universität wien

DISSERTATION

Titel der Dissertation

„Total Synthesis of the Antibiotic (+)–Branimycin“

Verfasser

Mag. Stefan Marchart

angestrebter akademischer Grad

Doktor der Naturwissenschaften (Dr.rer.nat.)

Wien, Dezember 2009

Studienkennzahl lt. Studienblatt:	A 091 419
Dissertationsgebiet lt. Studienblatt:	Chemie
Betreuerin / Betreuer:	Univ.-Prof. Dr. Johann Mulzer

Für meine Eltern Josef und Edith
und für Christa

Danksagung

Danken möchte ich an dieser Stelle allen, die in jeglicher Form an dem Entstehen dieser Dissertation mitgeholfen haben und mir mit ihrer Bereitschaft und Unterstützung zur Seite standen.

An erster Stelle möchte ich mich bei **Prof. Johann Mulzer** bedanken. Sein Interesse und Engagement für dieses außerordentlich herausfordernde Projekt, gemeinsam mit den unzähligen lehrreichen Gesprächen, Vorlesungen und Seminaren waren für mich von unschätzbarem Wert. Es war mir außerdem stets möglich unabhängig und eigenständig an diesem Projekt zu arbeiten.

Besonderer Dank gebührt meinen Laborkollegen Univ.-Doz. Dr. Valentin Enev und Dr. Alexey Gromov. Seit Beginn meiner Diplomarbeit teilten Sie stets bereitwillig ihr Wissen (und ihre Chemikalien) mit mir, und auch moralisch boten sie mir auf dem teilweise recht steinigen Pfad der Naturstoffsynthese die nötige Unterstützung. Der erfolgreiche Abschluß dieser Dissertation wurde in hohem Maße von ihnen beeinflußt.

Im Laufe der Jahre beteiligten sich viele Kollegen an der Totalsynthese von Branimycin: Dr. Wolfgang Felzmann, Dr. Christian Pilger, Dr. Daniele Castagnolo und Dr. Daniela Rosenbeiger sei an dieser Stelle ebenfalls recht herzlich gedankt. Ein großes Dankeschön möchte ich Ing. Martina Drescher aussprechen, durch deren tatkräftige Unterstützung vor allem die Endphase dieses Projekts merklich verkürzt werden konnte.

Für das nette Arbeitsklima und die schöne Zeit möchte ich mich bei all meinen Kollegen bedanken: Ass. Prof. Dr. Harry Martin, Dr. Uwe Rinner, Prof. Dr. Fritz Hammerschmidt, Dr. Konrad Tiefenbacher, Dipl. Ing. Harald Weinstabl, Dr. Roland Barth, Mag. Thomas Magauer, Dr. Tanja Gaich, Dr. Andreas Gollner, Dr. Kathrin Höferl-Prantz, Dr. Anna Innitzer, Dr. Marion Kögl (in ewiger Erinnerung), Dr. Peter Siengalewicz, Dipl. Chem. Lutz Kleemann, Dr. Anna Schweifer, Dr. Edyta Kuliszewska, Dr. Dagmar Kapeller, Dipl. Ing. Jürgen Ramharter**,** Mag. Martin Himmelbauer**,** Dr. Katja Jantos, Mag. Christian Aichinger, Mag. Rita Fürst, Mag. Christoph Lentsch, Mag. Christina Nowikow und Mag. Anna Wieczorek.

Dank Dr. Hanspeter Kählig, Dr. Lothar Brecker und Ing. Susanne Felsinger war stets ein hervorragender und reibungsloser NMR-Betrieb gewährleistet. Danke auch für die verlässlichen Messungen des MS-Teams: Ing. Peter Unteregger und Josef Plangger. Ein großes Dankeschön spreche ich dem HPLC-Team aus, deren Dienste ich besonders oft und auch für sehr große Mengen in Anspruch nehmen mußte: Ing. Sabine Schneider, Fikret Nasufi und Michael Zinke.

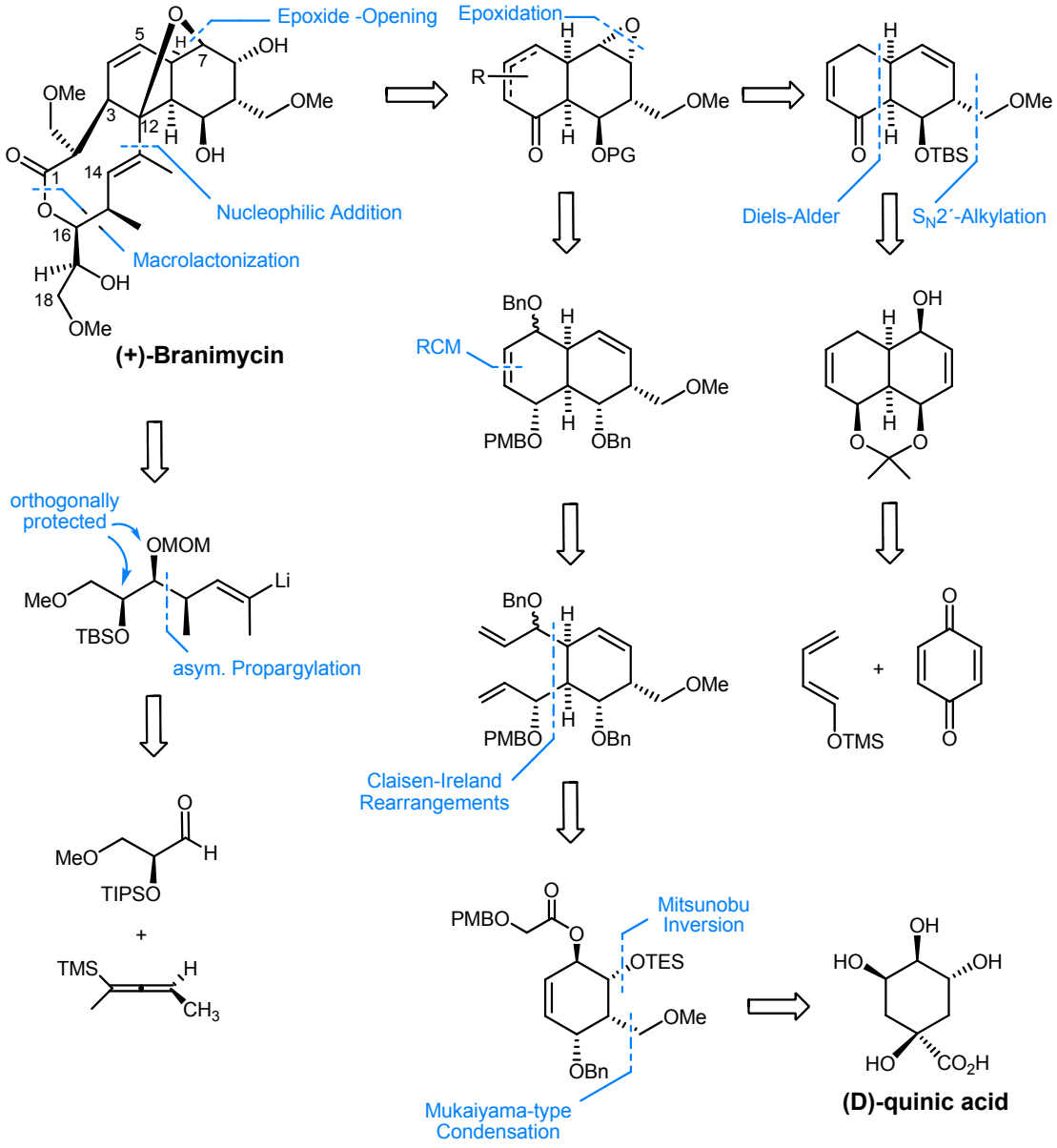
Bei Martin Lux-Amon, Jale Karolyi-Özgür, Sabine Brkovic und Walter Dietrich möchte ich mich ebenfalls für die angenehme Zusammenarbeit und deren Hilfsbereitschaft bedanken.

Wenn das seelische Gleichgewicht mal wieder zu kippen drohte warst du immer zur Stelle. Nicht nur dafür danke ich dir Christa.

Abschließend möchte ich meiner Familie meinen Dank aussprechen. Meinen Dank, für die jahrelangen Bemühungen und ihre immense Unterstützung. Ich hoffe, daß ich euch eines Tages etwas zurückgeben kann.

A. Graphical Abstract

Total Synthesis of (+)–Branimycin



B. Abstract

This Ph.D. thesis describes the first total synthesis of (+)–branimycin.

Branimycin, produced by *Actinomycete GW 60/1571* is a member of a new family of macrolide antibiotics known as the nargenicins. It exhibits activity against *Bacillus subtilis, Escherichia coli*, *Staphylococcus aureus* and in particular against *Streptomyces viridochromogenes*. The structure of branimycin, which was elucidated by multidimensional NMR experiments only, is unusually complex, as 24 out of the 25 carbon atoms are either functionalized and/or stereogenic.

We planned a convergent approach towards branimycin – formation of the diaxial 7,12-ether bridge should be accomplished *via* an intramolecular epoxide opening in the course of a 1,2-addition of the polyketide side chain to the *cis*-decalin nucleus. In this thesis, the densely functionalized *cis*-fused decalin core was accessed by the following two synthetic strategies: Starting from (-)–quinic acid all chiral centers were established *via* purely substrate controlled transformations applying a high yielding Claisen-Ireland rearrangement – RCM protocol. Furthermore an intermolecular quinone based Diels-Alder cycloaddition was used to establish the *cis*-decalin carbon framework right at the beginning. Anti-selective S_N2'-alkylation and regioselective allylic oxidation provided the desired substitution pattern.

By successive coupling of the *cis*-decalin nucleus with the lithiated side chain, the remote stereochemistry of the macrolide ring and the oxa-bridge of the nucleus could be incorporated in only one synthetic step. After several synthetic transformations the two-carbon ester portion of the branimycin macrolid system was introduced *via* a stereoselective 1,4-addition. Further synthetic manipulations culminated in the closure of the highly strained nine-membered lactone ring containing the internal *trans*-double bond, followed by the final global deprotection.

In addition, the proposed structure was validated and the absolute stereochemistry could be determined.

C. Zusammenfassung

Die vorliegende Dissertation beschreibt die erste Totalsynthese von (+)–Branimycin.

Branimycin, ein Antibiotikum das aus dem Stamm *Actinomycet GW 60/1571* isoliert wurde, ist Vertreter einer Familie neuartiger Makrolid-Antibiotika: den Nargenicinen. Es zeigt deutliche antimikrobielle Aktivität gegen *Bacillus subtilis, Escherichia coli*, *Staphylococcus aureus* und insbesondere gegen *Streptomyces viridochromogenes.* Die Struktur von Branimycin, welche ausschließlich mittels mehrdimensionaler NMR-Experimente ermittelt werden konnte, ist außergewöhnlich komplex, da 24 der 25 Kohlenstoffatome funktionalisiert und/oder stereogen sind.

Eine konvergente Synthesestrategie wurde verfolgt – mittels intramolekularer Epoxidöffnung im Zuge einer 1,2-Addition der polyketidischen Seitenkette an das *cis*-Dekalin Kernfragment sollte die 7,12-Etherbrücke aufgebaut werden.

In dieser Dissertation werden zwei verschiedene Zugänge zum Aufbau des hochfunktionalisierten *cis*-Dekalin Kerns beschrieben: Ausgehend von (-)–Chinasäure konnten alle chiralen Zentren ausschließlich unter Substratkontrolle in hohen Ausbeuten aufgebaut werden. Als Schlüsselschritte dienten hierzu zwei Claisen-Ireland Umlagerungen sowie eine ringschließende Metathese (RCM). Der zweite Zugang bediente sich einer intermolekularen Quinon-Diels-Alder Cycloaddition. Das *cis*-Dekalin Grundgerüst wurde hierbei bereits im ersten Syntheseschritt aufgebaut. Nach einer anti-selektiven S_N2'-Alkylierung sowie einer regioselektiven allylischen Oxidation konnte das Produkt zum gewünschten vollständig funktionalisierten *cis*-Dekalinepoxid umgesetzt werden.

Mittels 1,2-Addition der lithiierten polyketidischen Seitenkette an das *cis*-Dekalinepoxid konnten erfolgreich in nur einem Syntheseschritt die beiden Hauptfragmente verbunden, sowie die 7,12-Etherbrücke aufgebaut werden. Nach zwei weiteren Syntheseschritten wurde stereoselektiv die C1,C2-Esterkomponente über eine 1,4-Addition eingeführt. Die nach wenigen weiteren Transformationen erhaltene Seco-Säure wurde erfolgreich in ein sehr gespanntes, eine *trans*-Doppelbindung beinhaltendes neungliedriges Lakton überführt, durch darauffolgende Abspaltung der Schutzgruppen wurde (+)–Branimycin erhalten.

Mit dem erfolgreichen Abschluß dieser Totalsynthese konnte die vorgeschlagene Struktur von Branimycin bestätigt, als auch dessen Absolutkonfiguration bestimmt werden.

Publications and Conferences

Publications

"Toward the Synthesis of the Antibiotic Branimycin: Novel Approaches to Highly Substituted *cis*-Decalin Systems", Mulzer, J.; Castagnolo, D.; Felzmann, W.; Marchart, S.; Pilger, C.; Enev, V. S.; *Chem. Eur. J*. **2006**, *12*, 5992-6001.

"*cis*-Decalins from Quinic Acid: Toward a Synthesis of Branimycin", Marchart, S.; Mulzer, J.; Enev, V. S.; *Org. Lett*. **2007**, *9*, 813-816.

"Total Synthesis of the Antibiotic Branimycin", Marchart, S.; Gromov, A.; Mulzer, J. *Angew. Chem., Int. Ed*. **2009**, *accepted*.

A few other publications are in preparation.

Conference Contributions

31. Doktorandenworkshop der Universitäten Bayreuth, Leipzig, Wien, Würzburg, Halle und Jena, May 2006 (Würzburg, Germany):
Lecture title: "Auf dem Weg zum Branimycin"

The Vienna Symposium of Organic Chemistry, September 2007 (Vienna, Austria):
Lecture Title: "Towards the Total Synthesis of Branimycin"

Symposium of Organic Chemistry at ESPCI, February 2009 (Paris, France):
Poster Title: "Towards the Total Synthesis of Branimycin"

22. Irseer Naturstofftage der DECHEMA e. V., February 2010 (Irsee, Germany):
Lecture Title: "The Total Synthesis of the Antibiotic Branimycin"

39. Fränkisch-Mitteldeutsches Naturstofftreffen, April 2010 (Jena, Germany)
Lecture title: "Die Totalsynthese des Antibiotikums Branimycin"

Press-Releases

"In (noch) 30 Stufen zum hochwirksamen Bakterienkiller", **Die Presse** (02.05.2006).

Table of Contents

INTRODUCTION AND BACKGROUND

1. Branimycin and Related Natural Products 1

1.1 Branimycin 1

1.2 The Nargenicins: Isolation, Biological Activity and Structure Elucidation 2

1.3 Luminamicin/Coloradocin/Lustromycin 4

1.4 Biosynthesis 4

2. Synthetic Routes to *cis*-Decalins 7

2.1 Synthesis of *cis*-decalins from Wieland-Miescher type ketones 7

2.2 Diels-Alder cycloaddition 9

2.2.1 Intermolecular cycloaddition 9

2.2.2 Intramolecular cycloaddition 11

2.3 Cope rearrangements 14

2.4 Cyclization methods 16

3. Previous Synthetic Work 21

3.1 Approaches towards the nargenicin family 21

3.1.1 Kallmerten´s synthesis of 18-deoxynargenicin A_1 21

3.2 Approaches towards branimycin in the Mulzer group 23

3.2.1 Quinic acid based INOC approach 23

3.2.2 Lactone based INOC approach 24

3.2.3 *Trans*-Annular Diels-Alder approach 24

3.2.4 S_N2' oxa-bridge opening – RCM approach 25

3.2.5 Diepoxynaphthalene-desymmetrization approach 26

3.2.6 Synthesis of the C13-C18 side chain 27

4. Outline of the Synthetic Plan 29

RESULTS AND DISCUSSION

5. Toward the Synthesis of the Antibiotic Branimycin: Novel Approaches to Highly Substituted *cis*-Decalin Systems 32

6. *cis*-Decalins from Quinic Acid: Toward a Synthesis of Branimycin 43

6.1 Additional work on the quinic acid approach 77

7. Total Synthesis of the Antibiotic Branimycin 79

7.1 Additional remarks 140

7.1.1 Synthesis of decalin ketone 2 140

7.1.2 Modification of the C13-C18 side chain 141

7.1.3 Introduction of the C5-oxygen functionality 142

7.1.4 C2-C3 bond formation *via* conjugate addition and completion of the synthesis of branimycin (1) 142

7.2 Additional experimental procedures 145

8. Summary 149

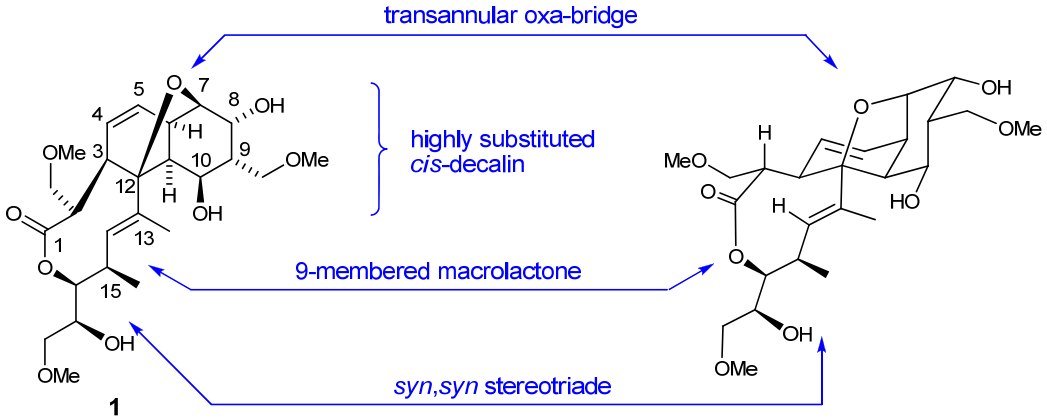
9. Abbreviations 150

INTRODUCTION AND BACKGROUND

1. Branimycin and Related Natural Products

1.1 Branimycin

In 1998, branimycin (**1**) has been isolated from *Actinomycete GW 60/1571* and structurally characterized by the Laatsch group at the University of Göttingen.[1] Biological tests have shown that **1** is active against *Bacillus subtilis, Escherichia coli*, *Staphylococcus aureus* and in particular against *Streptomyces viridochromogenes*. The basic C-C connectivities were determined by extensive NMR analysis. Full structural assignment was possible by comparison with the NMR data available for the related compound nargenicin A_1 (**2**) and also based on NOE-interactions.



1

Figure 1: Assigned structure of branimycin (**1**).

The structure of branimycin (**1**) is unusually complex, as 24 out of the 25 carbon atoms are either functionalized and/or stereogenic. It is characterized by a highly functionalized *cis*-decalin core, where C7 and C12 are spanned by a transannular oxa-bridge (Figure 1). Annulated to the decalin is a nine-membered macrolide ring with an internal *trans*-double bond, the stereocenters on the C13-C18 polyketide chain of the macrocycle are in a *syn,syn*-relationship. All in all, there are 12 stereocenters, 2 double bonds, 3 secondary OH- and 3 CH_2OMe functions.

[1] a) Speitling, M. *Dissertation*, Universität Göttingen, **1998**. (b) Speitling, M.; Grün-Wollny, I.; Hannske, F. G.; Laatsch, H. *12. And 13. IRSEER Naturstofftage der DECHEMA e.V. Irsee* **2000**, **2001**, poster sessions.

1.2 The Nargenicins: Isolation, Biological Activity and Structure Elucidation

In 1977 a novel family of antibiotics has been isolated by workers at Pfizer and Upjohn: the nargenicins. A stem of Nocardia, named *Nocardia argentinensis* nov. gen. (ATCC 31306), produced novel antibiotics upon aerobic submerged fermentation.[2] One of these antibiotics, CP 47,777 was subsequently patented, although without disclosing its structure. Some years later the structure was published, making it the first member of a new class of antibiotics, and the name nargenicin A_1 (**2**) was proposed.[3]

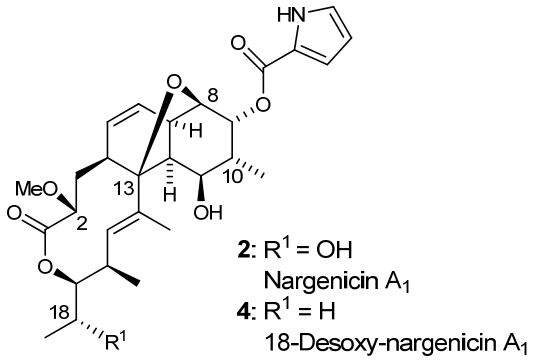


Figure 2: Nargenicin A_1 and its 18-Deoxy-derivative.

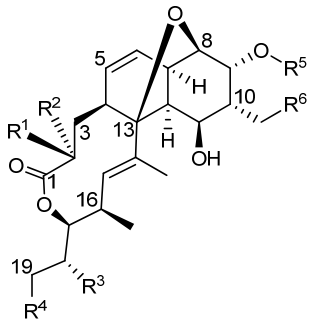
In general, the nargenicin family can be described by an oxygen-bridged *cis*-decalin system, annulated to a 10-membered macrolactone ring. So far, ten members of this new family of antibiotics have been published (Table 1).

Determination of the structure was based on extensive NMR-analysis which allowed initial assignment of all stereocenters of nargenicin A_1 except positions 2, 16, 17 and 18 residing on the flexible macrolactone ring (Figure 2). Shortly after the publication of the structure of nargenicin A_1 (**2**), scientists from Upjohn published the isolation of nodusmycin (**3**),[4] another antibiotic that differs only at the C9 position lacking the 2-pyrrol-carboxylate functionality. In contrast to nargenicin, nodusmycin (**3**) could be crystallized and X-ray analysis unambiguously proved the relative configuration of both the polyketide macrolactone and the *cis*-decalin core. Based on this information, the structure of **2** was also successfully elucidated. Non empirical CD exciton chirality method of Nakanishi showed a positive Cotton effect for the C11 *p*-nitrobenzoylated analog and thus identified the absolute configuration of nargenicin

[2] Celmer, W. D.; Cullen, W. P.; Moppett, C. E.; Jefferson, M. T.; Huang, L. H.; Shibakawa, R.; Tone, J. **U.S.** Patent 4,148,883, **1979**.
[3] Celmer, W. D.; Chmurny, G. N.; Moppett, C. E.; Ware, R. S.; Watts, P. C.; Whipple, E. B. *J. Am. Chem. Soc.* **1980**, *102,* 4203 - 4209.
[4] Whaley, H. A.; C. G. Chidester, C. G.; Mizsak, S. A.; Wnuk, R. J. *Tetrahedron Lett.* **1980**, *21*, 3659-3662.

A_1[5] which was additionally confirmed by feeding experiments (*vide infra*). Based on these results, the absolute configurations of other members of the nargenicin family were hypothesized.

In 1982, the structure of 18-deoxynargenicin (**4**), another constituent in these fermentations,[2] could be determined by selective deoxygenation of nargenicin A_1 (**2**) at the C18 position.[6]



Name	R^1	R^2	R^3	R^4	R^5	R^6	Ref.
Nodusmycin **(3)**	OMe	H	OH	H	H	H	4
Nargenicin A_1 **(2)**	OMe	H	OH	H	PC	H	2, 3
18-Deoxynargenicin **(4)**	OMe	H	H	H	PC	H	6
Nargenicin B_1 **(5)**	H	OH	OH	OMe	PC	OMe	7, 8
Nargenicin B_2 **(6)**	H	OH	H	OH	PC	OMe	7, 8
Nargenicin B_3 **(7)**	H	OH	OH	OMe	PC	H	7, 8
Nargenicin C_1 **(8)**	OMe	H	OH	OMe	PC	OMe	7, 8

PC =  2-pyrrole-carboxylate

Table 1: The nargenicin family.

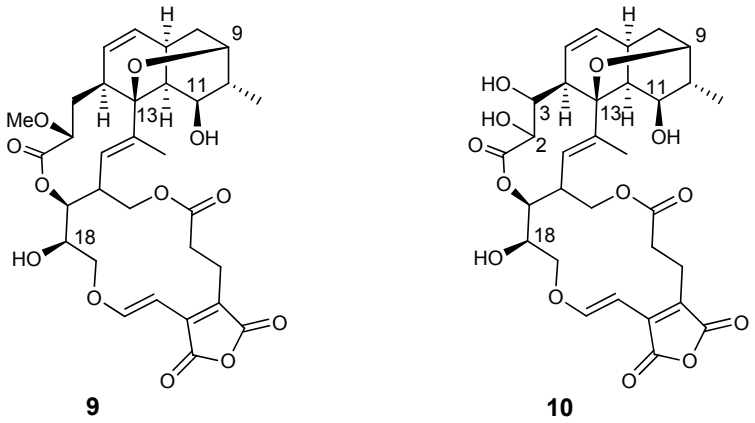
The Pfizer group also patented the isolation of the antibiotics CP 51,467, CP 52,726, and CP 52,748 from the species *Nocardia argentinensis* Huang ATCC 31438,[7] without disclosure of its structure. However, a few years later another antibiotic was patented by the same group: nargenicin C_1 (**8**).[8] In this patent the structure of **8** as well as the structures of nargenicins B_1-B_3 (**5-7**) were published.

[5] (a) Cane, D. E.; Yang, C.-C. *J. Antibiot.* **1985**, *38,*423-426. (b) Cane, D. E.; Yang, C.-C. *J. Am. Chem. Soc.* **1984**, *106,* 6633-6634.
[6] Magerlein, B. J.; Reid, R. J. *J. Antibiot.* **1982**, *35,* 254-255.
[7] Celmer, W. D.; Cullen, W. P.; Moppett, C. E.; Jefferson, M. T.; Huang, L. H.; Shibakawa, R.; Tone, J. *United States Patent* US 4,224,314, **1980**.
[8] Celmer, W. D.; Cullen, W. P.; Shibakawa, R.; Tone, J. *United States Patent* US 4,436,747, **1984**.

1.3 Luminamicin/Coloradocin/Lustromycin

Luminamicin (**9**) was isolated by Japanese scientists from a stem of genus Nocardioides.[9] It exhibits antibacterial activity against anaerobic bacteria, especially Clostridium. In 1987 researchers from Abbott Laboratories isolated coloradocin from *Actinoplanes coloradoensis*,[10] which proved identical to luminamicin. With a combination of molecular dynamics studies and Mosher ester derivatization at the C11 and C18 – hydroxyl groups the absolute configuration of luminamicin (**9**) could be determined. The structure of the closely related lustromycin (**10**) was only determined by NMR-analysis.[11] To date, the stereochemistry at C2 and C3 could not be elucidated (Figure 3).

Although the structures of **9** and **10** substantially differ from nargenicin A_1 (**2**) they also can be ascribed to this family. While the oxygen bridge connects C9 – C13, it also combines a *cis*-decalin core and a 10-membered lactone with a very closely related substitution pattern.



9 **10**

Figure 3: Luminamicin (**9**) and Lustromycin (**10**).

1.4 Biosynthesis

The biosynthetic origin of the nargenicins has been proposed on the basis of ^{13}C incorporation experiments in fermentations of *Norcardia argentinensis*.[12] These studies showed that the nargenicin skeleton, including the oxygens at C1, C9, C11 and C17 is apparently derived from 5 acetate and 4 propionate units, and the Me group of the C2-OMe from methionine (Figure 4). As none of these oxygens is derived from molecular oxygen, simple aldol and/or epoxide-

[9] Omura, S.; Iwata, R.; Iwai, Y.; Taga, S.; Tanaka, Y.; Tomoda, H. *J. Antibiot.* **1985**, *38*, 1322-1326.
[10] Jackson, M.; Karwowski, J. P.; Tehriault, R. J.; Fernandes, P. B.; Semon, R. C. *J. Antibiot.* **1987**, *40*, 1375-1381.
[11] (a) Omura, S.; Imamura, N.; Oiwa, R.; Kuga, H.; Iwata, R.; Masuma, R.; Iwai, Y. *J. Antibiot.* **1986**, *39*, 140. (b) Tomoda, T.; Iwata, R.; Takahashi, Y.; Iwai, Y.; Oiwa, R.; Omura, S. *J. Antibiot.* **1986**, *39*, 1205-1210.
[12] (a) Cane, D. E.; Yang, C.-C. *J. Antibiot.* **1985**, *38*,423-426. (b) Cane, D. E.; Yang, C.-C. *J. Am. Chem. Soc.* **1984**, *106,* 6633-6634. c) Snyder, W. C.; Rinehart, K. L. *J. Am. Chem. Soc.* **1984**, *106*, 787-789.

olefin condensations can be ruled out. Late stage oxidation studies executed in an $^{18}O_2$-atmosphere proved that the oxygens at C2, C8/13 and C18 are derived from molecular oxygen.[12a] Based on these informations Cane suggested that the *cis*-fused decalin core of **2** may be established *via* an intramolecular Diels-Alder cycloaddition mechanism in the polyketide chain **11**, a pathway which is consistent with the distribution of functionality and stereochemistry in the natural product (Scheme 1).

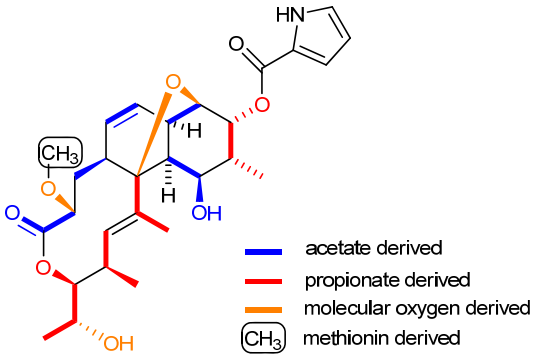
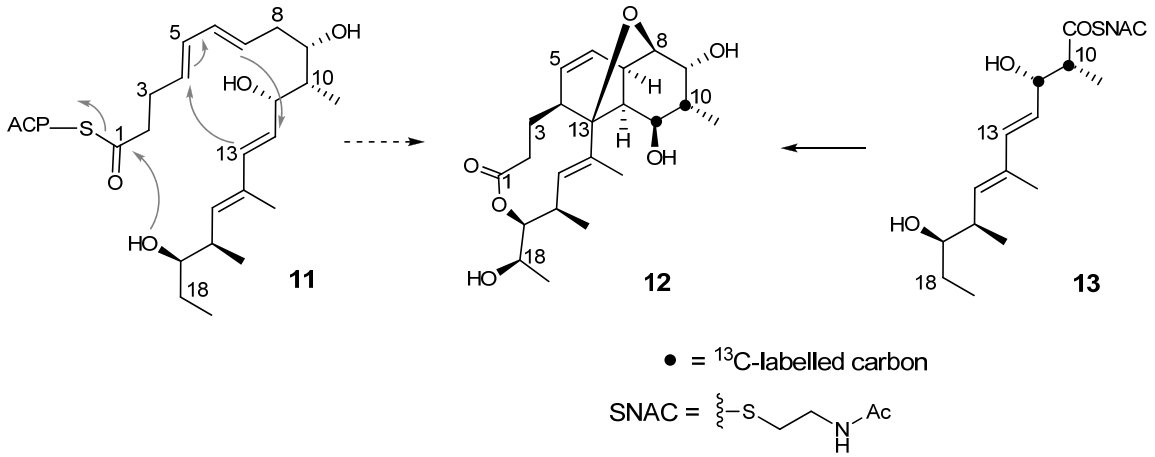


Figure 4: Biosynthetic origin of nargenicin A_1.

Diels-Alder adduct **12** is then further functionalized in late stage oxidation steps.

This hypothesis was corroborated by successful incorporation of ^{13}C-labelled chain elongation intermediate **13** into the nargenicin biosynthesis.[13]



Scheme 1: Proposed biosynthetic intramolecular Diels-Alder pathway.

Biosynthetic studies on luminamicin (**9**) proved unambiguously that the upper tricyclic ring system is also a polyketide whose biosynthesis generally follows the pattern established for nargenicin A_1 (**2**).[14] The path by which the carbons of the more unique lower bicyclic ring

[13] Cane, D. E.; Luo, G. *J. Am. Chem. Soc*. **1995**, *117*, 6633-6634.
[14] McAlpine, J. B.; Mitscher, L. A.; Jackson, M.; Rasmussen, R. R.; Velde D.V.; Veliz, E. *Tetrahedron* **1996**, *52*, 10327-10334.

system are assembled did not give an equally consistent picture. Feeding experiments with sodium (2,3-$^{13}C_2$)succinate provided direct evidence that C26 – C28 are derived from succinate, indicating the presence of an active citric acid cycle. It requires, however, that a carboxyl originally attached to C26 is lost along the sequence. Surprisingly, succinate being the source of C29 – C32 could be ruled out. They are synthesized in an uncommon pathway from acetate. The biosynthesis of this lower bicyclic ring system is definitely different from those few published for naturally occurring anhydrides. No ^{18}O-labelling studies have been reported so far, therefore the origin of this "abnormal" C9 – C13 oxa-bridge remains unclear.

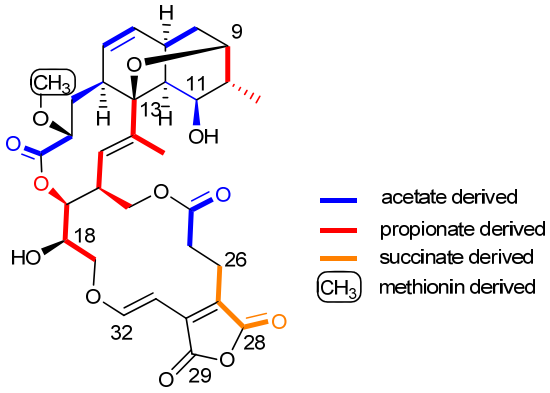


Figure 5: Biosynthesis of luminamicin.

So far no biosynthetic studies on branimycin (**1**) have been carried out. The similarity between nargenicin and branimycin from C4 upwards suggests a similar biosynthetic pathway. However, the C1 to C3 unit of branimycin cannot be constructed *via* two acetates. Also, the way of introducing the CH_2OMe group at C2 is not clear.

2. Synthetic Routes to *cis*-Decalins

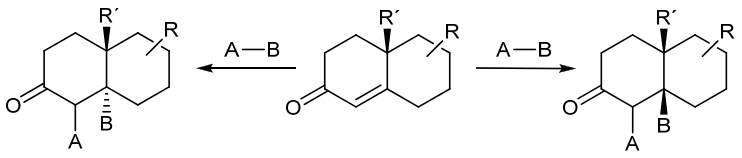
The *cis*-decalin ring system is present in a wide variety of polyterpenoids and many other natural products with interesting biological activity. The importance of *cis*-decalins in natural products has led to the development of an immense diversity of methods for its preparation. Containing eleven C-C bonds, many different bond disconnections are possible, and most of these disconnections have appeared in numerous publications over the years.

Among the various strategies for the synthesis of *cis*-fused decalin ring systems, Robinson annulation is one of the earliest and probably most well-known classical methods. The second most popular strategy involves the Diels-Alder (both intra- and intermolecular) reaction for the assembly of *cis*-decalins. As work in this area intensified, more and more new methods and strategies were developed. Broadly, most of these strategies for the construction of the *cis*-decalin framework can be divided into four categories: (a) syntheses starting with Wieland-Miescher type ketones, (b) Diels-Alder reactions, (c) Cope rearrangements and (d) cyclization strategies.

2.1 Synthesis of *cis*-decalins from Wieland-Miescher type ketones

Wieland-Miescher (WM) type ketones can of course be considered as part of a cyclization strategy, as they are normally made *via* Robinson annulation or Diels-Alder reaction. In order to arrange the classification of the various strategies more clearly, the syntheses of *cis*-decalins derived from WM type ketones are discussed separately.

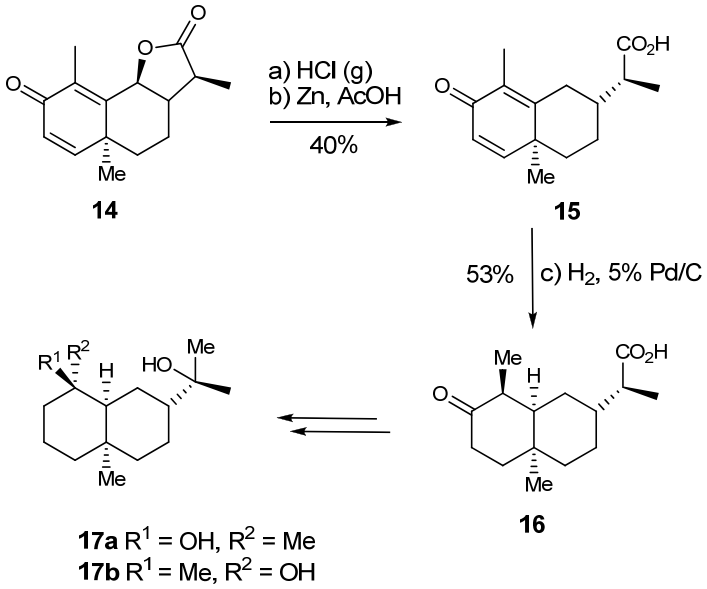
WM type ketones are venerable starting materials for the synthesis of *cis*-decalin-containing natural products. One of the key steps in the formation of the decalin core is saturation of the double bond at the ring junction (Scheme 2). Both, *cis*- and *trans*-decalins can be generated at this stage. Applying Birch conditions normally gives the *trans*-decalin skeleton whereas catalytic hydrogenation should give stereospecifically the *cis*-fused skeleton.



Scheme 2: Saturation at the ring junction of WM type ketones.

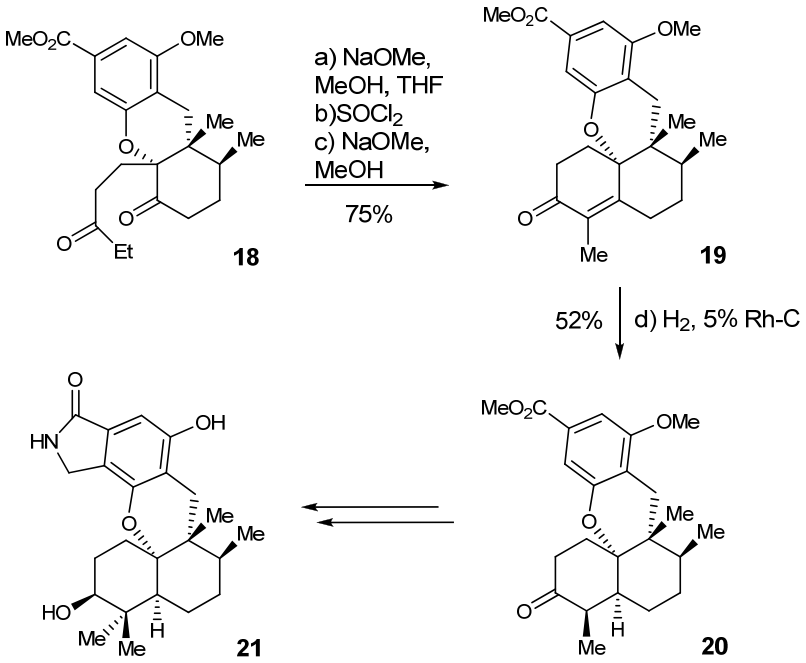
As a recent example Ando and co-workers synthesized in 1994 *cis*-decalin-based eudesmanes **17a** and **b** (Scheme 3). α–Santonin **14** was first transformed into 6-epi-santonin, which gave

carboxylic acid **15** upon reduction with Zn. Catalytic hydrogenation of **15** gave *cis*-fused decalin **16** which was then further transformed to the eudesmanes **17a,b**.



Scheme 3: Ando´s synthesis of eudesmanes **17a/b**.

In 1998, Mori and co-workers reported the first total synthesis of stachyflin (**21**).[15] Intramolecular aldol condensation on diketone **18** gave decalenone **19**, which on Rh-catalyzed



Scheme 4: Mori´s synthesis of stachyflin (**21**).

[15] Taishi, T.; Takechi, S.; Mori, S. *Tetrahedron Lett*. **1998**, *39*, 4347.

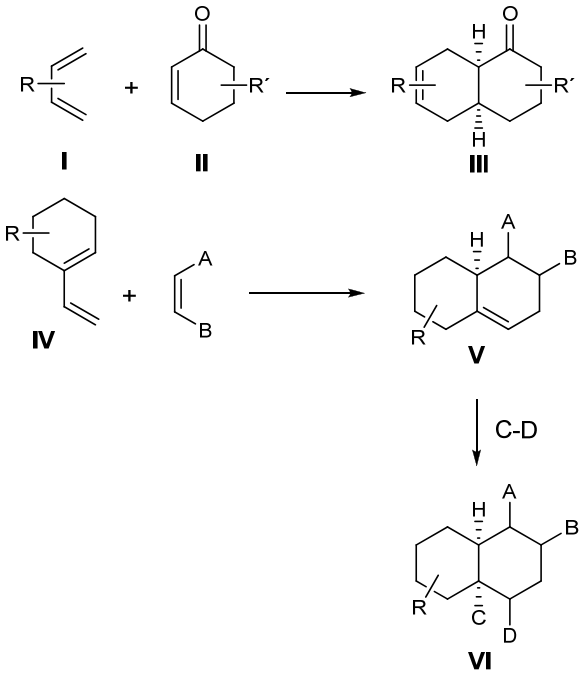
hydrogenation gave the desired *cis*-fused stachyflin precursor **20** as the major product (Scheme 4).

2.2 Diels-Alder cycloaddition

The Diels-Alder reaction is one of the most important and fascinating transformations in chemistry. Myriads of inter- and intramolecular Diels-Alder reactions have been employed to generate *cis*-decalin ring systems of any complexity.

2.2.1 Intermolecular cycloaddition

In general, two types of intermolecular Diels-Alder cycloadditions have been applied for the construction of *cis*-decalins (Scheme 5).

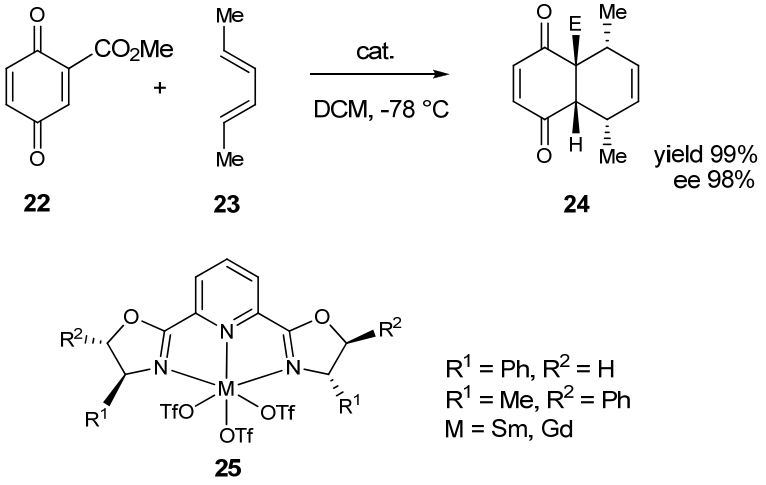


Scheme 5: Types of intermolecular Diels-Alder reactions.

In the first type an acyclic diene such as **I** reacts with a cyclic enone **II** directly to *cis*-fused decalin **III**, mostly in a stereo- and regioselective manner, provided both the diene and dienophile are appropriately activated. In the second type 1-vinylcyclohexene derivatives such as **IV** are used as Diels-Alder precursors. The resulting adduct **V** is unsaturated at the ring junction and has to be manipulated as discussed in section 2.1.

For more than 60 years the Diels-Alder reaction subtype using quinones as dienophiles has provided a powerful construction for functionalized *cis*-fused decalin systems. Examples include many of the most notable achievements in complicated synthetic chemistry: steroids,

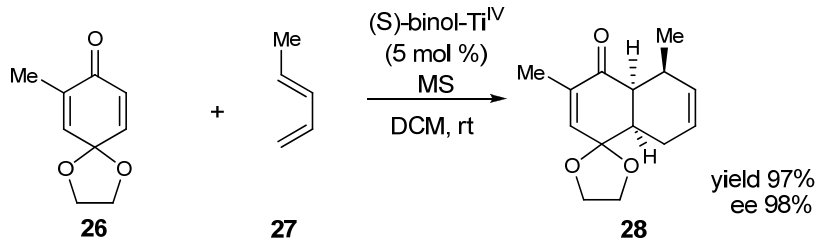
dendrobine, ibogamine, euonyminol, gibberellic acid, reserpine and trichodermol.[16] For many years there were no methods available for conducting these key quinone Diels-Alder reactions enantioselectively. This gap in methodology has just started to be filled. A recent example was described by Evans and Wu (Scheme 6).[17] They describe a new family of chiral Lewis acid complexes **25** derived from pyridyl-bis(oxazoline) ligands and gadolinium and samarium triflates. Reaction of quinone **22** with diene **23** gave adduct **24** in excellent yield and *ee*. The reaction was generally completed in less than 10 min; the product enantioselectivity was highly dependent on the choice of solvent system. The reaction is general and also gave high *ee´s* with other quinones and dienes.



Scheme 6: Evans´ enantioselective quinone Diels-Alder reaction of **22** and **23**.

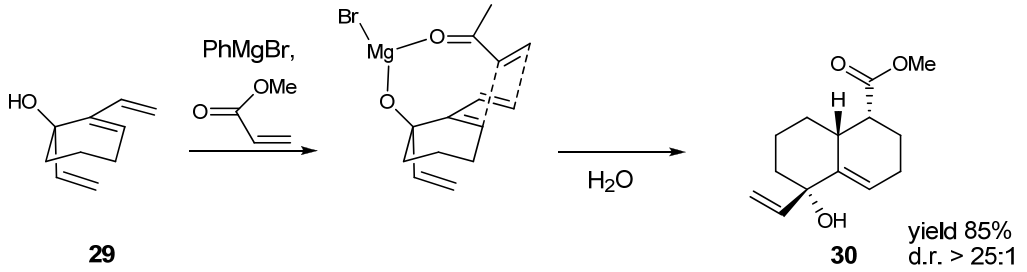
Corey *et al*. have focused on the use of 1,4-quinone monoketals [18] rather than the corresponding quinones as the monoketals are expected to be more Lewis basic and also the problem of aromatization could be avoided. Excellent results were obtained using e.g. 1,4-quinone monoketal **26** together with pentadiene **27** in the presence of binol-Ti^{IV} based catalyst. The use of molecular sieves that contain water was crucial, accelerating the reaction and making it more efficient (Scheme 7).

[16] a) Woodward, R. B.; Sondheimer, F. *J. Am. Chem. Soc.* **1952**, *74*, 4223. b) Salley, S. I. *J. Am. Chem. Soc.* **1967**, *89*, 6762. c) Kende, A. S.; Bently, T. J.; Mader, A. R.; Ridge, D. *J. Am. Chem. Soc.* **1974**, *96*, 4332. d) Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S.; Siret, P.; Keck, G. E.; Gras, J. *J. Am. Chem. Soc*. **1978**, *100*, 8031. e) Still, W. C.; Tsai, M. Y. *J. Am. Chem. Soc.* **1980**, *102*, 3654. f) White, J. D.; Cutshall, N. S.; Kim, T. S.; Shin, H. *J. Am. Chem. Soc*. **1995**, *117*, 9780.
[17] Evans, D. A.; Wu, J. *J. Am. Chem. Soc*. **2003**, *125*, 10162.
[18] Breuning, M.; Corey E. J. *Org. Lett*. **2001**, *3*, 1559.



Scheme 7: Corey´s enantioselective Diels-Alder reaction of quinone monoketal **26**.

Barriault *et al*. give an example for the second type of intermolecular Diels-Alder cycloadditions. [19] They successfully developed a method that controls regio- and stereoselectivity of the Diels-Alder reaction with PhMgBr of semicyclic dienes such as **29**

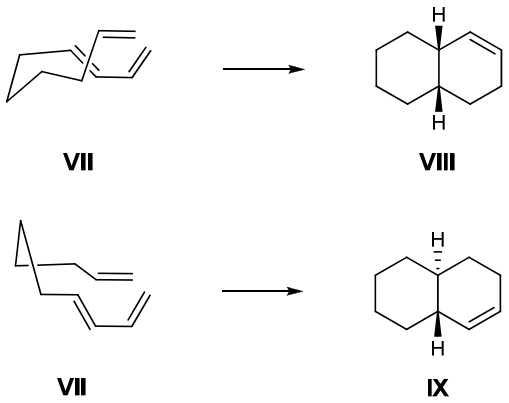


Scheme 8: Barriault´s hydroxyl group-directed Diels-Alder reaction.

possessing a secondary or tertiary allylic alcohol functionality in the β–position with activated dienophiles such as methyl acrylate, methacrolein and *N*-phenylmaleimide. Decalene **30** was obtained in a highly regio- and diastereoselective manner (Scheme 8).

2.2.2 Intramolecular cycloaddition

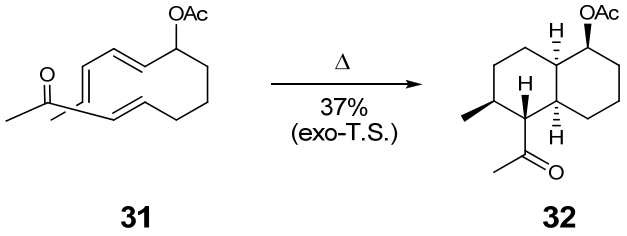
The intramolecular Diels-Alder cycloaddition (IMDA) has also been employed in numerous syntheses to construct the decalin skeleton. Depending on the transition state a triene such as



Scheme 9: Intramolecular Diels-Alder reaction.

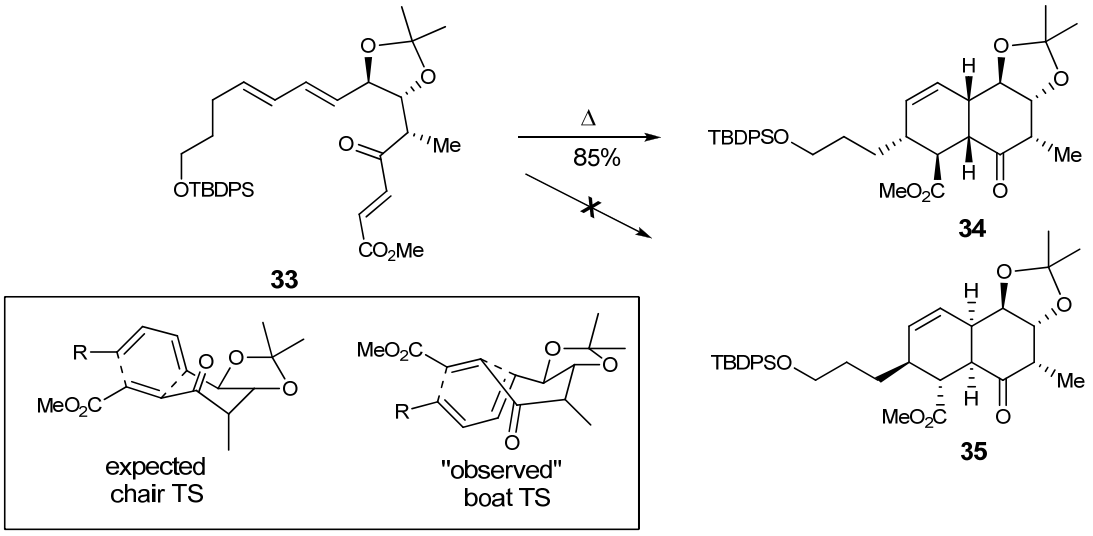
[19] Barriault, L.; Thomas, J. D. O.; Clement, R. *J. Org. Chem*. **2003**, *68*, 2317.

VII can either give *cis*-fused decalin **VIII** or the *trans*-fused decalin such as **IX** (Scheme 9). In intramolecular Diels-Alder reactions the prediction of the stereochemistry is not always easy as several factors such as steric, stereoelectronic and competing conformational effects can strongly influence the transition state.



Scheme 10: Jones´ IMDA approach.

In many cases, the use of Lewis acids favors an increased ratio of *endo:exo* products. It appears that secondary orbital interactions do not play a dominating role in intramolecular Diels-Alder reactions as quite often the stereochemical result turned out to be independent of the geometry of the dienophile moiety.



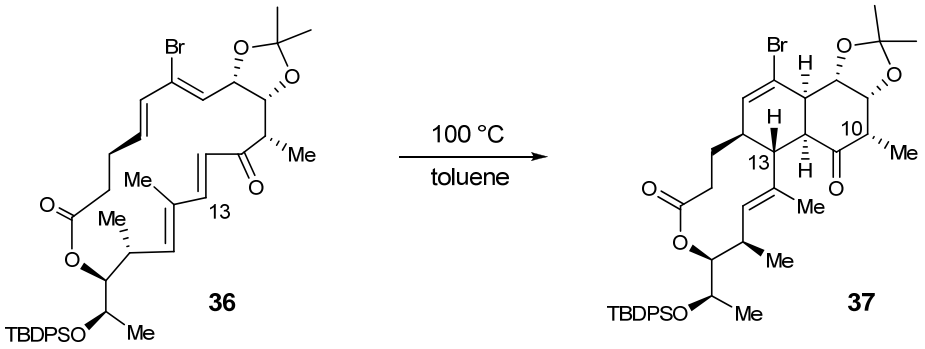
Scheme 11: Roush´s IMDA approach to the *cis*-decalin core of nargenicin A_1.

The placement of a functional group can change the product distribution. In many cases the presence of a carbonyl group in conjugation with the diene moiety helps in the formation of the *trans* product, whereas, if a carbonyl group is in conjugation with the double bond of the dienophile, the *cis* product is predominantely formed. Also in context of approaching the nargenicin family three IMDA strategies were applied.[20] In 1985, Jones *et al*. published a

[20] Also in the Mulzer group an IMDA strategy was applied to generate the decalin core of branimycin (*vide infra*).

model study on the construction of the oxa-bridged *cis*-decalin skeleton present in the nargenicin family.[21] Trienone **31** underwent an exo-cycloaddition to give *cis*-decalin **32**. Unfortunately, all attempts to introduce the oxa-bridge failed (Scheme 10).

Similar to the retrosynthetic considerations by Jones, Roush *et al*. also envisioned to construct the *cis*-decalin core (**35**) of nargenicin A_1 (**2**) *via* an IMDA cycloaddition.[22] Interestingly, upon heating, **33** underwent a clean cycloaddition to yield *cis*-decalin **34**, presumably *via* a boat-like transition state. Investigations of various diastereomeric substrates revealed that the involvement of a boat-like transition state in decatrienone intramolecular Diels-Alder reactions appears to be general (Scheme 11).

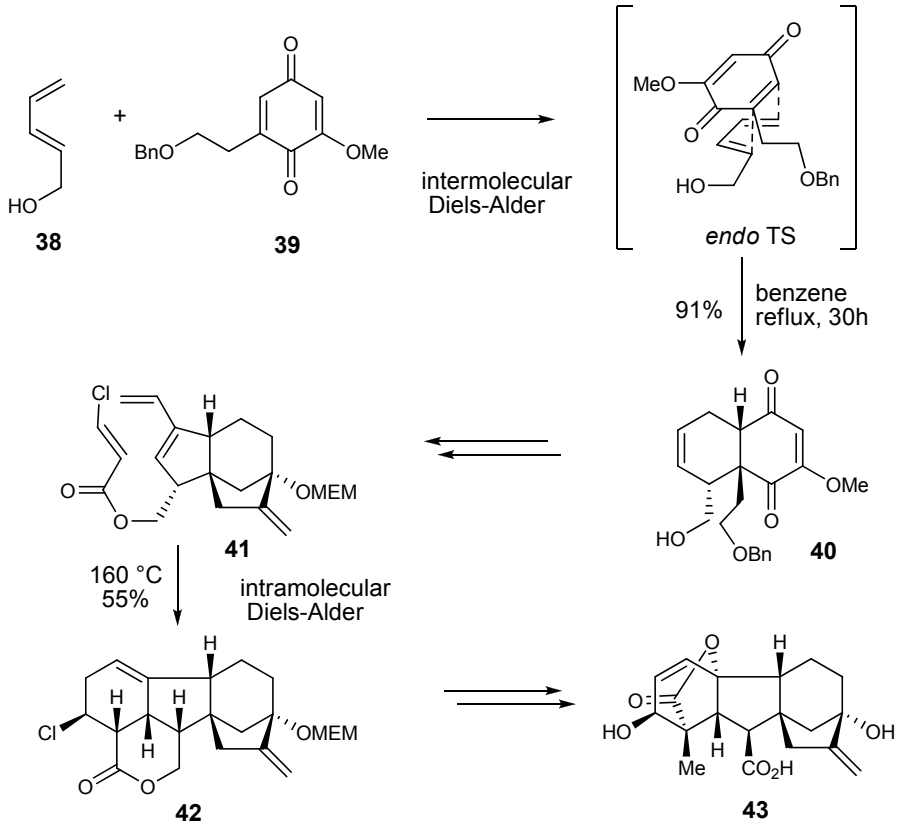


Scheme 12: Roush´s transannular Diels-Alder reaction of macrolactone **36**.

In continuation of their interest in this area, the Roush group turned their attention to an alternative strategy to create the entire carbon framework of nargenicin A_1 in one step *via* a transannular Diels-Alder reaction.[23] This strategy represents a biomimetic approach, as biosynthetic studies also propose a late stage intramolecular Diels-Alder reaction after full assembly of the polyketide chain.[12a] Under thermal conditions, macrolactone **36** converted selectively to *cis*-decalin **37** in high yields (85% b.r.s.m.). Also a minor amount of the C10-epimer was obtained. Unfortunately, also this route had to be abandoned as the C8-C13 ether bridge could not be introduced (Scheme 12).

Corey *et al*. used both inter- and intramolecular Diels-Alder reactions in the stereocontrolled synthesis of gibberellic acid (**43**).[24] An initial regio- and chemoselective Diels-Alder adduct between quinone **39** and diene **38** forged the relative stereochemistry in **40**. After a few steps the stage was set for a substrate-controlled intramolecular Diels-Alder reaction, which gave

[21] Jones, R. F.; Tunnicliffe, J. H. *Tetrahedron Lett*. **1985**, *26*, 5845-5848.
[22] Coe, J. W.; Roush, W. R. *J. Org. Chem.* **1989**, *54*, 915-930.
[23] Roush, W. R.; Koyama, K.; Curtin, M. L.; Moriarty, K. J**.** *J. Am. Chem. Soc.* **1996**, *118,* 7502-7512.
[24] Corey, E. J.; Danheiser, R. L.; Siret, P.; Keck, G. E.; Gras, J.-L. *J. Am. Chem. Soc*. **1978**, *100*, 8031-8034.



Scheme 13: Corey´s total synthesis of gibberelic acid (**43)**.

selectively desired **42** (Scheme 13). The outcome of this IMDA reaction was exactly as expected, based on the stereochemical requirements of the participating functionalities.

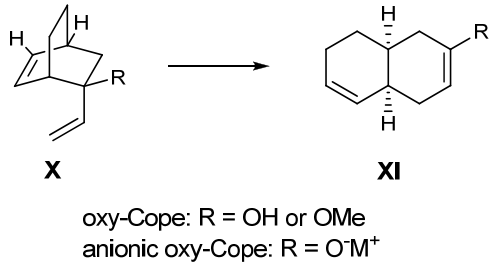
2.3 Cope rearrangements

Another very elegant route to *cis*-decalins is the Cope rearrangement of bicyclo[2.2.2]octene-derivatives of the types **X** to **XI** (Scheme 14). The Cope rearrangement itself is of minor synthetic importance as the yields are in general rather low due to the requirement of higher temperatures. Additionally, there are no general and flexible methods to synthesize such bicyclo-octenes. Oxy-Cope and oxy-anion Cope rearrangements,[25] however, have greatly extended their utility. They are often performed at or near room temperature and exhibit a considerable tolerance toward functional groups. Yields are also higher due to the irreversibility of these reactions. In addition **X** is easily accessible *via* addition of vinyl organometallics to a β,γ-unsaturated carbonyl group in the bridged bicyclic systems.

Also enormously attractive is the enhanced structural embellishment that often develops in the unsaturated ketone product, whose two new functional groups can be manipulated

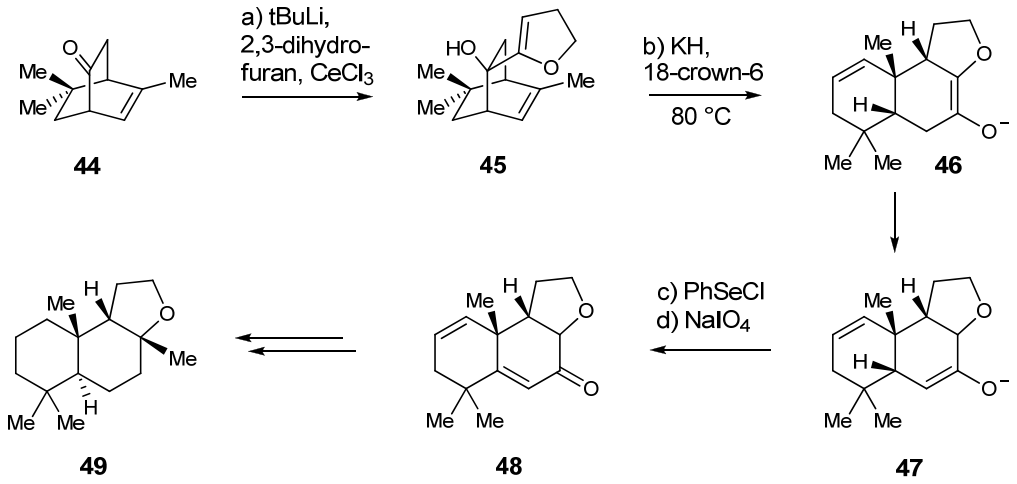
[25] Paquette, L. A. *Tetraehdron* **1997**, *53*, 13971.

independently for synthetic purposes.



Scheme 14: Cope rearrangement of bicyclo[2.2.2]octenes.

Paquette and co-workers have extensively examined the oxy-anion Cope rearrangements. In 1991 they published an enantioselective total synthesis of (-)-9-*epi*-ambrox (**49**) (Scheme 15).[26] Addition of lithiated 2,3-dihydrofuran to optically pure bicyclic ketone **44** gave **45** and its corresponding epimer in high yields (d.r. = 7:1). Heating the potassium salt of **45** induced the rearrangement *via* a boat transition state geometry for structural reasons.

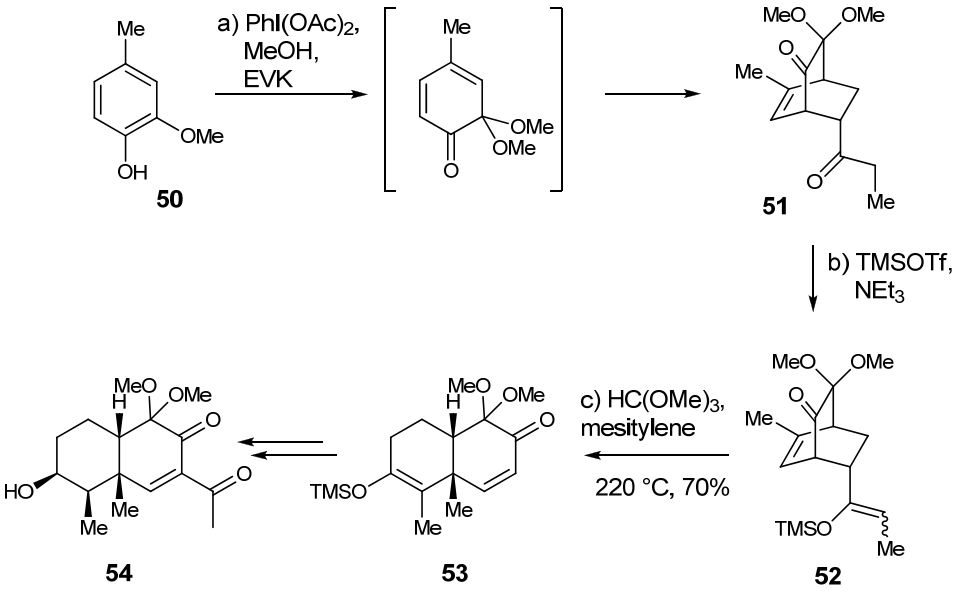


Scheme 15: Paquette´s synthesis of (-)-9-*epi*-ambrox.

The thermal activation also caused equilibration between enolates **46** and **47**, completely in favor of **47**. Quenching of the latter enolate with phenylselenyl chloride followed by oxidative elimination of the corresponding phenylseleno ketone gave **48** in good overall yield (54% from **45**), which was elaborated into **49** in four more steps.

Liao *et al*. have extensively exploited the cycloaddition of cyclohexadienone ketals for the synthesis of eremopetasidione (**54**). **51** was prepared by the Diels-Alder reaction of ethyl vinyl ketone with masked *o*-benzoquinone **50** generated *in situ via* oxidation with iodobenzene

[26] Paquette, L. A.; Guevel, R.; Sakamoto, S.; Kim, I. H.; Crawford, J. *J. Org. Chem*. **2003**, *68*, 6096.

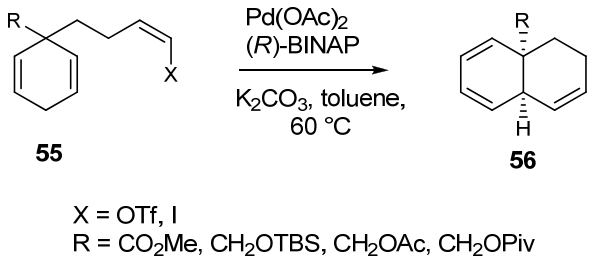


Scheme 16: Liao´s synthesis of eremopetasidione (**54**).

diacetate. Bicycle **51** was converted into silyl enol ether **52** which upon heating underwent Cope rearrangement smoothly furnishing *cis*-decalin **53** in high yields (Scheme 16).

2.4 Cyclization methods

The Robinson annulation has been extensively used for generating *cis*-fused decalins. However, various problems in efficiency, as well as in stereo- and regiocontrol made it necessary to develop alternative cyclization methods. Some recently developed methods are presented below.



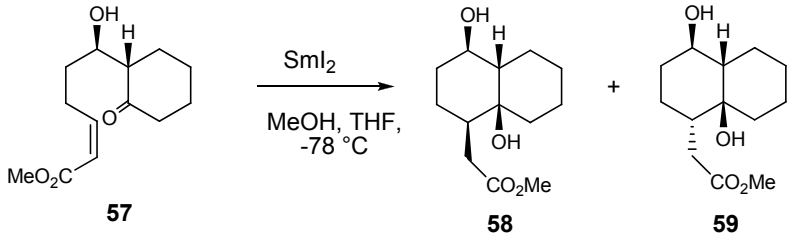
Scheme 17: *cis*-Decalins *via* asymmetric intramolecular Heck reaction.

Shibasaki *et al*. reported their results on screening BINAP and a range of oxazoline-containing phosphinamine ligands in the palladium-catalyzed asymmetric intramolecular Heck cyclization to form *cis*-decalins.[27] Palladium complexes derived from $Pd(OAc)_2$ and BINAP proved to be the most selective catalysts in the formation of **56** from either the alkenyl triflate

[27] Sato, Y.; Watanabe, S.; Shibasaki, M. *Tetrahedron Lett*. **1992**, *33*, 2589.

or the analogous alkenyl iodide **55**. For the alkenyl triflate, the optimum *ee* achieved was 91% in a yield of 54% (Scheme 17).

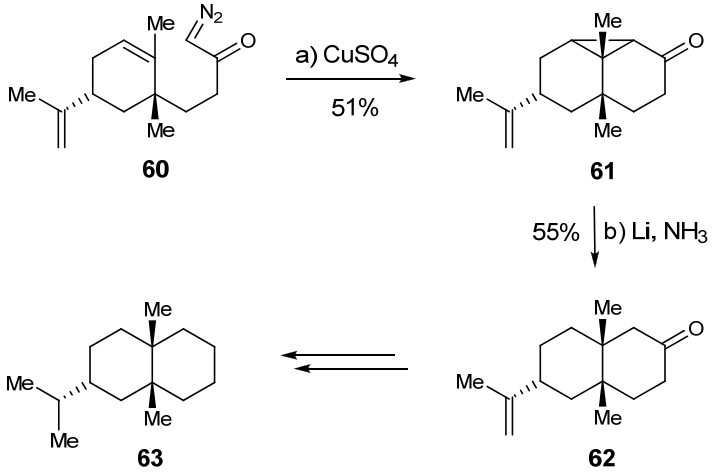
In 1993 Shirahama *et al*. reported samarium(II)iodide mediated ketone-olefin coupling cyclizations in a stereocontrolled manner, to give epimeric mixtures of *cis*-decalin diols **58** and **59** derived from (*Z*)-ester **57**.[28] Chelation of the samarium(III) cation with the incorporated hydroxyl group established the reported stereoselectivity. Exclusively *cis*-fused decalins were formed with d.r. = 6:1 (**58**:**59**) in 70% yield (Scheme 18).



57 **58** **59**

Scheme 18: Samarium(II)iodide mediated *cis*-decalin formation.

Srikrishna *et al*. reported enantiospecific routes to (+)-valerane **63**, starting from (*R*)-carvone, using intramolecular diazoketone cyclopropanation as a key step.[29] (*R*)-Carvone was converted into diazo-ketone **60**, which, on intramolecular diazo-ketone cyclopropanation (**61**), followed by reductive cleavage of the cyclopropane ring, gave ketone **62**, which was efficiently converted into (+)-valerane **63** (Scheme 19).



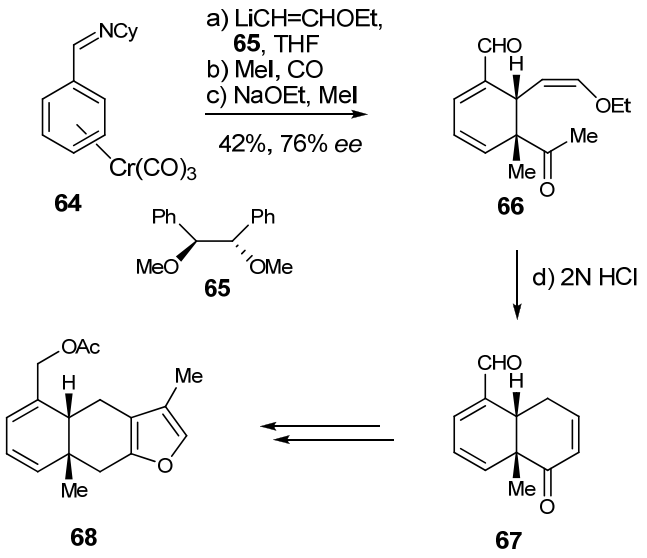
60 **61** **62** **63**

Scheme 19: Srikrishna´s intramolecular diazo-ketone cyclopropanation strategy.

Tricarbonylchromium-mediated dearomatization provides an efficient access to substituted cyclohexadienes. In the context of an application to the asymmetric synthesis of (-)-(*R,R*)-

[28] Kito, M.; Sakai, T.; Yamada, K.; Matsuda, F.; Shirahama, H. *Synlett* **1993**, 158.
[29] Srikrishna, A.; Viswajanani, R.; Dinesh, C. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4321.

acetoxytubipofuran (**68**), Kundig and co-workers reported a regio- and stereoselective one-pot sequence introducing up to three C-substituents (Scheme 20).[30] Nucleophilic addition of lithiated ethyl vinyl ether to imine complex **64** in the presence of **65** followed by acylation/alkylation and imine hydrolysis gave **66** in 76% *ee*. Hydrolysis of the vinyl ether followed by intramolecular aldol condensation gave **67** which was enantiomerically enriched *via* recrystallization (*ee* > 99%). Similarly the enantiomer of **68** was also synthesized.

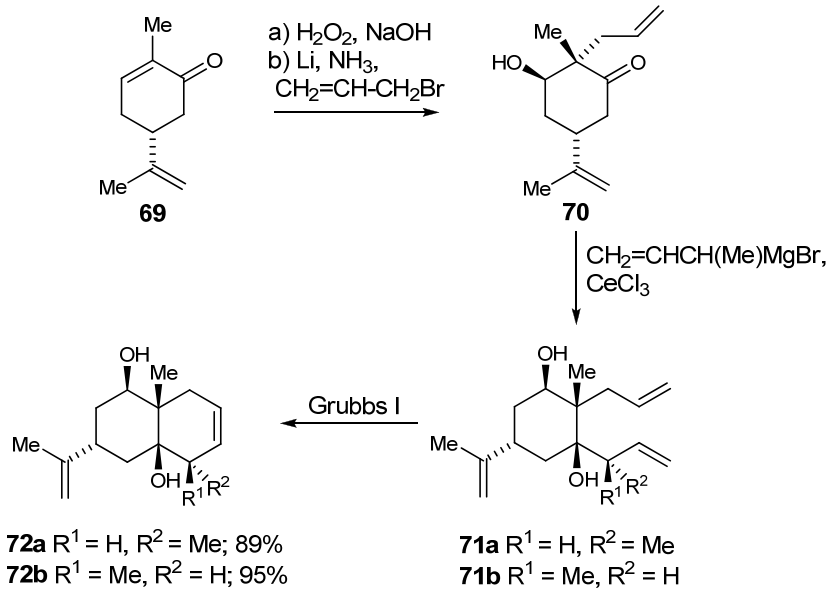


Scheme 20: Kundig´s tricarbonylchromium-mediated dearomatization.

Mehta *et al*. have developed a new approach to assemble functionalized eudesmanes from (-)-carvone (**69**) applying ring closing metathesis as key step (Scheme 21).[31] Epoxidation of **69** followed by reductive allylation under dissolving metal conditions gives ketone **70**. Addition of the Grignard reagent in the presence of Ce(III) furnished isomeric addition products **71a/b**. Ring-closing metathesis reaction then provided functionalized eudesmane frameworks **72a** and **b**.

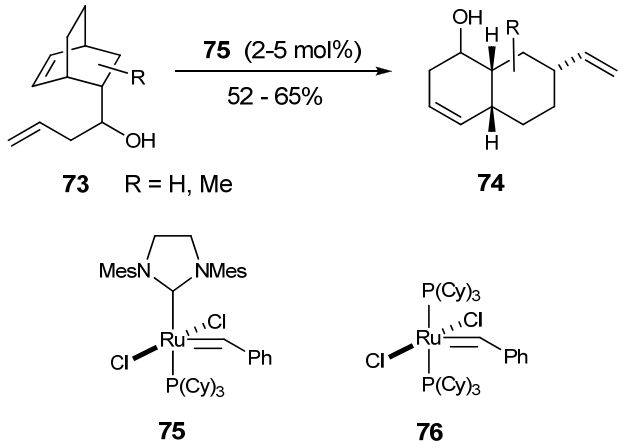
In 2002, Phillips and co-workers demonstrated that ruthenium alkylidene **75** is a competent catalyst for ring-opening-ring-closing metathesis of bicyclo[2.2.2]octenes such as **73**, providing a novel approach to the synthesis of functionalized decalins (**74**) and hydrindane ring systems.[32] Cyclization to give hydrindane ring systems proceeds readily at room temperature, whereas cyclization to give decalins requires higher temperatures - typically toluene at reflux. Employing carbene **76** failed to give any of the desired products (Scheme 22).

[30] Kundig, E. P.; Cannas, R.; Laxmisha, M.; Ronggang, L.; Tchertian, S. *J. Am. Chem. Soc*. **2003**, *125*, 5642.
[31] Mehta, G.; Kumaran, R. S. *Tetrahedron Lett*. **2003**, *44*, 7055.
[32] Minger, T. L.; Phillips, A. J. *Tetrahedron Lett*. **2002**, *43*, 5357.



Scheme 21: *cis*-Decalins *via* RCM.

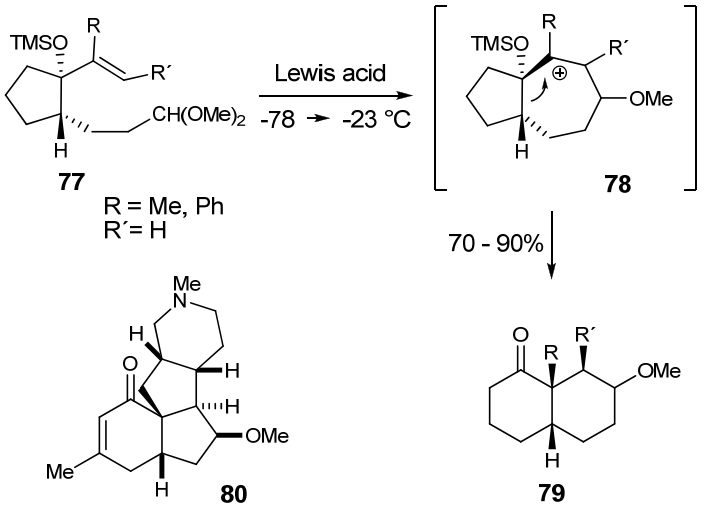
Overman *et al*. developed a ring-enlarging cyclohexane annulation method *via* Prins-pinacol rearrangement.[33] *Cis*-fused rings of various sizes can be formed including *cis*-decalins. Lewis acid-mediated ($SnCl_4$, TMSOTf) Prins reaction of substrates such as **77** give *via* kationic intermediates (**78**) decalones such as **79**.



Scheme 22: Ring-opening-ring-closing metathesis of bicyclo[2.2.2]octenes.

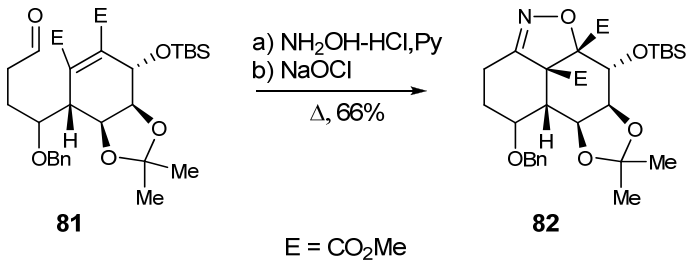
This method provides an efficient new route to *cis*-bicyclo[*n*.4.0]alkanones having angular aryl or alkyl substituents (Scheme 23). In the course of their total synthesis of (-)-magellanine (**80**) it was proven that this methodology can be applied for even quite complicated systems.

[33] Ando S.; Minor, K. P.; Overman, L. E. *J. Org. Chem*. **1997**, *62*, 6379.



Scheme 23: Overman´s ring-enlarging cyclohexane annulation method.

A highly oxygenated *cis*-decalin core was synthesized by Kozikowski *et al*. in their synthesis towards forskolin.[34] Aldehyde **81** was transformed into the corresponding nitrile oxide giving *cis*-fused isoxazol **82** in good yields *via* [3+2] dipolar cycloaddition (Scheme 24).



Scheme 24: Kozikowski´s INOC key step in the synthesis of forskolin.

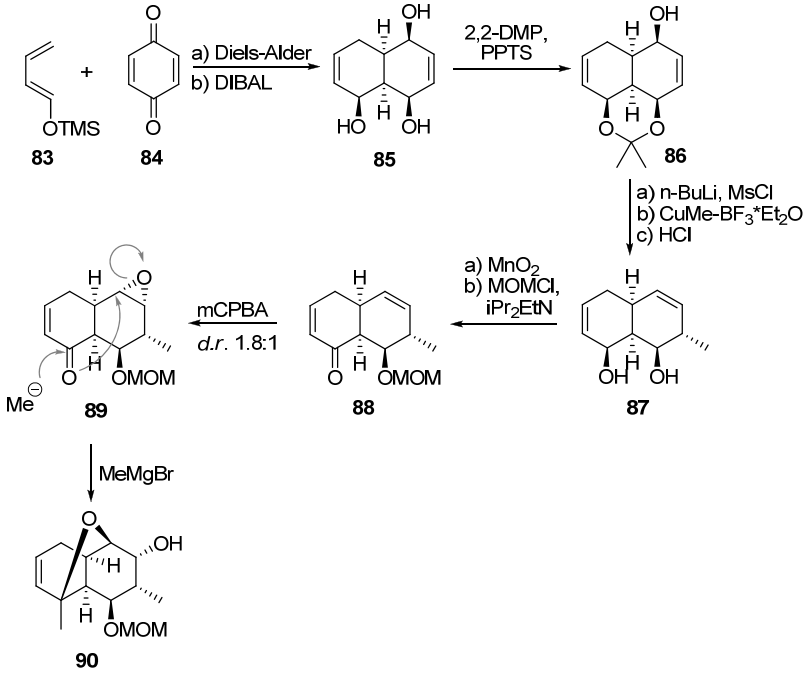
[34] Kozikowski, A. P.; Jung, S. H.; Springer, J. P. *J. Chem. Soc., Chem. Commun*. **1988**, 167.

3. Previous Synthetic Work

3.1 Approaches towards the nargenicin family

3.1.1 Kallmerten´s synthesis of 18-deoxynargenicin A$_1$

In 1984 Kallmerten *et al*. reported an elegant approach towards the oxa-bridged *cis*-decalin core of the nargenicins (Scheme 25).[35] The *cis*-decalin framework was synthesized in a racemic manner *via* intermolecular Diels-Alder cycloaddition of diene **83** and quinone **84**. The *endo* adduct was reduced to triol **85** which was further acetalized to leave only one OH-group free. **86** could be converted to **87** by a regio- and stereoselective introduction of a methyl group followed by acidic hydrolysis.

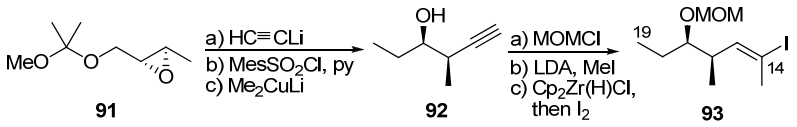


Scheme 25: Kallmerten´s synthesis of the "northern" fragment **89**.

Selective oxidation of the allylic alcohol followed by protection of the remaining free OH-group as a MOM-ether gave ketone **88**. Epoxidation of the more electron rich double bond gave a 1.8:1 diastereomeric ratio of expected epoxide **89** and its isomer. Treatment of **89** with methyl magnesium bromide as a test reaction furnished oxa-bridged bicycle **90**.

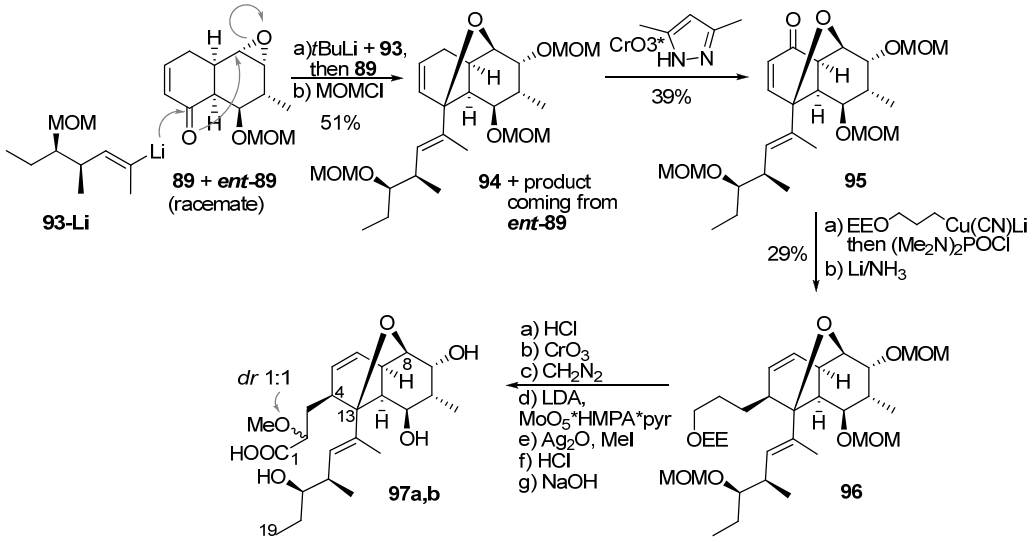
In 1988 the total synthesis of 18-deoxynargenicin was accomplished by the same authors.[36] Iodide **93** was obtained in analogy to a sequence published by Corey *et al*. (Scheme 26).[37]

[35] Kallmerten, J. *Tetrahedron Lett*. **1984**, *25*, 2843-2846.
[36] Plata, D. J.; Kallmerten, J. *J. Am. Chem. Soc.* **1988**, *110*, 4041-4042.



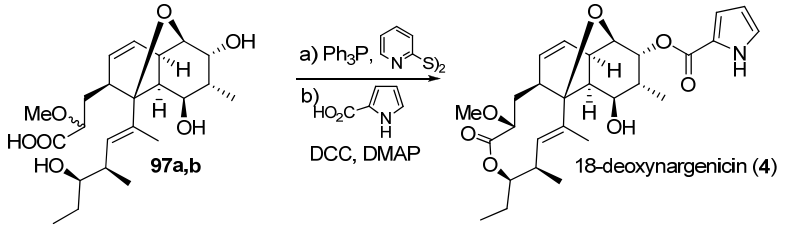
Scheme 26: Synthesis of polyketide side chain **93**.

Addition of **93-Li** to racemic **89** followed by direct transformation to the corresponding methoxymethyl ether gave a mixture of diastereomeric products **94**. Both diastereomers were converted further, until structural assignment *via* X-ray analysis was possible on a crystalline intermediate.



Scheme 27: Synthesis of seco acid **97a/b**.

Allylic oxidation of **94** gave enone **95** only in modest yield. Stereoselective conjugate addition of a mixed cuprate followed by immediate trapping as an enol phosphodiamidate and dissolving metal reduction afforded **96** again in poor yield. Selective deprotection of the



Scheme 28: Completion of the synthesis of **4**.

primary alcohol, conversion to the corresponding methyl ester, α–oxygenation, methylation, saponification and global deprotection gave seco acids **97a** and **b** as a mixture of

[37] Corey, E. J.; Trybulski, E. J.; Melvin, L. S.; Nicolaou, K. C.; Secrist, J. A.; Lett, R.; Sheldrake, P. W.; Falck, J. R.; Brunelle, D. J.; Haslanger, M. F.; Kim, S.; Yoo, S. *J. Am. Chem. Soc*. **1978**, *100*, 4618 – 4620.

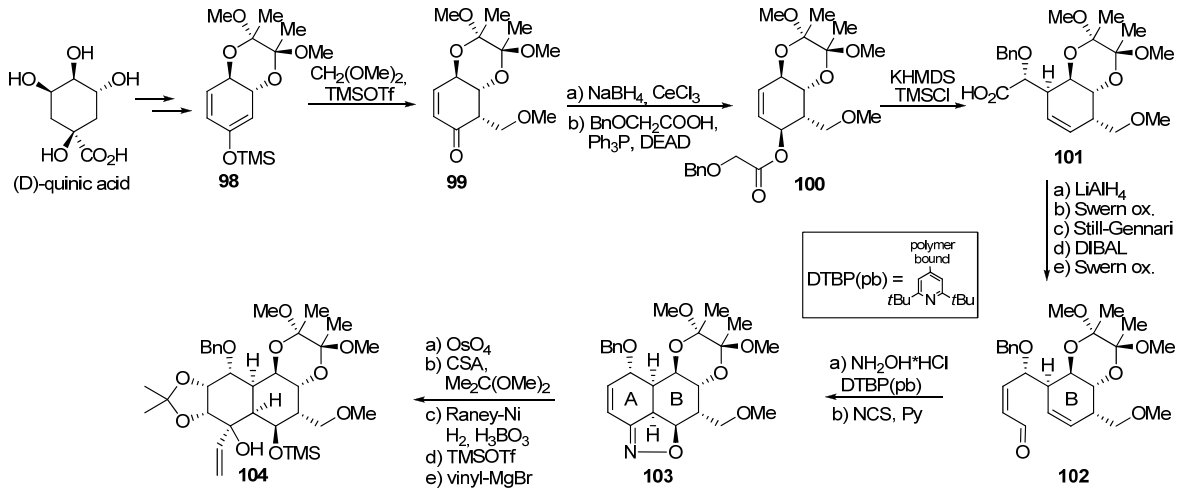
diastereomers (Scheme 27). Interestingly, applying Corey´s thiopyridyl ester procedure[38] on **97a/b** gave only the desired macrolide product. The absence of lactonic product arising from the undesired diastereomer can be attributed to unfavorable steric interactions in the transition state. Acylation at 9-OH then gave (+)-18-deoxynargenicin, identical with an authentic sample. So far it was the only complete synthesis of a member of the nargenicin family (Scheme 28).

3.2 Approaches towards branimycin in the Mulzer group

In the context of an ongoing study toward the total synthesis of branimycin and its unique, highly functionalized *cis*-decalin core, five alternative routes have been investigated previously.

3.2.1 Quinic acid based INOC approach

Quinic acid was used as a chiral scaffold for elaborating the *cis*-decalin core of branimycin via an Eschenmoser-Ireland rearrangement-INOC annulations sequence (Scheme 29).[39] Starting from known silyl-enol ether **98**, stereoselective alkylation under Mukaiyama conditions gave ketone **99**. Luche reduction, followed by Mitsunobu inversion provided allylic ester **100**. Chelation-controlled glycolate enolate Claisen rearrangement led to **101** as a single isomer.



Scheme 29: Quinic acid based INOC approach.

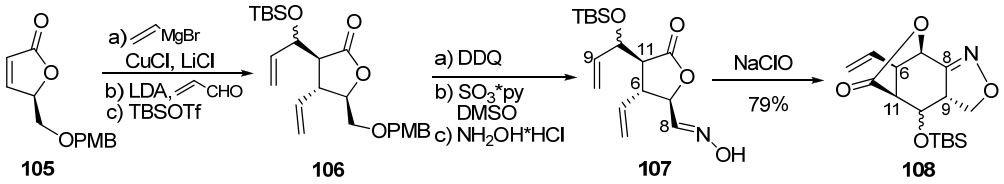
Conversion to the aldehyde and *Z*-selective Still-Gennari olefination followed by reduction gave enone **102**. After conversion to the corresponding *cis*-α,β–unsaturated oxime the stage for the key INOC reaction was set. Treatment of the oxime with NCS/pyridine resulted in

[38] Corey, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc*. **1974**, *96*, 5614-5616.
[39] Enev, V. S.; Drescher, M.; Mulzer, J. *Tetrahedron* **2007**, *63*, 5930-5939.

formation of a nitril oxide which immediately formed isoxazolidine **103** in excellent yields. After dihydroxylation of the double bond the cleavage of the isoxazolidine ring was possible, and 1,2-addition of vinylmagnesium bromide gave adduct **104** with high stereoselectiviy.

3.2.2 Lactone based INOC approach

Lactone **105** was converted into **106** *via* a copper catalyzed stereoselective Michael addition of vinyl Grignard, followed by an aldol reaction with acrolein and TBS-protection (Scheme 30). Unfortunately, **106** was obtained as an epimeric mixture. Some functional group interconversions of this mixture furnished oxime **107** which was oxidized to the corresponding

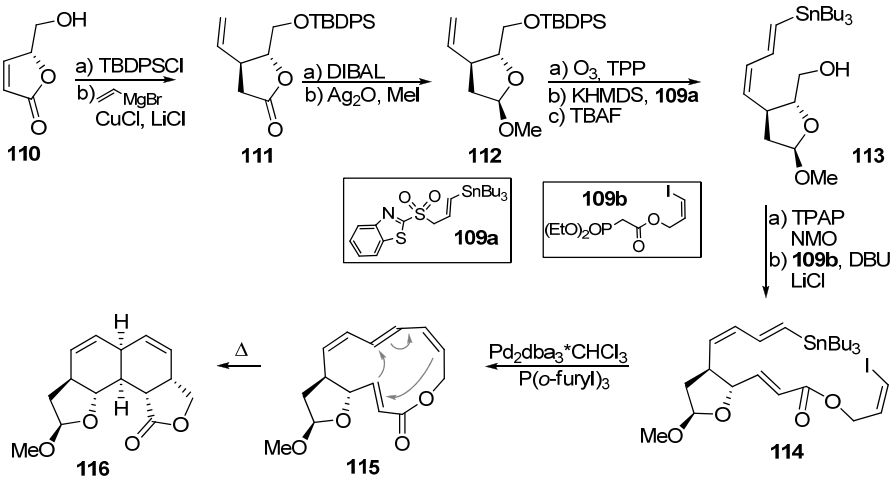


Scheme 30: Lactone based INOC approach.

nitrile oxide. The yield of the cyclization product **108** could be dramatically increased from initial 30% to 79% upon increase of the temperature (80 °C).[40]

3.2.3 Trans-Annular Diels-Alder approach

The synthesis was started from known butenolide **110**, which was protected as TBDPS ether followed by a stereoselective Michael addition of vinyl cuprate to give **111**.[41] Partial reduction and methylation gave methyl lactol **112** (Scheme 31).



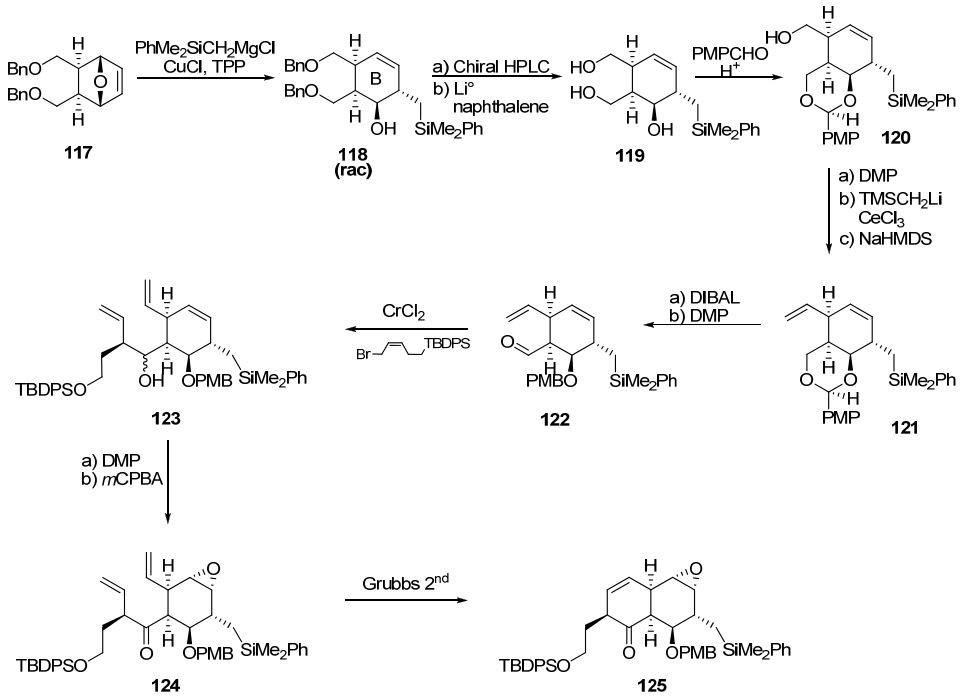
Scheme 31: Preparation of *cis*-fused decalin **116**.

[40] Gromov, A.; Enev, V. S.; Mulzer J. *Tetrahedron Lett.* **2009**, *50*, 5283-5284.
[41] Felzmann, W.; Arion, V. B.; Mieusset, J. L.; Mulzer, J. *Org. Lett.* **2006**, *8*, 3849−3851.

After ozonolysis of **112** the resulting aldehyde was used in a (*Z*)-selective, modified Julia olefination after which cleavage of the TBDPS group provided diene **113**. Using a TPAP-oxidation/Roush-Masamune olefination sequence *seco*-compound **114** was obtained in high yields. The key intramolecular Stille-coupling reaction under high-dilution conditions gave the desired macrocycle **115**, which under thermal conditions was converted smoothly to **116** as a single diastereomer. In this sequence six new stereogenic centers were established *via* purely substrate controlled transformations.

3.2.4 S_N2' oxa-bridge opening – RCM approach

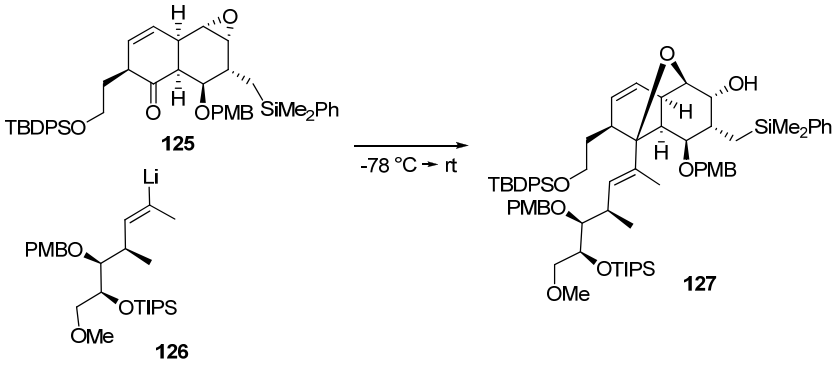
Starting from the readily available dibenzylether **117**, opening of the oxa-bridge with a Grignard reagent under copper catalysis provided **118** as a single diastereomer. Separation of racemic **118** *via* chiral HPLC followed by benzyl cleavage furnished triol **119**, which was treated with *p*-methoxybenzaldehyde to give alcohol **120**. The remaining free primary alcohol was oxidized and the resulting aldehyde was used in a modified Peterson olefination to give olefin **121** (Scheme 32).



Scheme 32: S_N2'oxa-bridge opening – RCM sequence to *cis*-decalin core **125**.

Regioselective opening of the PMB-acetal followed by Dess-Martin oxidation furnished aldehyde **122**, where simultaneously the second double bond required for RCM reaction as well as the C3-appendage were introduced to give a mixture of diastereomeric alcohols **123**. Oxidation to the ketone, followed by regio- and stereoselective epoxidation delivered epoxide

124. Finally RCM of **124** with Grubbs second-generation catalyst provided epoxyketone **125** in excellent yield.

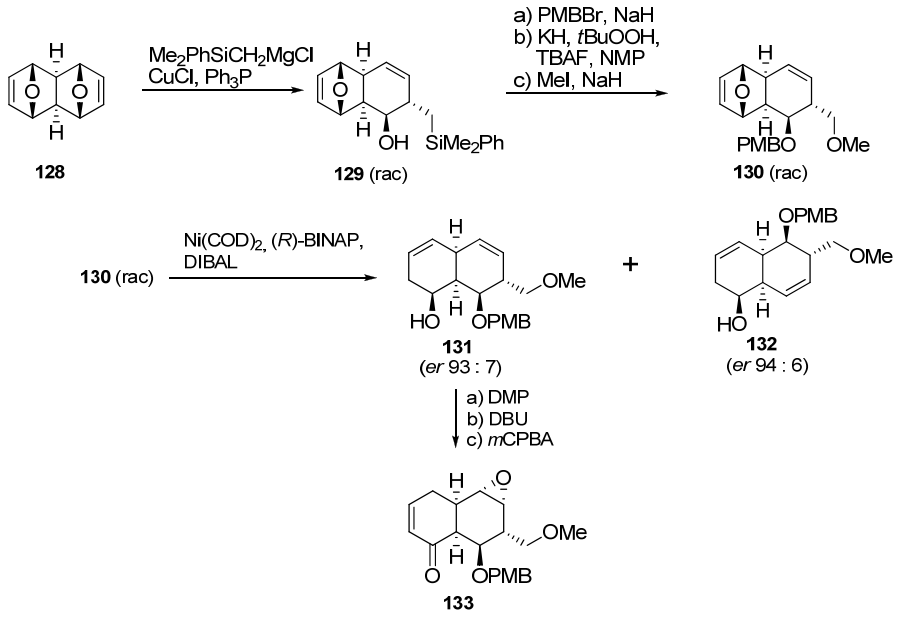


Scheme 33: Formation of the oxa-bridge.

Ketone **125** was reacted with pre-metalated side chain **126** (derived from its corresponding vinyl iodide)[42] where the addition to the carbonyl group was followed by transannular epoxide opening to give the desired alcohol **127** (Scheme 33).

3.2.5 Diepoxynaphthalene-desymmetrization approach

Starting from known diepoxynaphthalene **128**, organometallic catalyzed successive S_N2' openings of the oxa-bridges were used for desymmetrization (Scheme 34).[43]

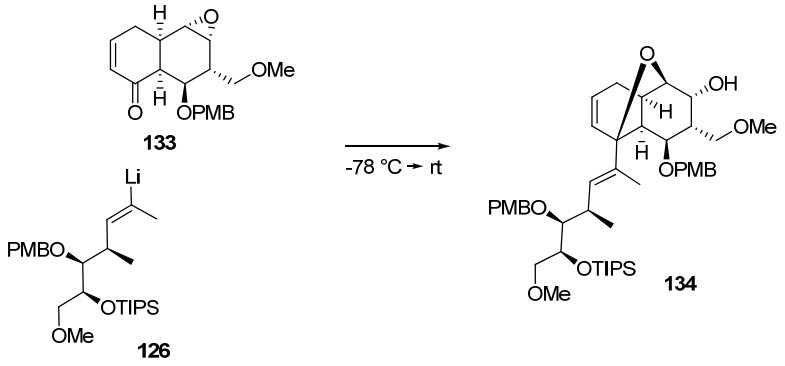


Scheme 34: Preparation of *cis*-decalin **133**.

An anti S_N2' opening of exclusively one of the oxa-bridges gave compound **129** in high

[42] Felzmann, W.; Castagnolo, D.; Rosenbeiger, D.; Mulzer, J. *J. Org. Chem.* **2007**, *72*, 2182-2186.
[43] Gromov, A.; Enev, V. S.; Mulzer J. *Org. Lett*. **2009**, *11*, 2884-2886.

yields. OPMB-Protection followed by oxidative cleavage of the C-Si bond gave the corresponding primary alcohol which was further converted to methyl ether **130**. Racemic **130** was treated with DIBAL and $Ni(COD)_2$/(R)-BINAP and a pseudoenantiotopos selective hydrogen attack was achieved to give enantiomerically enriched regioisomers **131** and **132**.

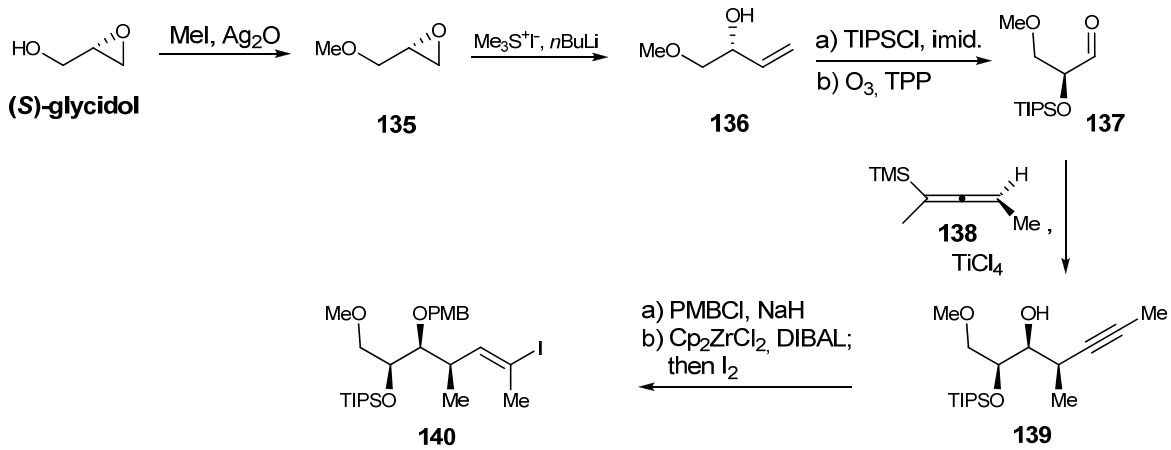


Scheme 35: Coupling of **133** and **126** and formation of the oxa-bridge.

Dess-Martin oxidation of **131** followed by base-catalyzed double bond isomerization and regioselective epoxidation gave a 3:1 mixture of diastereomeric epoxides. Finally, pursuing the strategy envisioned in our group, epoxyketone **133** and lithiated side chain **126** were coupled to give tricycle **134** with the desired oxa-bridge (Scheme 35).

3.2.6 Synthesis of the C13-C18 side chain

Based on the addition of chiral allenyl silane **138** to aldehyde **137** an elegant stereocontrolled synthesis of **140** was accomplished (Scheme 36).[42] (*S*)-Glycidol was *O*-methylated and upon treatment with trimethylsulfonium ylide alcohol **136** was furnished.



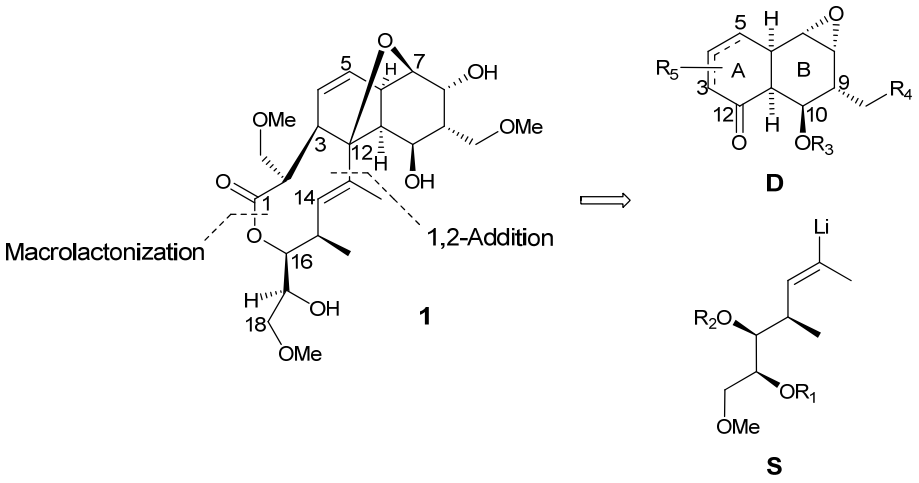
Scheme 36: Synthesis of the C13-C18 side chain **140**.

TIPS-protection and ozonolysis provided enantiomerically pure aldehyde **137**. The $TiCl_4$ mediated reaction of known allenyl silane **138** with **137** gave homopropargyl adduct **139** as a

20:1 diastereomeric mixture in good yields. The addition is the result of an allenyl-*re*-aldehyde-*si* face combination. Alcohol **139** was protected as its PMB ether followed by hydrozirconation, which, upon treatment with iodine, gave desired vinyliodide **140**.

4. Outline of the Synthetic Plan

Structural features of branimycin (**1**) that merit special attention include the nine-membered macrolide ring with an internal *trans*-double bond, the chirality at C15, C16 and C17, and the highly functionalized oxa-bridged *cis*-decalin core. The construction of the nine-membered lactone of **1** was expected to be a highly challenging synthetic task. Molecular modeling showed that the desirable macrolactone should be significantly strained, which also indicates a certain sensitivity towards hydrolysis suggesting that this structural element should be introduced only at a late stage. From an entropic point of view the formation of nine-membered rings can be regarded as an unfavourable process but on the other hand the connection of the macrocycle to the rigid oxa-bridged decalin nucleus should reduce the conformational mobility of the corresponding seco acid. In addition, the C13-C14 *trans* double bond is expected to significantly inhibit the rotational freedom of the C13-C18 side chain thus increasing the probability of intramolecular cyclization.

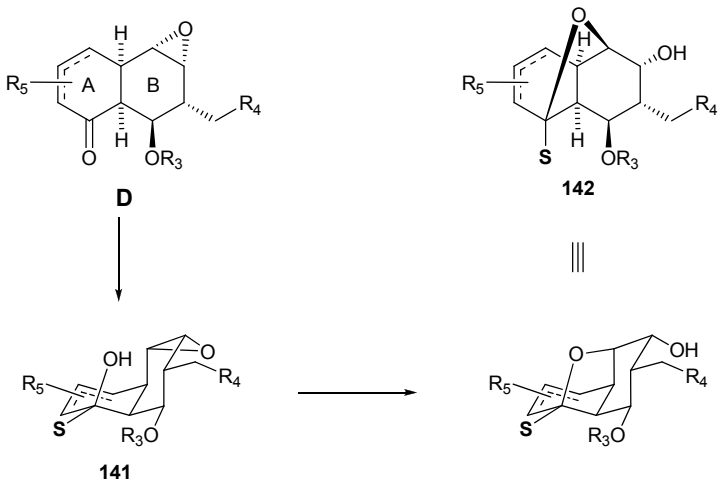


Scheme 37: Key disconnections of branimycin (**1**) into *cis*-decalins **D** and side chain **S**.

The C13-C18 substitution pattern of the branimycin macrolide offers a synthetic challenge as the number of methods for the selective generation of remote *syn,syn*-stereotriades is rather limited. The 7,12-oxa-bridged *cis*-decalin framework is unique to the nargenicin family, its exceptional stereochemical and structural complexity makes it also a formidable synthetic target.

We planned a convergent approach towards **1** (Scheme 37) – formation of the diaxial 7,12-ether bridge should be accomplished *via* a 1,2-addition of **S** to epoxy ketone **D** to give alcohol **141**, which upon warming would undergo intramolecular cyclization. Molecular modeling indicates that tricycle **142** features minimum torsional strain (Scheme 38). An 8,12-ether

bridge should not be formed as therefore an unfavourable boat-like conformation would be required. Application of this strategy requires a short and stereoselective synthesis of the C13-C18 framework, which has been previously reported in our group.[42] The C3-appendage was planned to be installed at a late stage, either *via* a Claisen rearrangement of an allylic hydroxyl-group at C5 or *via* conjugate addition at C3.

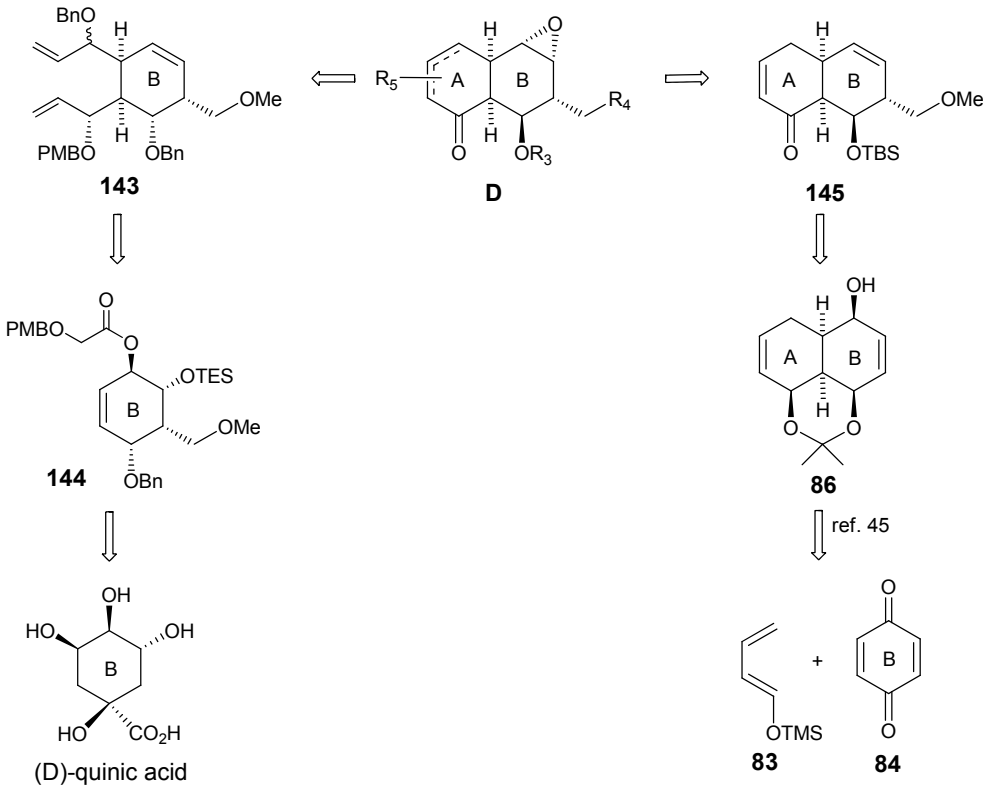


Scheme 38: Proposed formation of the branimycin 7,12-ether bridge.

(D)-Quinic acid seemed a reasonable starting material for the synthesis of **D**, expecting that all subsequent stereocenters should be constructed based on this chirality (Scheme 39). Ring A would be established by a ring closing metathesis of **143**, in which the required vinylic double bonds were to be installed *via* two successive chelation-controlled glycolate enolate Claisen rearrangements[44] from precursor **144**, which in turn should be arranged in stereoselective fashion from quinic acid. The absolute configuration would be ascertained, as quinic acid is a chiral pool molecule. Upon this strategy the OH-group at C5 would already be installed in the course of the second Claisen rearrangement.

Following an intermolecular quinone based Diels-Alder cycloaddition strategy, known tricycle **86** was also considered as a suitable precursor for **D** (Scheme 39).[45] As the *cis*-decalin skeleton is already constructed all following transformations would focus on establishing the functional group pattern. The enone functionality of **145** should be obtained *via* a regioselective allylic oxidation. Incorporation of a masked C9-methoxy methyl substituent

[44] Burke, S. D.; Fobare, W. F.; Pacofsky, G. J. *J. Org. Chem*. **1983**, *48*, 5221-5228 and references cited therein.
[45] a) White, J. D.; Choi, Y. *Helv. Chim. Acta* **2002**, *85*, 4306-4327 b) reference 35.



Scheme 39: Retrosynthetic analysis of *cis*-decalins **D**.

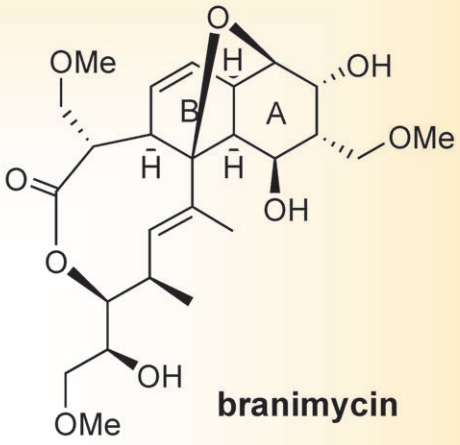
should be accomplished stereoselectively from the convex face by S_N2' displacement of mesylated **86**.This strategy requires a late stage allylic oxidation at C5.

RESULTS AND DISCUSSION

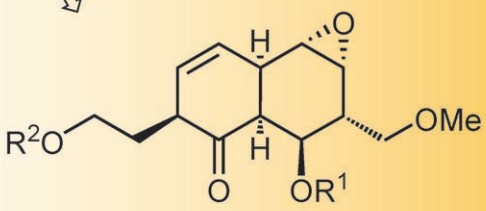
5. Toward the Synthesis of the Antibiotic Branimycin: Novel Approaches to Highly Substituted *cis*-Decalin Systems

Mulzer, J.; Castagnolo, D.; Felzmann, W.; Marchart, S.; Pilger, C.; Enev, V. S. *Chem. Eur. J.* **2006**, *12*, 5992-6001.

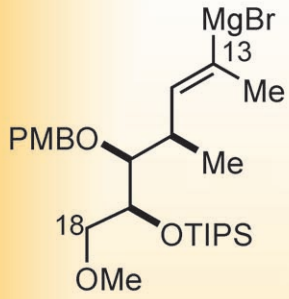
Towards the Synthesis of Antibiotic Branimycin



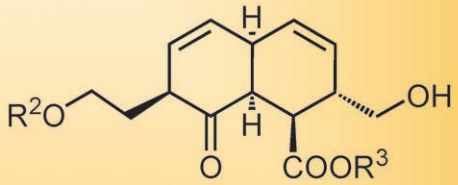
branimycin



octalin core



side chain



dehydrooctalin

DOI: 10.1002/chem.200600279

Toward the Synthesis of the Antibiotic Branimycin: Novel Approaches to Highly Substituted *cis*-Decalin Systems

Johann Mulzer,* Daniele Castagnolo, Wolfgang Felzmann, Stefan Marchart, Christian Pilger, and Valentin S. Enev*[a]

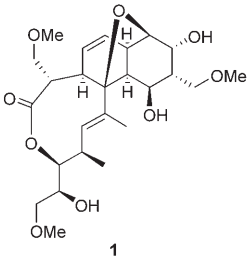
Dedicated to Professor Dieter Enders on the occasion of his 60th birthday

Abstract: A variety of highly functionalized *cis*-decalin systems have been prepared by means of the stereoselective transannular Diels–Alder (TADA) reaction of a (*Z*,*E*,*Z*,*Z*)-tetraene macrolide, and by means of intramolecular nitrile oxide olefin (INOC) or ring-closing metathesis (RCM) annulations to quinic acid derivatives.

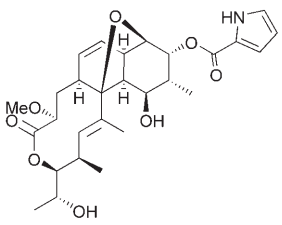
Keywords: annulation · Diels–Alder reaction · ring-closing metathesis · stereoselective synthesis · synthesis design

Introduction

The increasing resistance of bacterial pathogens against standard antibiotics combined with an emerging threat of bioterrorism has led to the urgent need for developing innovative anti-infective drugs.[1] Recently, branimycin (**1**) has been isolated by the Laatsch group from *actinomyces* GW 60/1571[2].



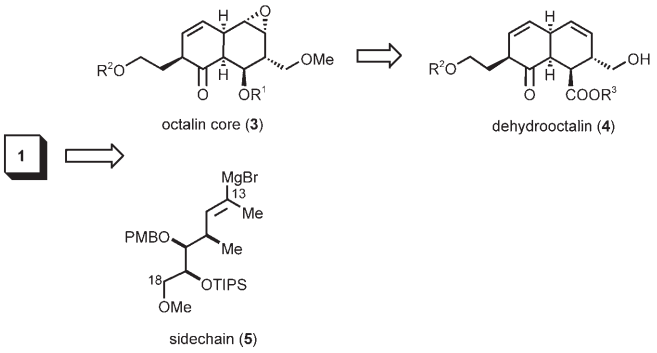
1



2

[a] Prof. Dr. J. Mulzer, D. Castagnolo, W. Felzmann, S. Marchart, Dr. C. Pilger, Dr. V. S. Enev
Institut für Organische Chemie, Universität Wien
Währinger Strasse 38, 1090 Wien (Austria)
Fax: (+43) 1-4277-52189
E-mail: johann.mulzer@univie.ac.at
valentin.enev@univie.ac.at

First biological tests have shown that **1** is highly active against *Streptomyces viridochromogenes*. The structure of **1** is related to that of the nargenicins[3] (e.g., nargenicin A1, **2**) and has been reliably elucidated by multidimensional ^{1}H and ^{13}C NMR experiments. The interesting biological activity and the complex molecular architecture make **1** an attractive target for total synthesis. Our retrosynthetic analysis (Scheme 1) features a disconnection of the molecule into a

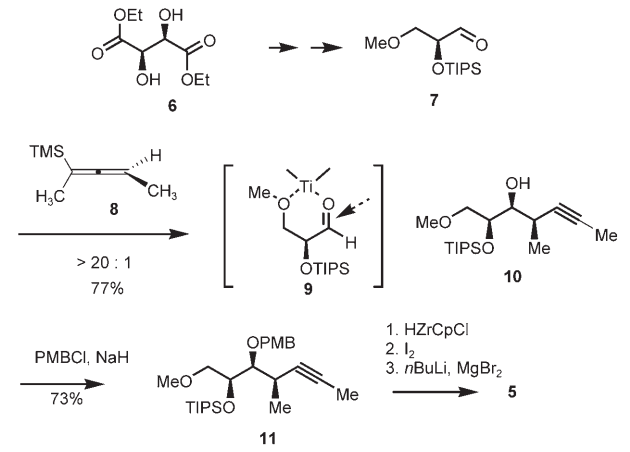


Scheme 1.

bicyclic *cis*-decalin type core (e.g., **3** or **4**) and a vinyl magnesium side chain (**5**). In this report we describe the synthesis of **5** and novel approaches to *cis*-fused decalin derivatives.

Synthesis of Side Chain 5

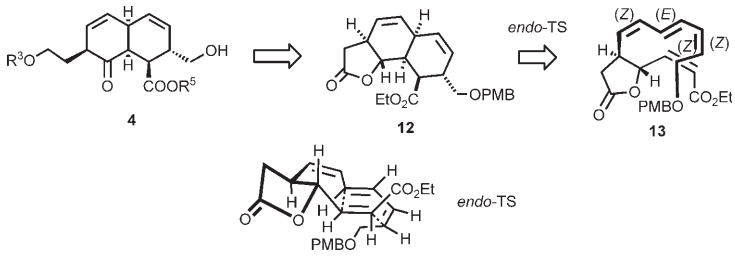
The synthesis started from natural (*R*,*R*)-diethyl tartrate (**6**), which was converted into the protected glyceraldehyde **7** (Scheme 2). Titanium tetrachloride mediated addition of the nonracemic allenylsilane **8**[4] resulted in the selective formation (d.r. >20:1) of the all-*syn* diastereomer **10**, presumably via a chelate intermediate **9**. Benzyl-protection led to **11** which was converted into **5** via a regio- and stereocontrolled hydrozirconation-iodination-metalation sequence.



Scheme 2.

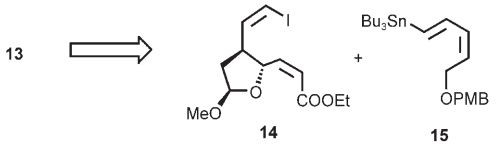
Synthesis of *cis*-Dehydrooctalin Lactone 12: The Transannular Diels–Alder (TADA) Approach

Following the retrosynthetic suggestion in Scheme 3, we aimed for a synthesis of **4** that should be prepared by means



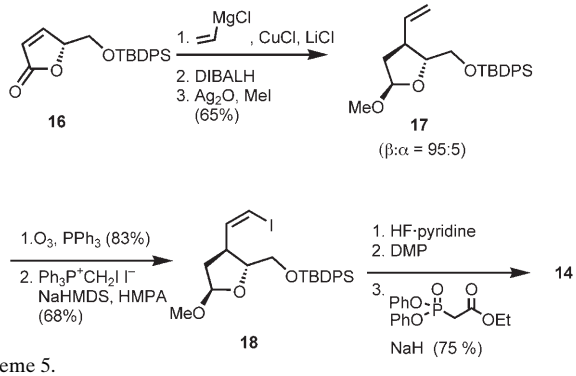
Scheme 3.

of a intramolecular Diels–Alder (IMDA) reaction[5] of tetraene **13**. In this manner, lactone **12** should be formed through an *endo*-transition state. Tetraene **13**, in turn, was to be constructed by a Stille coupling[6] of vinyl iodide **14** and vinyl stannane **15** (Scheme 4).



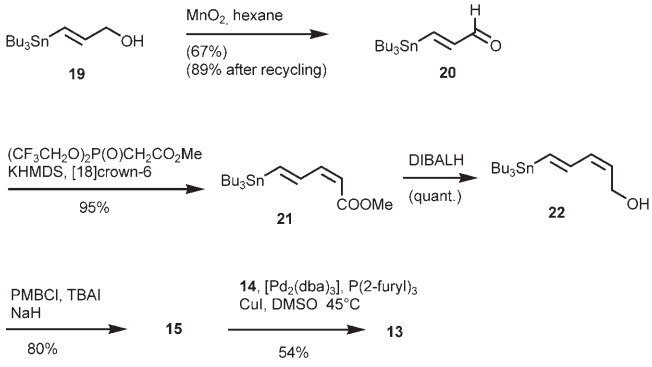
Scheme 4.

For the synthesis of **14**, lactone **16** was subjected to a stereoselective 1,4-addition of vinyl cuprate. As the lactone function turned out to be incompatible with the transformations envisaged later, it was reduced to the lactol and converted into acetal **17** with high stereocontrol. Oxidation of the olefinic sidechain to the aldehyde followed by a *cis*-selective Wittig olefination gave vinyl iodide **18** in good overall yield, which was transformed into (*Z*)-enoate **14** by means of an Ando olefination[7] (Scheme 5). The synthesis



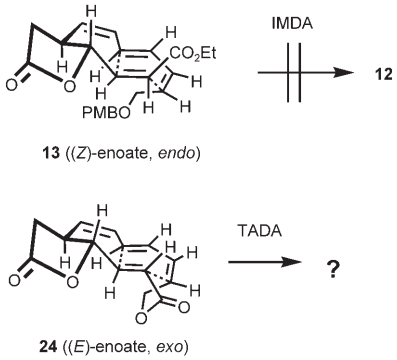
Scheme 5.

of dienyl-stannane **15** is outlined in Scheme 6. Allylic alcohol **19** was oxidized to aldehyde **20**, which was subjected to a Still–Gennari olefination to give ester **21** with high *Z* selectivity. Reduction with diisobutyl aluminium hydride and formation of the *p*-methoxybenzyl ether led to **15**. Stille coupling with **14** furnished geometrically pure tetraene **13** in satisfactory yield. The attempted IMDA reaction[5] failed under all conditions we tried (heating to 150 °C, addition of Lewis acids, high pressure up to 13 kbar). Instead, extensive *E*/*Z* isomerization was observed in the triene part of the molecule.

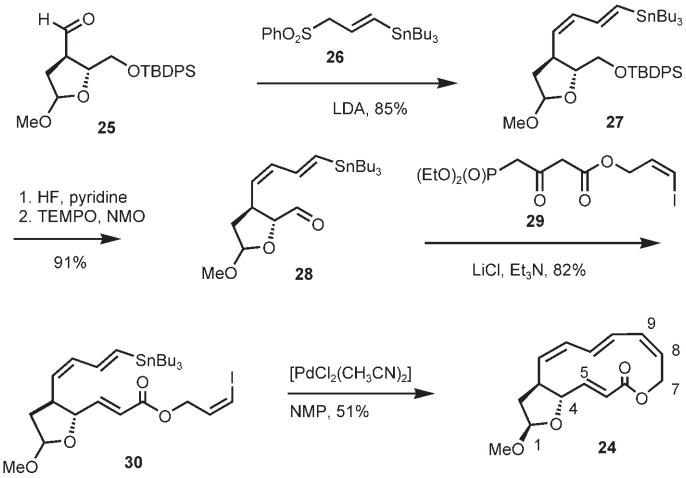


Scheme 6.

To remedy this situation, we decided to inhibit such isomerizations by incorporating the triene into a macrolide ring, such as **24**, and switch from IMDA to TADA[8] cyclization (Scheme 7). To achieve smooth macrocyclization, an (*E*)-enoate had to replace the former (*Z*)-enoate, and the former *endo* transition state had to be converted into the *exo* transition state. The synthesis of **24** (Scheme 8) was started with a (*Z*)-selective Julia olefination[9] of aldehyde **25** with sulfone **26** to give (*Z*,*E*)-diene **27**, which was oxidized to aldehyde **28** and olefinated to ester **30**. Stille macrocyclization[6] gave **24** in moderate yield.

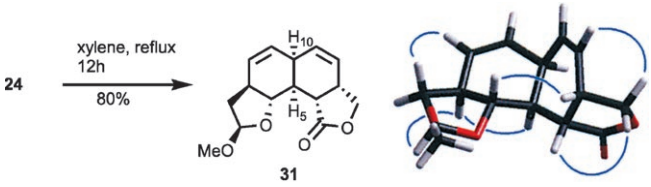


Scheme 7.



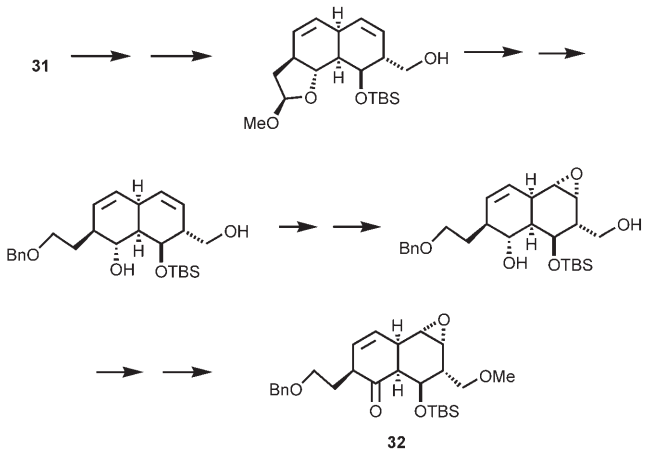
Scheme 8.

As expected, **24** underwent smooth TADA cyclization under thermal conditions (Scheme 9) to give the diastereomerically pure *cis*-dehydrooctalin lactone **31** according to



Scheme 9.

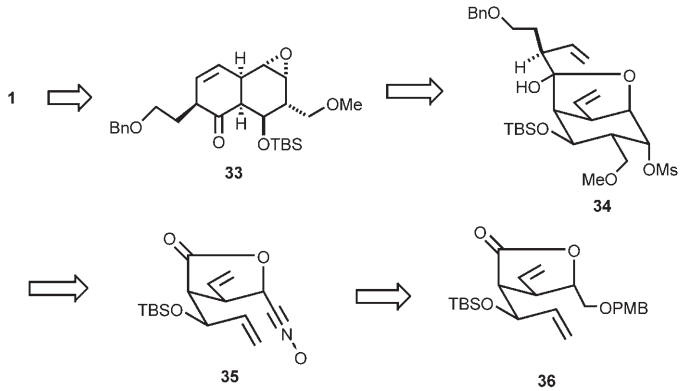
HPLC and NMR analysis. The relative configuration of **31** was elucidated by ^{1}NMR spectroscopy. Specifically, the low value of $J_{5,10}$ (6 Hz) and the NOE interactions shown in the three-dimensional representation strongly supported the configurations assigned. Further experiments are under way to convert **31** into octalin **32**, ready for connection with side chain **5** (Scheme 10).



Scheme 10.

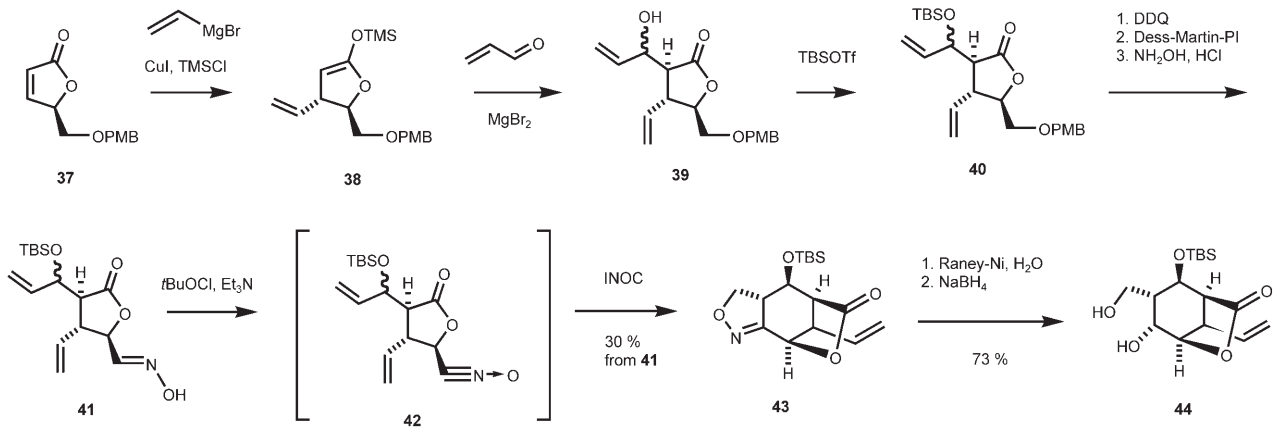
Intramolecular Nitrile Oxide Olefin (INOC) Cyclizations

In a second approach, the intramolecular nitrile oxide olefin (INOC) cyclization[10] was attempted for generating highly substituted cyclohexane and *cis*-decalin systems. Thus compound **33** was envisaged as a suitable core moiety of **1** (Scheme 11).



Scheme 11.

cis-Decalin **33** was to be derived from a ring-closing metathesis reaction[11] of diolefin **34**, which could be prepared from lactone **36** via nitrile oxide **35**. To probe the viability of this approach, lactone **37** was converted into **39** through the conjugate addition of vinyl cuprate and acrolein (Scheme 12). Unfortunately, **39** was obtained as an epimeric mixture and all attempts to generate **39** in epimerically pure form failed. Straightforward functional manipulation of this mixture furnished oxime **41**, which was oxidized to nitrile oxide **42**. Under the conditions in situ cyclization to diastereomerically pure isoxazoline **43** occurred, the configuration



Scheme 12.

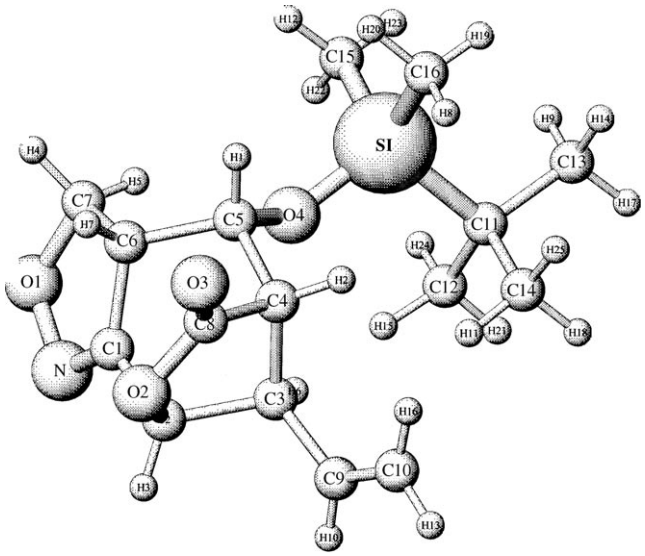
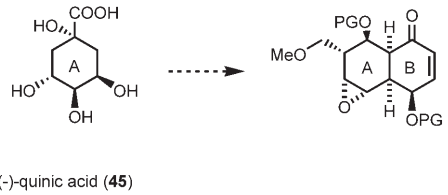
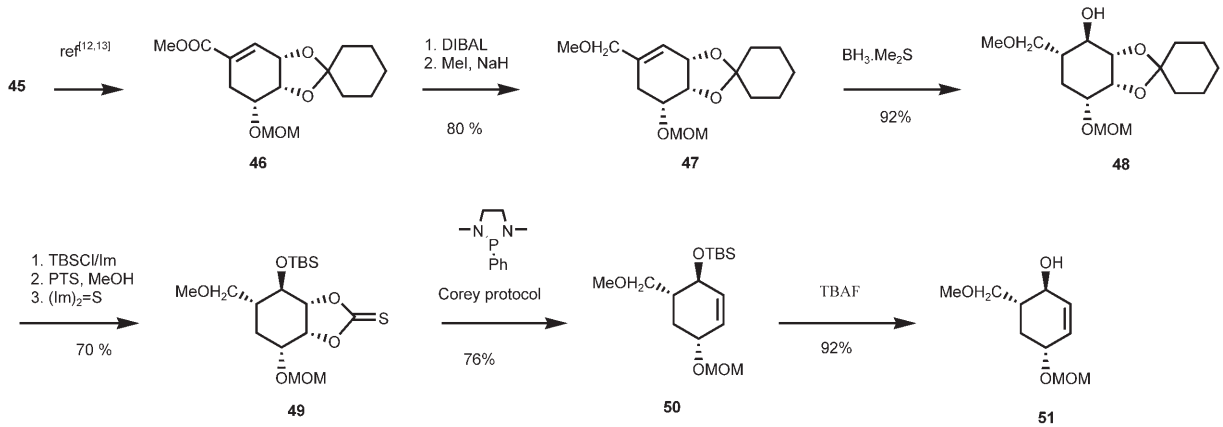


Figure 1. Crystal structure of compound **43**.



Scheme 13.

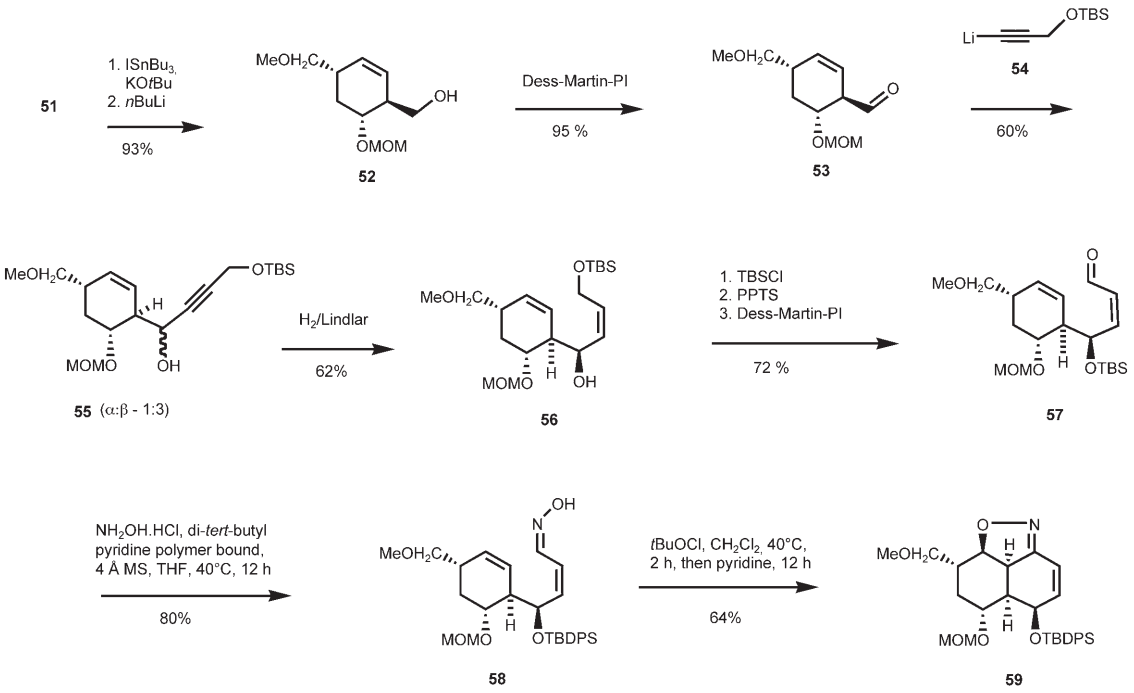
of which was elucidated by single-crystal diffraction (Figure 1). Only the β-OTBS diastereomer underwent the INOC reaction, the α-diastereomer did not give defined products. Although **43** could be converted into diol **44** with high stereocontrol, this approach was abandoned due to the low efficiency of the INOC step. Instead, it was decided to use the INOC reaction for an annulation of ring B to an already existing cyclohexene ring A, which should be derived from D-(−)-quinic acid (**45**) as an inexpensive chiral starting material (Scheme 13).



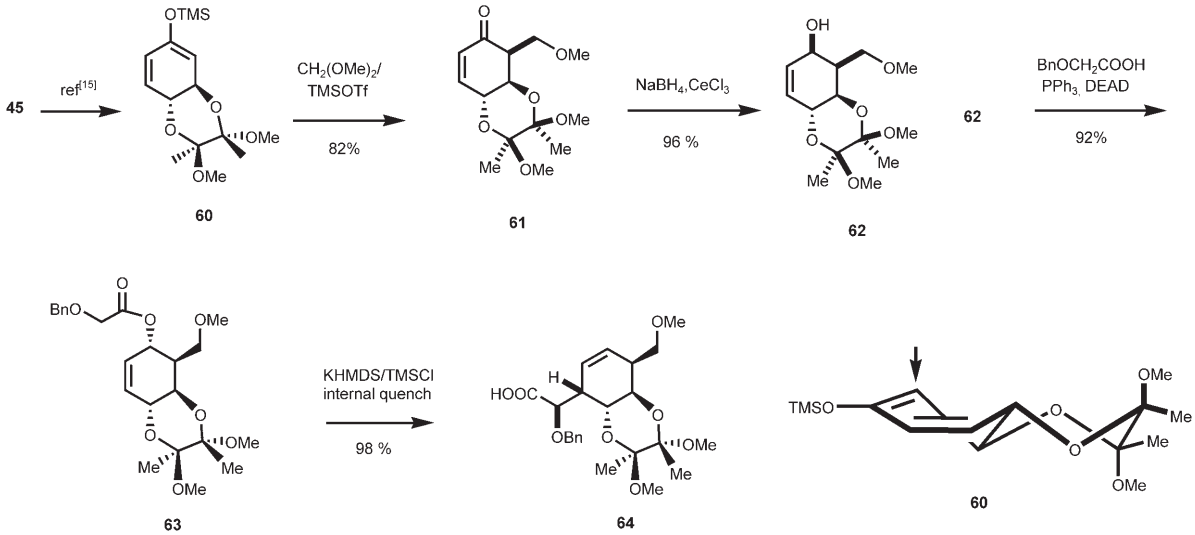
Scheme 14.

Hence, in a model study, **46** was prepared from **45** as described[12,13] and transformed into cyclohexene diol **51** by means of the sequence shown in Scheme 14, with stereocontrolled hydroboration/oxidation (**47** to **48**) and Corey–Hopkins elimination[14] (**49** to **50**) as the key steps.

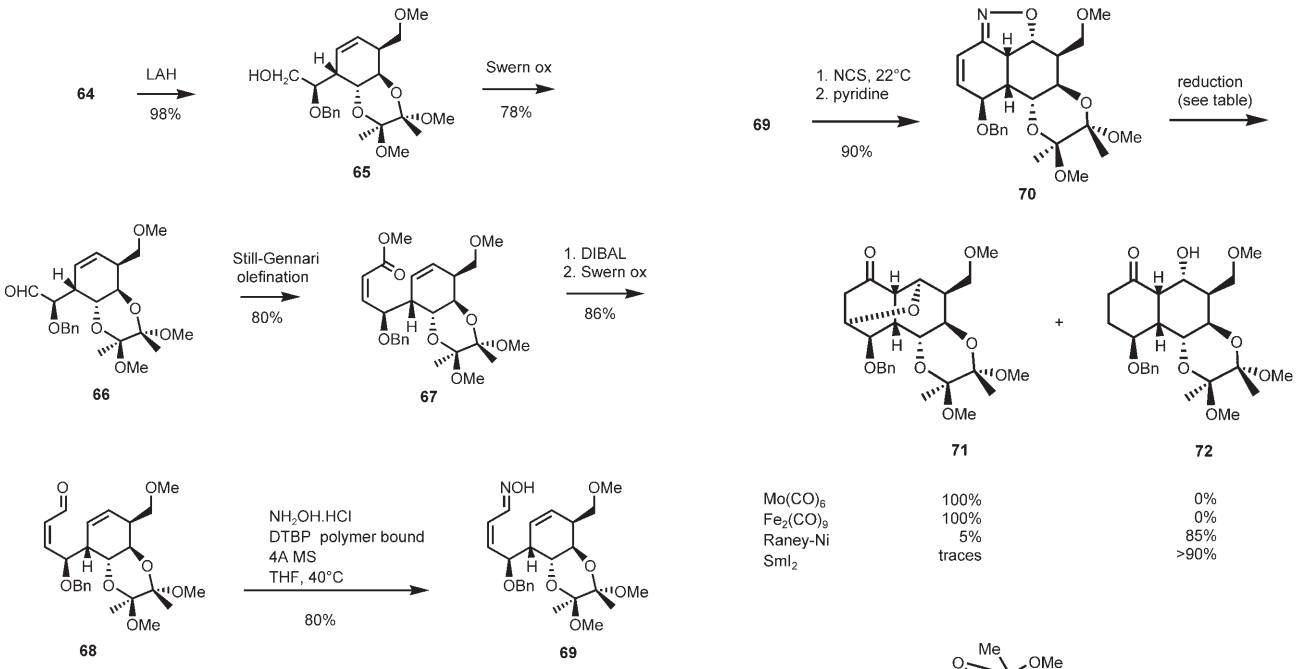
A Wittig–Still rearrangement was used to generate alcohol **52** (Scheme 15), which was oxidized to aldehyde **53**. Nonstereocontrolled addition of alkyne **54** furnished an epimeric mixture of alcohol **55** that was separated. The β-epimer was used in an INOC annulation via aldehyde **57** and oxime **58**, which were both stable towards *E*/*Z* isomerization. Nitrile oxide formation and cycloaddition occurred in situ to furnish isoxazoline **59** in a diastereomerically pure form. Encouraged by this success, we decided to prepare the fully substituted core compound. Thus, as shown in Scheme 16, **45** was converted into silyl dienol ether **60**,[15] to which dimethoxymethane was added under trimethylsilyl trifluoromethanesulfonate (TMSOTf) catalysis with high axial prefer-



Scheme 15.



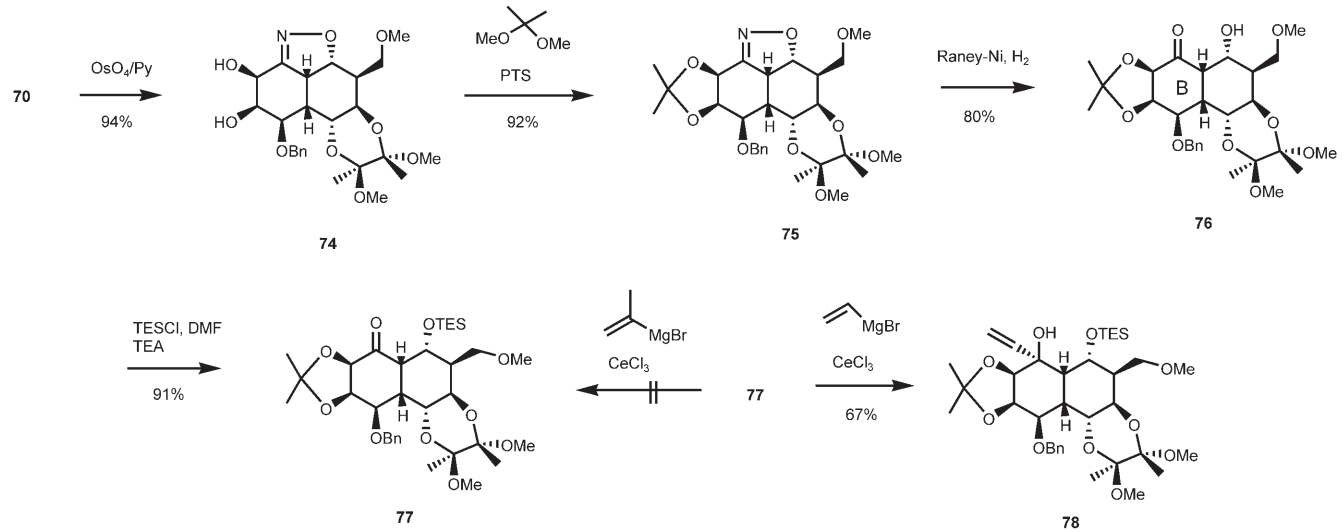
Scheme 16.



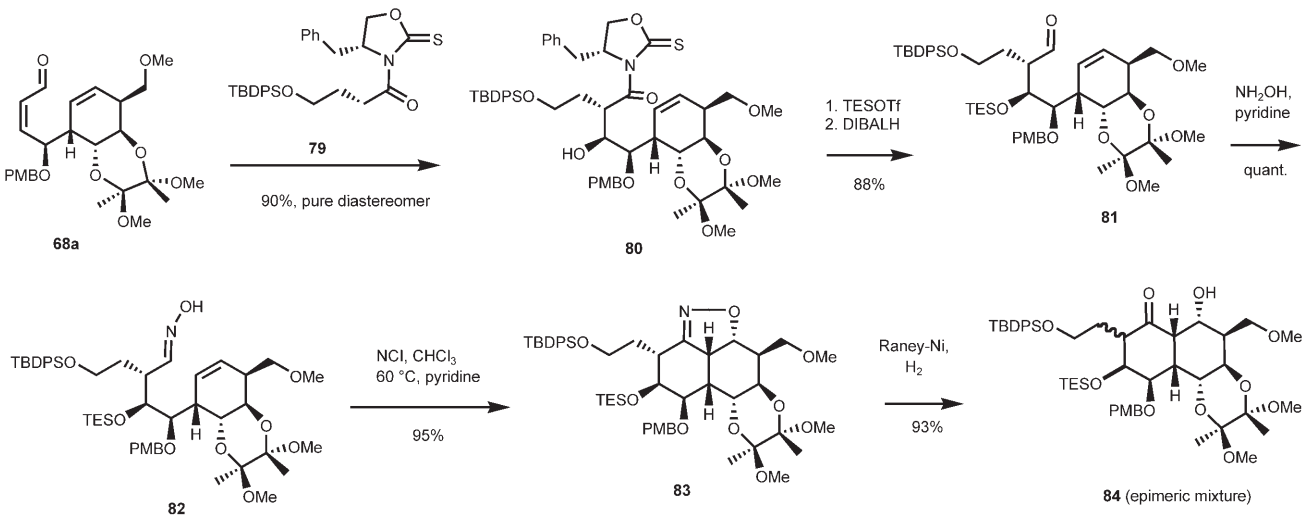
Scheme 17.

Scheme 18.

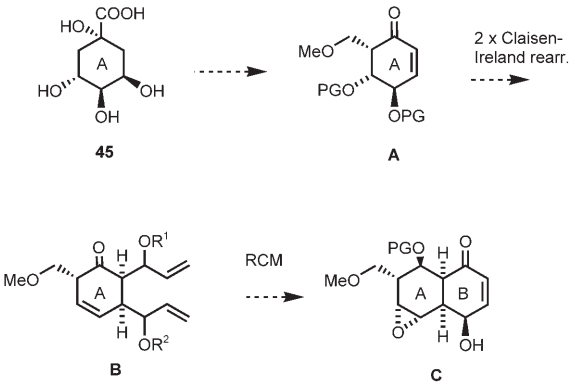
ence (indicated by vertical arrow) to give cyclohexenone derivative **61**. Reduction under Luche conditions furnished allylic alcohol **62** stereoselectively, which was converted into ester **63** under inversion of configuration. Claisen–Ireland rearrangement[16] smoothly gave acid **64** as a single stereoisomer. After reduction to alcohol **65**, the INOC annulation sequence was performed and indeed led to isoxazoline **70** in high overall yield (Schemes 17 and 18). However, all attempts to generate the desired hydroxy ketone failed. Either ether **71** was obtained (which demonstrated the proximity of functional groups in *cis*-decalin systems such as **73**) or over-reduction to **72** occurred. To rescue the approach, the double bond was protected as an acetonide in **75**. In fact, hydroxy ketone **76** was now formed without problems and protected as the triethylsilyl (TES) ether **77** (Scheme 19). However, although vinyl magnesium bromide could be



Scheme 19.



Scheme 20.



Scheme 21.

added to give **78** stereoselectively, isopropenyl magnesium bromide did not react at all.

To exploit the INOC approach further, the possibility of introducing the appendage in ring B prior to annulation was investigated (Scheme 20). Thus aldehyde **68a** was converted into adduct **80** through Crimmins aldolization[17] with oxazolidinethione **79**. Tesylation and reduction gave aldehyde **81** and after the usual INOC procedure, isoxazoline **83** was obtained. Reductive ring opening to hydroxy ketone **84** was successful; however, as extensive epimerization occurred, the INOC approach was abandoned as a whole.

Ring-Closing Metathesis (RCM) Annulation

Following the general retrosynthetic concept depicted in Scheme 21, intermediate **62** was chosen as a substrate for a Claisen–Ireland rearrangement (Scheme 22). It turned out that diol **86** could be acylated at the allylic alcohol position with high regioselectivity to give ester **88**. The remaining hydroxyl function was TES-protected and a Claisen–Ireland rearrangement was performed to give acid **90**, which was converted to olefin **93** as shown. After desilylation to **94**, an analogous sequence was performed that furnished the desired diolefin **98**.

RCM of **98** with Hoveyda's catalyst[18] gave *cis*-dehydrooctalin **99** (Scheme 23), which was converted into enone **101** with high yield. Stereo- and regioselective epoxidation of the electron-rich double bond led to epoxide **102**, diastereomerically pure according to the ^{1}H NMR spectrum (Figure 2) after chromatography, which is now ready for the addition of side chain **5**. From alkoxide **103**, the desired cyclic ether **104** should be formed.

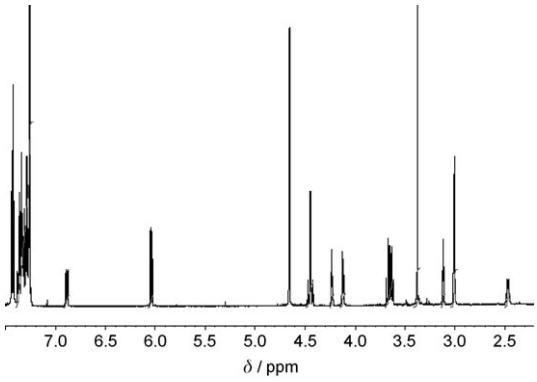
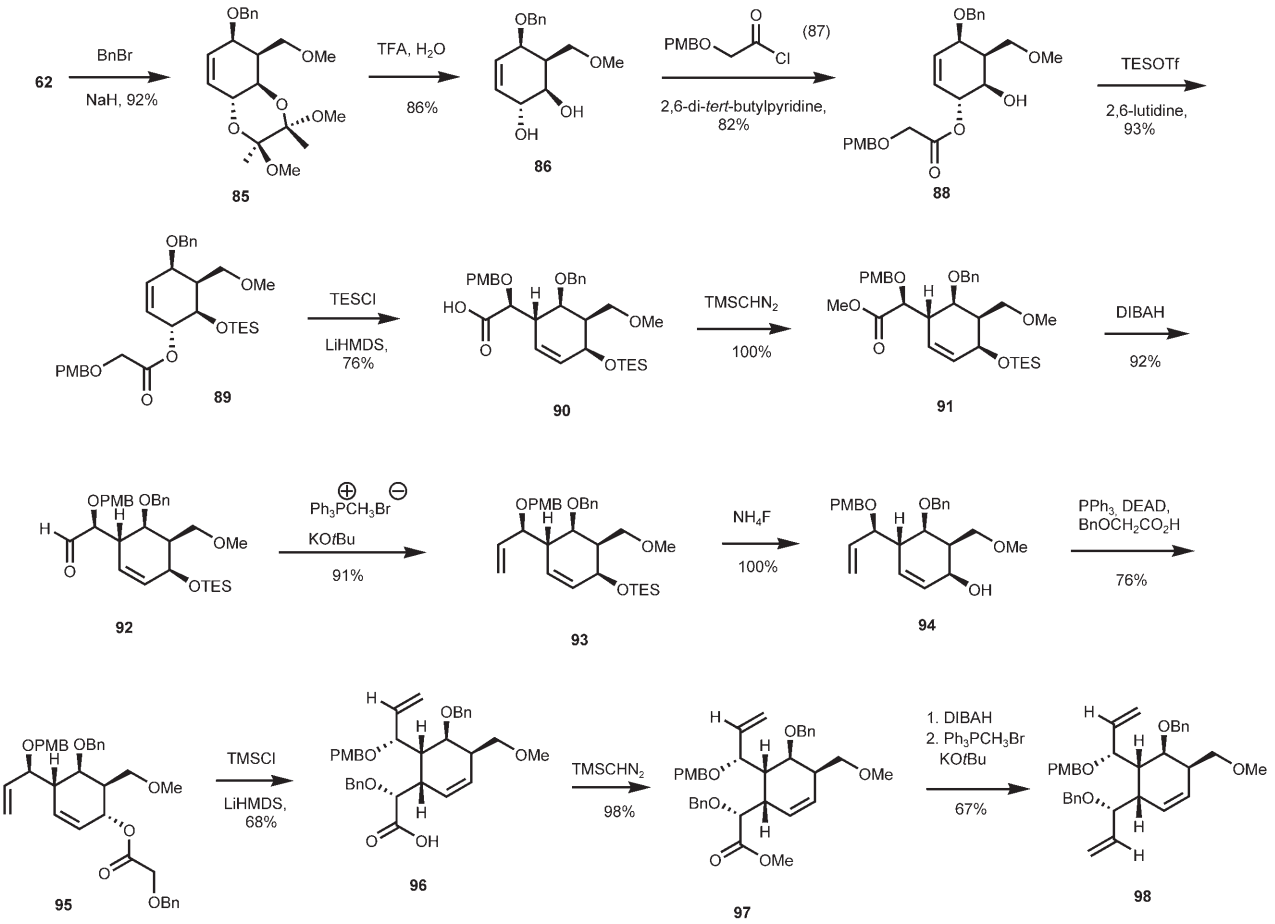


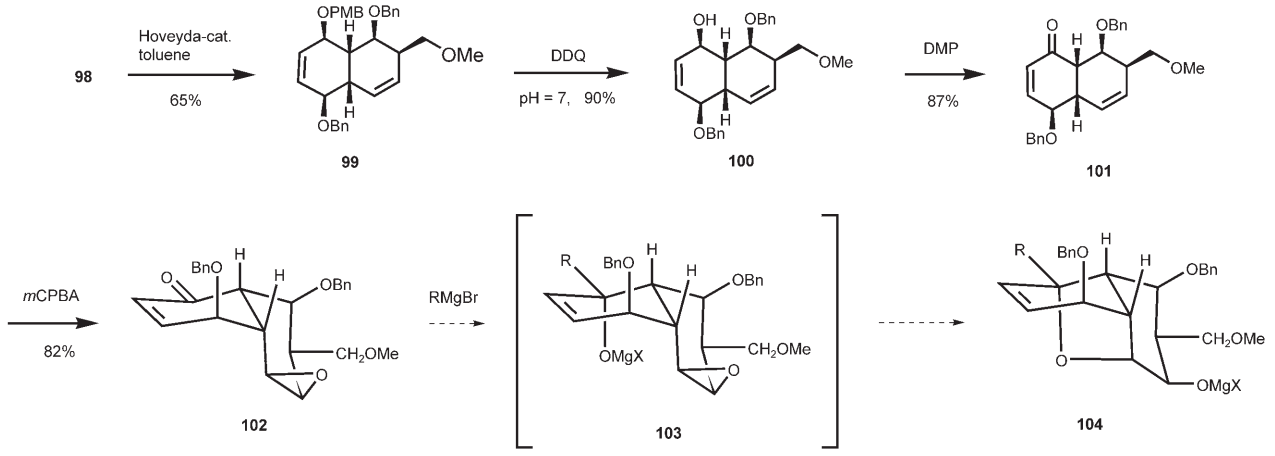
Figure 2. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of epoxide **102**.

Acknowledgements

We thank the Schering AG, Berlin, for chemicals, Drs. H. Kählig and L. Brecker for NMR spectroscopic measurements, and G. Giester for the X-ray analysis of compound **43**.



Scheme 22.



Scheme 23.

[1] a) *Antibiotic Resistance: Origin, Evolution, Selection and Spread* (Eds.: D. J. Chadwick, J. Goode), Wiley, Chichester, **1997**; b) S. B. Levy, *Sci. Am.* **1998**, *278*, 46, and references therein.

[2] M. Speitling, I. Grün-Wollny, F. G. Hannske, H. Laatsch, *12 and 13 IRSEER Naturstofftage der DECHEMA e.V. Irsee*, **2000** and **2001**, poster sessions.

[3] W. D. Celmer, C. N. Chmurny, C. E. Moppett, R. S. Ware, P. C. Watts, E. B. Whipple, *J. Am. Chem. Soc.* **1980**, *102*, 4203; Review: J. Kallmerten, *Studies in Natural Products Chemistry, Vol. 17* (Ed.: Atta-ur-Rahman), Elsevier, Amsterdam, **1995**, pp. 283–310, and references cited therein; synthesis: D. J. Plata, J. Kallmerten, *J. Am. Chem. Soc.* **1988**, *110*, 4041; L. T. Rossano, D. J. Plata, J. Kallmerten, *J. Org. Chem.* **1988**, *53*, 5189, and references therein.

[4] a) J. A. Marshall, *Chem. Rev.* **1996**, *96*, 31; b) J. A. Marshall, X. J. Wang, *J. Org. Chem.* **1992**, *57*, 1242; c) J. A. Marshall, H. Chobanian, P. Wipf, J. Pierce, *Org. Synth.* **2005**, *82*, 43; d) M. J. C. Buckle, I. Fleming, *Tetrahedron Lett.* **1993**, *34*, 2383; e) M. J. C. Buckle, I. Fleming, S. Gil, K. L. C. Pang, *Org. Biomol. Chem.* **2004**, *2*, 749.
[5] J. W. Coe, W. R. Roush, *J. Org. Chem.* **1989**, *54*, 915.
[6] Review: M. A. J. Duncton, G. Pattenden, *J. Chem. Soc. Perkin Trans. 1* **1999**, 1235.
[7] K. Ando, *J. Org. Chem.* **1999**, *64*, 8406.
[8] P. Soucy, A. L'Heureux, A. Toro, P. Deslongchamps, *J. Org. Chem.* **2003**, *68*, 9983, and references therein; W. R. Roush, K. Koyoma, M. L. Curtin, K. J. Moriarty, *J. Am. Chem. Soc.* **1996**, *118*, 7502.
[9] A. Sorg, R. Brückner, *Synlett* **2005**, 289.
[10] Review: J. Mulzer in *Organic Synthesis Highlights, Vol. I* (Eds.: J. Mulzer, H. J. Altenbach, M. Braun, K. Krohn, H. U. Reissig), VCH, Weinheim, **1990**, p. 77.
[11] Reviews on RCM: A. Fürstner, *Angew. Chem.* **2000**, *112*, 3140; *Angew. Chem. Int. Ed.* **2000**, *39*, 3012; T. M. Trnka, R. H. Grubbs, *Acc. Chem. Res.* **2001**, *34*, 18; R. R. Schrock, A. H. Hoveyda, *Angew. Chem.* **2003**, *115*, 4740; *Angew. Chem. Int. Ed.* **2003**, *42*, 4592; S. J. Connon, S. Blechert, *Angew. Chem.* **2003**, *115*, 1944; *Angew. Chem. Int. Ed.* **2003**, *42*, 1900; J. Mulzer, E. Öhler, *Top. Organomet. Chem.* **2004**, *13*, 269; K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem.* **2005**, *117*, 4564; *Angew. Chem. Int. Ed.* **2005**, *44*, 4490; T. Gaich, J. Mulzer, *Curr. Top. Med. Chem.* **2005**, *5*, 1473.
[12] G. Ulibarri, W. Nadler, T. Skrydstrup, H. Audrain, A. Chiaroni, C. Riche, D. Grierson, *J. Org. Chem.* **1995**, *60*, 2753.
[13] V. S. Enev, M. Drescher, H. Kählig, J. Mulzer, *Synlett* **2005**, 2227.
[14] E. J. Corey, P. B. Hopkins, *Tetrahedron Lett.* **1982**, *23*, 1979.
[15] L. M. Murray, P. O'Brien, R. J. K. Taylor, *Org. Lett.* **2003**, *5*, 1943.
[16] L. A. Paquette in *Comprehensive Organic Synthesis, Vol. 5* (Eds.: B. M. Trost, I. Fleming), Pergamon, New York, **1991**, pp. 785–898.
[17] M. T. Crimmins, J. She, *Synlett* **2004**, 1371.
[18] S. B. Garber, J. S. Kingsbury, B. L. Gray, A. H. Hoveyda, *J. Am. Chem. Soc.* **2000**, *122*, 8168; S. Gessler, S. Randl, S. Blechert, *Tetrahedron Lett.* **2000**, *41*, 9973.

Published online: May 19, 2006

6. *cis*-Decalins from Quinic Acid: Toward a Synthesis of Branimycin

Marchart, S.; Mulzer, J.; Enev, V. S. *Org. Lett*. **2007**, *9*, 813-816.

ORGANIC LETTERS

2007
Vol. 9, No. 5
813−816

cis-Decalins from Quinic Acid: Toward a Synthesis of Branimycin

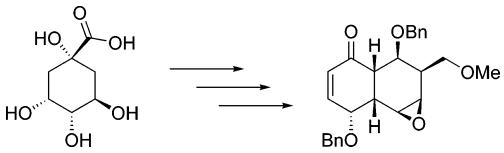
Stefan Marchart, Johann Mulzer,* and Valentin S. Enev*

Institut für Organische Chemie, Währingerstrasse 38, A-1090 Wien, Austria

valentin.enev@univie.ac.at; johann.mulzer@univie.ac.at

Received December 14, 2006

ABSTRACT



Starting from (−)-quinic acid an efficient synthesis of highly functionalized *cis*-α,*β*-unsaturated ketone 3, an advanced precursor of branimycin, has been accomplished via two key step reactions: a ring closing metathesis reaction to prepare the *cis*-decalin system, and a highly stereoselective epoxidation reaction.

The synthesis of highly functionalized *cis*-decalin systems has been a longstanding problem. In many cases Diels−Alder-based annulations to *p*-quinoids have been employed, but despite the conceptual simplicity of this approach the subsequent elaboration of stereogenic centers and appendages has proved problematic. Intrigued by the low price of quinic acid we looked for possibilities to annulate a second ring to this template. By using a non-Diels−Alder methodology, a richly elaborated *cis*-decalin system should be generated. As a target for this strategy we chose branimycin (**1**),[1,2] an unusual member of the nargenicin antibiotic family,[3] which has been isolated from *Streptomyces* by the Laatsch group in Göttingen.[4] Biological tests have shown that branimycin is active against *Escherichia coli*, *Bacillus subtilis*, *Staphylococcus aureus*, and in particular *Streptomyces viridochromogenes*. Apart form the biological activity, the complex *cis*-fused decalin core, the 1,4-oxygen bridge, and the 9-membered macrolide ring make **1** an attractive target for total synthesis.

The retrosynthetic concept is shown in Figure 1. As a key disconnection the 1,2-addition of vinyllithium subunit **2** to bicyclic 7,8-epoxy-12-ketone **3** was envisaged. This highly convergent approach necessitates efficient syntheses of both **2** and **3**. As outlined before, (−)-quinic acid[5] **7** was chosen as a starting material for **3**, to explore whether the existing chiral centers could be used to control the synthesis of an enantiomerically and diastereomerically pure *cis*-decalin system. Ring B should be constructed by a ring closing metathesis[6] (RCM) of **4**, in which the required monosubstituted double bonds were to be installed via two successive Claisen−Ireland rearrangements,[7] from protected diol precur-

(1) Enev, V. S.; Drescher, M.; Kaehlig, H.; Mulzer, J. *Synlett* **2005**, *14*, 2227−2229.

(2) Felzmann, W.; Arion, V. B.; Mieusset, J. L.; Mulzer, J. *Org. Lett.* **2006**, *8*, 3849−3851.

(3) (a) Review: Kallmerten, J. *Studies in Natural Procducts Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, The Netherlands, 1995; Vol. 17, pp 283−310 and references cited therein. (b) Celmer, W. D.; Chmurny, C. N.; Moppett, C. E.; Ware, R. S.; Watts, P. C.; Whipple, E. B. *J. Am. Chem. Soc.* **1980**, *102*, 4203−4209. (c) Tone, J.; Shibakawa, R.; Maeda, H.; Yamauchi, Y.; Niki, K.; Saito, M.; Tsukuda, K.; Whipple, E. B.; Watts, P. C.; Moppett, C. E.; Jefferson, M. T.; Huang, L. H.; Cullen, W. P.; Celmer, W. D. *20th Interscience Conference on Antimicrobial Agents and Chemotherapy*, New Orleans, LA, Abstract 62, Sep 22−24, 1980.

(4) Speitling, M.; Grün-Wollny, I.; Hannske, F. G.; Laatsch, H. *12 and 13 IRSEER Naturstofftage der DECHEMA e. V. Irsee*, 2000 and 2001.

(5) (a) Barco, A.; Benetti, S.; De Risi, C.; Marchetti, P.; Pollini, G. P.; Zanirato, V. *Tetrahedron*: *Asymmetry* **1997**, *8*, 3515−3545. (b) Usami, Y.; Ueda, Y. *Chem. Lett.* **2005**, *34*, 1062−1063.

(6) Fürstner A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012−3043. Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450. Trinka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18−29. Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371−388. Lee, C. W.; Grubbs, R. H. *Org. Lett.* **2000**, *2*, 2145−2147. Gaich, T.; Mulzer, J. *Curr. Top. Med. Chem.* **2005**, *5*, 1473−1494. Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490−4527.

(7) Paquette, L. A. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 5, pp 785−898.

10.1021/ol0630189 CCC: $37.00
Published on Web 02/01/2007

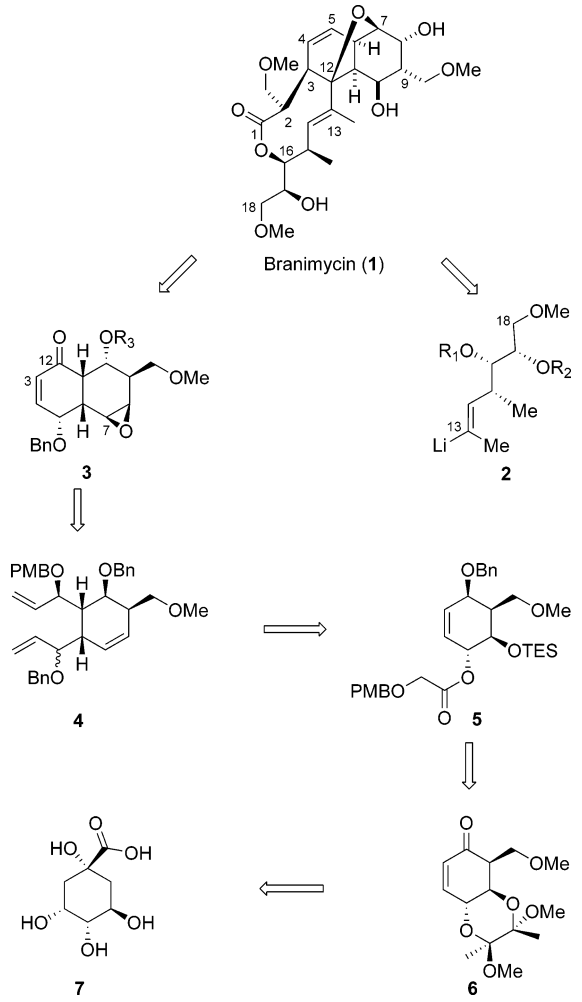


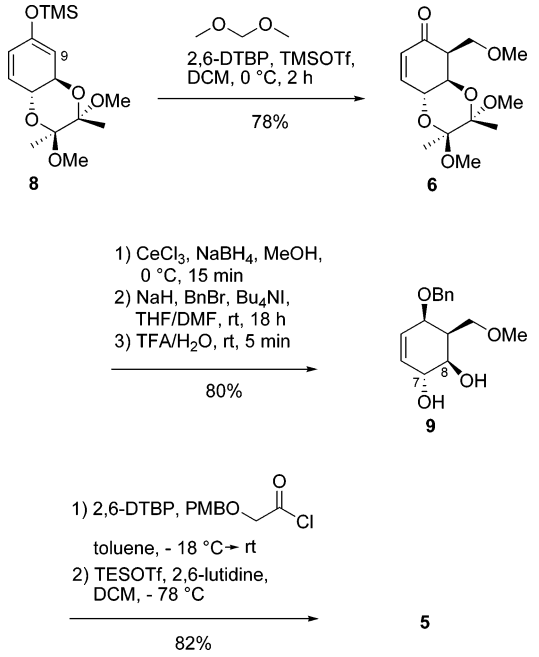
Figure 1. Retrosynthetic analysis.

sor **5**. In turn, **5** would be assembled in stereoselective fashion from enone **6**.

Our synthesis started from the known compound **8**,[8] which was subjected to a Mukaiyama-type condensation with dimethoxymethane[9] (Scheme 1) to afford **6** as a single diastereomer in moderate yield (55%, 78% after recycling). The same stereoselectivity has been observed with use of *m*-CPBA and NBS as electrophiles, which is a consequence of the conformational rigidity due to the trans-diequatorial-protected 1,2-diol. An axial attack on the electron-rich C9 avoids a twist boat conformation.[10]

Longer reaction times improved the yield remarkably, but with a sacrifice in diastereomeric ratio. Luche reduction of **6** occurred exclusively from the less hindered side. This

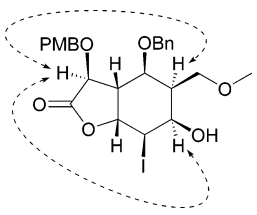
Scheme 1. Synthesis of Rearrangement Precursor **5**



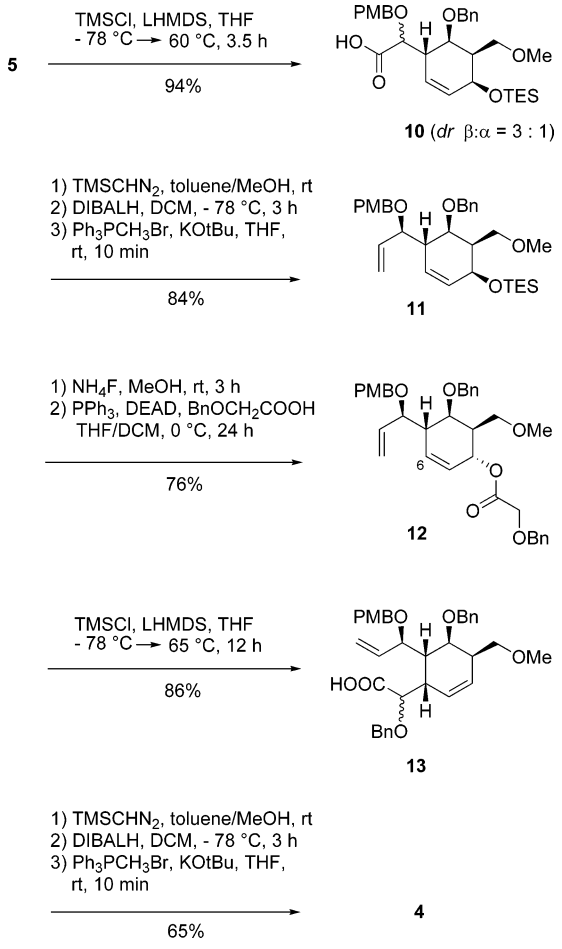
newly formed stereocenter is planned to be inverted in a later stage of the synthesis. Benzylation and removal of the BDA[11] group furnished diol **9** in 80% yield over three steps. Conversion of **9** to **5** was achieved in a two-step sequence—regioselective acylation of the C7-hydroxy group of **9** (p-$MeOC_6H_4OCH_2COCl$,[12] 2,6-di-*tert*-butylpyridine,[13] 82% yield) followed by TES protection at the C8-hydroxy group—which set the scene for the first Claisen−Ireland rearrangement. Following Corey's procedure[14] ester **5** was converted to the silylketene acetal under internal quench conditions (TMSCl/LHMDS) and subsequently heated to give **10** (94% after one recycling step) as a mixture of isomers (Scheme 2). The low stereoselectivity for C12 was inconsequential as this stereogenic center becomes oxidized later in the synthesis. Nevertheless, the diastereomers were separated to avoid ambiguous spectra information for the proximate reaction steps. The synthesis was carried on with pure main isomer **10**, whose configuration was assigned by 2D NMR studies of the corresponding iodolactone **10a**.[15]

Acid **10** was transformed to olefin **11** in 3 steps via reduction to the corresponding aldehyde and subsequent

(8) Murray, L. M.; O'Brien, P.; Taylor, R. J. K. *Org. Lett.* **2003**, *5*, 1943−1946.
(9) Murata, S.; Suzuki, M.; Noyori, R. *Tetrahedron* **1988**, *13*, 4259−4275.
(10) (a) Murray, L. M.; O'Brien, P.; Taylor, R. J. K. *Org. Lett.* **2003**, *5*, 1943−1946. (b) Mathews, R. S.; Girgenti, S. J.; Folkers, E. A. *J. Chem. Soc., Chem. Commun.* **1970**, 708−709. (c) House, H. O.; Umen, M. J. *J. Org. Chem.* **1973**, *38*, 1000−1003. (d) Skaddan, M. B.; Wüst, F. R.; Katzenellenbogen, J. A. *J. Org. Chem.* **1999**, *64*, 8108−8121.
(11) Ley, S. V.; Baeschlin, D. K.; Dixon, D. J.; Foster, A. C.; Ince, S. J.; Priepke, H. W. M.; Reynolds, D. J. *Chem. Rev.* **2001**, *101*, 53−80.
(12) Piers, E.; Lemieux, R. *Organometallics* **1995**, *14*, 5011−5012.
(13) It has to be pointed out that use of pyridine or 2,6-lutidine resulted in a 1:1 mixture of C-7/8 O-acyl regioisomers.
(14) Corey, E. J.; Gross, A. *Tetrahedron Lett.* **1984**, *25*, 495−498.
(15) Selected NOE data for **10a**.

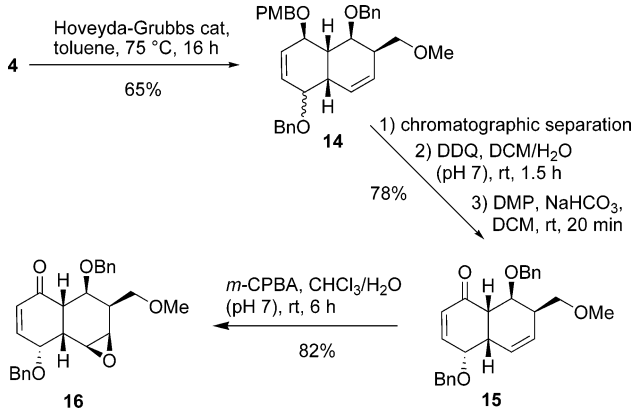


Scheme 2. Preparation of RCM Precursor **4**



Wittig olefination[16] in 84% overall yield. To initiate the second Claisen−Ireland rearrangement **11** was desilylated and the resulting allylic alcohol was acylated to give ester **12** via Mitsunobu inversion.[17] In the course of this reaction the C6-appendage was introduced simultaneously. The conversion of **12** to di-olefin **4** followed the established four-step sequence: rearrangement to **13**, followed by esterification, reduction to the corresponding aldehyde, and Wittig olefination (dr 2:1, 56% overall yield). The RCM reaction was carried out with either the Grubbs' second generation catalyst[18] or Hoveyda−Grubbs' second generation catalyst.[19] Unfortunately it turned out that Grubbs' second generation catalyst underwent decomposition in the course of the reaction at the required temperature (ca 75 °C), whereas Grubbs−Hoveyda catalyst was stable enough to give 65% of *cis*-decalin **14** with only starting material left, which could be recycled (Scheme 3). After chromatographic separation the pure isomer **14** was deprotected (DDQ/DCM/buffer) and

Scheme 3. Synthesis of Epoxyketone **16**



subsequently oxidized (DMP)[20] to give **15** in 78% yield (Scheme 3). 2D NMR spectra confirmed that none of the dreaded epimerization at C11 had occurred.

Stereo- and regioselective epoxidation of the C7−C8 double bond with *m*-CPBA furnished diastereomerically pure crystalline epoxyketone **16** whose relative configuration was established by single-crystal diffraction (Figure 2).

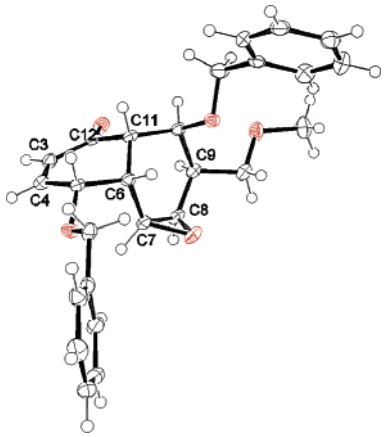


Figure 2. ORTEP-3[21] projection (ellipsoid: 50% probability) of epoxyketone **3**.

In conclusion, we have shown that quinic acid is a suitable substrate for stereocontrolled annulations via the Claisen−Ireland rearrangement; RCM protocol. Quite obviously the configurations at C6 and C11 can be manipulated at will by acylating diol **9** under retention or inversion of configuration so that *cis*- and *trans*-decalins with either absolute configuration should be available under perfect stereocontrol. Specifically, we have described an efficient route to the *cis*-decalin core of branimycin, whose further synthesis is actively pursued in our laboratory.

(16) Cadogan, J. I. G. *Orgnanophosphorus Reagents in Organic Synthesis*; Academic Press: New York, 1979.
(17) Mitsunobu, O. *Synthesis* **1981**, *1*, 1−28.
(18) Grubbs, R. H.; Schwab, B.; Ziller, J. W. *J. Am. Chem. Soc*. **1996**, *118*, 100−110.
(19) (a) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2000**, *122*, 8168−8179. (b) Gessler, S.; Randl, S.; Blechert, S. *Tetrahedron Lett*. **2000**, *41*, 9973−9976.
(20) Dess, D. B.; Martin, J. C. *J. Org. Chem*. **1983**, *48*, 4155−4156.
(21) Farrugia, L. J. *J. Appl. Crystallogr*. **1997**, *30*, 565.

We thank Dr. Hans-Peter Kaehlig, Dr. Lothar Brecker, and Susanne Felsinger for NMR analysis, M. Zinke for performing the HPLC separations, and Prof. Vladimir Arion (all University of Vienna) for crystallography. Moreover the financial support from the Austrian Science Fund (FWF) is gratefully acknowledged.

Supporting Information Available: Experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0630189

cis-Decalins from Quinic Acid: Toward a Synthesis of Branimycin – Supporting Information

Stefan Marchart, Johann Mulzer,* and Valentin S. Enev*

Institut für Organische Chemie, Währinger Strasse 38, A – 1090 Vienna, Austria

General Information

The following general procedures were used in all reactions unless otherwise noted. Reaction vessels were dried by repeated heating under vacuum (heat gun) followed by purging with dry argon. Oxygen- and moisture sensitive reactions were carried out under a slight argon overpressure (balloon) and in dry solvents. Sensitive liquids and solutions were transferred by double tipped needle or syringe through rubber septa. All reactions were stirred magnetically if not stated otherwise.

Solvents

The solvents used were purified and dried according to common procedures as follows. Dry solvents were stored under Argon over molsieve (4 Å).

• **Acetone** was distilled from phosphorpentoxide.

• **Benzene, toluene and xylene** were refluxed over potassium and freshly distilled.

• **Chloroform** was filtered through basic aluminium oxide (desiccant form), refluxed over phosphorpentoxide and freshly distilled.

• **Dichloromethane** was distilled from CaH_2 or phosphorpentoxide.

• **Diethyl ether** was predried over NaOH, refluxed over $LiAlH_4$ and freshly distilled.

• **Dimethylformamide** was refluxed over CaH_2 and distilled *in vacuum*.

• **Hexane** and **ethyl acetate** for chromatography were purified by distillation using a column.

• **Methanol** was treated with magnesium filings, refluxed for several hours and then distilled.

• **Pyridine** was distilled from KOH.

• **Tetrahydrofuran** was filtered through basic aluminium oxide (desiccant form), refluxed over sodium/benzophenone ketyl and freshly distilled. All other solvents were HPLC grade or were purified and dried by standard methods.

Chemicals

All commercially available reagents were purchased in the best quality available and used without further purification unless stated otherwise.

Chromatography

Thin-layer chromatography (TLC)

All reactions were monitored using Merck silica gel 60 F_{254} plates. The plates were usually developed with a mixture of hexane / ethyl acetate. Unless the compound was coloured, UV-active spots were detected at 254 nm. Most plates were additionally treated with one of the following visualization reagents: Anisaldehyde [anisaldehyde (6 g) in ethanol (250 ml) + conc. H_2SO_4 (25 mL)], Ceric sulfate [H_2SO_4 (10 %, 100 ml), phosphormolybdic acid (4.5 g), $Ce(IV)SO_4$ (0.1 g)], Vanillin [vanillin (6 g) in ethanol (250 ml) + conc. H_2SO_4].

Column chromatography

Preparative column chromatography and flash chromatography was performed with silica gel 60 from Merck (0.040-0.063 μm, 240 - 400 mesh).

Analytic and preparative HPLC

For the determination of diastereomeric ratios *etc.* in analytical scale module systems from *Jasco* (PU-980, UV-975 UV detector, RI-930 RI detector, 250 × 4 mm column) were used. The adsorbent was *Supersphere* Si 60 (4 μm, Merck) or *Nucleosil* 50 (4 μm, *Macherey-Nagel*). The semipreparative and preparative scale was covered by module systems from *Dynamax* (SD-1 pump, UV-1 UV detector) and *Knauer* (RI detector). Compounds separated by preparative HPLC were checked by analytical HPLC on homogenity.

NMR spectroscopy

NMR spectra were recorded on either a Bruker Avance DPX 250 MHz, a Bruker Avance DRX 400 MHz or a Bruker Avance DRX 600 MHz spectrometer. Unless otherwise stated, all NMR spectra were measured in $CDCl_3$ solutions and referenced to the residual $CDCl_3$ signal (^1H, δ = 7.26; ^{13}C, δ = 77.0) or the TMS signal (^1H, δ = 0.0; ^{13}C, δ = 0.0). The following abbreviations are used to describe spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, ddd = doublet of doublet of doublet, dddd = doublet of doublet of doublet

of doublet etc.; other combinations derive from those listed. Coupling constants *J* are given in Hz; assignments of proton resonances were confirmed, when possible, by selective homonuclear decoupling experiments or by correlation spectroscopy.

Mass spectroscopy

Mass spectra were measured on spectrometers from *Micro Mass*, *Fisions Instrument* and *Trio200*. Stated, is the kind of ionization (in most cases EI, **E**lectron **I**mpact; occasionally FAB, **F**ast **A**tom **B**ombardment) and electron activation energy (in eV). HRMS (**H**igh **R**esolution **M**ass **S**pectra) were taken with a *Finnigan* MAT 8230 with a resolution of 10000.

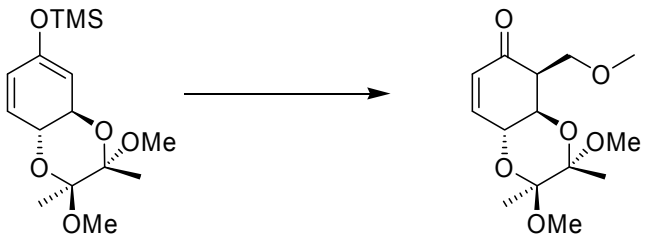
Infrared spectroscopy

IR spectra were recorded using a *Perkin-Elmer* 1600 Series FTIR spectrometer and are reported in wave numbers (cm^{-1}). All compounds were measured as a thin film on a silicon single crystal plate (Si-pellet).

Polarimetry

Optical rotations were measured on a P 341 *Perkin-Elmer* polarimeter. The length of the measuring chamber is 1 dm and the solution is kept at 20.0°C. The optical rotation is measured with monochromatic sodium light (589 nm) and unless otherwise stated $CHCl_3$ is used as solvent.

(2R, 3S, 4aR, 5S, 8aS)- 2,3-Dimethoxy-5-methoxymethyl-2,3-dimethyl-2,3,4a,8a-tetrahydro-5*H*-benzo[1,4]dioxin-6-one (6)



To a solution of the enol trimethylsilyl ether (13.0 g, 41.3 mmol) in DCM (80 mL) 2,6-di-tert-butylpyridine (0.94 mL, 4.2 mmol) and dimethoxymethane (6.3 g, 82.9 mmol) were added and the reaction mixture was cooled to 0 °C. TMSOTf (0.756 mL, 4.2 mmol) was added dropwise, the reaction was stirred for 2 h at 0 °C and quenched with a saturated $NaHCO_3$ solution. The phases were separated and extracted with DCM (3 x 70 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by HPLC to yield 6.5 g (55 %) of the desired product and 6.0 g of starting material.

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 6.80 (1H, dd, *J* = 10.1, 1.7 Hz), 5.99 (1H, dd, *J* = 10.2, 2.6 Hz), 4.88 (1 H, td, *J* = 9.3, 2.1 Hz), 4.16 (1H, dd, *J* = 9.4, 6.4 Hz), 3.87 (1 H, dd, *J* = 9.1, 3.9 Hz), 3.76 (1 H, dd, *J* =9.3, 3.9 Hz), 3.29 (3 H, s), 3.28 (3 H, s), 3.23 (3 H, s), 2.71 (1 H, m), 1.34 (3 H, s), 1.32 (3 H, s)

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 198.8, 148.5, 129.8, 100.7, 99.9, 69.3, 69.1, 66.1, 60.4, 59.2, 50.2, 48.0, 31.6, 22.6, 17.8, 17.6, 14.2

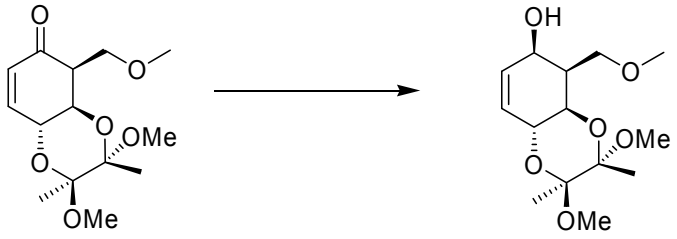
IR (Si, Film) ν_{max} = 3346, 2950, 2833, 1683, 1619, 1455, 1110, 1012, 931, 901, 611, 571

MS (EI, 70 eV, 40 °C): m/z = 255, 218, 197, 176, 154, 138, 123, 101, 73, 55

HRMS (EI, 70 eV, 60 °C) calc. for $C_{13}H_{19}O_5$ (= M^+ - MeOH): 255.1232;
found: 255.1236

$[\alpha]_D^{20}$ = + 77.8 (c = 0.65 $CHCl_3$)

(2R, 3S, 4aR, 5S, 6R, 8aS)- 2,3-Dimethoxy-5-methoxymethyl-2,3-dimethyl-2,3,4a,5,6,8a-hexahydro-benzo[1,4]dioxin-6-ol



A solution of ketone **6** (3 g, 10.5 mmol) in MeOH (50 ml) was cooled to 0 °C, $CeCl_3$ (472 mg, 1.3 mmol) was added and the solution was stirred for 15 min. $NaBH_4$ (472 mg, 12.5 mmol) was added portionwise and after 15 min. the reaction was quenched with NH_4Cl. The solvent was removed under reduced pressure and the product was hydrolysed with H_2O (20 mL) and EtOAc (100 mL). The two phases were separated and the aqueous phase was extracted with EtOAc (2 x 25 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure to give 3.1 g (100 %) of the desired alcohol as a viscous oil.

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 5.73 (1 H, dd, *J* = 10.3, 1.4 Hz), 5.55 (1 H, dd, *J* = 10.2, 2.0 Hz), 4.59 (1 H, m), 4.14 (1 H, m), 3.81 (3 H, m), 3.65 (1 H, t, *J* = 9.3 Hz), 3.36 (3 H, s), 3.25 (3 H, s), 3.23 (3 H, s), 2.59 (1 H, m), 1.30 (3 H, s), 1.29 (3 H, s)

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 133.1, 125.5, 100.8, 100.7, 70.9, 69.4, 68.9, 66.2, 59.3, 48.2, 48.2, 42.5, 18.2, 18.1

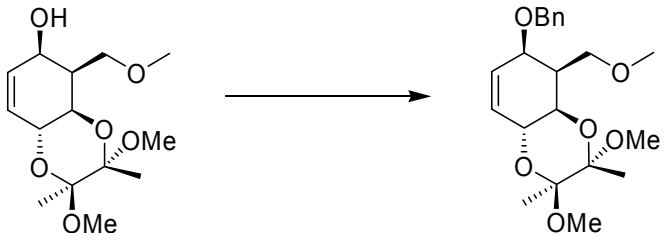
IR (Si, Film) ν_{max} = 3476, 2992, 2949, 2900, 2833, 1456, 1376, 1130, 1042, 933,

MS (EI, 70 eV, 60 °C): m/z = 257, 225, 156, 140, 101, 78, 55

HRMS (EI, 70 eV, 60 °C) calc. for $C_{13}H_{21}O_5$ (= M^+ - MeOH): 257.1389; found: 257.1384

$[\alpha]_D^{20}$ = + 47.3 (c = 1.11, $CHCl_3$)

(2R, 3S, 4aR, 5S, 6R, 8aS)-6-Benzyloxy-2,3-dimethoxy-5-methoxymethyl-2,3-dimethyl-2,3,4a,5,6,8a-hexahydro-benzo[1,4]dioxine



To a solution of the alcohol (1 g, 3.5 mmol) in THF (15 mL) NaH (220 mg, 5,25 mmol) was added and the reaction mixture was stirred until no gas evolution occurred anymore (0.5 h). Then DMF (15 mL), BnBr (0.623 mL, 5.25 mmol) and a catalytic amount of Bu_4NI were added and the reaction mixture was stirred at rt. for 18 h. The reaction was quenched with NH_4Cl, THF was removed under reduced pressure and the solution was diluted with toluene (100 mL). The organic layer was separated, extracted with H_2O (3 x 15 mL) and washed with brine. Toluene was removed under reduced pressure. The crude product was purified by column chromatography (hex:EtOAc = 3:1) to yield 1.22 g (93 %) of the desired product as a viscous oil.

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 7.40 – 7.23 (5H, m), 5.67 (1H, d, *J* = 10.4 Hz), 5.60 (1H, d, *J* = 10.4 Hz,), 4.85 (1H, d, *J* = 11.6 Hz,), 4.45 (1H, d, *J* = 11.4 Hz), 4.33 (1H, m), 4.23 (1H, m), 3.76 (1H, dd, *J* = 9.3, 4.0 Hz), 3.71 (1H, dd, *J* = 9.1, 2.0 Hz), 3.57 (1H, dd, *J* = 9.1, 7.1 Hz), 3.34 (3H, s), 3.26 (3H, s), 3.24 (3H, s), 2.69 (1H, m), 1.31 (3H, s), 1.30 (3H, s).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 139.0, 131.1, 128.7, 128.2, 127.9, 100.7, 100.6, 76.7, 71.2, 69.1, 68.2, 66.2, 59.2, 48.3, 48.2, 42.5, 42.0, 18.3, 18.2

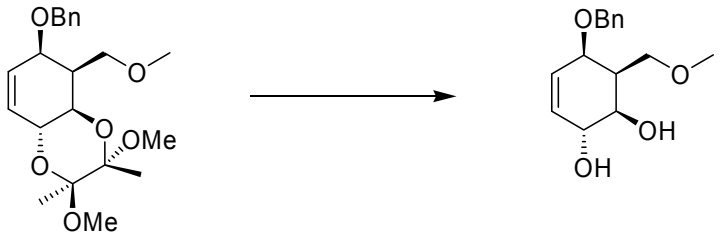
IR (Si, Film) ν_{max} = 2950, 1719, 1497, 1454, 1375, 1114, 1049, 902, 849, 811, 739, 698, 611, 514

MS (EI, 70 eV, 60 °C): m/z = 347, 270, 230, 185, 139, 91, 78

HRMS (EI, 70 eV, 60 °C) calc. for $C_{20}H_{27}O_5$ (= M^+ - CH_3OH): 347.1858; found: 347.1853

$[\alpha]_D^{20}$ = + 31.2 (c = 0.65, $CHCl_3$)

(1R, 2R, 5R, 6R)-5-Benzyloxy-6-methoxymethyl-cyclohex-3-ene-1,2-diol (9)



To a solution of the dioxine (2.6 g, 7 mmol) in H_2O (7 mL) was added TFA (20 mL, 261 mmol) and the reaction mixture was stirred for 5 min at rt. It was transferred slowly to a stirred mixture of a saturated Na_2CO_3 solution (150 mL) and Et_2O (200 mL). The aqueous layer was extracted with Et_2O (5 x 60 mL). The combined organic layers were washed with brine and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was filtered off over silica gel (hex:EtOAc = 2:1) to yield 1.55 g (86 %) of the diol.

^{1}H-NMR (400 MHz, $CDCl_3$): δ= 7.39 – 7.26 (5H, m), 5.90 (1H, ddd, *J* = 10.2, 2.8, 1.0 Hz), 5.85 (1H, ddd, *J* = 10.3, 2.8, 1.3 Hz), 4.59 (2H, s), 4.28 (1H, m), 4.20 (1H, m), 3.80 (2H, m), 3.67 (2H, m), 3.38 (3H, s), 2.72 (1H, m), 2.25 (1H, s)

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ= 138.2, 129.7, 129.3, 128.9, 128.3, 128.0, 74.7, 74.0, 71.7, 71.5, 70.5, 59.7, 40.4

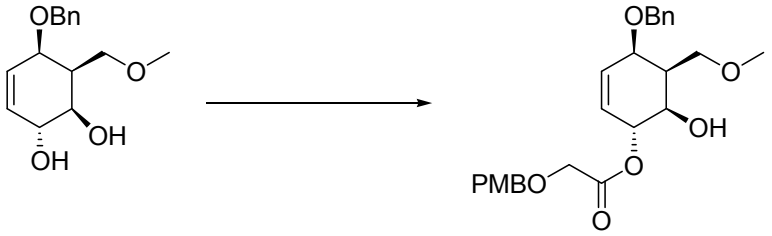
IR (Si, Film) ν_{max} = 3417, 3031, 2917, 1953, 1732, 1651, 1607, 1498, 1456, 1394, 1197, 1107, 803, 752, 698, 667, 514

MS (EI, 70 eV, 40 °C): m/z = 246, 176, 156, 140, 124, 107, 91, 78, 65

HRMS (EI, 70 eV, 40 °C) calc. for $C_{15}H_{18}O_3$ (= M^+ - H_2O): 246.1256; found: 246.1259

$[\alpha]_D^{20}$ = - 107.2 (c = 0.53, $CHCl_3$)

(1R, 4R, 5R, 6R)-(4-Methoxy-benzyloxy)-acetic acid 4-benzyloxy-6-hydroxy-5-methoxymethyl-cyclohex-2-enyl ester



A solution of **9** (1 g, 3.78 mmol) in toluene (10 mL) was cooled down to – 18 °C. Then 2,6-di-tert-butylpyridine (4 mL) was added, and after 5 min. p-methoxybenzoyl acetic acid chloride (810 mg, 3.78 mmol) was added dropwise over 15 min. After stirring at – 18 °C for 2 h the reaction mixture was warmed to rt. After 5 h the reaction was quenched with saturated $NaHCO_3$ solution and diluted with toluene (140 mL). The organic layer was separated, washed with H_2O (2 x 10 mL), and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (hex:EtOAc = 5:1) to yield 1.37 g (82 %) of the desired product.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.38 – 7.27 (7H, m), 6.88 (2H, d, *J* = 8.8 Hz), 6.10 (1H, ddd, *J* = 10.2, 3.8, 1.1 Hz), 5.87 (1H, dd, *J* = 10.1, 3.8 Hz), 5.42 (1H, dd, *J* = 4.8, 3.8 Hz), 4.63 (1H, d, *J* = 11.6 Hz), 4.57 (1H, d, *J* = 11.4 Hz), 4.56 (2H, s), 4.16 (1H, m), 4.10 (1H, d, *J* = 16.4 Hz), 4.04 (1H, d, *J* = 16.4 Hz), 3.85 (1H, m), 3.80 (3H, s), 3.76 (1H, dd, *J* = 11.5, 9.4 Hz), 3.68 (1H, dd, *J* = 9.8, 9.0 Hz), 3.39 (3H, s), 2.54 (1H, m)

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 170.3, 160.0, 138.0, 131.4, 130.2, 130.1, 129.6, 129.0, 128.8, 128.4, 128.1, 126.4, 114.3, 73.4, 72.4, 72.2, 72.0, 71.2, 70.6, 67.2, 67.1, 60.8, 59.7, 55.7, 40.6

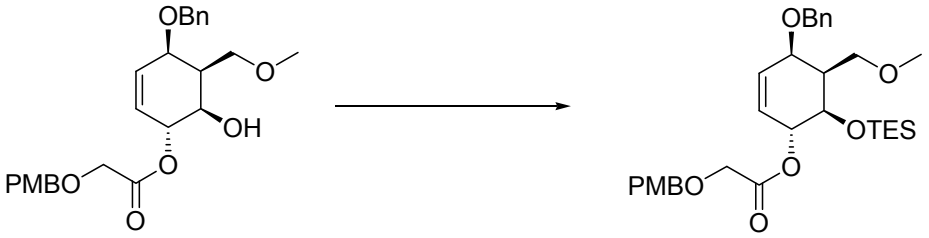
IR (Si, Film) ν_{max} = 3480, 2914, 1733, 1615, 1586, 1516, 1456, 1107, 823, 700, 514

MS (ESI): m/z = 465, 447, 441, 425, 395, 349, 328, 310, 287

HRMS (ESI) calc. for $C_{25}H_{30}O_7Na$ (= M^+ + Na): 465.1889; found: 465.1902

$[\alpha]_D^{20}$ = - 144.9 (c = 0.74, $CHCl_3$)

(1R, 4R, 5R, 6R)-(4-Methoxy-benzyloxy)-acetic acid 4-benzyloxy-5-methoxymethyl-6-triethylsilanyloxy-cyclohex-2-enyl ester (5)



To a solution of the starting material (3.9 g, 8.8 mmol) in DCM (100 mL), 2,6-lutidine (3.08 mL, 26.4 mmol) was added, and the mixture was cooled to – 78 °C. TESOTf (3.19 mL, 14.08 mmol) was added dropwise over 15 min. and the reaction mixture was stirred for 30 min. at – 78 °C. Then it was warmed to rt and after 1.5 h quenched with saturated $NaHCO_3$ solution. The mixture was diluted with toluene (600 mL) and H_2O (100 mL), the organic layer was separated and the aqueous phase was extracted with toluene (2 x 100 mL). The combined organic layers were washed with brine and the solvent was removed under reduced pressure. The crude product was filtered off over silica gel (hex:EtOAc = 5:1) to yield **5** (4.90 g, 100 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.40 – 7.25 (7H, m), 6.88 (2H, d, *J* = 8.8 Hz), 5.89 (1H, d, *J* = 10.4 Hz), 5.62 (1H, td, *J* = 10.2, 2.6 Hz), 5.28 (1H, ddd, *J* = 6.8, 4.6, 2.3 Hz), 4.73 (1H, d, *J* = 11.6 Hz), 4.58 (1H, d, *J* = 11.4 Hz), 4.54 (1H, d, *J* = 11.4 Hz), 4.52 (1H, d, *J* = 11.6 Hz), 4.18 (1H, m), 4.05 (2H, s), 3.93 (1H, dd, *J* = 6.8, 3.8 Hz), 3.80 (3H, s), 3.69 (1H, dd, *J* = 9.3, 3.5 Hz), 3.63 (1H, dd, *J* = 9.0, 6.4 Hz), 3.33 (3H, s), 2.51 (1H, m), 0.95 (9H, t, *J* = 8.0 Hz), 0.60 (6H, q, *J* = 8.0 Hz)

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 170.4, 159.9, 139.0, 132.6, 130.2, 129.5, 128.7, 128.1, 127.9, 125.5, 114.3, 74.3, 73.7, 73.3, 71.1, 70.2, 68.6, 67.2, 59.3, 55.7, 45.2, 7.1, 5.3

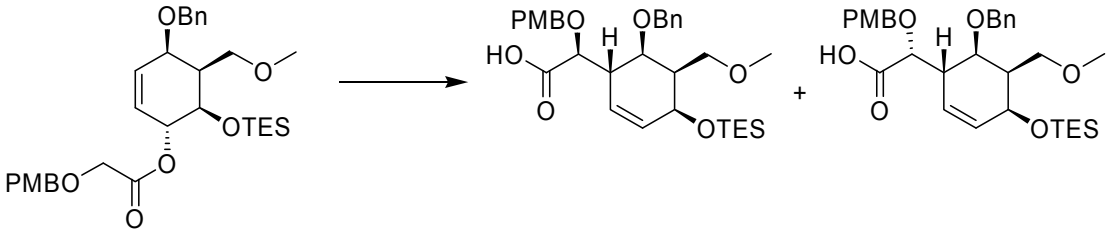
IR (Si, Film) ν_{max} = 2955, 2913, 1755, 1733, 1613, 1515, 1456, 1390, 1303, 1250, 1194, 1108, 1030, 961, 822, 743, 698

MS (ESI): m/z = 579, 521, 487, 465, 459, 415

HRMS (ESI) calc. for $C_{31}H_{44}O_7SiNa$ (= M^+ + Na): 579.2723; found: 579.2746

$[\alpha]_D^{20}$ = - 74.9 (c = 0.55, $CHCl_3$)

1-{[1(S),6(R)-Benzyloxy-5(R)-methoxymethyl-4(S)-triethylsilanyloxy-cyclohex-2-enyl]}-1{[1(S)-4-methoxy-benzyloxy]}-acetic acid (10)



A solution of compound **5** (510 mg, 0.92 mmol) in THF (20 mL) was cooled to - 78 °C and TMSCl (0.62 mL, 6.6 mmol, dissolved in 5 mL THF) was added. After 5 min. LiHMDS (3.3 mL, 1 M in toluene) was added quickly and the reaction was stirred for 30 min. at – 78 °C. Then it was allowed to warm to rt and heated at 60 – 65 °C for 3 h. The reaction mixture was quenched with a saturated $NaHCO_3$ solution and diluted with toluene (40 mL) and H_2O (3 mL). The phases were separated and the pH of the aqueous phase was lowered to 3 with HCl. It was extracted with toluene (3 x 10 mL), the combined organic layers were washed with brine and the solvent was removed under reduced pressure. The crude product was filtered off over silica gel (hex:EtOAc = 5:1) and the diastereomeric ratio was estimated from crude NMR *dr* = 3:1. The combined yield was 418 mg (82 %).

1-{[1(S),6(R)-Benzyloxy-5(R)-methoxymethyl-4(S)-triethylsilanyloxy-cyclohex-2-enyl]}-1{[1(S)-4-methoxy-benzyloxy]}-acetic acid methyl ester

To a solution of acid **10** (240 mg, 0.43 mmol) in toluene:MeOH = 5:1 (1.5 ml, 0.3 mL) $TMSCHN_2$ (0.216 ml, 2M in hexane) was added dropwise until no gas evolution occurred anymore. The reaction mixture was stirred for 10 min. The solvents were removed under reduced pressure to yield a crude product (244 mg, 99 %, *dr* = 3:1) which after column chromatography gave 180 mg of the desired product.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.38 – 7.22 (7H, m), 6.86 (2H, d, *J* = 8.6 Hz), 5.60 (1H, d, *J* = 10.1 Hz), 5.38 (1H, td, *J* = 10.1, 2.4 Hz), 4.70 (1H, d, *J* = 11.6 Hz), 4.61 (1H, d, *J* = 10.9 Hz), 4.38 (1H, m), 4.34 (1H, d, *J* = 11.8 Hz), 4.34 (1H, d, *J* = 10.4 Hz), 3.98 (1H, d, *J* = 3.3 Hz), 3.86 (1H, d, *J* = 8.6, 3.8 Hz), 3.80 (3H, s), 3.60 (1H, dd, *J* = 9.3, 4.5 Hz), 3.55 (1H, dd, *J* = 9.3, 4.3 Hz), 3.45 (3H, s), 3.27 (3H, s), 2.81 (1H, m), 2.48 (1H, m), 0.98 (9H, t, *J* = 8.0 Hz), 0.63 (6H, q, *J* = 7.9 Hz)

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 172.4, 159.8, 139.0, 133.3, 130.0, 130.0, 128.7, 128.4, 127.7, 126.7, 114.1, 77.2, 74.3, 72.4, 70.9, 68.7, 68.4, 59.0, 55.7, 51.9, 44.1, 42.9, 7.3, 5.3

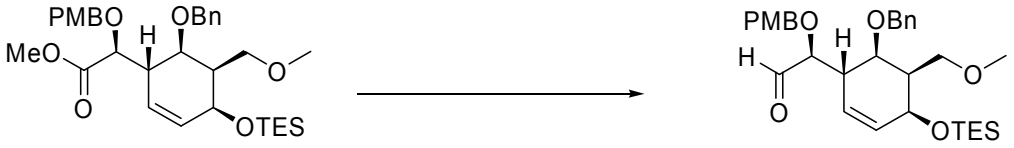
IR (Si, Film) ν_{max} = 3033, 2953, 2876, 1721, 1612, 1586, 1514, 1456, 1303, 1249, 1173, 1108, 1036, 849, 745, 700, 514

MS (ESI): m/z = 593, 577, 551, 503, 473, 439

HRMS (ESI) calc. for $C_{32}H_{46}O_7SiNa$ (= M^+ + Na): 593.2911; found: 593.2921

$[\alpha]_D^{20}$ = + 114.0 (c = 0.35, $CHCl_3$)

1-{[1(S),6(R)-Benzyloxy-5(R)-methoxymethyl-4(S)-triethylsilanyloxy-cyclohex-2-enyl]}-1{[1(R)-4-methoxy-benzyloxy]}-acetaldehyde



A solution of the methyl ester (1.719 g, 3.02 mmol) in DCM (50 ml) was cooled to – 78 °C. DIBALH (6.03 mL, 1 M in toluene) was added dropwise and stirred for 3 h. The reaction mixture was quenched with MeOH and Na-K-tartrate at – 78 °C, allowed to warm to rt and stirred for 18 h. It was diluted with toluene, the phases were separated and the aqueous phase was extracted with toluene (2 x 10 mL). The combined organic layers were washed with brine and the solvent

was removed under reduced pressure. The crude product was filtered off over silica gel (hex:EtOAc = 5:1) to yield 1.52 g (93 %) of the desired aldehyde.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.47 (1H, d, *J* = 1.0 Hz), 7.29-7.15 (7H, m), 6.81 (2H, d, *J* = 8.6 Hz), 5.53 (1H, d, *J* = 10.1 Hz), 5.35 (1H, td, *J* = 10.2, 2.2 Hz), 4.60 (1H, d, *J* = 11.6 Hz), 4.56 (1H, d, *J* = 11.1 Hz), 4.43 (1H, d, *J* = 11.6 Hz), 4.34 (1H, m), 4.30 (1H, d, *J* = 11.4 Hz), 3.77 (1H, d, *J* = 3.8 Hz), 3.76 (1H, m), 3.75 (3H, s), 3.53 (1H, dd, *J* = 9.6, 4.3 Hz), 3.47 (1H, dd, *J* = 9.5, 4.4 Hz), 3.20 (3H, s), 2.79 (1H, td, *J* = 8.9, 3.0 Hz), 2.46 (1H, m), 0.92 (9H, t, *J* = 8.0 Hz), 0.57 (6H, q, *J* = 7.8 Hz)

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 202.6, 159.9, 138.4, 134.0, 130.1, 129.8, 128.7, 128.0, 126.7, 114.2, 83.4, 74.2, 72.9, 70.8, 68.8, 68.3, 59.2, 55.7, 43.8, 42.8, 7.2, 5.2

IR (Si, Film) ν_{max} = 3034, 2954, 1742, 1739, 1733, 1729, 1616, 1520, 1516, 1467, 1248, 1204, 1173, 1107, 1030, 744, 699, 514,

MS (ESI): m/z = 563, 549, 533, 509, 505, 475, 445, 429, 413, 401, 393

HRMS (ESI): calc. for $C_{31}H_{44}O_6SiNa$ (= M^+ + Na): 563.2804; found: 563.2793

$[\alpha]_D^{20}$ = + 97.7 (c = 0.97, $CHCl_3$)

(1S)-{5(S)-Benzyloxy-4(S)-[1(R)-(4-methoxy-benzyloxy)-allyl]-6(R)-methoxymethyl-cyclohex-2-enyloxy}-triethyl-silane (11)

In THF (18 mL) Ph_3PCH_3Br (1.53 g, 4.07 mmol) and tBuOK (0.457 g, 4.07 mmol) were dissolved and refluxed for 5 min. The reaction mixture was cooled to rt and the aldehyde (1.465 g, 2.713 mmol in 10 ml THF) was added dropwise. After 10 min. the reaction was quenched with saturated NH_4Cl solution, the phases were separated and the aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was filtered off over silica gel (hex:EtOAc = 7:1) to yield 1.32 g (91 %) of the desired product.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.28 – 7.21 (5H, m), 7.19 (2H, d, *J* = 8.6 Hz), 6.82 (2H, d, *J* = 8.8 Hz), 5.65 (1H, td, *J* = 10.4, 2.4 Hz), 5.59 (1H, m), 5.57 (1H, m), 5.17 (1H, dd, *J* = 10.4, 1.8 Hz), 4.95 (1H, dd, *J* = 17.1, 1.8 Hz), 4.59 (1H, d, *J* = 11.6 Hz), 4.45 (1H, d, *J* = 11.4 Hz), 4.32 (1H, d, *J* = 11.6 Hz), 4.24 (1H, d, *J* = 11.4 Hz), 4.26 – 4.23 (1H, m), 3.91 (1H, dd, *J* = 8.6, 4.8 Hz), 3.76 (3H, s), 3.58 (1H, dd, *J* = 9.4, 4.7 Hz), 3.50 (1H, dd, *J* = 9.3, 5.0 Hz), 3.45 (1H, dd, *J* = 8.1, 3.5 Hz), 3.24 (3H, s), 2.65 (1H, m), 2.40 (1H, m), 0.94 (9H, t, *J* = 8.0 Hz), 0.59 (6H, q, *J* = 7.8 Hz)

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 159.4, 139.1, 136.5, 132.4, 131.2, 129.7, 128.6, 128.5, 127.8, 126.3, 119.8, 114.1, 80.3, 75.3, 70.7, 70.2, 69.4, 68.1, 59.1, 55.7, 44.4, 42.3, 7.3, 5.3

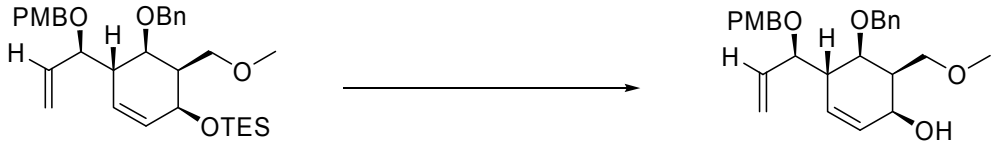
IR (Si, Film) ν_{max} = 3033, 2954, 2876, 1613, 1586, 1514, 1497, 1455, 1417, 1388, 1302, 1248, 1204, 1172, 1108, 1005, 849, 822, 743, 698

MS (ESI): m/z = 561, 525, 488, 469, 429, 393, 370, 342

HRMS (ESI): calc. for $C_{32}H_{46}O_5SiNa$ (= M^+ + Na): 561.3012; found: 561.3010

$[\alpha]_D^{20}$ = + 295.6 (c = 0.70, $CHCl_3$)

(1S)-{5(S)-Benzyloxy-4(S)-[1(R)-(4-methoxy-benzyloxy)-allyl]-6(R)-methoxymethyl}-cyclohex-2-enol



To a solution of compound **11** (1.27 g, 2.36 mmol) in MeOH (25 ml) NH_4F (2.41 g, 65.11 mmol) was added portionwise and the reaction mixture was stirred for 3 h at rt. Then the solvent was removed under reduced pressure. EtOAc (20 mL) and H_2O (20 mL) were added, the phases were separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure to yield 1 g (100 %) of the alcohol.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.35 – 7.24 (5H, m), 7.21 (2H, d, *J* = 8.6 Hz), 6.86 (2H, d, *J* = 8.6 Hz), 6.01 (1H, ddd, *J* = 10.1, 4.5, 1.8 Hz), 5.73 (1H, ddd, *J* = 17.2, 10.3, 8.1 Hz), 5.59

(1H, dd, *J* = 10.1, 4.3 Hz), 5.32 (1H, dd, *J* = 10.4, 1.5 Hz), 5.16 (1H, dd, *J* = 17.2, 1.0 Hz), 4.55 (1H, d, *J* = 11.9 Hz), 4.53 (1H, d, *J* = 11.4 Hz), 4.39 (1H, d, *J* = 11.9 Hz), 4.22 (1H, d, *J* = 11.4 Hz), 4.11 (1H, s), 4.00 (1H, m), 3.81 (3H, s), 3.70 (1H, dd, *J* = 9.4, 7.1 Hz), 3.50 (2H, dd, *J* = 9.1, 7.1 Hz), 3.29 (3H, s), 3.08 (1H, d, *J* = 10.6 Hz), 2.63 (1H, m), 2.04 (1H, m)

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 159.6, 138.6, 137.0, 131.7, 130.7, 129.9, 129.4, 129.0, 128.8, 128.3, 128.1, 126.4, 119.6, 114.2, 80.6, 75.3, 71.9, 71.6, 70.1, 65.7, 59.3, 55.7, 44.3, 39.7, 32.3, 30.1

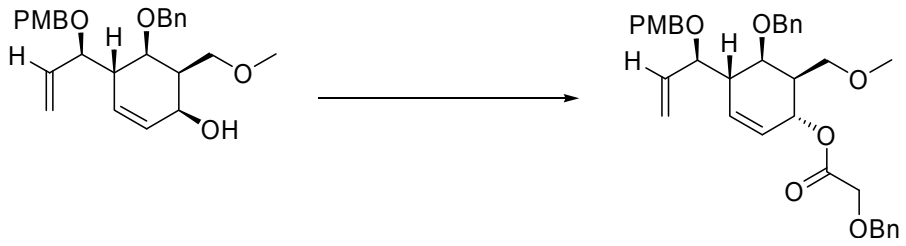
IR (Si, Film) ν_{max} = 3522, 2923, 1613, 1514, 1455, 1247, 1060, 821, 749, 698

MS (ESI): m/z = 447, 437, 393, 349, 327, 305

HRMS (ESI): calc. for $C_{26}H_{32}O_5Na$ (=M^+ + Na): 447.2147; found: 447.2142

$[\alpha]_D^{20}$ = + 56.9 (c = 0.84, $CHCl_3$)

(1R)-Benzyloxy-acetic acid 5(S)-benzyloxy-4(S)-[1(R)-(4-methoxy-benzyloxy)-allyl]-6(R)-methoxymethyl-cyclohex-2-enyl ester (12)



A solution of the alcohol (1.00 g, 2.36 mmol) in THF (25 ml) and DCM (25 mL) was cooled to 0 °C. Ph_3P (2.75 g, 10.50 mmol) and 5 min. later benzyloxy acetic acid (1.38 g, 8.3 mmol) were added. After additional 5 min. DEAD (2.75 mL, 17.4 mmol) was added dropwise and the reaction mixture was stirred for 30 min. at 0 °C. Then the solution was stored at + 4 °C for 24 h. The reaction mixture was diluted with toluene (80 mL) and concentrated under reduced pressure. The crude product was purified by column chromatography (hex:EtOAc = 4:1) to yield 1.02 g (76 %) of the desired product.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.40 – 7.25 (10H, m), 7.23 (2H, d, *J* = 8.6 Hz), 6.86 (2H, d, *J* = 8.6 Hz), 5.83 (1H, dd, *J* = 10.2, 2.9 Hz), 5.77 (1H, ddd, *J* = 10.3, 3.0, 1.7 Hz), 5.66

(1H, ddd, *J* = 17.3, 10.3, 8.2 Hz), 5.50 (1H, m), 5.27 (1H, dd, *J* = 10.2, 1.6 Hz), 5.12 (1H, dd, *J* = 17.2, 1.3 Hz), 4.64 (2H, s), 4.52 (1H, d, *J* = 11.4 Hz), 4.50 (1H, d, *J* = 11.6 Hz), 4.46 (1H, d, *J* = 11.6 Hz), 4.27 (1H, d, *J* = 11.4 Hz), 4.08 (2H, s), 3.94 (1H, dd, *J* = 5.6, 3.3 Hz), 3.80 (3H, s), 3.80 (1H, m), 3.53 (1H, dd, *J* = 9.4, 6.3 Hz), 3.29 (1H, dd, *J* = 9.2, 7.4 Hz), 3.23 (3H, s), 2.57 (1H, m), 2.30 (1H, ddd, *J* = 13.3, 6.7, 3.4 Hz)

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 170.4, 159.5, 138.8, 137.6, 136.4, 130.9, 130.5, 129.7, 128.9, 128.7, 128.4, 128.4, 128.3, 128.0, 126.3, 119.9, 114.2, 80.6, 73.7, 73.3, 71.3, 70.7, 70.4, 70.2, 67.7, 59.2, 55.7, 44.0, 40.4

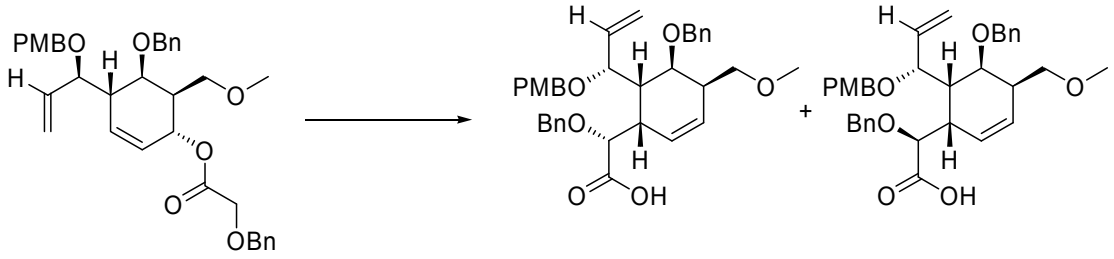
IR (Si, Film) ν_{max} = 3033, 2920, 1750, 1732, 1615, 1586, 1515, 1498, 1455, 1422, 1393, 1246, 1109, 823, 738, 698, 599, 515

MS (ESI): m/z = 595, 577, 537, 495, 470, 430, 417

HRMS (ESI): calc. for $C_{35}H_{40}O_7Na$ (=M^+ + Na): 595.2672; found: 595.2666

$[\alpha]_D^{20}$ = - 47.0 (c = 0.60, $CHCl_3$)

(1R)-Benzyloxy-1(S)-{5(S)-benzyloxy-6(S)-[1(R)-(4-methoxy-benzyloxy)-allyl]-4(R)-methoxymethyl-cyclohex-2-enyl}-acetic acid (13)



A solution of compound **12** (1.00 g, 1.75 mmol) in THF (43 mL) was cooled to – 78 °C and TMSCl (1.14 mL, 12.2 mmol) was added. After 5 min. LiHMDS (6.0 mL, 1 M in toluene) was added quickly and the reaction was stirred for 30 min. at – 78 °C. Then it was allowed to warm to rt and stirred over night at ~ 65 °C. The reaction mixture was quenched with a saturated $NaHCO_3$ solution and diluted with toluene (150 mL) and H_2O (10 mL). The phases were separated and the pH of the aqueous phase was lowered to 3 with HCl. It was extracted with toluene (3 x 15 mL), the combined organic layers were washed with brine and the solvent was removed under reduced pressure. The crude product was filtered off over silica

gel (hex:EtOAc = 5:1) and the diastereomeric ratio was estimated from crude NMR *dr* = 2:1. The combined yield was 692 mg (69 %) and the product was used immediately.

IR (Si, Film) ν_{max} = 3031, 2926, 1731, 1613, 1586, 1514, 1497, 1454, 1303, 1248, 1093, 931, 822, 738, 699

Following the same procedures as for the synthesis of **11**, compound **13** was converted to **4**.

(1S, 2R, 4aS, 5S, 8R, 8aS)-1,5-Bis-benzyloxy-8-(4-methoxy-benzyloxy)-2-methoxymethyl-1,2,4a,5,8,8a-hexahydro-naphthalene (14)

To a stirred solution of **4** (55 mg, 0.10 mmol) in degassed toluene (10 mL) a solution of Hoveyda – Grubbs catalyst 2nd generation (13 mg, 20 mol%) in degassed toluene (3.2 mL) was added via a syringe pump for 3.5 h and the reaction mixture was stirred over night at 75 °C. The reaction was cooled down to rt., air was bubbled through the solution and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (hex : EtOAc = 5:1) to yield 34 mg (65 %) of the two isomers (Spectroscopical data from the main isomer).

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.37 – 7.27 (10H, m), 7.20 (2H, d, *J* = 8.7 Hz), 6.85 (2H, d, *J* = 8.7 Hz), 5.94 (1H, d, *J* = 10.2 Hz), 5.85 (1H, dd, *J* = 10.5, 2.2 Hz), 5.81 (1H, dd, *J* = 10.4, 1.3 Hz), 5.61 (1H, dd, *J* = 10.2, 2.6 Hz), 4.67 (1H, d, *J* = 11.7 Hz), 4.61 (1H, d, *J* = 11.7 Hz), 4.53 (1H, d, *J* = 11.3 Hz), 4.52 (1H, d, *J* = 11.7 Hz), 4.49 (1H, d, *J* = 11.7 Hz), 4.35 (1H, d, *J* = 11.3 Hz), 4.18 (1H, dd, *J* = 6.0, 2.2 Hz), 4.00 (1H, t, *J* = 4.3), 3.90 (1H, dd, *J* = 8.5, 1.3 Hz), 3.80 (3H, s), 3.49 (1H, dd, *J* = 9.1, 7.2 Hz), 3.37 (1H, dd, *J* = 8.9, 7.4 Hz), 3.32 (3H, s), 3.28 (1H, m), 2.54 (1H, m), 2.35 (1H, m)

^{13}C-NMR (150.9 MHz, $CDCl_3$): δ = 159.3, 138.8, 138.4, 130.7, 130.5, 129.5, 128.4, 128.3, 127.9, 127.8, 127.6, 127.5, 127.4, 125.5, 113.8, 74.6, 73.4, 73.2, 72.2, 71.4, 70.4, 70.3, 58.8, 55.3, 40.4, 38.2, 32.9

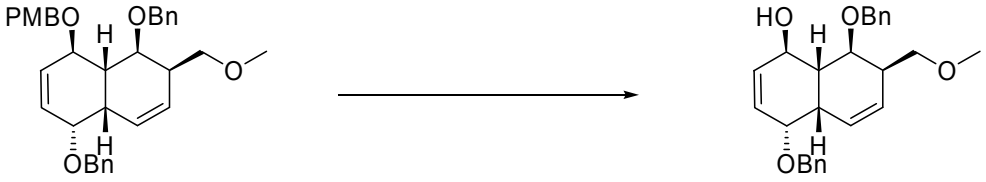
IR (Si, Film) ν_{max} = 3031, 2923, 1735, 1685, 1654, 1611, 1560, 1513, 1497, 1453, 1383, 1303, 1249, 1173, 1072, 821, 738, 698,

MS (ESI): m/z = 549, 507, 487, 459, 413, 393, 341, 309

HRMS (ESI): calc. for $C_{34}H_{38}O_5Na$ (=M^+ + Na): 549.2617; found: 549.2625

$[\alpha]_D^{20}$ = + 28.8 (c = 0.32, $CHCl_3$)

(1R, 4R, 4aS, 7R, 8S, 8aR)-4,8-Bis-benzyloxy-7-methoxymethyl-1,4,4a,7,8,8a-hexahydro-naphthalen-1-ol



To a solution of compound **14** (21 mg, 0.04 mmol) in DCM (2 mL) and buffer (2 mL, pH 7) on the ultrasound bath, DDQ (21 mg, 0.093 mmol) was added portionwise. After 1.5 h the reaction was quenched with a saturated $NaHCO_3$ solution, the phases were separated, and the aqueous phase was extracted with Et_2O (3 x 2 ml). The combined organic layers were dried over $MgSO_4$ and the solvents were removed under reduced pressure. The crude product was filtered off over silica gel (hex:EtOAc = 7:1) to yield 14.6 mg (90 %) of the alcohol.

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 7.40 – 7.22 (10 H, m), 5.94 (1 H, d, *J* = 10.0 Hz), 5.88 – 5.72 (2 H, m), 5.64 (1 H, td, *J* = 10.2, 2.9 Hz), 4.64 (1 H, d, *J* = 11.9 Hz), 4.63 (1 H, d, *J* = 11.6 Hz), 4.57 (1 H, d, *J* = 11.6 Hz), 4.52 (1 H, d, *J* = 11.8 Hz), 4.24 – 4.09 (3 H, m), 3.63 (1 H, dd, *J* = 8.9, 7.6 Hz), 3.43 (1 H, dd, *J* = 8.9, 7.1 Hz), 3.36 (3 H, s), 3.21 (1 H, m), 2.89 (1 H, m), 2.14 (1 H, m)

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 139.1, 134.6, 132.3, 130.3, 128.8, 128.5, 128.1, 128.0, 127.7, 127.6, 127.2, 126.6, 74.9, 74.4, 73.3, 72.2, 71.6, 70.7, 67.0, 59.3, 43.8, 34.6, 34.0

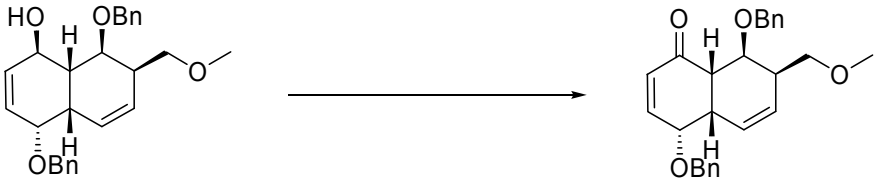
IR (Si, Film) ν_{max} = 3401, 3030, 2922, 1717, 1605, 1497, 1454, 1383, 1255, 1194, 1090, 1068, 1028, 738, 698

MS (ESI): m/z = 429, 393, 349, 339, 305, 232

HRMS (ESI): calc. for $C_{26}H_{30}O_4Na$ (=M^+ + Na): 429.2042; found: 429.2432

$[\alpha]_D^{20}$ = + 12.1 (c = 0.15, $CHCl_3$)

(4R, 4aS, 7R, 8S, 8aS)-4,8-Bis-benzyloxy-7-methoxymethyl-4a,7,8,8a-tetrahydro-4*H*-naphthalen-1-one (15)



To a stirred solution of $NaHCO_3$ (31 mg, 0.37 mmol) and DMP (39 mg, 0.092 mmol) in DCM (1.5 mL) a solution of alcohol (15 mg, 0.037 mmol), in DCM (1.5 mL) was added dropwise. After 20 min. the reaction mixture was filtered off over silica gel (hex:EtOAc = 5:1) to yield 13 mg (87 %) of the desired ketone.

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 7.40 – 7.28 (10 H, m), 6.74 (1 H, dd, *J* = 10.3, 1.8 Hz), 5.91 (1 H, m), 5.89 (1 H, dd, *J* = 10.3, 2.5 Hz), 5.64 (1 H, d, *J* = 10.4 Hz), 4.77 (1 H, d, *J* = 11.7 Hz), 4.62 (1 H, d, *J* = 11.9 Hz), 4.61 (1 H, d, *J* = 11.9 Hz), 4.58 (1 H, d, *J* = 11.8 Hz), 4.43 (2 H, m), 3.55 (1 H, t, *J* = 8.6 Hz), 3.53 (1 H, m), 3.37 (1 H, dd, *J* = 9.0, 7.0 Hz), 3.35 (3 H, s), 2.76 (1 H, t, *J* = 4.2 Hz), 2.66 (1 H, m)

^{13}C-NMR (150.9 MHz, $CDCl_3$): δ = 198.3, 149.4, 138.6, 137.6, 129.2, 128.6, 128.5, 128.4, 128.0, 127.7, 127.7, 124.4, 75.0, 73.5, 72.6, 72.2, 71.8, 70.8, 58.7, 46.8, 37.4, 34.4

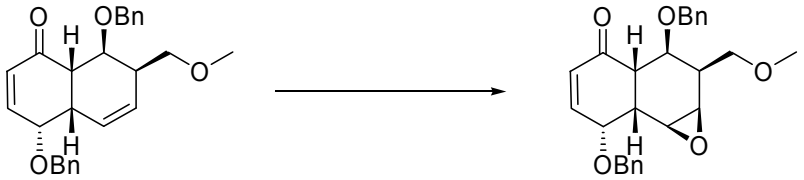
IR (Si, Film) ν_{max} = 3031, 2922, 1733, 1674, 1652, 1498, 1455, 1386, 1208, 1090, 813, 739, 699, 602

MS (ESI): m/z = 427, 393, 349, 305, 275, 235, 211

HRMS (ESI): calc. for $C_{26}H_{28}O_4Na$ (= M^+ + Na): 427.1885; found: 427.1896

$[\alpha]_D^{20}$ = + 66.3 (c = 0.12, $CHCl_3$)

(1aR, 2R, 3S, 3aS, 7R, 7aS, 7bS)-3,7-bis(benzyloxy)-2-(methoxymethyl)-1a, 2,3,3a,7,7a-hexahydronaphtho[1,2-b]oxiren-4(7bH)-one (16)



To a stirred solution of ketone **15** (12 mg, 0,03 mmol) in $CHCl_3$ (0.5 mL) and buffer (0.5 mL, pH 7) at rt *m*-CPBA (30 mg, 0.12 mmol) was added portionwise over a period of 4 h. After a total of 6 h the reaction was quenched with $Na_2S_2O_3$ and diluted with H_2O and $NaHCO_3$ solution. The aqueous phase was extracted with EtOAc (4 x 2 mL), the combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (hex:EtOAc = 5:1) to yield 10.3 mg (82 %) of the desired epoxide as colourless needles (mp = 68 - 69°C).

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.42 - 7.14 (10H, m), 6.91 (1 H, td, *J* = 10.5, 2.0 Hz), 5.94 (1 H, dd, *J* = 10.4, 2.4 Hz), 4.84 (1 H, d, *J* = 11.7 Hz), 4.63 (1 H, d, *J* = 11.7 Hz), 4.53 (1 H, d, *J* = 12.1 Hz), 4.48 (1 H, d, *J* = 12.1 Hz), 4.44 (1 H, m), 4.31 (1 H, t, *J* = 4.5 Hz), 3.67 (1 H, dd, *J* = 9.1, 7.5 Hz), 3.61 (1 H, dd, *J* = 9.1, 7.2 Hz), 3.41 (1 H, d, *J* = 4.2 Hz), 3.36 (3 H, s), 3.11 (1 H, m), 3.07 (1 H, t, *J* = 3.4 Hz), 2.51 (1 H, t, *J* = 4.3 Hz), 2.39 (1 H, m)

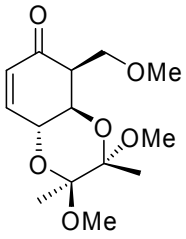
^{13}C-NMR (150.9 MHz, $CDCl_3$): δ = 197.7, 151.0, 138.7, 130.2, 129.5, 128.9, 128.8, 128.6, 128.3, 128.2, 128.1, 74.1, 73.9, 73.3, 71.6, 71.2, 59.4, 52.7, 51.1, 46.3, 36.6, 35.4

IR (Si, Film) ν_{max} = 2923, 1703, 1695, 1682, 1674, 1651, 1634, 1575, 1455, 1418, 1306, 1264, 1103, 1071, 898, 748

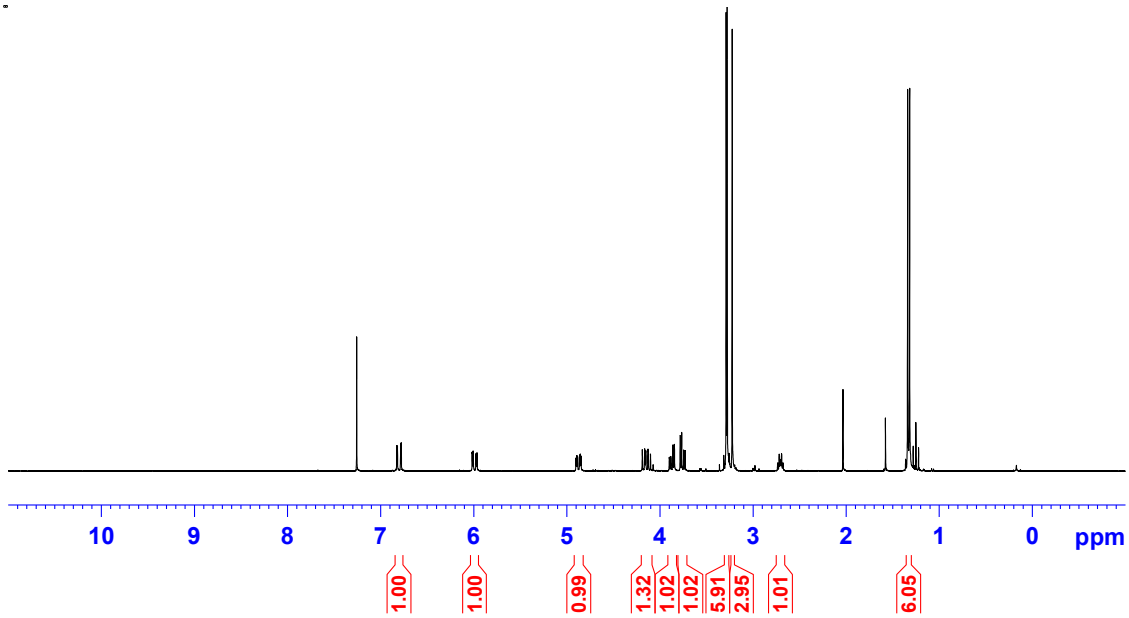
MS (ESI): m/z = 443.5, 421.5, 404, 390, 372, 354, 333, 317

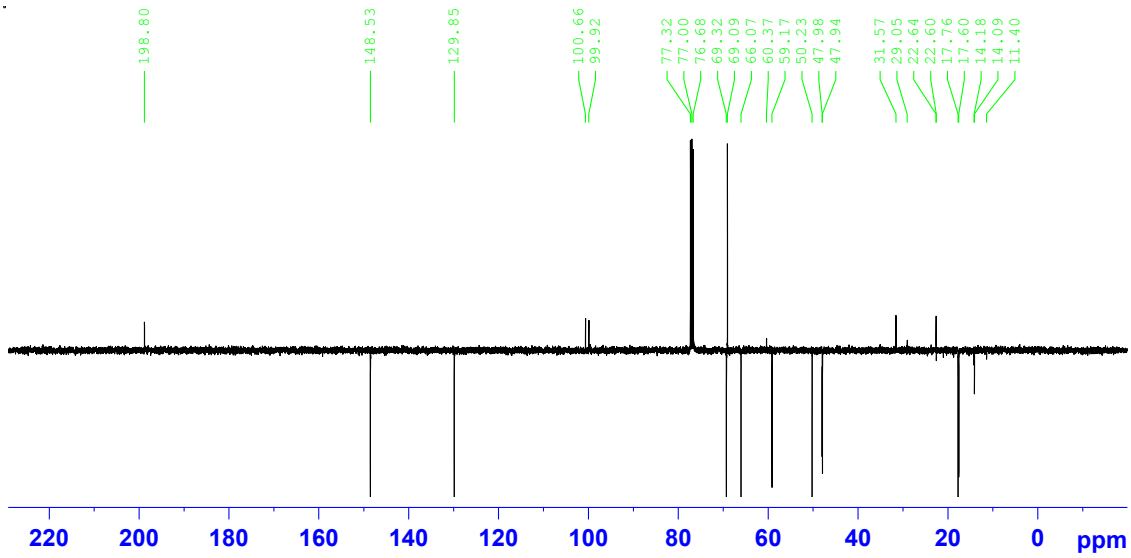
HRMS (ESI): calc. for $C_{26}H_{28}O_5Na$ (= M^+ + Na): 443.1834; found: 443.1840

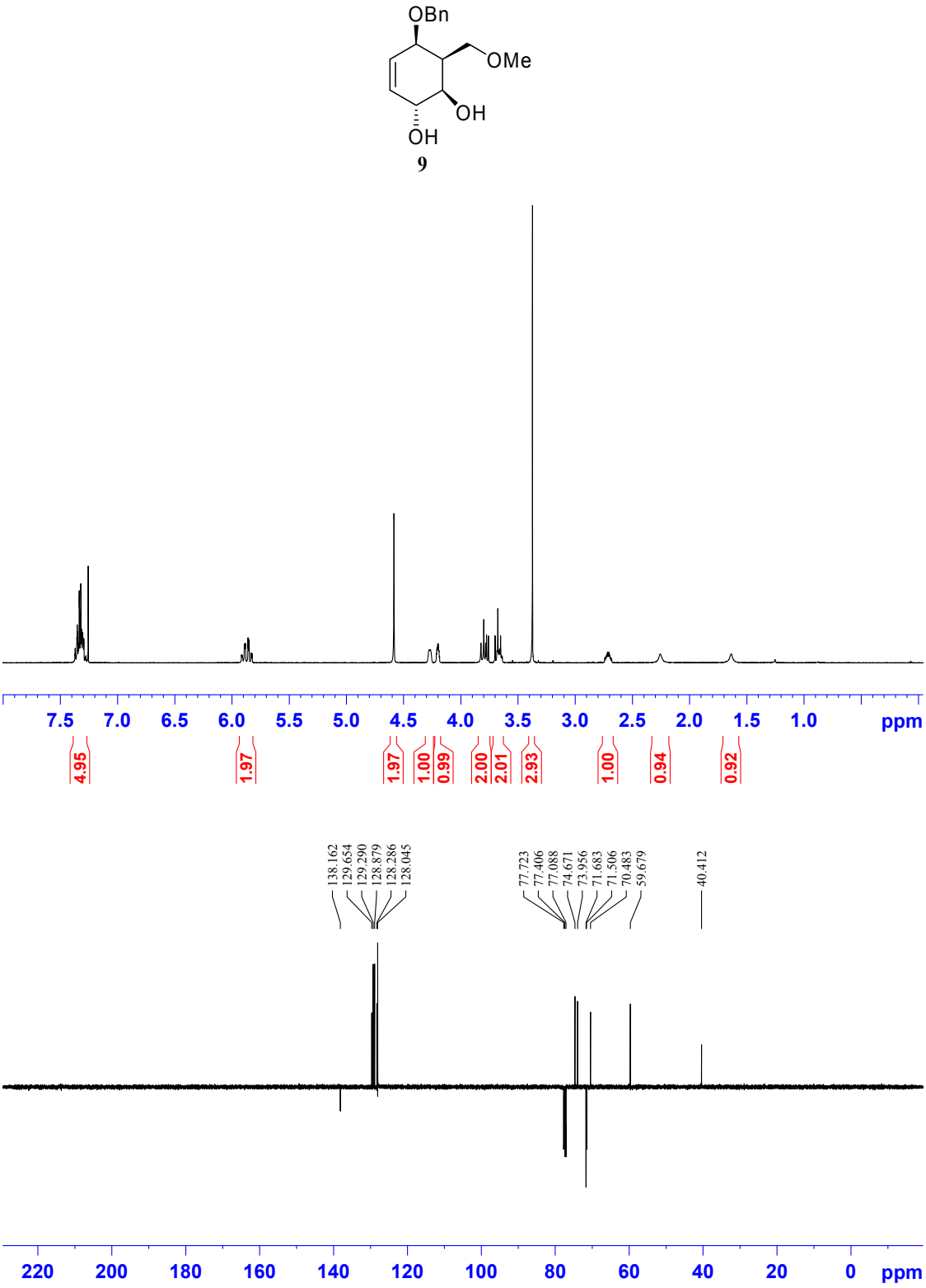
$[\alpha]_D^{20}$ = + 45.0 (c = 0.10, $CHCl_3$)

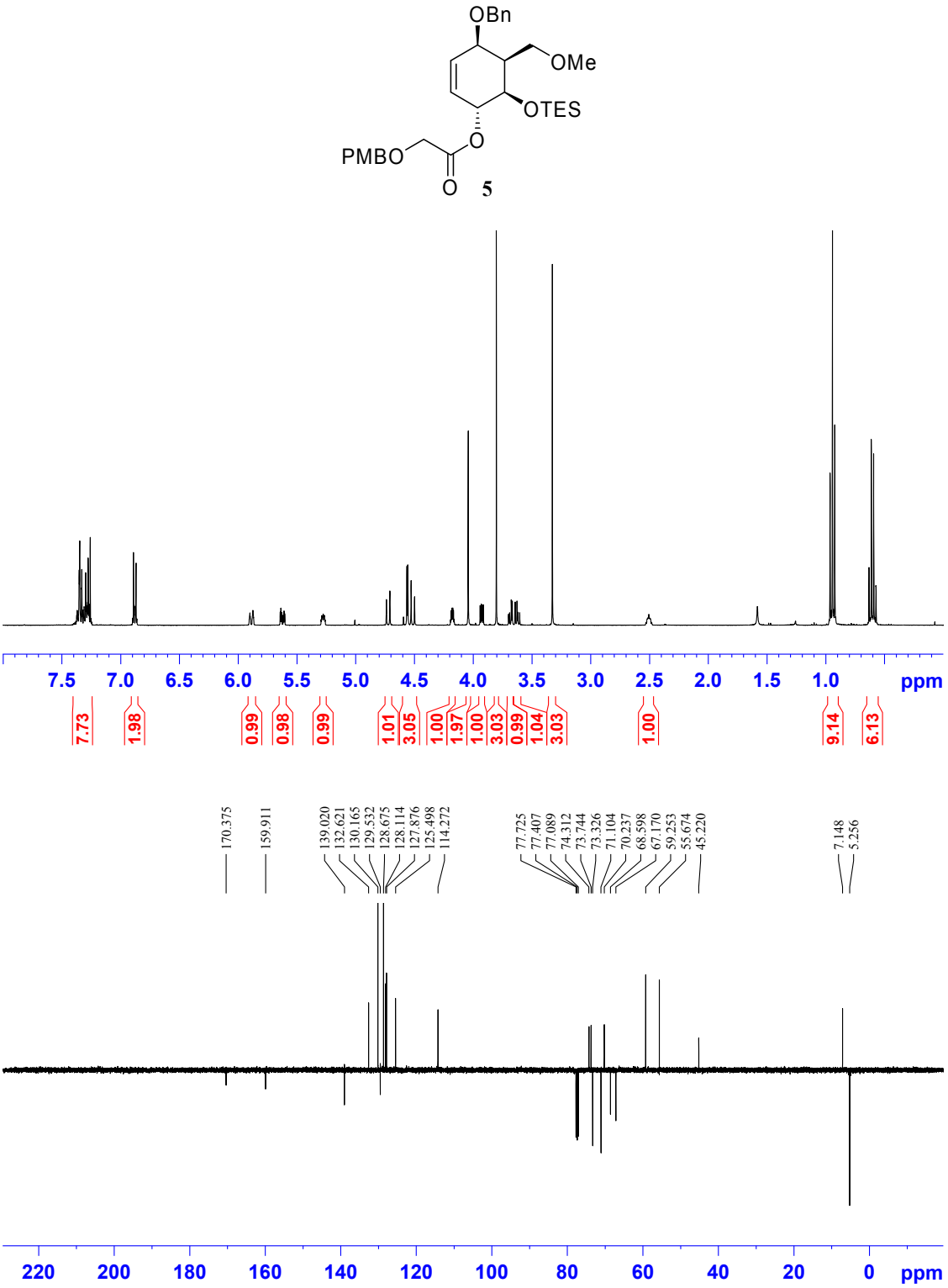

O
OMe
O
OMe
O
OMe

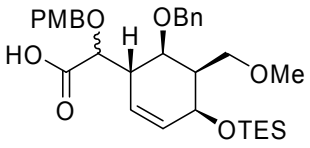
6


10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.00
0.99
1.32
1.02
1.02
5.91
2.95
1.01
6.05

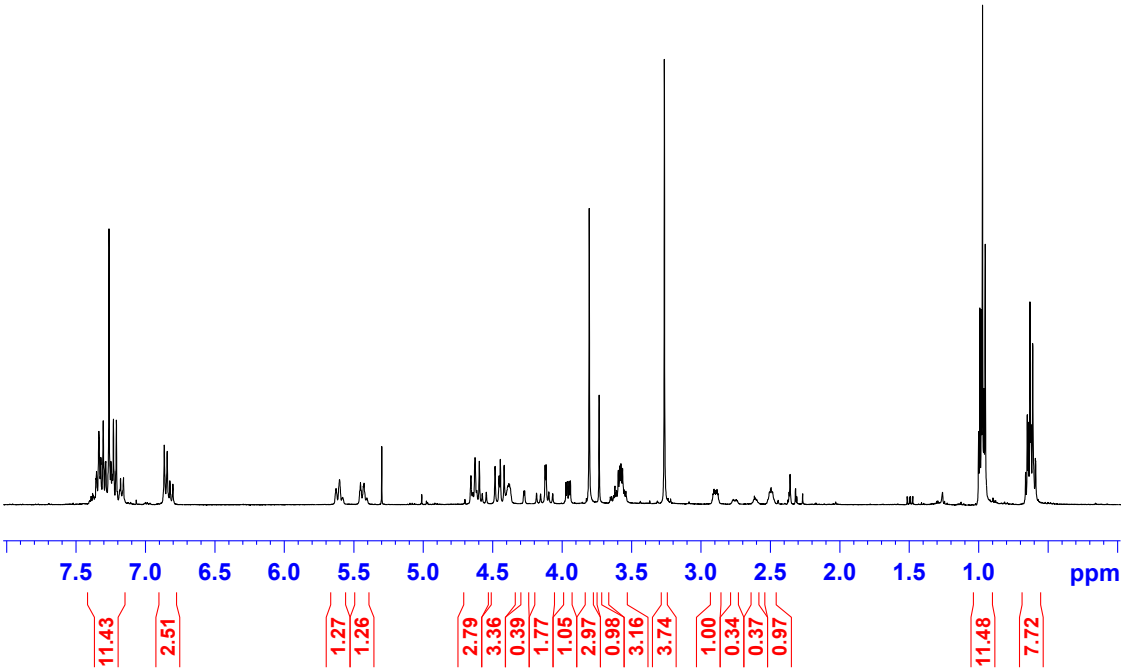

198.80
148.53
129.85
100.66
99.92
77.32
77.00
76.68
69.32
69.09
66.07
60.37
59.17
50.23
47.98
47.94
31.57
29.05
22.64
22.60
17.76
17.60
14.18
14.09
11.40
220
200
180
160
140
120
100
80
60
40
20
0
ppm

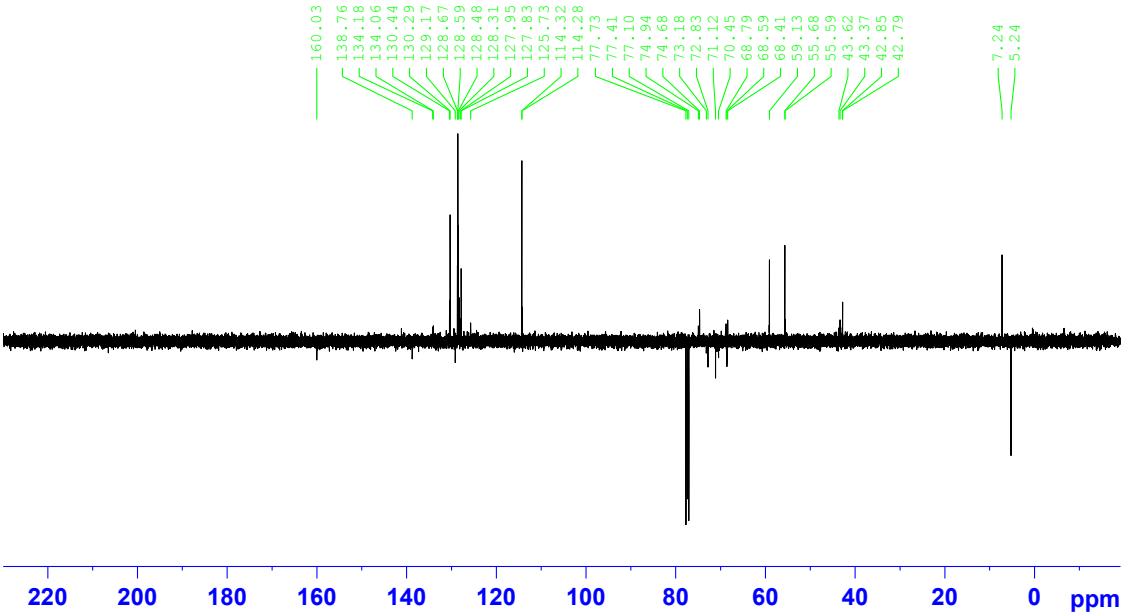

OBn
OMe
OH
OH
9
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
4.95 1.97 1.97 1.00 0.99 2.00 2.01 2.93 1.00 0.94 0.92
138.162 129.654 129.290 128.879 128.286 128.045
77.723 77.406 77.088 74.671 73.956 71.683 71.506 70.483 59.679
40.412
220 200 180 160 140 120 100 80 60 40 20 0 ppm

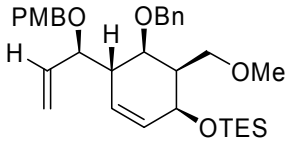

OBn
OMe
OTES
O
PMBO
O
5
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
7.73 1.98 0.99 0.98 0.99 1.01 3.05 1.00 1.97 1.00 3.03 0.99 1.04 3.03 1.00 9.14 6.13
170.375 159.911 139.020 132.621 130.165 129.532 128.675 128.114 127.876 125.498 114.272 77.725 77.407 77.089 74.312 73.744 73.326 71.104 70.237 68.598 67.170 59.253 55.674 45.220 7.148 5.256
220 200 180 160 140 120 100 80 60 40 20 0 ppm


PMBO
OBn
H
HO
OMe
O
OTES

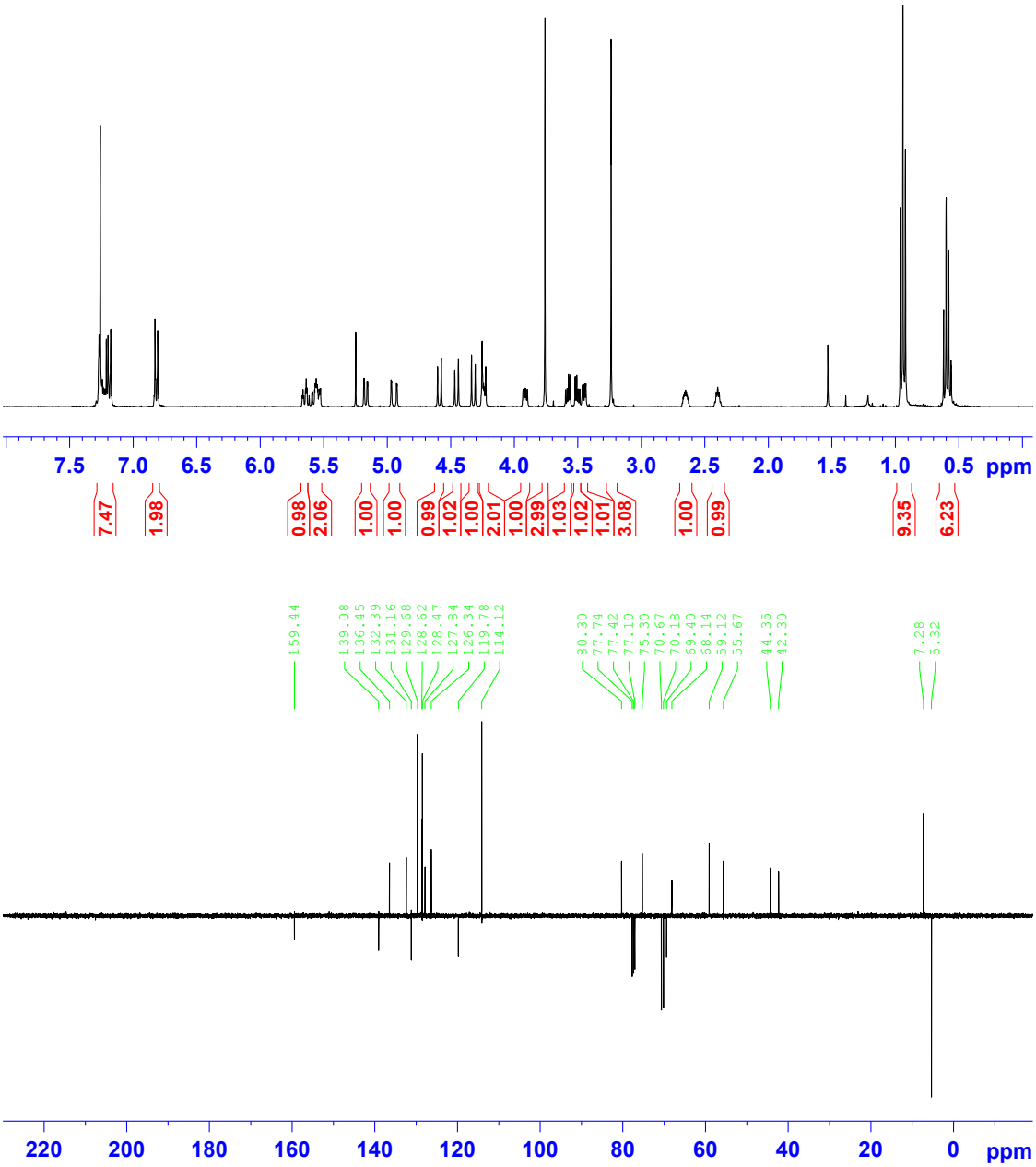
10

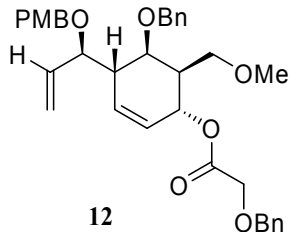

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
11.43
2.51
1.27
1.26
2.79
3.36
0.39
1.77
1.05
2.97
0.98
3.16
3.74
1.00
0.34
0.37
0.97
11.48
7.72


160.03
138.76
134.18
134.06
130.44
130.29
129.17
128.67
128.59
128.48
128.31
127.95
127.83
125.73
114.32
114.28
77.73
77.41
77.10
74.94
74.68
73.18
72.83
71.12
70.45
68.79
68.59
68.41
59.13
55.68
55.59
43.62
43.37
42.85
42.79
7.24
5.24
220
200
180
160
140
120
100
80
60
40
20
0
ppm

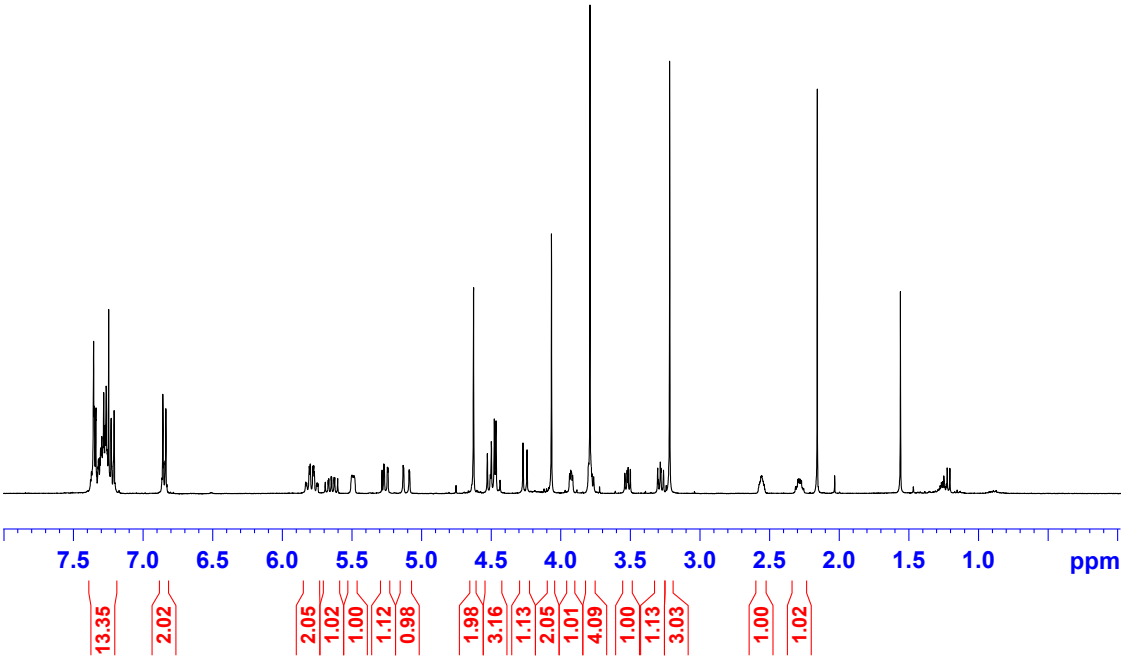

PMBO
H
H
OBn
OMe
OTES

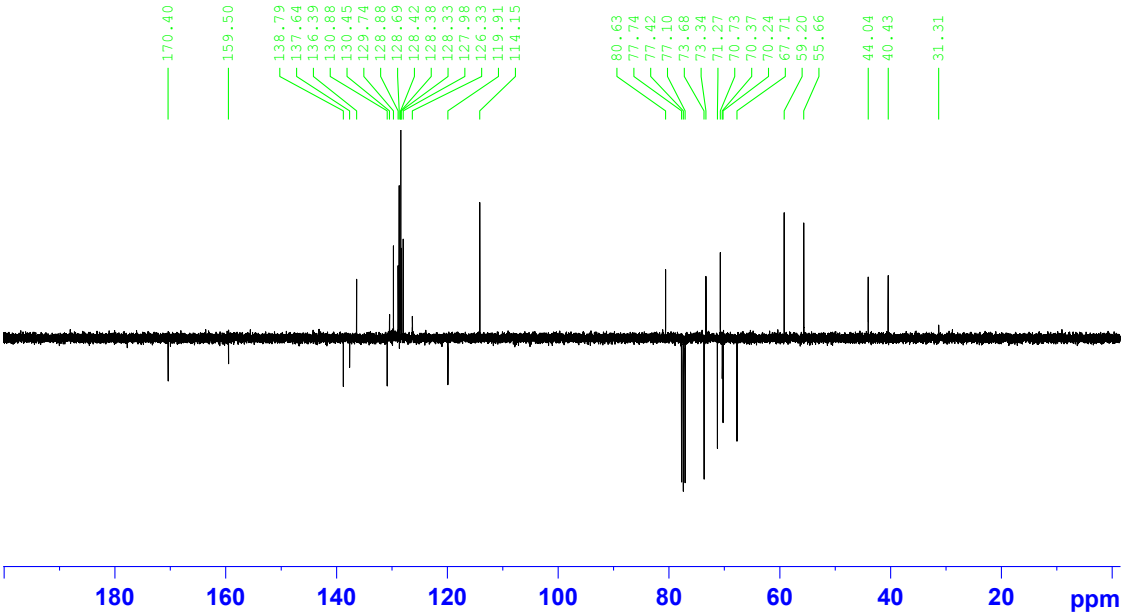
11

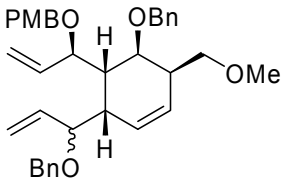

7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
7.47 1.98 0.98 2.06 1.00 1.00 0.99 1.02 1.00 2.01 1.00 2.99 1.03 1.02 1.01 3.08 1.00 0.99 9.35 6.23
159.44 139.08 136.45 132.39 131.16 129.68 128.62 128.47 127.84 126.34 119.78 114.12 80.30 77.74 77.42 77.10 75.30 70.67 70.18 69.40 68.14 59.12 55.67 44.35 42.30 7.28 5.32
220 200 180 160 140 120 100 80 60 40 20 0 ppm


PMBO
H
H
OBn
OMe
O
O
OBn

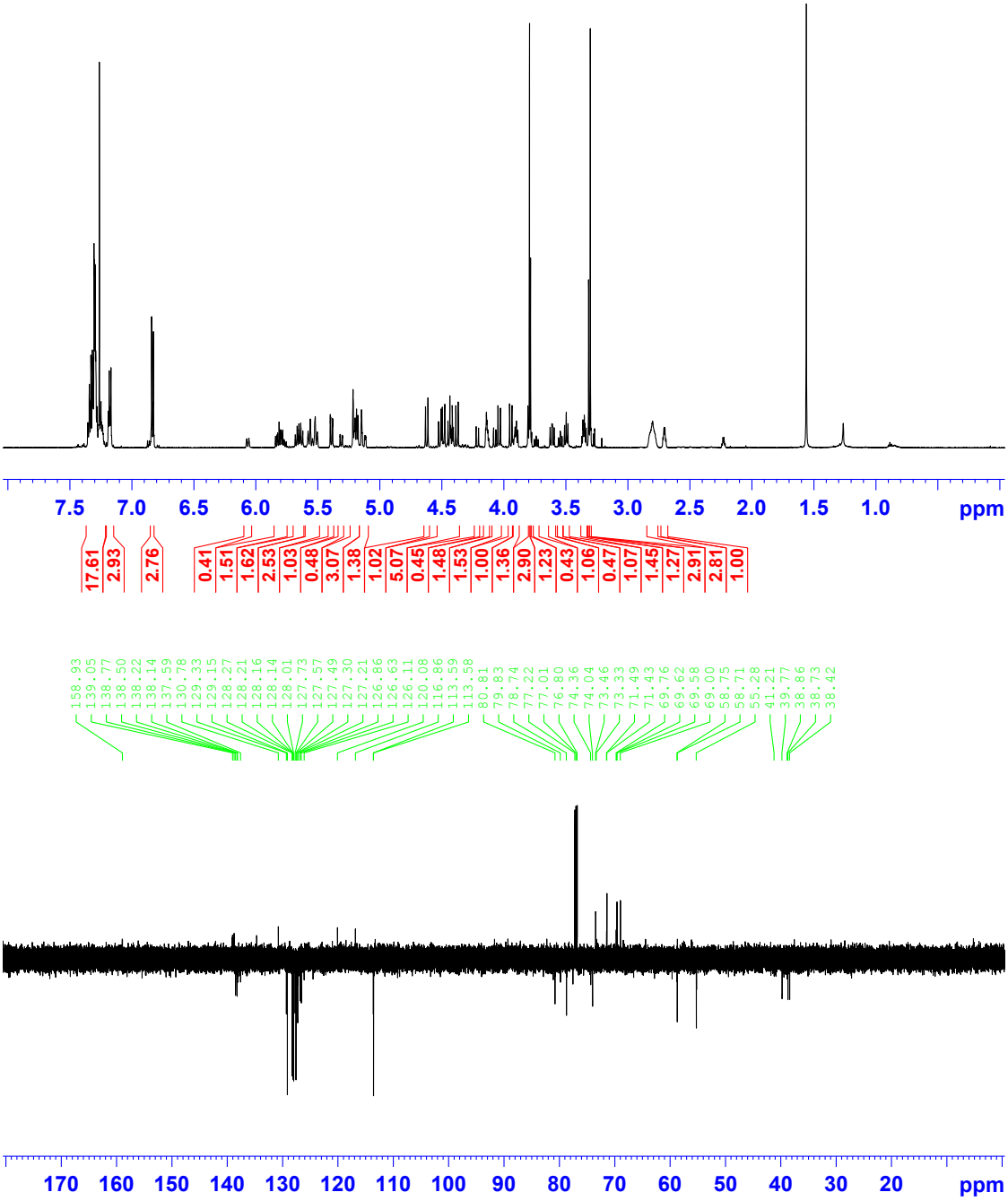
12

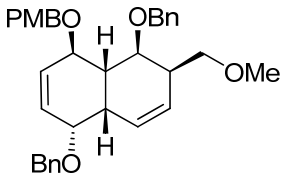

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
13.35
2.02
2.05
1.02
1.00
1.12
0.98
1.98
3.16
1.13
2.05
1.01
4.09
1.00
1.13
3.03
1.00
1.02


170.40
159.50
138.79
137.64
136.39
130.88
130.45
129.74
128.88
128.69
128.42
128.38
128.33
127.98
126.33
119.91
114.15
80.63
77.74
77.42
77.10
73.68
73.34
71.27
70.73
70.37
70.24
67.71
59.20
55.66
44.04
40.43
31.31
180
160
140
120
100
80
60
40
20
ppm

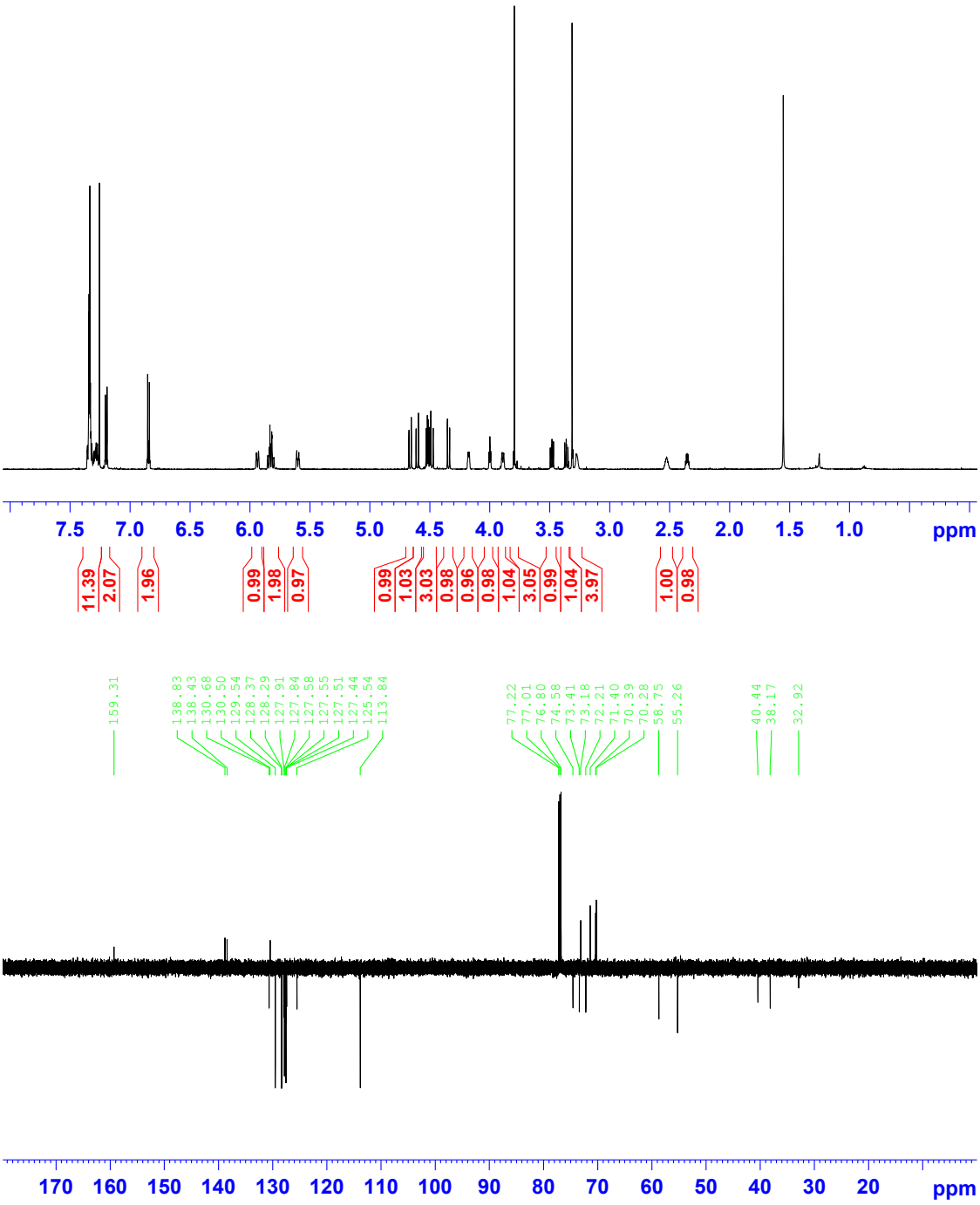

PMBO
H
OBn
OMe
H
BnO

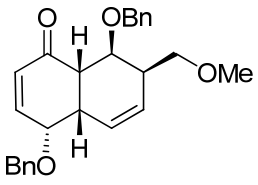
4


7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
17.61 2.93 2.76 0.41 1.51 1.62 2.53 1.03 0.48 3.07 1.38 1.02 5.07 0.45 1.48 1.53 1.00 1.36 2.90 1.23 0.43 1.06 0.47 1.07 1.45 1.27 2.91 2.81 1.00
158.93 139.05 138.77 138.50 138.22 138.14 137.59 130.78 129.33 129.15 128.27 128.21 128.16 128.14 128.01 127.73 127.57 127.49 127.30 127.21 126.86 126.63 126.11 120.08 116.86 113.59 113.58 80.81 79.83 78.74 77.22 77.01 76.80 74.36 74.04 73.46 73.33 71.49 71.43 69.76 69.62 69.58 69.00 58.75 58.71 55.28 41.21 39.77 38.86 38.73 38.42
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

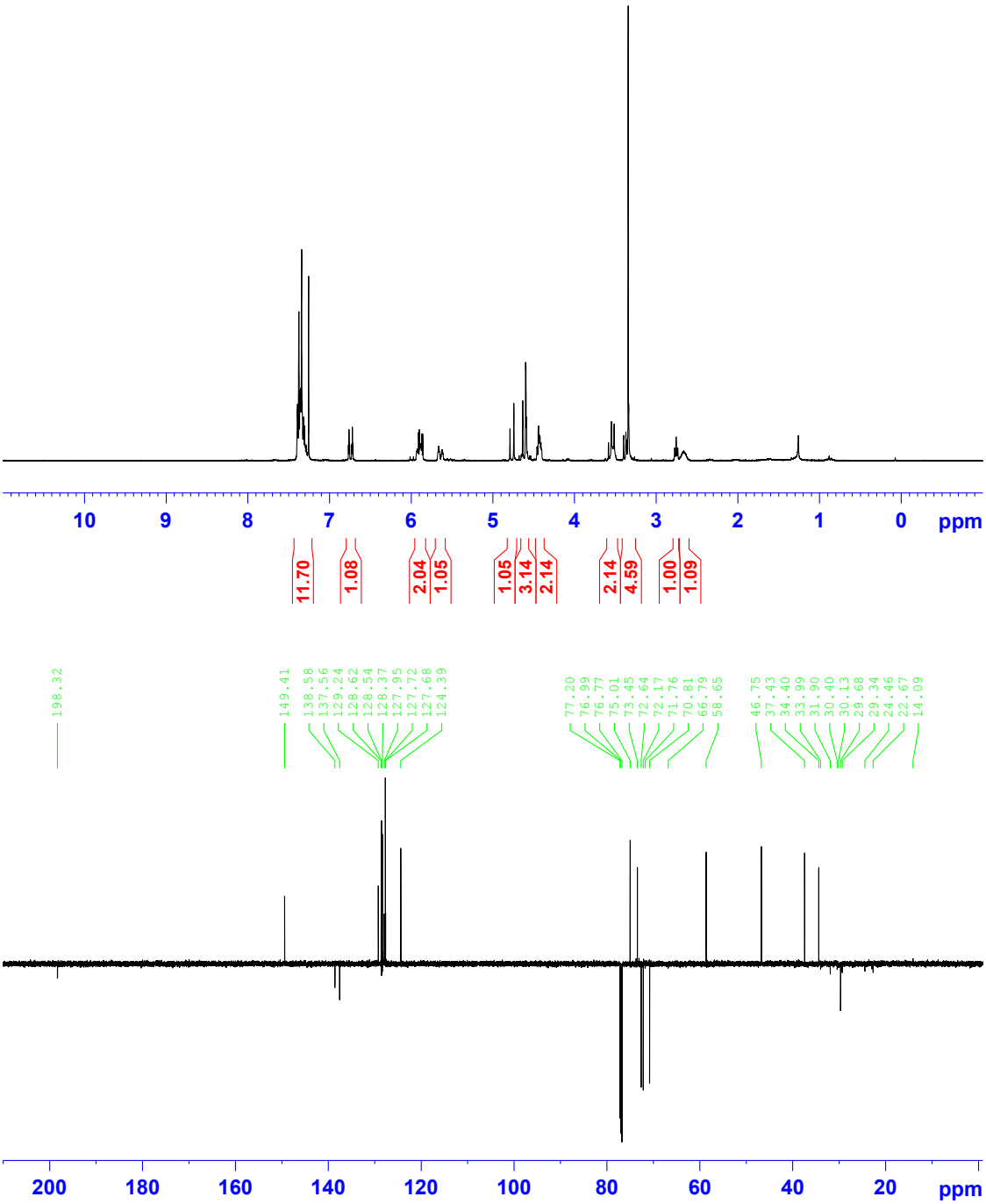

PMBO
H
OBn
OMe
H
BnO

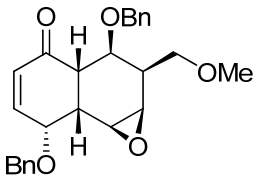
14


7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
11.39 2.07 1.96 0.99 1.98 0.97 0.99 1.03 3.03 0.98 0.96 0.98 1.04 3.05 0.99 1.04 3.97 1.00 0.98
159.31 138.83 138.43 130.68 130.50 129.54 128.37 128.29 127.91 127.84 127.58 127.55 127.51 127.44 125.54 113.84 77.22 77.01 76.80 74.58 73.41 73.18 72.21 71.40 70.39 70.28 58.75 55.26 40.44 38.17 32.92
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

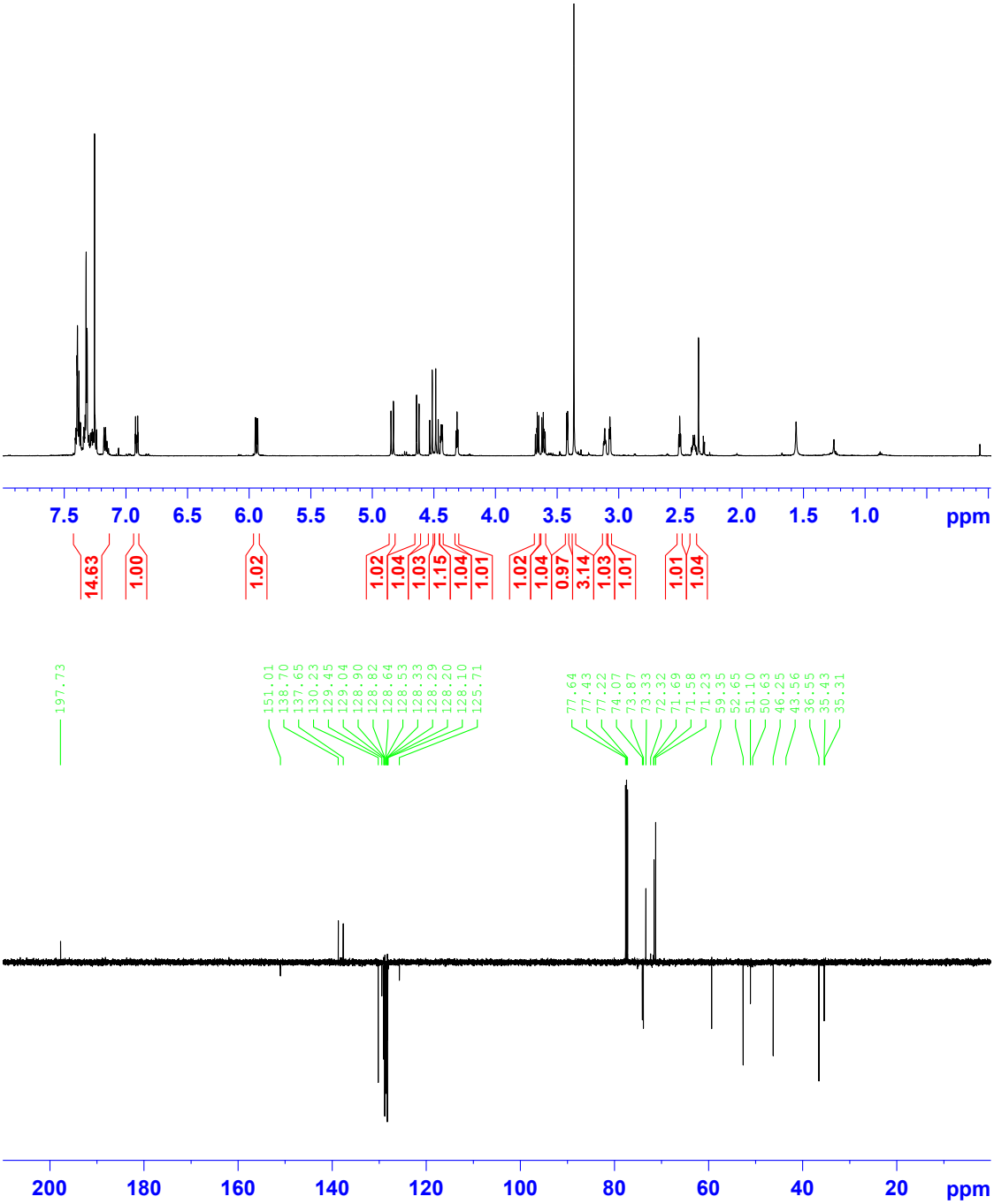

O
H
OBn
OMe
H
BnO

15


10
9
8
7
6
5
4
3
2
1
0
ppm
11.70
1.08
2.04
1.05
1.05
3.14
2.14
2.14
4.59
1.00
1.09
198.32
149.41
138.58
137.56
129.24
128.62
128.54
128.37
127.95
127.72
127.68
124.39
77.20
76.99
76.77
75.01
73.45
72.64
72.17
71.76
70.81
66.79
58.65
46.75
37.43
34.40
33.99
31.90
30.40
30.13
29.68
29.34
24.46
22.67
14.09
200
180
160
140
120
100
80
60
40
20
ppm

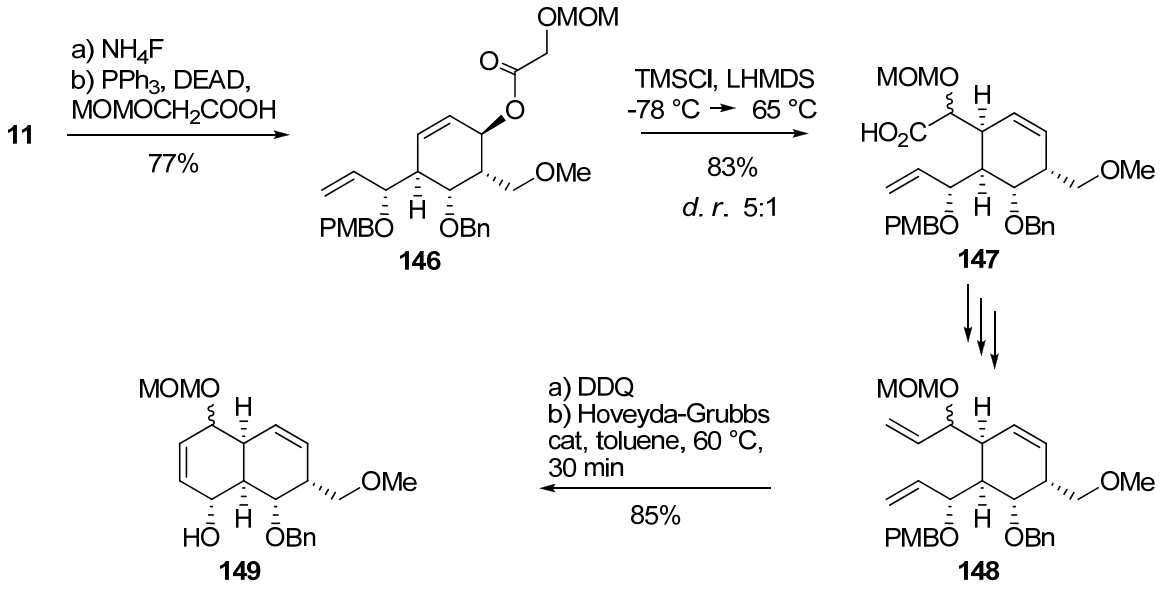

O
H
OBn
OMe
H
O
BnO

16


7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
14.63 1.00 1.02 1.02 1.04 1.03 1.15 1.04 1.01 1.02 1.04 0.97 3.14 1.03 1.01 1.01 1.04
197.73
151.01 138.70 137.65 130.23 129.45 129.04 128.90 128.82 128.64 128.53 128.33 128.29 128.20 128.10 125.71
77.64 77.43 77.22 74.07 73.87 73.33 72.32 71.69 71.58 71.23 59.35 52.65 51.10 50.63 46.25 43.56 36.55 35.43 35.31
200 180 160 140 120 100 80 60 40 20 ppm

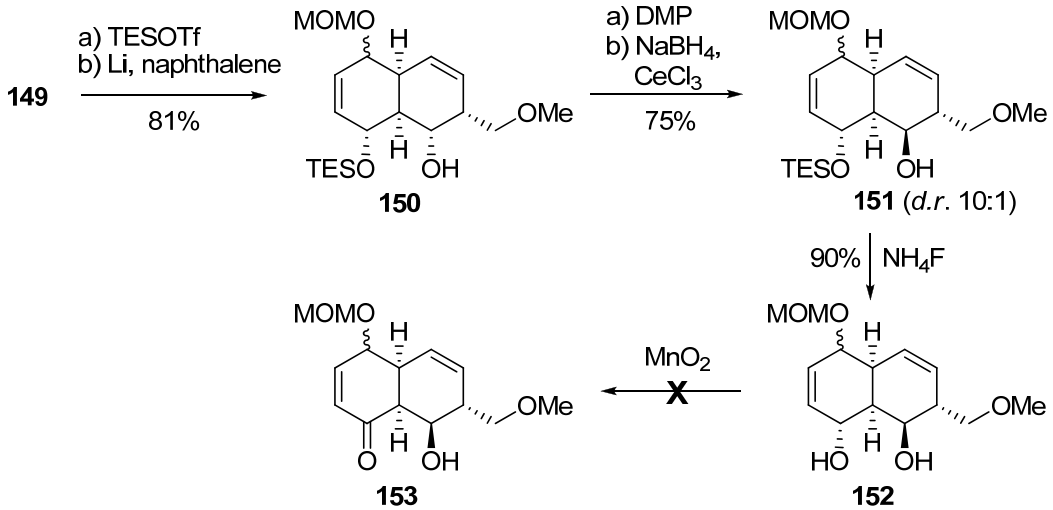
6.1 Additional work on the quinic acid approach

After desilylation of **11**[46] we also managed to introduce a MOM-protecting group in the course of an acylation *via* Mitsunobu inversion (Scheme 40). With this substitution pattern the Claisen-Ireland rearrangement gave **147** in 83% yield as a diastereomeric mixture.



Scheme 40: Preparation of *cis*-decalin **149**.

Interestingly, in the absence of the PMB-protecting group the RCM reaction proceeded smoothly to give **149** in 96% yield. After TES protection at the C12-hydroxy group a high yielding



Scheme 41: Attempted allylic oxidation of **152**.

[46] Numbering of publication.

and highly chemoselective debenzylation at C10 was conducted[47] (90%) to give **150** in 81% yield over 2 steps (Scheme 41). Subsequent oxidation (DMP) followed by Luche reduction afforded alcohol **151** as a 10:1 diastereomeric mixture. Removal of the OTES-protecting group gave diol **152**. Initial attempts to convert **152** into **153** were unsuccessful.

This approach shows that quinic acid is a suitable substrate to generate highly functionalized *cis*-decalins *via* a Claisen-Ireland rearrangement - RCM protocol. The synthesis proceeded with a high degree of diastereoselection and excellent yields for most of the steps. TBS-protection of enone **153** followed by regio- and stereoselective epoxidation will also furnish the desired *cis*-decalin core of branimycin with the C5 OH-group already being incorporated.

[47] Liu, H.; Yip, J.; Shia, K. *Tetrahedron Lett*. **1997**, *38*, 2253.

7. Total Synthesis of the Antibiotic Branimycin

Marchart, S.; Gromov, A.; Mulzer J. *Angew. Chem., Int. Ed*. **2009**, *accepted*.

Natural Product Synthesis

DOI: 10.1002/anie.200((will be filled in by the editorial staff))

Total Synthesis of the Antibiotic Branimycin

Stefan Marchart, Alexey Gromov and Johann Mulzer**
((Dedication----optional))

The nargenicin antibiotics[1] have repeatedly been the target of synthetic efforts over the past 20 years,[2-4] although only one synthesis was completed so far.[2] Branimycin (**1**), which has been isolated from *Actinomycete GW 60/1571* by the Laatsch group,[5] is the most complex member of this family so far. Biological tests have shown that branimycin is active against *Escherichia coli*, *Bacillus subtilis*, *Staphylococus aureus* and in particular against *Streptomyces viridochromogenes*. The structure of **1**, which was elucidated by multidimensional NMR experiments only, is unusually complex, as 24 out of the 25 carbon atoms are either functionalized and/or stereogenic. All in all, there are 12 stereocenters, 2 double bonds, 3 secondary OH- and 3 CH_2OMe functions. Additionally, the *cis*-fused dehydro-decalin core, the 7,12-ether bridge and the nine-membered macrolide ring make **1** an attractive target for total synthesis.[6] In this communication we report the first total synthesis of **1**, which also confirms the relative stereochemistry assigned by the Laatsch group. Additionally, the absolute configuration of **1** has been established.

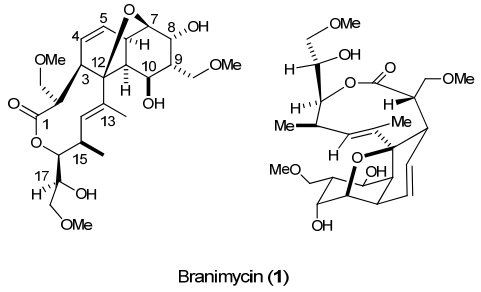
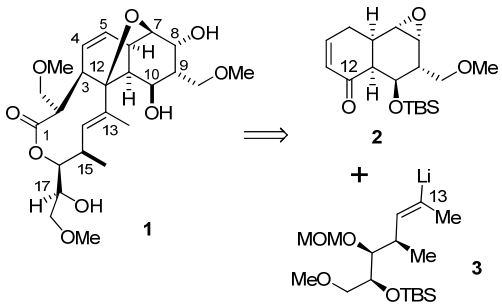


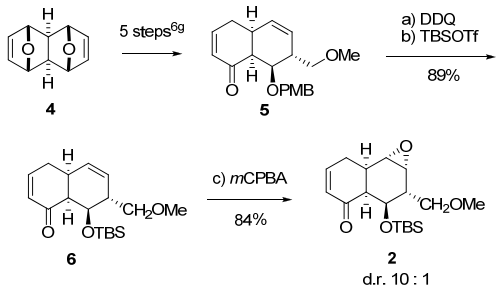
Figure 1 The structure of Branimycin.

In keeping with the retrosynthetic plan outlined previously (Scheme 1),[6c] we intended to assemble the target molecule *via* the addition of the organometallic side chain **3** to the *cis*-decalin ketone **2**. In a recent publication[6g] we have described the preparation of enantiopure decalin **5** *via* desymmetrization of the known precursor **4** (Scheme 2).



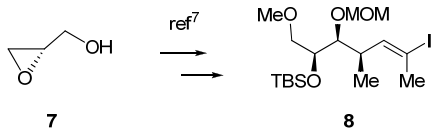
Scheme 1. Retrosynthetic analysis of **1**. TBS = *tert*-butyldimethylsilyl, MOM = methoxymethyl.

The protecting group was changed from PMB in **5** to TBS in **6** to ensure a decent stereoselectivity in the ensuing epoxidation step (**6** → **2**). Sidechain **8** was prepared in gram quantities from (*S*)-glycidol (**7**) by a modified version of our earlier approach[7] (Scheme 3) (see supporting information).



Scheme 2. Preparation of decalin ketone **2**. Reagents and conditions: a) DDQ, pH 7 buffer, DCM, 0-2 °C, 30 min, ultrasonic bath; b) TBSOTf, 2,6-di-*tert*-butyl-pyridine, THF, -78 °C, 1 h; c) *m*CPBA, DCM, 0 °C, 2 h. DDQ = 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone, Tf = trifluoromethanesulfonyl, *m*CPBA = 3-chloroperbenzoic acid, DCM = dichloromethane, THF = tetrahydrofuran.

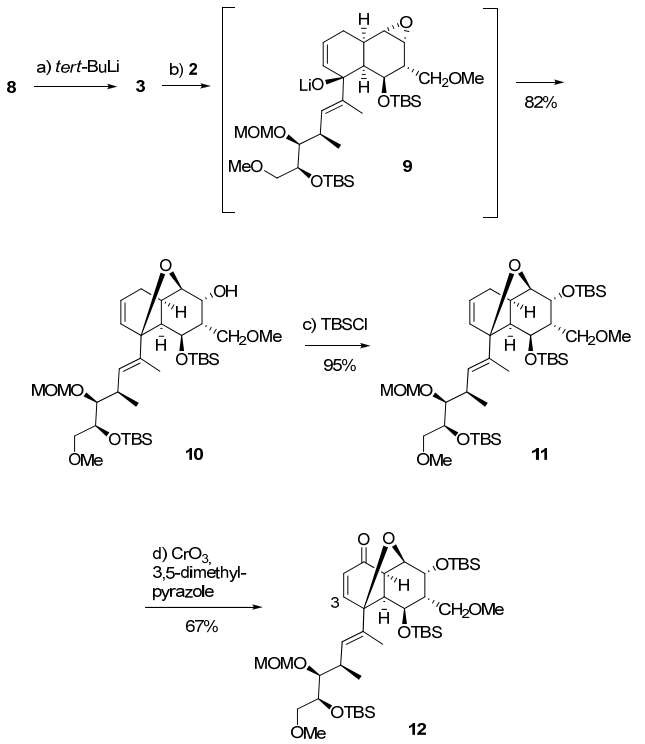
Vinyl iodide **8** was metallated to **3** with *tert*-butyllithium and the organolithium species was added to ketone **2** (Scheme 4). The primary adduct **9** could not be observed as the ether bridge was closed to form **10** directly, presumably under the influence of the lithium species as a Lewis acid catalyst.



[*] Mag. S. Marchart, Dr. A. Gromov, Prof. Dr. J. Mulzer
University of Vienna
Institute of Organic Chemistry
Waehringer Strasse 38
1090 Wien, Austria
Fax: (+) 431-427752189
E-mail: johann.mulzer@univie.ac.at

[**] We thank Dr. Valentin Enev for fruitful discussions, Ing. Martina Drescher for experimental work, Dr. Hanspeter Kählig and Ing. Susanne Felsinger for NMR spectra, Prof. H. Laatsch for an authentic sample of **1** and the Austrian Science Fund for financial support (P-15929-N08).
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

Scheme 3. Preparation of vinyl iodide **8**.

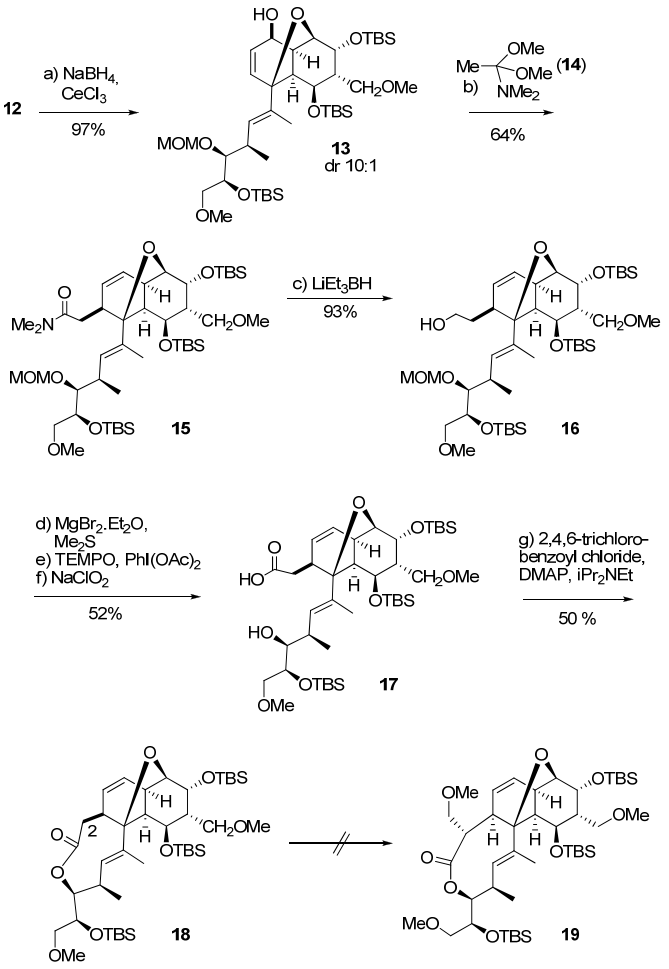


Scheme 4. Preparation of intermediate **12**. Reagents and conditions: a) **8** (1.7 equiv), *tert*-BuLi, THF, -78 °C, 2.5 h; b) **2** (1.0 equiv.), THF, -78 °C, 5 min, warmed to 22 °C overnight; c) TBSCl, imidazole, DMF, 22 °C, 12 h; d) CrO_3, 3,5-dimethyl-pyrazole, DCM, -20 °C, 2 h, then **11** in DCM, -20 °C, 2 h. DMF = dimethylformamide.

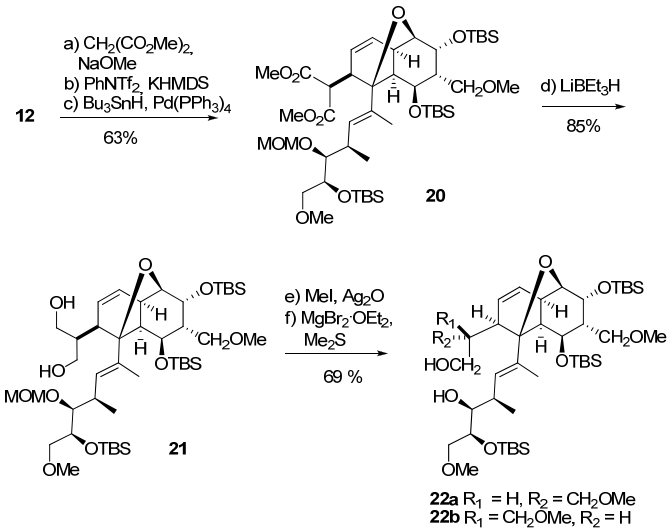
OTBS-protection to **11** was followed by allylic oxidation[8] to furnish enone **12**. The introduction of the sidechain at C3 was first attempted *via* Claisen-Eschenmoser rearrangement.[9] Thus, enone **12** was reduced to the allylic alcohol **13** with high stereocontrol and then treated with acetamide acetal **14** in DMF under microwave irradiation to obtain amide **15**. Direct hydrolysis to the acid was avoided due to the harsh conditions required. Therefore, alcohol **16** was prepared via reduction with Superhydride. Removal of the OMOM-protecting group was followed by a selective oxidation of the primary hydroxyl group with TEMPO[10] first to the aldehyde and then to *seco* acid **17**. Macrolactonization under modified Yamaguchi conditions[11] smoothly produced the nine-membered lactone **18**. Unfortunately all attempts to introduce the 2-CH_2OMe group were unsuccessful.

Therefore it was decided to install the crucial sidechain via Michael addition (Scheme 6). In fact, enone **12** added malonate anion stereoselectively from the top face. The enolate was trapped by vinyl triflate formation. Reduction with Bu_3SnH under Pd-catalysis gave diester **20** in good yield. Reduction furnished diol **21** which was converted into a mixture of monomethyl ethers **22a**/**b**. The ratio of **22a**/**b** strongly depended on the conditions. Thus, MeI and Ag_2O[12] furnished a 1:1-mixture, whereas the ratio was 1:4 with MeI, KHMDS.

After selective deprotection of the OMOM-group with $MgBr_2$, chromatographic separation of the two epimers was possible. In parallel experiments, the diastereomers **22a** and **b** were oxidized to *seco* acids **23a** and **b** in excellent yield. Yamaguchi lactonization led to elimination at the 2-CH_2OMe-group, presumably induced by the base present in the reaction mixture. Therefore we switched to the virtually neutral Corey-Nicolaou-Gerlach[13] conditions which did afford the nine-membered macrolactones **19** and **24** in acceptable yields. On treatment with TBAF in THF the least hindered 17-OTBS group in **19**/**24** was removed first, whereupon the two remaining TBS groups followed suit to give branimycin (**1**) and its C2-epimer **25** in high yield.[14]

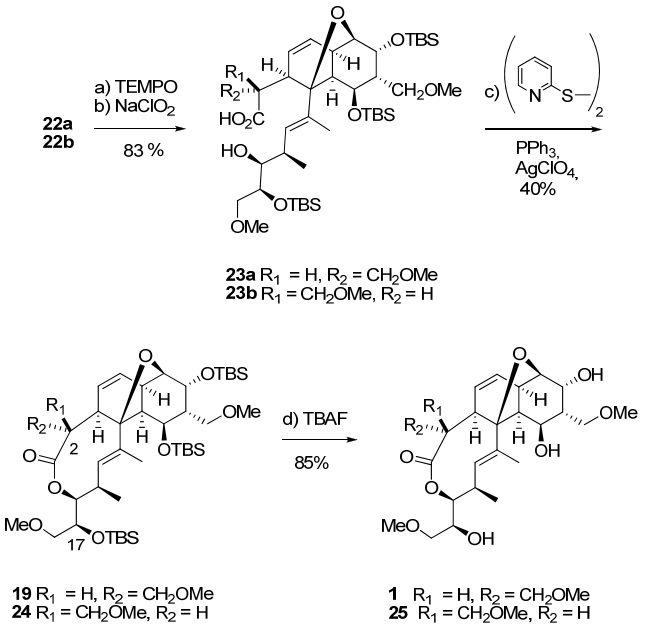


Scheme 5. Preparation of macrolactone **18**. Reagents and conditions: a) $NaBH_4$, $CeCl_3 \cdot 7\ H_2O$, MeOH, 0 °C, 12 h; b) **14**, DMF, microwave, 220 °C, 2 min; c) $LiBEt_3H$ (10 equiv), THF, 0 °C, 5h; d) $MgBr_2 \cdot Et_2O$, Me_2S, DCM, 40 °C, 12 h (70% b.r.s.m., 80% conversion); e) TEMPO (0.3 equiv), $PhI(OAc)_2$ (3 equiv), DCM, 22 °C, 2 h (87%); f) 2-methyl-2-butene, $NaClO_2$, NaH_2PO_4. H_2O, *tert*-BuOH, H_2O, 18 °C, 40 min, (85%); g) 2,4,6,-trichlorobenzoyl chloride, iPr_2NEt, DMAP, toluene, 110 °C, 4 h. TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy, DMAP = 4-(dimethylamino)pyridine.



Scheme 6. Preparation of monomethyl ethers **22a**/**b**. Reagents and conditions: a) $CH_2(CO_2Me)_2$, NaOMe, MeOH, -21 °C → 22 °C, 14 h (88%); b) $PhNTf_2$, KHMDS, THF, -78 °C → 22 °C, 30 min, (93%); c) Bu_3SnH, $Pd(PPh_3)_4$, LiCl, 2,6-lutidine, THF, 22 °C, 14 h (78%); d) $LiBEt_3H$, THF, 0 °C → 22 °C, 18 h; e) Ag_2O, MeI, 42 °C, 24 h, (99% b.r.s.m., 80% conversion); f) $MgBr_2.Et_2O$, Me_2S, DCM, 40 °C, 6 h, (70% b.r.s.m., 75% conversion). HMDS = hexamethyldisilazane, b.r.s.m. = based on recovered starting material.

According to the usual criteria (^1H and ^{13}C NMR as well as IR and MS spectra, R_f values in three different solvents) our synthetic sample of **1** was identical with authentic material. The optical rotation of the synthetic product ($[\alpha]_D^{25}$ = + 88 (*c* = 0.04, $CHCl_3$)) nicely matched the value of the natural product ($[\alpha]_D^{25}$ = + 80 (*c* = 0.045, $CHCl_3$)) and confirmed the absolute configuration depicted in formula **1**.



Scheme 7. Completion of the synthesis. Reagents and conditions: a) TEMPO, $PhI(OAc)_2$, DCM, 22 °C, 2 h (92%); b) 2-methyl-2-butene, $NaClO_2$, $NaH_2PO_4.H_2O$, *tert*-BuOH, H_2O, 15 °C, 30 min, (90%); c) $(PyS)_2$, PPh_3, $AgClO_4$, toluene, 85 °C, 2 h; d) TBAF, THF, 22 °C, 14 h. TBAF = tetra-*n*-butylammonium fluoride, $(PyS)_2$ = 2,2´-dithio-dipyridine.

In conclusion we have developed the first synthesis of branimycin along a convergent route with 22 steps in the longest linear sequence and an overall yield of 2%. Our route is flexible with respect to the substituents and configurations of the individual stereogenic centers. More specifically, some of the hydroxyl groups might be inverted, removed or replaced by other functions, e.g. amines. This should enhance the diversity of an envisaged library for detailed SAR-studies.

Received: ((will be filled in by the editorial staff))
Published online on ((will be filled in by the editorial staff))

Keywords: macrolides · *cis*-decalin · polyketides · natural products · antibiotics

[1] a) Review: J. Kallmerten, *Studies in Natural Procducts Chemistry*, Vol. *17* (Ed.: Atta-ur-Rahman), Elsevier, Amsterdam, **1995**, pp. 283-310 and references cited therein; b) W. D. Celmer, C. N. Chmurny, C. E. Moppett, R. S. Ware, P. C. Watts, E. B. Whipple, *J. Am. Chem. Soc.* **1980**, *102*, 4203-4209; c) J. Tone, R. Shibakawa, H. Maeda, Y. Yamauchi, K. Niki, M. Saito, K. Tsukuda, E. B. Whipple, P. C. Watts, C. E. Moppett, M. T. Jefferson, L. H. Huang, W. P. Cullen, W. D. Celmer, *20th Interscience Conf. Antimicr. Agents and Chemoth.*, New Orleans, LA, Abstract 62, Sep. 22-24, **1980;** d) H. A. Whaley, C. G. Chichester, S. A. Mizak, R. J. Wnuk,. *Tetrahedron Lett.* **1980**, *21*, 3659-3662; e) H. A. Whaley, J. H. Coates, *21th Interscience Conf. Antimicr. Agents and Chemoth*., Chicago, IL, Abstract 187, Nov. 4-6, **1981**; f) M. Jackson J. P. Karwowski, R. J. Theriault, P. B. Fernandes, R. C. Semio, W. H. Kohl, *J. Antibiot*. **1987**, *40*, 1375-1382; g) R. R. Rasmussen, M. H. Scherr, D. N.Whittern, A. M. Buko, J. B. McAlpine, *J. Antibiot*. **1987**, *40*, 1383-1393.

[2] 18-Deoxynargenicin A_1: a) D. J. Plata, J. Kallmerten,. *J. Am. Chem. Soc*. **1988**, *110*, 4041-4042; b) L. T. Rossano, D. J. Plata, J. Kallmerten,. *J. Org. Chem*. **1988**, *53*, 5189-5191, and cited earlier work.

[3] Nargenicin/Nodusmycin: a) J. W. Coe, W. R. Roush,. *J. Org. Chem*. **1989**, *54*, 915-930; b) W. R. Roush, K. Koyoma, M. L. Curtin, K. J. Moriarty, *J. Am. Chem. Soc*. **1996**, *118* , 7502-7512.

[4] Nodusmycin/Coloradocin: a) E. Gössinger, A. Schwartz, N. Sereinig, *Tetrahedron* **2001**, *57,* 3045-3061, and cited earlier work; b) E. Gössinger, A. Schwartz, N. Sereinig,. *Tetrahedron* **2000**, *56,* 2007-2014.

[5] M. Speitling, I. Grün-Wollny, F. G. Hannske, H. Laatsch,. *12 and 13 IRSEER Naturstofftage der DECHEMA e. V. Irsee*, **2000** and **2001**, poster presentations.

[6] a) V. S. Enev, M. Drescher, H. Kaehlig, J. Mulzer, *Synlett* **2005**, 2227-2229; b) W. Felzmann, V. B. Arion, J-L. Mieusset, J.Mulzer, *Org. Lett*. **2006**, *8*, 3849-3851; c) J. Mulzer, D. Castagnolo, W. Felzmann, S.; Marchart, C. Pilger, V. S. Enev, *Chem. Eur. J.*, **2006**, *12*, 5992-6001; d) S. Marchart, J. Mulzer, V. S Enev, *Org. Lett*. **2007**, *9*, 813-816; e) V. S. Enev, M. Drescher, J. Mulzer, *Tetrahedron* **2007**, *63*, 5930-5939; f) V. S. Enev, M. Drescher, J. Mulzer, *Org. Lett*. **2008**, *10*, 413-416; g) A. Gromov, V. S. Enev, J. Mulzer, *Org. Lett*. **2009**, *11,* 2884-2886.

[7] W. Felzmann, D. Castagnolo, D. Rosenbeiger, J. Mulzer, *J. Org. Chem.* **2007**, *72*, 2182-2186.

[8] W. G. Salmond, M. A. Rarta, J. L. Havens, *J. Org. Chem.* **1978**, *43*, 2057-2059.

[9] A. E. Wick, D. Felix, K. Steen, A. Eschenmoser, *Helv. Chim. Acta* **1964**, *47*, 2425-2429.

[10] A. E. J. de Nooy, A. C. Besemer, H. van Bekkum, *Synthesis* **1996**, 1153-1174.

[11] a) M. Hikota, H. Tone, K. Horita, O. Yonemitsu, *J. Org. Chem.* **1990**, *55,* 7 – 9. b) J. Inanga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989-1993.

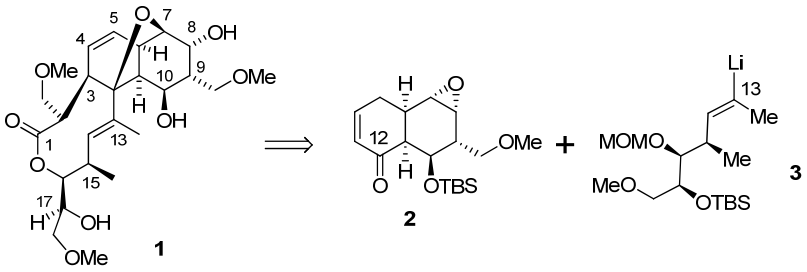
[12] A. Bouzide, G. Sauve, *Tetrahedron Lett.* **1997**, *38*, 5945-5948.

[13] a) E. J. Corey, K. C. Nicolaou, *J. Am. Chem. Soc*. **1974**, *96*, 5614-5616; b) H. Gerlach, A. Thalmann, *Helv. Chim. Acta* **1974**, *57*, 2661 – 2663.

[14] The relative configurations at C2 in **19**, **24**, **25** and **1** were safely assigned by NOE experiments.

Stefan Marchart, Alexey Gromov and Johann Mulzer_____ **Page – Page**

Total Synthesis of the Antibiotic Branimycin



The first total synthesis of branimycin (**1**) uses a highly convergent approach by adding the vinyl lithium derivative **3** to a *cis*-decalin ketone **2**. The original structural assignment has been confirmed by our scaleable and flexible route, which has 22 steps in the longest linear sequence with an overall yield of 2%.

Total Synthesis of the Antibiotic Branimycin

Supporting Information

Stefan Marchart*, Alexey Gromov and Johann Mulzer*

Institute of Organic Chemistry, University of Vienna

Waehringerstraße 38

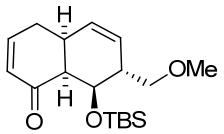
1090 Vienna

Austria

General Methods

All commercially available reagents were used as received. Thin layer chromatography (TLC) was performed on silica gel 60 F_{254} plates. Plates were visualized by dipping into ceric sulfate mixture [H_2SO_4 (10 vol %, 100 mL), phosphormolybdic acid (4.5 g), $Ce(IV)SO_4$ (0.1 g)] followed by heating with a heat gun. Flash column chromatography was carried out with silica gel 60 (0.040-0.063 μm, 240-400 mesh). Dichloromethane was dried by storage over MS 4Å. THF, diethyl ether, benzene and toluene were distilled from Na/benzophenone. Dry DMF and NMP (over molecular sieves) were purchased from Fluka. Molecule sieves 4Å (Aldrich) in powder (5 μ) or in beads (Merck) 4Å or 3Å were activated by heating at 350 °C in high vacuum for 8 h. All reactions were performed under atmosphere of Ar with flame-dried glassware unless otherwise stated. Microwave experiments were carried out on a Biotage Initiator (Biotage, Sweden) with reaction times specified as the ramp time and hold times at the final temperature. Temperatures were measured at the vessel surface by IR-sensors.

NMR spectra were recorded at 250, 400 or 600 MHz in $CDCl_3$ or C_6D_6 at 300 K. Chemical shift values were quoted in parts per million (ppm), and coupling constants were quoted in hertz. Residual signal of $CHCl_3$ (δ = 7.26 ppm) or C_6H_6 (δ = 7.16 ppm) were used as an internal reference for ^1H chemical shifts; signals of $CDCl_3$ (δ = 77.16 ppm) or C_6D_6 (δ = 128.06 ppm) were used as an internal reference for ^{13}C chemical shifts. ^{13}C NMR spectra were measured *J*-modulated and proton decoupled unless otherwise stated. Abbreviations for multiplicities are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. IR spectra were recorded with a FTIR spectrometer and are reported in wave numbers (cm^{-1}). All compounds were measured as a thin film on a silicon single crystal plate (Si-pellet). Optical rotations were measured on a P 341 Perkin-Elmer polarimeter. Mass spectra (HRMS) were performed with a Finnigan MAT 8230 with a resolution of 10000.



(4aS,7R,8R,8aS)-8-(tert-butyldimethylsilyloxy)-7-(methoxymethyl)-4,4a,8,8a-tetrahydro-naphthalen-1(7H)-one (6).

To a solution of enone **5** (50.0 mg, 0.151 mmol) in DCM (1.2 mL) was added aq. pH 7.0 buffer (1 mL). The mixture was immersed in an ultrasonic bath and sonicated at +1 to + 3 °C for 5 min. To this mixture DDQ (69.1 mg, 0.305 mmol) was added and the reaction mixture was sonicated for 30 min at +1 to +3 °C (maintaining the temperature in the bath by adding ice). The reaction mixture was transferred into a separation funnel, saturated aq. $Na_2S_2O_3$ (3 mL) was added and the mixture was vigorously shaked for 20 sec. Saturated aq. $NaHCO_3$ (30 mL) was added and the mixture was vigorously shaked for 1 min. The mixture was extracted with EtOAc (2x30 mL), the organic phase was washed with saturated aq. $NaHCO_3$ (30 mL). The combined water phases were extracted with EtOAc (4x30 mL). The combined organic phases were washed with brine (30 mL) and dried over $MgSO_4$. Solvents were removed *in vacuo* below 30 °C. The crude mixture (ca. 0.15 mmol) was dissolved in THF (1.4 mL) and cooled to -78 °C. To this solution 2,6-di-*tert*-butylpyridine (115 mg, 129 µL, 0.60 mmol) was added and the mixture was stirred until a clear solution was obtained. Then TBSOTf (86 µL, 99 mg, 0.375 mmol) was added dropwise and the mixture was stirred at -78 °C for 1h. The reaction was quenched by pouring into a vigorously stirred saturated aq. $NaHCO_3$ (30 mL), stirred for 5 min and extracted with EtOAc (3x30 mL). The combined organic phases were washed with brine (20 mL) and dried over $MgSO_4$. Volatiles were removed *in vacuo* and the residue was subjected to column chromatography (EtOAc/toluene) to obtain enone **6** in 89% (43.6 mg) over two steps.

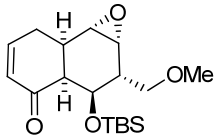
^{1}H-NMR (400MHz, $CDCl_3$): δ = 6.99 (ddd, *J*= 10.2, 6.1, 2.1 Hz, 1H), 6.09 (ddd *J*= 10.2, 2.7, 1.0 Hz, 1H), 5.87 (ddd, *J*= 10.2, 4.8, 1.6 Hz, 1H), 5.64 (ddd *J*= 10.2, 4.8, 1.3 Hz, 1H), 4.37 (bs, 1H), 3.33 (s, 3H), 3.31 (dd, *J*= 9.6, 5.1 Hz, 1H), 3.21 (dd, *J*= 9.6, 7.8 Hz, 1H), 2.87 - 2.72 (m, 1H), 2.61 (ddd, *J*= 18.4, 11.3, 2.5 Hz, 1H), 2.47 (dd, *J*= 6.9, 2.6 Hz, 1H), 2.48 - 2.40 (m, 1H), 2.38 (dddd, *J*= 18.3, 5.8, 5.8, 0.8 Hz, 1H), 0.79 (s, 9H), 0.01 (s, 3H), -0.01 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 201.9, 150.9, 130.5, 130.2, 125.3, 74.8, 71.7, 59.2, 46.8, 45.0, 33.1, 31.5, 25.8, 17.9, -4.9, -5.2.

IR (film): 3022, 2929, 2857, 2738, 1674, 1472, 1463, 1424, 1390, 1255, 1123, 1063, 1006, 890, 834, 777, 745 cm^{-1}.

HRMS (ESI): calc. for $C_{18}H_{30}NaO_3Si$ $[M+Na]^+$ 345.1862; found: 345.1862.

$[\alpha]_D^{20}$ = -91.88 (c = 0.690, $CHCl_3$).



(1aR,2S,3R,3aS,7aR,7bS)-3-(tert-butyldimethylsilyloxy)-2-(methoxymethyl)-1a,2,3,3a,7,7a-hexahydronaphtho[2,1-b]oxiren-4(7bH)-one (2).

To a solution of **6** (700 mg, 2.17 mmol) in DCM (40 mL) at 0 °C was added *m*CPBA (77%, 2.43 g, 10.8 mmol). The mixture was stirred for 2 h at 0 °C, washed with saturated aq. $Na_2S_2O_3$ (20 mL) and saturated aq. $NaHCO_3$ (2x20 mL). The combined water phases were extracted with DCM (5x50 mL). The combined organic phases were washed with brine, passed through a plug of cotton and concentrated *in vacuo*. The residue was subjected to column chromatography (EtOAc/hexane) to obtain starting **6** (281 mg) and epoxyketone **2** (371 mg, 84% b.r.s.m.).

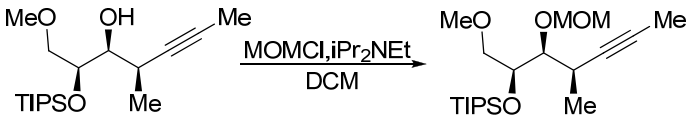
^{1}H-NMR (400 MHz, $CDCl_3$): 7.00 (ddd, *J*= 10.2, 6.1, 1.6 Hz, 1H), 6.08 (bd, *J*=10.2 Hz, 1H), 3.94 (bs, 1H), 3.50 (dd, *J*= 9.5, 7.1 1H), 3.16 (s, 3H), 3.34 - 3.28 (m, 2H), 3.25 (dd, *J*= 3.8, 1.0 1H), 2.87 - 2.76 (m, 2H), 2.45-2.33 (m, 2H), 2.28 (dd, *J*= 5.6, 2.4 1H), 0.8 (s, 9H), 0.14 (s, 3H), -0.14 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 200.8, 149.9, 131.0, 71.6, 69.5, 59.4, 55.4, 51.5, 43.9, 42.7, 32.0, 28.5, 25.9, -5.0, -5.3.

IR (film): 2928, 1733, 1674, 1557, 1388, 1326, 1253, 1212, 1067, 1035, 1006, 912, 828, 796, 778 cm^{-1}.

HRMS (ESI): calc. for $C_{18}H_{30}NaO_4Si$ $[M+Na]^+$ 361.1811; found: 361.1817.

$[\alpha]_D^{20}$ = -100.47 (c = 0.645, $CHCl_3$).



26

(5S,6S)-8,8-diisopropyl-6-(methoxymethyl)-9-methyl-5-((R)-pent-3-yn-2-yl)-2,4,7-trioxa-8-siladecane (27).

To a mixture of alcohol **26** (4.73 g, 14.4 mmol), *i*Pr_2NEt (7.0 g, 54.5 mmol) and DCM (2 mL) was added MOMCl (5.8 g, 72.0 mmol). The mixture was stirred at rt over 12 h. Reaction was quenched by stirring with aq. $NaHCO_3$ (100 mL) over 30 min. The water phase was extracted

with Et_2O (3x50 mL). The combined organic phases were washed with brine (50 mL) and dried over $MgSO_4$. Volatiles were removed *in vacuo* and the residue was subjected to column chromatography (EtOAc/hexanes) to obtain **27** in 95% yield (5.10 g).

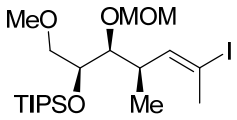
^{1}H-NMR (400MHz, $CDCl_3$): δ = 4.73 (d, *J* = 6.5 Hz, 1H), 4.70 (d, *J* = 6.5 Hz, 1H), 4.30 (ddd, *J* = 6.1, 6.1, 3.0 Hz, 1H), 3.53 (dd, *J* = 9.3, 6.1 Hz, 1H), 3.49 (dd, *J* = 7.7, 3.0 Hz, 1H), 3.41 (dd, *J* = 9.3, 6.1 Hz, 1H), 3.40 (s, 3H), 3.32 (s, 3H), 2.88-2.78 (m, 1H), 1.74 (d, *J* = 2.4 Hz 3H), 1.20 (d, *J* = 7.0 Hz, 3H), 1.12-1.02 (m, 21H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 98.1, 82.9, 82.0, 77.2, 74.5, 72.5, 58.8, 56.1, 27.7, 18.4, 18.3, 18.1, 13.0, 3.7.

IR (film): 2943, 2881, 2867, 1464, 1417, 1384, 1344, 1152, 1079, 1037, 983, 974, 938, 921, 902, 883, 836, 774, 714, 679, 419 cm^{-1}.

HRMS (ESI): calc. for $C_{20}H_{40}NaO_4Si$ $[M+Na]^+$ 395.2594; found: 395,2597.

$[\alpha]_D^{20}$ = +8.68 (c = 2.50, $CHCl_3$).



(5S,6S)-5-((R,E)-4-iodopent-3-en-2-yl)-8,8-diisopropyl-6-(methoxymethyl)-9-methyl-2,4,7-trioxa-8-siladecane (28).

To a solution of Cp_2ZrCl_2 (5.0 g, 17.1 mmol) in THF (120 mL) at 0 °C was added DIBAL (1.0 M in hexanes, 17.1 mL, 17.1 mmol). The reaction mixture was warmed to rt and the resulting slurry was stirred for 2 h. Then the stirring was stopped, and after 10 min the supernatant liquid was removed with a syringe. To the white precipitate a solution of **27** (2.20 g, 5.9 mmol) in benzene (160 mL) was added, and the mixture was stirred at rt over 12 h. Then the reaction mixture was cooled to 0 °C, and a solution of I_2 (5.0 g, 20 mmol) in benzene (100 mL) was added over 5 min. The reaction was quenched by pouring into a vigorously stirred aq. 3M $Na_2S_2O_3$ (100 mL). After both layers became colorless, the organic phase was separated, and the water phase was extracted with Et_2O (4x50 mL). The combined organic phases were washed with brine (50 mL) and dried over $MgSO_4$. Volatiles were removed *in vacuo* and the residue was subjected to column chromatography (EtOAc/hexanes) to obtain **28** in 83% yield (2.45 g).

^{1}H-NMR (400MHz, $CDCl_3$): δ = 6.23-6.18 (m, 1H), 4.74 (d, *J* = 6.8 Hz, 1H), 4.63 (d, *J* = 6.8 Hz, 1H), 4.01-4.02 (m, 1H), 3.53 (dd, *J* = 9.6, 3.9 Hz, 1H), 3.44 (dd, *J* = 5.8, 4.8 Hz, 1H), 3.40

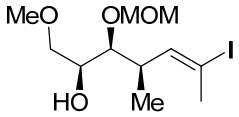
(s, 3H), 3.35 (dd, *J* = 9.6, 6.0 Hz, 1H), 3.32 (s, 3H), 2.77-2.66 (m, 1H), 2.38 (d, *J* = 1.5 Hz, 1H), 1.10-1.06 (m, 21H), 1.00 (d, *J* = 6.9 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 144.7, 98.0, 92.7, 82.9, 74.9, 73.5, 58.9, 56.0, 36.4, 27.8, 18.3, 16.4, 12.9.

IR (film): 2943, 2906, 2866, 1465, 1112, 1076, 1039, 937, 919, 882, 766, 679, 415, 406 cm^{-1}.

HRMS (ESI): calc. for $C_{20}H_{41}INaO_4Si$ $[M+Na]^+$ 523.1716; found: 523.1721.

$[\alpha]_D^{20}$ = +15.36 (c = 2.80, $CHCl_3$).



(2S,3S,4R,E)-6-iodo-1-methoxy-3-(methoxymethoxy)-4-methylhept-5-en-2-ol (29).

To a solution of **28** (2.50 g, 5.00 mol) in THF (18 mL) at rt was added TBAF (1.0 M in THF, 7 mL, 7 mmol) and the mixture was stirred for 1 h. Saturated aq. NH_4Cl (5 mL) was added and volatiles were removed *in vacuo*. The residue was diluted with half-saturated NH_4Cl (50 mL) and extracted with EtOAc (5x30 mL). The combined organic phases were washed with brine (30 mL) and dried over $MgSO_4$. Solvents were removed *in vacuo* and the residue was subjected to column chromatography (EtOAc/hexanes) to obtain **29** in 95% yield (1.63 g).

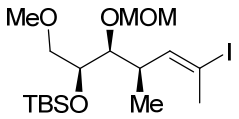
^{1}H-NMR (400MHz, $CDCl_3$): δ = 6.08-6.03 (m, 1H), 4.65 (d, *J* = 6.6 Hz, 1H), 4.62 (d, *J* = 6.6 Hz, 1H), 3.75-3.69 (m, 1H), 3.43-3.40 (m, 2H), 3.41 (s, 3H), 3.36 (dd, *J* = 6.1, 4.1 Hz, 1H), 3.36 (s, 3H), 2.81-2.73 (m, 1H), 2.79 (d, *J* = 5.8 Hz, 1H, O*H*), 2.40 (d, *J* = 1.5 Hz, 3H), 1.00 (d, *J* = 6.8 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 143.6, 98.6, 94.8, 83.1, 74.1, 70.4, 59.2, 56.3, 37.4, 28.0, 15.7.

IR (film): 3460, 3165, 2931, 2363, 1457, 1326, 1126, 1070, 1029, 809, 671, 611, 590, 587, 458, 452, 449, 434, 421, 410, 406, 403 cm^{-1}.

HRMS (ESI): calc. for $C_{11}H_{21}INaO_4$ $[M+Na]^+$ 367.0382; found: 367.0381.

$[\alpha]_D^{20}$ = +44.43 (c = 3.00, $CHCl_3$).



(5S,6S)-5-((R,E)-4-iodopent-3-en-2-yl)-6-(methoxymethyl)-8,8,9,9-tetramethyl-2,4,7-trioxa-8-siladecane (8).

A mixture of **29** (1.5 g, 4.36 mmol), imidazole (1.20 g, 20 mmol), TBSCl (1.4 g, 9 mmol) and DMF (3.0 mL) was stirred over 12 h at rt. The reaction mixture was quenched with saturated aq. $NaHCO_3$ (10 mL), stirred for 20 min, diluted with water (200 mL) and extracted with EtOAc (3x50 mL). The combined organic phases were washed with water (2x30 mL), brine (30 mL) and dried over $MgSO_4$. Volatiles were removed *in vacuo*, and the residue was subjected to column chromatography (EtOAc/hexanes) to obtain 1.90 g of **8** (95%).

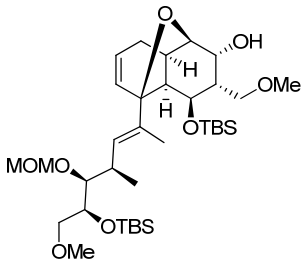
^{1}H-NMR (400MHz, $CDCl_3$): δ = 6.22-6.17 (m, 1H), 4.73 (d, *J* = 6.8 Hz, 1H), 4.62 (d, *J* = 6.8 Hz, 1H), 3.89-3.84 (m, 1H), 3.47 (dd, *J* = 9.9, 4.0 Hz, 1H), 3.41 (s, 3H), 3.39 (dd, *J* = 5.3, 5.3 Hz, 1H), 3.33 (dd, *J* = 9.7, 5.8 Hz, 1H), 3.33 (s, 3H), 2.73-2.63 (m, 1H), 2.38 (d, *J* = 1.5 Hz, 1H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 144.7, 98.1, 93.0, 82.5, 74.8, 73.2, 59.1, 56.1, 36.6, 27.8, 26.1, 18.3, 16.1, -4.4, -4.5.

IR (film): 2929, 2911, 2888, 2868, 2857, 2356, 1636, 1557, 1473, 1418, 1378, 1318, 1253, 1229, 1196, 1182, 1105, 1069, 1037, 999, 980, 836, 818, 778, 665, 631 cm^{-1}.

HRMS (ESI): calc. for $C_{17}H_{35}INaO_4Si$ $[M+Na]^+$ 481.1247; found: 481.1253.

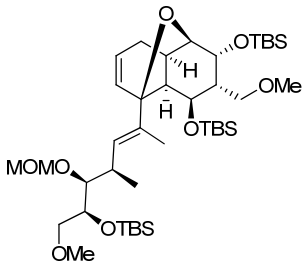
$[\alpha]_D^{20}$ = -0.41 (c = 2.45, $CHCl_3$).



Alcohol (10).

A solution of *t*BuLi (1.74 M in pentane, 1.13 mL, 1.96 mmol) was added within 10 min to THF (1.7 mL) cooled to -90 °C. The resulted yellow slurry was warmed to -80 °C, and a solution of **8** (451 mg, 0.98 mmol) in THF (1.2 mL) was added within 1.5 h. After stirring for additional 1 h, a solution of **2** (185 mg, 0.55 mmol) in THF (1.2 mL) was added within 5 min. The reaction mixture allowed to warm to rt overnight and stirred at rt for additional 3 h. Saturated aq. NH_4Cl (5 mL) was added and the mixture was concentrated to half its volume *in vacuo*. The mixture was extracted with EtOAc (3x20 mL), the combined organic phases were washed with brine (20 mL), dried over $MgSO_4$ and solvents were removed *in vacuo*. The residue was subjected to column chromatography (EtOAc/hexane) to obtain 282 mg of **10** (82%).

^{1}H-NMR (400 MHz, C_6D_6): δ = 6.12 (d, *J*=9.8 Hz, 1H), 5.96 (ddd, *J*= 9.3, 1.7, 1.8 Hz, 1H), 5.51 (ddd, *J*= 9.3, 3.2, 3.2 Hz, 1H), 4.76 (d, *J*=6.5 Hz, 1H), 4.64 (d, *J*=6.5 Hz, 1H), 4.33 - 4.26 (m, 2H), 4.18 - 4.09 (m, 2H), 3.72 - 3.66 (m, 2H), 3.62 (dd, *J*=5.4, 5.4 Hz, 1H), 3.57 (dd, *J*= 9.7, 3.5 Hz, 1H), 3.43 (dd, *J*= 9.7, 6.6 Hz, 1H), 3.33 (dd, *J*= 9.3, 3.0 Hz, 1H), 3.31 (s, 3H), 3.14 (s, 3H), 3.06 - 2.96 (m, 1H), 2.92 (s, 3H), 2.81 (d, *J*= 5.4 Hz, 1H), 2.78 - 2.71 (m, 1H), 2.41 - 2.32 (m, 1H), 2.37 (d, *J*= 2.5 Hz, 1H), 2.09 (d, *J*= 18.3 Hz, 1H), 1.93 (s, 3H), 1.27 (d, *J*= 6.8 Hz, 1H), 1.06 (s, 9H), 0.99 (s, 3H), 0.22 (s, 3H), 0.21 (s, 3H), 0.08 (s, 3H), 0.04 (s, 3H).
^{13}C-NMR (100 MHz, C_6D_6): δ = 139.1, 133.6, 128.2, 127.9, 98.4, 85.5, 85.1, 83.4, 75.8, 74.2, 73.8, 72.6, 72.2, 58.7, 58.4, 55.9, 49.6, 41.1, 38.0, 33.8, 33.6, 26.5, 26.4, 18.6, 18.5, 17.0, 16.4, -3.1, -4.0, -4.3, -5.6.
IR (film): 3468, 2930, 1473, 1423, 1388, 1349, 1253, 1223, 1103, 1083, 1039, 928, 898, 880, 835, 797, 775, 722, 671, 649, 611, 419 cm^{-1}.
HRMS (ESI): calc. for $C_{35}H_{66}NaO_8Si_2$ $[M+Na]^+$ 693.4194; found: 693.4200.
$[\alpha]_D^{20}$ = + 22.11 (c = 0.90, $CHCl_3$).



TBS-ether (11).

A mixture of **10** (200 mg, 0.30 mmol), TBSCl (230 mg, 1.5 mmol), imidazole (200 mg, 3 mmol) and DMF (0.3 mL) was stirred for 12 h at rt. Saturated aq. $NaHCO_3$ (5 mL) was added and stirring was continued for 10 min. The mixture was diluted with water (30 mL) and the water phase was extracted with EtOAc (3x30 mL). The combined organic phases were washed with brine (20 mL), dried over $MgSO_4$ and solvents were removed *in vacuo*. The residue was subjected to column chromatography (EtOAc/hexane) to obtain **11** in 95% yield (222 mg).
^{1}H-NMR (400 MHz, C_6D_6): δ = 6.20 (dd, *J*= 9.8, 1.1 Hz, 1H), 6.02 (ddd, *J*= 9.2, 1.8, 1.8 Hz, 1H), 5.55 (ddd, *J*= 9.2, 3.1, 3.1 Hz, 1H), 4.76 (d, *J*= 6.5 Hz, 1H), 4.64 (d, *J*= 6.5 Hz, 1H), 4.26 (dd, *J*= 4.5, 4.5 Hz, 1H), 4.19 - 4.14 (m, 2H), 3.79 (dd, *J*= 11.0, 2.7 Hz, 1H), 3.64 - 3.53 (m, 4H), 3.44 (dd, *J*= 9.6, 6.8 Hz, 1H), 3.31 (s, 3H), 3.23 (s, 3H), 3.14 (s, 3H), 3.16 - 3.00 (m, 2H), 2.70 (d, *J*= 5.4 Hz, 1H), 2.47 - 2.38 (m, 1H), 2.37 (d, *J*= 2.4 Hz, 1H), 2.10 (bd, *J*= 18.8 Hz,

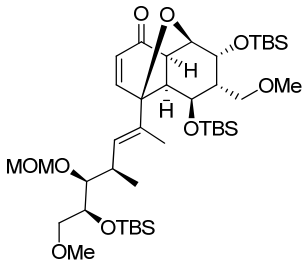
1H), 1.96 (d, *J*= 1.1 Hz, 3H), 1.32 (d, *J*= 6.9 Hz, 3H), 1.06 (s, 9H), 1.00 (s, 9H), 0.96 (s, 9H), 0.23 (s, 3H), 0.22 (s, 3H), 0.12 (s, 3H), 0.06 (s, 3H), 0.01 (s, 3H), 0.00 (s, 3H).

^{13}C-NMR (100 MHz, C_6D_6): δ = 139.4, 133.2, 128.5, 127.5, 98.4, 85.6, 85.3, 83.4, 75.9, 74.3, 73.9, 71.0, 70.6, 58.7, 58.3, 55.9, 49.8, 41.2, 38.0, 33.9, 33.6, 26.5, 26.4, 26.2, 18.6, 18.5, 18.4, 17.0, 16.3, -3.1, -3.9, -4.3, -4.6, -5.1, -5.3.

IR (film): 2955, 2944, 2929, 2911, 2889, 2871, 1557, 1388, 1253, 1117, 1030, 874, 836, 776, 705, 676, 619 cm^{-1}.

HRMS (ESI): calc. for $C_{41}H_{80}NaO_8Si_3$ $[M+Na]^+$ 807.5059; found: 807.5067.

$[\alpha]_D^{20}$ = + 44.30 (c = 1.00, $CHCl_3$).



Ketone (12).

To a suspension of CrO_3 (1.02 g, 10.2 mmol, dried overnight over P_2O_5) in DCM (7.5 mL) at -20 °C was added at once 3,5-dimethylpyrazole (0.98 g, 10.2 mmol) and the mixture was stirred until all solids dissolved to give a dark cherry-red solution. To this solution of CrO_3*3,5-dimethylpyrazole complex, a solution of **11** (0.200 g, 0.255 mmol) in DCM (2 mL) was added slowly and the mixture was stirred at -20 °C for 2h until TLC analysis showed full conversion of **11**. The reaction mixture was diluted with hexanes (10 mL) and washed with portions of aq. NaOH (3M, 30 mL) until the water phase remained colorless. The combined water phases were extracted with EtOAc (3x30 mL). The combined organic phases were washed with aq. HCl (1M, 3x30 mL), saturated aq. $NaHCO_3$ (30 mL), brine (30 mL) and dried over $MgSO_4$. Concentration *in vacuo* and purification by column chromatography gave 204 mg (67%) of **12** as a colorless oil.

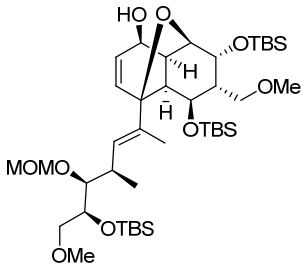
^{1}H-NMR (400 MHz, C_6D_6): δ = 6.92 (d, *J* = 9.5 Hz, 1H), 6.26 (dd, *J* = 9.8, 1.3 Hz, 1H), 6.03 (dd, *J* = 9.5, 1.4 Hz, 1H), 4.76 (d, *J* = 6.6 Hz, 1H), 4.60 (d, *J* = 6.6 Hz, 1H), 4.42 (dd, *J* = 4.6, 4.6 Hz, 1H), 4.15 – 4.09 (m, 2H), 3.67 (s, 1H), 3.64 – 3.45 (m, 5H), 3.41 (dd, *J* = 9.7, 6.5 Hz, 1H), 3.28 (s, 3H), 3.17 (s, 3H), 3.14 (s, 3H), 3.06 – 2.93 (m, 2H), 2.52 (d, *J* = 2.6 Hz, 1H), 1.81 (d, *J* = 1.2 Hz, 3H), 1.27 (d, *J* = 6.8 Hz, 3H), 1.04 (s, 9H), 0.99 (s, 9H), 0.94 (s, 9H), 0.21 (s, 3H), 0.20 (s, 3H), 0.07 (s, 3H), 0.03 (s, 3H), - 0.08 (s, 3H), - 0.10 (s, 3H).

^{13}C-NMR (100 MHz, C_6D_6): δ = 198.0, 159.9, 130.5, 130.4, 130.0, 98.3, 86.9, 83.2, 78.3, 75.7, 74.3, 72.0, 70.4, 70.1, 58.7, 58.4, 55.9, 55.5, 53.8, 41.5, 33.7, 26.3, 26.3, 26.1, 18.6, 18.4, 18.4, 16.7, 16.0, -3.3, -4.1, -4.3, -4.5, -5.2, -5.6.

IR (film): 2929, 2858, 1687, 1473, 1256, 1120, 1033, 838, 777, 674, 667, 515, 459, 438, 418, 402 cm^{-1}.

HRMS (ESI): calc. for $C_{41}H_{78}NaO_9Si_3$ $[M+Na]^+$ 821.4851; found: 821.4847.

$[\alpha]_D^{20}$ = + 79.1 (c = 0.22, $CHCl_3$)



Allylic alcohol (13).

A solution of $CeCl_3$*$7H_2O$ (746 mg, 2.00 mmol) in MeOH (20 mL) was added to ketone **12** (800 mg, 1.00 mmol). The mixture was cooled to 0 °C, and $NaBH_4$ (230 mg, 6 mmol) was added. The reaction was stirred at 0 °C for 12 h. Saturated aq. NH_4Cl (20 mL) was added, the mixture was warmed to rt and stirred for 30 min. The water phase was extracted with EtOAc (5x50 mL), combined organic phases were washed with brine (50 mL) and dried over $MgSO_4$. Volatiles were removed *in vacuo*, and the residue was repeatedly concentrated from MeOH (7x30 mL) *in vacuo*. The crude product was subjected to column chromatography (EtOAc/hexane) to obtain **13** in 97% yield (638 mg) as a mixture of diastereomers (dr 10:1). NMR data are given for the major diastereomer.

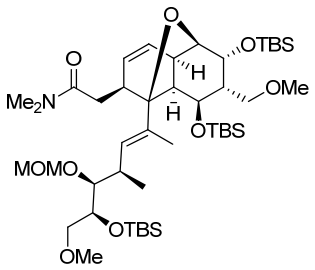
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.90 (dd, *J* = 9.3, 1.3 Hz, 1H), 5.73 (dd, *J* = 9.6, 1.2 Hz, 1H), 5.67 - 5.62 (m, 1H), 4.73 (d, *J* = 6.4 Hz, 1H), 4.69 - 4.64 (m, 1H), 4.62 (d, *J* = 6.4 Hz, 1H), 4.40 (d, *J* = 5.1 Hz, 1H), 4.09 (dd, *J* = 4.6, 4.6 Hz, 1H), 3.89 - 3.84 (m, 1H), 3.56 (dd, *J* = 11.0, 2.6 Hz, 1H), 3.47 (dd, *J* = 9.7, 4.2 Hz, 1H), 3.40 - 3.29 (m, 4H), 3.38 (s, 3H), 3.30 (s, 3H), 3.24 (s, 3H), 2.79 (d, *J* = 5.7 Hz, 1H), 2.79 - 2.68 (m, 2H), 2.32 (d, *J* = 2.4 Hz, 1H), 1.67 (s, 3H), 1.58 (d, *J* = 7.2 Hz, 1H), 1.02 (d, *J* = 6.9 Hz, 3H), 0.90 (s, 9H), 0.89 (s, 3H), 0.88 (s, 3H), 0.07 (s, 3H), 0.06 (s, 6H), 0.055 (s, 3H), 0.05 (s, 3H), 0.01 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 141.6, 132.1, 129.7, 128.0, 98.3, 84.4, 83.2, 76.7, 75.3, 73.3, 72.9, 70.7, 70.5, 69.4, 58.9, 58.4, 56.1, 51.9, 45.4, 41.2, 33.3, 26.3, 26.2, 26.1, 18.4, 18.3, 18.2, 16.6, 15.8, -3.1, -4.2, -4.2, -4.4, -5.2, -5.3.

IR (film): 3470, 2932, 1471, 1422, 1387, 1349, 1253, 1223, 1103, 1083, 1039, 928, 898, 880, 835, 797, 775, 722, 671, 649, 611, 419 cm^{-1}.

HRMS (ESI): calc. for $C_{41}H_{80}NaO_9Si_3$ $[M+Na]^+$ 823.5008; found: 823.5014.

Optical rotation for the mixture of diastereomers (10:1): $\mathbf{[\alpha]_D^{20}}$ = +66.63 (c = 2.05, $CHCl_3$).



Amide (15).

A Biotage® microwave vial (for 2-5 mL reactions) was charged with a stirring bar and 4Å molecular sieves (powder, 1.20 g), sealed with a cap and a septa. The septa was pierced with a needle (0.8x80 mm), the vial together with the needle were placed in a flask (250 mL, joint 29/42) and the system was subjected to evacuation-filling cycles with Ar. A solution of **13** (100 mg, 0.125 mmol, dr 10 : 1) in DMF (dry, degassed, 1.4 mL) was added, followed by N,N-dimethylacetamide dimethyl acetal (1.2 mL, 8.2 mmol). The mixture was irradiated at 220 °C for 2 min. Additional N,N-dimethylacetamide dimethyl acetal (0.3 mL, 2.05 mmol) was added and the mixture was irradiated for additional 2 min. All volatiles were removed *in vacuo*, the solid residue was suspended in EtOAc (10 mL) and passed through a plug of Celite. The filter cake was washed repeatedly with EtOAc (5x10 mL). The combined fractions were concentrated *in vacuo* and the residue was subjected to column chromatography (EtOAc/hexane) to yield **15** (64 mg, 64%) as a colorless oil.

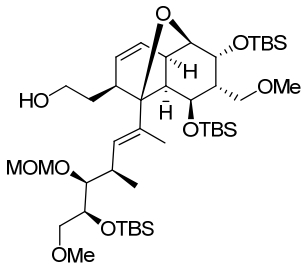
^{1}H-NMR (400 MHz, C_6D_6): δ = 6.28 (dd, *J* = 10.1, 0.8 Hz, 1H), 6.12 (dd, *J* = 9.5, 2.4 Hz, 1H), 6.00 - 5.95 (m, 1H), 6.12 (ddd, *J* = 9.2, 1.2, 3.0 Hz, 1H), 4.76 (d, *J* = 6.7 Hz, 1H), 4.62 (d, *J* = 6.7 Hz, 1H), 4.34 (d, *J* = 4.8 Hz, 1H), 4.30 (dd, *J* = 4.6, 4.0 Hz, 1H), 4.15 - 4.10 (m, 1H), 3.81 (dd, *J* = 10.9, 2.5 Hz, 1H), 3.74 - 3.69 (m, 1H), 3.60 - 3.55 (m, 3H), 3.52 (dd, *J* = 9.7, 3.7 Hz, 1H), 3.41 (dd, *J* = 9.7, 6.6 Hz, 1H), 3.31 (s, 3H), 3.24 - 3.16 (m, 1H), 3.22 (s, 3H), 3.09 (s, 3H), 3.08 - 3.01 (m, 1H), 2.85 (d, *J* = 6.5 Hz, 1H), 2.78 - 2.71 (m, 1H), 2.75 (s, 3H), 2.63 (s, 3H), 2.57 - 2.51 (m, 2H), 1.91 (d, *J* = 0.9 Hz, 3H), 1.34 (d, *J* = 6.8 Hz, 3H), 1.05 (s, 9H), 0.98 (s, 9H), 0.97 (s, 9H), 0.20 (s, 6H), 0.13 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H), 0.00 (s, 3H).

^{13}C-NMR (100 MHz, C_6D_6): δ = 170.7, 131.4, 131.1, 130.1, 127.6, 97.3, 89.4, 89.3, 85.2, 83.0, 74.6, 73.4, 72.0, 69.9, 69.3, 57.6, 57.4, 54.7, 49.6, 42.3, 39.9, 39.0, 35.6, 34.2, 33.1, 31.8, 25.5, 25.3, 25.1, 17.6, 17.5, 17.4, 15.9, 15.4, -4.1, -5.0, -5.4, -5.5, -6.1, -6.3.

IR (film): 2931, 1662, 1474, 1422, 1387, 1349, 1253, 1223, 1103, 1083, 1039, 928, 898, 880, 835, 797, 775, 722, 671, 649, 611, 419 cm^{-1}.

HRMS (ESI): calc. for $C_{45}H_{87}NNaO_9Si_3$ $[M+Na]^+$ 892.5586; found: 892.5581.

$[\alpha]_D^{20}$ = +98.9 (c = 0.37, $CHCl_3$).



Alcohol (16).

To a flask charged with amide **15** (179 mg, 0.206 mmol) under stirring was added dropwise Super-Hydride (1.0 M in THF, 3.2 mL, 3.2 mmol) at 0 °C, and the reaction was stirred for 5 h at 0 °C, 30 min at 5°C and 30 min at 10 °C. Saturated aq. NH_4Cl (5 mL) followed by MeOH (2 mL) were added carefully and the mixture was stirred for 10 min at rt. Most of organic solvents were removed *in vacuo* and the water phase was extracted with EtOAc (5x30 mL). Combined organic phases were diluted with toluene (40 mL), washed with brine (40 mL) and concentrated *in vacuo*. The residue was concentrated repeatedly from methanol (5x5 mL) and then subjected to column chromatography (EtOAc/hexane) to give 159 mg (93%) of **16**.

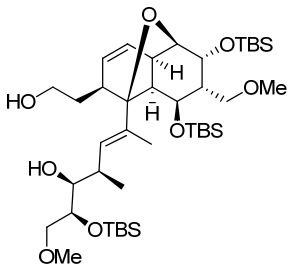
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.92 (ddd, *J* = 9.2, 6.7, 2.1 Hz, 1H), 5.74 (dd, *J* = 10.0, 1.0 Hz, 1H), 5.57 (dd, *J* = 9.5, 2.4 Hz, 1H), 4.74 (d, *J* = 6.7 Hz, 1H), 4.66 (d, *J* = 6.7 Hz, 1H), 4.05 (d, *J* = 5.0 Hz, 1H), 3.97 (dd, *J* = 4.3, 4.3 Hz, 1H), 3.94 - 3.89 (m, 1H), 3.71-3.61 (m, 1H), 3.62 (dd, *J* = 11.0, 2.5 Hz, 1H), 3.53 - 3.44 (m, 2H), 3.43 - 3.27 (m, 4H), 3.41 (s, 3H), 3.33 (s, 3H), 3.23 (s, 3H), 2.84 - 2.73 (m, 2H), 2.73 - 2.68 (m, 1H), 2.68 - 2.63 (m, 2H), 2.30 (d, *J* = 2.3 Hz, 1H), 1.75 - 1.66 (m, 1H), 1.68 (s, 3H), 1.55 - 1.45 (m, 1H), 1.04 (d, *J* = 6.7 Hz, 1H), 0.90 (s, 9H), 0.90 (s, 9H), 0.89 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 132.1, 130.1, 130.4, 129.0, 98.0, 90.1, 85.8, 83.0, 75.7, 73.6, 72.5, 70.5, 69.4, 60.8, 58.9, 58.4, 56.0, 50.4, 43.1, 40.2, 39.3, 34.4, 32.4, 26.4, 26.1, 26.0, 18.5, 18.4, 18.2, 17.1, 16.5, -3.1, -4.2, -4.3, -4.5, -5.2, -5.2.

IR (film): 3460, 1470, 1422, 1387, 1349, 1252, 1223, 1103, 1083, 1039, 921, 898, 880, 835, 797, 775, 722, 671, 649, 611, 419 cm^{-1}.

HRMS (ESI): calc. for $C_{43}H_{84}NaO_9Si_3$ $[M+Na]^+$ 851.5321; found: 851.5320.

$[\alpha]_D^{20}$ = +93.8 (c = 0.305, $CHCl_3$).



Diol (30).

A flask was charged with magnesium turning (400 mg, 16.6 mmol) and diethyl ether (10 mL), equipped with a reflux condenser and immersed in an ultrasound bath (20 °C). Dibromoethane (0.65 mL, 7.6 mmol) was added and the mixture was sonicated at 20 to 40 °C for 1h. The sonication was stopped and the mixture was allowed to stay at rt for 20 min. The separated bottom layer was transferred into a Schlenk flask (10 mL) with a syringe. Most of the solvent was blown away with Ar-stream and finally dried *in vacuo* for 2-3min to obtain a white powder. Into this flask Me_2S (2 mL) and a solution of substrate **16** (152 mg, 0.183 mmol) in 1.5 mL were added. The flask was immersed in an oil bath (40 °C), heated to reflux under Ar and the stop-cock to Ar-line was closed. The closed flask was heated at 40 °C for 12 h. Saturated aq. $NaHCO_3$ (5 mL) was added and the organic solvents were removed *in vacuo*. The water phase was extracted with EtOAc (4x15 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography (EtOAc/toluene) to obtain starting **16** (27 mg, 18%) and the desired diol **30** (83 mg, 70% b.r.s.m.) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.94 (ddd, *J* = 9.3, 6.7, 2.2 Hz, 1H), 5.57 (dd, *J* = 9.5, 2.3 Hz, 1H), 5.53 (dd, *J* = 10.0, 0.9 Hz, 1H), 4.08 (d, *J* = 5.0 Hz, 1H), 4.00 (d, *J* = 4.3 Hz, 1H), 3.88 (ddd, *J* = 7.0, 4.4, 1.2 Hz, 1H), 3.72-3.61 (m, 1H), 3.63 (dd, *J* = 10.9, 2.5 Hz, 1H), 3.54 - 3.45 (m, 1H), 3.43 (dd, *J* = 9.8, 4.4 Hz, 1H), 3.37 (dd, *J* = 9.7, 7.1 Hz, 1H), 3.35 - 3.30 (m, 2H), 3.32 (3H), 3.22 (s, 3H), 3.20 (dd, *J* = 9.4, 0.9 Hz, 1H), 2.82 (dd, *J* = 7.6, 5.3 Hz, 1H), 2.84 - 2.74 (m, 1H), 2.74 - 2.68 (m, 1H), 2.69 (d, *J* = 6.6 Hz, 1H), 2.56 (d, *J* = 9.4 Hz, 1H), 2.58 - 2.50 (m, 1H), 2.33 (d, *J* = 2.2 Hz, 1H), 1.79 (d, *J* = 0.90 Hz, 1H), 1.66 - 1.47 (m, 2H),

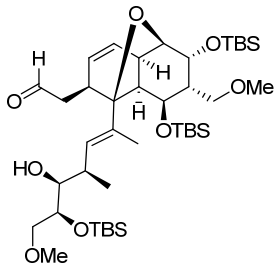
1.09 (d, *J* = 6.7 Hz, 1H), 0.91 (s, 9H), 0.90 (s, 9H), 0.88 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H), 0.07 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 133.4, 130.3, 129.9, 129.2, 90.3, 86.1, 76.5, 75.4, 72.4, 72.2, 70.3, 69.2, 60.3, 58.9, 58.4, 50.5, 43.1, 40.2, 39.3, 37.1, 32.4, 26.4, 26.1, 26.0, 18.5, 18.4, 18.2, 17.4, 17.0, -3.1, -3.7, -4.5, -4.6, -5.19, -5.22.

IR (film): 3470, 1474, 1422, 1387, 1349, 1252, 1223, 1103, 1083, 1039, 921, 898, 880, 835, 797, 775, 722, 671, 649, 611, 419 cm^{-1}.

HRMS (ESI): calc. for $C_{41}H_{80}NaO_8Si_3$ $[M+Na]^+$ 807.5059; found: 807.5063.

$[\alpha]_D^{20}$ = + 105.4 (c = 0.280, $CHCl_3$).



Aldehyde (31).

To diol **30** (46 mg, 0.060 mmol) at rt was added a solution of TEMPO (purified by sublimation *in vacuo*; 3.0 mg, 0.019 mmol) and $PhI(OAc)_2$ (45 mg, 0.140 mmol) in DCM (0.45 mL) and the clear solution was stirred at rt for 2 h. Then a mixture EtOAc/hexane (1:1, 3 mL) was added and the solution was passed through a short plug of silica gel (elution with EtOAc/hexanes 1:1) to remove $PhI(OAc)_2$. The resulting solution was concentrated, the residue was dissolved in toluene (3 mL) and passed through a short silica gel column (1.5 g SiO_2, elution with toluene; 2% EtOAc/toluene) to separate from most of TEMPO. (NOTE: slow column chromatography with oxidizing reagents cause partial oxidation of aldehyde **31** to the corresponding acid **17**; aq. saturated $Na_2S_2O_3$ in our hands was not effective enough to reduce oxidizing $PhI(OAc)_2$ and TEMPO). The fractions containing **31** were concentrated and subjected to column chromatography (EtOAc/toluene) to obtain aldehyde **31** (40 mg, 87%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.75 (d, *J* = 1.9 Hz, 1H), 5.96 (ddd, *J* = 9.4, 6.8, 2.2 Hz, 1H), 5.62 (dd, *J* = 9.6, 0.8 Hz, 1H), 5.54 (dd, *J* = 9.4, 2.5 Hz, 1H), 4.05 (d, *J* = 5.0 Hz, 1H), 4.00 (dd, *J* = 4.5, 4.5 Hz, 1H), 3.80 (ddd, *J* = 6.5, 4.9, 1.4 Hz, 1H), 3.63 (dd, *J* = 11.0, 2.5 Hz, 1H), 3.41 (dd, *J* = 9.5, 4.9 Hz, 1H), 3.36 (dd, *J* = 9.5, 6.6 Hz, 1H), 3.33 - 3.25 (m, 3H), 3.32 (s, 3H), 3.23 (s, 3H), 3.13 - 3.09 (m, 1H), 2.79 - 2.72 (m, 1H), 2.70 (d, *J* = 6.3 Hz, 1H), 2.58 -

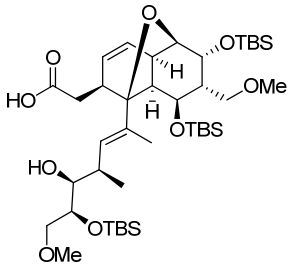
2.50 (m, 1H), 2.48 - 2.43 (m, 2H), 2.40 (dd, *J* = 8.4, 2.5 Hz, 1H), 2.32 (d, *J* = 2.2 Hz, 1H), 1.67 (d, *J* = 0.8 Hz, 1H), 1.09 (d, *J*= 6.9 Hz, 3H), 0.92 (s, 9H), 0.89 (s, 9H), 0.88 (s, 9H), 0.08 (s, 3H), 0.08 (s, 3H), 0.04 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.02(s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 202.1, 132.8, 130.3, 129.9, 129.5, 89.5, 86.1, 75.6, 75.3, 72.2, 72.1, 70.2, 69.1, 58.9, 58.4, 50.2, 43.4, 41.1, 40.1, 39.1, 36.6, 26.3, 26.0, 25.9, 18.3, 18.1, 16.9, 16.8, -3.3, 3.8, -4.6, -4.7, -5.3.

IR (film): 3464, 1730, 1479, 1421, 1387, 1345, 1252, 1223, 1103, 1082, 1039, 921, 898, 885, 835, 797, 770, 722, 671, 649, 611, 419 cm^{-1}.

HRMS (ESI): calc. for $C_{41}H_{78}NaO_8Si_3$ $[M+Na]^+$ 805.4902; found: 805.4898.

$[\alpha]_D^{20}$ = + 92.0 (c = 0.275, $CHCl_3$).



Seco acid (17).

To a solution of aldehyde **31** (25 mg, 0.032 mmol) in *t*BuOH (0.6 mL) was added 2-methyl-2-butene (1.4 mL) and the mixture was cooled to 17 °C. A solution of $NaClO_2$ (80%, 40 mg, 0.356 mmol) and NaH_2PO_4*H_2O (80mg, 0.580 mmol) in water (0.4 mL) was added and the mixture was stirred at 17 °C for 40 min. Chloroform (20 mL) was added and the organic phase was washed with water (2x5 mL). Combined aqueous phases were extracted with chloroform (4x15 mL) and the combined organic phases were washed with brine (20 mL), passed through a plug of cotton and concentrated *in vacuo*. The residue was subjected to column chromatography (EtOAc/hexane/1% *i*PrOH) to obtain acid **17** (21.9 mg, 85%).

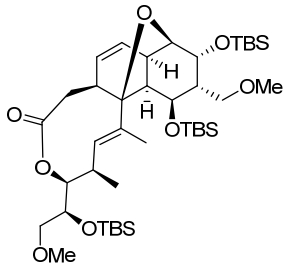
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.97 (ddd, *J* = 9.4, 6.9, 2.0 Hz, 1H), 5.60 (dd, *J* = 9.6, 0.8 Hz, 1H), 5.54 (dd, *J* = 9.4, 2.5 Hz, 1H), 4.11 (d, *J* = 5.0 Hz, 1H), 4.04 (dd, *J* = 4.5, 4.5 Hz, 1H), 3.82 (dd, *J* = 6.1, 1.1 Hz, 1H), 3.46 - 3.36 (m, 2H), 3.34-3.27 (m, 3H), 3.33 (s, 3H), 3.23 (s, 3H), 3.07 (m, 1H), 2.82 - 2.72 (m, 1H), 2.70 (d, *J* = 6.6 Hz, 1H), 2.60 - 2.49 (m, 2H), 2.32 (d, *J* = 2.2 Hz, 1H), 2.21 (dd, *J* = 16.0, 6.8 Hz, 1H), 1.72 (bs, 3H), 1.08 (d, *J* = 6.7 Hz, 3H), 0.92 (s, 9H), 0.82 (s, 9H), 0.78 (s, 3H), 0.08 (s, 3H), 0.04 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.5, 133.0, 130.4, 130.2, 129.7, 89.8, 86.2, 75.3, 74.6, 72.4, 71.9, 70.3, 69.2, 59.0, 58.5, 50.5, 42.4, 40.3, 39.0, 36.7, 34.2, 26.4, 26.1, 26.0, 18.42, 18.39, 18.2, 17.3, 16.9, -3.1, -3.7, -4.5, -4.7, -5.20, -5.23.

IR (film): 3460, 1710, 1479, 1421, 1387, 1345, 1252, 1223, 1103, 1082, 1039, 921, 898, 885, 835, 797, 770, 722, 671, 649, 611, 419 cm^{-1}.

HRMS (ESI): calc. for $C_{41}H_{78}NaO_9Si_3$ $[M+Na]^+$ 821.4851; found: 821.4857.

$[\alpha]_D^{20}$ = + 80.0 (c = 0.48, $CHCl_3$).



Macrolactone (18).

To acid **17** (2.5 mg, 0.003 mmol) was added a solution of *i*Pr_2NEt (3.8 µL, 2.9 mg, 0.023 mmol) and 2,4,6-trichlorobenzoyl chloride (2.2 µL, 3.4 mg, 0.014 mmol) in toluene (90 µL), and the mixture was stirred at rt for 6 h. The mixture was diluted with toluene (3.5 mL) and added *via* syringe pump to a solution of DMAP (17.0 mg, 0.14 mmol) in toluene (5.0 mL) at 110 °C over 2 h. Saturated aq. $NaHCO_3$ (10 mL) was added and the mixture was stirred for 15 min until phases became clear. The mixture was extracted with EtOAc (3x20 mL). The combined organic phases were washed with saturated aq. $NaHCO_3$ (20 mL), aq. NaH_2PO_4 (2M, 30 mL), saturated aq. $NaHCO_3$ (20 mL), brine (20 mL) and dried over $MgSO_4$. The solvents were removed *in vacuo* and the residue was subjected to column chromatography (SiO_2, EtOAc/hexanes) to obtain lactone **18** (1.2 mg, 50%).

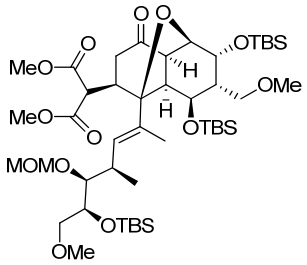
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 5.91 (ddd, *J* = 9.2, 6.7, 2.3 Hz, 1H), 5.74 (dd, *J* = 8.9, 1.2 Hz, 1H), 5.40 (dd, *J* = 9.5, 2.3 Hz, 1H), 4.94 (dd, *J* = 6.9, 6.9 Hz, 1H), 4.11 - 4.06 (m, 1H), 4.02 – 3.96 (m, 2H), 3.67 (dd, *J* = 11.3, 2.1 Hz, 1H), 3.47 (dd, *J* = 9.9, 6.6 Hz, 1H), 3.43 (dd, *J* = 9.9, 6.2 Hz, 1H), 3.39 – 3.28 (m, 2H), 3.36 (s, 3H), 3.22 (s, 3H), 3.15 (md, *J* = 11.6 Hz, 1H), 2.82 – 2.75 (m, 1H), 2.68 (d, *J* = 6.8 Hz, 1H), 2.57 – 2.49 (m, 2H), 2.33 (d, *J* = 1.8 Hz, 1H), 2.01 (dd, *J* = 9.3, 1.0 Hz, 1H), 1.65 (d, *J* = 1.1 Hz, 3H), 1.17 (d, *J* = 7.0 Hz, 3H), 0.89 (s, 9H), 0.89 (s, 9H), 0.88 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H).

^{13}C-NMR (150.9 MHz, $CDCl_3$): δ = 175.2, 135.9, 134.9, 131.0, 128.9, 89.0, 84.7, 80.1, 75.6, 72.4, 71.6, 70.2, 69.3, 68.3, 59.3, 58.2, 50.1, 49.7, 40.9, 40.1, 38.9, 36.6, 32.6, 30.5, 29.8, 29.1, 26.4, 26.0, 26.0, 18.5, 18.5, 18.2, 17.1, 15.8, -3.4, -3.9, -4.4, -4.7, -5.0, -5.2.

IR (film): 2928, 1729, 1577, 1464, 1388, 1258, 1116, 866, 836, 777, 671, 494, 448, 430, 411, 404 cm^{-1}.

HRMS (ESI): calc. for $C_{41}H_{76}NaO_8Si_3$ $[M+Na]^+$ 803.4746; found: 803.4742.

$[\alpha]_D^{20}$ = + 52.0 (c = 0.1, $CHCl_3$).



Diester (32).

To a solution of Na (6 mg, 0.263 mmol) in MeOH (0.8 mL) was added dimethyl malonate (0.18 mL, 1.579 mmol) at rt and the resulting mixture was stirred for 5 min. This mixture was then cooled to – 21 °C and a solution of enone **12** (140 mg, 0.175 mmol) in MeOH (0.8 mL) was added. The mixture was warmed to rt over night, then diluted with Et_2O and quenched with aq. saturated NH_4Cl. The water phase was extracted with Et_2O (3x3 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give a residue, which was purified by flash chromatography (EtOAc/hexane) on silica gel to afford 144 mg (88 %) of adduct **32** as an oil.

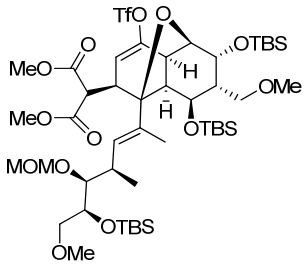
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 5.88 (d, *J* = 10.0 Hz, 1H), 4.76 (d, *J* = 6.6 Hz, 1H), 4.69 (d, *J* = 6.6 Hz, 1H), 4.02 – 3.94 (m, 3H), 3.68 (s, 3H), 3.66 (s, 3H), 3.58 (d, *J* = 2.6 Hz, 1H), 3.56 (dd, *J* = 11.2, 2.5 Hz, 1H), 3.51 (dd, *J* = 9.5, 4.7 Hz, 1H), 3.44 (dd, *J* = 4.6, 4.6 Hz, 1H), 3.42 (s, 3H), 3.38 (dd, *J* = 9.5, 6.4 Hz, 1H), 3.34 (s, 3H), 3.32 – 3.26 (m, 2H), 3.22 (s, 3H), 3.10 (dd, *J* = 17.4, 7.2 Hz, 1H), 3.04 (s, 1H), 2.94 – 2.87 (m, 2H), 2.87 – 2.80 (m, 1H), 2.56 (dd, *J* = 17.4, 8.7 Hz, 1H), 2.42 (d, *J* = 2.4 Hz, 1H), 1.71 (d, *J* = 1.1 Hz, 1H), 1.04 (d, *J* = 7.0 Hz, 1H), 0.91 (s, 9H), 0.89 (s, 9H), 0.87 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H), 0.04 (s, 6H), 0.03 (s, 3H), 0.00 (s, 3H).

^{13}C-NMR (150.9 MHz, $CDCl_3$): δ = 208.5, 169.6, 169.2, 133.0, 129.6, 100.1, 98.4, 89.8, 83.0, 80.9, 75.0, 73.3, 71.4, 69.9, 68.8, 58.9, 58.6, 55.9, 53.4, 52.8, 52.0, 49.6, 49.4, 42.2, 41.1, 37.1, 33.3, 26.3, 26.1, 26.0, 18.4, 18.3, 18.2, 16.7, 15.9, -3.2, -4.2, -4.4, -4.5, -5.3.

IR (film): 2928, 2851, 1792, 1735, 1539, 1473, 1307, 1254, 1177, 1118, 1060, 1028, 949, 837, 794, 777, 676, 420, 418, 416, 403 cm^{-1}.

HRMS (ESI): calc. for $C_{46}H_{86}O_{13}Si_3Na$ $[M + Na]^+$: 953.5274; found: 953.5291.

$[\alpha]_D^{20}$ = + 42.4 (c = 0.55, $CHCl_3$).



Vinyltriflate (33).

To a solution of N-Phenyltrifluoromethanesulfonimide (230 mg, 0.644 mmol) in THF (1.3 mL) at – 78 °C was added KHMDS (0.5 M in toluene, 1.3 mL, 0.644 mmol) and the resulting mixture was stirred for 5 min. A solution of **32** (150 mg, 0.161 mmol) in THF (2 mL) was added dropwise and after further 10 min at – 78 °C the reaction mixture was warmed to rt and stirred for 30 min. The reaction was diluted with toluene and quenched with aq. saturated NH_4Cl. The layers were separated and the organic phase was washed with H_2O (2x3 mL) and brine. The solvents were removed under reduced pressure and the residue was subjected to column chromatography (EtOAc/hexane) to yield 159 mg (93 %) of vinyl triflate **33**.

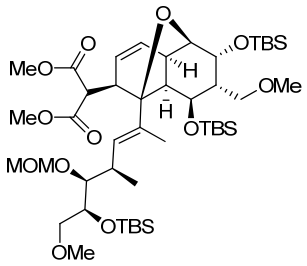
^{1}H-NMR (400 MHz, C_6D_6): δ = 6.32 (s, 1H), 6.26 (d, *J* = 10.2 Hz, 1H), 4.79 (d, *J* = 6.6 Hz, 1H), 4.71 (d, *J* = 6.6 Hz, 1H), 4.61 (d, *J* = 5.1 Hz, 1H), 4.34 – 4.28 (m, 1H), 4.20 (dd, *J* = 4.4, 4.4 Hz, 1H), 4.07 (d, *J* = 2.7 Hz, 1H), 3.85 (dd, *J* = 11.1, 2.5 Hz, 1H), 3.77 (dd, *J* = 2.8, 2.8 Hz, 1H), 3.67 – 3.61 (m, 2H), 3.59 (s, 3H), 3.52 – 3.45 (m, 3H), 3.30 (s, 3H), 3.27 (s, 3H), 3.26 – 3.18 (m, 2H), 3.16 (s, 3H), 3.14 (s, 3H), 3.11 – 3.02 (m, 1H), 2.67 (d, *J* = 2.2 Hz, 1H), 1.84 (d, *J* = 0.8 Hz, 3H), 1.31 (d, *J* = 6.9 Hz, 3H), 1.05 (s, 9H), 0.99 (s, 9H), 0.95 (s, 9H), 0.27 (s, 3H), 0.22 (s, 3H), 0.06 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H), -0.02 (s, 3H).

^{13}C-NMR (100.6 MHz, C_6D_6): δ = 169.5, 168.2, 149.4, 134.3, 123.8, 118.6, 99.0, 89.3, 85.5, 84.1, 75.3, 74.3, 71.9, 70.2, 69.3, 58.6, 58.5, 55.7, 52.4, 51.9, 51.5, 50.0, 46.0, 44.1, 41.2, 33.4, 26.4, 26.2, 26.1, 18.4, 18.2, 16.6, 16.2, -3.4, -3.8, -4.4, -4.5, -5.3, -5.4.

IR (film): 3175, 2956, 2932, 2893, 2858, 1738, 1700, 1473, 1463, 1423, 1388, 1361, 1255, 1212, 1143, 1120, 1045, 934, 868, 838, 778, 609 cm^{-1}.

HRMS (ESI): calc. for $C_{47}H_{85}F_3O_{15}SSi_3Na$ $[M + Na]^+$: 1085.4767; found: 1085.4784.

$[\alpha]_D^{20}$ = + 80.0 (c = 0.53, $CHCl_3$).



Diester (20).

To a solution of vinyl triflate **33** (103 mg, 0.097 mmol) in degassed THF (2.2 mL) was added LiCl (32 mg, 0.776 mmol), tetrakis(triphenylphosphine)palladium(0) (22 mg, 0.0194 mmol) and 2,6-lutidine (0.068 mL, 0.582 mmol), followed by dropwise addition of *n*-tributyltin hydride (0.103 mL, 0.388 mmol) at 15 °C. The reaction mixture was allowed to warm to rt and stirred for 14 h, then diluted with toluene and quenched with aq. saturated NH_4Cl. The layers were separated and the water phase was extracted with toluene (3x4 mL). The combined organic phases were washed with brine and the solvents were removed under reduced pressure. The residue was subjected to column chromatography (EtOAc/hexane) to obtain diester **20** (69 mg, 78 %) as a colorless oil.

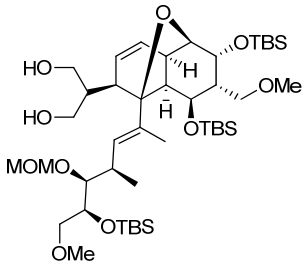
^{1}H-NMR (400 MHz, C_6D_6): δ = 6.27 (d, *J* = 10.1 Hz, 1H), 6.24 (dd, *J* = 9.6, 2.5 Hz, 1H), 6.07 (ddd, *J* = 9.6, 6.9, 2.3 Hz, 1H), 4.79 (d, *J* = 6.5 Hz, 1H), 4.72 (d, *J* = 6.5 Hz, 1H), 4.37 – 4.31 (m, 1H), 4.29 (d, *J* = 5.0 Hz, 1H), 4.21 (dd, *J* = 4.4, 4.4 Hz, 1H), 4.09 (d, *J* = 2.9 Hz, 1H), 3.86 (dd, *J* = 5.1, 2.5 Hz, 1H), 3.79 (dd, *J* = 11.0, 2.6 Hz, 1H), 3.69 - 3.62 (m, 2H), 3.61 (s, 3H), 3.56 – 3.49 (m, 3H), 3.38 (s, 3H), 3.30 (s, 3H), 3.31 – 3.22 (m, 1H), 3.20 (m, 3H), 3.17 – 3.08 (m, 1H), 3.14 (s, 3H), 2.83 (d, *J* = 6.9 Hz, 1H), 2.52 (d, *J* = 2.5 Hz, 1H), 1.95 (d, *J* = 0.9 Hz, 3H), 1.35 (d, *J* = 6.9 Hz, 3H), 1.07 (s, 9H), 0.98 (s, 9H), 0.95 (s, 9H), 0.28 (s, 3H), 0.24 (s, 3H), 0.08 (s, 3H), 0.00 (s, 3H), - 0.01 (s, 3H), 0.03 (s, 3H).

^{13}C-NMR (100.6 MHz, C_6D_6): δ = 170.3, 168.6, 133.0, 130.9, 129.3, 128.2, 98.9, 90.1, 86.5, 84.2, 75.5, 74.2, 72.9, 70.7, 69.9, 58.6, 58.5, 52.1, 51.5, 51.3, 47.8, 41.0, 39.6, 33.5, 26.5, 26.3, 26.1, 16.9, 16.5, - 3.2, - 3.8, - 4.5, - 5.2, - 5.3.

IR (film): 2932, 2914, 2771, 2703, 1738, 1651, 1573, 1488, 1391, 1254, 1101, 1023, 837, 781, 652, 543, 498, 475, 449, 419 cm^{-1}.

HRMS (ESI): calc. for $C_{46}H_{86}O_{12}Si_3Na$ $[M + Na]^+$: 937.5412; found: 937.5422.

$[\alpha]_D^{20}$ = + 104.9 (c = 0.47, $CHCl_3$).



Diol (21).

To a flask charged with diester **20** (60 mg, 0.066 mmol) was added dropwise under stirring Super-Hydride (1.0 M in THF, 2.0 mL, 2.00 mmol) at 0 °C. The resulting mixture was warmed to rt and stirred for 18 h. Pentaerythritol (540 mg, 4.00 mmol) was added carefully and the reaction mixture was stirred for 30 min. Aq. saturated NH_4Cl (2 mL) followed by MeOH (2 mL) were added and the water phase was extracted with EtOAc (5x10 mL). The combined organic phases were diluted with toluene (20 mL), washed with brine (10 mL) and concentrated *in vacuo*. The residue was concentrated repeatedly from methanol (5x2 mL) and then purified by flash chromatography (EtOAc/hexane) to afford 48 mg (85 %) of diol **21** as an oil.

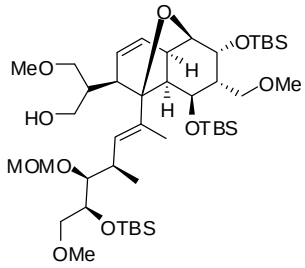
^{1}H-NMR (400 MHz, C_6D_6): δ = 6.13 (dd, *J* = 10.1, 1.0 Hz, 1H), 5.93 (ddd, *J* = 9.4, 6.6, 2.5 Hz, 1H), 5.55 (dd, *J* = 9.5, 2.4 Hz, 1H), 4.72 (d, *J* = 6.8 Hz, 1H), 4.64 (d, *J* = 6.8 Hz, 1H), 4.29 (d, *J* = 5.1 Hz, 1H), 4.25 – 4.16 (m, 2H), 4.13 (ddd, *J* = 8.2, 4.5, 3.8 Hz, 1H), 3.83 – 3.63 (m, 4H), 3.59 – 3.51 (m, 4H), 3.51 – 3.41 (m, 2H), 3.26 (s, 3H), 3.22 (s, 3H), 3.15 (s, 3H), 3.18 – 3.05 (m, 2H), 2.90 (dd, *J* = 3.8, 2.2 Hz, 1H), 2.83 (d, *J* = 6.7 Hz, 1H), 2.49 (d, *J* = 2.3 Hz, 1H), 2.36 – 2.19 (m, 2H), 1.91 (d, *J* = 1.0 Hz, 3H), 1.31 (d, *J* = 6.8 Hz, 3H), 1.07 (s, 9H), 0.99 (s, 9H), 0.96 (s, 9H), 0.25 (s, 6H), 0.10 (s, 3H), 0.03 (s, 3H), - 0.01 (s, 3H), - 0.03 (s, 3H).

^{13}C-NMR (100.6 MHz, C_6D_6): δ = 132.5, 131.6, 129.6, 128.4, 98.3, 91.5, 86.3, 83.5, 76.1, 74.3, 72.8, 70.7, 69.8, 65.7, 62.7, 58.7, 58.4, 55.7, 51.3, 46.6, 43.2, 40.8, 39.8, 34.7, 26.5, 26.3, 26.1, 18.7, 18.5, 18.3, 17.4, 16.5, - 3.1, - 4.0, - 4.1, - 4.5, - 5.2, - 5.3.

IR (film): 3436, 2954, 2929, 2891, 2857, 1472, 1463, 1389, 1361, 1253, 1196, 1117, 1034, 974, 914, 836, 802, 776, 668, 498, 436 cm^{-1}.

HRMS (ESI): calc. for $C_{44}H_{86}O_{10}Si_3Na$ $[M + Na]^+$: 881.5427; found: 881.5417.

$[\alpha]_D^{20}$ = + 70.9 (c = 0.55, $CHCl_3$).

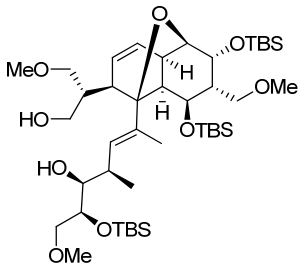


Alcohol (34).

To a solution of diol **21** (47 mg, 0.055 mmol) in MeI (0.7 mL, 11.24 mmol) was added Ag_2O (21.6 mg, 0.093 mmol) and the resulting mixture was refluxed for 24 h. The reaction mixture was diluted with DCM, filtrated through a pad of celite and the filtrate was concentrated *in vacuo* to give a residue which was flash chromatographed (EtOAc/hexane) to give 28.5 mg of diastereomers **34a/b** (99% b.r.s.m., 60% conversion, d.r. = 1:1) as a colorless oil.

IR (film): 3435, 2954, 2929, 2890, 2857, 1472, 1389, 1361, 1252, 1196, 1117, 1033, 974, 914, 836, 802, 776, 677, 424, 407 cm^{-1}.

HRMS (ESI): calc. for $C_{45}H_{88}O_{10}Si_3Na$ $[M + Na]^+$: 895.5583; found: 895.5568.



Diol (22a).

To a flask charged with $MgBr_2$*OEt_2 (905 mg, 3.51 mmol) were added Me_2S (2.9 mL) and a solution of alcohols **34a/b** (51 mg, 0.058 mmol) in 1.9 mL DCM. The reaction mixture was heated at 40 °C for 6 h. Saturated aq. $NaHCO_3$ (2 mL) was added and the water phase was extracted with EtOAc (4x5 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was subjected to column chromatography (EtOAc/hexane) to yield 25.5 mg of diols **22a/b** (70% b.r.s.m., 75% conversion) as a colorless oil.

^{1}H-NMR (400 MHz, C_6D_6): δ = 6.05 (dd, *J* = 9.8, 1.0 Hz, 1H), 5.97 (ddd, *J* = 9.5, 6.7, 2.5 Hz, 1H), 5.67 (dd, *J* = 9.6, 2.4 Hz, 1H), 4.26 (d, *J* = 5.0 Hz, 1H), 4.21 (dd, *J* = 4.3, 4.3 Hz, 1H), 4.12 (ddd, *J* = 6.7, 5.0, 1.2 Hz, 1H), 4.07 (dd, *J* = 9.4, 3.9 Hz, 1H), 3.96 (dd, *J* = 10.4, 5.9 Hz, 1H), 3.80 (dd, *J* = 11.1, 2.6 Hz, 1H), 3.64 – 3.56 (m, 1H), 3.56 – 3.47 (m, 3H), 3.44 – 3.34 (m, 3H), 3.23 – 3.17 (m, 1H), 3.20 (s, 3H), 3.14 (s, 3H), 3.03 (s, 3H), 2.97 – 2.93 (m, 1H), 2.93 –

2.87 (m, 1H), 2.84 (d, *J* = 6.7 Hz, 1H), 2.72 (d, *J* = 9.4 Hz, 1H), 2.48 (d, *J* = 2.3 Hz, 1H), 2.44 – 2.31 (m, 2H), 1.97 (d, *J* = 0.9 Hz, 3H), 1.51 (d, *J* = 6.8 Hz, 3H), 0.99 (s, 9H), 0.98 (s, 9H), 0.97 (s, 9H), 0.29 (s, 3H), 0.21 (s, 3H), 0.10 (s, 3H), 0.04 (s, 3H), 0.00 (s, 3H), - 0.03 (s, 3H).

^{13}C-NMR (100.6 MHz, C_6D_6): δ = 134.0, 130.9, 129.7, 128.4, 91.7, 86.0, 76.2, 75.5, 73.7, 73.0, 72.6, 70.7, 70.0, 65.6, 58.7, 58.5, 58.4, 51.5, 45.7, 40.7, 40.1, 39.9, 37.4, 26.5, 26.2, 26.1, 18.6, 18.5, 18.4, 17.7, 17.6, - 3.2, - 3.7, - 4.3, - 4.5, - 5.2, - 5.3.

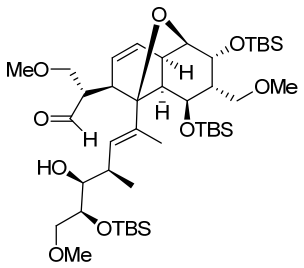
IR (film): 3511, 2926, 2855, 1472, 1462, 1388, 1360, 1251, 1196, 1116, 1085, 1024, 965, 911, 886, 836, 802, 776, 677, 595, 498, 436, 424, 420, 402 cm^{-1}.

HRMS (ESI): calc. for $C_{43}H_{84}O_9Si_3Na$ $[M + Na]^+$: 851.5321; found: 851.5311.

$[\alpha]_D^{20}$ = + 82.1 (c = 0.23, $CHCl_3$).

22b: **^{1}H-NMR** (400 MHz, C_6D_6): δ = 6.03 – 5.96 (m, 2H), 5.66 (dd, *J* = 9.7, 2.1 Hz, 1H), 4.30 (d, *J* = 5.0 Hz, 1H), 4.22 (ddd, *J* = 6.9, 5.9, 1.3 Hz, 1H), 4.16 (dd, *J* = 4.4, 4.4 Hz, 1H), 4.09 – 3.94 (m, 2H), 3.79 (dd, *J* = 11.1, 2.5 Hz, 1H), 3.56 – 3.46 (m, 4H), 3.43 (d, *J* = 1.2 Hz, 1H), 3.42 (s, 1H), 3.37 (dd, *J* = 9.1, 4.9 Hz, 1H), 3.32 (m, 1H), 3.20 (s, 3H), 3.20 (m, 1H), 3.10 (s, 3H), 3.09 (s, 3H), 3.09 (m, 1H), 2.96 – 2.90 (m, 1H), 2.87 (d, *J* = 6.9 Hz, 1H), 2.78 (d, *J* = 9.3 Hz, 1H), 2.59 (d, *J* = 2.2 Hz, 1H), 2.47 – 2.38 (m, 1H), 2.01 (d, *J* = 0.9 Hz, 3H), 1.52 (d, *J* = 6.7 Hz, 3H), 1.00 (s, 9H), 0.96 (s, 9H), 0.95 (s, 9H), 0.29 (s, 3H), 0.25 (s, 3H), 0.08 (s, 3H), - 0.01 (s, 3H), - 0.02 (s, 3H), - 0.08 (s, 3H).

^{13}C-NMR (100.6 MHz, C_6D_6): δ = 133.4, 131.2, 129.8, 128.4, 91.8, 86.6, 76.2, 75.8, 73.5, 72.9, 72.5, 70.6, 69.6, 61.3, 58.7, 58.6, 58.5, 51.7, 46.2, 41.7, 40.6, 40.2, 37.6, 26.4, 26.3, 26.1, 18.6, 18.5, 18.3, 17.6, 17.3, - 3.3, - 3.8, - 4.6, - 4.7, - 5.2, - 5.3.



Aldehyde (35a).

To diol **22a** (36 mg, 0.043 mmol) was added a solution of TEMPO (4.0 mg, 0.026 mmol) and $PhI(OAc)_2$ (70 mg, 0.217 mmol) in DCM (0.7 mL) and the mixture was stirred at rt for 2 h. Then a mixture EtOAc/hexanes (1:1, 2.5 mL) was added and the solution was passed through a short plug of silica gel (elution with EtOAc/hexanes 1:1). The fractions containing **35a** were

concentrated and subjected to column chromatography (EtOAc/toluene) to obtain aldehyde **35a** (33 mg, 92%) as a colorless oil.

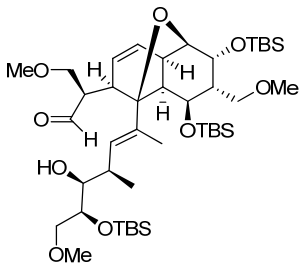
^{1}H-NMR (400 MHz, C_6D_6): δ = 10.09 (d, *J* = 2.3 Hz, 1H), 6.07 (d, *J* = 9.7 Hz, 1H), 5.97 (ddd, *J* = 9.3, 6.7, 2.3 Hz, 1H), 5.77 (dd, *J* = 9.6, 2.3 Hz, 1H), 4.24 (d, *J* = 5.0 Hz, 1H), 4.18 (dd, *J* = 4.3, 4.3 Hz, 1H), 4.09 (ddd, *J* = 5.8, 5.8, 1.5 Hz, 1H), 3.79 (dd, *J* = 11.0, 2.5 Hz, 1H), 3.57 (dd, *J* = 9.4, 5.1 Hz, 1H), 3.54 – 3.42 (m, 4H), 3.37 (d, *J* = 5.8 Hz, 2H), 3.28 (dd, *J* = 4.5, 2.2 Hz, 1H), 3.20 (s, 3H), 3.20 – 3.10 (m, 2H), 3.07 (s, 3H), 3.06 (s, 3H), 2.94 – 2.86 (m, 1H), 2.83 (d, *J* = 6.7 Hz, 1H), 2.70 (d, *J* = 8.9 Hz, 1H), 2.49 (d, *J* = 2.3 Hz, 1H), 1.95 (d, *J* = 0.8 Hz, 3H), 1.51 (d, *J* = 6.7 Hz, 3H), 0.98 (s, 9H), 0.97 (s, 9H), 0.96 (s, 9H), 0.23 (s, 3H), 0.20 (s, 3H), 0.09 (s, 3H), 0.01 (s, 3H), - 0.01 (s, 3H), - 0.06 (s, 3H).

^{13}C-NMR (100.6 MHz, C_6D_6): δ = 202.1, 133.3, 131.7, 130.8, 127.2, 91.0, 87.0, 76.1, 75.6, 72.8, 72.7, 70.6, 70.4, 69.7, 58.8, 58.6, 58.4, 51.2, 50.5, 46.6, 40.7, 39.9, 37.6, 26.4, 26.2, 26.1, 18.6, 18.5, 18.3, 17.5, 17.2, - 3.3, - 3.8, - 4.5, - 4.7, - 5.2, - 5.3.

IR (film): 3520, 2954, 2929, 2895, 2857, 1714, 1472, 1390, 1360, 1252, 1196, 1117, 1085, 1026, 966, 888, 837, 778, 680, 664, 595, 508, 483, 439, 430, 422, 418, 411, 404 cm^{-1}.

HRMS (ESI): calc. for $C_{43}H_{82}O_9Si_3Na$ $[M + Na]^+$: 849.5164; found: 849.5179.

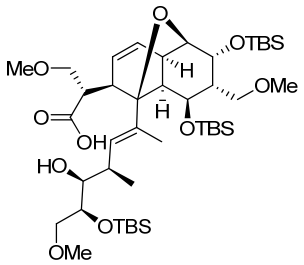
$[\alpha]_D^{20}$ = + 73.6 (c = 0.19, $CHCl_3$).



Aldehyde (35b).

^{1}H-NMR (400 MHz, C_6D_6): δ = 10.00 (d, *J* = 0.5 Hz, 1H), 6.08 (dd, *J* = 9.7, 0.8 Hz, 1H), 5.92 (ddd, *J* = 9.4, 6.7, 2.3 Hz, 1H), 5.53 (dd, *J* = 9.4, 2.3 Hz, 1H), 4.23 (d, *J* = 5.0 Hz, 1H), 4.20 – 4.17 (m, 1H), 4.13 (dd, *J* = 9.3, 4.4 Hz, 1H), 4.02 (ddd, *J* = 6.1, 6.1, 1.5 Hz, 1H), 3.78 (dd, *J* = 11.0, 2.5 Hz, 1H), 3.70 (dd, *J* = 9.2, 9.2 Hz, 1H), 3.58 – 3.49 (m, 4H), 3.36 (d, *J* = 6.0 Hz, 2H), 3.18 (s, 3H), 3.17 – 3.07 (m, 1H), 3.14 (s, 3H), 3.03 (s, 3H), 3.03 – 2.98 (m, 1H), 2.91 – 2.83 (m, 1H), 2.83 (d, *J* = 6.8 Hz, 1H), 2.61 (d, *J* = 9.3 Hz, 1H), 2.49 (d, *J* = 2.3 Hz, 1H), 1.92 (d, *J* = 0.8 Hz, 3H), 1.49 (d, *J* = 6.7 Hz, 3H), 0.96 (s, 9H), 0.95 (s, 9H), 0.94 (s, 9H), 0.19 (s, 3H), 0.17 (s, 3H), 0.09 (s, 3H), 0.01 (s, 3H), - 0.01 (s, 3H), - 0.04 (s, 3H).

^{13}C-NMR (100.6 MHz, C_6D_6): δ = 203.5, 133.6, 131.6, 130.3, 128.4, 91.2, 86.1, 75.7, 75.5, 72.9, 72.5, 70.6, 70.2, 69.9, 58.8, 58.5, 58.4, 51.5, 51.0, 43.8, 40.7, 39.9, 37.1, 26.4, 26.2, 26.1, 18.5, 18.5, 18.3, 17.4, 17.3, - 3.2, - 3.7, - 4.3, - 4.5, - 5.2, - 5.3.



Seco acid (23a).

To a solution of aldehyde **35a** (26 mg, 0.031 mmol) in *t*BuOH (0.9 mL) was added 2-methyl-2-butene (1.3 mL) and the mixture was cooled to 15 °C. A solution of $NaClO_2$ (80%, 39 mg, 0.35 mmol) and NaH_2PO_4*H_2O (78 mg, 0.57 mmol) in water (0.7 mL) was added and the mixture was stirred at 15 °C for 30 min. Chloroform (20 mL) was added and the organic phase was washed with water (2x4 mL). The combined aqueous phases were extracted with chloroform (4x15 mL) and the combined organic phases were washed with brine (10 mL), passed through a plug of cotton and concentrated *in vacuo*. The residue was subjected to column chromatography (EtOAc/hexanes/*i*PrOH) to afford 23.9 mg of seco acid **23a** (90%).

^{1}H-NMR (400 MHz, C_6D_6): δ = 6.00 (dd, *J* = 9.8, 1.0 Hz, 1H), 5.86 (ddd, *J* = 9.4, 6.6, 2.5 Hz, 1H), 5.70 (dd, *J* = 9.5, 2.3 Hz, 1H), 4.37 (d, *J* = 5.0 Hz, 1H), 4.11 (dd, *J* = 4.4, 4.4 Hz, 1H), 4.00 – 3.95 (m, 1H), 3.94 (dd, *J* = 9.6, 4.4 Hz, 1H), 3.74 (dd, *J* = 11.1, 2.5 Hz, 1H), 3.56 – 3.44 (m, 4H), 3.39 (dd, *J* = 2.2, 2.2 Hz, 1H), 3.36 – 3.30 (m, 2H), 3.27 (dd, *J* = 9.5, 6.5 Hz, 1H), 3.17 (s, 3H), 3.10 (s, 3H), 3.08 (s, 3H), 3.10 – 3.02 (m, 1H), 2.92 – 2.82 (m, 1H), 2.83 (d, *J* = 6.6 Hz, 1H), 2.51 (d, *J* =2.3 Hz, 1H), 2.00 (d, *J* = 0.9 Hz, 3H), 1.50 (d, *J* = 6.7 Hz, 3H), 0.96 (s, 9H), 0.94 (s, 9H), 0.92 (s, 9H), 0.20 (s, 3H), 0.16 (s, 3H), 0.05 (s, 3H), - 0.04 (s, 3H), - 0.05 (s, 3H), - 0.10 (s, 3H).

^{13}C-NMR (100.6 MHz, C_6D_6): δ = 170.9, 132.5, 130.4, 128.3, 126.9, 93.0, 87.1, 75.9, 75.1, 72.7, 72.4, 71.5, 70.3, 68.8, 58.8, 58.7, 58.5, 51.2, 44.8, 44.5, 40.8, 39.7, 38.0, 26.4, 26.1, 26.1, 18.5, 18.4, 18.2, 17.4, 16.9, - 3.3, - 4.0, - 4.6, - 5.0, - 5.3, - 5.4.

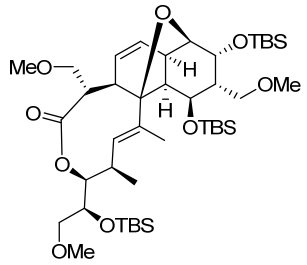
IR (film): 3546, 2953, 2929, 2894, 2858, 1735, 1707, 1472, 1462, 1388, 1361, 1253, 1116, 1085, 1027, 915, 862, 837, 776, 672, 495, 441, 424, 404 cm^{-1}.

HRMS (ESI): calc. for $C_{43}H_{82}O_{10}Si_3Na$ $[M + Na]^+$: 865.5114; found: 865.5110.

$[\alpha]_D^{20}$ = + 65.0 (c = 0.60, $CHCl_3$).

23b: **^{1}H-NMR** (400 MHz, C_6D_6): δ = 6.06 (d, *J* = 9.7 Hz, 1H), 5.95 (ddd, *J* = 9.1, 6.7, 2.1 Hz, 1H), 5.80 (dd, *J* = 4.4, 4.4 Hz, 1H), 4.24 – 4.18 (m, 2H), 4.12 – 4.06 (m, 2H), 3.78 (dd, *J* = 11.1, 2.4 Hz, 1H), 3.65 – 3.56 (m, 3H), 3.54 – 3.50 (m, 2H), 3.40 – 3.35 (m, 1H), 3.38 (dd, *J* = 6.1, 0.8 Hz, 1H), 3.27 – 3.21 (m, 1H), 3.18 (s, 3H), 3.17 – 3.09 (m, 1H), 3.05 (s, 3H), 2.98 (s, 3H), 2.96 – 2.86 (m, 1H), 2.82 (d, *J* = 6.9 Hz, 1H), 2.49 (d, *J* = 2.3 Hz, 1H), 1.99 (s, 3H), 1.49 (d, *J* = 6.7 Hz, 3H), 0.98 (s, 9H), 0.96 (s, 9H), 0.95 (s, 9H), 0.27 (s, 3H), 0.19 (s, 3H), 0.09 (s, 3H), 0.01 (s, 3H), - 0.01 (s, 3H), - 0.03 (s, 3H).

^{13}C-NMR (100.6 MHz, C_6D_6): δ = 172.8, 133.7, 131.5, 128.7, 128.3, 91.2, 86.0, 75.5, 75.1, 72.9, 72.3, 71.4, 70.6, 69.9,58.6, 58.4, 51.6, 44.3, 40.7, 39.7, 37.2, 30.2, 26.5, 26.2, 26.1, 18.5, 18.5, 18.3, 17.5, 17.4, - 4.4, - 4.3, -4.5, - 5.2, -5.2, -5.3.



Macrolactone (19).

To seco acid **23a** (6 mg, 0.007 mmol) was added a solution of 2,2´-dithiodipyridine (0.43M in toluene, 150 µL, 0.064 mmol) and a solution of PPh_3 (0.43M in toluene, 150 µL, 0.064 mmol), and the mixture was stirred at rt for 14 h. The resulting mixture was diluted by toluene (5 mL) and added *via* syringe pump to a solution of $AgClO_4$ (44 mg, 0.214 mmol) in toluene (15 mL) at 85 °C over 2 h. The resulting mixture was filtrated through a pad of celite and the filtrate was concentrated *in vacuo*. The residue was subjected to column chromatography (EtOAc/hexanes) to obtain lactone **19** (2.4 mg, 40 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.98 (ddd, *J* = 9.2, 7.0, 2.0 Hz, 1H), 5.66 (dd, *J* = 7.5, 1.0 Hz, 1H), 5.38 (dd, *J* = 9.8, 2.5 Hz, 1H), 4.95 (dd, *J* = 9.2, 6.2 Hz, 1H), 4.13 (ddd, *J* = 8.9, 7.1, 2.0 Hz, 1H), 4.03 – 3.97 (m, 2H), 3.69 (dd, *J* = 11.2, 1.8 Hz, 1H), 3.58 – 3.51 (m, 2H), 3.46 (dd, *J* = 8.6, 5.1 Hz, 1H), 3.41 – 3.33 (m, 2H), 3.33 – 3.25 (m, 1H), 3.31 (s, 3H), 3.29 (s, 3H), 3.24 (s, 3H), 3.07 (dm, *J* = 9.5 Hz, 1H), 3.03 – 2.94 (m, 1H), 2.85 – 2.77 (m, 1H), 2.69 (d, *J* = 7.0 Hz, 1H), 2.60 – 2.51 (m, 1H), 2.27 (s, 1H), 1.68 (s, 3H), 1.21 (d, *J* = 6.9 Hz, 3H), 0.90 (s, 18H), 0.89 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.03 (s, 6H).

^{13}C-NMR (150.9 MHz, $CDCl_3$): δ = 177.9, 138.5, 134.2, 131.2, 127.1, 89.1, 84.2, 80.7, 76.0, 73.7, 72.5, 71.1, 70.3, 69.2, 59.2, 58.7, 58.4, 52.4, 50.0, 46.3, 41.1, 40.1, 32.3, 29.9, 26.4, 26.3, 26.0, 18.6, 18.5, 18.2, 17.4, 15.8, -3.5, -3.6, -4.3, -4.9, -5.1, -5.2.

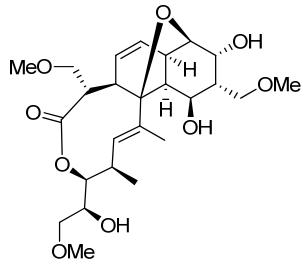
IR (film): 2955, 2929, 2857, 1721, 1472, 1389, 1361, 1252, 1211, 1116, 1084, 1057, 1031, 866, 837, 777, 668, 418, 404 cm^{-1}.

HRMS (ESI): calc. for $C_{43}H_{80}O_9Si_3Na$ $[M + Na]^+$: 847.5008; found: 847.5018.

$[\alpha]_D^{20}$ = + 173.3 (c = 0.05, $CHCl_3$).

24: **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 5.99 (ddd, *J* = 9.3, 6.8, 2.4 Hz, 1H), 5.74 (dd, *J* = 9.6, 1.0 Hz, 1H), 5.46 (dd, *J* = 9.4, 2.4 Hz, 1H), 4.98 (dd, *J* = 7.2, 5.1 Hz, 1H), 4.15 (dd, *J* = 10.1, 5.3 Hz, 1H), 4.06 – 3.98 (m, 2H), 3.95 (dd, *J* = 4.8, 3.9 Hz, 1H), 3.64 (dd, *J* = 11.3, 2.1 Hz, 1H), 3.50 – 3.47 (m, 2H), 3.44 (dd, *J* = 10.1, 2.0 Hz, 1H), 3.39 – 3.28 (m, 3H), 3.35 (s, 3H), 3.31 (s, 3H), 3.20 (s, 3H), 2.97 – 2.87 (m, 1H), 2.65 (d, *J* = 6.8 Hz, 1H), 2.62 – 2.56 (m, 1H), 2.55 – 2.46 (m, 1H), 2.30 (d, *J* = 2.0 Hz, 1H), 1.68 (d, *J* = 1.0 Hz, 3H), 1.19 (d, *J* = 7.0 Hz, 3H), 0.92 (s, 9H), 0.90 (s, 9H), 0.88 (s, 9H), 0.1 (s, 3H), 0.09 (s, 3H), 0.06 (s, 6H), 0.05 (s, 3H), 0.01 (s, 3H).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 174.6, 135.6, 134.3, 131.1, 130.8, 90.7, 85.2, 79.1, 75.8, 72.3, 71.9, 70.1, 69.4, 68.8, 59.2, 58.6, 58.2, 52.8, 51.3, 50.5, 40.7, 39.9, 32.6, 26.5, 26.2, 26.0, 18.5, 18.5, 18.2, 17.3, 15.5, -3.4, -3.7, -4.3, -5.0, -5.2.



Branimycin (1).

To a stirred solution of lactone **19** (1.6 mg, 0.002 mmol) in THF (0.15 mL) was added TBAF (1M in THF, 35µL) dropwise. The reaction mixture was then stirred for 14 h. The resulting mixture was diluted with THF and the reaction was quenched by addition of aq. saturated NH_4Cl. The water phase was extracted with EtOAc (4x1 mL), the combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude product was subjected to column chromatography (CCl_4/*i*PrOH) to yield Branimycin **(1)** (0.8 mg, 85%) as a colorless oil.

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 6.05 (ddd, *J* = 9.6, 7.2, 2.0 Hz, 1H), 5.68 (dd, *J* = 8.0, 1.2 Hz, 1H), 5.39 (dd, *J* = 9.7, 2.2 Hz, 1H), 5.04 (dd, *J* = 10.0, 6.7 Hz, 1H), 4.12 – 4.04 (m, 3H), 4.02 (ddd, *J* = 11.1, 5.3, 2.9 Hz, 1H), 3.78 (dd, *J* = 9.6, 4.6 Hz, 1H), 3.64 (dd, *J* = 9.6, 5.2 Hz, 1H), 3.59 – 3.54 (m, 2H), 3.48 (dd, *J* = 8.5, 4.8 Hz, 1H), 3.42 – 3.39 (m, 1H), 3.40 (s, 3H), 3.36 (s, 3H), 3.32 (s, 3H), 3.06 – 3.03 (m, 2H), 2.99 (d, *J* = 2.6 Hz, 1H), 2.91 – 2.84 (m, 1H), 2.72 (d, *J* = 7.2 Hz, 1H), 2.49 (d, *J* = 4.3 Hz, 1H), 2.48 (d, *J* = 2.5 Hz, 1H), 2.32 – 2.27 (m, 1H), 2.09 (d, *J* = 5.5 Hz, 1H), 1.69 (d, *J* = 0.9 Hz, 3H), 1.27 (d, *J* = 7.0 Hz, 3H).

^{13}C-NMR (150.9 MHz, $CDCl_3$): δ = 177.6, 138.7, 133.8, 131.5, 126.8, 88.7, 84.0, 79.4, 74.6, 73.7, 73.3, 72.0, 71.9, 68.1, 59.4, 59.3, 59.3, 51.8, 48.3, 46.2, 40.4, 38.6, 32.5, 17.0, 15.4.

IR (film): 3455, 2930, 1725, 1651, 1540, 1375, 1224, 1118, 944, 886, 874, 793, 685, 672, 668, 425, 421, 413 cm^{-1}.

HRMS (ESI): calc. for $C_{25}H_{38}O_9Na$ $[M + Na]^+$: 505.2414; found: 505.2420.

$[\alpha]_D^{25}$ = + 88.0 (*c* = 0.04, $CHCl_3$).

R_f = 0.27 ($CHCl_3$/5% MeOH), 0.22 (CCl_4/12.5% *i*PrOH), 0.35 (DCM/10% *i*PrOH).

25: **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 6.08 (ddd, *J* = 9.5, 6.8, 2.2 Hz, 1H), 5.66 (dd, *J* = 9.8, 1.1 Hz, 1H), 5.49 (dd, *J* = 9.6, 2.2 Hz, 1H), 5.04 (dd, *J* = 8.4, 2.8 Hz, 1H), 4.17 – 4.10 (m, 2H), 4.08 – 3.97 (m, 3H), 3.75 (dd, *J* = 9.6, 4.6 Hz, 1H), 3.63 (dd, *J* = 9.6, 5.2 Hz, 1H), 3.50 – 3.41 (m, 3H), 3.41 – 3.37 (m, 1H), 3.40 (s, 3H), 3.35 (s, 3H), 3.32 (s, 3H), 3.06 – 2.97 (m, 1H), 2.92 (d, *J* = 2.7 Hz, 1H), 2.71 (d, *J* = 7.0 Hz, 1H), 2.67 (dm, *J* = 10.4 Hz, 1H), 2.54 (d, *J* = 2.7 Hz, 1H), 2.27 – 2.20 (m, 1H), 2.18 – 2.12 (m, 1H), 2.08 (d, *J* = 5.5 Hz, 1H), 1.72 (d, *J* = 0.8 Hz, 3H), 1.29 (d, *J* = 7.0 Hz, 3H).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 177.6, 137.9, 136.8, 134.9, 130.0, 88.8, 82.9, 79.0, 74.9, 73.7, 73.4, 72.1, 71.9, 70.0, 59.5, 59.3, 58.8, 52.2, 48.9, 45.4, 40.6, 38.5, 33.0, 17.1, 15.6.

Comparison of the ^{1}H- and ^{13}C-NMR Data of Natural and Synthetic Branimycin.

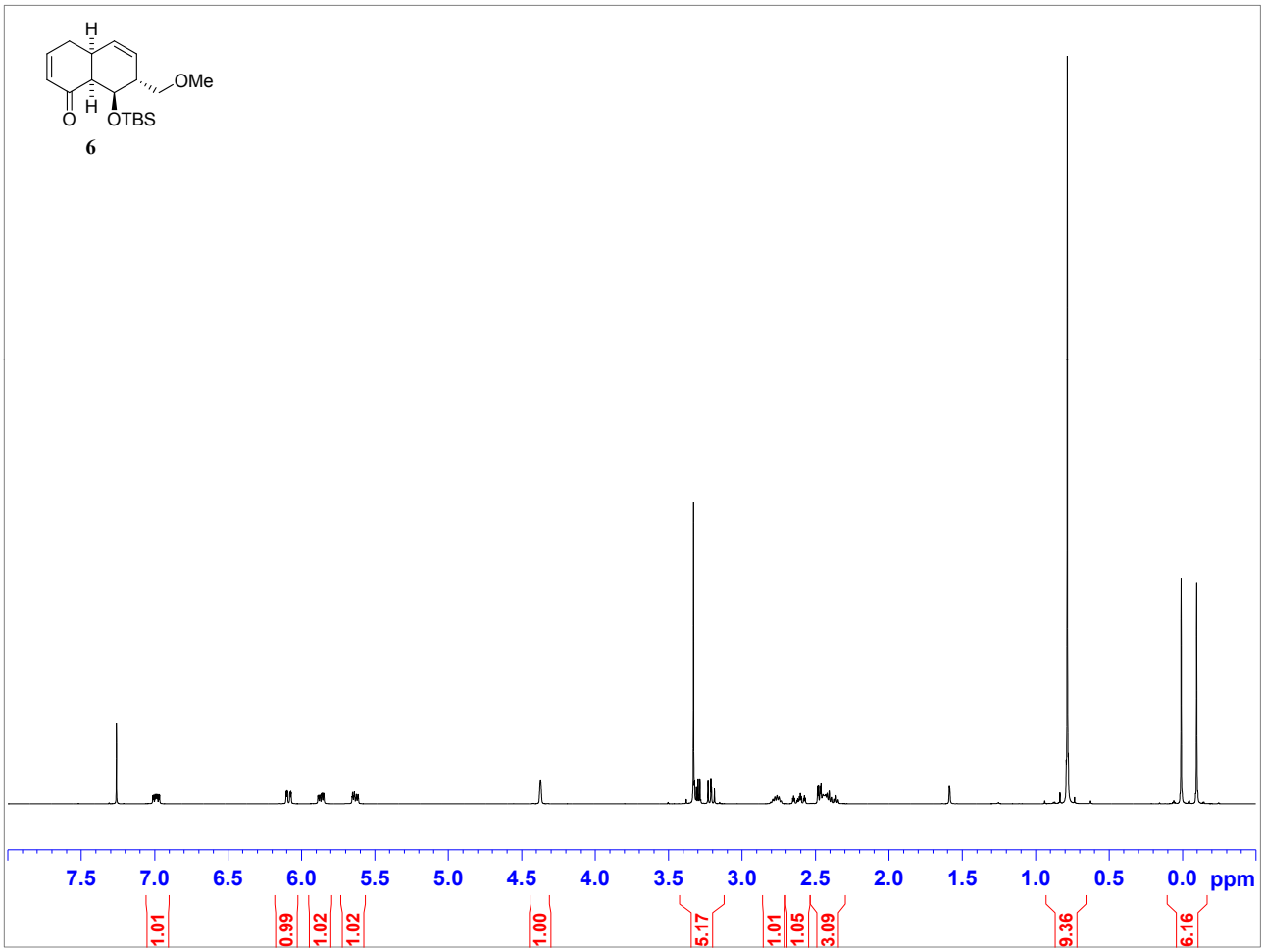
^{1}H-NMR (600 MHz, $CDCl_3$)		^{13}C-NMR (150.9 MHz, $CDCl_3$)	
Synthetic	Natural	Synthetic	Natural
6.05 (ddd, *J* = 9.6, 7.2, 2.0 Hz, 5-H)	6.05 (ddd, *J* = 9.5, 7.1, 2.0 Hz, 5-H)	177.6 (C-1)	177.6 (C-1)
5.68 (dd, *J* = 8.0, 1.2 Hz, 14-H)	5.68 (d, *J* = 8.1 Hz, 14-H)	138.7 (C-14)	138.7 (C-14)
5.39 (dd, *J* = 9.7, 2.2 Hz, 4-H)	5.38 (dd, *J* = 9.9, 2.3 Hz, 4-H)	133.8 (C-13)	133.7 (C-13)
5.04 (dd, *J* = 10.0, 6.7 Hz, 16-H)	5.04 (dd, *J* = 9.9, 6.8 Hz, 16-H)	131.5 (C-5)	131.5 (C-5)
4.12 – 4.04 (m, 7-H, 8-H, 17-H)	4.12 – 3.99 (m, 7-H, 8-H, 17-H, 10-H)	126.8 (C-4)	126.8 (C-4)
4.02 (ddd, *J* = 11.1, 5.3, 2.9 Hz, 10-H)		88.7 (C-12)	88.7 (C-12)
3.78 (dd, *J* = 9.6, 4.6 Hz, 9-CH_a)	3.78 (dd, *J* = 9.7, 4.7 Hz, 9-CH_a)	84.0 (C-7)	84.0 (C-7)
3.64 (dd, *J* = 9.6, 5.2 Hz, 9-CH_b)	3.64 (dd, *J* = 9.5, 5.1 Hz, 9-CH_b)	79.4 (C-16)	79.5 (C-16)
3.59 – 3.54 (m, 18-CH_a, 2-CH_a)	3.58 – 3.54 (m, 18-CH_a, 2-CH_a)	74.6 (C-18)	74.6 (C-18)
3.48 (dd, *J* = 8.5, 4.8 Hz, 2-CH_b)	3.48 (dd, *J* = 8.4, 4.6 Hz, 2-CH_b)	73.7 (2-CH_2)	73.7 (2-CH_2)
3.42 – 3.39 (m, 18-CH_b)	3.43 – 3.38 (m, 18-CH_b)	73.3 (9-CH_2)	73.3 (9-CH_2)
3.40 (s, 18-OCH_3)	3.40 (s, 18-OCH_3)	72.0 (C-10)	72.1 (C-10)
3.36 (s, 9-OCH_3)	3.36 (s, 9-OCH_3)	71.9 (C-8)	71.9 (C-8)
3.32 (s, 2-OCH_3)	3.32 (s, 2-OCH_3)	68.1 (C-17)	68.1 (C-17)
3.06 – 3.03 (m, 2-H, 3-H)	3.06 – 3.02 (m, 2-H, 3-H)	59.4 (9-OCH_3)	59.4 (9-OCH_3)
2.99 (d, *J* = 2.6 Hz, 8-OH)	3.00 (d, *J* = 2.1 Hz, 8-OH)	59.3(18-OCH_3)	59.3(18-OCH_3)
2.91 – 2.84 (m, 15-H)	2.91 – 2.84 (m, 15-H)	59.3 (2-OCH_3)	59.3 (2-OCH_3)
2.72 (d, *J* = 7.2 Hz, 6-H)	2.72 (d, *J* = 7.0 Hz, 6-H)	51.8 (C-3)	51.7 (C-3)
2.49 (d, *J* = 4.3 Hz, 17-OH)	2.50 (d, *J* = 4.0 Hz, 17-OH)	48.3 (C-11)	48.3 (C-11)
2.48 (d, *J* = 2.5 Hz, 11-H)	2.48 (d, *J* = 2.7 Hz, 11-H)	46.2 (C-2)	46.2 (C-2)
2.32 – 2.27 (m, 9-H)	2.32 – 2.26 (m, 9-H)	40.4 (C-9)	40.5 (C-9)
2.09 (d, *J* = 5.5 Hz, 10-OH)	2.09 (d, *J* = 5.5 Hz, 10-OH)	38.6 (C-6)	38.6 (C-6)
1.69 (d, *J* = 0.9 Hz, 13-CH_3)	1.69 (d, *J* = 0.8 Hz, 13-CH_3)	32.5 (C-15)	32.5 (C-15)
1.27 (d, *J* = 7.0 Hz, 15-CH_3)	1.27 (d, *J* = 7.0 Hz, 15-CH_3)	17.0 (13-CH_3)	17.0 (13-CH_3)
		15.4 (15-CH_3)	15.4 (15-CH_3)

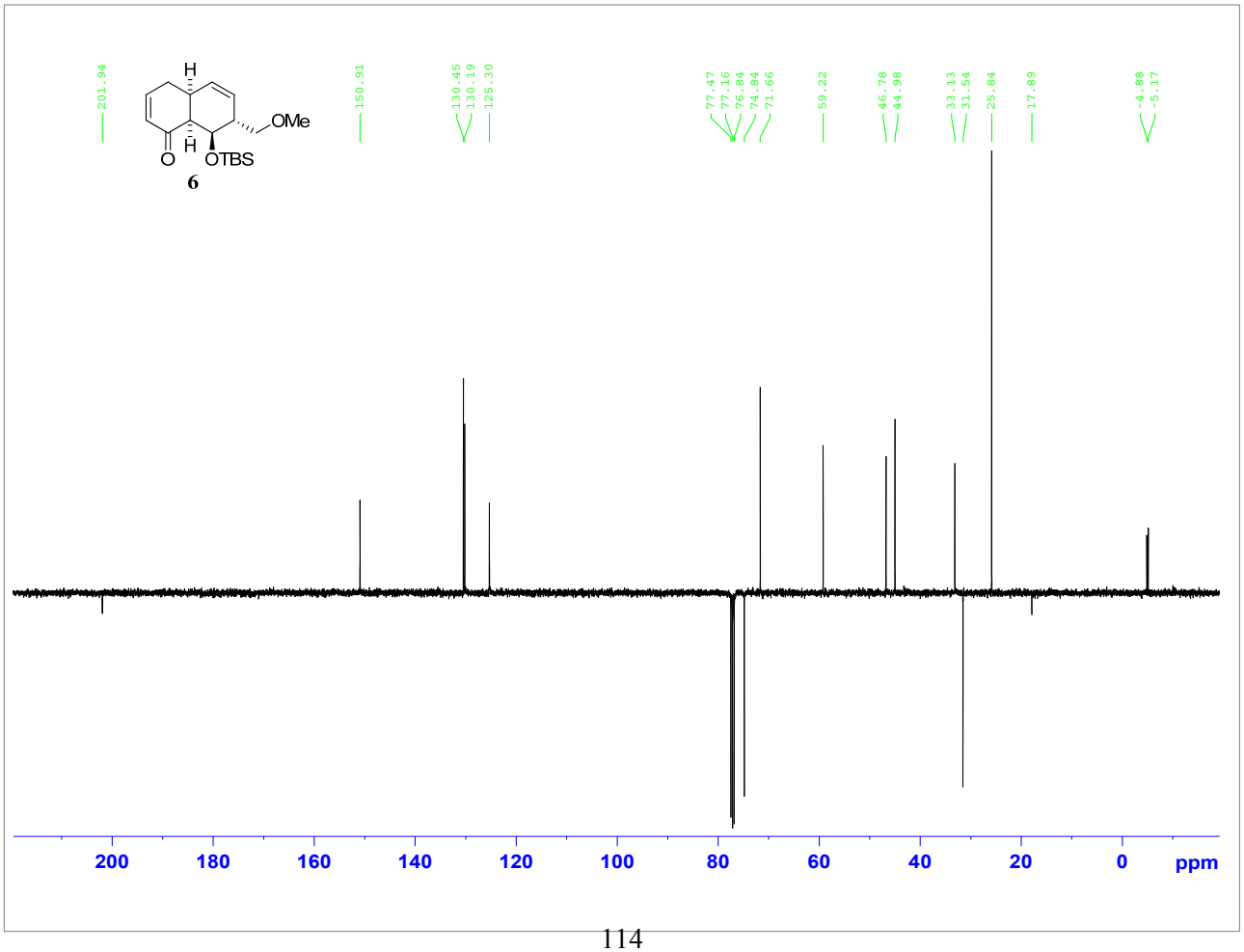
Total Synthesis of the Antibiotic Branimycin

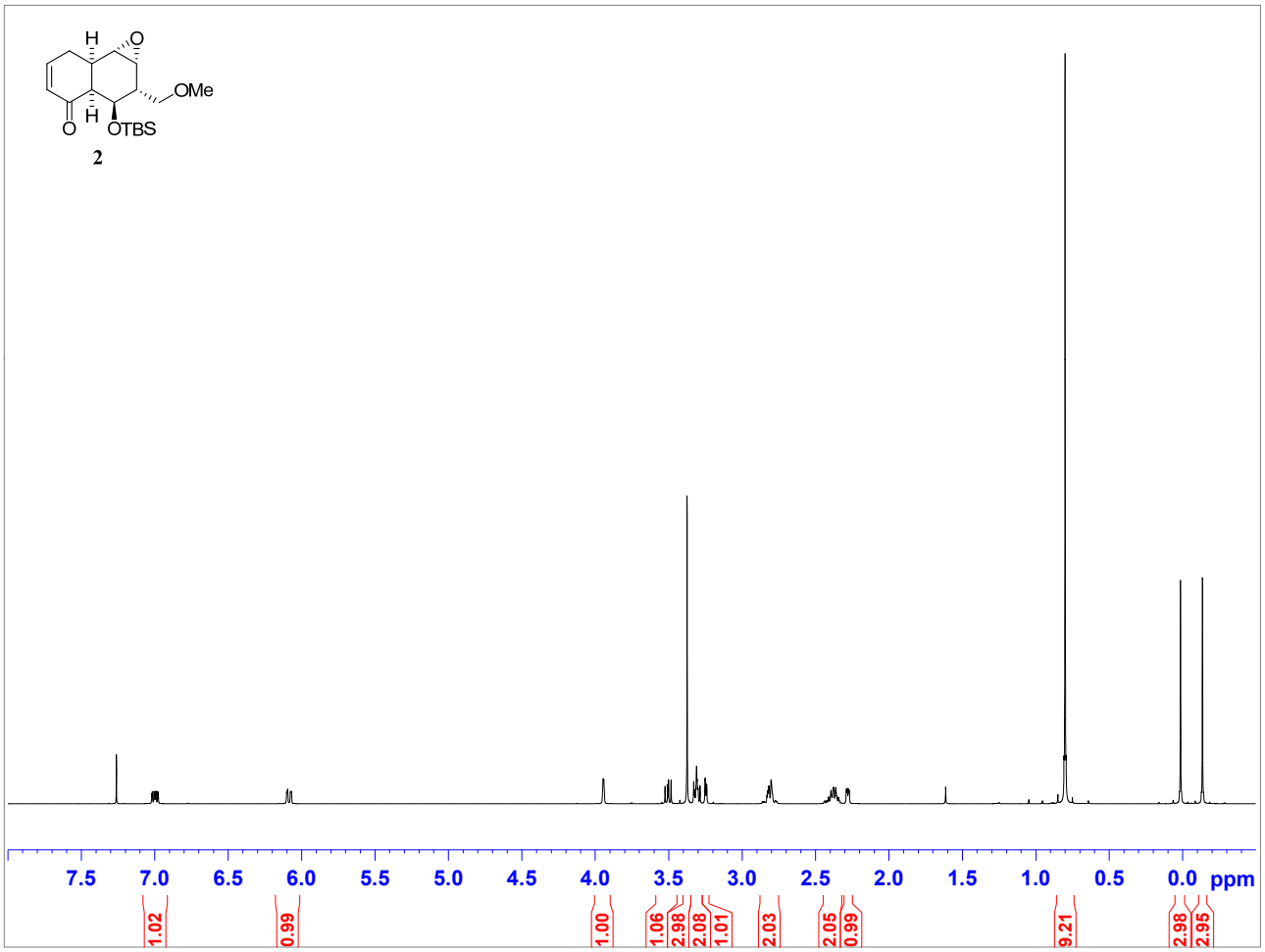
Supporting Information (^{1}H and ^{13}C NMR)

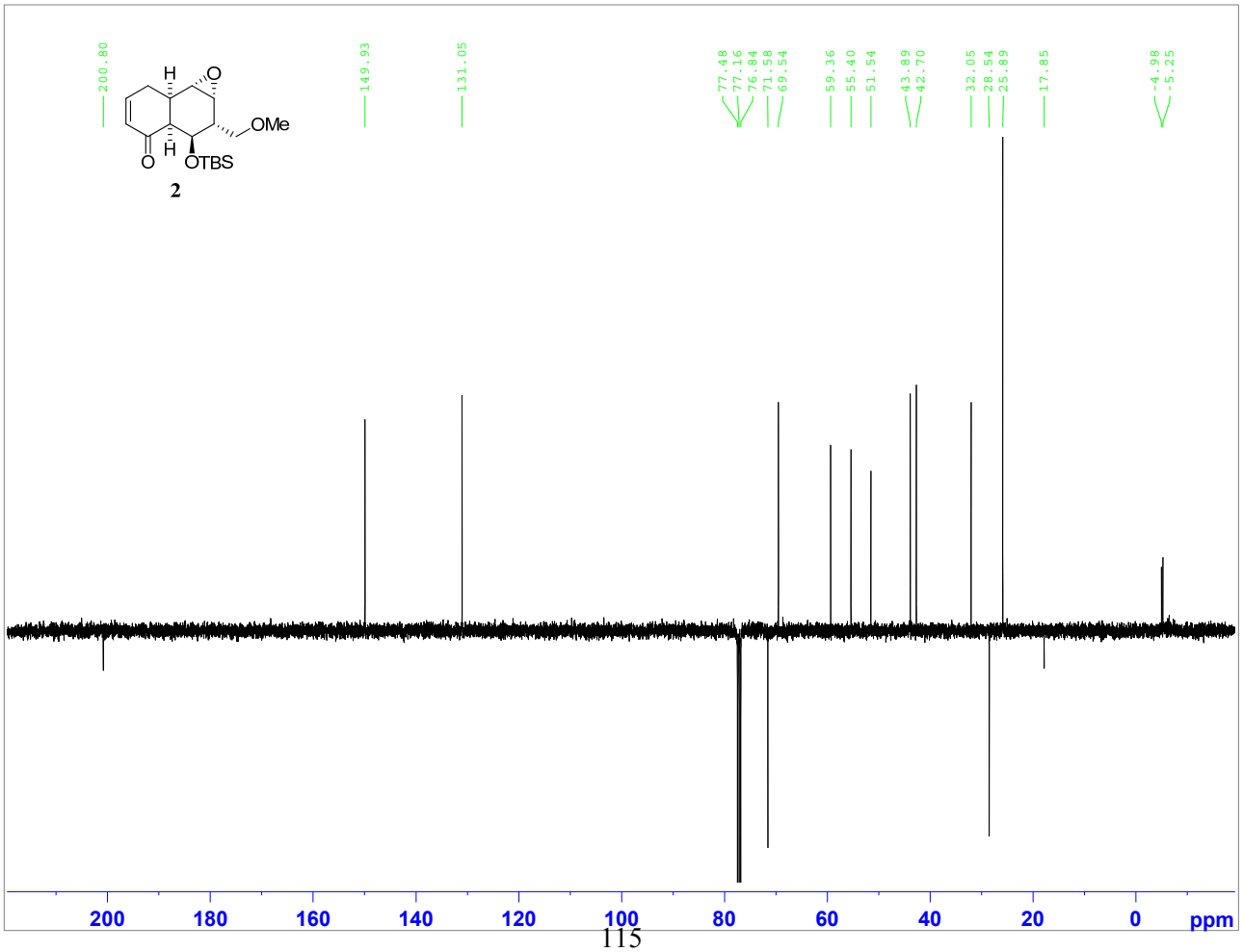
Stefan Marchart*, Alexey Gromov and Johann Mulzer*

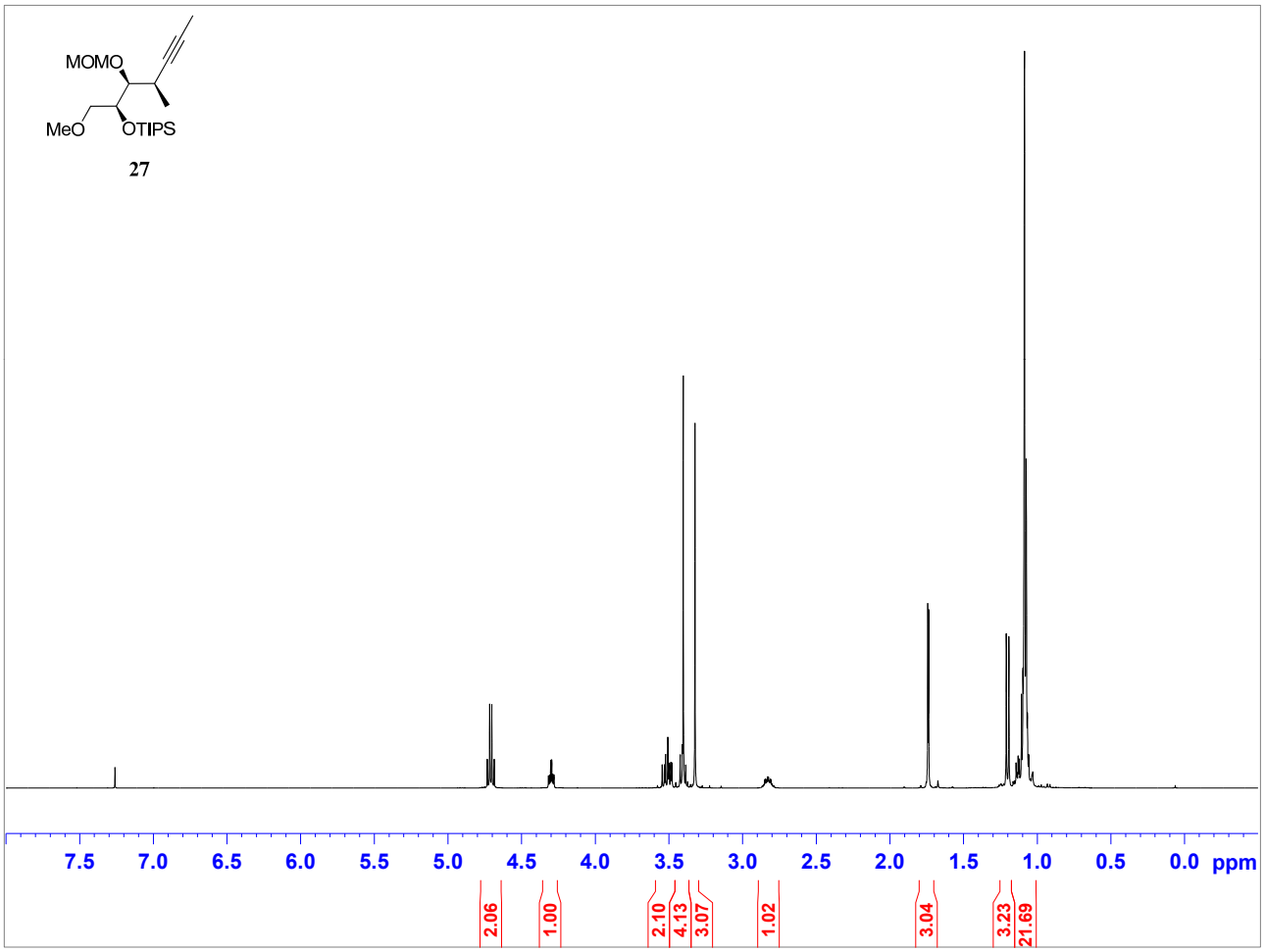
Institute of Organic Chemistry, University of Vienna,
Waehringerstr. 38, A-1090 Vienna, Austria

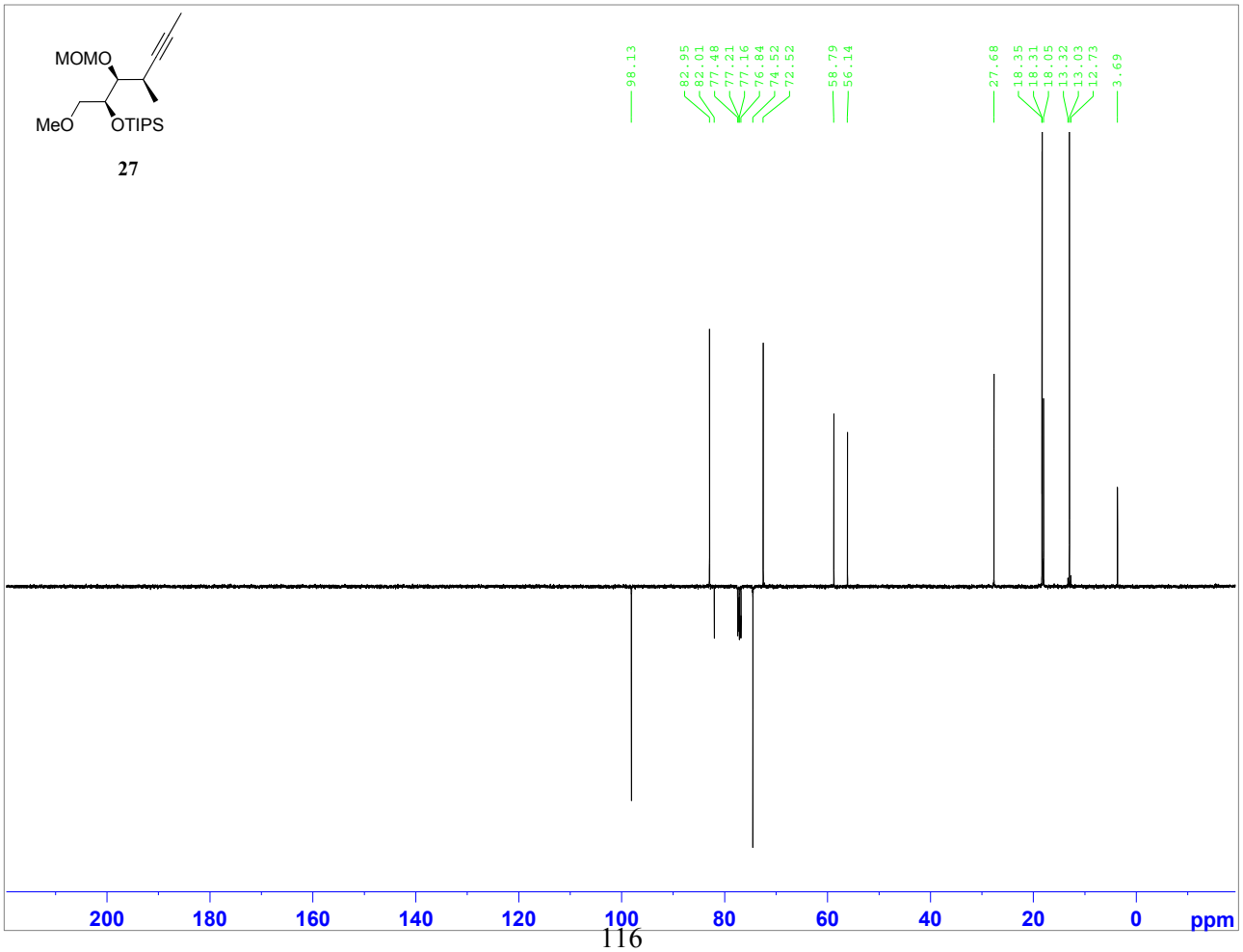

H
OMe
O
H
OTBS
6
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
1.01 0.99 1.02 1.02 1.00 5.17 1.01 1.05 3.09 9.36 6.16

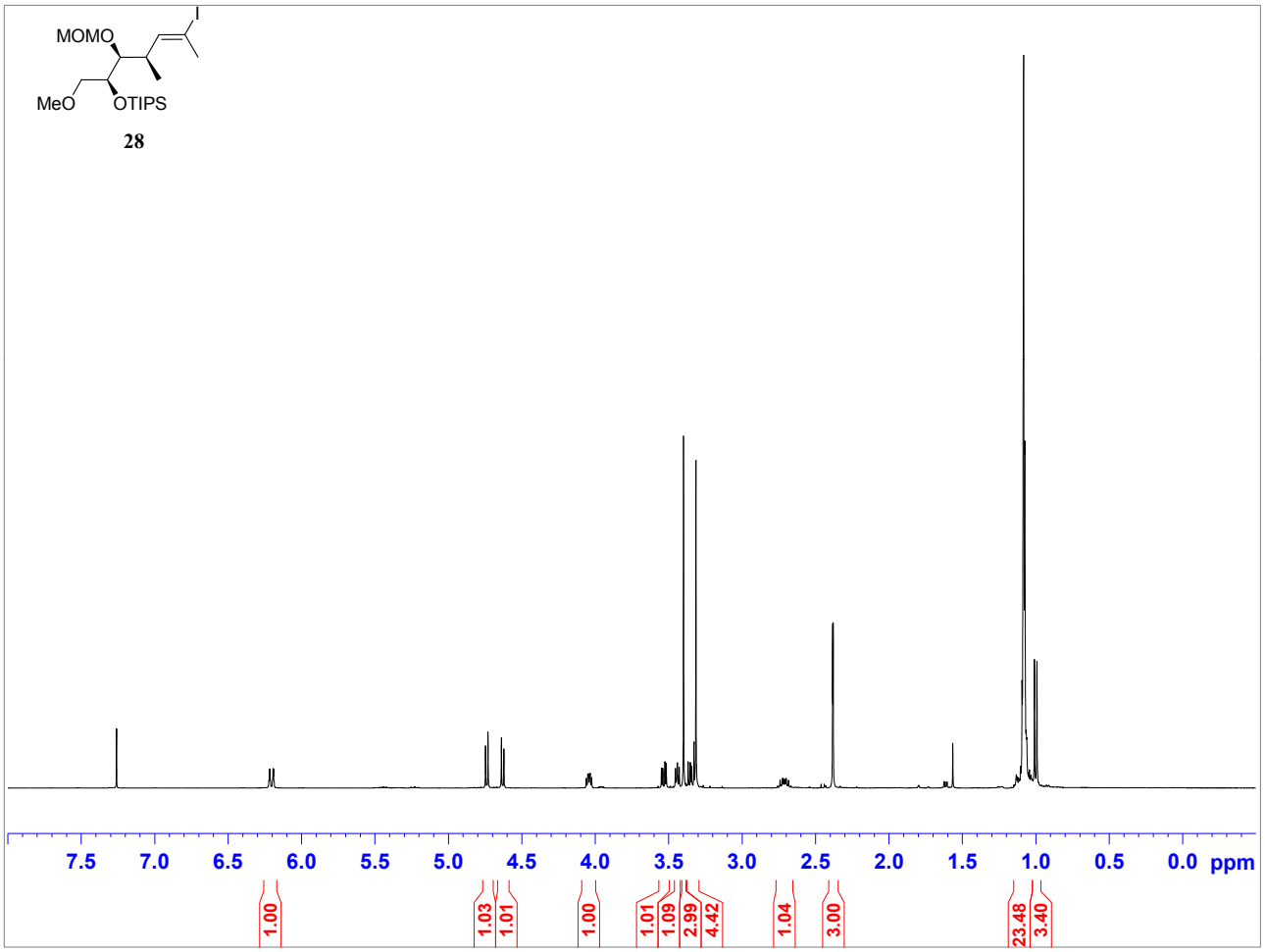

201.94
150.91
130.45
130.19
125.30
77.47
77.16
76.84
74.84
71.66
59.22
46.78
44.98
33.13
31.54
25.84
17.89
-4.88
-5.17
H
OMe
O
H
OTBS
6
200 180 160 140 120 100 80 60 40 20 0 ppm

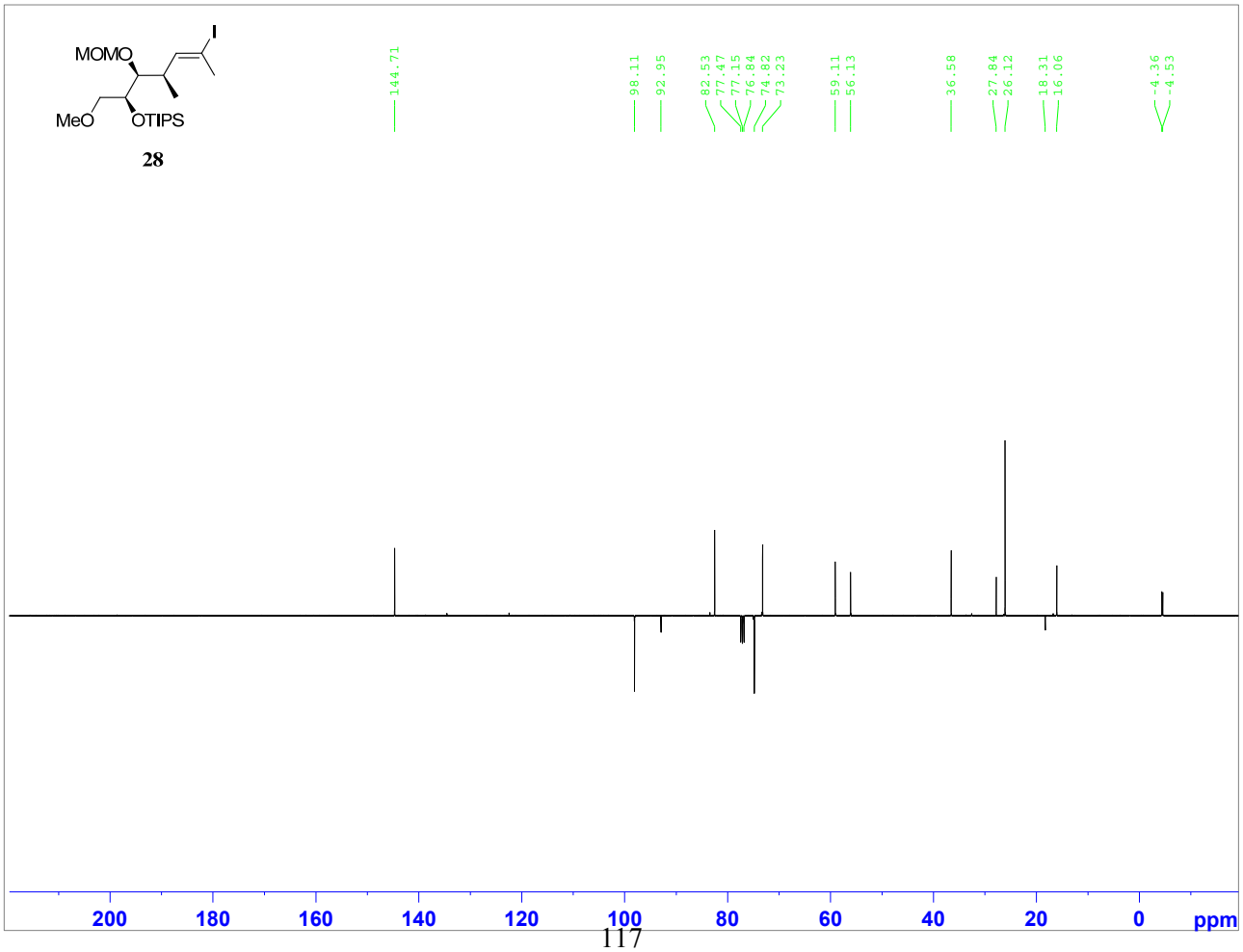

H
O
OMe
H
O
OTBS
2
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.02
0.99
1.00
1.06
2.98
2.08
1.01
2.03
2.05
0.99
9.21
2.98
2.95

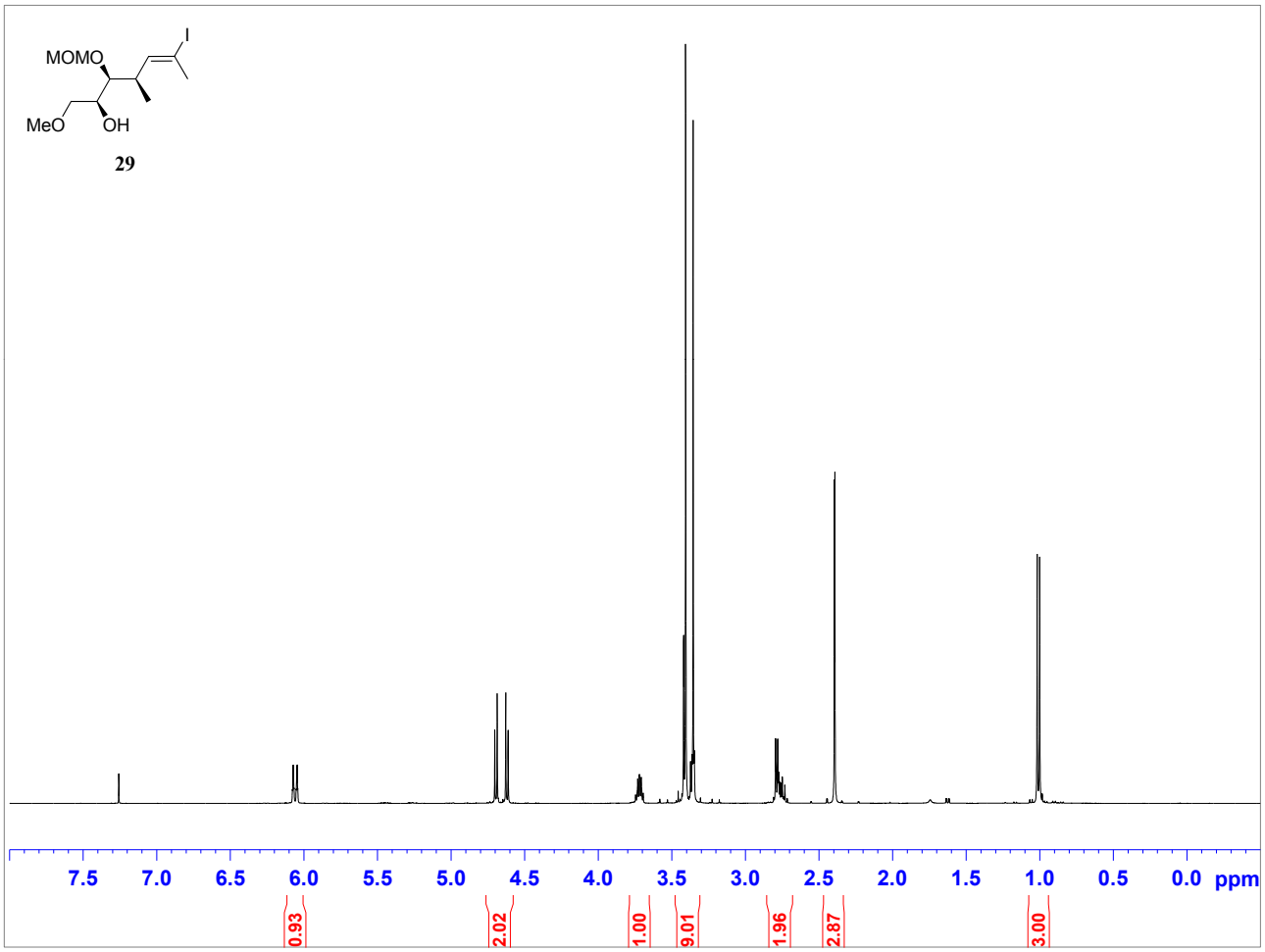

200.80
149.93
131.05
77.48
77.16
76.84
71.58
69.54
59.36
55.40
51.54
43.89
42.70
32.05
28.54
25.89
17.85
-4.98
-5.25
H
O
OMe
H
O
OTBS
2
200
180
160
140
120
100
80
60
40
20
0
ppm

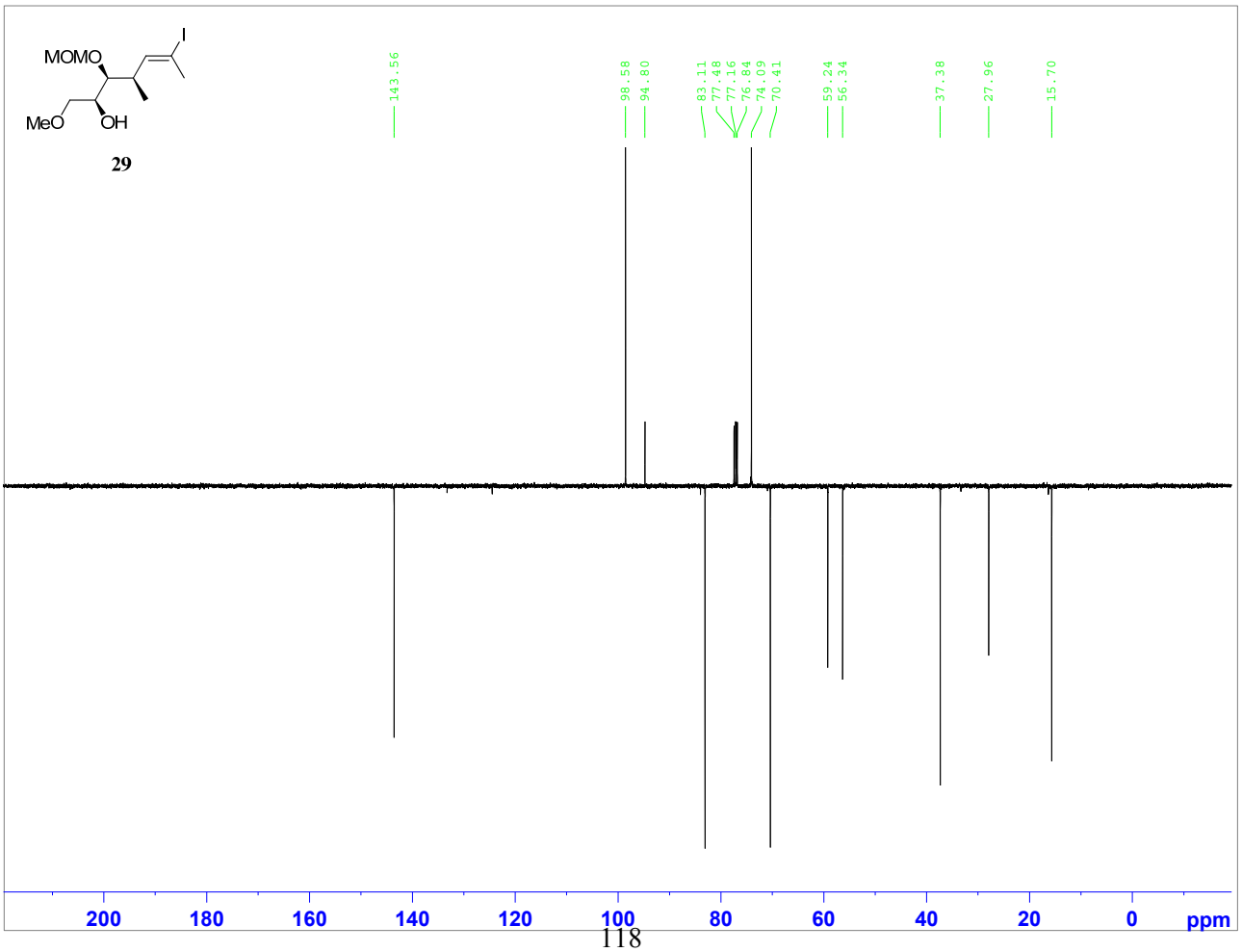

MOMO
MeO
OTIPS
27
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
2.06
1.00
2.10
4.13
3.07
1.02
3.04
3.23
21.69

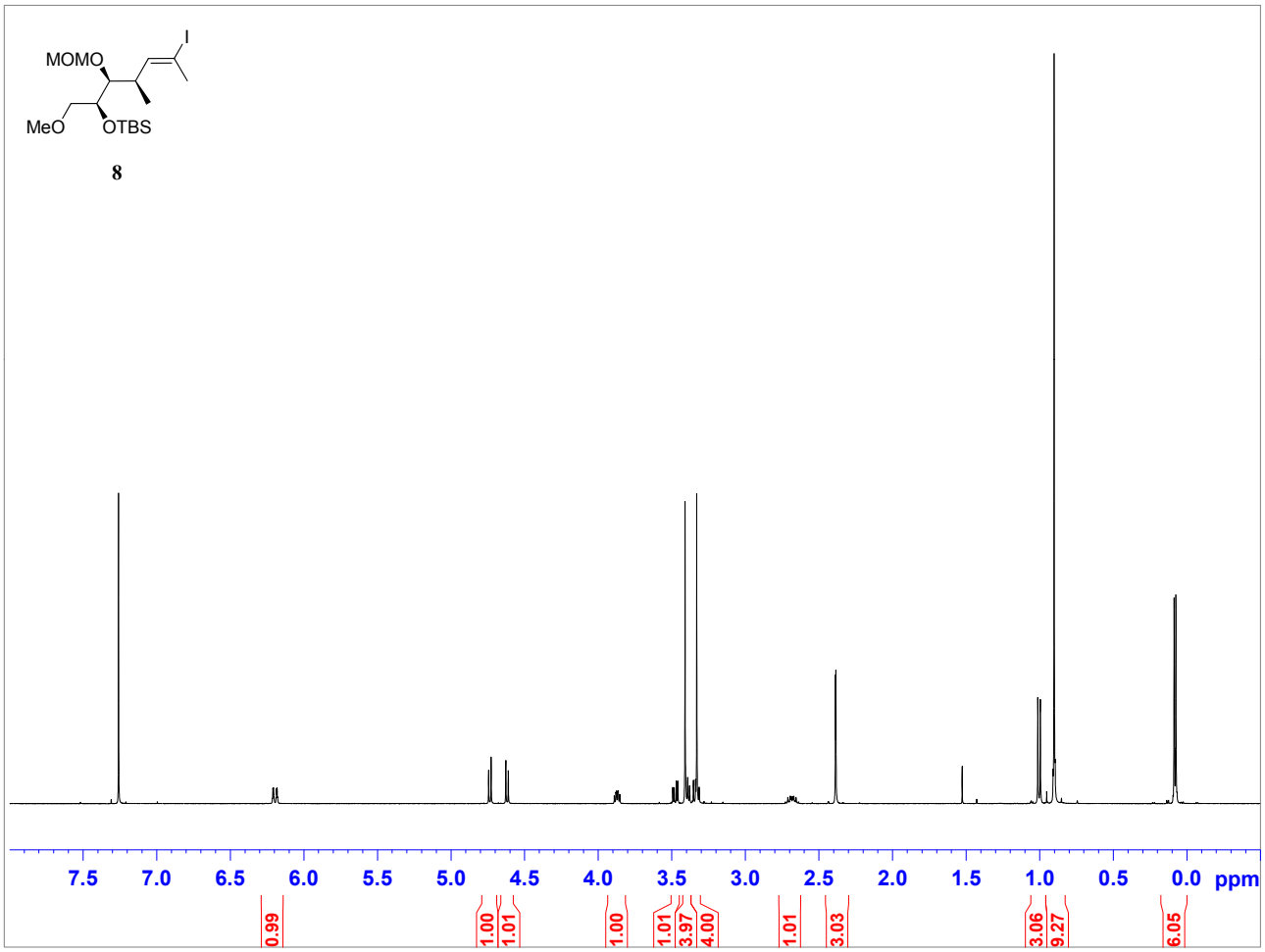

MOMO
MeO
OTIPS
27
98.13
82.95
82.01
77.48
77.21
77.16
76.84
74.52
72.52
58.79
56.14
27.68
18.35
18.31
18.05
13.32
13.03
12.73
3.69
200
180
160
140
120
100
80
60
40
20
0
ppm

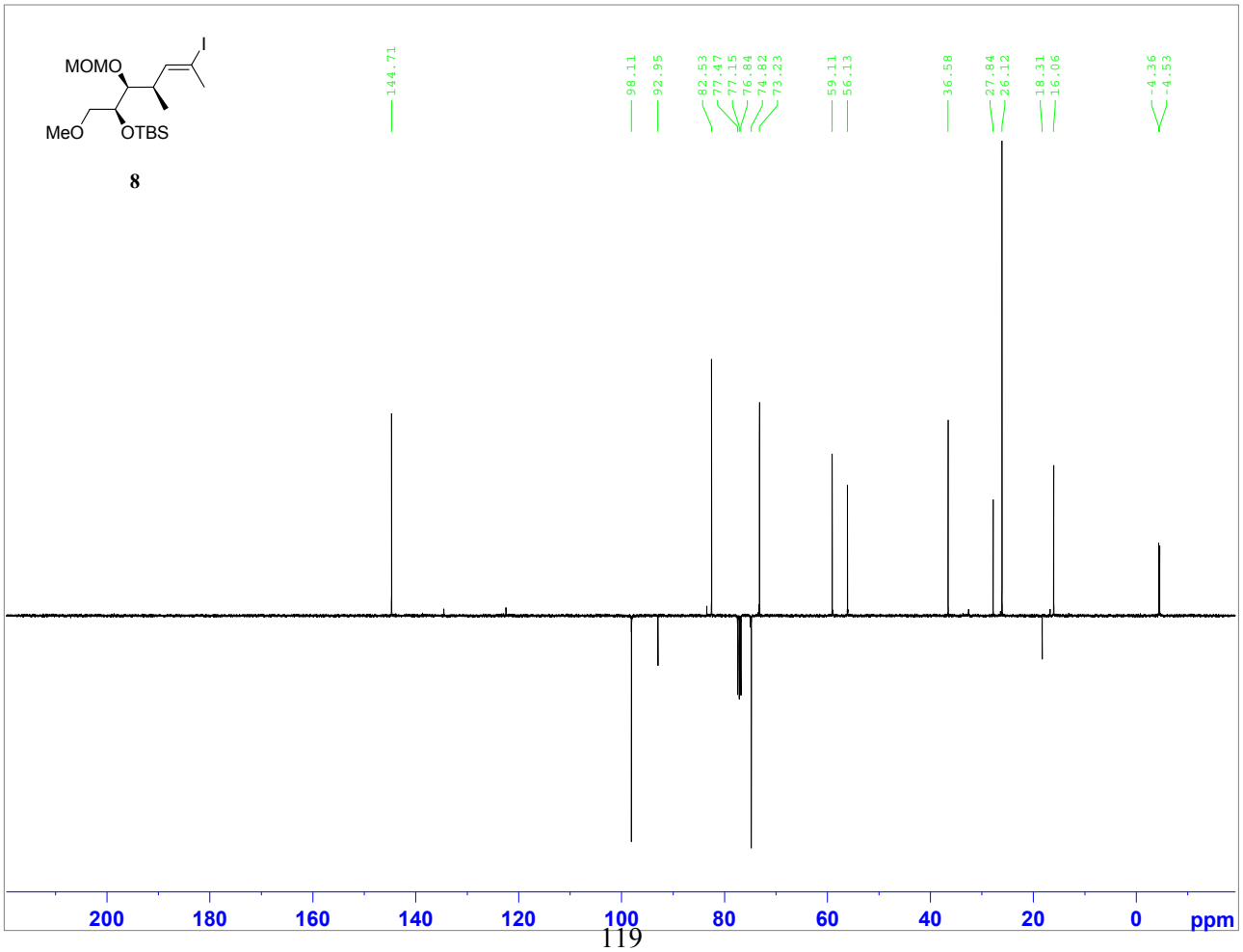

MOMO
MeO
OTIPS
28
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
1.00
1.03
1.01
1.00
1.01
1.09
2.99
4.42
1.04
3.00
23.48
3.40

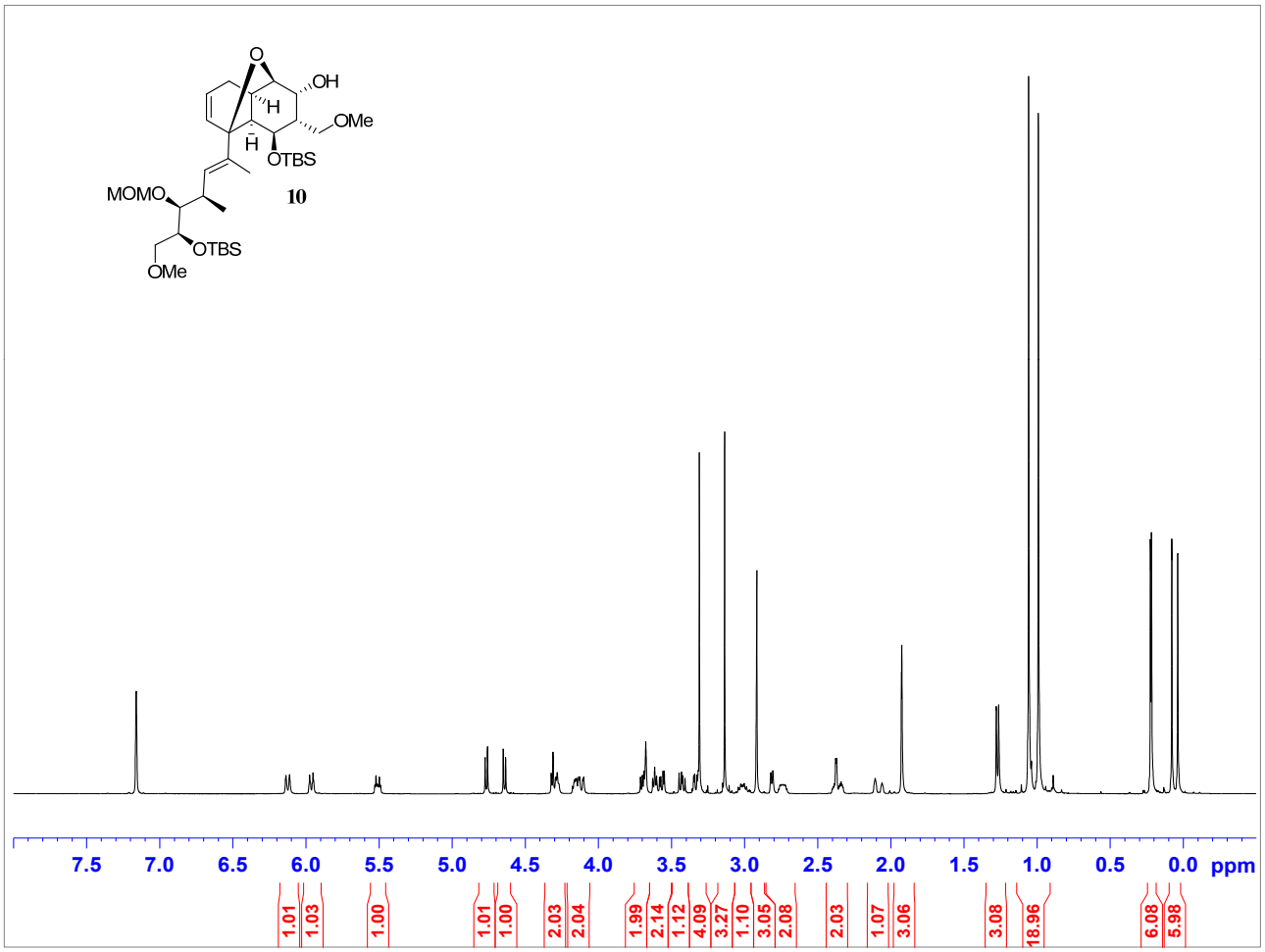

MOMO
MeO
OTIPS
28
144.71
98.11
92.95
82.53
77.47
77.15
76.84
74.82
73.23
59.11
56.13
36.58
27.84
26.12
18.31
16.06
-4.36
-4.53
200 180 160 140 120 100 80 60 40 20 0 ppm

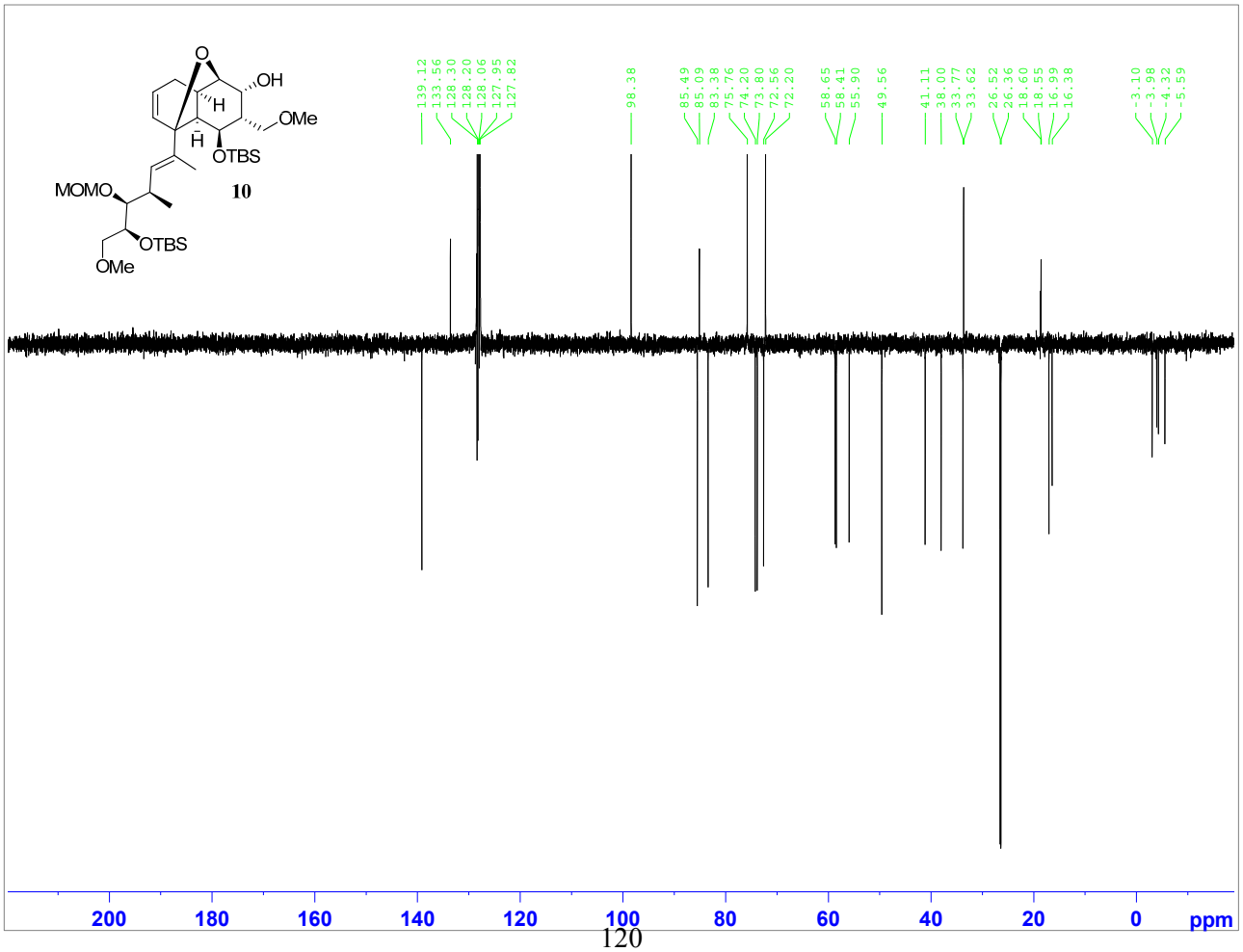

MOMO
MeO
OH
I
29
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
0.93
2.02
1.00
9.01
1.96
2.87
3.00

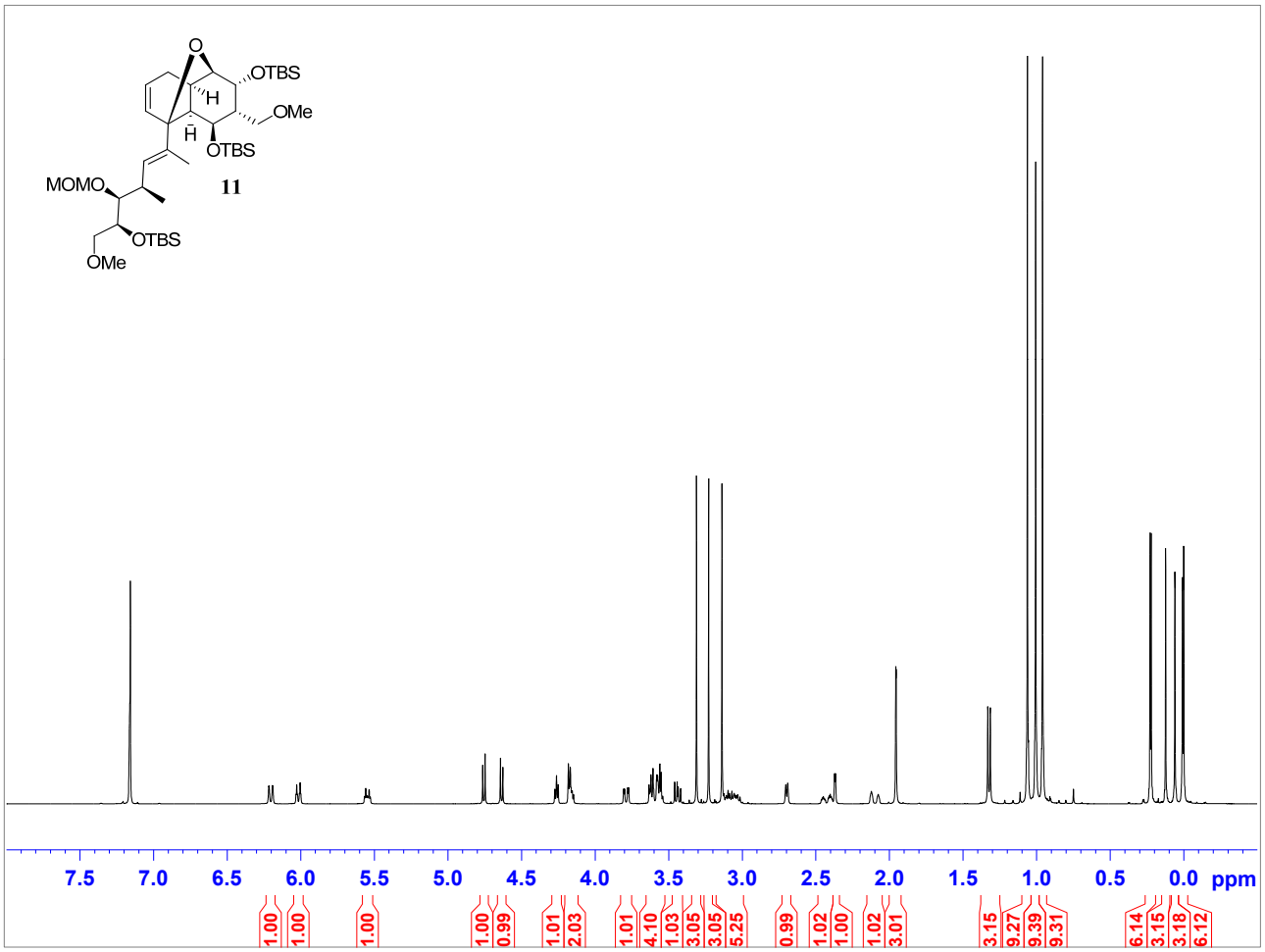

MOMO
MeO
OH
I
29
143.56
98.58
94.80
83.11
77.48
77.16
76.84
74.09
70.41
59.24
56.34
37.38
27.96
15.70
200
180
160
140
120
100
80
60
40
20
0
ppm

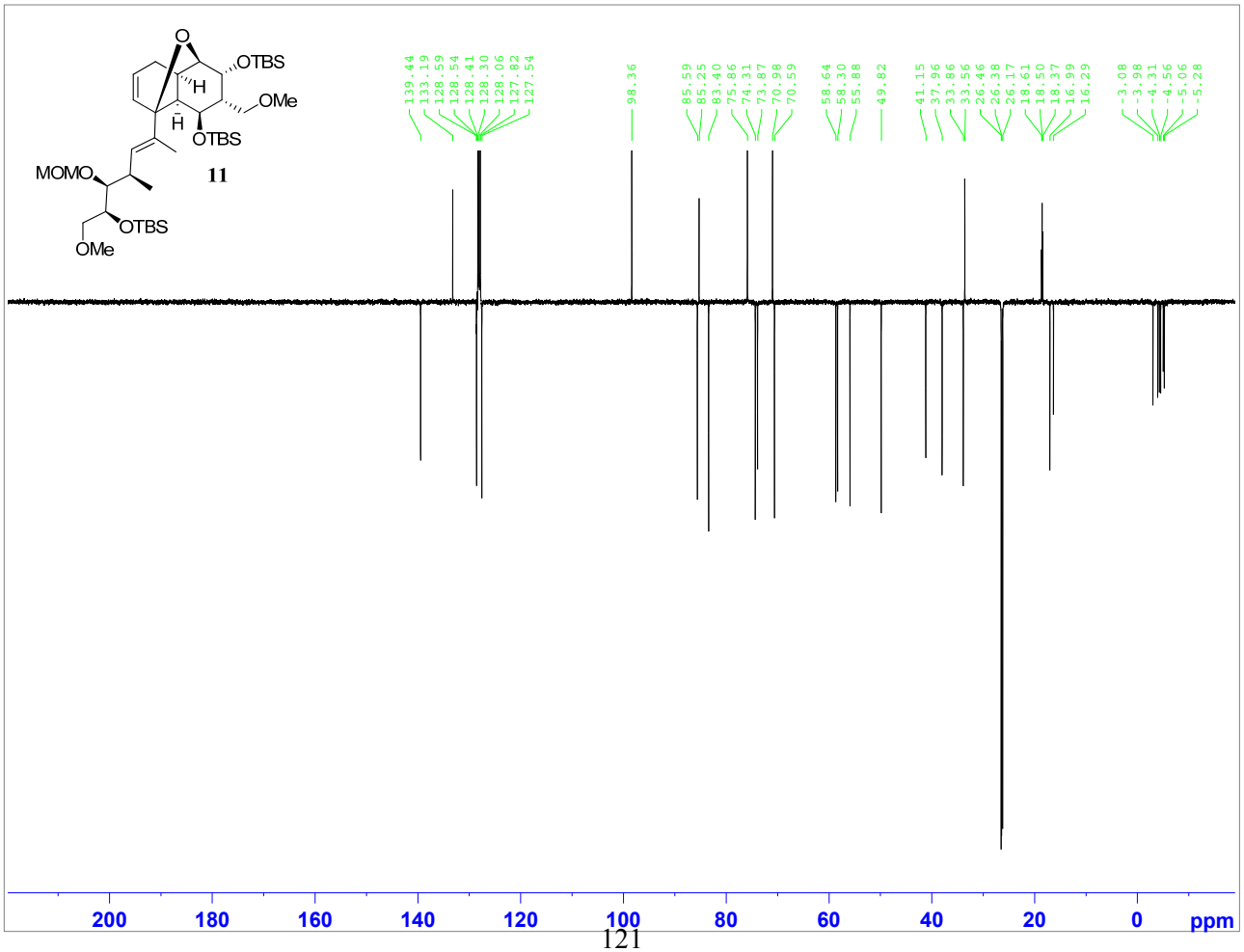

MOMO
I
MeO
OTBS
8
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
0.99
1.00
1.01
1.00
1.01
3.97
4.00
1.01
3.03
3.06
9.27
6.05

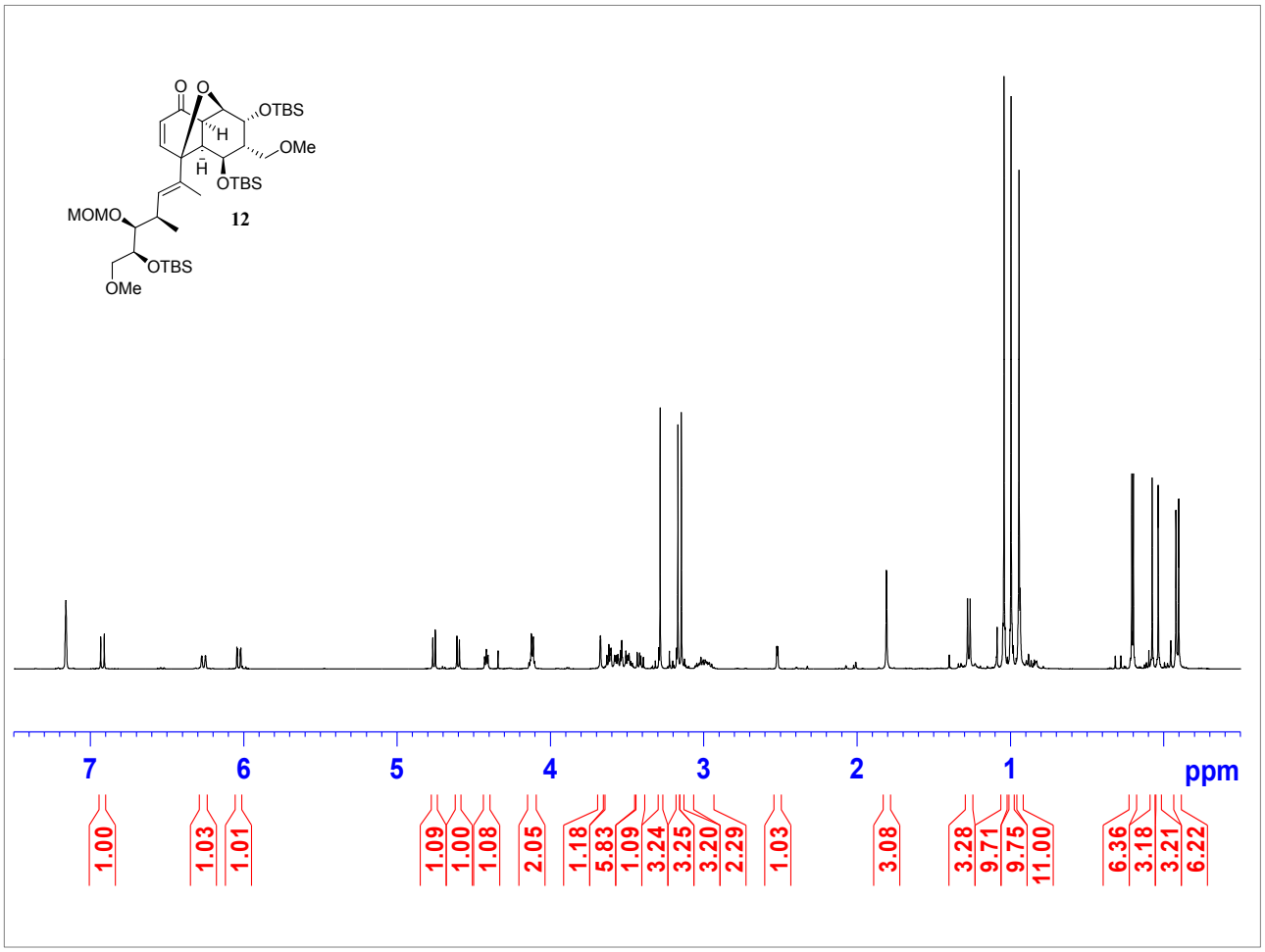

MOMO
I
MeO
OTBS
8
144.71
98.11
92.95
82.53
77.47
77.15
76.84
74.82
73.23
59.11
56.13
36.58
27.84
26.12
18.31
16.06
-4.36
-4.53
200 180 160 140 120 100 80 60 40 20 0 ppm

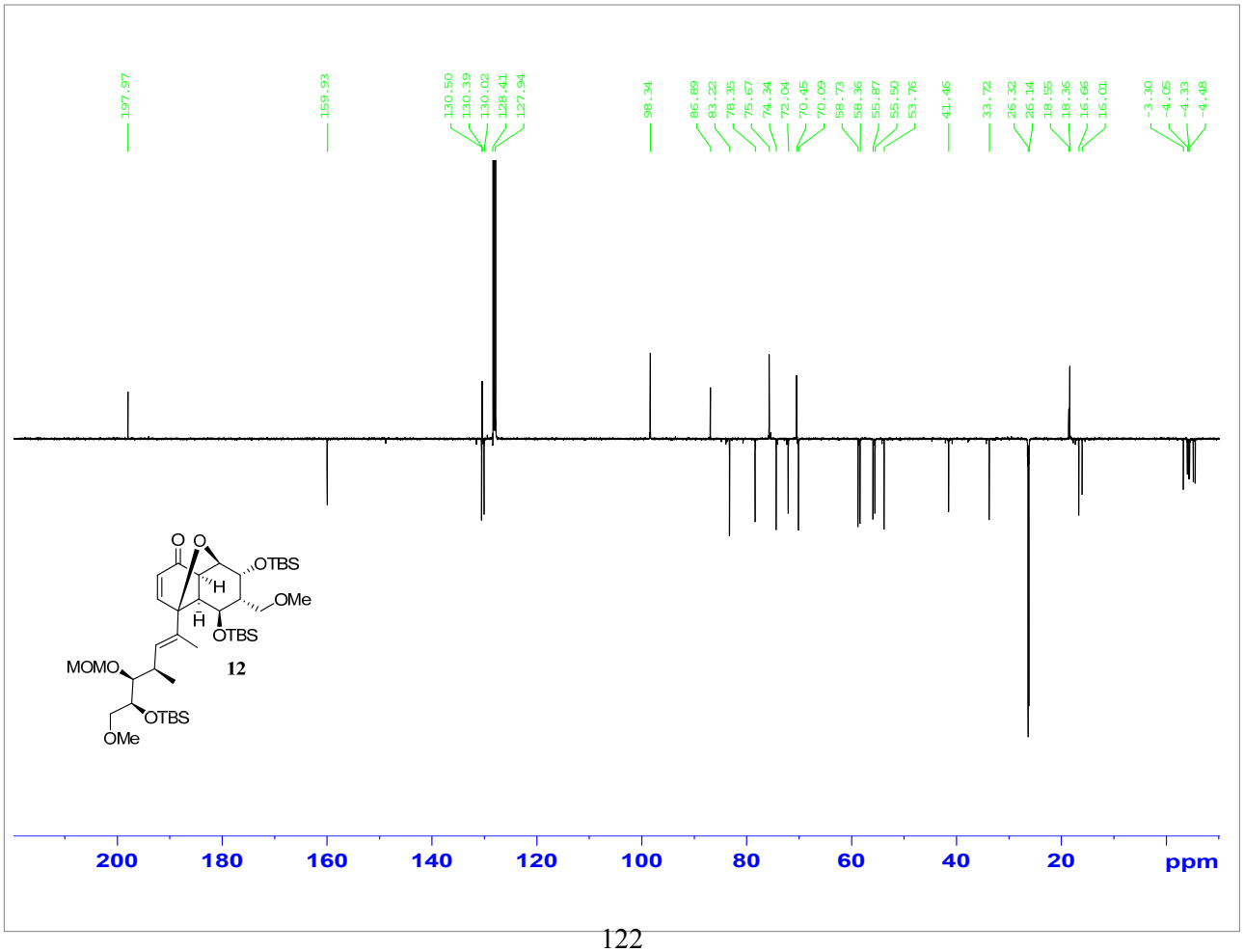

O
OH
H
OMe
H
OTBS
MOMO
10
OTBS
OMe
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
1.01 1.03 1.00 1.01 1.00 2.03 2.04 1.99 2.14 1.12 4.09 3.27 1.10 3.05 2.08 2.03 1.07 3.06 3.08 18.96 6.08 5.98

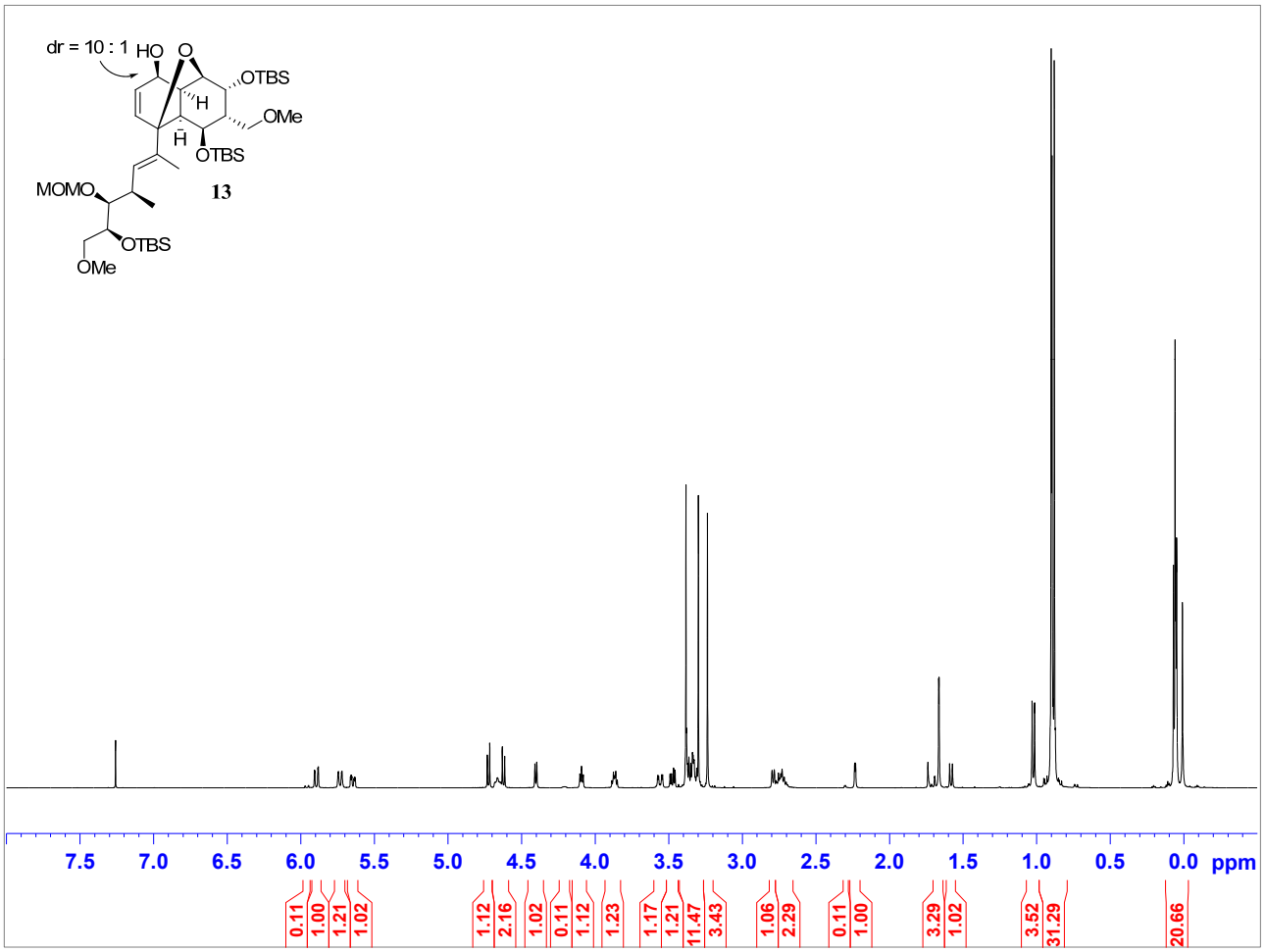

O
OH
H
OMe
H
OTBS
MOMO
10
OTBS
OMe
139.12
133.56
128.30
128.20
128.06
127.95
127.82
98.38
85.49
85.09
83.38
75.76
74.20
73.80
72.56
72.20
58.65
58.41
55.90
49.56
41.11
38.00
33.77
33.62
26.52
26.36
18.60
18.55
16.99
16.38
-3.10
-3.98
-4.32
-5.59
200 180 160 140 120 100 80 60 40 20 0 ppm

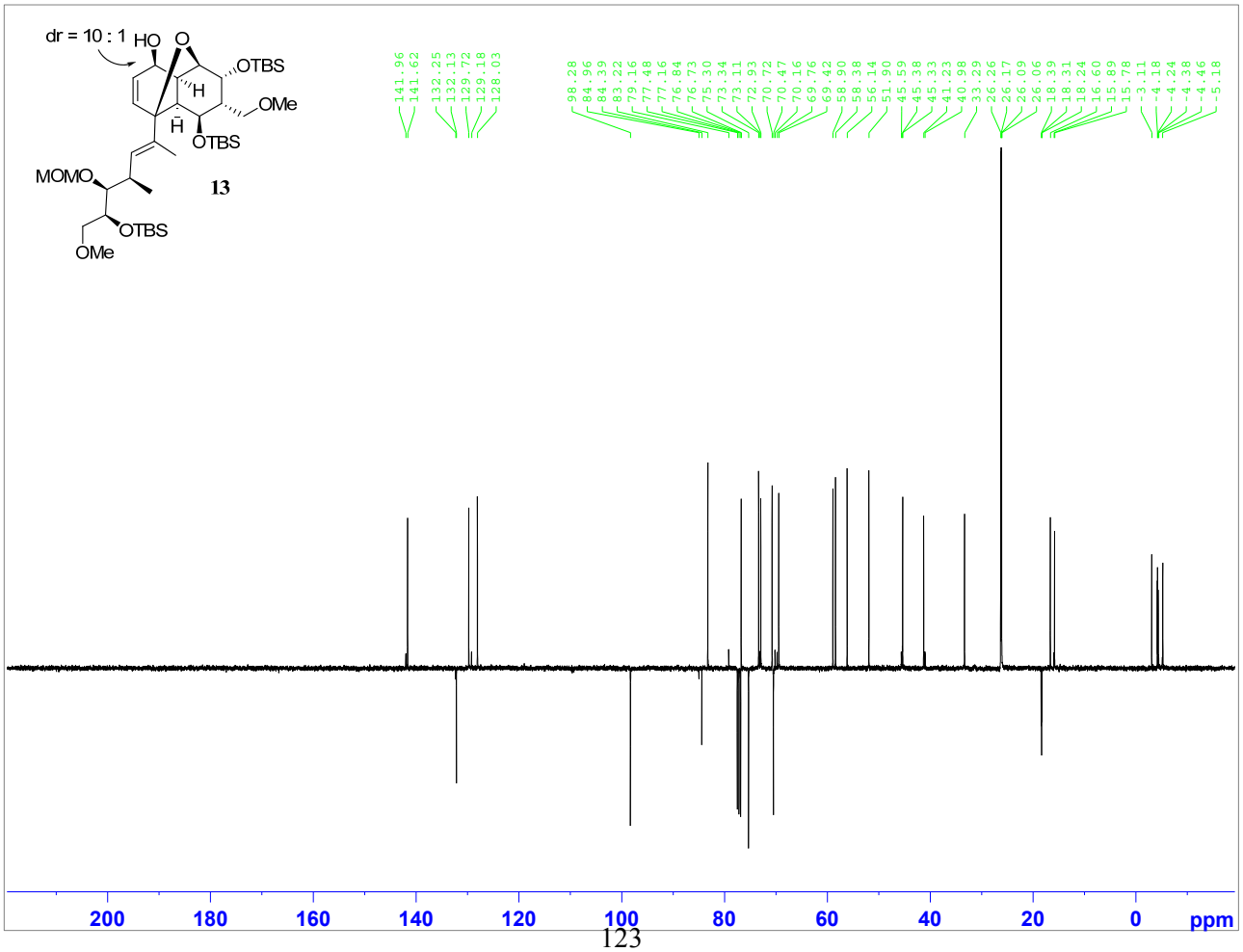

O
OTBS
H
OMe
H
OTBS
MOMO
11
OTBS
OMe
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
1.00 1.00 1.00 1.00 0.99 1.01 2.03 1.01 4.10 1.03 3.05 3.05 5.25 0.99 1.02 1.00 1.02 3.01 3.15 9.27 9.39 9.31 6.14 3.15 3.18 6.12

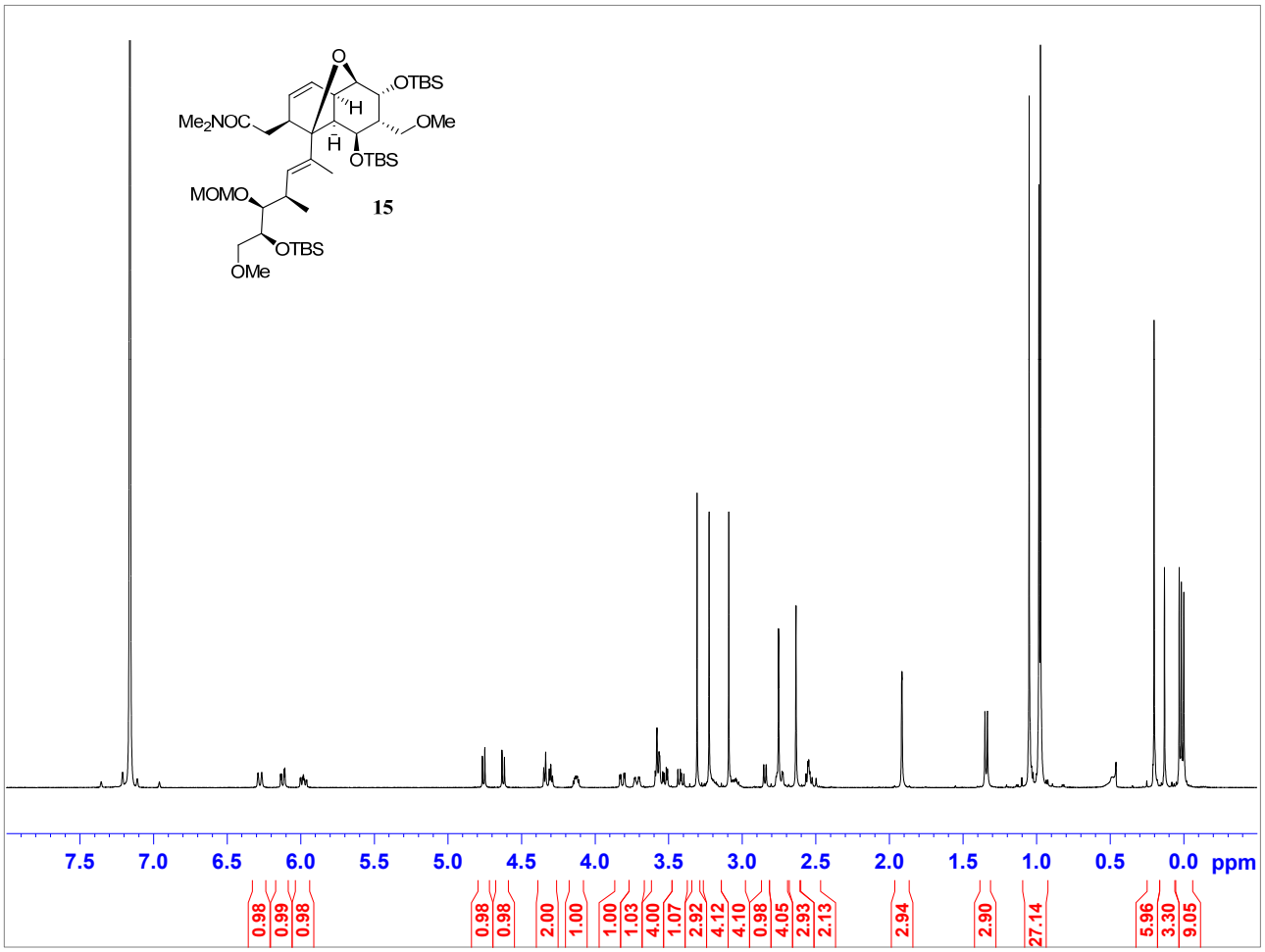

O
OTBS
H
OMe
H
OTBS
MOMO
11
OTBS
OMe
139.44
133.19
128.59
128.54
128.41
128.30
128.06
127.82
127.54
98.36
85.59
85.25
83.40
75.86
74.31
73.87
70.98
70.59
58.64
58.30
55.88
49.82
41.15
37.96
33.66
33.56
26.46
26.38
26.17
18.61
18.50
18.37
16.99
16.29
-3.08
-3.98
-4.31
-4.56
-5.06
-5.28
200 180 160 140 120 100 80 60 40 20 0 ppm

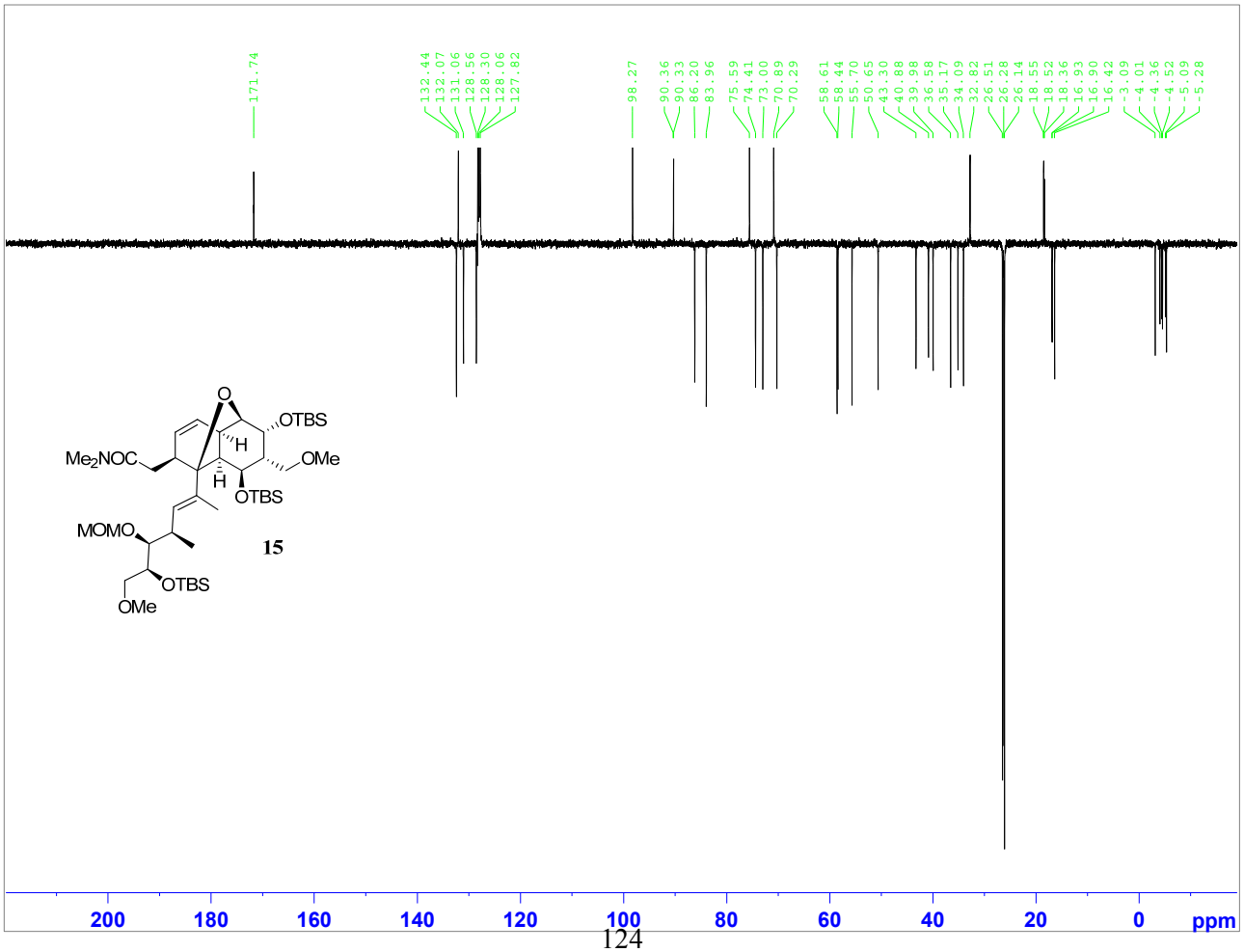

OTBS
OMe
OTBS
MOMO
OTBS
OMe
12
7
6
5
4
3
2
1
ppm
1.00
1.03
1.01
1.09
1.00
1.08
2.05
1.18
5.83
1.09
3.24
3.25
3.20
2.29
1.03
3.08
3.28
9.71
9.75
11.00
6.36
3.18
3.21
6.22

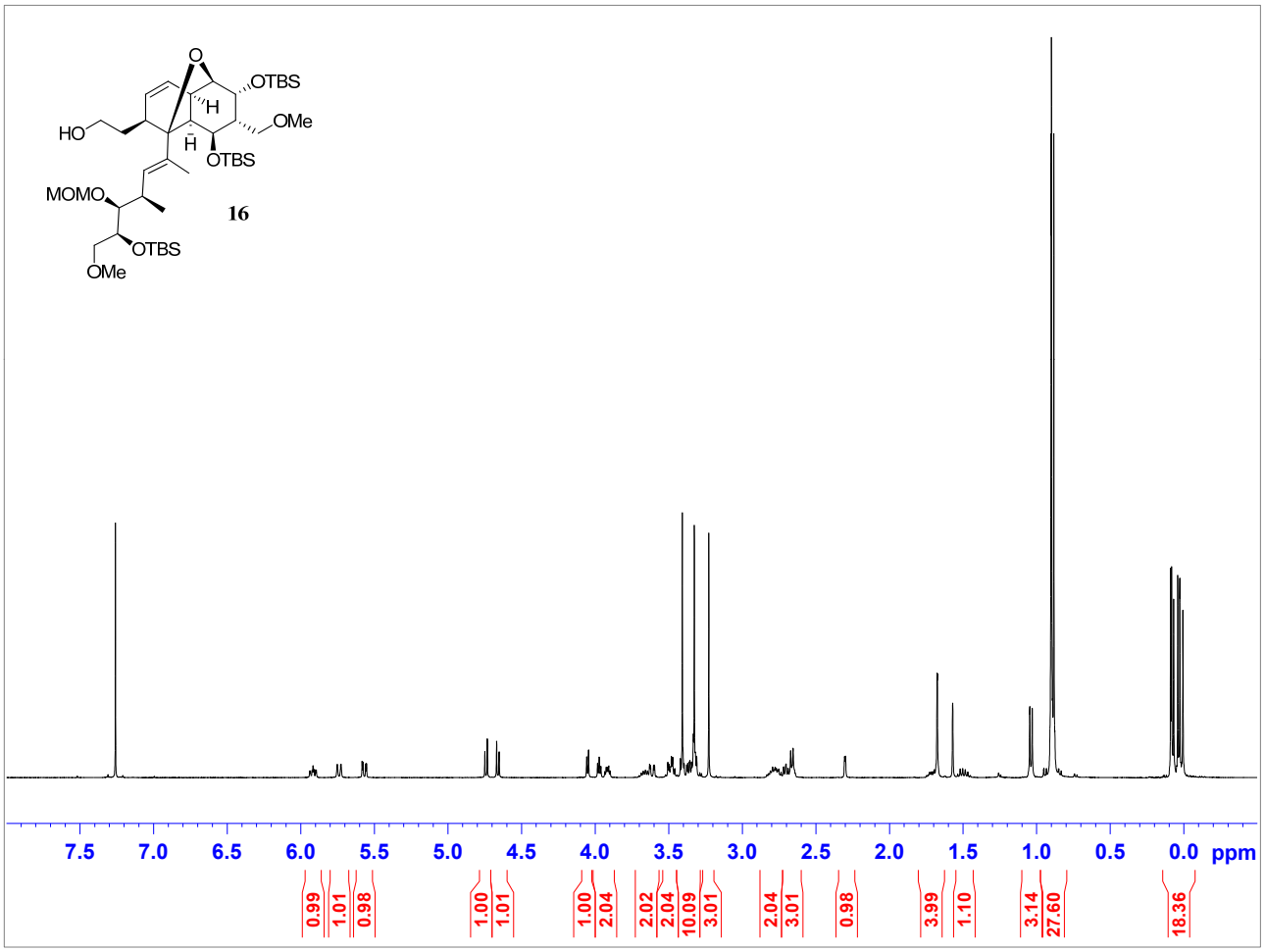

197.97
159.93
130.50
130.39
130.02
128.41
127.94
98.34
86.89
83.22
78.35
75.67
74.34
72.04
70.45
70.09
58.73
58.36
55.87
55.50
53.76
41.46
33.72
26.32
26.14
18.55
18.36
16.66
16.01
-3.30
-4.05
-4.33
-4.48
OTBS
OMe
OTBS
MOMO
OTBS
OMe
12
200
180
160
140
120
100
80
60
40
20
ppm

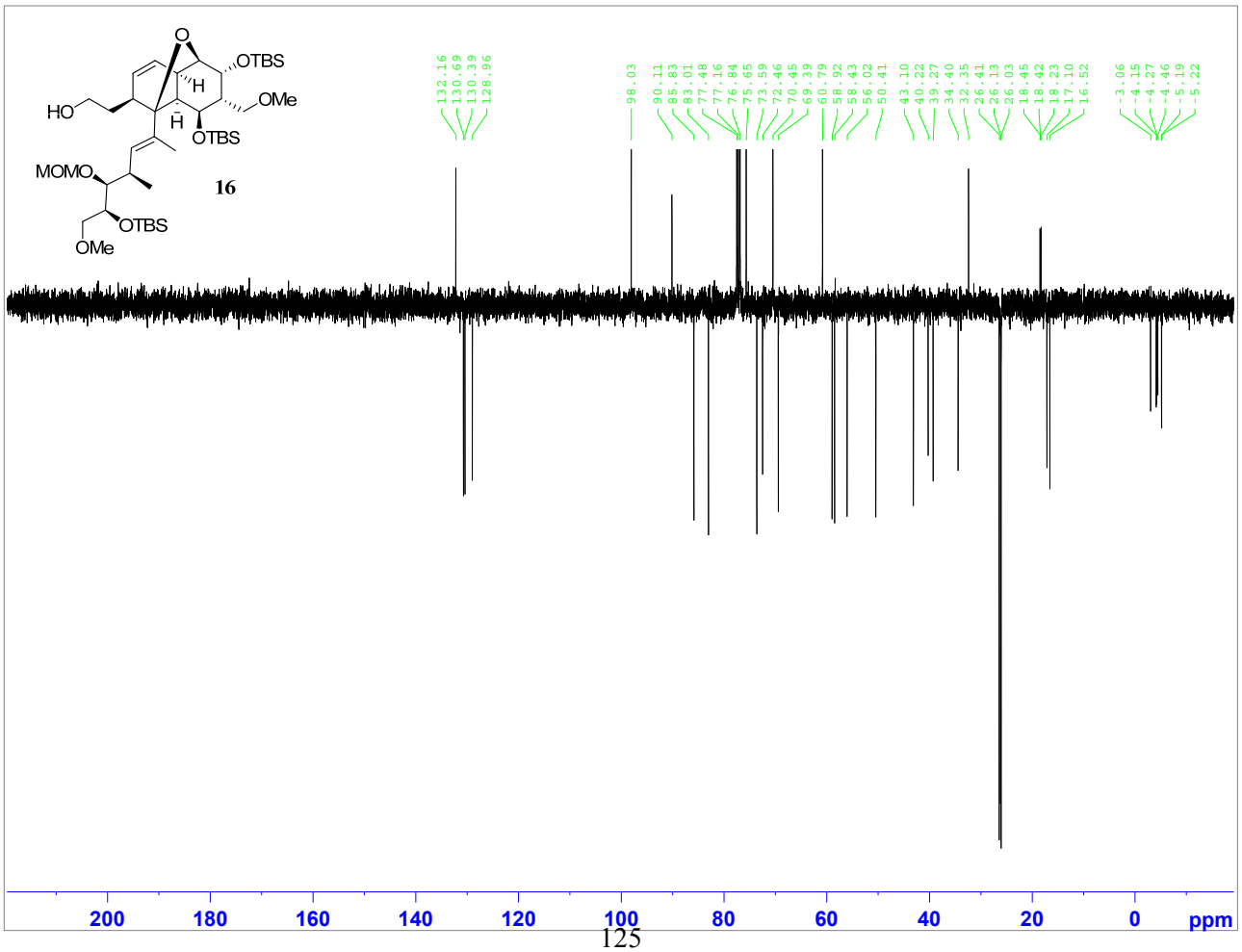

dr = 10 : 1
HO
O
OTBS
H
OMe
H
OTBS
MOMO
OTBS
OMe
13
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
0.11
1.00
1.21
1.02
1.12
2.16
1.02
0.11
1.12
1.23
1.17
1.21
11.47
3.43
1.06
2.29
0.11
1.00
3.29
1.02
3.52
31.29
20.66

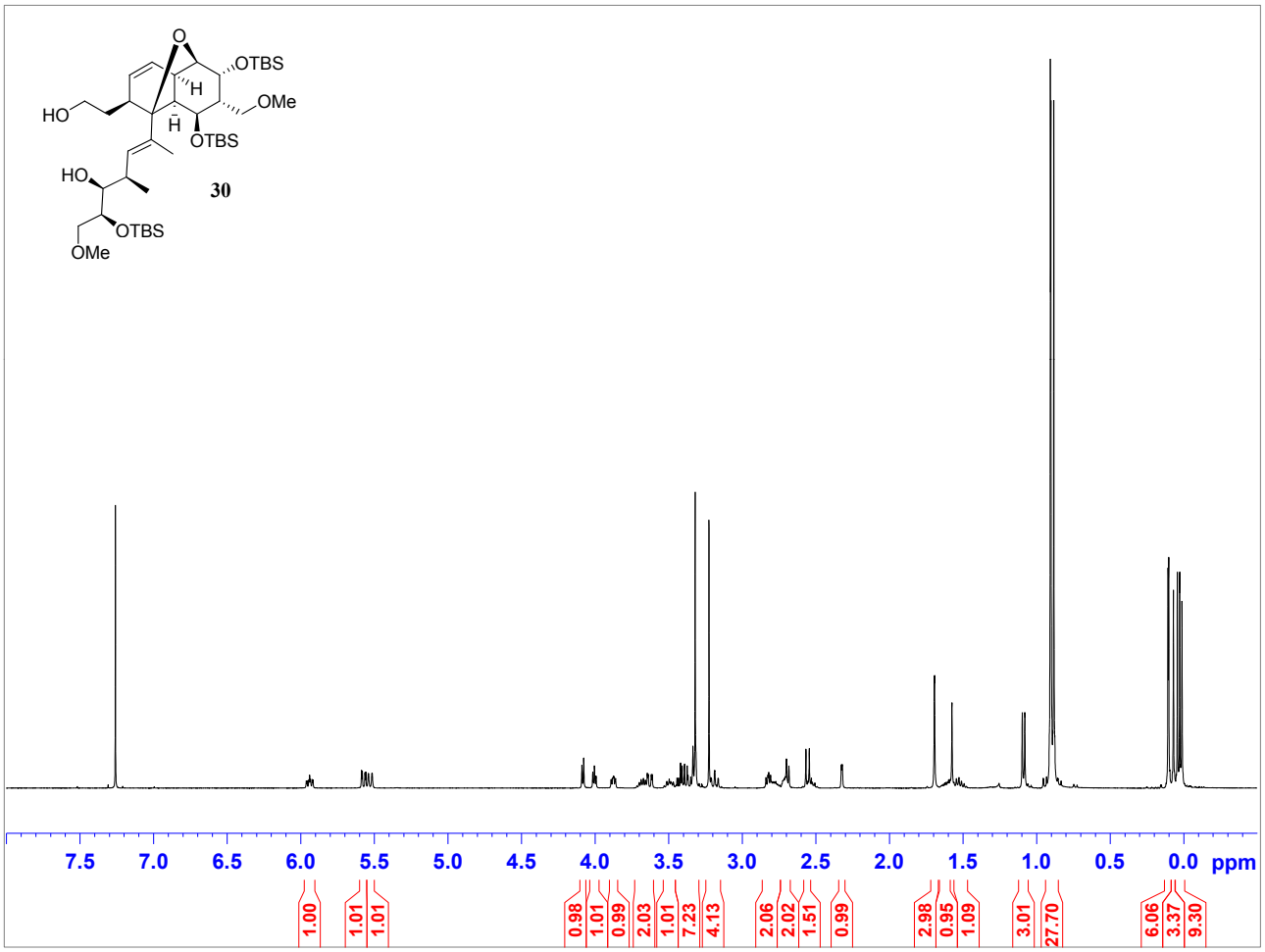

dr = 10 : 1
HO
O
OTBS
H
OMe
H
OTBS
MOMO
OTBS
OMe
13
141.96
141.62
132.25
132.13
129.72
129.18
128.03
98.28
84.96
84.39
83.22
79.16
77.48
77.16
76.84
76.73
75.30
73.34
73.11
72.93
70.72
70.47
70.16
69.76
69.42
58.90
58.38
56.14
51.90
45.59
45.38
45.33
41.23
40.98
33.29
26.26
26.17
26.09
26.06
18.39
18.31
18.24
16.60
15.89
15.78
-3.11
-4.18
-4.24
-4.38
-4.46
-5.18
200
180
160
140
120
100
80
60
40
20
0
ppm

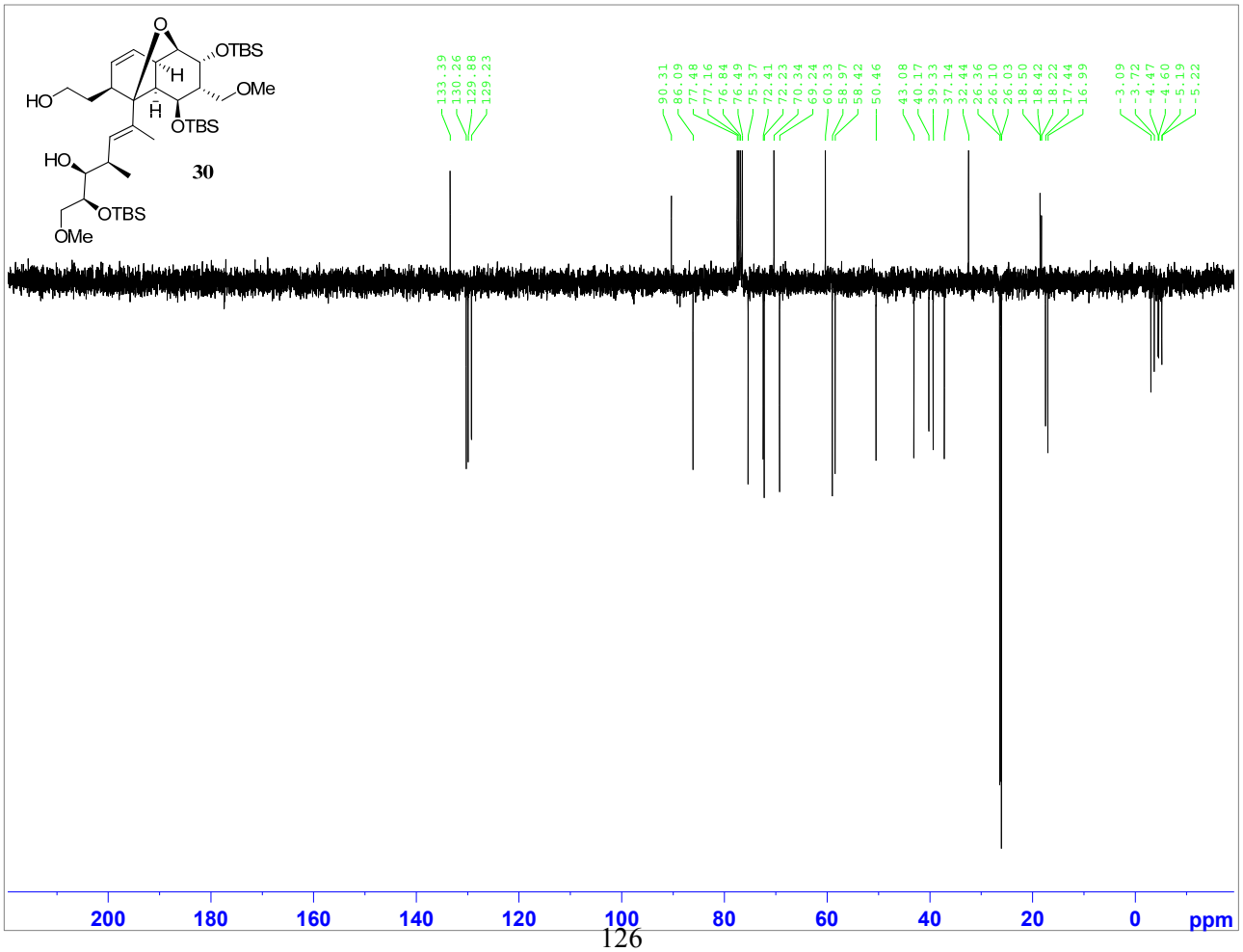

O
OTBS
H
Me2NOC
OMe
H
OTBS
MOMO
15
OTBS
OMe
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
0.98 0.99 0.98 0.98 0.98 2.00 1.00 1.00 1.03 4.00 1.07 2.92 4.12 4.10 0.98 4.05 2.93 2.13 2.94 2.90 27.14 5.96 3.30 9.05

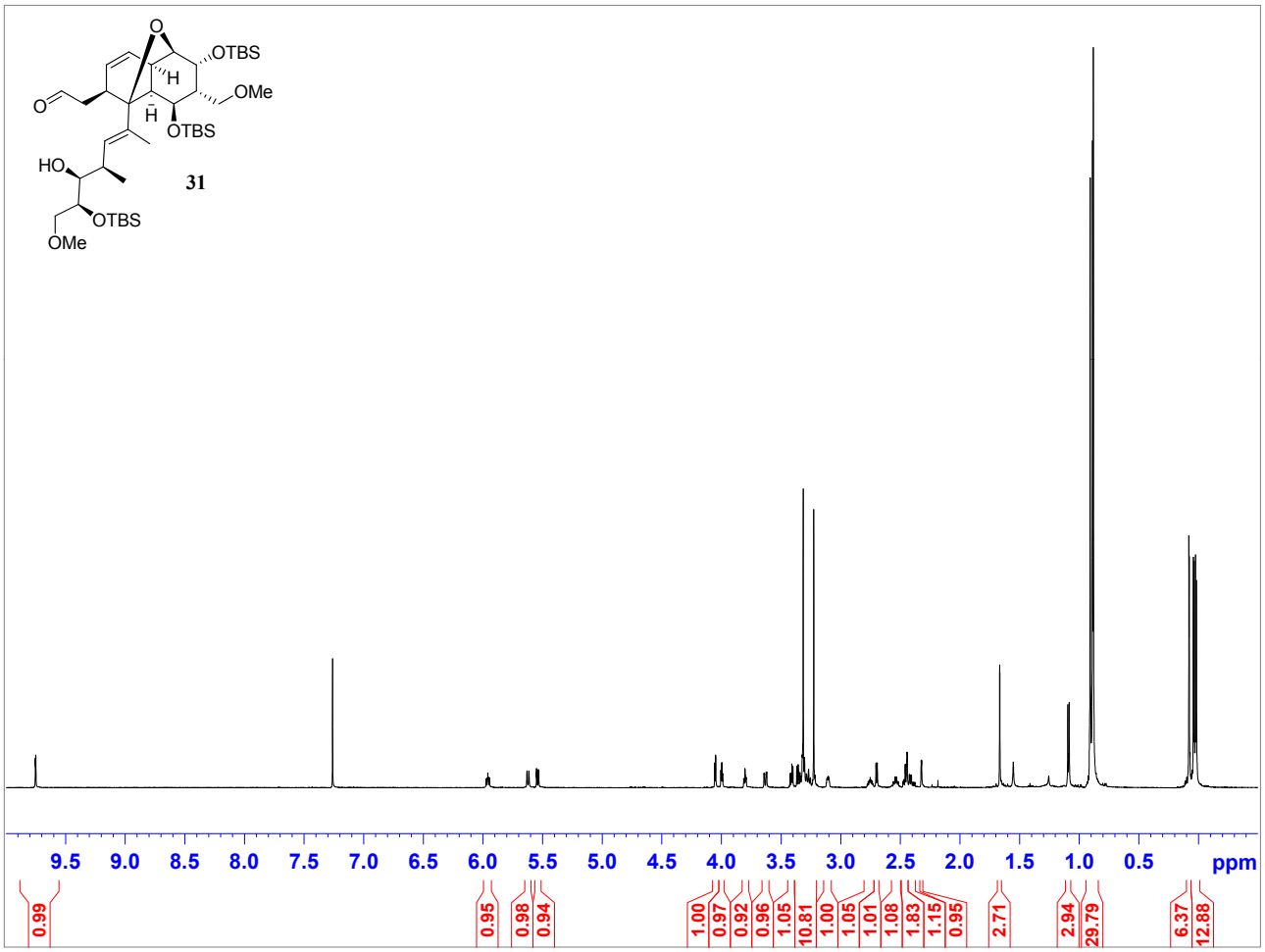

171.74
132.44 132.07 131.06 128.56 128.30 128.06 127.82
98.27
90.36 90.33 86.20 83.96
75.59 74.41 73.00 70.89 70.29
58.61 58.44 55.70 50.65 43.30 40.88 39.98 36.58 35.17 34.09 32.82 26.51 26.28 26.14 18.55 18.52 18.36 16.93 16.90 16.42 -3.09 -4.01 -4.36 -4.52 -5.09 -5.28
O
OTBS
H
Me2NOC
OMe
H
OTBS
MOMO
15
OTBS
OMe
200 180 160 140 120 100 80 60 40 20 0 ppm

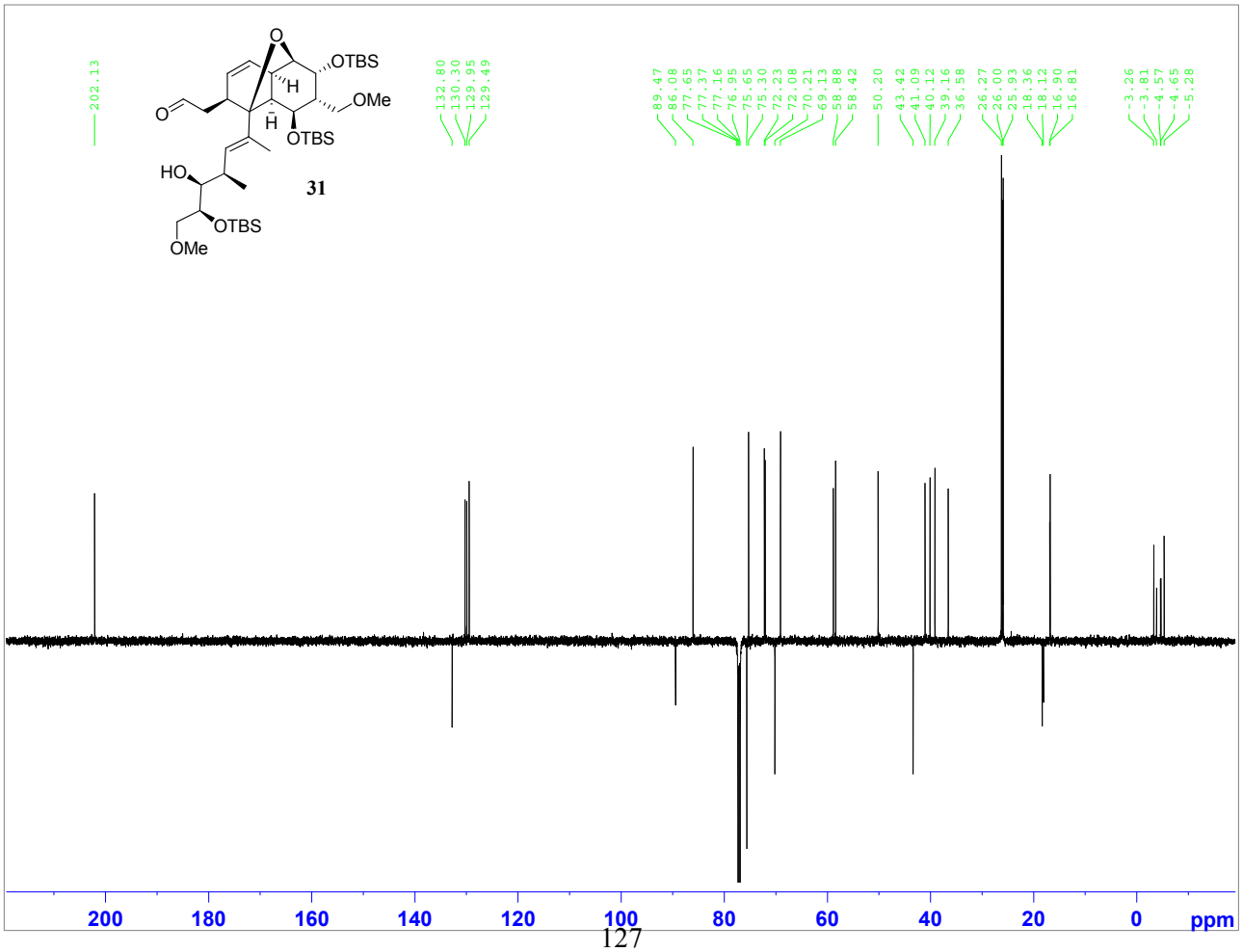

O
OTBS
H
HO
OMe
H
OTBS
MOMO
OTBS
OMe
16
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
0.99 1.01 0.98 1.00 1.01 1.00 2.04 2.02 2.04 10.09 3.01 2.04 3.01 0.98 3.99 1.10 3.14 27.60 18.36

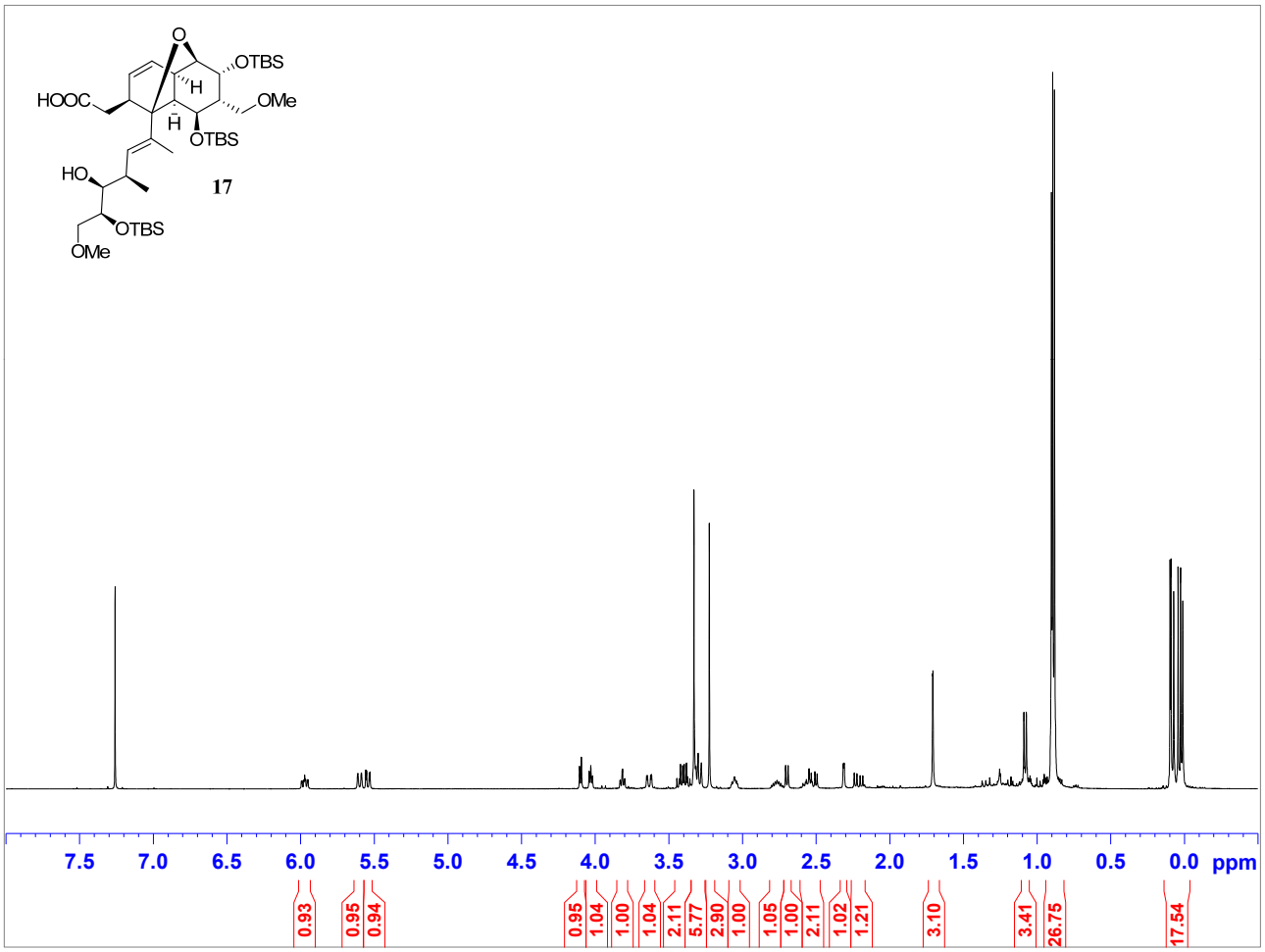

O
OTBS
H
HO
OMe
H
OTBS
MOMO
OTBS
OMe
16
132.16 130.69 130.39 128.96
98.03 90.11 85.83 83.01 77.48 77.16 76.84 75.65 73.59 72.46 70.45 69.39 60.79 58.92 58.43 56.02 50.41 43.10 40.22 39.27 34.40 32.35 26.41 26.13 26.03 18.45 18.42 18.23 17.10 16.52
-3.06 -4.15 -4.27 -4.46 -5.19 -5.22
200 180 160 140 120 100 80 60 40 20 0 ppm

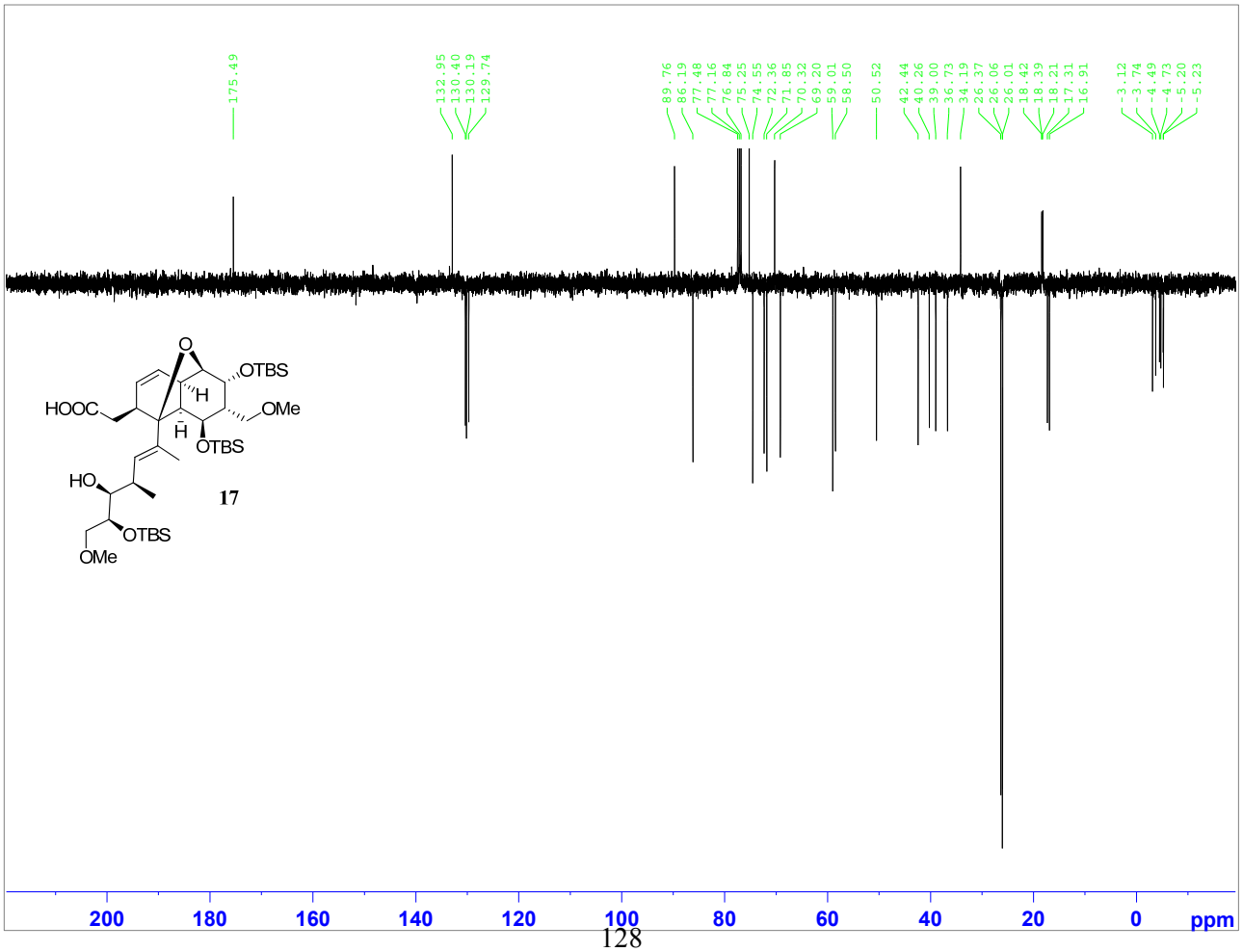

O
OTBS
H
HO
OMe
H
OTBS
HO
30
OTBS
OMe
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
1.00 1.01 1.01 0.98 1.01 0.99 2.03 1.01 7.23 4.13 2.06 2.02 1.51 0.99 2.98 0.95 1.09 3.01 27.70 6.06 3.37 9.30

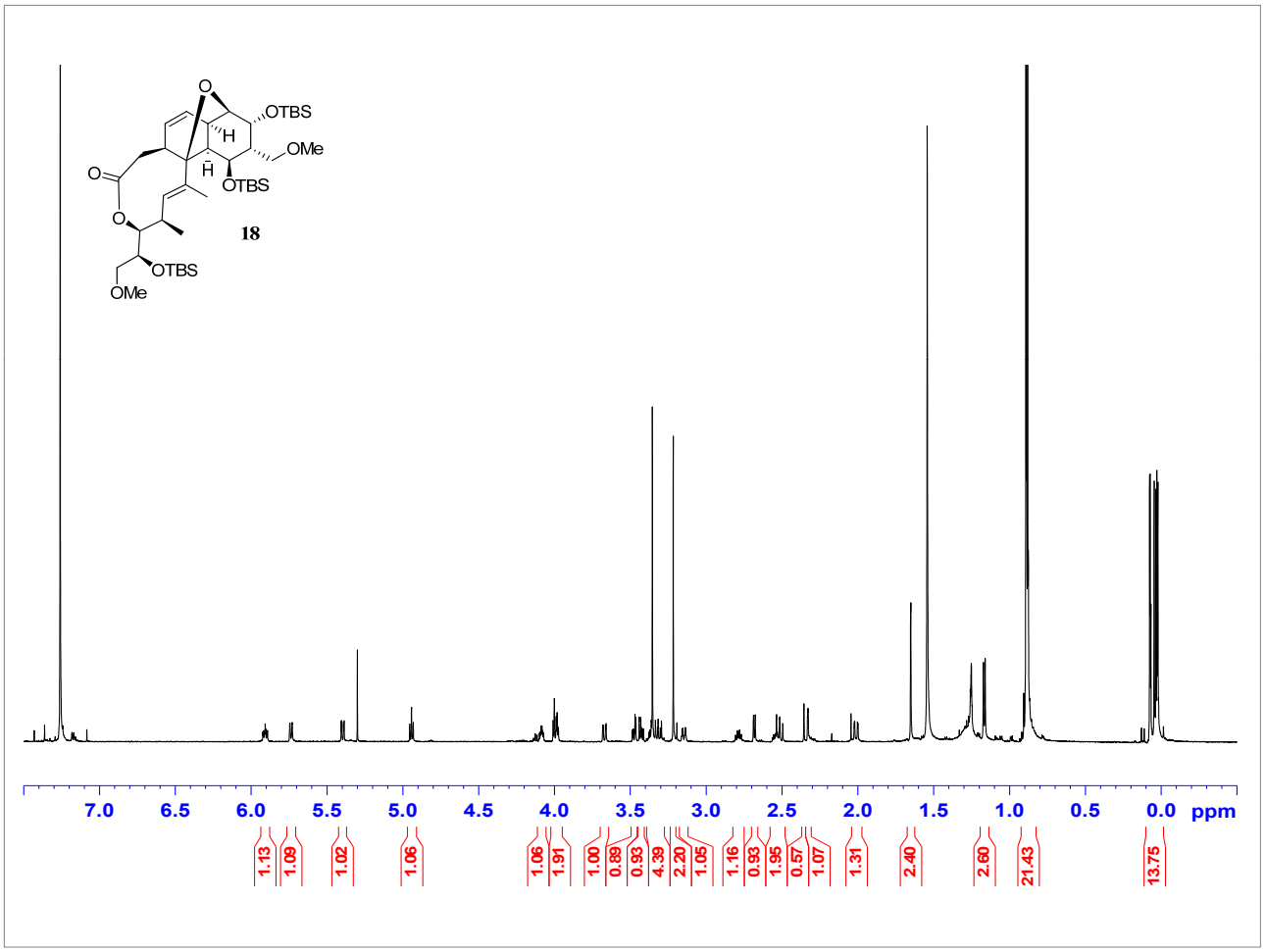

O
OTBS
H
HO
OMe
H
OTBS
HO
30
OTBS
OMe
133.39 130.26 129.88 129.23
90.31 86.09 77.48 77.16 76.84 76.49 75.37 72.41 72.23 70.34 69.24 60.33 58.97 58.42 50.46 43.08 40.17 39.33 37.14 32.44 26.36 26.10 26.03 18.50 18.42 18.22 17.44 16.99 -3.09 -3.72 -4.47 -4.60 -5.19 -5.22
200 180 160 140 120 100 80 60 40 20 0 ppm

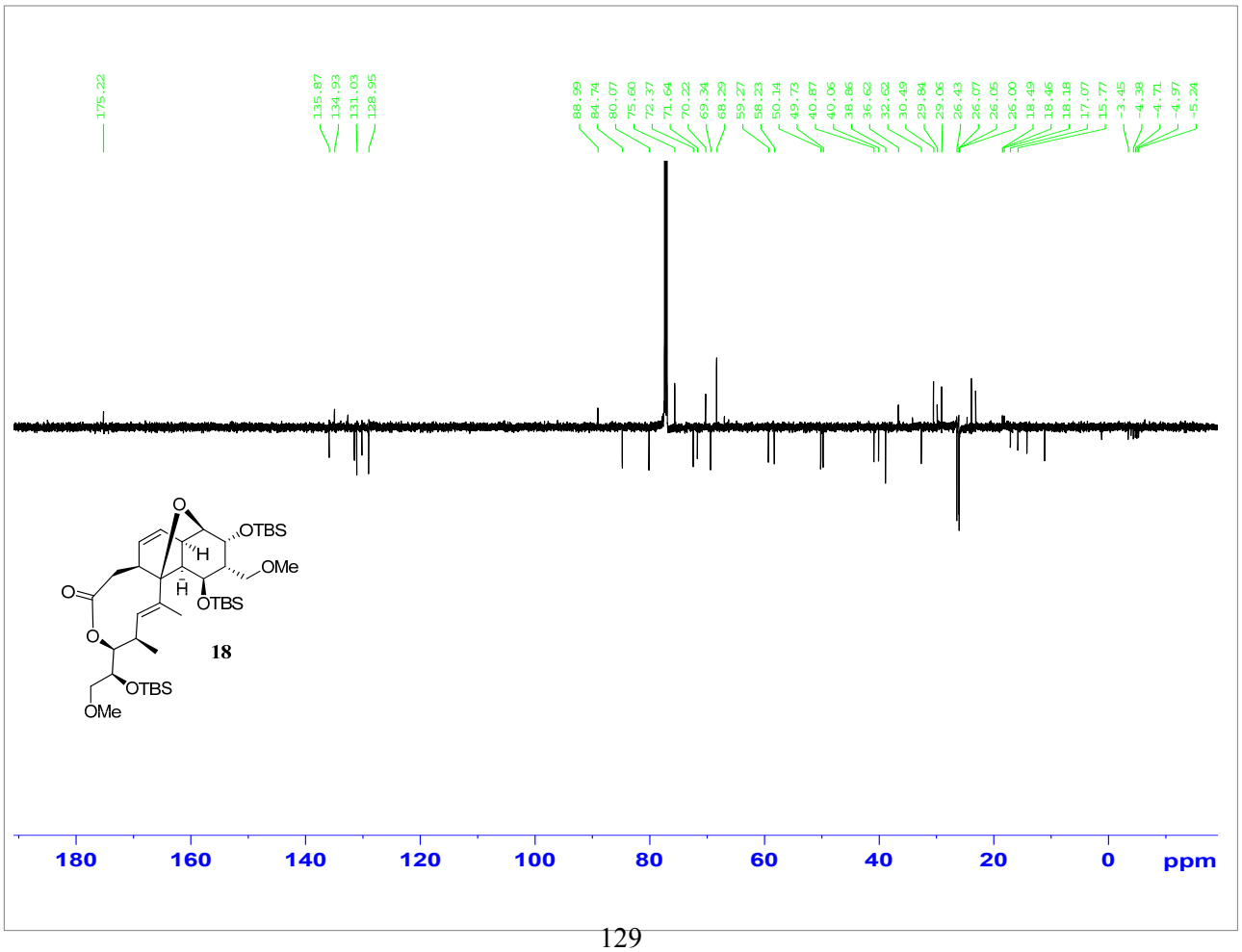

OTBS
OMe
OTBS
HO
OTBS
OMe
31
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.99 0.95 0.98 0.94 1.00 0.97 0.92 0.96 1.05 10.81 1.00 1.05 1.01 1.08 1.83 1.15 0.95 2.71 2.94 29.79 6.37 12.88

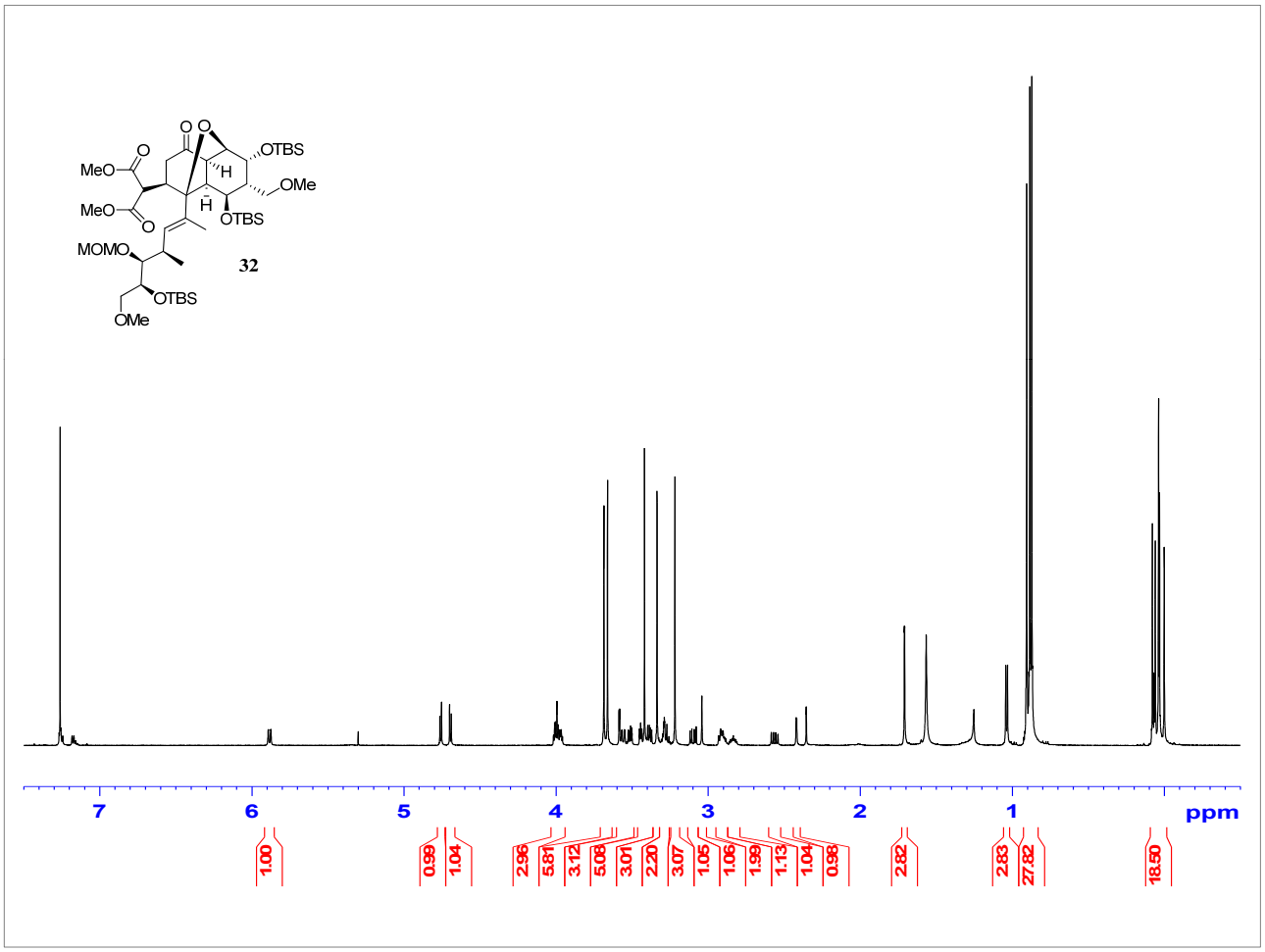

202.13
132.80 130.30 129.95 129.49
89.47 86.08 77.65 77.37 77.16 76.95 75.65 75.30 72.23 72.08 70.21 69.13 58.88 58.42
50.20
43.42 41.09 40.12 39.16 36.58
26.27 26.00 25.93 18.36 18.12 16.90 16.81
-3.26 -3.81 -4.57 -4.65 -5.28
OTBS
OMe
OTBS
HO
OTBS
OMe
31
200 180 160 140 120 100 80 60 40 20 0 ppm

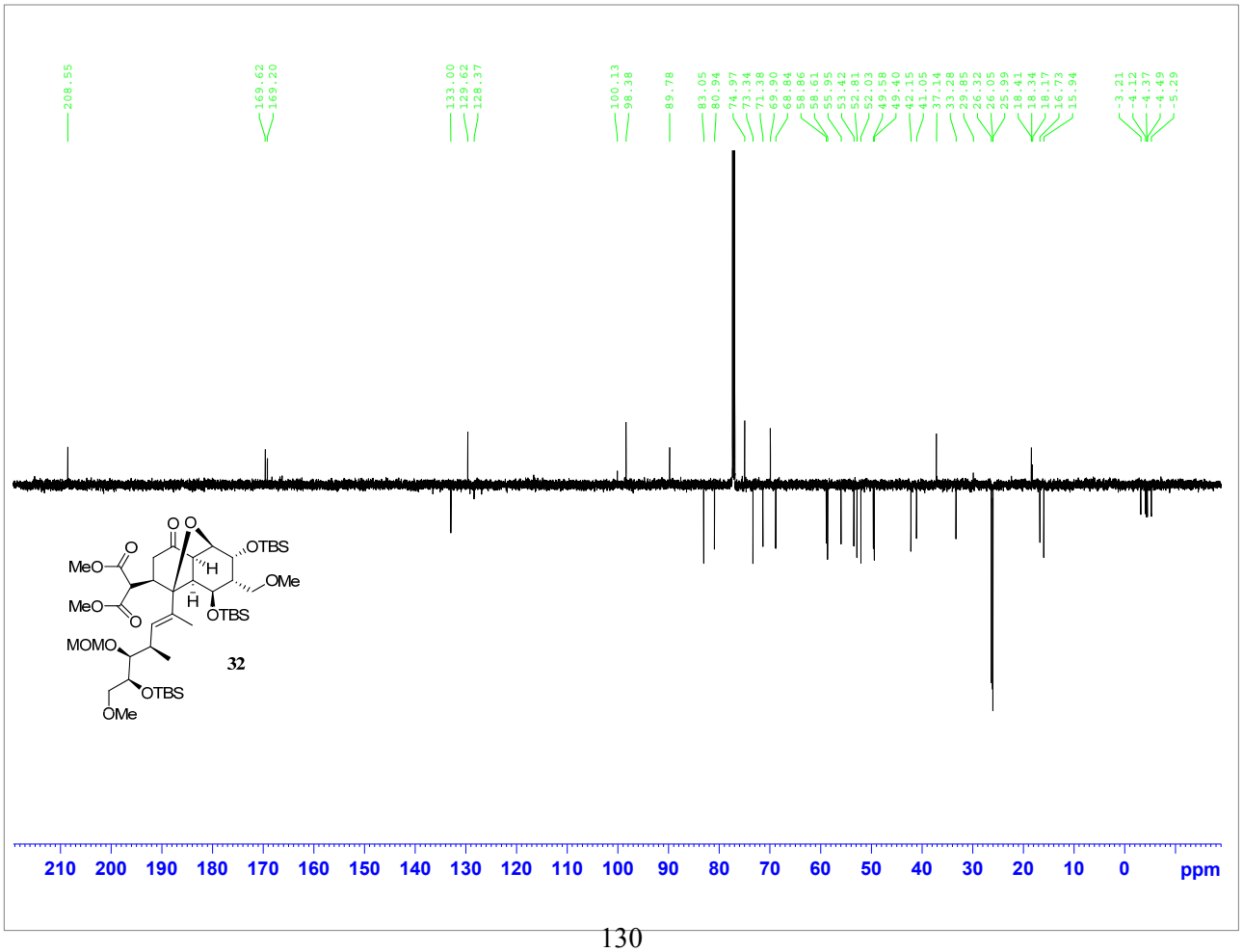

O
OTBS
H
HOOC
OMe
H
OTBS
HO
OTBS
OMe
17
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
0.93 0.95 0.94 0.95 1.04 1.00 1.04 2.11 5.77 2.90 1.00 1.05 1.00 2.11 1.02 1.21 3.10 3.41 26.75 17.54

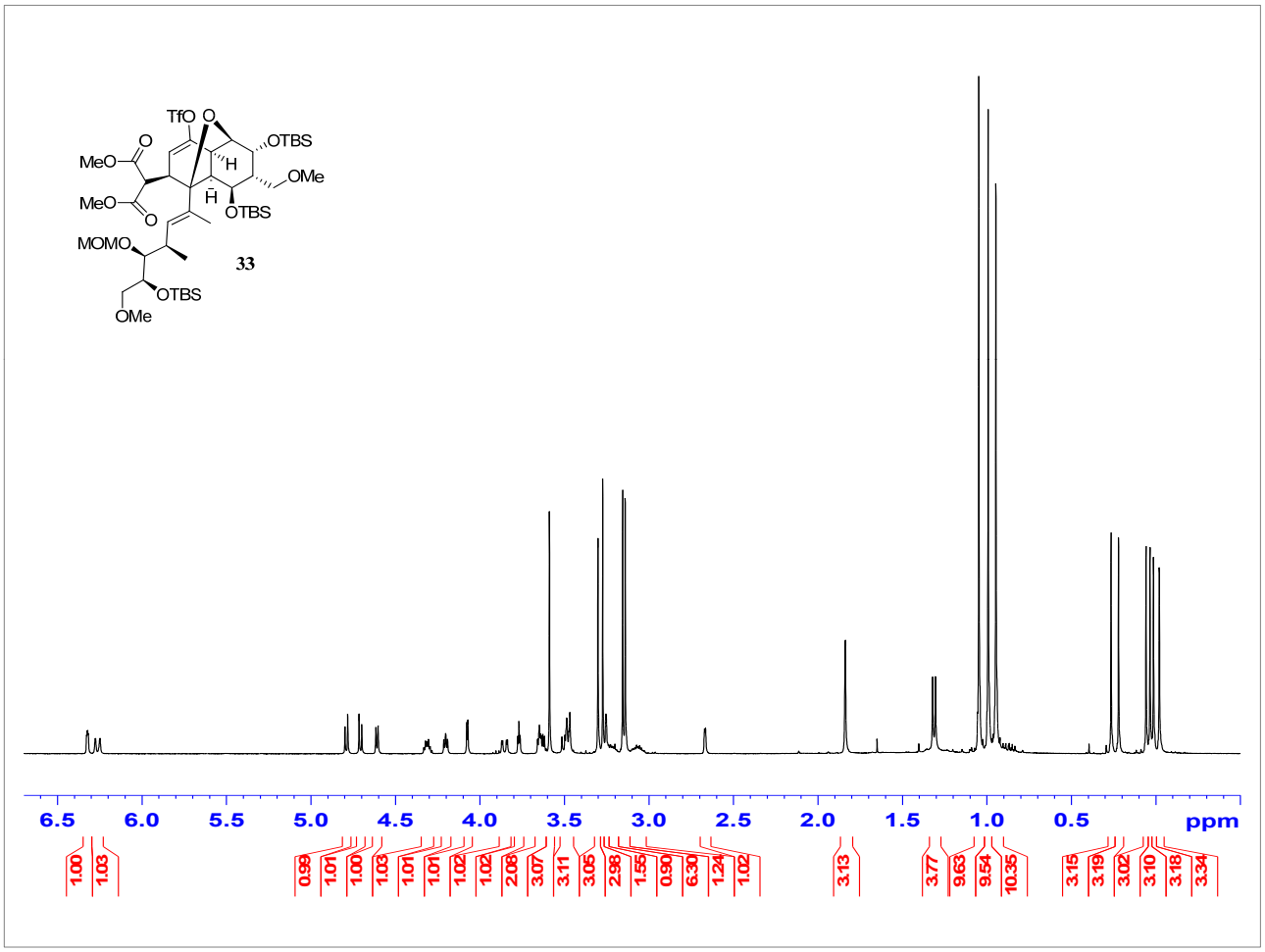

175.49
132.95 130.40 130.19 129.74
89.76 86.19 77.48 77.16 76.84 75.25 74.55 72.36 71.85 70.32 69.20 59.01 58.50
50.52
42.44 40.26 39.00 36.73 34.19 26.37 26.06 26.01 18.42 18.39 18.21 17.31 16.91
-3.12 -3.74 -4.49 -4.73 -5.20 -5.23
O
OTBS
H
HOOC
OMe
H
OTBS
HO
OTBS
OMe
17
200 180 160 140 120 100 80 60 40 20 0 ppm

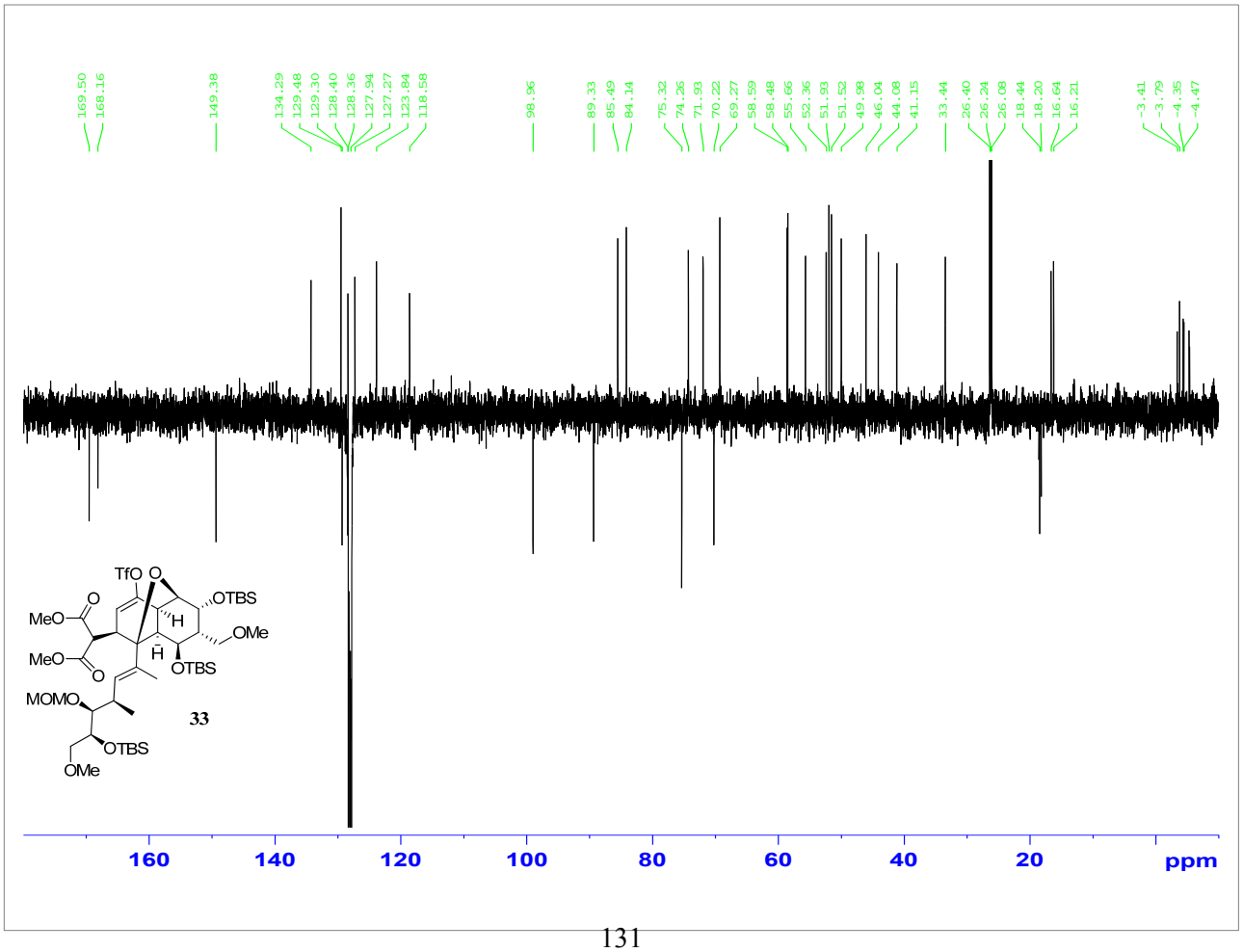

OTBS
OMe
OTBS
OTBS
OMe
18
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.13
1.09
1.02
1.06
1.06
1.91
1.00
0.89
0.93
4.39
2.20
1.05
1.16
0.93
1.95
0.57
1.07
1.31
2.40
2.60
21.43
13.75

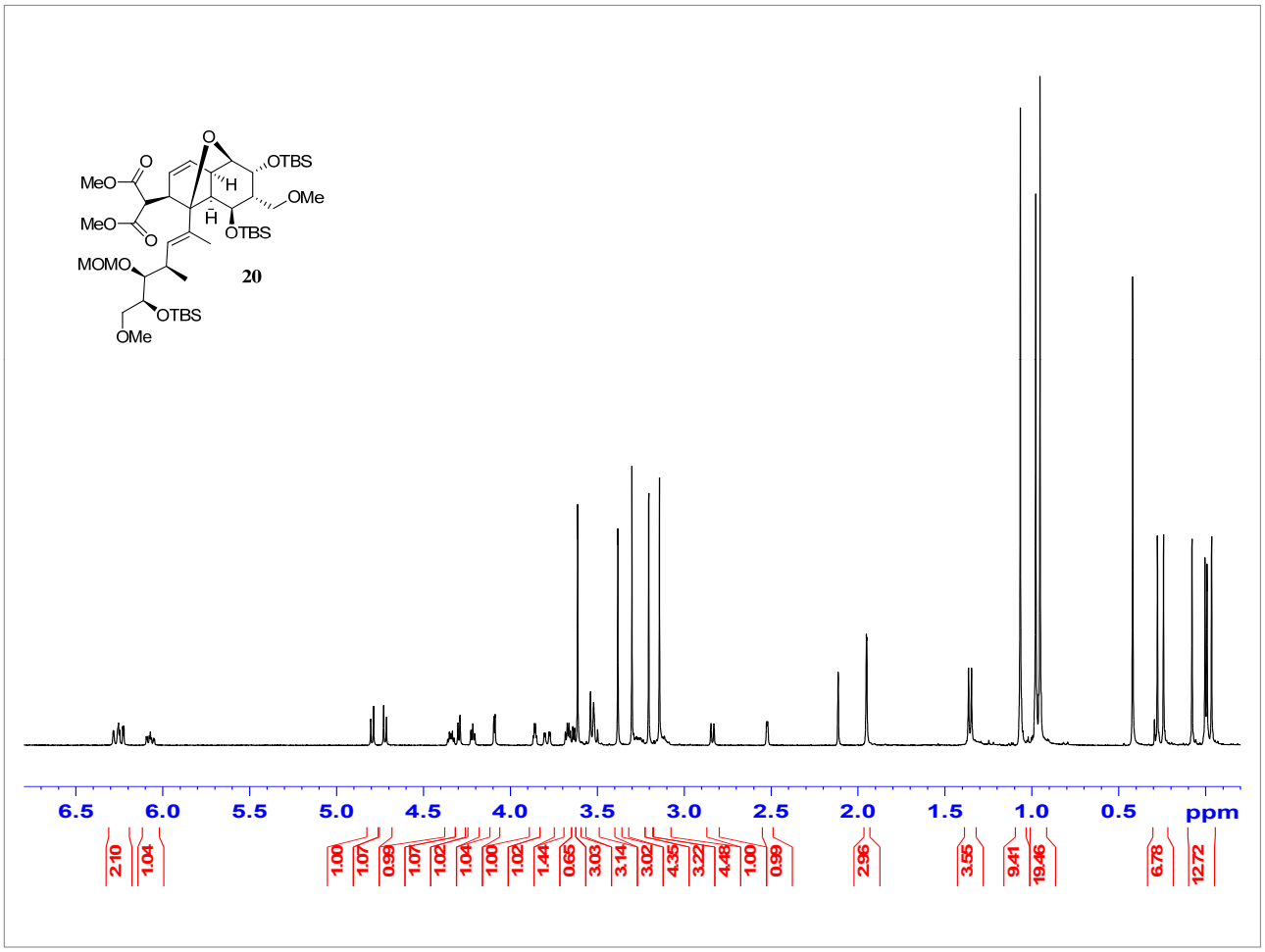

175.22
135.87
134.93
131.03
128.95
88.99
84.74
80.07
75.60
72.37
71.64
70.22
69.34
68.29
59.27
58.23
50.14
49.73
40.87
40.06
38.86
36.62
32.62
30.49
29.84
29.06
26.43
26.07
26.05
26.00
18.49
18.46
18.18
17.07
15.77
-3.45
-4.38
-4.71
-4.97
-5.24
OTBS
OMe
OTBS
OTBS
OMe
18
180
160
140
120
100
80
60
40
20
0
ppm

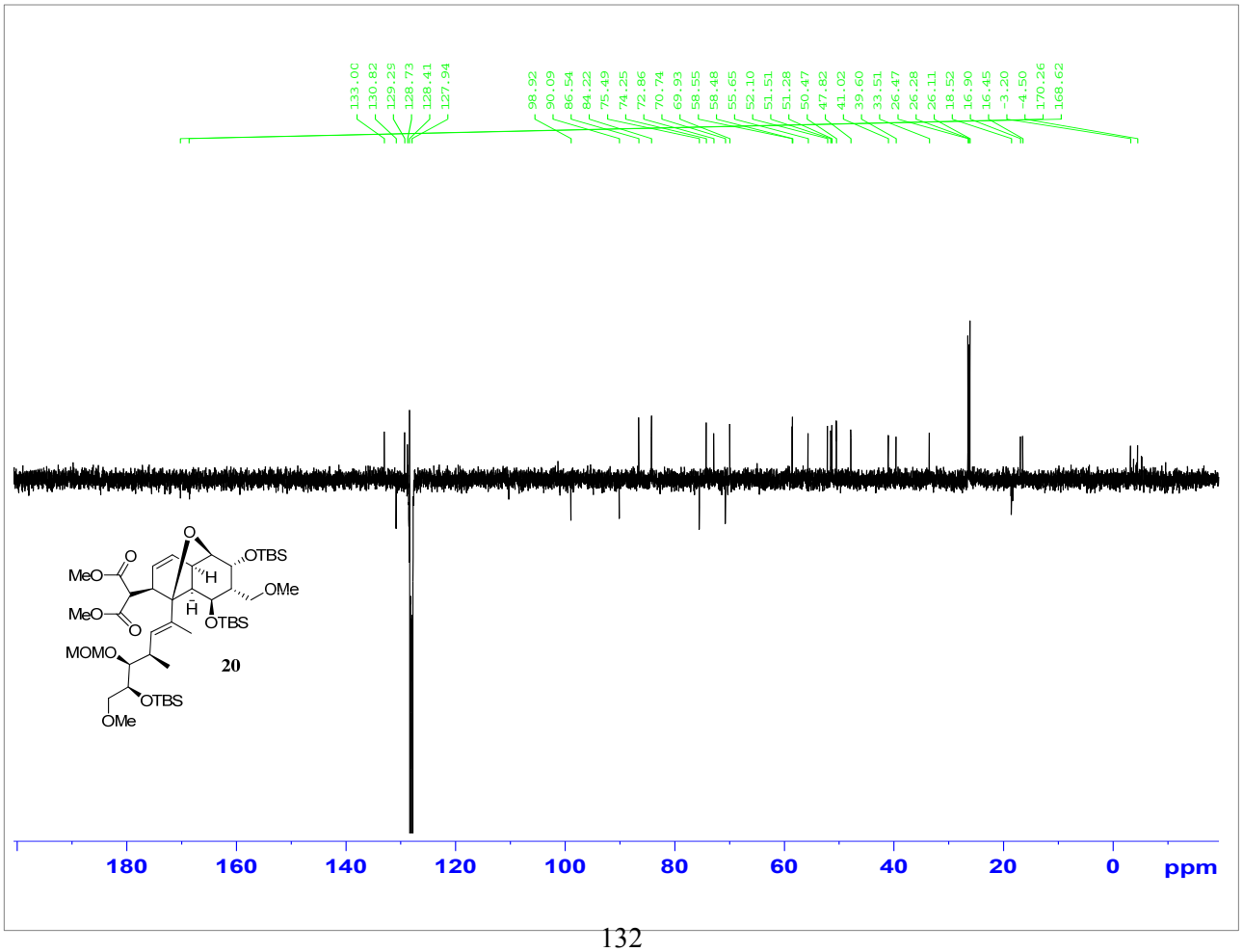

MeO
MeO
MOMO
OTBS
OMe
OTBS
OMe
OTBS
H
H
32
7
6
5
4
3
2
1
ppm
1.00
0.99
1.04
2.96
5.81
3.12
5.08
3.01
2.20
3.07
1.05
1.06
1.99
1.13
1.04
0.98
2.82
2.83
27.82
18.50

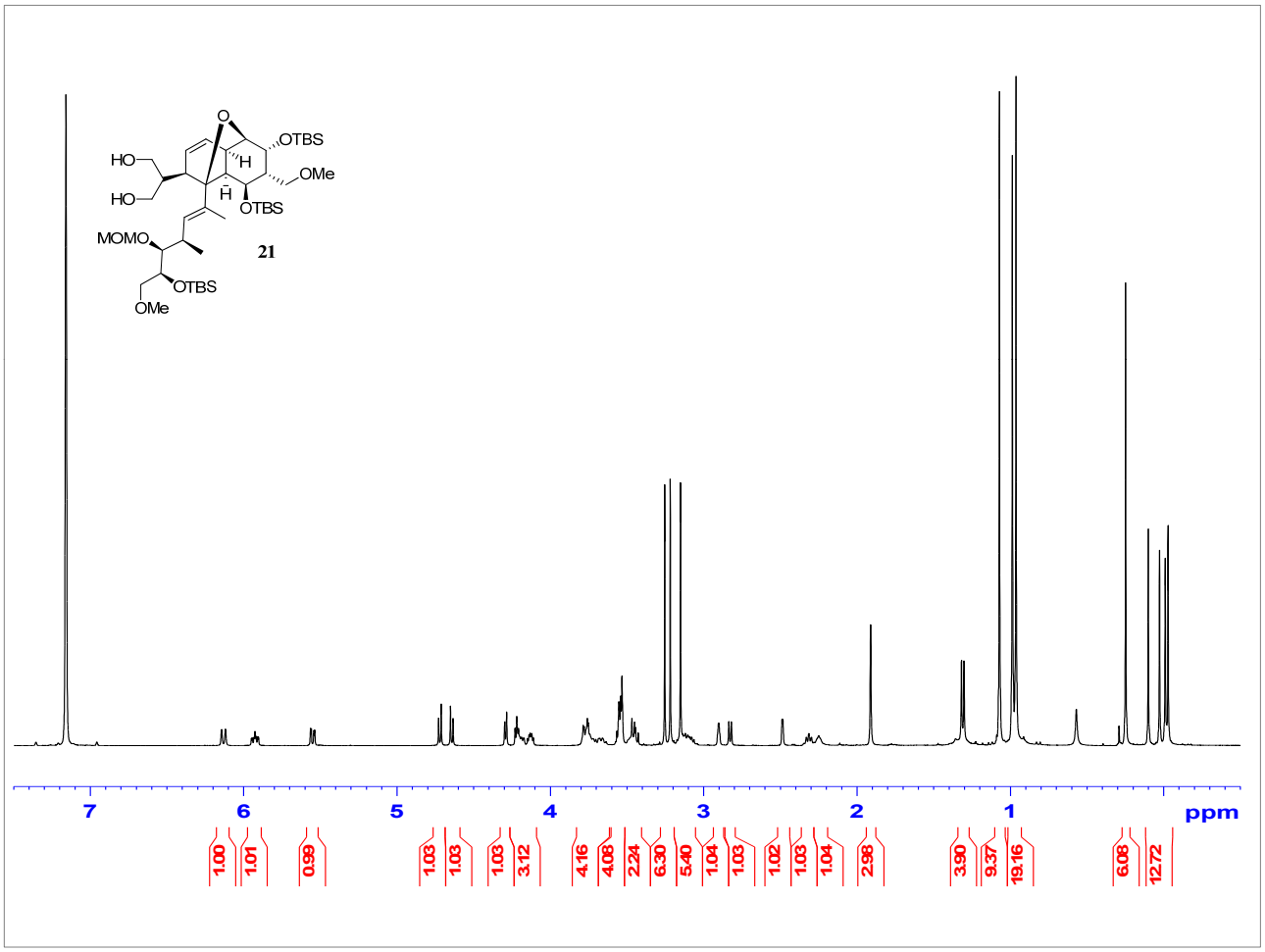

208.55
169.62
169.20
133.00
129.62
128.37
100.13
98.38
89.78
83.05
80.94
74.97
73.34
71.38
69.90
68.84
58.86
58.61
55.95
53.42
52.81
52.03
49.58
49.40
42.15
41.05
37.14
33.28
29.85
26.32
26.05
25.99
18.41
18.34
18.17
16.73
15.94
-3.21
-4.12
-4.37
-4.49
-5.29
MeO
MeO
MOMO
OTBS
OMe
OTBS
OMe
OTBS
H
H
32
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

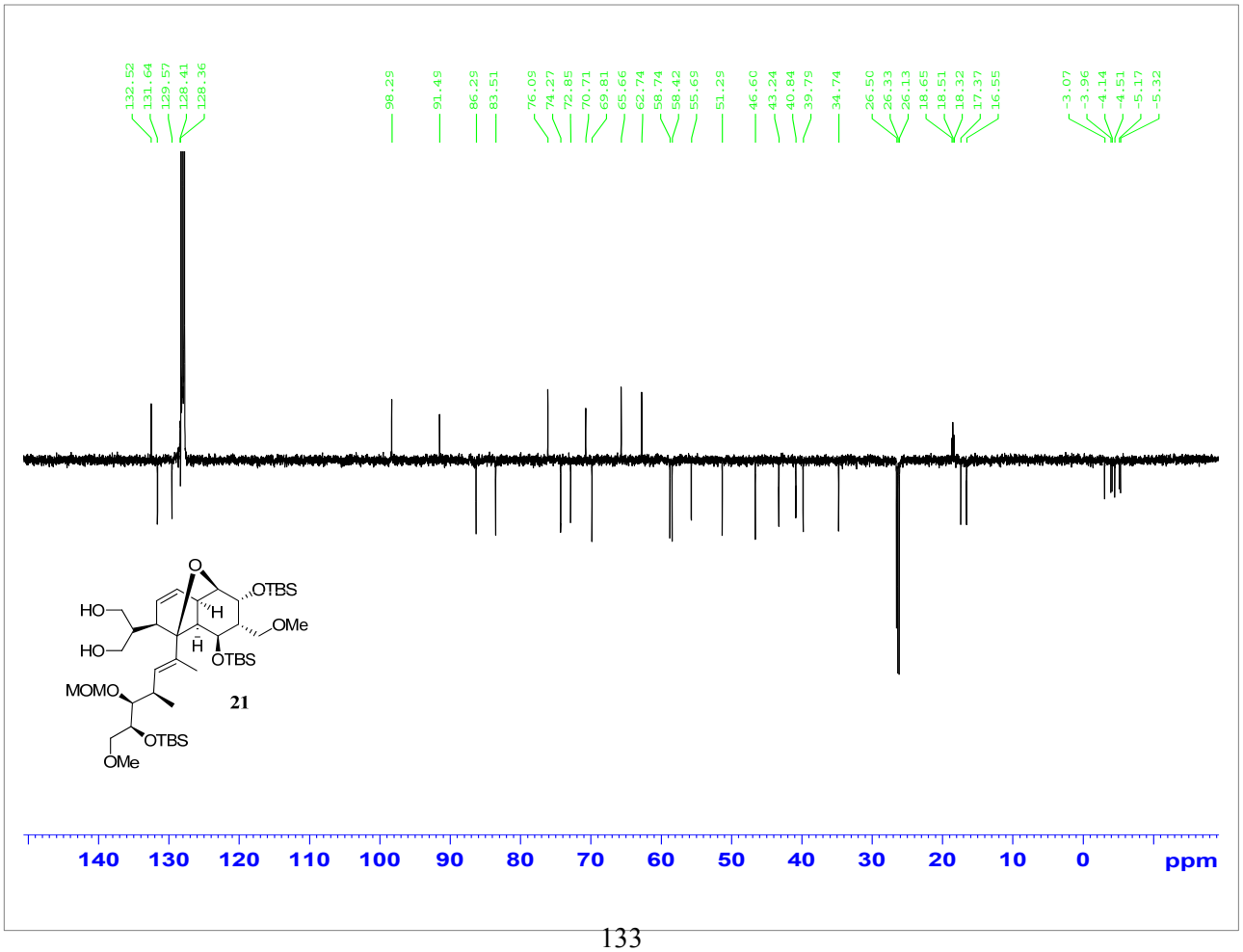

TfO
O
OTBS
MeO
H
OMe
MeO
H
OTBS
O
MOMO
OTBS
OMe
33
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
1.03
0.99
1.01
1.00
1.03
1.01
1.01
1.02
1.02
2.08
3.07
3.11
3.05
2.98
1.55
0.90
6.30
1.24
1.02
3.13
3.77
9.63
9.54
10.35
3.15
3.19
3.02
3.10
3.18
3.34

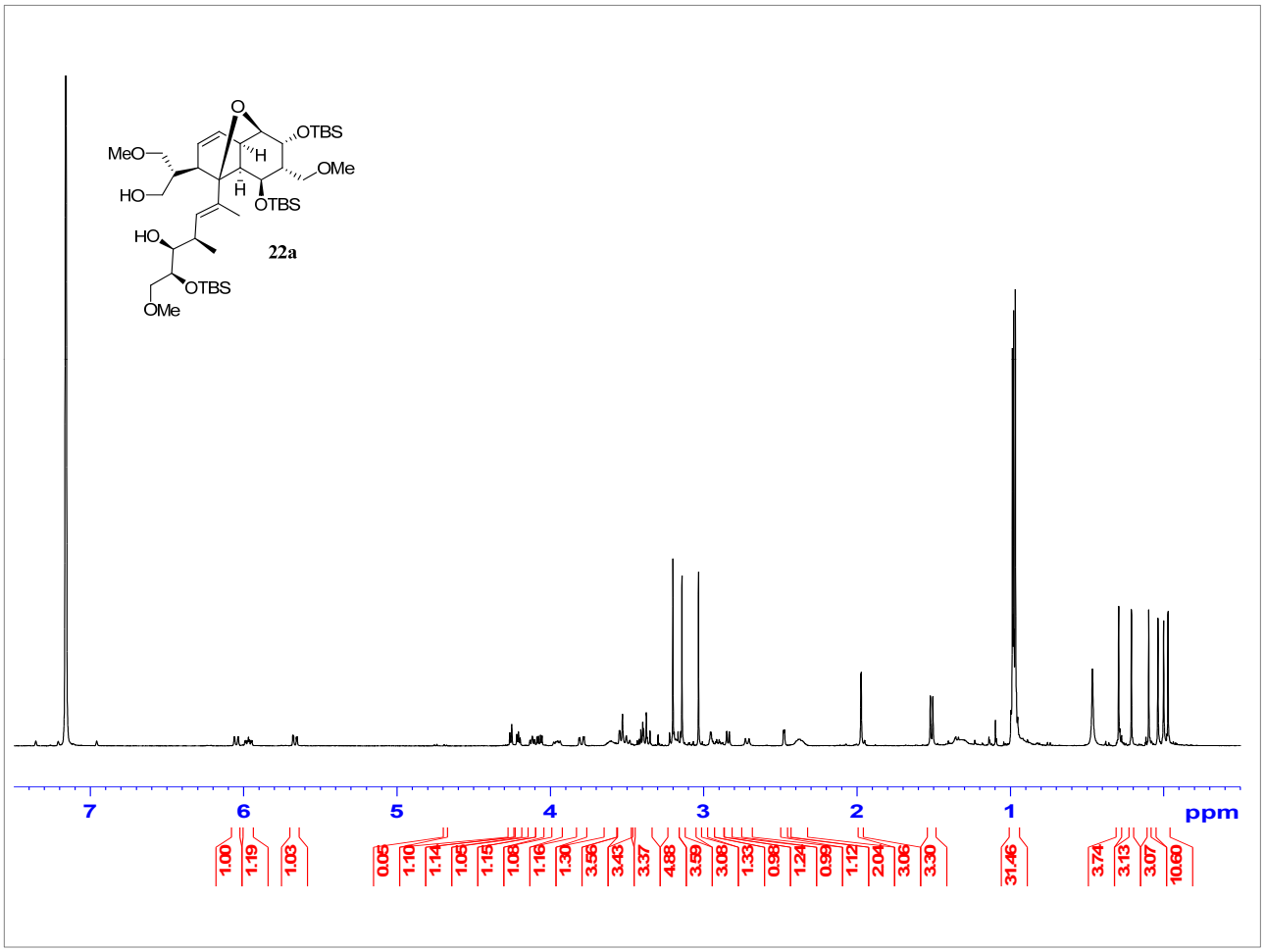

169.50
168.16
149.38
134.29
129.48
129.30
128.40
128.36
127.94
127.27
123.84
118.58
98.96
89.33
85.49
84.14
75.32
74.26
71.93
70.22
69.27
58.59
58.48
55.66
52.36
51.93
51.52
49.98
46.04
44.08
41.15
33.44
26.40
26.24
26.08
18.44
18.20
16.64
16.21
-3.41
-3.79
-4.35
-4.47
TfO
O
OTBS
MeO
H
OMe
MeO
H
OTBS
O
MOMO
OTBS
OMe
33
160
140
120
100
80
60
40
20
ppm

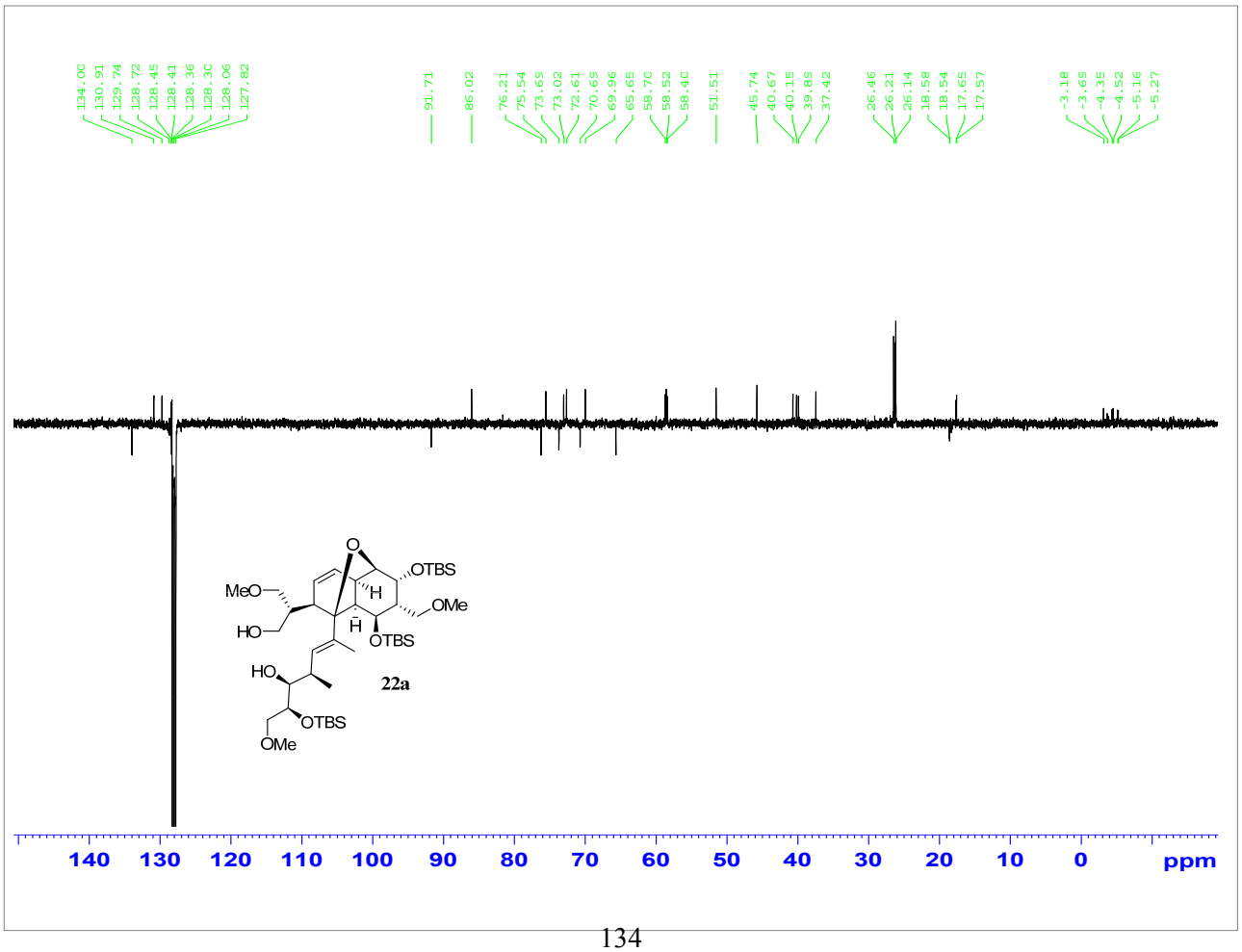

MeO
MeO
MOMO
OTBS
OMe
OTBS
OTBS
OMe
H
H
O
20
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.10
1.04
1.00
1.07
0.99
1.07
1.02
1.04
1.00
1.02
1.44
0.65
3.03
3.14
3.02
4.35
3.22
4.48
1.00
0.99
2.96
3.55
9.41
19.46
6.78
12.72

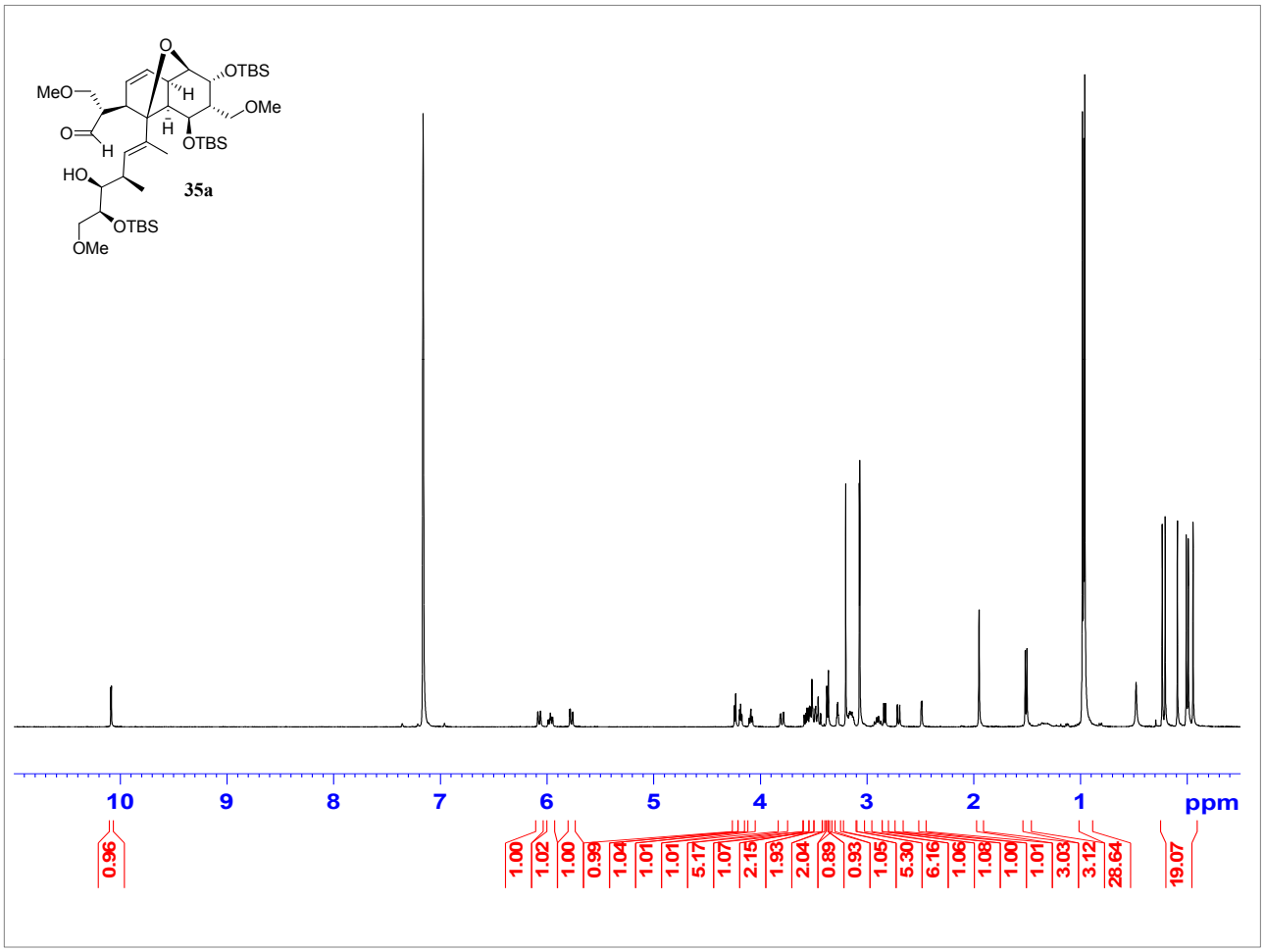

133.00
130.82
129.25
128.73
128.41
127.94
98.92
90.09
86.54
84.22
75.49
74.25
72.86
70.74
69.93
58.55
58.48
55.65
52.10
51.51
51.28
50.47
47.82
41.02
39.60
33.51
26.47
26.28
26.11
18.52
16.90
16.45
-3.20
-4.50
170.26
168.62
MeO
MeO
MOMO
OTBS
OMe
OTBS
OTBS
OMe
H
H
O
20
180
160
140
120
100
80
60
40
20
0
ppm

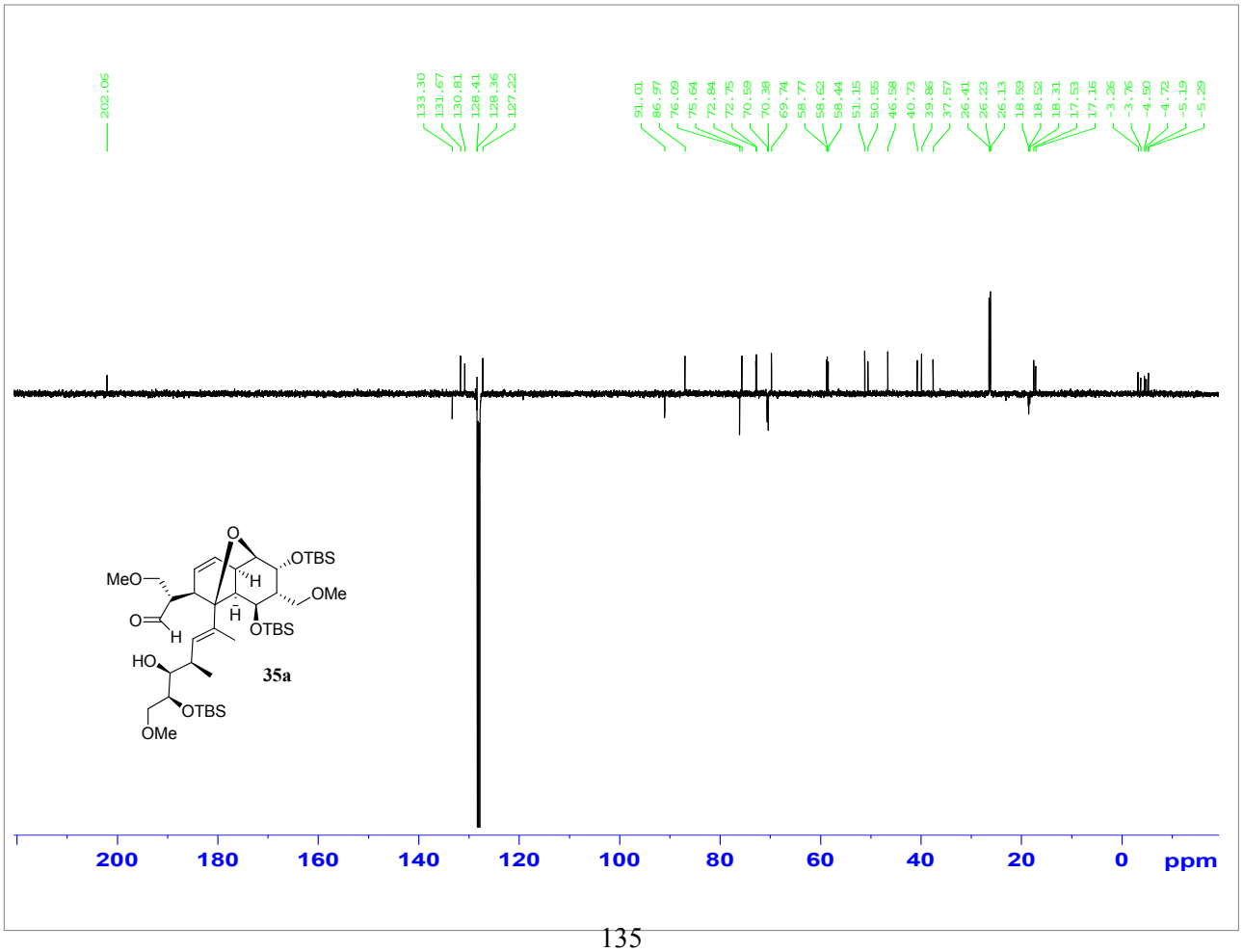

O
OTBS
HO
H
OMe
HO
H
OTBS
MOMO
21
OTBS
OMe
7
6
5
4
3
2
1
ppm
1.00
1.01
0.99
1.03
1.03
1.03
3.12
4.16
4.08
2.24
6.30
5.40
1.04
1.03
1.02
1.03
1.04
2.98
3.90
9.37
19.16
6.08
12.72

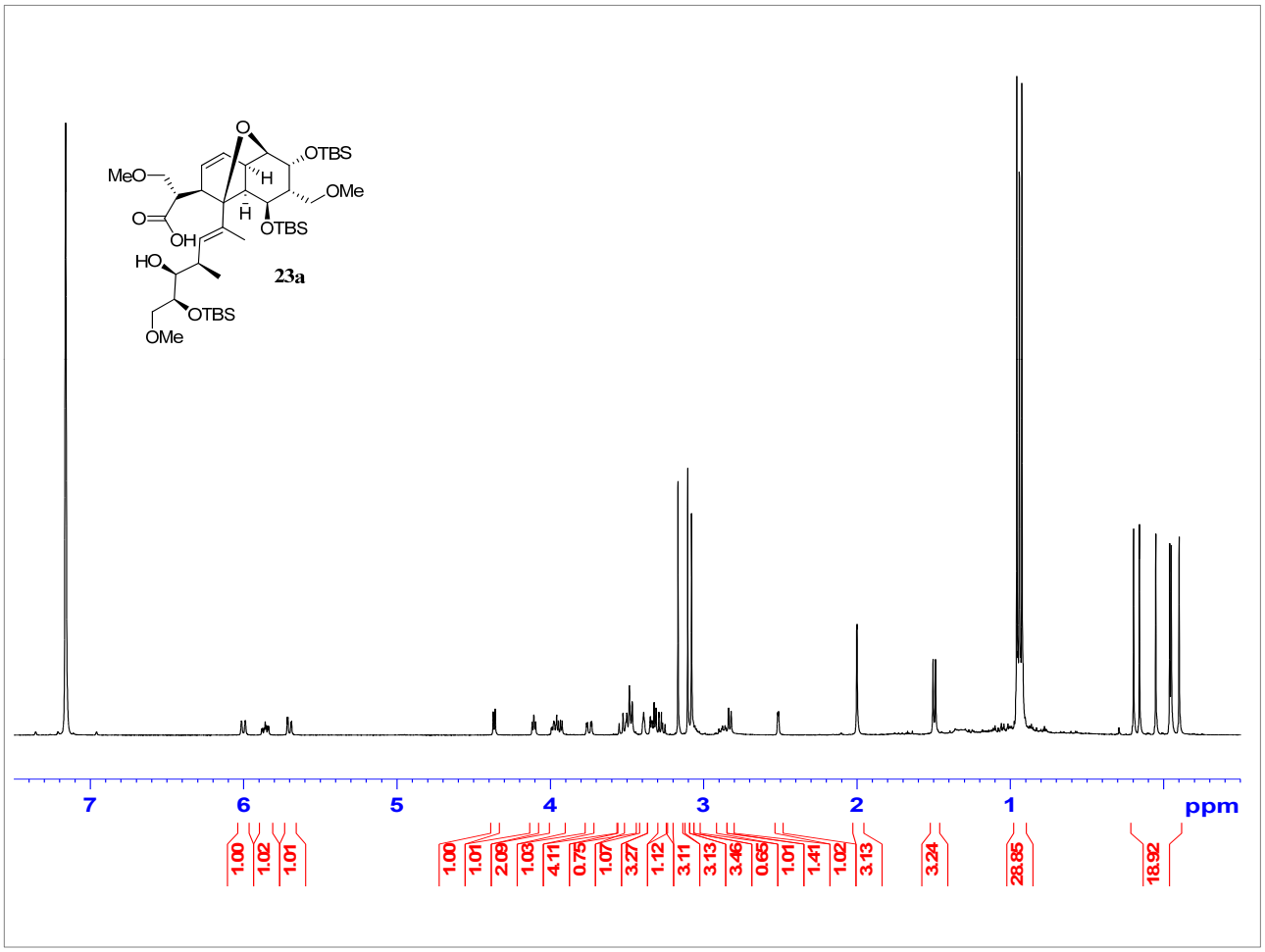

132.52
131.64
129.57
128.41
128.36
98.29
91.49
86.29
83.51
76.09
74.27
72.85
70.71
69.81
65.66
62.74
58.74
58.42
55.69
51.29
46.60
43.24
40.84
39.79
34.74
26.50
26.33
26.13
18.65
18.51
18.32
17.37
16.55
-3.07
-3.96
-4.14
-4.51
-5.17
-5.32
O
OTBS
HO
H
OMe
HO
H
OTBS
MOMO
21
OTBS
OMe
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

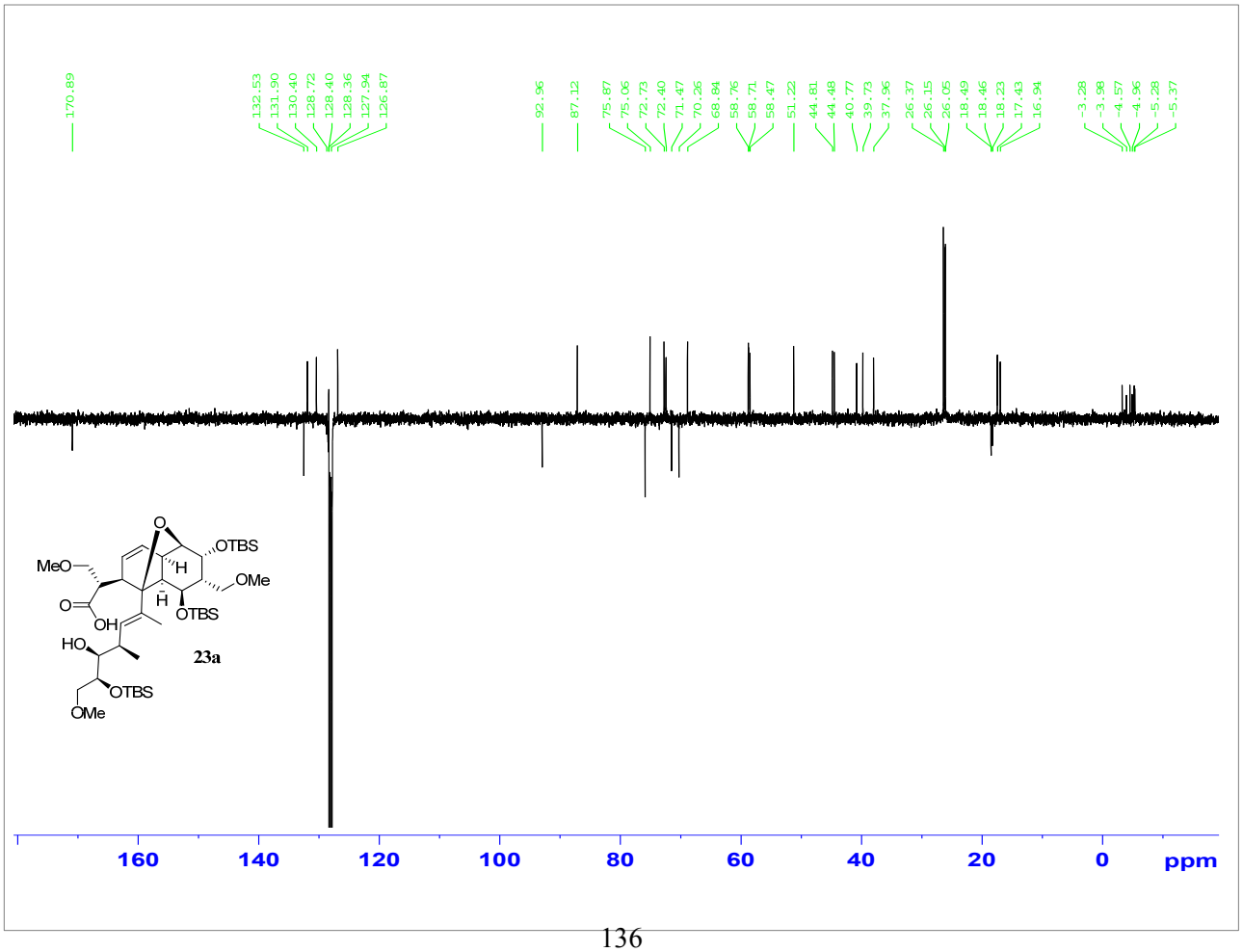

MeO
HO
O
OTBS
H
OMe
H
OTBS
HO
OTBS
OMe
22a
7
6
5
4
3
2
1
ppm
1.00
1.19
1.03
0.05
1.10
1.14
1.08
1.15
1.08
1.16
1.30
3.56
3.43
3.37
4.88
3.59
3.08
1.33
0.98
1.24
0.99
1.12
2.04
3.06
3.30
31.46
3.74
3.13
3.07
10.60

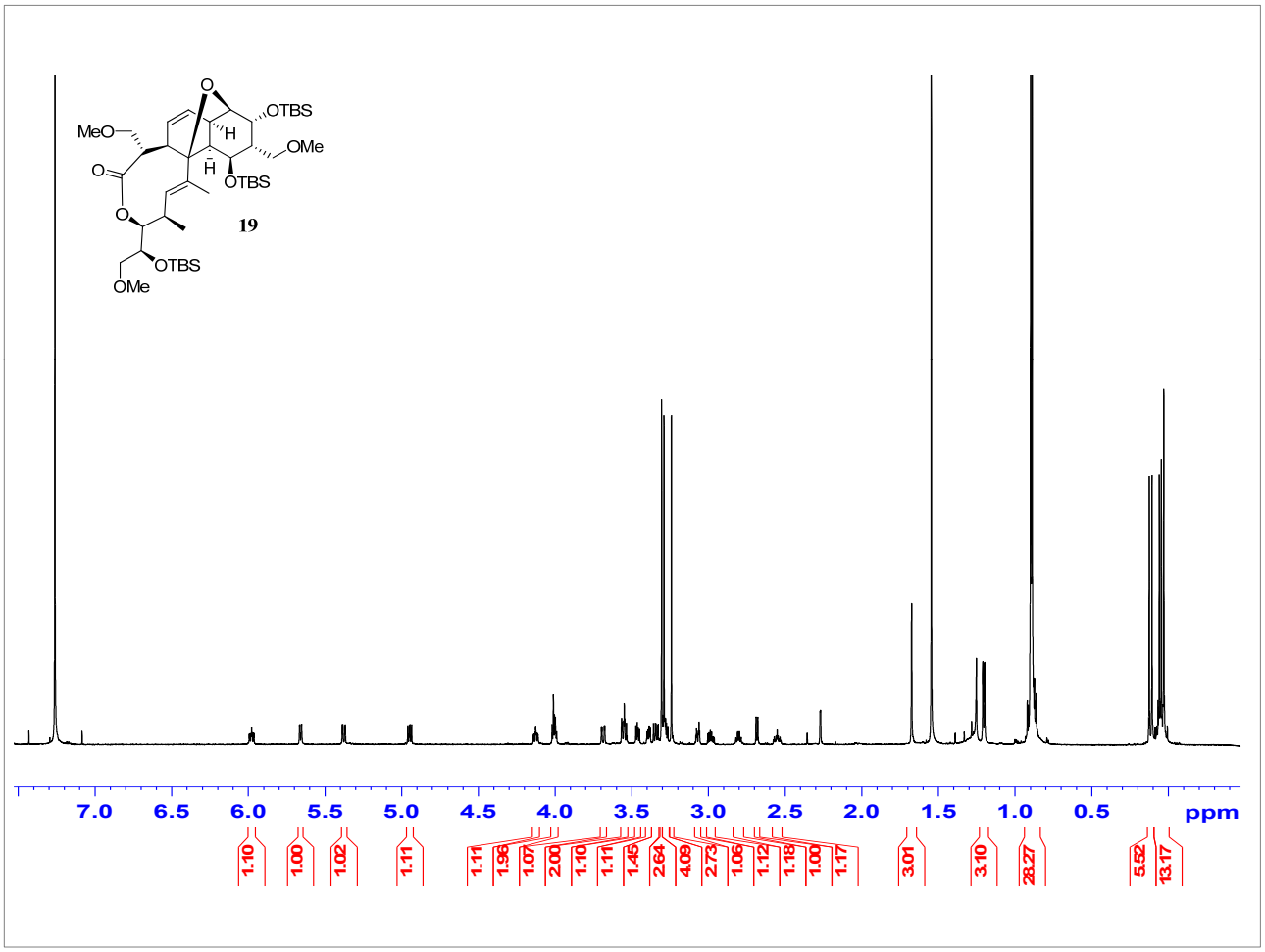

134.00
130.91
129.74
128.72
128.45
128.41
128.36
128.30
128.06
127.82
91.71
86.02
76.21
75.54
73.69
73.02
72.61
70.69
69.96
65.65
58.70
58.52
58.40
51.51
45.74
40.67
40.15
39.89
37.42
26.46
26.21
26.14
18.58
18.54
17.65
17.57
-3.18
-3.69
-4.35
-4.52
-5.16
-5.27
MeO
HO
O
OTBS
H
OMe
H
OTBS
HO
OTBS
OMe
22a
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

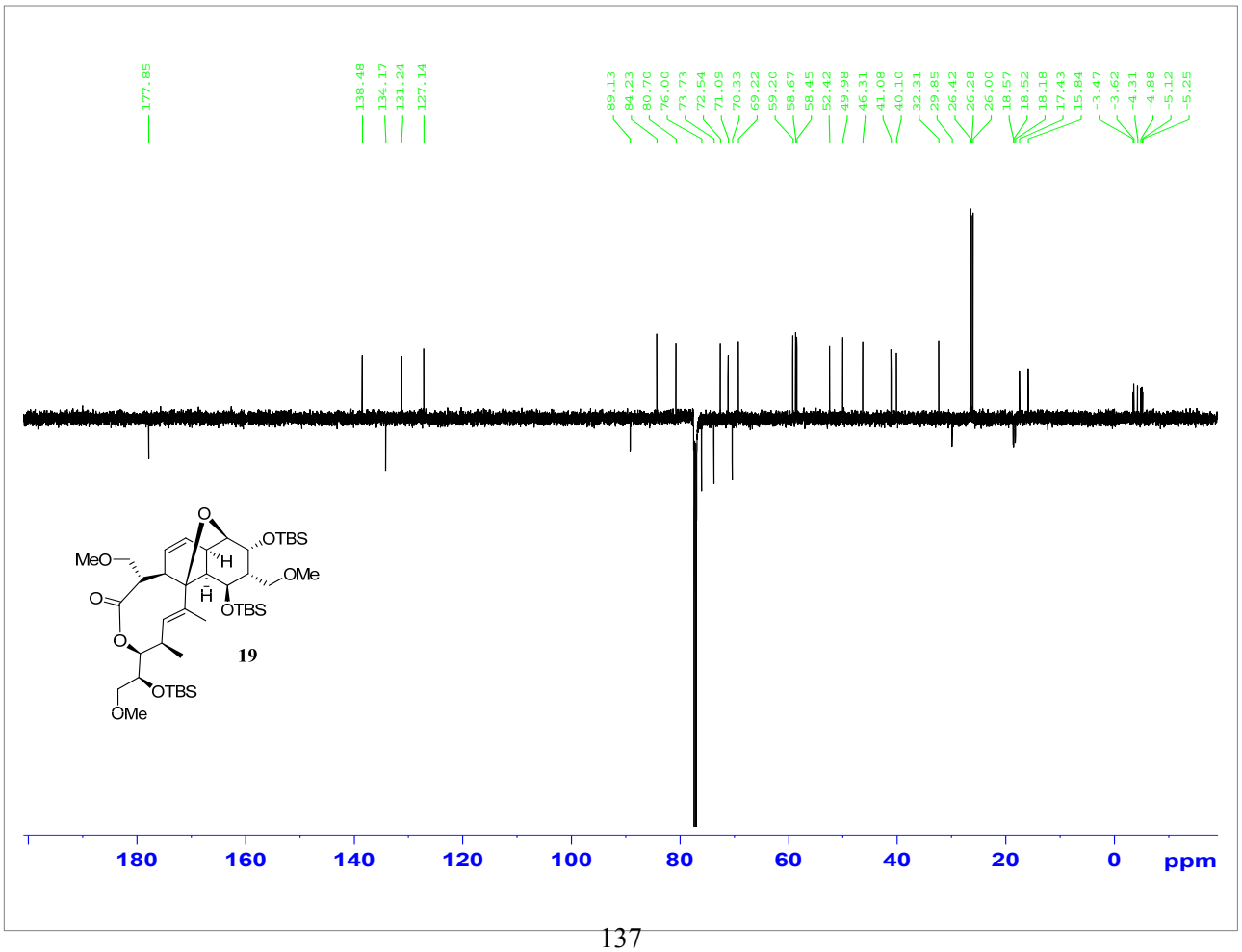

MeO
O
H
O
OTBS
H
H
OTBS
OMe
HO
OTBS
OMe
35a
10
9
8
7
6
5
4
3
2
1
ppm
0.96
1.00
1.02
1.00
0.99
1.04
1.01
1.01
5.17
1.07
2.15
1.93
2.04
0.89
0.93
1.05
5.30
6.16
1.06
1.08
1.00
1.01
3.03
3.12
28.64
19.07

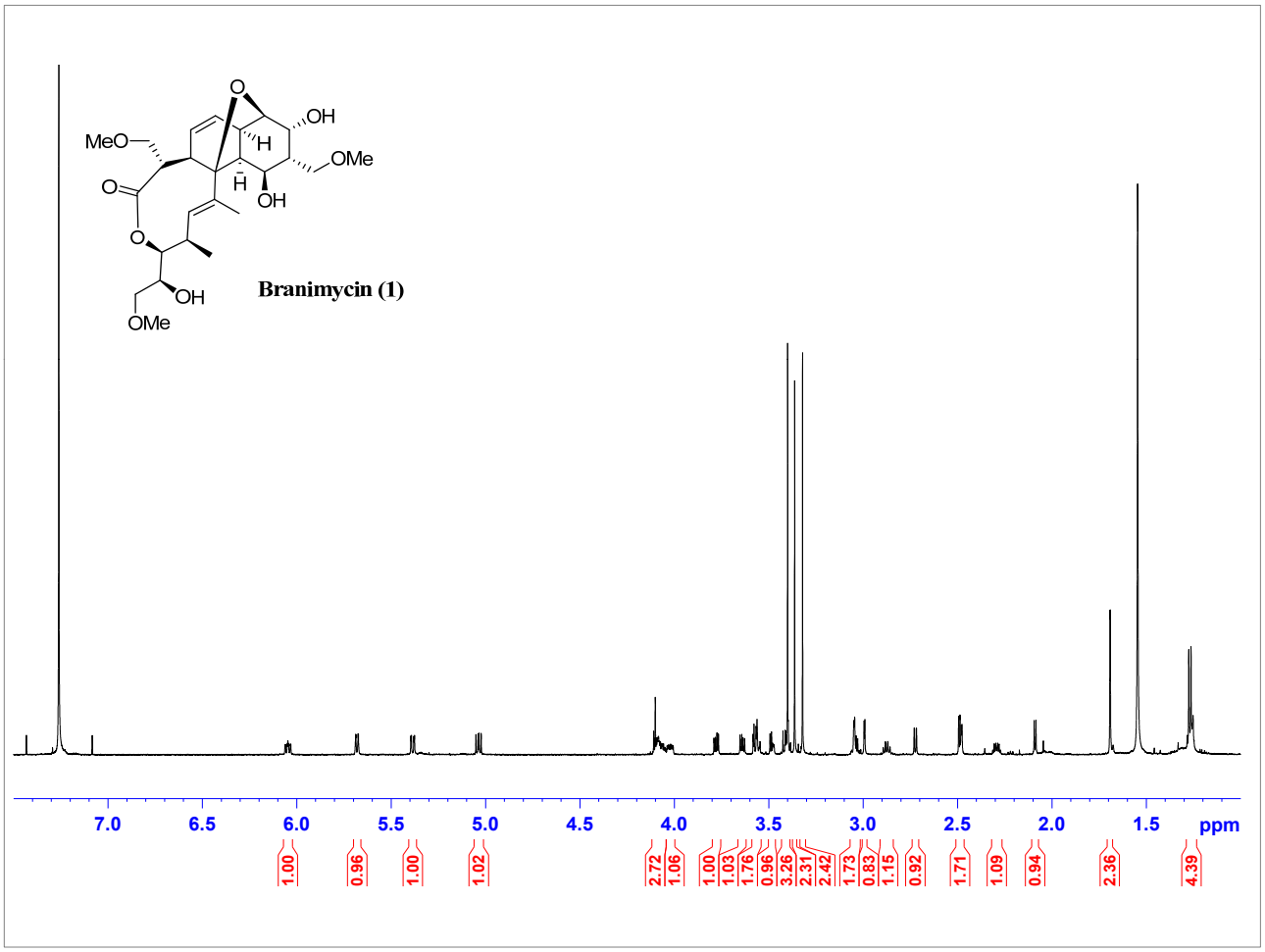

202.06
133.30
131.67
130.81
128.41
128.36
127.22
91.01
86.97
76.09
75.64
72.84
72.75
70.59
70.38
69.74
58.77
58.62
58.44
51.15
50.55
46.58
40.73
39.86
37.57
26.41
26.23
26.13
18.59
18.52
18.31
17.53
17.16
-3.26
-3.76
-4.50
-4.72
-5.19
-5.29
MeO
O
H
O
OTBS
H
H
OTBS
OMe
HO
OTBS
OMe
35a
200
180
160
140
120
100
80
60
40
20
0
ppm

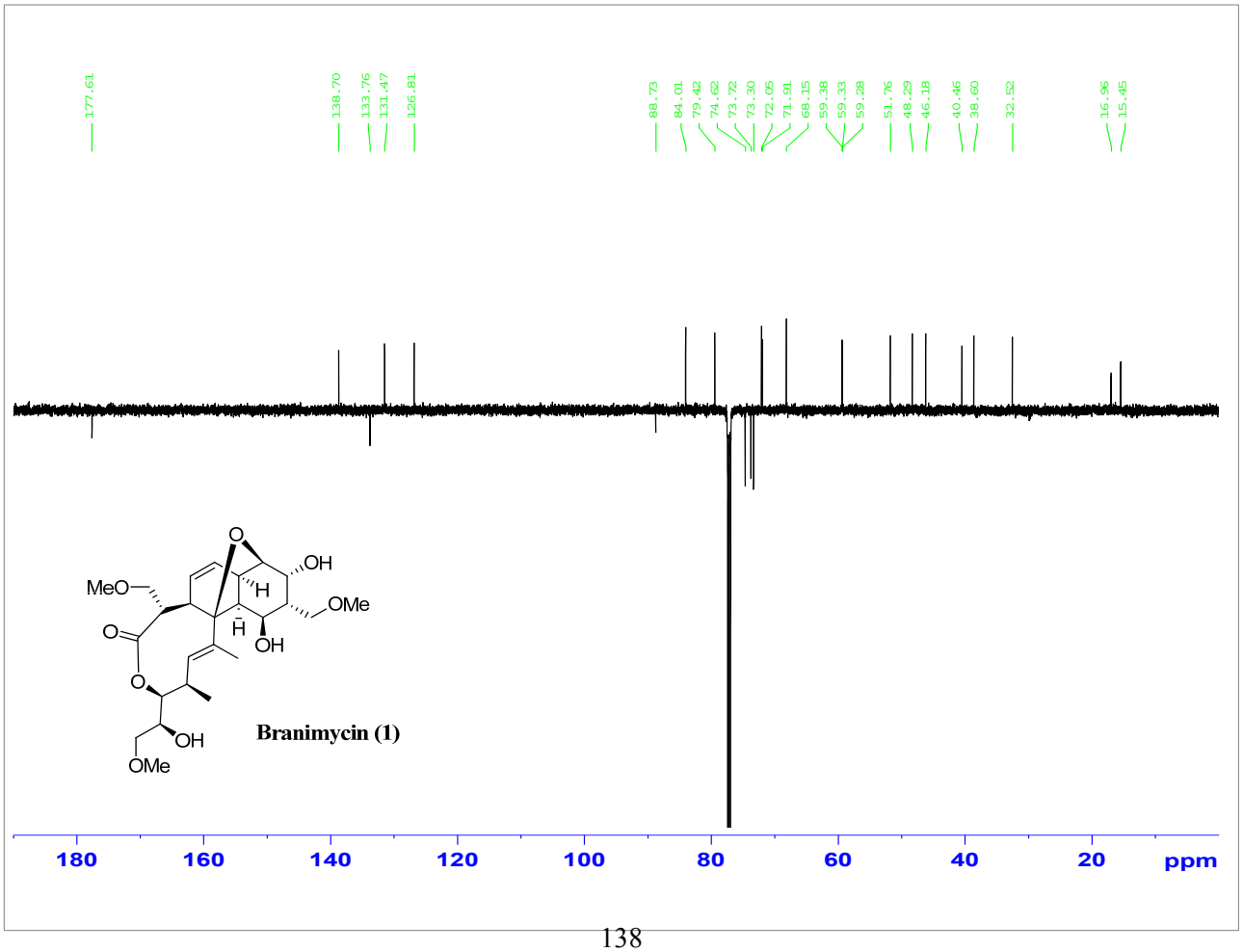

MeO
O
OH
HO
OTBS
OMe
H
OTBS
OTBS
OMe
23a
7
6
5
4
3
2
1
ppm
1.00
1.02
1.01
1.00
1.01
2.08
1.03
4.11
0.75
1.07
3.27
1.12
3.11
3.13
3.46
0.65
1.01
1.41
1.02
3.13
3.24
28.85
18.92

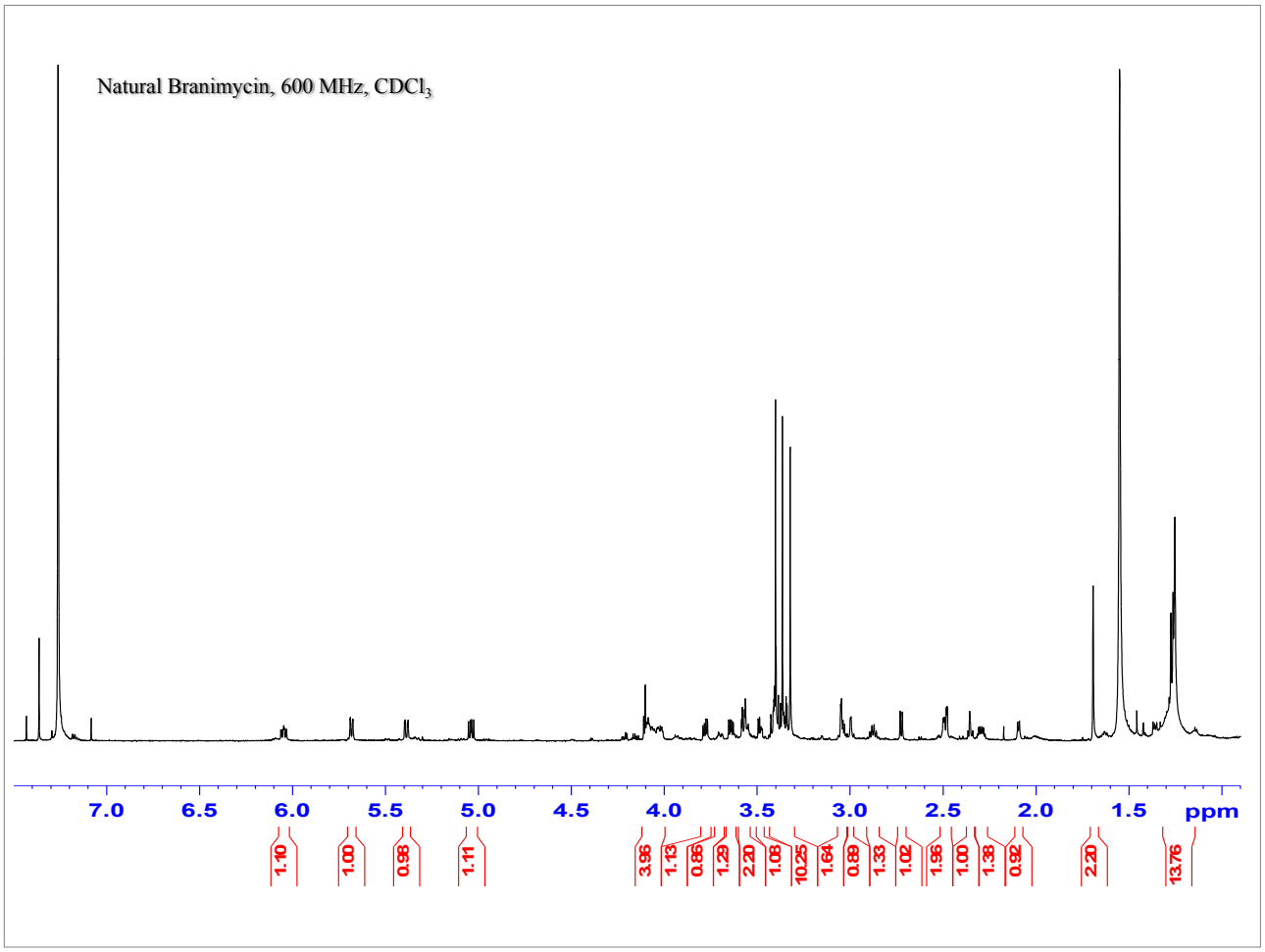

170.89
132.53
131.90
130.40
128.72
128.40
128.36
127.94
126.87
92.96
87.12
75.87
75.06
72.73
72.40
71.47
70.26
68.84
58.76
58.71
58.47
51.22
44.81
44.48
40.77
39.73
37.96
26.37
26.15
26.05
18.49
18.46
18.23
17.43
16.94
-3.28
-3.98
-4.57
-4.96
-5.28
-5.37
MeO
O
OH
HO
OTBS
OMe
H
OTBS
OTBS
OMe
23a
160
140
120
100
80
60
40
20
0
ppm

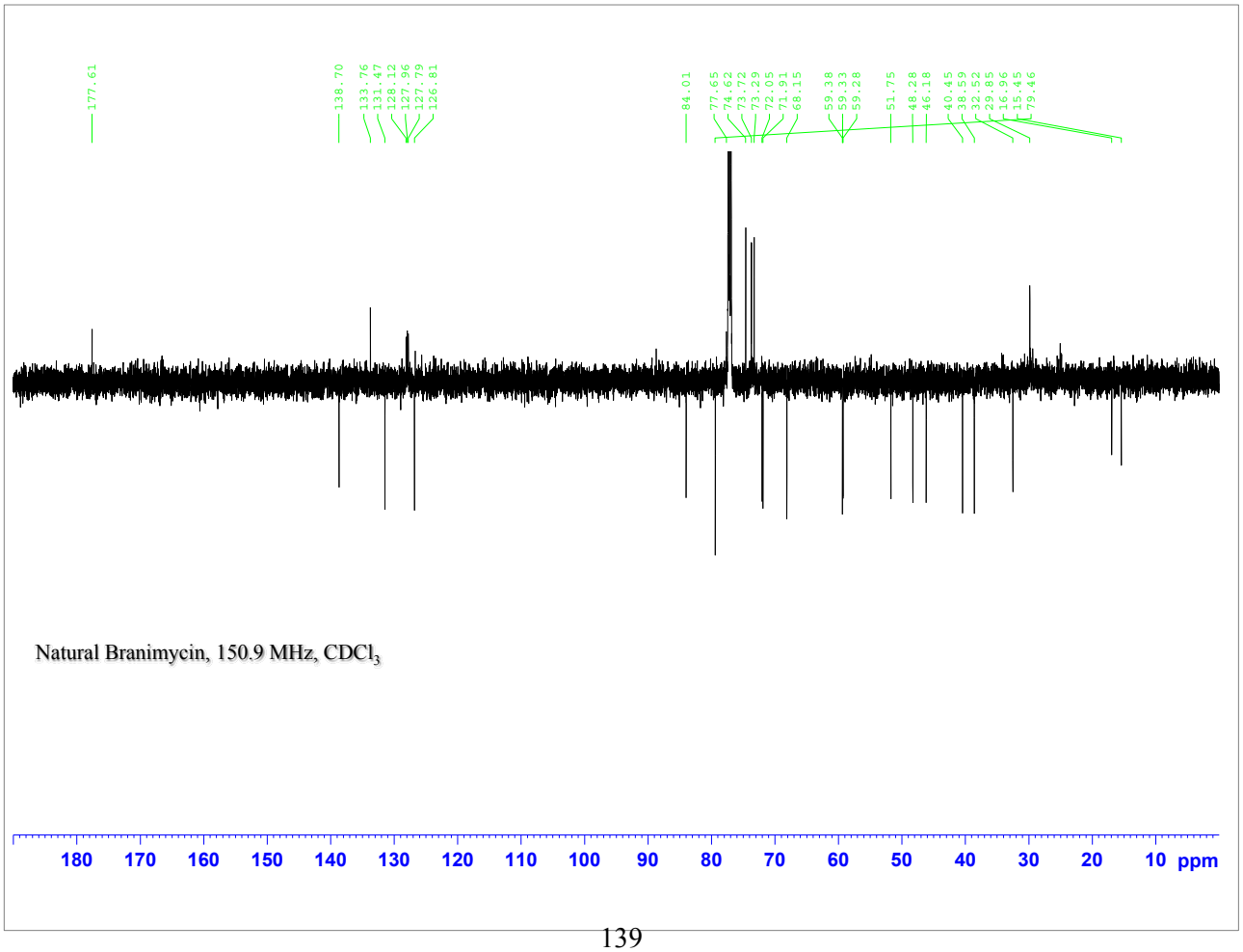

MeO
O
OTBS
H
OMe
H
OTBS
O
O
OTBS
OMe
19
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.10
1.00
1.02
1.11
1.11
1.96
1.07
2.00
1.10
1.11
1.45
2.64
4.09
2.73
1.06
1.12
1.18
1.00
1.17
3.01
3.10
28.27
5.52
13.17


177.85
138.48
134.17
131.24
127.14
89.13
84.23
80.70
76.00
73.73
72.54
71.09
70.33
69.22
59.20
58.67
58.45
52.42
49.98
46.31
41.08
40.10
32.31
29.85
26.42
26.28
26.00
18.57
18.52
18.18
17.43
15.84
-3.47
-3.62
-4.31
-4.88
-5.12
-5.25
MeO
O
OTBS
H
OMe
H
OTBS
O
O
OTBS
OMe
19
180
160
140
120
100
80
60
40
20
0
ppm


Branimycin (1)
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
1.00
0.96
1.00
1.02
2.72
1.06
1.00
1.03
1.76
0.96
3.26
2.31
2.42
1.73
0.83
1.15
0.92
1.71
1.09
0.94
2.36
4.39


177.61
138.70
133.76
131.47
126.81
88.73
84.01
79.42
74.62
73.72
73.30
72.05
71.91
68.15
59.38
59.33
59.28
51.76
48.29
46.18
40.46
38.60
32.52
16.96
15.45
Branimycin (1)
180
160
140
120
100
80
60
40
20
ppm

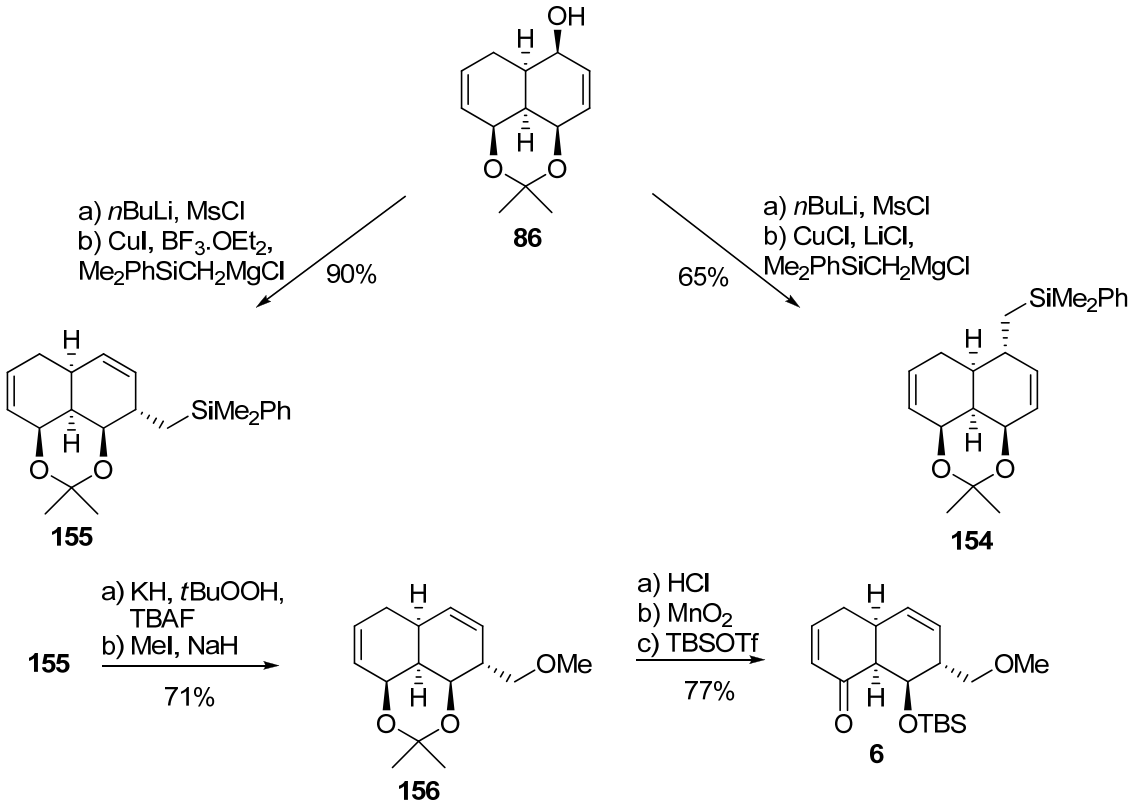

Natural Branimycin, 600 MHz, CDCl3
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
1.10
1.00
0.98
1.11
3.96
1.13
0.86
1.29
2.20
1.08
10.25
1.64
0.88
1.33
1.02
1.96
1.00
1.38
0.92
2.20
13.76


177.61
138.70
133.76
131.47
128.12
127.96
127.79
126.81
84.01
77.65
74.62
73.72
73.29
72.05
71.91
68.15
59.38
59.33
59.28
51.75
48.28
46.18
40.45
38.59
32.52
29.85
16.96
15.45
79.46
Natural Branimycin, 150.9 MHz, CDCl3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

7.1 Additional remarks[48]

7.1.1 Synthesis of decalin ketone 2

Decalin ketone **2** was also successively synthesized *via* the intermolecular quinone based Diels-Alder route (Scheme 39). Incorporation of the C9-methoxy methyl substituent from the convex face was accomplished by mesylation of the allylic hydroxyl group of **86** at -78 °C

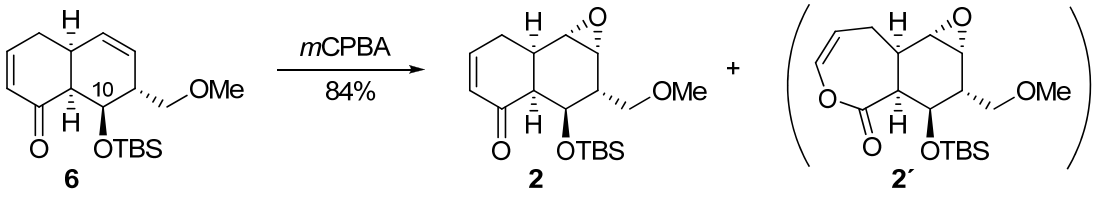


Scheme 42: Preparation of decalin ketone **6**.

followed by S_N2' displacement of this unstable mesylate *via* addition of a silylmethyl copper boron trifluoride etherate complex (derived from $Me_2PhSiCH_2MgCl$) and subsequent warming to room temperature according to the method of Yamamoto.[49] The resulting diene ketal **155** was unstable upon concentration in the presence of traces of $BF_3.OEt_2$. Work up with concentrated aqueous ammonia solution and repeated extraction of the reaction mixture with brine alleviated this problem (Scheme 42). Interestingly, by using CuCl or CuCN in a catalytic amount and in the absence of $BF_3.OEt_2$ mainly the corresponding S_N2 regioisomer **154** was formed (**154:155** = 4:1, 81% yield). Oxidative cleavage of the C-Si bond[50] followed by

[48] Numbering remains the same as in the publication for compounds which have been presented therein.
[49] Yamamoto, Y.; Maruyama, K. *J. Am. Chem. Soc*. **1978**, *100*, 3240.
[50] Tamao, K.; Akita, M.; Kumada, M. *J. Organomet. Chem*. **1983**, *254*, 13-22.

methylation of the corresponding primary alcohol gave ketal **156** in high yields. Cleavage of acetal **156** in aqueous HCl and THF was followed by allylic oxidation with manganese dioxide in DCM. The resulting β-hydroxy ketone was protected as TBS ether. Initial attempts using TBSCl/imidazole in DMF at 22 °C resulted in nearly exclusive formation of side products of intramolecular 1,4-addition. Applying TBSOTf at -78 °C gave the desired enone **6** in excellent yield.



Scheme 43: Regio- and stereoselective epoxidation of **6**.

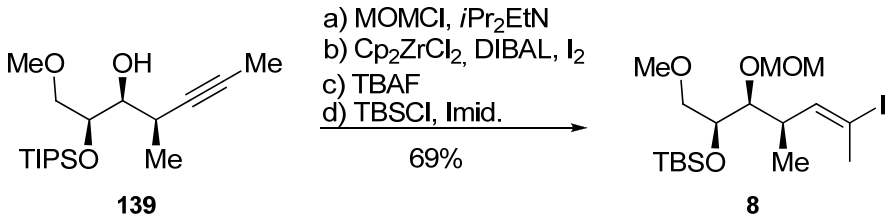
Epoxidation of **6** from the α-face was accomplished with high stereoselectivity by *m*CPBA (Scheme 43). The stereoselectivity is strongly influenced by the protecting group on C10. The PMB-ether affords a diastereomeric ratio of 3:1 whereas TBS-protection of the hydroxyl group increased the diastereomeric ratio to 10:1. The best yields were obtained at 60% conversion, whereas full conversion resulted in a decrease of isolable product (77%), mostly due to a competitive Bayer-Villiger oxidation yielding lactone **2´**. While facing scale-up problems when applying the reported enantioselective route to **86**[45a] we decided to work with the racemic mixture. Racemic **2** could be separated by chiral HPLC, being available in multigram quantities *via* this sequence. The racemates were unambiguously distinguished after addition of **3**, comparing ^{1}H and ^{13}C spectra of the resulting products with **10** derived from the recently published desymmetrization route.[43]

7.1.2 Modification of the C13-C18 side chain

Optimization studies of the preparation of the side chain became necessary because of the large quantities needed and also because of the rather high price of starting (*S*)-glycidol. Methylation of (*S*)-glycidol with MeI/Ag_2O required up to 48 h and never resulted in full conversion. Addition of molecular sieves[51] gave full conversion after only 2 h yielding **135** (see chapter 3.2.6) in decent 78% isolated yield. To our delight, also the addition of **138** to **137** could be optimized. Upon increasing the amount of $TiCl_4$ up to 1.7 mol eq. and performing the reaction at lower temperatures (-95 to -78 °C) the desired product **139** was obtained in 89%

[51] Reymond, S.; Cossy, J. *Tetrahedron* **2007**, *63*, 5918-5929.

yield. **139** was protected as its MOM-ether (Scheme 44). To avoid 1,2-migration of the TIPS-group, *i*Pr_2EtN was used as a base. After regioselective hydrozirconation, followed by iodination, the hydroxyl functionality was converted to the TBS-ether instead of the TIPS-ether (because of the possibility to cleave the protecting group under milder conditions), to yield **8** in 69% over 4 steps.



139 **8**

Scheme 44: Modification of the C13-C18 side chain.

7.1.3 Introduction of the C5-oxygen functionality

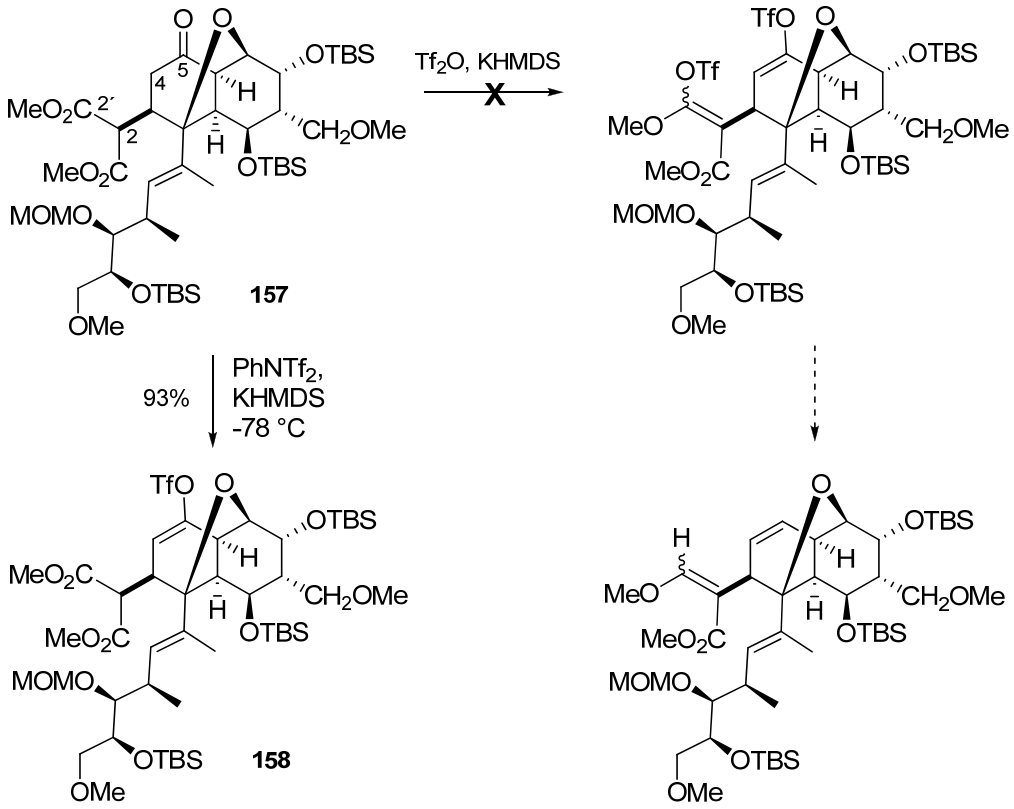
Allylic oxidation of tricycle **11** by selenium dioxide[52] was unsuccessful. Unfortunately, only decomposition was observed upon treatment of **11** with $PhIO_2$/$(PhSe)_2$. Oxidation with $Mn(OAc)_3$*$2H_2O$/*t*BuOOH gave **12** in only 30% yield. Further improvement was achieved by employing an excess of CrO_3*3,5-dimethylpyrazole in DCM, providing enone **12** in 67% yield. Performing the reaction in AcCN, EtOAc or PhCl gave the same result with respect to DCM, whereas no reaction was observed in THF or DMF. No product formation was observed when the reaction was performed at lower temperatures (-78 °C) even if the reaction mixture was subsequently warmed to -20 °C, most probably as too low temperatures result in precipitation of the complex and subsequent polymerization. On the other hand, if the complex is stored at 0 °C or room temperature, it also rapidly loses its activity due to polymerization.

7.1.4 C2-C3 bond formation via conjugate addition and completion of the synthesis of branimycin (1) [53]

1,4-Addition of dimethyl malonate occurred exclusively at the concave face of enone **12**[54] presumably due to steric hinderance of the opposing face by the C13-C18 side chain and by directing effects imposed by the ether bridge. We then intended to pave the way for stereoinduction *via* regio- and stereoselective hydrogenation of a double bond at C2-C2´ (Scheme 45). Unfortunately, treating **157** with Tf_2O/KHMDS to obtain 2,2´- and 4,5-bis-vinyl

[52] Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc*. **1977**, *99*, 5526.
[53] For a detailed discussion of sequence **12** -> **18** see: Gromov, A. *Dissertation*, Universität Wien, **2009**.
[54] The relative configuration at C3 was corroborated by NOE experiments, showing clear crosspeaks between H3 and H11.

triflates mainly caused decomposition of the molecule whereas $PhNTf_2$/KHMDS only gave mono-vinyl triflate **158** in excellent yield. Treatment of **158** with Tf_2O/KHMDS also caused decomposition.



Scheme 45: Vinyl triflate formation.

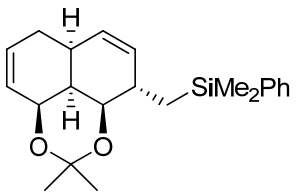
Pd-catalyzed reduction of vinyl triflate **158** failed using both Et_3SiH and formic acid/DIPEA respectively, where only starting material could be recovered. Reduction with Bu_3SnH gave desired diester **20** in good yield, the presence of LiCl and 2,6-lutidine turned out to be crucial for the outcome of the reaction. **20** was reduced to diol **21** by treatment with superhydride. The presence of pentaerythritol in the course of work up for re-complexation of boron from the product was important for obtaining high yields. Applying DIBAL or $LiAlH_4$ always caused partial cleavage of the TBS group located on the C13-C18 side chain whereas $LiBH_4$ gave no reaction. Enzyme mediated stereodifferentiation at the stage of diol **21** also failed. Using vinyl acetate and *Pseudomonas fluorescens* lipase, *Pseudomonas cepacia*, *candida Antarctica* lipase and *pig pancreatic* lipase respectively resulted only in the recovery of starting material. Exclusive mono *O*-methylation of **21** was achieved applying Ag_2O and MeI. The presence of molecular sieves or an excess of Ag_2O also gave the corresponding diether in up to 20% yield, applying HgO in place of Ag_2O gave no reaction.

Employing the Corey-Nicolaou double activation protocol[55] for the construction of the nine-membered lactone in **19**/**24** failed. The corresponding 2-thiopyridyl esters of **23a** and **b** were generated smoothly by treatment with 2,2´-dipyridyldisulfide and triphenylphosphine[56] but slow addition of the thiopyridyl esters to refluxing xylene and toluene respectively gave no further reaction, only starting material (**23a/b)** and the corresponding thiopyridyl esters could be recovered. A substantial increase in the rate of cyclization in the presence of metal ions has been described by several groups.[57] Applying Gerlach´s modification with an excess of $AgClO_4$ did afford the nine-membered macrolactones **19** and **24** in good yields. The reaction could be optimized from initial 20% to 40% yield. Decreasing temperature from 110 °C to 85 °C and a concomitant decrease in addition time of the 2-thiopyridyl ester from 8 h to only 2 h resulted in the substantial improvement to up to 40% yield.

The global deprotection of the three secondary hydroxyl groups of **19** and **24** with a 70% solution of HF.pyridine in either MeCN or THF gave no reaction. Eventually, the global deprotection step was smoothly effected with an excess of TBAF in THF to provide branimycin (**1**) in 85% yield. The relative configuration at C2 of **1**, **19**, **24** and **25** was unambiguously assigned by NOE experiments. **1** and **19** showed clear crosspeaks between H2 and H14, whereas C2 methylene protons did not interact with H14. On the other hand C2 methylene protons of **24** and **25** showed clear crosspeaks with H14, H2 did not.

[55] Corey, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc*. **1974**, *96*, 5614.
[56] Mukaiyama, T.; Matsueda, R.; Suzuki, M. *Tetrahedron Lett*. **1970**, 1901.
[57] a) Wollenberg, R. H.; Nimitz, J. S.; Gokcek, D. Y. *Tetrahedron Lett*. **1980**, *21*, 2791. b) Gerlach H.; Thalmann, A. *Helv. Chim. Acta* **1974**, *57*, 2661. c) Masamune, S.; Hayase, Y.; Schilling, W.; Chan, W. K.; Bates, G. S. *J. Am. Chem. Soc*. **1977**, *99*, 6756. d) Kim, S.; Lee, J. I. *J. Org. Chem*. **1984**, *49*, 1712. e) Palomo, C.; Oiarbide, M.; Garcia, J. M.; Gonzalez, A.; Pazos, R.; Odriozola, J. M.; Banuelos, P.; Tello, M.; Linden, A. *J. Org. Chem*. **2004**, *69*, 4126.

7.2 Additional experimental procedures



Ketal (**155**).

To a slurry of CuI (8.90 g, 46.85 mmol) in 67 mL of THF at 0 °C was added dimethyl-phenyl-silyl-methyl-magnesium chloride (9.04 g, 43.24 mmol). The suspension was stirred for 10 min and then cooled to -78 °C. Boron trifluoride etherate (5.66 mL, 45.05 mmol) was added and the resulting mixture was stirred for 20 min.

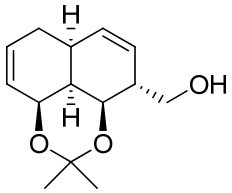
A solution of ketal **86** (4.00 g, 18.02 mmol) in 30 mL of THF was cooled to – 78 °C and *n*-butyllithium (1.6 M in hexanes, 12.95 mL, 20.72 mmol) was added. After 5 min methanesulfonyl chloride (1.68 mL, 21.62 mmol) was added slowly, and the solution was stirred for 5 min and then transferred *via* cannula into the cuprate suspension at – 78 °C, stirred for 40 min and then warmed to room temperature for 3.5 h. The reaction was quenched at 0 °C *via* addition of NEt_3 and after 5 min an ammonia solution (ca. 25% NH_3) was added. After warming to ambient temperature the mixture was filtered, the layers were separated and the aqueous layer was extracted with DCM. The combined organic layers were washed three times with $NaCl_{sat}$, dried ($MgSO_4$) and concentrated. The residue was subjected to column chromatography (EtOAc/hexane) to yield **155** (5.75 g, 90%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.54 – 7.48 (m, 3H), 7.37 – 7.32 (m, 3H), 6.30 (ddd, *J* = 9.6, 6.7, 2.8 Hz, 1H), 6.08 (ddd, *J* = 8.8, 5.8, 2.7 Hz, 1H), 5.72 (ddd, *J* = 9.6, 5.6, 2.3 Hz, 1H), 5.51 (dd, *J* = 10.0, 2.3 Hz, 1H), 4.46 (dd, *J* = 5.3, 5.3 Hz, 1H), 3.88 (dd, *J* = 3.3, 3.3 Hz, 1H), 2.38 (m, 1H), 2.29 – 2.13 (m, 2H), 2.07 (m, 1H), 1.96 (m, 1H), 1.40 (s, 3H), 1.29 (s, 3H), 0.90 (dd, *J* = 14.5, 5.7 Hz, 1H), 0.78 (dd, *J* = 14.5, 9.8 Hz, 1H), 0.35 (s, 3H), 0.31 (s, 3H).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 139.6, 136.5, 133.7, 133.5, 129.9, 129.4, 129.1, 128.0, 97.8, 71.6, 65.1, 36.8, 31.0, 30.9, 30.1, 29.7, 20.3, 19.9, -1.6, -2.4.

IR (film): 3069, 3045, 2991, 2954, 2905, 1773, 1487, 1378, 1301, 1250, 1170, 1113, 1045, 958, 834, 790, 728, 699, 467 cm^{-1}.

HRMS: calc. for $C_{21}H_{27}O_2Si$ $[M - CH_3]^+$: 339.1780; found: 339.1776.



Alcohol (**155a**).

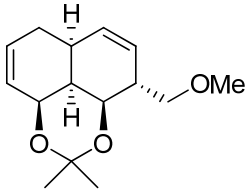
Potassium hydride (35 wt % suspension in mineral oil, 10.08 g, 88.14 mmol) was transferred in a dried flask under Ar and the mineral oil was removed by washing three times with dry pentane. *N*-Methyl-2-pyrrolidone (NMP, 54 mL) was added and the flask was cooled to 0 °C. *t*BuOOH (5-6 M in decane, 17.63 mL) was added dropwise, followed 10 min later by addition of a solution of **155** (5.20 g, 14.69 mmol) in NMP (97 mL). After another 10 min the mixture was warmed to rt, TBAF (1 M in THF, 33.80 mL, 33.80 mmol) was added and the stirring was continued for 3 h. The reaction was quenched with aqueous $Na_2S_2O_3$ (5 M, 200 mL) and stirred for 30 min. The mixture was diluted with water, the aqueous phase was extracted with EtOAc (4 x 100 mL) and the combined organic phases were dried ($MgSO_4$). Solvents were removed *in vacuo* (5 torr at ~ 100 °C to remove NMP) and the residue was subjected to column chromatography (EtOAc/hexane) to yield alcohol **155a** (2.78 g, 78 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.14 (m, 1H), 6.00 (ddd, *J* = 9.5, 4.4, 1.5 Hz, 1H), 5.72 (d, *J* = 10.0 Hz, 1H), 5.60 (ddd, *J* = 10.1, 4.2, 2.0 Hz, 1H), 4.60 (dd, *J* = 5.2, 5.2 Hz, 1H), 4.23 (dd, *J* = 4.8, 4.8 Hz, 1H), 3.73 (d, *J* = 10.3 Hz, 1H), 3.60 (dd, *J* = 10.6, 7.4 Hz, 1H), 2.65 – 2.58 (m, 1H), 2.42 – 2.32 (m, 3H), 2.28 – 2.19 (m, 1H), 2.13 – 2.05 (m, 1H), 1.51 (s, 3H), 1.40 (s, 3H).

^{13}C-NMR(100.6 MHz,$CDCl_3$): δ = 133.5, 132.9, 129.8, 125.0, 98.8, 69.3, 65.1, 65.0, 43.0, 33.8, 32.2, 30.3, 29.2, 22.3.

IR (film): 3417, 2990, 2910, 1681, 1613, 1482, 1379, 1204, 1085, 1024, 745, 713, 611 cm^{-1}.

HRMS: calc. for $C_{13}H_{17}O_3$ $[M - CH_3]^+$: 221.1178; found: 221.1177.



Ketal (**156**).

To a suspension of NaH (60 wt % in mineral oil, 1.38 g, 34.32 mmol) in THF (36 mL) at 0 °C was added a solution of **155a** (2.70 g, 11.44 mmol) in THF (18 mL), and the mixture was

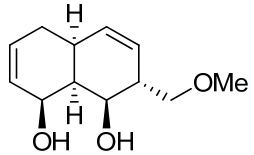
stirred for 30 min. DMF (54 mL) and MeI (10.70 mL, 171.61 mmol) were added and after 10 min the reaction mixture was warmed to ambient temperature. After 2 h the reaction was diluted with toluene and NH_4Cl_{sat} was added carefully. The organic phase was washed with water (2 x 30 mL) and brine (40 mL) and the solvents were removed under reduced pressure. The crude product was purified by column chromatography (EtOAc/hexane) to yield **156** (2.60 g, 91%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.19 (ddd, *J* = 9.8, 6.3, 3.8 Hz, 1H), 6.03 (ddd, *J* = 9.6, 4.9, 2.2 Hz, 1H), 5.73 – 5.65 (m, 2H), 4.61 (dd, *J* = 5.5, 5.5 Hz, 1H), 4.23 (dd, *J* = 4.5, 4.5 Hz, 1H), 3.40 – 3.31 (m, 5H), 2.69 – 2.60 (m, 1H), 2.37 – 2.14 (m, 4H), 2.13 – 2.04 (m, 1H), 1.49 (s, 3H), 1.37 (s, 3H).

^{13}C-NMR (100.6 MHz, $CDCl_3$):δ = 134.1, 132.7, 129.6, 125.3, 98.6, 73.4, 67.0, 65.2, 59.0, 41.1, 33.0, 31.9, 30.3, 29.4, 21.6.

IR (film): 3025, 2987, 2909, 2690, 1597, 1523, 1461, 1377, 1198, 1084, 961, 942, 865, 713, 523, 422, 418, 403 cm^{-1}.

HRMS: calc. for $C_{14}H_{19}O_3$ $[M - CH_3]^+$: 235.1334; found: 235.1331.



Diol (**156a**).

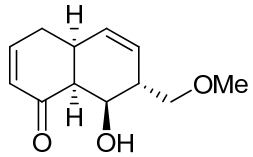
Ketal **156** (2.10 g, 8.40 mmol) in THF (18 mL) was cooled to 0 °C, 1N aqueous HCl (8.4 mL) was added and the reaction mixture was stirred for 30 min. The reaction was quenched at 0 °C by addition of pyridine (8 mL), the solvents were removed under reduced pressure and the residue was subjected to column chromatography (EtOAc/hexane) to obtain diol **156a** (1.59 g, 90 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.84 (t, *J* = 11.6 Hz, 2H), 5.68 (ddd, *J* = 10.0, 2.6, 2.6 Hz, 1H), 5.55 (ddd, *J* = 10.0, 3.2, 2.8 Hz, 1H), 4.54 – 4.46 (m, 1H), 4.22 (dd, *J* = 10.0, 4.4 Hz, 1H), 3.53 (dd, *J* = 8.9, 4.8 Hz, 1H), 3.39 (s, 3H), 3.33 (dd, *J* = 8.7, 8.7 Hz, 1H), 2.83 – 2.75 (m, 1H), 2.75 (d, *J* = 4.2 Hz, 1H), 2.56 – 2.48 (m, 1H), 2.32 (ddd, *J* = 6.7, 4.8, 4.8 Hz, 1H), 2.25 (ddd, *J* = 18.2, 6.9, 1.8 Hz, 1H), 2.20 – 2.11 (dm, *J* = 18.2 Hz, 1H), 2.05 (d, *J* = 7.8 Hz, 1H).

^{13}C-NMR (100.6 MHz, CDCl3): δ = 133.4, 129.8, 128.1, 127.3, 76.9, 72.7, 65.4, 59.3, 44.9, 40.3, 30.8, 30.6.

IR (film): 3423, 3018, 2891, 1685, 1475, 1452, 1418, 1384, 1193, 1119, 1044, 996, 938, 757, 739, 669, 408 cm^{-1}.

HRMS: calc. for $C_{12}H_{16}O_2$ $[M - H_2O]^+$: 192.1150; found: 192.1145.



Enone (**156b**).

Diol **156a** (1.6 g, 7.62 mmol) was dissolved in DCM (76 mL), and activated MnO_2 (2.52 g, 28.95 mmol) was added. After stirring for 26 h at rt, the reaction mixture was filtered through a pad of celite, concentrated *in vacuo* and the residue was subjected to column chromatography (EtOAc/hexane) to yield 1.49 g (94%) of enone **156b** as a colorless oil.

^{1}H-NMR (400 MHz, C_6D_6): δ = 6.00 (dddd, *J* = 9.9, 5.8, 2.3, 1.0 Hz, 1H), 5.81 – 5.74 (m, 2H), 5.03 (d, *J* = 9.9 Hz, 1H), 4.34 (d, *J* = 11.2 Hz, 1H), 3.77 (ddd, *J* = 11.2, 9.4, 4.1 Hz, 1H), 3.56 – 3.52 (m, 2H), 3.11 (s, 3H), 2.67 – 2.59 (m, 1H), 2.48 (dd, *J* = 4.5, 4.5 Hz, 1H), 2.38 – 2.31 (m, 1H), 1.82 – 1.73 (dm, *J* = 19.0 Hz, 1H), 1.62 – 1.53 (dm, *J* = 19.0 Hz, 1H).

^{13}C-NMR (100.6 MHz, C_6D_6): δ = 202.9, 147.1, 131.9, 130.0, 129.7, 73.4, 71.0, 58.7, 49.5, 43.6, 35.8, 31.1.

IR (film): 3481, 3051, 2999, 2886, 1652, 1423, 1393, 1312, 1258, 1116, 1076, 1029, 846, 741, 675, 588, 564, 460, 445, 419, 411, 403 cm^{-1}.

HRMS: calc. for $[C_{12}H_{16}O_3]^+$: 208.1099; found: 208.1097.

8. Summary

In summary, we have accomplished the first total synthesis of (+)–branimycin, an antibiotic isolated from *Actinomycete GW 60/1571*. This synthesis confirms the relative stereochemistry assigned by the Laatsch group. Additionally, the absolute configuration of branimycin has been established.

In accordance with our synthetic plan, we efficiently incorporated the oxa-bridged *cis*-decalin core of branimycin *via* an intramolecular epoxide opening. The C13-C18 side chain and the C7-C12 ether bridge of the nucleus were incorporated in one high yielding synthetic step. Improvement and modification of the side chain synthesis paved the way for the completion of the total synthesis of branimycin. The C3 appendage could be introduced exclusively at the concave face of the branimycin framework *via* 1,4-addition. The highly challenging construction of the strained nine-membered lactone of branimycin was successively achieved employing Gerlach´s modification of Corey-Nicolaou´s double activation protocol. This is a very rare, if not the first example of macrolactonization to provide such a nine-membered lactone containing a *trans*-double bond.

In this dissertation two approaches toward the *cis*-fused decalin nucleus of branimycin are presented. Starting from (-)–quinic acid a very flexible and stereoselective synthesis of the highly functionalized *cis*-decalin core was accomplished. Key-annulation of the A ring was conducted *via* a high yielding Claisen-Ireland rearrangement – RCM protocol.

Following an intermolecular quinone based Diels-Alder cycloaddition strategy the desired functional group pattern was established by a regio- and stereoselective introduction of a masked C9-methoxy methyl group and a regioselective allylic oxidation at C12. In both approaches epoxidation occurred nearly exclusively from the *exo*-face.

The longest linear sequence required only 20 steps from known easily accessible compounds (23 steps from commercially available *p*-benzoquinone). This route allows the preparation of sufficient material and it is very flexible with respect to the substituents and configurations of the individual stereogenic centers which should enhance the diversity for biological testing.

9. Abbreviations

Ac	acetyl
AIBN	2,2'-azobisisobutyronitrile
aq.	aqueous
Ar	aryl, aromatic
Bn	benzyl
Bu	butyl
cat.	catalyst, catalytic amount
DBU	1,8-diazabicyclo[5.4.0]undec-7-en
DDQ	2,3-dichloro-5,6-dicyano-p-quinone
DIBAL	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylaminopyridine
EE	1-ethoxyethyl
eq.	equivalent
Et	ethyl
er	enantiomeric ratio
et al.	latin: "et alii", meaning "and others"
EtOAc	ethyl acetate
Imid.	imidazole
INOC	intramolecular nitrile oxide cyclization
IR	infra red
J	coupling constant
KHMDS	potassium hexamethyldisilazide
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
*m*CPBA	*meta*-chloro peroxybenzoic acid
Me	methyl
min	minute
MOM	methoxymethyl
mp	melting point
MS	mass spectroscopy

4Å MS or 3Å MS	molecular sieves with pores of 4 or 3 Angstrom
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance spectroscopy
P or PG	unspecified protecting group
ppm	part per million
R, R', R'', R^1, R^2, R^3	unspecified substituents
RCM	ring closing metathesis
TBAF	tetrabutylammonium fluoride
THF	tetrahydrofuran
TBS	dimethyl-*tert*-butylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	tosyl

D. Curriculum Vitae

Personal Data

Name	Stefan Marchart
Date of Birth	23. 01. 1980
Place of Birth	Mistelbach, Austria
Citizenship	Austria
Marital Status	single
Address	Hernalser Hauptstr. 49/26, A-1170 Vienna
Degree	*Mag. rer. nat.*
Telephone	+43 6503900585
Email-Address	Stefan.Marchart@univie.ac.at Stefan_Marchart@gmx.at

Ph.D Thesis

February 2010	**PhD *viva*, Department of Organic Chemistry, University of Vienna**
February 2006 – October 2009	**PhD research, Department of Organic Chemistry, University of Vienna** PhD degree under the supervision of Prof. Dr. Johann Mulzer: "Total Synthesis of the Antibiotic (+)-Branimycin"

University Studies

October 2006 - date	**Vienna University of Economics and Business Administration** – Bachelor study of Business Administration, specialized in Accounting and Finance
22. 11. 2005	**University of Vienna** – Graduation with title Magister rer.nat. (equivalent to M.Sc.; cum laude)
March 2005 - October 2005	**University of Vienna** - Diploma thesis project: "Towards the Synthesis of Branimycin" in the research group of Prof. Dr. Johann Mulzer
October 2000 - November 2005	**University of Vienna** – Study of Chemistry, specialized in Organic Chemistry, Biochemistry and Analytical Chemistry (cum laude)

October 1999 - date	**Vienna University of Technology** – Study of Technical Physics

Education

1990 - 1998	**Bundes- und Bundesrealgymnasium Laa/Thaya** – focusing on math and science
1986 - 1990	**Primary School Mistelbach**

Professional Career

January 2007 - date	**University of Vienna** – Assistant Position. Teaching, supervision, tutoring and grading students in organic chemistry
February 2006 – December 2006	**University of Vienna** – Research assistant.
March 2005 – October 2005	**University of Vienna** – tutor of undergraduate students in the organic chemistry lab
July 1998 – February 1999	**Military Service** (public body, Baden, Austria)

Other Qualifications

Languages	▪ German – mother tongue ▪ English – spoken - excellent, written - excellent, comprehension - excellent ▪ French – spoken – basic, written – basic, comprehension – basic
Technical	▪ Skilled operator of NMR, IR and HPLC instruments and software ▪ Extensive knowledge of office tools and operating systems (MacOS, Linux, Windows, Ms Office) ▪ Experienced with a variety of chemistry software (Beilstein, CS ChemOffice, IsisBase, IsisDraw, SciFinder)

Extracurricular Activities

Member of GÖCH	Membership (Gesellschaft Österr. Chemiker)
Member of GDCH	Membership (Gesellschaft Deutscher Chemiker)
Active Member of AG NaWi	Students Representative Doctorate Natural Sciences

Hobbies

Sports	Running, Skiing, Volleyball, Swimming, Sailing
Other	Traveling, Reading, Chess, Piano