Towards the Synthesis of the Cornexistins


a 251 Nieuwland Hall of Science, University of Notre Dame, Notre Dame, IN 46556, USA
b Discovery Research, Dow Agrosciences, Inc., 9330 Zionsville Road, Indianapolis, IN 46268-1054, USA

Fax +1(574)6316652; E-mail: taylor.61@nd.edu

Received 1 March 2007
Dedicated to Professor Paul Wender on the occasion of his 60th birthday

Abstract: A concise synthetic route to the carbocyclic core of the cornexistins is reported. The route is highlighted by a Diels–Alder cycloaddition/oxidative cleavage strategy to generate the central highly functionalized nine-membered ring. A silyl-tethered ring-closing metathesis strategy is utilized to control trisubstituted alkene geometry.

Key words: Diels–Alder, oxidative cleavage, natural products, ring expansion, ring-closing metathesis, carbocycle

Cornexistin (1) (Figure 1) was isolated by Sankyo and reported in 1991.1 A fungal metabolite of Paeilomyces variotiitii SANK 21086, cornexistin has potent herbicidal activity against broadleaf weed species. At that level of activity, maize plants are insensitive to cornexistin’s effects. In 1991, an additional metabolite was found by Dow Agrosciences to be the 14-hydroxy analogue of cornexistin;2 14-hydroxycornexistin (2) is at least as active as cornexistin, if not more. Both of these molecules are of practical interest to the agrochemical community and are interesting to the synthetic community in terms of their unique structure and functionality.

Figure 1 Cornexistin (1) and 14-hydroxycornexistin (2), herbicidal natural products

Clark has published synthetic routes to cornexistin, including the use of ring-closing metathesis (RCM) technology to close the nine-membered ring.7 Our retrosynthesis of the cornexistins (Figure 2) began with the recognition of inherent symmetry of functionality within the nine-membered-ring system. By bisecting the molecule horizontally and noting that oxidation state is fungible, each substituent is mirrored across the ring with the exception of the C3 propyl group. Such a reductionist approach brought us to 3, where a chemoselective oxidative cleavage would expose a nine-membered cyclic diketone. This cyclohexa-1,4-diene could be clearly derived from a Diels–Alder reaction of dienophile dimethyl acetylenedicarboxylate and readily available 4 as the necessary diene. This strategy is quite reminiscent of Wender’s metathetical approach to medium-ring carbocycles.8

SYNTHESIS 2007, No. 15, pp 2388–2396
Advanced online publication: 26.07.2007
DOI: 10.1055/s-2007-983769; Art ID: C00907SS
© Georg Thieme Verlag Stuttgart · New York
The synthesis of the cyclopentadiene (Scheme 1) began with the aldehyde 5, which was reacted with lithiated pentyne to give the desired alcohol in 91% yield. The resulting alcohol was protected as the 4-methoxybenzyl ether, the tert-butylidemethylsilyl ether was removed using tetrabutylammonium fluoride, and the resulting alcohol oxidized using Swern conditions to provide the desired aldehyde 7 in three steps in 70% yield. Aldehyde 7 was immediately used in the following reaction, where it was reacted with lithiated (trimethylsilyl)acetylene to provide the syn- and anti-diastereomers. Through careful column chromatography, the diastereomers were separated and the desired syn-diastereomer was obtained in good yield. (A Mitsunobu inversion was used to convert the anti-diastereomer into the syn in moderate yield.)

The desilylation of the terminal alkyne was carried out with tetrabutylammonium fluoride deprotection and the free alcohol was protected under standard conditions as the tert-butyldimethylsilyl ether. Diyne 8 was subjected to Trost reductive cyclization conditions to provide the cyclopentadiene 4 in excellent yield. It was then reacted with dimethyl acetylenedicarboxylate to provide the desired cyclohexadiene 3 in moderate yield. The stereochemical relationship between the propyl group and the 4-methoxybenzyl (PMB) ether was under question and ROESY analysis was unfortunately equivocal.

With this key intermediate in hand, 3 was oxidatively cleaved to reveal the diketone (Scheme 2). Despite the exploration of several different reagents and conditions for alkenation of the C7 ketone, Tebbe’s reagent and an excess of pyridine gave the desired alkene 9 in moderate yield. Then, sodium borohydride reduction of the C2 ketone gave product alcohol 10 in excellent yield as a single diastereomer.

A number of attempts were made to crystallize this product, including derivatization to the 4-bromobenzoate or the phenyl carbamate. Unfortunately, neither compound was crystalline. NMR analysis of the corresponding acetate 11 revealed a strong NOE between the C2 and C3 hydrogens. Additionally, the multiplicity of the C2 proton supported the 1,2-trans,2,3-cis relationship. Moreover, computer-based molecular modeling experiments provided a number of low energy conformations that fit this analysis. Although this was not definitive proof, it suggested the assignments of 10 and 11 in Scheme 2.

Completion of the carbon skeleton of the cornexistins required stereoselective alkylation of the 1,1-disubstituted...
alkene. To achieve this aim, we considered the use of a temporary silicon tether. Silyl group exchange provided ring-closing metathesis precursor \( \text{13} \) (Scheme 3). Unfortunately, only dimeric products were obtained regardless of the choice of ring-closing metathesis catalyst.

Scheme 3

It was suspected that the molecule was in an inappropriate conformation for the ring-closing metathesis. To alter the conformation of \( \text{13} \), inversion of the alcohol stereocenter at C8 was accomplished. While Mitsunobu inversion resulted in elimination, an oxidation–reduction sequence was quite fruitful. Dess–Martin oxidation of \( \text{12} \) followed by simple sodium borohydride reduction provided the inverted C8 of \( \text{15} \) (Scheme 4) in good yield with a moderate diastereomeric ratio (4:1). Silyl protection gave desired allyldimethylsilyl ether \( \text{16} \) in 50% yield, which was refluxed in dichloromethane with a catalytic amount of Grubbs’ second-generation ruthenium catalyst \( \text{14} \); this gave desired siloxacycle \( \text{17} \) in quantitative yield.

Having generated \( \text{17} \) successfully, we turned to the manipulation of said siloxacycle to provide both cornexistin and hydroxycornexistin. Initial attempts at protodesilylation of \( \text{17} \) have thus far demonstrated a surprising lack of reactivity. However, inclusion of hydrogen peroxide led to Tamao–Fleming oxidation and diol \( \text{18} \) was obtained in quantitative yield (Scheme 5).

In summary, we have generated complex nine-membered-ring carbocycles through the use of a Diels–Alder strategy and subsequent oxidative cleavage. This route has the ability to install the required functionality towards the herbicidal natural products hydroxycornexistin and cornexistin, including the use of ring-closing metathesis technology to install the desired geometry of an exocyclic ethylidene. Further efforts will be reported in due course.

Unless otherwise noted, all materials were used as received from a commercial supplier and used without further purification. All reactions were performed using oven-dried glassware and under an \( \text{N}_2 \) atmosphere unless otherwise noted. THF, \( \text{CH}_2\text{Cl}_2 \), \( \text{Et}_2\text{O} \), and toluene were filtered through activated alumina under \( \text{N}_2 \). DMSO was purchased from a commercial supplier. All reactions were monitored by E. Merck analytical TLC plates (silica gel 60 GF, glass back) and analyzed with 254 nm UV light and anisaldehyde/H\(_2\text{SO}_4 \) treatment. Silica gel for column chromatography was purchased from E. Merck (Silica Gel 60, 230–400 mesh). Biotage chromatography was performed using Flash 12+M, 25+S, 25+M, and 40+M KP-Sil Silica (32–63 \( \mu \text{m}, 60 \text{ Å}, \text{nominally 500 m}^2/\text{g} \) silica) cartridges. All \( ^1\text{H} \) and \( ^{13}\text{C} \) NMR spectra were obtained on Varian Unity Plus 300 and 500 spectrometers (operating at 299.701 and 499.864 MHz for \( ^1\text{H} \) and 75.368 MHz and 127.706 MHz for \( ^{13}\text{C} \), respectively); \( \text{CHCl}_3 \) was used as an internal reference (\( ^1\text{H}: \delta = 7.26, ^{13}\text{C}: \delta = 77.00 \)). FT-IR spectra were obtained on a Perkin-Elmer Paragon 1000 spectrophotometer. MS (FAB) were obtained using 3-nitrobenzyl alcohol (NBA) as a matrix using either a JEOL AX505HA or JEOL JMS-GCmate mass spectrometer.

1-(tert-Butyldimethylsiloxy)oct-4-yn-3-ol (6)

To a soln of pent-1-yn (6.09 mL, 0.062 mol, 1.2 equiv) in THF (50 mL) cooled to –78 °C was added 2.5 M BuLi in hexanes (26.83 mL, 0.067 mol, 1.3 equiv) and the mixture was stirred for 30 min. The bath temperature was then warmed to 0 °C for 5 min and then re-cooled to –78 °C. 3-(tert-Butyldimethylsiloxy)propanal (5, 9.7 g, 0.052 mol) in THF (25 mL) was added slowly to the mixture. The round-bottom flask was transferred to a 0 °C ice bath and stirred for 4 h. After TLC analysis revealed the completion of the reaction, the
reaction was quenched using sat. NH₄Cl soln and diluted with EtOAc. The aqueous layer was extracted with water and the combined organic layers were washed with sat. NaHCO₃ soln, brine, and H₂O. After drying (MgSO₄), the organic layer was concentrated to give a crude yellow oil (12.24 g, 91%). The material was used further without purification.

IR (thin film): 2957, 2931, 2857, 2234, 1613, 1586, 1514, 1463, 1249, 1098, 834, 776 cm⁻¹.

H NMR (300 MHz, CDCl₃): δ = 4.64–4.54 (m, 1 H, CHO), 4.08–3.98 (m, 1 H, CH₂(OTBS)), 3.86–3.75 (m, 1 H, CH₂(OTBS)), 3.30 (d, J = 5.12 Hz, 1 H, CHO), 2.19 (dt, J = 6.96, 2.2 Hz, 2 H, CH₂(CHOH)), 2.02–1.88 (m, 8 H, C₂H₅CH₂CH₂), 1.54 (sextet, J = 6.96 Hz, 2 H, C(CH₃)₂CH₂CH₂), 1.0 (t, J = 7.2 Hz, 3 H, C₆H₄(CH₂)₂). 1H NMR (375 MHz, CDCl₃): δ = 86.6, 79.5, 70.3, 55.5, 39.5, 26.2, 22.5, 21.0, 13.8, –5.1

HRMS-FAB: m/z [M + H⁺] calcd for C₁₆H₂₂O₃Si: 262.1553; found: 262.1509.

1-(tert-Butyldimethylsiloxy)-3-(4-methoxybenzyl)oxy)-oct-4-yne (3.4 g, 0.016 mol) in anhyd DMF (40 mL) at –10 °C and H₂O. After drying (MgSO₄), the material was used further without purification. The reaction was quenched using sat. NH₄Cl soln and diluted with water. After drying (MgSO₄), the organic layer was concentrated to give a crude yellow oil (1.02 g, 72% yield), which was subjected to careful chromatography (silica gel) to give the desired product (0.78 g, 71% yield), which was subjected to column chromatography (silica gel). This gave 7 as a pale yellow oil (1.02 g, 72% yield), which was subjected immediately to the following reaction.

IR (thin film): 2963, 2934, 2871, 2837, 2727, 2273, 1728, 1613, 1514, 1464, 1336, 1302, 1249, 1174, 1073, 1035, 823, 758 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 9.34 (t, J = 2.2 Hz, 1 H, CH₂(CHOH)), 12.79 (d, J = 8.8 Hz, 2 H, CH₂(CHOH)), 6.89 (d, J = 8.8 Hz, 2 H, C₆H₄(OMe)), 4.78 (d, J = 8.8 Hz, 2 H, C₆H₄(OMe)), 8.57, 1.96 Hz, 1 H, CH₂(CHOH)), 4.45 (t, J = 11.4 Hz, 1 H, OCH₂(CHOH)), 5.12, 1.96 Hz, 1 H, OCH₂(CHOH)), 5.72, 1.96 Hz, 1 H, CHO(OMPB)), 3.80–3.85 (m, 3 H, C₆H₄(OMe)), 3.78–3.75 (m, 1 H, CHO), 2.82–2.78 (m, 2 H, CH₂(CHOH)), 2.17–2.08 (m, 5 H, C₆H₄(OMe)), 1.96 Hz, 1 H, OCH₂(CHOH)), 4.52 (tt, J = 5.86, 1.96 Hz, 1 H, CH₂(CHOH)), 3.79–3.69 (m, 2 H, CH₂(OTBS)), 3.30 (s, 3 H, OCH₃), 2.33 (dd, J = 6.96, 1.95 Hz, 2 H, CH₂(CHOH)), 2.05–1.80 (m, 2 H, C₆H₄(OMe)), 1.10 (t, J = 7.2 Hz, 3 H, C₆H₄(OMe)), 0.93 [s, 9 H, Osi(C(CH₃)₃)Me₂], 0.51 [s, 6 H, Osi-Bu(CHOH)₂].

13C NMR (75 MHz, CDCl₃): δ = 159.4, 130.6, 129.9, 114.0, 86.6, 79.5, 70.3, 65.9, 59.6, 55.5, 39.5, 26.2, 22.5, 21.0, 13.8, –5.1

HRMS-FAB: m/z [M + H⁺] calcd for C₃₆H₃₉O₆Si: 575.2333; found: 575.2355.

(3-Methoxybenzyl)oxy)-oct-4-ynal (0.78 g) and its diastereomer (0.45 g) (71% yield) were subjected to careful purification via column chromatography (silica gel) to give the desired product (0.29 g) (71% yield) and its anti-diastereomer (0.11 g) (71% yield).

5-(4-Methoxybenzyl)oxy)-1-(trimethylsilyl)deca-1,6-diyn-3-ol (2.0 g, 1.6 mmol) was added slowly to the THF (20 mL) was added slowly to the solution with a catalytic amount of TBAI and the reaction was stirred at 0 °C. Stirred for 30 min. 4-Methoxybenzyl bromide (4.7 g, 0.023 mol) dissolved in anhyd THF (20 mL) was added slowly to the solution with a catalytic amount of TBAI and the reaction was stirred at 0 °C. Stirred for 30 min. After completion of the reaction, the reaction was quenched using sat. NH₄Cl soln and diluted with water. After drying (MgSO₄), the organic layer was concentrated to give a crude yellow oil (12.24 g, 91%). The material was used further without purification.

IR (thin film): 2957, 2931, 2857, 2234, 1613, 1514, 1463, 1249, 1098, 834, 776 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 7.32 (d, J = 8.5 Hz, 2 H, C₆H₄(OMe)), 6.90 (d, J = 8.5 Hz, 2 H, C₆H₄(OMe)), 4.71 (d, J = 11 Hz, 1 H, OCH₂(CHOH)), 4.45 (d, J = 11 Hz, 1 H, OCH₂(CHOH)), 4.21 (dd, J = 7.2 Hz, 3 H, C₆H₄(OMe)), 3.98 (m, 1 H, C₆H₄(OMe)), 3.94–3.91 (m, 1 H, C₆H₄(OMe)), 2.92–2.88 (m, 2 H, C₆H₄(OMe)), 1.61–1.50 (sextet, 2 H, C₆H₄(OMe)), 1.0 (t, J = 7.2 Hz, 3 H, C₆H₄(OMe)), 0.93 [s, 9 H, Osi(C(CH₃)₃)Me₂], 0.1 [s, 6 H, Osi-Bu(CHOH)₂].

13C NMR (75 MHz, CDCl₃): δ = 159.4, 130.6, 129.9, 114.0, 86.6, 79.5, 70.3, 65.9, 59.6, 55.5, 39.5, 26.2, 22.5, 21.0, 13.8, –5.1


Synthesis 2007, No. 15, 2388–2396 © Thieme Stuttgart · New York
3.97, 2.14 Hz, 1 H, CH(OH)3), 3.81 (s, 3 H, CH2OCH3), 2.75 (d, J = 4.27 Hz, 1 H, CH(OH)), 2.30–2.19 [m, 2 H, CH2OCH3], 2.19 (s, 3 H, OSi(C(CH3)3)).

\[ \text{[M} - 1\text{]}^+ \text{calcd for C21H29O3Si: 357.1886; found: 357.1867.} \]

J. C. Tung et al.

**anti-Diastereomer**

IR (thin film): 3449, 2962, 2934, 2872, 2837, 2172, 1617, 1587, 1514, 1224, 1104, 1074, 803, 755, 710, 710 cm\(^{-1}\).

**HRMS-FAB:** m/z [M – 1]\(^+\) calc for C30H43O7Si: 543.2668; found: 543.2649.

**3-([1R]-Butylidimethylsiloxy)-5-(4-methoxybenzyl)oxy-deca-1,6-diyne-3(3)ol**

To a soln of 5-([4-methoxybenzyl])oxo-1-(trimethylsilyl)deca-1,6-diyne-3(3)ol (0.781 g, 2.18 mmol) dissolved in THF (25 mL) and additive TBAF in THF (3.27 mL, 3.27 mmol, 1.5 equiv.). The mixture was stirred for 3 h. Upon completion of the reaction, it was quenched with sat. NaHCO3. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine and H2O, dried, and concentrated. The crude product was not purified but subjected immediately to the next reaction. The crude alcohol mixture was dissolved in DMF (25 mL) and added 4.54 (M, 2, 1.9 Hz, CH(OMe)2), 2.19 (s, 3 H, OCH2CH3), 2.75 (d, J = 6.05 Hz, 1 H, CHO), 2.24–2.06 (m, 6 H, C6H2(OMe)2), C6H2(CH2CH3), 1.59 (sextet, J = 7.2 Hz, 2 H, C6H2(CH3)2), 1.03 (s, 3 H, C6H2(CH3)3), 0.1 [s, 9 H, OSi(CH3)3]).

**HRMS-FAB:** m/z [M – 1]\(^+\) calc for C21H29O3Si: 543.1867; found: 543.1866.

**3-([1R]-Butylidimethylsiloxy)-5-(4-methoxybenzyl)oxy-deca-1,6-diyne-3(3)ol**

To a soln of 5-([4-methoxybenzyl])oxo-1-(trimethylsilyl)deca-1,6-diyne-3(3)ol (0.781 g, 2.18 mmol) dissolved in THF (25 mL) and additive TBAF in THF (3.27 mL, 3.27 mmol, 1.5 equiv.). The mixture was stirred for 3 h. Upon completion of the reaction, it was quenched with sat. NaHCO3. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine and H2O, dried, and concentrated. The crude product was not purified but subjected immediately to the next reaction. The crude alcohol mixture was dissolved in DMF (25 mL) and added 4.54 (M, 2, 1.9 Hz, CH(OMe)2), 2.19 (s, 3 H, OCH2CH3), 2.75 (d, J = 6.05 Hz, 1 H, CHO), 2.24–2.06 (m, 6 H, C6H2(OMe)2), C6H2(CH2CH3), 1.59 (sextet, J = 7.2 Hz, 2 H, C6H2(CH3)2), 1.03 (s, 3 H, C6H2(CH3)3), 0.1 [s, 9 H, OSi(CH3)3]).

**HRMS-FAB:** m/z [M – 1]\(^+\) calc for C21H29O3Si: 543.1867; found: 543.1866.

**Synthesis 2007, No. 15, 2389–2396 © Thieme Stuttgart · New York**
Dimethyl 7-(tert-Butyldimethylsiloxy)-5-(4-methoxybenzyl-oxy)-4,8-dioxo-3-propylcyclonon-1-ene-1,2-dicarboxylate

A solution of 3 (1.78 g, 3.29 mmol) and Sudan III dye (1.5 mL, 0.1 wt%) dissolved in CH2Cl2-MeOH (2:1, 40 mL) at −78 °C was saturated with O2 gas for 10 min. The mixture was subjected to ozone until the solution color had gone from a deep red to a light pink or orange. The mixture was again saturated with O2 gas for 10 min; following this, thiourea (3 g) was added and the mixture was stirred at r.t. for 4 h. The mixture was then filtered to remove solids, concentrated to a thick oil, redissolved in Et2O and then washed with brine and H2O. The organic layer was then dried (MgSO4) and concentrated to give a viscous yellow oil. The oil was subjected to column chromatography (silica gel) to give a pale, viscous yellow oil (1.57 g, 83%).

IR (thin film): 2955, 1727, 1613, 1514, 1465, 1462, 1256, 1106, 1076, 913, 837, 781 cm−1.

1H NMR (300 MHz, CDCl3): δ = 7.27 (d, J = 6.4 Hz, 2 H, C2H2OMe), 6.82 (d, J = 6.4 Hz, 2 H, C2H2OMe), 4.59 (dd, J = 8.99, 4.50 Hz, 1 H, CH(OTBS)CHa), 4.43 (d, J = 9.0 Hz, 1 H, OCH(CH2)C2H2OCH3), 4.40 (t, J = 4.71 Hz, 1 H, CH2), 4.39 (d, J = 10.7 Hz, 1 H, OCH(CH2)C2H2OCH3), 3.84–3.79 (2 s, 6 H, 2 CO2C6H4OMe), 2.41 (dd, J = 14.55, 4.72 Hz, 1 H, CH(OTBS)-CH2CH2OH), 2.15–2.02 (2 m, 1 H, CH2CH(CH2)CH2), 1.97 (ddd, J = 14.34, 10.2, 4.02 Hz, 1 H, CH(OTBS)-CH2CH2OH), 1.41–1.10 (m, 3 H, CH2CH(CH2)CH2OCH3), 0.93 (t, J = 7.36 Hz, 3 H, CH2CH(CH2)CH2), 0.01 (s, 9 H, OSi(CH3)2Me2), 0.01 (2 s, 6 H, OSi-Bu(CHOH))-.

13C NMR (75 MHz, CDCl3): δ = 142.5, 131.6, 130.3, 113.9, 78.9, 76.0, 72.9, 71.5, 55.5, 52.4, 50.1, 44.8, 31.0, 29.4, 26.0, 20.7, 18.4, 14.4, –5.0.


Towards the Total Synthesis of the Cornexistins
CH(CH₂)₂CH₂CH₃), 1.52–2.12 [m, 3 H, CH₂CH₂CH₂CH₂CH₃], 0.93 [t, J = 7.36 Hz, 3 H, CH₃CH₂CH₂CH₂CH₃], 0.90 [s, 9 H, OSi(CH₃)₃Me], 0.01 [2 s, 6 H, OSi-Bu₂(CH₂)₃] ¹³C NMR (75 MHz, CDCl₃): δ = 170.4, 168.7, 168.3, 159.3, 148.5, 142.3, 134.6, 130.9, 129.5, 116.0, 113.9, 74.4, 72.5, 55.5, 52.6, 51.9, 43.7, 40.8, 32.6, 29.5, 26.0, 21.1, 20.9, 18.3, 14.5, –4.6, –6.5.


Dimethyl 4-Acetoxy-7-hydroxy-5-(4-methoxybenzyl)oxy)-8-methylene-3-propenylcyclonon-1-ene-1,2-dicarboxylate (15)

To a solution of ketone (10 mg, 0.022 mmol) in THF (1 mL) was added 1 M TBAF in THF (45 μL, 0.045 mmol, 2 equiv) and stirred for 2 h. After completion of the reaction, the reaction was quenched with sat. NaHCO₃ and separated. The aqueous layer was extracted with EtOAc; the recombined organic layers were washed with brine and subsequently dried and concentrated. Purification (silica gel) gave product alcohol 15 as a pale yellow oil (6 mg, 87%).

IR (thin film): 3512, 2954, 2873, 1724, 1613, 1514, 1434, 1373, 1247, 1077, 1038, 971, 917, 851, 821, 734, 664 cm⁻¹.

¹¹H NMR (500 MHz, CDCl₃): δ = 7.18 (d, J = 8.5 Hz, 2 H, C₆H₄OMe), 6.85 (d, J = 8.6 Hz, 2 H, C₆H₄OMe), 5.22 (s, 1 H, C=CH₂), 5.11 (s, 1 H, C=CH₂), 5.08 (dd, J = 9.47, 2.44 Hz, 1 H, CHOAc), 4.60 (dd, J = 8.85, 3.55 Hz, 1 H, CHOAc), 4.46 (dd, J = 8.85, 3.55 Hz, 1 H, OCH₂CH₂CH₂OMe), 3.80–3.76 (2 s, 6 H, 2 CO₂CH₃), 3.79–3.76 (2 s, 6 H, 2 CO₂CH₃), 3.68 (s, 3 H, CH₃OCH₃), 3.52–3.42 (m, 1 H, CH₃OH) and d. j = 15.39 Hz, 1 H, C₆ methylene), 3.38–3.30 [m, 1 H, CH(OPMB)], 3.12 (d, J = 15.74 Hz, 1 H, C₆ methylene), 2.18 [d, d, J = 15.75, 3.66, 2.93 Hz, 1 H, CH(OH)CH₃H₂CH₂CH₃), 2.04–1.88 [m, 1 H, CH(OH)CH₃H₂CH₂CH₃], 1.98 (s, 3 H, COOCH₃), 1.73–1.56 [m, 2 H, CH₂CH₂CH₂CH₂CH₃), 1.48–1.20 [m, 2 H, CH₂CH₂CH₂CH₂CH₃), 0.88 [t, J = 6.96 Hz, 3 H, CH₃(CH₂)₂CH₃].

¹³C NMR (75 MHz, CDCl₃): δ = 170.3, 168.4, 168.1, 159.4, 150.4, 142.7, 133.5, 130.7, 129.6, 115.7, 113.9, 77.9, 77.1, 74.0, 71.9, 55.6, 52.8, 52.0, 41.1, 40.7, 32.4, 31.7, 21.1, 20.7, 14.2.

HRMS-FAB: m/z [M⁻]⁺ calculated for C₃₅H₅₀O₆Si: 503.2281; found: 503.2271.

Dimethyl 4-Acetoxy-7-(allyldimethyloxilo)-5-(4-methoxybenzyl)oxy)-8-methylene-3-propenylcyclonon-1-ene-1,2-dicarboxylate (16)

To a solution of alcohol 15 (0.005 g, 0.01 mmol) was added allyldimethyloxilo chloride (7 μL, 0.05 mmol, 5 equiv) and Et,N (25 μL, 0.177 mmol, 15 equiv). The mixture was stirred overnight at r.t. and subsequently quenched with sat. NaHCO₃. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine and H₂O. The organic layers were then dried (MgSO₄) and concentrated. The compound was then subjected to column chromatography (silica gel), which yielded silly ether 16 as a pale yellow oil (6 mg, 50%, 63% based on recovered 15).

IR (thin film): 3074, 2954, 2872, 1736, 1630, 1613, 1514, 1458, 1369, 1301, 1248, 1120, 1091, 1039, 954, 931, 900 cm⁻¹.

¹¹H NMR (300 MHz, CDCl₃): δ = 7.18 (d, J = 8.2 Hz, 2 H, C₆H₄OMe), 6.84 (d, J = 8.2 Hz, 2 H, C₆H₄OMe), 5.80 [ddd, J = 8.43, 10.41, 16.86 Hz, 1 H, OSiMe(CH₂CH₂CH₃)], 5.09 (s, 1 H, C=CH₂), 5.08 (dd, J = 9.47, 2.44 Hz, 1 H, CHOAc), 4.60 (dd, J = 8.85, 3.55 Hz, 1 H, CHOAc), 4.46 (dd, J = 8.85, 3.55 Hz, 1 H, OCH₂CH₂CH₂OMe), 3.80–3.76 (2 s, 6 H, 2 CO₂CH₃), 3.79–3.76 (2 s, 6 H, 2 CO₂CH₃), 3.68 (s, 3 H, CH₃OCH₃), 3.52–3.42 (m, 1 H, CH₃OH) and d. j = 15.39 Hz, 1 H, C₆ methylene), 3.38–3.30 [m, 1 H, CH(OPMB)], 3.12 (d, J = 15.74 Hz, 1 H, C₆ methylene), 2.18 [d, d, J = 15.75, 3.66, 2.93 Hz, 1 H, CH(OH)CH₃H₂CH₂CH₃), 2.04–1.88 [m, 1 H, CH(OH)CH₃H₂CH₂CH₃], 1.98 (s, 3 H, COOCH₃), 1.73–1.56 [m, 2 H, CH₂CH₂CH₂CH₂CH₃), 1.48–1.20 [m, 2 H, CH₂CH₂CH₂CH₂CH₃), 0.88 [t, J = 6.96 Hz, 3 H, CH₃(CH₂)₂CH₃].

¹³C NMR (75 MHz, CDCl₃): δ = 170.3, 168.4, 168.1, 159.4, 150.4, 141.1, 134.0, 130.9, 129.6, 115.2, 113.9, 77.5, 74.8, 72.4, 72.1, 55.5, 52.8, 52.0, 42.4, 41.1, 34.4, 32.5, 21.1, 20.8, 14.4.

HRMS-FAB: m/z [M⁻]⁺ calculated for C₃₅H₅₀O₆Si: 503.2281; found: 503.2271.

Synthesis 2007, No. 15, 2388–2396 © Thieme Stuttgart · New York
CH(CH₂CH₃), 1.64 [dd, J = 7.94, 13.89 Hz, 2 H, OSiMe₂(CH₂CH₃H₄)], 1.46–1.38 [m, 1 H, CH(CH₂CH₃H₄)], 1.32–1.22 [m, 1 H, CH₂CH₂CH₂CH₂CH₃], 0.88 [t, J = 7.33 Hz, 3 H, CH₃(CH₂CH₃)], 0.13 [s, 6 H, OSi(CH₃)₂(CH₂CH₃)].

¹¹C NMR (75 MHz, CDCl₃): δ = 170.4, 168.9, 167.9, 151.2, 141.8, 134.2, 133.4, 129.2, 114.1, 113.9, 113.3, 77.6, 74.8, 72.1, 71.5, 55.5, 52.6, 51.8, 44.2, 39.9, 34.6, 32.5, 24.7, 21.1, 20.8, 14.4, –20.2. –20.2.


Dimethyl 9-Acetoxy-10-(4-methoxybenzoxo)-2,2-dimethyl-8-propyl-3,8,10,11,11a-hexahydro-2H,11a-oxa-2-silabenzo-cyclononene-6,7-dicarboxylate (17)

Silyl ether 16 (4 mg, 0.001 mol) was dissolved in CH₂Cl₂ (10 mL) and heated to reflux for 10 min. Grubs 2nd generation CCM cata-
yst 14 (cat.) was added and the mixture was heated to reflux for 3 h. The mixture was then concentrated to dryness, redissolved in hexanes and subjected to column chromatography (silica gel), which yielded a quantitative amount of silacycle 17 as a brown oil.

IR (thin film): 2923, 2852, 1740, 1612, 1514, 1458, 1373, 1250, 1043, 855 cm⁻¹.

¹¹B NMR (500 MHz, CDCl₃): δ = 7.20 (d, J = 9 Hz, 2 H, CH₂CH₂CH₃), 6.83 (d, J = 8 Hz, 2 H, CH₂CH₂CH₃), 6.10 (d, J = 8.55, 3.67 Hz, 1 H, C₂=CHCH₂SiMe₂OR), 5.12 (dd, J = 10.07, 2.44 Hz, 1 H, CHOAc), 4.34 [dd, J = 8.85, 3.35 Hz, 1 H, CH₃(OSiMe₂R)], 4.46 (d, J = 11.6 Hz, 1 H, OCH₂CH₂CH₂OCH₃), 4.42 (d, J = 11.3 Hz, 1 H, OCH₂CH₂CH₂OCH₃), 3.80–3.76 (2 s, 6 H, 2 CO₂CH₃), 3.70 (s, 3 H, C₂=CH₂OCH₃), 3.42–3.34 (m, 1 H, CH₂CH₃), 3.38 (d, J = 13.44 Hz, 1 H, C₆H₆methylene), 2.88–2.84 [m, 1 H, CH(OPMB)], 2.68 (d, J = 14.35 Hz, 1 H, C₆H₆methylene), 2.12–2.04 [m, 1 H, CH(OSi(CH₂CH₂OCH₂CH₃)], 1.98 (s, 3 H, OCOC₂H₅), 1.99–1.90 [m, 1 H, CH(OSi(CH₂CH₂OCH₂CH₃)], 1.90–1.80 (m, 2 H, C=CH₂SiMe₂OR), 1.58–1.38 [m, 2 H, CH₂CH₂CH₂CH₃], 1.18–1.12 [m, 2 H, CH₂CH₂CH₂CH₃], 0.88 [t, J = 7.33 Hz, 3 H, CH₃(CH₂CH₃)], 0.13 (s, 3 H, CH₃(OSi(CH₂CH₂OCH₂CH₃)], 0.07 (s, 3 H, CH₃(OSi(CH₂CH₂OCH₂CH₃)]).

¹¹C NMR (75 MHz, CDCl₃): δ = 178.7, 170.0, 159.1, 140.9, 138.5, 130.7, 129.4, 129.2, 129.8, 113.7, 75.4, 75.4, 74.9, 72.8, 55.3, 52.3, 51.8, 46.0, 42.4, 41.0, 35.4, 32.0, 20.8, 14.1, 13.1, 1.04.

HRMS-FAB: m/z [M + H]+ calculated for C₆H₆OSi: 575.2676; found: 575.2655.

Dimethyl 4-Acetoxy-7-hydroxy-8-(2-hydroxyethylidene)-5-(4-methoxyphenyl)-5,5-dimethylcyclohexane-1,2-dicarboxylate (18)

For assistance with detailed NMR analysis and Chris Nicholson for support of this work. J.C.T. acknowledges Dow Agrosciences for a research fellowship. We would like to thank Jaroslav Zajicek for assistance with detailed NMR analysis and Chris Nicholson for computer modeling experiments.

Acknowledgment

R.E.T. gratefully acknowledges Paul A. Wender for his continual mentorship, inspiration, and support. We would like to acknowledge the progressive views of Professor Anthony K. Ryder (University of Notre Dame) and the Embedded Center Research Fund for support of this work. J.C.T. acknowledges Dow Agrosciences for a research fellowship.

References

(9) Aldehyde 5 was derived from the monoprotection of propane-1,3-diol (BuLi, TBSCI, THF, –78 °C to reflux) and TEMPO/bleach oxidation.
crystallographic Data Centre and may be retrieved at www.ccdc.cam.ac.uk by citing CCDC 642483.


