Total Synthesis of Allocyathin B_2, a Metabolite of Bird's Nest Fungi

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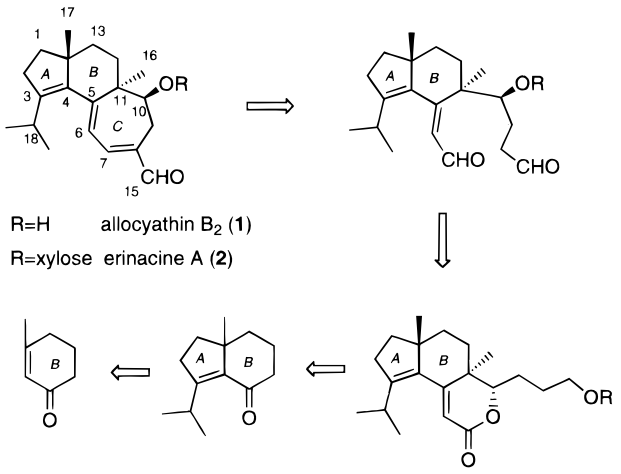
Allocyathin B_2 has been synthesized using aldol reactions for construction of rings A and B, introduction of the side chain for ring B, cyclization of the acetyl group into a lactone, and construction of the seven-membered diene aldehyde during the last step.

Introduction

The fruit bodies of *Cyathus earlei* are small and they look like a tiny "bird's nest".[1e] The metabolites of this fungi have been found by Ayer and co-workers to have cyathane diterpene skeletons successively consisting of five-, six-, and seven-membered rings, to constitute one of the most unusual terpenoid frameworks thus far discovered.[1,2] This kind of terpenoid has also been found in other mushrooms studied by Shibata et al.[3] and Kawagishi et al.[4] and in liverworts by Asakawa and his group.[5] Although there has been considerable effort to synthesize these molecules,[6] only recently has Snider succeeded in the total synthesis of allocyathin B_2 (**1**) as well as its xyloside, erinacine A (**2**).[7] We have been interested in structurally unusual natural products as well as biologically active compounds. Kawagishi reported the isolation and structure elucidation of erinacine A (**2**) and its congeners, which show strong nerve-growth-inducing activities.[4] We have started our synthetic work as outlined in Scheme 1, during which time Snider reported the first total synthesis of both allocyathin B_2 (**1**) and erinacine A (**2**).[7] This synthetic plan has three unique features: (1) the stereochemistry at the C-11 position can be controlled by the order of the alkylation reaction, (2) introduction of the two-carbon unit for C-6 and C-7 can be accomplished by the intramolecular aldol cyclization, which is difficult because of the hindered nature at the C-5 position, and (3) the *E* arrangement of the C-5 and C-6 double bond is advantageous for intramolecular aldol cyclization in the last step.

Scheme 1



Results and Discussion

Construction of Rings A and B. The 1,4-addition of the Grignard reagent of 4-bromo-1-butene to 3-methyl-2-cyclohexen-1-one (**3**) in the presence of $CuBr{\cdot}Me_2S$ followed by ketalization afforded **5**. Ozonolysis and alkylation with isopropylmagnesium bromide afforded the alcohol **6**, which was subjected to Jones oxidation to give the diketone **7**, with concomitant deprotection of the ketal group. Finally, base-catalyzed aldol cyclization gives the desired bicyclic enone **8** in high yield (Scheme 2).

Preparation of the Four-Carbon Side Chain. We have prepared two types of aldehydes, **11** and **14**, and acid chloride **16** as outlined in Scheme 3. γ-Butyrolactone (**9**) was hydrolyzed, methylated, and protected to give the methyl ester **10**, which was converted to the aldehyde **11** in high yield. The silyl-protected aldehyde **14** was prepared from butane-1,4-diol (**12**) in two steps. The acid chloride **16** was prepared from **12** through alcohol **15**, as previously described.[8]

Introduction of the Four-Carbon Side Chain to Ring B. We first thought that alkylation at the C-11 position may occur from the convex face of the ring, so methylation was first carried out (to **17**) and then aldol condensation with the four-carbon aldehyde **11** was attempted (Scheme 4). This assumption turned out to be incorrect. The product **18** was a mixture of two

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(1) (a) Ayer, W. A.; Taube, H. *Tetrahedron Lett.* **1972**, 1917. (b) Ayer, W. A.; Taube, H. *Can. J. Chem.* **1973**, *51*, 3842. (c) Ayer, W. A.; Browne, L. M.; Mercer, J. R.; Taylor, D. R.; Ward, D. E. *Can. J. Chem.* **1978**, *56*, 717. (d) Ayer, W. A.; Yoshida, T.; VanSchie, D. M. J. *Can. J. Chem.* **1978**, *56*, 2113. (e) Ayer, W. A.; Lee, S. P. *Can. J. Chem.* **1979**, *57*, 3332. (f) Ayer, W. A.; Lee, S. P.; Nakashima, T. T. *Can. J. Chem.* **1979**, *57*, 3338.

(2) Ayer, W. A.; Browne, L. M. *Tetrahedron* **1981**, *37*, 2199.

(3) Shibata, H.; Tokunaga, T.; Karasawa, D.; Hirota, A. *Agric. Biol. Chem.* **1989**, *53*, 3373.

(4) Kawagishi, H.; Shimada, A.; Shirai, R.; Okamoto, K.; Ojima, F.; Sakamoto, H.; Ishiguro, Y.; Furukawa, S. *Tetrahedron Lett.* **1994**, *35*, 1569.

(5) Toyota, M.; Nakaisi, E.; Asakawa, Y. *Phytochemistry* **1996**, *43*, 1057.

(6) (a) Ayer, W. A.; Browne, L. M. *Tetrahedron* **1981**, *37*, 2199. (b) Ward, D. E. *Can. J. Chem.* **1987**, *65*, 2380. (c) Dahnke, K. R.; Paquette, L. A. *J. Org. Chem.* **1994**, *59*, 885.

(7) Snider, B. B.; Vo, N. H.; O'Neil, S. V.; Foxman, B. M. *J. Am. Chem. Soc.* **1996**, *118*, 7644.

(8) Jacobi, P. A.; Murphree, S.; Rupprecht, F.; Zheng, W. *J. Org. Chem.* **1996**, *61*, 2413.

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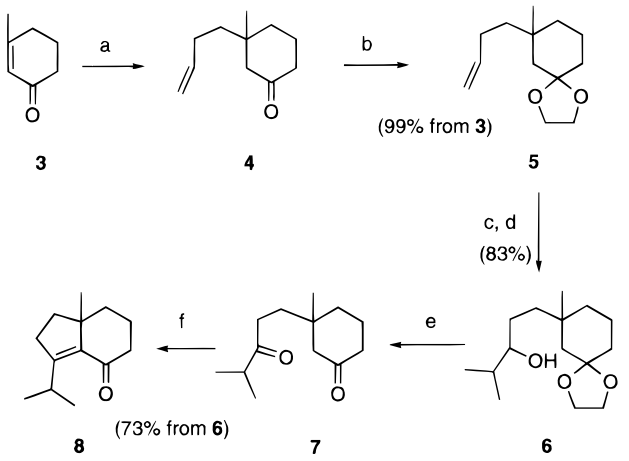
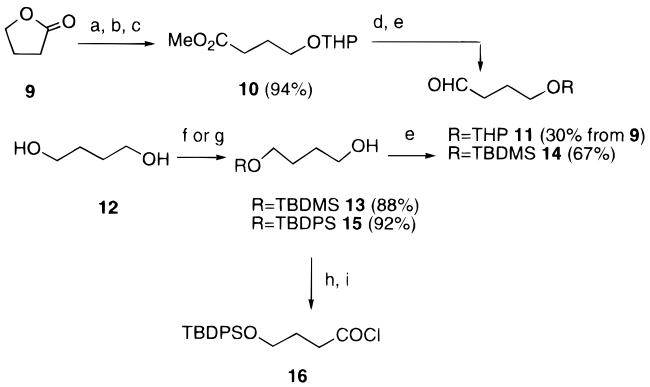
Scheme 2[a]



[a] Reagents: (a) $CH_2{=}CHCH_2CH_2Br$, Mg, CuBr/Me_2S, THF; (b) $HOCH_2CH_2OH$, TsOH, C_6H_6; (c) O_3; then Zn, AcOH; (d) $CH_3CH(Br)CH_3$, Mg, Et_2O; (e) Jones oxidation; (f) 5% KOH−MeOH.

Scheme 3[a]



[a] Reagents: (a) KOH, MeOH, reflux; (b) MeI, acetone, reflux; (c) dihydropyrane, PPTS, CH_2Cl_2; (d) $LiAlH_4$, ether; (e) Swern oxidation; (f) TBDMSCl, NEt_3, DMAP, CH_2Cl_2; (g) TBDPSCl, BuLi, THF; (h) PDC, DMF; (i) $(COCl)_2$, C_6H_6.

diastereoisomers,[9] whose structures were later revealed to be isomers at the C-10 position, the four-carbon side chain being on the α-side at the C-11 position. These results were revealed by Swern oxidation of the mixture of TBDMS ether **24** into the diketone **25**, which was a single isomer, stereochemically pure, showing that the second alkylation occurred exclusively from the α-side of the molecule at C-11. The mixture of the alcohols **18** was acetylated (to **19**), and two acetoxyl signals were observed in the NMR spectrum.

Introduction of the C2 Unit at the C-5 Position (Cyclization to the Lactone). The mixture of acetates **19** was treated with LDA to isolate the hydroxy lactone **20** and acetate **21**. Both **20** and **21** were stereochemically pure single isomers. The lactone **20** was dehydrated using $SOCl_2$ to afford the α,β-unsaturated lactone **22** and its isomer **23**. The stereochemistries at both the C-10 and 11 positions of **22** were determined from the NOESY spectrum. NOE's between the methyl group at C-11 and that at C-14 and between the protons at C-9, coupled with H-10, were observed. Thus the two methyl groups are cis to each other, the aldol condensation occurred exclusively from the α face of the ring, and the configuration at C-10 of **20** is *R**. The acetate **21** is the C-10 isomer, the configuration of which must be *S**. These results are attributed to the fact that the oncoming electron acceptor reacted from the opposite side of the C-14 methyl group of compound **17**. This is presumably due to the steric hindrance of the C-14 methyl group of the enolate **17′** (Figure 1) and also to the electronic requirement that the α-position (axial) is more accessible at C-11. This suggests that in order to synthesize the desired stereochemistry, we should first introduce the side chain and then the methyl group in ketone **8** (vide infra).

Preparation of Isoallocyathin B_2 (29). Although the stereochemistry at the two tertiary methyl groups is opposite to that desired, we attempted to synthesize isoallocyathin B_2 (**33**) in order to establish the synthetic route (Scheme 5). The lactone **22** was first reduced by $LiAlH_4$. The diol **26** was isolated in only 25% yield along with the dihydro diol **27** in 14% yield. This step was studied in detail in the case of allocyathin B_2 (*vide infra*). The primary alcohol of the diol **26** was protected by a TBDMS group and the secondary hydroxyl group was protected with a MOM group to afford **29** in high yield. Deprotection of both the THP and TBDMS groups was simply achieved by treatment of **29** with PPTS in MeOH to afford the diol **30** in quantitative yield. The final steps were accomplished by the Swern oxidation of **30** to the aldehyde **31** followed by intramolecular aldol condensation to give the dienal **32** in moderate yield. Although, deprotection of the MOM group was realized in only poor yield,[10] the synthesis of isoallocyathin B_2 (**33**), the unnatural diastereoisomer of natural allocyathin B_2 (**1**), was thus completed. The protons for the C-10 and C-11 positions of **33** appeared at δ 6.18 and 6.91, which suffered slightly downfield shifts than those of **1**. It is interesting to note that most other peaks were almost the same as those of diastereomeric natural allocyathin B_2 (**1**).

Acylation of the Ketone 8. The ketone **8** was alkylated using aldol conditions with the aldehyde **14** to acetates **34** in 87% yield (Scheme 6). However, the second alkylation of the acetates **34** was not an easy task, since elimination was facile. We next attempted acylation of the ketone **8** with the acid chloride **16**.[8] Although a considerable amount of the O-acylated product **36**, which was isolated by HPLC, was obtained, the product mixture was hydrolyzed without separation to give the C-acylated product **35** in 37% and the starting ketone **8**, which can be recycled, in 60% yield. The diketone was methylated using tBuOK/MeI in 91% yield. The product was stereochemically homogeneous judging from the ^{13}C NMR spectrum. Since reasonable evidence concerning the stereochemistry could not be obtained by spectral analysis, compound **37** was deprotected to the alcohol **38** and its spectral data were compared with those of the isomeric alcohol **25** (vide supra), which had completely different spectral data.[11] Therefore, the stereochemistry of **38** was established as depicted in the formula.

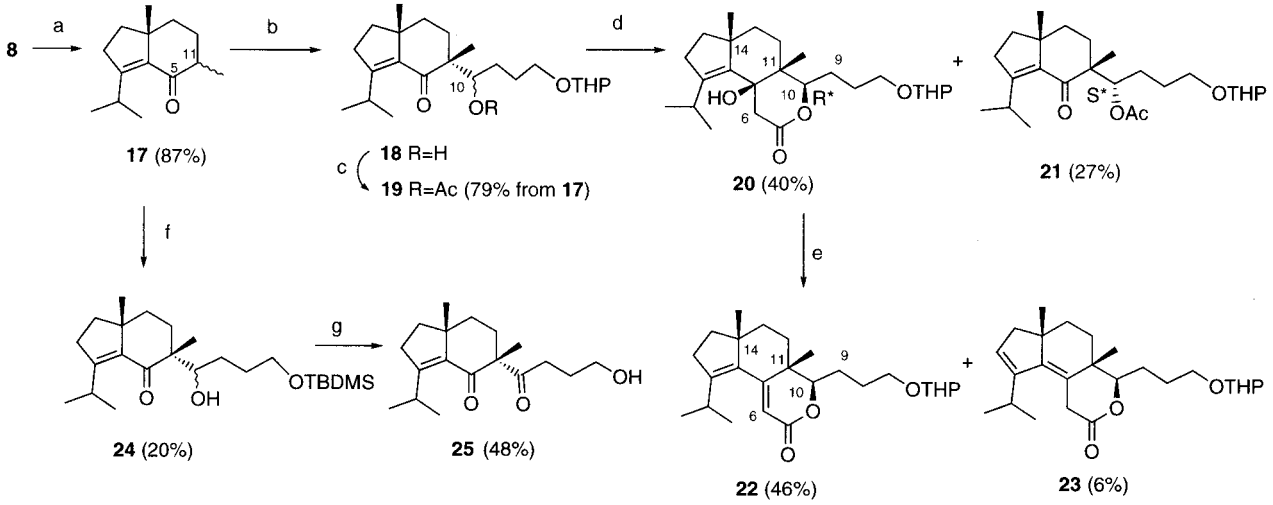
Preparation of the Lactone 44. The next problem was the regioselective and stereoselective reduction of the

(9) Heathcock, C. H. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: San Diego, 1984; Vol. 3, pp 111−206.

(10) The poor yield is presumably due to the instability of the aldehyde group under acidic conditions.

(11) Even after **38** was purified by preparative TLC or HPLC, the sample showed two spots or two peaks in TLC or HPLC, respectively. Therefore, compound **38** should exisit in equilibrium with its intramolecular acetal form, although **25** does not.

Scheme 4[a]



[a] Reagents: (a) LDA, MeI, THF, −78 °C; (b) LDA, Et_2O, **11**, −78 °C; (c) Ac_2O, DMAP, Py; (d) LDA, THF; (e) $SOCl_2$, Py, CH_2Cl_2, 0 °C; (f) LDA, THF, **14**, −78 to −55 °C; (g) Swern oxidation.

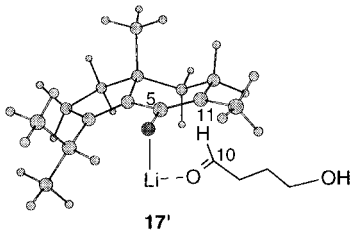
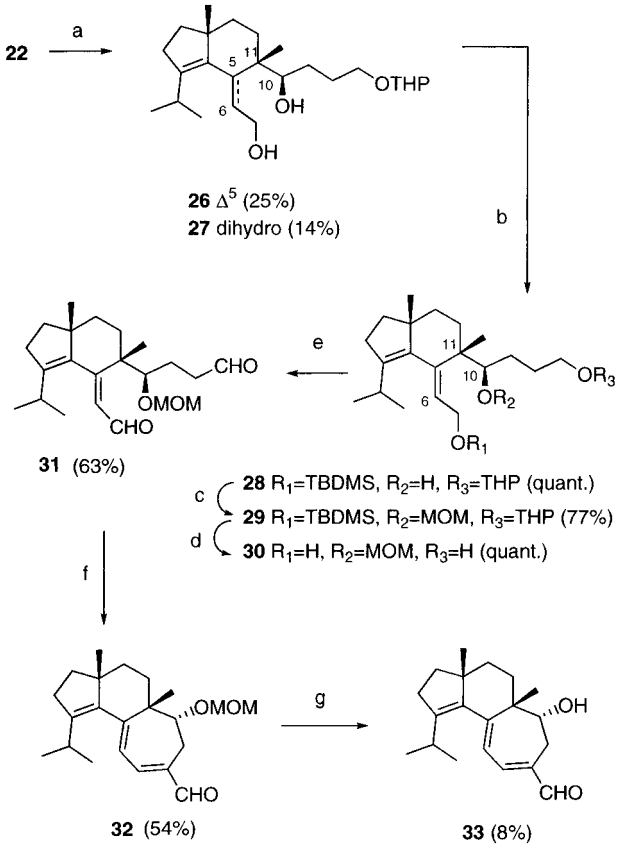


Figure 1. Transition state model in the reaction of **17**.

diketone **37** (Scheme 7). Sodium borohydride reduction in MeOH gave a mixture of the two diastereoisomers **39** and **40** in 62% yield in a 1:1.4 ratio. However, zinc borohydride reduction in ether at −78 °C afforded **39** and **40** in 50% yield in the ratio of 15:1.[12] When L-Selectride was used, the ratio of **39** and **40** was 1:12. These ratios were obtained by transformation into the corresponding acetates **41** and **42**. The stereochemistry was determined by the following transformation. The acetate **41** was treated with LHMDS to yield a hydroxy lactone **43** in 80% yield. The NOESY cross peaks were observed between the methyl group at δ 1.00 (at C-11) and the protons at C-9 and between the methyl group at δ 0.96 (C-14) and the proton at δ 2.78 (H-6β). Thus the stereochemistry of the hydroxy lactone **43** was determined as depicted in the formula. Therefore, this compound was the desired one with all the correct stereochemistries. Compound **43** was dehydrated with $SOCl_2$ and pyridine in CH_2Cl_2 to afford the α,β-unsaturated lactone **44** in 50% yield along with the isomeric lactone **45** in 22% yield. The latter could be transformed into **44** by treatment with potassium carbonate in MeOH under reflux. The stereochemistry was also confirmed by the NOESY spectrum for **44**. The isomeric acetate **42** was transformed into the lactone **46** by LDA followed by dehydration to yield the lactone **47**. The NOESY spectrum indicated cross peaks between the proton at δ 4.16 (H-10) and the methyl group at δ 1.21 (C-11). Thus, zinc borohydride reduction was presumably involved the chelation of the zinc atom to the diketone moiety and the hydride attacked from the convex side of this chelate ring to afford predominantly the *S** isomer, realizing regio- and stereoselective reduction.

(12) (a) Gensler, W. J.; Johnson, F.; Sloan, A. D. B. *J. Am. Chem. Soc.* **1960**, *82*, 6074. (b) Crabbé, P.; Garcia, G. A.; Rius, C. *J. Chem. Soc., Perkin Trans. 1* **1973**, 810.

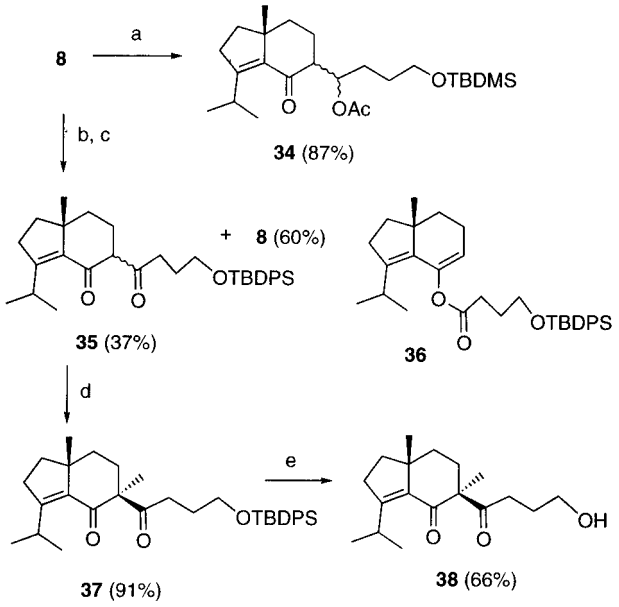
Scheme 5[a]



[a] Reagents: (a) $LiAlH_4$, THF, reflux; (b) TBDMSCl, NEt_3, DMAP, CH_2Cl_2; (c) MOMCl, $(i\text{-}Pr)_2NEt$, CH_2Cl_2; (d) PPTS, MeOH; (e) Swern oxidation; (f) 5% KOH−MeOH; (g) HCl, MeOH.

Synthesis of Allocyathin B_2 (1). The lactone **44** was then reduced by $LiAlH_4$ in THF under reflux to afford the deprotected triol **48**, which was isolated by transformation into the bis-TBDMS ether **49** in 37% overall yield (Scheme 8). This low yield was also observed in the six-membered lactone in the case of isoallocyathin B_2. When

Scheme 6[a]



[a] Reagents: (a) LDA, THF, **14**, −78 °C; then Ac_2O, rt; (b) LDA, THF, **16**, −78 °C; (c) 5% KOH−MeOH; (d) tBuOK, MeI, THF; (e) TBAF, THF.

DIBALH was used for the reduction, the lactol **52** was isolated in high yield. The lactol **52** was reduced again with $LiAlH_4$ in THF under reflux to yield the triol **48** in poor yield. When it was reduced by $NaBH_4$ in dioxane, the lactol **52** was obtained in high yield.[13] Super hydride reduction failed to give the diol. Therefore, the best method so far is to reduce the lactone with $LiAlH_4$ in THF under reflux for several hours. This is presumably due to the presence of the double bond at the C-5 and C-6 positions and the fact that the conformation is very rigid. Since the acetate can be easily removed at the cyclization step, this may not cause problems with the aldol cyclization. The alcohol **49** was treated with Ac_2O in pyridine followed by deprotection of the TBDMS group with PPTS to afford the diol **51** in 52% yield in two steps. Swern oxidation of the diol **51** afforded the dial **53**, and the final intramolecular aldol cyclization as well as deprotection of the acetate gave allocyathin B_2 (**1**) in 74% yield. The spectral data were identical with those of the natural one. Since the total synthesis of erinacine A (**2**) was achieved using *dl*-allocyathin B_2 (**1**) by Snider et al.,[7] this also constitutes the formal total synthesis of erinacine A (**2**).

In summary, we have achieved the total synthesis of allocyathin B_2 (**1**) using aldol reactions in (1) the construction of ring A; (2) the introduction of the two-carbon unit into the C-5 position, replacing the Wittig processes; and (3) the preparation of the seven-membered dienal by intramolecular cyclization. The introduction of an alkyl group at the C-11 position occurred solely from the α-side of the molecule (the side opposite the methyl group at C-14), which means that bond formation selectively occurred from the axial direction.

Experimental Section

General. Silica gel 60 (70−230 mesh, Merck) was used for column chromatography, and silica gel $60F_{254}$ plates (0.25, 0.5, 1.0 mm, Merck) were used for TLC.

(13) Ohmori, K.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1995**, *36*, 6519.

Synthesis of 3-Methyl-3-(3-butenyl)cyclohexanone (4). A solution of the Grignard reagent in THF was prepared from 4-bromo-1-butene (4.80 mL, 47.4 mmol) and Mg (0.93 g, 38.4 mmol) in THF (12 mL). A solution of $CuBr{\cdot}Me_2S$ (1.55 g, 7.55 mmol) in THF (10 mL) was added into this solution. In 10 min, a solution of 3-methyl-2-cyclohexen-1-one (1.41 g, 12.8 mmol) in THF (3 mL) was added and the mixture was stirred at −30 °C for 2 h. Saturated NH_4Cl solution (10 mL) was added and the mixture was extracted with ether. The organic phase was washed with water and brine, dried ($MgSO_4$), and evaporated to afford the ketone **4** (2.78 g) as an oil: FTIR 1725, 1650 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.94 (3 H, s), 4.94 (1 H, ddt, J = 10.0, 1.9, 1.0 Hz), 5.01 (1 H, dq, J = 16.9, 1.9 Hz), 5.80 (1 H, ddt, J = 16.9, 10.0, 6.5 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.9 (t), 24.7 (q), 27.7 (t), 35.6 (t), 38.4 (s) 40.7 (t), 40.8 (t), 53.5 (t), 114.2 (t), 138.6 (d), 211.8 (s); MS (EI) m/z 166 (M^+), 151, 111 (base), 95, 81, 69, 55; EI-HRMS m/z calcd for $C_{11}H_{18}O$: 166.1358. Found: 166.1374.

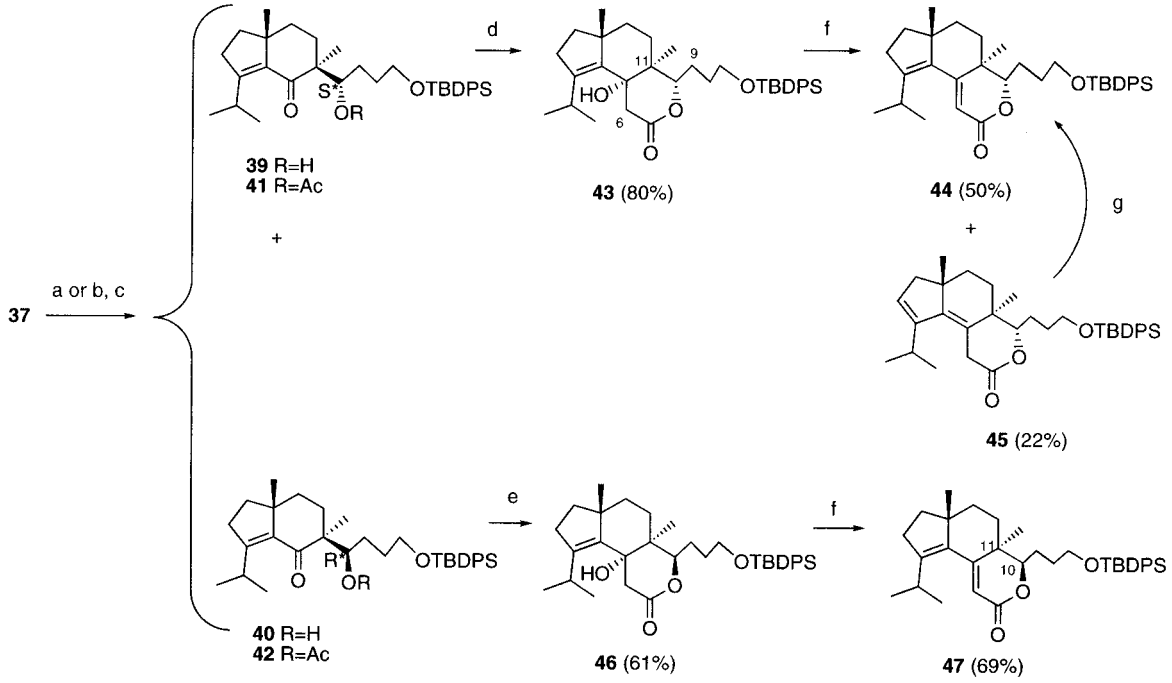
Synthesis of 3-Methyl-3-(3-butenyl)cyclohexanone Ethylene Ketal (5). A solution of the ketone **4** (2.78 g), ethylene glycol (1.31 g, 21.1 mmol), and $TsOH{\cdot}H_2O$ (0.27 g) in C_6H_6 (150 mL) was heated under reflux for 15 h with the aid of a Dean−Stark water separator. The mixture was washed with saturated $NaHCO_3$ solution, water, and brine. The aqueous layer was extracted with ether and the ethereal solution was washed with water and brine. The combined organic layer was dried ($MgSO_4$) and evaporated to afford a residue, which was purified by silica gel column chromatography (hexanes−EtOAc in gradient) to give the ketal **5** (2.66 g, 99%, two steps) as an oil: FTIR 1650 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.96 (3 H, s), 3.91 (4 H, m), 4.91 (1 H, ddt, J = 10.2, 1.6, 1.2 Hz), 5.00 (1 H, dq, J = 16.8, 1.6 Hz), 5.82 (1 H, ddt, J = 16.8, 10.2, 6.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.7 (t), 25.3 (q), 28.1 (t), 34.4 (s), 35.0 (t), 37.1 (t) 42.1 (t), 44.8 (t), 63.9 (t), 64.1 (t), 109.4 (s), 113.7 (t), 139.7 (d); MS (EI) m/z 210 (M^+), 195, 167, 155, 153, 139, 126, 113, 99 (base), 86; EI-HRMS m/z calcd for $C_{13}H_{22}O_2$: 210.1620. Found: 210.1633.

Synthesis of 3-Methyl-3-(3-hydroxy-4-methylpentyl)-cyclohexanone Ethylene Ketal (6). Ozone was bubbled through a solution of the ketal **5** (1.32 g, 44.5 mmol) in CH_2Cl_2 (150 mL) at −78 °C for 15 min. Acetic acid (3 mL) and Zn powder (2.33 g) were added, and the mixture was kept at rt overnight. The filtrate was washed with water, saturated $NaHCO_3$ solution, and brine, dried ($MgSO_4$), and evaporated to afford an aldehyde (1.87 g) as an oil: FTIR 1735 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.95 (3 H, s), 3.91 (4 H, m), 9.78 (1 H, t, J = 1.9 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.6 (t), 25.8 (q), 33.3 (t), 33.6 (s), 34.1 (t) 37.1 (t), 39.0 (t), 44.6 (t), 63.9 (t), 64.1 (t), 109.2 (s), 203.2 (d); MS (CI) m/z 213 $(M + H)^+$, 195, 184, 169, 155, 141, 113, 99 (base), 86; CI-HRMS m/z calcd for $C_{12}H_{21}O_3$ $(M + H)^+$: 213.1491. Found: 213.1507.

A solution of the aldehyde (1.87 g) in dry ether (40 mL) was added to a solution of the Grignard reagent prepared from 2-bromopropane (10 mL, 0.11 mol) and Mg (2.17 g, 89.3 mmol) in dry ether (60 mL) during 1 h. The mixture was further stirred at rt for 1 h. Saturated NH_4Cl (100 mL) was added at 0 °C and the mixture was extracted with ether. The organic phase was washed with water and brine, dried ($MgSO_4$), and evaporated to afford the alcohol **6** (1.36 g, 83%, two steps) as an oil: FTIR 3470 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.92 (6 H, d, J = 7.3 Hz), 0.95 (3 H, s), 3.30 (1 H, m), 3.91 (4 H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.1 (q), 18.9 (q), 19.6 (t), 25.8 (q), 28.0 (t) 33.1 (d), 34.3 (s), 34.9 (t), 37.6 (t), 38.0 (t), 44.5 (t), 63.9 (t), 64.0 (t), 77.3 (d), 109.8 (s); MS (EI) m/z 256 (M^+), 241, 213, 195, 155 (base), 111, 99, 86; EI-HRMS m/z calcd for $C_{15}H_{28}O_3$: 256.2038. Found: 256.2045.

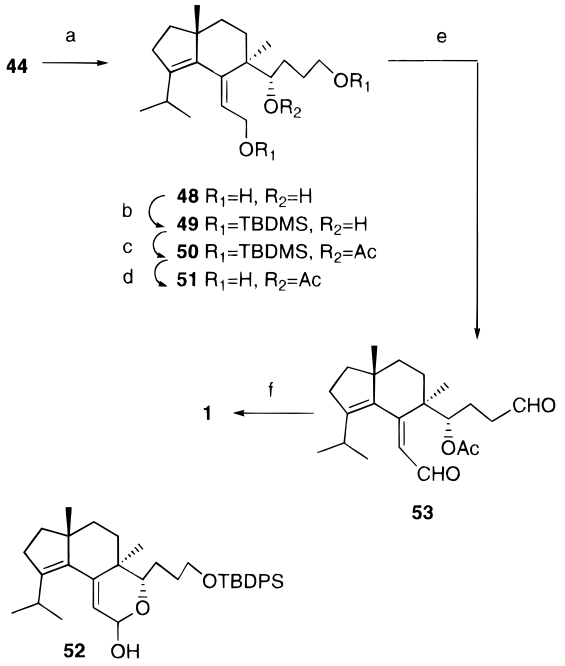
Synthesis of 3-Methyl-3-(4-methyl-3-oxopentyl)cyclohexanone (7). A solution of the alcohol **6** (3.75 g, 14.6 mmol) in acetone (30 mL) was treated with the Jones reagent (12.0 mL) at 0 °C. The mixture was stirred for 25 min and 2-propanol (15.0 mL) was added. Water was added and acetone was evaporated. The mixture was extracted with ether and the organic solution was washed with brine to afford the diketone **7** (3.33 g) as an oil: FTIR 1725 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.91 (3 H, s), 1.10 (3 H, d, J = 6.9 Hz),

Scheme 7[a]



[a] Reagents: (a) $NaBH_4$, MeOH, 0 °C; (b) $Zn(BH_4)_2$, Et_2O, −78 °C; (c) Ac_2O, DMAP, Py; (d) LHMDS, THF, −78 °C; (e) LDA, THF, −78 °C; (f) $SOCl_2$, Py, CH_2Cl_2, 0 °C; (g) K_2CO_3, MeOH, reflux (52%, **44**:**45** = 3:1).

Scheme 8[a]



[a] Reagents: (a) $LiAlH_4$, THF, reflux; (b) TBDMSCl, NEt_3, CH_2Cl_2 (37% from **44**); (c) Ac_2O, DMAP, Py; (d) PPTS, MeOH (52% from **49**); (e) Swern oxidation; (f) 5% KOH−MeOH (74% from **51**).

2.62 (1 H, septet, J = 6.9 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.2 (q × 2), 21.9 (t), 24.2 (q), 34.3 (t), 35.0 (t) 35.8 (t), 37.9 (s), 40.7 (t), 40.8 (d), 53.1 (t), 211.4 (s), 214.1 (s); MS (EI) m/z 210 (M^+), 192, 167, 149, 121, 111 (base), 95, 81, 71; EI-HRMS m/z calcd for $C_{13}H_{22}O_2$: 210.1619. Found: 210.1615.

Synthesis of 9-Isopropyl-6-methylbicyclo[4.3.0]non-1(9)-en-2-one (8). The diketone **7** (2.00 g) was treated with 5% KOH in MeOH (5 mL) under reflux for 12 h. The solvent was evaporated and the mixture was extracted with ether. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated to afford a residue, which was purified by silica gel column chromatography (hexanes−EtOAc in gradient) to give the enone **8** (1.24 g, 73%, 2 steps) as an oil: FTIR 1690, 1630 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.94 (3 H, d, J = 6.9 Hz), 0.98 (3 H, s), 1.00 (3 H. d, J = 6.9 Hz), 3.42 (1 H, septet, J = 6.9 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.0 (q × 2), 21.4 (t), 24.2 (q), 27.2 (d), 28.5 (t) 38.6 (t), 40.2 (t), 41.8 (t), 48.6 (s), 138.6 (s), 159.1 (s), 201.3 (s); MS (EI) m/z 192 (M^+), 177 (base), 159, 149, 135, 121, 107, 93, 79, 67; EI-HRMS m/z calcd for $C_{13}H_{20}O$: 192.1515. Found: 192.1496.

Synthesis of 35. A solution of the ketone **8** (543.0 mg, 2.83 mmol) in dry THF (5 mL) was treated with a solution of LDA prepared from BuLi (1.68 M, 2.20 mL, 3.70 mmol) and ^{i}Pr$_2$-NH (0.56 mL, 4.27 mmol) at −78 °C for 1 h. The acid chloride **16** (prepared from 1.17 g of the corresponding carboxylic acid **15** by treatment with oxalyl chloride) was added to this solution and the mixture was stirred for 30 min. Saturated NH_4Cl solution and ether were added, and the organic layer was washed with brine, dried ($MgSO_4$), and evaporated to afford a residue. The residue was treated with 5% KOH in MeOH (10 mL) at 0 °C for 30 min. Water was added and the mixture was extracted with ether. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated to afford a residue, which was purified by silica gel column chromatography (hexanes−EtOAc in gradient) to give the diketone **35** (486.3 mg, 33%) and the ketone **8** (325 mg, 60%) each as an oil.

35: FTIR 1630, 1590, 1560 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.95 (3 H, s), 1.04 (3 H, d, J = 6.8 Hz), 1.04 (3 H, d, J = 6.8 Hz), 1.05 (9 H, s), 3.72 (2 H, t, J = 6.0 Hz), 3.83 (1 H, septet, J = 6.8 Hz), 7.39 (6 H, m), 7.65 (4 H, m), 16.17 (1 H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.2 (s), 21.1 (q), 21.3 (q), 21.9 (q), 22.5 (t) 26.9 (q × 3), 27.3 (t), 27.9 (d), 29.7 (t), 34.3 (t), 36.1 (t), 38.3 (t), 46.0 (s), 63.2 (t), 106.4 (s), 127.6 (d × 4), 127.8 (s), 129.6 (d × 2), 133.9 (s × 2), 135.6 (d × 4), 159.3 (s), 171.5 (s), 203.0 (s); MS (CI) m/z 517 $(M + H)^+$, 501, 459 (base), 439, 381, 361, 261; CI-HRMS m/z calcd for $C_{33}H_{45}O_3Si$ $(M + H)^+$: 517.3138. Found: 517.3147.

Synthesis of 37. A solution of the diketone **35** (486.3 mg, 0.94 mmol) in dry THF (5 mL) was added to a solution of KO^t-Bu (118.0 mg, 1.05 mmol) in dry THF (5 mL) at 0 °C. Then the mixture was stirred at rt for 1 h before addition of MeI

(0.12 mL, 1.93 mmol). The mixture was stirred at rt for 1.5 h and then water was added. The mixture was extracted with ether and the organic layer was washed with brine, dried ($MgSO_4$), and evaporated to afford a residue. The residue was purified by silica gel column chromatography (hexanes−EtOAc in gradient) to give the diketone **37** (454.5 mg, 91%) as an oil: FTIR 1715, 1665, 1610 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.96 (3 H, d, J = 6.8 Hz), 1.03 (3 H, d, J = 6.8 Hz), 1.03 (9 H, s), 1.12 (3 H, s), 1.28 (3 H, s), 1.49 (1 H, dt, J = 13.8, 3.6 Hz), 3.38 (1 H, septet, J = 6.8 Hz), 3.68 (2 H, t, J = 6.0), 7.39 (6 H, m), 7.65 (4 H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.2 (s), 20.8 (q × 2), 21.2 (q), 24.8 (q), 26.9 (q × 3) 27.3 (d), 27.3 (t), 29.1 (t), 31.0 (t), 34.6 (t), 36.2 (t), 40.1 (t), 48.9 (s), 62.7 (s), 63.2 (t), 127.6 (d × 4), 129.5 (d × 2), 133.9 (s × 2), 135.5 (d × 4), 136.3 (s), 162.9 (s), 202.1 (s), 210.6 (s); MS (CI) m/z 531 $(M + H)^+$, 515, 473, 453, 395, 375, 325, 275 (base), 199, 151; CI-HRMS m/z calcd for $C_{34}H_{47}O_3Si$ $(M + H)^+$: 531.3294. Found: 531.3293.

Synthesis of 38. The diketone **37** (28.1 mg, 0.053 mmol) was treated with TBAF (1.0 M, 0.10 mL) at rt for 2.5 h. Water was added and the mixture was extracted with ether. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated to afford a residue. The residue was chromatographed over silica gel (hexanes−EtOAc in gradient) to give the alcohol **38** (10.2 mg, 66%) as an oil: FTIR 3400, 1715, 1670 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.96 (3 H, d, J = 6.9 Hz), 1.02 (3 H, d, J = 6.9 Hz), 1.13 (3 H, s), 1.30 (3 H, s), 3.14 (1 H, septet, J = 6.9 Hz), 3.67 (2 H, t, J = 5.6 Hz; MS (CI) m/z 291 $(M - H)^+$, 275 $(M - H_2O + H)^+$ (base), 259, 205, 151, 124, 87; CI-HRMS m/z calcd for $C_{18}H_{27}O_3$ $(M - H)^+$: 291.1960. Found: 291.1958.

Reduction of 37 by $NaBH_4$. A solution of **37** (454.5 mg, 0.86 mmol) in MeOH (5 mL) was added to a suspension of $NaBH_4$ (40.0 mg, 1.06 mmol) in MeOH (5 mL) at 0 °C. More $NaBH_4$ (10 mg) was added in 1.5 h, 9 mg in 2.5 h, and 12 mg in 4 h, respectively. Water and ether were added, and the organic layer was washed with brine, dried ($MgSO_4$), and evaporated to afford a residue. The residue was purified by silica gel column chromatography (hexanes−EtOAc in gradient) to give a mixture of alcohols **39** and **40** (282.7 mg, 1:1.4, 62%).

Reduction of 37 by $Zn(BH_4)_2$. A solution of diketone **37** (76.9 mg, 0.15 mmol) in dry ether (2 mL) was treated with $Zn(BH_4)_2$ in ether (60 mL) at −78 °C for 11 h. Water and AcOH were added, and the organic layer was washed with brine, dried ($MgSO_4$), and evaporated to afford a residue. The residue was purified by silica gel column chromatography (hexanes−EtOAc in gradient) to give a mixture of alcohols **39** and **40** (38.9 mg, 15:1, 50%) as an oil.

Data corresponding to the *S**-alcohol **39**: FTIR 3480, 1660, 1610 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.98 (3 H, d, J = 7.0 Hz), 1.02 (3 H, s), 1.04 (3 H, d, J = 7.0 Hz), 1.07 (9 H, s), 1.04 (3 H, s), 3.28 (1 H, septet, J = 7.0 Hz), 3.72 (1 H, td, J = 11.5, 5.9), 3.78 (1 H, td, J = 11.5, 5.9 Hz), 3.83 (1 H, br d, J = 10.4 Hz), 7.38 (6 H, m), 7.70 (4 H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.8 (q), 19.2 (s), 20.8 (q), 21.3 (q), 24.4 (q), 26.8 (q × 3) 27.0 (t), 27.2 (d), 29.3 (t), 29.5 (t), 31.0 (t), 34.9 (t), 40.0 (t), 49.4 (s), 51.2 (s), 63.9 (t), 75.4 (d), 127.5 (d × 4), 129.5 (d × 2), 134.0 (s × 2), 135.5 (d × 4), 137.5 (s), 160.0 (s), 210.0 (s); MS (CI) m/z 533 $(M + H)^+$, 515, 475, 455, 397, 377, 327, 269, 249, 207 (base), 191, 71; CI-HRMS m/z calcd for $C_{34}H_{49}O_3Si$ $(M + H)^+$: 533.3451. Found: 533.3445.

A solution of the alcohols (187.2 mg, 0.35 mmol) in pyridine (7 mL) was treated with Ac_2O (5 mL) and DMAP (42 mg) at rt for 10 h. Methanol (10 mL) and water were added, and the solvent was removed. The mixture was extracted with ether and the organic layer was washed with water, 1 M HCl solution, saturated $NaHCO_3$ solution, and brine, dried ($MgSO_4$), and evaporated to afford a residue. The residue was purified by silica gel column chromatography (hexanes−EtOAc in gradient) to give the acetates **41** (186.4 mg, 92%) and **42** (12.0 mg, 6%), each as an oil.

41: FTIR 1740, 1670, 1610 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.95 (3 H, d, J = 6.8 Hz), 1.01 (3 H, d, J = 6.8 Hz), 1.01 (3 H, s), 1.03 (9 H, s), 1.06 (3 H, s), 2.04 (3 H, s), 2.41 (1 H, dd, J = 7.6, 2.0 Hz), 2.44 (1 H, t, J = 9.0), 3.37 (1 H, septet, J = 6.8 Hz), 3.65 (2 H, br t, J = 5.6), 5.51 (1 H, br d, J = 8.8 Hz), 7.38 (6 H, m), 7.63 (4 H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.2 (s), 20.8 (q), 21.0 (q), 21.2 (q), 23.1 (q), 24.4 (q) 26.8 (q × 3), 27.1 (d), 27.6 (t × 2), 29.1 (t), 29.9 (t), 34.5 (t), 40.0 (t), 49.0 (s), 52.1 (s), 63.7 (t), 78.0 (d), 127.6 (d × 4), 129.5 (d × 2), 134.1 (s × 2), 135.5 (d × 4), 137.0 (s), 160.9 (s), 170.8 (s), 203.8 (s); MS (CI) m/z 575 $(M + H)^+$, 559, 543, 517, 497, 457, 437 (base), 419, 319, 259, 199, 177; CI-HRMS m/z calcd for $C_{36}H_{51}O_4Si$ $(M + H)^+$: 575.3557. Found: 575.3567.

42: FTIR 1740, 1675, 1610 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.93 (3 H, d, J = 6.9 Hz), 0.99 (3 H, d, J = 6.9 Hz), 1.028 (3 H, s), 1.033 (3 H, s), 1.04 (9 H, s), 1.94 (3 H, s), 3.40 (1 H, septet, J = 6.9 Hz), 3.70 (2 H, m), 5.46 (1 H, br dd, J = 10.4, 2.4 Hz), 7.38 (6 H, m), 7.64 (4 H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.2 (s), 20.8 (q), 21.1 (q), 21.3 (q), 21.9 (q), 24.0 (q) 25.6 (t), 26.9 (q × 3), 26.9 (d), 28.2 (t), 29.1 (t), 29.4 (t), 35.0 (t), 39.7 (t), 48.8 (s), 51.8 (s), 63.5 (t), 76.2 (d), 127.6 (d × 4), 129.5 (d × 2), 134.0 (s × 2), 135.5 (d × 4), 136.9 (s), 160.6 (s), 170.1 (s), 203.0 (s); MS (CI) m/z 575 $(M + H)^+$, 559, 515, 497, 457, 437 (base), 259, 61; CI-HRMS m/z calcd for $C_{36}H_{51}O_4Si$ $(M + H)^+$: 575.3556. Found: 575.3532.

Reduction of 37 by L-Selectride. A solution of **37** (72.2 mg, 0.14 mmol) in THF (2.5 mL) was treated with L-Selectride in THF (6.0 mL) at −78 °C for 4.5 h. Water and ether were added, and the organic layer was washed with brine, dried ($MgSO_4$), and evaporated to afford a residue. The residue was purified by silica gel column chromatography (hexanes−EtOAc in gradient) to give a mixture of alcohols **39** and **40** (51.6 mg, 0.097 mmol, 71%). The mixture of alcohols (49.5 mg, 0.093 mmol) in pyridine (0.7 mL) was treated with Ac_2O (0.5 mL) and DMAP (23.8 mg, 0.19 mmol) at rt for 18.5 h. MeOH (3 mL) was added at 0 °C and the solvent was evaporated. The mixture was extracted with ether and the organic layer was washed with brine, dried ($MgSO_4$), and evaporated to afford a residue. The residue was separated by silica gel column chromatography (hexanes−EtOAc in gradient) to give the acetates **41** and **42** (48.2 mg, 90%) in a ratio of 1:12.

Synthesis of 43. A solution of the acetate **41** (39.3 mg, 0.069 mmol) in dry THF (0.4 mL) was treated with LHMDS (1.0M, 0.08 mL) at −78 °C for 1 h. More LHMDS (1.0 M, 0.15 mL) was added and the mixture was further stirred for 1.5 h. Ether and saturated NH_4Cl solution were added and the organic layer was washed with brine, dried ($MgSO_4$), and evaporated to afford a residue. The residue was purified by silica gel column chromatography (hexanes−EtOAc in gradient) to give the hydroxy lactone **43** (31.2 mg, 80%) as an oil: FTIR 3500, 1750 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.93 (3 H, d, J = 6.8 Hz), 0.96 (3 H, s), 1.00 (3 H, d, J = 6.8 Hz), 1.00 (3 H, s), 1.05 (9 H, s), 2.18 (1 H, ddd, J = 16.0, 8.7, 0.4 Hz), 2.33 (1 H, ddd, J = 16.0, 10.9, 6.1 Hz), 2.66 (1 H, d, J = 15.1 Hz), 2.78 (1 H, dd, J = 15.1, 2.4 Hz), 3.48 (1 H, septet, J = 6.8 Hz), 3.67 (1 H, ddd, J = 10.2, 6.7, 5.6 Hz), 3.73 (1 H, ddd, J = 10.0, 5.8, 5.8 Hz), 3.92 (1 H, dd, J = 6.5, 6.1 Hz), 7.38 (6 H, m), 7.64 (4 H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.6 (q), 19.2 (s), 21.3 (q), 22.1 (q), 23.6 (q) 26.4 (t), 26.9 (q × 3), 27.3 (d), 28.0 (t), 29.5 (t), 33.4 (t × 2), 40.8 (t), 42.0 (s), 42.9 (t), 47.2 (s), 63.4 (t), 75.6 (s), 86.4 (d), 127.7 (d × 4), 129.6 (d × 2), 133.9 (s × 2), 135.6 (d × 4), 140.1 (s), 148.1 (s), 172.1 (s); MS (CI) m/z 575 $(M + H)^+$, 533, 497, 472, 439, 373, 327, 269, 249, 221, 207, 193, 179, 71 (base); CI−HRMS m/z calcd for $C_{36}H_{51}O_4Si$ $(M + H)^+$: 575.3556. Found: 575.3572.

Synthesis of 44. A solution of $SOCl_2$ (0.12 mL) in CH_2Cl_2 (2 mL) was added to a solution of the hydroxy lactone **43** (73.3 mg, 0.13 mmol) in pyridine (0.54 mL) and CH_2Cl_2 (4 mL) at 0 °C. The mixture was stirred for 15 min. Water was added and the mixture was extracted with CH_2Cl_2. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated to afford a residue. The residue was purified by silica gel column chromatography (hexanes−EtOAc in gradient) to give a mixture of the lactones **44** and **45** (59 mg). HPLC separation (Nucleosil 50−5, 4.6 × 250, hexane−EtOAc 96.5:3.5, 3.0 mL/min) afforded **44** (31.9 mg, 50%) and **45** (15.9 mg, 22%), each as an oil.

44: FTIR 1715, 1630, 1610 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.96 (3 H, s), 0.97 (3 H, s), 0.97 (3 H, d, J = 6.9 Hz), 1.03 (3

H, d, J = 6.9 Hz), 1.05 (9 H, s), 1.75 (1 H, m), 1.80 (1 H, ddd, J = 12.4, 7.7, 2.6 Hz), 2.00 (1 H, m), 2.43 (1 H, ddd, J = 16.7, 9.6, 2.5 Hz), 2.47 (1 H, ddd, J = 17.3, 9.6, 7.7 Hz), 2.91 (1 H, septet, J = 6.9 Hz), 3.69 (1 H, ddd, J = 10.4, 6.6, 5.2 Hz), 3.77 (1 H, ddd, J = 10.4, 6.3, 4.9 Hz), 4.03 (1 H, dd, J = 10.4, 1.9 Hz), 5.72 (1 H, s), 7.38 (6 H, m), 7.65 (4 H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 16.8 (q), 19.2 (s), 21.4 (q), 21.6 (q), 23.4 (q), 25.1 (t) 26.9 (q × 3), 26.9 (d), 28.8 (t), 29.2 (t), 32.7 (t), 36.0 (t), 39.0 (t), 39.4 (s), 48.6 (s), 63.3 (t), 85.4 (d), 114.2 (d), 127.6 (d × 4), 129.6 (d × 2), 133.9 (s × 2), 134.6 (s), 135.6 (d × 4), 151.2 (s), 160.7 (s), 166.1 (s); MS (CI) m/z 557 $(M + H)^+$, 499 (base), 479, 421, 242, 199; CI-HRMS m/z calcd for $C_{36}H_{49}O_3Si$ $(M + H)^+$: 557.3451. Found: 557.3456.

45: FTIR 1735 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.00 (3 H, s), 1.01 (3 H, d, J = 6.2 Hz), 1.03 (3 H, s), 1.05 (9 H, s) 1.14 (3 H, d, J = 6.2 Hz), 3.40 (1 H, d, J = 21.7 Hz), 3.67 (1 H, d, J = 21.7), 3.67 (1 H, dt, J = 10.1, 5.6 Hz), 3.78 (1 H, dt, J = 10.1, 5.2 Hz), 4.07 (1 H, br d, J = 10.5 Hz), 5.77 (1 H, br t, J = 0.7 Hz), 7.38 (6 H, m), 7.65 (4 H, m); MS (CI) m/z 557 $(M + H)^+$, 499 (base), 479, 421, 199; CI-HRMS m/z calcd for $C_{36}H_{49}O_3Si$ $(M + H)^+$: 557.3451. Found: 557.3479.

Isomerization of 45 to 44. A mixture of **45** (15.9 mg, 0.028 mmol), K_2CO_3 (130 mg), and MeOH (10 mL) was heated under reflux for 21 h. MeOH was removed and the mixture was extracted with ether. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated to afford a residue. The residue was purified by silica gel column chromatography (hexanes−EtOAc in gradient) to give a mixture of **44** and **45** (8.3 mg, 52%) in the ratio of 2:1.

Synthesis of 46. A solution of the acetate **42** (33.8 mg, 0.059 mmol) in dry THF (1 mL) was treated with LDA prepared from BuLi (1.63 M, 0.19 mL, 0.30 mmol) and ^{i}Pr$_2$-NH (0.05 mL, 0.38 mmol) in dry THF (1 mL) at −78 °C for 40 min. Ether and 1 M HCl solution were added, and the organic layer was washed with brine, dried ($MgSO_4$), and evaporated to afford a residue. The residue was purified by silica gel column chromatography (hexanes−EtOAc in gradient) to give the hydroxy lactone **46** (20.7 mg, 61%) as an oil: FTIR 3480, 1720, 1640 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.88 (3 H, s), 0.94 (3 H, d, J = 6.8 Hz), 1.02 (3 H, d, J = 6.8 Hz), 1.04 (3 H, s), 1.05 (9 H, s), 2.78 (1 H, dd, J = 18.9, 0.8 Hz), 2.92 (1 H, dd, J = 18.9, 1.6 Hz), 3.49 (1 H, septet J = 6.8 Hz), 3.68 (1 H, ddd, J = 10.6, 5.3, 5.3 Hz), 3.78 (1 H, ddd, J = 10.6, 6.0, 4.8 Hz), 4.52 (1 H, br dd, J = 9.8, 2.0 Hz), 7.38 (6 H, m), 7.65 (4 H, m); ^{13}C NMR (100 MHz, C_6D_6) δ 17.8 (q), 19.5 (s), 21.4 (q), 22.3 (q), 24.8 (t) 25.3 (q), 25.9 (t), 27.1 (d), 27.2 (q × 3), 28.4 (t), 29.9 (t), 34.1 (t), 41.6 (s), 42.5 (t), 42.6 (t), 42.7 (s), 63.8 (t), 76.8 (s), 81.3 (d), 128.1 (d × 4), 130.0 (d × 2), 134.4 (s × 2), 136.0 (d × 4), 140.5 (s), 145.5 (s), 169.2 (s); MS (CI) m/z 575 $(M + H)^+$, 573 $(M - H)^+$, 517, 497, 479 (base), 419, 401, 199; CI-HRMS m/z calcd for $C_{36}H_{49}O_4Si$ $(M - H)^+$: 573.3400. Found: 573.3390.

Synthesis of 47. A solution of $SOCl_2$ (0.06 mL) in CH_2Cl_2 (1 mL) was added to a solution of the hydroxy lactone **46** (17.2 mg, 0.030 mmol) in pyridine (0.13 mL) and CH_2Cl_2 (1 mL) at 0 °C. The mixture was stirred for 15 min. Water was added and the mixture was extracted with CH_2Cl_2. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated to afford a residue. The residue was purified by silica gel column chromatography (hexanes−EtOAc in gradient) to give the lactone **47** (11.5 mg, 69%) as an oil: FTIR 1715, 1610 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.97 (3 H, d, J = 6.9 Hz), 0.98 (3 H, s), 1.04 (9 H, s), 1.04 (3 H, d, J = 6.9 Hz), 1.21 (3 H, s), 1.27 (1 H, dt, J = 13.5, 3.3 Hz), 2.41 (1 H, ddd, J = 14.9, 9.8, 2.2 Hz), 2.46 (1 H, ddd, J = 17.0, 9.8, 7.7 Hz), 2.92 (1 H, septet, J = 6.9 Hz), 3.68 (1 H, ddd, J = 10.2, 6.5, 5.1 Hz), 3.75 (1 H, ddd, J = 10.2, 6.6, 5.2 Hz), 4.16 (1 H, dd, J = 11.0, 3.3 Hz), 5.72 (1 H, s), 7.38 (6 H, m), 7.64 (4 H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 19.2 (s), 21.4 (q), 21.5 (q), 23.8 (q), 24.7 (q), 26.2 (t) 26.9 (q × 3), 27.1 (d), 28.7 (t), 29.2 (t), 30.0 (t), 35.8 (t), 39.1 (t), 39.7 (s), 48.5 (s), 63.1 (t), 85.3 (d), 114.0 (d), 127.6 (d × 4), 129.6 (d × 2), 133.8 (s), 133.9 (s), 134.7 (s), 135.5 (d × 4), 151.9 (s), 157.3 (s), 164.7 (s); MS (CI) m/z 557 $(M + H)^+$, 521, 499, 479 (base), 199; CI-HRMS m/z calcd for $C_{36}H_{49}O_3Si$ $(M + H)^+$: 557.3451. Found: 557.3425.

Reduction of 44. A solution of **44** (31.9 mg, 0.057 mmol) in dry THF (5 mL) was heated under reflux with $LiAlH_4$ (60.0 mg, 1.58 mmol) for 1 h. Wet ether and water were added, and the organic layer was washed with brine, dried ($MgSO_4$), and evaporated to afford the triol **48** (25.0 mg) as an oil: FTIR 3310, 1650, 1620 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.94 (3 H, s), 0.95 (3 H, d, J = 6.4 Hz), 0.99 (3 H, d, J = 6.4 Hz), 1.05 (3 H, s), 2.84 (1 H, septet, J = 6.4 Hz), 3.71 (2 H, t, J = 5.6), 3.97 (1 H, br d, J = 10.0 Hz), 4.18 (1 H, dd, J = 13.2, 6.8 Hz), 4.28 (1 H, dd, J = 13.2, 6.8 Hz), 5.26 (1 H, t, J = 6.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.4 (q), 21.7 (q), 22.8 (q), 24.1 (q), 26.5 (d), 28.1 (t), 29.5 (t), 29.7 (t), 30.5 (t), 36.3 (t), 38.8 (t), 46.8 (s), 48.1 (s), 59.8 (t), 62.7 (t), 77.4 (d), 125.5 (d), 141.5 (s), 141.6 (s), 143.0 (s); MS (CI) m/z 323 $(M + H)^+$, 322, 304, 287 (base), 269, 234, 217, 201, 71; CI-HRMS m/z calcd for $C_{20}H_{35}O_3$ $(M + H)^+$: 323.2586. Found: 323.2581.

Synthesis of 49. A solution of the triol **48** (12.0 mg, 0.037 mmol) in CH_2Cl_2 (3 mL) was treated with NEt_3 (0.10 mL, 0.72 mmol), DMAP (31.9 mg, 0.26 mmol), and TBDMSCl (43.6 mg, 0.29 mmol) at rt for 1.3 h. Water was added and the mixture was extracted with CH_2Cl_2. The organic layer was washed with 1 M HCl solution, saturated $NaHCO_3$ solution, and brine, dried ($MgSO_4$), and evaporated to afford a residue. The residue was purified by silica gel column chromatography (hexanes−EtOAc in gradient) to give the monoalcohol **49** (23.1 mg) as an oil: FTIR 3400 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.07 (12 H, s), 0.90 (18 H, s), 0.92 (3 H, s), 0.95 (3 H, d, J = 6.8 Hz), 0.97 (3 H, d, J = 6.8 Hz), 1.04 (3 H, s), 2.28 (2 H, br dd, J = 8.9, 5.9 Hz), 2.89 (1 H, septet, J = 6.8 Hz), 3.64−3.81 (3 H, m), 4.21 (1 H, dd, J = 13.9, 5.1 Hz), 4.39 (1 H, dd, J = 13.9, 6.4 Hz), 5.15 (1 H, dd, J = 6.4, 5.1 Hz); MS (CI) m/z 551 $(M + H)^+$, 533, 493, 418, 401, 361, 269, 203 (base), 145, 71; CI-HRMS m/z calcd for $C_{32}H_{63}O_3Si_2$ $(M + H)^+$: 551.4316. Found: 551.4337.

Synthesis of 51. A solution of **49** (23.1 mg) in pyridine (3.5 mL) was treated with Ac_2O (2.5 mL) and DMAP (27.8 mg) at rt for 3.5 h. MeOH (10 mL) was added at 0 °C and the solvent was evaporated. The mixture was extracted with ether and the organic layer was washed with brine, dried ($MgSO_4$), and evaporated to afford the acetate **50**. A solution of **50** in MeOH (2 mL) was treated with PPTS (98.1 mg) at rt for 4 h. Water was added and the solvent was evaporated. The mixture was extracted with ether and the organic layer was washed with brine, dried ($MgSO_4$), and evaporated to afford a residue. The residue was purified by silica gel column chromatography (hexanes−EtOAc in gradient) to give the diol **51** (7.1 mg, 52%, three steps) as an oil: FTIR 3350, 1730, 1660 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.92 (3 H, s), 0.94 (3 H, d, J = 6.8 Hz), 0.97 (3 H, s), 0.99 (3 H, d, J = 6.8 Hz), 2.09 (3 H, s), 2.81 (1 H, sept, J = 6.4 Hz), 3.63 (1 H, dd, J = 7.4, 5 Hz), 3.75 (2 H, t, J = 5 Hz), 4.25 (1 H, dd, J = 13.2, 6.2 Hz), 4.38 (1 H, dd, J = 13.2, 8.8 Hz), 5.28 (1 H, dd, J = 8.8, 6.2 Hz); MS (CI) m/z 363 $(M - 1)^+$, 319, 303, 287 (base), 269, 243, 233, 215; CI-HRMS m/z calcd for $C_{22}H_{35}O_4$ $(M - H)^+$: 363.2535. Found: 363.2509.

Synthesis of Allocyathin B$_2$ (1). A solution of the diol **51** (3.1 mg, 0.085 mmol) in dry CH_2Cl_2 (0.34 mL) was treated with oxalyl chloride (0.04 mL, 0.46 mmol) and DMSO (0.06 mL, 0.85 mmol) in CH_2Cl_2 (1 mL) at −50 °C. In 15 min, NEt_3 (0.24 mL, 1.72 mmol) was added and the mixture was stirred for 5 min. Water and more CH_2Cl_2 were added, and the organic layer was washed with brine, dried ($MgSO_4$), and evaporated to afford the dialdehyde **53**. A solution of the dialdehyde **53** was treated with 5% KOH in MeOH (2 mL) at rt for 1 h. Water was added and the solvent was removed. The mixture was extracted with EtOAc and the organic layer was washed with brine, dried ($MgSO_4$), and evaporated to afford a residue. The residue was purified by silica gel column chromatography (hexanes−EtOAc in gradient) to give allocyathin B$_2$ (**1**) (1.9 mg, 74% for 2 steps) as an oil: FTIR 3450, 1670, 1630, 1570 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.96 (3 H, s), 0.97 (3 H, d, J = 6.9 Hz), 1.00 (3 H, s), 1.05 (3 H, d, J = 6.9 Hz), 1.34 (1 H, dt, J = 14.0, 3.6 Hz), 1.61 (1 H, d, J = 9.9 Hz, −OH), 1.65−1.69 (3 H, m), 1.74 (1 H, ddd, J = 12.9, 7.7, 4.9 Hz), 2.41 (1 H, d, J = 13.7 Hz), 2.42 (1 H, dd, J = 9.3, 2.7

Hz), 2.53 (1 H, dd, J = 19.5, 5.8 Hz), 2.55 (1 H, br d, J = 18.4 Hz), 2.83 (1 H, septet, J = 6.9 Hz), 3.17 (1 H, dd, J = 18.4, 5.8 Hz), 3.72 (1 H, br dd, J = 9.9, 5.8), 5.94 (1 H, d, J = 8.2 Hz), 6.82 (1 H, dd, J = 8.2, 2.5 Hz), 9.45 (1 H, s); MS (EI) m/z 300 (M^+) (base), 285, 267, 239, 211, 197, 183, 155, 128, 105, 91; EI-HRMS m/z calcd for $C_{20}H_{28}O_2$: 300.2089. Found: 300.2100.

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Supporting Information Available: Copies of ^{1}H NMR spectra and experimental details for compounds **10**−**34** (51 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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