Total Synthesis of (−)-Cylindricine C

Gary A. Molander* and Magnus Rönn

Department of Chemistry and Biochemistry, University of Colorado, Boulder, Colorado 80309-0215

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(−)-Cylindricine C has been synthesized from commercially available (*S*)-(−)-1,2,4-butanetriol in 11 steps with an overall yield of 12%. The key step utilizes a $CrCl_2$ reduction of an azide to form the corresponding amine with a subsequent double Michael addition to create the tricyclic skeleton of cylindricine from a monocyclic substrate.

Cylindricines A−J (**1a**−**j**) were first isolated by Blackman et al.[1] from the ascidian *Calvelina cylindrica* off the coast of Tasmania. These alkaloids represent one class of a family of compounds with similar structures that include the clavepictines[2] and fasicularin[3] (Figure 1). Lepadiformine[4] is also presumably among this class, but its published structure has been questioned by the groups of Weinreb[5] and Pearson.[6] Members of this general ensemble of compounds exhibit bioactivity against brine shrimp in a bioassay[1a] and a DNA-repair-deficient yeast strain[3] and also inhibit growth of murine leukemia and human solid tumor cell lines.[2] Moreover, the tricyclic system of the cylindricines is comprised of a spirocyclic amine that makes them an interesting target for total synthesis.

Several approaches to the cylindricines and related compounds have been recorded. Pearson and co-workers utilized their elegant 2-azapentadienyl anion cycloaddition chemistry in conjunction with an intramolecular reductive amination to construct the perhydropyrrolo[2,1-*j*]quinoline system of these marine alkaloids.[6] A convergent, stereoselective approach comprising an intramolecular nitrone/diene dipolar cycloaddition was employed by Weinreb and co-workers en route to the putative structure of lepadiformine.[5] Finally, a double Michael addition of NH_3 to a conjugated dienone system served as the key step in the highly efficient synthesis of (±)-cylindricines A, D, and E, as reported by Snider and Liu.[7] Herein, we report the first enantioselective total synthesis of (−)-cylindricine C.

Retrosynthetic analysis (Scheme 1) reveals a potentially convenient route to cylindricine C via the azide **2a**. Reduction of this azide to the corresponding amine followed by a double Michael addition would provide cylindricine C (**1c**) in a single step. (*S*)-(−)-1,2,4-Butanetriol, cyclohexanone, and *E*-trimethyl-1-octenylstannane were envisioned as the three major building blocks for the construction of **2a**. Challenges to overcome in this approach would include the prevention of a hydroxyl group Michael addition en route from the enol triflate to the azide **2a**, selective reduction of the azide to the amine in the presence of the dienone, and realization of the double Michael addition of the resulting amine to the highly hindered dienone system. Should these obstacles be conquered, the route designed would be highly con-

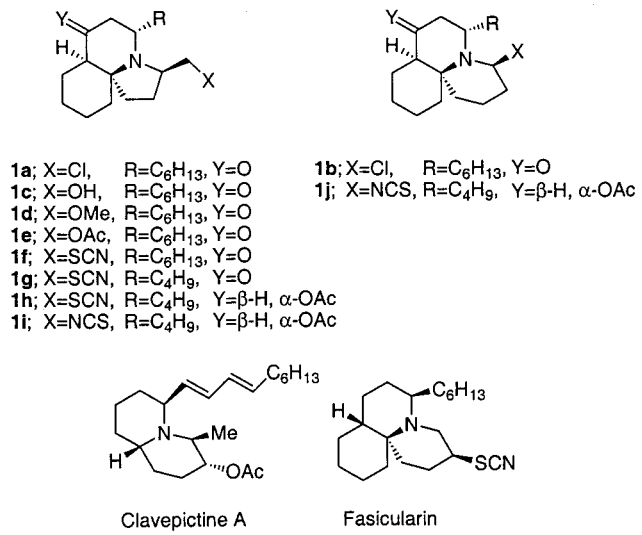
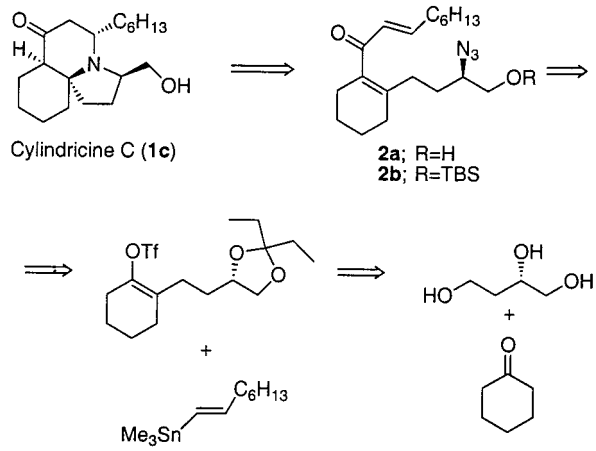


Figure 1.

Scheme 1



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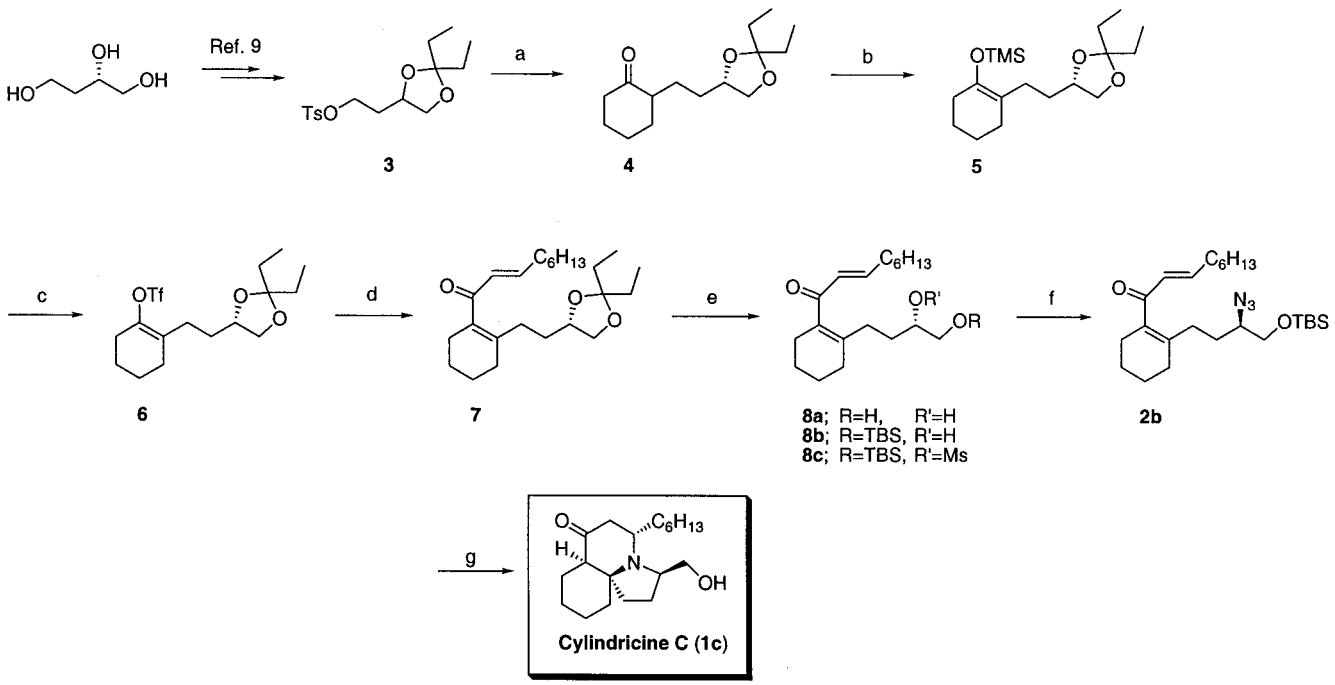
Scheme 2



(a) *i.* cyclohexanone dimethylhydrazone, LDA then **3**, THF, *ii.* $Cu(OAc)_2$, THF/H_2O, 77%; (b) *i.* $(i\text{-}Pr)_2NMgBr$, Et_2O. *ii.* TMSCl, NEt_3, HMPA; (c) *i.* MeLi, THF, *ii.* Tf_2NPh, TMEDA, 86% from **4**; (d) *E*-Trimethyl-1-octenylstannane, LiCl, $Pd(PPh_3)_4$, CO(g), 55 °C, 79%; (e) $PdCl_2(MeCN)_2$ cat. $MeCN:H_2O$ 9:1, 83%; (f) *i.* TBSCl, NEt_3, DMAP, CH_2Cl_2, *ii.* MsCl, NEt_3, *iii.* NaN_3, DMF, 60 °C, 86% from **8a**; (g) *i.* $CrCl_2$, H_3O^+, *ii.* TBAF, THF, 45% from **2b**.

vergent as well as efficient. Thus, the final cascade of reactions leading to cyclindricine would establish two of the three rings as well as three stereogenic centers in a single process.

Results and Discussion

With the strategic analysis in place, attention was directed toward execution of the synthetic plan (Scheme 2). Selective protection of the commercially available (*S*)-(−)-1,2,4-butanetriol as its five-membered ring pentylidene ketal,[8] followed by tosylation of the primary alcohol, provided the known tosylate **3**[9] in 72% overall yield. Coupling of tosylate **3** and the cyclohexanone moiety was best accomplished using the anion of cyclohexanone dimethylhydrazone as the alkylating agent. Hydrolysis of the hydrazone using standard acidic conditions gave, in addition to the free carbonyl, a considerable amount of deprotected diol, which in turn internally protected the newly formed ketone. To prevent this, a metal-ion-promoted procedure involving Cu(II)[10] was used for the hydrolysis of the hydrazone to provide a 1:1 diastereomeric mixture of the ketone **4** in 77% yield. With this near neutral procedure, no detectable amount of diol or internally protected ketone was observed.

Formation of the more substituted enol triflate **6** from **4** was examined using $(i\text{-}Pr)_2NMgBr/Tf_2NPh$,[11] LDA/Tf_2Ph,[12] and Tf_2O/di-*tert*-butylpyridine.[13] Unfortunately, all of these protocols gave low yields of the desired product or an unacceptably high amount of the undesired, less substituted, enol triflate. As a result, a two-step procedure was employed. Treating the ketone **4** with $(i\text{-}Pr)_2NMgBr$ in Et_2O followed by entrapment of the enolate with TMSCl[14] smoothly furnished the more substituted TMS-enol ether **5**, containing around 3% of the undesired enolate.[15] The TMS-enol ether was converted to the corresponding enol triflate **6** by treatment with MeLi followed by trapping the enolate with Tf_2NPh[16] in THF/TMEDA to give **6** in 89% yield from **4**, which was also contaminated with 3% of the undesired isomer. Performing this reaction using only THF as solvent gave a higher amount of the undesired isomer (5−15%) as the temperature had to be elevated to room temperature to allow complete trapping of the enolate. Thus, it proved advantageous to use TMEDA as a cosolvent, thereby allowing the reaction to be performed at 0 °C. At this temperature, no further isomerization of the intermediate enolate was observed. Carbonylative Stille coupling[11] of **6** with *E*-trimethyl-1-octenylstannane[17] afforded the dienone **7** in 79% yield.

Hydrolysis of **7** using acidic conditions, such as MeOH/cat. TsOH or MeOH/cat. PPTS gave the desired diol **8a** in low yield. The major product from these reactions was a less polar component, most likely the Michael addition product resulting from addition of the secondary alcohol to the enone resulting in the formation of a spirofuran. As a viable alternative, hydrolysis to the desired diol **8a** was accomplished in 83% yield under metal-ion-promoted

(8) Protection as an acetonide gives a higher amount of the six-membered ketal. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1991.
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(14) Krafft, M. E.; Holton, R. A. *Tetrahedron Lett.* **1983**, *24*, 1345.
(15) According to ^1H NMR analysis.
(16) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979.

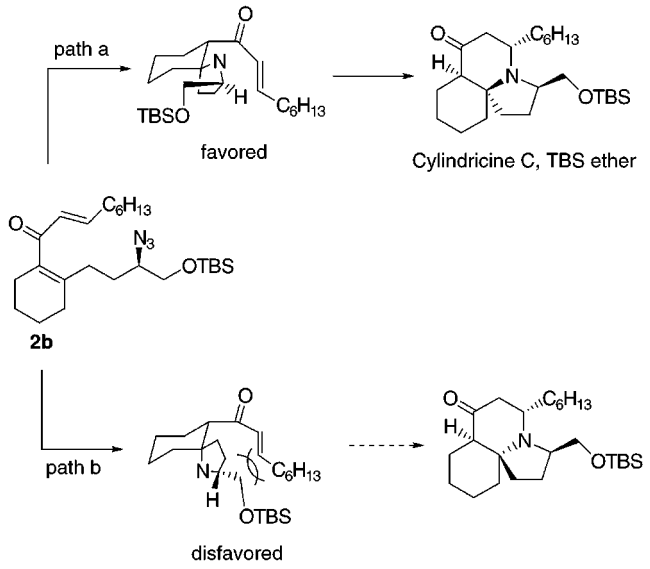
conditions, using catalytic amounts of Pd(II) in MeCN/H_2O.[18] Again, the remainder of the reaction mixture was a less polar component, probably the Michael addition product. The reaction could be quenched before all the substrate was consumed, giving about 70% yield of the diol **8a** and 25% recovered substrate **7**, the latter of which could be recycled.

The primary alcohol in **8a** was selectively protected using TBSCl/NEt_3/DMAP to give the monoprotected diol **8b** in 98% yield. A subsequent Mitsunobu reaction using $(PhO)_2PON_3$[19] gave the azide **2b** in 76% yield. However, as the Mitsunobu reaction did not perform consistently well and purification of the product proved to be difficult, we examined other routes to **2b**. Fortunately, it was discovered that a more expedient entry to the azide **2b** could be achieved by treatment of the diol **8a** with TBSCl/NEt_3/DMAP immediately followed by addition of MsCl/NEt_3 to form the mesylate **8c** in essentially quantitative yield from the diol. Aqueous workup, without further purification, followed by heating the crude mesylate in DMF with NaN_3 gave the azide **2b** in 86% yield (over three transformations).

Selective reduction of azide **2b** initially proved to be problematic. Employing a transition metal catalyst[20] in combination with H_2(g) gave low yields or no yield of the desired product because of competitive hydrogenation of the disubstituted double bond; use of $SnCl_2$ or $SnCl_2$/$AlCl_3$[21] gave a complex mixture of products. Propane-1,3-dithiol[22] was examined as a reductant, but this reagent added to the enone in a Michael fashion. Promising results were achieved in the reduction of the azide, using trialkyl or triaryl phosphines as well as trialkyl phosphites, followed by the hydrolysis of the resulting iminophosphorane.[23] The best results along these lines were achieved using Me_3P followed by hydrolysis of the corresponding intermediate iminophosphorane with boiling wet THF. In this case, the TBS-protected cylindricine C was isolated in 5−25% yield, but the reaction was capricious, and an alternative reduction of the azide was sought.

The groups of Kirk[24] and Goto[25] have reported the reduction of azides to the corresponding amines, using a fresh solution of $CrCl_2$. Thus, treating the azide **2b** with an aqueous acidic solution of $CrCl_2$ gave, with concomitant gas evolution, a complex mixture of amines after basic workup. Instead of isolating the various products, the crude mixture was dissolved in THF and treated with TBAF to deprotect the primary alcohol, giving (−)-cylindricine C **1c** in 45% yield[26] directly from the azide **2b** (Scheme 2).[27] The absolute configuration of the natural product is unknown, and additionally, the optical rotation has not been determined. Furthermore, apparently no sample remains of the isolated cylindricine C.[28] Thus, *rac*-cylindricine C was prepared by the same route as described above using *rac*-1,2,4-butanetriol as substrate. Both enantiopure and racemic cylindricine C were converted to the corresponding Mosher ester and analyzed by ^{1}H NMR. These studies revealed the synthetic (−)-cylindricine C to be of >98% ee.

Scheme 3



The formation of three new stereocenters from one is a highlight of this synthesis and demands further discussion. The stereoinduction at the quaternary center most likely arises from steric hindrance in the transition state leading to product. The amine can approach the tetrasubstituted enone from two different directions (Scheme 3). If the amine attacks to give the desired isomer (path a), the bulky OTBS-group will project away from the unsaturated side chain. Severe steric interactions are encountered between the OTBS-group and the enone side chain if approach is ventured from the opposite face (path b). The stereochemistry in the second Michael attack is undoubtedly created by reversibility in the attack (Michael/retro-Michael), allowing the C_6-chain to occupy an equatorial orientation. Finally, the stereochemistry α to the ketone is established by equilibration with base to afford the stable *cis*-fusion of the cyclohexanone moiety, with the proton in an axial orientation.

To our knowledge, no examples of a double Michael reaction forming a tricyclic skeleton that includes a spirocyclic center have been described previously in the literature. The mono-Michael attack of amines, forming spirocyclic amines, is well described,[29] although it seems advantageous to trap the Michael product as an acetal using ethylidene glycol to allow complete formation of the adduct.[30] Thus, in Corey's synthesis of perhydrohistri-

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(26) Average of five attempts using 20−40 mg of substrate giving 37−55% (−)-cylindricine C.
(27) Spectral data (^{1}H NMR, ^{13}C NMR, LRMS, HRMS) are in accordance with those presented in the literature, ref 1.
(28) Blackman, A. J., personal communication.
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onicotoxin the formation of a spirocyclic amine proved to be difficult, and mixtures of the Michael adduct and the starting amino enone were isolated.[31] On the other hand, in a similar study Magnus et al. isolated the Michael product with no detectable traces of the amine enone moiety.[32] In their synthesis of racemic cylindricines, Snider and co-workers performed a double Michael addition, although this procedure did not include the formation of a spirocyclic amine.[7]

Conclusions

An efficient, enantioselective synthesis of (−)-cylindricine C has been developed with an overall yield of 17% over nine steps, starting from tosylate **3**. The key step is the reduction of an azide to the corresponding amine with a subsequent double Michael addition. In this step, two rings and three new stereocenters are created with good selectivity.

Experimental Section

General. NMR spectra were recorded in $CDCl_3$ at 500 MHz for ^1H and 100 MHz for ^{13}C using chloroform (7.24 ppm for ^1H, 77.00 ppm for ^{13}C) as an internal reference unless otherwise stated. Optical rotations were measured using the D-line of Na at 25 °C. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel plates using UV light, *p*-anisaldehyde, or ceric ammonium nitrate solutions for visualization. Flash chromatography was performed using Scientific Adsorbent Inc. silica gel (40 μm). All reactions were performed under a dry atmosphere of argon using oven- and/or flame-dried glassware, except for those reactions utilizing water as solvent, which were run under air. THF and Et_2O were distilled from Na-benzophenone ketyl radical immediately before use. CH_2Cl_2, TMEDA, NEt_3, and *i*-Pr_2NH were distilled from CaH_2. *E*-Trimethyl-1-octenylstannane,[17] (*S*)-4-tosyloxy-1,2-*O*-3-pentylidene-1,2-butanediol (**3**),[9] and the $CrCl_2$-solution[33] were prepared according to the literature. Alkyllithium reagents were titrated before use using diphenylacetic acid. Other reagents were purchased from Aldrich and were used without further purification.

(2*R/S*)-{[(3*S*,4)-*O*-3-Pentylidene-3,4-dihydroxybutan]-1-yl}cyclohexanone (4). A solution of LDA was prepared by adding *n*-BuLi (6.3 mL of a 1.5 M solution in hexanes, 9.4 mmol) to diisopropylamine (0.99 g, 9.8 mmol) in THF (15 mL) at 0 °C. After 30 min, cyclohexanone dimethylhydrazone (1.37 g, 9.8 mmol) was added, and the anion was allowed to form during 1 h at 0 °C. A solution of **3** (2.7 g, 8.2 mmol) in THF (5 mL) was added dropwise to the resulting solution, and after 3 h, the mixture was poured into a solution of $Cu(OAc)_2$ (2.0 g, 11 mmol) in H_2O (100 mL) and THF (50 mL). The resulting bluish suspension was vigorously stirred for 1 h at which time a brown suspension had formed. The organic solvents were evaporated under reduced pressure, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with H_2O and brine, dried over $MgSO_4$, and evaporated. The crude product was purified by flash chromatography using 9:1 hexanes/EtOAc as solvent to give **4** (1.6 g, 77%) as a clear oil. $R_f = 0.18$ (9:1 hexanes/EtOAc). ^1H NMR: δ 4.02 (m, 2H), 3.44 (m, 1H), 2.36 (m, 1H), 2.27 (m, 2H), 2.10 (m, 1H), 2.09 (m, 1H), 1.15−1.90 (m, 12H), 0.86 (m, 6H). ^{13}C NMR: δ 212.98, 212.94, 112.5, 76.5, 76.2, 70.1, 70.0, 50.7, 50.4, 42.1, 42.0, 34.2, 33.8, 31.4, 30.8, 29.9, 29.74, 29.67, 28.1, 28.0, 26.0, 25.4, 25.0, 24.9, 8.2, 7.9. IR ($CDCl_3$): 1706, 1077, 921 cm^{-1}. LRMS (EI): *m/z* 225 (55), 151 (91), 57 (100), 29 (44). Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H 10.30. Found: C, 70.90; H, 10.30.

4-[2-(Trimethylsilanyloxy)cyclohex-1-enyl]-(1,2*S*)-butanediol, *O*-3-Pentylidine Acetal (5). To a solution of diisopropylamine (3.1 g, 30 mmol) in Et_2O (80 mL) was added MeMgBr (10.2 mL of a 3.0 M solution in Et_2O, 30 mmol). After the mixture was stirred for 12 h at room temperature, a white thick slurry had been formed to which ketone **4** (6.2 g, 24 mmol) in Et_2O (20 mL) was added dropwise. After 15 min, TMSCl (8.0 g, 73 mmol), NEt_3 (8.0 g, 79 mmol), and HMPA (2.1 g, 12 mmol) were added consecutively. After the mixture was stirred for 20 h, Et_2O was added, and the organic solution was washed with an ice-cooled saturated solution of $NaHCO_3$, dried over $MgSO_4$, and evaporated. The crude material was dissolved in 9:1 hexanes/EtOAc and filtered through a short silica plug to remove polar impurities. The silica plug was washed with an additional portion of 9:1 hexanes/EtOAc, the organic layers were combined, and the solvent was evaporated to give **5** in essentially quantitative yield. The silyl enol ether **5** was used in the subsequent step without any further purification. $R_f = 0.56$ (9:1 hexanes/EtOAc). ^1H NMR: δ 4.03 (m, 2H), 3.46 (app t, J = 7.2 Hz, 1H), 2.07 (m, 1H), 1.99 (m, 2H), 1.93 (m, 3H), 1.73 (m, 1H), 1.60 (m, 6H), 1.52 (m, 3H), 0.88 (t, J = 7.5 Hz, 3H), 0.87 (t, J = 7.5 Hz, 3H), 0.14 (s, 9H). ^{13}C NMR: δ 143.5, 114.7, 112.3, 76.4, 70.2, 31.6, 30.3, 29.9, 29.8, 27.7, 26.3, 23.6, 23.0, 8.3, 8.0, 0.8. IR ($CDCl_3$): 1254, 1190, 1165, 1078 cm^{-1}. HRMS calcd for $C_{18}H_{34}O_3Si$ 326.2277, found 326.2260. LRMS (EI): *m/z* 326 (52), 297 (64), 223 (70), 183 (92), 133 (65), 73 (100).

4-[2-(Trifluoromethylsulfonyloxy)cyclohex-1-enyl]-(1,2*S*)-butanediol, *O*-3-Pentylidine Acetal (6). The crude silyl enol ether **5** was dissolved in THF (50 mL) and cooled to 0 °C, and MeLi (19 mL of a 1.4 M solution in Et_2O, 27 mmol) was added dropwise. After the mixture was stirred for 30 min at 0 °C, Tf_2NPh (10.5 g, 29 mmol) in THF (20 mL) was added followed by TMEDA (20 mL). After 30 min at 0 °C, the THF and Et_2O were evaporated under reduced pressure and 7:3 hexanes/EtOAc was added to the residual solution. The organic layer was washed with H_2O, 0.1 M HCl, and H_2O, dried over $MgSO_4$, and evaporated. The crude product was purified by flash chromatography using 95:5 hexanes/EtOAc as solvent to give **6** (8.0 g, 86% over two steps) as a clear oil. This material contained 3% of the less substituted, undesired vinyl triflate, according to ^1H NMR analysis. $R_f = 0.29$ (9:1 hexanes/EtOAc). ^1H NMR: δ 4.03 (m, 2H), 3.48 (m, 1H), 2.29 (m, 2H), 2.20 (m, 2H), 2.14 (m, 2H), 1.73 (m, 3H), 1.60 (m, 7H), 0.88 (t, J = 7.5 Hz, 3H), 0.87 (t, J = 7.5 Hz, 3H). ^{13}C NMR: δ 143.3, 129.7, 118.3 (q, J = 318 Hz), 112.7, 75.7, 69.8, 31.1, 29.9, 29.6, 28.4, 27.5, 27.0, 23.1, 21.7, 8.2, 7.9. IR ($CDCl_3$): 1409, 1216, 1142 cm^{-1}. HRMS calcd for $C_{16}H_{26}F_3SO_5$: 387.1453 (m + H)$^+$, found 387.1471. LRMS (EI): *m/z* 357 (87), 133 (86), 91 (72), 57 (100), 41 (56).

1-{[1-(3*S*,4)-Dihydroxybutyl]cyclohex-1-enyl}non-2-en-1-one, *O*-3-Pentylidine Acetal (7). To LiCl (1.2 g, 28 mmol) and $Pd(PPh_3)_4$ (0.66 g, 0.6 mmol) were added **6** (4.4 g, 11 mmol) and *E*-trimethyl-1-octenylstannane (3.8 g, 14 mmol) in THF (60 mL). A flow of CO (g) was bubbled through the solution during 30 min. A balloon containing CO (g) was connected to the vessel, and the temperature was elevated to 55 °C. After 48 h, the solvent was evaporated and replaced by 7:3 hexanes/EtOAc. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and evaporated. The crude product was purified by flash chromatography using 95:5 hexanes/EtOAc as eluent to give **7** (3.4 g, 79%) as a pale yellow oil. $R_f = 0.27$ (9:1 hexanes/EtOAc). ^1H NMR: δ 6.75 (dt, J = 7.0, 15.6 Hz, 1H), 6.10 (dt, J = 1.6, 15.6 Hz, 1H), 3.97 (m, 2H), 3.39 (m, 1H), 2.19 (app ddd, J = 1.6, 7.0, 7.8 Hz, 2H), 2.11 (m, 2H), 2.04 (m, 3H), 1.96 (m, 1H), 1.71 (m, 1H), 1.61 (m, 3H), 1.56 (m, 4H), 1.42 (m, 2H), 1.26 (m, 8H), 0.85 (t, J = 6.9 Hz, 3H), 0.84 (t, J = 7.6 Hz, 3H), 0.83 (t, J = 7.6 Hz, 3H). ^{13}C NMR: δ 200.5, 150.3, 137.6, 133.6, 130.2, 112.5, 76.0, 69.9, 32.5, 32.3, 31.5, 31.1, 29.9, 29.6, 28.9, 28.7, 28.0, 27.3, 22.5, 22.4, 22.2, 14.0, 8.2, 7.9. IR ($CDCl_3$): 1640, 1464 cm^{-1}. HRMS calcd for $C_{22}H_{35}O_3$: 347.2586 (m − C_2H_5)$^+$, found 347.2581. LRMS (EI): *m/z* 347 (100), 273 (82), 57 (54). $[\alpha]_D^{25}$ 12.4 (c = 1.0, CH_2Cl_2).

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1-{2-[(3*S*,4)-Dihydroxybutyl]cyclohex-1-enyl}non-2-en-1-one (8a). To acetal **7** (600 mg, 1.6 mmol) in MeCN/H_2O (9:1) (10 mL) was added $PdCl_2(MeCN)_2$ (21 mg, 0.08 mmol). After the resulting light yellow solution was stirred at room temperature for 20 h, 1:1 hexanes/EtOAc was added, and the mixture was filtered through silica to remove Pd-salts. The silica was washed with 1:1 hexanes/EtOAc, and the combined organic portions were evaporated under reduced pressure. The crude product was purified by flash chromatography using 1:1 hexanes/EtOAc as eluent to give **8a** (410 mg, 83%) as a pale yellow oil. R_f = 0.20 (1:1 hexanes/EtOAc). ^{1}H NMR: δ 6.85 (dt, J = 7.0 Hz, 15.6 Hz, 1H), 6.17 (dt, J = 1.6, 15.6 Hz, 1H), 4.25 (br, 1H), 3.61 (m, 1H), 3.51 (dd, J = 3.2, 10.9 Hz, 1H), 3.41 (dd, J = 7.7, 10.9 Hz, 1H), 2.50 (br, 1H), 2.34 (ddd, J = 6.6, 9.7, 13.4 Hz, 1H), 2.21 (m, 4H), 2.09 (m, 2H), 1.97 (m, 2H), 1.68 (m, 2H), 1.39−1.62 (m, 5H), 1.27 (m, 6H), 0.86 (t, J = 7.1 Hz, 3H). ^{13}C NMR: δ 200.3, 151.2, 139.8, 134.3, 129.1, 70.0, 66.7, 32.6, 31.5, 30.4, 30.3, 28.85, 28.77, 28.0, 27.4, 22.5, 22.3, 22.2, 14.0. IR ($CDCl_3$): 3406, 1664, 1638 cm^{-1}. HRMS calcd for $C_{19}H_{32}O_3$: 308.2351, found 308.2337. LRMS (EI): *m*/*z* 308 (16), 247 (92), 149 (100), 41 (54). $[\alpha]_D^{25}$ 38.2 (c = 1.0, CH_2Cl_2).

1-{2-[(3*S*)-Methanesulfonyloxy-4-*tert*-butyldimethylsilyloxybutyl]cyclohex-1-enyl}non-2-en-1-one. To diol **8a** (150 mg, 0.49 mmol) in CH_2Cl_2 (5 mL) was added NEt_3 (74 mg, 0.73 mmol) followed by TBSCl (88 mg, 0.58 mmol) and DMAP (12 mg, 98 μmol). After the mixture was stirred for 6 h at room temperature, **8a** was completely transformed to the monoprotected alcohol **8b**[34] according to TLC. NEt_3 (74 mg, 0.73 mmol) was added followed by MsCl (67 mg, 0.58 mmol), and the mixture was stirred for an additional 3 h. The solvent was removed under reduced pressure, and the crude mixture was dissolved in 7:3 hexanes/EtOAc. The crude mixture was filtered through a short silica plug, and the solvent was evaporated to give the mesylate **8c** in essentially quantitative yield, which was used in the subsequent step without further purification. ^{1}H NMR: δ 6.77 (dt, J = 6.9, 15.7 Hz, 1H), 6.11 (dt, J = 1.6, 15.7 Hz, 1H), 4.56 (app pent, J = 5.5 Hz, 1H), 3.67 (m, 2H), 3.01 (s, 3H), 2.21 (app ddd, J = 1.6, 6.9, 14.9 Hz, 2H), 2.12 (m, 2H), 2.10−2.02 (m, 4H), 1.75 (m, 2H), 1.62 (m, 4H), 1.44 (m, 2H), 1.34−1.22 (m, 6H), 0.87 (br s, 12H), 0.05 (s, 3H), 0.04 (s, 3H). ^{13}C NMR: δ 200.1, 150.6, 137.3, 134.1, 130.0, 84.1, 64.5, 38.4, 32.5, 31.5, 30.4, 30.1, 28.9, 28.7, 28.0, 27.3, 25.8, 22.5, 22.4, 22.1, 18.3, 14.0, −5.47, −5.49.

1-{2-[(3*S*)-Hydroxy-4-*tert*-butyldimethylsilyloxybutyl]-cyclohex-1-enyl}non-2-en-1-one (8b). ^{1}H NMR: δ 6.79 (dt, J = 6.9, 15.7 Hz, 1H), 6.13 (dt, J = 1.6, 15.7 Hz, 1H), 3.52 (m, 2H), 3.42 (m, 1H), 2.99 (br, 1H), 2.22 (dd, J = 1.6, 6.9 Hz, 1H), 2.19 (dd, J = 1.6, 6.9 Hz, 1H), 2.18−2.00 (m, 6H), 1.68−1.51 (m, 5H), 1.44 (m, 3H), 1.27 (m, 6H), 0.87 (m, 12H), 0.035 (s, 6H). ^{13}C NMR: δ 200.5, 150.5, 138.7, 133.6, 129.9, 70.9, 67.0, 32.5, 31.5, 31.1, 30.7, 28.8, 28.6, 28.0, 27.3, 25.8, 22.5, 22.4, 22.3, 18.2, 14.0, −5.4. IR ($CDCl_3$): 1640, 1257, 920 cm^{-1}. Anal. Calcd for $C_{25}H_{46}O_3Si$: C, 71.03; H,10.97. Found: C, 71.37; H, 11.09. LRMS (EI): *m*/*z* 422 (18), 365 (60), 247 (65), 161 (74), 139 (87), 75 (100). $[\alpha]_D^{25}$ 15.4 (c = 0.5, CH_2Cl_2).

1-{2-[(3*R*)-Azido-4-*tert*-butyldimethylsilyloxybutyl]cyclohex-1-enyl}non-2-en-1-one (2b). The crude mesylate **8c** was dissolved in DMSO (2 mL), and NaN_3 (160 mg, 25 mmol) was added. After the mixture was stirred at 60 °C for 20 h, the solution was cooled to room temperature, and 9:1 hexanes/EtOAc was added. The organic layer was washed with H_2O, and the aqueous layer was extracted with 9:1 hexanes/EtOAc. The combined organic layers was washed with brine, dried ($MgSO_4$), and evaporated. The crude product was purified by flash chromatography using 95:5 hexanes/EtOAc as eluent to give **2b** (187 mg, 86%) as a pale yellow oil. R_f = 0.32 (95:5 hexanes/EtOAc). ^{1}H NMR (C_6D_6): 6.85 (dt, J = 7.0, 15.7 Hz, 1H), 6.23 (dt, J = 1.5, 15.7 Hz, 1H), 3.53 (dd, J = 3.7, 10.5 Hz, 1H), 3.43 (dd, J = 6.6, 10.5 Hz, 1H), 3.17 (m, 1H), 2.17 (m, 4H), 1.94 (dd, J = 1.5, 7.0 Hz, 1H), 1.91 (dd, J = 1.5, 7.0 Hz, 1H), 1.85 (m, 2H), 1.52 (m, 2H), 1.41 (app pent, J = 2.9 Hz, 4H), 1.22 (m, 4H), 1.14 (m, 4H), 0.97 (s, 9H), 0.87 (t, J = 7.1 Hz, 3H), 0.056 (s, 3H), 0.046 (s, 3H). ^{13}C NMR (C_6D_6): δ 197.8, 148.7, 137.8, 134.8, 130.5, 66.6, 63.6, 32.6, 31.93, 31.88, 29.3, 29.19, 29.16, 28.4, 27.5, 26.0, 22.9, 22.8, 22.6, 18.4, 14.2, −5.4. IR ($CDCl_3$): 1640, 1254 cm^{-1}. HRMS calcd for $C_{25}H_{42}N_3O_2Si$ (m-CH_3): 432.3046, found 432.3041. LRMS (EI): *m*/*z* 362 (100), 274 (97), 73 (88). $[\alpha]_D$25 13.3 (c = 0.4, CH_2Cl_2).

(−)-Cylindricine C. To azide **2b** (20 mg, 45 μmol) in THF (1 mL) was added a fresh solution of $CrCl_2$ (0.5 mL of a 1.4 M solution, 0.70 mmol). The solution was stirred for 1 h at room temperature, then K_2CO_3 (s) (ca. 1 g) was added along with EtOAc (5 mL). The solution was dried by addition of $MgSO_4$ (s) and stirred until the solids formed a homogeneous mixture (ca. 30−60 min). The organic layer was filtered through a short silica plug, and the solids were washed with EtOAc and EtOAc with 5% NEt_3, which also was filtered through the silica plug. The combined organic layers were evaporated under reduced pressure, and the residue was dissolved in THF. This solution was cooled with an icewater bath, and Bu_4NF (54 μL of a 1 M solution in THF, 54 μmol) was added dropwise. After 30 min, the solution was allowed to warm to room temperature and was stirred for 10 h. The THF was evaporated, and the crude mixture was purified by flash chromatography using 9:1 hexanes/EtOAc and 5% NEt_3 as eluent to give (−)-cylindricine C (6.2 mg, 45%)[26] as a pale yellow oil with spectral data in accordance with those reported in the literature.[1,35] ^{1}H NMR: δ 3.51 (m, 2H), 3.41 (m, 1H), 3.26 (m, 1H), 2.85 (br, 1H), 2.28 (t, J = 12.6 Hz, 2H), 2.21 (dd, J = 2.8, 13.3 Hz, 2H), 2.10 (dd, J = 7.8, 12.2 Hz, 1H), 1.81 (dd, J = 8.5, 13.3 Hz, 1H), 1.70−1.17 (m, 19H), 0.85 (t, J = 7.1 Hz, 3H). $[\alpha]_D^{25}$ −64 (c = 0.2, CH_2Cl_2).

(−)-Cylindricine C, Mosher Ester. To *rac*- or enantiopure cylindricine C (2.0 mg, 6.5 μmol) in CH_2Cl_2 (0.5 mL) at 0 °C was added NEt_3 (1.3 mg, 13 μmol) followed by (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (2.0 mg, 7.8 μmol). After the mixture was stirred for the mixture for 10 h at 0 °C, the solvent was evaporated and the crude mixture was purified by flash chromatography using 9:1 hexanes/EtOAc as eluent to give the Mosher ester of cylindricine C (2.5 mg, 3.5 μmol). The ^{1}H NMR for the enantiopure ester revealed two dd's at 3.85 and 4.36 ppm whereas the racemic ester had these signals and in addition two dd's at 3.87 and 4.31 ppm, respectively.[36]

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for **1c**, **2b**, and **5**−**8**. ^{1}H NMR for pertinent regions of the spectra for the Mosher ester of enantiopure (−)-cylindricine C and (±)-cylindricine C. This material is available free of charge via the Internet at http://pubs.acs.org.

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(34) Alcohol **8b** was initially isolated and fully characterized.

(35) The ^{13}C NMR was consistently ca. 0.6 ppm lower than the value reported in the literature. This is also in accordance with the values reported by Snider et al., ref 7.

(36) Copies of the relevant ^{1}H NMR spectra have been submitted in the Supporting Information.