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Lewis acid mediated control of allylic epoxide opening in carbocyclization and halide addition pathways

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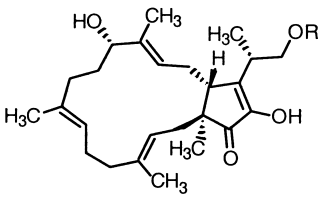
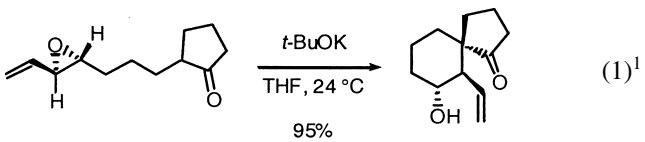
Abstract—Various novel carbocyclization processes were observed to occur in Lewis acid mediated cyclizations of an allylic epoxide substrate with a tethered enol(ate) function as nucleophile. Both cation-olefin polycyclization pathways and S_N-prime macrocyclization processes were observed to occur in the presence of different Lewis acid additives. Lewis acid additives were also observed to direct the stereochemistry of allylic epoxide opening by S_N-prime addition of halide ions. This provided a route to the corresponding *E*- or *Z*-allylic halides, which served as substrates in an alternative, successful approach to the terpestacin/fusaproliferin ring system by a subsequent alkylative macrocyclization reaction.

1. Introduction

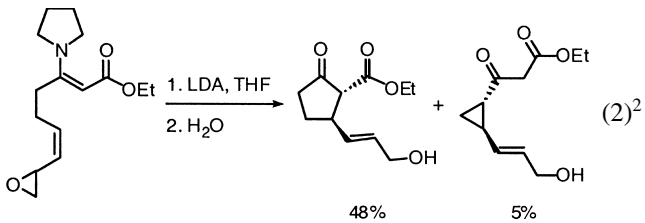
The use of allylic epoxides as electrophiles in internal carbocyclization reactions with enolate derivatives is well precedented in synthesis. The Stork cyclization of allylic epoxides to form 6-membered rings by internal displacement of the allylic C–O bond is a classic example of a stereocontrolled enolate alkylation reaction (Eq. (1)).[1] The formation of smaller rings is also precedented (Eq. (2))[2] and, by using palladium catalysts and stabilized enolates as nucleophiles, cyclization reactions producing a wide range of ring sizes, to include macrocyclic products, have been achieved.[3] In the course of research leading to the enantioselective syntheses[4] of the syncytium formation inhibitor (−)-terpestacin (**1**)[5,6] and the maize pathogen metabolite (−)-fusaproliferin (**2**)[7] we found that a variety of interesting, unprecedented cyclization pathways could be realized by Lewis acid activation of an allylic epoxide in the presence of a tethered enol or enolate derivative as nucleophile, as discussed herein. We also describe the S_N-prime opening of an allylic epoxide by halide addition, with control of olefin geometry by the choice of the Lewis acid activator.



Terpestacin (**1**) R = H
Fusaproliferin (**2**) R = Ac



(1)[1]



(2)[2]

2. Results and discussion

As one means of achieving the transformation of the allylic epoxide **3**[4] to the macrocyclic product **5**, envisioned to be a synthetic precursor to both **1** and **2**, we investigated several protocols to generate the enolate **4** from **3** with the goal of trapping it internally by addition to the electrophilic allylic epoxide group (Scheme 1). Many potential modes of cyclization were envisioned for **4**; two critical issues

Keywords: allylic epoxide; Lewis acid; allylic halide; cation-olefin cyclization; macrocyclization; terpestacin; fusaproliferin.

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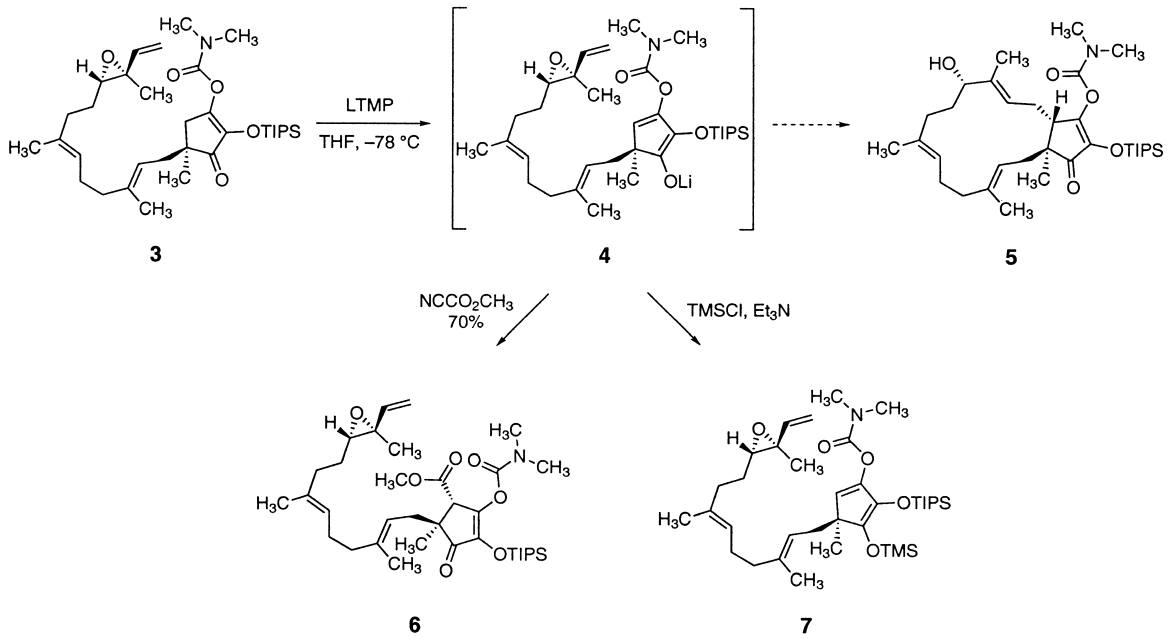
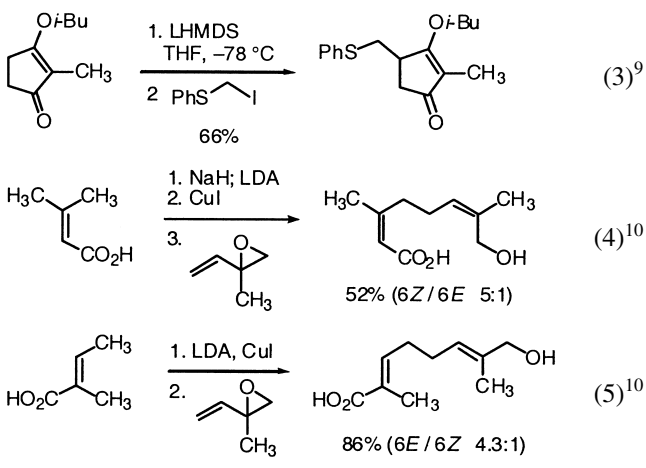
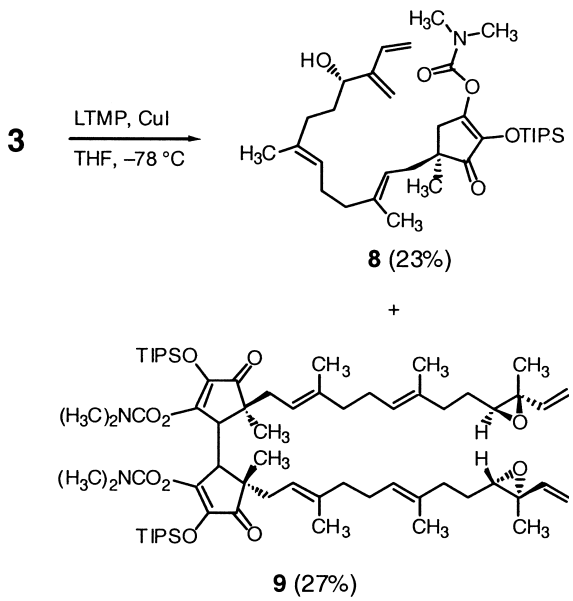


Scheme 1.

determining the cyclization outcome were the regioselectivity of the allylic epoxide opening (S_N versus S_N-prime displacement)[8] and the site of alkylation of the extended enolate (α- versus γ-alkylation). Concerning the first issue, the examples of Eqs. (1) and (2) provide precedence for both S_N and S_N-prime modes of addition of an enolate to an allylic epoxide, respectively. It was felt that the substrate **4** would exhibit a propensity for S_N-prime opening by virtue of the greater substitution of the site of the alternative direct S_N epoxide opening, as well as the presumed greater facility of 15-membered ring formation over 13-membered ring formation. Concerning the issue of α- versus γ-reactivity of the enolate, precedent for the desired γ-reactivity of 3-alkoxy-2-cyclopentenones is found in the work of Koreeda et al. as summarized in Eq. (3);[9] the examples of Eqs. (4) and (5) are also instructive, and provide additional support for a γ-alkylation pathway.[10] The complexity of these issues when compounded in the context of an unexplored macrocyclization reaction, however, clearly required experimental investigation for resolution.

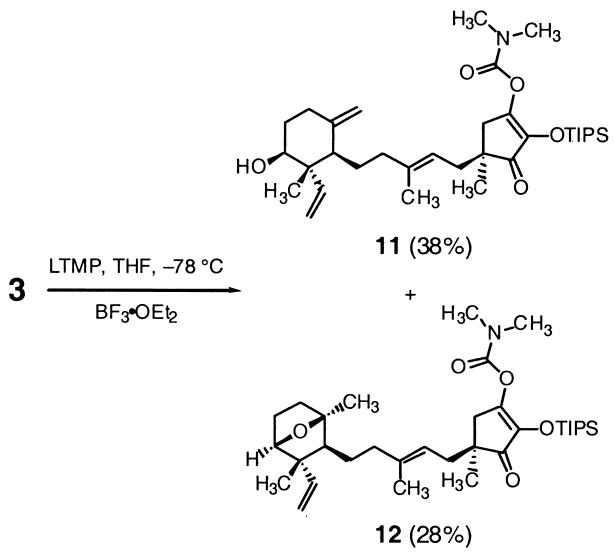


Formation of the lithium enolate **4** was readily achieved by the treatment of **3** with lithium 2,2,6,6-tetramethylpiperidide (LTMP) in tetrahydrofuran at −78°C (Scheme 1). Trapping of **4** with methyl cyanoformate gave the γ-alkylation product **6** as a single stereoisomer (stereochemistry not established, tentatively assigned as α, see structure **6**) in 70% yield, whereas trapping with chlorotrimethylsilane afforded the corresponding trimethylsilyl enol ether (**7**, unstable toward silica gel). Although the lithium enolate **4** was readily formed, under no circumstance was it observed to undergo macrocyclization in the absence of Lewis acid additives. Transmetalation of **4** to the corresponding copper(I) enolate in deoxygenated tetrahydrofuran (−78°C)[10] led to elimination within the allylic epoxide to form the diene alcohol **8** and slow dimerization of **4** to form one of the two possible C_2-symmetric dimers **9** (27%, Scheme 2). Because basic conditions alone did not effect macrocyclization, activation of the allylic epoxide



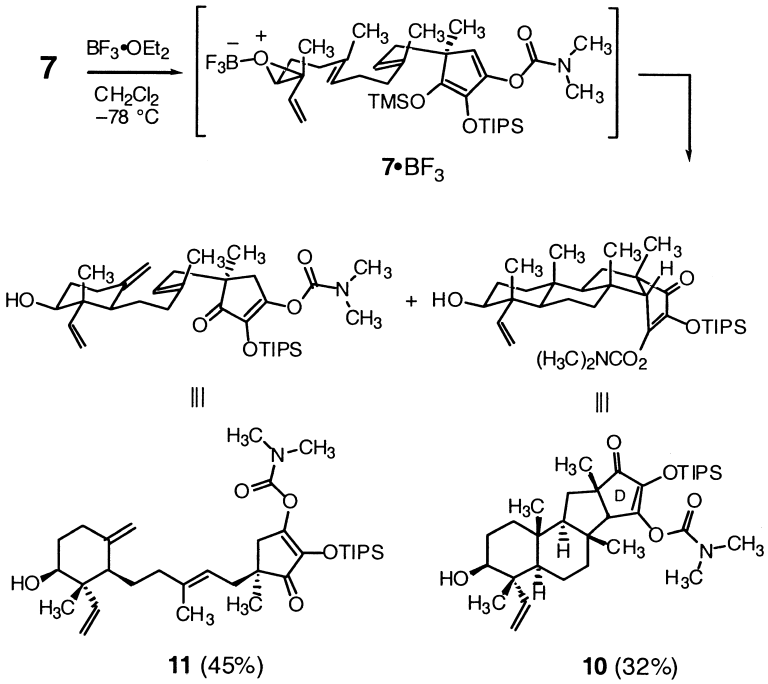
Scheme 2.

with Lewis acid additives was investigated. Both the lithium enolate **4** and the trimethylsilyl enol ether **7** were studied as substrates for Lewis acid activated ring closure. Addition of boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$) to a solution of the crude trimethylsilyl enol ether **7** (CH_2Cl_2, −78°C) resulted in rapid (<5 min) cation-olefin cyclization affording stereoselectively the tetracycle **10** and the cyclohexanol **11** in 32 and 45% yields, respectively (Scheme 3). The epoxide group of **7** is believed to determine the stereochemistry of the polycyclization; *trans*-addition to the trisubstituted olefins follows from the Stork–Eschenmoser postulate (Scheme 3).[11] Nuclear Overhauser enhancements between the adjacent angular methyl groups and the D-ring methine hydrogen of **10** (NOESY experiment) supported these stereochemical assignments. A related experiment using boron trifluoride diethyl etherate to activate the epoxy group of the lithium enolate **4** in tetrahydrofuran gave the cation-olefin cyclization products **11** and **12** in 38 and 28% yields, respectively (Scheme 4).

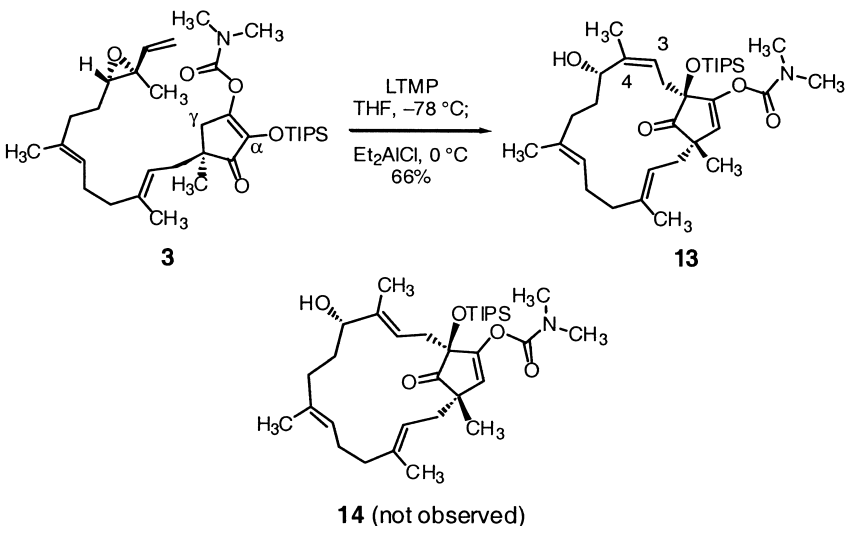


Scheme 4.

Macrocyclization could be achieved, albeit not in the desired sense, by treatment of the enolate **4** with the milder Lewis acid diethylaluminum chloride in THF (−78→0°C),[12] affording the macrocycle **13** in 66% yield (Scheme 5). Olefin and ring fusion stereochemistries were determined by NOESY experiments; approximately 7% of **3** was also recovered from the cyclization reaction. In this reaction, macrocyclization occurred by S_N-prime addition of the enolate derivative to the allylic epoxide; however, the extended enolate reacted at the α-position and not the γ-position as hoped, in spite of the presence of the bulky triisopropylsilyloxy α-substituent. It is believed that this outcome reflects the greater steric hindrance toward electrophilic approach at the γ-position, which is effectively a neopentyl center. The selective generation of the *Z*-stereoisomer of the newly formed trisubstituted olefin is interesting and merits brief comment. This, too, may arise as a consequence of steric interactions; the alternative *E*-isomeric product (**14**), which was not observed, is believed to suffer from specific steric interactions between the epoxy methyl group and cyclopentenone enolate, interactions that are avoided in the formation of the *Z*-product **13**. Another possible rationale for the selective formation of the *Z*-stereoisomer of the C3–C4 olefin may be that diethylaluminum chloride mediates opening of the allylic epoxide to an intermediate *Z*-allylic halide (or *Z*-allylic oxonium, by reaction with THF), which subsequently undergoes in situ macrocyclization. This latter hypothesis originates from consideration of results we obtained later (vide infra) wherein Lewis acid mediated *Z*-selective allylic epoxide opening by bromide ion was observed.



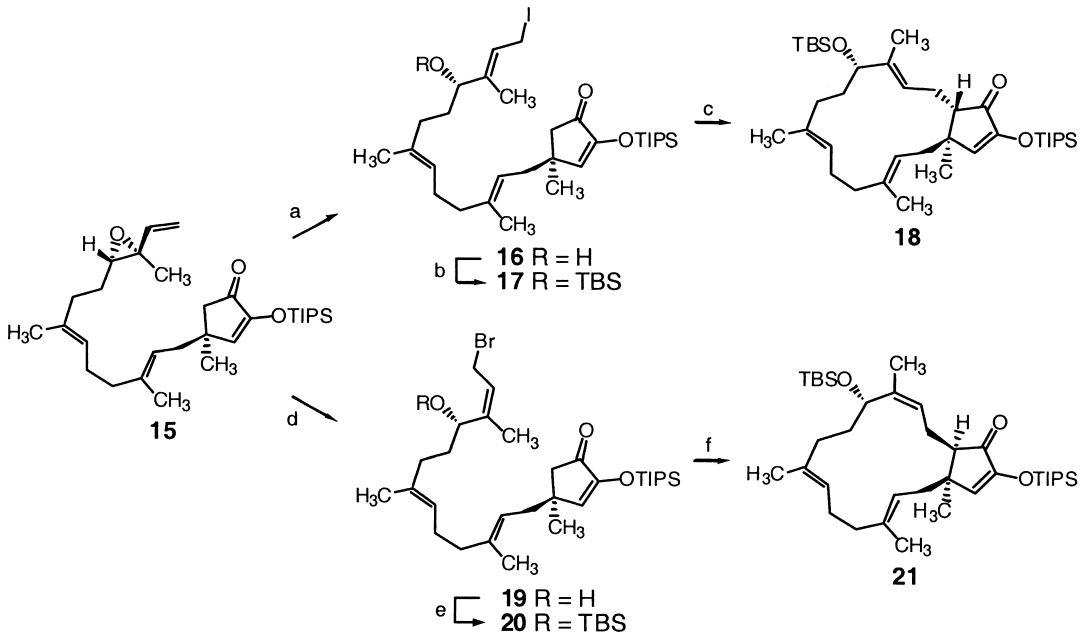
Scheme 3.



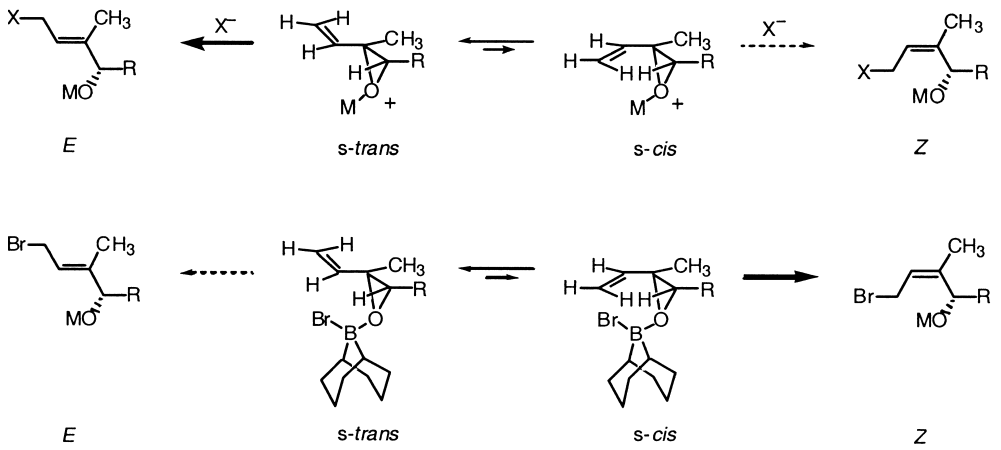
Scheme 5.

Ultimately, to bring about macrocyclization in the desired sense, the cyclopentenone component of the substrate **3** was modified to decrease its steric encumbrance, and by carbonyl transposition, so as to allow for only one mode of *C*-alkylation (see substrate **15**, Scheme 6).[4] In addition, Lewis acid mediated epoxide activation and enolate alkylation were decoupled. That is, the allylic epoxide was transformed into an allylic halide derivative and, after protection of the resultant allylic alcohol as the corresponding *tert*-butyldimethylsilyl ether, enolization and intramolecular allylic halide displacement readily occurred (Scheme 6). The transformation of the allylic epoxide group of **15** stereoselectively into the isomeric allylic halides **16** and **19** could be achieved by proper choice of the Lewis acid activator. Specifically, we observed that treatment of a mixture of **15** and lithium iodide (5 equiv.) with scandium trifluoromethanesulfonate (1 equiv., hydrate) in tetrahydrofuran (−78→−25°C) gave the corresponding *E*-allylic iodide selectively, whereas addition of 9-bromo-9-borabicyclo[3.3.1]nonane to **15** (THF, 0°C; H_2O_2, H_2O, MeOH) selectively furnished the *Z*-allylic bromide in 64% yield, presumably by intramolecular bromide delivery to the s-*cis* epoxide conformer (Schemes 6 and 7).[13] In the latter transformation, dihydrofuran formation was a primary side reaction.

Addition of lithium diphenyltetramethyldisilazide to a solution of **17** (THF, 0.002 M, 0°C) led to enolization and macrocyclization, providing the macrocycle **18** (53%, 4.8:1 *trans*–*cis* ring fusions, NOESY analysis). Cyclization of the bromide **20** (LHMDS, THF, 0°C) furnished the macrocycle **21** in 52% yield (2.4:1 *cis*–*trans* ring fusions, NOESY analysis) where, interestingly, altering the geometry of the allylic halide apparently led to a reversal in the diastereoselectivity of the alkylation reaction (*cis*- versus *trans*-ring fusion).



Scheme 6. (a) LiI, $Sc(OTf)_3$, THF, −25°C, 92%; (b) TBSOTf, 2,6-lutidine, THF, −78°C, 97%; (c) $LiN(Si(CH_3)_2Ph)_2$, THF, 0°C, 53% (4.8:1 *trans*–*cis*); (d) *B*-Br-9-BBN, THF, 0°C; MeOH, 30% H_2O_2, 0°C, 64%; (e) TBSOTf, 2,6-lutidine, THF, −78°C, 82%; (f) LHMDS, THF, 0°C, 54% (2.4:1 *cis*–*trans*).



Scheme 7.

3. Conclusion

It is evident from the studies described that the specific choice of Lewis acid activator in intramolecular allylic epoxide-enol(ate) carbocyclization processes can be a critical determinant of the mode of cyclization that occurs. Novel cation-olefin cyclization reactions, to include macrocyclization and polycyclization pathways, were found to occur in the presence of different Lewis acids. The choice of Lewis acid activator in S_N-prime allylic epoxide opening by halide ions also provided a sensitive determinant of the reaction outcome, here with respect to the stereochemistry of the resultant allylic halide. Both *Z*- and *E*-selective processes were developed; the latter was of utility in a two-step macrocyclization sequence to produce the terpestacin/fusaproliferin ring system.

4. Experimental

4.1. Data for compounds

4.1.1. Tetracycle 10 and cyclohexanol 11. A solution of lithium tetramethylpiperidide (LTMP) was prepared by the addition of a solution of *n*-butyllithium in hexanes (104 μL, 0.172 mmol, 9.2 equiv., 1.65 M) to a solution of 2,2,6,6-tetramethylpiperidine (32.0 μL, 0.191 mmol, 10.2 equiv.) in THF (300 μL) at −78°C. After 15 min, the reaction flask was transferred to an ice bath for 5 min, then was cooled to −78°C. A solution of the enol carbamate **3** (11.0 mg, 0.0187 mmol, 1 equiv.) in THF (500 μL) at −78°C was then added via cannula to the cold solution of LTMP. The transfer was quantitated with additional THF (500 μL). After 23 min, the orange reaction mixture was warmed to 0°C for 5 min, then was cooled to −78°C and a 1:1 mixture by volume of chlorotrimethylsilane and triethylamine (48 μL) was added to the reaction mixture at −78°C. After 1 h, the reaction mixture was warmed to 0°C for 5 min and saturated aqueous $NaHCO_3$ solution (3 mL) and saturated aqueous NaCl solution (2 mL) were added sequentially. The resulting mixture was extracted with pentane (3×5 mL), and the collected organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude dienol trimethylsilyl ether **7** was lyophilized from benzene (5 mL).

Boron trifluoride diethyl etherate (15.0 μL, 0.118 mmol, 6.3 equiv.) was added to a solution of the crude dienol trimethylsilyl ether **7** (prepared above) in CH_2Cl_2 (500 μL) at −78°C. After 5 min, Et_2O (6 mL) and saturated aqueous $NaHCO_3$ solution (2 mL) were added to the reaction mixture. The organic layer was separated, and the aqueous layer was extracted with Et_2O (2×5 mL). The combined organic layers were washed with saturated aqueous NaCl solution (2 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated. The resulting yellow oil was purified by preparative thin layer chromatography (3:2 hexanes–Et_2O, 4 elutions) to provide separately the tetracycle **10** (3.5 mg, 32%) and the cyclohexanol **11** (4.9 mg, 44%).

Tetracycle **10**. ^{1}H NMR (500 MHz, C_6D_6), δ: 5.21 (dd, 1H, *J*=17.0, 11.0 Hz), 4.95 (dd, 1H, *J*=10.5, 1.5 Hz), 4.89 (dd, 1H, *J*=17.5, 1.0 Hz), 3.04 (m, 1H), 3.00 (s, 1H), 2.57 (s, 3H), 2.51 (s, 3H), 1.93 (m, 1H), 1.76 (dt, 1H, *J*=12.5, 3.0 Hz), 1.48 (m, 3H), 1.28 (s, 3H), 1.24 (d, 18H, *J*=16.5 Hz), 1.15–1.53 (m, 7H), 0.90 (s, 3H), 0.88 (s, 3H), 0.82 (m, 2H), 0.70 (d, 1H), 0.68 (s, 3H). FTIR (neat), cm^{-1}: 3488 (br w), 2925 (s), 2865 (s), 1738 (s), 1714 (s), 1651 (m), 1461 (m), 1337 (m), 1312 (m), 1233 (m), 1146 (s), 1118 (m), 1016 (m), 881 (w), 686 (w). HRMS (FAB): calcd for $C_{34}H_{57}NNaO_5Si$ $[M+Na]^+$: 610.3904; Found: 610.3896. TLC (4:1 hexanes–Et_2O), R_f: 0.23 (UV, CAM).

Cyclohexanol **11**. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 5.63 (dd, 1H, *J*=17.6, 10.6 Hz), 5.28 (d, 1H, *J*=9.5 Hz), 5.10 (d, 1H, *J*=16.8 Hz), 4.96 (t, 1H, *J*=7.5 Hz), 4.92 (s, 1H), 4.62 (s, 1H), 3.41 (dd, 1H, *J*=11.7, 4.4 Hz), 3.04 (s, 3H), 2.97 (s, 3H), 2.77 (A of AB, 1H, J_{AB}=17.6 Hz), 2.52 (B of AB, 1H, J_{AB}=17.6 Hz), 2.30–2.36 (m, 1H), 2.16 (d, 2H, *J*=7.7 Hz), 1.72–2.09 (m, 5H), 1.33–1.50 (m, 3H), 1.17–1.30 (m, 3H), 1.11 (s, 3H), 1.05 (d, 18H, *J*=7.3 Hz), 0.74 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 205.8, 159.7, 152.1, 146.4, 145.8, 138.8, 137.1, 119.7, 116.4, 109.2, 74.6, 49.1, 48.4, 45.2, 38.8, 37.1, 36.9, 36.8, 36.0, 34.7, 30.2, 24.3, 24.2, 18.10, 18.09, 16.3, 13.3, 9.3. FTIR (neat), cm^{-1}: 2936 (s), 2864 (s), 1738 (s), 1715 (s), 1647 (m), 1456 (w), 1320 (s), 1147 (s), 1005 (w). HRMS (ES): calcd for $C_{34}H_{58}O_5NSi$ $[MH]^+$: 588.4084; Found: 588.4085. TLC (4:1 hexanes–Et_2O), R_f: 0.18 (UV, CAM).

4.1.2. Bicyclic ether 12. A solution of lithium tetramethylpiperidide (LTMP) was prepared by the addition of a solution of *n*-butyllithium in hexanes (93.8 μL, 0.151 mmol, 8.0 equiv., 1.61 M) to a solution of 2,2,6,6-tetramethylpiperidine (31.9 μL, 0.189 mmol, 10.0 equiv.) in THF (400 μL) at −78°C. After 20 min, the reaction flask was transferred to an ice bath for 5 min, then was cooled to −78°C. A solution of the enol carbamate **3** (11.1 mg, 0.0189 mmol, 1 equiv.) in THF (800 μL) was added via cannula to the cold solution of LTMP. After 20 min, the orange reaction mixture was warmed to 0°C for 5 min, where it became yellow. The yellow solution was cooled to −78°C, and after 15 min, $BF_3{\cdot}OEt_2$ (24.0 μL 0.189 mmol, 10.0 equiv.) was added at −78°C. Additional portions of $BF_3{\cdot}OEt_2$ were added at 1 and 2 h intervals (24.0 μL, 0.189 mmol, 10.0 equiv., and 72.0 μL, 0.568 mmol, 30.1 equiv., respectively). After 7 h, Et_2O (3 mL) and saturated aqueous $NaHCO_3$ solution (3 mL) were added sequentially to the reaction mixture. The aqueous layer was extracted with Et_2O (3×2 mL). The combined organic layers were washed with saturated aqueous NaCl solution, dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography (15:2 hexanes–Et_2O) afforded the cyclohexanol **11** (4.3 mg, 38%) and the bicyclic ether **12** (3.1 mg, 28%).

See above for spectroscopic data for cyclohexanol **11**. ^{1}H NMR (400 MHz, C_6D_6), δ: 5.79 (dd, 1H, *J*=17.2, 11.0 Hz), 5.24 (t, 1H, *J*=7.3 Hz), 4.98–5.03 (m, 2H), 3.71 (d, 1H, *J*=5.5 Hz), 2.94 (d, 1H, *J*=17.6 Hz), 2.54 (d, 1H, *J*=17.6 Hz), 2.52 (s, 3H), 2.46 (s, 3H), 2.42 (dd, 1H, *J*=13.9, 8.1 Hz), 2.16 (dd, 1H, *J*=13.9, 8.1 Hz), 1.34–2.04 (m, 8H), 1.54 (s, 3H), 1.42–1.50 (m, 3H), 1.35 (s, 3H), 1.23 (m, 18H), 1.21 (s, 3H), 1.12 (s, 3H). FTIR (neat), cm^{-1}: 2943 (s), 2866 (m), 1740 (s), 1716 (s), 1660 (m), 1462 (w), 1322 (m), 1237 (w), 1148 (s), 1007 (m), 882 (w), 829 (w), 686 (w). TLC (4:1 hexanes–EtOAc), R_f: 0.40 (UV, CAM).

4.1.3. Macrocyclic ketone 13. A solution of lithium tetramethylpiperidide (LTMP) was prepared by the addition of a solution of *n*-butyllithium in hexanes (130 μL, 0.221 mmol, 13.0 equiv., 1.70 M) to a solution of 2,2,6,6-tetramethylpiperidine (43.0 μL, 0.255 mmol, 15.0 equiv.) in deoxygenated THF (500 μL) at −78°C. After 15 min, the reaction flask was transferred to an ice bath for 5 min, then was cooled to −78°C. A solution of the enol carbamate **3** (10.0 mg, 0.0170 mmol, 1 equiv.) in deoxygenated THF (1 mL) at −78°C was added via cannula to the cold solution of LTMP. After 1.25 h at −78°C, a solution of Et_2AlCl in toluene (189 μL, 0.340 mmol, 20.0 equiv., 1.8 M) was added to the reaction mixture. The reaction mixture was warmed to 0°C after 3 min and was held at that temperature for 50 min. Methanol (125 μL), saturated aqueous potassium sodium tartrate solution (4 mL), and hexanes (2 mL) were then added to the reaction mixture in sequence. The resulting emulsion was stirred vigorously for 30 min at 24°C. The organic layer was separated, and the aqueous layer was extracted with EtOAc (4×2 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography (3:1 hexanes–Et_2O) gave **13** (6.6 mg, 66%). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 5.88 (s, 1H), 5.53 (t, 1H, *J*=7.1 Hz), 5.02 (m, 2H), 4.19 (br t, 1H), 3.01 (s, 3H), 2.97 (s, 3H), 2.54 (dd, 2H, *J*=15.4, 7.3 Hz), 2.46 (dd, 1H, *J*=18.0, 8.4 Hz), 2.35 (dd, 1H, *J*=18.4, 6.6 Hz), 2.05–2.17 (m, 6H), 1.86 (br s, 1H), 1.73 (m, 2H), 1.69 (s, 3H), 1.55 (s, 3H), 1.54 (s, 3H), 1.23 (m, 3H), 1.23 (s, 3H), 1.03 (s, 18H). FTIR (neat), cm^{-1}: 3480 (br w), 2924 (s), 2866 (m), 1738 (br s), 1462 (w), 1390 (w), 1146 (m), 883 (w), 680 (w). HRMS (FAB): calcd for $C_{34}H_{58}NO_5Si$ $[MH]^+$: 588.4084; Found: 588.4088. TLC (5:1 hexanes–EtOAc), R_f: 0.39 (CAM).

4.1.4. *E*-Allylic iodide 16. A solution of scandium trifluoromethanesulfonate hydrate (61.8 mg) in THF (0.5 mL) was added over 10 min to a solution of the epoxide **15** (49.3 mg, 0.0984 mmol, 1 equiv.) and lithium iodide (69 mg, 0.51 mmol, 5.1 equiv.) in THF (3 mL) at −78°C. After 15 min, the reaction mixture was warmed to −25°C and was maintained at that temperature for 70 min. The reaction mixture was then cooled to −78°C, and water (5 mL) and saturated aqueous NaCl solution (3 mL) were added sequentially. The product mixture was extracted with EtOAc (3×10 mL). The combined organic layers were washed with saturated aqueous sodium thiosulfate solution (3 mL), then were dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography (4:1 hexanes–EtOAc) gave the *E*-allylic iodide **16** (56.9 mg, 92%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 6.38 (s, 1H), 5.78 (t, 1H, *J*=8.8 Hz), 5.05–5.10 (m, 2H), 3.99 (t, 1H, *J*=6.5 Hz), 3.93 (d, 2H, *J*=9.8 Hz), 2.28 (A of AB, 1H, J_{AB}=18.2 Hz), 2.08 (B of AB, 1H, J_{AB}=18.6 Hz), 1.95–2.18 (m, 8H), 1.64 (s, 3H), 1.60–1.65 (m, 2H), 1.59 (s, 3H), 1.58 (s, 3H), 1.24 (m, 3H), 1.18 (s, 3H), 1.08 (d, 18H, *J*=6.8 Hz). TLC (5:1 hexanes–EtOAc), R_f: 0.26 (UV, CAM).

4.1.5. *tert*-Butyldimethylsilyl ether 17. *tert*-Butyldimethylsilyl trifluoromethanesulfonate (42.4 μL, 0.181 mmol, 2.00 equiv.) was added to a solution of the *E*-allylic iodide **16** (56.9 mg, 0.090 mmol, 1 equiv.) and 2,6-lutidine (42.2 μL, 0.362 mmol, 4.00 equiv.) in THF (4.5 mL), at −78°C. After 15 min, methanol (11 μL) was added to quench any excess silyl triflate. After 5 min, aqueous pH 7 phosphate buffer solution (4 mL) was added, and the resulting mixture was warmed to 24°C. After dilution with saturated aqueous NaCl solution (3 mL), the mixture was extracted with EtOAc (3×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography (21:1 hexanes–EtOAc) afforded the *tert*-butyldimethylsilyl ether **17** (65.1 mg, 97%). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 6.38 (s, 1H), 5.67 (t, 1H, *J*=8.8 Hz), 5.07–5.11 (m, 2H), 3.92 (d, 2H, *J*=8.7 Hz), 3.90 (m, 1H), 2.28 (A of AB, J_{AB}=18.7 Hz), 2.09 (B of AB, J_{AB}=18.7 Hz), 1.82–2.20 (m, 8H), 1.59 (s, 3H), 1.57 (s, 3H), 1.55 (s, 3H), 1.52 (m, 2H), 1.23 (m, 3H), 1.17 (s, 3H), 1.08 (d, 18H, *J*=9.3 Hz), 0.88 (s, 9H), 0.02 (s, 3H), −0.01 (s, 3H). FTIR (neat), cm^{-1}: 2926 (s), 2865 (s), 1722 (s), 1625 (m). TLC (5:1 hexanes–EtOAc), R_f: 0.73 (UV, CAM).

4.1.6. Macrocycle 18. A solution of lithium diphenyltetramethyldisilazide in THF (500 μL, 0.18 mmol, 2.1 equiv., 0.37 M) was added over 5 min to an ice-cooled solution of the *tert*-butyldimethylsilyl ether **17** (65.1 mg, 0.0876 mmol, 1 equiv.) in THF (45 mL). After 10 min,

additional base (0.37 M lithium diphenyltetramethyldisilazide in THF, 210 μL, 0.078 mmol, 0.87 equiv.) was added. After 40 min, saturated aqueous NH_4Cl solution (3 mL) and saturated aqueous NaCl solution (25 mL) were added sequentially to the reaction mixture. The organic layer was separated, and the aqueous layer was extracted with EtOAc (2×40 mL). The combined organic layers were dried over anhydrous Na_2SO_4, then were filtered and concentrated. Purification was achieved by successive flash column chromatography (29:1 hexanes–Et_2O, 3:2 benzene–hexanes) to provide separately *trans*-ring fusion macrocycle **18** (23.7 mg, 44%) and *cis*-ring fusion macrocycle **18** (4.9 mg, 9%).

trans-ring fusion macrocycle **18**. ^{1}H NMR (500 MHz, $CDCl_3$), δ: 6.42 (s, 1H), 5.35 (t, 1H, *J*=5.4 Hz), 5.21 (m, 1H), 5.09 (m, 1H), 4.00 (dd, 1H, *J*=9.1, 4.7 Hz), 2.51 (br d, 1H, *J*=17.4 Hz), 2.40 (dd, 1H, *J*=13.8, 10.6 Hz), 2.27–2.31 (m, 3H), 2.09 (m, 1H), 1.94–1.99 (m, 3H), 1.77–1.81 (m, 2H), 1.65 (m, 2H), 1.62 (s, 3H), 1.61 (s, 3H), 1.50 (s, 3H), 1.24 (m, 3H), 1.09 (d, 18H, *J*=7.4 Hz), 1.01 (s, 3H), 0.85 (s, 9H), 0.00 (s, 3H), −0.04 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 206.2, 150.8, 147.3, 137.4, 137.2, 133.2, 125.9, 123.7, 122.1, 76.7, 52.7, 42.2, 41.8, 40.4, 34.6, 31.5, 27.0, 25.8, 23.8, 20.8, 18.2, 17.8, 15.8, 15.4, 12.6, 10.2, −4.6, −4.9. FTIR (neat), cm^{-1}: 2944 (s), 2866 (s), 1715 (s), 1632 (m). HRMS (FAB): calcd for $C_{37}H_{66}NaO_3Si_2$ $[M+Na]^+$: 637.4448; Found: 637.4447. TLC (21:1 pentane–ether), R_f: 0.66 (UV, CAM).

cis-ring fusion macrocycle **18**. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 6.27 (s, 1H), 5.42 (t, 1H, *J*=7.1 Hz), 5.36 (m, 1H), 4.90 (br d, 1H, *J*=9.1 Hz), 3.85 (dd, 1H, *J*=8.9, 4.8 Hz), 2.50 (m, 1H), 1.97–2.42 (m, 7H), 1.70 (m, 2H), 1.65 (m, 2H), 1.58 (s, 3H), 1.56 (s, 3H), 1.54 (s, 3H), 1.21 (m, 3H). 1.08 (m, 21H), 0.84 (s, 9H), −0.05 (s, 3H), −0.07 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 204.3, 150.8, 137.8, 136.1, 133.2, 124.5, 124.1, 122.0, 77.7, 56.2, 42.2, 39.5, 37.2, 34.8, 31.2, 27.1, 25.9, 24.3, 23.6, 18.2, 17.8, 15.24, 15.15, 12.6, 10.1, −4.6, −4.9. FTIR (neat), cm^{-1}: 2939 (s), 2864 (s), 1721 (s), 1630 (m), 1462 (w), 1249 (w), 1069 (m), 834 (s). HRMS (FAB): calcd for $C_{37}H_{70}NO_3Si_2$ $[M+NH_4]^+$: 632.4894; Found: 632.4899. TLC (21:1 pentane–ether), R_f: 0.50 (UV, CAM).

4.1.7. *Z*-Bromoalcohol 19. *B*-Br-9-BBN (130 μL, 0.13 mmol, 1.20 equiv., 1.0 M in CH_2Cl_2) was added dropwise to an ice-cooled solution of the cyclopentenone **15** (54.3 mg, 0.108 mmol, 1 equiv.) in THF (10 mL). After 40 min, methanol (25 μL), aqueous pH 7 phosphate buffer solution (5 mL), EtOAc (5 mL), and saturated aqueous NaCl solution (5 mL) were added sequentially to the reaction mixture. The solution was extracted with EtOAc (3×25 mL). The organic layers were combined and dried over anhydrous Na_2SO_4, then were filtered and concentrated. The resulting colorless oil was dissolved in 2:1 methanol–30% aqueous hydrogen peroxide solution (9 mL), and the resulting solution was stirred at 0°C for 1 h. After concentration in vacuo (25 mm Hg), the largely aqueous mixture was diluted with water (10 mL) and the resulting solution was extracted with CH_2Cl_2 (4×30 mL). The combined organic extracts were washed with saturated aqueous sodium thiosulfate solution (40 mL), then were dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography (9:2 hexanes–EtOAc) yielded the bromoalcohol **19** as a colorless oil (40.4 mg, 64%). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 6.38 (s, 1H), 5.60 (m, 1H), 5.06–5.12 (m, 2H), 4.57 (dd, 1H, *J*=8.0, 5.6 Hz), 4.04 (d, 2H, *J*=8.7 Hz), 2.28 (A of AB, 1H, J_{AB}=18.7 Hz), 2.09 (B of AB, 1H, J_{AB}=18.7 Hz), 1.96–2.10 (m, 8H), 1.78 (s, 3H), 1.72 (m, 2H), 1.61 (s, 3H), 1.59 (s, 3H), 1.21 (m, 3H), 1.19 (s, 3H), 1.08 (d, 18H, *J*=7.2 Hz). FTIR (neat), cm^{-1}: 3434 (br w), 2943 (s), 2866 (s), 1720 (s), 1623 (s), 1461 (m), 1333 (m), 1214 (m), 1114 (m), 883 (m), 686 (m). HRMS (ES): calcd for $C_{31}H_{54}BrO_3Si$ $[MH]^+$: 581.3025; Found: 581.3001. TLC (5:1 hexanes–EtOAc), R_f: 0.22 (UV, CAM).

4.1.8. *tert*-Butyldimethylsilyl ether 20. *tert*-Butyldimethylsilyl trifluoromethanesulfonate (24.5 μL, 0.104 mmol, 1.50 equiv.) was added to a solution of the bromoalcohol **19** (40.5 mg, 0.070 mmol, 1 equiv.) and 2,6-lutidine (24.3 μL, 0.209 mmol, 3.00 equiv.) in THF (3 mL) at −78°C. After 23 min, methanol (25 μL) was added to quench any excess silyl triflate. After 5 min, aqueous pH 7 phosphate buffer solution (2 mL) was added, and the resulting mixture was warmed to 24°C. After dilution with EtOAc (5 mL) and saturated aqueous NaCl solution (2 mL), the organic layer was separated. The aqueous layer was extracted with EtOAc (3×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, then were filtered and concentrated. Purification by flash column chromatography (19:1 hexanes–EtOAc) yielded the *tert*-butyldimethylsilyl ether **20** as a colorless oil (39.5 mg, 82%). ^{1}H NMR (400 MHz, C_6D_6), δ: 6.24 (s, 1H), 5.24–5.31 (m, 2H), 5.11 (t, 1H, *J*=7.5 Hz), 4.55 (dd, 1H, *J*=7.9, 5.3 Hz), 3.79 (m, 2H), 2.19 (A of AB, J_{AB}=18.5 Hz), 1.92 (B of AB, J_{AB}=18.4 Hz), 1.83–2.15 (m, 8H), 1.66 (s, 3H), 1.61 (s, 3H), 1.52 (m, 2H), 1.46 (s, 3H), 1.30 (m, 3H), 1.17 (d, 18H, *J*=6.5 Hz), 0.98 (s, 9H), 0.13 (s, 3H), 0.08 (s, 3H). FTIR (neat), cm^{-1}: 2928 (s), 2865 (s), 1722 (s), 1624 (m), 1462 (w), 1250 (w), 1083 (m), 836 (m). TLC (5:1 hexanes–EtOAc), R_f: 0.62 (UV, CAM).

4.1.9. Macrocycle 21. A solution of lithium bis(trimethylsilyl)amide in THF (48.0 μL, 0.017 mmol, 1.2 equiv., 0.36 M) was added over 5 min to a solution of the *tert*-butyldimethylsilyl ether **20** (10.1 mg, 0.0145 mmol, 1 equiv.) in THF (0.8 mL) at −78°C. After 35 min, the reaction mixture was warmed to −45°C for 30 min, then was warmed to 0°C and maintained at that temperature. After 3.7 h, aqueous pH 7 phosphate buffer solution (2 mL) and saturated aqueous NaCl solution (1 mL) were added sequentially to the reaction mixture. The resulting mixture was extracted with EtOAc (3×5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, then were filtered and concentrated. Purification by flash column chromatography (3:2 hexanes–toluene→toluene) provided separately the *trans*-ring fusion macrocycle **21** (1.4 mg, 16%) and *cis*-ring fusion macrocycle **21** (3.4 mg, 38%).

cis-ring fusion macrocycle **21**. ^{1}H NMR (500 MHz, $CDCl_3$), δ: 6.32 (s, 1H), 5.61 (t, 1H, *J*=7.6 Hz), 5.12 (t, 1H, *J*=6.6 Hz), 5.07 (t, 1H, *J*=6.3 Hz), 4.56 (m, 1H), 2.34 (m, 2H), 1.92–2.22 (m, 9H), 1.68 (m, 2H), 1.66 (s, 3H), 1.58 (s, 3H), 1.57 (s, 3H), 1.22 (m, 3H), 1.09 (m, 18H), 1.06 (s, 3H),

0.88 (s, 9H), 0.05 (s, 3H), −0.02 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 205.5, 151.2, 144.4, 138.9, 137.4, 135.2, 123.4, 122.3, 120.2, 68.8, 52.9, 41.8, 40.5, 39.3, 34.3, 34.2, 25.8, 25.6, 24.6, 22.9, 18.6, 18.2, 17.8, 16.7, 16.4, 12.5, −4.6. FTIR (neat), cm^{-1}: 2945 (s), 2866 (s), 1718 (s), 1629 (m), 1462 (w), 1250 (w), 1083 (m), 835 (m), 774 (m). HRMS (FAB): calcd for $C_{37}H_{66}NaO_3Si_2$ $[M+Na]^+$: 637.4448; Found: 637.4438. TLC (3:2 toluene–hexanes), R_f: 0.30 (UV, CAM).

trans-ring fusion macrocycle **21**. ^{1}H NMR (500 MHz, C_6D_6), δ: 6.19 (s, 1H), 5.74 (t, 1H, J=7.2 Hz), 5.20 (m, 1H), 5.16 (m, 1H), 4.71 (t, 1H, J=6.4 Hz), 2.60 (m, 1H), 2.41 (m, 1H), 2.33 (t, 1H, J=6.6 Hz), 1.81–2.20 (m, 10H), 1.76 (s, 3H), 1.55 (s, 3H), 1.43 (s, 3H), 1.29 (m, 3H), 1.17 (m, 18H), 1.01 (s, 9H), 0.92 (s, 3H), 0.15 (s, 3H), 0.13 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 205.3, 151.4, 145.2, 138.6, 137.5, 134.7, 123.2, 122.5, 120.4, 69.1, 53.5, 42.2, 40.7, 39.3, 34.0, 33.5, 25.8, 25.4, 24.5, 23.4, 18.1, 17.8, 17.1, 16.2, 12.5, −4.6, −4.8. FTIR (neat), cm^{-1}: 2944 (s), 2866 (s), 1719 (s), 1629 (m), 1462 (w), 1250 (w), 1069 (m), 836 (m), 774 (m), 685 (w). HRMS (ES): calcd for $C_{37}H_{67}O_3Si_2$ $[MH]^+$: 615.4629; found: 615.4634. TLC (3:2 toluene–hexanes), R_f: 0.44 (UV, CAM).

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