Total Synthesis of (−)-Maytansinol

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A total synthesis of maytansinol (**1**) was achieved, in a convergent way, using (3*S*,6*S*,7*S*)-aldehyde **4** and (*S*)-*p*-tolyl sulfoxide **3** as fragments. When the anion of **3** was condensed with aldehyde **4**, some induction at C(10) was observed (60% de), giving the C(1)−N(19)-open-chain compound **7**, after thermal elimination of sulfinate. Pure *E*/*E* stereochemistry of the 11,13-diene was obtained. Selective modifications of the functionalities permitted macrocyclization and further elaboration to maytansinol.

Maytansine is a naturally occurring ansamacrolide, isolated originally by Kupchan in 1972[1] from *Maytenus serrata*, which exhibits potent antitumor and antileukemic activity and has been the subject of extensive chemical[2] and biological[3] studies. Two independent total syntheses of maytansine[4] and two total syntheses of maytansinol[5] have been reported to date.

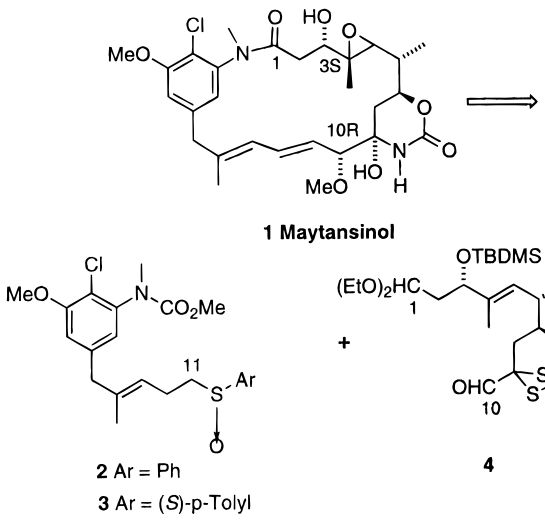
In a previous paper, we had proposed a new synthetic approach that could lead to modified skeleton maytansinoids,[6] which could replace maytansine in order to overcome its toxicity[7] in clinical use.[8] The synthesis of a C(1)−N(19) open-chain derivative in the 4,6-didemethyl series was carried out to improve our methodology and to test its feasability. Accesses to the 4-demethyl and 6-demethyl C(1)−C(9)-fragments were also described.[6]

In the present paper, we report the synthesis of (−)-maytansinol (**1**), by condensation of two fragments, phenyl sulfoxide **2** or (*S* -(−)-*p*-tolyl sulfoxide **3** and (3*S*,6*S*,7*S*)-aldehyde **4** (Scheme 1).

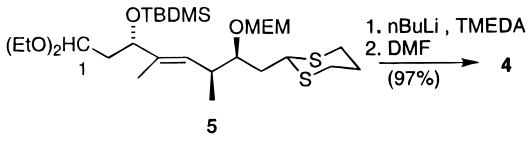
The synthesis of phenyl sulfoxide **2** was realized from vanillin in 12 steps as previously described.[6] We prepared aldehyde **4** by formylation[9] of the anion α to the dithiane group of the (3*S*,6*S*,7*S*)-C(1)−C(9) fragment **5** (Scheme 2). It was observed that deprotonation of the dithianyl group needed TMEDA when the C(7)-hydroxyl was protected as MEM ether. It was not necesary when a TBDMS protecting group was used for this position.[6]

Regioselective opening of 2(*S*),3(*S*)-epoxy-1-(tosyloxy)-butane by diethylpropynylalane was the first step of the chiral synthesis of **5**, which was performed in seven steps, with a 26% yield, as reported previously (Scheme 3).[10]

Scheme 1



Scheme 2



The best conditions to realize the coupling of aldehyde **4** with the anion α to the sulfoxide group of **2** (R = Ph) were to add 1 equiv of LDA to an equimolar solution of **2** and **4**, in DME/pentane at −78 °C. After 1 h at −78 °C, the reaction was quenched at this temperature by acetic acid. Workup gave sulfoxide−alcohol intermediates (73% yield) plus some starting materials. This reaction seems to be reversible, and if the temperature was permitted to raise to ambient before quenching, both starting materials were recovered with few condensation products. When THF or ether were used the yield decreased (Scheme 4).

Crude sulfoxide−alcohols were transformed to diols **7** and **8** as a 1/1 mixture of epimers at C(10) by warming at 80 °C in toluene solution (Scheme 4). Pure *E*/*E* stereochemistry of the 11,13-dienic system was obtained. These alcohols could be separarated by chromatography. The absolute configuration at C(10) of each alcohol was determined by Horeau's method.[11]

[⊗] Abstract published in *Advance ACS Abstracts*, August 15, 1996.

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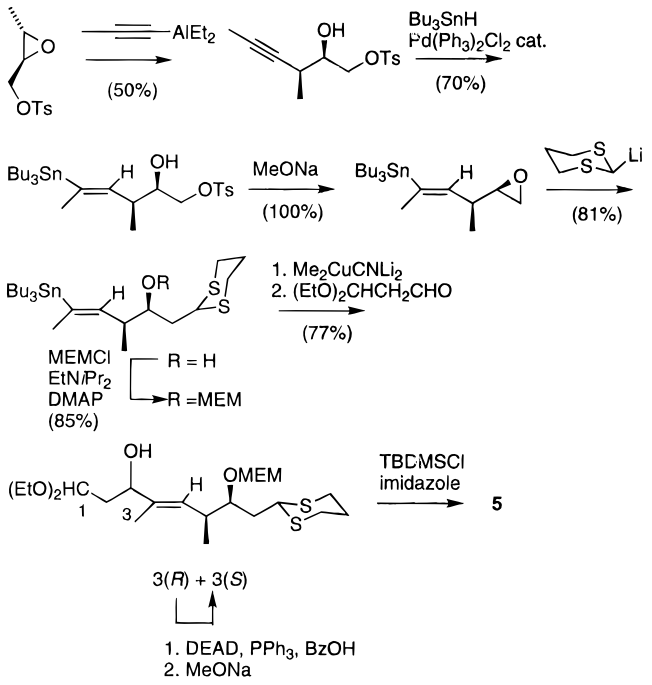
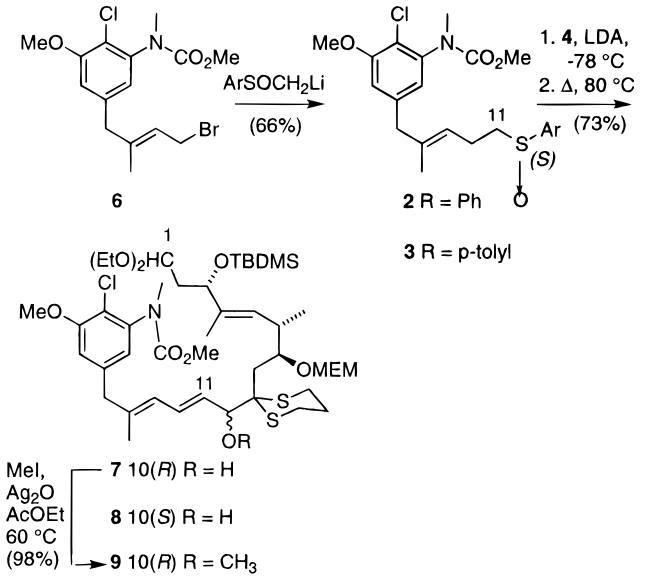
Scheme 3



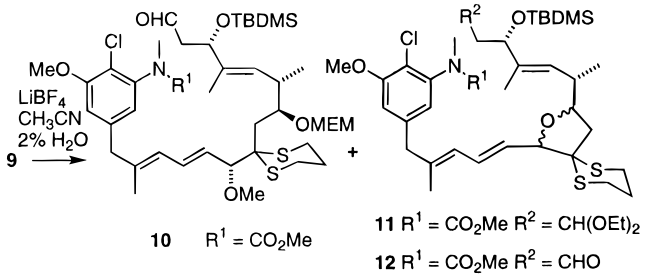
Scheme 4



Various attempts to obtain neighboring asymmetric induction by modification of the conditions of the reaction were unsuccessful. Addition of $ZnCl_2$ to fix the geometry of the MEM group in the transition state by chelation gave (*R*)-alcohol **7** as the only product, but the chemical yield was only 9%. Addition of other divalent salts was inefficient.

Therefore, in spite of the poor stereoselectivity that was obtained with most previous examples, we tried to induce asymmetric condensation by the use of a chiral sulfoxide.[12] Preliminary approaches with (*R*)-(+)- and (*S*)-(−)-phenyl sulfoxide **2** showed that (*S*)-(−)-sulfoxide was required to obtain 10(*R*)-induction. We prepared chiral (*S*)-(−)-*p*-tolyl sulfoxide **3** by alkylation of the lithio derivative of (*S*)-(−)-methyl *p*-tolylmethyl sulfoxide[13] with

Scheme 5



the previously described[6] allylic bromide **6**. The condensation reaction between **3** and **4**, followed by thermal elimination of sulfinate using the conditions previously described, gave a mixture of **7** and **8** in a 4/1 ratio (60% de) (Scheme 4). This result confirms the importance of the steric bulk of the reactants in improving the stereoselectivity.[12c] Attempts to increase this diastereomeric excess using various transmetalations were unsuccessful.[14]

After chromatographic separation of **7** and **8**, 10(*R*)-alcohol **7** was methylated with excess methyl iodide in the presence of Ag_2O, giving the C(1)−N(19)-open-chain compound **9** in 98% yield. The C(9)-dithianyl group was unaffected by these conditions.

The next steps before ring closure involved hydrolysis of the C(1)-diethyl acetal protective group, oxidation of the resulting aldehyde into the acid, and hydrolysis of the carbamate moiety to give the free N(19)-methylamino function.

In our first experiments, we tried the selective cleavage of the C(1)-diethyl acetal group. With $LiBF_4$,[15] three compounds were obtained, the desired aldehyde **10** in 70% yield and the cyclized compounds **11** and **12** (Scheme 5). Unfortunately, the unstable aldehyde **10** was not useful, as elimination of the TBDMS-oxy group occurred during the next oxidation step.

The successful hydrolysis of the diethyl acetal group, after *n*-Bu_4NF cleavage of the *tert*-butyldimethylsilyl group, was achieved with 0.1 M HCl in THF/H_2O at room temperature. The very sensitive aldehyde intermediate was not isolated but oxidized into acid **14** with Ag_2O (modified Meyers' procedure).[5a] Selective protection of the C(3)-hydroxyl as its *tert*-butyldimethylsilyl ether was carried out; and the hydrolysis of the carbamate protective moiety of **15** was then studied. The use of bases or strong nucleophiles, such as 4-mercaptopyridine,[16] gave unsatisfactory results. Clean cleavage could be obtained by DIBAH-controlled reduction of this carbamate when this reaction was performed at $-78\ °C < \theta < -60\ °C$ in toluene. The secondary amine **16** was obtained in 72% yield. There is some formation of the corresponding dimethylamino-derivative (8%). Ring closure of the amino acid **16** was effected using Mukayama's procedure,[4b,17] under high dilution conditions, to give **17** in 66% yield (Scheme 6). In solution, macrolactam **17** exists as a mixture of conformers as shown by the complexity of its ^1H NMR spectrum.

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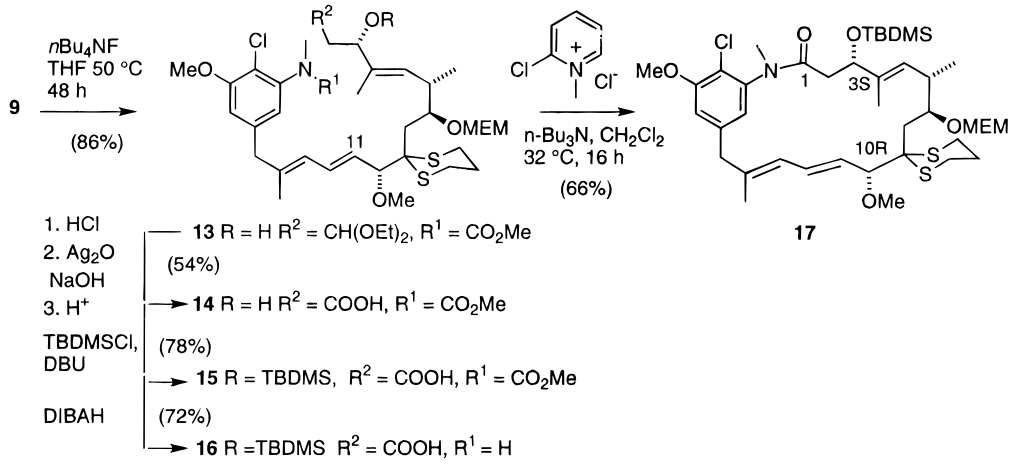
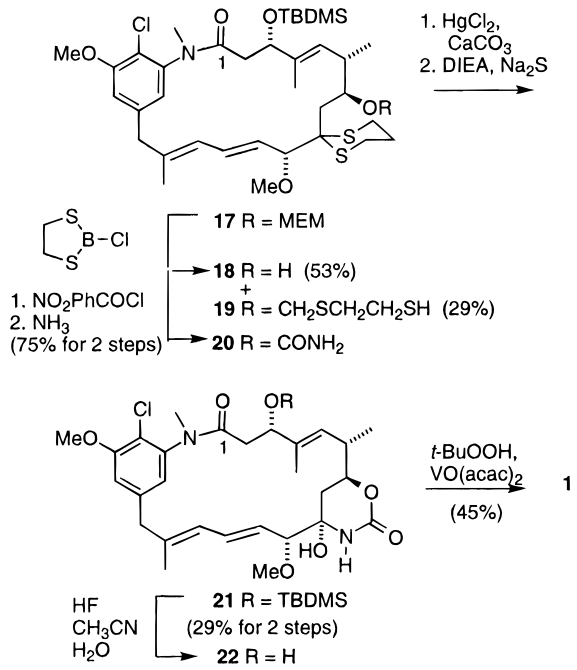
Scheme 6



Scheme 7



The synthesis of (−)-maytansinol (**1**) was achieved from **17** by elaboration of the cyclic carbamate between C(7) and C(9) and epoxidation of the 4,5 double bond. For these transformations, we adapted the reactions used for the previously achieved total syntheses of maytansine and maytansinol[4,5] (Scheme 7).

Selective cleavage of the MEM group was carried out by 2-chloro-1,3,2-dithioborolane according to William's procedure.[18] Alcohol **18** was obtained in 53% yield but had to be separated from thiol **19** formed as byproduct in 29% yield. The formation of **19**, which had not been pointed out before, could be explained by competitive attack of the oxonium intermediate by ethanedithiol.[19]

The free hydroxyl of **18** was transformed into carbamate **20** by reaction with 4-nitrophenyl chloroformate in pyridine followed by treatment with methanolic NH_3. Hydrolysis of the dithiane by $HgCl_2/CaCO_3$ in aqueous acetonitrile gave cyclic carbamate **21**. Cleavage of the C(3)-silyl ether was carried out with HF in CH_3CN at −78 °C, giving 4,5-deoxymaytansinol that was identical to that previously described.[4b,20] Epoxidation of the C(4)−C(5)-double bond of **22** was performed with *tert*-butyl hydroperoxide and $VO(acac)_2$. Following the experimental conditions described by Pan and al.,[4b] we obtained (−)-maytansinol (**1**) in a yield of 45%. Comparison with an authentic sample, prepared from maytansine,[21] led to the identification of our synthetic material. In this total synthesis, the chirality was introduced by L-tartaric acid, which was used in catalytic amounts in the Sharpless epoxidation of (*E*)-crotyl alcohol and in the preparation of (*S*)-*p*-tolyl sulfoxide.

Experimental Section

Melting points (mp) were determined in capillary tubes and are uncorrected. Optical rotations, $[\alpha]_D$, were measured in $CHCl_3$ with 0.5% EtOH, at 20 °C. Tetrahydrofuran was distilled from sodium benzophenone ketyl, diethyl ether from lithium aluminum hydride, dichloromethane from phosphorus pentoxide, and toluene from sodium. Other solvents and reagents were purified by standard procedures as necessary. Numbering for compounds follows the numbering for maytansinol (**1**). Column chromatography was performed on Merck Kieselgel 60, flash chromatography on Merck Kieselgel 60H. Standard workup means addition of water to the reaction mixture, extraction with an organic solvent (CH_2Cl_2, ether, or AcOEt), washing of the organic phases successively with brine and water, and evaporation of the solvent *in vacuo*. 2D $^1H-^1H$, $^1H-^{13}C$, and HMBC experiments led to the interpretation of the ^1H and ^{13}C NMR spectra. Chemical shifts, δ, are expressed in ppm and coupling constants, *J*, in Hz.

17-[14-Methyl-11-(*p*-tolylsulfoxy)penten-13-enyl]-18-(*N*-methyl-*N*-carbomethoxyamino)-19-chloro-20-methoxybenzene (3). (*S*)-(−)-Methyl *p*-tolyl sulfoxide was prepared according to Kagan's procedure.[13] After recrystallization in heptane, it had mp 74 °C, $[\alpha]_D$ −144 (*c* = 1, acetone) (99% ee). A solution of LDA (4 mmol) in THF (10 mL) was prepared at −5 °C by addition of *n*-BuLi (3.2 mL of a 1.28 M solution in hexane) to a solution of DIPA (0.56 mL, 4 mmol). After the solution was cooled at −78 °C, (*S*)-(−)-methyl *p*-tolyl sulfoxide (569 mg, 3.7 mmol) in THF (3 mL) and HMPA (3.5 mL, 20 mmol) were added.The mixture was stirred at this temperature for 10 min, and then **6** (1.24 g, 3.3 mmol) in THF (8 mL) was added. The solution was warmed to −20 °C over ca. 90 min. After being quenched with aqueous ammonium chloride, the mixture was extracted three times with ether. The organic phases were washed with brine, dried over $MgSO_4$, and

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evaporated *in vacuo* without heating. Flash chromatography of the residue gave **3** (980 mg, 66%) as an oil. $[\alpha]_D$: -86 ($CHCl_3$, $c = 1.1$). Anal. Calcd for $C_{23}H_{28}ClNO_4S$: C, 61.39; H, 6.27. Found: C, 61.20; H, 6.37. EIMS: M^+ 451 and 449, m/z 435 and 433. ^{1}H NMR (250 MHz, $CDCl_3$) δ ppm: 1.56 (3H, s, C(14)-CH_3), 2.34 and 2.55 (2H, 2 m, C(12)-H_2), 2,42 (3H, s, Ar-CH_3), 2.8 (2H, m, C(11)-H_2), 3.18 (3H, s, NCH_3), 3.25 (2H, bs, C(15)-H_2), 3.62 (major rotamer) and 3.78 (minor rotamer), (3H, 2 s, CO_2CH_3), 3.88 (3H, s, C(20)-OCH_3), 5.26 (1H, t, $J = 7.5$ Hz, C(13)-H), 6.61 and 6.68 (2H, 2s, C(17)-H and C(21)-H), 7.32 and 7.51 (4H, $J = 8$ Hz, A_2B_2, C_6H_4). ^{13}C NMR, ($CDCl_3$) δ: 15.8 (C(14)-CH_3), 20.9 (C-12), 21.1 (Ar-CH_3), 36.8 (NCH_3), 45.5 (C-15), 52.7 (CO_2CH_3), 56.2 (C(20)-OCH_3), 56.8 (C-11), 111.2 (C-21), 118.8 (C-19), 121.1 (C-17), 123.2 (C-13), 123.8 and 129.7 (4 CH, tolyl), 136.5 (C-14), 139.6, 140.5, 141.2, 141.2, (4 C Ar), 155.5, 155.8 (C-20 and C=O).

3*S*,6*S*,7*S*-1,1-Diethoxy-3-[(*tert*-butyldimethylsilyl)oxy]-7-[(methoxyethoxy)methoxy]-9-(1,3)-dithian-2′-yl-4,6-dimethylnon-4-en-10-aldehyde (4). *n*-BuLi (1 mL of a 1.5 M solution in hexane, 1.5 equiv) was added at −30 °C to **5** (600 mg, 1.03 mmol) and TMEDA (2 mL) in THF (40 mL). After 3 h at −20 °C, the mixture was cooled to −78 °C, and freshly distilled DMF (720 mg, 10 mmol) was added. The solution was warmed to 0 °C and stirred for 30 min. The reaction was quenched with aqueous ammonium chloride. The mixture was extracted with CH_2Cl_2. The organic phases washed with brine and evaporated *in vacuo* gave a residue that, when purified by flash chromatography, led to **4** (612 mg, 97%) as a colorless oil. $[\alpha]_D$: +72 ($c = 1.4$, $CHCl_3$). Anal. Calcd for $C_{29}H_{56}O_7S_2Si$: C, 57.23; H, 9.21. Found: C, 57.40; H, 9.23. MS (EI): M^+ 608, m/z 579, 551. ^{1}H NMR (250 MHz, $CDCl_3$) δ: −0.06 (3H, s, $SiCH_3$), −0.02 (3H, s, $SiCH_3$), 0.85 (9H, s, *t*-Bu), 0.87 (3H, d, $J = 7$ Hz, C(6)-CH_3), 1.16 (3H, t, $J = 7$ Hz, CH_2CH_3), 1.19 (3H, t, $J = 7$ Hz, CH_2CH_3), 1.53 (3H, d, $J = 1$ Hz, C(4)-CH_3), 1.57−1.87 (3H, m, C(2)-H_2, SCH_2CH), 1.89 (1H, dd, $J = 14$, 2.5 Hz, C(8)-H_a), 2.07 (1H, m, SCH_2CH), 2.07 (1H, dd, $J = 14$, 9.5 Hz, C(8)-H_b), 2.42−2.67 (3H, m, SCH, SCH_2), 2.77 (1H, m, C(6)-H), 3.33 (3H, s, OCH_3), 3.33−3.69 (9H, m, 4 OCH_2, SCH), 3.77 (1H, m, C(7)-H), 4.07 (1H, dd, $J = 8$, 4 Hz, C(3)-H), 4.49 (1H, dd, $J = 7$, 4 Hz, C(1)-H), 4.61 (2H, s, OCH_2O), 5.18 (1H, d, $J = 10$ Hz, C(5)-H), 8.78 (1H, s, CHO). ^{13}C NMR, ($CDCl_3$) δ: −5.1 ($SiCH_3$), −4.3 ($SiCH_3$), 11.3 (C(4)-CH_3), 15.4 (2 CH_2CH_3), 17.1 (C(6)-CH_3), 18.1 (CMe_3), 24.7 (CH_2), 25.85 (CMe_3), 26.53 (SCH_2), 26.62 (SCH_2), 35.16 (C-6), 39.18 (CH_2), 40.83 (C-2), 55.67 (C-9), 58.9 (OCH_3), 60.8 (OCH_2-CH_3), 61.1 (OCH_2CH_3), 68.1 (OCH_2), 71.7 (OCH_2), 75.1 (C-3), 77.1 (C-7), 95.5 (OCH_2O), 100.6 (C-1), 126 (C-5), 138.9 (C-4), 187.1 (CHO).

(3*S*,6*S*,7*S*,10*R*)-17-[1,1-Diethoxy-3-[(*tert*-butyldimethylsilyloxy]-7-[(methoxyethoxy)methoxy]-4,6,14-trimethyl-10-hydroxy-9-(1,3)-dithian-2′-ylpentadeca-4,11,13-trienyl]-18-(*N*-methyl-*N*-carbomethoxyamido)-19-chloro-20-methoxybenzene (7). (a) LDA (0.35 mL of a 0.7 M solution in DME, 0.25 mmol) was added at −78 °C to **2** (100 mg, 0.23 mmol) in DME/heptane 3/1 (5 mL). After 30 min, a preformed chelate (−78 °C, 1 h) from aldehyde **4** (90 mg, 0.15 mmol) and $ZnCl_2$ (0.2 mL of a 1 M solution in ether, 0.2 mmol) in DME (3 mL) was added. The mixture was stirred at −78 °C for 1 h. After the mixture was quenched at −78 °C with acetic acid in toluene, standard workup led to a residue which was dissolved in benzene (2 mL) and refluxed in the presence of solid sodium bicarbonate (70 mg). Thermolysis was monitored by TLC. Upon completion of the reaction, the solution was poured on silica gel column and flash chromatography (Hept/AcOEt) afforded **4** (48 mg, 53%) and **7** (12 mg, 9%).

(b) LDA (5 mL of a 0.7 M solution in DME, 3.5 mmol) was added at −78 °C to **3** (1.30 g, 2.90 mmol) and **4** (1.5 g, 2.46 mmol) in DME / heptane 3/1(40 mL). This mixture was stirred at −78 °C for 3 h. After the mixture was quenched at −78 °C with acetic acid in toluene, standard workup led to a residue that was dissolved in benzene (30 mL) and refluxed in the presence of solid sodium bicarbonate (1 g). Thermolysis was monitored by TLC. Upon completion of the reaction, the solution was poured onto a silica gel column, and flash chromatography (Hept/AcOEt) afforded **4** (0.25 g, 17%) and the mixture of **7** and **8** (81/19, 1.64 g, 73%), which was resolved by preparative HPLC. Pure **7** was obtained (1.25 g, 55%) as a colorless oil, but we also obtained **8** contaminated with 5% of **7**.

Absolute configuration, Horeau's method: **7** (10*R*), recovered α-phenylbutyric acid had $[\alpha]_D$ +4.5; **8** (10*S*), recovered α-phenylbutyric acid had $[\alpha]_D$ −3.1.

7. $[\alpha]_D$: +16 ($CHCl_3$, $c = 2.4$). Anal. Calcd for $C_{45}H_{76}ClNO_{10}S_2Si$: C, 58.88; H, 8.28. Found: C, 58.86; H, 8.26. EIMS: M^+ 919 and 917, m/z 899 $(M - 18)^+$, 860 $(M - 57)^+$, 579, 452. UV, λ_{max} (nm, EtOH): 240.4 (ϵ =28 300), 285 (ϵ = 4400). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.0 (3H, s, $SiCH_3$), 0.04 (3H,s, $SiCH_3$), 0.88 (9H, s, C(CH_3)$_3$), 0.92 (3H,d, $J = 7$ Hz, C(6)-CH_3), 1.20 (3H, t, $J = 7$ Hz, CH_3CH_2O), 1.22 (3H, t, $J = 7$ Hz, CH_3CH_2O), 1.6 (3H, s, C(4)-CH_3), 1.71 (3H, s, C(14)-CH_3), 1.76−1.88 (4H, m, C(2)-H_2, C(8)-H_a, SCH_2CH), 2.05 (1H, m, SCH_2CH), 2.13 (1H, dd, $J = 15$, 2.5 Hz, C(8)-H_b), 2.65 (2H, m, CH_2S), 2.77 (1H, m, C(6)-H), 2.98 (2H, m, CH_2S), 3.19 (3H, s, N-CH_3), 3.33 (2H, s, C(15)-H_2), 3.39 (3H, s, OCH_3), 3.4−3.8 (8H, m, 4 OCH_2), 3.63 (3H, s, CO_2CH_3), 3.89 (3H, s, C(20)-OCH_3), 3.95 (1H, m, C(7)-H), 4.10 (1H, dd, $J = 4$, 9 Hz, C(3)-H), 4.56 (1H, dd, $J = 4$, 6 Hz, C(1)-H), 4.68 (1H, d, $J = 5.5$ Hz, C(10)-H), 4.82 and 4.89 (2H, AB, $J = 7$ Hz, OCH_2O), 5.35 (1H, d, $J = 9$ Hz, C(5)-H), 5.97 (1H, dd, $J = 14$, 5.5 Hz, C(11)-H), 5.98 (1H, d, $J = 11$ Hz, C(13)-H), 6.66 (1H, dd, $J = 14$, 11 Hz, C(12)-H), 6.70 (2H, s, C(17)-H and C(21)-H); ^{13}C NMR ($CDCl_3$) δ: −5.28 ($SiCH_3$), − 4.47 ($SiCH_3$), 11.40 (C(4)-CH_3), 15.28 (2 OCH_2-CH_3), 16.02 (C(6)-CH_3), 16.4 (C(14)-CH_3), 17.9 (C-Me$_3$), 24.3 (CH_2), 25.7 (C-(CH_3)$_3$ and 2 SCH_2), 36.5 (C-6), 36.9 (NCH_3), 37.6 (CH_2), 40.8 (CH_2), 45.9 (C-15), 52.8 (OCH_3), 56.2 (C(20)-OCH_3), 57.7 (C-9), 58.8 (OCH_3), 60.6 and 60.9 (2 OCH_2-CH_3), 67.7 and 71.7 (OCH_2-CH_2O), 72.5 (C-10), 74.8 (C-3), 79.2 (C-7), 95.7 (OCH_2O), 100.6 (C-1), 111.4 (C-21), 119.1 (C-19), 121.3 (C-17), 126.7 and 128.5 (C-11 and C-13), 127.2 (C-5), 128.8 (C-12), 136.6, 137.7, 139.5, 141.1 (4 C), 155.6 and 155.9 (C-20 and C=O).

8. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.0 (3H, s), 0.04 (3H, s), 0.88 (9H, s), 0.93 (3H, d, $J = 7$ Hz), 1.20 (3H, t, $J = 7$ Hz), 1.22 (3H, t, $J = 7$ Hz), 1.60 (3H, s), 1.71 (3H, s), 1.70 (1H, m), 1.80 (1H, ddd, $J = 13$, 9, 4 Hz), 1.96 (2H, m), 2.19 (2H, m), 2.66−3.02 (5H, m), 3.19 (3H, s), 3.33 (2H, s), 3.38 (3H, s), 3.4−3.8 (8H, m), 3.63 (3H, s), 3.89 (3H, s), 3.96 (1H, m), 4.12 (1H, dd, $J = 4$, 9 Hz), 4.54 (2H, m, C(1)-H and C(10)-H), 4.79 and 4.84 (2H, AB, $J = 7$ Hz), 5.37 (1H, d, $J = 9$ Hz), 5.97 (1H, dd, $J = 14$, 5.5 Hz), 5.98 (1H, d, $J = 11$ Hz,), 6.63 (1H, dd, $J = 15$, 11 Hz), 6.70 (2H, s).

(3*S*,6*S*,7*S*,10*R*)-17-[1,1-Diethoxy-3-[(*tert*-butyldimethylsilyl)oxy]-7-[(methoxyethoxy)methoxy]-4,6,14-trimethyl-10-methoxy-9-(1,3)-dithian-2′-ylpentadeca-4,11,13-trienyl]-18-(*N*-methyl-*N*-carbomethoxyamido)-19-chloro-20-methoxybenzene (9). A suspension of **7** (1 g, 1.09 mmol), MeI (1 mL), and freshly prepared Ag_2O (1 g) in ethyl acetate (20 mL) was stirred at 60 °C for 90 min. The suspension was filtered off through a silica gel column to afford **9** (1 g, 98%). Anal. Calcd for $C_{46}H_{78}ClNO_{10}S_2Si$: C, 59.26; H, 8.44. Found: C, 59.22; H, 8.25. $[\alpha]_D$: +14 ($CHCl_3$, $c = 2$). EIMS: M^+ 931, m/z 900, 886, 874, 856, 814, 602, 579, 473, 352. UV, λ_{max} (nm (EtOH)): 242.7 (ϵ = 25 600), 285 (ϵ = 3700). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 0.0 (3H, s, $SiCH_3$), 0.04 (3H, s, $SiCH_3$), 0.87 (9H, s, *t*-Bu), 0.91 (3H, d, $J = 7$ Hz, C(6)-CH_3), 1.17 (3H, t, $J = 7$ Hz, CH_2CH_3), 1.20 (3H, t, $J = 7$ Hz, CH_2CH_3), 1.58 (3H, d, $J = 1$ Hz, C(4)-CH_3), 1.71 (3H, d, $J = 1$ Hz, C(14)-CH_3), 1.56−2.3 (6H, m, 3CH_2), 2.78 (3H, m, SCH_2 and C(6)-H), 2.94 (2H, m, SCH_2), 3.17 (3H, s, NCH_3), 3.29 (3H, s, OCH_3), 3.32 (2H, s, C(15)-H_2), 3.37 (3H, s, OCH_3), 3.42−3.81 (8H, m, 4 OCH_2), 3.61 (3H, broad s, CO_2CH_3), 3.87 (1H, m, C(7)-H), 3.89 (3H, s, C(20)-OCH_3), 3.93 (1H, d, $J = 8$ Hz, C(10)-H), 4.11 (1H, dd, $J = 8$, 4 Hz, C(3)-H), 4.53 (1H, dd, $J = 5$, 7 Hz, C(1)-H), 4.76 and 4.86 (2H, AB, $J = 7$ Hz, OCH_2O), 5.38 (1H, d, $J = 9$ Hz, C(5)-H), 5.71 (1H, dd, $J = 15$, 8 Hz, C(11)-H), 5.97 (1H, d, $J = 10$ Hz, C(13)-H), 6.47 (1H, dd, $J = 15$, 10 Hz, C(12)-H), 6.70 (2H, s); ^{13}C NMR ($CDCl_3$) δ: −5.3 ($SiCH_3$), −4.5 ($SiCH_3$), 11.2 (C(4)-CH_3), 15.2 (2 CH_2CH_3), 15.6 (C(6)-CH_3), 16.4 (C(14)-CH_3), 17.9 (CMe_3), 24.6 (CH_2), 25.6 (CMe_3), 26.5 (SCH_2), 26.5 (SCH_2), 36.5 (C(6)-H or NCH_3), 36.8 (NCH_3 or C(6)-H), 38.6 (C-8), 40.6 (CH_2), 45.8 (C-15), 52.7 (OCH_3), 55.7 (C-9), 56.1 (C(20)-OCH_3), 56.9 (OCH_3), 58.7 (OCH_3), 60.6 (OCH_2CH_3, 60.8

(OCH_2CH_3), 67.5 and 71.6 (OCH_2CH_2O), 74.9 (C-3), 79.5 (C-7), 88.5 (C-10), 95.8 (OCH_2O), 100.5 (C-1), 111.5 (C-21), 119.0 (C-19), 121.3 (C-17), 126.1 (C-13), 127.6 (C-5), 127.9 (C-11), 130.7 (C-12), 137.3 (2C), 139.2 (C), 141.1 (C), 155.6 and 155.7 (C-20) and C═O).

Reaction of 9 with $LiBF_4$. Compounds 10−12. $LiBF_4$ (17 mg, 0.18 mmol) was added to a solution of **9** (152 mg, 0.163 mmol) in wet CH_3CN (2% H_2O) at rt. After 2 h, TLC indicated the complete disappearance of the starting material. Addition of ether was followed by careful neutralization (aqueous $NaHCO_3$). Standard workup and flash chromatography (heptane/ether 2/1) led to compounds **10** (98 mg, 70%), **11** (8 mg, 6%), and **12** (5 mg, 4%).

10, $C_{42}H_{68}ClNO_9S_2Si$. EIMS: M^+ 857, *m/z* 800 $(M-57)^+$, 725 $(M-132)^+$. ^1H NMR (250 MHz, $CDCl_3$) δ: 0.03 (3H, s), 0.06 (3H, s), 0.84 (9H, s), 0.91 (3H, d, J = 7 Hz), 1.62 (3H, s), 1.72 (3H, d, J = 1 Hz), 1.90−3.10 (8H, m), 2.20 (1H, dd, J = 15, 7 Hz), 2.39 (1H, ddd, J = 15, 5 Hz, 2 Hz), 2.63 (1H, ddd, J = 15, 8, 2 Hz), 3.18 (3H, s), 3.29 (3H, s), 3.33 (2H, s), 3.36 (3H, s), 3.42−3.95 (6H, m), 3.63 (3H, s), 3.89 (3H, s), 4.50 (1H, dd, J = 8, 5 Hz), 4.76 and 4.86 (2H, AB, J = 7.5 Hz), 5.51 (1H, d, J = 9.5 Hz), 5.80 (1H, dd, J = 15, 9 Hz), 5.98 (1H, d, J = 11 Hz), 6.42 (1H, dd, J = 15, 11 Hz), 6.68 (2H, s), 9.72 (1H, t, J = 2 Hz).

11, $C_{41}H_{66}ClNO_7S_2Si$. EIMS: M^+ 811. ^1H NMR (250 MHz, $CDCl_3$) δ: 0.02 (3H, s), 0.06 (3H, s), 0.89 (9H, s), 1.06 (3H, d, J = 6 Hz), 1.20 (3H, t, J = 7 Hz), 1.22 (3H, t, J = 7 Hz), 1.65 (3H, s), 1.72 (3H, s), 1.75−2.90 (11H, m), 3.20 (3H, s), 3.3 (2H, s), 3.42−3.90 (5H, m), 3.64 (3H, s), 3.89 (3H, s), 4.12 (1H, dd, J = 8, 5 Hz), 4.43 (1H, d, J = 7.5 Hz), 4.53 (1H, dd, J = 5, 7 Hz), 5.12 (1H, d, J = 10 Hz), 5.78 (1H, dd, J = 15, 7.5 Hz), 5.99 (1H, d, J = 11 Hz), 6.62 (1H, dd, J = 15, 11 Hz), 6.69 (2H, s).

12, $C_{37}H_{56}ClNO_6S_2Si$. EIMS: M^+ 737, *m/z* 680, 605. ^1H NMR (250 MHz, $CDCl_3$) δ: 0.05 (3H, s), 0.07 (3H, s), 0.86 (9H, s), 1.06 (3H, d, J = 7 Hz), 1.67 (3H, s), 1.72 (3H, d, J = 1 Hz), 1.90−2.95 (9H, m), 2.44 (1H, ddd, J = 15, 5, 2.5 Hz), 2.64 (1H, ddd, J = 15, 7.5, 2.5 Hz), 3.19 (3H, s), 3.34 (2H, s), 3.64 (3H, s), 3.87 (3H, s), 4.42 (1H, d, J = 8 Hz), 4.50 (1H, dd, J = 7.5, 5 Hz), 5.26 (1H, d, J = 10 Hz), 5.76 (1H, dd, J = 15, 8 Hz), 5.99 (1H, d, J = 11 Hz), 6.60 (1H, dd, J = 15, 11 Hz), 6.69 (2H, s), 9.77 (1H, t, J = 2.5 Hz).

(3*S*,6*S*,7*S*,10*R*)-17-[1,1-Diethoxy-3-hydroxy-7-[(methoxyethoxy)methoxy]-4,6,14-trimethyl-10-methoxy-9-(1,3)-dithian-2′-ylpentadeca-4,11,13-trienyl]-18-(*N*-methyl-*N*-carbomethoxyamido)]-19-chloro-20-methoxybenzene (13). Tetrabutyl ammonium fluoride (142 mg 0.54 mmol) was added to a solution of **9** (432 mg, 0.46 mmol) in THF (20 mL). This mixture was warmed to 50 °C for 48 h. After addition of water, standard workup led to a residue that afforded, after flash chromatography, **13** (326 mg, 86%) as a colorless oil. $[\alpha]_D$: +32 ($CHCl_3$, c = 2.8). Anal. Calcd for $C_{40}H_{64}ClNO_{10}S_2$. EIMS: M^+ 817, *m/z* 800, 772. ^1H NMR (250 MHz, $CDCl_3$) δ: 0.96 (3H, d, J = 7 Hz, C(6)-CH_3), 1.21 (6H, t, J = 7 Hz, 2 OCH_2CH_3), 1.65 (3H, s, C(4)-CH_3), 1.73 (3H, d, J = 1 Hz, C(14)-CH_3), 1.83−2.05 (4H, m, C(2)-H_2, SCH_2CH_2), 2.01 (1H, dd J = 15 Hz, 6 Hz, C(8)-Ha), 2.21 (1H, dd, J = 15 Hz, 2 Hz, C(8)-Hb), 2.78 (3H, m, SCH_2, C(6)-H), 2.96 (2H, m, SCH_2), 3.19 (3H, s, NCH_3), 3.31 (3H, s, OCH_3), 3.33 (2H, broad s, C(15)-H_2), 3.37 (3H, s, OCH_3), 3.40 −3.90 (9H, m, 4 OCH_2 and C(7)-H), 3.63 (3H, bs, CO_2CH_3), 3.90 (3H, s, C(20)-OCH_3), 3.93 (1H, d, J = 8 Hz, C(10)-H), 4.16 (1H, dd, J = 3, 8 Hz, C(3)-H), 4.63 (1H, t, J = 5 Hz, C(1)-H), 4.76 and 4.91 (2H, AB, J = 7 Hz, OCH_2O), 5.46 (1H, d, J = 9 Hz, C(5)-H), 5.75 (1H, dd, J = 15, 8 Hz, C(11)-H), 5.98 (1H, d, J = 11 Hz, C(13)-H), 6.48 (1H, dd, J = 15, 11 Hz, C(12)-H), 6.70 (2H, s, C(17)-H and C(21)-H). ^{13}C NMR, ($CDCl_3$) δ: 12.0 (C(4)-CH_3), 15.3 and 15.4 (2 CH_2CH_3), 15.8 (C(6)-CH_3), 16.6 (C(14)-CH_3), 24.7 (SCH_2CH_2), 26.6 and 26.7 (2 SCH_2), 37.0 (C-6 and NCH_3), 38.8 and 38.9 (C-8 and C-2), 46.0 (C-15), 53.0 (OCH_3), 55.7 (C-9), 56.4 (C(20)-OCH_3), 57.2 (OCH_3), 58.9 (OCH_3), 61.3 and 62.0 (2 OCH_2CH_3), 67.8 and 71.8 (OCH_2CH_2O), 74.1 (C-3), 79.7 (C-7), 88.6 (C-10), 96.0 (OCH_2O), 101.8 (C-1), 111.6 (C-21), 119.1 (C-19), 121.5 (C-17), 126.2 (C(13), 128.0 (C-11), 128.6 (C-5), 131.0 (C-12), 136.9 and 137.6 (2 C), 139.4 (C16), 141.2 (C18), 156.8 and 157.1 (C-20 and C═O).

Acids 14 and 15. Aqueous HCl (0.1 N, 2 mL) was added to **13** (120 mg, 0.147 mmol) in THF (8 mL) at rt. The hydrolysis was monitored by TLC. After 2 h, the solution was made alkaline (pH = 8) with 0.5 N aqueous NaOH, and freshly prepared Ag_2O (340 mg, 10 equiv) was added. The black suspension was vigorously stirred until completion of the oxidation (45 min). After acidification with methanolic oxalic acid and filtration through a Celite pad to remove silver residue, extraction with $CHCl_3$ and flash chromatography ($CHCl_3/CH_3OH$, 85/15) afforded **14** (61 mg, 54%). This polar compound will be described as its O-silylated derivative **15**.

14. ^1H NMR (250 MHz,$CDCl_3$) δ: 0.92 (3H, d, J = 7 Hz), 1.66 (3H, s), 1.72 (3H, d, J = 1 Hz), 1.83−3.06 (11H, m), 3.19 (3H, s, NCH_3), 3.30 (3H, s), 3.34 (2H, broad s), 3.36 (3H, s), 3.57 and 3.80 (5H, m,), 3.62 (3H, broad s, CO_2CH_3), 3.90 (3H, s), 3.91 (1H), 4.44 (1H, broad d, J = 8 Hz), 4.73 and 4.87 (2H, AB, J = 7 Hz), 5.47 (1H, d, J = 9 Hz), 5.73 (1H, dd, J = 14.5, 8 Hz), 5.97 (1H, d, J = 11 Hz), 6.47 (1H, dd, J = 14.5, 11 Hz), 6.70 (2H, s).

15. DBU (225 mg, 4 equiv), and TBDMSCl (100 mg, 1.4 equiv) were added to a solution of **14** (348 mg, 0.46 mmol) in dry CH_2Cl_2 (10 mL). This mixture was stirred at rt for 18 h. After addition of water, standard workup led to a residue that was treated with 1 N methanolic K_2CO_3 (10 mL) at rt, for 10 min. After careful acidification and addition of ether, the organic phase was washed with water, dried, and concentrated. The residue was purified by flash chromatography (SiO_2, eluting with CH_2Cl_2/CH_3OH, 9/1, to give **15** (313 mg, 78%) as a colorless oil. $[\alpha]_D$: +16 ($CHCl_3$, c = 2); HRMS (FAB, thio + NaCl), for $C_{42}H_{68}ClNO_{10}S_2SiNa$: found 896.3612, calcd 896.3640 $(M + Na)^+$. IR ν cm^{-1}: 3412 and 3225 (OH), 1715, (C═O), 1587 (C═C), 1462, 1080 (CO). ^1H NMR (250 MHz, $CDCl_3$) δ: 0.02 (3H, s), 0.04 (3H, s), 0.86 (9H, s), 0.92 (3H, d, J = 7 Hz), 1.62 (3H, s), 1.72 (3H, d, J = 1 Hz), 1.80−3.0 (11H, m), 3.20 (3H, s), 3.31 (3H, s), 3.34 (2H, bs), 3.38 (3H, s), 3.52−3.90 (5H, m), 3.63 (3H, bs), 3.89 (3H, s), 3.92 (1H, d, J = 7.5 Hz), 4.47 (1H, dd, J = 3, 8 Hz), 4.76 and 4.88 (2H, AB, J = 7 Hz), 5.49 (1H, d, J = 9 Hz), 5.76 (1H, dd, J = 15, 7.5 Hz), 5.98 (1H, d, J = 11 Hz), 6.47 (1H, dd, J = 15, 11 Hz), 6.70 (2H, s). ^{13}C NMR ($CDCl_3$) δ: −5.3, −4.4, 11.8, 15.8, 16.7, 18.2, 24.8, 25.8, 26.7, 26.9, 36.9, 37.0, 38.8, 42.4, 46.1, 53.2, 55.8, 56.5, 57.2, 59.1, 67.6 and 71.9, 75.2, 80.0, 88.6, 96.3, 111.8, 119.0, 121.5, 126.4, 128.1, 128.9, 131.1, 136.2 and 137.7, 139.5, 141.3, 155.8 and 156.2, 175.9.

DIBAH Reduction of the Carbamate Protective Group, Amino Acid 16. DIBAH (1.5 N in toluene, 0.45 mL, 4 equiv) was added to **15** (153 mg, 0.17 mmol) in toluene (5 mL) at −78 °C. This mixture was warmed to −60 °C, and upon completion of the reaction monitored by TLC, oxalic acid in methanol was added. After addition of $CHCl_3$, standard workup afforded a residue that was purified on a silica gel column (eluent: toluene/AcOEt: 3/1), giving **16** (103 mg, 72%) and the dimethylamino acid (8%). **16.** $[\alpha]_D$: +20 ($CHCl_3$, c = 0.7). HRMS (FAB) for $C_{40}H_{67}ClNO_8S_2Si$ $(MH)^+$: found 816.3760, calcd 816.3766. IR ($CHCl_3$), ν cm^{-1}: 3420, 2958, 2929, 1729 (w), 1590, 1480, 1250. ^1H NMR (250 MHz, $CDCl_3$) δ: 0.05 (3H, s), 0.08 (3H, s), 0.87 (9H, s), 0.93 (3H, d, J = 6 Hz), 1.64 (3H, s), 1.76 (3H, d, J = 1 Hz), 1.95 (2H, m), 2.04 (1H, dd, J = 16, 2.5 Hz), 2.19 (1H, dd, J = 16, 6 Hz), 2.46 (1H, dd, J = 15, 8 Hz), 2.59 (1H, dd, J = 15, 5 Hz), 2.70−3.10 (5H, m), 2.90 (3H, s), 3.32 (5H, bs), 3.39 (3H, s), 3.52−3.90 (5H, m), 3.87 (3H, s), 3.92 (1H, d, J = 8 Hz), 4.47 (1H, dd, J = 5, 8 Hz), 4.78 and 4.89 (2H, AB, J = 7 Hz), 5.52 (1H, d, J = 8 Hz), 5.76 (1H, dd, J = 15, 8 Hz), 5.99 (1H, d, J = 11 Hz), 6.16 (1H, s), 6.17 (1H, s), 6.49 (1H, dd, J = 15, 11 Hz). ^{13}C NMR ($CDCl_3$) δ: −5.2, −4.4, 11.9, 15.6, 16.7, 18.1, 24.9, 25.84 26.8, 26.87, 30.7, 37.1, 39.2, 42.2, 46.9, 55.8, 56.2, 57.1, 59.0, 67. and 71.9, 75.1, 79.9, 89.1, 96.3, 101.7 and 107.2, 125.7, 127.5, 129.2, 131.5, 135.9, 138.9, 139.4, 145.9, 155.3, 175.3.

Macrocyclization. Lactam 17. 16 (115 mg, 0.14 mmol) and tri-*n*-butylamine (83 mg, 3.2 equiv) in dry CH_2Cl_2 (100 mL) were added over ca. 10 h to a well-stirred suspension of 2-chloro-1-methylpyridinium iodide (107 mg, 3 equiv) in CH_2Cl_2 (30 mL) at 32 °C. After complete addition, the mixture was stirred, at this temperature, for 16 h, and then cooled to rt and diluted with ether. The organic phase was washed with

brine, dried, and concentrated in vacuo. The residue was chromatographed over silica gel (toluene/AcOEt: 9/1) to afford **17** (74 mg, 66%) in addition to **16** (8 mg).

17. HR EIMS for $C_{40}H_{64}ClNO_7SiS_2$: M^+ calcd 797.3582, found 797.3556. EIMS: M^+ 797, *m/z* 782, 740, 559. IR, ν cm^{-1}: 1662 and 1575 (C═O). ^1H NMR (300 MHz,$CDCl_3$) δ for the major conformer: −0.07(3H, s), −0.04 (3H, s), 0.86 (9H, s), 0.94 (3H, d, $J = 6$ Hz,), 1.52 (3H, s), 1.86 (3H, d, $J = 1$ Hz), 3.14 (3H, s), 3.33 (3H, s), 3.37 (3H, s), 3.92 (3H, s), 4.04 (1H, d, $J = 7.5$ Hz), 4.35 (1H, m), 4.81 and 4.91 (2H, AB, $J = 7$ Hz), 5.3 (1H, m), 5.6 (2H, m), 6.46 (1H, dd, $J = 15$, 11 Hz), 6.72 (1H, s), 6.76 (1H, s).

Cleavage of the MEM group. Compound 18. Freshly prepared 2-chloro-1,3,2-dithioborolane[22] (23 mg, 2.5 equiv) in dry CH_2Cl_2 (1 mL) was added to a well-stirred solution of **17** (60 mg, 0.075 mmol) in dry CH_2Cl_2 (5 mL) at −78 °C. The mixture was kept at −60 °C for 2 h. Then saturated aqueous solutions of NH_4Cl (1 mL) and $(NH_4)_2CO_3$ (2 mL) were added successively. The mixture reached rt over ca. 1 h. After addition of ether, standard workup gave a residue that was chromatographed on silica gel (heptane/ether: 2/1) to afford two compounds (46 mg), **18** (53%) and **19** (29%). **18**, $C_{36}H_{56}ClNO_5SiS_2$. EIMS: M^+ 709, *m/z* 691, 677, 652, 620, 559. ^1H NMR (250 MHz,$CDCl_3$) δ for the major conformer: −0.05 (3H, s), 0.01 (3H, s), 0.86 (9H, s), 0.99 (3H, d, $J = 6$ Hz), 1.56 (3H, s), 1.94 (3H, d, $J = 1$ Hz), 3.17 (3H, s), 3.36 (3H, s), 3.93 (3H, s), 5.22 (1H, m), 5.48 (2H, m), 6.54 (1H, dd, $J = 15$, 11 Hz), 6.69 (1H, s), 6.77 (1H, s).

19, $C_{39}H_{62}ClNO_5SiS_4$. EIMS: M^+ 815, *m/z* 800 $(M - 15)^+$, 758 $(M - 57)^+$, 691, 559. ^1H NMR (250 MHz, $CDCl_3$) δ for the major conformer: 0.0 (3H, s), 0.02 (3H, s), 0.84 (9H, s), 0.93 (3H, d, $J = 6$ Hz), 1.50 (3H, s), 1.88 (3H, d, $J = 1$ Hz), 3.16 (3H, s), 3.31 (3H, s), 3.93 (3H, s), 4.0 (1H, d, $J = 6$ Hz), 4.38 (1H, m), 4.60 and 4.90 (2H, AB, $J = 10$ Hz), 5.29 (1H, d, $J = 9$ Hz), 5.51 (2H, m), 6.46 (1H, dd, $J = 15$, 11 Hz), 6.72 (1H, s), 6.76 (1H, s).

Preparation of Carbamate 20. *p*-Nitrophenyl chloroformate (50 mg, 0.25 mmol, 9.2 equiv) in CH_2Cl_2 (0.5 mL) was added to a solution of **18** (19 mg, 0.027 mmol) in CH_2Cl_2 (1 mL) and pyridine (1 mL) at 0 °C. After 24 h at rt, a saturated methanolic solution of ammonia (5 mL) was added. The mixture was stirred for 14 h at rt. After concentration *in vacuo*, the residue was dissolved in ether (40 mL). After standard workup the solid material that was obtained was chromatographed (SiO_2, eluent pentane/ether 1:1) to give to the carbamate **20** (15 mg, 75%), $C_{37}H_{57}ClN_2O_6SiS_2$. EIMS: M^+ 752, *m/z* 737 $(M - 15)^+$, 695 $(M - 57)^+$, 691 $[M - (H_2NCO_2H)]^+$, 559 $[M - (132+18)]^+$. ^1H NMR (250 MHz, $CDCl_3$) δ for the major conformer: −0.05 (3H, s), 0.00 (3H, s), 0.88 (9H), 0.93 (3H, d, $J = 6$ Hz), 1.46 (3H, s, CH_3), 1.89 (3H, d, $J = 1$ Hz), 3.14 (3H, s), 3.33 (3H, s), 3.91 (3H, s), 6.40 (1H, dd, $J = 15$, 11 Hz), 6.67 (1H, s), 6.70 (1H, s).

3-*O*-(*tert*-Butyldimethylsilyl)-4,5-deoxymaytansinol (21). $CaCO_3$ (30 mg, 033 mmol) and $HgCl_2$ (30 mg, 0.11 mmol) were added to a solution of **20** (14 mg, 0.0186 mmol) in CH_3CN/H_2O (3 mL, 5/1). This mixture was stirred for 18 h at rt. The addition of diisopropylethylamine (0.1 mL) was followed after 30 min by that of an aqueous solution of Na_2S (2%, 1 mL), giving a black precipitate. After 30 min, dilution with AcOEt, filtration through a Celite pad, and standard workup gave, after filtration (silica gel), an impure cyclic carbamate (8 mg), which was desilylated without further purification.

4-Deoxymaytansinol (22). Aqueous HF (48%, 70 μL) was added to a solution of **21** (8 mg, 0.012 mmol). This mixture was stirred for 2 h at rt, neutralized with solid Na_2CO_3, and diluted with AcOEt (20 mL). The organic phase was washed successively with brine and water, dried, and concentrated. The residue was chromatographed by passing on a silica gel column, eluting with ether/AcOEt, 3/1, giving 4,5-deoxymaytansinol (**22**) (3 mg, 29% for two steps). HR CIMS, for $C_{28}H_{37}ClN_2O_7$: $(MH)^+$ found 549.2328, calcd 549.2367. CIMS: MH^+ 549, *m/z* 488, 455. IR ($CHCl_3$), ν (cm^{-1}): 3370−3260 (NH), 1710 and 1655 (C═O), 1575. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.05 (1H, t, $J = 13$ Hz, C(8)-H_a), 1.16 (3H, d, $J = 6$ Hz, C(6)-CH_3), 1.32 (3H, s, C(4)-CH_3), 1.69 (1H, d, $J = 14$ Hz), 1.81 (3H, d, $J = 1$ Hz, C(14)-CH_3), 2.21 (1H, dd, $J = 16$, 2 Hz, C(2)-H_a), 2.45 (1H, m, C(6)-H), 3.20 (3H, s, NCH_3), 3.33 (3H, s, C(10)-OCH_3), 3.39 (1H, d, $J = 13$ Hz, C(15)-H_b), 3.46 (1H, d, $J = 8.5$ Hz, C(10)-H), 3.97 (3H, s, C(20)-OCH_3), 4.23 (2H, m), 5.21 (1H, broad s), 5.42 (2H, m, C(5)-H) and C(11)-H), 5.92 (1H, d, $J = 11$ Hz, C(13)-H), 6.14 (1H, broad s, NH), 6.37 (1H, dd, $J = 15$, 11 Hz, C(12)-H), 6.71(1H, d, $J = 1.5$ Hz, C(17)-H), 6.82 (1H, d, $J = 1.5$ Hz, C(21)-H). ^{13}C NMR ($CDCl_3$) δ: 14.3 (CH_3), 16.7 (C(14)-(CH_3), 17.3 (CH_3), 34.8 (CH_2), 35.8 (NCH_3), 37.6 (C-6), 38.8 (CH_2), 46.5 (C-15), 56.5 (OCH_3), 56.6 (OCH_3), 70.8 (C-3), 77 6 (C-7), 81.5 (C-9), 89.1 (C-10), 112.6 (C-21), 118.8 (C-19), 121.6 (C-17), 124.2 (C-5), 124.3 (C-13), 126.3 (CH), 132.7 (CH), 136. 0 (C-4), 139.6 (C-16), 140.4 (C-14), 141.7 (C-18), 152.8 (C═O), 156.1 (C-20), 175.3 (C-1).

Maytansinol (1). A solution of 2,6-lutidine (100 μL, 2×10^{-2} mmol) in dry toluen was added, at 0 °C, to **22** (1.7 mg, 3×10^{-3} mmol) in toluene (3 mL). Then, anhydrous *t*-Bu-OOH (3×10^{-3} mmol) in toluene (100 μL) and $VO(acac)_2$ (20 μL of a 0.1% solution in toluene) were added. This well-stirred mixture was allowed to warm to rt. Then ten 10 μL portions of the $VO(acac)_2$ solution were successively every 1 h, while five portions of *t*-BuOOH (10^{-3} mmol) were added every 2 h. After 24 h, analysis of the crude mixture using MS (FAB) showed starting material in addition to maytansinol. Lutidine (10^{-2} mmol), *t*-BuOOH (5×10^{-3} mmol), and the $VO(acac)_2$ solution were added again as previously described. After 24 h, MS analysis showed almost no starting material left, and the crude solution was poured on a silica gel column. Elution (AcOEt/Heptane) led to the maytansinol (**1**) (0.8 mg, 45%) identical to reference sample. $[\alpha]_D$: −185 ($CHCl_3$, $c = 0.09$). $C_{28}H_{37}ClN_2O_8$. MS (FAB, thio + NaCl), *m/z* 589, 587 $(M + Na)^+$. UV, λ_{max} (nm (EtOH)): 250.4 ($\epsilon = 27\,000$), 279 and 285 ($\epsilon = 6500$). IR ($CHCl_3$), ν (cm^{-1}): 3375 (NH), 1709 and 1656 (C═O), 1581. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.84 (3H, s, CH_3), 1.29 (3H, s, CH_3), 1.54 (3H, s, CH_3), 1.68 (3H, s, CH_3), 2.14 (2H, broad s), 2.28 (1H, dd, $J = 11$ Hz, 13 Hz), 2.56 (1H, d, $J = 10$ Hz), 3.13 (1H, d, $J = 12$ Hz), 3.21 (3H, s, NCH_3), 3.36 (3H, s, OCH_3), 3.46 (1H, d, $J = 12$ Hz), 3.50 (1H, d, $J = 9$ Hz), 3.55 (1H, m), 3.99 (3H, s), 4.34 (1H, broad t), 5.52 (1H, dd), 6.15 (1H, d, $J = 11$ Hz), 6.29 (1H, broad s), 6.46 (1H, dd, $J = 15$, 11 Hz), 6.11 (1H, d, $J = 1$ Hz), 6.97 (1H, d, $J = 1$ Hz). ^{13}C NMR ($CDCl_3$) δ: 11.5, 14.65, 15.95, 35.25, 35.85, 35.95, 37.95, 47.05, 56.65, 62.8, 66.2, 75.2, 75.7, 81.2, 88.6, 112.7, 123.3, 124.9, 127.1, 133.3, 139.55, 140.2, 142.2, 152.5, 171.2. C(19) is missing.

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Supporting Information Available: NMR spectra for **3**, **4**, **7**−**20**, **22**, and **1** (18 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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