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Synthesis and X-Ray Crystal Structure of (-)-Calicheamicinone†

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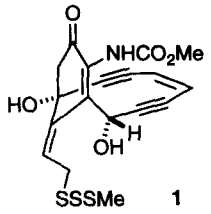
Abstract: Diels-Alder reaction between ketene acetal **3** and the β-nitroacrylate ester **12** of (-)-8-phenylmenthol gave optically pure ketone **17**. This substance was modified in such a way as to remove the chiral auxiliary and afford the epimeric silyl ethers **20M** and **20m**. Following procedures worked out using racemic materials, both **20M** and **20m** were converted into optically pure (-)-calicheamicinone (**1**). This is a crystalline substance, and an X-ray structure determination was carried out.

We report full details for the synthesis of optically pure (-)-calicheamicinone (**1**),[1a] the aglycon of the antitumor antibiotic[2] calicheamicin γ_1^I. The material we made is crystalline, and its detailed structure in the solid state was established by X-ray analysis.



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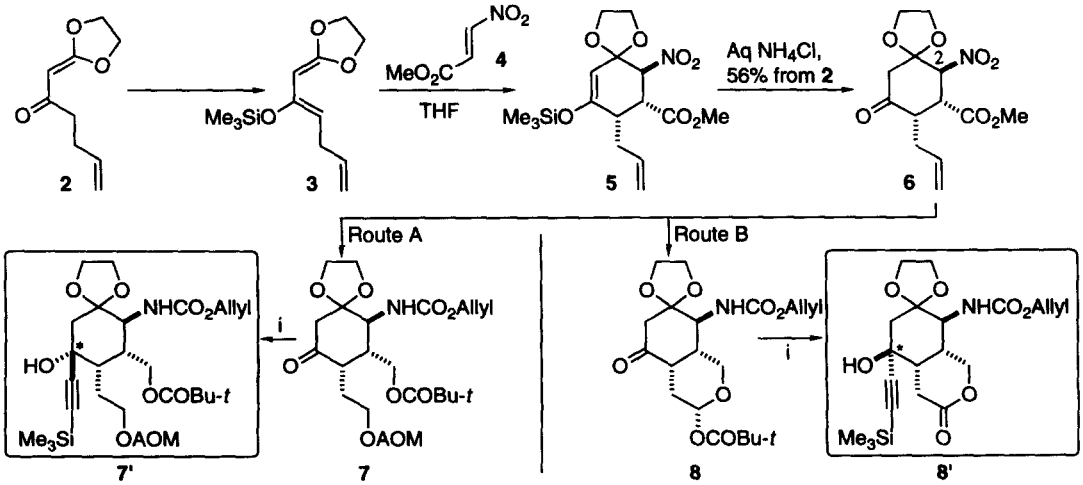
Our route[1a] is based on a synthesis of *racemic* calicheamicinone reported from this laboratory.[3] That work (see Scheme 1 for the early stages) began with a Diels-Alder reaction between ketene acetal **3** and methyl

Scheme 1[a]



[a]All chiral compounds are racemic. AOM = $CH_2OC_6H_4OMe$-*p*. (i) Lithium trimethylsilylacetylide, $CeCl_3$, THF.

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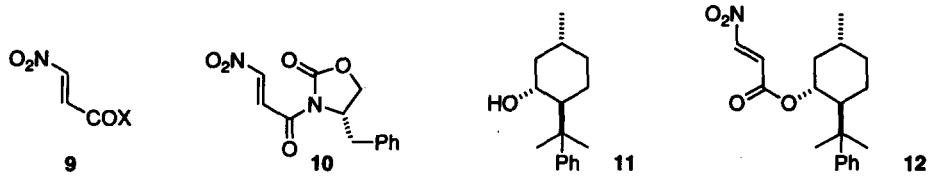
3-nitropropenoate (**4**). The product (**5**) was subjected to mild acid hydrolysis so as to afford the highly functionalized ketone **6**, and this was then elaborated by two routes. One gave ketone **7** and the other ketone **8**. Each of these substances was treated with the cerium salt of trimethylsilylacetylene, and both gave in excellent yield the product of acetylide attack at the ketone carbonyl; however, the stereochemical outcome was different in the two reactions. With ketone **7** the acetylide entered *syn* to the carbamate nitrogen (**7** → **7'**), while with **8** it entered *anti* to the nitrogen (**8** → **8'**). When **7'** and **8'** are converted into (±)-calicheamicinone, all the stereogenic centers except C* (see **7'** and **8'**) are changed to sp^2 hybridization, so that in the *racemic* series both advanced intermediates **7'** and **8'** afford the same final product [(±)-**1**]. A consequence of this situation is that *either* enantiomer of **6** can serve equally well for the preparation of (-)-calicheamicinone: the enantiomer with 2*S* absolute configuration would be processed by route B (see Scheme 1), while that with 2*R* configuration could also be converted into **1**, but would require use of route A.

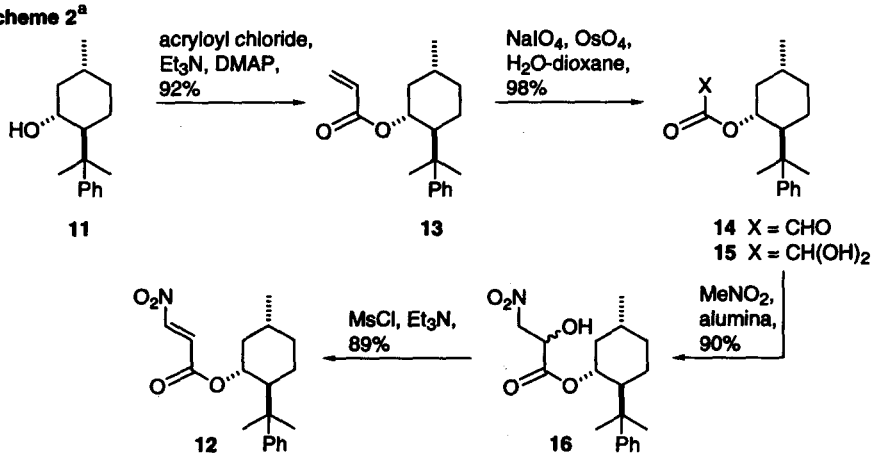
Because of these unusual circumstances, synthesis of **1** can be based on an asymmetric Diels-Alder in which the absolute configuration of the Diels-Alder product is immaterial, although it must be established, so that the appropriate choice between routes A and B can be made. With this information as background, we tried to prepare a nitroalkene **9** in which group X is part of a chiral auxiliary. Our initial choice fell on oxazolidinones,[4] because of our very satisfactory experience in using these compounds,[5] but we could not prepare the



required oxazolidinone derivative **10** — at least within the short time we devoted to the problem — and so we turned next to (-)-8-phenylmenthol (**11**), which also has a fine reputation as a chiral auxiliary in asymmetric Diels-Alder reactions,[6] and can be made[7] easily from *R*-pulegone.

Conversion of **11** into the required nitropropenoate **12** was surprisingly troublesome to begin with, but a satisfactory and reliable method (Scheme 2) was eventually found. Acylation of **11** with acryloyl chloride

Scheme 2[a]

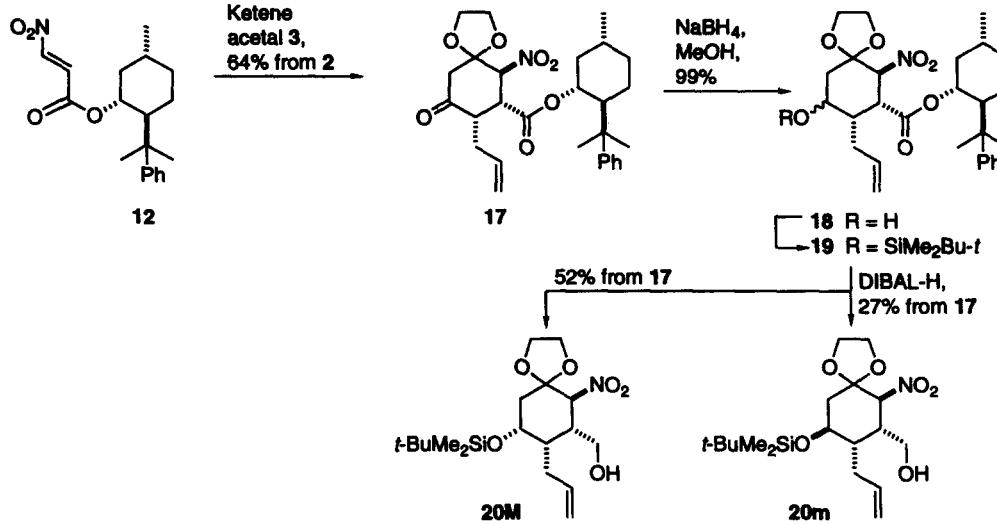


[a]All compounds optically pure.

(Et_3N, DMAP, 92%) gave ester **13**,[8] and the double bond was then cleaved under the classical Lemieux-Johnson conditions[9] to afford a mixture (98%) of the glyoxylate **14** and the corresponding hydrate (**15**). These compounds underwent efficient (90%) Henry reaction in the presence of neutral alumina[10] to give the diastereoisomeric alcohols **16**, which were easily converted (89%) into the required nitropropenoate **12** by mesylation[11] and spontaneous elimination.

With the chiral nitropropenoate in hand, we were ready to try the critical asymmetric Diels-Alder reaction (Scheme 3). As in our earlier work in the racemic series, the diene component **3** was generated from

Scheme 3[a]



[a]All compounds optically pure.

the acyl ketene acetal **2**, and used *in situ*. Very mild acidic hydrolysis (aqueous ammonium chloride) allowed us to isolate the desired adduct **17**, which was obtained in 64% yield from **2**, after chromatography and recrystallization. This yield is a modest improvement over the corresponding reaction in the racemic series (formation of **6**) for which the yield was 56%.

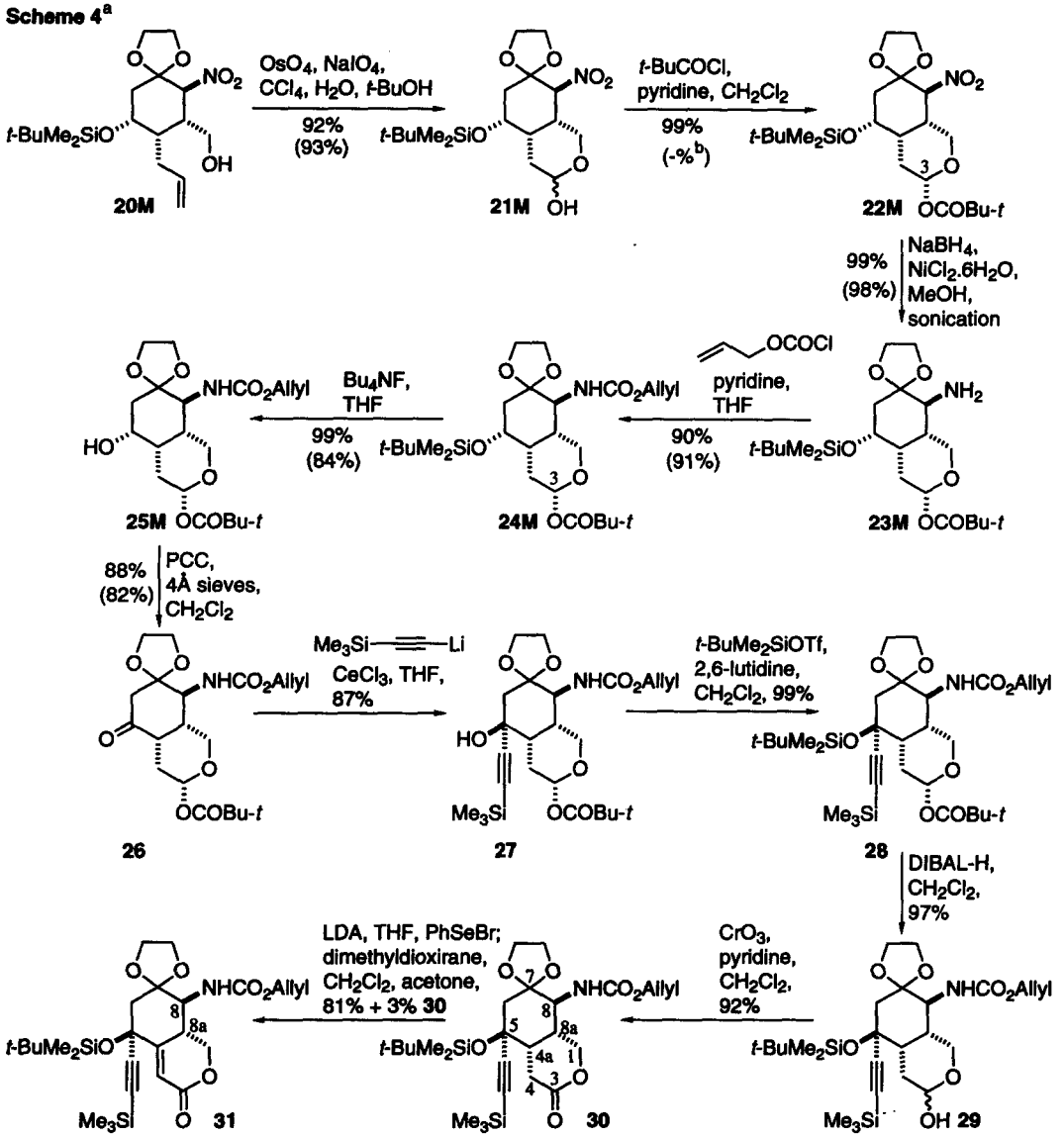
X-ray analysis of **17** established that the absolute configuration is as shown, and this information indicated that route B of Scheme 1 should be followed in order to make calicheamicinone of natural configuration. To this end, the ketone carbonyl of **17** was reduced with sodium borohydride (99%), and the resulting mixture of epimeric alcohols was protected in the form of their *t*-butyldimethylsilyl ethers (**18** → **19**, *ca* 100%).

The next task was to disengage the chiral auxiliary [**19** → **20M** + **20m** (M = major isomer, m = minor isomer]. This was accomplished by treatment with DIBAL-H, but the experiment has to be done under carefully defined conditions. At -75 °C reaction is very slow, while at room temperature the silyl group is removed.[12] After considerable experimentation, a reliable and efficient procedure was found: DIBAL-H (2 equiv.) is added to a solution of **19** at -78 °C and, after 1 h the reaction flask is transferred to a bath at -30 °C. Another portion of DIBAL-H (2 equiv.) is added 24 h after the first batch, and stirring at -30 °C is continued for 48 h. At this point the epimeric silyl ethers **20M** (52% from **17**) and **20m** (27% from **17**) are easily isolated. The chiral auxiliary, (-)-8-phenylmenthol, is recovered (96%), and can be recycled. The optical purity of the two alcohols **20M** and **20m** was confirmed by converting each one, as well as samples of the corresponding racemic materials,[13] into the Mosher esters[14] and then examining the ^{19}F NMR spectra. The alcohols in the present series were optically pure, the CF_3-signals for the esters of the racemic alcohols (there are two CF_3-signals in each case) being well separated (22 and 57 Hz).

Once the chiral auxiliary had been removed, we were in a position to follow the procedures (see Scheme 4) we had used earlier in the racemic series, because racemic material corresponding to **20M** and **20m** had been converted into (±)-calicheamicinone.[3] In Scheme 4 the yields in brackets refer to the corresponding experiments for the series beginning with **20m**, but only the structures for compounds derived from **20M** are shown.

Double bond cleavage of **20M** (Scheme 4) under Lemieux-Johnson conditions gave a mixture of epimeric lactols (**20M** → **21M**, 92%), and treatment with pivaloyl chloride served to convert them into the

Scheme 4[a]



[a]All compounds optically pure. Yields in brackets refer to the series from **20m**. [b]See text.

pivaloate **22M** (99%). Evidently, as we had found with the racemic compounds,[3] the epimeric lactols equilibrate, and one of them reacts faster than the other, so as to give a single product (**22M**) in which the bulky pivaloyl group is equatorial. In this particular transformation, use of **21m** (not shown in the Scheme) gave a different result from that obtained with racemic compounds. In our earlier work,[3] the mixture of racemic lactols corresponding to **21m** afforded a single pivaloate, but in the present case, we obtained (94%) a 4:1 separable mixture of epimeric pivaloates. The undesired (minor) isomer could be reconverted (83%) into a 1:1 mixture of lactols by the action of DIBAL-H, and this lactol mixture was resubjected to reaction with pivaloyl chloride, so as to obtain more of the desired product. We do not know why our result for pivaloylation of the lactols derived from **21m** is different from what we observed when working with

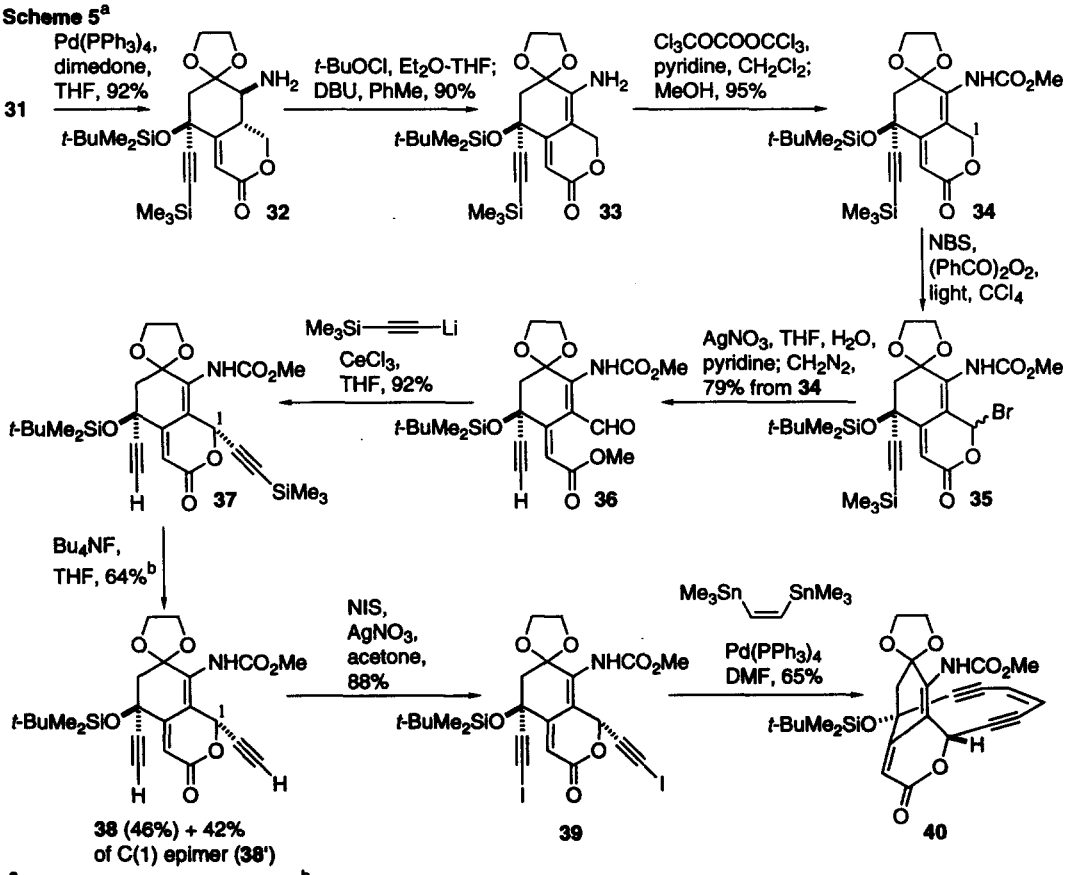
corresponding racemic compounds but, in any event, the stereochemistry can be adjusted by recycling, as described.

Reduction of the nitro group, using the reagent generated from nickel(II) chloride and sodium borohydride, gave the corresponding amine in high yield (99%), and this was then converted efficiently (90%) into its allyl carbamate under standard conditions (**22M** → **23M** → **24M**). Finally, desilylation (**24M** → **25M**, Bu_4NF, 99%) and PCC oxidation (**25M** → **26**, 88%) brought the work to a stage where the series from **20M** and **20m** converge to a single compound. In the desilylation step the yield with **24m** was significantly lower (84% as compared with 99%) than with the C(3)-epimer (**24M**) — in the racemic series the two corresponding yields were almost identical (95 and 97%) — but, apart from this, and the earlier complication with the pivaloylation, the results in the two series (from **20M** and **20m**) were very similar, and were also close to those obtained with racemic compounds.

Treatment of ketone **26** with the cerium salt of trimethylsilylacetylene, under the special conditions previously worked out,[3] served to introduce an acetylene unit *anti* to the nitrogen (87% yield), and the resulting tertiary hydroxyl was protected by silylation (**27** → **28**, 99%). Next, the pivaloyl group was removed by the action of DIBAL-H (97%), and oxidation (92%) of the resulting mixture of epimeric lactols with the Collins reagent led to the advanced intermediate **30**.

The next phase of the synthesis involved desaturation at both C(8)-C(8a) and C(4)-C(4a), and oxidation at C(1). Introduction of a double bond at C(4)-C(4a) was effected by phenylselenenylation (LDA, PhSeBr) and oxidation of the resulting selenide with dimethyldioxirane [**30** → **31**, 81% not corrected for recovered **30**

Scheme 5[a]



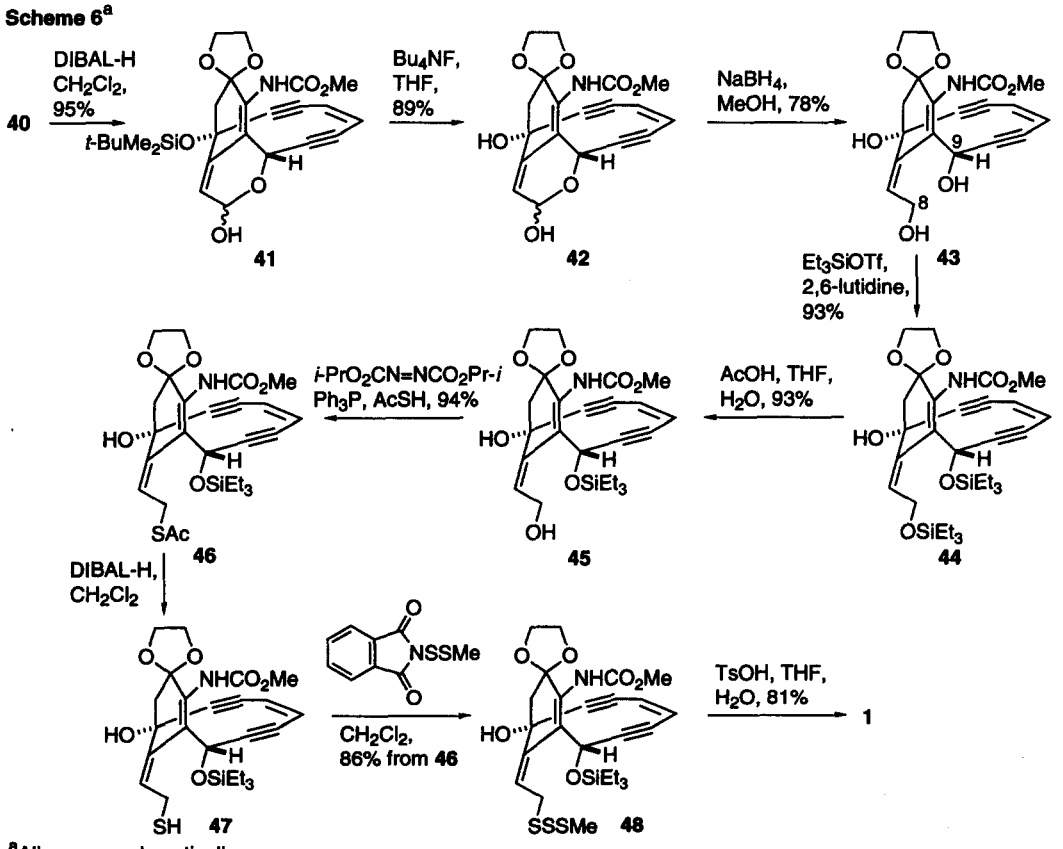
[a]All compounds optically pure. [b]Yield of **38** after one recycling of *anti* bis-acetylene.

(3%)]. At this point the free amine was liberated (Scheme 5, **31** → **32**, 92%) by deprotection with tetrakis(triphenylphosphine)palladium(II) in the presence of dimedone,[15] and the amine was chlorinated on nitrogen (*t*-BuOCl) and treated with DBU.[16] That experiment afforded (90%) the fully conjugated amine **33**, which was immediately converted (95%) into its methyl carbamate **34**.

Oxidation at C(1) was then achieved by free radical bromination (**34** → **35**), hydrolysis of the intermediate bromides **35**, without purification, and trapping of the liberated carboxylic acid[17] with diazomethane (**35** → **36**). During the hydrolysis the acetylenic silyl group is lost, but this was an advantage, as it would have had to be removed, in any case. When the bromination, hydrolysis, and methylation sequence is performed carefully, we were able to obtain an overall yield of 79% for the conversion of **34** into **36**. This result is marginally better than in our earlier work.[3] Treatment of **36** with the cerium salt of trimethylsilylacetylene, again under our special conditions,[3] led directly to the *syn* bis-acetylene **37**, and desilylation produced a mixture of *syn* bis-acetylene **38** and the corresponding C(1) epimer in 46% and 42% yields, respectively. The two compounds were separated, and the undesired *anti* bis-acetylene was treated with tetrabutylammonium acetate in order to equilibrate the epimers. In the racemic series we had used a reaction period of several h; we now find that the reaction must be stopped after a few minutes in order to obtain a quantitative recovery of the two epimers (44% *syn*, 56% *anti*). After one recycling the yield of the desired *syn* bis-acetylene was 64% (a further recycling would have raised it to 74%). Finally, the acetylenic hydrogens were replaced by iodine (**38** → **39**, NIS, $AgNO_3$, 88%), and ring closure by a double Stille coupling gave the initial target **40** in 65% yield — a value somewhat lower than in the racemic series (72%).

With the calicheamicinone core structure in hand, the remaining tasks were introduction of the trisulfide

Scheme 6[a]



[a]All compounds optically pure.

unit and removal of protecting groups. Reduction of lactone **40** gave a mixture of lactols (95%) (Scheme 6); these were desilylated with tetrabutylammonium fluoride (89%), and reduced (78%) further with sodium borohydride (**40** → **41** → **42** → **43**). Bis-silylation of the triol (**43** → **44**, Et_3SiOTf, 2,6-lutidine, 93%), and selective deprotection of the primary hydroxyl, by storage overnight in an aqueous acidic solution (**44** → **45**, 93%), set the stage for introduction of the first sulfur without interference from the secondary hydroxyl (which was now blocked). Mitsunobu reaction with thiolacetic acid (**45** → **46**), followed by treatment with DIBAL-H, gave thiol **47**. This was chromatographed and immediately treated with an excess of recrystallized *N*-(methyldithio)-phthalimide[18,19] to afford trisulfide **48** in 86% yield from thioacetate **46**. Finally, mild acidic hydrolysis[20] (TsOH, THF, H_2O, 81%) served to remove the ketal and silyl protecting groups and release synthetic and optically pure calicheamicinone. The material was obtained as a white solid. Slow recrystallization from a mixture of dichloromethane and ethanol produced faintly yellow crystals suitable for X-ray analysis, and the X-ray structure[21] is shown in Figure 1 (which has its own numbering system).

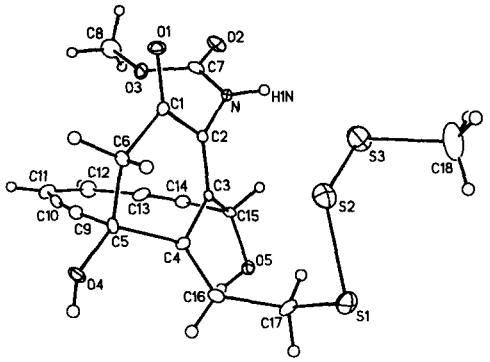


Figure 1

Although model compounds have been subjected to X-ray analysis, the actual core of calicheamicin γ_1^I has never been examined in this way, and its dimensions were unknown. The present measurements show that the C(9)-C(14) (crystallographic numbering system) distance is 3.429(9) Å, and the C(10)-C(13) distance is 2.747(10) Å. The two acetylenic units are bent to different extents, with the bond angles about C(13) [165.4(7)°] and C(14) [167.3(7)°] deviating slightly more from linearity than those about C(9) [172.4(7)°] and C(10) [168.5(8)°]. In the crystal, the carbamate adopts a conformation in which the nitrogen lone pair is nearly parallel to the attached double bond (lone pair-double bond torsional angle *ca* 15°), and the amide hydrogen is *syn* to the carbamate carbonyl. This *syn* relationship (torsion angle about the N-C bond of the carbamate H-N-C=O subunit ≤25°) in carbamates is rare — we found 11 cases out of 506 carbamates[22] in the Cambridge Structural Database. Finally, a search for acyclic CS_3C units showed that this segment in calicheamicinone is unexceptional with respect to bond lengths and angles, including the fact that the S(1)-C(17) and S(3)-C(18) bond vectors point from opposite faces of the S(1)S(2)S(3) plane (see Figure 1). Our remaining sample of (-)-calicheamicinone was examined by NMR, in an attempt to establish whether the same conformation was maintained in solution. However, the results of a ROESY experiment were inconclusive.

Experimental

General procedures.

The same general procedures as used previously[23] were followed. DMF was stirred overnight with crushed CaH_2, and then distilled under water pump vacuum, with protection from moisture. Optical rotations were measured at 25 °C. The symbols s', d', t', and q' used for ^{13}C NMR signals indicate zero, one, two, or three attached hydrogens, respectively. In cases where the number of signals is less than expected, we assume this is due to coincident chemical shifts. Except where different from corresponding data obtained on racemic compounds, the FTIR, ^1H NMR, and ^{13}C NMR data are not repeated here; the information is available elsewhere.[3b] The type of characterization data obtained for each compound, and the scale and yield, are, however, indicated in brackets. Mass spectral and combustion analysis data are quoted, wherever measured.

[1*R*-(1α,2β,5α)]-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Oxoacetate (14) and [1*R*-(1α,2β,5α)]-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Dihydroxyacetate (15).[8] A

procedure previously applied[9] to a stereoisomer was followed. OsO_4 (2.5% w/w in *t*-BuOH, 6.5 mL, 0.50 mmol) was added to a stirred mixture of **13**[8] (22.83 g, 79.71 mmol), water (50 mL) and dioxane (150 mL). After 5 min, the mixture had become dark brown. $NaIO_4$ (51.22 g, 239.5 mmol) was then added in portions over 10 min, and the resulting mixture was stirred for 2 h. Brine (100 mL) was added, and the mixture was extracted with Et_2O (4 x 100 mL). The combined organic extracts were washed with water (*ca* 100 mL) and 10% aqueous $NaHSO_3$ (200 mL), dried (Na_2SO_4) and evaporated, and the residue was filtered through a short column (5 x 20 cm) of silica gel, using 1:1 EtOAc-hexane, to afford the gummy product,[24] which exists partly (IR) as the hydrate **15** (24.09 g, 98%).

[1*R*-(1α,2β,5α)]-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl 2-Hydroxy-3-nitropropanoate (16). Neutral alumina (grade I) was heated in an oven at 150 °C for 24 h, and cooled in a desiccator. A portion of this material (18.5 g, i.e. 1 g per 2 mmol of **15**) was added over 10 min to a stirred and cooled (0 °C) solution of **14** and its hydrate **15** (11.40 g, 37.21 mmol, assuming all the material is the hydrate) in freshly-distilled (same day) $MeNO_2$ (25.0 mL, 462 mmol). After 30 min, the ice-bath was removed and stirring was continued for 3 h. CH_2Cl_2 (300 mL) was added to the resulting suspension, and the mixture was filtered through a pad (1.5 x 7 cm) of Celite, using CH_2Cl_2. The filtrate was evaporated and the residue was passed through a short column of silica gel (5 x 25 cm), using 1:4 EtOAc-hexane, to afford **16** (11.81 g, 90% yield) as a thick gum: FTIR (CH_2Cl_2, cast) 3491, 1735, 1560 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.35-7.10 (m, 5 H), 5.00-4.82 (m, 1 H), 4.30-3.85 (m, 2 H), 3.57-3.47 (m, 0.55 H), 2.96 (d, *J* = 6 Hz, 0.42 H), 2.30-0.80 [m including s at δ 1.27, s at δ 1.16, and d (*J* = 8.4 Hz) at δ 0.89, 18 H); exact mass *m/z* calcd for $C_{19}H_{27}NO_5$ 349.18893, found 349.18913. Anal. Calcd for $C_{19}H_{27}NO_5$: C 65.31, H 7.79, N 4.01. Found: C 65.07, H 8.03, N 3.77.

[1*R*-[1α(*E*),2β,5α)]]-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl 3-Nitro-2-propenoate (12). $MeSO_2Cl$ (2.75 mL, 35.5 mmol) was added at a fast dropwise rate to a stirred and cooled (0 °C) solution of **16** (11.81 g, 33.80 mmol) in dry CH_2Cl_2 (200 mL) (Ar atmosphere), and Et_3N (18.87 mL, 135.4 mmol) was then added dropwise over 5 min with stirring.[11] The mixture was stirred at 0 °C for 2 min after the end of the addition, and then diluted with Et_2O (500 mL). (These times must be adhered to for maximum yield.) The resulting solution was washed with 5% hydrochloric acid (100 mL) and brine, and dried (Na_2SO_4). The solvent was evaporated and the residue was filtered through a short column (5 x 25 cm) of silica gel, using 3:17 EtOAc-hexane, to give **12** (10.02 g, 89% yield) as a dark, yellowish oil: $[\alpha]_D$ -57.0 (*c* 2.0, EtOH); FTIR (CH_2Cl_2 cast) 1723, 1538 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.30-7.20 (m, 4 H), 7.12-7.05 (m, 1 H), 6.50 (AB q, *J* = 14.4 Hz, $\Delta\nu_{AB}$ = 186.7 Hz, 2 H), 4.92 (dt, *J* = 10.8, 4.8 Hz, 1 H), 2.16 (dt, *J* = 10.8, 3.6 Hz, 1 H), 2.06-1.97 (m, 1 H), 1.90-1.80 (m, 1 H), 1.80-1.72 (m, 1 H), 1.56-1.44 (m, 1 H), 1.38-1.13 (m including s at δ 1.30 and s at δ 1.20, 7 H), 1.09-0.80 [m including d at δ 0.91 (J = 7.2 Hz), 5 H]; ^{13}C NMR ($CDCl_3$, 100.6 MHz) 161.8 (s'), 151.9 (s'), 147.8 (d'), 128.2 (d'), 127.2 (d'), 125.2 (d'), 76.1 (d'), 50.2 (d'), 41.4 (t'), 39.3 (t'), 34.4 (t'), 31.3 and 30.7 (d' and q'), 26.0 (t'), 21.7 (q'), 21.6 (q'); exact mass *m/z* calcd for $C_{19}H_{25}NO_4$ 331.17834, found 331.17820. Anal. Calcd for $C_{19}H_{25}NO_4$: C 68.86, H 7.60, N 4.23. Found: C 69.08, H 7.82, N 4.17.

[6*S*-[6α,7β,(1*S,2*R**,5*S**),8β]]-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl 6-Nitro-9-oxo-8-(2-propenyl)-1,4-dioxaspiro[4.5]decane-7-carboxylate (17).** *n*-BuLi (1.6 M in hexanes, 43.4 mL, 69.45 mmol) was added over 5 min to a stirred and cooled (0 °C) solution of $(Me_2PhSi)_2NH$[25] (20.78 g, 72.78 mmol) in dry THF (300 mL) (Ar atmosphere). Stirring at 0 °C was continued for 45 min, the mixture was cooled to -78 °C, and a solution of **2**[3] (11.1127 g, 66.071 mmol) in dry THF (60 mL) was added dropwise over 10 min. The mixture was stirred (-78 °C) for 45 min after the end of the addition, and was then quenched by rapid addition (over *ca* 1 min) of dry Me_3SiCl (9.64 mL, 76.0 mmol). The resulting mixture was stirred at -78 °C for 20 min, and then a solution of **12** (20.80 g, 62.76 mmol) in dry THF (60 mL) was added over 5 min by cannula. The mixture was stirred for 35 min, the cold bath was removed, and saturated aqueous NH_4Cl (300 mL) was added. Stirring was continued for 4 h, and the mixture was then extracted with EtOAc (4 x 150 mL). The combined organic extracts were washed with brine, and dried (Na_2SO_4). Evaporation of the solvent, and flash chromatography of the oily residue over silica gel (6 x 30 cm), using 1:4 EtOAc-hexane, gave **17** as a solid, which was contaminated with traces of $(Me_2PhSi)_2NH$. The material was recrystallized from 1:4 EtOAc-hexane (dissolve in EtOAc first) to give **17** (21.13 g, 64% based on **2**) as pure (^1H NMR, 400 MHz), colorless crystals: mp 143 °C; $[\alpha]_D$ -4.0 (*c* 1.9, CCl_4); FTIR (CH_2Cl_2 cast) 1726, 1559 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.40-7.29 (m, 4 H), 7.20-7.08 (m, 1 H), 5.60-5.46 (m, 1 H), 5.13 (d, *J* = 12 Hz, 1 H), 5.05-4.92 (m, 2 H), 4.78-4.66 (m 1 H), 4.05-3.90 (m, 1 H), 3.16 (dd, *J* = 12, 6 Hz, 1 H), 2.60 (AB q, *J* = 15.6 Hz, $\Delta\nu_{AB}$ = 77 Hz, 2 H), 2.46-2.40 (m, 1 H), 2.18-1.96 (m, 3 H), 1.96-1.76 (m, 2 H), 1.74-1.65 (m, 1 H), 1.55-1.40 (m, 1 H), 1.25 (s, 3 H), 1.22-1.03 (m including s at δ 1.20, 4 H), 1.00-0.80 (m, including d at δ 0.90, 5 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 202.5 (s'), 168.8 (s'), 151.7 (s'), 133.1 (d'), 128.0 (d'), 125.2 (d'), 118.0 (t'), 107.0 (s'), 84.6 (d'), 76.8 (d'), 65.8 (t'), 50.2 (d'), 49.1 (d'), 47.9 (t'), 44.1 (d'), 41.0 (t'), 39.3 (s'), 34.4 (t'), 32.2 (t'), 31.1 (d'), 29.0 (q'), 26.1 (t'), 23.2 (q'), 21.7 (q'); exact mass *m/z* calcd for $C_{28}H_{37}NO_7$ 499.25699, found 499.25594.

Anal. Calcd for $C_{28}H_{37}NO_7$: C 67.32, H 7.46, N 2.80. Found: C 67.37, H 7.60, N 2.78.

[6*S*-[6α,7β,(1*S,2*R**,5*S**),8β]]-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl 9-Hydroxy-6-nitro-8-(2-propenyl)-1,4-dioxaspiro[4.5]decane-7-carboxylate (18).** A solution of crystalline **17** (12.20 g, 24.42 mmol) in distilled THF (60 mL) (the compound is sparingly soluble in MeOH) was diluted with bench MeOH (225 mL) and the resulting solution was stirred in an ice-water bath. $NaBH_4$ (924.9 mg, 24.45 mmol) was added in one lot, and the mixture was stirred for 15 min after the addition. The mixture was then concentrated to a thick oil (rotary evaporator at room temperature) and half-saturated aqueous NH_4Cl (350 mL) was added. The mixture was extracted with EtOAc (4 x 100 mL), and the combined organic extracts were washed with water (100 mL) and brine (100 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (5 x 25 cm), using 2:3 EtOAc-hexane, gave a pure (TLC, silica, 2:3 EtOAc-hexane) mixture of epimeric alcohols **18** (12.13 g, 99%), which was used directly for the next stage.

[6*S*-[6α,7β,(1*S,2*R**,5*S**),8β,9α]]- and [6*S*-[6α,7β,(1*S**,2*R**,5*S**),8β,9β]]-5-Methyl-2-(1-methyl-1-phenyl)ethyl)cyclohexyl 9-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-6-nitro-8-(2-propenyl)-1,4-dioxaspiro[4.5]decane-7-carboxylate (19).** *t*-$BuMe_2SiOTf$ (10.08 mL, 43.89 mol) was added over 15 min to a stirred solution of **18** (14.66 g, 29.23 mmol) and 2,6-lutidine (6.82 mL, 58.6 mol) (used as purchased) in dry CH_2Cl_2 (320 mL). Stirring was continued for 3 h at room temperature, and then water (320 mL) was added. The mixture was shaken and the aqueous phase was extracted with Et_2O (3 x 150 mL). The combined organic extracts were washed with water (100 mL) and brine (100 mL), and dried (Na_2SO_4). Evaporation of the solvents and flash chromatography of the residue over silica gel (5 x 25 cm), using 1:4 EtOAc-hexane, gave **19**, as a mixture of epimers (17.99 g, 100%). A small portion was separated into its two components by flash chromatography over silica gel, using 1:19 EtOAc-hexane, and data were obtained on the individual components. Compound **19M** had: $[\alpha]_D$ 15.8 (*c* 2.3, CCl_4); FTIR (CH_2Cl_2 cast) 1727, 1557 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.42-7.32 (m, 4 H), 7.20-7.15 (m, 1 H), 5.73-5.60 (m, 1 H), 4.94-4.80 (m, 2 H), 4.75 (d, *J* = 12 Hz, 1 H), 4.69-4.59 (m, 1 H), 4.00-3.87 (m, 4 H), 3.82-3.74 (m, 1 H), 2.75 (dd, *J* = 12, 6 Hz, 1 H), 2.30-2.20 (m, 1 H), 2.18-2.08 (m, 1 H), 2.04-1.94 (m, 1 H), 1.88-1.65 (m, 6 H), 1.50-1.38 (br s, 1 H), 1.30 (s, 3 H), 1.20 (s, 3 H), 1.18-1.05 (m, 1 H), 1.00-0.80 (m including s at δ 0.9, 14 H), 0.01 (s, 6 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 170.0 (s'), 152.3 (s'), 137.8 (d'), 128.0 (s'), 125.5 (s'), 124.6 (s'), 115.8 (t'), 107.5 (s'), 84.6 (d'), 76.6 (d'), 69.0 (d'), 65.4 (t'), 65.2 (t'), 50.2 (d'), 45.5 (d'), 42.0 (d'), 41.0, 40.2, 39.2 (last three signals comprise two t' and one s'), 34.5 (t'), 31.1 (d'), 29.4 (q'), 27.9 (t'), 26.2 (t'), 25.7 (q'), 22.7 (q'), 21.7 (q'), 17.9 (s'), -4.7 (q'), -4.9 (q'); exact mass *m/z* calcd for $C_{14}H_{22}NO_7Si$ (M - *t*-Bu - $C_{16}H_{22}$) 344.11655, found 344.11588. Anal. Calcd for $C_{34}H_{53}NO_7Si$: C 66.31, H 8.67, N 2.27. Found: C 66.49, H 8.97, N 2.23. Compound **19m** had: FTIR (CH_2Cl_2 cast) 1727, 1557 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.36-7.22 (m, 4 H), 7.20-7.13 (m, 1 H), 5.73-5.60 (m, 1 H), 5.10-5.00 (m, 2 H), 4.89 (d, *J* = 12 Hz, 1 H), 4.82-4.74 (m, 1 H), 4.04-3.82 (m, 5 H), 2.32-2.22 (m, 1 H), 2.10-1.75 (m, 5 H), 1.55-1.15 (m including s at δ 1.42 and s at δ 1.30, 9 H), 1.00-0.80 (m including s at δ 0.9, 17 H), 0.05 (s, 3 H), 0.09 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 171.3 (s'), 150.2 (s'), 135.0 (d'), 128.0 (s'), 125.7 (s'), 125.3 (s'), 117.2 (t'), 107.8 (s'), 84.8 (d'), 76.4 (d'), 66.6 (d'), 65.4 (t'), 64.7 (t'), 50.6 (d'), 43.9 (d'), 43.4 (d'), 41.3, 40.2, 37.2 (last three signals comprise two t' and one s'), 34.4 (t'), 31.7 (t'), 31.2 (d'), 30.3 (q'), 27.2 (t'), 25.7 (q'), 23.4 (q'), 21.7 (q'), 18.0 (s'), -4.7 (q'), -4.9 (q'); exact mass *m/z* calcd for $C_{14}H_{22}NO_7Si$ (M - *t*-Bu - $C_{16}H_{22}$) 344.11655, found 344.11601.

[6*S*-(6α,7β,8β,9β)]-9-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-6-nitro-8-(2-propenyl)-1,4-dioxaspiro[4.5]decane-7-methanol (20M), [6*S*-(6α,7β,8β,9α)]-9-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-6-nitro-8-(2-propenyl)-1,4-dioxaspiro[4.5]decane-7 methanol (20m), and establishment of optical purity. The following conditions are better than those reported in reference 1a. A well-insulated cooling bath filled with a magnetically stirred mixture of ethylene glycol and water (1:1) and provided with an immersion cooling coil (Haake, Model EK 51-1) was used for this reaction. It normally took 10 h for the bath to settle at -30 °C (with the instrument set at -50 °C).

DIBAL (1 M in CH_2Cl_2, 49.6 mL, 0.0496 mol) was added over 30 min to a stirred and cooled (-78 °C) solution of **19** (mixture of epimers) (15.25 g, 24.76 mmol) in dry CH_2Cl_2 (400 mL). Stirring was continued for 1 h at -78 °C, and the flask was then transferred to the -30 °C bath. Stirring was continued at -30 °C for 24 h, and a second batch of DIBAL (52 mL, 0.052 mol) was added over 30 min. Stirring at -30 °C was continued for a further 48 h, and the mixture was then quenched by slow (over 5 min) addition of bench MeOH (15 mL). Then Na_2SO_4 (50 g), water (12 mL), and Celite (25 g) were added sequentially at -30 °C with continued stirring. The cold bath was removed and stirring was continued for 1 h. The mixture was filtered through a pad [9 (breadth) x 2.5 (height) cm] of Celite, using EtOAc. Evaporation of the filtrate and flash chromatography of the residue over silica gel (5 x 25 cm), using first 1:9 EtOAc-hexane, gave the pure (^1H NMR, 400 MHz) chiral auxiliary (5.5494 g, 96%). Further elution with 3:22 EtOAc-hexane gave alcohol **20M** (5.090 g, 52%). Continued elution with 13:87 EtOAc-hexane served to elute an impurity, after which elution with 3:17 EtOAc-hexane gave the minor isomeric alcohol (**20m**) (2.592 g, 27%). Compound **20M**

had: (FTIR, ^{1}H NMR, ^{13}C NMR); $[\alpha]_D$ -20.7 (*c* 2.0, CCl_4); exact mass *m/z* calcd for $C_{18}H_{33}NO_6Si$ 387.20770, found 387.20695. Anal. Calcd for $C_{18}H_{33}NO_6Si$: C 55.79, H 8.58, N 3.61. Found: C 55.70, H 8.92, N 3.57. Compound **20m** had: (^{1}H NMR, ^{13}C NMR); FTIR (CH_2Cl_2 cast) 3450 cm^{-1}; exact mass *m/z* calcd for $C_{14}H_{24}NO_6Si$ 330.13730, found 330.13416. Anal. Calcd for $C_{18}H_{33}NO_6Si$: C 55.79, H 8.58, N 3.61. Found: C 55.59, H 8.44, N 3.40.

The optical purity of the two alcohols was established as follows:[14,26] DCC (37.1 mg, 0.18 mmol) was added to a stirred solution of one of the above alcohols (20.0 mg, 0.052 mmol), (*S*)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (42.0 mg, 0.179 mmol) and DMAP (1 mg) in CH_2Cl_2 (3 mL). Reaction was complete after 30 min (TLC control, silica, 4:1 EtOAc-hexane). The solvent was evaporated and the residue was filtered through a small pad of silica gel, using 4:1 EtOAc-hexane. Care was taken to elute all organic products derived from the starting alcohol. The combined fractions were evaporated and examined by ^{19}F NMR. The experiment was done using the optically active major isomer (**20M**), the optically active minor isomer (**20m**), and corresponding racemic materials.[3] The latter showed clearly resolved NMR signals (Δν *ca* 22 and 57 Hz for the major and minor isomers, respectively), and the products from the individual isomers in the optically active series were found to be optically pure. Racemic **20M**: ^{19}F NMR ($CDCl_3$, 188.33 MHz) δ -71.95, -72.07. Optically pure **20M**: ^{19}F NMR ($CDCl_3$, 188.33 MHz) δ -71.95. Racemic **20m**: ^{19}F NMR ($CDCl_3$, 188.33 MHz) δ -71.86, -72.16. Optically pure **20m**: ^{19}F NMR ($CDCl_3$, 188.33 MHz) δ -71.85.

[3*S*-(3α,4aβ,5α,8β,8aβ)]- and [3*R*-(3α,4aα,5β,8α,8aα)]-5-[[(1,1-Dimethylethyl)-dimethylsilyl]oxy]hexahydro-8-nitrospiro[1H-2-benzopyran-7(3H),2'-[1,3]dioxolan]-3-ol (21M).[27] Compounds **21M**: (9.29 g, 92%): (^{1}H NMR, ^{13}C NMR); FTIR (CH_2Cl_2 cast) 3540, 3433 cm^{-1}; exact mass *m/z* calcd for $C_{16}H_{28}NO_7Si$ 374.16351, found 374.16424. Anal. Calcd for $C_{17}H_{31}NO_7Si$: C 52.42, H 8.02, N 3.60. Found: C 52.45, H 8.18, N 3.49.

[3*R*-(3α,4aα,5α,8α,8aα)]- and [3*S*-(3α,4aβ,5α,8β,8aβ)]-5-[[(1,1-Dimethylethyl)-dimethylsilyl]oxy]hexahydro-8-nitrospiro[1H-2-benzopyran-7(3H),2'-[1,3]dioxolan]-3-ol (21m).[27] Compounds **21m**: (5.63 g, 93%): (FTIR, ^{1}H NMR, ^{13}C NMR); exact mass *m/z* calcd for $C_{13}H_{221}NO_7Si$ 332.11655, found 332.11710.

[3*R*-(3α,4aβ,5α,8β,8aβ)]-5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]hexahydro-8-nitrospiro[1H-2-benzopyran-7(3H),2'-[1,3]dioxolan]-3-yl 2,2-Dimethylpropanoate (22M).[27] Compound **22M**: (11.183 g, 99%): (FTIR, ^{1}H NMR, ^{13}C NMR); $[\alpha]_D$ -52.7 (*c* 1.7, CCl_4); exact mass *m/z* calcd for $C_{18}H_{309}NO_8Si$ 416.17407, found 416.17470. Anal. Calcd for $C_{22}H_{39}NO_8Si$: C 55.79, H 8.30, N 2.96. Found: C 55.70, H 8.31, N 2.82.

[3*R*-(3α,4aβ,5β,8β,8aβ)]-5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]hexahydro-8-nitrospiro[1H-2-benzopyran-7(3H),2'-[1,3]dioxolan]-3-yl 2,2-Dimethylpropanoate (22m). *t*-BuCOCl (14.28 mL, 115.9 mmol) was injected over *ca* 30 min into a stirred solution of **21m** (mixture of epimers) (9.020 g, 23.16 mmol) and dry pyridine (18.75 mL, 231.8 mmol) in dry CH_2Cl_2 (200 mL). Stirring was continued at room temperature for 40 h, and then saturated aqueous $NaHCO_3$ (200 mL) was added. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 200 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (5 x 25 cm), using 3:17 EtOAc-hexane, gave the derived pivaloates (10.36 g, 94%) as a pure (^{1}H NMR, 400 MHz) solid, consisting of a 4:1 mixture of **22m** and its C(3) epimer. The epimers were separable by TLC (silica, 1:9 EtOAc-hexane, developed twice). This mixture was fractionally crystallized (1:9 EtOAc-hexane) to obtain a single isomer (**22m**) (5.65 g), and the material in the mother liquor was recycled as described below. In the racemic series only one pivaloate was obtained. Compound **22m** had: (FTIR, ^{1}H NMR, ^{13}C NMR); exact mass *m/z* calcd for $C_{182}H_{30}NO_8Si$ (M - *t*-Bu) 416.17407, found 416.17360. Anal. Calcd for $C_{22}H_{39}NO_8Si$: C 55.79, H 8.30, N 2.96. Found: C 55.95, H 8.49, N 3.05.

[3*R*-(3α,4aα,5α,8α,8aα)]- and [3*S*-(3α,4aβ,5α,8β,8aβ)]-5-[[(1,1-Dimethylethyl)-dimethylsilyl]oxy]hexahydro-8-nitrospiro[1H-2-benzopyran-7(3H),2'-[1,3]dioxolan]-3-ol (21m) from the C(3)-epimer of 22m. The mother liquor from the above experiment was evaporated, and flash chromatography of the residue over silica gel (4 x 20 cm), using 3:17 EtOAc-hexane, gave a 1:1 mixture of epimeric pivaloates.

DIBAL-H (1 M in CH_2Cl_2, 29.44 mL, 0.02944 mol) was added dropwise by syringe over *ca* 20 min to a stirred and cooled (-78 °C) solution of the above pivaloates (4.280 g, 9.036 mmol) in dry CH_2Cl_2 (200 mL). Stirring at -78 °C was continued for 30 min, and then MeOH (5 mL) was added slowly (over *ca* 2 min), followed successively by Na_2SO_4 (6 g), Celite (16 g), and water (6 mL). The cold bath was removed, and stirring was continued for 30 min. The mixture was then filtered through a pad (2 x 7 cm) of Celite, and the solid was washed with EtOAc. Evaporation of the filtrate, and flash chromatography of the residue over silica gel (3 x 24 cm), using 1:4 EtOAc-hexane, gave **21m** (2.94 g, 83%) as a pure (TLC, silica, 1:1 EtOAc-hexane), white solid, consisting (^{1}H NMR, 400 MHz) of a 1:1 mixture of epimers.

[3*R*-(3α,4aβ,5α,8β,8aβ)]-8-Amino-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]hexahydrospiro[1H-2-benzopyran-7(3H),2'-[1,3]dioxolan]-3-yl 2,2-Dimethylpropanoate

(23M).[27] Compound **23M**: (4.59 g, 99%): (FTIR, ^{1}H NMR, ^{13}C NMR); $[\alpha]_D$ -17.8 (*c* 2.3, CCl_4); exact mass *m/z* calcd for $C_{22}H_{41}NO_6Si$ 443.27032, found 443.26995.

[3*R*-(3α,4aβ,5β,8β,8aβ)]-8-Amino-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]hexahydrospiro[1H-2-benzopyran-7(3H),2'-[1,3]dioxolan]-3-yl 2,2-Dimethylpropanoate (23m).[27] Compound **23m**: (702.8 mg, 98%): (FTIR, ^{1}H NMR, ^{13}C NMR); exact mass *m/z* calcd for $C_{22}H_{41}NO_6Si$ 443.27032, found 443.27023.

[3*R*-(3α,4aβ,5α,8β,8aβ)]-5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]hexahydro-8-[[(2-propenyloxy)carbonyl]amino]spiro[1H-2-benzopyran-7(3H),2'-[1,3]dioxolan]-3-yl 2,2-Dimethylpropanoate (24M). The procedure used with the corresponding racemic compound was followed, except that the proportions of allyl chloroformate and pyridine were doubled. The reagents were each added in two equal portions, the second portion after 1 h. Compound **24M**: (6.85 g, 90%): (^{1}H NMR, ^{13}C NMR); $[\alpha]_D$ -37.7 (*c* 2.2, CCl_4); FTIR (CH_2Cl_2 cast) 3357, 1739 cm^{-1}; exact mass *m/z* calcd for $C_{26}H_{45}NO_8Si$ 527.29144, found 527.29190. Anal. Calcd for $C_{26}H_{45}NO_8Si$: C 59.18, H 8.59, N 2.65. Found: C 59.22, H 8.63, N 2.56.

[3*R*-(3α,4aβ,5β,8β,8aβ)]-5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]hexahydro-8-[[(2-propenyloxy)carbonyl]amino]spiro[1H-2-benzopyran-7(3H),2'-[1,3]dioxolan]-3-yl 2,2-Di-methylpropanoate (24m).[27] Compound **24m**: (815.1 mg, 91%): (FTIR, ^{1}H NMR, ^{13}C NMR); exact mass *m/z* calcd for $C_{22}H_{36}NO_8Si$ (M - *t*-Bu) 470.22101, found 470.21974. Anal. Calcd for $C_{26}H_{45}NO_8Si$: C 59.18, H 8.59, N 2.65. Found: C 59.15, H 8.87, N 2.59.

[3*R*-(3α,4aβ,5α,8β,8aβ)]-Hexahydro-5-hydroxy-8-[[(2-propenyloxy)carbonyl]amino]spiro[1H-2-benzopyran-7(3H),2'-[1,3]dioxolan]-3-yl 2,2-Dimethylpropanoate (25M).[27] Compound **25M**: (11.040g, 99%): (FTIR, ^{1}H NMR, ^{13}C NMR); $[\alpha]_D$ -57.6 (*c* 2.2, EtOH); exact mass *m/z* calcd for $C_{16}H_{26}NO_5$ (M - *t*-Bu) 312.18109, found 312.18023. Anal. Calcd for $C_{20}H_{31}NO_8$: C 58.08, H 7.56, N 3.39. Found: C 58.08, H 7.77, N 3.29.

[3*R*-(3α,4aβ,5β,8β,8aβ)]-Hexahydro-5-hydroxy-8-[[(2-propenyloxy)carbonyl]amino]spiro[1H-2-benzopyran-7(3H),2'-[1,3]dioxolan]-3-yl 2,2-Dimethylpropanoate (25m).[27] Compound **25m**: (178.5 mg, 84%): (FTIR, ^{1}H NMR, ^{13}C NMR); exact mass *m/z* calcd for $C_{20}H_{31}NO_8$ 413.20496, found 413.20450.

[3*R*-(3α,4aβ,8β,8aβ)]-Hexahydro-5-oxo-8-[[(2-propenyloxy)carbonyl]amino]spiro-[1H-2-benzopyran-7(3H),2'-[1,3]dioxolan]-3-yl 2,2-Dimethylpropanoate (26) from 25M.[27] Compound **26**: (2.36 g, 88%): ^{1}H NMR, ^{13}C NMR); $[\alpha]_D$ -5.4 (*c* 1.9, CCl_4); FTIR (CH_2Cl_2 cast) 3354, 1722 cm^{-1}; exact mass *m/z* calcd for $C_{20}H_{29}NO_8$ 411.18933, found 411.18996. Anal. Calcd for $C_{20}H_{29}NO_8$: C 58.38, H 7.10, N 3.40. Found: C 58.07, H 7.27, N 3.46.

[3*R*-(3α,4aβ,8β,8aβ)]-Hexahydro-5-oxo-8-[[(2-propenyloxy)carbonyl]amino]spiro-[1H-2-benzopyran-7(3H),2'-[1,3]dioxolan]-3-yl 2,2-Dimethylpropanoate (26) from 25m.[27] Compound **26**: (869 mg, 82%).

[3*R*-(3α,4aβ,5β,8β,8aβ)]-Hexahydro-5-hydroxy-8-[[(2-propenyloxy)carbonyl]amino]-5-[(trimethylsilyl)ethynyl]spiro[1H-2-benzopyran-7(3H),2'-[1,3]dioxolan]-3-yl 2,2-Dimethylpropanoate (27).[27] Compound **27**: (2.810 g, 87%): (FTIR, ^{1}H NMR, ^{13}C NMR); exact mass *m/z* calcd for $C_{20}H_{30}NO_6Si$ (M - *t*-$BuCO_2$) 408.18423, found 408.18463. Anal. Calcd for $C_{25}H_{39}NO_8Si$: C 58.92, H 7.71, N 2.75. Found: C 58.66, H 7.68, N 2.53.

[3*R*-(3α,4aβ,5β,8β,8aβ)]-5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]hexahydro-8-[[(2-propenyloxy)carbonyl]amino]-5-[(trimethylsilyl)ethynyl]spiro[1H-2-benzopyran-7(3H),2'-[1,3]dioxolan]-3-yl 2,2-Dimethylpropanoate (28).[27] Compound **28**: (4.460 g, 99%): (FTIR, ^{1}H NMR, ^{13}C NMR); $[\alpha]_D$ -28.7 (*c* 2.2, CCl_4); exact mass *m/z* calcd for $C_{27}H_{44}NO_8Si_2$ (M - *t*-Bu) 566.26056, found 566.26149. Anal. Calcd for $C_{31}H_{53}NO_8Si_2$: C 59.68, H 8.56, N 2.26. Found: C 59.67, H 8.96, N 2.13.

2-Propenyl [3*R*-(3α,4aα,5α,8α,8aα)]- and [3*S*-(3α,4aβ,5β,8β,8aβ)]-[5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]hexahydro-3-hydroxy-5-[(trimethylsilyl)ethynyl]spiro-[1H-2-benzopyran-7(3H),2'-[1,3]dioxolan]-8-yl]carbamate (29).[27] Compounds **29**: (6.880 g, 97%): (FTIR, ^{1}H NMR, ^{13}C NMR); exact mass *m/z* calcd for $C_{22}H_{36}NO_7Si_2$ (M - *t*-Bu) 482.20303, found 482.20252. Anal. Calcd for $C_{26}H_{45}NO_7Si_2$: C 57.85, H 8.40, N 2.59. Found: C 57.59, H 8.56, N 2.47.

2-Propenyl [4a*S*-(4aα,5α,8α,8aα)]-[5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]hexahydro-3-oxo-5-[(trimethylsilyl)ethynyl]spiro[1H-2-benzopyran-7(3H),2'-[1,3]dioxolan]-8-yl]carbamate (30).[27] Compound **30**: (3.1548 g, 92%): (FTIR, ^{1}H NMR, ^{13}C NMR); $[\alpha]_D$ 19.8 (*c* 2.6, CCl_4); exact mass *m/z* calcd for $C_{25}H_{40}NO_7Si_2$ (M - CH_3) 522.23431, found 522.23378. Anal. Calcd for $C_{26}H_{43}NO_7Si_2$: C 58.07, H 8.06, N 2.60. Found: C 58.06, H 8.17, N 2.64.

2-Propenyl [5*R*-(5α,8α,8aα)]-[5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-5,6,8,8a-tetrahydro-3-oxo-5-[(trimethylsilyl)ethynyl]spiro[1H-2-benzopyran-7(3H),2'-[1,3]-dioxolan]-8-yl]carbamate (31).[27] Compound **31**: (476.1 mg, 81% over two steps): (FTIR, ^{1}H NMR,

^{13}C NMR); exact mass *m/z* calcd for $C_{22}H_{32}NO_7Si_2$ (M - *t*-Bu) 478.17172, found 478.17048. Some starting material (**30**) (20 mg, 3.4%) was also recovered.

[5*R*-(5α,8α,8aα)]-8-Amino-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-5,6,8,8a-tetrahydro-5-[(trimethylsilyl)ethynyl]spiro[1H-2-benzopyran-7(3H),2'-[1,3]dioxolan]-3-one (32).[27] Compound **32**: (554.2 mg, 92%): (FTIR, ^{1}H NMR, ^{13}C NMR); exact mass *m/z* calcd for $C_{22}H_{37}NO_5Si_2$ 451.22104, found 451.22019.

(5*R*)-8-Amino-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-5,6-dihydro-5-[(trimethylsilyl)ethynyl]spiro[1H-2-benzopyran-7(3H),2'-[1,3]dioxolan]-3-one (33).[27] Compound **33**: (920 mg, 90% over two steps): (FTIR, ^{1}H NMR, ^{13}C NMR); exact mass *m/z* calcd for $C_{22}H_{35}NO_5Si_2$ 449.20538, found 449.20462. Some starting amine (15 mg, 2.7 %) was recovered.

Methyl 5*R*-[5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-5,6-dihydro-3-oxo-5-[(trimethylsilyl)ethynyl]spiro[1H-2-benzopyran-7(3H),2'-[1,3]dioxolan]-8-yl]carbamate (34).[27] Compound **34**: (1.555 g, 95%): (FTIR, ^{1}H NMR, ^{13}C NMR); $[\alpha]_D$ 52.5 (*c* 2.0, CCl_4); exact mass *m/z* calcd for $C_{24}H_{37}NO_7Si_2$ 507.21085, found 507.21096.

Methyl 1*R*-*cis*- and 1*S*-*trans*-[1-Bromo-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-5,6-dihydro-3-oxo-5-[(trimethylsilyl)ethynyl]spiro[1H-2-benzopyran-7(3H),2'-[1,3]-dioxolan]-8-yl]carbamate (35).[27] The total brominated product obtained from lactone **34** (110 mg) was used directly in the next step.

Methyl (8*E*,9*R*)-[9-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-9-ethynyl-7-formyl-6-[(methoxycarbonyl)amino]-1,4-dioxaspiro[4.5]dec-6-en-8-ylidene]acetate (36).[27] Compound **36**: (80 mg, 79% over three steps): (FTIR, ^{1}H NMR, ^{13}C NMR); mp 123-125 °C; exact mass *m/z* calcd for $C_{22}H_{31}NO_8Si$ 465.18188, found 465.18071.

Methyl 1*S*-*trans*-[5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-5-ethynyl-5,6-dihydro-3-oxo-1-[(trimethylsilyl)ethynyl]spiro[1H-2-benzopyran-7(3H),2'-[1,3]dioxolan]-8-yl]carbamate (37).[27] Compound **37**: (351 mg, 92%): (FTIR, ^{1}H NMR, ^{13}C NMR); mp 152-154 °C; $[\alpha]_D$ 254 (*c* 0.8, CCl_4); exact mass *m/z* calcd for $C_{26}H_{37}NO_7Si_2$ 531.21088, found 531.21220.

Methyl 1*S*-*trans*-[5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-1,5-diethynyl-5,6-dihydro-3-oxospiro[1H-2-benzopyran-7(3H),2'-[1,3]dioxolan]-8-yl]carbamate (38) and Methyl 1*S*-*cis*-[5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-1,5-diethynyl-5,6-dihydro-3-oxospiro[1H-2-benzopyran-7(3H),2'-[1,3]dioxolan]-8-yl]carbamate (38').[27] Compound **38**: (159 mg, 46%): (FTIR, ^{1}H NMR, ^{13}C NMR); $[\alpha]_D$ -239 (*c* 1.4, CH_2Cl_2); exact mass *m/z* calcd for $C_{23}H_{29}NO_7Si$ 459.17133, found 459.17062. Compound **38'**: (145 mg, 42%): (FTIR, ^{1}H NMR, ^{13}C NMR); exact mass *m/z* calcd for $C_{23}H_{29}NO_7Si$ 459.17133, found 459.17095.

Methyl 1*S*-*trans*-[5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-1,5-diethynyl-5,6-dihydro-3-oxospiro[1H-2-benzopyran-7(3H),2'-[1,3]dioxolan]-8-yl]carbamate (38) from 38'. The procedure used with the corresponding racemic compound was followed, except that the reaction time was shortened to 10 min. Compound **38**: (18 mg, 43.5%) and recovered **38'** (23.3 mg, 56%). Use of a longer reaction time gives a poor yield.

Methyl 1*S*-*trans*-[5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-5,6-dihydro-1,5-bis-(iodoethynyl)-3-oxospiro[1H-2-benzopyran-7(3H),2'-[1,3]dioxolan]-8-yl]carbamate (39).[27] Compound **39**: (191 mg, 88%): (^{1}H NMR, ^{13}C NMR); mp >210 °C dec; $[\alpha]_D$ -170 (*c* 0.6, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 3292, 2181, 1720 cm^{-1}; exact mass *m/z* calcd for $C_{23}H_{27}I_2NO_7Si$ 710.96466, found 710.96470.

Methyl [1'*S*-(1'*R,5'*S**,11'*Z*)]-[5'[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-5',6'-dihydro-3'-oxospiro[1,3-dioxolane-2,7'(3'H)-[1,5][3]hexene[1,5]diyno[1H-2]benzopyran]-8'-yl]carbamate (40).**[27] Compound **40**: (57.2 mg, 65%): (FTIR, ^{1}H NMR, ^{13}C NMR); mp >225 °C dec.; $[\alpha]_D$ -703 (*c* 1.0 CH_2Cl_2); exact mass *m/z* calcd for $C_{25}H_{29}NO_7Si$ 483.17133, found 483.17087.

Methyl [1*S*-(1'*R,3'*R**,5'*S**,11'*Z*)]- and [1*S*-(1'*R**,3'*S**,5'*S**,11'*Z*)]-[5'-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-5',6'-dihydro-3'-hydroxyspiro[1,3-dioxolane-2,7'(3'H)-[1,5][3]hexene[1,5]diyno[1H-2]benzopyran]-8'-yl]carbamate (41).**[27] Compounds **41**: (48 mg, 95%): (FTIR, ^{1}H NMR); mp >220 °C dec.; $[\alpha]_D$ -588 (*c* 0.5, CH_2Cl_2); exact mass *m/z* calcd for $C_{25}H_{31}NO_7Si$ 485.18698, found 485.18782.

Methyl [1*S*-(1'*R,3'*R**,5'*S**,11'*Z*)]- and [1*S*-(1'*R**,3'*S**,5'*S**,11'*Z*)]-[5',6'-Dihydro-3',5'-dihydroxyspiro[1,3-dioxolane-2,7'(3'H)-[1,5][3]hexene[1,5]diyno[1H-2]-benzopyran]-8'-yl]carbamate (42).**[27] Compounds **42**: (26 mg, 89%): (FTIR, ^{1}H NMR); exact mass HRFAB *m/z* calcd for $C_{19}H_{17}NO_7Na$ (M + Na) 394.09027, found 394.09072.

Methyl [1*R*-(1*R,4*Z*,8*S**,13*E*)]-[1,8-dihydroxy-13-(2-hydroxyethylidene)spiro-[bicyclo[7.3.1]trideca-4,9-diene-2,6-diyne-11,2'-[1,3]dioxolan]-10-yl]carbamate (43).**[27] Compound **43**: (20.6 mg, 78%): (FTIR, ^{1}H NMR); exact mass HRFAB *m/z* calcd for $C_{19}H_{19}NO_7Na$ (M + Na) 396.10592, found 396.10500.

Methyl [1*R*-(1*R,4*Z*,8*S**,13*E*)]-[1-Hydroxy-8-[(triethylsilyl)oxy]-13-[2-[(triethylsilyl)oxy]ethylidene]spiro[bicyclo[7.3.1]-trideca-4,9-diene-2,6-diyne-11,2'-[1,3]dioxolan]-10-yl]carbamate (44).**[27] Compound **44**: (33 mg, 93%): (^{1}H NMR); $[\alpha]_D$ -177 (*c* 0.4, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 3412, 3359, 1741, 1712 cm^{-1}; exact mass *m/z* calcd for $C_{31}H_{47}NO_7Si_2$ 601.28912, found 601.28947.

Methyl [1*R*-(1*R,4*Z*,8*S**,13*E*)]-[1-Hydroxy-13-(2-hydroxyethylidene)-8-[(triethylsilyl)oxy]spiro[bicyclo[7.3.1]trideca-4,9-diene-2,6-diyne-11,2'-[1,3]dioxolan]-10-yl]-carbamate (45).** Compound **45**: (25 mg, 93%): (FTIR, ^{1}H NMR); $[\alpha]_D$ -237.5 (*c* 0.3, CH_2Cl_2); exact mass HRFAB *m/z* calcd for $C_{25}H_{31}O_7NSiNa$ (M + Na) 510.19240, found 510.19437.

[1*R*(1*R,4*Z*,8*S**,13*E*)-*S*-[2-[1-Hydroxy-10-[(methoxycarbonyl)amino]-8-[(triethylsilyl)oxy]spiro[bicyclo[7.3.1]trideca-4,9-diene-2,6-diyne-11,2'-[1,3]dioxolan]-13-ylidene]ethyl] ethanethioate (46).**[27] Compound **46**: (7.8 mg, 94%): (FTIR, ^{1}H NMR); $[\alpha]_D$ -128 (*c* 0.4, CH_2Cl_2); exact mass *m/z* calcd for $C_{27}H_{35}O_7NSSi$ 545.19037, found 545.18918.

Methyl [1*R*-(1*R,4*Z*,8*S**,13*E*)]-[1-hydroxy-13-(2-mercaptoethylidene)-8-[(triethylsilyl)oxy]spiro[bicyclo[7.3.1]trideca-4,9-diene-2,6-diyne-11,2'-[1,3]dioxolan]-10-yl]carbamate (47).**[27] The product obtained from **46** (8.8 mg) was chromatographed and used immediately, without characterization.

Methyl [1*R*-(1*R,4*Z*,8*S**,13*E*)]-[1-Hydroxy-13-[2-(methyltrithio)ethylidene]-8-[(triethylsilyl)oxy]spiro[bicyclo[7.3.1]trideca-4,9-diene-2,6-diyne-11,2'-[1,3]dioxolan]-10-yl]-carbamate (48).** Compound **48**: (8.1 mg, 86% over two steps): (FTIR, ^{1}H NMR); $[\alpha]_D$ -154 (*c* 0.3, CH_2Cl_2); exact mass HRFAB *m/z* calcd for $C_{26}H_{35}NO_6S_3SiNa$ (M + Na) 604.12935, found 604.12884.

Methyl [1*R*-(1*R,4*Z*,8*S**,13*E*)]-[1,8-Dihydroxy-13-[2-(methyltrithio)ethylidene]-11-oxobicyclo[7.3.1]trideca-4,9-diene-2,6-diyne-10-yl]carbamate (1) [(-)-calicheamicinone)].** TsOH.H_2O (5.30 mg, 0.028 mmol) was added to a stirred solution of **48** (8.1 mg, 0.014 mmol) in a mixture of THF (0.6 mL) and water (1 drop), and stirring was continued at room temperature for 8 h, the flask being wrapped in aluminum foil. (The foil wrapping and shorter reaction time are the only differences from the experiment done in the racemic series, in which we had used a reaction period of 16 h and had also monitored the reaction by TLC.) Hexane (1 mL) was added, and the mixture was applied directly to a flash chromatography column (0.6 x 8 cm) packed with silica gel, a little 1:1 Et_2O-hexane being used as a rinse. The column was developed with 1:1 Et_2O-hexane, to obtain pure (^{1}H NMR, 400 MHz) (-)-calicheamicinone (**1**) (4.8 mg, 81%) as a white solid: (FTIR, ^{1}H NMR); mp >125 °C, decomp.; $[\alpha]_D$ -509 (*c* 0.2, CH_2Cl_2);[28] exact mass HRFAB *m/z* calcd for $C_{18}H_{17}NO_5S_3Na$ (M + Na) 446.01658, found 446.01698. The material was used for an X-ray structure determination.

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References and footnotes

† This synthesis was first reported on the 26th February, 1998 at a Conference (Kuredu Island, Maldive Islands) intended as an 80th Birthday Tribute to Professor D. H. R. Barton, FRS. Sadly, the work must now be dedicated to the memory of this great scientist.

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