16-6; **35** (6-*endo*-Me_3Si), 89657-11-4; **35** (6-*exo*-Me_3Si), 89657-12-5; **36**, 89657-13-6; **37**, 89657-14-7; *cis*-**38**, 89657-15-8; *trans*-**38**, 89657-16-9; *cis*-**39** (isomer 1), 89657-17-0; *cis*-**39** (isomer 2), 89708-66-7; *trans*-**39** (isomer 1), 89708-67-8; *trans*-**39** (isomer 2), 89708-68-9; **40**, 89657-18-1; **41**, 71342-13-7; **42**, 89657-19-2; **43**, 53723-46-9; (*E*)-**46**, 89657-21-6; (*Z*)-**46**, 89657-22-7; **48**, 87729-87-1; LDMAN, 74379-76-3; $(CH_3)_2C(SPh)_2$, 14252-46-1; $(CH_3)_2C(OMe)_2$, 77-76-9; $CH_3CH_2CH(SPh)_2$, 15486-58-5; CH_3CH_2CHO, 123-38-6; c-$C_6H_{11}CH(SPh)_2$, 54905-14-5; c-$C_6H_{11}CHO$, 2043-61-0; Me_3SiCl, 75-77-4; CH_3CHO, 75-07-0; $MeOC_6H_4$-*p*-CHO, 123-11-5; *n*-$C_6H_{13}CHO$, 111-71-7; *n*-$C_5H_{11}CHO$, 66-25-1; $CH_2{=}C(CH_3)CHO$, 78-85-3; KH, 7693-26-7; 1-(dimethylamino)naphthalene, 86-56-6; 1,1-bis(phenylthio)-4-*tert*-butylcyclohexane, 85895-63-2; 4-*tert*-butylcyclohexanone, 98-53-3; *exo*-7-(phenylthio)norcarane, 89657-20-5; *endo*-7-(phenylthio)norcarane, 37942-20-4.

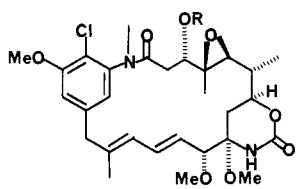
Stereocontrolled Total Synthesis of (-)-Maytansinol

Masato Kitamura, Minoru Isobe,* Yoshiyasu Ichikawa, and Toshio Goto

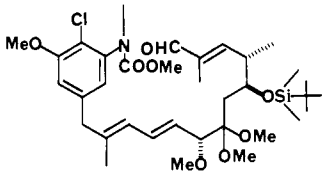
Contribution from the Laboratory of Organic Chemistry, Faculty of Agriculture, Nagoya University, Chikusa, Nagoya 464, Japan. *Received September 14, 1983. Revised Manuscript Received January 25, 1984*

Abstract: Chiral maytansinol (**1**) was synthesized stereoselectively from D-mannose. Asymmetric centers of **1** were induced intramolecularly from an asymmetric carbon corresponding to C-7 via the common key intermediate **3** for maytansinoids. Key points are (i) the usage of a carbohydrate as a chiral template for acyclic asymmetric induction and (ii) a remote stereochemical control in aldol reaction to elaborate the C-3 asymmetric center by intramolecular asymmetric induction.

Maytansinol (**1**) is the key compound in preparing ansa macrolactams such as maytansine (**2a**) found in *Maytenus serrata*,[1]



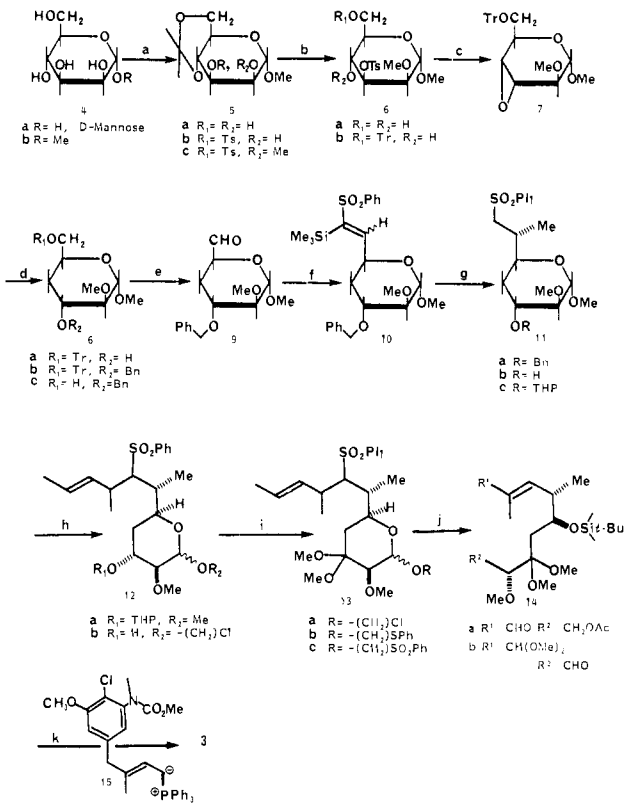
1 R= H
2a R= COCHMeNMeAc
b R= $COCHMe_2$



3

ansamitosin (**2b**) found in *Nocardia* sp. C-15003(N-1),[2] and others, which have remarkable antitumor activity with different accompanying toxicity depending upon the ester side chain at C-3 position.[3] We have recently reported the total synthesis of racemic maytansinol in a highly stereocontrolled manner involving diastereotopic induction of all the asymmetric centers of (±)-**1** from only one asymmetric carbon corresponding to C-7.[4] This success prompted us to the studies on the synthesis of optically active **1** via the same key intermediate **3** as the racemic case.

Scheme I[a]



[a] (a) $(CH_3)_2C(OMe)_2$-PPTS, TsCl/Py, NaH-MeI; (b) H^+, TrCl-Py; (c) *t*-BuOK/THF; (d) super hydride, BnBr-NaH, H^+; (e) $(COCl)_2$/Me_2SO/Et_3N; (f) $PhS(Me_3Si)_2CLi$/THF, *m*-CPBA; (g) MeLi/THF, KF-MeOH, H_2/Pd-black, DHP-PPTS; (h) *n*-BuLi-4-bromopent-2-ene/THF-HMPA, CSA/$HOCH_2CH_2Cl$; (i) CrO_3-2Py, CSA/HC-$(OMe)_3$-MeOH, PhSNa, *m*-CPBA; (j) $NaBH_4$, AcCl/Py, *t*-$BuMe_2$-SiCl-imidazole/DMF, O_3/CH_2Cl_2, Et_3N; (k) PPTS/$CH(OMe)_3$-MeOH, NaOMe/MeOH, CrO_3-2Py, **15**/THF-DMF (2:1), AcOH-$THF-H_2O$ (4:1:1).

Synthesis of the Chiral Key Intermediate (-)-3. The key intermediate (-)-**3** was prepared from D-mannose (**4a**) both as the chiral starting material and as the chiral template for the induction

(1) Kupchan, S. M.; Komoda, Y.; Branfman, A. R.; Sneden, A. T.; Court, W. A.; Thomas, G. J.; Hintz, H. P. J.; Smith, R. M.; Karim, A.; Howie, G. A.; Verma, A. K.; Nagao, Y.; Dailey, R. G., Jr.; Zimmerly, V. A.; Sumner, W. C. Jr. *J. Org. Chem.* **1977**, *42*, 2349.

(2) Asai, M.; Mizuta, E.; Izawa, M.; Haibara, K.; Kishi, T. *Tetrahedron* **1979**, *35*, 1079.

(3) (a) Komoda, Y.; Kishi, T. "Anticancer Agents Based on Natural Product Models"; Ed. Cassady, J. M., Douros, J. D., Eds.; Academic Press: New York, 1980; Chapter 10, pp 353-389. (b) Corey, E. J.; Hua, D. H.; Seitz, S. P. *Tetrahedron Lett.* **1984**, *25*, 3.

(4) (a) Isobe, M.; Kitamura, M.; Goto, T. *J. Am. Chem. Soc.* **1982**, *104*, 4997. (b) Kitamura, M.; Isobe, M.; Ichikawa, Y.; Goto, T., manuscript submitted for publication in *J. Org. Chem.* (c) Other synthetic works, see the following papers and the references cited therein: Meyers, A. I.; Reider, P. J.; Campbell, A. L. *J. Am. Chem. Soc.* **1980**, *102*, 6597. Corey, E. J.; Weigel, L. O.; Chamberlin, A. R.; Cho, H.; Hua, D. H. *J. Am. Chem. Soc.* **1980**, *102*, 6615.

0002-7863/84/1506-3252$01.50/0

of the asymmetric centers as summarized in Scheme I. Methyl D-mannopyranoside (**4b**) was converted (with 2,2-dimethoxypropane in DMF at 5 °C for 36 h in the presence of pyridinium *p*-toluenesulfonate) into the crystalline 4,6-monoacetonide **5a** [mp 103 °C, $[\alpha]_D$ +73.6° ($CHCl_3$) and +60.3° (MeOH)].[5] The two hydroxy groups of **5a** at C-2 and C-3 were selectively tosylated [with *p*-tosyl chloride in CH_2Cl_2 and pyridine (2:1), **5b**] and then methylated (with methyl iodide and NaH in THF, **5c**, mp 116 °C, 60% yield), respectively. In this case, little pinacolone-type rearrangement was observed. Hydrolysis of the acetonide of **5b** with Dowex 50W (H^+) in MeOH afforded **6a** (mp 99 °C) in quantitative yield. Monotritylation of the diol **6a** (with trityl chloride in pyridine at 70 °C for 1.5 h) gave **6b** (mp 156 °C), which was cyclized to the epoxide **7** with KO-*t*-Bu in THF at 0 °C for 30 min (86% yield). Reductive opening of the epoxide **7** was effected with $LiBHEt_3$ at −20 °C for 5 days and then at room temperature to afford **8a**. The hydride attacked largely at the quasi-equatorial C-4 position with a little attack at C-3 (in a ratio of 7:1), but these isomers were not separated at this stage. After the hydroxy group in **8a** was protected as the benzyl ether (**8b**) (with benzyl chloride with NaH in THF and Me_2SO at room temperature for 1 day), the trityl group of **8b** was hydrolyzed with HCl in $CHCl_3$ by stirring overnight at room temperature and then purified to give the alcohol **8c** in 67% overall yield from **7**. **8c** was oxidized with CrO_3–2Py in CH_2Cl_2 to the aldehyde **9** (69% yield). The aldehyde could also be made by Swern oxidation in higher yield.[6] Condensation of **9** with [bis(trimethylsilyl)(phenylsulfenyl)methyl]lithium in a mixture of THF–hexane (3:2), at −45 °C for 5 min and at room temperature for 30 min, was followed by oxidation with MCPBA and gave the heteroolefin **10** (72% yield), the geometry of the heteroolefin being a mixture of *E* and *Z* isomers. Although it was not necessary to separate these isomers for the following step, a part of the sample was purified for analysis to give crystalline (*E*)-**10** (mp 138 °C). The mixture of isomers (**10**) was mixed with MeLi in THF at −78 °C for 30 min and then with KF in a mixture of hot MeOH and CH_2Cl_2 to afford a single (exceeding 99% purity) isomer **11a** in quantitative yield.

The following steps are concerned with some necessary protecting group manipulation on the way to aldehyde **14**. The protective group R of **11** was converted from benzyl to THP ether in two steps, involving first hydrogenolysis of **11a** with Pd-black under H_2 for 2 days in refluxing EtOH containing AcOH and, second, protection of the resultant alcohol (**11b** in 97.5% yield) with dihydropyran in CH_2Cl_2 in the presence of PPTS to give **11c**. Compounds **11c**–**13c** were a mixture of diastereoisomers and were used without chromatographic purification. Alkylation of **11c** with *n*-BuLi and 4-bromopent-2-ene gave **12a**, which was treated with 2-chloroethanol and trimethyl orthoformate in the presence of *dl*-10-camphorsulfonic acid (CSA) giving **12b**. After the alcohol **12b** had been oxidized to the corresponding ketone with CrO_3–2Py in CH_2Cl_2 and then ketalized into the dimethyl ketal (**13a**) with trimethyl orthoformate in MeOH in the presence of CSA, the glycosidic group of **13a** was converted into a base-labile (phenylsulfonyl)ethyl glycoside (**13c**) in two steps involving substitution with NaSPh followed by oxidation with MCPBA. Treatment of **13c** with $NaBH_4$ in refluxing EtOH containing THF afforded a diol, which was monoacetylated and then silylated. Subsequent ozonolysis and reduction of the ozonide with Et_3N (used as reducing agent and at the same time as promoter of elimination of the $PhSO_2$ group) produced the pure unsaturated aldehyde (**14a**) in 38% overall yield in seven steps from **11b**. The stereochemically pure **14a**, $[\alpha]_D$ +26.9°, was shown to be structurally identical with the racemic **14a**, which contains three properly oriented asymmetric carbons. After ketalization of the aldehyde **14a**, the ketal

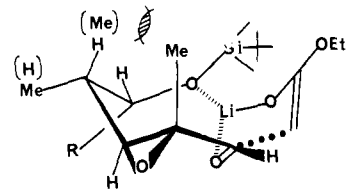
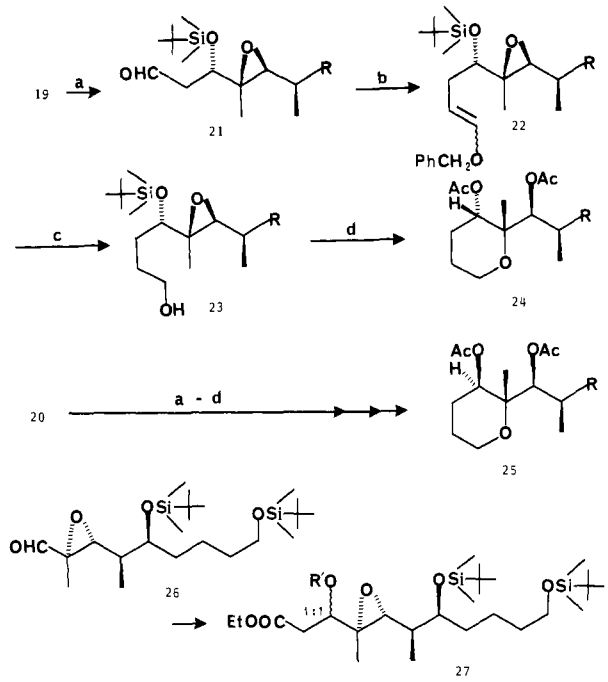


Figure 1.

Scheme II[a]



[a] (a) LAH/THF; CrO_3–2Py. (b) $Ph_3P{=}CHOCH_2Ph$/THF; (c) 0.1 N HCl–THF (1:5); $PhCOCl/Et_3N$–CH_2Cl_2; H_2/Pd-C; (d) CSA/MeOH; Ac_2O/Py.

was converted into the key intermediate **3**, first by hydrolysis of the acetate and oxidation to the aldehyde **14b** and then by condensation with the aromatic counterpart **15** and final hydrolysis of the acetal to **3**.[7]

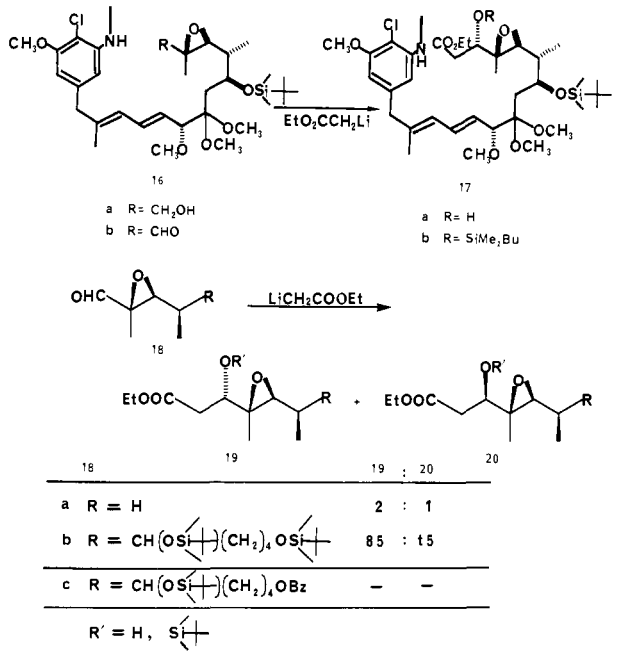
Remote-Controlled Aldol Reaction to α-Epoxy Aldehydes and Anti Selectivity. The conversion of the key intermediate **3** into the epoxy aldehyde **16** was accomplished by (i) reduction of the aldehyde with $NaBH_4$, (ii) hydrolysis with KOH (**3b**), (iii) diastereoselective epoxidation with *tert*-butyl hydroperoxide in the presence of Ti(IV) (**16a**), and (iv) oxidation with SO_3–Py (**16b**).[7] The aldol reaction of (−)-**16b** with lithium ethyl acetate and protection of the resulting hydroxy group afforded (−)-**17b**, which was the only isolable stereoisomer. This unusually high selectivity was found to be effected by C-7 oxygen atom with its taking part in chelation at the transition state (Figure 1) in the aldol reaction. This was concluded from the following comparison experiments.

The first example used the epoxy aldehyde **18a** (R = H), which was treated with lithium ethyl acetate (generated with LDA) at −78 °C in THF to produce a mixture of **19a** and **20a** (R′ = H). After the hydroxy group was protected as the *tert*-butyldimethylsilyl ether, the mixture was separated by silica gel TLC to give anti isomer **19a** and syn isomer **20a** (R′ = $SiMe_2Bu$) in a ratio of 2:1. The major isomer **19a** was converted as shown in Scheme II into a six-membered cyclic compound. This transformation involves the addition of one carbon fragment to **21** by a Wittig reaction (**22**) and six-membered ether ring formation (**23** → **24**) with concomitant opening of the epoxide ring. Compound **24a** showed the ^1H NMR signal corresponding to C-3

(5) The value in $CHCl_3$ was consistent with that of Evans' $[\alpha]_D$ +73° (*c* 0.99); see: Evans, M. E.; Parrish, F. W. *Carbohydr. Res.* **1977**, *54*, 105. C. L. Stevens et al. reported the optical rotation of **5a** as +68.3° (c 1.15 in MeOH), see: Stevens, C. L.; Glinski, R. P.; Taylor, K. G.; Suokman, F. *J. Org. Chem.* **1970**, *35*, 592. Isobe, M.; Ichikawa, Y.; Kitamura, M.; Goto, T. *Chem. Lett.* **1981**, 457.

(6) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *3*, 2480.

(7) The experimental detail of the procedure from **14** to **3** via **15** is the same as for the racemic case described in ref 4b.



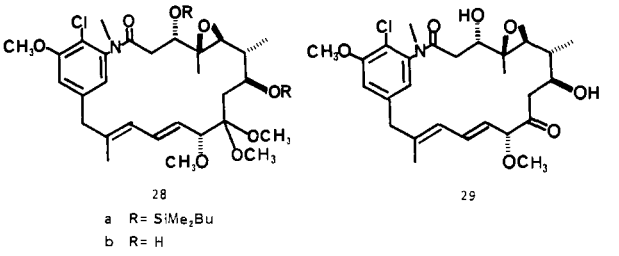
position at δ 4.72 ppm (dd, J = 3.5, 2.5 Hz). The major isomer **20a** was similarly converted into **25a** showing the corresponding proton at δ 4.83 ppm (dd, J = 8.2, 4.0 Hz) proving the presence of an axial H.[8] Therefore, the major product **19a** has the anti configuration of the hydroxyl to the epoxide ring, which is the desired relative configuration for **1**. The same aldol reaction was examined on a functionalized epoxy aldehyde **18b**, having a side chain with additional syn asymmetric centers, under the same condition with lithium ethyl acetate as above to afford largely anti product **19b** [δ 2.86 ppm (d, J = 9 Hz)] in 65.9% isolated yield together with the corresponding syn product (**20b**) [δ 2.97 ppm (d, J = 9 Hz)] in 11.6% yield, the ratio of these product being 85:15. Each isomer (**19b** and **20b**) was respectively converted into **24b** and **25b** as shown in Scheme II. The ^{1}H NMR signal corresponding to C-3 position in **24b** appeared at δ 4.31 (dd, J = 3.0, 1.5 Hz), while the axial proton in the minor product (**25b**) was at δ 4.93 (dd, J = 10.0, 2.5 Hz), showing the anti orientation of the aldol adduct **19b**. On the other hand, the *anti*-epoxy aldehyde **26** afforded a contrasting result on condensation with the lithium enolate of ethyl acetate. In this case the product, analyzed as the silyl ether, was a mixture of the two diastereoisomers **27** (syn and anti ones) in ca. 50:50 judging from the epoxidic proton signals appearing at δ 2.83 and 2.88, respectively.

Three different results were obtained in the above aldol reactions using the similar epoxyaldehydes, **18a**, **18b**, and **26**, giving product ratios of syn:anti of 67:33, 85:15, and 50:50, respectively. These facts imply uncommon transition states and different mechanisms for the stereocontrol. Comparing **18b** and **26**, the particularly high selectivity of the former might be derived from the contribution of the silyl oxygen atom by taking part in an efficient chelation[9] in the aldol reaction. Thus, one of the possible transition states might be the pseudo-bicyclo[5,3,1]undecene shown in Figure 1. This large ring transition state would explain the difficult formation of such a chelate ring with the *anti*-epoxy aldehyde **26** due to 1,3-steric repulsion of the two methyl groups shown in parentheses. These phenomena are the first examples to our knowledge, that the stereochemistry of an aldol addition can be controlled by factors caused by four and five atoms away from the electrophilic center.

(8) The corresponding lactones, prepared by oxidation of **23** and by its acidic cyclization, showed similar coupling constants in ^{1}H NMR spectra: major isomer in J = 5.7 and 4.3 Hz, minor isomer in J = 5.9 and 2.1 Hz. This was due to a conformational ambiguity of the latter being in boat-like form.

(9) (a) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1–115. (b) Mukaiyama, T. *Org. React. (N.Y.)* **1982**, *28*, 203–331. (c) Masamune, S.; Choy, W. *Aldrichimica Acta* **1982**, *15*, 47. (d) Heathcock, C. H. *Science (Washington, D.C.)* **1981**, *214*, 395.

Total Synthesis of Optically Active Maytansinol (1). Proper introduction of all the necessary asymmetric centers into (−)-**17b** leads us to the final stage of the total synthesis. (−)-**17b** was hydrolyzed with 3 N KOH in a mixture of THF and EtOH (2:5) at 45 °C for 7 h to give the carboxylic acid, which was cyclized to the 19-membered lactam via conversion of its tetrabutylammonium salt to the mixed anhydride (with mesitylenesulfonyl chloride).[4c] After the chromatographic separation, the product was isolated in pure state as **28a** showing $[\alpha]_D$−33.4° in 53% yield.



Since the starting material contained ca. 55% of **17b** (with (*E*)-**11** geometry) and 45% of the **11** (*Z*)-isomer of **17b**, the isolation of **28a** in 53% yield corresponds a 96% cyclization yield. Desilylation of the cyclized product **28a** was effected with n-Bu_4NF in a mixture of acetonitrile and THF at 60 °C for 12 h. After isolation of the diol **28b**, it was first attempted to perform the carbamoylation and then the deketalization to produce **1**, but this gave only a low yield. On the other hand, first deketalization followed by carbamoylation via **29** gave maytansinol (−)-**1** in 58% overall yield as crystals, mp 192 °C and $[\alpha]_D$ −195° (lit. mp 195 °C and $[\alpha]_D$ −198°). All other physical properties were identical with the authentic material.

Maytansinol exhibited a strong aromatic stacking, which was observed in $CDCl_3$ during the NMR measurements of the synthetic sample, as well as of the natural product. One of the two aromatic protons of **1** appeared at two different chemical shifts around δ 7.0 (in the range of δ 7.04–6.91 as a double (J = 2 Hz)) depending upon the concentration (15–0.5 mM), at higher chemical shift in lower concentration, while the other aromatic signal appeared at δ 6.80, constant irrespective of the concentration. The position of all other signals was independent of concentration.

The total synthesis of racemic and optically active maytansinol provides a new synthetic concept in the use of carbohydrates as chiral templates. Thus, the carbon chain elongation used the mannose nucleus to produce high-asymmetric induction via *intramolecular* chelation. Heteroconjugate addition to establish the asymmetry at C-6, diastereoselective epoxidation to establish that at C-4 and C-5, and remote controlled aldol reaction to set up C-3, all derived from the original C-7 asymmetric center of the starting material. The use of a carbohydrate for chiral synthesis remains highly effective.

Experimental Section

Preparation of 5c from Methyl D-Mannopyranoside. A mixture of **4b** [100.0 g, 0.52 mmol in DMF (2.5 L) and acetone (0.8 L)] and 2,2-dimethoxypropane (160 mL) was stirred with PPTS (9.0 g) at 5 °C for 24 h. Additional dimethoxypropane (50 mL × 3) was added every 24 h. Amberlite IRA 402 was added to this mixture to neutralize the catalyst, and then stirring was continued overnight. The resin was removed by filtration, and the filtrate was concentrated to give syrup, which was evacuated at 80 °C to remove the remaining DMF. The product **5a** was crystallized by allowing the residue to stand at room temperature. Recrystallization from Et_2O and petroleum ether provided the pure sample **5a**: 57.4 g, 47.1% yield, mp 101–103 °C: ^{1}H NMR δ 1.38 (3 H, s), 1.48 (3 H, s), 2.90 (2 H, br s), 3.28 (3 H, s), 3.4–3.9 (6 H, m), 4.64 (1 H, s); $[\alpha]_D$ +60.3° (MeOH, c 1.00), 73.6° ($CHCl_3$, c 1.00) (lit. by Evans[5] $[\alpha]_D$ 73° ($CHCl_3$), Stevens[5] 68.3°). Calcd for $C_{10}H_{18}O_6$: C, 51.27; H, 7.75. Found: C, 51.30; H, 7.79.

p-Toluenesulfonyl chloride (36.0 g, 19 mmol) was added to a solution of the monoacetonide **5a** (30.0 g, 0.128 mmol) in a mixture of dichloromethane (2 L) and pyridine (1 L). An additional 8 g each of the chloride was added 3 times, after 24, 36, and 48 h, respectively. After 60 h, TLC analysis showed the absence of starting material. The reaction mixture was washed with water, and the aqueous layer was extracted

with CH_2Cl_2. The combined organic layer was dried over anhydrous sodium sulfate and evaporated to afford a crude oil, which was diluted with ether and filtered through a short column of silica gel. The filtrate was concentrated under reduced pressure to give the monotosylate **5b** (53.2 g, used without further purification).

A mixture of THF (350 mL), MeI (40 mL, 6.5 mol), and petroleum ether–washed NaH (12.0 g, 2.5 mol) was placed in a flask equipped with a mechanical stirrer and a dropping funnel, through which was introduced **5b** [53.2 g, 0.128 mol dissolved in THF (150 mL)] over 1.5 h at room temperature with vigorous stirring. After the addition, MeOH was added cautiously until the evolution of H_2 ceased. The reaction mixture was diluted with aqueous NH_4Cl and then extracted with ether. The combined organic layer was washed with water and saturated NaCl and then dried. Removal of the solvent under reduced pressure afforded the crude crystals (39.7 g), which were recrystallized from ether to give the analytically pure crystals **5c**: 30.8 g, 60% yield, mp 116 °C; ^{1}H NMR δ 1.10 (3 H, s), 1.34 (3 H, s), 2.22 (3 H, s), 3.32 (3 H, s), 3.52 (3 H, s), 3.7–3.8 (3 H, m), 4.02 (1 H, t, J = 9 Hz), 4.61 (1 H, dd, J = 9, 4 Hz), 4.69 (1 H, d, J = 3 Hz), 7.3 (2 H, m), 7.8 (2 H, m); $[\alpha]_D$ +14.7° (MeOH, c 1.01). Calcd for $C_{18}H_{26}O_8S$: C, 53.72; H, 6.51. Found: C, 53.57; H, 6.48.

Preparation of the Trityl Ether 6b. A solution of the acetonide **5c** [31.0 g, 77 mmol in MeOH (1 L)] was stirred vigorously in the presence of Dowex 50W (H^+) (30 mL) at room temperature for 3.5 h. Removal of the resin and then the solvent afforded crystals of **6a**, which was recrystallized from ether and hexane. **6a**: 28.4 g, 100%, mp 97–99 °C; ^{1}H NMR δ 1.88 (3 H, s), 3.04 (3 H, s), 3.26 (3 H, s), 3.4–4.0 (5 H, m), 4.18 (1 H, dt, J = 8, 5 Hz), 4.54 (1 H, s), 4.88 (1 H, J = 9, 3 Hz), 6.6–6.8 (2 H, m), 7.7–7.9 (2 H, m); $[\alpha]_D$ +30.1° (MeOH, c 1.03). Calcd for $C_{15}H_{2i}O_8S$: C, 49.72; H, 6.12. Found: C, 49.81; H, 6.16.

A solution of the diol **6a** (26.9 g, 74.3 mmol) and trityl chloride (25.6 g, 90 mmol) dissolved in pyridine (135 mL) was heated at 70 °C for 1.5 h. After cooling to room temperature the reaction mixture was poured into water and then extracted with CH_2Cl_2. Crude solid **6b** (55.0 g) was recrystallized from ether to give pure **6b**: 38.6 g, 86% yield, mp 156 °C dec; ^{1}H NMR δ 1.20 (1 H, br t, J = 7 Hz), 2.38 (3 H, s), 3.32 (3 H, s), 3.34 (3 H, s), 3.4–4.0 (5 H, m), 4.6–4.7 (2 H, m), 7.0–7.4 (18 H, m), 7.6–7.8 (2 H, m); $[\alpha]_D$ +20.0° ($CHCl_3$, c 1.02). Calcd for $C_{34}H_{36}O_8S$: C, 67.54; H, 6.00. Found: C, 67.45; H, 6.00.

Preparation of 8. Potassium *tert*-butoxide (1.17 M, 68 mL) was added dropwise at 0 °C to a solution of **6b** [16.0 g, 26.5 mmol in THF (500 mL)] under N_2. After 30 min, the mixture was diluted with NH_4Cl and then extracted with ether. The combined organic layer was washed with water and aqueous NaCl, dried, and then concentrated to afford the crude unstable epoxide **7** (12.8 g), which was subjected to the next step.

To a solution of the epoxide **7** [12.8 g, 26.5 mmol in THF (30 mL)] was added dropwise at −78 °C a 1 M solution of $LiBEt_3H$ (200 mL), and the reaction mixture was kept at −20 °C (in a freezer) for 5 days and then at room temperature when TLC analysis showed absence of the starting material. The mixture was treated with 30% H_2O_2 (45 mL, dropwise addition at −78 °C) and then with aqueous Na_2SO_3 until the organic layer became negative to KI–starch test paper. Extraction with ether followed by washing (aqueous Na_2SO_3, water, and aqueous NaCl) and drying over Na_2SO_4 gave **8a** (15.1 g, crude in quantitative yield). The purity of this product was determined as follows. Part of the mixture of **8a** (0.67 g) was heated with *tert*-butyldimethylchlorosilane (0.8 g) and imidazole (0.71 g) as a solution in DMF (3 mL) at 75 °C for 6 h. The reaction mixture was worked up to give the crude *tert*-butyldimethylsilyl ether (1.33 g). Separation of the resulting mixture of silyl ethers by HPLC (Partisil, Whatman, ether:hexane = 8:1) afforded the products in a 7:1 ratio of **8a** and its 3-deoxy isomer. *tert*-Butyldimethylsilyl ether of **8a**: ^{1}H NMR δ 0.05 (3 H, s), 0.09 (3 H, s), 0.90 (9 H, s), 1.4–1.9 (2 H, m), 2.9–3.4 (3 H, m), 3.38 (6 H, s), 3.90 (1 H, br q, J = 4.5 Hz), 4.22 (1 H, br m), 4.58 (1 H, d, J = 2.5 Hz), 7.1–7.5 (15 H, m).

The alcohol **8a** [15.1 g, 26.5 mmol in Me_2SO (40 mL)] was added to a suspension of NaH (3.8 g) in THF (350 mL). After the evolution of H_2 ceased, benzyl bromide (4.7 mL) was added dropwise. The mixture was stirred for 1 day, diluted with saturated aqueous NH_4Cl and then extracted with ether to give the benzyl ether **8b**: 15.4 g; ^{1}H NMR δ 1.6–1.7 (2 H, m), 2.92 (1 H, dd, J = 10, 4 Hz), 3.20 (1 H, m), 3.28 (3 H, s), 3.46 (3 H, s), 3.60 (1 H, m), 4.20 (1 H, m), 4.56 (2 H, s), 4.66 (1 H, s), 7.1–7.5 (15 H, m).

A solution of **8b** [15.4 g, 26.5 mmol in $CHCl_3$ (370 mL)] was stirred with HCl (0.9 mL) overnight at room temperature, the mixture was neutralized by saturated $NaHCO_3$, and the separated aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with water and half-saturated NaCl, dried over Na_2SO_4, and evaporated to give a residue, which was separated by a silica gel column (100 g) with a mixture of ether and hexane (1:1) to afford the alcohol **8c** (5.0 g, 67% overall yield from **6** in 4 steps). **8c**: ^{1}H NMR δ 1.5–1.9 (2 H, m), 2.23 (1 H, br m), 3.24 (1 H, br s), 3.32 (3 H, s), 3.36 (3 H, s), 3.5–3.8 (3 H, m), 4.1 (1 H, m), 4.58 (2 H, s), 4.70 (1 H, s), 7.26 (5 H, br s).

Preparation of the Heteroolefin 10. To a suspension of CrO_3–2Py (12.6 g) in CH_2Cl_2 (130 mL) was addded **8c** [1.38 g, 4.9 mmol in CH_2Cl_2 (10 mL)] dropwise at room temperature with vigorous stirring. After 10 min, the mixture was diluted with a mixture of ether and EtOAc and then decanted to leave a gum, which was thoroughly washed with ether. The combined organic solution was filtered through Hyflo Supercell, and the filtrate cake was washed with ether. The filtrate was passed through a short column of silica gel to remove trace amounts of chromium species. Condensation of the filtrate under reduced pressure gave the aldehyde **9** (0.95 g, 69% yield): ^{1}H NMR δ 1.94 (2 H, m), 3.22 (1 H, dd, J = 4, 2 Hz), 3.38 (3 H, s), 3.46 (3 H, s), 3.68 (1 H, dd, J = 4, 4 Hz), 4.4 (1 H, dd, J = 8, 8 Hz), 4.60 (2 H, s), 4.72 (1 H, d, J = 2 Hz), 7.26 (5 H, br s), 9.68 (1 H, s).

An alternative method for **9** by Swern oxidation follows. To a mixture of oxalyl chloride [33 mL, 387 mmol, 2.5 equiv] and Me_2SO (55 mL) in CH_2Cl_2 (1.4 L) was added **8c** (44.2 g, 157 mmol) over a period of 5 min at −70 °C. After stirring for 15 min, the mixture was treated with Et_3N (218 mL, 1550 mmol) and stirred for 5 min at this temperature and for 45 min without external cooling, the final temperature being ca. 0 °C. The reaction mixture was diluted with water (1.5 L), extracted with ether (1.4 L × 3), washed with 1 N HCl to pH ca. 5 then with $NaHCO_3$, water, and brine, dried over Na_2SO_4, and evapted to give 45.7 g of the crude aldehyde **9** in almost quantitative yield.

To a solution of bis(trimethylsilyl)(phenylthio)methane (2.5 mL) in THF (50 mL) cooled to −78 °C under Ar was added *n*-BuLi [1.5 M in hexane, 8.9 mmol (5.5 mL)] portionwise, and then the temperature was regulated as follows: (i) warmed up to −40 °C gradually in 2.5 h, (ii) kept at −45 ± 5 °C for 2 h, (iii) allowed to warm to room temperature in 3 h, and (iv) cooled to −45 °C. To this mixture was introduced the aldehyde **9** [0.95 g, 3.4 mmol in THF (5 mL)]. After stirring for 5 min at −45 °C and then for 30 min at room temperature, the reaction mixture was diluted with saturated NH_4Cl and extracted with ether to give crude oil, which was purified by chromatography to give a sulfide [1.13 g, 72% yield, as a mixture of E/Z isomers in 3:1]. MCPBA [80%, 1.16 g] was added to a solution of the sulfide [1.13 g, 2.46 mmol in CH_2Cl_2 (40 mL)] at 0 °C. After stirring for 30 min, the mixture was treated with Na_2SO_3, and then the cooling bath was removed. Aqueous workup gave the heteroolefin **10** (1.18 g, 98% yield). Part of the product was separated for analytical purpose by preparative TLC to give (*Z*)-**10** (mp 136–138 °C) and (*E*)-**10** (oil), respectively. (*Z*)-**10**: ^{1}H NMR δ 0.34 (9 H, s), 1.6–2.1 (2 H, m), 2.92 (3 H, s), 3.18 (1 H, br s), 3.32 (3 H, s), 3.80 (1 H, br s), 4.54 (1 H, s), 4.60 (1 H, d, J = 12 Hz), 4.84 (1 H, d, J = 12 Hz), 5.20 (1 H, ddd, J = 10, 9, 3 Hz), 6.48 (1 H, d, J = 9 Hz), 7.3 (8 H, m), 7.8 (2 H, m); $[\alpha]_D$ −64.3° (MeOH, c 1.00). Calcd for $C_{25}H_{34}O_6Si_1S$: 61.20; H, 6.93. Found: C, 61.10; H, 6.90. (*E*)-**22**: ^{1}H NMR δ 0.22 (9 H, s), 1.4–2.1 (2 H, m), 3.24 (1 H, br s), 3.32 (3 H, s), 3.28 (3 H, s), 3.70 (1 H, br s), 4.58 (2 H, s), 4.68 (1 H, s), 5.02 (1 H, ddd, J = 10, 10, 7 Hz), 7.10 (1 H, d, J = 10 Hz), 7.3–7.6 (8 H, m), 7.7–7.8 (2 H, m).

Heteroconjugate Addition of MeLi to 10. To a stirred solution of **10** [113 mg, 0.23 mmol in THF (3.8 mL)] was added MeLi [1.5 M, 1.6 equiv (0.25 mL)] dropwise at −78 °C under N_2. After it was stirred for 10 min, the resulting yellow mixture was mixed with aqueous NH_4Cl and then extracted with ether to give an adduct (113 mg), which was stirred in MeOH (3.5 mL) containing KF (46 mg) at room temperature for 1 h. The solvent was removed and the resulting residue was taken up with CH_2Cl_2 to give **11** as the sole isolable product: 98 mg, 100% yield; ^{1}H NMR δ 1.08 (3 H, d, J = 7 Hz), 1.55 (2 H, m), 2.20 (1 H, br), 2.90 (1 H, dd, J = 14 9 Hz), 3.16 (1 H, br s), 3.26 (6 H, s), 3.62 (1 H, m), 3.90 (1 H, ddd, J = 10, 4, 3 Hz), 4.50 (1 H, s), 4.53 (2 H, s), 7.2 (5 H, br s), 7.5 (3 H, m), 7.8 (2 H, m); ^{13}C NMR δ 14.6, 27.5, 32.0, 55.5, 58.2, 59.2, 66.2, 71.0, 71.9, 76.3, 100.4, 127.6, 127.9, 128.3, 129.2, 133.5, 138.3, 140.0; $[\alpha]_D$ +40.0° ($CHCl_3$, c 1.60).

Preparation of 12. A solution of **11a** [36.2 g, 83.4 mmol in EtOH (900 mL)] was stirred with Pd-black (10 g) and AcOH (5 mL) under H_2 at reflux temperature for 2 days. Filtration and evaporation of the mixture gave colorless oil **11b**: 28.0 g, in 97.5% yield; ^{1}H NMR δ 1.12 (3 H, d, J = 7 Hz), 1.3–2.0 (2 H, m), 2.24 (1 H, m), 3.00 (1 H, dd, J = 14.5, 8 Hz), 3.16 (1 H, m), 3.40 (1 H), 3.36 (3 H, s), 3.40 (3 H, s), 4.00 (2 H, m), 4.72 (1 H, br s), 7.6 (3 H, m), 7.9 (2 H, m).

The alcohol **11b** (30 g, 87.2 mmol) was stirred with dihydropyran 15 mL, 164.4 mmol) in CH_2Cl_2 (600 mL) in the presence of PPTS (3 g) at ambident temperature for 5 h. The usual workup afforded **11c** (crude 40 g) as a slightly yellow oil. ^{1}H NMR of **11c**: δ 1.14 (3 H, d, J = 7 Hz), 1.4–2.0 (8 H, m), 2.24 (1 H, m), 3.00 (1 H, dd, J = 14, 8 Hz), 3.30 (3 H, 2s), 3.40 (3 H, 2s), 3.4 (4 H, m), 3.92 (2 H, m), 4.58 (1 H, br s), 4.70 (1 H, m), 7.6 (3 H, m), 7.9 (2 H, m). After it was pumped at 10^{-2} torr for 5 h, **11c** (40 g, 93 mmol) was dissolved in a mixture of THF (720

mL) and HMPA (180 mL) and then cooled to −78 °C. To this solution was added *n*-BuLi [1.65 M, 132 mmol (80 mL)] dropwise at −78 °C and the temperature was raised to −40 °C in 20 min. The mixture was again cooled to −78 °C and mixed with 3-bromopent-2-ene (20 mL, 166 mmol). The stirring was continued at −20 °C for 2 h, and the mixture was then worked up by addition of NH_4Cl(aq) followed by extraction with ether. The crude product **12a** (48.3 g) was treated under the following reaction conditions without further purification.

Preparation of 13. The alkylated product **12a** (48.3 g) was heated in 2-chloroethanol (800 mL) containing trimethyl orthoformate (16 mL) and CSA (4 g) at 60 °C for 12 h. The mixture was poured into ice-cold 5% $NaHCO_3$ and then extracted with CH_2Cl_2 to give crude **12b** (53 g), which was oxidized with CrO_3–2Py (140 g, 5 equiv) in CH_2Cl_2 (800 mL) at room temperature for 30 min. The total amount of the product (52.4 g) was dissolved in a mixture of MeOH (800 mL) and trimethyl orthoformate (80 mL) and stirred with CSA at room temperature for 12 h. The usual aqueous workup with CH_2Cl_2 afforded the dimethyl ketal **13a** (43.4 g). The residual oil was dissolved in THF (600 mL) to which was added a solution of PhSNa [prepared from PhSH (13 mL) and NaH (6 g) in THF] at 0 °C over 15 min. After it was stirred overnight at room temperature, the mixture was diluted with water and then extracted with ether to give crude **13b** (44.9 g). The sulfide **13b** was oxidized with MCPBA (42 g) in CH_2Cl_2 (1 L) at 0 °C for 1 h to give crude **13c** (45.7 g), which was reduced with $NaBH_4$ (14 g) in a mixture of EtOH (800 mL) and THF (200 mL) at refluxing temperature for 1.5 h. The product was extracted with CH_2Cl_2 (2.6 L) and passed through a silica gel column to afford crude diol (40.3 g), monoacetylation of which (40.3 g) was effected with acetyl chloride (7.8 mL, 1.1 equiv) in CH_2Cl_2 in the presence of pyridine (74 mL, 10 equiv) at 0 °C for 20 min. After the usual aqueous workup with CH_2Cl_2, the acetate (40.7 g) was treated with *tert*-butyldimethylchlorosilane (50 g, 4 equiv) and imidazole (48 g, 8 equiv) in DMF (100 mL) at 80 °C for 12 h. The silyl ether (crude 51.2 g) was purified with silica gel (700 g) and a mixture of ether–hexane (1:2), to give 19.0 g of pure material, as an oil, in 38.1% isolated overall yield from **11b** in seven steps. Ozone was introduced into a cold solution (−78 °C) of the silyl ether [15.0 g in CH_2Cl_2 (400 mL)] for 4 h when Et_3N (30 mL) was added to the mixture. The mixture was stirred at room temperature for 12 h, and then the CH_2Cl_2 solution was washed with ice-cold water, dried, and concentrated to yield **14a** (11.0 g, quantitative yield). Part of this aldehyde was purified on a silica gel column (ether–hexane 1:3) to afford pure unsaturated aldehyde **14a**, $[\alpha]_D$ +26.9° ($CHCl_3$, *c* 1.82): all other physical properties are the same as the racemic ones.

Preparation of 3. The unsaturated aldehyde **14a** (11.0 g) was stirred in MeOH (250 mL) with trimethyl orthoformate (46 mL) and PPTS (1.1 g) at 0 °C for 12 h. The mixture was poured into 5% $NaHCO_3$ and extracted with ether to give the corresponding acetal (12.1 g), which was hydrolyzed with MeONa (1 M, 1.5 equiv) in MeOH (300 mL) at room temperature for 1 h. Usual workup with ether afforded an alcohol (10.5 g in 95.5% yield), which was then oxidized with CrO_3–2Py (60 g) in CH_2Cl_2 (300 mL) at room temperature for 30 min to afford the aldehyde **14b** (9.8 g in 94.0% yield). A solution of **14b** in THF (50 mL) was introduced to a solution of the ylide of **15** [prepared from 17.8 g with *t*-BuLi (1.85 M, 17.3 mL) in a mixture of THF (294 mL) and DMF (147 mL)] at −67 °C over a period of 1 h. The mixture was stirred at −67 °C for 1 hr and then heated to 40 °C for 1 hr. Usual aqueous workup afforded crude product (23.9 g), which was purified with silica gel (350 g) column chromatography (ether–hexane 1:2) to afford the adduct (13.0 g, 81.3% yield). A solution of this adduct in a mixture of THF (220 mL), water (55 mL), and acetic acid (55 mL) was stirred at 0 °C for 2 days to give the key intermediate **3** (12.3 g in quantitative yield). The series of materials, after this Wittig and before closing the ansa ring, were comprised from a mixture of (*E*)- and (*Z*)-**11** in a ratio of 55:45, which were not separable. Part of (−)-**3** was purified with HPLC to give 85% purity of the (*E*)-**11** isomer, which showed $[\alpha]_D$ −5.9° (*c* 0.29, $CHCl_3$).

Preparation of 17b. The crude key intermediate (−)-**3** (12 g) was reduced with $NaBH_4$ (0.85 g) in MeOH (280 mL) at 0 °C for 1 h, and the usual workup gave the crude allyl alcohol (12.5 g), which was heated in EtOH (426 mL) with 12 N KOH (142 mL) at reflux temperature for 24 h and the ethereal workup afforded crude amino alcohol (10 g). A solution of this material in CH_2Cl_2 (430 mL) was treated with Ti(O-*i*-Pr)$_4$ (1 M, 24 mL) and *tert*-butyl hydroperoxide (5.1 M, 25 mL) at −23 °C for 1.5 h. The reaction mixture was then stirred for 1 h with Me_2S (10 mL) and NaF (200 mL). The CH_2Cl_2 extracts (**16a**, crude 10 g) were oxidized with SO_3–Py (12 g) and Et_3N (22 mL) in Me_2SO (220 mL) at room temperature for 45 min, and the mixture was extracted with ether to afford chiral **16b** (9.1 g).

Freshly distilled ethyl acetate (6.6 mL) was added slowly at −78 °C into a solution LDA in THF (180 mL) [prepared from diisopropylamine (9.6 mL) and *n*-BuLi (1.6 M, 42 mL) in hexane at 0 °C for 1 h]. To this mixture was added dropwise a solution of **16b** [8.8 g in THF (60 mL)]. The mixture was stirred for 30 min at −78 °C, mixed with saturated NH_4Cl and extracted with ether to provide **17a** (10.2 g). This product was dissolved in DMF (75 mL) and treated with *tert*-butyldimethylchlorosilane (11 g) and imidazole (13 g) with stirring for 12 h at 35 °C. MeOH (20 mL) was added to the mixture at such a rate that no exothermic reaction occurred, and the resulting solution was extracted with ether to afford crude oil, which was purified by silica gel column chromatography to give **17b** (3.5 g in 23.3% overall yield from **3**). (−)-**17b**: $[\alpha]_D$ −19.7° ($CHCl_3$, *c* 1.21); ^1H NMR δ 0.00 (3 H, s), 0.04 (3 H, s), 0.08 (6 H, s), 0.83 (9 H, s), 0.89 (9 H, s), 1.00 (Me-6, d, J = 6.6 Hz), 1.34 (3 H, t, J = 7 Hz), 1.27 (Me-4, s), 1.73 (Me-14, s), 2.0 (H-8 × 2, m), 2.54 (H-2 × 2, m), 2.88 (NMe, s), 2.99 (H-5, d, J = 9.5 Hz), 3.23 (OMe-9 × 2, s), 3.28 (OMe-10, s), 3.76 (H-10, d, J = 7 Hz), 3.85 (Ar OMe, s), 4.08 (H-3, m), 4.12 (2 H, q, J = 7 Hz), 4.40 (NH, br s), 5.51 (H-11, dd, J = 15.0, 7.0 Hz), 5.95 (H-13, d, J = 11.0 Hz), 6.15 (2 H, Ar H × 2, br s), 6.48 (H-12, dd, J = 15.0, 11.0 Hz); IR ($CHCl_3$) ν 3450, 1730, 1595, 1460 cm^{-1}; mass spectrum, m/z 807 (M^+ − 34), 793, 644, 546, 514.

Cyclization of the 19-Membered Lactam. Compound **17b** (550 mg, 0.67 mmol) was dissolved in a mixture of 3 N KOH (2 mL),EtOH (10 mL), and THF (2 mL) and the solution was heated at 45 °C for 7 h. The mixture was neutralized with 1 N HCl at 0 °C and then extracted 3 times with CH_2Cl_2. The organic layer was passed through a column containing Na_2SO_4 and then concentrated to an oil, which was purified by silica gel TLC with ether–hexane (1:1) to give carboxylic acid, which was dissolved in toluene (30 mL) and mixed with *n*-Bu_4NOH (10%, 2.2 mL in MeOH at room temperature). The mixture was concentrated to dryness to remove water by azeotropic distillation, and the residue was redissolved and concentrated to dryness under reduced pressure below 25 °C 4 succiessive times. The resulting light brown material (0.8 g) was dissolved in benzene 1 L) and added dropwise in a mixture of 2-mesitylenesulfonyl chloride (3.5 g, 16 mmol) and diisopropylethylamine (2.8 mL, 16 mmol) in benzene (2 L) and pyridine (400 mL) at 40 °C over a period of 40 h. The reaction mixture was concentrated to 1/5 volume and extracted 4 times with ether. The extracts were washed with water and brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo to afford crude **28a**, which was chromatographed on a silica gel column. Elution with ether–hexane (1:3) removed excess 2-mesitylenesulfonyl chloride and side products. Elution with ethyl acetate provided in 31% yield as colorless oil (−)-**28a** [160 mg; $[\alpha]_D$ −33.4° ($CHCl_3$ *c* 0.58)]. This yield was 53% in 1/10 scale, and the corresponding **11** *Z* isomer of **28a** was too unstable to isolate. ^1H NMR (400 MHz) δ −0.28 (3 H, s), −0.07 (3 H, s), 0.03 (3 H, s), 0.135 (3 H, s), 0.83 (9 H, s), 0.84 (9 H, s), 0.99 (Me-6, d, J = 6.4 Hz), 1.05 (Me-4, s), 1.79 (H-6, d, J = 10.0, 7.0 Hz), 1.95 (Me-14, s), 1.9–2.2 (m), 2.91 (H-5, d, J = 10.0 Hjz), 3.01 (OMe-10, s), 3.14 (OMe-9 × 2, s), 3.26 (NMe, s), 3.3 (2 H), 3.67 (1 H, d, J = 10 Hz), 3.72 (1 H, d, J = 10.0 Hz), 3.91 (Ar OMe, s), 4.48 (1 H, *d*, J = 10.0 Hz), 5.24 (H-13, d, J = 10.0 Hz), 5.40 (H-11, dd, J = 15.0, 10.0 Hz), 6.46 (H-12, dd, J = 15.0, 10.0 Hz), 6.56 (Ar H, d, J = 2 Hz), 6.72 (Ar H, d, J = 2 Hz); IR ($CHCl_3$) ν 1660, 1575, 1455, 1120, 1080 cm^{-1}; mass spectrum, m/z 795 (M^+), 780, 764, 739. Optically active material was prepared similarly from **5** in 30.8% yield (ca. 160 mg from 550 mg); $[\alpha]_D$ = −33.4° ($CHCl_3$, *c* 0.580).

Total Synthesis of Maytansinol 1. Compound **28a** [95 mg, 0.12 mmol dissolved in MeCN (4 mL)] was treated with *n*-Bu_4NF [1 M, in THF (2 mL)] at 60 °C for 12 h. The reaction mixture was partitioned between CH_2Cl_2 and water, and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were washed with water, dried over Na_2SO_4, and concentrated under reduced pressure to afford crude oil **28b**, which was passed through a silica gel short column (elution first with CH_2Cl_2 and then with ethyl acetate) to give **28b**, which was used for the next step. When it was purified in the racemic material, the yield was 77%. ^1H NMR of **28b** (200 MHz) δ 1.05 (Me-6, d, J = 7 Hz), 1.30 (Me-4, s), 1.76 (Me-14, s), 1.8–2.3 (m), 2.91 (H-5, d, J = 9.2 Hz), 3.18 (OMe-9, s), 3.19 (OMe-9, s), 3.27 (OMe-10, s), 3.41 (NMe, s), 3.96 (Ar OMe, s), 3.4–4.0 (m), 5.60 (H-11, dd, J = 15.5, 5 Hz), 5.99 (H-13, d, J = 11 Hz), 6.52 (H-12, ddd, J = 15.5, 11, 1 Hz), 6.73 (Ar H, d, J = 2 Hz), 6.78 (Ar H, d, J = 2 Hz); IR ($CHCl_3$) 3500, 1642, 1580, 1118, 1095 cm^{-1}; mass spectrum m/z 567 (M^+), 548, 533, found 567.2586, calcd ($C_{29}H_{42}O_8N_1Cl_1$) 567.2596.

The diol **28b** was dissolved in a mixture of acetic acid (1 mL), THF (0.5 mL), and water (0.5 mL), and the mixture was stirred for 11 h at 35 °C. The reaction mixture was extracted with CH_2Cl_2, and the organic layer was washed with aqueous 5% $NaHCO_3$, water, and brine, dried over anhydrous Na_2SO_4, and evaporated to afford almost pure **29** (39.0 mg, 62.7% overall yield from **28a**), $[\alpha]_D$ −410° ($CHCl_3$, *c* 0.432), and the racemic material was also prepared from 7.0 mg of **28b** in quantitative yield of **29** (6.7 mg) as colorless oil: ^1H NMR (200 MHz) δ 0.87

(Me-4, s), 1.16 (Me-6, d, J = 6.6 Hz), 1.76 (Me-14, s), 2.18 (2 H, m), 2.32 (H-6, m), 2.55 (H-5, d, J = 9.5 Hz), 2.56 (H-8, dd, J = 17.5, 9.5), 2.76 (H-8, dd, J = 17.5 3 Hz), 3.14 (H-15, d, J = 12 Hz), 3.20 (OMe-10, s), 3.37 (NMe, s), 3.46 (H-15, d, J = 12 Hz), 3.62 (1 H, m), 3.88 (1 H, m), 3.98 (Ar OMe, s), 4.19 (H-10, d, J = 8 Hz), 5.42 (H-11, dd, J = 15, 8 Hz), 5.98 (H-13, d, J = 11 Hz), 5.60 (H-12, dd, J = 15, 11, 1 Hz), 6.81 (Ar, H, d, J = 2 Hz), 6.83 (Ar H, d, J = 2 Hz); IR ($CHCl_3$) ν 3400, 1724, 1644, 1576, 1095 cm^{-1}; mass spectrum m/z 521 (M^+), 503, 488, found 521.1105, calcd ($C_{27}H_{36}O_7N_1Cl_1$) 521.2178.

To a solution of the keto diol (−)-**29** [21.6 mg in CH_2Cl_2 (0.5 mL)] was added 0.5 M pyridine (0.3 mL) in CH_2Cl_2 with stirring at 0 °C. The stirring was continued for 15 min, and the reaction mixture was cooled down to −78 °C and mixed with excess ammoniacal MeOH (0.7 mL). After removal of the cooling bath, the resultant yellow solution was stirred for 20 min and then diluted with CH_2Cl_2. The organic layer was separated, washed with 5% $NaHCO_3$, water, and brine, dried over anhydrous Na_2SO_4, and then concentrated in vacuo affording the crude maytansinol **1**, which was purified by silica gel TLC with 5% MeOH–CH_2Cl_2 to give (−)-**1**, [13.6 mg in 58.1% yield, mp 190–192 °C, $[\alpha]_D$ −195° ($CHCl_3$, c 0.272)]. The racemic material (ca. 6.7 mg of ±**29**) was also converted into (±)-**1** in 67% yield (4.7 mg of white powder). ^1H NMR (400 MHz) δ 0.84 (Me-4, s), 1.29 (Me-6, d, J = 6.5 Hz), 1.54 (H-6, m), 1.69 (Me-14, s), ~1.25 (H-8, overlap), 2.15 (H-8, d, J = 14 Hz, s), 2.10 Hz (H-2, dd, J = 13.5, 2.0 Hz), 2.28 (H-2, dd, J = 13.5, 11.0 Hz), 2.57 (H-5, d, J = 9.5 Hz), 3.11 (H-15, d, J = 12.5 Hz), 3.47 (H-15, d, J = 12.5 Hz), 3.20 (OMe-10, s), 3.35 (NMe, s), 3.49 (H-10, d, J = 9.0 Hz), 3.54 (H-3, dd, J = 11.0, 2.0 Hz), 3.98 (Ar OMe, s), 4.34 (H-7, t, J = 11.0 Hz), 5.51 (H-11, dd, J = 15.0, 9.0 Hz), 6.14 (H-13, d, J = 11.0 Hz), 6.35 (NH, s), 6.43 (H-12, dd, J = 15.0, 11.0 Hz), 6.80 (Ar H, d, J = 2 Hz), 6.98 (Ar H, d, J = 2) (This signal appeared at δ 7.04 in a concentration of **1** being 15 mg/0.5 mL ($CDCl_3$), δ 6.98 (2.1 mg/0.5 mL), 6.94 (1 mg/0.5 mL), 6.91 (0.25 mg/0.5 mL), while the other aromatic H appeared at δ 6.80 in these concentrations.); IR ($CHCl_3$) ν 3420, 2920, 2850, 1703, 1650, 1575, 1455, 1341, 1095, 1080 cm^{-1}; mass spectra m/z 503 (M^+ − 61), 485 ,468, 450; found 503.2095, calcd ($C_{27}H_{34}O_6N_1Cl_1$) 503.2073 [M^+ − (H_2O + HNCO)].

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Supplementary Material Available: ^1H NMR and IR spectra of **1**, **17a**, **17b**, **28a**, **28b**, and **29** (14 pages). Ordering information is given on any current masthead page.

Nucleophilic Addition to Olefins. 10.[1] Kinetics of Cleavage of the Piperidine and Morpholine Adducts of α-Cyano-4-nitrostilbene and α-Cyano-2,4-dinitrostilbene

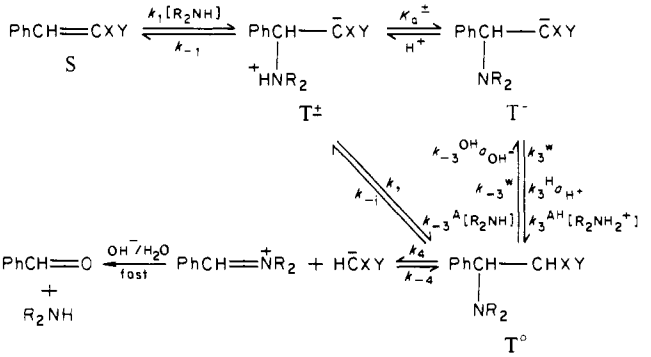
Claude F. Bernasconi* and Christopher J. Murray

Contribution from the Thimann Laboratories of the University of California, Santa Cruz, California 95064. *Received September 26, 1983. Revised Manuscript Received January 5, 1984*

Abstract: Rates of cleavage of the anionic piperidine and morpholine adducts (T^-) of α-cyano-4-nitrostilbene (**1**-NO_2) and α-cyano-2,4-dinitrostilbene (**1**-$(NO_2)_2$) into $PhCH{=}{}^+NR_2$ and 2-X-4-nitrophenylacetonitrile anion were determined. For the adducts of **1**-$(NO_2)_2$ there is a change from rate-limiting carbon protonation (to form T^0) at low amine concentrations to rate-limiting cleavage of T^0 into products at high concentrations. For the adducts of **1**-NO_2 cleavage is rate limiting throughout. Compared to the protonation of the anion of (2,4-dinitrophenyl)acetonitrile (**2**-$(NO_2)_2^-$), protonation of T^- derived from **1**-$(NO_2)_2$ is slightly enhanced when the acid is water, strongly reduced when the acid is morpholinium or piperidinium ion ($R_2NH_2^+$), and strongly enhanced with H_3O^+. The slightly enhanced rate of the water reaction is attributed to an enhanced pK_a^0 of the adduct, the strongly depressed rate for the $R_2NH_2^+$ reactions to a steric effect. The enhanced rate with H_3O^+ is ascribed either to an intramolecular pathway via the nitrogen-protonated adduct ($T^\pm$) or to a stabilization, by the adjacent amine moiety, of the transition state for protonation by H_3O^+. Problems with either interpretation exist, though, and are discussed. Even after taking into account the different leaving group basicities, the cleavage of T^0 derived from **1**-NO_2 is much slower than that of the previously studied T^0 derived from benzylidenemalononitrile, indicating a higher intrinsic barrier for the departure of the more delocalized (4-nitrophenyl)acetonitrile anion compared to $^-CH(CN)_2$. This is consistent with similar patterns observed with other carbanion-forming reactions such as deprotonations of C–H acids and nucleophilic additions to olefins. If one allows for a steric enhancement of the cleavage of T^0 derived from **1**-$(NO_2)_2$, it appears that the intrinsic barrier for departure of **2**-$(NO_2)_2^-$ is also higher than that for the somewhat less delocalized (4-nitrophenyl)acetonitrile anion.

The cleavage of activated olefins in the presence of an amine proceeds by a complex, multistep mechanism. This mechanism is shown in Scheme I for a benzylidene-type substrate PhCH=CXY where X and/or Y are electron-withdrawing groups. The reaction $T^\pm \rightleftharpoons T^-$ is shown as a rapid equilibrium even though in some cases the k_{-1} step is of comparable magnitude to the rate of deprotonation of $T^\pm$.[1-4] $k_i - k_{-i}$ refer to an intramolecular proton switch which might occur in competition with the $T^\pm \rightleftharpoons T^- \rightleftharpoons T^0$ pathway.[5]

Scheme I



Detailed kinetic studies have recently been reported for the $Ph_2C{=}C(NO_2)_2$/morpholine,[2] $PhCH{=}C(COO)_2C(CH_3)_2$/

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