Synthesis of Maytansinoid. A General Approach via Heteroconjugate Addition Strategy and the Total Synthesis of (±)-Maysine and (±)-*N*-Methylmaysenine

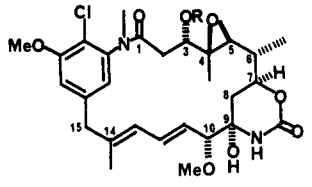
Masato Kitamura, Minoru Isobe,* Yoshiyasu Ichikawa, and Toshio Goto

Laboratory of Organic Chemistry, Faculty of Agriculture, Nagoya University, Chikusa, Nagoya 464, Japan

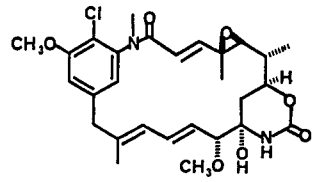
Received January 18, 1984

A general strategy for maytansinoid synthesis is described based on the retrosynthetic analysis in Scheme I. The synthetic problems were largely solved by developing a heteroconjugate addition strategy involving stereoselective introduction of the C-6 methyl group followed by carbon chain elongation and functionalization assisted by heteroatoms. The stereochemistry at C-6 was controlled by a chelational and conformational differentiation at the transition state of the addition and the reaction system was further developed with pyranosyl heteroolefin. These methods enabled us to prepare a key intermediate "A" from acrolein dimer according to the retrosynthesis in Scheme I. The total synthesis of racemic *N*-methylmaysenine (**4b**) was accomplished as the first example of the application of this synthetic scheme to the maytansinoids. An acyclic diastereoselective epoxidation mediated by Ti(IV) was developed and applied to the synthesis of racemic maysine (**3**).

Maytansine (**1**), a novel ansa-macrocyclic lactam occurring in plants such as *Maytenus serrata* in Kenia and *M. buchananii* in South Africa, was found to have significant in vitro cytotoxicity (AC) and in vivo antitumor activity against Leukemia P-388 and Melanoma B-16.[1] Congeners of maytansine are maytansinol (**2**), maysine (**3**), and maysenine (**4a**).[2] Since the elucidation of their



1 R = COCHMeNMeCOMe
2 R = H



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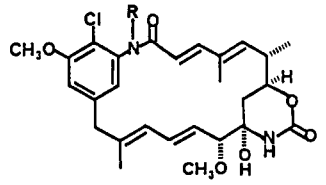
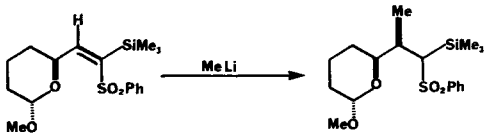


4a R = H
4b R = Me

structures by Kupchan et al. in 1972, the maytansinoids have become important targets for organic synthesis. Analogous compounds, the ansamycins [e.g., ansamitocin P-3 being maytansinol-3-isobutylate], were found in the fermented broth of a *Nocardia* sp.[3,4] A new class of maytansinoid containing two fused macrocyclic rings has been reported as a tumor inhibitor.[5] Several total syntheses have been reported.[6-8]

We would like to describe here a general synthetic strategy directed toward the maytansinoids via a common intermediate "A" as well as the total synthesis of racemic *N*-methylmaysenine. A total synthesis of (±)-maysine which features an acyclic diastereoselective formation of the epoxide ring of **3** is also discussed.

Retrosynthetic Analysis of Maytansinoids. The process we have called heteroconjugate addition[9] was developed for the synthesis of maytansinoids to provide an appropriate methodology capable of achieving highly selective asymmetric induction at the same time as it constructs the carbon skeleton. The principle of stereocontrol is illustrated, as a general transition-state model for the addition reaction, in Figure 1, where E represents a planar electrophile (with sp^2 orbital) located next to an asymmetric carbon atom bearing a protected secondary alcohol. N represents a nucleophile. Employment of a bulky substituent will restrict the conformational relation with the neighboring asymmetric carbon and thus leads to stereocontrol. Addition of methyllithium occurred as eq 1 in a



(1)

(1) Kupchan, S. M.; Komoda, Y.; Court, W. A.; Thomas, G. J.; Smith, R. M.; Karim, A.; Gilmore, C. J.; Haltiwanger, R. C.; Bryan, R. F. *J. Am. Chem. Soc.* **1972**, *94*, 1354.

(2) (a) Kupchan, S. M.; Komoda, Y.; Branfman, A. R.; Dailey, R. G., Jr.; Zimmerly, V. A. *J. Am. Chem. Soc.* **1974**, *96*, 3706. (b) Kupchan, S. M.; Branfman, A. R.; Sneden, A. T.; Verma, A. K.; Dailey, R. G., Jr.; Komoda, Y.; Nagao, Y. *J. Am. Chem. Soc.* **1975**, *97*, 5294. (c) 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.

(3) (a) Higashide, E.; Asai, M.; Ootsu, K.; Kozai, Y.; Hasegawa, T.; Kishi, T.; Sugino, Y.; Yoneda, M. *Nature (London)* **1977**, *270*, 721. (b) Asai, M.; Mizuta, E.; Izawa, M.; Haibara, K.; Kishi, T. *Tetrahedron* **1979**, *35*, 1079.

(4) Komoda, Y.; Kishi, T. "Anticancer Agents Based on Natural Product Models"; Ed. by Cassady, J. M., Douros, J. D., Eds.; Academic Press New York, 1980; Chapter 10, pp 353–389.

(5) Powell, R. G.; Weisleder D.; Smith, C. R., Jr.; Kozlowski, J.; Rohwedder, W. K. *J. Am. Chem. Soc.* **1982**, *104*, 4929.

(6) Meyers, A. I.; Reider, P. J.; Campbell, A. L. *J. Am. Chem. Soc.* **1980**, *102*, 6597.

(7) Corey, E. J.; Weigel, L. Q.; Chamberlin A. R.; Cho, H., Hua, D. H. *J. Am. Chem. Soc.* **1980**, *102*, 6615.

(8) Isobe, M.; Kitamura, M.; Goto, T. *J. Am. Chem. Soc.* **1982**, *104*, 4997.

(9) Isobe, M.; Kitamura, M.; Goto, T. *Tetrahedron Lett.* **1979**, 3465.

(10) Heathcock, C. H.; Young, S. D.; Hagen, J. P.; Pirrung, M. C.; White, C. T.; VanDerveer, D. *J. Org. Chem.* **1980**, *45*, 3846. (b) Still, W. C.; McDonald, J. H., III *Tetrahedron Lett.* **1980**, *21*, 1031.

(11) Isobe, M.; Kitamura, M.; Goto, T. *Tetrahedron Lett.* **1981**, *22*, 239.

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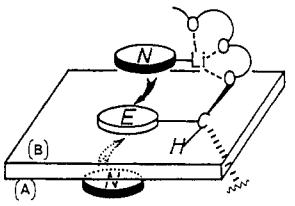


Figure 1.

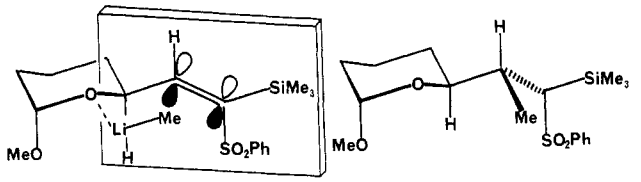


Figure 2.

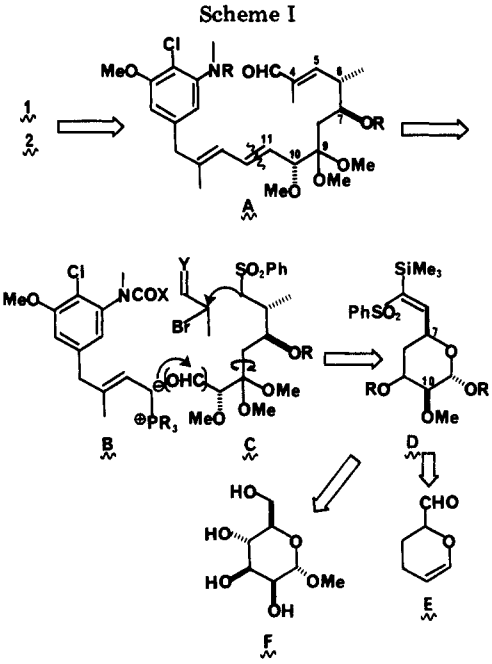
syn-diastereoselective manner (irrespective of E/Z geometry of the heteroolefin). The stereochemical process is shown in Figure 2, where MeLi first chelates with the ethereal oxygen atoms to make the selective attack of the methyl anion pseudointramolecularly. Second, MeLi is located over the sp^2 orbital of the heteroolefin in the transition state. As a rule, the nucleophile attacks from the oxygen face when the least bulky substituent (H) is brought near to the olefin.

Retrosynthetic analysis of maytansinol (**2**) led us to a key intermediate "A" (Scheme I) via the following operations involving (i) retroaldol reaction to cleave the C-2/C-3 bond, (ii) reduction of the epoxide into an olefin, and (iii) hydrolysis of the carbamate ring to the intermediate (A) possesses the three common asymmetric centers (C-6, 7, and 10) of the maytansinoids. Further disconnection of the double bond of A at C-11/C-12 and at C-4/C-5 affords a hypothetical right-hand side segment "C", while the left-hand one may be the phosphonium ylide "B". Cyclization of C suggests its precursor to be "D" in which a C-10 methoxy group corresponds to the 2β position of a pyranose sugar. The sulfonyl group in "C" assists bond formation between C-4 and 5 and would result from heteroconjugate addition to a heteroolefin "D" as Figure 2. These considerations then led us to acrolein dimer "E" as the starting material for racemic maytansinoids, while a D-hexopyranoside such as D-mannose "F" was selected for the synthesis of an optically active one. The synthesis of racemic "A" (**20**) from acrolein dimer "E" (**5**) follows.

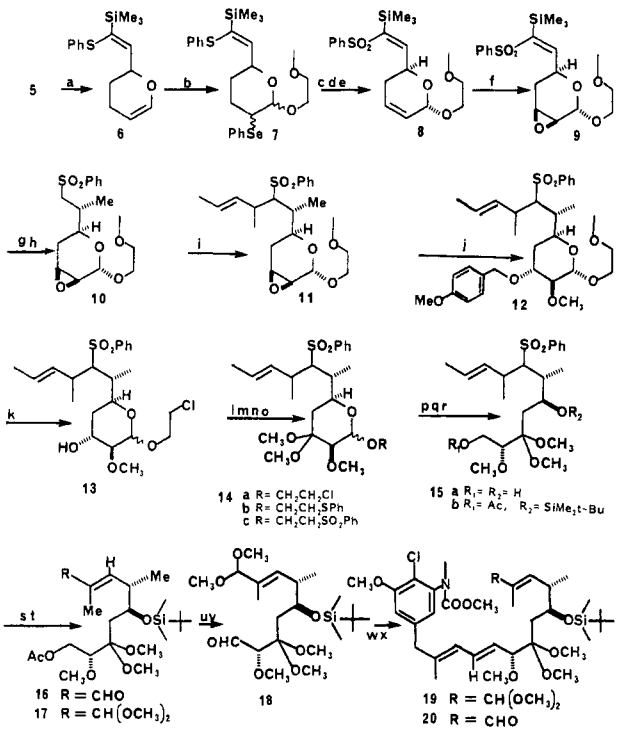
Synthesis of the Key Intermediates. The pyranosyl heteroolefin **8** was prepared in 50% overall yield by successive treatment of acrolein dimer **5**: (i) Peterson's olefination with [bis(trimethylsilyl)(phenylthio)methyl]lithium[12] (into **6**), (ii) oxy selenation with benzeneselenenyl chloride in the presence of methoxyethanol (into **7**), and (iii) oxidation of the sulfide and selenide with 3 equiv of MCPBA followed by heating to form **8**. When **8** was epoxidized with an additional equivalent of MCPBA in CH_2Cl_2 at room temperature in the dark for 3 days, it gave a mixture of **9** and its α isomer (in a ratio of 85:15), which was separated to give **9** in 79.1% yield. Addition of MeLi to a solution of **9** in THF at −78 °C for 5 min and treatment of the adduct with KF in MeOH yielded **10** quantitatively. The complete diastereoselective addition was confirmed by ^{13}C NMR spectroscopy, indicating no evidence of another isomer. The carbanion of the sulfone **10**, generated by *n*-BuLi, was alkylated with 4-bromo-pent-2-ene at 0 °C for 30 min to afford **11**. Opening of the oxirane ring of **11** with sodium *p*-anisyl oxide and subsequent methylation of the resultant alkoxide with methyl iodide in THF gave **12** in 80% yield. The *p*-anisyl group allowed liberation of the hydroxyl in mild acidic media. Further functional group transformations in **12**–**16** to distinguish the hydroxy groups or acetal groups were performed by highly chemoselective protections and de-

(12) Groebel, B.-Th.; Seebach, D. *Chem. Ber.* **1977**, *110*, 852.

Scheme I

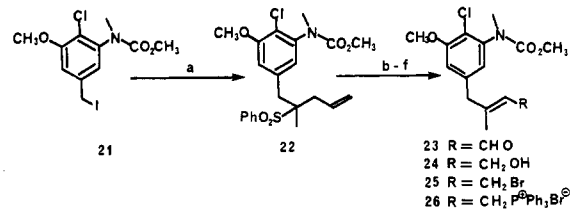


Scheme II[a]



[a] (a) $PhS(Me_3Si)_2CLi$/THF; (b) PhSeCl/$HOCH_2CH_2OCH_3$, Py; (c) 3 equiv MCPBA; (d) Δ; (e) CSA/$HOCH_2CH_2OCH_3$; (f) MCPBA in the dark; (g) MeLi/THF; (h) KF-MeOH; (i) *n*-BuLi/4-bromopent-2-ene (j) *p*-$MeOC_6H_4CH_2ONa$/THF, MeI; (k) CSA/CH_2Cl_2-$HOCH_2CH_2Cl$; (l) CrO_3-2Py; (m) CSA/$HC(OMe)_3$-MeOH; (n) PhSNa/THF; (o) MCPBA; (p) $NaBH_4$/EtOH; (q) AcCl/Py; (r) *t*-$BuMe_2SiCl$-imidazole/DMF; (s) O_3/CH_2Cl_2, Et_3N; (t) PPTS/$HC(OMe)_3$-MeOH; (t) NaOMe-MeOH; (v) CrO_3-2Py; (w) **26**, *t*-BuLi/THF-DMF (2:1); (x) AcOH-THF-H_2O (4:1:1).

Scheme III[a]



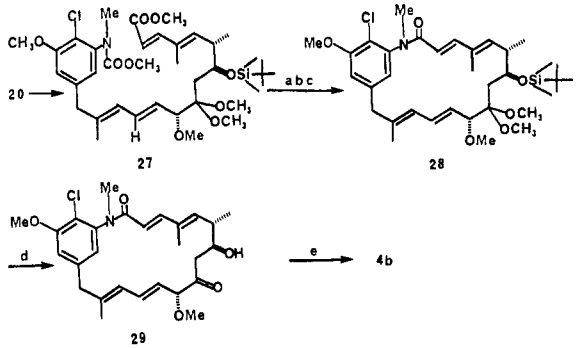
[a] (a) LiC(SO_2Ph)(CH_3)$CH_2CH{=}CH_2$/THF; (b) O_3/CH_2Cl_2, Et_3N; (c) $NaBH_4$; (d) PBr_3-LiBr/collidine-THF-Et_2O; (e) $PPh_3/MeNO_2$; (f) *t*-BuLi/THF-DMF (2:1).

protections. For example, the glycosidic bond must be cleaved at the step from **14c** to **15a** under basic conditions because of the emergence of the carbonyl function protected as a ketal in **14c**. First of all, trans glycosidation of **12** was effected under acidic conditions in the presence of chloroethanol with concomitant hydrolysis to the alcohol **13**. After oxidation of this alcohol with dipyridinium chromate, the resulting ketone was ketalized to **14a** with trimethyl orthoformate and CSA. The chloroethyl moiety of **14a** was converted by sodium thiophenolate and MCPBA via **14b** into **14c** in 78% overall yield from **13**. This particular glycoside in **14c** was extremely alkaline labile.[13] For example, when **14c** was treated with sodium hydride in THF, it was converted into an equilibrium mixture of the corresponding hemiacetal and aldehyde. It was also converted by sodium borohydride which was basic enough to cleave this glycoside with concomitant reduction in a mixture of ethanol and THF (4:1), at 80 °C for 1 h, to produce the open chain diol **15a** in 70% yield. The primary and the secondary hydroxy groups of **15a** were selectively protected first with acetyl chloride and pyridine at 0 °C, and then with dimethyl-*tert*-butylchlorosilane and imidazole in DMF at 70 °C for 30 h to give **14b** in 90% overall yield. Ozonolysis of the double bond of **15b** was followed by a workup with triethylamine, which reduced the ozonide at −78 °C and also promoted the elimination of the phenylsulfonyl group as the temperature rose to room temperature to yield, in a one pot operation, the stereochemically pure unsaturated aldehyde **16** in 99% yield.

The aldehyde **16** was converted into another aldehyde **18** in three steps (91%) overall yield): (i) ketalization of the aldehyde **16** with trimethyl orthoformate in the presence of pyridinium tosylate at 0 °C for 2 days, (ii) alcoholysis of the acetate with MeONa (1.5 equiv) in MeOH at room temperature for 45 min, and (iii) oxidation with CrO_3–2Py (6 equiv) in CH_2Cl_2. The acetal **18** was now ready for condensation with the aromatic counterpart **26**, which was prepared separately.

Preparation of **26** is summarized in Scheme III; the phosphorous ylide **26** was synthesized in seven steps in 45% overall yield from the iodide **21**.[14] Thus, **21** was treated with 4-lithio-4-(phenylsulfonyl)pent-1-ene in THF at −78 °C for 15 min. Ozonolysis of the product **22** and workup with Et_3N gave unsaturated aldehyde as an isomeric mixture (*E*/*Z* 5:1) which was separated by silica gel chromatography.[15] The major *E* isomer **23** was reduced with $NaBH_4$ in EtOH to **24** which was then brominated with phosphorous tribromide (1.3 equiv) in the presence

Scheme IV[a]



[a] (a) 12 N KOH-dioxane-MeOH (1:2:1); (b) *n*-Bu_4NOH/toluene, azeotropically dried; (c) 2-mesitylenesulfonyl chloride, *N,N*-diisopropylethylamine/benzene; (d) CSA/aqueous MeOH; (e) *p*-$NO_2C_6H_4OCOCl$/Py, NH_3-MeOH.

of LiBr and collidine to afford **25**. Treatment of **25** with PPh_3 in CH_3NO_2 and then with *t*-BuLi in a mixture of THF and DMF (2:1) at low temperatures afforded the reactive ylide from **26** to which was added the aldehyde **18**. The product **19** which showed a single spot on TLC was separated from the reagent by silica gel column chromatography to give the diene **19** in 78% yield. This product was eventually found to be a mixture of *E*/*Z* isomers at the C-11/C-12 double bond in the ratio of 55:45.[16] Since the allylic acetal **19** was very unstable, it was selectively hydrolyzed with a mixture of THF–AcO-H–H_2O (4:1:1) at −10 °C for 2 days to yield the unsaturated aldehyde **20**, which was used without further purification for the following steps. A part of the sample was separated by HPLC with silica gel to give the pure key intermediate **20** corresponding to "A" in Scheme I.

Total Synthesis of (±)-*N*-Methylmaysenine (4b). The validity of our strategy was demonstrated by the synthesis of racemic *N*-methylmaysenine as shown in Scheme IV. The key intermediate **20** was condensed with the sodium salt of methyl (diethoxyphosphinyl)acetate at −78 °C for 30 min and then at room temperature for 4.5 h to give **27**. After hydrolysis of the ester and urethane of **27** with KOH [in a mixture of H_2O–MeOH–dioxane (1:1:2) at 90 °C for 12 h in 65% overall yield], the lactam ring was formed in 70% yield by treatment with *n*-Bu_4OH and then with 2-mesitylenesulfonyl chloride in the presence of diisopropylethylamine in benzene at 40 °C under very dilute conditions, as described by Corey et al.[17a] Interestingly, both of the 11-*E* and 11-*Z* isomers of **20** did cyclize and the products were separated by preparative silica gel TLC (ether–hexane 1:1) to give **28** and (11-*Z*)-**28** in 36.2% and 24.3% isolated yield, respectively.[16] The major product **28**, was transformed with CSA in MeOH at room temperature for 12 h to the ketol **29**, which was converted into the cyclic carbamate in a one-pot reaction (involving *p*-nitrophenyl chloroformate and then ammonia at 0 °C) to afford *N*-methylmaysenine (**4b**) in 73% overall yield

(13) Narang, S. A.; Bhanot, O. S.; Goodchild, J.; Wightman, R. J.; Dheer, S. K. *J. Am. Chem. Soc.* **1972**, *94*, 6183.
(14) Gotschi, E.; Schneider, F.; Wagner, H.; Bernauer, K. *Org. Prep. Proced. Int.* **1981**, *13*, 23.
(15) Chromatographic separation was not necessary in a large scale preparation, since only the desired *E* isomer crystallized in the phosphonium salts (**26**).
(16) The key intermediate (**20**) was used as a mixture with its C-11 *Z* isomer without separation due to the nonstereoselective Wittig reaction and because of an impractical separation of the isomer. The 11-*Z* isomer was readily separated at the lactam cyclization step as **28** and **39**. As for the cyclization yield, the secoacids contained ca. 55% of the 11-*E* isomer (**27** and **38**), the isolation of **28** and **39** in 36.2% and 46% is counted as 66% and 84% of the theoretical amount, respectively.
(17) (a) Corey, E. J.; Weigel, L. O.; Floyd, D.; Bock, M. G. *J. Am. Chem. Soc.* **1978**, *100*, 2916. (b) Corey, E. J.; Weigel, L. O.; Chamberlin A. R.; Lipshutz, B. *J. Am. Chem. Soc.* **1980**, *102*, 1439. (c) Meyers, A. I.; Roland, D. M.; Comins, D. L.; Henning, R.; Fleming, M. P.; Schimizu, K. *J. Am. Chem. Soc.* **1979**, *101*, 4732. (d) Isobe, M.; Kitamura, M.; Goto, T. *Chem. Lett.* **1982**, 1907.

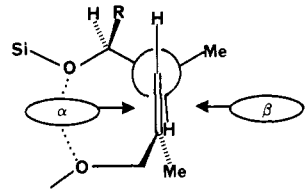
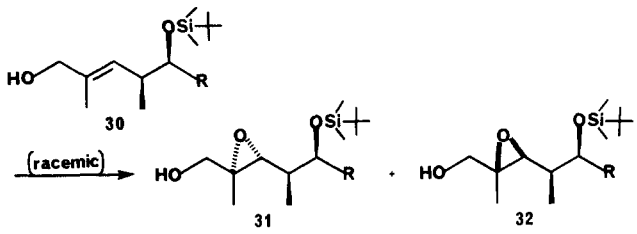


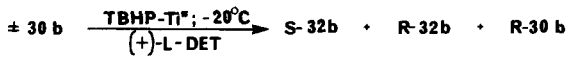
Figure 3.

Scheme V



MCPBA	a	99	:	1
"	b	40	:	1
TBHP-Ti"	a	1	:	10
"	b	1	:	99

a R= $(CH_2)_4OSi$ b R= $CH_2C(OMe)_2CH(OMe)CH_2OAc$



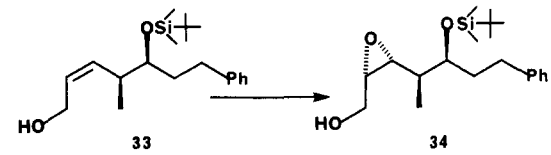
12 hr	3	: 2	: 1
5 hr	2	: 1	: 1

after purification by silica gel chromatography. The ^1H NMR spectrum at 400 MHz, IR, MS (high resolution), and chromatographic behavior were all identical with those of an authentic sample.[17]

Diastereoselective Epoxidation. A precursor of the epoxide ring for maysine (**3**) is a corresponding trisubstituted olefin such as **30**. The predicted stereochemistry of the epoxide, using MCPBA,[18] is anti orientation as in **31**. Maytansinoids, however, demand syn epoxides such as **32** which were unavailable until we found the following highly syn selective process.[19] General acyclic stereocontrol in the epoxidation is well explained by a transition-state model in the Newman projection illustrated in Figure 3; thus, the olefin is oriented by the asymmetric carbon so that the least bulky substituent (H) comes close to the substituted olefin. In this case, the secondary alkoxy group is located over the α face of the olefin, usually chelating with the reagent to accelerate attack from the α side to afford predominantly the anti epoxide.[18a] As a working hypothesis to achieve the required syn selectivity for the maytansinoids, the chelation face must be blocked so that the reagent could attack the olefin intermolecularly only from the opposite (nonchelated) face to afford the syn orientation. A proper *diastereo*selective protocol was found during the course of a study on *enantio*selective epoxidation as described below.

When the racemic trisubstituted olefin **30** was treated with titanium tetraisopropoxide, diethyl L-(+)-tartrate, and *tert*-butyl hydroperoxide (TBHP) in CH_2Cl_2 at −20 °C for 12 h under Sharpless conditions,[20] it was epoxidized in 80% yield together with some starting material (15%). The stereochemistry of this epoxidation had been expected to yield largely enantiomerically pure *S* epoxide, part of a diastereomeric mixture consisting of both syn and anti configuration. Contrary to this prediction, the epoxide was in fact a 3:2 mixture of enantiomers of the *S* epoxide ((*S*)-**32**) and *R* epoxide (*R*)-**32**) but the relative stereochemistry of the epoxides was pure syn.[21] A small amount (15%) of the starting material was recovered in optically active form.[21] When the reaction was interrupted after a shorter period (5 h at −20 °C) the ratio of *S* and *R* epoxide became ca. 2:1, while the olefin was recovered in optically pure form in 45% yield of the theoretical amount. The optical purity was determined by converting the alcohols (**30**, **31**, and **32**) into the corresponding (+)-MTPA esters of **32**. The pure anti epoxide **31** was prepared from **30** with MCPBA at −20 °C for 10 min. The assignment of the stereochemistry was based on the ^1H NMR signal of the epoxidic protons which appeared at δ 2.82 (d, J = 9.0 Hz) for the syn epoxide and at δ 2.87 (d, J = 8.5 Hz) for the anti epoxide, respectively. In conclusion, *no enantioselective epoxidation took place at all, but a highly diastereoselective epoxidation and partially kinetic resolution was observed.*

Since the epoxidation took place in a diastereoselective manner under Sharpless conditions in the special case of olefin **30**, the reaction conditions were improved by leaving out the chiral auxiliary. When the olefin **30a** was simply treated with $Ti(OiPr)_4$ and TBHP at −20 °C, it was converted largely into the syn epoxide **32a** together with a very small amount of the anti epoxide **31a** in a ratio of ca. 10:1. A more functionalized olefin (**30b**) was also converted into the syn epoxide (**32b**) exclusively without a detectable amount of anti product, the ratio exceeding 99:1. Another example of the cis olefin (**33**) was similarly converted into 85% syn epoxide **34** and 15% anti isomer in 82% yield. The real intermediate (**35**) for maysine was subjected to the same conditions at −20 °C for 1.5 h to afford, almost exclusively, **36** in 70% yield (vide infra).



Total Synthesis of (±)-Maysine. The high selectivity in the acyclic epoxidation prompted us to accomplish the total synthesis of racemic maysine (**3**), which is summarized in Scheme VI. The key intermediate (**20**) was converted into the epoxy aldehyde **37** via diastereoselective syn epoxidation (vide supra) of the allylic alcohol **35** [formed by $NaBH_4$ followed by hydrolysis with 12 N KOH–EtOH (1:3)]. The olefin of **35** was epoxidized

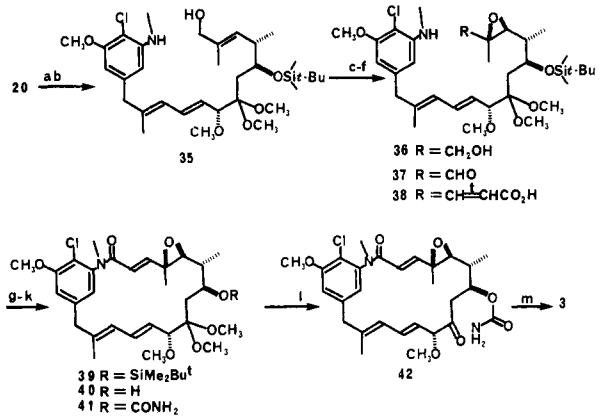
(18) (a) Rossiter, B. E.; Verhoeven, T. R.; Sharpless, K. B. *Tetrahedron Lett.* **1979**, 4733. (b) Mihelich, E. D. *Ibid.* **1979**, 4729. (c) Dehnel, R. B.; Whitham, G. H. *J. Chem. Soc. Perkin Trans. 1* **1979**, 953. (d) Itoh, T.; Jitsukawa, K.; Kaneda, K.; Teranishi, S. *J. Am. Chem. Soc.* **1979**, *101*, 159. (e) Mihelich, E. D.; Daniels, K.; Eickhoff, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 7690. (f) Tomioka, H.; Suzuki, T.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1982**, *23*, 3387. (g) Narula, A. S. *Tetrahedron Lett.* **1982**, *23*, 5579.

(19) Isobe, M.; Kitamura, M.; Mio, S.; Goto, T. *Tetrahedron Lett.* **1982**, *23*, 221.

(20) Katsuki, T., Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.

(21) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237. *R–S* epoxides of **32** were assigned from the *S* epoxidation which is presumed to proceed faster than the other.

Scheme VI[a]



[a] (a) $NaBH_4$; (b) 12 N KOH-EtOH (1:3); (c) TBHP-Ti(O-*i*-Pr)$_4$/CH_2Cl_2; (d) SO_3-Py/DMSO-Et_3N; (e) $MeO_2CCHNaPO(OEt)_2$/THF; (f) 1 N KOH-THF-EtOH (2:5:5); (g) *n*-Bu_4NOH/toluene azeotropically dried; (h) 2-mesitylenesulfonyl chloride, *N,N*-diisopropylamine/benzene; (i) *n*-Bu_4NF/CH_3CN-THF (2:1); (j) *p*-$NO_2C_6H_4OCOCl$/Py; (k) NH_3-MeOH; (l) AcOH-THF-H_2O (2:1:1); (m) NH_3-MeOH.

[TBHP, Ti(OiPr)$_4$ in CH_2Cl_2 at −20 °C] to **36** (60% from **20**) whose hydroxy group was converted into the aldehyde **37** [SO_3–Py in Me_2SO in the presence of Et_3N]. Addition of a two-carbon fragment to the aldehyde (**37**) with sodium methyl diethyl phosphonoacetate in THF and a basic hydrolysis of the ester group of the product [1 N KOH in a mixture of THF and EtOH] gave the carboxylic acid **38** (72% overall yield from **36**). Lactam formation took place by treatment of its tetrabutylammonium salt with 2-mesitylenesulfonyl chloride and diisopropylethylamine under high dilution conditions to give the cyclized product **39** in 46% yield.[16] Hydrolysis of the silyl ether of **39** with tetrabutylammonium fluoride afforded alcohol **40** (70% yield) which was then carbamoylated [*p*-nitrobenzoyl chloride and then ammonia] into **41** (83% yield). [Initial deketalization, followed by carbamoylation, produced a very low yield of maysine (**3**)]. Deketalization of the dimethyl acetal (**41**) was done with a mixture of acetic acid–THF–water (2:1:1) at 35 °C for 2 h.[22] When the reaction mixture was neutralized with ammonia, the intermedite was converted immediately into a polar product, which was purified with silica gel TLC by using ethyl acetate as the developing agent, to give pure (±)-maysine (**3**) in 71% isolated yield.[23]

The success of the total synthesis of (±)-*N*-methylmaysenine (**4b**) provided a chemical proof that the key intermediate "A" = **20** has the right configuration at three common asymmetric centers of the maytansinoids. The stereocontrolled total synthesis of racemic maysine (**3**) demonstrated the value of a new diastereoselective epoxidation. These developments prompted us to devise a total synthesis of racemic maytansinol as well as of the chiral substance starting from a D sugar. This is described in a separate paper.[24]

(22) Interestingly, the TLC analysis of the reaction mixture showed an intermediate which was assigned to **42** as a less polar substance than the authentic maysine (**3**).

(23) (a) Meyers, A. I.; Comins,D. L.; Roland, D. M.; Henning, R.; Shimizu, K. *J. Am. Chem. Soc.* **1979**, *101*, 7104. (b) Meyers, A. I.; Babiak, K. A.; Campbell, A. L.; Comins, D. L.; Fleming, M. P.; Henning, R.; Heuschmann, M.; Hudspeth, J. P.; Kane, J. M.; Reider, P. J.; Roland, D. M.; Shimizu, K.; Tomioka, K.; Walkup, R. C. *J. Am. Chem. Soc.* **1983**, *105*, 5015.

Experimental Section

Melting points were determined by using a Mitamura Riken direct hot stage melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a JASCO IR-A3 spectrophotometer and are reported in wavenumber (cm^{-1}). Proton nuclear magnetic resonance spectra were recorded on a JEOL MH-100, or FX-100 except where "200 MHz" or "400 MHz" denotes spectra recorded on a JEOL FX-200 or FX-400. All spectra were dissolved in $CDCl_3$ and chemical shifts are reported as δ values in parts per million relative to tetramethylsilane (δ 0.0) as internal standard. Data are reported as follows: chemical shift (integrated intensity, multiplicity, coupling constants in Hz). Carbon nuclear magnetic resonance (^{13}C NMR) were recorded on a JEOL FX-100 spectrometer in $CDCl_3$. Chemical shifts are reported as δ values in parts per million relative to tetramethylsilane (δ 0.0) as an internal standard. Low-resolution electron-impact mass spectra were recorded on JEOL D-100 machine using direct probe insertion. High-resolution mass spectra were performed by JEOL 01-SG-2 instrument.

Analytical thin-layer chromatography (TLC) was conducted on precoated TLC plates: silica gel 60 F-254, layer thickness 0.25 mm, supplied by E. Merck(Art 7734) Darmstadt, Germany. Silica gel columns for chromatography utilized Fuji Devison (BW 820-MH) or E. Merck (Art no. 7734). Fiji Devison micro beads silica gel (B-20) used for medium-pressure column chromatography.

Dry solvents and reagents were distilled shortly before use from an apparatus under nitrogen atmosphere, except ether which was purchased from Sanraku Ocean Whisky Co. in a can as absolute grade. Tetrahydrofuran (THF) and dimethoxyethane (DME) were distilled from potassium metal with potassium benzophenone ketyl as an indicator. Dimethyl sulfoxide (Me_2SO), dimethylformamide (DMF), and hexamethylphosphoramide (HMPA) were distilled under reduced pressure from calcium hydride. Dichloromethane was dried over alumina and used without distillation.

Preparation of the Pyranosyl Heteroolefin 8. Acrolein dimer **5** [40 mL, 0.37 mol dissolved in THF (100 mL)] was added to a solution of lithium bis(trimethylsilyl)(phenylthio)methylide [0.36 mol in a mixture of THF (1.9 L) and hexane (0.2 L), generated from the corresponding methane derivative with *n*-butyllithium] at −78 °C under argon atmosphere. After the addition, the reaction mixture was warmed to room temperature by removing the dry ice bath, and then it was worked up with ammonium chloride solution and hexane. The organic layer was separated, washed with water and brine, dried over sodium sulfate, passed through a short column of silica gel [1 kg, washed with a mixture of ether–hexane 1:15] and then evaporated to give 76 g (72%) as *E* and *Z* regioisomers of **6**, which can be used for the following reactions. If necessary, one can separate the mixture completely by preparative liquid chromatography [Waters-S-500 with a mixture of ether and hexane (1:30 v/v) eluant] to obtain the pure *E* and *Z* isomer in a ratio of 43:57. (*E*)-**6**: ^1H NMR δ 0.24 (9 H, s), 1.7 (2 H, m), 1.9 (2 H, m), 4.50 (1 H, dd, J = 9, 3), 4.60 (1 H, m), 5.92 (1 H, d, J = 9), 6.30 (1 H, brd, J = 6), 7.3 (5 H, m). (*Z*)-**15**: δ 0.10 (9 H, s), 1.88 (2 H, m), 2.04 (2 H, m), 4.76 (1 H, m), 5.08 (1 H, dt, J = 7.5, 4), 6.42 (1 H, brd, J = 6), 6.56 (1 H, d, J = 7.5), 7.28 (5 H, m). To a solution of (*E*) and/or (*Z*)-**6** [20 g, 69 mmol dissolved in dichloromethane (400 mL) containing ethylene glycol monomethyl ether (130 mL) and pyridine (17 mL, 210 mmol)] was added phenylselenenyl chloride [14 g, 73.1 mmol] at 0 °C in one portion and then another 14 g of the chloride in 10 min. The reaction was completed in 30 min, and the mixture was washed with ice cold sodium bicarbonate [5%, 200 mL]. The aqueous layer was extracted three times with dichloromethane. The combined organic layer was washed with water, dried over sodium sulfate, and then evaporated in vacuo to give crude selenide **7**. The excess reagent was separated by silica gel column chromatography [SiO_2, 200 g, hexane], and pure **7** was eluted with a mixture of hexane and ether (4:1) to give 32 g (92%). To an ice cold solution of **7** [32.4 g, 62.4 mmol in dichloromethane (800 mL)] was added MCPBA [80% 50 g, 232 mmol] and the mixture

(24) Kitamura, M.; Isobe, M.; Ichikawa, Y.; Goto, T. *J. Am. Chem. Soc.* **1984**, *106*, 3252.

was stirred for 1 h at 0 °C and then further mixed with saturated aqueous sodium sulfite (100 mL) and 5% aqueous sodium bicarbonate (100 mL). After 15 min of vigorous stirring, the aqueous layer was extracted twice with dichloromethane. The combined organic layer (2 L) was washed with water, dried over anhydrous sodium sulfate, and evaporated to $^1/_3$ volume. The remaining solution was refluxed for 20 h with pyridine [30 mL, 0.37 mmol] and then vigorously stirred at 0 °C, while 30% H_2O_2 was added dropwise to decompose diphenyl diselenide to the selenenic acid. The resulting colorless solution was partitioned between dichloromethane and water, and the organic layer was washed successively with 5% sodium bicarbonate, saturated sodium sulfite, and water, dried over anhydrous sodium sulfate, and evaporated to give the crude mixture of α- and β-glycoside **8** (1:1, 26 g). This crude anomeric mixture (26 g) was dissolved in dichloromethane (480 mL) and ethylene glycol monomethyl ether (160 mL) and then treated with *d,l*-10-camphorsulfonic acid (1 g) at room temperature for 20 h. After the usual workup, the yellow oil was chromatographed on SiO_2 (200 g) with 1:1 ether-hexane as eluant to give a small amount (5%) of the β-isomer of **8** and pure **8** [in 70% overall yield from **6**]. **8**: ^{1}H NMR δ 0.28 (9 H, s), 2.06 (2 H, m), 3.3 (3 H, s), 3.50 (4 H, m), 4.98 (1 H, br s), 5.28 (1 H, dt, J = 5, 8), 5.5–6.2 (2 H, m), 6.50 (1 H, d, J = 8), 6.56 (3 H, m), 6.88 (2 H, m); IR_{CCl_4} ν 1660, 1605 cm^{-1}; m/z 396 (M^+), 381, 321.

Epoxidation of 8 and Heteroconjugate Addition. A solution of **8** [1.75 g, 4.4 mmol in dichloromethane (58 mL)] was stirred with 80% MCPBA [1.5 g, 6.95 mmol] at room temperature in the dark for 3 days. The reaction mixture was treated with sodium sulfite and sodium bicarbonate and then partitioned between dichloromethane and water. The organic layer was washed successively with sodium bicarbonate, water, and half-saturated brine, dried over anhydrous sodium sulfate, and evaporated to give the practically pure product **9** (1.7 g, in 93% yield). The mixture of α-**9**: β-**9** (15:85) was readily separated by column chromatography on SiO_2 (30 g) eluted with ether–hexane 1:1 to give the epoxide **9**: ^{1}H NMR δ 0.24 (9 H, s), 1.5–2.2 (2 H, m), 3.06 (1 H, d, J = 4), 3.36 (1 H, m), 3.38 (3 H, s), 3.52 (4 H, brs), 5.02 (1 H, brs), 5.20 (1 H, m), 6.38 (1 H, d, J = 8), 7.6 (3 H, m), 7.86 (2 H, m). A solution of **9** [20 g, 48.5 mmol in THF (450 mL)] was cooled to −78 °C with a dry ice acetone bath. To this cold solution was added at −78 °C an ethereal solution of methyllithium [lithium bromide complex, 1.5 M, 40 mL, 60 mmol]. After 5 min, the resulting yellow mixture was mixed with saturated ammonium chloride (30 mL), and then extracted with ether three times. The combined extracts were washed successively with water and brine and dried over anhydrous sodium sulfate. The solution (ca. 260 mL) was mixed with potassium fluoride (8 g, 137 mmol) and methanol (130 mL) at room temperature for 1 h. After washing the reaction mixture with water, the mixture was dried on anhydrous sodium sulfate and evaporated to give in quantitative yield the pure **10** (17 g): ^{1}H NMR δ 1.06 (3 H, d, J = 7), 1.6–1.9 (2 H, m), 2.16 (1 H, m), 2.88 (1 H, dd, J = 8, 15), 2.94 (1 H, d, J = 4), 3.30 (3 H, s), 3.1–4.0 (7 H, m), 4.88 (1 H, s), 7.3–7.9 (5 H, m); ^{13}C NMR δ 14.6, 24.7, 32.1, 49.0, 49.8, 58.7, 59.0, 65.8, 67.5, 71.6, 95.4, 127.8, 129.2, 133.4, 140.1; IR_{CCl_4} ν 1445, 1320, 1310, 1150 cm^{-1}; MS, m/z 356 (M^+), 297, 281, 262.

Alkylation and Functionalization of 10. To a solution of **10** [6.1 g, 17.1 mmol in THF (100 mL) and HMPA (25 mL)] was added dropwise a solution of *n*-butyllithium [1.6 M, 13.5 mL 21.6 mmol in hexane] at −78 °C and, after 10 min, 4-bromopent-2-en [2.6 mL 21.6 mmol]. The reaction mixture was allowed to warm to 0 °C and was stirred for 30 min at this temperature. It was poured into saturated ammonium chloride and ether and extracted with ether three times. The organic layer was washed successively with saturated ammonium chloride, water, and brine, dried over anhydrous sodium sulfate, and evaporated to give practically pure **11** (7.3 g) in almost quantitative yield. This materials was used in the following experiments without further purification. Sodium 4-methoxybenzyl alkoxide [prepared from 4-methoxybenzyl alcohol (10 mL, 80.2 mmol) and sodium hydride in THF (100 mL) at 0 °C under a nitrogen atmosphere] was added dropwise to a solution of **11** (7.3 g, 17.2 mmol) in THF (104 mL) at 0 °C with subsequent heating at reflux for 20 h under a nitrogen atmosphere. After cooling, the resulting alkoxide was further mixed with a large excess of methyl iodide at room temperature to give the crude **12** as a red oil. After stirring for 1 h, the reaction mixture was worked up. The excess of 4-methoxybenzyl methyl ether was distilled off by Kugelrohr (130 °C (0.3 mmHg)), and the resulting residue was chromatographed on SiO_2 [100 g, eluted with ether–hexane 1:1 and then 3:1] to afford pure **12** [8.7 g, 87% yield] as a slightly yellow oil. **12**: ^{1}H NMR δ 0.8–2.4 (13 H), 3.0–4.0 (8 H), 3.3–3.4 (OMe × 2), 3.75 (Ar-OMe), 4.0–5.0 ($ArCH_2O$, H-11), 5.0–6.0 (H-2, 3), 6.84 (ArH × 2), 3.75 (Ar-OMe), 4.0-5.0 ($ArCH_2O$, H-11), 5.0–6.0(H-2, 3), 6.84 (ArH × 2), 7.30 (ArH × 2), 7.5 (3 H, m), 7.8 (2 H, m); IR_{CCl_4} ν 1610, 1580, 1510, 1445, 1305, 1245, 1145 cm^{-1}; MS, m/z 501 (M^+ − 75, OCH_2CH_2OMe), 468 (M^+ − 108), 435 (M^+ − 141, SO_2Ph).

A mixture of **12** [7.5 g, 13.0 mmol)], *d,l*-10-camphorsulfonic acid [800 mg, 3.4 mmol], methyl orthoformate [3 mL], and 2-chloroethanol [180 mL] was heated at 80 °C for 18 h. The reaction mixture was poured into ice cold 5% sodium bicarbonate and dichloromethane, and then extracted two times with dichloromethane. The extracts were combined, washed with water and brine, dried over anhydrous sodium sulfate, and evaporated to give a drak colored residue (10 g). This product was passed through a short column of silica gel [silica gel, 80 g, eluant, ether–hexane (1:3) removing chloroethyl 4-methoxybenzyl ether and then ether–hexane (3:1)] to afford pure **13** as a slightly red oil in 92% yield. **13**: -H NMR δ 0.8–2.4 (13 H), 3.0–4.4 (8 H), 3.9 (OH), 3.3–3.5 (OMe × 3), 4.5–5.0 (H-11, m), 5.0–6.0 (H-2, 3, m), 7.5 (3 H, m), 7.8 (2 H, m); IR_{CCl_4} ν 3550, 1450, 1305, 1145, 1115, 1080, 980 cm^{-1}; MS, m/z 381 (M^+ -79, OCH_2CH_2Cl), 319 (M^+ - 141, SO_2Ph), 281, 279.

To a vigorously stirred solution of **13** [5.8 g, 12.6 mmol in dichloromethane (120 mL)] was added dipyridinium chromate [20 g, 77.5 mmol] at room temperature. After 30 min, the dark brown reaction mixture was diluted with ether (300 mL) and then filtered through Cellite and silica gel. A lump of excess reagent in the flask was crushed to a fine powder, washed with five 50-mL portions of ether and filtered. The combined filtrate was concentrated under reduced pressure to give a ketone [5.6 g, IR_{CHCl_3} ν 1730 cm^{-1}], which was dissolved in methanol (170 mL) and methyl orthoformate (17 mL). The solution was stirred in the presence of a ctalytic amount of *d,l*-10-camphorsulfonic acid (500 mg) for 12 h at room temperature and then poured into 5% sodium bicarbonate containing cracked ice and dichloromethane. The organic layer was separated, washed with water and brine, dried over anhydrous sodium sulfate, and then concentrated under reduced pressure to afford **14a** (5.8 g) as a mixture of diastereoisomers in 94% yield. This material was used for the next step without further purification.

Sodium thiophenolate [prepared from thiophenol (1.8 mL, 17.5 mmol) and sodium hydride (850 mg, 17.7 mmol washed with dry petroleum ether) in THF (40 mL) for 30 min at 0 °C under a nitrogen atmosphere] was added dropwise to a solution of **14a** [5.8 g, 11.5 mmol in THF (125 mL)] at 0 °C. After the addition was completed, the ice bath was removed, and the reaction mixture was stirred at room temperature for 12 h. Aqueous workup with ether gave **14b** (6.2 g) as a slightly yellow oil in 97% yield. **14b**: ^{1}H NMR δ 0.8–2.4 (13 H), 2.8–4.4 (7 H), 3.1–3.7 (OMe × 3), 4.4–5.0 (H-11, m), 5.0–6.0 (H-2, 3, m), 7.3 (SPh, m), 7.5 (3 H), 7.8 (2 H); IR_{CCl_4} ν 1580, 1445, 1305, 1145, 1115, 1085, 970 cm^{-1}; MS, m/z 578 (M^+), 515, 505, 469, 437; found 578.238, calcd for $C_{30}H_{42}O_7S_2$ 578.237.

The sulfide **14b** [6.2 g, 10.7 mmol in dichloromethane (200 mL)] was oxidized with 80% MCPBA [5.1 g, 23.6 mmol] for 30 min at 0 °C. Excess MCPBA was decomposed with saturated sodium sulfite. The organic layer was washed with 5% sodium bicarbonate and water, dried over anhydrous sodium sulfate, and evaporated to yield **14c** (6.6 g) as a colorless oil. This material was used for the next step without further purification. Purification of a part of this oil by SiO_2 TLC with ether as developing agent afforded pure sulfone (**14c**) as a diastereomixture in 93% yield from **14a**. **14c**: ^{1}H NMR δ 0.8–2.4 (13 H), 2.8–4.4 (7 H), 3.0–3.5 (OMe × 3), 4.6–4.9 (H-11), 4.9–5.0 (H-2, 3, m), 7.6 (6 H, m), 7.9 (4 H, m); IR_{CCl_4} ν 1580, 1445, 1320, 1305, 1145, 1115, 1080, 970 cm^{-1}; MS, m/z 610 (M^+), 469 (M^+ − 141), 437, 362, 360, 328.

Opening of the Pyranosyl Ring of 14c. The sulfone **14c** [6.6 g, 10.8 mmol dissolved in a mixture of ethanol (176 mL) and THF (44 mL)] was stirred with sodium borohydride [1.7 g, 45.0 mmol] for 1 h at 80 °C under a nitrogen atmosphere. After the reaction

was cooled, acetone was added to the reaction mixture to decompose excess sodium borohydride. The resulting solution was evaporated to half of its volume, poured into cold 0.1 N HCl, and then extracted four times with dichloromethane. The combined extracts were washed with water and brine, dried with anhydrous sodium sulfate, and then evaporated to afford the crude **15a** (6.3 g), which was used for the next reaction without purification. Purification of a part of this crude product **15a** by silica gel [first washed out with ether–hexane (5:1) and then eluted with ether] afforded the pure diol **15a** in 70% isolated yield. **15a**: ^{1}H NMR δ 1.0–2.3 (13 H), 3.1–3.6 (OMe × 3), 3.4–4.6 (4 H), 5.0–6.0 (H-2,3), 7.55 (3 H), 7.85 (2 H); IR_{CCl_4} ν 3550, 1445, 1305, 1145, 1120, 1085, 1045, 970 cm^{-1}; MS, m/z 385 (M^+ – 59), 382, 369, 350, 338.

Preparation of Diastereomerically Pure Compound 16. To an ice cold solution of **15a** [4.8 g, 10.8 mmol and pyridine (4.4 mL, 54.4 mmol) in dichloromethane (160 mL)] was added acetyl chloride [0.85 mL, 12.0 mmol] was added acetyl chloride [0.85 mL, 12.0 mmol] dropwise at 0 °C under a nitrogen atmosphere in 10 min. After 10 min, the reaction mixture was poured into ice cold water and extracted three times with dichloromethane. After the combined extracts were dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure, and the residual pyridine was removed in vacuo by repeated addition of toluene. The resulting acetate (5.0 g, 95% crude yield) was used for silylation in two portions. A solution of the crude acetate [2.7 g, 5.6 mmol] was stirred with imidazole [2.8 g, 41.1 mmol] and *tert*-butyldimethylchlorosilane [2.5 g, 16.6 mmol in DMF (15 mL)] for 30 h at 70 °C. The mixture was partitioned between ether and water. The water layer was throughly extracted three times with ether. After the combined extracts were washed with water and brine and dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure. The residue was chromatographed on silica gel [70 g, ether–hexane (1:2)] to give pure **15b** (3.2 g) in 95% yield. The overall yield of **15b** was 49% without intermediary purification from **13**. **15b**: ^{1}H NMR δ 0.14 (6 H, s), 0.86–0.92 (9 H, s), 1.0–1.4 (Me × 2), 1.5–1.7 (6 H) 1.3–2.5 (4 H), 2.1 (Ac), 2.8 (H-4, m), 3.2–3.26 (OMe × 2, s × 4), 3.5 (OMe, s × 2), 3.3–4.6 (5 H), 5.0–5.9 (H-2, 3), 7.5 (3 H), 7.8 (2 H); IR_{CCl_4} ν 1742, 1445, 1365, 1305, 1230, 1145, 1085, 1040, 970 cm^{-1}; MS, m/z 511, 483, 395, 369.

Ozone was passed through a solution of **15b** [3.2 g, 5.3 mmol] in dichloromethane (100 mL) at –78 °C until the solution turned light purple. After purging excess ozone, the ozonide was reduced with triethylamine by addition of 10 mL at –78 °C, and the solution was allowed to warm to room temperature. After standing for 20 h at room temperature, the mixture was poured into water, washed with water and brine, dried over anhydrous sodium sulfate, and evaporated to give **16** (2.3 g) in almost quantitative yield. **16**: ^{1}H NMR (400 MHz) δ 0.001 (3 H, s), 0.062 (3 H, s), 0.869 (9 H, s), 1.03 (Me-6, d, J = 6.8), 1.75 (Me-4, d, J = 0.8), 1.76 (H-8, dd, J = 4.0, 15.5), 2.05 (H-8, dd, J = 7.4, 15.5), 2.08 (OAc-11, s), 3.03 (H-6, m), 3.21 (OMe-9, s), 3.24 (OMe-9, s), 3.48 (OMe-10, s), 3.61 (H-10, dd, J = 2.4, 8.0), 4.02 (H-11, dd, J = 8.0, 11.6), 4.07 (H-7, m), 4.38 (H-11, dd, J = 2.4, 11.6), 6.51 (H-5, dd, J = 0.8, 9.8), 9.37 (H-3, s); ^{13}C NMR δ –4.7 (q), –4.1 (q), 9.3 (s), 12.4 (q), 18.2 (q), 20.9 (q), 26.0 (3 C, q), 37.5 (t), 38.7 (d), 48.4 (2 C, q), 59.6 (q), 65.6 (t), 70.5 (d), 80.7 (d), 101.6 (s), 137.9 (s), 158.9 (d), 170.6 (s), 195.6 (d); IR (neat) ν 1744, 1690, 1250, 1235, 1120, 1040 cm^{-1}; MS, m/z 345 (M^+ – 101).

Preparation of the Diketal Aldehyde.[18] The unsaturated aldehyde **16** [1.58 g 3.54 mmol dissolved in methanol (30 mL) and trimethyl orthoformate (6 mL)] was treated with pyridinium tosylate [150 mg, 0.60 mmol] at 0 °C for 2 days. The reaction mixture was poured into ice cold sodium bicarbonate and then extracted with ether. The extract was washed with water and brine, dried over anhydrous sodium sulfate, and concentrated to give the acetal **17** (1.66 g). This material was dissolved at room temperature in methanol (35 mL) containing sodium methoxide (1 N, 5 mL). After 45 min, the mixture was diluted with ether, washed with water and brine, dried over anhydrous sodium sulfate, and evaporated to afford the alcohol (1.67 g), which was dissolved in dichloromethane (60 mL) and oxidized with dipyridinium chromate (10 g, 38.8 mmol) at room temperature. After vigorous stirring for 15 min, the dark brown sticky mixture was diluted with ether (150 mL) and filtered through Celite and SiO_2. The filtrate was evaporated to give **18** [1.45 g, 91% yield from **16**]; this material was immediately used for the next reaction. **18**: ^{1}H NMR δ 0.06 (6 H, s), 0.88 (9 H, s), 1.00 (3 H, d, J = 7), 1.66 (3 H, s), 1.7–2.1 (3 H, m), 3.26 (12 H, s x 2), 3.44 (3 H, s), 3.90 (1 H, brs), 3.96 (1 H, m), 4.40 (1 H, brs), 5.52 (1 H, d, J = 9) 9.56 (1 H, brs); IR (neat) ν 1732 cm^{-1}.

Preparation of the Aromatic Counterpart 26. The iodide **21** was prepared from the corresponding benzyl alcohol via its mesylate with sodium iodide in dimethoxyethane at 0 °C. The crude iodide (**21**) was purified by passing through an aluminum oxide (Wako Chem. Ltd) column right before use, and the purified **21** [6.2 g, 16.8 mmol in THF (18 mL)] was added to a solution of 4-lithio-4-(phenylsulfonyl)pent-1-en [19.0 mmol in THF (66 mL) prepared from 4-(phenylsulfonyl)pent-1-en (4 g, 19.0 mmol) and 1.6 M *n*-butyllithium (12 mL, 19.2 mmol) in THF at –78 °C for 15 min] at –78°C under a nitrogen atmosphere. After 15 min at –78 °C, the mixture was mixed with ammonium chloride, extracted with ether, washed with water and brine, dried over anhydrous sodium sulfate, and evaporated to give the crude **22** (8.1 g), which was separated on a silica gel column [eluted with ether–hexane (2:1)] to yield the pure **22** (7.3 g) as a slightly yellow oil in 93.5% yield from **21**. **22**: ^{1}H NMR δ 1.26 (Me-14, s), 2.40 (H-13, × 2, d, J = 8), 3.08 (H-15 × 2, s), 3.16 (3 H, s), 3.60 (NMe, brs), 3.88 (3 H, s), 5.08 (H-11 × 2, dd, J = 10, 16), 5.84 (H-12, m), 6.64 (ArH, brs), 6.72 (ArH, brs), 7.3–7.9 (5 H, m); IR_{CHCl_3} ν 2850, 1700, 1580, 1450 cm^{-1}; MS, m/z 451 (M^+), 416, 310; found 451.120, calcd for $C_{22}H_{26}O_5N_1Cl_1S_1$ 451.122.

Cold ozone was introduced through a cold spiral glass tubing into a solution of **22** [6.7 g, 14.4 mmol in dichloromethane (170 mL)] at –78 °C until the blue color persisted. The excess ozone was purged by bubbling oxygen through the solution at –78 °C, and triethylamine (17 mL) was added to the mixture. After removing the bath, the reaction mixture was stirred for 1 h, extracted with dichloromethane, washed with water, dried over anhydrous sodium sulfate, and evaporated to yiled the crude **23**, (4.7 g) as a mixture of *E*:*Z* 5:1, which was analyzed by HPLC (Develosil 100-5, 4.6 × 250 mm, solvent, ether–hexane (6:1), flow rate, 3.5 mL/min, detector, UV 256 nm)]. The minor isomer (*Z*)-**23** was in equilibrium with **23** in dichloromethane at room temperature in the presence of triethylamine; after the reaction had stirred for 24 h, the ratio of *E*:*Z* became 3:1. The geometric mixture of **23** (5:1) could be used without separation, since the isomers were separated at a later stage by crystallization of the phosphonium salt. **23**: 1H NMR δ 2.04 (3 H, s), 3.20 (3 H, s), 3.50 (2 H, s), 3.64 (3 H, brs), 3.91 (3 H, s), 5.88 (1 H, d, J = 8), 7.69 (2 H, s), 10.0 (1 H, d, J = 8); IR_{CHCl_3} ν 2850, 1705, 1675, 1580 cm^{-1}; MS, m/z 311 (M^+), 292, 276.

A solution of **23** [4.6 g, 1 4.8 mmol in ethanol (120 mL)] was treated with sodium borohydride [1 g, 26.4 mmol] with stirring for 30 min at 0 °C. To the reaction mixture was added acetone (7 mL) dropwise at 0 °C and then cold 1 N HCl (50 mL) was added. The mixture was extracted three times with dichloromethane, washed successivly with water, sodium bicarbonate, water, and half saturated sodium chloride, and then dried over anhydrous sodium sulfate. The solvent was evaporated to yield crude **24** (4.4 g, 95% yield). **24**: ^{1}H NMR δ 1.64 (3 H, s), 2.82 (1 H, brs, D_2O exchangable), 3.18 (3 H, s), 3.30 (2 H, brs), 3.62 (3 H, s), 3.88 (3 H, s), 4.18 (2 H, d, J = 7), 5.49 (1 H, t, J = 7), 6.70 (2 H, brs); IR_{CHCl_3} ν 3470, 2850, 1700, 1580 cm^{-1}; MS, m/z 313 (M^+), 295, 279.

To a solution of **24** [2.15 g, 6.87 mmol in ether (36 mL) and THF 16.5 mL)] was added lithium bromide (3 g, 34.5 mmol), collidine (5 mL, 37.8 mmol), and phosphorous tribromide (0.85 mL, 9.04 mmol) at 0 °C under a nitrogen atmosphere. After stirring for 30 min at 0 °C, the reaction mixture was mixed with 5% sodium bicarbonate (20 mL) and partitioned between ether and water. The aqueous layer was thoroughly extracted three times with ether. The combined extracts were washed with water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give crude alkyl bromide **25**: 1.88 g; ^{1}H NMR δ 1.74 (3 H, s), 3.20 (3 H, s), 3.35 (2 H, s), 3.64 (3 H, s), 3.90 (3 H, s), 4.04 (2 H, d, J = 8), 5.67 (1 H, t, J = 8), 6.72 (2 H, s); 73% yield. This product was used for the next step without further purification. The bromide (**25**) was treated with triphenylphosphine [1.5 g, 5.7 mmol] in nitromethane (60 mL) at 60 °C for 24 h. The reaction mixture was concentrated and the residue was purified by silica gel [eluted with ether and then

dichloromethane–methanol (95:5)] to afford **26** (2.0 g, 74%) and (*Z*)-**26** (0.65 g, 24%). Overall yield from the benzyl alcohol was 45%. In the case of a large scale preparation, the *E*/*Z* isomers could be separated by crystallization [dissolving in a minimum amount of acetone and then diluting with toluene to afford crystals of the *E* isomer]. **26**: ^{1}H NMR δ 1.32 (3 H, d, J = 4), 3.10 (3 H, s), 3.22 (2 H, d, J = 4), 3.58 (3 H, s), 3.82 (3 H, s), 4.4–4.9 (2 H, m), 5.30 (1 H, m), 6.42 (1 H, brs), 6.58 (1 H, brs), 7.4–8.2 (15 H, m); mp 200–201 °C.

Coupling of the Right (18) and Left (26) Segments. To a vigorously stirring dark red solution of the ylide of **26** [prepared from **26** (2 g, 3.13 mmol) in THF (34 mL), DMF (17 mL), and 1.85 M *tert*-butyllithium (2 mL, 3.7 mmol) in pentane at −78 °C for 30 min and then −63 °C for 15 min] was added **18** [1.24 g, 2.76 mmol) in THF (10 mL)] at −63 °C and then stirring was continued for 17 h without external cooling. Ethereal aqueous workup gave the crude **19** (3 g), which was chromatographed on a silica gel column [40 g of SiO_2, eluted with ether–hexane (1:2)] to afford **19** (2 g, 78%) as an *E*/*Z* mixture (ca. 1:1). Since this compound was unstable, it was immediately used for the next reaction after this purification. The allyl dimethyl acetal (**19**) [1.56 g, 2.14 mmol] was dissolved at −10 °C in a mixture of THF (26 mL), water (6.5 mL), and acetic acid (6.5 mL), and the mixture was allowed to stand at −10 °C for 2 days. Workup under slightly basic conditions furnished in quantitative yield the key intermediate **20** (1.46 g), which was used without purification for the following step. For analytical purposes, **20**/(*Z*)-**20** (20 mg) was separated by HPLC (Develosil 100-5, flow rate, 2.0 mL/min, eluant, ether–hexane (2:3), detector, UV at 256 nm) to afford the pure **20** (2 mg), (*Z*)-**20** (4 mg), and a mixture (12 mg). **20**: ^{1}H NMR (200 MHz) δ 0.00 (3 H, s), 0.007 (3 H, s), 0.88 (9 H, s), 1.02 (Me-6, d, J = 7), 1.70 (Me-14, s), 1.76 (Me-4, s), 1.82 (1 H, dd, J = 2, 15), 2.06 (H-8, dd, J = 7, 15), 3.04 (H-6, m), 3.19 (OMe-10, s), 3.25 and 3.27 (OMe-9 × 2), 3.33 (3 H, s), 3.63 (NMe), 3.90 (ArOMe), 3.85 (1 H, d, J = 7), 4.08 (H-7, ddd, J = 2, 4, 7), 5.53 (H-11, dd, J = 7, 15), 5.92 (H-13, d, J = 11), 6.47 (H-12, dd, J = 11, 15), 6.51 (H-5, d, J = 9), 6.68 (ArH × 2), 9.33 (1 H, s); IR_{CCl_4} ν 2850, 1719, 1688, 1640 cm^{-1}; MS, m/z 681 (M$^+$), 680, 653, 621, 591, 523, 426. (*Z*)-**20**: ^{1}H NMR (200 MHz) δ 0.00 (3 H, s), 0.07 (3 H, s), 0.88 (9 H, s), 1.05 (3 H, d, J = 7), 1.72 (3 H, s), 1.77 (3 H, d, J = 1), 1.80 (1 H, dd, J = 4, 15), 2.12 (1 H, dd, J = 7, 15), 3.08 (1 H, m), 3.18, 3.22, 3.25, 3.27 and 3.63 (Me × 5), 3.36 (2 H), 3.87 (3 H, s), 4.07 (1 H, m), 4.23 (1 H, d, J = 10), 5.32 (1 H, t, J = 10), 6.26 (1 H, d, J = 11), 6.55 (1 H, t, J = 10), 6.51 (1 H, d, J = 9), 6.66 (2 H, s), 9.35 (1 H, s); IR_{CCl_4} ν 2850, 1720, 1688, 1640 cm^{-1}.

Condensation of the Two-Carbon Segment with 20. To a solution of **20** [271 mg, 0.04 mmol in THF (5 mL)] was added at −78 °C lithium methyl (diethoxyphosphinyl)acetate [prepared from methyl (diethoxyphosphinyl)acetate (388.5 mg, 2.00 mmol) and *n*-butyllithium (1.3 mL, 2.08 mmol) in THF (5 mL) in the presence of triphenylmethane as an anion indicator at 0 °C to room temperature for 2 h], and the reaction mixture was stirred for 4.5 h at room temperature. Extraction of the mixture with ether and the usual workup gave **27** (280 mg) in 95% yield. **27**: ^{1}H NMR (400 MHz) δ 0.00 (3 H, s), 0.04 (3 H, s), 0.88 (9 H, s), 0.95 (3 H, d, J = 7), 1.0–1.4 (2 H, m), 1.72 (3 H, s), 1.80 (3 H, s), 3.20 (3 H, s), 3.24 (3 H, s), 3.26 (3 H, s), 3.32 (3 H, s), 3.50 (2 H, m), 3.64 (3 H, s), 3.74 (3 H, s), 3.90 (3 H, s), 4.02 (1 H, m), 4.20 (1 H, d, J = 7), 5.52 (1 H, dd, J = 7, 15), 5.80 (1 H, d, J = 16), 5.92 (2 H, d, J = 11), 6.48 (1 H, dd, J = 11, 15), 7.52 (1 H, d, J = 16), 6.70 (2 H, brs); IR_{CCl_4} ν 2850, 1720, 1623 cm^{-1}; MS, m/z 737 (M$^+$), 704, 673, 645, 623.

Formation of the Lactam Ring of 28. Compound **27** [39.2 mg, 0.0532 mmol] was heated at 90 °C for 12 h with a mixture of 12 N KOH (0.33 mL), methanol (0.33 mL), and 1,4-dioxane (0.66 mL). The reaction mixture was poured into ice cold water and extracted four times with ether. The combined ether extracts were washed with water (three times) and brine, dried on sodium sulfate, and evaporated to give the crude oil, which was purified by silica gel TLC [ether–hexane (2:1)] to afford pure amino acid (23.5 mg) in 66.3% yield. The tetra-*n*-butylammonium salt of the amino acid [obtained by treatment of 57.9 mg, 0.087 mmol, in toluene (2 mL) with *n*-butylammonium hydroxide (10% in methanol, 0.23 mL) at room temperature for 20 min] was azeotropically dried with toluene three times in vacuo below 25 °C to give a crude salt (84.4 mg), which was dissolved in benzene (100 mL). This solution was added dropwise over 40 h at 40 °C to a solution of 2-mesitylenesulfonyl chloride (500 mg, 2.29 mmol) and diisopropylethylamine (0.4 mL, 2.30 mmol) in benzene (230 mL). The reaction mixture was evaporated to $^1/_5$ volume and partitioned between ether and water. The aqueous layer was extracted with four portions of ether, and the combined ether layers were washed with sodium bicarbonate, water, and brine, dried over anhydrous sodium sulfate, and then concentrated to afford the crude oil (480 mg), from which excess 2-mesitylene sulfonyl chloride was removed with a short column of silica gel [1.6 g, eluant, ether–hexane (1:3) and then ether] to give the mixture of **28** and (*Z*)-**28**. Chromatography of this material (47.8 mg) by silica gel TLC [eluted with ether–hexane (1:1)] gave **28** (20.4 mg, 36.2%) and the *Z* isomer (13.7 mg, 24.3%). **28**: ^{1}H NMR δ 0.07 (3 H, s), 0.13 (3 H, s), 0.92 (9 H, s), 1.00 (3 H, d, J = 7), 1.50 (3 H, s), 1.6 (2 H), 1.70 (3 H, s), 2.58 (1 H, m), 3.2 (2 H, brs), 3.26 (9 H, s), 3.30 (3 H, s), 3.86 (1 H, m), 3.96 (3 H, s), 4.04 (1 H, d, J = 9), 5.4 (1 H, dd, J = 9, 15), 5.44 (1 H, d, J = 15), 5.48 (1 H, d, J = 10), 5.78 (1 H, d, J = 11.5), 6.44 (1 H, dd, J = 11.5, 15), 6.60 (1 H, d, J = 1.5), 6.76 (1 H, d, J = 1.5), 7.12 (1 H, d, J = 15); IR_{CCl_4} ν 2850, 1658, 1610, 1572, 1095 cm^{-1}; MS m/z 647 (M$^+$), 616, 587; found 647.342, calcd for $C_{35}H_{54}O_8N_1Cl_1Si_1$ 647.341. (*Z*)-**28**: ^{1}H NMR δ 0.05 (3 H, s), 0.10 (3 H, s), 0.88 (9 H, s), 0.94 (3 H, d, J = 6), 1.50 (3 H, s), 1.6 (2 H), 1.80 (3 H, s), 2.72 (1 H, m), 3.16 (3 H, s), 3.25 (3 H, s), 3.3 (2 H), 3.36 (3 H, s), 3.38 (3 H, s), 3.8 (1 H, m), 3.89 (3 H, s), 4.28 (1 H, d, J = 10), 5.36 (1 H, dd, J = 10, 11), 5.42 (1 H, d, J = 11), 5.50 (1 H, d, J = 16), 6.20 (1 H, d, J = 11), 6.44 (1 H, d, J = 1.5), 6.60 (1 H, t, J = 11), 6.68 (1 H, d, J = 1.5), 6.76 (1 H, d, J = 16); IR_{CCl_4} ν 2850, 1660, 1620, 1570, 1095 cm^{-1}; MS, m/z 647 (M$^+$).

Preparation of the Ketol 29. Compound **28** [5.5 mg, 8.5 μmol dissolved in aqueous methanol (0.2 mL)] was treated with a trace of *d,l*-10-camphorsulfonic acid at room temperature for 12 h. The reaction mixture was extracted with dichloromethane and the extract was washed with sodium bicarbonate, water, and half saturated sodium chloride, dried over anhydrous sodium sulfate, and evaporated to give **29** (4.9 mg) in almost quantitative yield. **29**: ^{1}H NMR δ 1.11 (3 H, d, J = 6.2), 1.38 (3 H, d, J = 0.5), 1.74 (3 H, s), 2.2–2.8 (3 H, m), 3.20 (2 H, brs), 3.26 (3 H, s), 3.34 (3 H, s), 3.66 (1 H, m), 3.98 (3 H, s), 4.12 (1 H, d, J = 8.5), 5.36 (1 H, dd, J = 8.5, 15.5), 5.42 (1 H, d, J = 11), 5.44 (1 H, d, J = 15), 5.92 (1 H, d, J = 11), 6.54 (1 H, dd, J = 11, 15.5), 6.61 (1 H, d, J = 1.5), 6.78 (1 H, d, J = 1.5), 7.18 (1 H, d, J = 15); IR_{CCl_4} ν 3460, 1720, 1645, 1605, 1580, 1090 cm^{-1}; MS, m/z found 487.212, calcd for $C_{27}H_{34}O_5N_1Cl_1$ 487.212.

Synthesis of (±)-*N*-Methylmaysenine (4b). A solution of **29** [4.9 mg in THF (0.25 mL) and pyridine (8 μL)] was stirred with *p*-nitrophenyl chloroformate [20 mg in THF (0.1 mL)] cooled in an ice bath and mixed with excess ammoniacal methanol to result in a light yellow solution. After 30 min at 0 °C, the mixture was extracted with dichloromethane. The extract was washed successively with sodium bicarbonate, water, and half saturated sodium chloride, dried over anhydrous sodium sulfate, and evaporated to yield the crude **4b** (8 mg). Silica gel TLC [eluted with ethyl acetate] afforded the pure *N*-methylmasenine (**4b**) (3.3 mg) in 73% overall yield from **28**. **4b**: ^{1}H NMR (400 MHz) δ 1.16 (H-8, t, J = 12.5), 1.65 (H-8, dt, J = 12.5, 2.0), 1.23 (Me-6, d, J = 6.5), 1.41 (Me-4, d, J = 1), 1.67 (Me-14, s), 2.63 (H-6, m), 3.14 (H-15, d, J = 12.5), 3.41 (H-15, d, J = 12.5), 3.26 (OMe-10, s), 3.34 (NMe), 3.48 (H-10, d, J = 9), 3.98 (ArOMe, s), 4.14 (H-7, ddd, J = 2.0, 10.0, 12.5), 5.46 (H-11, dd, J = 9.0, 15.5), 5.48 (H-2, d, J = 15.0), 5.49 (H-5, d, J = 11.0), 6.05 (H-13, d, J = 11.0), 6.15 (NH, brs), 6.36 (H-12, dd, J = 11.0, 15.5), 6.61 (ArH, d, J = 2), 6.79 (ArH, d, J = 2), 7.22 (H-3, d, J = 15.0); IR_{CCl_4} ν 3420, 1700, 1645, 1603, 1575, 1455, 1340, 1185, 1085 cm^{-1}; MS m/z 530 (M$^+$), 512, 469, 454, 434; found 469.202 (M − H_2O − HNCO), calcd for $C_{27}H_{32}O_4N_1Cl_1$ 469.202.

Syn Diastereoselective Epoxidation of 30a and 30b. To a cold (−20 °C) solution of **30** [303 mg, 0.704 mmol in dichloromethane (8 mL)] was added dropwise titanium (IV) isopropoxide (0.42 mL, 1.41 mmol) with a hypodermic syringe. After 10 min, tert-butyl hydroperoxide (TBHP) [3.6 M, 0.58 mL] was added and the mixture was stirred for 10 h at −20 °C. Dimethyl sulfide (0.3 mL) and aqueous saturated sodium fluoride (5 mL) was added at −20 °C. The cooling bath was removed and the mixture was stirred for 1 h to result in a white emulsion, which was filtered

through Celite. The filtrate, a clear solution, was extracted with dichloromethane, washed with water, dried over anhydrous sodium sulfate, evaporated, and chromatographed on a silica gel column (ether–hexane 1:4) to produce the pure **32a**: 267 mg; 85.1% yield; ^{1}H NMR δ 0.00 (6 H, s), 0.04 (6 H, s), 0.88 (18 H, s), 1.06 (3 H, d, J = 6.8), 1.30 (3 H, s), 1.2–1.8 (m), 2.98 (1 H, d, J = 9.3), 3.6 (m); ^{13}C NMR δ –5.38 (2 C, q), –4.79 (q), –4.03 (q), 11.18 (q), 14.52 (q), 18.05 (s), 18.22 (s), 21.86 (t), 25.91 (6 C, q), 32.90 (t), 34.66 (t), 36.54 (d), 62.08 (s), 62.73 (d), 63.78 (t), 65.72 (t), 73.35 (d). The above product was treated with benzoyl chloride (0.16 mL) and triethylamine (1 mL) at room temperature for 2 h, separated with silica gel TLC (ether–hexane, 1:4) to afford the benzoate of pure syn epoxide **32a** [^{1}H NMR δ 0.00 (6 H, s), 0.04 (6 H, s), 0.88 (18 H, s), 1.08 (3 H, d, J = 7), 1.42 (3 H, s), 1.2–1.8 (m), 2.94 (1 H, d, J = 9.1), 3.6 (m), 4.18 (1 H, d, J = 11), 4.44 (1 H, d, J = 11), 7.5 (3 H, m), 8.06 (2 H, m)] and anti epoxide benzoate in 200 mg and 20 mg, respectively.

Under the same condition as above, **30b** [77 mg, 0.18 mmol] was treated with titanium tetra-*O*-isopropoxide (0.15 mL) and TBHP (2.6 M, 0.35 mL) in dichloroethane (2 mL) at –20 °C for 11 h to give **32b**: 79.8 mg; 80% yield; ^{1}H NMR δ 0.04 (3 H, s), 0.08 (3 H, s), 0.86 (9 H, s), 1.08 (3 H, d, J = 7), 1.32 (3 H, s), 1.5–2.0 (m), 2.07 (3 H, s), 3.00 (1 H, d, J = 9), 3.20 (6 H, s), 3.46 (3 H, s), 3.60 (m), 3.8–4.6 (m). To obtain a high reproducibility of this epoxidation, the following care must be taken. An anhydrous solution of TBHP [3.6 M in 1,2-dichloroethane] was prepared by mixing TBHP (70%, 15 mL) and Na_2SO_4 in dichloroethane (25 mL) for 10 h, passing through a column with Na_2SO_4, and distilling the eluant. After collecting ca. 8 mL of the distillate at 72 °C, the vapor became transparent. After an additional 2 mL was collected, the residual solution was rapidly cooled by flowing water, and the ^{1}H NMR was measured to determine its concentration [comparing the intensity of *tert*-butyl vs. methylene signals].

Partial Kinetic Resolution and Nonenantioselective Epoxidation of 30b. To a cold (–20 °C) solution of titanium tetraisopropoxide [0.05 mL, 0.168 mmol in dichloromethane (2 mL)] was added diethyl L-(+)-tartrate [35 mg, 0.170 mmol in dichloromethane (0.2 mL)]. After stirring for 10 min at –20 °C, the racemic olefin **30b** [50 mg, 0.112 mmol in dichloromethane (0.2 mL)] and anhydrous TBHP [4 M, 0.085 mL, 0.34 mmol in 1,2-dichloroethane, azeotropically dried] were added to the solution. The mixture was stirred for 12 h at –20 °C, and 10% aqueous tartaric acid solution (0.5 mL) was added. The resulting mixture was stirred at –20 °C for 30 min and at room temperature for 1 h. The organic layer was diluted with dichloromethane, washed with water, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give an oil which was separated by silica gel TLC (ether–hexane 2:1) to provide (*R*-**30b** (5.1 mg, 10.2%) and **32b** (25 mg, 48.3%). A solution of the epoxide **32b** [25 mg in dichloromethane (0.5 mL)] was further treated with (+)-MTPACl (20 mg) and pyridine (20 mg) for 2 h at room temperature. The usual workup and chromatography on silica gel TLC (ether–hexane 1:1) gave MTPA-**32b** in 80% yield as a mixture of MTPA-(*S*)-**32** and MTPA-(*R*)-**32b** in a 3:2 [the ratio being determined by the ^{1}H NMR signals at δ 2.82 (d, J = 9); 2.87 (d, J = 8.5)]. The recovered starting material (*R*)-**32b** was epoxidized with titanium(IV)–TBHP without any tartrate and acylated with (+)-MTPACl and pyridine to afford MTPA-(*R*)-**32b** as a single isomer in 90% overall yield: ^{1}H NMR δ –0.06 (3 H, s), 0.06 (3 H, s), 0.84 (9 H, s), 1.06 (3 H, d, J = 7), 1.36 (3 H, s), 1.4–2.3 (m), 2.08 (3 H, s), 2.87 (1 H, d, J = 8.5), 3.20 (6 H, s), 3.44 (3 H, s), 3.57 (3 H, d, J = 1.5), 3.8–4.6 (m), 7.48 (5 H, m).

Anti Diastereoselective Epoxidation of 30a and 30b. A solution of **30a** [267 mg, 0.621 mmol in dichloromethane (6.5 mL)] was stirred with MCPBA (80%, 175 mg, 0.81 mmol) at –20 °C for 10 min resulting in a white precipitate. Aqueous sodium sulfite was added to this suspension until the KI–starch test paper became negative. After addition of 5% sodium bicarbonate, the mixture was extracted with dichloromethane, and the extract was washed with water, dried over anhydrous sodium sulfate, and concentrated to provide the epoxide **31a** in 99.6% yield as a single product. The purity was established on its benzoate as in the case of syn epoxidation. **31a**: ^{1}H NMR δ 0.04 (6 H, s), 0.06 (6 H, s), 0.90 (18 H, s), 0.88 (3 H, d), 1.28 (3 H, s), 1.0–1.8 (m), 2.97 (1 H, d, J = 9.6), 3.6 (4 H, m), 3.8 (1 H, m); ^{13}C NMR δ –5.26 (2 C, q), –4.73 (q), –4.15 (q), 9.89 (q), 14.17 (q), 18.16 (s), 18.28 (s), 21.57 (t), 25.97 (6 C, q), 33.08 (t), 35.04 (t), 36.42 (d), 61.14 (s), 62.14 (d), 62.96 (t), 65.84 (t), 72.82 (d). Benzoate of **31a**: ^{1}H NMR δ 0.00 (6 H, s), 0.06 (6 H, s), 0.88 (18 H, s), 0.92 (3 H, d), 1.44 (3 H, s), 1.2–1.7 (m), 2.98 (1 H, d, J = 9), 3.6 (4 H, m), 3.8 (1 H, m), 4.18 (1 H, d, J = 12), 4.43 (1 H, d, J = 12), 7.5 (3 H, m), 8.04 (2 H, m).

The olefin **30b** [52.9 mg, 0.118 mmol in dichloromethane (1.1 mL) was also epoxidized by the same method with MCPBA (30 mg in 0.5 mL) to give a single epoxide **31b**: 34.7 mg; 70.1% yield; ^{1}H NMR δ 0.08 (3 H, s), 0.10 (3 H, s), 0.88 (9 H, s), 0.88 (3 H, s, J = 7), 1.28 (3 H, s), 1.4–2.1 (m), 2.07 (3 H, s), 2.97 (3 H, d, J = 10), 3.21 (3 H, s), 3.23 (3 H, s), 3.48 (3 H, s), 3.6 (2 H, brs), 3.9–4.5 (m). The benzoate of **31b** showed the epoxidic signal at 2.89 (d, J = 10).

Epoxidation of the Allylic Alcohol 35. The key intermediate **20** [612 mg, 0.90 mmol, 11-*E*/*Z* (ca. 1:1) dissolved in methanol (15 mL)] was treated with sodium borohydride [50 mg, 1.31 mmol] at 0 °C for 15 min and the product was taken with dichloromethane. After passing through an anhydrous sodium sulfate column, the solvent was evaporated under reduced pressure to give a residue which was dissolved in a mixture of 12 N KOH (7.5 mL) and ethanol (22.5 mL). The mixture was heated at reflux for 22 h, and after cooling, it was poured into ice cold water (20 mL) and extracted with ether. The extracts were washed with water until pH test paper showed neutral. The solution was dried over anhydrous sodium sulfate and evaporated in vacuo to give crude **35**, which was purified by silica gel to afford **35** [473 mg, 84% yield as a mixture of 11-*E*/*Z* (ca. 1:1)]. **35**: ^{1}H NMR δ 0.0 (6 H, s), 0.88 (9 H, s), 0.8–2.2 (6 H, m), 1.64 (3 H, brs), 1.72 (3 H, brs), 2.82 (3 H, s), 3.0–4.2 (13 H, m), 3.8 (3 H, s), 3.94 (2 H, brs), 5.0–7.0 (4 H, m), 6.12 (2 H, brs); IR_{CCl_4} ν 3610, 3450, 1590, 1460, 1420, 1245 cm^{-1}; MS, m/z 625 (M^+), 592, 561, 535, 504, 493.

To a cold solution of **35** [463 mg, 0.740 mmol in dichloromethane (20 mL)] was added dropwise at –20 °C titanium tetraisopropoxide (1.1 mL, 3.70 mmol) and in 10 min *tert*-butyl hydroperoxide [3.6 M anhydrous solution in 1,2-dichloroethane, 5.6 mmol (1.5 mL)] with a hypodermic syringe. The mixture was stirred for 1.5 h at –20 °C, and dimethyl sulfide (1 mL) and aqueous sodium fluoride [5%, 20 mL] were added. The resulting mixture was stirred for a further 10 min at –20 °C and 1 h at room temperature and then filtered through Celite. The filtrate was extracted with dichloromethane, and the combined extract was washed with water, dried with anhydrous sodium sulfate, and evaporated to afford a crude oil, which was purified by TLC (eluted with ether–hexane 1:1) to yield **36** (332 mg, 70.0% yield). **36**: ^{1}H NMR δ 0.00 (3 H, s), 0.08 (3 H, brs), 0.88 (9 H, s), 1.08 (3 H, d, J = 8), 1.34 (3 H, s), 1.75 (3 H, s), 1.0–2.2 (3 H, m), 2.87 (3 H, s × 2), 3.00 (1 H, d, J = 9), 3.20, 3.29 (3 H, s × 2), 3.24 (6 H, s), 3.3–4.3 (6 H, m), 3.83, 3.85 (3 H, s × 2), 5.0–6.8 (3 H, m), 6.15 (2 H, brs); IR_{CCl_4} ν 3550, 3450, 1595, 1460 cm^{-1}; MS, m/z 609 (M^+ – 33), 594.

To a stirred solution of **36** [310 mg, 0.48 mmol in dimethylsulfoxide (10 mL) containing triethylamine (1 mL, 7.17 mmol)] was added sulfur trioxide–pyridine complex [560 mg, 3.52 mmol dissolved in Me_2SO (3 mL)] dropwise at room temperature. The mixture was stirred for 15 min and diluted with water (50 mL) and ether (50 mL). The separated aqueous layer was thoroughly extracted with ether and the combined organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and concentrated in vacuo to give the crude aldehyde **37** (440 mg), which was purified on a silica gel column with ether–hexane (1:1) as eluant to provide the pure **37** as a ca. 1:1 11-*E*/*Z* mixtute. The epoxy aldehyde **37**: ^{1}H NMR δ 0.00 (3 H, s × 2), 0.05 (3 H, s × 2), 0.84 (9 H, s), 1.15, 1.16 (3 H, d × 2), 1.45 (3 H, s), 1.73 (3 H, s), 1.8–2.2 (3 H, m), 2.87 (3 H, brs), 3.12 (1 H, d), 3.17, 3.28 (3 H, s × 2), 3.20 (6 H, s), 3.82, 3.84 (3 H, s × 2), 3.2–4.5 (4 H, m, NH), 5.20 (0.5 H, t, J = 11), 5.46 (0.5 H, dd, J = 15, 7), 5.92 (0.5 H, d, J = 11), 6.12 (1 H, s), 6.14 (1 H, s), 6.2–6.8 (1.5 H, m), 8.92 (1 H, s); IR_{CCl_4} ν 3450, 2850, 1728 cm^{-1}; MS, m/z 639 (M^+), 608, 582, 550.

Synthesis of (±)-Maysine (3). Sodium methyl diethyl phosphonoacetate [prepared from methyl diethyl phosphonoacetate (83.4 mg, 0.43 mmol) in THF (1.1 mL) and 50% sodium hydride (21 mg, 0.43 mmol, washed with dry petroleum ether prior to use) at 0 °C for 10 min and at room temperature for 3 h] was added to a solution of **37** (110 mg, 0.172 mmol) dissolved in THF

(1 mL) at −78 °C. After the cooling bath was removed, the reaction mixture was stirred for 2 h, and extracted with ether. The extracts were washed with water and brine, dried over anhydrous sodium sulfate, and evaporated affording the crude oil. Chromatography of this product [silica gel TLC with ether–hexane (1:3) as eluant] provided the corresponding methyl ester in 84.7% yield. About half of this material [61.0 mg, 87.7 μmol] was hydrolyzed by stirring in a mixture of 1 N KOH (0.53 mL), ethanol (1.33 mL), and THF (1.33 mL) at room temperature for 17 h. The mixture was diluted with dichloromethane and 1 N HCl (0.55 mL) was added slowly. The aqueous layer was extracted three times with dichloromethane and the usual workup gave the crude oil **38**, which was purified by silica gel TLC [ether–hexane (2:1)] to give the amino acid **38** (50.9 mg) as the mixture of *E*/*Z* isomers at C-11 in 85.2% yield. **38**: ^{1}H NMR δ −0.07 (3 H, s × 2), −0.05 (3 H, s × 2), 0.07 (3 H, s × 2), 0.85 (9 H, s), 1.08 (1.5 H, d, *J* = 6.6), 1.10 (1.5 H, d, *J* = 7.1), 1.50 (3 H, s), 1.75 (3 H, s), 2.0 (m), 2.85 (1 H, d, *J* = 8.7), 2.86, 2.89 (3 H, s × 2), 3.19, 3.29 (3 H, s × 2), 3.22 (6 H, s), 3.83, 3.85 (3 H, s × 2) 4.12 (m), 5.27 (0.5 H, t, *J* = 10), 5.53 (0.5 H, dd, *J* = 15, 7), 6.00 (1 H, d, *J* = 16), 6.86 (1 H, d, *J* = 16), 5.8–6.7 (2 H, m), 6.14, 6.15 (2 H, s × 2); IR_{CHCl_3} ν 3450, 2950, 1700, 1655, 1600, 1460 cm^{-1}; MS, *m*/*z* 661, 647.

To a solution of **38** [20.8 mg, 0.03 mmol in toluene (0.7 mL)] was added *n*-Bu_4NOH [10%, 0.087 mL, 0.03 mmol in MeOH] dropwise at room temperature. After stirring for 20 min, the solvent was removed under reduced pressure at low temperature to give a light brown oil. This material was azeotropically dried with toluene four times at ambient temperature and dissolved in dry benzene (30 mL). the resulting solution was added at 40 °C over a period of 32 h to a mixture of 2-mesitylenesulfonyl chloride [176.5 mg, 0.807 mmol] and diisopropylethylamine (0.145 mL, 0.832 mmol) in benzene (90 mL). After the addition was completed, pyridine (0.2 mL) was added to the reaction mixture which was concentrated to one fifth under reduced pressure at 35 °C and then extracted three times with ether. The ether extracts were washed with aqueous 5% sodium bicarbonate, water, and brine, dried over anhydrous sodium sulfate, and evaporated to afford the crude product contaminated with the excess reagent. The residue was passed through a short column of silica gel. Mesitylenesulfonyl chloride was eluted with ether–hexane (1:3) and then the crude **39** with ether. Separation with silica gel TLC with ether–hexane (2:1) as eluant afforded the pure **39** (9.5 mg, 46%) and the pure *Z* isomer of **39** (5.1 mg, in 25% yield). **39** ^{1}H NMR δ −0.24 (3 H, s), −0.03 (3 H, s), 0.87 (9 H, s), 1.07 (Me-6, d, *J* = 6.6), 1.23 (Me-4, s), 1.84 (m), 1.93 (Me-14, brs), 2.80 (H-5, d, *J* = 9.5), 3.14, 3.20, 3.26 (OMe × 6), 3.49 (NMe, s), 3.7 (m), 3.99 (ArOMe, s), 5.35 (H-13, d, *J* = 11), 5.41 (H-11, dd, *J* = 15, 4), 5.78 (H-2, d, *J* = 15.5), 6.5 (H-3, d, *J* = 15.5), 6.56 (ArH, d, *J* = 2), 6.81 (ArH, d, *J* = 2), 6.7 (H-12, m); IR_{CHCl_3} ν 1662, 1630, 1575, 1460, 1095 cm^{-1}; MS *m*/*z* 663 (M^+), 648, 632, 606; found *m*/*z* 663.3385, calcd $C_{35}H_{54}O_7N_1Cl_1Si_1$ *m*/*z* 663.3357. Cyclized compound from (*Z*)-**39**: ^{1}H NMR δ −0.20 (3 H, s), −0.12 (3 H, s), 0.82 (9 H, s), 1.03 (Me-6, d, *J* = 6.6), 1.25 (Me-4, s), 1.8 (m), 1.96 (Me-14, brs), 2.77 (H-5, d, *J* = 9.8), 3.15 (Me-10, s), 3.23, 3.25 (OMe-9, s × 2), 3.30 (NMe, s), 3.84 (ArOMe, s), 5.48 (H-11, t, *J* = 11), 5.80 (H-13, d, *J* = 11), 5.77 (H-2, d, *J* = 16), 6.52 (H-3, d, *J* = 16), 6.60, 6.77 (ArH × 2, d, *J* = 2), 6.6 (H-12, m); IR_{CHCl_3} ν 1660, 1630, 1573, 1460, 1095 cm^{-1}; found m/z 663.3350, calcd 663.3357.

Compound **39** [9.3 mg, 0.014 mmol dissolved in acetonitrile (0.15 mL)] was treated with tetra-*n*-butylammonium fluoride [1 M, 0.07 mL, 0.07 mmol in THF] at 50 °C for 20 h, and the mixture was diluted with dichloromethane and separated. The organic layer was washed with water and half-saturated sodium chloride, dried over anhydrous sodium sulfate, and concentrated to provide crude **40**, which was purified by silica gel TLC (eluted with ether) affording pure **40** (5.4 mg) as colorless oil in 70% yield. **40**: ^{1}H NMR δ 1.06 (Me-6, d, *J* = 6.1), 1.35 (Me-4, s), 1.70 (Me-14, brs), 3.20 (OMe-9, s), 3.21 (OMe-9, s), 3.28 (OMe-10, s), 3.44 (NMe, s), 3.98 (ArOMe, s), 5.53 (H-2, d, *J* = 15), 5.58 (Me-11, dd, *J* = 11, 16), 6.06 (H-13, d, *J* = 11.0), 6.56 H-12, dd, *J* = 16, 11), 6.56, 6.76 (ArH × 2, d, *J* = 2), 6.94 (H-3, d, *J* = 15); IR_{CCl_4} ν 3520, 1662, 1624, 1580 cm^{-1}; MS, *m*/*z* 549 (M^+), 534, 518; found *m*/*z* 549.250, calcd for $C_{29}H_{40}O_7N_1Cl_1$ 549.249.

To a solution of **40** [5.4 mg, 0.0098 mmol in dichloromethane (0.1 mL)] was added pyridine [0.1 mL of 0.5 *M* in dichloromethane] and then *p*-nitrophenyl chloroformate [0.1 mL of 0.5 *M* in dichloromethane] at room temperature, resulting in a white precipitate. The mixture was stirred for 2 h at room temperature and then cooled to −78 °C with dry ice acetone. Ammoniacal methanol was added to the cold mixture and then the cooling bath was removed. The yellow solution was stirred for 1 h at ambient temperature and extracted with dichloromethane. The organic layer was washed with sodium bicarbonate, water, and brine, dried over anhydrous sodium sulfate, and evaporated to give the crude **41**. This material was separated on silica gel TLC (eluted with ethyl acetate) to afford the pure carbamate **41** (4.8 mg) as a colorless oil in 83% yield. **41**: ^{1}H NMR δ 1.17 (Me-6, d, *J* = 6.1), 1.14 (Me-4, s), 1.82 (Me-14, s), 2.2 (m), 2.71 (H-5, d, *J* = 9.5), 3.21 (OMe-10, s), 3.26 (OMe-9, s), 3.27 (OMe-9, s), 3.30 NMe, s), 3.98 (ArOMe, s), 4.48 (NH_2, brs), 5.78 (H-11, dd, *J* = 15.5, 8), 5.80 (H-2, d, *J* = 16), 6.00 (H-13, d, *J* = 11), 6.47 (H-3, d, *J* = 16), 6.5 (H-12, m), 6.74 (ArH, d, *J* = 2), 6.81 (ArH, d, *J* = 2); IR_{CHCl_3} ν 3540, 3430, 1726, 1660, 1622, 1580 cm^{-1}; MS, *m*/*z* 592, 548.

The carbamate **41** [4.8 mg, 0.0081 mmol] was hydrolyzed in a mixture of acetic acid (0.1 mL), THF (0.05 mL), and water (0.05 mL) at 35 °C. After standing for 2 h, the mixture showed a different R_f value (0.55/ethyl acetate) from authentic natural product maysine (R_f 0.40). This intermediate presumably the open chain carbamate **42**, was treated with ammoniacal methanol (0.1 mL) to make the medium basic. This immediately afforded racemic maysine **3**, which was purified on silica gel TLC with ethyl acetate as eluant. Evaporation of the eluant provided the pure **3** (3.2 mg) in 71% yield. (±)-**3**: ^{1}H NMR δ 1.07 (Me-4, s), 1.24 (H-8, t, *J* = 12.5), 1.59 (H-8, dt, *J* = 12.5, 1.5), 1.34 (Me-6 , d, *J* = 6.5), 1.62 (H-6, m), 1.71 (Me-14, s), 2.68 (H-5, d, *J* = 9.5), 3.09 (H-15, d, *J* = 12.5), 3.46 (H-15, d, *J* = 12.5), 3.27 (MeO-10, s), 3.34 (NMe, s), 3.47 (H-10, d, *J* = 9.0), 3.99 (ArOMe, s), 4.31 (H-7, ddd, *J* = 12.5, 10.0, 1.5), 5.50 (H-11, dd, *J* = 15.0, 9.0), 5.74 (H-2, d, *J* = 15.5), 6.11 (H-13, d, *J* = 11), 6.28 (NH, s), 6.41 (H-12, dd, *J* = 15.0, 11.0), 6.45 (H-3, d, *J* = 15.5), 6.70 (ArH, d, *J* = 2), 6.82 (ArH, d, *J* = 2); IR_{CHCl_3} ν 3420, 1710, 1664, 1625, 1578, 1455, 1345, 1090 cm^{-1}; MS, *m*/*z* 546 (M^+), 511, 485 (base), 470, 450, 386; found 485.1979, calcd for $C_{27}H_{32}O_5N_1Cl_1$ 485.1967 [M^+ − (H_2O + HNCO)].

Acknowledgment. Support of this work by a Grant-in-aid for Scientific Research from the Japanese Ministry of Education, Science and Culture, by the Naito Science Foundation, by the Yamada Science Foundation, and by the Aichi Cancer Research Foundation are gratefully acknowledged. The authors are also indebted to Professor H. Seto of the University of Tokyo and to Dr. T. Kondo of Nagoya University for the high-field ^{1}H NMR measurements. We thank Professor G. Stork of Columbia University for correcting the manuscript. Thanks are also due to Nippon Daicel Co. Ltd. for their kind gift of acrolein dimer and Takeda Chem. Ind., for authentic samples of **3** and **4b** for comparison.

Registry No. **3**, 72880-43-4; **4b**, 67045-55-0; **5**, 100-73-2; (*E*)-**6**, 77890-81-4; (*Z*)-**6**, 77890-82-5; **7**, 77890-89-2; **8** α-isomer, 77943-80-7; **8** β-isomer, 91422-78-5; **9**, 77943-81-8; **10**, 77890-94-9; **11**, 82598-93-4; **12**, 82598-94-5; **13**, 82598-95-6; **13** ketone deriv, 91365-89-8; **14a**, 82614-13-9; **14b**, 89874-07-7; **14c**, 82598-96-7; **15a**, 82598-97-8; **15a** acetate, 89874-18-0; **15b**, 82598-98-9; **16**, 82598-99-0; **17**, 91423-65-3; **18**, 82614-14-0; (*E*)-**19**, 82599-05-1; (*Z*)-**19**, 91422-79-6; (*E*)-**20**, 82599-06-2; (*Z*)-**20**, 91422-80-9; **21**, 82599-00-6; **22**, 82599-02-8; (*E*)-**23**, 67705-17-3; (*Z*)-**23**, 82599-21-1; (*E*)-**24**, 67705-16-2; (*Z*)-**24**, 74510-48-8; (*E*)-**24** acetate, 91365-90-1; (*E*)-**25**, 74510-49-9; (*Z*)-**25**, 91365-91-2; (*E*)-**26**, 82599-03-9; (*Z*)-**26**, 91384-60-0; **26** ylide, 82599-04-0; (*E*)-**27**, 85621-27-8; (*Z*)-**27**, 91422-81-0; **27** decarboxy deriv, 85621-28-9; (*E*)-**28**, 85621-29-0; (*Z*)-**28**, 91422-84-3; **29**, 85648-78-8; **30a**, 91365-92-3; **30b**, 81679-52-9; **31a**, 91422-85-4; **31a** benzoate, 91365-93-4; **31b**, 81679-55-2; **31b** benzoate, 91365-94-5; **32a**, 91423-66-4; **32a** benzoate, 91423-67-5; MTPA-**32b**, 81679-53-0; (*E*)-**35**, 82599-07-3; (*Z*)-**35**, 91423-68-6; **36**, 82599-08-4; (*E*)-**37**, 82599-15-3; (*Z*)-**37**, 91423-69-7; 27 decarboxy ammonium salt, 91422-83-2; (*E*)-**38**, 85621-22-3; (*Z*)-**38**, 91422-86-5; **38** methyl ester, 91365-95-6; (*E*)-**39**, 85621-23-4; (*Z*)-**39**, 91423-70-0; **40**, 85621-24-5; **41**, 85621-25-6; **42**, 85621-26-7; lithium bis(trimethylsilyl)(phenylthio)methylide, 91384-61-1; 4-bromopent-2-ene,

23068-95-3; 4-methoxybenzyl alcohol, 105-13-5; 2-chloroethanol, 107-07-3; 4-lithio-4-(phenylsulfonyl)pent-1-ene, 82599-01-7; lithium methyl(diethoxyphosphinyl)acetate, 67393-41-3; sodium methyldiethylphosphonoacetate, 61961-70-4.

Supplementary Material Available: ^{1}H NMR spectra of **16** (400 MHz), **20** (200 MHz), (*Z*)-**20** (200 MHz), **22**, **23**, the acetate of **24**, **26**, **27**, (*Z*)-**27** (400 MHz), **28**, (*Z*)-**28**, **29**, **4b** (400 MHz), **35**, **36**, **37**, **38**, **38** Me ester, **39**, **40**, **41**, and (±)-**3**; ir spectra of **16**, **20**, (*Z*)-**20**, **22**, **23**, **24**, **27**, **28**, (*Z*)-**28**, **29**, **4b**, **35**, **36**, **38**, **38** Me ester, **39**, **40**, **41**, and (±)-**3** (44 pages). Ordering information is given on any current masthead page.

Synthesis of N^{α},N^{δ}-Protected N^{δ}-Hydroxy-L-ornithine from L-Glutamic Acid

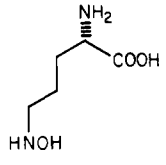
Richard K. Olsen,* K. Ramasamy, and Thomas Emery

Department of Chemistry and Biochemistry, Utah State University, Logan, Utah 84322

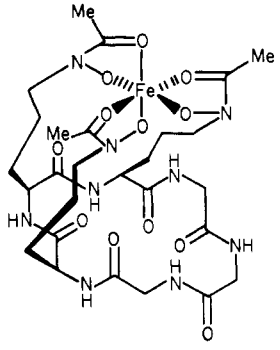
Received January 10, 1984

The synthesis of N^{α}-(*tert*-butyloxycarbonyl)-N^{δ}-acetyl-N^{δ}-(benzyloxy)-L-ornithine (**3**) has been accomplished by alkylation of the anion of *O*-benzyl acetohydroxamate with the chiral 2-amino-5-bromopentanoic acid **4**, the latter substance being derived from L-glutamic acid. In a similar manner, N^{δ}-(benzyloxy)-N^{δ}-tosyl-L-ornithine (**16**) was prepared and was shown to be optically pure. Two other approaches to the ornithine **3** were investigated; however, these approaches were not successful due to (1) the propensity of the urethane nitrogen to undergo intramolecular cyclization with a δ-aldehyde function present in glutamic semialdehyde derivatives generated in situ and (2) the occurrence of transamidation rearrangement processes upon attempted reduction of the δ-carboxyl group in certain glutamic acid α-hydroxamate derivatives.

Methods for the synthesis of optically active amino acids are of continuing interest.[1] Preparation and resolution of DL-α-amino acids commonly afford the desired optically active amino acids. Transformation of one chiral amino acid into another chiral amino acid also has received considerable attention.[2] By application of the latter approach, we report a convenient synthesis from L-glutamic acid of N^{δ}-hydroxy-L-ornithine, a component of several peptidyl hydroxamate antibiotics such as ferrichrome (**2**),[3]



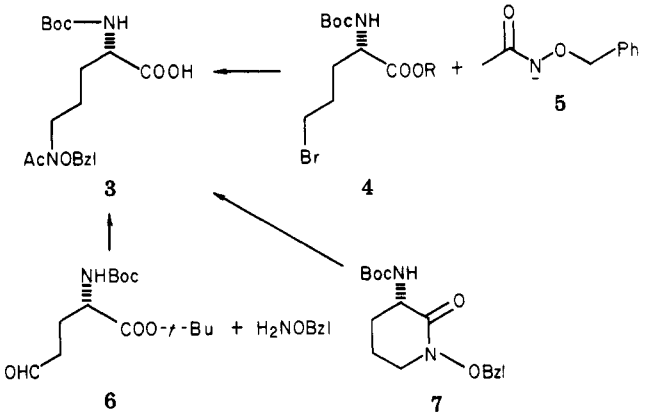
1



ferrichrome (**2**)

fusarinine,[4] dimeric acid,[5] rhodotorulic acid,[6] and related antibiotics.[7] The problems associated with the preparation and utilization of N^{δ}-hydroxy-L-ornithine in the total synthesis of ferrichrome,[8] dimeric acid,[9] and rhodotorulic acid[10] have prompted interest in a practical synthesis of the above amino acid.

Scheme I



Syntheses of N^{δ}-hydroxyornithine (**1**) have been reported. A racemic synthesis of **1** by Rogers and Neilands[11] involved reduction of an ω-nitro derivative to the hydroxyamino group with zinc dust, a reaction that pro-

(1) For some recent examples, see: Schollkopf, U.; Neubauer, H-J. *Synthesis* **1982**, 861. Bajgrowicz, J. A.; Cossec, B.; Pigiere, Ch.; Jacquier, R.; Viallfont, Ph. *Tetrahedron Lett.* **1983**, *24*, 3721. MacNeil, P. A.; Roberts, N. K.; Bosnich, B. *J. Am. Chem. Soc.* **1981**, *103*, 2273. Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *Ibid.* **1980**, *102*, 7932. Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J.; Bachman, G. L.; Weinkauff, D. J. *Ibid.* **1977**, *99*, 5946. Nakajima, K.; Oda, H.; Okawa, K. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 520.

(2) For some recent examples, see: Seebach, D.; Aebi, J. B. *Tetrahedron Lett.* **1983**, *24*, 3311. Seebach, D.; Weber, T. *Ibid.* **1983**, *24*, 3315. Bernardini, A.; Hallaoui, A. E.; Jacquier, R.; Pigiere, Ch.; Viallefont, Ph.; Bajgrowicz, J. *Ibid.* **1983**, *24*, 3717. Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. *J. Am. Chem. Soc.* **1983**, *105*, 5390. Noguchi, N.; Kurada, T.; Hatanaka, M; Ishimaru, T. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 633. Schollkopf, U.; Nozulak, J.; Groth, U. *Synthesis* **1982**, 868. Rich, D. H.; Sun, E. T.; Boparai, A. S. *J. Org. Chem.* **1978**, *43*, 3624. Ramasamy, K.; Olsen, R. K.; Emery, T. *Synthesis* **1982**, 42. Scott, A. I; Wilkinson, T. J. *Synth.* Commun. **1980**, *10*, 127.

(3) Neilands, J. B.; *J. Am. Chem. Soc.* **1952**, *74*, 4846. Rogers, S.; Neilands, J. B. *Biochemistry* **1965**, *4*, 1410.

(4) Emery, T. *Biochemistry* **1965**, *4*, 1410.

(5) Diekmann, H. *Arch. Mikrobiol.* **1970**, *73*, 65.

(6) Atkin, C. L.; Neilands, J. B. *Biochemistry* **1968**, *7*, 3734.

(7) Giaribaldi, J. A.; Neilands, J. B. *J. Am. Chem. Soc.* **1955**, 77, 2429. Emery, T.; Neilands, J. B. *J. Am. Chem. Soc.* **1961**, *83*, 1626. Atkin, C. L.; Neilands, J. B.; Phaff, H. J. *J. Bacteriol.* **1970**, *103*, 722. Keller-Schierlein, W.; Deer, A. *Helv. Chim. Acta* **1963**, *46*, 1907. Tadenuma, M.; Sato, S. *Agric. Biol. Chem.* **1967**, *31*, 1482. Keller-Schierlein, W.; Deer, A. *Helv. Chim. Acta* **1963**, *46*, 1920. Sayer, J. M.; Emery, T. *Biochemistry* **1968**, *7*, 184. Moore, R. E.; Emery, T. *Ibid.* **1976**, *15*, 2719. Diekmann, H. *Agnew. Chem.* **1968**, *7*, 551. Pidacks, C.; Whitehill, A. R.; Pruess, L. M.; Hesseltine, C. W.; Hutchings, B. L.; Bohonos, N.; Williams, J. H. *J. Am. Chem. Soc.* **1953**, *75*, 6064. Keller-Schierlein, W.; Diekmann, H. *Helv. Chim. Acta* **1970**, *53*, 2035. Maurer, B.; Muller, A.; Keller-Schierlein, W..; Zahner, H. *Arch. Microbiol.* **1968**, *60*, 326. Maehr, H. *Pure Appl. Chem.* **1971**, *28*, 603. Poddubnaya, N. A.; Krysin, E. P. *J. Gen. Chem. USSR* (Engl. Transl.) **1962**, *32*, 990.

(8) (a) Keller-Schierlein, W. *Helv. Chim. Acta* **1969**, *52*, 603. (b) Isowa, Y.; Takashima, T.; Ohmori, M.; Kurita, H.; Sato, M.; Mori, K. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 215.

(9) Widmer, J.; Keller-Schierlein, W. *Helv. Chim. Acta* **1974**, *57*, 1904.

(10) Isowa, Y.; Takashima, T.; Ohmori, M.; Kurita, H.; Sato, M.; Mori, K. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 1467.

(11) Rogers, S.; Neilands, J. B. *Biochemistry* **1963**, *2*, 6.

0022-3263/84/1949-3527$01.50/0