of 5 mL of dichloromethane. After addition of 420 mg (3.25 mmol) of diisopropylethylamine and the usual workup, flash chromatography (2:1 hexane/ethyl acetate) gave 184 mg (93%) of an oil that slowly crystallized, mp 118-9 °C: IR ($CDCl_3$) 1709, 1448, 1301, 1140 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.85-7.95 (m, 2 H), 7.45-7.75 (m, 3 H), 4.68 (dt, J = 13.4, 1.9 Hz, 2 H), 4.04 (dd, J = 9.5, 3.5 Hz, 1 H), 2.65-2.95 (m, 3 H), 2.35-2.55 (m, 2 H), 2.20-2.3 (m, 4 H), 1.45-1.75 (m, 3 H); calcd for $C_{17}H_{20}O_3S$ 304.1133, found 304.1101.

(c) 2-Methylene-1,2,3,4,5,6-hexahydroinden-4-one (67, n = 1). A suspension of 0.5 g of Woelm alumina in 2 mL of dry dichloromethane containing 69 mg (0.24 mmol) of keto sulfone **66** (n = 1) was stirred until TLC indicated disappearance of starting material (reaction must be promptly stopped since extended contact time promotes isomerization). The alumina was removed by filtration and washed with additional dichloromethane. The combined organic layers were concentrated in vacuo to give 31 mg (88%) of the title compound: IR ($CHCl_3$) 1655, 1630, 1452, 1438, 1408 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.0 (m, 2 H), 3.27 (m, 2 H), 3.21 (m, 2 H), 2.39 (m, 4 H), 2.33 (m, 2 H); calcd for $C_{10}H_{12}O$ 148.0888, found 148.0887.

(d) 2-Methylene-2,3,5,6,7,8-hexahydroazulen-4-one (67, n = 2). As above, 56 mg (0.184 mmol) of keto sulfone **66** (n = 2) was treated with 0.5 g of neutral Woelm alumina in 2 mL of dry dichloromethane to give 28 mg (93%) of the enone **67** (n = 2): IR ($CDCl_3$) 1640, 1618, 1450, 1420, 1382 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.94 (m, 2 H), 3.30 (m, 4 H), 2.59 (m, 2 H), 2.42 (m, 2 H), 1.80 (m, 4 H); calcd for $C_{11}H_{14}O$ 162.1045, found 162.1048.

(e) 2-Methyl-4,5,6,7-tetrahydroinden-7(1*H*)-one (68, n = 1). A suspension of 1.0 g of neutral Woelm alumina in 2 mL of dry dichloromethane containing 129 mg (0.44 mmol) of keto sulfone **66** and 0.1 mL of triethylamine was stirred 24 h at room temperature. The reaction was filtered, and the alumina was washed with dichloromethane. Concentration of the combined organic layers and flash chromatography (2:1 ether/hexane) gave 55 mg (84%) of conjugated dienone **68** (n = 1): IR ($CDCl_3$) 1636, 1539, 1420, 1407 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.13 (q, J = 1.3 Hz, 1 H), 3.15 (td, J = 3.0, 1.1 Hz, 2 H), 2.52 (m, 2 H), 2.38 (t, J = 6.3 Hz, 2 H), 2.11 (d, J = 1.3 Hz, 3 H), 1.95-2.0 (m, 2 H); calcd for $C_{10}H_{12}O$ 148.0888, found 148.0887.

(f) 2-Methyl-3,4,5,6,7,8-hexahydroazulen-4-one (68, n = 2). A solution of 106 mg (0.349 mmol) of keto sulfone **66** (n = 2) and 106 mg (0.697 mmol) of DBU in 2 mL of dry dichloromethane was stirred 1 h at room temperature. Removal of solvent in vacuo and flash chromatography (2:1 ether/hexane) gave 40 mg (70%) of conjugated dienone **68** (n = 2): IR ($CDCl_3$) 1618, 1605, 1545, 1395 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.02 (m, 1 H), 3.26 (td, J = 3.0, 0.8 Hz, 2 H), 2.64 (m, 4 H), 2.05 (d, J = 1.4 Hz, 3 H), 1.8 (m, 4 H); calcd for $C_{11}H_{14}O$ 162.1045, found 162.1047.

(g) Diels-Alder Reaction of Dienone (68, n = 1). A solution of 20 mg (0.13 mmol) of dienone **68**, n = 1, and 26 mg (0.27 mmol) of maleic anhydride in 0.5 mL of dry benzene was stirred 24 h at room temperature. Direct flash chromatography (2:1 hexane/ethyl acetate) gave 16 mg (48%) of adduct **69** as a crystalline solid, mp 105-6 °C: IR ($CDCl_3$) 1858, 1775, 1705, 1448, 1228 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.08 (d, J = 1.8 Hz, 1 H), 3.82 (d, J = 8.2 Hz, 1 H), 3.40 (d, J = 8.2 Hz, 1 H), 2.66 (d, J = 4.4 Hz, 1 H), 2.61 (d, J = 4.4 Hz, 1 H), 2.53 (dt, J = 16.3, 3.5 Hz, 1 H), 2.0-2.33 (m, 2 H), 1.90 (d, J = 8.8 Hz, 1 H), 1.6-1.8 (m, 1 H), 1.59 (d, J = 8.8 Hz, 1 H), 1.55 (s, 3 H); calcd for $C_{14}H_{14}O$ 246.0892, found 246.0901.

Reductive Desulfonylation of Cycloadducts. (a) 2-Methylene-3aβ-octahydroinden-4β-ol (71 + 72, n = 1). Powdered sodium amalgam (6%, 690 mg, 1.8 g-atom) was added portionwise to 135 mg (0.459 mmol) of hydroxysulfone (**32**, R = H, n = 1) and 262 mg of disodium acid phosphate in 4 mL of dry methanol at room temperature. After 3 h, additional portions of the acid phosphate (200 mg) and 6% sodium amalgam (400 mg, 1.04 g-atom) were added, and stirring was continued an additional 2 h. Addition of water was followed by pentane extraction. The pentane layers were dried ($MgSO_4$) and concentrated in vacuo, and the residue was flash chromatographed (2:1 ether/hexane) to give 48 mg (68%) of the desulfonylated products. VPC analysis showed two peaks at 6.3 min (65%) and 7.1 min (35%): IR ($CDCl_3$) 3605, 1450, 1435 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.87 (m, 2 H), 3.41 (m, 1 H), 0.8-2.8 (m, 13 H); calcd for $C_{10}H_{16}O$ 152.1201, found 152.1189.

(b) 2-Methylene-3aβ-decahydroazulen-4β-ol (71 and 72, n = 2). By using the above procedure, 143 mg (0.464 mmol) of hydroxy sulfone (**32**, R = H, n = 2) was reductively desulfonylated with 6% sodium amalgam (690 mg, 1.8 g-atom and 300 mg, 0.783 g-atom) to give 63 mg (81%) of product. VPC analysis shows equal amounts of two isomers of retention times, 11.5 and 11.8 min: IR ($CDCl_3$) 3605, 1656, 1630, 1449, 1430 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.75 (m, 2 H), 3.25-3.60 (m, 1 H), 2.40-3.15 (m, 3 H), 1.2-2.4 (m, 12 H); calcd for $C_{11}H_{18}O$ 166.1358, found 166.1359.

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health, Institute of General Medical Sciences, for their generous support of our programs, Rhone-Poulenc for a fellowship to S.M.M., and the Swiss National Science Foundation for a fellowship to M.A. We are grateful to the Bioorganic, Biomedical Mass Spectrometry Resource (A. L. Burlingame, Director) supported by the NIH Division of Research Resources Grant RRD1614 for some of the mass spectral data. Some of the molecular mechanics calculations were performed by A. Trost.

Synthesis of Hydroxylated 1-Azabicyclo[3.1.0]hexane and Prolinol Derivatives by Stereo- and Regiocontrolled Staudinger Aminocyclization. Application to the Nonproteinogenic Amino Acid (2*S*,3*S*,4*S*)-3-Hydroxy-4-methylproline (HMP) and Its Enantiomer

Johann Mulzer,* Roland Becker, and Erich Brunner

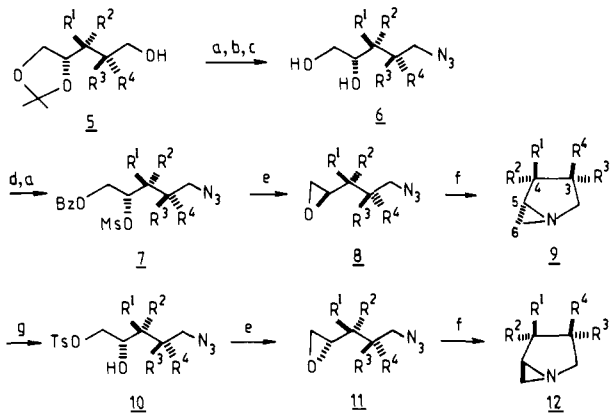
Contribution from the Institut für Organische Chemie, Freien Universität Berlin, Takustrasse 3, D 1000 Berlin 33, F.R.G. *Received February 27, 1989*

Abstract: On treatment with triphenylphosphine the azido epoxides **8/11** form enantio- and diastereomerically pure 1-azabicyclo[3.1.0]hexanes (**9/12**) via a Staudinger type aminocyclization reaction. Benzoic acid anhydride opens the aziridine ring in **9/12** to give prolinol derivatives (**20/23**) exclusively, whereas Boc anhydride shows a strong preference for the formation of hydroxypiperidine derivatives (**21/22**). The bicyclic amines **12** may also be prepared by aminocyclization of the ditosylates **25** and, analogously, prolinols **24** may be obtained from the monomesylates **7**. This novel methodology is applied to the synthesis of the rare amino acid HMP (**4**) and its enantiomer.

1-Azabicyclo[3.1.0]hexanes (**1**) are interesting synthetic intermediates.[1] They are found as an important structural feature in complex natural products (azinomycins) with antitumor activity.[2] On the other hand, proline derivatives such as **2** have

0002-7863/89/1511-7500$01.50/0

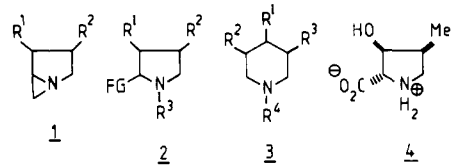
Scheme I[a]



a: R^1 = OBn; R^2 = H; R^3 = H; R^4 = Me
b: R^1 = H; R^2 = OBn; R^3 = Me; R^4 = H
c: R^1 = OBn; R^2 = H; R^3= OBn; R^4 = H
d: R^1 = OBn; R^2 = H; R^3 = H; R^4 = H
e: R^1 = H; R^2 = OBn; R^3 = H, R^4 = H

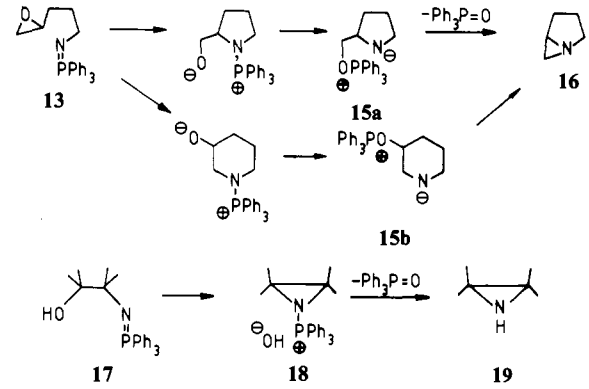
[a] (a) MsCl, pyridine, DMAP, 14 h, 22 °C, 2 h, 50 °C, 90–95%; (b) NaN_3, DMF, 24 h, 45 °C, 90–97%; (c) *p*-TsOH, MeOH, 45 °C, 12 h, 95–99%; (d) BzCl, pyridine, DMAP, 1 h, 0 °C, 87–92%; (e) MeONa, MeOH, 30 min, 0 °C, 90–95%; (f) PPh_3, THF or hexane, 3 h, 22 °C, 65–75%; (g) TsCl, pyridine, DMAP, 24 h, 0 °C, 95–100%.

aroused wide interest as chiral auxiliaries[3] or, with 3- or 4-hydroxy functions, as glycosidase inhibitors.[4] We describe an efficient synthesis of enantiomerically and diastereomerically pure derivatives of **1**, and their conversion into proline (**2**) and piperidine (**3**) derivatives. As an application, (2*S*,3*S*,4*S*)-3-hydroxy-4-methylproline (HMP, **4**), a nonproteinogenic amino acid found in the cyclopeptides echinocandin B-D,[5] was prepared together with its enantiomer, in a regio- and stereocontrolled manner.



The tetrol derivatives **5**, readily available from D-mannitol, either directly (**5c**) or via (*R*)-2,3-*O*-isopropylidene glyceraldehyde (**5a**,**b**,**d**,**e**),[6] were converted into the azides **6** in nearly quantitative yields. (Scheme I). To gain access to both configurations at C-5 of the envisaged target molecules **9**/**12**, the 1,2-diol moiety of **6** was transformed into the epoxide with retention and inversion of configuration. Thus, **6** was first benzoylated and then mesylated to give **7** with perfect regiocontrol, which was cyclized with base to epoxide **8**. Alternatively, **6** was regioselectively converted into the monotosylate **10**, which gave epoxide **11** on treatment with base. Both epoxides were diastereomerically pure according to the usual criteria (HPLC, ^1H and ^{13}C NMR). With triphenylphosphine under aprotic conditions (THF or, better, hexane), **8** and **11** smoothly formed the desired compounds **9** and **12**, respectively, with complete regio- and stereocontrol in ca. 70% isolated yield. The ^1H NMR data, in particular the characteristic high-field position of H-6, are in good agreement with literature values, as far as available.[1] Further confirmation of the structures was given by the conversion into known derivatives (e.g., **4**, vide infra). As expected, **8a**/**11b**, **8b**/**11a**, **8d**/**11e**, **8e**/**11d**, **9a**/**12b**, **9b**/**12a**, **9d**/**12e**, and **9e**/**12d** are enantiomers according to NMR and HPLC comparison and optical rotation.

Scheme II



A mechanism for the cyclization of **8**/**11** to **9**/**12** is suggested in Scheme II. The first step undoubtedly is the formation of an iminophosphorane **13** (Staudinger reaction[7]). The strongly nucleophilic nitrogen[8] opens the epoxide either in a 5-exo or a 6-endo fashion[9] to generate betaines **14a**/**b**, which undergo an N–O migration of the phosphorus to give **15a**/**b** in analogy to the Mitsunobu reaction.[10] Triphenylphosphine oxide is eliminated from **15a**/**b** and the bicyclic amine **16** is formed via a S_N2-type cyclization. Thus, with respect to the final product the 5-exo and the 6-endo pathways are indistinguishable, which renders the overall aminocyclization regioconvergent. As the conversion of **15a** to **16** has literature precedence,[11] the 5-exo mode appears more likely. To explain the cyclization of **17** to aziridine **19**, Blum postulated[12] the intermediate **18**. However, this mechanism requires a proton source, in contrast to our azides, which react smoothly in aprotic solvents like THF or hexane.

We next turn to the regiochemistry of the aziridine ring opening in **9**/**12**. With acids, **1** is opened to give pyrrolidines (**2**) under kinetically and piperidines (**3**) under thermodynamically controlled conditions.[13a] By contrast, anhydrides react irreversibly with **9**/**12** and it depends on the nature of the anhydride as to which product is formed.[13b] We found that benzoic acid anhydride leads to the five-membered ring. For instance, **23** was obtained from **12c** **20a** was obtained from **9a** exclusively. In contrast, Boc anhydride reacted with **9a** to give a 3:1 mixture of **20**/**21b** and furnished **22** from **9c**. The piperidine structure of **22** clearly follows from the fact that a meso compound was obtained after removal of the protecting groups. The reason for this pronounced difference in the regioselectivity of each anhydride is unclear. It has to be

(1) See, for example: Black, D. St. C.; Doyle, J. E. *Adv. Heterocycl. Chem.* **1980**, *27*, 1. Hudlicky, T.; Frazier, J. O.; Seoane, G.; Tiedje, M.; Seoane, A.; Kwart, L. D.; Beal, C. *J. Am. Chem. Soc.* **1986**, *108*, 3755. Harding, K. E.; Burke, S. R. *J. Org. Chem.* **1984**, *49*, 40. Alverne, G.; Frazier, J. D.; Touhami, K. *J. Fluorine Chem.* **1985**, *29*, 363.

(2) Ishizeki, S.; Ohtsuka, M.; Irinoda, K.; Kukita, K.; Nagaoka, K.; Nakashima, T. *J. Antibiot.* **1987**, *40*, 60.

(3) See, for example: Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1987**, *28*, 651, and earlier papers. Enders, D. *Selectivity—A Goal for Synthetic Efficiency*; Bartmann, W., Trost, B. M., Eds.; Verlag Chemie, Weinheim, West Germany, 1983; p 65.

(4) Scofield, A. M.; Fellows, L. E.; Nash, R. J.; Fleet, G. W. J.; *Life Sci.* **1986**, *39*, 645. Elbein, A. D. *Annu. Rev. Biochem.* **1987**, *56*, 497.

(5) Benz, F.; Knüsel, F.; Nüesch, J.; Treichler, H.; Voser, W.; Nyfelder, R.; Keller-Schierlein, W. *Helv. Chim. Acta* **1974**, *57*, 2459. Keller-Juslen, C.; Kuhn, M.; Loosli, H. R.; Petcher, T. J.; Weber, H. P.; Wartburg, A. v. *Tetrahedron Lett.* **1976**, 4147.

(6) Mulzer, J.; Lasalle, P. de; Freissler, A. *Liebigs Ann. Chem.* **1986**, 1152. Mulzer, J.; Angermann, A.; Münch, W. *Liebigs Ann. Chem.* **1986**, 825.

(7) Staudinger, R.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635. Review: Gololobov, Y. G.; Zhmurova, I. N.; Kasukhin, L. F. *Tetrahedron* **1981**, *37*, 437.

(8) Vaultier, M.; Knouzi, N.; Carrié, R. *Tetrahedron Lett.* **1983**, *24*, 763, and references therein.

(9) Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. *J. Chem. Soc., Chem. Commun.* **1976**, 736. Mulzer, J.; Schulze, T.; Strecker, A.; Denzer, W. *J. Org. Chem.* **1988**, *53*, 4098.

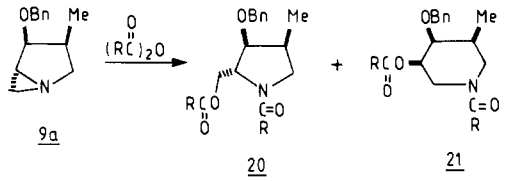
(10) Hughes, D. L.; Reamer, R. A.; Bergan, J. J.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1988**, *110*, 6487. Mitsunobu, O. *Synthesis* **1981**, 1. In the intermolecular reaction of epoxides with iminophosphoranes, 1,3,2λ^5-oxazaphospholidines are postulated as intermediates: Appel, R.; Halstenberg, M. *Chem. Ber.* **1976**, *109*, 814.

(11) Buyle, R. *Chem. Ind. (London)* **1966**, 195. See also: Gassman, P. G.; Fentiman, A. *J. Org. Chem.* **1967**, *32*, 2388.

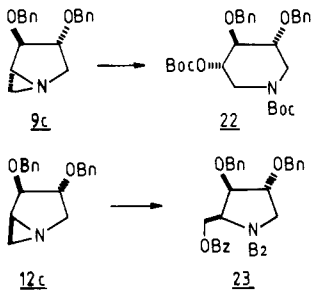
(12) Ittah, Y.; Sasson, Y.; Shahak, I.; Tsaroom, S.; Blum, J. *J. Org. Chem.* **1978**, *43*, 4271.

(13) (a) Harding, K. E.; Burks, S. R. *J. Org. Chem.* **1984**, *49*, 40. (b) **1** (R^1,R^2 = H) gives a 1.86:1 mixture of **3** and **2** with acetic anhydride: Wong, J. L.; Helton, D. O. *J. Chem. Soc., Chem. Commun.* **1973**, 352.

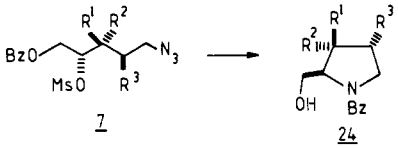
clarified whether a concerted or a stepwise mechanism under participation of an immonium ion may be responsible for this phenomenon; also, the substituents at C-4 and C-5 have to be varied to study their regiodirecting influence on the ring opening for each anhydride. Additionally, other anhydrides have to be tried.



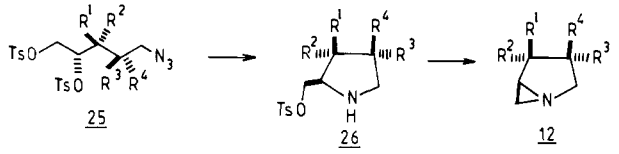
20a, **21a**: R = Ph
20b, **21b**: R = O*t*Bu



To extend the scope of our approach, direct aminocyclization[14] of **7b,c** with triphenylphosphine under aqueous conditions was also tested. In fact, the prolinol derivatives **24a,b** were obtained in ~80% isolated yield, indicating that an O–N migration of the benzoyl group has taken place subsequent to the cyclization. By selective O-debenzoylation with methoxide in methanol **23** was converted into **24b**, whereas **20a** gave **27a**, the enantiomer of **24a**, in total agreement with our expectation. Similarly, the ditosylates **25a–c**, quantitatively obtained from **6a–c** with an excess of tosyl chloride in pyridine, furnished **12a–c** in good yield, identical with the compounds obtained from **11** under aprotic conditions. In the presence of water, the cyclizations of **7** and **25** most likely proceed via the free amino base; the unstable monotosylate **26** rapidly undergoes a second S_N2 cyclization to form **12**. Again, as in the conversion of **8**/**11** into **9**/**12**, the primary tosylate may be attacked first by the nitrogen; again, both alternatives are indistinguishable with respect to the product.



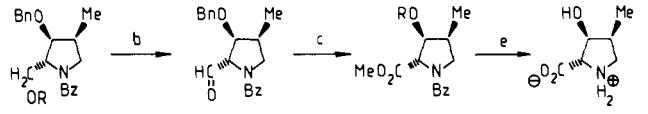
7b, **24a**: R^1 = H; R^2 = OBn; R^3 = Me
7c, **24b**: R^1 = OBn; R^2 = H, R^3 = OBn



a: R^1 = OBn; R^2 = H; R^3 = H; R^4 = Me
b: R^1 = H; R^2 = OBn; R^3 = Me; R^4 = H
c: R^1 = OBn; R^2 = H; R^3 = OBn; R^4 = H

As an application, and to confirm the structural assignment, **20a** was elaborated into the rare amino acid HMP (**4**). So far, only one synthesis has been reported of **4**,[15] and one of the methyl ester hydrochloride;[16] in both syntheses the chiral centers are created under the influence of suitable auxiliaries. In our case (Scheme III) **27a** was oxidized to the aldehyde **27b** under Swern conditions, and further to the carboxylic acid with potassium permanganate by using Masamune's conditions.[17] Esterification of the crude acid with diazomethane furnished the ester **27c**, which was debenzylated to **27d**. Hydrolysis of the ester and amide functions delivered **4**, identical with the compound described[15] (^{1}H NMR, optical rotation). The overall yield from **20a** to **4** is ~30%: no isolation of the intermediates **27b** and **c** is necessary. An analogous sequence starting from **24a** led to ent-**4**, as expected.

Scheme III[a]



20a: R = Bz
27a: r = H
27b
27c: R = Bn
27d: R = H
4

[a] (a) 2 N NaOH, 5 h, 22 °C, quantitative; (b) $(COCl)_2$, DMSO, CH_2Cl_2, NEt_2iPr, −55 °C; (c) $KMnO_4$, H_2O–*t*BuOH, pH 6, 22 °C, CH_2N_2, ether, 0 °C, yield over b–c 68%; (d) H_2/Pd, MeOH, HCl, 3 bar, 22 °C, 3 h, 94%; (e) 40% NaOMe in MeOH–H_2O (1:1), reflux, 36 h, then addition of HCl until neutral. Isolation of **4** by acidic ion-exchange resin Dowex 50×4 and elution with 1 N NH_3, 64%.

In conclusion, efficient and stereochemically flexible syntheses have been presented for the amino compounds **1** and **2** from the acyclic precursors **5**, which are readily available in a variety of substitution patterns from carbohydrate sources. Extension of this approach to other pyrrolidine (and also piperidine[18]) type natural products is under current investigation.

Experimental Section

NMR experiments were performed at 270 MHz (^{1}H) and 62.5 MHz (^{13}C). For the sake of brevity, only the synthetic sequence starting from **5a** is described in detail; the others are quite analogous. A detailed description of some important intermediates is given in the Supplementary Material.

(2*R*,3*S*,4*S*)-3-*O*-Benzyl-1,2-*O*-isopropylidene-4-methylpentane-1,2,3,5-tetrol (5a). (2*R*,3*S*,4*S*)-1,2-*O*-Isopropropylidene-3-*O*-benzyl-4-methyl-5-hexene (40.0 g, 143.5 mmol) in methanol (1.5 L) was ozonized at −78 °C until the solution was faintly blue. The mixture was warmed to 20 °C, and sodium borohydride (10.3 g, 270 mmol) was added in small portions. Water (250 mL) was added and the mixture was stirred for 30 min, concentrated under reduced pressure, and extracted with chloroform. The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure to give after column chromatography (hexane–ethyl acetate 3:1, silica gel) **5a** (28.1 g, 88%) as a colorless oil: $[\alpha]^{20}_D$ 14.3° (*c* 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.05 (d, *J* = 7 Hz, CH_3), 1.38, 1.45 (s, 2 CH_3), 2.00 (sept, *J* = 7 Hz, H-4), 2.68 (s, OH), 3.36 (t, *J* = 6 Hz, H-3), 3.65 (m, H-2, H-3), 3.92 (dd, *J* = 6, 8 Hz, H-1), 4.10 (dd, *J* = 6, 8 Hz, H-1), 4.25 (q, *J* = 6 Hz, H-2), 4.64 (d, *J* = 11 Hz, benzyl H), 4.70 (d, *J* = 11 Hz, benzyl H), 7.28–7.38 (m, phenyl H); ^{13}C NMR ($CDCl_3$) δ 13.05, 25.27, 26.46, 37.16, 65.41, 66.58, 73.91, 76.00, 82.81, 109.10, 127.66, 128.45, 138.00; IR (film) 3400, 2990, 2940, 2890, 1455, 1380, 1370, 1215, 1160, 1100–1030, 700 cm^{-1}. Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63. Found: C, 68.21; H, 8.66.

(2*R*,3*S*,4*S*)-5-Azido-3-*O*-benzyl-4-methylpentane-1,2,3-triol (6a). **5a** (27.0 g, 96.5 mmol) in pyridine (10 g, 145 mmol) and DMAP (500 mg) was treated dropwise with methanesulfonyl chloride (13.3 g, 125 mmol) in THF (40 mL) at 0 °C. The mixture was stirred 14 h at 20 °C and 2 h at 45 °C, then concentrated, filtered, and evaporated to give after column chromatography (silica gel, hexane-ethyl acetate 3:1) analytically pure mesylate (31.8 g, 92%). The mesylate (30.0 g, 83.7 mmol) in DMF (250 mL) was treated with sodium azide (6.00 g, 92 mmol), and the suspension was stirred 24 h at 45 °C. After cooling to room temperature, water, hexane, and ether were added and the mixture was stirred for 5

(14) Similar cyclizations have been studied: Fleet, G. W. J.; Son, J. C. *Tetrahedron* **1988**, *44*, 2637, 2649, and earlier papers. Shing, T. K. M. *Tetrahedron* **1988**, *44*, 7261, and earlier papers. Jones, D. W. C.; Nash, R. J.; Bell, E. A.; Williams, J. M. *Tetrahedron Lett.* **1985**, *26*, 3125. Card, P. J.; Hitz, W. D. *J. Org. Chem.* **1985**, *50*, 891. Le Merrer, Y.; Dufeault, A,; Gravier, C.; Languin, D.; Depezay, J. C. *Tetrahedron Lett.* **1985**, *26*, 319. Ewing, W. R.; Harris, B. D.; Bhat, K. L.; Joullie, M. M. *Tetrahedron* **1986**, *42*, 242.

(15) Kurokawa, N.; Ohfune, Y. *J. Am. Chem. Soc.* **1986**, *108*, 6041.
(16) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1987**, *109*, 7151.
(17) Abiko, A.; Roberts, J. C.; Takemasa, T.; Masamune, S. *Tetrahedron Lett.* **1986**, *27*, 4536.
(18) Hydroxylated piperidines are known as glycosidase inhibitors: Lalegerie, P.; Legler, G.; Yon, J. M. *Biochemie* **1982**, *64*, 877. Bernotas, R. C.; Ganem, B. *Tetrahedron Lett.* **1985**, *26*, 4981, and references therein.

min. The organic phase was washed with water, dried ($MgSO_4$), evaporated, and purified by column chromatography (silica gel, hexane–ethyl acetate 3:1) to furnish 23.2 g (91%) of the azide as an analytically pure colorless oil. The azide (22.0 g, 71.9 mmol) was stirred in methanol (2 L) with *p*-TsOH (1 g) at 45 °C until the starting material had disappeared (TLC monitoring). The mixture was concentrated under reduced pressure, and the residue was purified by column chromatography (silica gel, hexane–ethyl acetate 1:1) to give **6a** (17.9 g, 94%) as colorless crystals: mp 62–63 °C; $[\alpha]^{20}_D$ 1.4° (*c* 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.11 (d, J = 7 Hz, CH_3), 2.07 (m, H-4), 2.61 (s, 2 OH), 3.35 (dd, J = 13, 6 Hz, H-5), 3.50 (t, J = 5 Hz, H-3), 3.58 (dd, J = 13, 5 Hz, H-5), 3.72 (m, 2 H-1), 3.80 (m, H-2), 4.60 (d, J = 11 Hz, benzyl H), 4.66 (d, J = 11 Hz, benzyl H), 7.32–7.39 (m, phenyl H); ^{13}C NMR ($CDCl_3$) δ 14.94, 35.27, 54.12, 63.58, 71.72, 74.46, 82.08, 127.80–128.47 (3 lines), 137.94; IR (KBr) 3450, 2970, 2100, 1280, 1100–1055, 738, 700 cm^{-1}. Anal. Calcd for $C_{13}H_{19}N_3O_3$: C, 58.84; H, 7.22; N, 15.84. Found: C, 58.96; H, 7.17; N, 15.94.

(2*R*,3*S*,4*S*)-5-Azido-1-*O*-benzoyl-3-*O*-benzyl-2-*O*-(methylsulfonyl)-4-methylpentane-1,2,3-triol (7a). **6a** (16.0 g, 60.3 mmol) in pyridine (7 g) and DMAP (500 mg) was treated dropwise with freshly distilled benzoyl chloride (10.2 g, 72.4 mmol) in ether (20 mL) at 0 °C for 1 h. The solvents were evaporated under reduced pressure, and the residue was chromatographed (silica gel, hexane–ethyl acetate 3:1) to furnish the monobenzoate (18.9 g, 87%) as an analytically pure colorless oil. The monobenzoate (10.0 g) was mesylated as described for **6a** to give **7a** (10.4 g, 86%) as a colorless oil: $[\alpha]^{20}_D$ 9.2° (*c* 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.16 (d, J = 7 Hz, CH_3), 2.04 (m, H-4), 3.03 (s, CH_3), 3.44 (dd, J = 13, 6 Hz, H-5), 3.54 (dd, J = 13, 5 Hz, H-5), 3.80 (dd, J = 8, 2.5 Hz, H-3), 4.55 (dd, J = 13, 8 Hz, H-1), 4.64 (d, J = 11 Hz, benzyl H), 4.76 (dd, J = 13, 2.5 Hz, H-1), 4.88 (d, J = 11 Hz, benzyl H), 5.22 (dt, J = 8, 2.5 Hz, H-2), 7.30–7.74 (m, phenyl H); ^{13}C NMR ($CDCl_3$) δ 14.80, 35.89, 38.73, 54.01, 62.75, 74.88, 81.04, 81.38, 128.06, 128.47, 128.55, 129.33, 129.64, 133.42, 137.38, 166.20; IR (film) 2100, 1720, 1450, 1360, 1340, 1270, 1175, 1110, 1098, 1070, 1027, 970, 740 cm^{-1}. Anal. Calcd for $C_{21}H_{25}O_6N_3S$: C, 56.36; H, 5.63; N, 9.39. Found: C, 56.55; H, 5.59; N, 9.43.

(2*S*,3*S*,4*S*)-5-Azido-3-*O*-benzyl-1,2-epoxy-4-methylpentan-3-ol (8a). **7a** (9.00 g, 36.4 mmol) in methanol (10 mL) was treated dropwise with a solution of sodium (1.00 g) in methanol (10 mL) at 0 °C. After 30 min the mixture was neutralized with ammonium chloride and extracted with ether. The ether phase was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (silica gel, hexane–ethyl acetate 3:1) to give **8a** (4.70 g, 94%) as a colorless oil: $[\alpha]^{20}_D$ −29.8° (*c* 2.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.05 (d, J = 7 Hz, CH_3), 2.04 (m, H-4), 2.56 (dd, J = 5, 2.5 Hz, H-1), 2.84 (dd, J = 5, 4 Hz, H-1), 2.94 (t, J = 8 Hz, H-3), 3.09 (ddd, J = 8, 4, 2.5 Hz, H-2), 3.45 (d, J = 5 Hz, H-5), 4.56 (d, J = 11 Hz, benzyl H), 4.88 (d, J = 11 Hz, benzyl H), 7.32–7.40 (m, phenyl H); ^{13}C NMR ($CDCl_3$) δ 14.72, 36.84, 43.53, 53.69, 53.98, 72.26, 81.81, 127.58, 127.85, 128.28, 138.25; IR (film) 2100, 1190, 1070 cm^{-1}. Anal. Calcd for $C_{13}H_{17}N_3O_2$: C, 63.14; H, 6.93; N, 16.99. Found: C, 63.30; H, 6.79; N, 16.72.

(1*R*,3*S*,4*S*,5*R*)-4-*O*-Benzyl-3-methyl-1-azabicyclo[3.1.0]hexan-4-ol (9a). **8a** (3.50 g, 14.1 mmol) in THF (35 mL) was treated with triphenylphosphine (3.90 g, 14.8 mmol) at 22 °C. The reaction was monitored by TLC. At first the starting material was converted into the iminophosphorane (evolution of nitrogen, polar spot on TLC). Overnight, the product (**9a**) and triphenylphosphine oxide were formed. The oxide was removed by filtration, and the product was isolated from the filtrate by column chromatography (silica gel, ethyl acetate) to give **9a** (1.90 g, 66%) as a colorless oil, which solidified in the refrigerator: $[\alpha]^{20}_D$ −105.7° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.03 (d, J = 7 Hz, CH_3), 1.24 (d, J = 3 Hz, H-6), 1.64 (d, J = 5.5 Hz, H-6), 2.05 (m, H-3), 2.54 (dd, J = 5.5, 3 Hz, H-5), 2.72 (dd, J = 11, 10 Hz, H-2), 2.98 (dd, J = 11, 8 Hz, H-2), 3.96 (d, J = 5 Hz, H-4), 4.60 (d, J = 11 Hz, benzyl H), 4.94 (d, J = 11 Hz, benzyl H), 7.28–7.40 (m, phenyl H); ^{13}C NMR ($CDCl_3$) δ 10.69, 27.72, 33.08, 42.82, 58.81, 71.72, 80.57, 127.46, 128.30, 138.74; IR (film) 2885, 1455, 1095, 1070, 1045, 1030, 740, 700 cm^{-1}; MS (Cl, 40 °C, 160 eV) *m/e* (relative intensity) 204 ($M^+ + H$) (100), 174 (M^+ − HCN, 52), 96 (81), 91 (72). Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.74; H, 8.45; N, 6.97.

(2*R*,3*S*,4*S*)-5-Azido-3-*O*-benzyl-1,2-epoxy-4-methylpentan-3-ol (11a). **6a** (2.50 g, 9.42 mmol) in pyridine (2 mL) was treated with DMAP (100 mg) and tosyl chloride (2.08 g, 10.9 mmol) in pyridine (3 mL) at 0–22 °C for 14 h. The mixture was poured into water and extracted with ether. The ethereal phase was dried ($MgSO_4$), concentrated, and chromatographed (silica gel, hexane–ethyl acetate 3:1) to give the monotosylate (10a) as a colorless oil. No secondary tosylate could be detected (HPLC analysis). The monotosylate was then treated with sodium methoxide in methanol as described for **8a**. The epoxide **11a** was isolated by column chromatography (silica gel, hexane–ethyl acetate 5:1) as a colorless oil: yield 2.11 g (83%); $[\alpha]^{20}_D$ −19.5° (*c* 1.15, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.11 (d, J = 7 Hz, CH_3), 2.07 (m, H-4), 2.72 (dd, J = 5.5, 3 Hz, H-1), 2.80 (dd, J = 5.5, 4 Hz, H-1), 3.00 (dt, J = 6, 4.5 Hz, H-2), 3.19 (t, J = 6 Hz, H-3), 3.36 (dd, J = 12, 7 Hz, H-5), 4.48 (d, J = 11 Hz, benzyl H), 4.69 (d, J = 11 Hz, benzyl H), 7.32–7.39 (m, phenyl H); ^{13}C NMR ($CDCl_3$) δ 14.25, 37.47, 45.13, 51.60, 53.81, 72.95, 79.70, 127.58, 127.85, 128.25, 138.26; IR (film) 2100, 1185, 1070, 740 cm^{-1}. Anal. Calcd for $C_{13}H_{17}N_3O$: C, 63.14; H, 6.93; N, 16.99. Found: C, 63.25; H, 7.10; N, 16.74.

(1*S*,3*S*,4*S*,5*S*)-4-*O*-Benzyl-3-methyl-1-azabicyclo[3.1.0]hexan-4-ol (12a). **11a** (1.60 g, 6.45 mmol) was converted into **12a** as described for the reaction of **8a** to **9a**. The yield was 921 mg (70%) of **12a** as a colorless oil: $[\alpha]^{20}_D$ −154° (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.99 (d, J = 7 Hz, CH_3), 1.84 (d, J = 3.5 Hz, H-6), 2.10 (d, J = 5.5 Hz, H-6), 2.14 (t, J = 11 Hz, H-2), 2.56 (m, H-2, H-3, and H-5), 3.34 (dd, J = 11, 9 Hz, H-2), 4.16 (dd, J = 6, 4 Hz, H-4), 4.40 (d, J = 12 Hz, benzyl H), 4.61 (d, J = 12 Hz, benzyl H), 7.26–7.37 (m, phenyl H); ^{13}C NMR ($CDCl_3$) δ 11.98, 37.32, 45.01, 45.30, 61.65, 70.26, 79.08, 127.12, 127.25, 128.13, 138.43; IR (film) 2920, 2870, 1450, 1090, 1060, 730, 695 cm^{-1}; MS *m/e* calcd for M^+ − H 202.123 19, found 202.122 77.

Ring Opening of 9a with Benzoic Acid Anhydride To Give 20a. **9a** (1.58 g, 7.78 mmol) in THF (5 mL) was treated with benzoic acid anhydride (2.28 g, 10.0 mmol) in small portions at −10 °C. The reaction was complete in 10 min. The mixture was concentrated, and the residue was chromatographed (silica gel, hexane–ethyl acetate 3:1) to give **20a** (2.64 g, 79%) as a colorless oil.

(2*R*,3*S*,4*S*)-*N*-Benzoyl-1-[(benzoyloxy)methyl]-3-(benzyloxy)-4-methylpyrrolidine (20a): $[\alpha]^{20}_D$ −80.4° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.05 (d, J = 7 Hz, CH_3), 2.51 (m, H-4), 3.25 (t, J = 10 Hz, H-5), 3.60 (dd, J = 10, 7.5 Hz, H-5), 3.97 (dd, J = 3.5, 1.5 Hz, H-3), 4.52 (d, J = 11.5 z, benzyl H), 4.69 (d, J = 11.5 Hz, benzyl H), 4.52–4.77 (m, H-2, H-3, and H-1′), 7.24–7.55 (m, 12 phenyl H), 7.58 (m, 1 phenyl H), 8.02 (m, 2 phenyl H); ^{13}C NMR ($CDCl_3$) δ 11.18, 35.75, 54.55, 60.70, 62.47, 71.14, 80.49, 126.81, 127.64, 128.28, 128.31, 129.46, 129.72, 129.78, 133.00, 136.64, 137.64, 165.98, 170.72; IR (film) 1720, 1640–1630, 1410, 1270, 1115, 715, 702 cm^{-1}. Anal. Calcd for $C_{27}H_{27}NO_4$: C, 75.50; H, 6.34; N, 3.26. Found: C, 75.13; H, 6.43; N 3.24.

Saponification of 20a To Give 27a. **20a** (2.50 g, 5.82 mmol) was treated with sodium methoxide in methanol for 14 h at 20 °C as described for the conversion of **8a** to **9a**. Aqueous workup and chromatography (silica gel, ethyl acetate) furnished **27a** (1.79 g, 95%) as colorless crystals. **(2*R*,3*S*,4*S*)-*N*-Benzoyl-3-(benzyloxy)-4-methylprolinol (27a):** mp 101–102 °C; $[\alpha]^{20}_D$ −84.1° (*c* 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.02 (d, J = 7 Hz, CH_3), 2.36 (m, H-4), 3.31 (dd, J = 10, 9 Hz, H-5), 3.35 (dd, J = 10, 8 Hz, H-5), 3.76 (dd, J = 12, 7 Hz, H-1′), 3.80 (t, J = 4 Hz, H-3), 3.83 (dd, J = 12, Hz, H-1′), 4.56 (dd, J = 7, 4 Hz, OH), 4.45 (dt, J = 7, 4 Hz, H-2), 4.54 (d, J = 12 Hz, benzyl H), 4.67 (d, J = 12 Hz, benzyl H), 7.28–7.59 (m, phenyl H); ^{13}C NMR ($CDCl_3$) δ 11.21, 35.76, 54.96, 64.75, 65.21, 71.25, 81.21, 126.84, 127.60, 127.71, 128.30, 128.35, 129.94, 136.33, 137.82, 172.03; IR (KBr) 3400, 1615, 1580, 1450, 1430, 1100, 915, 705 cm^{-1}. Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.73; H, 7.07; N, 4.33.

Aminocyclization of 7b To Give 24a. **7b** (4.28 g, 9.56 mmol) in THF (60 mL) was treated with triphenylphosphine (2.63 g, 10.0 mmol) at 20 °C until the evolution of nitrogen had ceased. Water (300 mg) was added, and the mixture was stirred for 14 h at 20 °C. The mixture was treated with 2 N NaOH until the pH was 11 and stirred for 5 h. Workup with ether and column chromatography (silica gel, ethyl acetate) delivered pure crystalline **24a** (2.48 g, 85%). The compound is enantiomeric to **20a**. ^1H and ^{13}C NMR spectra are superimposable: mp 101–102 °C; $[\alpha]^{20}_D$ 84.3° (*c* 1.5, $CHCl_3$).

Aminocyclization of the Ditosylate 25a To Give 12a. **6a** (4.00 g, 15.1 mmol) was treated with tosyl chloride (8.59 g, 45.3 mmol) as described for the conversion of **6a** into **11a**. After column chromatography (silica gel, hexane–ethyl acetate 4:1) **25a** (8.57 g, 95%) was obtained as colorless crystals. **(2*R*,3*S*,4*S*)-5-Azido-3-*O*-benzyl-1,2-di-*O*-tosylpentane-1,2,3-triol (25a):** mp 56–57 °C; $[\alpha]^{20}_D$ −6.4° (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.98 (d, J = 7 Hz, CH_3), 1.77 (m, H-4), 2.46, 2.48 (s, Tos CH_3), 3.24 (dd, J = 12.5, 7 Hz, H-5), 3.36 (dd, J = 12.5, 7 Hz, H-5), 3.72 (dd, J = 8, 3 Hz, H-3),4.12–4.25 (m, H-2), 4.50 (d, J = 11 Hz, benzyl H), 4.72 (d, J = 11 Hz, benzyl H), 4.82 dt, J = 6, 3 Hz, H-2), 7.20–7.79 (phenyl H); IR (KBr) 2100, 1365, 1190, 1175, 1045, 925, 915 cm^{-1}. Anal. Calcd for $C_{29}H_{31}N_3O_7S_2$: C, 58.27; H, 5.23; N, 7.03. Found: C, 58.62; H, 5.27; N, 7.10. **25a** (7.50 g, 12.6 mmol) was treated with triphenylphosphine as described for the conversion of **7b** into **24a**. **12a** (2.09 g, 82%) was obtained, identical in NMR spectra and optical rotation with the compound obtained from **11a**.

Synthesis of HMP (4) from 20a. Oxalyl chloride (1.74 g, 13.5 mmol) in dichloromethane (27 mL) was treated dropwise at −60 °C with DMSO

(1.05 g, 13.2 mmol) in dichloromethane (12 mL). After 10 min, **20a** (4.20 g, 12.9 mmol) in dichloromethane (25 mL) was added. After 15 min, diisopropylethylamine (9.0 g, 69 mmol) was added and the mixture was allowed to warm to 20 °C. Workup with water furnished the crude aldehyde (**27a**), which was immediately oxidized to the acid. Crude **27a** (4.0 g) in *tert*-butyl alcohol (25 mL) was treated with phosphate buffer until pH 6 was reached. Aqueous 1 M potassium permanganate was added dropwise, until no starting material was left (TLC). Sodium sulfite was added to destroy unreacted permanganate, and the mixture was acidified to pH 3 with diluted HCl and extracted with ether. The ether phase was dried ($MgSO_4$) and concentrated to give the crude acid (**27b**). **27b** in ether (10 mL) was treated dropwise at 0 °C with ethereal diazomethane, until the mixture was faintly yellow. One drop of acetic acid was added, and the ether was removed under reduced pressure. The residue was purified by column chromatography to give **27c** (3.10 g, 68%) as a colorless oil.

(2*S*,3*S*,4*S*)-*N*-Benzoyl-3-(benzyloxy)-4-methylproline methyl ester (27c): $[\alpha]^{20}_D$ −22.1° (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.06 (d, *J* = 7 Hz, CH_3), 2.48 (m, H-4), 3.39 (t, *J* = 10 Hz, H-5), 3.66 (dd, *J* = 10, 2.5 Hz, H-5), 3.80 (s, OMe), 3.94 (d, *J* = 5 Hz, H-3), 4.55 (d, *J* = 11 Hz, benzyl H), 4.80 (d, *J* = 11 Hz, benzyl H), 4.86 (br s, H-2), 7.28–7.56 (phenyl H); ^{13}C NMR ($CDCl_3$) δ 10.81, 37.11, 52.31, 54.14, 64.54, 71.28, 81.74, 127.11, 127.73, 127.82, 128.15, 128.37, 128.98, 136.03, 137.41, 169.70, 170.45; IR (film) 1745, 1635, 1400, 1415, 1210, 1180, 735 cm^{-1}. Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.52; H, 6.40; N, 3.87.

(2*S*,3*S*,4*S*)-*N*-Benzoyl-3-hydroxy-4-methylproline Methyl Ester (27d). **27c** (3.00 g, 8.48 mmol) in methanol (150 mL) was treated with 0.5 mL of concentrated HCl. Pd/C (10%) (300 mg) was added, and the mixture was hydrogenated at 22 °C (3 bar). After 3 h, the catalyst was removed by filtration and the solvent was evaporated. Column chromatography (silica gel, hexane–ethyl acetate 1:1) furnished **27d**: 2.10 g, 94%; colorless crystals, mp 106–107 °C; $[\alpha]^{20}_D$ −13.8° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.03 (d, *J* = 7 Hz, CH_3), 1.73 (s, OH), 2.44 (m, H-4), 3.38 (dd, *J* = 10, 9 Hz, H-5), 3.67 (dd, *J* = 10, 7.5 Hz, H-5), 3.80 (s, OMe), 4.28 (br s, H-3), 4.68 (s, H-2), 7.36–7.60 (m, phenyl H); ^{13}C NMR ($CDCl_3$) δ 10.81, 37.45, 52.41, 53.75, 68.27, 75.23, 127.20, 128.25, 130.17, 170.63; IR (KBr) 1745, 1625–1610, 1450, 1432, 1206, 1178, 732 cm^{-1}; MS *m/e* calcd. for $C_{14}H_{17}NO_4^{\bullet+}$ 263.115 759, found 263.115 862.

(2*S*,3*S*,4*S*)-3-Hydroxy-4-methylproline (HMP) (4). Sodium methoxide (40% in methanol, 70 mL) was diluted with water (30 mL). **27d** (2.00 g, 7.57 mmol) in methanol (5 mL) was added, and the mixture was refluxed for 36 h. After neutralization with diluted HCl, the solvent was evaporated and the solid residue was dried under reduced pressure and then extracted with methanol. The methanol solution was evaporated to deliver crude **4**, which was purified by dissolving it in diluted HCl (pH 2) and treating the solution with acidic ion-exchange resin (Dowex 50×4). The resin was washed with water and then eluted with 1 N aqueous ammonia. Evaporation of the elute delivered **4** (710 mg, 64%) as a colorless solid: $[\alpha]^{22}_D$ −26.4° (*c* 1.3, H_2O) [lit.[15] −27° (*c* 0.8, H_2O)]; ^1H NMR (D_2O) δ 1.08 (d, *J* = 7 Hz, CH_3), 2.26 (m, H-4), 3.05 (t, *J* = 12 Hz, H-5), 3.60 (dd, *J* = 12, 8 Hz, H-5), 4.06 (s, H-2), 4.45 (d, *J* = 4 Hz, H-3); ^{13}C NMR (D_2O + acetone-d_6) δ 11.79, 38.95, 51.63, 71.73, 78.20, 174.05; IR (KBr) 3320, 3030, 1620, 1575, 1380 cm^{-1}. Anal. Calcd for $C_6H_{11}NO_3$: C, 49.65, H, 7.64; N, 9.65. Found: C, 50.11; H, 7.58; N, 9.69.

Acknowledgment. This work was generously supported by Fonds der Chemischen Industrie and the Schering AG Berlin-Bergkamen.

Registry No. 4, 54615-51-9; **5a**, 121964-06-5; **5a** (mesylate), 121964-11-2; **5b**, 122045-92-5; **5c**, 121964-07-6; **5d**, 93170-28-6; **5e**, 122045-93-6; **6a**, 121964-08-7; **6a** (1,2-*O*-isopropylidene), 121964-12-3; **6a** (1-*O*-benzoate), 121964-16-7; **6b**, 122045-94-7; **6c**, 121964-09-8; **6d**, 121964-10-1; **6e**, 122045-95-8; **7a**, 121964-13-4; **7b**, 122045-96-9; **7c**, 121964-14-5; **7d**, 121964-15-6; **7e**, 122045-97-0; **8a**, 121964-17-8; **8b**, 122045-98-1; **8c**, 121964-18-9; **8d**, 121964-19-0; **8e**, 122045-99-2; **9a**, 121964-21-4; **9b**, 122046-04-2; **9c**, 121964-22-5; **9d**, 121964-23-6; **9e**, 122046-05-3; **10a**, 121964-24-7; **10b**, 122046-11-1; **10c**, 121964-25-8; **10d**, 121964-26-9; **10e**, 122087-62-1; **11a**, 122046-00-8; **11b**, 122046-01-9; **11c**, 122046-02-0; **11d**, 122046-03-1; **11e**, 121964-20-3; **12a**, 122046-06-4; **12b**, 122046-07-5; **12c**, 122046-08-6; **12d**, 122046-09-7; **12e**, 122046-10-0; **20a**, 121964-27-0; **20b**, 121964-28-1; **21b**, 121964-29-2; **21b** (3-*O*-deblocked), 121964-39-4; **22**, 121964-30-5; **22** (triol), 121964-40-7; **22** (triol, *N*-deblocked), 13042-55-2; **23**, 121964-31-6; **24a**, 121964-32-7; **24b**, 121964-33-8; **25a**, 121987-72-2; **25b**, 122087-63-2; **25c**, 121987-73-3; **27a**, 121964-34-9; **27a** (*N*-BOC analog), 121964-38-3; **27b**, 121964-35-0; **27c**, 121964-36-1; **27c** (free acid), 121964-41-8; **27d**, 121964-37-2; (2*R*,3*S*,4*S*)-1,2-*O*-isopropylidene-3-*O*-benzyl-4-methyl-5-hexene, 100572-69-8; (2*R*,3*R*,4*R*)-1,2-*O*-isopropylidene-3-*O*-benzyl-4-methyl-5-hexene, 100758-79-0; (2*R*,3*S*)-1,2-*O*-isopropylidene-3-*O*-benzyl-5-hexene, 87604-53-3; (2*R*,3*R*)-1,2-*O*-isopropylidene-3-*O*-benzyl-5-hexene, 87604-54-4; D-mannitol, 69-65-8; 3,4-di-*O*-benzyl-1,2:5,6-di-*O*-isopropylidene-D-mannitol, 111476-62-1; 3,4-di-*O*-benzyl-1,2-*O*-isopropylidene-D-mannitol, 121964-05-4.

Supplementary Material Available: Experimental details for the preparation of **5c** and ^1H and ^{13}C NMR and IR data and optical rotation for compounds **5c**, **8**, **9**, **10b,c**, **11**, **12b–d**, **23**, **25b,c**, and some derivatives of **20**/**21b** and **23** (9 pages). Ordering information is given on any current masthead page.

Total Synthesis of (±)-Suaveoline†

Mark L. Trudell and James M. Cook*

Contribution from the Department of Chemistry, University of Wisconsin—Milwaukee, Milwaukee, Wisconsin 53201. *Received March 2, 1989. Revised Manuscript Received May 15, 1989*

Abstract: The first total synthesis of the indole alkaloid (±)-suaveoline (**1**) (a macroline-related base and a member of the sarpagine/ajmaline class of alkaloids) was completed in a stereocontrolled fashion. The serial synthesis employed three intramolecular reactions, the Pictet–Spengler cyclization (**2** → **3**), the Dieckmann condensation (**3** → **4**), and the ortho ester Claisen rearrangement (**7** → **9**), all of which occurred with high stereoselectivity. Construction of the unique 3,4,5-trisubstituted pyridine ring (*E*) of **1** was executed by addition of hydroxylamine hydrochloride to an ethanolic solution of the corresponding 1,5-dialdehyde **13** followed by heating.

The indole alkaloid suaveoline (**1**) was first isolated from *Rauwolfia suaveolens* S. Moore in 1972.[1,2] The structure of **1** was elucidated by mass spectrometry, ^1H NMR (100 MHz) and UV spectroscopies, and partial synthesis from ajmaline.[1,2] Suaveoline (**1**) is a member of the sarpagine/ajmaline family of alkaloids and is structurally reminiscent of the macroline-related

† This paper is dedicated to Elmer Fike on the occasion of his 70th birthday.

(1) Majumdar, S. P.; Potier, P.; Poissen, J. *Phytochemistry* **1973**, *12*, 1167.
(2) Majumdar, S. P.; Potier, P.; Poissen, J. *Tetrahedron Lett.* **1972**, 1563.

0002-7863/89/1511-7504$01.50/0