was extracted with ether (3 × 20 mL). The organic layer was washed and dried. The crude product obtained after the removal of solvent was charged on a silica gel column (20 g). Elution with 5% ethyl acetate–benzene furnished the *gem*-dimethylated product **35**: 22 mg (67% based on the recovery of starting material); mp 66–67 °C; IR (KBr) 3075, 2950, 1700, 1635, 1460, 880 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.90 (3 H, d, J = 7 Hz), 1.04 (3 H, s), 1.08 (3 H, s), 1.5–1.88 (6 H, m), 2.0–2.42 (6 H, m), 3.34 (1 H, t, J = 6 Hz), 4.68 (1 H, br s), 4.84 (1 H, br s); ^{13}C NMR (25.0 MHz, $CDCl_3$) δ 218.4, 148.5, 114.5, 51.6, 49.0, 48.3, 40.6, 40.0, 37.9, 35.2, 31.9, 30.5, 27.2, 21.4, 16.3. Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.56; H, 10.99. Further elution of the column with 10% ethyl acetate–benzene resulted in the recovery of the starting material (20 mg).

(3aβ,9aβ)-3α,5,5,8-Tetramethyl-1,2,3,3a,5,6,9,9a-octahydro-4*H*-cyclopentacycloocten-4-one (36). A solution of *gem*-dimethylated compound **35** (25 mg, 0.11 mmol) and $RhCl_3 \cdot 3H_2O$ (12 mg, 0.05 mmol) in absolute ethanol (2 mL) was heated to reflux in a 5-mL round-bottomed flask fitted with reflux condensor for 6 h. The reaction mixture was passed through a short alumina column. The crude product obtained after removal of the solvent was charged on a silica gel column (5 g). Elution with 10% ethyl acetate in benzene furnished the isomerized keto olefin **36** [20 mg (80%)], which was bulb-to-bulb distilled at 110 °C (0.5 mm): IR (neat) 3050, 2950, 1695, 1660, 1460 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.86 (3 H, d, J = 7 Hz), 1.08 (3 H, s), 1.2 (3 H, s), 1.76 (3 H, s), 1.6–2.3 (10 H, m), 3.24 (1 H, dd, J = 6 Hz), 5.44 (1 H, t, J = 8 Hz); exact mass calcd for $C_{15}H_{24}O$ m/e 220.1827, found m/e 220.1817.

(3aβ,9aβ)-3α,5,5,8-Tetramethyl-4-hydroxy-1,2,3,3a,5,6,9,9a-octahydro-4*H*-cyclopentacyclooctene (37). Into a two-necked 20-mL round-bottomed flask fitted with a rubber septum and mercury seal was placed LAH (5 mg, excess) in dry ether (5 mL). To this suspension was added keto olefin **37** (20 mg, 0.09 mmol) in dry ether (5 mL) slowly through a syringe. The reaction mixture was stirred for 30 min. A few drops of ethyl acetate were then added to destroy excess hydride. The reaction mixture was diluted with water and extracted with ether (3 × 10 mL). The ethereal layer was washed and dried. Removal of solvent gave hydroxy olefin **37**: 16 mg (80%); IR (neat) 3550, 2950, 1460, 1030 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.84 (3 H, s), 0.98 (3 H, d, J = 8 Hz), 1.02 (3 H, s), 1.74 (3 H, s), 1.2–2.0 (10 H, m), 2.2–3.0 (2 H, m), 3.48 (1 H, d, J = 2 Hz), 5.36 (1 H, t, J = 8 Hz); exact mass calcd for $C_{15}H_{26}O$ m/e 222.1983, found m/e 222.1981.

(±)-Precapnelladiene (1). Hydroxy olefin **37** (15 mg, 0.06 mmol) in dry pyridine (0.5 mL) was placed in a 5-mL round-bottomed flask fitted with a drying tube. To this stirred solution was added phosphorous oxychloride (0.2 mL) at 0–5 °C, and the mixture was stirred for $4^1/_2$ days at room temperature (30 °C). DBU (0.1 mL) was added to the reaction mixture and then stirred at 60 °C for 2 h. The reaction mixture was diluted with pentane (5 mL) and slowly quenched with water (2 mL) to hydrolyze the excess phosphorous oxychloride. The reaction mixture was extracted with pentane (3 × 5 mL) and washed with dilute hydrochloric acid (20%, 3 × 5 mL) and brine. Removal of solvent gave crude diene **12** (12 mg), which was charged on a $AgNO_3$-impegnated silica gel (5 g) column. Elution with pentane removed all oily impurities. Further elution with 50% benzene–pentane furnished pure diene **1**: 9 mg (70%); IR (neat) 2900, 1440, 1370, 1360, 850 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.97 (6 H, s), 1.07 (3 H, d, J = 8 Hz), 1.64 (3 H, s), 1.08–1.9 (6 H, m), 2.14–2.54 (2 H, m), 2.7–3.08 (1 H, m), 3.34–3.64 (1 H, m), 5.0 (1 H, br s), 5.34 (1 H, t, J 8 Hz). These were found to be identical (IR, ^1H NMR) with naturally occurring precapnelladiene (**1**).

Acknowledgment. A.N.M. thanks the CSIR for a Junior Research Fellowship. We thank Professors C. Djerassi and G. Pattenden for the comparison spectra. We appreciate many useful discussions with our colleague Dr. M. Nagarajan. This research was supported through a Special Assistance Programme in Organic Chemistry.

Registry No. **1**, 92841-66-2; **13**, 108169-59-1; **14**, 94475-26-0; **15**, 108169-60-4; **16**, 108169-61-5; **17**, 108169-62-6; **18**, 108169-63-7; **19**, 108169-64-8; **20**, 108169-65-9; **20** (thioketal), 108169-73-9; **21**, 108266-43-9; **21** (thioketal), 108266-44-0; **22**, 108169-66-0; **23**, 108169-67-1; **24**, 108169-68-2; **25**, 108169-69-3; **26**, 108169-70-6; **27**, 108169-71-7; **28**, 94475-27-1; **29**, 94475-28-2; **31**, 108169-72-8; **32**, 94475-29-3; **33**, 94535-87-2; **34**, 94475-30-6; **34** (monoalkylated), 108169-74-0; **35**, 94475-31-7; **36**, 94475-32-8; **37**, 94475-33-9.

A Short Synthesis of Enantiomerically Pure (2*S*,3*R*,4*R*,6*E*)-3-Hydroxy-4-methyl-2-(methylamino)-6-octenoic Acid, the Unusual C-9 Amino Acid Found in the Immunosuppressive Peptide Cyclosporine

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Received December 30, 1986

A new and efficient synthesis of enantiomerically pure (2*S*,3*R*,4*R*,6*E*)-3-hydroxy-4-methyl-2-(methylamino)-6-octenoic acid (MeBmt, **2**) is reported. Reaction of (2*R*,4*E*)-2-methyl-4-hexenal (**6c**) with *p*-methoxybenzyloxycarbonylsarcosine *tert*-butyl ester (Pmz-Sar-O-*t*-Bu, **5**) gave MeBmt (**2**) in 18–20% overall yield. The lithium enolate of the *tert*-butyl ester is more stable than the corresponding methyl ester at higher temperature (room temperature vs. −78 °C) and reacts selectively with aldehydes even in the presence of impurities. Room temperature conditions were needed in order to increase the desired anti-Cram product **9a**. The Pmz group proved superior to other amino protecting groups (e.g., Cbz) because residual Pmz-sarcosine derivatives could be easily removed from products **9a** and **9b** by cleavage of the Pmz group by reaction with TFA/anisole. This procedure eliminated the need for column chromatography after the aldol reaction. Reaction of the lithium enolate of Pmz-Sar-O-*t*-Bu (**5**) with aldehyde **6c** afforded only the two trans-substituted 2-oxazolidinones **9a** and **9b** and none of the cis-substituted 2-oxazolidinones. The chemically pure diastereomeric mixture of 2-oxazolidinones **9a** and **9b** was resolved by using (1*S*,2*R*)-(+)-ephedrine to give enantiomerically and diastereomerically pure **9a** in 18–20% overall yield (from aldehyde **6c**). Hydrolysis of **9a** gave the desired MeBmt (**2**) in quantitative yield. This amino acid was incorporated into cyclosporin A (CSA, **1**) by known literature procedures. In order to demonstrate that the synthetic methodology described in this paper can be utilized in the synthesis of a number of MeBmt (**2**) analogues, 1′-desmethyl-2-oxazolidinone **10a** was also prepared by similar procedures.

The structure of the immunosuppressive agent cyclosporine A (CSA, **1**)[1] is distinguished by two novel features: the highly N-methylated cyclic undecapeptide (seven N-methyl amino acids) and the presence of the unique

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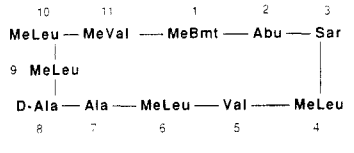
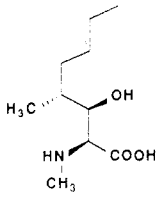
amino acid (4*R*)-4-[(*E*)-2-butenyl]-4,*N*-dimethyl-L-threonine (MeBmt or C-9-ene, **2**)[1] located in the 1-position.[2]



1



2

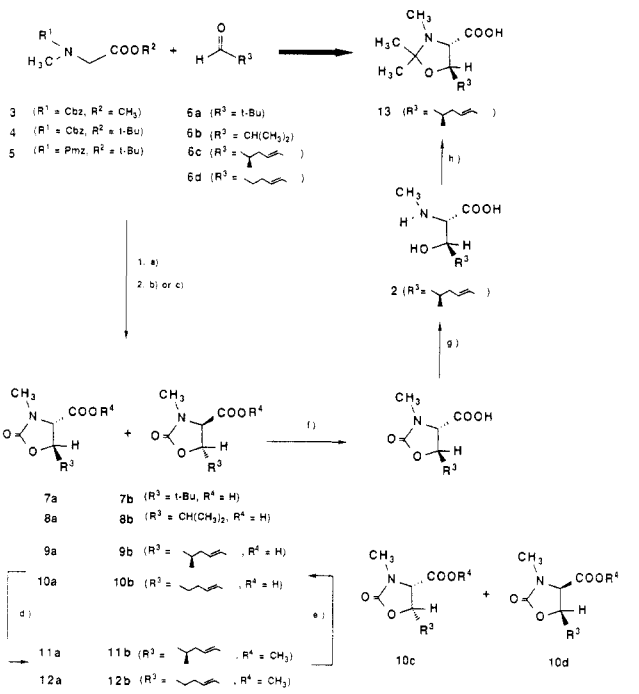
Work by Wenger[3] has led to the successful synthesis of CSA and CS analogues. In addition, the biological activities of several synthetic analogues that contain modified amino acids in the 1-position and in other positions have been reported.[4,5] These results have shown that alteration of MeBmt (**2**) in CSA (**1**) dramatically decreases the biological activity.[6] Thus, biologically active analogues of CSA (**1**) are likely to require MeBmt (**2**) in the 1-position.

MeBmt (**2**) is characterized by three contiguous asymmetric centers, an N-methyl amino group, and a trans double bond. This amino acid is not available from degradation of CSA (**1**)[2a] and was therefore synthesized by Wenger[7] via a 24-step procedure that used diethyl tartrate as the chiral building block. More recently, Evans and Weber[8] reported an asymmetric synthesis of MeBmt (**2**) that utilized an asymmetric glycine–enolate aldol reaction *and* an oxazolidinone chiral auxilary.

We required a MeBmt (**2**) synthesis that is fast, easy, and can be adapted to large-scale preparation of enantiomerically pure amino acid. Our basic idea was to start from a Gly synthon and to synthesize MeBmt (**2**) by an aldol reaction. We considered a chiral auxiliary attached to the nitrogen[9] ($R^*_2C{=}NCH_2COOR$) or to the carboxylic group[10] ($R_2NCH_2COXR^*$). However, most of these enolates do not react with the required stereoselectivity and have been added stereoselectively to aldehydes for the synthesis of α-amino-β-hydroxy acids[9a,f] in only a few cases. The highest selectivities in aldol reactions with chiral glycyl derivatives were reported for Schöllkopf's bislactim ethers,[11] Seebach's imidazolidinone,[12] and, after this work was completed, by Evans and Weber who used an (isothiocyanoacetyl)oxazolidinone.[8] More recently, a diastereo- and enantioselective aldol reaction was reported with isocyanoacetate in which the reaction was catalyzed by a chiral ferrocenylphosphine–gold(I) complex.[13]

In most of these examples, the synthesis of the chiral Gly synthon or the synthesis of the chiral catalyst requires additional synthetic steps utilizing expensive reagents, plus one or more steps for the N-methylation of the final amino acid. Therefore, we decided to develop a synthetic route beginning with an *N*-methylglycine (sarcosine, Sar) derivative and to follow the reaction methodology developed by Shanzer et al.[14] for the diastereoselective synthesis of

Scheme I[a]



[a] (a) LDA, then addition of the aldehyde; (b) hydrolysis during aqueous workup (for **3**); (c) 1 N KOH/EtOH/reflux (for **4** and **5**); (d) CH_2N_2 in ether; (e) NaOH in MeOH/H_2O; (f) crystallization with (1*S*,2*R*)-(+)-ephedrine; (g) 2 N KOH, heat under reflux, 5 h; (h) acetone, heat under reflux, 24 h.

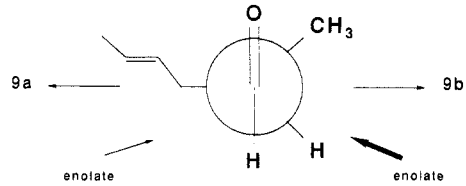


Figure 1. Enolate attack to the aldehyde **6c** according to the Anh–Felkin model.[20]

(1) IUPAC-IUB Joint Commission on Biochemical Nomenclature. Nomenclature and symbolism for amino acids and peptides, recommendations 1983. *Eur. J. Biochem.* **1984**, *138*, 9. Additional abbreviations used are EDCI, 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide; LDA, lithium diisopropylamide; Pmz, *p*-methoxybenzyloxycarbonyl; Teoc, (trimethylsilyl)ethoxycarbonyl; TFA, trifluoro acetic acid; % ds, % diastereoselectivity. For a discussion, see: Izumi, Y. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 871 and also ref 12. Threo and erythro are defined according to Fischer's nomenclature. The threo diastereomer **9a/b** corresponds to the *u* (unlike) diastereomer **9a/b** according to Seebach, D.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 654.

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(6) For example, exchange of MeBmt (**2**) in the 1-position of CSA (**1**) with (OAc)MeBmt, 3'-Desoxy-MeBmt, MeThr, Ser, Me-β-cyclohexyl Ser, MeLeu(3-OH), MeAbu led to CS analogues of significantly decreased biological activity.

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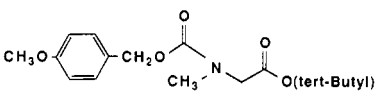
Table I. Yield of Anti-Cram Aldol Adducts as a Function of Temperature and Sarcosine Protecting Groups

starting material	aldehyde (cpd, equiv)	T (°C) of the aldehyde addition	after aldol reaction[a] crude yield	after aldol reaction[a] unreacted starting material	diastereoselectivity **9a:9b**[a]	overall yield after purification (%)	overall yield after crystallization (%)[28]
Z-Sar-OMe (**3**)							
(5 mmol)	**6c**, 1.3[b]	−78	53	4	43:57		
(10 mmol)	**6c**, 1.3[b]	0	49	12	47:53		
(10 mmol)	**6c**, 0.79[c]	0	44	3	54:46	25 (54:46)	10
Z-Sar-O-*t*-Bu (**4**)							
(3 mmol)	**6c**, 1.02[c]	−78	76	9	47:53		
(17 mmol)	**6c**, 1.00[c]	−78	76	13	47:53	59 (48:52)	23
(3 mmol)	**6c**, 1.05[c]	23	74	9	47:53		
Pmz-Sar-O-*t*-Bu (**5**)							
(1 mmol)	**6c**, 0.90[c]	−78	83	9	44:56		
(1 mmol)	**6c**, 0.98[c]	23	71	6	47:53	60 (47:53)	18
(10 mmol)	**6c**, 1.00[d]	23	76	13	47:53	72 (47:53)	20
					10a/b:10c/d[a]	**10a,b**	**10a**
3 (35 mmol)	**6d**, 0.93[e]	−78	47	10	92:8	30	11

[a] Ratio of diastereomers in crude products determined by 200-MHz ^{1}H NMR. [b] The aldehyde used was racemic and had 10–15% of precursor alcohol as byprodyct. [c] The aldehyde used was enantiomerically pure and had 4–7 mol % Me_2SO as contaminant. [d] The aldehyde used was not distilled[22,25] and contained 16 mol Me_2SO as contaminant. [e] Aldehyde **6d** contained 3 mol % Me_2SO.

threo-α-amino-β-hydroxy acids.[1] We report herein the synthesis of enantiomerically pure MeBmt (**2**) from *p*-methoxybenzyloxycarbonylsarcosine *tert*-butyl ester (Pmz-Sar-O-*t*-Bu, **5**) and (2*R*,4*E*)-2-methyl-4-hexenal (**6c**) (see Scheme I). The required enantiomerically pure aldehyde **6c** was synthesized by the procedure reported by Evans and Weber.[8,15]



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As a model reaction for the synthesis of MeBmt (**2**), the enolate of Cbz-Sar-OMe (**3**) was allowed to react with either pivalaldehyde (**6a**) or isobutyraldehyde (**6b**) (−78 °C to room temperature). Neutralization of the reaction mixture with acetic acid at −78 °C gave a mixture of open-chain aldol adducts.[16] Addition of methanol at 0 °C to the reaction, followed by warming to ambient temperature, evaporation of the solvent, and aqueous workup gave the 2-oxazolidinones **7a/b** and **8a/b**, respectively.[17] These results were analogous to aldol reactions carried out with the enolate of Cbz-Gly-OEt.[14]

When a chiral aldehyde is used, four diastereomeric aldol products are possible. Reaction of (2*R*,4*E*)-2-methyl-4-hexenal (**6c**) at −78 °C with Cbz-Sar-OMe enolate produced a mixture of two diastereomeric 2-oxazolidinones **9a** and **9b** in a ratio of 43:57 (see Table I),[18] a ratio consistent with Cram's rule[19] (see Figure 1). The ratio of the anti-Cram to Cram product (**9a:9b**) was increased from 43:57 to 47:53 when the enolate was warmed to 0 °C prior to the addition of aldehyde **6c**. But this modification also increased the amount of side products formed.[21] The moderate yield (44–53%) of crude product obtained from this aldol reaction is attributable to three factors: (1) the presence of Me_2SO (4–7%) in the aldehydes **6c** and **6d**, which was not completely removed by distillation;[22] (2) the instability of the protected Sar enolate at the higher reaction temperature (0 °C vs. −78 °C); and (3) the possibility of an increase in entropically favored retroaldol reactions at higher temperatures and subsequent decomposition of the reformed enolate.

In order to find a more stable enolate or an enolate that preferentially forms the desired anti-Cram product **9a**, different protecting groups of Sar were evaluated.[23] Reaction of (±)-2-methylvaleraldehyde with enolates of Boc-Sar-OMe, Cbz-Sar, Pmz-Sar-OMe, Teoc-Sar-OMe, and Cbz-Sar-OSi(Me)$_3$ gave a mixture of trans- and cis-substituted 3-methyl-5-(1-methylbutyl)-1-oxo-2-oxazolidine-4-carboxylic acids in ratios (trans:cis) from 2:8 to 1:1. Since enolates of *tert*-butyl esters are thermally more stable than less hindered ester enolates,[24] Cbz-Sar-O-*t*-Bu

(14) Shanzer, A.; Somekh, L.; Butina, D. *J. Org. Chem.* **1979**, *44*, 3967.
(15) Aldehyde **6c** is prepared in a six-step synthesis from (±)-1-buten-3-ol (Aldrich). The intermediate (4*R*)-3-[(2*R*,4*E*)-2-methyl-4-hexenoyl]-4-(phenylmethyl)-2-oxazolidinone is obtained as a 10:1 mixture of C(2′) epimers, which can be separated by column chromatography (MPLC). Studies are currently in progress in our group to make this synthetic route more amenable to large-scale preparation of aldehyde **6c**.
(16) It was not determined if the aldol adducts were a mixture of rotamers or erythro/threo diastereomers.
(17) The crude yields were ca. 80% with at least a 9:1 preference for the trans-substituted 2-oxazolidinones **7a/b**, **8a/b**, respectively (200-MHz ^{1}H NMR). The minor cis-substituted 2-oxazolidinones could not be assigned. Small amounts of starting material (5–10%) were also present in the reaction mixture.
(18) The assignments of 2-oxazolidinones **9a** and **9b** were made by comparison of the high-field NMR spectra (200 MHz) with the 2-oxazolidinone **9a**, which had been prepared by Wenger.[7]
(19) Cram, D. J.; Abd Elhafez, F. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828. See also: (a) Morrison, J. D.; Mosher, H. S. *Asymmetric Organic Reactions*; Prentice-Hall: Englewood Cliffs, 1971. (b) Izumi, Y.; Tai, A. *Stereodifferentiating Reactions*; Academic Press: New Yor, 1977. (c) Masamune, S.; Kaiho, T.; Garvey, D. S. *J. Am. Chem. Soc.* **1982**, *104*, 5521.
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(21) The crude yield of 2-oxazolidinones **9a** and **9b** does not change. With increased temperature, the decomposed enolate undergoes a variety of reactions that were not characterized. The multiple products made the separation of the desired aldol products more difficult.
(22) To prevent racemization, it was important to keep the temperature below 70 °C during distillation.[8] We did not try to purify **6c** by other methods.
(23) Commercially available (±)-2-methylvaleraldehyde (Aldrich) was shown to have a selectivity similar to aldehyde **6c**.
(24) (a) Seebach, D.; Amstutz, R.; Laube, T.; Schweizer, W. B.; Dunitz, J. D. *J. Am. Chem. Soc.* **1985**, *107*, 5403. (b) Seebach, D.; Coquoz, M. *Chimia* **1985**, *39*, 20.

(4) was synthesized and deprotonated with lithium diisopropylamide (LDA) at −78 °C. Reaction of aldehyde **6c** at −78 °C or at ambient temperature with the preformed enolate of *tert*-butyl ester **4** gave a mixture of anti-Cram/Cram products (**9a/9b**) in a ratio of 47:53 in 74–76% crude yield. The aldol adducts were cyclized to the 2-oxazolidinones **9a** and **9b** by heating the reaction solution under reflux with ethanolic KOH. The crude products were surprisingly free of side products[25] but were contaminated with a small quantity (9–13%) of Cbz-Sar, which complicated the subsequent separation of the two diastereomers. Diastereomer **9a** was resolved by crystallization as the (1*S*,2*R*)-(+)-ephedrine salt.[26,27] It is important to note that for purification of these diastereomers, it is essential to first remove all Cbz-Sar from the mixture of **9a/b**, otherwise the resolved (1*S*,2*R*)-(+)-ephedrine salts were still contaminated with traces of Cbz-Sar. Removal of Cbz-Sar was best achieved by converting **9a/b** to the methyl esters **11a/b** and **3** (CH_2N_2/ether) and then separating these by MPLC. Hydrolysis (aqueous 1 N NaOH in methanol) gave acids **9a/b**.

This procedure was used to prepare pure **9a/b** in 25% and 59% yields starting from Cbz-Sar-OMe (**3**) and Cbz-Sar-O-*t*-Bu (**4**), respectively (Table I). The desmethyl analogue **10a** was synthesized following the same procedure. Reaction of Cbz-Sar-OMe (**3**) with aldehyde **6d** gave pure acid **10a/b** in 30% yield (Table I). The cis-substituted 2-oxazolidinone **10c/d**, which was detected in the crude aldol product **10** (ca. 8%), was separated during chromatography of the appropriate methyl ester **12**. Crystallization of these acids (**9a/b** and **10a/b**) with (1*S*,2*R*)-(+)-ephedrine and acidic extraction of the (+)-ephedrine (aqueous HCl) gave diastereomerically pure enantiomers **9a** and **10a**.[28] The 2-oxazolidinone **9a** was isolated in 10% overall yield starting from Cbz-Sar-OMe (**3**) or in 23% overall yield beginning with Cbz-Sar-O-*t*-Bu (**4**).[29] The desmethyl analogue **10a** was isolated in 11% overall yield by using Cbz-Sar-OMe (**3**) as starting material.

In order to eliminate the additional esterification, chromatography, and hydrolysis steps that were needed to remove Cbz-Sar from the aldol product, we decided to use Pmz-Sar-O-*t*-Bu (**5**) as starting material. Reaction of aldehyde **6c** at −78 °C with the preformed enolate from *tert*-butyl ester **5** produced only the trans-substituted 2-oxazolidinones **9a** and **9b** in 83% crude yield and in a ratio of 44:56.[30] When aldehyde **6c** was added at room temperature, a 71–76% crude yield of 2-oxazolidinones **9a** and **9b** was obtained in a ratio of 47:53 (see Table I). The amino protecting group of Pmz-Sar was removed by reaction with TFA/anisole[31] to give, after standard extractive workup, Sar-free oxazolidinones **9a/b** in 60–72% crude yield. Crystallization with (1*S*,2*R*)-(+)-ephedrine gave the enantiomerically and diastereomerically pure (+)-ephredrine salt of **9a** in 18–20% yield.

Extractive separation of acid **9a** from (1*S*,2*R*)-(+)-ephedrine (1 N HCl/ether) gave pure **9a**.[32] Hydrolysis (2 N KOH, 5 h, 100 °C) of 2-oxazolidinone **9a** gave, after neutralization (Dowex 50 WX8, H^+) and elution with 1.5 N aqueous ammonia, crude MeBmt (**2**) in quantitative yield.[33]

The MeBmt (**2**), which was obtained after ion-exchange chromatography, was then converted quantitatively to the acetonide **13** and coupled to amino-deprotected Abu-Sar-MeLeu-Val-MeLeu-Ala-OBzl by using the methods described by Wenger.[3a,34]

The procedure described in this paper provides a useful and general method for obtaining both enantiomers of diastereomerically pure *threo*-β-hydroxy-α-*N*-methyl amino acids (even pivalaldehyde **6a** reacts with the enolate). The N-methylated β-hydroxy-α-amino acids are obtained directly, thereby obviating additional synthetic steps needed to introduce the N-methyl group. The Pmz-Sar-O-*t*-Bu ester enolate is more thermally stable than other protected Sar derivatives and even can be reacted with impure aldehydes[25] without a significant loss in yield. In general, the aldol products obtained from Pmz-Sar-O-*t*-Bu do not require column chromatography for either the removal of side products or starting material because these are easily removed by acid deprotection and extraction. With completion of this practical synthesis of MeBmt (**2**) by an aldol reaction and by subsequent chemical resolution of the resulting diastereomers, we have developed a useful method for obtaining large quantities of this important amino acid.

Experimental Section

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. ^1H NMR spectra were recorded on a Bruker WP-200 instrument. Coupling constants are reported in hertz and chemical shifts in ppm (δ units) downfield from tetramethylsilane. Silica gel chromatography was carried out under low pressure (5–15 psi) by using Merck grade 60 silica, 230–400 mesh. Thin layer chromatograms were run on Merck Kieselgel 60-F_{254} with fluorescent indicator visualized with 7% phosphomolybdic acid in ethanol. Optical rotations were recorded on a Perkin-Elmer 241 automatic polarimeter. Elemental analyses were determined by Galbraith Laboratories, Inc., Knoxville, TN.

Tetrahydrofuran (THF) was distilled from sodium metal/benzophenone ketyl. Diisopropylamine was distilled from calcium hydride. Aldehydes were distilled and used immediately. All other commercial reagents were used as received. All nonaqueous reactions were carried out under a dry argon atmosphere in oven-dried (140 °C, 12 h) glassware.

Cbz-Sar was purchased from Bachem Inc.; Cbz-Sar-OMe (**3**) was prepared with CH_2N_2 starting from Cbz-Sar;[35] (2*R*,4*E*)-2-methyl-4-hexenal (**6c**) and (4*E*)-hexenal (**6d**) were synthesized by the procedure reported by Evans and Weber.[8]

Cbz-Sar-O-*t*-Bu (4). Following the procedure of Roeske,[36] a solution of Cbz-Sar (10.50 g, 47.04 mmol) in CH_2Cl_2 (20 mL)

(25) Even when the reaction was carried out with undistilled aldehyde **6c** (with up to 16% Me_2SO left after the Swern oxidation), there was no increase of side products. This was especially important for the thermally labile aldehyde **6c**.[22]

(26) (a) Hegedüs, B.; Krassó, A. F.; Noack, K.; Zeller, P. *Helv. Chim. Acta* **1975**, *58*, 147. (b) Oki, K.; Suzuki, K.; Tuchida, S.; Saito, T.; Kotake, H. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 2554.

(27) Attempts to separate **9a** and **9b** by chromatography on silica gel as the free acids **9a/b**, the methyl esters **11a/b**, the *l*-menthyl esters, or the 4-(phenylmethyl)-2-oxazolidinones failed. Attempts to resolve by crystallization of salts formed with triethylamine, *N*-methylmorpholine, *l*-cinchonidine, brucine, and quinine also were unsuccessful.

(28) The diastereomeric purity of **9a** and the enantiomeric purity of **10a** were determined by 200-MHz ^1H NMR (in $CDCl_3$) of their respective (1*S*,2*R*)-(+)-ephedrine salts. We observed a better separation of the amino acid N-methyl peaks in **10a/b** when the ^1H NMR spectrum of the diastereomeric salts were recorded in benzene-d_6.

(29) In order to improve the chemical resolution of 2-oxazolidinones **9a** and **9b**, the mother liquor was treated with (1*R*,2*S*)-(−)-ephedrine. This resulted in crystallization of **9b**-(−)-ephedrine salt and in an enrichment of the desired acid **9a** remaining in the mother liquor.

(30) The results were unanticipated because the aldol reaction with Pmz-Sar-OMe gave under several different reaction conditions mixtures of cis- and trans-substituted 2-oxazolidinones.

(31) Weygand, F.; Hunger, K. *Chem. Ber.* **1962**, *95*, 1.

(32) All physical data were identical with those reported by Wenger.[7]

(33) For analytical purposes, a sample was purified with Sephadex LH-20. The physical data were identical with the reported values.[7]

(34) The resulting MeBmt-containing heptapeptide had the same physical and spectral characteristics as previously reported.[3a] The yield was also comparable.

(35) Class, E.; Prijs, B.; Erlenmeyer, H. *Helv. Chim. Acta* **1959**, *42*, 1612.

(36) Roeske, R. *J. Org. Chem.* **1963**, 28, 1251.

was treated at −78 °C with concentrated H_2SO_4 (10 drops) and isobutene (100 mL) and was kept for 3 days at room temperature in a high-pressure bottle. The bottle was then chilled and opened, and the contents were diluted with ether (150 mL) and washed with saturated $NaHCO_3$ (50 mL). After drying ($MgSO_4$) and evaporation in vacuo of the organic phase, 12.22 g (93%) of *tert*-butyl ester **4** was obtained as a light yellow oil: IR ($CHCl_3$) 3100–2850, 1740, 1700, 1476, 1454, 1405, 1368, 1359, 1209, 1145 cm^{-1}; ^1H NMR ($CDCl_3$; 2 rotamers 1:1) δ 1.42, 1.47 (s, 9 H, *tert*-butyl), 2.98, 3.00 (s, 3 H, N-CH_3), 3.88, 3.95 (s, 2 H, CH_2), 5.14, 5.16 (s, 2 H, benzyl H), 7.33, 7.36 (s, 5 H, Ar H). MS, *m/e* (relative intensity) 279 (M^+, 3), 223 ($M^+ + 1 - t$-Bu, 11), 178 (8), 134 (8), 92 (11), 91 (100), 65 (9), 57 (51), 44 (21), 41 (36), 40 (67). Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.53; H, 7.47; N, 5.04.

Pmz-Sar. The title compound was synthesized following the method reported for the synthesis of Pmz-Gly.[37] A solution of *p*-methoxybenzyloxycarbonyl azide (10.00 g, 48.26 mmol; Aldrich) in 35 mL of THF was added dropwise over 10 min to a vigorously stirred ice-cold solution of Sar (4.07 g, 45.68 mmol) that was dissolved in 96 mL of a solution of 1 N NaOH in water/THF (76:20). The reaction mixture was allowed to warm to room temperature and was stirred overnight. The light yellow solution was evaporated in vacuo to three-fourths of its original volume and was then washed with ether (2 × 100 mL), cooled to 0 °C, and acidified (6 N HCl, pH <2). After extraction of the aqueous phase with EtOAc (2 × 100 mL), the organic phase was dried ($MgSO_4$) and evaporated in vacuo to afford 7.20 g (62%) of Pmz-Sar as a white crystalline solid. An analytical sample was prepared by recrystallization from CH_2Cl_2/ether: mp 89.5–90.0 °C; IR ($CHCl_3$) 3300–2800, 1730 sh, 1700, 1512, 1402, 1204, 1155 cm^{-1}; ^1H NMR ($CDCl_3$, 2 rotamers 3:2) δ *2.96*, 3.00 (s, 3 H, NCH_3), 3.80, *3.82* (s, 3 H, *p*-CH_3O), 4.01, *4.10* (s, 2 H, CH_2), 5.08, *5.12* (s, 2 H, benzyl H), 6.76–6.85 and 7.18–7.38 (m, 4 H, Ar H), 8.97 (s br, 1 H, COOH); MS, *m/e* (relative intensity) 253 (M^+, 10), 149 (9), 121 (19), 45 (17), 44 (60), 43 (21), 40 (100). Anal. Calcd for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97; N, 5.53. Found: C, 56.85; H, 5.96; N, 5.46.

Pmz-Sar-O-*t*-Bu (5). Following the procedure of Dhaon et al.,[38] a solution of Pmz-Sar (6.87 g, 27.13 mmol), 4-(dimethylamino)pyridine (0.99 g, 8.14 mmol), and *tert*-butyl alcohol (3.02 g, 40.68 mmol) in 35 mL of CH_2Cl_2 was cooled with stirring in an ice bath. 1-Ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDCI, 5.72 g, 29.84 mmol) was added and the reaction mixture was stirred at 0 °C for 2 h and at room temperature for 20 h. The solution was concentrated to dryness in vacuo and the residue was taken up in EtOAc (2 × 100 mL) and water (1 × 50 mL). The combined organic layers were washed with 1 N HCl (50 mL), saturated $NaHCO_3$ (50 mL), and water (50 mL) and dried ($MgSO_4$). The solvent was removed in vacuo to afford 7.83 g (93%) of *tert*-butyl ester **5** as a colorless oil: IR ($CHCl_3$) 3050–2820, 1740, 1697, 1612, 1512, 1475, 1455, 1404, 1367, 1302, 1209, 1145 cm^{-1}; ^1H NMR ($CDCl_3$; 2 rotomers 1:1) δ 1.41, 1.46 (s, 9 H, *tert*-butyl), 2.95, 2.97 (s, 3 H, NCH_3), 3.79 (s, 3 H, *p*-CH_3O), 3.83, 3.93 (s, 2 H, CH_2), 5.07, 5.10 (s, 2 H, benzyl H), 6.81–6.93 and 7.21–7.36 (m, 4 H, Ar H); MS, *m/e* (relative intensity) 309 (M^+, 5), 253 ($M^+ + 1 - t$-Bu, 7), 121 (25), 91 (31), 57 (36), 44 (41), 40 (100). Anal. Calcd for $C_{16}H_{23}NO_5$: C, 62.12; H, 7.49; N, 4.53. Found: C, 62.33; H, 7.62; N, 4.67.

(4*S*,5*R*)-3-Methyl-5-[(1*R*,3*E*)-1-Methyl-3-pentenyl]-1-oxo-2-oxazolidine-4-carboxylic Acid (9a). Method A: Using Pmz-Sar-O-*t*-Bu (5) as Starting Material. A cooled solution (−78 °C) of lithium diisopropylamide[39] (LDA; 12.60 mmol, 1.2 equiv) in THF/hexane (57 mL, 6:1) was treated dropwise with Pmz-Sar-O-*t*-Bu (**5**) (3.25 g, 10.53 mmol, 1 equiv) in 6 mL of THF. After 20 min (−78 °C) the colorless solution was warmed to room temperature (water bath) and, after 10 min, freshly prepared (2*R*,4*E*)-2-methyl-4-hexenal (**6c**) (1.18 g, 10.53 mmol, 1 equiv contaminated with additional 16% Me_2SO resulting from the Swern oxidation) was added to the light yellow enolate solution (the syringe was washed with a total of 5 mL of THF).[40] Stirring was continued for 40 min at room temperature;[41] then 1 N KOH in anhydrous EtOH (12.2 mL) was added.[42] The solution was then heated under reflux (bath temperature 120 °C) for 25 min, cooled (0 °C), concentrated in vacuo (40 °C), and treated with ether (40 mL)/water (40 mL). The aqueous phase was extracted a second time with ether (40 mL), then cooled (0 °C), and acidified (6 N HCl, pH <2). After extraction of the aqueous phase with ether (3 × 50 mL), the organic phase was dried ($MgSO_4$) and concentrated in vacuo to give 2.15 g of crude acids [according to the ^1H NMR: 1.81 g (76%) of **9a:9b** (47:53) and 0.34 g of Pmz-Sar].

The mixture of these acids **9a/b** and Pmz-Sar was treated with anisole (2.8 mL) and at 0 °C with TFA (12 mL).[31] After 1 h (0 °C) the solvents were evaporated in vacuo (25 °C, 16 Torr and the residue was dissolved in saturated $NaHCO_3$/ether (60 mL/30 mL). The aqueous phase was washed a second time with ether (30 mL), cooled (0 °C), and acidified (6 N HCl, pH <2). After extraction of the water phase with ether (3 × 60 mL), the organic phase was dried ($MgSO_4$) and evaporated in vacuo to give 1.73 g (72%) of **9a/b** as a pale brown oil.

This mixture of isomers (1.69 g, 7.43 mmol) was treated with 1.0 equiv of (1*S*,2*R*)-(+)-ephedrine (1.22 g, 7.43 mmol) and crystallized from CH_2Cl_2 (minimal amount to dissolve the salt)/ether. Crystallization at −25 °C[43] gave 0.28 g (7%) of the **9a**·(+)-ephedrine salt. The mother liquor was concentrated and ether and a seed crystal were added. A second crop of 0.13 g (3%) of the **9a**·(+)-ephedrine salt was collected. The mother liquor was concentrated and treated with 30 mL of ether and 30 mL of 1 N HCl. The aqueous layer was extracted twice with ether (30 mL), and the ether extracts were combined, washed with 1 N HCl (40 mL), dried ($MgSO_4$), and concentrated to 1.22 g (5.37 mmol) of yellow oil. This material was treated with 0.6 equiv of (1*R*,2*S*)-(−)-ephedrine (0.53 g, 3.22 mmol) to obtain 0.70 g of the **9b**·(−)-ephedrine salt by analogous crystallizations. The mother liquor was again concentrated and the mixture of diastereomeric carboxylic acids **9a/9b** isolated by HCl extraction as described above. This produced 0.48 g of yellow oil, which was treated with 0.35 g (2.11 mmol, 1 equiv) of (1*S*,2*R*)-(+)-ephedrine and crystallized as above from ether/CH_2Cl_2. An additional four crops of **9a**·(+)-ephedrine salt (0.45 g, 11%) were obtained. All crops of **9a**·(+)-ephedrine salt (0.86 g, 21%) were recrystallized from ether/CH_2Cl_2 to give 0.82 g (20% yield based on aldehyde **6c**) of diastereo- and enantiomerically pure **9a**·(+)-ephedrine salt.[28]

This material was treated in 60 mL of ether with 1 N HCl (40 mL) followed by two extractions with ether (40 mL). Each organic phase was washed with 1 N HCl (40 mL), combined, dried ($MgSO_4$), and concentrated to yield crystalline **9a** (0.48 g, 20% yield based on aldehyde **6c**). An analytical sample was crystallized from ether/pentane.[32]

Method B: Using Cbz-Sar-O-*t*-Bu (4) as Starting Material. Following the same procedure as described in method A, the crude acids **9a/b** and Cbz-**sar** [3.47 g total; according to the ^1H NMR 2.96 g (13.02 mmol, 76% yield starting from aldehyde **6c**) **9a:9b** (47:53) and 0.51 g of Cbz-Sar] were esterified with etheral CH_2N_2 (0 °C, 15 min). The separation on a MPLC column (hexane/EtOAc, 8:2) gave pure methyl esters **11a/b** [0.10 g (3%) of **11a:11b** (~1:3) and 2.45 g (78%) of **11a:11b** (~1:1)]. The 1:1 diastereomeric mixture of **11a/b** (see below for spectral data) was hydrolyzed (20 mL of MeOH, 13 mL of 1 N NaOH, 0 °C → room temperature, 2 h), evaporated in vacuo and extracted with ether (3 × 50 mL) from 1 N HCl (40 mL). The organic phase was dried ($MgSO_4$) and evaporated in vacuo to give a 1:1 mixture of acids

(37) Sōfuku, S.; Mizumura, M.; Hagitani, A. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 177.

(38) Dhaon, M. K.; Olsen, R. K.; Ramasamy, K. *J. Org. Chem.* **1982**, *47*, 1962.

(39) For a description of the procedure for formation of LDA and lithium enolates, see: Seebach, D.; Aebi, J.; Wasmuth, D. *Org. Synth.* **1985**, *63*, 109.

(40) When the aldehyde was added at −78 °C to the enolate solution, the solution was allowed to stir for 40 min at −78 °C in order to ensure complete enolate formation (see Table I).

(41) When the aldehyde was added at −78° C, the reaction was stirred for 0.5–1 h at −78 °C and then warmed up to 0 °C (0.5–1 h) (see Table I).

(42) In the case of the aldol reaction with Cbz-Sar-OMe (**3**), methanol was added at 0 °C (0.8 mL/1 mmol **3**), then the reaction solution was stirred at room temperature for 15 min.

(43) In order to prevent the ephedrine salts of **9a** and **9b** from oiling out, it was necessary to add 1 drop of EtOH.

9a/b [2.31 g (78%, 10.17 mmol)]. Crystallizations with (1*S*,2*R*)-(+)- and (1*R*,2*S*)-(−)-ephedrine followed by extraction (ether/1 N HCl) gave crystalline **9a** (0.89 g, 23%, starting from aldehyde **6c**, >95% ds,[1] according to the ^{1}H NMR): mp 78–79 °C; $[\alpha]_D$ +35.5° (*c* 1.07, $CHCl_3$) [lit.[7] mp 81–82 °C; $[\alpha]^{22}_D$ +33.5° (*c* 1.0, $CHCl_3$)]; IR ($CHCl_3$) 3560–2380, 1755, 1440, 1401, 1205, 1145, 1040, 970 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.96 (d, 3 H, *J* = 6.5, $CHCH_3$); 1.67 (d, 3 H, *J* = 6.5, $CH{=}CHCH_3$), 1.81–2.06 (m, 2 H, $CHCH_2CH{=}CH$), 2.11–2.31 (m, 1 H, $CHCH_2CH{=}CH$), 2.96 (s, 3 H, NCH_3), 4.01 (d, 1 H, *J* = 5, C_4-H), 4.36 (dd, 1 H, *J* = 5, 6, C_5-H), 4.70 (br s, 1 H, COOH), 5.26–5.65 (m, 2 H, CH=CH); MS, *m/e* (relative intensity) 228 (M^+ + 1, 10), 227 (M^+, 29), 182 (20), 128 (46), 55 (92), 44 (45), 43 (36) 42 (100), 41 (54).

Mixture (ca. 1:1) of methyl (4*S*,5*R*)-3-methyl-5-[(1*R*,3*E*)-1-methyl-3-pentenyl]-1-oxo-2-oxazolidine-4-carboxylate (11a) and methyl (4*R*,5*S*)-3-methyl-5-[(1*R*,3*E*)-1-methyl-3-pentenyl]-1-oxo-2-oxazolidine-4-carboxylate (11b): R_f 0.13 (hexane/EtOAc, 7:3); ^{1}H NMR ($CDCl_3$) δ 0.95, 0.97 (d, 3 H, *J* = 6, $CHCH_3$), 1.68 (d, 3 H, *J* = 5.5, $CH{=}CHCH_3$), 1.72–2.05 (m, 2 H, $CHCH_2CH{=}CH$), 2.10–2.19 (m, 1 H, $CHCH_2CH{=}CH$), 2.91, 2.92 (s, 3 H, NCH_3), 3.83 (s, 3 H, OCH_3), 3.96, 3.97 (d, 1 H, *J* = 5, C_4-H), 4.28 (dd, 0.5 H, *J* = 5, 5.5, C_5-H), 4.35 (t, 0.5 H, *J* = 5, C_5-H), 5.26–5.62 (m, 2 H, CH=CH).

(4*S*,5*R*)-3-Methyl-5-[(3*E*)-pentenyl]-1-oxo-2-oxazolidine-4-carboxylic Acid (10a). Following the procedure described for the synthesis of 2-oxazolidinone **9a**, reaction of Cbz-Sar-OMe (**3**) (7.93 g, 33.44 mmol, 1 equiv) with (4*E*)-hexenal (**6d**) (3.07 g, 31.28 mmol, 0.93 equiv) at −78 °C gave 3.81 g of crude acids [after ^{1}H NMR, 3.10 g (47%, 92% ds[1]) of **10a/b** and 0.71 g of Cbz-Sar]. Esterification (→**12a/b**) followed by purification on a MPLC column (hexane/EtOAc, 7:3) gave 2.09 g (30%, >95% ds[1]) of pure methyl ester **12a/b** (see below for spectral data). Hydrolysis (5 mL of MeOH, 11 mL of 1 N NaOH, 1.5 h at room temperature) and two crystallizations with (1*S*,2*R*)-(+)-ephedrine (0.84 g, 5.06 mmol, 0.55 equiv) first in EtOAc/pentane at −25 °C and then in CH_2Cl_2/ether at room temperature gave diastereomerically pure **10a**·(+)-ephedrine salt (1.27 g, 11%, >95% ds[1], according to ^{1}H NMR). After extractive workup (0.5 N HCl/ether) enantiomerically pure crystalline 2-oxazolidinone **10a** (0.70 g, 11%) was isolated.[44] An analytical sample was prepared by recrystallization from ether/pentane: mp 92–93 °C; $[\alpha]_D$ +35.1° (*c* 1.14, $CHCl_3$); IR ($CHCl_3$) 3540–2360, 1755, 1436, 1400, 1229, 1203, 1145, 1040, 968 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.67 (d, 3 H, *J* = 5.5, $CH{=}CHCH_3$), 1.78–1.94 (m, 2 H, $CH_2CH_2CH{=}CH$), 2.08–2.28 (m, 2 H, $CH_2CH_2CH{=}CH$), 2.97 (s, 3 H, NCH_3), 3.94 (d, 1 H, *J* = 5.5, C_4-H), 4.50 (q, 1 H, *J* = 5.5, C_5-H), 5.30–5.64 (m, 2 H, CH=CH), 6.64 (br s, 1 H, COOH); MS, *m/e* (relative intensity) 213 (M^+, 20), 168 (37), 149 (28), 124 (28), 81 (29), 69 (66), 57 (51), 55 (87), 45 (39), 44 (88), 43 (97), 42 (82), 41 (100). Anal. Calcd for $C_{10}H_{15}NO_4$: C, 56.33; H, 7.09; N, 6.57. Found: C, 56.32; H, 7.21; N, 6.49.

Racemic *trans*-Methyl 3-Methyl-5-[(3*E*)-pentenyl]-1-oxo-2-oxazolidine-4-carboxylate (12a/b). R_f 0.10 (hexane/EtOAc, 7:3); ^{1}H NMR ($CDCl_3$) δ 1.66 (d, 3 H, *J* = 5.5, $CH{=}CHCH_3$), 1.73–1.90 (m, 2 H, $CH_2CH_2CH{=}CH$), 2.09–2.25 (m, $CH_2CH_2CH{=}CH$), 2.94 (s, 3 H, NCH_3), 3.83 (s, 3 H, OCH_3), 3.90 (d, 1 H, *J* = 5.5, C_4-H), 4.41 (q, 1 H, *J* = 5.5, C_5-H), 5.32–5.60 (m, 2 H, CH=CH).

(2*S*,3*R*,4*R*,6*E*)-3-Hydroxy-4-methyl-2-(methylamino)-6-octenoic Acid (2). The solution of 2-oxazolidinone **9a** [0.100 g (0.44 mmol)] in 2 mL of 2 N KOH was heated under reflux for 5 h, cooled (room temperature), acidified with Dowex H^+ (50 × 8-100) (pH <4), and heated for 5 min at 80 °C. The mixture of Dowex H^+/water was filtered through 10 mL of Dowex H^+ (1.7 × 5 cm column) and eluted with 150–200 mL of 1.5 M aqueous ammonia. The aqueous eluant was evaporated (16 Torr, 30 °C) and dried (1 Torr, room temperature, 16 h). MeBmt (**2**) was received quantitatively (0.10 g) as a white solid. In order to obtain an analytically pure sample of MeBmt (**2**), the amino acid was purified by Sephadex LH-20 chromatography (methanol)[7,8] and crystallized from ethanol/water: mp 240–241 °C (decomposition with scintering at 200–225 °C); $[\alpha]_D$ +12.0° (*c* 0.38 H_2O at pH 7 (phosphate buffer Titrisol pH 7.00 from Merck)) [lit.[7] mp 240–241 °C; $[\alpha]_D$ +13.5° (*c* 0.50, H_2O at pH 7 (phosphate buffer Titrisol pH 7.00 from Merck)); lit.[8] mp 242–243 °C; $[\alpha]_D$ +11.4° (*c* 0.50, H_2O at pH 7 (phosphate buffer Titrisol pH 7.00 from Merck))]; ^{1}H NMR (D_2O, HDO = 4.63 ppm) δ 0.74 (d, 3 H, *J* = 6.5, C_4-CH_3), 1.46 (d, 3 H, *J* = 5, C_8-H), 1.35–1.92 (m, 2 H, C_4-H, C_5-H), 2.00–2.17 (m, 1 H, C_5-H), 2.54 (s, 3 H, NCH_3), 3.44 (d, 1 H, *J* = 5.5, C_2-H), 3.58 (t, 1 H, *J* = 5.5 C_3-H), 5.18–5.47 (m, 2 H, CH=CH); ^{1}H NMR (CD_3OD, CHD_2OD = 3.30) δ 0.93 (d, 3 H, *J* = 6.5, C_5-CH_3), 1.64 (d, 3 H, *J* = 4, C_8-H), 1.60–1.96 (m, 2 H, C_4-H, C_5-H), 2.29–2.44 (m, 1 H, C_5-H), 2.67 (s, 3 H, NCH_3), 3.45 (d, 1H, *J* = 5.5, C_2-H), 3.71 (t, 1 H, *J* = 5.5, C_3-H), 5.32–5.58 (m, 2 H, CH=CH). Anal. Calcd for $C_{10}H_{19}NO_3$: C, 59.68; H, 9.52; N, 6.96. Found: C, 59.45; H, 9.46; N, 6.90.

Acknowledgment. This work was supported in part by a grant from the National Institutes of Health (AM 32007). We thank C. Q. Sun for a sample of **6d**, V. S. Goodfellow for helpful comments on the synthetic procedures, and Prof. David Evans for sending a copy of ref 8 prior to publication.

(44) The absolute configuration of 2-oxazolidinone **10a** was deduced by comparing to **9a**. The optical rotation for 10a was nearly idential with the optical rotation for 2-oxazolidinone **9a**.

Alkaline and Enzymatic Hydrolysis of Isobutyl 3,4-Anhydro-2,6-dideoxy-DL-hexopyranosides. Preparation of Enantiomeric Boivinopyranosides through a Highly Efficient Kinetic Resolution

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Received October 27, 1986

Racemic isobutyl 3,4-anhydro-2,6-dideoxy-β-*ribo*-hexopyranoside and -*lyxo*-hexopyranoside have been prepared starting from the cycloadduct between 3-buten-2-one and isobutyl vinyl ether. Alkaline hydrolysis converted the lyxo isomer exclusively into isobutyl 2,6-dideoxy-β-DL-*xylo*-hexopyranoside (isobutyl β-DL-boivinopyranoside), the ribo isomer into a 57:43 mixture of the same glycoside, and its arabino diastereomer (isobutyl β-DL-olivopyranoside). Rabbit microsomal epoxide hydrolase similarly converted the racemic lyxo epoxide into the xylo diol in a regiospecific way and exhibited a high degree of enantioselectivity: when the enzymatic reaction was stopped at 50% conversion, isobutyl β-L-boivinopyranoside and isobutyl 3,4-anhydro-2,6-dideoxy-β-D-*lyxo*-hexopyranoside were obtained, both with an enantiomeric excess of at least 96%.

Carbohydrates with nonconventional structures, such as branched chain, deoxy, and aminodeoxy sugars, are often found as components of biologically relevant compounds, such as glycoside antibiotics and cardioactive

0022-3263/87/1952-2886$01.50/0