Chelation-Controlled Enantioselective Synthesis of Key Intermediates for the Preparation of Carbapenem Antibiotics PS-5 and 1β-Methyl-PS-5

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Reaction of the *E* silyl ketene acetal derived from (1*S*,2*R*)-*N*-methylephedrine butyrate (**7**) with $TiCl_4$ and β-alkoxy aldehyde **5** gave the aldol product in 75% yield as a 78:11:11 mixture of stereoisomers. In agreement with a chelated transition structure model, the major isomer is syn (2*R*,3*S*). The condensation product was transformed into **3**, a key intermediate for the preparation of (+)-PS-5 [8:1 trans–cis; ee(trans) = 75%]. The stereoselectivity of the aldol reaction was substantially improved by using α-methyl-β-alkoxy aldehyde **6**, which was synthesized in 91% enantiomeric excess and 50% overall yield starting from (1*S*,2*R*)-*N*-methylephedrine propionate *E* silyl ketene acetal **13**. In this case the reaction of silyl ketene acetal **7** with $TiCl_4$ and aldehyde **6** gave the aldol product in 70% yield as a *single* isomer out of the eight possible isomers. The result is in agreement with a chelated transition structure model and with a kinetic resolution–matched pair mechanism. The condensation product was transformed into **4** and **18**, key intermediates for the preparation of 1β-methyl-PS-5 (ee > 99%). Via a different approach, the reaction of enantiomerically pure aldehyde (*S*)-(+)-**6**, prepared from (*R*)-(−)-methyl 3-hydroxy-2-methylpropionate, with $TiCl_4$ and achiral *E* or *Z* silyl ketene acetals **19** or **20** gave the aldol product in high yield respectively as a 99:1:0:0 or 96:3:1:0 mixture of stereoisomers. The major isomer **21**, obtained in agreement with a chelated transition structure model, was transformed into the key intermediate **18** via the same reaction sequence.

In the synthesis of carbapenem antibiotics, the control of the relative and absolute stereochemistry of the contiguous chiral centers and the construction of the β-lactam ring remain difficult synthetic tasks.[1] Recently we reported the asymmetric synthesis of various β-lactams via the $TiCl_4$-mediated condensation of *N*-methylephedrine-derived silyl ketene acetals with aldehydes and imines.[2a,b] Herein we describe a straightforward enantio- and diastereoselective synthesis of key intermediates **3** and **4** of carbapenem antibiotics PS-5 (**1**)[3] and 1β-methyl-PS-5 (**2**), based on a highly selective $TiCl_4$-mediated chelation-controlled aldol reaction (Scheme I). The novelty of our synthesis, compared with those already reported,[3] is the double role played by the oxygen function at C-2[4] of **3** and **4**, which is both necessary for the subsequent routine elaboration to PS-5[3b,f,g] and essential for controlling—through chelation—the simple and relative diastereoselectivity of the aldol process.[5]

Results and Discussion

Reaction of the *E* silyl ketene acetal derived from (1*S*,2*R*)-*N*-methylephedrine butyrate[6] **7** (0.75 molar equiv) with aldehyde **5** (1.0 molar equiv) and $TiCl_4$ (1.0 molar equiv) in methylene chloride at −78 °C gave the aldol condensation product **8** in 75% yield[7] as a 78:11:11 mixture of stereoisomers (Scheme II). In contrast with the usual anti selectivity of reagent **7** with aldehydes,[2b,6a,b,e] the major isomer of this mixture is syn (2*R*,3*S*), in accord with the chelated transition structure model A (Figure 1). The crude condensation product was saponified (LiOH, MeOH–H_2O, room temperature, 5 days) to give acid **9** (90%),[8,9] which was treated with methoxyamine hydrochloride and the water-soluble carbodiimide[10] to give the desired hydroxamate **10** cleanly (75%). Treatment of **10** with methanesulfonyl chloride (pyridine, 0 °C) gave the mesylate, which was directly cyclized[11] (K_2CO_3, acetone, reflux) to give *N*-methoxyazetidinone **11** in 70% overall yield from **10**, as a 8:1 trans–cis mixture. The major by-products (15–20%) of the cyclization reaction were identified as the *E* and *Z* α,β-unsaturated hydroxamates. The enantiomeric excess of the major trans isomer was shown to be 75% by 200-MHz ^1H NMR spectroscopy in the presence of the chiral shift reagent Eu(hfc)$_3$.[12] Dissolving

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(4) PS-5 numbering.

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(7) The mass balance in this process was largely accounted for by recovered aldehyde and (1*S*,2*R*)-*N*-methylephedrine butyrate.

(8) Optically pure *N*-methylephedrine was recovered at this stage in 90% yield (see the Experimental Section).

(9) In order to be sure that no epimerization had occurred during the LiOH treatment, compound **8** was hydrogenolyzed (H_2, Pd–C, MeOH, 3.5 h; see the Experimental Section) to give acid **9** in quantitative yield and successively transformed into β-lactam **11** with the same stereoisomeric ratio [Eu(hfc)$_3$, 200-MHz ^1H NMR] as that obtained via LiOH.

(10) *N*-Ethyl-*N'*-[3-(dimethylamino)propyl]carbodiimide; see: (a) Miller, M. J.; Bajwa, J. S.; Mattingly, P. G.; Peterson, K. *J. Org. Chem.* **1982**, *47*, 4928. (b) Miller, M. J. *Acc. Chem. Res.* **1986**, *19*, 49.

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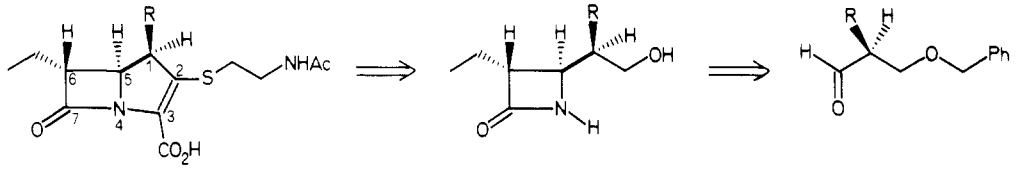
Scheme I

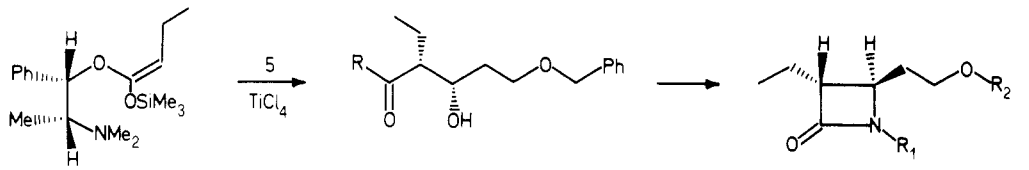


1 R = H
2 R = Me

3 R = H
4 R = Me

5 R = H
6 R = Me

Scheme II

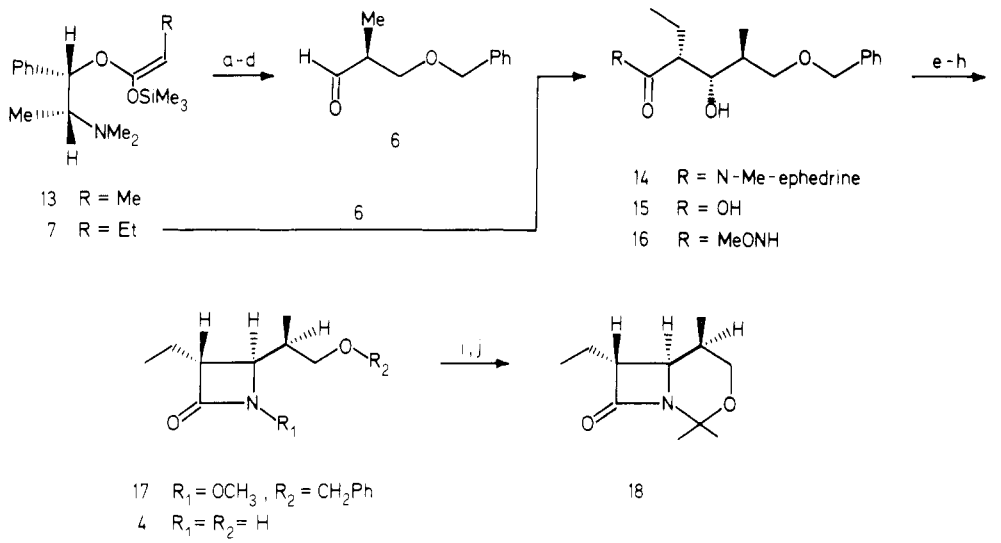


7

8 R = N-Me-ephedrine
9 R = OH
10 R = MeONH

11 $R_1 = OCH_3$, $R_2 = CH_2Ph$
3 $R_1 = R_2 = H$
12 $R_1 = R_2 = SiMe_2Bu^t$

Scheme III[a]



13 R = Me
7 R = Et

6

14 R = N-Me-ephedrine
15 R = OH
16 R = MeONH

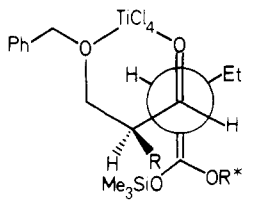
17 $R_1 = OCH_3$, $R_2 = CH_2Ph$
4 $R_1 = R_2 = H$

18

[a] Reagents and yields: (a) $TiCl_4$, $HC(OMe)_3$, CH_2Cl_2, −78 °C (62%). (b) LAH, Et_2O, room temperature (95%). (c) NaH, $PhCH_2Br$, n-Bu_4NI cat., THF (90%). (d) AcOH–H_2O 1:1, room temperature, 20 h (95%). (e) LiOH, MeOH–H_2O, room temperature, 5 days (90%). (f) $MeONH_2$–HCl, WSC (70%). (g) MsCl, Py, 0 °C (100%). (h) K_2CO_3, acetone, reflux (65%). (i) THF, NH_3, 6 equiv of Na, −78 °C, 1 h (70%). (j) CH_2Cl_2, 2,2-dimethoxypropane, BF_3·OEt_2 (85%).

metal reduction (THF, NH_3, 6 equiv of Na, −78 °C, 1 h)[11] cleanly effected both N–O and O–CH_2Ph bond cleavage to afford **3** in 70% yield (trans–cis 8:1). Finally, silylation of **3** (TBDMS-OTf, CH_2Cl_2, lutidine)[13] and flash chromatography gave 100% trans disilyl β-lactam **12** in 85% yield and 76% optical purity.[14] Both **12** and a 7:3 trans–cis mixture of **3** had previously been transformed into (+)-PS-5 (**1**) by standard operations.[3b,f,g]

The selectivity of the aldol condensation was substantially improved by α-methyl substitution on the aldehyde. (*S*)-(+)-3-(Benzyloxy)-2-methylpropionaldehyde (**6**) was synthesized in 91% enantiomeric excess and 50% overall yield, starting from (1*S*,2*R*)-*N*-methylephedrine propionate *E* silyl ketene acetal **13** and trimethyl orthoformate[6c] (Scheme III). Reaction of aldehyde **6** (1.0 molar equiv) and $TiCl_4$ (1.0 molar equiv) with *E* silyl ketene acetal **7** (0.9 molar equiv) in methylene chloride at −78 °C gave the aldol condensation product **14** in 70% yield[7] as a *single* isomer

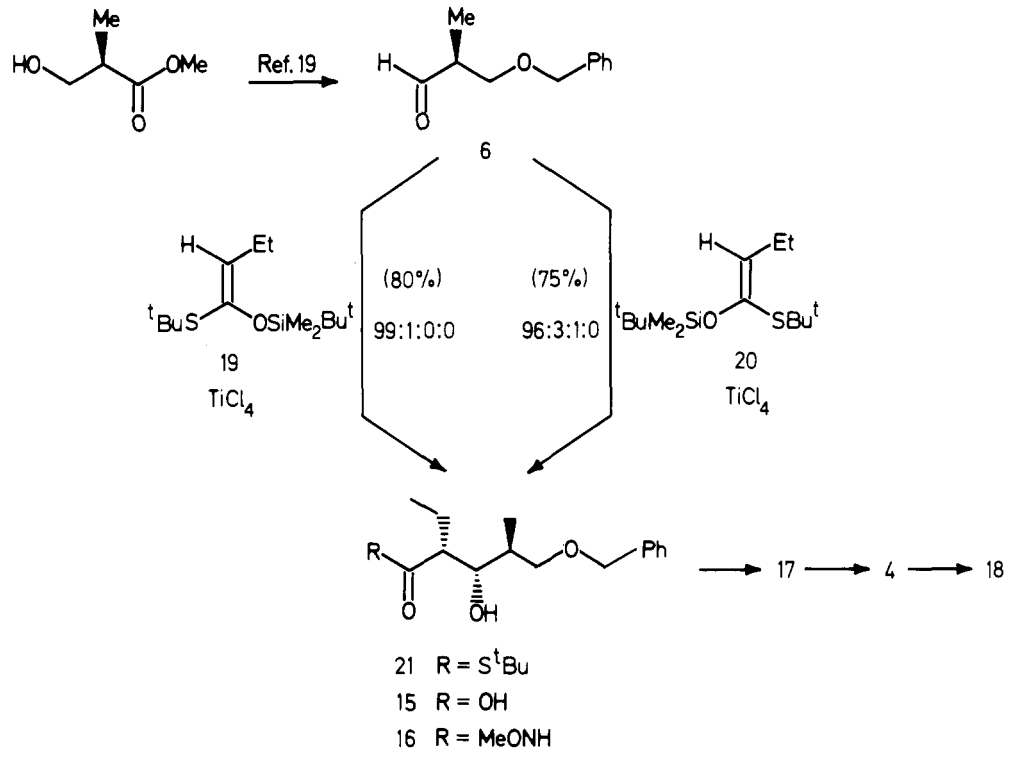


A R = H
B R = Me

Figure 1.

(12) Tris[3-[(heptafluoropropyl)hydroxymethylene]-(+)-camphorato]europium(III) derivative.
(13) Corey, E. J.; Cho, H.; Rucker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455.
(14) $[\alpha]^{25}_D$ −30.1° (*c* 2.9, $CHCl_3$) [lit.[3g] $[\alpha]^{25}_D$ −39.59° (*c* 2.92, $CHCl_3$)].

Scheme IV



out of the eight possible isomers.

Our explanation for this excellent selectivity is the following: both the (1*S*,2*R*)-*N*-methylephedrine derived silyl ketone acetal **7** and (*S*)-**6** have an intrinsic preference for establishing a 2*R*,3*S* absolute configuration at C-2,C-3, as is evident from the reaction of **7** with the achiral aldehyde **5** (see Scheme II) and from the reaction of (*S*)-**6** with the achiral silyl ketene acetals **19**, **20** (see Scheme IV). As **7** and (*S*)-**6** form a matched pair (they cooperate to realize the same stereochemical result) while **7** and (*R*)-**6** form a mismatched pair, only the *S* enantiomer of the starting 95.5/4.5 *S*/*R* mixture of aldehyde **6** reacts with **7**, and the condensation occurs with concomitant kinetic resolution.[15] The relative stereochemistry of the three contiguous chiral centers is a result of chelation control[16] (C-3,C-4 anti) and syn simple stereoselection (C-2,C-3 syn) in agreement with the transition structure model B (Figure 1).[15]

14 was transformed into β-lactam **17** via the same reaction sequence described above (41% overall). The enantiomeric excess of **17** was shown to be >99% by 200-MHz ^{1}H NMR spectroscopy in the presence of the chiral shift reagent Eu(hfc)$_3$.[12] Dissolving metal reduction gave **4** (70%), which was treated with 2,2-dimethoxypropane in CH_2Cl_2 in the presence of BF_3·OEt_2[17] to give the bicyclic acetonide **18** (85%), characterized by the proton coupling

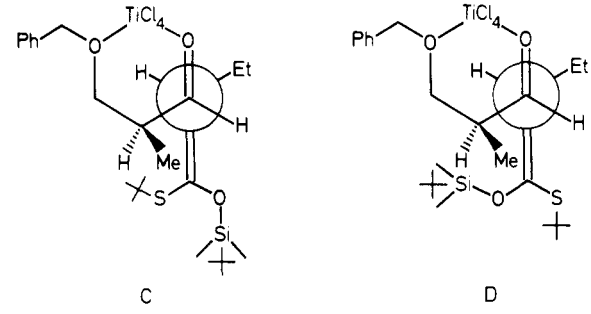


Figure 2.

pattern typical of 1β-methyl substitution.[17b] Both **4**- and **18**-type compounds had previously been transformed into 1β-methylcarbapenem antibiotics[17a,c,d] that possess improved chemical stability at high concentrations and decreased susceptibility to renal dipeptidase-I while retaining an excellent antibacterial profile.[18]

The approach described above is based on the triple role played by the chiral *N*-methylephedrine-derived silyl ketene acetals: first they are used to synthesize aldehyde **6** in 91% enantiomeric excess, second to establish the relative stereochemistry of the three contiguous chiral centers of the aldol product **14** with >99% selectivity, and third to upgrade the enantiomeric excess from 91 to >99%.

An alternative approach, based on the use of the achiral thiolester derived silyl ketene acetals **19** and **20**,[6c] is shown in Scheme IV. In this case aldehyde (*S*)-(+)-**6** was prepared in the enantiomerically pure form, starting from *R*-(−)-methyl 3-hydroxy-2-methylpropionate.[19] *E* Silyl ketene acetal **19** (*E*/*Z* ≥ 95:5) and *Z* silyl ketene acetal **20** (*Z*/*E*) ≥ 95:5) were prepared from *tert*-butyl thiobutyrate

(15) For a discussion of this selectivity and an example of the mismatched pair, i.e. reaction of *S* aldehyde **6** (91% ee) with (1*R*,2*S*)-*N*-methylephedrine derived silyl ketene acetal, see ref 6e.

(16) The 1:1 complex between titanium tetrachloride and aldehyde **6** was recently characterized by NMR spectroscopy and shown to be quite rigid and essentially "conformationally locked"; see: Keck, G. E.; Castellino, S. *J. Am. Chem. Soc.* **1986**, *108*, 3847; *Tetrahedron Lett.* **1987**, *28*, 281.

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(18) Shih, D. H.; Baker, F.; Cama, L.; Christensen, B. G. *Heterocycles* **1984**, *21*, 29.

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with LDA, THF–HMPA, *t*-BuMe$_2$SiCl and LDA, THF, *t*-BuMe$_2$SiOTf, respectively, according to our published methodology.[20,21] The condensation reaction established the relative stereochemistry of the three contiguous chiral centers with good selectivity: reaction of aldehyde **6** (1.0 molar equiv) and $TiCl_4$ (1.0 molar equiv) with silyl ketene acetal **19** (1.5 molar equiv) in methylene chloride at −78 °C gave the aldol condensation product in 80% yield as a 99:1:0:0 mixture of the four possible diastereoisomers (200-MHz ^{1}H and ^{13}C NMR). The major isomer **21** is the result of chelation control[16] (C-3,C-4 anti) and syn simple stereoselection (C-2,C-3 syn) in agreement with the transition structure model C (Figure 2).[6c,20] Almost the same ratio (96:3:1:0) and yield (75%) were obtained with the *Z* silyl ketene acetal **20** (transition structure model D, Figure 2).[6c,20] Adduct **21** was then treated with $Hg(OCOCF_3)_2$ in acetonitrile–water[22] to give acid **15** in 70% yield, which was transformed into β-lactam **17** via the same reaction sequence described above. The diastereoisomeric ratios were confirmed at this stage by 200-MHz ^{1}H NMR spectroscopy in the presence of Eu(fod)$_3$[23] (≥99:≤1 starting from **19** and ≥96:≤3:1 starting from **20**). Unfortunately, but not unexpectedly,[6c] ^{1}H NMR analysis with Eu(hfc)$_3$[12] revealed the presence of variable amounts of the enantiomer of β-lactam **17** (up to 4% starting from **20** and up to 10% starting from **19**). This result, probably due to partial racemization of aldehyde **6** during the $TiCl_4$-mediated condensation,[6c] points out very clearly the superiority of the kinetic resolution–matched pair process based on the use of the chiral silyl ketene acetal **7**.

In conclusion, these experiments provide a simple route to optically active β-lactams. Extensions of this methodology to the preparation of other optically pure 1β-methylcarbapenam antibiotics (1β-methylthienamycin and analogues) are in progress.

Experimental Section

General Procedures. ^{1}H and ^{13}C NMR spectra were recorded with Varian XL-200 or Bruker WP-80 instruments in the FT mode. Optical rotations were measured in 1-dm cells of 1-mL capacity on a Perkin-Elmer Model 241 polarimeter. IR spectra were recorded with a Perkin-Elmer 681 spectrophotometer. Elemental analyses were performed with a Perkin-Elmer Model 240 instrument. Silica gel 60 F_{254} plates (Merck) were used for TLC; 273–400-mesh silica gel (Merck) was used for flash chromatography. Organic extracts were dried over Na_2SO_4. Dry solvents were distilled under nitrogen immediately before use: THF and ethyl ether from sodium/benzophenone, CH_2Cl_2 and diisopropylamine from CaH_2. All reactions were run under nitrogen atmosphere (from liquid nitrogen).

Aldehyde 5. A suspension of NaH (80% in oil, 1.578 g, 52.56 mmol) in THF (100 mL) was treated dropwise with 1,3-propanediol (3.846 mL, 52.56 mmol), and the mixture was stirred at room temperature for 45 min. Benzyl bromide (5.638 mL, 47.31 mmol) and tetrabutylammonium iodide (0.6 g, 1.62 mmol) were added, and the mixture was stirred at room temperature for 60 h and then refluxed for 2 h. The reaction was quenched with 10% potassium carbonate (150 mL) and extracted with ethyl ether (4 × 200 mL). The organic extracts were washed with saturated brine (150 mL), dried, and evaporated to give a crude product, which was purified by flash chromatography (*n*-hexane–ethyl acetate 6:4) to give the monobenzyl-protected diol in 70% yield: ^{1}H NMR ($CDCl_3$) δ 1.86 (2 H, quintet, *J* = 6.1 Hz), 2.0–2.4 (1 H, br s), 3.68 (2 H, t, *J* = 6.1 Hz), 3.80 (2 H, t, *J* = 6.1 Hz), 4.52 (2 H, s), 7.33 (5 H, s).

A solution of oxalyl chloride (0.558 mL, 6.62 mmol) in methylene chloride (15 mL) was treated with a solution of DMSO (1.02 mL, 11.4 mmol) in methylene chloride (3 mL) during 10 min, at −60 °C, under nitrogen, with stirring. After 15 min at −60 °C the monoprotected diol (0.466 g, 3.66 mmol) was added in methylene chloride (3 mL) during 5 min. After 15 min at −60 °C triethylamine (4.18 mL, 30 mmol) was added during 15 min, and the mixture was slowly warmed up to room temperature (during 1 h). The reaction was quenched with water (15 mL) and extracted with methylene chloride. The organic extracts were concentrated and flash chromatographed (*n*-hexane–ethyl acetate 85:15) to give aldehyde **5** in 75% yield: ^{1}H NMR ($CDCl_3$) δ 2.68 (2 H, dt, *J* = 6.0, 2.0 Hz), 3.80 (2 H, t, *J* = 6.0 Hz), 4.50 (2 H, s), 7.32 (5 H, s), 9.78 (1 H, t, *J* = 2.0 Hz). Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.05; H, 7.42.

(1*S*,2*R*)-(+)-*N*-Methylephedrine Butyrate. This compound was prepared via the general procedure described in ref 6e: $[\alpha]^{25}_D$ +42.2° ($CHCl_3$, *c* 1.2); ^{1}H NMR ($CDCl_3$) δ 0.93 (t, 3 H, *J* = 7.7 Hz), 1.06 (d, 3 H, *J* = 6.6 Hz), 1.4–1.9 (m, 2 H), 2.2–2.5 (m, 2 H), 2.3 (s, 6 H), 2.87 (dq, 1 H, *J* = 5.4, 6.6 Hz), 5.95 (d, 1 H, *J* = 5.4 Hz), 7.30 (s, 5 H); ^{13}C NMR ($CDCl_3$) δ 9.47, 13.67, 18.37, 36.56, 41.30, 63.67, 75.17, 126.31, 127.38, 128.18, 140.34, 172.50; IR (liquid film) ν 1740, 1495, 1455, 1175, 740, 695 cm^{-1} (selected values). Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.28; H, 9.23; N, 5.62. Found: C, 72.20; H, 9.30; N, 5.58.

(1*S*,2*R*)-*N*-Methylephedrine Butyrate Derived *E* Silyl Ketene Acetal 7. A solution of diisopropylamine (1.45 mL, 10.2 mmol) in THF (20.5 mL) was treated with *n*-BuLi (1.5 N in *n*-hexane, 6.8 mL, 10.2 mmol) at 0 °C, under nitrogen, with stirring. After 30 min at 0 °C, the solution was cooled to −78 °C, and a solution of (+)-*N*-methylephedrine butryate (8.5 mmol) in THF (17.0 mL) was slowly added. After 1 h at −78 °C, TMSCl (1.29 mL, 10.2 mmol) was slowly added. After 1 h at −78 °C the mixture was slowly warmed up to room temperature (during 1 h). The mixture was then evaporated and pumped. The residue (*THF free*!) was taken up in methylene chloride (8.5 mL), and the 0.8 M solution so obtained could be stored at −20 °C for several weeks and used as stock solution: ^{1}H NMR ($CDCl_3$) δ 0.00 (s, 9 H), 0.90 (t, 3 H, *J* = 6.9 Hz), 1.09 (d, 3 H, *J* = 6.7 Hz), 2.05 (m, 2 H), 2.30 (s, 6 H), 2.80 (m, 1 H), 3.48 (t, 1 H, *J* = 6.9 Hz), 5.25 (d, 1 H, *J* = 4.0 Hz), 7.25 (s, 5 H); spectroscopic yield (^{1}H NMR) >95%; *E*–*Z* ratio (^{1}H NMR) >95:5, based on an authentic *E*–*Z* mixture obtained with $LiN(SiMe_3)_2$ as base instead of LDA.

Aldol Condensation Product 8. A solution of aldehyde **5** (2.4 mmol) in methylene chloride (7.3 mL) was treated with a 1.0 M solution of $TiCl_4$ in methylene chloride (2.4 mL), at −78 °C, under nitrogen, with stirring. Immediately after, a 0.8 M solution of silyl ketene acetal **7** in methylene chloride (2.24 mL) was slowly added at −78 °C. After 3 h at −78 °C, the reaction was quenched with 10% K_2CO_3 and 2 NaOH aqueous solution and filtered through Celite. The aqueous phase was extracted with methylene chloride, and the combined organic extracts were dried and evaporated. The crude product was then filtered through silica gel (CH_2Cl_2–MeOH 95:5) to give the aldol condensation product in 75% yield as a 78(major):11(minor):11(minor) mixture of stereoisomers: ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 3 H, *J* = 7.5 Hz), 1.03 (d, 3 H, *J* = 6.8 Hz), 1.58–1.96 (m, 4 H), 2.27 (s, 6 H), 2.38–2.48 (m, 1 H), 2.71 (dq, 1 H, *J* = 6.8, 5.0 Hz, major), 3.5–3.8 (m, 2 H), 3.9–4.02 (m, 1 H), 4.48 (s, 2 H, major), 4.52 (s, 2 H, minor), 4.53 (s, 2 H, minor), 6.07 (d, 1 H, *J* = 5.0 Hz, major), 6.16 (d, 1 H, *J* = 4.4 Hz, minor), 6.31 (d, 1 H, *J* = 3.1 Hz, minor), 7.2–7.4 (m, 10 H).

Acid 9. A solution of the aldol condensation product **8** (0.4 g, 0.969 mmol) in 4:1 MeOH–H_2O (9.7 mL) was treated with LiOH (0.203 g, 4.85 mmol) at room temperature with stirring. After 5 days at room temperature, the mixture was diluted with water (1.5 mL), and methanol was evaporated in vacuo. The resulting aqueous mixture was treated with 1 N HCl (10 mL) and extracted with CH_2Cl_2. The combined organic extracts were dried and evaporated to give the crude acid. The aqueous phase containing *N*-methylephedrine hydrochloride was treated with NaOH and extracted with CH_2Cl_2: the combined organic extracts were dried and evaporated to give optically pure *N*-methylephedrine (90%

(20) Gennari, C.; Beretta, M. G.; Bernardi, A.; Moro, G.; Scolastico, C.; Todeschini, R. *Tetrahedron* **1986**, *42*, 893.

(21) Note that silyl ketene acetals derived from thiolesters have the opposite *Z*/*E* descriptors compared to esters due to change of sequence rule priority associated with the sulfur atom.

(22) Masamune, S.; Kamata, S.; Schilling, W. *J. Am. Chem. Soc.* **1975**, *97*, 3515. Masamune, S.; Hayase, Y.; Schilling, W.; Kit Chan, W.; Bates, G. S. *J. Am. Chem. Soc.* **1977**, *99*, 6756.

(23) Tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium.

recovery). The crude acid was purified by flash chromatography (CH_2Cl_2–MeOH 94:6) to give acid **9** in 90% yield: IR ($CHCl_3$) ν 3500, 2960, 2860, 1750, 1710, 1085 cm^{-1} (selected values); ^1H NMR ($CDCl_3$) δ 0.98 (t, 3 H, J = 7.2 Hz), 1.5–1.9 (m, 4 H), 2.3–2.6 (m, 1 H), 3.6–3.8 (m, 2 H), 3.85–4.15 (m, 1 H), 4.50 (s, 2 H), 6.40 (br s, 1 H), 7.32 (s, 5 H). Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.55; H, 8.03. Alternatively the aldol condensation product **8** (2.18 mmol) was dissolved in methanol (21.8 mL) and hydrogenated in the presence of 10% Pd–C (0.231 g). After 3.5 h at room temperature, the catalyst was filtered off and washed with methanol. The solvent was evaporated and the crude product flash chromatographed (CH_2Cl_2–MeOH 94:6) to give acid **9** in quantitative yield.

Hydroxamate 10. A solution of acid **9** (0.64 g, 2.54 mmol) in 6:1 THF–H_2O (24 mL) was treated with methoxyamine hydrochloride (0.382 g, 4.572 mmol) and the pH was adjusted to 4.5 with 2 N aqueous HCl. A solution of WSC[10] (1.217 g, 6.35 mmol) in water (21 mL) was then added. After being stirred for 5 h at room temperature, the mixture was acidified with 2 N HCl to pH 2 and extracted with ethyl acetate. The combined organic extracts were dried and evaporated to give a crude product, which was purified by flash chromatography (CH_2Cl_2–MeOH 94:6) to give hydroxamate **10** in 75% yield: IR ($CHCl_3$) ν 3480, 3400, 2890, 1690, 1460, 1090 cm^{-1} (selected values); ^1H NMR ($CDCl_3$) δ 0.9 (t, 3 H, J = 7.2 Hz), 1.5–1.9 (m, 4 H), 1.9–2.25 (m, 1 H), 3.6–3.8 (m, 2 H), 3.7 (s, 3 H), 3.80–4.05 (m, 1 H), 4.47 (s, 2 H), 7.3 (s, 5 H), 8.95 (br s, 1 H). Anal. Calcd for $C_{15}H_{23}NO_4$: C, 64.04; H, 8.24; N, 4.98. Found: C, 64.00; H, 8.34; N, 4.89.

***N*-Methoxyazetidinone 11.** A solution of hydroxamate **10** (0.334 g, 1.19 mmol) in dry pyridine (1.19 mL) at 0 °C was treated with methanesulfonyl chloride (2.38 mmol). The mixture was stirred at 0 °C for 3 h, then diluted with ethyl acetate (24 mL), and treated with 1 N aqueous HCl. The organic extracts were washed with 1 N HCl (until acidic), followed by saturated $NaHCO_3$ and finally brine. The extracts were dried and evaporated to give the crude mesylate in quantitative yield. A solution of the crude mesylate (0.416 g, 1.19 mmol) in dry acetone (24 mL) was heated at reflux temperature and treated with powdered potassium carbonate (0.82 g, 5.95 mmol) with *vigorous* stirring. After refluxing for 1 h, the mixture was cooled, diluted with ethyl acetate (50 mL), and filtered through Celite (washing with ethyl acetate). The solvent was evaporated to give a crude product, which was purified by flash chromatography (*n*-hexane–acetone 80:20) to give *N*-methoxyazetidinone **11** in 70% yield as a 8:1 trans–cis mixture: IR ($CHCl_3$) ν 2960, 2940, 2860, 1760, 1450, 1380, 1360, 1100 cm^{-1} (selected values); ^1H NMR ($CDCl_3$) δ 0.99 (t, 3 H, J = 7.4 Hz, trans), 1.06 (t, 3 H, J = 7.4 Hz, cis), 1.5–1.8 (m, 2 H), 1.8–2.0 (m, 1 H), 2.05–2.22 (m, 1 H), 2.56 (ddd, 1 H, J = 2.0, 6.25, 8.12 Hz, trans), 2.76–2.87 (ddd, 1 H, cis), 3.60 (t, 2 H, J = 6.5 Hz), 3.64–3.74 (ddd, 1 H, trans), 3.71 (s, 3 H, cis), 3.74 (s, 3 H, trans), 4.02–4.14 (ddd, 1 H, cis), 4.50 (s, 2 H, trans), 4.52 (s, 2 H, cis), 7.25–7.40 (m, 5 H); ^1H NMR [$CDCl_3$ + Eu(hfc)$_3$] racemic δ 6.27 (50%, MeO, s, trans), 6.31 (50%, MeO, s, trans), optically active 6.27 (12.5%, MeO, s, trans), 6.31 (87.5%, MeO, s, trans). Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.33; H, 8.11; N, 5.30.

β-Lactam 3. To a solution of Na (26.2 mg, 1.14 mmol) in 10:1 NH_3–THF (2.7 mL) at −78 °C a solution of *N*-methoxyazetidinone **11** (50 mg, 0.19 mmol) in THF (0.430 mL) was added. The resulting blue solution was stirred at −78 °C for 1 h, then solid NH_4Cl (137 mg, 2.565 mmol) was added, and the resulting colorless solution was diluted with ethyl ether (3.0 mL). The ammonia was then allowed to distill off, while the solution was heated to room temperature, and 5 mL of ethyl ether was added to the white slurry. After filtration and washing of the solids with additional ethyl ether, the organic phase was concentrated to give a crude product, which was purified by flash chromatography (CH_2Cl_2–MeOH 89:11) to give lactam **3** in 70% yield as a 8:1 trans–cis mixture: IR ($CHCl_3$) ν 3620, 3420, 2960, 2940, 1750, 1380, 1050 cm^{-1} (selected values); ^1H NMR ($CDCl_3$) δ 1.02 (t, 3 H, J = 7.4 Hz, trans), 1.05 (t, 3 H, J = 7.4 Hz, cis), 1.55–1.95 (m, 4 H), 2.77 (ddd, 1 H, J = 2.0, 6.0, 8.0 Hz, trans), 3.06–3.16 (m, 1 H, cis), 3.45 (ddd, 1 H, J = 2.0, 5.80, 7.75 Hz, trans), 3.65–3.86 (m, 2 H), 6.25 (br s, 1 H). Anal. Calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.63; H, 9.22; N, 9.69.

Disilyl β-Lactam 12. A solution of **3** (26 mg, 0.182 mmol) in methylene chloride (3.6 mL) was treated with lutidine (0.22 mL, 1.93 mmol) and then with TBDMS-OTf (0.166 mL, 0.726 mmol) at 0 °C, under nitrogen, with stirring. After 1 h at 0 °C, the reaction was quenched with methanol (0.5 mL) and the mixture was evaporated. The crude product was purified by flash chromatography (*n*-hexane–ethyl acetate 92:8) to give disilyl β-lactam **12** (100% trans) in 85% yield: IR ($CHCl_3$) ν 2960, 2920, 2860, 1720, 1470, 1460, 1250, 1100, 830 cm^{-1} (selected values); ^1H NMR ($CDCl_3$) δ 0.03 (s, 6 H), 0.19 (s, 3 H), 0.23 (s, 3 H), 0.88 (s, 9 H), 0.94 (s, 9 H), 1.0 (t, 3 H, J = 7.5 Hz), 1.48–1.83 (m, 3 H), 1.98–2.15 (m, 1 H), 2.78 (ddd, 1 H, J = 2.5, 6.3, 8.25 Hz), 3.36 (ddd, 1 H, J = 2.5, 2.5, 10.5 Hz), 3.54–3.74 (m, 2 H); $[\alpha]^{25}_D$ −30.1° (*c* 2.9, $CHCl_3$) [lit.[3g] $[\alpha]^{25}_D$ −39.59° (*c* 2.92, $CHCl_3$)]. Anal. Calcd for $C_{19}H_{41}NO_2Si_2$: C, 61.39; H, 11.12; N, 3.77. Found: C, 61.30; H, 11.20; N, 3.70.

(1*S*,2*R*)-*N*-Methylephedrine Propionate. This compound was prepared via the general procedure described in ref 6e: $[\alpha]^{25}_D$ +46.3° ($CHCl_3$, *c* 1.2); ^1H NMR ($CDCl_3$) δ 1.05 (d, 3 H, J = 6.7 Hz), 1.15 (t, 3 H, J = 7.7 Hz), 2.25 (s, 6 H), 2.38 (q, 2 H, J = 7.7 Hz), 2.88 (dq, 1 H, J = 5.4, 6.7 Hz), 5.94 (d, 1 H, J = 5.4 Hz), 7.25 (s, 5 H); ^{13}C NMR ($CDCl_3$) δ 9.02, 9.36, 27.95, 41.11, 63.73, 75.00, 126.13, 127.27, 128.07, 140.12, 172.81; IR ($CHCl_3$) ν 2980, 2940, 1735, 1460, 1450, 1375, 1185 cm^{-1} (selected values). Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.45; H, 9.00; N, 5.95. Found: C, 71.30; H, 9.11; N, 5.87.

(1*S*,2*R*)-*N*-Methylephedrine Propionate Derived *E* Silyl Ketene Acetal 13. The reaction was run under the same experimental conditions described for the preparation of **7**. **13**: ^1H NMR ($CDCl_3$) δ 0.00 (s, 9 H), 1.10 (d, 3 H, J = 6.7), 1.55 (d, 3 H, J = 6.7 Hz), 2.30 (s, 6 H), 2.80 (dq, 1 H, J = 4.0, 6.7 Hz), 3.48 (q, 1 H, J = 6.7 Hz), 5.29 (d, 1 H, J = 4.0 Hz), 7.27 (s, 5 H); spectroscopic yield (^1H NMR) >95%; *E*–*Z* ratio (^1H NMR) >95:5, based on an authentic *E*–*Z* mixture obtained with $LiN(SiMe_3)_2$ as base instead of LDA.

(*S*)-(+)-3-(Benzyloxy)-2-methylpropionaldehyde (6) (Scheme III) (91% ee). A solution of trimethyl orthoformate (0.875 mL, 8.0 mmol) in methylene chloride (24 mL) was treated with a 1 M solution of $TiCl_4$ in methylene chloride (8.0 mL, 8.0 mmol), at −78 °C, under nitrogen, with stirring. Immediatley after, a 0.8 M solution of silyl ketene acetal **13** in methylene chloride (10.0 mL, 8.0 mmol) was slowly added at −78 °C. After 2 h at −78 °C, the reaction was quenched with 10% K_2CO_3 and 2 N NaOH aqueous solution and filtered through Celite. The aqueous phase was extracted with methylene chloride and the combined organic extracts were dried and evaporated. The crude product was filtered through silica gel (CH_2Cl_2–MeOH 95:5) to give the condensation product in 62% yield as a 21:1 mixture of stereoisomers (the mass balance in this process was largely accounted for by recovered (1*S*,2*R*)-*N*-methylephedrine propionate): ^1H NMR ($CDCl_3$, 300 MHz) δ 1.08 (d, 3 H, J = 6.7 Hz), 1.20 (d, 3 H, J = 7.5 Hz), 2.38 (s, 6 H), 2.6–3.0 (dq, 1 H), 2.6–3.0 (dq, 1 H), 3.30 (s, 3 H), 3.33 (s, 3 H), 4.48 (d, 0.955 H, J = 7.5 Hz), 4.50 (d, 0.045 H, J = 7.5 Hz), 5.98 (d, 1 H, J = 5.0 Hz), 7.27 (s, 5 H). A solution of the condensation product described above (2 g, 6.27 mmol) in ethyl ether (31 mL) was treated with $LiAlH_4$ (0.476 g, 12.53 mmol) at 0 °C under nitrogen, with stirring. The mixture was stirred at room temperature for 2 h and then quenched with water (0.48 mL), 15% NaOH (0.48 mL), and water (0.96 mL). After 30 min the mixture was treated with Na_2SO_4 and filtered and the organic phase was evaporated in vacuo. The crude product was distilled at reduced pressure (16 mmHg) to give (1*S*,2*R*)-*N*-methylephedrine (120–125 °C) (95%) and the desired alcohol (105–110 °C) (95%): ^1H NMR ($CDCl_3$) δ 0.91 (d, 3 H, J = 7.2 Hz), 1.75–2.25 (m, 1 H), 2.50 (br s, 1 H), 3.37 (s, 3 H), 3.45 (s, 3 H), 3.55 (d, 2 H, J = 5.30 Hz), 4.20 (d, 1 H, J = 6.50 Hz).

A suspension of NaH (80% in oil, 0.359 g, 14.9 mmol) in THF (20 mL) was treated at 0 °C with a solution of the alcohol described above (1 g, 7.46 mmol) in THF (17.8 mL). After 30 min a catalytic amount of n-Bu_4NI (0.137 g, 0.37 mmol) and benzyl bromide (1.774 mL, 14.93 mmol) were added. The mixture was stirred at room temperature for 2 h, then quenched with NH_4Cl saturated solution, and worked up as usual. The crude product was purified by flash chromatography (*n*-hexane–ethyl acetate 9:1) to give the benzyl ether in 90% yield: IR ($CHCl_3$) ν 2920, 1445, 1350, 1060 cm^{-1} (selected values); ^1H NMR ($CDCl_3$) δ 0.98

(d, 3 H, J = 6.9 Hz), 1.9–2.3 (m, 1 H), 3.38 (s, 6 H), 3.25–3.60 (m, 2 H), 4.25 (d, 1 H, J = 6.13 Hz), 4.50 (s, 2 H), 7.27 (s, 5 H); $[\alpha]^{25}_D$ −7.6° (c 1.25, $CHCl_3$).

A solution of the dimethyl acetal described above (1.0 g, 4.46 mmol) in 1:1 AcOH–H_2O (4.46 mL) was stirred under nitrogen at room temperature (with vigorous stirring) for 20 h. Then the mixture was treated with solid $NaHCO_3$ and extracted with ethyl ether. The organic extracts were washed with saturated $NaHCO_3$ solution and saturated brine, dried, and evaporated. The crude aldehyde **6** (95% yield) was used without further purification: ^1H NMR ($CDCl_3$) δ 1.15 (d, 3 H, J = 7.2 Hz), 2.45–2.85 (m, 1 H), 3.6–3.7 (m, 2 H), 4.53 (s, 2 H), 7.27 (s, 5 H), 9.71 (d, 1 H, J = 1.7 Hz); IR (film) ν 2740, 1730 cm^{-1}; $[\alpha]^{25}_D$ +25.8° (c 1.0, $CHCl_3$) [lit.[6c] $[\alpha]^{25}_D$ +28.4° (c 1.56, $CHCl_3$)]. Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.06; H, 7.99.

Aldol Condensation Product 14. A solution of aldehyde **6** (2.4 mmol) in methylene chloride (7.3 mL) was treated with a 1.0 M solution of $TiCl_4$ in methylene chloride (2.4 mL), at −78 °C, under nitrogen, with stirring. Immediately after, a 0.8 M solution of silyl ketene acetal **7** in methylene chloride (2.7 mL, 2.16 mmol) was slowly added at −78 °C. The aldol condensation product **14** was obtained in 70% yield, as a single stereoisomer, following the work-up procedure described above for the preparation of **8**: ^1H NMR ($CDCl_3$) δ 0.95 (t, 3 H, J = 7.5 Hz), 0.99 (d, 3 H, J = 6.5 Hz), 1.02 (d, 3 H, J = 6.25 Hz), 1.58–1.95 (m, 3 H), 2.26 (s, 6 H), 2.46 (ddd, 1 H, J = 3.75, 5.34, 10.0 Hz), 2.72 (dq, 1 H, J = 5.22, 6.25 Hz), 3.48 (A part of an ABX system, 1 H, J = 9.16, 3.66 Hz), 3.64 (B part of an ABX system, 1 H, J = 9.16, 5.20 Hz), 3.65 (dd, 1 H, J = 5.34, 6.44 Hz), 4.47, 4.52 (AB system, 2 H, J = 12.06 Hz), 6.05 (d, 1 H, J = 5.22 Hz), 7.20–7.40 (m, 10 H).

Hydroxamate 16 (Scheme III). The aldol condensation product **14** was transformed into acid **15** (90% yield) and hydroxamate **16** (70% yield) as previously described for the preparation of **9** and **10**. **16**: ^1H NMR ($CDCl_3$) δ 0.86 (d, 3 H, J = 7.0 Hz), 0.93 (t, 3 H, J = 7.4 Hz), 1.54–1.80 (m, 2 H), 1.90–2.10 (m, 1 H), 2.18–2.30 (m, 1 H), 3.50–3.76 (m, 4 H), 3.66 (s, 3 H), 4.48, 4.52 (AB system, 2 H, J = 11.5 Hz), 7.25–7.40 (m, 5 H), 9.12 (s, 1 H); IR ($CHCl_3$) ν 3480, 3400, 2890, 1690, 1460, 1090 cm^{-1} (selected values). Anal. Calcd for $C_{16}H_{25}NO_4$: C, 65.06; H, 8.53; N, 4.74. Found: C, 65.00; H, 8.60; N, 4.67.

***N*-Methoxyazetidinone 17 (Scheme III).** Hydroxamate **16** was transformed into *N*-methoxyazetidinone **17** as previously described for the preparation of **11**. Flash chromatography (*n*-hexane–ethyl acetate 75:25) gave **17** in 65% yield: ^1H NMR ($CDCl_3$) δ 0.99 (t, 3 H, J = 7.5 Hz), 1.06 (d, 3 H, J = 6.3 Hz), 1.48–1.80 (m, 2 H), 2.08 (m, 1 H, J = 6.3 Hz), 2.66 (ddd, 1 H, J = 2.2, 6.3, 7.5 Hz), 3.40 (d, 2 H, J = 6.3 Hz), 3.63 (dd, 1 H, J = 2.2, 6.3 Hz), 3.72 (s, 3 H), 4.48, 4.49 (AB system, 2 H, J = 12.2 Hz), 7.25–7.40 (m, 5 H); ^1H NMR ($CDCl_3$ + Eu(hfc)$_3$), a single isomer was observed δ 5.44 (100%, MeO, s); $[\alpha]^{25}_D$ +20.2° (c 1.4, $CHCl_3$); IR ($CHCl_3$) ν 2960, 2940, 2860, 1760, 1450, 1380, 1360, 1100 cm^{-1} (selected values). Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.19; H, 8.43; N, 4.99.

β-Lactam 4 (Scheme III). *N*-Methoxyazetidinone **17** was transformed into β-lactam **4** (70% yield) as previously described for the preparation of **3**: ^1H NMR ($CDCl_3$) δ 0.96 (d, 3 H, J = 7.0 Hz), 1.01 (t, 3 H, J = 7.5 Hz), 1.54–1.92 (m, 3 H), 2.1 (br s, 1 H), 2.87 (ddd, 1 H, J = 2.1, 6.5, 8.0 Hz), 3.29 (dd, 1 H, J = 2.1, 6.5 Hz), 3.58 (d, 2 H, J = 5.5 Hz), 6.25 (br s, 1 H); $[\alpha]^{25}_D$ +8.5° (c 1.4, $CHCl_3$); IR ($CHCl_3$) ν 3620, 3420, 2960, 2940, 1750, 1380, 1050 cm^{-1} (selected values). Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.03; H, 9.69; N, 8.88.

Acetonide 18 (Scheme III). A solution of β-lactam **4** (140 mg, 0.8917 mmol) in methylene chloride (8.9 mL) was treated with 2,2-dimethoxypropane (1.78 mmol) and with BF_3·OEt_2 (0.134 mmol) at room temperature, under nitrogen. After 1 h the reaction was quenched with Et_3N (1 drop), the mixture was evaporated, and the crude product was purified by flash chromatography (*n*-hexane–ethyl acetate 6:4) to give acetonide **18** in 85% yield: ^1H NMR ($CDCl_3$) δ 0.98 (t, 3 H, J = 7.5 Hz), 1.08 (d, 3 H, J = 7.25 Hz), 1.38 (s, 3 H), 1.71 (s, 3 H), 1.50–2.00 (m, 3 H), 2.93 (ddd, 1 H, J = 1.83, 6.10, 8.25 Hz), 3.42 (dd, 1 H, J = 1.83, 4.89 Hz), 3.55 (dd, 1 H, axial, J = 3.05, 12.05 Hz), 3.91 (dd, 1 H, equatorial, J = 2.52, 12.05 Hz); $[\alpha]^{25}_D$ +26.0° (c 0.6, $CHCl_3$); IR ($CHCl_3$) ν 2960, 1735, 1370, 1090, 900 cm^{-1} (selected values). Anal. Calcd for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 66.88; H, 9.80; N, 7.01.

(*S*)-(+)-3-(Benzyloxy)-2-methylpropionaldehyde (6) (Scheme IV) (100% ee). Enantiomerically pure aldehyde **6** was prepared from (*R*)-(−)-methyl 3-hydroxy-2-methylpropionate (Aldrich) according to the procedure reported in ref 19 and used without further purification: $[\alpha]^{25}_D$ +28.4° (c 1.0, $CHCl_3$) [lit.[6c] $[\alpha]^{25}_D$ +28.4° (c 1.56, $CHCl_3$)].

***tert*-Butyl Thiobutyrate.** A solution of pyridine (22 mL) in chloroform (100 mL) at 0 °C was treated dropwise with butyryl chloride (28.78 mL) during 1 h. Then *tert*-butyl thioalcohol (26.7 mL) was slowly added at 0 °C during 3 h, and the mixture was stirred at room temperature for 3 days. The mixture was then quenched with water, and the organic phase was washed with 5% HCl, 5% $NaHCO_3$, water, dried, and evaporated. The crude product was distilled at reduced pressure (65 °C/20 mmHg) to give the desired compound in 71% yield: ^1H NMR ($CDCl_3$) δ 0.9 (t, 3 H, J = 7.3 Hz), 1.45 (s, 9 H), 1.30–1.85 (m, 2 H), 2.40 (t, 2 H, J = 7.3 Hz). Anal. Calcd for $C_8H_{16}OS$: C, 59.95; H, 10.06. Found: C, 59.87; H, 10.10.

***E* and *Z* Silyl Ketene Acetals 19 and 20.** These compounds were prepared from *tert*-butyl thiobutyrate according to the general procedure reported in ref 20. **19**: ^1H NMR ($E/Z \geq 95:5$)[21] δ 0.19 (s, 6 H), 0.95 (s, 9 H), 0.95 (t, 3 H, J = 7.3 Hz), 1.32 (s, 9 H), 2.08 (quint, 2 H, J = 7.3 Hz), 5.18 (t, 1 H, J = 7.3 Hz). **20**: ^1H NMR ($Z/E \geq 95:5$)[21] δ 0.16 (s, 6 H), 0.95 (s, 9 H), 0.95 (t, 3 H, J = 7.3 Hz), 1:38 (s, 9 H), 2.20 (quint, 2 H, J = 7.3 Hz), 5.27 (t, 1 H, J = 7.3 Hz).

Aldol Condensation Product 21. A solution of enantiomerically pure aldehyde **6** (0.946 g, 5.28 mmol) in methylene chloride (12 mL) at −78 °C, under nitrogen, with stirring, was treated during 10 min with a 1.0 M solution of $TiCl_4$ in methylene chloride (5.28 mL). Immediately after, the silyl ketene acetal **19** (2.17 g, 7.92 mmol) was added dropwise during 10 min and the mixture was stirred at −78/−80 °C for 1.5 h. The reaction was then quenched with 1 N KOH and filtered through Celite. The aqueous phase was extracted with methylene chloride, and the combined organic extracts were dried and evaporated. The crude product was analyzed by ^1H and ^{13}C NMR spectroscopy and flash chromatographed twice (*n*-hexane–ethyl acetate 85:15 and benzene–ethyl ether 95:5) to give the pure aldol condensation product as a 99:1 mixture of stereoisomers (80% yield): IR ($CHCl_3$) ν 3480, 2960, 1665, 1450, 1360, 1080, 970 cm^{-1} (selected values); ^1H NMR ($CDCl_3$) δ 0.94 (t, 3 H, J = 7.5 Hz), 1.06 (d, 3 H, J = 7.0 Hz), 1.445 and 1.457 (s, 8.91 H and s, 0.09 H), 1.76 (quint, 2 H, J = 7.5 Hz), 1.80–1.95 (m, 1 H), 2.50 (q, 1 H, J = 7.0 Hz), 3.26 (d, 1 H, J = 6.0 Hz, exchangeable with D_2O), 3.54 (A part of an ABX system, 1 H, J = 4.0, 9.5 Hz), 3.67 (q, 1 H, J = 6.0 Hz), 3.78 (B part of an ABX system, 1 H, J = 4.5, 9.5 Hz), 4.51 (s, 2 H), 7.25–7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ [10.78 (1%), 11.92 (99%)], 15.24, 21.17, 29.69, 35.81, [46.80 (1%), 48.25 (99%)], 59.86, 73.13, 73.47, 75.95, 127.67, 127.73, 128.42, 137.91, 203.73. Anal. Calcd for $C_{19}H_{30}O_3S$: C, 67.42; H, 8.93. Found: C, 67.39; H, 8.99. Analogously, reaction with silyl ketene acetal **20** gave the aldol condensation product as a 96:3:1 mixture of stereoisomers (75% yield): ^1H NMR ($CDCl_3$, selected values) δ 1.445 (s, 8.64 H), 1.457 (s, 0.27 H), 1.470 (s, 0.09 H).

***N*-Methoxyazetidinone 17 (Scheme IV).** A solution of the aldol condensation product **21** (1.10 g, 3.33 mmol) in 4:1 acetonitrile–water (17.7 mL) was treated with $Hg(OCOCF_3)_2$ (1.563 g, 3.663 mmol). The mixture was stirred at 60–65 °C for 3 h. More $Hg(OCOCF_3)_2$ (0.426 g, 1.0 mmol) was added and the mixture was stirred at 60–65 °C for additional 3 h. Then the mixture was cooled to room temperature, diluted with ethyl acetate (50 mL), and filtered through Celite, washing the Celite cake with ethyl acetate (80 mL). The solution was then treated with H_2S (10 min bubbling) and filtered again through Celite. The resulting solution was evaporated to give a crude compound, which was purified by flash chromatography (CH_2Cl_2–MeOH from 93:7 to 70:30) to give acid **15** (70–85% yield) contaminated by variable amounts (0–15%) of Hg-containing byproducts. Via the procedure described for the preparation of **10**, this compound was transformed into hydroxamate **16** (70% yield) contaminated by variable amounts of Hg-containing byproducts. Hydroxamate **16** was then transformed into *N*-methoxyazetidinone **17** via the procedure described for the preparation of **11**; flash chromatography (*n*-hexane–ethyl acetate 75:25) gave pure **17** in 60–65% yield: ^1H

NMR ($CDCl_3$) δ 0.99 (t, 3 H, J = 7.5 Hz), 1.06 (d, 3 H, J = 6.3 Hz), 1.48–1.80 (m, 2 H), 2.08 (m, 1 H, J = 6.3 Hz), 2.66 (ddd, 1 H, J = 2.2, 6.3, 7.5 Hz), 3.40 (d, 2 H, J = 6.3 Hz), 3.63 (dd, 1 H, J = 2.2, 6.3 Hz), 3.72 (s, 3 H), 4.48, 4.49 (AB system, 2 H, J = 12.2 Hz), 7.25–7.40 (m, 5 H); ^{1}H NMR [$CDCl_3$ + Eu(hfc)$_3$] of **17** obtained from silyl ketene acetal **20**, δ 5.62 (≥96%, MeO, s), 5.68 (≤4%, MeO, s); ^{1}H NMR [$CDCl_3$ + Eu(fod)$_3$] of **17** obtained from silyl ketene acetal **20**, δ 5.56 (≥96%, MeO, s), 5.45 (1%, MeO, s), 5.33 (≤3%, MeO, s); ^{1}H NMR [$CDCl_3$ + Eu(hfc)$_3$] of **17** obtained from silyl ketene acetal **19**, δ 6.37 (≥90%, MeO, s), 6.45 (≤10%, MeO, s); ^{1}H NMR [$CDCl_3$ + Eu(fod)$_3$] of **17** obtained from silyl ketene acetal **19**, δ 6.10 (>99%, MeO, s).

Synthesis of Benzobicyclo[3.2.1]octanes Involving Inversion of Configuration via an N to O Acetyl Migration[1]

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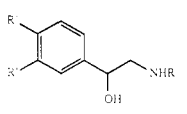
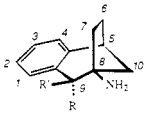
Two conformationally defined analogues of phenylethanolamine, 8-amino-6,7,8,9-tetrahydro-5,8-methano-5*H*-benzocyclohepten-*endo*-9-ol (**5**) and 8-amino-6,7,8,9-tetrahydro-5,8-methano-5*H*-benzocyclohepten-*exo*-9-ol (**6**), have been synthesized. The benzobicyclo[3.2.1]octane skeleton was constructed by an intramolecular cyclization of 3-phenylcyclopentane-1,1-dicarboxylic acid (**10**). The sodium borohydride reduction of 8-amino-9-oxo-6,7,8,9-tetrahydro-5,8-methano-5*H*-benzocycloheptene (**12**) gave the endo alcohol **5**. The greater stability of the exo alcohol **6** compared to **5** was confirmed by AM1 calculations. The exo alcohol **6** was obtained from **5** by an N to O acetyl migration. A possible mechanism for this migration in the inversion of the stereochemistry at C-9 is discussed. Structural assignments using 2-D NMR spectra and an NOE difference spectrum are presented.

Epinephrine (**1**) is synthesized by phenylethanolamine *N*-methyltransferase (PNMT) from norepinephrine (**2**). As part of a continuing study to explore the binding requirements at the active site of PNMT for both substrates and inhibitors,[2,3] we had need of compounds **5** and **6** with the benzobicyclo[3.2.1]octane skeleton. These amines were designed as conformationally defined analogues of phenylethanolamine (**3**), a good substrate of PNMT.



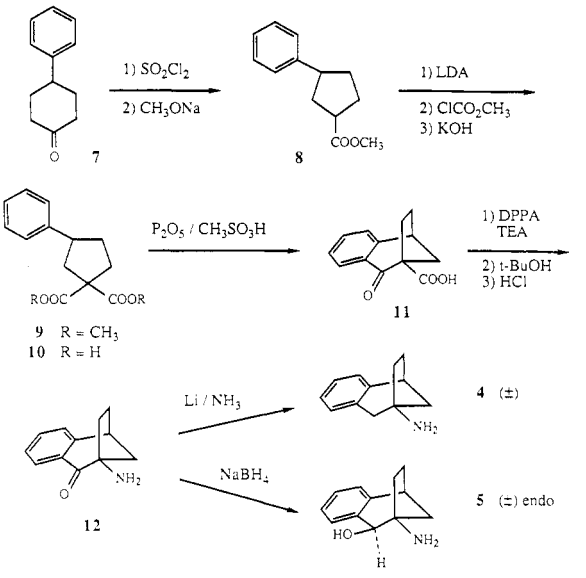
1 R = Me, R' = OH
2 R = H, R' = OH
3 R = R' = H



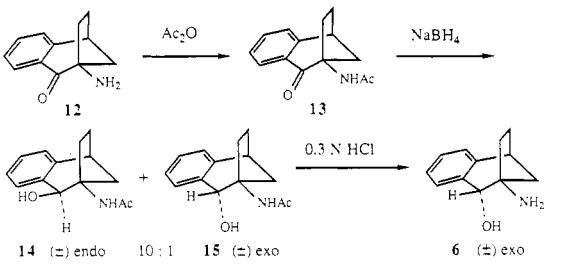
4 R = R' = H (±)
5 R = H, R' = OH (±) endo
6 R = OH, R' = H (±) exo

Although several synthetic approaches to benzobicyclo[3.2.1]octanes are available, only a few compounds with substitution at bridgehead position 8 in this ring system were known.[4,5] Entry into this ring system via rearrangement of the benzobicyclo[2.2.2]octane ring system has been studied by us[4] and by others.[6] Boger and Mullican[7] proposed a novel approach to this ring system in which the aliphatic portion was constructed prior to an aromatic annulation sequence. Considering the availability of starting material and our specific targets, we developed

Scheme I



Scheme II



(1) (a) Presented in part at the 194th National Meeting of the American Chemical Society, New Orleans, LA, Aug 30–Sept 4, 1987. (b) Paper 13 in our series "Conformationally Defined Adrenergic Agents"; for paper 12, see: Grunewald, G. L.; Sall, D. J.; Monn, J. A. *J. Med. Chem.* **1988**, *31*, 433.

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