Synthetic Studies of Carbapenem and Penem Antibiotics. VI.[1] Stereoselective Reduction of Enamino Ketone and Lactonization of the Reduction Product for the Synthesis of 1β-Methylcarbapenem

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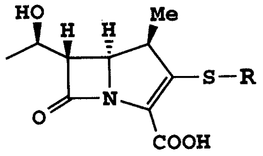
Received July 6, 1994; accepted August 22, 1994

The synthesis of the 1β-methylcarbapenem key intermediate 2 from the enamino ketone 6 was investigated. Stereoselective reduction of 6 and effective lactonization of the crude reduction product are described. The methyl group in 6 was shown to play an important role in these steps.

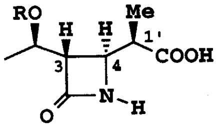
Keywords enamino ketone; stereoselective reduction; δ-lactone; 3-(1-hydroxyethyl)-2-azetidinone; 1β-methylcarbapenem

Much effort has been directed toward the synthesis of 1β-methylcarbapenem antibiotics (**1**), because of their excellent characteristics; good chemical and metabolic stability, in addition to potent and broad-spectrum antibacterial activity.[2] In the synthesis of **1**, a (3*S*,4*S*)-4-[(*R*)-1-carboxyethyl]-3-[(*R*)-1-hydroxyethyl]-2-azetidinone derivative (**2**) is a key intermediate, and a number of synthetic methods for **2** have been developed.[3] In the practical synthesis of thienamycin starting from 1,3-acetonedicarboxylate, Melillo *et al.* reported that reduction of the enamino ketone (**3a**) proceeded stereoselectively to afford the amino alcohol (**4**) as an all-*syn* single isomer, which was easily converted to the δ-lactone (**5**) by treatment with hydrogen chloride.[4] We considered that this method would be applicable to a practical synthesis of 1β-methylcarbapenems, if the reduction of **6** stereoselectively afforded an all-*syn* amino alcohol isomer. Therefore, we initiated studies on the approach to racemic **2** from the enamino ketone (**6**) by the application of Melillo's method and found that the methyl group in **6** played a significant role not only in the stereoselective reduction of dimethyl 2-acetyl-3-benzylamino-4-methyl-2-pentenedioate (**6**), but also in the formation of the δ-lactone (**8**) from the amino alcohol (**7**). The present paper describes these results.

Stereoselective Reduction of the Enamino Ketone (6) The reduction of **6**, which was easily prepared from dimethyl 2-acetyl-3-benzylamino-2-pentenedioate (**3b**) by treatment with methyl iodide and sodium hydride in tetrahydrofuran (THF) at 45°C, was carried out with



1



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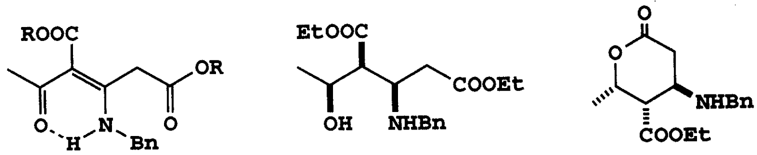
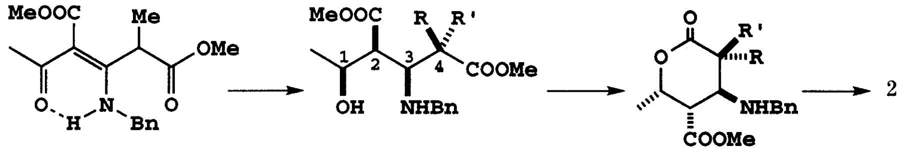


3a: R=Et
3b: R=Me

4

5

Fig. 1



6

7a: R=Me, R'=H
7b: R=H, R'=Me

8a: R=Me, R'=H
8b: R=H, R'=Me

Chart 1

$NaBH_3CN$ (2.0 eq) in AcOH at 10 °C for 2 h to give the saturated amino alcohol as a mixture of two isomers (**7a** and **7b**) in 77% yield. The ratio of the two isomers was determined to be 3 : 1 based on the integration of the H-3 signal in the ^{1}H-NMR spectrum, and no other isomers could be observed. The stereochemistry at C1, C2 and C3 in **7a** and **7b** was expected to be all-*syn* from literature precedents, and the relative configuration of C3 and C4 was assigned as *syn* in **7a** and *anti* in **7b** on the basis of the coupling constant between H-3 and H-4 in the ^{1}H-NMR spectra. The stereochemistry of **7a** and **7b** was confirmed by transforming **7a,b** into a mixture of azetidinones (**10a** and **10b**) as follows. It was reported that aqueous barium hydroxide in THF hydrolyzed a less hindered ester more rapidly,[5] so the selective saponification of the 3 : 1 mixture of **7a** and **7b** was examined with $Ba(OH)_2$. As expected, the sterically congested ester was not hydrolyzed and a mixture of terminal carboxylic acids (**9a** and **9b**) was obtained in 50% yield. The ratio of **9a** and **9b** was 10 : 3 by ^{1}H-NMR analysis. Subsequently, the mixture of **9a** and **9b** was cyclized with 2,2′-dipyridyl disulfide and triphenylphosphine[6] to afford a mixture of **10a** and **10b** in 62% yield and in the ratio of 7 : 2 on the basis of the ^{1}H-NMR spectrum. Comparing the NMR spectra of **10a** and **10b** in the mixture, the coupling constant between H-3 and H-4 of the major product (**10a**) was 5.3 Hz, which showed that **10a** was a *cis*-β-lactam, while that of the minor product (**10b**) was 2.0 Hz, showing a *trans*-β-lactam. Consequently, **7a** was the (all-*syn*) compound and **7b** was the (*syn*-*syn*-*anti*) compound (Chart 2).

In order to improve the stereoselectivity, we attempted the reduction at lower temperature using catecholborane[4c] and then $NaBH_3CN$ in AcOH. Treatment of **6** with catecholborane (1.1 eq) in THF at −78 °C gave the 1,4-adduct (**11**), whose NMR spectrum showed it to be almost the sole product. Subsequently **11** was subjected to further reduction with $NaBH_3CN$ (2 eq) in AcOH at 10 °C to afford a 98 : 2 mixture of **7a** and **7b** in 80% yield from **6** (Chart 3).

From these results, the stereoselectivity of reduction was due to the effect of the methyl substituent at C4, but it could not be explained just in terms of the formation of a rigid hydrogen-bond in the enamino ketone moiety of **6**. It seemed that a bicyclic chelation system as shown in **6′** was constructed in the reduction step, and the steric hindrance of the methyl group caused the higher stereoselectivity in the rigid system.

Lactonization of the Amino Alcohols When HCl gas was passed through a solution of the 3 : 1 mixture of **7a** and **7b** in CH_2Cl_2 at room temparature, the desired lactone (**8a**) was obtained as a sole product, which was isolated as its HCl salt by crystallization from Et_2O in 65% yield (87% yield from **7a**).[7] The other stereoisomer (**8b**) was not observed in the reaction mixture. This result showed that the course of the lactonization could be controlled by the stereochemistry of the methyl group and kinetic separation of **7a** and **7b** could be easily achieved. Consequently, **8a** was obtained from **6** without purification by column chromatography. The relative configuration of **8a** was determined by leading **8a** to the azetidinone (**10**) using the same procedure as described above, after ring cleavage by treatment with $Ba(OH)_2$. The obtained

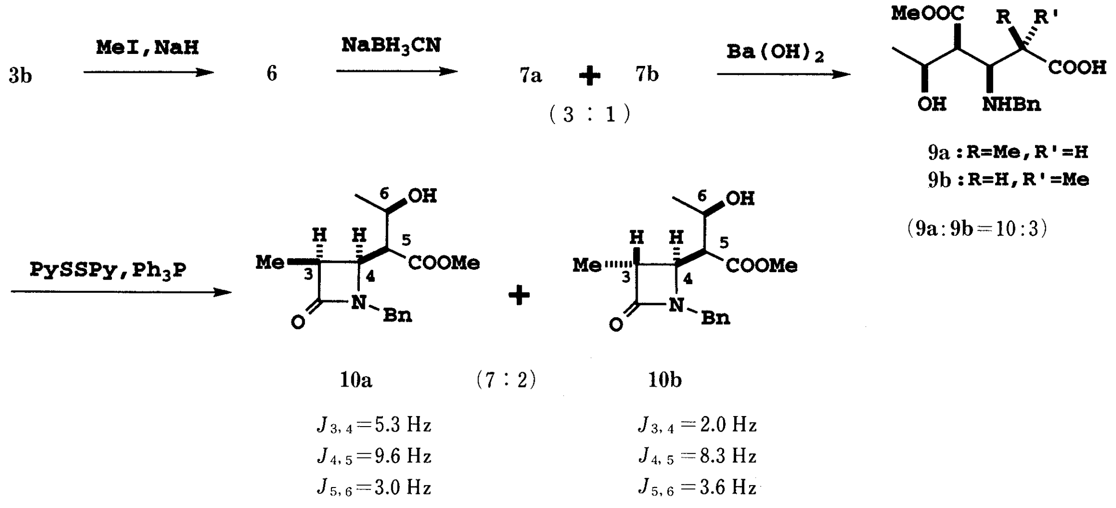


Chart 2

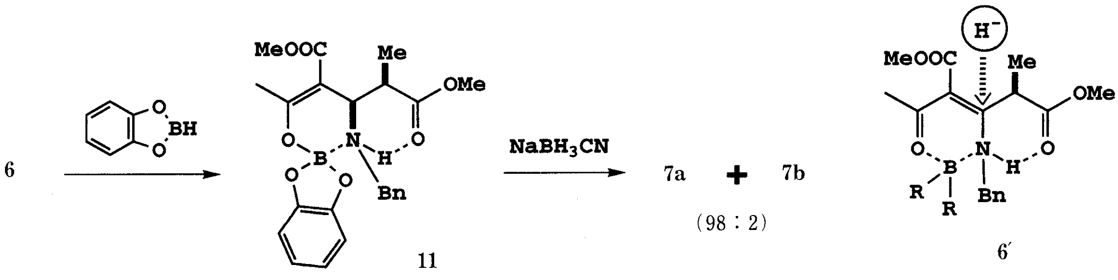
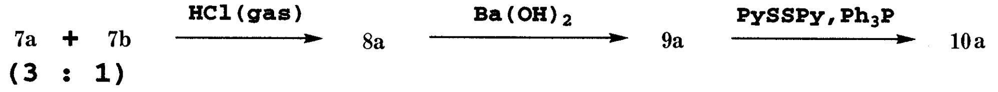
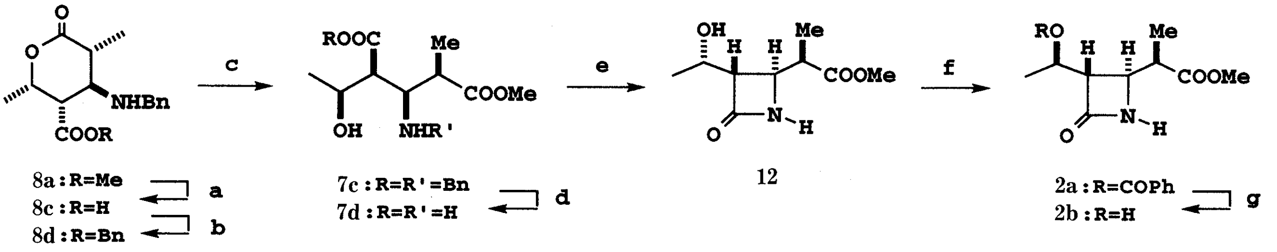


Chart 3



$$\underset{(3\ :\ 1)}{7a + 7b} \xrightarrow{HCl(gas)} 8a \xrightarrow{Ba(OH)_2} 9a \xrightarrow{PySSPy, Ph_3P} 10a$$

Chart 4



reagents: (a) conc HCl; (b) BnBr, NEt_3; (c) i) $Ba(OH)_2$, ii) MeI, NEt_3, (d) H_2/Pd-C; (e) DCC; (f) PhCOOH, Ph_3P, DEAC; (g) NaOMe

Chart 5

azetidinone was identical with **10a** derived from **7a**. It was found that **8a** possessed the desired relative configuration for the synthesis of **2**, except for that of the hydroxy group (Chart 4).

Finally the stereochemistry of **7a** and **8a** was confirmed by transforming them into the known key intermediate (**2**). The conversion of **8a** to **2** was accomplished as shown in Chart 5. Acid hydrolysis of **8a** with concentrated HCl followed by esterification with benzyl bromide gave the benzyl ester (**8d**) in 63% yield from **8a**. Conversion of **8d** to the amino acid (**7d**) was achieved in 72% yield by hydrolysis with $Ba(OH)_2$, esterification and then hydrogenolysis over Pd–C. Cyclization of **7d** with dicyclohexylcarbodiimide (DCC) afforded the azetidinone (**12**) in 60% yield. The inversion of hydroxyl group was performed by using the Mitsunobu reaction[8)] to give the benzoate (**2a**), which was then treated with sodium methoxide in a mixture of CH_3CN and MeOH to afford the racemic 3-[1-hydroxyethyl]-2-azetidinone (**2b**) in 64% yield from **12**. The spectral data of **2b** were identical with reported values.[7a)]

Conclusion

We have demonstrated that the synthetic route to thienamycin starting from 1,3-acetonedicarboxylate was applicable to a practical synthesis of 1β-methylcarbapenems (**1**). Owing to the effect of the methyl group, the reduction of the enamino ketone (**6**), which is the key step of this route, proceeded stereoselectively to give the desired amino alcohol (**7a**). Furthermore, the isomerically pure lactone (**8a**) was easily isolated as crystals after lactonization of the crude reduction product. The highly stereoselective reduction of **6** strongly suggested the formation of a bicyclic ring system (**6'**) by chelation.

A synthetic study of optically active analogues of **2** using this established procedure will be reported in the near future.

Experimental

Melting points were determined with a Thomas-Hoover capillary melting points apparatus without correction. Infrared (IR) spectra were measured with a Hitachi 260-10 spectrophotometer. ^{1}H-NMR spectra were recorded with a JEOL GX-270 FT spectrometer in the designated solvent using tetramethylsilane as an internal reference. Thin layer chromatography (TLC) was performed on Silica gel 60 F_{254} TLC plates (E. Merck). Column chromatography was done on Silica gel 60 (70—230 mesh, E. Merck). The organic solutions were dried over $MgSO_4$ before vacuum evaporation.

Dimethyl 2-Acetyl-3-benzylamino-4-methyl-2-pentene-dioate (6) A solution of dimethyl 2-acetyl-3-benzylamino-2-pentenedioate (**3b**) (6.2 g, 20 mmol) in THF (10 ml) was added dropwise to a suspension of 60% NaH (1.68 g, 42 mmol) in THF (10 ml) with ice-cooling and the mixture was stirred for 15 min. Then methyl iodide (5.68 g, 40 mmol) was added. Stirring was continued for 1 h at room temperature and then at 40 °C for 1 h. After addition of water to quench the reaction, the reaction mixture was diluted with EtOAc. The organic layer was washed with water, 1 N HCl and brine. Drying followed by evaporation and purification of the residue by silica gel chromatography gave **6** (5.0 g, 78%). mp 123.5—124 °C. IR (neat): 1735, 1698 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.43 (3H, d, J=6.9 Hz), 2.30 (3H, s), 3.61 (3H, s), 3.71 (3H, s), 3.95 (1H, q, J=6.9 Hz), 4.49 (2H, m), 7.22—7.39 (5H, m). *Anal.* Calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.86; H, 6.40; N, 4.82.

Mixture of Dimethyl (2*SR*,3*RS*,4*RS*)- and (2*SR*,3*RS*,4*SR*)-2-[1(*SR*)-Hydroxyethyl]-3-benzylamino-4-methylpentanedioate (7a and 7b) ⟨Method A⟩ A solution of **6** (15 g, 47 mmol) in AcOH (180 ml) was added dropwise to a solution of $NaBH_3CN$ (5.90 g, 94 mmol) in AcOH (180 ml) at 10 °C and the mixture was stirred at the same temperature for 2 h. After removal of AcOH under reduced pressure, the oily residue was dissolved in EtOAc and washed with 5% $NaHCO_3$ three times and then brine. Drying followed by evaporation and purification of the residue by silica gel chromatography gave a mixture of **7a** and **7b** (11.7 g, 77%, **7a** : **7b** = 3 : 1 by ^{1}H-NMR analysis). IR (neat): 3340, 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) of **7a** δ: 1.18 (3H, d, J=6.9 Hz), 1.23 (3H, d, J=6.6 Hz), 2.57 (1H, dd, J=2.3, 4.0 Hz, 2-H), 3.03 (1H, m, 4-H), 3.14 (1H, t, J=4.6 Hz, 3-H), 3.70 (6H, s), 4.02 (1H, m). ^{1}H-NMR ($CDCl_3$) of **7b** δ: 2.53 (1H, dd, J=2.6, 4.3 Hz, 2-H) 2.89 (1H, m, 4-H) 3.32 (1H, dd, J=4.3, 6.9 Hz, 3-H).

⟨Method B⟩ A 0.55 N THF solution of catecholborane (0.2 ml) was added dropwise to a solution of **6** (32 mg, 0.10 mmol) in THF (0.1 ml) at −78 °C and the mixture was stirred at the same temperature for 2 h. The reaction mixture was warmed to room temperature, then concentrated *in vacuo* to give 1,4-adduct (**11**) ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H, d, J=7.3 Hz), 2.44 (3H, s), 3.27 (1H, m), 3.60 (3H, s), 3.69 (3H, s). The residue was dissolved in AcOH (0.1 ml), and $NaBH_3CN$ (13 mg, 0.2 mmol) was added at 10 °C. The mixture was stirred at 10 °C for 1 h and at room temperature for 1.5 h. After removal of AcOH under reduced pressure, the residue was dissolved in $CHCl_3$ and washed with 5% $NaHCO_3$ six times and with brine. Drying followed by evaporation and purification of the residue by silica gel chromatography gave a mixture of **7a** and **7b** (26 mg, 80%, **7a** : **7b** = 98 : 2 by ^{1}H-NMR analysis).

Methyl (2*SR*,3*SR*,4*RS*,5*RS*)-Tetrahydro-2,5-dimethyl-6-oxo-4-benzyl-

amino-2*H*-pyrane-3-carboxylate Hydrochloride (8a) Gaseous hydrogen chloride was passed through a solution of the 3 : 1 mixture **7a** and **7b** (5.90 g, 18.3 mmol) in CH_2Cl_2 (50 ml) for 1 h at room temperature and the whole was stirred for 1 h. After evaporation, the residue was crystallized from Et_2O to give **8a** as crystals (3.89 g, 65%). mp 159.5—161 °C (dec.). IR (neat): 1728 cm^{-1}. ^{1}H-NMR ($CDCl_3$) 8: 1.34 (3H, d, J=6.9 Hz), 1.43 (3H, d, J=6.6 Hz), 2.38 (1H, m), 2.81 (1H, dd, J=2.0, 3.0 Hz), 3.02 (1H, dd, J=2.0, 6.3 Hz), 3.71 (3H, s), 3.80 (2H, ABq), 4.74 (1H, dq, J=3.0, 6.6 Hz), 7.24—7.37 (5H, m). *Anal.* Calcd for $C_{16}H_{22}NO_4Cl$: C, 58.62; H, 6.76; N, 4.27. Found: C, 58.54; H, 6.75; N, 4.35.

(2*RS*,3*RS*,4*SR*,5*SR*)-2-Methyl-3-benzylamino-4-methoxycarbonyl-5-hydroxyhexanoic Acid (9a) A suspension of **8a** (0.98 g, 3.0 mmol) and $Ba(OH)_2$–$8H_2O$ (1.99 g, 6.3 mmol) in THF (20 ml) and water (10 ml) was vigorously stirred at room temperature for 1.5 h. Insoluble materials were removed by filtration and washed with EtOH. The filtrate and washings were combined and acidified with 6 N HCl (pH 4—5). After evaporation, the oily residue was purified by preparative TLC ($CHCl_3$: MeOH = 9 : 1) to give **9a** (0.68g, 73%). IR (Nujol): 3300, 1715 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, d, J=6.6 Hz), 1.27 (3H, d, J=6.3 Hz), 2.63 (1H, t, J=3.0 Hz), 3.17 (1H, m), 3.84 (1H, dq, J=3.0, 6.3 Hz), 3.71 (3H, s), 3.94 (2H, ABq), 7.26—7.38 (5H, m).

(3*SR*,4*SR*)-1-Benzyl-4-[1-methoxycarbonyl-2(*SR*)-hydroxy]propyl-3-methyl-2-azetidinone (10a) A solution of **9a** (14 mg, 0.046 mmol), 2,2′-dipyridyl disulfide (14 mg, 0.064 mmol) and triphenylphosphine (19 mg, 0.073 mmol) in CH_3CN (3.5 ml) was stirred for 5 h at 80 °C. After cooling to room temperature and evaporation, the residue was purified by preparative TLC ($CHCl_3$: acetone = 3 : 1) to give **10a** (9 mg, 67%). IR (neat): 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.21 (3H, d, J=6.6 Hz), 1.31 (3H, d, J=7.6 Hz), 2.69 (1H, dd, J=3.0, 9.6 Hz, H-5), 3.44 (1H, m, H-3), 3.58 (3H, s), 3.88 (1H, m, H-6), 3.99 (1H, d, J=15.5 Hz), 4.16 (1H, dd, J=5.3, 9.6 Hz, H-4), 4.55 (1H, d, J=15.5 Hz).

Mixture of (3*SR*,4*SR*)- and (3*RS*,4*SR*)-1-Benzyl-4-[1-methoxycarbonyl-2(*SR*)-hydroxy]propyl-3-methyl-2-azetidinone (10a and 10b) A suspension of the 3 : 1 mixture of **7a** and **7b** (130 mg, 0.4 mmol) and $Ba(OH)_2$–$8H_2O$ (0.25 g, 0.8 mmol) in THF (4 ml) and water (2 ml) was vigorously stirred at room temperature for 45 min. The same work-up as described for the preparation of **9a** from **8a** gave a mixture of the amino acids **9a** and **9b** (62 mg, 50%, **9a** : **9b** = 10 : 3 by ^{1}H-NMR analysis). ^{1}H-NMR ($CDCl_3$) of **9b** δ: 1.22 (3H, d, J=6.6 Hz), 3.69 (3H, s). The mixture of **9** was treated with 2,2′-dipyridyl disulfide (60 mg, 0.27 mmol) and triphenylphosphine (78 mg, 0.3 mmol) in CH_3CN (12 ml) in the same manner as described for the preparation of **10a** from **9a** to afford a mixture of **10a** and **10b** (36 mg, 62%, **10a** : **10b** = 7 : 2 by ^{1}H-NMR analysis). ^{1}H-NMR ($CDCl_3$) of **10b** δ: 1.33 (3H, d, J=7.3 Hz), 2.53 (1H, dd, J=3.6, 8.3 Hz, H-5), 3.12 (1H, dq, J=2.0, 7.6 Hz, H-3), 3.60 (1H, dd, J=2.0, 8.3 Hz, H-4), 3.60 (3H, s), 4.62 (1H, d, J=15.5 Hz).

(2*SR*,3*SR*,4*RS*,5*RS*)-Tetrahydro-2,5-dimethyl-6-oxo-4-benzylamino-2*H*-pyrane-3-carboxylic Acid Hydrochloride (8c) **8a** (2.0 g, 6.1 mmol) was heated with concentrated HCl (18 ml) at 90 °C for 3 h. After cooling to room temperature, the precipitate was collected by filtration, washed with concentrated HCl (1.5 ml × 2) and dried *in vacuo* to give **8c** (1.47 g, 77%) as a colorless solid. mp 160—164 °C (dec.). IR (neat): 1722 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 1.37 (3H, d, J=6.6 Hz), 1.53 (3H, d, J=6.6 Hz), 3.07 (1H, m), 3.65 (1H, dd, J=2.0, 8.6 Hz), 4.40 (2H, ABq), 5.04 (1H, m), 7.47—7.57 (5H, m). *Anal.* Calcd for $C_{15}H_{20}NO_4Cl$: C, 57.42; H, 6.42; N, 4.46. Found: C, 57.29; H, 6.37; N, 4.65.

Benzyl (2*SR*,3*SR*,4*RS*,5*RS*)-Tetrahydro-2,5-dimethyl-6-oxo-4-benzylamino-2*H*-pyrane-3-carboxylate (8d) A mixture of **8c** (174 mg, 0.55 mmol), benzyl bromide (162 mg, 0.95 mmol) and Et_3N (127 mg, 1.26 mmol) in *N*,*N*-dimethylformamide (DMF) (5 ml) was stirred for 20 h at room temperature. The reaction mixture was diluted with EtOAc, then washed with 1 N HCl and water. Drying followed by evaporation and purification of the residue by silica gel chromatography gave **8d** (166 mg, 82%). IR (neat): 1728 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.29 (3H, d, J=6.6 Hz), 1.39 (3H, d, J=6.6 Hz), 2.37 (1H, m), 2.82 (1H, dd, J=2.3, 3.0 Hz), 3.00 (1H, dd, J=3.0, 8.6 Hz), 3.76 (2H, ABq), 4.73 (1H, dq, J=3.0, 6.6 Hz), 5.15 (2H, ABq), 7.25—7.34 (10H, m).

Methyl (2*RS*,3*RS*,4*SR*,5*SR*)-2-Methyl-3-benzylamino-4-benzyloxycarbonyl-5-hydroxyhexanoate (7c) A suspension of **8d** (92 mg, 0.25 mmol) and $Ba(OH)_2$–$8H_2O$ (213 mg, 0.68 mmol) in THF (4 ml) and water (2 ml) was vigorously stirred at room temperature for 2.5 h. The same work-up as described for the preparation of **9a** from **8a** gave an oily residue, which was dissolved in DMF (5 ml). Methyl iodide (40 mg, 0.28 mmol) and Et_3N (30 mg, 0.3 mmol) were added to the DMF solution and the whole was stirred at room temperature overnight. The reaction mixture was diluted with water and extracted with EtOAc. The extract was washed with water and brine. Drying followed by evaporation and purification of the residue by preparative TLC gave **7c** (72 mg, 72%). IR (neat): 3340, 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.17—1.22 (6H, m), 2.19 (1H, s), 2.61 (1H, dd, J=2.3, 4.0 Hz), 2.96—3.03 (1H, m), 3.18 (1H, t, J=4.6 Hz), 3.64 (3H, s), 3.72 (1H, d), 4.01—4.07 (2H, m), 5.11 (2H, ABq), 7.22—7.38 (10H, m).

Methyl (2*RS*,3*RS*,4*SR*,5*SR*)-2-Methyl-3-amino-4-carboxy-5-hydroxyhexanoate (7d) A suspension of **7c** (123 mg, 0.31 mmol) and 10% Pd–C (123 mg) in MeOH (10 ml) was stirred under a hydrogen atmosphere for 2.5 h. The catalyst was filtered off and the filtrate was concentrated *in vacuo* to give **7d** (68 mg, quantitative). IR (neat): 3300, 1722 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, d, J=7.3 Hz), 1.31 (3H, d, J=6.3 Hz), 2.42 (1H, m), 3.00 (1H, m), 3.73 (3H, s), 4.11 (1H, m), 4.90 (1H, br s).

(3*SR*,4*SR*)-3-[1(*SR*)-Hydroxyethyl]-4-[1(*RS*)-methoxycarbonyl]ethyl-2-azetidinone (12) DCC (40 mg, 0.19 mmol) was added to a solution of **7d** (40 mg, 0.18 mmol) in CH_3CN (2.0 ml) and the whole was stirred for 3 h at 60 °C, then diluted with EtOAc, and the insoluble material was removed by filtration. The filtrate was concentrated *in vacuo* and the residue was purified by preparative TLC to give **12** (22 mg, 60%). IR (neat): 3410, 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, d, J=7.3 Hz), 1.33 (3H, d, J=6.3 Hz), 2.67 (1H, m), 3.06 (1H, dd, J=2.3, 5.9 Hz), 3.69 (1H, d, J=2.3 Hz), 3.71 (3H, s), 4.11 (1H, m), 6.11 (1H, br s).

(3*SR*,4*SR*)-3-[1(*RS*)-Benzoyloxyethyl]-4-[1(*RS*)-methoxycarbonyl]ethyl-2-azetidinone (2a) Benzoic acid (27 mg, 0.22 mmol) was added to a solution of **12** (36 mg, 0.18 mmol) and triphenylphosphine (70 mg, 0.27 mmol) in THF (2.0 ml) with ice-cooling and the mixture was stirred for 5 min. After addition of diethylazodicarboxylate (41 mg, 0.24 mmol), stirring was continued at room temperature for 3 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by preparative TLC to give **2a** (51 mg, 93%). IR (neat): 3331, 1772, 1734, 1718 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, d, J=6.9 Hz), 1.48 (3H, d, J=6.3 Hz), 2.73 (1H, m), 3.33 (1H, m), 3.63 (3H, s), 3.89 (1H, dd, J=2.2, 6.1 Hz), 5.50 (1H, m), 6.16 (1H, br s), 7.44 (2H, dd, J=7.6, 8.3 Hz), 7.57 (1H, dd, J=1.5, 7.6 Hz), 8.02 (2H, dd, J=1.5, 8.3 Hz).

(3*SR*,4*SR*)-3-[1(*RS*)-Hydroxyethyl]-4-[1(*RS*)-methoxycarbonyl]ethyl-2-azetidinone (2b) A 10% MeOH solution of sodium methoxide (108 mg, 0.2 mmol) was added dropwise to a solution of **2a** (51 mg, 0.17 mmol) in CH_3CN (1.5 ml) with ice-cooling and the mixture was stirred for 3 h, then diluted with EtOAc, and washed with brine, 0.2 N HCl and brine. Drying followed by evaporation and purification of the residue by preparative TLC gave **2b** (23 mg, 69%). IR (neat): 3406, 1734 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, d, J=6.9 Hz), 1.31 (3H, d, J=6.3 Hz), 2.67 (1H, m), 2.98 (1H, dd, J=2.0, 6.6 Hz), 3.73 (3H, s), 3.77 (1H, dd, J=2.0, 7.3 Hz), 4.16 (1H, m), 6.07 (1H, br s).

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