

ENANTIOSELECTIVE SYNTHESIS OF (R)- AND (S)-4-[(METHOXYCARBONYL)-
METHYL]-2-AZETIDINONES FROM D-GLYCERALDEHYDE ACETONIDE

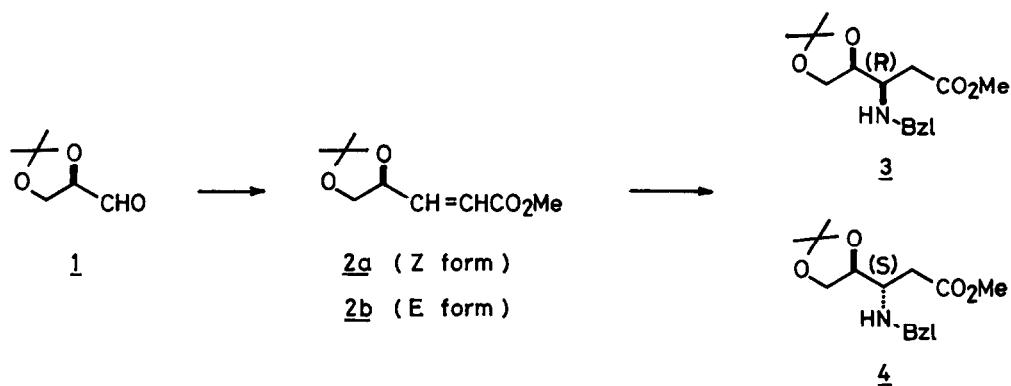
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Summary: (R)-N-Benzyl-4-[(methoxycarbonyl)methyl]-2-azetidinone (10) and (S)-4-[(methoxycarbonyl)methyl]-2-azetidinone (17) were enantioselectively synthesized from the benzylamino ester 3, which was prepared by the highly stereoselective 1,4-addition of benzylamine to the α,β -unsaturated ester 2 derived from D-glyceraldehyde acetonide (1).

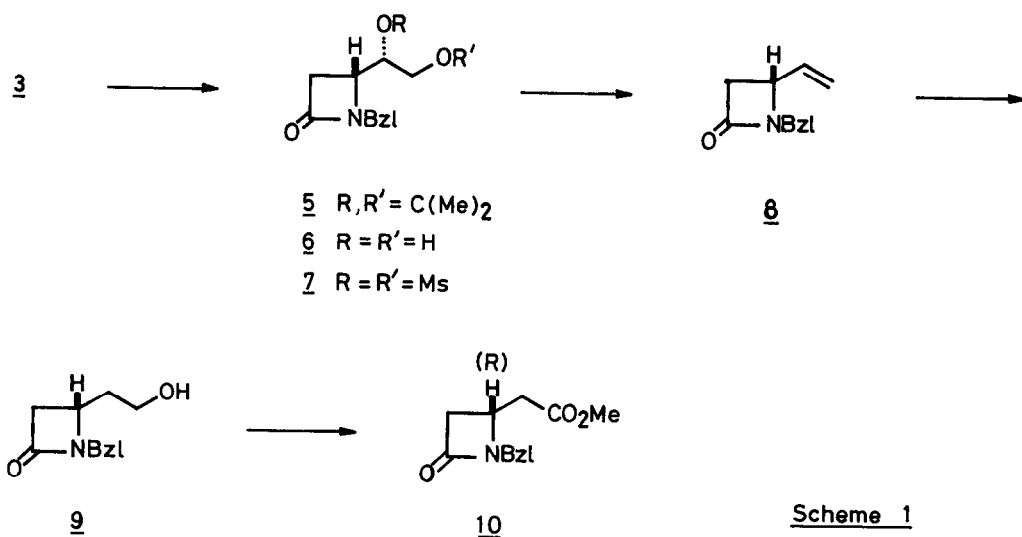
D-Glyceraldehyde acetonide (1) easily prepared from D-mannitol is known to be a useful and inexpensive starting material for the synthesis of various optically active natural products.¹ In the course of our investigation on the synthetic utility of 1, we have accomplished the conversion of 1 into optically active β -lactams. This paper describes the highly stereoselective 1,4-addition reaction of benzylamine to α,β -unsaturated ester 2 derived from 1, and the enantioselective synthesis of (R)-N-benzyl-4-[(methoxycarbonyl)methyl]-2-azetidinone (10) and (S)-4-[(methoxycarbonyl)methyl]-2-azetidinone (17) from the resulting β -amino ester 3.

The Wittig reaction of 1 with $\text{Ph}_3\text{P}=\text{CHCO}_2\text{CH}_3$ (MeOH, 0°C) gave a separable mixture of the α,β -unsaturated ester 2a (Z form) and 2b (E form) (8:1). The reaction of 2a with benzylamine (2 equiv.) in the absence of solvent at -50°C for 50 h afforded exclusively (3R)-benzylamino ester 3,^{2,3} $[\alpha]_{\text{D}} -8.0^\circ$ (c=1.3, EtOH), in 85% yield. The stereoselectivity was found to be dependent on the reaction temperature; at -20°C, 2a gave a 15:1 mixture⁴ of 3 and its stereoisomer 4, $[\alpha]_{\text{D}} +14.6^\circ$ (c=1.0, EtOH); at 0°C, 2a gave a 4:1 mixture of 3 and 4. The similar stereoselectivity and yield were obtained on the reaction of the (E)-



isomer 2b with benzylamine under the same conditions as in 2a. These findings allowed the use of a mixture of 2a and 2b for the synthesis of the β -amino ester 3 (85% yield). The amino ester 3 thus obtained was enantioselectively converted into β -lactam 10 with (R)-configuration and 17 with (S)-configuration at the C-4 position of the β -lactams. The former β -lactam can be transformed into unnatural series of carbapenem antibiotics and the latter one is the versatile intermediate for the synthesis of natural (+)-thienamycin.⁵

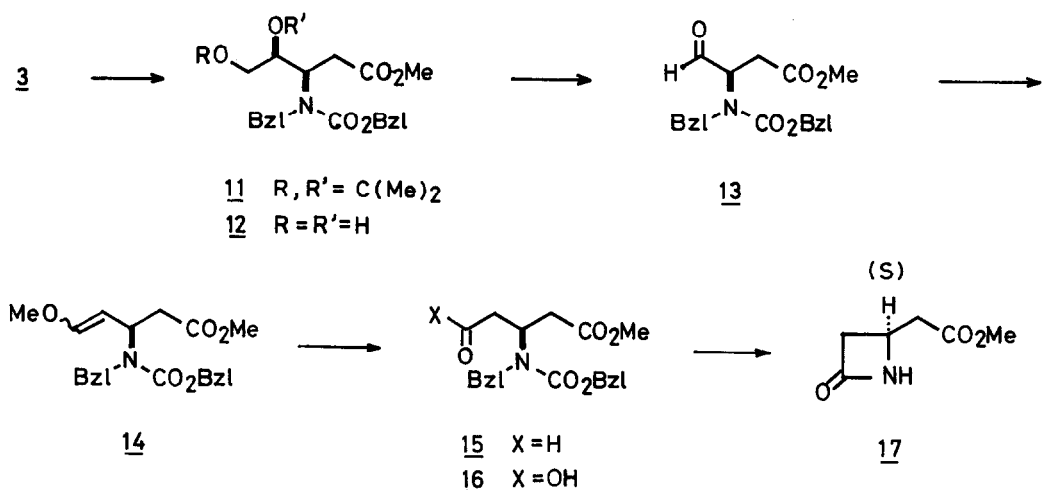
The synthesis of 10 from 3 is outlined in Scheme 1. Saponification of 3 with 0.01 M ethanolic sodium hydroxide (20°C, 15 h) gave the sodium carboxylate,



Scheme 1

which was treated with thionyl chloride (benzene, 80°C), and then with triethylamine (20°C, 12 h) to furnish the azetidinone 5, $[\alpha]_D -74.9^\circ$ ($c=0.6$, benzene), in 46% yield from 3. The acetonide group in 5 was removed by acid treatment (80% aq. AcOH, 40°C) to afford the diol 6, $[\alpha]_D -71.3^\circ$ ($c=0.94$, EtOH), in 80% yield. The diol 6 was converted via the dimesylate 7 (3.5 equiv. of MsCl, 4.5 equiv. of Et₃N, CH₂Cl₂, 0°C) to the olefin 8, $[\alpha]_D -93.6^\circ$ ($c=1.28$, CHCl₃), (10 equiv. of NaI, 10 equiv. of Zn, DMF, reflux, 8 h) in 92% overall yield. Treatment of 8 with diborane (THF, 20°C), followed by oxidative work-up (H₂O₂, NaOH) gave the alcohol 9, $[\alpha]_D -7.6^\circ$ ($c=0.2$, CHCl₃), in 54% yield. Jones oxidation of 9 and the subsequent methylation with CH₂N₂ afforded (R)-N-benzyl-4-[(methoxycarbonyl)-methyl]-2-azetidinone 10, $[\alpha]_D -22.1^\circ$ ($c=0.28$, benzene). The spectral data of this product were all identical with those reported for the enantiomer of 10, $[\alpha]_D +23.8^\circ$ ($c=1.0$, benzene), prepared from L-aspartic acid by Koga et al.⁶ except for the sign of the optical rotation.

The synthesis of (S)-17 from 3 is shown in Scheme 2. The protection of the amino group in 3 with benzyloxycarbonyl chloride in the presence of potassium carbonate (THF, rt) gave 11 in 94% yield. Exposure of 11 to 75% aqueous acetic acid (40°C, 3.5 h) gave diol 12 (70% yield), $[\alpha]_D +34.4^\circ$ ($c=1.2$, CHCl₃),



Scheme 2

which was then converted into the aldehyde 13 (1.1 equiv. of sodium metaperiodate, DME - H₂O, 0°C). The aldehyde 13 was subjected to Wittig reaction (Ph₃P=CHOCH₃, THF, -43°C) to give the enol ether 14 in 75% yield (from 12) as a 1:1 isomeric mixture. Acid treatment of 14 with 75% aqueous acetic acid (40°C, 8 h) afforded the aldehyde 15, [α]_D+11.7° (c=0.67, CHCl₃), which was treated with Jones reagent to give the carboxylic acid 16, [α]_D+116.1° (c=0.55, CHCl₃) in 92% yield from 14. The removal of the benzyl and the benzyloxycarbonyl groups from nitrogen in 16 by catalytic reduction (H₂, 10% Pd-C, MeOH, 50°C), followed by treatment with Ph₃P - (PyS)₂ in acetonitrile⁷ afforded (S)-4-[(methoxycarbonyl)methyl]-2-azetidinone (17) (81% yield from 16), [α]_D+64.5° (c=0.2, CHCl₃), whose spectral data were all identical with those reported.^{7,8}

The above-mentioned methods thus provide access to enantioselective synthesis of both (+)- and (-)-thienamycin from D-glyceraldehyde acetonide.

References and Notes

- 1) E.J.Corey, H.Shirahama, H.Yamamoto, S.Terashima, A.Venkateswarlu, and T.K. Schaaf, J.Am.Chem.Soc., 93, 1490 (1971); G.Stork and T.Takahashi, J.Am.Chem. Soc., 99, 1275 (1977); H.Yamaguchi and T.Mukaiyama, Chemistry Lett., 1005 (1982); N.Minami, S.S.Ko, and Y.Kishi, J.Am.Chem.Soc., 104, 1109 (1982).
- 2) The absolute configuration of the benzylamino group was confirmed by the conversion of 3 into 10.⁶ The high asymmetric induction was also observed on the 1,4-addition reaction of the α,β -unsaturated ester 2 with ammonia and amines such as methylamine. These Michael type addition will be published in a separate paper.
- 3) All new compounds have been fully characterized by IR, ¹H-NMR (200 MHz), and high resolution mass spectroscopy and/or combustion analysis.
- 4) The ratios of the products were determined by HPLC analysis.
- 5) K.Okano, T.Izawa, and M.Ohno, Tetrahedron Lett., 24, 217 (1983).
- 6) N.Ikota, H.Shibata, and K.Koga, Heterocycles, 14, 1077 (1980).
- 7) M.Ohno, S.Kobayashi, T.Iimori, Y-F.Wang, and T.Izawa, J.Am.Chem.Soc., 103, 2405 (1981).
- 8) Here we have accomplished a formal total synthesis of (+)-thienamycin from D-mannitol.

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