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

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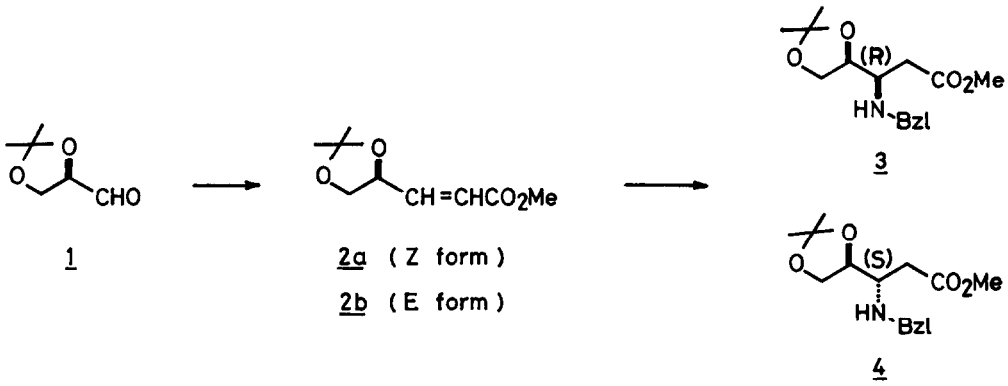
Summary: (R)-N-Benzyl-4-[(methoxycarbonyl)methyl]-2-azetidinone (10) and (S)-4-[(methoxycarbonyl)methyl]-2-azetidinone (17) were enantioselectively synthesized from the benzylamino ester 3, which was prepared by the highly stereoselective 1,4-addition of benzylamine to the α,β-unsaturated ester 2 derived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

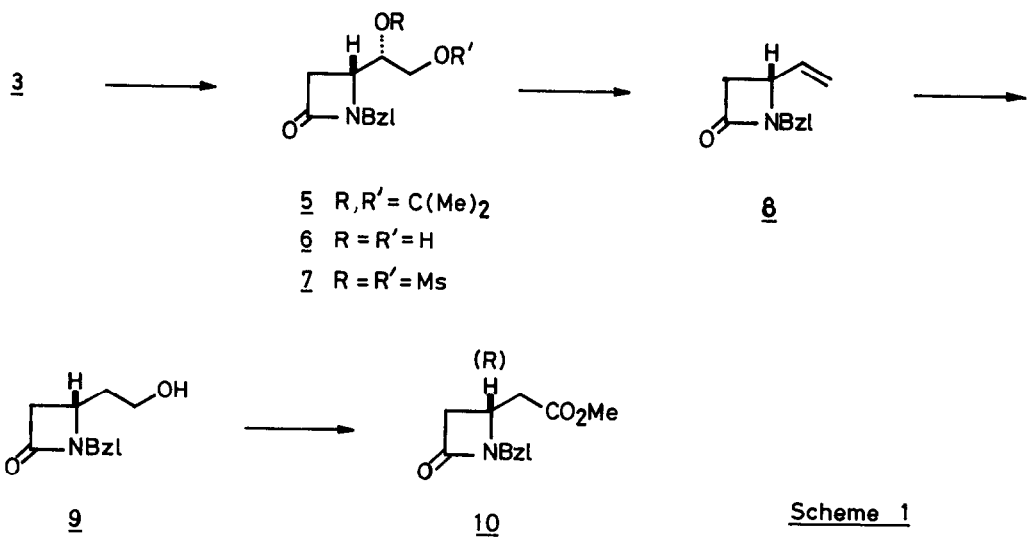
The Wittig reaction of 1 with $Ph_3P{=}CHCO_2CH_3$ (MeOH, 0°C) gave a separable mixture of the α,β-unsaturated ester 2a (Z form) and 2b (E form) (8:1). The reaction of 2a with benzylamine (2 equiv.) in the absence of solvent at -50°C for 50 h afforded exclusively (3R)-benzylamino ester 3,[2,3] $[\alpha]_D$-8.0° (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 mixture[4] of 3 and its stereoisomer 4, $[\alpha]_D$+14.6° (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)-



1 2a (Z form) 2b (E form) 3 4

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,



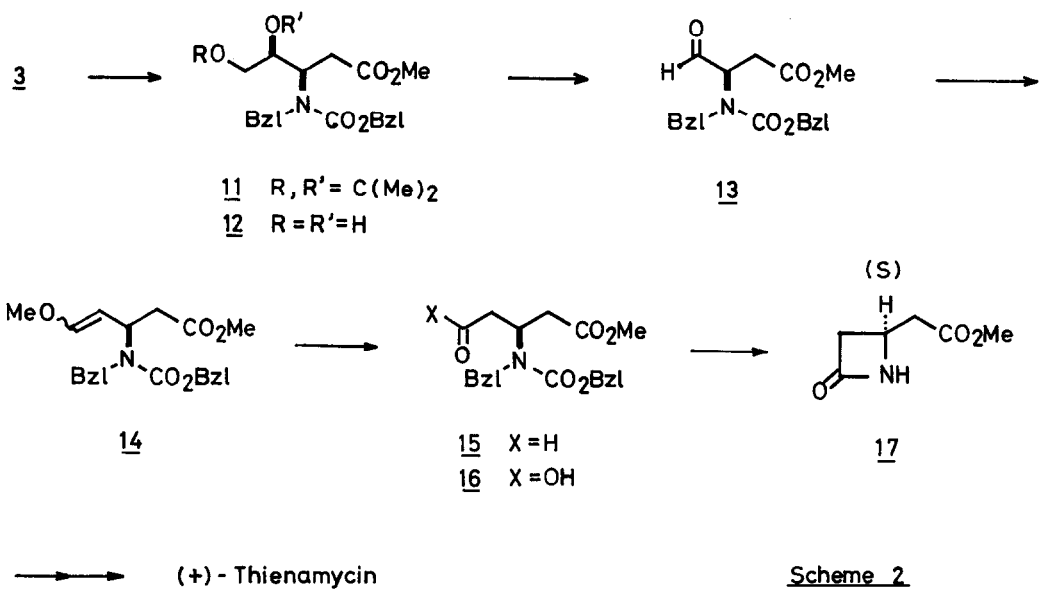
5 R,R' = C(Me)2
6 R = R' = H
7 R = R' = Ms

8 9 10

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° (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° (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 Et_3N, CH_2Cl_2, 0°C) to the olefin 8, $[\alpha]_D$-93.6° (c=1.28, $CHCl_3$), (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 (H_2O_2, NaOH) gave the alcohol 9, $[\alpha]_D$-7.6° (c=0.2, $CHCl_3$), in 54% yield. Jones oxidation of 9 and the subsequent methylation with CH_2N_2 afforded (R)-N-benzyl-4-[(methoxycarbonyl)-methyl]-2-azetidinone 10, $[\alpha]_D$ -22.1° (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° (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)-β-lactam 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° (c=1.2, $CHCl_3$),



Scheme 2

which was then converted into the aldehyde 13 (1.1 equiv. of sodium metaperiodate, DME - H_2O, 0°C). The aldehyde 13 was subjected to Wittig reaction ($Ph_3P=CHOCH_3$, 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, $[\alpha]_D$+11.7° (c=0.67, $CHCl_3$), which was treated with Jones reagent to give the carboxylic acid 16, $[\alpha]_D$+116.1° (c=0.55, $CHCl_3$) in 92% yield from 14. The removal of the benzyl and the benzyloxycarbonyl groups from nitrogen in 16 by catalytic reduction (H_2, 10% Pd-C, MeOH, 50°C), followed by treatment with Ph_3P - $(PyS)_2$ in acetonitrile[7] afforded (S)-4-[(methoxycarbonyl)methyl]-2-azetidinone (17) (81% yield from 16), $[\alpha]_D$+64.5° (c=0.2, $CHCl_3$), 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, ^{1}H-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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