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A Synthesis of (3S,4R)-3-[(R)-1-(t-Butyldimethylsilyloxy)ethyl]-4-carboxymethyl-2-azetidinone, the Thienamycin Intermediate, from (S)-Ethyl Lactate

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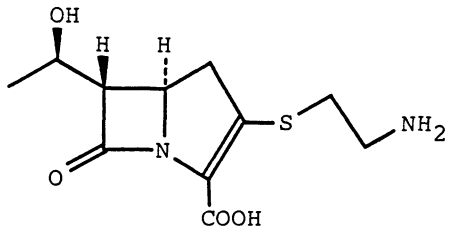
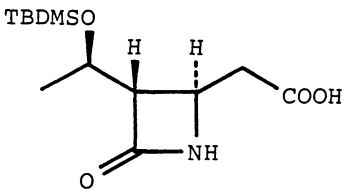
The title thienamycin intermediate was efficiently synthesized from (S)-ethyl lactate (3) by subjecting (3S,4S)-3-acetyl-4-[(S)-1-benzyloxyethyl]-2-azetidinone readily obtainable from 3, to sequential reactions in which base catalyzed elimination and regioselective hydroboration were employed as the key processes.

Thienamycin (1) constitutes the recent synthetic challenge because of its potent antibacterial activity and broad spectrum.[1] The title compound (2) or its equivalents have ingeniously been employed as a key synthetic intermediate in the synthesis of 1, and various novel synthetic routes have hitherto been explored for producing these important compounds.[2,3]

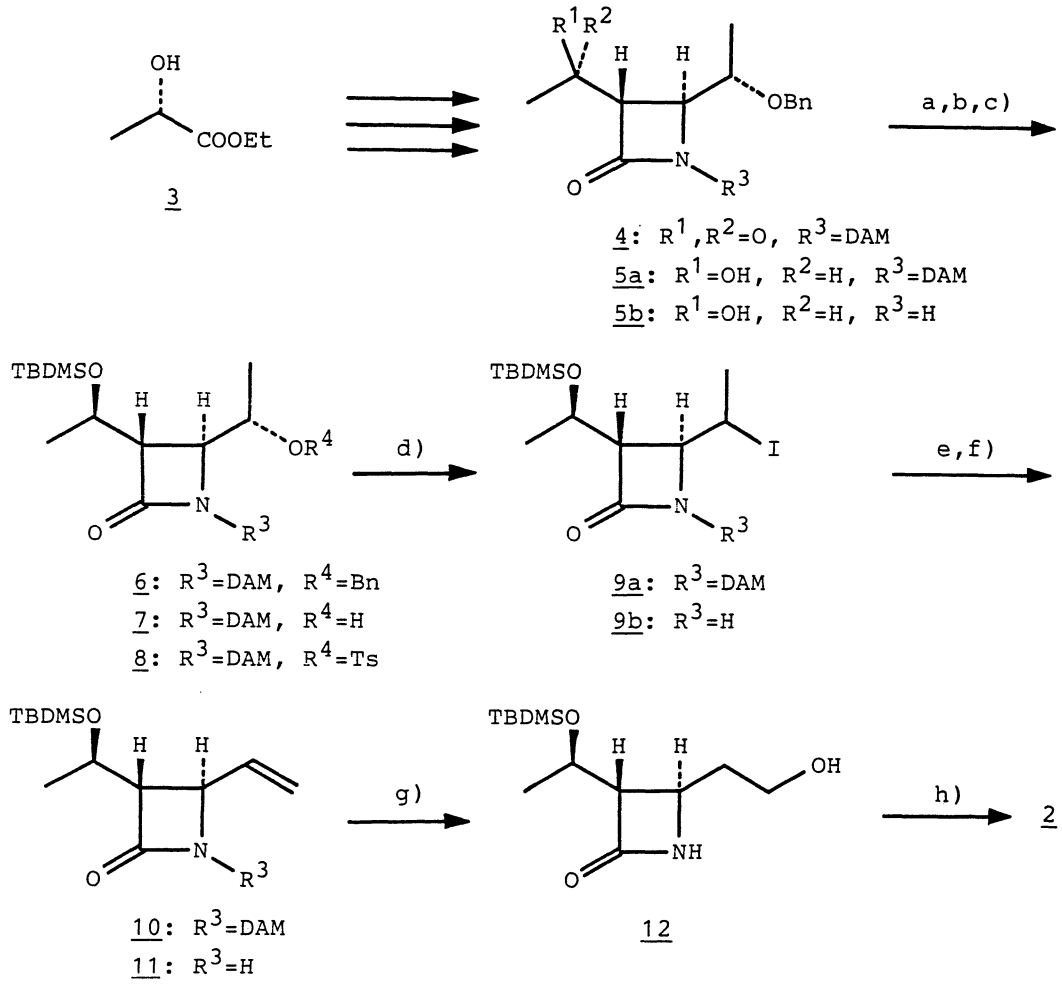


1



2

Recently, it was reported from these laboratories that [2+2] cycloaddition reaction of diketene with the chiral imine readily obtainable from inexpensive (S)-ethyl lactate (3), occurred efficiently in the presence of imidazole to produce (3S,4S)-3-acetyl-4-[(S)-1-benzyloxyethyl]-2-azetidinone (4) in a stereoselective manner.[4] The cycloaddition product (4) could be effectively converted to (3R,4R)-4-acetoxy-3-[(R)-1-(t-butyldimethylsilyloxy)ethyl]-2-azetidinone, another versatile intermediate of carbapenem synthesis.[3,5] We wish to report here that 4 can be further elaborated to 2 by the process in which base catalyzed



a) TBDMSCl-Imidazole in DMF, rt, 96% b) H_2-Pd/C-HCl (cat.) in EtOAc, 85% c) TsCl in pyridine, 0 °C, 82% d) NaI in acetone, reflux, 12 h, 90% e) DBU (2 equiv.) in toluene, 100 °C, 91% f) CAN in aq CH_3CN, at -10 °C, 1 h, 74% g) 9-BBN (2 equiv.) in THF-Et_2O, rt, 3 h then H_2O_2-aq NaOH, 0 °C, 77% h) $RuCl_3$ (2 mol%)-$NaIO_4$ in CCl_4-CH_3CN-H_2O, rt, 69%

elimination of the secondary iodide (9a) and regioselective hydroboration of the 4-vinyl-2-azetidinone derivative (11) constitute the key synthetic reactions.

As shown in the scheme, the hydroxy group of (3S,4S)-4-[(S)-1-benzyloxyethyl]-3-[(R)-1-hydroxyethyl]-2-azetidinone (5a) stereoselectively prepared in 5 steps from 3 by way of 4 according to the reported method,[4] was protected with a t-butyldimethylsilyl (TBDMS) group to give the silyl ether (6), $[\alpha]_D^{25}$ -17.7° (c 2.47, $CHCl_3$). After hydrogenolysis of the benzyl (Bn) ether of 6, the produced secondary alcohol (7), $[\alpha]_D^{25}$ -29.1° (c 3.32, $CHCl_3$), was transformed to the p-toluenesulfonate (tosylate) (8), $[\alpha]_D^{25}$ -22.2° (c 2.51, $CHCl_3$). Attempts to effect elimination of the tosyl group by treating 8 with bases such as 1,8-diazabicyclo-

[5,4,0]-7-undecene (DBU), KO^tBu, pyridine, etc., turned out to be fruitless. Accordingly, preparation of 10 was examined by way of the iodide (9a). Thus, treatment of 8 with sodium iodide in acetone gave rise to 9a as a mixture of the two diastereomers. The isomeric ratio could be roughly estimated as 5:2 by the ^1H NMR spectrum. This can be explained by epimerization of the initially formed iodide during the substitution reaction. Without separation of the diastereoisomers, treatment of 9a with DBU cleanly produced 11, $[\alpha]_D^{25}$ +52.5° (c 1.18, $CHCl_3$). Oxidative removal of the di-p-anisylmethyl group (DAM) was effected with cerium (IV) ammonium nitrate (CAN) at low temperature without a cleavage of the TBDMS ether, yielding 11[6] as colorless crystals, mp 63-64.5 °C, $[\alpha]_D^{25}$ -24.5° (c 1.05, $CHCl_3$).

On the other hand, the DAM group was removed at the stage of 5a and the deprotected 2-azetidinone derivative (5b) was derived to the iodide 9b by the same procedure as that employed for preparing 9a from 5a. When 9b was treated under the same elimination conditions as those employed for 9a, only a 24% yield of 11 was obtained due to partial decomposition of 9b and/or 11.

Hydroboration of 11 with borane in THF followed by the usual oxidative workup gave a mixture of the primary alcohol (12) and its regioisomer [the 4-(1-hydroxyethyl)-2-azetidinone derivative]. These isomers could be readily separated by preparative TLC [SiO_2: Hexane-EtOAc (1:4)] (the formation ratio = 11:9). However, the use of 9-borabicyclo-[3,3,1]-nonane (9-BBN) in place of borane in THF furnished 12,[7] mp 85-87 °C, $[\alpha]_D^{25}$ -22.3° (c 1.01, $CHCl_3$) as a single product in a high yield. Oxidation of 12 was achieved smoothly by the procedure reported by Sharpless, et al.,[8] to afford 2,[9] mp 150-154 °C (dec.), $[\alpha]_D^{20}$ +16.1° (c 0.69, $CHCl_3$) [lit.,[2f] $[\alpha]_D^{20}$ +16.19° (c 1.00, $CHCl_3$)].

In summary, we have succeeded in developing a new synthetic route to the thienamycin intermediate (2) from commercially available inexpensive (S)-ethyl lactate (3). The method developed here can be characterized by the efficient utilization of all the framework of 3 for constructing 2. The overall process may hold promise as one of the most practical preparation method for 2.

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6) 11: IR (KBr) 1760, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.08(6H, s), 0.88(9H, s), 1.21(3H, d, J=6.4 Hz), 2,87(1H, m), 4.0-4.4(2H, m), 5.15(1H, d, J=10 Hz), 5.29(1H, d, J=16 Hz), 5.96(1H, ddd, J=6.8, 10, 16 Hz), 5.98(1H, bs); MS m/e 198(M^+-^{t}Bu). Found: C, 60.96; H, 9.78; N, 5.43%. Calcd for $C_{13}H_{25}NO_2Si$: C, 61.13; H, 9.86; N, 5.48%.

7) 12: IR (KBr) 1732 cm^{-1} ^1H NMR ($CDCl_3$) δ=0.10(6H, s), 0.89(9H, s), 1.28(3H, d, J=6.2 Hz), 2.34(1H, t, J=5.7 Hz), 2.91(1H, dq, J=1.1, 7.0 Hz), 3.73(3H, m), 4.16(1H, m), 6.17(1H, bs); MS m/e 258(M^+-Me), 216(M^+-^{t}Bu). Found: C, 57.05; H, 10.12; N, 4.99%. Calcd for $C_{13}H_{27}NO_3Si$: C, 57.10; H, 9.95; N, 5.12%.

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9) 2: IR ($CHCl_3$) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.07(6H, s), 0.88(9H, s), 1.21(3H, d, J=6.2 Hz), 2.65(2H, m), 2.81(1H, m), 3.95(1H, m), 4.18(1H, quint, J=6 Hz), 6.0-7.4(1H, b), 7.11(1H, bs); MS m/e 272(M^+-Me), 230(M^+-^{t}Bu). Found: C, 54.38; H, 8.69; N, 4.94%. Calcd for $C_{13}H_{25}NO_4Si$: C, 54.32; H, 8.77; N, 4.87%.

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