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ASYMMETRIC SYNTHESIS OF α-HYDROXYETHYL β-LACTAM DERIVATIVES: AN APPROACH TO THIENAMYCIN

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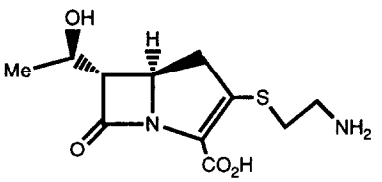
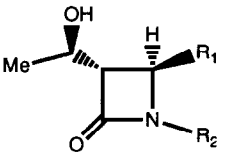
Summary: The asymmetric synthesis of a β-lactam ring with three contiguous chiral centers, including a hydroxyethyl side chain, was accomplished by the preparation and oxidative cyclization of the appropriate β,γ-unsaturated hydroxamate.

The unique structure of thienamycin and related β-lactam antibiotics consists of a hydroxyethyl side chain and a β-lactam ring system with three contiguous chiral centers. The hydroxyethyl side chain and the stereochemisty of these three chiral centers is important for antibiotic activity.[1] The development of efficient approaches to the asymmetric synthesis of β-lactams which contain those three chiral centers remains a topic of considerable interest. Recently, the stereoselective syntheses of various forms of substituted hydroxyethyl β-lactams (**1**) have been achieved by several groups.[2]



[+] - thienamycin

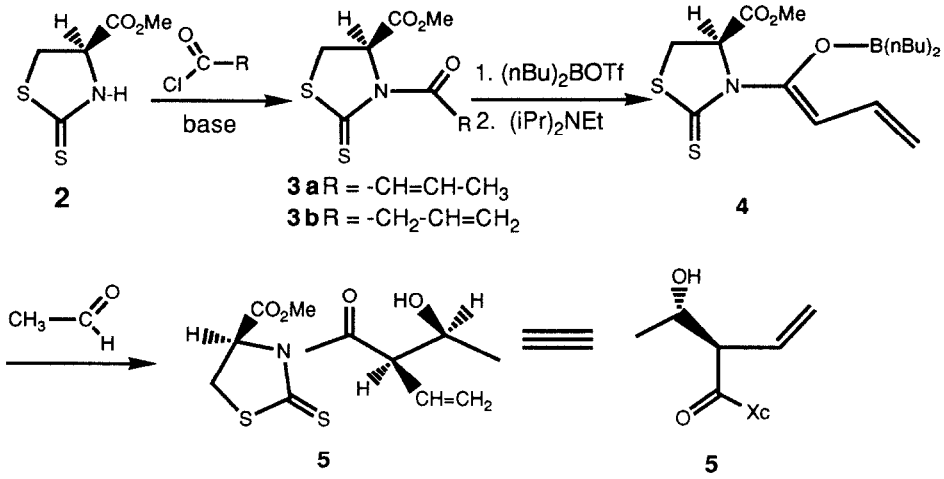


1

In this paper, we describe a short enantioselective synthesis of the mirror image of β-lactam **1** [R_1=CH_2Br, R_2=$O_2CC(CH_3)_3$] using a combination of a stereoselective aldol condensation and oxidative cyclization. The starting material chosen for the synthesis was thiazolidinethione **2**, a chiral auxiliary previously utilized by our group for asymmetric aldol condensation reactions.[4] The

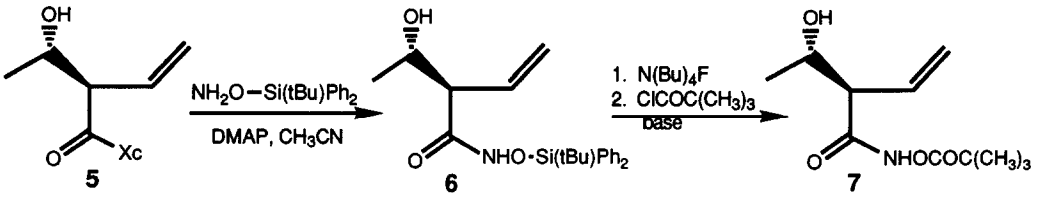
corresponding acyl thiazolidinethiones **3a** and **3b** were prepared by adding the appropriate acid chlorides to the chiral auxiliary in the absence of base. While aldol reactions of either **3a** or **3b** produced the desired aldol products, the ß,γ-isomer **3b** was more effective. Thus, treatment of **3b** with $(n\text{-}Bu)_2BOTf$ under argon for 5 min at 0°C in CH_2Cl_2 followed by the slow addition of diisopropyl ethyl amine at 0°C gave a light yellow solution which was stirred for another 30 min at 0°C. The solution was cooled to -78°C at which time acetaldehyde was added. The mixture was allowed to warm to 0°C over a period of 30 min. Excess pH7 phosphate buffer solution was added and the mixture was stirred vigorously at 0°C for 3 min. The CH_2Cl_2 solution was separated and concentrated. The residue was chromatographed on silica gel to provide the optically active aldol product **5** (Scheme 1) in > 96% de. The stereoselectivity and reaction mechanism of this type of chiral aldol reaction have been discussed previously.[4]

Scheme 1



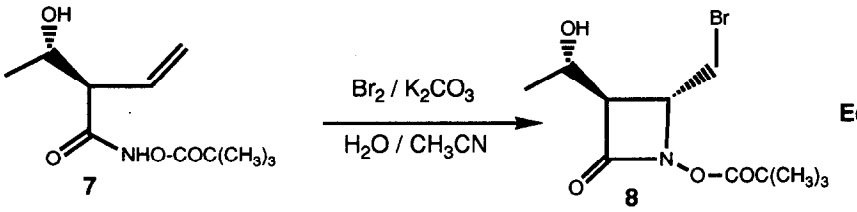
Since acylthiazolidinones also behave as active esters, compound **5** was reacted with O-t-butyldiphenylsilylhydroxylamine[5] in acetonitrile with a catalytic amount of DMAP to produce hydroxamate **6** in 36% yield after chromatography on silica gel. O-t-Butyldimethylsilyl-hydroxylamine was also used to remove the chiral auxiliary, but the yield was lower (16%) because the t-butyldimethylsilyl group is not as stable. Hydroxamate **6** was treated with tetrabutylammonium fluoride followed by exposure to trimethylacetyl chloride and pyridine in THF. After quenching, the reaction mixture was extracted with ethyl acetate. The extract was washed with water, 5% oxalic acid, and brine, dried and filtered. Evaporation and chromatography provided the more acidic O-pivaloylhydroxamate **7** (Scheme 2).

Scheme 2



To a solution of compound **7** in acetonitrile was added 1.05 eq of solid K_2CO_3 followed by 5-10 volume % of water. The mixture was stirred vigorously for 1 min. Then 110 mol% of bromine was added over a one min period. After the addition was complete, the mixture was stirred for 1 min before being transferred to a separatory funnel containing ethyl acetate. The mixture was then successively washed with water, 10% sodium sulfite and brine before drying over Na_2SO_4. Filtration and evaporation of the ethyl acetate provided light yellow crystals which were recrystallized from ethyl acetate-hexanes to give the pure *trans* isomer of ß-lactam **8** in 89% yield.

The stereoselectivity of oxidative cyclization of β,γ–unsaturated O-acyl hydroxamates to β-lactams has been described earlier.[3] The α-substitutent has a profound affect on the stereochemical outcome of the reaction. α-Alkyl substituents induce preferential formation of the *trans* β-lactams whereas an α-amino substituent promotes formation of *cis* β-lactams as the major product. The NMR of crude ß-lactam product **8** indicated that the *trans* isomer was formed exclusively, indicating that the important hydroxylethyl group has the same stereochemical influence as a bulky alkyl group in the cyclization reaction. Thus, the combination of an effective asymmetric aldol condensation and a subsequent oxidative cyclization results in complete control of the three contiguous chiral centers characteristic of many potent carbapenem antibiotics.



Eq 1

Changing the absolute configuration of the chiral auxiliary in the initial aldol condensation will provide the appropriate absolute stereochemistry for thienamycin. Future investigations will study the use of that chiral auxiliary as well as application of this methodology to the synthesis of a number of bicyclic β-lactams.

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References and Notes

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6 Selected data for **3a**: (70%) ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.0 (d, 3H), 3.45 (dd, 1H), 3.85 (dd, 1H), 3.90 (s, 3H), 5.65 (dd, 1H), 7.20 (dt, 1H), 7.45 (d, 1H); IR (KBr): 1170, 1630, 1685, 1740, 2960, 3040 cm^{-1}; MS (CI) m/e 290(M+1), 205, 178, 164; $[\alpha]_D$ =101.5 (c = 1.492 in $CHCl_3$); mp: 92-94^{o}C. **3b**: (52%) ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.50 (dd, 1H), 3.82 (m, 1H), 3.89 (s, 3H), 4.05 (dd, 1H), 4.25 (dd, 1H), 5.24 (d, 1H), 5.73 (dd, 1H), 5.96 (m, 1H). **5**: (28%) ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.12 (d, 3H), 2.75 (br, 1H), 3.30 (d, 1H), 3.68 (dd, 1H), 3.73 (s, 3H), 4.10 (m, 1H), 4.25 (dd, 1H), 5.19 (dd, 1H), 5.32 (m, 2H), 5.87 (ddd, 1H); IR (thin film) 3300(b), 2980, 2940, 2880, 1750, 1710, 1695, 1685, 1435, 1400, 1310, 1170, 925 cm^{-1}; MS (CI) m/e, 290(m+1), 272, 178. **6**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.96 (d, 3H), 1.12 (s, 9H), 2.56 (dd, 1H), 3.95 (5 peaks, 1H), 5.03 (d, 1H), 5.15 (d, 1H), 5.72 (m, 1H), 7.41 (m, 6H), 7.73 (m, 4H); ^{13}C NMR (75 MHz) 19.1, 19.6, 26.6, 55.0, 67.4, 120.8, 128.0, 130.5, 131.0, 131.5, 135.7, 169.9; IR (KBr) 3240(b), 3080, 3050, 2970, 2940, 2900, 2860, 1740, 1660, 1430, 1110, 820 cm^{-1}; MS (CI) m/e 384(M+1), 326, 306, 257, 199; CH anal calcd. C 68.89, H 7.62; found C 69.02, H 7.40. **7**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.10 (d, 3H), 1.30 (s, 9H), 3.02 (dd, 1H), 4.18 (m,1H), 5.45 (m, 2H), 5.97 (m, 1H), 9.12 (b, 1H); ^{13}C NMR (75MHz) 19.6, 27.0, 38.3, 55.3, 67.9, 121.3, 131.1, 170.6, 176.8; IR (KBr) 3200(b), 2980, 2940, 2880, 1780, 1755, 1675, 1480, 1380, 1270, 1080 cm^{-1}; MS (CI) m/e 230(M+1), 177, 128, 118. **8**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 9H), 1.36 (d, 3H, J = 5.9 Hz), 2.91 (dd, 1H, J_1= 2.4 Hz, J_2 = 5.8 Hz), 3.59 (d, 1H, J = 5.9 Hz), 3.59 (d, 1H, J = 6.1 Hz), 4.28 (5 peaks, 1H, J = 6.0 Hz), 4.37 (dt, 1H, J_1= 2.4 Hz, J_2 = 6.0 Hz); IR (KBr) 3400(br), 2980, 2940, 2915, 2875, 1800, 1765,1475, 1370, 1015 cm^{-1}; ^{13}C NMR (75 MHz) δ 21.7, 26.8, 31.4, 38.3, 59.0, 61.9, 65.0, 164.2, 175.7; MS (CI) m/e, 310, 308 (M+1), 292, 290 (M+1-18), 230 (M+1-Br).

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