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A Formal Total Asymmetric Synthesis of (+)-Thienamycin

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Abstract: Synthesis of an enantiomerically pure intermediate to (+)-thienamycin is presented: the pivotal reaction in this sequence is the highly diastereoselective Michael addition of a differentially protected lithium amide.

The differentially protected lithium amide derived from N-allyl-N- α -methylbenzylamine 1 has been shown to undergo a highly diastereoselective Michael addition to a range of α , β -unsaturated esters.¹ Following the selective removal of the allyl group, transesterification allowed cyclisation of the resulting β amino methyl esters to a range of N-protected β -lactams. This versatile methodology allows access to homochiral (enantiomerically pure) β -lactams, and herein we describe its application in a formal synthesis of (+)-thienamycin 2.



Thienamycin possesses an excellent antibacterial profile,² and this biological activity has provided the impetus for the synthesis of further carbapenem analogues. In a recent strategy for the assembly of the carbapenem bicyclic structure the aldehyde **16** was a crucial intermediate.³ Our synthesis of this bis-silylated β -lactam employs the diastereoselective Michael addition of lithium *N*-allyl-*N*- α -methylbenzylamide to an $\alpha,\beta,\gamma,\delta$ -doubly unsaturated ester **3**,⁴ with the vinyl silane moiety serving as a latent carbonyl group.⁵ The 1,4-conjugate addition of lithium *N*-allyl-*N*- α -methylbenzylamide **1** to the $\alpha,\beta,\gamma,\delta$ -unsaturated ester **3** yielded a single diastereoisomer **4** {[α]_D²³ -17.5 (*c* 0.60, CHCl₃); yield 94%, >98% d.e.}, with no 1,2- or 1,6-addition being observed. Selective removal of the allyl group was then achieved using Wilkinson's catalyst in aqueous acetonitrile giving the secondary amine **5** {[α]_D²³ +31.9 (*c* 1.65, CHCl₃)} in 93% yield.⁶ Although cyclisation of the resultant β -amino ester to the required β -lactam was satisfactorily accomplished by transesterification of **5** to the methyl ester {[α]_D²³ -23.2 (*c* 0.95, CHCl₃)} under Ohno's conditions. Cyclisation of the resulting β -amino acid **6** {[α]_D²³ -23.2 (*c* 0.95, CHCl₃)} under Ohno's conditions (dipyridyl disulphide-triphenylphosphine in acetonitrile)⁷ gave an excellent overall yield of β -lactam **7** {[α]_D²³ -25.4 (*c* 2.00, CHCl₃)} form *tert*-butyl ester **5** (Scheme 1).

Dedicated to the memory of Professor Hidemasa Takaya, deceased on 5 October 1995



Scheme 1: *Reagents*: i) 1, NH₄Cl (94%, >98% d.e.); ii) (Ph₃P)₃RhCl, H₂O, CH₃CN (93%) iii) CF₃CO₂H, CH₂Cl₂ (100%); iv) PPh₃, (PyS)₂, CH₃CN (100%).

Epoxidation of the vinyl silane was effected using *m*-CPBA in dichloromethane giving a mixture of diastereoisomeric α,β -epoxy silanes (9:4; 97% yield). Treatment of this mixture of diastereoisomeric epoxides under aqueous acidic conditions yielded the diastereoisomeric dihydroxy silanes, which were resistant to further transformation both under acidic conditions or by Peterson-Hudrlik reaction *via* an α - or β -oxidosilane.⁸ However, a two-step transformation involving the formation of the α -methoxy- β -hydroxy silane (H₂SO₄, MeOH) and the subsequent base induced *syn*-elimination of the resulting β -hydroxy silane (NaH in THF) successfully transformed the vinyl silane 7 into the methyl enol ether 12 {[α]_D²³ -11.3 (*c* 1.55, CHCl₃)}.⁹ The poor diastereofacial selectivity of epoxidation but high stereospecificity of ring opening and subsequent elimination resulted in the isolation of a single *trans* methyl enol ether, evidenced by the coupling constant between the olefinic protons (*J* 12.6 Hz) in the ¹H nmr spectrum. Having accomplished transformation of the vinyl silane to enol ether, reductive removal of the *N*- α -methylbenzyl group was efficiently carried out by treatment of the β -lactam 12 with sodium in liquid ammonia which yielded 13 {[α]_D²³ -13.7 (*c* 1.09, CHCl₃)}.¹⁰ Subsequent *N*-silylation (TBDMSCl, Et₃N in DMF) of β -lactam 13 was achieved in excellent vield.



Scheme 2: Reagents: i) m-CPBA, CH₂Cl₂ (98%); ii) H₂SO₄, MeOH (65%); iii) NaH, THF (90%); iv) Na, NH₃ (l), EtOH (91%).

The stereoselective incorporation of the hydroxyethyl side-chain required for (+)-thienamycin was achieved following literature precedent, an inverse addition of the β -lactam enolate to a cooled solution containing N-acetyl imidazole.¹¹ The desired β -keto- β -lactam 14 {[α]_D²³ +11.9 (c 1.00, CHCl₃)} was isolated as a single diastereoisomer in 72% yield; its stereochemistry assigned on the basis of the coupling constant between H₃ and H₄ (J 2.7 Hz) in the ¹H nmr spectrum.¹² Transformation of this intermediate into the desired (R)-alcohol was efficiently carried out by reduction using the bulky ionic K-Selectride in the presence of potassium iodide in diethyl ether at ambient temperature, yielding the desired (R)-alcohol in good yield and diastereoselectivity. Following silylation of the carbinol (TBDMSCl in DMF), deprotection of the methyl enol ether while retaining the N and O silyl groups was required to complete the formal synthesis of (+)-thienamycin. Treatment of the bis-silyl enol ether 15 {[α]_D²³ -31.2 (c 1.10, CHCl₃)} with acid selectively cleaved the N-Si bond, leaving the enol ether intact. Encouragingly, treatment of the β -lactam 15 with trimethylsilyl iodide in acetonitrile¹³ or an *in situ* formation of the reagent¹⁴ yielded some of the desired product, however, treatment of the enol ether with mercury (II) acetate and potassium iodide furnished the aldehyde 16 in moderate yield.¹⁵ The spectroscopic data, melting point and specific rotation of this material¹⁶ were all in good agreement to that for authentic material.¹⁷



Scheme 3: *Reagents*: i) Bu^tMe₂SiCl, Et₃N, DMF (98%); ii) LDA (3.5 equiv.), *N*-acetyl imidazole (72%); iii) K(Bu^s)₃BH, KI, Et₂O (83%, 88:12 d.s.); iv) Bu^tMe₂SiCl, imidazole, DMF (97%); v) Hg(OAc)₂, KI, 10% aq. THF (48%).

In conclusion, the stereoselective formal synthesis of (+)-thienamycin 2 has been accomplished following the highly diastereoselective Michael addition of the differentially protected lithium amide derived from N-allyl-N- α -methylbenzylamine to an $\alpha,\beta,\gamma,\delta$ -unsaturated ester. The overall yield of the 13 steps was 12.5%, isolation of the known crystalline aldehyde confirming both the absolute stereochemistry of all intermediates¹⁸ and proved the sense of addition of the lithium amide.

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- 16; m.p. 110-111°C; [α]_D²³ -65.3 (*c* 1.26, CHCl₃); δ_H (CDCl₃, 300 MHz) 9.79 (1H, t, *J* 2.2, CH₂C<u>H</u>O),
 4.15 [1H, m, CH₃C<u>H</u>(OH)], 3.96 (1H, ddd, *J* 8.7, 4.4 and 2.6, CHC<u>H</u>CH₂), 2.95 (1H, dd, *J* 5.5 and 2.6,
 CHCO), 2.88 (1H, ddd, *J* 16.0, 4.4 and 2.2, C<u>H₂</u>CHO), 2.67 (1H, ddd, *J* 16.0, 8.7 and 2.2, C<u>H₂</u>CHO),
 1.21 [3H, d, *J* 6.3, C<u>H₃</u>CH(OH)], 0.95 [9H, s, SiC(C<u>H₃)₃], 0.88 [9H, s, SiC(C<u>H₃)₃], 0.23 [3H, s,
 Si(C<u>H₃)₂], 0.22 [3H, s, Si(C<u>H₃)₂], 0.08 [3H, s, Si(C<u>H₃)₂], 0.05 [3H, s, Si(C<u>H₃)₂]; δ_C (CDCl₃, 50 MHz)
 199.4 (CHO), 172.4 (CO), 66.0 (CH), 65.1 (CH), 49.6 (NCH), 47.3 (<u>C</u>H₂CHO), 26.2 [SiC(<u>C</u>H₃)₃], 25.8 [SiC(<u>C</u>H₃)₃], 22.6 [<u>C</u>H₃CH(OH)], 18.2 [Si<u>C</u>(CH₃)₃], 17.9 [Si<u>C</u>(CH₃)₃], -4.6 [Si(<u>C</u>H₃)₂], -5.2 [Si(<u>C</u>H₃)₂], -5.9 [Si(<u>C</u>H₃)₂]; *m/z* (CI, NH₃) 386 (MH⁺, 40%), 97 (100%).
 </u></u></u></u></u></u>
- 17 Data for **16** supplied by Dr G.B. Feigelson,³ American Cyanamid Company; m.p. 112-113°C; $[\alpha]_D^{25}$ -62 ± 1 (*c* 1.26, CHCl₃); δ_H (CDCl₃, 300 MHz) 9.79 (1H, t, *J* 2.2, CH₂CHO), 4.16 [1H, m, CH₃CH(OH)], 3.97 (1H, ddd, *J* 8.6, 4.3 and 2.6, CHCHCH₂), 2.95 (1H, dd, *J* 5.5 and 2.6, CHCO), 2.88 (1H, ddd, *J* 16.0, 4.3 and 2.2, CH₂CHO), 2.67 (1H, ddd, *J* 16.0, 8.6 and 2.2, CH₂CHO), 1.22 [3H, d, *J* 6.2, CH₃CH(OH)], 0.96 [9H, s, SiC(CH₃)₃], 0.88 [9H, s, SiC(CH₃)₃], 0.23 [3H, s, Si(CH₃)₂], 0.22 [3H, s, Si(CH₃)₂], 0.09 [3H, s, Si(CH₃)₂], 0.07 [3H, s, Si(CH₃)₂]; δ_C (CDCl₃, 75 MHz) 199.3 (CHO), 172.3 (CO), 66.1 (CH), 65.2 (CH), 49.6 (NCH), 47.4 (CH₂CHO), 26.2 [SiC(CH₃)₃], 25.8 [SiC(CH₃)₃], 22.6 [CH₃CH(OH)], 18.2 [SiC(CH₃)₃], 18.0 [SiC(CH₃)₃], -4.5 [SiC(CH₃)₃(CH₃)₂], -4.6 [Si(CH₃)₂], -5.2 [SiC₄H₃)₂], -5.8 [Si(CH₃)₂].
- 18 Satisfactory data including elemental analysis were obtained for all new compounds.