Pergamon

Tetrahedron: Asymmetry Vol. 6, No. 10, pp. 2507-2510, 1995
Elsevier Science Ltd
Printed in Great Britain
0957-4166/95 $9.50+0.00

0957-4166(95)00327-4

A Formal Total Asymmetric Synthesis of (+)-Thienamycin

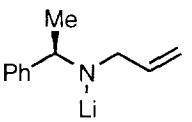
Stephen G. Davies,*[a] Charles J.R. Hedgecock[b] and Jeffrey M. McKenna[a]

[a]The Dyson Perrins Laboratory, University of Oxford, South Parks Road, Oxford, UK OX1 3QY.

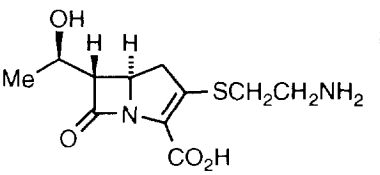
[b]Roussel Laboratories Ltd., Kingfisher Drive, Covingham, Swindon, UK SN3 5BZ.

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.

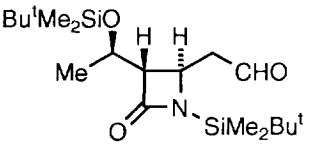
The differentially protected lithium amide derived from *N*-allyl-*N*-α-methylbenzylamine **1** has been shown to undergo a highly diastereoselective Michael addition to a range of α,β-unsaturated esters.[1] Following the selective removal of the allyl group, transesterification allowed cyclisation of 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**.



1



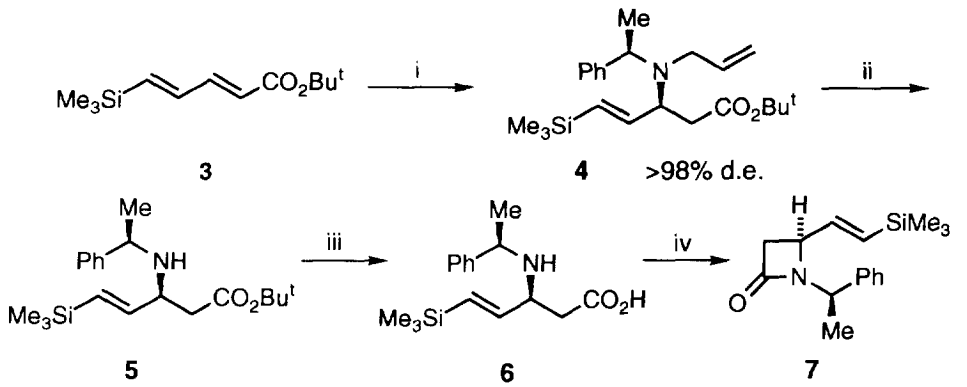
2



16

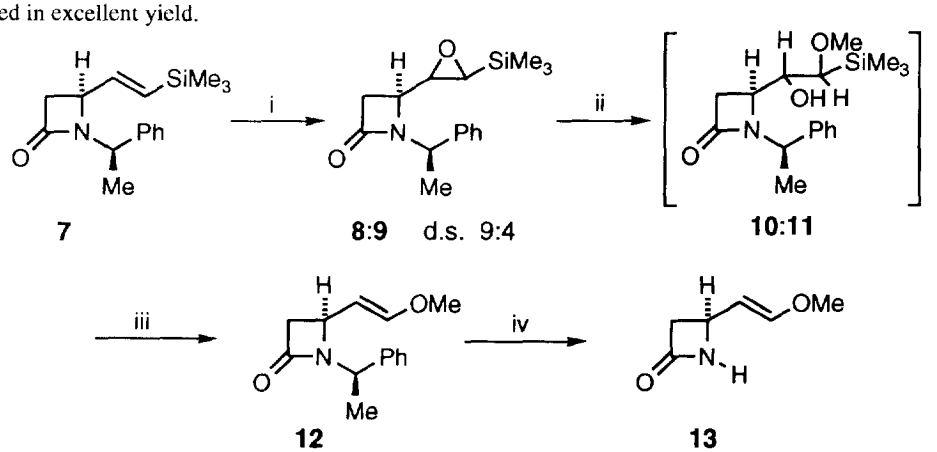
Thienamycin possesses an excellent antibacterial profile,[2] and this biological activity has provided the impetus for the synthesis of further carbapenem analogues. In a recent strategy for the assembly of the carbapenem bicyclic structure the aldehyde **16** was a crucial intermediate.[3] Our synthesis of this bis-silylated β-lactam employs the diastereoselective Michael addition of lithium *N*-allyl-*N*-α-methylbenzylamide to an α,β,γ,δ-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 α,β,γ,δ-unsaturated ester **3** yielded a single diastereoisomer **4** {$[\alpha]_D^{23}$ -17.5 (*c* 0.60, $CHCl_3$); 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** {$[\alpha]_D^{23}$ +31.9 (*c* 1.65, $CHCl_3$)} 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 {$[\alpha]_D^{23}$ +36.5 (*c* 2.10, $CHCl_3$)} followed by the Grignard-mediated cyclisation, a more efficient procedure involved cleavage of the *tert*-butyl ester under acidic conditions. Cyclisation of the resulting β-amino acid **6** {$[\alpha]_D^{23}$ -23.2 (*c* 0.95, $CHCl_3$)} under Ohno's conditions (dipyridyl disulphide-triphenylphosphine in acetonitrile)[7] gave an excellent overall yield of β-lactam **7** {$[\alpha]_D^{23}$ -25.4 (*c* 2.00, $CHCl_3$)} from *tert*-butyl ester **5** (Scheme 1).

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



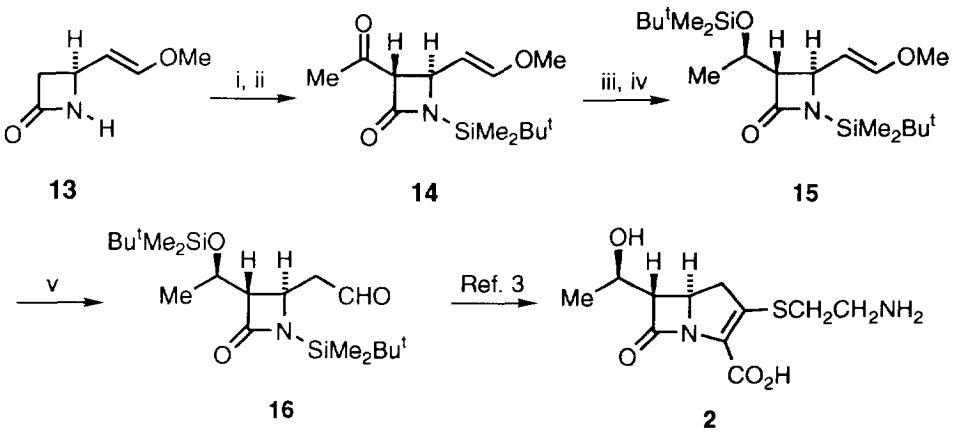
Scheme 1: *Reagents*: i) **1**, NH_4Cl (94%, >98% d.e.); ii) $(Ph_3P)_3RhCl$, H_2O, CH_3CN (93%); iii) CF_3CO_2H, CH_2Cl_2 (100%); iv) PPh_3, $(PyS)_2$, CH_3CN (100%).

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 (H_2SO_4, 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** {$[\alpha]_D^{23}$ -11.3 (*c* 1.55, $CHCl_3$)}.[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** {$[\alpha]_D^{23}$ -13.7 (*c* 1.09, $CHCl_3$)}.[10] Subsequent *N*-silylation (TBDMSCl, Et_3N in DMF) of β-lactam **13** was achieved in excellent yield.



Scheme 2: *Reagents*: i) *m*-CPBA, CH_2Cl_2 (98%); ii) H_2SO_4, MeOH (65%); iii) NaH, THF (90%); iv) Na, NH_3 (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** {$[\alpha]_D^{23}$ +11.9 (*c* 1.00, $CHCl_3$)} was isolated as a single diastereoisomer in 72% yield; its stereochemistry assigned on the basis of the coupling constant between H_3 and H_4 (*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** {$[\alpha]_D^{23}$ -31.2 (*c* 1.10, $CHCl_3$)} with acid selectively cleaved the N-Si bond, leaving the enol ether intact. Encouragingly, treatment of the β-lactam **15** with trimethylsilyl iodide in acetonitrile[13] or an *in situ* formation of the reagent[14] 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 material[16] were all in good agreement to that for authentic material.[17]



13 **14** **15** **16** **2**

Scheme 3: *Reagents*: i) Bu^tMe_2SiCl, Et_3N, DMF (98%); ii) LDA (3.5 equiv.), *N*-acetyl imidazole (72%); iii) $K(Bu^s)_3BH$, KI, Et_2O (83%, 88:12 d.s.); iv) Bu^tMe_2SiCl, 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 α,β,γ,δ-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 intermediates[18] and proved the sense of addition of the lithium amide.

Acknowledgements We thank EPSRC and Roussel Laboratories Ltd for a CASE award (to JMM) and Dr G.B. Feigelson of the American Cyanamid Company for his helpful and prompt supply of all data requested on compound **16**.

References

1 S.G. Davies and D.R. Fenwick, *J. Chem. Soc., Chem. Comm.*, 1995, 1109; S.G. Davies, C.J.R. Hedgecock and J.M. McKenna, *Tetrahedron: Asymmetry*, 1995, **6**, 827.

2 J.S. Kahan, F.M. Kahan, R. Goegelman, S.A. Currie, M. Jackson, E.O. Stapley, T.W. Miller, A.K. Miller, D. Hendlin, S. Mochales, S. Hernandez, H.B. Woodruff and J. Birnbaum, *J. Antibiot.*, 1979, **32**, 1.

3 G.B. Feigelson, *Tetrahedron Lett.*, 1993, **34**, 4747.

4 The ester was obtained from reaction between *tert*-butyl diethylphosphonoacetate and (*E*)-3-trimethylsilyl-propenal, itself prepared by the method of S.E. Denmark and T.K. Jones, *J. Org. Chem.*, 1982, **47**, 4595 and M.J. Carter, I. Fleming and A. Percival, *J. Chem. Soc., Perkin Trans. I*, 1981, 2415.

5 G. Stork and E. Colvin, *J. Am. Chem. Soc.*, 1971, **93**, 2080.

6 B.C. Laguzza and B. Ganem, *Tetrahedron Lett.*, 1981, **22**, 1483.

7 S. Kobayashi, T. Iimori, T. Izawa and M. Ohno, *J. Am. Chem. Soc.*, 1981, **103**, 2406.

8 P.F. Hudrlik, A.M. Hudrlik and A.K. Kulkarni, *J. Am. Chem. Soc.*, 1985, **107**, 4260.

9 P.F. Hudrlik, A.M. Hudrlik, R.J. Rona, R.N. Misra and G.P. Withers, *J. Am. Chem. Soc.*, 1977, **99**, 1993.

10 S.T. Hodgson, D.M. Hollinshead and S.V. Ley, *Tetrahedron*, 1985, **41**, 5871.

11 F.A. Bouffard and B.G. Christensen, *J. Org. Chem.*, 1981, **46**, 2208.

12 K.D. Barrow and T.M. Spotswood, *Tetrahedron Lett.*, 1965, 3325.

13 G. Majetich and J. Defauw, *Tetrahedron*, 1988, **44**, 3833.

14 Z. Kosarych and T. Cohen, *Tetrahedron Lett.*, 1980, **21**, 3959.

15 (a) K.C. Nicolaou, R.L. Magolda, J.B. Smith, D. Aharony, E.F. Smith and A.M. Lefer, *Proc. Natl. Acad. Sci. (USA)*, 1979, **76**, 2566. (b) M.F. Ansell, M.P.L. Caton and K.A.J. Stuttle, *J. Chem. Soc., Perkin Trans. I*, 1984, 1069.

16 **16**; m.p. 110-111°C; $[\alpha]_D^{23}$ -65.3 (*c* 1.26, $CHCl_3$); δ_H ($CDCl_3$, 300 MHz) 9.79 (1H, t, *J* 2.2, $CH_2C\underline{H}O$), 4.15 [1H, m, $CH_3C\underline{H}(OH)$], 3.96 (1H, ddd, *J* 8.7, 4.4 and 2.6, $CHC\underline{H}CH_2$), 2.95 (1H, dd, *J* 5.5 and 2.6, CHCO), 2.88 (1H, ddd, *J* 16.0, 4.4 and 2.2, $C\underline{H}_2CHO$), 2.67 (1H, ddd, *J* 16.0, 8.7 and 2.2, $C\underline{H}_2CHO$), 1.21 [3H, d, *J* 6.3, $C\underline{H}_3CH(OH)$], 0.95 [9H, s, $SiC(C\underline{H}_3)_3$], 0.88 [9H, s, $SiC(C\underline{H}_3)_3$], 0.23 [3H, s, $Si(C\underline{H}_3)_2$], 0.22 [3H, s, $Si(C\underline{H}_3)_2$], 0.08 [3H, s, $Si(C\underline{H}_3)_2$], 0.05 [3H, s, $Si(C\underline{H}_3)_2$]; δ_C ($CDCl_3$, 50 MHz) 199.4 (CHO), 172.4 (CO), 66.0 (CH), 65.1 (CH), 49.6 (NCH), 47.3 ($\underline{C}H_2CHO$), 26.2 [$SiC(\underline{C}H_3)_3$], 25.8 [$SiC(\underline{C}H_3)_3$], 22.6 [$\underline{C}H_3CH(OH)$], 18.2 [$Si\underline{C}(CH_3)_3$], 17.9 [$Si\underline{C}(CH_3)_3$], -4.6 [$Si(\underline{C}H_3)_2$], -4.6 [$Si(\underline{C}H_3)_2$], -5.2 [$Si(\underline{C}H_3)_2$], -5.9 [$Si(\underline{C}H_3)_2$]; *m/z* (CI, NH_3) 386 (MH^+, 40%), 97 (100%).

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, $CHCl_3$); δ_H ($CDCl_3$, 300 MHz) 9.79 (1H, t, *J* 2.2, $CH_2C\underline{H}O$), 4.16 [1H, m, $CH_3C\underline{H}(OH)$], 3.97 (1H, ddd, *J* 8.6, 4.3 and 2.6, $CHC\underline{H}CH_2$), 2.95 (1H, dd, *J* 5.5 and 2.6, CHCO), 2.88 (1H, ddd, *J* 16.0, 4.3 and 2.2, $C\underline{H}_2CHO$), 2.67 (1H, ddd, *J* 16.0, 8.6 and 2.2, $C\underline{H}_2CHO$), 1.22 [3H, d, *J* 6.2, $C\underline{H}_3CH(OH)$], 0.96 [9H, s, $SiC(C\underline{H}_3)_3$], 0.88 [9H, s, $SiC(C\underline{H}_3)_3$], 0.23 [3H, s, $Si(C\underline{H}_3)_2$], 0.22 [3H, s, $Si(C\underline{H}_3)_2$], 0.09 [3H, s, $Si(C\underline{H}_3)_2$], 0.07 [3H, s, $Si(C\underline{H}_3)_2$]; δ_C ($CDCl_3$, 75 MHz) 199.3 (CHO), 172.3 (CO), 66.1 (CH), 65.2 (CH), 49.6 (NCH), 47.4 ($\underline{C}H_2CHO$), 26.2 [$SiC(\underline{C}H_3)_3$], 25.8 [$SiC(\underline{C}H_3)_3$], 22.6 [$\underline{C}H_3CH(OH)$], 18.2 [$Si\underline{C}(CH_3)_3$], 18.0 [$Si\underline{C}(CH_3)_3$], -4.5 [$SiC(CH_3)_3(\underline{C}H_3)_2$], -4.6 [$Si(\underline{C}H_3)_2$], -5.2 [$Si\underline{C}H_3)_2$], -5.8 [$Si(\underline{C}H_3)_2$].

18 Satisfactory data including elemental analysis were obtained for all new compounds.

(*Received in UK 27 July 1995, accepted 20 September 1995*)