Tetrahedron Letters, Vol. 34, No. 50, pp. 8163-8166, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

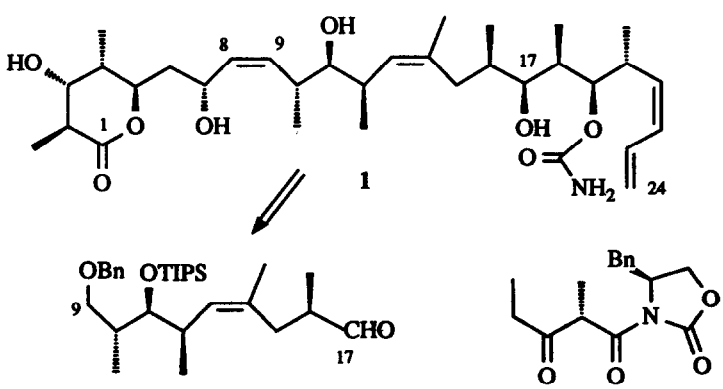
The Synthesis of a C_9-C_{17} Fragment of Discodermolide

Philip L. Evans, Julian M. C. Golec* and Roger J. Gillespie

Roussel Laboratories Ltd., Kingfisher Drive, Covingham, Swindon, Wiltshire, SN3 5BZ, England

Abstract: The asymmetric synthesis of a synthetically useful fragment corresponding to the C_9-C_{17} region of the immunosuppressant lactone discodermolide is reported. The route incorporates the use of an unsaturated lactone to provide a trisubstituted olefin with absolute control of geometry.

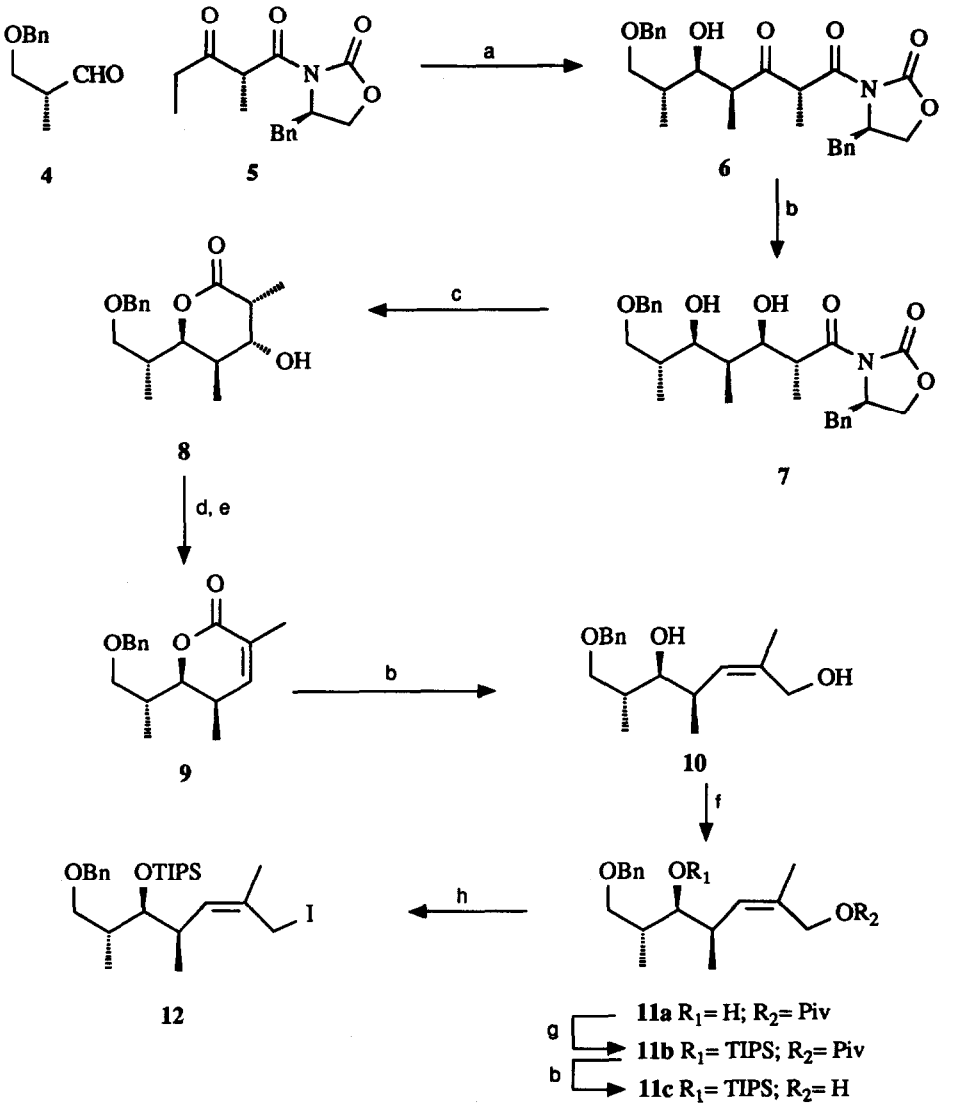
In the preceding paper we outlined a route for the total synthesis of the immunosuppressant lactone discodermolide[1,2] with absolute stereochemistry described as compound **1**. Our retrosynthetic analysis relied on the diastereoselective aldol reactions of β-keto imides described by Evans *et al*[3,4]. The intention was that this technology should provide access to all the stereocentres in discodermolide with the exception of those at C_7, C_{10} and C_{16}. The previous paper described how one of these aldol reactions may be used to provide a fragment corresponding to the tetrasubstituted lactone region (C_1-C_8) of discodermolide. We now describe the application of the tin(II) triflate mediated aldol reaction of a β-keto imide[3] to the synthesis of a fragment **2** corresponding to the C_9-C_{17} region.



1

2 **3**

Scheme 1



a) $Sn(OTf)_2$ / NEt_3; b) DIBAL-H /CH_2Cl_2; c) LiOH / H_2O_2; d) $MeSO_2Cl$ / NEt_3; e) NEt_3
f) pivaloyl chloride / pyridine; g) TIPSOTf / 2,6-lutidine; h) methyl triphenoxyphosphonium iodide

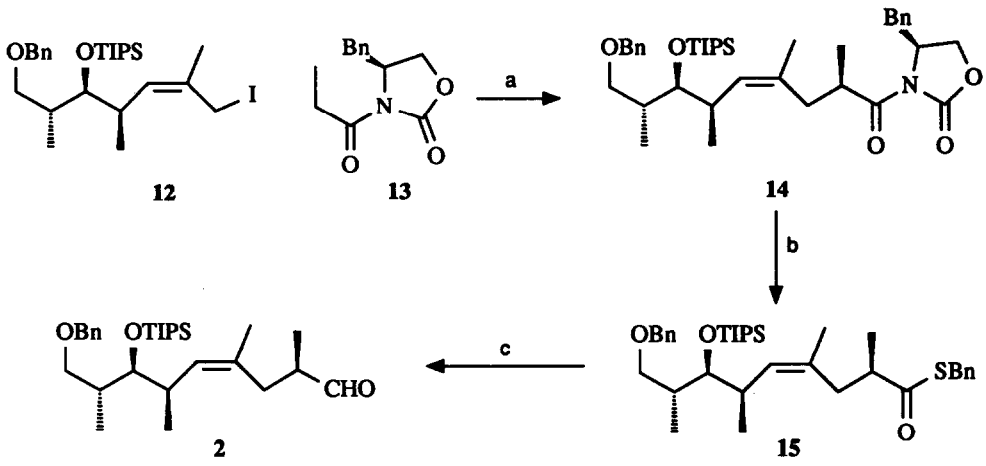
Aldehyde **2** was chosen as a synthetic target because we expected that its tin(II) triflate mediated aldol condensation with β-keto imine **3**[3] would provide us with a suitable substrate for elaboration to the a fragment corresponding to the C_9-C_{24} region of discodermolide. The first part of the synthesis (Scheme 1) started with the tin (II) triflate mediated[3] aldol condensation between aldehyde **4**[5] and β-keto imide **5**[4]. This gave the aldol product **6** (94%) which yielded the diol **7** (99%) on treatment with DIBAL-H[3]. Although the the stereocentres created at C_{13} and C_{14} would eventually be lost, the conditions for *syn-anti* aldol reaction and *syn* reduction were carefully chosen so that the lactone **8** would incorporate the correct stereochemistry

for facile elimination.

The diol **7** was converted to the unsaturated lactone **9**[6] (72%) by use of a three step procedure which did not involve isolation of the intermediates[7]. These were (i) removal of the chiral auxiliary (LiOOH) and immediate lactonisation, (ii) mesylation of the free hydroxyl group (methanesulphonyl chloride), and (iii) base catalysed elimination (triethylamine). Treatment of the lactone **9** with DIBAL-H afforded the diol **10**[8] (62%). This sequence provided a Z-trisubstuted olefin with absolute control of the geometry[9]. A variation of this protocol was used by Grieco *et al* in the synthesis of tylonolide hemiacetal[10].

The synthesis continued with a three step protection sequence. Esterification of diol **10** with pivaloyl chloride afforded the primary hydroxyl protected compound **11a** (91%), which on treatment with triisopropylsilyl triflate afforded the fully protected compound **11b** (100%). Deprotection of the primary hydroxyl (DIBAL-H) yielded the desired alcohol **11c** (96%). The labile allylic iodide **12** was obtained in 92% yield by treatment of alcohol **11c** with methyl triphenoxyphosphonium iodide[11].

Scheme 2



a) $NaN(TMS)_2$ / THF; b) n-BuLi / BnSH; c) DIBAL-H / CH_2Cl_2

The synthesis of aldehyde **2** from the iodide **12** is represented by Scheme 2. The stereoselective alkylation[12] of the propionyl oxazolidinone **13** with iodide **12** provided the amide **14** (90%) as a single stereoisomer. Although double bond geometry remained stable during the alkylation reaction, the iodide **12** was prone to isomerisation on storage. Treatment of **14** with benzylmercaptan and n-butyl lithium afforded the thioester **15**[13] (81%). The synthesis was completed by reduction of the thioester **15** (DIBAL-H) to the aldehyde **2**[14] (88%).

REFERENCES AND NOTES

1. Gunasekera, S. P.; Gunasekera, M.; Longley, R. E.; Schulte, G. K. *J. Org. Chem.* **1990**, *55*, 4912. *ibid* **1991**, *56*, 1346.
2. Longley. R. S.; Caddigan, D.; Harmody, D.; Gunasekera, M.; Gunasekera, S. P. *Transplantation* **1991**, *52*, 650. *ibid* **1991**, *52*, 656.
3. Evans, D. A.; Clark, J. S.; Metternich, R.; Novack, V. J.; Sheppard, G. S. *J. Am. Chem. Soc.*

1990, *112*, 866.

4. Evans, D. A.; Ng, H. P.; Clark, J. S.; Rieger, D. L. *Tetrahedron* **1992**, *48*, 2127.
5. Meyers, A. I.; Babiak, K. A.; Campbell, A. L.; Comins, D. L.; Fleming, M. P.; Henning, R; Heuschmann, M.; Hudspeth, J. P.;Kane, M. K.; Reider, P. J.; Roland, D. M.; Shimizu, K.; Tomioka, K.; Walkup, R. D. *J. Am. Chem. Soc.* **1983**, *105*, 5015.
6. Analytical data for lactone **9**. $[\alpha]^{D}_{21}$ -85.9° (c 1.09, CH_2Cl_2); IR (film) 2970, 2920, 2870, 2850, 1724, 1708, 1446, 1362, 1218, 1126, 1092, 1074, 1046, 986, 734, 694; ^1H NMR ($CDCl_3$) δ 7.22-7.36 (5H, m, Ar), 6.68 (1H, dd *J*= 6.6, 1.4, $C_{13}H$), 4.51 (2H, s, Bn), 4.25 (1H, dd *J*= 10.6, 3.1, $C_{11}H$), 3.62-3.69 (2H, m, C_9H_2), 2.33-2.42 (1H, m, $C_{12}H$), 2.08 (1H, m, $C_{10}H$), 1.9 (3H, br s, $C_{14a}H_3$), 1.01 (3H, d *J*= 7, $C_{10a}CH_3$), 0.99 (3H, d *J*=7, $C_{12a}CH_3$); ^{13}C NMR 166.0 (C_{15}), 145.8 (C_{13}) 138.5 (C_{14}), 128.2, 127.4, 126.9, 80.2 (C_{11}), 73.1, 71.1 (C_9), 34.7 (C_{10}), 30.2 (C_{12}), 16.8 (C_{14a}), 12.9 (C_{10a}), 10.74 (C_{12a}). Anal. Calcd. for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.33; H, 8.09.
7. The lactone **8** was unstable, however ^1H NMR data provides evidence to discount alternative relative stereochemistry. ^1H NMR δ ($CDCl_3$) 4.62 (1H, dd $J_{11,12}$= 2.7, H_{11}), 3.85 (1H, t $J_{12,13}$ and $J_{13,14}$= 3.7, H_{13}), 2.58 (1H, dq $J_{13,14}$= 3.7, H_{14}).
8. Analytical data for diol **10**. $[\alpha]^{D}_{21}$ +7.94 (c 1.16, CH_2Cl_2); IR (film) 3403, 2965, 2932, 2917, 1454, 1366, 1089, 1076, 1009, 739, 698; ^1H NMR ($CDCl_3$) δ 7.35 (5H, m, Ar), 5.22 (1H, d *J*= 9.8, $C_{13}H$), 4.50 (2H, dd), 4.10 (1H, d *J*= 11.8, $C_{15}H$), 3.92 (1H, d *J*= 11.8, $C_{15}H$), 3.56 (1H, dd *J*= 9.2, 4.1 C_9H), 3.45 (1H, dd *J*= 9.2, 6.5, C_9H), 3.31 (1H, m, $C_{11}H$), 2.65 (1H, m, $C_{12}H$), 1.94 (1H, m, $C_{10}H$), 1.79 (3H, d *J*= 1.4, $C_{14a}H_3$), 1.01 (3H, d *J*= 6.7, $C_{12a}H_3$), 0.97 (3H, d *J*= 7, $C_{10a}H_3$); ^{13}C NMR ($CDCl_3$) δ 137.5, 134.3, 131.4 (C_{13}), 128.5, 127.9, 80.3 (C_{11}), 74.3 (C_9), 73.6, 61.7 (C_{15}), 36.2 (C_{12}), 35.4 (C_{10}), 21.8 (C_{14a}), 16.4 (C_{12a}), 15.2 (C_{10a}). Anal. Calcd. for $C_{17}H_{26}O_3$: C, 73.35; H, 9.41. Found: C, 73.72; H, 9.74.
9. Z-olefin geometry is confirmed by the observation of significant NOEs between $C_{14}CH_3$ and $C_{13}H$.
10. Grieco, P. A.; Inanaa, J.; Lin, N.-H.; Yanami, T. *J. Am. Chem. Soc.* **1982**, *104*, 5781.
11. Landauer, S. R.; Rydon, H. N. *J. Chem. Soc.* **1953**, 2224.
12. Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.
13. Analytical data for thioester **15**. $[\alpha]^{D}_{21}$ -30.44° (c 0.338, CH_2Cl_2); IR (film) 2965, 2944, 2866, 1690, 1497, 1454, 1379, 1246, 1092, 1028, 1015, 966, 883, 735, 698, 679; ^1H NMR ($CDCl_3$) δ 7.28 (10H, m, Ar), 5.14 (1H, d *J*= 10, $C_{13}H$), 4.45 (2H, s), 4.09 (2H, s), 3.71 (1H, dd *J*= 5, $C_{11}H$), 3.45(1H, dd *J*= 9, 5.9, $C_{11}H$), 3.25 (1H, m, C_9H), 2.76 (1H, m, $C_{16}H$), 2.54 (1H, m, $C_{12}H$), 2.34 (1H, dd *J*= 13.5, 9.3, $C_{15}H$), 2.18 (1H, dd *J*= 13.5, 5.5, $C_{15}H$), 2.06 (1H, m, $C_{10}H$), 1.57 (3H, s, $C_{14a}H_3$), 1.09 (3H, d, $C_{16a}H_3$), 1.07 (21H, s), 0.98 (3H, d *J*= 6.8, $C_{10a}H_3$), 0.96 (3H, d *J*= 6.5, $C_{12a}H_3$): ^{13}C NMR ($CDCl_3$) δ 202.7 (C_{17}), 138.8, 137.6, 133.1(C_{13}), 129.5 (C_{14}), 128.8, 128.6, 128.2, 127.5, 127.3, 127.2, 77.9 (C_{11}), 73.2 (C_{11}), 72.9, 46.4 (C_{16}), 39.8 (C_{10}), 35.9 (C_{15}), 35.3 (C_{12}), 33.1, 23.1, 18.4, 17.1 (C_{12a}), 16.7 (C_{16a}), 13.5 (C_{10a}), 13.4. Anal. Calcd. for $C_{36}H_{56}O_3SSi$: C, 72.43; H, 9.46; S, 5.37. Found: C, 72.39; H, 9.43; S, 5.31.
14. Analytical data for aldehyde **2**. $[\alpha]^{D}_{21}$ -12.79° (c 0.9, CH_2Cl_2); IR (film) 3031, 2962, 2943, 2867, 1728, 1455, 1092, 1028, 1014, 883, 697, 678, 651; ^1H NMR ($CDCl_3$) δ 9.62 (1H, d *J*= 1.6, $C_{17}H$), 7.29 (5H, m, Ar), 5.17 (1H, d *J*= 10, $C_{13}H$), 4.46 (2H, s, Bn), 3.72 (1H, dd *J*= 5.7 *J*=4.3, $C_{11}H$), 3.46 (1H, dd, *J*= 9, 6, C_9H), 3.26 (1H, dd *J*= 9, 7.6, C_9H), 2.52 (1H, m, $C_{12}H$), 2.5 (1H, m, $C_{16}H$), 2.18 (2H, d *J*= 7.7, $C_{15}H_2$), 2.08 (1H, m, $C_{10}H$), 1.61 (3H, d *J*= 1.2, $C_{14a}H_3$), 1.08 (21H), 1.01 (3H, d *J*= 7, $C_{16a}H_3$), 0.97 (3H, d *J*= 7.1, $C_{10a}H_3$), 0.96 (3H, d *J*= 6.7, $C_{12a}H_3$); ^{13}C NMR δ 204.7 (C_{17}), 138.8, 133.2 (C_{13}), 129.3 (C_{14}), 128.2, 127.5, 127.4, 78.0 (C_{11}), 73.1 (C_9), 73.0, 44.5 (C_{16}), 39.8 (C_{10}), 35.4 (C_{12}), 32.4 (C_{15}), 23.0 (C_{14a}), 18.4, 17.1, 13.6, 13.4, 12.9. Anal. Calcd. for $C_{29}H_{50}O_3Si$: C, 73.36; H, 10.61; Found: C, 73.34; H, 10.47.
15. NMR assignments refer to discodermolide numbering.

(Received in UK 16 September 1993; accepted 8 October 1993)