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Synthesis of C1–C8 and C9–C24 fragments of (−)-discodermolide: use of asymmetric alkylation and stereoselective aldol reactions †

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Abstract

The C1–C8 and C9–C24 fragments of (−)-discodermolide, the antipode of the marine natural product (+)-discodermolide, have been synthesized with excellent stereoselectivities. These syntheses feature the utilization of the isoxazolidine-mediated asymmetric alkylation methodology and fragment–fragment coupling aldol reactions.

Discodermolide [(+)-**1**] was isolated from the marine sponge *Discodermia dissoluta* in 1990,[1] and is noted for its potent immunosuppressive and anti-cancer activities.[1,2] Due to the potential therapeutic applications and the extreme scarcity of discodermolide [0.002% (w/w) from frozen marine sponge], interest in the chemical synthesis of this natural product still continues unabated.[3] In this communication we wish to describe our approach to highly stereoselective syntheses of the C1–C8 (**A**) and C9–C24 (**B**) fragments of (−)-discodermolide. These syntheses feature the utilization of our isoxazolidine-mediated asymmetric alkylation methodology and fragment–fragment coupling aldol reactions.

A logical retrosynthetic analysis of (−)-**1** involves the dissection of the C8–C9 double bond to afford two fragments, **A** and **B** (Scheme 1). Indeed, the feasibility of the reconstruction of the *Z* double bond via a Wittig reaction has been demonstrated by Smith et al.[3b] Our stereoselective syntheses of fragments **A** and **B** are summarized below.

The synthesis of fragment **B** started with the known chiral aldehyde **2**[4] (Scheme 2). The trisubstituted *Z*-double bond was constructed with complete stereocontrol through the use of Still's procedure[5] to afford the α,β-unsaturated ester **3**. We envisioned establishing the stereogenic center at C16 via an asymmetric alkylation reaction using chiral isoxazolidine auxiliaries which were recently developed in our laboratories.[6] Thus, compound **3** was first converted into the unstable iodide **4**,[7] which was then allowed to react with the enolate derived from the chiral propylamide (+)-**5** to furnish compound **6**. This

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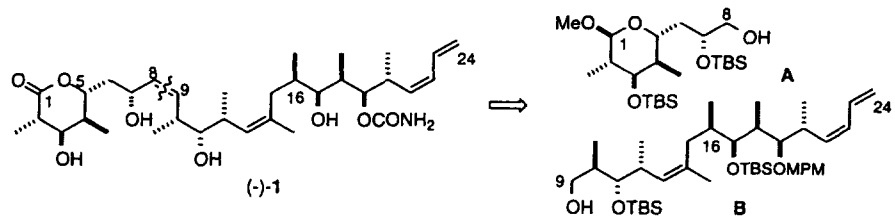
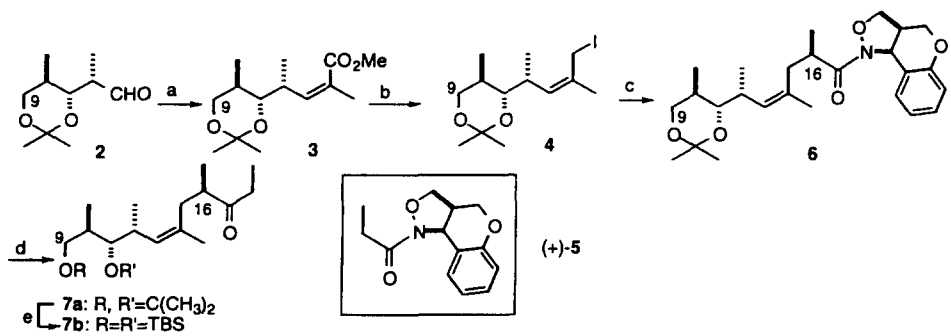


Scheme 1.

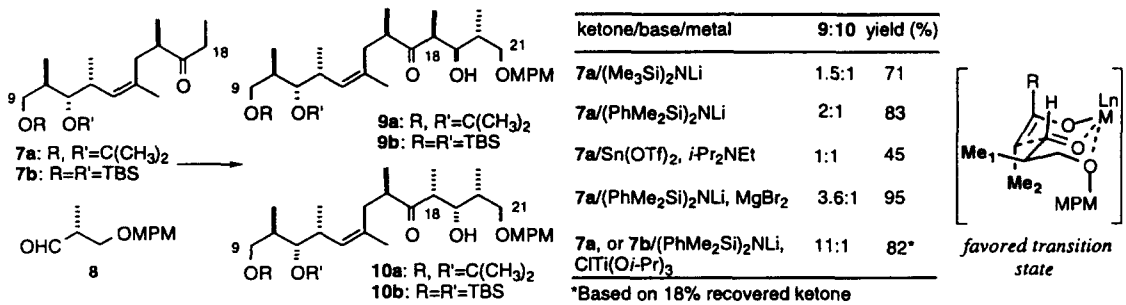
double asymmetric alkylation proceeded with a diastereoselectivity greater than 96%. One of the distinct advantages of this isoxazolidine-mediated alkylation methodology is that the alkylated products can be transformed into the corresponding ketones, alcohols and aldehydes in a single operation. This is best exemplified by the conversion of compound **6** to the ethyl ketone **7a** upon treatment with EtMgBr. At this point, the acetonide group in **7a** was changed to the TBS groups (**7b**) which was necessary for subsequent manipulations.



Scheme 2. Conditions: (a) KHMDS, $(CF_3CH_2O)_2P(O)CH(CH_3)CO_2Me$, 18-c-6, THF, −78°C then **2**, −30°C (77%); (b) i. DIBAL-H, ether, −78°C (92%), ii. I_2, Ph_3P, imidazole, CH_3CN/ether (1/3), −20°C; (c) (+)-**5**, KHMDS, THF, −78°C, then **4**, (76% for 2 steps); (d) EtMgBr, THF, −78°C to 0°C, (70%); (e) i. CSA, MeOH/THF/H_2O (93%); ii. TBSOTf, 2, 6-lutidine (91%)

The next stage of the synthesis involved a stereoselective aldol reaction of ethyl ketone **7a** (or **7b**) with aldehyde **8** (Scheme 3).[8] Coupling of two chiral fragments via stereoselective aldol reactions has been a subject of extensive investigation because of its great utility in the convergent syntheses of polyketide natural products.[9] The stereochemistry of our desired compounds **9a** (or **9b**) is very similar to, or the same as, the stereochemistry encountered earlier in the syntheses of 6-deoxyerythronolide B[10] and rifamycin S.[11] The stereochemical course of this aldol reaction is extremely sensitive to both the metal counter ion used, and the substituents on the C_β of the aldehyde. The results of a systematic survey of metals are summarized in Scheme 3. As can be seen from the Scheme, while the aldol reaction of aldehyde **8** with the lithium *Z* (*O*)-enolate of **7a** proceeded with only modest stereoselectivity (2:1), the use of magnesium and titanium as counter ions brought about good stereocontrol, with ratios of 3.6:1 and 11:1, respectively.[12] The stereochemical outcome of the aldol addition could be rationalized by considering the transition state depicted in Scheme 3. Both the chelation effect and the avoidance of the g^+g^- pentane interaction of Me_1 and Me_2 stabilized this transition state.[10,11,13]

Directed reduction[14] of the β-hydroxyketone **9b** afforded the *syn*-diol,[15] which was treated with DDQ in anhydrous CH_2Cl_2[16] to provide compound **11** (Scheme 4). Protection of the C17 alcohol as its TBS ether followed by reaction with an excess of DIBAL-H resulted in the exclusive formation of the C21 primary alcohol.[17] Swern oxidation of the alcohol afforded the corresponding aldehyde **12**. The terminal *Z*-diene was installed via a two-step procedure involving a Wittig olefination with the phosphorane **14**.[18]

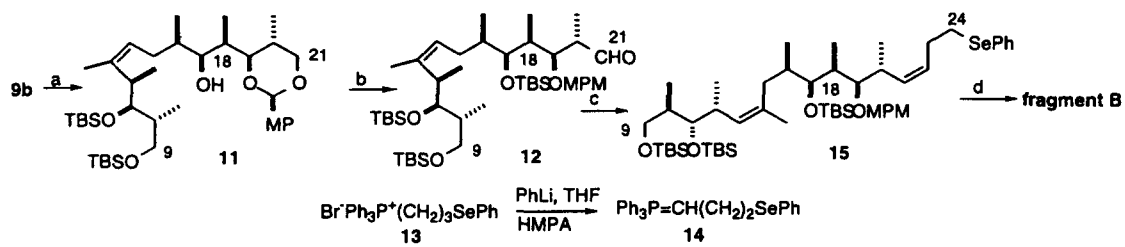


ketone/base/metal	9:10	yield (%)
7a/$(Me_3Si)_2NLi$	1.5:1	71
7a/$(PhMe_2Si)_2NLi$	2:1	83
7a/$Sn(OTf)_2$, i-Pr_2NEt	1:1	45
7a/$(PhMe_2Si)_2NLi$, $MgBr_2$	3.6:1	95
7a, or 7b/$(PhMe_2Si)_2NLi$, $ClTi(Oi\text{-}Pr)_3$	11:1	82*

*Based on 18% recovered ketone

Scheme 3.

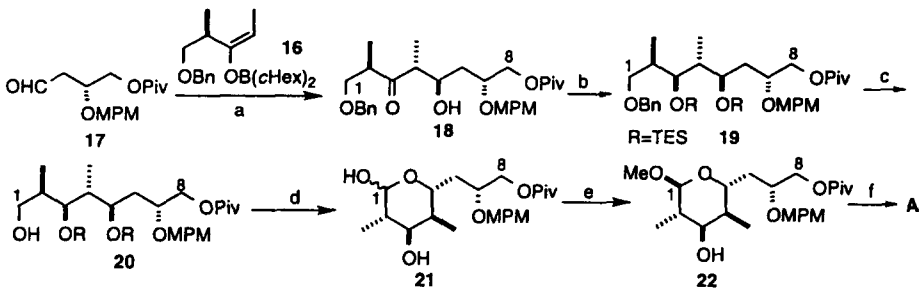
Treatment of the phosphonium salt **13** with PhLi in THF/HMPA generated **14**, which was condensed with aldehyde **12** to afford alkene **15** as a single isomer in good yield. The phenylselenium moiety was then oxidized and eliminated to give the desired *Z*-diene. Finally, the primary TBS group was removed selectively with buffered HF–py, thereby concluding the synthesis of fragment **B**.[19]



Scheme 4. Conditions: (a) i. Et_2BOMe, $NaBH_4$, THF/MeOH (3/1) (84%); ii. DDQ, 4Å molecular sieves, CH_2Cl_2 (81%); (b) i. TBSOTf, 2, 6-lutidine, CH_2Cl_2, –78°C (98%); ii. DIBAL-H, toluene, –78°C to 0°C (89%); iii. $(COCl)_2$, DMSO, TEA, CH_2Cl_2, –78°C (95%); (c) **13**, PhLi, THF/HMPA, –78~0°C, then **12** (77%); (d) i. H_2O_2, $NaHCO_3$, THF (87%); ii. HF–py, py, THF, (87%)

The synthesis of fragment **A** commenced with an *anti*-selective aldol reaction of the *E* (*O*)-enolate **16**[20] with the readily synthesized aldehyde **17** (Scheme 5). Extensive studies by Paterson and coworkers have determined that the diastereofacial selectivity (ds) of **16** is extremely high and that it can often adequately override the ds of many chiral aldehydes. In the present case, the double asymmetric aldol reaction proceeded in the expected manner to provide compound **18** exclusively. Directed reduction of **18** afforded the *syn*-diol,[14,15] then the hydroxy groups were protected as TES ethers to provide **19**. Selective removal of the benzyl group with Raney-Ni furnished the primary alcohol **20**, which was subsequently oxidized to the aldehyde. Deprotection of silyl groups with 50% acetic acid resulted in spontaneous cyclization to the hemi-acetal **21**. Treatment of **21** with a catalytic amount of CSA in MeOH led to the formation of the methylglycoside **22** (β:α=1.5:1). Protecting group adjustment then completed the synthesis of fragment **A**.[21]

In the syntheses described above, every step proceeded with high stereoselectivity, leading to the efficient construction of both fragments **A** and **B** of (–)-discodermolide. As earlier noted, the feasibility of the coupling of **A** and **B** via a Wittig reaction has been demonstrated by Smith et al.[3b]



Scheme 5. Conditions: (a) **16** and **15**, ether, –78°C to 0°C (73%); (b) i. Et_2BOMe, $NaBH_4$, MeOH/THF (1/3), –78°C (83%); ii. TESOTf, 2, 6-lutidine, CH_2Cl_2, -78°C (97%); (c) Raney-Ni, EtOH, 25°C (86%); (d) i. PDC, CH_2Cl_2 (99%); ii. 50% AcOH/H_2O, THF; (e) CSA (cat. amt.) MeOH (96%, 2 steps); (f) i. DDQ, CH_2Cl_2/H_2O (77%); ii. TBSOTf, 2, 6-lutidine, CH_2Cl_2, –78°C; iii. MeLi, ether, 0°C (83% for 2 steps)

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References

1. Gunasekera, S. P.; Gunasekera, M.; Longley, R. E.; Schulte, G. K. *J. Org. Chem.* **1990**, *55*, 4912; (Erratum) *ibid.* **1991**, *56*, 1346.
2. (a) Longley, R. E.; Caddigan, D.; Harmody, D.; Gunasekera, M.; Gunasekera, S. P. *Transplantation* **1991**, *52*, 650. (b) Longley, R. E.; Caddigan, D.; Harmody, D.; Gunasekera, M.; Gunasekera, S. P. *ibid.* **1993**, *55*, 236.
3. For total syntheses, see: (a) Hung, D. T.; Nerenberg, J. B.; Schreiber, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 11054. (b) Smith III, A. B.; Qiu, Y.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **1995**, *117*, 12011. (c) Harried, S. S.; Yang, G.; Strawn, M. A.; Myles, D. C. *J. Org. Chem.* **1997**, *62*, 6098. (d) Marshall, J. A.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 7885. For other synthetic efforts, see: (e) Paterson, I.; Schlapbach, A. *Synlett* **1995**, 498. (f) Paterson, I.; Wren, S. P. *J. Chem. Soc., Chem. Commun.* **1993**, 1790. (g) Golec, J. M. C.; Jones, S. D. *Tetrahedron Lett.* **1993**, *34*, 8159. (h) Evans, P. L.; Golec, J. M. C.; Gillespie, R. J. *ibid.* **1993**, *34*, 8163. (i) Golec, J. M. C.; Gillespie, R. J. *ibid.* **1993**, *34*, 8167. (j) Clark, D. L.; Heathcock, C. H. *J. Org. Chem.* **1993**, *58*, 5878.
4. Ziegler, F. E.; Cain, W. T.; Kneisley, A.; Stirchak, E. P.; Wester, R. T. *J. Am. Chem. Soc.* **1988**, *110*, 5442.
5. Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.
6. (a) Abiko, A.; Moriya, O.; Filla, S. A.; Masamune, S. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 793. (b) Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1996**, *37*, 1081.
7. Garregg, P. J.; Samuelsson, B. *J. Chem. Soc., Chem. Commun.* **1979**, 978.
8. Nakamura, S.; Shibasaki, M. *Tetrahedron Lett.* **1994**, *35*, 4145.
9. (a) Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151 and references cited therein; (b) McCarthy, P. A.; Kageyama, M. *J. Org. Chem.* **1987**, *52*, 4681.
10. Masamune, S.; Ellingboe, J. W.; Choy, W. *J. Am. Chem. Soc.* **1982**, *104*, 5526.
11. Masamune, S.; Imperiali, B.; Garvey, D. S. *J. Am. Chem. Soc.* **1982**, *104*, 5528.
12. For Mg enolate: (a) Ref. 11. (b) Devant, R.; Mahler, H.; Braun, M. *Chem. Ber.* **1988**, *121*, 397. For Ti enolate: (c) Siegel, C.; Thornton, E. R. *J. Am. Chem. Soc.* **1989**, *111*, 5722. (d) Evans, D. A.; Ng, H. P.; Rieger, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 11446.
13. (a) Ref. 9a. (b) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1.
14. Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155.
15. The *syn* relationship of the diol was confirmed through the conversion of the diol to its acetonide and analysis of the chemical shifts of the acetonide carbons in the ^{13}C NMR spectrum. (a) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945. (b) Evans, D. A.; Rieger, D. L.; Gage, J. R. *ibid.* **1990**, *31*, 7099. (c) Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511.

16. Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 889.
17. (a) Kloosterman, M.; Shghek, T.; Hermans, J. P. G.; van Boom, J. H. *J. Royal Neth. Chem. Soc.* **1984**, *103*, 335. For recent applications, see: (b) Nakatsuka, M.; Ragan, J. A.; Sammakia, T.; Smith, D. B.; Uehling, D. E.; Schreiber, S. *J. Am. Chem. Soc.* **1990**, *112*, 5583. (b) Evans, D. A.; Ng, H. P.; Rieger, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 11446.
18. For a preparation of the bromide, see: Middleton, D. S.; Simpkins, N. S.; Begley, M. J.; Terrett, N. K. *Tetrahedron* **1990**, *46*, 545. The phosphonium salt was generated from the bromide under the standard conditions (toluene, 110°C, 24 h). For a recent application, see: Nicolaou, K. C.; Reddy, K. R.; Skokotas, G.; Sato, F.; Xiao, X.-Y.; Hwang, C.-K. *J. Am. Chem. Soc.* **1993**, *115*, 3558.
19. ^{1}H NMR data for fragment **B**: (300 MHz, C_6D_6) δ 7.30 (d, *J*=9.0 Hz, 2H), 6.83 (d, *J*=9.0 Hz, 2H), 6.72 (dt, *J*=10.5, 16.8 Hz, 1H), 6.13 (t, *J*=10.8 Hz, 1H), 5.70 (t, *J*=10.5 Hz, 1H), 5.26 (dd, *J*=2.4, 17.1 Hz, 1H), 5.11 (d, *J*=10.2 Hz, 2H), 4.60 (d, *J*=10.5 Hz, 1H), 4.51 (d, *J*=10.2 Hz, 1H), 3.55–3.71 (m, 3H), 3.46 (dd, *J*=3.9, 6.6 Hz, 1H), 3.34 (dd, *J*=3.6, 6.9 Hz, 1H), 3.32 (s, 3H), 3.11 (m, 1H), 2.78 (m, 1H), 2.33 (t, *J*=12.9 Hz, 1H), 1.74–2.04 (m, 5H), 1.66 (s, 3H), 1.23 (d, *J*=6.6 Hz, 3H), 1.13 (d, *J*=7.1 Hz, 3H), 1.09 (d, buried, 3H), 1.08 (s, 9H), 1.02 (d, *J*=6.9 Hz, 3H), 1.00 (s, 9H), 0.95 (d, *J*=6.7 Hz, 3H), 0.20 (s, 3H), 0.18 (s, 3H), 0.11 (s, 3H), 0.09 (s, 3H).
20. (a) Paterson, I.; Goodman, J. M.; Isaka, M. *Tetrahedron Lett.* **1989**, *30*, 7121. (b) Paterson, I.; Perkins, M. V. *J. Am. Chem. Soc.* **1993**, *115*, 1608.
21. ^{1}H NMR data for fragment **A**, (300 MHz, C_6D_6) δ 4.24 (d, *J*=3.0 Hz, 1H), 3.89–4.05 (m, 2H), 3.60–3.69 (m, 2H), 3.46 (dd, *J*=4.5, 5.7 Hz, 1H), 3.27 (s, 3H), 1.94 (m, 1H), 1.58–1.80 (m, 3H), 1.03 (s, 9H), 0.99 (s, 9H), 0.90 (d, *J*=6.6 Hz, 6H), 0.18 (s, 3H), 0.13 (s, 3H), 0.07 (s, 3H), 0.02 (s, 3H).