A Practical Synthesis of (+)-Discodermolide and Analogues: Fragment Union by Complex Aldol Reactions

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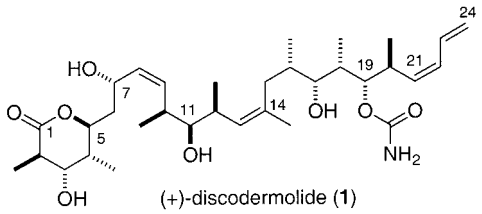
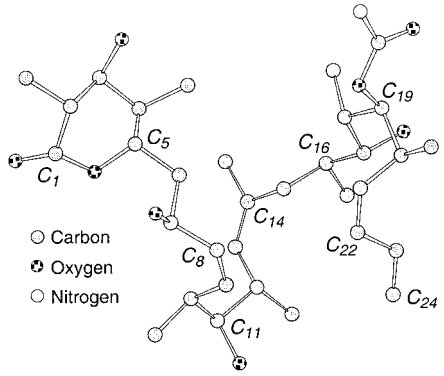
Abstract: A practical stereocontrolled synthesis of (+)-discodermolide (**1**) has been completed in 10.3% overall yield (23 steps longest linear sequence). The absolute stereochemistry of the C_1-C_6 (**7**), C_9-C_{16} (**8**), and $C_{17}-C_{24}$ (**9**) subunits was established via substrate-controlled, boron-mediated, aldol reactions of the chiral ethyl ketones **10**, **11**, and **12**. Key fragment coupling reactions were a lithium-mediated, *anti*-selective, aldol reaction of aryl ester **8** (under Felkin-Anh induction from the aldehyde component **9**), followed by in situ reduction to produce the 1,3-diol **40**, and a (+)-diisopinocampheylboron chloride-mediated aldol reaction of methyl ketone **7** (overturning the inherent substrate induction from the aldehyde component **52**) to give the (7*S*)-adduct **58**. The flexibility of our overall strategy is illustrated by the synthesis of a number of diastereomers and structural analogues of discodermolide, which should serve as valuable probes for structure−activity studies.

Introduction

Discodermolide (**1**) is a unique polyketide isolated by Gunasekera and co-workers at the Harbor Branch Oceanographic Institute in 1990 from the Caribbean deep sea sponge *Discodermia dissoluta*.[1,2] Its gross structure was determined by extensive spectroscopic studies and the relative stereochemistry was assigned by single-crystal X-ray crystallography. Structurally, it bears 13 stereogenic centers, a tetrasubstituted δ-lactone (C_1-C_5), one di- and one trisubstituted (*Z*)-double bond, a pendant carbamate moiety (C_{19}), and a terminal (*Z*)-diene ($C_{21}-C_{24}$). In the solid state, discodermolide adopts the U-shaped conformation shown in Figure 1, where the two internal (*Z*)-olefins in the side chain act as conformational locks by minimizing A(1,3) strain between their respective substituents in concert with the avoidance of *syn*-pentane interactions, while the tetrasubstituted δ-lactone prefers a boatlike conformation. The 24-membered polyketide carbon skeleton of discodermolide appears to be made up of eight propionate and four acetate units. It is likely that this dodecaketide is biosynthesized by a symbiotic microorganism associated with *Discodermia dissoluta* species, involving a modular polyketide synthase.

Discodermolide was initially found to be a potent immunosuppressive agent, both in vivo and in vitro, as well as displaying antifungal activity.[3] It inhibited T-cell proliferation with an IC_{50} of 9 nM and graft versus host disease in transplanted mice. Further biological screening of this compound revealed startling cytotoxicity, causing cell cycle arrest in the G2/M phase in a variety of human and murine cell lines.[4] Discodermolide joins the group of antimitotic agents shown in Figure 2 now known to act by microtubule stabilization whose number include Taxol (**2**),[5a] epothilones A and B (**3**, **4**),[5b] eleutherobin (**5**),[5c] and most recently, laulimalide (**6**).[5d] Discodermolide has been recognized





View of the X-ray structure of (+)-discodermolide (Hydrogens omitted for clarity)

Figure 1.

(1) Gunasekera, S. P.; Gunasekera, M.; Longley, R. E.; Schulte, G. K. *J. Org. Chem.* **1990**, *55*, 4912. Additions and corrections: *J. Org. Chem.* **1991**, *56*, 1346.

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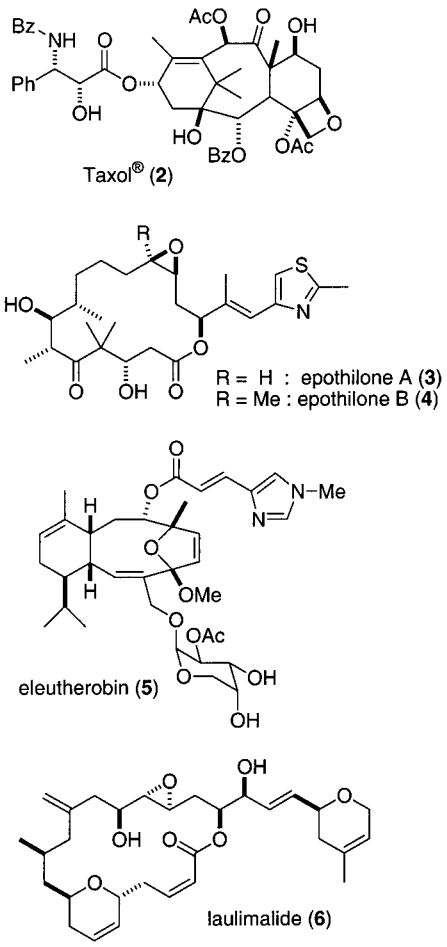

Figure 2.

as one of the most potent tubulin polymerizing agents presently known. Despite having no apparent structural similarities, discodermolide has been found to stabilize microtubules more potently than Taxol (**2**, paclitaxel) and competitively inhibit its binding to tubulin polymers.[4,6] The growth of Taxol-resistant ovarian and colon cancer cells is inhibited by discodermolide with an IC_{50} of <2.5 nM,[7] while the timing and type of DNA fragmentation induced is consistent with the induction of apoptosis.[8]

In recent comparative studies of discodermolide, the epothilones and eleutherobin against a Taxol-dependent human lung carcinoma cell line (A549-T12),[9] it was found that discodermolide was unable to act as a substitute for Taxol, whereas the epothilones and eleutherobin were able to maintain the viability of the cell line. Significantly, the presence of low concentrations of Taxol amplified the cytotoxicity of discodermolide 20-fold against this cell line. However, this synergistic effect in vitro was not observed with combinations of the epothilones or eleutherobin with Taxol.

The highly encouraging biological profile of discodermolide (**1**) makes it a promising candidate for clinical development as a chemotherapeutic agent for Taxol-resistant breast, ovarian, and colon cancer and other multi-drug-resistant cancers. Clinical development, though, is severely hampered by the extremely scarce supply of discodermolide (0.002% w/w frozen sponge) from the natural source (a rare, deep-sea sponge only found in the Caribbean that requires the use of manned submersibles for collection). Thus, total synthesis presently provides the only viable route to useful quantities of this novel cytotoxic polyketide. Consequently, there has been considerable synthetic effort toward discodermolide, culminating in several total syntheses[10] and numerous fragment syntheses.[11] Indeed, the absolute configuration of discodermolide was established by Schreiber and co-workers by their initial syntheses of both (+)- and (−)-discodermolide.[10a,b] Herein, we report full details of the development of a novel, aldol-based, total synthesis[12a] of (+)-discodermolide to provide useful quantities of this important marine natural product, with improved fragment syntheses and couplings, and some novel structural analogues.[12b] Notably, our optimized synthesis involves a highly effective fragment coupling strategy, distinct from all previously reported approaches, which leads to a 10.3% overall yield (over 23 linear steps) and offers the potential for producing substantial quantities of (+)-discodermolide, thus helping to relieve the supply problem and enabling its further development in cancer chemotherapy.

Results and Discussion

Synthesis Plan. At the outset, a revised synthetic strategy was designed to overcome the problems associated with our earlier route,[11a,h] which were encountered in fragment coupling and installation of the synthetically challenging trisubstituted (*Z*)-alkene. Specific objectives were to design a practical synthesis employing a high level of convergency, involving efficient and scaleable chemistry, that both has the potential to deliver multigram quantities of discodermolide and is amenable to analogue synthesis. Our resulting retrosynthesis of discodermolide (Scheme 1) is based on two key aldol-type disconnections, across C_6-C_7 and $C_{16}-C_{17}$, leading back to the C_1-C_6 methyl ketone **7**, the C_9-C_{16} aryl ester **8**,[13] and the $C_{17}-C_{24}$ diene aldehyde **9**. These three fragments are of similar stereochemical and functional group complexity. We viewed these subunits as being readily accessible by boron-mediated *anti-*

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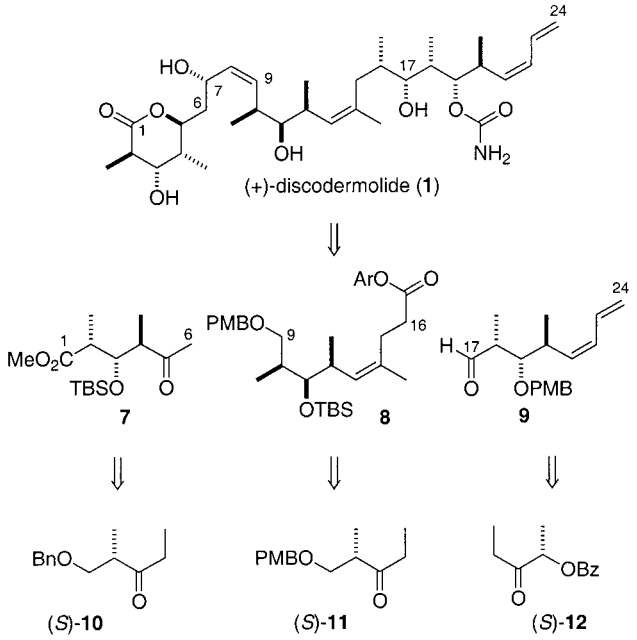
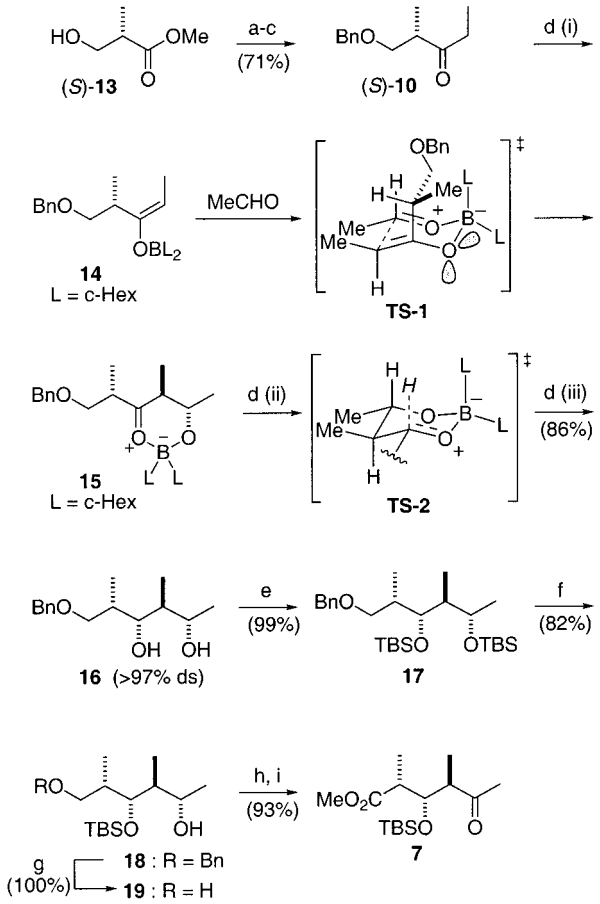
Scheme 1. Retrosynthetic Analysis



aldol reactions of the chiral ethyl ketones (*S*)-**10**,[14] (*S*)-**11**,[15] and (*S*)-**12**,[16] which should serve to construct the requisite stereochemical motifs in a rapid and efficient manner.[17]

Synthesis of the C_1-C_6 Subunit, 7. The α-chiral ethyl ketone (*S*)-**10** required for the sequence was readily synthesized in three steps (71% overall yield) from commercially available methyl (*S*)-2-methyl-3-hydroxypropionate, (*S*)-**13**.[14a] Enolization of (*S*)-**10** under standard conditions, $(c\text{-Hex})_2BCl/Et_3N$, led to the selective generation of the (*E*)-boron enolate **14** (Scheme 2), which underwent addition to acetaldehyde through a highly ordered chairlike transition state (**TS-1**).[14] This was followed by in situ reduction of the intermediate boron aldolate **15** with $LiBH_4$, via axial hydride delivery (**TS-2**), to provide, after oxidative workup, the 1,3-*syn* diol **16** (86%, >97% ds).[18,19] Thus, the initial substrate-controlled aldol addition is extended to allow the one-pot assembly of the specific stereotriad found in the C_1-C_6 unit. Treatment of the 1,3-*syn* diol **16** with TBSOTf and 2,6-lutidine in CH_2Cl_2 provided the bis-TBS ether **17** in 99% yield. Selective removal of the less sterically encumbered TBS ether at C_5 was then achieved by using

Scheme 2[a]



[a] Key: (a) $BnOC(=NH)CCl_3$, $TfOH_{cat.}$, Et_2O, 20 °C; (b) *i*PrMgCl, MeNH(OMe)·HCl, THF, −30 → −10 °C; (c) EtMgBr, THF, 0 °C; (d) (*i*) $c\text{-Hex}_2BCl$, Et_3N, Et_2O, 0 °C; MeCHO, −78 → −20 °C; (*ii*) $LiBH_4$, −78 °C; (*iii*) H_2O_2(30% aq)/MeOH, NaOH(10% aq), 0 °C; (e) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C; (f) CSA, MeOH/CH_2Cl_2, 0 °C; (g) 20% $Pd(OH)_2/C$, H_2, EtOH, 20 °C; (h) (*i*) $(COCl)_2$, DMSO, CH_2Cl_2, −78 → −50 °C; (*ii*) Et_3N, −50 → −20 °C; (i) (*i*) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, H_2O, 20 °C; (*ii*) CH_2N_2, Et_2O, 20 °C.

catalytic CSA in 1:2 MeOH/CH_2Cl_2 at 0 °C, to provide alcohol **18** in 82% yield, along with diol **16** and recovered bis-TBS ether **17**, which could be recycled accordingly. Subsequent hydrogenolysis of the benzyl ether **18** provided diol **19** in quantitative yield. The diol was cleanly converted into the required C_1-C_6 fragment **7** in a further three steps. In general, this sequence was carried out without isolation of the intermediates, affording the C_1-C_6 fragment **7** in excellent yield (93%). Double oxidation of **19** to the corresponding keto aldehyde was possible by using a modified Swern protocol.[20] Further oxidation[21] with sodium chlorite provided the intermediate carboxylic acid, which was esterified directly with diazomethane to give **7**. This sequence was readily performed on a multigram scale to provide the C_1-C_6 fragment **7** in 46% overall yield from the starting ester (*S*)-**13**.

Synthesis of the C_9-C_{16} Subunit, 8. One of the most synthetically challenging aspects of discodermolide is the efficient introduction of the $C_{13}-C_{14}$ trisubstituted (*Z*)-olefin. Previous syntheses have adopted conventional methods for its

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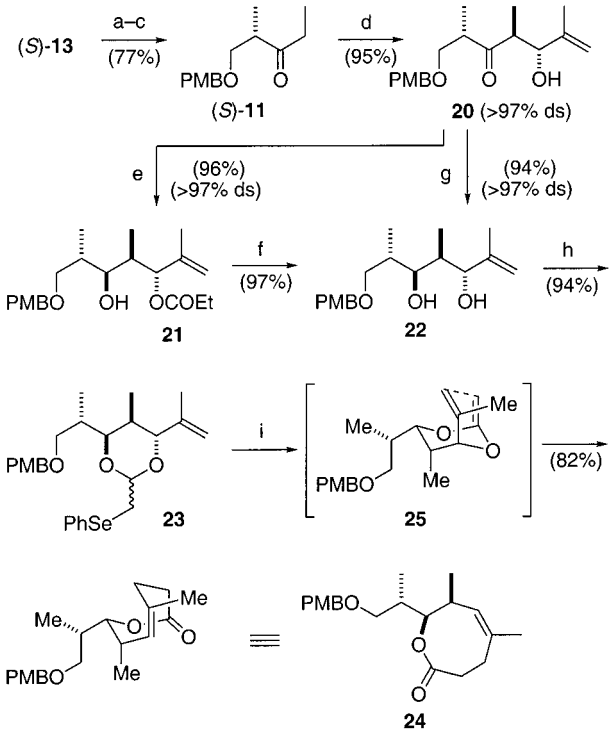
Scheme 3[a]

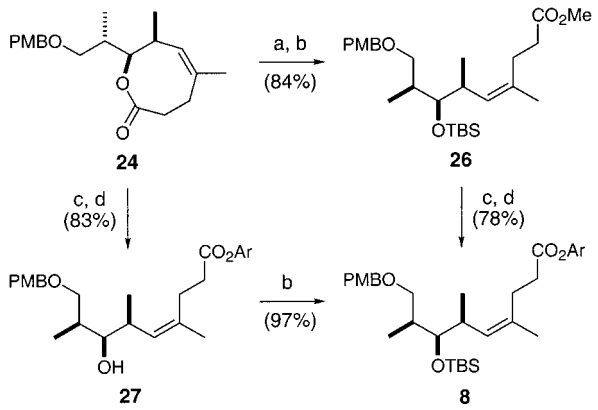


[a] Key: (a) PMBOC(=NH)CCl_3, $TfOH_{cat.}$, Et_2O, 20 °C; (b) *i*PrMgCl, MeNH(OMe)·HCl, THF, −15 °C; (c) EtMgBr, THF, 0 °C; (d) (*i*) c-Hex_2BCl, Et_3N, Et_2O; H_2C=C(Me)CHO, −78 → −20 °C; (*ii*) H_2O_2(30% aq)/MeOH, pH 7 buffer, 0 °C; (e) SmI_2, EtCHO, THF, −10 °C; (f) K_2CO_3, MeOH, 20 °C; (g) $Me_4NBH(OAc)_3$, MeCN/AcOH, −40 → −23 °C; (h) $PhSeCH_2CH(OEt)_2$, PhMe, $PPTS_{cat.}$, reflux; (i) (*i*) $NaIO_4$, $NaHCO_3$, MeOH/H_2O, 20 °C; (*ii*) DBU, H_2C=C(OMe)OTBS, xylenes, reflux.

construction, e.g. Wittig olefinations, but these have often proved unreliable, exhibiting variable yields and selectivities.[10c,g] Our C_9-C_{16} fragment **8** required a carbonyl functionality attached to C_{16} to allow aldol-based fragment coupling. The elegant Claisen-type ring expansion methodology, developed extensively by Holmes and co-workers for the synthesis of medium ring lactones, allows the installation of this functionality and the $C_{13}-C_{14}$ trisubstituted olefin simultaneously.[22]

The synthesis of the C_9-C_{16} aryl ester fragment **8** started from the PMB protected ketone (*S*)-**11** (Scheme 3).[15] This was accessed in three steps (77% overall yield, 0.2 mol scale) from methyl (*S*)-3-hydroxy-2-methylpropionate, (*S*)-**13**, under similar conditions to that described above for the benzyl protected ketone (*S*)-**10**. Under our standard conditions (c-Hex)$_2$BCl/Et_3N,[14] (*E*)-enolization of the ketone (*S*)-**11**, and reaction with methacrolein gave, after oxidative workup, the expected *anti*-aldol product **20** (95%, >97% ds).[23] Substrate-controlled 1,3-*anti* reduction of the *β*-hydroxy ketone was achieved under the Evans−Tischenko conditions,[24] with SmI_2 and propionaldehyde, to provide 1,3-diol monoester **21** (96%, >97% ds). Methanolysis

Scheme 4[a]



[a] Key: (a) NaOMe, MeOH, 0 °C → 20 °C; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C; (c) KOH (1 M aq), MeOH, reflux; (d) 2,6-dimethylphenol, DCC, 4-DMAP, CH_2Cl_2, 20 °C. Ar = 2,6-dimethylphenyl.

(K_2CO_3, MeOH) then provided the 1,3-*anti* diol **22** (97%). Alternatively, reduction of *β*-hydroxy ketone **20** was achieved by using $Me_4NBH(OAc)_3$ in MeCN and AcOH to provide directly the 1,3-*anti* diol **22** (94%, >97% ds). While the latter method shortens the synthetic route, it was somewhat less amenable to material throughput than the two-step procedure. Following the Holmes protocol,[22e] the phenylselenoacetal **23** was accessed by acetal exchange of 2-phenylselenoacetaldehyde diethylacetal with diol **22** under acidic conditions. This gave the expected Claisen precursor **23** as an inconsequential 2:1 diastereomeric mixture at the acetal carbon (94%). Oxidation of selenide **23** to the selenoxide was readily achieved with $NaIO_4$. The crude product was then directly subjected to the conditions of Claisen rearrangement providing the desired eight-membered lactone **24** in 82% yield, along with recovered selenide **23** (18%), which could be recycled. The exclusive formation of the $C_{13}-C_{14}$ (*Z*)-trisubstituted olefin can be attributed to the preferred bicyclic-chair conformation adopted by the ketene acetal **25**, as shown in Scheme 3. These conditions were amenable to the production of multigram quantities of the eight-membered lactone **24**.

The conversion of lactone **24** to the aryl ester **8** was now required (Scheme 4). Initially, a four-step sequence was employed, whereby methanolysis of **24** and TBS protection of the resulting hydroxy ester provided **26** (84%, 2 steps), and saponification and esterification with 2,6-dimethylphenol under Steglich conditions[25] afforded the key fragment **8** (78%, 2 steps). Subsequently, a shorter three-step sequence was developed to provide the key fragment **8** in 81% overall yield. This involved direct opening of the lactone **24** to the intermediate hydroxy acid and esterification[25] with 2,6-dimethylphenol to provide the hydroxy ester **27**, followed by TBS protection to give **8**. In summary, the optimized multigram synthesis of the C_9-C_{16} fragment **8** was completed in 10 steps with 43% overall yield from the starting ester (*S*)-**13**.

Synthesis of the $C_{17}-C_{24}$ Subunit, 9. The synthesis of the $C_{17}-C_{24}$ fragment **9** required the union of two chiral coupling partners to configure the stereotriad (Scheme 5). The ethyl ketone (*S*)-**12** was prepared in three steps from commercial ethyl (*S*)-lactate in 65% yield, as previously described.[16a] Enolization of the ketone (*S*)-**12**, using (c-Hex)$_2$BCl/Me_2NEt, generates the (*E*)-boron enolate **28** exclusively. Addition of the α-chiral aldehyde **29** (prepared from (*S*)-**13**) provides, after oxidative

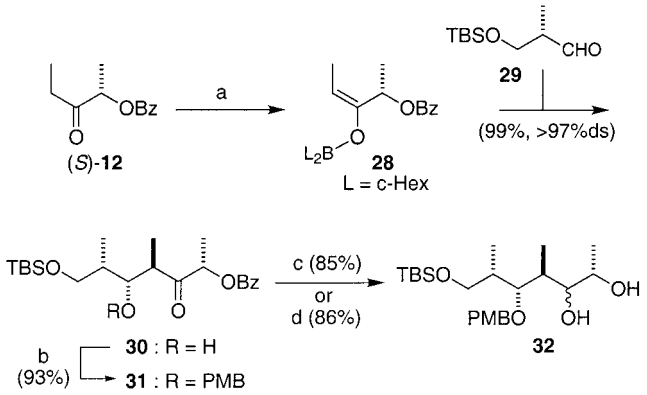
(22) (a) Carling, R. W.; Holmes, A. B. *J. Chem. Soc., Chem. Commun.* **1986**, 325. (b) Curtis, N. R.; Holmes, A. B.; Looney, M. G. *Tetrahedron* **1991**, *47*, 7171. (c) Congreve, M. S.; Holmes, A. B.; Looney, M. G. *J. Am. Chem. Soc.* **1993**, *115*, 5815. (d) Fuhry, M. A. M.; Holmes, A. B.; Marshall, D. R. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2743. (e) Burton, J. W.; Clark, J. S.; Derrer, S.; Stork, T. C.; Bendall, J. G.; Holmes, A. B. *J. Am. Chem. Soc.* **1997**, *119*, 7483. (f) Harrison, J.; Holmes, A. B. *Synlett* **1999**, 972.

(23) The 1,2-*anti* relative stereochemistry of the aldol bond construction in **20** was supported by the observed vicinal coupling constant (^3J = 8.5 Hz): Heathcock, C. H.; Pirrung, M. C.; Sohn, J. E. *J. Org. Chem.* **1979**, *44*, 4294.

(24) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447.

(25) Nieses, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522.

Scheme 5[a]



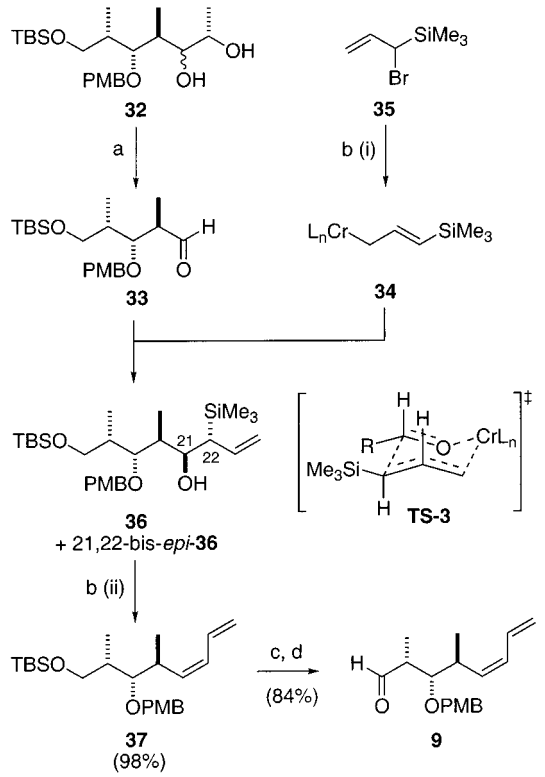
[a] Key: (a) (*i*) c-Hex$_2$BCl, Me$_2$NEt, Et$_2$O, 0 °C; −78 → −20 °C; (*ii*) H$_2$O$_2$(30% aq)/MeOH, 0 °C; (b) PMBOC(═NH)CCl$_3$, TfOH$_{cat.}$, Et$_2$O, 20 °C; (c) LiAlH$_4$, THF −78 → −20 °C; (d) (*i*) NaBH$_4$, MeOH, H$_2$O, 0 → 20 °C; (*ii*) K$_2$CO$_3$, MeOH, 20 °C.

workup, the expected *anti*-aldol product **30** in excellent yield and selectivity (99%, >97% ds).[16,26] Optimum conditions required a 1.5- to 2-fold excess of aldehyde **29** with respect to the enolate. After considerable experimentation, protection of the β-hydroxy group was achieved by using high-purity *p*-methoxybenzyl-trichloroacetimidate and triflic acid (0.3 mol %) to provide the ketone **31** in 93% yield.[27] With the protected ketone in hand, conversion to the 1,2-diol **32** was now required. This was achieved by one of two methods: (i) reduction with LiAlH$_4$ (85%) or (ii) ketone reduction (NaBH$_4$) followed by benzoate hydrolysis (K$_2$CO$_3$, MeOH) (86%), where the latter procedure proved somewhat more amenable to multigram synthesis.[16]

Introduction of the terminal C$_{21}$−C$_{24}$ (*Z*)-diene unit of discodermolide was achieved in a highly efficient manner following our previously developed protocol.[11h] This required first, the oxidative cleavage of the 1,2-diol **32** with NaIO$_4$ to afford the aldehyde **33** (Scheme 6). Nozaki−Hiyama reaction between crude aldehyde **33** and allyl chromium reagent **34**, generated in situ from 1-bromo-1-trimethylsilyl-2-propene **35** and chromium(II) chloride in THF,[28] provided (via **TS-3**) the intermediate *anti* β-hydroxy silanes **36**. These crude products were then directly subjected to Peterson-type *syn* elimination,[29] with KH in THF, to provide the desired (*Z*)-diene **37** exclusively in excellent yield (98% from **32**). Deprotection of the TBS ether (CSA, MeOH/CH$_2$Cl$_2$) and Dess−Martin oxidation[30] of the intermediate alcohol completed the synthesis of the C$_{17}$−C$_{24}$ diene aldehyde **9** (84%, 2 steps). In summary, the optimized synthesis of the key fragment **9** from ethyl (*S*)-lactate was achieved in 10 steps with 42% overall yield, on a multigram scale.

Fragment Union and Completion of the Total Synthesis of (+)-Discodermolide. With the three key subunits in place, attention was now focused on the stereocontrolled union of these components to advance our synthesis. As our fragment coupling

Scheme 6[a]



[a] Key: (a) NaIO$_4$, MeOH, H$_2$O, 20 °C; (b) (*i*) CrCl$_2$, THF, 20 °C; (*ii*) KH, THF, 0 °C; (c) CSA$_{cat.}$, MeOH/CH$_2$Cl$_2$, 20 °C; (d) Dess−Martin periodinane, CH$_2$Cl$_2$, 20 °C.

strategy was totally different from that adopted by other researchers, efficient aldol-based protocols needed to be developed in this demanding case. We first concentrated on realizing the C$_{16}$−C$_{17}$ bond connection. The stereoselective, lithium-mediated, aldol reaction of C$_9$−C$_{16}$ fragment **8** with the C$_{17}$−C$_{24}$ aldehyde **9** was expected to afford the desired *anti*-aldol adduct **38a** with high levels of Felkin−Anh selectivity (Scheme 7).[13d,31] Selective enolization of the Heathcock-type aryl ester **8** was best achieved by employing LiTMP/LiBr[32] at −100 °C (external bath temperature) to provide the (*E*)-lithium enolate **39**. Addition of aldehyde **9** then proceeded via **TS-4** preferentially, which provided on workup the desired aldol product **38a** in an optimized 81% yield with >97% ds.[33] In practice, a 2-fold excess of enolate was employed relative to aldehyde **9**, as partial α-epimerisation of the aldehyde component was periodically observed. The low reaction temperature (−100 °C) proved a

(26) The 1,2-*anti* relative stereochemistry of the aldol bond construction in **30** was supported by the observed vicinal coupling constant (^3J = 9.5 Hz) in accord with ref 23.

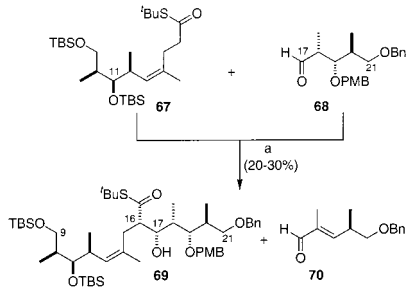
(27) (a) Iverson, T.; Bundle, D. R. *J. Chem. Soc., Chem. Commun.* **1981**, 1240. (b) Nakajima, N.; Horita, K.; Abe, R.; Yonemitsu, O. *Tetrahedron Lett.* **1988**, *29*, 4139.

(28) (a) Cintas, P. *Synthesis* **1992**, 248. (b) Hodgson, D. M.; Wells, C. *Tetrahedron Lett.* **1992**, *33*, 4761. (c) Andringa, H.; Heus Kloos, Y. A.; Brandsma, L. *J. Organomet. Chem* **1987**, *336*, C41.

(29) For a review of Peterson-type eliminations, see: Ager, D. *Org. React.* **1990**, *38*, 1.

(30) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

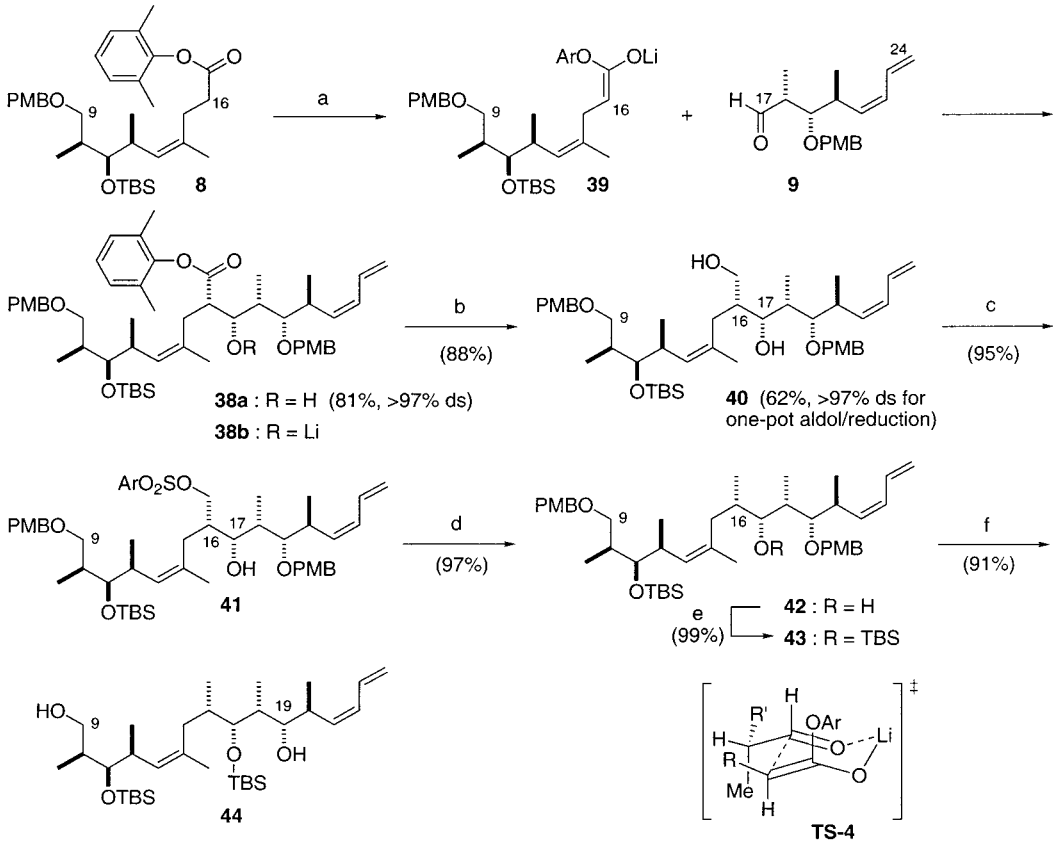
(31) Initial studies into a stereoselective C$_{16}$−C$_{17}$ boron-mediated aldol coupling of a *tert*-butyl thioester derivative **67** and a truncated C$_{17}$−C$_{21}$ aldehyde **68** led to the formation of the desired aldol product **69** (20−30%) and the β-OPMB elimination product **70**.



Conditions: (a) (*i*) **67**, (c-Hex)$_2$BBr, Et$_3$N, Et$_2$O, 0 °C.; **68**, −78 → −20 °C; (*ii*) H$_2$O$_2$ (30%)/MeOH.

(32) Hall, P. L.; Gilchrist, J. H.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 9571.

Scheme 7[a]

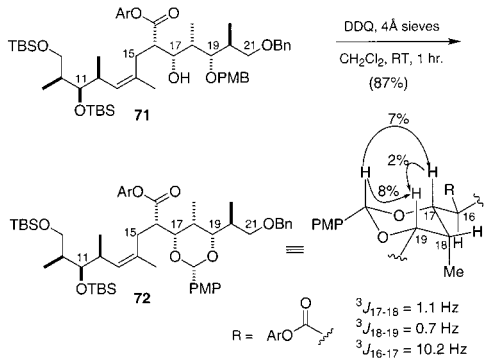


[a] Key: (a) **8**, LiTMP, LiBr, THF, −100 °C; **9**, −100 °C; (b) $LiAlH_4$, THF, −30 °C; (c) 2,4,6-$Me_3(C_6H_2)SO_2Cl$, Et_3N, CH_2Cl_2, 20 °C; (d) $LiAlH_4$, THF, −10 °C; (e) TBSOTf, Et_3N, CH_2Cl_2, 20 °C; (f) DDQ, CH_2Cl_2/pH 7 buffer, 20 °C; Ar = 2,4,6-trimethylphenyl.

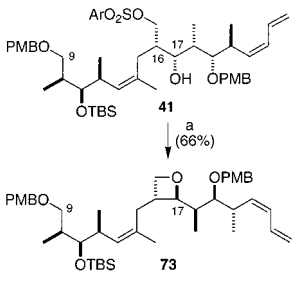
key determinant, as significant levels of α-elimination of the enolate, generating the 2,6-dimethylphenolate, were observed at higher temperatures. However, no other aldol products were observed, which suggested that elimination only occurred from the enolate and equilibration was avoided. With the aldol adduct **38a** in hand, $LiAlH_4$ reduction of the aryl ester provided the 1,3-diol **40** in 88% yield. To further streamline the synthesis, we subsequently developed an alternative in situ aldol/reduction sequence. By now employing an excess of aldehyde **9** (2 equiv) over ester **8**, the lithium aldol coupling was performed in a similar fashion but instead of working up as above to give **38a**, the intermediate lithium aldolate **38b** was treated directly with $LiAlH_4$. This convenient one-pot procedure gave the 1,3-diol **40** in 62% isolated yield (from **8**) with complete diastereoselectivity (cf. 71% overall yield for the two-pot process), along with the alcohol corresponding to the precursor of fragment **9** which was easily recyclable.

With the 1,3-diol **40** in hand, controlled deoxygenation was now required to introduce the C_{16} methyl group. The regioselective derivatization of the primary hydroxyl in diol **40** was achieved by using 2,6-mesitylenesulfonyl chloride and Et_3N to afford the mono-sulfonate **41** in excellent yield with complete selectivity. The deoxygenation sequence was then completed by hydride displacement of **41** with $LiAlH_4$ to give alcohol **42** in 97% yield.[34] The C_{17}−OH was readily protected as its TBS ether to provide **43** (99%). Subsequent deprotection of both

(33) The 1,2-anti relative stereochemistry of the aldol bond construction in **38** was supported by the observed vicinal coupling constant (^3J = 8.5 Hz) in accord with ref 23. The absolute stereochemistry was not proven directly but by correlation with the related aldol product **71**, which was readily transformed into the corresponding PMP-acetal **72** (Oikawa, Y.; Yoskioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 889). Strong nOe contacts were observed between H_{17}, H_{19} and the acetal proton, consistent with their axial orientations in the preferred chairlike conformation. The small vicinal coupling constants between H_{17} and H_{18} ($^3J_{17-18}$ = 1.1 Hz), and H_{18} and H_{19} ($^3J_{18-19}$ = 0.7 Hz) established the 1,3-*syn* relative stereochemistry between the C_{17} and C_{19} oxygen functionalities and the absolute stereochemistry at C_{17}.

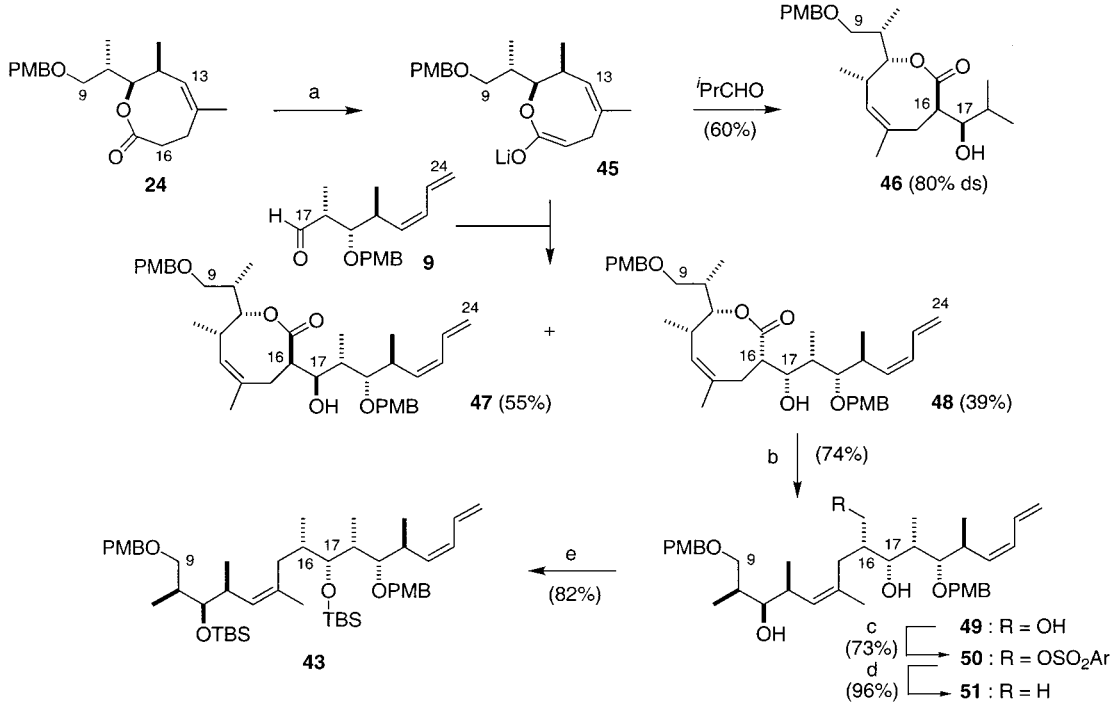


(34) Interestingly, in preliminary investigations into the deoxygenation of **41** treatment with Super-Hydride led to the exclusive formation of an oxetane **73**.



Conditions: (a) Super-Hydride, Et_3N, THF, −10 → 20 °C.

Scheme 8[a]



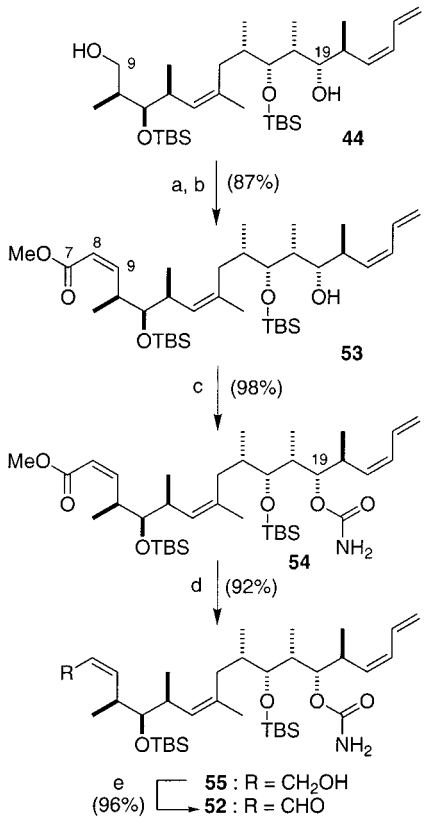
[a] Key: (a) **24**, LiTMP, LiBr, THF, −100 °C; RCHO, −100 °C; (b) $LiAlH_4$, THF, −30 °C; (c) 2,4,6-$Me_3(C_6H_2)SO_2Cl$, Et_3N, CH_2Cl_2, 20 °C; (d) $LiAlH_4$, THF −10 °C; (e) TBSOTf, Et_3N, CH_2Cl_2, 20 °C. Ar = 2,4,6-trimethylphenyl.

PMB ethers at C_9 and C_{19} with DDQ then proceeded uneventfully to give diol **44** (91%).

In efforts to further shorten our synthetic route, the viability of a $C_{16}-C_{17}$ aldol coupling with the eight-membered lactone **24** was investigated (Scheme 8). First, the π-facial bias of the lithium enolate **45** derived from lactone **24** was determined by reaction with an achiral aldehyde. Enolization of lactone **24** using LiTMP/LiBr[32] at −100 °C generated the lithium enolate **45** and addition of isobutyraldehyde gave the aldol product **46** in 60% yield with 80% ds. Under these same conditions, the lithium-mediated aldol reaction of lactone **24** and the $C_{17}-C_{24}$ aldehyde **9** gave the two diastereomeric adducts **47** (55%) and **48** (39%). This result was not unexpected, as the enolate facial bias was expected to oppose the Felkin−Anh influence of the aldehyde **9** in this situation.[35] To demonstrate the applicability of this result in our synthesis, the aldol product **48**, bearing the correct $C_{16}-C_{17}$ stereochemistry, was converted to the known intermediate **43**. Following $LiAlH_4$ reduction, the triol **49** was converted to the sulfonate **50** in 73% yield. Deoxygenation with $LiAlH_4$ then provided the diol **51** (96%). Finally, bis-TBS protection of **51** was achieved using TBSOTf and Et_3N to provide **43** in 82% yield. While representing a saving of two steps over the one-pot aldol/reduction of aryl ester **8**, this sequence gives an unacceptable overall yield of **43** (17% in 5 steps from the lactone **24**). Although this leads overall to the realization of a 20-step synthesis of (+)-discodermolide, the longer route was obviously preferable, providing **43** in 46% yield over 7 steps from **24**, and proved suitable for multigram synthesis.

At this stage, the two distinct stereochemical arrays found in the C_7-C_{24} section of discodermolide were complete and elaboration of the C_9-C_{24} fragment **44** was now required to furnish the requisite C_7-C_{24} aldehyde **52** (Scheme 9). The introduction of the C_8-C_9 (*Z*)-olefin required the selective oxidation of the C_9 terminus and (*Z*)-selective olefination. Employing catalytic TEMPO (0.2 equiv, iodobenzene diacetate, CH_2Cl_2, 20 °C) as a sterically demanding oxidant,[36] the diol **44**

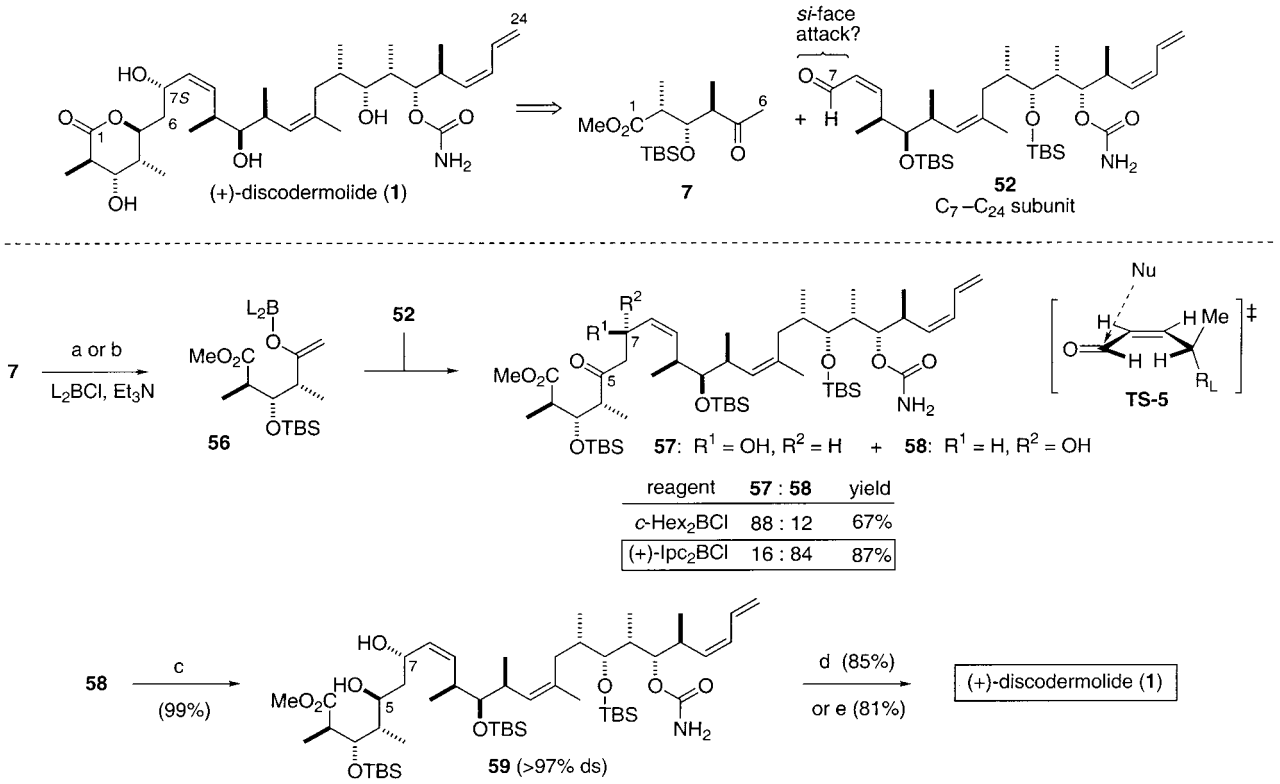
Scheme 9[a]



[a] Key: (a) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, 20 °C; (b) $(CF_3CH_2O)_2P(O)$-CH_2CO_2Me, 18-crown-6, K_2CO_3, PhMe, −20 → 0 °C; (c) (*i*) $Cl_3CC(O)NCO$, CH_2Cl_2, 20 °C; (*ii*) K_2CO_3, MeOH, 20 °C; (d) DIBAL, CH_2Cl_2, −78 °C; (e) Dess−Martin periodinane, CH_2Cl_2, 20 °C.

(35) Anderson, E. A.; Holmes, A. B.; Collins, I. *Tetrahedron Lett.* **2000**, *41*, 117.

Scheme 10[a]



[a] Key: (a) (*i*) **7**, c-Hex$_2$BCl, Et$_3$N, Et$_2$O, 0 °C; **52**, −78 → −20 °C; (*ii*) H_2O_2(30% aq)/MeOH, 0 °C; (b) (*i*) **7**, (+)-Ipc$_2$BCl, Et$_3$N, Et$_2$O, 0 °C; **52**, −78 → −20 °C; (*ii*) H_2O_2(30% aq)/MeOH, 0 °C; (c) $Me_4NBH(OAc)_3$, MeCN/AcOH, −20 → 0 °C; (d) HF·pyr, THF, 20 °C; (e) 3 N HCl, MeOH, 20 °C.

was cleanly converted to the intermediate aldehyde without any detectable oxidation of the hindered C_{19} hydroxyl group. The (*Z*)-olefin was then introduced selectively under the milder HWE conditions (K_2CO_3, 18-crown-6) reported by Still and Gennari[37] to provide the desired (*Z*)-enoate **53**, exclusively, in 87% yield over two steps. The C_7-C_{24} aldehyde **52** was completed in a further three steps. The C_{19} carbamate moiety was installed following a modification of the Kocovsky protocol.[10g,38] Reaction of the hydroxy ester **53** with trichloroacetylisocyanate, followed by methanolysis (K_2CO_3/MeOH), provided the carbamate ester **54** in 98% yield. Chemoselective reduction of **54** with DIBAL at −78 °C then furnished allylic alcohol **55** in 92% yield on a gram scale. Finally, the alcohol **55** was oxidized cleanly to the C_7-C_{24} aldehyde **52** in 96% yield, using Dess−Martin periodinane,[30] in preparation for the final, and most challenging, C_6-C_7 aldol coupling.

In planning our synthesis of discodermolide, we envisaged the late stage C_6-C_7 aldol coupling between the (*Z*)-enal **52**, containing the entire C_7-C_{24} section of discodermolide, with a suitable enolate derivative of **7** (Scheme 10). To avoid competing intramolecular Claisen condensation of the methyl ketone with the ester in **7**, it was essential to identify a metal enolate with the appropriate reactivity/selectivity characteristics, such as were anticipated to be provided by use of the corresponding boron enolate. However, the stereochemical requirement for setting up the (7*S*) carbinol center by *si*-face attack in this complex aldol coupling situation proved particularly challenging. While extensive studies of structurally related boron enolates are available,[17,39] the π-facial bias of such an unusual chiral aldehyde substrate as **52** was an unknown quantity. Following a detailed stereochemical investigation,[12b,40] it was apparent that the boron-mediated C_6-C_7 aldol coupling of ketone **7** and the C_7-C_{24} subunit **52** would be a mismatched situation. Enolization of **7** with (c-Hex)$_2$BCl/Et$_3$N provided the boron enolate **56** (L = c-Hex). Reaction of this preformed enolate **56** with (*Z*)-enal **52** gave, after oxidative work up, the (7*R*) adduct **57** (major) in 71% yield with high levels of remote 1,4-stereoinduction (88%

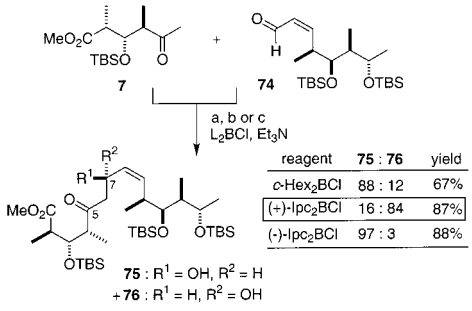
(36) De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974.

(37) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.

(38) Kocovsky, P. *Tetrahedron Lett.* **1986**, *27*, 5521.

(39) (a) Paterson, I.; Goodman, J. M.; Lister, M. A.; Schumann, R. C.; McClure, C. K.; Norcross, R. D. *Tetrahedron* **1990**, *46*, 4663. (b) Paterson, I.; Cumming, J. G.; Smith, J. D.; Ward, R. A. *Tetrahedron Lett.* **1994**, *35*, 441. (c) Paterson, I.; Oballa, R. M.; Norcross, R. D. *Tetrahedron Lett.* **1996**, *37*, 8581. (d) Paterson, I.; Gibson, K. R.; Oballa, R. M. *Tetrahedron Lett.* **1996**, *37*, 8585. (e) Paterson, I.; Oballa, R. M. *Tetrahedron Lett.* **1997**, *38*, 8241. (f) Mulzer, J.; Berger, M. *J. Am. Chem. Soc.* **1999**, *121*, 8393.

(40) Initial boron-mediated aldol reactions of **7** with the model truncated (*Z*)-enal **74** demonstrated the viability of controlling this C_6-C_7 coupling step (ref 12b).

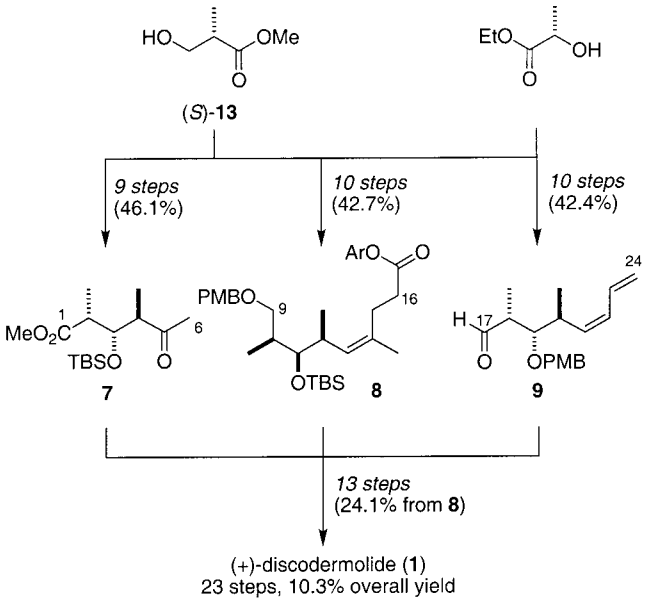


Conditions: (a) (*i*) **7**, c-Hex$_2$BCl, Et$_3$N, Et$_2$O, 0 °C; **74**, −78 → −20 °C; (*ii*) H_2O_2(30% aq)/MeOH, 0 °C; (b) (*i*) **7**, (+)-Ipc$_2$BCl, Et$_3$N, Et$_2$O, 0 °C; **74**, −78 → −20 °C; (*ii*) H_2O_2(30% aq)/MeOH, 0 °C; (c) (*i*) **7**, (−)-Ipc$_2$BCl, Et$_3$N, Et$_2$O, 0 °C; **74**, −78 → −20 °C, 19 h; (*ii*) H_2O_2(30% aq)/MeOH, 0 °C.

ds) in the wrong sense for discodermolide. This undesired outcome can be attributed to preferential *re*-face addition of the boron enolate **56** (L = c-Hex) to the γ-chiral aldehyde. The π-facial selectivity can be rationalized by steric control, considering the preferred *s*-trans conformation that the aldehyde **52** adopts, where A(1,3) strain is minimized (**TS-5**).[41] Addition of the boron enolate **56** (L = c-Hex) will then occur favorably from the less sterically congested *re*-face of the aldehyde. Gratifyingly, when (+)-Ipc_2BCl/Et_3N[39,42] was employed for enolization, the dominating selectivity of the aldehyde **52** could be overturned in favor of *si*-facial attack, leading to isolation of the desired (7*S*) adduct **58** in 74% yield (84% ds). Notably, this represents the first successful example of this chiral boron reagent overturning the intrinsic substrate selectivity of a complex aldol coupling between two chiral carbonyl components.[17] The desired (7*S*) aldol product **58** was readily separable by chromatography from the minor (7*R*) epimer **57**. To achieve good overall conversion of the valuable aldehyde component, it was best to employ a 10-fold excess of the ketone. The excess ketone **7** could be recovered in 90−95% yield without any degradation. In this way, optimum diastereoselection and conversion could be realized in this highly challenging, mismatched aldol reaction.

Following the successful union of **7** and **52**, the C_1-C_{24} carbon skeleton of (+)-discodermolide was now in place. The completion of the synthesis required the substrate-directed reduction of the C_5 ketone and subsequent global deprotection with concomitant δ-lactonization (Scheme 10). The 1,3-*anti* reduction of the β-hydroxy ketone **58** was conveniently achieved under the Evans−Saksena conditions,[43] using $Me_4NBH(OAc)_3$ in MeCN and AcOH, to provide the 1,3-*anti* diol **59** in quantitative yield, introducing the final stereocenter at C_5 with >97% diastereoselectivity. Final deprotection and δ-lactonisation was achieved by treatment of the protected C_1-C_{24} precursor **59** with HF·py in THF over 16 h, or 3 N HCl/MeOH for 4 days, to provide (+)-discodermolide (**1**) in 85% and 81% yield, respectively. Our synthetic (+)-discodermolide was identical in all respects by ^1H NMR ($CDCl_3$), ^{13}C NMR ($CDCl_3$), IR, and TLC to a natural sample. The specific rotation of our material at the sodium D-line was measured as +13.0 (*c* 1.1, MeOH), in fair agreement with that reported for authentic material +7.2 (*c* 0.7, MeOH),[1] while matching better that reported by Schreiber: +14.0 (*c* 0.6, MeOH),[10a,b] along with that of other research groups.[10c,g] Our synthetic discodermolide was also shown to be equipotent to natural material in tubulin binding assays conducted by Novartis Pharma AG.[44a] In summary, a highly efficient and practical stereocontrolled synthesis of (+)-discodermolide (**1**) has been completed in 10.3% overall yield over 23 steps (longest linear sequence via fragment **8**) from methyl (*S*)-3-hydroxy-2-methylpropionate, (*S*)-**13**. As summarized in Scheme 11, this improved route involves the formation of the three subunits **7**, **8**, and **9** and their efficient union, exploiting stereocontrolled aldol reactions. To date, this synthesis has been used to produce gram quantities of the advanced C_7-C_{24} intermediate **55**, thus enabling the SAR exploration of analogues, inter alia with permutations in the δ-lactone section.

Scheme 11. Total Synthesis of (+)-Discodermolide (**1**).



Application to the Synthesis of Discodermolide Analogues. The foregoing approach to discodermolide presents a variety of options for analogue chemistry. We have the ability to selectively access both C_7 epimers in the final C_6-C_7 aldol coupling and this should then allow the synthesis of three further epimeric discodermolides **60**−**62** by stereocontrolled reduction of the C_5 ketone and subsequent deprotection (Figure 3). These three epimers may in turn provide valuable information about the effect that altering the configuration at C_5 and the internal C_7-hydroxyl, and hence the conformation of the C_1-C_6 segment, has on the biological profile.[44b]

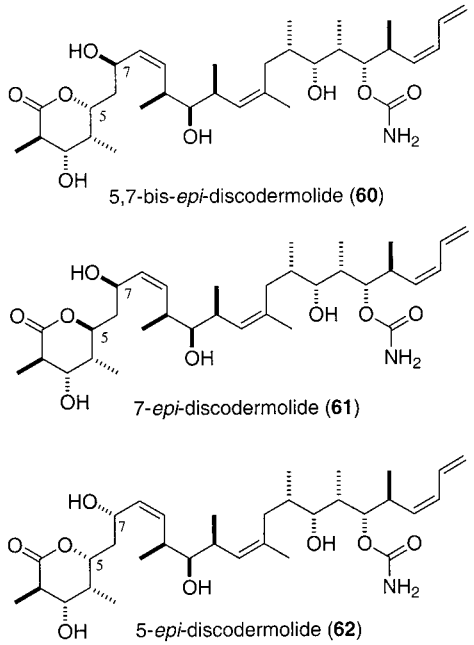


Figure 3.

The synthesis of the 5,7-bis-*epi*-discodermolide (**60**) first required the stereoselective 1,3-*anti* reduction of the (7*R*) aldol product, **57** (Scheme 12).[12b] In an analogous fashion to the approach used to complete discodermolide, the β-hydroxy ketone **57** was reduced by using $Me_4NBH(OAc)_3$ to provide

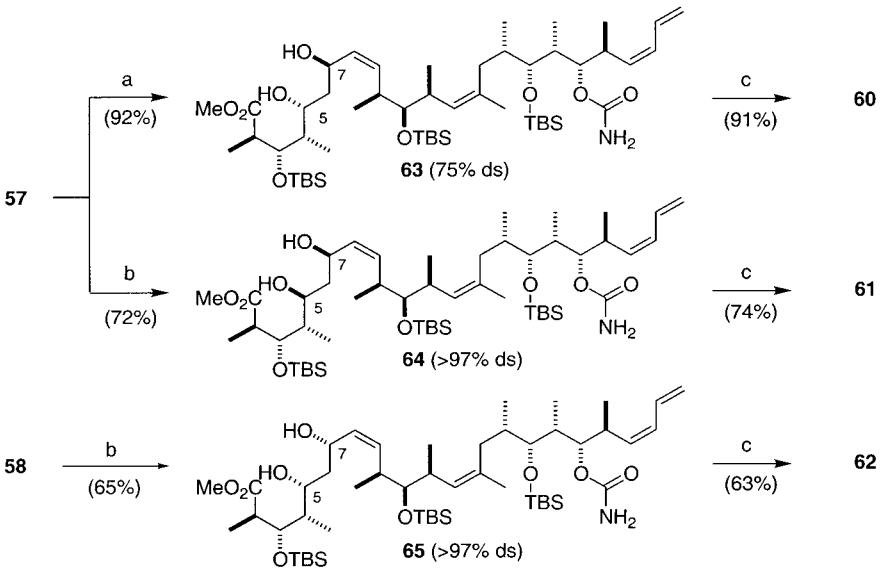
(41) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.

(42) Depending on the precise experimental conditions, the (+)-Ipc_2BCl mediated aldol coupling between **7** and **52** leads to selectivities in the range 3.5−6:1 in favor of **58**. The Ipc_2BCl reagents are available from Aldrich under the name DIPCl.

(43) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.

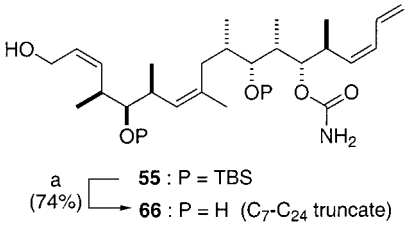
(44) (a) We are grateful to Dr. Walter Fuhrer of Novartis Pharma AG (Basel) for arranging these studies. (b) The biological results for these analogues will be reported elsewhere.

Scheme 12[a]



[a] Key: (a) $Me_4NBH(OAc)_3$, MeCN/AcOH, −20 → 0 °C; (b) (*i*) c-Hex_2BCl, Et_3N, THF, −78 °C; $LiBH_3(OMe)$, −78 °C; (*ii*) H_2O_2(30% aq)/MeOH, 0 °C; (c) 3 N HCl, MeOH, 20 °C.

Scheme 13[a]



[a] Key: (a) 3 N HCl/MeOH, 20 °C.

the 1,3-*anti* diol **63** with 75% ds.[43] Chromatographic separation, deprotection, and concomitant lactonisation of **63**, employing 3 N HCl in MeOH, provided 5,7-bis-*epi*-discodermolide (**60**) in 91% yield (63% yield, over 2 steps). To furnish 7-*epi*-discodermolide (**61**) and 5-*epi*-discodermolide (**62**), stereocontrolled 1,3-*syn* reductions of the *β*-hydroxy-ketones **57** and **58** were performed utilizing a modified Narasaka−Prasad protocol.[18,45,46] Treatment of the *β*-hydroxy ketones **57** and **58** with $(c\text{-Hex})_2BCl/Et_3N$ reformed the corresponding boron aldolates and subsequent reduction with $LiBH_3(OMe)$ gave, after oxidative workup, the expected 1,3-*syn* diols **64** and **65** in 72% and 65% yield, respectively, both with >97% diastereoselectivity. The conversion of diols **64** and **65** to the corresponding epimeric discodermolides **61** and **62** was achieved by exposure to 3 N HCl in MeOH, in 74% and 63% yield, respectively. To further address the role of the C_1-C_5 *δ*-lactone moiety in the binding of discodermolide to tubulin, the truncated C_7-C_{24} analogue **66** was prepared from alcohol **55** in 74% yield, by deprotection under acidic conditions (Scheme 13).

Conclusions

The stereocontrolled synthesis of compounds **60**−**62** and **66** demonstrates the ready applicability of our synthetic route to analogues. The use of the intrinsic 1,4-stereoinduction from the aldehyde **52** should also allow the synthesis of structurally less complex discodermolide analogues,[12b] where the full C_7-C_{24} skeleton is retained while the C_1-C_6 unit can be varied, probing the role of the C_1-C_5 *δ*-lactone moiety. Moreover, such stereoinduction in other nucleophilic additions to *γ*-chiral (*Z*)-enals may be found to be a useful process for achieving remote stereocontrol in acyclic systems. Work is now underway to explore this effect, along with further studies into the tubulin binding and polymerization properties of (+)-discodermolide (**1**) and related structural analogues. Finally, the practical route to (+)-discodermolide described herein should be amenable to the preparation of multigram quantities, enabling further biological and clinical studies in cancer chemotherapy.

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Supporting Information Available: Experimental details and analytical data for all new compounds and comparison data for natural and synthetic (+)-discodermolide (**1**) (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA011211M

(45) (a) Narasaka, K.; Pai, F.-C. *Tetrahedron* **1984**, *40*, 2233. (b) Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repic, O. *Tetrahedron Lett.* **1987**, *28*, 155.

(46) Paterson, I.; Donghi, M.; Gerlach, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3315.