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A Second-Generation Total Synthesis of (+)-Discodermolide: The Development of a Practical Route Using Solely Substrate-Based Stereocontrol

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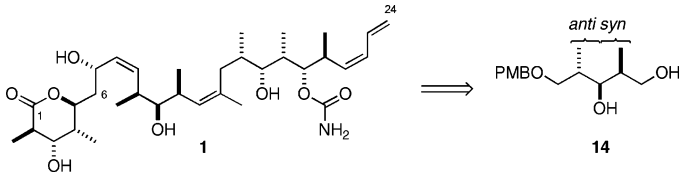

A novel total synthesis of the complex polyketide (+)-discodermolide, a promising anticancer agent of sponge origin, has been completed in 7.8% overall yield over 24 linear steps, with 35 steps altogether. This second-generation approach was designed to rely solely on substrate control for introduction of the required stereochemistry, eliminating the use of all chiral reagents or auxiliaries. The common 1,2-*anti*-2,3-*syn* stereotriad found in each of three subunits, aldehyde **9** (C_1−C_5), ester **40** (C_9−C_{16}), and aldehyde **13** (C_{17}−C_{24}), was established via a boron-mediated aldol reaction of ethyl ketone **15** and formaldehyde, followed by hydroxyl-directed reduction to give 1,3-diol **14**. Alternatively, a surrogate aldehyde **22** was employed for formaldehyde in this aldol reaction, leading to the β-hydroxy aldehyde **20** as a common building block, corresponding to the discodermolide stereotriad. Key fragment unions were achieved by a lithium-mediated *anti* aldol reaction of ester **40** and aldehyde **13** under Felkin−Anh control to provide (16*S*,17*S*)-adduct **51** and a boron-mediated aldol reaction between enone **10** and aldehyde **9**, exploiting unprecedented remote 1,6-stereoinduction, to give the (5*S*)-adduct **57**.

Introduction

Discodermolide (**1**, Figure 1) is a unique cytotoxic polyketide, originally isolated in 1990 by Gunasakera and co-workers from the Caribbean deep-sea sponge *Discodermia dissoluta*.[1] Samples of this marine sponge were collected by scuba at a depth of 33 m and following exhaustive extraction and purification provided discodermolide in 0.002% w/w from frozen sponge.

Initial studies revealed the immunosuppressive properties of discodermolide both *in vivo* and *in vitro*.[2] In 1996, it was disclosed that discodermolide was a potent cell growth inhibitory agent, arresting cell development at the boundary of the G2-M phase by binding and stabilizing mitotic spindle microtubules.[3] This novel mechanism of action, identified for the first time in paclitaxel (**2**, Taxol),[4] is shared by several other antimitotic agents, including epothilone B (**3**),[5] eleutherobin (**4**),[6] laulimalide (**5**),[7] sarcodictyin A (**6**),[6b] peloruside A (**7**),[8] and dictyostatin (**8**).[9] Comparative studies showed that

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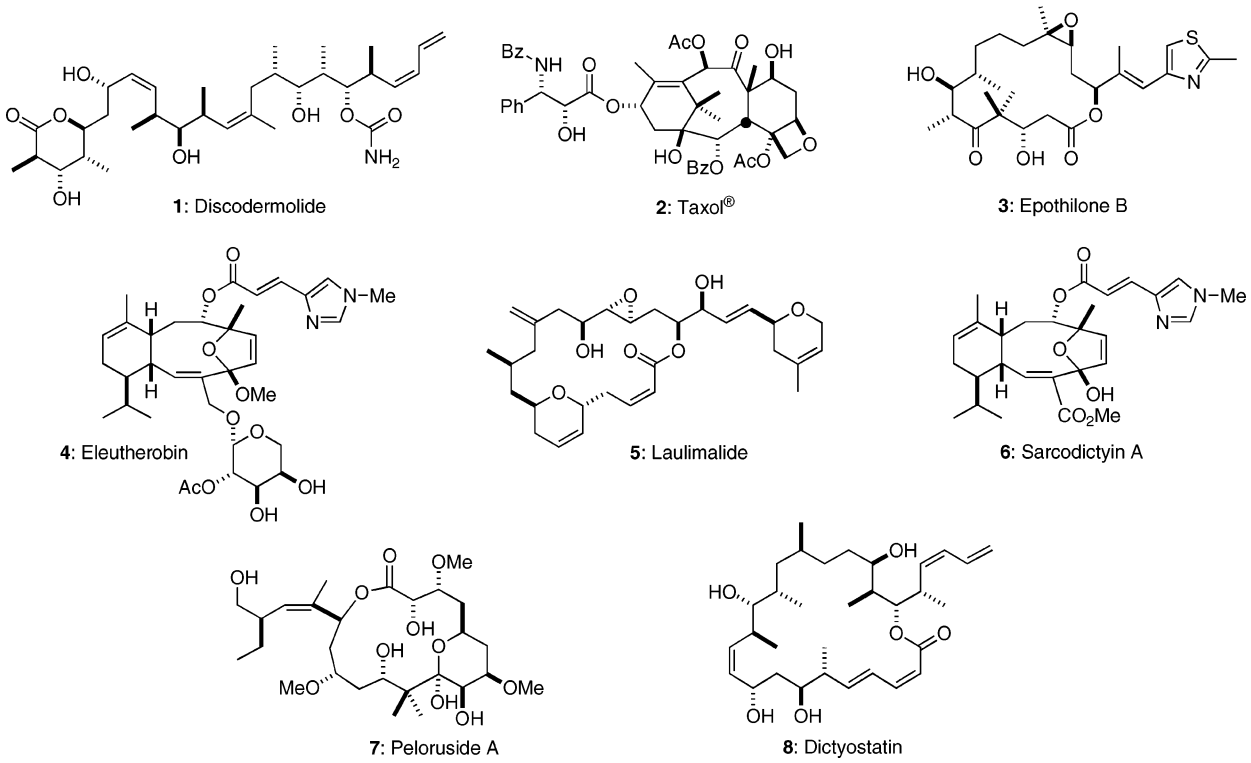

FIGURE 1. Discodermolide and other microtubule-stabilizing natural products.

discodermolidewas 1000-fold more active than paclitaxel in promoting the same microtubule polymerization/bundling. Furthermore, multidrug-resistant human colon and ovarian cancer cells retained significant sensitivity to discodermolide. More recently, further studies regarding the precise mechanism by which discodermolide binds to β-tubulin and induces its polymerization have been performed.[10] These findings highlighted that binding of discodermolide and paclitaxel to β-tubulin are mutually exclusive, although it could not be ascertained whether they share the same or an overlapping binding site. Interestingly, the synergistic effect observed for both anticancer drugs prompted the suggestion that a combination of paclitaxel and discodermolide may form a more effective chemotherapeutic treatment. Additional support for this hypothesis was gained in a study of discodermolide and its effect on microtubule dynamics, where it was found to possess significant additional stabilizing effects, which in turn may reflect the difference in binding site to paclitaxel.[11] Discodermolide also demonstrated significant human tumor growth inhibition in hollow fiber and xenograft mouse models. This remarkable biological profile has been recognized by Novartis Pharmaceutical Corporation, leading to discodermolide entering clinical trials as a new generation anticancer agent.

In comparison with paclitaxel[12] and epothilone B,[13] where semisynthetic and fermentation approaches have been employed successfully, total synthesis remains the only means at present of providing the quantities of discodermolide required to support clinical development. Consequently, there has been considerable synthetic effort directed toward providing a practical supply of discodermolide,[14] culminating in several total syntheses[15–19] and numerous fragment syntheses.[20] Notable contributions from academic groups achieving completed discodermolide syntheses have come from Schreiber and coworkers,[15] followed by the groups of Smith,[16] Myles,[17] and Marshall,[18] as well as ourselves.[19] Within the pharma-

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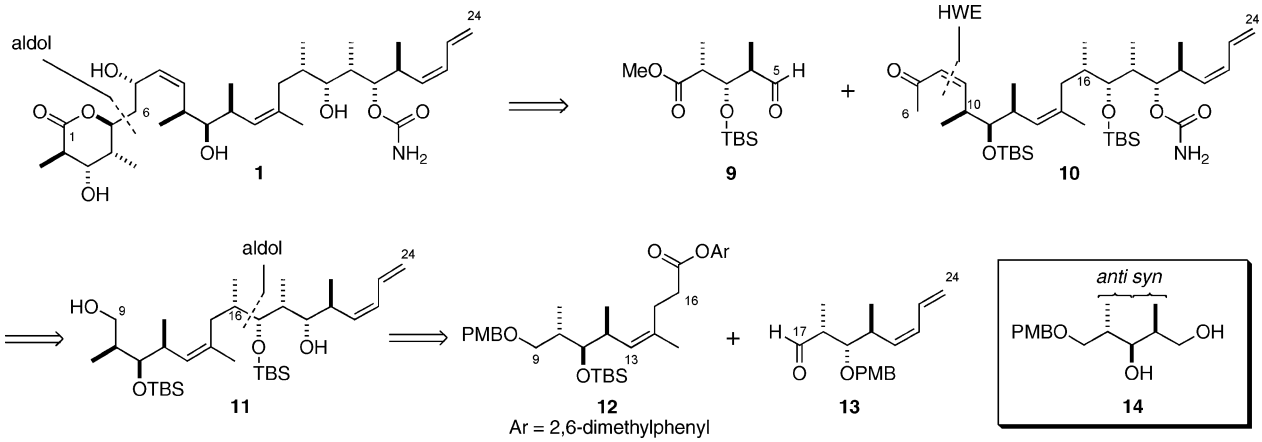
SCHEME 1. Retrosynthesis of Discodermolide (1) Based on C_5–C_6 and C_{16}–C_{17} Aldol Disconnections



ceutical industry, the landmark synthesis of over 60 g of discodermolide for Phase I clinical trials has been achieved by Novartis chemists, following a hybrid Smith–Paterson route, as reported recently by Mickel and co-workers.[21,22] Despite these impressive efforts, there is still a pressing demand for developing a more practical and efficient synthesis of discodermolide, particularly one that can be adapted to provide a manufacturing route. Herein, we report full details of our improved second-generation total synthesis,[19d] which has the potential to be scaled up to provide significant quantities of discodermolide.

Results and Discussion

Synthesis Plan. In 2000, we reported an initial total synthesis of discodermolide, based on the novel application of complex aldol reactions, that proceeded in 10.3% yield over 23 steps in the longest linear sequence and 42 total steps.[19a–c] Following on from this work, we sought further refinements to enable the large-scale synthesis of discodermolide within industry.[19d] Our revised strategy (Scheme 1) was designed to rely upon substrate-based stereocontrol only, thereby eliminating the use of all chiral reagents and auxiliaries, while reducing the total number of synthetic operations required. To achieve these specific goals, a novel aldol coupling was envisaged between C_1–C_5 aldehyde **9** and C_6–C_{24} methyl ketone **10**, relying on the possibility of exploiting remote 1,6-asymmetric induction from the C_{10} stereocenter in **10**. The methyl ketone **10** would then arise from diol **11**, an advanced intermediate from our first-generation synthesis (also used in the Novartis large-scale synthesis of discodermolide[21]), which would arise from the aldol union of Heathcock-type[23] ester **12** and aldehyde **13**. The second goal of our campaign was to be achieved by recognition of the common 1,2-*anti*-2,3-*syn* stereotriad in each of our key fragments **9**, **12**, and **13**, which could arise from the 1,3-diol **14**. A related common precursor strategy was utilized by Smith and co-workers, to great effect.[16]

Synthesis of the Common Building Block. The synthesis of the common building block **14** needed to address several criteria. In particular, a concise, efficient and stereocontrolled preparation, amenable to large-scale operation, was required. We chose to exploit the boron-mediated aldol reaction of the versatile dipropionate equivalent **15** and formaldehyde to configure the requisite 1,3-*anti* methyl groups in diol **14** (Scheme 2).[24,25] The ethyl ketone **15** was readily prepared in three steps (84%

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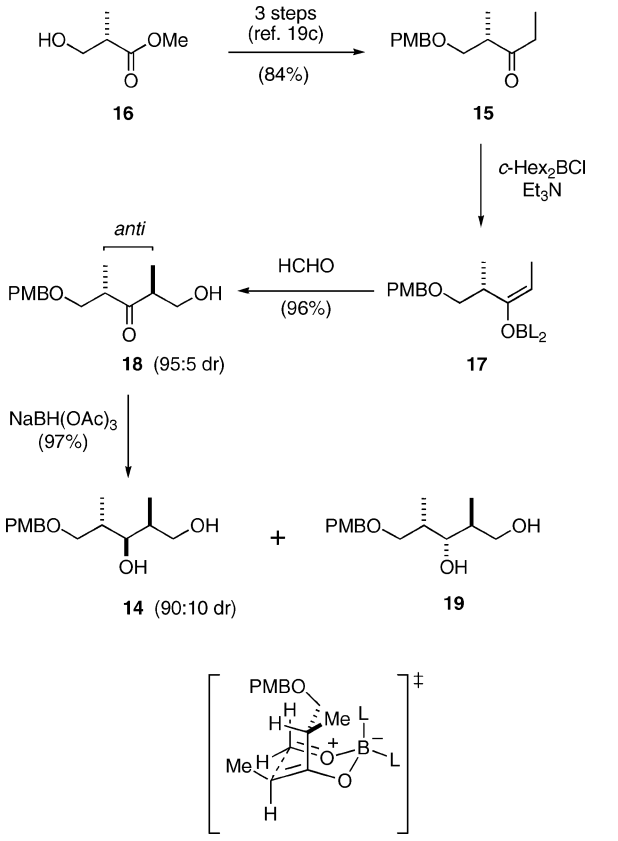
SCHEME 2. Synthesis of Common Building Block 14

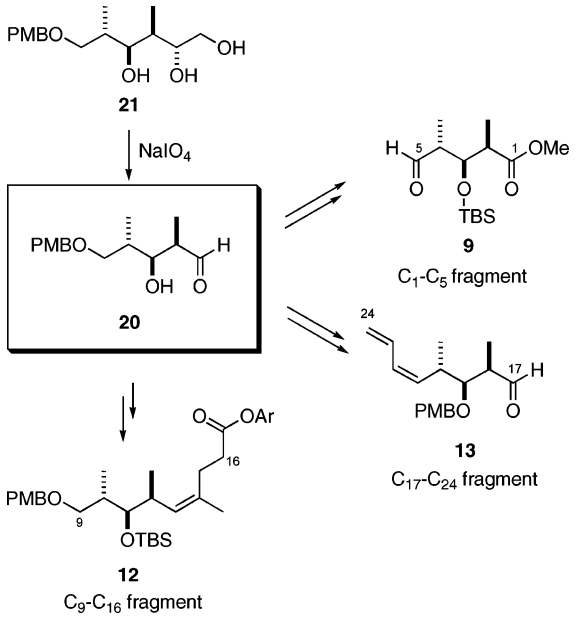


overall yield) from commercially available Roche ester **16** and purified via reduced pressure distillation.[19c,26] Enolization of **15** under our standard conditions with *c*-Hex_2BCl/Et_3N led to the selective generation of the (*E*)-boron enolate **17**, which was then treated at −78 °C with an ethereal solution of monomeric formaldehyde,[27] to provide aldol adduct **18** (96%, 95:5 dr), via a chairlike transition state.[28]

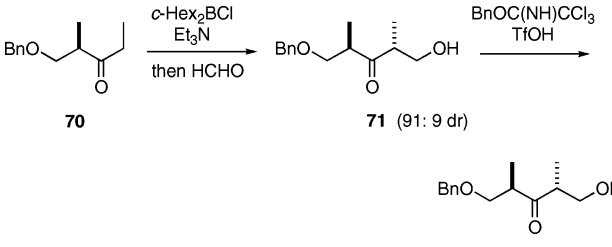
With ketone **18** in hand, we now needed to configure the remaining hydroxyl-bearing center. We explored a variety of reduction conditions to generate the required 1,3-diol **14**. Under a modified Narasaka−Prasad protocol,[29,30] employing *c*-Hex_2BCl and Et_3N in Et_2O to regenerate the boron aldolate, reduction with $LiBH_4$ proceeded in good yield to provide a diastereomeric mixture of 1,3-diols, favoring the undesired epimer **19** (96%, 67:33 dr). However, under standard Evans−Saksena-type hydroxyl-directed reduction conditions, using $Me_4NBH(OAc)_3$ in AcOH/MeCN, the desired 1,2-*syn* diol **14** could be obtained in high yield with a reasonable level of stereocontrol (97%, 80:20 dr).[31] Further optimization led to the use of $NaBH(OAc)_3$ in AcOH/THF at −20 °C, to provide diol **14** with improved diastereoselectivity (85%, 90:10 dr) which was isolated conveniently in pure form by recrystallization from diethyl ether/hexanes (1:1) in 66% yield. Notably, this five-step synthesis of the common building block **14**, starting from ester **16**, was performed readily on a multigram scale without recourse to chromatographic purification.

This synthesis of the common precursor diol **14**, though efficient and amenable to multigram synthesis in our laboratory, has some possible limitations in an industrial setting due primarily to the problems of preparing and handling solutions of monomeric formaldehyde. It is also apparent that a more stereoselective aldol-reduction sequence would be advantageous to obtain higher yields of the 1,3-diol **14**. The use of a formaldehyde "surrogate", bearing an additional substituent, to enable a more selective 1,3-*anti* reduction was envisaged and removal at a later stage would then reveal a synthetic equivalent of **14**. As shown in Scheme 3, our revised common precursor was selected to be β-hydroxy aldehyde **20** in place of the corresponding diol **14**. This would allow a convenient synthesis from oxidative cleavage of the glycol

SCHEME 3. Revised Common Building Block Strategy Based on β-Hydroxy Aldehyde 20



(24) In the course of previous studies, the viability of this asymmetric aldol reaction had been demonstrated with the analogous benzyl-protected ethyl ketone.



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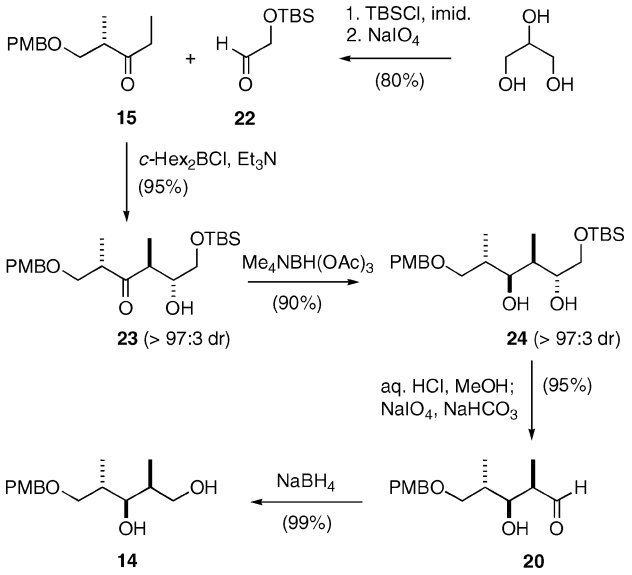
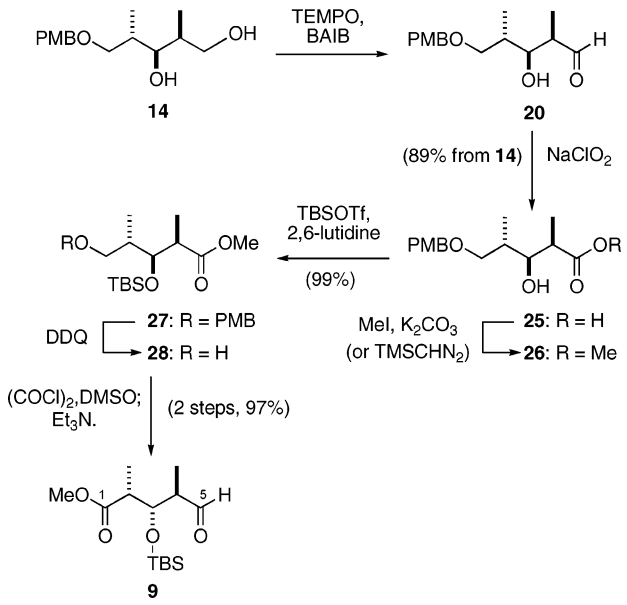
SCHEME 4. Synthesis of Common Building Blocks 14 and 20



SCHEME 5. Synthesis of C_1-C_5 Subunit 9



21. Indeed, two of our key fragments C_1-C_5 aldehyde **9** and C_9-C_{16} ester **12** require this aldehyde oxidation state in their synthesis.

To this end, the starting aldehyde **22** was prepared conveniently via mono-TBS protection of glycerol, followed by sodium periodate cleavage (Scheme 4). Reaction of **22** with the (*E*)-boron enolate of ethyl ketone **15**, under standard conditions, provided the expected *anti*-aldol adduct **23** in 95% yield with essentially complete stereoselectivity (>97:3 dr).[26] Gratifyingly, hydroxyl-directed reduction of the β-hydroxy ketone **23** under standard Evans–Saksena conditions with $Me_4NBH(OAc)_3$ provided the required 1,3-*anti* diol **24** in 90% yield as the sole product, without the need for chromatographic purification.[31] Methanolysis of the TBS group and subsequent glycol cleavage with sodium periodate were performed in one pot, to afford common precursor aldehyde **20** in 95% yield. This aldehyde could then be used directly in the synthesis of C_1-C_5 fragment **9** and C_9-C_{16} fragment **12**. The synthesis of the remaining $C_{17}-C_{24}$ fragment **13** first required the reduction of **20**, which was conveniently achieved with sodium borohydride.

By employing aldehyde **22** as a surrogate for formaldehyde, we have been able to refine the synthesis of the common precursor diol **14** and utilize the more advanced aldehyde **20**. Furthermore, this sequence provides both **14** and **20** with greater overall stereoselectivity and yields than our original route (80% compared with 62% yield, from ethyl ketone **15**). In addition, this revised route is more economic, allowing operationally simpler preparation of the common precursor on larger scales, as required for industrial application.

Synthesis of C_1-C_5 Subunit 9. The synthesis of the C_1-C_5 aldehyde **9** began with the selective primary oxidation of 1,3-diol **14** under Piancatelli conditions, employing TEMPO and bis-acetoxyiodobenzene (BAIB) to provide aldehyde **20** (Scheme 5).[32] Further oxidation with sodium chlorite provided carboxylic acid **25**,[33] which was readily converted into its methyl ester **26** employing either MeI/K_2CO_3 or TMS-diazomethane. Subsequent hydroxyl protection with TBSOTf/2,6-lutidine proceeded smoothly to provide **27** in excellent yield. Oxidative cleavage of the primary PMB group with DDQ to provide alcohol **28** required rigorously neutral conditions to avoid δ-lactonization of the product. The propensity of **28** to δ-lactonize under acidic or basic conditions or under prolonged storage in solution also proved troublesome in the following oxidation to aldehyde **9**. However, Swern oxidation provided the desired aldehyde **9** cleanly in 97% yield over two steps.[34] Overall, the synthesis of the C_1-C_5 aldehyde **9** was completed in six steps from the common precursor diol **14** (or in five steps from aldehyde **20** prepared as shown in Scheme 4) in 85% yield to provide multigram quantities when required.

Synthesis of C_9-C_{16} Subunit 12. The second key subunit **12** was accessed utilizing the common precursor aldehyde **20** (Scheme 6). Following the protocol of Still and Gennari,[35] treatment of phosphonate **29** with KHMDS in the presence of 18-crown-6 at −78 °C, followed by the addition of **20**, provided enoate **30** in excellent yield with essentially complete selectivity for the trisubstituted (*Z*)-olefin.[15] Subsequent TBS protection of the C_{11} hydroxyl group then gave **31** in 72% yield over three steps from diol **14**. Homologation of the ester terminus was now required to complete the C_9-C_{16} subunit **12**. Treatment of **31** with DIBAL provided the corresponding allylic alcohol **32**, which could be readily converted into either iodide **33** (90% over two steps) or bromide **34** (94% over two steps).[36] On a multigram scale, only two chromatographic purifications were required throughout this sequence.

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

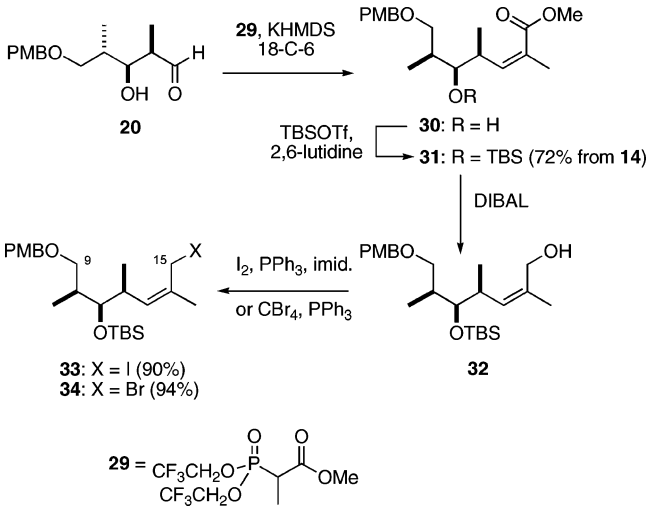
(33) (a) Lindgren, B. O.; Nilsson, T. *Acta Chem. Scand.* **1973**, *27*, 888. (b) Bal, B. S.; Childers, W. E. J.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091. (c) Mann, J.; Thomas, A. *Tetrahedron Lett.* **1986**, *27*, 3533.

(34) (a) Omura, K.; Swern, D. *Tetrahedron Lett.* **1978**, *34*, 1651. (b) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2231.

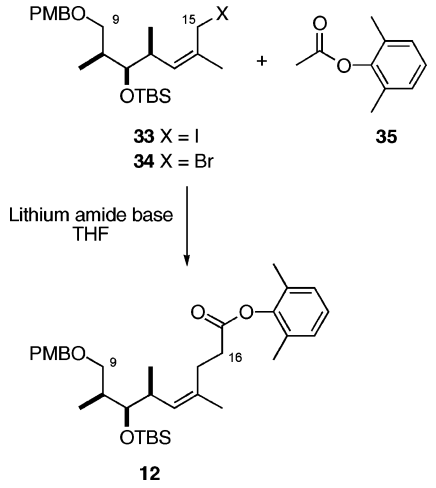
(35) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.

(36) Katritzky, A. R.; Nowak-Wydra, B.; Marson, C. M. *Chem. Scr.* **1987**, *27*, 477.

SCHEME 6. Synthesis of Allylic Halides 33 and 34

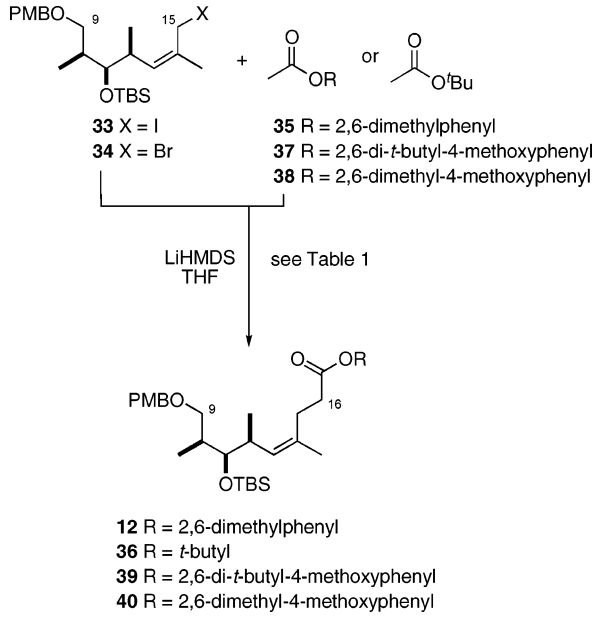


SCHEME 7. Initial Alkylation Studies with 35 (See Table 1)



With ready access to iodide **33** and bromide **34**, our attention focused on employing these in enolate alkylations with a range of alkyl and aryl acetates. Initially, the alkylation of 2,6-dimethylphenyl acetate (**35**) was investigated (Scheme 7), which would provide access to the C_9-C_{16} subunit **12** from our first-generation synthesis of discodermolide. However, the lithium enolate of 2,6-dimethylphenyl acetate **35**, generated by a range of lithium amide bases (LiHMDS, LDA, LiTMP), proved unreactive toward bromide **34** at −78 °C, even on addition of DMPU or HMPA. At higher temperatures, the alkylation product could be isolated in poor yield (<20%). The enolate alkylation of **35** with the more reactive iodide **33** proved equally unsuccessful in the absence of additives. However, employing either HMPA or DMPU, the desired product **12** could be isolated, again in disappointing yield (15−38%). In all cases, where the allylic halide (**33** or **34**) was totally or partially consumed, 2,6-dimethylphenol was observed in the product mixture. In our first-generation synthesis, 2,6-dimethylphenol was also observed when 2,6-dimethylphenyl ester **12** was enolized with LiTMP or LDA at −100 °C, which was attributed to α-elimination of phenolate to produce the ketene.[19c] The low reactivity of iodide **33** or bromide **34** implied the use of long reaction times and higher temperatures, leading to increased levels of decomposition. Unfortunately, extensive optimization failed to provide an adequate solution to this problem, and it was clear that modifications to the C_9-C_{16} ester subunit **12** were required.[37]

SCHEME 8. Further Enolate Alkylation Studies (See Table 1)



We then turned to screening the alkylation of alternative ester enolates (Scheme 8, Table 1). Reaction of bromide **34** with the lithium enolate of *tert*-butyl acetate provided ester **36** in 98% yield. However, we doubted its effectiveness in realizing high levels of stereocontrol in the pivotal $C_{16}-C_{17}$ aldol coupling with the aldehyde **13**. It was essential to find an ester moiety that met two key requirements: first, its acetate should be cleanly alkylated by allylic halide **33** or **34**; second, the resulting C_9-C_{16} ester should undergo aldol addition with α-chiral aldehyde **13** in a stereocontrolled manner. Heathcock and co-workers have employed a range of substituted phenyl esters to impart high levels of 1,2-*anti* selectivity in their aldol reactions with α-branched aldehydes.[23b] The 2,6-di-*tert*-butyl-4-methoxy and 2,6-dimethyl-4-methoxy phenyl ester derivatives **37** and **38** were chosen as promising candidates, on the basis that the *ortho* substituents would

(37) An indirect solution to this problem required a three-step sequence to provide **12** in 70% yield.

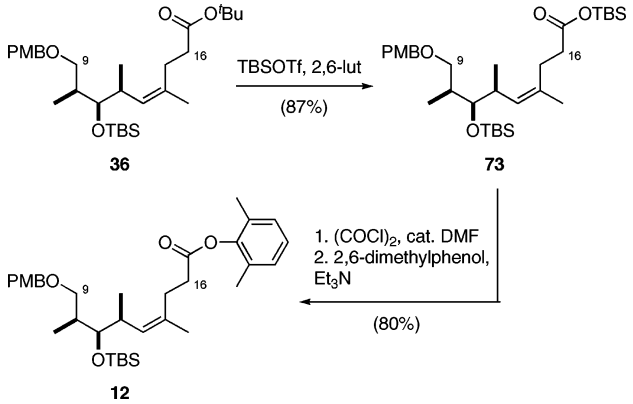
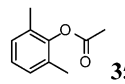
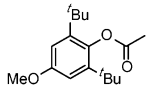
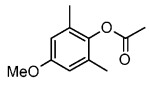


TABLE 1. Enolate Alkylation Studies with a Range of Acetates (see Schemes 7 and 8)

Entry	Acetate	Halide	Yield (%)	Product
1	 **35**	**33**[a]	38	**12**
2		**34**	98	**36**
3	 **37**	**34**[a]	65	**39**
4	 **38**	**33**	72	**40**

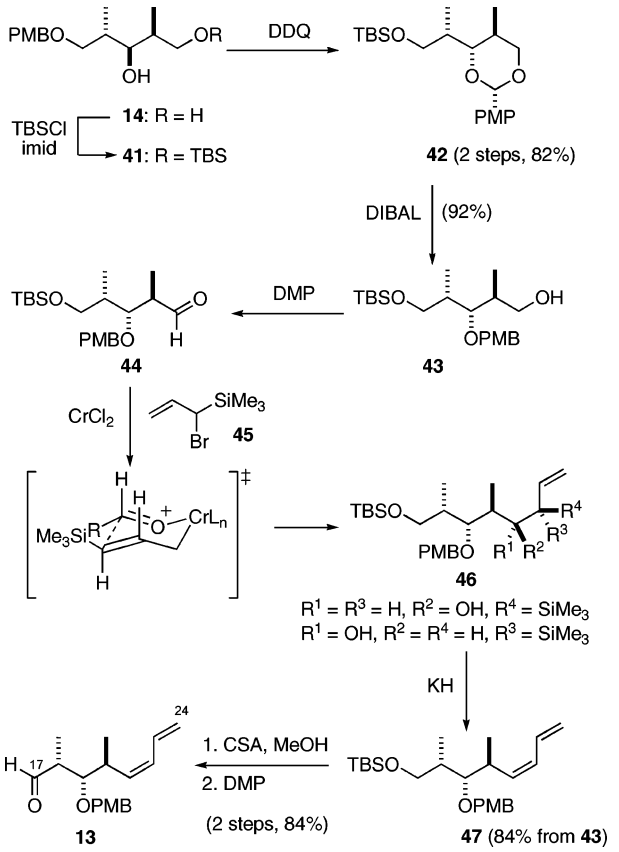
[a] HMPA as additive.

provide the steric hindrance required in the aldol reaction and the *p*-methoxy group would enhance reactivity in the enolate alkylation.

Gratifyingly, alkylation of the lithium enolate of either aryl acetate **37** or **38** with iodide **33** or bromide **34** provided the corresponding esters **39** and **40** cleanly (Scheme 8, Table 1). Treatment of 2,6-di-*tert*-butyl-4-methoxyphenyl acetate **37** with LiHMDS, in the presence of HMPA, and reaction with bromide **34** provided the ester **39** in 65% yield (entry 3). The corresponding 2,6-dimethyl-4-methoxyphenyl acetate **38**[38] was also alkylated by the more reactive iodide **33**, without HMPA, to provide **40** in 72% yield. With a reliable access to esters **36**, **39**, and **40** established, we were now in a position to investigate their effectiveness in the crucial $C_{16}-C_{17}$ aldol coupling reaction with aldehyde **13**.

Synthesis of $C_{17}-C_{24}$ subunit 13. The synthesis of the third key subunit **13** from 1,3-diol **14** started with a sequence of protecting group manipulations (Scheme 9). Selective TBS protection of the primary hydroxyl of **14**, followed by anhydrous DDQ treatment, provided the PMP acetal **42** in 82% yield.[39] Regioselective opening of the acetal **42** with DIBAL at 0 °C gave primary alcohol **43** (92%),[40] although performing this reaction at room temperature led to some TBS deprotection. Dess–Martin oxidation of alcohol **43** readily provided aldehyde **44** in readiness for the installation of the terminal (*Z*)-diene

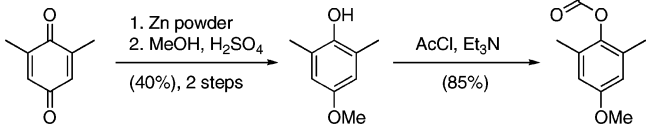
SCHEME 9. Synthesis of $C_{17}-C_{24}$ Aldehyde 13



moiety.[41] Following the methodology developed previously in our group,[20f] this was introduced efficiently by Nozaki–Hiyama allylation[42] and subsequent Peterson-type elimination.[43] Addition of aldehyde **44** and 1-bromo-1-trimethylsilyl-2-propene (**45**) to chromium(II) chloride in THF led to the formation of the intermediate *anti*-β-hydroxysilanes **46**. Direct treatment with KH to induce 1,2-*syn* elimination afforded the requisite (*Z*)-diene **47** exclusively in 84% yield. With the diene **47** in hand, methanolysis of the primary TBS group and Dess–Martin oxidation of the liberated hydroxyl completed the synthesis of the $C_{17}-C_{24}$ aldehyde **13**, as in our previous synthesis.[19c]

$C_{16}-C_{17}$ Aldol coupling. With access to the $C_{17}-C_{24}$ aldehyde **13** and a range of C_9-C_{16} esters (**36**, **39**, and **40**) achieved, their compatibility in the *anti*-selective aldol coupling was now explored (Scheme 10, Table 2). In our first-generation route, the lithium aldol coupling of aryl ester **12** with aldehyde **13** provided the corresponding aldol adduct **48** in 81% yield as essentially a single diastereomer (>97:3 dr, entry 1).[19a,c] Treatment of *tert*-butyl ester **36** with LiTMP/LiBr at −78 °C, conditions introduced by Collum and co-workers for (*E*)-selective ester enolate formation,[44] and addition of aldehyde **13** gave a complex mixture of diastereomeric adducts **49** (52% yield, approximate ratio 1.4:1.2:1, entry 2).

(38) Compound **38** was synthesized in 3 steps from commercially available 2,6-dimethyl-*p*-benzoquinone **74**:



(39) Oikawa, Y.; Yoskioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885.

(40) Takano, S.; Akiyama, M.; Sato, S.; Ogasawara, K. *Chem. Lett.* **1983**, 1593.

(41) (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.

(42) (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.

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

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

SCHEME 10. Lithium-Mediated Aldol Coupling (See Table 2)

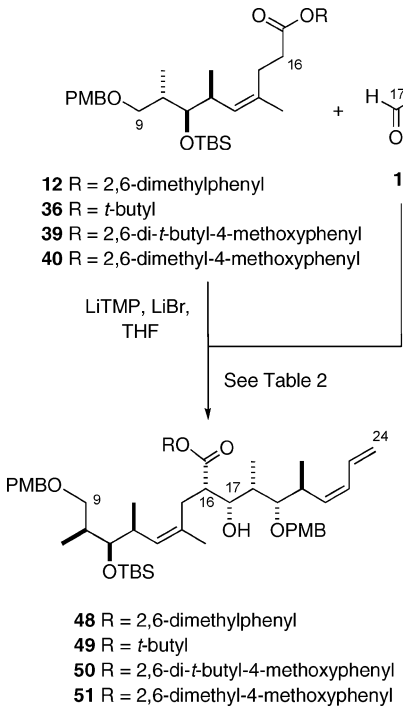


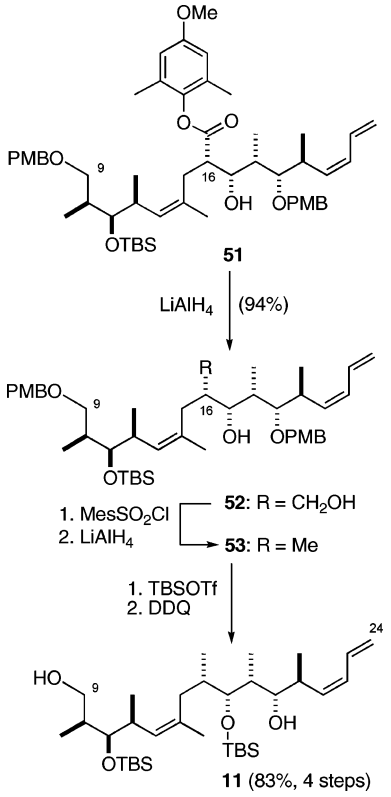
TABLE 2. Lithium-Mediated Aldol Coupling (see Scheme 10)

entry	ester	temp (°C)	product	dr	yield (%)[a]
1	**12**	−100	**48**	>97:3	81
2	**36**	−78	**49**	1.4:1.2:1	52
3	**39**	−78	**50**		0
4	**40**	−78	**51**	11:3:1	85 (61)[b]
5	**40**	−100	**51**	26:4:1	85 (67)[b]

[a] Yield of combined diastereomers. [b] Yield of major diastereomer separated by silica gel chromatography.

Clearly, an aryl ester appeared to be required to obtain stereocontrol in this aldol coupling reaction. However, the attempted reaction of the lithium enolate of 2,6-di-*tert*-butyl-4-methoxyphenyl ester **39** and aldehyde **13** failed to generate any of the expected aldol adduct **50** (entry 3). This negative result was attributed to the increased steric constraints imposed by the flanking *ortho tert*-butyl groups. Heathcock had reported previously that, in some instances, undesired retro-aldolization was observed in the reactions of this class of aryl esters.[23b] Gratifyingly, the lithium enolate of 2,6-dimethyl-4-methoxyphenyl ester **40** reacted with aldehyde **13** at −78 °C to provide the desired Felkin−Anh product **51** (61% isolated yield) accompanied by two further diastereomers (approximate ratio 11:3:1 dr, entry 4). Reducing the reaction temperature to −100 °C led to improved diastereoselectivity for **51** (26:4:1 dr, entry 5). Fortunately, the desired aldol product **51** was readily separated by flash chromatography in 67% yield. Notably, the revised C9−C16 fragment **40** does not show any enolate decomposition under the reaction conditions, and therefore it is possible to perform this key aldol coupling employing equimolar quantities of the respective carbonyl components **40** and **13**. These findings are important for any large-scale use of this route.

SCHEME 11. Elaboration of 51 into Diol 11



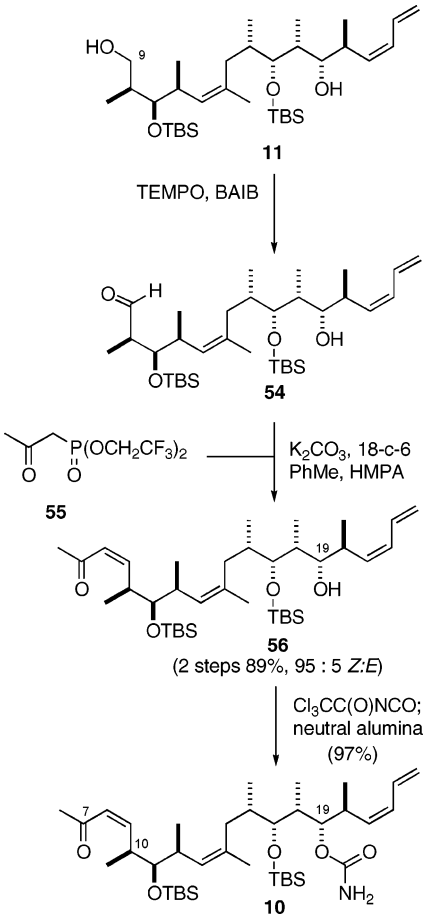
With access to the revised aldol adduct **51**, a further five steps were required to provide diol **11** (Scheme 11). Following our first generation approach, treatment with $LiAlH_4$ gave the 1,3-diol **52** in 94% yield.[19c] A two-step deoxygenation sequence was then performed to reveal the C_{16} methyl group, via selective sulfonylation of the primary alcohol followed by hydride displacement. TBS protection of **53** and removal of both PMB groups with DDQ gave diol **11** in 83% yield over four steps.

In preparation for the final and most challenging bond construction of the synthesis, diol **11** was transformed first into the C_6-C_{24} enone **10** (Scheme 12). Selective primary oxidation of **11** under Piancatelli conditions, with catalytic TEMPO and BAIB, provided the corresponding aldehyde **54**.[28] The aldehyde was then reacted with phosphonate **55** under modified Still−Gennari conditions to yield (*Z*)-enone **56**.[36,45] After extensive optimization, it was found that the addition of HMPA in conjunction with K_2CO_3 and 18-crown-6, in toluene at −5 °C, was beneficial in leading to the formation of **56** in excellent yield, with essentially complete Z-selectivity (89% yield, 95:5 *Z*:*E*). Introduction of the C_{19} carbamate moiety was then achieved by the reaction of **56** with trichloroacetyl isocyanate and subsequent treatment with neutral alumina to provide **10** in 97% yield.[46] In contrast, employing K_2CO_3 in MeOH, a standard procedure to hydrolyze the trichloroacetyl adduct intermediate, led to both partial *Z*−*E* isomerization of the enone and epimerization of the C_{10} stereocenter.

C_5-C_6 Aldol coupling. The final key aldol coupling of methyl ketone **10** and aldehyde **9** was now addressed

(45) Yu, W.; Su, M.; Jin, Z. *Tetrahedron Lett.* **1999**, *40*, 6725.
(46) Kocovsky, P. *Tetrahedron Lett.* **1986**, *27*, 5521.

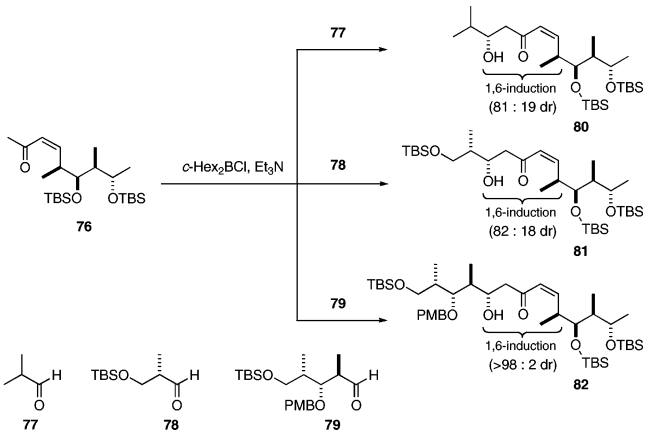
SCHEME 12. Completion of C_6–C_{24} Enone 10



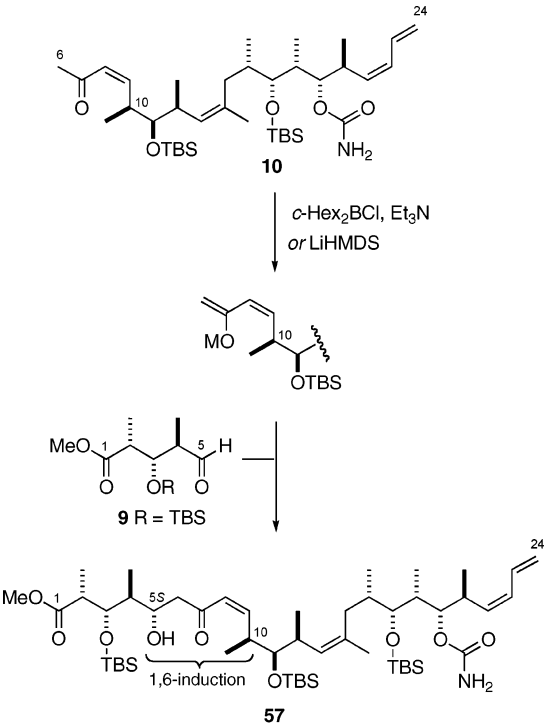
(Scheme 13). Following encouraging results from preliminary model studies that explored the potential influence of the γ-stereogenic center of methyl ketone **10** in its boron-mediated aldol reaction with α-chiral aldehydes, we planned to exploit this beneficial remote influence of 1,6-stereoinduction to configure the new hydroxyl-bearing stereocenter at C_5.[47]

Methyl ketone **10** was enolized with *c*-Hex_2BCl/Et_3N in Et_2O at 0 °C and reacted with aldehyde **9** (1.1–2 equiv) at −78 °C to afford aldol adduct **57** in 83% yield with excellent levels of control over the (5*S*)-center (92:8 dr).

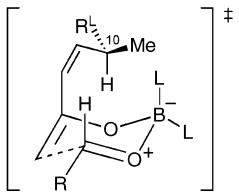
(47) Initial boron-mediated aldol reactions of truncated enone **76** with achiral and α-chiral aldehydes demonstrated that significant levels of remote 1,6-asymmetric induction could be obtained.



SCHEME 13. C_5–C_6 Aldol Coupling between 9 and 10

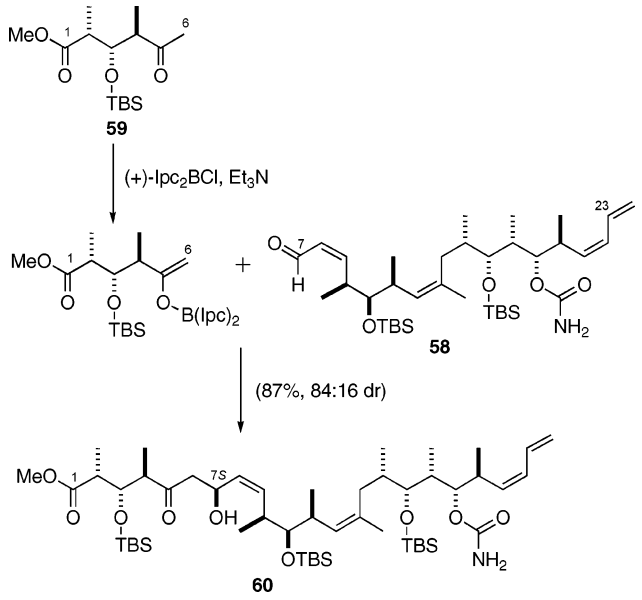


M	Yield (%)	dr (5*S* : 5*R*)
B(*c*-Hex)$_2$	83	92 : 8
Li	33	<3 : >97

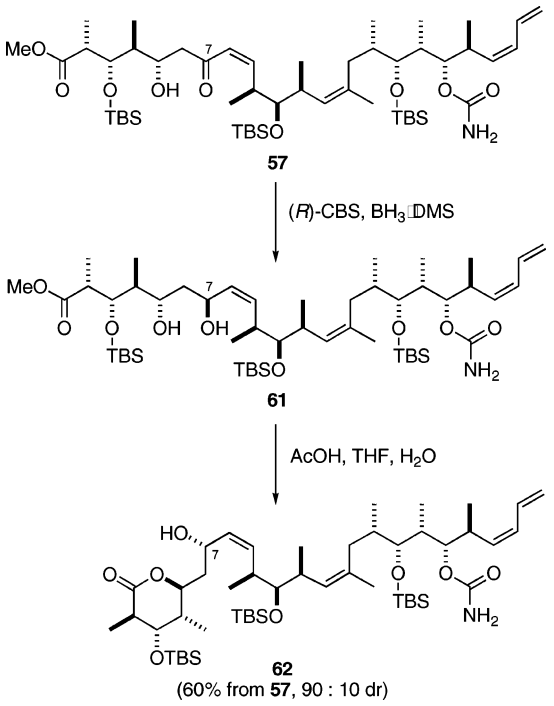


Preferential *si*-face attack of the boron enolate on the aldehyde can be rationalized by invoking a chair transition state in which the dienolate is constrained in the lower energy *s-trans* conformation, A(1,3) strain is minimized, and other steric clashes are avoided. This key aldol reaction required extensive optimization, and the isolation conditions proved critical to ensure a reproducible yield. Indeed, it was found that a neutral aqueous workup followed by reverse-phase chromatography provided the best recovery of the product **57**. In contrast, the analogous lithium-mediated reaction of ketone **10** with aldehyde **9** gave the undesired (5*R*)-adduct exclusively, as expected from Felkin–Anh 1,2-induction, underscoring the importance of the boron-mediated protocol. Notably, this new C_5–C_6 aldol coupling offers a significant improvement over our original route (Scheme 14), which was used by Mickel and co-workers to prepare 60 g of discodermolide, in which the reversed aldol coupling at C_6–C_7 depended on the influence of a chiral boron reagent to overturn the π-facial bias of aldehyde **58** and required an excess of the C_1–C_6 ketone **59** (5 equiv) to

SCHEME 14. First-Generation C_6–C_7 Aldol Coupling between 58 and 59



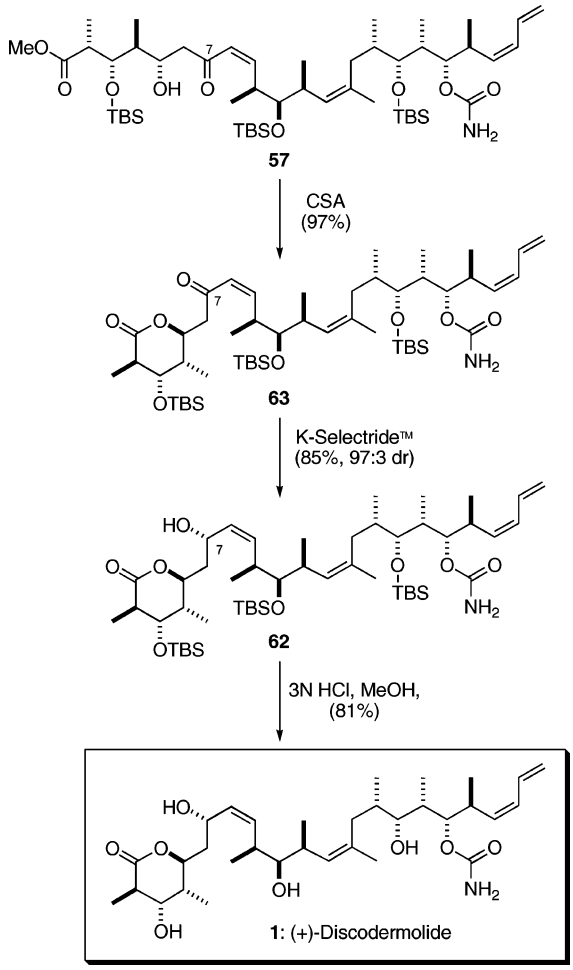
SCHEME 15. Reagent-Controlled Reduction of 57



afford the desired (7*S*)-adduct **60** in good yield with a diastereomeric ratio of 84:16.[19c, 21e]

To complete our second-generation synthesis of discodermolide, a 1,3-*anti* reduction and δ-lactonization were still required. Initial studies concentrated on reduction of the β-hydroxy ketone **57** and subsequent δ-lactonization (Scheme 15). However, the reduction of **57** proved troublesome, affording mixtures of epimeric alcohols at C_7 with various reagents, such as sodium borohydride, Luche conditions, K-Selectride, Evans–Saksena conditions, or lithium tris(*tert*-butoxy)aluminum hydride. It was apparent that the poor results obtained in this reduction step were due to the competitive δ-lactonization taking place under the reaction conditions. The only

SCHEME 16. Endgame for (+)-Discodermolide



reducing agent to provide good levels of selectivity with **57** was (*R*)-CBS and BH_3·DMS complex, giving the desired isomer **61** with 90:10 dr (Scheme 15).[48] However, up to 2 equivalents of the chiral reducing agent were required. Acid-promoted lactonization of **61** then afforded **62**, which could be isolated in 60% yield. Deprotection of **61** or **62**, as in our first-generation synthesis, would then have provided discodermolide.

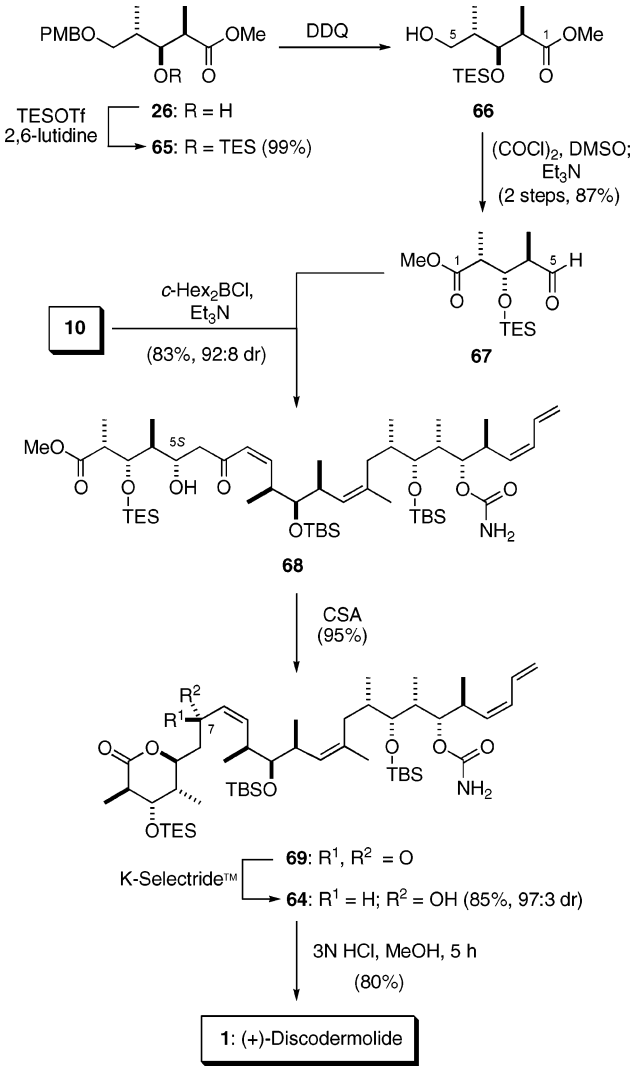
Up to the preparation of β-hydroxy ketone **57**, all of the new stereocenters had been configured relying solely on substrate control. To continue with this paradigm, an alternative reagent system for our endgame should be feasible, giving both a high yield and good selectivity without recourse to a chiral reagent system. Even though this would require the addition of an extra step to the longest linear sequence, we decided to lactonize **57** first and then reduce the ketone at C_7 (Scheme 16). Thus β-hydroxy ketone **57** was treated with catalytic camphorsulfonic acid in dichloromethane to afford the corresponding δ-lactone **63** in 97% yield. Reduction of **63** was then investigated. Gratifyingly, treatment with the sterically demanding reducing agent K-Selectride in toluene proceeded smoothly in favor of the desired (7*S*)-alcohol **62** (85%, 97:3 dr).[16c] Global deprotection was then routinely performed under acidic conditions, by treatment

(48) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551.

of **62** with 3 N HCl in methanol over 96 h at ambient temperature,[19d,21e] to afford (+)-discodermolide (**1**) in 81% yield, which was identical to an authentic sample in all respects.

Further Refinement of the Endgame. In the final deprotection step, three TBS groups are cleaved under acidic conditions. Using 3 N HCl in MeOH, it took 96 h to remove the TBS ethers in **62**. Moreover, in the Novartis large-scale synthesis of discodermolide, it was found that prolonged exposure to acidic conditions led to degradation by participation of the electron-rich trisubstituted alkene in cyclization reactions.[22] Previous studies within our group had shown that the TBS ether attached at C_3 within the δ-lactone was the last silyl group to be cleaved. We therefore anticipated that a more labile silyl protecting group at this position would lead to an increased rate of deprotection, thus minimizing the intervention of degradation pathways on large-scale production.[21e] Thus, the analogous TES ether **64** was prepared as shown in Scheme 17. Treatment of hydroxy ester **26** with TESOTf and 2,6-lutidine afforded **65**, which was submitted to DDQ to give **66**, and Swern oxidation then provided the revised TES-protected aldehyde **67** (86% over three steps). Efficient C_5-C_6 aldol coupling between methyl ketone **10** and aldehyde **67** was then achieved, employing the conditions we had developed previously, to provide adduct **68** in 83% yield (92:8 dr). Unsurprisingly, the presence of the less bulky TES ether at C_3 did not have a detrimental effect on the diastereoselectivity of this reaction. Following our previous route, treatment of **68** with CSA cleanly promoted δ-lactonization without any loss of the TES ether. K-Selectride reduction of **69** then provided the desired alcohol **64** in 85% yield with excellent selectivity at C_7 (97:3 dr). Gratifyingly, submitting **64** to 3 N HCl in MeOH led to complete silyl deprotection in only 5 h at ambient temperature to afford discodermolide in 80% yield, which potentially offers advantages for large-scale work.

SCHEME 17. Revised Synthesis for the C_3-OTES-Protected Series



Conclusions

We have completed a revised, highly convergent, and practical second-generation synthesis of (+)-discodermolide. This route proceeds in 7.8% yield over 24 linear steps, with 35 steps in total. This approach substantially reduces the total number of steps required to complete discodermolide, by utilizing the 1,3-diol **14** as a common building block for the synthesis of the three key subunits **9**, **13**, and **40**. In contrast to other reported syntheses of discodermolide that start out from the Roche ester **16**,[15−18,19a−c] the present route relies solely on substrate control to configure all of the remaining stereocenters. Moreover, by eliminating the use of all chiral reagents and auxiliaries, a more cost-effective approach has been realized. A practical alternative to the use of monomeric formaldehyde has also been developed, such that the chemistry is more robust and scalable. With suitable development, this new route should be applicable to the preparation of substantial quantities of discodermolide, enabling further clinical studies of its antitumor efficacy.

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Supporting Information Available: Detailed experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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