Evolution of a Gram-Scale Synthesis of (+)-Discodermolide

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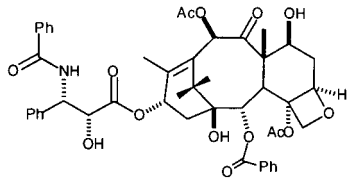
Abstract: An efficient, highly convergent, stereocontrolled total synthesis of the potent antimitotic agent (+)-discodermolide (**1**) has been achieved on gram scale. Key elements of the successful strategy include (1) elaboration of three advanced fragments from a common precursor (**CP**) which embodies the repeating stereochemical triad of the discodermolide backbone, (2) σ-bond installation of the *Z* trisubstituted olefin, exploiting a modified Negishi cross-coupling reaction, (3) synthesis of a late-stage phosphonium salt utilizing high pressure, and (4) Wittig installation of the *Z* disubstituted olefin and the terminal (*Z*)-diene.

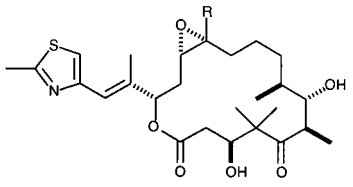
In 1990, Gunasekera and co-workers[1] at the Harbor Branch Oceanographic Institute reported the isolation of (+)-discodermolide (**1**), an architecturally novel antitumor agent derived from the deep-water marine sponge *Discodermia dissoluta*. The structure of (+)-discodermolide comprises a linear polypropionate backbone punctuated by (*Z*)-olefinic linkages at C(8,9), C(13,14), and C(21,22). Structure elucidation entailed extensive spectroscopic studies, including a combination of 1-D and 2-D NMR techniques; the relative stereochemistry was subsequently revealed by X-ray crystallography.[1] The absolute configuration however remained undefined until Schreiber and co-workers[2] synthesized both antipodes. Interestingly, the unnatural (−)-antipode also displays significant cytotoxicity.[3]

Initial biological studies revealed that (+)-discodermolide suppresses both the two-way mixed-lymphocyte reaction and the concanavalin A-induced mitogenesis of murine splenocytes in vitro (IC_{50} 0.24 and 0.19 mM, respectively), with no associated cytotoxicity.[4] (+)-Discodermolide also inhibits the graft vs host-splenomegaly response induced by injection of parental splenocytes into F1 recipient mice, with potency intermediate between those of cyclosporin A and FK506.[5] These findings stimulated considerable interest in discodermolide as a possible immunosuppressant.

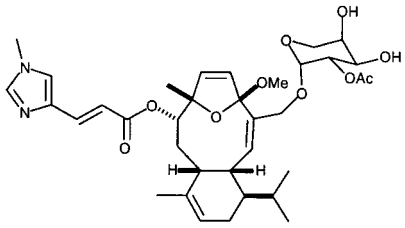
Subsequently, ter Haar et al. reported that (+)-discodermolide is a potent cell growth inhibitory agent, which arrests cell development at the M phase by binding and stabilizing mitotic spindle microtubules.[6] Thus, the ability of (+)-**1** to inhibit cell growth was suggested to resemble the clinically proven anticancer agent Taxol (**2**, Figure 1). (Taxol is a registered trademark of Bristol-Myers Squibb.) Significantly, the binding affinity to microtubules is higher.[6]



Taxol® (**2**)



Epothilone A (**3**, R=H)
Epothilone B (**4**, R=Me)



Eleutherobin (**5**)

Figure 1.

That the cell growth inhibitory effects of (+)-discodermolide and Taxol are indeed similar was confirmed by Day and co-workers.[7] (+)-Discodermolide (**1**) also displays potent activity against multi-drug-resistant (MDR) carcinoma cell lines, includ-

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

(2) Nerenberg, J. B.; Hung, D. T.; Somers, P. K.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 12621. (b) Hung, D. T.; Nerenberg, J. B.; Schreiber, S. L. *Chem. Biol.* **1994**, *1*, 67. (c) Hung, D. T.; Nerenberg, J. B.; Schreiber, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 11054.

(3) The mode of action involves blocking the S phase of the cell cycle; see ref 2.

(4) Gunasekera, S. P.; Cranick, S.; Longley, R. E. *J. Nat. Prod.* **1989**, *52*, 757.

(5) (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.* **1991**, *52*, 656. (c) Longley, R. E.; Gunasekera, S. P.; Faherty, D.; McLane, J.; Dumont, F. *Ann. N. Y. Acad. Sci.* **1993**, *696*, 94.

(6) (a) ter Haar, E.; Kowalski, R. J.; Hamel, E.; Lin, C. M.; Longley, R. E.; Gunasekera, S. P.; Rosenkranz, H. S.; Day, B. W. *Biochemistry* **1996**, *35*, 5, 243. (b) Hung, D. T.; Chen, J.; Schreiber, S. L. *Chem. Biol.* **1996**, *3*, 287.

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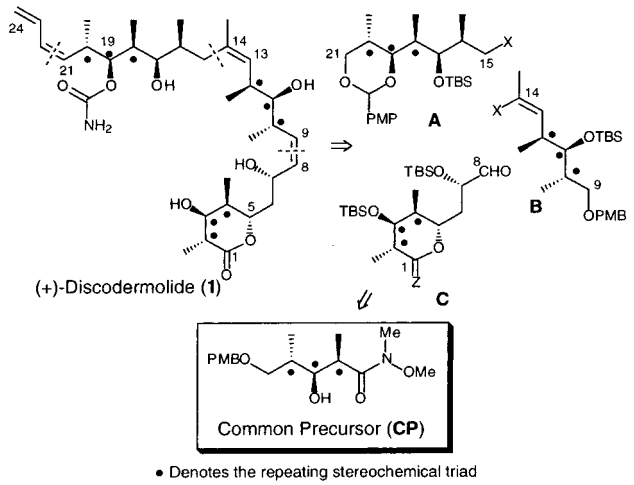
ing Taxol-resistant lines.[8] In this regard, Horwitz et al.[9] reported that **1** was unable to replace Taxol in a newly discovered Taxol-dependent human lung carcinoma cell line (A549-T12), whereas the natural products epothilone A and B (**3**, **4**) and eleutherobin (**5**) were able to serve as substitutes for Taxol and thus maintain viability of the cell line.[9] Importantly, the Taxol-dependent cell line proved to be 20-fold more sensitive to **1** in the presence of low concentrations of Taxol than in its absence.[9] The significance of these results is 2-fold: (1) (+)-discodermolide may bind to microtubules at a site distinct from that of Taxol, the epothilones (**3**, **4**), and eleutherobin (**5**) and (2) the combination of (+)-discodermolide and Taxol may constitute a promising synergistic cancer chemotherapeutic treatment regime. Unfortunately, the current scarcity of natural material (0.002% w/w from frozen sponge) has precluded further evaluation as an anticancer agent.

Not surprisingly the remarkable biological activity and novel structure, in conjunction with the scarcity of the natural material**,** has led to considerable interest in discodermolide as a synthetic target.[10] To date, six total syntheses of discodermolide, including our first-generation synthesis of the unnatural levorotatory congener, have been reported.[2,11] In this, a full paper, we describe the evolution of a synthetic strategy which recently culminated in the preparation of 1 g of the natural congener.[11b]

Synthetic Plan. Analysis of the discodermolide structure revealed a repeating triad of contiguous stereocenters (Scheme 1), separated by (*Z*)-olefinic linkages at C(8,9) and C(13,14). From the synthetic perspective we sought an efficient, highly convergent approach taking full advantage of this structural element, while also exploiting the dithiane coupling and σ- and π-bond construction tactics that had proven so effective in our syntheses of FK506 and rapamycin.[12] Thus, disconnections at C(8,9), C(14,15), and C(21,22) generated fragments **A**, **B**, and **C**, each envisioned to arise from a common precursor (**CP**) possessing the recurring triad of contiguous stereogenic centers. Union of **A** and **B** via either cuprate chemistry[13] or palladium-catalyzed cross-coupling[14] would then lead to an **AB** fragment possessing the C(13,14) trisubstituted (*Z*)-olefin; in turn the ylide derived from the **AB** fragment would be coupled via Wittig olefination with aldehyde **C** to generate the C(8,9) *cis*-alkene. Introduction of the terminal *Z*-diene would also exploit a Wittig olefination or like process. Completion of the discodermolide venture would then only require elaboration of the C(1) lactone carbonyl, selective incorporation of a carbamate moiety at C(19), and global deprotection.

Scheme 1



The Common Precursor. The critical role of the common precursor **CP** demanded development of a route that would be amenable to large-scale production. To orchestrate the triad of contiguous stereogenic centers, we selected the Evans *syn*-aldol protocol.[15] Given that the absolute stereochemistry of (+)-discodermolide was unknown at the outset (early 1993), we arbitrarily chose the commercially available (*R*)-(−) antipode of methyl 3-hydroxy-2-methylpropionate (**6**) as starting material. Ultimately this choice led to the unnatural (−)-antipode of **1**.[11a] As detailed here, this strategy is equally amenable to the synthesis of (+)-discodermolide, utilizing the commercially available (*S*)-(+) antipode of **6**. Although some of the transformations described in this paper were developed during our initial synthesis of (−)-discodermolide, for clarity of presentation, all transformations are depicted in the optical series of the natural product. The absolute stereochemistries with associated chiropic properties of all intermediates are available in the Supporting Information.

Our point of departure for the construction of the common precursor **CP** required for natural (+)-discodermolide entailed protection of hydroxy ester (+)-**6** as the *p*-methoxybenzyl (PMB) ether (Scheme 2), exploiting the Bundle trichloroimidate protocol.[16] Reduction with $LiAlH_4$ and distillation provided

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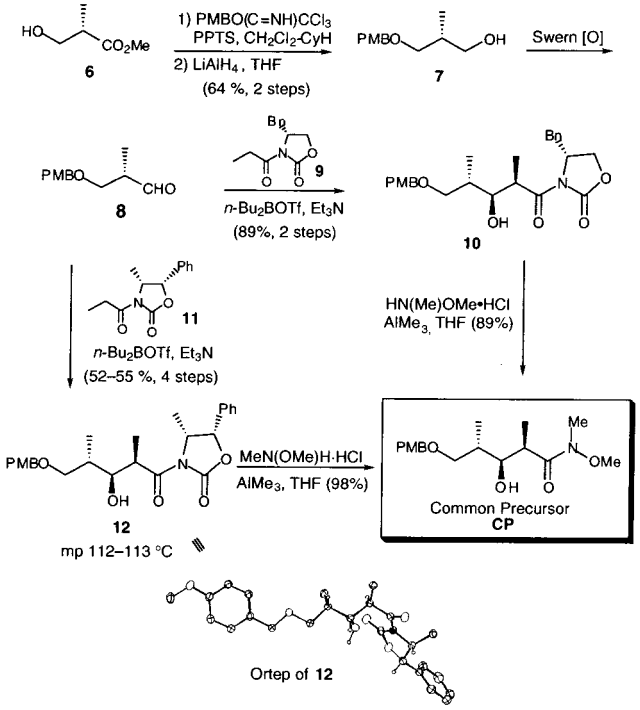
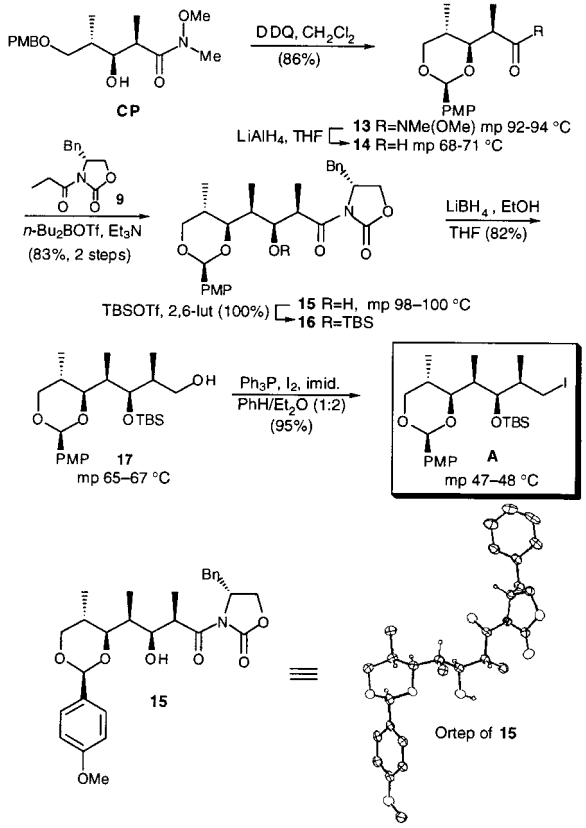
Scheme 2



Scheme 3



alcohol **7**; Swern oxidation[17] then furnished aldehyde **8**, which was used without purification in an Evans aldol condensation with oxazolidinone **9**.[18] Weinreb amide formation[19] completed construction of the common precursor **CP**.

While preparing for the large-scale synthesis of natural discodermolide (vide infra), we became aware of a report by Walkup and co-workers[20] describing aldol adduct **12** as a crystalline solid. Since the phenylalaninol-derived oxazolidine **10** is noncrystalline and thus purified by silica gel chromatography, the prospect of utilizing **11** in place of **9** appeared attractive for the large-scale production of **CP**. Gratifyingly, the dibutylboron enolate of **11**, readily prepared from (1*S*,2*R*)-norephedrine,[15] did indeed produce a crystalline adduct with aldehyde **8**. The yield of **12** was 64−70% on a 60−70 g scale. Significantly, **12** could be isolated directly from the reaction mixture by crystallization. In practice, the first three intermediates were carried forward without purification, and **12** was isolated by crystallization (55%, four steps, 60 g scale). The structure of **12** was confirmed by single-crystal X-ray analysis.[21] Subsequent conversion of **12** to the common precursor **CP** proceeded as before without complication (98% yield). Purification of **CP** was facilitated by crystallization of the oxazolidinone auxiliary from the reaction mixture (80−90% recovery). The readily recovered auxiliary further augmented the efficiency of this sequence.

Fragment A. The polypropionate structural motif of fragment **A** suggested a second asymmetric aldol reaction (Scheme 3). Initial generation of the *p*-methoxybenzylidene (PMP) acetal[22] was intended to permit eventual late-stage deprotection of the C(21) and C(19) hydroxyls, facilitating selective introduction in turn of the terminal diene and carbamate moieties. Accordingly, treatment of **CP** with DDQ furnished crystalline acetal **13**. Controlled reduction of the Weinreb amide[23] provided crystalline aldehyde **14** which was directly coupled with oxazolidinone **9** via an Evans aldol reaction to provide crystalline alcohol **15** (83% yield, two steps), possessing the requisite five contiguous stereogenic centers of subunit **A**. The structures of **13** and **15** were confirmed by single-crystal X-ray analyses.[21] Protection of the secondary hydroxyl as the TBS ether and removal of the chiral auxiliary ($LiBH_4$, EtOH, THF)[24] then furnished crystalline **17** (82% yield, two steps). Alcohol **17** was then converted to iodide **A** (95% yield), completing the synthesis of the C(17−21) subunit **A** in six steps and 56% overall yield from **CP**.[25] The remarkable number of crystalline intermediates en route made this sequence well suited for the routine production of **A** on a large scale.[26]

Fragment B. As outlined in Scheme 1 our synthetic plan called for construction of a vinyl halide possessing the (*Z*)-configuration to couple with fragment **A**. We selected bromide **23** as our initial target (Scheme 4). Beginning again with **CP**, protection of the hydroxyl as the TBS ether, followed by DIBAL reduction, afforded aldehyde **19** in 89% overall yield. Unfor-

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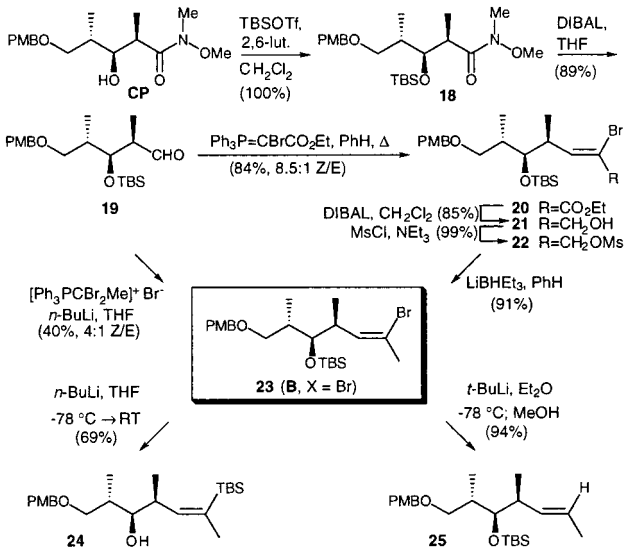
(25) Alcohol **17** could also be converted to iodide **A** in 94% overall yield via tosylation (TsCl, pyridine) followed by displacement with sodium iodide in DMF.

(26) We also explored the use of the norephedrine-derived oxazolidinone **11** employed in the synthesis of **CP**. Unfortunately the corresponding aldol product was obtained as an oil. In addition, reductive removal of the auxiliary resulted in competitive opening of the oxazolidinone ring; thus, oxazolidinone **9** was the auxiliary of choice for the construction of fragment **A**.

Scheme 4

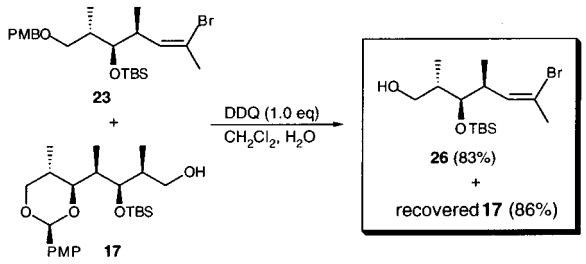


tunately the one-step protocol of Smithers[27] to introduce the vinyl halide via an α-bromoalkylylide was not synthetically useful (e.g., 40% yield, 4:1 *Z*/*E*). We therefore adopted a stepwise approach, whereby **19** was first converted to the *Z* α-bromo unsaturated ester **20** ($Ph_3P{=}CBrCO_2Et$,[28] PhH, reflux; 75% yield). Reduction, followed by mesylation and displacement with hydride ($LiBHEt_3$) then furnished the *(Z)*-vinyl bromide **23** in 77% yield from **20**.

In seeking to verify the olefin geometry in **23** by sequential metalation, protonation, and ^1H NMR analysis, we discovered that the initially formed vinyl anion was prone to 1,5-silyl migration, affording **24** when the lithium−halogen exchange (*n*-BuLi) was performed in THF.[29] Although the unexpected retro-[1,5]-Brook rearrangement[30] provided evidence that bromide **23** indeed possessed the desired (*Z*)-configuration (vide infra), our synthetic plan was now in jeopardy, unless the migration could be suppressed. Toward this end, halogen exchange with *t*-BuLi at −78 °C in THF resulted in only 20% rearrangement, while treatment with *t*-BuLi *in Et2O* (−78 °C) completely circumvented the problem. We attribute the observed difference in reactivity to stronger solvation of the organolithium aggregate in THF, an effect that renders the carbanion more nucleophilic.[31] Protonation of the vinyl anion then led to **25** in 94% yield; the *trans*-olefinic geometry was confirmed by the vinylic coupling constant (e.g., $J = 15.3$ Hz).[32]

While the protecting groups in subunits **A** and **B** were carefully chosen to exploit most efficiently **CP**, our long-term strategy demanded removal of the primary PMB ether (derived from **23**) in the presence of the PMP acetal in the **AB** coupled product (Scheme 1). It thus appeared prudent to explore the feasibility of this unprecedented tactic before committing to this protecting group scheme. Accordingly, exposure of an equimolar mixture of PMB ether **23** and PMP acetal **17** to DDQ (1.1 equiv) in CH_2Cl_2/H_2O[22] (Scheme 5) furnished acetal **17** largely intact

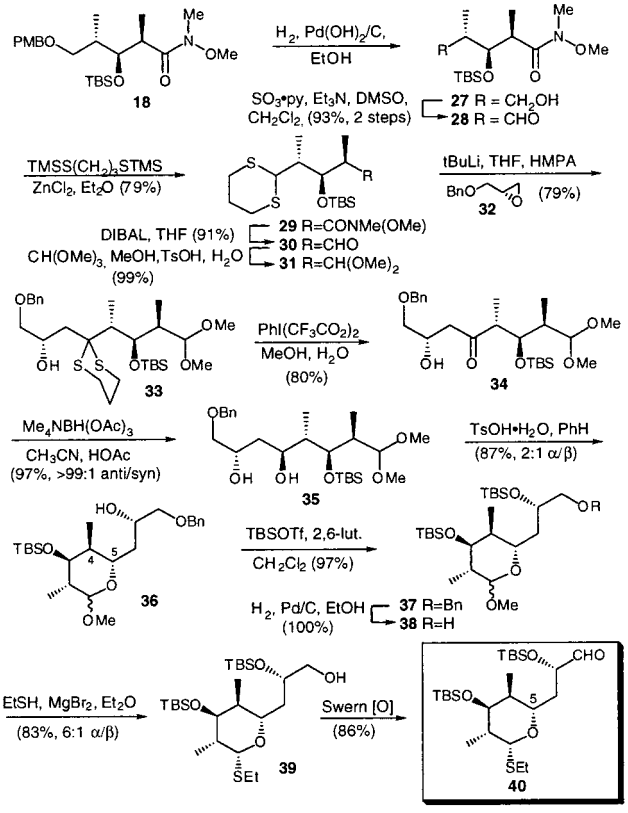
Scheme 5



and alcohol **26** in 83% yield. Presumably, the observed selectivity is due to the higher oxidation potential of the acetal which contains two electron-withdrawing oxygens. With these results in hand, we proceeded with confidence.

Fragment C. Our point of departure was TBS ether **18** (Scheme 6), previously prepared during the synthesis of

Scheme 6



fragment **B** (vide supra). Oxidative removal of the PMB group (DDQ, CH_2Cl_2, H_2O) provided an unstable alcohol, **27**, in yields ranging from 60% to 86%, accompanied by significant amounts of the corresponding δ-lactone, which could be recycled.[33] Better results were obtained by hydrogenolysis of **18** with Pearlman's catalyst, which provided **27** in 95% yield. Oxidation with SO_3•pyridine[34] then furnished aldehyde **28** (98% yield); the two steps were routinely performed without purification of **27**. Dithiane generation via modification of the Evans protocol[35] [e.g., $(TMSSCH_2)_2CH_2$, $ZnCl_2$, Et_2O] minimized elimination of the TBS ether, permitting efficient production of dithiane **29** (79%). DIBAL reduction (91% yield), followed by dimethyl acetal

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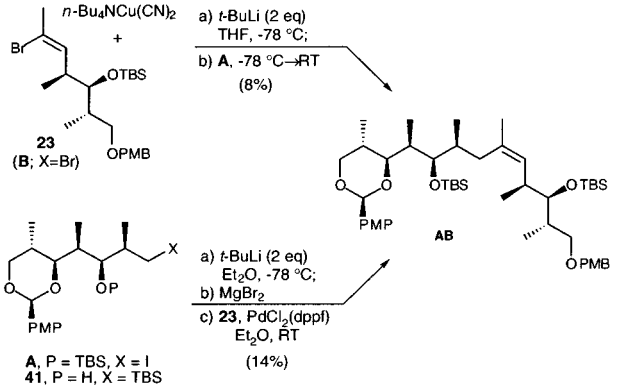
(34) Parikh, J. R.; Doering, W. von E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.
(35) $ZnCl_2$ was used instead of ZnI_2; see: Qui, Y. Ph.D. Thesis, University of Pennsylvania, Philadelphia, PA, 1997. Evans, D. A.; Truesdale, L. K.; Grimm, K. G.; Nesbitt, S. L. *J. Am. Chem. Soc.* **1977**, *99*, 5009.

formation, then gave **31** (99%). Coupling of the dithiane with benzyl (*S*)-(+)-glycidyl ether **32** exploited the conditions developed earlier in our laboratory in connection with our FK506 and rapamycin syntheses.[12] This sequence provided alcohol **33** in 79% yield. Unmasking of the ketone [$(CF_3CO_2)_2$-IPh, 80%][36] followed by Evans directed reduction[37] furnished the *anti*-diol **35** (97%), which embodied all of the stereogenic centers required for fragment **C**. Acid-catalyzed cyclization then provided methoxy pyran **36** in 87% yield, as a separable mixture of α and β anomers (2:1). The large coupling constant in **36**α ($J_{4,5}$ = 9.8 Hz), diagnostic of the diaxial arrangement of the C(4) and C(5) hydrogens, confirmed the selectivity of the directed reduction.[38] The configuration of the methoxy group was deduced by a series of NOE experiments.[39] The epimeric mixture **36** was then converted to the corresponding TBS ethers **37** (α:β = 2:1, 97% yield).

In our initial synthetic strategy, we had planned to mask the C(1) carbonyl in fragment **C** as the mixed methyl acetal. However, under a variety of conditions, we were unable to hydrolyze the acetal moiety in the presence of the TBS ethers, a required endgame transformation. To circumvent this obstacle we converted **37** to the ethylthio derivative **39**, a tactic first reported by Schreiber and co-workers in their discodermolide syntheses.[2] Toward this end, hydrogenolysis of **37** afforded alcohol **38** quantitatively; exposure to ethanethiol and $MgBr_2$ in Et_2O[40] then furnished a separable mixture of hemithioacetal **39** and the β anomer (6:1) in 83% yield.[39] Although in principle both epimers could be carried forward, it was more expedient to work with homogeneous material. Swern oxidation of **39** led to **40** (86% yield), our first-generation fragment **C**. The overall sequence proceeded in 14 steps from **CP** and in 24% overall yield (average yield/step 90%).

Union of Fragments A and B. At the outset, we had planned to employ a vinyl cuprate to effect σ-bond construction of the C(13−14) *Z* trisubstituted olefin.[13] Unfortunately, attempts to couple iodide **A** (Scheme 7) with the cuprate prepared from

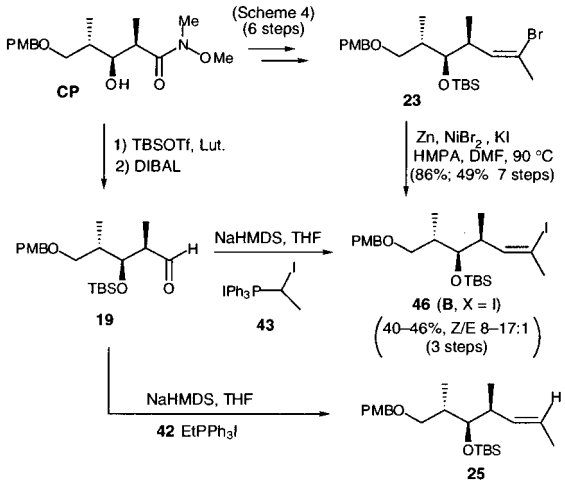
Scheme 7



vinyl bromide **23**, via lithium halogen exchange followed by the addition of a variety of Cu(I) salts [i.e., CuCN, CuI, (Th)-Cu(CN)Li], by and large proved unsuccessful. Only the higher order cuprate exploiting the Corey reagent *n*-$Bu_4NCu(CN)_2$[41] furnished the desired **AB** segment, albeit in only 8% yield.

Attention quickly shifted to palladium-catalyzed cross-coupling reactions.[14] Initial studies targeted the coupling of bromide **23** with organomagnesium, organozinc, or organoboron reagents prepared from **A**.[14] To this end, lithiation of iodide **A** (2 equiv of *t*-BuLi, −78 °C) followed by the addition of $MgBr_2$, $ZnCl_2$, or *B*-methoxy-9-BBN furnished the requisite organometallic species.[42] Not surprisingly, the initial lithio species also proved susceptible to silyl migration to form **41**, a significant side reaction at −45 °C in Et_2O or at −78 °C in THF (cf. Scheme 4). Best results were obtained by metalation with *t*-BuLi at −78 °C for ca. 10 min followed by addition of $MgBr_2$. Although **AB** was only obtained in 14% yield, we were encouraged by the observation that most of the vinyl bromide could be recovered. The high recovery of **23** suggested slow oxidative insertion of the palladium into the carbon−bromine bond. We therefore examined the more reactive vinyl iodide **46** (Scheme 8). Initially, iodide **46** was prepared in one step

Scheme 8

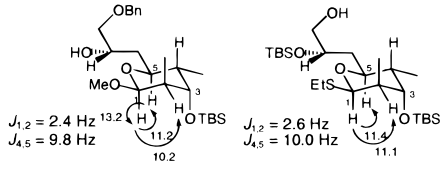


(86% yield) from bromide **23** via Nickel-catalyzed bromine−iodine exchange.[43] The overall length of this sequence from **CP** however was not acceptable (i.e., seven steps). We therefore explored the Zhao one-step protocol.[44] Treatment of aldehyde **19** with the ylide derived from **43**[44] afforded **46** in 40−46% overall yield from **CP**.[45] The *Z*/*E* selectivity ranged from 8:1 to 17:1. In practice, the sequence required only a single chromatographic purification, and could be performed routinely on a 30 g scale.

Upon scale-up, we noted the formation of significant amounts of an olefin lacking the iodide. A similar result was recently reported by Marshall and Johns.[11] This side product **25** proved to be the direct result of incomplete incorporation of iodine in

(36) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 287.
(37) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.
(38) See ref 32, Chapter 11.

(39) Selected NOE values (%) and ^{1}H NMR coupling constants for **36** and **39**. We thank Dr. Peter Dormer for technical assistance.

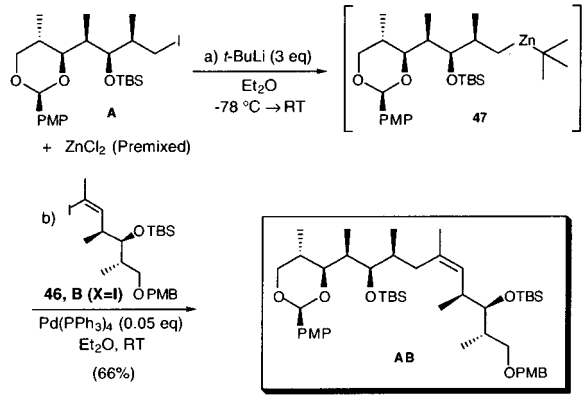


(40) Kim, S.; Park, J. H.; Lee, S. *Tetrahedron Lett.* **1989**, *30*, 6697.
(41) Corey, E. J.; Kyler, K.; Raju, N. *Tetrahedron Lett.* **1984**, *25*, 5115.
(42) (a) Bailey, W. F.; Punzalan, E. R. *J. Org. Chem.* **1990**, *55*, 5404. (b) Negishi, E.; Swanson, D. R.; Rousset, C. *J. Org. Chem.* **1990**, *55*, 5406.
(43) Takagi, K.; Hayama, N.; Inokawa, S. *Chem. Lett.* **1978**, 1435.
(44) Chen, J.; Wang, T.; Zhao, K. *Tetrahedron Lett.* **1994**, *35*, 2827.
(45) While attempting to optimize the formation of **46** via the Zhao protocol, we observed significant formation of methyl ketone and epoxide byproducts. These results suggest that formation of an epoxyphosphonium salt is competitive with Wittig olefination. A detailed discussion of the Zhao chemistry has been published and will not be repeated here; see: Arimoto, H.; Kaufman, M. D.; Kobayashi, K.; Qui, Y.; Smith, A. B., III. *Synlett* **1998**, 765.

phosphonium salt **42**, thereby leading to a mixture of ylides upon deprotonation with NaHMDS. The poor iodine incorporation was in turn the result of the low solubility of iodine in THF; increasing the amount of THF (0.1 M I_2) during the preparation of **43**, in conjunction with vigorous stirring at ambient temperature prior to cooling, circumvented this problem.

As anticipated vinyl iodide **46** proved superior to bromide **23** in the palladium-catalyzed cross-coupling reactions, although not without significant initial experimentation. Best results involved modification of a Negishi protocol (Scheme 9).[14b]

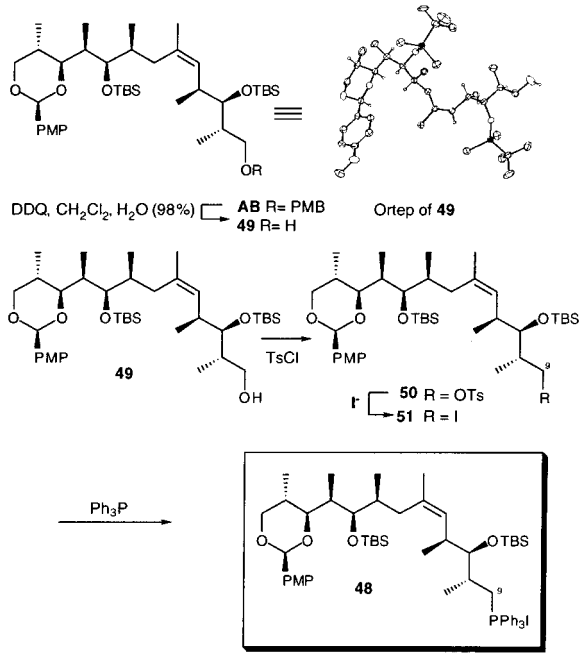
Scheme 9



Specifically, treatment of iodide **A** and 1 equiv of $ZnCl_2$ in ether with 3 equiv of *t*-BuLi at −78 °C, followed by warming to ambient temperature and transfer to an intimate mixture of vinyl iodide **46** and $Pd(PPh_3)_4$ (5 mol %), furnished **AB** after workup in 66% yield (recrystallized). The efficiency of this cross-coupling reaction is particularly noteworthy. In contrast to most cross-coupling reactions which require a minimum of 1.5 equiv of alkyl iodide for comparable efficiency, only 1.1 equiv of **A** was required.[46] Importantly, 3 equiv of *t*-BuLi is required for complete consumption of **A**. Treatment with 2 equiv of *t*-BuLi, followed by quenching with water, leads to a 1:1 mixture of starting iodide and the expected alkane. Accordingly, we speculate that a mixed *tert*-butyl−alkyl zinc intermediate (e.g., **47**) is the reactive alkyl donor in the coupling process.

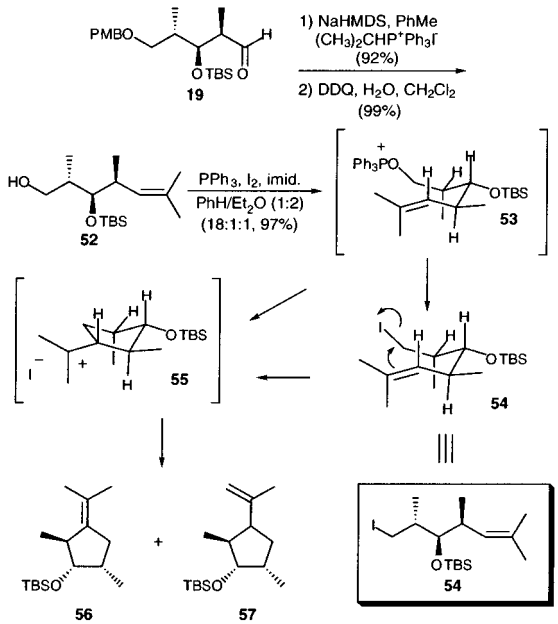
The AB Wittig Reagent. Conversion of **AB** to the requisite phosphonium iodide **48** (Scheme 10) began with selective removal of the PMB group. As anticipated from our earlier model study (Scheme 5), exposure of **AB** to 1 equiv of DDQ (CH_2Cl_2, H_2O) effected selective removal of the PMB ether in the presence of the PMP acetal, furnishing **49** in 91% yield. The relative stereochemistry of **49** was confirmed by single-crystal X-ray analysis.[21] Further elaboration of **49**, however, presented unforeseen difficulties. Quite surprisingly, attempts to convert **49** to iodide **51** via tosylate **50** proved unsuccessful. While some tosylate appeared to be present in the reaction mixture (^1H NMR), attempts to chromatograph the tosylate failed. Attempts to convert the tosylate directly to iodide **51** also proved unrewarding. Detailed ^1H NMR analysis of the product mixture revealed the loss of the trisubstituted olefin, presumably the result of olefin-assisted displacement at C(9). Analogous olefin-assisted solvolyses of 5-hexenylsulfonates are well-known.[47] However, such reactions usually require more vigorous conditions (e.g., formic acid, 75 °C).[47]

Scheme 10



To understand better the nature of this reaction, we turned to model alcohol **52** (Scheme 11), prepared from aldehyde **19** via reaction with the ylide derived from isopropyltriphenylphosphonium iodide, followed by oxidative removal (DDQ) of the PMB ether. Again attempts to generate the iodide **54** from **52** via the tosylate proved unsuccessful. However, a modification

Scheme 11



of the Garegg conditions (PPh_3, I_2, imidazole, 3:1 Et_2O/CH_3CN)[48] did permit conversion of **52** to iodide **54** (74%); minor amounts of **56** and **57** were also isolated and characterized (8% each). The observation of cyclopentanes **56** and **57** provides clear evidence for the competitive solvolysis process.[49]

Analysis of the competing transition states (e.g., intramolecular vs bimolecular displacement) suggested that solvent

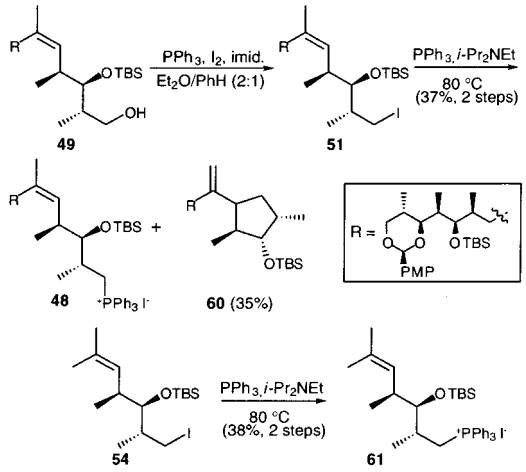
(46) In the Marshall synthesis of **1**, a Suzuki coupling strategy was employed requiring 2 equiv of the alkyl iodide; see ref 11d.

(47) (a) Johnson, W. S.; Bailey, D. M.; Owyang, R.; Bell, R. A.; Jaques, B.; Crandall, J. K. *J. Am. Chem. Soc.* **1964**, *86*, 1959. (b) Johnson, W. S.; Owyang, R. *J. Am. Chem. Soc.* **1964**, *86*, 5593.

(48) (a) Corey, E. J.; Pyne, S. G.; Su, W.-G. *Tetrahedron Lett.* **1983**, *24*, 4883. (b) Garegg, P. J.; Samuelsson, B. *J. Chem. Soc., Perk. Trans. 1* **1980**, 2866.

polarity should influence the product distribution.[50] Indeed, the use of CH_3CN or CH_3CN/Et_2O (3:1) as solvent significantly increased cyclization vs displacement (e.g., **54**:**56**:**57** = 9:1:1; 90% yield) whereas the less polar medium, Et_2O/PhH (2:1), provided a greater proportion of iodide **54** (18:1:1; 97% yield). To our delight similar treatment of alcohol **49** [PPh_3, I_2, Et_2O/PhH (2:1)] furnished the requisite iodide **51** in near quantitative yield (Scheme 12). The sensitive iodide could be either purified

Scheme 12

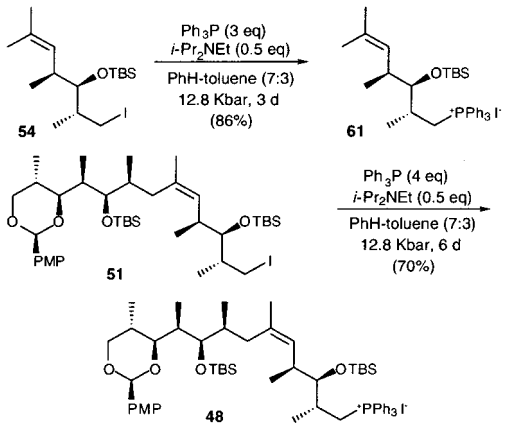


by rapid silica gel chromatography (pretreated, Et_3N) or used without purification.

Turning next to the preparation of the requisite Wittig reagent (Scheme 12), initial efforts involved treatment of **51** with PPh_3 in solvent (not shown); again extensive cyclization and some decomposition occurred. To circumvent intramolecular cyclization, we turned to molten PPh_3. In the event, treatment of **51** with excess triphenylphosphine (15 equiv) and *i*-Pr_2NEt (3 equiv) at 80 °C in the absence of additional solvent generated **48** in 37% yield from **49**. The major byproduct was again cyclopentane **60** (35% yield). Critical to the success of this reaction was the use of an amine base to prevent the HI, produced during cyclization, from promoting decomposition. Similar treatment of model iodide **54** furnished phosphonium salt **61** in 38% overall yield from **52**. In marked contrast, the fully saturated congener obtained by hydrogenation of olefin **52** afforded the corresponding saturated phosphonium salt (via the iodide) in almost quantitative yield (94%).

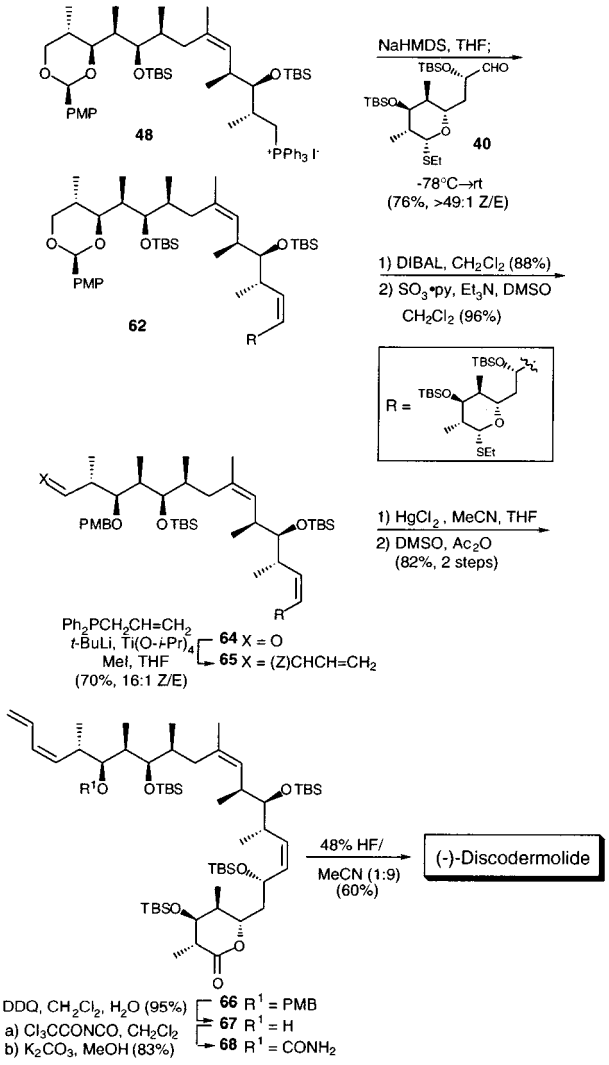
Phosphonium Salts via Ultrahigh Pressure. Although the use of molten triphenylphosphine as solvent led to displacement of the iodide, the 37% yield was not acceptable for large-scale material advancement. We therefore turned to high pressure to facilitate displacement. In 1984 Dauben and co-workers reported that alkylation of phosphines can be dramatically accelerated by ultrahigh pressure.[51] In the event, reaction of a mixture of iodide **54**, triphenylphosphine (3 equiv), and *i*-Pr_2NEt (0.5 equiv) in benzene/toluene (7:3) at 12.8 kbar (185 000 psi) for 72 h furnished an 86% yield of phosphonium salt **61** (Scheme 13). Gratifyingly, iodide **51** was similarly transformed into **48** via these conditions (6 d; 70% overall yield from alcohol **49**).

Scheme 13



A First-Generation Endgame. Deprotonation of phosphonium salt **48** with sodium bis(trimethylsilyl)amide in THF gave rise to an ylide which underwent high *Z*-selective coupling (>49:1 *Z*/*E*) with aldehyde **40**, to furnish **62** in 76% yield (Scheme 14). DIBAL reduction[52] then led to a primary alcohol

Scheme 14



(88% yield), which in turn was oxidized to aldehyde **64** (96% yield). The terminal (*Z*)-diene **65** was next installed via the Yamamoto protocol[53] in 70% yield, completing assembly of the discodermolide backbone; the selectivity was 16:1 Z/E.[54]

(49) Interestingly a Monte Carlo conformational analysis of iodide **54** using the MM2* force field (Macromodel, v. 5.0) revealed that the substituents on **54** enforce a half-chair arrangement in a large percentage of the lower energy conformers. In particular, 12% of the lowest energy conformers (E_{rel} = 0−5.48 kJ/mol) were judged suitably disposed to facilitate displacement of the iodide by the olefin. Of these conformers, the average distance between C(1) and C(5) was only 3.05 Å (SD = 0.02 Å) while the average I−C(1)−C(5) angle was 161.2° (SD = 0.4°).

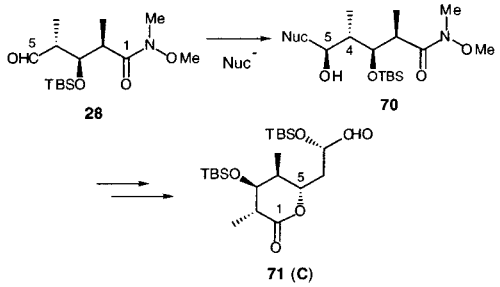
(50) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*; VCH: Weinheim, 1990.

Hydrolysis of the hemithio acetal followed by Kuzuhara−Fletcher oxidation[55] provided lactone **66** in 82% yield for the two steps. Removal of the PMB group (DDQ, CH_2Cl_2, H_2O, 95%) and introduction of the carbamate via the Kocovsky protocol ($Cl_3CCONCO$, CH_2Cl_2; K_2CO_3, MeOH, 83%)[56] then led to **68**. Final deprotection with HF/CH_3CN (48%, 1:9) furnished (−)-discodermolide (60% yield), identical in all respects, with an authentic sample provided by Schreiber (e.g., 500 MHz ^{1}H NMR, 125 MHz ^{13}C NMR, IR, HRMS, optical rotation, and TLC in four solvent systems).[57]

A Second-Generation Endgame. Although the endgame shown in Scheme 14 permitted completion of (−)-discodermolide in 1995 (40 total steps; 28 in the longest linear sequence),[11] the synthesis was far from optimal. Having subsequently learned of the potential of (+)-discodermolide as an anticancer agent, we felt compelled both to shorten the existing synthetic route and to improve the overall efficiency of the synthesis to permit preparation of significant quantities of this natural product for further clinical development. We set as our goal the synthesis of 1 g.

Fragment C: A Second-Generation Strategy. In our initial synthesis of (−)-discodermolide, elaboration of subunit **C** (**40**) from the common precursor **CP** was clearly the least efficient aspect of the synthetic venture, requiring 14 steps (**CP** → **40**; Scheme 6). The length of this sequence was due, at least in part, to our desire to exploit the coupling of dithiane **31** with an epoxide (**31** → **33**; Scheme 6), a tactic utilized to great advantage in earlier syntheses in our laboratory. While the above protocol proved effective, a direct three-carbon extension of aldehyde **28** appeared more expedient (Scheme 15). The

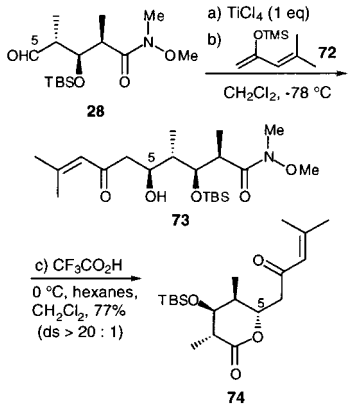
Scheme 15



challenge, however, would entail stereocontrol in the addition of an appropriate nucleophile to **28**, to generate the required anti relationship between C(4) and C(5) in **70**.[58] This strategy also held the promise of allowing the unprotected C(1) lactone to be carried throughout the endgame sequence. We thus set lactone−aldehyde **71** as our second-generation fragment C.[59]

We selected as our initial nucleophile the silyl enol ether derived from mesityl oxide (**72**) (Scheme 16).[60] There was of

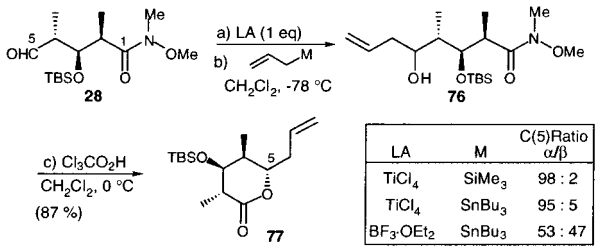
Scheme 16



course no guarantee that we would be able to control the facial selectivity of aldehyde **28**. Two options were however available. One would be to replace the TBS ether of **28** with a more Lewis basic protecting group to direct nucleophilic addition to the aldehyde via metal ion chelation.[10k,l] The alternative would be to use an external asymmetric promoter. In the interest of synthetic economy and the demonstrated effectiveness of the C(14) TBS ether in the first-generation endgame (vide supra), we elected to explore initially the addition of enol ether **72** to **28** (Scheme 16). To our delight treatment of a solution of **28** and $TiCl_4$ (1 equiv) with enol ether **72** at −78 °C proceeded in 77% yield with near complete anti-Felkin selectivity (ds > 20:1); lactone **74** was then available after acid-catalyzed cyclization of the intermediate hydroxy amide **73**.[61]

Anti-Felkin addition was also observed in the $TiCl_4$-promoted reactions of allyltrimethylsilane and allyltributylstannane with **28** (ca. 49:1 and 19:1, respectively; Scheme 17). In contrast,

Scheme 17



LA	M	C(5)Ratio α/β
$TiCl_4$	$SiMe_3$	98 : 2
$TiCl_4$	$SnBu_3$	95 : 5
$BF_3{\cdot}OEt_2$	$SnBu_3$	53 : 47

$BF_3{\cdot}OEt_2$-promoted the addition of allyltributylstannane with no selectivity.[62] Taken together, these results suggest that bidentate complexation of the $TiCl_4$ with the carbonyl groups of the Weinreb amide and the aldehyde, via an eight-membered chelate, is responsible for the observed high anti-Felkin selectivity.[63,64]

(51) Dauben, W. G.; Gerdes, J. M.; Bunce, R. A. *J. Org. Chem.* **1984**, *49*, 4293. For reviews on the use of high pressure in organic synthesis, see: (a) *Organic Synthesis at High Pressure*; Matsumoto, K., Morrin Acheson, R., Eds.; John Wiley: New York, 1991. (b) Matsumoto, K.; Sera, A.; Uchida, T. *Synthesis* **1985**, 1. (c) Matsumoto, K.; Sera, A. *Synthesis* **1985**, 999.

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

(53) Ikeda, Y.; Ukai, J.; Ikeda, N.; Yamamoto, H. *Tetrahedron* **1987**, *43*, 723.

(54) Heathcock has also utilized the Yamamoto protocol; see ref 10b.

(55) Kuzuhara, H.; Fletcher, H. G., Jr. *J. Org. Chem.* **1967**, *32*, 2531.

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

(57) We thank Professor Schreiber (Harvard University) for providing a sample of synthetic (−)-discodermolide.

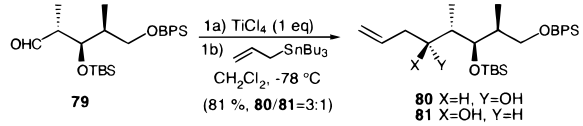
(58) For a general discussion of nucleophilic additions to α-chiral carbonyl compounds, see: Devant, R. M.; Radunz, H.-E. In *Methods of Organic Chemistry*; Helmchen, G., Hoffman, R. W., Mulzer, J., Schaumann, Eds.; Thieme Verlag: New York, 1995; Vol. E21b, Chapter 1.3.

(59) Paterson reported the synthesis of the enantiomer of **71**; see ref 10a. However, use as a substrate for Wittig olefination was not reported.

(60) Paterson, I. *Tetrahedron Lett.* **1979**, 1519.

(61) The relative stereochemistries of **74** and the C(5) epimer **75** were established by NMR: **74**, $J_{4,5} = 10.0$ Hz; **75**, $J_{4,5} = 2.4$ Hz, $J_{2,3} = 9.8$ Hz.

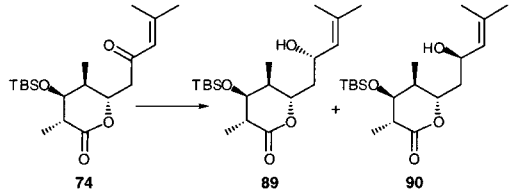
(62) The BPS ether aldehyde **79**, a substrate lacking the Weinreb amide moiety furnished the Felkin addition product **80** over the anti-Felkin adduct **81** (3:1):



With a method available to access **73**, **74**, and **77** with excellent stereocontrol at C(5), attention turned to introduction of the requisite α-hydroxy aldehyde functionality. Initial studies entailed asymmetric dihydroxylation of olefin **77**.[65] Attempts to effect this transformation led, at best, only to a 3:1 mixture of diols. Attention thus shifted to the acyclic Mukaiyama aldol adduct **73**. We reasoned that the stereogenicity of the C(5) hydroxyl could be employed to direct reduction of the enone carbonyl to the *anti*-diol similiar to a reduction reported by Evans.[37,66]

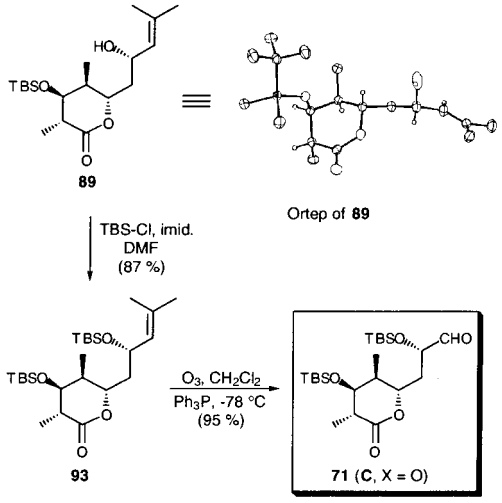
Having failed to observe high selectivity in the directed reduction of the C(7) enone in **73**, we explored the reduction of the enone in lactone **74** (Scheme 18), readily available (77% yield) from **73** by acidic treatment (Scheme 16). A variety of reducing conditions were examined. Only the Selectride reagents furnished the desired allylic alcohol **89** as the predominant product.[67] Higher selectivities were obtained in toluene compared to THF or ether. The selectivies also proved sensitive to the counterion; K-Selectride (**89**:**90** = 9:1) was notably more selective than both N-Selectride (**89**:**90** = 3:1) and L-Selectride (**89**:**90** = 1.2:1). The stereochemistry of alcohol **89** was subsequently secured via single-crystal X-ray analysis (Scheme 19).

Scheme 18



Reducing Conditions	Yield	**89:90**
K-Selectride, PhMe-THF (19:1), -78 °C	50-79 %	9 : 1
N-Selectride, PhMe-THF (19:1), -78 °C	80 %	3 : 1
L-Selectride, PhMe-THF (19:1), -78 °C	86 %	1.2 : 1
(S)-Alpine Hydride, THF (19:1), -78 °C	59 %	1 : 2.5
(R)-Alpine Hydride, THF (19:1), -78 °C	63 %	1 : 7
$LiAl(OtBu)_3$, PhMe-THF (19 : 1), -78 °C	84 %	1 : 4
$NaBH_4$, EtOH, -78 °C	54 %	1 : 2

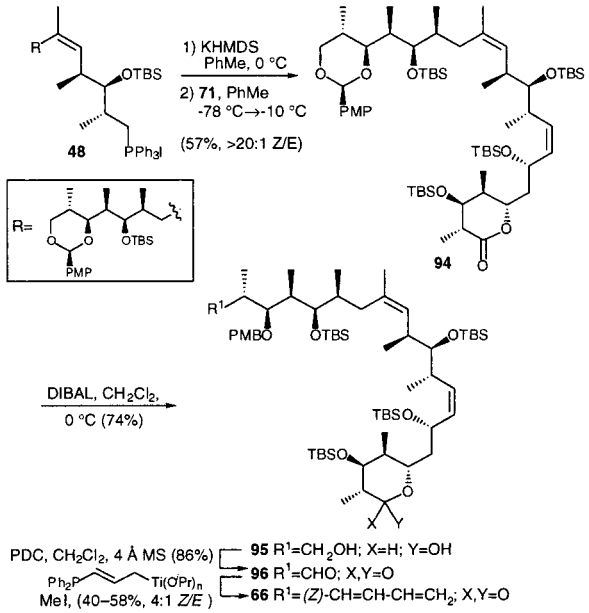
Scheme 19



With alcohol **89** in hand, conversion to our second-generation fragment **C** (**71**) proved straightforward. Protection as the TBS ether furnished **93** (87% yield), which was then subjected to ozonolysis to give **71** (95% yield). Thus, our second-generation subunit **C** was available in seven steps (47% overall yield, 89% average) from **CP**. While this synthesis was considerably shorter and more efficient than that of **40** (e.g.,14 steps, 24% overall yield), the vitality of **71** as a Wittig coupling partner was yet to be established.

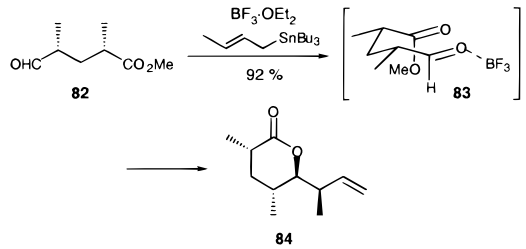
Chemoselectivity in the Wittig Coupling. Treatment of **71** (Scheme 20) with the ylide derived from **48** (KHMDS, toluene, 0 °C) furnished olefin **94** in 57% yield with excellent *Z*/*E* selectivity (>20:1). The choice of both base and solvent proved

Scheme 20



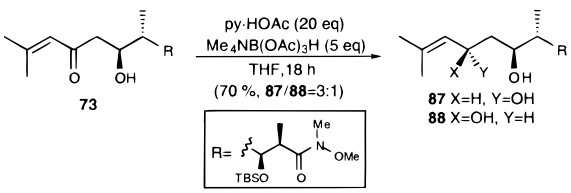
(63) For a discussion of chelation-controlled carbonyl additions see: Reetz, M. T. *Acc. Chem. Res.* **1993**, *26*, 462.

(64) Interestingly the structurally similar aldehyde ester **82** has also been postulated to participate in bidentate coordination with both $TiCl_4$ and $SnCl_4$ to afford anti-Felkin products upon reaction with crotylsilanes and crotylstannanes. ^{13}C NMR data strongly supports coordination of Sn(IV) with the carbonyls of **82**. (a) Santelli-Rouvier, C. *Tetrahedron Lett.* **1984**, *25*, 4371. (b) Yamamoto, Y.; Yatagai, H.; Ishihara, Y.; Maeda, N.; Maruyama, K. *Tetrahedron* **1984**, *40*, 2239. (c) Yamamoto, Y.; Nemoto, H.; Kikuchi, R.; Komatsu, H.; Suzuki, I. *J. Am. Chem. Soc.* **1990**, *112*, 8598.

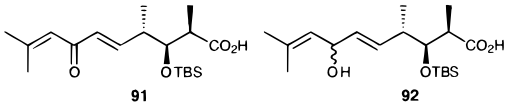


(65) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

(66) Surprisingly, treatment of **73** with $Me_4NB(OAc)_3H$ again afforded only a 3: 1 mixture of diols.



(67) Minor amounts of elimination products **91** and **92** were also observed.

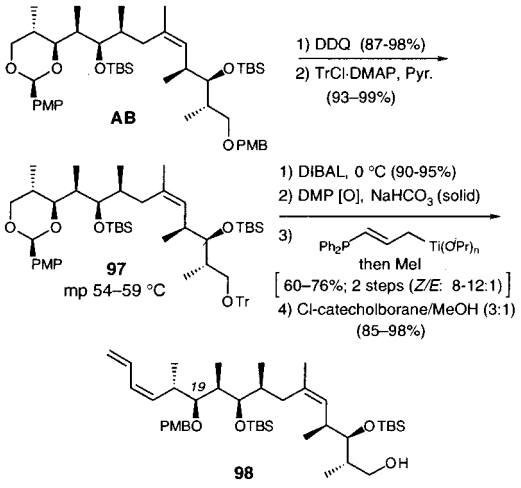


critical for this coupling reaction. Subsequent exposure of **94** to excess DIBAL (10 equiv, −78 °C → 0 °C) effected reductive cleavage of the PMP acetal, with concomitant reduction of the lactone carbonyl, to furnish **95**. Reduction of the lactone proved of little consequence, since pyridinium dichromate (PDC) readily converted the primary hydroxyl and the lactol to lactone aldehyde **96** (62% yield, two steps).

The stage was thus set for incorporation of the terminal diene. Although our first synthesis of discodermolide (cf. **64**, Scheme 14) made efficient use of the Yamamoto protocol for this transformation (70% yield, 16:1 *Z/E*), in this case only a modest yield of **66** with significantly lower *Z* selectivity (40−58%, 4:1 *Z/E*) was observed. Apparently the lactone moiety is sensitive to the reaction conditions, although it is difficult to account for the low *Z* selectivity (e.g., **65**).[68] The low efficiency of the diene installation stimulated us to explore an alternative route in which the diene would be incorporated at an earlier stage.

Early Installation of the Terminal Diene: Completion of a Gram-Scale Synthesis of (+)-Discodermolide. We began with the previously prepared C(9−22) **AB** fragment (Scheme 21). To maintain eventual discrimination of the C(19) PMB

Scheme 21



ether, a protecting group interchange was required. Initially we selected the TBS moiety to protect the primary hydroxyl. However, during reductive-opening of the acetal, we experienced competitive removal of the silyl group.[69] Accordingly, we exploited the trityl group. Reduction of **97** with DIBAL then gave the primary alcohol (Scheme 21) which in turn was subjected to oxidation with buffered Dess−Martin periodinane,[70] installation of the diene via the Yamamoto diene protocol,[53] and removal of the trityl group[71] to furnish **98** in yields ranging from 50% to 74% (four steps) with good diastereocontrol (8−12:1 *Z/E*, 10 g scale). As will be described, the undesired (*E*)-congener eventually proved inconsequential since it could be readily removed at a later stage in the synthesis (vide infra).

Conversion of alcohol **98** to the corresponding phosphonium salt via our previously optimized high-pressure conditions proceeded without difficulty, providing phosphonium salt **99** in 75−82% yield on a multigram scale (Scheme 22). Chemoselective addition of the derived ylide also proceeded in good yield and with excellent selectivity (*Z/E* 15−24:1). Again the solvent of choice (vide supra) proved to be THF, with aldehyde **71** added to the ylide at −20 °C. Addition at lower temperature resulted in considerable decomposition. The phosphonium salt **99** proved to be highly hygroscopic; thus, great care was necessary to remove residual water, which if present led to the formation of the corresponding diphenylphosphine oxide upon addition of base.[72] Best results were obtained by azeotropic removal of water from the salt with toluene (three times), followed by drying in vacuo at 50 °C for 12 h (ca. 0.1 Torr). Attention to these details led to **66** reproducibly in 59−69% yield up to the 2.0 g scale; importantly the phosphonium salt **99** could be recovered. The yield of **66** based on recovered **99** was 85−95%.

Having achieved assembly of the discodermolide carbon skeleton, we were poised to complete the large-scale synthesis. However, the *Z/E* selectivity (8−12:1) obtained in the diene synthesis demanded attention. Previously the minor (*E*)-diene was removed via $AgNO_3$-impregnated silica gel chromatography; however, for large-scale work this was less than optimal. Fortunately we discovered that when **66**, an 8:1 *Z/E* mixture at C(22,23), was subjected to DDQ oxidation to remove the C(19) PMB group, **67** was obtained as a single diastereomer along with an easily separable byproduct (not shown). The byproduct proved to be the result of a fortuitous Diels−Alder reaction between the (*E*)-diene and DDQ. The ability of the (*E*)-diene to adopt the *s-cis*-conformation required for cycloaddition to DDQ leads to the observed chemoselectivity, whereas the desired (*Z*)-isomer is prevented from adopting a planar conformation due to significant steric interaction between the C(24) vinyl and C(20) methine moieties.

With pure **67** in hand, completion of the 1 g synthesis of (+)-discodermolide now only required installation of the carbamate and global desilylation. Importantly, carbamate formation ($Cl_3CCONCO$; Al_2O_3) proceeded in 90−95% yield. For global deprotection we had employed HF/CH_3CN in our 1995 synthesis. However, on scale-up we found these conditions to be capricious (e.g., yields ranging from 20% to 60%). Screening a series of conditions revealed that slow addition of 3 N HCl to a methanol solution of **68** over a 12 h period produced the natural product cleanly and reproducibly up to the 200 mg scale. Utilizing this route, we were able to prepare 1.06 g of (+)-discodermolide; crystallization from acetonitrile[73] furnished 1.043 g of the natural product (mp 117−120 °C). Importantly, in contrast to the original report on the isolation, we found (+)-discodermolide to be stable as a crystalline solid. However, when (+)-discodermolide was concentrated from $CDCl_3$, decomposition occurred, due to residual acid derived from the deuteriochloroform. Thus, the reported instability of natural discodermolide is most likely an artifact.

Summary. A highly convergent total synthesis of discodermolide (**1**) has been achieved, exploiting a common precursor (**CP**) to permit rapid and efficient construction of three advanced subtargets. The subtargets, each of which embody the common triad of contiguous stereogenic centers, were then coupled via highly stereoselective σ-bond (palladium-catalyzed cross-coupling) and π-bond (Wittig) constructions. Importantly, the synthesis is highly efficient, proceeding in 6% overall yield (longest linear sequence, 24 steps), stereocontrolled, and

(68) Both Myles and Paterson employed a two-step diene synthesis in their syntheses of discodermolide. In our hands this route did successfully deliver discodermolide in 31 total steps (22 in the longest linear sequence); however, due to the capricious yields observed, this approach was not conducive to large-scale synthesis.

(69) All attempts to remove selectively the primary PMB ether in the presence of the secondary PMB ether proved unsuccessful.

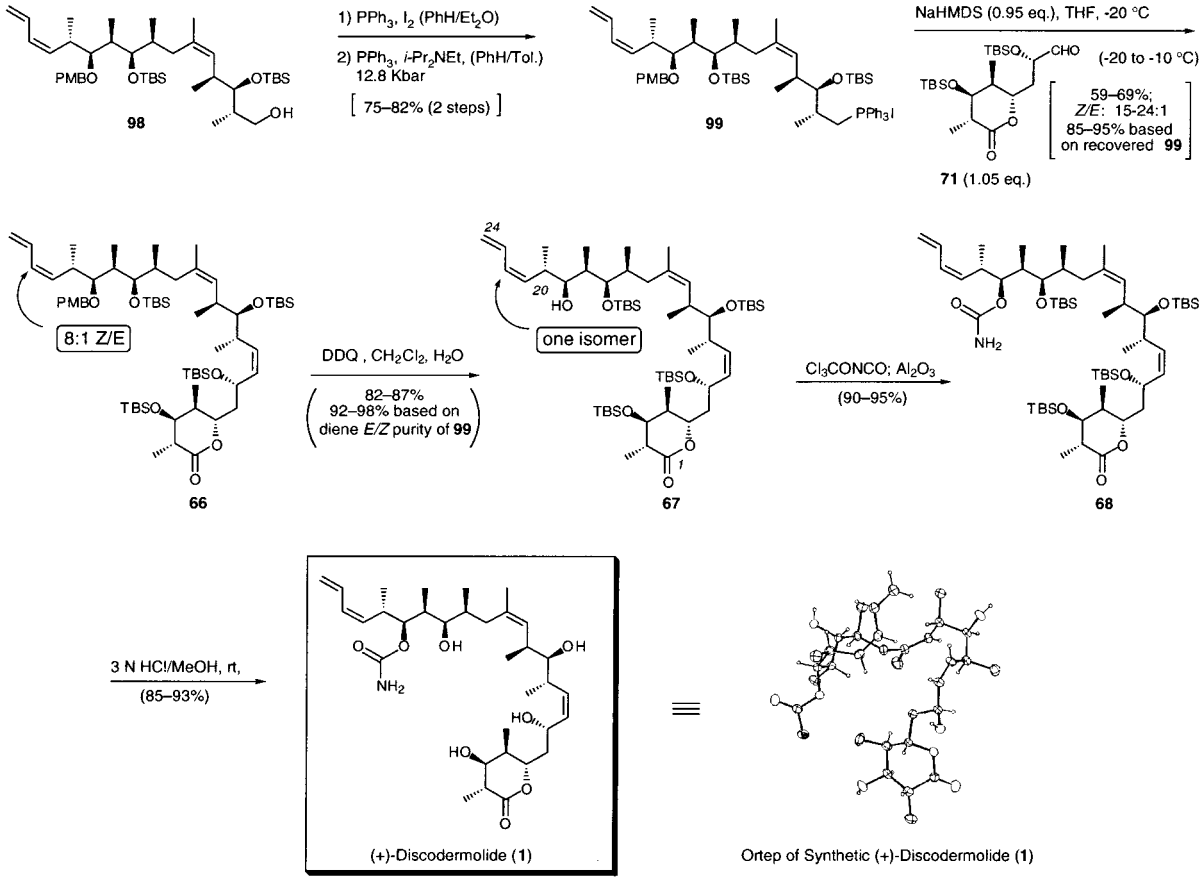
(70) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

(71) Boeckman, R. K, Jr.; Potenza, J. C.; *Tetrahedron Lett.* **1985**, *26*, 11, 1411.

(72) For a discussion on this side reaction see: Schnell, A.; Tebby, J. C. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1883.

(73) We thank Novartis for informing us that discodermolide is stable in acetonitrile.

Scheme 22



amenable to gram-scale production of this potentially important natural product.

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Supporting Information Available: Experimental procedures and characterization data for all synthetic intermediates (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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