Pure Appl. Chem., Vol. 79, No. 4, pp. 685–700, 2007.
doi:10.1351/pac200779040685

Total synthesis of the marine natural product (+)-discodermolide in multigram quantities*

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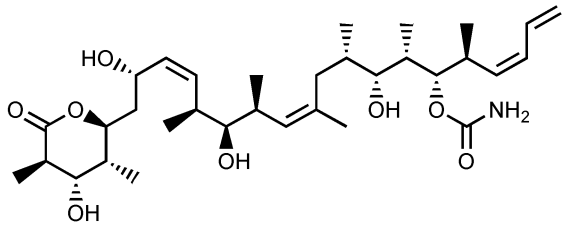
Abstract: The novel polyketide (+)-discodermolide was isolated in very small quantities from sponge extracts. This compound is one of several microtubule stabilizers showing promise as novel chemotherapeutic agents for the treatment of cancer. The clinical evaluation of this and similar compounds is hampered by lack of material, and at present, the only way to obtain the necessary quantities is total chemical synthesis.

Keywords: discodermolide; boron aldol reaction; isolation; side products; olefination.

INTRODUCTION

The marine natural product (+)-discodermolide **1** was isolated by workers at the Harbor Branch Oceanographic Institute from the deep-sea sponge *Discodermia dissoluta* in 1990 [1]. It is obtained from the sponge in extremely small quantities, 0.002 % in the frozen material. This compound is one of several natural products exhibiting inhibition of microtubule depolymerization and as such shows considerable promise as a novel chemotherapeutic agent for the treatment of cancer [2]. In contrast to Taxol®, another microtubule stabilizer, (+)-**1** shows activity in the Taxol-resistant cell lines which overexpress P-glycoprotein, the multidrug-resistant transporter. The similarities and differences between (+)-**1** and Taxol have recently been discussed in detail [3].



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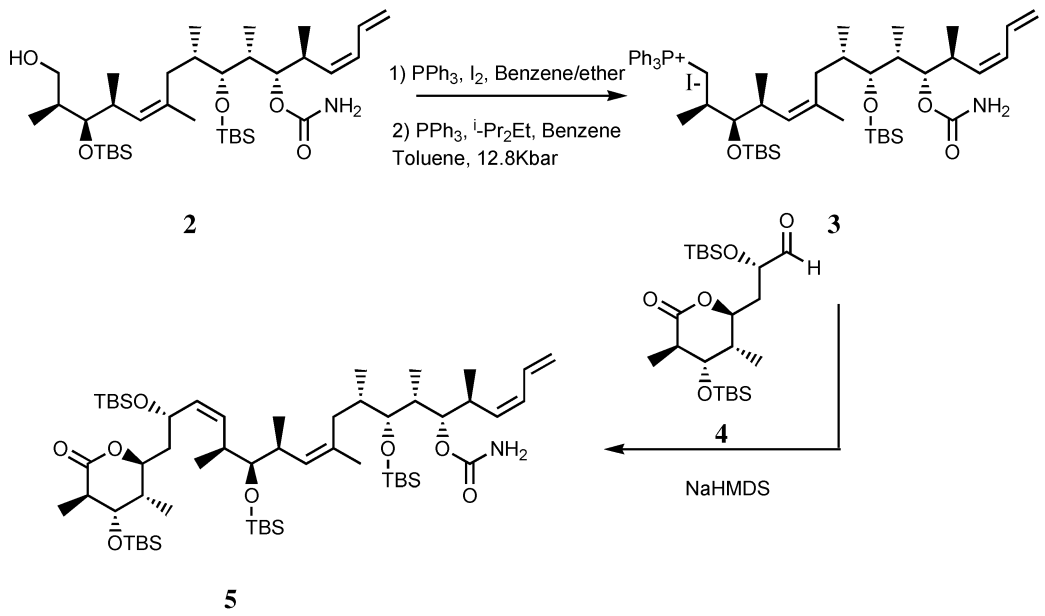
The structure of (+)-**1** consists of a linear polypropionate chain interrupted by 3 *cis*-olefins. It contains 13 chiral centers, 6 of which are hydroxyl groups, one esterified as a lactone, another as a carbamic acid ester. It has 7 chiral methyl groups and 3 cis double bonds, one of which is part of a terminal diene. Also present in the structure is a common stereo triad. The Schreiber group has synthesized antipodes, thus establishing the absolute configuration of (+)-**1** [4].

Pure Appl. Chem.* **79, 467–823 (2007). An issue of reviews and research papers based on lectures presented at the 25th International Symposium on Chemistry of Natural Products (ISCNP-25) and 5th International Conference on Biodiversity (ICOB-5), held jointly in Kyoto, Japan, 23–28 July 2006, on the theme of natural products.

This compound represents a considerable synthetic challenge, and since Schreiber's original publications, several total synthesis [5–8] and the synthesis of various discodermolide fragments [9] have appeared in the literature. A useful review of the available synthetic approaches has recently appeared [10].

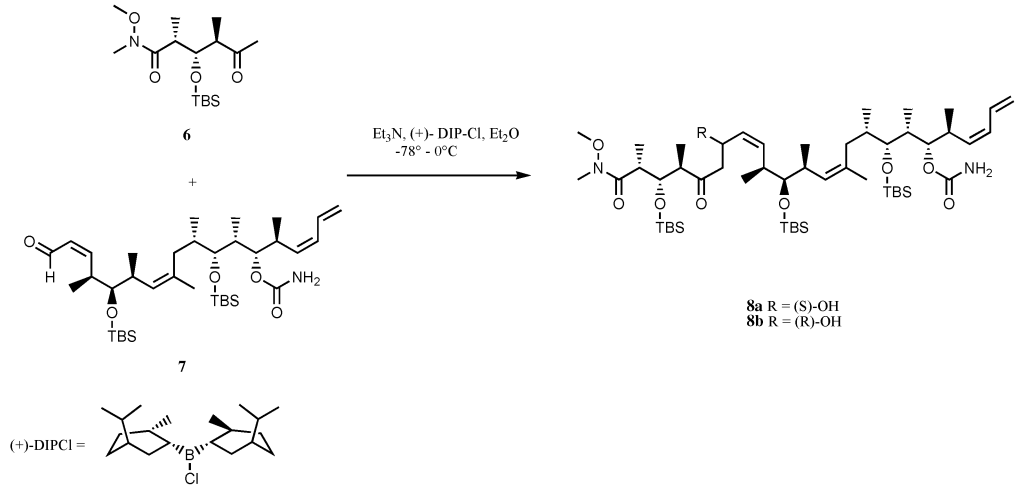
As a part of our anticancer program, we were interested in obtaining quantities of (+)-**1** for clinical development; this, however, is hampered by its scarcity. Fermentation methods are, at the moment, not capable of delivering the desired quantities. This is also the case with biotechnology approaches utilizing polyketide synthatases [11], which have been reported to deliver polyketide fragments useful in the synthesis of erythromycin and other such structures; however, the application has not been demonstrated on a significant scale, and, therefore, at the moment total synthesis is the only viable way to obtain quantities of this cytotoxic polyketide for clinical evaluation. Consequently, we examined the various published total synthesis with a view to scale-up in order to obtain at least 50 g of (+)-**1**. Unfortunately, while the chemistry described in these syntheses is very attractive, none of the described routes lends itself readily to scale-up. For example, many of them are extremely long, >40 synthetic steps with virtually every intermediate requiring chromatographic purification. Several reactions lead to unfavorable mixtures of isomers, requiring extensive separation, thus producing a lot of unusable material. Some of the intermediates used can be considered as "high energy", thus constituting a safety hazard, particularly when they occur at the beginning of the synthesis, where large amounts would be required. For example, the route described by Marshall and coworkers [7], while being very attractive, contains many acetylenic intermediates.

In the gram scale synthesis described by Smith et al. [5c], a high-pressure reaction (12.8 Kbar) is required to prepare the triphenylphosphonium salt **3** necessary for the Wittig reaction, which introduces the C8–C9 cis double bond (Scheme 1). Smith realized this limitation at a later date and by simply altering the protecting group was able to carry out this reaction under more reasonable conditions [12]. Unfortunately, this solution was not available to us at the time we began the project.



Scheme 1 High-pressure phosphonium salt formation.

This reaction was, for us, not a viable proposition. The route as a whole is quite attractive but requires a different approach to the end game. Fortunately, such an end game was available through the work of Paterson [8a], who had been studying complex aldol coupling reactions for the construction of natural products. Scheme 2 outlines Paterson's approach to the end game.



Scheme 2 Paterson end game.

The Paterson aldehyde **7** and the ketone **6** may be easily obtained via advanced intermediates that were described by Smith [5c]. Thus, it seemed to us that a combination of these two approaches offered a viable opportunity to synthesize significant quantities of **1**. The chosen synthesis in abbreviated form is outlined in Fig. 2. The synthesis consists of a total of 35 steps, with 27 being in the longest linear chain, and still contains an unknown number of chromatographic steps and some difficult chemistry, which we felt had a chance of being scalable. We estimated the overall yield to be around 0.1 %.

Figure 1 summarizes these "difficult" reactions, and Fig. 2 outlines the chosen synthesis in abbreviated form [13a–e]. The entire synthesis has been described in great detail in a book chapter [14].

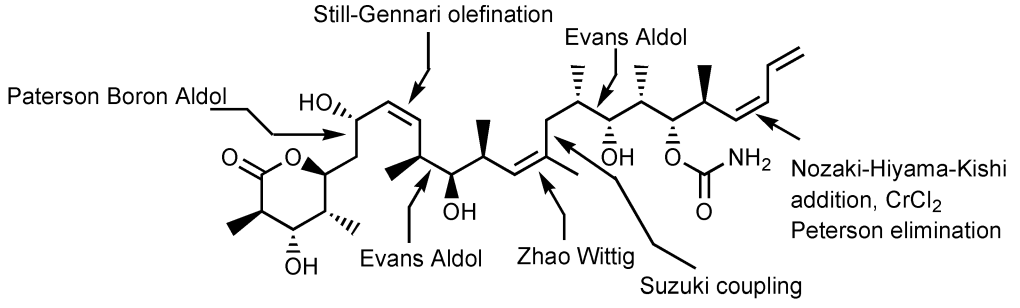


Fig. 1 Difficult coupling reactions.

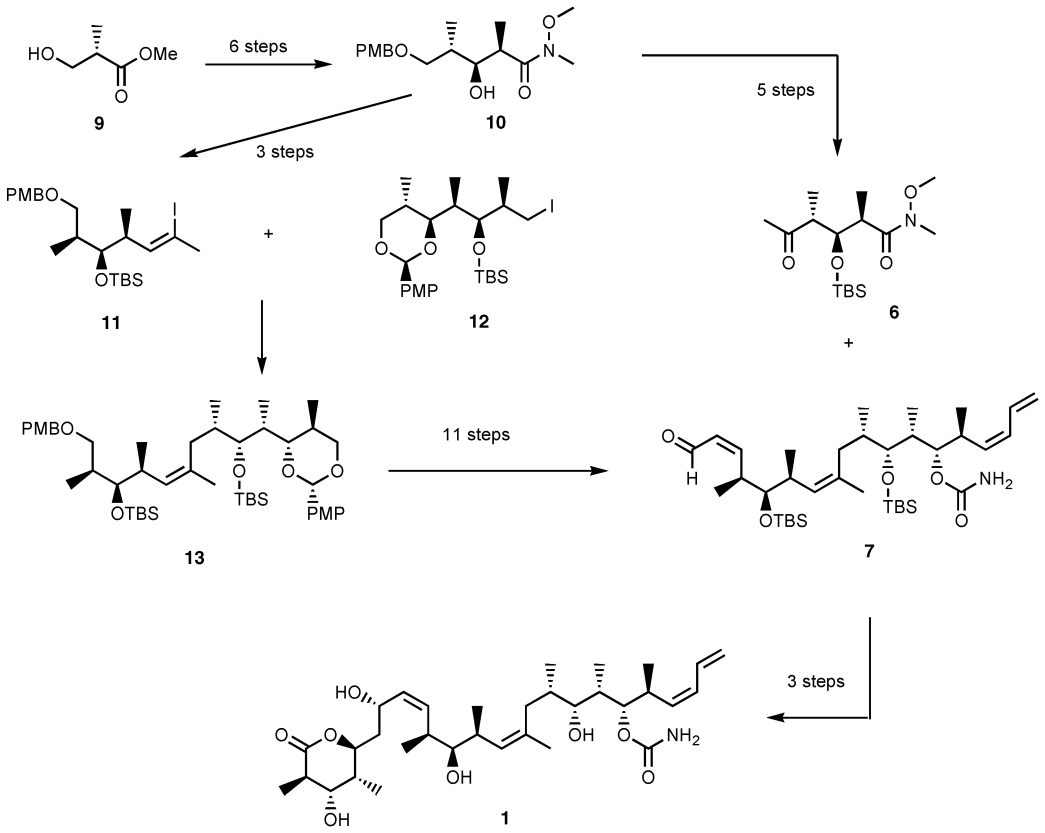


Fig. 2 Abbreviated synthetic scheme.

RESULTS AND DISCUSSION

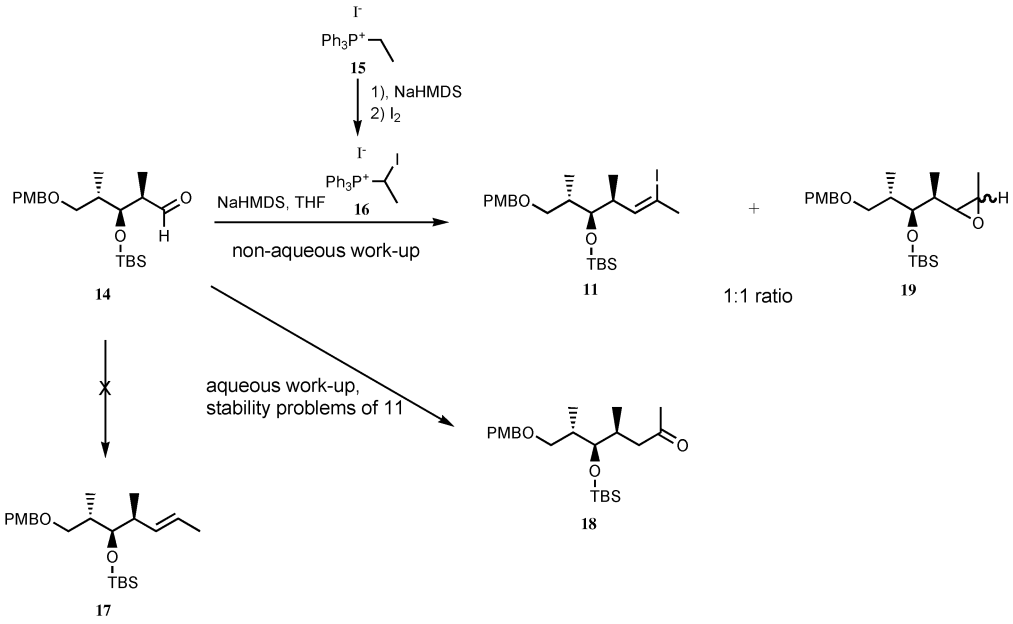
We have carried out this synthesis twice, to make 5 and 60 g of **1** and were two-thirds of the way toward 500 g of **1** [13a–e,14] when the project was terminated due to toxicity issues in the clinic.

Space precludes a detailed discussion of all the steps involved in the synthesis. Therefore, I have selected three key reactions and will explain in further detail how we managed to achieve the scale-up in order to achieve the most complex and challenging substance ever synthesized in Novartis chemical development. The Evans aldol chemistry turned out not to be difficult on scale, the only problems were reagent stability issues, which were readily overcome

SYNTHESIS OF *CIS*-VINYL IODIDE 11

The crucial step (**14** to **11**) here is the so-called Zhao olefination [15]; Scheme 3 outlines the chemistry involved. The reaction is a variation of the Wittig reaction and is fraught with problems.

For the first (6 g) and the second (60 g) campaign, utilizing the Zhao olefination procedure, also used by Smith [5a] and Marshall [7], we obtained the desired *cis*-vinyl iodide **11** in between 20 to 31 % yield after chromatographic purification on silica gel. Only small amounts of the undesired *trans*-isomer were detected (*cis:trans* = 10:1 to 15:1), which could not be separated from the desired *cis* compound. This is fortunately not a problem as they can be separated after the next step in the synthetic sequence.



Scheme 3 Zhao olefination.

On a positive note, we did not observe any *des*-iodo olefin **17**, suggesting that the formation of the iodo ylide **16** from ethyltriphenylphosphonium iodide via ylide iodination (Scheme 3) had been completed before it was added to aldehyde **14**.

This olefination step was one of the most difficult reactions to scale-up. We consistently obtained variable and low yields on a maximum scale of around 2 kg of aldehyde **14**. This lack of reproducibility indicated that we did not have the process under any sort of control. Complicated work-up procedures and apparent instability of **11** to the work-up conditions most certainly contribute to the low yield.

Smith utilized iodine for the conversion of ethyltriphenylphosphonium iodide **15** into the iodo ylide **16**. During process optimization work for the third campaign (500 g), we found that *N*-iodosuccinimide can be used to replace iodine without detriment. While this makes the reaction easier to handle and increased the reproducibility of the process, it did not contribute to an increase in yield.

During the first and second synthetic campaigns, we observed the formation of the methyl ketone **18** [16] during the work-up. For the third campaign, we changed this to a nonaqueous work-up [13b]. Consequently, this by-product and the aforementioned stability problems completely disappeared! This allowed a scale-up to 3 kg per reaction, and the yield over 10 reactions on a scale of 3 kg per reaction of **14** was 31 ± 0.5 %.

It was found, as reported [16], that the reaction of 2-iodo-ethyltriphenylphosphonium iodide **16** with **14** afforded epoxide **19** as a mixture of isomers in addition to the desired **11** in a 1:1 ratio. Alternative approaches were investigated in an attempt to minimize this major by-product, however, they were unsuccessful. For example, employing a method described by Shen [17] (where the initially formed betaine intermediate was deprotonated with a second equivalent of base and then iodinated) produced des-iodo olefin **17**. Utilizing Hanessian's phosphonates [18] in this process also resulted in only des-iodo olefin **17**.

A mechanism has been proposed [16] for the formation of epoxide **19** in which intermediate betaine **A** plays an important role. This ring closes to the corresponding epoxyphosphonium salt **B** with the elimination of iodine (Fig. 3). Phosphonium salt **B** can then eliminate triphenylphosphine oxide after an aqueous or methanolic work-up to deliver the epoxide.

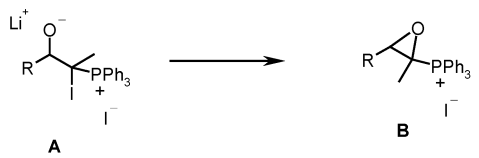


Fig. 3 Proposed mechanism for the formation of epoxide **19**.

Apart from triphenylphosphine oxide, we found significant amounts of triphenylphosphine to be present, and interestingly this was **not** observed during reaction monitoring. Triphenylphosphine was isolated after the chromatography on silica gel. This suggested the presence of an intermediate that decomposed during the contact with silica gel delivering the observed triphenylphosphine. If one accepts that the mechanism proposed by Smith is correct, the protonated form of intermediate **A** can also collapse to an unstable iodo epoxide with the elimination of triphenylphosphine. This may especially relevant during a nonaqueous work-up. Table 1 indicates the overall yield and the absolute quantities of **11** for this modified sequence.

Table 1 Summary of the three campaigns to produce *cis*-vinyl iodide **11**.

Campaign	Overall yield from **14**	Absolute quantities of **11**
1st (6 g)	22 %	0.5 kg
2nd (60 g)	20–30 %	3.4 kg
3rd (500 g)	30.5 %	11.8 kg

THE PATERSON END GAME

This complex aldol coupling, shown in Scheme 2, proceeds via reagent-control to reverse the intrinsic substrate selectivity at C-15, i.e., it is a mismatched reaction [8a,19] and completes the carbon skeleton of discodermolide.

Paterson [8a] described the use of 10 equiv of (+)-DIPCl; we decided to reduce this rather large excess [13e]. Thus, treatment of 6.6 equiv of the corresponding boron enolate of **6**, prepared by treatment of **6** with (+)-B-chlorodiisopinocampheylborane (DIP-Cl) and triethylamine in diethyl ether at 0 °C, followed by aldol reaction, at –78 °C, with *cis*-α,β-unsaturated aldehyde **7** led to alcohol **8a** in 50–55 % yield after chromatography on reverse-phase silica gel, together with its epimer **8b** in a ratio of ~4:1.

This sounds like a simple process, however, in the event this conversion of **7** to produce **8a** turned out to be one of the most difficult reactions that I have ever had to scale-up. The problems are manifold and complex. As of writing, they still have not all been solved and the solutions presented here, while allowing the isolation of the product, are by no means optimal, and significant effort will have to be invested in order to make this a reasonable, well-behaved process!

During the first (6 g) campaign, we observed a considerable variation in the yield of this reaction, from 30 to 60 %. While this was sufficient for the 6 g of discodermolide, such variation would not have allowed us to successfully prepare the larger quantities. The reason for this became clear after the first experiments during process research before the second campaign began. The quality of commercial (+)-DIP-Cl was capricious.

We initially used commercially available solid (+)-DIP-Cl. This reagent is difficult to obtain and handle in large quantities, as it is hygroscopic and inherently unstable. On storage, it eliminates pinene, which reduces the quality of the reagent and produces undefined boron species. Obtaining a well-defined quality reagent on a large scale from a commercial supplier was problematic. Routine analytical

methods are not really suitable for monitoring the quality of this boron reagent, and the only method of testing its quality it to use it!

When the reaction worked with solid (+)-DIP-Cl, we did not obtain the desired **8a**, but the compounds depicted in Fig. 4, *trans*-aldol **20** together with its epimer **21** in a 3:1 ratio together with isomerized aldehyde **22**.

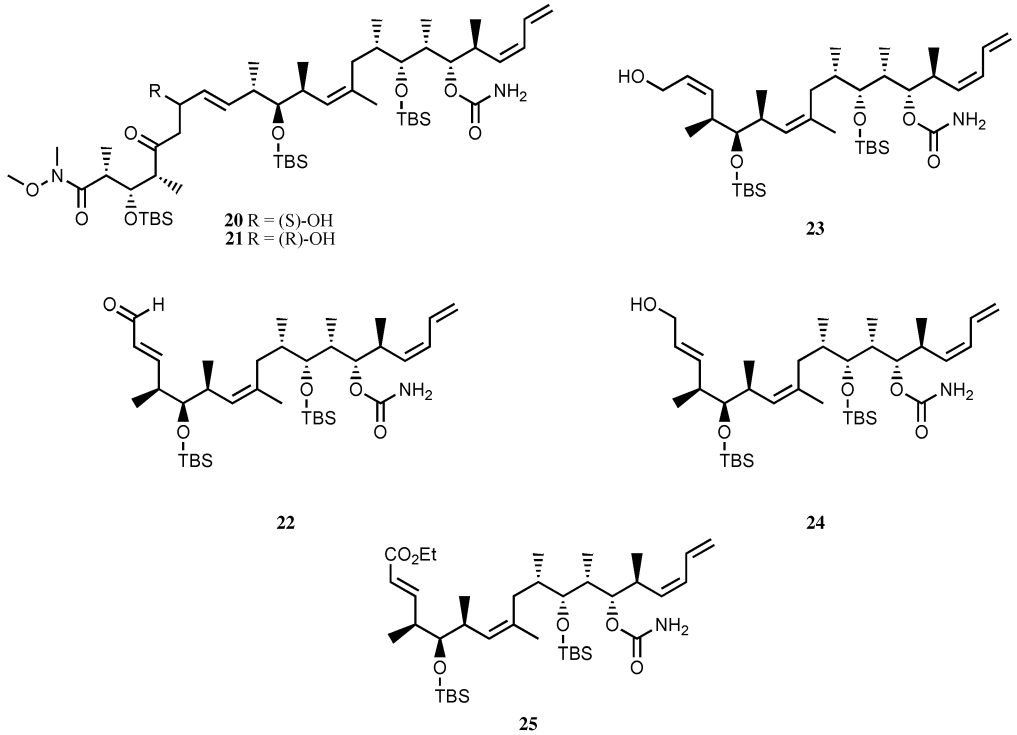


Fig. 4 Products obtained by using solid (+)-DIP-Cl in the Paterson aldol reaction.

We also obtained significant amounts of allyl alcohol **23** and its *trans*-isomer **24** resulting from the reduction of the aldehyde **22**. The structures were confirmed by comparison with authentic samples that were prepared from the *trans* Still–Gennari olefin **25** [13e].

The mechanism of this double-bond isomerization is not clear. It occurs at –78 °C even before the aldol reaction takes place and may be the consequence of an addition/elimination process of chloride or triethylamine induced by boron coordination to the aldehyde oxygen atom, but this is speculative. Although it should be noted at this point that exposing aldehyde **7** separately to all the reagents used in the process produces no change apart from minimal reduction in the presence of (+)-DIP-Cl.

By employing a 70 % solution of the reagent in hexane, these problems were eliminated. This is commercially available and according to the manufacturer indefinitely stable! In this form, it is easier to handle and is readily transferred into the reaction vessel from the cylinder it is supplied in. The aldol reaction now proceeded in a reproducible 50 % yield on a small scale. Neither reduction nor isomerization was observed, and the product **8a** was easily isolated by filtration through reverse-phase silica gel.

The time had now come to attempt the first large-scale reaction, 50 g of aldehyde **7**. Utilizing the conditions we had worked out on the small scale gave 23 % yield of the aldol **8a**! What happened? We actually obtained significant reduction of **7** back to **24** that could not be re-isolated from the vast ex-

cesses of the reagent. We surmised that the reason for this result was incomplete enolization of ketone **6** (2 h at 0 °C), causing the (+)-DIP-Cl to simply reduce **7**. We examined the enolization time on a small scale and extended it to 16 h at 0 °C. Once again on the 50 g scale, 23 % yield of aldol **8a** was obtained, this time with no reduction observed.

We examined the fate of the aldol product at every stage of the process. Before work-up, the desired product is formed in 65 % yield together with the epimer in 33 % yield. That is, the aldol reaction proceeds almost quantitatively! The reaction solvent is diethyl ether (no other solvent produced a viable result); therefore, safety considerations demand that before the standard oxidative work-up, the solvent must be changed (ether peroxides). After an aqueous quench, solvent evaporation, and redissolution in methylene chloride examination of the fate of **8a** revealed that some 20 % less was present in the mixture. Carrying out the oxidative work-up resulted in a further 15–20 % loss. The product was not stable (in the reaction mixture) to the work-up conditions. To overcome this problem, we simply omitted these steps, and after quenching the reaction mixture with water it was diluted with the chromatography solvent eluent and chromatographed directly on reverse-phase silica gel. This led to a 60 % yield of the desired alcohol **8a** epimer-free! The epimer **8b** was isolated by further elution and recycled as described below. The summarized column conditions are outlined in Table 2.

Table 2 Chromatography conditions.

700 g reaction mixture	Dilute with **368** kg acetonitrile/*t*-butylmethyl ether/water 85/15/10
Apply to	120 × 30 cm column packed with **20 kg** RP-18 silica gel
Elute	With **1060 kg** acetonitrile/*t*-butylmethyl ether/water 85/15/10
Change eluent to	Acetonitrile/*t*-butylmethyl ether 1/1
Fractionate	**20 kg** fractions (**8**)

Combining and evaporating product fractions to 10 % of original volume followed by extraction with ethyl acetate and re-evaporation to dryness provides 150 g of pure **8a**.

Prior to the third (500 g) campaign, we re-examined the stoichiometry of the reaction with the aim of reducing the reagent excesses and increasing the product stability to the work-up conditions [20]. Several factors were examined:

- The effect of additives: Here, the aim was to attempt to trap out any "reactive boron species" which may have been causing the product instability. The addition of various aldehydes, or dienes, boron-specific ion exchange resins or other boron-trapping agents just before work-up had no effect on the product stability.
- Solvent: As already mentioned, diethyl ether is not the solvent of choice for industrial applications. Dichloromethane and *tert*-butylmethyl ether were evaluated. Both solvent systems were detrimental to the ratio of **8a/8b**.
- Alternative enolization method: Other methods of enolate generation could well be of use in reducing the reagent quantities. We examined firstly generating the lithium enolate with lithium diisopropylamide (LDA) and then carrying out a lithium–boron exchange. In a model system, this worked well, as demonstrated by following the reaction by Fourier transform-infrared (FT-IR) [20]. However, when applied to the real system a 1/1 mixture of **8a/8b** was obtained.
- Enolate excess: We examined the optimum stoichiometry of the reaction by systematically reducing the excesses of ketone **6**, (+)-DIP-Cl, and triethylamine (Table 3).

Table 3 Optimization of enolate excess.

Entry	Equiv of **6**	Equiv DIP-Cl	Equiv Et_3N	Yield of **8a** (%)	Ratio **8a/8b**	Ratio **8a/21**	Ratio **8/7**
1	6.6	5.4	6.6	55	3.9/1	25/1	28/1
2	4.0	3.0	4.0	56	3.9/1	30/1	30/1
3	3.3	2.7	3.3	48	4/1	28/1	35/1
4	**3.3**	**2.5**	**3.3**	**68**	**3/1**	**22/1**	**22/1**
5	2.4	2.0	2.4	49	3.6/1	28/1	5/1
6	1.5	1.2	1.5	34	3.6/1	64/1	1/1
7	1.5	1.2	1.5	31	3.4/1	60/1	1/1
8	3.3	2.5	3.3	0	Trace of water added		

The observed yields in entries 2 and 3 are still a result of the product stability to reagent excesses and work-up conditions. Entries 5 and 6 indicate that when the enolate excess falls below a certain value the reaction is very slow and incomplete conversion is observed. Entry 8 shows the remarkable effect of water. Here, the (+)-DIP-Cl was exposed to atmospheric moisture for 1–2 s simply by removing the stopper of the weighing flask. No aldol product was formed, and a 1/1 mixture of **7** and its isomer **23** was observed. The conditions of entry 4 are apparently optimal. However, the reaction is very intolerant of manipulative errors, and very narrow limits between slow reaction and product stability are apparent. These conditions brought a benefit. The crude product was found to be stable indefinitely to the reagents and the work-up system. Stability tests of **8a** showed no loss in yield even when the mixture was kept at 40 °C.

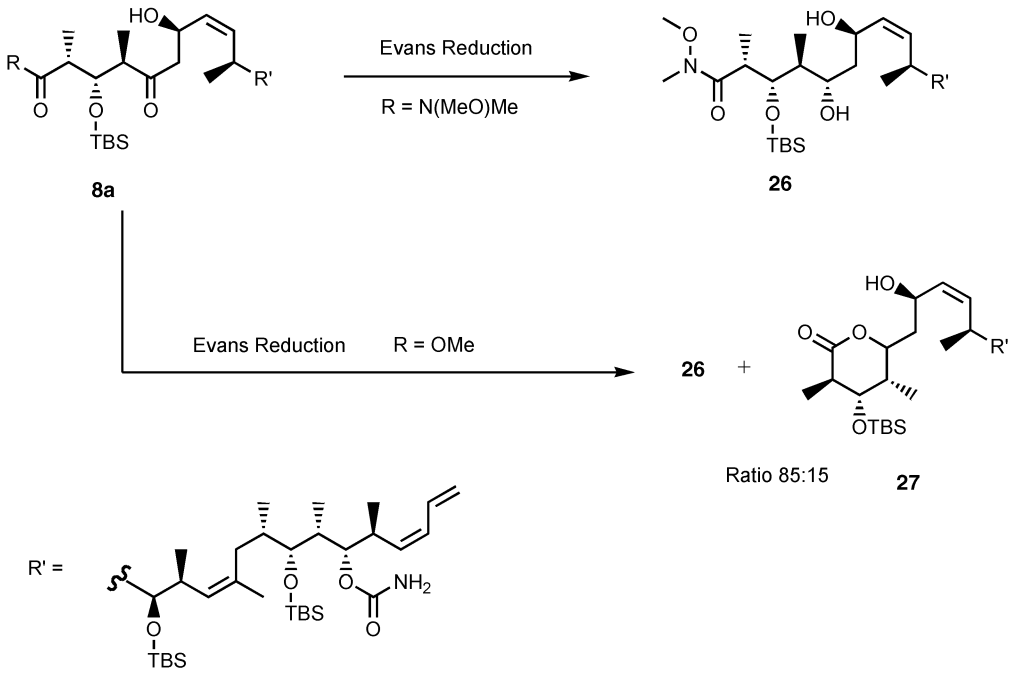
The purification procedure is not optimal. For the 60 g campaign, we required some 20 m^3 of solvent, and we have still not perfected the purification process a larger production run. Therefore, they will probably not be significantly different from those described above. For larger-scale processes (i.e., >2 kg of reaction mixture), one would require oceans of solvent, and indeed for any production quantities (>10 kg discodermolide) an entire planet full! Thus, this process, while it works, still needs intensive optimization.

THE FINAL STEPS

Evans reduction [21] of **8a** with tetramethylammonium triacetoxyborohydride delivered the *anti*-diol **26** in high stereoselectivity and reasonable yield after chromatography (Scheme 4). Contrary to the corresponding methyl ester used by Paterson [8a,19], where the product from the reduction was a mixture of *anti*-diol and the corresponding lactone in a ratio of 85:15, no lactone **27** derived from *anti*-diol **26** was observed in the case of the Weinreb amide.

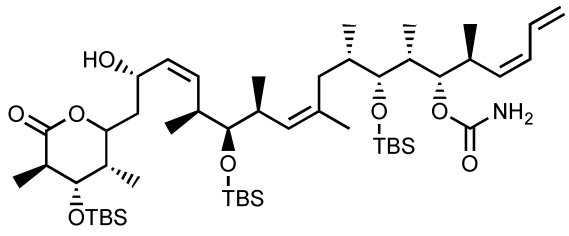
After the problems encountered with the final fragment coupling, we did not expect too many problems with the final step. As it turned out, the cyclization and concomitant acidic hydrolysis of the three silyl ethers provided us with a few nasty surprises.

The reaction is quite complex, and intensive investigation was required in order to maximize product and minimize side-product formation. The literature is unclear on the best method for this transformation. Some authors use HF/pyridine, some HCl/MeOH, others employ HCl/THF, or *para*-toluenesulphonic acid. There is no obvious reason to be gleaned for utilizing differing acidic systems, especially within the same publication!



Scheme 4 Evans reduction, differences between esters and Weinreb amide.

We settled on running three batches under carefully optimized HCl/MeOH conditions after a brief examination of the alternatives. The first reaction we attempted with **26** during the 60 g campaign produced a 40 % yield of **1** after chromatography! The reason was simple although not immediately obvious. The first reaction to occur is cyclization to the fully silylated discodermolide **28**. This compound oils out of the reaction mixture and distributes itself around the walls of the reactor. During the reaction monitoring, this is not obvious and only becomes so after work-up. The tri-silylated discodermolide **28** can be isolated and separately hydrolyzed, see below.



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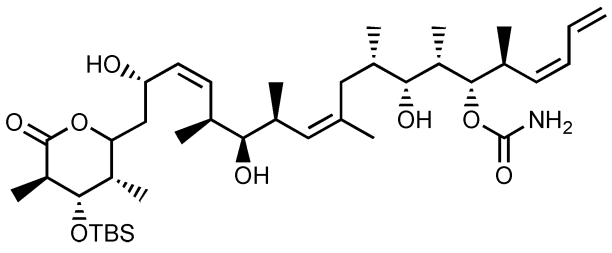
This problem may be avoided by continually washing the walls of the vessel with methanol in order to maintain **28** in solution and adding the HCl in portions over several hours, if this is done (+)-**1** can be isolated in 70 % yield after reverse-phase chromatography.

All the possible permutations of bis-silyl-protected **1** can be observed in the high-performance liquid chromatography (HPLC) of the reaction mixture. The slowest silyl group to cleave is that at the C_3-position, and we were able to isolate this compound (**29**) after column chromatography of the reac-

tion mixture. Forcing the reaction conditions results in significant formation of side products, the isolation and formation of these will be discussed below.



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ISOLATION OF (+)-DISCODERMOLIDE

The discodermolide isolated from the 6 g campaign proved to be a monohydrate. In agreement with our quality assurance department, we could only use the material from the 60 g campaign and eventually the 500 g campaign without repeating the toxicology if the following conditions were met: (a) the synthetic route was identical, (b) the material produced had the same side-product profile, (c) the material was equally pure or better, and (d) the same crystal modification was produced (8 or 9 modifications are known), and (e) the material was sterile.

The material isolated from the chromatography after the cleavage was anhydrous. So we now had to prepare the monohydrate and the required crystal modification and combine the three separate batches into one. This was done in this case because normally samples from each batch are taken for the analysis, leading to release for human use. In this case, we could not "donate" this amount of material (i.e., several grams from each batch). So we were forced to combine the material, obtain one batch, and negotiate the analytical department down with respect to the quantities required for release analytics!

The anhydrous material turned out to be an equilibrium mixture of the lactone and the acid, around 9/1. This caused some consternation until we realized what was going on.

The solution was simple: Adjusting the pH to 4 kept the lactone ring closed. This behavior turned out to be of assistance in preparing the combined batch. Thus, the material isolated from the three columns was redissolved in acetonitrile/water 9/1 and the pH adjusted to 4 with HCl. After partial evaporation and crystallization, (+)-discodermolide was isolated in 95 % yield as the monohydrate with the desired crystal modification formed. The purity was 99.9 % with loss on drying of 3.1 %. The optical rotation was (+) 19° (0.5 % in acetonitrile). It contained around 600 ppm of acetonitrile as residual solvent. This could not be removed by drying. The quantities and yields from the two campaigns are summarized in Table 4.

The isolation was carried out in a special laboratory in a laminar flow fume hood in order to ensure sterility and provide personal protection. All solvents were rendered sterile by filtration through a 4 μm filter. The number of spores was <20 cfu/g, and the material was endotoxin-free.

Table 4 Summary of the two campaigns for **1**.

Campaign	Overall yield from **8**	Absolute quantities of **1**
1st (6 g)	30 %	6 g
2nd (60 g)	20 %	60 g

SIDE PRODUCTS

The tri-silyl derivative **28** isolated from the chromatography of the first cleavage reaction can be separately cleaved to **1**, which may then be isolated by crystallization. The mother liquors from this crystallization contained several side products formed during the cleavage process. They were isolated by extensive chromatography on silica gel [22]. Their structures are shown in Fig. 5. These compounds are all formed under the acidic cleavage conditions in similar amounts. The trick here is to push the de-silylation to completion while at the same time minimizing their formation.

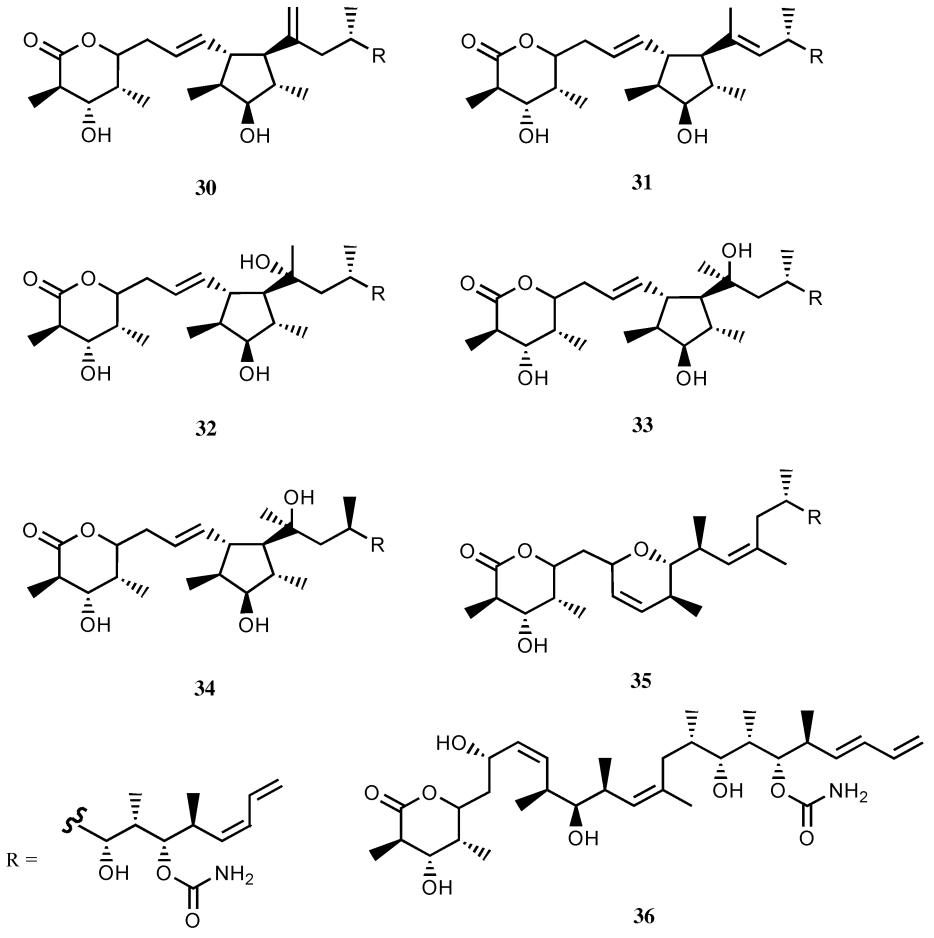

Fig. 5 Side products isolated from the acid hydrolysis of **26**.

The stereochemistry was determined by NMR experiments [22]. Compounds **32–34** are presumably formed by hydration of the double bond. In **34**, the C_{16} methyl group apparently has the opposite configuration to that observed in discodermolide. This stereocenter is formed in an aldol reaction; therefore, it is reasonable to assume that traces of the diastereoisomer have been formed in the aldol reaction and carried through the synthesis, although we did not observe the corresponding C_{16} (*R*)-isomer of discodermolide.

One more side product was found, *trans*-diene **36**. This compound runs immediately after **1** on HPLC and unfortunately co-crystallizes with discodermolide. It is apparently formed in small amounts

during the acid cleavage of the silyl groups, although its formation as a consequence of the Nozaki–Hiyama–Kishi reaction cannot be ruled out.

STATISTICS

A few figures relating to the second (60 g) campaign) will help illustrate the magnitude of this synthetic effort. We began the synthesis on 21 July 2000 (first reaction started in pilot plant), and finished (compound released for human use) 1 March 2002. This process took 20 months, which equates to about 2 weeks per step! Here again, we did not run the campaign in an overlapping mode, but rather progressed in a linear fashion. Therefore, there is a lot of scope to obtain a quicker lead time; probably one could prepare the final product in around 12 months. Around 100 persons were involved. This figure contains all laboratory and pilot plant personnel. The analytic effort is not included, but as an estimate, around 10 more could be added.

The amount of discodermolide produced would equate to around 3000 kg of sponge—a quantity that probably does not exist! The total number of steps is 36 with an overall yield of 0.2 % (main chain). This is on the low side, but it should be remembered that the yields for each step have not been optimized. The description of the various optimization processes in this article have only related to the various scale-up and reproducibility issues, not to obtaining the maximum possible yield, so there is plenty of scope for increasing the yield. There were, in this second campaign, some 18 chromatographic purifications. This has now been somewhat reduced to 15. The number of crystalline intermediates stands currently at 7.

OUTLOOK

The synthesis described here will probably never be the one of choice for chemical production. Two examples suffice to illustrate this: For the required submission of 60 g of (+)-**1** (120 g were actually produced), we used an estimated 300 tons of solvent per kg of **1** (Fig. 6) and around 1600 kg of silica gel for the chromatography together with 40 kg of RP-18 reverse-phase silica gel for the final purification before crystallization. This quantity may seem a bit low, but in most of the chromatographies we were able to re-use the silica gel several times.

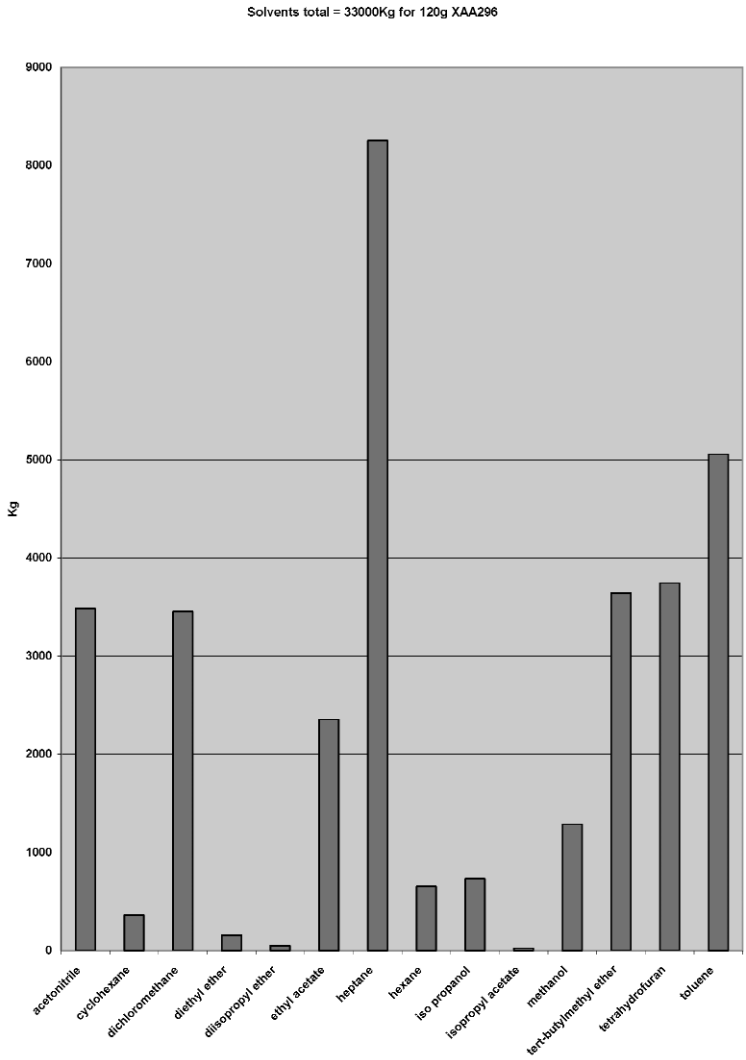

Fig. 6 Solvent quantities used for the production of 120 g of (+)-discodermolide.

ACKNOWLEDGMENTS

Many people were involved in the work described here, and this lecture and paper are dedicated to them to thank them for all the support they gave.

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