The Development of a Practical Total Synthesis of Discodermolide, a Promising Microtubule-Stabilizing Anticancer Agent

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Dedicated to the memory of D. John Faulkner[‡]

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Marine organisms provide an important source of natural product diversity with an associated range of significant biological activities. Discodermolide, isolated in microscopic quantities from a deep-water sponge, shares the same microtubule-stabilizing mechanism as Taxol and has a promising antitumor profile. There is, however, a chronic supply problem hampering clinical development and so a practical total synthesis of discodermolide is an important goal. This review highlights the completed total syntheses of discodermolide, focusing on the various methods and strategies employed for achieving stereocontrol and realising the pivotal fragment couplings.

1. Introduction

The vast ecosystem in our oceans provides a practically unlimited reservoir of structurally diverse secondary metabolites.[1,2] The biological activity of these marine natural products is often startling, demonstrating, for example, potent cytotoxic properties.[3,4] The low natural abundance, however, of many of these compounds, as isolated from sponges, corals and other marine organisms, dictates that alternative means of supply are usually required to further investigate and exploit their biological activities. These factors, coupled with their often complex molecular architectures and elaborate stereochemistry, offer compelling challenges for contemporary organic synthesis.[5,6] Along with other synthetic groups, we have sought innovative strategies and methods to deliver these precious compounds and their analogues for further biological studies and preclinical de-

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Ian Paterson was born in Dundee, Scotland. He received his B.Sc. degree in Chemistry from St. Andrews University. In 1979, he obtained his PhD from Cambridge University, working with Professor Ian Fleming on the development of new synthetic methods using allylsilanes and silyl enol ethers. After spending a postdoctoral year with Professor Gilbert Stork at Columbia University, working on the total synthesis of erythromycin A, he joined the faculty at University College London. In 1983, he moved back to Cambridge University, where he is now Professor of Organic Chemistry and a Professorial Fellow of Jesus College. His research interests are centred on the design and development of new synthetic methods for the control of stereochemistry and their application to the total synthesis of a range of biologically active compounds. He has developed novel strategies and general methods for the asymmetric synthesis of polyol building blocks, particularly by using substrate- and reagent-controlled aldol reactions, which facilitate the practical synthesis of structurally complex, polyketide natural products. Within his group, this research has enabled the total synthesis of rare anticancer agents, including spongistatin 1 (altohyrtin A), swinholide A and discodermolide, as well as antibiotics, such as concanamycin F and oleandolide.

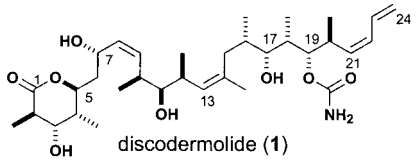
Gordon J. Florence was born in Manchester, England, in 1975. He gained a B.A. degree in Natural Sciences from Cambridge University in 1997. He received his PhD from Cambridge University in 2001, under the supervision of Professor Ian Paterson, working on the total synthesis of discodermolide, which included the development and application of new asymmetric aldol methodology. From 2001 to 2002, he was a Postdoctoral Research Associate with Professor Craig J. Forsyth at the University of Minnesota, working toward the synthesis of azaspiracid. In 2002, he returned to Cambridge as a Research Fellow of Emmanuel College and is currently focussing on the development of new stereoselective methods and their application to the total synthesis of several marine macrolides.

MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

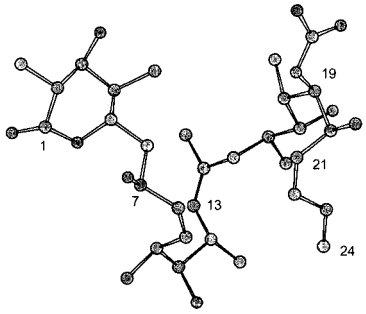
velopment. A notable example, and a primary focus of our group's research over the past decade, is discodermolide, a promising microtubule-stabilizing anticancer agent of sponge origin.[7−9]

2. Isolation and Biological Activity of Discodermolide

Discodermolide (**1**, Figure 1) is a unique polyketide that was isolated by Gunasekera and co-workers at the Harbor Branch Oceanographic Institution in 1990 from the Caribbean deep-sea sponge *Discodermia dissoluta*.[10−12] Initially, the sponge was collected off the Bahamas by manned submersibles at a depth in excess of 33 m.[11] These samples were exhaustively extracted and purified to provide crystalline discodermolide, $C_{33}H_{55}NO_8$, in 0.002% w/w isolation yield from the frozen sponge. Discodermolide's structure, as determined by extensive spectroscopic studies and single-crystal X-ray crystallography, features 13 stereogenic centres, a tetrasubstituted δ-lactone, one di- and one trisubstituted (*Z*)-alkene, a carbamate moiety and a terminal (*Z*)-diene. Discodermolide adopts a U-shaped conformation, where the internal (*Z*)-alkenes act as conformational locks by minimising 1,3-allylic strain between their respective substituents and *syn*-pentane interactions along the backbone are avoided, while the δ-lactone is held in a boat-like conformation.



discodermolide (**1**)



X-ray structure of discodermolide (**1**);
hydrogen atoms omitted for clarity

Figure 1. Structure and conformation of discodermolide (**1**)

Discodermolide was found initially to be a potent immunosuppressive agent,[13,14] similar to FK-506 and rapamycin, as well as displaying antifungal activity. Further biological screening revealed striking cytotoxicity in a variety of human and murine cell lines (IC_{50} 3−80 nM), causing cell cycle arrest at the G2/M phase boundary and subsequent cell death by apoptosis.[15,16] Discodermolide is a member of an elite group of natural products (Figure 2) that act as microtubule-stabilizing agents and mitotic spindle poisons,[7−9,17] which currently include Taxol® (paclitaxel) (**2**),[18] epothilones A (**3**) and B (**4**),[19] sarcodictyin A (**5**),[20] eleutherobin (**6**),[21] laulimalide (**7**),[22] FR182877 (**8**),[23] peloruside A (**9**),[24] and dictyostatin (**10**).[25] Despite showing no apparent structural similarities, discodermolide stabilizes microtubules more potently than the clinically important anticancer drug Taxol® and competitively inhibits the binding of radiolabelled Taxol to microtubules, suggesting that it occupies the same or an overlapping binding site on β-tubulin.[15,26]

Notwithstanding the general resemblance in mechanism of action to Taxol® and its analogues, such as Taxotere® (**11**),[27] discodermolide has some unique activities. Notably, the growth of Taxol-resistant ovarian and colon carcinoma cells that overexpress P-glycoprotein are inhibited by discodermolide at low-nanomolar concentrations.[28] Furthermore, unlike the epothilones and eleutherobin, discodermolide cannot substitute for Taxol in a Taxol-resistant carcinoma cell line that requires low concentrations of Taxol for normal growth.[29] Significantly, the presence of low concentrations of Taxol amplified the toxicity of discodermolide by 20-fold against this cell line, a feature that was not observed with the epothilones or eleutherobin. Hence, the combination of discodermolide with Taxol and other anticancer drugs may offer potential synergies. Moreover, in hollow fiber and xenograft mouse models, discodermolide demonstrates significant growth inhibition of human tumors in vivo, including those that are Taxol-resistant.[30]

The highly encouraging biological profile of discodermolide makes it a promising candidate for clinical development as a chemotherapeutic agent for the treatment of breast cancer and other drug-resistant solid tumors. This feature has been recognised by Novartis Pharmaceuticals Corporation, who licensed discodermolide from the Harbor Branch Oceanographic Institution in 1998 to develop it as a new-generation anticancer drug.

3. Total Synthesis

While the early clinical development of Taxol (**2**) was severely hampered by its supply, this problem was eventually resolved by semi-synthesis from 10-deacetylbaccatin III, which is obtained by extracting the needles of the European Yew tree.[31] In comparison, the epothilones, which are currently in clinical trials as anticancer agents, can be obtained by fermentation.[32] Unfortunately, this approach is not possible for discodermolide as yet, even though as a polyketide it is likely to be produced by a symbiotic microorganism associated with the sponge source. Therefore, the supply problem for discodermolide is chronic and can be solved at present only by total synthesis, rather than semi-synthesis as with Taxol. Consequently, there has been considerable synthetic effort directed towards discodermolide, culminating in several total syntheses[33−37] and numerous fragment

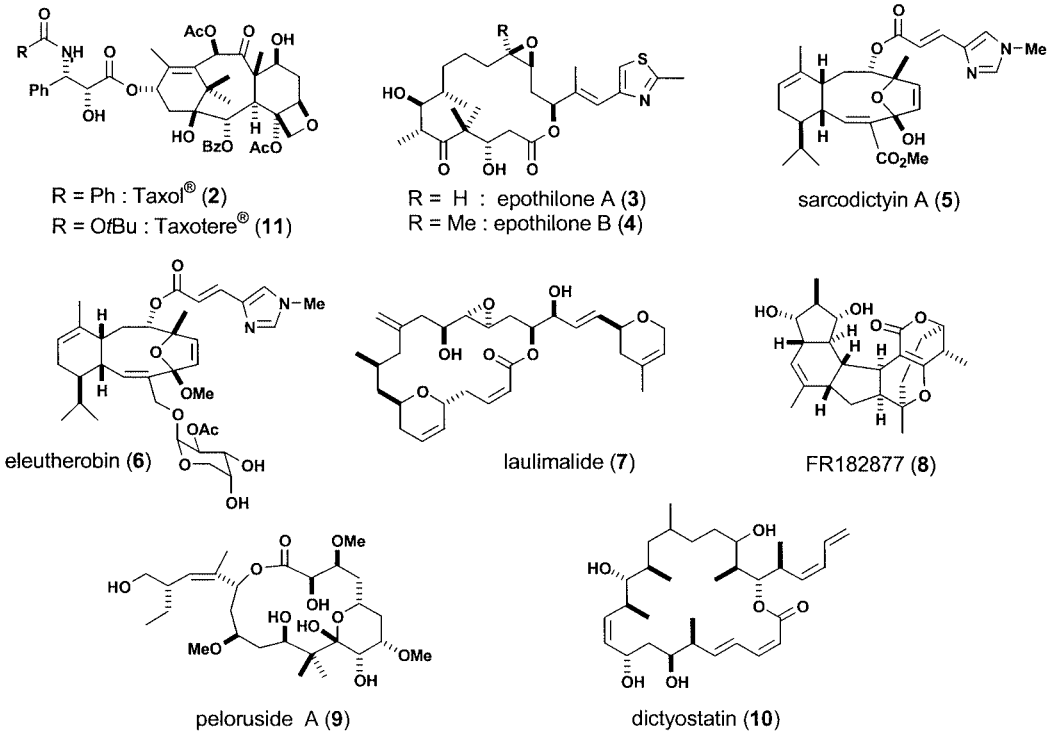


Figure 2. Microtubule-stabilizing agents; the configurational assignments of peloruside A and dictyostatin have not been rigorously established

syntheses.[38] This Microreview highlights the completed syntheses of discodermolide by ourselves and the groups of Schreiber, Smith, Myles and Marshall. In particular, we focus on the strategies employed to configure the multiple stereogenic centres and (*Z*)-alkenes, and the pivotal fragment coupling steps.

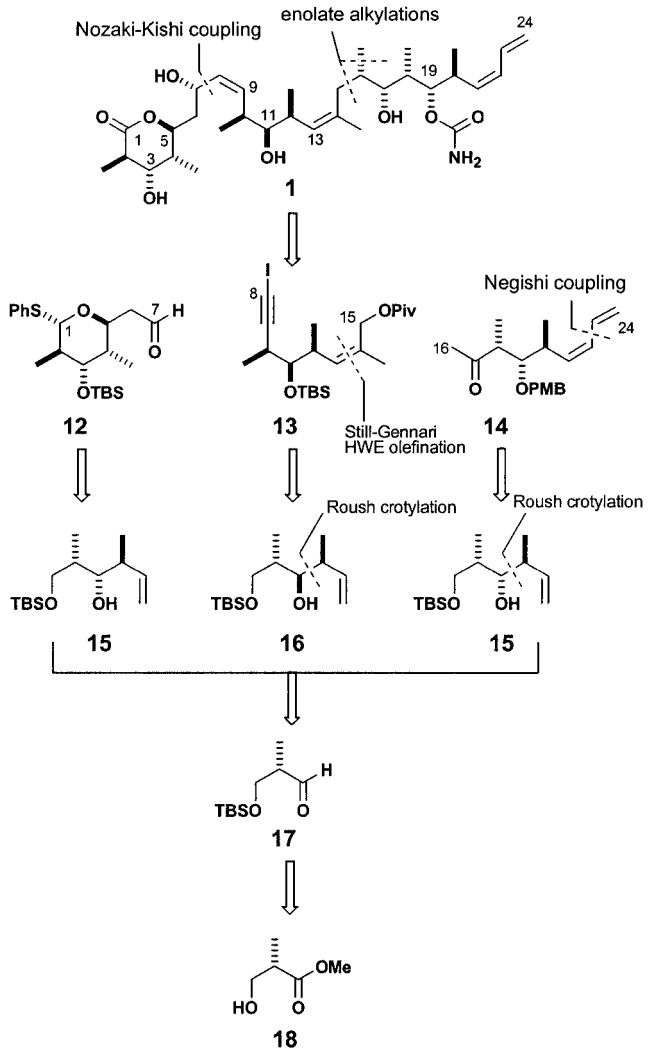
3.1 Schreiber Syntheses of Discodermolide[33]

Schreiber and co-workers disclosed their total synthesis of *ent*-discodermolide (*ent*-**1**) in 1993, which served to establish the absolute configuration.[33b] In 1996, they reported the first synthesis of the natural antipode (+)-discodermolide (**1**), essentially using the same route performed in the correct enantiomeric series (Scheme 1), along with several analogues designed to study their tubulin-binding and microtubule-stabilizing properties.[33a] Their synthetic route to (+)-discodermolide involved two key fragment couplings at C7−C8 and C15−C16, based on a Nozaki−Kishi addition[39] and an enolate alkylation, respectively. This approach relied on the use of three subunits **12** (C1−C7), **13** (C8−C15) and **14** (C16−C24) that were accessed from the homoallylic alcohols **15** and **16**, where the characteristic stereotriads were configured by two separate Roush asymmetric crotylation reactions[40] performed on the chiral aldehyde **17**, derived from the Roche ester **18**.

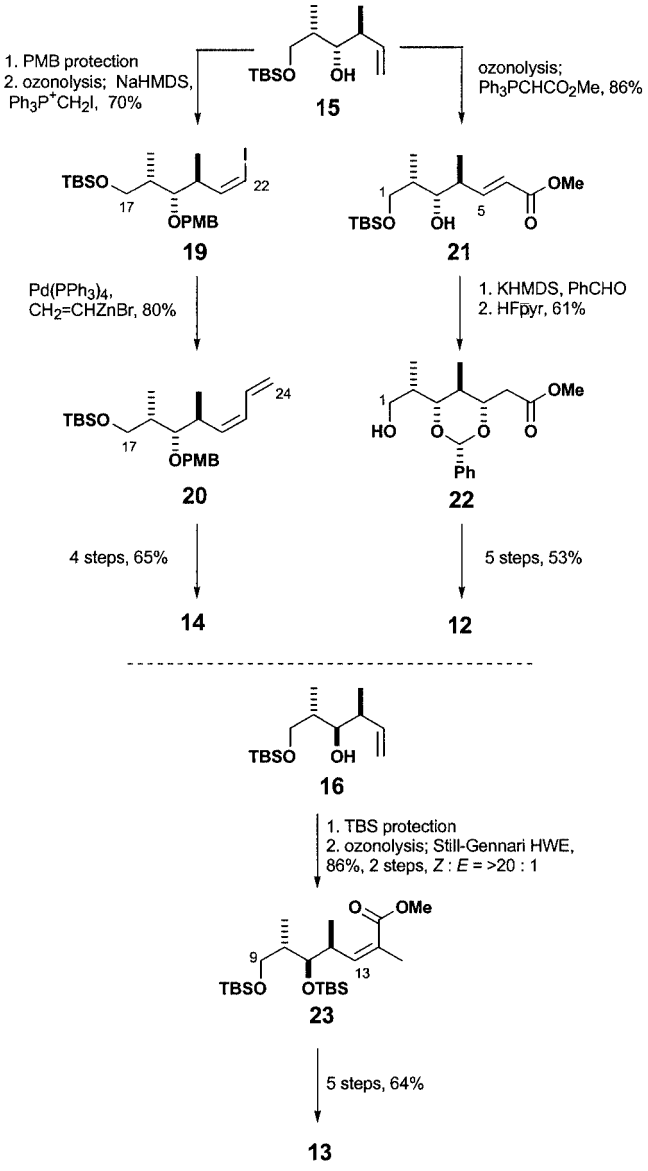
The C16−C24 segment **14** was synthesised in seven steps from homoallylic alcohol **15** (Scheme 2), in which the terminal (*Z*)-diene unit was introduced by a palladium-catalysed Negishi coupling[41] of vinyl iodide **19** with vinylzinc bromide to give **20**. The C1−C7 aldehyde **12**, as precursor to the δ-lactone, was prepared in eight steps from homoallylic alcohol **15**. The sequence included an intramolecular Michael addition of a hemiacetal to the (*E*)-enoate **21**, which proceeded with complete stereoselectivity at C5.[42] A further five-step sequence, performed on the acetal **22**, completed the synthesis of the thioacetal **12**. The trisubstituted (*Z*)-alkene was introduced efficiently by Still−Gennari HWE olefination [(*Z*)/(*E*) > 20:1], following silyl protection and ozonolysis of **16**. The resulting (*Z*)-enoate **23** was then converted into iodoacetylene **13** in a further five steps.

The Nozaki−Kishi coupling reaction of iodoacetylene **13** and aldehyde **12**, in the presence of $CrCl_2$/$NiCl_2$, gave propargylic alcohol **24** with *dr* = 2:1 at C7 (Scheme 3).[39] The low level of stereocontrol in this addition represents a disadvantage of this disconnection. The minor, undesired epimer can be recycled, however, by an oxidation/CBS reduction[43] protocol. Following elaboration, the resulting bromide **25** was coupled to the methyl ketone **14** via the lithium enolate. Further alkylation of the lithium (*Z*)-enolate of **26** with methyl iodide gave **27**, introducing the C16 stereocentre with *dr* = 3:1. Installation of the carbamate was followed by the presumed chelation-controlled reduction of the ketone **28** to introduce the OH group at C17 with *dr* = 30:1. Global deprotection completed the synthesis of discodermolide (**1**), with an overall yield of 4.3% achieved over 24 steps in the longest linear sequence.

The Schreiber synthesis is particularly noteworthy in that the absolute stereochemistry of discodermolide was assigned unambiguously, and through the preparation of nu-



Scheme 1. Strategy for the total synthesis of discodermolide developed by Schreiber et al.



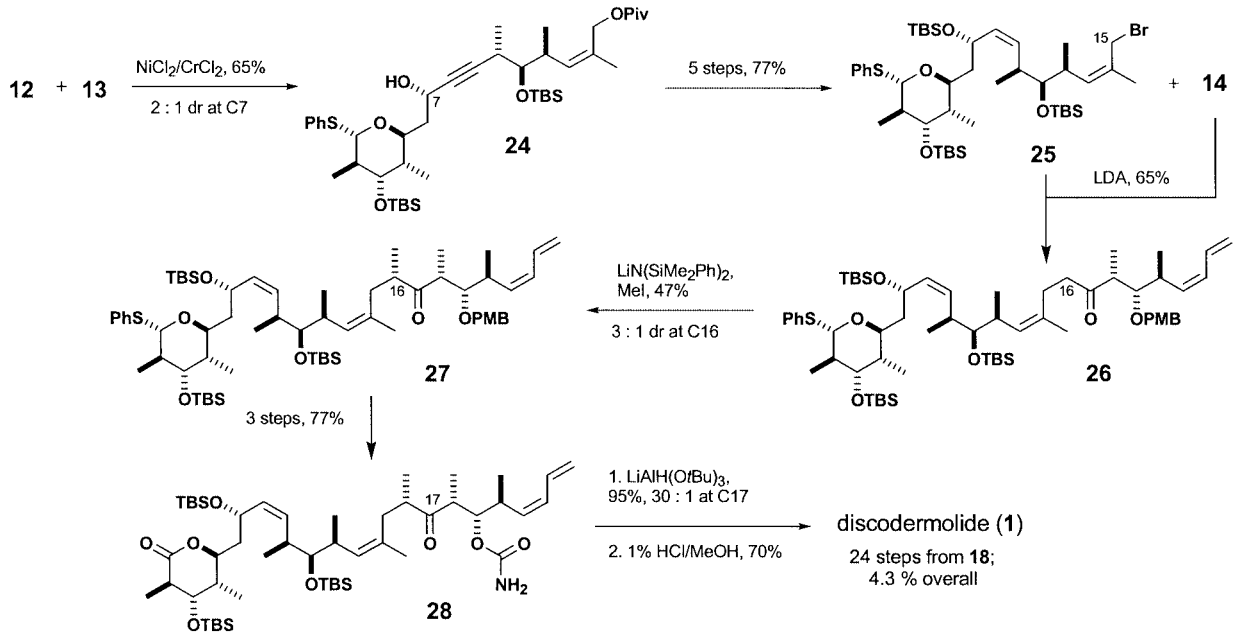
Scheme 2. Synthesis of the C1−C7, C8−C15 and C16−C24 segments of discodermolide according to Schreiber et al.

merous analogues the first structure−activity relationship study was possible.[33a] Perhaps most surprising was the discovery that the unnatural antipode (*ent*-**1**) is also cytotoxic and causes cell cycle arrest in the S-phase.[44]

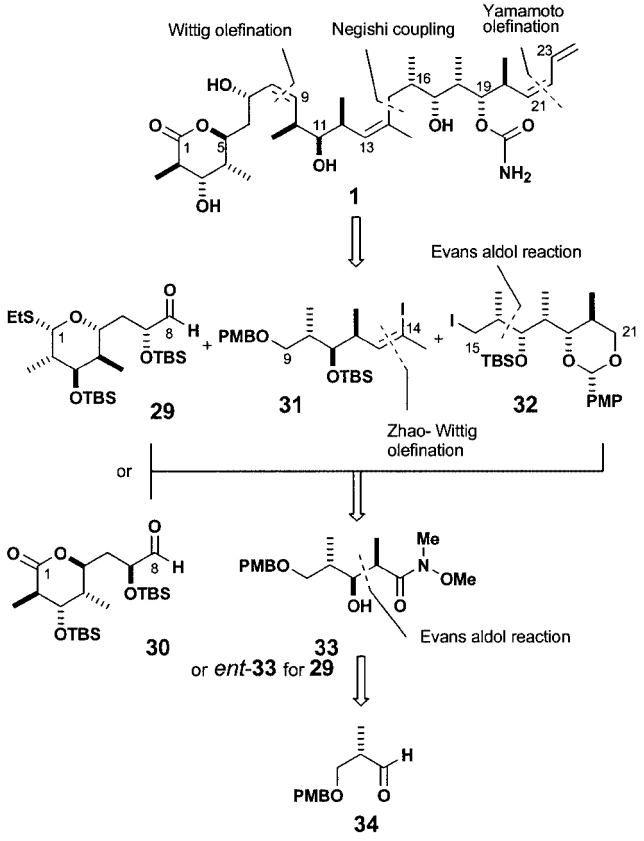
3.2 Smith Syntheses of Discodermolide[34]

Smith and co-workers first achieved the total synthesis of *ent*-discodermolide (*ent*-**1**) and subsequently developed a second-generation approach to provide discodermolide itself.[34] Their strategy involved key fragment couplings at C8−C9 and C14−C15 using a Wittig olefination and a Negishi[41] cross-coupling reaction, respectively (Scheme 4). The modifications to their original route involved the earlier introduction of the terminal (*Z*)-diene unit by a Yamamoto olefination[45] and the replacement of thioacetal aldehyde **29** with δ-lactone aldehyde **30** for the C1−C8 subunit. The segments **31** (C9−C14) and **32** (C15−C21) were used in both syntheses in the appropriate enantiomeric series. In their second-generation route, all three segments were derived from the common precursor **33**, which incorporates the repeating stereotriad sequence of discodermolide.

The common precursor **33** was configured using the *syn*-aldol reaction of the α-chiral aldehyde **34**, which is derived in three steps from Roche ester **18**, with the Evans propionimide **35** (Scheme 5).[46] The (*Z*)-alkenyl iodide at C14 was introduced directly in moderate yield and variable selectivity [(*Z*)/(*E*) = 8:1−17:1] by the Zhao−Wittig olefination protocol[47,48] performed on aldehyde **36**, following silyl protection and DIBAL reduction of **33**. The synthesis of C15−C21 segment **32** utilised a second Evans-aldol reaction to configure the *syn* relationship of C16−C17 to provide **37** and was completed in a further three steps. Palladium-catalysed cross-coupling of the zincate derived from the vinyl iodide **31** with primary iodide **32** then gave the C9−C21 segment **38**.[41]



Scheme 3. Total synthesis of discodermolide according to Schreiber et al.



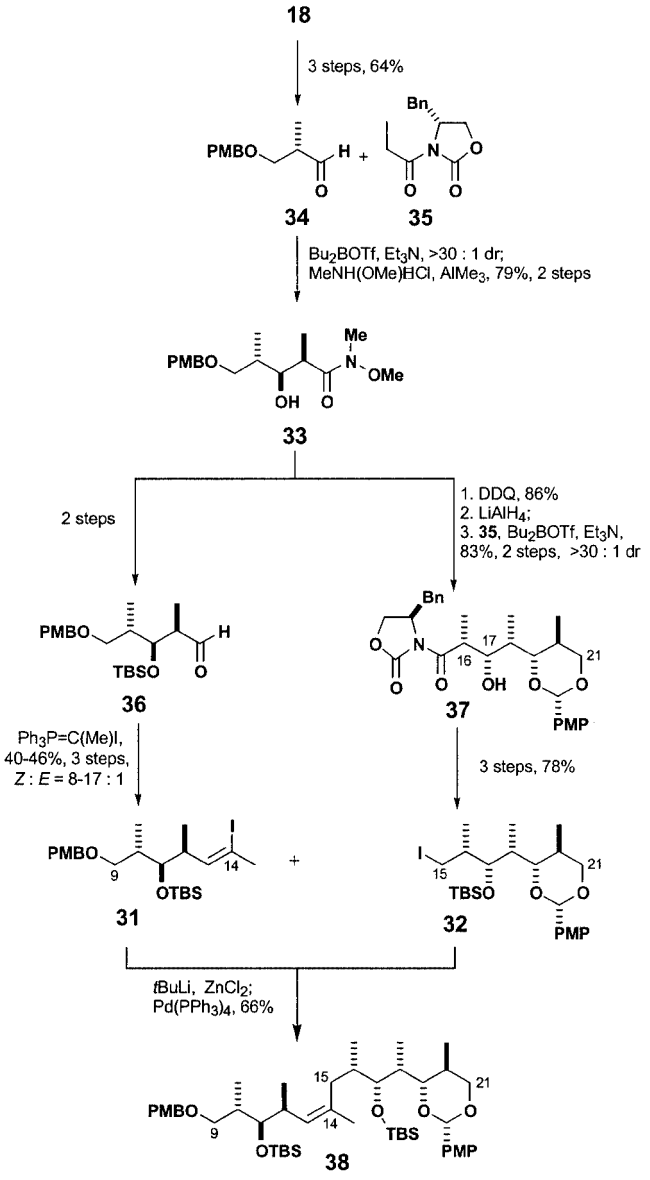
Scheme 4. Strategy for the total synthesis of discodermolide developed by Smith et al.

In the initial Smith synthesis of *ent*-discodermolide,[34c] the C1−C8 thioacetal aldehyde **29** was prepared in 14 steps from *ent*-**33**, exploiting the coupling of dithiane **39** with epoxide **40**, derived from (*R*)-glycidol, to complete the carbon skeleton in **41** (Scheme 6).

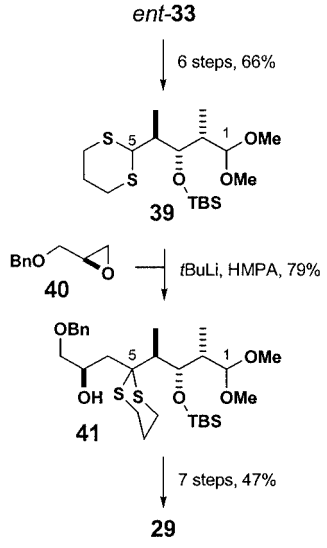
The elaboration of the C9−C21 fragment *ent*-**38** to phosphonium salt **42** proved troublesome and required the treatment of intermediate iodide **43** with triphenylphosphane at ultrahigh pressure (12.8 kbar = 12.6 × 10^3 atm) for 6 d using a specialised reactor (Scheme 7).[49,50] Subsequent (*Z*)-selective Wittig coupling of aldehyde **29** and phosphonium salt **42** gave the advanced C1−C21 intermediate **44**. The terminal (*Z*)-diene unit was then introduced by a three-step sequence utilising the Yamamoto olefination protocol to give **45**.[45] A further five-step sequence was required to complete the synthesis of *ent*-discodermolide (*ent*-**1**), with 2.2% overall yield obtained over 28 steps (longest linear sequence).

The Smith second-generation approach was designed both to reduce the number of steps and to generate a gram of the natural (+)-enantiomer of discodermolide (**1**), and the common-precursor strategy was used to access the δ-lactone aldehyde **30** that now replaced **29** (Scheme 4). The synthesis of the aldehyde **30** was achieved in eight steps from the Weinreb amide **33** (Scheme 8). A remarkable non-Felkin-selective addition of silyl enol ether **46** to aldehyde **47** gave ketone **48**, after acid-catalysed δ-lactonisation, followed by K-Selectride reduction at C7 to give alcohol **49** with *dr* = 9:1. The sequence was completed by TBS protection and ozonolysis to produce **30**, corresponding to a total of 13 steps in 21% yield. In comparison, *ent*-**30** was synthesised earlier by the Paterson group in 12 steps and 29% yield when a similar Wittig strategy was employed.[38a]

The earlier installation of the terminal diene unit was addressed with the C9−C21 fragment **38** (Scheme 9). The diene was installed in a five-step sequence to give the C9−C24 intermediate **50**, with a (*Z*)/(*E*) ratio of 8:1−12:1,



Scheme 5. Synthesis of the C9−C21 segment of discodermolide according to Smith et al.



Scheme 6. Synthesis of the C1−C8 segment of *ent*-discodermolide according to Smith et al.

again utilising the Yamamoto olefination.[45] The phosphonium salt **51** was prepared from **50** in a further two steps, again requiring ultrahigh-pressure conditions. The key Wittig coupling of phosphonium salt **51** and aldehyde **30** gave **52** with a (*Z*)/(*E*) ratio of 15:1−24:1. A further three steps were required to complete this second-generation synthesis of discodermolide, which proceeded in an improved 6% yield over 24 steps (longest linear sequence).

The Smith synthesis is notable in that it provided an impressive 1.043 g of discodermolide, which was considerably more than had ever been isolated from the sponge source, and this synthesis proved to be timely to enable further biological and preclinical evaluation. Further scale-up of this route, however, would pose significant technical challenges, in particular because of the limited availability of ultrahigh-pressure reactors for performing large-scale preparations of the phosphonium salt **51**, as required for the late-stage fragment coupling.

3.3 Myles Synthesis of *ent*-Discodermolide[35]

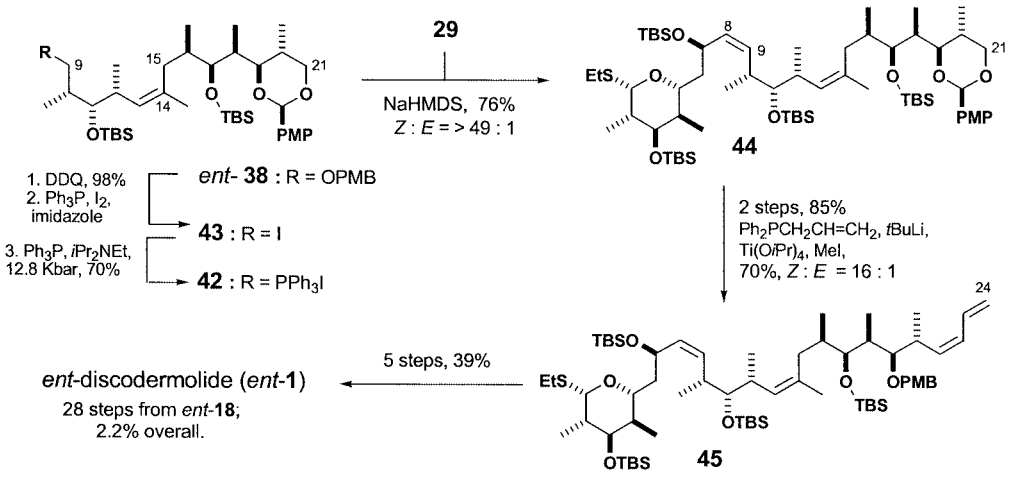
In the total synthesis of *ent*-discodermolide (*ent*-**1**) reported by Myles and co-workers,[35] the three segments **53** (C1−C7), **54** (C9−C15) and **55** (C16−C21) were employed, as shown in Scheme 10, with key couplings performed at C7−C8 based on a Nozaki−Kishi addition[39] and C15−C16 relying on an ambitious enolate alkylation step.

The synthesis of the C9−C15 segment **54** exploited methodology developed in the Danishefsky group[51] to introduce the trisubstituted (*Z*)-olefin (Scheme 11), where $TiCl_4$-mediated cyclocondensation of the chiral aldehyde **56** and diene **57**, gave the dihydropyrone **58**.[35b]

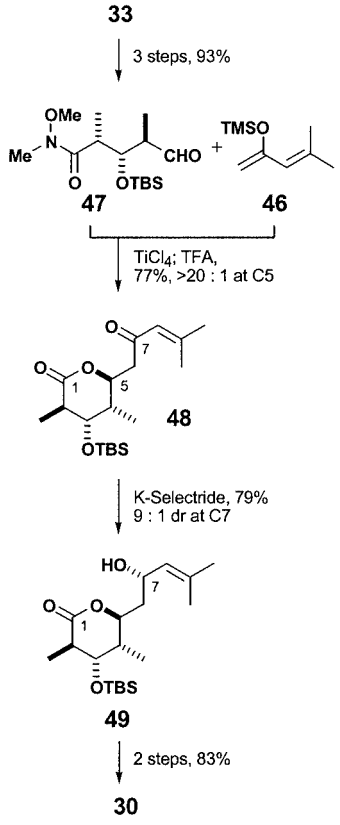
Subsequent Luche reduction and Ferrier rearrangement provided the lactol **59**, which was then converted into the iodide **54** in five further steps. The lithium-mediated aldol reaction of pentan-3-one and the Roche ester derived aldehyde *ent*-**34**, followed by hydroxy protection, allowed access to the C16−C21 segment **55**.[35c]

The C1−C7 aldehyde **53** was prepared in 10 steps from homoallylic alcohol **60**, where the C5-OH group was introduced by a Brown asymmetric allylation on aldehyde **61**. The resulting alcohol **62** was then converted into **53** by a five-step sequence.

The adventurous ethyl ketone alkylation strategy to form the C15−C16 bond had also been explored by Schreiber[33] and Heathcock.[38b] Both of these groups, however, were unable to obtain the C16 configuration of discodermolide with useful selectivity using the ethyl ketone. In contrast, Myles found that in the alkylation of **54** with the lithium (*Z*)-enolate of **55**, the MOM protection of the C19-OH group and the judicious choice of lithium base and solvent system were critical to provide the desired C9−C21 segment **63** with *dr* = 6:1 (Scheme 12).[35a] Subsequent manipu-



Scheme 7. Total synthesis of *ent*-discodermolide according to Smith et al.



Scheme 8. Synthesis of the C1−C8 segment of discodermolide according to Smith et al.

lations, including reduction at C17 (*dr* = 8:1), and a Stork−Wittig olefination gave the C8−C21 vinyl iodide **64**.[52] Following PMB deprotection and oxidation, the terminal diene unit was installed using the modified Roush allylation reagent **65** with subsequent Peterson-type *syn* elimination.[53,54] Introduction of the carbamate followed to afford the vinyl iodide **66**. In a manner similar to the Schreiber synthesis,[33] the Nozaki−Kishi coupling to form the C7−C8 bond through addition of iodide **64** to aldehyde **53** proceeded, at best, in moderate yield to give **67** with *dr* = 2:1 at C7. Global deprotection and concomitant δ-lactonisation of **67** gave *ent*-discodermolide (*ent*-**1**) in a synthesis that proceeded in ca. 1.4% overall yield from iodide **54** (the yields and full details of this synthesis are not available in the literature).

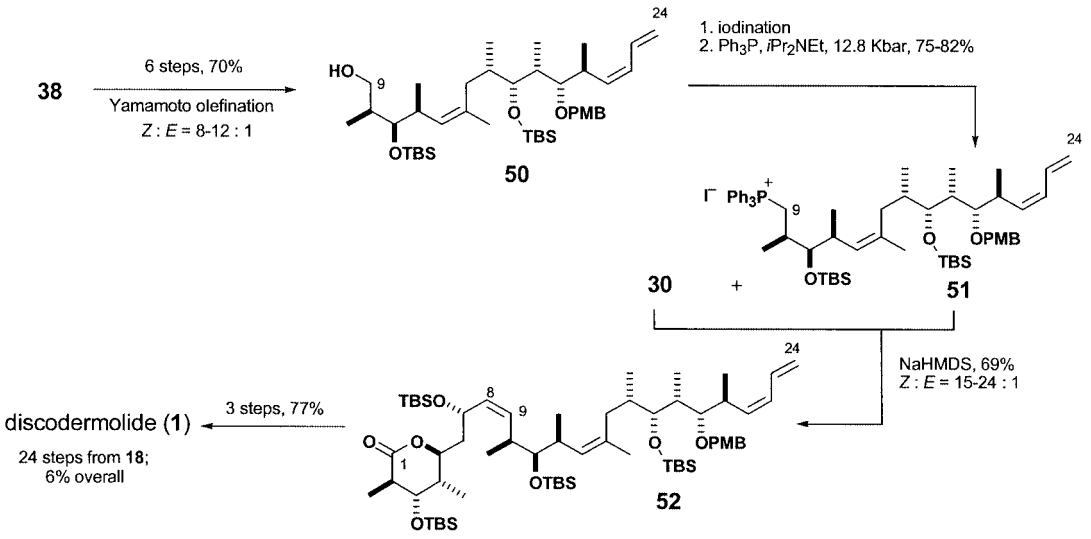
3.4 Marshall Synthesis of Discodermolide[36]

The synthetic plan adopted by Marshall and co-workers[36] for (+)-discodermolide involved the three segments **68** (C1−C7), **69** (C8−C13) and **70** (C15−C24), with key coupling steps performed at C7−C8 by lithium acetylide addition to an aldehyde and C14−C15 using a novel Suzuki cross-coupling reaction (Scheme 13).[55]

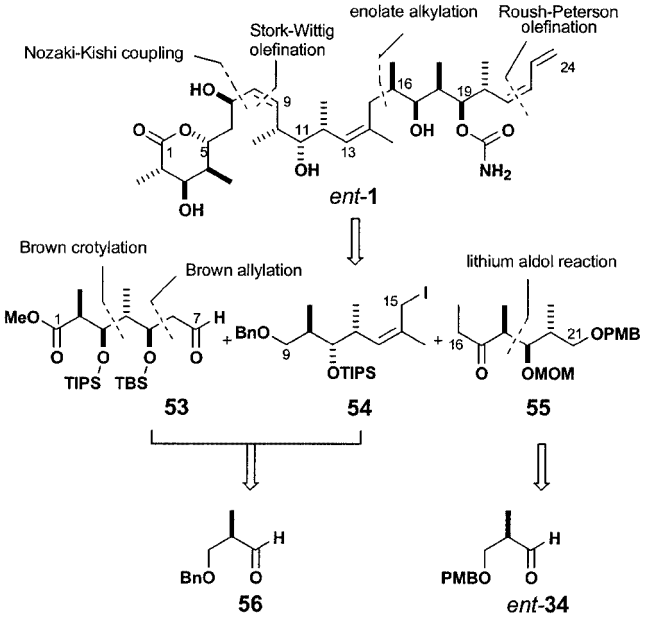
The stereopentad found in the C15−C24 segment **70** was built using methodology developed within the Marshall group,[56] involving the addition of chiral allenylstannane **71** to the Roche ester derived aldehyde **17** to give **72** with *dr* > 20:1 (Scheme 14). Introduction of the C19 and C20 stereocentres utilised a sequence of reduction, Sharpless epoxidation, and methyl cuprate opening of the resulting epoxide to afford diol **73**.[36b]

Installation of the terminal diene unit was performed using the Nozaki−Hiyama/Peterson protocol developed in the Paterson group,[38f] and protecting group transformations completed the synthesis of the iodide **70** in a further eight steps.

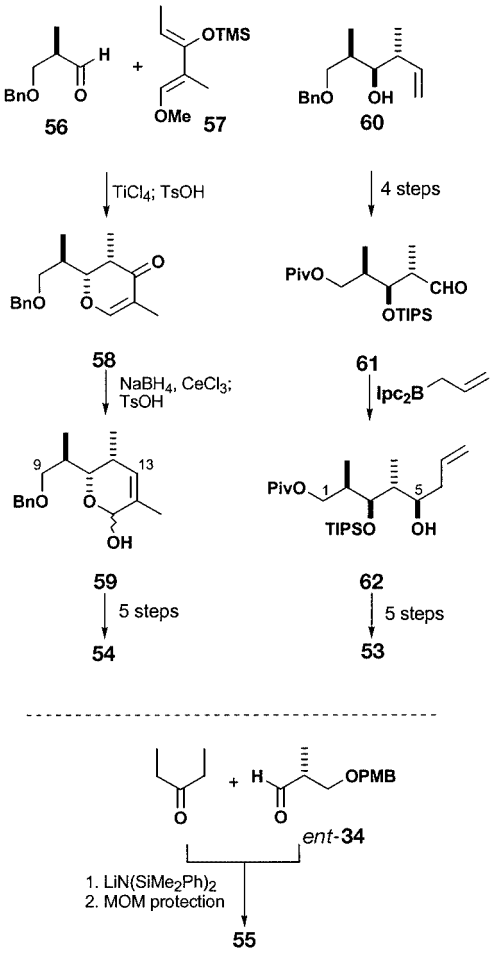
The common stereotriad found in **68** (C1−C7) and **69** (C8−C13) was accessed with *dr* = 9:1 by the addition of a chiral allenylzinc species, prepared in situ from the treatment of propargylic mesylate **74** with Et_2Zn and catalytic Pd^0, to the α-chiral aldehyde **75**. Protection of the resulting alcohol **76** as the MOM ether gave the C8−C13 segment **69**. A further nine-step sequence performed on **76** provided the C1−C7 segment **68**, which involved Red-Al reduction, Sharpless epoxidation, and hydride opening of the resulting epoxide to introduce the C5-OH group.[36b]



Scheme 9. Total synthesis of discodermolide according to Smith et al.

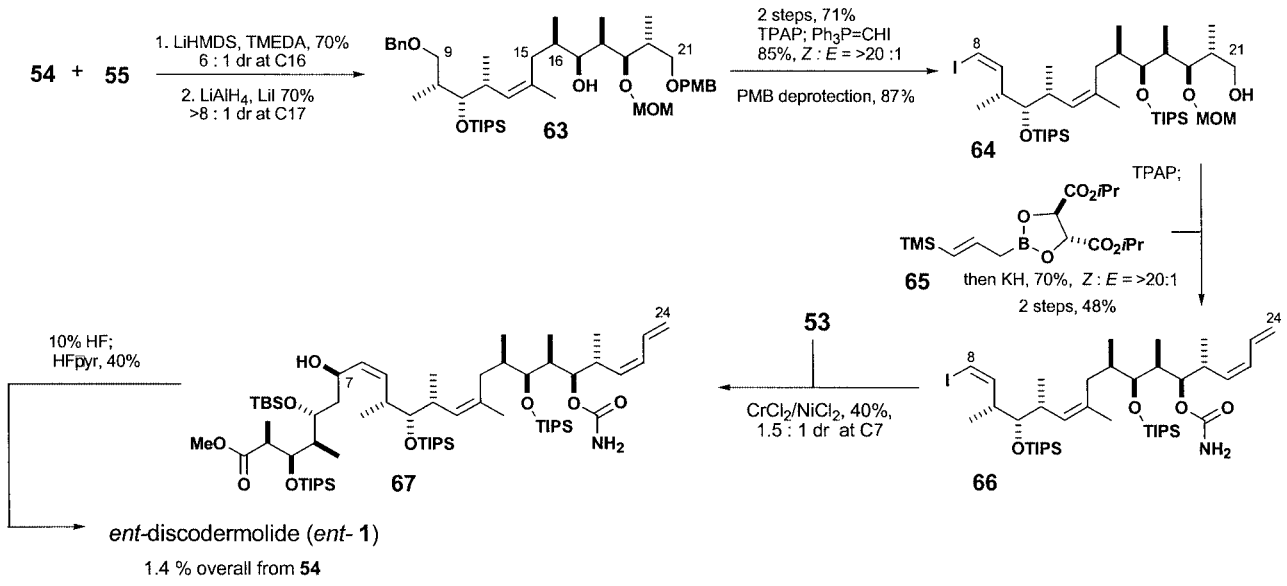


Scheme 10. Strategy for the total synthesis of *ent*-discodermolide developed by Myles et al.

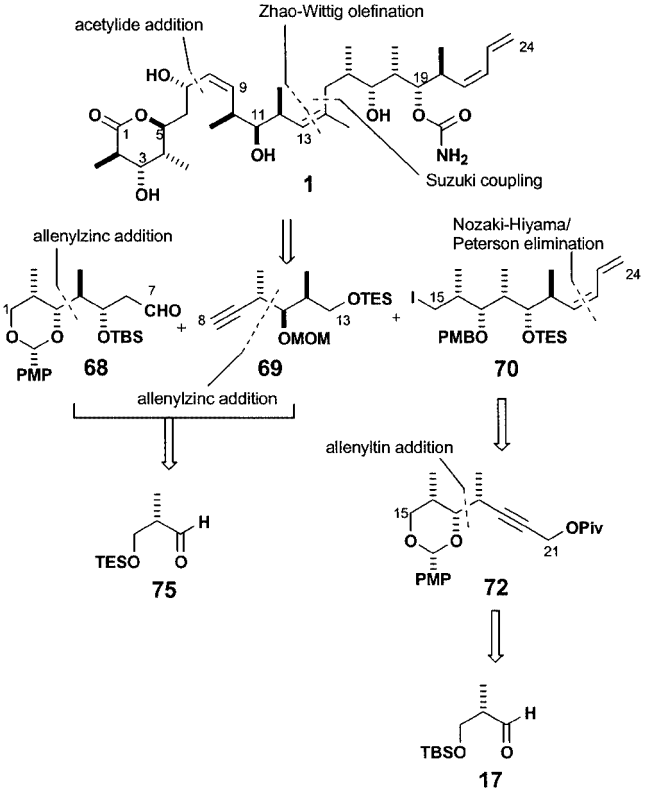


Scheme 11. Synthesis of the C1−C7, C9−C15 and C16−C21 segments of discodermolide according to Myles et al.

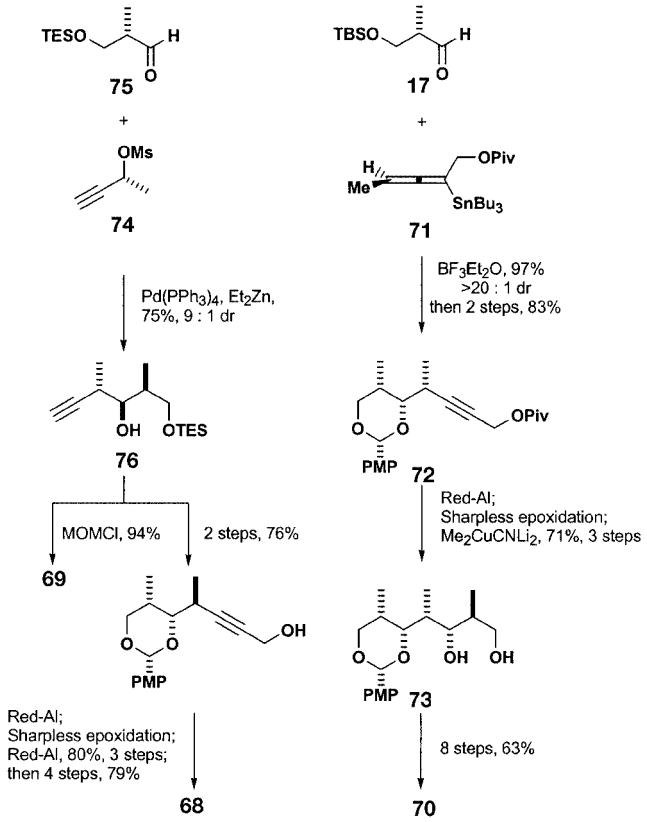
As shown in Scheme 15, the addition of the lithium acetylide derivative of alkyne **69** to the aldehyde **68** proceeded in high yield to give alcohol **77** as a 6:1 ratio of epimers at C7 (where the minor epimer could be recycled by Mitsunobu inversion). Following the Lindlar hydrogenation of the alkyne moiety and protecting group manipulations, the Zhao−Wittig protocol was employed on **78** to introduce the (*Z*)-alkenyl iodide,[47] which was characterised by variable yields and selectivity [(*Z*)/(*E*) = 1.3:1−9:1). The efficient Suzuki cross-coupling[55] of vinyl iodide **79** and C15−C24 boronate **80**, derived from primary iodide **70**, facilitated the assembly of the advanced C1−C24 intermediate **81**. After a series of manipulations and deprotections, the synthesis of discodermolide (**1**) was completed in 2.2% overall yield achieved over 29 steps (longest linear sequence). The Marshall synthesis clearly demonstrated the



Scheme 12. Total synthesis of *ent*-discodermolide according to Myles et al.



Scheme 13. Strategy for the total synthesis of discodermolide developed by Marshall et al.

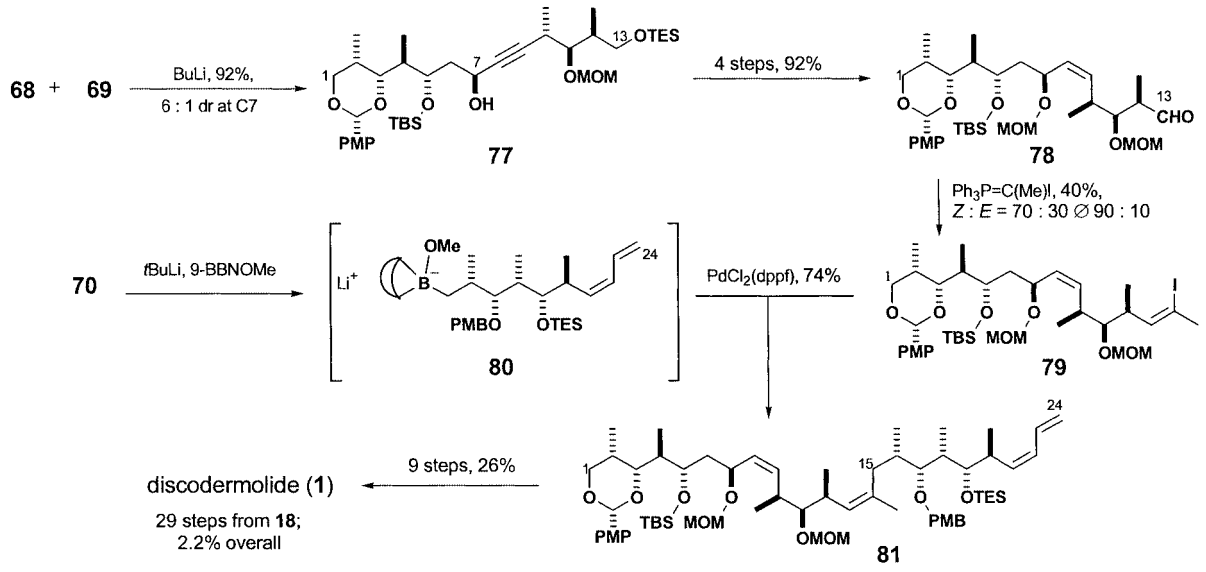


Scheme 14. Synthesis of the C1−C7, C8−C13 and C15−C24 segments of discodermolide according to Marshall et al.

versatility of their chiral allenylmetal methodology for the preparation of polypropionate arrays and the utility of the Suzuki cross-coupling for complex fragments.

3.5 Paterson Syntheses of Discodermolide[37]

The synthesis of discodermolide and structural analogues has been the subject of extensive effort within our grou-

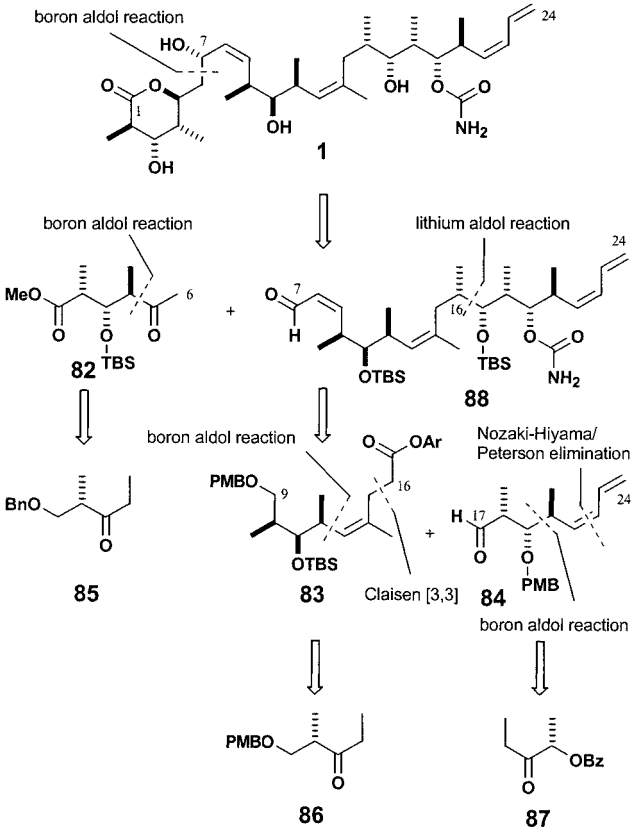


Scheme 15. Total synthesis of discodermolide according to Marshall et al.

p.[37][38a][38f] The construction of the requisite polypropionate arrays found in discodermolide was accomplished, at an early stage,[38a][38f] with relative ease using our aldol-based methodology.[57–59] Problems were encountered, however, in the fragment-coupling steps and introducing the trisubstituted (*Z*)-olefin, such that a revised strategy was designed to circumvent these difficulties. As shown in Scheme 16, this approach was based on the application of two aldol reactions to unite three subunits **82** (C1–C6), **83** (C9–C16) and **84** (C17–C24).[37a–37c] The stereochemical motifs present in each of these compounds were configured, utilising our group's methodology, by employing the ethyl ketones **85**, **86** and **87** as chiral building blocks.[58][59] The full carbon backbone was completed by an adventurous aldol coupling reaction at C6–C7 between methyl ketone **82** and the advanced (*Z*)-enal **88**. The latter compound was assembled by a lithium-mediated aldol reaction at C16–C17 between aryl ester **83** and aldehyde **84**. This approach constituted a novel construction of the carbon skeleton of (+)-discodermolide by installing three stereogenic centres in two fragment-coupling steps, while the trisubstituted (*Z*)-alkene was installed efficiently by a Claisen rearrangement using Holmes methodology.[60]

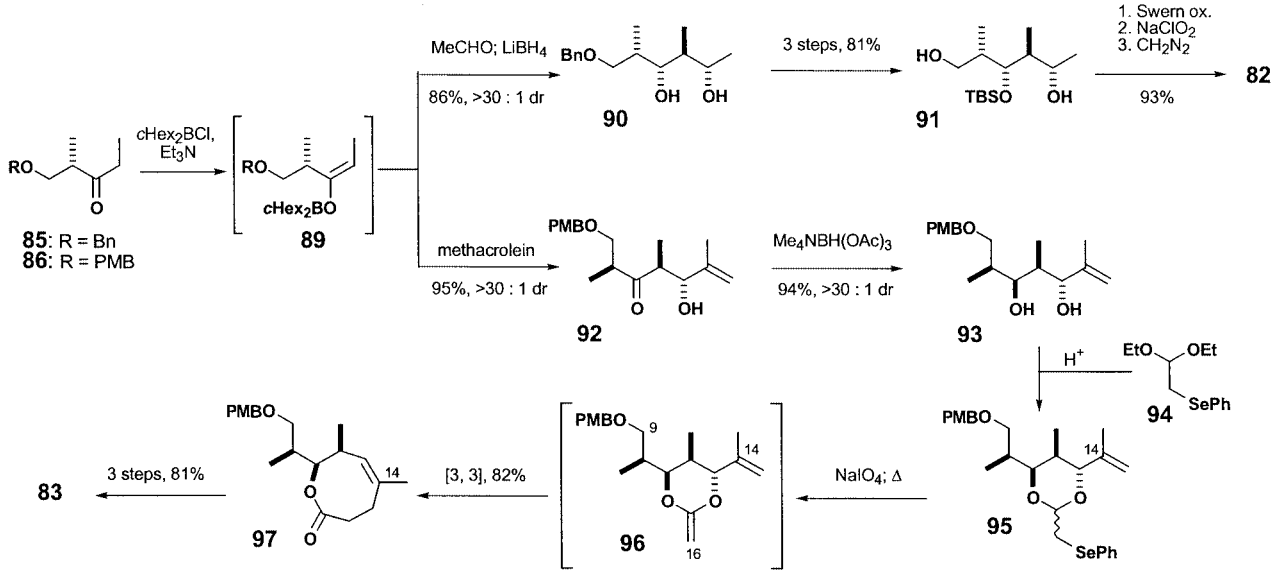
Our synthesis of the C1–C6 methyl ketone **82** started with an *anti*-aldol reaction between the ethyl ketone **85**, prepared in three steps from Roche ester **18**, and acetaldehyde (Scheme 17).[58] Enolization with *c*Hex$_2$BCl/Et$_3$N and addition of acetaldehyde to enolate **89** provided the intermediate aldolate, where an in situ reduction with LiBH$_4$ gave diol **90** (*dr* > 30:1).[61] Subsequent protecting group manipulations provided **91** and the synthesis of **82** was completed through oxidation at C1 and C5, and subsequent methyl ester formation.

Our synthesis of the C9–C16 aryl ester **83** began with the *anti*-aldol reaction of ethyl ketone **86** with methacrolein to provide **92** with *dr* > 30:1 (Scheme 17). An Evans *anti*



Scheme 16. Strategy for the first-generation synthesis of discodermolide developed by Paterson et al.; Ar = 2,6-dimethylphenyl

reduction provided diol **93** (*dr* > 30:1),[62] which then underwent transacetalisation with **94** to give acetal **95**. Following the Holmes protocol,[60] oxidation and thermal elimination of the phenyl selenoxide gave the intermediate ketene acetal **96**, which in turn underwent Claisen [3,3] re-

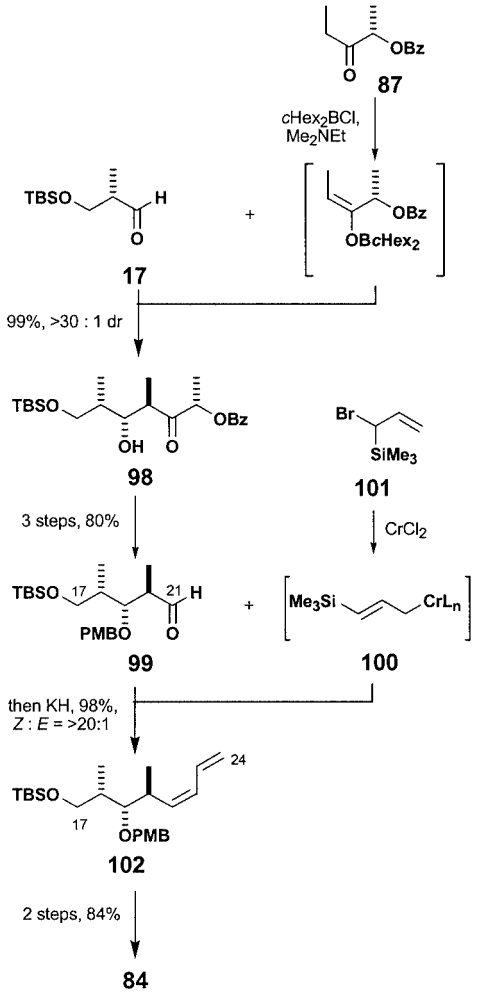


Scheme 17. Synthesis of the C1−C6 and C9−C16 segments of discodermolide according to Paterson et al.

arrangement to afford the lactone **97**, leading to complete selectivity for introduction of the trisubstituted (*Z*)-alkene. A further three-step sequence was then required to complete the ester **83**.

As shown in Scheme 18, our synthesis of the C17−C24 aldehyde **84** began with the boron-mediated aldol reaction of the lactate-derived ethyl ketone **87** with the α-chiral aldehyde **17** to give the *anti* adduct **98** exclusively.[59] Subsequent protecting group manipulations and oxidative cleavage gave aldehyde **99**. Following the protocol that we had developed earlier, the terminal (*Z*)-diene moiety was introduced efficiently by sequential Nozaki−Hiyama allylation and Peterson elimination reactions.[38f] Addition of the allylchromium compound **100**, generated from bromide **101**, to aldehyde **99**, provided the (*Z*)-diene **102** after *syn* elimination of the intermediate adducts. Silyl deprotection and oxidation completed the synthesis of **84**.

As shown in Scheme 19, the lithium-mediated *anti*-aldol reaction of the Heathcock-type aryl ester **83** with aldehyde **84** gave the expected adduct **103** with *dr* = 30:1 based on Felkin−Anh stereoinduction.[63] Following ester reduction, either in situ or after isolation of **103**, a two-step deoxygenation sequence was performed on **104**, to introduce the C16-CH_3 group. TBS protection of the C17-OH group and subsequent PMB deprotection gave diol **105**. Following selective primary oxidation with TEMPO,[64] the C8−C9 (*Z*)-olefin was introduced efficiently by a Still−Gennari HWE reaction to give **106** with (*Z*)/(*E*) > 30:1. Subsequent carbamate installation at C19 and a reduction/oxidation sequence at the C7 terminus gave enal **88** in readiness for the pivotal C6−C7 aldol coupling. This step proved to be particularly challenging and required considerable effort to secure the desired C7 configuration.[37a−37c] Enolization of **82** with *c*Hex_2BCl/Et_3N provided the boron enolate **107**, which on addition to **88** gave the undesired (7*R*) adduct



Scheme 18. Synthesis of the C17−C24 segment of discodermolide according to Paterson et al.

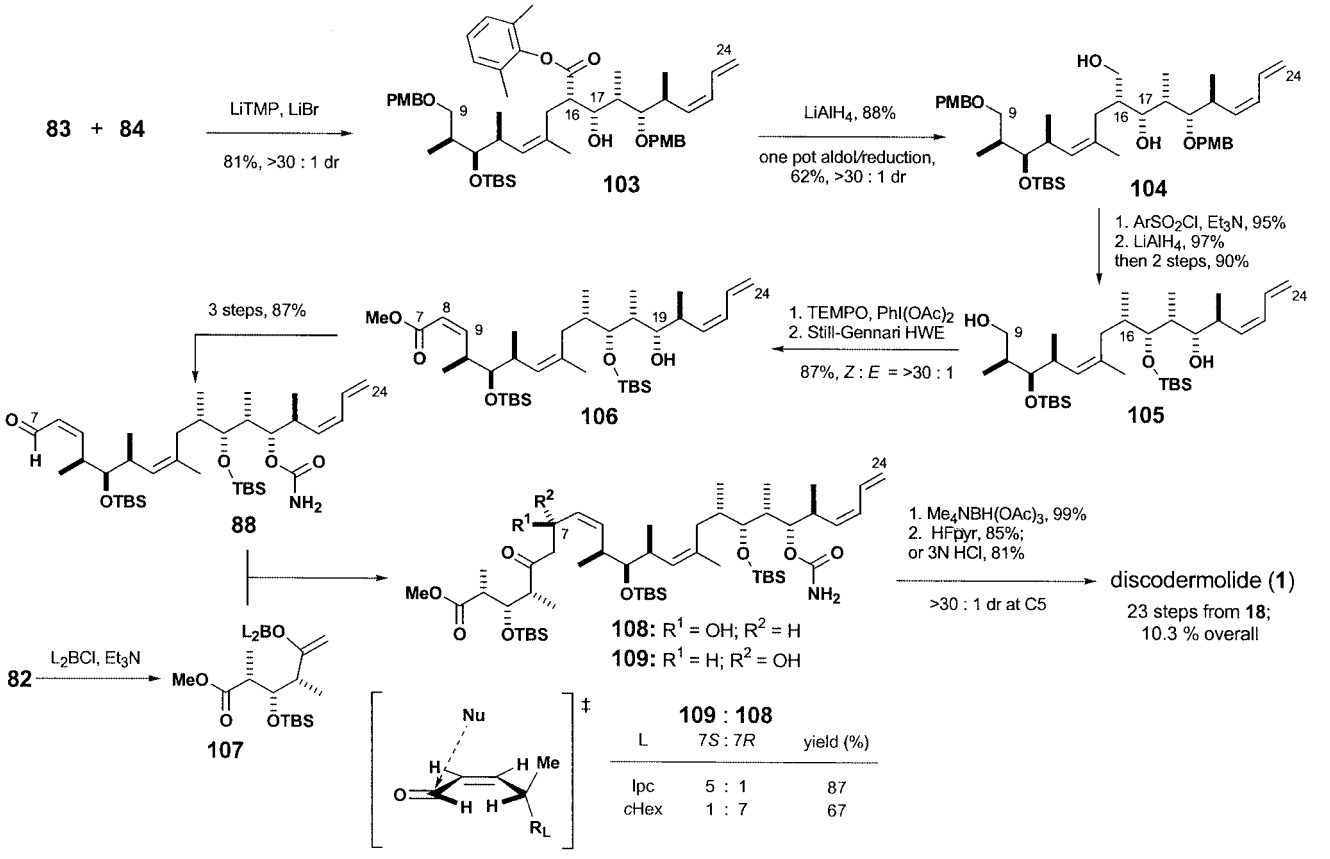
108 with *dr* = 7:1, arising from high levels of remote 1,4-stereoinduction from the (*Z*)-enal with preferred attack on the sterically less congested *re* face as indicated. Therefore, to obtain the desired (7*S*) adduct **109**, it was necessary to employ a chiral boron reagent to overturn the π-facial bias of aldehyde **88**. Gratifyingly, enolisation of **82** with (+)-Ipc_2BCl/Et_3N and addition of **107** to enal **88** gave the desired aldol adduct **109** with *dr* = 5:1.[65] This result represents a rare example of the use of reagent control to reverse the intrinsic substrate selectivity successfully in a complex aldol coupling of two chiral carbonyl components. An Evans 1,3-*anti* reduction on **109** introduced the final stereogenic centre at C5 with *dr* > 30:1. Global deprotection and δ-lactonisation then completed our synthesis of discodermolide (**1**) in 10.3% yield over 23 steps (longest linear sequence).

This first-generation synthesis of discodermolide demonstrated the novel application of complex aldol reactions in key fragment unions and achieved essentially complete control over the double-bond geometry. The only step that proceeded with less-than-perfect stereocontrol was the final aldol coupling, but we have since developed an effective sequence to convert also the minor (7*R*) adduct **108** into discodermolide.[66]

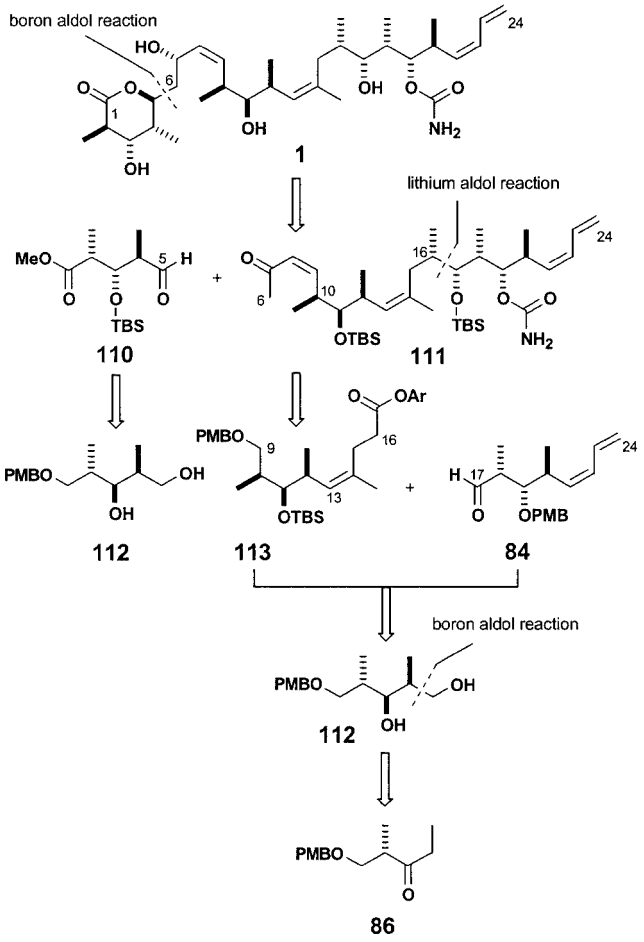
Following our first-generation synthesis, a revised strategy towards discodermolide was devised (Scheme 20) both to eliminate the use of all chiral reagents and auxiliaries, thus relying solely on substrate control, and to reduce the total number of steps.[37d] To achieve these specific goals, a novel aldol coupling across C5−C6 was employed between aldehyde **110** and methyl ketone **111**, relying on long-range asymmetric induction from the C10 γ-stereocenter. The use of a common building block **112**, containing the repeating *anti-syn* stereotriad found in the three subunits **110**, **113** and **84**, helped to reduce the total number of steps.

Our synthesis of the common building block **112** started with the boron-mediated aldol reaction of ethyl ketone **86** with formaldehyde to give adduct **114** with *dr* = 20:1, containing the required 1,3-*anti*-configured methyl groups (Scheme 21).[58] A hydroxy-directed reduction then gave diol **112** with *dr* = 10:1, which was isolated conveniently in stereochemically pure form by recrystallization. Notably, the five-step synthesis of **112**, starting from Roche ester **18**, can be performed on a large scale without recourse to chromatographic purification.

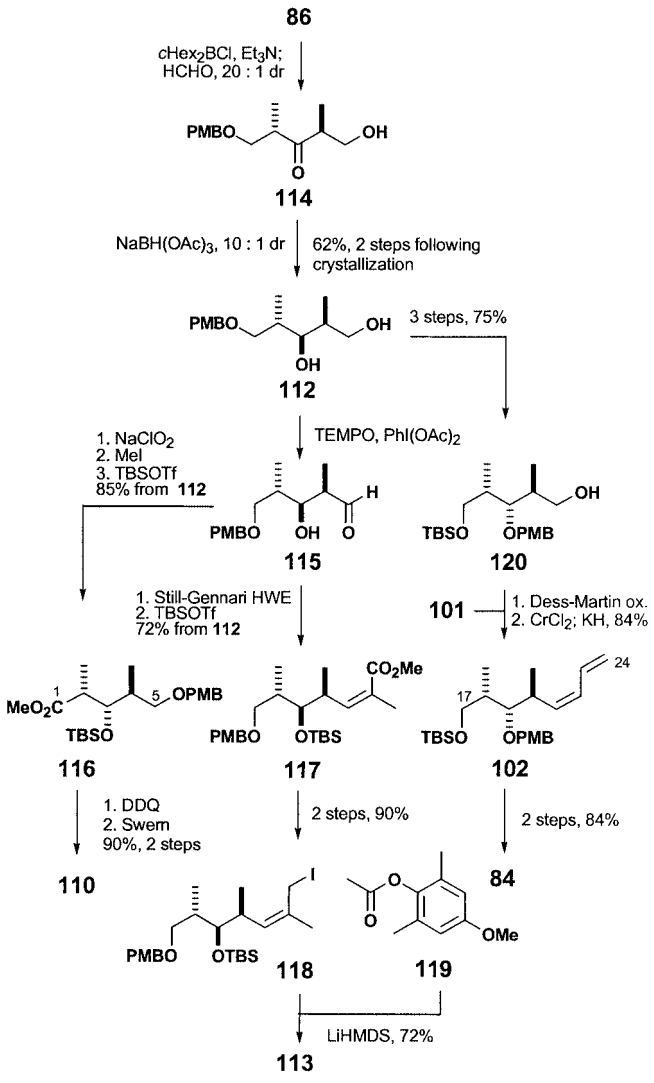
Our synthesis of the C1−C5 subunit **110** from the common precursor **112** began with a selective TEMPO oxidation of the C1−OH group to give **115**. Further oxidation to the carboxylic acid and conversion into the methyl ester was followed by TBS protection. Deprotection of **116** at the C5 terminus and oxidation completed the C1−C5 aldehyde **110** in six steps. In parallel, the C9−C16 subunit **113** was accessed in five steps utilising aldehyde **115**. The trisubstituted (*Z*)-olefin was introduced by Still−Gennari HWE olefination, as used in the Schreiber synthesis,[33] and TBS protection of the C11-OH group then provided **117**. Re-



Scheme 19. Completion of first-generation synthesis of discodermolide according to Paterson et al.; Ar = 2,4,6-trimethylphenyl



Scheme 20. Strategy for the second-generation synthesis of discodermolide developed by Paterson et al.; Ar = 4-methoxy-2,6-dimethylphenyl

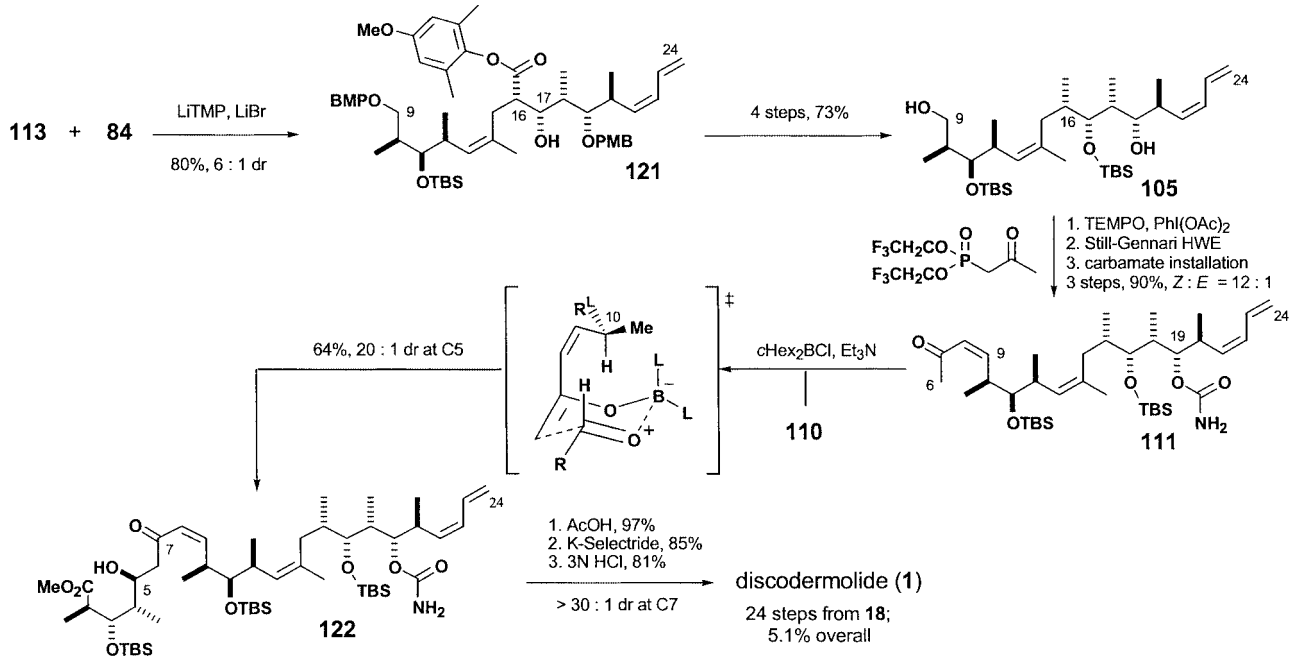


Scheme 21. Synthesis of the C1−C5, C9−C16 and C17−C24 segments of discodermolide according to Paterson et al.

duction of the methyl ester and conversion into the iodide **118** was followed by alkylation with the lithium enolate of the novel aryl ester **119**, to complete the C9−C16 subunit **113**. The revised synthesis of the C17−C24 subunit **84** from the common precursor **112** began with a three-step sequence of protecting group manipulation to give **120**. Oxidation of the primary hydroxy group was followed by installation of the terminal (*Z*)-diene by our usual method[38f] to provide the known intermediate **102**, which was converted into **84** as before.[37a]

The lithium-mediated aldol coupling of **113** and **84** provided **121** with *dr* = 6:1,[63] which was then converted into alcohol **105** (Scheme 22) by following our previously established route.[37a,37b] Selective primary oxidation of **105** and introduction of the (*Z*)-enone moiety under modified Still−Gennari HWE conditions provided **111** with (*Z*)/(*E*) = 12:1,[67] following carbamate installation at C19. The novel boron-mediated aldol reaction of methyl ketone **111** and aldehyde **110** exploited remote 1,6-asymmetric induction from C10 as in the indicated transition state. Enolisation of **111** with *c*Hex_2BCl/Et_3N and reaction with **110** gave the desired (5*S*) adduct **122** with *dr* = 20:1. In contrast, the analogous lithium-mediated reaction gave the (5*R*) adduct exclusively, as expected from Felkin−Anh control. Acid-promoted δ-lactonisation of **122** was followed by K-Selectride reduction at C7,[34a] introducing the final stereogenic centre with *dr* > 30:1. Global deprotection then completed our second-generation synthesis of discodermolide (**1**), which proceeded in 5.1% yield over a 24-step longest linear sequence (35 total steps).

In comparison with our original route, this second-generation approach reduced substantially the total number of steps required to complete discodermolide. The use of chiral reagents and auxiliaries was eliminated, altogether achieving a more cost-effective route. In contrast to the earlier syntheses of discodermolide by the groups of Schreiber, Smith, Myles and Marshall, which start out from the ubiquitous Roche ester **18**, our second route relies solely on substrate control to configure all the remaining stereocentres.



Scheme 22. Completion of second-generation synthesis of discodermolide according to Paterson et al.

4. Outlook

The different synthetic approaches developed to date clearly demonstrate the feasibility of chemical synthesis providing useful quantities of discodermolide, and this feature has enabled further biological and preclinical evaluation of this potent microtubule-stabilizing antimitotic agent, as well as inspiring the development and application of new methods for acyclic stereocontrol. It is evident that lengthy total syntheses of such complex natural products are no longer limited to delivering milligrams of product.[68] The prospect of realising the crossover of discodermolide from laboratory to clinic as a new-generation anticancer agent will require a practical and scaleable synthesis that can ultimately deliver kilogram quantities. Rising to this challenge, the Chemical Development Group of Novartis Pharma AG in Basel has recently succeeded in synthesising discodermolide on a sufficiently large scale for Phase I clinical trials. Thanks to the power of modern organic synthesis, the problem of discodermolide supply is certainly not insurmountable!

Abbreviations

Ac: acetyl; Ar: unspecified aryl group; 9-BBNOMe: 9-borabicyclo[3.3.1]nonyl methoxide; Bn: benzyl; Bz: benzoyl; DDQ: 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DIBAL: diisobutylaluminium hydride; dppf: 1,1′-bis(diphenylphophino)ferrocene; *dr*: diastereomeric ratio; HMPA: hexamethylphosphoramide; HWE: Horner−Wadsworth−Emmons; Ipc: isopinocampheyl; KHMDS: potassium bis(trimethylsilyl)amide; L: unspecified ligand; LiHMDS: lithium bis(trimethylsilyl)amide; LDA: lithium diisopropylamide; MOM: methoxymethyl; Ms: methylsulfonyl; NaHMDS: sodium bis(trimethylsilyl)amide; OTf: trifluoromethanesulfonate; PMB: *p*-methoxybenzyl; PMP: *p*-methoxyphenyl; PPTS: pyridinium *p*-toluenesulfonate; Piv: pivaloyl; pyr: pyridine; TBS: *tert*-butyldimethylsilyl; TES: triethylsilyl; TFA: trifluoroacetic acid; TIPS: triisopropylsilyl; TMEDA: *N*,*N*,*N*′,*N*′-tetramethylethylenediamine; TMS: trimethylsilyl; TMP: 2,2,6,6-tetramethylpiperidine; TPAP: tetrapropylammonium perruthenate; TsOH: *p*-toluenesulfonic acid.

Acknowledgments

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