A Ruthenium-Mediated Asymmetric Hydrogenation Approach to the Synthesis of Discodermolide Subunits

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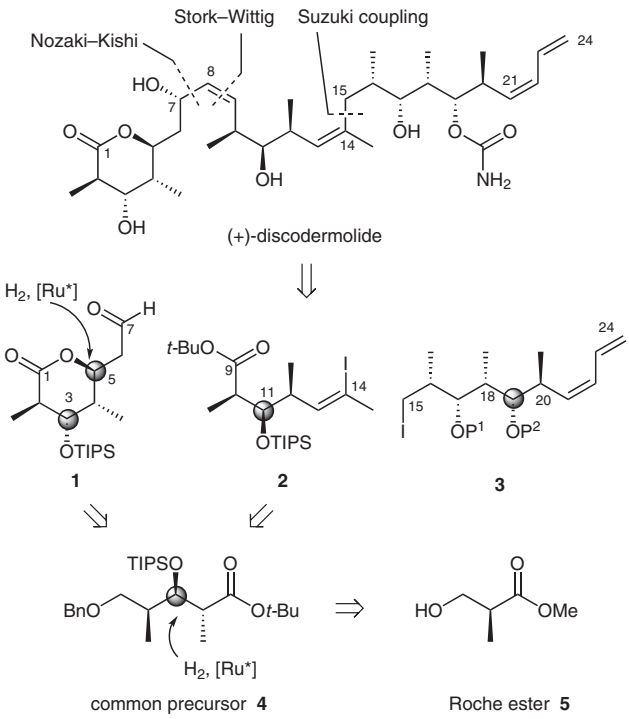
Abstract: The C1–C7 and C9–C14 subunits of (+)-discodermolide have been synthesized using ruthenium-SYNPHOS-mediated asymmetric hydrogenation reactions of β-keto esters to set the C3, C5 and C11 hydroxy-bearing stereocenters with very high levels of diastereoselectivity.

Key words: asymmetric catalysis, hydrogenation, ruthenium, total synthesis, natural products

The polypropionate-derived marine metabolite discodermolide was first isolated by Gunasekera and co-workers[1] in 1990 from the Caribbean deep-sea sponge *Discodermia dissoluta*. Preliminary biological evaluations showed this compound to possess potent immunosuppressive activity.[2] It was later demonstrated that discodermolide exhibited excellent microtubule-stabilizing capabilities[3] as well as synergism with taxol.[4] This promising biological profile and the potential as chemotherapeutic agent[5] have prompted considerable synthetic efforts toward the total synthesis of discodermolide.[6]

As part of our ongoing projects involving the synthesis of biologically relevant natural products via ruthenium-promoted asymmetric hydrogenation,[7] we were particularly interested in the linear polypropionate backbone of discodermolide, because the C2–C4, C10–C12, and C18–C20 motifs appeared ideally suited for construction through hydrogenation reactions. From a retrosynthetic point of view, all of the reported total syntheses disconnect discodermolide into three major fragments of equal complexity, each subunit possessing a *syn*,*anti* methyl–hydroxy–methyl stereotriad. On this basis, we chose to disconnect discodermolide into compounds **1**, **2**, and **3**, corresponding to C1–C7,[8] C9–C14 and C15–C24 fragments of the natural product, as depicted in Scheme 1. Formation of the C14–C15 bond would result from a Suzuki coupling reaction between (*Z*)-alkenyl iodide **2** and compound **3**. The C7–C8 bond would be created by a Nozaki–Kishi reaction between aldehyde **1** and a (*Z*)-vinyl iodide derived from an ester at C9.

Herein we report the preparation of key discodermolide intermediates **1** and **2**. In our retrosynthetic plan, both fragments would be prepared from a common precursor **4**



Scheme 1 Retrosynthetic analysis for (+)-discodermolide

which in turn would be derived from methyl (*S*)-3-hydroxy-2-methylpropionate (Roche ester) **5**. Among the seven stereocenters of the target subunits, three would be created via ruthenium-mediated asymmetric hydrogenation[9] of β-keto esters using the atropisomeric ligand SYNPHOS[10] as the chiral diphosphine.

The common precursor **4** was readily prepared in five steps starting from commercially available Roche ester **5**. After protection of the hydroxy function as a benzyl ether, subsequent chain extension with lithio *tert*-butyl acetate[11] delivered the β-keto ester **6** required for the asymmetric hydrogenation reaction (Scheme 2).

The stereoselective reduction of the ketone function was accomplished using 2 mol% of the chiral complex {Ru[(*R*)-SYNPHOS]Br_2} prepared in situ from commercially available [Ru(cod)(2-methylallyl)$_2$][12] and afforded β-hydroxy ester **7** in high yield and with excellent diastereoselectivity (99% de, as determined by HPLC analysis). Subsequent diastereoselective methylation of **7** using the Fráter–Seebach conditions[13] (>95% de, only one diastereomer detected by ^{1}H NMR) followed by protection of the

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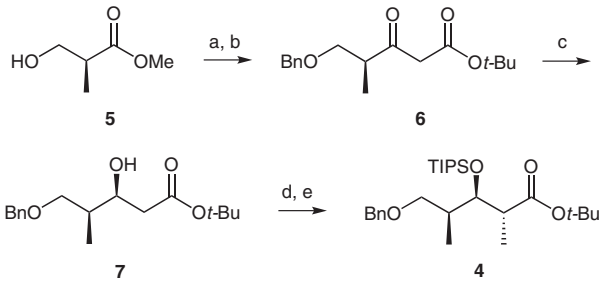
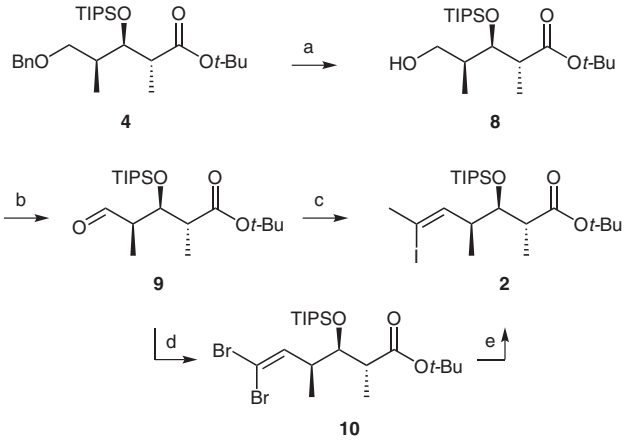


Scheme 2 Synthesis of the common precursor (**4**). *Reagents and conditions*: (a) $BnOC(=NH)CCl_3$, TfOH, CH_2Cl_2, r.t., 3.5 h, 85%; (b) LDA, *t*-BuOAc, THF, –40 °C, 3 h, 80%; (c) H_2 (75 bar), 2 mol% {Ru[(*R*)-SYNPHOS]Br_2}, *t*-BuOH–MeOH (4:1), 50 °C, 24 h, 96%, 99% de; (d) LDA, THF, –40 °C to 0 °C, 1 h; then HMPA, MeI, THF, –10 °C to r.t., 3 h, 73%, 95% de; (e) TIPSOTf, 2,6-lutidine, CH_2Cl_2, –30 to –15 °C, 4 h, quant.

hydroxy function then furnished the common precursor **4** which was thereby obtained in 48% overall yield from **5**.

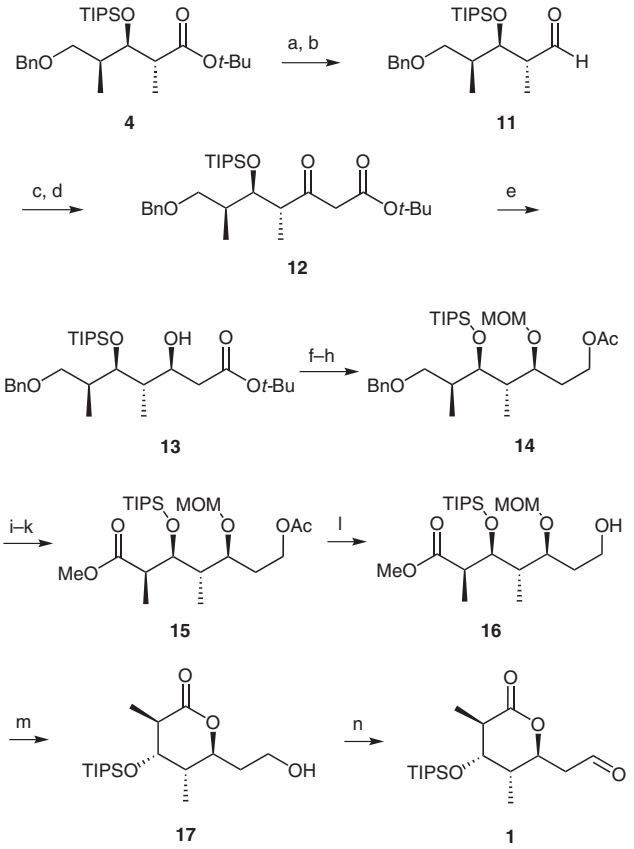
With compound **4** in hand, we could address the preparation of the C1–C7 (**1**) and C9–C14 (**2**) fragments of discodermolide. Thus, compound **2** was obtained in three steps from **4** after deprotection of the primary hydroxy function, followed by oxidation to the aldehyde and (*Z*)-alkenyl iodide introduction under Zhao conditions[14] (Scheme 3).



Scheme 3 Synthesis of the C9–C14 (**2**) subunit of discodermolide. *Reagents and conditions*: (a) H_2 (1 atm), Pd/C (5%), THF, r.t., 105 min, 79%; (b) Dess–Martin periodinane, CH_2Cl_2, 0 °C to r.t., 4 h, 83%; (c) Ph_3PEtI, *n*-BuLi, THF, I_2, –78 °C to –20 °C, 20 min; then NaHMDS, THF, 2 min; then **9**, THF, –78 °C to r.t., 4.5 h, 12%; (d) CBr_4, PPh_3, Et_3N, CH_2Cl_2, r.t., 30 min, 84%; (e) MeLi, CuI, Et_2O, 0 °C then r.t., 30 min, then **10**, Et_2O, –90 to –70 °C, 1 h, then I_2, THF, r.t., 45 min, 72%.

This Zhao olefination reaction has been employed by Smith,[15] Marshall,[16] and the Novartis group[17] on related substrates in their syntheses of discodermolide, delivering the corresponding (*Z*)-vinyl iodides in modest yields. In our hands, however, the reaction proved even more troublesome and provided **2**[18] in only 12% yield. To circumvent this restrictive step, aldehyde **9** was converted into dibromoolefin **10**[19] in order to install the critical (*Z*)-alkenyl iodide using the procedure reported by Tanino and Miyashita.[20] Thus, treatment of **10** with an excess amount of Me_2CuLi (4.5 equiv) generated stereoselectively a (*Z*)-vinyl copper species which was trapped with iodine to afford **2** in 72% yield along with 14% of the *E*-isomer. It should be noted that this particular reaction required extensive investigation of the experimental parameters before achieving a satisfactory result. Indeed, variations in reaction time, temperature, or Me_2CuLi amount resulted invariably in lower yields of **2**. Not only lower conversions were usually observed but the corresponding 1,1-dimethylalkene as well as the (*Z*)-alkenyl bromide were also formed in addition to the (*E*)-alkenyl iodide. Starting from the common precursor **4**, the C9–C14 (**2**) subunit of discodermolide was thereby generated in four steps in 40% overall yield.

Preparation of the C1–C7 subunit (**1**) began with a four-step sequence from **4** to afford the β-keto ester **12** required for the diastereoselective hydrogenation reaction to install the C5 hydroxy-bearing stereocenter (Scheme 4).



Scheme 4 Synthesis of the C1–C7 (**1**) subunit of discodermolide. *Reagents and conditions*: (a) DBAL-H, toluene, –78 °C to –60 °C, 2 h, 78%; (b) Dess–Martin periodinane, CH_2Cl_2, 0 °C to r.t., 3.5 h, 95%; (c) LDA, *t*-BuOAc, THF, –78 °C, 15 min, 99%; (d) Dess–Martin periodinane, CH_2Cl_2, 0 °C to r.t., 1.5 h, quant.; (e) H_2 (80 bar), 4 mol% [{RuCl[(*R*)-SYNPHOS]}(μ-Cl)$_3$][Me_2NH_2], MeOH, r.t., 22 h, 94%, 99% de; (f) MOMCl, DIPEA, CH_2Cl_2, 0 °C to r.t., 22 h, 82%; (g) $LiAlH_4$, Et_2O, r.t., 3.5 h, 97%; (h) Ac_2O, DMAP, pyridine, CH_2Cl_2, r.t., 30 min, 99%; (i) H_2 (1 atm), Pd/C (5%), THF, r.t., 25 min, quant.; (j) $NaIO_4$, $RuCl_3$, MeCN–CCl_4–H_2O, r.t., 2 h; (k) MeI, K_2CO_3, DMF, r.t., overnight, 76% (2 steps); (l) K_2CO_3, MeOH, r.t., 30 min, 84%; (m) PPTS, *t*-BuOH, 80 °C, overnight, 58%; (n) Dess–Martin periodinane, CH_2Cl_2, 0 °C to r.t., 6 h, 69%.

First, conversion of **4** into aldehyde **11** was performed using a hydride reduction–Dess–Martin oxidation sequence. Addition of lithio *tert*-butyl acetate to **11** afforded the corresponding β-hydroxy ester as a mixture of diastereomers (7:3 in favor of the undesired Felkin *syn*-product) which was directly subjected to Dess–Martin oxidation, leading to compound **12** in quantitative yield. The following hydrogenation reaction was initially performed in methanol at 80 °C under 80 bar of hydrogen, using 2 mol% of the chiral complex {Ru[(*R*)-SYNPHOS]Br_2}. However, under these conditions, the expected β-hydroxy ester **13** was obtained in only 52% yield along with recovered starting material as well as some transesterified hydrogenated product. Variation of the reaction conditions (temperature, hydrogen pressure, reaction time, solvent, and/or catalyst loading) did not allow any improvement. As the use of {Ru[(*R*)-SYNPHOS]Br_2} in the hydrogenation reaction failed to afford reasonable yields of **13**, we tried an Ikariya-type complex[21] bearing (*R*)-SYNPHOS as a ligand.[22] The reaction was conducted in methanol at room temperature under 80 bar of hydrogen using 1 mol% of the complex [{RuCl[(*R*)-SYNPHOS]}(μ-Cl)$_3$][Me_2NH_2]. Under these conditions, the corresponding β-hydroxy ester was obtained in 68% yield with no transesterification product observed. Finally, using 4 mol% of the ruthenium complex under the otherwise aforementioned conditions, the hydrogenation reaction proceeded in a satisfactory 94% yield and with a high level of diastereoselectivity (99% de, as determined by HPLC analysis). Having compound **13** in hand, a few functional transformation steps remained in order to obtain aldehyde **1**. Thus, after MOM protection, the ester function was reduced to the corresponding alcohol which was acylated to furnish compound **14**. The benzyl ether was then converted into ester **15** by deprotection of the primary alcohol, $RuCl_3/NaIO_4$ oxidation and methylation of the resulting carboxylic acid. After hydrolysis of the acetate function, access to compound **1** required a lactonization step. To this end, **16** was treated with a catalytic amount of PPTS in refluxing *tert*-butanol, which resulted in cleavage of the MOM ether and subsequent lactonization at the C5 position. Finally, Dess–Martin oxidation of **17** completed the synthesis of the C1–C7 fragment (**1**)[23] of discodermolide which was thereby prepared in 14 steps from **4** in 14% overall yield.

In conclusion, discodermolide subunits **1** and **2** have been efficiently prepared from a common precursor **4**, possessing a *syn*,*anti* methyl–hydroxy–methyl stereotriad. The C3, C5, and C11 hydroxy-bearing stereocenters have been set through ruthenium-promoted asymmetric hydrogenation reactions using SYNPHOS as a ligand. This route provides good yields and high levels of diastereoselectivity. Efforts are currently under way to complete the C15–C24 subunit of discodermolide as well.

Acknowledgment

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(18) **Spectroscopic Data for Compound 2**
$[\alpha]_D^{25}$ +3.6 (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 5.22 (dq, *J* = 9.1, 1.1 Hz, 1 H), 4.32 (dd, *J* = 7.0, 4.1 Hz, 1 H), 2.64 (qd, *J* = 7.1, 4.1 Hz, 1 H), 2.43–2.50 (m, 1 H), 2.42 (d, *J* = 1.1 Hz, 3 H), 1.45 (s, 9 H), 1.19 (d, *J* = 7.1 Hz, 3 H), 1.10 (br s, 18 H), 0.98–1.15 (m, 3 H), 1.01 (d, *J* = 7.0 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.0, 137.6, 100.3, 80.2, 75.7, 47.1, 45.3, 33.7, 28.1, 18.3, 16.1, 13.1, 10.9. IR (film): 1732, 1640, 1257, 883 cm^{-1}. MS (DCI/NH_3): *m/z* = 551 $[M + H]^+$, 472 $[M + NH_4t\text{-}Bu]^+$.

(19) **Spectroscopic Data for Compound 10**
$[\alpha]_D^{25}$ +5.5 (*c* 1.05, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 6.23 (d, *J* = 9.8 Hz, 1 H), 4.28 (dd, *J* = 6.8, 4.1 Hz, 1 H), 2.52–2.67 (m, 2 H), 1.47 (s, 9 H), 1.13 (d, *J* = 7.2 Hz, 3 H), 1.10 (s, 18 H), 1.04–1.13 (s, 3 H), 1.07 (d, *J* = 7.0 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.7, 140.8, 88.8, 80.7, 75.1, 46.9, 42.0, 28.2, 18.2, 15.5, 13.1, 9.4. IR (film): 1733, 1460, 1255, 882 cm^{-1}. MS (DCI/NH_3): *m/z* = 529 $[M + H]^+$. Anal. Calcd for $C_{21}H_{40}Br_2O_3Si$: C, 47.73; H, 7.63. Found: C, 47.81; H, 7.51.

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(23) **Spectroscopic Data for Compound 1**
$[\alpha]_D^{25}$ –2.5 (*c* 0.8, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 9.85 (dd, *J* = 2.5, 1.3 Hz, 1 H), 4.91 (ddd, *J* = 10.5, 7.4, 4.0 Hz, 1 H), 3.87 (t, *J* = 2.3 Hz, 1 H), 2.80 (td, *J* = 7.5, 2.3 Hz, 1 H), 2.78 (td, *J* = 16.7, 4.0, 1.3 Hz, 1 H), 2.68 (ddd, *J* = 16.7, 7.4, 2.5 Hz, 1 H), 2.04–2.15 (m, 1 H), 1.28 (d, *J* = 7.5 Hz, 3 H), 0.98–1.10 (m, 24 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.5, 173.1, 76.3, 75.0, 46.5, 44.4, 33.6, 18.1, 16.7, 13.9, 12.7. IR (film): 2731, 1735, 1223, 883 cm^{-1}. MS (DCI/NH_3): *m/z* = 360 $[M + NH_4]^+$, 343 $[M + H]^+$.