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TETRAHEDRON: *ASYMMETRY*

Convenient syntheses of (2*R*,3*S*,4*R*)-3-(*tert*-butyldimethylsilanyloxy)-2,4-dimethyl-5-oxopentanoic acid methoxymethylamide from methacrolein. Preparation of C1–C7 and C17–C24 fragments of (+)-discodermolide

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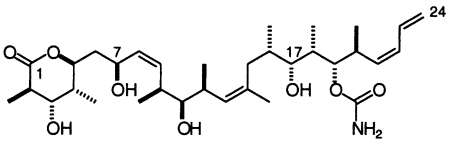
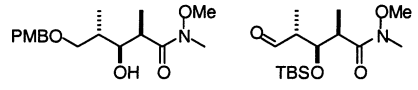
Abstract—Two new highly stereoselective routes to (2*R*,3*S*,4*R*)-3-(*tert*-butyldimethylsilanyloxy)-2,4-dimethyl-5-oxopentanoic acid methoxymethylamide, an important intermediate in natural product synthesis, are described. Both schemes are considerably shorter and less expensive than methods previously reported. The title compound was then converted to direct precursors of C1–C7 and C17–24 fragments of the potent microtubule stabilizer (+)-discodermolide.

1. Introduction

The unique natural product (+)-discodermolide is a C24:4 fatty acid lactone bearing three (*Z*)-double bonds, four hydroxy groups, eight methyl substituents, a carbamate moiety and thirteen stereogenic centers (Fig. 1). It was originally isolated from the Caribbean deep sea sponge *Discodermia dissoluta*[1] and was initially proposed to be a potential immunosuppressant.[2–4]



(+)-Discodermolide



(–)-CP 1

Figure 1.

Its mechanism of action, however, was first predicted computationally, then shown biochemically and in cell culture to involve potent induction of tubulin assembly and stabilization of microtubules,[5,6] properties that lead to cell cycle arrest at mitosis and death by apoptosis.[7–10] The microtubule-based actions of (+)-discodermolide are superior to those of other mechanistically-related agents like paclitaxel (Taxol). This, coupled with its effectiveness against paclitaxel- and other multidrug-resistant cancers, make it a promising candidate for clinical development as a chemotherapeutic agent.[9,11,12] (+)-Discodermolide is, however, present in only minute quantities in the sponge, which is itself difficult to obtain. Several ingenious total syntheses of both (+)-discodermolide and its less active (–)-enantiomer have been reported.[13–22] The development of an economical synthetic route to (+)-discodermolide, as well as to simpler and more diverse analogs, is therefore an important goal in the medicinal chemistry of this agent.

Smith et al. achieved the herculean task of preparing (+)-discodermolide on gram scale by constructing a common precursor [(–)-**CP**: (2*R*,3*S*,4*S*)-3-hydroxy-5-(4-methoxybenzyloxy)-2,4-dimethylpentanoic acid methoxymethylamide] to all three subunits of the molecule.[17] In one branch of their synthesis, (–)-**CP** was further elaborated by TBS protection, PMB group removal by hydrogenolysis with catalytic $Pd(OH)_2/C$

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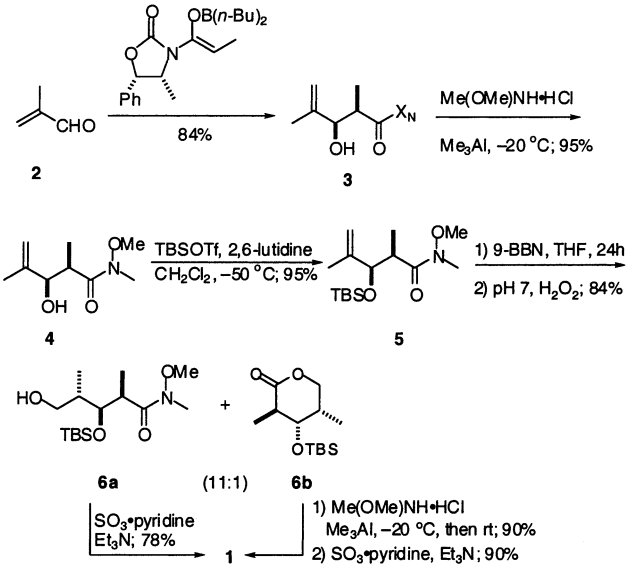
and subsequent oxidation of the resulting primary alcohol to furnish (2*R*,3*S*,4*R*)-3-(*tert*-butyldimethylsilanyloxy)-2,4-dimethyl-5-oxopentanoic acid methoxymethylamide **1**. Their routes to **1** from the starting material, (*S*)-3-hydroxy-2-methylpropionic acid methyl ester (aka 'Roche ester'), were performed in seven or eight steps with a very respectable overall yield of 45–50%. Having repeated these methods at various molar scales, we found them to possess certain drawbacks, including, among others,[23,24] the fact that the starting Roche ester is expensive. We envisaged **1** to be an important intermediate in our preparation of various versions of the left side lactone and right side diene displays of (+)-discodermolide for analogue building, and therefore sought a more efficient and economical synthesis of **1**.

2. Results and discussion

We reasoned that all stereochemistry in the target molecule could be selectively and reliably installed, and originate entirely from the easily recyclable chiral auxiliaries developed by Evans.[24] Thus, the boron enolate derived from the acylated oxazolidinone derivative of (1*S*,2*R*)-norephedrine was reacted with inexpensive methacrolein **2** to give the desired aldol product **3** in 85% yield as the sole diastereomer (Scheme 1).[25] Reaction of **3** with Me_3Al and Me(OMe)NH·HCl[26,27] yielded the Weinreb amide **4**, whose secondary hydroxyl group was silyl protected with TBSOTf to give compound **5**.[28] *gem*-Disubstituted olefins can be converted to primary alcohols with high levels of *anti* or *syn* diastereoselectivity between the newly formed and pre-existing stereocenters by using 9-borabicyclo[3.3.1]nonane (9-BBN) or catecholborane/$RhCl(Ph_3P)_3$ (Wilkinson's catalyst), respectively.[29–32] Hydroboration of the terminal alkene moiety in **5** with 9-BBN in THF therefore gave the desired *anti* intermediate **6a** in good yield (85%) as a 9:1–11:1 mixture with a minor product **6b**, a δ-lactone also encountered in the Smith synthesis as a byproduct in their hydrogenolysis reaction.[17] Oxidation of alcohol **6a** with SO_3·pyridine then afforded aldehyde **1**. Compound **1** was identical in all respects with that reported, with the only exception being a minor difference in optical rotation ($[\alpha]_D^{18}$ −54.1 (*c* 0.79, $CHCl_3$) for one batch, $[\alpha]_D^{18}$ −57.0 (*c* 13.5, $CHCl_3$) for another; lit.[17] $[\alpha]_D^{23}$ −65.0 (*c* 1.38, $CHCl_3$)).



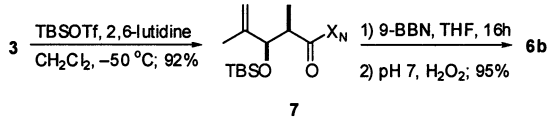
Scheme 1. New 'second generation' synthesis of **1**.

This 'second generation' five-step preparation of **1** was achieved in an overall yield of 50% with no attempts to optimize reaction conditions. This is comparable to the yields reported previously,[17] but is at least two steps shorter. Furthermore, using prices from the most common chemical vendors in the calculation, the route in Scheme 1 via **6a** allows the synthesis of **1** for one-half the cost necessary to prepare **1** by the method reported in Ref. 17.

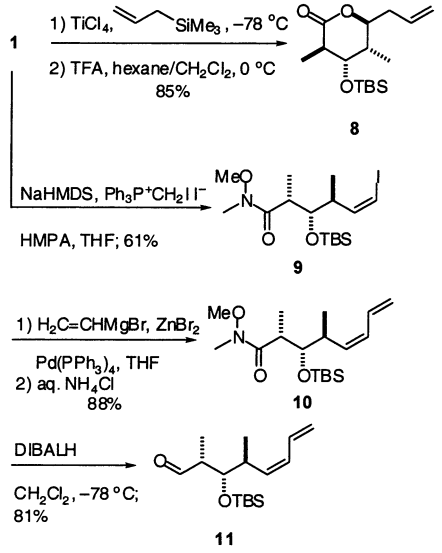
The δ-lactone **6b** from the hydroboration reaction was easily 'recycled' to **1** by reproducible ring-opening Weinreb amide formation followed by oxidation with SO_3·pyridine. The formation of **6b**, which is a solid,[33] in the hydroboration reaction led to the supposition that the Weinreb amide formation could be postponed in the synthesis of **1**. We reasoned that the more easily displaced Evans auxiliary might, if used in place of a Weinreb amide, lead directly to **6b** during hydroboration. Therefore, the auxiliary-bearing aldol adduct **3** was TBS protected to give intermediate **7**. Compound **7** was converted, as envisioned, directly and in high yield (95%) by reaction with 9-BBN to **6b** (Scheme 2), which was converted to **1** by the methods outlined above. Thus, this 'third generation' route to **1** via **6b** is also a five-step preparation that leads to an overall yield of 60%, again without attempts to optimize yields, and at a lower cost even than our 'second generation' synthesis.

Compound **1** was then elaborated to the direct precursors of the C1–C7 and C17–C24 fragments of (+)-discodermolide (Scheme 3). Allyltrimethylsilane was added with anti-Felkin selectivity (>50:1) to **1** in a $TiCl_4$-promoted reaction.[17] The product was cyclized with TFA in hexane/CH_2Cl_2 to afford the left side, C1–C7 fragment of (+)-discodermolide, lactone **8** ($[\alpha]_D^{18}$ +13.8 (*c* 1.30, $CHCl_3$); lit.[17] $[\alpha]_D^{23}$ +14.2 (*c* 0.12, $CHCl_3$)) in 85% yield from **1**.

As further proof of principle, **1** was converted to the right side C17–C24 fragment of (+)-discodermolide in three steps. Compound **1** was transformed to the (*Z*)-vinyl iodide **9** in 61% yield by Stork's procedure,[34] then to diene **10** in 88% yield via palladium-catalyzed reaction with vinyl zinc bromide.[35] The Weinreb amide was then readily cleaved with DIBALH to give aldehyde **11** in 81% yield.



Scheme 2. 'Third generation' synthetic route.



Scheme 3. Elaboration of **1** to the lactone and diene displays of (+)-discodermolide.

3. Conclusions

Methods used in previous syntheses of discodermolide subunits have all relied upon an enantiomerically pure substrate, most often the Roche ester, as a starting material for stereoselective introduction of substituents by various methodologies. Schreiber's group utilized the separate additions of Roush's (*E*)- and (*Z*)-crotyl boronates to the Roche ester in their synthesis.[13,14] Marshall and Johns used chiral allenyl metal reagents in homoaldol reactions with the Roche ester to prepare alkyne intermediates to the subunits.[19] Paterson et al. prepared early intermediates in their recent full synthesis through boron-mediated *anti*-selective aldol reaction of chiral ketones built from the Roche ester and (*S*)-ethyl lactate.[20–22] With the exception of the Smith procedure,[15–17] all other methods have suffered at least one point in the synthetic scheme from the appearance of a substantial level of undesired diastereomers. The methods reported here rely solely on the Evans auxiliary for introduction of all stereochemistry and, at least for preparation of left- and right-side arrays of discodermolide, give no undesired diastereomer output.

In summary, we have achieved two less costly and more expedient syntheses of an important intermediate in the preparation of (+)-discodermolide displays. These two new stereoselective routes have several advantages, including an overall shortening of the number of operations required to synthesise **1**, the elimination of the costly Roche ester from the synthetic scheme, and provide alternatives for the timing of introduction of the Weinreb amide protecting group. These improvements are noteworthy and could significantly lower the cost of producing **1** and the products derived from it. These routes and displays will be useful in the medicinal chemistry of (+)-discodermolide, a rare natural product with exciting anti-cancer potential.

4. Experimental

4.1. General procedures

Reactions were carried out under a dry nitrogen atmosphere in anhydrous solvents using oven-dried glassware. Solvents and bases were distilled from CaH_2 and stored under argon over 4 Å molecular sieves or CaH_2. Methacrolein was distilled immediately prior to use. Melting points were determined on a Fisher–Johns open stage apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on Varian Mercury 400 spectrometer at 400 and 100 MHz, respectively, with compounds dissolved in $CDCl_3$. Chemical shifts are reported in ppm downfield from tetramethylsilane with the solvent resonance acting as the internal standard (residual $CHCl_3$ in $CDCl_3$ δ 7.26 ppm in ^1H spectra; $CDCl_3$ δ 77.0 ppm in ^{13}C spectra). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constant (Hz), integration. ^{13}C NMR spectra were recorded with complete proton decoupling. Gas chromatography–mass spectrometry (GC–MS) was carried out on a Hewlett Packard 5890 Series II gas chromatograph equipped with a 30 m HP-5 (5% phenyl methylsilicone) Hewlett Packard capillary column and a Hewlett Packard 5971 mass selective detector in the positive chemical ionization (PCI) mode using CH_4 as the reagent bath gas. Low and high resolution electron ionization (EI) mass spectra (LRMS and HRMS) were determined on a Micromass Autospec double focusing instrument by direct insertion probe at the High Resolution Mass Spectrometry Facility at the Department of Chemistry, University of Pittsburgh. Optical rotations were recorded on a Perkin–Elmer 241 digital polarimeter with a sodium lamp at ambient temperature and are reported as follows: $[\alpha]^{^\circ C}_{\lambda}$ (cg/100 mL). Only new entities are described below. All data reported is from chromatographically homogeneous compounds.

4.1.1. (3*R*,4*S*,5*S*)-4-(*tert*-Butyldimethylsilanyloxy)-3,5-dimethyltetrahydropyran-2-one 6b. A solution of 9-BBN (132 mL, 66 mmol, 0.5 M in THF) was treated with (4*R*,5*S*)-3-[(3*R*,4*R*)-3-(*tert*-butyldimethylsilanyloxy)-2,4-dimethylpent-4-enoyl]-4-methyl-5-phenyloxazolidin-2-one **7** (9.2 g, 22 mmol) in THF (60 mL). The reaction mixture was stirred at rt for 24 h, then treated sequentially with 1:1 EtOH–THF (8 mL), 50 mM phosphate buffer (pH 7, 8 mL) and 30% aq. H_2O_2 (8 mL) and then stirred for 12 h at rt. The mixture was extracted with diethyl ether (3×30 mL). The combined organic layers were washed with H_2O (20 mL) and saturated aq. NaCl (20 mL) then dried over $MgSO_4$. Filtration, concentration in vacuo and purification by flash chromatography (4:1 hexanes–ethyl acetate) gave **6b** as a white crystalline solid (5.4 g, 94%). Mp: 55–55.5°C (pentane); $[\alpha]_D^{18}$ +20.4 (*c* 0.22, $CHCl_3$); ^1H NMR δ 4.30 (m, 1H), 4.12 (m, 1H), 3.66 (t, J = 3.7, 1H), 2.68 (dq, J = 7.9, 1H), 2.14 (m, 1H), 1.25 (d, J = 7.9, 3H), 0.93 (d, J = 7.5, 3H), 0.85 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR δ 173.7, 73.5, 70.1, 43.6, 30.3, 25.7, 17.9, 16.2, 12.0; GC–MS (PCI) m/z (relative abundance, %): 259 ([M+H]$^+$, 26), 157 (18), 145 (17), 127 (95), 115 (39), 99 (15),

83 (100), 75 (59); LRMS (EI) m/z (relative abundance, %): 201 ($M-C_4H_9^{+\bullet}$, 15), 171 (7), 157 (70), 145 (93), 115 (86), 101 (9), 99 (10), 85 (11) 75 (100), 73 (49), 59 (37); HRMS (EI) m/z 201.0947 found ($M-C_4H_9^{+\bullet}$), 201.0941 calculated for $C_9H_{17}O_3Si$.

4.1.2. (2*R*,3*S*,4*S*,5*Z*)-3-(*tert*-Butyldimethylsilanyloxy)-6-iodo-2,4-dimethylhex-5-enoic acid methoxymethylamide 9. A suspension of (iodomethyl)triphenylphosphonium iodide (2.90 g, 5.36 mmol) in THF (15 mL) was treated with NaHMDS (1.0 M in THF, 5.36 mL, 5.36 mmol) and the resulting solution was stirred for 20 min at rt. The resulting dark red solution was cooled to −78°C and HMPA (1.2 mL) was added followed by (2*R*,3*S*,4*R*)-3-(*tert*-butyldimethylsilanyloxy)-2,4-dimethyl-5-oxopentanoic acid methoxymethylamide **1** (0.85 g, 2.68 mmol) in THF (5 mL). After 20 min of stirring at −78°C, the reaction mixture was warmed to rt and stirred for an additional 1 h. The mixture was diluted with hexane (20 mL), filtered through silica gel (60 g), and concentrated in vacuo. Chromatography of the resulting residue (10:1 hexane–diethyl ether) afforded **9** (720 mg, 61%). $[\alpha]_D^{18}$ +65.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 6.35 (dd, $J=7.3$, 8.7 Hz, 1H), 6.20 (d, $J=7.3$ Hz, 1H), 3.97 (d, $J=9.6$ Hz, 1H), 3.7 (s, 3H), 3.18 (s, 3H), 2.82 (unresolved m, 1H), 2.63 (ddq, $J=$ 10.3, 3.3, 7.0 Hz, 1H), 1.14 (d, $J=7.0$ Hz, 3H), 1.01 (d, $J=6.9$ Hz, 3H), 0.94 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H). ^{13}C NMR δ 142.5, 82.7, 76.3, 61.2, 44.4, 26.2, 22.6, 18.4, 17.4, 15.4, −3.4, −3.5; GC–MS (PCI) m/z (relative abundance, %): 442 ($[M+H]^+$, 31), 426 (32), 384 (74), 310 (55), 260 (100), 57 (79); LRMS (EI) m/z (relative abundance, %): 441 ($M^{+\bullet}$, 1), 426 (3), 384 (7), 188 (18), 181 (28), 75 (56), 73 (60), 59 (45), 57 (100); HRMS (EI) m/z: 441.1212 found ($M^{+\bullet}$), 441.1196 calculated for $C_{16}H_{32}NO_3SiI$.

4.1.3. (2*R*,3*S*,4*S*,5*Z*)-3-(*tert*-Butyldimethylsilanyloxy)-2,4-dimethylocta-5,7-dienoic acid methoxymethylamide 10. Vinylmagnesium bromide (1.0 M in THF, 6.35 mL, 6.35 mmol) was added to a solution of $ZnBr_2$ (1.43 g, 6.35 mmol) in THF (5 mL) under argon and the white slurry was stirred for 15 min at rt. The resulting gray reaction mixture was cooled to 0°C and treated with vinyl iodide **9** (0.70 g, 1.59 mmol) in THF (3 mL) followed by addition of $Pd(PPh_3)_4$ (0.18 g, 0.16 mmol) in THF (8 mL). The mixture was stirred and allowed to warm to rt. After 24 h at rt, the reaction was quenched by the addition of saturated aq. NH_4Cl (30 mL). The aqueous layer was separated and extracted with hexane (3×20 mL). The combined organic layers were washed with saturated aq. NaCl (30 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. Flash chromatography of the residue (20:1 diethyl ether–hexane) provided **10** (480 mg, 88%). $[\alpha]_D^{18}$ +53.2 (*c* 0.01, $CHCl_3$); ^{1}H NMR δ 6.50 (ddd, $J=16.7$, 10.6, 10.2 Hz, $1H_7$), 6.01 (dd, $J=11.4$, 11.4 Hz, $1H_6$), 5.62 (dd, $J=10.4$, 10.4 Hz, 1H), 5.17 (d, $J=17.0$ Hz, 1H), 5.07 (d, $J=10.7$ Hz, 1H), 3.93 (d, $J=10.8$ Hz, 1H), 3.61 (s, 3H), 3.13 (s, 3H), 2.85–2.78 (m, 2H), 1.13 (d, $J=7.2$ Hz, 3H), 1.03 (d, $J=7.0$ Hz, 3H), 0.94 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR δ 133.9, 132.7, 129.6, 117.1, 61.0, 36.7, 26.2, 26.1, 19.4, 18.5, 15.4, −3.4, −3.5; GC–MS (PCI) m/z (relative abundance, %): 342 ($[M+H]^+$, 45), 326 (58), 284 (61), 260 (57), 210 (100); LRMS (EI) m/z (relative abundance, %): 341 ($M^{+\bullet}$, 1) 326 (4), 284 (66), 260 (73), 204, 149, 73; HRMS (EI) m/z: 341.2398 found ($M^{+\bullet}$), 341.2386 calculated for $C_{18}H_{35}NO_3Si$.

4.1.4. (2*R*,3*S*,4*S*,5*Z*)-3-(*tert*-Butyldimethylsilanyloxy)-2,4-dimethylocta-5,7-dienal 11. A solution of amide **10** (0.45 g, 1.32 mmol) in THF (10 mL) was treated with DIBALH (1 M in hexanes, 2.77 mL) at −78°C. The solution was stirred at −78°C for 2 h, then treated with CH_3OH (2 mL) followed by saturated aqueous solution of Rochelle's salt (10 mL). The mixture was diluted with ethyl acetate (20 mL) and stirred for 3 h at ambient temperature. The organic phase was separated, washed with saturated aq. $NaHCO_3$ and saturated aq. NaCl, dried over $MgSO_4$, filtered and concentrated under vacuum. Flash chromatography of the residue (20:1 hexane–diethyl ether) provided **11** (300 mg, 81%). $[\alpha]_D^{18}$ −16.7 (*c* 1.30, $CHCl_3$) ^{1}H NMR δ 9.76 (s, 1H), 6.51 (ddd, $J=16.8$, 10.7, 10.6 Hz, $1H_7$), 6.0 (dd, $J=$ 11.0, 11.0 Hz, $1H_6$), 5.44 (dd, $J=10.7$, 10.7 Hz, 1H), 5.23 (d, $J=16.8$ Hz, 1H), 5.12 (d, $J=10.2$ Hz, 1H), 3.99 (dd, $J=4.7$, 4.7 Hz, 1H), 2.85 (m, 1H), 2.52–2.46 (m, 2H), 1.08 (d, $J=7.0$ Hz, 3H), 1.04 (d, $J=6.7$ Hz, 3H), 0.91 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR δ 204.2, 133.2, 132.1, 130.4, 118.2, 75.9, 51.5, 36.2, 25.9, 18.7, 18.2, 9.5, −4.1, −4.2; GC–MS (PCI) m/z (relative abundance, %): 283 ($[M+H]^+$, 3), 267 (8), 225 (100), 201, (19), 151 (25), 123 (18), 107 (27), 95 (7), 93 (14), 81 (11), 75 (6), 73 (4); LRMS (EI) m/z (relative abundance, %): 225 ($M-C_4H_9^{+\bullet}$, 52), 201 (73), 173 (44), 145 (33), 115 (77), 93 (32), 81 (30), 75 (65) 73 (100), 59 (45); HRMS (EI) m/z: 225.1302 found ($M-C_4H_9^{+\bullet}$), 225.1311 calculated for $C_{12}H_{21}O_2Si$.

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