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A short synthesis of the C_{15}–C_{21} segment of (+)-discodermolide, based on an asymmetric approach from achiral 2-methyl-1,3-propanediol to versatile enantiopure stereotriads

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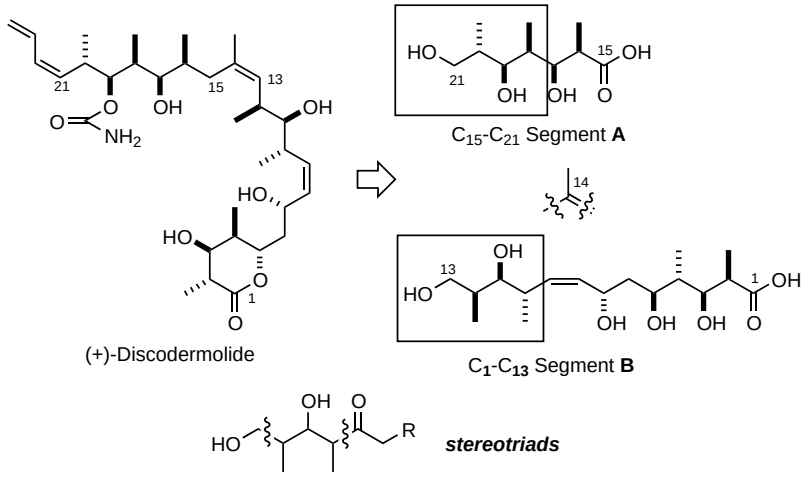
Abstract—A new approach was developed to versatile enantiopure stereotriads using chiral oxazaborolidinone-promoted asymmetric aldol reaction of a racemic aldehyde with a bromo silyl nucleophile. A short synthesis of the C_{15}–C_{21} segment of (+)-discodermolide was achieved by elongation of one of the stereotriads with further diastereoselective aldol reaction with the same nucleophile. © 2002 Elsevier Science Ltd. All rights reserved.

(+)-Discodermolide is a polypropionate-derived natural product known as a potent microtubule-stabilizing agent which retains activity against Taxol®-resistant cancer.[1] Due to the potential therapeutic development and the extreme scarcity of the natural product, the chemical synthesis of this compound is necessary, especially for making possible its supply in large scale. Although the total syntheses of (+)- and (−)-isomers were achieved by several groups to date,[2] the highly stereoselective construction of the complex framework is still a challenging and attractive target for synthetic chemists. Our retrosynthetic analysis dissected the target molecule at both sides of C-14 to generate segments **A** and **B**, which contain the necessary 13 stereogenic centers (Scheme 1). A two-carbon unit at C-14 is incorporated into segment **B** as a (*Z*)-vinyl iodide by



Scheme 1.

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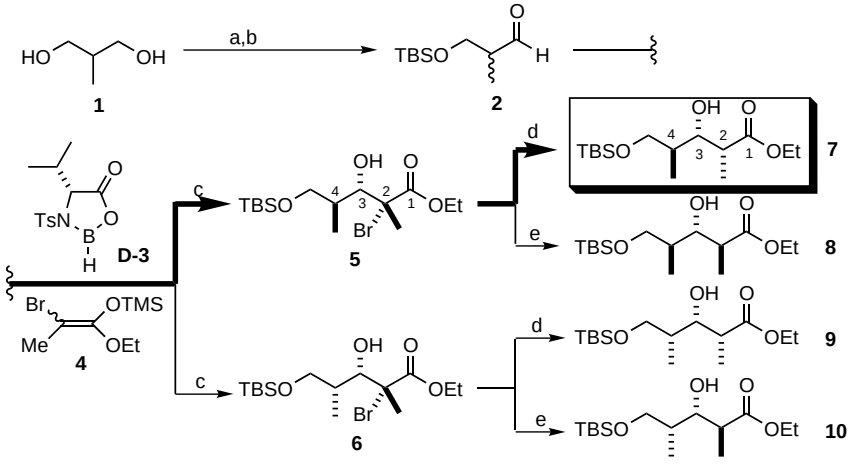
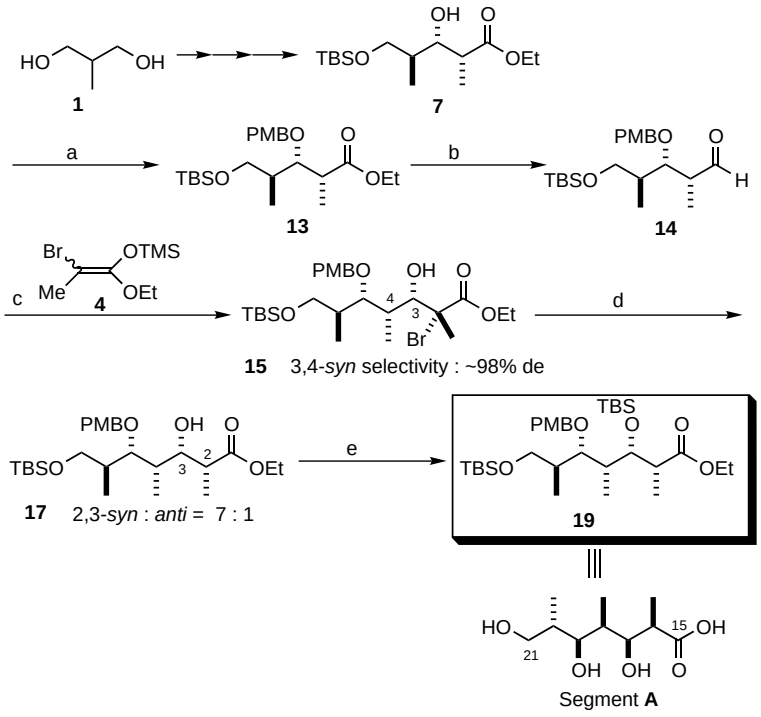
the known method[2d,2e,3] before the developed palladium(0) cross-coupling reaction between C-13 and C-14. Segments **A** and **B** have similar fragments, as depicted by squares in Scheme 1, which bound to stereotriads.[4] If an easier synthetic access to enantiopure equivalents of the stereotriads is developed, it may more directly permit a systematic approach to the synthesis of polyketides containing a variety of polypropionate units. Smith has effectively utilized a stereotriad[5] as a common precursor in the total synthesis of (+)-discodermolide.[2e] We describe herein a versatile asymmetric approach from an achiral diol **1** via a racemic aldehyde, **2**, to enantiopure stereotriads, **7**∼**10**, and a short synthesis of C_{15}–C_{21} segment **A** of (+)-discodermolide by using one of them, which has the same stereochemistry with different functionality to Smith's stereotriad.

Our strategy toward the quite effective enantioselective synthesis of versatile stereotriads is designed in a sequence of the chiral oxazaborolidinone-promoted asymmetric aldol reactions of the racemic aldehyde **2**, derived from the cheap achiral diol **1**,[6] with silylketene acetal **4**[7] and the following radical debromination reaction.[8] After mono protection of **1** with TBSCl/NaH, Swern oxidation gave **2** in good yield. In the presence of a stoichiometric amount of chiral borane **D-3**, which was prepared in situ by stirring D-TsVal and BH_3·THF in CH_2Cl_2 at 0°C, the aldol reaction of **2** with **4** was carried out at −78°C for 3 h.[8] The reaction proceeded smoothly to give a mixture of products in 85% yield. The mixture was constituted of an almost 1:1 ratio of 2,3-*syn*-3,4-*anti* **5** and 2,3-*syn*-3,4-*syn* **6** with a small amount of isomers at C-2. The 2,3-*syn* selection, though considered unnecessary for the sequence, is known to be characteristic of the chiral oxazaborolidinone-promoted aldol reaction with **4**.[9] The most important point of the strategy is the almost complete selection of the stereogenic center at C-3 (>98% ee, determined by chiral HPLC), which is controlled only by the stereocenter of promoter **D-3** without any influence of the existing α-chirality of aldehyde **2**; the so-called 'catalyst (promoter) control in acyclic stereoselection'.[10] The desired **5** was easily separated by silica-gel flash column chromatography. When a solution of **5** in CH_2Cl_2 was exposed to Bu_3SnH (5 equiv.) and Et_3B (1 equiv.) in the presence of $MgBr_2$·OEt_2 (7 equiv.) at 0°C for 3 h, a smooth debromination reaction took place to give 2,3-*syn*-3,4-*anti* stereotriad **7**[11] in 80% yield. *syn* Selection (chelation control) was observed in a 10:1 ratio of *syn* and *anti*.[12] On the other hand, *anti* selection of the debromination (Bu_3SnH/Et_3B/toluene) was achieved with the corresponding MOM-protected compound in good selectivity (10:1). Although further improvement of the debromination processes is being awaited for excellent diastereoselection, our present method to give four enantiopure stereotriads, **7**∼**10**, is remarkably efficient along with easy purification (Scheme 2). Indeed, when chiral borane **L-3** (derived from L-valine) is applied to the sequence, the other four stereotriads are available.

The synthesis of a synthetic equivalent **19** to segment **A** is shown in Scheme 3. Alcohol **7** was protected with the treatment of PMBCO(=NH)CCl_3 and TfOH to the corresponding *p*-methoxybenzyl ether **13** in 67% yield. DIBALH reduction of **13** gave directly aldehyde **14**. The BF_3·OEt_2-mediated diastereoselective aldol reaction (CH_2Cl_2, −78°C, 1 h) of **14** with **4** resulted in the highly 3,4-*syn* selective formation of 2,3-*syn*-3,4-*syn* aldol adduct **15**[13] in 65% yield along with very high selection at C-2.[14] The following debromination reaction (Bu_3SnH, Et_3B, CH_2Cl_2) in the presence of $MgBr_2$·OEt_2 at −78°C for 3 h[15] gave the desired 2,3-*syn*-3,4-*syn*-4,5-*syn*-5,6-*anti* compound **17**[16] in 81% yield (2,3-*syn* selectivity = 7:1). This diastereoselective sequence using the Mukaiyama aldol reaction and the



Scheme 2. *Reagents and conditions*: (a) TBSCl, NaH, THF, rt, 15 h, 88% yield. (b) $(COCl)_2$, DMSO, CH_2Cl_2, −78°C, Et_3N, 0°C, 82% yield. (c) Chiral oxazaborolidinone-promoted aldol reaction of **2** with **4** in the presence of a stoichiometric amount of D-3 in CH_2Cl_2 at −78°C for 3 h gave a 1:1 mixture of enantiopure **5** and **6** in 85% yield and then by using flash column chromatography **5** was easily separated. (d) Bu_3SnH, Et_3B, $MgBr_2$·OEt_2 at 0°C for 3 h: Chelation-controlled debromination resulted in good 2,3-*syn* selection. With *syn* selection (10:1) **7** was obtained in 80% yield. (e) Bu_3SnH, Et_3B: After MOM protection of hydroxy group at C-3, 2,3-anti stereoisomer was predominantly obtained.



Scheme 3. *Reagents and conditions*: (a) $PMBCO(=NH)CCl_3$, TfOH, Et_2O, rt, 15 h, 67% yield. (b) DIBALH, CH_2Cl_2, −78°C, 3 h, 86% yield. (c) $BF_3{\cdot}OEt_2$, **4**, CH_2Cl_2, −78°C, 1 h, 65% yield. (d) Bu_3SnH, Et_3B, CH_2Cl_2, $MgBr_2{\cdot}OEt_2$, −78°C, 3 h, 81% yield. (e) TBSOTf, 2,6-lutidine, 95% yield.

following debromination reaction apparently turned out to be effective as an approach to the construction of polypropionate frameworks. A similar approach also has been reported.[17] Protection of alcohol **17** was carried out without incident to TBS ether **19**, which is a synthetic equivalent of segment **A**, in 95% yield.[18]

In conclusion, a versatile, systematic asymmetric approach was developed to enantiopure stereotriads available for the synthesis of polyketides, based on catalyst (promoter) control with respect to the chiral oxazaborolidinone-promoted asymmetric aldol reaction of racemic aldehyde **2** with **4**. The above results suggest that the sequence of enantioselective and/or diastereoselectiove aldol reactions with silylketene acetal **4** and the following diastereoselective debromination reactions surely provide a practical methodology for a series of polypropionate syntheses. A short synthesis of the C_{15}–C_{21} segment of (+)-discodermolide has been achieved, based on the strategy.

Acknowledgements

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5. The Weinreb ester of 2,3-*syn*-3,4-*anti* isomer was obtained via a double differential, asymmetric aldol reaction of a chiral aldehyde with a chiral Evans' nucleophile in ~50% yield over five steps, according to a similar procedure of Heathcock, see: Clark, D. L.; Heathcock, C. H. *J. Org. Chem.* **1993**, *58*, 5878.

6. 2-Methyl-1,3-propanediol was purchased from Aldrich (1 L, ¥ 4.100; 2000–2001 catalog).
7. The silylketene acetal **4** (*Z*:*E*=3:1), which accompanies the corresponding *C*-silyl ester, by trapping the lithium enolate with TMSOTf.
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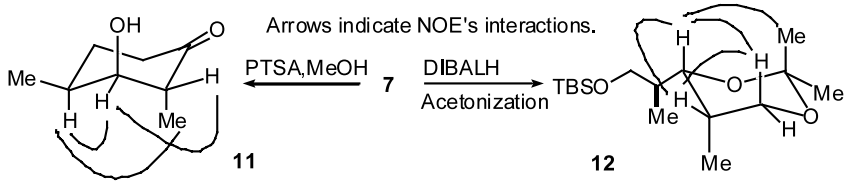
11. The stereochemistry of **7** was confirmed by *J* values and NOE measurements of **11** and **12**.



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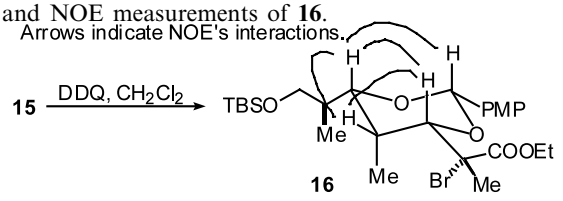
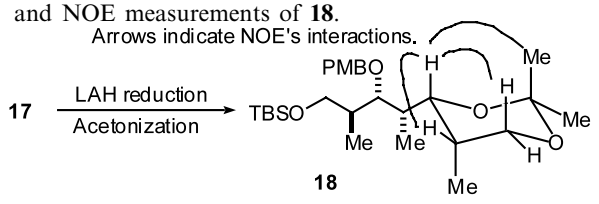
13. The stereochemistry of **15** was determined by *J* values and NOE measurements of **16**.



14. Kiyooka, S.-i.; Shahid, K. A.; Murai, K.; Li, Y.-N.; Okazaki, M.; Shuto, Y. *Tetrahedron: Asymmetry* **2001**, *12*, 2343.
15. Even in the presence of non-protected β-OH, the chelation-controlled products can be predominantly obtained (Ref. 12).
16. The stereochemistry of **17** was determined by *J* values and NOE measurements of **18**.



17. In a more simple system, the diastereoselective synthesis of 2,3-*anti*-3,4-*anti* and 2,3-*anti*-3,4-*syn* propionates has recently been reported by using a tandem sequence of Mukaiyama aldol reaction of α-methyl-β-protected-oxypropanal with a selenoenoxysilane and the following hydrogen transfer reaction: Guindon, Y.; Prévost, M.; Mochirian, P.; Guérin, B. *Org. Lett.* **2002**, *4*, 1019.
18. Spectroscopic data for selected compounds.

Compound **5**: $[\alpha]_D^{26}$ +17.5 (*c* 4.24, $CHCl_3$). IR (neat) 3528, 2935, 1720 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.0 (s, 6H), 0.80 (d, J=7.1 Hz, 3H), 0.82 (s, 9H), 1.24 (t, J=7.1 Hz, 3H), 1.69–1.82 (m, 1H), 1.82 (s, 3H), 3.60 (dd, J=10.0, 5.84 Hz, 1H), 3.72 (dd, J=10.0, 4.4 Hz, 1H), 3.91 (d, J=3.7 Hz, 1H), 4.10 (dd, J=7.1, 3.68 Hz, 1H), 4.16 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) −5.6, −5.6, 13.8, 14.8, 18.2, 22.0, 25.8, 37.9, 62.0, 67.1, 68.0, 78.1, 170.7.

Compound **7**: $[\alpha]_D^{29}$ +10.9 (*c* 2.58, $CHCl_3$). IR (neat) 3493, 2932, 1732 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.06 (s, 6H), 0.81 (s, 9H), 0.88 (d, J=6.8 Hz, 3H), 1.18 (d, J=7.1 Hz, 3H), 1.24 (t, J=7.1 Hz, 3H), 1.68–1.74 (m, 1H), 2.57 (dq, J=6.8, 2.4 Hz, 1H), 3.64 (dd, J=9.8, 6.1 Hz, 1H), 3.72 (d, J=3.7 Hz, 1H), 3.80–3.86 (m, 2H), 4.14 (q, J=7.1 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) −5.7, 10.2, 13.7, 14.1, 18.1, 25.8, 37.0, 42.8, 60.4, 67.5, 76.2, 175.7.

Compound **15**: $[\alpha]_D^{28}$ +18.2 (*c* 0.11, $CHCl_3$). IR (neat) 3539, 2955, 2932, 2858, 1736 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.06 (s, 3H), 0.07 (s, 3H), 0.85 (d, J=6.8 Hz, 3H), 0.91 (s, 9H), 0.92 (d, J=6.8 Hz, 3H), 1.34 (t, J=7.1 Hz, 3H), 1.74–1.83 (m, 2H), 1.88 (s, 3H), 2.73 (d, J=2.9 Hz, 3H), 3.48 (dd, J=9.0, 2.4 Hz, 1H), 3.60 (dd, J=9.8, 2.7 Hz, 1H), 3.80 (s, 3H), 3.82 (dd, J=9.8, 4.2 Hz, 1H), 3.17 (dd, J=2.7, 1.2 Hz, 1H), 4.18 (dq, J=7.1, 1.7 Hz, 2H), 4.39 (ABq, J=10.7 Hz, v=37.5 Hz, 2H), 6.88 (d, J=8.5 Hz, 2H), 7.29 (d, J=8.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) −5.5, −5.3, 7.7, 14.0, 14.6, 18.3, 23.1, 25.9, 36.5, 38.1, 55.3, 62.1, 64.5, 66.6, 74.4, 78.1, 85.5, 114.0, 129.6, 130.7, 159.4, 170.6.

Compound **19**: $[\alpha]_D^{24}$ +20.0 (*c* 0.10, $CHCl_3$). IR (neat) 2957, 2930, 2857, 1738 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.0 (s, 3H), 0.03 (s, 3H), 0.04 (s, 3H), 0.07 (s, 3H), 0.89 (s, 9H), 0.90 (s, 9H), 0.95 (d, J=6.8 Hz, 3H), 1.02 (d, J=6.8 Hz, 3H), 1.06 (d, J=7.1 Hz, 3H), 1.24 (t, J=7.1 Hz, 3H), 1.91–1.99 (m, 1H), 2.01–2.08 (m, 1H), 2.73 (dq, J=7.1, 5.4 Hz, 1H), 3.39 (t, J=5.6 Hz, 1H), 3.62 (dd, J=10.0, 6.6 Hz, 1H), 3.68 (dd, J=9.8, 3.9 Hz, 1H), 3.80 (s, 3H), 3.88 (t, J=5.4 Hz, 1H), 4.06–4.15 (m, 2H), 4.51 (ABq, J=11.0 Hz, v=51.8 Hz, 2H), 6.86 (d, J=8.5 Hz, 2H), 7.26 (d, J=8.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) −5.4, −5.3, −4.1, −3.9, 10.4, 14.2, 14.4, 15.3, 18.3, 18.4, 26.0, 26.1, 38.6, 38.8, 44.8, 55.3, 60.2, 64.4, 74.4, 75.4, 81.8, 113.7, 129.0, 131.5, 159.1, 174.4.