

## Multi-gram-scale synthesis of a versatile *syn-anti* stereotriad by a short and cost-effective route

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Dedicated to Professor George A. Kraus in tribute to his many contributions  
to synthetic methodology and total synthesis

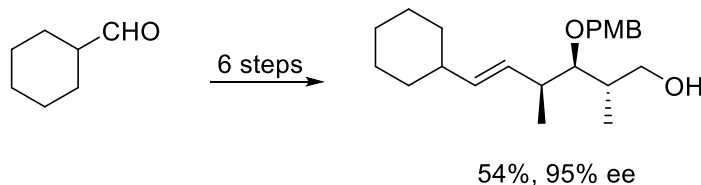
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### Abstract

The polyketide family of natural products includes numerous biologically important molecules that exhibit a variety of complex structures. The biosynthesis of these diverse structures relies on the iterative assembly of individual segments controlled by the enzymes of the polyketide synthase (PKS) family. In the synthesis laboratory, access to stereospecifically-prepared ketide building blocks can be both challenging and cost-limiting. We report an efficient, multigram-scale synthesis of the *syn-anti* synthon (2*S*,3*R*,4*S*)(*E*)-6-cyclohexyl-3-[(4-methoxybenzyl)oxy]-2,4-dimethylhex-5-en-1-ol from the commercially available cyclohexane-carboxaldehyde in excellent overall yield and purity.

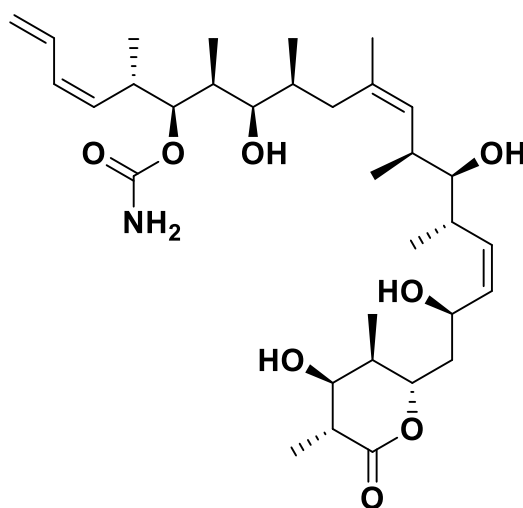


**Keywords:** Polyketides, polypropionates, enantioselection, synthon, catalysis

## Introduction

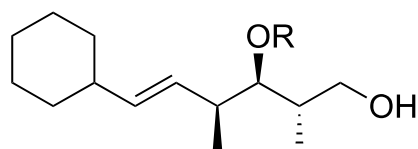
The polyketides are complex and diverse natural products.<sup>1,2</sup> Many are in drug trials<sup>1</sup> and clinical use.<sup>2</sup> About 22% of prescription drugs that are derived from natural products contain polyketide units.<sup>3</sup> The large number of asymmetric centers in most of these substances, often in contiguous runs, pose major obstacles to their synthetic construction.

The asymmetric synthesis of polyketide compounds is performed in nature by polyketide synthetases (PKSs) which direct the necessary aldol couplings, reductions, and, in some cases, dehydrations.<sup>4-6</sup> An often-used strategy in the laboratory synthesis of polyketides is the iterative coupling of small chiral building blocks.<sup>6</sup> Such syntheses, which have largely focused on stereospecificity, can be costly on a large scale.<sup>7,8</sup> For example, the practical total synthesis of discodermolide (Figure 1), a marine polyketide, remains a formidable challenge. We describe the multi-gram, catalytic, asymmetric preparation of stereotriad (**1a**) by a six-step route that offers convenience and promises further scalability.



**Figure 1.** The natural polyketide (+)-discodermolide.

In earlier work on an approach to discodermolide, we designed the chiral *syn-anti* stereotriad (**1**) and reported a small-scale, five-step, catalytic asymmetric preparation of the *syn-anti* stereotriad building blocks (**1b**) and (**1c**).<sup>9-11</sup> These synthons and their equivalents offer particularly attractive options for extending the polyketide chain in both directions. Of special note is the potential for ozonolysis as a method of liberating an aldehyde at one terminus.



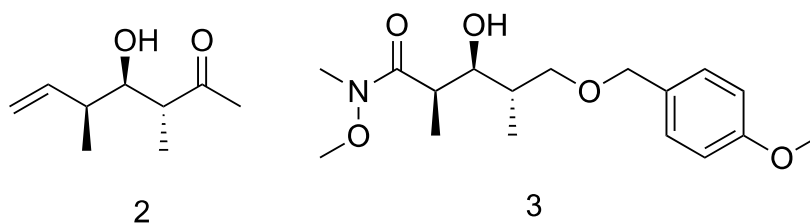
1a: R = PMB

1b: R = TES

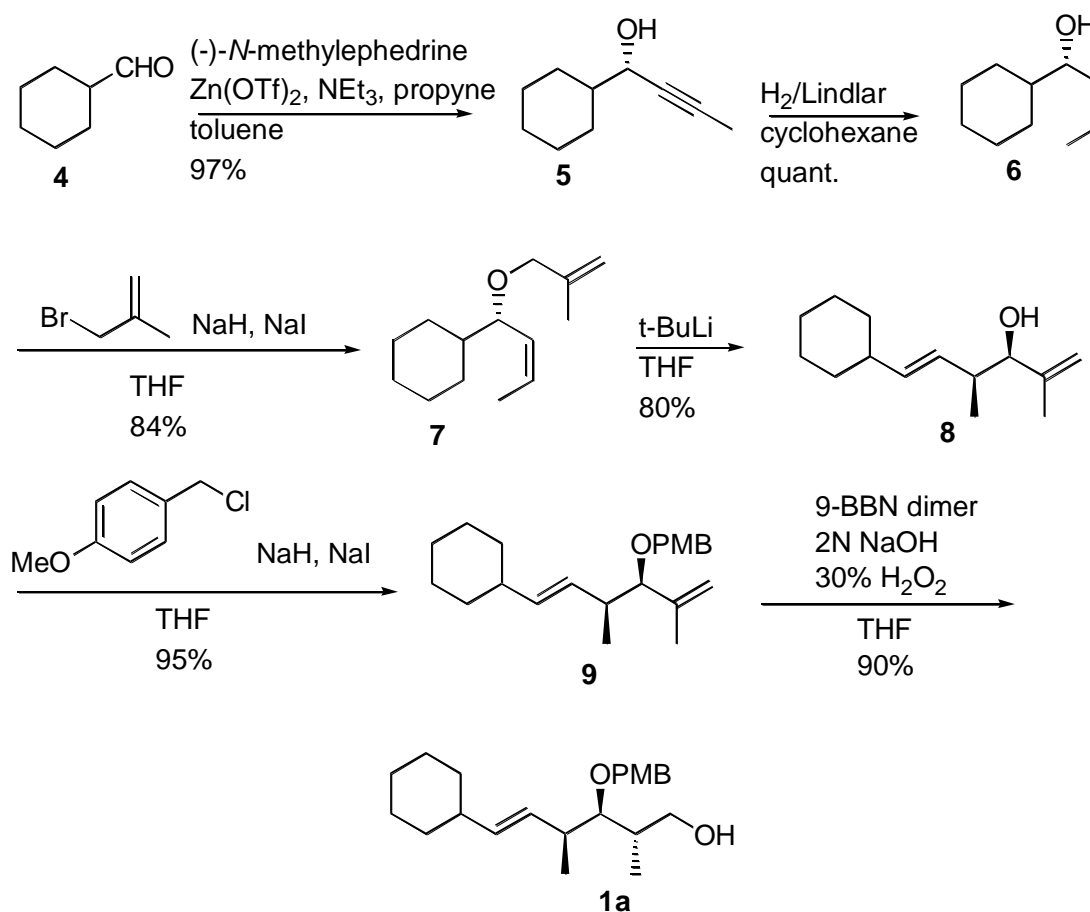
1c: R = MOM

To date, the *syn-anti* stereotriad unit (**2**) from Leighton,<sup>12,13</sup> (**3**) from Smith,<sup>14,15</sup> and the identical Novartis-Smith-Paterson<sup>16-20</sup> unit are the only examples of *syn-anti* building blocks that have been prepared on multi-

gram scales. Each of these substances is easily modifiable at each terminus for ease of continued synthetic elaboration.



We report the large-scale synthesis of synthon **1a** using Carreira's asymmetric addition reaction<sup>21-24</sup> as a key step in an expansion of our previous approach. This preparation is outlined in Scheme 1.



**Scheme 1.** The synthesis of synthon **1a** (54% overall yield, 95% ee).

## Results and Discussion

Our previously reported approach to stereotriad (**1**) was modified to improve the yield and ease of handling. In the earlier work,<sup>9-11</sup> (-)-*N*-methylephedrine was used as a chiral auxiliary to direct a propenylation of cyclohexanecarboxyaldehyde (**4**) to produce the alcohol (**6**) in one step. These reaction conditions proved to be highly moisture sensitive, difficult to maintain in large batches, and challenging to reproduce. This step was

replaced by a two-step procedure: Carreira propynylation and hydrogenation. The Carreira reaction<sup>21-24</sup> afforded the alcohol (**5**) in 97% yield with 95% *ee*.

We note, however, that zinc triflate is an expensive source of zinc(II) ion. Thus, other zinc salts were considered to reduce the cost of this step while retaining yield and *ee*. These results (Table 1) highlight the clear advantage of zinc triflate over zinc bromide and zinc chloride. Despite the variation in overall yield depending on the zinc salt, the overall *ee* of the product remained unaffected. Although we were unable to find an acceptable alternative to zinc triflate, we were able to reduce the amount of salt to 10 mol % without sacrificing yield using extended reaction times. (–)-*N*-Methylephedrine can be recovered, quantitatively, from aqueous extraction.<sup>25</sup>

**Table 1.** Summary of the optimization of Carreira's conditions<sup>a</sup>

Salt	Mol %	Reaction time	Yield (%)
Zinc(II) chloride	100	48 h	36
Zinc(II) bromide	100	48 h	45
Zinc(II) triflate	100	48 h	96
Zinc(II) triflate	60	48 h	97
Zinc(II) triflate	10	7 d	94

<sup>a</sup> All reactions were performed with toluene as the solvent. The *ee*, as determined by Mosher ester analysis, was unaffected by the Zn(II) source.

The subsequent reduction of alcohol (**5**) with Lindlar's catalyst provided the necessary (*Z*)-olefinic alcohol (**6**) in quantitative yield. Formation of ether (**7**) was performed under Finkelstein conditions.<sup>26</sup> Our synthetic intermediate *syn* diad (**8**) was easily isolated after a [2,3]-Wittig rearrangement of **7**.<sup>27-33</sup> Optimum conditions for this rearrangement required the use of excess *t*-BuLi (Table 2). This protocol afforded the rearranged **8** without side products.<sup>33</sup> Unreacted starting material was easily recovered by chromatography.

**Table 2.** Optimization of the [2,3]-Wittig rearrangement<sup>a</sup>

Base	Temperature	Yield (%) <sup>c</sup>
<i>n</i> -BuLi, <i>t</i> -BuOK	-78 °C to 0 °C	35
<i>n</i> -BuLi, <i>t</i> -BuOK, HMPA	-78 °C to 0 °C	0
<i>n</i> -BuLi, LDA	-78 °C to 0 °C	0
<i>n</i> -BuLi, <i>t</i> -BuOK	-78 °C to 0 °C, then 0 °C to -78 °C	66
<i>n</i> -BuLi	-78 °C to 0 °C	50
<i>sec</i> -BuLi	-78 °C to 0 °C	55
<i>t</i> -BuLi <sup>b</sup>	-78 °C to 0 °C	60
<i>t</i> -BuLi <sup>b</sup>	-90 °C to -20 °C	80

<sup>a</sup>All reactions were performed with 100 mg of substrate (**7**) in THF under argon atmosphere for 4h. <sup>b</sup>No byproduct was observed. <sup>c</sup>Yields reflect product isolated following chromatography.

Finally, alcohol (**8**) was converted to the desired *syn-anti* synthon (**1a**) by a two-step procedure, i.e., protection with *p*-methoxybenzyl chloride (PMB-Cl) followed by selective oxidation of the terminal olefin with crystalline 9-borabicyclo[3.3.1]nonane (9-BBN).

We imagine that synthon (**1a**) may be incorporated into large polyketides through easily performed transformations.<sup>34-40</sup>

## Conclusions

In summary, we have successfully completed a multi-gram asymmetric synthesis of the *syn-anti* synthon (**1a**) in six steps in 54% overall yield with 95% ee. We envision this stereotriad to be a precursor to a variety of synthetically useful compounds that contain contiguous stereochemical centers. We believe that the cost effectiveness of this approach is advantageous for large-scale polyketide synthesis.

## Experimental Section

**General.** Solvents were dried over calcium hydride. Thin-layer chromatography was performed on Agela plates, 0.25mm thickness, 60Å F254. Plates were stained with 15-20% phosphomolybdic acid (PMA) or visualized by UV (254 nm). Commercially-available reagents were purchased from Alfa Aesar. All NMR spectra were recorded on Bruker 500 MHz and 700 MHz spectrometers. NMR solvents were purchased from Cambridge Isotope Laboratories (Tewksbury, Massachusetts, USA). High-resolution mass spectra (HRMS) were acquired with electrospray ionization (positive mode) at the Stony Brook University Mass Spectrometry Lab on an Agilent LC-UV-TOF model G6224A oaTOF. IR spectra were collected on a Thermo Scientific Nicolet iS10 FTIR spectrophotometer.

**(S)-1-Cyclohexylbut-2-yn-1-ol (5).**<sup>23</sup> Triethylamine (25.0 g, 246 mmol), Zn(OTf)<sub>2</sub> (39.0 g, 107 mmol), and (-)-*N*-methylephedrine (21.0 g, 117 mmol) were added to an argon-filled 2 L pressure vessel along with 1.2 L of dry toluene. The mixture was stirred for 2 h at room temperature after which cyclohexanecarboxyaldehyde (20.3 g, 181 mmol) was added. The vessel was chilled to -78 °C in an acetone/dry ice bath. Propyne gas (9.8 g, 245 mmol) was added and the vessel was sealed with a Teflon screw cap. The reaction mixture was warmed to room temperature and stirred for 72 h. The reaction was quenched with a saturated solution of NH<sub>4</sub>Cl. The organic phase was washed three times with 500 mL saturated NH<sub>4</sub>Cl solution, dried over MgSO<sub>4</sub>, and concentrated under reduced pressure to afford a clear, colorless oil. Yield: 26.6 g (97.0%).

**(S)(Z)-1-Cyclohexylbut-2-en-1-ol (6).**<sup>9</sup> Alcohol **5** (20.0 g, 131 mmol) was dissolved in 200 mL of dry cyclohexane and added to a 500 mL Parr shaker flask. Lindlar's catalyst (1.67 g, 0.790 mmol) was added. The vessel was then flushed with hydrogen and pressurized to 52.0 psi four times until the hydrogen uptake ceased. The mixture was then filtered through Celite and washed through with cyclohexane. The filtrate was concentrated under reduced pressure to afford a pale yellow oil. Yield: 22 g (quantitative).

**(S)(Z)-{1-[(2-Methylallyl)oxy]but-2-en-1-yl}cyclohexane (7).**<sup>9</sup> Dry THF (300 mL) was added to a 500 mL argon-flushed two-neck round-bottom flask which was cooled in an ice bath. Sodium hydride (60%, 29.0 g, 720 mmol) was slowly added into the reaction vessel and the reaction mixture was stirred for 15 minutes. 3-Bromo-2-methylpropene (32.4 g, 240 mmol), was then added, followed by the dropwise addition of alcohol **(6)** (22.0 g, 143 mmol) in THF (10 mL). The reaction mixture was stirred for an additional 10 minutes then sodium iodide (21.4 g, 143 mmol) was added. The solution was warmed to room temperature and left overnight. The mixture was chilled in an ice bath and quenched with the slow addition of water until two layers formed. The aqueous phase was then extracted three times with ether (300 mL portions). The combined organic-phase solution was dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified using column chromatography (silica gel, 20:1 hexanes:ethyl acetate) to afford a pale yellow oil. Yield: 25.3 g (84%).

**(3R,4S)(E)-6-Cyclohexyl-2,4-dimethylhexa-1,5-dien-3-ol (8).**<sup>9</sup> A flame-dried 500 mL three-neck round-bottom flask was purged with argon and cooled to -90 °C. *tert*-Butyllithium (100 mL, 160 mmol) was transferred into an argon-purged addition funnel via cannula, then, slowly dripped into the reaction vessel over 20 minutes. Ether **(7)** (11.0 g, 53.0 mmol) in dry THF (10 mL) was then added dropwise to the reaction vessel followed by 12-crown-4 (0.26 mL) and the mixture was stirred for 4h at -90 °C. The reaction was quenched by slow dropwise addition of water and warmed to room temperature over 2 h. The aqueous phase was extracted three times with ethyl acetate (100 mL portions). The combined organic solution was dried over anhydrous MgSO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by column chromatography (silica gel 20:1 hexanes:ethyl acetate) to afford product as a yellow oil. Yield: 8.55 g (78%).

**(3R,4S)(E)-1-[[[6-Cyclohexyl-2,4-dimethylhexa-1,5-dien-3-yl]oxy]methyl]-4-methoxybenzene (9).** Dry THF (100 mL) was added to a 250 mL argon-flushed two-neck round-bottom flask and cooled in an ice bath. Sodium hydride (60%, 1.72 g, 72.0 mmol) was slowly added to the reaction vessel and the resulting suspension was stirred for 15 minutes. Alcohol **(8)** (3.00 g, 14.4 mmol) was dissolved in dry THF (15 mL) and added into the reaction vessel followed by para-methoxybenzyl chloride (5.88 mL, 43.2 mmol). After 10 minutes of stirring, sodium iodide (2.15 g, 14.4 mmol) was added and the reaction mixture was brought to room temperature and left for 72 h. The reaction mixture was chilled in an ice bath and quenched by the slow addition of water until two layers formed. The aqueous phase was extracted three times with ether (50 mL portions). The combined organic solution was dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by column chromatography (silica gel, 20:1 hexane:ethyl acetate) to afford the product as a pale yellow oil. Yield: 4.50 g (95.0%). R<sub>f</sub> 0.66 (20 : 1 hexane : ethyl acetate) <sup>1</sup>H-NMR (CDCl<sub>3</sub>,

500 MHz):  $\delta$  7.25 (d, *J* 8 Hz, 2H), 6.87 (d, *J* 8 Hz, 2H), 5.30 (m, 1H), 5.12 (m, 1H), 4.94 (s, 1H), 4.82 (s, 1H), 4.44 (d, *J* 11 Hz, 1H), 4.15 (d, *J* 11 Hz, 1H), 3.80 (s, 3H), 3.34 (d, *J* 9 Hz, 1H), 2.28 (m, 1H), 1.84 (m, 1H), 1.64 (m, 8H), 1.19 (m, 3H), 1.05 (d, *J* 7 Hz, 3H), 0.99 (m, 2H).  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ , 125 MHz):  $\delta$  159.0, 143.7, 135.7, 131.0, 129.6, 129.4, 129.3, 114.6, 114.7, 113.7, 113.5, 87.7, 69.7, 55.3, 40.6, 39.5, 33.11, 33.08, 26.2, 26.1, 17.5, 17.1. IR  $\text{cm}^{-1}$  (NaCl): 3069, 2923, 2850, 1650, 1613, 1586, 1513, 1449, 1370, 1348, 1301, 1247, 1207, 1172, 1109, 1073, 1039, 1011, 967, 899, 844, 821, 756, 637. HRMS (ESI<sup>+</sup>):  $\text{C}_{22}\text{H}_{32}\text{O}_2$  328.2402, calc for (M+H): 329.2475, found 329.2474.

**(2S,3R,4S)(E)-6-Cyclohexyl-3-[(4-methoxybenzyl)oxy]-2,4-dimethylhex-5-en-1-ol (1a)**. In an argon-filled round-bottom flask was added dry THF (25 ml) and ether (**9**) (1.00 g, 3.03 mmol). The solution was cooled to -5 °C, and 9-borabicyclo[3.3.1]nonane (9-BBN) dimer (1.48 g, 6.06 mmol) in THF (5 mL) was added dropwise. The reaction mixture was warmed to room temperature and tracked by TLC. The reaction was complete after 12 h, and the mixture was cooled back to -5 °C. Over 20 minutes, 2N NaOH (18 mL, 36 mmol) was added followed by 30%  $\text{H}_2\text{O}_2$  (18 mL). The reaction mixture was warmed to room temperature and left to stir for 5 h, then diluted with ether (50 mL) and washed three times with sat.  $\text{NH}_4\text{Cl}$  (25 mL portions). The organic solution was dried over  $\text{MgSO}_4$ , filtered, and concentrated under reduced pressure. The crude oil was purified by column chromatography (silica gel, 10:1 hexane:ethyl acetate) to afford a clear colorless oil. Yield: 954 mg (90%).  $R_f$  0.15 (10:1 hexane:ethyl acetate)  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  7.28 (d, *J* 8 Hz, 2H), 6.89 (d, *J* 8 Hz, 2H), 5.42 (m, 2H), 4.61 (d, *J* 11 Hz, 1H), 4.48 (d, *J* 11 Hz, 1H), 3.81 (s, 3H), 3.72 (dd, *J* 8 Hz, 3 Hz, 1H), 3.56 (d, *J* 6 Hz, 1H), 3.26 (t, *J* 6 Hz, 1H), 2.82 (s, 1H), 2.47 (m, 1H), 1.92 (m, 3H), 1.71 (m, 6H), 1.52 (m, 3H), 1.29 (m, 2H), 1.17, (tt, *J* 12 Hz, 3Hz, 1H), 1.09 (d, *J* 7 Hz, 3H), 1.06 (m, 1H), 1.00 (d, *J* 7 Hz, 3H)  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ , 125 MHz):  $\delta$  159.2, 136.1, 130.9, 129.4, 88.9, 74.7, 66.0, 55.2, 40.7, 39.8, 37.2, 34.7, 33.1, 33.0, 27.4, 26.1, 26.0, 22.6, 15.5. IR  $\text{cm}^{-1}$  (NaCl): 3418, 2919, 2236, 2061, 1878, 1739, 1613, 1586, 1514, 1448, 1348, 1301, 1247, 1173, 1036, 975, 892, 822, 757, 733. HRMS (ESI<sup>+</sup>):  $\text{C}_{22}\text{H}_{34}\text{O}_3$  346.2508, calc for (M+H): 347.2581, found 347.2583

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## Supplementary Material

Supplementary data associated with this article can be found in the online version.

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