Asymmetric Iterative Hydration of Polyene Strategy to Cryptocaryols A and B

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Abstract The development of two iterative asymmetric hydration approaches to the synthesis of all syn- and syn/anti-syn-1,3,5,7-tetraol motifs was described. These pseudo-symmetric products are synthetic precursors for 1,3-hexol products. The utility of the route to the all syn-1,3,5,7-tetraol diastereoisomer was demonstrated with its use in the synthesis of cryptocaryols A and B, as well as, stereoisomers.

Key words Asymmetric synthesis, iterative hydration, cryptocaryol A, cryptocaryol B, 1,3-polyols

Cryptocaryols A and B (1 and 2) are two members of a class of 5,6-dihydro-α-pyrone/1,3-polyol natural products that were reported in 2011 by Gustafson (Figure 1). Using a high-throughput PDCD4 stabilization assay, eight cryptocaryols were found in extracts from the plant cryptocarya sp. with EC50 ranging from 1.3 to 4.9 μM. Using detailed NMR, HRMS and CD analyses, the structures for cryptocaryols A and B were tentatively assigned as the purported structures 3 and 4. These initial structures had the correct connectivity but lacked certainty in terms of their absolute and relative stereochemistry. This stereochemical uncertainty was not resolved until the purported and actual structures succumbed to total synthesis by us and others. In addition to elucidating the structure of the cryptocaryols, our successful synthetic efforts provided material for the initial SAR studies of this class of natural products as both stabilizers of PDCD4 and anti-cancer agents. Thus, both enantiomers of cryptocaryols A (1) and B (2) as well as their diastereomers were prepared and studied.

Our approach to the 1,3-syn-diol motif builds on the idea that a 3,5-dihydroxy carboxylic ester would result from the iterative alkene hydration of 2,4-dienoate (Scheme 2). Key to controlling the sequence and regiocontrol of the first hydration step comes from the recognition that an asymmetric hydration of the distal double bond of a 2,4-dienoate to a 5-hydroxy-1-enoate would result in an asymmetric oxidation and reduction sequence. Finally the remaining alkene can be diastereoselectively hydrated by the in situ trapping of a

Figure 1 Cryptocaryol A and B

Our strategy focused on the synthesis of the all syn-tetraol relative configuration of the C-5 to C-15 portion of the cryptocaryols. This approach resulted from the recognition that the complete natural product could be constructed by diastereoselectively appending the C-5/C-15 pyranone and the C-15/C-5 alkyl side chain to a single enantiomer of syn-8. This stereo-divergent approach takes advantage of the pseudo-symmetry of syn-8, which allows for its stereoselective elaboration into any of the eight most likely stereoisomers of the cryptocaryols. Herein, we disclose the development of the synthetic chemistry that underpinned this effort. Specifically this includes the development of a dieneoate iterative asymmetric hydration, its elaboration to the asymmetric synthesis of C8 and C5 symmetric protected tetroal precursors and finally the use of one of these stereoisomeric polyols for the synthesis, structure elucidation and medicinal chemistry study of the cryptocaryols.

Scheme 1 Retrosynthetic analysis of cryptocaryol A and B
hemiacetal using the Evans protocol resulting in the benzylidene protected 3,5-dihydroxy carboxylic ester 12.  

Our first attempt to execute the initial hydration step began with the Sharpless dihydroxylation of ethyl sorbate 13a to give 4,5-dihydroxy-1-enolate 14a (71%, 80% ee). 15 We next explored converting the allylic alcohol into ester and carbonate type Pd-π-allyl leaving groups 15a-c (Table 1). 15 When 15a-b were exposed to our typical π-allyl Pd-hydride reducing conditions (2.5% Pd(dba)2•CHCl3/6.3% PPh3), a significant amount of reductive elimination occurred along with the benzole 16a and ethyl carbonate 16b. In contrast, the cyclic carbonate 15c was reduced under the same conditions to give the desired 5-hydroxy-1-enolate 16c without any elimination (70%). 16

### Table 1 Optimization of the asymmetric hydration of dienoates

<table>
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<tr>
<th>Entry</th>
<th>Cmpd</th>
<th>R1</th>
<th>R2</th>
<th>Yield</th>
<th>ee</th>
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<tbody>
<tr>
<td>1</td>
<td>15a : 13a</td>
<td>Bz</td>
<td>Bz</td>
<td>43%</td>
<td>4:1</td>
</tr>
<tr>
<td>2</td>
<td>16b : 13a</td>
<td>CO2Et</td>
<td>CO2Et</td>
<td>47%</td>
<td>4:1</td>
</tr>
<tr>
<td>3</td>
<td>16c : 13a</td>
<td>(CO2)3</td>
<td>H</td>
<td>70%</td>
<td>1:0</td>
</tr>
</tbody>
</table>

Reagents and conditions: a) 1% OsO4, 1.1% (DHQ)2PHAL, K3FeCN6/MeSO2NH2; a') 1% OsO4, 1.1% (DHQD)2PHAL, K3FeCN6/MeSO2NH2; b) BzCl, Et3N, CH2Cl2; c) ClCO2Et, Et3N, CH2Cl2; d) (Cl3CO)2CO, Pyridine, CH2Cl2; e) HCO2H/Et3N, Pd2(dba)3•CHCl3, PPh3, THF, 66 °C.

We next explored the applicability of the protocol on a variety of δ-substituted dienoates 13a-g (Table 2). When the variously substituted dienoates 13a-g were exposed to the Sharpless dihydroxylation and carbonate forming conditions, carbonates 17a-g were obtained in improved yields and enantiomeric excesses. Similar yields and enantiomeric purities were obtained from the (DHQ)2PHAL or the (DHQD)2PHAL ligand system (80-95% ee). Exposing the cyclic carbonates 17a-g to our optimized Pd-reduction conditions (2.5% Pd(dba)2•CHCl3/6.3% PPh3) gave homoallylic alcohols 18a-g (66-93 %) with no loss of enantiomeric excess (80-95% ee). With the demonstrated generality for the first asymmetric hydration set, we next pursued the subsequent hydration/protection step.

### Table 2 Scope of asymmetric hydration of polyene

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cmpd</th>
<th>R1</th>
<th>R2</th>
<th>Yield</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19a</td>
<td>Me</td>
<td>Et</td>
<td>71%</td>
<td>80%</td>
</tr>
<tr>
<td>2</td>
<td>19b</td>
<td>Pr</td>
<td>Me</td>
<td>81%</td>
<td>95%</td>
</tr>
<tr>
<td>3</td>
<td>19c</td>
<td>Ph</td>
<td>Et</td>
<td>79%</td>
<td>95%</td>
</tr>
</tbody>
</table>

Reagents and conditions: a) 1 equiv PhCHO, 11% KOt-Bu, 3 times, THF, 0 °C.

As with the first three steps, we found a broad substrate scope for the Evans acetal forming reaction. Thus, when exposing the δ-hydroxy enoates 18a-g to the Evans procedure (1.1 equiv of benzaldehyde and 0.11 equiv of KOt-Bu, 0 °C, repeat 3 times every 15 min), all but one proceeded smoothly to the desired benzylidene protected 3,5-dihydroxy carboxylic esters 19a-g. Typical yields for these transformations are in the 60% range. The exception to this was the substrate with the C-6 t-butylmethylisoxyl group in entry 4. Unfortunately, under the basic conditions, the TBS-group migrated to the C-5 alkoxide leaving behind a C-6 alkoxy group which was ideally poised to intramolecularly add across the enolate to give tetrahydrofurran 20. This issue with silyl-group migration issue was easily solved by simply switching the TBS-group to a base stable PMB-group (19f and 19g).
Building upon this observation, we decided to use the benzylidene protected 3,5-dihydroxy carboxylic esters with a C-7 OPMB group to build the next 1,3-syn-diol unit (Scheme 3). To accomplish this we first needed to append another dieneoate functional group onto the carbon chain. This undertaking was most easily accomplished by a Dibal-H reduction of the methyl ester in ent-19f, which cleanly provided aldehyde 21 (93%). A subsequent vinylogous Horner-Wadsworth-Emmons olefination of aldehyde 21 with phosphonate 25 and base gave the desired dieneoate 22 (66%). With the E,E-dieneoate in place in 22, it can then been elaborated into a second 1,3-syn-diol unit subunit. Simply repeating the four-step iterative hydration sequence of 22 would install the second benzylidene acetal as in ent-syn-8. Thus exposing 21 to the typical Sharpless asymmetric dihydroxylation conditions (1% OsO₄, 1.1% (DHQD)₂PHAL, K₂Fe₆C₆, MeSO₂NH₂), diol 23 was produced as a single diastereomer (71%). Treating diol 23 with triphosgene and base readily converted the diol into a cyclic carbonate, which when exposed to the Pd-reduction conditions (HCO₂H/Et₃N, THF, 66 °C, 90%); f) 1 equiv PhCHO, 10% KOtBu, 3 times, THF, 0 °C, 63%.

Concerns over the scale-ability and dieneoate stability inspired us to pursue an alternative approach for the stereoselective installation of the second benzylidene unit (i.e., 21 to syn-8). In this regard, we devised an allylation/cross metathesis strategy (Scheme 4). This alternative approach began with a one-pot reduction/allylation sequence, which involved an in situ addition of the allyl Grignard reagent directly to the ester 19f/DibalH reaction mixture. When this reaction was warmed to room temperature and quenched a 1:2.1 ratio of homoallylic alcohols syn-26 and anti-26 were isolated in good overall yield (91% yield). Unfortunately all of our efforts to improve upon this modest selectivity in the allylation reaction were unsuccessful. These efforts included the addition of various chelating Lewis acids (Al, Ti, Zn) in combination with an allylanion, in an attempt to take advantage of the β-alkoxy group. While these homoallylic alcohols can be separated by silica gel chromatography, the ratio would be improved by an oxidation/reduction reaction sequence. Thus, treatment of a diastereomeric mixture of syn-26 and anti-26 with Dess-Martin reagents gave a clean conversion to the β,γ-unsaturated ketone 28, without any double bond isomerization (90%). Then, treating a THF solution of 28 with L-selectride at −90 °C provided syn-26 in a 4:1 ratio (89% yield).
With access to the C5 and C2 symmetric protected tetraol precursors syn-8 and anti-8, we next looked to install the remaining C5/C15 stereochemistry of the cryptocaryols (Scheme 6). Because we wanted to be able to install both R and S-stereochemistry at the C5/C15, we looked into using a reagent-controlled approach. We found that this was most easily accomplished with the use of the Leighton reagent for the C5 position and the Noyori hydrogen transfer reaction for the C15 position. For the Noyori reduction to occur with high stereocontrol, an ynone functionality needed to be introduced, as in 29. This was most easily accomplished by removing the PMB-group (DDQ, 92%) and oxidizing the primary alcohol with the Dess-Martin reagent (81%) to give 28. An unsel ective addition of 1-lithiopentadec-1-yn e to aldehyde 28 and a subsequent Dess-Martin oxidation was used to give 29 (62%). Exposure of 29 to our typical Noyori reduction conditions (5% (S,S)-Noyori, Et,N, formic acid, 94%) gave a propargyl alcohol as a single diastereomer, which upon exposure to excess dimide gave secondary alcohol 30 with the desired (R)-stereochemistry at C15. The (R)-stereochemistry at C5 was installed by reducing the ester to an aldehyde with Dibal-H (87%), acylating the C5 alcohol (Ac,O, 72%) and finally a diastereoselective addition of an allyl anion with the (S,S)-Leighton reagent (75%) resulting in homallylic alcohol 31. A similar approach was used to convert 30 into 32 with the (S)-stereochemistry at C5 (TBSCI, Dibal-H and (R,R)-Leighton, 82%). However in this alternative approach the C15 alcohol was protected as a TBS-group.

To install the C5/C15 with the opposite tetraol stereochemistry (ent-32), all we need to do is apply the same sequences to the opposite ends of the tetraol precursors syn-8 (Scheme 6). This began with a Dibal-H reduction of syn-8 followed by an unsel ective 1-lithiopentadec-1-yn e to resulting aldehyde and a subsequent Dess-Martin oxidation was used to give ynone 33 (62%). Noyori reduction of 33 (5% (R,R)-Noyori, Et,N, formic acid, 98%) gave a propargyl alcohol as a single diastereomer, which upon exposure to excess dimide gave secondary alcohol 34 with the desire (S)-stereochemistry at C-15. TBS protection of the secondary alcohol (94%) and DDQ-promoted removal of the PMB-group (92%) gave 35. Finally the C5 (R)-stereochemistry was installed by oxidation of the primary alcohol and addition of the (S,S)-Leighton reagent (95%).

With all the stereochemistry installed in homallylic alcohols ent-32, it was readily converted into cryptocaryol A (1), by a three-step procedure. This began with an acrylation of the C5 alcohol, ring closing metathesis with the Grubbs I reagent and aqueous acetic acid deprotection to give 1 (42% over three steps). By replacing the C15 TBS group with an acetal (TBAF then Ac2O) after the acrylation at C5, homallylic alcohol ent-32 could also be converted into cryptocaryol B (2) (28% over five steps). Applying the identical 3- and 5-step sequences to 32 provided ent-cryptocaryol A (ent-1) and ent-cryptocaryol B (ent-2). Both synthetic cryptocaryols A and B, gave identical spectral data as was reported for the natural material. Finally the homallylic alcohol 31 was converted into purported cryptocaryol B (4), the initially assigned structure for cryptocaryol B, by a 3-step acylation of the C5 alcohol, ring closing metathesis with the Grubbs I reagent and aqueous acetic acid deprotection (35%, three steps).

In conclusion, we have described the full account of our recently completed synthesis of cryptocaryol A (1) and cryptocaryol B (2). The route featured three different approaches to the C5 and C2 symmetric protected tetraol precursors syn-8 and anti-8, which are key building blocks for the synthesis of many poly-acetate type natural products. The utility of this approach was demonstrated in the application of various stereoisomeric analogues of the cryptocaryols, which in turn enabled structure activity relationship studies.
Ethyl (2E,4E)-6-(2545,6R)-6-2-(4-methoxybenzyl)oxy)ethyl)-2-phenyl-1,3-dioxan-4-yl)hexa-2,4-diene orange (22): To a 25 mL round bottom flask containing 131 mg (0.28 mmol) of dienoate 22 was added 2 mL of t-BuOH, 2 mL of water, K2Fe(CN)6·3H2O (277 mg, 0.84 mmol), K2CO3 (116 mg, 0.84 mmol), MeSO2NH2 (27 mg, 0.28 mmol) and (DIPDCl)2PF6 (13 mg, 0.18 mmol). The mixture was stirred at room temperature for 15 minutes and then cooled to 0°C. To this solution was added OsO4 (3.6 mg, 14 μmol) and the reaction was stirred vigorously at 0°C overnight. The reaction was quenched with saturated aqueous sodium sulfite (4 mL) at room temperature. Ethyl acetate (5 mL) was added to the reaction mixture, and after separation of the layers, the aqueous phase was further extracted with the organic solvent (2 x 10 mL). The combined organic layers were washed with 2N KOH (10 mL) to remove the methanesulfonamide, and then dried over anhydrous sodium sulfate. After removal of the solvents in vacuo, flash chromatography on silica gel afforded 99 mg (71% yield) of 23 as a colorless oil: Rf = 0.16 (3:2 hexanes:EtOAc), [α]D = +18.6 (c 1.2, CH2Cl2); IR (neat) 3478, 2914, 1713, 1660, 1613, 1586, 1547, 1514, 1463, 1454, 1304, 1100 cm−1; 1H NMR (CDCl3, 300 MHz) δ 7.41 (m, 2H), 3.53 (m, 3H), 7.26 (d, J = 9 Hz, 2H), 6.96 (dd, J = 15.5, 5 Hz, 1H), 6.87 (d, J = 9 Hz, 2H), 6.14 (dd, J = 15.5, 2 Hz, 1H), 5.56 (s, 1H), 4.45 (d, J = 11.5 Hz, 1H), 4.45 (d, J = 11.5 Hz, 1.20 (q, J = 7 Hz, 2H), 4.19 (m, 2H), 4.07 (d, J = 10.5, 7.5, 4.2 Hz, 1H), 3.93 (d, J = 9.5, 4.5, 2.5 Hz, 1.27 (s, 3H), 3.65 (dd, J = 9, 8, 5 Hz, 1H), 3.56 (dd, J = 9, 5.5, 5.5 Hz, 1H), 1.92 (m, 2H), 1.84 (s, 1H), 1.77 (dd, J = 15, 3.3 Hz, 1H), 1.62 (m, 1H), 1.52 (dd, J = 13, 11, 11 Hz, 1.29 (t, J = 7 Hz, 3H); 13C NMR (CDCl3, 125 MHz) 0663, 159.2, 146.8, 1381, 130.5, 129.4, 129.0, 128.4, 126.0, 122.4, 121.0, 112.1, 100.8, 87.7, 77.1, 73.1, 72.7, 65.4, 60.5, 55.3, 38.6, 37.0, 36.14, 14.35; HRMS (ESI) calcd for [C13H16O5+Na]+: 523.2308 Found: 523.2297.

Ethyl (E)-3-(4(RR)-5)-{(2E,4R)-6-2-[((4-methoxybenzyl)oxy)ethyl]-2-phenyl-1,3-dioxan-4-yl)ethyl]octa-2,3-dienoylate (23a): To a 10 mL volumetric flask containing 90 mg (0.18 mmol) of diol 23 and 57 μL pyridine was placed 2 mL of CH2Cl2. This mixture was cooled to 0°C and 27 mg of triphosgene (0.09 mmol) dissolved in 1 mL of CH2Cl2 was added slowly using an addition funnel.

The experimental section has no title; please list this line here.
Ethyl (S,E)-5-hydroxy-6-((2R,4S,6R)-6-((4-methoxybenzyl)oxy)ethyl)-2-phenyl-1,3-dioxan-4-yllactate (ent-syn-8): To a solution of alcohol syn-24 (75 mg, 0.155 mmol) in 1.5 mL of THF at 0 °C was added 15 μL (0.16 mmol) of benzaldehyde, followed by 1.7 mg (0.016 mmol) of t-BuOK. The solution was stirred for 15 min. The addition of benzaldehyde/t-BuOK was repeated 3 more times and the reaction was quenched with 1 mL of pH 7 phosphate buffer and diethylether (3 mL). The layers were separated, and the aqueous layer was extracted with ether (3 x 5 mL). The combined organic layers were washed with brine, dried over anhydrous Na2SO4, filtered, and concentrated in vacuo. The crude product was purified by silica gel chromatography to produce (syn, syn) dibenzylidene ent-8 (58 mg) in 63% yield as a clear oil. Rf = 0.26 (4:1 hexanes:EtOA): [α]23 = +19.3 (c 1.7, CH2Cl2); IR (neat) 2920, 2864, 1732, 1614, 1586, 1545, 1436, 1303, 1248, 1112, 1028 cm⁻¹; 1H NMR (CDCl3, 300 MHz) δ 7.49 (m, 4H), 7.36 (m, 6H), 7.27 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 5.59 (s, 1H), 5.54 (s, 1H), 4.50 (d, J = 11.7 Hz, 1H), 4.44 (d, J = 11.7 Hz, 1H), 4.35 (d, J = 11.1, 6.6, 6.2, 1.1 Hz, 1H), 4.18 (q, J = 7.2 Hz, 2H), 4.02-4.18 (m, 3H), 3.79 (s, 3H), 3.69 (d, J = 9, 8.1, 5.1 Hz, 1H), 3.60 (d, J = 9, 6.6, 5.7, 11 Hz, 2H). 2.76 (dd, J = 15.6, 7.2, 11 Hz, 2H), 2.54 (dd, J = 15.6, 6.8, 11 Hz, 1H), 2.16 (dd, J = 15.6, 7.2, 11 Hz, 1H), 1.64-2.00 (m, 5H), 1.45-1.62 (m, 2H), 1.28 (t, J = 7.2 Hz, 3H); 13C NMR (CDCl3, 75 MHz) δ 170.6, 160.0, 138.6, 138.2, 130.4, 129.7, 128.5, 128.0, 128.0, 125.9, 125.9, 113.6, 100.4, 100.3, 73.6, 73.1, 72.9, 72.9, 72.5, 65.0, 60.5, 55.1, 41.6, 40.9, 36.7, 36.2, 36.0, 14.1; HRMS (ESI) calcd for [C26H32O6Na+] = m/z 434.2377 Found: m/z 434.2375.

Ethyl 2-((2R,4R,6R)-6-((2-(4-methoxybenzyl)oxy)ethyl)-2-phenyl-1,3-dioxan-4-yllactyl)pent-4-en-2-yl (28): Into a 10 mL round bottomed flask was added 90 mg of alcohol in 2 mL of CH2Cl2. To this solution was added Dess-Martin periodane (140 mg, 0.33 mmol). The reaction was stirred for 1.5 hours. Ether was added to the reaction and the solution was filtered through a pad of silica gel, followed by removal of the solvents under reduced pressure. The crude product was purified by silica gel chromatography to produce 80 mg (99% yield) of ketone 28 as a clear oil. [α]23 = 22.3 (c 10, CH2Cl2); IR (neat) 2922, 1714, 1644, 1614, 1586, 1515, 1455, 1350, 1347, 1245, 1174, 1098, 1028 cm⁻¹; 1H NMR (CDCl3, 500 MHz) δ 8.74 (m, 2H), 7.33 (m, 3H), 7.26 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 5.59 (s, 1H), 5.54 (s, 1H), 4.50 (d, J = 11.7 Hz, 1H), 4.44 (d, J = 11.7 Hz, 1H), 4.35 (d, J = 11.1, 6.6, 6.2, 1.1 Hz, 1H), 3.79 (s, 3H), 3.69 (d, J = 9, 8.1, 5.1 Hz, 1H), 3.60 (d, J = 9, 6.6, 5.7, 11 Hz, 2H). 2.76 (dd, J = 15.6, 7.2, 11 Hz, 2H), 2.54 (dd, J = 15.6, 6.8, 11 Hz, 1H), 2.16 (dd, J = 15.6, 7.2, 11 Hz, 1H), 1.64-2.00 (m, 5H), 1.45-1.62 (m, 2H), 1.28 (t, J = 7.2 Hz, 3H); 13C NMR (CDCl3, 75 MHz) δ 170.6, 160.0, 138.6, 138.2, 130.4, 129.7, 128.5, 128.0, 128.0, 125.9, 125.9, 113.6, 100.4, 100.3, 73.6, 73.1, 72.9, 72.9, 72.5, 65.0, 60.5, 55.1, 41.6, 40.9, 36.7, 36.2, 36.0, 14.1; HRMS (ESI) calcd for [C26H32O6Na+] = m/z 434.2377 Found: m/z 434.2375.

(R)-1-(254.5465)-6-2-((4-methoxybenzyl)oxy)ethyl-2-phenyl-1,3-dioxan-4-yllactylpent-4-en-2-yl (syn-26): To a solution of ester 19f in 10 mL of CH2Cl2 at -78 °C was added 3.75 mL (1.0 M solution in CH2Cl2) of disiobutylaluminum hydride. This solution was allowed to stir for 1 h when 2.5 mL of allylmagnesium chloride (2 M solution in THF) was added to the flask. The reaction was allowed to warm to room temperature and stirred for 3 h, after which 1 mL of methanol and 10 mL of a 20% sodium potassium tartrate solution were added. This solution was stirred vigorously until the layers separated rapidly upon cessation of stirring. The aqueous layer was extracted with CH2Cl2 (3 x 10 mL). The organic layers were combined and washed with brine and dried over anhydrous sodium sulfate. Removal of the solvents in vacuo followed by passage through a short pad of silica gel yielded the alcohol (876 mg, 85%) as a clear oil and a mixture of diastereomers.
over anhydrous Na2SO4, filtered and concentrated under reduced pressure.

Ethyl 2-((2R,6R,6)-6-((2-((4-methoxybenzyl)oxy)ethyl)-2-phenyl-1,3-dioxan-4-yly)methyl)-2-phenyl-1,3-dioxan-4-ylacetate(anti-B): To a stirred solution of anti-C (0.35 g, 1.6 mmol) in tetrahydrofuran (30 mL) at 0 °C was added benzaldehyde (0.18 mL, 1.75 mmol), followed by potassium tert-butoxide (0.02 g, 0.175 mmol) under N2. The resulting mixture was stirred for 15 min. Then the addition of benzaldehyde/potassium tert-butoxide was repeated three more times. The mixture was passed through a pad of silica gel, and the silica gel was washed with EtOAc (100 mL). The filtrate was concentrated, and the crude residue was purified by flash chromatography (5 to 40% EtOAc in hexanes) on silica gel to afford anti-B (0.72 g, 77%) as a colorless oil: Rf = 0.41 (10% EtOAc in hexanes); [α]D21 = +18.0 (CH2Cl2, c = 1.72); IR (neat): 3376, 2918, 2859, 1712, 1512, 1470, 1247, 1107, 1010 cm–1; 1H NMR (500 MHz, CDCl3) δ 171.0, 159.4, 139.0, 138.6, 130.7, 129.6, 129.0, 128.9, 128.4; 13C NMR (125 MHz, CDCl3) δ 171.0, 159.4, 139.0, 138.6, 130.7, 129.6, 129.0, 128.9, 128.4, 128.38, 128.26, 126.26, 114.0, 100.8, 100.7, 74.0, 73.5, 73.7, 72.20, 72.9, 65.9, 60.9, 55.5, 41.9, 41.2, 37.1, 36.6, 36.4, 14.5; HRMS (ESI) calcd for C31H29NO4 Na+: 507.2345; Found: 507.2324.

Acknowledgment
We are grateful to NIH (GM090259) and NSF (CHE-1213596) for financial support of this research.

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6 Mohapatra reported the synthesis of purported crytopcaryol A (3) and mistakenly reported it as Cryptopcaryol A (1), see: Reddy, D. S.; Mohapatra, D. K. Eur. J. Org. Chem. 2013, 1051-1057.


