Asymmetric Iterative Hydration of Polyene Strategy to Cryptocaryols A and B

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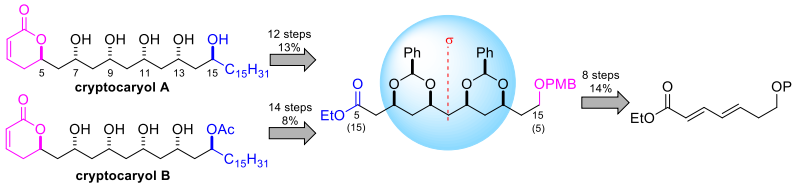

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Abstract The development of two iterative asymmetric hydration approaches to the synthesis of all syn- and syn/anti/syn-1,3,5,7-tetraol motifs was described. These pseudo-symmetric products are synthetic precursors for 1,3-hexol products. The utility 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-pyranone/1,3-polyol natural products that were reported in 2011 by Gustafson (Figure 1).[1] Using a high-throughput PDCD4 stabilization assay, eight cryptocaryols were found in extracts from the plant *cryptocarya sp.* with EC_{50} ranging from 1.3 to 4.9 μM. Using detailed NMR, HRMS and CD analyses,[2,3] 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.[4,5,6] 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.[7] Thus, both enantiomers of cryptocaryols A (**1**) and B (**2**) as well as their diastereomers were prepared and studied.

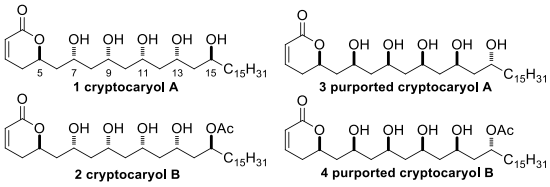
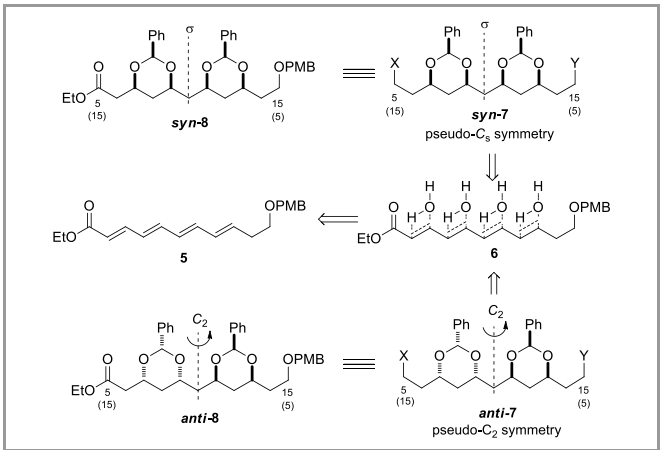


Figure 1 Cryptocaryol A and B

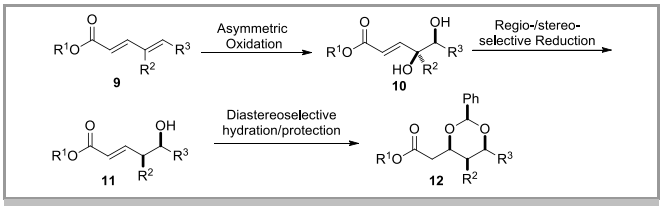
Our strategy focused on the synthesis of the all *syn*-tetraol relative configuration of the *C*-5 to *C*-15 portion of the cryptocaryols.[8] This approach resulted from the recognition that the complete natural product could be constructed by diastereoselectively appending the *C*-5/*C*-15 pyranone 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 dienoate iterative asymmetric hydration, its elaboration to the asymmetric synthesis of C_s and C_2 symmetric protected tetraol 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

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).[9,10,11] 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 by an asymmetric oxidation and reduction sequence. Finally the remaining alkene can be diastereoselectively hydrated by the *in situ* trapping of a

hemiacetal using the Evans protocol resulting in the benzylidene protected 3,5-dihydroxy carboxylic ester **12**.[12]



Scheme 2 Asymmetric hydration route to *syn*-1,3-diol

Our first attempt to execute the initial hydration step began with the Sharpless dihydroxylation of ethyl sorbate **13a** to give 4,5-dihydroxy-1-enoate **14a** (71%, 80%ee).[13,14] 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% $Pd_2(dba)_3$•$CHCl_3$/6.3% PPh_3), a significant amount of reductive elimination occurred along with the benzoate **16a** and ethyl carbonate **16b**. In contrast, the cyclic carbonate **15c** was reduced under the same conditions to give the desired 5-hydroxy-1-enoate **16c** without any elimination (70%).[16]

Table 1 Optimization of the asymmetric hydration of dienoates

Entry	Cmpd	R	R'	Yield	Ratio
1	**16a : 13a**	Bz	Bz	43%	4:1
2	**16b : 13a**	CO_2Et	CO_2Et	47%	4:1
3	**16c : 13a**	-(CO)-	H	70%	1:0

Reagents and conditions: a) 1% OsO_4, 1.1% $(DHQ)_2PHAL$, K_3FeCN_6/$MeSO_2NH_2$, 71%; b) BzCl, Et_3N, CH_2Cl_2, 57%; c) $ClCO_2Et$, Et_3N, CH_2Cl_2, 81%; d) $(Cl_3CO)_2CO$, Pyridine, CH_2Cl_2, 87%; e) HCO_2H/Et_3N, $Pd_2(dba)_3$•$CHCl_3$, PPh_3, 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% $Pd_2(dba)_3$•$CHCl_3$/ 6.3% PPh_3) 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.

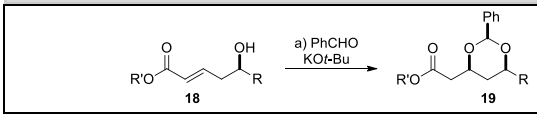
Table 2 Scope of asymmetric hydration of polyene

Entry	Cmpd	R^1	R^2	Yield **14**, ee	Yield **17**	Yield **18**
1	**a**	Me	Et	71%, 80%	87%	70%
2	**b**	Pr	Me	81%, 95%	94%	80%
3	**c**	Ph	Et	79%, 95%	91%	72%

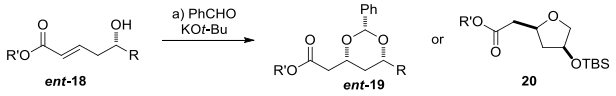
Entry	Cmpd	R	R'	Yield, ee ***ent*-14**	Yield ***ent*-17**	Yield ***ent*-18**
4	***ent*-d**	CH_2OTBS	Et	82%, 95%	94%	88%
5	***ent*-e**	$(CH_2)_2OTBS$	Et	91%, 95%	95%	87%
6	***ent*-f**	$(CH_2)_2OPMB$	Me	79%, 95%	95%	93%
7	***ent*-g**	CH_2OPMB	Et	NA	57%	66%

Reagents and conditions: a) 1% OsO_4, 1.1% $(DHQ)_2PHAL$, K_3FeCN_6/$MeSO_2NH_2$; a') 1% OsO_4, 1.1% $(DHQD)_2PHAL$, K_3FeCN_6/$MeSO_2NH_2$; b) $(Cl_3CO)_2CO$, Pyridine, CH_2Cl_2; c) HCO_2H/Et_3N, $Pd_2(dba)_3$•$CHCl_3$, PPh_3, THF, 66 °C.

Table 3 Evans acetal formation



Entry	Cmpd	R	R'	Yield
1	**19a**	Me	Et	60%
2	**19b**	Pr	Me	60%
3	**19c**	Ph	Et	52%



Entry	Cmpd	R	R'	Yield
4	**20**	CH_2OTBS	Et	88%
5	***ent*-19e**	CH_2 CH_2OTBS	Et	68%
6	***ent*-19f**	CH_2 CH_2OPMB	Me	62%
7	***ent*-19g**	CH_2OPMB	Et	61%

Reagents and conditions: a) 1.1 equiv PhCHO, 11% KO*t*-Bu, 3 times, THF, 0 °C.

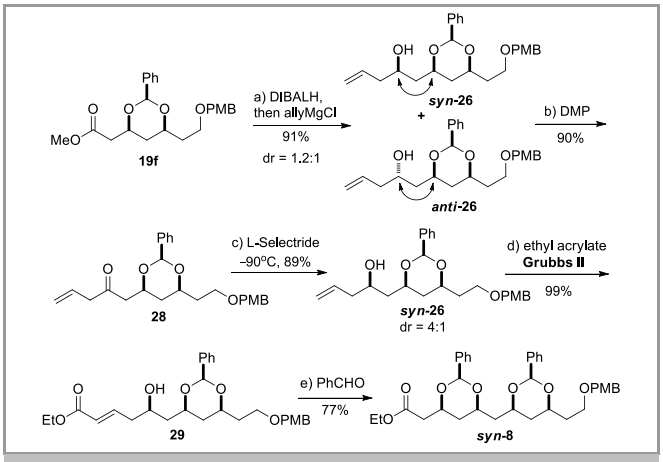
As with the first three steps, we found a broad substrate scope for the Evans acetal forming reaction. Thus, when exposing the δ-hydroxy enoates **18a-g** to the Evans procedure (1.1 equiv of benzaldehyde and 0.11 equiv of KO*t*-Bu, 0 °C, repeat 3 times every 15 min), all but one proceeded smoothly to 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*-butyldimethylsiloxy 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 enoate to give tetrahydrofuran **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**).

Scheme 3 Iterative Oxidation/Reduction Approach to *syn*-1,3- Polyols

Reagents and conditions: a) DIBALH, CH_2Cl_2, −78 °C, 93%; b) LiOH·H_2O, phosphonate **25,** 4Å molecular sieves, THF, 66%; c) 1% OsO_4, 1.1% $(DHQD)_2PHAL$, K_3FeCN_6, $MeSO_2NH_2$, 71%; d) $(Cl_3CO)_2CO$, Pyridine, CH_2Cl_2, 90%; e) 1% $Pd_2(dba)_3$•$CHCl_3$, PPh_3, HCO_2H/Et_3N, THF, 66 °C, 90%; f) 1 equiv PhCHO, 10% KO-*t*Bu, 3 times, THF, 0 °C, 63%.

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 dienoate 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 dienoate **22** (66%).[17] With the *E*,*E*-dienoate in place in **22**, it can then be elaborated into a second 1,3-*syn*-diol unit subunit. Simply repeating the four-step iterative hydration sequence of **22** would install the second benzylidine acetal as in ***ent*-*syn*-8**. Thus exposing **21** to the typical Sharpless asymmetric dihydroxylation conditions (1% OsO_4, 1.1% $(DHQD)_2PHAL$, K_3FeCN_6, $MeSO_2NH_2$), 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 (HCO_2H/Et_3N, 1% $Pd_2(dba)_3$•$CHCl_3$/2.5% PPh_3) cleanly gave the 5-hydroxy-1-enoate ***syn*-24** (90%). Finally exposing ***syn*-24** to the Evans acetal formation condition(1.1 equiv PhCHO, 0.11 equiv KO*t*-Bu, 3 times, THF, 0 °C) easily converted it into the bis-benzylidene-protected ester ***ent*-*syn*-8** in good yield (63%).

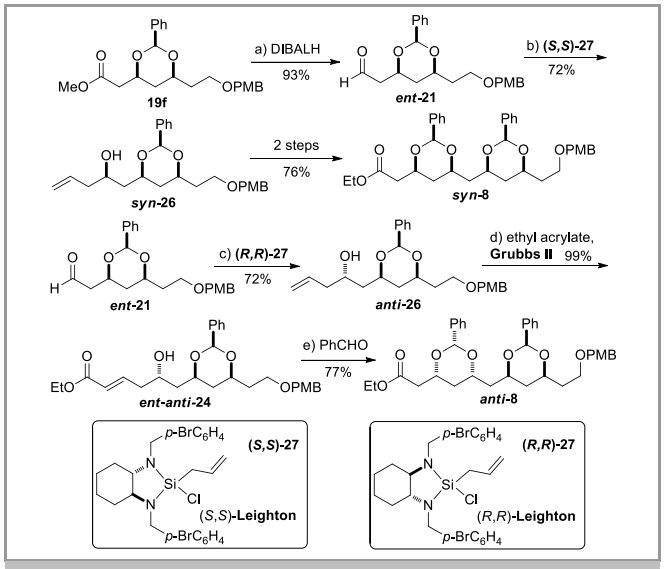
Concerns over the scale-ability and dienoate stability inspired us to pursue an alternative approach for the stereoselective installation of the second benzylidene unit (*i.e.*, **21** to ***syn*-8**). In this regard, we devised an allylation/cross metathesis strategy (Scheme 4). This alternative approach 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.[10] 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).



Scheme 4 Second generation to protected 1,3-*syn*-Polyol

Reagents and conditions: a) DIBALH, CH_2Cl_2, −78 °C, 1 h then allyMgCl (2M THF solution), r.t., 91%; b) Dess-Martin reagent, CH_2Cl_2, 90%; c) L-Selectride, −90 °C, 89%, dr = 4:1; c) ethyl acrylate, 2.5% Grubbs II, CH_2Cl_2 , 99%; d) 1.1 equiv PhCHO, 0.11 equiv KO*t*-Bu, 3 times, THF, 0 °C, 77%.

In spite of our desire to try to use a substrate controlled approach to control the stereochemistry in the next benzylidene subunit, a much more practical and simplified procedure resulted when we turned to a reagent control approach in the allylation reaction. This involved turning to the Leighton allylation reagents **27**.[18] Thus, this revised procedure to the installation of the second protected diol fragment of **19f** began with the same ester to aldehyde reduction with Dibal-H (**19f** to ***ent*-21**, 93%). In this alternative approach exposure of purified aldehyde ***ent*-21** to the (*S,S*)-Leighton reagent cleanly afforded homoallylic alcohol ***syn*-26** as a single diastereoisomer. A Grubbs II type cross metathesis reaction between ***syn*-26** and ethyl acrylate gave a single alkene isomer, which we previously have shown can be converted into bis-benzylidene-protected ester ***syn*-8**.[19] The stereodivergent aspect of the synthesis can be seen in its ability to just as easily be used for the conversion of **19f** into the diastereomeric bis-benzylidene-protected ester ***anti*-8.** This involves the switching of the (*S,S*)-Leighton reagent to the (*R,R*)-Leighton reagent in the allylation of ***ent*-21**. Thus when ***ent*-21** is treated with the (*R,R*)-Leighton reagent homo-allylic alcohol ***anti*-26** is produced as a single diastereomer. The diastereomeric alcohol ***anti*-26** reacted similarly under the Grubbs II cross metathesis condition to give the 5-hydroxy-1-enoate ***ent*-*anti*-24** (90%). Finally the Evans acetal forming reaction (1.1 equiv PhCHO, 11% KO*t*-Bu, 3 times, THF, 0 °C, 77%) is used to install the final benzylidene unit in the diastereomeric bis-benzylidene-protected ester ***anti*-8**.

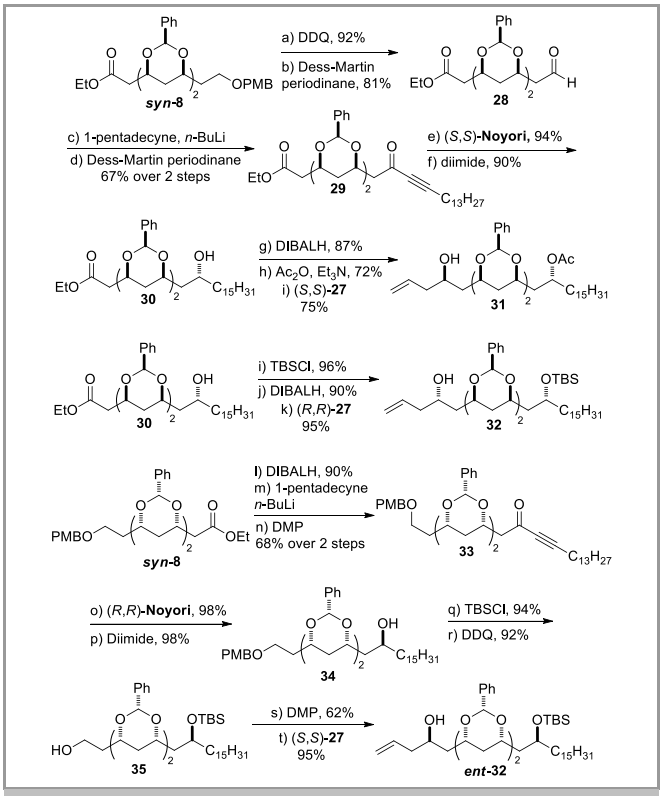


Scheme 5 Synthesis of protected *syn* and *anti*-1,3-polyols

Reagents and conditions: a) DIBALH, CH_2Cl_2, −78 °C, 93%; b) **(*S,S*)-27**, 2.5% $Sc(OTf)_3$, CH_2Cl_2, -10 °C, 72%; c) ethyl acrylate, 2.5% Grubbs II, 99%; d) 1 equiv PhCHO, 10% KO*t*-Bu, 3 times, THF, 0 °C, 77%; e) (*R,R*)-27, 2.5% $Sc(OTf)_3$, CH_2Cl_2, –10 °C, 72%; f) ethyl acrylate, 2.5% Grubbs II, 99%; g) PhCHO, 10% KO*t*-Bu, 3 times, THF, 0 °C, 78%.

With access to the *Cs* and C_2 symmetric protected tetraol precursors ***syn*-8** and ***anti*-8**, we next looked to install the remaining *C*-5/*C*-15 stereochemistry of the cryptocaryols (Scheme 6). Because we wanted to be able to install both *R* and *S*-stereochemistry at the *C*-5/*C*-15, 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 *C*-5 position and the Noyori hydrogen transfer reaction for the *C*-15 position.[20] 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 unselective addition of 1-lithiopentadec-1-yne 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_3N, formic acid, 94%) gave a propargyl alcohol as a single diastereomer, which upon exposure to excess diimide gave secondary alcohol **30** with the desired (*R*)-stereochemistry at *C*-15. The (*R*)-stereochemistry at *C*-5 was installed by reducing the ester to an aldehyde with Dibal-H (87%), acylating the C-15 alcohol (Ac_2O, 72%) and finally a diastereoselective addition of an allyl anion with the (*S,S*)-Leighton reagent (75%) resulting in homoallylic alcohol **31**. A similar approach was used to convert **30** into **32** with the (*S*)-stereochemistry at *C*-5 (TBSCl, Dibal-H and (*R,R*)-Leighton; 82%). However in this alternative approach the *C*-15 alcohol was protected as a TBS-group.

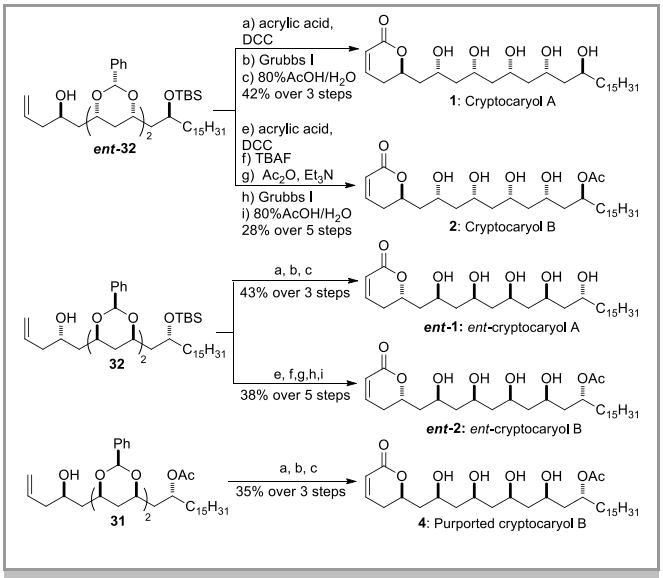
To install the *C*-5/*C*-15 with the opposite tetraol stereochemistry (***ent*-32**), all we need to do is apply the same sequences to the opposite ends of the tetraol precursors ***syn*-8** (Scheme 6). This began with a Dibal-H reduction of ***syn*-8** followed by an unselective 1-lithiopentadec-1-yne 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_3N, formic acid, 98%) gave a propargyl alcohol as a single diastereomer, which upon exposure to excess diimide 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 *C*-5 (*R*)-stereochemistry was installed by oxidation of the primary alcohol and addition of the (*S,S*)-Leighton reagent (95%).



Scheme 6 Synthesis of protected tetraol intermediates

With all the stereochemistry installed in homoallylic alcohol ***ent*-32**, it was readily converted into cryptocaryol A (**1**), by a three-step procedure. This began with an acrylation of the *C*-5 alcohol, ring closing metathesis with the Grubbs I reagent and aqueous acetic acid deprotection to give **1** (42% over three steps).[21] By replacing the *C*-15 TBS group with an acetate (TBAF then Ac_2O) after the acrylation at *C*-5, homoallylic 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.[1] Finally the homoallylic alcohol **31** was converted into purported cryptocaryol B (**4**), the initially assigned structure for cryptocaryol B, by a 3-step acrylation of the *C*-5 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 C_s and C_2 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.



Scheme 7 Synthesis of 1,3-*syn*-ploly/pyranones

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^{1}H and ^{13}C NMR spectra were recorded on a Varian 300, 400 or 500 MHz spectrometer. Chemical shifts were reported relative to internal tetramethylsilane (δ 0.00 ppm) or $CDCl_3$ (δ 7.26 ppm) or CD_3OD (δ 3.30 ppm) for ^{1}H NMR and $CDCl_3$ (δ 77.2 ppm) or CD_3OD (δ 49.05 ppm) for ^{13}C NMR. In the case of ^{19}F NMR, trifluoroacetic acid (δ –76.55 ppm) was used as an external reference for Mosher ester analyses. Infrared (IR) spectra were obtained on a FT-IR spectrometer. Optical rotations were measured with a digital polarimeter in the solvent specified. Melting points were determined with a standard melting point apparatus. Flash column chromatography was performed on 60-200 or 230-400 mesh silica gel. Analytical thin-layer chromatography was performed with precoated glassbacked plates and visualized by quenching of fluorescence and by charring after treatment with *p*-anisaldehyde or potassium permanganate stain. R_f values were obtained by elution in the stated solvent ratios. Diethyl ether, tetrahydrofuran, methylene dichloride and triethylamine were dried by passing through activated alumina column with argon gas pressure. Commercial reagents were used without purification unless otherwise noted. Air- and/or moisture-sensitive reactions were carried out under an atmosphere of argon/nitrogen using oven- or flame-dried glassware and standard syringe/septa techniques.

Procedures

2-((2R,4R,6R)-6-(2-((4-methoxybenzyl)oxy)ethyl)-2-phenyl-1,3-dioxan-4-yl)acetaldehyde (21): Diisobutylaluminum hydride (11.5 mL of a 1 M solution in CH_2Cl_2) was added to a –78 °C solution of the ester (3.06 g, 7.64 mmol) in CH_2Cl_2 (40 mL). After 30 minutes, acetone was added to quench the reaction and it was stirred for 10 minutes before warming to room temperature. A 20% solution of sodium potassium tartrate (30 mL) was added and the biphasic mixture was stirred until the two layers rapidly separated on cessation of stirring. The aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layer was washed with brine, filtered, and concentrated. The crude product was purified by silica gel chromatography to produce benzylidene protected diol **21** (2.63 g) in 93 % yield as a clear oil: R_f = 0.58 (3:2 hexanes:EtOAc), $[\alpha]_D$ = +37.0 (*c* 1.0, CH_2Cl_2) IR (neat) 3035, 3002, 2858, 2729, 2358, 2060, 1732, 1614, 1586, 1515, 1455, 1345, 1302, 1248, 1176, 1101 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.86 (dd, *J* = 2, 2 Hz, 1H), 7.44 (m, 2H), 7.34 (m, 3H), 7.26 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.57 (s, 1H), 4.47 (d, *J* = 12 Hz, 1H), 4.43 (d, *J* = 12 Hz, 1H), 4.42 (m, 1H), 4.09 (dddd, *J* = 11, 8, 4.5, 2.5 Hz, 1H), 3.79 (s, 3H), 3.67 (ddd, *J* = 9.5, 8.5, 5.5 Hz, 1H), 3.56 (ddd, *J* = 9.5, 5.5, 5.5 Hz, 1H), 2.80 (ddd, *J* = 17, 7.5, 2 Hz, 1H), 2.61 (ddd, *J* = 17, 5, 2 Hz, 1H), 1.92 (dddd, *J* = 13.5, 8, 5, 5 Hz, 1H), 1.84 (m, 1H), 1.69 (ddd, *J* = 13, 2.5, 2.5 Hz, 1H), 1.50 (ddd, *J* = 12.5, 11, 11 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 200.4, 159.2, 138.3, 130.5, 129.3, 128.7, 128.2, 128.2, 126.0, 113.8, 100.6, 73.7, 72.7, 71.9, 65.5, 55.3, 49.4, 36.7, 36.0; HRMS (ESI) calcd for [$C_{22}H_{26}O_5$ + Na + MeOH]$^+$: 425.1940 Found: 425.1952.

Ethyl (2E,4E)-6-((2S,4S,6R)-6-(2-((4-methoxybenzyl)oxy)ethyl)-2-phenyl-1,3-dioxan-4-yl)hexa-2,4-dienoate (22): To phosphonate **25** (469 mg, 2.11 mmol) in 8 mL of THF was added 81 mg (1.94 mmol) $LiOH·H_2O$ and 1.5 g of 4Å molecular sieves. This mixture was heated at reflux for 30 min. before 625 mg (1.69 mmol) of aldehyde **21** dissolved in 2 mL of THF was added. This mixture was heated at reflux for 6 h and then filtered through a plug of celite. The solvent was removed under reduced pressure and the crude product was purified by silica gel chromatography to produce dienoate **22** (523 mg) in 66% yield as a clear oil: R_f = 0.71 (3:2 hexanes:EtOAc), $[\alpha]_D$ = + 7.8 (*c* 1.16, CH_2Cl_2), IR (neat) 2948, 1714, 1644, 1614, 1586, 1514, 1454, 1367, 1302, 1250, 1173, 1097 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.46 (m, 2H), 7.35 (m, 3H), 7.26 (d, *J* = 9 Hz, 2H), 7.26 (m, 1H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.28 (dd, *J* = 15.3, 9.6 Hz, 1H), 6.20 (ddd, *J* = 15, 6.3, 6.3 Hz, 1H), 5.82 (d, *J* = 15.3 Hz, 1H), 5.51 (s, 1H), 4.48 (d, *J* = 11.7 Hz, 1H), 4.42 (d, *J* = 11.7 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 4.02 (dddd, *J* = 12, 7.5, 4.5, 2.5 Hz, 1H), 3.91 (m, 1H), 3.79 (s, 3H), 3.66 (ddd, *J* = 9, 9, 5.1 Hz, 1H), 3.56 (ddd, *J* = 9.6, 5.4, 5.4 Hz, 1H), 2.53 (ddd, *J* = 14.7, 6.3, 6.3 Hz, 1H), 2.42 (ddd, *J* = 14.4, 6.6, 6.6 Hz, 1H), 1.76-1.98 (m, 2H), 1.60 (ddd, *J* = 13.2, 2.4, 2.4, Hz, 1H), 1.44 (ddd, *J* = 13.2, 11.1, 11.1 Hz, 1H), 1.30 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.9, 159.0, 144.3, 138.8, 138.5, 130.6, 130.4, 129.1, 128.4, 128.0, 125.9, 120.0, 113.6, 100.3, 75.7, 73.5, 72.5, 65.4, 60.1, 55.1, 39.2, 36.5, 35.9, 14.2; HRMS (ESI) calcd for [$C_{28}H_{34}O_6$ + Na]$^+$: 489.2253 Found: 489.2227.

Ethyl (4R,5R,E)-4,5-dihydroxy-6-((2R,4S,6R)-6-(2-((4-methoxybenzyl)oxy)ethyl)-2-phenyl-1,3-dioxan-4-yl)hex-2-enoate(23): Into 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, $K_3Fe(CN)_6$ (277 mg, 0.84 mmol), K_2CO_3 (116 mg, 0.84 mmol), $MeSO_2NH_2$ (27 mg, 0.28 mmol) and $(DHQD)_2$-PHAL (13 mg, 16.8 μmol). The mixture was stirred at room temperature for 15 minutes and then cooled to 0°C. To this solution was added OsO_4 (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 brine, 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 clear oil: R_f = 0.16 (3:2 hexanes:EtOAc), $[\alpha]_D$ = +18.6 (*c* 1.2, CH_2Cl_2);), IR (neat) 3478, 2914, 1713, 1660, 1613, 1586, 1547, 1514, 1463, 1454, 1304, 1100 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.41 (m, 2H), 7.35 (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, 1H), 4.20 (q, *J* = 7 Hz, 2H), 4.19 (m, 2H), 4.07 (dddd, *J* = 10.5, 7.5, 4, 2 Hz, 1H), 3.93 (dddd, *J* = 9.5, 4.5, 2.5, 2.5 Hz, 1H), 3.79 (s, 3H), 3.65 (ddd, *J* = 9, 8, 5 Hz, 1H), 3.56 (ddd, *J* = 9.5, 5.5, 5.5 Hz, 1H), 1.92 (m, 2H), 1.84 (m, 1H), 1.77 (ddd, *J* = 15, 3, 3 Hz, 1H), 1.62 (m, 1H), 1.52 (ddd, *J* = 13, 11, 11 Hz, 1H), 1.29 (t, *J* = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ166.3, 159.2, 146.8, 138.1, 130.5, 129.4, 129.0, 128.4, 126.0, 122.4, 113.8, 100.7, 80.7, 77.1, 73.8, 73.1, 72.7, 65.4, 60.5, 55.3, 38.6, 37.0, 36.0, 14.3; HRMS (ESI) calcd for [$C_{28}H_{36}O_8$ + Na]$^+$: 523.2308 Found: 523.2329.

Ethyl (E)-3-((4R,5R)-5-(((2R,4R,6R)-6-(2-((4-methoxybenzyl)oxy)ethyl)-2-phenyl-1,3-dioxan-4-yl)methyl)-2-oxo-1,3-dioxolan-4-yl)acrylate(23a): Into a 10 mL volumetric flask containing 90 mg (0.18 mmol) of diol **23** and 57 μL pyridine was placed 2 mL of CH_2Cl_2. This mixture was cooled to 0 ºC and 27 mg of triphosgene (0.09 mmol) dissolved in 1 mL of CH_2Cl_2 was added slowly using an addition funnel.

The reaction was stirred for 1.5 h and quenched with saturated aqueous NH_4Cl (4 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate (10 mL), brine (10 mL), and dried over anhydrous sodium sulfate. After removal of the solvents in vacuo, flash chromatography on silica gel afforded **23a** as a clear, colorless oil (87 g, 92%): R_f = 0.11 (4:1 hexanes:EtOAc); $[\alpha]_D$ = +39.3 (*c* 1.7, CH_2Cl_2); IR (neat) 2920, 1810, 1716, 1668, 1615, 1586, 1560, 1516, 1456, 1248 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.42 (m, 2H), 7.36 (m, 3H), 7.27 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.83 (dd, *J* = 15.6, 5.7 Hz, 1H), 6.14 (dd, *J* = 15.6, 1.5 Hz, 1H), 5.51 (s, 1H), 5.14 (ddd, *J* = 7.2, 5.7, 1.5 Hz, 1H), 4.63 (ddd, *J* = 6.6, 5.1, 5.1 Hz, 1H), 4.48 (d, *J* = 11.7 Hz, 1H), 4.43 (d, *J* = 11.7 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 4.02-4.18 (m, 2H), 3.80 (s, 3H), 3.66 (ddd, *J* = 9.3, 8.1, 5.1 Hz, 1H), 3.57 (ddd, *J* = 11.1, 5.4, 5.4 Hz, 1H), 2.08-2.18 (m, 2H), 1.80-1.98 (m, 2H), 1.58 (m, 2H), 1.29 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): 164.7, 159.0, 153.5, 139.1, 137.9, 130.3, 129.2, 128.7, 128.1, 125.8, 124.8, 113.6, 100.5, 79.4, 78.0, 73.6, 72.5, 71.9, 65.2, 60.9, 55.1, 37.7, 36.2, 35.8, 14.0; HRMS (ESI) calcd for $[C_{29}H_{34}O_9 + Na]^+$: 549.2101 Found: 549.2082.

Ethyl (*S*,*E*)-5-hydroxy-6-((2*R*,4*S*,6*R*)-6-(2-((4-methoxybenzyl)oxy) ethyl)-2-phenyl-1,3-dioxan-4-yl)hex-2-enoate(*syn*-24): Into a 10 mL, round bottomed flask fitted with a condenser and maintained under nitrogen was placed 80 mg (0.152 mmol) of **23a**, 1.6 mg (1.5 μmol) of $Pd_2(dba)_3{\cdot}CHCl_3$, 1 mg (3.8 μmol) of PPh_3, and 1.5 mL of THF. Triethylamine (63 μL, 0.46 mmol) and formic acid (17 μL, 0.46 mmol) were added and the mixture was allowed to reflux for three hours. The reaction was cooled to room temperature and quenched with saturated aqueous sodium bicarbonate (2 mL). The aqueous layer was extracted with ether (3 x 5 mL). The organic layer was washed with brine (5 mL) and dried with anhydrous sodium sulfate. After removal of the solvents in vacuo, flash chromatography on silica gel afforded ***syn*-24** as a yellow oil (66 mg, 90%): R_f = 0.22 (3:2, hexanes:EtOAc); $[\alpha]_D$ = +7.7 (*c* 1.0, CH_2Cl_2); IR (neat) 3518, 3035, 2938, 2863, 1886, 1722, 1714, 1658, 1652, 1614, 1586, 1514, 1463, 1454, 1368, 1302, 1248, 1174 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.41 (m, 2H), 7.34 (m, 3H), 7.26 (d, *J* = 9 Hz, 2H), 6.98 (ddd, *J* = 15.5, 7.5, 7.5 Hz, 1H), 6.86 (d, *J* = 8.5 Hz, 2H), 5.90 (ddd, *J* = 15.5, 1.5, 1.5 Hz, 1H), 5.56 (s, 1H), 4.46 (d, *J* = 12 Hz, 1H), 4.42 (d, *J* = 12 Hz, 1H), 4.18 (q, *J* = 7 Hz, 2H), 4.03-4.15 (m, 3H), 3.79 (s, 3H), 3.65 (ddd, *J* = 9.5, 8.5, 5 Hz, 1H), 3.55 (ddd, *J* = 9.5, 5.5, 5.5 Hz, 1H), 2.39 (m, 2H), 1.92 (dddd, *J* = 14, 8.5, 5.5, 5.5 Hz, 1H), 1.76-1.86 (m, 2H), 1.68 (ddd, *J* = 14.5, 2.5, 2.5 Hz, 1H), 1.60 (ddd, *J* = 13, 2.5, 2.5 Hz, 1H), 1.50 (ddd, *J* = 13, 11, 11 Hz, 1H), 1.29 (q, *J* = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.3, 159.2, 145.0, 138.2, 130.5, 129.3, 128.9, 128.3, 126.0, 123.8, 113.8, 100.6, 77.4, 73.8, 72.7, 70.0, 65.5, 60.3, 55.3, 42.1, 40.2, 37.1, 36.0, 14.3; HRMS (ESI) calcd for $[C_{28}H_{36}O_7 + Na]^+$: 507.2359 Found: 507.2348.

Ethyl 2-((2R,4R,6R)-6-(((2R,4R,6R)-6-(2-((4-methoxybenzyl)oxy) ethyl)-2-phenyl-1,3-dioxan-4-yl)methyl)-2-phenyl-1,3-dioxan-4-yl)acetate (*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 diluted with ether (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 Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by silica gel chromatography to produce (*syn, syn, syn*) dibenzylidene ***ent-syn-8*** (58 mg) in 63% yield as a clear oil: R_f = 0.26 (4:1 hexanes:EtOAc); $[\alpha]_D$ = +18.9 (*c* 0.9, CH_2Cl_2); IR (neat) 2920, 2864, 1732, 1614, 1586, 1514, 1455, 1346, 1303, 1248, 1216, 1112, 1028 cm^{-1}; ^1H NMR ($CDCl_3$, 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 (dddd, *J* = 11.1, 6.6, 6.6, 2.1 Hz, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 4.02-4.18 (m, 3H), 3.79 (s, 3H), 3.69 (ddd, *J* = 9, 8.1, 5.1 Hz, 1H), 3.60 (ddd, *J* = 9.6, 5.7, 5.7 Hz, 1H), 2.76 (dd, *J* = 15.6, 7.2 Hz, 1H), 2.54 (dd, *J* = 15.6, 6 Hz, 1H), 2.16 (ddd, *J* = 15.6, 7.2 Hz, 1H), 1.64-2.00 (m, 5H), 1.45-1.62 (m, 2H), 1.28 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.6, 160.0, 138.6, 138.2, 130.4, 129.2, 128.5, 128.4, 128.0, 128.0, 125.9, 125.9, 113.6, 100.4, 100.3, 73.6, 73.1, 72.9, 72.9, 72.5, 65.5, 60.5, 55.1, 41.6, 40.9, 36.7, 36.2, 36.0, 14.1; HRMS (ESI) calcd for $[C_{35}H_{42}O_8 + Na]^+$: 613.2777 Found: 613.2785.

(*R*)-1-((2*S*,4*R*,6*S*)-6-(2-((4-Methoxybenzyl)oxy)ethyl)-2-phenyl-1,3-dioxan-4-yl)pent-4-en-2-ol (*syn*-26): To a solution of ester **19f** in 10 mL of CH_2Cl_2 at –78 ºC was added 3.75 mL (1.0 M solution in CH_2Cl_2) of diisobutylaluminum 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 CH_2Cl_2 (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. Spectroscopic data for the *syn* diastereomer ***syn*-26**: R_f = 0.19 (4:1 hexanes:EtOAc); $[\alpha]_D^{21}$ = –19.2 (*c* 0.92, CH_2Cl_2); IR (neat) 3532, 3071, 2918, 1727, 1641, 1614, 1586, 1515, 1455, 1303, 1247, 1174, 1102 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.43 (m, 2H), 7.33 (m, 3H), 7.26 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.85 (dddd, *J* = 17.5, 10.5, 7, 7 Hz, 1H), 5.56 (s, 1H), 5.13 (m, 2H), 4.47 (d, *J* = 11.5 Hz, 1H), 4.43 (d, *J* = 11.5 Hz, 1H), 4.12 (dddd, *J* = 11.5, 8.5, 3.5, 2.5 Hz, 1H), 4.06 (dddd, *J* = 11, 8, 4.5, 2.5 Hz, 1H), 3.98 (dddd, *J* = 9, 6, 6, 2.5 Hz, 1H), 3.79 (s, 3H), 3.66 (ddd, *J* = 9.5, 8.5, 5 Hz, 1H), 3.56 (ddd, *J* = 9.5, 5.5, 5.5 Hz, 1H), 2.26 (m, 2H), 1.92 (dddd, *J* = 14, 8.5, 5.5, 5.5 Hz, 1H), 1.84 (m, 1H), 1.79 (ddd, *J* = 14.5, 9.5, 9.5 Hz, 1H), 1.70 (ddd, *J* = 14.5, 3.5, 2.5 Hz, 1H), 1.62 (ddd, *J* = 13, 2.5, 2.5 Hz, 1H), 1.50 (ddd, *J* = 13.5, 11.5, 11.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.2, 138.3, 134.8, 130.5, 129.3, 128.8, 128.2, 126.0, 117.6, 113.8, 100.6, 77.3, 73.9, 72.7, 70.4, 65.5, 55.3, 42.0, 42.0, 37.2, 36.0; HRMS (ESI) calcd for $[C_{25}H_{32}O_5 + Na]^+$: 435.2147 Found: 435.2132.

Spectroscopic data for the *anti* diastereomer ***anti*-26**: R_f = 0.19 (4:1 hexanes:EtOAc); $[\alpha]_D$ = –25.6 (*c* 1.0, CH_2Cl_2); IR (neat) 3446, 3069, 2917, 2861, 1718, 1700, 1684, 1654, 1637, 1613, 1586, 1514, 1456, 1405, 1100, 1028 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.44 (m, 2H), 7.34 (m, 3H), 7.26 (d, *J* = 9 Hz, 2H), 6.87 (d, *J* = 9 Hz, 2H), 5.84 (dddd, *J* = 17.5, 11, 7.5, 7.5 Hz, 1H), 5.54 (s, 1H), 5.15 (m, 2H), 4.47 (d, *J* = 11.5 Hz, 1H), 4.43 (d, *J* = 11.5 Hz, 1H), 4.17 (m, 1H), 4.04 (m, 2H), 3.79 (s, 3H), 3.67 (ddd, *J* = 9, 8.5, 5 Hz, 1H), 3.57 (ddd, *J* = 9.5, 5.5, 5.5 Hz, 1H), 2.30 (m, 2H), 1.93 (dddd, *J* = 14, 8.5, 5.5, 5.5 Hz, 1H), 1.84 (m, 1H), 1.78 (ddd, *J* = 15, 8.5, 3 Hz, 1H), 1.69 (ddd, *J* = 14.5, 9, 3 Hz, 1H), 1.55 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.2, 138.7, 134.8, 130.6, 129.3, 128.6, 128.2, 126.0, 118.0, 113.8, 100.6, 74.2, 73.9, 72.7, 67.0, 65.6, 55.3, 42.3, 42.1, 36.9, 36.1; HRMS (ESI) calcd for $[C_{25}H_{32}O_5 + Na]^+$: 435.2147 Found: 435.2132.

1-((2*S*,4*S*,6*S*)-6-(2-((4-methoxybenzyl)oxy)ethyl)-2-phenyl-1,3-dioxan-4-yl)pent-4-en-2-one (28): Into a 10 mL round bottomed flask was placed 90 mg of alcohol in 2 mL of CH_2Cl_2. To this solution was added of 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 (89% yield) of ketone **28** as a clear oil. $[\alpha]_D$ = +22.3 (*c* 1.0, CH_2Cl_2); IR (neat) 2922, 1714, 1644, 1614, 1586, 1515, 1455, 1360, 1347, 1245, 1174, 1098, 1028 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.42 (m, 2H), 7.33 (m, 3H), 7.26 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.93 (dddd, *J* = 17.1, 10.2, 7.2, 7.2 Hz, 1H), 5.54 (s, 1H), 5.18 (m, 2H), 4.47 (d, *J* = 11.7 Hz, 1H), 4.43 (d, *J* = 11.7 Hz, 1H), 4.34 (m, 1H), 4.06 (dddd, *J* = 10.5, 7.5, 4.5, 2.7 Hz, 1H), 3.79 (s, 3H), 3.66 (ddd, *J* = 9, 7.8, 5.4 Hz, 1H), 3.56 (ddd, *J* = 9.3, 5.7, 5.7 Hz, 1H), 3.25 (m, 2H), 2.90 (dd, *J* = 16.2, 7.2 Hz, 1H), 2.57 (dd, *J* = 16.2, 5.7 Hz, 1H), 1.84 (m, 2H), 1.70 (ddd, *J* = 12.9, 2.4, 2.4 Hz, 1H), 1.40 (ddd, *J* = 12.9, 11.1, 11.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 206.2, 159.0, 138.3, 130.3, 130.0,

129.1, 128.4, 128.0, 125.8, 119.0, 113.6, 100.3, 73.5, 72.9, 72.5, 65.4, 55.1, 48.7, 48.0, 36.7, 35.9; HRMS (ESI) calcd for $[C_{25}H_{30}O_5 + Na]^+$: 433.1991 Found: 433.1997.

(*R*)-1-((2*S*,4*R*,6*S*)-6-(2-((4-Methoxybenzyl)oxy)ethyl)-2-phenyl-1,3-dioxan-4-yl)pent-4-en-2-ol (*syn*-26):To a solution of ketone (55 mg, 0.13 mmol) in THF (1.5 mL) at −90°C was added a 1.0M solution of L-selectride in THF (0.26 mL, 0.26 mmol). After stirring for 3 h a solution of 30% H_2O_2 and 1 M NaOH was added and the reaction was allowed to warm to room temperature and diluted with Et_2O. The organic layer was separated, washed with a saturated solution of sodium thiosulfate, brine, and then dried (Na_2SO_4), filtered, and concentrated. The crude material was purified by flash chromatography to provide 48 mg (89%) of alcohol **26** as a mixture (4:1) of diastereomers.

(*R*)-1-((2*S*,4*R*,6*S*)-6-(2-((4-Methoxybenzyl)oxy)ethyl)-2-phenyl-1,3-dioxan-4-yl)pent-4-en-2-ol (*syn*-26): To a stirred solution of ***ent*-21** (2.23 g, 6.02 mmol) in dichloromethane (20 mL) at −10 °C was added a solution of (*S*,*S*)-Leighton reagent (5.01 g, 9.03 mmol) in dichloromethane (10 mL) slowly via syringe, followed by scandium triflate (74.1 mg, 0.151 mmol) under N_2. Then the resulting mixture was transferred to freezer at −10 °C. After 12 h, the reaction was quenched by adding 1 N hydrochloric acid (20 mL). The formed solid was filtered through a fritted funnel, and the filtrate was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography (10 to 30% EtOAc in hexanes) on silica gel (50 mL) to afford ***syn*-26** (1.79 g, 72%, dr = 8.7:1.0) as a colorless oil.

(*R*)-1-((2*S*,4*R*,6*S*)-6-(2-((4-Methoxybenzyl)oxy)ethyl)-2-phenyl-1,3-dioxan-4-yl)pent-4-en-2-ol (*anti*-26): To a stirred solution of ***ent*-21** (1.10 g, 3.0 mmol) in dichloromethane (10 mL) at −10 °C was added a solution of (*R*,*R*)-Leighton reagent (2.50 g, 4.51 mmol) in dichloromethane (5 mL) slowly via syringe, followed by scandium triflate (37 mg, 0.075 mmol) under N_2. Then the resulting mixture was transferred to freezer at −10 °C. After 12 h, the reaction was quenched by adding 1 N hydrochloric acid (10 mL). The formed solid was filtered through a fritted funnel, and the filtrate was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography (10 to 30% EtOAc in hexanes) on silica gel (50 mL) to afford ***anti*-26** (1.79 g, 72%, dr = 8:1) as a colorless oil.

Ethyl (S,E)-5-hydroxy-6-((2S,4R,6S)-6-(2-((4-methoxybenzyl)oxy)ethyl)-2-phenyl-1,3-dioxan-4-yl)hex-2-enoate(*ent-anti*-24): To a stirred solution of ***anti*-26** (2.95 g, 7.15 mmol) in dichloromethane (10 mL) at room temperature was added ethyl acrylate (30.4 mL, 0.286 mol), followed by the Grubbs second-generation catalyst (146 mg, 0.179 mmol) under N_2. The resulting mixture was degassed by two freeze−pump−thaw cycles, then warmed to room temperature and stirred at the same temperature. After 3 h, the mixture was diluted with hexanes (100 mL), and purified by flash chromatography (20 to 50% EtOAc in hexanes) on silica gel (100 mL) to afford ***anti*-29** (3.43 g, 99%) as a colorless oil: R_f = 0.34 (50% EtOAc in hexanes); $[\alpha]_D^{21}$ = −15.6 (*c* 1.79, CH_2Cl_2); IR (neat) 3501, 3037, 2917, 1888, 1715, 1698, 1652, 1614, 1586, 1515, 1456, 1246 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.42 (m, 2H), 7.34 (m, 3H), 7.26 (d, *J* = 8.7 Hz, 2H), 6.98 (ddd, *J* = 15.6, 7.2, 7.2 Hz, 1H), 6.86 (d, *J* = 8.7 Hz, 2H), 5.91 (ddd, *J* = 15.6, 1.5, 1.5 Hz, 1H), 5.52 (s, 1H), 4.47 (d, *J* = 11.7 Hz, 1H), 4.42 (d, *J* = 11.7 Hz, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 4.17 (m, 2H), 4.05 (m, 1H), 3.78 (s, 3H), 3.65 (ddd, *J* = 9.3, 8.1, 5.4 Hz, 1H), 3.56 (ddd, *J* = 9.6, 5.4, 5.4 Hz, 1H), 2.40 (m, 2H), 1.80-1.98 (m, 2H), 1.72-1.78 (m, 2H), 1.55 (m, 2H), 1.28 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.1, 159.0, 144.9, 138.4, 130.3, 129.1, 128.5, 128.0, 125.8, 123.7, 113.6, 100.4, 73.9, 73.7, 72.5, 66.7, 65.4, 60.2, 55.1, 41.9, 40.3, 36.5, 35.9, 14.2; HRMS (ESI) calcd for $[C_{28}H_{36}O_7 + Na]^+$: 507.2359 Found: 507.2329.

Ethyl 2-((2R,4R,6R)-6-(((2S,4S,6S)-6-(2-((4-methoxybenzyl)oxy)ethyl)-2-phenyl-1,3-dioxan-4-yl)methyl)-2-phenyl-1,3-dioxan-4-yl)acetate(*anti*-8): To a stirred solution of ***anti*-29** (0.75 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 (0.02g, 0.175 mmol) under N_2. 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*-8** (0.72 g, 77%) as a colorless oil: R_f = 0.41 (30% EtOAc in hexanes); $[\alpha]_D^{21}$ = −18.0 (CH_2Cl_2, c = 1.72); IR (neat): 2918, 2859, 1732, 1512, 1247, 1107, 1010 cm-1 ; ^1H NMR (500 MHz, CDCl3) δ 7.57–7.41 (m, 4H), 7.43– 7.28 (m, 6H), 7.26 (d, *J* = 9.0 Hz, 2H), 6.86 (d, *J* = 9.0 Hz, 2H), 5.58 (s, 1H), 5.53 (s, 1H), 4.45 (d, *J* = 11.6 Hz, 1H), 4.43 (d, *J* = 11.5 Hz, 2H), 4.34 (dddd, *J* = 11.5, 7.0, 7.0, 2.5 Hz, 1H), 4.17 (q, *J* = 7.0 Hz, 2H), 4.13 (m, 3H), 3.78 (s, 3H), 3.68 (ddd, *J* = 8.5, 8.5, 5.0 Hz, 1H), 3.58 (ddd, *J* = 9.5, 5.5, 5.5 Hz, 1H), 2.74 (dd, *J* = 15.5, 7.0 Hz, 1H), 2.53 (dd, *J* = 15.5, 6.0 Hz, 1H), 2.15 (ddd, *J* = 14.0, 7.0, 7.0 Hz, 1H), 1.93 (dddd, *J* = 14.0, 8.0, 5.0, 5.0 Hz, 1H), 1.86 (dddd, *J* = 14.0, 8.0, 5.5, 4.5 Hz, 1H), 1.81 (ddd, *J* = 13.0, 2.5, 2.5 Hz, 1H), 1.76 (ddd, *J* = 14.0, 6.0, 6.0 Hz, 1H), 1.68 (ddd, *J* = 13.0, 2.5, 2.5 Hz, 1H), 1.55 (ddd, *J* = 13.0, 11.5, 11.5 Hz, 1H), 1.51 (ddd, *J* = 13.0, 11.5, 11.5 Hz, 1H), 1.27 (t, *J* = 7.2, 3H); 13C NMR (100 MHz, $CDCl_3$) δ 171.0, 159.4, 139.0, 138.6, 130.7, 129.6, 129.0, 128.9, 128.41, 128.38, 126.29, 126.26, 114.0, 100.8, 100.7, 74.0, 73.5, 73.27, 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 $C_{35}H_{42}O_8Na$ $[M+Na]^+$: 613.2777 Found: 613.2785.

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Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO (this text will be deleted prior to publication)

References

1 Grkovic, T.; Blees, J. S.; Colburn, N. H.; Schmid, T.; Thomas, C. L.; Henrich, C. J.; McMahon, J. B.; Gustafson, K. R. *J. Nat. Prod.* **2011**, *74*, 1015-1020.

2 (a) Kobayashi, Y.; Tan, C.-H.; Kishi, Y. *Helv. Chim. Acta* **2000**, *83*, 2562-2571. (b) Higashibayashi, S.; Czechtizky, W.; Kobayashi, Y.; Kishi, Y. *J. Am. Chem. Soc.* **2003**, *125*, 14379-14393.

3 Snatzke, G. *Angew. Chem. Int. Ed.* **1968**, *7*, 14-25.

4 Wang, Y.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2013**, *135*, 9334-9337.

5 (a) Dias, L. C.; Kuroishi, P. K.; de Lucca, E. C. *Org. Biomol. Chem.* **2015**, *13*, 3575-3584. (b) Brun, E.; Bellosta, V.; Cossy, J. *J. Org. Chem.* **2015**, *80*, 8668-8676. (c) Bredenkamp, A.; Wegener, M.; Hummel, S.; Haring, A. P.; Kirsch, S. F. *Chem. Commun.* **2016**, *52*, 1875-1878.

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

7 Cuccarese, M. F.; Wang, Y.; Beuning, P. J.; O'Doherty, G. A. *ACS Med. Chem. Lett.* **2014**, *5*, 522-526.

8 For other approach to 1,3-syn-polyols, see: (a) Rychnovsky, S. D. *Chem. Rev.* **1995**, *95*, 2021–40. (b) Rychnovsky, S. D.; Hoye, R. C. *J. Am. Chem. Soc.* **1994**, *116*, 1753-1765. (c) Rychnovsky, S. D.; Khire, U. R.; Yang, G. *J. Am. Chem. Soc*. **1997**, *119*, 2058-2059. (d) Carreira, E. M.; Singer, R. A.; Lee, W. *J. Am. Chem. Soc*. **1994**, *116*, 8837-8838. (e) Evans, D. A.; Murry, J. A.; Kozlowski, M. C. *J. Am. Chem. Soc*. **1996**, *118*, 5814-5815. (f) Evans, D. A.; Coleman, P. J.; Cote, B. *J. Org. Chem*. **1997**, 62, 788-789. (g) Paterson, I.; Oballa, R. M.; Norcross, R. D. *Tetrahedron Lett.* **1996**, 37, 8581-8584. (h) Paterson, I.; Gibson, K. R.; Oballa, R. M. *Tetrahedron Lett*. **1996**, *37*, 8585-8588.

9 Iterative asymmetric hydration of polyenes: (a) Wang, Y.; Xing, Y.; Zhang, Q.; O'Doherty, G. A. *Chem. Commun.* **2011**, *47*, 8493-8505. (b) Ahmed, Md. M.; Mortensen, M. S.; O'Doherty, G. A. *J. Org. Chem.* **2006**, *71*, 7741-7746. (c) Hunter, T. J.; O'Doherty, G. A. *Org. Lett*. **2001**, *3*, 1049-1052.

10 Syntheses of related 1,3-polyol-natural products: (a) Hunter, T. J.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 2777-2780. (b) Smith, C. M.; O'Doherty, G. A. *Org. Lett.* **2003**, *5*, 1959-1962. (c) Garaas, S. D.; Hunter, T. J.; O'Doherty, G. A. *J. Org. Chem.* **2002**, *67*, 2682-2685. For alternative approaches, see, ref. 5 and (d) Melillo, B.; Smith, A. B. *Org. Lett*. **2013**, *15*, 2282-2285.

11 (a) Guo, H.; Mortensen, M. S.; O'Doherty, G. A. *Org. Lett.* **2008**, *10*, 3149-3152. (b) Gao, D.; O'Doherty, G. A. *Org. Lett.* **2010**, *12*, 3752-3755. (c) Li, M.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 6087-6090. (d) Li, M.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 3987-3990.

12 Evans, D. A.; Gauchet-Prunet, J. A. *J. Org. Chem.* **1993**, *58*, 2446-2453.

13 (a) Xu, D.; Crispino, G. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7570-7571. (b) Y. Zhang and G. A. O'Doherty, *Tetrahedron* **2005**, *61*, 6337–6351. (c) Becker, H.; Soler, M. A.; Sharpless, K. B. *Tetrahedron* **1995**, *51*, 1345-76. (d) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev*., **1994**, *94*, 2483–2547.

14 All levels of enantioinduction were determined by HPLC analysis (8% IPA/Hexane, Chiralcel OD) and/or Mosher ester analysis. a) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143. b) Yamaguchi, S.; Yasuhara, F.; Kabuto, K. T. *Tetrahedron* **1976**, *32*, 1363.

15 (a) Tsuji, J.; Minami, I. *Acc. Chem. Res*. **1987**, *20*, 140. (b)Hughes, G.; Lautens, M.; Wen, C. *Org. Let.* **2000**, *2*, 107-110.

16 For alternative approaches to δ-hydroxy-1-enoates see: (a) Fleming, I. *Bull. Soc. Chem. Fr*. **1981**, *2*, 7-13. (b) Barloy-Da Silva, C.; Benkouider, A.; Pale, P. *Tetrahedron Lett*. **2000**, *41*, 3077-3081. (c) Albaugh-Robertson, P.; Katzenellenbogen, J. A. *J. Org. Chem.* **1983**, *48*, 5288-302. (d) Miyazawa, M; Matsuoka, E.; Sasaki, S.; Oonuma, S.; Maruyam, K. Miyashita, M. *Chem. Lett.* **1998**, 109-110. (e) Keck, G. E.; Palani, A.; McHardy, S. F. *J. Org. Chem.* **1994**, *59*, 3113. (f) Solladie, G.; Gressot, L.; Colobert, F. *Eur. J. Org. Chem*. **2000**, 357-364.

17 (a) Burden, R. S.; Crombie, L. *J. Chem. Soc. C* **1969**, 2477. (b) Bohlmann, F.; Zdero, C. *Chem. Ber*. **1973**, *106*, 3779. (c) Roush, W. R. *J. Am. Chem. Soc*. **1980**, *102*, 1390. (d) Evans, D. A.; Fitch, D. M. *J. Org. Chem*. **1997**, *62*, 454. (e) Posner, G. H.; Lee, J. K.; White, M. C.; Hutchings, R. H.; Dai, H.; Kachinski, J. L.; Dolan, P.; Kensler, T. W. *J. Org. Chem*. **1997**, *62*, 3299. (f) Barrett, A. G. M.; Hamprecht, D.; White, A. J. P.; Williams, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 8608. (g) Takacs, J. M.; Jaber, M. R.; Clement, F.; Walters, C. *J. Org. Chem*. **1998**, *63*, 6757. (h) Nazare, M.; Waldmann, H. *Chem. Eur. J.* **2001**, *7*, 3363. (i) Sun, M.; Deng, Y.; Batyreva, E.; Sha, W.; Salomon, R. G. *J. Org. Chem*. **2002**, *67*, 3575. (j) Tsuzuki, T.; Tanaka, K.; Kuwahara, S.; Miyazawa, T. *Lipids* **2005**, *40*, 147. (k) Barth, R.; Mulzer, *J. Angew. Chem., Int. Ed*. **2007**, *46*, 5791. Markiewicz, J. T.; Schauer, D. J.; Lofstedt, J.; Corden, S. J.; Wiest, O.; Helquist, P. *J. Org. Chem*. **2010**, *75*, 2061–2064.

18 (a) Kubota, K.; Leighton, J. L. *Angew. Chem. Int. Ed.* **2003**, *115*, 976-978. (b) Chalifoux, W. A.; Reznik, S. K.; Leighton, J. L. *Nature* **2012**, *487*, 86-89.

19 Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247-2250.

20 Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 7562-7563.

21 (a) Grubbs, R. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 3760–3765. (b) Gosh, A. K.; Bilcer, G. *Tetrahedron Lett.* **2000**, *41*, 1003-1006. (c) Boger, D. L.; Ichikawa, D.; Zhong, W. *J. Am. Chem. Soc.* **2001**, *123*, 4161. (d) Reddy, M. V. R.; Rearick, J. P.; Hoch, N.; Ramachandran, P. V. *Org. Lett.* **2001**, *3*, 19-20. (e) Smith, A. B.; Brandt, B. M. *Org. Lett.* **2001**, *3*, 1685-88. (f) Reddy, M. V. R.; Yucel, A. J.; Ramachandran, P. V. *J. Org. Chem.* **2001**, *66*, 2512-14. (g) S. D. Garaas, T. J. Hunter, and G. A. O'Doherty, *J. Org. Chem.* **2002**, *67*, 2682-2685.

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1 Grkovic, T.; Blees, J. S.; Colburn, N. H.; Schmid, T.; Thomas, C. L.; Henrich, C. J.; McMahon, J. B.; Gustafson, K. R. *J. Nat. Prod.* **2011**, *74*, 1015-1020.

2 (a) Kobayashi, Y.; Tan, C.-H.; Kishi, Y. *Helv. Chim. Acta* **2000**, *83*, 2562-2571. (b) Higashibayashi, S.; Czechtizky, W.; Kobayashi, Y.; Kishi, Y. *J. Am. Chem. Soc.* **2003**, *125*, 14379-14393.

3 Snatzke, G. *Angew. Chem. Int. Ed.* **1968**, *7*, 14-25.

4 Wang, Y.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2013**, *135*, 9334-9337.

5 (a) Dias, L. C.; Kuroishi, P. K.; de Lucca, E. C. *Org. Biomol. Chem.* **2015**, *13*, 3575-3584. (b) Brun, E.; Bellosta, V.; Cossy, J. *J. Org. Chem.* **2015**, *80*, 8668-8676. (c) Bredenkamp, A.; Wegener, M.; Hummel, S.; Haring, A. P.; Kirsch, S. F. *Chem. Commun.* **2016**, *52*, 1875-1878.

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

7 Cuccarese, M. F.; Wang, Y.; Beuning, P. J.; O'Doherty, G. A. *ACS Med. Chem. Lett.* 2014, 5, 522-526.

8 For other approach to 1,3-syn-polyols, see: (a) Rychnovsky, S. D. *Chem. Rev.* **1995**, *95*, 2021–40. (b) Rychnovsky, S. D.; Hoye, R. C. *J. Am. Chem. Soc.* **1994**, *116*, 1753-1765. (c) Rychnovsky, S. D.; Khire, U. R.; Yang, G. *J. Am. Chem. Soc.* **1997**, *119*, 2058-2059. (d) Carreira, E. M.; Singer, R. A.; Lee, W. *J. Am. Chem. Soc.* **1994**, *116*, 8837-8838. (e) Evans, D. A.; Murry, J. A.; Kozlowski, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 5814-5815. (f) Evans, D. A.; Coleman, P. J.; Cote, B. *J. Org. Chem.* **1997**, 62, 788-789. (g) Paterson, I.; Oballa, R. M.; Norcross, R. D. *Tetrahedron Lett.* **1996**, 37, 8581-8584. (h) Paterson, I.; Gibson, K. R.; Oballa, R. M. *Tetrahedron Lett.* **1996**, *37*, 8585-8588.

9 Iterative asymmetric hydration of polyenes: (a) Wang, Y.; Xing, Y.; Zhang, Q.; O'Doherty, G. A. *Chem. Commun.* **2011**, *47*, 8493-8505. (b) Ahmed, Md. M.; Mortensen, M. S.; O'Doherty, G. A. *J. Org. Chem.* **2006**, *71*, 7741-7746. (c) Hunter, T. J.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 1049-1052.

10 Syntheses of related 1,3-polyol-natural products: (a) Hunter, T. J.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 2777-2780. (b) Smith, C. M.; O'Doherty, G. A. *Org. Lett.* **2003**, *5*, 1959-1962. (c) Garaas, S. D.; Hunter, T. J.; O'Doherty, G. A. *J. Org. Chem.* **2002**, *67*, 2682-2685. For alternative approaches, see, ref. 5 and (d) Melillo, B.; Smith, A. B. *Org. Lett.* **2013**, *15*, 2282-2285.

11 (a) Guo, H.; Mortensen, M. S.; O'Doherty, G. A. *Org. Lett.* **2008**, *10*, 3149-3152. (b) Gao, D.; O'Doherty, G. A. *Org. Lett.* **2010**, *12*, 3752-3755. (c) Li, M.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 6087-6090. (d) Li, M.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 3987-3990.

12 Evans, D. A.; Gauchet-Prunet, J. A. *J. Org. Chem.* **1993**, *58*, 2446-2453.

13 (a) Xu, D.; Crispino, G. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7570-7571. (b) Y. Zhang and G. A. O'Doherty, *Tetrahedron* **2005**, *61*, 6337–6351. (c) Becker, H.; Soler, M. A.; Sharpless, K. B. *Tetrahedron* **1995**, *51*, 1345-76. (d) Kolb, H. C.; VanNieuwenhze, M. S.; K. Barry Sharpless, K. B. *Chem. Rev.*, **1994**, *94*, 2483–2547.

14 All levels of enantioinduction were determined by HPLC analysis (8% IPA/Hexane, Chiralcel OD) and/or Mosher ester analysis. a) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143. b) Yamaguchi, S.; Yasuhara, F.; Kabuto, K. T. *Tetrahedron* **1976**, *32*, 1363.

15 (a) Tsuji, J.; Minami, I. *Acc. Chem. Res.* **1987**, *20*, 140. (b)Hughes, G.; Lautens, M.; Wen, C. *Org. Let.* **2000**, *2*, 107-110.

16 For alternative approaches to -hydroxy-1-enoates see: (a) Fleming, I. *Bull. Soc. Chem. Fr*. **1981**, *2*, 7-13. (b) Barloy-Da Silva, C.; Benkouider, A.; Pale, P. *Tetrahedron Lett*. **2000**, *41*, 3077-3081. (c) Albaugh-Robertson, P.; Katzenellenbogen, J. A. *J. Org. Chem.* **1983**, *48*, 5288-302. (d) Miyazawa, M; Matsuoka, E.; Sasaki, S.; Oonuma, S.; Maruyam, K. Miyashita, M. *Chem. Lett.* **1998**, 109-110. (e) Keck, G. E.; Palani, A.; McHardy, S. F. *J. Org. Chem.* **1994**, *59*, 3113. (f) Solladie, G.; Gressot, L.; Colobert, F. *Eur. J. Org. Chem*. **2000**, 357-364.

17 (a) Burden, R. S.; Crombie, L. *J. Chem. Soc. C* **1969**, 2477. (b) Bohlmann, F.; Zdero, C. *Chem. Ber*. **1973**, *106*, 3779. (c) Roush, W. R. *J. Am. Chem. Soc*. **1980**, *102*, 1390. (d) Evans, D. A.; Fitch, D. M. *J. Org. Chem*. **1997**, *62*, 454. (e) Posner, G. H.; Lee, J. K.; White, M. C.; Hutchings, R. H.; Dai, H.; Kachinski, J. L.; Dolan, P.; Kensler, T. W. *J. Org. Chem*. **1997**, *62*, 3299. (f) Barrett, A. G. M.; Hamprecht, D.; White, A. J. P.; Williams, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 8608. (g) Takacs, J. M.; Jaber, M. R.; Clement, F.; Walters, C. *J. Org. Chem*. **1998**, *63*, 6757. (h) Nazare, M.; Waldmann, H. *Chem.;Eur. J.* **2001**, *7*, 3363. (i) Sun, M.; Deng, Y.; Batyreva, E.; Sha, W.; Salomon, R. G. *J. Org. Chem*. **2002**, *67*, 3575. (j) Tsuzuki, T.; Tanaka, K.; Kuwahara, S.; Miyazawa, T. *Lipids* **2005**, *40*, 147. (k) Barth, R.; Mulzer, *J. Angew. Chem., Int. Ed*. **2007**, *46*, 5791. Markiewicz, J. T.; Schauer, D. J.; Lofstedt, J.; Corden, S. J.; Wiest, O.; Helquist, P. *J. Org. Chem*. **2010**, *75*, 2061–2064.

18 (a) Kubota, K.; Leighton, J. L. *Angew. Chem. Int. Ed.* **2003**, *115*, 976-978. (b) Chalifoux, W. A.; Reznik, S. K.; Leighton, J. L. *Nature* **2012**, *487*, 86-89.

19 Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247-2250.

20 Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 7562-7563.

21 (a) Grubbs, R. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 3760–3765. (b) Gosh, A. K.; Bilcer, G. *Tetrahedron Lett*. **2000**, *41*, 1003-1006. (c) Boger, D. L.; Ichikawa, D.; Zhong, W. *J. Am. Chem. Soc.* **2001**, *123*, 4161. (d) Reddy, M. V. R.; Rearick, J. P.; Hoch, N.; Ramachandran, P. V. *Org. Lett.* **2001**, *3*, 19-20. (e) Smith, A. B.; Brandt, B. M. *Org. Lett.* **2001**, *3*, 1685-88. (f) Reddy, M. V. R.; Yucel, A. J.; Ramachandran, P. V. *J. Org. Chem.* **2001**, *66*, 2512-14. (g) S. D. Garaas, T. J. Hunter, and G. A. O'Doherty, *J. Org. Chem.* **2002**, *67*(8); 2682-2685.