Communication

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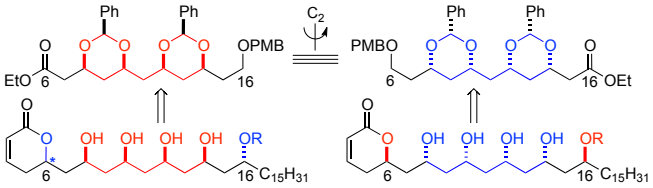

***ent*-cryptocaryol A**: C-6 (*S*) R = H
***ent*-cryptocaryol B**: C-6 (*S*) R = Ac
purported cryptocaryol B : C-6 (*R*) R = Ac
(*i.e.*, **6-*epi*-*ent*-cryptocaryol B**)

cryptocaryol A: R = H
cryptocaryol B: R = Ac

Cryptocaryol A and B: Total Syntheses, Stereochemical Revision, Structure Elucidation and Structure-Activity Relationship

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Supporting Information Placeholder

ABSTRACT: The first total syntheses and structural elucidation of cryptocaryol A and cryptocaryol B were achieved in 23 and 25 linear steps, respectively. The synthesis relied on the use of a key pseudo-C_s symmetric pentaol intermediate, which in a stereochemically divergent manner was converted into either enantiomer as well as diastereomers. This synthetic effort enabled the first structure-activity relationships of this class of PDCD4 stabilizing natural products.

The early success and subsequent limitation found with the development of PKC as a target for cancer and other diseases, have led to the search for alternative downstream kinase targets for development (e.g., mTOR, Akt).[1] It is believed that the regulation of these new targets will selectively produce all the desired outcomes (e.g., tumor suppression) without side effects (e.g., non-cancer cell toxicity).[2] Programmed cell death 4 (PDCD4), a downstream target of Akt, is a novel tumor suppressor protein. PDCD4 interaction with eukaryotic initiation factor 4A (eIF4A) inhibits protein synthesis.[3] In addition, PDCD4 suppresses the activation of activator protein-1 (AP-1) through c-Jun.[4] Not surprisingly, the stabilization of PDCD4 is linked to the induction of apoptosis.[5] Conversely, its low expression levels are linked with the progression of several cancers (e.g., lung, liver, ovary and brain).[6]

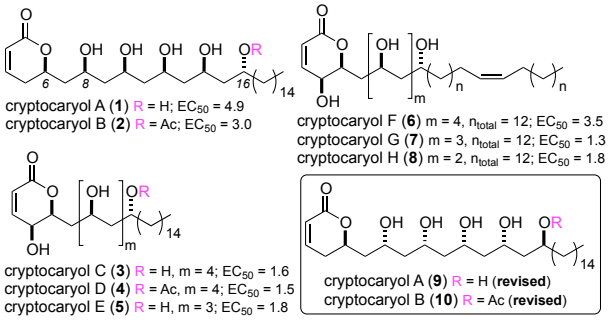
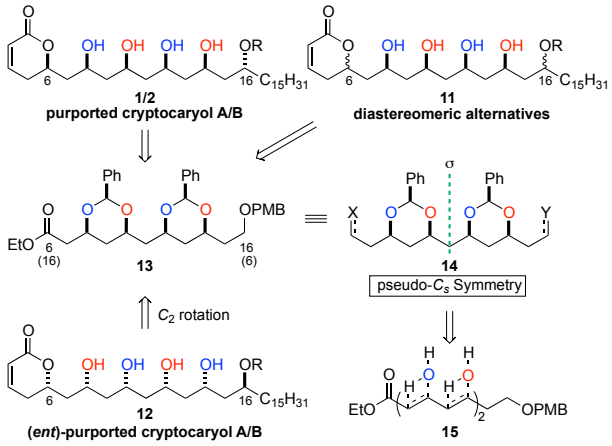


Figure 1. Purported structures of cryptocaryols A–H and revised structures of cryptocaryol A (**9**) and B (**10**). EC_{50} = mM conc. for recovery of 50% PDCD4 concentration from TPA-induced degradation.[7]

In an effort to find natural products that stabilize levels of PDCD4, Gustafson *et al*. developed a high-throughput *in vivo* cell-based assay that identified cryptocaryols A–H (**1**–**8**) (Figure 1).[7] This class of natural products isolated from *cryptocarya sp*. shares a 5,6-dihydro-α-pyranone and a 1,3-polyol segment. In addition, the eight cryptocaryols stablized PDCD4 in 12-*O*-tetradecanoylphorbol-13-acetate (TPA) challenged cells with EC_{50} ranging from 1.3 to 4.9 mM. The structures of these compounds were elucidated by a combination of NMR, HRMS and CD analyses. The all *syn*-tetraol relative configuration was assigned using Kishi's ^{13}C NMR database,[8] and the absolute configuration of pyranone at C-6 was assigned as *R* from its Cotton effect.[9] Unfortunately, knowledge gained from the structure-activity relationship (SAR) study was limited by the ambiguities associated with the absolute and relative stereochemistry of these structures.[10]

Scheme 1. Retrosynthetic analysis of cryptocaryol A and B

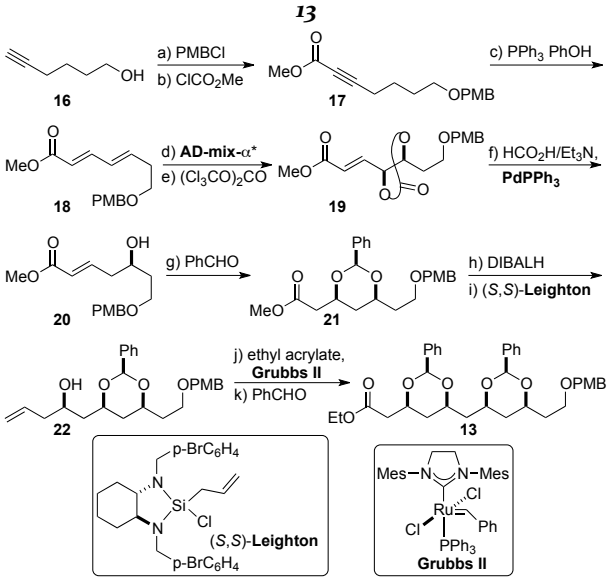


Thus, we devised a plan for the synthesis of cryptocaryol A and B with the aims of establishing the 3D structure and providing material for SAR studies (Scheme 1). In particular, we envisioned an approach that would take advantage of the pseudo-C_s symmetry of a tetraol fragment in **13**,[11] which would be amenable for the synthesis of the purported structures of these natural products (**1** and **2**), along with their enantiomer (**12**) and C6/16-diastereomers (e.g., **9**, **10** and **11**). Recently, we developed an iterative hydration of polyene strategy to build 1,3-polyols,[12] which has proved to be extremely successful for the syntheses of related 1,3-polyol-natural products[13] as well as more complicated variants.[14]

Towards this end, we began with the synthesis of orthogonally protected pentaol **13** from commercially available 5-hexyn-1-ol (**16**) (Scheme 2). The primary alcohol was protected as a PMB ether and the terminal alkyne was homologated (*n*-BuLi/methyl chloroformate, **16** to **17**) and then subsequently isomerized (PPh_3/PhOH)[15] to give dienoate **18** in excellent overall yield for 3 steps (88%). The distal double bond of dienoate **18** was asymmetrically oxidized under the Sharpless conditions ($(DHQ)_2PHAL$) to give a 2-enoate-4,5-diol,[16] which upon treatment with triphosgene and pyridine gave carbonate **19**. A Pd-catalyzed regioselective

reduction of **19** with (Et_3N/HCO_2H, catalytic Pd/PPh_3) produced *δ*-hydroxy enoate **20**. Acetal formation using the Evans' conditions (benzaldehyde/KO*t*-Bu) diastereoselectively transformed **20** into benzylidene protected *syn*-1,3-diol **21**.[17] Thus in 4 steps, the initial protected diol fragment of **13** was installed in **21** from **18**.

Scheme 2. *Synthesis of pseudo-C_s symmetric intermediate 13*



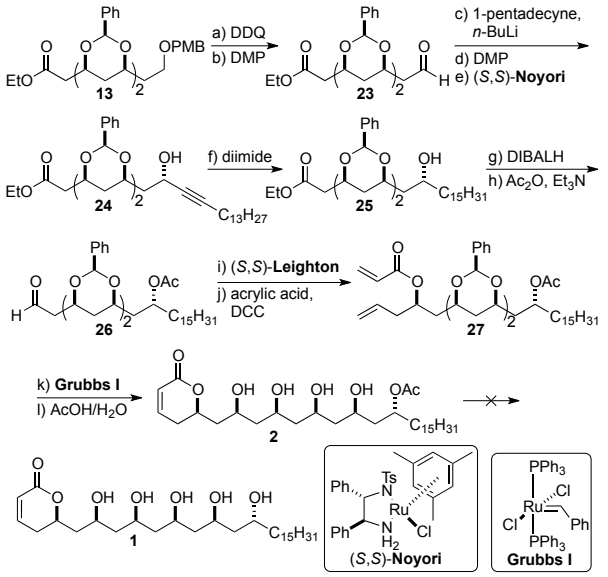
Reagents and conditions: a) PMBCl, NaH, DMF, TBAB, 0 °C, 99%; b) $ClCO_2Me$, *n*-BuLi, THF, –78 to 0 °C, 99%; c) PPh_3, PhOH, benzene, 50 °C, 90%; d) **AD-mix-α*** = $K_3Fe(CN)_6$ (3 equiv), K_2CO_3 (3 equiv), $MeSO_2NH_2$ (1 equiv), $(DHQ)_2PHAL$ (2 mol %), OsO_4 (1 mol %), *t*-BuOH/H_2O, 0 °C, 85%; e) triphosgene, pyridine, DMAP, CH_2Cl_2, –78 °C, 89%; f) **PdPPh$_3$** = $Pd_2(dba)_3$•$CHCl_3$/PPh_3 (0.3 mol %), Et_3N, HCO_2H, THF, reflux, 95%; g) PhCHO, KO*t*-Bu, THF, 0 °C, 67%; h) DIBALH, CH_2Cl_2, –78 °C, 95%; i) (*S*,*S*)-**Leighton**, $Sc(OTf)_3$ (2.5 mol %), CH_2Cl_2, –10 °C, 72%, dr = 8.7:1.0; j) ethyl acrylate, **Grubbs II** (1.5 mol %), CH_2Cl_2, 99%; k) PhCHO, KO*t*-Bu, THF, 0 °C, 77%.

The installation of the second protected diol fragment of **13** began with an ester to aldehyde reduction of **21** (DIBALH) followed by Leighton allylation to give homoallylic alcohol **22**.[18] The homoallylic alcohol stereochemistry of **22** was used to stereospecifically install the final benzylidene protected diol fragment. This was accomplished with a 2-step cross metathesis (ethyl acrylate/Grubbs II) and Evans' acetal formation sequence to furnish the pentaol **13**.[19]

With the key pentaol **13** in hand, our efforts were turned to the synthesis of the purported cryptocaryol A (**1**) and B (**2**). The PMB group in **13** was deprotected with DDQ to release the primary alcohol, which then was oxidized with DMP to afford aldehyde **23** (Scheme 3). Nucleophilic alkyne addition (1-pentadecyne/*n*-BuLi, –78 °C) to aldehyde **23** gave a propargyl alcohol, which upon oxidation (Dess-Martin) and reduction (Noyori) diastereoselectively gave propargyl alcohol **24**.[20] The alkyne in **24** was reduced to alkane **25** with excess diimide (NBSH/Et_3N). A 2-step DIBALH reduction and alcohol acylation procedure on ester **25** produced aldehyde **26**. The final stereocenter in **2** was installed with the use of a second Leighton allylation, which after acylation (acrylic acid/DCC) was then converted into diene **27**. A ring closing metathesis (Grubbs I) installed the desired pyranone, which after benzylidene deprotection (AcOH/H_2O) furnished the structure purported to be cryptocaryol B (**2**).[10,21]

Although great similarities existed between the ^1H and ^{13}C NMR spectra of **2** and the data reported for cryptocaryol B,[7] our analysis led us to conclude that they did not match.[10] This included discrepancies in the ^1H NMR (e.g., H-5a/H-5b, H-6, H-7a/H-7b, and H-8) and the ^{13}C NMR (C-6, C-7 and C-8), with the variances (0.6 to 0.9 ppm) in the ^{13}C NMR values being the hardest to reconcile. In order to gain a locus for further comparison, we attempted to convert **2** into the structure reported for cryptocaryol A (**1**). Unfortunately, we were unable to find conditions to selectively hydrolyze the C-16 acetate without concomitant hydrolysis of the pyranone ring. Next, we targeted the C-6 diastereomers of **1** and **2** (**30a** and **30b**, respectively), as the stereochemical relationship between the C-6 and C-8 positions was ambiguously assigned by Gustafson.[7] Moreover, we found the greatest variance in the C-5 to C-9 positions in our comparison of the ^1H and ^{13}C NMR.

Scheme 3. *Synthesis of 6-epi-ent-cryptocaryol B (2)*



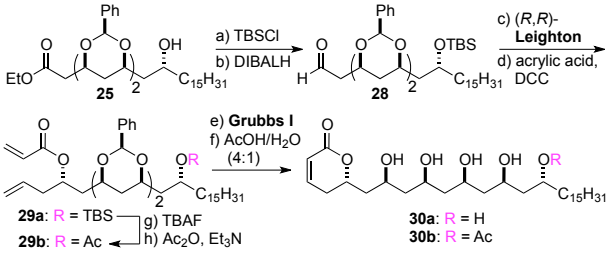
Reagents and conditions: a) DDQ, CH_2Cl_2, H_2O, 0 °C, 92%; b) Dess-Martin periodinane, CH_2Cl_2, 0 °C, 81%; c) 1-pentadecyne, *n*-BuLi, THF, –78 °C; d) Dess-Martin periodinane, CH_2Cl_2, 0 °C, 67 % (two steps); e) (*S*,*S*)-**Noyori** (5 mol %), Et_3N, HCO_2H, 94%; f) NBSH, Et_3N, CH_2Cl_2, 90%; g) DIBALH, CH_2Cl_2, –78 °C, 87%; h) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0 °C, 72%; i) (*S*,*S*)-**Leighton**, $Sc(OTf)_3$ (5 mol %), CH_2Cl_2, –10 °C, 75%; j) acrylic acid, DCC, DMAP, CH_2Cl_2, 61%; k) **Grubbs I** (5 mol %), CH_2Cl_2, reflux, 75%; l) AcOH/H_2O (4:1), 80 °C, 75%.

These revised efforts returned to alcohol **25** and involved the use of the enantiomeric (*R*,*R*)-Leighton reagent (Scheme 4). In practice, we protected the secondary alcohol in **25** as a TBS ether and reduced the ester to aldehyde **28**. Application of the diastereomeric Leighton allylation, acylation (acrylic acid/DCC) gave diene **29a**, which in 2 steps (Grubbs I; AcOH/H_2O) was converted into **30a**. The ^1H NMR and ^{13}C NMR spectral data for synthetic **30a** were found to be identical to the data reported for cryptocaryol A. While the optical rotation data was consistent in magnitude, it was opposite in sign (reported: $[\alpha]_D$ = +12 (c = 0.1, MeOH); synthetic: $[\alpha]_D^{21}$ = –13.4 (c = 0.1, MeOH)). Replacing the TBS group in **29a** with an acetate group (TBAF; Ac_2O/EtN_3) gave **29b**, the precursor for *ent*-cryptocaryol B, which in 2 steps (Grubbs I; AcOH/H_2O) was converted into **30b**. Once again, the spectral data for synthetic **30b** were identical to the data reported for cryptocaryol B.[22] Thus the structures for cryptocaryol A and B should be reassigned to **9** and **10**, respectively.[21]

With the elucidation of the structures for the cryptocaryol A and B, we set out to undertake their enantioselective synthesis and biological evaluation as anticancer agents. This effort began with pseudo-C_s symmetric protected pentaol **13**, and requires the reversal in the order of pyranone and side chain installation (Scheme

5). The revised route begins with the conversion of ester **13** into ynone **31** (DIBALH; 1-penadecyne; Dess-Martin). The C-16 stereochemistry was installed in alcohol **32** by a 2-step Noyori asymmetric and diimide reduction procedure. Adjustments of the protecting groups involved the protection of the C-16 alcohol of **32** as a TBS group (TBSCl) followed by PMB-deprotection (DDQ) to give **33a**. Oxidation of the primary alcohol in **33a** (Dess-Martin) followed by Leighton allylation and acrylate acylation (acrylic acid/DCC) provided diene **34a**, from which **34b** was prepared with the required C-16 acetate group.

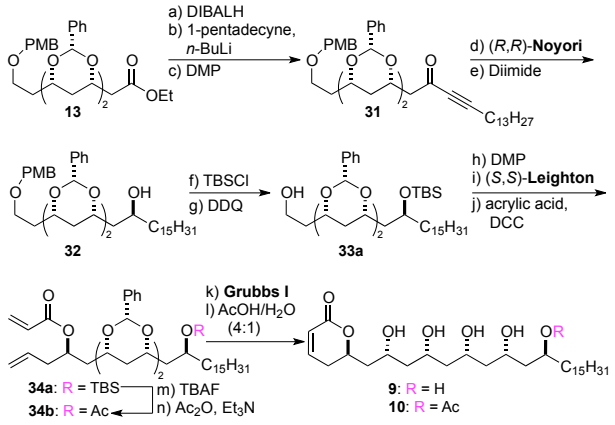
Scheme 4. *Synthesis of ent-cryptocaryol A and B (**30a/b**)*



Reagents and conditions: a) TBSCl, imidazole, DMF, 96%; b) DIBALH, CH_2Cl_2, –78 °C, 90%; c) (*R,R*)-**Leighton**, $Sc(OTf)_3$ (5 mol %), CH_2Cl_2, –10 °C, 95%; d) acrylic acid, DCC, DMAP, CH_2Cl_2, 64%; e) **Grubbs I** (5-10 mol %), CH_2Cl_2, reflux, 87% or 78%; f) AcOH/H_2O (4:1), 80 °C, 77% or 75%; g) TBAF, THF, 91%; h) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0 °C, 96%.

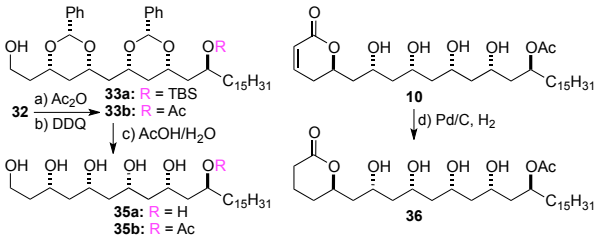
Using the same ring closing metathesis/deprotection sequence, the dienes **34a** and **34b** were uneventfully converted into cryptocaryol A (**9**) and B (**10**). The ^1H and ^{13}C NMR data for the synthetic material were identical to the data reported for the isolated material.[21] In addition to providing ample material for structural elucidation, the route also provided enough material for the cancer cell cytotoxicity studies. As part of these SAR studies, additional analogues (hexaol **35a**, hexaol acetate **35b** and saturated pyranone compound **36**) were required for evaluation. These analogues were readily prepared from intermediates **33a/b** and cryptocaryol B (**10**) by deprotection of benzylidene and hydrogenation of alkene, respectively (Scheme 6).

Scheme 5. Synthesis of cryptocaryol A and B (**9** and **10**)



Reagents and conditions: a) DIBALH, CH_2Cl_2, –78 °C, 90%; b) 1-pentadecyne, *n*-BuLi, THF, –78 °C; c) Dess–Martin periodinane, CH_2Cl_2, 0 °C, 68 % (2 steps); d) (*R,R*)-**Noyori** (5 mol %), Et_3N, HCO_2H, 98%; e) NBSH, Et_3N, CH_2Cl_2, 98%; f) TBSCl, imidazole, DMF, 94%; g) DDQ, CH_2Cl_2, H_2O, 0 °C, 92%; h) Dess-Martin periodinane, CH_2Cl_2, 0 °C, 62%; i) (*S,S*)-**Leighton**, $Sc(OTf)_3$ (5 mol %), CH_2Cl_2, –10 °C, 95%; j) acrylic acid, DCC, DMAP, CH_2Cl_2, 80%; k) **Grubbs I** (5-10 mol %), CH_2Cl_2, reflux, 76% or 70%; l) AcOH/H_2O (4:1), 80 °C, 70%; m) TBAF, THF, 92%; n) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0 °C, 72%.

Scheme 6. Synthesis of cryptocaryol analogues for SAR



Reagents and conditions: a) Ac_2O, pyridine, DMAP, CH_2Cl_2, 0 °C, 98%; b) DDQ, CH_2Cl_2, H_2O, 0 °C, 72%; c) AcOH/H_2O (4:1), 80 °C, 65% or 69%; d) Pd/C (10% wt/wt, 10 mol %), H_2 (1 atm), 66%.

While other PDCD4 stabilizers are known to be cytotoxic, there is very little data to correlate their activity to PDCD4 stabilization.[23] With access to cryptocaryol A and B, two known PDCD4 stabilizers (4.9 and 3.0 mM, see Gustafson's assay), this comparison can be made. We chose to study MCF-7 breast cancer cells (Table 1 and Figure 2),[24] because of their high expression level of PDCD4.[25] We found that both cryptocaryol A and B possessed growth inhibitory activity against MCF-7 in the mircomolar range and their relative activity was consistent with their PDCD4 stabilizing activity (i.e., **10** slightly more active than **9**). The two analogues without a pyranone ring **35a/b** (>10 fold) and the one without the double bond **36** (>100 fold) were the least active. The surprisingly greater loss in activity for **36**, could be a result of its propensity to ring open (e.g., unstable in CD_3OD). The diastereomer **2** (with only the C-6 pyrano-stereocenter retained) had a small loss in activity (~2 fold). The effect of C-16 acylation could be seen in the comparison between cryptocaryol A and B (**9**/**10**), as well as, **35a/35b**. Surprisingly, the stereochemistry of natural products did not have a significant effect on activity as *ent*-cryptocaryol A (**30a**) had only a ~3 fold loss of activity.

Table 1. Cytotoxicity of cryptocaryol analogues (MCF-7)

Compounds	IC_{50} (μM)[a]
cryptocaryol A (**9**)	8.5 ± 2.6
cryptocaryol B (**10**)	6.0 ± 1.6
6-*epi*-*ent*-cryptocaryol B (**2**)	14.0 ± 4.5
ent-cryptocaryol A (**30a**)	28.0 ± 10.7
hexaol (**35a**)	242 ± 180
hexaol acetate (**35b**)	170 ± 104
2H-cryptocaryol B (**36**)	>500
etoposide	1.2 ± 0.6

[a] The IC_{50} values were measured from 72 h treatment of MCF-7 cells in a MTT assay. All values represent the standard error of the mean value of three independent experiments with two duplicate determinations.

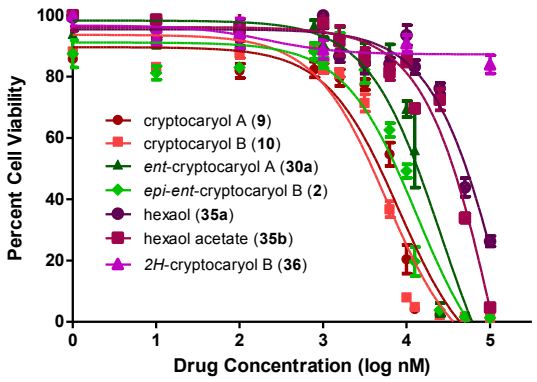


Figure 2. Graph of MCF-7 cell viability for cryptocaryols and their analogues. The dose-response curve of cell viability from a 72 h drug treatment (1 nM to 100 μM).

In conclusion, the first total synthesis, structural elucidation/correction and SAR of cryptocaryol A and B have been achieved. The enantioselective synthesis was accomplished in 23 and 25-step linear sequence, respectively, from commercially available 5-hexyn-1-ol. The stereochemically divergent synthesis concisely enabled the exact stereochemical assignment, as well as, the SAR for cryptocaryol A and B in a cancer cell cytotoxicity assay. It is worth noting that the difficulties in distinguishing between the two diastereomers (e.g., **1** and **9**) demonstrate the need for stereochemically divergent approaches for structural determination, as well as, enabling SAR-studies that probe the effects of stereochemistry on activity.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, full characterization data, and copies of spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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Cryptocaryol A and B: Total Syntheses, Stereochemical Revision, Structure Elucidation and Structure-Activity Relationship

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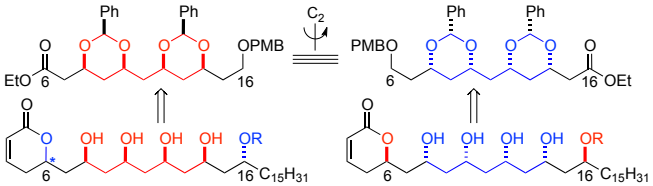

***ent*-cryptocaryol A**: C-6 (*S*) R = H
***ent*-cryptocaryol B**: C-6 (*S*) R = Ac
purported cryptocaryol B : C-6 (*R*) R = Ac
(*i.e.*, **6-*epi*-*ent*-cryptocaryol B**)

cryptocaryol A: R = H
cryptocaryol B: R = Ac