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Cryptocaryols A and B: Total Syntheses, Stereochemical Revision, Structure Elucidation, and Structure–Activity Relationship

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Supporting Information

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., noncancer 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]

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* spp. shares a 5,6-dihydro-α-pyranone and a 1,3-polyol segment. In addition, the eight cryptocaryols stabilized 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]

Thus, we devised a plan for the synthesis of cryptocaryols 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]

Toward 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

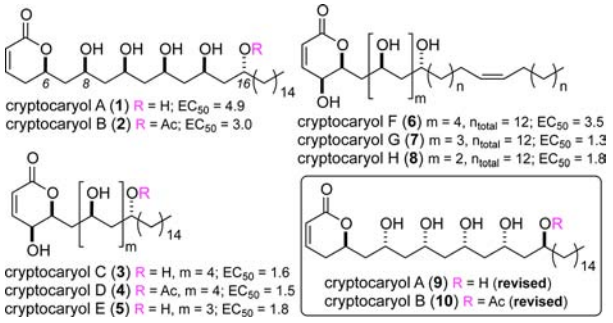
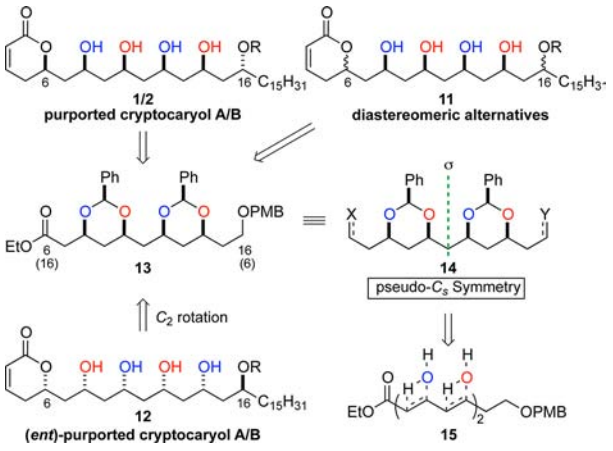


Figure 1. Purported structures of cryptocaryols A–H and revised structures of cryptocaryols A (**9**) and B (**10**). EC_{50} = mM conc. for recovery of 50% PDCD4 concentration from TPA-induced degradation.[7]

Scheme 1. Retrosynthetic Analysis of Cryptocaryols A and B



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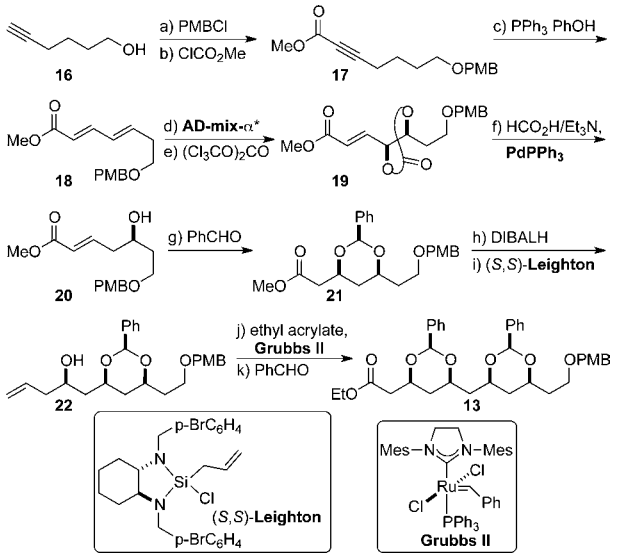
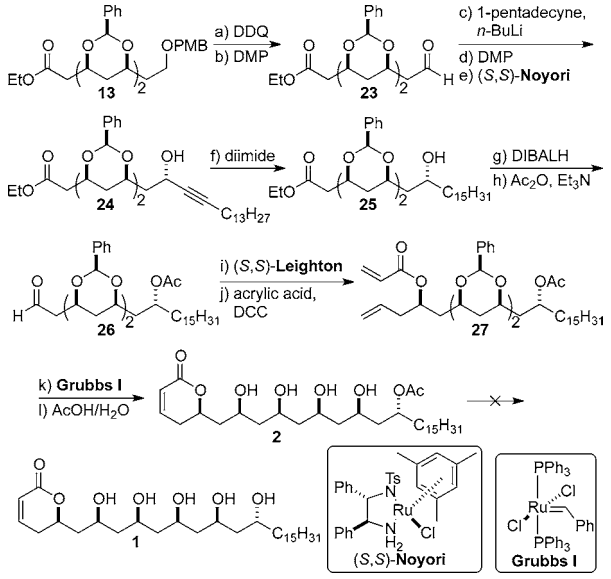
Scheme 2. Synthesis of Pseudo-C_s Symmetric Intermediate 13[a]



[a]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%.

Scheme 3. Synthesis of 6-*epi*-*ent*-Cryptocaryol B (2)[a]



[a]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%.

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 three 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 four steps, the initial protected diol fragment of **13** was installed in **21** from **18**.

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 two-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 cryptocaryols 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 two-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.

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 diasteromeric Leighton allylation, acylation (acrylic acid/DCC) gave diene **29a**, which in two steps (Grubbs I; AcOH/H_2O) was converted into **30a**. The ^1H NMR and ^{13}C NMR spectral

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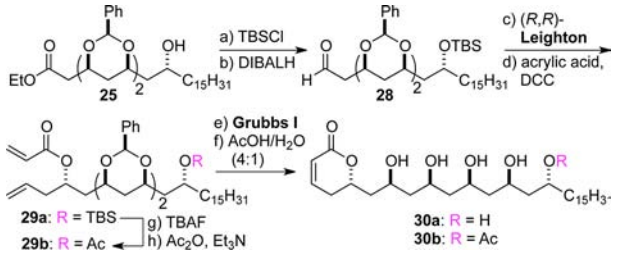
Scheme 4. Synthesis of *ent*-Cryptocaryols A and B (30a/b)[a]

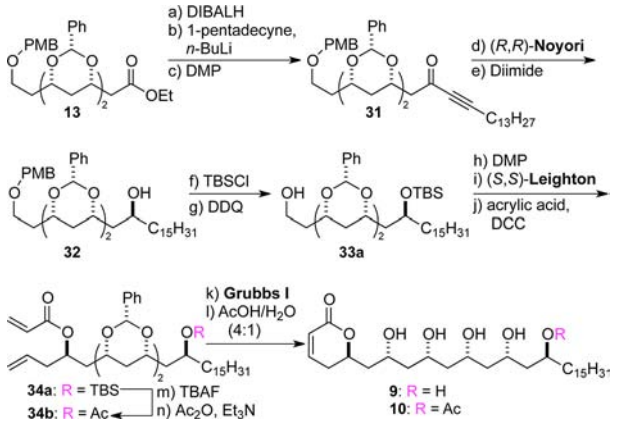


[a]Reagents and conditions: a) TBSCl, imidazole, DMF, 96%; b) DIBALH, CH_2Cl_2, −78 °C, 90%; c) (*R*,*R*)-Leighton, $Sc(OTf)_3$ (5 mol %), CH_2Cl_2, −10 °C, 95%; d) acrylic acid, DCC, DMAP, CH_2Cl_2, 64%; e) Grubbs I (5−10 mol %), CH_2Cl_2, reflux, 87% or 78%; f) $AcOH/H_2O$ (4:1), 80 °C, 77% or 75%;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

data for synthetic **30a** were found to be identical to the data reported for cryptocaryol A. While the optical rotation data were 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 two 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 cryptocaryols A and B should be reassigned to **9** and **10**, respectively.[21]

With the elucidation of the structures for the cryptocaryols 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 two-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.

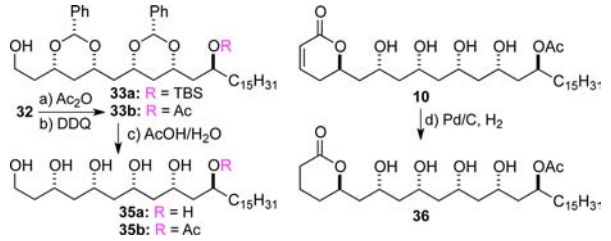
Scheme 5. Synthesis of Cryptocaryols A and B (9 and 10)[a]



[a]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% (two 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%.

Using the same ring-closing metathesis/deprotection sequence, the dienes **34a** and **34b** were uneventfully converted into cryptocaryols 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**/**33b** and cryptocaryol B (**10**) by deprotection of benzylidene and hydrogenation of alkene, respectively (Scheme 6).

Scheme 6. Synthesis of Cryptocaryol Analogues for SAR[a]



[a]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 are very little data to correlate their activity to PDCD4 stabilization.[23] With access to cryptocaryols 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 S1),[24] because of their high expression level of PDCD4.[25] We found that both cryptocaryols A and B possessed growth inhibitory activity against MCF-7 in the micromolar range and their relative

Table 1. Cytotoxicity of Cryptocaryol Analogues (MCF-7)

cmpds	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
2*H*-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.

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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 for ring-opening (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 cryptocaryols 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.

In conclusion, the first total synthesis, structural elucidation/correction, and SAR of cryptocaryols 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 cryptocaryols 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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(21) The absolute and relative configuration for all stereocenters was confirmed by a combination of Mosher and ^{1}H NMR analyses, see SI.

(22) Unfortunately, no optical rotation data for cryptocaryol B were reported, see ref 7.

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