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The Asymmetric Syntheses of Cryptocaryols A and B

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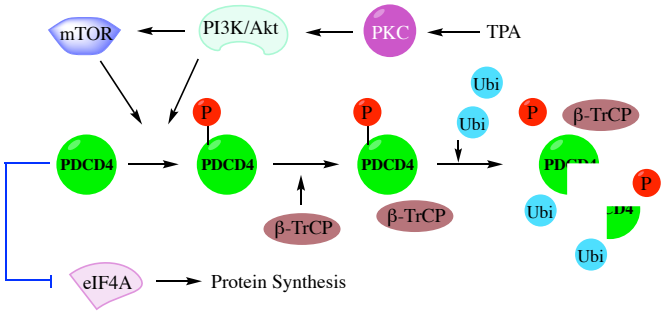
The recent total syntheses of cryptocaryols A and B are reviewed. These efforts include the correction of the initially assigned absolute and relative stereochemistry of this class of natural products. In addition to enabling the initial structure activity relationships for this class of natural products, these syntheses demonstrated the practical utility of several novel synthetic approaches.

Introduction

As the early enthusiasm for the development of Protein Kinase C (PKC) as a target for cancer and other diseases has waned, there has been a renewed search for alternative downstream kinase targets (*e.g.*, mTOR, Akt).[1] Central to these efforts is the hope that the selective inhibition of these new kinase targets will produce all the desired outcomes (*e.g.*, tumor suppression) without the undesired effects (*e.g.*, non-cancer cell toxicity).[2] One potentially interesting downstream target is programmed cell death 4 (PDCD4). PDCD4 is activated by mTOR[3] and Akt,[4] and regulates protein synthesis by binding to translation eukaryotic initiation factor 4A (eIF4A). PDCD4 interaction with eIF4A leads to the inhibition of protein synthesis[3,5] PDCD4 expression levels are controlled by ubiquitination and subsequent proteasome degradation. Down-regulation and/or reduced expression of PDCD4 has been shown to increase translation and in turn tumor cell transformation and invasion.[5a,6] Not surprisingly, low expression levels are linked with the progression of several cancers (*e.g.*, lung, liver, ovary, and brain). Conversely, the stabilization of PDCD4 is linked to the induction of apoptosis.[7]

Thus, molecules that increase levels of PDCD4 in its active form hold potential as target for the development as novel antineoplastic agents. The degradation (aka, destabilization) of PDCD4 in the cell occurs via a discrete pathway, which begins with its phosphorylation by Akt and leads to ubiquitination and digestion by proteasomes.[8] This destabilization is increased in some tumors.[9] As a result, stabilization of PDCD4 has been identified as a potential way to increase cancer cell sensitivity to chemotherapy. For example, rapamycin is known to both stabilize PDCD4 and sensitize cancer cells to chemotherapy.[10] Unfortunately, rapamycin well known immunosuppressive effects limit its use to cancer treatments.[11]



Scheme 1: Tumor-suppressive effects of PDCD4/inhibition of eIF4A.

In 2011, as part of an effort to find compounds that sensitize cancer cells to cancer drugs, Gustafson discovered a class of natural products called cryptocaryols (A-H). These products were identified as PDCD4 stabilizers.[12] As a result of their novel mode of action and unique structure, the cryptocaryols have garnered the attention of the synthetic chemistry community. This interest has resulted in the total synthesis of two members of this family of natural products, cryptocaryols A and B. Specifically, there has been five syntheses of cryptocaryol A and one synthesis of cryptocaryol B. In addition, these synthetic efforts have resulted in the reassignment of the absolute and relative stereochemistry for the cryptocaryols A and B, as well as their initial structure activity relationship studies.

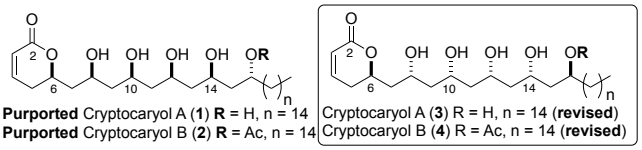


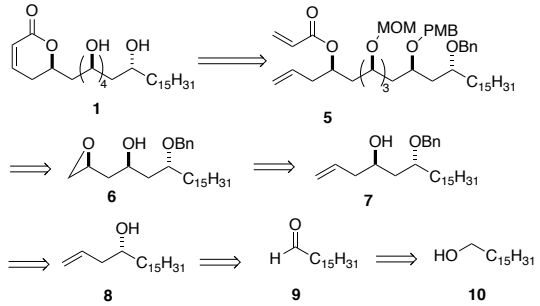
Figure 1: Purported and revised cryptocaryols A and B.

The structure of cryptocaryol A consists of a 5,6-dihydro-α-pyranone terminated penta-hydroxy-polyketide, with a repeating 1,3-polyol fragment (Figure 1). The *C*-7 to *C*-15 pentaol fragment of cryptocaryol A was initially assigned with a *syn*,*syn*,*syn*,*anti*-relationship. Cryptocaryol B has the same core structure with the addition of a *C*-15 acetyl group, which leads to an increase in PDCD4

[a] *Address here.*
[b] *Address here.*
[c] *Address here.*
† Footnotes relating to the title and/or authors should appear here.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

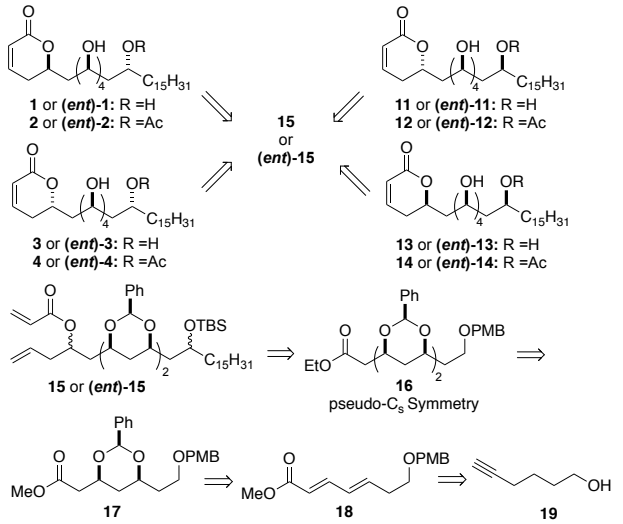
stabilization ability. Using the optical rotation data, the absolute stereochemistry of the *C*-5 pyranone configuration was assigned with the (*R*)-configuration. As a result of the stereo-divergent synthetic efforts by the O'Doherty group, the absolute and relative stereochemistry of cryptocaryols A and B were revised (*cf*, **3** and **4**).[13] They found that the revised structures for both cryptocaryols A and B had opposite stereochemistry at all but the (*R*)-stereochemistry of the C-5 pyranone.

Since the initial disclosure of the structure and activity of the cryptocaryols in 2011, there have been several syntheses of both cryptocaryols A and B. This work has been carried out by five synthetic groups from around the world, Mohapatra,[14] O'Doherty,[13] Dias,[15] Cossy[16] and Krische.[17] While each route has its own synthetic uniqueness, four of the five syntheses (Mohapatra, O'Doherty, Cossy and Krische) used a Grubbs ring-closing metathesis (RCM) to install the pyranone ring.[18] In contrast, Dias used an Ando-olefination[19] in combination with an acid catalyzed ring closure to install the pyranone. All five syntheses used different strategy to install the repeating the 1,3-polyol subunits, however, Dias, Cossy and Krische all used a boron aldol reaction for stitching together portions of the polyol. Mohapatra, O'Doherty and Krische used asymmetric allylation for portions of the polyols. Herein, we review the five total syntheses of cryptocaryols.



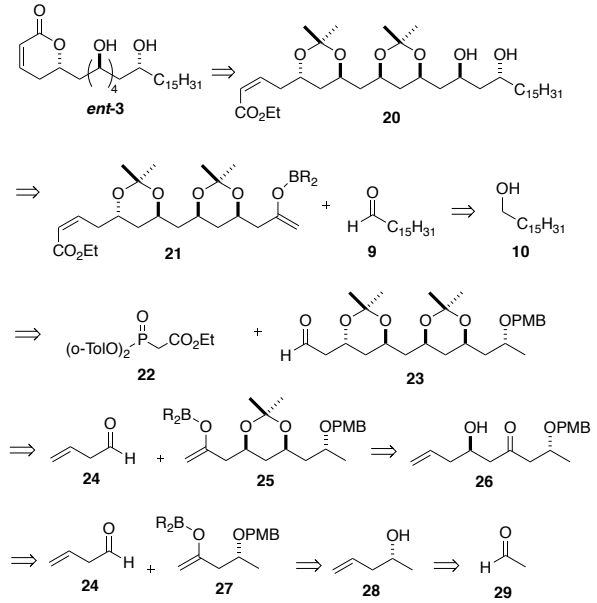
Scheme 2: Mohapatra's approach to purported cryptocaryol A

In 2013, Mohapatra reported the first synthesis of a cryptocaryol (Scheme 2). Their synthesis was the first to report a 28 step synthesis of the purported structure of cryptocaryol A**.** Retrosynthetically, they envisioned cryptocaryol A **1** coming from a RCM reaction of diene **5**.[20] The polyol portion of **5** would be made by an iterative use of an allylation/epoxidation and cuprate ring opening reaction.[21] The key features of the Mohapatra's approach were the diasteroselective epoxidation via a diastereoselective Bartlett-Smith[22] iodocarbonate formation and epoxide ring closure (**7** to **6**). A chelate controlled Keck allylation was used to install the stereochemistry in **7**, whereas, the absolute stereochemistry was installed via an asymmetric Keck allylation[23] of aldehyde **9** to give homoallylic alcohol **8**. An oxidation of primary alcohol **10** was achieved to give the aldehyde **9**.



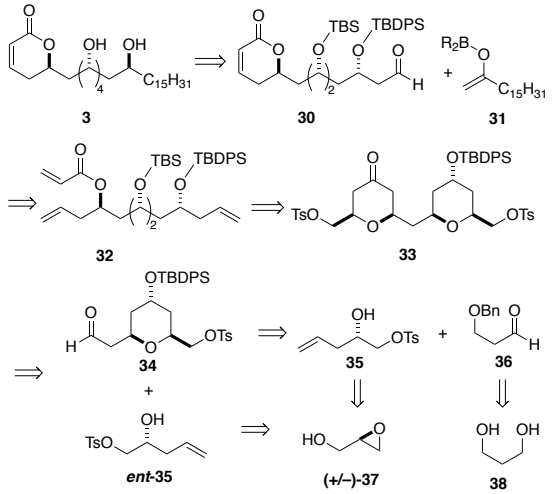
Scheme 3: O'Doherty's approach to cryptocaryols A and B.

In 2013, the O'Doherty group was the first to recognize a problem with the purported structure of the cryptocaryols and to correctly assign the structure via total synthesis (Scheme 3). This effort was the first to complete the total synthesis of both cryptocaryols A and B, which were accomplished in a total of 23 and 25 steps respectively. Retrosynthetically, the O'Doherty group devised a synthesis that was amenable for the synthesis of eight possible diastereomers **1-4, (*ent*)-1-4, 11-14** and **(*ent*)-11-14** of both cryptocaryols A and B. Key to the success of this stereodivergent approach was the recognition that all the desired cryptocaryol diastereomers **1-4, (*ent*)-1-4, 11-14** and **(*ent*)-11-14** could be accessed from **15** and **(*ent*)-15**. In turn, **15** and **(*ent*)-15** could be prepared by the reagent control stereoselective appending of the desired functionality onto *pseudo*-Cs symmetric protected tetraol **16**. The tetraol portion of **16** could be installed diastereoselectively from **17**, which in turn could be prepared by the iterative asymmetric hydration of dienoate **18**.[24] Finally, the desired dienoate **18** could be readily prepared from hex-5-ynol **19** via protection of the primary alcohol and carbomethoxylation of the terminal alkyne followed by isomerization.



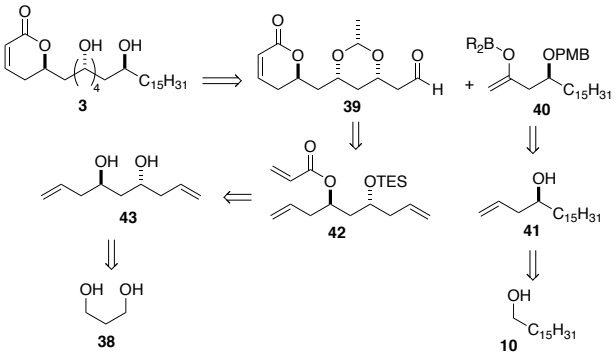
Scheme 4: Dias's approach to *ent*-cryptocaryol A**.**

In 2015, Dias reported the second synthesis of the correct enantiomer of *ent*-cryptocaryol A, which was accomplished in 17-steps (Scheme 4). In this approach five of the six-stereogenic centers were controlled by three boron-aldol/reduction sequences. Dias's retrosynthesis began with a concomitant acid catalyzed deprotection lactonization sequence that provided *ent*-**3** from **20**. The diol in **20** could be derived from a boron enolate aldol followed by an anti-reduction between boron enoate **21** and aldehyde **9**. The *cis*-enoate in **21** could result from an Ando-olefination between **22** and **23**. Another boron enolate aldol/anti-reduction between **25** and **24** followed by oxidative cleavage of the alkene should provide **23**. A Wacker oxidation of **26** should install the desired ketone of enolate **25**. The first boron enolate aldol/anti-reduction between **24** and **27** should provide **26**. Finally, the ketone precursor for **27** can be prepared by a Wacker oxidation of **28**, which in turn can be prepared by a Brown allylation of acetaldehyde **29**.



Scheme 5: Cossy's approach to cryptocaryol A**.**

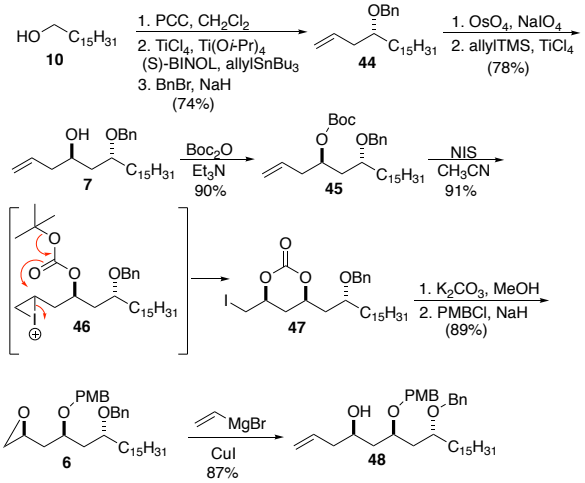
In 2015, Cossy's completed a 20-step synthesis of the natural enantiomer, (+)-cryptocaryol A, by a very elegant route that used two Prins cyclization to control four stereogenic centers (Scheme 5). Retrosynthetic analysis of Cossy's route began with aldol coupling of aldehyde **30** and methyl ketone **31** to produce **3.** The pyranone ring of aldehyde **30** could result from a ring-closing metathesis of triene **32**. Two of the alkenes in **32** could be revealed in a Zn mediated ring-opening of bis-tosylate **33**. The two Prins cyclizations could be used to prepare the two pyran rings in **33**. The first Prins was between aldehyde **34** and homoallylic alcohol **35** to produce **33**. The second Prins occurred between aldehyde **36** and alcohol ***ent*-35** to form **34**. Both enantiomers of homoallylic alcohol **35** can be prepared from racemic epoxide **(+/-)-37**.



Scheme 6: Krische's approach to cryptocaryol A.

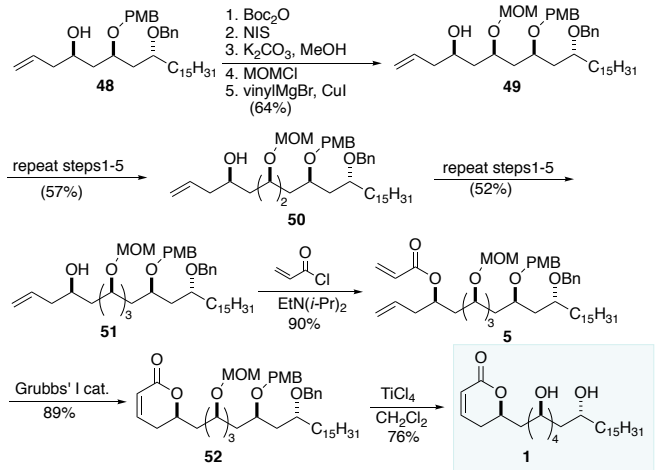
In 2016, Krische completed a total synthesis of cryptocaryol A. This route was by far the most concise route to cryptocaryol A and in its brevity in reveals both its elegance and the power of the suite redox carbon-carbon bond formation transformations developed by Krische (Scheme 6).[25] Thus in only 8 longest linear steps (12 total steps), Krische is able to prepare cryptocaryol A. In Krische's retrosynthesis, **3** was prepared via boron-mediated aldol addition between aldehyde **39** and boron enolate **40** followed by reduction and global deprotection. The aldehyde fragment **39** was readily prepared by ring–closing metathesis and Bi(III)-promoted acetal formation of **42**.[26] A mono-acylation and then TES protection of the diol **43** was used to produce **42**. The diol **43** was prepared by a double allylation of **38** to generate C_2-symmetric. The other half of the molecule, boron enolate **40** could be formed from homoallylic alcohol **41** via a Wacker oxidation and enolization of compound **41**, which was formed by a Krische allylation of alcohol **10**.

Herein we detail the five total syntheses reported for cryptocaryols A and B. Each synthetic approach offers a unique approach to this class of polyketide natural product. In combination, the syntheses offer an excellent view at the rapid evolution total synthesis can undergo in a short three-year time span (2013 to 2016).



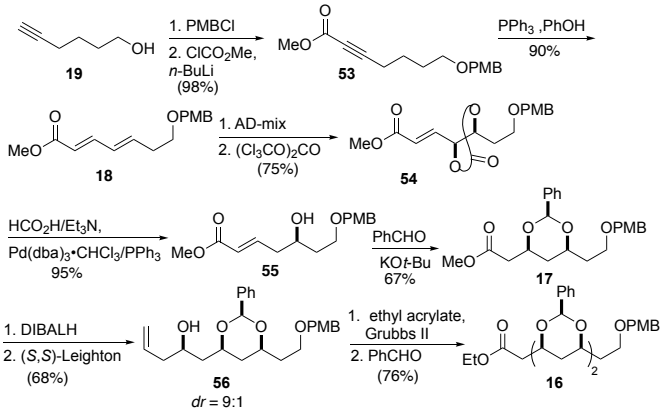
Scheme 7: Mohapatra's approach to the C-16 to C-10 portion of **1**.

The first synthesis of a cryptocaryol was of the purported structure **1** by Mohapatra. The Mohapatra synthesis started with oxidation of alcohol **10** followed by Keck allylation (Ti(O*i*-Pr)$_4$ and (S)-BINOL) of the aldehyde intermediate **9** to install the first stereocenter in homoallylic ether **44** which was formed after a subsequent benzyl protection. An oxidative cleavage of the double bond (OsO_4/$NaIO_4$) followed by a Keck chelation allylation of the aldehyde intermediate gave the anti-1,3 mono-protected diol **7**.[27] Protection of the other alcohol with Boc-anhydride gave **45**. Next, a diastereoselective epoxidation was achieved through a three step iodo-carbonate formation/methanolysis/epoxide ring closure followed by PMB-protection to give **6**. Key to stereoselectivity in the iodo-carbonate cyclization reaction is that in occurs via a six-member ring intermediate **46**. Finally, a cuprate opening (vinylMgBr/CuI) of **6** was used to give **48** with the third desired stereocenter set.



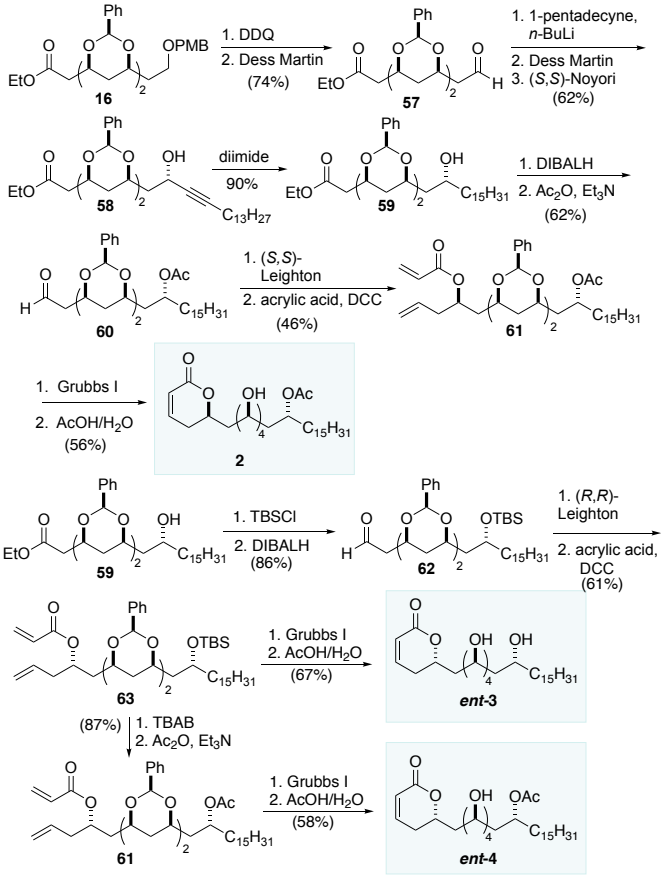
Scheme 8: Mohapatra's synthesis of purported cryptocaryol A.

Mohapatra used the same diastereoselective epoxidation/ring opening sequence (**48** to **49**) to install the remaining stereocenters. Two more applications of the five-step sequence were used to install the remaining stereocenters in homoallylic alcohol **51** (*via* homoallylic alcohol **50**). The synthesis of the purported structure of cryptocaryol A (**1**) was completed by a three-step esterification (**51** to **5**), RCM (**5** to **52**) and deprotection (**52** to **1**) reaction sequence. While it was clear at the conclusion of this effort, this synthetic material matched spectroscopically with the *C*-5 diastereomer of cryptocaryol A, (*vide infra*).



Scheme 9: O'Doherty's approach C-6 to C-14 fragment of the cryptocaryols A.

In 2013, the O'Doherty group disclosed a synthesis of purported cryptocaryol B **2**, identified the structural misassignment, and corrected the structure via synthesis of both enantiomers of cryptocaryols A and B. Their route started with protection of 5-hexyn-1-ol **19** followed by treatment with *n*-BuLi and then $ClCO_2Me$ to homologate the terminal alkyne to form a ynoate **53**. The ynoate **53** was isomerized into its more stable isomer dienoate **18** (PPh_3/PhOH). A regioselective asymmetric Sharpless dihydroxylation[28] was performed on the dienoate followed by a treatment with triphosgene to form carbonate **54**. A regioselective Pd-catalyzed reduction of **54** with formic acid was used to form alcohol **55**. Using the Evans hemi-acetal **55** was converted into **17**. A DibalH reduction produced an aldehyde intermediate, which was diastereoselectively allylated with the (*S,S*)-Leighton reagent. This cleanly converted ester **17** into homoallylic alcohol **56**. A Grubbs-II catalyzed cross metathesis of homoallylic alcohol **56** with ethyl acylate followed by a subsequent Evans condidtion benzylidene acetal reaction gave the desired pseudo-Cs symmetric protected tetraol **16**.

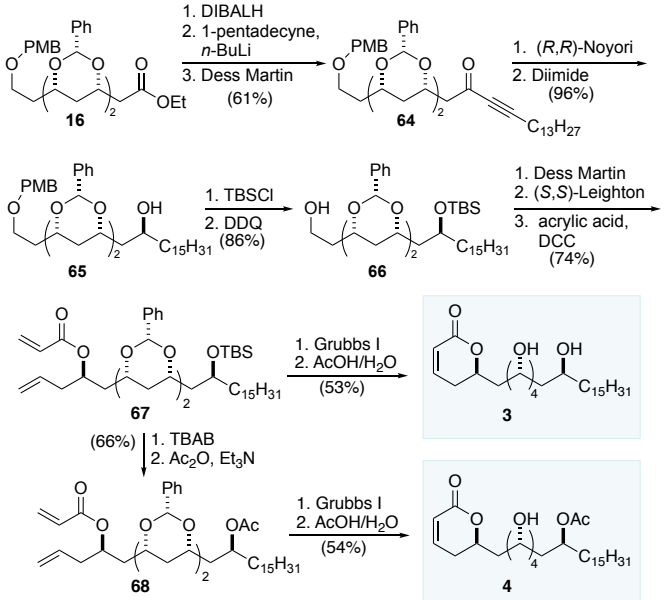


Scheme 10: O'Doherty's synthesis of the cryptocaryol stereoisomers.

A DDQ promoted deprotection of **16** followed by Dess-Martin periodinane oxidation gave aldehyde **57**. An unselective lithium acetylide addition to **57**, followed by Dess-Martin periodinane oxidation and Noyori asymmetric ketone hydrogenation resulted in a net stereoselective addition of **57** to form alcohol **58**. An exhaustive reduction of alkyne **58** with excess diimide gave the saturated alcohol **59**. A DibalH reduction to an aldehyde and alcohol acylation of **59** was used to form aldehyde **60**. A diastereoselective allylation of **60** with the (*S,S*)-Leighton reagent followed by alcohol acylation was used to form diene **61**. A Grubbs ring-closing metathesis and acid catalyzed deprotection of the two benzylidene protecting groups gave **2**, which is the purported structure of cryptocaryol B **2**. However, the spectra did not match that reported for cryptocaryol B.

The difference between the ^1H and ^{13}C NMR spectra for the two structures was greatest for the C-5 to C-7 positions. Thus, the C-5 epimer was targeted for synthesis. To accomplish this, the synthesis returned to alcohol **59**, which was TBS-protected. The ester was reduced with DibalH to form aldehyde **62**. At this point, the synthesis diverged with a diastereoselective allylation of **62** with the (*R,R*)-Leighton reagent followed by alcohol acylation, Grubbs ring-closing metathesis and acid catalyzed global deprotection of the TBS and two benzylidene protecting groups to give ***ent*-3**. The ^1H and ^{13}C NMR spectra matched those for cryptocaryol A, albeit its optical rotation was opposite of that reported for the natural material. Thus, it was the structure of (*ent*)-cryptocaryol A **3.** Thus, (*ent*)-cryptocaryol B (**(*ent*)-4**) was formed from **63** in 4 steps, which included a TBS-

deprotection, alcohol acylation (diene **61**), a Grubbs ring-closing metathesis and acid catalyzed deprotection of the two benzylidene protecting groups gave ***(ent)*-4.**



Scheme 11: O'Doherty's approach to cryptocaryols A and B.

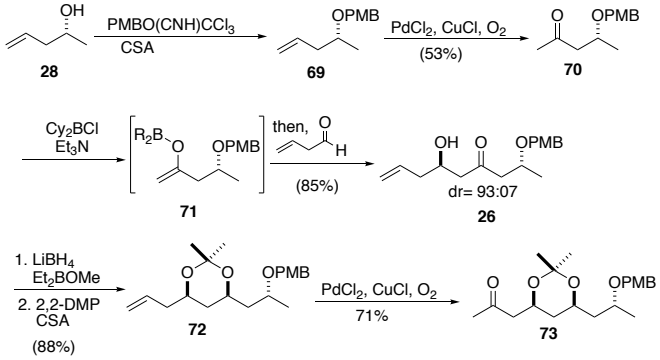
Once the correct relative stereochemistry for cryptocaryols A and B were established, the O'Doherty group returned to the pseudo-C_s symmetric protected pentaol **16** to complete the synthesis. As was part of their retrosynthetic design, all that was required was to reverse the order of pyranone and side chain installation. Their revised approach began with a DibalH reduction of **16** followed by acetylide anion addition and Dess-Martin oxidation to give ynone **64**. A reagent controlled Noyori asymmetric hydrogenation followed by diimide reduction was used to convert **64** into alcohol **65**. A TBSCl protection of **65** followed by PMB deprotection was used to form **66**. A three-step Dess-Martin oxidation followed by a reagent controlled Leighton allylation and acylation of **66** was used to convert **66** into diene **67**. A Grubbs I RCM and per-benzylidene deprotection was performed on **67** to give cryptocaryol A **3**. Returning to **67** a four-step procedure was used to convert it into cryptocaryol B **4**. Specifically, TBS deprotection followed by acylation was used to form **68**. Then, as before, a Grubbs ring-closing metathesis and global benzylidene deprotection was used to form cryptocaryol B **4**.

Table 1: PDCD4 stabilization and cytotoxicity data.

Compound	[rel.] [a]	Cell Line, IC_{50} (μM) [b]		
	PDCD4	MCF-7	HT-29	H460
cryptocaryol A (**3**)	3.6	8.1	4.2	5.4
cryptocaryol B (**4**)	4.5	5.8	2.9	3.8
ent-cryptocaryol A ((*ent*)-**3**)	3.8	25.8	4.1	7.9
ent-cryptocaryol B ((*ent*)-**4**)	3.6	9.0	2.4	4.0
6-*epi*-*ent*-cryptocaryol B (**2**)	1.9	13.3	4.9	7.8

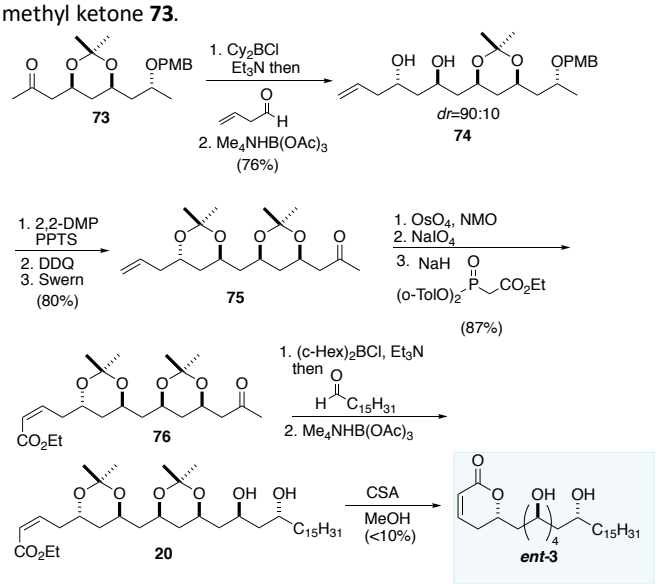
a PDCD4 stabilization is presented as a relative value over cells treated only with TPA (See Fig. 1). b IC50 was determined via MTT colorimetric analysis and curve fitting in Graphpad® Prism.

The O'Doherty approach provided enough material to enable their evaluation of the cryptocaryols' PDCD4 stabilization and cancer cell cytotoxicity Table 1.[29] Both cryptocaryols A and B, as well as their stereoisomers (**2**, **3**, **(*ent*)-3**, **4**, **(*ent*)-4**) possessed growth inhibitory activity against three cell lines in the micromolar range. Interestingly, the most cytotoxic cryptocaryol family member, cryptocaryol B, is also the best PDCD4 stabilizer. The relative cytotoxicity of the cryptocaryols was consistent with their PDCD4 stabilizing activity (*i.e.*, **4** slightly more active than **3**) for each cell line; however, the cell line sensitivity to a given compound did not correlate with the cell line's PDCD4 expression levels. Thus, HT-29 cell lines, with the medium level of PDCD4 expression, were the most sensitive; whereas MCF-7 cells, with the highest level of PDCD4 expression, were the least sensitive.



Scheme 12: Dias's approach to *ent*-cryptocaryol A.

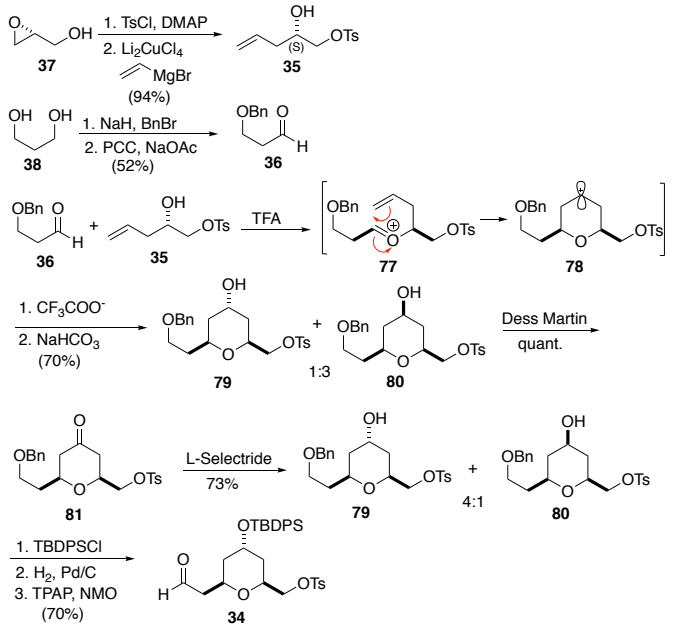
Dias's synthesis to (*ent*)-cryptocaryol A **3** started with PMB-protection of (*R*)-4-penten-2-ol **28**, which can be readily prepared by a Brown allylation of acetaldehyde to give **69**. A Wacker oxidation of **69** (O_2, Li_2PdCl_4 and CuCl) was used to convert the double bond to a methyl ketone **70**.[30] Ketone **70** was converted into boron enolate **71** (Cy_2BCl/Et_3N) which was reacted with 3-butenal to give *β*-hydroxyketone **26**. A chelation-controlled reduction of ketone **26** was used to give syn-1,3 diol which was subsequently protected to form acetonide **72**. Another Wacker oxidation was preformed to give methyl ketone **73**.



Scheme 13: Dias's approach to *ent*-cryptocaryol A

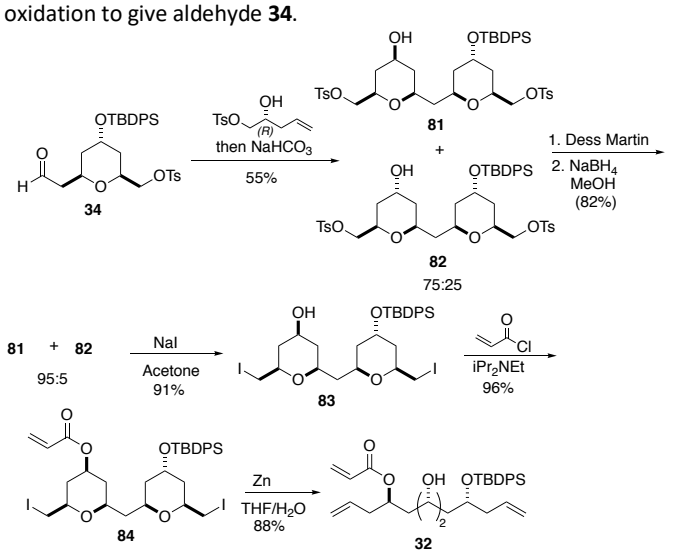
Once again, a boron mediated aldol between methyl ketone **73** and 3-butenal was used to give *β*-hydroxyketone, which was then reduced to anti-1,3-diol **74**. A three-step acetonide-protection, PMB-deprotection and Swern oxidation sequence was used to give **75**. The alkene in **75** was converted into the cis-enoate **76** by a dihydroxylation followed by diol oxidative cleavage and Ando olefination. Reacting at the methylketone side of **76**, another boron mediated aldol followed by anti-reduction was used to combine

methyl ketone **76** with hexadecanal to form anti-1,3-diol **20**. Finally, a one pot global acetonide deprotection and lactonization reaction was used to form *ent*-cryptocaryol A **3**.



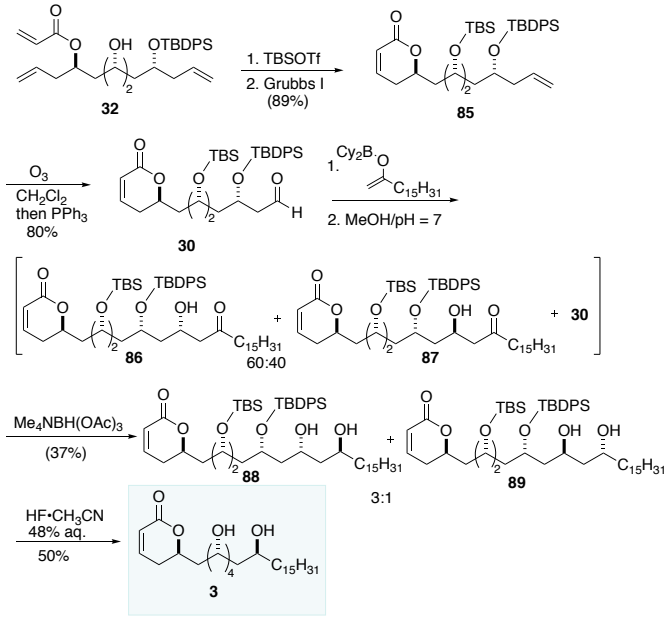
Scheme 14: Cossy's approach to cryptocaryol A

In 2015, Cossy reported a synthesis of the correct enantiomer of cryptocaryol A. The Cossy synthesis began with the coupling of homoallylic alcohol **35** and aldehyde **36** in a Prins-type pyran cyclization reaction.[31] Aldehyde **36** was prepared from 1,3-propane diol **38** via a two-step mono-protection and oxidation sequence. Homoallylic alcohol **35** was prepared from (*R*)-glycidol **37** by a two-step tosylation and cuprate epoxide opening sequence. The Prins cyclization between **36** and **35** occurred to give mixture of diastereomers **79** and **80** in a 1:3 ratio. A Dess-Martin periodinane oxidation of the mixture was used to form ketone **81**. A stereoselective reduction of ketone **81** with L-Selectride gave a 4:1 mixture of **79** and **80** with the desired isomer being major. A TDBPS-protection of alcohol **79** was applied followed by hydrogenolysis and oxidation to give aldehyde **34**.



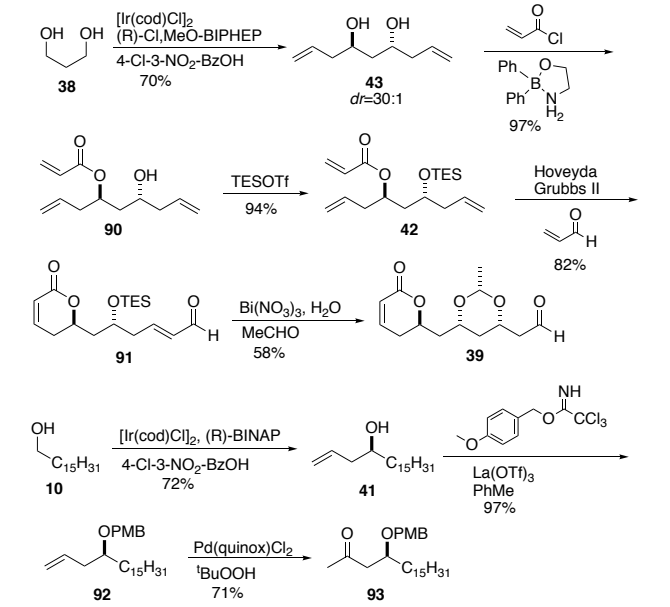
Scheme 15: Cossy's approach to cryptocaryol A.

With the first pyran ring set, the synthesis continued with a second Prins cyclization between **34** and *ent*-**35** to form a 3:1 mixture of diastereomers **81** and **82**. A Dess-Martin periodinane oxidation followed by reduction of the ketone intermediate were used to produce the desired diastereomer **81** in a 95:5 *dr* ratio. A Finkelstein reaction was used to convert bis-tosylate **81** into the bis-iodide **83**. An esterification of the equatorial alcohol in **83** gave **84**, which after a Zinc promoted reductive cleavage produced the key triene **32**.



Scheme 16: Cossy's approach to cryptocaryol A

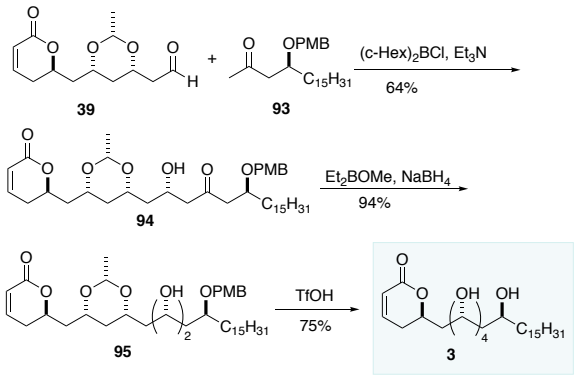
Triene **32** was chemoselectively cyclized into pyranone **85** by a two-step TBS-protection and Grubbs ring-closing metathesis reaction sequence. Ozonolysis of the terminal double bond in **85** was used to form aldehyde **30**. An aldol reaction between aldehyde **30** and a boron enolate was used to form a 6:4 mixture of diastereomers **86** and **87,** along with some unreacted aldehyde **30**. An anti-selective reduction of the mixture of **86** and **87** was applied to form **88** and **89**. Finally, a treatment of the major diastereomer **88** with HF•CH_3CN removed the silyl-protecting group to form cryptocaryol A **3**.



Scheme 17: Krische's approach to cryptocaryol A.

The most recent synthesis of cryptocaryol A was accomplished by Krische in 2016. As it is late to the game, Krische's synthesis uses

some of the same features of the earlier syntheses (*e.g.*, RCM, boron aldol, Wacker oxidation, etc.). However, it reorganizes these transformations and combines them with new in-house reactions, resulting in a well-honed synthetic effort that maximizes synthetic efficiency (*e.g.*, atom economy) in the minimal number of synthetic steps. The Krische synthesis began with the iterative Krische allylation of 1,3-propane **38** to stereoselectively create diol **43**. A mono-acylation of diol **43** catalyzed by Taylor catalyst formed triene **90**.[32] A TES-ether protection of the remaining alcohol was used to give **42**. A regioselective Hoveyda-Grubbs catalyzed ring-closing methathesis/cross methathesis of triene **42** gave the desired pyranone **91**. A Bi(III) mediated oxa-conjugate addition under Evans conditions converted **91** into aldehyde **39** which is the aldehyde half for the key aldol coupling reactions. The ketone partner was prepared in three steps from hexadecanol **10**. Specifically, a Krische allylation of **10** gave the homoallylic alcohol **41**, which after PMB-protection was converted into **92.** A Wacker oxidation of the allylic alcohol in **92** converted the alcohol into the desired ketone **93**.



Scheme 18: Krische's approach to cryptocaryol A.

Finally, the synthesis was completed by a three-step reaction sequence as laid out in (Scheme 18). Thus, the ketone **93** was converted into a dicyclohexylboron enolate and coupled with aldehyde **39** to give β-hydroxy-ketone **94**. A boron-mediated chelation controlled reduction of **94** gave protected cryptocayol A **95**. Global deprotection of the acetal and PMB ether was accomplished with triflic acid to form cryptocaryol A **3**.

In conclusion, the total syntheses of cryptocaryols A and B have been reviewed. Five unique approaches were developed to address this class of biologically active polyketide natural product. In 2013, Mohapatra reported the first synthesis of purported structure of cryptocaryol A. In the same year, O'Doherty reported the first total synthesis of cryptocaryols A and B and its enantiomers while revising the structure of cryptocaryols A and B. In 2015, Dias and Cossy completed the total synthesis of *ent*-cryptocaryol A and cryptocaryol A, respectively. In 2016, Krische reported the most efficient route to cryptocaryol A. Amazingly, in only two years, the structure of the cryptocaryols was reassigned by synthesis (23 total steps) and two alternative novel strategies were developed (22 and 17 total steps). Then one year later, these approaches inspired a revolutionary retrosynthetic redesign of the molecule culminating in the 8-step synthesis. These five diverse synthetic strategies shared some key transformations including RCM, boron aldol reaction/reduction and asymmetric allylation to form the pyranone or portions of the polyols. Each synthesis accomplished the goals of preparing the desired material and proved the merit of the synthetic methodologies used in that effort. Thus, one can expect that the lessons learned from these synthetic endeavors will enable further synthetic and medicinal chemistry efforts.

Conflicts of interest

There are no conflicts to declare.

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