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Total Synthesis of Cryptocaryol A *via* Enantioselective Iridium Catalyzed Alcohol C-H Allylation**

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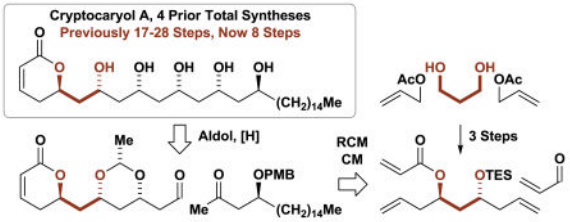
Less is More

The polyketide natural product Cryptocaryol A is prepared in 8 steps *via* iridium catalyzed enantioselective diol double C-H allylation, which directly generates an acetate-based triketide stereodiad. In 4 previously reported total syntheses, 17-28 steps were required.



Keywords

Iridium; Transfer Hydrogenation; Polyketide; Enantioselective; Total Synthesis

Downregulation of the tumor suppressor protein PDCD4 (programmed cell death 4)[1] has been linked to diverse human cancers, including liver,[2a] colorectal, [2b] brain,[2c]; ovarian,[2d] and gastric carcinomas.[2e] Conversely, murine epidermal cells resistant to tumor promotion possess elevated levels of PDCD4.[;1a] Hence, PDCD4 has emerged as a target for the development of anticancer drugs.[3] In 2011, using a high-throughput cell-based reporter assay[4] to screen extracts of a Papua New Guinea collection of the plant *Cryptocarya* sp. (Lauraceae, NSC number N098347), Gustafson and coworkers identified a new class of small-molecule PDCD4-stabilizers, the amphiphilic type I polyketides cryptocaryols A-H (Figure 1).[5] In 2013, Mohapatra reported the total synthesis of the purported structure of cryptocaryol A.[6a] In elegant contemporaneous work, O'Doherty completed total syntheses of cryptocaryols A and B,[6b] revising their structural assignments and enabling the first structure-activity studies within this compound class.[7] Recently, two additional total syntheses of cryptocaryol A were reported by Cossy[6c] and Dias.[6d]

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The interesting biology, recurring 1,3-polyol motif and prior synthetic work associated with cryptocaryol A made it an interesting compound to further benchmark the utility of catalytic C-C couplings developed in our laboratory.[8] These processes, which directly convert lower alcohols to higher alcohols, merge the characteristics of transfer hydrogenation with carbonyl addition, exploiting the native reducing ability of alcohols to drive generation of transient carbonyl-organometal pairs. Unlike synthetic routes involving conventional carbonyl addition chemistry, discrete alcohol-to-carbonyl redox reactions and use of premetalated carbanions are not required. This technology, which includes methods for stereo- and site-selective primary alcohol C-H allylation[9] and crotylation,[10] has been used in total syntheses of several iconic type I polyketide natural products.[8b,11] By evoking strategies beyond those accessible *via* conventional carbanion chemistry, our technology has provided the most concise routes reported in all cases where it has been applied.

In the context of cryptocaryol A, the double allylation of 1,3-propane diol,[9c] which directly generates a *C*2-symmetric acetate-based triketide stereodiad, was envisioned as a means of constructing the C3-C9 substructure (Scheme 1). This method has proven especially effective in type I polyketide construction, as illustrated in remarkably concise total syntheses of roxaticin,[11a]; bryostatin 7,[11b] neopeltolide,[11c] psymberin (irciniastatin A),[11d] cyanolide A,[11e] mandelalide,[11f,g] cryptolatifolione[11h] and cryptomoscatone E3.[11i] Another key feature of the proposed route involved concomittant ring-closing metathesis-cross metathesis[12] to convert the acrylic ester **3** to an α,β-unsaturated aldehyde, the immediate precursor to the α-pyrone, Fragment **A**. Stereoselective substrate directed aldol addition-ketone reduction followed by global deprotection unites Fragment **A** and Fragment **B** to deliver cryptocaryol A (Scheme 1).

Our route to Fragment **A** is as follows (Scheme 2). The previously reported double C-H allylation of 1,3-propane diol provides the *C*2-symmetric diol **1**.[9c] On gram scale, use of (*R*)-BINAP was preferred due to its relatively low cost, although isolated yields were diminished. Selective monoacylation of diol **1** using the method of Taylor was remarkably efficient, delivering the acrylic ester **2** in 97% yield.[13] Protection of the hydroxyl moiety of acrylate **2** to form TES-ether **3** was required to increase efficiency in the subsequent 2 steps. Treatment of compound **3** with acrolein in the presence of the Hoveyda-Grubbs-II catalyst in toluene solvent provided the desired RCM-CM product, α-pyrone **4**, in 58% yield. The efficiency of the RCM-CM process was improved significantly upon use of F8-toluene as solvent,[14] which enabled acquisition of α-pyrone **4** in 82% yield. Under these conditions, but in the absence of the TES-ether, the desired RCM-CM product was formed in only 14% yield. Related metathesis reactions were explored in Pilli's recently reported synthesis of cryptolatifolione.[11h] Finally, exposure of α-pyrone **4** to Evans' conditions for oxa-conjugate addition delivered Fragment **A** as a single stereoisomer.[15] Attempts to purify Fragment **A** *via* flash silica gel chromatography resulted in substantial decomposition. Chromatography on florisil gave better results, providing pure Fragment **A** in 58% yield. However, crude Fragment **A** (>90% pure by 1H NMR) could be obtained in 91% yield, which served equally well in subsequent steps compared to the chromatographically purified material. Notably, in the synthesis of Fragment **A**, 4 of the required 5 steps are catalytic transformations and all 4 C-C bonds are forged *via* metal catalysis.

The synthesis of Fragment **B** begins with the enantioselective C-H allylation of cetyl alcohol using the iridium catalyst assembled *in situ* from [Ir(cod)Cl]2, (*R*)-BINAP, allyl acetate and 4-chloro-3-nitrobenzoic acid.[9] The homoallylic alcohol **5** was obtained in 72% isolated yield and >95% ee, as determined by Mosher ester analysis.[16] Exposure of alcohol **5** to *p*-methoxybenzyl trichloroacetimidate in the presence of lanthanum triflate delivered the PMB-ether **6** in 97% yield.[17] Finally, using Sigman's modification of the Wacker oxidation,[18] PMB-ether **6** is transformed into the methyl ketone in 71% isolated yield, completing the synthesis of Fragment **B** (Scheme 3).

The union of Fragment **A** and Fragment **B** takes advantage of substrate-directed boron-mediated aldol addition (Scheme 4). Whereas enolborinate additions to β-alkoxy aldehydes typically do not display high levels of 1,3-asymmetric induction, exceptional 1,5-*anti*-diastereoselectivity is observed in enolborinate additions involving β-alkoxy methyl ketones as nucleophilic partners.[19] In the event, Fragment **B** was exposed to dicyclohexylboron chloride in the presence of triethylamine to form the enol borinate,[20] which upon exposure to Fragment **A** under cryogenic conditions (-78 °C) delivered the aldol product **7** in 64% yield as a single stereoisomer. As established in the parent methodological studies,[19] this level of stereocontrol is significantly higher than that reported for stereochemically related aldol additions between corresponding silyl-protected partners.[21] Hydroxy-directed reduction of the aldol product **7** delivers the diol **8** in 94% yield with good levels of 1,3-diastereoselectivity (15:1).[22] Finally, global deprotection of the acetal and PMB ether using triflic acid/1,3-dimethoxybenzene[23] delivers cryptocaryol A in a total of 8 steps (LLS) from 1,3-propane diol, fewer than half the steps of any prior synthesis.

In summary, despite impressive methodological advances, the vast majority of *de novo* chemical syntheses remain distant from the Hendricksonian ideal.[24,25] Using step-count as the most fundamental metric to evaluate strategic efficiency,[26] it is evident that classical carbanion chemistry, which requires separate treatment of redox and C-C bond construction events, contributes significantly to this inefficiency. As borne out by an expanding body of work,[8,11] technologies that merge redox and C-C bond construction events streamline chemical synthesis. In the specific context of cryptocaryol A, the chemistry of carbonyl addition and transfer hydrogenation are united in the form of a double enantioselective alcohol C-H allylation, which directly delivers an acetate-based triketide motif that would otherwise require numerous steps to prepare.[9c] This transformation, applied in combination with recent advances in alkene metathesis (RCM/CM)[12] and catalytic diol mono-functionalization,[13] have enabled a total synthesis of cryptocaryol A in fewer than half the steps previously required, and one can easily envision application of this approach to other members of this compound class. It is our hope the present exposition in chemical synthesis (along with prior demonstrations)[11] will motivate further developments in the area of redox-economic C-C bond formation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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"Given the fact that every reaction may be optimized… the total number of chemical transformations is the only variable in the determination of strategic efficiency. Obviously, the fewer the total number of reactions steps in a synthetic design, the higher the level of strategic efficiency." Qiu F. Can J Chem. 2008; 86:903–906.

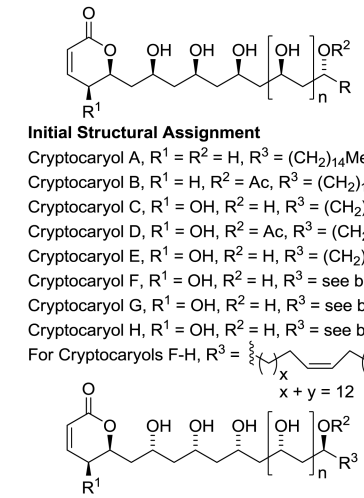
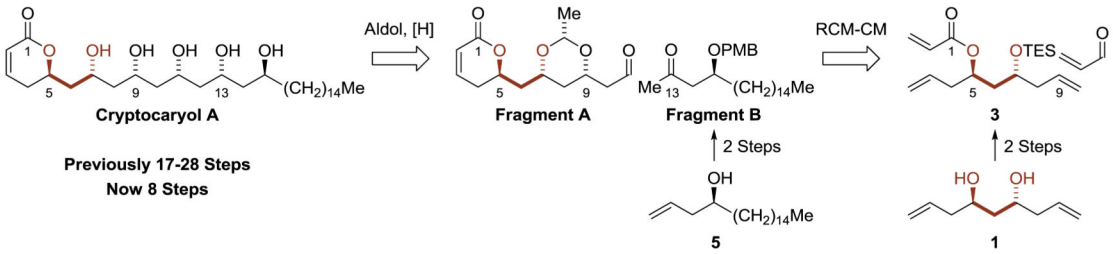
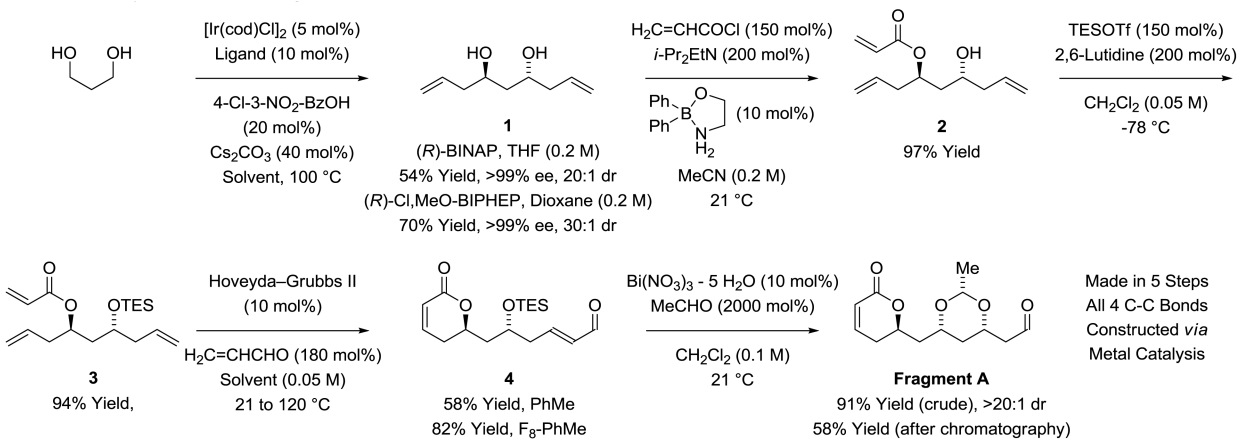


Figure 1. Initially proposed structures of cryptocaryols A-H, revised structures of cryptocaryols A and B and total syntheses of cryptocaryol A

*For graphical summaries of prior total syntheses, see Supporting Information. Longest Linear Sequence (LLS); Total Steps (TS).

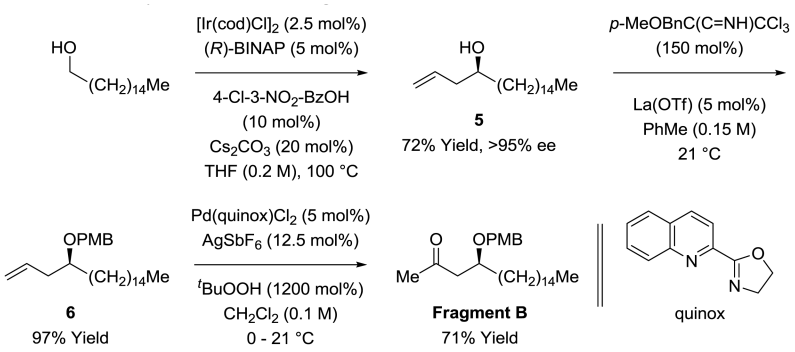


Scheme 1. Retrosynthetic analysis of cyanolide A *via* direct generation acetate-based triketide stereodiad



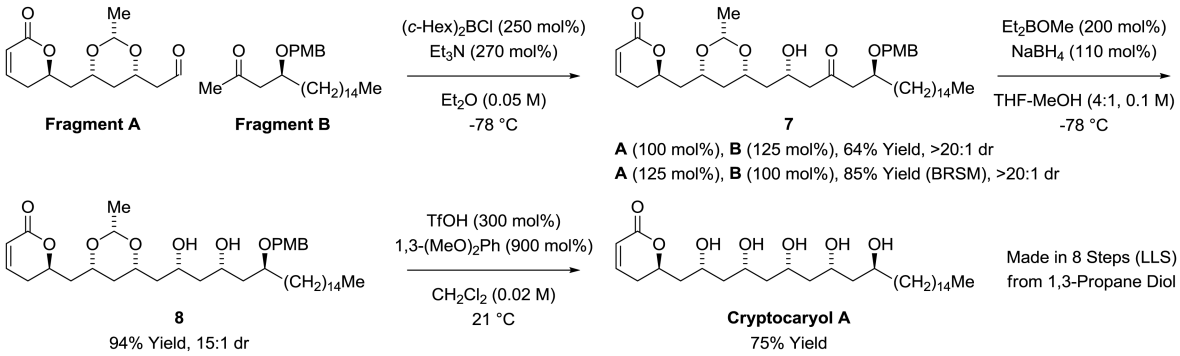
Scheme 2. Synthesis of Fragment A.[a]

[a]Yields are of material isolated by silica gel chromatography. See Supporting Information for further experimental details



Scheme 3. Synthesis of Fragment B.[a]

[a]Yields are of material isolated by silica gel chromatography. See Supporting Information for further experimental details



Scheme 4. Union of Fragment A and Fragment B and total synthesis of cryptocaryol A.[a]

[a]Yields are of material isolated by silica gel chromatography. See Supporting Information for further experimental details