Total Synthesis of (+)-Cryptocaryanone A

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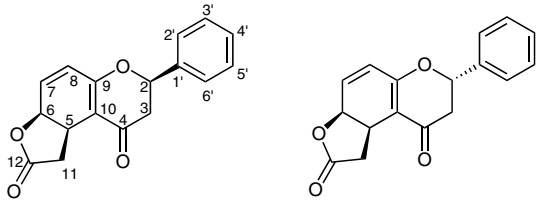
Abstract: The first total synthesis of (+)-cryptocaryanone A is described. The synthesis features a Mukaiyama aldol reaction, one-pot saponification/lactonization sequences, and TsOH-assisted dihydropyrone formation as key steps.

Key words: total synthesis, natural products, aldol reaction, saponification, lactonization

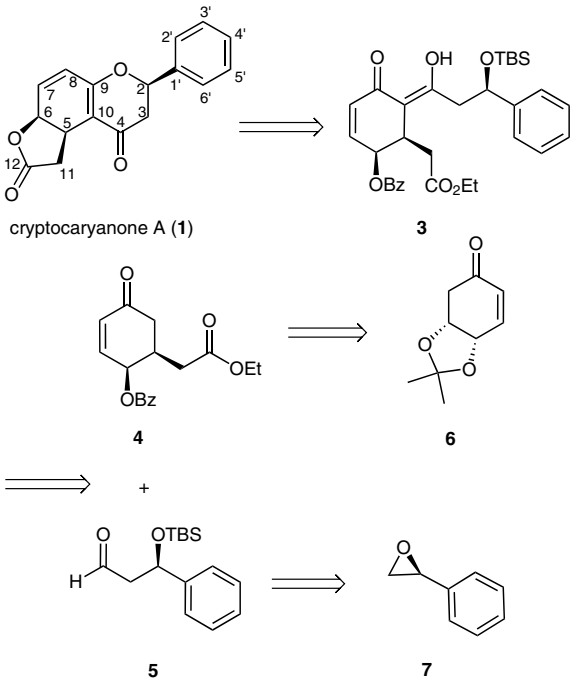
Flavonoids are a large class of natural products with diverse structures and good bioactivities that have been used to treat diseases for centuries.[1] In 2001, Guéritte and coworkers reported the isolation of two new dihydroflavanones, cryptocaryanones A (**1**) and B (**2**), from the trunk bark of *Cryptocarya infectoria* (Figure 1).[2] Both compounds exhibit modest cytotoxicity against KB cell lines, with IC_{50} values of 2.5 μM for **1** and 2.1 μM for **2**. In addition, cryptocaryanone A also shows cytotoxicities against MCF-7, NCI-H460, and SF-268 cell lines.[3] Structurally, these dihydroflavanones contain a tricyclic [6,6,5] skeleton comprising a γ-lactone and a dihydropyrone subunit. To date, to the best of our knowledge, no synthetic efforts towards these natural products have been reported. Attracted by its biological activity and unique chemical structure, we sought to develop a flexible synthetic route to these dihydroflavanones. Herein, we reported a concise synthesis of (+)-cryptocaryanone A.



cryptocaryanone A (**1**) cryptocaryanone B (**2**)

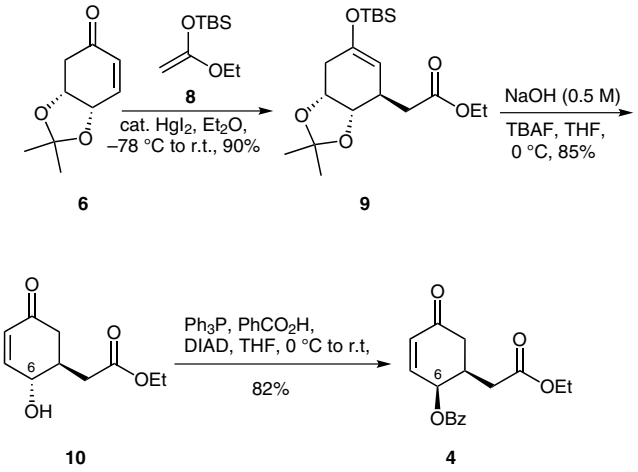
Figure 1 Structures of cryptocaryanone A and B

Retrosynthetically, cryptocaryanone A (**1**) could be obtained from enone **3** via lactonization and dihydropyrone formation (Scheme 1). Enone **3** was convergently disconnected into two segments, cyclohexenone **4** and aldehyde **5**, which would be easily prepared from known chiral enone **6** and epoxide **7** respectively.



Scheme 1 Retrosynthetic analysis of cryptocaryanone A

The synthesis of cyclohexenone **4** commenced from the known chiral enone **6** as shown in Scheme 2.[4] Conjugate addition of TBS-enol ether **8** to enone **6** smoothly afford-



Scheme 2 Synthesis of cyclohexenone (**4**)

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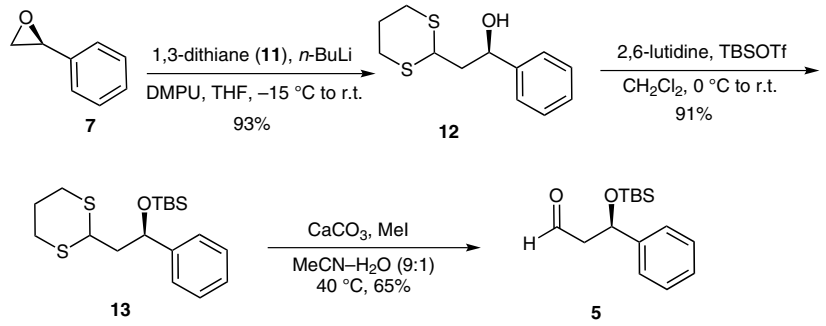


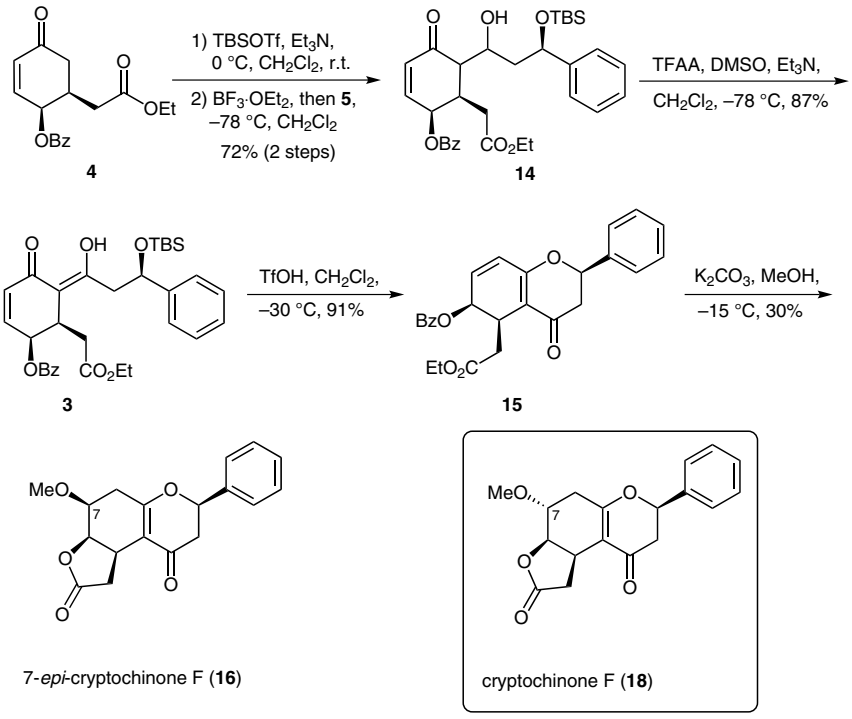
Scheme 3 Synthesis of aldehyde **5**

ed **9** as a single isomer.[5] Treatment of **9** with sodium hydroxide and tetrabutylammonium fluoride (TBAF) gave **10** in 85% yield.[4,6] Compound **10** was subjected to a Mitsunobu reaction with benzoic acid and the stereochemistry of the C6 secondary hydroxy group was inverted to give the desired cyclohexenone **4** in 82% yield.

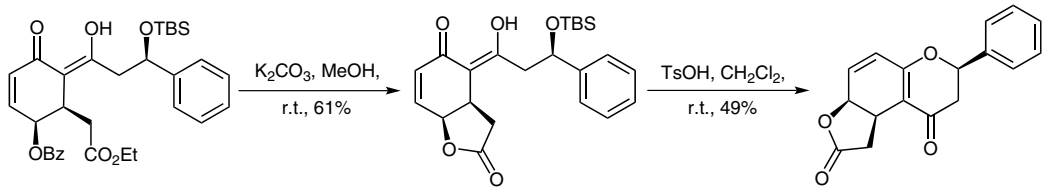
The synthesis of aldehyde **5** is depicted in Scheme 3: lithiation of 1,3-dithiane **11**, followed by addition of epoxide **7**, afforded alcohol **12** in 93% yield.[7] Protection of the free alcohol as the TBS ether and removal of the 1,3-dithiane group gave aldehyde **5** in 59% overall yield for two steps.

With cyclohexenone **4** and aldehyde **5** in hand, we turned our attention to the completion of the total synthesis of cryptocaryanone A (Scheme 4). Ketone **4** was first converted into the corresponding silyl enol ether, which was treated with aldehyde **5** in the presence of $BF_3{\cdot}OEt_2$ to afford alcohol **14** in 72% overall yield for two steps.[8] Subsequent oxidation of **14** was more problematic; attempted oxidations (PCC, 2-iodoxybenzoic acid, Dess–Martin reagent) were all unsuccessful. Gratifyingly, the use of TFAA-assisted Swern condition was effective and furnished ketone **3** in 87% yield.[9] Treatment of **3** with TfOH in dichloromethane at –15 °C for five hours led to cleavage of the TBS ether and cyclization in one pot to provide hydropyranone **15** in excellent yield.[10] At this time, we anticipated that cryptocaryanone A (**1**) could be obtained from ester **15** by a lactonization reaction.[11] Surprisingly, when ester **15** was treated with potassium carbonate in methanol at –15 °C, 7-*epi*-cryptochinone F (**16**)[12] was obtained, the structure of which was assigned by means of comprehensive spectroscopic analysis, including ^1H, ^{13}C NMR, H–H COSY, HMBC and NOE experiments.[3,13]

The synthetic route was adjusted slightly to construct the γ-lactone subunit first. Lactone **17** was readily obtained in 61% yield by treating ketone **3** with potassium carbonate in methanol. Subjecting **17** to the TsOH-promoted dihydropyrone formation reaction smoothly furnished cryptocaryanone A (**1**) in 49% isolated yield (Scheme 5). The optical rotation and spectroscopic data of synthetic cryp-



Scheme 4 Synthesis of 7-*epi*-cryptochinone F (**16**)



Scheme 5 Synthesis of cryptocaryanone A

tocaryanone A (**1**) were in agreement with those of the isolated natural product.[14]

In summary, an enantioselective total synthesis of cryptocaryanone A (**1**) has been accomplished that involved a Mukaiyama aldol reaction and a one-pot saponification/lactonizaton sequence as key steps. The 7-*epi*-cryptochinone F (**16**) was also achieved accidently and the developed strategy can be used to access other cryptochinone analogues.

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(12) **7-*epi*-Cryptochinone F (16)**: $[\alpha]_D^{20}$ +40 (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 2.35 (dd, *J* = 18.0, 5.2 Hz, 1 H), 2.50 (dd, *J* = 18.4, 5.6 Hz, 1 H), 2.71 (dd, *J* = 17.0, 3.4 Hz, 1 H), 2.76 (dd, *J* = 19.8, 3.8 Hz, 1 H), 2.92 (dd, *J* = 16.8, 13.6 Hz, 1 H), 3.03 (dd, *J* = 18.2, 8.6 Hz, 1 H), 3.47 (s, 3 H), 3.61 (br dd, *J* = 14.4, 6.4 Hz, 1 H), 3.83 (br dd, *J* = 10.6, 5.4 Hz, 1 H), 4.67 (t, *J* = 6.6 Hz, 1 H), 5.48 (dd, *J* = 13.2, 3.6 Hz, 1 H), 7.37–7.43 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.24, 32.05, 34.89, 43.01, 58.18, 74.75, 78.26, 80.94, 110.75, 126.27, 129.11, 129.24, 137.88, 167.88, 176.16, 190.80. IR (KBr): 2985, 2547, 2256, 1739, 1374, 1245, 915, 734 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{19}O_5^+$: 315.1227; found: 315.1223.

(13) Cryptochinone F was isolated from the evergreen tree *Cryptocarya chinensis* by Chou et al. (see ref. 3).

(14) **Cryptocaryanone A (1)**: To a solution of diketone **17** (9 mg, 0.022 mmol) in CH_2Cl_2 (5 mL) at r.t., was added $TsOH·H_2O$ (41 mg, 0.22 mmol). The reaction mixture was stirred for 3 days, then quenched with sat. aq $NaHCO_3$ (2 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. Flash chromatography (hexanes–EtOAc, 3:1) afforded cryptocaryanone A (**1**; 3 mg, 49%) as a white powder. $[\alpha]_D^{20}$ +217 (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 2.41 (dd, *J* = 17.9, 10.5 Hz, 1 H), 2.73 (dd, *J* = 16.8, 3.6 Hz, 1 H), 2.94 (dd, *J* = 17.2, 14.0 Hz, 1 H), 2.99 (dd, *J* = 18.0, 9.2 Hz, 1 H), 3.88 (dd, *J* = 19.8, 10.4 Hz, 1 H), 5.46–5.50 (m, 2 H), 6.10 (dd, *J* = 10.1, 1.8 Hz, 1 H), 6.29 (dd, *J* = 10.1, 2.7 Hz, 1 H), 7.41–7.45 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.75, 33.34, 42.94, 76.70, 81.08, 109.00, 124.30, 126.36, 129.13, 129.34, 134.87, 137.71, 162.77, 175.58, 190.47. IR (KBr): 2923, 2253, 1782, 1652, 1589, 1428, 910 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{19}O_5^+$: 283.0965; found: 283.0959.

