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A Flexible and Divergent Strategy to Flavonoids with a Chiral A-Ring Featuring Intramolecular Michael Addition: Stereoselective Synthesis of (+)-Cryptocaryone, (+)-Cryptogione F, and (+)-Cryptocaryanones A and B, as Well as (+)-Cryptochinones A and C

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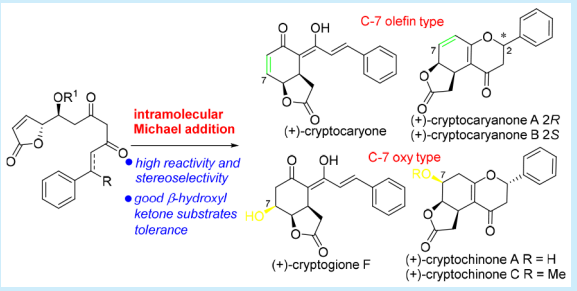
Supporting Information

ABSTRACT: A flexible strategy has been developed to synthesize divergent flavonoids bearing a chiral A-ring. As two key steps, the coupling via a boron-mediated aldol condensation and the cyclization via a highly stereoselective intramolecular Michael addition of 1,3-diketone proceed under mild conditions; thus, the chiral flavonoids bearing C-7 oxy functional groups or olefinic bonds are both easily accessible. Using this approach, the first synthesis of (+)-cryptogione F, (+)-cryptocaryanone B, and (+)-cryptochinones A and C, as well as stereoselective synthesis of (+)-cryptocaryone and (+)-cryptocaryanone A, were achieved from 2-deoxy-D-ribose in high overall yields.



Flavonoids are a large family of natural products with diverse structures and important bioactivities. A special group of chiral flavonoids such as **1**−**9**, only isolated from *Cryptocarya* species, are distinguished from other members by their dearomative A-ring containing a C-5 acetic acid/lactone group (see Figure 1). This unique feature of these skeletal molecules could be used as a chemotaxonomic marker. As the first member of this group, cryptocaryone (**2**) was isolated from *Cryptocarya bourdilloni* in 1972.[1] Since 2001, more and more flavonoids and biflavonoids bearing a chiral A-ring were reported.[2] Some members of these chiral flavonoids displayed significant cytotoxicity against a series of human cancer cells.[2a−c,g,3] In recent years, the cell antiproliferation effect and the mechanism of cryptocaryone on oral and androgen refractory prostate cancer cells were studied exclusively.[4] These skeletal compounds were also found to possess a variety of other bioactivities, such as anti-inflammatory,[2e] antimicrobial,[2g] antituberculosis,[2d] tyrosine kinase inhibitory,[2b] glucose transport inhibitory,[3] and NF-*k*B inhibitory activity.[5] Moreover, several members bearing C-7 oxy functional groups, including cryptochinones A (**6**) and C (**7**),[2c] can act as farnesoid X receptor agonists.[6] Therefore, these flavonoids and analogues are a type of potential agent for the treatment of cancer and other diseases.

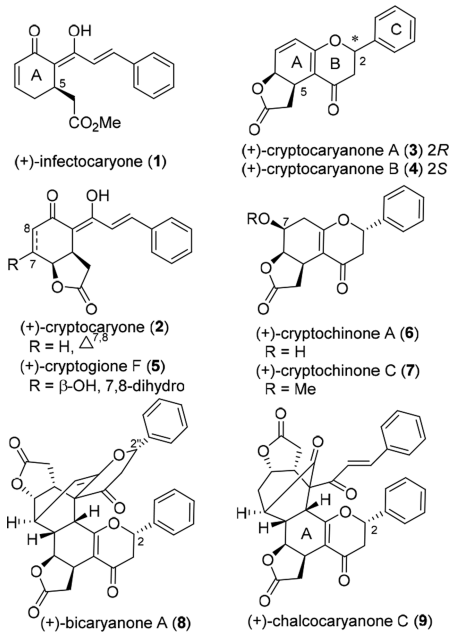


Figure 1. Several flavonoids and biflavonoids bearing a chiral A-ring.

The increasing group member and bioactivity discovery make these unique chiral flavonoids become attractive synthetic targets. In 2010, the first synthesis of cryptocaryone and the enantioselective synthesis of cryptocaryone and infectocaryone (**1**)[2a] were reported by the Fujioka group[7] and the Helmchen group,[8] respectively. The third member, cryptocaryanone A (**3**),[2a] was synthesized by She and co-workers in 2012.[9] Two years later, an alternative approach to infectocaryone was also developed by our laboratory.[10] All of the above syntheses are achieved via the prior construction of chiral A-ring cores,

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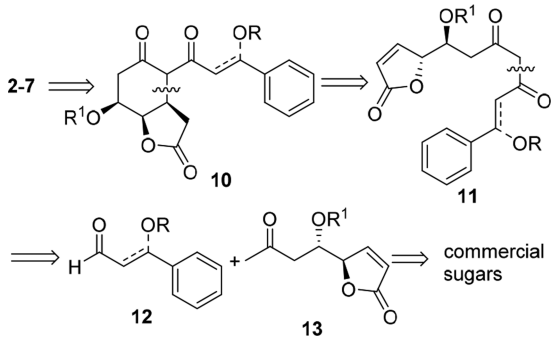
followed by the coupling with the appropriate partners containing an aryl ring. Although these useful approaches to the chiral flavonoids containing C-7 olefinic bond are developed, those members with oxy groups at C-7, such as cryptogione F (**5**),[2e] e.g., cryptochinones A and C, are not conveniently synthesized yet. Herein, we describe a distinctive and flexible strategy to the chiral flavonoids with more structural variation, in which the chiral A-ring is constructed in the final stage via an intramolecular Michael addition. Via this approach, the first synthesis of cryptogione F, cryptocaryanone B,[2a] and cryptochinones A and C, as well as stereoselective synthesis of cryptocaryone and cryptocaryanone A, are achieved.

Our retrosynthetic strategy for these divergent flavonoids is delineated (see Scheme 1). It was envisioned that **2**–**7** could be

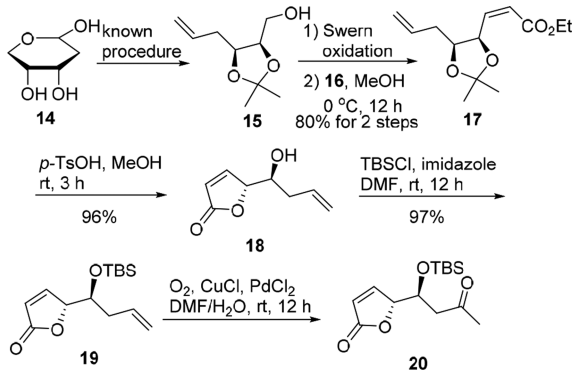
Scheme 1. Retrosynthetic Analysis of Flavonoids 2–7



accessed from advanced intermediate **10** via modification or dihydropyrone formation. The critical polysubstituted cyclohexanone core of **10** could be constructed via a stereoselective intramolecular Michael addition from the corresponding 1,3-diketone substrates (**11**). The cyclization precursor **11** containing all carbons of the final targets should be generated via an aldol condensation between appropriate aldehydes (**12**) and methyl ketone (**13**), the latter of which could be prepared readily from commercially available carbohydrates. Some cases regarding the Michael addition of 1,3-diketones have been reported;[11] however, the reaction has not yet been employed in the synthesis of chiral flavonoids.

Our synthesis began with the preparation of chiral ketone **13** from 2-deoxy-D-ribose **14** (see Scheme 2). According to the literature procedures,[12] **14** was converted to the known terminal alkene (**15**) with 72% yield in two steps. Swern oxidation of primary alcohol **15** gave the corresponding

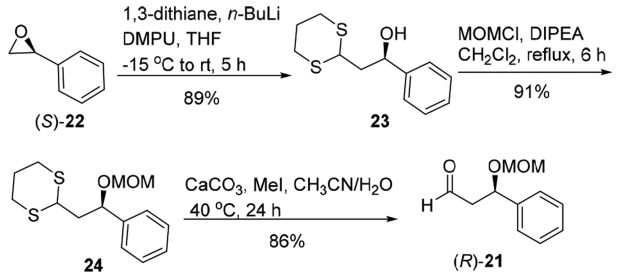
Scheme 2. Synthesis of Methyl Ketone 20



aldehyde, which was treated with (carbethoxymethylene)-triphenylphosphorane (**16**) to result in the *Z*-conjugated ester **17** with good yield. To achieve better stereoselectivity in the subsequent cyclization, we decided to construct unsaturated lactone unit prior to the formation of the A-ring. Thus, following the similar procedure in our synthesis of botryolide-E,[13] concurrent removal of the isopropylidene group in **17** and lactonization smoothly occurred under acidic conditions to afford the desired lactone **18**. After protection of the remaining alcohol functionality as TBS ether, terminal olefin **19** was subjected to Wacker oxidation,[14] which furnished the target methyl ketone (**20**).

The chiral aldehydes (*R*)- and (*S*)-**21** are conveniently prepared following She's procedure[9] (see Scheme 3).

Scheme 3. Synthesis of Aldehydes (*R*)- and (*S*)-21



Regioselective opening of (*S*)-2-phenyloxirane ((*S*)-**22**) by 1,3-dithiane anion gave benzylic alcohol **23**, which was converted to **24** via treatment with MOMCl. The subsequent removal of the 1,3-dithiane group afforded aldehyde (*R*)-**21** in higher yield than that reported in the literature, because of employment of the MOM protecting group, instead of the TBS group. Via the same route, (*S*)-**21** was synthesized from (*R*)-**22**.

Next, we turned our attention to the aldol union of the ketone and aldehyde subunits. Cinnamaldehyde (**25**) was first tested in the coupling with methyl ketone **20**. The aldol reactions under basic conditions gave unsatisfactory results, because of the occurrence of some side reactions of **20** such as *β*-elimination and intramolecular nucleophilic attack. On the other hand, in the boron-mediated aldol condensation (Cy_2BCl,[15] Ipc_2BCl[15c,16]) or the titanium-mediated aldol condensation ($TiCl_4$[15a,17]), the target adducts were obtained. After optimization of the reaction conditions, methyl ketone **20** was treated with Cy_2BCl and Et_3N at −78 °C to produce the corresponding kinetic boron enolate, which reacted with **25** to afford a mixture of diastereoisomeric adducts **26** and **27** in good total yield. Although the aldol diastereoselectivity is not high (diastereomeric ratio (dr) = 1.8:1), the absolute configuration of the new stereogenic center was not important to the overall synthetic plan. Thus, Dess–Martin periodinane oxidation of the mixture afforded the 1,3-dione, which isomerized to enol ketone **28** immediately. Following the same procedures as applied to **25**, chiral aldehydes (*R*)- and (*S*)-**21** were also converted to enol ketones **29** and **30**, respectively (see Scheme 4).

With cyclization precursors **28**–**30** prepared, the key intramolecular Michael addition was investigated. Upon treatment of **28** with Cs_2CO_3 in THF, the desired *cis*-cyclization product **31** and its *trans*-isomer **32** were obtained in 44% and 20% yield, respectively (Table 1, entry 1). The stereochemistry of the two cyclic adducts were subsequently identified by their transformation to the natural product and its

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Scheme 4. Synthesis of Enol Ketones 28−30

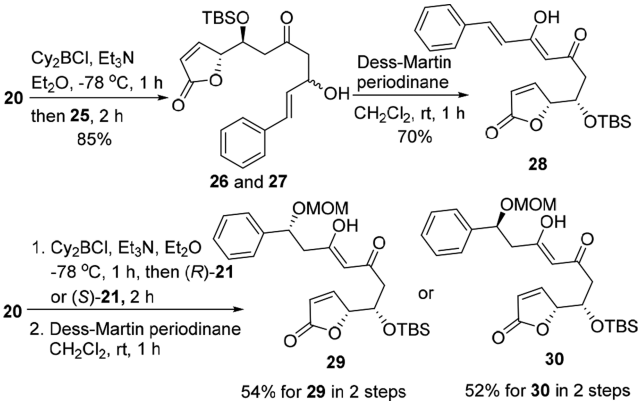
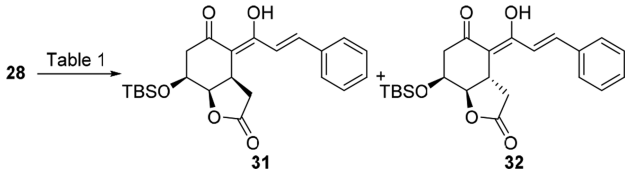


Table 1. Optimization of the Cyclization of 28[a]



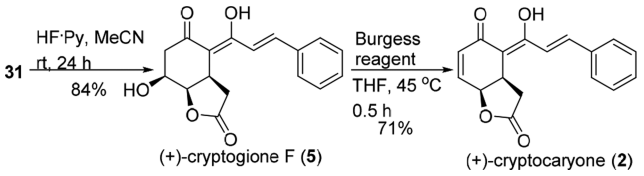
entry	base	solvent	temperature (°C)	time (h)	yield of **31** (%)	yield of **32** (%)
1	Cs_2CO_3	THF	rt	3	44	20
2	K_2CO_3	THF	rt	55	48	15
3	K_2CO_3	acetone	rt	48	40	17
4	K_2CO_3	CH_3CN	rt	24	34	14
5	DBU	CH_2Cl_2	rt	1	65	11
6	DBU	CH_2Cl_2	0	1	83	8
7	DBU	CH_2Cl_2	0	2	71	7
8	DBU	THF	0	4	50	12
9	DBU	DMF	0	4	38	10
10[b]	DBU	CH_2Cl_2	−20	8	60	10

[a]General conditions: **28**/base = 1/1.1, concentration (c) = 0.05 M. [b]20% of **28** was recovered.

epimer. Under K_2CO_3-mediated conditions, the cyclization of **28** showed similar yield and dr values. However, prolonged reaction times are necessary for full consumption of **28** (entries 2−4 in Table 1). Gratifyingly, the velocity and stereoselectivity of the reaction were remarkably improved when DBU was used as a base. The cyclization of **28** could completed within 1 h in CH_2Cl_2 at room temperature to afford **31** and **32** in a ratio of 6:1 (entry 5 in Table 1). The better results were obtained by decreasing the temperature to 0 °C, and the target **31** was produced in 83% yield, together with a small amount of **32** (8%) (Table 1, entry 6). Increased reaction times led to a decrease in yield, likely due to the slow deterioration of products (Table 1, entry 7). In other solvents, such as tetrahydrofuran (THF) or dimethylformamide (DMF), the catalytic effect of DBU decreased to give inferior results (see entries 8 and 9 in Table 1). Lower reaction temperature did not show an improvement in the stereoselectivity, but the reaction ran sluggishly (Table 1, entry 10).

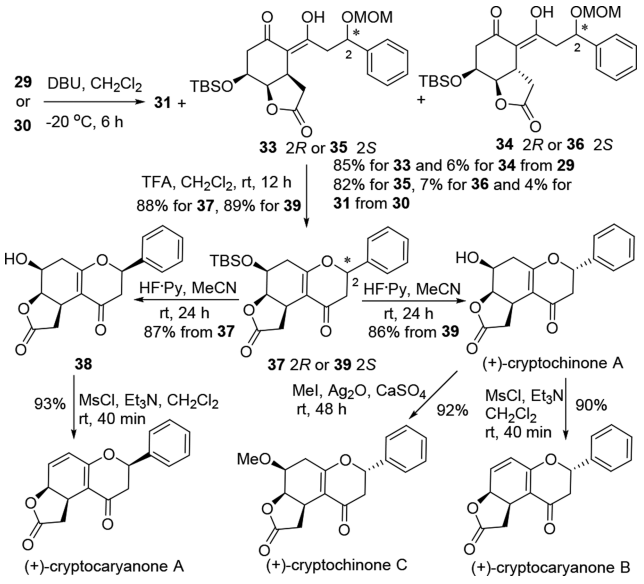
After optimizing conditions to provide useful quantities of **31**, the transformation of this key intermediate to **2** and **5** is easy. The silyl group of **31** was removed smoothly with HF·Py to give (+)-cryptogione F. Further β-elimination of the hydroxyl group in **5** with Burgess reagent[18] furnished (+)-cryptocaryone (see Scheme 5). The spectroscopic properties of the synthetic samples were identical to those of the natural products.[1,2e]

Scheme 5. Synthesis of (+)-2 and (+)-5



Subsequently, we set out to utilize enol ketone **29** and **30** to synthesize other chiral flavonoids via similar cyclization. Under the same conditions as for **28** (Table 1, entry 6), the intramolecular Michael addition of **29** furnished the resulting *cis*- and *trans*-lactones **33** (68%) and **34** (13%); however, in the cyclization of **30**, **31** was also obtained in 12% yield, because of β-elimination of the OMOM group besides two normal adducts (**35** (58%) and **36** (15%)). To suppress the elimination, we must optimize the reaction conditions again. To our delight, the temperature exerted a noticeable influence on the reaction, with better results being obtained upon decreasing the temperature. Remarkable enhancement of stereoselectivity and inhibition of β-elimination both were achieved by performing the reactions at −20 °C to afford the target *cis*-adduct predominantly. Under the optimized conditions, **29** and **30** cyclized with higher dr value to afford *cis*-fused lactones **33** and **35** in good yield, respectively (see Scheme 6).

Scheme 6. Synthesis of (+)-3, (+)-4, (+)-6, and (+)-7



Finally, construction of the B-ring was achieved by TFA-mediated cleavage of the MOM protecting group in **33**, concomitant formation of hemiacetal, and dehydration to produce hydropyranone (**37**). After deprotection of the TBS group, the resulting alcohol (**38**) was subjected to one-pot sulfonylation and elimination to furnish (+)-cryptocaryanone A. Following the similar manipulation involving closure of the B-ring and removal of the TBS group, the other adduct (**35**) was transformed to (+)-cryptochinone A, which underwent *O*-methylation using MeI and Ag_2O to give (+)-cryptochinone C (7-*O*-methylcryptochinone A). On the other hand, (+)-crypto-

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caryanone B was easily obtained by the treatment of **6** with MsCl and Et_3N. All spectroscopic and spectrometric data for the synthesized products were in good accord with the data reported for natural molecules.[2a,c]

In summary, we have developed a versatile synthetic strategy to flavonoids with a chiral A-ring featuring boron-mediated aldol condensation and highly stereoselective intramolecular Michael addition. Because of the high nucleophilicity of the 1,3-diketone substrates, the construction of the A-ring at the final stage can proceed under mild conditions, which allows one to tolerate the oxy functional groups, which are prone to β-elimination. Therefore, the chiral flavonoids bearing C-7 oxy functional groups or olefinic bonds are both easily accessible. The utility of the flexible strategy has been demonstrated by the first synthesis of cryptogione F, cryptocaryanone B, and cryptochinones A and C, as well as stereoselective synthesis of cryptocaryone and cryptocaryanone A, in good overall yields. More of this type of chiral flavonoids should be accessed via the versatile approach by fine-tuning methyl ketone partners.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00479.

Detailed experimental procedures and copies of ^1H and ^{13}C NMR spectra of the compounds (PDF)

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Notes

The authors declare no competing financial interest.

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