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Total Synthesis of Cryptotrione

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Dedicated to Shanghai Institute of Organic Chemistry, The Chinese Academy of Sciences on the occasion of its 70th Anniversary

Abstract: The first total synthesis of cryptotrione (**1**) has been achieved through substrate-controlled diastereoselective construction of the bicyclo[3.1.0]hexene framework *via* platinum-catalyzed enyne cycloisomerization, Lewis-acid induced polyene cyclization to construct the abietane type tricyclic diterpene skeleton, as well as diastereo-divergent conjugate addition to generate the tertiary carbon center on the side chain.

In 2010, cryptotrione (**1**) (Figure 1), a novel C_{35}-terpene with an unprecedented skeleton, was isolated from the bark of *Cryptomeria japonica* by the Kuo group.[1] Since the isolation of the first cryptotrione member from the *Cryptomeria japonica* family in 1983 nine cryptotrione family members, including chamaecydin (**2**), isochamaecydin (**3**) and cryptoquinonemethides D and E (**4**, **5**), have been isolated.[1-2] All share this unprecedented skeleton possessing an abietane-type diterpene quinone methide spiro-annulated with a thujone-type bicyclo[3.1.0]hexane ring system. Cryptotrione (**1**), the structurally most complex member of this family, interestingly exhibits anticancer activity against human oral epidermoid carcinoma KB cells with an IC_{50} value of 6.44 ± 2.23 μM, only slightly weaker than that of the clinically used anticancer drug, etoposide (VP-16, IC_{50}~2.0 μM).[1] To the best of our knowledge, there have been no reports of its total synthesis, although the Shi group demonstrated the construction of its bicyclo[3.1.0]hexane core.[3] The promising bioactivity of these unprecedented molecules, coupled with the synthetic challenges arising from their bicyclo[3.1.0]hexane unit, attracted our interest. Here we report the first total synthesis of cryptotrione (**1**) employing the efficient platinum-catalyzed assembly of the bicyclo[3.1.0]hexane structural unit and quinone methide moiety.

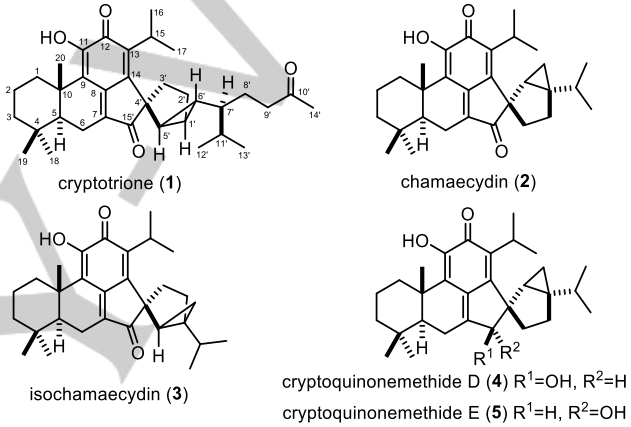

Figure 1. Representative Structures of Cryptotrione Family.

Our retrosynthetic analysis of the structure of cryptotrione (**1**) has revealed the bicyclo[3.1.0]hexane unit and quinone methide species as the structural features common to the cryptotrione family. Based on our preliminary results and reports of gold- or platinum-catalyzed cycloisomerization of 1,*n*-enynes into bicyclo[n.1.0]hexane derivatives[4,5] (Figure 2), we proposed to assemble the bicyclo[3.1.0]hexane moiety in compound **9** from 1,5-enyne species **10**. Moreover, in consideration of the steric effect of the isopropyl group on the benzene ring, we reasoned that the enyne cycloisomerization of a substrate with an isopropyl group could lead to the undesired stereochemistry of the bicyclo[3.1.0]hexane moiety. This could also facilitate efficient synthesis of other cryptotrione family members through functional group modification of the 1,5-enyne substrate.[5f,5i,5m] The 1,5-enyne precursor **10** could be readily prepared from commercially available homoveratric acid (**11**) through a known procedure.[6] Once alcohol **9**, with a bicyclo[3.1.0]hexane unit, was achieved, alkylation of relevant ketone derivative of alcohol **9** could lead to polyene **8**. Compound **8**, with an α-alkyl group, would then undergo Lewis acid-mediated stereoselective cyclization followed by isopropylation to provide the corresponding *trans*-polycyclic species **7**, in which the stereocyclization could be controlled by the stereochemistry of the relevant α-alkyl group in ketone **8**. Subsequent installation of the side chain on **7** could afford alkene **6**. The generation of the

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relevant quinone methide species followed by Wacker oxidation would eventually afford synthetic cryptotrione (**1**).

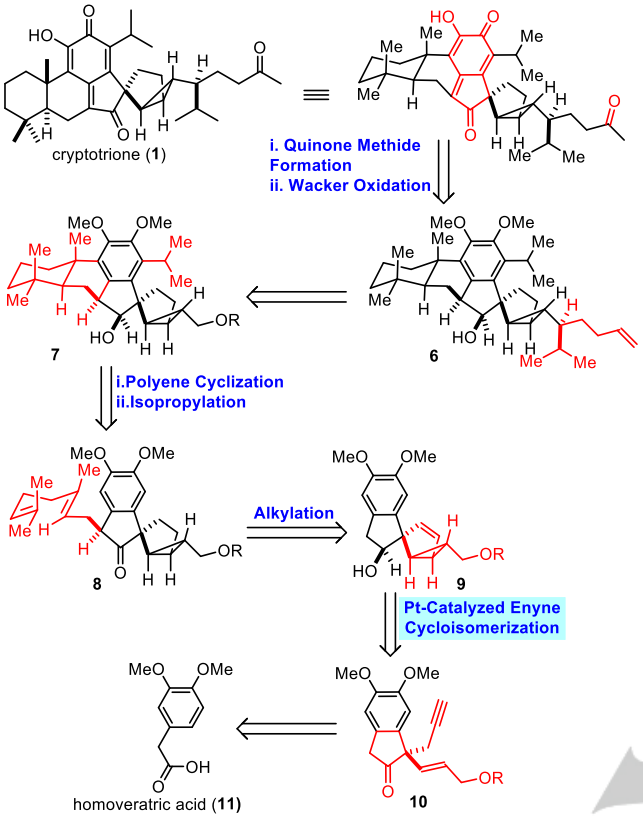
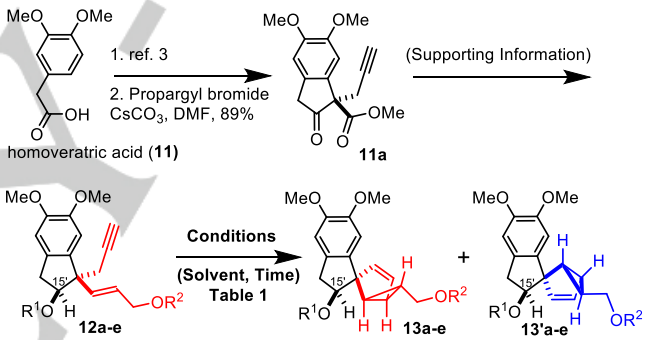


Figure 2. Retrosynthetic Analysis of Cryptotrione (**1**).

Thus, we commenced our synthesis by developing an assembly protocol for the bicyclo[3.1.0]hexane structural unit. Starting from the commercially available homoveratric acid (**11**), various enynes **12a-e** were prepared, via a known carbene-insertion procedure,[3] followed by a series of classic transformations (Scheme 1 and Supporting Information). Next, we focused on the conversion of enynes **12a-e** into the desired bicyclo[3.1.0]hexene species **13a-e**, as opposed to the undesired **13´a-e**. In order to understand the stereoeffects of the protective hydroxyl groups in enynes **12a-e**, we prepared both C15'-α-silyloxy-1,5-enyne species and C15'-β-silyloxy-1,5-enyne species via diastereoselective reduction. Treatment of the α-silyloxy-1,5-enyne under Toste's Au-catalyzed conditions[5i] generated the undesired bicyclo[3.1.0]hexene compound whose relative configuration of the cyclopropane ring differed from that of cryptotrione (**1**) (Supporting Information). We therefore turned our attention to cycloisomerization of C15'-β-silyloxy-1,5-enynes **12a-e** as a way to generate the bicyclo[3.1.0]hexane unit for total synthesis of cryptotrione (**1**), expecting that the C15'-β-silyloxy group would cause substantial steric hindrance to impact relevant cycloisomerization, leading to key precursors **13a-e** with the desired stereochemistry. Unfortunately, in the presence of 10% $Ph_3PAuCl/AgSbF_6$,[5i] enyne **12a** decomposed completely (Entry 1), and enyne **12c** with a β-benzyloxy group even initiate a novel gold-catalyzed tandem cycloisomerization.[4] We therefore turned to platinum-catalyzed enyne isomerization.[5h-n]

To our pleasure, the $PtCl_2$-catalyzed enyne isomerization[5k,5l,5m] of **12a** occurred smoothly with 20 mol% $PtCl_2$ at 100 °C in toluene for 18 hours, affording **13a** in 44% isolated yield with a *dr* > 30:1 (Table 1, entry 2). While **12b** containing smaller protection group (TBS vs *i*Pr_3Si) gave slightly lower yield under the same conditions (Table 1, entry 3). Enyne **12c** with a β-benzyloxy group also gave the desired **13c** in 30% yield with a similar *dr* > 30:1(Table 1, entry 3).[4] In contrast, enyne **12d** with a methoxyl group (Table 1, entry 6) gave poor yield (20%) and *dr* (12:1), presumably due to insufficient steric hindrance. Replacing the acetyl protection group on R^2 to pivaloyl improved the yield only slightly (Table 1, entries 4 *vs* 5), implying that the β-triisopropylsiyl group at C15' dominated stereoselectivity. We then further optimized cycloisomerization for catalyst and solvent using enyne **12e** (Supporting Information). After varying the platinum(II) or platinum(IV) halides, 10 mol% of $PtCl_4$ gave the best result of 75% isolated yield (entries 7-8). Screening of solvents showed that 1,4-dioxane gave even better yields than those know cases usually using toluene as the solvent.[5f,5k-n] Moreover, this isomerization was easily scaled up to 15g using 10 mol% $PtCl_4$ catalyst at 115 °C, affording **13e** in 71% yield (entry 8).



12a: R^1 = *i*Pr_3Si, R^2 = Ac; **12b**: R^1 = TBS, R^2 = Ac
12c: R^1 = Bn, R^2 = Ac; **12d**: R^1 = Me, R^2 = Ac
12e: R^1 = *i*Pr_3Si, R^2 = Piv

Scheme 1. Synthesis of Bicyclo[3.1.0]hexene Species

Table 1. Optimization of 1,5-Enyne Cycloisomerization[a].

Entry	Enyne	Catalyst (mol%)	Solvent	Ratio[b] (13:13')	t(h)	Yield[c] (%)
1	**12a**	$Ph_3PAuSbF_6$	CH_2Cl_2	–	0.5	0
2	**12a**	$PtCl_2$ (20)	Toluene	>30:1	18	44
3	**12b**	$PtCl_2$ (20)	Toluene	>30:1	18	32
4	**12c**	$PtCl_2$ (20)	Toluene	>30:1	18	30
5	**12d**	$PtCl_2$ (20)	Toluene	12:1	6	20
6	**12e**	$PtCl_2$ (20)	Toluene	>30:1	18	47
7	**12e**	$PtCl_4$ (10)	Dioxane	>30:1	4	75
8[d]	**12e**	$PtCl_4$ (10)	Dioxane	>86:1	7	71

[a] Standard conditions: **12** (0.05 mmol) and platinum catalyst in solvent (5 mL) at 100 °C under argon. [b] *dr* ratio determined by ^1H NMR spectra after global deprotection of **13** and **13'**. [c] Isolated yield. [d] 15g scale at 115 °C.

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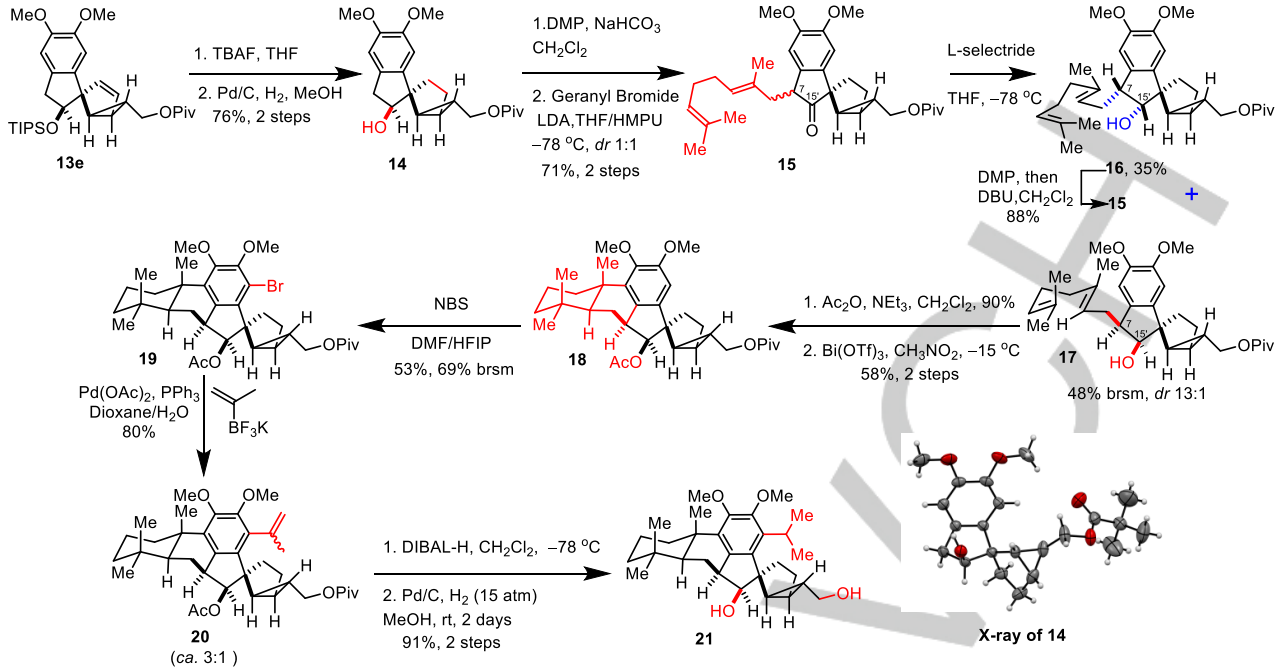

Scheme 2. Synthesis of Diol **21**.

With crucial precursor **13e** in hand, we turned to the synthesis of diol **21**. Desilylation of **13e** followed by hydrogenation yielded alcohol **14** in 75% yield (Scheme 2) and X-ray crystallographic analysis showed the bicyclo[3.1.0]hexane skeleton to have the same relative configuration as in natural cryptotrione (**1**).[24] Oxidation of **14** with Dess-Martin periodinane furnished the corresponding ketone, which then underwent monoalkylation with geranyl bromide using one equivalent of LDA in a mixed solvent (THF:DMPU 10:1) to afford a diastereomeric mixture of monoalkylated polyene ketones **15** in 72% yield (84% brsm) together with 15% yield of the dialkylated by-product. The mixture of ketones **15** was inseparable by column chromatography and, since it also proved unstable and prone to decomposition. We then sought to stabilize ketones **15** by reducing the carbonyl groups to hydroxyl groups, because we reasoned that the hydroxyl group would decrease the acidity of the α-proton, preventing the cyclization precursor from potential epimerization. Screening of various reducing reagents showed ketone **15** was reduced diastereoselectively by L-selectride at low temperature (see Table S3 in Supporting Information for details), affording *syn*-C7,15'-β,β-polyene alcohol **17** as a major diastereomer (*dr* = 13:1) in 33% yield (48% brsm), as well as *syn*-C7,15'-α,α-polyene alcohol **16** as a single isomer in 35% yield. Alcohol **16** was able to undergo oxidation followed by epimerization to regenerate ketones **15** (*dr* = 1:1) in 88% yield. To stabilize the polyene alcohol **17** and prevent it from undergoing cation-olefin cyclization under acidic conditions,[7] we converted its hydroxyl group into the acetate in high yield, containing the polyene and hydroxyl groups on the β-side (Supporting Information).

To construct the abietane-type skeleton, we explored Lewis acid-induced polyene cyclization of the acetate of alcohol **17** to yield the *trans*-decalin product **18**.[8] Based on Stork–Eschenmoser's rule,[9] we anticipated that cyclization of the C7-β-*trans*-polyene acetate of compound **17** would favorably proceed *via* a double-chair transition state to afford the *trans*-decalin product **18**, containing a C10-β-angular methyl. After careful optimization (see Table S4 in Supporting Information), $Bi(OTf)_3$-induced polycyclization[10] was indeed able to convert the acetate of **17** into the abietane-type product **18** in 67% yield as a single diastereomer, after further cyclization of partially cyclized intermediates.

After constructing the *trans*-decalin skeleton, we began to install the isopropyl group onto the benzene ring. Neither N-bromosuccinimide (NBS) with various promoters ($Ph_3P{=}S$,[11] $AgNTf_2$,[12] $AuCl_3$,[13] or zwitterionic-salt[14]) nor NBS with a strong Brønsted acid in DMF, such as H_2SO_4, were able to deliver a successful bromination, but bromide **19** was produced in 30% yield (50% brsm) using NBS and AcOH. Employing two equivalents of NBS in the co-solvents hexafluoroisopropanol (HFIP) and DMF, the yield of bromide **19** was increased to 53% yield (69% brsm). Our efforts to direct isopropylation of bromide **19**, using newly developed direct isopropylation conditions,[15] yielded only reductive product **18** and n-propyl-substituted product (Supporting Information). We then tried to introduce the isopropyl group stepwise under Stoltz's conditions.[16] As expected, bromide **19** smoothly underwent sterically hindered Suzuki-Miyaura coupling with potassium isopropenyltrifluoroborate to produce the alkene **20** in 80% yield as an inseparable atropisomeric mixture (*ca.* 3:1). Attempts at direct hydrogenation of alkene **20** using a variety of classic

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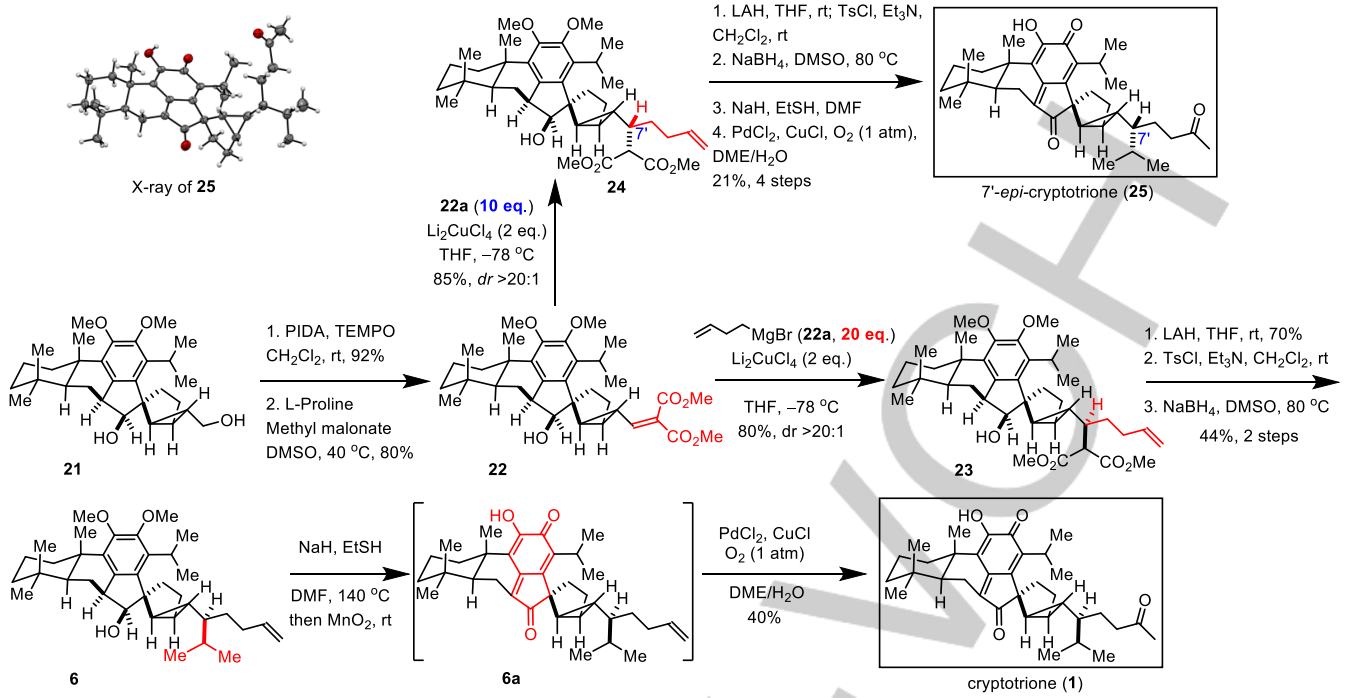

Scheme 3. Total Synthesis of Cryptotrione (**1**)

protocols were completely unsuccessful, probably retarded by the steric hindrance from acetyl and pivaloyl groups. Reduction of **20** with DIBAL-H to relieve this steric hindrance, followed by subsequent hydrogenation, however, successfully led to diol **21** in 91% yield over the two steps.

After establishment of the structural framework of cryptotrione (**1**), we then focused on the installation of the side chain. As shown in Scheme 3, selective oxidation of the primary hydroxyl group of **21** using PIDA-TEMPO[17] led to its aldehyde in 92% yield, which subsequently underwent Knoevenagel condensation with dimethyl malonate to afford *α*,β-unsaturated malonate **22**,[18] the precursor for conjugate addition, in 80% yield. In our initial studies, conjugate addition of **22** and homoallylmagnesium bromide (**22a**) in the presence of CuI formed **23** and its isomer with poor diastereoselectivity.[19] When two equivalents Li_2CuCl_4 were used as the copper source in the presence of 20 equivalents of homoallylmagnesium bromide (**22a**) at –78 °C,[20] the desired conjugate addition product **23** was smoothly achieved in 80% yield with *dr* > 20:1. Interestingly, further optimizations (see Supporting Information) showed that the stereoselectivity of the conjugate addition was totally reversed in the presence of 10 equivalents of homoallylmagnesium bromide (**22a**) and Li_2CuCl_4 (2 equivalents) at –78 °C with different reagent addition mode (see Supporting Information), forming **24** (C7'-epimer of **23**) with excellent *dr* (> 20:1 at C7'). Thus, the stereochemistry at C7' could be fully controlled using different amounts of homoallylmagnesium bromide and addition mode, presumably due to the formation of different copper magnesium complexes.

Thus, alkenes **23** and **24** are ready for the syntheses of cryptotrione (**1**) and 7'-*epi*-cryptotrione (**25**), respectively. In Scheme 3, the Michael acceptor **22** hence served as a diastereo-divergent intermediate for the syntheses of both cryptotrione (**1**) and its C7'-epimer (**25**). Upon treatment of **23** with $LiAlH_4$, subsequent selective tosylation and hydride replacement[21] of the resulting tosylate, alkene **6** was formed in 30% yield over the 3 steps. Demethylation of **6** under alkaline conditions[22] then afforded the dihydroxyl intermediate, which unfortunately could not be auto-oxidized in air to its corresponding *ortho*-quinone. Instead, this dihydroxyl phenol intermediate was treated with MnO_2, generating the *para*-quinone methide **6a**, which was directly subjected to Wacker oxidation[23] without further purification, eventually affording synthetic cryptotrione (**1**) in 40% yield. Moreover, subjection of alkene **24** to the similar aforementioned procedures from alkene **23** to cryptotrione (**1**), 7'-*epi*-cryptotrione (**25**) was successfully achieved in 18% yield over 5 steps. The structure of 7'-*epi*-cryptotrione (**25**) was unambiguously confirmed using X-ray crystallographic analysis.[24]

In summary, we achieved the first total synthesis of cryptotrione (**1**) from commercially available homoveratric acid (**11**) in a diastereoselective and diastereo-divergent manner. This synthetic protocol features with a novel platinum(IV) chloride-catalyzed diastereoselective cycloisomerization of 1,5-enynes to construct the bicyclo[3.1.0]hexane core, a Lewis acid-induced diastereoselective polyene cyclization, and a stereo-divergent conjugate addition to construct the tertiary carbon center of the side chain with full stereocontrol. This synthetic route would be practical for synthesizing other members of the structurally unprecedented cryptotrione family and its analogs for further biological evaluation.

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Keywords: total synthesis • cryptotrione • enyne • isomerization • cyclization

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Natural Product Synthesis

Total Synthesis of Cryptotrione

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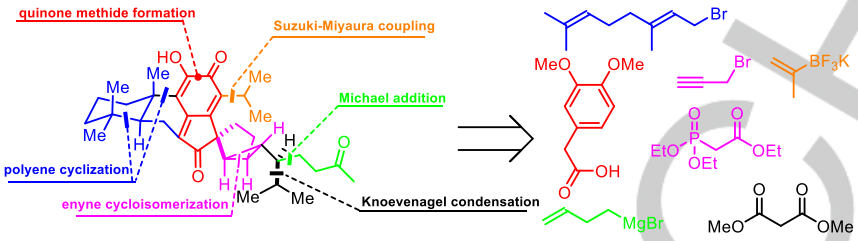

The first total synthesis of cryptotrione has been acheived *via* platinum-catalyzed enyne cycloisomerization from commercially available homoveratric acid in a diastereoselective and diastereo-divergent manner. This synthetic strategy would be practical for synthesizing other members of the structurally unprecedented cryptotrione family.

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