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Expedient Synthesis of the Proposed Structure of Cryptoconcatone H Exploiting Hidden Symmetry

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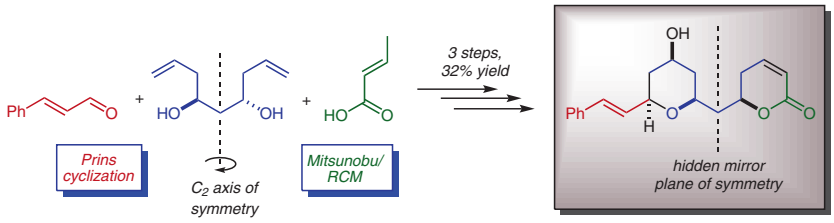

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Abstract Synthesis of the originally assigned structure of the styryl tetrahydropyranol-dihydropyranone natural product cryptoconcatone H from C_2-symmetric (±)-1,8-nonadiene-4,6-diol is reported. Desymmetrization by Mitsunobu reaction with crotonic acid established the requisite inter-ring stereochemical relationship and was followed by a highly diastereoselective Re_2O_7-catalyzed Prins cyclization with cinnamaldehyde to construct the 2,4,6-*cis*-tetrahydropyranol ring. Ring-closing metathesis resulted in formation of the dihydropyranone ring and completed the synthesis in three steps and 32% overall yield. The brevity of the synthesis is the result of the recognition of hidden, inter-ring symmetry in the target and the ensuing choice of an appropriately symmetric diol as our starting material.

Key words cryptoconcatone H, total synthesis, hidden symmetry, Mitsunobu reaction, Prins cyclization, ring-closing metathesis

The cryptoconcatones are a family of structurally related natural products isolated by Luo, Kong, and coworkers from the leaves and branches of *Cryptocarya concinna*, a monsoon evergreen found in subtropical mainland China.[1] Although the majority of cryptoconcatones contain terminal styryl and dihydropyranone groups tethered by a linear trisubstituted, six-carbon chain, three members (cryptoconcatones H, K, and L) possess a central 2,4,6-tetrahydropyranol ring (Figure 1). Cryptoconcatone H was originally assigned to be 2,4,6-*cis*-tetrahydropyranol **1**; however, combined computational and synthetic studies by Pilli and coworkers led to structural revision of the putative structure to diastereomer **2**, which differs in configurations at C2′ and C4′ (cryptoconcatone numbering).[2] The assignments of cryptoconcatones K (**3**) and L (**4**) have also been called into question by similar computational analysis, which, for example, identified **5**, possessing the opposite relative inter-ring stereochemistry as **3**, as the most plausible structure of cryptoconcatone K.[2b]

Given the structural ambiguity associated with the tetrahydropyranol cryptoconcatones, we aimed to develop a stereochemically versatile synthetic approach to this class of compounds. Herein, we report an efficient synthesis of (±)-**1** and its C6 diastereomer that we believe may hold potential in facilitating the assignment of cryptoconcatone K.

To date, synthetic studies on the tetrahydropyranol cryptoconcatones have resulted the synthesis of *ent*-**2**[2a] as well as two syntheses of **1**.[2b,3] NMR data of synthetic materials has confirmed the reassignment of **2** as the correct structure of naturally occurring cryptoconcatone H. Strategically, the reported approaches to **1** are related (Scheme 1). In both, stereoselective tetrahydropyranol formation (Pd-catalyzed cyclization of diol **6** by Pilli and workers and tandem deprotection/oxa-Michael addition of acetonide **7** by Csókás and Bates) preceded diastereoselective allylation to establish the C6 stereocenter and ring-closing metathesis

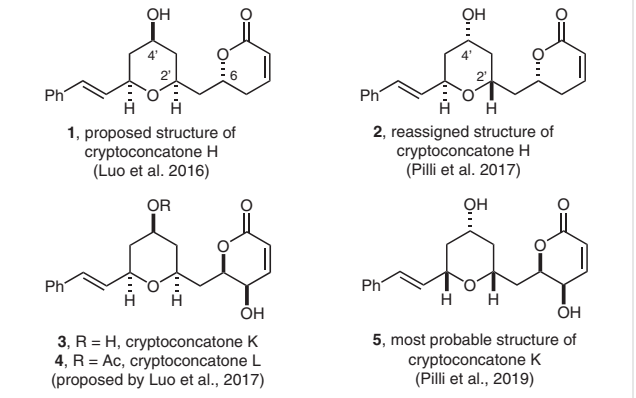

Figure 1 Tetrahydropyranol cryptoconcatones from *C. concinna*

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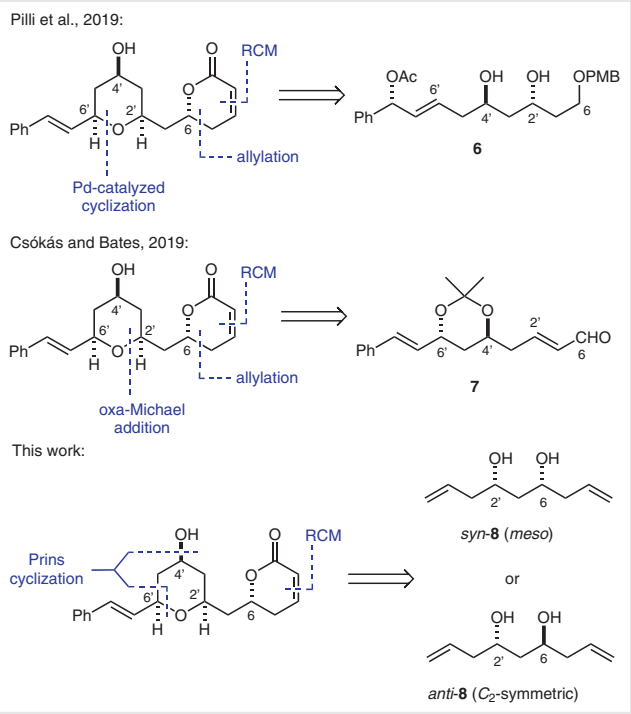
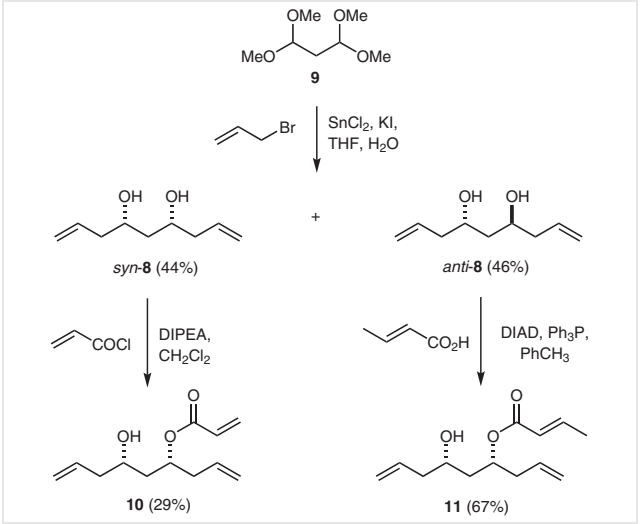
(RCM) to construct the dihydropyranone ring. The Pilli and Bates syntheses of **1** were also similar in step count – requiring ten and eleven steps, respectively, from known compounds. We envisioned an alternate approach to **1** that takes advantage of the latent symmetry about the core methylene-ring junction that could significantly streamline the synthesis.[4] Specifically, we recognized that the tetrahydropyranol and dihydropyranone rings could both be derived from homoallylic alcohols, by Prins cyclization and RCM, which revealed symmetric diols *syn*- or *anti*-**8**, in which the inter-ring, C2′,C6-stereochemical relationship is fixed, as potential starting points.



Scheme 1 Synthetic approaches to **1**

Diols *syn*- and *anti*-**8** were readily accessible from 1,1,3,3-tetramethoxypropane (**9**) as a chromatographically separable 1:1 mixture following the procedure of Samoshin and coworkers (Scheme 2).[5] The first step in our synthetic plan was a symmetry-breaking acylation of either *syn*- or *anti*-**8** in order to set up the RCM and 'protect' the C6 hydroxyl during the Prins cyclization. Monoacylation of *syn*-**8**, which possesses the requisite C2′,C6-relative stereochemistry, with acryloyl chloride led to only poor isolated yields of acrylate **10**. Fortunately, synthetic equivalent **11** could be prepared in 67% yield from *anti*-**8** by invertive Mitsunobu esterification with crotonic acid as reported previously by Walleser and Brückner.[6] The Mitsunobu reaction of *anti*-**8** failed to produce acrylate **10** if acrylic acid was used.

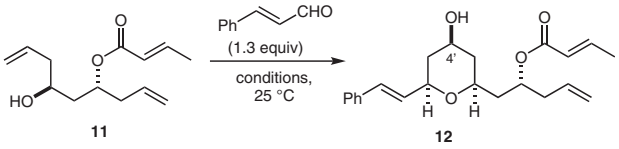


Scheme 2 Synthesis and monoacylation of *syn*- and *anti*-**8**

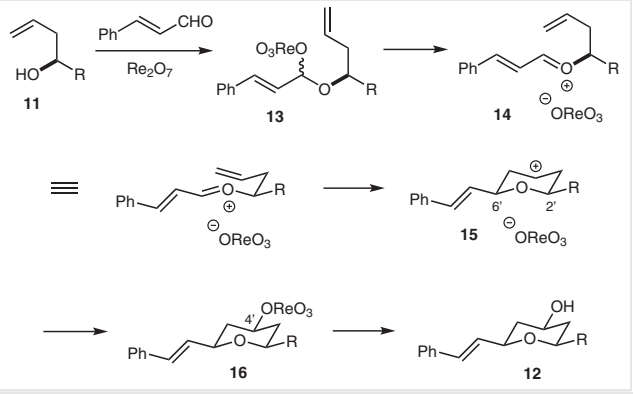
The key step in our synthesis was the Prins cyclization of homoallylic alcohol **11** with cinnamaldehyde to provide the 2,4,6-*cis*-tetrahydropyranol ring present in **1** (Table 1). A limited number of Prins promotors have been reported that result in direct incorporation of a hydroxyl substituent at the 4-position.[7] In our hands, three of these (Montmorillonite,[7a] Amberlyst-15,[7b] $Bi(OTf)_3$[7c]) led to no discernable formation of **12** from **11**. However, we were pleased to find that use of either 40 mol% or 10 mol% phosphomolybdic acid (PMA)[7d] in water successfully produced **12** as a single diastereomer,[8] albeit in low isolated yields. Conducting the reaction with 10 mol% PMA in CH_2Cl_2 led to significantly shorter reaction time and modestly increased yield, but a quantifiable amount of the C4′ epimer, which could not be separated from **12**, was also detected in the ^{1}H NMR spectrum. Catalysis by Re_2O_7[7e] proved to be much more effective, leading to the formation of a 10:1 mixture of **12** and its C4′ epimer in 69% yield in just 4 h when CH_2Cl_2 was used as solvent. In their initial study on Re(VII) catalysis of Prins cyclizations, Tadpetch and Rychnovsky found that yields and stereoselectivities were strongly influenced by solvent in reactions employing $O_3ReOSiPh_3$, and we made similar observations using Re_2O_7.[7e,9] Changing the solvent to $CHCl_3$ had little effect on the outcome of the reaction; however, use of hexanes resulted in a slower and lower-yielding reaction, but with excellent equatorial selectivity for hydroxyl incorporation. We found that optimal isolated yield and selectivity (64%, >20:1) could be achieved by using a 9:1 mixture of hexanes and CH_2Cl_2.[10] The rapid reaction times and high levels of diastereoselectivity observed in the formation of **12** using commercially available Re_2O_7 as a catalyst are particularly notable.[11]

The stereochemical outcome of the Prins cyclization can be rationalized by considering the mechanism outlined in Scheme 3. Condensation of homoallylic alcohol **11** and cin-

Table 1 Prins Cyclization of Homoallylic Alcohol **11** and Cinnamaldehyde



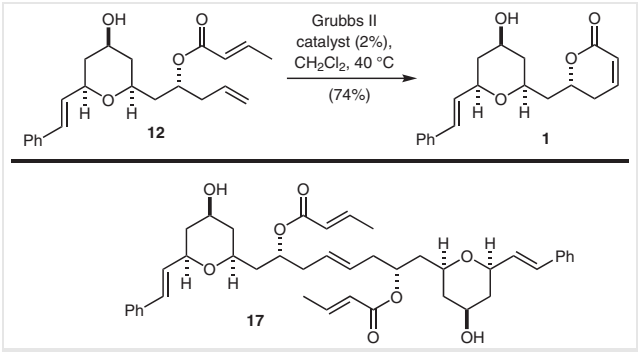
Conditions	Yield (*dr*, **12**:4' epimer)
PMA (40%), H_2O, 6 h	10% (> 20:1)
PMA (10%), H_2O, 17 h	24% (> 20:1)
PMA (10%), CH_2Cl_2, 6 h	35% (12:1)
Re_2O_7 (10%), CH_2Cl_2, 4 h	69% (10:1)
Re_2O_7 (10%), $CHCl_3$, 4 h	59% (9:1)
Re_2O_7 (10%), hexanes, 9 h	47% (> 20:1)
Re_2O_7 (10%), 9:1 hexanes/CH_2Cl_2, 5 h	64% (> 20:1)



Scheme 3 Stereochemical rationale for the formation of tetrahydropyranol **12**

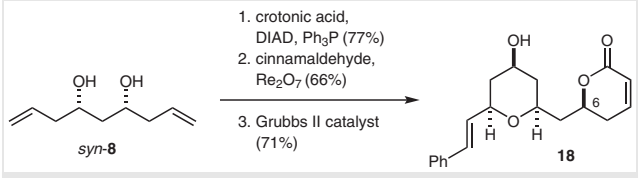
namaldehyde in the presence of Re_2O_7 leads to the formation of activated perrhenate ester **13**, which readily ionizes to produce oxonium ion **14**. Cyclization of **14** via a chairlike transition state in which both the C2′ and C6′ substituents adopt pseudoequatorial orientations establishes the *cis*-stereochemical relationship between them that is typical of Prins reactions and results in the formation of carbocation **15**. Equatorial attack is sterically more accessible and overwhelmingly observed for Prins reactions involving oxygen nucleophiles.[7] In our case, this leads to perrhenate ester **16**, which undergoes reaction with perrhenic acid (produced during the formation of **13**) to generate the desired 2,4,6-*cis*-tetrahydropyranol **12** and to regenerate the Re_2O_7 catalyst.

Completion of the synthesis required only RCM of crotonate **12** to construct the dihydropyranone ring. Initial attempts using the first-generation Grubbs catalyst in either the absence or presence of Ti(O*i*-Pr)$_4$[12] led to the formation of cross-metathesis dimer **17** as the major product even at elevated temperatures (Scheme 4).[13] Gratifyingly, use of the second-generation Grubbs catalyst in CH_2Cl_2 gave conversion of **12** into **1** as a viscous pale yellow oil in 74% yield.[14] Dimer **17** was observed by TLC in reactions using the second-generation Grubbs catalyst at room temperature but it was cleanly converted into **1** upon heating to 40 °C. NMR data of **1** produced in this manner is consistent with the extensive analysis presented for these compounds by the Pilli[2b] and Bates[3] groups and is clearly different from naturally occurring cryptoconcatone H.



Scheme 4 RCM of crotonate **12**

Using the same sequence of steps, C6 diastereomer **18** was prepared from *syn*-**8** as shown in Scheme 5. Yields for the individual steps were comparable to those in the conversion of *anti*-**8** into **1**. The ^{1}H and ^{13}C NMR spectra of **18** were identical to those reported for this compound by Bates.[3] With efficient access to both **18** and **1**, efforts are currently underway to convert them into **3** and **5** (Figure 1) in order to aid in the unambiguous assignment of cryptoconcatone K.



Scheme 5 Synthesis of **18** from *syn*-**8**

In summary, we have completed syntheses of the originally proposed structure of cryptoconcatone H (**1**) and its C6 epimer **18** in just three steps and 32% and 36% yields, respectively, from (±)- and *meso*-1,8-nonadiene-4,6-diol. Our approach is distinct from those previously reported, requires no protecting group or redox manipulations, highlights the unique utility of Re_2O_7 as a Prins cyclization catalyst, and provides further confirmation of the reassignment of cryptoconcatone H. Moreover, this work serves as an instructive illustration of the step economy and efficiency

created by the recognition of hidden symmetry in retrosynthetic planning and the streamlining effect it can provide in organic synthesis.

Conflict of Interest

The authors declare no conflict of interest.

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1972-3587.

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(8) The assignment of **12** as the 2,4,6-*cis*-tetrahydropyranol was based on the typically observed stereochemical outcome of Prins reactions and later confirmed by comparison of NMR data of **1**.

(9) The primary focus of ref. 7e is the study of the catalytic activity of $O_3ReOSiPh_3$ in Prins cyclizations. Only a single example of the use of Re_2O_7 is presented.

(10) **Preparation of Tetrahydropyranol 12**
To a solution of alcohol **11**(61.0 mg, 0.27 mmol) and cinnamaldehyde (44 μL, 0.35 mmol) in hexanes (2.4 mL) and CH_2Cl_2 (0.3 mL) at room temperature was added Re_2O_7 (13.1 mg, 0.027 mmol). The reaction mixture was stirred for 5 h, at which time TLC analysis indicated complete consumption of starting material. The solvent was removed in vacuo to give a black oil. Purification by silica gel flash column chromatography (2:1 hexanes/EtOAc) provided 61.6 mg (64%) of **12** as a yellow oil.
Analytical Data for 12
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 (br d, *J* = 7.2 Hz, 2 H), 7.28 (t, *J* = 7.2 Hz, 2 H), 7.21 (tt, *J* = 7.2, 1.7 Hz, 1 H), 6.92 (dq, *J* = 15.4, 6.9 Hz, 1 H), 6.55 (d, *J* = 16.0 Hz, 1 H), 6.17 (dd, *J* = 16.0, 5.9 Hz, 1 H), 5.81 (dq, *J* = 15.4, 1.7 Hz, 1 H), 5.76 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1 H), 5.18 (dtd, *J* = 9.8, 6.1, 4.0 Hz, 1 H), 5.11–5.05 (m, 2 H), 3.93 (ddt, *J* = 11.4, 6.0, 1.5 Hz, 1 H), 3.83 (tt, *J* = 11.0, 4.5 Hz, 1 H), 3.53–3.47 (m, 1 H), 2.42–2.31 (m, 3 H), 2.06–1.97 (m, 3 H), 1.77 (dd, *J*= 6.9, 1.7 Hz, 3 H), 1.72 (ddd, *J* = 14.4, 5.8, 4.0 Hz, 1 H), 1.35 (q, *J* = 11.3 Hz, 1 H), 1.20 (q, *J* = 11.3 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.3, 144.8, 136.9, 133.6, 130.6, 129.6, 128.6, 127.7, 126.6, 123.1, 118.1, 76.1, 73.2, 70.5, 68.0, 41.1, 40.9, 40.1, 39.2, 18.0. IR (thin film): 3406, 2943, 2916, 2850, 1714, 1655, 1495, 1444, 1361, 1310, 1292, 1266, 1184, 1102, 1068, 1016, 998, 914, 837, 746, 732, 693 cm^{-1}. HRMS (ESI): *m/z* calcd for $C_{22}H_{28}O_4Na$ [M + Na$^+$]: 379.1885; found: 379.1895.

(11) For a recent review on the use of Re_2O_7 as a catalyst in organic synthesis, see: Floreancig, P. E. *Synlett* **2021**, *32*, 1406.

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(13) Others have observed similar cross-metathesis products in attempted RCM reactions of crotonates. For example, see ref. 6.

(14) **Preparation of Dihydropyranone 1**
To a solution of **12** (53.3 mg, 0.15 mmol) in CH_2Cl_2 (15 mL) at room temperature was added Grubbs second-generation catalyst (2.5 mg, 0.003 mmol). The reaction was heated to reflux for 1 h, at which time TLC analysis indicated complete consumption of starting material. After cooling to room temperature, the crude reaction mixture was concentrated in vacuo. Purification by silica gel flash column chromatography (EtOAc) gave 35.8 mg (97% pure, 74% yield) of **1**as viscous pale yellow oil.
Analytical Data for 1
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (br d, *J* = 7.2 Hz, 2 H), 7.31 (t, *J* = 7.2 Hz, 2 H), 7.23 (tt, *J* = 7.2, 1.8 Hz, 1 H), 6.89 (ddd,*J* = 9.7, 5.9, 2.6 Hz, 1 H), 6.57 (d, *J* = 16.0 Hz, 1 H), 6.19 (dd, *J* = 16.0, 5.9 Hz, 1 H), 6.02 (br dd, *J* = 9.8, 2.5 Hz, 1 H), 4.67 (dtd, *J* = 11.4, 6.0, 4.5 Hz, 1 H), 4.00 (ddt, *J* = 11.2, 5.8, 1.5 Hz, 1 H), 3.90 (tt, *J* = 11.0, 4.6 Hz, 1 H), 3.74–3.68 (m, 1 H), 2.49 (ddt, *J* = 18.4, 11.4, 2.6 Hz, 1 H), 2.40 (br ddd, *J* = 18.4, 5.7, 4.3 Hz, 1 H), 2.21–2.14 (m, 2 H), 2.09 (ddt, *J* = 12.3, 4.5, 2.0 Hz, 1 H), 2.03 (ddt, *J* = 12.3, 4.5, 2.0 Hz, 1 H), 1.88 (dt, *J*= 14.4, 5.6 Hz, 1 H), 1.37 (q, *J* = 11.3 Hz, 1 H), 1.30 (q, *J* = 11.3 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.7, 145.7, 136.7, 130.4, 129.5, 128.6, 127.8, 126.6, 121.2, 76.1, 75.1, 71.5, 67.8, 41.1, 40.6, 40.5, 29.3. IR (thin film): 3405, 2921, 2850, 2849, 1698, 1494, 1448, 1390, 1312, 1251, 1188, 1153, 1069, 1037, 969, 814, 750, 734, 696 cm^{-1}. HRMS (ESI): *m/z* calcd for $C_{19}H_{23}O_4$ [M + H$^+$]: 315.1596; found: 315.1591.