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Total Synthesis of Cryptoacetalide

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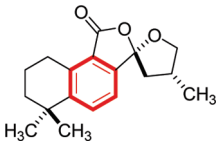

We are reporting the first total synthesis of the tetracyclic terpene natural product cryptoacetalide. Key steps of the synthesis are a microwave-mediated [2+2+2] cyclotrimerization reaction to construct the central benzene ring, and a light-mediated radical cyclization to assemble the spiro-ketal moiety.

Cyclotrimerization reactions are versatile reactions for the assembly of highly substituted benzene and pyridine rings.[1−6] Despite their versatility and several recent advances in the design of new cyclotrimerization catalysts (such as Co,[7−9] Ni,[10−12] Ru,[13] Pd,[14,15] Rh,[16−20] Co/Zn,[21,22] and Ni/Zr[23,24]) and the application of microwave irradiation[25−30] to facilitate these reactions, only a surprisingly small number of natural products have been assembled with benzene-forming [2+2+2] cyclotrimerization reactions.[27,28,31−41] Here, we are reporting the synthesis of the tetracyclic terpene cryptoacetalide (**1**) via a cyclotrimerization key step.

The diterpenoids cryptoacetalide (**1**) and epicryptoacetalide (*epi*-**1**) were isolated in 1990 from Dan-shen, the dried root of *Salvia miltiorrhiza* (Lamiaceae),[42] which is commonly used as a Chinese medicine for the treatment of a wide range of human diseases.[43] Cryptoacetalide and *epi*-cryptoacetalide were isolated as an inseparable mixture (**1**/*epi*-**1** = 3:1), together with danshenspiroketallactone (**2**), and its epimer.[42] They both contain a lactone group, a benzene ring, and also a spiroacetal moiety (Figure 1). To date, no synthesis of cryptoacetalide and epicryptoacetalide has been reported.

Our strategy is shown in Scheme 1. We envisioned the D ring of cryptoacetalide **1** to be formed from **3** through a light-mediated spiro-ketalization. The A, B, and C rings of **1** could be assembled simultaneously by an intramolecular [2+2+2] cyclotrimerization reaction of the triyne **4** to the benzene **3**. The tryine **4** would be synthesized by a coupling of the acid **5** to the corresponding secondary alcohol. The X and Y substituents represent the geminal dimethyl group, or a suitable precursor functionality, e.g. a protected hydroxyl group (X = H, Y = OTBS) that can be oxidized to a ketone, which in turn could be converted to the geminal dimethyl group by a Reetz reaction.[44]

First, we investigated the intramolecular cyclotrimerization reaction of different model triynes (Table 1). We first used

(1) Chopade, P. R.; Louie, J. *Adv. Synth. Catal.* **2006**, *348*, 2307.
(2) Yamamoto, Y. *Curr. Org. Chem.* **2005**, *9*, 503.
(3) Kotha, S.; Brahmachary, E.; Lahiri, K. *Eur. J. Org. Chem.* **2005**, 4741.
(4) Heller, B.; Hapke, M. *Chem. Soc. Rev.* **2007**, *36*, 1085.
(5) Varela, J. A.; Saá, C. *Chem. Rev.* **2003**, *103*, 3787.
(6) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901.
(7) Bönnemann, H. *Angew. Chem., Int. Ed.* **1985**, *24*, 248.
(8) Agenet, N.; Gandon, V.; Vollhardt, K. P. C.; Malacria, M.; Aubert, C. *J. Am. Chem. Soc.* **2007**, *129*, 8860.
(9) Fatland, A. W.; Eaton, B. E. *Org. Lett.* **2000**, *2*, 3131.
(10) Hsieh, J. C.; Cheng, C. H. *Chem. Commun.* **2005**, 2459.
(11) Sato, Y.; Nishimata, T.; Mori, M. *Heterocycles* **1997**, *44*, 443.
(12) Sato, Y.; Nishimata, T.; Mori, M. *J. Org. Chem.* **1994**, *59*, 6133.
(13) Yamamoto, Y.; Arakawa, T.; Ogawa, R.; Itoh, K. *J. Am. Chem. Soc.* **2003**, *125*, 12143.
(14) Jhingan, A. K.; Maier, W. F. *J. Org. Chem.* **1987**, *52*, 1161.
(15) Lin, Y.-Y.; Tsai, S.-C.; Yu, S. J. *J. Org. Chem.* **2008**, *73*, 4920.
(16) Witulski, B.; Stengel, T. *Angew. Chem., Int. Ed.* **1999**, *38*, 2426.
(17) Konno, T.; Moriyasu, K.; Kinugawa, R.; Ishihara, T. *Org. Biomol. Chem.* **2010**, *8*, 1718.
(18) Komine, Y.; Tanaka, K. *Org. Lett.* **2010**, *12*, 1312.
(19) Dachs, A.; Osuna, S.; Roglans, A.; Solà, M. *Organometallics* **2010**, *29*, 562.
(20) Dachs, A.; Torrent, A.; Roglans, A.; Parella, T.; Osuna, S.; Solà, M. *Chem.—Eur. J.* **2009**, *15*, 5289.
(21) Kase, K.; Goswami, A.; Ohtaki, K.; Tanabe, E.; Saino, N.; Okamoto, S. *Org. Lett.* **2007**, *9*, 931.
(22) Saino, N.; Amemiya, F.; Tanabe, E.; Kase, K.; Okamoto, S. *Org. Lett.* **2006**, *8*, 1439.
(23) Takahashi, T.; Tsai, F. Y.; Kotora, M. *J. Am. Chem. Soc.* **2000**, *122*, 4994.
(24) Takahashi, T.; Tsai, F. Y.; Li, Y. Z.; Wang, H.; Kondo, Y.; Yamanaka, M.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc.* **2002**, *124*, 5059.
(25) Saaby, S.; Baxendale, I. R.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 3365.
(26) Zhou, Y.; Porco, J. A.; Snyder, J. K. *Org. Lett.* **2007**, *9*, 393.
(27) Teske, J. A.; Deiters, A. *Org. Lett.* **2008**, *10*, 2195.
(28) Teske, J. A.; Deiters, A. *J. Org. Chem.* **2008**, *73*, 342.
(29) Young, D. D.; Sripada, L.; Deiters, A. *J. Comb. Chem.* **2007**, *9*, 735.
(30) Young, D. D.; Deiters, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 5187.
(31) Anderson, E. A.; Alexanian, E. J.; Sorensen, E. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 1998.
(32) Senaiar, R. S.; Teske, J. A.; Young, D. D.; Deiters, A. *J. Org. Chem.* **2007**, *72*, 7801.
(33) Ramana, C. V.; Salian, S. R.; Gonnade, R. G. *Eur. J. Org. Chem.* **2007**, 5483.
(34) Sato, Y.; Tamura, T.; Mori, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2436.
(35) Alayrac, C.; Schollmeyer, D.; Witulski, B. *Chem. Commun.* **2009**, 1464.
(36) Witulski, B.; Alayrac, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3281.
(37) Witulski, B.; Zimmermann, A.; Gowans, N. D. *Chem. Commun.* **2002**, 2984.
(38) Kalogerakis, A.; Groth, U. *Synlett* **2003**, 1886.
(39) Nicolaou, K. C.; Tang, Y. F.; Wang, J. H. *Angew. Chem., Int. Ed.* **2009**, *48*, 3449.
(40) Germanas, J.; Aubert, C.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1991**, *113*, 4006.
(41) Funk, R. L.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1980**, *102*, 5253.
(42) Asari, F.; Kusumi, T.; Zheng, G. Z.; Cen, Y. Z.; Kakisawa, H. *Chem. Lett.* **1990**, 1885.
(43) Chang, H. M.; But, P. P. H. *Pharmacollogy and Applications of Chinese Meteria Medica*; World Scientific: Singapora, 1986; Vol. 1, pp 237−249.
(44) Reetz, M. T.; Westermann, J.; Kyung, S. H. *Chem. Ber.* **1985**, *118*, 1050.
(45) Bhatarah, P.; Smith, E. H. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2163.

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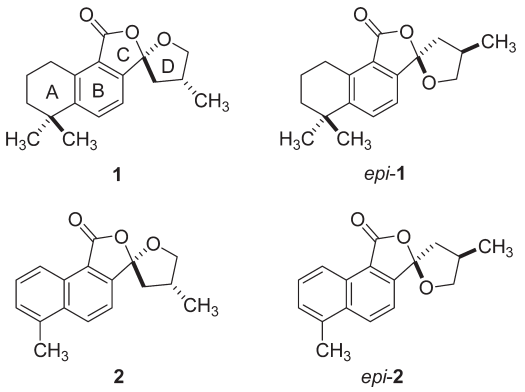
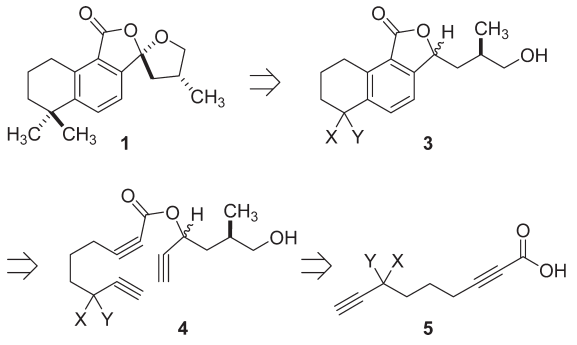


FIGURE 1. Structures of cryptoacetalide (**1**), *epi*-cryptoacetalide, danshenspiroketallactone (**2**), and *epi*-danshengspiroketallactone.

SCHEME 1. Retrosynthetic Analysis of 1[a]



[a]X, Y represent the geminal dimethyl substituents (X, Y = CH_3), or a suitable precursor (e.g., X = H and Y = OTBS).

the triyne ether **6** as a model system, since it is the simplest triyne based on our retrosynthetic analysis. The triyne **6** underwent a smooth cyclotrimerization reaction to **10** in the presence of 10 mol % of Cp*RuCl(COD) and microwave irradiation in 88% yield (entry 1). A literature reported cyclotrimerization of the same compound furnished **10** in the absence of any catalyst in 80% yield, using microwave irradiation (Biotage AG Emrys microwave synthesizer) in DMF at 200 °C for 1 h.[25] However, we were not able to reproduce this result using **6** under identical reaction conditions (except we used a CEM Discover microwave synthesizer). A model triyne **7**, more similar to the compound **4** due to its ester linkage, underwent an efficient cyclotrimerization reaction to **11** using the same catalyst (Cp*RuCl(COD), 10 mol %) and microwave irradiation (entry 3). Good yields were also obtained by employing $(Ph_3P)_2Ni(CO)_2$ (10 mol %) at room temperature (entry 4). We then increased the complexity of the triyne to investigate the effects of additional substituents. The triyne **8** was transformed smoothly in a microwave-assisted [2+2+2] cyclotrimerization reaction under Ru or Ni catalysis in 78−81% yield (entry 6 and 7). The TBS protected propargyloxy triyne **9** underwent cyclotrimerization under microwave irradiation with Cp*RuCl(COD) in 84% yield (entry 8). To our surprise, the triyne **9** underwent a cyclotrimerization reaction even in the absence of any catalysts (in contrast to **6** and **7**) with only microwave irradiation (DMF, 200 °C, 1 h), yielding **13** in 81% yield (entry 9).

Our synthesis of the acid **19** commenced with the TBDMS protection of the known 6-chlorohex-2-yn-1-ol (**14**),[46] followed by a Finkelstein[47] reaction with NaI to provide the iodide **15** in excellent yield. The installation of the geminal dimethyl group was accomplished by deprotonation of isobutyronitrile with LDA followed by a nucleophilic substitution with **15**, delivering the nitrile **16** in 86% yield.[48] Reduction of the nitrile **16** with DIBAL-H[49] at −78 °C afforded the aldehyde **17** in 93% yield. The second triple bond was then installed via a Corey−Fuchs reaction[50] directly followed by a deprotection, providing the diyne **18**. A Jones oxidation[51] of the alcohol **18** then delivered the acid **19** in 97% yield (Scheme 2).

To assemble the triyne [2+2+2] cyclotrimerization precursor, the secondary alcohol **21** was generated as a 1:1 diastereomeric mixture in 90% yield by the addition of ethynylmagnesium bromide into the known, enantiomerically pure aldehyde **20** (synthesized in five steps from methyl (*S*)-3-hydroxy-2-methylpropionate).[52] The coupling reaction between the acid **19** and the alcohol **21** in the presence of DCC and DMAP provided the cyclotrimerization precursor **22** in 79% yield. On the basis of the model studies shown in Table 1, the [2+2+2] cyclotrimerization reaction was conducted with Cp*RuCl(COD) in toluene under microwave irradiation (300 W) affording the tricyclic product **23** in 90% yield. Deprotection of the PMB ether with DDQ generated the corresponding alcohol **24**, which set the stage for the spiroketalization reaction.[53] The lacton **24** was irradiated with light (200 W Xe/Hg lamp) in the presence of iodine and iodobenzene diacetate for 1 h. The natural products cryptoacetalide (**1**) and *epi*-cryptoacetalide (*epi*-**1**) were isolated as a 2:1 mixture in an excellent yield of 84% (Scheme 3). As previously reported, **1** and *epi*-**1** could not be separated by column chromatography, HPLC, or GC. The NMR spectrum of the mixture matches the NMR spectrum of the material isolated from nature.[42]

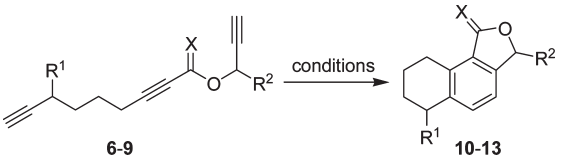
In summary, the first synthesis of the terpene natural product cryptoacetalide was accomplished in 12 steps in an overall yield of 26% from known, easily accessible starting materials. Key steps of the developed synthetic approach are a microwave-mediated intramolecular [2+2+2] cyclotrimerization reaction and a light-mediated spiro-ketalization. Moreover, the intramolecular cyclotrimerization reactions of different triynes were investigated under various conditions with different catalyst systems in the absence and presence of microwave irradiation.

Experimental Section

(5*R*)-6-(4-Methoxybenzyloxy)-5-methylhex-1-yn-3-yl 7,7-Dimethylnona-2,8-diynoate (22). At 0 °C, the solution of the acid

(46) Roy, C. D.; Soundararajan, R.; Brown, H. C. *Monatsh. Chem.* **2008**, *139*, 241.
(47) Hodgson, D. M.; Labande, A. H.; Pierard, F. Y. T. M.; Castro, M. A. E. *J. Org. Chem.* **2003**, *68*, 6153.
(48) Yun, S. Y.; Kim, M.; Lee, D.; Wink, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 24.
(49) Kesharwani, T.; Verma, A. K.; Emrich, D.; Ward, J. A.; Larock, R. C. *Org. Lett.* **2009**, *11*, 2591.
(50) de Meijere, A.; Kozhushkov, S. I. *Chem.—Eur. J.* **2002**, *8*, 3195.
(51) Ferrié, L.; Reymond, S.; Capdevielle, P.; Cossy, J. *Org. Lett.* **2006**, *8*, 3441.
(52) Carley, S.; Brimble, M. A. *Org. Lett.* **2009**, *11*, 563.
(53) Brimble, M. A.; Horner, G. M.; Stevenson, R. J. *Aust. J. Chem.* **1996**, *49*, 189.

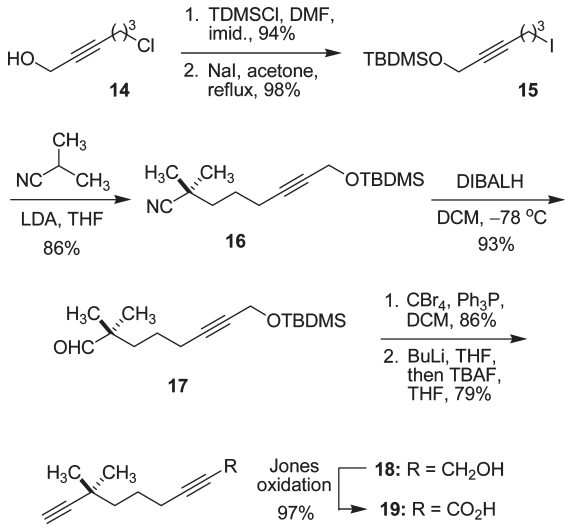
TABLE 1. Cyclotrimerization Reactions of Model Substrates 6−9



entry	compd	X	R^1	R^2	catalyst R^1	product	yield, %
1	**6**	H_2	H	H	Cp*RuCl (COD)[a]	**10**	88
2	**6**	H_2	H	H	none [b]	**10**	–[c]
3	**7**	O	H	H	Cp*RuCl (COD)[a]	**11**	83
4	**7**	O	H	H	$(Ph_3P)_2Ni(CO)_2$[d]	**11**	70
5	**7**	O	H	H	none [b]	**11**	–
6	**8**	O	H	C_3H_6OTBS	Cp*RuCl (COD)[a]	**12**	81
7	**8**	O	H	C_3H_6OTBS	$(Ph_3P)_2Ni(CO)_2$[a]	**12**	78
8	**9**	O	OTBS	C_3H_6OTrt	Cp*RuCl (COD)[a]	**13**	84
9	**9**	O	OTBS	C_3H_6OTrt	none [b]	**13**	81

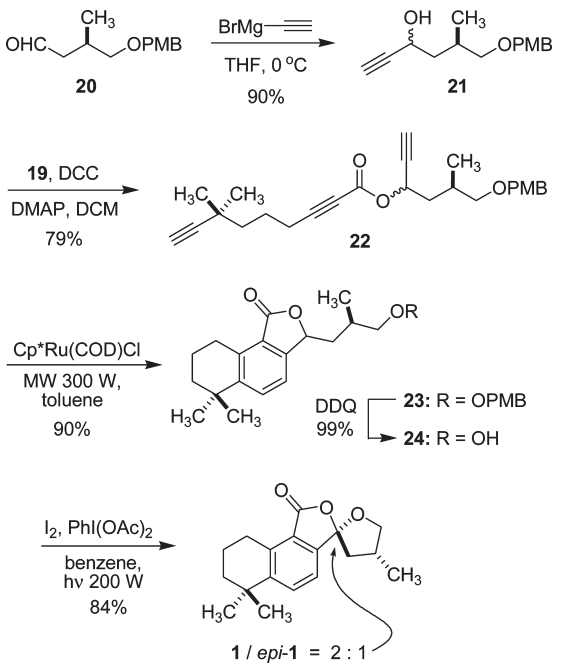
[a]Conditions: toluene, catalyst, MW 300 W, 130 °C, 20 min. [b]Conditions: DMF, MW 200 W, 200 °C, 1 h. [c]Conditions: ref 25 reported an 80% yield. [d]Conditions: THF, rt, 17 h; see ref 45.

SCHEME 2. Synthesis of the Diyne 19



19 (19.1 mg, 0.107 mmol) in the DCM (0.7 mL) was added dropwise to the solution of the alcohol **21** (22.1 mg, 0.0891 mmol) and DMAP (6.5 mg, 0.053 mmol) in DCM (0.7 mL). The solution was stirred at 0 °C for 10 min and a solution of DCC (23.9 mg, 0.116 mmol) in DCM (0.7 mL) was added dropwise at 0 °C and the resulting mixture was stirred at rt overnight. The mixture was cooled to 0 °C and additional DCC (23.9 mg, 0.116 mmol) in DCM (0.7 mL) was added and the resulting mixture was stirred overnight. The mixture was concentrated and the crude was purified by column chromatography on SiO_2 (eluted with hexanes/ethyl acetate = 50:1, 25:1, 10:1, and 5:1), delivering 28.7 mg (79% yield) of triyne **22** as colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25−7.20 (m, 2H), 6.85 (d, J = 8.4 Hz, 2H), 5.52−5.44 (m, 1H), 4.41 (s, 2H), 3.79 (s, 3H), 3.28 (d, J = 7.8 Hz, 2H), 2.47 (t, J = 0.8 Hz, 1H), 2.35 (t, J = 7.2 Hz, 2H), 2.07 (s, 1H), 2.01−1.96 (m, 2H), 1.78−1.65 (m, 3H), 1.55−1.45 (m, 2H), 1.20 (s, 6H), 0.96 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 152.9, 130.77, 130.74, 129.4, 114.0, 91.4, 90.50, 90.48, 81.0, 80.6, 75.1, 74.9, 74.6, 74.4, 73.1, 72.92, 72.86, 68.5, 64.3, 63.9, 55.5, 42.4, 39.0, 38.6, 31.0, 30.4, 30.2, 29.3, 23.8, 19.3, 17.3, 17.2; HRMS calcd for $[M + Na]^+$ $C_{26}H_{32}NaO_4$ 431.2198, found 431.2195.

SCHEME 3. Synthesis of the Alcohol 21, the Cyclotrimerization Precursor 22, and Completion of the Total Synthesis of 1



3-((*R*)-3-(4-Methoxybenzyloxy)-2-methylpropyl)-6,7,8,9-tetrahydro-6,6-dimethylnaphtho[2,1-*c*]furan-1(3*H*)-one (23). To a flame-dried microwave vial was added the triyne **22** (10.0 mg, 0.025 mmol) and toluene (1 mL) under argon. Cp*RuCl(COD) (0.9 mg, 0.0025 mmol) was added and the vial was sealed and heated in a CEM Discover microwave synthesizer (power mode, 300 W, 130 °C final temperature) for 20 min. An additional 0.1 equiv (0.9 mg) of Cp*RuCl(COD) was added and the reaction was continued for 30 min. The solid was filtered off and solvent was removed in vacuo. The product was purified by column chromatography on SiO_2 (eluted with hexanes/ethyl acetate = 10:1), delivering the product **23** (9.0 mg, 90% yield) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 7.6 Hz, 1H), 7.28−7.25 (m, 2H), 7.19−7.16 (m, 1H), 6.90−6.87 (m, 2H), 5.45−5.40 (m, 1H), 4.48 (s, 1H), 4.43 (s, 1H), 3.81 (s, 3H), 3.52−3.48 (m, 0.5H), 3.41−3.34 (m, 0.5H), 3.37−3.34 (m, 1H), 3.24 (t, J = 6.4 Hz, 2H), 2.25−2.21 (m, 1H),

1.86−1.84 (m, 0.5H), 1.86−1.78 (m, 3H), 1.72−1.69 (m, 2H), 1.52−1.47 (m, 0.5H), 1.32 (s, 6H), 1.10 (d, J = 6.0 Hz, 1.5H), 1.05 (d, J = 6.0 Hz, 1.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 159.4, 159.3, 149.08, 149.06, 147.3, 138.1, 132.8, 130.8, 129.43, 129.37, 123.0, 122.9, 119.03, 118.98, 114.02, 113.96, 79.1, 78.3, 75.5, 74.8, 73.0, 72.8, 55.5, 40.0, 39.7, 38.7, 34.2, 32.1, 32.0, 31.0, 30.6, 29.9, 26.1, 18.8, 18.3, 17.0; HRMS calcd for $[M + Na]^+$ $C_{26}H_{32}NaO_4$ 431.2198, found 431.2198.

3-((*R*)-3-Hydroxy-2-methylpropyl)-6,7,8,9-tetrahydro-6,6-dimethylnaphtho[2,1-*c*]furan-1(3*H*)-one (24). The PMB ether **23** (9.0 mg, 0.022 mmol) was dissolved in DCM (0.8 mL) and H_2O (0.03 mL), and the solution was cooled to 0 °C. DDQ (5.5 mg, 0.024 mmol) was added and the reaction mixture was stirred at rt overnight. Saturated NH_4Cl (1 mL) was added to quench the reaction and the mixture was extracted with DCM (4 × 2 mL). The combined organic layers were washed with brine (2 mL), dried over anhydrous Na_2SO_4, and filtered and the filtrate was concentrated in vacuo. The product was purified by column chromatography on SiO_2 (eluted with hexanes/ethyl acetate = 5:1 to 2:1), delivering the alcohol **24** (6.3 mg, 99% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, J = 8.0 Hz and J = 1.2 Hz, 1H), 7.16 (dd, J = 8.0 Hz and J = 3.6 Hz, 1H), 5.46−5.38 (m, 1H), 3.68−3.57 (m, 1H), 3.55−3.53 (m, 1H), 3.21 (t, J = 6.0 Hz, 2H), 2.14−2.02 (m, 1.5H), 1.86−1.77 (m, 2.5H), 1.69−1.64 (m, 2H), 1.62−1.49 (m, 2H), 1.28 (s, 6H), 1.07 (d J = 6.8 Hz 1.5H), 1.02 (d J = 6.8 Hz 1.5H); 147.49, 147.45 ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 148.94, 148.91, 138.2, 134.7, 132.95, 132.92, 122.8, 118.96, 118.88, 78.8, 78.5, 68.3, 67.5, 39.5, 39.3, 38.7, 34.2, 33.3, 33.1, 32.1, 32.0, 29.9, 26.1, 18.7, 17.7, 16.7; HRMS calcd for $[M + Na]^+$ $C_{18}H_{24}NaO_3$ 311.1623, found 311.1626.

Cryptoacetalide (1). The alcohol **24** (6.2 mg, 0.022 mmol) was dissolved in dry benzene (1.5 mL). Iodobenzene diacetate (20.8 mg, 0.065 mmol) and iodine (10.9 mg, 0.043 mmol) were added under nitrogen. The vial was sealed and irradiated with a 200 W Xe/Hg lamp (Newport) for 1 h. After cooling to rt, 10 mL of ether was added and the mixture was washed with H_2O (2 mL) and brine (2 mL), dried over anhydrous Na_2SO_4, and filtered and the filtrate was concentrated in vacuo. The product was purified by column chromatography on SiO_2 (eluted with hexanes/ethyl acetate = 20:1, 10:1), delivering 5.2 mg (84% yield) of the natural product **1** as a yellow solid. ^{1}H NMR showed a 2:1 diastereomeric ratio of **1** to *epi*-**1**. HRMS calcd for $[M + H]^+$ $C_{18}H_{23}O_3$ 287.1647, found 287.1647. Cryptoacetalide (**1**): ^{1}H NMR (300 MHz, $CDCl_3$) 7.62 (d, J = 8.1 Hz, 1H), 7.24 (d, J = 8.1 Hz, 1H), 4.37 (t, J = 8.1 Hz, 1H), 3.71 (t, J = 8.1 Hz, 1H), 3.18 (t, J = 6.3 Hz, 2H), 2.88−2.80 (m, 1H), 2.42 (dd, J = 6.8 Hz and J = 13.3 Hz, 1H), 2.00−1.90. (m, 1H), 1.85−1.75 (m, 2H), 1.69−1.60 (m, 2H), 1.29 (s, 3H), 1.28 (s, 3H), 1.18 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 149.2, 144.9, 138.0, 133.3, 124.4, 119.5, 113.2, 77.2, 45.7, 38.6, 34.3, 32.7, 32.0, 26.2, 18.7, 17.6. *epi*-Cryptoacetalide (*epi*-**1**): ^{1}H NMR (300 MHz, $CDCl_3$) 7.62 (d, J = 8.1 Hz, 1H), 7.20 (d, J = 8.1 Hz, 1H), 4.31 (t, J = 8.1 Hz, 1H), 3.81 (t, J = 8.1 Hz, 1H), 3.18 (t, J = 6.3 Hz, 2H), 2.70−2.60 (m, 1H), 2.58 (dd, J = 9.4 Hz and J = 13.3 Hz, 1H), 2.10 (dd, J = 4.5 Hz and J = 13.3 Hz, 1H), 2.05−2.01 (m, 1H), 1.85−1.75 (m, 2H), 1.69−1.60 (m, 2H), 1.29 (s, 3H), 1.28 (s, 3H), 1.24 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 149.1, 145.7, 137.8, 133.4, 124.0, 119.3, 113.1, 77.2, 44.7, 38.6, 34.3, 33.6, 29.9, 26.2, 18.4, 17.6.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of all new compounds, additional experimental procedures, and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.