Notes

An Enantioselective Synthesis of Tarchonanthuslactone

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Abstract: An enantioselective synthesis of tarchonanthuslactone has been achieved in eight steps from ethyl sorbate. The asymmetry of the route was introduced via a Sharpless asymmetric dihydroxylation allowing access to either enantiomer. The synthesis utilizes a palladium-catalyzed reduction and a diastereoselective base-catalyzed acetal formation as the key steps. The pyran ring of tarchonanthuslactone was established by a Still-olefination/lactonization sequence. DCC-mediated attachment of dihydrocaffeic acid completed the synthesis of tarchonanthuslactone in a 19% overall yield.

The 1,3-polyol/5,6-dihydro-2*H*-pyran-2-one motif is a common structural unit found in several natural products that possess a wide range of biological properties. These biological activities include plant growth inhibition as well as antifeedent, antifungal, antibacterial, and antitumor properties.[1,2] Due to the interest in their biological activities, several synthetic approaches to these molecules have been reported by us[3] and others.[4] The simplest structure isolated with the *syn*-1,3-diol/5,6-dihydropyran-2-one motif is the dihydrocaffeic ester, tarchonanthuslactone (**1**).[4a,5] Some more complex examples of these structures are cryptocarya diacetate (**2**), cryptocarya triacetate (**3**), and passifloricin A (**4**) (Figure 1).[6]

The absolute and relative stereochemistries of tarchonanthuslactone and the cryptocarya acetates have been established by a combination of Mosher ester analysis and Rychnovsky ^{13}C NMR/acetonide analysis.[7] Ultimately, the structural studies for three of these structures (**1**−**3**) were confirmed by enantioselective total synthesis.[8]

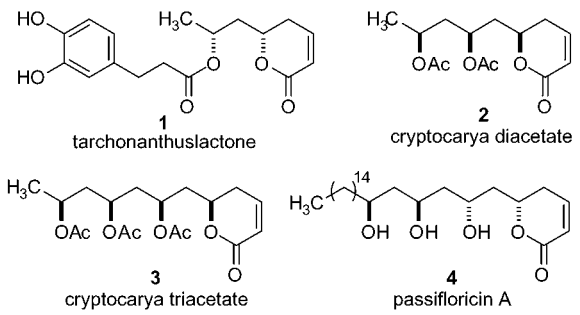

Figure 1.

Tarchonanthuslactone (**1**) was isolated by Bohlmann from *Tarchonanthustrilobus compositae*.[9] Hsu et al. have shown that tarchonanthuslactone lowers plasma glucose in diabetic rats.[10] Because of its interesting biological activity, there have been several approaches to tarchonanthuslactone (**1**).[4b−f] To date, all of these approaches derive the asymmetry from the stoichiometric use of either chiral auxiliaries or chiral reagents. For example, Mori and co-workers synthesized **1** from a chiral dithiane using a 16-step sequence.[4a,b] Solladié and co-workers utilized a chiral sulfoxide to induce chirality during their 12-step synthesis of **1**.[4d] More recently, Ramachandran has used a reagent-controlled approach to **1** utilizing a consecutive Ipc_2Ballyl asymmetric allyl anion addition to establish the relative stereochemistry of **1**.[4f] All of the above procedures for the synthesis of **1** involve the use of stoichiometric reagents and/or substrates to control the absolute asymmetry of tarchonanthuslactone.

We have been interested in the development of practical and concise enantioselective approaches to biologically important substituted 1,3-polyol-5,6-dihydropyran-2-one-containing natural products.[3,11] These efforts have culminated in an efficient route to cryptocarya diacetate (**2**) from benzylidine-protected *syn*-3,5-dihydroxy carboxylic ester **7** (Scheme 1).[3,12] In our route to **2**, asymmetry was installed by the Sharpless asymmetric dihydroxylation of the dienoate ethyl sorbate (**8**).[13] As a model study for the synthesis of the more complex even-numbered 1,3-polyol/pyranone natural products (**3** and **4**), we decided

† University of Minnesota-NSF-REU Program Participant−2001.

(1) Jodynis-Liebert, J.; Murias, M.; Bloszyk, E. *Planta Med.* **2000**, *66*, 199.

(2) Drewes, S. E.; Schlapelo, B. M.; Horn, M. M.; Scott-Shaw, R.; Sandor, O. *Phytochemistry* **1995**, *38*, 1427.

(3) Hunter, T. J.; O'Doherty, G. A. *Org. Lett.* **2001**, *3* (17), 2777.

(4) (a) Nakata, T.; Hata, N.; Iida, K.; Oishi, T. *Tetrahedron Lett.* **1987**, *28*, 5661. (b) Mori, Y.; Suzuki, M. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1809. (c) Mori, Y.; Kageyama, H.; Suzuki, M. *Chem. Pharm. Bull.* **1990**, *38*, 2574. (d) Solladié, G.; Gressot-Kempf *Tetrahedron: Asymmetry* **1996**, *7* (8), 2371. (e) Jorgensen, K. B.; Suenaga, T.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 8855−8858. (f) Reddy, M. V. R.; Yucel, A. J.; Ramachandran, P. V. *J. Org. Chem.* **2001**, *66*, 2512. (g) Gosh, A. K.; Bilcer, G. *Tetrahedron Lett.* **2000**, *41*, 1003. (h) Boger, D. L.; Ichikawa, D.; Zhong, W. *J. Am. Chem. Soc.* **2001**, *123*, 4161. (i) Reddy, M. V. R.; Rearick, J. P.; Hoch, N.; Ramachandran, P. V. *Org. Lett.* **2001**, *3*, 19. (j) Smith, A. B.; Brandt, B. M. *Org. Lett.* **2001**, *3*, 1685.

(5) Echeverri, F.; Arango, V.; Quinones, W.; Torres, F.; Escobar, G.; Rosero, Y.; Archbold, R. *Phytochemistry* **2001**, *56*, 881−885.

(6) (a) Andrianaivoravelona, J. O.; Sahpaz, S.; Terreaux, C.; Hostettmann, K.; Stoecki-Evans, H.; Rasolondramanitra, J. *Phytochemistry* **1999**, *52*, 265−269. (b) Echeverri, F.; Arango, V.; Quinones, W.; Torres, F.; Escobar, G.; Rosero, Y.; Archbold, R. *Phytochemistry* **2001**, *56*, 881−885.

(7) Collett, L. A.; Cavies-Coleman, M. T.; Rivett, D. E. A.; Drewes, S. E.; Horn, M. M. *Phytochemistry* **1997**, *44*, 935−938.

(8) Cryptocarya acetates **1** and **2** were prepared by 16- and 24-step routes, respectively, from the (*S*)-*tert*-butyl 3-hydroxybutyrate by Nakata; see: ref 4e. Nakata has also prepared racemic tarchonanthuslactone and passifloricin A in 16 and 27 steps, respectively; see: ref 4a. More recently, we have enantioselectively prepared **1** in 10 steps and a 14% overall yield from ethylsorbate; see: ref 3.

(9) Bohlmann, F.; Suwita, A. *Phytochemistry* **1979**, *18*, 677.

(10) Hsu, F. L.; Chen, Y. C.; Cheng, J. T. *Planta Med.* **2000**, *66*, 228.

(11) (a) Harris, J. M.; O'Doherty, G. A. *Tetrahedron* **2001**, *57*, 5161−5171. (b) Harris, J. M.; O'Doherty, G. A. *Org. Lett.* **2000**, *2*, 2983.

(12) Hunter, T. J.; O'Doherty, G. A. *Org. Lett.* **2001**, *3* (7), 1049.

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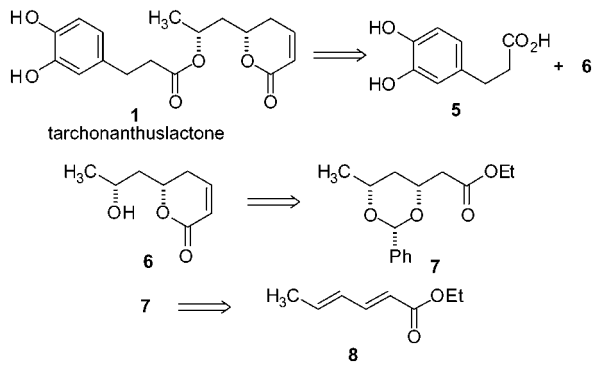
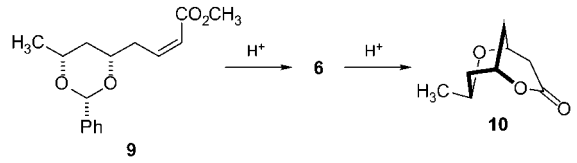
Scheme 1



to apply this methodology toward an enantioselective synthesis of tarchonanthuslactone (**1**).

Specifically, we wanted to test the viability of constructing the pyranone ring in **6** from ester **7** by a three-step sequence utilizing a Still cis-olefination[14] and acid-catalyzed lactonization. Critical for the successful implementation of this strategy was the discovery that acidic conditions both deprotect the benzylidene acetal of **9** as well as induce the resulting diol to selectively lactonize to form pyranone **6** without catalyzing a subsequent 1,4-addition to form bicyclic-lactone **10** (Scheme 2). Presumably, once a reliable procedure has been developed, it can be applied toward the other even-numbered polyols such as cryptocarya triacetate (**3**) and passifloricin A (**4**). Herein, we describe our successful implementation of this strategy toward the synthesis of the *syn*-1,3-diol-containing tarchonanthuslactone (**1**). In addition, access to the intermediate lactone **6** allows for access to the enantiomer of the naturally occurring bicylic lactone **10** (Scheme 2).[15]

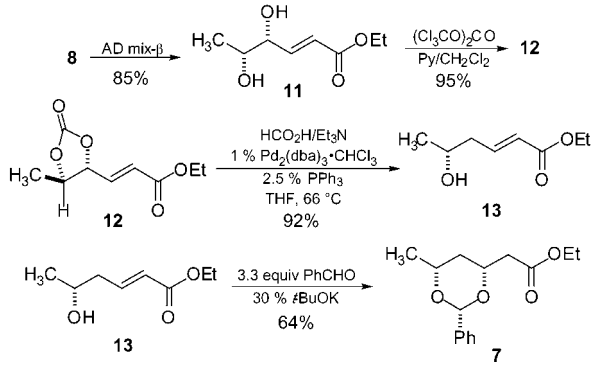
Scheme 2



Following our previously reported protocol allowed conversion of ethyl sorbate[16] (**8**) into the protected diol **7** in four steps and a 35% overall yield (Scheme 3).[12] The sequence starts with a Sharpless dihydroxylation of ethyl sorbate (**8**) yielding diol **11** in 85% yield. Either enantiomer of diol **11** can be obtained by Sharpless dihydroxylation reactions with enantiomeric excesses on the order of 80% from the $(DHQ)_2PHAL$ ligand system and >90% from the $(DHQD)_2PHAL$ ligand.[17]

The cyclic carbonate **12** was prepared by treating a pyridine/CH_2Cl_2 solution of diol **11** with triphosgene, providing **12** in a 95% yield. At this stage, the two

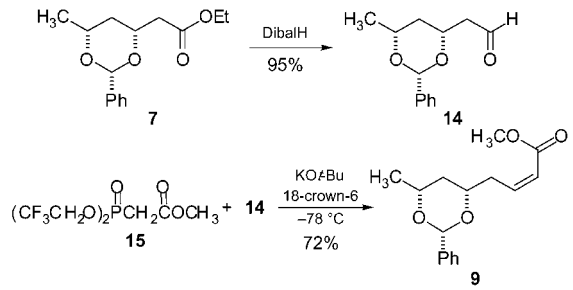
Scheme 3



hydroxyl groups were readily differentiated by taking advantage of the fact that allylic carbonates are good leaving groups for the formation of *p*-allyl palladium complexes.[18] Treatment of **12** with a catalytic amount of palladium/triphenylphosphine (1.0% $Pd_2(dba)_3{\cdot}CHCl_3$/2.5% PPh_3)[19] and a mild hydride source (1:1, Et_3N/HCO_2H) afforded an excellent yield (92%) of the desired δ-hydroxy ester **13** with no loss of enantiomeric excess. Exposing the δ-hydroxy enoate **13** to 3−4 equiv of benzaldehyde and a catalytic amount of KO*t*-Bu (30−40 mol %) led to a 65% yield of the benzylidene-protected 3,5-dihydroxy carboxylic ester **7**.[20] Thus, the ester **7** was conveniently prepared as a single diastereomer (>95% de) in four steps and a 35% overall yield.

Having established a general procedure for the enantioselective synthesis of either enantiomer of benzylidine acetal **7**, we turned our attention to the installation of the pyranone functionality of tarchonanthuslactone. To this end, we planned to convert ester **7** into the *cis*-enoate **9**, which possesses all of the desired carbon atoms and the correct double-bond stereochemistry of **1**. The aldehyde **14** was easily prepared in a nearly quantitative yield (>95%) by exposure of a THF solution of ester **7** to 1.1 equiv of DibalH at −78 °C (Scheme 4). Treatment of

Scheme 4



14 with the potassium salt of **15** afforded a 70% yield of **9** with a 9:1 double-bond cis/trans stereoselectivity.[14]

Having established the double-bond stereochemistry and the C-5/C-7 stereocenters of tarchonanthuslactone in **9**, we looked to investigate the selective deprotection

(13) For other approaches to *syn*-3,5-dihydroxy carboxylic esters, see: (a) Miyazawa, M.; Matsuoka, E.; Sasaki, S.; Oonuma, S.; Maruyam, K. Miyashita, M. *Chem. Lett.* **1998**, 109. (b) Evans, D. A.; Trotter, B. W.; Coleman, P. J.; Cote, B.; Dias, L. C.; Rajpakse, H. A.; Tyler, A. N. *Tetrahedron* **1999**, *55* (29), 8671−8726. (c) Solladié, G.; Wilb, N.; Bauder, C.; Bonini, C.; Viggiani, L.; Chiummiento, L. *J. Org. Chem*. **1999**, *64*, 5447. (d) Sarraf, S. T.; Leighton, J. L. *Org. Lett*. **2000**, *2*, 3205−3208.

(14) Still, W. C.; Gennari, C. *Tetrahedron Lett*. **1983**, *24*, 4405.

(15) Takeda, Y.; Yoshihiro, O.; Toshiya, M.; Hirata, E.; Shinzato, T.; Takishi, A.; Yu, Q.; Otsuka, H. *Chem. Pharm. Bull.* **2000**, *48* (5) 752.

(16) The Aldrich Chemical Co. sells ethyl sorbate for $0.30/g.

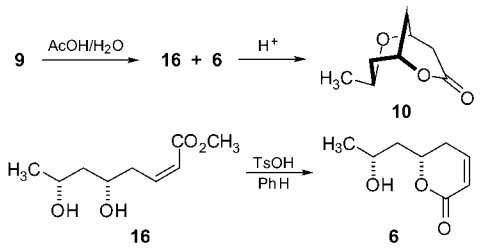
(17) All levels of enantioinduction were determined by HPLC analysis (8% IPA/hexane, Chiralcel OD) and/or Mosher ester analysis. (a) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem*. **1973**, *38*, 2143. (b) Yamaguchi, S.; Yasuhara, F.; Kabuto, K. T. *Tetrahedron* **1976**, *32*, 1363.

(18) (a) Tsuji, J.; Minami, I. *Acc. Chem. Res*. **1987**, *20*, 140. (b) Hughes, G.; Lautens, M.; Wen, C. *Org. Lett*. **2000**, *2*, 107.

(19) This lower than normal (1.25:1 as opposed to 2:1) phosphine-to-palladium ratio gave higher yields and faster reaction times.

(20) Evans, D. A. Gauchet-Prunet, J. A. *J. Org. Chem*. **1993**, *58*, 2446.

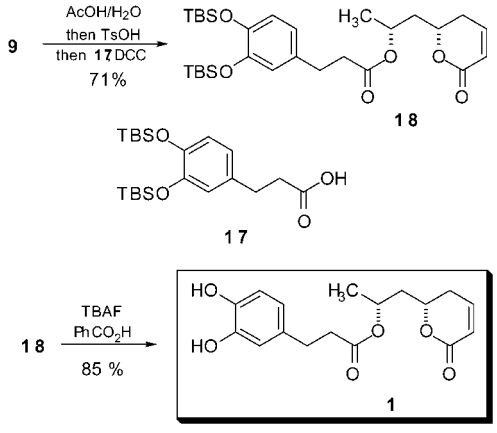
Scheme 5



and lactonization reaction sequence to convert enone **9** to pyranone **6** and not bicyclic lactone **10** (Schemes 2 and 5).[21] In the course of our cryptocyara diacetate (**2**) synthesis, we found that the benzylidene protecting group could be easily removed by refluxing in 80% aqueous acetic acid. These conditions were more troublesome when applied to **9** in that refluxing enone **9** for 12 h in 80% aqueous acetic acid provided a nearly quantitative yield of a 1:1 mixture of lactone **6** and bicyclic lactone **10**.[22] Reducing the reaction time along with careful monitoring of the reaction mixture led to a more selective conversion of **9** to diol **16**.[23] The penchant of diol **16** to cyclization made it difficult to isolate in a pure form; however, crude solutions of **16** were easy to prepare and use. For instance, exposure of the crude diol **16** to catalytic acid in THF at room temperature provided mixtures of **6** and **10**.[24] Switching the reaction solvent from THF to benzene proved to be a desirable solution. Hence, treating the crude diol product **16** with catalytic amounts of TsOH in benzene yielded lactone **6** (95%) with only minor amounts of the undesired bicyclic lactone **10** (5%).

The hydroxylactone **6** that was prepared by this sequence had spectral properties identical to that of the material prepared by Solladié.[4d] Following the Solladié procedure allowed acylation of pyranone **6** using **17** and DCC to give **18**, which was deprotected with TBAF to give tarchonanthuslactone **1** (Scheme 6). While this

Scheme 6



three-step procedure provided adequate yields of **18** from **9**, a simpler and higher-yielding procedure for the conversion of **9** to **18** was accomplished with a one-pot procedure. Thus, after the deprotection of **9** to produce diol **16**, the solvent (AcOH) was switched to benzene and a catalytic amount of TsOH was added producing a solution of **6** with less than 5% of starting material **9** and/or bicyclic lactone **10**. At this stage, **6** was acylated first by neutralization (solid $NaHCO_3$) and solvent exchange (CH_2Cl_2), followed by the addition of 1.1 equiv of DCC and the carboxylic acid **17**. This one-pot protocol for the conversion of **9** to protected tarchonanthuslactone **18** provided an excellent yield (71%) of product with spectral data identical to that of the material prepared by Solladié.[4d]

In conclusion, this highly enantio- and diastereocontrolled route illustrates the utility of our recently developed Os/Pd route to benzylidene-protected *syn*-1,3-diols. The synthesis provides tarchonanthuslactone in eight steps and 19% overall yield (82% average yield) and is amenable to the preparation of either enantiomer by use of asymmetric catalysis. Further studies on the use of these chiral building blocks toward the synthesis of *syn*-1,3-polyol-containing natural products such as **3** and **4** will be reported in due course.

Experimental Section[25]

***cis*-Enoate (9).** To a stirred solution of bis(2,2,2-trifluoroethyl)methoxycarbonylmethylphosphonate (101 mg, 0.32 mmol) and 18-crown-6 (212 mg, 0.8 mmol) in THF (1 mL) at −78 °C was added $KN(TMS)_2$ (0.48 mL of a 0.5 M solution in toluene). The mixture was stirred for 1 h. The aldehyde **14**, dissolved in THF (1 mL), was added dropwise, and the resulting mixture was stirred for 20 min. After this period, the reaction was quenched with saturated sodium bicarbonate and warmed to room temperature. The layers were separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. Removal of the solvent and purification by silica gel chromatography yielded 27 mg (72%) of a 9:1 mixture of the cis and trans esters: R_f 0.61 (hexane/EtOAc, 4:1); $[\alpha]_D$ −27.3 (*c* 0.80, $CHCl_3$); IR (neat, cm^{-1}) 2973, 2855, 1723, 1648, 1439, 1405, 1379, 1339; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.53 (m, 2H), 7.37 (m, 3H), 6.49 (ddd, J = 11, 7.5, 7 Hz, 1H), 5.91 (ddd, J = 11, 2, 2 Hz, 1H), 5.55 (s, 1H), 3.98 (m, 2H), 3.73 (s, 3H), 3.10 (dddd, J = 16, 8, 4.5, 2 Hz, 1H), 2.91 (dddd, J = 16, 7, 7, 2 Hz, 1H), 1.66 (ddd, J = 13, 2.5, 2.5 Hz, 1H), 1.50 (ddd, J = 13, 11, 11 Hz, 1H), 1.32 (d, J = 6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.9, 146.1, 138.8, 128.8, 128.3, 126.3, 120.9, 100.9, 76.0, 73.1, 51.2, 38.3, 35.1, 21.7; HRMS (CI) calcd for $[C_{16}H_{20}O_4 + H]^+$ 277.1440, found 277.1445. Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 69.15; H, 7.51.

TBS-Protected Tarchonanthuslactone (18).[26] A solution of *cis*-enoate **9** (12 mg, 0.043 mmol, 1.9 mL 80% AcOH) was heated to 60 °C and stirred for 4 h. The solvent was then removed under reduced pressure, and 1 mL of benzene along with 1 mg of *p*-toluenesulfonic acid was added to the flask. The reaction mixture was stirred for 2 h when solid sodium bicarbonate was added to the reaction. The solution was filtered through a plug of glass wool, and the solvent was removed under reduced pressure and replaced with methylene chloride (1 mL). To this solution were added 27.5 mg (0.067 mmol) of TBS-protected dihydrocaffeic acid,[13] 13 mg (0.067 mmol) of DCC, and catalytic DMAP (<1 mg). This reaction was stirred for 3 h. Ether was added to the solution, and the mixture was filtered through a pad of Celite. Removal of the solvent under reduced pressure provided crude **18**. Purification of the crude material with silica gel chromatography yielded TBS-protected tarchonanthuslactone **18** (17 mg, 71% yield for the three steps): R_f 0.42 (hexane/EtOAc, 4:1).

(21) Others have had success at removing an acetonide protecting group to provide **16**; see: ref 4d.

(22) Hayakawa, H.; Miyashita, M. *Tetrahedron Lett.* **2000**, *41*, 707.

(23) At this stage of the reaction, there can be a small amount of compound **6** detected.

(24) These procedures provide a ca. 50% yield of **10**; however, no efforts were made to optimize this procedure for the production of **10**.

(25) For full experimental details for all compounds shown and general experimental details, see Supporting Information.

(26) These data match spectral data for the compounds reported in ref 4d.

NMR Data for Agylcon (6):[26] ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.89 (ddd, J = 10, 4.4, 3.8 Hz, 1H), 6.02 (ddd, J = 10, 2, 2 Hz, 1H), 4.64 (dddd, J = 8, 8, 8, 5 Hz, 1H), 4.10 (ddq, J = 8.4, 6.4, 4.2 Hz, 1H), 2.37−2.44 (m, 2H), 2.01 (ddd, J = 14, 8, 8 Hz, 1H), 1.76 (ddd, J = 14.4, 5.2, 4.2 Hz, 1H), 1.26 (d, J = 6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.1, 145.4, 121.3, 76.7, 65.4, 43.6, 29.6, 23.8.

NMR Data for Bicyclic Compound 10:[27] ^{1}H NMR (1:1 $CDCl_3$−C_6D_6, 300 MHz) δ 4.39 (dddd, J = 4, 4, 4, 2 Hz, 1H), 3.88 (m, 1H), 3.67 (ddq, J = 12, 6, 3 Hz, 1H), 2.59 (br d, J = 19 Hz, 1H), 2.30 (dd, J = 19, 5.4 Hz, 1H), 1.67 (br d, J = 13.8 Hz, 1H), 1.47 (dddd, J = 14, 4, 2, 2 Hz, 1H), 1.32 (dddd, J = 14, 4, 2, 2 Hz, 1H), 1.10 (m, 1H), 0.98 (d, J = 6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.9, 73.2, 65.9, 62.0, 38.6, 36.5, 29.6, 21.4.

NMR Data for TBS-Protected Tarchonanthuslactone (18):[26] ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.85 (ddd, J = 10, 5.5, 2.5 Hz, 1H), 6.72 (d, J = 8 Hz, 1H), 6.64 (m, 2H), 6.01 (ddd, J = 9.5, 2, 1 Hz, 1H), 5.10 (ddq, J = 8, 6, 4.5 Hz, 1H), 4.42 (dddd, J = 13, 6.5, 6.5, 4 Hz, 1H), 2.81 (t, J = 8 Hz, 2H), 2.55 (t, J = 8 Hz, 2H), 2.35 (dddd, J = 18.5, 4.5, 4.5, 1 Hz, 1H), 2.26 (dddd, J = 18, 11.5, 3, 3 Hz, 1H), 2.16 (ddd, J = 14, 8.5, 6 Hz, 1H), 1.81 (ddd, J = 14.5, 6.5, 4 Hz, 1H), 1.26 (d, J = 6.5 Hz, 3H), 0.98 (s, 9H), 0.97 (s, 9H), 0.19 (s, 6H), 0.18 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.5, 163.9, 146.6, 145.2, 144.8, 133.4, 121.4, 121.2, 121.1, 120.9, 74.9, 67.1, 40.8, 36.2, 30.2, 29.1, 25.9, 20.3, 18.4, −4.1.

(27) These data match spectral data for the enatiomer of compound **10** as reported in ref 15.

Tarchonanthuslactone (1).[26] Benzoic acid (5 mg, 0.044 mmol) was added to a solution of protected tarchonanthuslactone (8 mg, 0.015 mmol) and THF (1 mL). A 1.0 M solution of TBAF in THF (30 μL) was added to the solution. The mixture was stirred at room temperature for 2 h. The solvent was evaporated and extracted with ethyl acetate (3 × 5 mL). Evaporation of the solvent and purification by silica gel chromatography yielded tarchonanthuslactone (4 mg, 85% yield): R_f 0.3 (ether), ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.85 (ddd, J = 10, 6, 3 Hz, 1H), 6.77 (d, J = 8 Hz, 1H), 6.75 (d, J = 3 Hz, 1H), 6.62 (dd, J = 8, 2.5 Hz, 1H), 6.02 (ddd, J = 10, 3, 1 Hz, 1H), 5.07 (ddq, J = 10, 6, 4 Hz, 1H), 4.17 (dddd, J = 11.5, 6.5, 6, 4.5 Hz, 1H), 2.86 (t, J = 7 Hz, 2H), 2.63 (t, J = 7 Hz, 2H), 2.36 (dddd, J = 18, 4, 4, 1 Hz, 1H), 2.24 (dddd, J = 18, 11.5, 3, 3 Hz, 1H), 2.08 (ddd, J = 14.5, 8.5, 6 Hz, 1H), 1.77 (ddd, J = 14.5, 7, 4 Hz, 1H), 1.27 (d, J = 6 Hz, 3H).

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Supporting Information Available: Complete experimental procedures and spectral data for the known compounds prepared by this route. This material is available free of charge via the Internet at http://pubs.acs.org.

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