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Synthesis of (−)-Tetrodotoxin: Preparation of an Advanced Cyclohexenone Intermediate

Douglass F. Taber* and Pierre H. Storck

Department of Chemistry and Biochemistry, University of Delaware, Newark, Delaware 19716

taberdf@udel.edu

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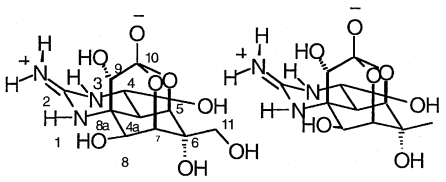
The preparation of an advanced intermediate toward the enantioselective synthesis of tetrodotoxin is outlined. The enantiomerically pure cyclopentene **15** was generated from ketone **14** by alkylidene carbene insertion with retention of absolute configuration. An ozonolysis/aldol sequence first produced the trans cyclohexenone, which upon epimerization gave the more stable cis enone **18**.

Introduction

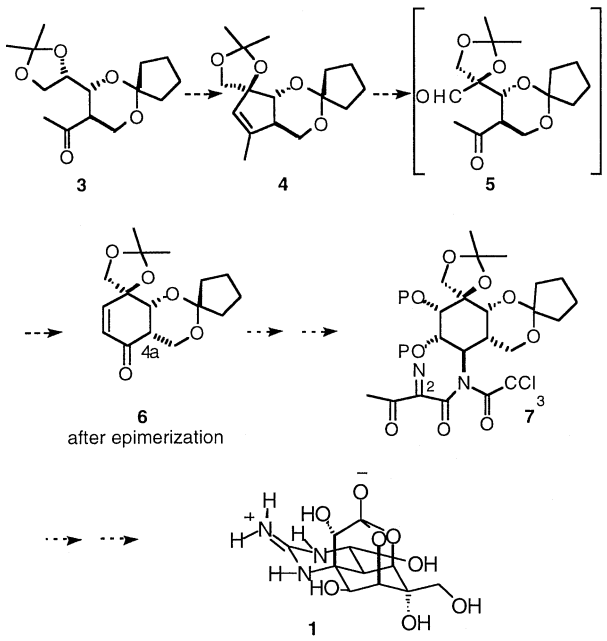
Tetrodotoxin **1**, a potent blocker of sodium ion channels originally isolated from the puffer fish,[1] has become a useful tool for physiological studies.[2] The pentacyclic structure of **1** is unusual in that there are as many heteroatoms as carbons and 9 of the 11 carbons are stereogenic centers. In 1972, Kishi reported[3a,b] a synthetic tour de force leading to the preparation of racemic tetrodotoxin. The most concerted effort toward **1** since that time has been by Isobe, who recently reported the synthesis of the naturally occurring 11-deoxy derivative **2**.[3c]



1 **2**

Both the synthesis of **1** and the synthesis of **2** were based on the extensive oxidative derivatization of a cyclohexene prepared by Diels−Alder cycloaddition. Alternative approaches[4] based on the cyclization of fully functionalized carbohydrate precursors have not yet been brought to fruition. We propose a third approach (Scheme 1), based on the functionalization of cyclohexenone **6**. We plan to prepare the cyclohexenone **6** by an intramolecular alkylidene carbene cyclization[5] of the readily available ketone **3**.

SCHEME 1



We expected the aldolization reaction to be difficult. A cyclic ketal was therefore incorporated into the synthesis to prevent the otherwise likely decomposition by β-elimination of the intermediate keto aldehyde **5**. Base-catalyzed epimerization to the more stable cis enone **6** would establish the correct relative configuration at C-4a (tetrodotoxin numbering). Further elaboration of the cyclohexenone core by C−H insertion of **7** would then lead to **1**.

Intramolecular Alkylidene Carbene Insertion To Form 15. For reasons of convenience, and in an attempt

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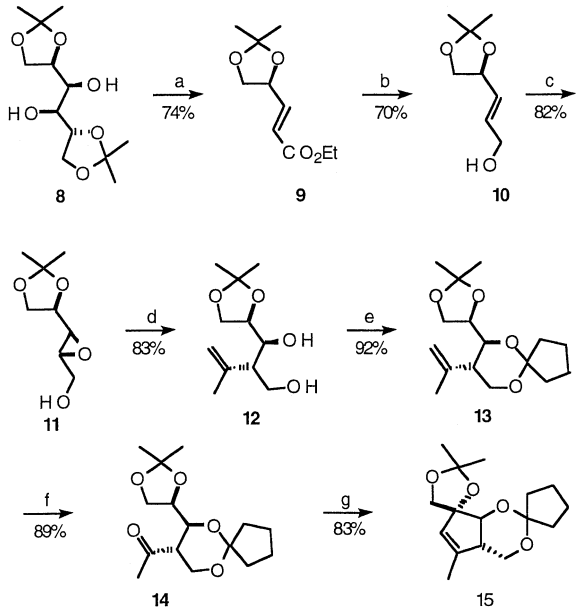
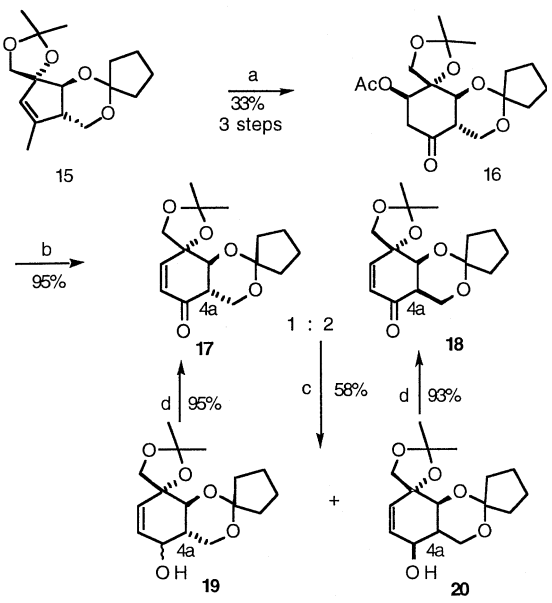
SCHEME 2 [a]



[a] Conditions: (a) $NaIO_4$, $NaHCO_3$, H_2O then triethyl phosphonoacetate, K_2CO_3; (b) DIBAH, CH_2Cl_2, −78 °C; (c) SAE; (d) isopropenylmagnesium bromide, CuBr·$S(CH_3)_2$, Et_2O, −20 °C; (e) cyclopentanone, trimethyl orthoformate, PTSA, CH_2Cl_2, rt, 3 min; (f) O_3, CH_2Cl_2, rt then Ac_2O, DMAP; (g) TMS diazomethane, *n*-BuLi, THF, −78 then 0 °C.

SCHEME 3 [a]



[a] Conditions: (a) (i) O_3, CH_2Cl_2, −78 °C then $S(CH_3)_2$; (ii) DBU, CH_2Cl_2, rt 24 h then Ac_2O, DMAP; (b) DBU, CH_2Cl_2, rt, overnight; (c) $NaBH_4$·$CeCl_3$·$7H_2O$, MeOH, 0 °C; (d) Dess−Martin periodinane, CH_2Cl_2, rt.

to quickly evaluate the feasibility of our strategy, the synthesis of the advanced cyclohexenone intermediate **6** was explored using the readily available D-mannitol as the starting material. The absolute configuration of this series would lead ultimately to the unnatural enantiomer of tetrodotoxin.

Allylic alcohol **10**[6] was prepared from glyceraldehyde acetonide, prepared in situ by $NaIO_4$-mediated cleavage of 1,2;5,6-di-*O*-isopropylidene-D-mannitol **8**. Condensation with triethyl phosphonoacetate afforded predominantly the desired *E*-conjugated ester **9**, along with a minor amount of the *Z* isomer (Scheme 2).

After separation of the two geometric isomers by chromatography, DIBAH reduction of **9** provided **10**. Sharpless asymmetric epoxidation with D-(−)-diethyl tartrate then gave the epoxy alcohol **11**.[7] Opening of the epoxide with isopropenylmagnesium bromide/CuBr·$S(CH_3)_2$ in ether as described by Tius[8] afforded diol **12** in good yield. The 1,3-diol was protected as a cyclopentylidene ketal using a very short exposure time (3 min) to avoid the formation of mixtures.

We were concerned about the efficiency of the alkylidene carbene insertion into the somewhat congested methine of **14** to form the strained trans 6,5 bicyclic alkene **15**. In fact, the cyclopentene **15** was generated in an efficient two-step procedure: ozonolyzis of the alkene **13** produced the ketone **14**, which upon exposure to lithiated trimethylsilyl diazomethane cleanly underwent intramolecular alkylidene carbene insertion into the activated methine C−H with the expected retention of absolute configuration.[5]

Aldol Condensation Leading to 18. The aldol condensation to form the cyclohexenone **17** and **18** was not trivial (Scheme 3). Attempts to isolate the keto aldehyde from ozonolysis of **15** led only to decomposition. We were, however, able to trap the intermediate hydroxy ketone as the corresponding acetate **16**.

Exposure of **16** to DBU effected elimination to give the trans-fused enone **17**. On continued exposure to DBU (rt, overnight) the enone was smoothly converted to the equilibrium 1:2 mixture of **17** and the desired cis-fused enone **18**. Unfortunately, the two enones were not separable by chromatography. The mixture was therefore reduced according to Luche's procedure.[9] The diastereoisomeric allylic alcohols **19** and **20** (the former as a mixture of α and β isomers) were separated and individually reoxidized with the Dess−Martin periodinane[10] to produce the enantiomerically pure cyclohexenones **17** and **18**. The confirmation of the structure of **18** as the

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cis enone was based on NMR evidence. In **18**, H-5 is equatorial and does not couple with the axial H-4a. It therefore appears as a simple singlet. In **17**, in contrast, these two protons, both axial, share a coupling constant at 4.8 Hz. Moreover, in the carbon NMR, C-4a of **18** appears at a higher field (δ 41.8) than in **17** (δ 46.4). The structures of **17** and **18** were confirmed by X-ray crystallographic analysis. The pure ketones **17** and **18** were each efficiently equilibrated by DBU to the 1:2 mixture of **17** and **18**.

Conclusion

As we had hoped, the synthesis of the enantiopure cyclohexenone **18** has been successfully completed using an alkylidene carbene insertion/ozonolysis/aldol sequence. The alkyidene carbene insertion proceeds with retention of absolute configuration, so it can be used for the asymmetric construction of quaternary stereogenic centers. Our efforts toward the enantioselective synthesis of (−)-tetrodotoxin are continuing.

Experimental Section

Diol 12. A freshly made solution of isopropenylmagnesium bromide in THF (1.0 M, 210 mL) was added over 20 min to a slurry of CuBr·SMe_2 (17.2 g, 83.7 mmol) in dry ether (320 mL) cooled to −50 °C. The mixture was stirred for 10 min at −20 °C, after which time a solution of the epoxy alcohol **11**[7] (4.19 g, 24.1 mmol) in ether (100 mL) was added over 10 min. The mixture was stirred at −20 °C for 36 h. The reaction mixture was partitioned between ether (200 mL) and, sequentially, 75% saturated aqueous NH_4Cl (400 mL) and brine (200 mL). The combined organic extract was dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed to yield the diol **12** as white crystals (4.45 g, 86% yield from **11**): TLC R_f = 0.38 (petroleum ether-ethyl acetate, 1:1); $[\alpha]^{20}_D$ +22 (c = 1.0, CH_2Cl_2); mp 51−53 °C (petroleum ether-ethyl acetate); ^{1}H NMR δ 1.36 (s, 3H), 1.44 (s, 3H), 1.73 (s, 3H), 2.19 (m, 1H), 3.09 (d, 1H, J = 2.7 Hz), 3.12 (m, 1H), 3.69 (m, 1H), 3.91 (m, 1H), 3.95 (s, 1H), 3.98 (s, 1H), 4.10 (m, 2H), 4.83 (d, 1H, J = 0.5 Hz), 4.92 (t, 1H, J = 1.5 Hz); ^{13}C NMR δ u 142.4, 114.7, 109.1, 65.0, 63.7; d 76.7, 72.4, 51.1, 26.6, 25.3, 21.2; IR (film) 3418, 1645 cm^{-1}; HRMS calcd for $C_{11}H_{20}O_4$ 217.1440 ($M + H^+$), found 217.1438.

Ketal 13. A mixture of cyclopentanone (0.43 mL, 4.86 mmol), trimethyl orthoformate (0.51 mL, 4.66 mmol). and PTSA (48 mg, 0.25 mmol) in CH_2Cl_2 (10 mL) was aged for 10 min at rt and then cooled to 0 °C. A solution of diol **12** (1.00 g, 4.63 mmol) in CH_2Cl_2 (10 mL + 2 mL rinse) was then added in one portion. After 3 min, the reaction mixture was partitioned between a saturated solution of $NaHCO_3$ (10 mL) and CH_2Cl_2 (10 mL). The combined organic extract was dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed to yield the alkene **13** as a colorless oil (1.00 g, 76% yield from **12**, 90% yield based on the recovered starting material): TLC R_f = 0.55 (petroleum ether−MTBE, 9:1); $[\alpha]^{20}_D$ +27 (c = 1.0, CH_2Cl_2); ^{1}H NMR δ 1.36 (s, 3H), 1.39 (s, 3H), 1.55−1.91 (m, 9H), 2.00 (m, 1H), 2.20 (m, 1H),; ^{13}C NMR δ u 142.1, 114.2, 110.2, 109.2, 65.8, 64.7, 40.1, 30.8, 24.4, 22.7; d 76.8, 73.0, 45.9, 26.1, 26.1, 21.6; IR (film) 3076, 1644 cm^{-1}; MS (CI, 70 eV) m/z 284 (36), 269 (26), 255 (62), 183 (60), 125 (100); HRMS calcd for $C_{16}H_{26}O_4$ 284.1625 (M^+), found 284.1624. Anal. Calcd for $C_{16}H_{26}O_4$: C, 68.06; H, 9.28. Found: C, 68.28; H, 9.33.

Ketone 14. A solution of the alkene **13** (890 mg, 3.13 mmol) and a crystal of Sudan III in CH_2Cl_2 (18 mL) was chilled at −78 °C and ozonized until the red color faded. Nitrogen was bubbled through the solution for 10 min before triphenylphosphine (910 mg, 3.47 mmol) was added. The reaction mixture was brought to room temperature, stirred for 1 h, and then concentrated in vacuo. The residue was chromatographed to yield the ketone **14** as a colorless solid (790 mg, 89% yield from **13**): TLC R_f = 0.40 (petroleum ether−MTBE, 8:2); $[\alpha]^{20}_D$ +2.2 (c = 1.0, CH_2Cl_2); mp 53−55 °C (ethanol); ^{1}H NMR δ 1.29 (s, 3H), 1.30 (s, 3H), 1.52−2.00 (m, 8H), 2.25 (s, 3H), 3.01 (m, 1H), 3.77−4.08 (m, 6H); ^{13}C NMR δ u 207.9, 110.3, 110.1, 67.5, 63.3, 39.8, 31.0, 24.4, 22.6; d 78.2, 74.7, 52.2, 32.3, 26.1, 25.4; IR (KBr) 3440, 1706 cm^{-1}. Anal. Calcd for $C_{15}H_{24}O_5$: C, 63.36; H, 8.5. Found: C, 63.22; H, 8.55.

Cyclopentene 15. A solution of *n*-BuLi (1.86 M in hexane, 2.0 mL) was added over 2 min to a solution of TMS diazomethane (2 M in hexanes, 2.12 mL) in THF (8 mL) chilled at −78 °C. After 1 h, a solution of ketone **14** (790 mg, 2.74 mmol) in THF (2 mL) was added over 2 min, and the mixture was stirred 1 h at −78 °C and 1 h at 0 °C. The reaction mixture was partitioned between dichloromethane (10 mL) and, sequentially, 50% saturated aqueous NH_4Cl (10 mL) and brine (10 mL). The combined organic extract was dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed to yield the cyclopentene **15** (650 mg, 83% yield from **14**) as a colorless oil: TLC R_f = 0.45 (petroleum ether−MTBE, 9:1); $[\alpha]^{20}_D$ +13.1 (c = 1.0, CH_2Cl_2); ^{1}H NMR δ 1.28 (s, 3H), 1.29 (s, 3H), 1.48−1.90 (m, H), 2.24 (m, 1H), 3.52 (d, 1H, J = 8.39 Hz), 3.62 (dd, 1H, J = 11.2, 10.2 Hz), 3.67 (d, 1H, J = 9.3 Hz), 3.97 (dd, 1H, J = 10.2, 4.1 Hz), 4.25 (d, 1H, J = 8.3 Hz), 5.25 (m, 1H); ^{13}C NMR δ u 140.3, 112.2, 109.0, 89.4, 66.2, 65.2, 40.2, 32.3, 24.6, 22.9; d 128.9, 83.1, 46.0, 26.6, 15.0; IR (film) 1631 cm^{-1}. Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63. Found: C, 68.19; H, 8.85.

Acetate 16. A solution of the alkene **15** (500 mg, 1.78 mmol) and a crystal of Sudan III in dichloromethane (10 mL) was chilled at −78 °C and ozonized until the red color faded. Nitrogen was bubbled through the solution for 10 min before methyl sulfide (1 mL) was added. The reaction mixture was brought to room temperature and stirred for 3 h before being concentrated in vacuo. The residue was dissolved in 10 mL of dry dichloromethane and cooled at 0 °C, and a solution of DBU (272 mg, 1.80 mmol) in CH_2Cl_2 (1 mL) was added. The mixture was stirred for 24 h at rt before a solution of Ac_2O (185 μL, 1.96 mmol) in CH_2Cl_2 (1 mL) and DMAP (10 mg) were sequentially added. After 60 min, the reaction was partitioned between water (10 mL) and CH_2Cl_2 (10 mL). The combined organic extract was dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed to yield the acetate **16** (213 mg, 33% yield from **15**) as a colorless solid: TLC R_f = 0.25 (petroleum ether−MTBE, 4:1); $[\alpha]^{20}_D$ +21.1 (c = 1.47, CH_2Cl_2); mp 133−138 °C (petroleum ether−ethyl acetate); ^{1}H NMR δ 1.4−*1.9 (*m, 9H), 1.47 (s, 3H), 1.49 (s, 3H), 2.12 (s, 3H), 2.44 (m, 1H), 2.73 (dd, 1H, J = 14.6, 11.7 Hz), 2.83 (dd, 1H, J = 14.6, 5.6 Hz), 3.26 (dd, 1H, J = 11.7, 3.2 Hz), 3.75 (dd, 1H, J = 3.4 Hz), 4.0 (AB system, 2H), 4.12 (d, 1H, J = Hz), 4.57 (d, 1H, J = 11.7 Hz), 5.33 (dd, 1H, J = 11.9 Hz, J = 5.61 Hz); ^{13}C NMR δ u 204.7, 170.1, 111.3, 110.9, 81.4, 68.0, 59.3, 43.3, 40.0, 30.5, 24.5, 22.6; d 74.3, 68.2, 44.2, 27.8, 25.9; IR (KBr) 3426, 1744, 1722 cm^{-1}; MS (CI, 70 eV) m/z, 354 (36), 325 (62),153 (71),135 (100); HRMS calcd for $C_{18}H_{26}O_7$ 354.1679 (M^+), found 354.1669.

Allylic Alcohols 19 and 20. To a solution of the acetate **16** (162 mg, 0.46 mmol) in dichloromethane (4.6 mL) was added DBU (72 mL, 0.48 mmol), and the mixture was stirred for 24 h at rt. The reaction was then partitioned between water (10 mL) and CH_2Cl_2 (10 mL). The combined organic extract was dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed to yield a 2:1 mixture of *trans*- and *cis*-cyclohexenones **17** and **18** (127 mg, 95% yield from **16**) as a colorless oil.

To a solution of ketones **17** and **18** (177 mg, 0.6 mmol) in dry MeOH (6 mL) was added $CeCl_3$·$7H_2O$ (225 mg, 0.61 mmol). The mixture was cooled with an ice−water bath, and solid $NaBH_4$ (24 mg, 0.63 mmol) was added over a 5 min period. The mixture was stirred for 30 min and was then partitioned

between Et_2O (5 mL) and, sequentially, 50% saturated aqueous NH_4Cl (5 mL) and brine (5 mL). The combined organic extract was dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed to yield cyclohexenol **19** (65 mg, 37% yield from **16**) as a colorless solid and **20** (38 mg, 21% yield from **16**) as a colorless oil.

Allylic alcohol 19: TLC $R_f = 0.40$ (petroleum ether−EtOAc, 7:3); $[\alpha]^{20}_D$ +162.8 ($c = 0.47$, CH_2Cl_2); mp 89−91 °C (petroleum ether−MTBE); ^{1}H NMR δ 1.42 (s, 6H), 1.55−2.15 (m, H), 3.56 (d, 1H, $J = 8.3$ Hz), 3.80 (d, 1H, $J = 9.3$ Hz), 3.97 (m, 1H), 4.15−4.23 (m, 2H), 4.29−4.38 (m, 2H), 5.70 (dt, 1H, $J = 10.0$ Hz, $J = 1.22$ Hz), 6.16 (dd, 1H, $J = 10.0$ Hz, $J = 4.4$ Hz); ^{13}C NMR δ u 111.8, 110.1, 77.6, 71.1, 64.5, 64.4, 40.5, 30.5, 24.5, 22.7; d 134.3, 134, 3, 127.0, 72.6, 72.5, 65.0, 65.0, 31.9, 27.3, 27.2; IR (KBr) 3495 cm^{-1}; MS (CI, 70 eV) *m*/*z*, 296 (10), 268 (12), 195 (36), 183 (47), 156 (64), 137 (100); HRMS calcd for $C_{16}H_{24}O_5$ 296.1623 (M^+), found 296.1624.

Allylic alcohol 20: TLC $R_f = 0.45$ (petroleum ether−EtOAc, 1:1); ^{1}H NMR δ 1.40, (s, 3H),1.43 (s, 3H), 1.58−2.1 (m, 9H), 3.65−3.84 (m, 2H), 3.75 (d, 1H, $J = 8.3$ Hz), 3.95 (m, 1H), 4.21 (m, 1H), 4.47, (d, 1H, $J = 8.3$ Hz), 5.68 (bs AB system, 2H); ^{13}C NMR δ u 110.8, 110.1, 81.7, 69.0, 64.4, 40.3, 30.6, 24.5, 22.6; d 133.0, 131.4, 72.8, 68.3, 43.7, 27.4, 24.5; IR (film) 3443 cm^{-1}; MS (CI, 70 eV) *m*/*z*, 296 (16), 267 (24),137 (88); HRMS calcd for $C_{16}H_{24}O_5$ 296.1623 (M^+) found 296.1617.

Cyclohexenone 17. Dess−Martin reagent (46 mg, 0.11 mmol) was added in one portion to a solution of cyclohexenol **19** (21.1 mg, 0.07 mmol) in dry CH_2Cl_2 (1 mL). After 10 min, the mixture was partitioned between CH_2Cl_2 (5 mL) and, sequentially, saturated aqueous $Na_2S_2O_3$ (5 mL) and 5% aqueous $NaHCO_3$ (5 mL). The combined organic extract was dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed to yield the cyclohexenone **17** (19 mg, 95% yield from **19**) as a colorless solid: TLC $R_f = 0.36$ (petroleum ether−MTBE, 4:1); mp 108−112 °C (petroleum ether/MTBE); $[\alpha]^{20}_D$ −18.3 ($c = 0.75$, CH_2Cl_2); ^{1}H NMR δ 1.45 (s, 3H), 1.50 (s, 3H), 1.68 (m, 4H), 1.88 (m, 2H), 1.96 (m, 2H), 2.53 (dt, 1H, $J = 11.6$, 4.8 Hz), 3.83 (m, 1H), 3.94 (d, 1H, $J = 8.8$ Hz), 4.20 (m, 2H), 4.66 (d, 1H, $J = 8.4$ Hz), 5.94 (d, 1H, $J = 10.0$ Hz), 6.83 (d, 1H, $J = 10.0$ Hz); ^{13}C NMR δ u 196.3, 196.3, 111.4, 111.0, 81.4, 67.4, 61.1, 61.1, 40.2, 30.7, 24.5, 22.6; d 153.2, 153.1, 128.3, 74.0, 74.0, 46.4, 27.4, 25.8; IR (KBr) 3445, 1682 cm^{-1}; MS (CI, 70 eV) *m*/*z*, 294(12), 265(25), 207(26), 135(55), 121(100), M^+ too weak for high resolution. Structure confirmed by X-ray crystallography

Cyclohexenone 18. Dess−Martin reagent (66 mg, 0.15 mmol) was added in one portion to a solution of cyclohexenol **20** (31 mg, 0.10 mmol) in dry CH_2Cl_2 (1 mL). After 10 min, the mixture was partitioned between CH_2Cl_2 (5 mL) and, sequentially, saturated aqueous $Na_2S_2O_3$ (5 mL) and 5% aqueous $NaHCO_3$ (5 mL). The combined organic extract was dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed to yield the cyclohexenone **18** (29 mg, 93% yield from **20**) as a colorless solid: TLC $R_f = 0.36$ (petroleum ether−MTBE, 4:1); mp 86−89 °C (petroleum ether/MTBE); $[\alpha]^{20}_D$ +104 ($c = 1.7$, CH_2Cl_2); ^{1}H NMR δ 1.42 (s, 6H), 1.56 (m, 2H), 1.68 (m, 4H), 1.91 (m, 2H), 3.81 (d, 1H, $J = 11.6$ Hz), 3.92 (d, 1H, $J = 9.6$ Hz), 4.16 (d, 1H, $J = 9.6$ Hz), 4.22 (s, 1H), 4.60 (d, 1H, $J = 11.6$ Hz), 6.13 (d, 1H, $J = 10.0$ Hz), 6.57 (d, 1H, $J = 10.0$ Hz); ^{13}C NMR δ u 196.1, 196.1, 111.0, 110.9, 76.9, 71.6, 60.6, 60.5, 40.0, 30.5, 24.3, 22.5; d 145.1, 130.8, 74.0, 73.9, 42.0, 27.4, 26.6; IR (KBr) 3424, 1676 cm^{-1}; MS (CI, 70 eV) *m*/*z* 294 (20), 265 (40), 135 (100); HRMS calcd for $C_{16}H_{22}O_5$ 294.1472 (M^+), found 294.1467. Structure confirmed by X-ray crystallography.

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

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