Novel Preparation of Orthoquinol Acetates and Their Application in Oxygen Heterocyclization Reactions

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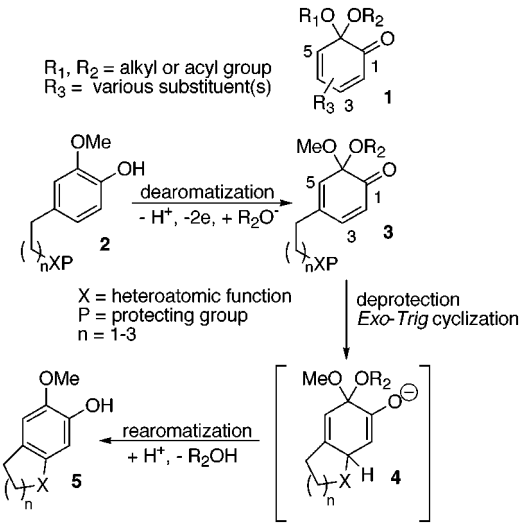
Orthoquinone monoketals (**1**), i.e., 6,6-dioxocyclohexa-2,4-dienones, are underutilized synthons in organic chemistry despite their considerable synthetic potential.[1] Most successful synthetic applications are usually limited to utilizing their dienone moiety as either a dienic[2,3] or a dienophilic[3a−c,4] component in [4_π+2_π] cycloaddition reactions. A few other applications in natural product synthesis have been reported,[5] but further systematic exploitations of the electrophilic reactivity and differentially activated double bonds of these orthoquinonoid species are sporadic.[6] A program aimed at exploring other avenues for the utilization of these species in organic synthesis has been initiated. One possibility is to exploit the reactivity of adequately functionalized orthoquinone monoketals in intramolecular nucleophilic addition reactions to construct polyoxygenated carbocycle-fused heterocyclic systems, which are found in many bioactive natural products and synthetic drugs. Conceptually, monoketal synthons of type **3** bearing protected heteroatomic appendages of varied length can be prepared from dearomatization of phenols **2** by two-electron oxidation in the presence of an oxygen-based trapping species. Deprotection will unmask the appended heteroatom which could then attack the electrophilic ketal moiety to form phenol-fused heterocycles of various sizes, such as **5**, via *in situ* aromatization of transient enolates **4** (Scheme 1). These intramolecular 1,4-additions (i.e., attack at C-3 of **3**) would follow an *Exo-Trig* cyclization pathway. According to Baldwin's rules, 5-*Exo-Trig* nucleophilic ring closures are preferred to 5-*Endo-Trig* closures (i.e., 1,6-addition at C-5 of **3**), but both pathways may compete for 6- and 7-membered ring closures.[7] Steric congestion at C-5 adjacent to the tetrahedral C-6 ketal center could however favor ring closure at C-3 of **3**. We report here a novel and convenient method for the preparation of relatively stable orthoquinone monoketals **3** and their regiocontrolled conversion into benzannulated 5- to 7-membered ether rings **5** (n = 1−3, X = O).

Scheme 1



Phenols **2a**−**e** were prepared from commercially available 2-methoxyphenols (see Supporting Information). Silyl protective groups were chosen in anticipation of inducing the heterocyclization event by desilylation (Scheme 1, **3** → **5**; P = TBDPS, TBDMS, TES).[8] Two-electron oxidizing systems commonly used today to generate orthoquinone monoketals from 2-methoxyphenols are $PhI(O_2CCF_3)_2$ or $PhI(OAc)_2$ in MeOH (oxidative methoxylation)[2,3a−f] and $Pb(OAc)_4$ in AcOH or CH_2Cl_2 (Wessely oxidative acetoxylation).[9] Oxidative methoxylation furnishes 6,6-dimethoxycyclohexa-2,4-dienone derivatives (e.g., **1**, R_1, R_2 = Me). These ketals are particularly sensitive to Diels−Alder dimerization *in situ* unless the system bears either relatively bulky substitutent(s) at the 3- or 5-position[3g,10] or a bromine at the 4-position.[2] However, we observed that a 6-acetoxy-6-methoxycyclohexa-2,4-dienone derivative, a so-called orthoquinol acetate (i.e., **1**, R_1 = Me, R_2 = Ac), did not dimerize in contrast to its 6,6-dimethoxy counterpart (see Supporting Information). On the basis of this result, phenols **2a**−**e** were systematically converted into orthoquinol acetates **3a**−**e** (Scheme 1, R_2 = Ac); this was initially accomplished by performing the Wessely oxidative acetoxylation in CH_2Cl_2.[9] These orthoquinone monoketal variants do not bear any substituent at their 3- or 5-position, but do not dimerize *in situ*, and are stable enough to be extracted from the reaction mixture. We then found that the use of $PhI(OAc)_2$ in CH_2Cl_2 also led to the formation of stable **3a**−**e** in quasi-quantitative yields (see Table 1). The

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(8) Variation in the choice of the silyl protecting group was due to incompatibilities caused by the lack of reactivity of the silylating reagents used, β-elimination of the silyloxy group, or difficulties in achieving TBAF-mediated desilylation (see Supporting Information).

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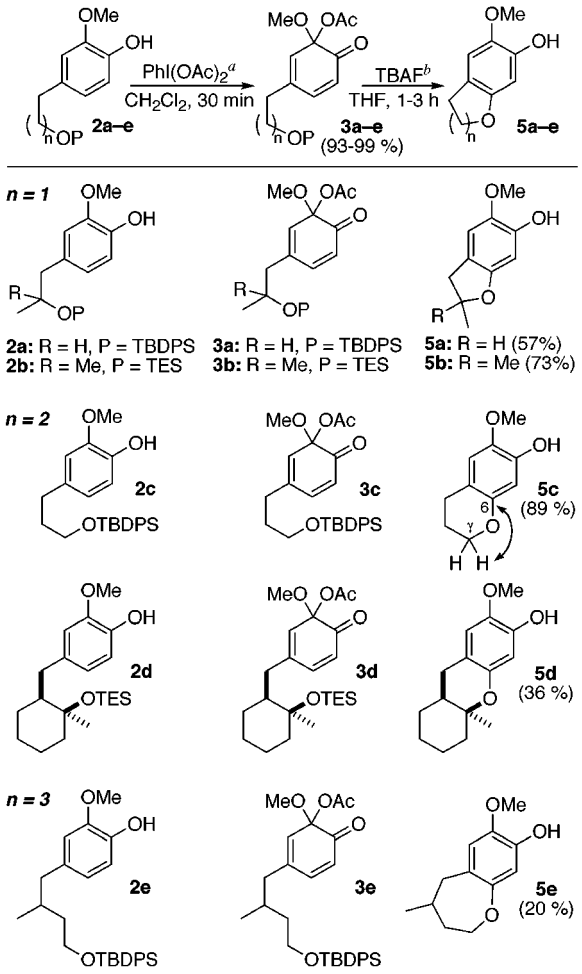
Table 1. Preparation of Orthoquinol Acetates and Their Oxygen Heterocyclizations



[a] 1.0 equiv. [b] Best results were obtained by adding a 12 mM solution of the orthoquinol acetate to a 30 mM solution of TBAF (2.0 equiv) in dry THF.

advantages of using $PhI(OAc)_2$ instead of $Pb(OAc)_4$ are the absence of toxic lead salts, and the convenient removal of PhI and residual AcOH byproducts by drying under vacuum; no purification by silica gel chromatography was necessary. Compounds **3a**−**e** can be stored as dry oils for several days at −20 °C without any noticeable degradation.

Heterocyclizations are then induced upon fluoride-mediated desilylation of **3a**−**e** using TBAF in THF (Table 1). As expected, cyclization and concomitant rearomatization via elimination of the acetoxy groups of ketals **3a** and **3b** furnished the 5-*Exo*-*Trig* cyclized benzofurans products **5a** and **5b** in good yields.[11] Ketal **3c** furnished the 6-*Exo*-*Trig* cyclized product **5c** as the sole regioisomer in 89% optimized yield. No 6-*Endo*-*Trig* cyclized products were observed. The regiochemistry is readily determined by the observation of two aromatic singlets in the ^{1}H NMR spectrum. The cyclic connectivity was further confirmed by the detection of a diagnostic three-bond response between the 6-carbon and the γ-protons of **5c** in its long-range C−H correlation spectrum.[12] This successful regioselective formation of **5c** is particularly interesting, for the same methodology can be tailored to novel approaches to the synthesis of numerous benzopyran-containing[13] natural products, notably including marine shikimate-sesquiterpenoids. These natural products, exemplified by puupehenone,[14] are currently the focus of a renewed synthetic interest because of their potent biological activities.[15] Orthoquinone monoketals can serve as precursors of their vicinally dioxygenated shikimate moieties, and constitute ideal synthons for annulation of their terpenoid units to their shikimate units. The feasibility of this approach was demonstrated by subjecting phenol **2d** to the oxidation−cyclization conditions (Table 1). This two-step sequence gave the shikimate-terpenoid model compound **5d** again as the sole cyclized regioisomer in 36% yield (not optimized) from **2d**.

Orthoquinol acetate **3e** was used to test the feasibility of generating benzannulated seven-membered ether rings. A method based on ring-closing metathesis has recently been reported to provide a solution to this challenging synthetic endeavor.[16] Here, we hoped that the rearomatization event would help overcome the energetically disfavored direct closure of these medium-sized rings.[17] The TBAF-mediated desilylation of **3e**, performed at room temperature for 1h, gave rise to the *Exo*-*Trig* cyclized benzoxepin **5e** in 20% yield. No other cyclized regioisomers were observed; the other main products were some recovered **2e** derived from *in situ* reduction of **3e**, and its desilylated counterpart. Thus, optimization of this reaction by varying the reaction time and the nature of the silyl group may offer an efficient alternative to the formation of phenolic benzoxepin compounds.

In summary, this preliminary study has demonstrated the synthetic utility and potential of orthoquinol acetates in oxygen heterocyclization chemistry. These relatively stable orthoquinone monoketal variants are easily prepared from $PhI(OAc)_2$-mediated oxidation of 2-methoxyphenols. This protocol constitutes a convenient alternative to the lead salt-based Wessely oxidation. The combined oxidation−cyclization of silyloxy derivatives of functionalized 2-methoxyphenols into benzannulated 5- to 7-membered ether rings, as described therein, should find valuable applications in organic synthesis. The application of this promising two-step methodology to the synthesis of marine shikimate-sesquiterpenoids, and its extension to nitrogen nucleophilic ring closures for the

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synthesis of lycorine-type Amaryllidaceae alkaloids are in progress.

Experimental Section

General. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were purified by distillation from sodium/benzophenone under Ar immediately before use. EtOAc and CH_2Cl_2 were distilled from CaH_2 prior to use. Light petroleum refers to the fraction boiling in the 40−60 °C range. Moisture and oxygen sensitive reactions were carried out in flame-dried glassware under Ar. Evaporations were conducted under reduced pressure at temperatures less than 45 °C unless otherwise noted. Column chromatography was carried out under positive pressure using 32−63 μm silica gel (Bodman) and the indicated solvents. Melting points are uncorrected. One- and two-dimensional NMR spectra of samples in the indicated solvent were run at 300 MHz (^{1}H). Carbon multiplicities were determined by DEPT135 experiments.[18] Diagnostic correlation information was obtained using the Bruker pulse program XHCORR[12a] for ^{1}H−^{13}C two- and three-bond connectivities; delay times $\Delta1$ and $\Delta2$[19] of 35 ms (d3) and 25 ms (d4) were used, respectively.[12b] Electron impact mass spectra (EIMS) were obtained at 50−70 eV. Chemical ionization low and high-resolution mass spectrometric analyses (CIMS, HRMS) were obtained from the mass spectrometry laboratory at the University of Texas at Austin. Combustion analyses were performed by Desert Analytics (Tucson, AZ). ^{1}H and ^{13}C NMR spectra are provided to establish purity for those compounds which were not subject to combustion analyses.

Preparation of Orthoquinol Acetates 3a−e. A solution of the phenol **2a−e** (ca. 250 mg, 1.0 equiv) in dry CH_2Cl_2 (2 mL) was added dropwise to a stirring solution of the oxidizing agent [$Pb(OAc)_4$, 1.1 equiv, or $PhI(OAc)_2$, 1.0 equiv] in 5 mL of dry CH_2Cl_2 at −78 °C. The reaction mixture immediately became bright yellow. After 1 h, TLC monitoring [hexanes−EtOAc (4:1)] indicated complete consumption of the starting material. The mixture was poured into ice-cold saturated aqueous $NaHCO_3$ (20 mL), extracted with CH_2Cl_2 (2 × 20 mL), washed with brine (20 mL), dried over Na_2SO_4 (vide infra), filtered and evaporated at room temperature. The residue was further dried under high vacuum overnight to give the corresponding orthoquinol acetate **3a−e** as a bright yellow oil which was used without further purification.

Orthoquinol acetate 3a. Yellow oil: $Pb(OAc)_4$ ⇒ 96%, $PhI(OAc)_2$ ⇒ 94%. IR (NaCl) 1738, 1694 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.04 (s, 18H, 2 × tBu), 2.05 (s, 6H, 2 × AcO), 2.29−2.32 (m, 4H, 2 × CH_2), 3.39 (s, 3H, MeO), 3.40 (s, 3H, MeO), 3.94−3.96 (m, 2H, 2 × CH), 5.82 (bs, 1H, H-2), 5.86 (bs, 1H, H-2), 5.95 (d, J = 10.0 Hz, 1H, H-5), 5.97 (d, J = 10.0 Hz, 1H, H-5), 6.39 (dd, J = 2.0, 10.0 Hz, 1H, H-6), 6.52 (dd, J = 2.0, 10.0 Hz, 1H, H-6), 7.33−7.70 (m, 20H, 4 × Ph); ^{13}C NMR ($CDCl_3$) δ 191.7, 169.3, 143.5, 142.8, 135.8, 134.1, 133.9, 131.5, 131.4, 129.7, 129.6, 127.7, 127.6, 125.4, 125.1, 92.9, 68.9, 68.2, 51.2, 45.0, 44.8, 26.9, 22.4, 22.3, 20.5, 19.1; CIMS m/z (relative intensity) 478 (MH$^+$, 6), 421 (23), 419 (33), 401 (23), 198 (100); HRMS (CI) calcd for $C_{28}H_{33}O_5Si$ 477.2097, found 477.2079.

Orthoquinol acetate 3b. Yellow oil: $Pb(OAc)_4$ ⇒ 98%, $PhI(OAc)_2$ ⇒ 98%. IR (NaCl) 1737, 1684 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.54 (q, J = 7.9 Hz, 6H, 3 × CH_2−TES), 0.90 (t, J = 7.9 Hz, 9H, 3 × CH_3−TES), 1.20 (s, 3H, Me), 1.22 (s, 3H, Me), 2.06 (s, 3H, AcO), 2.30 (s, 2H, CH_2), 3.42 (s, 3H, MeO), 5.89 (bs, 1H, H-2), 5.99 (d, J = 10.0 Hz, 1H, H-5), 6.97 (dd, J = 2.1, 10.0 Hz, 1H, H-6); ^{13}C NMR ($CDCl_3$) δ 191.9, 169.2, 144.9, 136.3, 132.2, 124.1, 93.0, 73.8, 51.2, 50.0, 29.8, 29.7, 20.5, 6.9, 6.6; EIMS m/z (relative intensity) 369 (MH$^+$, 41), 368 (M$^+$, 37), 367 (80), 309 (20). Anal. Calcd for $C_{19}H_{32}O_5Si$: C, 61.92; H, 8.76. Found: C, 61.91; H, 9.04.

Orthoquinol acetate 3c. Yellow oil: $Pb(OAc)_4$ ⇒ 97%, $PhI(OAc)_2$ ⇒ 98%. IR (NaCl) 1739, 1689 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.04 (s, 9H, tBu), 1.67−1.76 (m, 2H, CH_2-β), 2.06 (s, 3H, AcO), 2.35 (bt, J = 7.6 Hz, 2H, CH_2-α), 3.41 (s, 3H, MeO), 3.68 (t, J = 6.0 Hz, 2H, CH_2-γ), 5.91 (bs, 1H, H-2), 6.09 (d, J = 10.0 Hz, 1H, H-5), 6.75 (dd, J = 2.1, 10.0 Hz, 1H, H-6), 7.33−7.65 (m, 10H, 2 × Ph); ^{13}C NMR ($CDCl_3$) δ 191.8, 169.4, 142.7, 138.4, 135.5, 133.7, 129.6, 128.9, 127.6, 125.7, 93.0, 62.5, 51.2, 31.3, 30.6, 26.8, 20.5, 19.2; EIMS m/z (relative intensity) 479 (MH$^+$, 19), 421 (59), 419 (49), 401 (79), 343 (100). Anal. Calcd for $C_{28}H_{34}O_5Si$: C, 70.26; H, 7.17. Found: C, 70.17; H, 6.95.

Orthoquinol acetate 3d. Yellow oil: $Pb(OAc)_4$ ⇒ 99%. IR (NaCl) 1742, 1689 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.45−0.67 (m, 12H, 6xCH_2), 0.87−0.98 (m, 18H, 6xCH_3), 1.13−1.62 (m, 18H), 1.23 (s, 3H, Me), 1.24 (s, 3H, Me), 1.93−2.06 (m, 2H), 2.07 (s, 6H, 2 × AcO), 2.52−2.58 (m, 2H), 3.43 (s, 3H, MeO), 3.44 (s, 3H, MeO), 5.86 (bs, 1H, H-2), 5.88 (bs, 1H, H-2), 6.07 (d, J = 10.0 Hz, 1H, H-5), 6.09 (d, J = 10.0 Hz, 1H, H-5), 6.71−6.76 (m, 2H, 2 × H-6); ^{13}C NMR ($CDCl_3$) δ 191.9, 169.4, 169.2, 143.0, 142.8, 138.2, 130.1, 125.6, 93.2, 93.0, 73.8, 51.3, 46.0, 45.9, 40.7, 35.7, 28.8, 26.7, 26.3, 25.7, 25.6, 21.9, 21.8, 20.6, 7.2, 7.0, 6.9, 6.8; CIMS m/z (relative intensity) 423 (MH$^+$, 10), 422 (M$^+$, 13), 363 (73), 291 (100); HRMS (CI) calcd for $C_{23}H_{38}O_5Si$ 422.2488, found 422.2477.

Orthoquinol acetate 3e. Yellow oil: $Pb(OAc)_4$ ⇒ 99%, $PhI(OAc)_2$ ⇒ 93%. IR (NaCl) 1737, 1684 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.82 (d, J = 6.4 Hz, 3H, Me-β), 0.86 (d, J = 6.4 Hz, 3H, Me-β), 1.06 (s, 18H, 2 × tBu), 1.32−1.46 (m, 2H), 1.61−1.69 (m, 2H), 1.85−2.06 (m, 4H), 2.07 (s, 6H, 2 × AcO), 2.21−2.34 (m, 2H), 3.44 (s, 3H, MeO), 3.45 (s, 3H, MeO), 3.68−3.73 (m, 4H, 2 × CH_2-δ), 5.89 (bs, 2H, 2 × H-2), 6.09 (d, J = 10.0 Hz, 2 × H-5), 6.72 (dd, J = 1.8, 10.0 Hz, 2H, 2 × H-6), 7.33−7.72 (m, 20H, 4 × Ph); ^{13}C NMR ($CDCl_3$) δ 191.9, 169.3, 142.9, 142.7, 137.5, 135.8, 135.5, 134.8, 133.8, 130.2, 129.7, 127.7, 127.6, 125.7, 125.6, 93.1, 61.7, 51.2, 42.6, 42.5, 39.2, 39.0, 28.4, 28.2, 26.8, 26.5, 20.5, 19.2, 19.1, 18.9; CIMS m/z (relative intensity) 507 (MH$^+$, 9), 449 (47), 447 (23), 429 (23), 357 (100); HRMS (CI) calcd for $C_{30}H_{39}O_5Si$ 507.2566, found 507.2553.

Heterocyclization of Orthoquinol Acetates 3a−e. To a stirring ice-cold solution of commercial TBAF (1 M in THF, 2.0 equiv) in dry THF (ca. 30 mM) was added dropwise a solution of the orthoquinol acetate (**3a−e**, 1.0 equiv) in dry THF (ca. 12 mM). After 10 min, the ice bath was removed, and the reaction mixture was stirred at room temperature for 1−3 h. Progression of the reaction was monitored by the disappearance of the orthoquinol acetate, as indicated by TLC [hexanes−EtOAc, (4:1)]. The mixture was quenched by adding dropwise a 1:1 mixture of ice-cold water and 1 M H_3PO_4, and then diluted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered and evaporated to give a dark oil, which was subjected to column chromatography, eluting with hexanes−EtOAc (9:1), to give the cyclized product.

Benzofuran 5a. Brown oil (57%): IR (NaCl) 3432 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.42 (d, J = 6.2 Hz, 3H, Me), 2.72 (ddd, J = 0.6, 7.7, 14.8 Hz, 1H, CH_2), 3.20 (dd, J = 8.7, 14.8 Hz, 1H, CH_2), 3.80 (s, 3H, MeO), 4.80−4.92 (m, 1H, CH), 5.59 (bs, 1H, OH), 6.39 (s, 1H, $H_{arom.}$), 6.68 (s, 1H, $H_{arom.}$); ^{13}C NMR ($CDCl_3$) δ 153.9, 140.7, 135.9, 116.6, 108.5, 97.2, 79.9, 57.0, 37.7, 21.6; CIMS m/z (relative intensity) 181 (MH$^+$, 100), 180 (25), 166 (11); HRMS (CI) calcd for $C_{10}H_{12}O_3$ 180.0786, found 180.0784.

Benzofuran 5b. Brown oil (73%): IR (NaCl) 3440 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 6H, 2 × Me), 2.90 (s, 2H, CH_2), 3.79 (s, 3H, MeO), 5.61 (s, 1H, OH), 6.37 (s, 1H, $H_{arom.}$), 6.67 (s, 1H, $H_{arom.}$); ^{13}C NMR ($CDCl_3$) δ 153.3, 145.8, 140.5, 116.6, 108.7, 97.3, 86.9, 57.1, 43.0, 28.1; EIMS m/z (relative intensity) 194 (M$^+$, 96), 179 (100). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.01; H, 7.27. Found: C, 67.85; H, 7.20.

Benzopyran 5c. Yellow oil (89%): IR (NaCl) 3436 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.91−1.99 (m, CH_2-β), 2.68 (t, J = 6.5 Hz, CH_2-α), 3.79 (s, MeO-3), 4.09 (t, J = 5.1 Hz, CH_2-γ), 5.55 (bs, OH), 6.40 (s, H-5), 6.49 (s, H-2); ^{13}C NMR ($CDCl_3$) δ 149.1 (C-6), 144.7 (C-4), 140.7 (C-3), 112.5 (C-1), 111.8 (C-2), 103.2 (C-5), 66.2 (CH_2-γ), 56.5 (MeO-3), 24.5 (CH_2-α), 22.6 (CH_2-β); EIMS m/z (relative intensity) 180 (M$^+$, 28), 165 (58), 69 (100). Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.64; H, 6.72. Found: C, 66.71; H, 7.00.

Benzopyran 5d. White crystals (36%): mp 115−116 °C; IR (KBr) 3424 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.15 (s, Me-γ), 1.19−1.64 (m, 8H), 1.87−1.91 (m, 1H), 2.22 (dd, J = 1.0, −16.3 Hz, 1H, CH_2-α), 3.01 (dd, J = 6.3, −16.3 Hz, 1H, CH_2-α), 3.79 (s, MeO-3), 5.44 (bs, OH), 6.39 (s, H-5), 6.48 (s, H-2); ^{13}C NMR ($CDCl_3$) δ 147.3 (C-6), 144.8 (C-4), 140.5 (C-3), 111.9 (C-2), 110.1 (C-1), 103.6 (C-5), 74.5 (C-γ), 56.5 (MeO-3), 38.5 (CH_2), 37.0 (CH-β),

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29.1 (CH_2-α), 28.4 (CH_2), 25.6 (CH_2), 25.3 (Me-*γ*), 21.7 (CH_2); CIMS *m*/*z* (relative intensity) 249 (MH^+, 100), 248 (M^+, 36), 154 (35), 153 (39); HRMS (CI) calcd for $C_{15}H_{20}O_3$ 248.1412, found 248.1415.

Benzoxepin 5e. White crystals (20%): mp 67−68 °C; IR (KBr) 3413 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 0.99 (d, *J* = 6.3 Hz, Me-*β*), 1.59−1.89 (m, 3H), 2.46−2.70 (m, 2H), 3.62 (ddd, *J* = 2.1, 7.9, −12.3 Hz, 1H, CH_2-*δ*), 3.82 (s, MeO-3), 4.21 (ddd, *J* = 2.9, 7.6, −12.3 Hz, 1H, CH_2-*δ*), 5.46 (bs, OH), 6.57 (s, H-5), 6.58 (s, H-2); ^{13}C NMR ($CDCl_3$) *δ* 154.5 (C-6), 144.0 (C-4), 142.2 (C-3), 124.9 (C-1), 112.8 (C-2), 108.0 (C-5), 72.2 (CH_2-*δ*), 56.3 (MeO-3), 42.0 (CH_2), 40.7 (CH_2), 31.9 (CH-*β*), 22.4 (Me-*β*); EIMS *m*/*z* (relative intensity) 208 (M^+, 100), 193 (51), 153 (52); HRMS (CI) calcd for $C_{12}H_{16}O_3$ 208.1099, found 208.1107.

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Supporting Information Available: Experimental procedures and spectral characterizations for **2a**−**e** and their intermediates (16 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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