

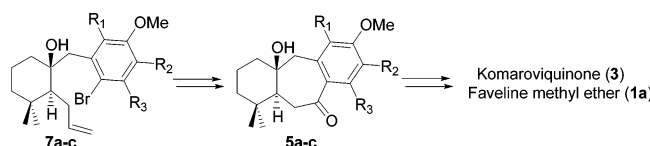
Stereoselective Syntheses of (±)-Komaroviquinone and (±)-Faveline Methyl Ether through Intramolecular Heck Reaction

Sujaya Sengupta,[†] Michael G. B. Drew,[‡] Ranjan Mukhopadhyay,[†] Basudeb Achari,[†] and Asish Kr. Banerjee^{*,†}

Medicinal Chemistry Division, Indian Institute of Chemical Biology, 4 Raja S. C. Mullick Road, Kolkata-700 032, India, and School of Chemistry, University of Reading, Whiteknights, Reading RG6 6AD, U.K.

ashisbanerjee@iicb.res.in

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An efficient, flexible, and stereoselective convergent route for constructing the *trans*-10-hydroxy-1,1-dimethyloctahydrodibenzo[*a,d*]cyclohepten-7-ones (**5a–c**) was achieved via intramolecular Heck reaction. This strategy has been successfully implemented for the syntheses of (±)-komaroviquinone (**3**) through (±)-coulterone dimethyl ether (**5c**) and (±)-faveline methyl ether (**1a**).

Introduction

A number of cytotoxic compounds have been isolated from the bark of the Brazilian plant favela (*Cnidocolus phyllacanthus*).¹ Faveline methyl ether (**1a**), faveline (**1b**), and deoxofaveline (**1c**) are typical members of rearranged 9(10→20)-*abeo*-16,17-dinorabieta-8,11,13-triene diterpenes (Figure 1). These molecules display significant activity against P-388 murine leukemia cells.¹ Several other rearranged abietane diterpenes, for example, pisiferin (**1d**),^{2a,b} isopisiferin (**1e**),^{2c} and barbatusol (**1f**),^{2d} have also been described. Recently, isolation of coulterone (**2**)^{3,4} and two new compounds in the icetexane group of rearranged abietane diterpenes komaroviquinone (**3**)⁴ and cyclocoulterone (**4**)⁴ have been reported from *Dracocephalum komarovi*. Komaroviquinone (**3**) displays a strong trypanocidal activity against epimastigotes of *Trypanosoma cruzi*, the causative agent of American trypanosomiasis.⁴

A number of total syntheses of the rearranged diterpenoids **1d**,⁵ **1e**,^{5b,6} and **1f**^{5c,7} incorporating functionalized 6–7–6-fused tricycles have appeared in the literature. The reported total syntheses^{5c,8} of (±)-faveline methyl ether (**1a**), (±)-faveline (**1b**), and (±)-deoxofaveline (**1c**) involve generation of the basic tricyclic skeleton mainly through acid-catalyzed cyclacylation⁸ or cyclialkylation^{5c} reactions. However, introduction of the 7-oxo group in deoxofaveline (**1c**) was plagued with problems.^{5c,8b} No report exists so far for the synthesis of coulterone (**2**), komaroviquinone (**3**), and cyclocoulterone (**4**). In continuation of our studies on the palladium-mediated synthesis of rearranged polycyclic diterpenoids,^{9,10} we report herein the first total synthesis of (±)-komaroviquinone (**3**) through (±)-coulterone dimethyl ether (**5c**) as well as a simple route to (±)-faveline methyl ether (**1a**).

[†] Indian Institute of Chemical Biology.

[‡] University of Reading.

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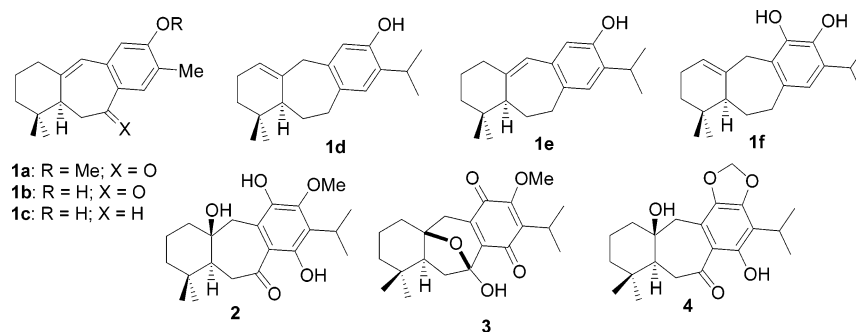
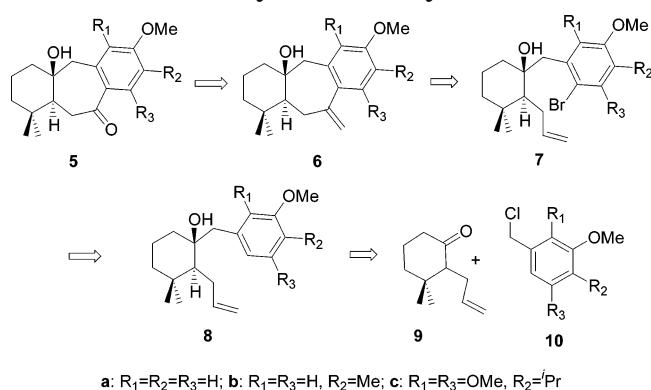


FIGURE 1. Rearranged 9(10→20)-abeo-abietane diterpenoids.

SCHEME 1. Retrosynthetic Analysis



Results and Discussion

A short, flexible, and stereoselective convergent route for the construction of the intermediate *trans*-10-hydroxy-1,1-dimethyloctahydrodibenzo[*a,d*]cyclohepten-7-one core structures (**5a–c**) was developed by employing the intramolecular Heck reaction as the crucial carbon–carbon bond-forming step, and the retrosynthetic analysis of the tricyclic systems is shown in Scheme 1.

The key step involves the formation of the cycloheptene ring (**6a–c**) by a palladium-catalyzed 7-*exo* cyclization¹¹ of the allyl *o*-bromobenzylcyclohexanols (**7a–c**) with the *exo*-methylene group in the correct position for oxidative transformation to the hydroxycycloheptenones (**5a–c**). The desired olefinic substrates **7a–c** for the intramolecular Heck reaction were prepared from the corresponding benzylcyclohexanols **8a–c**, which were obtained by Barbier coupling^{12a,b} of the benzyl chlorides **10a–c**

with the allylcyclohexanone **9**. The chlorides **10b** and **10c** were prepared from *p*-toluic acid and 1,2,4-trimethoxybenzene via the modification of known sequences of reactions^{13–17} involving intermediates **11–19** (schemes given in the Supporting Information).

The *gem*-dimethylcyclohexanone **9** was prepared (Scheme 2) by the conjugate addition of a methyl group¹⁸ to the allylcyclohexenone **21**,¹⁹ obtained in turn from **20**, the methyl ester analogue of Hagemann's ester.²⁰ Barbier reaction of **10a–c** with **9** was initially carried out under sonication according to the method of Abad et al.^{12a} The resulting crude mixture furnished the expected desired products (**8a–c**) in low yield, along with a lot of undesired byproducts including aromatic dimeric compounds. Switching on to reaction without sonication improved the yield of the desired products, isolated in pure form as single diastereoisomers as determined by spectral analysis. The *trans* OH/H stereochemistry in the products, deduced by analogy,¹⁰ received support from the X-ray structure determination of **24b** subsequently done.²¹ Thus, the Barbier reaction of **10a–c** with **9** appears to proceed diastereoselectively, in line with the addition of Grignard or alkylolithium reagents to 2-alkylcyclohexanones where a steric approach control of the addition has been suggested^{12b} to determine the course of reaction.

Treatment of each of the benzylcyclohexanols **8a–c** with NBS in acetonitrile²² led to the corresponding unstable bromomethylfurans **23a–c** via formation of the bromonium intermediate **22** followed by the intramolecular participation of the hydroxy group as depicted in Scheme 2. Further reaction of these intermediates **23a–c** with an excess of NBS gave the respective aromatic ring brominated products **24a–c**.

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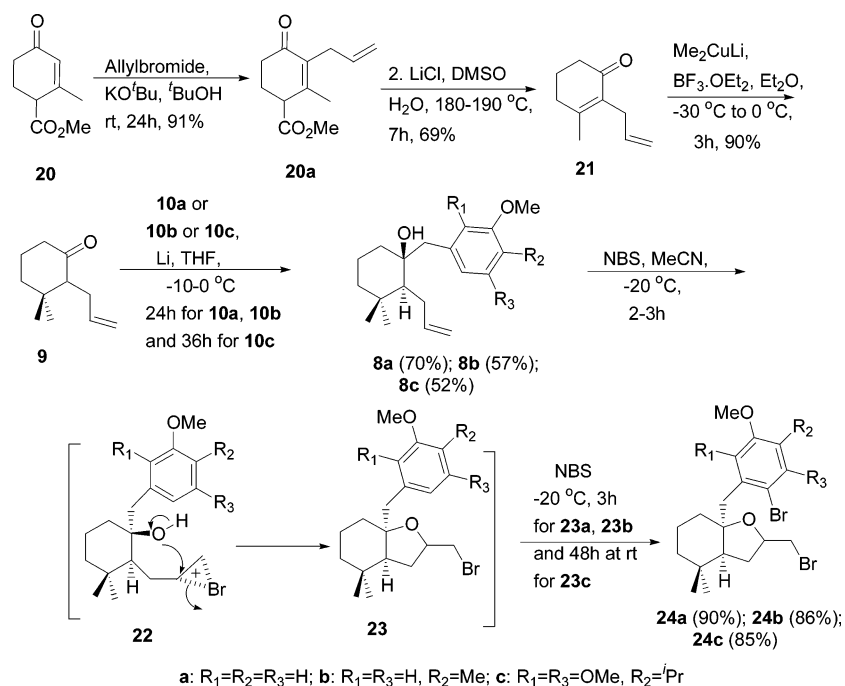
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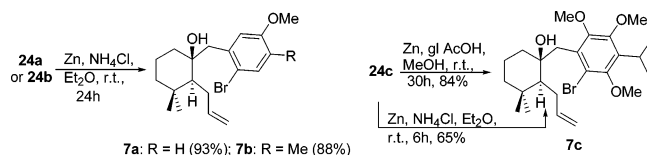
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SCHEME 2. Preparation of 24a–c



SCHEME 3. Preparation of 7a–c



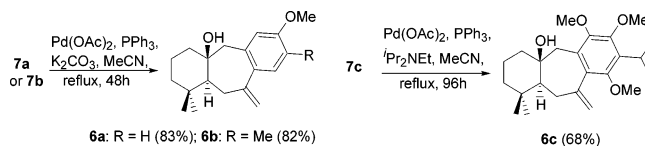
Regeneration of the allyl *o*-bromobenzylcyclohexanols (**7a–c**) from the bromomethylfuran derivatives (**24a–c**) was planned to be effected by using a zinc-mediated debromination fragmentation reaction.²³ Treatment of **24a** and **24b** with activated Zn dust and saturated NH₄-Cl solution indeed led to the allyl *o*-bromobenzyl cyclohexanols **7a** and **7b** in excellent yields (Scheme 3). In contrast, application of the same reaction to the highly substituted bromoaryl analogue **24c** proved troublesome and resulted in the formation of the expected fragmentation product **7c** along with the aromatic ring debrominated compound **8c**. This was probably due to the buttressing effect²⁴ caused by the fully substituted phenyl ring in **24c**, which makes the bromine atom relatively labile in comparison to that in the analogues **24a–b**. The aromatic ring debromination could be suppressed by reducing the reaction time to 6 h. Although the reaction was incomplete, remarkably the formation of **8c** was not observed, and the desired **7c** could be obtained in 65% yield (Scheme 3). However, fragmentation of **24c** with acetic acid and activated zinc in methanol at room temperature²⁵ proved to be the method of choice, affording **7c** in a substantially improved yield (84%). The

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SCHEME 4. Preparation of 6a–c



assignment of *trans*-stereochemistry to the allyl *o*-bromobenzylcyclohexanols **7a–c** and the corresponding precursors **8a–c** was based on the established structure of **24b**.

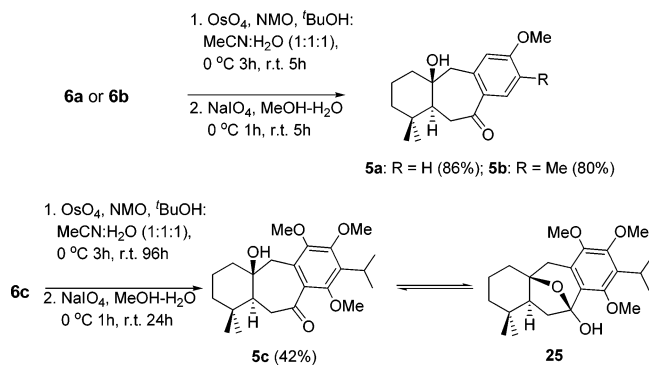
With the precursors **7a–c** in hand, the synthetic exercise was next directed toward the Heck reaction. To our gratification, the intramolecular Heck cyclization of **7a** and **7b** with Pd(OAc)₂, K₂CO₃, and PPh₃ in acetonitrile under reflux²⁶ led to the seven-membered *exo*-cyclic alkenes **6a** and **6b** in excellent yields (Scheme 4). Not surprisingly, the highly crowded bromobenzyl cyclohexanol **7c** produced under similar conditions only a small amount of the cyclized product **6c** with most of the starting material remaining unchanged. However, the 7-*exo* product **6c** could be obtained in 30% yield under forcing conditions (120 h reflux, 61% based on recovered starting material). Replacement of K₂CO₃ by triethylamine in acetonitrile under reflux for 120 h resulted in the formation of **6c** in 58% yield (95% based on recovered starting material). The yield of **6c** could be further improved (Scheme 4) by using diisopropylethylamine as the base and heating the reaction mixture under reflux for 96 h (68%, 93% based on recovered starting material).

Finally, oxidative cleavage²⁷ of the *exo*-olefins **6a** and **6b** with OsO₄ and NaIO₄ gave the respective *trans*-hydroxy ketones **5a** and **5b** in good yields (Scheme 5). The structure of **5a** was confirmed by X-ray diffraction analysis.²²

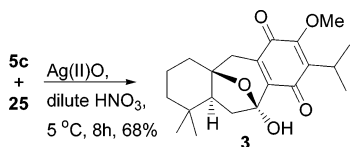
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SCHEME 5. Preparation of 5a–c



SCHEME 6. Preparation of 3



Similar oxidative cleavage²⁷ of the highly crowded *exo*-olefin **6c** produced the corresponding hydroxy ketone **5c**, albeit only in moderate yield (Scheme 5). Although it appeared that **5c** exists in equilibrium with the hemiketal form **25** in solution as revealed by the ¹H and ¹³C NMR spectra,²⁸ direct oxidation²⁹ of this mixture of **5c** and **25** with Ag(II)O in dilute HNO₃ afforded (±)-komaroviquinone (**3**) as the only isolable product (Scheme 6).

With an expedient synthesis of (±)-komaroviquinone (**3**) accomplished, the remaining task of converting the key intermediate hydroxycycloheptenone **5b** to (±)-faveline methyl ether (**1a**) was undertaken. While reaction of **5b** with BF₃·Et₂O in CH₂Cl₂ at 0 °C^{5c} led (Scheme 7) only to the olefin **26** (isofaveline methyl ether), the use of SOCl₂ in pyridine³⁰ (at -10 °C for 5 h) produced a mixture of the known tetrasubstituted olefinic ketone **27**³¹ along with **26** in a ratio of 2:1 (as shown by ¹H NMR). Finally, dehydration of **5b** with KHSO₄^{8b} furnished an easily separable mixture of (±)-faveline methyl ether (**1a**) and its isomer **26** (in 2:3 ratio as shown by ¹H NMR).

The present strategy for the synthesis of faveline methyl ether (**1a**) thus affords better overall yield of the product (4.48%) compared to that (1.95%) of Majetich et al.^{5c} and is also more flexible in approach to permit synthesis of many other related natural products.

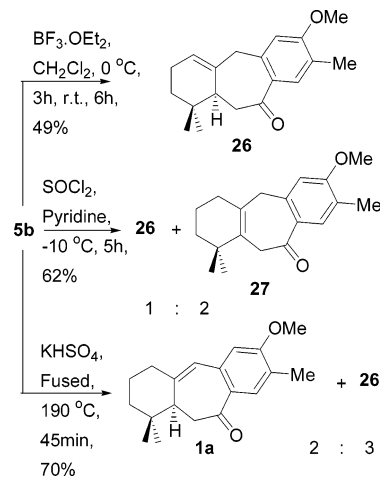
(28) The ¹H NMR spectrum of the hydroxy ketone **5c** in CDCl₃ solution showed additional peaks (see the Experimental Section) indicating the possible presence of two equilibrating forms. Recording the spectrum of a freshly prepared solution of **5c** in C₅D₅N, however, suggested the presence of only one form (**5c**). The ¹³C NMR spectrum was recorded later to establish if the keto (**5c**) or the hemiketal form (**25**) was present. Unfortunately, conversion to the other form (**25**) had taken place in the meantime and the solution showed peaks both for a carbonyl carbon (δ 207.4) and a hemiketal carbon (δ 102.9), with the former about four times more intense than the latter. The ¹H NMR spectrum of the same solution, recorded again, now showed additional peaks supporting the presence of both the forms. The exchange appears to occur at a faster rate in CDCl₃ solution (where the presence of traces of acid is not unexpected) and after a week's time, the minor form appeared to have become the major one.

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SCHEME 7. Dehydration of 5b



Conclusion

The facile intramolecular Heck reaction of the olefinic intermediates **7a–c** provides a simple convergent route to rearranged diterpenoids incorporating a tricyclic dibenzo[*a,d*]cycloheptenone skeleton and led to the first total synthesis of (±)-komaroviquinone (**3**) through (±)-coulterone dimethyl ether (**5c**). The methodology also constitutes a convenient alternative route to (±)-faveline methyl ether (**1a**).

Experimental Section

2-Allyl-3,3-dimethylcyclohexanone (9). To a stirred suspension of CuI¹⁸ (14 g, 73.5 mmol) in dry Et₂O (86 mL) was added MeLi (75 mL, 1.6 M solution in Et₂O, 120 mmol) dropwise during 30 min (-25 °C). The resulting yellow suspension was cooled to -50 °C, and BF₃·OEt₂ (10.2 mL, 80.5 mmol) was added. After 10 min, the temperature was raised to -30 °C, a solution of **21** (3 g, 20 mmol) in Et₂O (25 mL) added dropwise during 1 h, and stirring was continued for 30 min at -30 °C. An additional aliquot of BF₃·OEt₂ (10.2 mL, 80.5 mmol) was added to the mixture and stirring continued for 2 h at -30 °C. The temperature of the bath was allowed to warm to -10 °C, and thereafter the reaction was quenched by dropwise addition of saturated NH₄Cl solution. The reaction mixture was filtered and the residue thoroughly washed with Et₂O. The combined organic extracts were washed with saturated NH₄Cl solution, saturated Na₂S₂O₃ solution, and brine and dried. After removal of the solvent, the crude product was purified by column chromatography over silica gel (100–200 mesh) using 2–4% EtOAc in hexane as eluent to afford **9** (3 g, 90%) as a colorless oil: IR (neat) ν 1710 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.79 (s, 3H), 1.07 (s, 3H), 1.57–1.66 (m, 2H), 1.71–1.92 (m, 2H), 2.03–2.11 (m, 1H), 2.21–2.36 (m, 3H), 2.40–2.47 (m, 1H), 4.90–4.98 (m, 1H), 5.02–5.03 (m, 1H), 5.70–5.83 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 21.7, 22.8, 28.3, 29.2, 38.9, 39.4, 41.0, 60.6, 114.9, 137.6, 212.2; EI-MS *m/z* 166 (M⁺, 66), 111 (61), 95 (84), 69 (100). Anal. Calcd for C₁₁H₁₈O: C, 79.46; H, 10.91. Found: C, 79.32; H, 11.08.

(1S*,2S*)-2-Allyl-1-(3-methoxybenzyl)-3,3-dimethylcyclohexanol (8a). To a well-stirred suspension of small chips of Li (590 mg, 85 mmol) in dry THF (160 mL) was added dropwise a mixture of **9** (2.6 g, 15.7 mmol) and **10a** (1.4 g, 8.9 mmol) in dry THF (50 mL) during 4 h at -10 °C. The reaction mixture was then stirred at 0 °C for 24 h. It was filtered and quenched with cold saturated solution of NH₄Cl. The layers were separated, and the organic part was evaporated under reduced pressure; the residue was taken in EtOAc (50 mL). The aqueous part was extracted with EtOAc (2 × 20 mL); the

combined organic extracts were washed with brine, dried, and concentrated. Column chromatography of the residue over silica gel (100–200 mesh) using 2–5% EtOAc in hexane yielded **8a** (1.7 g, 70%) as a colorless oil: IR (neat) ν 3573, 2934, 1597, 1488, 1460, 1367, 1262, 1155 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 0.94 (s, 3H), 1.01 (s, 3H), 1.15–1.24 (m, 2H), 1.28–1.46 (m, 3H), 1.51–1.65 (m, 2H), 2.21–2.29 (m, 1H), 2.38 (d, $J = 13$ Hz, 1H), 2.50–2.58 (m, 1H), 3.12 (d, $J = 13$ Hz, 1H), 3.79 (s, 3H), 4.96 (ddd, $J = 2, 3, 10$ Hz, 1H), 5.09 (ddd, $J = 2, 3, 17$ Hz, 1H), 5.89–6.02 (m, 1H), 6.72–6.80 (m, 3H), 7.21 (t, $J = 8$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 17.7, 21.5, 30.1, 32.2, 35.0, 38.0, 41.9, 48.1, 53.0, 54.9, 74.4, 111.5, 113.8, 116.3, 123.0, 128.9, 138.7, 142.0, 159.3; EI-MS m/z 288 (M^+ , 2), 273 (11), 167 (100). Anal. Calcd for $\text{C}_{19}\text{H}_{28}\text{O}_2$: C, 79.12; H, 9.78. Found: C, 79.31; H, 9.65.

(2S*,3aS*,7aS*)-7a-(2-Bromo-5-methoxybenzyl)-2-bromomethyl-4,4-dimethyloctahydrobenzofuran (24a). To a well-stirred solution of **8a** (1.17 g, 4.06 mmol) in dry CH_3CN (20 mL) was added NBS²² (0.795 g, 4.46 mmol) portionwise at -20 °C. The reaction mixture was stirred for 2 h at the same temperature. Then another lot of NBS (0.795 g, 4.46 mmol) was added and the reaction mixture further stirred for 2 h at -20 °C. Aqueous $\text{Na}_2\text{S}_2\text{O}_3$ solution (10%) was then added, and the layers were separated. The organic part was evaporated under reduced pressure, and the crude product was extracted with Et_2O . The Et_2O extract was washed with $\text{Na}_2\text{S}_2\text{O}_3$ solution (5%, 50 mL) and brine, dried, and then evaporated to leave an oil. The crude oil was chromatographed over silica gel (100–200 mesh) using 1–2% EtOAc in hexane to yield **24a** (1.6 g, 88%) as an oil, which solidified after cooling: mp 70–71 °C; IR (KBr) ν 2958, 1590, 1467 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 0.95 (s, 3H), 1.17 (s, 3H), 1.14–1.25 (m, 3H), 1.34–1.45 (m, 1H), 1.47–1.62 (m, 1H), 1.67–1.82 (m, 1H), 1.85–1.94 (m, 2H), 2.08–2.21 (m, 1H), 2.81 (d, $J = 14$ Hz, 1H), 3.30 (dd, $J = 7, 10$ Hz, 1H), 3.40 (dd, $J = 5, 10$ Hz, 1H), 3.52 (d, $J = 14$ Hz, 1H), 3.78 (s, 3H), 4.15–4.22 (m, 1H), 6.64 (dd, $J = 3, 9$ Hz, 1H), 7.16 (d, $J = 3$ Hz, 1H), 7.39 (d, $J = 9$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 19.9, 28.8, 30.5, 31.1, 32.6, 33.2, 33.7, 37.6, 44.5, 53.1, 55.3, 74.3, 85.0, 114.2, 116.6, 118.6, 132.8, 138.9, 158.1; EI-MS m/z 448 (M^+ for $2 \times \text{Br}^{81}$, 0.02), 446 (M^+ for Br^{79} and Br^{81} , 0.04), 444 (M^+ for $2 \times \text{Br}^{79}$, 0.02), 247 (66), 245 (62), 69 (100). Anal. Calcd for $\text{C}_{19}\text{H}_{26}\text{Br}_2\text{O}_2$: C, 51.14; H, 5.87. Found: C, 51.06; H, 5.99.

(2S*,3aS*,7aS*)-7a-(2-Bromo-4-isopropyl-3,5,6-trimethoxybenzyl)-2-bromomethyl-4,4-dimethyloctahydrobenzofuran (24c). To a well-stirred solution of **8c** (2 g, 5.13 mmol) in dry CH_3CN (170 mL) was added NBS²² (1.1 g, 6.18 mmol) portionwise at -20 °C. The reaction mixture was stirred for 3 h at the same temperature. Then an additional lot of *N*-bromosuccinimide (1.1 g, 6.18 mmol) was added and stirring continued for another 48 h at room temperature. After usual workup, the product was chromatographed over silica gel (100–200 mesh) using 1–2% EtOAc in hexane to yield **24c** (2.39 g, 85%) as a white solid: mp 116–118 °C; IR (KBr) ν 2955, 1581, 1450 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 0.83–0.92 (m, 1H), 0.97 (s, 3H), 1.18 (s, 3H), 1.26–1.46 (m, 1H), 1.31 (d, $J = 7$ Hz, 6H), 1.51–1.74 (m, 3H), 1.75–1.83 (m, 1H), 1.93–2.19 (m, 3H), 3.01 (d, $J = 13$ Hz, 1H), 3.21 (t, $J = 9$ Hz, 1H), 3.35–3.49 (m, 3H), 3.73 (s, 3H), 3.76 (s, 3H), 3.84 (s, 3H), 4.08–4.15 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 19.6, 20.9, 22.0, 26.8, 28.6, 31.2, 31.8, 32.5, 32.9, 33.6, 36.6, 39.6, 53.2, 59.4, 60.0, 61.3, 75.2, 85.5, 116.8, 131.1, 134.5, 149.3, 151.0, 151.7; EI-MS m/z 550 (M^+ for $2 \times \text{Br}^{81}$, 1), 548 (M^+ for Br^{79} and Br^{81} , 3), 546 (M^+ for $2 \times \text{Br}^{79}$, 1), 533 (3), 505 (4), 245 (100). Anal. Calcd for $\text{C}_{24}\text{H}_{36}\text{Br}_2\text{O}_4$: C, 52.57; H, 6.62. Found: C, 52.66; H, 6.57.

(1S*,2S*)-2-Allyl-1-(2-bromo-5-methoxybenzyl)-3,3-dimethylcyclohexanol (7a). A mixture of **24a** (1 g, 2.24 mmol), zinc²³ (2.5 g, 38.2 mmol), and NH_4Cl solution (10 mL, 50%) in Et_2O (15 mL) was vigorously stirred at room temperature for 6 h. Then another lot of zinc (2.5 g, 38.2 mmol) was added, and the reaction mixture was stirred for 6 h. The mixture was

diluted with Et_2O (100 mL) and filtered. The organic part was washed with brine, dried, and concentrated. The crude product was chromatographed over silica gel (100–200 mesh) using 2–5% EtOAc in hexane to provide **7a** (720 mg, 88%) as white solid: mp 62–63 °C; IR (KBr) ν 3523, 2936, 1587 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 0.95 (s, 3H), 1.01 (s, 3H), 1.23–1.62 (m, 9H), 2.24–2.31 (m, 1H), 2.48–2.58 (m, 1H), 2.65 (d, $J = 13$ Hz, 1H), 3.27 (d, $J = 13$ Hz, 1H), 3.77 (s, 3H), 4.98 (dd, $J = 1, 10$ Hz, 1H), 5.12 (dd, $J = 1, 17$ Hz, 1H), 5.90–6.04 (m, 1H), 6.65 (dd, $J = 3, 9$ Hz, 1H), 6.84 (d, $J = 3$ Hz, 1H), 7.42 (d, $J = 9$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 17.7, 21.7, 30.2, 32.2, 35.2, 37.4, 41.9, 46.9, 53.7, 55.4, 76.1, 113.8, 114.1, 116.8, 117.9, 133.4, 138.4, 141.8, 158.5; EI-MS m/z 368 (M^+ for Br^{81} , 19), 366 (M^+ for Br^{79} , 11), 353 (91), 351 (100). Anal. Calcd for $\text{C}_{19}\text{H}_{27}\text{BrO}_2$: C, 62.13; H, 7.41. Found: C, 62.29; H, 7.56.

(1S*,2S*)-2-Allyl-1-(2-bromo-4-isopropyl-3,5,6-trimethoxybenzyl)-3,3-dimethylcyclohexanol (7c). **Method A**. A mixture of **24c** (1 g, 1.82 mmol), activated zinc²³ (4.47 g, 68.4 mmol), NH_4Cl solution (40 mL, 50%), and ether (40 mL) was vigorously stirred at room temperature for 6 h. The reaction mixture was diluted with ether (100 mL) and filtered. After usual workup, the crude residue was flash chromatographed over silica gel (230–400 mesh); 0.5–1% EtOAc in hexane eluted **7c** (554 mg, 65%) as a colorless oil (which solidified on cooling) while 2–4% EtOAc in hexane eluted the starting material **24c** (275 mg). **7c**: mp 80–81 °C (crystallized from MeOH); IR (KBr) ν 3484, 2935, 1452 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 0.83–1.00 (m, 1H), 0.94 (s, 3H), 1.00 (s, 3H), 1.12–1.68 (m, 7H), 1.31 (d, $J = 7$ Hz, 3H), 1.33 (d, $J = 7$ Hz, 3H), 2.28–2.32 (m, 1H), 2.44–2.54 (m, 1H), 2.85 (d, $J = 14$ Hz, 1H), 3.32 (d, $J = 14$ Hz, 1H), 3.38–3.50 (m, 1H), 3.74 (s, 3H), 3.81 (s, 3H), 3.86 (s, 3H), 4.96 (d, $J = 10$ Hz, 1H), 5.10 (d, $J = 17$ Hz, 1H), 5.96–6.05 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 18.1, 21.6, 21.9, 22.0, 26.8, 30.6, 32.2, 35.4, 37.5, 42.1, 43.0, 54.4, 59.8, 60.5, 61.4, 76.7, 113.6, 116.5, 130.8, 134.9, 142.5, 148.3, 151.7, 151.9; EI-MS m/z 470 (M^+ for Br^{81} , 2), 468 (M^+ for Br^{79} , 2), 304 (100). Anal. Calcd for $\text{C}_{24}\text{H}_{37}\text{BrO}_4$: C, 61.40; H, 7.94. Found: C, 61.29; H, 8.06.

Method B. To a solution of **24c** (20 mg, 0.04 mmol) in MeOH (0.4 mL) were added freshly activated zinc (20 mg, 0.31 mmol) and glacial acetic acid (0.3 mL), and the mixture was stirred at room temperature.²⁵ After 6 h, an additional lot of freshly activated zinc (30 mg, 0.47 mmol) and MeOH (0.4 mL) was added, and the stirring was continued for another 24 h. The reaction mixture was filtered, diluted with H_2O , and extracted with EtOAc (2×10 mL). The combined organic extracts were washed with saturated NaHCO_3 solution and brine, dried, and concentrated. The crude product was purified by column chromatography over silica gel (100–200 mesh) using 2–4% EtOAc in hexane to furnish **7c** (14.5 mg, 84%).

(4aS*,11aS*)-7-Methoxy-1,1-dimethyl-10-methylene-1,2,3,4,5,10,11,11a-octahydrodibenzo[*a,d*]cyclohepten-4-ol (6a). A mixture of **7a** (500 mg, 1.36 mmol), K_2CO_3 (1.13 g, 8.2 mmol), and PPh_3 (140 mg, 0.53 mmol) in dry CH_3CN (50 mL) was degassed by sonication for 30 min. $\text{Pd}(\text{OAc})_2$ (60 mg, 0.267 mmol) was added to the reaction mixture. The mixture was stirred for 1 h at room temperature and then heated to reflux²⁶ for 24 h under nitrogen atmosphere. The mixture was cooled and filtered through Celite, and the residue washed with dry ethyl acetate. The combined filtrate was evaporated under reduced pressure to leave a residue. The crude product was chromatographed over silica gel (100–200 mesh) using 2% EtOAc in hexane to afford **6a** (325 mg, 83%) as a colorless oil: IR (neat) ν 3473, 2932, 1606 cm^{-1} ; ^1H NMR (300 MHz, CD_3OD) δ 0.94 (s, 3H), 0.96 (s, 3H), 1.23–1.53 (m, 6H), 1.67–1.73 (m, 1H), 1.90–1.94 (m, 1H), 2.36–2.45 (m, 1H), 2.53 (d, $J = 13$ Hz, 1H), 2.64 (d, $J = 14$ Hz, 1H), 2.76 (d, $J = 14$ Hz, 1H), 3.77 (s, 3H), 4.96 (d, $J = 2$ Hz, 1H), 5.07 (s, 1H), 6.65 (d, $J = 3$ Hz, 1H), 6.73 (dd, $J = 3, 8$ Hz, 1H), 7.10 (d, $J = 8$ Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 19.6, 22.0, 32.4, 32.8, 35.1, 42.1, 43.3, 52.7, 55.6, 56.9, 72.8, 112.3, 112.6, 117.6, 129.3, 137.9,

138.4, 153.9, 160.3; EI-MS m/z 286 (M^+ , 53), 202 (64), 167 (100). Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.75; H, 9.21.

(4aS*,11aS*)-8-Isopropyl-6,7,9-trimethoxy-1,1-dimethyl-10-methylene-1,2,3,4,5,10,11,11a-octahydrodibenzo[*a,d*]cyclohepten-4a-ol (6c). **Method A.** A mixture of **7c** (40 mg, 0.09 mmol), K_2CO_3 (70.6 mg, 0.51 mmol), and PPh_3 (8.9 mg, 0.03 mmol) in dry CH_3CN (5 mL) was degassed by sonication for 30 min. $Pd(OAc)_2$ (3.8 mg, 0.02 mmol) was added to the reaction mixture, and the mixture stirred for 1 h at room temperature. It was then heated²⁶ at 90 °C for 120 h. Usual workup gave a crude product which was chromatographed over silica gel (60–120 mesh). Eluting with 1–2% EtOAc in hexane afforded starting material **7c** (20 mg), while 2–4% EtOAc in hexane furnished the cyclized product **6c** (10 mg, 30%; 61% based on recovered starting material) as a thick oil, which solidified on cooling: mp 124–126 °C (crystallized from dry methanol); IR (KBr) ν 3478, 2936, 1581 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$) δ 0.92 (s, 3H), 1.01 (s, 3H), 1.22–1.35 (m, overlapped, 2H), 1.32 (d, $J = 7$ Hz, 3H), 1.34 (d, $J = 7$ Hz, 3H), 1.43–1.56 (m, 3H), 1.64 (s, 1H), 1.78–2.04 (m, 3H), 2.46 (d, $J = 14$ Hz, 1H), 2.69 (brd, $J = 13$ Hz, 1H), 3.14 (d, $J = 14$ Hz, 1H), 3.45 (sep, $J = 7$ Hz, 1H), 3.61 (s, 3H), 3.76 (s, 3H), 3.84 (s, 3H), 5.08 (s, 1H), 5.35 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.7, 21.4, 22.07, 22.10, 25.9, 32.1, 33.1, 34.3, 41.6, 42.0, 42.2, 59.7, 60.4, 60.5, 61.0, 70.7, 115.5, 126.8, 133.9, 145.8, 148.5, 150.5, 151.0 [one carbon signal could not be identified due to overlap]; EI-MS m/z 388 (M^+ , 100), 247 (11), 224 (16). Anal. Calcd for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 74.06; H, 9.27.

Method B. A mixture of **7c** (280 mg, 0.60 mmol), triethylamine (362.5 mg, 0.5 mL, 3.58 mmol), and PPh_3 (62.6 mg, 0.24 mmol) in dry acetonitrile (25 mL) was sonicated for 30 min. Palladium acetate (26.8 mg, 0.12 mmol) was added to the reaction mixture and the mixture stirred for 1 h at room temperature. It was then heated at 90 °C for 120 h. After usual workup, the crude product was chromatographed over silica gel (60–120 mesh) to afford the starting material **7c** (110 mg) and **6c** (134 mg, 58%; 95% based on recovered starting material).

Method C. A mixture of **7c** (445 mg, 0.95 mmol), diisopropylethylamine (1.23 g, 1.65 mL, 9.49 mmol), and PPh_3 (99.5 mg, 0.38 mmol) in dry CH_3CN (40 mL) was sonicated for 30 min. $Pd(OAc)_2$ (42.6 mg, 0.19 mmol) was added, and the mixture was stirred for 1 h at room temperature. It was then heated at 90 °C for 96 h. After usual workup, the crude product was chromatographed over silica gel (60–120 mesh) to afford **7c** (120 mg) and **6c** (250 mg, 68%; 93% based on recovered starting material).

(4aS*,11aS*)-4a-Hydroxy-7-methoxy-1,1-dimethyl-1,2,3,4,4a,5,11,11a-octahydrodibenzo[*a,d*]cyclohepten-10-one (5a). To a solution of **6a** (200 mg, 0.7 mmol) in a mixture of t BuOH (9 mL), acetone (9 mL), and H_2O (9 mL) was added N -methylmorpholine oxide (495 μ L, 50% aqueous solution). Three small crystals of OsO_4 ²⁷ were then added at 0 °C. The mixture was stirred for 5 h at 0 °C and for 2 h at room temperature. A solution of Na_2SO_3 (14 mL, 45% aqueous solution) was added, and the reaction mixture was stirred for 45 min. The solid was filtered and the filtrate evaporated to leave a residue, which was taken up in EtOAc. The solid mass was dissolved in H_2O and extracted with EtOAc (50 mL). The combined organic extracts were washed with brine and dried, and solvent was removed in a rotary evaporator under reduced pressure to leave the crude trihydroxy compound as a white solid, which was directly used in the next step without purification.

To the solution of the white solid in MeOH (10 mL) was added a solution of $NaIO_4$ (prepared by dissolving 222 mg in 3 mL of water) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 2 h, then at room temperature for 3 h, and filtered. The residue was dissolved in H_2O and extracted with EtOAc (100 mL). The combined organic extracts were washed

with brine and then dried. The solvent was evaporated under reduced pressure to give a white solid. The crude solid was chromatographed over silica gel (60–120 mesh) using 10–15% ethyl acetate in hexane to afford **5a** as a white solid (180 mg, 86%): mp 125–127 °C (crystallized from 5% EtOAc in hexane); IR (KBr) ν 3470, 2937, 1657 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$) δ 0.82 (s, 3H), 0.99 (s, 3H), 1.09–1.18 (m, 1H), 1.39–1.73 (m, 5H), 1.82–1.95 (m, 2H), 2.62 (d, $J = 14$ Hz, 1H), 2.67 (d, $J = 9$ Hz, 1H), 2.85 (2 \times d, $J = 11, 18$ Hz, 1H), 3.11 (d, $J = 14$ Hz, 1H), 3.85 (s, 3H), 6.62 (d, $J = 2$ Hz, 1H), 6.84 (brd, $J = 7$ Hz, 1H), 7.70 (d, $J = 9$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.5, 21.5, 32.1, 33.7, 38.5, 39.1, 40.7, 48.3, 49.9, 55.4, 73.4, 111.8, 115.9, 131.0, 131.3, 139.5, 162.5, 205.3; EI-MS m/z 288 (M^+ , 28), 149 (100). Anal. Calcd for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 75.09; H, 8.31.

(4aS*,11aS*)-4a-Hydroxy-8-isopropyl-6,7,9-trimethoxy-1,1-dimethyl-1,2,3,4,4a,5,11,11a-octahydrodibenzo[*a,d*]cyclohepten-10-one (5c). To a solution of **6c** (166 mg, 0.43 mmol) in a mixture of t BuOH (7 mL), acetone (7 mL), and H_2O (7 mL) was added N -methylmorpholine oxide (1 mL, 50% aqueous solution). OsO_4 ²⁷ (22 mg, 0.866 mmol, 20 mol %) was then added at 0 °C. The mixture was stirred at 0 °C for 3 h and then at room temperature for 96 h. A solution of Na_2SO_3 (40 mL, 45% aqueous solution) was added to the reaction mixture, which was stirred for 1 h. After usual workup as described for **5a**, the crude product obtained was chromatographed over silica gel (60–120 mesh). Elution with 2% EtOAc in hexane furnished the starting olefin **6c** (76 mg), while 30% ethyl acetate in petroleum ether afforded the trihydroxy compound (96 mg) (as revealed from 1H NMR and IR spectra), which was directly used in the next step.

To the solution of above trihydroxy compound (95 mg) in MeOH (7 mL) was added a solution of $NaIO_4$ (prepared by dissolving 175 mg in 2 mL of water) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 2 h and then at room temperature for 24 h and filtered. Usual workup furnished the crude product which was chromatographed over silica gel (60–120 mesh) using 10–15% EtOAc in hexane to afford **5c** (70 mg, 42% in two steps; 77% based on recovered starting material **6c**) as a white solid: mp 138–140 °C (crystallized from 2% ethyl acetate in petroleum ether); IR (KBr) ν 3484, 2944, 1673, 1574 cm^{-1} ; 1H NMR (300 MHz, pyridine- d_5) δ 0.85 (s, 3H), 1.07 (brd t, $J = 12$ Hz, 1H), 1.21 (s, 3H), 1.37 (d, $J = 7$ Hz, 3H), 1.39 (d, $J = 7$ Hz, 3H), 1.35–1.48 (m, overlap, 2H), 1.61–1.71 (m, 1H), 1.80 (d, $J = 11$ Hz, 1H), 2.02 (d, $J = 13$ Hz, 1H), 2.14–2.23 (m, 1H), 2.86 (d, $J = 17$ Hz, 1H), 3.06–3.10 (m, 1H), 3.21 (m, 1H), 3.39 (dd, $J = 12, 16$ Hz, 1H), 3.58 (sept, $J = 7$ Hz, 1H), 3.77 (s, 3H), 3.88 (s, 6H), 5.80 (s, D_2O exchangeable, 1H); ^{13}C NMR (75 MHz, pyridine- d_5) [a mixture of **5c** (major) and the hemiketal **25** (minor); only the major peaks shown] δ 19.2, 22.02, 22.06, 22.09, 32.1, 34.1, 40.4, 40.6, 41.6, 60.4, 63.4, 72.5, 128.1, 134.3, 147.6, 151.8, 154.4, 207.4 [additional peaks at δ 78.6 and 102.8 are assignable to **25**]; EI-MS m/z 390 (M^+ , 73), 267 (29), 251 (100). Anal. Calcd for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.87; H, 8.83.

(±)-Komaroviquinone (3). To a stirred solution containing **5c** and **25** (28 mg, 0.07 mmol) in dioxane (1.4 mL, redistilled over sodium) and silver(II) oxide²⁹ (36 mg, 0.29 mmol) was added HNO_3 (717 μ L, 6 N) at 5 °C. After the mixture was stirred for 4 h at 5 °C, another portion of silver(II) oxide (36 mg) and HNO_3 (717 μ L, 6 N) was added and the stirring continued for 4 h at the same temperature. The mixture was diluted with water and extracted with EtOAc (50 mL). The organic extract was washed with brine, dried, and evaporated to give an orange oil. The product was purified over silica gel (60–120 mesh) using 5% EtOAc in hexane to give **3** (18 mg, 69%) as a yellow-orange solid: mp 123–124 °C [natural (+)-**3** was reported⁴ as an orange oil]; IR (KBr) ν 3404, 2944, 1651, 1606, 1455 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$) δ 0.86 (s, 3H), 0.95 (s, 3H), 1.21 (d, $J = 7$ Hz, 3H), 1.21 (d, $J = 7$ Hz, 3H), 1.11–1.25 (m, overlapped, 1H), 1.56–1.66 (m, 2H), 1.68–1.75 (m, 2H), 1.78–1.90 (m, 1H), 1.99–2.08 (m, 2H), 2.25 (d, $J =$

19 Hz, 1H), 2.30 (dd, $J = 13$, 9 Hz, 1H), 2.55 (d, $J = 19$ Hz, 1H), 3.23 (septet, $J = 7$ Hz, 1H), 3.98 (s, 3H), 5.98 (brs, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 15.6, 20.38, 20.42, 24.3, 27.0, 29.8, 30.3, 31.3, 32.0, 39.0, 45.7, 51.5, 61.1, 79.3, 100.9, 137.1, 138.9, 142.2, 156.1, 183.6, 189.1 [^1H NMR and ^{13}C NMR of (\pm)-**3** are identical with those of the natural (+)-**3**]; EI-MS m/z 360 (M^+ , 16), 316 (100), 301 (40). Anal. Calcd for $\text{C}_{21}\text{H}_{28}\text{O}_5$: C, 69.98; H, 7.83. Found: C, 69.83; H, 7.96.

Reaction of 5b with $\text{BF}_3 \cdot \text{OEt}_2$: Formation of (11aS*)-7-Methoxy-1,1,8-trimethyl-1,2,3,5,11,11a-hexahydrodibenzo[*a,d*]cyclohepten-10-one (26). To a stirred solution of **5b** (20 mg, 0.066 mmol) in dry CH_2Cl_2 (2 mL) was added $\text{BF}_3 \cdot \text{OEt}_2$ (10 μL) at 0 $^\circ\text{C}$.^{5c} The reaction mixture was stirred at 0 $^\circ\text{C}$ for 3 h and then at room temperature for 6 h. The reaction mixture was quenched with saturated NaHCO_3 solution (5 mL) and extracted with CH_2Cl_2 (20 mL). The organic part was washed with brine and dried and the solvent evaporated to give a yellow oil. The crude oil was purified by preparative TLC (multiple run in 2% ethyl acetate–hexane) to give **26** (9.3 mg, 49%) as the only isolable product as a white solid: mp 135–136 $^\circ\text{C}$ (crystallized from EtOAc in hexane); IR (KBr) ν 2916, 1654, 1601 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 0.80 (s, 3H), 0.99 (s, 3H), 1.37–1.39 (m, 2H), 2.03–2.19 (m, 3H), 2.19 (s, 3H), 2.59 (dd, $J = 11$, 17 Hz, 1H), 2.88 (d, $J = 17$ Hz, 1H), 3.31 (d, $J = 15$ Hz, 1H), 3.83 (d, $J = 15$ Hz, 1H, overlapped by 3H singlet at 3.89), 3.89 (s, 3H), 5.67 (s, 1H), 6.60 (s, 1H), 7.73 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 15.6, 19.2, 23.1, 29.4, 32.4, 37.2, 42.8, 43.1, 43.7, 55.5, 110.3, 121.9, 125.2, 128.8, 131.8, 135.6, 140.4, 161.6, 203.0; EI-MS m/z 284 (M^+ , 61), 256 (97), 200 (100). Anal. Calcd for $\text{C}_{19}\text{H}_{24}\text{O}_2$: C, 80.24; H, 8.51. Found: C, 80.39; H, 8.46.

Reaction of 5b with SOCl_2 in Pyridine: Formation of 26 and 7-Methoxy-1,1,8-trimethyl-1,2,3,4,5,11-hexahydrodibenzo[*a,d*]cyclohepten-10-one (27). To a stirred solution of **5b** (20 mg, 0.07 mmol) in pyridine (714 μL) was added SOCl_2 ³⁰ (72 μL , 0.99 mmol) at -10 $^\circ\text{C}$. The reaction mixture was stirred for 5 h at the same temperature. The reaction mixture was diluted with Et_2O (25 mL), and the organic part was washed successively with HCl (10 mL, 5%), water, and brine, and dried. The solvent was evaporated to give a mixture

of **26** and **27** as an oil. The crude oil was purified by preparative TLC (multiple run in 2% EtOAc–hexane) to give **26** (5.6 mg, 30%) and **27**³¹ (6 mg, 32%) as an oil.

Reaction of 5b with KHSO_4 : Formation of (\pm)-Faveline Methyl Ether (1a) and 26. The keto alcohol **5b** (40 mg, 0.132 mmol) was fused with KHSO_4 ⁸ (40 mg, 0.294 mmol) at 190 $^\circ\text{C}$ under N_2 atmosphere for 45 min, and the resulting mixture was sublimed at 140–145 $^\circ\text{C}$ (0.1 mm of Hg) to give a solid. The product was purified by preparative TLC (multiple run in 2% EtOAc–hexane) to give **1a** (10.8 mg, 28%) and **26** (15.8 mg, 42%) as white solids.

1a: mp 137–138 $^\circ\text{C}$ [lit.^{8b} mp 138–140 $^\circ\text{C}$]; IR (KBr) ν 2929, 1655, 1600 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 0.75 (s, 3H), 1.12 (s, 3H), 1.42–1.62 (m, 2H), 1.64–1.76 (m, 2H), 2.18 (s, 3H), 2.30–2.38 (m, 3H), 3.01–3.03 (m, 2H), 3.87 (s, 3H), 6.29 (s, 1H), 6.59 (s, 1H) 7.62 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 15.5, 20.7, 25.1, 28.9, 38.4, 40.2, 42.5, 43.0, 51.3, 55.4, 112.9, 124.7, 125.5, 129.7, 131.2, 136.3, 147.7, 160.9, 201.3; EI-MS m/z 284 (M^+ , 100), 215 (81), 202 (94). Anal. Calcd for $\text{C}_{19}\text{H}_{24}\text{O}_2$: C, 80.24; H, 8.51. Found: C, 80.11; H, 8.65.

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Supporting Information Available: Schemes 2 and 3 (containing compounds **11–19**); experimental procedures for **5b**, **6b**, **7b**, **8b,c**, **10b,c**, **12–19**, **20a**, **21**, and **24b**; ^1H NMR and ^{13}C NMR spectral data of compounds **1a**, **3**, **5a–c**, mixture of **5c** and **25**, **6a–c**, **7a–c**, **8a–c**, **24a–c**, and **26**; IR spectral data of **3**; and ORTEP diagrams of **5a** and **24b**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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