Convenient Formal Synthesis of (±)-Cuparene, (±)-Enokipodins A and B, and (±)-Cuparene-1,4-Quinone

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Abstract: A Brønsted or Lewis acid mediated semi-pinacolic rearrangement effected on the diastereomers of cyclobutanol derivatives leads efficiently to useful intermediates in the synthesis of cuparene-type sesquiterpenes. The cyclobutanols are themselves easily obtainable from cyclopropyl phenyl sulfide.

Key words: antifugal agents, aldol reactions, rearrangements, ring expansion, ketones

Cuparene (**1**) (Figure 1), found in the essential oil of *Glehnia littoralis*,[1] shows interesting anti-inflammatory activity.[2] Likewise, enokipodins A (**2**), B (**3**)[3] and related compounds such as cuparene-1,4-quinone (**4**)[4] isolated in 2000 from a mushroom (*Flammulina velutipes*) exhibits antimicrobial and antifungal activities.

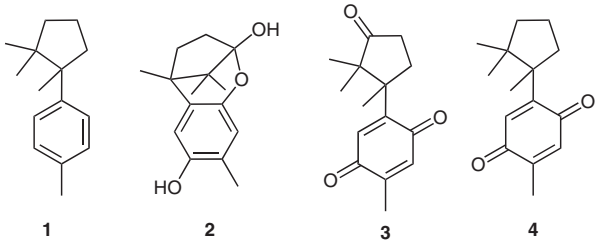
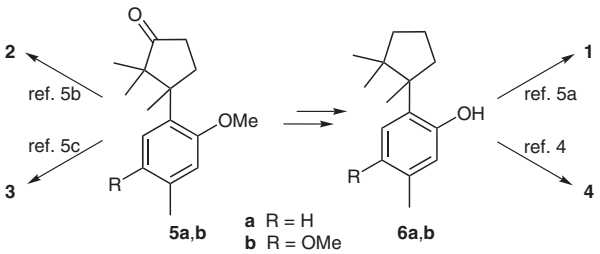


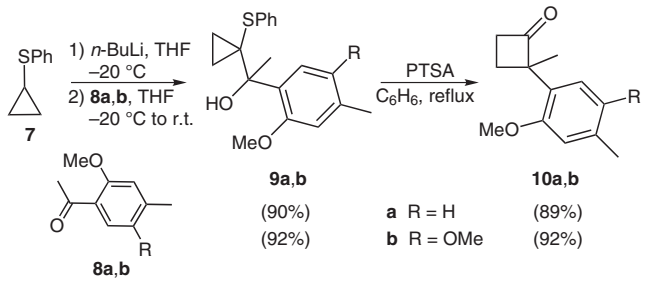
Figure 1 Cuparene-type sesquiterpenes

According to the literature,[5] all these natural compounds can be synthesized from common intermediates **5a**,**b** possessing the same basic 3-aryl-4-methylphenyl-2,2,3-trimethylcyclopentanone skeleton (Scheme 1).

Applying a successful method previously described by us in the synthesis of monoterpenoids fragranol and grandisol,[6] cyclopropyl phenyl sulfide **7**[7] gave the carbinols **9a**,**b**, after metalation and reaction with the methyl ketones **8a**[8] or **8b**,[9] respectively. The carbinols then underwent acid-catalyzed ring expansion[10] to yield cyclobutanones **10a**,**b** (Scheme 2).



Scheme 1



Scheme 2

Subsequent addition of isopropenylmagnesium bromide to the ketones **10a**,**b** led to cyclobutanols **11a** and **11b**, respectively, as mixtures of diastereomers. Isomers **11a** and **11a′** were obtained in 84% yield as a 60:40 inseparable mixture, while isomers **11b** and **11b′** were obtained in 88% yield as an 80:20 mixture which were separated chromatographically (Scheme 3).

The relative configuration of *trans*-**11a**,**b** and *cis*-**11a′**,**b′** was assigned by two-dimensional NOESY NMR spectroscopy. However, the semi-pinacolic rearrangement, induced by catalytic *p*-toluenesulfonic acid in benzene[11] or by catalytic boron trifluoride etherate in dichloromethane on a mixture of *trans*-**11a**/*cis*-**11a′** as well as *trans*-**11b**/*cis*-**11b′**, yielded cyclopentanones **5a** and **5b**, respectively.

While the synthesis of natural products **2**, **3** and **4** from the cyclopentanone **5b** has been previously reported in the literature,[5b–d] the synthesis of (±)-cuparene (**1**) from the intermediate **5a** required some additional steps. Thus, Huang–Minlon reduction[12] led to the cyclopentane **12**[13] which underwent demethylation to give the 3-hydroxycu-

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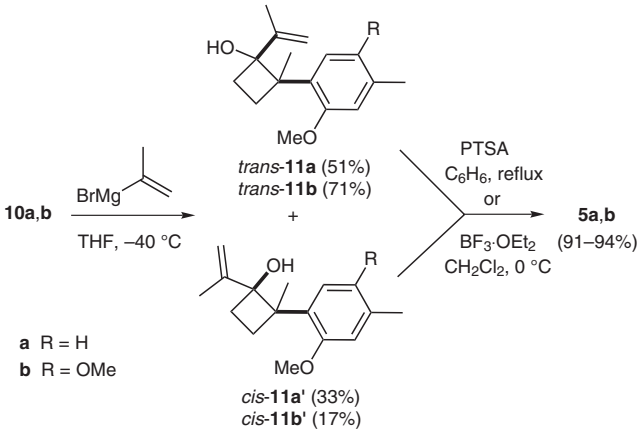
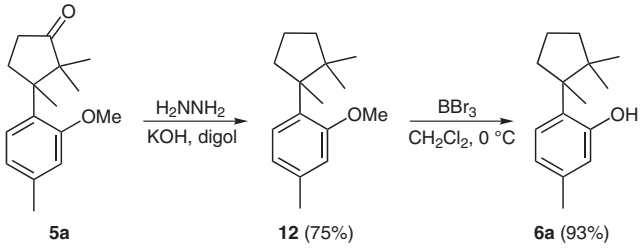


Scheme 3



Scheme 4

parene (**6a**),[14] an intermediate previously used in the total synthesis of cuparene (**1**)[5a] (Scheme 4).

In conclusion, we have developed a new and concise access to intermediates for the efficient preparation of (±)-cuparene, (±)-enokipolins A, B, and (±)-cuparene-1,4-quinone. The extension of this pathway to the enantioselective synthesis of these biologically active natural products is under current investigation.

Preparative column chromatography was performed on SDS flash silica gel (35–70 mesh). IR spectra were recorded as thin films on a FT-IR PerkinElmer Spectrum One. ^{1}H NMR (300 MHz and 400 MHz) and ^{13}C NMR (63 MHz and 75 MHz) spectra were recorded in $CDCl_3$ on Varian 300, Bruker DRX 400 and Bruker AM 250 spectrometers and the data are reported in δ (ppm) from $CDCl_3$ (^{1}H = 7.27 and ^{13}C = 77). Mass spectra (electron impact or chemical ionization) were measured with a Nermag R-10 coupled with a OK1 DP 125 gas chromatograph and a Agilent 5973 Network coupled with a 6890N gas chromatograph. Relative percentages are shown in brackets; high-resolution mass spectra (electron impact or electrospray) were recorded with a Finnigan MAT 95S spectrometer. Microanalyses were carried out on a Carlo Erba 1106 Elemental Analyzer.

Cyclopropyl Carbinols 9a,b

To a solution of cyclopropyl phenyl sulfide (**7**; 0.390 g, 26 mmol) in anhyd THF (150 mL) was added dropwise at –20 °C, a 1.5 M solution of *n*-BuLi (18.66 mL, 0.028 mmol) and stirring was continued at this temperature for 4 h. Then, after cooling down to –78 °C, a solution of the ketones **8a** or **8b** (26 mmol) in anhyd THF (20 mL) was added. The mixture was slowly warmed to r.t., diluted with Et_2O (100 mL) and quenched with aq NH_4Cl (20 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, hexanes–Et_2O, 5:1) to afford the corresponding cyclopropylphenylthio carbinols **9a** or **9b**.

1-(2-Methoxy-4-methylphenyl)-1-[1-(phenylthio)cyclopropyl]ethanol (9a)

Yellow oil; yield: 0.734 g (90%).

IR (neat): 3487, 3000, 2989, 2870 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.97–1.09 (m, 2 H, 2H-*c*Pr), 1.21–1.26 (m, 1 H, H-*c*Pr), 1.28–1.35 (m, 1 H, H-*c*Pr), 1.72 (s, 3 H, CH_3COH), 2.18 (s, 3 H, ArCH_3), 3.69 (s, 3 H, OCH_3), 4.75 (br s, 1 H, OH), 6.57 (d, *J* = 8.4 Hz, 1 H, H-6′ Ar), 6.86 (dd, *J* = 8.4, 1.5 Hz, 1 H, H-5′ Ar), 6.96–7.08 (m, 5 H, SC_6H_5), 7.15 (d, *J* = 1.5 Hz, 1 H, H-3′ Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.6 (CH_2 *c*Pr), 13.9 (CH_2 *c*Pr), 20.4 (*C*H_3COH), 26.3 (Ar*C*H_3), 34.4 (PhS*C c*Pr), 55.1 (OCH_3), 77.2 (CH_3*C*OH), 111.8 (C-3′ Ar), 124.1 (C-5′ Ar), 126.3 (C Ph), 126.7 (C Ph), 127.9 (C Ph), 128.8 (C Ph), 129.5 (C-6′ Ar), 130.1 (C-1′ Ar), 130.8 (C Ph), 131.7 (C-4′ Ar), 137.1 (C Ph), 154.8 (C-2′ Ar).

Anal. Calcd for $C_{19}H_{22}O_2S$ (314.45): C, 72.58; H, 7.05; S, 10.20. Found: C, 72.62; H, 7.15; S, 10.12.

1-(2,5-Dimethoxy-4-methylphenyl)-1-[1-(phenylthio)cyclopropyl]ethanol (9b)

Yellow oil; yield: 0.823 g (92%).

IR (neat): 3460, 2980, 1656 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05–1.23 (m, 2 H, 2H-*c*Pr), 1.30–1.34 (m, 1 H, H-*c*Pr), 1.43–1.50 (m, 1 H, H-*c*Pr), 1.80 (s, 3 H, CH_3COH), 2.18 (s, 3 H, ArCH_3), 3.76 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 4.90 (br s, 1 H, OH), 6.58 (s, 1 H, H-6′ Ar), 6.92 (s, 1 H, H-3′ Ar), 7.07–7.12 (m, 5 H, SC_6H_5)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8 (CH_2 *c*Pr), 14.0 (CH_2 *c*Pr), 15.9 (*C*H_3COH), 26.6 (Ar*C*H_3), 34.5 (PhS*C c*Pr), 55.8 (OCH_3), 56.1 (OCH_3), 78.1 (CH_3*C*OH), 112.3 (C-3′ Ar), 114.2 (C-6′ Ar), 125.3 (C-1′ Ar), 127.1 (C Ph), 128.0 (C Ph), 129.0 (C Ph), 130.5 (C Ph), 131.7 (C Ph), 132.1 (C-4′ Ar), 136.9 (C Ph), 153.0 (C-5′ Ar), 154.6 (C-2′ Ar).

FAB-MS: *m*/*z* = 367 [M + Na$^+$].

HRMS (EI): *m*/*z* calcd for $C_{20}H_{24}O_3S$: 344.2102; found: 344.2051.

Cyclobutanones 10a,b

A solution of the cyclopropylphenylthio carbinols **9a** or **9b** (3 mmol) and PTSA (516 mg, 3 mmol) in wet benzene (50 mL) was refluxed for 6 h. Then, the mixture was allowed to cool to r.t., diluted with H_2O (100 mL), and washed with aq 2 N NaOH (2 × 5 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was readily purified by flash column chromatography (silica gel, hexanes–Et_2O, 10:1) to afford the corresponding cyclobutanones **10a** or **10b**.

2-(2-Methoxy-4-methylphenyl)-2-methylcyclobutanone (10a)

Yellow oil; yield: 89%.

IR (neat): 2998, 1780, 1670 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.52 (s, 3 H, H_3CC *c*Bu), 1.98 (dt, *J* = 8.7, 8.1 Hz, 1 H, H-*c*Bu), 2.01 (dt, *J* = 11.4, 8.1 Hz, 1 H, H-*c*Bu), 2.25 (s, 3 H, ArCH_3), 3.13 (t, *J* = 8.1 Hz, 2 H, 2H-*c*Bu), 3.77 (s, 3 H, OCH_3), 6.77 (d, *J* = 8.1 Hz, 1 H, H-5′ Ar), 7.02 (d, *J* = 8.1 Hz, 1 H, H-6′ Ar), 7.08 (s, 1 H, H-3′ Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.6 (*C*H_3C *c*Bu), 21.7 (Ar*C*H_3), 26.7 (CH_2 *c*Bu), 42.4 (CH_2 *c*Bu), 55.3 (OCH_3), 64.6 (CH_3*C c*Bu), 111.2 (Ar C-3), 127.0 (Ar C-5′), 128.3 (Ar C-6′), 129.7 (Ar C-1′), 130.5 (Ar C-4′), 154.8 (Ar C-2′), 213.1 (C=O).

MS (EI): *m*/*z* (%) = 204 (9, M^+), 162 (67), 147 (100), 119 (58), 105 (24) 91 (25), 77 (19).

Anal. Calcd for $C_{13}H_{16}O_2$ (204.27): C, 76.44; H, 7.90. Found: C, 76.37; H, 7.86.

2-(2,5-Dimethoxy-4-methylphenyl)-2-methylcyclobutanone (10b)

Yellow oil; yield: 92%.

IR (neat): 2959, 1779, 1505 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.57 (s, 3 H, H_3CC *c*Bu), 2.03–2.16 (m, 1 H, H-*c*Bu), 2.24 (s, 3 H, ArCH_3), 2.36–2.48 (m, 1 H, H-*c*Bu), 3.15 (t, *J* = 8.7 Hz, 2 H, H-*c*Bu), 3.78 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 6.74 (br s, 1 H, H-5′ Ar), 6.88 (br s, 1 H, H-3′ Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.0 (CH_3C *c*Bu), 27.0 (CH_2 *c*Bu), 28.2 (ArCH_3), 42.5 (CH_2 *c*Bu), 54.5 (CH_3C *c*Bu), 55.9 (OCH_3), 56.1 (OCH_3), 109.4 (C-3′ Ar), 114.6 (C-6′ Ar), 126.0 (C-4′ Ar), 129.1 (C-1′ Ar), 149.5 (C-5′ Ar), 151.6 (C-2′ Ar), 213.5 (C=O).

FAB-MS: *m*/*z* = 257 [M + Na^+].

HRMS (EI): *m*/*z* calcd for $C_{14}H_{18}O_3$: 234.1251; found: 234.1255.

Cyclobutanols 11a,b

To a stirred solution of the cyclobutanols **10a** or **10b** (1 mmol) in anhyd THF (45 mL), was added dropwise a 1.5 M solution of isopropenylmagnesium bromide in CH_2Cl_2 (1 mL, 1.5 mmol) at –40 °C. Then, the mixture was allowed to warm to r.t., diluted with Et_2O (20 mL) and quenched with aq NH_4Cl (5 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, hexanes–Et_2O, 10:1) to give from **10a** a 60:40 inseparable mixture of cyclobutanols *trans*-**11a** and *cis*-**11a′** and from **10b** an 80:20 separable mixture of cyclobutanols *trans*-**11b** and *cis*-**11b′**.

2-(2-Methoxy-4-methylphenyl)-2-methyl-1-(prop-1-en-2-yl)cyclobutanol (*trans*-11a and *cis*-11a′)

Colorless oil; yield: 84% (**11a/11a′** = 60:40).

IR (neat): 3450, 2997, 1620 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.47 (s, 3 H, H_3CC *c*Bu, *trans*), 1.53 (s, 3 H, H_3CC *c*Bu, *cis*), 1.65 (s, 3 H, $H_3CC{=}CH_2$, *trans*), 1.67 (s, 3 H, $H_3CCH{=}CH_2$, *cis*), 1.71–1.78 (m, 1 H, H-*c*Bu, *cis*), 1.83 (t, *J* = 9.3 Hz, 1 H, H-*c*Bu, *trans*), 1.93 (s, 3 H, ArCH_3, *cis*), 2.01–2.13 (m, 1 H, H-*c*Bu, *trans*), 2.26 (s, 3 H, ArCH_3, *trans*), 2.32–2.45 (m, 2 H, H-*c*Bu, *trans*), 2.34–2.45 (m, 1 H, H-*c*Bu, *cis*), 2.55–2.65 (m, 2 H, H-*c*Bu, *cis*), 2.87 (br s, 1 H, OH, *trans*), 3.22 (br s, 1 H, OH, *cis*), 3.67 (s, 3 H, OCH_3, *trans*), 3.78 (s, 3 H, OCH_3, *cis*), 4.59 (br s, 1 H, $H_3CC{=}CH_2$, *trans*), 4.86 (br s, 1 H, $H_3CC{=}CH_2$, *trans*), 4.93 (br s, 1 H, $H_3CC{=}CH_2$, *cis*), 5.09 (br s, 1 H, $H_3CC{=}CH_2$, *cis*), 6.65 (s, 1 H, H-3′ Ar, *cis*), 6.68 (s, 1 H, H-3′ Ar, *trans*), 6.71–6.82 (m, 2 H, Ar H-5′ and H-6′, *trans*), 6.93–7.03 (m, 2 H, Ar H-5′ and H-6′, *cis*).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 16.1 (CH_3C *c*Bu, *trans*), 16.2 (CH_3C *c*Bu, *cis*), 20.5 ($H_3CC{=}CH_2$, *trans*), 22.5 ($H_3CC{=}CH_2$, *cis*), 25.3 (CH_2 *c*Bu, *cis*), 25.3 (CH_2 *c*Bu, *trans*), 26.7 (ArCH_3, *trans*), 28.3 (ArCH_3, *cis*), 29.6 (CH_2 *c*Bu, *cis*), 29.9 (CH_2 *c*Bu, *trans*), 49.8 (H_3CC *c*Bu, *cis*), 50.6 (H_3CC *c*Bu, *trans*), 56.1 (OCH_3, *cis*), 56.3 (OCH_3, *trans*), 75.7 (COH, *cis*), 79.8 (COH, *trans*), 109.2 (C=CH_2, *cis*), 109.7 (C=CH_2, *trans*), 110.2 (Ar C-3′, *cis*), 110.9 (*C*=CH_2, *trans*), 112.8 (Ar C-3′, *trans*), 113.6 (*C*=CH_2, *cis*), 128.2 (Ar C-5′, *trans*), 128.6 (Ar C-6′, *trans*), 128.8 (Ar C-5′, *cis*), 129.2 (Ar C-6′, *cis*), 129.4 (Ar C-1′, *trans*), 129.6 (Ar C-1′, *cis*), 130.3 (Ar C-4′, *cis*), 130.3 (Ar C-4′, *trans*), 154.4 (Ar C-2′, *cis*), 154.7 (Ar C-2′, *trans*).

MS (EI): *m*/*z* (%) (*trans* **11a**) = 246 (5, M^+), 162 (38), 147 (100), 131 (20), 119 (69), 105 (21), 91 (47), 69 (43), 41 (64).

HRMS (EI): *m*/*z* calcd for $C_{16}H_{22}O_2$: 246.1619; found: 246.1621.

MS (EI): *m*/*z* (%) (*cis* **11a′**) = 246 (4, M^+), 162 (45), 147 (100), 131 (15), 119 (79), 115 (34), 105 (15), 91 (44), 69 (33), 41 (49).

HRMS (EI): *m*/*z* calcd for $C_{16}H_{22}O_2$: 246.1619; found: 246.1620.

***trans*-2-(2,5-Dimethoxy-4-methylphenyl)-2-methyl-1-(prop-1-en-2-yl)cyclobutanol (*trans*-11b)**

Colorless oil; yield: 71%.

IR (neat): 3429, 2966, 2867, 1464 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.48 (s, 3 H, H_3CC *c*Bu), 1.57 (s, 3 H, $H_3CC{=}CH_2$), 1.79–1.96 (m, 1 H, H-*c*Bu), 2.11–2.13 (m, 1 H, H-*c*Bu), 2.20 (s, 3 H, ArCH_3), 2.21–2.28 (m, 1 H, H-*c*Bu), 2.35–2,43 (m, 1 H, H-*c*Bu), 2.90 (br s, 1 H, OH), 3.68 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 4.63 (br s, 1 H, $H_3CC{=}CH_2$), 4.88 (br s, 1 H, $H_3CC{=}CH_2$), 6.52 (s, 1 H, H-5′ Ar), 6.60 (s, 1 H, H-6′ Ar).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 16.2 (CH_3C *c*Bu), 20.5 ($H_3CC{=}CH_2$), 25.3 (CH_2 *c*Bu), 26.7 (ArCH_3), 29.9 (CH_2 *c*Bu), 50.7 (H_3CC *c*Bu), 55.4 (OCH_3), 56.2 (OCH_3), 79.8 (COH), 109.1 (Ar C-3′), 109.2 (C=CH_2), 110.8 (*C*=CH_2), 113.6 (Ar C-6′), 124.1 (Ar C-4′), 134.1 (Ar C-1′), 149.7 (Ar C-5'), 151.9 (Ar C-2′).

FAB-MS: *m*/*z* = 299 [M + Na^+].

HRMS (EI): *m*/*z* calcd for $C_{17}H_{24}O_3$: 276.17254; found: 276.17293.

***cis*-2-(2,5-Dimethoxy-4-methylphenyl)-2-methyl-1-(prop-1-en-2-yl)cyclobutanol (*cis*-11b')**

Colorless oil; yield: 17%.

IR (neat): 3429, 2966, 1504 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.30 (s, 3 H, H_3CC *c*Bu), 1.51 (s, 3 H, $H_3CC{=}CH_2$), 1.20–1.75 (m, 3 H, H-*c*Bu), 1.77 (br s, 1 H, OH), 2.13 (s, 3 H, ArCH_3), 2.20–2.24 (m, 1 H, H-*c*Bu), 3.68 (s, 3 H, OCH_3), 3.71 (s, 3 H, OCH_3), 4.61 (br s, 1 H, $H_3CC{=}CH_2$), 4.83 (br s, 1 H, $H_3CC{=}CH_2$), 6.37 (s, 1 H, H-3′ Ar), 6.60 (s, 1 H, H-6′ Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.2 (CH_3C *c*Bu), 22.5 ($H_3CC{=}CH_2$), 25.3 (CH_2 *c*Bu), 28.2 (ArCH_3), 29.7 (CH_2 *c*Bu), 51.7 (H_3CC *c*Bu), 55.7 (OCH_3), 56.1 (OCH_3), 75.7 (COH), 108.5 (C=CH_2), 109.6 (Ar C-3'), 110.1 (*C*=CH_2), 113.6 (Ar C-6′), 124.6 (Ar C-4′), 132.6 (Ar C-1′), 149.6 (Ar C-5′), 152.1 (Ar C-2′).

FAB-MS: *m*/*z* = 299 [M + Na^+].

HRMS (EI): *m*/*z* calcd for $C_{17}H_{24}O_3$: 276.1725; found: 276.1731.

Cyclopentanones 5a and 5b

Method A: A solution of the cyclobutanols **11a**,**a′** or **11b**,**b′** (1 mmol) and PTSA (172 mg, 1 mmol) was refluxed in benzene (20 mL) for 30 min. Then, the mixture was cooled to r.t., diluted with Et_2O (100 mL) and washed with aq sat. $NaHCO_3$ solution (2 × 10 mL) and brine (10 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude oil was readily purified by flash column chromatography (silica gel, hexanes–Et_2O, 10:1) to afford the corresponding cyclopentanones **5a** or **5b.**

Method B: To a stirred solution of the cyclobutanols **11a**,**a′** or **11b**,**b′** (1 mmol) in Et_2O (20 mL), $BF_3{\cdot}OEt_2$ (0.5 mmol) was added dropwise at –40 °C. After stirring for 4 h at this temperature, the mixture was allowed to warm to r.t. and stirred for one additional hour. Then, the mixture was diluted with Et_2O (50 mL), washed with aq sat. $NaHCO_3$ solution (2 × 10 mL) and brine (10 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude oil was readily purified by flash column chromatography (silica gel, hexanes–Et_2O, 10:1) to afford the corresponding cyclopentanones **5a** or **5b**.

3-(2-Methoxy-4-methylphenyl)-2,2,3-trimethylcyclopentanone (5a)

Yellow oil; yield: 91% (Method A); 94% (Method B).

IR (neat): 3000, 2987, 1760, 1220 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.66 (s, 3 H, CH_3C-2 *c*Pent), 1.23 (s, 3 H, CH_3C-2 *c*Pent), 1.38 (s, 3 H, CH_3C-3 *c*Pent), 1.98–2.47 (m, 1 H, H-*c*Pent), 2.29 (s, 3 H, ArCH_3), 2.41–2.54 (m, 3 H, H-*c*Pent), 3.72 (s, 3 H, OCH_3), 6.75 (d, *J* = 8.1 Hz, 1 H, H-5′ Ar), 7.01 (d, *J* = 8.1 Hz, 1 H, H-6′ Ar), 7.12 (s, 1 H, H-3′ Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.9 (CH_2 *c*Pent), 21.8 (CH_3C-2 *c*Pent), 23.4 (CH_3C-2 *c*Pent), 29.6 (ArCH_3), 32.6 (CH_3C-3 *c*Pent), 34.5 (CH_2 *c*Pent), 48.7 (CH_3C-3 *c*Pent), 52.6 (CH_3CCH_3), 54.2 (OCH_3), 110.9 (Ar C-3′), 127.6 (Ar C-5′), 128.6 (Ar C-6′), 129.2 (Ar C-1′), 134.4 (Ar C-4′), 155.9 (Ar C-2′), 223.1 (C=O).

MS (EI): *m*/*z* (%) = 246 (26, M^+), 189 (4), 162 (56), 147 (100), 119 (61), 91 (39), 77 (19), 56 (28).

Anal. Calcd for $C_{16}H_{22}O_2$ (246.35): C, 78.01; H, 9.00. Found: C, 78.15; H, 9.13.

1-Methoxy-2-(1,2,2-trimethylcyclopentyl)benzene (12)

To a solution of the cyclopentanone **5a** (370 mg, 1.5 mmol) in diethylene glycol (digol, 25 mL), was added dropwise hydrazine hydrate (65 mg, 1.5 mmol) at 70 °C. After stirring for 3 h, *t*-BuOK (358 mg, 3.2 mmol) was added portionwise and the temperature was maintained for 4 h. Then, the mixture was cooled to r.t., diluted with Et_2O (50 mL), and washed with brine (2 × 5 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude oil was readily purified by flash column chromatography (silica gel, hexanes–Et_2O, 10:1) to furnish the cyclopentane **12**; yellow oil; yield: 0.208 g (75%). We noted omissions in the reported data of this compound.[13]

^1H NMR (300 MHz, $CDCl_3$): δ = 0.66 (s, 3 H, CH_3CCH_3), 1.13 (s, 3 H, CH_3C-2 *c*Pent), 1.34 (s, 3 H, CH_3C-2 *c*Pent), 1.45–1.84 (m, 5 H, H-*c*Pent), 2.26 (s, 3 H, ArCH_3), 2.47–2.60 (m, 1 H, H-*c*Pent), 3.75 (s, 3 H, OCH_3), 6.74 (d, *J* = 8.1 Hz, 1 H, H-5′ Ar), 7.00 (d, *J* = 8.1 Hz, 1 H, H-6′ Ar), 7.10 (s, 1 H, H-3′ Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.8 (CH_3CAr), 21.1 (CH_3CCH_3), 23.3 (CH_3CCH_3), 26.3 (ArCH_3), 30.0 (CH_3CCH_3), 40.1 (CH_2CH_2), 42.3 (CH_2CH_2), 44.2 CH_2CH_2), 51.3 (CH_3CAr), 54.8 (OCH_3), 111.0 (Ar C-3′), 127.8 (Ar C-5′), 129.2 (Ar C-6′), 134.5 (Ar C-1′), 135.9 (Ar C-4′), 156.7 (Ar C-2′).

5-Methyl(-2-(1,2,2-trimethylcyclopentyl)phenol (6a, Hydroxycuparene)

To a solution of the cyclopentane **12** (280 mg, 1.21 mmol) in CH_2Cl_2 (20 mL) cooled at – 20 °C, was added dropwise BBr_3 (303 mg, 1.21 mmol). After stirring for 3 h, the mixture was allowed to warm to r.t. and stirred for one additional hour. The mixture was diluted with CH_2Cl_2 (50 mL), washed with aq sat. $NaHCO_3$ solution (2 × 5 mL), and brine (5 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (silica gel, hexanes–Et_2O, 10:1) to give the cyclopentane **6a**[14] (245 mg, 93%).

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