Synthesis of *dl*-3-Hydroxycuparene by a Claisen Rearrangement of Allyl Aryl Ether

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The Claisen rearrangement of 1-methyl-2-[(3-methylphenoxy)methyl]cyclopentene in *N,N*-dimethylformamide gave 5-methyl-2-(1-methyl-2-methylenecyclopentyl)phenol(**5**) *via* its trimethylsilyl ether. The methylation of **5**, followed by a Simmons-Smith reaction and by the catalytic hydrogenolysis, afforded 3-hydroxycuparene.

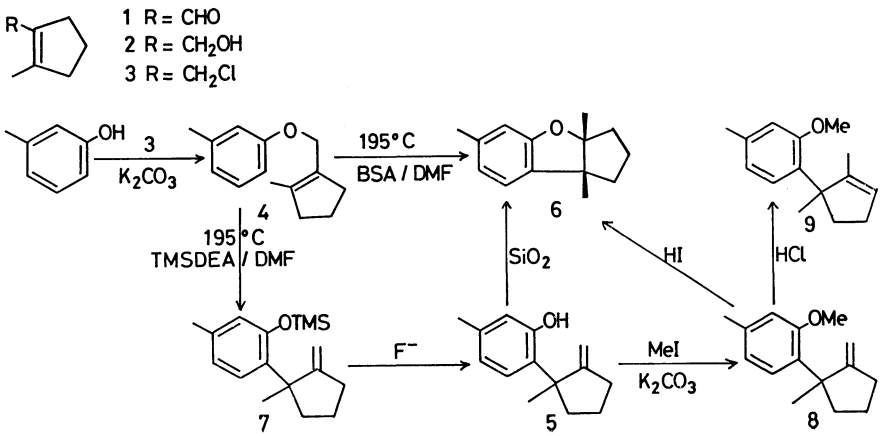
Claisen rearrangement[1] is one of the most attractive synthetic methods in natural-product chemistry because a new C–C bond can be created at the relatively hindered site of a molecule, where such intermolecular reactions as alkylation or acylation are frequently unsuccessful because of their steric demands. Several successes have been reported.[2] Most of them, however, have utilized the thermal reorganization of allyl vinyl ethers to γ,δ-unsaturated aldehydes or their variants.

We wish to report here the synthesis of hydroxycuparene *via* *o-t*-alkylphenol **5**, which is itself obtained by means of the Claisen rearrangement[3] of allyl aryl ether **4**.[4] This hydroxycuparene is expected to be a valuable intermediate for the synthesis of various cuparene derivatives found in the organisms.

6-Oxoheptanal, prepared from 1-methylcyclohexene, was cyclized with piperidinium acetate[5] to give 2-methyl-1-cyclopentenecarbaldehyde (**1**), which was then reduced with sodium borohydride to the corresponding alcohol **2**. The conversion of **2** into chloride **3** was problematic, however, because **3** was very unstable and, when isolated, immediately changed into unidentifiable green materials. Moreover, **3** was volatile, and an extraction procedure was undesirable. On this account, the alcohol **2** was treated with hexachloroacetone–triphenylphosphine,[6] after which the chloride **3** was isolated by flash distillation from the reaction mixture into a cooled (−70 °C) receiver containing small pieces of galvinoxyl. The immediate treatment of **3** with *m*-cresol in the presence of potassium carbonate gave 1-methyl-2-[(3-methylphenoxy)-methyl]cyclopentene (**4**), though the yield was low (18%). The structure of **4** was confirmed by the presence of an aromatic methyl at 2.37 ppm and an olefinic methyl at 1.82 ppm, together with the –O–CH_2–C= group at 4.49 ppm in the NMR spectrum of **4**.

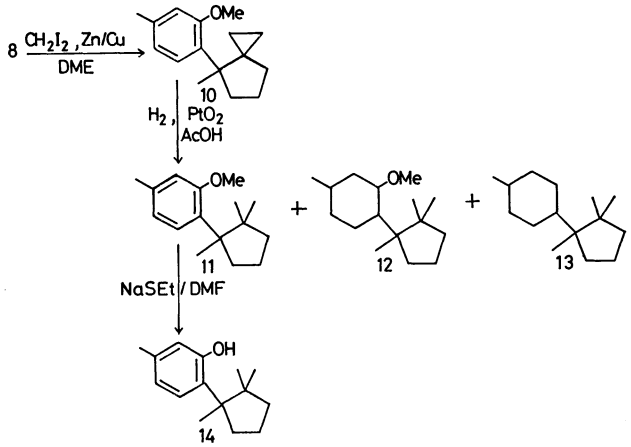
The Claisen rearrangement of simple allyl aryl ethers has been extensively investigated by Schmid *et al.*;[7] they showed that *N,N*-dimethylformamide (DMF) was the most effective solvent in giving an ortho-rearranged phenol.

When **4** was heated in DMF at 195 °C, the rearrangement occurred slowly in the anticipated direction to afford 5-methyl-2-(1-methyl-2-methylenecyclopentyl)phenol (**5**); however, a prolonged heating caused the gradual isomerization of **5** into the cyclic ether **6**. Thus, **5** could not be isolated in a pure form. The trapping of the initially rearranged phenol **5** as a trimethylsilyl derivative was successively performed when the reaction was carried out in the presence of *N*-trimethylsilyldiethylamine (TMSDEA). The GC analysis of the crude products showed the absence of any material other than **7**. On the other hand, *N,O*-bis(trimethylsilyl)acetamide (BSA) was undesirable because the decomposition of BSA at a high temperature accelerated the isomerization of **5** into **6** (see Experimental). The pure **5** was obtained in a 71% yield from **4** by the treatment of **7** with benzyltrimethylammonium fluoride[8] and by subsequent chromatography on neutral alumina. The structures of **5** and **6** were confirmed by their spectroscopic properties. Besides three aromatic protons which are located in a 2,5-dialkylphenol, two methyl groups at 1.38 and 2.18 ppm, and one exocyclic methylene group at 4.82 and 4.98 ppm as broad singlets are recognized in the NMR spectrum of **5**. On the other hand, in **6** three methyl groups appear, at 1.25, 1.30, and 2.20 ppm, while the signals due to the exocyclic methylene protons in **5** vanish completely. The chemical



shifts of 1.25 and 1.30 ppm of the two methyl groups on the ring juncture show the *cis*-relationship of these groups in comparison with those of aplysin (1.25 and 1.30 ppm).[9]

As **5** was sensitive toward acid, the phenolic hydroxyl group was protected by methylation. Attempted hydrohalogenations of the exocyclic methylene group in **8** were unsucessful; the treatment of **8** with potassium iodide/85% phosphoric acid[10] or hydrogen iodide/carbon tetrachloride gave **6** exclusively, while the action of hydrogen chloride/ether on **8** converted it into the endocyclic olefin **9**.



The Simmons-Smith reaction of **8** in the presence of 1,2-dimethoxyethane (DME) afforded the cyclopropane derivative **10**, which was then subjected to a careful catalytic hydrogenolysis (PtO_2 in acetic acid, 1.5 atom, 15 min) to give 3-hyrdoxycuparene methyl ether **11** in a crystalline form, together with a small amount of the octahydro compound **12** and the deoxy compound **13**.

The ether **11** was treated with sodium ethanethiolate in DMF to give oily *dl*-3-hydroxycuparene (**14**); the chemical shifts of four methyl signals (0.71, 1.13, 1.35, and 2.19 ppm) and the signal pattern of an aromatic region [6.29(br.s), 6.49(br.d, J=8 Hz), and 7.01 (d, J=8 Hz)] in the NMR spectrum of **14** are quite different from those reported for isomeric 2-hydroxycuparene.[11]

Experimental

All the melting points are uncorrected. The IR spectra were recorded with a Hitachi 215 grating spectrophotometer. The NMR spectra were measured with Hitachi H-60 and JEOL MH-100 spectrophotometers, using TMS as the internal standard. The mass spectra were obtained with a Hitachi RMU-6MG mass analyzer. The gas chromatograms were taken on a Shimadzu 3B-F analyzer, using a glass column (3 mϕ×1.7 m, 5% OV-1). The flash chromatographies were performed using Wakogel C-300 as the adsorbent.

6-Oxoheptanal. 1-Methylcyclohexene (29.5 g) was dissolved in 1400 ml of water–dioxane (2:5) in a 3-liter three-necked flask equipped with a mechanical stirrer and a nitrogen-inlet tube. $NaIO_4$ (177 g) was added, and the mixture was cooled to 0 °C. After the system had been flushed with nitrogen, a solution of 1 g of OsO_4 in 100 ml of water was added; the whole was then allowed to warm to room temperature. After 15 hours' stirring under nitrogen, white precipitates were removed by filtration, and the filtrate was extracted with ether. The subsequent removal of the solvent gave an oil, which was then purified by distillation to afford 17.8 g (43%) of 6-oxoheptanal as a slight yellow oil; bp 57—58 °C/0.7 mmHg (1 mmHg≈133.322 Pa) (Lit,[12]: bp 91—96 °C/4 mmHg): δ ($CDCl_3$): 1.46—1.76 (m, 4H), 2.14 (s, 3H), 2.22—2.68 (m, 4H), and 9.76 (t, 1H, J=1.5 Hz).

(2-Methyl-1-cyclopentenyl)methanol (2). 6-Oxoheptanal (8.49 g) was dissolved in 350 ml of dry benzene in a 1-liter three-necked flask equipped with a mechanical stirrer and a condenser. Traces of hydroquinone and a solution of dry piperidine (2.5 ml)–acetic acid (1.5 ml) in dry benzene (20 ml) were added, after which the mixture was stirred under nitrogen for 9 h at 60 °C. Water (300 ml) was then added, and the products were taken up in ether. The organic layer was washed with water and brine, and dried over Na_2SO_4. The subsequent evaporation of the solvent gave 6.89 g of crude 2-methyl-1-cyclopentenecarbaldehyde (**1**); ν ($CHCl_3$): 1660 cm^{-1}; δ ($CDCl_3$): 1.64—2.00 (m, 2H), 2.08 (s, 3H), 2.36—2.68 (m, 4H), and 9.84 (s, 1H).

The crude aldehyde **1** (6.89 g) was dissolved in 200 ml of methanol. After cooling to 0 °C, 4.13-g portions of $NaBH_4$ were gradually added; stirring was then continued for 80 min at 0 °C. Water was added, and the products were extracted with ether. The organic layer was washed with water and brine. After concentrating *in vacuo*, the oil which remained was purified by distillation to afford 3.77 g (51%) of **2** as a colorless oil; bp 42—43 °C/10 mmHg; ν ($CHCl_3$): 3600, 3400br, and 990 cm^{-1}; δ ($CDCl_3$): 1.70 (s, 3H), 1.75—2.10 (m, 2H), 2.10—2.68 (m, 4H), 2.88 (br.s, 1H), and 4.15 (br.s, 2H).

Elementray analysis was performed on its *p*-nitrobenzoate derivative; mp 71—72 °C; ν (KBr): 1720 and 1520 cm^{-1}. Found: C, 64.39; H, 5.81; N, 5.46%. Calcd for $C_{14}H_{15}NO_5$: C, 64.35; H, 5.78; N, 5.36%.

1-Methyl-2-[(3-methylphenoxy)methyl]cyclopentene (4). The alcohol **2** (736 mg) was mixed with 5 ml of hexachloroacetone[6] in a three-necked flask equipped with a thermomether and a distillor connected to a trap cooled with a Dry Ice–acetone bath. Traces of galvinoxyl were then added to the flask and the trap. Triphenylphosphine (5.2 g) was stirred in small portions into the mixture, during which the temperature of the content was controlled below 10 °C. The mixture was then allowed to warm to room temperature, and stirring was continued for a further 4 h. Crude 1-chloromethyl-2-methylcyclopentene (**3**) was flashly distilled (room temperature/0.2—0.3 mmHg) into the trap; *m/e* of **3**: 132 (11%, M^++2), 130 (33%, M^+), and 95 (100%, M^+−Cl). The chloride **3** was quite unstable and changed into a green material in the absence of galvinoxyl. Thus, the crude **3** was used immediately in the subsequent reaction.

A mixture of 0.75 ml of *m*-cresol and 1.05 g of K_2CO_3 in 5 ml of dry acetone was placed in a flask under nitrogen. A solution of **3** in 2 ml of acetone was then added into the above flask. The whole was then stirred at room temperature for 48 h. The reaction mixture was poured into water, and the products were taken up in ether. The organic layer was washed with 1 M (1 M=1 mol dm^{-3}) NaOH and water, and dried over Na_2SO_4. After concentrating *in vacuo*, the residual oil was chromatographed on alumina (15 g) with hexane to give crude **4** (348 mg). A pure sample was obtained by repeated flash chromatographies (3 times, 1.0 ϕ, hexane) to give 239 mg (18%) of **4**; Kugelrohr dist: bath temp 80—83 °C/0.3 mmHg; ν (CCl_4): 1590, 1580,

1480, 1250br, and 1150 cm^{-1}; δ (CCl_4): 1.82 (br. s, 3H), 2.37 (s, 3H), 4.49 (s, 2H), and 6.5—7.3 (m, 4H). Found: C, 82.89; H, 9.04%. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.96%.

Claisen Rearrangement[7] *of* ***4***. *A)*: A mixture of 68 mg of **4**, 0.01 ml of BSA, and 0.25 ml of dry DMF was sealed in a test tube under argon. The tube was heated for 19 h at 195 °C. The whole was then poured into water, and the products were extracted with ether. The organic layer was washed with water and brine, dried, and concentrated *in vacuo* to give crude **6** (51 mg), which was subsequently purified by chromatography on silica gel with hexane–ethyl acetate (1:1) to give pure **6**; Kugelrohr dist: bath temp 50—65 °C/0.3 mmHg; ν ($CHCl_3$): 1640, 1615, 1590, 1490, 1110, and 945 cm^{-1}; δ ($CDCl_3$, 100 MHz): 1.25 (s, 3H), 1.30 (s, 3H), 2.20 (s, 3H), 6.24 (br.s, 1H), 6.57 (br.d, 1H, J=7 Hz), and 6.63 (d, 1H, J=7 Hz); *m/e*: 202 (67%, M$^+$) and 187 (100%). Found: C, 83.01; H, 9.09%. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.96%.

B): A mixture of 225 mg of **4**, 0.5 ml of freshly distilled TMSDEA, and 4 ml of dry DMF was placed in a sealed tube under argon. The tube was heated for 30 h at 195 °C. The reaction mixture was then worked up as in A) to give crude **7**; *m/e*: 274 (M$^+$) and 259 (base). The GC analysis (140 °C) showed **7** was a single product. Crude **7** was treated with benzyltrimethylammonium fluoride[5] (20 mg) in 5 ml of THF for 4 h, and the products subsequently obtained by evaporating the solvent were chromatographed on neutral alumina (activity grade III, 10 g) with hexane to give **5** (159 mg, 71%). Some (20 mg) of the **4** was recovered from the earlier fractions.

An analytical sample of **5** was obtained by Kugelrohr dist: bath temp 67—70 °C/0.05 mmHg; ν (CCl_4): 3480, 1620, 1240, 1160, and 895 cm^{-1}; δ (CCl_4, 100 MHz): 1.38 (s, 3H), 2.18 (s, 3H), 4.82 (br.s, 1H), 4.98 (br.s, 1H), 5.32 (br.s, 1H), 6.42 (br.s, 1H), 6.49 (br.d, 1H, J=8 Hz), and 6.98 (d, 1H, J=8 Hz). Found: C, 83.00; H, 8.99%. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.96%.

*1-(2-Methoxy-4-methylphenyl)-1-methyl-2-methylenecyclopentane (****8****).* To a stirred mixture of 159 mg of **5** and 2 ml of methyl iodide in 5 ml of acetone, 1 g of K_2CO_3 was added, after which the whole was stirred at room temperature for 43 h. The solids were removed by filtration, and the filtrate was evaporated to give an oil, which was chromatographed on silica gel (5 g). From the hexane eluates, 141 mg (83%) of methyl ether **8** was obtained. Kugelrohr distillation gave a pure sample; bath temp 70—75 °C/0.05 mmHg; ν (CCl_4): 1645, 1600, 1250, 1170, 895, and 880 cm^{-1}; δ (CCl_4, 100 MHz): 1.38 (s, 3H), 2.22 (s, 3H), 3.66 (s, 3H), 4.54 (br.s, 1H), 4.82 (br.s, 1H), 6.46 (br.s, 1H), 6.46 (br. d, 1H, J=8 Hz), and 7.00 (d, 1H, J=8 Hz). Found: C, 83.29; H, 9.32%. Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.31%.

Attempted Hydrohalogenation of ***8****. With KI–85% H_3PO_4*:[10] A mixture of 15 mg of **8**, 35 mg of KI, and 0.5 ml of 85% H_3PO_4 was heated at 80 °C for 3 h. The products were taken up in ether to give **6**.

With HI–CCl_4. Through a cooled (0 °C) solution of 12 mg of **8** in 1.5 ml of CCl_4 there was passed a dry HI gas, prepared from I_2 and tetralin, for 2 h. The product was found to be **6**.

With HCl–Ether. A dry HCl gas was passed through a solution of 11 mg of **8** in 2 ml of anhydrous ether at 0 °C, and then the mixture was allowed to warm to room temperature. A work-up as usual gave 8.5 mg (77%) of **9** by chromatography on silica gel (hexane). Kugelrohr dist: bath temp 40—50 °C/0.03 mmHg; ν (CCl_4): 1605, 1250, 1185, 1165, 1060, and 1035 cm^{-1}; δ (CCl_4, 100 MHz): 1.37 (s, 3H), 1.51 (br.s, 3H), 2.24 (s, 3H), 3.68 (s, 3H), 5.28 (m, 1H), 6.44 (br.d, 1H, J=8 Hz), 6.46 (br.s, 1H), and 6.75 (d, 1H, J=8 Hz). Found: C, 83.09; H, 9.34%. Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.31%.

*4-(2-Methoxy-4-methylphenyl)-4-methylspiro[2.4]heptane (****10****).* To a suspension of 280 mg (4.3 mmol) of a freshly prepared Zn–Cu couple in 5 ml of dry ether, 0.35 ml (4.3 mmol) of diiodomethane was added, after which the mixture was irradiated with IR lamp for 2 min. The whole was stirred at 40 °C for 1.5 h, after which 0.45 ml (4.3 mmol) of DME was added. A solution of 95 mg (0.43 mmol) of **8** in 3 ml of ether was then added, and the mixture was stirred at that temperature for 48 h. After the removal of the precipitates, the filtrate was washed with water and brine, dried, and evaporated to give an oil. The oil was subjected to flash chromatography with hexane to afford **10** (44 mg, 44%).

Kugelrohr dist: bath temp 75—80 °C/0.04 mmHg; ν (CCl_4): 3075, 1610, 1250, and 1170 cm^{-1}; δ (CCl_4, 100 MHz): 0.0—0.8 (m, 4H), 1.09 (s, 3H), 1.2—2.0 (m, 5H), 2.23 (s, 3H), 2.4—2.7 (m, 1H), 3.71 (s, 3H), 6.46 (br.s, 1H), 6.47 (br.d, 1H, J=8 Hz), and 7.13 (d, 1H, J=8 Hz); *m/e*: 230 (35%, M$^+$), 215 (64%), and 202 (100%). Found: C, 83.38; H, 9.46%. Calcd for $C_{16}H_{22}O$: C, 83.43; H, 9.63%.

*1-(2-Methoxy-4-methylphenyl)-1,2,2-trimethylcyclopentane (****11****).* A solution of 54 mg of **10** in 10 ml of acetic acid was shaken with 50 mg of PtO_2 under a hydrogen atmosphere (1.5 atm) for 15 min. The catalysts were then removed by filtration, and the filtrate was evaporated to give an oil (49 mg; GC showed the presence of four compounds, **10**:**11**:**12**:**13**=1.5:7.0:2.5:1.0). Repeated flash chromatographies with hexane separated the components:

11: mp 44—45 °C (from pentane, −78 °C); ν (CCl_4): 1615, 1255, 1060, and 1040 cm^{-1}; δ (CCl_4, 100 MHz): 0.64 (s, 3H), 1.10 (s, 3H), 1.29 (s, 3H), 2.24 (s, 3H), 3.71 (s, 3H), 6.45 (br.s, 1H), 6.48 (br.d, 1H, J=9 Hz), and 6.96 (d, 1H, J=9 Hz); *m/e*: 232 (67%, M$^+$), 217 (22%), 175 (41%), 162 (63%), and 149 (100%). Found: C, 82.97; H, 10.54%. Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41%.

12: Kugelrohr dist: bath temp 50—60 °C/0.5 mmHg; ν (CCl_4): 1120 and 1095 cm^{-1}; δ (CCl_4, 100 MHz): 0.87 (s, 3H), 0.93 (s, 3H), 0.97 (s, 3H), 1.08 (br.d, 3H, J=7 Hz), and 3.18 (s, 3H); *m/e*: 238 (7%, M$^+$), 206 (53%,) 149 (78%), and 82 (100%). Found: C, 81.15; H, 12.63%. Calcd for $C_{16}H_{30}O$: C, 80.60; H, 12.68%.

13: oil; ν (CCl_4): 1460br and 1375 cm^{-1}; *m/e*: 208 (20%, M$^+$) and 124 (100%).

*5-Methyl-2-(1,2,2-trimethylcyclopentyl)phenol (****14****,3-hydroxycuparene).* A solution of 11 mg of the ether **11** in 0.5 ml of DMF in the presence of 25 equivalents of NaSEt was heated at 160 °C for 3 h. The mixture was then poured into dil hydrochloric acid, and the products were extracted with ether. The ether was dried over Na_2SO_4 and evaporated to give an oil. The oil was purified by flash chromatography with hexane to give phenol **14** (8 mg, 70%). Kugelrohr dist: bath temp 85—90 °C/0.04 mmHg; ν (CCl_4): 3630sh, 3600, 1620, 1290, and 1140 cm^{-1}; δ (CCl_4, 100 MHz): 0.71 (s, 3H), 1.13 (s, 3H), 1.35 (s, 3H), 2.19 (s, 3H), 4.42 (s, 1H), 6.29 (br.s, 1H), 6.49 (br.d, 1H, J=8 Hz), and 7.01 (d, 1H, J=8 Hz); *m/e*: 218 (50%, M$^+$), 203 (10%), 161 (30%), 148 (100%), and 135 (56%). Found: C, 82.34; H, 10.25%. Calcd for $C_{15}H_{22}O$: C, 82.51; H, 10.15%.

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