Synthesis of cuparene and herbentene via a common intermediate

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A dihydroisobenzofuran (13) was obtained from β-ionone in 10 steps via an intramolecular Diels–Alder reaction. On further oxidation, reductive ring opening and decarboxylation, cuparene and herbentene were synthesized.

Introduction

Cuparene (1) and herbentene (2) are prototypes of sesquiterpenes containing interconnecting cyclopentane and benzene rings. Cuparene occurs in the heartwood of conifers (e.g., Chamaecyparis thyoides) while herbentene is a constituent of the leafy liverwort Herberta adunca. The popularity of cuparene, α-cuparenone, β-cuparenone, and herbentene as synthetic targets is attested by the appearance of more than sixty publications, addressing various aspects of establishing two adjacent quaternary carbon atoms. Because the only difference between cuparene and herbentene is the substitution pattern of the benzene nucleus, any synthetic method relying on the construction of the cyclopentane unit is applicable to a synthesis of the other sesquiterpene when a route to either cuparene or herbentene has been delineated. However, we were intrigued by the possibility of accessing both types of terpenes from a common intermediate for the sake of attendant synthetic economy. Necessarily it entails the employment of a tetrasubstituted cyclopentane derivative for attachment or de novo construction of the aromatic ring. The divergent strategy is indicated in eqn. (1).

To maximize the strategic advantage, we considered the preparation of a series of intermediates possessing a local symmetry. In other words, we desired to delay the branching of the route as long as feasible in order to save our efforts. To that end we focused on a dihydroisobenzofuran, with the expectation that oxidation would give rise to two isomeric phthalides which would be processed further to complete the synthesis of cuparene and herbentene [eqn. (2)].

Results and discussion

We chose to start our synthesis from diketone 3, which is readily accessible from β-ionone by epoxidation at the cyclic double bond, boron trifluoride induced rearrangement (ring contraction), and hydrogenation. The cyclocondensation of 3 with hydrazine hydrate in refluxing ethanol in the presence of oxygen yielded pyridazine 4 (Scheme 1). The idea was to functionalize the benzylic methyl group for a subsequent introduction of a pendant group, and execution of an intramolecular Diels–Alder reaction. At this point, we investigated the dienophilicity of 4, but failed to observe any reaction with either methyl vinyl ketone or acrylic acid. Eventually, the conversion of 4 to the N-oxide 5 with MCPBA was effected. Because of the differential steric shieldings, the regioisomer 6 was not formed in the oxidation.

Next, 5 was treated with acetic anhydride at refluxing temperature to provide the Polonovski product 7 which was then saponified. Several attempts at using the benzylic alcohol 8 thus obtained did not succeed to generate the desired products. For example, pyrolysis of the silyl ether 9 furnished aldehyde 10, presumably due to intervention of a more favorable retroene decomposition [eqn. (3)]. Finally, 8 was derivatized to the propargyl ether (prop-2-ynyl ether) 11, subjected to isomerization with t-BuOK to an allenyl ether 12 which was directly thermolyzed in a sealed tube at 200 °C. The Diels–Alder reaction followed by elimination of dinitrogen occurred, albeit in low yield.

At this point we had passed the most crucial stage of our
Scheme 1  Reagents and conditions: (i) $\text{NH}_2\text{H}_2\text{O}, \text{EtOH (AIR), } \Delta$; (ii) $3\text{-ClC}_6\text{H}_4\text{CO}_3\text{H}, \text{CH}_2\text{Cl}_2, 0\degree\text{C}$; (iii) $\text{Ac}_2\text{O}, \Delta$; (iv) $\text{NaOH, EtOH, H}_2\text{O, } \Delta$; (v) $\text{HC}/\text{H}_2\text{O}/\text{H}_2\text{O}/\text{H}_2\text{O}$, $50\% \text{NaOH} - \text{CH}_2\text{Cl}_2, n\text{-Bu}_4\text{NBr}$; (vi) $t\text{-BuOK, t}\text{-BuOH, } \Delta$; (vii) $\text{PCC, THF, } \Delta$; (viii) $\text{Me}_3\text{SiCl, NaI, MeCN, } \Delta$; (ix) $\text{Cu, quinoline, } 220\degree\text{C}$.

synthesis, and were ready to process the dihydroisobenzofuran 13 by oxidation. This desymmetrization operation was carried out with PCC in 1,2-dichloroethane at 80–90 $\degree\text{C}$. An equimolar mixture of phthalides 14 and 15 was obtained. We were rather disappointed at not having been able to separate the lactone mixture but even in capillary GC they elute very closely. Accordingly, these lactones were submitted to a reductive ring cleavage using $\text{Me}_3\text{SiCl} - \text{NaI}$ in refluxing acetonitrile. The two different carboxylic acids 16 and 17 thus produced were now separable by recrystallization in hexane. Our use of the procedure was based on a conjecture that the benzylic iodides would undergo reduction under the reaction conditions.

The final step was decarboxylation. Thus, in heating with copper powder in quinoline each acid provided the corresponding hydrocarbon in reasonable yield. The products were identified as cuparene and herbertene.

As a corollary, we should mention an assay for a short approach to cuparene using the enedione derived from rearrangement of $\beta$-ionone monoepoxide. This route involves a Wittig reaction with ethylidenetriphenylphosphorane to give the diene and a subsequent electrocycloaddition to afford a cyclohexadienol. Unfortunately, the photoinduced cyclization was not realized.

Our previous efforts in demonstrating the power of symmetry considerations in facilitating synthesis design has resulted in an elaboration of u-cuparenone. The present work illustrates a new approach to both the cuparane and herbertane series while taking advantage of local symmetry of an intermediate. Subsequent to our preliminary report, a paper describing the creation of the aromatic ring of herbertene in emulation of our Diels–Alder method has appeared. Their modification, however, could not reach cuparene.

Experimental

IR spectra were measured on a JASCO FT/IR-200 spectrophotometer. $^1\text{H}$- and $^{13}\text{C}$-NMR spectra were recorded in CDCl$_3$ on a Varian UNITY-300 instrument at 300 and 75 MHz respectively; chemical shifts are reported in parts per million downfield from TMS. The EIMS were obtained from a TRIO-2000 mass spectrometer. Melting points were uncorrected. Merck Kieselgel 60 of 70–230 mesh was used for column...
chromatography. During workup of reactions, organic solutions were dried over anhydrous Na$_2$SO$_4$ and evaporated in vacuo using a Buchi rotary evaporator.

3-Methyl-6-(1,2,2-trimethylcyclopentan-1-yl)pyridazine (4)

A solution of hydrazine hydrate (0.6 g, 18.7 mmol) in 95% ethanol (20 mL) was mixed with diketene (3.2 g, 9.4 mmol) while being stirred magnetically. The mixture was refluxed for 1 h, cooled to room temperature, and the solvent was removed in vacuo. The crude product was chromatographed over silica gel using EtOAc–n-hexane (1:8) as eluent to give pyridazine (1.6 g, 84%). IR (film): 2873, 2858, 1460, 1424 cm$^{-1}$; $^1$H-NMR $\delta$ 7.27 (d, 1H, J = 9 Hz), 7.14 (d, 1H, J = 9 Hz), 2.80–2.60 (m, 1H), 2.58 (s, 3H), 1.82–1.40 (m 5H), 1.27 (s, 3H), 1.06 (s, 3H), 0.49 (s, 3H); $^{13}$C-NMR $\delta$ 165.5 (s), 157.0 (s), 125.8 (d), 124.6 (d), 51.8 (s), 44.7 (s), 39.8 (t), 35.9 (t), 25.8 (q), 24.2 (q), 23.4 (q), 21.6 (q), 19.7 (t); MS m/z 204 (M$^+$, 18), 187 (17), 163 (11); HRMS (EI) 204.1617 (204.1628 Caled for C$_{13}$H$_{12}$_N$_2$).

5-(1,2,2-Trimethylcyclopentan-1-yl)-1,3-dihydroisobenzofuran (13)

A solution of ether (1.1 g, 2.2 mmol) and potassium tert-butoxide (1.0 g, 8.9 mmol) in tert-butanol (2-methylpropan-2-ol) (10 mL) was refluxed for 5 h. After cooling to room temperature, the mixture was concentrated in vacuo. Silica gel chromatography using ElOAc–n-hexane (1:10) as eluent furnished the prop-2-ynyl ether (11) (0.51 g, 75%). IR (film) 3307, 2960, 2873, 1438, 1468, 1368, 1111 cm$^{-1}$; $^1$H-NMR $\delta$ 7.50 (d, 1H, J = 9 Hz), 7.46 (d, 1H, J = 9 Hz), 4.91 (s, 2H), 4.28 (d, 2H, J = 2.4 Hz), 2.90–2.70 (m, 1H), 2.47 (d, 1H, J = 2.4 Hz), 1.90–1.50 (m, 5H), 1.36 (s, 3H), 1.14 (s, 3H), 0.55 (s, 3H); $^{13}$C-NMR $\delta$ 167.5 (s), 157.2 (s), 125.2 (d), 124.6 (d), 79.0 (d), 75.1 (s), 70.8 (s), 58.2 (t), 52.2 (s), 45.0 (s), 39.9 (t), 36.1 (t), 26.0 (q), 24.4 (q), 23.5 (q), 19.8 (t); MS m/z 285 (M$^+$, 13), 190 (14), 189 (100); HRMS (EI) 258.1718 (258.1733 Caled for C$_{15}$H$_{12}$O$_2$).

2-Methyl-5-(1,2,2-trimethylcyclopentan-1-yl)benzoic acid (16) and 2-methyl-4-(1,2,2-trimethylcyclopentan-1-yl)benzoic acid (17)

To a stirred mixture of 14–15 (0.24 g, 1 mmol) and sodium iodide (3 g, 20 mmol) in dry acetonitrile (10 mL) was added...


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chlorotrimethylsilane (2.16 g, 20 mmol) slowly. The reaction mixture was refluxed for 4 days. The cooled reaction mixture was taken up in ether, washed with water, sodium thiosulfate solution (10%), and brine. The ether solution was dried, evaporated, and the residue (0.19 g, 78.4%) was recrystallized from n-hexane to separate the less soluble Cuparene (1) from the more soluble 17.

Compound 17 mp: 190–192 °C; IR (film) 3340, 2970, 2870, 1672, 1458 cm⁻¹; ¹H-NMR δ 7.91 (d, 2H, J = 7.8 Hz), 7.30–7.10 (m, 2H), 2.59 (s, 3H), 2.50–2.40 (m, 1H), 1.80–1.40 (m, 5H), 1.21 (s, 3H), 1.01 (s, 3H), 0.50 (s, 3H); ¹³C-NMR δ 171.2 (s), 153.4 (s), 140.5 (s), 131.0 (d), 130.7 (d), 125.3 (d), 124.7 (s), 123.8 (d), 127.8 (d), 127.4 (d), 126.1 (d), 124.1 (d), 50.5 (s), 44.4 (s), 39.9 (t), 36.9 (t), 26.6 (q), 24.5 (q), 24.4 (q), 21.9 (q), 19.8 (t).

H-NMR 7.20 (d, 2H, J = 7.8 Hz), 7.43 (dd, 1H, J = 2.7 Hz), 7.17 (d, 1H, J = 8.4 Hz), 2.64 (s, 3H), 2.50–2.40 (m, 1H), 1.80–1.40 (m, 5H), 1.27 (s, 3H), 1.01 (s, 3H), 0.55 (s, 3H); ¹³C-NMR δ 173.4 (s), 145.3 (s), 138.2 (s), 131.7 (d), 131.2 (d), 130.1 (d), 127.3 (s), 50.3 (s), 44.3 (s), 39.7 (t), 26.8 (t), 26.5 (q), 24.2 (q), 21.6 (q), 19.7 (t); MS m/z 246 (M⁺, 38), 245 (100), 176 (95), 145 (60), 115 (21); HRMS (EI) 246.1615 (246.1620 Calculd for C₁₂H₁₈O₂).

Cuparene (1)

A mixture of 16 (50 mg, 0.2 mmol), Cu powder (38 mg, 0.6 mmol) and quinoline (6 mL) was stirred at 220 °C for 6 h. On cooling to room temperature, the mixture was filtered and the filtrate was washed with ice-cold HCl (8 mL, 20 g ice), and the organic layer was dried over Na₂SO₄ and concentrated in vacuo. The crude product was chromatographed over silica gel using n-hexane as eluent to give cuparene (1) (29.5 mg, 71.9%). ¹H-NMR δ 7.72 (d, 2H, J = 8.1 Hz), 7.06 (d, 2H, J = 8.1 Hz), 2.60–2.40 (m, 1H), 2.34 (s, 3H), 1.80–1.40 (m, 5H), 1.23 (s, 3H), 1.07 (s, 3H), 0.57 (s, 3H); ¹³C-NMR δ 144.5 (s), 134.6 (s), 128.2 (d), 126.9 (d), 50.3 (s), 44.3 (s), 39.8 (t), 36.8 (t), 27.0 (q), 24.4 (q), 20.9 (q), 19.8 (q).

Herbertene (2)

A mixture of acid 17 (80.5 mg, 0.3 mmol), Cu powder (57 mg, 0.9 mmol) and quinoline (8 mL) was manipulated in the same manner as above. The crude product was chromatographed over silica gel using n-hexane as eluent to give Herbertene (2) (51.4 mg, 73.7%). ¹H-NMR 7.20–7.10 (m, 3H), 7.00–6.90 (m, 1H), 2.60–2.40 (m, 1H), 2.34 (s, 3H), 1.80–1.40 (m, 5H), 1.25 (s, 3H), 1.05 (s, 3H), 0.55 (s, 3H); ¹³C-NMR δ 147.5 (s), 136.6 (s), 127.8 (d), 127.4 (d), 126.1 (d), 124.1 (d), 50.5 (s), 44.4 (s), 39.9 (t), 36.9 (t), 26.6 (q), 24.5 (q), 24.4 (q), 21.9 (q), 19.8 (t).

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