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1-Iodomethyl-3,4-diphenyl-2,6-dioxabicyclo[2.2.0]hexane: the first example of a [2.2.0] fused ketal

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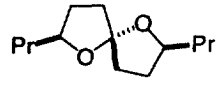
Abstract

The preparation of 1-iodomethyl-3,4-diphenyl-2,6-dioxabicyclo[2.2.0]hexane (**12**) is described. This represents the first reported example of a [2.2.0] fused ketal. The key step involved the iodoetherification of a 2-methyleneoxetane **11** containing a pendant alcohol.

Spiroketals occur widely in nature and display a broad spectrum of biological activities.[1] They are manifest in systems that are structurally simple, such as the insect pheremone **1** and in structures of great complexity, such as the avermectins. However, no [*n*.3] bicyclic systems have been reported as natural products. The very few examples of [3.3],[2,3] [4.3][2] and [5.3][4] systems result mostly from Paterno–Büchi reactions with allenes or enol cyclic ethers. Although not as prevalent, biologically interesting fused ketals are found in nature and in rationally designed drug candidates.[5] Fused [3.2.0][6] and [4.2.0][7,8] ketals are known. Again, these are largely accessed via the Paterno–Büchi reaction. There have been no examples, to our knowledge, of a [2.2.0] fused ketal reported in the literature. We believe that the uncommon ketal systems **4** and **5** represent moieties of untapped potential, both biologically and synthetically. Such systems might be accessed by electrophile mediated cyclization of appropriately substituted 2-alkylidene oxetanes **2** and **3** (Eq. 1). Recently, we reported the first straightforward preparation of 2-methyleneoxetanes.[9] We decided to examine a 'proof of concept' for electrophile mediated cyclizations of 2-alkylidene oxetanes by attempting the preparation of a fused ketal system. Herein, we report the synthesis of a hitherto unknown [2.2.0] fused ketal system by iodoetherification of 2-methyleneoxetane **11**.



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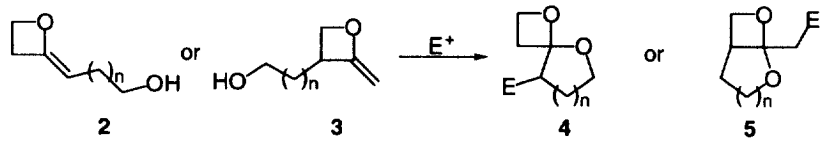
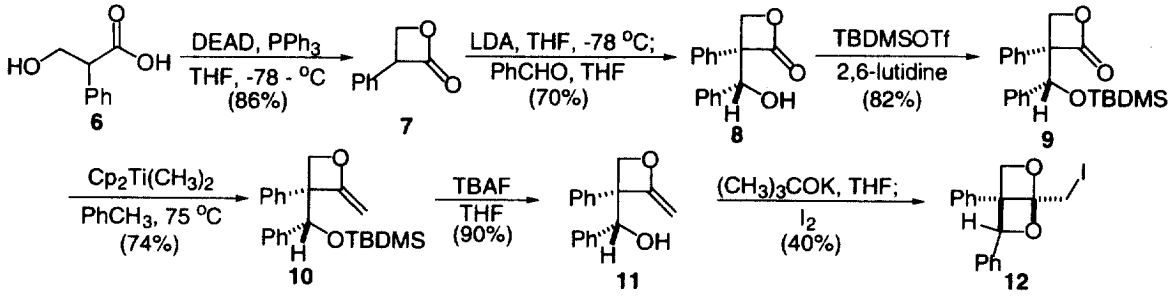


(1)

Our approach to 2-methyleneoxetane **11** and its conversion to the [2.2.0] fused ketal **12** are delineated in Scheme 1. Thus, commerically available (±) tropic acid (**6**) was converted into β-lactone **7** under Mitsunobu conditions.[10] Condensation with benzaldehyde (3 equiv.) provided alcohol **8**, as a separable 6:1 mixture of diastereomers. The relative stereochemistry of the major diastereomer (shown) was deduced by X-ray crystallography of the minor diastereomer.[11] Interestingly, if less than one equivalent (0.8) of benzaldehyde was employed, the alternate diastereomer predominated. Although we have previously demonstrated that β-lactones can be methylenated with dimethyltitanocene in the presence of a remote free hydroxyl group, an attempt to directly convert alcohol **8** to 2-methyleneoxetane **11** was unsuccessful. Protection with TBDMSOTf afforded alcohol **9**, which was smoothly converted into methyleneoxetane **10**. Deprotection of **10** with TBAF provided the key intermediate **11** for examining the feasibility of an iodoetherification reaction. Although the deprotection proceeded efficiently, it was essential to use the product immediately, as it was unstable. Finally, treatment of **11** with potassium *t*-butoxide, followed by iodine, provided the desired [2.2.0] fused ketal **12**.[12]



Scheme 1.

In conclusion, we have demonstrated that electrophile mediated cyclization of 2-methyleneoxetanes is feasible, potentially offering a novel protocol for the prepartion of little investigated [*n*.2.0] fused ketals and [*n*.3] spiroketals. Further, the first example of a [2.2.0] fused ketal has been reported.

Acknowledgements

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11. Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre.
12. 3-[Hydroxy(phenyl)methyl]-3-phenyl-2-methyleneoxetane (**11**). *n*-Bu_4NF (0.55 mL of 1 M solution in THF, 0.55 mmol) and **10** (0.10 g, 0.28 mmol) in THF (1.05 mL) were stirred at rt for 1 h. TLC (petroleum ether:EtOAc 1:1, $KMnO_4$ visualized) showed remaining **10**, and more *n*-Bu_4NF (0.2 mL, 0.2 mmol) was added to the reaction mixture. After another 2 h most of the solvent was evaporated, and the residue was purified by flash chromatography on silica gel (NEt_3:EtOAc:petroleum ether 0.5:15:84.5). Compound **11** (0.05 g, 75%) was isolated as a colorless oil: IR (film) 3481, 3028, 2898, 1684, 1448 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.23 (m, 6H), 7.01 (m, 2H), 6.95 (m, 2H), 5.17 (d, *J*=5.0 Hz, 1H), 5.10 (s, 1H), 4.80 (d, *J*=5.0 Hz, 1H), 4.44 (d, *J*=4.0 Hz, 1H), 4.12 (d, *J*=4.0 Hz, 1H), 2.48 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 167.4, 138.8, 138.7, 128.0, 127.6, 127.5, 127.3, 127.1, 83.2, 77.7, 77.0, 60.1; MS (EI) *m/z* 222 (M^+-CH_2O), 179 (100), 152, 115, 103, 77; HRMS calcd for $C_{17}H_{17}O_2$ (M^++1) 253.1229. Found: 253.1226. 2-Iodomethyl-3,4,-diphenyl-2,6-dioxabicyclo[2.2.0]hexane (**12**). To a stirred solution of **11** (50 mg, 0.20 mmol) in THF (7 mL), $(CH_3)_3COK$ (38 mg, 0.24 mmol) was added under N_2 at rt. After 15 min the solution was cooled to 0°C, iodine (61 mg, 0.24 mmol) was added, and after 10 min the reaction mixture was allowed to warm to rt and was further stirred 1.5 h. The reaction mixture was cooled to 0°C and quenched with saturated aqueous $Na_2S_2O_3$ (10 mL). The mixture was then extracted with Et_2O (3×15 mL). The combined organic extracts were dried ($MgSO_4$), and the solvent was removed in vacuo. Purification of the residue by flash chromatography on silica gel (petroleum ether:EtOAc 95:5) afforded fused ketal **12** (30 mg, 40%) as a light yellow oil: IR (film) 3060, 2960, 2854, 1685, 1496, 1448, 1261 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38 (m, 10H), 6.18 (s, 1H), 4.73 (d, *J*=6.5 Hz, 1H), 4.57 (d, *J*=6.5 Hz, 1H), 3.61 (d, *J*=10.6 Hz, 1H), 3.54 (d, *J*=10.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 137.1, 135.9, 129.2, 128.6, 128.2, 128.1, 126.0, 125.6, 114.5, 86.2, 72.1, 55.6, 3.9; MS (EI) *m/z* 378 (M^+), 251, 191 (100), 165, 115, 77; HRMS calcd for $C_{17}H_{15}O_2I$ (M^+) 378.0117. Found: 378.0125.