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Tetrahedron Letters 46 (2005) 3835–3837
Tetrahedron Letters

A new tricyclic triketone from tandem condensation reactions

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Received 16 March 2005; revised 25 March 2005; accepted 28 March 2005
Available online 11 April 2005

Abstract—Perhydrophenanthrene-1,5,10-trione (**6**) was isolated from the reaction of methyl 3-(carboxymethyl)cyclohexanone and cyclohexenone in a tandem Michael–Claisen reaction. NMR and X-ray analysis confirmed the structure of the product.
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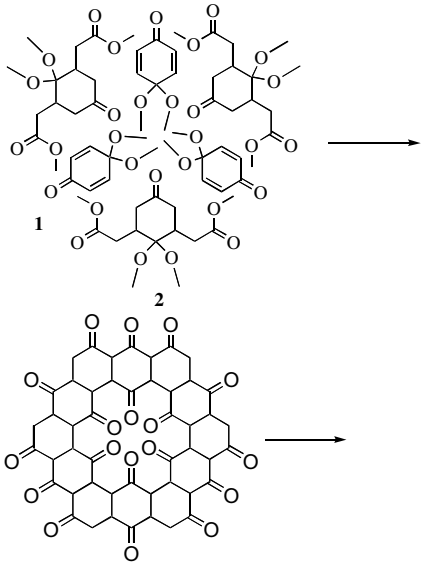
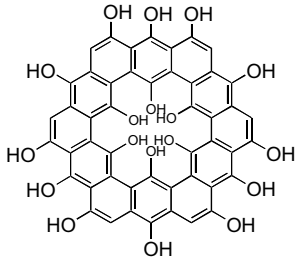
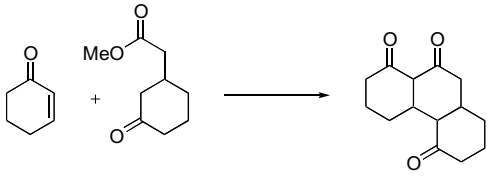
We are engaged in a long-term project to create novel aromatic structures by multiple tandem Michael–Claisen reactions. For example, one of our goals is the polyhydroxykekulene **3**, which could in principle be formed from **1** and **2**.





3

To demonstrate the viability of this approach to large molecules, we set out to prepare the simple tricyclic triketone **6** using tandem condensations.



4 **5** **6**

Compound **5** (as the ethyl ester) was synthesized by McMurry in 94% yield by reaction of cyclohexenone with the magnesium double salt of monoethyl malonate.[1] Several attempts at this reaction were unsuccessful. However, we have been able to prepare **5** much more conveniently by Michael addition of dimethyl malonate to cyclohexenone followed by Krapcho decarbomethoxylation[2] using the microwave conditions reported by Loupy et al.[3]

Keywords: Michael; Claisen; Tricyclic; Triketone; Modeling; Tandem condensations; Kekulene; Perhydrophenanthrene.
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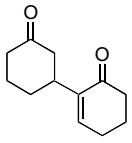
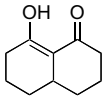
doi:10.1016/j.tetlet.2005.03.182

Our first attempt at the tandem cyclization used methoxide as base and led, not surprisingly, to Michael addition of methoxide to cyclohexenone. Switching to potassium *tert*-butoxide produced diketone **7**.[4] This was formed by a process related to the Baylis–Hillman reaction[5] involving addition of extraneous hydroxide to cyclohexenone, addition of the resulting anion to a second molecule of cyclohexenone, followed by elimination of the original hydroxide. Use of dryer potassium *tert*-butoxide reduced (but did not eliminate) the production of **7** and led to only trace amounts of the desired product; for the most part there was no reaction under these conditions.



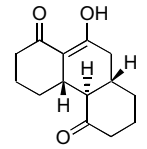
7

In contrast, when ketoester **5** and cyclohexenone were treated with sodium hydride in THF and worked up by acidification of the reaction mixture, concentration, and chromatography, a sample of **6** was obtained in 10% yield. Triketone **6** was obtained as colorless crystals from ethanol–water, mp 122–123 °C, IR 1698 cm^{-1} (sharp), 1599 (broad), consistent with a broad peak at 1608 cm^{-1} reported for **8**.[6]

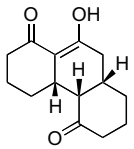


8

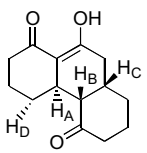
The 300 MHz proton NMR displayed a one-proton multiplet at 1.2 ppm, a complex pattern accounting for 15 protons between 1.6 and 2.7 ppm, a one-proton triplet of doublets at 2.9 ppm, and a sharp singlet at 16.1 ppm. The latter peak is consistent with the enolic proton in **8**, which appears at 16.3 ppm.[7] The peak at 2.9 ppm was assigned to H_A by analogy with the single proton reported for **8** at a similar chemical shift, and the multiplet at 1.2 ppm was judged to be due to a proton in the shielding zone of the third carbonyl group.



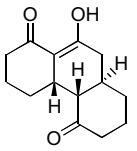
6a



6b



6c



6d

In order to gain more insight into the structure of this molecule, MM+ calculations were done using the Hyperchem molecular modeling software. According to the results, **6a** has the lowest energy, calculated to be 26.5 kcal/mol. Compound **6b** has an energy of 27.95 kcal/mol followed by **6c** and **6d** at about 29.5 kcal/mol. Of course, the reaction may not have produced the most stable isomer, since only H_B is epimerizable. The relative stereochemistry of H_A and H_C is set in the Michael reaction. Least hindered approach arguments suggest that H_A and H_C should end up cis to each other in the Michael reaction, leading to either **6a** or **6b**. However, in **6c** H_D is much more directly in the shielding zone of the isolated carbonyl group than in any other isomer. Thus kinetic and thermodynamic arguments both suggest that we should have **6a**, and the NMR seems more consistent with **6c**.

Despite extensive 2-dimensional NMR analysis, we were not able to confirm which isomer we had. Thus a crystal of **6** was submitted for X-ray analysis.[8] The X-ray experiment revealed the positions of all hydrogen atoms as they are depicted in Figure 1; as the structure was further refined, observed H's were replaced by calculated ones to improve accuracy. The X-ray showed that H_A is trans to H_B, and H_C is cis to H_B. Enolic hydrogens could also be located: from the residual electron density map, and also from bond lengths, it was concluded that the enol hydrogen was about 66% in the enol form shown in **6a**–**d** and 34% in the alternate enol form.[9] Thus drawing **6c** most accurately represents the structure of this molecule. We currently have no explanation for why this isomer is the one formed.

We are continuing our work on improving this reaction and expanding it to larger, polyfunctional examples.

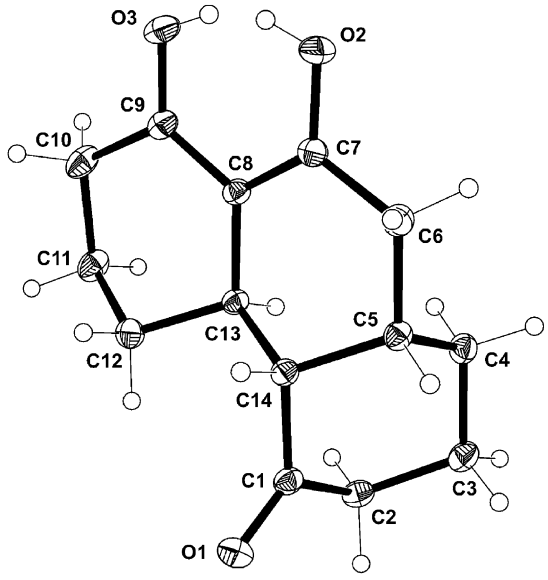


Figure 1. Molecular structure of **6** with 50% probability ellipsoids. Both positions for the disordered enol H atom are shown, however experimental data for H occupancy factors are 66:34 in favor of H located on O2.

Acknowledgements

We gratefully acknowledge the National Science Foundation's REU Program and the von Liebig Foundation for financial support of this work. We thank Professors R. Brisbois, N. Mills, T. Mitzel, K. Mondanaro, and K. C. Russell (the TIM Consortium) and Richard Hark for exciting discussions of chemistry, and Dr. Jeff Wolbach for helping with the calculations. Dr. Philip Coppens (UB) is gratefully acknowledged for providing access to the X-ray diffractometer.

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8. Crystal data for **6**: $C_{14}H_{18}O_3$, $M = 234.28$, $0.25 \times 0.20 \times 0.15\,mm^3$, monoclinic, space group $P2_1/n$ (No. 14), $a = 9.5611(2)$, $b = 13.8471(3)$, $c = 9.6146(2)$ Å, $\beta = 116.708(1)°$, $V = 1137.10(4)$ Å^3, $Z = 4$, D_c 1.369 g cm^{-3}, μ (Mo K$_\alpha$) = 0.95 cm^{-1}, $T = 90$ K, $2\theta_{max} = 61.00°$, 15344 reflections collected, 3462 unique ($R_{int} = 0.0119$). The refinement (157 variables, 0 restriction) based on F^2 converged with $R = 0.0357$, $R_w = 0.0974$, and GOF = 1.039 using 3218 unique reflections with $I > 2\sigma(I)$. CCDC 262378 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).
9. We saw no spectroscopic evidence of individual tautomers, so presumably interconversion is fast on the time scale of the measurements.