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The INOC Approach to the Hydroazulenone Ring System - A Potential Entry to the Guaianolides and Pseudoguaianolides.

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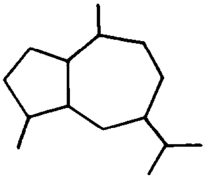
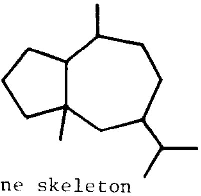
Summary: The intramolecular nitrile oxide cycloaddition reaction has been examined as a method for preparing the hydroazulene ring system.

In this letter we wish to communicate a new process for generating the hydroazulenone ring system. We believe that the strategy outlined herein should find important application in the construction of sesquiterpene natural products of both the guaianolide and pseudoguaianolide families.[1]

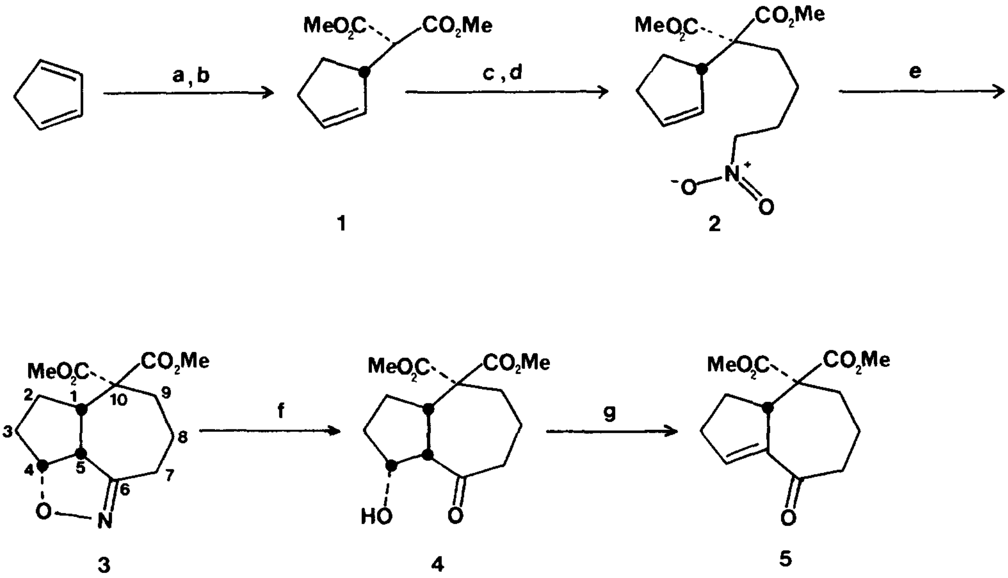

guaiane skeleton


pseudoguaiane skeleton

As has been discussed recently by Heathcock,[2] several different topological approaches for the construction of the hydroazulene skeleton can be discerned. These consist of: (a) the affixation of a seven-membered ring onto an existing five-membered ring; (b) the reverse of this, i.e., the affixation of a five-membered onto a functionalized seven-membered ring; (c) the transannular cyclization of a cyclodecane to hydroazulene; (d) the skeletal rearrangement of a hydronaphthalene to hydroazulene; and (e) the conversion of an acyclic olefin or diene precursor to a hydroazulene by way of an intramolecular [3+2] or [3+4] cycloaddition process.[3]

Of these methods, the first has found the greatest success in the synthesis of the pseudoguaianolides. Our method for hydroazulenone synthesis does also belong to this type (a) category, and it is based on a very simple extension of our previously reported route to carbocyclic ring systems via the INOC process.[4] To our knowledge, there exists but one example of the preparation of a seven-membered ring employing such a reaction, and this example consists of the construction of an oxygen containing ring in but 17% yield.[5]

It thus became of some immediate interest to ascertain whether we could generate a seven-membered carbocyclic ring through such dipolar cycloaddition chemistry at all. We chose initially to carry out the following relatively simple model study. 3-Chlorocyclopent-1-ene, readily available from the addition of hydrogen chloride to cyclopentadiene,[6] was treated with dimethyl sodiomalonate to furnish **1**.[7] Deprotonation of this malonate derivative with sodium hydride and alkylation with 1-bromo-4-chlorobutane in the presence of HMPA delivered the 4-chlorobutyl substituted malonate. The chloro group of the disubstituted malonate was thence converted to a nitro group by reaction of its derived iodide with silver nitrite.[8] With the key nitrolefin 2 in hand, we were now ready to test the crucial ring-forming reaction. The nitro compound was simply boiled in benzene with a trace of triethylamine while phenyl isocyanate in benzene was added dropwise from an addition funnel. With this but slight modification of the orginial Mukaiyama conditions for nitrile oxide generation,[9] an 83% yield of the beautifully crystalline product 3 was generated!



(a) HCl, ϕCH_3; (b) $(MeO_2C)_2CHNa$, ϕCH_3 (74% overall); (c) NaH; $Cl(CH_2)_4Br$, THF, HMPA (93%); (d) NaI, MeCOMe; $AgNO_2$, Et_2O (64% overall); ϕNCO (2 equiv), Et_3N (cat.), ϕH, Δ (83%); (f) O_3, MeOH, -78°C; (g) *p*-TsOH, MeOH (80% overall).

Examination of the 300 MHz ^1H NMR coupling constants of 3 confirmed the syn nature of the C1, C4 and C5 hydrogens.[10] The hydrogen at C5 is coupled equally to the C1 and C4 hydrogens, a fact consistent with the *cis*-ring fused structure 3. From model building, it is fairly clear why this stereochemistry obtains in the INOC process. Considerable non-bonded interactions must develop in

the transition state A which leads to the trans-fused product. The steric interactions involving the C5, C7, C8 triad are avoided in the transition state B which leads to the cis-fused product 3. An x-ray analysis has confirmed independently our NMR-based structural assignment (Figure 1).[11]

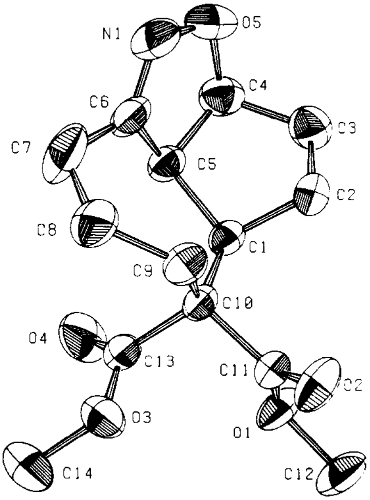


Figure 1. X-ray structure of 3 with hydrogen atoms omitted for clarity.

Upon attempting to cleave the isoxazoline ring of 3 to the β-hydroxy ketone 4 using our recently reported Raney Ni/AlCl$_3$ or BCl$_3$ procedures[12] (or any other hydrogenolytic method), it was found that dehydration occurred under the reaction conditions, for much of the corresponding saturated ketone was generated. However, ozonolytic cleavage proceeded in good yield to give presumably 4 which was further converted by *p*-TsOH promoted dehydration to the enone 5.[13]

While intermediate 3 could be converted to a suitable guaianolide precursor by a number of fairly conventional steps, the incorporation of the extra methyl group required at C4 or C5 for guaianolide or pseudoguaianolide construction, respectively, at a much earlier stage should allow for the more efficient buildup of an advanced intermediate. Additionally, the incorporation of a more suitable carbonyl synthon at C10 should further expedite the overall process envisioned.

The contents of this letter again substantiate the importance of isoxazolines generated by the [3+2] cycloaddition process as *aldol equivalents*, but one of the many equivalencies that link chemically these heterocycles with other functional group pairs.[14,15]

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References and Notes

1. For reviews of the pseudoguaianolides and the guaianolides, see C. H. Heathcock, S. L. Graham, M. C. Pirrung, F. Plavac and C. T. White in "The Total Synthesis of Natural Products", Vol. 5, J. W. ApSimon, Ed., Wiley, New York, 1982 and C. H. Heathcock, *Ibid*., Vol. 2.
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3. For examples of routes a-d, see reference 2. For an example of route e, see R. Noyori, M. Nishizawa, F. Shimizu, Y. Hayakawa, K. Maruoka, S. Hashimoto, H. Yamamoto, and H. Nozaki, *J. Am. Chem. Soc.*, **101**, 220 (1979).
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10. Physical and spectral data for **3**: mp 94-96°C; IR (thin film) 2930, 1720, 1440, 1320-1100, 1090, 1075, 1060, 1030, 1000, 975, 960, 940, 920-845, 830, 770, 730, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.98 (dd, 1 H, *J* = 8.1, 5.2 Hz), 3.97 (dd, 1 H, *J* = 8.1, 8.1 Hz), 3.68 (s, 3 H), 3.60 (s, 3 H), 2.72-2.53 (m, 2 H), 2.27-2.12 (m, 2 H), 1.94 (dd, 1 H, *J* = 13.6, 6.1 Hz), 1.88-1.52 (m, 3 H), 1.41-1.10 (m, 3 H); Exact mass calcd for $C_{14}H_{19}NO_5$ 281.1263, found 281.1257. **5**: mp 73-74°C; IR (thin film) 2930, 1730, 1670, 1595, 1430, 1345, 1320, 1300-1130, 1080, 1055, 1035, 1015, 1000, 955, 880-845, 770-730, 720-685 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 6.98-6.92 (m, 1 H), 3.77 (s, 3 H), 3.68 (s, 3 H), 3.63-3.52 (m, 1 H), 2.67-2.50 (m, 4 H), 2.49-2.34 (m, 1 H), 2.31-2.11 (m, 2 H), 2.05-2.89 (m, 2 H), 1.83-1.67 (m, 1 H); Exact mass calcd for $C_{14}H_{18}O_5$ 266.1154, found 266.1154.
11. Details of the x-ray structure will be reported elsewhere.
12. A. P. Kozikowski and S. Goldstein, *J. Org. Chem.*, **48**, 1139 (1983).
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14. For some other recent examples from these laboratories, see: A. P. Kozikowski and A. K. Ghosh *J. Am. Chem. Soc.*, **104**, 5788 (1982); *idem*, *Tetrahedron Lett.*, in press; A. P. Kozikowski and J. G. Scripko, submitted.
15. Attempts to prepare both the eight- and nine-membered ring systems via the appropriate homologs of **2** have proven unsuccessful. The outcome of these reactions may be changed, however, by minimizing non-bonded interactions in the transition state through removal of one or both of the carbomethoxy groups.

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