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A General Synthesis of cis Perhydro 3,6-Isoquinolinediones Related to the Alloyohimbane Alkaloids

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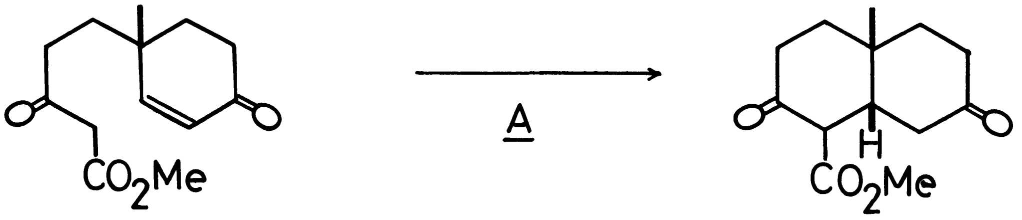
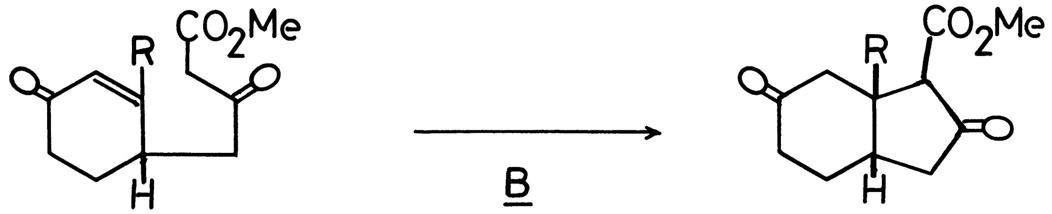
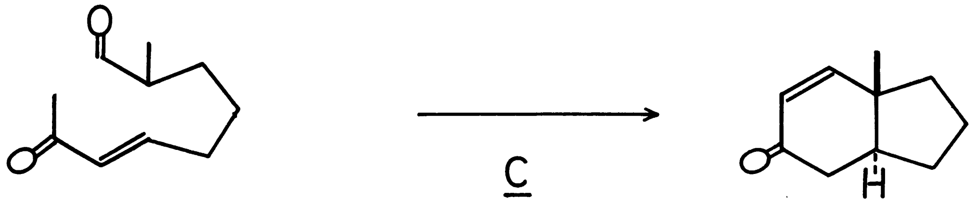
The intramolecular annulation of malonic acid derivatives of 4-aminomethyl cyclohexenones is shown to be an efficient route to 3,6-diketoderivatives of cis perhydroisoquinolines.

The synthesis of complex structures often requires the specific construction of either cis or trans bicyclic elements. We have shown earlier that the intramolecular Michael reaction is particularly valuable in that connection since it can be used in two different versions, leading either to cis (A[1a]; B[1b]) or to trans (C)[1c] bicyclic systems.



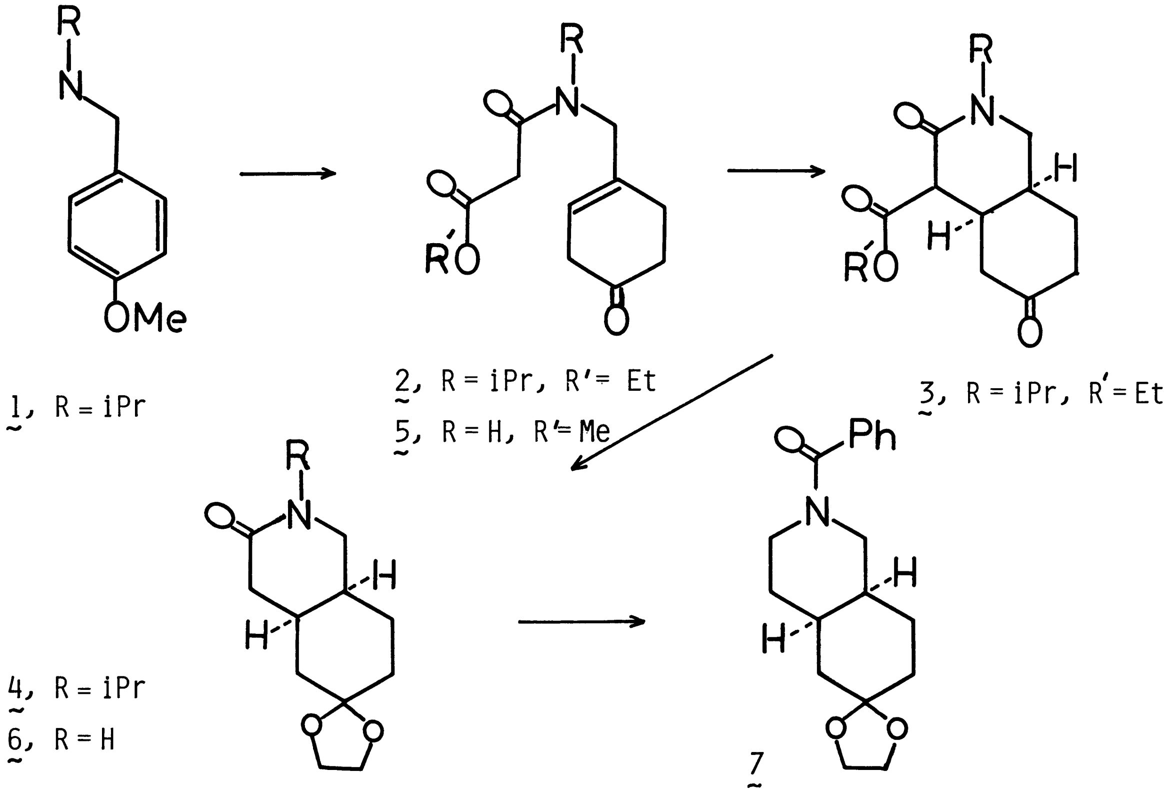




Dedicated to Professor T. Mukaiyama on the occasion of his sixtieth birthday.

We now show that the intramolecular annulation of type A is also very effective in the stereospecific construction of cis-fused bicyclic heterocyclic systems.[2] We specifically illustrate this with a general synthesis of cis perhydro 3,6-isoquinolinediones. These systems are related, for example, to reserpine and other alloyohimbane alkaloids.[3]

Birch reduction of N-isopropyl-4-methoxylbenzylamine (1)[4] (lithium-liquid ammonia, 5 equiv. lithium, 5 min; 97%), followed by acylation with carbethoxyacetyl chloride (10% excess in benzene with 4 equiv. triethylamine) and acid hydrolysis (1% aq hydrochloric acid in ethanol) gave the malonic acid derivative 2 (chromatographed on silica with 10% ethyl acetate in hexane) which spectral data clearly showed to be the unconjugated isomer. Treatment of 2 with sodium ethoxide (1 equiv.) in ethanol (30 min, room temperature, followed by quenching with acetic acid) gave the carbethoxyisoquinolinedione 3, mp 100-102 °C (66% after silica chromatography; IR: 1635, 1725 cm^{-1}), obviously via conjugate addition to the α,β-unsaturated tautomer. Refluxing 3 with 10% sodium hydroxide in THF, followed by acidification and evaporation of the solvent under vacuum, gave the corresponding carboxylic acid which underwent decarboxylation under the usual conditions for dioxolane formation. The quinolinedione ketal 4 was thus produced, as a single isomer, in 25% overall yield from 4-methoxybenzaldehyde.



1, R = iPr

2, R = iPr, R' = Et
5, R = H, R' = Me

3, R = iPr, R' = Et

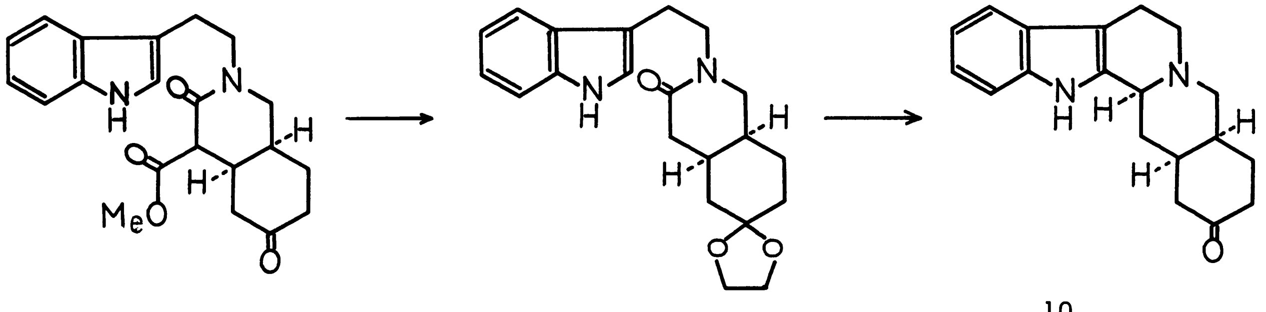
4, R = iPr
6, R = H

7

The construction of the related N-unsubstituted cis quinolinedione ketal 6 was carried out in a similar manner[5] via the unsaturated amide 5, mp 92.5 -

94 °C,6) to produce the crystalline ketal of hexahydroisoquinoline-3,6-dione (6), mp 160-161 °C7) (22% overall yield from commercially available 4-methoxybenzylamine). The cis stereochemistry of 6 was proved by reduction (LAH - THF), followed by treatment with benzoyl chloride, to give the ethylene glycol ketal of N-benzoyl hexahydro-6(2H)isoquinolone (7), mp 108-109 °C, identical in all respects (including mp of mixture) with an authentic sample.3a)

The efficient synthesis of cis hexahydro-3,6(2H,5H)isoquinolinediones which we have just described provides a simple entry into a number of alkaloid systems. For example, the above sequence of steps, starting with the Birch reduction8) of the imine from 4-methoxybenzaldehyde and tryptamine led, via the lactam ketoester 8, mp 181-183 °C, to the ketal lactam 99) which could easily be transformed to alloyohimbone: Cyclization (2 h reflux in phosphorus oxychloride), followed by reduction of a methanol solution of the resulting iminium salt (sodium borohydride), and hydrolysis of the ketal with hydrochloric acid let to (±)-alloyohimbone (10) (dec. 246 °C).10)



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References

1) a) G. Stork, D.F. Taber, and M. Marx, Tetrahedron Lett., 1978, 2444; b) G. Stork, R.K. Boeckmann, Jr., D.F. Taber, W.C. Still, and J. Singh, J. Am. Chem. Soc., 101, 7107 (1979); c) G. Stork, C.S. Shiner, and J.D. Winkler, ibid., 104, 310 (1982).

2) Strong indications of the feasibility of this route had been obtained in earlier experiments. Cf D.F. Taber, Ph.D. thesis, Columbia University, 1974.

3) For other syntheses of cis perhydroisoquinolones, see inter alia, a) M. Uskokovic, J. Gutzwiller, and T. Henderson, J. Am. Chem. Soc., 92, 203 (1970); b) P.A. Wender, J.M. Schaus, and A.W. White, ibid., 102, 6157 (1980); c) S.A. Godleski and E.B. Villhauer, J. Org. Chem., 49, 2246 (1984).

4) Bp 140-141 °C (20 mmHg): made by sodium borohydride reduction of the imine from 4-methoxybenzaldehyde and isopropylamine.

5) Using carbomethoxyacetyl chloride: V. Grakauskas, J. Org. Chem., 43, 3485 (1978); H. Leden, G. Linstrumelle, and S. Julia, Tetrahedron, 29, 3609 (1973).

6) Found, C 58.42; H, 6.70%. The corresponding conjugated isomer of 2 was sometimes obtained instead: mp 78-79 °C; Found: C, 58.66; H, 6.71%.

7) Found: C, 62.23; H, 7.84%. The very polar compound is soluble in an equal weight of water. The corresponding keto lactam (aq. hydrochloric acid), the parent 1,4,4a,7,8,8a hexahydro 3,6 (2H,5H) dione, had mp 155-155.5 °C; Found: C, 64.52; H, 7.84%.

8) By addition of its solution in THF-t-butyl alcohol to 10 equiv. of lithium in anhydrous ammonia, followed by quenching with benzoic acid after 45 min.

9) Ketalization-decarboxylation required refluxing in toluene, in this case.

10) The infrared spectrum agreed with the literature: A. LeHir, M.M. Janot, and R.Goutarel, Bull. Soc. Chim. Fr., 1953, 1027.

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