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A GENERAL METHOD FOR CIS-HYDROISOQUINOLINE SYNTHESIS

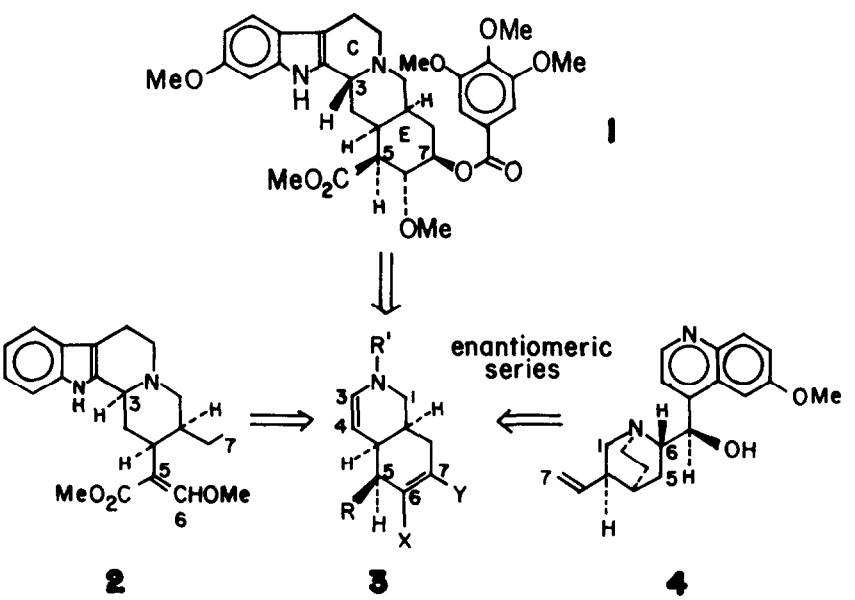
Paul A. Wender,* John M. Schaus,[1a] and David C. Torney[1b]

Department of Chemistry, Harvard University, Cambridge, MA 02138

A method is described which allows for the conversion of N-carbomethoxy-1,2-dihydropyridine to *cis* hydroisoquinolines *via* a Diels-Alder/Cope rearrangement sequence.

As part of our continuing interest in the development of general methodology for the synthesis of key naturally occurring ring systems, we have initiated studies on methods for the preparation of *cis*-hydroisoquinolines. This ring system is a key sub-unit of or potential precursor to demonstrated chemotherapeutic agents such as reserpine (1)[2] and quinine (4)[3] and a wide range of indole alkaloids[4] (Scheme I). For example, with respect to a synthesis of reserpine or its

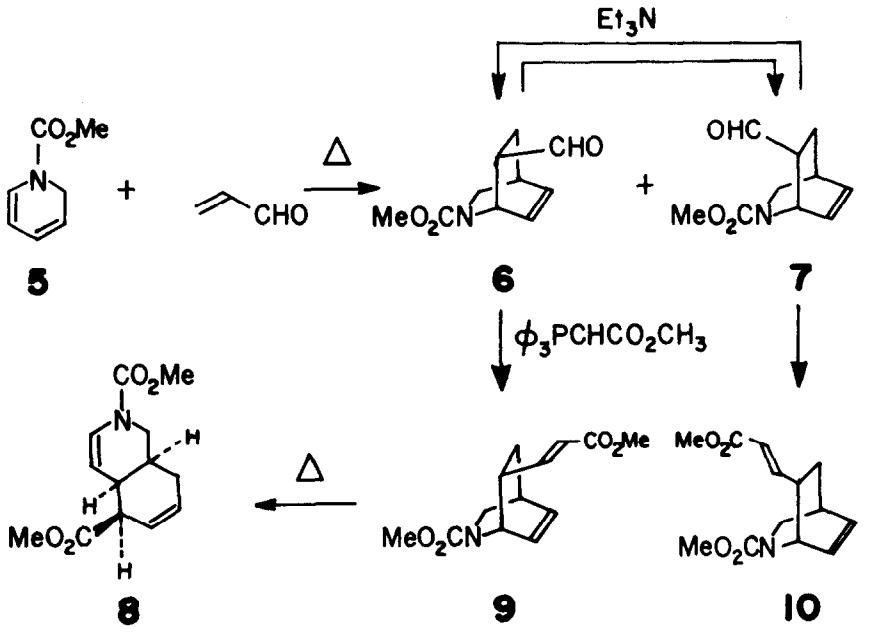
Scheme I



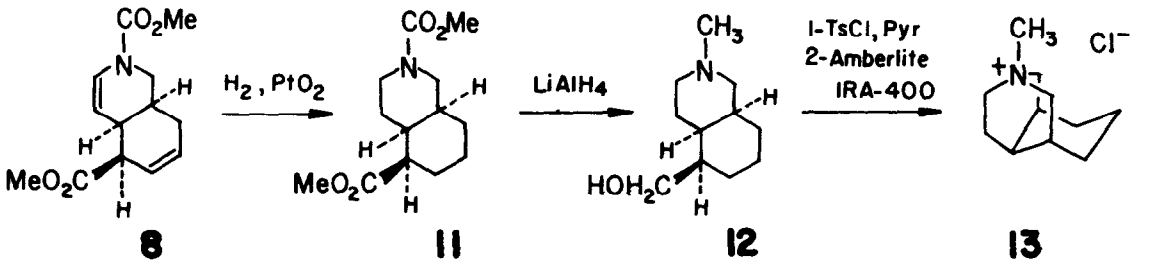
analogues, the C-3, C-4 double-bond of hydroisoquinoline 3 (R'=6-methoxytryptophyl) is suitably situated for regio-controlled Pictet-Spengler cyclization to form ring C while the chemically differentiated C-6, C-7 double-bond could be utilized for introduction of the E-ring functionality Alternatively, oxidative cleavage of the C-6, C-7 double-bond of such hydroisoquinolines would provide the basis for approaches to alkaloids such as corynantheidine (2) or quinine depending on

the choice of peripheral appendages. We expected that a general method for the preparation of the *cis*-hydroisoquinolines required in these strategies could be derived from the Diels-Alder/Cope rearrangement sequence outlined in Scheme II.[5] The viability of this method for hydroisoquinoline synthesis is reported herein.

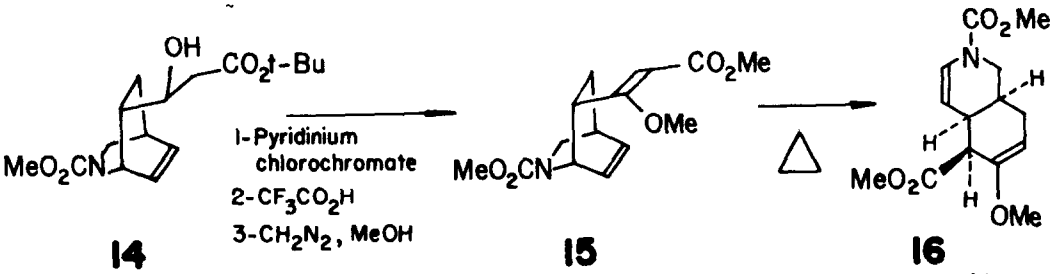
Scheme II



N-carbomethoxy-1,2-dihydropyridine (5) (prepared from pyridine according to the procedure given by Fowler[6]) and acrolein (Eastman, 0.1% hydroquinone) when heated under reflux in toluene for ca. 28 h provided aldehydes (6) and (7) in the ratio of 7:3 (70% yield).[7] This ratio did not significantly change when the reaction temperature or time or solvent was varied and was different from the equilibrium ratio (ca. 1:1) obtained by heating aldehyde 7 or a 7:3 mixture of aldehydes 6 and 7 in triethylamine. The latter process can be used to convert the minor adduct (7) to aldehyde 6. The stereochemical assignments for these aldehydes are based on the expected preference for an *endo*-mode of cycloaddition and are further supported by studies on the pyrolysis of esters (9) and (10) obtained by reaction of the aldehydes with carbomethoxymethylenetriphenylphosphorane.[8] Specifically, pyrolysis (246°C, 5 h) of a toluene solution of ester (9) in a resealable Pyrex tube provided the expected hydroisoquinoline (8)[9] in 79% yield, whereas under the same conditions, ester (10) was recovered in high yield. Similarly, pyrolysis of a 7:3 mixture of esters (9) and (10) gave hydroisoquinoline (8) (52%) and unreacted ester (10) (21%). These data are in accord with the expectation that rearrangement of ester (9) would proceed *via* a [3,3]sigmatropic shift involving a boat transition state whereas a similar low energy pathway for the rearrangement of ester (10) would be geometrically impossible. The stereochemistry of hydroisoquinoline 8 would follow from a concerted or operationally equivalent Cope rearrangement of ester (9) and was proved by conversion of 8 to the symmetrical salt 13. This conversion serves to uniquely distinguish the reserpine-related stereochemistry established in this sequence from any other stereochemical outcome.[10]



In an extension of this study, we have found that the above sequence can be readily modified to allow for the preparation of C-6 substituted hydroisoquinoline derivatives. For example, hydroxy-ester (14), obtained from the reaction of aldehyde (6) with the lithium enolate of *tert*-butyl acetate, was converted to ester (15)[11] by the indicated three-step sequence. Thermolysis (258°C, 2.5 h, toluene-pyridine) of this ester provided (64% yield) hydroisoquinoline (16),[12] a potential precursor to various pentacyclic indole alkaloids. Finally, while we have restricted the above studies for mechanistic purposes to elaboration of the Diels-Alder adducts of acrolein and (5), it is noteworthy that (5) will undergo cycloaddition with a variety of dienophiles including methyl



vinyl ketone, methyl acrylate, α-acetoxy-acrylonitrile, and methyl α-acetoxyacrylate.[13] The utilization of these adducts in the above strategy would allow for considerable variation in the functionality of the hydroisoquinoline product.

In summary, this method provides a facile and, considering the ready availability of the starting materials, economically attractive route to *cis*-hydroisoquinolines. Studies directed toward the further development and application of this method are in progress.

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References and Notes

1. (a) National Science Foundation Predoctoral Fellow, 1975-1978.
   (b) Harvard University Undergraduate Research Participant, 1976-1977.
2. R.B. Woodward, F.E. Bader, H. Bickel, A.J. Frey & R.W. Kierstaed, *Tetrahedron* 2, 1 (1958).
3. M. Uskoković, T. Henderson, C. Reese, H.L. Lee, G. Grethe & J. Gutzwiller, *J. Am. Chem. Soc.* 100, 571 (1978) and the subsequent papers in this series.
4. J. Gutzwiller, G. Pizzolato & M. Uskoković, *J. Am. Chem. Soc.* 93, 5907 (1971); G. Grethe, H.L. Lee, T. Mitt & M. Uskoković, *J. Am. Chem. Soc.* 100, 589 (1978). For the most recent study in this area, see: F.V. Brutcher & H. Hinney, *Tetrahedron Letts.*, 679 (1979).

5. A similar sequence has been used in carbocyclic synthesis; for examples, see: M.E. Jung & J. Hudspeth, *J. Am. Chem. Soc.* 100, 4309 (1978); W.L. Scott & D.A. Evans, *J. Am. Chem. Soc.* 94, 4779 (1972); J.A. Berson & M. Jones, Jr., *J. Am. Chem. Soc.* 86, 5019 (1964); and references cited therein. For an amino-Claisen approach to hydroisoquinolines, see: P.S. Mariano, D. Dunaway-Mariano & P.L. Huesmann, *J. Org. Chem.* 44, 124 (1979). Added note: a conceptually related approach to an analogue of ester 8 has recently been reported by R.V. Stevens & J.R. Moran (Orgn 289, ACS/CJS Chemical Congress, April 1-6, 1979).

6. F.W. Fowler, *J. Org. Chem.* 37, 1321 (1972).

7. Satisfactory spectroscopic data and elemental or exact mass analysis were obtained for all new compounds.

8. NMR ($CDC\ell_3$) δ 1.04-1.39 (m, 1H), 1.92 (ddd, 1H, J=2, 10, 10 Hz), 2.60-3.10 (m, 3H), 3.23 (dd, 1H, J=2, 10 Hz), 3.66 (s, 3H), 3.68 (s, 3H), 4.38-4.80 (m, 1H), 5.75 (d, 1H, J=16 Hz), 6.15-6.50 (m, 2H), 6.50 (dd, 1H, J=8, 16 Hz). IR (film) 1725, 1700, 1655 cm^{-1}. UV λ_{max}^{EtOH} = 221 nm, ε = 6,400. Mass spectrum m/e 251 (M^+), 139 (base).

9. NMR ($CDC\ell_3$) δ 1.90-2.12 (m, 2H), 2.12-2.46 (m, 1H), 2.98-3.20 (m, 1H), 3.26-3.56 (m, 2H), 3.74 (s, 3H), 3.76 (s, 3H), 3.75-4.08 (m, 1H), 4.30-4.58 (m, 1H), 5.74 (bs, 2H), 6.60-6.92 (m, 1H). IR (film) 1745, 1710, 1650 cm^{-1}. UV $\lambda_{max}^{CC\ell_4}$ = 265 nm, ε = 950. Mass spectrum m/e 251 (M^+), 139 (base).

10. NMR (D_2O) δ 3.66-3.08 (m, 6H), 2.99 (s, 3H), 2.48-1.82 (m, 5H), 1.58 (bs, 6H). For related experiment, see: E. van Tamelen & P.D. Hance, *J. Am. Chem. Soc.* 77, 4692 (1955).

11. NMR ($CDC\ell_3$) δ 1.15-1.55 (m, 1H), 1.88 (ddd, 1H, J=2, 10, 10 Hz), 2.62-3.03 (m, 3H), 3.18 (dd, 1H, J=2, 8 Hz), 3.58 (s, 3H), 3.62 (s, 3H), 3.82 (s, 3H), 4.55-4.94 (m, 1H), 4.81 (s, 1H), 6.09-6.50 (m, 2H). IR (film) 1720, 1695, 1640 cm^{-1}. UV λ_{max}^{EtOH} = 245 nm, ε = 8,600. Mass spectrum m/e 281 (M^+), 139 (base).

12. NMR ($CDC\ell_3$) δ 1.94-2.36 (m, 1H), 2.18 (bs, 2H), 2.71-2.98 (m, 1H), 3.27-3.99 (m, 3H), 3.51 (s, 3H), 3.67 (s, 3H), 3.73 (s, 3H), 4.55-5.01 (m, 2H), 6.54-6.96 (m, 1H). IR (KBr) 1755, 1700, 1670, 1645 cm^{-1}. UV $\lambda_{max}^{CC\ell_4}$ = 266 nm, ε = 1,300. Mass spectrum m/e 281 (M^+), 139 (base).

13. John M. Schaus & David C. Torney, unpublished results. For further studies, see: ref. 6; H. Sliwa & Y. LeBot, *Tetrahedron Letts.*, 4129 (1977); P.S. Mariano, D. Dunaway-Mariano, P. Huesmann & R. Baemer, *Tetrahedron Letts.*, 4299 (1977); R.J. Sundberg & J.D. Bloom, *Tetrahedron Letts.*, 5157 (1978).

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