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SYNTHESIS APPLICATIONS OF AZA-COPE REARRANGEMENTS. STEREOSELECTIVE SYNTHESIS OF TRANS-2-ALKYL-CIS-3a-ARYLOCTAHYDROINDOLONES.[1a]

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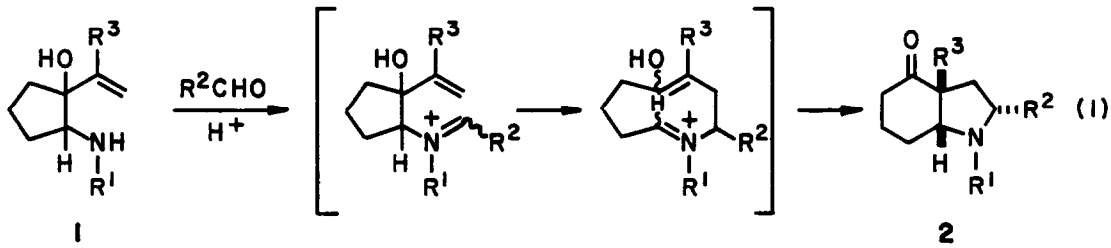
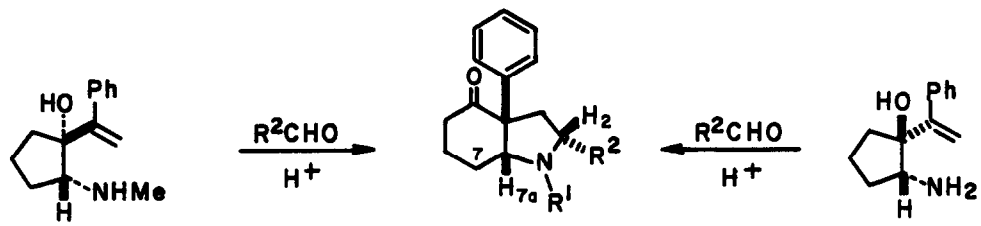
Summary: The reaction of both cis- and trans-2-amino-1-(1-phenylvinyl)-cyclopentanols with aldehydes affords trans-2-alkyl-cis-3a-aryl-4-oxo-octahydro indoles stereoselectively.

The cis-3a-aryloctahydroindole ring system is found in a variety of natural products and pharmaceutical agents.[2] We recently reported the facile reaction of aminocyclopentanols 1 with formaldehyde and acid to give cis-3a-aryl-4-oxo-octahydroindoles stereoselectively and in good yield via a "Mannich-directed" cationic aza-Cope rearrangement[3,4] (eq 1, R^2=H, R^3=Ar). In this Letter, we report that if an aldehyde is employed in this reaction, trans-2-alkyl-cis-3a-aryloctahydroindolones 2 are produced with high (>95%) stereoselectivity.



(1)

Reaction[4] of aminoalcohol 3[3] with acetaldehyde(2 equiv) and d-10-camphor-sulfonic acid(0.95 equiv) for 5 h in refluxing ethanol afforded a single product 4[5] (>98% pure by capillary GC analysis) in 81% yield after purification on silica gel. Octahydroindolone 4 showed characteristic cyclohexanone carbonyl absorption at 1710 cm^{-1} in the IR spectrum, a narrow multiplet at δ 3.19 for H_{7a}



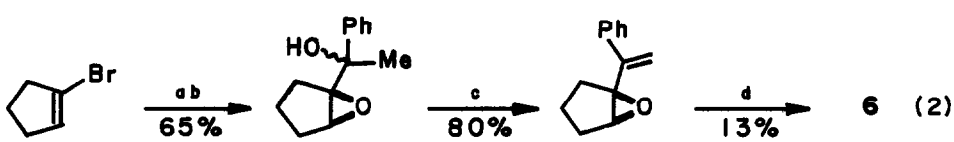
4; $R^1 = R^2 = Me$

5; $R^1 = Me$, $R^2 = n\text{-}C_6H_{13}$

7; $R^1 = H$, $R^2 = Me$

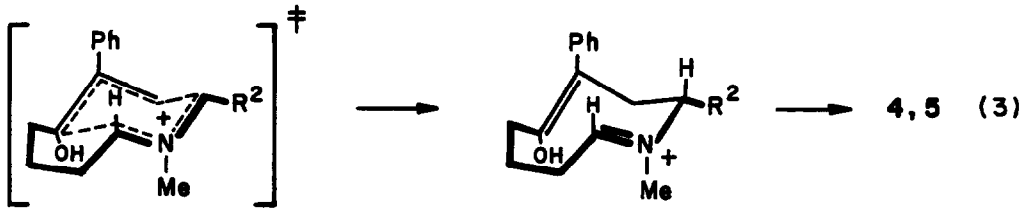
(half-height width = 5 Hz; consistent only with a cis ring-fusion[3,6]), and complex absorption at δ 2.36 for H_2 (collapses to a dd, J = 5.5 and 10 Hz when the C_2-Me is irradiated). The reaction of 3 with heptanal proceeded similarly and gave cis-octahydroindolone 5[5] (IR: 1710 cm^{-1}; ^1H NMR: δ 3.16, broad s, half-height width = 5 Hz) in 77% yield. In this case, GC analysis of the crude reaction mixture showed the presence of a minor product of similar retention time (~ 5%, assumed to be an isomer). The reaction of aminoalcohol 6,[5] which has cis-oriented amine and vinyl groups (prepared as summarized in eq 2), with acetaldehyde (4 equiv, 0.9 equiv RSO_3H, ethanol, reflux, 4 h) proceeded with similar selectivity to give a single product 7[5] in 66% yield. Octahydroindolone 7 showed a narrow multiplet in the ^1H NMR spectrum at δ 4.10 for H_{7a} (half-height width = 6 Hz)[3,6] and complex absorption at δ 3.30 for H_2 (dd, J = 5.9 and 9.6 Hz when the C_2-Me is irradiated). Methylation of 7 (NaH, MeI, rt) gave 4 in 92% yield.

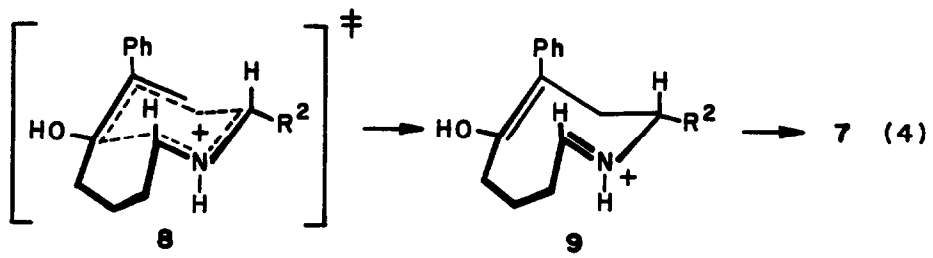
The stereochemistry at C-2 for 4 and 7 follows from the unusual upfield positions of H_{7a} and H_2 in the ^1H NMR spectrum of 4. In particular, N-methylation of 7 resulted in identical upfield shifts for H_{7a} (0.91 ppm) and H_2 (0.94 ppm).[7] cis-Octahydroindolone 4 should exist preferentially in a conformation with the N-Me group on the β-face (trans to C_7 and the C_2-Me) and, thus, the C_{7a} and C_2 hydrogens should be identically shielded[8] by the syn N-Me group and the anti electron pair. Large stereochemistry-dependent ^1H NMR shielding effects for hydrogens alpha to nitrogen have been observed for many N-alkylpyrrolidines.[8,9]

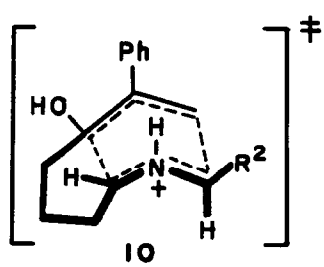


(a) Mg, THF; PhCOMe, reflux (b) m-CPBA, rt; (c) $SOCl_2$, 1:1 Et_3N-THF, -10°C; $KOBu^t$, 18-C-6, pentane, reflux; (d) NH_4OH, NH_4Cl, Pr^iOH, 170°C.

Preferential formation of the less stable trans-2-substituted-cis-octahydroindolone isomers must reflect kinetic control in the ring-enlarging pyrrolidine annulation reaction. If iminium ion formation is readily reversible, it is reasonable that cyclopentanol 3, which has trans-oriented amine and vinyl groups, should give 4 and 5. This prediction follows from an expected kinetic preference for pericyclic rearrangement of the E-iminium ion isomer (via a chair transition state[3,10] with R^2 quasi equatorial, see eq. 3). A cis-octahydroindolone could be formed from cyclopentanol 6 (cis-oriented amine and vinyl groups) via two topologically different pericyclic transition states (8 and 10).[10] Preferential rearrangement of the E-iminium ion isomer in this case would lead[10] to the observed product 7, only if rearrangement occurred via transition state 8. This conclusion is somewhat surprising since cis,trans-1,5-cyclononadiene (the carbocyclic analog of intermediate 9) is less stable[11] than the cis,cis-isomer. Nonetheless, rearrangement of 6 by the sequence described in eq 4 best rationalizes the experimental results obtained to date.[12]







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References and Notes:

1. (a) Part 7 in the series. For part 6, see: Overman, L.E.; Sworin, M.; Bass, L.S.; Clardy, J. Tetrahedron, 1981, 37, 4041. (b) NIH Postdoctoral Fellow 1980-81.
2. This ring system is found, for example, in alkaloids of the mesembrine, Amaryllidaceae, Aspidosperma, and Strychnos families. Cf. Dalton, D.R. "The Alkaloids. The Fundamental Chemistry", Marcel Dekker: New York, 1979.
3. Overman, L.E.; Mendelson, L.T. J. Am. Chem. Soc. 1981, 103, 5579.
4. Cf. Overman, L.E.; Kakimoto, M. J. Am. Chem. Soc. 1979, 101, 1310.
5. New compounds showed IR, 250 MHz ^{1}H NMR, ^{13}C NMR, and mass spectra consistent with their assigned structures, and had correct molecular compositions by high resolution mass spectral or combustion analysis.
6. Cf. Stevens, R.V.; Dupree, L.E.; Lowenstein, R.L. J. Org. Chem. 1972, 37, 977.
7. If the stereochemistry at C-2 were reversed, either (a) small upfield shifts would have been observed for these hydrogens resulting from a mixture of N-methyl conformers, or (b) only one of these hydrogens (the one syn to the N-Me group) would be shifted upfield.
8. Cf. Lambert, J.B.; Oliver, W.L. J. Am. Chem. Soc. 1969, 91, 7774; Breuer, E.; Melumad, D. J. Org. Chem. 1973, 38, 1601; Pitner, T.P.; Edwards, W.B.; Bassfield, R.L.; Whidby, J.F. J. Am. Chem. Soc. 1978, 100, 246.
9. For leading references to similar effects in the piperidine series, see: Vierhapper, F.W.; Eliel, E.L.; Zuniga, G. J. Org. Chem. 1980, 45, 4844.
10. We assume that Mannich ring closure of the presumed azacyclononadiene intermediates is more rapid than loss of their stereochemical integrity. All results obtained to date are consistent with this assumption.
11. ΔH° = 4.3 kcal/mol: Turner, R.B.; Mallon, B.J.; Tichy, M.; von E. Doering, W.; Roth, W.R.; Schröder, G. J. Am. Chem. Soc. 1973, 95, 8605.
12. Although an isomeric aminoalcohol was not detected in the rearrangement of 6, its formation and subsequent rearrangement cannot be rigorously excluded at this time.

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