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ROUTES TO BICYCLO [X.3.0] RING SYSTEMS: STEREOSELECTIVE SYNTHESES OF CIS AND TRANS-8-METHYLHYDRINDANS

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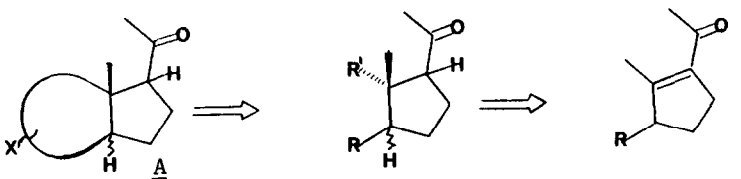
Conjugate additions to 3-alkyl-2-methyl-1-acetylcyclopentenes via diethyl aluminum cyanide and via lithium divinylcuprate lead with good or essentially complete stereoselectivity, respectively, to cis 2-cyano-3-alkyl- and trans 2-vinyl-3-alkyl-1-acetyl-2methylcyclopentanes. The latter may be useful precursors of trans [X,3,0] bicyclic systems such as trans hydrindanes.

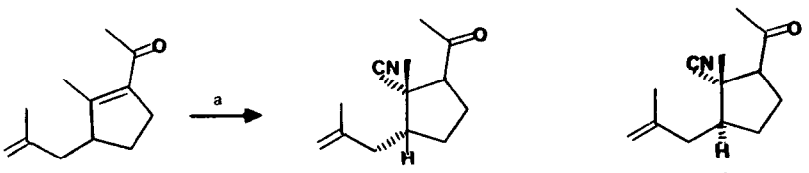
We wish to report an approach to the stereoselective synthesis of [X.3.0] bicyclic systems such as A, [1] in which the junction to the cyclopentane ring can be either cis or trans. As examples, we now record synthesis of angularly methylated [4.3.0] bicyclic ring systems (hydrindanes) from a common acyl-cyclopentene.



A

Steric control is achieved by the stereoselective construction of a cyclopentane suitably functionalized for cyclization to the bicyclic structure (Scheme 1). [2] Treatment of enone 1 [3] with Et_2AlCN [4] produces, in quantitative yield, an 80:20 mixture of the isomeric ketonitriles 2 and 3, respectively. [5] The major isomer 2 has the cis stereochemistry of the cyano and methallyl groups which is required for the construction of a cis bicyclic system. This was proved by the synthesis of a known hydrindane. Ketalization of ketonitrile 2, [6] reduction of the resulting cyanoketal with DIBAL H, and hydrolysis gave aldehyde 5 (86%,

SCHEME 1



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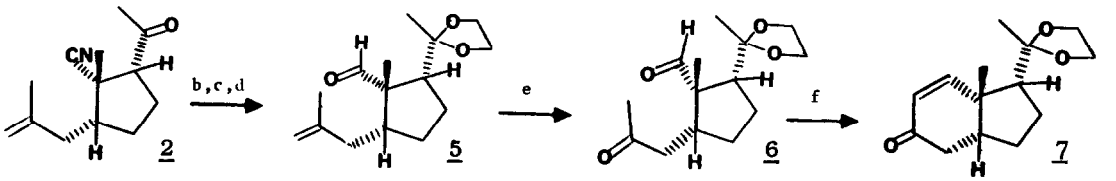
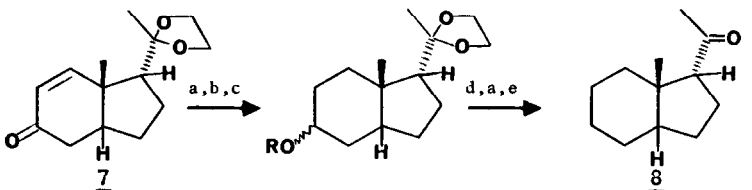


a) Et_2AlCN, benzene:THF [2·3], 0°→25°C, 7 hrs.; b) $HOCH_2CH_2OH$, p-toluenesulfonic acid, benzene, Δ; c) DIBAL H, -78°C→25°C; d) 10% HOAc; e) OsO_4(5%)-$NaIO_4$, ether-water, 25°C, 18 hrs.; f) potassium t-butoxide ether, 25°C, 5 min.

bp. 120° C/0.05mm). Reaction of 5 with OsO_4-$NaIO_4$[7] led to ketoaldehyde 6 (94%)[8] which, on treatment with potassium t butoxide, was cyclized to yield hydrindenone 7 (98%).[9]

Conversion of hydrindenone 7 to the known cis-1α-acetyl-8β-methylhydrindane[10] 8 (outlined in Scheme 2)[11] confirmed the cis ring junction, thereby proving that ketonitrile 2 results from conjugate addition cis to the C_3-methallyl substituent.

SCHEME 2



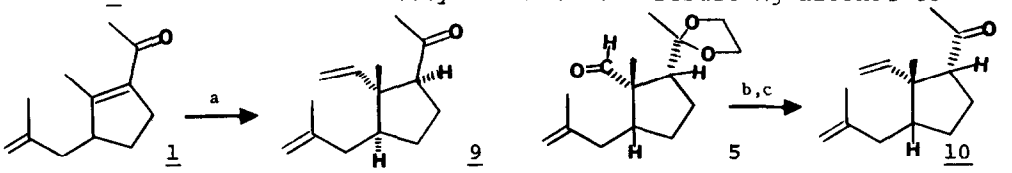
a) H_2, $Pd/CaCO_3$, THF; b) $NaBH_4$, MeOH, 25°C; c) MsCl-pyridine, 0°C; d) DBU, dioxane, Δ; e) H^+, acetone, 25°C.

While this route led to a cis-hydrindane, it is the less stable trans-isomer which is of greater interest. The latter isomer is found naturally as the C,D ring of steroids and has proven to be more difficult to synthesize. Cuprate addition to enone 1 which, in contrast to cyanide addition, is uncomplicated by possible equilibration following addition could be expected to lead to the trans-bicyclic systems.[12] Indeed, we found that treatment of enone 1 with lithium divinylcuprate[13] affords ketone 9 (77%).[14] Prior to conversion of ketone 9 to a trans-hydrindane, confirmation of the indicated stereochemistry was obtained by direct chemical correlation with ketonitriles 2 and 3 (Scheme 3). This was accomplished by Wittig condensation of aldehyde 5 (derived from 2) with triphenylphosphine methylide followed by deketalization to afford ketone 10 (70%). Ketones 9 and 10 were isomers, but equilibration of their C_1-acetyl groups with NaOMe revealed that the two compounds were not solely isomeric at C_1. A similar reaction sequence on ketonitrile 3 (the Nagata reactions's minor product) afforded only a mixture of the two C_1-acetyl isomers of ketone 9, in 35% overall yield. With the relative C_2, C_3 stereochemistry of ketone 9 thus substantiated the route to trans annulated cyclopentanes is clear; and for most purposes (e.g. C/D ring of steroids), the stereochemistry of the C_1 acetyl group is not particularly relevant. We have nevertheless deter-

mined it for the sake of completeness. For both the cis and trans 1 [α,β] - acetyl-8β-methylhydrindanes[10] and for the equilibrium mixture of ketones derived from 10 (vide supra) we noted that the chemical shifts (δ) of the quaternary methyl groups (^{1}H NMR) were 0.33± 0.4ppm further upfield for the isomer in which the methyl and acetyl groups are cis. Application of this observation to the equilibrium mixture of ketones derived from 9 (vide supra), revealed that the major isomer produced in the cuprate reaction had the indicated stereochemistry.[15]

Transformation of ketone 9 to a trans-hydrindane system (Scheme 4) starts by reduction of 9 with DIBAL H and acetylation of the resulting alcohol to

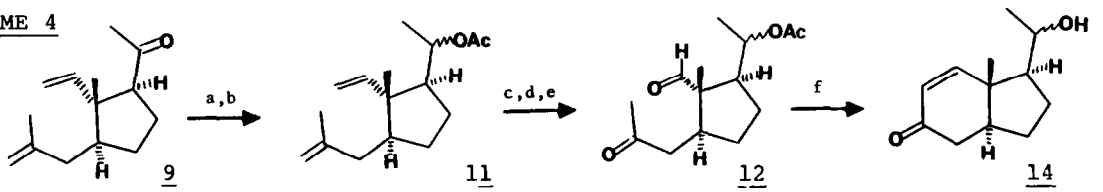
SCHEME 3



a) lithiumdivinylcuprate , ether:THF:DMS [10:1:1.5], -78°C-0°C; b) $Ph_3P=CH_2$, ether, 25°C; c) H^+, acetone.

afford acetate 11 (90%).[16] Selective cleavage of the C_3-methallyl group in 11 with OsO_4-$NaIO_4$[7] followed by ozonolysis furnishes impure ketoaldehyde 12 (75%).[17] Treatment of this ketoaldehyde with NaOMe results in simultaneous aldolization and deacetylation affording, after chromatography, trans-hydrindenone 14 (50%).[18]

SCHEME 4



a) DIBAL H, toluene, 0°C; b) Ac_2O, pyridine, 25°C; c) OsO_4(5%)-$NaIO_4$, ether-water, 25°C; d) O_3, CH_2Cl_2, -78°C, e) Zn, 30%HOAc, f) NaOMe, ether, 25°C.

The above sequence is obviously applicable to the synthesis of [x.3.0] ring systems in general.

Acknowledgment. Financial support from the National Science Foundation and the National Institutes of Health is gratefully acknowledged.

References and Notes

1. This communication is taken in part from the Ph.D. Thesis of P.R. Bernstein, Columbia University (1977).

2. For related approaches to [4.3.0] ring systems see; a) W. Oppolzer, M. Petrizlka, and K. Battig, Helv. Chim. Acta, 60, 2964(1977) and 61, 1945(1978), and b) C.M. Lentz and G.H. Posner, Tetrahedron Lett., 3769(1978).

3. Enones of this general structure are available in high yield from their corresponding unsaturated aldehydes by the addition of methyllithium and oxidation with Sharpless'-reagent, ruthenium trichloride-N-methylmorpholine-N-oxide (K.B. Sharpless, K. Akashi, and K. Oshmira, Tetrahedron Lett., 2503(1976). The synthesis of such aldehydes is the subject of the accompanying communication.

4. W. Nagata, M. Yoshioka, and T. Terasawa, J. Amer. Chem. Soc., 94, 4672(1972).

5. All structures are in accord with NMR, IR, and low resolution MS. Selected intermediates were subjected to either combustion or exact mass analysis.

6. Chromatography on silica gel using ether:hexane 1:4 as the eluent affords a 60% yield of isomerically pure ketonitrile 2a from the product mixture.

7. R. Pappo, D.S. Allen, Jr., R.U. Lemieux, and W.S. Johnson, J. Org. Chem., 21, 478(1956).

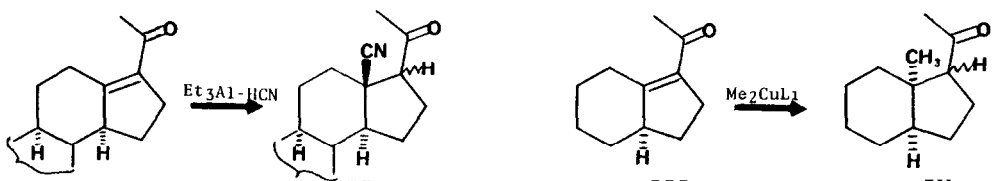
8. This product was an unstable low melting solid which could be recrystallized to afford a sample mp. 69-70.5°C. The instability of this sample precluded a satisfactory combustion analysis.

9. IR(film) 3040(w), 1680(s), 1060(m), 1040(m); NMR($CDCl_3$) 90MHz-δ ppm 7.00(br d, 10Hz, 1H), 5.87(d, 10Hz, 1H), 4.1-3.8(m, 4H), 2.5-1.5(mm, 8H), 1.33(s, 6H); MS(E.I. 30ev) 236 P^+(8%), 221(10)m 149(10), 87(9); Anal. calcd. for $C_{14}H_{20}O_3$ C 71.15, H 8.39: found C 70.78, H. 8.53.

10. B. Zeeh, G. Jones, and C. Djerassi, Chem. Ber., 101, 1018(1965).

11. Attempted direct conversion of the carbonyl to a methylene by a Wolff-Kishner reduction or by treatment with Tosylhydrazine-Sodium Cyanoborohydride afforded a mixture of products.

12. Nagata (ref. 4) has noted that treatment of enone I with Et_3Al-HCN results in predominant formation of ketone II. Whereas Lansbury (P.T. Lansbury, T.R. Demmin, G.E. Dubois, and U.R. Haddon, J. Amer. Chem. Soc. 97, 394[1975]) found that the addition of lithium dimethylcuprate to III affords ketone IV. Furthermore it should be noted that in the case of enone 1a the use of either Et_3Al-HCN or Et_2AlCN produces an identical mixture of products.



I II III IV

13. H.O. House, C.Y. Chu, J.M. Wilkins, and M.J. Umen, J. Org. Chem., 40, 1460 (1975).

14. Ketone 9 contains ∿5% of the epimeric C_1-acetyl isomer. IR(film) 3080(w), 1710(s), 1630(m), 920(m), 890(m); NMR($CDCl_3$) δ ppm. 5.95(dd, 11Hz, 16Hz, 1H), 5.20(dd, 11Hz, 1.5Hz, 1H), 5.03(dd, 16Hz, 1.5Hz, 1H), 4.00(br s, 2H), 2.9(br t, 9Hz, 1H), 2.25(m, 2H), 2.06(s, 3H), 1.95-1.75(mass, 3H), 1.68(br s, 3H), 1.6-1.0(mass, 2H), 0.72(s, 3H); MS(E.I. 12ev) P^+ 206(3%), 163(55), 107(100), 87(75); Anal. calcd. for $C_{14}H_{22}O$ 206.1669 found 206.1670.

15. Angular CH_3 ^1H NMR ($CDCl_3$) δppm. ketone 10 1.33, C_1-isomer of ketone 10 0.98; ketone 9 0.72, C_1-isomer of ketone 9 1.07; cis-1α-acetyl-8β-methylhydrindane* 1.22, cis-1β-acetyl-8β-methylhydrindane* 0.85; trans-1α-acetyl-8β-methylhydrindane* 0.88, trans-1β-acetyl-8β-methylhydrindane* 0.58. * values are taken from B. Zeeh, G. Jones, and C. Djerassi, Chem. Ber., 101, 1018(1968).

16. A similar sequence utilizing protection of the ketone as an ethylene ketal afforded generally lower yields.

17. Oxidative cleavage of diene 9 with O_3 results in a complex mixture of products which contains only a small amount of the desired keto-aldehyde.

18. IR(film) 3640-3200(OH), 3060(w), 1680(s), 1600(w), 1120(m); NMR($CDCl_3$) δ ppm. 7.71(d, 10Hz, 1H), 5.80(d, 10Hz, 1H), 3.80(m, 1H), 2.65-2.25(mm, 2H), 2.24-2.04(mass, 2H [OH]), 2.0-1.3(mass, 5H), 1.20(d, 6.2Hz, 3H), 0.97(s, 3H); MS (C.I.-methane) 223 P^{+29} (10%0, 195(100), 182(20).

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