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SUPERIOR METHODOLOGY FOR γ-LACTONE ANNULATION: INTRAMOLECULAR ALKOXYHYDRIDE REDUCTION OF CONJUGATED NITRILES

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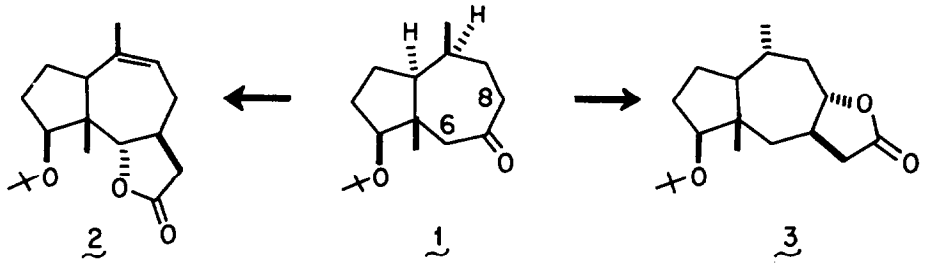
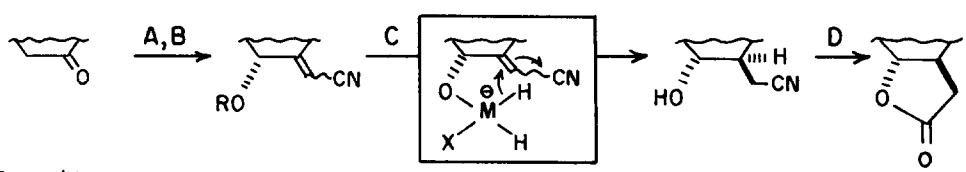
Abstract: Metal hydride reduction of acetate groups adjacent on rings to exocyclic α,β-unsaturated nitriles generates alkoxyhydrides which perform stereospecific intramolecular hydride transfers to the β-position of the conjugated system; hydrolysis of the γ-hydroxynitriles so formed gives, after lactonization, trans-fused γ-butyrolactones whose relative stereochemistry is derived from the configuration of the original acetate.

The ubiquitous α-methylene-γ-butyrolactone moiety is cis- or trans-fused upon the carbocyclic framework of many sesquiterpenes of the germacrane, eudesmane, guaiane and pseudoguaiane types inter alia.[1] Our strategic plans[2] for synthesizing a variety of helenanolides[3] (pseudoguaianolides with α C-10 methyl groups) called for a general and reliable method for site- and diasteroselective annulation of trans-fused γ-lactones[4] onto hydroazulenone 1,[2] with α-methylenation to be performed at a later stage.



2 1 3

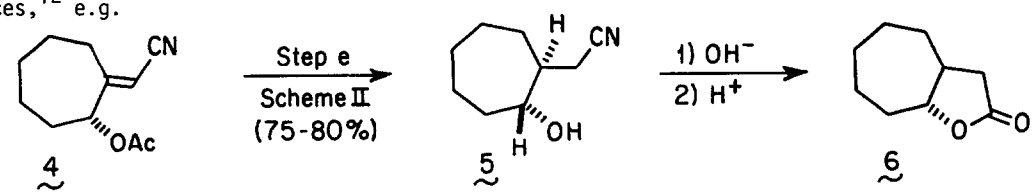
Such a process should be directable to each side of the carbonyl group in any unsymmetrical ketone, so as to create either 6α,7β- or 7β,8α-lactones,[1] exemplified by 2 and 3, respectively. We have devised the following mechanism-based sequence for conveniently solving this problem.



Scheme I: (M=B or Al; X=OC_2H_5 when R=Ac, H when R=H)

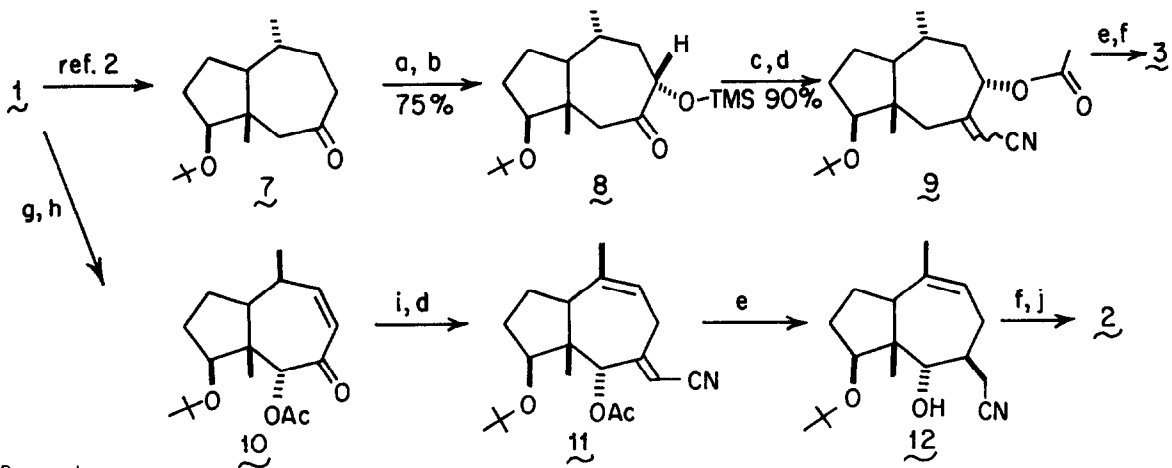
Steps A and B involve well-known operations, i.e. $Pb(OAc)_4$[5] or peracid oxidation (of silyl enolates[6]) adjacent to carbonyl groups, followed by Wadsworth-Emmons olefination,[7]

respectively. In step C, an appropriate complex metal hydride, e.g. $LiBH_4$, chosen to attack initially at the strategically placed acetoxy (or hydroxy) substituent, presumably generates an alkoxyhydride[8] (box in Scheme I) which is uniquely located for stereocontrolled, intramolecular 1,4-conjugate hydride addition. An α,β-unsaturated nitrile was considered the ideal "pre-lactonic" substrate, being essentially inert to intermolecular borohydride attack,[9] and also easiest to incorporate at sterically hindered carbonyl centers such as those in 1, 11 and 13. With $LiAlH_4$, which reduces conjugated nitriles to α,β-unsaturated imines and/or amines,[10] the intended outcome (Scheme I, step C) seemed less certain. Nevertheless there was reason for optimism, since esters are more readily reduced than nitriles[8a] and the carbanionoid reduction product formed in situ would be "electronically protected"[11] from further attack under suitably mild conditions. Final steps (D) for elaboration into trans-fused lactones (or cis-fused lactones via carbinol inversion[4b]) involve well established nitrile hydrolysis and esterification sequences (vide infra). The viability of these speculations was shown by several model sequences,[12] e.g.



The stage was now set for implementing the above described intramolecular reduction strategy for the elaboration of 1 into 2 and 3 (Scheme II).[14]

Scheme II



Reagents:

a) LDA-HMPA, Me_3SiCl; b) MCPBA/CH_2Cl_2, 0°; c) Ac_2O, Et_3N, DMAP/CH_2Cl_2; d) $(EtO)_2POCH_2CN$, NaH/DME; e) 1.3 mol $LiAlH_4$/THF, 0°→RT, 10 min, or 3-4 mol $LiBH_4$/THF, 4-6 h reflux; f) NaOH/EtOH, Δ, then H^+; g) $C_6H_5SO_2CH_3$, NaH/DME, then Δ, $BrCH_2CO_2CH_3$; h) $Pb(OAc)_4/C_6H_6$, Δ; i) DBU/CH_2Cl_2; j) Ac_2O/C_5H_5N, 2 h, RT or p-TsCl/C_5H_5N, 20 h, RT.

Ketone 7, accessible from 1 by epimerization through vinyl activation,[2] was kinetically enolized and the derived trimethylsilyl enol ether (C-8 H, δ 4.9) oxidized[6] to the isomerically pure α-trimethylsiloxy-ketone 8 (C-8 H, δ 4.0). The labile silyl substituent was immediately exchanged with acetic anhydride so that both E and Z isomers of 9 once formed could be kept (and used) without unwanted iminolactone formation (from Z). Inverse addition of $LiAlH_4$ to 9 (0°→RT,10m) gave saturated nitrile in 92% yield, followed by saponification and acidification, whereupon pure 3,[4b] mp 88-89°, was obtained (in 40% overall yield for six steps from 7). This stereoselective route to 3 is superior to our previous sequence for this vital aromaticin-aromatin precursor.[4b] For approaching lactone 2, an 8,9-double bond was first introduced into 1 by C-8 sulfoxide[2] pyrolysis (65% yield), after which lead tetraacetate oxidation[5] at C-6 proceeded stereoselectively in ca. 80% yield. The crucial α-orientation of the acetate group in 10, mp 113°, (ν 1740, 1680 cm^{-1}), was established by observing "W-coupling" (J_4 = 1.8 Hz) in the NMR spectrum between the coplanar C-6 and C-8 protons. Deconjugation of 10 allowed the Wadsworth-Emmons reaction[7] (→11) to proceed without complicating Michael addition at C-9 and set the stage for later functionalization of 2 (see following paper). Rapid $LiAlH_4$ reduction of 11 (95% of 12 after 5 min at RT!) was preferable to slower $LiBH_4$; nevertheless verification of the intramolecular reduction path was achieved using $LiBD_4$, from which reaction the C-6 proton signal appeared as a broad singlet (δ 3.5, H-D coupling) instead of a doublet (J = 11 Hz) as in 12. Saponification of 12 (85%) and lactonization (90%) gave pure 2, mp 109-109.5°, (ν 1780 cm^{-1}). This compound is destined to play a key role in pseudoguaianolide synthesis, so an alternative approach was simultaneously undertaken,[15] particularly to verify beyond any doubt that the annulated γ-lactone ring had the assigned 6α,7β-stereochemistry. Suffice it to say, we have reached the synthetic goals set forth in the first paragraph; further studies will include mechanistic investigations as well as applications in other natural products synthesis.[12]

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b) For trans→cis lactone inversion (at the carbinol center), see P. T. Lansbury, D. G. Hangauer, Jr. and J. P. Vacca, J. Am. Chem. Soc., 102, 3964 (1980) and references cited.
c) For a recent review on γ-lactone synthesis, see S. Kano, S. Shibuya and T. Ebata, Heterocycles, 14, 611 (1980).

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9. Simple α,β-unsaturated nitriles, with no other electron-withdrawing groups at C_α (or C_β), are not reduced by $NaBH_4$ in isopropanol, Y. Pepin, H. Nazemi and D. Payette, Can. J. Chem., 56, 41 (1978) and we have observed comparable inertness of several β,β-dialkylacrylonitriles during 4-6 h exposure to refluxing $LiBH_4$/THF.

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12. Compound 4 was prepared from α-acetoxycycloheptanone according to reagents d, Scheme II, and gave a 1:1 isomeric hydrogenation product mixture (H_2,Pd-C); the lactone 6 (ca. 6:1 trans/cis ratio) is a known substance: J. A. Marshall and N. Cohen, J. Org. Chem., 30, 3475 (1965). Cycloheptylideneacetonitrile is recovered unchanged from extended reflux with $LiBH_4$. Among alternative reductions of conjugated nitriles, dissolving metal reduction (e.g. ref. 13) might not be stereospecific at C_β; moreover, the γ-acetate group would be vulnerable to cleavage. A variety of additional substrates, in which acetate "director groups" are more distant from the conjugated nitrile, also undergo intramolecular alkoxyborohydride reduction (P. T. Lansbury and J. M. Messinger, II, unpublished observations).

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