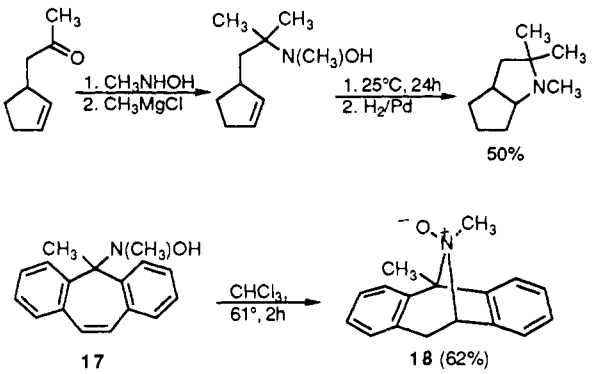
given above indicate that the reverse reaction proceeds by the same mechanism (shown in **13b**-D, Scheme II) rather than by the radical-chain mechanism proposed by House and co-workers[1] for the cyclization of N-monosubstituted unsaturated hydroxylamines to cyclic hydroxylamines (Scheme III). Pertinent observations are: (1) Only one of two possible *N*-oxides is formed; for *N*-oxide **7**, the newly formed methyl group and the *N*-oxide oxygen were shown to be cis as required by the concerted mechanism. It is reasonable to assume that the same stereochemical relationship holds for all other *N*-oxides as well. (2) In suitably substituted substrates the reaction is reversible at room temperature. (3) The observed influence of double bond substitution on the rate of cyclization is inconsistent with a radical mechanism, particularly the rapid cyclization of the internally substituted hydroxylamine **13d** as compared to the very slow cyclization of the terminally disubstituted hydroxylamine **13c**. (4) The specific transfer of deuterium in the transformation of **13b**-D to **14b**-D (Scheme II) is consistent only with a concerted mechanism.

The rate of cyclization of monosubstituted hydroxylamines (Scheme III) has been shown subsequently[3a] to be unaffected by radical inhibitors. We propose that it proceeds by a concerted reverse Cope elimination as well, the only difference being that the secondary *N*-oxide **16** (Scheme III) formed initially rearranges irreversibly[11] to the *N*-hydroxy isomer.

(11) In this connection we have found that no 1-decene is formed when *N*-decyl-*N*-methylhydroxylamine is heated, either neat at 200 °C or in dimethyl sulfoxide at 180 °C.

Scheme IV



The potential use of the reverse Cope elimination in synthesis is under investigation. Two examples are shown in Scheme IV.[12] The reverse Cope elimination discussed here has an analogy in the recently reported[13] intramolecular addition of certain oximes to double bonds to give derivatives of 3,4,5,6-tetrahydropyridine *N*-oxide.

(12) The transformation of **17** into **18** is analogous to the cyclization of *N*-[5-(5-methyl-5*H*-dibenzo[*a*,*d*]cycloheptenyl)]hydroxylamine to 5-methyl-12-hydroxy-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine, which is the key step in the synthesis of the *N*-methyl-D-aspartate receptor antagonist MK-801.[3d]

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Carbohydrates to Carbocycles: A Synthesis of (-)-α-Pipitzol[1]

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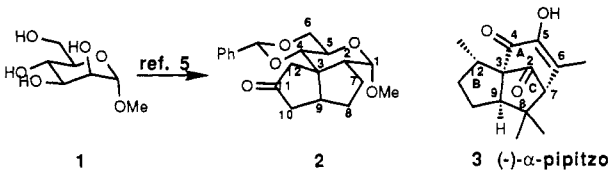
Summary: A 2-deoxy-3-keto sugar derived from methyl α-D-mannopyranoside has been processed to give a multibranched-chain sugar which undergoes serial radical cyclization, affording a pyranosidodiquinane as the key intermediate. The diquinane moiety represents the BC ring system of pipitzol, the A ring being obtained from the pyranosido moiety. A late intermediate is identified by comparison with the racemic modification prepared by Funk and Bolton, and, following their procedure, (-)-α-pipitzol was obtained spectroscopically identical with the racemic modification but with $[\alpha]_D = -141°$.

Studies in this laboratory have been concerned with the development of synthetic routes to complex polycyclic hydrocarbons from sugars,[4] and recently, radical cyclization avenues have been examined for preparation of the requisite annulated pyranoside precursors.[5,6] Central features of this approach are the use of the pyranoside core for several purposes: (i) easy stereocontrol in the creation of off-template stereocenters; (ii) for proof of structure via NMR analyses; (iii) as a source of varied latent functionalities; and, as a bonus, (iv) for its optical activity. In this paper, we exploit these attributes to achieve a stereospecific synthesis of (-)-α-pipitzol, **3**,[7-9] which makes this type

Scheme I



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(3) I.I.C. is grateful to the Government of Spain for a Post Doctoral Fellowship. Permanent address: Departmento de Quimica Organica, Universidad de Alcala, Madrid, Spain.

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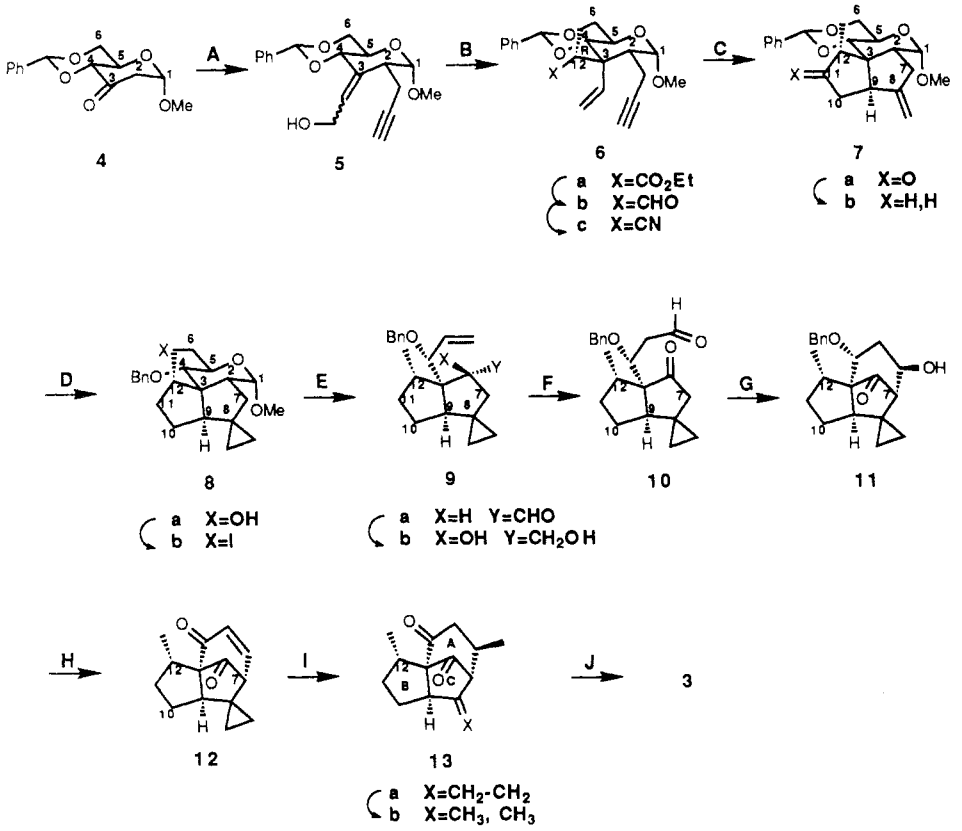
Scheme II[a]



[a] (A) (i) KH, THF, propargyl bromide, 0 °C (50%); (ii) $(EtO)_2POCH_2COOEt$, NaH, THF, 0 °C then DIBAL (53%); (B) (i) $CH_3CH_2C(OEt)_3$, CH_3CH_2COOH, xylene, reflux (85%); (ii) DIBAL then PCC then NaOMe (85%); (iii) NH_2OH·HCl, NaOAc/AcOH then $(CF_3CO_2)_2O$ (65%); (C) (i) (a) Bu_3SnH, AIBN, PhH, reflux; (b) silica gel, CH_2Cl_2 (65%); (ii) DIBAL (88%); (iii) PhOCSCl then Bu_3SnH (70%); (D) (i) Et_2Zn, CH_2I_2, $PhCH_3$, 60 °C (94%); (ii) DIBAL (60%); (E) (i) Ph_3P, I_2 (90%); (ii) Zn(Hg) (70%); (F) (i) (a) $KN(TMS)_2$, TBSCl, DMF, −60 °C, (b) MCPBA, (c) Bu_4NF, (d) $NaBH_4$, [64% a–d]; (ii) (a) BH_3·Me_2S, (b) $NaIO_4$, (c) PDC, [25% a–c]; (G) 0.25% Na_2CO_3, 4:3 MeOH/H_2O (90%); (H) (i) TsCl; (ii) H_2, Pd/C; (iii) LiBr, DMF, reflux; (iv) Dess–Martin periodinane, CH_2Cl_2; (I) (i) Me_2CuLi, THF, −78 °C; (ii) H_2, PtO_2, AcOH, 3–4 atm; (iii) Dess–Martin periodinane [24% for H and I]; (J) SeO_2, dioxane/H_2O, reflux, 18 h (47%).

of cedranoid sesquiterpene available in optically pure form for the first time (see Scheme I).

The above-mentioned radical cyclization studies[5] provided a route from the mannoside **1** to the pyranosidodiquinane **2**.[10] Juxtaposition of **2** with pipitzol **3** shows that a major task would be the development of a strategy for connecting C-6 to C-7. With respect to the C-8 and C-12 methyl groups, our hope was that provisions for these substituents could be made at early stages of the synthesis.

Indeed, the C-12 methyl group was furnished by using an orthopropionate[11] for the spiro Claisen rearrangement[12] of **5** (obtained from **4** by previously described[6b] methodology), while the exocyclic methylene group, generated in the radical cyclization of the derived nitrile[13,14] **6c**, provided the implement for *gem*-dimethyl substitution at C-8. The last reaction afforded ketone **7a** as a single isomer from which the C-11 deoxy analogue **7b** was obtained by DIBAL reduction and subsequent deoxygenation by Robins' variation[15] of the Barton/McCombie process.[16]

After Simmons/Smith cyclopropanation,[17] the benzylidene ring was cleaved by treatment with DIBAL according to Garegg's procedure,[18] and the resulting alcohol in **8a** was converted into the iodide **8b**. Reductive elimination[19] now afforded the enal **9a**.

The task of constructing the A ring could now be addressed, and since the C-2 center of **9** would eventually have to be ketonic, it seemed expeditious to base our A-ring strategy on an aldol condensation. However, aldol ring

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closures to give [3:2:1] bicyclic systems, such as the AC rings of **3**, can be troublesome, although strategies for success have been reported by Coates,[20] based on elegant pioneering studies of Raphael and co-workers.[21]

The most effective synthon for the C-2 carbonyl group proved to be the vicinal diol **9b**, obtained via a Rubottom reaction.[22] Sodium periodate cleavage, followed by routine processing of the olefinic group, led to the keto aldehyde **10**. In view of the aforementioned prospects for the aldol condensation, we were gratified to find that treatment of **10** with a dilute solution of sodium carbonate in aqueous methanol afforded **11** in 90% yield.

It now remained to install the functionality on the A ring, and we planned to intersect with intermediate **13b**, which had been prepared (in racemic form) by Funk and Bolton in their elegant synthesis of α-pipitzol.[9] Of several routes examined, the one preferred involved conversion of **11** into the α-enone **12**, followed by conjugate addition of methyl to give **13a**. Hydrogenolytic cleavage of the cyclopropane ring, followed by reoxidation of the secondary alcohol, then afforded **13b** in chiral nonracemic form. This material had spectroscopic (^{1}H NMR, FTIR, MS) and TLC properties[23] identical with those of a sample of the racemic modification prepared by Funk and Bolton.[9] In keeping with their precedent, selenium dioxide oxidation then afforded (−)-α-pipitzol **3**, which was spectroscopically identical with the racemic material[9] except for the optical rotation, $[\alpha]_D = -141°$.

Acknowledgment. We are grateful to Professor R. Funk for samples and spectra of racemic modifications of compounds **13b** and **3**.

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Articles

Copper-Mediated Oxygenation of Aldehydes and Internal Cannizzaro-like Rearrangement of Phenylglyoxal

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Under the influence of Cu(II) in MeOH containing py and Et_3N, $PhCH_2CHO$ undergoes competitive O_2-dependent conversions to PhCHO and phenylglyoxal. The latter, as the MeOH hemiacetal, undergoes a Cu(II)-catalyzed rearrangement to PhCHOHCOOMe and a Cu(II) oxidation to PhCOCOOMe, and there appears to be an independent O_2-mediated production of PhCOCOOH. Phenylglyoxal also undergoes oxidative cleavage to PhCOOH, but does not give rise to PhCHO. The homologous aldehyde $PhCH_2CH_2CHO$ is converted mainly via $PhCH_2CHO$ to a product mixture derived from the latter. This result is interpreted in terms of preferential C–C cleavage of an α-hydroxyperoxide intermediate initially formed from $PhCH_2CH_2CHO$. The alternative pathway for this intermediate, dehydration to α-keto aldehyde $PhCH_2COCHO$, is barely competitive, because the independently prepared α-keto aldehyde gives a distinct set of products under the reaction conditions. The preference for cleavage over dehydration explains the previously published finding of a stepwise degradation of long-chain aldehydes to formate units by the Cu(II)–py–Et_3N–MeOH–O_2 system. Product comparisons using either an O_2 atmosphere or a N_2 atmosphere (with varying equivalents of Cu^{II}) permit a distinction between stoichiometric Cu(II) oxidations and O_2-dependent reactions. Mechanisms are proposed for the observed transformations.

In the mid 1960s Backman and co-workers reported that aliphatic aldehydes could be autoxidized to α-keto aldehydes under the influence of a Cu(II) salt in MeOH containing excess pyridine and Et_3N,[1] but the synthetic utility was limited on account of competing C–C cleavage reaction(s) leading to a stepwise chain shortening of the aldehyde. These workers presumed that the chain-shortening process involved mainly a methoxide-induced cleavage of α-keto aldehyde to methyl formate and the next lower aldehyde homologue. We recently studied the autoxidation of benzylic ketones using the Cu(II)–py–Et_3N–MeOH system and found that in this case, the aldehyde-forming C–C cleavage occurs in competition with, and not subsequent to, generation of α-dicarbonyl compound.[2] Furthermore, when C–C cleavage of α-diketone did occur, this required the presence of water and Cu(II) as oxidant and led to chain-shortened *acid* rather than aldehyde. On the basis of substantial precedent in published studies on base-catalyzed[3,4] and/or metal-cata-

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