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A TOTAL SYNTHESIS OF THE KESSANOLS

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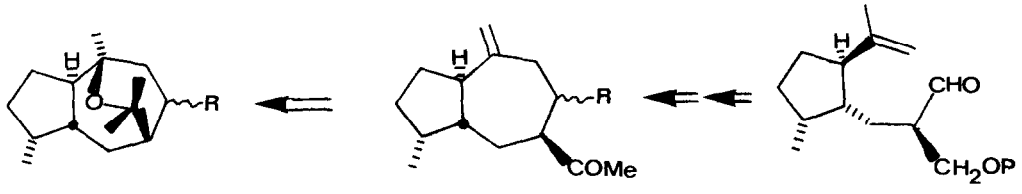
The synthesis of hydroazulenic sesquiterpenes, particularly those with more than one functional group and multiple chiral centers in the cycloheptane ring, remains a challenge.[1] As an example, although the synthesis of kessane (1) was reported in 1970,[2] no syntheses of the kessanols (2, 3), prominent constituents of a number of valerians used as folk medicines,[3,4] have appeared. Our approach to kessanol was originally based on the scheme, 5 → → 4α → → 2, in which oxymercuration of the tert-carbinol derived from 4α was viewed as the last ring-forming step: the ene reaction of olefinic aldehyde 5 serving for the formation of the seven-membered ring.[5] However numerous attempts to obtain cyclization products from aldehyde 5 (P = $SiMe_2tBu$, THP, $OCONEt_2$, $OCH_2\emptyset$, among others) have failed. Although cyclization could be demonstrated under some conditions (SiO_2 chromatography or $SnCl_4$ in CH_2Cl_2) elimination of the oxygen function β to the carbonyl with the formation of the enal was always competitive.[6] We now report a practical synthesis of the kessanols in



1 kessane R = H
2 kessanol R = αOH
3 8-epikessanol R = βOH

4α R = α$OSiMe_2tBu$
4β R = β$OSiMe_2tBu$

5

which the OP group of 5 is replaced by the poorer leaving group, -NHAc, and nitrosative deamination is employed to restore the requisite oxygen functionality at a later stage.

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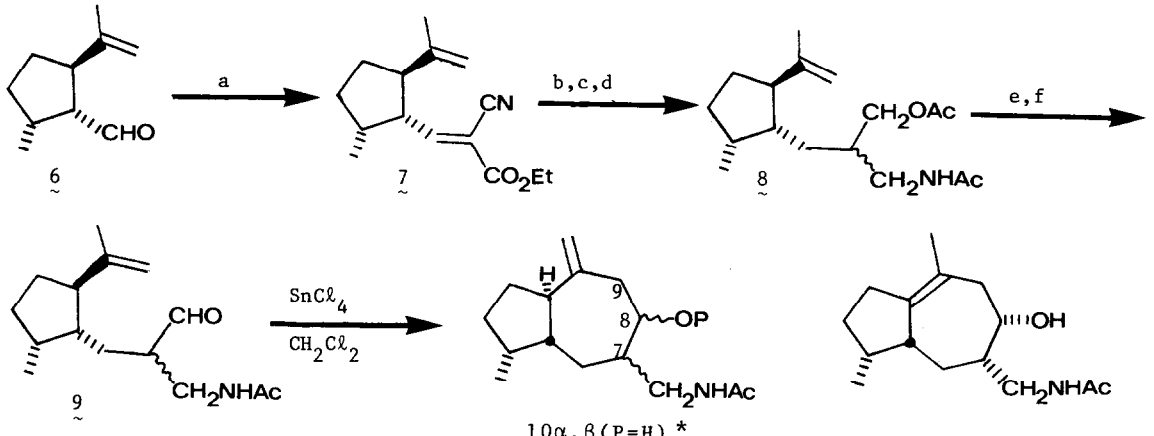
The synthesis of the aldehyde (9) and the results of cyclization experiments are collected in scheme I. The Kno venagel condensation of $CNCH_2CO_2Et$ and photocitral-A (6)[7] proceeds in essentially quantitative yield affording a single isomer (7).[8,9a] A two stage reduction[10] affords the aminoalcohol which is acetylated and purified by column chromatography on SiO_2 affording 8 (53% overall from photocitral-A):[9a] IR (CCl_4) 1750 and 1695 (C=O), 3090, 900 ($C=CH_2$) cm^{-1}; δ ($CDCl_3$) 0.82 (Me, d), 1.67 (vinyl-Me), 1.97 (OAc, Me), 2.07 (NAc, Me), 3.24 ($\underline{CH}_2N$), 4.09 ($\underline{CH}_2O$), 4.72 ($C=CH_2$), and 5.89 (NH) ppm. Selective saponification followed by oxidation (74-85%[11]) affords a 1:1 diastereomeric mixture of aldehyde 9 (barely distinguishable by HPLC):[9b] ν_{CHO} 1730 cm^{-1}. The $SnCl_4$ (0.5 equiv. in CH_2Cl_2 containing powdered NaOAc, 0°) catalyzed cyclization of 9 affords (85% yield) three major products:[9b] 10α, 10β, and 12. The ratio varies with time with the initial product (10α) converting to the more stable endocyclic isomer (12) via a cycloreversion mechanism.[13] The cyclization products are more readily separated after silation,[12c] with 11β (40% from 9) eluting first from a silica column: $C_{21}H_{39}NO_2Si$;[9a,b] mp 108-108.5°; δ ($CDCl_3$) 0.11 ($SiMe_2$, s), 0.83 (Me, d, 7), 0.92 (tBu), 1.96 (MeCO, s), 2.61 (H_2-9, AB of ABX), 3.39 ($\underline{CH}_2NHAc$, AB of ABMX), 4.06 (H-8, J_7=2.3, J_9=6 and 8 Hz), 4.81 ($C=CH_2$), and 6.6 ppm (NH).

Protection of the olefinic linkage (Br_2, pyr-CH_2Cl_2, -78°)[12d] was essential for successful nitrosative deamination.[12e] Debromination[12f] fol-



SCHEME I

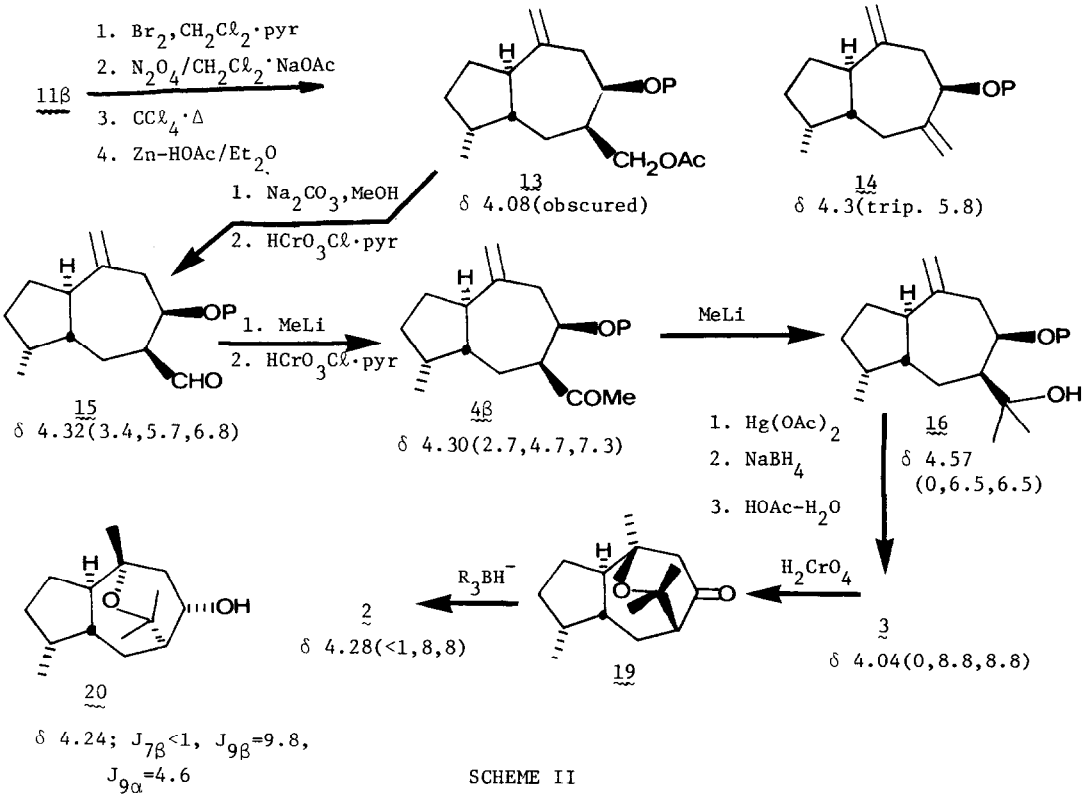
a) $CNCH_2CO_2Et$/β-alanine/95% EtOH; b) $NaBH_4$/MeOH, 0°C; c) $LiAlH_4$/THF at reflux; d) Ac_2O/pyridine; e) KOH-H_2O/MeOH; f) $CrO_3 \cdot 2pyr/CH_2Cl_2$[11].

* The substituents at C-7 and -8 are cis in all the major products: α and β indicates the configuration of the C-8 substituent.[13]

lowed by column chromatography affords the desired product 13 (20% from 11β) but nearly equal quantities of the elimination product (14) were also obtained indicating a cationic mechanism for this nitrosoamide rearrangement. Further efforts to improve the yield of this process have failed, but the minor products have been characterized. The diastereomer (11α) undergoes the sequence with equally poor results: the silyl ether of 12 affords only further rearrangement products.

The further stages in the synthesis leading to 8-epi-kessanol (3) are shown below (scheme II). All compounds are fully characterized,[9b] but only the chemical shift (and vicinal coupling constants) for H-8 are shown. Transesterification and oxidation ($HCrO_3Cl\cdot pyr$)[12g] proceeded without incidence (80% over-all) affording aldehyde 15. Step-wise MeLi additions gave carbinol 16 (60% from 15). The conformational change signalled by the NMR parameters of 16, sets the stage for a high-yield (85+%) mercuricyclization.[14] Desilation (3:1:1, HOAc: H_2O: THF, 70°, $t_{1/2}$=24 hr) proceeds slowly, but without side-reactions, affording racemic 8-epi-kessanol (3), mp 134-134.5°, identical to an authentic sample[15] by NMR, TLC, and GC. The synthesis of kessanol (2) was completed via oxidation to kessanone (19) and the known $LiAlH_4$ reduction[3] which affords a 3:2 mixture of 2 and 3. The use of hindered borohydrides gives ratios approaching 10:1 in favor of kessanol.

When the other exocyclic ene product 10β is subjected to the same



SCHEME II

sequence of reactions, 7-epi-kessanol (20) is obtained, but the mercuricyclization yield is much lower in our preliminary trials. The stereochemical assignment follows from the observed H-8 coupling pattern.

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8. Cyanoester 7 when prepared from epimerically pure photocitral-A displays a single vinyl-H resonance (δ 7.63, d, 11 Hz). More typically, we use photocitral containing 5-10% of the isomer epimeric α to the carboxaldehyde. In such cases a fractional distillation (85% yield, center-cut) of cyanoester 7 provides diastereomerically pure material.

9. This compound was characterized by NMR, IR, and GLC (or HPLC) and a) C,H,N combustion analysis (±0.3%) or b) high resolution (±5 mmass) mass spectral data for the molecular ion and significant fragments.

10. With limited quantities of $NaBH_4$ (or limited time of reaction) in ethanol only the activated double bond is reduced. With $NaBH_4$/MeOH the ester is also reduced, for precedents, see: G.W.K. Cavill and F. B. Whitfield, Proc. Chem. Soc., 380 (1962); Aust. J. Chem., 17, 1260 (1964); J. A. Meschino and C. H. Bond, J. Org. Chem., 28, 3129 (1963); J. A. Marshall and R. D. Carroll, J. Org. Chem., 30, 2748 (1965).

11. The "in situ" Collins oxidation[12a] gave the most reliable results on a large scale (>6g, 74-76%). On a <2g scale a Moffat oxidation using diethylcarbodiimide/pyr H^+ $CF_3CO_2^-$/ CMSO/ϕH[12b] was the best (85+% yield).

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13. The details of studies allowing assignment of the stereochemistry here and in model trans-hydroazulenol synthesis will appear in the full report of these studies. For now, the conversion to the kessanols[3] confirms the assignment.

14. Modeled after the work of H. C. Brown and P. J. Geohegan, Jr, J. Org. Chem., 35, 1844 (1970).

15. Authentic (+)-kessanol and (-)-8-epi-kessanol were kindly supplied by Prof. H. Hikino (Tohoku Univ. School of Medicine).