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CYCLIZATION OF POLYENES XIV[1]. EASY SYNTHESIS OF A/B RING SYSTEM OF HIGHER TERPENOIDS

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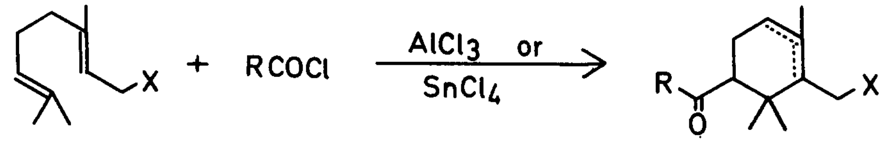
In previous papers[4] we described the results of inter- and intramolecular acylation reaction of polyenes using $AlCl_3$-, or $SnCl_4$ complex of suitable acid chlorides. In particular, we revealed that the acylation occurred selectively at the terminal double bond of geranyl derivatives (I) to give the cyclic acylated products (II) in moderate yields.

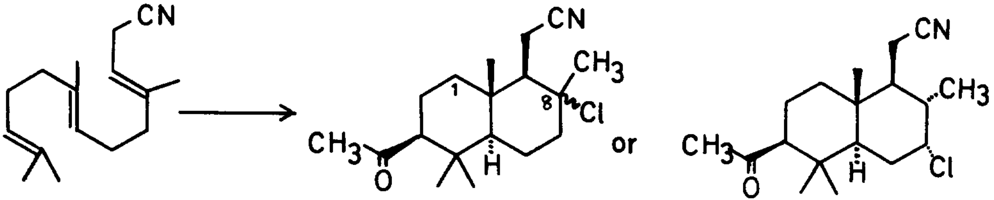
It is of interest to extend the acylation reaction to farnesyl cyanide (III) since it possesses in a molecule three double bonds capable for the involvement of further cyclization.



(I)

(II)

X = CN, CH_2OAc or CH_2CN



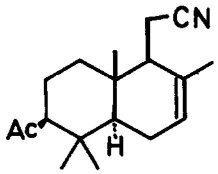
(III) (IV) (V)

Actually, the acylation took place easily to afford bicyclic products (IV, or V) and we observed that the acylation of III is convenient for the construction of A/B ring system of higher terpenoids. The details are reported in this communication.

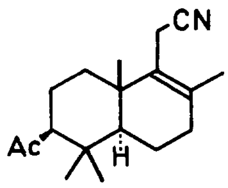
Trans farnesyl cyanide (III) was prepared from nerolidol by successive reactions with PBr_3 (1 mol equivalent) in isooctane (0°C, 3 hr) to farnesyl bromide followed by treatment with NaCN in DMF (room temp., 24 hr). Distillation of crude product under reduced pressure and subsequent chromatography on SiO_2 (n-hexane : AcOEt 40:1) provided the starting material in practical yield. To a freshly prepared CH_3COCl-$AlCl_3$ complex in CH_2Cl_2 was added 1 mol equivalent of trans farnesyl cyanide (III) at 0°C and the mixture was kept for an hour at the same temperature. The acylated cyclic derivative (IV)[5], mp 141-142°, was isolated in 29% yield after usual work up and succeeding chromatography on SiO_2 (benzene : isopropyl ether 4:1). On the other hand, when III was treated with 5 mol equivalents of CH_3COCl-$AlCl_3$ complex under the same conditions, isomeric compound (V), mp 114-115°, was obtained as a major product. The yield of V varies seriously depending mainly on the amounts of the starting material (III) and V was isolated in $30\sim50$% yield when ca 1 g of III was subjected to the acylation reaction.

The structure of IV and V was determined as follows excepting the stereochemistry of chlorine atom of IV. V was submitted to crystallographic X-ray analysis[6] and the structure was unequivocally solved [space group, $P2_12_12_1$ (Z = 4); a = 21.156, b = 13.497, c = 5.981 A°]. V ν^{KBr}_{max}, 2250, 1700 cm^{-1}; δ CCl_4 0.90 and 1.00 (C_4-Me x 2 and C_{10}-Me), 1.13 (C_8-Me, d, 6.5 Hz), 2.18 ($C\underline{H}_3CO$), and 4.50 (C_7-H, q, 3.0 Hz). By treatment with LiCl in DMF, V was selectively converted to the corresponding trisubstituted olefine derivative (VI) in high yield. Under similar conditions, IV was transformed into 6:4 mixture of VI and tetrasubstituted olefine isomer (VII), which were easily separated by preparative TLC on SiO_2 plates (n-hexane : AcOEt 20:1). IV ν^{KBr}_{max} 2250, 1700 cm^{-1}; δ CCl_4 0.88, 0.90 and 1.02 (c_4-Me x 2 and C_{10}-Me), 1.51 (C_8-Me), and 2.18 ($C\underline{H}_3CO$-).

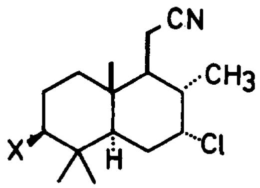
Although the stereochemistry of C_8 of IV is not certain at present, Cl atom of IV is suspected to be α equatorial since chemical shifts of methyl groups at



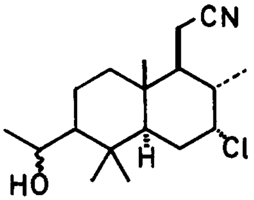
(VI)



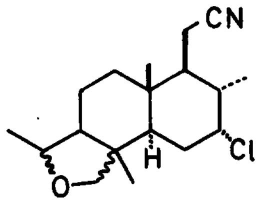
(VII)



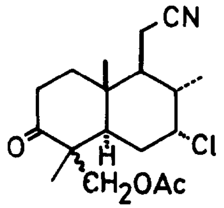
(VIII) X = OAc
(IX) X = OH



(X)



(XI)



(XII)

C_4- and C_{10} of IV are quite similar to those of V. If Cl atom is β axial orientation, remarkable down field shift is expected[7] on the chemical shift of C_{10}-methyl of IV. Treatment of IV with $AlCl_3$ (5 mol equivalents) in CH_2Cl_2 at 0°C resulted in the formation of equilibrium mixture, from which isomer (V) was isolated in ca 40% yield. This finding suggests that the isomer (V) is presumably derived from IV.

The introduced acetyl group is effectively used for the construction of terpenoid A/B ring system. 3-Hydroxy derivative (IX), mp 150-151°, is obtained from V by successive treatments with perbenzoic acid to the acetate (VIII), mp 158-159°, followed by hydrolysis with ethanolic KOH in 50% overall yield. In addition, one of gem-dimethyls at C_4 could be oxidized as follows. Reduction of V with $NaBH_4$ yielded quantitatively ca 1:1 mixture of epimeric alcohols (X), which were separated with high pressure liquid chromatography[8] into Xa, mp 170° and Xb, mp 164°, respectively. Oxidation of Xb with $Pb(OAc)_4$ afforded ether (XI), mp 238-240° in 44% yield after purification with SiO_2 column chromatography (benzene : isopropyl ether 6:1). Treatment of the ether (XI) with CrO_3-H_2SO_4 in mixed solvents of CH_2Cl_2 and acetone gave unexpectedly keto-acetate (XII), mp 138-139° in 34% yield accompanied with recovered ether (42%). XII

ν_{max} 2250, 1740 and 1705 cm^{1}; δ 1.06 and 1.20 (C_4- and C_{10}-Methyls), 1.20 (d, C_8-Me), 2.03 (O$\underline{A}$c), 4.10 and 4.20 (-C$\underline{H}_2$OAc), and 4.50 (C_7-H). XII afforded the corresponding ketal by usual work up. The stereochemistry at C_4 of XII remains unsolved and is the subject of future investigation.

References

1. Part XIII of this series, T. Kobayashi, S. Kumazawa, T. Kato, and Y. Kitahara, Chem. Letts., 301 (1975)
2. Present address, Central Research Center, Kureha Co. Ltd., (Tokyo)
3. To whom correspondence should be addressed.
4. S. Kumazawa, Y. Nakano, T. Kato, and Y. Kitahara, Tetrahedron Letts., 1757 (1974) and references of previous papers are cited therein.
5. All new compounds described herein have been analyzed satisfactorily.
6. Measured by a Rigaku automatically controlled four circle diffractiometer using Mo-Kα radiation.
7. For an example, T. Kato, I. Ichinose, S. Kumazawa, and Y. Kitahara, Bioorg. Chem., in press
8. Chromatographed with Waters Chromatograph provided by the aid of Toray Science Foundation, to which we deeply acknowledge.