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CYCLIZATION OF POLYENES XXIX[1]
SYNTHESIS OF SECO-TAXANE SKELETON BASED ON BIOGENETICAL CONSIDERATION

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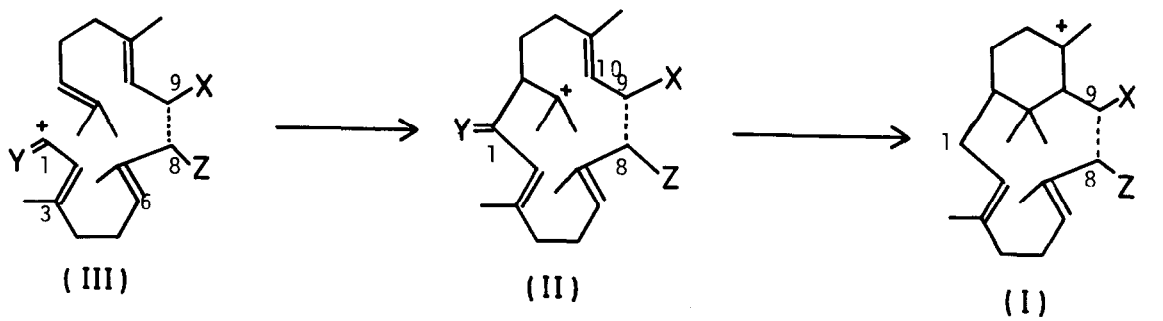
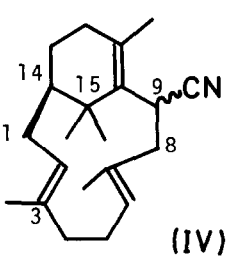
From a biogenetical point of view[3], seco-taxane skeleton(I) is related with cembrene framework(II), both of which are considered to be biosynthesized from acyclic geranylgeranyl cation(III, Y = H_2) as shown below (in each skeleton, C_8-C_9 is bonding). After we have developed an efficient construction method of the cembrene skeleton(II, Y = O) starting from the acyl cation(III, Y = O) derived from geranylgeranic acid chloride[4], we have further continued our synthetic effort for building up the seco-taxane skeleton based on this biogenetical scheme.

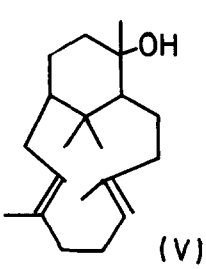
This paper is concerned with our recent exploitation of the construction method of a seco-taxane derivative(IV). Naturally occurring verticillol(V) is a typical example possessing the seco-taxane skeleton[5]. Our synthetic strategy is based on the slight modification of the biogenetical scheme in such a way that C_8-C_9 bond of I is connected <u>after</u> construction of A ring by C-C bond formation



(III) (II) (I)

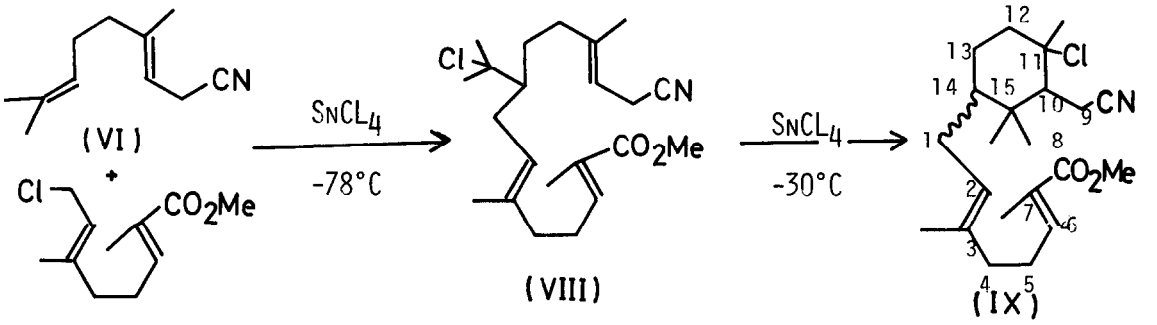


(IV)

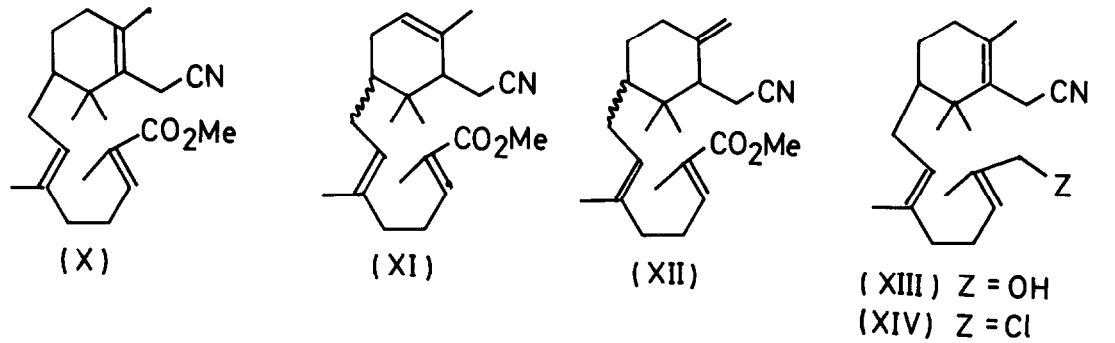


(V)

between isopropyl cation and C_{10}-position of an intermediate(II)(C_8-C_9 is not connected). The seco-cembrene(II) is prepared by head to tail coupling reaction of two geranyl units, both of which are properly functionalized by X and Z groups so as to make the C_8-C_9 bonding at the final stage



a, Cl : CH_2CN = cis
b, Cl : CH_2CN = trans



The regioselective C-C bond formation of the terminal double bond of geranyl cyanide(VI) with allyl chloride(VII)[6] was performed when two geranyl derivatives were kept at -78°C for 1 h in CH_2Cl_2 containing 1 mol equivalent of $SnCl_4$, resulting in the formation of a 10 : 1 mixture of acyclic(VIII) and cyclic(IX) chlorides in 61% yield. The mixture was separated by SiO_2 column chromatography and the former could be transformed into the latter in good yield by treatment with 1 mol equivalent of $SnCl_4$ in CH_2Cl_2 at -30°C for 1 h. In the meanwhile, the cyclic isomer(IX) was formed predominantly and was isolated in 41% yield when the coupling reaction of VI and VII was carried out at -30°C under the same conditions. The PMR spectrum of the resultant cyclic chloride(IX)[7] revealed that it was a ca 1 : 1 mixture of two stereoisomers, IXa and b, which was separated by repeated SiO_2 column chromatography with n-hexane - AcOEt(8 : 1). The evidence described above indicated that the cyclic chlorides, IXa and b, were formed through the acyclic intermediate(VIII).

PMR and IR. VIII δ(ppm), 1.55(3H x 2, s, C_{15}-Me x 2), 1.66(3H x 2, bs, C_3- and C_{11}-Me), 1.81(3H, bs, C_7-Me), 3.03(2H, d, 6.5 Hz, C_9-$\underline{H}_2$), 3.72(s, $CO_2\underline{Me}$), 5.20(2H, bt, 6.5 Hz, C_2- and C_{10}-H), and 6.68 ppm(1H, m, C_6-H): IXa δ(ppm)($CDCl_3$), 0.84 and 1.05(each 3H, s, C_{15}-Me x 2), 1.61(bs, C_3-Me), 1.67(s, C_{11}-Me), 1.83(bs, C_7-Me), 2.48(1H, dd, 3.5 and 18.0 Hz, C_9-Ha), 2.60(1H, dd, 5.5 and 18.0 Hz, C_9-Hb), 3.71(CO_2Me), 5.12(1H, bt, 7.5 Hz, C_2-H), and 6.73 ppm(1H, m, C_6-H); ν_{max}^{neat} 2250, 1710, and 1645 cm^{-1}: IXb δ(ppm)($CDCl_3$), 0.79 and 1.17(each 3H, s, C_{15}-Me x 2), 1.51(s, C_{11}-Me), 1.59(bs, C_3-Me), 1.84(bs, C_7-Me), 2.43(1H, dd, 7.0 and 17.0 Hz, C_9-Ha), 2.78(1H, dd, 3.0 and 17.0 Hz, C_9-Hb)[8], 3.71(CO_2Me), 5.09(1H, bt, 7.0 Hz, C_2-H), and 6.71 ppm(1H, m, C_6-H); ν_{max}^{neat} 2250, 1710, and 1645 cm^{-1}.

Table 1
CMR Spectra of IV, IXa, and IXb

compound	IV	IXa	IXb	compound	IV	IXa	IXb
carbon				carbon			
1	25.9*	28.6	27.9	11	128.6**	74.0	75.4
2	126.1**	124.4	124.0	12	33.8	42.7	44.3
3	131.9**	134.7	134.5	13	32.2	23.0	25.0
4	39.8	38.1	37.8	14	42.5	48.1	47.8
5	26.7*	26.8	26.5	15	38.5	38.4	39.9
6	121.2**	141.8	141.4	3-Me	15.3***	15.8*	15.5
7	132.0**	120.8	120.4	7-Me	16.5***	12.2	11.9
8	42.0	168.0	167.6	11-Me	22.0	15.6*	15.5
9	27.2	14.8	14.4	15-Me	24.2	28.2	24.7
10	132.9**	55.0	56.7	15-Me	32.6	33.8	28.4
				CN	122.8		

Values with *, **, and *** in each vertical column may be reversed

The structure of the chlorides, VIII and IX(a and b), was supported by physical evidence including CMR spectra in table 1. When IXa was submitted to dehydrochlorination with LiCl in DMF (100°C, 3 h), tetrasubstituted olefinic product(X) was exclusively formed in 91% yield while IXb afforded a 1 : 1 mixture of isomers, XI and XII, in 90% yield, which was separated by HPLC or $AgNO_3$(5%) - SiO_2 column chromatography. Although stereochemistry of C_{14}-position of IX(a and b) remains uncertain with respect to the remaining asymmetric carbons at C_{10}- and C_{11}-positions on the cyclohexane ring, it can be deduced on the basis of the dehydrochlorination experiments that the relative stereochemistry of Cl atom at C_{11}-position and the neighboring -CH_2CN group is cis in IXa and trans in IXb, respectively.

PMR. X δ(ppm)(CCl_4), 0.90 and 1.12(each 3H, s, C_{15}-Me x 2), 1.60(bs, C_3-Me), 1.72(s, C_{11}-Me), 1.81(3H, d, 1.5 Hz, C_7-Me), 2.93(2H, bs, C_9-$\underline{H}_2$), 3.65($CO_2\underline{Me}$), 5.12(1H, bt, 7.0 Hz, C_2-H), and 6.62 ppm(1H, m, C_6-H): XI δ(ppm)(CCl_4), 0.80 and 1.05(each 3H, s, C_{15}-Me x 2), 1.61(bs, C_3-Me), 1.83(3H x 2, bs, C_7- and C_{11}-Me), 5.10(1H, bt, 7.0 Hz, C_2-H), 5.53(1H, m, C_{12}-H), and 6.63 ppm(1H, m, C_6-H): XII δ(ppm)(CCl_4), 0.60 and 1.12(each 3H, s, C_{15}-Me x 2), 1.60(bs, C_3-Me), 1.83 (bs, C_7-Me), 4.66 and 4.97(each 1H, bs, C_{11}=C$\underline{H}_2$), 5.13(1H, bt, 7.0 Hz, C_2-H), and 6.63 ppm(1H, m, C_6-H).

The dehydrochlorinated product(X) was reduced with $LiAlH_4$ (-25°C, 2 h) to the allyl alcohol(XIII), which was then converted to the corresponding chloride (XIV) with PPh_3 (1.3 mol equiv) in refluxing CCl_4 for 1 h in 75% overall yield from X. The freshly prepared $LiN(SiMe_3)_2$ (1.3 mol equiv) in anhydrous THF was added to the allyl chloride(XIV) in THF at -78°C under argon atmosphere and the mixture was then kept for 2 h at 0°C. The reaction was quenched by adding MeOH - Et_2O (1 : 1) and the reaction products were passed through a SiO_2 column to give the seco-taxane(IV) in 15% yield as white crystals, mp 149 - 150°C (from MeOH).

The structure of IV was supported by PMR and CMR spectra. It is worthy to note that each coupling mode of two olefinic protons is quite similar in the PMR spectra of both synthesized seco-taxane(IV) and naturally occurring verticillol (V). Each of the two olefinic protons of V is reported to appear as a broad doublet at 4.91 and 5.65 ppm with the coupling constants of 12 and 13 Hz, respectively[9].

PMR. XIV δ(ppm)(CCl_4), 0.95 and 1.15(each 3H, s, C_{15}-Me x 2), 1.63(bs, C_3-Me), 1.72(3H x 2, s, C_7- and C_{11}-Me), 2.90(2H, bs, C_9-$\underline{H}_2$), 3.91(2H, s, C_8-$\underline{H}_2$), 5.05(1H, bt, 7.0 Hz, C_2-H), and 5.41 ppm(1H, m, C_6-H): IV δ(ppm)($CDCl_3$), 0.85 and 1.11(each 3H, s, C_{15}-Me x 2), 1.49, 1.53, and 1.89(each 3H, s, C_3-, C_7-, and C_{11}-Me), 2.90(1H, t, 12.7 Hz, C_8-Ha), 3.42(1H, dd, 12.7 and 3.8 Hz, C_9-H), 4.82(1H, bd, 11.0 Hz, C=C$\underline{H}$), and 5.09 ppm(1H, bd, 12.0 Hz, C=C$\underline{H}$).

Application of the present methodology for the synthesis of verticillol and several kinds of taxinines is now in progress[10].

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6. On the synthesis of VII, see ref. 1.
7. Numbering of all the compounds described herein is conventionally based on that of the biogenetical precursor, geranylgeraniol. All the new compounds have the satisfactory analytical and/or mass spectral data.
8. Description of Ha and Hb means no stereochemical argument.
9. See ref. 5.
10. Ph. D. Thesis of H. Takayanagi submitted to Tohoku University (1978).