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SYNTHESIS OF TRANS-4,8,12,15,15-PENTAMETHYLBICYCLO[9,3,1]PENTADECA-3E,7Z,12Z-TRIENE, A GEOMETRICAL ISOMER OF ANHYDROVERTICILLOL[1]

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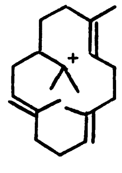
A 7Z-isomer of anhydroverticillol skeleton was constructed in 15% yield when the 7E allyl bromide having secoverticillol framework was treated with $LiN(TMS)_2$. Reductive removal of the SO_2Ph group furnished a geometrical isomer of anhydroverticillol.

Verticillol (1)[2], a constituent of conifer wood of *Sciadopitys verticillata* Sieb. et Zucc. represents a class of structurally fascinating diterpenes that have not yet yielded to chemical synthesis. Its carbon skeleton is biogenetically envisaged as correlating with that of cembrenoid such as neocembrene (2)[3]. Both may be derived from a common precursor (3) arisen from geranylgeraniol in the conifer wood.

After achievement of the synthesis[4] of cembrene type compounds, our effort has been expended to develop the construction method of the former skeleton[5]. A strategy of our synthesis is based on the biogenetical consideration on its formation and a key feature is to apply the regioselective coupling reaction of properly functionalized allyl chloride (6) with the terminal double bond of phenyl prenyl sulfones (7a and b) by virtue of $SnCl_4$ followed by ring closure to make seco-verticillol



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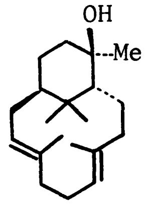
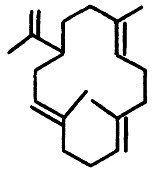


(1)



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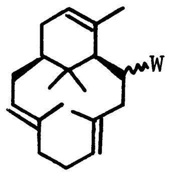

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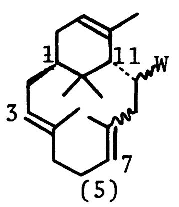
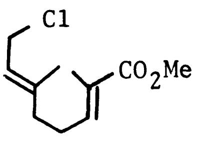
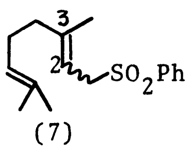


(5)

a $C_7{=}C_8$; Z
b $C_7{=}C_8$; E

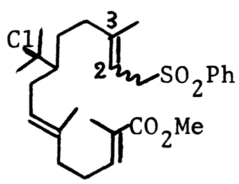


(6)



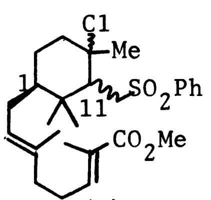
(7)

a $C_2{=}C_3$; Z
b $C_2{=}C_3$; E



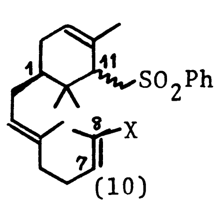
(8)

a $C_2{=}C_3$; Z
b $C_2{=}C_3$; E



(9)

a C_1,C_{11}=cis
b C_1,C_{11}=trans



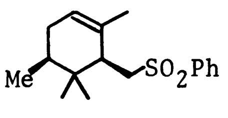
(10)

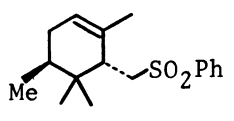
a C_1,C_{11}=cis
b C_1,C_{11}=trans

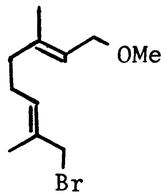
framework (9). The final C-C bond formation would provide the requisite skeleton of anhydroverticillol (4 and 5). We report here the result of our approach which has led to a synthesis of a geometrical isomer of anhydroverticillol (5a, W = H).

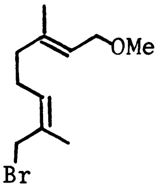
To a 1:1 mixture of neryl phenyl sulfone (7a)[6] and the allyl chloride (6)[7] in CH_2Cl_2 was added 1 mol equivalent of $SnCl_4$ at -78°C. When the reaction was quenched with pyridine at the same temperature after 2 hr, the coupling product (8a) was obtained in 44% yield accompanied with the corresponding isopropenyl derivative[8] in 16% yield. On the other hand, the isomeric cyclic chloride (9b)[9] was formed if the reaction was carried out at -30°C for 2 hr after addition of $SnCl_4$ at -78°C. Due to its instability to silica gel, the crude products were treated, without purification, with LiCl in DMF at 100°C for 3 hr to give the dehydrochlorinated compound (10b, X = CO_2Me) as a sole product in 34% yield after purification with silica gel column chromatography[10].

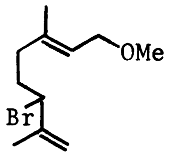
When geranyl phenyl sulfone (7b) was subjected to the coupling reaction with the allyl chloride (6) in a manner same to that used for the preparation of 9b, a mixture of cyclic chlorides[11] was obtained, which was similarly dehydrochlorinated to afford a 3:2 mixture of 10a and 10b in 29% yield. The gross structure of these compounds was fully supported by the physical evidence[12] and the relative stereochemistry at C_{11}-phenyl sulfonylmethyl group[13] with respect to the C_1-side chain was determined by the comparison of the coupling patterns of CH_2SO_2ph group of 10a and 10b with those of Torii and Uneyama's compounds (11a and b)[14] in their PMR spectra.


(11a)


(11b)


(12)


(13)


(14)

The next step requires only manipulation of C-C bond formation to make B ring of the verticillol skeleton. The ester group of 10b (X = CO_2Me) was converted into the corresponding allyl bromide (10b, X = CH_2Br) in 95% overall yield by the sequential reactions of reduction with AlH_3 in ether followed by treatment with CBr_4 and PPh_3 in CH_3CN. The allyl bromide was submitted to the reaction with 1.8 mol equivalents of $LiN(TMS)_2$ in THF containing 3.6 mol equivalents of N,N,N',N'-tetramethylethylenediamine at -78°C and then at 0°C for 24 hr in argon atmosphere, resulting in the formation of the verticillol skeleton (5a, W = SO_2ph) in 15% isolated yield after purification with silica gel column chromatography[15]. Reductive removal of the phenyl sulfonyl group with Li in ethylamine at -78°C led to the isolation of hydrocarbon (5a, W = H)[16] in 60% yield after purification with 10% $AgNO_3$-silica gel column chromatography.

Fragmentation pattern of the hydrocarbon (5a, W = H) in the mass spectrum is quite similar, excepting the relative intensities, to that of anhydroverticillol (5b, W = H)[17], readily obtainable from the natural verticillol (1). PMR, CMR and retention time of GLC[18] are, however, somewhat different from those of anhydroverticillol. In particular, CMR of the hydrocarbon indicates the existence of only one cis (Z) olefinic methyl at 14.5 ppm. The anhydroverticillol (5b, W = H) shows two signals at 15.2 and 15.7 ppm due to the cis olefinic methyls. This fact suggests that the geometrical isomerization took place at $C_7=C_8$ bond to afford an equilibrium mixture of 7E and 7Z isomers of 10b, the latter of which might be converted into 5a (W = SO_2Ph) under the basic conditions. In fact, it was revealed that the geometrically pure model compound (12) gave a 5:1 mixture of 12 and its isomers (13 plus 14) when treated with $LiN(TMS)_2$ in THF at -78°C for 1 hr[19].

The ester group of the cis isomer (10a, X = CO_2Me) was similarly transformed in 95% overall yield into allyl bromide (10a, X = CH_2Br), from which construction of anhydroverticillol skeleton corresponding to 4 was attempted by the same procedure. It was, however, in marked contrast to the reaction of the cis allyl bromide where no C-C bond formation occurred entirely under a variety of conditions including $LiN(TMS)_2$ in THF.

Our present experiments have led to the conclusion that cis-trans isomerization takes place at the allyl bromide moiety of 10b and presumably of 10a prior to the requisite C-C-bond formation when treated with $LiN(TMS)_2$ and that only 7Z isomer of 10b can make the C-C bond, resulting in the formation of a geometrical isomer of anhydroverticillol skeleton.

References

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2. B. Karlsson, Anne-M. Pilotti, Anne-C. Soderholm, T. Norin, S. Sundin, and M. Sumimoto, Tetrahedron, 34, 2349 (1978).
3. Concerning the synthesis of 2, see ref. 1.
4. H. Takayanagi, T. Uyehara, and T. Kato, Chem. Commun., 359 (1978) and references cited therein.
5. T. Kato, H. Takayanagi, T. Suzuki, and T. Uyehara, Tetrahedron Lett., 1201 (1978).
6. The phenyl prenyl sulfones (7a and b) were prepared from the corresponding alcohols by the sequential treatments with CBr_4 and PPh_3 followed by $NaSO_2Ph$.
7. For the preparation of 6, see ref. 4.
8. Dehydrochlorination of 8a with silica gel[4] afforded exclusively the isopropenyl derivative.
9. 9b was also prepared from the isolated 8a in 70% yield by the action of $SnCl_4$ at -30°C for 2 hr.
   8a PMR (CCl_4)δ1.51 and 1.54 (each 3H, sharp s, $CCl\underline{Me}_2$), 1.66, 1.74 and 1.81 (each 3H, bs, $C{=}C\underline{Me}$), 3.64 (2H, d, 7 Hz, $C\underline{H}_2SO_2Ph$), 5.08 (t, 7 Hz), 5.17 (t, 7 Hz), and 6.63 (m)(each 1H, $C{=}C\underline{H}$) ppm.
10. All the silica gel column chromatographies were carried out using a mixed solvent of hexane:AcOEt in the ratio of 5:1 ∼ 3:1.
11. From the mixture of the cyclic chlorides was isolated pure 9a by high pressure LC. 9a was converted into 10a in 81% yield with LiCl in DMF at 100°C.
   9a PMR δ 0.82, 0.98, 1.61, 1.63, 1.82 (each 3H, s, $\underline{Me}$s), 3.07 (dd, 3 and 15 Hz) and 3.24 (dd, 4 and 15 Hz)(each 1H, CH_2SO_2Ph), 5.11 (bt, 7 Hz) and 6.61 (m)(each

1H, C=CH) ppm: CMR δ Mes (q) 12.4, 16.1, 17.1, 28.6, 34.9 and 51.7; CH_2 (t) 23.3, 27.2, 29.0, 38.4, 43.2, and 56.6; CH (d) 48.5, 50.5, 124.8, 127.7, 129.4, 133.6, and 142.2; quart. C (s) 38.7, 75.0, 135.0, 141.1, and 141.8; CO_2Me 170.3 ppm.

12. Physical evidence supports the structures. 10a (X = CO_2Me) PMR δ 0.69 and 0.90 (each 3H, s, C_{15}-Mes), 1.58, 1.73, and 1.81 (each 3H, bs, C=CMes), 3.00 (dd, 4 and 15 Hz) and 3.09 (dd, 3 and 15 Hz)(each 1H, CH_2SO_2Ph), 5.07 (m), 5.35 (bs), and 6.59 (m)(each 1H, C=CHs) ppm: CMR δ Mes (q) 12.4, 16.0, 17.4, 22.4, 26.8, 51.7; CH_2 (t) 27.1, 28.0, 28.5, 38.3, 56.0; CH (d) 43.8, 44.0, 123.3, 124.7, 128.2, 129.3, 133.6, 142.1; quart. C (s) 36.1, 127.5, 132.6, 134.7, 141.8; CO_2Me 170.2 ppm. 10b (X = CO_2Me) PMR δ 0.87 and 0.98 (each 3H, s, C_{15}-Mes), 1.61, 1.67, and 1.80 (each 3H, C=CMes), 2.78 and 3.19 (dd, 4 and 15 Hz) (each 1H, CH_2SO_2Ph), 5.09 (bt, 7 Hz), 5.23 (bs), and 6.65 (m)(each 1H, C=CHs) ppm: CMR δ Mes (q) 12.5, 16.1, 21.5, 22.5, 25.5, 51.8; CH_2 (t) 27.2, 28.0, 29.4, 38.5, 59.2; CH (d) 38.5, 45.3, 122.4, 124.7, 128.3, 129.6, 133.9, 142.5; quart. C (s) 35.4, 127.8, 134.8, 135.6, 140.9; CO_2Me 162.5 ppm.
13. The numbering of 9 and 10 is based tentatively on that of anhydroverticillol.
14. S. Torii, K. Uneyama, and S. Matsumoto, J. Org. Chem., 45, 16 (1980). The stereochemistry of 11a was unequivocally confirmed by an X-ray analysis by Dr. C. Kabuto (Tohoku University), to whom we appreciate. We are indebted to professors S. Torii and K. Uneyama for their kind supply of 11a and b.
15. The isomeric compound corresponding to 5a (W = SO_2Ph) could not be obtained at all.
16. Physical evidence supports the structure of 5a. 5a (W = SO_2Ph) PMR δ 0.80 and 0.82 (each 3H, s, gem-Mes), 1.67 (3H) and 1.80 (6H)(C=CMes), 4.93 (bd, 7 Hz), 5.31 (bt, 7 Hz), and 5.55 (bs)(each 1H, C=CHs) ppm. 5a (W = H) PMR δ 0.73 and 0.83 (each 3H, s, gem-Mes), 1.60, 1.62, and 1.69 (each 3H, bs, C=CMes), 5.03 (bd, 9 Hz), 5.39 (t, 9 Hz), and 5.44 (bs)(each 1H, C=CHs) ppm: CMR Mes (q) 14.5, 21.8, 22.8, 22.9, 26.6; CH_2 (t) 22.0, 24.6, 26.4, 28.5, 32.2, 34.9; CH (d) 40.9, 54.1, 123.1, 125.8, 127.9; quart. C (s) 34.2, 134.0, 134.4, and 135.4 ppm.
17. Dehydration of verticillol (1), kindly provided by professor M. Sumimoto, with several reagents described in the literatures[20] afforded a mixture of 5a (W = H) and the exocyclic isomer. Refluxing the mixture in toluene with iodine converted the latter into the former exclusively. Anhydroverticillol (5a, W = H) PMR δ 0.73 and 0.80 (each 3H, s, gem-Mes), 1.49, 1.57, and 1.76 (each 3H, bs, C=CMes), 4.75 (bd, 9 Hz), 5.22 (bd, 14 Hz), and 5.30 (bs)(each 1H, C=CHs) ppm: CMR δ Mes (q) 15.2, 15.7, 23.0, 23.7, 27.1; CH_2 (t) 21.5, 26.7, 30.8, 34.1, 39.6, 41.0; CH (d) 38.0, 42.5, 121.6, 124.7, 129.9; quart. C (s) 35.7, 132.7, 132.9, 135.9 ppm.
18. GLC was carried out using a Golay column Z-45 with column temperature at 200°C.
19. The isomers (13 plus 14) were separated by high pressure LC with hexane:AcOEt = 30:1.
20. a, H. Erdtman, T. Norin, M. Sumimoto, and A. Morrison, Tetrahedron Lett., 3879 (1964); b, C. Kaneko, S. Hayashi, and M. Ishikawa, Chem. Pharm. Bull. Jpn., 12, 1510 (1964).

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