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SELECTIVE OZONOLYSIS OF METHYL *TRANS*-COMMUNATE. SYNTHESIS OF DRIMANES

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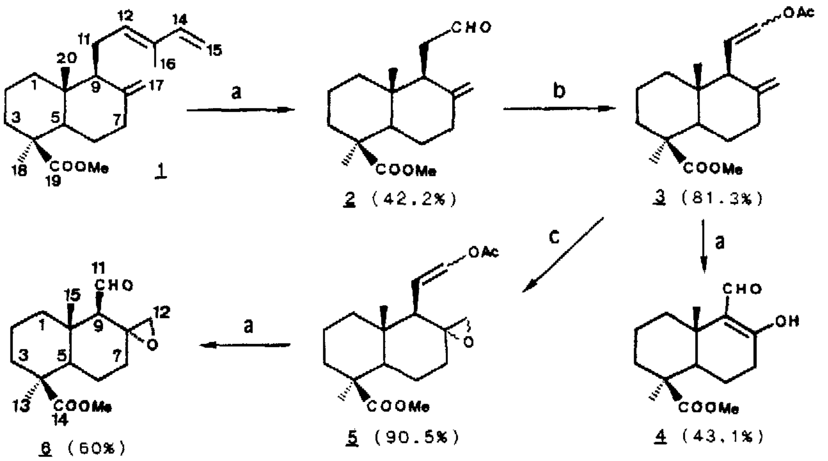
Abstract: *Trans*-communic acid (1), found in important quantities in species belonging the *Cupresaceas* family, is used as starting material for the synthesis of drimanes, in four steps. The present study establishes the conditions for selective ozonolysis of 1 over Δ^{12}, leading to aldehyde 2 (42.2%), transformed into enol-acetate 3 (81.3%), and which, in protecting the exocyclic double bond by selective epoxidation with MCPBA (90.5%) and subsequent ozonolysis (60%), yields drimane 6.

Given the interesting and multiple biological properties observed in drimanic sesquiterpenoids polygodial and warburganal, different total synthesis and semisynthesis pathways have been developed. Semisynthesis have the added advantage of offering one stereoisomer, and frequently uses diterpenes as starting material. Warburganal, for example, is obtained from abietic[1] and levopymaric[2] acids, while other related drimanes have been obtained using both dehydroabietic and podocarpic acids[3] (as well as their phenolic derivatives[4]), and from manool[5] and hispanolone[6].

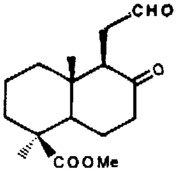
While studying the reactivity of communic acids[7] and their conversion into certain perfumery goods and biologically-active compounds of interest, we developed a methyl *trans*-communate (1) transformation pathway in drimanic sesquiterpenoid 6 (scheme 1), from which the enal-aldehyde grouping is chemically easy to obtain.

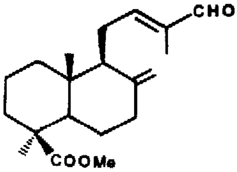
Scheme 1

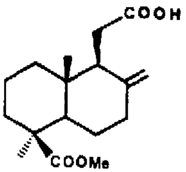


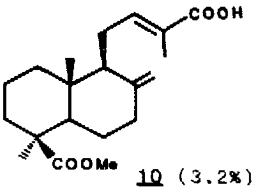
a) O_3, -78°C, CH_2Cl_2; Me_2S. b) Ac_2O, Et_3N, DMAP, reflux 20h (N_2).
c) MCPBA, CH_2Cl_2, room temperature.

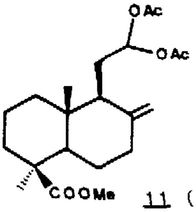
1, is a major component in apolar extracts of plant species from the *Cupresaceas* family. Given its chirality and functionality, we considered it a successful substrate for the synthesis of biologically-active drimanes. Taking into account the major reactivity of double bond Δ^{12} in electrophylic additions (such as epoxidation with MCPBA[8]), we studied its selective degradation by ozonolysis. Several reactions on 1 were carried out under differing conditions, such as type of solvent (hexane, methanol, CH_2Cl_2), temperature (room temperature, 0ºC, and -78ºC) and ozone stream[9]. We observed that the test performed in CH_2Cl_2 at -78ºC showed the greatest selectivity towards double bond Δ^{12} degradation. Under these conditions, 42.2% aldehyde 2[10] was obtained. Even though aldehyde is the first product to form (TLC and ^{1}H-NMR control), once an approximate 30% conversion has occurred, the degradation product of $\Delta^{8(17)}$ and Δ^{12} (7), progressively begins to appear. Moreover, compounds 8 (exclusive degradation of Δ^{14}), 9 and 10 (oxidation of 2 and 8, respectively)[11] are also obtained.


7 (13.0%)


8 (3.2%)


9 (5.0%)


10 (3.2%)


11 (5.4%)

The acetylation of 2 using 4-N,N-dimethylaminopyridine (DMAP) as a catalyst[12], primarily yields enol-acetate 3[13], showing double bond Δ^{11} adequately positioned for its subsequent degradation to drimane. Acylal 11[14] also is formed as a product of the addition of HOAc to the enolic double bond of 3.

The ozonolysis of 3 under the same conditions applied to methyl *trans*-communate (1), predominately gives rise to the simultaneous degradation of both double bonds, producing nor-drimane 4 (mainly in enolic form)[15], found not to be appropriate as an intermediate for this type of synthesis.

Consequently, a third stage is the selective funtionalitation of the exocyclic double bond $\Delta^{8(17)}$ by epoxydation of 3 with MCPBA at room temperature, yielding the mixture of oxyranes 5[16] (90.5%) which, by direct ozonolysis of the double bond Δ^{11}, finally leads to drimane 6 (60%)[17].

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9.- General procedure used in the different tests for ozonolysis consisted in bubbling an ozone stream (mixture of O_3/O_2 obtained using a oxygen-feed Fischer apparatus), through a solution of 1 at a given temperature. After a variable period of time, the ozonide mixture is treated with Me_2S for 2 hours at room temperature and the DMSO formed is removed from the reaction crude by filtering through a silica gel column with ether as an eluent.

10.- Methyl 12-oxo-13,14,15,16-tetranor-labd-8(17)-en-19-oate (**2**) is a colourless oil: $[\alpha]_D$= +18.5° ($HCCl_3$, 1.15). MS: m/z 278 (M$^+$, 3%, $C_{17}H_{26}O_3$), 121 (100%). IR: ν 2716 (CHO), 1721 (CHO, COOMe). ^{1}H-NMR (300MHz, $DCCl_3$): δ 4.37 (1H, brs, H_{17}), 4.81 (1H, brs, $H_{17'}$), 9.61 (1H, dd, J_1=2.8Hz, J_2=1.4Hz, H_{12}). ^{13}C-NMR (75MHz, $DCCl_3$): δ 147.97 (C_8), 108.05 (C_{17}), 177.45 (C_{19}), 203.03 (C_{12}).

11.- **7**: $[\alpha]_D$= -9.7° ($HCCl_3$, 1.10). MS: *m/z 280 (M$^+$, 0.3%, $C_{18}H_{24}O_4$), 123* (100%). IR: ν 2725 (CHO), 1721 (CHO, COOMe, ketone). ^{1}H-NMR (300MHz, $DCCl_3$): δ 0.52 (3H, s, Me-C_{10}), 9.77 (1H, s, H_{12}). ^{13}C-NMR (75MHz, $DCCl_3$): δ 39.47 (C_1), 19.46 (C_2), 37.78 (C_3), 44.17 (C_4), 54.41 (C_5), 24.86 (C_6), 41.82 (C_7), 209.68 (C_8), 56.96 (C_9), 41.95 (C_{10}), 37.09 (C_{11}), 200.99 (C_{12}), 28.66 (C_{18}), 176.88 (C_{19}), 13.53 (C_{20}), 53.34 (C_{21}).
8: $[\alpha]_D$= +35.8° ($HCCl_3$, 1.02). MS: m/z 318 (M$^+$, 3%, $C_{20}H_{30}O_3$), 121 (100%). IR: ν 2710, 1686 (α,β-unsaturated aldehyde with s-*trans* conformation). ^{1}H-NMR (80MHz, $DCCl_3$): δ 0.60 (3H, s, Me-C_{10}), 1.76 (3H, d, J=1Hz, Me-C_{13}), 6.42 (1H, brt, J=7Hz, H_{12}), 9.32 (1H, s, H_{14}).
9: m.p. 127-8ºC (MeOH). $[\alpha]_D$= +11.8° ($HCCl_3$, 1.13). MS: m/z 294 (M$^+$, 2%, $C_{17}H_{26}O_4$), 249 (M$^+$-COOH, 0.7%), 235 (M$^+$-CH_2COOH, 5%). IR: ν 2500-3400, 1721 (COOH). ^{1}H-NMR (80MHz, $DCCl_3$): δ 0.54 (3H, s, Me-C_{10}), 4.55 (1H, brs, H_{17}), 4.81 (1H, brs, $H_{17'}$).
10: IR: ν 2500-3400, 1686 (COOH α,β-unsaturated). ^{1}H-NMR (80MHz, $DCCl_3$): δ 0.57 (1H, s, Me-C_{10}), 1.85 (3H, s, Me-C_{13}), 4.37 (1H, brs, H_{17}), 4.82 (1H, brs, $H_{17'}$), 6.79 (1H, brt, J=6Hz, H_{12}).

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13.- **3**, formed by mixing the two configurational isomers in Δ^{11} as deduced from data on H_{11} and H_{12} in ^{1}H-NMR (80MHz, $DCCl_3$): δ 5.44 (dd,

$J_{11,12}$=13Hz, $J_{11,9}$=10Hz, H_{11} en Δ^{11E}), 7.01 (d, $J_{12,11}$=13Hz, H_{12} en Δ^{11E}), 4.91 (dd, $J_{11,12}$=6Hz, $J_{11,9}$= 10Hz, H_{11} en Δ^{11Z}), 7.14 (d, $J_{12,11}$=6Hz, H_{12} en Δ^{11Z}), 2.96 (d, $J_{9,11}$=10Hz, H_9 en $\Delta^{11E/Z}$). In ^{13}C-NMR both are differentiated mainly in the δ value of C_9: 55.18 (Δ^{11E}), 51.31 (Δ^{11Z}).

14.- <u>11</u>: m.p. 128-9ºC (MeOH). $[\alpha]_D$= +27.1° ($HCCl_3$, 0.77). MS: m/z 380 (M^+, 3%, $C_{21}H_{32}O_6$), 320 (M^+-HOAc, 7%), 278 (M^+-HOAc-ketene, 71%), 120 (100%), 43 (CH_3CO, 77%). IR: ν 1761, 1246, 1201, 1011, 968 (acetoxy groups). ^{1}H-NMR (80MHz, $DCCl_3$): δ 0.51 (3H, s, Me-C_{10}), 2.05 (3H, s, AcO-12), 2.08 (3H, s, AcO-12'), 4.76 (1H, brs, H_{17}), 4.91 (1H, brs, $H_{17'}$), 6.68-6.87 (1H, m, H_{12}).

15.- <u>4</u> is a white solid of m.p. 108-9ºC (MeOH) and $[\alpha]_D$= +85.7° ($HCCl_3$, 0.99). MS: m/z 266 (M^+, 12%, $C_{15}H_{22}O_4$), 251 (M^+-CH_3, 100%), 191 (M^+-CH_3-HCOOMe, 83%). IR: ν 1596 (CO, strong broad band of conjugated chelate, Rasmussen, R.S.; Tunnicliff, D.D. and Brattain, R.R., (1949) *J. Am. Chem. Soc.* 71, 1068). ^{1}H-NMR (300MHz, $DCCl_3$): δ 15.34 (d, J=3.1Hz, strongly bound enolic proton), 8.91 (d, J=3.1Hz, H_{11}). ^{13}C-NMR (75MHz, $DCCl_3$): δ 38.77 (C_1), 19.51* (C_2), 37.35 (C_3), 43.56 (C_4), 51.89 (C_5), 19.26* (C_6), 33.08 (C_7), 184.94 (C_8), 120.36 (C_9), 35.50 (C_{10}), 187.84 (C_{11}), 28.38 (C_{13}), 177.18 (C_{14}), 22.52 (C_{15}), 51.32 (C_{16}).

16.- In the ^{1}H-NMR (80MHz, $DCCl_3$) spectrum, we observed a predominance of the 8α,17-epoxy-derivate as compared to the 8β,17-epoxy-derivate (approximately 3:1) using signals corresponding to Me-C_{10} at 0.71 ppm and 0.80 ppm, respectively (Grant, P.K. and Weavers, R.T., (1974) *Tetrahedron* 30, 2385). Hydrogens H_{17} from both epoxydes appear as a multiplet at 2.40-2.80 ppm.

17.- In the ^{1}H-NMR (80MHz, $DCCl_3$) spectrum, an AX system formed by hydrogens H_9 (δ 2.66) and H_{11} (δ 9.51) with J=4Hz is observed, as well as an AB system of the epoxydic protons H_{12} (δ 2.45) and $H_{12'}$ (δ 3.03) with the same coupling constant.

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