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A NOVEL SYNTHESIS OF (±)-TRANS-CHRYSANTHEMIC ACID

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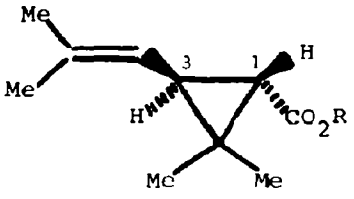
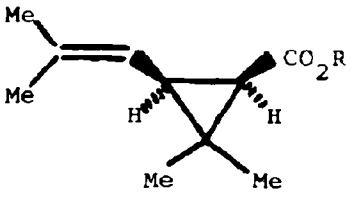
A novel approach to ± trans chrysanthemic acid, from commercially available 2,5-dimethyl 3 hexyne 2-5 diol (30 % overall yield) is described.

As (±)-trans-chrysanthemic acid (1a) is the most accessible and effective component of the Pyrethroid group of insecticides[1], its synthesis has been the subject of several investigations over the years[2].



1

a : R = H ; b : R = Me

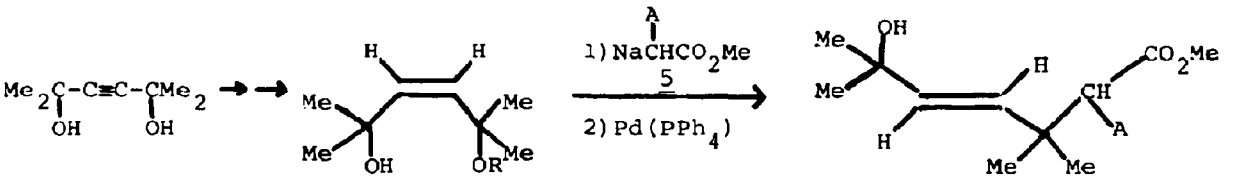


2

a : R = H ; b : R = Me

We now describe a new strategy for obtaining (1a) from an easily available precursor, 2,5-dimethyl-3-hexyne-2,5-diol (3) which already possesses eight of the ten carbon atoms present in the chrysanthemic acid molecule. Our strategy is based on two key steps : an alkylation which adds the two carbon atoms of the acetic acid moiety to complete the basic structure needed to form chrysanthemic acid and a cyclization which forms the C_1-C_3 linkage of the 3-membered ring.

The first step is the palladium-catalyzed alkylation[3] 4 ⟶ 6 which is carried out on the monoacetate 4b[4,5] of the cis diol 4a[6,7] obtained by the selective reduction of the commercially available 3 (75 % overall yield).



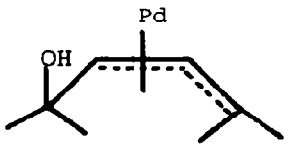
3 4 6

a : R = H ; b : R = Ac

a : A = SO_2Ph ; b : A = COOMe

The success of the alkylation step 4b ⟶ 6b by esters 5 is dependent of the use of tetrakis (triphenylphosphine) palladium catalyst[3]. The acetyl group would not otherwise be displaced by malonate derivatives and halides, which are better leaving groups than acetates, are known to undergo substitution followed by elimination reaction under similar conditions[9]. In the presence of a catalytic amount (10 %) of tetrakis (triphenylphosphine) palladium, alkylation with malonate derivatives occurs easily (60°C, 15 h) to afford regio-and stereoselectively esters 6a[10] (85 % yield) and 6b[11] (80 % yield).

The regio and stereoselectivities of this alkylation are very high. On one hand, one observes a complete isomerization of the cis double bond of acetate 4 to a trans double bond in esters 6, attributable, to the greater stability of complexes of type 8 compared to those of type 7 which are formed initially[3b].



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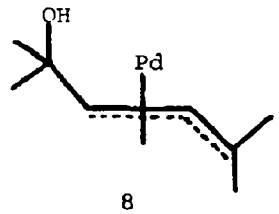

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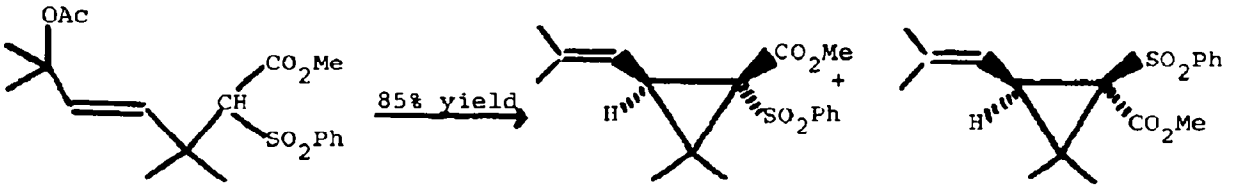
On the other hand, as could be expected, only the reaction at acetate, a better leaving group than hydroxyl, is observed. A less expected result is the regioselective alkylation of the most substituted end of complex 8. It is plausible that in such case the secondary center of a neopentyl type may be sterically more crowed than the tertiary position and therefore directs the reaction towards the end of the chain.

The second key step of this synthesis involves a cyclization which was performed under several conditions in order to investigate the steric course of this intramolecular SN' reaction.

One approach dealt with the cyclization of sulfoester 9[12] after acetylation[5] of the corresponding alcohol 6a ; the other approach involved cyclization of ester 12[13], after decarbomethoxylation[14] of 6b followed by benzylation[5] of the allylic alcohol leading to 12.

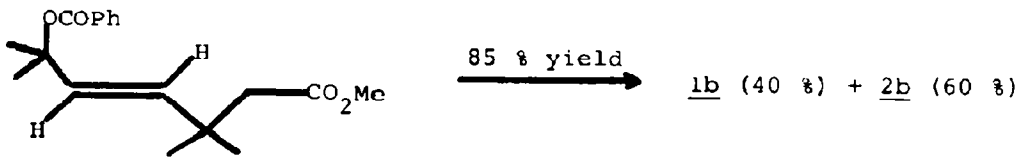
The cyclization of sulfoester 9 with sodium hydride is facile (1 eq NaH, THF, 65°C, 15 h) and affords a 1:1 mixture of cis 10[15] and trans 11[16] substituted cyclopropanes in 85 % yield.



9 10 (50 %) 11 (50 %)

The presence of a catalytic amount (10 %) of tetrakis (triphenylphosphine) palladium increases the rate of the reaction but does not modify appreciably the steric course of the reaction (10/11 = 3/2). The reduction (Na/Hg in ethanol, $HNaPO_4$ according to reference[17]) of the sulfone groups of derivatives 10 and 11 affords quantitatively a 1:1 mixture of cis (2b) and trans (1b) methyl chrysanthemates from which trans-chrysanthemic acid (1a)[18] is obtained quantitatively.

Cyclization of ester 12 requires a stronger base than sodium hydride, and may be accomplished with lithium diisopropylamide (1.2 eq, THF, -78°C, 30 min. then 25°C, 4 h) to afford a mixture of methyl chrysanthemates (85 % yield) in a 3:2 ratio (cis 2b : trans 1b). It is remarkable and worth noting that the less stable cis cyclization product is kinetically formed in a considerable quantity. The exact reason for this surprising result is not clear at this time. Isomerization of this mixture according to the directions previously cited and hydrolysis to the (+) trans-chrysanthemic acid (1a) were then carried out.



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The two routes to (+) trans-chrysanthemic acid we have described allow the preparation of (1a) from a commercially available acetylenic diol (3) in 30 % overall yield. An additional interest of this new strategy is its application in the synthesis of cis-chrysanthemic acid ; we are investigating this possibility.

References and Notes :

1) J.E. Casida : Pyrethrum. The natural Insecticide, Academic Press, New York (1973).

2) For a review, see : reference 1, page 56 ; For more recent syntheses, see, for instance : M.J. Devos, L. Hevesi, P. Bayet, A. Krief, Tetrahedron Letters, 3911 (1976) ; S.C. Welch, T.A. Valdes, J. Org. Chem., 42, 2108 (1977) ; S. Torii, H. Tanaka, Y. Nagai, Bull. Soc. Chim. Japan, 50, 2828 (1977) ; T. Aratani, Y. Yoneyoshi, T. Nagase, Tetrahedron Letters, 2599 (1977) ; M.J. Devos, J.N. Denis, A. Krief, ibid, 1847 (1978) ; K. Ohkata, I. Isako, T. Hanafusa, Chem. Industry, 8, 274 (1978) ; H. Lehmkuhl, K. Mehler, Liebigs Ann. Chem. 1841 (1978) ; M.J. Devos, A. Krief, Tetrahedron Letters, 1515, 1891 (1979).

3) a) For a review, see : B.M. Trost, Tetrahedron, 33 2615 (1977).
b) B.M. Trost, J.P. Klun, J. Amer. Chem. Soc., 101, 6758 (1979).

4) Pure Z mono acetate 4b: bp 55°C (0.1 mm) ; IR (neat) : 3400, 1730 cm^{-1} ; NMR 1.25(s,6H), 1.65(s,6H), 2(s,3H), 5.25(s,2H) is obtained according to 5 with 75 % yield by slow addition (3 h) of acetic anhydride in a methylene chloride solution (1M) of 4a containing diethylamine (excess) and 4-dimethylamino pyridine as catalyst (10 %).

5) For acetylation and benzoylation of tertiary allylic alcohols, see : W. Steglich, G. Höfle, Angew. Chem. Int. Ed., 8, 981 (1969) ; see also a review : G. Höfle, W. Steglich, H. Vorbruggen, Angew. Chem. Int. Ed., 17, 569 (1978).

6) Pure Z diol 4a (already described[7]) is obtained quantitatively according to ref. 8 by semi-hydrogenation of 3 with $Pd/CaCO_3$ and quinoleine.

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8) Catalytic semi-hydrogenation of triple bond, E.N. Marvell and T. Li, Synthesis, 457 (1973).

9) F. Korte, D. Scharf, K.H. Büchel, Liebigs Ann. Chem., 664, 97 (1963).

10) Purified by chromatography on silicagel, ether/hexane-3/1 ; IR (neat) 3400, 1740 cm^{-1} ; NMR ($CDCl_3$) : 1.25(s,6H), 1.4(s,6H), 2(OH), 3.45(s,3H), 3.95 (s,1H), 5.75(d,d,J 16 Hz,2H), 7.55(m,3H), 7.75(m,2H) ppm.

11) bp 120-130°C (0.01 mm) ; IR (neat) 3400, 1735 cm^{-1} ; NMR ($CDCl_3$) 1.20(s,6H), 1.2(s,6H), 2(O-H), 3.2(s,1H), 3.5(s,3H), 5.6(d,d,J 16 Hz,2H) ppm.

12) 9 IR (neat) 1720 cm^{-1} ; ^1H NMR ($CDCl_3$) 1.4(s,6H), 1.5(s,6H), 1.95(s,3H), 3.45(s,3H), 4(s,1H), 5.8(s,2H), 7.6(m,3H), 7.9(m,2H) ; ^{13}C NMR 21.0, 22.25 25.2, 26.6, 26.9, 40.2, 52.25, 78.3, 80.2, 126.5, 128.6, 129, 129.5, 133.3, 134, 134.4, 140.2, 165.8, 169.8 ppm.

13) 12 IR (neat) 1710,1600,1580 cm^{-1} ; ^1H NMR (CCl_4) 1.13(s,6H), 1.6(s,6H), 2.2 (s,2H), 3.5(s,3H), 5.7 (s,2H), 7.25(m,3H), 7.8(m,2H) ; ^{13}C NMR ($CDCl_3$) 27.2 , 27.4, 35.2 , 47.05, 51.0 , 81.2 , 128.2, 129, 129.5, 131.3, 132.1, 132.45, 137.30, 165.25, 171.9 ppm.

14) A.P. Krapcho, J.F. Weinaster, J.M. Eldridge, E.G.E. Jahngen Jr., A.J. Lovey, W.P. Stephens, J. Org. Chem., 43, 138 (1978).

15) 10 IR(neat) 1730 cm^{-1} ; ^1H NMR(CCl_4) 1.03(s,3H), 1.56(s,3H), 1.73(s,6H), 2.9(d,1H,J 8 Hz), 3.43(s,3H), 5.1(d(broad),1H), 7.6(m,5H) ppm.

16) 11 IR(neat) 1730 cm^{-1} ; ^1H NMR(CCl_4) 1.16(s,3H), 1.61(s,3H), 1.7 (s(broad, 6H), 2.7(d,1H,J 8 Hz), 3.43(s,3H), 5.56(d(broad),1H), 7.6(m,5H) ppm.

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