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BASE-PROMOTED CYCLIZATION OF A δ-CHLORO ESTER: APPLICATION TO THE TOTAL SYNTHESIS OF (±)-GRANDISOL[1]

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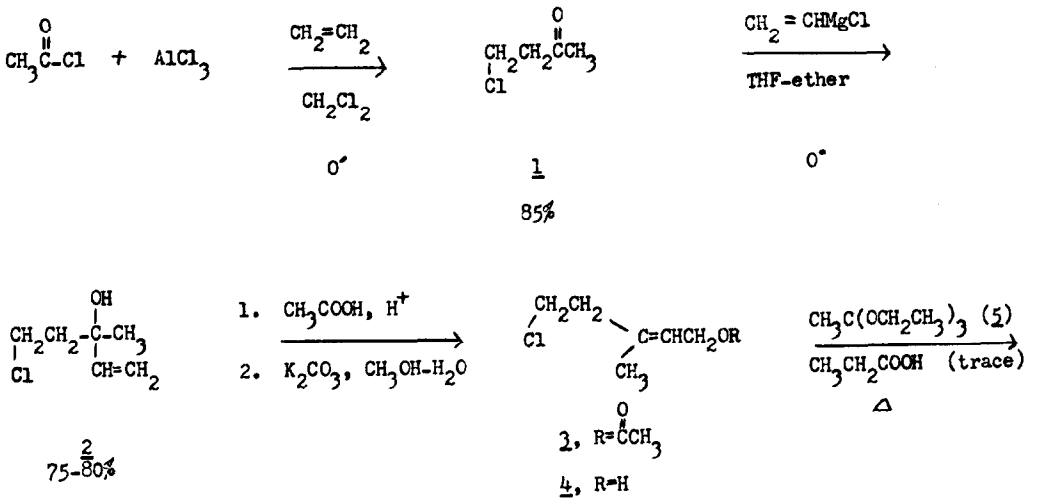
A recent communication[2] by Stork and Cohen describing the synthesis of functionally substituted cyclobutanes via cyclization of appropriate epoxynitriles and the application of this method to the total synthesis of (±)-grandisol[3] (9) prompts this report of a related nonphotochemical route to cyclobutanes that has been successfully developed as part of a total synthesis of this same pheromone (9). The key step in the synthesis, outlined in Scheme I, involves treatment of ethyl 3-[2-chloroethyl]-3-methyl-4-pentenoate[4] (6) with lithium diisopropylamide[5] to effect closure of the four-membered ring. A thorough study of the optimum conditions for effecting this intramolecular alkylation so as to obtain the Z-stereoisomer 7a, the one necessary for a stereoselective synthesis of (±)-grandisol (9), has been undertaken as well as attempts to epimerize the mixture of esters 7a and 7b. These results will be reported in a full paper on this synthesis in the near future. If the cyclization is effected at 0° in a tetrahydrofuran solution containing a catalytic amount of hexamethylphosphoramide, the ratio of esters[4] 7a : 7b is 65:35.[6]

The starting material in the synthesis was the previously reported[7] 4-chloro-2-butanone (1), easily prepared via a Friedel-Crafts acylation of ethylene. Subsequent treatment of ketone 1 with vinylmagnesium chloride afforded tertiary vinyl carbinol 2[4] in

Scheme I


CH3C(=O)-Cl + AlCl3
CH2=CH2
CH2Cl2
0°
1
85%
CH2=CHMgCl
THF-ether
0°
2
75-80%
1. CH3COOH, H+
2. K2CO3, CH3OH-H2O
3, R=CCH3
4, R=H
CH3C(OCH2CH3)3 (5)
CH3CH2COOH (trace)
Δ
6
76%
2 LiN[CH(CH3)2]2
THF-HMPA
0°
2 CH3Li
0°
80%
7a, R1=H; R2=CO2CH2CH3
b, R1=CO2CH2CH3; R2=H
8
100%
1. BH3
2. H2O2, OH-
3. Ac2O
4. KOH
9

75-80% yield. This alcohol (2), when treated overnight at room temperature with a mixture of acetic acid-acetic anhydride containing a catalytic amount of p-toluenesulfonic acid[8], afforded in 80% yield a 2:1 mixture[9] of E:Z stereoisomers of the rearranged 1° allylic acetate (3). Saponification of this acetate mixture (3), followed by a Claisen-type reaction of the corresponding alcohol mixture (4)[9] with triethyl orthoacetate (5),[10] proceeded smoothly to yield the δ-chloro ester 6 necessary for the cyclization step. The total synthesis was formally completed by addition of ester mixture 7a and 7b to excess methyllithium to obtain the previously reported[11] alcohol 8 as the major product, along with the corresponding E-stereoisomer.

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3. For other recent syntheses of grandisol, see: (a) J. H. Tumlinson, R. C. Gueldner, D. D. Hardee, A. C. Thompson, P. A. Hedin, and J. P. Minyard, J. Org. Chem., 36, 2616 (1971); (b) R. C. Gueldner, A. C. Thompson, and P. A. Hedin, ibid., 37, 1854 (1972); (c) R. Zurflüh, L. L. Dunham, V. L. Spain, and J. B. Siddall, J. Amer. Chem. Soc., 92, 425 (1970); (d) W. E. Billups, J. H. Cross, and C. V. Smith, ibid., 95, 3438 (1973); (e) P. D. Hobbs and P. D. Magnus, J. Chem. Soc., Chem. Commun., 856 (1974).

4. Satisfactory elemental analysis (±0.30%), VPC analysis, and IR and NMR spectral analysis of all novel intermediates in the synthesis have been obtained. ^{1}H-NMR (CCl_4 vs TMS, δ in ppm) for the key intermediate, δ-chloro ester 6 : 1.25 (t, J=7 Hz, $-OCH_2\underline{CH_3}$); 1.17 (s, CH_3); 2.27 (s, $\underline{CH_2}\overset{O}{\overset{\|}{C}}$); 4.11 (quartet, J=7Hz, $-O\underline{CH_2}CH_3$); 6.09 to 4.82 (complex pattern, 3 vinyl H's, peaks at 6.09, 5.90, 5.81, 5.62, 5.15, 5.12, 4.93, 4.95, 4.84, and 4.82).

5. R. J. Cregge, J. L. Herrmann, C. S. Lee, J. E. Richman, and R. H. Schlessinger, Tetrahedron Lett., 2425, 2429 (1973).

6. Obtained by NMR analysis of the mixture. The Z-isomer has an NMR spectrum which is characterized by a 3-proton singlet at 1.34δ and a 2-proton quartet at 4.06δ. The corresponding E-isomer absorptions are respectively, 1.13δ and 4.11δ.

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9. Obtained by NMR analysis of the mixture as well as VPC analysis (using a 6' x 1/8" SE-30 column). Satisfactory elemental analysis ($\pm$0.30%) was obtained for both the acetate mixture 3 as well as the corresponding alcohol mixture 4. Since both stereoisomers can be used in the subsequent step, no attempt was made to separate them.

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