

ELECTROPHILIC ADDITION REACTIONS IN TERPENOID SYNTHESIS. VI.¹⁾ (+)-CHRYSANTHEMIC ACID AND ANALOGUES THEREOF

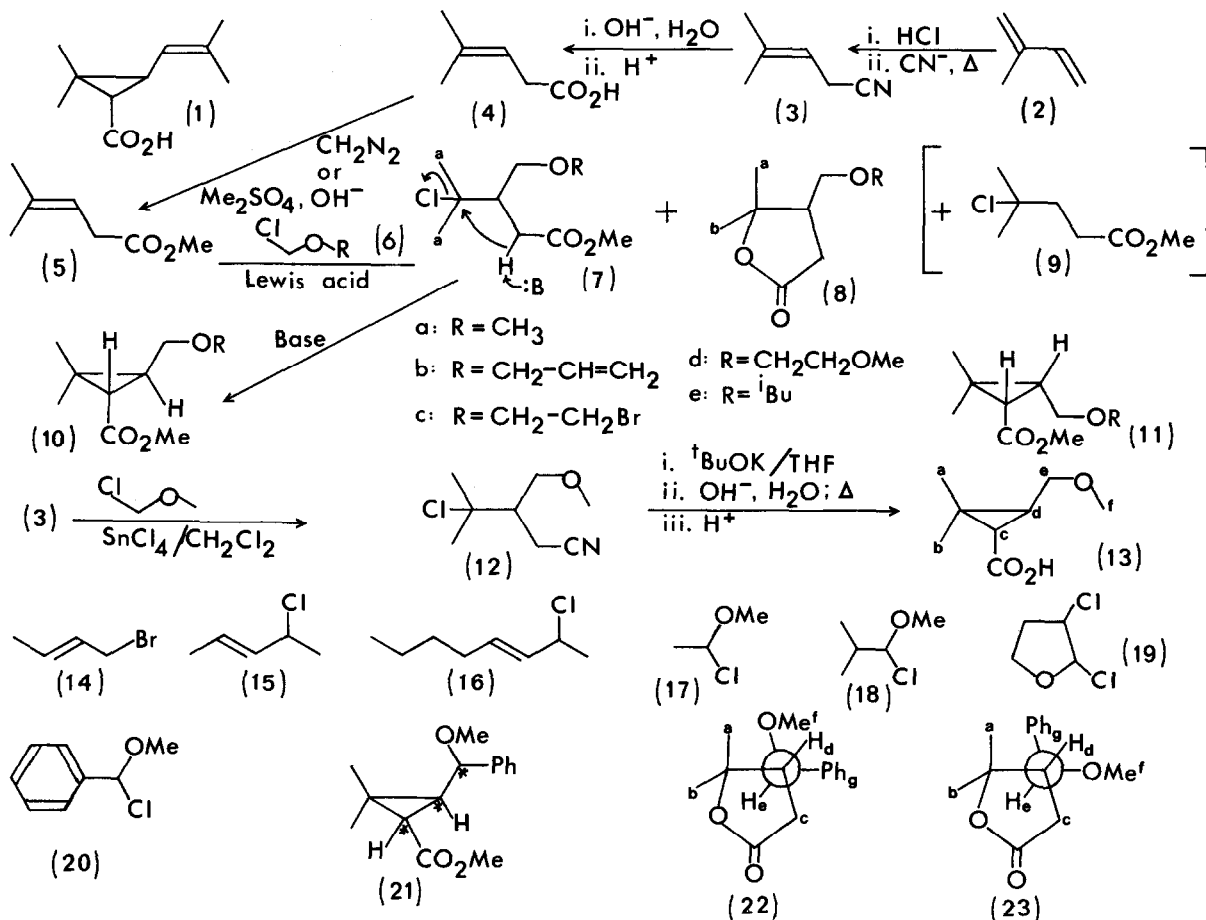
C.F. Garbers^{*}, Martha S. Beukes, Christine Ehlers,²⁾ and Margaret J. McKenzie
Department of Chemistry, University of Stellenbosch, South Africa

(Received in UK 19 October 1977; accepted for publication 11 November 1977)

Apart from the well established industrial pathways to chrysanthemic acid (1),³⁾ new approaches to its preparation are actively investigated.⁴⁾ We herewith report an alternative synthesis of chrysanthemic acid (1) and analogues thereof from readily available starting materials. The method is based on the electrophilic addition of α -halo-ethers⁵⁾ to methyl 4-methyl-pent-3-enoate (5) and subsequent cyclisation with base of the condensation product to the corresponding cyclopropane carboxylates.⁶⁾

The ester (5), obtained from isoprene (2) via the nitrile (3) and acid (4), on treatment with an α -chloromethyl ether (6) in the presence of a Lewis acid gave a mixture of the γ -chloro-ester (7), the γ -lactone (8), and the hydrochloric acid addition product (9) of the starting ester (5). The ratio of these products varied with the Lewis acid employed and with the nature of the chloromethyl ether. Although not exhaustively investigated, SnCl_4 proved to be superior to other Lewis acids employed.⁷⁾ Utilisation of bromomethyl ethers and extended reaction times favoured lactone (8) formation at the expense of some initially formed ester (7). Consequently this approach also constitutes an effective lactone (8) synthesis.⁸⁾ Although the yields for the individual condensations were not optimised, it was observed that e.g. the reaction of the chloro-ether (6b) with ester (5) at -25° in CH_2Cl_2 with SnCl_4 as catalyst gave predominantly ($> 60\%$, nmr analysis) the required ester (7b) (δ_a 1.61) with some of lactone (8b) (29% ; δ_a 1.33 and δ_b 1.45).⁹⁾ Generally the mixture of ester (7) and the corresponding lactone (8) from the condensation, was converted into a mixture of the cyclopropane carboxylate (10) and the lactone (8) by treatment with base (e.g. $^t\text{BuOK}/\text{THF}$) prior to separation. Formation of the cis-cyclopropane carboxylates (11) was not observed.¹⁰⁾ Lactone formation could be avoided by the Lewis acid catalysed reaction of nitrile (3) with the chloro-ether e.g. the condensation of the nitrile (3) with ether (6a) gave the chloro-nitrile (12) (66% isolated yield; $\text{SnCl}_4/\text{CH}_2\text{Cl}_2$). which on treatment with base ($^t\text{BuOK}/\text{THF}$), saponification and acidification, yielded the trans-cyclopropane carboxylic acid (13) (δ_a 1.18,s; δ_b 1.26,s; δ_c 1.35,d,J_{cd} 5.5; δ_p 3.31,s; δ_{e1} 3.33,dd, J_{e1e2} 13.5; J_{e1d} 7; δ_{e2} 3.51,dd, J_{e2d} 6).

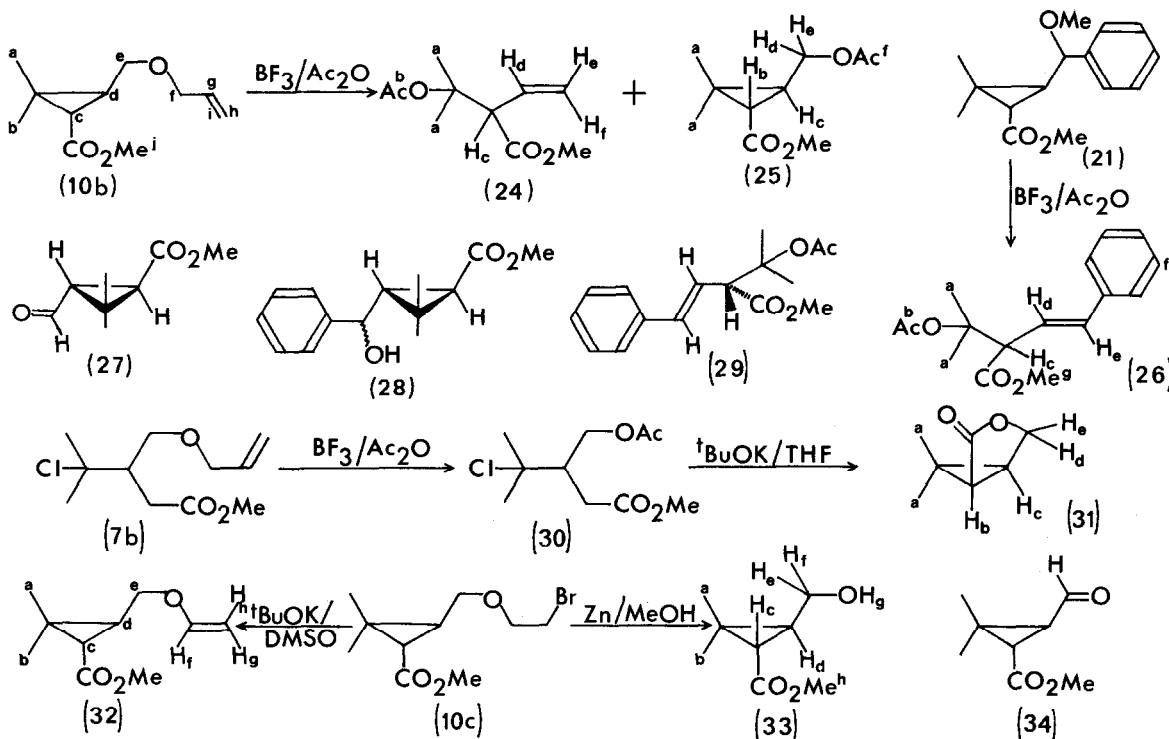
Whereas utilisation of ether (6) gave 2,2-dimethylcyclopropane carboxylates (10) and lactones (8) with a C-O-C side chain, the underlying reactions were successfully employed in the synthesis of 2,2-dimethylcyclopropane carboxylates and 4-methylpentan-4-olides with a C-C-C side chain. This was effected by utilisation of e.g. the allylic halides (14) - (16) and the chloro-ethers (17) - (20). These halogen derivatives, except crotyl bromide, introduced an additional chiral centre in the final products, leading to the formation of diastereo-isomers, illustrated by the compounds (21), (22) (m.p. $94-98^\circ$; δ_a 1.44,s; δ_b 1.62,s; δ_c & δ_d ca. 2.32-2.96,m; δ_p 3.10,s,



δ_e 4.01, d, J_{ed} 9.5; δ_g 7.31, s) and (23) (m.p. 93-95°; δ_a 1.12, s; δ_b 1.39, s; δ_c & δ_d ca. 2.37-2.93, m; δ_f 3.14; δ_e 4.17, d, J_{ed} 4.8; δ_g 7.31), which were isolated, after cyclisation by base, from the condensation product of chloro-ether (20) with ester (5).

Since the allyloxymethyl group may be converted into the hydroxymethyl group,¹¹⁾ we investigated whether the cyclopropane carboxylate (10b) could serve as an intermediate in the preparation of either ester (25) or the hydroxymethyl ester (33). On oxidation the latter compound yields the corresponding aldehyde (34), which has been converted into chrysanthemic acid (1).^{4b)} The aldehyde (34) also serves as starting material for the preparation of chrysanthemic acid analogues,¹²⁾ from which pyrethroids¹³⁾ are obtainable of much greater insecticidal activity compared to the naturally occurring pyrethrins.

Treatment of the ester (10b) (δ_a 1.18, s; δ_b 1.23, s; δ_c 1.38, d, J_{cd} 5.2; δ_d ca. 1.71, ddd, J_{de} 7.5, J_{de2} 7; J_{dc} 5.2; δ_{e1} 3.36, dd, J_{e1e2} 10.5; δ_{e2} 3.69, dd; δ_f 3.65, s; δ_f 3.98, ddd, J_{fg} 5.0, $J_{fi} \approx J_{fn} \approx 1$; δ_h 5.16, tdd, J_{hg} 9.4; J_{hi} 3.5; δ_i 5.21, tdd, J_{ig} 17; δ_g 5.93, tdd) with $\text{BF}_3/\text{Ac}_2\text{O}$ reagent, gave compounds (24) (δ_a 1.43, s; δ_b 1.87, s; δ_g 3.61, s; δ_c 3.79, d, J_{cd} 9; δ_e & δ_f ca. 4.95-5.25, m; δ_d 5.90, ddd, J_{df} 18; J_{de} 9) and (25) (δ_a 1.20, s; δ_b 1.35, d, J_{bc} 5.3; δ_c ca. 1.45-1.85, m; δ_f 1.99, s; δ_g 3.60; δ_d 3.88, dd, J_{de} 12, J_{dc} 7.8; δ_e 4.17, dd, J_{ec} 7) in an approximate ratio of 7:1 (glc). A similar opening of the cyclopropane



ring¹⁴⁾ was also observed with other cyclopropane derivatives with an oxygen function in the side chain e.g. ester (21) gave with $\text{BF}_3/\text{Ac}_2\text{O}$ reagent the (E)-olefinic acetate (26) (δ_a 1.56, s; δ_b 1.94, s; δ_g 3.68, s; δ_c 4.02, d, J_{cd} 8; δ_d 6.24, dd, J_{de} 15.6; δ_e 6.51, d; δ_f ca. 7.31, m) in excellent yield (97%). The corresponding diastereo-isomeric alcohols (28) reacted similarly to give the (E)-olefinic acetate (29) [nmr identical to that of compound (26)]. The alcohols (28) were prepared by selective reaction with PhLi of the aldehyde (27), obtained from methyl (1R,3R)-chrysanthemate by ozonolysis.¹⁵⁾ It is interesting to note, that these conversions constitute a method for the construction of part of the 25-hydroxy-ergosterol side chain.

The opening of the cyclopropane ring during the ether cleavage reaction, was circumvented by cleavage of the allyl ether moiety in chloro-ether (7b), prior to conversion into the cyclopropane carboxylate with base. However, treatment of the chloro-ester (30) with base ($t\text{BuOK}/\text{THF}$) gave the cis- γ -lactone¹⁶⁾ (31) (δ_a 1.17, s; δ_b 1.91, ddd, J_{bc} 7.4, J_{bd} ~1, J_{be} ~1; δ_c 2.05, ddd, J_{cd} 1.6, J_{ce} 4.6; δ_d 4.09, ddd, J_{de} 9.8; δ_e 4.37, br. dd.) Synthesis of the required compound (33) (δ_a 1.23, s; δ_b 1.25, s; δ_c 1.40, d, J_{cd} 5.4; δ_d 1.69, ddd, J_{de} 7.3, J_{df} 7.2; δ_e 3.55, dd; δ_f 3.78, dd, J_{ef} 11.6; δ_g 1.72; δ_h 3.66) was successfully achieved by refluxing the cyclopropane carboxylate (10c) with Zn/MeOH .¹⁷⁾ The alternative to hydrolyse the vinyl ether (32) (δ_a 1.19, s; δ_b 1.25, s; δ_c 1.44, d, J_{cd} 5.5; δ_d 1.78, ddd, J_{de} 7.8, J_{de} 6.5; δ_{e_1} 3.58, dd, $J_{e_1e_2}$ 10.5; δ_{e_2} 3.85, dd; δ_g 4.00, dd, J_{gf} 7.0, J_{gh} 2.0; δ_h 4.15, dd, J_{hf} 14; δ_f 6.46, dd; δ_i 3.67), obtained by dehydrobromination of the cyclopropane carboxylate (10c) proved less effective.

Financial assistance by the University of Stellenbosch, the South African Council for Scientific and Industrial Research, the South African Inventions Development Corporation is gratefully acknowledged.

REFERENCES AND FOOTNOTES

- Part V. C.F. Garbers and F. Scott, *Tetrahedron Lett.*, 1625 (1976).
- Abstracted in part from a thesis by C. Ehlers (to be submitted at the Univ. of Stellenbosch).
- For a recent summary see M. Elliott and N.F. Janes in "Pyrethrum the Natural Insecticide", ed. J.E. Casida Academic Press (1973), p. 65.
- e.g. (a) R.W. Mills, R.D.H. Murray, and R.A. Raphael, *J. Chem. Soc., Perkin Trans. I*, 133, (1973); (b) H. Babler and A.J. Tortorello, *J. Org. Chem.*, 41, 885 (1976); (c) J. Ficini and J. d'Angelo, *Tetrahedron Lett.*, 2441 (1976); (d) Kiyoshi Kondo, Kiyohide Matsui, and Yuriko Takahatake, *Tetrahedron Lett.*, 4359 (1976); (e) T. Aratani, Y. Yoneyoshi, and T. Nagase, *Tetrahedron Lett.*, 2599 (1977); (f) S.C. Welch and T.A. Valdes, *J. Org. Chem.*, 42, 2108 (1977).
- H. Gross and E. Höft, *Angew. Chem. internat. Edit.*, 6, 335 (1967).
- cf. C.F. Garbers, J.A. Steenkamp and H.E. Visagie, *Tetrahedron Lett.*, 3753 (1975).
- Approximate ratios of products formed in trial experiments in the reaction:

$$\text{Ester(5) + Ether(6a)} \xrightarrow{\text{Lewis acid}} \gamma\text{-chloro-ether(7a) + lactone(8a) + HCl-addition product(9)}$$
 Yields are not optimised. Analysis by nmr.

Catalyst	Total Yield	Ether (7a)	Lactone (8a)	HCl-Add. Product (9)
TiCl ₄ /CH ₂ Cl ₂	82%	27%	33%	40%
ZnCl ₂	80%	15%	64%	21%
SnCl ₄ /CH ₃ NO ₂	49%	-	48%	52%
BF ₃	49%	-	65%	35%
SnCl ₄ /CH ₂ Cl ₂	86%	56%	44%	-

- The conversion of 4-methylpentan-4-olides to cyclopropane carboxylates by successive treatment with SOCl₂, MeOH, and base, is a known procedure e.g. M. Julia, *Fr. 356 954*; M. Julia, S. Julia and M. Langlois, *Bull. Soc. Chim. Fr.*, 4, 1014 (1965).
- Apart from some t-chloroderivatives (7) which partially decomposed during purification, all new compounds or known compounds prepared by new methods, gave satisfactory combustion analyses. The spectral properties of all compounds are in accord with the assigned structures. Pmr. spectral data were obtained from CDCl₃ solutions of the relevant samples.
- Deducted from the vicinal coupling constants of the cyclopropane ring hydrogens: $J_{\text{trans}} \sim 5.5$ Hz; $J_{\text{cis}} \sim 8.7$ Hz. See A.F. Bramwell, L. Crombie, P. Helmesley, G. Pattenden, M. Elliott, and N.F. Janes, *Tetrahedron*, 25, 1727 (1967).
- E.J. Corey and P. Grieco, *Tetrahedron Lett.*, 1972, 107; B. Ganem and V.R. Small, *J. Org. Chem.*, 39, 3728 (1974); E.J. Corey and B. Snider, *J. Org. Chem.*, 39, 256 (1975). See also ref. 6.
- M. Elliott, N.F. Janes, and D.A. Pulman, *B.P. 24 809/72*; *24 810/72*; *30 838/72*; *59 184/72*; and *20 539/73*.
- e.g. M. Elliott, A.W. Farnham, N.F. Janes, P.H. Needham, and D.A. Pulman, *Nature*, 248, 710 (1974)
- This reaction is analogous to the Julia-reaction: cf. M. Julia, S. Julia, and R. Guégan, *Bull. Soc. chim. France*, 1072 (1960), S.F. Brady, M.A. Ilton, and W.S. Johnson, *J. Amer. Chem. Soc.*, 90, 2882 (1968); H. Babler, M.J. Coghlan, and D.J. Giacherio, *J. Org. Chem.*, 42, 2172 (1977).
- J. Martel, *Ger. Offen* 1 935 386 (1970).
- M. Franck-Neumann, *Angew. Chem. internat. Edit.*, 7, 65 (1968).
- H.O. House and R.S. Ro, *J. Amer. Chem. Soc.*, 80, 182 (1958).