Tetrahedron Letters No. 36, pp 3417 - 3420. 0040-4039/79/0901-3417$02.00/0

THE PREPARATION OF SYNTHONS ON ROUTE TO TERPENOIDS OF MARINE ORIGIN

Francis ROUESSAC,
Laboratoire de Synthèse Organique - Faculté des Sciences, route de Laval - 72017 Le Mans Cédex,

And

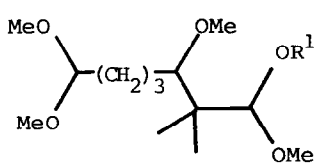
Henri ZAMARLIK,
Laboratoire de Chimie Organique et Biologique - Faculté des Sciences, avenue Monge - 37200 Tours.

An approach to versatile intermediates by Claisen rearrangements followed by chemical purification gave a stable γδ-unsaturated acid useful for title mentioned compounds.

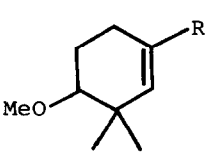
Several authors have explored biogenetic-type syntheses of brominated terpenoids from marine origin (1). However the selective C-halogen bond formation with concomitant ring closure remains at present hampered by the low yields of purified compounds obtained in this fashion (1c, 2).

In this article we wish to report an alternative way to prepare compounds of known stereochemistry which may be valuable intermediates in syntheses of β-snyderol (3), aplysistatine (4) and obtusadiol (5) now in progress in our laboratory.

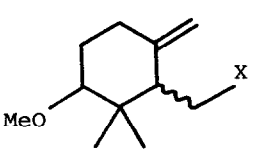
Treatment (0°, then for 4 h at 30°) of an excess of 1,1,5,5-tetramethoxypentane (6) with isobutenyl ethyl (or methyl) ether (7) in the presence of a catalytic amount of BF_3/Et_2O gave the adduct 1 (R^1 = Et or Me) in ≃ 45 % yield. This was converted to the aldehyde 2 bp 100°/14 mm, in 80 % yield, by reflux for 2 h with AcONa in 95 % AcOH, followed by reduction with $NaBH_4$ in CH_3OH-H_2O mixture to the alcohol 3, bp 112°/10 mm, yield 90 % (8).



1



	R
2	CHO
3	CH_2OH
4	$CH_2OCH=CH_2$
6	CH_2OCOCH_3



I

Then, among the numerous [3.3] sigmatropic rearrangements that are known to transform an allylic alcohol as 3 into a structure of type I (X = CHO, CO_2H ...) in which we had an interest, we have investigated the Claisen transposition and two of its variants in order to estimate the stereochemistry of this transformation.

Thus, heating at 550° in vapour phase (10), the vinyl allyl ether 4, obtained by transvinylation of 3 catalyzed by mercuric acetate (11) (bp 95°/10 mm, yield 78 %) gave 5 with a nearly quantitative yield, as a mixture of two epimers 5a/5b (bp ≃ 77°/0.1 mm - ratio 65 : 35, $\sigma_{n-1} = \pm 1,7$ (8, 12).

^1H n.m.r. ($CDCl_3$/TMS) 5a δ : 0.82 ; 1.01 ; 3.33 (3 CH_3, s) ; 4.50 ; 4.85 (2H ethyl.) ; 9.56 (CHO, dd J ≃ 2.5/2.5 Hz) - 5b δ : 0.76 ; 1.03 ; 3.34 (3 CH_3, s) ; 9.62 (CHO, dd J ≃ 3, 1.5 Hz) (13) - $\frac{m}{e}$ = 196.1461 (CAMECA, 250 MHz).

(Spectra unambiguously assigned a posteriori by chemical transformations on these epimers, vide infra). Unfortunately this transposition which takes place via a pseudo cyclic chair transition state might not proceed with a great stereoselectivity due to the location of the methoxyl group.

Two other Claisen-type rearrangements were also used that gave acids 7a and 7b at lower temperatures.

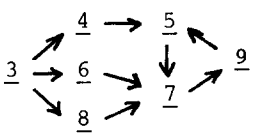
In the first sequence, treatment of acetate 6, bp : 77°/0.1 mm, (Ac_2O, pyr., 20°, 24 h, yield 90 %) with lithium isopropylcyclohexylamide then t-$BuMe_2SiCl$ according to (14), then subsequent hydrolysis of the rearranged silyl-ester with 10 % HCl (20°, 24 h) gave 7a/7b in approximatively the same ratio (70 : 30) as for aldehydes 5 (yield 40 %).

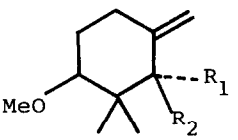
^1H n.m.r. ($CDCl_3$/TMS) 7a δ : 0.84 ; 0.98 ; 3.34 (3 CH_3, s) ; 4.64 and 4.80 (2H ethyl.) - 7b δ : 0.76 ; 1.03 ; 3.34 (3 CH_3, s) (13).

Finally ketene acetal rearrangement using the triethylorthoacetate pathway (15) was investigated which proved to be the most efficient means for the conversion of 3 to 7. Thus, condensation of 3 with an excess of triethylorthoacetate in the presence of a catalytic amount of acetic acid (15) produced the corresponding esters 8a/8b (ratio 70 : 30) at 120°C.

^1H n.m.r. ($CDCl_3$/TMS) 8a δ : 0.85 ; 0.98 ; 3.33 (3 CH_3, s) - 8b δ : 0.75 ; 1.02 ; 3.33 (3 CH_3, s) (13).

8a/8b were hydrolysed to 7a/7b with Claisen's alkali (16), then acidification (overall yield 3 ⟶ 7 : 60 %).





For b serie, R_1 and R_2 must be exchanged

	R_1	R_2
5a	CH_2CHO	H
7a	CH_2CO_2H	H
8a	CH_2CO_2Et	H
9a	CH_2CO_2Me	H

Transformations of 5 to 7 (Jones oxydation, yield 70 %) and of 7 to 5 - DIBAH, -30° on 8 (y : 80 %) or on 9 derived from 7 with CH_3OH-BF_3 (y > 95 %) were also achieved to correlate the different compounds 5, 7, 8, 9.

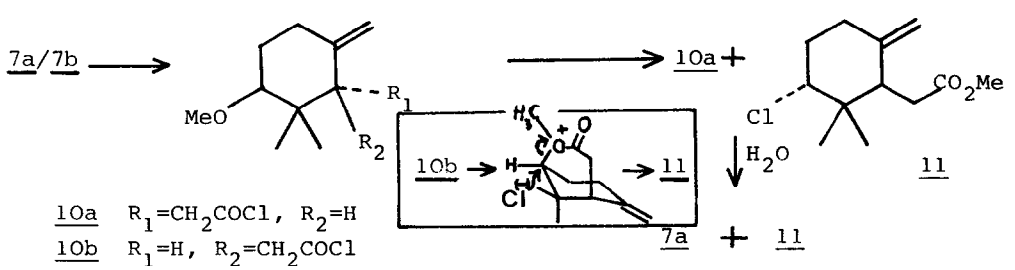
^1H n.m.r. ($CDCl_3$,TMS) of 9a δ : 0.86 ; 0.97 ; 3.32 ; 3.61 (4 CH_3, s) ; 4.55 ; 4.75 (2H ethyl.) - 9b δ : 0.77 ; 1.01 ; 3.32 ; 3.61 (4 CH_3, s) (13).

The lack of stereospecificity in the above rearrangements compared with the methoxyl group and the difficulties encountered to separate properly both isomers on a preparative scale by column chromatography (close R_F for a and b compounds) made it necessary to carry out chemical transformations to isolate pure 7a which after S_N2 substitution of the CH_3O group should have the expected stereochemistry.

For this purpose 7a/7b were transformed (quantitative yield) into acid chlorides 10a/10b (reflux with 1,5 eq. of $SOCl_2$ in C_6H_6 for 1 h).

^1H n.m.r. of mixture 10 ($CDCl_3$, TMS) δ : 0.82 ; 1.01 ; 3.32 (3 CH_3) ; 4.60 ; 4,85 (2H ethyl.).

When reflux was lengthened (even in the absence of $SOCl_2$) acid chloride 10a was unaffected but 10b rearranged mainly to chloroester 11 (17). Since 11 derived from the minor compound 10b, its yield didn't allow to use it as a useful intermediate. But hydrolysis of the crude reaction mixture (hot water 10 mn) then subsequent extraction in a classical way furnished pure 7a (overall yield 50 % from 7a/7b).



10a R_1=CH_2COCl, R_2=H
10b R_1=H, R_2=CH_2COCl

We are confident that the sequences described represent an interesting process to obtain acid 7a on a preparative scale.

References and notes

1 - a) P.J. Scheuer "Marine Natural Products", Vol. 1, Acad. Press, N.Y., 1978
b) G.R. Pettit, C.L. Herald, J.J. Einck, L.D. Vanell, P. Brown and D. Gust, J. Org. Chem., 43, 4685 (1978).
c) D.J. Faulkner, Tetrahedron, 33, 1421 (1977).

2 - Cf. Inter alia (a) E.E. Van Tamelen and E.J. Hessler, J. Chem. Soc., Chem. Comm., 411 (1966) ; (b) A.G. Gonzales, J.D. Martin, C. Perez and M.A. Ramirez, Tetrahedron Letters, 137 (1976).

3 - B.M. Howard and W. Fenical, Tetrahedron Letters, 41 (1976).

4 - G.R. Pettit, C.L. Herald, M.S. Allen, R.B. Von Dreele, L.D. Vanell, J.P.Y. Kao and W. Blake, J. Amer. Chem. Soc., 99, 262 (1977).

5 - B.M. Howard and W. Fenical, Tetrahedron Letters, 2453 (1978).

6 - S.M. Makin, V.M. Likhosherstov and M.I. Berezhnaya, Zh. Org. Khim., 3, 1419 (1967) ; Chem. Abstr., 67, 116,787z.

7 - K.C. Brannock, J. Org. Chem., 25, 258 (1959).

8 - This sequence is closely related to interesting analogues 3, 4 and 5 prepared by Julia et al (9). In our work, overall yield is yet greater (20 % instead 3 %, from commercially available compounds) and stereochemistry is also defined.

9 - S. Julia, M. Julia, H. Linares and J.C. Blondel, Bull. Soc. Chim. Fr., 1952 (1962).

10 - This reaction was made under vacuum (0.2 mm) is an apparatus already described : J. Haslouin and F. Rouessac, C.R. Acad. Sci. Paris, 274 (C), 1691 (1973). If temperature is lower, reaction was incomplete.

11 - W. Watanabe and L. Conlon, J. Amer. Chem. Soc., 79, 2828 (1957).

12 - Accurate n.m.r. analyses based on $6\,^{13}C$ atoms and ^{1}H methyl groups.

13 - In the text, for b compounds, only most significant differences with a serie are given.

14 - J.A. Katzenellenbogen and K.J. Christy, J. Org. Chem., 39, 3315 (1974).

15 - W.S. Johnson, L. Werthemann, W.R. Bartlett, T.J. Brocksom, T.T. Li, D.J. Faulkner and M.R. Petersen, J. Amer. Chem. Soc., 92, 741 (1970).

16 - L. Fieser and M. Fieser, Reagents for Org. Synth., Vol. I, Wiley, N.Y., p. 153, 1967.

17 - We thank the referees for bringing to our attention similar transformations. e.g. : V. Prelog and S. Heinbach-Juhasz, Chem. Ber., 74,1702 (1941).

- D.S. Noyce and H.I. Weingarten, J. Amer. Chem. Soc., 79, 3093 (1957).

(Received in France 13 June 1979)