Tetrahedron Letters,Vol.24,No.1,pp 103-106,1983 0040-4039/83/010103-04$03.00/0
Printed in Great Britain

ENANTIOSELECTIVE SYNTHESIS OF CHIRAL CARONIC ESTERS : APPLICATION TO THE SYNTHESES OF (1R)-TRANS-CHRYSANTHEMIC ACID AND ITS (1R)-CIS-DIBROMO VINYL ANALOGUE FROM DIMENTHYL FUMARATES

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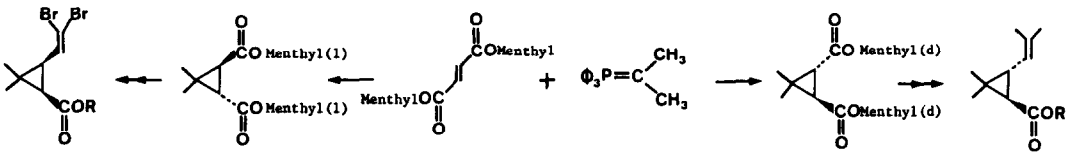
(1R) trans chrysanthemic acid and the (1R) cis gem dibromovinyl analogue, constituents respectively of the natural Pyrethrins and of Deltamethrin, the most potent insecticides known, have been stereoselectively prepared from isopropylidene triphenyl phosphorane and di(d)-menthyl or di(l)-menthyl fumarates respectively.

Suitable esters of (1R) trans chrysanthemic acid 1 and of its (1R) cis dibromovinyl analogue 2 are potent insecticides [1] sold respectively for domestic and agriculture uses. They have an important economical value since their world turnover has reached 450 million dollars in 1981.

We have recently reported that dimethyl caronates are valuable key intermediates for the synthesis of racemic [2] or optically active [3] 1 and 2. We now disclose our preliminary results concerning the enantioselective synthesis of (1R) 1 and (1R) 2 (Scheme 1).

Scheme 1



2 5b 4 3 5a 1

The key step of that synthesis is without contest the enantioselective synthesis of trans caronic diester from a fumarate bearing a chiral alkoxy moiety and a suitable isopropylidene precursor [2,4].

Best results were obtained (85% yield, 74%d.e. [diastereoisomeric excess [5]])on reaction of isopropylidene triphenyl phosphorane 3 [1.2 mol.eq., 7.2 10^{-2}M,THF/hexane 95/5, from $(C_6H_5)_3\overset{+}{P}-CH(CH_3)_2I^-$ and n-BuLi] with dimenthyl fumarates [6] 4 (5.10^{-2}M, THF, addition at -78°C then warmed at 20° for 0.5h). The (1S,3S) stereoisomer 5b is obtained if (l)menthyl group is used as the inductor.

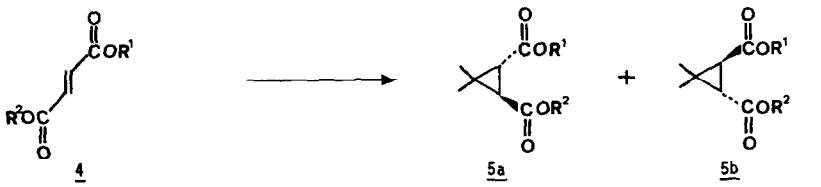
The reaction proceeds in two steps. The addition of isopropylidene triphenyl phosphorane on the dimenthyl fumarates already occurs at -100° whereas the cyclization requires at least -30°C to start. The first step is the one which controls the induction : till now we were unable to prove if it is reversible. The nature of the solvent and the temperature at which the reaction is initiated do not have a dramatic influence on the diastereoselection [-100° (74% d.e.) ; -78° (74% d.e.);+20°(56% d.e.)] . However, the concentration appears to play an important role since

a 44% d.e. instead of the 74% d.e. was found when the reacting solutions were ten times more concentrated.

Among the different isopropylidene precursors (i.e. isopropylidene triphenyl phosphorane[4], isopropylidene diphenylsulfurane [8], 2-diazopropane [7]) used for the asymmetric cyclopropanation of chiral fumarates (Scheme 2), the phosphorus reagent was found to be superior by far. For example, only 22% d.e. was observed on the caronate resulting from the reaction of isopropylidene diphenylsulfurane (prepared according to Corey)[8] with di(l)menthyl fumarate ($3.6\ 10^{-2}$M final concentration, DME/hexane, -78°, 0.2h then 20°) whereas under identical reaction conditions, isopropylidene triphenylphosphorane led to a caronate with a much higher diastereoselection (66% d.e.)[9]

Interestingly, the (1S,3S) stereoisomer 5b predominates in all the cases studied in which the (l)menthyl group is present.

Scheme 2



	Reagents and conditions	Overall yield %	5a/5b	d.e. %
$R^1=R^2$ = l-menthyl	$(CH_3)_2C{=}P\phi_3$, 0.025 M†, THF, -78° to +20°	85	13/87	74
d-menthyl	" " " "	85	87/13	74
l-menthyl	$(CH_3)_2CN_2$/Cu xylene 0° to 160° [7]	56	47/53	6
l-menthyl	$(CH_3)_2C{=}S\phi_2$, 0.036 M†, DME, -78° to +20°	79	39/61	22
l-bornyl	$(CH_3)_2C{=}P\phi_3$, 0.025 M†, THF, -78° to +20°	68	41/59 *	18
trans chrysanthemyl[10]	" " " "	70	51/49	2
d-stigmastanyl[11]	" " " "	57	70/30	40
d-dimethyl-3,3-butanyl-2[12]	" " " "	83	75/25	50
l-phenyl menthyl[13]	" " " "	80	09/91	82
R^1 = l-menthyl R^2 = methyl	" " " "	75	39/61	22

† This refers to the final concentration.

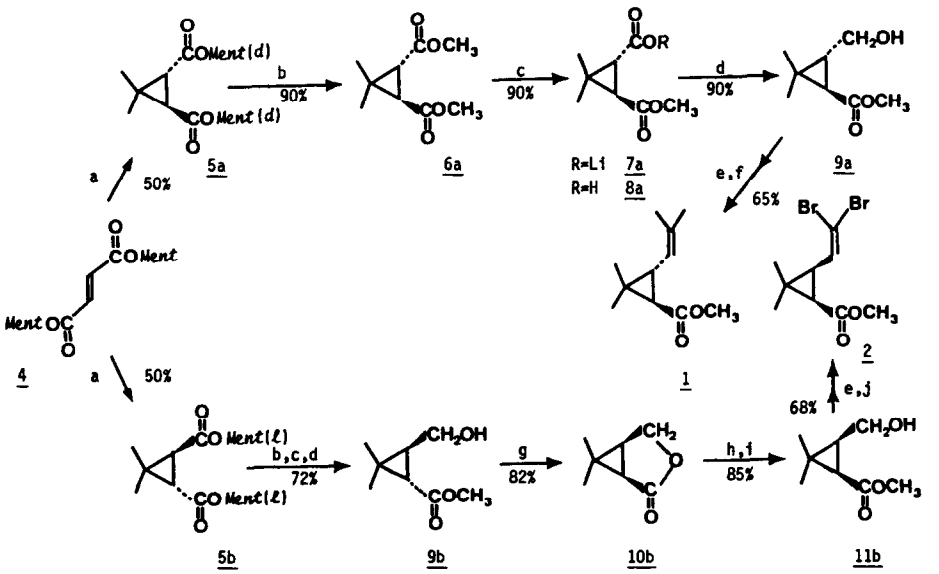
* The stereochemical assignment has not been realized in that specific case.

We have achieved the synthesis of (1R) trans chrysanthemic acid 1 and its (1R) cis dibromo vinyl analogue 2 from the fumarates respectively derived from unnatural d-menthol and its natural enantiomer (Scheme 1). Each major diastereoisomer 5 present in the crude mixture of dimenthyl caronates obtained from 4a or 4b and isopropylidene triphenylphosphorane (see table, entries 1 and 2, 85% overall yield, 74% d.e.) was isolated diastereoisomerically pure in 50% overall yield from the fumarates after only one recrystallization from ethanol (0.1M, reflux then 20°, 24h).

We planned to apply to 5a (1R,3R) the synthetic scheme we already published [2], for the synthesis of (dl) trans chrysanthemic acid. That would require the synthesis of mono menthyl caronic acid by the selective saponification of one of the two menthyl esters. All our trials were unsuccessful. We therefore decided to achieve first the transesterification of 5a to the dimethyl ester 6a and to perform later its monosaponification to 8a. The dimethyl ester 6a was readily obtained from the dimenthylcaronate 5a and sodium methylate (1 mol.eq. methanol, 75°, 16h).

We were however disappointed to find that it, in fact, consists of a 70/30 mixture of the (1R,3R) and (1S,3S) enantiomers. This requires two consecutive epimerizations at the C_1 and C_3 carbons of the cyclopropane ring. We found that it already occurs during the reaction, on the (1R,3R) di (d)menthyl caronate 5a [after 1hr reaction, (1R,3R), (1S,3S) ratio : 70/30 by $|GC|^2$]. However, if the dimenthyl caronate 5a is reacted with lithium methylate (1 mol.eq., methanol, 75°) instead of sodium methylate not only is the reaction faster (4h instead of 16h) but also the dimethyl caronate 6a was isolated, after acidic work up, enantiomerically pure, and in 90% yield. The monomethyl ester of caronic acid 8a, required for the completion of the synthesis, was obtained by a slight variation of the above mentioned reaction. Addition of water instead of acidic work up, transforms the lithium alcoholate to lithium hydroxide (1 mol.eq.) which on heating (75°, 3h) performs the monosaponification of 6a to 7a. Extraction of the crude mixture with ether allows the easy recovery of the menthol (96%), from the acid 8a isolated after acidic work up (90% yield, e.e.: 98.6%). The synthesis of (1R,3R) trans chrysanthemic ester 1 (R = CH_3) was achieved from that stage in 65% overall yield along the line we already reported[2,3] (Scheme 3).

Scheme 3



a) 1.2 mol.eq. $(C_6H_5)_3P{=}C(CH_3)_2$, THF/hexane, -78° then 20°, 0.5h ; b) 1 mol.eq. CH_3OLi, CH_3OH, 75°, 4h ; c) then addition of H_2O, 75°, 3h ; d) 1.5 mol.eq. $H_3B{:}S(CH_3)_2$, THF, 20°, 0.5h ; e) $C_5H_5\overset{+}{N}HCrO_3Cl^-$ (PCC), CH_2Cl_2, 20°, 1h ; f) 1.2 mol.eq. $(C_6H_5)_3P{=}C(CH_3)_2$, THF/hexane, 0°, 1h ; g) 1 mol.eq. t-BuOK, benzene, 80°, 1h then H_2SO_4 conc., 20°, 0.2h ; h) 3 mol.eq. KOH, CH_3OH, 20°, 1.5h then 1N HCl ; i) 1.1 mol.eq. CH_2N_2, ether, 20°, 0.2h ; j) 2 mol.eq. CBr_4, 4 mol.eq. $(C_6H_5)_3P$, CH_2Cl_2.

The synthesis of the (1R,3S) cis dibromovinyl chrysanthemic acid takes advantage of the reactions just reported. Applied to the (1S,3S)di(1)menthyl caronate 5b, they allow the easy synthesis of the alcohol 9b (36% yield from the fumarate). This must be transformed by an "enantioselective contrathermodynamic isomerization" to its cis (1R,3S) analogue 11b in order to obtain the required stereochemistry.

This was achieved in two steps, in 73% overall yield and 98.1% e.e. through the cis butyrolactone 10b.

Thus reaction of 9b with potassium t-butoxide in benzene (1 mol.eq., 0.55 M /C_6H_6,80°,1h) afforded the lactone 10b. An acidic work up (conc. H_2SO_4,20°,0.2h) was required in order to avoid its ring opening. It was isolated in 82% yield after the removal ($NaHCO_3$,aq.sol.) of some products belonging to the cis series.

Ring opening of the lactone 10b was readily achieved in basic media (3 mol.eq. KOH, 2N/CH_3OH,20°, 1.5h) ; *in situ* acidic work up (aq. HCl,1N) followed by esterification of the resulting (1R,3S)cis acid alcohol (1.1 mol.eq. CH_2N_2,ether,20°) provided the (1R,3S) cis ester alcohol 11b, formed in 85% overall yield from 10b.

Finally, the cis dibromo vinyl derivative 2 (R = CH_3) is obtained in two steps and 68% yield from that stage by oxidation of the hydroxy moiety to the corresponding aldehyde and its further reaction with carbon tetrabromide and triphenyl phosphine [3].

This work was first reported by one of us (AK) at the Euchem conference "Methods in Organic Synthesis", held in Louvain-la-Neuve (Belgium), July 5-9, 1982.

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6. a) Unnatural d-menthol was kindly provided by Professor Weyersthal (W. Berlin). It is now available from Aldrich (personal communication from Dr. Bader).
   b) Natural l-menthol used without purification for this work, has been purchased from Aldrich M.278.0.

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9. Other asymmetric inductions involving isopropylidene triphenyl phosphorane and α,β-unsaturated esters bearing a chiral alkoxy group or a chiral acetal moiety attached in position 4 have already been performed in our laboratory and will be published in due course (first report of that work A. Krief 28th congress of IUPAC held in Vancouver (Canada) August 16-21 (1981)).

10. Prepared by reduction ($LiAlH_4$/ether) of 1R trans chrysanthemic acid prepared according to ref. 3.

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(Received in UK 6 October 1982)