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ALLYLIC STEREOCENTRE DIRECTED CYCLOPROPANATION. A NEW HIGHLY ENANTIOSELECTIVE SYNTHESIS OF HEMICARONIC ALDEHYDE

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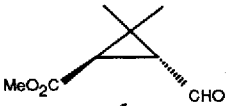
Abstract: isopropylidenetriphenylphosphorane reacts with oxazolidine **4** with excellent π-face selectivity. The title compound is obtained in high optical purity after removal of the chiral auxiliary.

Pyrethroids (like chrysantemic acid **2** and its *cis* dibromo vinyl analog **3**) are among the most powerful insecticides known (Scheme 1).[1] Their biological activity is associated with the (1R) configuration, the (1S) isomers being in many cases less effective. The key intermediate for most syntheses of pyrethroids is (1R,3R)-hemicaronic aldehyde **1**, which has been frequently obtained by ozonization of naturally occurring (+)-trans-chrysantemic acid.[1] More recently, alternative routes to enantiomerically pure **1** have been actively investigated and a few asymmetric syntheses have appeared in the literature.



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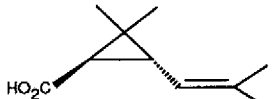

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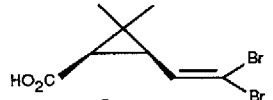
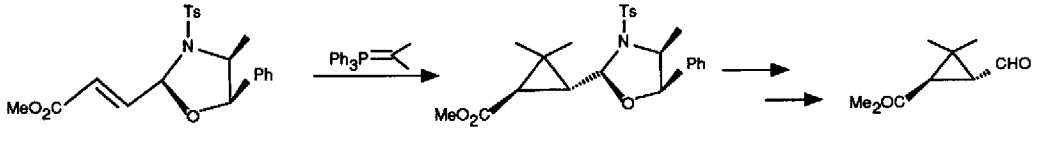


3

Oxazolidine **4**, recently introduced as an effective C-4 chiral synthon,[3] is perfectly suited to be a precursor of **1** provided that stereoselective cyclopropanation can be achieved. Since this substrate has proved to be an excellent Michael acceptor, adding nucleophiles selectively on the *si* face,[3] we decided to investigate its reactivity toward nucleophilic cyclopropanating agents. To this end, **4** was prepared in pure diastereomeric form and high yield by cyclization of N-tosyl (1R,2S) norephedrine and the appropriate α,β-unsaturated dimethyl acetal as previously reported.[3]

After much experimentation, the best cyclopropanation conditions were found to involve the use of 3 eq of isopropylidene triphenylphosphorane[4] in benzene-hexane at R.T. for 30 min and afforded **5** as a single detectable isomer in 60 % yield (Scheme 1).[5,6]

SCHEME 1



4 **5** **1**

Standard removal of the chiral auxiliary (1.$BF_3.Et_2O$, $HSCH_2CH_2SH$ / 2.MeI, H_2O, $CaCO_3$)[3] afforded **1**

in 70 % yield. The thus obtained aldehyde has $[\alpha]_D^{25}$=+19.2° (c=2.78,acetone) and was therefore assigned the (1R,3R) configuration.[7] Nucleophilic addition to **4** therefore takes place, also in this case, from the substrate *si* face and can be rationalized on the basis of MO considerations[8] using the transition structures previously proposed.[3]

The optical purity of **1** was further confirmed by $NaCNBH_3$ reduction to the corresponding alcohol followed by NMR analysis of the Mosher ester. The racemic sample was obtained by hydrolysis with Amberlyst-15[9] of the corresponding dimethyl acetal (purchased from Fluka Chemical Co.)

In conclusion, this sequence constitutes a very short and highly enantioselective route to the important intermediate hemicaronic aldehyde **1**.

REFERENCES AND NOTES

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3. *a*)Bernardi,A., Cardani,S., Pilati,T., Poli,G., Scolastico,C., Villa,R., *J. Org. Chem.* **1987**, *53*, 1600; *b*)Bernardi,A., Cardani,S., Poli,G., Scolastico,C., *J. Org. Chem.* **1986**, *51*, 5041; *c*)Cardani,S., Poli,G., Scolastico,C., Villa,R., *Tetrahedron* **1988**, *44*, 5929; *d*)Cardani,S., Bernardi,A., Colombo,L., Gennari,C., Scolastico,C., Venturini,I, *Tetrahedron*, **1988**, *44*, 5563.
4. Grieco,P.A., Finkelhar,R.S., *Tetrahedron Lett.* **1972**, 3781.
5. All attempts to improve on this yield, including use of different solvents (THF, toluene), lower reaction temperatures (-20°C, 0°C) and different nucleophiles [diphenylsulfonium isopropylide, N,N dimethylamino phenyloxosulfonium isopropylide and the stabilized carbanions of S,S-diisopropyl and S-phenyl-S-isopropyl-N-(*p*-tolylsulfonyl) sulfoximines] were unsuccessful.
6. Conditions for cyclopropanation reaction and characterization of **5** follow: a solution of isopropyl triphenylphosphonium iodide (4971 mg, 9.55 mmol) in C_6H_6 (38 ml) is treated with n-BuLi 1.6 M in hexane (5.97 ml, 9.55 mmol) at room temperature. After one hour a solution of **4** (1534 mg, 3.18 mmol) in C_6H_6 (19 ml) is added, and the reaction is allowed to stand 30 min at room temperature. The reaction is quenched with water (20 ml) and extracted with CH_2Cl_2 (3 x 15 ml). The organic layer is dried (Na_2SO_4) and the solvent is evaporated at reduced pressure. The crude product is purified by flash chromatography using n-hexane/AcOEt (80:20) affording **5** as a pale yellow syrup; yield: 1016 mg (61%); $[\alpha]_D^{25}$= -32.4° (c= 1.33; $CHCl_3$); IR ($CHCl_3$): ν= 1730 (O-CO) cm^{-1}; ^{1}H-NMR (C_6D_6): δ= 0.91 (d, 3H, J= 6.7Hz, *CH_3*-CH); 1.40 (s, 6H, 2 CH_3); 1.95 (s, 3H, *$CH_3C_6H_4$*) 2.04 (d, 1H, J= 5.8Hz, *CH*-CO_2Me); 2.42 (dd, 1H, J= 5.8Hz, 5.5Hz, *CH*-CHNO); 3.43 (s, 3H, CO_2CH_3); 4.02-4.43 (m,1H, *CH*-CH_3); 4.38 (d, 1H, J=5.1Hz, *CH*-Ph); 5.16 (d, 1H, J= 5.5Hz, CHNO); 6.83-7.88 (m, 9H, H_{arom}). ^{13}C-NMR ($CDCl_3$) (selected data) : δ= 17.3; 20.6; 21.6; 21.9; 28.1; 29.5; 38.2; 51.7; 58.5; 81.4; 88.7; 172.2.
7. For the (1R,3R) aldehyde obtained by ozonolysis of methyl chrisantemate see note *2d*: $[\alpha]_D^{25}$=+19.2° (c=18.25, acetone).
8. For a theoretical discussion on the transition structures in nucleophilic additions to double bond: Houck,K.N., Paddon-Row,M.N., Rondan,N.G., Wu,Y.D., Brown,F.K., Spellmeyer,D.C., Metz,J.T., Li,Y., Loncharich,R.J., *Science* **1986**, *231*, 1108 and references therein.
9. For Amberlyst-15 hydrolysis of acetals: Gree,R., Tourbah,H., Carrié,R., *Tetrahedron Lett.***1986**, *27*, 4983.

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