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Enantiospecific Synthesis of a Chrysanthemic Acid Precursor by the Katsuki-Sharpless Epoxidation and the Stork Cyclisation

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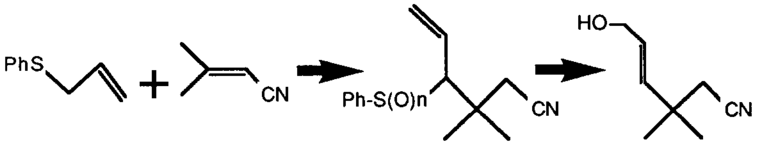
Abstract: The 1,4 addition of the anion of allylphenylthioether to 3,3-dimethylacrylonitrile occured in 76% at the α position to the sulfur. The allylic alcohol 5 obtained from thioether 3 was asymetrically epoxidised with the Katsuki-Sharpless procedure to [4S,5R] epoxyalcohol 6 (ee > 94%). The silyl ether 8 was cyclised to the cis and trans nitrile 9. Cleavage of the glycol 10 gave the cis 11 and trans-aldehyde 12. Later 12 was converted to [1R,3R] trans chrysanthemic nitrile 13 (ee 92%).

Enantiospecific synthesis of chrysanthemic acid (1,2) are of interest considering the high biological activity of the ester of [1R,3R] enantiomer (3). Combining the asymetric Katsuki-Sharpless epoxidation (4) and the requirement of inversion for SN_2 reaction in the Stork cyclisation (5), we have prepared starting from allylic alcohol 5 the [1R,3R] nitrile 13, a precursor of [1R,3R] chrysanthemic acid (2).

The planned synthesis required the cyano-alcohol 5 not described in the literature. The 1,4 addition at the α center of the lithium carbanion (6) derived from allylphenyl thioether 1 in THF at -78° in presence of HMPA (3eq) and of lithium bromide (2eq) to dimethylacrylonitrile 2 (1.5eq) provided 3, in a yield of 76%.

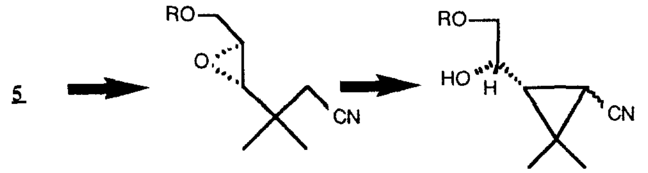
The thioether 3 was oxidised to sulfoxide 4, which was transformed to alcohol 5 by [2,3] sigmatropic shift to the sulfenate and by reaction of the sulfenate with diethylamine (7) (yield 3 → 5 : 86%).



1 2 3 n=0 4 n=1 5

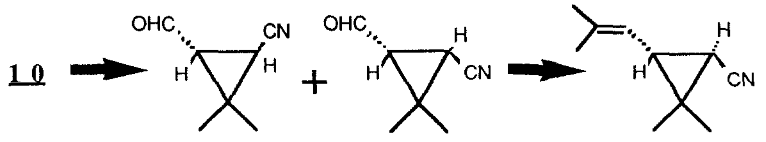
The allylic alcohol 5 was epoxidised to [4S,5R] epoxy alcohol 6 in methylene chloride at -8° in presence of molecular sieves 4Å with t-butylhydroperoxide (3eq) in presence of titanium tetra-isopropoxide (0.3eq) and (+)diethyltartrate (0.3eq) (8). The enantiomeric excess of the [4S,5R] epoxy alcohol 6 was determined on its acetate 7 using chiral europium shift reagent (9) : ee>94% with a yield 5 → 8 : 62%.

The Stork cyclisation (5) was performed at 20° in 3 hr on the silyl ether 8 converted to its anion with LDA at 0°. The product (yield 85% ; isomer ratio 1/2.2) was a mixture of cis and trans isomers 9. After removal of the silyl ether (tetrabutylammonium fluoride: 90%), the glycols 10 were cleaved with sodium periodate.



6 R=H
7 R=Ac
8 R=Me$_2$tBuSi

9 R=Me$_2$tBuSi
10 R=H



11 12 13

The cis and trans aldehydes 11 and 12 were separated by chromatography on silica gel. The yield of both aldehydes 11 and 12 from thioether 1 was 15%.

The trans aldehyde 12 was converted by Wittig reaction to the nitrile 13 of chrysanthemic acid, showing an $[\alpha]_D$ +27° (EtOH ; c=0.04) to be compared to $[\alpha]_D$ +29.3 (EtOH; c=1.31) for the nitrile 13 obtained from pantolactone (2). Thus the [1R,3R] nitrile 13 prepared through our sequence had an ee of 92%.

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