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SYNTHESIS OF PYRETHROIDS VIA EPOXYAMIDE CYCLIZATION

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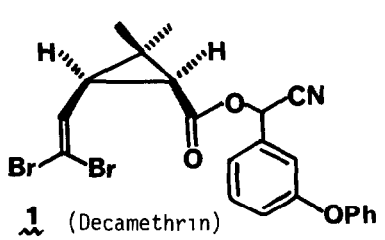
Summary. LDA-induced cyclization of 4 yields 5, the trans-isomer of which undergoes dehydration using $Ph_2S[OC(CF_3)_2Ph]_2$ to give the pyrethroid amide 6.

The recent development of synthetic pyrethroids (e.g 1) as a most promising class of insecticides[1] has triggered a flurry of new synthetic activity [2] Since "almost all active pyrethroids are esters,"[1a] it is surprising that, with a few exceptions,[1a] reports concerning systematic variation to functional groups at the same oxidation state (e.g. thioesters, amides, thioamides) have not appeared. We report a short, direct route to pyrethroid amide 6 via base-induced epoxyamide cyclization. The key step, involving a crucial dehydration step of the cyclopropylcarbinol trans-5 which had thwarted an analogous strategy using α-metalated esters,[3] was achieved using Martin's sulfurane reagent, $Ph_2S[OC(CF_3)_2Ph]_2$.[4]



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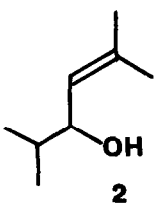

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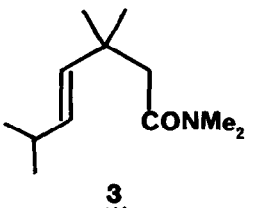

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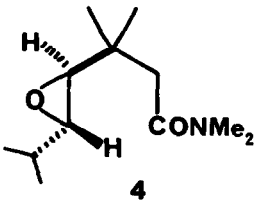

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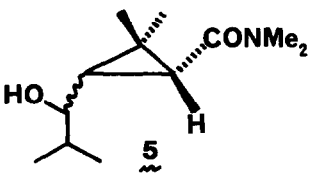

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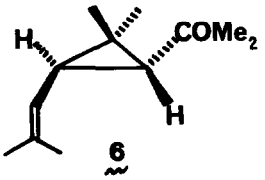

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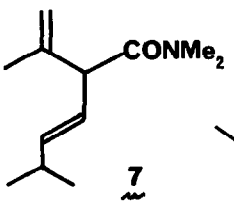

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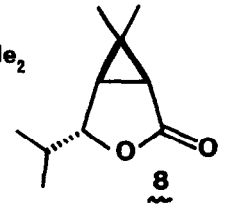

8

The readily available alcohol 2[5] was subjected to the Claisen-Eschenmoser rearrangement[6] ($MeC(OMe)_2NMe_2$/xylene/Δ/4h) to give the unsaturated amide 3[7] in 91% yield Epoxidation (MCPBA/CH_2Cl_2/aq. $NaHCO_3$) gave the unstable epoxide 4 which without purification was treated with 3 equiv of LDA (THF/-78°C → RT/8h) to afford the cyclopropane amide 5 in 72% yield as a 1.3 mixture of cis trans isomers which were clearly separated by hplc (Waters Prep 500, SiO_2/

EtOAc-hexane, 1:1).[7] Attempts to dehydrate 5 (as a mixture or as the separate isomers) under ten different acidic, basic, and thermal conditions led, as expected[9], to complex mixtures which contained <3% of the desired product 6. Use of Burgess' reagent ($Et_3\overset{+}{N}SO_2\text{-}\overline{N}CO_2Me$/PhH/30-60°C)[10] on trans-5 produced a 1·4 mixture of 6[7,11] and diene 7[7], the latter resulting from a fragmentation predictable on the basis of a favorable bisected cyclopropyl conformation.[12] However, treatment of trans-5 with $Ph_2S[OC(CF_3)_2Ph]_2$ (Et_2O/-78°C/1h) furnished the trans-pyrethroid amide 6[7,12] in 92% yield without detectable formation of 7. When cis-5 was treated under the same conditions, only lactone 8[7] was isolated (80% yield)

Based-induced intramolecular epoxyamide cyclization,[13] like its predecessor, the corresponding epoxynitrile method,[14] may have broader implications for carbocyclic construction.[15]

References and Footnotes

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4. Arhart, R.J.; Martin, J C J Am Chem Soc. 1972, 94, 5003.
5. Prepared in three steps from iso-butyryl chloride (1 $CH_2=CMe_2/SnCl_2/CH_2Cl_2$/-78°C, 50%; 2. LiCl/DMF/Δ/4h, 60%, 3. LAH/Et_2O/0°C, 90%) by a modification of a literature method (ref 3)
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7. All isolated products show analytical and spectral data (IR($CHCl_3$), NMR($CDCl_3$)] in accord with their structures. Selected properties are 3. bp 75-80°C/0 03 mm; IR ν max 1640 cm^{-1}; NMR δ 2.20, 1H, m, 5.42, 2H, m, ABX, J=5.0, 16.0 Hz. cis-5 bp 105-107°C/0.2 mm; IR ν max 3440, 1630 cm^{-1}, 400 MHz NMR δ 1 10, 1H, dd, J=8.0, 9 0 Hz, 1 56, 1H, d, J=9 0 Hz, 4.11, 1H, dd, J=4.5, 8.0 Hz. trans-5· mp 64-65°C (Et_2O-pet ether), IR ν max 3440, 1630 cm^{-1}, 400 MHz NMR δ 1 44, 1H, d, J=6.0 Hz, 1.58, 1H, dd, J=6.0, 10.0 Hz. 6. bp 120-125°C/0.02 mm, IR ν max 1640 cm^{-1}, NMR δ 1.40, 1H, d, J=5 8 Hz, 2.10, 1H, dd, J=9 0, 5 8 Hz, 4.90, 1H, dh, J=9 0, 1 0 Hz 7: bp 88-92°C/0.01 mm, IR ν max 1645 cm^{-1}; NMR δ 3.78, 1H, d, J=8.0 Hz, 4 85, 2H, m, 5 40, 1H, dd, J=5 1, 16.0 Hz, 5 71, 1H, dd, J=8.0, 16.0 Hz 8: bp 90-95°C/0.01 mm; IR ν max 1760 cm^{-1}; NMR δ 1.25, 1H, d, J=7.0 Hz, 1.90, 1H, dd, J=7.0, 8.0 Hz, 4.11, 1H, dd, J=3.0, 8.0 Hz.
8. Attempts to purify by SiO_2 chromatography led to 4,4-dimethyl-5(1'-hydroxyisobutyl)butyrolactone [mp 63-64°C (Et_2O-pet ether), IR ν max 3460, 1770 cm^{-1}, NMR δ 3 65, 1H, dd, J=2 7 Hz, 4.0, 1H, d, J=7 Hz]
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11. Identical with a sample prepared by standard methods from trans-chrysanthemic acid furnished by Prof. L. Crombie.
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15. We are indebted to Prof. J.C Martin for a munificent sample of his reagent, to Prof. L Crombie for a sample of trans-chrysanthemic acid, and to Agriculture Canada for financial support.

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