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Stereospecific Synthesis of cis-2-Alkenylcyclopropane Carboxylic Acids; A Total Synthesis of (±)-cis-Chrysanthemic Acid

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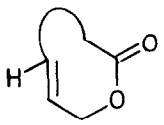
Summary: A stereospecific route to cis-2,2-dimethyl-3-alkenylcyclopropanecarboxylic Acids is illustrated by a total synthesis of (±)-cis-Chrysanthemic Acid (11). The key step consists of an alicyclic Claisen rearrangement of O-silyl enolates derived from appropriately substituted (Z)-4-hexen-6-olides [e.g.(9)].

The less thermodynamically stable cis-2-alkenyl cyclopropanecarboxylic acids are of considerable interest especially because of their use in the synthesis of non-natural analogues of the Pyrethrin insecticides. The naturally-occurring Pyrethrins all contain a trans-2,2-dimethyl-3-alkenylcyclopropanecarboxylic acid unit[1] and, although these are powerful insecticides, more potent totally synthetic analogues have been developed which contain the corresponding cis-substituted cyclopropanes.[2] Understandably, stereoselective routes to these cis-substituted cyclopropanes are significantly less numerous than ones to the corresponding trans-isomers.[3] We were attracted by the possibility of utilising the alicyclic Claisen rearrangement[4] in a potentially general and stereoselective approach to this type of cis-substituted cyclopropanecarboxylic acid. This particular version of the Claisen rearrangement, illustrated by the sequence (1) → (2) → (3), proceeds via a boat-like transition state (2), and hence affords only the cis-1,2-disubstituted carbocycles (3), when the (Z)-lactones (1) are 12-membered or smaller. Participation of the corresponding chair-like conformations is prevented by the constraints imposed by the remainder of the lactone ring. However, during attempts to extend the utility of the alicyclic Claisen rearrangement, we have observed[5] that in certain cases involving highly-substituted lactones, alternative reaction pathways, notably [1,3]-sigmatropic rearrangements, are followed[6]. The presence of two gem-dimethyl groups in the intermediate lactone which could lead to chrysanthemic acid (11) will impose considerable constraints on the transition state and it was therefore unclear to us whether or not this particular version of the Claisen rearrangement could be used to prepare acid (11) and indeed 2,2-dimethyl-3-alkenylcyclopropanecarboxylic acids in general.

Our investigations began with the preparation of the 4-pentynoic acid (4)[7] by alkylation of diethyl malonate with 3-chloro-3-methyl-1-butyne followed by saponification and decarboxylation in hot pyridine[8]. Although this overall sequence is far from efficient, it can easily be carried out on a large scale. The only other isolable products were the doubly-alkylated diester (5) and the butyrolactone (6)[8], the latter being formed in the final decarboxylation step. Both were easily separated from the desired products by distillation. Condensation of the dilithium salt of acid (4) with acetone gave the hydroxy-acid (7) (m.p. 76-77°C)[9], but only in 24% yield, improved to 54% by using the bis-Grignard salt of (4). Attempted semi-hydrogenation of (7) using Lindlar catalyst (Fluka) in methanol failed, but when unpoisoned 5%Pd-$CaCO_3$ was used as catalyst in the same solvent, uptake of hydrogen proceeded smoothly. After one equivalent had been absorbed, filtration and evaporation gave an oil which consisted of a mixture of the hydroxy-acid (8) and the desired lactone (9). This spontaneous lactonisation continued slowly on leaving the sample overnight at ambient temperature and was completed by chromatography over silica gel to give (9) (m.p. 39-40°C) in 85% isolated yield. Initial attempts to enolise and O-silylate lactone (9) using the usual conditions[4] [LDA-THF-HMPA, -78°C, 0.5 h., then t-$BuMe_2SiCl$] failed to produce significant amounts of the desired silyl enolate (10). However, by the simple expedient of allowing the reaction mixture to warm to ca. -40°C before silylation, the enolate (10) was obtained in essentially quantitative yield after a simple aqueous work-up. The material was not sufficiently stable to permit further purification; chromatography resulted in hydrolysis back to the lactone (9). However, when a solution of the crude enolate (10) in toluene was refluxed for 2 h, the Claisen rearrangement proceeded smoothly. Desilylation of the product using aqueous HF in acetonitrile finally gave (±)-cis-chrysanthemic acid (11) in 81% yield after crystallisation from EtOAc-petrol. The material was identical to authentic material[10] according to m.p., mixed m.p., n.m.r. and t.l.c. analysis. $A^{13}C$ n.m.r. spectrum showed no contamination by the corresponding trans-isomer. It is notable that rearrangement of the enolate (10) does not take place to any significant extent at ambient temperature in view of an example reported by Funk et.al.[4a] in which the less substituted enolate (12) rearranged to cyclopropane (13) before or during work-up. Undoubtedly, this reflects the much more crowded nature of the transition state. No products arising from alternative modes of rearrangement of (10) were detected.

As expected from the foregoing results, this approach can also be applied to less substituted chrysanthemic analogues. Thus, condensation of the bis-Grignard salt of (4) with formaldehyde gave the hydroxy-acid (14) (m.p. 47-48°C) in 73% yield which underwent smooth semi-hydrogenation using Lindlar catalyst in methanol to give the cis-hydroxy-acid (15) which was lactonised



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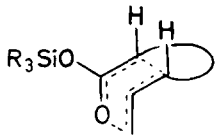

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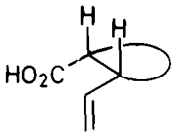

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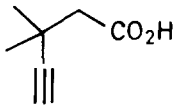

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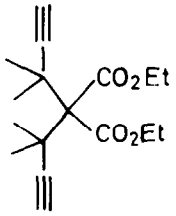

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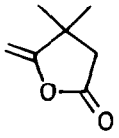

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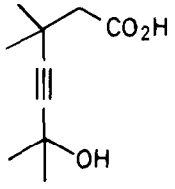

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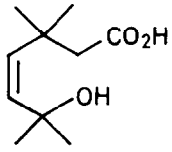

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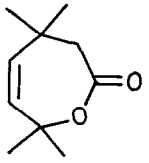

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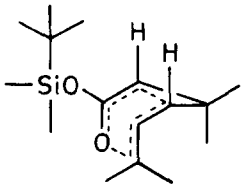

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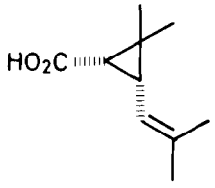

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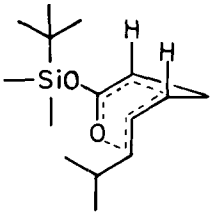

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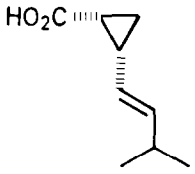

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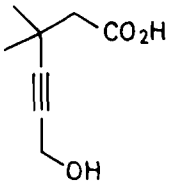

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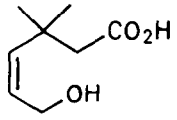

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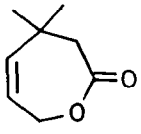

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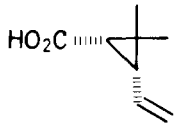

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using $EtO_2CN{=}NCO_2Et$-Ph_3P[11] to give (16)(oil) in 82% yield. Claisen rearrangement and desilylation as described above for (9) then gave the cis-3-ethenylcyclopropanecarboxylic acid (17) (m.p. 50-51°C)[12] in 84% isolated yield as a single isomer.

Overall, these results suggest that the alicyclic Claisen rearrangement represents a relative brief and stereospecific approach to alkenylcyclopropanecarboxylic acids which will be applicable to a wide range of highly substituted derivatives. Furthermore, the well-defined nature of the transition state suggests that this method could well be used in the synthesis of chiral cyclopropane derivatives; investigations along these lines are now in progress.[13]

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