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ELABORATION OF A TRICYCLIC GIBBERELLIC ACID INTERMEDIATE

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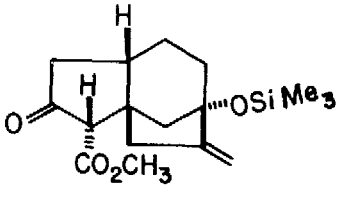
Summary: The synthesis of an important tricyclic intermediate for gibberellic acid synthesis is described.

We recently reported[1] on the synthesis of the tricyclic β-ketoester 1 which embodies a number of the features of gibberellic acid 2. We were interested in using 1 as an intermediate for the construction of the unsaturated lactone aldehyde 3, a substance which cyclizes readily to gibberellic acid.[2]



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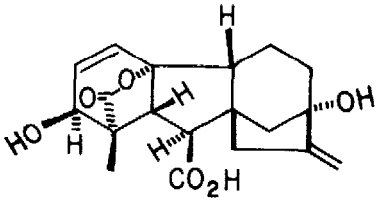

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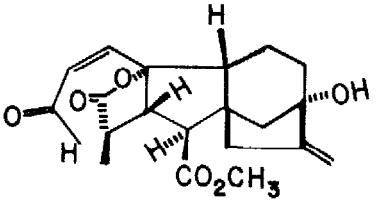

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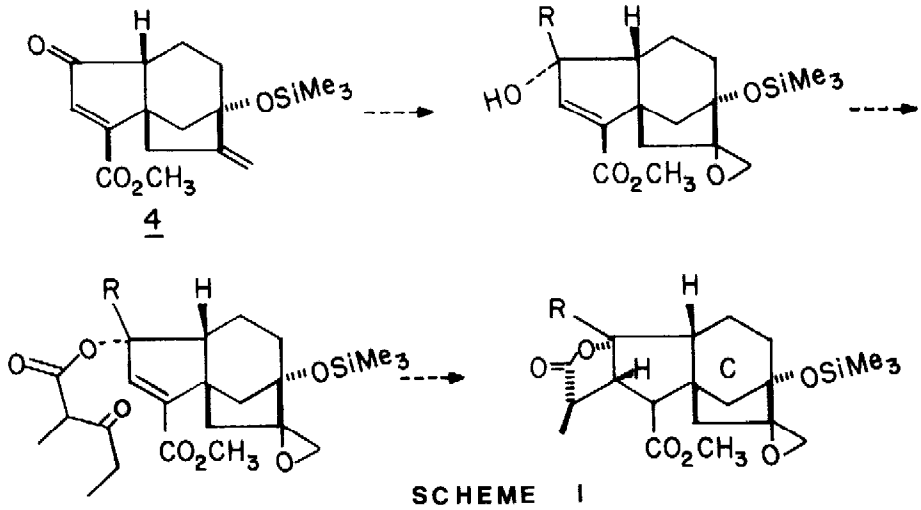
The most obvious route to 3 seemed to require the unsaturated ketoester 4 which might then be transformed to 3 by a route involving the intramolecular addition of a β-ketoester[3] (cf Scheme 1).

We have become aware that the same general scheme has been followed, and

brought to a successful conclusion, by L.N. Mander et al.,[4] and are, therefore, not planning further work in this area. We describe here, however, the formation of the β-ketoester to a close relative of 4 in which the exocyclic methylene is protected as an epoxide, since our route to structures of type 4 is unrelated to that of the Australian route.



SCHEME I

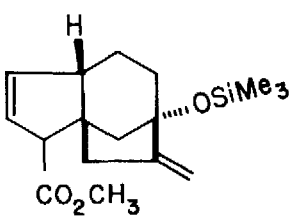
A solution of the β-ketoester 1 was reduced ($NaBH_4$ in CH_3OH, 0°, 5-10 min) and benzoylated (2 equiv benzoyl chloride in 7 ml/mmol pyridine; room temp., 14 hr) to the corresponding benzoate which led directly to the β,γ-unsaturated ester by elimination-deconjugation. (lithium dicyclohexylamide in 5:1 THF - HMPA, -30°, 30 min; quenching with 1:1 THF - ACOH) to give 5, R_f 0.75 in 1:1 EtOAc-pentane, as a 1:1 mixture of C_3 epimers (singlets at δ 3.53 and 3.48, 5.66 s, $W_{\frac{1}{2}}$ = 2 Hz; H_1 and H_2). The overall yield from 1 was ∿ 50%.

Regiospecific introduction of the cyclopentenone carbonyl of 4 started with

the formation of the diepoxide of 5 (2.8 equiv of MCPBA, $NaHCO_3$, 0^o to room temp., overnight). Base-catalyzed elimination (KOtBu in t BuOH, 5 min at room temperature) gave the two allylic alcohols 6-A and 6-B (1:1 mixture) in 70% yield.

Although the mixture of epimers is suitable for the necessary oxidation to a cyclopentenone, the two isomers could be separated by chromatography with 15% methyl acetate-pentane, followed by crystallization from 1:1 pentane-ether which gave 6A, mp 88-90° (NMR: δ 6.75 (d, 1H, J AB 2.5 Hz), 4.65 (b d 2H, J BC = 6.0 Hz); 3.74 (s, 3 H) and 6B (NMR: δ 6.68 (d, 1 H, J AB = 1.5 Hz); 4.48 (b d, 2 H, J BC = 7.5 Hz); 3.73 (s, 3 H). The R_f values of 6A and 6B in 1:1 EtOAc-pentane were 0.62 and 0.50, respectively.

Finally, oxidation of the mixture of epimeric alcohols 6A and 6B with chromic acid-2 pyridine in the presence of 2 equiv of acetic acid in methylene chloride at room temperature gave 85% of the desired carbomethoxycyclopentenone 7, in which the exocyclic methylene carbinol of 4 is protected as an epoxide[5] trimethylsilylether (NMR: δ 6.70 (s, 1 H); 3.86 (s, 3 H); IR: 1720, 1605 cm^{-1}; $\lambda_{max}^{CH_3OH}$ 243 nm; ms: (CI) M + 1 = 337. R_f: 0.34 (1:1 ether-pentane).



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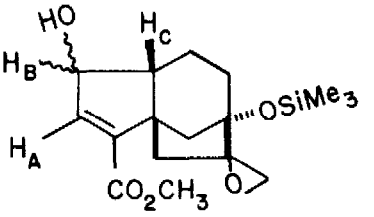

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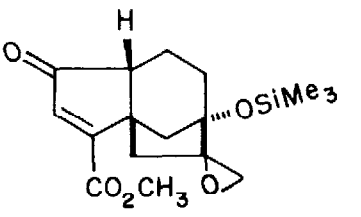

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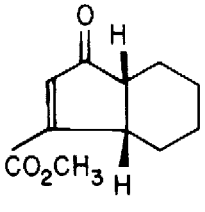
The feasibility of the construction shown in scheme I was demonstrated, inter alia by the model conversion 8→10: The bicyclic indenone 8, mp 43-44°, was transformed (lithium salt of the ethoxyethyl derivative of propynol, ether, -20° to 0° 15 min) into the ethynylcarbinol 9 (NMR: 6.58, s, 1 H, $W_{\frac{1}{2}}$ 2 Hz; IR: 1720, 3435 cm^{-1}) in

66% yield (50% conversion). Sequential treatment of 9 with the diketene from propionyl chloride (2 equiv in THF with 4-dimethylaminopyridine, 3 h at room temperature) and then methanolic potassium carbonate for 15 h, to effect cyclization of the β-ketoester intermediate, and deacylation (cf. Scheme I) gave the acetylenic lactone ester (74% yield) which was then deprotected (30% acetic acid, 30 min) and semihydrogenated (Pd-$BaSO_4$ in ethyl acetate with quinoline poison) to give in 74% yield the crystalline cis-vinylcarbinol lactonic ester 10, mp 98-100° (NMR ($CDCl_3$): δ 5.62, m, 2 H; 4.35, d, 2 H; 3.75, s, 3 H; 1.32 & 1.1 (2d, 3 H, J = 7.5 Hz. Mass Spectrum: (CI) M + 1 309).



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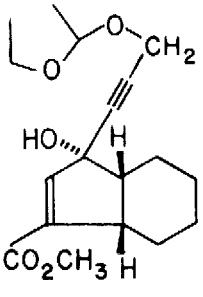

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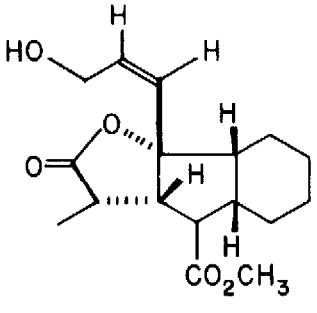

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References and Notes

1. G. Stork, W. Clark Still and J. Singh, Tetrahedron Lett., 5077 (1979).

2. G. Stork and J. Singh, J. Am. Chem. Soc., 101, 7109 (1979).

3. We demonstrated the feasibility of this intramolecular route to the ring A lactone with simple model systems a number of years ago: cf. D.F. Taber, Ph.D. Thesis, Columbia University, 1974, pp 75-76.

4. L.N. Mander et al, submitted to J. Am. Chem. Soc., 102 (1980).

5. We have shown that chromous ion reduction is suitable for regeneration of the exocyclic methylene group in related substances. Cf. J.K. Kochi, D.M. Singleton and L.J. Andrews, Tetrahedron, 24, 3503 (1968).

6. J.C. Sauer, J. Am. Chem. Soc., 69, 2444 (1947).

7. This substance, although crystalline and giving a single peak on HPLC (corasil) is evidently (NMR) a mixture either at the carbomethoxyl or the methyl-bearing center.

8. We thank the National Institutes of Health and the National Science Foundation for supporting this work.

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