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CYCLIZATION OF OLEFINIC β-KETOESTERS. A NOVEL SYNTHESIS OF $\Delta^{8(14)}$-PODOCARPEN-13-ONE

Richard W. Skeean, Gary L. Trammell,[1] and James D. White*
Department of Chemistry, Oregon State University
Corvallis, Oregon 97331

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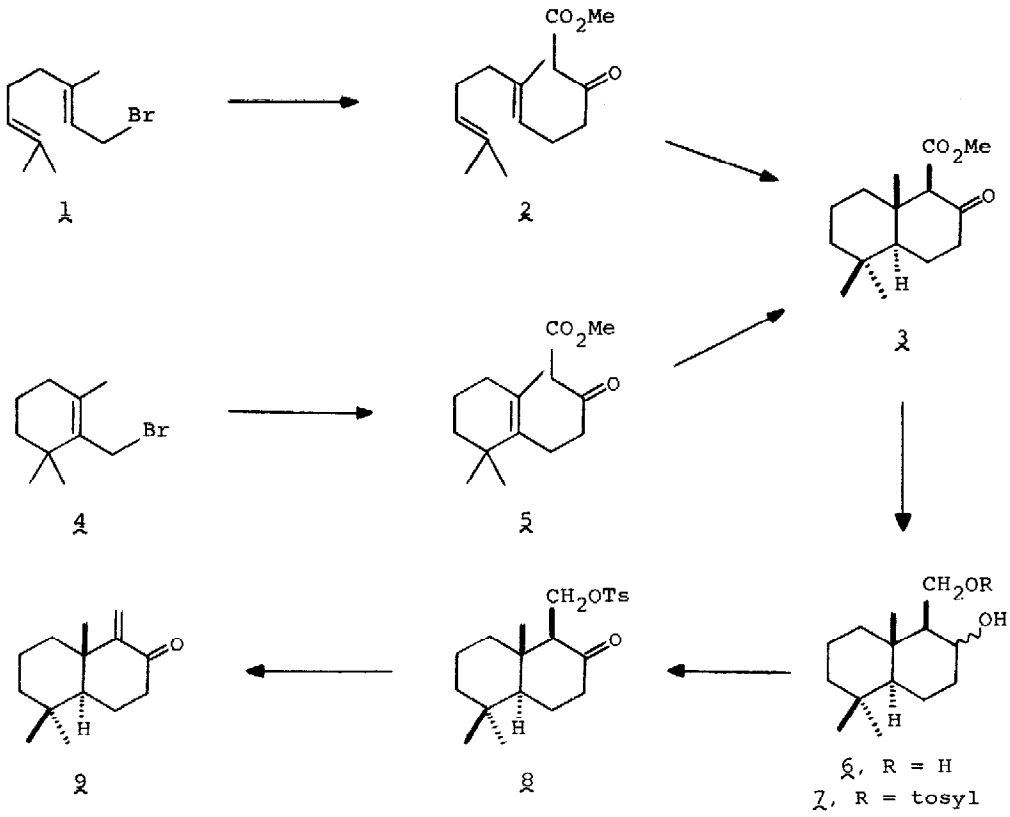
The biogenetic-like cyclization of polyolefins pioneered by Eschenmoser[2] and by Stork,[3] and developed extensively by Johnson,[4] has proved to be exceedingly useful for the construction of terpenoid systems. The possibility of extending this concept to olefinic β-ketoesters is attractive for several reasons, not the least of which are the ready access to ketoester precursors, as well as the favorable prospect for elaboration of residual functionality after cyclization. Moreover, the β-ketoester moiety through its enol tautomer, should be a particularly effective participant in the annelation process. We wish to report an efficient cyclization of this type, which affords direct entry to a decalin system of broad, potential utility in diterpene synthesis.

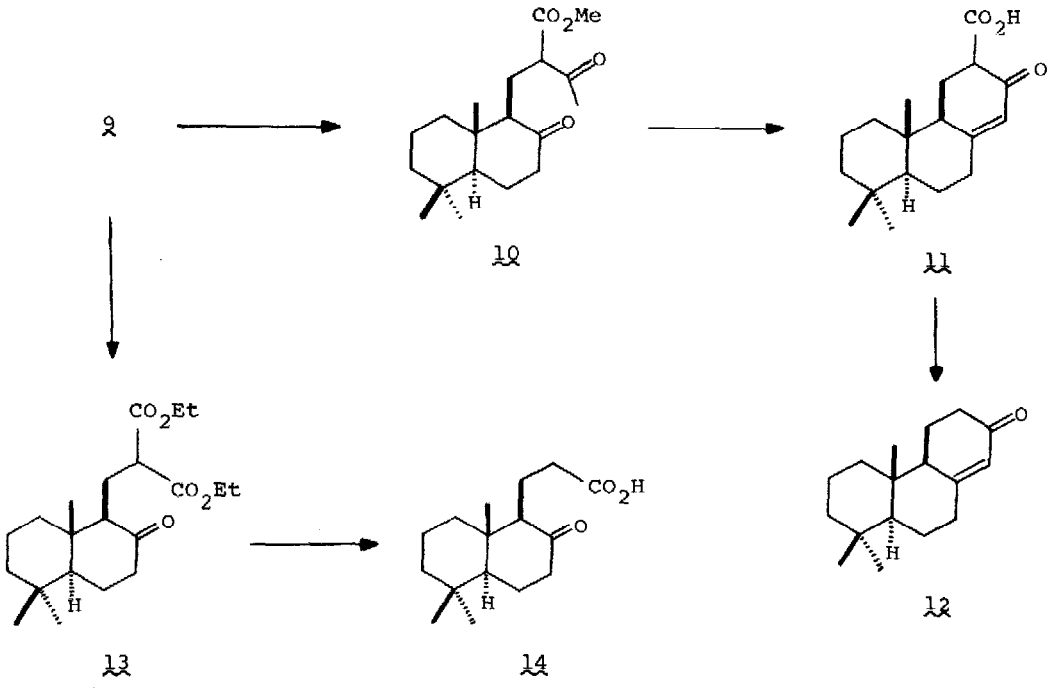
Alkylation of the dianion derived from methyl acetoacetate[5] with geranyl bromide (1)[6] afforded ketoester 2 as an oil, bp 140-144° (0.6 mm), in 61% yield.[7] After exploring a variety of conditions for the acid-catalyzed cyclization of 2, it was found that exposure of 2, in CH_2Cl_2, to 1 molar equivalent of stannic chloride (0°, then room temperature for 17 hr) gave a single cyclic product (3), mp 85.5-87°, in 68% yield following chromatography on Florisil. The structure of 3 was apparent from its nmr spectrum [δ^{CDCl_3} 0.88 (3H, s), 0.98 (3H, s), 1.13 (3H, s), 3.06 (1H, s), 3.63 (3H, s)], which showed the absence of olefinic hydrogen, and from a comparison of its properties with those reported.[8] Stannic chloride-catalyzed cyclization of 5, prepared by alkylation of the dianion of methyl acetoacetate with β-cyclogeranyl bromide (4),[9] gave a 70% yield of 3. Thus, no significant yield advantage pertains to the use of a monocyclic precursor in this reaction although removal of byproducts is somewhat simplified.

Attempts to alkylate ketoester 3 via its enolate anion were unsuccessful and, hence, 3 was converted to enone 9, which was expected to be an active receptor in the Michael reaction with enolates. The transformation 3→9 followed closely the sequence of steps previously described.[8] Thus, reduction of 3



($LiAlH_4$, ether) furnished 97% of a crystalline mixture of epimeric diols 6, mp 83-84.5°, which without separation were converted to the corresponding primary tosylates 7 (p-toluenesulfonyl chloride, pyridine, 0°, 18 hr). Oxidation of 7 with Jones' reagent, followed by elimination of p-toluenesulfonic acid from 8 with 1,5-diazobicyclo[5.4.0]-undec-5-ene (CH_2Cl_2, 18 hr), gave 9 [1700, 1620 cm^{-1}; δ^{CCl_4} 4.76 (1H, d, J=2Hz), 5.30 (1H, d, J=2Hz)] in 62% yield based on 6.

Treatment of 9 with methyl acetoacetate in the presence of sodium methoxide (0.1N in methanol) afforded Michael adduct 10 in good yield as a mixture of epimers with respect to the carboxyl group [δ^{CCl_4} 0.75, 0.88, 0.98 (3H each, s) 2.10 and 2.23 (3H total, s), 3.4 (1H, broad), 3.65 and 3.70 (3H total, s).[10] Saponification of 10 (5N NaOH) resulted in concomitant Robinson annelation to 11[11] which, upon warming to 80°, underwent decarboxylation to $\Delta^{8(14)}$-podocarpen-13-one (12), mp 90.5-91.5° (lit[12] 92.5-93.5°); 1680, 1630 cm^{-1}; δ^{CDCl_3} 5.85 (1H s), obtained in 50% overall yield from 9. The tricyclic ketone 12 has proven to be a "versatile starting material"[13] for diterpene synthesis, including



recently phyllocladene[14] and hibaone,[15] which customarily has been prepared by degradation of manool.[16,17]

The Michael reaction of 9 with diethyl malonate (0.1N sodium methoxide in methanol) gave ketodiester 13 which, without purification, was saponified (6N sodium hydroxide) and decarboxylated (140°), to yield ketoacid 14 (mp 130-132°) in 73% overall yield from 9. Compound 14, which can also be prepared by ozonolysis of 12, has been previously utilized in the reconstitution of ambreinolide and related labdanoid systems.[10] Ketoester 3 and the derived enone 9 thus represent useful synthons for the construction of certain diterpenoid skeletons and are now readily accessible via total synthesis.[18]

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