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A METHOD FOR THE STEREOSPECIFIC SYNTHESIS OF THE A AND B RINGS OF GIBBERELLIC ACID

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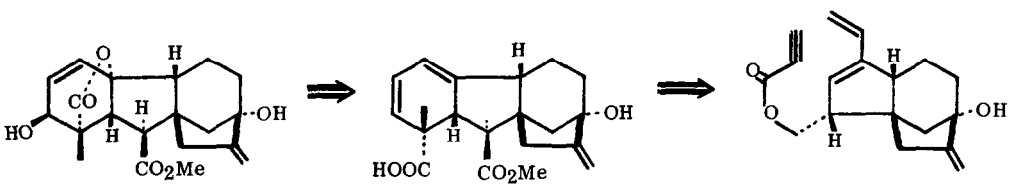
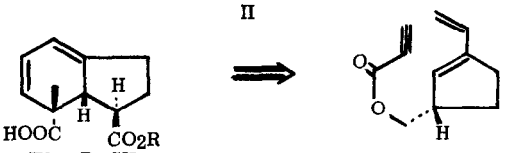
A previous report from these Laboratories[1] described the partial synthesis of gibberellic acid (I) from the trienic acid II and recognized III as an attractive precursor to this key intermediate.

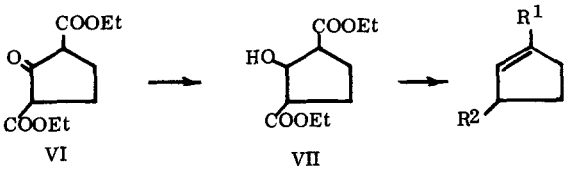


I II III



IVa, R=CH_3
IVb, R=$CH_2COPhPh$ V

This report demonstrates synthetic methodology for effecting the conversion III→II by a stereospecific synthesis of the model system IV. The key step in this sequence is the internal Diels-Alder cyclization of V, conveniently prepared via intermediates VI-XI as outlined below.



VI VII

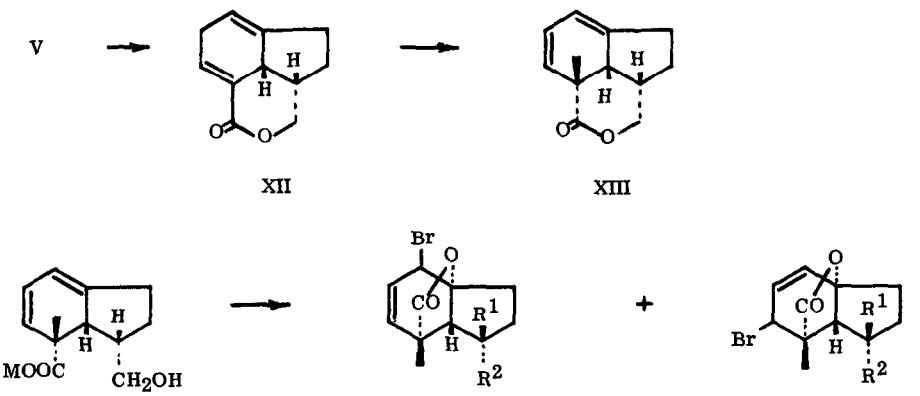
VIII $R^1=R^2=CO_2Et$
IX $R^1=R^2=CH_2OH$
X $R^1=CHO$, $R^2=CH_2OH$
XI $R^1=CH=CH_2$, $R^2=CH_2OH$

Sodium borohydride reduction (1.2 equiv, -24°, 17.5 hr) of 2,5-diethyl-1-cyclopentanone dicarboxylate VI[2] gave VII[3a] in 90% yield. Treatment of VII with 1.1 equiv of methanesulfonyl chloride and 2.5 equiv of 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) (benzene, 0.5 hr at 0°, 5 hr at 23°) afforded

VIII[3a] in more than 90% yield[4] after distillation (bp 107-114°/0.45 mm). Reduction of VIII with aluminum hydride or diisobutylaluminum hydride followed by evaporative distillation from a small amount of anhydrous K_2CO_3 (oven temp 120-130°/0.4 mm) gave IX[3a] in 50-70% yield.

Manganese dioxide oxidation of IX gave the α,β-unsaturated aldehyde X[3a] which was transformed to the diene XI[3a] by treatment with 3 equiv of methylenetriphenylphosphorane in THF (0°, 1.5 hr). Esterification of XI with propiolic acid was accomplished using N,N'-dicyclohexylcarbodiimide in methylene chloride. The ester V[3] was obtained in 35% overall yield from VIII in this manner.

The diene ester V underwent intramolecular cycloaddition[5] above 135° affording the lactone XII[3a]. Yields of up to 70% were obtained by refluxing V in acetic anhydride[6] for 20 hr. The lactone XII was best converted to XIII without purification because of its propensity toward aromatization. This was readily accomplished by adding XII to a solution of 1 equiv of lithium isopropylcyclohexylamide[8] and 3 equiv of hexamethylphosphoramide in THF at -78° and treating the reaction mixture with 1.3 equiv of methyl iodide (-78° to 23° over 7 hr). Isolation and purification by column chromatography on florisil afforded the tricyclic lactone XIII[3] mp 60.5-61° in 40-50% overall yield from V. The stereochemistry of XII and XIII follow unambiguously from the method of synthesis.



XIVa	M = H	XVa	R^1 = H, R^2 = CH_2OH
b	M = K^+	XVIa	R^1 = H, R^2 = CHO
		XVIIa	R^1 = CHO, R^2 = H
		XVIIIa	R^1 = COOH, R^2 = H
		XIXa	R^1 = $COOCH_3$, R^2 = H
		XXa	R^1 = $COOCH_2COPhPh$, R^2 = H

XVb
XVIb
XVIIb
XVIIIb
XIXb
XXb

Oxidation of XIVa could not be achieved without substantial relactonization; XIVb was therefore bromolactonized to permit the required operations at ring B. An aqueous solution of XIVb, obtained by saponification of XIII (KOH, anhydrous CH_3OH, 23°, 6.5 hr) and neutralization to pH 7 at 0° with

CO_2, was treated with KBr_3 (1 equiv, -10°, 30 sec) affording a mixture[3a] of bromolactones XVa and XVb. Oxidation of this mixture with Collins reagent (-23°, 1.5 hr) provided the aldehydes XVIa,b and XVIIa,b, a mixture of epimers. Preparative layer chromatography on silica gel effected purification and concomitant epimerization (ca. 90% as judged by NMR[9]) affording XVIIa,b in 40-56% overall yield from XIII. Oxidation of XVIIa,b with Jones reagent[10] (0°, 30 sec) and esterification of the crude acid with excess CH_2N_2 (ether, 0°) gave the methyl esters XIXa,b[3a]. Treatment of XIXa,b with excess activated zinc[11] (ethanol, 23°, 2 hr) provided the dienic acid IVa[3] mp 75-81° in 63% overall yield from XVII.

Alternatively, the acids XVIIIa,b may be protected as p-phenylphenacyl esters for subsequent elaboration of the A ring. This allows for convenient purification and analysis by thin layer chromatography. Reaction of XVIIIa,b with 1 equiv of p-phenylphenacyl bromide and 1 equiv triethylamine (DMF, 0°, 1 hr)[14a] yielded the esters XXa,b[3a] which were selectively cleaved to IVb[3a] upon treatment with excess zinc-silver couple[15] and 1 drop of glacial acetic acid[12] (5:1 ether-ethanol, 23°, 4.5 hr, 55% overall yield from XVIIa,b). Cleavage of phenacyl esters may be readily accomplished in high yield by exposure to 1 equiv of LiSPr in HMPA for 5 min at 0°.[14]

An investigation of routes to the key intermediate III is now in progress.[16]

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