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INTRAMOLECULAR DIELS-ALDER REACTION WITH FURAN-DIENE[1]. AN EXPEDITIOUS ENTRY INTO A FUNCTIONALIZED GIBBANE.

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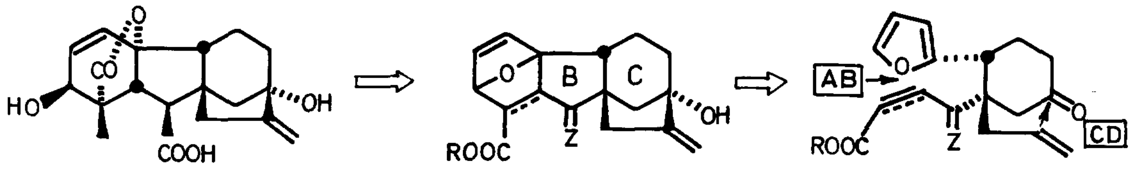
ABSTRACT

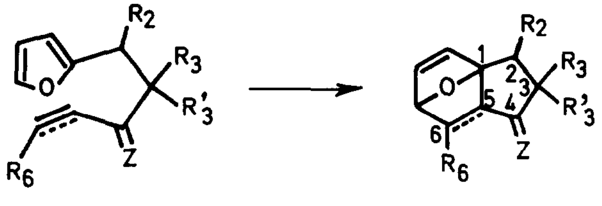
A short synthesis of a functionalized gibbane is described. The key-step involves the intramolecular Diels-Alder reaction of furan-diene 12, leading to a 3:1 ratio of two diastereoisomers, tentatively identified as 14a and 14b. The precursor 12 is obtained from m-methoxybenzoic acid in 7 steps.

The continuous search for syntheses of gibberellin phytohormones has recently culminated in the total synthesis of its most prestigious member, gibberellic acid (GA$_3$, 1)[3]. In connection with synthetic approaches to natural products we have been investigating in recent years the synthetic potential of the intramolecular Diels-Alder reaction with furan as diene partner. One powerful application of this strategy rests in the simultaneous AB-ring formation to a functionalized gibbane (i.e., 2), thereby providing directly for an oxygenated A-ring. In view of the planned CD-ring closure (cf. 3), a retrosynthesis calls for an adequately functionalized 4-furyl-3,3-dialkylcyclohexanone, the synthesis of which we recently reported on[4]. We now wish to describe the successful application of this overall CD/AB-strategy with the expeditious synthesis (8 steps from m-methoxybenzoic acid) of potential gibberellin precursors 14a and 14b.



1 2 3

At the outset of our study the sole report on a successful Diels-Alder transformation of the type 4 → 5 involved the 40 % conversion (benzene, reflux, 5 days) of 4a to 5a[5]. Subtle conformational effects are probably responsible for this result since both allylic alcohol 4b and enone 4c were unreactive under the same conditions[6]. No cycloadduct could be obtained from 4d (undefined stereochemistry at 2,3), where a β-phenyl-α,β-acetylenic ketone serves as the dienophile[7] (Scheme).



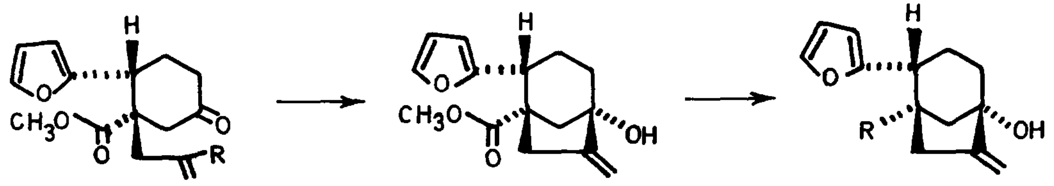
4 5

a $\Delta^{5,6}$; R_2=R_6=H; Z=H_2; R_3'=COOEt=R_3
b $\Delta^{5,6}$; R_2=R_6=R_3=R_3'=H; Z=H, OH
c $\Delta^{5,6}$; R_2=R_6=R_3=R_3'=H; Z=O
d 5,6-acet.; R_2, R_3 = cyclohexene; R_3'=H and Me; R_6=phenyl; Z=O

Scheme

Ketone 6, available from m-methoxybenzoic acid (3 steps, 40 % overall yield)[4], possesses the correct set-up for CD-ring closure to 7 according to Corey's method[8a]. Thus, 7 (m.p. 59-61°C)[9] was obtained in 65 % yield upon reaction with 9 eq di-n-butylcopperlithium in THF-hexane (3:1) at -50°C (1 h), the sole isolated by-product being ketone 8. Consistent with the original findings[8b], the reaction is critically dependent on both solvent and reaction temperature. Indeed, the same procedure in ether (ether-hexane, 2.7:1) gave a mixture of 7, 8 and 9 (ratio ∿ 1:1:1). Higher temperatures (0°C) or solvent ratios in favor of hexane (e.g., ether-hexane, 1:6) led to complex reaction mixtures without any appreciable amount of ring closed 7. The reduction of ester 7 with LAH (THF, 0°C, quantitative), followed by PDC/pyridinium trifluoroacetate oxidation (CH_2Cl_2-THF, 12 h)[10] led to a mixture of diol 10 (m.p. 115-118°C) and aldehyde 11[9] (50 % isolated yield of 11; silica gel, EtOAc-isooctane, 3:7). Reaction of 11 with lithium ethyl propiolate[11] (-78°C, 60 min) gave a ∿ 4:1 mixture of two diastereoisomeric alcohols (94 % yield), from which the major isomer (12) was separated by chromatography (silica gel; EtOAc-isooctane, 4:6); the stereochemistry at C-6 remains yet to be clarified. Upon reflux in benzene for 24 h 12 was clearly converted to a 3:1 mixture of two adducts diastereoisomeric at C-10 (70 % isolated next to starting material; silica gel, EtOAc-isooctane, 1:1). Both isomers 14a (m.p. 65-67°C) and 14b (m.p. 55-58°C) are separated by HPLC (ether-hexane, 8:2). Although no absolute proof for the respective configurations at C-10 has been obtained so far, the presence of a long range coupling between H-2 and H-9 (1.0 Hz; proven by double irradiation) in the minor isomer suggests 14b for its structure[12]. Upon prolonged heating in benzene (160 h) a 1:1 ratio of both adducts is obtained (70 % conversion). At room temperature (CH_2Cl_2) only trace amounts (TLC) of adduct were observed. The preferred formation of 14a is as yet not fully understood.

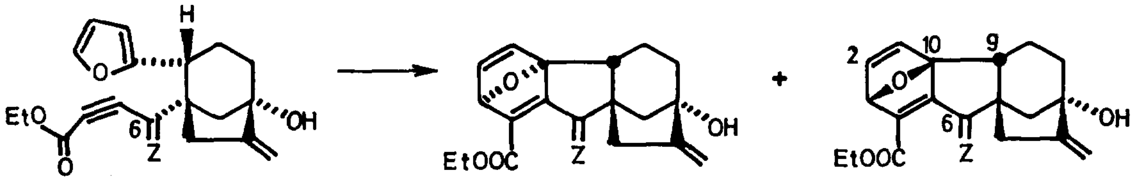
The successful Diels-Alder reaction of 12 is especially noteworthy in view of the failure for reaction of the analogous 4d. Both adducts 14a and 14b



6 R = Br
8 R = n.Bu
9 R = H

7

10 R = CH_2OH
11 R = CHO



12 Z = H, OH
13 Z = OH, H

14a Z = H,OH

14b Z = H,OH

possess the gibbane skeleton and carry the necessary functionalities for introduction of the two remaining carbons at C-4 and at C-6 (cf. 1) and for realizing the gibberellic acid A-ring. The expeditious way in which they are obtained (8 steps from m-methoxybenzoic acid) makes them especially attractive for further gibberellin synthesis[13]. Results obtained along this route will be reported in due course.

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9. ^{1}H-NMR data were obtained at 360 MHz in CDCl$_3$ unless otherwise stated, 7 : ν 3420, 1730 cm^{-1}; δ 7.27 (1H, d; 1.75 Hz), 6.26 (1H, dd; 1.75, 3.25 Hz), 6.05 (1H, d; 3.25 Hz), 5.12 (1H, t; 2.5 Hz), 4.93 (1H, t; 1.75 Hz), 3.67 (3H, s), 3.38 (1H, bd; 5.75 Hz) , 2.64 (2H, m), 2.4 (1H, OH) ppm; m/z 262 ($M^{+\cdot}$, 35), 244 (10), 94 (100). 10 : ν 3500 cm^{-1}; δ (acetone-d$_6$) 3.61 (1H, t; 5.3 Hz), 3.42 (1H, ABd; 10.75, 5.6 Hz), 3.17 (1H, ABd; 10.75, 5.0 Hz) ppm; m/z 234 ($M^{+\cdot}$, 100). 11 : ν 3260, 1710 cm^{-1}; δ 9.74 (1H, s) ppm; m/z 232 ($M^{+\cdot}$, 20), 203 (10), 94 (100). 12 : ν 3400, 2230, 1700 cm^{-1}, δ 4.28 (1H, s), 4.24 (2H, q; 7.0 Hz), 1.32 (3H, t; 7.0 Hz) ppm; m/z 330 (M^{+}), 43 (100). 13 : ν 3400, 2220, 1700 cm^{-1}; δ 4.39 (1H, s). 14a : δ 7.17 (1H, dd; 5.0, 2.0 Hz), 6.84 (1H, d; 5.0 Hz), 5.72 (1H, d; 2.0 Hz), 5.17 (1H, $\sim$t; 2.25 Hz), 5.07 (1H, bt; 1.5 Hz), 4.71 (1H, s). 14b : 7.31 (1H, ddd; 5.5, 2.25, 1.0 Hz), 7.11 (1H, d; 5.5 Hz), 5.68 (1H, d; 2.25 Hz), 5.20 (1H, bt; 2.5 Hz), 5.10 (1H, bt; 1.5 Hz), 4.52 (1H, s).
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