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A C_6, C_7 Oxygen Functionalized Intermediate for the Synthesis of Forskolin: Stereochemical Control in an Intramolecular Diels-Alder Reaction

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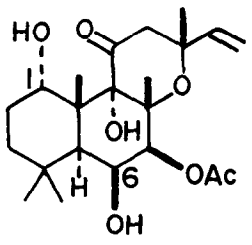
ABSTRACT: Stereospecific intramolecular Diels-Alder reactions of aldehydes **3a** and **3b** afford lactones **4** and **5**, respectively. The mechanism of the reactions is considered. Lactone **4** is elaborated further to provide acetonide **14b**, an important intermediate in an approach to the synthesis of forskolin (**1**).

Forskolin (**1**), a highly oxygenated labdane diterpene isolated from Coleus Forskolii[1], displays a wide variety of physiological properties, among which are bronchospasmolytic[2], antihypertensive[3], and ionotropic activity[3]. In addition, forskolin has been demonstrated to effect adenylate cyclase activation[4] and has reduced intraocular pressure in man[5].

An intramolecular Diels-Alder reaction of the E-ester **3a** presented itself as an attractive source of a tricyclic lactone that would contain useful functionality for further skeletal elaboration. Cognizant of the reluctance of acrylate esters of structural type **3** (R_1,R_2 = H, alkyl) to undergo an intramolecular Diels-Alder reaction[6], we incorporated an aldehyde group into the dienophile of **3**, first to direct the endo-transition state and then to establish the appropriate oxidation level of ring B[7].

Methylenation of hydroxy aldehyde **2a**[8] ($Ph_3P{=}CH_2$, THF, 25°C, 2 h) followed by esterification (DCC, DMAP)[9] with E-3-methyl-4-oxo-2-butenoic acid[10] provided ester **3a** in 91% yield. Thermolysis of **3a** (C_6H_6, 120°C, N_2, 2,6-di-tert-butylphenol, sealed tube, 0.2 M, 85 h) gave rise to a single Diels-Alder adduct **4** (37%) and recovered starting material **3a** (55%). When the thermolysis was conducted at 160°C, the aldehyde **4** was isolated (47%) in addition to 7% of isomeric aldehyde **5** and 28% of esters **3a** and **3b** in a 1:1 ratio. Exposure of aldehyde **5** to base (CH_3ONa, CH_3OH, 25°C, 16 h) provided aldehyde **4**, demonstrating that the relative stereochemistry at C_8 and C_{10} is the same in both aldehydes. Aldehyde **5** arises from the Z-ester **3b** via an endo-(CHO) transition state. Since the ratio of esters **3a** and **3b** remains essentially constant with time at 160°C, the activation energy for the formation of aldehyde **4** from E-ester **3a** is lower than that required to convert Z-ester **3b** to aldehyde **5**.



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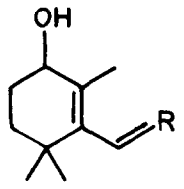
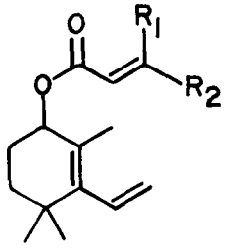
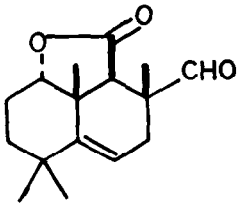


2a, R=O
b, R=CH_2



3a, R_1 = CH_3, R_2 = CHO
b, R_1 = CHO, R_2 = CH_3
c, R_1 = $CO_2C_2H_5$, R_2 = H
d, R_1 = H, R_2 = $CO_2C_2H_5$



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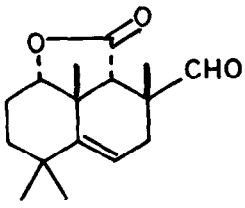

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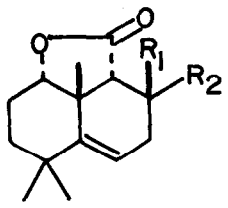
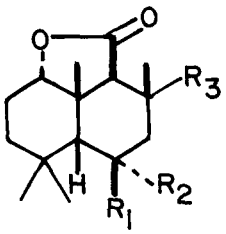


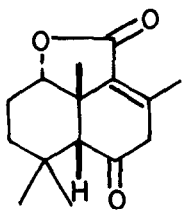
6a, $R_1 = CO_2C_2H_5$, $R_2 = H$

b, $R_1 = H$, $R_2 = CO_2C_2H_5$



7a, $R_1 = OH$, $R_2 = H$, $R_3 = CH_2OH$

b, $R_1, R_2 = O$; $R_3 = CO_2H$



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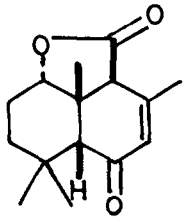

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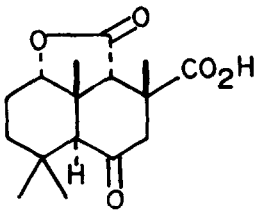

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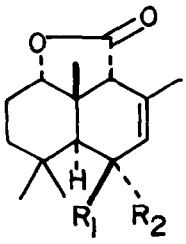
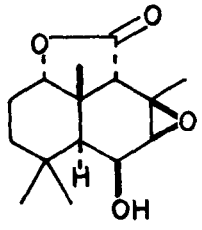


11a, $R_1, R_2 = O$

b, $R_1 = OH$, $R_2 = H$



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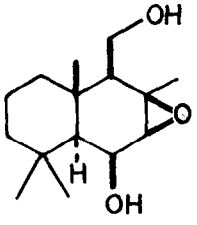

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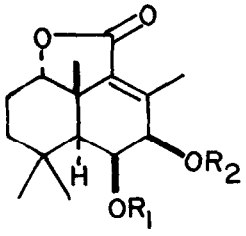

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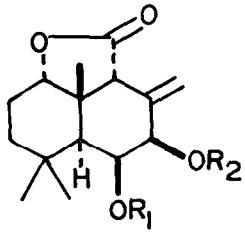

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a, $R_1 = R_2 = H$

b, $R_1, R_2 = C(CH_3)_2$

The mechanism for the E,Z-isomerization cannot involve a 1,5-hydrogen shift from the methyl group to the ester carbonyl because no pathway exists for the reverse reaction. Moreover, methyl E-3-methyl-4-oxo-2-butenoate was shown not to isomerize under the reaction conditions. In a related study, Jenkins and coworkers[7] observed that the thermolysis of maleate **3c** provided a 1:3 ratio of lactones **6a** and **6b**, respectively, while the related fumarate gave a different stereoisomer (endo-ester), presumably related to aldehyde **4**. These authors have suggested the reasonable argument that isomerization occurs through a nonsynchronous diradical intermediate. The absence of a C_8 stereoisomer of aldehyde **5** is noticeably contrary to the maleate case.

Hydroboration (BH_3/THF, 0°C, 20 h; 4% aq. NaOOH, 4 h) of aldehyde **4** gave rise to diol **7a** which was directly oxidized with Jones reagent (0°C, 2 h) to afford keto acid **7b** (mp 215-216°C) in 60% yield. The stereochemistry of **7b** was determined by a single crystal X-ray analysis. The cis-ring juncture stereochemistry was established during the hydroboration step[11], since oxidation with Jones reagent, prepared with D_2O, showed no incorporation of deuterium in the keto acid **7b**.

Although keto acid **7b** proved unsuitable for our synthetic objectives, its oxidative decarboxylation is worthy of comment. When a benzene solution of **7b** was refluxed in the presence of $Pb(OAc)_4$ (1 equiv.) and pyridine (2 equiv.), the deconjugated ketone **8** was produced; whereas, in the absence of pyridine, the conjugated ketone **9** was formed. Exposure of ketone **9** to pyridine in benzene at 25°C effected deconjugation to **8**, indicating that ketone **9** is formed kinetically. The C_9-H bond of ketone **9** maintains overlap with the π-framework of the lactone and the enone function, thereby contributing to the enhanced kinetic acidity. The deconjugation of ketone **9** manifested itself in all attempts to reduce the carbonyl function with metal hydride reagents. Deconjugated isomer **8** is anticipated as the thermodynamic product owing to the cis-ring fusion.

Successful elaboration of the C_6-C_7 oxygen functionality required circumvention of conjugated ketone **9**. This goal was realized in the following way. Keto acid **7b** was epimerized (CH_3OK/CH_3OH, 2 equiv., 0.5M, reflux, 2 h) to afford keto acid **10** (mp 240-241°C) in 95% yield. When the epimerization was conducted in CH_3OH-d_1, the NMR spectrum of **10** was devoid of the singlets for the C_5-H and C_9-H, and the doublets for the two C_7-H. While deuterium incorporation at C_5 and C_9 does not necessarily indicate that both centers have been epimerized, MM2 calculations indicate a strain energy of 36.3 Kcal/mol for keto acid **10** (C_5-H epimer, 40.2 Kcal/mol) and 40.5 Kcal/mol for keto acid **7b** (C_5-H epimer, 48.5 Kcal/mol). The strained trans-lactone of keto acid **7b** (as well as aldehyde **4**, lactone **7a**, and unsaturated lactones **8** and **14**) displays the C_1-H as a doublet of doublets (δ 4.17, J = 11.0, 6.7 Hz) in its NMR spectrum, resulting from the twist boat conformation of ring A. This strain is relieved in lactone **10** (as well as **5**, **11**, **12**, and **15**), which has ring A in a chair conformation with the C_1-H appearing as a triplet (δ 4.23, J = 3.0 Hz).

Oxidative decarboxylation of keto acid **10** with $Pb(OAc)_4$, with or without pyridine, gave only the conjugated ketone **11a** (mp 109-110°C) in 95% yield. Reduction ($LiBH_4$, Li_2CO_3, ethanol, 3 h, 25°C) of ketone **11a** provided after chromatography the axial alcohol **11b** (mp 133-134°C) in 52% yield. Sharpless[12] directed epoxidation (tert-BuOOH, 2 equiv., $VO(AcAc)_2$, 0.05 equiv., CH_2Cl_2, 25°C, 16 h) of the allylic alcohol **11b** provided a single epoxy alcohol **12** (mp 191-192°C, 95%). The C_5-H of uvidin-C **13**[13] is reported to appear at high field (δ 0.80) with J = 4.0 Hz, values which are in good agreement with the C_5-H signal in **12** (δ 0.95, J = 4.0 Hz).

Treatment of epoxide **12** with $LiNEt_2$ (2.0 equiv., -78° - 25°C, THF) afforded diol **14a**, as witnessed by the presence of three high field methyl singlets in its NMR spectrum in addition to a vinylic methyl singlet at 2.22. When 4 equiv. of $LiNEt_2$ were employed, the exocyclic olefin **15** (vinylic protons, δ 5.24 and 5.52, 2 x 1H, brd. s) was formed. The stereochemistry of the lactone was once again established by the appearance of the C_1-H as a triplet (δ 4.15). Conjugated lactone **14a** is formed kinetically and, in the presence of excess base, is deprotonated at the vinylic methyl. Kinetic protonation of the enolate occurs from the β-face, through the less strained transition state. However, the acetonide **15b** (2,2-dimethoxypropane, p-TsOH, 25°C, 16 h) was completely isomerized to the conjugated isomer **14b** by kinetic protonation of the ester enolate ($LiNEt_2$) or by equilibration (CH_3OK/CH_3OH). Acetonide **14b** (mp 99-100°C) was also prepared directly from diol **14a**.[14]

Our current efforts are being directed toward elaboration of the tetrahydropyran ring of forskolin **1**.

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FOOTNOTES AND REFERENCES:

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14. All new compounds gave correct spectral and/or analytical data. Yields are not optimized.

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