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A STEREOSELECTIVE SYNTHESIS OF 1,2-DIOLS FROM α-HYDROXYALDEHYDES

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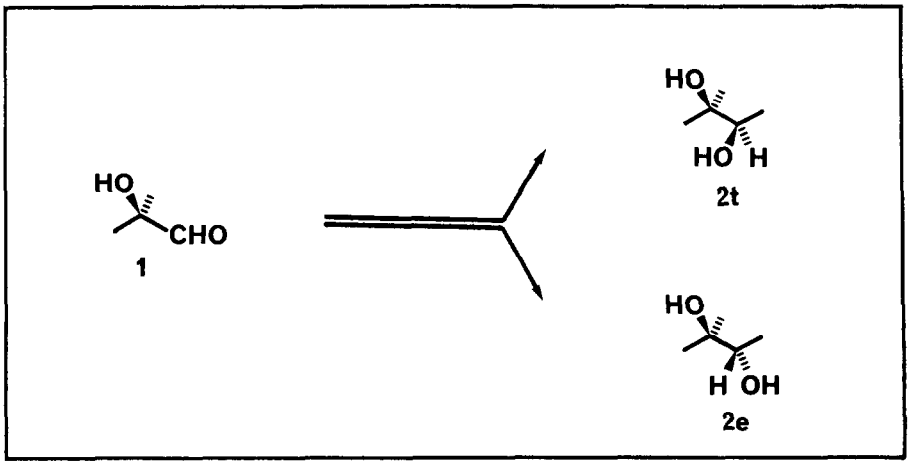
Abstract. The addition of lithium acetylides to (20R)-20-hydroxypregnane-22-carboxaldehydes in the absence and in the presence of BF_3 afforded predominantly 20R,22R- or 20R,22S-diols, respectively, characteristic of ecdysones.

The addition of nucleophiles to chiral α-hydroxyaldehydes **1** constitutes a valuable procedure for the diastereoselective synthesis of 1,2-diols **2**. In connection with our interest in the partial synthesis of ecdysones,[1] we examined the addition of lithium acetylides to (20R)-20-hydroxypregnane-22-carboxaldehydes **5** and observed that certain Lewis acids dramatically altered the stereoselectivity of the addition process. In particular, the addition of boron trifluoride[2] altered the usual outcome leading to the threo-diastereomer **2t** and led instead to the erythro-diastereomer **2e**. This finding provided a convenient solution to the partial synthesis of either the ecdysone or the 22-epiecdysone side chain.



The Darzens condensation of pregnan-20-ones **3** and the subsequent ring opening of epoxysulfones **4** furnished the desired substrates, the α-hydroxyaldehydes[3] **5**, in a highly stereoselective reaction. As summarized in Table I, the condensation of **5x** or **5y** with $LiC{\equiv}CC(CH_3)_2OTHP$ (**10**) or $BrMgC{\equiv}CC(CH_3)_2OTHP$ (**11**) followed the anticipated stereochemical course to give predominantly the 20R,22R-diastereomer[4] **6**. According to Cram's "cyclic" model[5] or the Felkin model,[6] the transition state leading preferentially to **6** involves nucleophilic attack on the "chelated" substrate[7] from the less hindered direction (as indicated by the emboldened arrow).

When boron trifluoride was added to the acetylide **10** prior to the addition of **5**, this preference for the 20R,22R- diastereomer **6** was inverted and the 20R,22S-diastereomer **7** was the principal product. Independent experiments established that the predominance of **7x** was not due to the selective destruction of the epimer **6x** or to the epimerization of **6x** during the course of the condensation. Reetz[8] has recently reported a similar inversion in the reaction of crotyltitanium reagents with simple aldehydes in which a non-cyclic mechanism was suggested to account for erythro-diastereoselectivity in the presence of boron trifluoride. Our own observations involving α-hydroxyaldehydes are also consistent with a non-cyclic mechanism involving either Cram's "dipolar" model or the Felkin model[6] in which the α-hydroxyaldehyde is transformed to a boron "ate" complex prior to nucleophilic addition. Other Lewis acids ($B(OCH_3)_3$, $AlCl_3$, etc.) were less effective than boron trifluoride in this particular reaction.

Manipulation of the proparyl alcohols **6** and **7** provided convenient access to the side chains **8** and **9**, respectively, characteristic of the ecdysones and the 22-epiecdysones. The stereochemical assignments of these C-22 epimers relied on ^{13}C NMR data (pyridine-d_5) in which the C-22 signal appeared at 77.1-78 ppm for the 22R-epimer and at 76.0-76.8 for the 22S-epimer. In addition, it was important to develop hydrolytic conditions for deprotecting the C-25 tetrahydropyranyl ether that would be compatible with a C-14α hydroxyl group in a projected synthesis of the natural ecdysones. Standard hydrolytic conditions (PPTS, CH_3OH) fail to remove C-14α tetrahydropyranyl ether-protected hydroxyl groups,[9] but we have found that 1:50 70% perchloric acid (9.0 equivalents) in methanol cleanly deprotects tetrahydropyranyl ethers at either C-25, as in **6** and **7** (90% yield) or at C-14 as in **12** (63% yield) to furnish the desired tertiary alcohols without concomitant elimination. Application of this strategy to the partial synthesis of ecdysones will be reported in due course.

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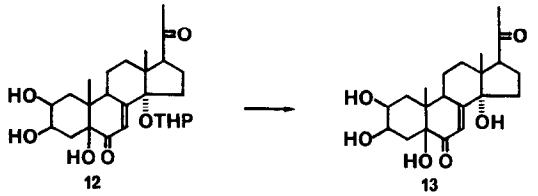
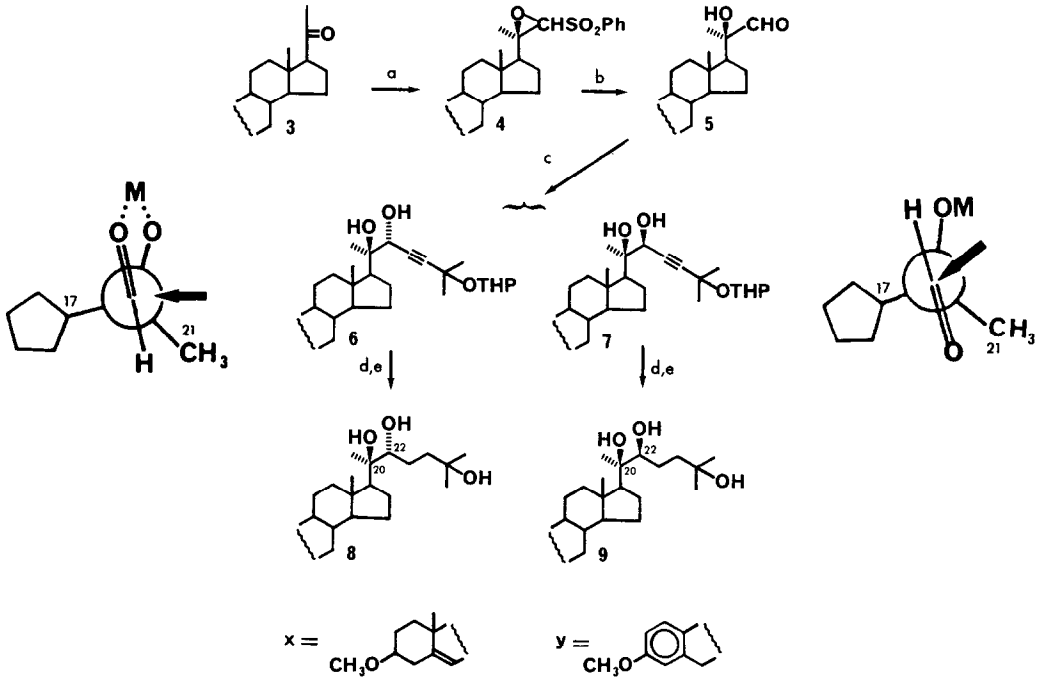


Scheme I.



a, KOtBu (2.1 eq), $ClCH_2SO_2Ph$ (2.1 eq), 1:2 tBuOH-THF, 72h (**3x** ⟶ **4x** in 56% yield; **3y** ⟶ **4y** in 60% yield); b, H_2O (5 eq) in 70.5% KOtBu-tBuOH (15 eq) followed by 1:1 10% HCl-THF, 72h (**4x** ⟶ **5x** in 91% yield; **4y** ⟶ **5y** in 95% yield); c, $MC{\equiv}CC(CH_3)_2OTHP$ (see Table I); d, 1:50 70% $HClO_4/CH_3OH$; e, H_2 PtO_2.

Table I.

Substrate	Conditions	Lewis Acid	Isolated Yield (%)	Ratio of 6 to 7
5x	10, THF, -26°C	---	91	2.3:1
5x	11, THF, -26°C	---	76	6.9:1
5y	11, THF, -26°C	---	87	6.9:1
5x	10, THF, -26°C	$MgBr_2$	80	6.9:1
5x	10, THF, -26°C	$ZnCl_2$	76	2.1:1
5x	10, THF, -26°C	$Ti(OiPr)_4$	78	1.5:1
5x	10, THF, -26°C	BF_3	37	1.0:13
5x	10, THF, -78°C	BF_3	40	22S only

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