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A novel one-pot annelation, decarboxylation reaction: synthesis of (±)-*trans*-benzohydrindane

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Abstract—A novel one-pot annelation, decarboxylation protocol is utilized in the synthesis of *trans*-2,3,4,5-tetrahydro-3*a*-methyl-7-methoxybenz[*e*]indan-3-one **1**.

A-nor B-aromatic steroids[1] have attracted much attention because of their hormonal and antihormonal activity[2] and their potential importance as intermediates in the synthesis of 19-nor-testosterone, 19-nor-progesterone, estradiol, 9,11-dehydrotestosterone, adrenosterone, and cortisone.[3] Due to the potential synthetic flexibilities in constructing the A-ring and introducing functional groups at C-9 and C-11, synthetic studies towards the B–C–D skeleton of steroids is an important synthetic challenge.

It would therefore be very important to search for an efficient method for construction of the B–C–D steroidal ring system with an appropriate functional group at the C-17 position for further elaboration. Keeping in mind the above facts, we undertook the stereoselective synthesis of the steroidal B–C–D ring system.

Herein we report the synthesis of a (±)-*trans*-benzohydrindane derivative using a simple one-pot annelation, decarboxylation strategy, whose construction had been otherwise difficult and which had provided one of the main unresolved problems in the total synthesis of steroids.[4]

In our synthesis, 6-methoxy-2-methyltetralone **2** was prepared from 6-methoxytetralone by modifying the methods of Chang[5] and Chatterjee.[6] Thus, the hydroxymethylene compound of 6-methoxytetralone was prepared in good yield using NaH/ethylformate. Benzoylation of the hydroxymethylene tetralone using NaOH and benzoyl chloride[7] furnished the corresponding benzoyl derivative in good yield and its reduction with PtO_2 in isopropanol[8] afforded **2**. The ester–aldehyde **3** was prepared according to Linstead's procedure[9] from pent-4-enoic acid by esterification[10,11] and ozonolysis. The pent-4-enoic acid in turn was prepared by monoalkylation of diethyl malonate with allyl bromide and potassium carbonate in the presence of a phase transfer catalyst followed by hydrolysis and decarboxylation in refluxing acetonitrile and copper oxide[12] in 78% overall yield.

Having obtained the desired tetralone **2** and aldehyde **3** they were next subjected to a condensation reaction.

Thus, the enolate of 6-methoxy-2-methyltetralone **2** was reacted with ester–aldehyde **3**, at −78°C, to afford the desired aldol **4a** in 56% yield. The attempted protection of the aldol **4a** as its tetrahydropyran derivative using DHP (dihydropyran) and *p*-TSA[13] in $CHCl_3$ afforded the undesired lactone **5** in 87% yield (Scheme 1). This problem was overcome by performing the protection of the secondary alcohol under mild conditions using PPTS[14] (pyridine *p*-toluenesulfonate) in dichloromethane and DHP to afford the -OTHP ether **4b** in practically quantitative yield as an inseparable diastereomeric mixture. Having obtained the -OTHP ether the key cyclization was carried out with NaH in anhydrous xylene at reflux to afford tricyclic -OTHP ether **6** in a distereomeric mixture. The formation of **6** can be explained by a novel one-pot cyclization, decarboxylation reaction and the probable mechanism of the reaction is depicted in Scheme 2. In order to ascertain the mechanism of the reaction (path A or path B), an attempt was made to trap the liberated isobutene by employing a trap maintained at –78°C at the outlet.

Keywords: aldol; cyclization; annelation; steroid skeleton.

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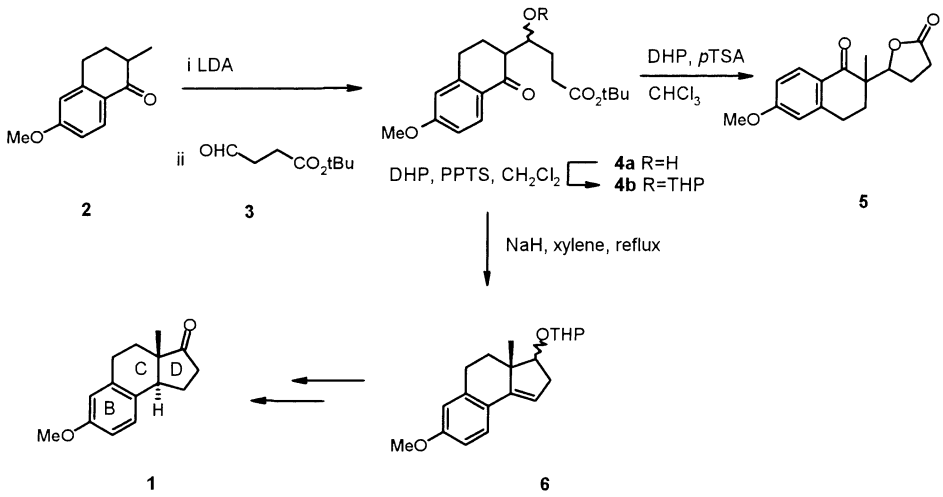
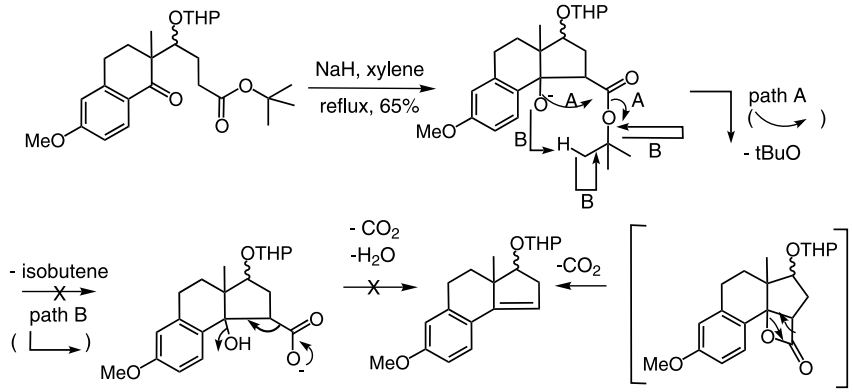


Scheme 1.

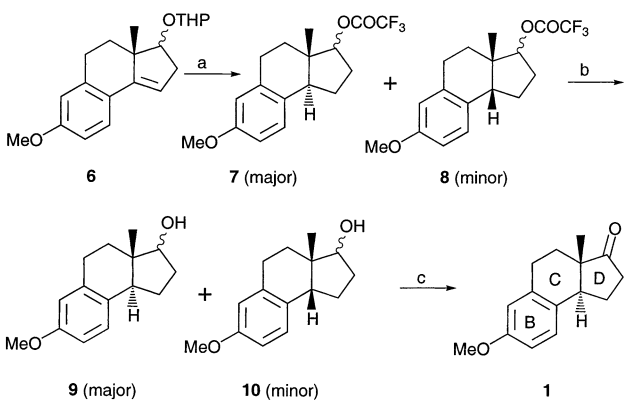


Scheme 2.

Since the formation of isobutene was not detected, the most probable mechanism is formation of a four-membered lactone and loss of CO_2 as shown in path A.

Having successfully achieved the synthesis of tricyclic -OTHP ether **6**, the next task was stereoselective reduction of the double bond to achieve the CD ring (steroidal ring) with *trans* geometry and its further conversion to *trans*-benzohydrindane **1**.

Catalytic hydrogenation and deprotection with *p*-TSA as well as deprotection with *p*-TSA and then hydrogenation with Pd/C afforded *trans–anti* alcohol **9** as a minor product and the undesired *cis–anti* alcohol **10** as the major product in 63% yield (4:96). Representations of stereoisomers refer to the CD ring juncture and the relative arrangements of the angular methyl and hydroxy group at the C-17 position, respectively. Other reagents such as lithium/naphthalene and Lindlar's catalyst also failed to give *trans–anti* alcohol **9**. We then turned our attention towards chemical reduction. Ionic hydrogenation reduction usually exhibits a high degree of selectivity and yield. Accordingly the ionic hydrogenation of **6** using triethylsilane and trifluoroacetic acid[15] at 0°C (Scheme 3) afforded an isomeric mixture of trifluoroacetates **7** and **8** (44%, 2:1) and alcohols **9** and **10** (28%, 2:1). The direct saponification of the reaction mixture using NaOH and ethanol afforded alcohols **9** and **10** in 72% in a 2:1 mixture. The geometry of the CD rings was established by the characteristic chemical shift of the angular methyl group.[16–19] The characteristic doublet at 3.95 δ (d, $J=6.3$ Hz, 1H(CH-OH)) supported the assigned structure of **9** as the *trans–anti* alcohol. The ^{13}C NMR spectrum of the mixture of alcohols displayed 27 peaks for the 15



Scheme 3. (a) Et_3SiH, CF_3COOH, CH_2Cl_2, 0°C, 2 h (44% of **7**, **8** and 28% **9**, **10**); (b) NaOH, EtOH, rt, 72% **9** and **10** from **6**; (c) Jones' oxidation and seperation, 42%.

carbons of each alcohol. A comparison of the ^{13}C NMR spectrum of alcohol **9** and **10** prepared by catalytic hydrogenation was superimposable with that of the alcohols obtained by chemical hydrogenation except for the peak ratios. Efforts to crystallize the mixture of alcohols were unsuccessful. Thus, from the above mentioned points, it is clear that alcohol **9** has a CD *trans* ring junction while the C-17-OH is in an *anti* configuration, i.e. -OH is in the α orientation, which can be readily changed to the β orientation by simple oxidation and $NaBH_4$ reduction.

Having prepared the *trans* alcohol **9** as the major product, the next task was to separate these alcohols and convert them to *trans* benzohydrindane **1**. Accordingly, Jones' oxidation of the mixture of alcohols **9** and **10** afforded a mixture of ketones. Careful separation of the ketones by column chromatography on silica gel using hexane and ethyl acetate (10:1) as eluent afforded a mixture of *cis* and *trans* isomers as an oil in 42% yield followed by the solid, *trans* benzohydrindane **1** in 42% as colorless needles, mp 112°C (reported 113°C)[17] with all spectral data matching that reported in the literature.[20] Thus, the synthesis of *trans*-2,3,4,5-tetrahydro-3*a*-methyl-7-methoxybenz[*e*]indan-3-one **1** has been achieved from the simple precursor, 6-methoxytetralone, by utilizing a novel one-pot annelation, decarboxylation protocol, involving stereoselective chemical reduction for the formation of the *trans* CD ring junction. All the steps involved are simple and convenient to perform. Additionally, by performing the aldol condensation mediated by a chiral amine/amide (base) the BCD skeleton of steroids can be accessed in an enantioselective manner and this study is underway in our laboratories.

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