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A Novel and Efficient Synthetic Approach to Polyfunctional Bicyclo[3.1.0]hexane Derivatives#

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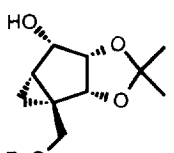
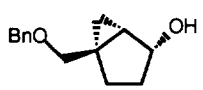
Abstract. *1,3-Dipolar cycloaddition of diazomethane and nucleophilic oxirane-ring opening are the key steps in the synthesis of chiral and highly functionalized title compounds all of them bearing two quaternary carbons and three other stereocenters. Hydroxy esters and hydroxy amino esters have been prepared in good yields as representative instances of the versatility of the method described.*

The cyclopropane-fused 6-oxabicyclo[3.1.0]hexane system is present in the structures of some nucleosides showing antiviral activity, whose syntheses have already been reported.[1] This type of skeleton, in its carbocyclic version, has been used to prepare carbocyclic nucleoside analogues structurally related to neplanocin C, in order to evaluate their anti-HIV activity. They are described by Marquez as conformationally locked nucleoside analogues,[2] and their use as building blocks for the synthesis of antisense nucleotides,[3] an emerging and potential new class of therapeutic agents, is being subjected to investigation by some pharmaceutical laboratories.[4]

Differently substituted methano-cyclopentane derivatives have been prepared by a Simmons-Smith[4] or a samarium-promoted[2] cyclopropanation reaction of convenient antecedent cyclopentenols, affording **1** and **2**, respectively. In a third case, Rapoport has used an 1-aminocyclopropane carboxylic acid derivative as a precursor to aminoalcohol **3**.[5]



1



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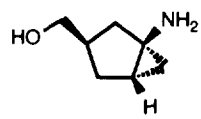


3

With the purpose of developing new rigid carbocycle-based potential drugs we have achieved the synthesis of some molecules containing a α-hydroxy-ester or a α-hydroxy-β-amino-ester fragment linked to a bicyclo[3.1.0]hexane moiety that, in turn, bears other functional groups. These structures are highly

Dedicated to Professor Félix Serratosa, *in memoriam.*

functionalized and present two quaternary carbons, one in the ring-fusion and another in the side-chain, and, at least, three additional stereogenic centers, all of them with controlled absolute configuration.

We published in an initial communication the synthesis of the enantiomer of epoxy diester **4** and its reactions with some nucleophiles.[6] Later, we have achieved the multigram synthesis of **4** in 80% ee and its reaction with lithium dimethylcuprate to give alcohol **5** in 70% yield.[7] Starting from **4** we now describe herein alternative synthetic routes that differ in the order of performing nucleophilic oxirane-ring opening and cyclopropanation reaction of the double carbon-carbon bond in an intermediate cyclopentene derivative (Scheme 1). Cyclopropanes were produced through 1,3-dipolar cycloaddition of diazomethane to suitable ester-conjugated cyclopentenes. The stereoselective syntheses of alcohol **15** and aminoalcohol **16** have been achieved in a very efficient manner by reaction of epoxide **14**, as a key intermediate compound, with lithium dimethylcuprate or (*R*)-α-methylbenzylamine, respectively.

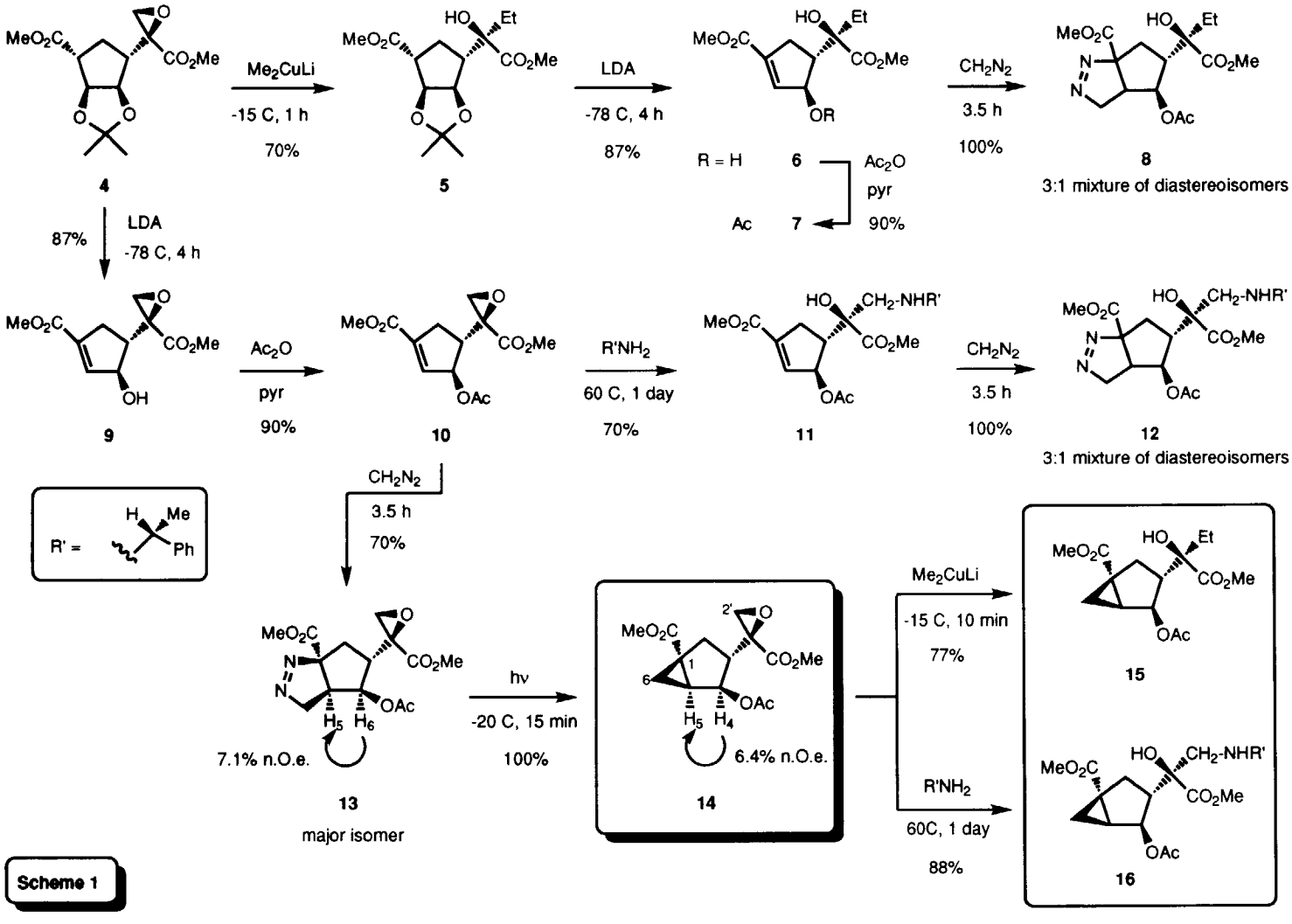
In the first route, cyclopentene **6**[8] was obtained in 87%, by LDA-promoted elimination of acetone,[6] at -78 C for 4 h. Then, the secondary alcohol was selectively acetylated to give **7** which was subjected to treatment with an ethereal diazomethane solution at room temperature for 3.5 h, affording quantitatively a 3:1 mixture of diastereomeric pyrazolines **8**. Cyclopentene **10** was prepared in a similar manner by reaction of **4** with LDA followed by acetylation, in 80% yield for the two steps. Subsequent reaction with (*R*)-α-methylbenzylamine in DMF at 60 C for one day produced a mixture of diastereomeric amino alcohols the major isomer being isolated by column chromatography to provide pure **11** in 70% yield. Products from conjugate addition of the amine to the double bond were not detected. Finally, reaction with diazomethane in the same conditions as above gave a mixture of pyrazolines **12** also in a 3:1 ratio of diasteroisomers.

Unfortunately, diastereomerically pure pyrazolines could not be obtained from **8** or **12** by using crystallization or chromatographic techniques. Therefore, the next synthetic step, involving their decomposition to cyclopropane containing compounds, was not performed.

Following an alternative pathway, conjugated ester **10** was reacted with diazomethane. Since a 3:1 mixture of pyrazolines was obtained also in this case, the stereoselectivity of the cycloaddition was shown to be the same as in the cases of **7** and **11**, these last products resulting from oxirane ring opening previous to cyclopropanation. In contrast, separation of the two diastereoisomers was now easily accomplished by column chromatography to furnish diastereomerically pure **13** (80% ee) in 70% yield. Photochemically promoted decomposition of **13** was realised as a dichloromethane solution contained in a Pyrex reactor by irradiation with a 125 W medium-pressure mercury-lamp, at -20 C for 15 minutes, in the presence of benzophenone as a photosensitizer, to afford compound **14** in quantitative yield. On the other hand, when irradiation was performed on a toluene solution of **13** at -78 C in absence of benzophenone, **14** was obtained as a major product along with the insertion olefin and enoate **10**, this last compound proceding from cycloreversion of pyrazoline **13**.

Stereochemistry of pyrazoline **13** and cyclopropane **14** was assigned on the basis of n.O.e. difference experiments, considering the high enhancements obtained on H_5 when H_6 in **13** or H_4 in **14** were selectively irradiated (Scheme 1).

Once the carbo-bicyclic framework had been stereoselectively assembled, we proceeded to achieve the synthetic goals. Thus, in a later step, reaction of epoxide **14** with lithium dimethylcuprate at -15 C for 10 minutes gave alcohol **15** in 77% yield (42% from **4**).


Me2CuLi
-15 C, 1 h
70%
LDA
-78 C, 4 h
87%
CH2N2
3.5 h
100%
Ac2O
pyr
90%
R'NH2
60 C, 1 day
70%
hν
-20 C, 15 min
100%
7.1% n.O.e.
6.4% n.O.e.
R' =
4
5
6
7
8
9
10
11
12
13
14
15
16
3:1 mixture of diastereoisomers
major isomer

Scheme 1

Furthermore, treatment of **14** with (*R*)-α-methylbenzylamine in a DMF solution at 60 C for one day gave **16** in 88% yield (48% from **4**). The reactions of **14** with chiral amines are specially attractive since they provide an easy procedure to prepare enantiomerically pure derivatives. In addition, the α-hydroxy-β-amino carboxylic acid fragment is constituent of several biologically active products. This functionalization along with the presence of the bulky bicyclic system confer, therefore, of promising interest to these type of constrained molecules.

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8. All new products were fully charaterized by their physical constants and spectral data, and gave satisfactory microanalysis. Selected data for the most representative compounds follow.
   Compound **7**: Oil, $[\alpha]_D$ +132.2 (c 1.77, chloroform). Compound **10**: Oil, $[\alpha]_D$ +151.7 (3.23 chloroform). Compound **11**: Oil, $[\alpha]_D$ +133.8 (c 1.39, chloroform). Compound **13**: Crystals, m. p. 115 C (dec) (from ethyl acetate-pentane); $[\alpha]_D$ +229.5 (c 1.54, chloroform). Compound **14**: Oil, $[\alpha]_D$ +135.4 (c 1.30, chloroform); 250-MHz ^{1}H NMR ($CDCl_3$) δ 1.15 (dd, J = J' = 5.1 Hz, H_{6a}), 1.35 (dd, *J* = 8.4 Hz, *J'* = 5.1 Hz, H_{6b}), 2.01 (s, OCOC*H*$_3$), 2.22 (complex abs, H_{2a} and H_{2b}), 2.28 (ddd, *J* = 8.6 Hz, *J'* = 8.4 Hz, *J"* = 5.1 Hz, H_5), 2.55 (m, H_3), 2.67 (d, *J* = 5.3 Hz, $H_{2'a}$), 3.01 (d, *J* = 5.3 Hz, $H_{2'b}$), 3.62 (s, OC*H*$_3$), 3.72 (s, OC*H*$_3$), 4.86 (dd, *J* = 8.6 Hz, *J'* = 4.9 Hz, H_4) (see Scheme 1 for proton numeration). Compound **15**: Oil, $[\alpha]_D$ +129.5 (c 1.83, chloroform). Compound **16**: Oil, $[\alpha]_D$ +126.0 (c 1.23, chloroform).

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