Pergamon

Tetrahedron: Asymmetry Vol. 5, No. 1, pp. 37-40, 1994
Elsevier Science Ltd
Printed in Great Britain
0957-4166/94 $6.00+0.00

0957-4166(93)E0040-4

Stereoselective Synthesis of New Homochiral Polyfunctional Side-Chain Cyclopentane Derivatives

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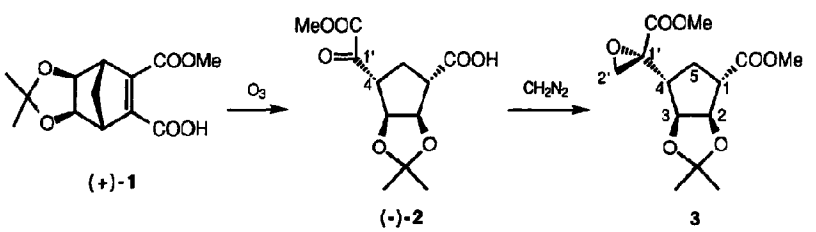
Abstract: A new homochiral polyfunctional cyclopentane derivative, containing an oxirane ring in a side-chain, has been synthesized stereoselectively . This compound is an useful intermediate in the synthesis of products such as hydroxyesters, polyols or aminoalcohols.

The cyclopentane ring moiety is a structural feature present at molecules such as prostanoids, carbocyclic nucleosides, and carba-sugars, among other interesting compounds. These products are attractive owing to their biological properties such as inhibitors of the platelet aggregation,[1] antibiotics,[2] or antiviral agents.[3]

In the synthesis of the carbocyclic nucleosides (-)-aristeromycin and (-)-neplanocin described by Ohno and coworkers, the cyclopentane structure is produced by ozonolysis of the C-C double bond in hemiester (-)-1 that through oxidative cleavage and concomitant reductive decarboxylation affords (+)-2. This compound was not characterized but subsequently transformed in other intermediates in the synthetic route towards the target molecules.[4]

We have performed the ozonolysis of the previously synthesized hemiester (+)-1,[5] obtaining quantitatively (-)-2, $[\alpha]_D$ -12.5 (Scheme 1).[6] In this communication we report the reaction of (-)-2 with



Scheme 1

diazomethane to give the epoxide **3**. The assignment of absolute configuration for this compound, as well as some exploratory reactions leading to polyfunctional branched cyclopentane derivatives are also described.

Excess diazomethane reacts with (-)-**2** at room temperature for 1 h giving epoxide **3** in 85% yield as a single stereoisomer which results from both methylation of the carboxyl group and addition to the ketone carbonyl. These two processes are simultaneous as verified when the reaction was monitored by GLC. Epoxide **3** was characterized as a solid, m.p. 72-74 °C, $[\alpha]_D$ +1.3. The absolute configuration of the new stereogenic center was determined by X-ray analysis of a single crystal and shown to be *R* (Fig 1). The high stereoselectivity of the addition of diazomethane to the ketone allowing the stereocontrolled creation of a stereogenic center in a flexible fragment is noteworthy. In order to verify whether a marked conformational bias in (-)-**2** was responsible for the observed stereoselection, the energies associated to the conformations resulting from considering rotations around the C_4-$C_{1'}$ bond were calculated. No conclusion could be deduced, however, and at present the theoretical study of the addition stereochemical outcome is being carried out in our laboratory.

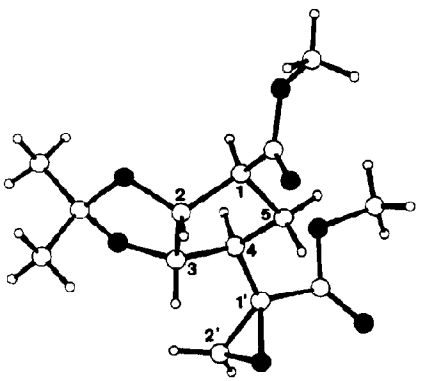
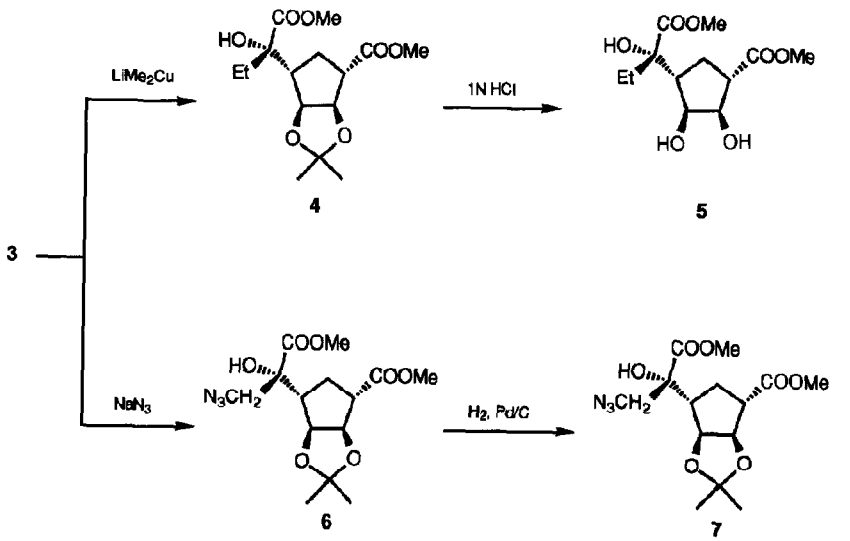


Fig 1. Structure of compound 3 as determined by X-ray structural analysis. The atomic coordinates and thermal parameters for structure 3 are available on request from the Director of the Cambridge Crystallographic Data Center. Any request should be accompannied by a full literature citation for this paper. Please note that the crystallographic numbering differs from that used in this communication.

Molecule **3** contains five stereogenic centers and offers an enormous synthetic potential for obtaining polysubstituted five-membered rings containing heteroatom functions, such as hydroxyesters, polyols, aminoalcohols, etc. We report herein the first results obtained from the reactions of **3** with lithium dimethylcuprate and sodium azide, respectively, as well as some simple transformations of the produced compounds (Scheme 2).

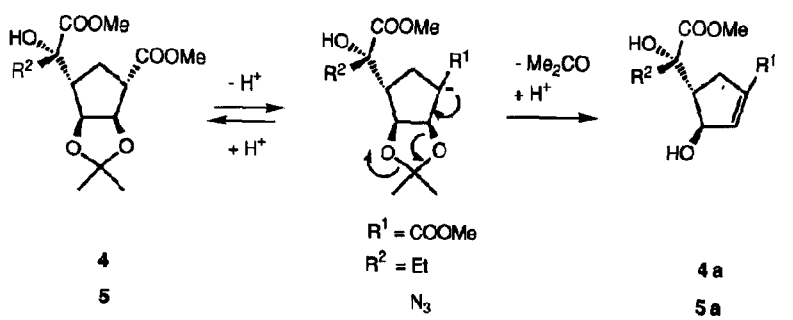
Reaction of **3** with lithium dimethylcuprate at 0 °C for 4 h resulted in regioselective nucleophilic oxirane-ring opening to give alcohol **4** in 60% yield which is a crystalline solid, m.p. 52-53 °C, $[\alpha]_D$ +35.6. In turn, treatment of **4** with 1N HCl afforded the triol **5**. On the other hand, reaction of **3** with sodium azide in DMF at

room temperature for four days furnished azide **6** in 35% yield (yield not optimized) as an oil, $[\alpha]_D$ +46.23. Finally, catalytic hydrogenation (Pd/C) of **6** led quantitatively to aminoalcohol **7**.



Scheme 2

In the reactons between epoxide **3** and the mentioned nucleophiles, compounds **4a** and **5a** were obtained, respectively, as minor products. β-Elimination of acetone from the intermediate enolate (Scheme 3) leads to alkoxide species that give **4a** or **5a** after protonation. Related elimination processes have previously been



Scheme 3

observed in lactonic carbohydrate derivatives.[7] Structural assignment for these products was mainly made on the basis of MS and NMR spectral data.[8] Compounds **4a** and **5a** would be the equivalent to glycals in branched carba-sugar series and, in addition, could behave as Michael-type acceptors affording a variety of products. Therefore, specific synthetic methods to prepare such moleules in good yields are under study.

Thus, epoxide 3 has proved its usefulness and versatility as an intermediate in the synthesis of polyfunctional cyclopentane derivatives. The reactions with other nucleophiles and the preparation of several new products is the subject of active investigation.

Acknowledgements. M.D. thanks the Ministerio de Educación y Ciencia and J.I. thanks the Direció General de Universitats (CIRIT) for respective grants. Financial support from DGICYT through the project PB91-0502 is gratefully acknowledged.

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6. Full characterization of all new products will be reported in a futur.
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8. For instance, the ^{13}C NMR spectrum for both products showed signals at 136 and 143 ppm corresponding to the C_α and C_β olefinic carbons, repectively, the last one being quaternary, and a peak at 165 ppm for the conjugated ester-carbonyl carbon. In addition, a multiplet centered at 6.5 ppm was observed in the ^1H NMR spectra which corresponds to the olefinic H_β.

(*Received in UK 26 November* 1993)