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The first synthesis of spirocyclopentyl derivatives of lupane triterpenoids by radical nitrocyclization of C-2-diallyl substituted betulonates

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ABSTRACT

Radical cyclization of the 1,6-hexadiene moiety in 2,2-diallyl substituted methyl or benzyl dihydrobetulonates initiated by $Fe(NO_3)_3{\cdot}9H_2O$ in the presence of $FeCl_3$ or LiCl gave hitherto unknown spirocyclic compounds in which ring A of the lupane triterpenoid at position C-2 is spiro coupled with a vicinally substituted nitromethyl- and chloromethylcyclopentane. Based on a quantum-chemical assessment of the energy characteristics of this reaction, the most probable configurations of the chiral atoms in the spirocyclopentane ring were determined for the major diastereomers isolated in individual form.

Pentacyclic triterpenoids of lupane series constitute an important class of bioactive compounds possessing a broad scope of activity. These compounds are of special interest due to their antitumor and antiviral properties.[1] Lupane triterpenoids manifest low toxicity against animals even in high concentrations, but the relatively weak potential of their biological effect hinders considerably the use of these compounds in clinical practice. In view of this, studies on the synthesis of betulin and betulinic acid derivatives by the modification of functional groups at C-3 and C-28 atoms have been under way in the past years. These studies resulted in a group of compounds that had superior antitumor and antiviral activities in comparison with native compounds.[2,3] However, studies aimed at modifications of ring A in betulinic or betulonic acids[1,3–5] are no less promising. We have recently developed a facile and efficient method for synthesizing 2,2-diallyl-substituted 3-ketolupanes **1** and **2** that are of interest as polyfunctional blocksynthons for new derivatives of lupane triperpenoids with modified ring A.[6] These compounds can be converted into potentially bioactive spirocyclic systems by cyclization of the 1,6-hexadiene moiety under conditions of radical[7,8] or catalytic reactions on treatment with transition metal complexes,[9,10] including olefin metathesis catalysts.[11]

In this work, we have studied the radical cyclization of 2,2-diallyl-substituted methyl and benzyl dihydrobetulonates **1** and **2** initiated by $Fe(NO_3)_3{\cdot}9H_2O$ (under its thermal degradation conditions) in the presence of $FeCl_3$ or LiCl as radical traps. The reaction performed by short refluxing of the reagents in THF gave a mixture of diastereomeric compounds **3** and **4**, respectively, in good yields (Scheme 1).[12]

MALDI TOF mass spectra of a mixture of compounds **3** or **4** contained molecular ion peaks corresponding to their molecular formulas (for compound **3**, *m/z* 654.98 $[M+Na]^+$, 670.96 $[M+K]^+$; for compound **4**, 730.40 $[M+Na]^+$, 746.37 $[M+K]^+$).

^1H NMR spectra of cyclization products **3** and **4** contained signals of CH_2NO_2 and CH_2Cl moieties as broad multiplets that resonate at δ 4.30–4.75 and 3.45–3.65, respectively. In the ^{13}C NMR spectra, these groups manifested themselves as characteristic methylene signals: δ 75.81 and 44.45 for compounds **3**; δ 75.83, and 44.46 for compounds **4**.

Analysis of NMR spectra of these compounds did not allow us to determine their stereoisomeric compositions. Major isomers **3a** and **4a** were isolated as individual compounds from hardly-separable diastereomeric mixtures of **3** and **4** using column chromatography on silica gel (Fig. 1). The structures of compounds **3a** and **4a** were partially confirmed by the analysis of one-dimensional ^1H and ^{13}C NMR spectra, two-dimensional homo-(COSY, NOESY) and heteronuclear experiments (HSQC, HMBC).

The ^1H and ^{13}C NMR spectra, with a slight difference in chemical shifts between compounds **3a** and **4a**, totally matched their

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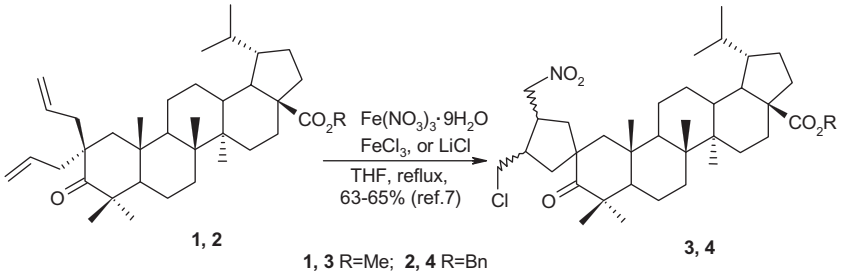

Scheme 1. Radical nitrocyclization of dihydrobetulonates **1** and **2**.

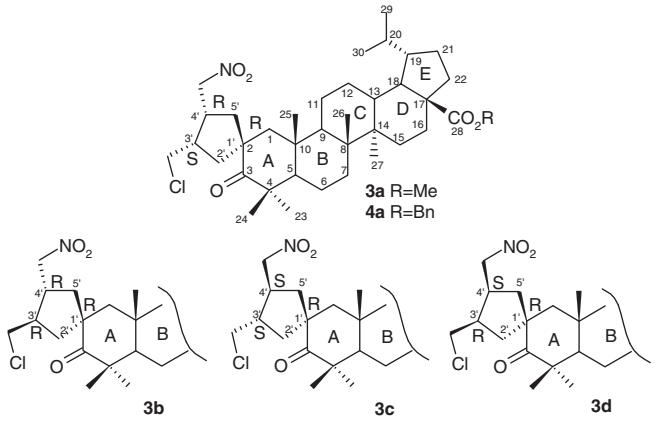

Figure 1. Diastereomeric spiro compounds **3a–d** with an *R*-configuration of the spiro atom.

structure; each spectrum contained a single set of characteristic signals of the lupane and cyclopentane moieties and those of the respective substituents. Their ^{13}C NMR spectra showed an upfield shift of the singlet signal of the quaternary C-2 carbon in ring A ($\Delta\ \delta$ 5.7 ppm) in comparison with its positions in the spectra of the original esters **1** and **2**. The coupling constant of vicinal protons HC-3́ (δ 2.7) and HC-4́ (δ 3.0) observed in ^1H NMR spectra, which amounted to 8 Hz, suggested a mutual *cis*-orientation of these protons and hence a *cis*-arrangement of the CH_2NO_2 and CH_2Cl groups in the spirocyclopentane moiety. The mutual *cis*-orientation of substituents was confirmed by intense cross peaks in the NOESY spectrum between the protons of CH_2Cl (δ 3.5) and CH_2NO_2 (δ 4.4).

However, NMR spectroscopy did not allow us to make an exhaustive conclusion about the stereochemical structure of the spiro compounds. In order to obtain information about the absolute configuration of the chiral carbon atoms of the cyclopentane ring, we performed a theoretical analysis of the stereochemical features of the reaction in question.[13]

Using 2,2-diallyl substituted cyclohexanone **1′** (Fig. 2) as a model compound whose conformational structure matches the structure of ring A in the starting lupane terpenoids (**1**, **2**), we studied the mechanism of radical cyclization that occurs by Scheme 1 (*cf.* Ref. 7) by means of DFT and ab initio methods.*exo*-Cyclization of 1,6-hexadiene moiety in methyl dihydrobetulonate **1** (or model compound **1′**) to cyclopentane can result in eight diastereomers: four pairs of molecules with *cis*- and *trans*-arrangement of vicinal CH_2NO_2 and CH_2Cl groups that differ in arrangement of the latter with respect to the plane of ring A of the lupane frame (Figs. 1 and 3; only diastereomers **3a–d** and **3a′–d′** with an *R*-configuration of the spiro atom are shown).

Calculations of the full energies of optimized structures of all isomers of model compounds **3a′–d′** (Fig. 3) in B3LYP/6–31G(d) approximation suggest unambiguously that *trans*-isomers are energetically favorable: the energy difference between the least stable *trans*-isomer **3b′** and the most stable *cis*-isomer **3a′** (or reaction products **3b** and **3a**) amounted to 9 kJ/mol, while the energy

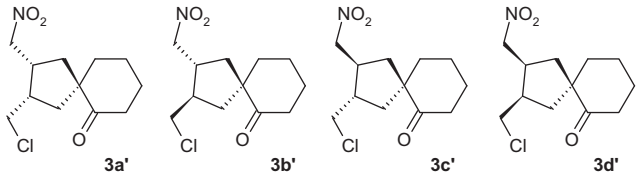

Figure 3. Diastereomeric model spiro compounds **3a′–d′** with an *R*-configuration of the spiro atom.

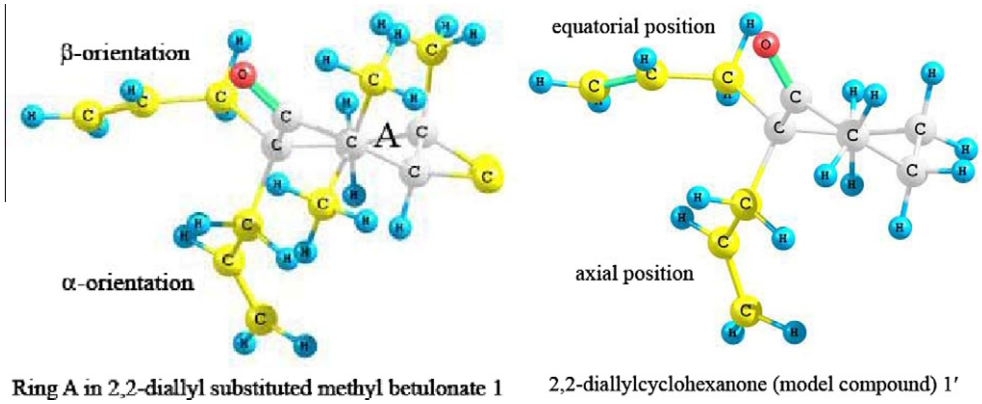

Figure 2. Conformational structure of model 2,2-diallyl substituted cyclohexanone **1′** and ring A in 2,2-diallyl substituted methyl betulonate **1** (both rings have the 'twist' conformation).