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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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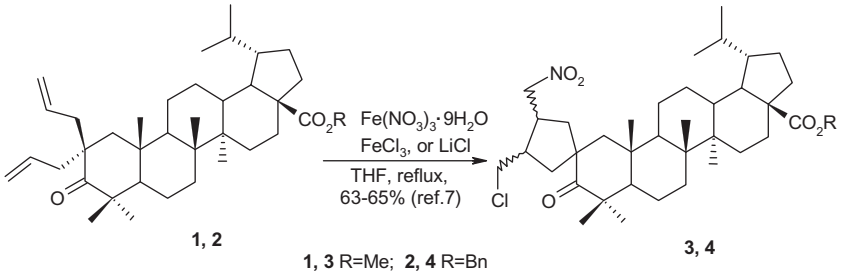


Scheme 1. Radical nitrocyclization of dihydrobetulonates **1** and **2**.

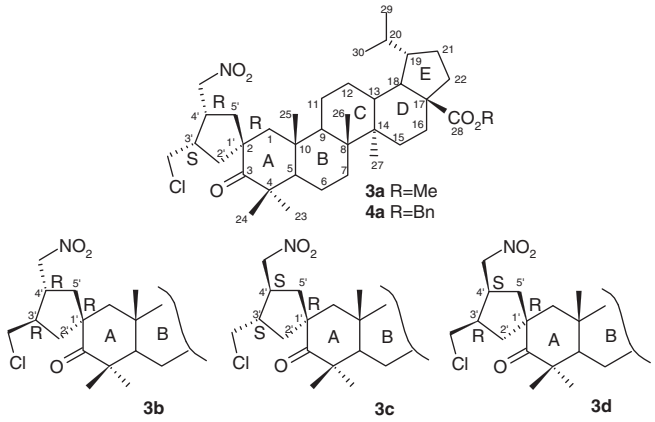


Figure 1. Diastereomeric spiro compounds **3a–d** with an *R*-configuration of the spiro atom.

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

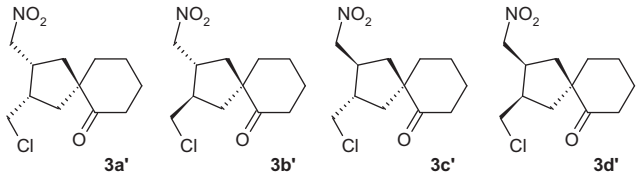


Figure 3. Diastereomeric model spiro compounds **3a′–d′** with an *R*-configuration of the spiro atom.

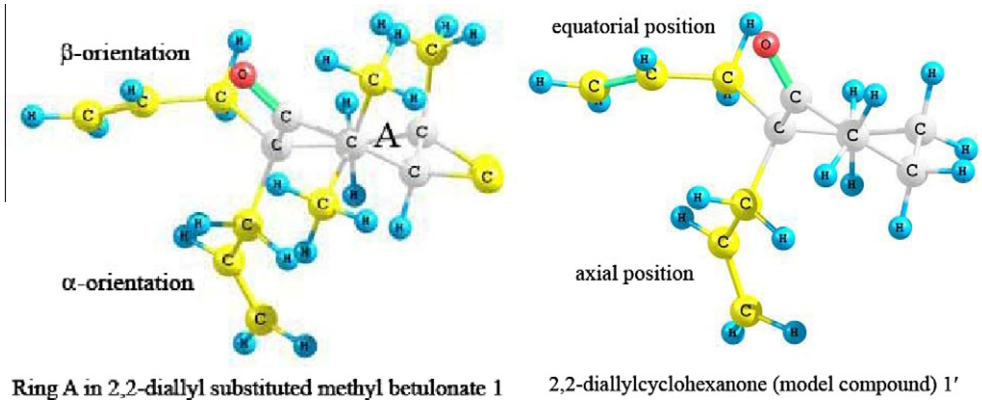
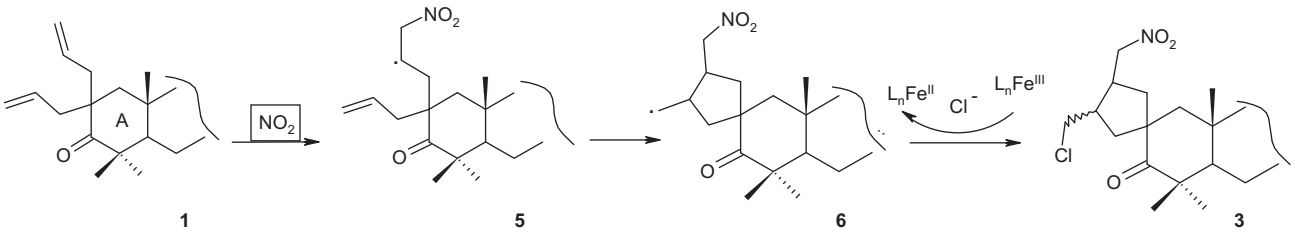


Figure 2. Conformational structure of model 2,2-diallyl substituted cyclohexanone **1′** and ring A in 2,2-diallyl substituted methyl betulonate **1** (both rings have the 'twist' conformation).



Scheme 2. Assumed mechanism of radical nitrocyclization of methyl betulonate **1**.

difference between the most stable *trans*-isomer **3c**′ and isomer **3a**′ (or reaction products **3c** and **3a**) is 15 kJ/mol (see Tables 1 and 2 in Supplementary data).

However, it follows from our experimental data that *cis*-isomers that are less stable thermodynamically are formed in major amounts. In fact, the yield of *cis*-isomer **3a** amounted to 60% of the diastereomer mixture **3**.[12] To explain this apparent contradiction, it was assumed that the selective formation of the *cis*-isomer, which is less stable thermodynamically, is determined by the kinetics and mechanism of the reaction in question. This hypothesis is supported by known facts[14] about the preferential formation of *cis*-substituted cyclopentanes in the radical cyclization of 1,6-hexadienes.

According to the hypothetical mechanism suggested for radical nitrocyclization of 1,6-dienes,[7] the reaction of C-2-diallyl substituted dihydrobetulonates, for example, methyl dihydrobetulonate **1**, starts with radical addition of nitrogen dioxide to one of the double bonds of the 1,6-diene moiety followed by 5-*exo*-cyclization of intermediate **5** to intermediate **6** that contains a cyclopentylmethyl group spiro coupled with ring A of the lupane triterpenoid. Radical intermediate **6** is trapped by the chlorine atom to give reaction product **3** (Scheme 2).

When selecting the theoretical method to study the assumed nitrocyclization mechanism of compound **1**, it was taken into account that the B3LYP hybrid functional overstates the contribution of the pathway that results in the *trans*-isomer in radical cyclization of substituted hexenyl radicals, which occurs in a manner similar to the reaction in question.[14] It is recommended to use the HandHLYP (BHLYP) hybrid functional for this purpose and, if possible, verify the reliability of the calculation results using the com-

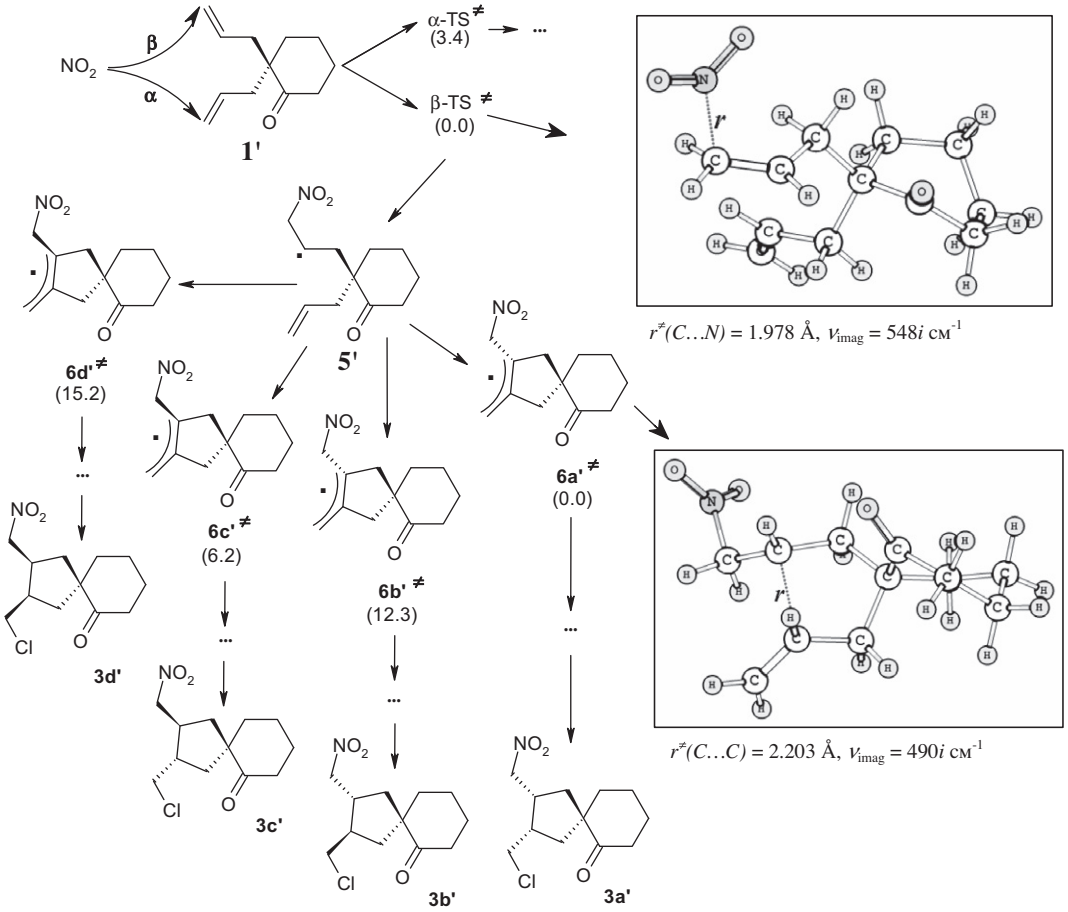


Figure 4. Radical cyclization mechanism for model compound, 2,2-diallylcyclohexanone **1**′, as an example. The relative Gibbs energies (kJ/mol) of the transition states calculated in the BHLYP/cc-pVTZ approximation with nonspecific solvation (tetrahydrofuran) taken into account are shown in parentheses.

posite method. Therefore, the BHLYP functional combined with the Danning basis set with cc-pVTZ triple splitting was chosen as the main calculation method.

Calculations of relative Gibbs energies of the β-TS$^{\neq}$ and α-TS$^{\neq}$ transition states for the two pathways of the first cyclization steps of model compound **1′** (Table 3 in Supplementary data) showed the preferability of nitrogen dioxide reaction with the allyl substituent in compound **1′** having an equatorial configuration (β-orientation of the allyl moiety in **1**) to give intermediate **5′** (Fig. 4). The ratio of the rate constants ($k_\beta/k_\alpha = 3$, $T = 338$ K) calculated using the Eyring equation and the relative nonequilibrium Gibbs energy ($\Delta\Delta G^{\neq}_{\alpha\text{-}\beta}$). Hence, based on the data for model compound **1′**, it can be assumed that the formation of four diastereomers **3a–d** with an *R*-configuration of the C-2 spiro atom is preferential in the series of isomeric compounds **3**.

In calculations of the relative Gibbs energies for transition states **6a′$^{\neq}$–d′$^{\neq}$** (Table 4 in Supplementary data) that lead to model compounds **3a′–d′**, the relative energies of transition states **6a′$^{\neq}$** and **6c′$^{\neq}$** were refined by the G3MP2B3 composite method in accordance with published recommendations.[14] As one can see from Figure 4, transition state **6a′$^{\neq}$** that leads to isomer **3a′** has the lowest energy barrier. The $\Delta\Delta G^{\neq}_{c-a}$ value was found to be 8.1 kJ/mol. The reaction rate ratio $k_a/k_c = 15$ ($T = 338$ K) calculated from this value, that is, the rate constant of cyclization that occurs toward model compound **3a′** or reaction product **3a** is by an order of magnitude higher than the rate constants for the competing pathways. Hence, the experimentally observed formation of *cis*-isomers **3a** and **4a** of spirocyclopentane derivatives of betulonates can be reasonably explained by analyzing data obtained in the framework of theoretical studies, which eliminate the apparent contradiction noted above between the isomerism thermodynamics and NMR data for diastereomeric mixtures of compounds **3** or **4**.

To conclude, we have synthesized hitherto unknown spirocyclic derivatives of lupane terpenoids. Theoretical analysis of the reaction mechanism allowed us to establish the most probable structures of major reaction products **3a** and **4a** that were isolated in individual form from diastereomeric mixtures: methyl 3-oxo-3′*S*-(chloromethyl)-4′*R*-(nitromethyl)spiro[2(1′)*R*-cyclopentane]-dihydrobetulonate (**3a**) and benzyl 3-oxo-3′*S*-(chloromethyl)-4′*R*-(nitromethyl)spiro[2(1′)*R*-cyclopentane]-dihydrobetulonate (**4a**).

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.11.020.

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12. *Typical procedure*: To a solution of **1** (0.10 g, 0.18 mmol) and $FeCl_3$ (0.04 g, 0.27 mmol) or LiCl (0.01 g, 0.27 mmol) in THF (3 ml) was added $Fe(NO_3)_3{\cdot}9H_2O$ (0.09 g, 0.22 mmol), and the mixture was heated at reflux for 3 h. After cooling to room temperature, the resulting suspension was diluted with EtOAc (5 ml) and filtered. After removal of solvent under reduced pressure, the residue was purified by silica gel chromatography ($CHCl_3$) to give **3** (0.07 g, 65%) as a mixture of diastereomeres. Re-chromatography on SiO_2 (hexane:EtOAc, 30→1) separate of **3a** (0.04 g, 60% relative to initial diastereomeric mixture **3**. Methyl 3-oxo-3′*S*-(chloromethyl)-4′*R*-(nitromethyl)spiro[2(1′)*R*-cyclopentane]-dihydrobetulonate (**3a**): White solid mp = 160–162 °C (EtOH), $[\alpha]_D^{20}$ + 30.30 (*c* 1.12, $CHCl_3$). IR (ν/cm^{-1}): 1760 (C=O). MS, *m/z* 654.98 [M+Na]$^+$, 670.96 [M+K]$^+$. Anal. Calcd for $C_{37}H_{58}ClNO_5$: C, 70.28; H, 9.25; Cl, 5.61; N, 2.22. Found: C, 70.03; H, 9.72; Cl, 5.66; N, 2.52. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.71, 0.95, 0.99, 1.10, 1.12 (all s, 3H each, H(25), H(26), H(27), H(24), H(23)), 0.77, 0.88 (both d, *J* = 6.0 Hz, 3H each, H(30), H(29)), 1.18 (m, 1H, H^a(15)), 1.19 (m, 1H, H^a(21)), 1.22 (m, 1H, H^a(12)), 1.24 (m, 1H, H^a(22)), 1.36 (m, 1H, H^a(11)), 1.37 (m, 1H, H^a(16), 1H, H^b(15); 2H, H(5)), 1.39 (m, 1H, H(18)), 1.43 (m, 2H, H(6)), 1.44 (m, 2H, H(7)), 1.50 (d, ^2J = 13.0 Hz, 1H, H^a(1)), 1.51 (m, 1H, H^b(11)), 1.56 (m, 1H, H(9)), 1.60 (m, 1H, H^a(5′)), 1.73 (m, 1H, H^b(12), 1H, H^a(2′)), 1.82 (m, 1H, H^b(20), 1H, H^b(21), 1H, H^b(22)), 2.02 (m, 1H, H^b(2′)), 2.04 (d, ^2J = 13.0 Hz, 1H, H^b(1)), 2.24 (m, 1H, H(19)), 2.25 (m, 1H, H^b(16)), 2.27 (m, 1H, H(13)), 2.43 (dd, ^2J = 13.0 Hz, ^3J = 8.0 Hz, 1H, H^b(5′)), 2.71 (sext, ^3J = 8.0 Hz, 1H, H(3′)), 3.01 (sext, ^3J = 8.0 Hz, 1H, H(4′)), 3.53 (dd, 2H, ^2J = 14.0 Hz, ^3J = 7.0 Hz, CH_2Cl), 3.67 (s, 3H, OMe), 4.46, 4.65 (both dd, ^2J = 13.0 Hz, ^3J = 8.0 Hz, 2H, CH_2NO_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.53 (C(27)), 14.69 (C(30)), 15.50 (C(26)), 15.75 (C(25)), 20.36 (C(6)), 21.87 (C(11)), 22.56 (C(24)), 22.96 (C(29)), 27.02 (C(12)), 29.58 (C(21)), 29.69 (C(15)), 29.76 (C(20)), 30.25 (C(23)), 32.00 (C(16)), 33.08 (C(7)), 37.28 (C(22)), 37.97 (C(4′)), 38.23 (C(13)), 40.46 (C(2)), 40.48 (C(8)), 42.66 (C(14)), 43.13 (C(3′)), 44.13 (C(19)), 44.45 (CH_2Cl), 45.00 (C(5′)), 45.87 (C(4)), 48.10 (C(2′)), 48.36 (C(5)), 48.83 (C(18)), 51.21 (OMe), 51.52 (C(10)), 53.21 (C(9)), 55.93 (C(1)), 56.98 (C(17)), 75.81 (CH_2NO_2), 176.81 (C(28)), 221.23 (C(3)). Benzyl 3-oxo-3′*S*-(chloromethyl)-4′*R*-(nitromethyl)spiro[2(1′)*R*-cyclopentane]-dihydrobetulonate (**4a**): White solid mp = 120–122 °C (EtOH), $[\alpha]_D^{20}$ + 37.50 (*c* 0.08, $CHCl_3$). IR (ν/cm^{-1}): 1725 (C=O). MS, *m/z* 730.40 [M+Na]$^+$, 746.37 [M+K]$^+$. Anal. Calcd for $C_{43}H_{62}ClNO_5$: C, 72.90; H, 8.82; Cl, 5.00; N, 1.98. Found: C, 72.52; H, 8.44; Cl, 5.21; N, 1.89. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.73, 0.93, 0.98, 1.09, 1.12 (all s, 3H each, H(25), H(26), H(27), H(24), H(23)), 0.88, 0.90 (both d, *J* = 6.0 Hz, 3H each, H(30), H(29)), 1.21–2.32 (m, 28H, CH, CH_2 in the betulin residue), 2.43 (dd, ^2J = 13.0 Hz, ^3J = 8.0 Hz, 1H, H(5′)), 2.71 (sext, ^3J = 8.0 Hz, 1H, H(3′)), 3.01 (sext, ^3J = 8.0 Hz, 1H, H(4′)), 3.52 (dd, ^2J = 14.0 Hz, ^3J = 7.0 Hz, 2H, CH_2Cl), 4.46, 4.64 (both dd, ^2J = 13.0 Hz, ^3J = 8.0 Hz, 2H, CH_2NO_2), 5.08–5.17 (m, 2H, OCH_2Ph); 7.32–7.37 (m, 10H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.49 (C(27)), 14.68 (C(30)), 15.37 (C(26)), 15.74 (C(25)), 20.35 (C(6)), 21.86 (C(11)), 22.55 (C(24)), 22.96 (C(29)), 27.04 (C(12)), 28.44 (C(21)), 29.46 (C(15)), 29.76 (C(20)), 30.25 (C(23)), 31.95 (C(16)), 33.07 (C(7)), 36.85 (C(22)), 37.26 (C(4′)), 37.97 (C(13)), 38.17 (C(2)), 40.46 (C(8)), 42.67 (C(14)), 43.13 (C(3′)), 44.13 (C(19)), 44.45 (CH_2Cl), 45.00 (C(5′)), 45.86 (C(4)), 48.09 (C(2′)), 48.36 (C(5)), 48.82 (C(18)), 51.51 (C(10)), 53.21 (C(9)), 55.93 (C(1)), 56.95 (C(17)), 65.65 (CH_2-Ph), 75.82 (CH_2NO_2), 128.03, 128.28, 128.47, 136.55 (Ph), 175.95 (C(28)), 221.25 (C(3)).
13. Conformations of the structures in question were calculated by the B3LYP/6-31G(d) method.[15–17] In the case of the most stable isomers, the structures were additionally optimized and the vibrational problem was solved in the B3LYP/6-311G(d,p) approximation.[18] Transition states were localized using the B3LYP/6-311G(d,p), BHandHLYP/cc-pVTZ,[19,20] and G3MP2B3[21] methods. Energy parameters of the compounds were calculated at 298 K. Nonspecific solvation by the solvent (tetrahydrofuran) was taken into account in the framework of the polarized continuum method[22] in the BHLYP/cc-pVTZ approximation. Calculations were performed using Gaussian 09 software, Revision A.01.[23]
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