Mendeleev Communications

Mendeleev Commun., 2025, **35**, 521–523

Synthesis of 3-amino triterpenes involving the $NaBH_3CN/MoCl_5$ reduction of the oxime precursors

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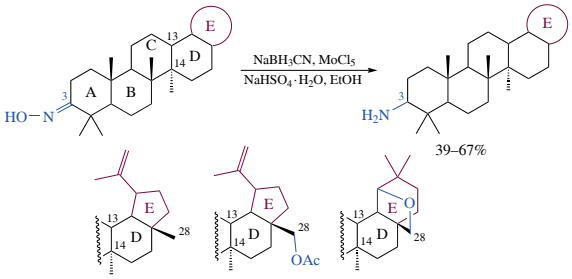
DOI: 10.71267/mencom.7744

A new efficient method for the preparation of 3-amino derivatives of pentacyclic lupane and germanicane triterpenoids, valuable precursors for the rational design of physiologically active agents, is presented. The key step involves the reduction of triterpenoid 3-oximes with sodium cyanoborohydride in the presence of molybdenum(V) chloride.



Keywords: triterpenes, betulin, allobetulin, lupane type, molybdenum(V) chloride, reduction reaction, sodium cyanoborohydride, oximes, amines.

Pentacyclic triterpenoids attract much attention due to their diverse biological activity conveniently combined with low systemic toxicity, so they are considered as new versatile platforms for the design of pharmaceutical compounds.[1] Many triterpenoids are components of medicinal plants that confer antitumour,[2] anti-inflammatory, hepatoprotective, analgesic, antimicrobial,[3] antifungal,[4] antidiabetic,[5] antioxidant, antiviral, immunomodulatory and tonic properties[6] to their extracts. The antitumour activity of triterpenoids has been confirmed in both *in vitro* and *in vivo* studies using various animal models.[7] Triterpenoids are capable of inducing apoptosis in tumour cells and cell cycle arrest in the S-phase by inhibiting DNA replication processes.[8,9] Many triterpenoid derivatives induce apoptosis of cancer cells through an intrinsic mitochondrial pathway; this is accompanied by an increase in mitochondrial membrane permeability and release of pro-apoptotic molecules from the mitochondrial intermembrane space into the cytoplasm.[10]

The poor solubility in aqueous medium and insufficient bioavailability in the gastric medium are important reasons that limit the further use of triterpene compounds in clinical practice. These properties can be improved by directed chemical modification.

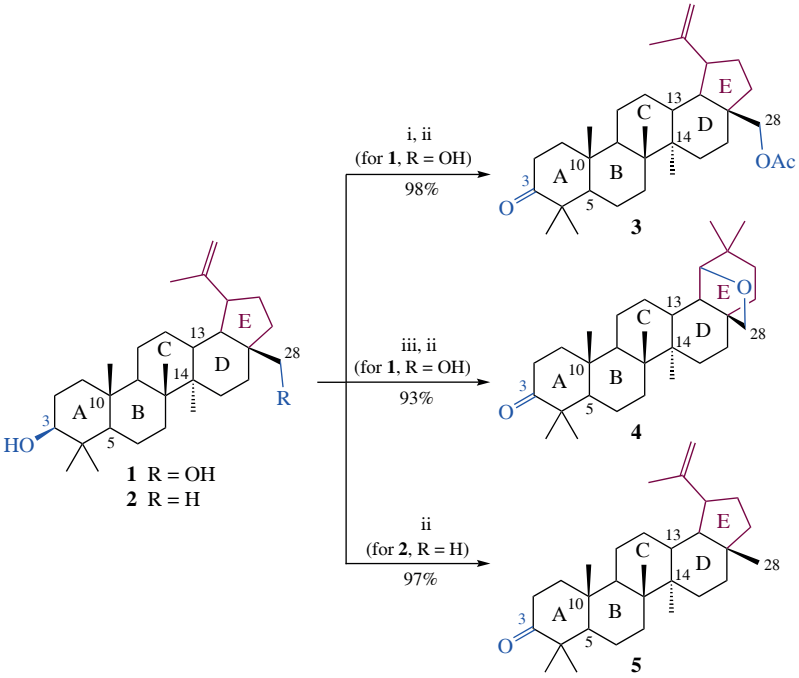
Lupane triterpenoids have a high synthetic potential due to the presence of functional groups (in rings A and E) that can be easily converted to carboxy, carbonyl, phosphate, ether or amino functions, so the derivatives thus obtained can often be considered as prodrugs.[11] The facile incorporation of functional substituents into the structure of pentacyclic triterpenoids allows their physical and pharmacokinetic characteristics to be improved. In fact, replacement of the hydroxy group at the C^3 position of ursolic acid with an amino group resulted in increased cytotoxicity against the HL-60, Bel-7402 and HeLa cell lines, with the 3-β-amino derivative of ursolic acid being more efficient by a factor of 20 than the 3-α-amino derivative.[12] Modification of betulonic acid with α,ω-amino acids and a dipeptide resulted in a number of new amides whose apoptosis-inducing effect was significantly higher than that of the starting betulonic acid.[13] Thus, the search for new methods to produce amino derivatives of triterpenoids aimed at expanding the scope of synthetic methods for directed design of practically important substances and materials remains a current challenge.

The majority of approaches for synthesizing 3-amino triterpenoids reported to date employ a method based on the reduction of oximes with sodium cyanoborohydride in the presence of titanium(III) chloride in concentrated hydrochloric acid.[14,15] This method has significant drawbacks: the synthesis duration is 18 h or longer; the use of concentrated hydrochloric acid significantly restricts the range of natural compounds that can be reduced under these drastic conditions without modifying the backbone of the molecule.

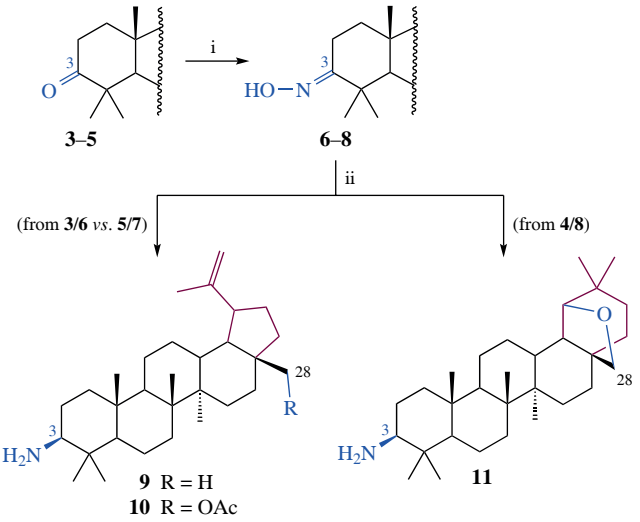
In this work, we suggested a new procedure for synthesizing 3-amino derivatives of pentacyclic triterpenoids by reduction of the corresponding oximes with sodium cyanoborohydride in the presence of molybdenum(V) chloride. This method was previously suggested for reduction of substituted aromatic oximes.[16]

Initially, based on triterpenoids betulin **1** and lupeol **2** isolated from natural sources (bark of *Betula pendula* birch), we synthesized their functional derivatives: 28-acetylbetulone **3**, allobetulone **4** (a product of primary isomerization of betulin followed by oxidation) and lupenone **5** (Scheme 1).

Further, the reaction of 3-keto derivatives of triterpenoids **3**–**5** with hydroxylamine resulted in oximes **6**–**8** in 74–89% yields (Scheme 2). The final stage of the synthesis of amino triterpenoids involved the reduction of the oximes with sodium cyanoborohydride in the presence of molybdenum(V) chloride and



Scheme 1 *Reagents and conditions*: i, Ac_2O, DMAP; ii, PDC, CH_2Cl_2; iii, CF_3CO_2H.



Scheme 2 *Reagents and conditions*: i, $NH_2OH \cdot HCl$, Py; ii, $NaBH_3CN$, $MoCl_5$, $NaHSO_4 \cdot H_2O$, EtOH.

excess sodium hydrosulfate monohydrate in ethanol. The use of anhydrous ethanol and an inert medium are important conditions for the successful implementation of this approach, since molybdenum(V) chloride is easily hydrolyzed. The reaction occurs on heating for 4 h to give amino triterpenoids **9**–**11** as mixture of 3α- and 3β-epimers with significant predominance of the latter (the ratio of isomers for amine **9** is 1 : 3, for **10** is 1 : 5, for **11** is 1 : 4). Some of the known techniques can be used to separate the α- and β-isomers: chromatographic separation on silica gel in the $CHCl_3$/MeOH[17] and CH_2Cl_2/MeOH/NH_4OH[18] systems, or separation using their *N*-Boc derivatives.[15] We have found that the chromatographic separation of *N*-Boc derivatives of 3-aminotritepenoids gave the best results.

The successful completion of each stage in the suggested approach can be conveniently monitored by NMR (see Online Supplementary Materials, Figure S1). The differences in the ^{1}H NMR spectra of 3β-hydroxy-28-acetoxylup-20(29)-ene and products of its transformation 3, 6 and 10 in the region of δ 2.1–4.8 ppm are diagnostic. These signals correspond to the resonances for the protons at carbon atoms with functional groups (C^3, C^{28}) and the protons at C^{19} and C^{20}=$C^{29}H_2$. The oxidation of 3-hydroxy triterpenoids to 3-oxo derivatives results in the disappearance of the signal at C^3 in the δ 3.1 ppm region (see Figure S1, part *c*). Upon incorporating an oxime group, a downfield shift of the proton signal at C^2 to the δ 2.75 ppm region is observed. Reduction of oximes gives rise to appearance of a signal at C^3 in the δ 2.15 ppm region (part *d*). The invariability of the positions of the signals corresponding to the internal rings (B, C, D) of the triterpenes in the ^{1}H and ^{13}C NMR spectra indicates that the pentacyclic structure is preserved under these experimental conditions.

To conclude, a new convenient access to 3-amino derivatives of lupane and germanicane triterpenoids involving the reduction of the corresponding 3-oximes with the $NaBH_3CN/MoCl_5$ reagent system at the key step is suggested.

A. A. Shalina and L. R. Idrisova acknowledge the State Program in the field of scientific activities (FZSM-2023-0018) (synthesis of 3-aminotriterpenes) and the Kazan Federal University Strategic Academic Leadership Program (PRIORITY-2030). A. V. Nemtarev and V. F. Mironov acknowledge the Ministry of Science and Higher Education of the Russian Federation (government assignment for FRC Kazan Scientific Center of RAS, synthesis of 3-oxo triterpenes). T. I. Abdullin acknowledges the Russian Science Foundation (grant no. 20-73-10105, synthesis of allobetulone, allobetulone oxime and 3-amino-28-acetoxylup-20(29)-ene). The measurements have been carried out using the equipment of the Distributed Spectral-Analytical Center of Shared Facilities for the Study of Structure, Composition and Properties of Substances and Materials of the FRC Kazan Scientific Center of

† *General procedure for the synthesis of 3-β-aminotriterpenes* **9**–**11**. Reagents $NaBH_3CN$ (0.03 g, 4 mmol), $MoCl_5$ (0.03 g, 1 mmol) and $NaHSO_4 \cdot H_2O$ (0.04 g, 3 mmol) were successively added to a triterpenoid oxime **6**–**8** (1 mmol) in absolute ethanol (5 ml). The mixture was stirred under argon for 4 h at 80 °C. The reaction completion was monitored by TLC (light petroleum/EtOAc = 1 : 1), after which 5% $NaHCO_3$ solution (30 ml) was added, then the mixture was extracted with CH_2Cl_2 (2×40 ml) and dried over Na_2SO_4. Column chromatography in the CH_2Cl_2 : 5 N NH_3 (in MeOH) (95 : 5 v/v) system (R_f = 0.3) gave the target compounds.

the Russian Academy of Sciences and Interdisciplinary Centre for Shared Use of Kazan Federal University.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7744.

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Received: 7th February 2025; Com. 25/7744