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Synthesis of terminal acetylenes using $POCl_3$ in pyridine as applied to natural triterpenoids

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Four new triterpenoids with alkyne moieties have been synthesized by the proposed procedure; among them, 3β,28-dihydroxy-29-norlup-20(30)-yne has demonstrated antiviral activity against papilloma virus and HCV replicon.

The appearance of synthetic approaches to the design of new acetylenic structures, which are based on cross-coupling reactions catalyzed by transition metal complexes, has revolutionized the assembling of acetylene-containing systems and ensembles.[1,2]

Recently, the alkyne moiety became one of the most commonly used substituents in the design of new medicinal agents.[3] A high biological activity of acetylenic metabolites isolated from a wide variety of plant species, cultures of higher fungi, and marine invertebrates has been established.[4]

A classical route to acetylenes based on the reaction of aldehydes or ketones with phosphorus halides involves formation of *gem*-dichlorides or vinyl chlorides as by-products.[5] To overcome this shortage, we propose a new efficient pathway to terminal acetylenes by the reaction of methyl ketones with phosphorus oxychloride in pyridine.

As a starting material, we used the derivatives of natural lupane triterpenoid betulin **1** as a helpful platform for the discovery of new biologically active compounds, for example, with antiviral, anticancer and immunomodulating properties.[6] Only a few tertiary acetylenic alcohols of the triterpenoid family (derived from 3-ketoglycyrrhetic acid)[7] and betulonic acid–acetylene hybrids with hepatoprotective and anti-inflammatory activities[8] have been described.

At first, methyl ketones **2**, **3**, **6** and **7** were synthesized by ozonolysis of isopropenyl groups of betulin acetoxy derivatives and 2-cyano-3,4-secotriterpenoids **4** and **5** (Scheme 1).

Then, the reaction of 3β,28-diacetoxy-20-oxo-29-norlupane **2** with $POCl_3$ in pyridine under reflux[†] led to the formation of 3β,28-diacetoxy-29-norlup-20(30)-yne **8**[‡] in 78% yield. Most probably, the reaction occurs through the stage of C(20)-*gem*-dichloro derivative with following elimination of two HCl molecules to form a pyridinium salt and an ethynyl fragment in the C20(30) position. When phosphorus pentachloride in pyridine was used for reaction with **2** according to a published procedure,[5] the yield of **8** after purification was not higher than 55%.

The reaction of 3β-acetoxy-28-hydroxy-20-oxo-29-norlupane **3** with $POCl_3$ in pyridine led to compound **9**[§] with a terminal ethynyl group. In this case, the participation of C(28) hydroxy group in the Wagner–Meerwein rearrangement giving 22(17→28)-*abeo*-lupene fragment under the action of $POCl_3$ in pyridine was also observed. The structures of compounds **8** and **9** were found from X-ray crystal analysis[¶] (Figures 1 and 2).

Triterpenoid **10**[††] with both ethynyl and cyano groups in cycle A was synthesized from 3-azanylidyne-19β,28-epoxy-4,28-dioxo-3,4-seco-23-noroleane **6** with good yield. When methyl 3-azanylidyne-3,4-seco-23,29-dinorlup-4,20-dioxo-28-oate **7** was taken for the reaction with $POCl_3$ in pyridine, derivative **11**[‡‡] with bis(ethynyl) architecture was obtained. The NMR spectra of triterpenoids **8**–**11** consist of characteristic doublets of acetylene proton at δ 2.03–2.08 ppm, the signals of C20(30)

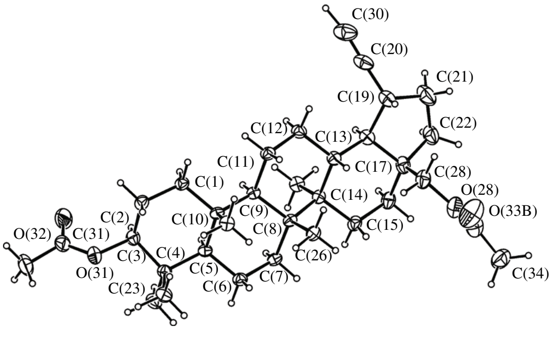
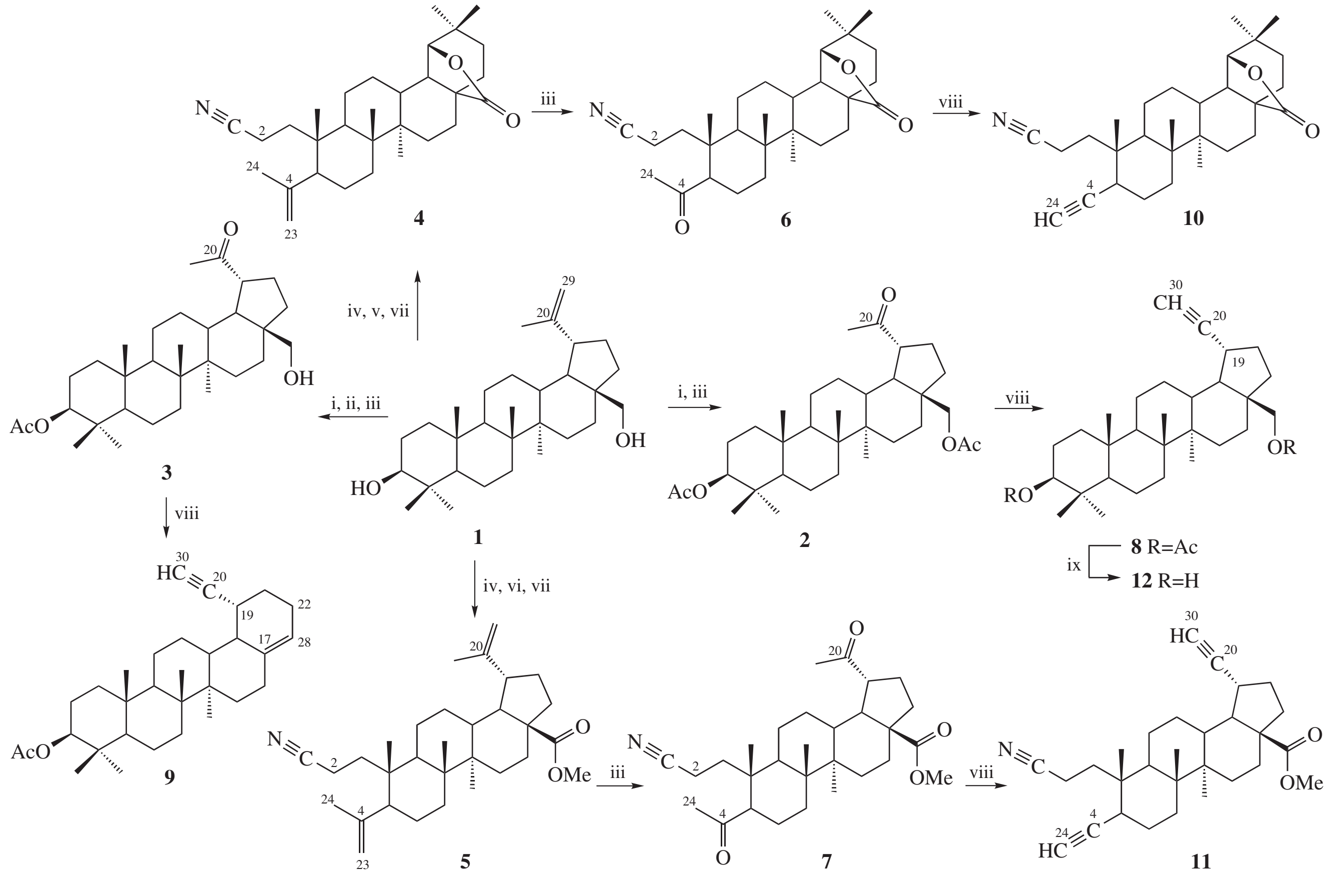


Figure 1 Molecular structure of compound **8**.

[†] *General procedure for the synthesis of compounds* **8**–**11**: freshly distilled $POCl_3$ (4–6 ml) was added to a solution of triterpenoids **4**–**7** (1 mmol) in anhydrous pyridine (10–15 ml). The reaction mixture was refluxed with a backflow condenser for 3 h and carefully poured out on ice (50 g). The precipitate was filtered off, washed with water and dried. The product was purified by column chromatography and crystallized from benzene.

[‡] *3β,28-Diacetoxy-29-norlup-20(30)-yne* **8**: yield 78%, mp 198–200 °C, $[\alpha]_D^{20}$ –33 (*c* 2.60, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ: 0.80, 0.81, 0.82, 0.87, 0.93 (5s, 15H, 5Me), 1.15–1.85 (m, 25H, CH, CH_2), 1.99 and 2.01 (2s, 6H, OAc), 2.03 (d, 1H, 30-H, *J* 2.2 Hz), 3.65 and 4.15 (2d, 2H, 28-H, *J* 7 Hz), 4.42–4.50 (m, 1H, 3-H). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 171.1, 170.7, 89.8 (20-C), 80.6 (3-C), 68.6 (30-C), 62.0 (28-C), 55.2, 53.8, 49.9, 45.9, 42.5, 40.7, 38.2, 37.6, 36.9, 36.9, 33.9, 30.8, 29.6, 29.4, 27.8, 26.7, 26.4, 23.5, 21.1, 21.1, 20.8, 20.5, 18.0, 16.3, 15.9, 15.8, 14.4. Found (%): C, 77.48; H, 9.97. Calc. for $C_{33}H_{50}O_4$ (%): C, 77.60; H, 9.87.

[§] *3β-Acetoxy-22(17→28)-*abeo*-29-norlup-17(28)-en-20(30)-yne* **9**: yield 73%, mp 232–234 °C, $[\alpha]_D^{20}$ –13.8 (*c* 3.00, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ: 0.84, 0.86, 0.87, 0.94, 1.05 (5s, 15H, 5Me), 1.20–1.74 (m, 23H, CH, CH_2), 2.05 (1s, 3H, OAc), 2.08 (d, 1H, 30-H, *J* 2.3 Hz), 2.50 (m, 1H, 19-H), 4.45 (dd, 1H, 3-H, *J* 5.5 and 10.5 Hz), 5.40 (br. s, 2H, 28-H). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 170.9, 140.1 (28-C), 118.0 (17-C), 89.9 (20-C), 80.9 (3-C), 68.0 (30-C), 55.4, 50.3, 45.4, 43.9, 42.3, 40.9, 38.5, 37.7, 37.0, 34.0, 33.7, 32.6, 28.4, 27.9, 26.7, 26.4, 23.7, 22.7, 21.3, 21.0, 18.2, 16.5, 16.3, 15.2, 14.6. Found (%): C, 82.88; H, 10.07. Calc. for $C_{31}H_{46}O_2$ (%): C, 82.61; H, 10.29.



Scheme 1 *Reagents and conditions*: i, Ac_2O; ii, 0.1 N NaOH/EtOH; iii, O_3, CH_2Cl_2; iv, Jones' oxidation; v, HCOOH; vi, CH_2N_2/Et_2O; vii, $NH_2OH{\cdot}HCl$/EtOH, *p*-$TsCl/C_5H_5N$; viii, $POCl_3/C_5H_5N$; ix, 5% KOH/EtOH.

and C4(24) carbon atoms were observed at δ 89–90 (68) and 84–85 (65–70) ppm, respectively.

The synthetic value of compounds **8–11** with the ethynyl group is determined by a high acidity of the HC≡C– fragment, which makes it possible to carry out both the functionalization of the molecule and the formation of new C–C bonds.

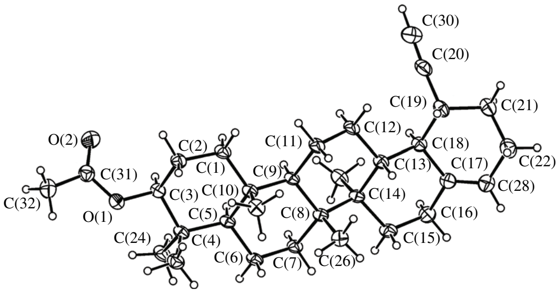


Figure 2 Molecular structure of compound **9**.

[¶] *Crystallographic data for* **8**: $C_{33}H_{50}O_4$, $M = 510.73$, orthorhombic, space group $P2_12_12_1$, at 296 K: $a = 7.1694(10)$, $b = 17.062(2)$ and $c = 24.700(3)$ Å, $V = 3021.5(7)$ Å^3, $Z = 4$, $d_{calc} = 1.123$ g cm^{-3}, μ(MoKα) = 0.72 cm^{-1}, $F(000) = 1120$. Intensities of 36611 reflections ($R_{int} = 0.0768$) and 7504 independent reflections were measured with a Bruker AXS SMART APEX II CCD diffractometer [λ(MoKα) = 0.71073 Å, graphite monochromator, ω and φ-scans, $2.39° \leq \theta \leq 28.55°$], and 7504 independent reflections were used in the further refinement. Final *R* values are $R_1 = 0.0540$, $wR_2 = 0.1031$ for 3530 observed reflections with $I > 2\sigma(I)$, and $R_1 = 0.1475$, $wR_2 = 0.1315$, GOF on $F^2 = 0.954$ for all independent reflections.

Crystallographic data for **9**: $C_{31}H_{46}O_2$, $M = 450.68$, monoclinic, space group $P2_1$, at 296 K: $a = 12.5132(5)$, $b = 7.4096(2)$ and $c = 14.7627(5)$ Å, $\beta = 109.761(2)°$, $V = 1288.16(8)$ Å^3, $Z = 2$, $d_{calc} = 1.162$ g cm^{-3}, μ(CuKα) = 5.32 cm^{-1}, $F(000) = 496$. Intensities of 8416 reflections ($R_{int} = 0.0312$) and 2754 independent reflections were measured with a Bruker AXS KAPPA APEX II CCD detector [λ(CuKα) = 1.54178 Å, graphite monochromator, ω and φ-scans, $6.21° \leq \theta \leq 66.92°$]. Final *R* values are $R_1 = 0.0426$, $wR_2 = 0.1097$ for 2576 observed reflections with $I > 2\sigma(I)$, and $R_1 = 0.0453$, $wR_2 = 0.1128$, GOF on $F^2 = 1.035$ for all independent reflections.

The structures were solved by a direct method and refined by the least-squares technique firstly in the isotropic, and secondly in the anisotropic approximation. The positions of hydrogen atoms were calculated on the basis of stereochemical criteria and refined in the riding model. The absolute configurations of molecules in the crystal were not determined. All calculations were performed using the SHELXTL v.6.12 and the WinGX 1.64.05 programs.

CCDC 735896 and 735897 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2010.

[††] *3-Azanylidyne-19β,28-epoxy-28-oxo-3,4-seco-23-norolean-4(24)-yne* **10**: yield 87%, mp 271–275 °C, $[\alpha]_D^{20}$ +127 (*c* 0.2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.89, 0.95, 0.95, 0.97, 1.03, (5s, 15H, 5Me), 1.08–1.97 (m, 21H, CH, CH_2), 2.08 (d, 1H, 24-H, *J* 2.3 Hz), 2.16–2.20 (m, 1H, 5-H), 2.29–2.32 (t, 2H, 2-H, *J* 4.9 and 2.5 Hz), 3.94 (s, 1H, 19-H). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 179.6 (28-C), 120.1 (3-C), 85.8 (19-C), 84.8 (4-C), 65.8 (24-C), 46.5, 46.0, 40.3, 40.3, 40.1, 38.5, 36.8, 35.8, 35.1, 33.5, 32.2, 31.8, 31.3, 28.7, 27.6, 25.7, 25.4, 25.1, 23.9, 21.9, 18.9, 15.3, 13.3, 11.5. Found (%): C, 80.03; H, 9.35; N, 3.35. Calc. for $C_{29}H_{41}NO_2$ (%): C, 79.95; H, 9.49; N, 3.22.

[‡‡] *Methyl 3-azanylidyne-3,4-seco-23,29-dinorlup-4(24),20(30)-diyn-28-oate* **11**: yield 76%, mp 138–141 °C, $[\alpha]_D^{20}$ –150 (*c* 0.25, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.93, 0.95, 0.95 (3s, 9H, 3Me), 1.07–1.94 (m, 21H, CH, CH_2), 2.06 (d, 1H, 30-H, *J* 1.4 Hz), 2.07 (d, 1H, 24-H, *J* 2.2 Hz), 2.10–2.17 (m, 1H, 5-H), 2.21–2.26 (t, 2H, 2-H, *J* 6.9 and 7.1 Hz), 2.94–3.04 (m, 1H, 19-H), 3.64 (s, 3H, OMe). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 176.0 (28-C), 120.0 (3-C), 90.4 (20-C), 85.0 (4-C), 70.8 (24-C), 68.2 (30-C), 55.9, 54.6, 51.4, 42.7, 40.2, 39.7, 38.1, 37.9, 37.0, 36.2, 35.4, 31.9, 31.6, 31.5, 29.5, 29.4, 26.2, 25.3, 21.9, 18.4, 14.4, 14.4, 11.6. Found (%): C, 80.25; H, 9.00; N, 3.32. Calc. for $C_{29}H_{39}NO_2$ (%): C, 80.33; H, 9.07; N, 3.23.

Note that 3β,28-dihydroxy-29-norlup-20(30)-yne **12** demonstrated a high antiviral activity against papilloma virus (strain HPV-11; SI 30), whereas it was not active against viruses of respiratory panel [Adeno, Flu A (H1N1, H3N2, H5N1), Flu B, SARS, Rhinovirus Type 2].[§§] Compound **12** has low toxicity ($CC_{50} > 100$ μM) and no influence on HBV DNA replication at 10 μM concentration, and it was active against HCV replicon ($SI_{90} > 1.19$). To our knowledge, this is the first example of the antiviral activity of synthetic triterpenoids against papilloma virus.

In conclusion, the interaction of methyl ketones with phosphorus oxychloride in pyridine is an efficient method for the synthesis of terminal acetylenes, including those of triterpenoid family. The method has such advantages as a short-stage route, a simple experimental procedure and no by-product formation.

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References

1 E. Negishi and L. Anastasia, *Chem. Rev.*, 2003, **103**, 1979.

2 B. A. Trofimov and N. K. Gusarova, *Usp. Khim.*, 2007, **76**, 550 (*Russ. Chem. Rev.*, 2007, **76**, 507).

3 (*a*) J. E. Moses and A. D. Moorhouse, *Chem. Soc. Rev.*, 2007, **36**, 1249; (*b*) R. Chinchilla and C. Najera, *Chem. Rev.*, 2007, **107**, 874; (*c*) M. Meldal and C. W. Tornoe, *Chem. Rev.*, 2008, **108**, 2952.

4 V. M. Dembitsky and D. O. Levitsky, *Nat. Prod. Commun.*, 2006, **1**, 405.

5 C. M. Wong and T.-L. Ho, *Synth. Commun.*, 1974, **4**, 25.

6 (*a*) G. A. Tolstikov, E. E. Shults, L. A. Baltina and T. G. Tolstikova, *Khimiya v Interesakh Ustoichivogo Razvitiya*, 1997, **5**, 57 (*Chem. Sustainable Dev.*, 1997, **5**, 57); (*b*) G. A. Tolstikov, E. E. Shults, L. A. Baltina, T. G. Tolstikova and O. B. Flekhter, *Khimiya v Interesakh Ustoichivogo Razvitiya*, 2005, **13**, 1 (*Chem. Sustainable Dev.*, 2005, **13**, 1); (*c*) P. A. Krasutsky, *Nat. Prod. Rep.*, 2006, **23**, 919; (*d*) P. Dzubak, M. Hajduch, D. Vydra, A. Hustova, M. Kvasnicsa, D. Biedermann, L. Markova, M. Urban and J. Sarek, *Nat. Prod. Rep.*, 2006, **23**, 394; (*e*) G. A. Tolstikov, L. A. Baltina, V. P. Grankina, R. M. Kondratenko and T. G. Tolstikova, *Licorice: Biodiversity, Chemistry and Application in Medicine*, Academic Publishing House 'Geo', Novosibirsk, 2007.

7 G. A. Tolstikov, M. I. Goryaev and L. F. Tolstikova, *Dokl. Akad. Nauk*, 1967, **5**, 1110 (in Russian).

8 S. F. Vasilevsky, A. I. Govdi, E. E. Shults, M. M. Shakirov, I. V. Sorokina, T. G. Tolstikova, D. S. Baev, G. A. Tolstikov and I. V. Alabugin, *Bioorg. Med. Chem.*, 2009, **17**, 5164.

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[§§] The protocols and explanations of the test results are available at the AACF website (www.niaid-aacf.org).