Mendeleev Communications

Mendeleev Commun., 2025, **35**, 57–59

Diels–Alder adduct of levoglucosenone and isoprene in the syntheses of the key synthon for loganin

Liliya Kh. Faizullina,*[a] Yuliya A. Khalilova,[a] Marsel G. Yalalov,[b] Artur R. Tagirov,[c] Shamil M. Salikhov,[a] El'za M. Minnibaeva[b] and Farid A. Valeev[a]

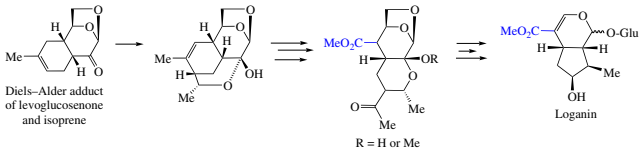
[a] *Ufa Federal Research Centre of the Russian Academy of Sciences, 450054 Ufa, Russian Federation. E-mail: sinvmet@anrb.ru*

[b] *Institute of Chemistry and Protection in Emergency Situations, Ufa University of Science and Technology, 450076 Ufa, Russian Federation*

[c] *Ufa State Petroleum Technical University, 450064 Ufa, Russian Federation*

DOI: 10.71267/mencom.7537

Based on the hemiketal obtained by the carbonyl ene-ketalization of the Diels–Alder adduct of levoglucosenone and isoprene with acetaldehyde, two methods have been suggested for incorporating the carboxy group of loganin at the pyran ring. The first method involved one-pot conversion employing ozonolytic cleavage of the double bond, ozonide reduction, *in situ* aldehyde oxidation and esterification. An alternative five-step sequential conversion of the ketal, with isolation and identification of intermediate compounds, involved ketalization, Wagner *vic*-hydroxylation of the double bond, periodate cleavage of diols, *in situ* oxidation of the aldehyde to an acid, and esterification.

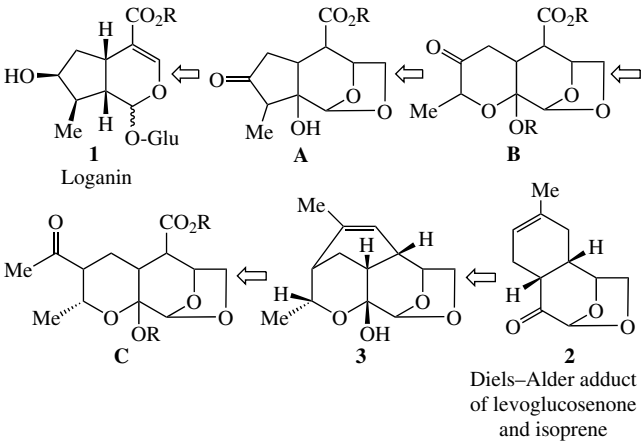


Keywords: levoglucosenone, loganin, Diels–Alder adduct, Wagner *vic*-hydroxylation, periodate cleavage, oxidation.

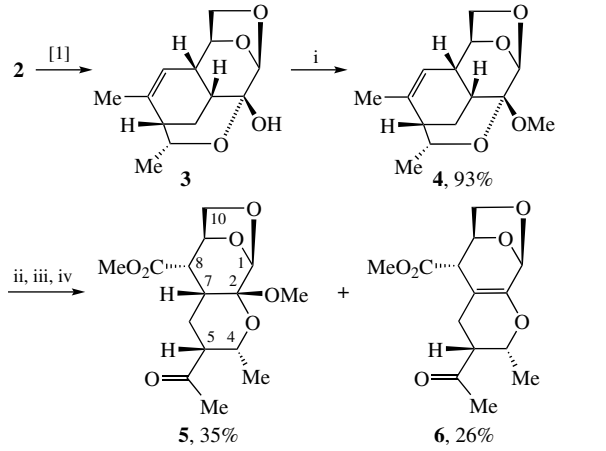
Diels–Alder adducts of levoglucosenone and 1,3-dienes react with aldehydes to give products of the ene reaction, *i.e.* alcohols, whose hydroxy group then adds to the keto group in intramolecular manner to afford a cyclic hemiketal.[1,2] In this process, the double bond undergoes a 1,2-shift, thus opening new prospects for employing the compound obtained as a chiral matrix. In this case, it appears that the use of products of the ene reaction, *i.e.* ketalization, in the synthesis of cyclopentanoids (known to be a broad family of biologically active natural products) is the most attractive approach. Of these compounds, monoterpene iridoid loganin **1**, which is a key precursor in the biogenetic synthesis of a number of indole alkaloids,[3,4] is of continuing interest. Loganin **1** itself possesses antidiabetic, anti-inflammatory (arthritis and acute renal failure), and neuroprotective (Alzheimer's and Parkinson's diseases) effects.[5–8] To date, many approaches to the synthesis of loganin **1** have already been developed. Its total syntheses[9–17] are also known and have become classical.

The retrosynthetic sequence based on the use of the product of the ene reaction, *i.e.* ketalization of the Diels–Alder adduct of levoglucosenone and isoprene **2**,[18,19] is shown in Scheme 1. According to the retrosynthetic scheme, cleavage of the double bond in compound **3**, the product of the ene reaction of the Diels–Alder adduct of levoglucosenone and isoprene with acetaldehyde,[1,2] would allow the incorporation of the carboxy group of loganin at the pyran ring **C**. It is intended to use the Bayer–Villiger oxidation, deoxygenation and aldol condensation steps in order to create the methylcyclopentane moiety **A**, while the steps of 1,6-anhydro bridge opening and reaction involving hydroxy groups would complete the synthesis of the loganin aglycone (Scheme 1).

Ozonolysis seems to be an obvious way to cleave the double bond. However, taking into account the facts that ozonolytic cleavage of the double bond in Diels–Alder adducts of levoglucosenone and 1,3-dienes is complicated by the formation of a number of products in low yields,[20,21] hemiketal **3** was converted to ketal **4** (Scheme 2). Then one-pot conversion of olefin **4** into methyl ester **5** was carried out. Ozonolysis of the double bond in ketal **4** at –50 °C in CH_2Cl_2 followed by reduction of peroxide ozonolysis products with Me_2S, Jones oxidation of the intermediate aldehyde to the acid and esterification with CH_2N_2 gave the desired ester **5** in 35% yield over the three steps. In addition, enol ether **6** was isolated from the reaction mixture in 26% yield (see Scheme 2). It should be noted that with an



Scheme 1



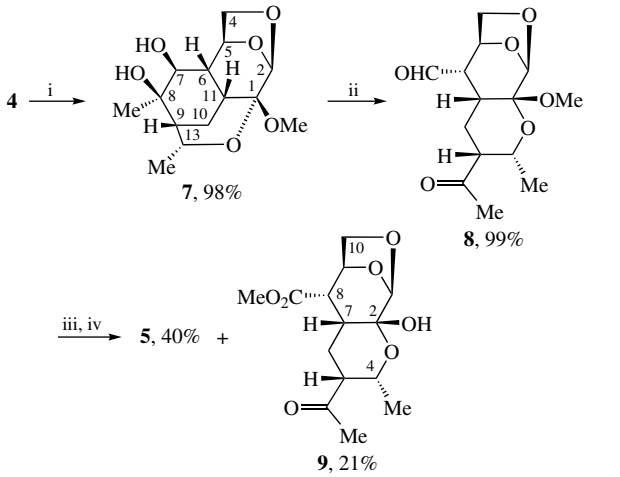
Scheme 2 *Reagents and conditions*: i, HCl/MeOH, 0–25 °C, 2 h; ii, O_3, CH_2Cl_2, –50 °C, 15 min, Me_2S, –78 °C, 15 min; iii, Jones reagent, 0 °C, 10 min; iv, CH_2N_2, room temperature, 10 min.

excess of the Jones reagent, the yield of compound **6** increased to 38%, while the yield of the target ester **5** became 21%.

The HMBC spectrum of ester **5** showed H^4/C^2, H^{10}/C^1, $H^8/C^{C=O}$ and H^{OMe}/C^2 correlation peaks, indicating the formation of methyl ester with preservation of the trioxatricyclic framework. Experiment NOE H^{10}/H^8 makes it possible to determine the relative configuration of C^8 and C^9, while NOE H^7/H^4 provided the relative configuration of C^7 and C^4. The orientation of the H^5 proton was determined from the coupling constant $^3J_{5–4}$ = 7.0 Hz.[22]

An alternative method for opening the cyclohexene ring in ketal **4** by the Wagner oxidation of the double bond with $KMnO_4$ in EtOH at 0 °C led to *vic*-diol **7** in 98% yield (Scheme 3). Periodate cleavage of glycol **7** by treatment with $NaIO_4$ resulted in keto aldehyde **8** in 99% yield. Attempts to oxidize aldehyde **8** with chromate oxidants or $KMnO_4$ to the corresponding acid for subsequent synthesis of target ester **5** yielded difficult-to-identify reaction products. The desired ester **5** was obtained by the reaction with Br_2. Hemiketal **9**, a hydrolysis product of ketal **5**, was isolated from the reaction mixture. Both products appear interesting for further transformations. Though additional steps were introduced, the second method of incorporating a carboxy group is more convenient and allows the yield of the target synthon **C** to be improved.

The proton of the hydroxy group at C^7 of diol **7** manifests itself as a signal at 4.40 ppm in ^{1}H NMR spectrum with a coupling constant of 9.3 Hz. Its carbon is detected at 71.58 ppm



Scheme 3 *Reagents and conditions*: i, $KMnO_4$, EtOH, H_2O, 0 °C, 30 min; ii, $NaIO_4$, room temperature, 1 h; iii, Br_2, 1,4-dioxane, H_2O, room temperature, 1 h; iv, CH_2N_2, room temperature, 15 min.

in the ^{13}C NMR spectrum. The presence of H^{4A}/H^6, H^{4A}/H^{11}, H^7/H^5 and H^7/H^{Me} correlation peaks in the NOESY spectrum is a result of the *S*-configuration of the C^7 center and the *R*-configuration of the C^6, C^8 and C^{11} centers. The H^{13}/C^1 and H^{OMe}/C^1 correlation peaks are observed in the HMBC spectrum, indicating the preservation of the original trioxatetracyclic system. The *S*-configuration of the C^8 center in hemiketal **9** was determined from the NOE effect between the H^8 and H^{10} protons and the coupling constant value of $^3J_{8,7}$ 5.1 Hz. The H^4/C^2 and H^{OMe}/C^2 correlation peaks are observed in the HMBC spectrum, indicating the preservation of the trioxatricyclic framework and the spatial orientation of the OH group (δ_H 5.57) in the C^2 position.

To summaruze, two methods for the preparation of the key synthon for the synthesis of loganin were developed. They are based on the product of the ene ketalization of the Diels–Alder adduct of levoglucosenone and isoprene. The first method of incorporating the carboxy group of loganin at the pyran ring involves a one-pot transformation through the steps of ozonolytic cleavage of the double bond, ozonide reduction by Me_2S, oxidation of the intermediate aldehyde to the acid, and esterification. The alternative sequential transformation of the hemiketal consists of ketalization, the Wagner *vic*-hydroxylation, periodate cleavage, oxidation, and esterification.

This work was carried out under subjects nos. 122031400259-1 and 122031400282-9 of the government assignment. The authors are grateful to the Circa Group who provided industrial grade levoglucosenone. NMR spectra were recorded using the equipment of the Center for Collective Use of Scientific Equipment ‘Chemistry’ and the Regional Center for Collective Use ‘Agidel’ of the Ufa Institute of Chemistry of the Russian Academy of Sciences.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7537.

References

1 L. Kh. Faizullina, A. R. Tagirov, Sh. M. Salikhov and F. A. Valeev, *Mendeleev Commun.*, 2022, **32**, 100; https://doi.org/10.1016/j.mencom.2022.01.032.
2 L. Kh. Faizullina, A. R. Tagirov, Sh. M. Salikhov and F. A. Valeev, *Mendeleev Commun.*, 2023, **33**, 9; https://doi.org/10.1016/j.mencom.2023.01.002.
3 A. I. Scott, *Acc. Chem. Res.*, 1970, **3**, 151; https://doi.org/10.1021/ar50029a002.
4 J. J. Partridge, N. K. Chaddha and M. R. Uskokovic, *J. Am. Chem. Soc.*, 1973, **95**, 532; https://doi.org/10.1021/ja00783a037.
5 C. J. Coscia, R. Guarnaccia and L. Botta, *Biochemistry*, 1969, **8**, 5036; https://doi.org/10.1021/bi00840a054.
6 R. Guarnaccia, L. Botta and C. J. Coscia, *J. Am. Chem. Soc.*, 1974, **96**, 7079; https://doi.org/10.1021/ja00829a041.
7 R. Benkrief, A.-L. Skaltsounis, F. Tillequin, M. Koch and J. Pusset, *J. Nat. Prod.*, 1991, **54**, 532; https://doi.org/10.1021/np50074a028.
8 F. Zhang, Y. Yan, J. Zhang, L. Li, Y.-W. Wang, C.-Y. Xia, W.-W. Lian, Y. Peng, J. Zheng, J. He, J.-K. Xu and W.-K. Zhang, *Phytother. Res.*, 2022, **36**, 2272; https://doi.org/10.1002/ptr.7347.
9 G. Buechi, J. A. Carlson, J. E. Powell, Jr. and L. F. Tietze, *J. Am. Chem. Soc.*, 1970, **92**, 2165; https://doi.org/10.1021/ja00710a078.
10 G. Buechi, J. A. Carlson, J. E. Powell and L. F. Tietze, *J. Am. Chem. Soc.*, 1973, **95**, 540; https://doi.org/10.1021/ja00783a038.
11 J. J. Partridge, N. K. Chadha, S. Faber and M. R. Uskoković, *Synth. Commun.*, 1971, **1**, 233; https://doi.org/10.1080/00397917108082702.
12 L. F. Tietze, *J. Am. Chem. Soc.*, 1974, **96**, 946; https://doi.org/10.1021/ja00810a067.
13 G. Kinast and L. F. Tietze, *Chem. Ber.*, 1976, **109**, 3626; https://doi.org/10.1002/cber.19761091116.
14 M. Nakane and C. R. Hutchinson, *J. Org. Chem.*, 1980, **45**, 4233; https://doi.org/10.1021/jo01309a037.

15 M. Demuth, S. Chandrasekhar and K. Schaffner, *J. Am. Chem. Soc*., 1984, **106**, 1092; https://doi.org/10.1021/ja00316a046.
16 T. Ikeda, S. Yue and C. R. Hutchinson, *J. Org. Chem.*, 1985, **50**, 5193; https://doi.org/10.1021/jo00225a042.
17 H.-M. Tai, M.-Y. Chang, A.-Y. Lee and N.-C. Chang, *J. Org. Chem.*, 1999, **64**, 659; https://doi.org/10.1021/jo9817624.
18 M. S. Miftakhov, I. N. Gaisina and F. A. Valeev, *Russ. Chem. Bull.*, 1996, **45**, 1942; https://doi.org/10.1007/BF01457782.
19 A. M. Sarotti, A. G. Suárez and R. A. Spanevello, *Tetrahedron Lett*., 2011, **52**, 3116; https://doi.org/10.1016/j.tetlet.2011.04.021.
20 F. A. Valeev, I. N. Gaisina, Kh. Kh. Gainullin, L. V. Spirikhin and M. S. Miftakhov, *Russ. J. Org. Chem.*, 1997, **33**, 331; https://elibrary.ru/leeayb.
21 I. M. Biktagirov, L. Kh. Faizullina, Sh. M. Salikhov, M. G. Safarov and F. A. Valeev, *Russ. J. Org. Chem.*, 2015, **51**, 1457; https://doi.org/10.1134/S1070428015100188.
22 Yu. M. Volovenko, V. G. Kartsev, I. V. Komarov, A. V. Turov and V. P. Khilya, *Spektroskopiya yadernogo magnitnogo rezonansa dlya khimikov (Nuclear Magnetic Resonance Spectroscopy for Chemists)*, ICSPF, Moscow, 2011 (in Russian).

Received: 13th June 2024; Com. 24/7537