Available online at www.sciencedirect.com

ScienceDirect

Mendeleev Commun., 2024, **34**, 521–522

Mendeleev Communications

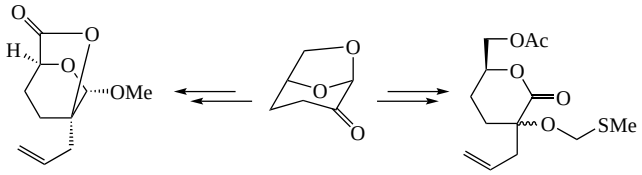
Synthesis of functional allyl-α-tetrahydropyrones from cyrene

Yuliya A. Khalilova, Liliya Kh. Faizullina, Shamil M. Salikhov and Farid A. Valeev*

Ufa Institute of Chemistry, Ufa Federal Research Centre of the Russian Academy of Sciences, 450054 Ufa, Russian Federation. E-mail: sinvmet@anrb.ru

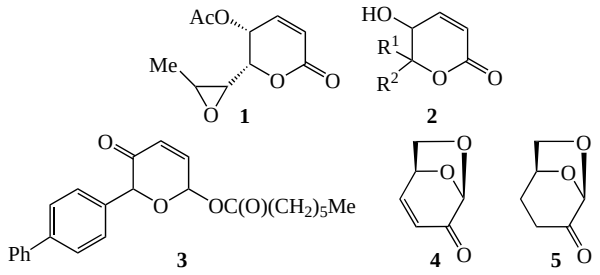
DOI: 10.1016/j.mencom.2024.06.016

Addition of allylzinc to cyrene affords diastereomeric 4-allyl-6,8-dioxabicyclo[3.2.1]octan-4-ols. Opening of their 1,6-anhydro bridge with Ac_2O followed by selective deacetylation of the resulting tertiary and acetal acetates yields diastereomeric 2-acetoxymethyl-5-allyl-tetrahydropyran-5,6-diols whose oxidation by the action of DMSO–Ac_2O system is accompanied by etherification of tertiary hydroxy groups leading to methylthiomethoxy pyrone derivatives. The opening of 1,6-anhydro bridge in 4-allyl-6,8-dioxabicyclo[3.2.1]octan-4-ols with MeOH–HCl followed by oxidation with PCC gives individual (4*S*,6*S*)-1-allyl-6-methoxy-2,5-dioxabicyclo[2.2.2]octan-3-one.



Keywords: cyrene, asperlin, 1,2-addition reaction, tetrahydropyrans, α-tetrahydropyrones, methylthiomethyl ethers.

In the 2nd half of the past century, antibiotic asperlin **1** was isolated from *Aspergillus nidulans* fungus.[1] Subsequently, synthetic analogs including compounds **2** and **3** were obtained on its basis.[2] In addition to antimicrobial properties, they showed fungicidal and antiparasitic activity, which was most pronounced in analog **3**. Comparison of the structures of asperlin **1** and levoglucosenone **4** showed that they were somewhat similar and that levoglucosenone had the structural elements required for the synthesis of asperlin **1** analogs. On the other hand, the study of biological properties of levoglucosenone **4** revealed its cytotoxic,[3] fungicidal, bactericidal,[4] anti-aggregation and anticoagulant activities.[5] Therefore, we aimed to study the transformations of the dihydro derivative of levoglucosenone, cyrene **5**, into chiral tetrahydropyran derivatives.

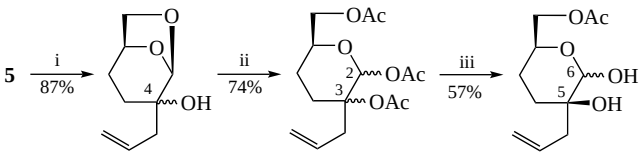


1 **2** **3** **4** **5**

Previously,[6] we obtained derivatives of cyrene **5** by modification of the pyran ring at the α-position with respect to the keto group *via* aldol transformations. Development of the synthesis of tetrahydropyran derivatives, α-tetrahydropyrones in particular, by 1,2-addition of an allylic moiety to cyrene **5** is promising in terms of the subsequent modification of the resulting compounds by the double bond for studying the structure–activity relationship. To this end, cyrene **5** was involved into the Barbier reaction with allyl bromide in the presence of zinc metal. The reaction led to diastereomeric adducts **6a**,**b** in 87% yield (Scheme 1).

In attempt to convert the 1,2-addition products **6a**,**b** to α-tetrahydropyrones, their 1,6-anhydro bridge was opened in acetic anhydride by the treatment with $ZnCl_2$.[7] Selective deacetylation of acetates **7a**,**b** was performed in acetonitrile in the presence of $BF_3 \cdot Et_2O$,[8] which preserved primary acetoxy group (see Scheme 1). Oxidation of lactols **8a**,**b** with Br_2 in a dioxane–water solution resulted in annulated tetrahydrofuran diastereomers **9a**,**b** in 36% yield (Scheme 2). The structure of bromides **9a**,**b** is manifested by the signals of the $C^{1'}$ methylene carbon atom at δ 36.41 [35.11] {δ_H 3.48–3.52 [3.43–3.55]} and of the C^2 carbon bound to oxygen at δ 75.01 [75.36]}.† The HMBC spectrum shows the H^{7a}/C^2, H^6/C^{7a} and $H^{1'}/C^3$ correlation peaks which indicate the presence of a tetrahydrofuran moiety annulated with tetrahydropyran with the H^{7a} acetal proton between them. The existence of a NOE effect between the $H^{1''}/H^{7a}$ protons in both diastereomers and between $H^{1'}/H^{7a}$ only in the main diastereomer is an evidence for the *R*-configuration of the C^{7a} center in both epimers and the *R*-configuration of the C^2 center in the main diastereomer.

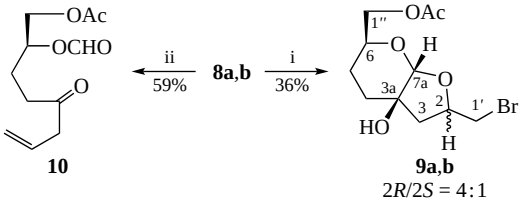
Unfortunately, all attempts to oxidize epimers **8a**,**b** with chromium reagents to produce α-pyrone function resulted in



4*R*-**6a**/4*S*-**6b** 2.5:1 | 2*R*,3*R*-**7a**/2*S*,3*R*-**7b**/ 2*R*,3*S*-**7c**/2*S*,3*S*-**7d** 20.8:7.7:1.2:1.0 | 5*R*,6*S*-**8a**/5*R*,6*R*-**8b** 1.7:1

Scheme 1 *Reagents and conditions*: i, $CH_2{=}CHCH_2Br$, Zn, DMF, 0 °C, 30 min; ii, Ac_2O, $ZnCl_2$, 0 → 25 °C, 3 h; iii, $BF_3 \cdot Et_2O$, MeCN–H_2O, 0 °C, 8 h.

† For convenience of the interpretation of NMR spectra, the numbering of atoms is given according to IUPAC rules based on the names of the compounds obtained (see Online Supplementary Materials).



Scheme 2 *Reagents and conditions*: i, Br_2, dioxane, H_2O, 25 °C, 30 min; ii, PCC, CH_2Cl_2, 25 °C, 2 h.

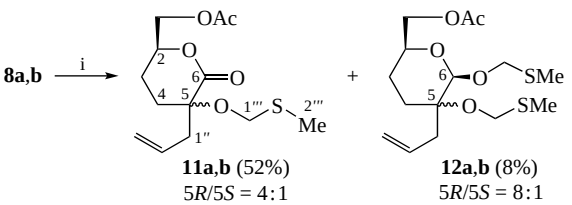
cleavage of the vicinal diol C(OH)–C(OH) bond. For example, oxidation of adducts **8a**,**b** in dichloromethane in the presence of PCC or Py–CrO_3 resulted in ring opening to give keto formate **10** (see Scheme 2). Attempts to oxidize acetals **8a**,**b** with oxidizing agents such as DCC–DMSO–P_2O_5, DMSO–P_2O_5–Et_3N–CH_2Cl_2, Py*SO_3–DMSO or Pd/C–O_2–EtOAc or Ag_2O were unsuccessful; the starting materials remained intact. Oxidation of lactols **8a**,**b** with DMSO–Ac_2O system resulted in the conversion of the hemiacetal centers into lactone moieties with simultaneous etherification of the tertiary hydroxy groups into methylthiomethyl ethers **11a**,**b** (Scheme 3). In addition, diastereomeric diethers **12a**,**b** were also isolated from the reaction mixtures as minor products. The probable mechanism of formation of such methylthiomethyl ethers is reported elsewhere.[9]

We have found previously that incorporation of a methylthiomethyl group into the levoglucosenone molecule with preservation of the double bond increases the fungicidal activity.[4(*b*)] This successfully discovered reaction makes it possible to simultaneously perform the oxidation of the acetal center and etherification of the tertiary hydroxy group into a methylthiomethyl ether, allowing the synthesis to be completed at the stage of the more biologically promising diastereomers **11a**,**b**. Hydrolysis of such ethers is well studied and, if necessary, it can be performed by a reported method.[9(*e*)]

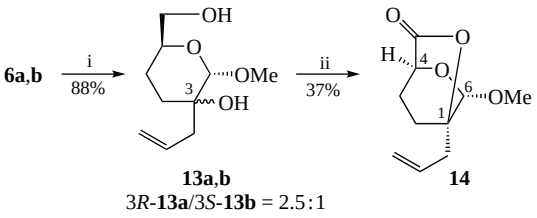
The structure of lactones **11a**,**b** is confirmed by the signals of the ester carbonyl carbon C^6 at δ 168.77 [168.94] that correlates with the $H^{1''}$ proton in the HMBC spectrum. Moreover, the $H^{1''}/C^4$, $H^{1''}/C^5$, $H^{2'''}/C^{1'''}$ and $H^{1'''}/C^5$ correlation peaks are observed in the HMBC spectrum, indicating the formation of a bond of the methylthiomethylene moiety with the oxygen at C^5.

Based on diastereomeric adducts **6a**,**b**, an alternative route to the synthesis of α-tetrahydropyrone moiety by formation of a lactone function from the 1,6-anhydro bridge and a tertiary hydroxy group looked promising. For this purpose, we performed the opening of the 1,6-anhydro bridge by treatment with HCl–MeOH.[10] Subsequent oxidation of diols **13a**,**b** with PCC resulted in spontaneous formation of individual 6-allylated *R*-enantiomer of α-tetrahydropyrone **14** (Scheme 4). Attempts to perform the Swern oxidation of primary alcohols **13a**,**b** with DMSO–$(COCl)_2$ system led to resinification of the reaction mixture.

The structure of **14** is confirmed by the downfield shift of the signal for the quaternary carbon atom C^1 at δ 82.26 (compared to the initial signal) and appearance of the ester carbonyl signal at δ



Scheme 3 *Reagents and conditions*: i, Ac_2O, DMSO, 25 °C, 7 days.



Scheme 4 *Reagents and conditions*: i, HCl–MeOH, 0 → 25 °C, 60 h; ii, PCC, CH_2Cl_2, 25 °C, 3 h.

171.25. Correlation peaks H^{OMe}/C^6, H^4/C=O and H^4/C^6 observed in the HMBC spectrum indicate that the methylpyranoside moiety is preserved in lactone **14**.

In summary, the reaction of cyrene and allyl bromide in the presence of Zn gave a 1,2-addition product, which was converted by two alternative routes to allylated α-tetrahydropyrone derivatives, including 2-methylthiomethyl ethers.

The authors are grateful to the Circa Group for providing them with industrial grade cyrene. This work was carried out under subjects (no. 122031400259-1) of the government assignment. 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: 10.1016/j.mencom.2024.06.016.

References

1 (*a*) A. D. Argoudelis and J. F. Zieserl, *Tetrahedron Lett.*, 1966, **18**, 1969; (*b*) A. D. Somoza, K.-H. Lee, Y.-M. Chiang, B. R. Oakley and C. C. C. Wang, *Org. Lett.*, 2012, **14**, 972.
2 R. Laliberté, G. Médawar and Y. Lefebvre, *J. Med. Chem.*, 1973, **16**, 1084.
3 G. F. Giri, M. Danielli, R. A. Marinelli and R. A. Spanevello, *Bioorg. Med. Chem. Lett.*, 2016, **26**, 3955.
4 (*a*) G. F. Giri, G. Viarengo, R. L. E. Furlán, A. G. Suárez, G. V. Eleonora and R. A. Spanevello, *Ind. Crops Prod.*, 2017, **105**, 113; (*b*) B. T. Sharipov, A. N. Davidova, A. S. Ryabova, N. F. Galimzyanova and F. A. Valeev, *Chem. Heterocycl. Compd.*, 2019, **55**, 31.
5 L. Kh. Faizullina, Yu. A. Khalilova, F. A. Valeev, V. N. Pavlov and A. V. Samorodov, *Chem. Heterocycl. Compd.*, 2021, **57**, 966.
6 (*a*) L. Kh. Faizullina, Yu. A. Khalilova, L. Sh. Karamysheva, Sh. M. Salikhov and F. A. Valeev, *Mendeleev Commun.*, 2022, **32**, 546; (*b*) Yu. A. Khalilova, L. Kh. Faizullina, Sh. M. Salikhov and F. A. Valeev, *Mendeleev Commun.*, 2023, **33**, 648.
7 (*a*) M. Isobe, Y. Fukuda, T. Nishikawa, P. Chabert, T. Kawai and T. Goto, *Tetrahedron Lett.*, 1990, **31**, 3327; (*b*) L. Kh. Faizullina, A. R. Tagirov, Sh. M. Salikhov and F. A. Valeev, *Russ. J. Org. Chem.*, 2019, **55**, 1832 (*Zh. Org. Khim.*, 2019, **55**, 1834).
8 D. Askin, C. Angst and D. J. Danishefsky, *J. Org. Chem.*, 1987, **52**, 622.
9 (*a*) J. D. Albright and L. Goldman, *J. Am. Chem. Soc.*, 1965, **87**, 4214; (*b*) K. Omura, A. K. Sharma and D. Swern, *J. Org. Chem.*, 1976, **41**, 957; (*c*) S. L. Huang, K. Omura and D. Swern, *J. Org. Chem.*, 1976, **41**, 3329; (*d*) K. Omura and D. Swern, *J. Org. Chem.*, 1978, **34**, 1651; (*e*) P. M. Pojer and S. J. Angyal, *Aust. J. Chem.*, 1978, **31**, 1031.
10 (*a*) S. Aburaki, N. Konishi and M. Kinoshita, *Bull. Chem. Soc. Jpn.*, 1975, **48**, 1254; (*b*) L. Kh. Faizullina, Y. A. Khalilova, Sh. M. Salikhov and F. A. Valeev, *Chem. Heterocycl. Compd.*, 2018, **54**, 598.

Received: 21st February 2024; Com. 24/7401