Available online at www.sciencedirect.com
ScienceDirect
Mendeleev Commun., 2019, **29**, 200–202

Mendeleev Communications

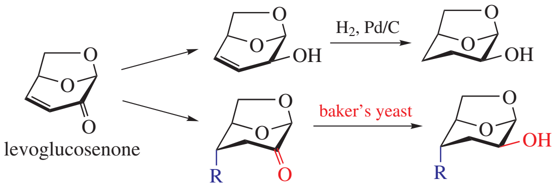
Preparation of the diastereomerically pure 2*S*-hydroxy derivative of dihydrolevoglucosenone (cyrene)

Bulat T. Sharipov,* Anna N. Davydova, Liliya Kh. Faizullina and Farid A. Valeev

Ufa Institute of Chemistry, Russian Academy of Sciences, 450054 Ufa, Russian Federation.
E-mail: sharipovbt@anrb.ru

DOI: 10.1016/j.mencom.2019.03.029

Diastereomerically pure levoglucosenone alcohol, synthesized from levoglucosenone, upon hydrogenation on Raney Ni or Pd/BaSO$_4$ undergoes epimerization at C^2 atom caused by formation of cyrene by-product and its subsequent non-specific reduction. A microbiological stereospecific technique using baker's yeast (*Saccharomyces cerevisiae*) has been developed for cyrene reduction into cyrene alcohol and also applied to reduce 4-alkoxy and 4-benzyloxy derivatives of cyrene.



R = H (cyrene), OMe, OEt, OBn

Pure optically active substances are highly demanded in organic synthesis. Levoglucosenone (1,6-anhydro-3,4-dideoxy-β-D-*glycero*-hex-3-enopyranos-2-ulose) and its derivatives are of growing interest as precursors for stereospecific synthesis of natural compounds,[1] chiral auxiliary reagents,[1–3] and also as bio-based alternatives for dipolar aprotic solvents.[4] For example, some chiral alcohols can be derived directly from levoglucosenone or through its derivative, dihydrolevoglucosenone (cyrene, 1,6-anhydro-3,4-dideoxy-β-D-*glycero*-hexopyranos-2-ulose). These chiral alcohols demonstrate good regio- and stereoselectivity when used as auxiliary reagents in asymmetric Diels–Alder reactions.[2,3] In addition, they deserve attention as substrates for the reduction of unsymmetrical ketones by hydride reagents and as precursors for the synthesis of chiral solvents.

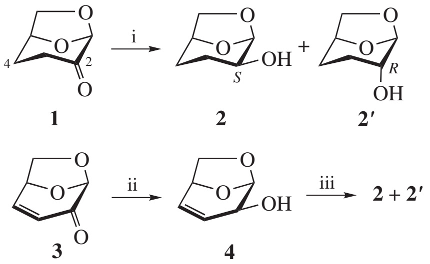
The known reduction techniques for cyrene **1** and levoglucosenone **3** result predominantly in the formation of a diastereomeric mixture of alcohols enriched in 2*S*-epimers (Scheme 1). The pure 2*S*-epimer of cyrene alcohol **2** is typically prepared by indirect approach from other carbohydrates.[5,6] Available data on the reduction of cyrene to cyrene alcohol with various reagents show that the use of NaBH$_4$ in methanol results in an inseparable mixture of compounds **2** and **2′** (89 : 11),[6,7] with $[\alpha]_D^{25}$ –117.3° (*c* 2.00 in CHCl$_3$).[8] The use of LiAlH$_4$ for the reduction of cyrene has been extensively investigated.[9–11] In the early work,[9] the configuration of the alcohol reduction product at C^2 was determined incorrectly, and later it was clarified.[7,10] After that, the content of cyrene alcohol **2** in the resulting diastereomeric mixture was established to be 91%. The use of hydrogen under pressure on various palladium catalysts affords the diastereomeric ratio of 4.7 in favor of compound **2**.[12] The hydrogenation of pure 2*S*-epimer of unsaturated levoglucosenone alcohol **4** on Pd/C leads to alcohol **2** containing 11 to 29% of cyrene,[2] in contrast to the hydrogenation on Pd/BaSO$_4$,[9] although these latter results do not specify the diastereomeric purity of alcohol **2**.

To obtain the data in addition to the published ones and to arrange the resulting information, we have investigated and when necessary reproduced various approaches to the preparation of alcohols **2** and **2′** (Scheme 1, Table 1).

According to the data in Table 1, our results on borohydride reduction of cyrene **1** in methanol are close to the published ones.[6,7] The addition of CeCl$_3$ to the reaction mixture during borohydride reduction improves the diastereomeric purity.[13] In our hands, repeating the process in the presence of CeCl$_3$ resulted in increased diastereomeric ratio in favor of 2*S*-epimer **2**.

In the reduction of cyrene **1** with Bu$^i_2$AlH in dichloromethane, the temperature had more significant effect on the total yield than on the ratio of alcohols. The use of LiAlH$_4$ in diethyl ether afforded product mixture with even better cyrene alcohol **2** content.

Taking into account the fact that the reduction of levoglucosenone **3** with NaBH$_4$ in water proceeds stereoselectively



Scheme 1 *Reagents and conditions*: i, see Tables 1 and 2; ii, NaBH$_4$, H$_2$O, 0 °C; iii, H$_2$, see Table 1.

Table 1 Preparation of alcohols **2** and **2′** from cyrene **1** or levoglucosenone alcohol **4**.

Starting compound	Reaction conditions	Yield of **2** + **2′** (%)	*dr* **2** : **2′** [a]
1	NaBH$_4$, MeOH, 0 °C	99	85 : 15[b]
1	NaBH$_4$, CeCl$_3$·7H$_2$O, MeOH, 0 °C	86	90 : 10
1	LiAlH$_4$, Et$_2$O, 0 °C	75	79 : 21[c]
1	Bu$^i_2$AlH, CH$_2$Cl$_2$, 0 °C	68	69 : 31
1	Bu$^i_2$AlH, CH$_2$Cl$_2$, –78 °C	86	67 : 33
3	H$_2$, Raney Ni, EtOAc, ~20 °C	90	59 : 41
4	H$_2$, Raney Ni, EtOAc, ~20 °C	99	91 : 9
4	H$_2$, Raney Ni, EtOAc, AcOH, ~20 °C	98	94 : 6
4	H$_2$, Pd/BaSO$_4$, EtOAc, ~20 °C	87[d]	98 : 2
4	H$_2$, Pd/C, EtOAc, ~20 °C	71[e]	>99

[a] *dr* is diastereomeric ratio. [b] Lit.,[6,7] 89 : 11. [c] Lit.,[11] 6 : 1 and lit.,[9] content of **2** 91%. [d] Yield of cyrene was 12%. [e] Yield of cyrene was 28%.

to form alcohol **4** with only 2% impurity of its 2*R*-epimer,[14] and that alcohol **4** is further readily isolated in a diastereomerically pure form by recrystallization from light petroleum–CH_2Cl_2, the attractive direct way to the pure alcohol **2** may be the hydrogenation of the double bond in the pure unsaturated alcohol **4**.

In our hands, the hydrogenation of alcohol **4** on Raney Ni resulted in a mixture of alcohols **2** and **2′** in a ratio of 91:9. Most probably, similar to the known evidence of ketone production on Raney Ni,[15] such an outcome may be rationalized by formation of small amount of cyrene **1**, which is further hydrogenated to afford mixture of **2** and **2′**. The addition of acetic acid to inhibit the Raney Ni activity slightly reduced the yield of undesired diastereomer **2′**. The use of levoglucosenone **3** as starting compound in the hydrogenation on Raney Ni did not improve the specificity and yielded a mixture of **2** and **2′** in a ratio of 59:41.

The most effective method to prepare the diastereomerically pure alcohol **2** turned out to be the hydrogenation of unsaturated alcohol **4** on Pd/C in ethyl acetate;[2] it was accomplished in less than an hour and was only slightly complicated by the formation of cyrene **1** as by-product. Hydrogenation of alcohol **4** on Pd/$BaSO_4$ in ethyl acetate proceeded with complete conversion in 24 h with the formation of alcohol **2** in 87% yield and cyrene **1** in 12% yield. The formation of cyrene under these conditions has not been previously reported.[9] The hydrogenation with Pd/$BaSO_4$ afforded alcohol **2** with lower purity, which was associated with a longer reaction time when non-specific reduction of cyrene **1** occurred.

Given the fact that microbiological syntheses are widely used for preparation of chiral products, we investigated the reduction of cyrene **1** in the presence of baker's yeast (*Saccharomyces cerevisiae*), which is known to turn the stereoselectivity of ketone reduction in favor of (*S*)-alcohol for simple arylmethyketones, ethyl acetoacetate or substituted bicyclo[3.3.0]octane-2,8-diones.[16] Although the laboratory strains of baker's yeast are used in these biotransformations, organic chemists typically employ the commercial ones, so we utilized baker's yeast purchased from Pakmaya Company (Turkey). The results of our experiments are presented in Table 2.

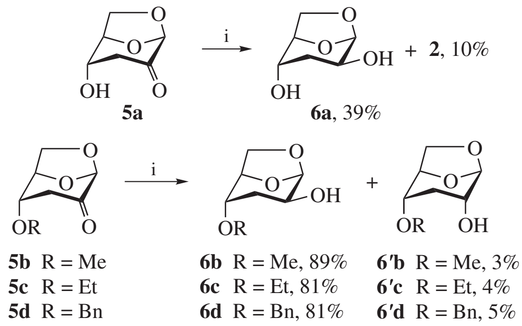
The reaction was carried out in water at 30 °C with constant stirring, both in the absence of carbohydrates and in the presence of D-glucose or sucrose as a growth medium. In the presence of sucrose the reaction proceeded slowly, and with D-glucose[†] its rate increased significantly. Thus, the most effective run proceeds stereospecifically with D-glucose to give alcohol **2** with $[\alpha]_D^{20}$ –134.2° (*c* 1.0 in $CHCl_3$) and $[\alpha]_D^{20}$ –132.8° (*c* 1.0 in H_2O).[‡]

In addition, we investigated the reduction of hydroxy-functionalized cyrene derivatives **5a–d** (Scheme 2) that were easily prepared from levoglucosenone **3** by the oxa-Michael reaction.[14,17]

Table 2 Microbiological reduction of cyrene **1**.[a]

Baker's yeast/g	Carbohydrate	*t*/h	Yield of **2** (%)
2.0	sucrose	50	65
2.0	D-glucose	24	99
4.0	–	7	78

[a] Conditions: cyrene **1** (200 mg, 1.56 mmol), 30 °C.



Scheme 2 *Reagents and conditions*: i, baker's yeast, H_2O, D-glucose, 30 °C.

It is known that the reduction of hydroxy ketone **5a** with $NaBH_4$ gives a mixture of alcohol **6a** and its 2*R*-epimer in a ratio of 71:14 determined from the mass yields of the corresponding diacetate derivatives.[14] The reduction of methoxy ketone **5b** yields a mixture of alcohols **6b** and **6′b** in a ratio of 10:11;[17] while alcohols **6d** and **6′d** in the borohydride reduction of benzyloxy derivative **5d**[18] are formed in almost equal amounts.

In our hands, the reduction of hydroxy ketone **5a** with baker's yeast proceeded for **5d** to form pure alcohol **6a** in a yield of 39% together with small amount of alcohol **2**. The reduction of ketones **5b–d** took less than 24 h; the reaction was characterized by high stereoselectivity, good yields of alcohols **6b–d**, and the formation of small amount of diastereomeric alcohols **6′b–d**, which could be easily separated from the main products. It was noted that the selectivity of the reduction of levoglucosenone keto derivatives with baker's yeast decreased for compounds bearing bulky substituents at C^4; however, this microbial technique is still more effective than all those described above.

Thus, methods for the reduction of cyrene and the hydrogenation of unsaturated alcohol, prepared from borohydride reduction of levoglucosenone, have been tested to synthesize a diastereomerically pure cyrene 2*S*-alcohol. The data obtained demonstrate that the most efficient chemical method to gain this purpose is hydrogenation on Pd/C. The reduction of cyrene by microbiological method using baker's yeast (*S. cerevisiae*) proceeds stereospecifically. This latter technique also turned out well in the reduction of oxa-Michael adducts of levoglucosenone with methanol, ethanol or benzyl alcohol. The microbial reduction technique for levoglucosenone derivatives is a promising way to synthesize chiral functionalized alcohols, including large scale processes.

This study was performed in the framework of the State contract (AAAA-A17-117011910022-5) and supported by the Russian Foundation for Basic Research (grant no. 17-43-020166 r_a).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.03.029.

[†] *General procedure for the reduction of ketones with baker's yeast.* A suspension of baker's yeast (1.3 g) and D-glucose (1 g) in water (10 ml) was stirred at *ca.* 30 °C for 1 h, then a solution of ketone (1 mmol) in water (3 ml) was added. The reaction mixture was stirred at *ca.* 30 °C. The reaction was monitored by silica-gel TLC until the disappearance of the starting ketone (*ca.* 24 h). Then ethanol (10 ml) was added, the precipitate was filtered off, washed with ethanol and the solution obtained was combined with filtrate. The filtrate was evaporated *in vacuo* and the residue was purified by column chromatography.

[‡] *1,6-Anhydro-3,4-dideoxy-β-D-*threo*-hexopyranose* **2**. Alcohol **2** was prepared from cyrene **1** (200 mg, 1.56 mmol) according to the general procedure as a clear oil that partially crystallized; 201 mg (99%); $[\alpha]_D^{20}$ –134.2° (*c* 1.0, $CHCl_3$); $[\alpha]_D^{20}$ –132.8° (*c* 1.0, H_2O) {lit.,[5] mp ~28 °C (unsharp), $[\alpha]_D^{25}$ –133° (*c* 0.6 in H_2O)}. IR (ν/cm^{-1}): 3418 (OH), 2954 (C–H), 1131 and 1070 (C–O–C), 985 and 900 (O–C–O). ^1H NMR (500 MHz, $CDCl_3$) δ: 1.49 (dtd, 1H, H-3, *J* 12.9, 10.0, 6.1 Hz), 1.57 (dd, 1H, H-4, *J* 13.9, 6.1 Hz), 1.82–1.91 (m, 1H, H-4), 1.98–2.04 (m, 1H, H-3), 2.18 (br. s, 1H, OH), 3.58 (dd, 1H, H-2, *J* 10.0, 6.2 Hz), 3.79 (dd, 1H, H-6, *J* 7.1, 5.4 Hz), 3.83 (d, 1H, H-6, *J* 7.1 Hz), 4.46–4.49 (m, 1H, H-5), 5.30 (s, 1H, H-1). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 26.02 (C^3), 27.82 (C^4), 68.17 (C^6), 69.98 (C^2), 72.80 (C^5), 102.92 (C^1). MS (APCI), *m*/*z*: 130.1 $[M]^+$. Found (%): C, 55.45; H, 7.79. Calc. for $C_6H_{10}O_3$ (%): C, 55.37; H, 7.74.

References

1 (*a*) M. S. Miftakhov, F. A. Valeev and I. N. Gaisina, *Russ. Chem. Rev*., 1994, **63**, 869 (*Usp. Khim*., 1994, **63**, 922); (*b*) A. M. Sarotti, M. M. Zanardi, R. A. Spanevello and A. G. Suárez, *Curr. Org. Synth*., 2012, **9**, 439; (*c*) M. B. Comba, Y.-h. Tsai, A. M. Sarotti, M. I. Mangione, A. G. Suárez and R. A. Spanevello, *Eur. J. Org. Chem*., 2018, 590; (*d*) B. T. Sharipov, A. A. Pershin and F. A. Valeev, *Mendeleev Commun*., 2017, **27**, 119; (*e*) K. P. Stockton and B. W. Greatrex, *Org. Biomol. Chem*., 2016, **14**, 7520.

2 M. M. Zanardi and A. G. Suárez, *Tetrahedron Lett*., 2009, **50**, 999.

3 (*a*) A. M. Sarotti, R. A. Spanevello and A. G. Suárez, *Org. Lett*., 2006, **8**, 1487; (*b*) A. M. Sarotti, I. Fernández, R. A. Spanevello, M. A. Sierra and A. G. Suárez, *Org. Lett*., 2008, **10**, 3389; (*c*) A. M. Sarotti, R. A. Spanevello and A. G. Suárez, *Tetrahedron*, 2009, **65**, 3502; (*d*) J. Klepp, C. J. Sumby and B. W. Greatrex, *Synlett*, 2018, **29**, 1441; (*e*) M. M. Zanardi, M. C. Botta and A. G. Suárez, *Tetrahedron Lett*., 2014, **55**, 5832.

4 (*a*) J. Sherwood, M. De bruyn, A. Constantinou, L. Moity, C. R. McElroy, T. J. Farmer, T. Duncan, W. Raverty, A. J. Hunt and J. H. Clark, *Chem. Commun*., 2014, **50**, 9650; (*b*) A. A. C. Pacheco, J. Sherwood, A. Zhenova, C. R. McElroy, A. J. Hunt, H. L. Parker, T. J. Farmer, A. Constantinou, M. De bruyn, A. C. Whitwood, W. Raverty and J. H. Clark, *ChemSusChem*, 2016, **9**, 3503; (*c*) J. Zhang, G. B. White, M. D. Ryan, A. J. Hunt and M. J. Katz, *ACS Sustainable Chem. Eng*., 2016, **4**, 7186; (*d*) K. L. Wilson, A. R. Kennedy, J. Murray, B. Greatrex, C. Jamieson and A. J. B. Watson, *Beilstein J. Org. Chem*., 2016, **12**, 2005; (*e*) K. L. Wilson, J. Murray, C. Jamieson and A. J. B. Watson, *Synlett*, 2018, **29**, 650.

5 J. Halbych, T. Trnka and M. Černý, *Collect. Czech. Chem. Commun*., 1973, **38**, 2151.

6 J. Pecka, J. Staněk Jr. and M. Černý, *Collect. Czech. Chem. Commun*., 1974, **39**, 1192.

7 J. Pecka and M.Černý, *Collect. Czech. Chem. Commun*., 1978, **43**, 1720.

8 G. F. Giri, G. Viarengo, R. L. E. Furlán, A. G. Suárez, E. Garcia Véscovi and R. A. Spanevello, *Ind. Crops Prod*., 2017, **105**, 113.

9 F. Shafizadeh and P. P. S. Chin, *Carbohydr. Res*., 1977, **58**, 79.

10 J. S. Brimacombe, F. Hunedy and L. C. N. Tucker, *Carbohydr. Res*., 1978, **60**, C11.

11 M. E. Jung and M. Kiankarimi, *J. Org. Chem*., 1998, **63**, 8133.

12 S. H. Krishna, D. J. McClelland, Q. A. Rashke, J. A. Dumesic and G. W. Huber, *Green Chem*., 2017, **19**, 1278.

13 G. A. Molander, *Chem. Rev*., 1992, **92**, 29.

14 F. Shafizadeh, R. H. Furneaux and T. T. Stevenson, *Carbohydr. Res*., 1979, **71**, 169.

15 (*a*) E. C. Kleiderer and E. C. Kornfeld, *J. Org. Chem*., 1948, **13**, 455; (*b*) J. Foršek, *Tetrahedron Lett*., 1980, **21**, 1071; (*c*) V. N. Odinokov, R. V. Shafikov, R. G. Savchenko, S. R. Afon'kina, I. V. Galyautdinov, L. M. Khalilov and A. S. Shashkov, *Russ. J. Org. Chem*., 2008, **44**, 671 (*Zh. Org. Khim*., 2008, **44**, 681).

16 (*a*) G. Fantin, M. Fogagnolo, M. E. Guerzoni, A. Medici, P. Pedrini and S. Poli, *J. Org. Chem*., 1994, **59**, 924; (*b*) B. Wipf, E. Kupfer, R. Bertazzi and H. G. W. Leuenberger, *Helv. Chim. Acta*, 1983, **66**, 485; (*c*) T. Inoue, K. Hosomi, M. Araki, K. Nishide and M. Node, *Tetrahedron: Asymmetry*, 1995, **6**, 31.

17 T. Kawai, M. Isobe and S. C. Peters, *Aust. J. Chem*., 1995, **48**, 115.

18 R. H. Furneaux, G. J. Gainsford, F. Shafizadeh and T. T. Stevenson, *Carbohydr. Res*., 1986, **146**, 113.

Received: 15th October 2018; Com. 18/5719