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SCIENCE DIRECT
Carbohydrate Research 341 (2006) 1945–1947
Carbohydrate RESEARCH

Note

A new synthesis of α-arbutin via Lewis acid catalyzed selective glycosylation of tetra-*O*-benzyl-α-D-glucopyranosyl trichloroacetimidate with hydroquinone

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Received 17 January 2006; received in revised form 7 April 2006; accepted 11 April 2006
Available online 15 May 2006

Abstract—α-Arbutin has huge application potentials in the cosmetic industry, as its inhibitory effect on human tyrosinase is stronger than that of its naturally occurring anomer arbutin (4-hydroxyphenyl β-D-glucopyranoside). Enzymatic synthesis was preferred for α-arbutin previously, and now a new chemical synthesis is reported. The reaction of tetra-*O*-benzyl-α-D-glucopyranosyl trichloroacetimidate, as glycosyl donor, with hydroquinone was initiated by catalytic amounts of trimethylsilyl trifluoromethanesulfonate (TMSOTf), resulting in 4-hydroxyphenyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside with high stereoselectivity and yield, and then to α-arbutin quantitatively after deprotection.

Keywords: α-Arbutin; Trichloracetimidate; Hydroquinone; Glycosylation

α-Arbutin (4-hydroxyphenyl α-D-glucopyranoside, **1**) is the anomer of the naturally occurring arbutin. It is a potent suppressor of melanin synthesis in human skin without apparent side effects.[1–3] It was reported that α-arbutin inhibited human tyrosinase much more effectively than arbutin. The IC_{50} value of α-arbutin is 2.1 mM, whereas that of arbutin is higher than 30 mM.[4] This indicates that α-arbutin is a more effective skin-whitening agent than arbutin. Moreover, arbutin inhibits normal cellular growth with increasing concentration while α-arbutin does not,[5] which suggests that α-arbutin is more safe than arbutin.

α-Arbutin used to be produced by enzymatic synthesis.[6,7] There are very few reports on its chemical synthesis. Kariyone et al. prepared α-arbutin in 16% yield by reaction of penta-*O*-acetyl-β-D-glucopyranose and hydroquinone at 120–130 °C under diminished pressure.[8] Onodera et al. reported the direct acid-catalyzed glycosylation of D-glucose with hydroquinone at 100 °C for 10 h giving α-arbutin and its β-anomer in 11% and 4% yield, respectively.[9] Cepanec et al. patented recently a chemical synthesis of α-arbutin involving reaction of penta-*O*-acetyl-α-D-glucopyranose and 4-hydroxyphenyl acetate at reflux for about 3 days. α-Arbutin was obtained in 27% yield after deacetylation.[10] In all these methods, the reaction time was long and the yields were low.

We now describe a synthesis of α-arbutin with high stereoselectivity involving tetra-*O*-benzyl-α-D-glucopyranosyl trichloroacetimidate[11–13] as glucosyl donor in reaction with hydroquinone to afford α-arbutin in two steps and 65% yield (Scheme 1).

As could be seen in Table 1, the selectivity of glycosylation of **3** was greatly dependent on the catalyst and reaction temperature. Dichloromethane was selected as the best solvent after screening. The presence of 4 Å molecular sieves was an important parameter since it significantly improved the yield of glycosylation, though it tended to give β-arbutin as a major product (entries 8–10). Several Lewis acids have been tried for their impact

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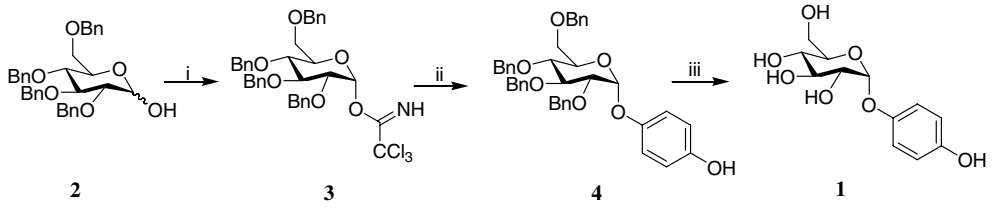
doi:10.1016/j.carres.2006.04.022



Scheme 1. Synthesis of α-arbutin (**1**). Reagents and conditions: (i) $CCl_3CN/DBU/CH_2Cl_2$; (ii) hydroquinone, TMSOTf, −60 °C → rt; (iii) Pd–C, H_2.

Table 1. Glycosylation of **3** and **3β** with hydroquinone

Entry	Donor	Catalysts	Temperature (°C)	Time (h)	Yield (%)	Isomer distribution (α:β)
1	**3**	TMSOTf/4 Å ms	rt	~1	86	2:1
2	**3**	TMSOTf/4 Å ms	0 to rt	~1	83	1:1
3	**3**	TMSOTf/4 Å ms	−20 to rt	~1	82	1:2
4	**3**	TMSOTf/4 Å ms	−40 to rt	~1	80	1:1
5	**3**	TMSOTf/4 Å ms	−60 to rt	~1	81	4:1
6	**3**	TMSOTf/4 Å ms	−80 to rt	~1	81	2:3
7	**3**	TMSOTf	−60 to rt	~1	79	5:1
8	**3**	4 Å ms	rt	~1	86	1:4
9	**3**	4 Å ms	0 to rt	~1	79	1:4
10	**3**	4 Å ms	−60 to rt	~1	78	2:9
11	**3**	$BF_3{\cdot}Et_2O$/4 Å ms	rt	~1	85	3:2
12	**3**	$ZnCl_2$/4 Å ms	40	~1	89	1:1
13	**3**	$ZnCl_2$/4 Å ms	rt	~1	96	2:3
14	**3**	$ZnCl_2$/4 Å ms	−30 to rt	~1	86	2:5
15	**3β**	TMSOTf	−60 to rt	~3	58	5:1
16	**3β**	$BF_3{\cdot}Et_2O$	rt	~3	56	5:1
17	**3β**	$ZnCl_2$	rt	~3	23	1:2

on selectivity and yield. TMSOTf, $BF_3{\cdot}Et_2O$ and $ZnCl_2$ gave good yields, but only TMSOTf gave a good α-selectivity (entries 5 and 7). The best α-selectivity was achieved using TMSOTf as the catalyst in the absence of 4 Å molecular sieves (entry 7). Low yields were obtained when Lewis acids such as $AlCl_3$, $TiCl_4$, YCl_3 and $LaCl_3$ were used as catalysts.

2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl trichloroacetimidate[14] (**3β**) was also used as donor in reaction with hydroquinone (entries 15–17), but the reaction proceeded slowly (~3 h) and the yields were not so high.

1. Experimental

1.1. General

Melting points are uncorrected. ^1H NMR spectra were obtained on a DRX-500 equipment using TMS as internal standard. IR spectra were recorded on a Nicolet 5SXC equipment with KBr films. ESIMS spectra were recorded on a HP-5989A spectrometer. Elementary analyses were done on Elementar Vario EL III. Optical rotations were measured on a WZZ-1S polarimeter. Chromatography was performed on silica gel (200–300 mesh). TLC was performed on Silica Gel $HSGF_{254}$.

1.2. 4-Hydroxyphenyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside (4)

At −60 °C, under Ar, a soln of hydroquinone (49.5 mg, 0.45 mmol) and **3** (205.4 mg, 0.30 mmol) in anhyd CH_2Cl_2 (15 mL) was treated with TMSOTf (33.3 mg, 0.15 mmol), and the mixture was stirred for 20 min. The temperature was gradually allowed to rise to room temperature over a period of 1 h. The reaction was quenched by the addition of aq saturated $NaHCO_3$ (2 mL) and stirring was continued for ~10 min, and then saturated aq NaCl was added. The mixture was extracted with CH_2Cl_2 (3 × 5 mL), and the organic layer was dried over anhyd $MgSO_4$. The solvent was evaporated under diminished pressure, and the residue was chromatographed on a silica gel column (10:1 petroleum ether–EtOAc) to give **4** (125.1 mg, 66%) and its anomer **4β** (24.6 mg, 13%) both as oily materials.

Compound **4**: $[\alpha]_D^{20}$ +84.0 (*c* 1,$CHCl_3$); IR (KBr): *v* 3350, 2930, 2870, 1450, 1210, 1080 cm^{-1}; ^1H NMR (500.13 MHz, $CDCl_3$): δ 7.25 (m, 20H, 4-Ar), 6.93 (d, 2H, *J* 8.8 Hz, ArH), 6.68 (d, 2H, *J* 8.8 Hz, ArH), 5.33 (d, 1H, *J* 3.4 Hz, 1-H), 5.04 (d, 1H, $-CH_2$), 4.96 (br s, 1H, –OH), 4.89–4.39 (m, 7H, $-CH_2$), 4.18 (dd, 1H, *J* 9.3 Hz, *J* 9.3 Hz, 3-H), 3.92–3.55 (m, 5H, H-2,4-6,6′); ESIMS: *m*/*z* 632 $[M]^+$, 655 $[M+Na]^+$, 671 $[M+K]^+$,

1287 $[2M+Na]^+$. Anal. Calcd for $C_{40}H_{40}O_7$: C, 75.95; H, 6.33. Found: C, 76.06; H, 6.09.

Compound **4β**: $[\alpha]_D^{20}$ +1.41 (*c* 1, $CHCl_3$). IR (KBr): *v* 3380, 2930, 1650, 1520, 1260, 1180, 1080 cm^{-1}; ^1H NMR (500.13 MHz, $CDCl_3$): δ 7.26 (m, 20H, 4-Ar), 6.96 (d, 2H, *J* 8.8 Hz, ArH), 6.70 (d, 2H, *J* 8.8 Hz, ArH), 5.04 (d, 1H, $-CH_2$), 4.94 (d, 1H, *J* 10.9 Hz, 1-H), 4.84 (m, 4H, $-CH_2$), 4.75 (br s, 1H, –OH), 4.56 (m, 3H, $-CH_2$) 3.79–3.55 (m, 6H, H-2-6,6′); ESIMS: *m*/*z* 633 $[M+1]^+$, 655 $[M+Na]^+$. Anal. Calcd for $C_{40}H_{40}O_7$: C, 75.95; H, 6.33. Found C, 75.66; H, 6.23.

1.3. 4-hydroxyphenyl α-D-glucopyranoside (α-arbutin, 1)

A soln of **4** (316 mg, 0.5 mmol) and 10% Pd–C (50 mg) in EtOAc (5 mL) and EtOH (5 mL) was stirred at room temperature for 1.5 h under H_2. After filtering the catalyst, the filtrate was concentrated to give **1** (133.5 mg, 98%) as white crystals; mp 195–196 °C, lit.[8] 195.5–196 °C. R_f 0.16 (1:1 EtOAc–Me_2CO); $[\alpha]_D^{20}$ +155.07 (*c* 1, $CHCl_3$); ^1H NMR (500.13 MHz, D_2O): δ 6.96 (d, 2H, *J* 8.9 Hz, ArH), 6.77 (d, 2H, *J* 8.9 Hz, ArH), 5.38 (d, 1H, *J* 3.7 Hz, 1-H), 3.81–3.37 (m, 6H, H-2,3,4,5,6,6′).

Acknowledgements

This work was supported by the Natural Science Foundation of China (No. 20576034) and Shanghai Science and Technology Community. (Grant No. 044307011).

References

1. Funayama, M.; Arakawa, H.; Yamamoto, R.; Nishino, T.; Shin, T.; Murao, S. *Biosci., Biotechnol., Biochem.* **1995**, *59*, 143–144.
2. Nishimura, T.; Kometani, T.; Okada, S.; Uendo, N.; Yamamoto, T. *Yakugaku Zasshi* **1995**, *115*, 626–632.
3. Tehara, T.; Hachimaki, H. Jpn. Kokai Tokkyo Koho JP 277,261, 2003; *Chem. Abstr*. **2003**, *139*, 265423k.
4. Sugimoto, K.; Nishimura, T.; Nomura , K.; Sugimoto, K.; Kuriki, T. *Chem. Pharm. Bull.* **2003**, *51*, 798–801.
5. Yao, B.; Shen, X.-L.; Pan, Y.-J. *Chin. JMAP* **2005**, *22*, 32–33.
6. Kitao, S.; Sekine, H. *Biosci., Biotechnol., Biochem.* **1994**, *58*, 38–42.
7. Kurosu, J.; Sato, T.; Yoshida, K.; Tsugane, T.; Shimura, S.; Kirimura, K.; Kino, K.; Usami, S. *J. Biosci. Bioeng.* **2002**, *93*, 328–330.
8. Kariyone, T.; Takahashi, M.; Takaishi, K. *Yakugaku Zasshi* **1952**, *72*, 13–16.
9. Onodera, J.-I.; Takano, M.; Kishi, Y.; Yokoyama, N.; Ishida, R. *Chem. Lett.* **1983**, 1487–1488.
10. Cepanec, I.; Melnjak, A.; Koretic, S.; Litvic, M.; Mikotic-Mihun, Z. Croat. Pat. Appl. HR 2010190, 2001; *Chem. Abstr.* **2003**, *139*, 323746f.
11. Schmidt, R. R.; Michel, J. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 731–732.
12. Schmidt, R. R.; Stumpp, M. *Liebigs Ann. Chem.* **1983**, 1249–1256.
13. Koto, S.; Morishima, N.; Miyata, Y. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 2639–2640.
14. Schmidt, R. R.; Michel, J. *Tetrahedron Lett.* **1984**, *25*, 821–824.