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Synthesis of 3,4,5-Trimethoxyphenyl 5''-*O*-caffeoyl-β-D-*erythro*-apiofuranosyl-(1→6)-β-D-glucopyranoside: Kelampayoside B

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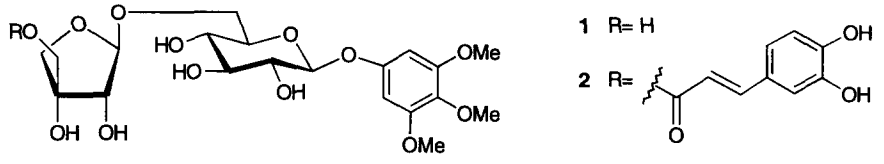
Abstract. Chemoselective NIS/ cat. TfOH-mediated glycosylation of ethyl 2,3,4-tri-*O*-benzoyl-1-thio-β-D-glucopyranoside (**4**) with ethyl 2,3-di-*O*-acetyl-5-*O*-benzyl-1-thio-α/β-D-*erythro*-apiofuranoside (**3**) gave dimer **5** in an excellent yield. $BF_3{\cdot}Et_2O$-catalysed condensation of the α-trichloroacetimidate **18**, accessible in two steps from **5**, with 3,4,5-trimethoxyphenol gave β-linked derivative **19** which could be transformed in five steps into the title compound.

Ten years ago, Shiraga *et al.*[1] showed that 3,4,5-trimethoxyphenyl β-D-*erythro*-apiofuranosyl-(1→6)-β-D-glucopyranoside (**1**), isolated earlier[2] from the dried stem bark of *Cinnamomum cassia* Blume, exhibits antiulcerogenic activity in rats. Recently, Kitagawa *et al.*[3] isolated the same active compound as well as its 5''-*O*-caffeoyl derivative **2** (so-called Kelampayoside A and B, respectively) from the bark of *Anthocephalus chinensis*. Both compounds are characterised by the presence of the rare apiofuranose sugar and the rather electron-rich aryl moiety. Thus far, only scarce information[4] on the glycosylating properties of apiofuranose, the occurrence of which is restricted[5] to the plant kingdom, is available. Moreover, it was anticipated that Fries-type rearrangement[6] of the initially formed *O*-3,4,5-trimethoxyphenyl moiety would give rise to the formation of the unwanted *C*-aryl derivative. The aforementioned chemical and, to a lesser extent, pharmacological aspects seemed to us a justifiable objective in preparing Kelampayosides A (**1**) and B (**2**).

Figure 1



In line with the retrosynthetic analysis of target compounds **1-2**, we first explored (see Scheme 1) the feasibility of preparing the functionalized dimer **5** via a chemoselective glycosylation of the partially benzoylated ("disarmed")[7] thioethyl glucosyl acceptor **4**[8] with the also in principle "disarmed" ethyl 2,3-di-*O*-acetyl-5-*O*-benzyl-1-thio-α/β-D-*erythro*-apiofuranoside (**3**). Donor **3** is readily available by treatment of 1,2,3-tri-*O*-acetyl-5-*O*-benzyl-α/β-D-*erythro*-apiofuranoside[4a] with ethanethiol in the presence of $SnCl_4$. It was established that NIS/catalytic triflic acid (TfOH) mediated[7] glycosylation of the glycosyl acceptor **4** with donor **3** proceeds with a high degree of chemoselectivity to give the β-linked dimer **5** in 92% yield. The outcome of this experiment indicates that de deactivating effect of the 2-*O*-acetyl group in donor **3** is more than fully compensated by the intrinsically higher reactivity of a glycosylating species derived from a furanosyl than a pyranosyl donor. The latter effect may also explain the unexpected high chemoselectivity in the NIS / cat. TfOH-assisted glycosylation of the partially benzylated ("armed") acceptor **6**[9] with **3**. The

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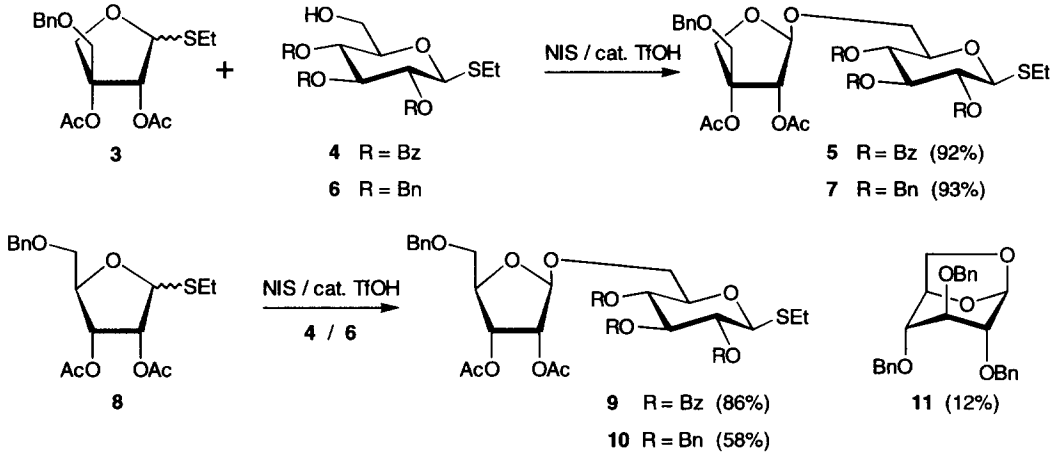
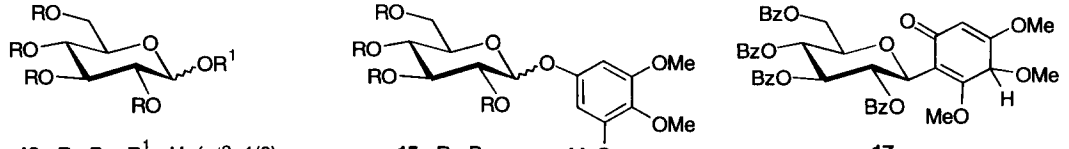
general nature of the furanosyl effect was also demonstrated (see Scheme 1) in the high chemoselective glycosylation of the ethylthio ribofuranosyl donor **8** with **4** and to a lesser extent with **6**, as evidenced by the relatively low yield of **10** as well as the formation of the 1,6-anhydro derivative **11**.

Scheme 1



Attention was now focused on the introduction of the requisite β-linked trimethoxyphenyl moiety in the target compounds **1-2**. To this end, the glucopyranose derivatives **12-14** were condensed with commercially available 3,4,5-trimethoxyphenol (antiarol) under Mitsunobu[10] and mild Lewis acid conditions[6]. The results of these pilot experiments are summarised in Table 1. It can be seen (entry 1) that Mitsunobu glycosidation of antiarol with anomerically pure **12** (α) proceeds as expected[10] with inversion of configuration to give the *O*-β-glycoside **15**. It is also evident (entry 2) that the β-directing effect of the 2-*O*-benzoyl group in the anomerically impure donor **13** is reflected in the predominant formation of the β-*O*-glucoside **16**. On the other hand, condensation of the corresponding α-trichloracetimidate **14** with antiarol under the influence of a

Figure 2

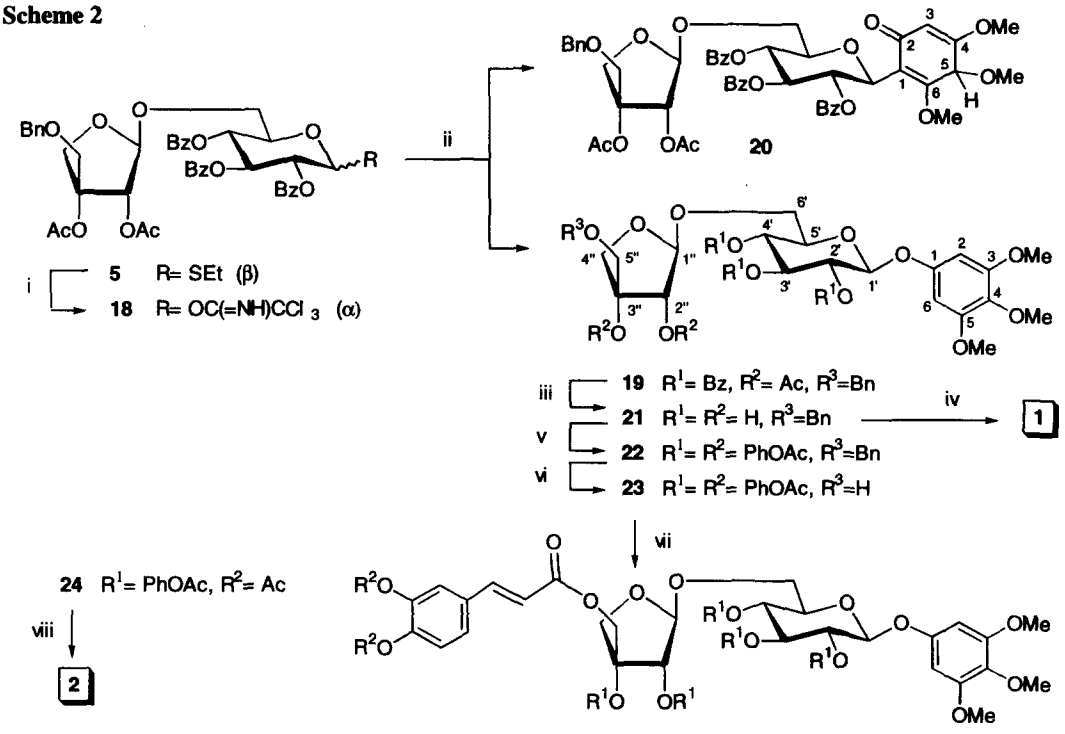


12 R= Bn, R^1= H (α/β, 1/0)
13 R= Bz, R^1= H (α/β, 4/1)
14 R= Bz, R^1= C(=NH)CCl$_3$ (α)
15 R= Bn
16 R= Bz
17

Table 1 Relevant data on the glycosidation of 3,4,5-trimethoxyphenol with the glucopyranosyl donors **12-14**.

Entry	Donor	Activator	Solvent	*O*-aryl	*C*-aryl
1	**12**	DEAD, Ph_3P	THF	62% (**15**: α/β, 0/1)	-
2	**13**	DEAD, Ph_3P	THF	55% (**16**: α/β, 1/7)	-
3	**14**	$BF_3 \cdot Et_2O$ (0.25 equiv.)	CH_2Cl_2	41% (**16**: α/β, 0/1)	18% (**17**)
4	**14**	$BF_3 \cdot Et_2O$ (0.25 equiv.)	CH_2Cl_2/THF, (10/1)	64% (**16**: α/β, 0/1)	5% (**17**)

Scheme 2



Reagents and conditions: i) a) NIS / cat. TfOH, wet CH_2Cl_2 (89%); b) Cs_2CO_3, CCl_3CN, CH_2Cl_2 (81%); ii) antiarol, 0.25 equiv. $BF_3{\cdot}Et_2O$, CH_2Cl_2 / THF (10/1, v/v), (**19**: 63%, **20**: 4%); iii) NaOMe, MeOH / CH_2Cl_2 (5/1, v/v), (88%); iv) H_2, 10% Pd/C, *i*-PrOH / H_2O (10/1, v/v), (91%); v) PhOAcCl, CH_2Cl_2, 3 equiv. pyridine (88%); vi) H_2, 10% Pd/C, *i*-PrOH / EtOAc / H_2O (12/8/1, v/v/v), (86%); vii) di-*O*-acetylcaffeoyl chloride, CH_2Cl_2, 3 equiv. pyridine (77%); viii) 0.005 M K_2CO_3, MeOH / CH_2Cl_2 (1/1, v/v), (49%).

small amount[11] of the weak Lewis acid catalyst $BF_3{\cdot}Et_2O$ gave apart from the β-*O*-glucoside **16** an unacceptable quantity of the β-*C*-glucoside **17** (entry 3). It was therefore gratifying to find that **16** was the main product (entry 4) by executing the same glycosidation in the solvent CH_2Cl_2 containing a small amount of THF[12]. Moreover, β-*O*-glucoside **16** could be readily separated by silica gel chromatography from the undesired β-*C*-glycoside **17**. On the basis of the latter results, dimer **5** seemed to be a convenient starting compound for the synthesis of Kelampayoside A (**1**) and B (**2**). Thus, condensation (see Scheme 2) of the α-trichloroacetimidate **18**, easily accessible in two steps from **5**, with antiarol in the presence of cat. $BF_3{\cdot}Et_2O$ in CH_2Cl_2 / THF (10/1, v/v) gave, after purification by silica gel chromatography, the β-antiaryl glycoside **19**[13] and the corresponding β-*C*-aryl derivative **20**[13] in a yield of 63 and 4%, respectively. Zémplen deacetylation of **19** and subsequent hydrogenolysis of **21** gave homogeneous Kelampayoside A (**1**), the physical data of which were in full accord with those reported[3] by Kitagawa *et al.* It was expected that Kelampayoside B (**2**) could be prepared by regioselective acylation of Kelampayoside A (**1**) with 3,4-di-*O*-acetylcaffeoyl chloride[14]. However, the latter possibility was thwarted by the poor solubility of **1** and impelled us to adopt the following four-step approach. Acylation of **21** with phenoxyacetyl chloride followed by debenzylation of **22** gave **23**. Treatment of the latter compound with excess 3,4-di-*O*-acetylcaffeoyl chloride, and then mild deesterification

of the phenoxyacetyl and acetyl groups of **24**, gave Kelampayoside B (**2**) in a yield of 29% over four steps. The ^{1}H- and ^{13}C-NMR data of the target compound **2** were in excellent agreement with those reported[3] for Kelampayoside B (**2**).

The results described in this paper clearly show that apiofuranoide **3** is an effective and highly potent glycosylating agent. In addition, $BF_3{\cdot}Et_2O$ catalysed Fries-type rearrangement (*O→C*-aryl migration) of an electron-rich aryl group at the anomeric centre of sugars can be attenuated by the addition of THF to the reaction mixture. The implementation of these findings in the design and synthesis of other biologically interesting oligosaccharides will be published in due course.

References and Notes

1. Shiraga, Y.; Okana, K.; Akira, T.; Fukaya, C.; Yokayama, K.; Tanaka, S.; Fukui, H.; Tubata, M. *Tetrahedron*, **1988**, *44*, 4703.
2. Miyamura, M.; Nohara, T.; Tomimatsu, T.; Nishioka, I. *Phytochemistry*, **1983**, *22*, 215.
3. Kitagawa, H.; Wei, H.; Nagao S.; Mahmud, T.; Hori, K.; Kobayashi, M.; Uji, T.; Shibuya H. *Chem. Pharm. Bull.*, **1996**, *44*, 1162.
4. a) Mbaïraroua, O.; Ton-That, T.; Tapiéro, C. *Carbohydrate Research*, 253, **1994**, 79. b) Suzuki, Y.; Yamaguchi, I.; Morofushi, N.; Takahashi, N.; Sugawara, F.; Yoshita, S.; Nukada, T.; Ogawa, T. *Agric. Biol. Chem.*, **1988**, *52*, 1261. c) Hettinger, P.; Schildknecht, H. *Liebigs Ann. Chem.*, **1984**, 1230.
5. Watson, R.R.; Orenstein, N.S. *Adv. Carbohydr. Chem. Biochem.*, **1975**, 31, 135.
6. a) Mahling, J-A.; Schmidt, R.R. *Synthesis*, **1993**, 325. b) Mahling, J-A.; Jung, K-H.; Schmidt, R.R. *Liebigs Ann.*, **1995**, 461. c) Schmidt, R.R.; Hoffmann, M. *Tetrahedron Lett.*, **1982**, *23*, 409. d) Matsumoto, T.; Hosoya, T.; Suzuki, K. *Tetrahedron Lett.*, **1990**, *32*, 4629. e) Matsumoto, T.; Katsuki, M.; Suzuki, K. *Tetrahedron Lett.*, **1988**, *29*, 6935.
7. Veeneman, G.H.; Van Leeuwen, S.H.; Van Boom, J.H. *Tetrahedron Lett.*, **1990**, *31*, 1331.
8. Bochkov, A.F; Snuatkova, V.I.; Voznyi Ya, V.; Kochetkov, N.K. *J. Gen. Chem. USSR*, **1971**, *41*, 2808.
9. Ray, A.K.; Roy, N. *Carbohydr. Res.*, **1990**, *196*, 95.
10. a) Roush, W.R.; Lin, X-L. *J. Am. Chem. Soc.*, **1995**, *117*, 2236. b) Roush, W.R.; Lin, X-L. *J. Org. Chem.*, **1991**, *56*, 5740. c) Kometani, T.; Kondo, H.; Fujimori, Y. *Synthesis*, **1988**, 1005.
11. Glycosidation of 3,4,5-trimethoxyphenol with **14** using excess (*i.e.* 1.0 equiv.) $BF_3{\cdot}Et_2O$ resulted, as evidenced by ^{1}H NMR and ^{13}C NMR, in the exclusive formation of the *C*-aryl derivative **17** (84%).
12. In an attempt to completely suppress *O→C* migration, the glycosidation was also carried out at –20°C. However, under these conditions no reaction of **14** with antiarol was observed.
13. Relevant data for compound **19** and **20**.
    19: ^{1}H NMR ($CDCl_3$): δ 3.70 (s, 6H, 3-OMe, 5-OMe), 3.77 (s, 3H, 4-OMe), 5.00 (d, 2H, H-2"), 5.26 (d, 1H, H-1' $J_{1',2'}$ 7.8 Hz), 5.28 (d, 1H, H-1" $J_{1",2"}$ 0.8 Hz), 6.26 (s, 2H, H-2, H-6). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 55.9 (3-OMe, 5-OMe), 60.7 (4-OMe), 65.9, 69.0, 73.1 (C-4", C-5", C-6', CH_2, Bn), 69.1, 71.6, 72.5, 73.7, 76.2 (C-2', C-3', C-4', C-5', C-2"), 85.0 (C-3"), 95.5 (C-2, C-6), 100.4 (C-1'), 105.8 (C-1"), 133.6 (C-4), 152.7 (C-1), 153.4 (C-3, C-5).
    20: ^{1}H NMR ($CDCl_3$): δ 2.91 (s, 3H, 5-OMe), 3.72, 3.80 (2 x s, 6H, 4-OMe, 6-OMe), 4.35 (d, 1H, H-1' $J_{1',2'}$ 9.7 Hz), 4.84 (d, 2H, H-2"), 5.60 (d, 1H, H-3 or H-5 $J_{3,5}$ 1.4 Hz), 5.63 (d, 1H, H-3 or H-5). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 52.1 (5-OMe), 55.9, 56.5 (4-OMe, 6-OMe), 66.6, 69.1, (C-4", C-5", C-6', CH_2, Bn), 73.0, 73.1, 75.1, 75.8, 78.3, 78.4 (C-1', C-2', C-3', C-4', C-5', C-2"), 79.8 (C-1), 85.3 (C-3"), 104.5, 105.4, 106.3 (C-1", C-3, C-5), 128.0-133.4 (CH, Bz), 128.7 129.0, 130.1 (Cq, Bz), 165.7, 165.1, 165.7 (C=O, Bz), 166.6, 167.7 (C-4, C-6), 186.7 (C-2).
14. Li, Z.; Huang, H.; Cai, M. *Chem. Abstr.* **1993**, *119*, 95041b.