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Stereoselective synthesis of β-rhamnopyranosides *via* gold(I)-catalyzed glycosylation with 2-alkynyl-4-nitro-benzoate donors†

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Stereoselective β-rhamnopyranosylation remains a challenge, due to the unfavorable anomeric effect and steric hindrance of the C2-substituent; herein, this challenge is addressed with a gold(I)-catalyzed S_N2-like glycosylation protocol employing α-rhamnopyranosyl 2-alkynyl-4-nitro-benzoates as donors.

The stereoselective synthesis of β-rhamnopyranosides is a relevant problem compared to that of β-mannopyranosides, involving the formation of the equatorial 1,2-*cis*-glycopyranosidic bond which is unfavorable due to the anomeric and steric effects.[1,2] The latter problem has been addressed brilliantly by the Crich protocol in which an S_N2-like glycosylation pathway is exploited *via* an intermediacy of a mannopyranosyl α-triflate or a relevant contact ion-pair.[2] The formation of these intermediates is secured *via* tethering the 4,6-OH groups so as to provide the requisite torsional strain and the electron-withdrawing effect of O6 at a fixed C5–C6 *trans–gauche* (tg) conformation to discourage the formation of the solvent-separated oxocarbenium species, which would lead predominantly to α-mannopyranosides.[3] Applying Crich's β-mannosylation protocol to the synthesis of β-rhamnopyranosides requires subsequent defunctionalization at C6.[4] The indirect methods for the synthesis of β-rhamnopyranosides also include intramolecular aglycon delivery (which requires pre-installation of the aglycon),[5] glycosylation with ulosyl donors (followed by reduction of the ketone),[6] and glycosylation with 6-thio-6-deoxy-mannosyl donors (followed by desulfurization).[7] Direct β-selective rhamnosylation has been realized *via* a judicious choice of the protecting groups and glycosylation conditions, employing such rhamnopyranosyl donors as 2,3 or 3,4-*O*-carbonates,[8] 2,3-*O*-alkylidenes,[9] those in $^4C_1$ conformation,[10] 2-*O*-sulfonates,[11] and 1,2-*O*-stannylene acetal donors.[12] However, satisfactory β-selectivity is limited only to those coupling with reactive acceptors.

Recently, we disclosed that β-mannosylation could be effected with mannopyranosyl *ortho*-alkynylbenzoate donors[13] under the catalysis of a gold(I) complex bearing a noncoordinating counter anion (*i.e.*, $Ph_3PAuBAr^F_4$; $^-BAr^F_4$ = tetrakis[3,5-bis-(trifluoromethyl)phenyl]borate), in that a 1-α-glycosyloxy-isochromenylium-4-gold(I) intermediate was invoked.[14] High β-selectivity could be attained even employing mannosyl donors without a tethering but instead with only electron-withdrawing groups at O4 and O6.[14,15] Inspired by these results, we embarked on exploration of the challenging β-rhamnopyranosylation with *ortho*-alkynylbenzoate donors (Fig. 1).

We commenced the study with the coupling of 2,3,4-tri-*O*-benzyl-α-rhamnosyl *o*-hexynylbenzoate **1** and galactoside alcohol **9a**, wherein the highly armed donor **1** was expected to render poor β-selectivity. Applying the previously optimized conditions for β-mannosylation (0.1 equiv. $Ph_3PAuBAr^F_4$, freshly prepared by mixing Ph_3AuCl and $AgBAr^F_4$ in Et_2O (0.45 M), PhCl, 5 Å MS, −20 °C),[14] the glycosylation led to the coupled disaccharide **10** within 3 h in an excellent 97% yield with an

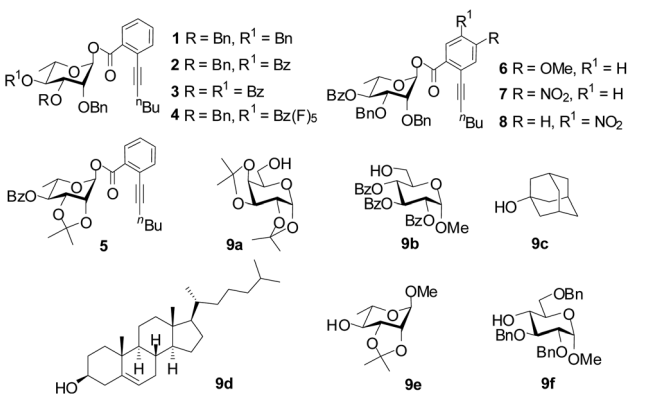

Fig. 1 α-L-Rhamnopyranosyl *ortho*-hexynylbenzoates **1–8** and alcoholic acceptors **9a–9f**.

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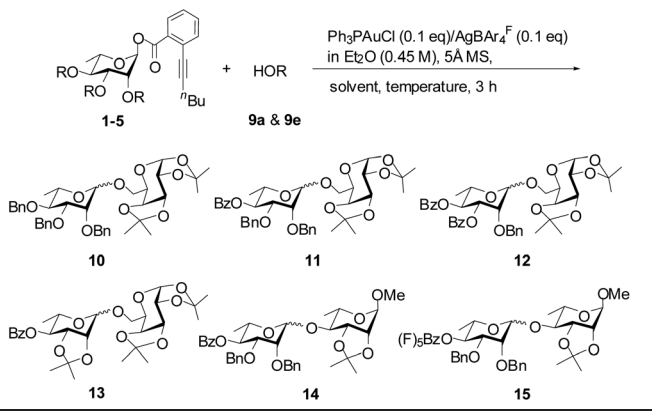
encouraging β/α-selectivity of 3.2 : 1 (Table 1, entry 1). Lowering the reaction temperature to −42 °C increased the β/α ratio to 5.5 : 1 while the yield was maintained (entry 2). To obtain a further lower temperature, the solvent PhCl (m.p. −45 °C) was replaced with toluene (m.p. −95 °C), and the glycosylation at −60 °C in toluene did give a better β-selectivity (β/α = 7.2 : 1; entry 3) in nearly quantitative yield. The β-selectivity was further increased at −70 °C (β/α = 10 : 1; entry 4), however, the coupling yield decreased dramatically to 38% with the rest of the donor **1** being fully recovered.

According to the precedent β-mannosylation/rhamnosylation,[14–16] replacement of the electron-donating 4-*O*-benzyl group with an electron-withdrawing benzoyl group in donor **1**, resulting in rhamnosyl donor **2**, would lead to better β-selectivity in the glycosylation. Indeed, the glycosylation of **9a** with **2** gave the coupled disaccharide **11** in an excellent β/α-selectivity of 14 : 1 (95%) in PhCl at −42 °C in 3 h (Table 1, entry 5). In contrast, the glycosylation of **9a** with donor **3**, which bears one more benzoyl group at O3, resulted in α-disaccharide **12** exclusively in 99% yield (entry 6); this could be attributable to the remote participation of the 3-*O*-benzoyl group.[15b] Additionally, similar glycosylation with donor **5**, which has its O2 and O3 being locked by isopropylidene acetal, provided a β/α ratio of 6.4 : 1 (entry 7), indicating no beneficial effect of such fixation of conformation on the β-rhamnosylation (*cf.*, entries 7 and 5).

The optimal donor **2** and rhamnosylation conditions (entry 5) were then applied to the coupling with rhamnoside alcohol **9e**, with which as the acceptor the previous mannosylation/rhamnosylation led to poor β-selectivity. As expected, the present $Ph_3PAuBAr^F_4$-catalyzed rhamnosylation of **2** and **9e** in PhCl at −42 °C afforded the coupled disaccharide **14** quantitatively but without stereoselectivity (β/α = 1.1 : 1; entry 8). Replacement of the 4-*O*-benzoyl group with a more electron-withdrawing pentafluorobenzyl group resulted in donor **4**. Although **4** was indeed much less reactive, so that completion of the glycosylation of **4** and **9e** required 12 h, the β-selectivity was increased marginally (β/α = 1.3 : 1; entry 9).

Now that the β-selective rhamnosylation of a secondary sugar alcohol such as **9e** was hardly achieved *via* modification of the protecting groups in the rhamnosyl donors, we turned our attention to the modification of the *ortho*-hexynylbenzoate leaving group. This could also affect the population and reactivity of the glycosylation intermediates and therefore possibly to streamline the S_N2-like β-rhamnosylation pathway. Thus, 4-*O*-benzoyl-2,3-di-*O*-benzyl-α-L-rhamnosyl 2-hexynyl-4-methoxybenzoate **6**, 2-hexynyl-4-nitrobenzoate **7**, and 2-hexynyl-5-nitrobenzoate **8** were prepared (see the ESI† for preparation) and subjected to the glycosylation with the difficult acceptor **9e** (Table 2). Compared to the non-substituted donor **2** (Table 1, entry 8), the 4-methoxy-substituted donor **6** was found much less reactive; the glycosylation led to the coupled disaccharide **14** in only 75% yield in 24 h, with 24% of **6** being recovered. Moreover, the β/α-selectivity remained poor (β/α = 1 : 1.5; Table 2, entry 1). Gratifyingly, the nitro-substituted donors **7** and **8** were more reactive than donor **2**, their glycosylation with **9e** completed within 0.5 and 1 h, respectively, and led to disaccharide **14** with a decent β/α-selectivity of ~3.3 : 1 (entries 2 and 3). Thus, these glycosylation reactions were further explored at lower temperatures (entries 4–8). With toluene as the solvent at −60 °C, the glycosylation of **8** and **9e** led to **14** in

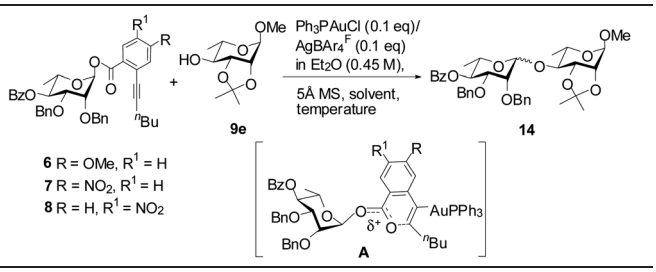
Table 1 The $Ph_3PAuBAr^F_4$-catalyzed glycosylation of rhamnosyl *ortho*-hexynylbenzoates **1–5** and acceptors **9a**/**9e**



Entry	Donor	Acceptor	Solvent	T [°C]	Product (yield)	β/α ratio[a]
1	**1**	**9a**	PhCl	−20	**10** (97%)	3.2 : 1
2	**1**	**9a**	PhCl	−42	**10** (99%)	5.5 : 1
3	**1**	**9a**	Toluene	−60	**10** (99%)	7.2 : 1
4	**1**	**9a**	Toluene	−70	**10** (38%)	10 : 1
5	**2**	**9a**	PhCl	−42	**11** (95%)	14 : 1
6	**3**	**9a**	PhCl	−42	**12** (99%)	α only
7	**5**	**9a**	PhCl	−42	**13** (99%)	6.4 : 1
8	**2**	**9e**	PhCl	−42	**14** (99%)	1.1 : 1
9[b]	**4**	**9e**	PhCl	−20	**15** (99%)	1.3 : 1

[a] The β/α ratio was determined by ^{1}H NMR. [b] The reaction was performed for 12 h.

Table 2 The $Ph_3PAuBAr^F_4$-catalyzed glycosylation of acceptor **9e** with L-rhamnosyl *ortho*-hexynylbenzoates **6–8**



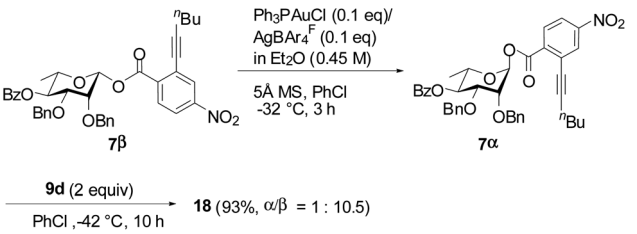
Entry	Donor	Solvent	T [°C]	t [h]	Yield	β/α ratio[a]
1[b]	**6**	PhCl	−42	24	75%	1 : 1.5
2	**7**	PhCl	−42	0.5	95%	3.2 : 1
3	**8**	PhCl	−42	1	87%	3.4 : 1
4	**8**	Toluene	−60	5	66%	4.9 : 1
5	**7**	CH_2Cl_2	−60	10	90%	5.8 : 1
6	**8**	CH_2Cl_2	−60	10	80%	7.2 : 1
7	**7**	CH_2Cl_2	−72	15	71%	8.0 : 1
8	**8**	CH_2Cl_2	−72	15	16%	β only

[a] The β/α ratio was determined by ^{1}H NMR. [b] 24% **6α** was recovered.

only 66% yield in 5 h, although the β-selectivity was slightly improved (β/α = 4.9 : 1; entry 4). CH_2Cl_2 was then found to be a better solvent at −60 °C for the present rhamnosylation; the coupling of **7**/**8** with **9e** (in 10 h) led to **14** in satisfactory yields and β-selectivities (90%, β/α = 5.8 : 1 and 80%, β/α = 7.2 : 1, respectively; entries 5 and 6). Further lowering the reaction temperature to −72 °C, the glycosylation of the 4-nitro donor **7** afforded **14** in 71% yield (15 hour) with a further improved β/α-selectivity of 8.0 : 1 (entry 7); whereas the glycosylation of the 5-nitro donor **8** hardly proceeded, leading to the β-product exclusively but in only 16% yield (entry 8).

At this junction, we examined with NMR the possible formation of the corresponding 1-α-glycosyloxy-isochromenylium-4-gold(I) intermediates (**A**) from the α-rhamnosyl *ortho*-hexynylbenzoates **6**, **7** and **2** upon activation with $Ph_3PAuBAr^F_4$ (1.0 equiv.).[14] At −42 °C in CD_2Cl_2, the corresponding intermediates **A** were detected from **2** and **6** (the poorer donors for β-rhamnosylation) but not from **7** (the better donors) (see the ESI†). These results imply that the covalent **A** is not a glycosylation intermediate, more likely a contact ion pair collapsed from **A** is the species which undergoes the present β-rhamnosylation. Indeed, the S_N1 character has already been experimentally proven in the Crich type β-mannosylation.[17]

Considering both the β-selectivity and the glycosylation yield, 4-nitrobenzoate **7** turned out to be the optimal donor in coupling with **9e** (Table 2); therefore, **7** was selected for glycosylation with a variety of alcohols (**9b–9d** and **9f**) to examine the scope of the present β-rhamnosylation protocol (Table 3). With adamantanol **9c** and cholesterol **9d** as the acceptors, the glycosylation catalyzed by 0.1 equiv. of $Ph_3PAuBAr^F_4$ led to the coupled glycosides **16** and **18**, respectively, in excellent yields (~96%) and β-selectivity (β/α = ~13 : 1) at −42 °C in PhCl (Table 3, entries 1 and 2). The coupling with sugar-6-OH acceptor **9b** proceeded smoothly at −60 °C in CH_2Cl_2 to provide the coupled disaccharide **17** in 95% yield with a satisfactory β/α ratio of 9.8 : 1 (entry 3). Under the same conditions, rhamnosylation of the hindered sugar-4-OH acceptor **9f** still led to an acceptable yield (75%) and β-selectivity (β/α = 4.2 : 1) of the coupled product **19** (entry 4). The same glycosylation at −72 °C proceeded much slower, leading to **19** in a similar yield (67%) within 20 h with a slightly better β-selectivity (β/α = 5.6 : 1, entry 5).

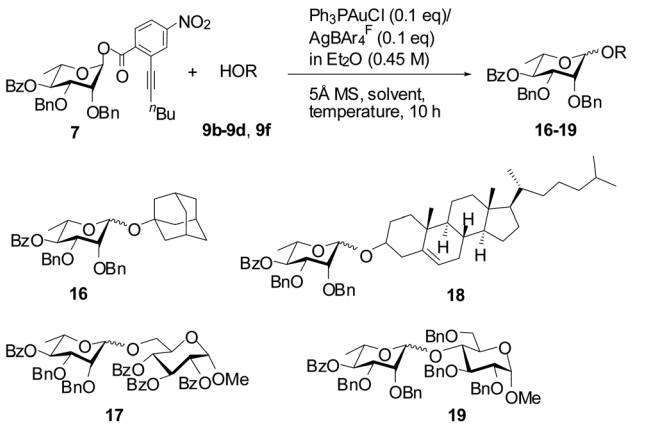


Scheme 1 The one-pot anomerization and β-rhamnosylation of acceptor **9d** with the β-donor **7β**.

Similar to the mannopyranosyl *o*-alkynylbenzoates,[14] the rhamnopyranosyl α/β-alkynylbenzoates could undergo anomerization in the presence of the gold(I) catalyst to give predominantly the α-anomers; therefore, the present β-rhamnosylation could also be realized using the β-anomer or the α/β-mixture of the donors (Scheme 1). Thus, the β-donor **7β** in PhCl was firstly treated with $Ph_3PAuBAr^F_4$ (0.1 equiv.) at −32 °C, TLC indicated that most of **7β** was converted into its α-donor **7** (α/β = ~10 : 1) after 3 h. The mixture was then cooled to −42 °C and acceptor **9d** (2 equiv.) was added; rhamnosylation proceeded smoothly to furnish **18** in an excellent 93% yield and β/α-selectivity of 10.5 : 1. Similar results were attained starting from a mixture of **7**/**7β** (1 : 1) employing the same procedure.

In summary, an effective β-rhamnopyranosylation protocol has been developed by employing rhamnopyranosyl *ortho*-hexynylbenzoates as donors under the catalysis of $Ph_3PAuBAr^F_4$. Both the electron-withdrawing protecting group on O4 and the electron-withdrawing nitro group on the leaving group have been found effective in enhancing the β-selectivity. Satisfactory coupling yields and β-selectivity are attainable even when coupling with hindered acceptors. The application of this protocol to the synthesis of the β-rhamnopyranosidic linkages occurring in the bacterial capsular and lipopolysaccharides is undergoing and the results will be reported in due course.

Table 3 The scope of acceptors in the $Ph_3PAuBAr^F_4$-catalyzed β-selective glycosylation of α-rhamnosyl 2-hexynyl-4-nitrobenzoate **7**



Entry	Acceptor	Solvent	T [°C]	Product (yield)	β/α ratio[a]
1	**9c**	PhCl	−42 °C	**16** (95%)	13.5 : 1
2	**9d**	PhCl	−42 °C	**18** (97%)	13.1 : 1
3	**9b**	CH_2Cl_2	−60 °C	**17** (95%)	9.8 : 1
4	**9f**	CH_2Cl_2	−60 °C	**19** (70%)	4.2 : 1
5[b]	**9f**	CH_2Cl_2	−72 °C	**19** (67%)	5.6 : 1

[a] The β/α ratio was determined by ^1H NMR. [b] The reaction was performed for 20 h.

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