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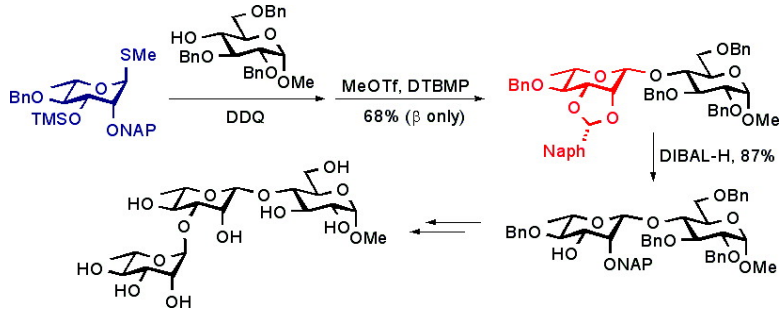

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Stereoselective Synthesis of β-L-Rhamnopyranosides

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In spite of remarkable progress in *O*-glycoside bond forming reactions, the stereoselective synthesis of β-L-rhamnopyranosides (β-L-Rha) remains challenging. Although its difficulty derives from structural features similar to β-D-mannopyranosides (β-D-Man) (i.e., equatorial, 1,2-*cis*),[1] the formation of β-L-Rha is by far more difficult. The direct glycosylation strategy employed for β-D-Man is not effective for β-L-Rha because the 6-deoxy structure of Rha excludes the use of a donor with 4,6-*O*-cyclic (e.g., benzylidene) protection,[2] which is essential for the stereoselective β-D-Man formation. Although β-D-Rha may be formed from β-D-Man through deoxygenation,[3] this strategy is not suitable for β-L-Rha because of the limited availability of L-Man. In spite of various attempts using structurally modified donors, such as 2,3-*O*-carbonate,[4] 2,3-*O*-alkylidene,[5] 3,4-*O*-carbonate,[6] 2-ulosyl[7] or 2-*O*-sulfonate,[8] 1,2-*O*-stanylene acetal,[9] and allyl-mediated IAD,[10] there was limited selectivity. We report herein the unprecedented stereoselective synthesis of β-L-Rha through intramolecular aglycon delivery (IAD).

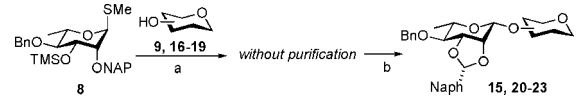
Our strategy exploits 2-naphthylmethyl (NAP) ether[11,12] to make a temporary linkage between donor and acceptor as a mixed acetal. We recently found that NAP ether is highly favorable as a tether for IAD. NAP-mediated IAD was found to be versatile, providing β-D-mannopyranosides, β-D-arabinofuranosides, and α-D-glucopyranosides in high yields and complete selectivity.[13] β-L-Rha has been discovered in various bacterial polysaccharides, such as *Sphaerotilus natans*,[14] *Azotobacter beijerinckii* TNM1,[15] *Salmonella* serogroup,[16] *Shigella boydii* type 18,[17] and *Vibrio cholerae* NRT36S.[18] These polysaccharides have (1→3)-β-L-Rha*p* substructures that are linked to Glc$^{O\text{-}4}$, Glc$^{O\text{-}3}$, Man$^{O\text{-}2}$, Rha$^{O\text{-}4}$, and GlcNAc$^{O\text{-}4}$, respectively. From examination of these structures, the corresponding derivatives **9**, **16**, **17**, **18**, and **19** were chosen as acceptors for this study (Table 1). As rhamnosyl donors, 2-*O*-NAP equipped thioglycosides **4**, **5**, and **8** were designed, which were all synthesized from thiorhamnoside **1**.

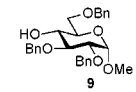
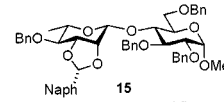
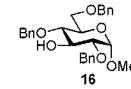
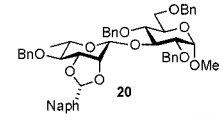
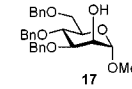
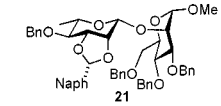
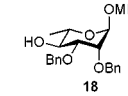
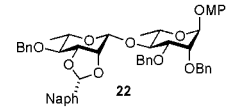
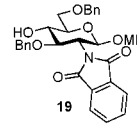
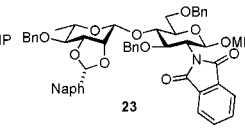
Thus, compounds **4** and **5** were prepared through 3,4-*O*-diacetal **2** and 2-*O*-NAP ether **3**, while preparation of compound **8** was conducted via monobenzyl ether **6**, which was regioselectively alkylated to give compound **7** (Scheme 1). The capacity of these donors was compared using the glucose derivative **9** as an acceptor. The formation of mixed acetals (MAs) with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) under anhydrous conditions afforded **10** (89%, diastereomeric ratio 12:1), **11** (75%, diastereomeric ratio 7:1), and **12** (93%, diastereomeric ratio 25:1). To our delight, subsequent IAD under standard conditions with MeOTf and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) proceeded smoothly. From **10** and **11**, β-L-rhamnosides **13** (72%, J_{C1-H} = 162 Hz)[20] and **14** (56%, J_{C1-H} = 164 Hz)[20] were obtained as single isomers, after acidic treatment and acetylation (Protocol A).

A more favorable result was obtained with 3-*O*-TMS protected MA **12** (Protocol B). In this case, the TMS ether intramolecularly trapped the transiently generated benzylic cation to give the naphthylidene cyclic acetal **15**,[21] which was obtained in 83% yield (J_{C1-H} = 164 Hz)[20] (Scheme 2).

The operationally simple IAD of crude **12** was attempted (Protocol C, Table 1), which gave **15** in a satisfactory yield of 68% based on **9**. The stereochemistry of the acetal carbon was assigned as endo, based on a ^{1}H NMR NOE experiment. Namely, NOE correlations were observed between the naphthylidene acetal proton

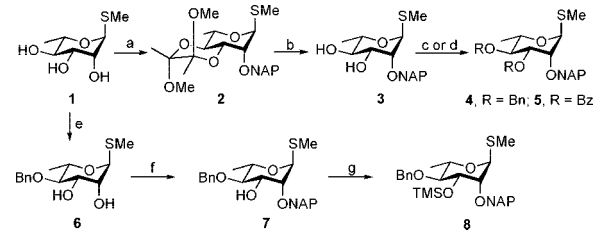
Table 1. Results of β-L-Rhamnopyranosylations (Protocol C)[a]



entry	Acceptor	Product	yield (%)[b]	J_{C1-H} (Hz)
1	 9	 15	68 (β only)	164
2	 16	 20	64 (β only)	166
3	 17	 21	67 (β only) endo/exo = 32:1	166
4	 18	 22	71 (β only)	162
5	 19	 23	69 (β only)	163

[a] Conditions: (a) DDQ, MS 4Å, CH_2Cl_2, 0 °C, 4 h; (b) MeOTf, DTBMP, MS 4Å $(CH_2Cl)_2$, 48 h. [b] Determined by ^{1}H NMR after isolation.

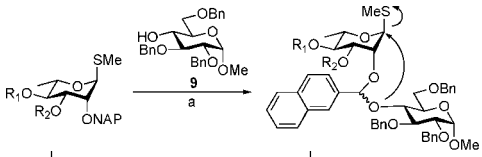
Scheme 1. Synthesis of Rhamnosyl Donors **4**, **5**, and **8**[a]



[a] Conditions: (a) (i) 2,3-butanedione, $CH(OMe)_3$, CSA, MeOH, 86%, (ii) NAPBr, NaH, DMF, 96%; (b) TFA, H_2O, CH_2Cl_2, 97%; (c) for **4**, BnBr, NaH, DMF, 88%; (d) for **5**, BzCl, DMAP, CH_2Cl_2, Et_3N, 92%; (e) see ref 19; (f) NAPBr, NaH, DMF, 71%; (g) TMSCl, imidazole, DMF, 93%.

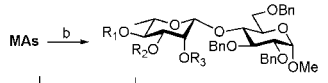
10.1021/ja801574q CCC: $40.75

Scheme 2. NAP-Mediated IAD (Protocols A, B)[a]



D	R_1	R_2
4	Bn	Bn
5	Bz	Bz
8	Bn	TMS

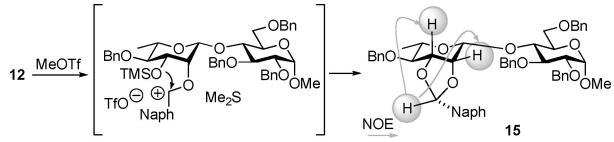
MA	R_1	R_2	Yield (%)[b]
10	Bn	Bn	89
11	Bz	Bz	75
12	Bn	TMS	93



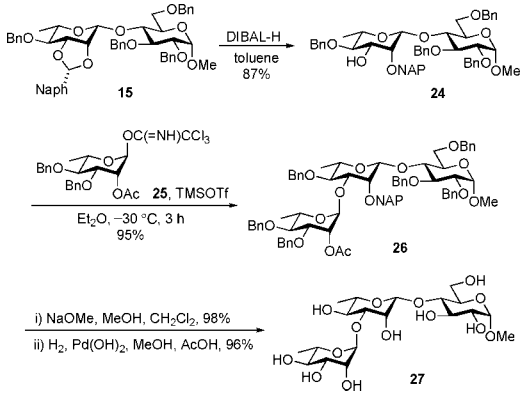
MA	P	R_1	R_2	R_3	Yield (%)[b]
10	**13**	Bn	Bn	Ac	72 (β only)
11	**14**	Bz	Bz	Ac	56 (β only)
12	**15**	Bn	>CHNaph		83 (β only)

[a] Conditions: (a) DDQ, MS 4Å, CH_2Cl_2; (b) Protocol A for MA **10** and **11**, (i) MeOTf, DTBMP, MS 4Å, $(CH_2Cl)_2$; (ii) TFA, CH_2Cl_2, then Ac_2O, DMAP, pyridine; Protocol B for MA **12**, only (i). [b] Determined by ^{1}H NMR after isolation.

Scheme 3. Determination of Stereochemistry for **15** as endo



Scheme 4. Complete Stereoselective Synthesis of a Trisaccharide



and the ring protons at C-2 and C-3 in the rhamnopyranoside (Scheme 3).[22]

Having achieved the stereoselective synthesis of β-L-Rha*p*(1→4)Glc (**15**), acceptors that correspond to $Glc^{3\text{-OH}}$ (**16**), $Man^{2\text{-OH}}$ (**17**), $Rha^{4\text{-OH}}$ (**18**), and $GlcNAc^{4\text{-OH}}$ (**19**) were examined. As expected, reactions with **8** gave desired products **20** [β-L-Rha*p*(1→3)Glc], **21** [β-L-Rha*p*(1→2)Man], **22** [β-L-Rha*p*(1→4)Rha], and **23** [β-L-Rha*p*(1→4)GlcN] in 64−71% yields (Table 1).

With the aim of synthesizing bacterial glycans, regioselective opening of the naphthylidene acetal was conducted to liberate the 3-OH of β-L-Rha*p*. DIBAL-H was suitable for this purpose, solely giving 2-*O*-NAP ether **24** from **15**. Subsequent α-L-rhamnopyranosylation of **24** with trichloroacetimidate **25**[23] cleanly afforded the desired trisaccharide **26** in high yield, which was deprotected under standard conditions to achieve the synthesis of **27**, corresponding to the substructure of *S. natans* polysaccharide[14] (Scheme 4).

In conclusion, application of the novel naphthylmethyl ether-mediated IAD toward the stereoselective construction of β-L-Rha*p* was achieved with various acceptors in good yield. The complete stereoselective synthesis of a trisaccharide, α-L-Rha*p*-(1→3)-β-L-Rha*p*-(1→4)Glc*p* from *S. natans*, was successfully accomplished, clearly suggesting the utility of NAP-IAD for β-L-rhamnopyranosylation.

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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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