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Efficient Generation of β-L-Rhamnosidic Linkages via the Ulosyl Bromide Approach

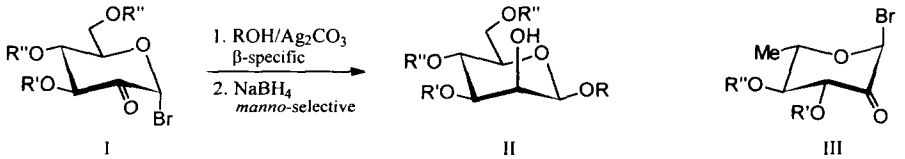
Frieder W. Lichtenthaler* and Thomas W. Metz

Institut für Organische Chemie, Technische Universität Darmstadt, Petersenstraße 22, D-64287 Darmstadt, Germany

Abstract: Practical protocols have been developed for the acquisition of ulosyl bromides of type III from L-rhamnose, i.e. 6-deoxy-α-L-*arabino*-2-ketohexosyl bromides **6** - **8**. They have high potential as indirect β-L-rhamnosyl donors, as they undergo β-specific glycosidations under Koenigs-Knorr conditions, and carbonyl reductions of the resulting β-L-ulosides proceed with high β-L-*rhamno* selectivity. © 1997 Elsevier Science Ltd.

For the generation of β-D-mannosidic linkages, the *ulosyl bromide approach*[1] has proved highly expedient, since the 2-oxo-glycosyl (glycos-*ulosyl*) bromides of type I, e.g. **1** - **5** [2-4], are well accessible from glucose and constitute efficient „indirect" β-D-mannosyl donors as they undergo β-specific glycosidations under Koenigs-Knorr conditions[2-4], and the resulting β-D-ulosides are reduced to the β-D-mannosides II with high selectivities, reaching 20:1 to 50:1 *manno/gluco* ratios in cases with 3-*O*-benzyl groups[3]. Accordingly, the 3-*O*-benzyl-protected ulosyl bromides **4** and **5** have quite advantageously been applied to the synthesis of a number of fairly complex trisaccharides with β-D-mannose units[4,5] as well as a bioactive β-D-mannosylated fungal metabolite[6].

In view of the various bacterial antigens containing β-L-rhamnopyranose units[7], ulosyl bromides of type III, i.e. 6-deoxy-L-enantiomers of I, would provide, if fairly well accessible, an expedient protocol for the straightforward synthesis of β-L-rhamnosides which have the additional advantage to accumulate with a free 2-OH amenable to direct further glycosylation. As a consequence, we have opted to evaluate this concept and here present practical syntheses of the ulosyl bromides **6** - **8** from L-rhamnose, as well as proof of their utility as indirect β-L-rhamnosyl donors.



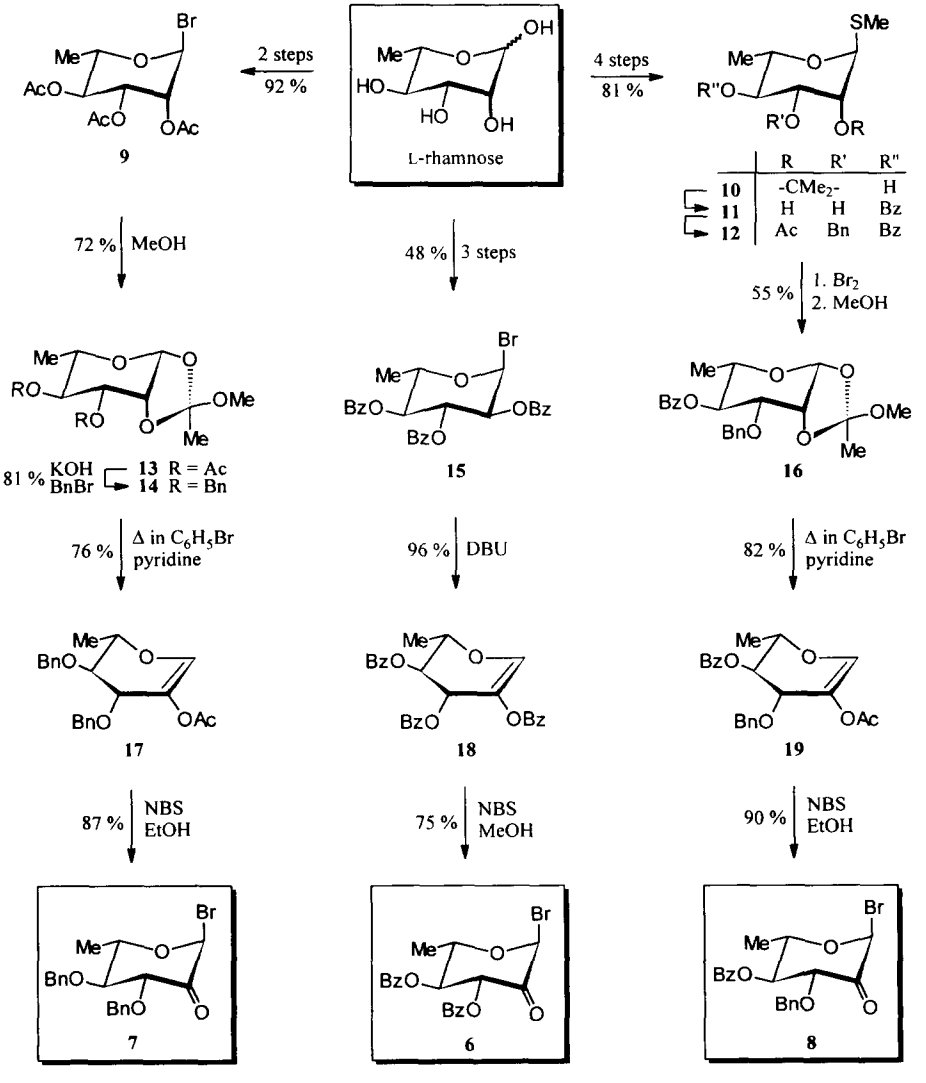
I II III

	R'	R"
1	Ac	Ac
2	Piv	Piv
3	Bz	Bz
4	Bn	Bn
5	Bn	Bz

	R'	R"
6	Bz	Bz
7	Bn	Bn
8	Bn	Bz

The practical acquisition of the indirect β-L-rhamnosyl donors **6** - **8** relied on L-rhamnose as a most suitable, readily available starting material, and on the 2-acyloxy-L-rhamnals **17** - **19** as key intermediates, as these were expected to smoothly elaborate the desired ulosyl bromides by brief exposure to NBS/methanol[2,3].

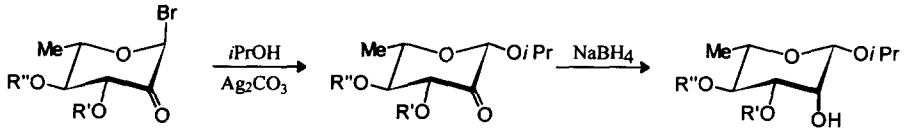
The preparation of the benzoyl-protected α-L-rhamnosulosyl bromide **6** comprised the conversion of L-rhamnose – by molybdate-catalyzed C-2-epimerization[8a], benzoylation, and HBr/HOAc treatment[8b], feasible in 48 % overall yield – into the 6-deoxy-L-glucosyl bromide **15**, in which HBr-elimination to the 2-benzoyloxy-L-rhamnal **18**[9] could smoothly be effected by DBU treatment. Subsequent exposure to NBS/methanol in dichloromethane (30 min, 25 °C) provided the desired **6** in crystalline form[9] and in quite satisfactory overall yield (39 %) for the five steps from L-rhamnose.



The 3,4-di-*O*-benzyl-blocked ulosyl bromide **7** similarly required a five-step sequence from L-rhamnose, involving conversion into its acetobromo derivative **9** [10] and then into orthoester **13** by treatment with methanol/lutidine[11]. Subsequent exchange of acetyl against benzyl blocking groups (**13** → **14**) was effected in a one-pot operation with benzyl bromide/KOH in THF (81 %), and followed by thermal fragmentation[3] (reflux in bromobenzene/pyridine for 5 h), which elaborated the 2-acetoxy-L-rhamnal **17** [9] via excision of methanol. The concluding exposure of **17** to NBS/ethanol gave ulosyl bromide **7** [9] in high yield.

For generation of L-rhamnosulosyl bromide **8** carrying different protecting groups at *O*-3 and *O*-4, L-rhamnose was first converted into its α-methylthio 2,3-*O*-isopropylidene derivative **10** [12], which was subjected to benzoylation, TFA-induced deacetonation (→ **11**, 83 %), dibutyltin oxide-assisted selective benzylation at *O*-3, and acetylation (77 % for **11** → **12**). Subsequent exposure of **12** to bromine in dichloromethane (20 min, 0 °C) followed by in situ treatment with methanol/lutidine gave the nicely crystalline orthoester **16**, which – like its benzylated analog **14** – yielded to thermal fragmentation to give the 2-acetoxy-L-rhamnal **19** [9]; finally treatment with NBS/ethanol smoothly elaborated the desired ulosyl bromide **8**. Although somewhat lengthy, the conversion L-rhamnose → **8** is not unefficient as four of the altogether nine steps can be combined into one-pot operations, allowing an overall yield of 25 %.

The utility of ulosyl bromides **6** - **8** as indirect β-L-rhamnosyl donors followed from the essential β-specificity attainable in the crucial glycosidation step: under standard Koenigs-Knorr conditions (Ag_2CO_3 in dichloromethane at 25 °C), alcoholysis is complete within 15-30 min, no α-anomeric products being detectable in the reaction mixture by TLC or ^1H NMR, and the β-ulosides **20** - **22** are isolable in yields of 80 - 90 %. Similar results are obtained with diacetone-galactose and with methyl 2,3-*O*-isopropylidene-α-L-rhamnose or its methylthio analog **10** as the alcohol components.



	R'	R"
6	Bz	Bz
7	Bn	Bn
8	Bn	Bz

	R'	R"
20	Bz	Bz
21	Bn	Bn
22	Bn	Bz

	R'	R"
23	Bz	Bz
24	Bn	Bn
25	Bn	Bz

The *rhamno*/6-deoxy-*gluco* selectivities obtained in the carbonyl reductions of glycosiduloses **20** - **22** confirmed previous findings[3] that the outcome depends on the nature of the 3-*O*-protection: uloside **20**, on exposure to $NaBH_4$ in dichloromethane/methanol (2 h, 0 °C → room temperature) gave a 3:1 mixture of the L-*rhamno* (**23**) and 6-deoxy-L-*gluco* epimers, whereas hydride reductions of the 3-*O*-benzylated compounds **21** and **22** take an essentially stereospecific course to the β-L-rhamnosides **24** and **25**, no 2-epimer being detectable in the reaction mixtures.

By way of summation, the exploratory results described amply demonstrate the potential of the uloside bromide approach for the generation of β-L-rhamnopyranosidic linkages – an approach that favorably compares with existing methodologies[13,14], in its β-specific glycosylation even reaching Ziegler's strategy of intramolecular β-L-rhamnosylation via pre-linked donor and acceptor substrates[14]. More elaborate glycosyl acceptors, most notably those with notoriously unreactive secondary OH groups, are presently being evaluated for glycosylations with **7** and **8**, as well as the application of this methodology to the synthesis of various biologically relevant oligosaccharides with β-L-rhamnose units. These and related efforts will be disclosed in due time.

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References and Notes

1. For an early review, see: Kaji, E.; Lichtenthaler, F. W. *Trends Glycosci. Glycotechnol.* **1993**, *5*, 121-142.
2. Lichtenthaler, F. W.; Kläres, U.; Lergenmüller, M.; Schwidetzky, S. *Synthesis* **1992**, 179-184.
3. Lichtenthaler, F. W.; Schneider-Adams, T. *J. Org. Chem.* **1994**, *59*, 6728-6734.
4. Lichtenthaler, F. W.; Kläres, U.; Szurmai, Z.; Werner, B. *Carbohydr. Res.* **1997**, in press.
5. Lichtenthaler, F. W.; Schneider-Adams, T.; Immel, S. *J. Org. Chem.* **1994**, *59*, 6735-6738.
6. Fürstner, A.; Konetzki, I. *Tetrahedron* **1996**, *52*, 15071-15078.
7. Jones, C. *Carbohydr. Res.* **1985**, *139*, 75-83. – Richards, J. C.; Perry, M. B. *Biochem. Cell Biol.* **1988**, *66*, 758-771; Moreau, M.; Richards, J. C.; Perry, M. B.; Kniskern, P. J. *Carbohydr. Res.* **1988**, *182*, 79-99; *Can. J. Chem.* **1989**, *67*, 1038-1050. – van Dam, J. E. G.; Fleer, A.; Snippe, H; van Leeuwenhoek, A. J. *Microbiol. Serol.* **1990**, *58*, 1-47.
8. (a) Bilik, V.; Voelter, W.; Bayer, E. *Angew. Chem.* **1971**, *83*, 967; *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 909. – (b) Kamiya, S.; Esaki, E.; Konishi, F. *Agric. Biol. Chem.* **1976**, *40*, 273-276.
9. Significant physical data of 6-deoxy-α-L-*arabino*-hexopyranos-2-ulosyl bromides **6** - **8** and 2-acyloxy-L-rhamnals **17** - **19** (rotations at $c = 1$ in $CHCl_3$, ^1H NMR at 300 MHz in $CDCl_3$):
   6: colorless needles (solvent), m.p. 124-125 °C, $[\alpha]_D^{20} = -195.2°$; ^1H NMR δ 1.44 (d, 3H, 6-H_3), 4.65 (qd, 1H, 5-H), 5.64 (dd, 1H, 4-H), 6.44 (d, 1H, 3-H), 6.46 (s, 1H, 1-H), $J_{3,4} = J_{4,5} = 10.3$, $J_{5,6} = 6.3$ Hz. The D-enantiomer of **6** had m.p. 125-126 °C and $[\alpha]_D^{22} = +191.4°$, as well as identical ^1H NMR data[15].
   7: syrup, $[\alpha]_D^{20} = -229.2°$. – ^1H NMR δ 1.35 (d, 3H, 6-H_3), 3.46 (dd, 1H, 4-H), 4.21 (qd, 1H, 5-H), 4.87 (d, 1H, 3-H), 6.27 (s, 1H, 1-H), $J_{3,4} = J_{4,5} = 9.6$, $J_{5,6} = 6.2$ Hz.
   8: syrup, $[\alpha]_D^{20} = -132.5°$; ^1H NMR δ 1.34 (d, 3H, 6-H_3), 4.41 (qd, 1H, 5-H), 4.85 (d, 1H, 3-H), 5.36 (dd, 1H, 4-H), 6.37 (s, 1H, 1-H), $J_{3,4} = 10.2$, $J_{4,5} = 10.1$, $J_{5,6} = 6.3$ Hz.
   17: syrup, $[\alpha]_D^{20} = -11.6°$.
   18: m.p. 95-96 °C, $[\alpha]_D^{20} = +176.8°$. – ^1H NMR δ 1.57 (d, 3H, 6-H_3), 4.56 (qd, 1H, 5-H), 5.56 (dd, 1H, 4-H), 6.11 (dd, 1H, 3-H), 6.90 (d, 1H, 1-H), $J_{1,3} = 0.6$, $J_{3,4} = 4.4$, $J_{4,5} = 5.6$, $J_{5,6} = 6.8$ Hz.
   19: syrup, $[\alpha]_D^{20} = +37.7°$.
10. Roth, W.; Pigman, W. *Methods Carbohydr. Chem.* **1963**, *2*, 407.
11. (a) Mazurek, M.; Perlin, A. S. *Can. J. Chem.* **1965**, *43*, 1918-1923. – (b) Bundle, D. R.; Josephson, S. *Can. J. Chem.* **1979**, *57*, 662-668.
12. Pozsgay, V.; Jennings, H. J. *J. Org. Chem.* **1988**, *53*, 4042-4052.
13. Bakinovsky, L. J.; Balan, N. F.; Shashkov, S. S.; Kochetkov, N. K. *Carbohydr. Res.* **1980**, *84*, 225-235. – Iversen, T.; Bundle, D. R. *Carbohydr. Res.* **1980**, *84*, C13-C15. – Paulsen, H.; Kutschker, W.; Lockhoff, O. *Chem. Ber.* **1981**, *114*, 3233-3241; *Carbohydr. Res.* **1983**, *120*, 25-42. – van Steijn, A. M. P.; Kamerling, J. P.; Vliegenthart, J. F. G. *Carbohydr. Chem.* **1992**, *11*, 665-689.
14. Lau, R.; Schüle, G.; Schwaneberg, U.; Ziegler, T. *Liebigs Ann.* **1995**, 1745-1754. – Schüle, G.; Ziegler, T. *Liebigs Ann.* **1996**, 1599-1607.
15. Lichtenthaler, F. W.; Cuny, E.; Weprek, S. *Angew. Chem.* **1983**, *95*, 906-907; *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 891-892.

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