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Convenient syntheses of isomaltose derivatives from amygdalin

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Abstract—The isomaltose trichloroacetimidate **7** was synthesized in five steps from D-amygdalin. The key step in this series of reactions was the acid catalyzed rearrangement of the inter-glycosydic bond to give the thermodynamically more stable α-anomer. The reaction was also applied to different di-, tri-, and tetrasaccharide derivatives of amygdalin giving the corresponding rearrangement products.

The synthesis of isomaltose (**1**) (Fig. 1), from monosaccharide precursors was first reported by Wolfram in 1961.[1] Since then, a multitude of papers have reported the chemical synthesis of this simple molecule.[2] Its synthetic challenge resides in the stereoselective 1,2-*cis* *O*-glycosylation reaction used to couple the monosaccharide derivatives. Total selectivity in these types of reactions has proven to be more difficult to achieve than with the corresponding 1,2-*trans* reactions.[3] The majority of synthetic routes to isomaltose use a bromide as the glycosyl donor with a nonparticipating group in position 2, thus taking advantage of the halide ion catalyzed glycosylation introduced by Lemieux et al.[4] to achieve 1,2-*cis* stereoselectivity in disaccharide formation. To our knowledge, only one example exists in the literature concerning the synthesis of isomaltose from a disaccharide precursor. In it, isomaltose was prepared by titanium tetrachloride mediated rearrangement of gentiobiose, followed by treatment with mercuric acetate in acetic acid to achieve the final isomaltose octaacetate in 37% yield.[5]

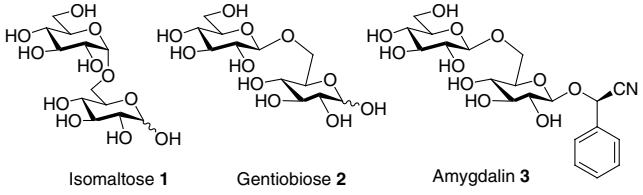

Figure 1.

In the course of our work related to saponin syntheses,[6] we wished to prepare a trichloroacetimidate derivative of gentiobiose (**2**). It was found that the treatment of per-benzoylated gentiobiose with HBr in acetic acid, followed by hydrolysis of the anomeric bromide and formation of the trichloroacetimidate gave a mixture of products in low yield. To our surprise, the major isolated product proved to be benzoylated isomaltose trichloroacetimidate. Since the source of our gentiobiose was D-amygdalin (**3**), we surmised that application of the same reaction conditions to amygdalin might lead to an isomaltose derivative. The advantage of using amygdalin instead of gentiobiose as an access to isomaltose was evident when comparing the initial cost of the two commercially available compounds. We would now like to report an efficient synthesis of isomaltose from an existing disaccharide precursor, D-amygdalin.

The starting point of our study was the preparation of the per-benzoylated amygdalin derivative **4**. Treatment of D-amygdalin with benzoyl chloride in pyridine gave **4** in 93% yield. HBr (33% in acetic acid) was then added to a solution of **4** in CH_2Cl_2 at room temperature. The reaction was complete in 4–6 h, and a mixture of two

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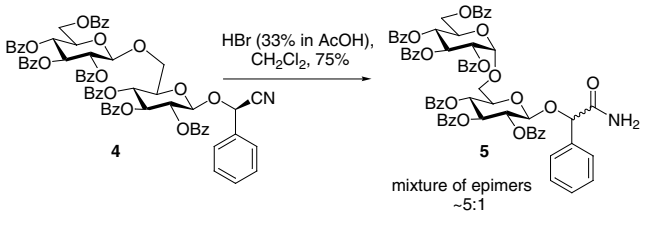
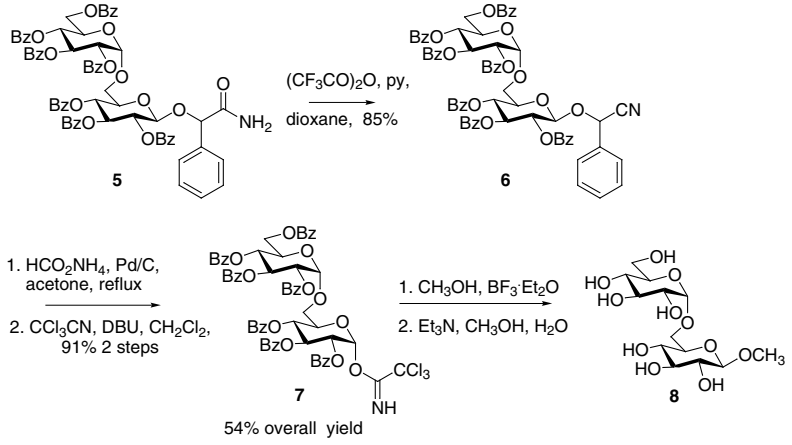


Scheme 1.

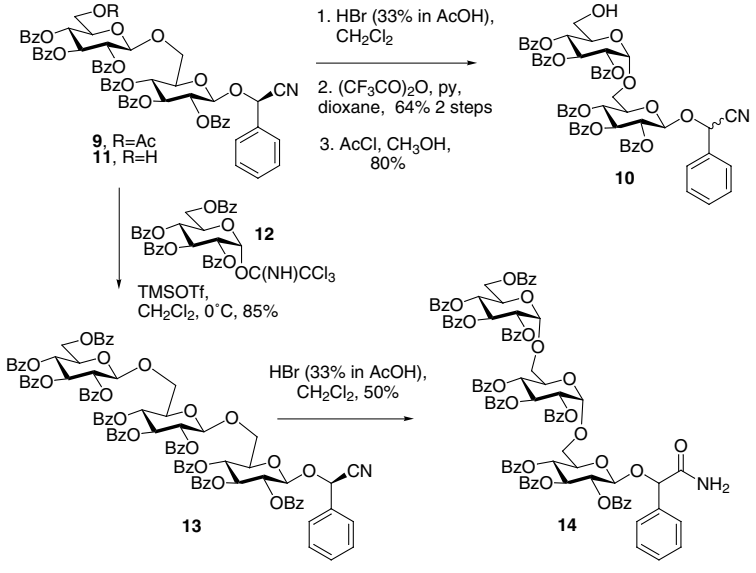
products (**5**) was obtained in 75% yield (Scheme 1). NMR analysis of the separated products showed that the acid catalyzed rearrangement had occurred, along with hydrolysis of the nitrile group into a primary amide and epimerization at the mandeloamide moiety.[7] It should be noted that no 'amygdalin' amide was detected, the reaction being completely stereoselective.

The primary amide was easily converted back into the nitrile **6** in 85% yield in the presence of trifluoroacetic anhydride and pyridine.[8] Hydrogenation of **6** followed by trichloroacetimidate formation gave the isomaltose derivative **7** in 54% overall yield from D-amygdalin (Scheme 2). The isomaltose derivative was fully characterized at this stage because the α-trichloroacetimidate was the unique reaction product and thus facilitated NMR interpretation.[9] The overall yield could be improved to 60% by performing the reactions without intermediate purification or separation of the epimers at the amide stage. Further structural confirmation was obtained by preparation of methyl β-D-isomaltoside (**8**) from trichloroacetimidate **7** in two steps. ^{1}H and ^{13}C NMR data were identical in all respects to previously published data.[10]

The acidic rearrangement conditions were then applied to another amygdalin derivative **9** with an acetate on the terminal 6′-hydroxyl group. Isomerization was successful, and two additional steps led to compound **10** having a free hydroxy group in the 6′ position, thus creating the possibility for further transformations on the non-reducing sugar (Scheme 3).



Scheme 2.



Scheme 3.

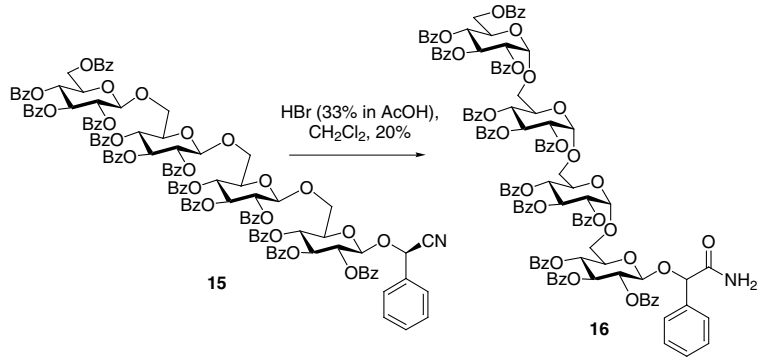
To further explore the limits of this reaction, we wished to see if it would be successful on tri- or tetrasaccharides derived from amygdalin. The trisaccharide **13** was synthesized from compound **11** and 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl trichloroacetimidate **12** in 85% yield. Treatment with HBr gave the desired rearrangement at *both* internal anomeric centers furnishing the isomaltotriose amide derivative **14** in 50% yield (Scheme 3). It was interesting to observe that no apparent epimerization took place as only one amide was isolated. Attempts to optimize the reaction conditions at this point were unsuccessful. Starting the reaction at low temperature (0 °C) and leaving it for long periods of time or letting it slowly warm to room temperature was detrimental. Leaving the reaction at room temperature overnight also caused the yield to drop to 20%.

The reaction was then tried with the tetrasaccharide derivative **15** (synthesized from 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl-(1 → 6)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranosyl trichloroacetimidate[11] and **11** in 68% yield). Rearrangement occurred at *three* anomeric centers to give the isomaltotetraose amide derivative **16** in 20% yield (Scheme 4).

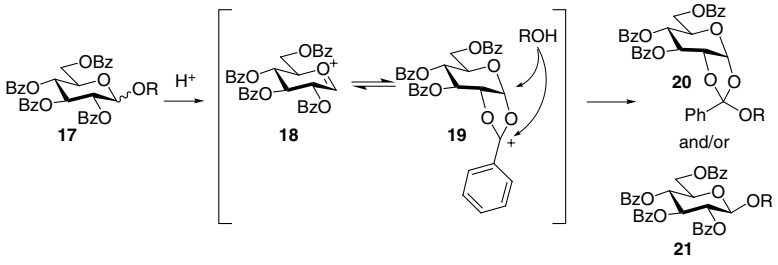
The surprising stereochemical outcome of the acid catalyzed rearrangement of the di-, tri-, and tetrasaccharides **4**, **13**, and **15**, remains unexplained. The reaction mechanism is unclear for several reasons; if bond rupture occurs to give the oxonium intermediate **18**, this exists in equilibrium with the benzoxonium intermediate **19** (Scheme 5). Expected reaction products would thus be orthoester **20** and/or the β-glycosylation product **21**. It has been the authors experience that glycosylation with benzoylated glucose derivatives often gives the orthoester before acid catalyzed rearrangement to the β-glycosylation product. A complex mixture of products could then be expected resulting from the formation of all possible alcohols, as well as their eventual recombinations.

The observed outcome of the reaction is contrary to the above arguments in that the acid catalyzed rearrangement gave the thermodynamically more stable α anomers in spite of possible neighboring group participation. No benzoyl orthoesters were detected. The reaction mixtures gave one easily isolated major product (as a mixture of 'amido' epimers for the disaccharide). We initially hypothesized that a rupture of the internal O-(C-1) bond (endocyclic cleavage) could result in a 'pre-β' linear intermediate **23** where rotation around the C–O bond could lead to the 'pre-α' intermediate **24**. Ring closure would then result in the formation of the more stable α-anomer **25** (Scheme 6).

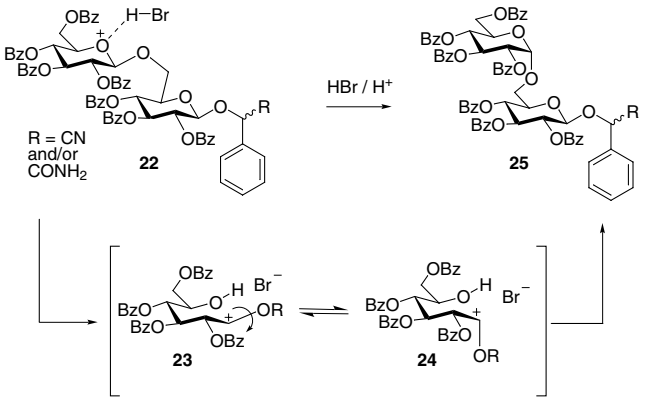
Based on very recent work of Deslongchamps, endocyclic cleavage is possible under these conditions, but the involvement of the free cationic species and bond rotation appear unlikely as the β-anomer tends to reform in nonpolar solvents.[12] A modified mechanism could be proposed[13] involving the bromide ion as a transient nucleophile/leaving group. First, endocyclic C–O bond cleavage (**23**), accompanied or followed by formation of a cationic benzoate species, ring opening by the nucleo-philic bromide (**26**) followed by displacement of the bromide by the free 5 hydroxyl group (**27**) (Scheme 7).



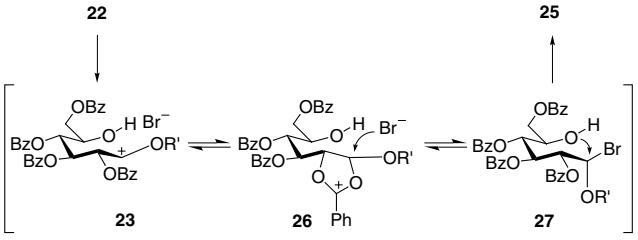
Scheme 4.



Scheme 5.



Scheme 6.



Scheme 7.

Exocyclic bond cleavage with orthoester formation and a complex mixture of products may also be a part of the reaction mechanism and cannot be excluded. In the tri- and tetrasaccharide reactions, small quantities of mono- and diglucosyl bromides were detected as nonpolar impurities. Analysis of the polar reaction impurities for these reactions was also attempted, but the complexity of the mixtures prevented characterization of any of these compounds.

In conclusion, isomaltose trichloroacetimidate was conveniently synthesized from D-amygdalin in five steps and 60% overall yield. In spite of the fact that isomaltose is commercially available (although expensive), and can be produced in large quantities through hydrolysis or enzymatic processes, this synthesis is easily accessible, and avoids the preparation of monosaccharide precursors as well as the necessity of controlling the glycosylation reaction for 1,2-*cis* bond formation. We have shown that this reaction is applicable to tri- and tetrasaccharide precursors, and further investigation is underway to better determine the mechanism as well as the scope and limitations of this reaction.

Acknowledgements

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References and notes

1. (a) Wolfram, M. L.; Pittet, A. O.; Gillam, I. C. *Proc. Natl. Acad. Sci. U.S.A.* **1961**, *47*, 700–705; (b) Wolfram, M. L.; Lineback, D. R. In *Methods in Carbohydrate Chemistry and Biochemistry*; Whistler, R. L., Wolfram, M. L. , Eds.; Academic: New York, London, 1963; Vol. 2, pp 341–345.
2. A few selected references are: (a) Wolfram, M. L.; Igarashi, K.; Koizumi, K. *J. Org. Chem.* **1965**, *30*, 3841–3844; (b) Koto, S.; Uchida, T.; Zen, S. *Chem. Lett.* **1972**, 1049–1052; (c) Pfaffli, P. J.; Hixon, S. H.; Anderson, L. *Carbohydr. Res.* **1972**, *23*, 195–206; (d) Takiura, K.; Kakehi, K.; Honda, S. *Chem. Pharm. Bull.* **1973**, *21*, 523–527; (e) Koto, S.; Uchida, T.; Zen, S. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 2520–2523; (f) Berry, J. M.; Dutton, G. S. *Carbohydr. Res.* **1974**, *38*, 339–345.
3. Demchenko, A. V. *Synlett* **2003**, *9*, 1225–1240.
4. Lemieux, R. U.; Hendriks, K. B.; Stick, R. V.; James, K. *J. Am. Chem. Soc.* **1975**, *97*, 4056–4062.
5. Lindberg, B. *Acta Chem. Scand.* **1949**, *3*, 1355–1357.
6. Plé, K.; Chwalek, M.; Voutquenne-Nazabadioko, L. *Eur. J. Org. Chem.* **2004**, 1588–1603.
7. Typical procedure for the acid catalyzed rearrangement: Hydrogen bromide (33% in AcOH; 10 mL) was added dropwise to a solution of amygdalin heptabenzoate **4** (2.0 g, 1.55 mmol) in CH_2Cl_2 (20 mL) at room temperature. The reaction was stirred for 6 h before pouring into ice water and extracting with CH_2Cl_2. The combined organic layers were washed with H_2O and $NaHCO_3$ (sat.) before drying over Na_2SO_4. Column chromatography of the crude reaction mixture (30% EtOAc, 5% CH_2Cl_2, 65% cyclohexane) gave 1.25 g of the major epimer of **5** along with 0.25 g of the minor one.
   Compound **5** major epimer: $R_f = 0.4$ (cyclohexane/EtOAc, 1:1); Selected NMR data: ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.82 (d, 1H, $J = 10.6$ Hz, H-6), 3.94 (m, 1H, H-5), 4.06 (dd, 1H, $J = 11.6$, $J = 5.5$ Hz, H-6), 4.45 (dd, 1H, $J = 12.1$, $J = 5.9$ Hz, H-6′), 4.59 (m, 1H, H-5′), 4.69 (d, 1H, $J = 7.8$ Hz, H-1), 4.70 (dd, 1H, $J = 12.0$, $J = 2.2$ Hz, H-6′), 5.29 (m, 2H, H-2, CH), 5.42 (dd, 1H, $J = 10.2$, $J = 3.7$ Hz, H-2′), 5.46 (t, 1H, $J = 9.8$ Hz, H-4), 5.57 (d, 1H, $J = 3.7$ Hz, H-1′), 5.68 (d, 1H, $J = 2.7$ Hz, NH), 5.75 (t, 1H, $J = 9.6$ Hz, H-3), 5.77 (t, 1H, $J = 9.7$ Hz, H-4′), 6.37 (t, 1H, $J = 9.9$ Hz, H-3′), 7.05 (d, 1H, $J = 2.6$ Hz, NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 62.9 (C-6′), 65.6 (C-6), 68.2 (C-5′), 68.7 (C-4), 69.3 (C-4′), 70.3 (C-3′), 71.9 (C-2), 72.0 (C-2′), 72.3 (C-3), 73.6 (C-5′), 80.2 (CH), 96.0 (C-1′), 98.4 (C-1), 171.8 ($CONH_2$); ESI-MS m/z 1227 $(M+Na)^+$; Anal. Calcd for $C_{69}H_{58}NO_{19}$: C, 68.76; H, 4.85; N, 1.16. Found: C, 68.45; H, 4.79; N, 1.28.
   Compound **5** minor epimer: $R_f = 0.32$ (cyclohexane/EtOAc, 1:1); Selected NMR data: ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.53 (d, 1H, $J = 10.3$ Hz, H-6), 3.91 (m, 2H, H-5, H-6), 4.37 (dd, 1H, $J = 12.0$, $J = 5.7$ Hz, H-6′), 4.43 (m, 1H, H-5′), 4.55 (dd, 1H, $J = 12.1$, $J = 2.6$ Hz, H-6′), 4.93 (d, 1H, $J = 7.9$ Hz, H-1), 5.19 (s, 1H, CH), 5.21 (d, 1H, $J = 3.7$ Hz, H-1′), 5.30 (dd, 1H, $J = 9.7$, $J = 7.9$ Hz, H-2), 5.39 (dd, 1H, $J = 10.1$, $J = 3.8$ Hz, H-2′), 5.44 (d, 1H, $J = 2.8$ Hz, NH), 5.56 (t, 1H, $J = 9.7$ Hz, H-4), 5.69 (t, 1H, $J = 9.9$ Hz, H-4′), 5.83 (t, 1H, $J = 9.7$ Hz, H-3), 6.29 (t, 1H, $J = 9.9$ Hz, H-3′), 6.84 (d, 1H, $J = 2.8$ Hz, NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 62.8 (C-6′), 65.9 (C-6), 68.0 (C-5′), 68.6 (C-4), 69.4 (C-4′), 70.5 (C-3′), 71.6 (C-2′), 72.3 (C-2), 72.6 (C-3), 73.5 (C-5), 82.0 (CH), 96.2 (C-1′), 100.1 (C-1), 172.0 ($CONH_2$); ESI-MS m/z 1227 $(M+Na)^+$.
8. Campagna, F.; Carroti, A.; Casini, G. *Tetrahedron Lett.* **1977**, 1813–1816.

9. Compound **7**: Selected NMR data: ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.72 (dd, 1H, $J = 10.9$, $J = 1.1$ Hz, H-6), 4.05 (dd, 1H, $J = 11.0$, $J = 6.6$ Hz, H-6), 4.39 (dd, 1H, $J = 12.4$, $J = 5.6$ Hz, H-6′), 4.53 (dd, 1H, $J = 10.4$, $J = 5.5$ Hz, H-5), 4.63 (dd, 1H, $J = 12.2$, $J = 2.2$ Hz, H-6′), 4.66 (m, 1H, H-5′), 5.35 (m, 2H, H-2, H-2′), 5.4 (d, 1H, $J = 3.7$ Hz, H-1′), 5.54 (t, 1H, $J = 10.1$ Hz, H-4), 5.67 (t, 1H, $J = 10.0$ Hz, H-4′), 6.22 (m, 2H, H-3, H-3′), 6.69 (d, 1H, $J = 3.8$ Hz, H-1), 9.0 (s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 62.7 (C-6′), 65.4 (C-6), 67.8 (C-5′), 68.6 (C-4), 69.4 (C-4′), 70.3 (C-3), 70.5 (C-3′), 70.6 (C-2), 71.2 (C-5), 71.7 (C-2′), 92.7 (C-1), 95.4 (C-1′), 160.0 (CNH); Anal. Calcd for $C_{63}H_{50}Cl_3NO_{18}$: C, 62.26; H, 4.15; N, 1.15. Found: C, 62.21; H, 4.07; N, 1.07.
10. ^{1}H NMR: (a) Jansson, P. E.; Kenne, L.; Kolare, I. *Carbohydr. Res.* **1994**, *257*, 163–174; (b) ^{13}C NMR: Forsgren, M.; Jansson, P. E.; Kenne, L. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2383–2388.
11. This compound was synthesized from D-amygdalin in three steps and 60% overall yield.
12. Deslongchamps, P.; Li, S.; Dory, Y. L. *Org. Lett.* **2004**, *6*, 505–508.
13. Following the referee's suggestion.