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Efficient synthesis of triazoles from D-arabinose and L-fucose

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Abstract

The efficient synthesis of sugar-derived triazoles via a one-pot substitution–cyclization–oxidation procedure is presented. Starting from D-arabinose and L-fucose, triazole structures as potential enzyme inhibitors were obtained in six to eight steps.

Keywords: carbohydrates; iminosugars; triazoles.

Various iminosugars have been shown to be very potent inhibitors of glycosidases[1] and glycosyltransferases.[2] Due to their ability to resemble the transition states[3] of the sugars involved in these processes, a variety of monocyclic[4] and bicyclic[5] iminosugars have been synthesized or isolated from natural sources over the years.

We have been involved in the synthesis of numerous compounds designed to inhibit glycosyl transfer enzymes, especially α-fucosidase and the family of fucosyltransferases.[5a] Herein, we would like to report a short and efficient synthesis of novel bicyclic triazoles starting from naturally occurring carbohydrates. The main structural features of triazoles include: an sp^2-configured anomeric carbon, the presence of lone-pair donating nitrogens, and flattened conformation of the six-membered ring, that might closely resemble the proposed transition state conformation of the natural substrates in the enzyme catalyzed reaction. Even though triazoles have been shown to be generally poor inhibitors of numerous β-glycosidases, possibly due to a lack of a lone-pair donating heteroatom next to the anomeric center in the triazole system,[6] we considered them as useful targets for synthesis and as interesting structures for evaluation as enzyme inhibitors.

Starting from D-arabinose **1** and L-fucose **2** the sugars were transformed into their tri-*O*-2,3,4-benzyl-derivatives **3** and **4** by known procedures (Scheme 1).[7,8] The α,β-unsaturated esters **5** and

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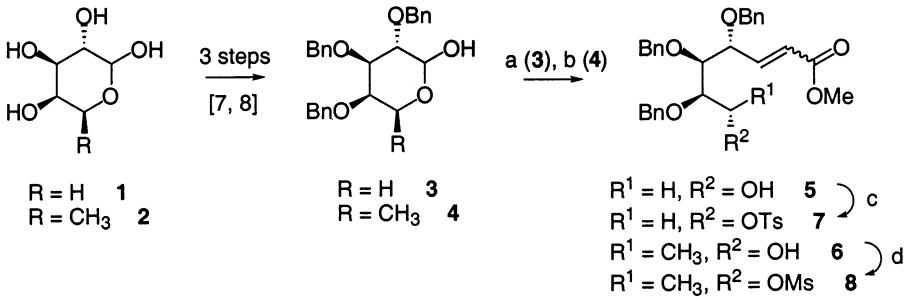
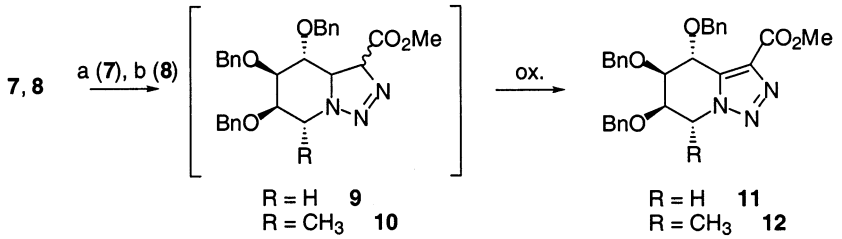
6 were formed in high yields from **3** and **4** as a 2:1 mixture of *trans*:*cis* isomers after Horner–Wittig–Emmons reaction.[9] Subsequently, **5** and **6** were converted to the tosylate **7** and the mesylate **8**, respectively.



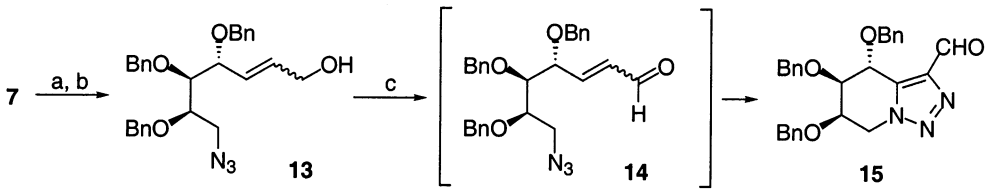
Scheme 1. *Reagent and conditions*: (a) methyl-(triphenylphosphoranylidene)-acetate, toluene, 80°C, 16 h, 94%; (b) methyl-(triphenylphosphoranylidene)-acetate, toluene, 80°C, 16 h, 81%; (c) TsCl, DMAP, pyridine, 40°C, 24 h, 89%; (d) MsCl, DMAP, pyridine, rt, 24 h, 91%

Even though the formation of triazolines by intramolecular addition to α,β-unsaturated esters has been studied,[10] lengthy routes accompanied the introduction of the azido group. In hopes to introduce the azide and directly convert this intermediate to the triazoline in a one-pot procedure, by first displacement with azide and then subsequent cyclization with the unsaturated ester, both the tosylate **7** and the mesylate **8** were treated with sodium azide followed by 1,8-diazabicyclo-[5.4.1]-undec-7-ene (DBU)[11] in DMF (Scheme 2).[12] Surprisingly, triazoles **11** and **12** were obtained in 30% overall yield.[13] It is likely that the triazoline intermediates **9** and **10** in this three-step–one-pot reaction were easily aromatized by air oxidation.



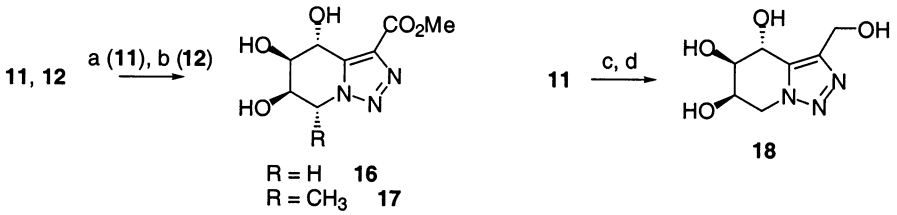
Scheme 2. (a) i: NaN_3, DMF, 80°C, 1 h, ii: DBU, 80°C, 1 h, 30%; (b) i: NaN_3, DMF, 80°C, 1 h, ii: DBU, 80°C, 1 h, 30%

In order to investigate the one-pot cyclization sequence of an azide with an unsaturated aldehyde, tosylate **7** was converted to the allylic alcohol **13** in two steps (Scheme 3). The allylic alcohol **13** was then oxidized with tetrapropylammonium perruthenate (TPAP)[14] to give the aldehyde intermediate **14** which was transformed to triazole **15** after further oxidation with TPAP with NMO (1.5 equiv.) as co-oxidant.



Scheme 3. (a) 1 M DIBAL in THF, toluene, 0°C, 35 min, 85%; (b) NaN_3, DMF, 70°C, 73% (+11% of starting material); (c) TPAP, NMO, molecular sieves, CH_2Cl_2, rt, 5 h, 26%

The triazoles were deprotected to give the corresponding compounds **16** and **17**; reduction of the methyl ester, followed by deprotection gave the corresponding compound **18** (Scheme 4).[15] Future plans include the use of these triazoles as building blocks for the development of enzyme inhibitors and further development of the three-step process described herein.



Scheme 4. (a) Pd/C, H_2, MeOH/AcOH 1/1, rt, 48 h, 95%; (b) Pd/C, H_2, MeOH/AcOH 1/1, rt, 40 h, 77%; (c) $LiAlH_4$, THF, 0°C, 10 min, 88%; (d) Pd/C, H_2, MeOH/AcOH 1/1, rt, 48 h, 95%

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11. DBU was added to the reaction mixture in order to avoid side products resulting from Michael-type reaction of azide to the unsaturated ester.
12. Standard procedure for the formation of triazoles from tosylate **7** (same procedure starting from mesylate **8**): 850 mg (1.348 mmol) of the tosylate **7** and 350 mg (5.390 mmol) of sodium azide were stirred in 8 ml of DMF at 80°C for 45 min. 405 μl (2.696 mmol) of DBU were added at room temperature. After 30 min at 80°C the reaction mixture was poured into a 1/1 mixture of H_2O/Et_2O, extracted with Et_2O, washed with H_2O and brine, and dried over Na_2SO_4. Purification via column chromatography (EtOAc/hexanes 1/4) yielded 202 mg (30%) of the triazole **11**.
13. The comparable stepwise cyclization–oxidation sequence starting from an appropriate azide-containing alkene gives a yield of 45% over two steps (Ref. 10).
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15. Selected analytical data for the deprotected triazoles **16**, **17**, and **18**. **16**: ^{1}H NMR (500 MHz, CD_3OD): $\delta = 3.89$ (s, 3 H), 4.04 (dd, $J = 4.4$, 1.8 Hz, 1 H), 4.23 (dd, $J = 12.9$, 8.5 Hz, 1 H), 4.41 (ddd, $J = 8.5$, 5.5, 1.8 Hz, 1 H), 4.58 (dd, $J = 12.9$, 5.5 Hz, 1 H), 5.09 (d, $J = 4.4$ Hz, 1 H); HRMS: MH^+ calcd for $M = C_8H_{11}N_3O_5$ 230.0771, found 230.0777. **17**: ^{1}H NMR (600 MHz, CD_3OD): $\delta = 1.71$ (d, $J = 6.5$ Hz, 3 H), 3.84 (s, 3 H), 3.95 (dd, $J = 8.8$, 2.2 Hz, 1 H), 4.00 (dd. $J = 4.0$, 2.2 Hz, 1 H), 4.32 (dq, $J = 8.3$, 6.6 Hz, 1 H), 5.06 (d, $J = 4.0$ Hz, 1 H); ^{13}C NMR (150 MHz, CD_3OD): $\delta = 17.37$, 52.53, 56.81, 64.39, 71.41, 72.50, 137.70, 139.92, 162.71; HRMS: MH^+ calcd for $M = C_9H_{13}N_3O_5$ 244.0928, found 244.0933. **18**: ^{1}H NMR (500 MHz, D_2O): $\delta = 4.12$ (m, 1 H), 4.53 (m, 1 H), 4.57 (m, 1 H), 4.64 (m, 1 H), 4.80 (m, 1 H), 4.82 (m, 1 H), 5.06 (d, $J = 7.4$ Hz, 1 H); ^{13}C NMR (125 MHz, CD_3OD/D_2O): $\delta = 50.66$, 55.90, 65.48, 67.60, 74.02, 134.47, 145.88.