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Radical Cyclization of Sugar-Derived β-(Alkynyloxy)acrylates: Synthesis of Novel Fused Ethers

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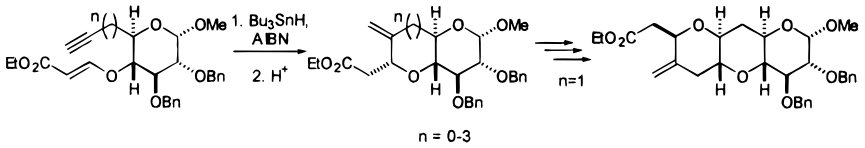
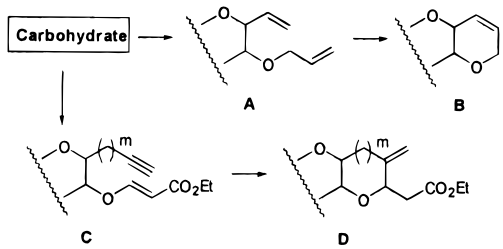
ABSTRACT



Tributyltin radical mediated cyclization of carbohydrate-derived β-(alkynyloxy)acrylates leading to highly functionalized *cis*- and *trans*-fused bicyclic ethers of various ring sizes is described. The efficacy of the radical cyclization is nicely illustrated in the iterative construction of a *trans*-fused tricyclic tetrahydropyran.

The development of synthetic procedures toward fused oxacycles, which are key structural elements in many marine toxins such as the brevetoxins[1] and ciguatoxins,[2] has received considerable attention over the past decade.[3] In this respect, we[4] and others[5] recently showed the versatility of carbohydrate-derived dienes (**A**, Scheme 1) and enynes in the ring closing

Scheme 1



metathesis mediated synthesis of *cis*- and *trans*-fused bicyclic (**B**) as well as tricyclic ether systems. Some years ago, Lee et al.[6] revealed that β-(alkynyloxy)acrylates could be converted into monocyclic ethers via tributyltin radical mediated cyclization and subsequent acidic destannylation. It occurred to us that this interesting two-step methodology could be adopted for the conversion of appropriate carbohydrate-derived β-(alkynyloxy)acrylates **C** (see Scheme 1) into highly functionalized bicyclic ethers of type **D**.

We here report the general usefulness of this approach in the construction of *cis*- and *trans*-fused bicyclic ethers of various ring sizes (i.e., **D**, $n = 0-3$), as well as the feasibility

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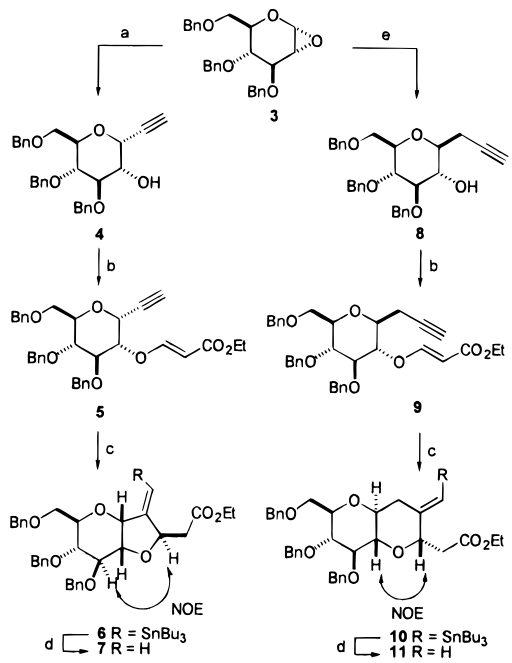
of transforming **C** ($n = 1$) into a tricyclic ether system via an iterative process.

In the first instance, the transformation of the known[7] perbenzylated α-1,2-anhydro-D-glucose **3** (Scheme 2) into

Scheme 2[a]

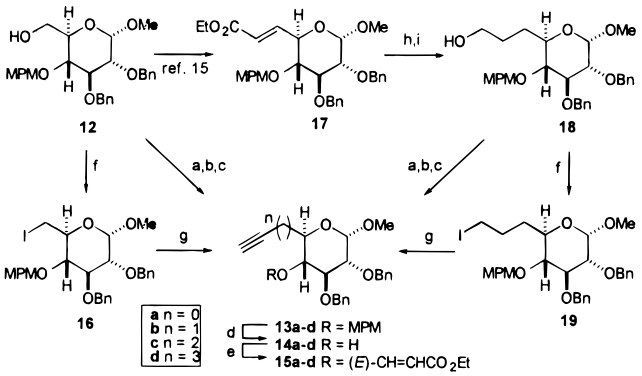


[a] Reagents and conditions: (a) NaCCH, $ZnCl_2$, THF, 0 °C to room temperature, 85%; (b) ethyl propiolate, NMM, CH_2Cl_2, 98% **5**, 95% **9**; (c) Bu_3SnH, AIBN, added over 5 h, toluene, 80 °C, 59% **6**, 72% **10**; (d) *p*-TsOH, CH_2Cl_2, 97% **7**, 99% **11**; (e) $Bu_3SnCH{=}C{=}CH2$, *n*-BuLi, then $ZnCl_2$, then **3**, −50 °C to room temperature, 72%.

the respective *cis*-5,6- and *trans*-6,6-bicyclic ethers **7** and **11** was explored. To this end, **3** was treated with sodium acetylide in the presence of zinc chloride to give exclusively the α-ethynyl-*C*-glucoside **4**.[8,9] Hetero-Michael addition of **4** to ethyl propiolate under the influence of *N*-methylmorpholine gave the sugar-derived β-(alkynyloxy)acrylate **5** in 83% yield based on **3**. The radical cyclization of **5** by syringe pump addition of Bu_3SnH and AIBN in toluene at 80 °C led to the isolation of *cis*-fused 5,6-bicyclic vinylstannane derivative **6** in a yield of 59%. Acidic destannylation of **6** afforded in near quantitative yield **7**, the stereochemistry of which was firmly established by NOESY spectroscopy. On the other hand, the *trans*-fused 6,6-bicyclic ether system **11** was also readily accessible from **3** by the following sequence of reactions. Ring opening of epoxide **3** with allenyllithium, generated in situ by transmetalation of allenyltributyltin[10] with *n*-butyllithium, under the influence of zinc chloride proceeded with virtually complete stereoselectivity to give the β-propargyl-*C*-glucoside **8**.[9] Subjection of the corresponding Michael adduct **9** to the same two-step procedure mentioned for the conversion of **5** into **7** gave the expected *trans*-fused pyranopyran **11** as the single diastereoisomer in 71% over the two steps.

The high stereoselectivity and acceptable yield of the radical cyclization of **9** was an incentive to explore the feasibility of converting the known[11] partially protected methyl α-D-glucoside **12** (Scheme 3) into the *trans*-fused

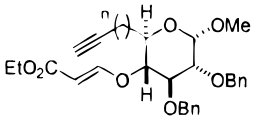
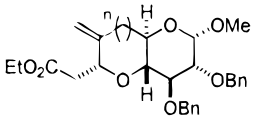
Scheme 3[a]



[a] Reagents and conditions: (a) Dess−Martin periodinane, CH_2Cl_2; (b) PPh_3, CBr_4, CH_2Cl_2, 82%-83% (two steps); (c) *t*-BuLi, THF, −50 °C, 76% **13a**, 92% **13c**; (d) DDQ, H_2O, CH_2Cl_2, 79% **14a**, 77% **14b**, 77% **14c**, 88% **14d**; (e) ethyl propiolate, NMM, CH_2Cl_2, 94% **15a**, 99% **15b**, 97% **15c**, 96% **15d**; (f) I_2, imidazole, toluene, 92% **16**, 78% **19**; (g) HCCLi ethylenediamine complex, DMSO, 74% **13b**, 82% **13d**; (h) H_2, PtO_2, EtOAc/hexanes; (i) $LiAlH_4$, THF, 0 °C, 76% (two steps).

five- to eight-membered bicyclic ethers **20a**−**d** (Table 1). Accordingly, **12** was subjected to Dess−Martin oxidation[12] and the resulting aldehyde was transformed into alkyne **13a**

Table 1. Formation of Five- through Eight-Membered Rings

starting compound	product[a]	yield[b]
		
15a n=0	**20a**	85%
15b n=1	**20b**	85%
15c n=2	**20c**	76%
15d n=3	**20d**	13%[c]

[a] Conditions: (a) 2 equiv of Bu_3SnH and 0.25 equiv of AIBN, added over 5 h to the acrylate in toluene at 80 °C, followed by stirring for 10 h; (b) 1.5 equiv of *p*-TsOH, CH_2Cl_2, 1.5 h. [b] Overall isolated yield of the cyclization and destannylation. [c] Bu_3SnH and AIBN were added over 24 h.

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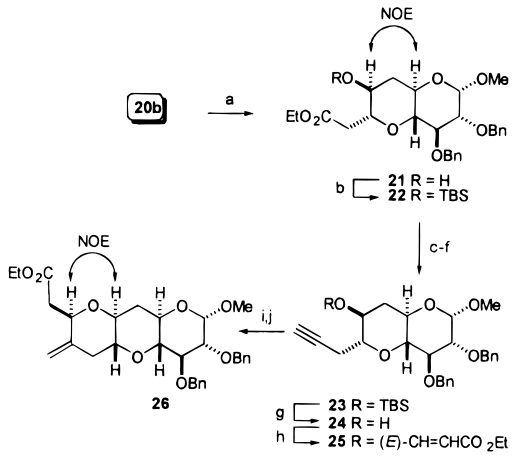
(9) Details on the synthesis of this and related *C*-glycosides from α-1,2-anhydrosugars will be reported soon.

via a slightly modified two-step Corey−Fuchs procedure.[13,14] Removal of the *p*-methoxybenzyl (MPM) group in **13a** with DDQ was followed by hetero-Michael addition of alkynol **14a** to afford five-membered ring precursor **15a** in an overall yield of 47% from **12**. The corresponding six-membered ring precursor **15b** was also readily accessible by treatment of primary iodide **16**, prepared by reaction of **12** with I_2/PPh_3/imidazole in toluene, with lithium acetylide ethylenediamine complex. Subsequent deprotection of HO-4 in the resulting **13b** and hetero-Michael addition of **14b** afforded *β*-(alkynyloxy)acrylate **15b**. On the other hand, known[15] ethyl D-*gluco*-oct-6-enuronate **17** served as the starting compound for the 7,6- and 8,6-bicyclic ether precursors **15c** and **15d**. Thus, selective hydrogenation of the double bond in **17** under the influence of platinum(IV) oxide followed by reduction of the saturated ester with lithium aluminum hydride gave alcohol **18** (76%, two steps). Transformation of **18** into the corresponding aldehyde and sequential dibromoolefination and elimination yielded alkyne **13c** in 76% over the three steps. Intermediate alkyne **13d** was prepared from alcohol **18** by executing the earlier mentioned two-step protocol (cf. **12** → **13b**) in an overall yield of 64%. Deprotection of **13c** and **13d** at the 4-positions and installation of the acrylate functionalities yielded **15c** and **15d**, respectively.

The results of the ensuing tributyltin radical mediated cyclizations of **15a**−**d** and subsequent acidic destannylations to afford compounds **20a**−**d** are summarized in Table 1. First of all, it is of interest to note that the formation of the *trans*-5,6 bicyclic ether **20a** proceeded more efficiently than the *cis*-5,6 system **7**. This may be explained by taking into consideration that the acrylate moiety in **15a**, in contrast to acrylate **5**, adopts a more favorable equatorial conformation. It is also evident that there is a dramatic drop in yield going from the seven- to eight-membered rings (**20c** to **20d**). In this particular case, the desired product **20d** could only be isolated in 8% yield and the major product proved to be the result of hydrostannylation of the triple bond (60−70%). Prolonging the time of addition (i.e., from 5 to 24 h) of Bu_3SnH and AIBN in order to suppress quenching of the intermediate vinylic radical by Bu_3SnH only led to a slight increase in the yield of **20d**.

An additional merit of the radical cyclization process is the formation of an exocyclic double bond. The latter feature offers the opportunity to install an equatorially oriented hydroxyl group, thus opening the way for an iterative radical cyclization process. The feasibility of this concept is demonstrated in the conversion of bicyclic **20b** into the tricyclic system **26** (Scheme 4). In this respect, it was gratifying to establish that subjection of **20b** to ozonolysis and in situ reduction of the intermediate ozonide with sodium borohydride was a highly efficient and stereoselective process, giving equatorial alcohol **21** as the sole isomer, as evidenced by NOESY spectroscopy. Temporary protection of the newly formed secondary alcohol with a *tert*-butyldimethylsilyl (TBS) group and reduction of the ester in **22**, followed by oxidation and a Corey−Fuchs procedure, gave alkyne **23** in 64% yield over the five steps. Fluoride-ion mediated desilylation and reaction of alkynol **24** with ethyl propiolate furnished bicyclic *β*-(alkynyloxy)acrylate **25**, cyclization and destannylation of which afforded homogeneous tricyclic ether **26** in an overall yield of 87%.

Scheme 4[a]



[a] Reagents and conditions: (a) O_3; $NaBH_4$, MeOH/CH_2Cl_2 (7:1), −70 °C to room temperature, 92%; (b) TBSOTf, *i*-Pr_2EtN, CH_2Cl_2, 0 °C, 89%; (c) $LiAlH_4$, Et_2O, 0 °C, 91%; (d) Dess−Martin periodinane, pyridine, CH_2Cl_2; (e) CBr_4, PPh_3, CH_2Cl_2, 86% (two steps); (f) *n*-BuLi, THF, −50 °C, 92%; (g) TBAF, THF, 91%; (h) ethyl propiolate, NMM, CH_2Cl_2, 99%; (i) Bu_3SnH, AIBN, added over 5 h, toluene, 80 °C, 90%; (j) *p*-TsOH, CH_2Cl_2, 97%.

In summary, an efficient method for the preparation of functionalized fused ethers of various ring sizes by radical cyclization of sugar-derived *β*-(alkynyloxy)acrylates is presented. The versatility of this approach is highlighted by the iterative expansion of **20b** to give **26** in an overall yield of 48% over 10 steps and nicely complements recently reported related radical cyclization protocols.[16] At present, we are studying in detail whether an appropriately protected sugar can be extended at both the reducing and nonreducing end.

Acknowledgment. We thank Fons Lefeber for recording the 2D-NMR spectra, Hans van den Elst for the mass spectra, and Han Peeters (University of Amsterdam) and Peter van Veelen for the high-resolution mass measurements.

Supporting Information Available: General experimental procedures for the acrylation, radical cyclization, and acidic destannylation. Full characterization data for compounds **7**, **11**, **20a**−**d**, and **26**. This material is available free of charge via the Internet at http://pubs.acs.org.

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