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Radical-Based Asymmetric Synthesis: An Iterative Approach to 1, 3, 5, ... (2*n* + 1) Polyols

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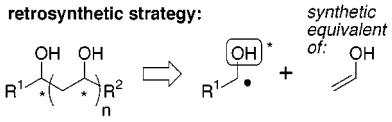
ABSTRACT



A conceptually novel approach to 1, 3, 5, ... (2*n* + 1) polyols based on iterative stereocontrolled homologation of chiral hydroxyalkyl radicals is reported. Starting from α-keto ester precursors, the general sequence of (1) ketone reduction, (2) auxiliary attachment, (3) saponification, (4) Barton esterification, and (5) radical addition provided the two-carbon homologue in 70–80% overall yield. The simplicity and generality of this iterative strategy for 1, 3, 5, ... (2*n* + 1) polyol synthesis suggests an attractive alternative for the preparation of molecules containing this structural motif.

The 1, 3, 5, ... (2*n* + 1) polyol array is a structural theme found in many macrolide antibiotics (cf., roflamycoin in Figure 1) that continues to attract the attention of synthetic chemists.[1] Perhaps the simplest and most general retrosynthetic disconnection of any 1, 3, 5, ... (2*n* + 1) polyol system of variable stereochemistry would follow Nature's iterative use of two-carbon (acetate) building blocks.[2] Surprisingly few iterative 1, 3, 5, ... (2*n* + 1) polyol syntheses have been demonstrated over the years,[3] despite the successful application of iterative strategies to other molecules made up of repeating subunits (polypeptides and oligonucleotides, for example). We now report an iterative approach to 1, 3, 5, ... (2*n* + 1) polyols based on the stereocontrolled homologation of chiral hydroxyalkyl radicals.[4] Advantages of this protocol include (1) chemical reactions that are high-yielding and convenient to perform, (2) the ability to introduce either (*R*)- or (*S*)-configured secondary alcohols selectively during the C−C bond-forming event, and (3) use of multifunctional and reusable chiral auxiliaries derived from D-glucose. The chemistry described herein may also be amenable to eventual polymer-supported synthesis of 1, 3, 5, ... (2*n* + 1) polyols.

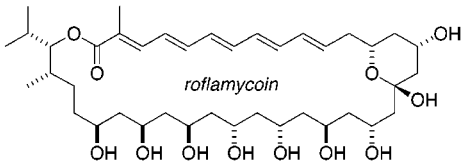


Figure 1.

(1) (a) Oishi, T.; Nakata, T. *Synthesis* **1990**, 635. (b) Rychnovsky, S. D. *Chem. Rev.* **1995**, *95*, 2021.

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(4) (a) Garner, P. P.; Cox, P. B.; Klippenstein, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 4183. (b) Garner, P.; Leslie, R.; Anderson, J. T. J. *Org. Chem.* **1996**, *61*, 6754.

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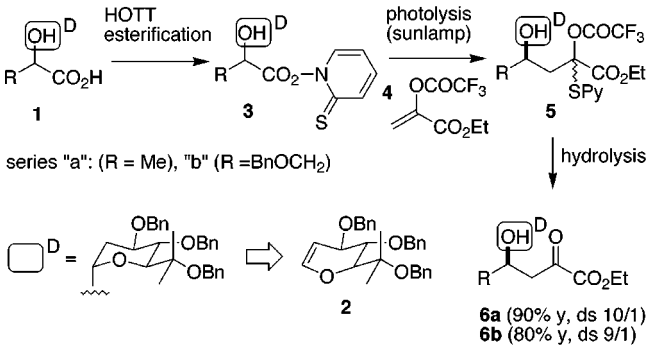
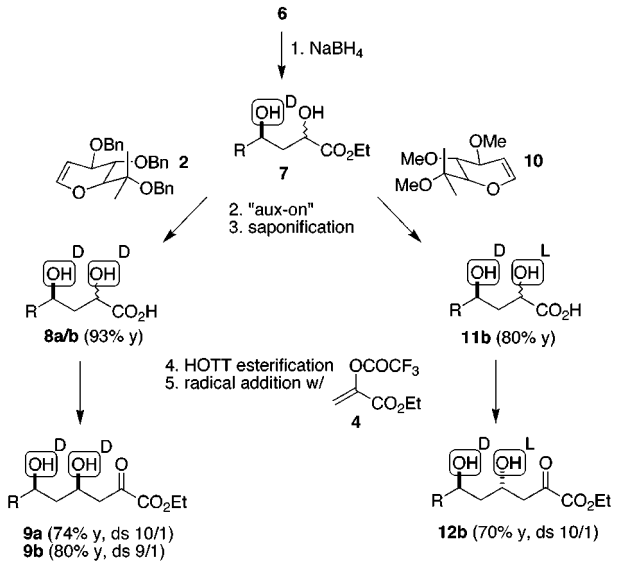
Scheme 1



Scheme 2



The sequence (Scheme 1) begins with an O-glycosylated α-hydroxy acid such as **1**, which is readily prepared from the corresponding α-hydroxy ester and D-glucal derivative **2**[5] using chemistry that we have previously described (ref 4). Since the substrate's stereocenter will be lost during radical formation, the configurational integrity of the starting α-hydroxy ester has no bearing on subsequent chemistry. Note that the chiral auxiliary used differs from our original version in that C-6 is now fully substituted ($CH_2OBn \rightarrow CMe_2OBn$). This modification leads to enhanced stereocontrol in accord with an earlier study[6] yet also retains other favorable properties such as exclusive formation of the α-anomer during glycosylation and increased stability of the 2-deoxyglucoside. Application of our improved Barton esterification protocol[7] resulted in fast (<30 min) and quantitative conversion to **3** which was then photolyzed using a sunlamp in the presence of excess ethyl trifluoroacetoxyacrylate (**4**), an easily prepared compound which is known[8] to be an efficient radical trap. The initial adduct **5** was not isolated but hydrolyzed directly (in situ?) to produce the α-keto ester **6** in 80−90% yield after flash chromatography. The diasteoselectivity was on the order of 10/1 when the radical addition was performed at 0 °C but can be raised significantly simply by going to lower reaction temperatures (diasteoselectivity >20/1 at −78 °C). The absolute configuration shown for the newly formed stereocenter in **6** is that expected from our previously proposed TS model (see ref 4a).

The iterative homologation sequence (Scheme 2)[9] commenced with the reduction of **6** by $NaBH_4$ to produce a mixture of diastereomeric α-hydroxy esters **7** in nearly quantitative yield. (Recall that the configuration at this center is irrelevant.) At this point, the synthetic path diverged depending on what configuration was desired at the incipient stereocenter. Introduction of a second D-auxiliary followed by ester saponification led to the carboxylic acids **8**. Subjection of these free acids to HOTT-mediated Barton esterification followed by photolytic radical addition to a 10-fold excess of **4** resulted in the clean formation of "DD" or "syn" product **9**. Access to the complementary "DL" or "anti" product **12** was effected using the same chemistry but simply employing the easily obtainable pseudo-antipodal glucal **10**[10] instead of **2** in the "aux-on" step. It should be mentioned that no evidence of β-anomer formation was detected during the introduction of either the D- or L-auxiliaries. The overall yield of both sequences was 70−80% and the diastereoselectivity (at 0 °C) was about 10/1 as judged by ^{1}H NMR integration.

Conclusive proof of structure came from the conversion[11] of **9** and **12** to the diastereomeric acetonides **13** and **15** followed by analysis of their respective ^{13}C NMR spectra according to Rychnovsky (see Figure 2).[12] The complementary stereochemical course of these two routes (**6** → **9** and **6** → **12**) showed that the radical additions are exclusively under auxiliary control. Accordingly, it should be possible

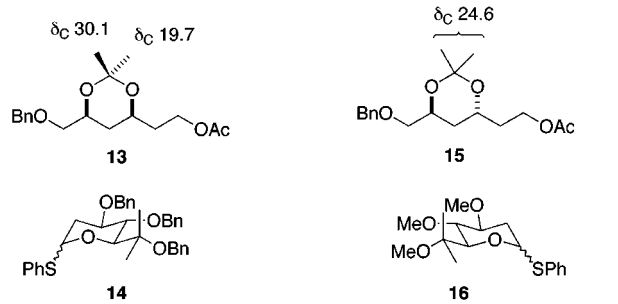


Figure 2.

(5) Prepared in 24% overall yield from inexpensive ($0.20/g) D-(+)-glucurono-6,3-lactone via the following six-step sequence: (1) MeOH, catalytic NaOMe; (2) Ac_2O, catalytic $HClO_4$; (3) 30 wt % HBr/AcOH; (4) Zn dust, $CuSO_4 \cdot 5H_2O$, buffered aqueous HOAc; (5) excess MeMgCl, THF, 0 °C → rt; (6) NaH, BnBr, Bu_4NI, DMSO. See: Fehlhaber, H.-W.; Snatzke, G.; Vlahov, I. *Liebigs Ann. Chem.* **1987**, 637.

(6) Garner, P.; Anderson, J. T. *Tetrahedron Lett.* **1997**, *38*, 6647.

(7) HOTT = (*S*-1-oxido-2-pyridinyl) 1,1,3,3-tetramethylthiouronium hexafluorophosphate: Garner, P.; Anderson, J. T.; Dey, S.; Youngs, W. J.; Galat, K. *J. Org. Chem.* **1998**, *63*, 5732.

(8) Barton, D. H. R.; Chern, C.-Y.; Jaszberenyi, J. Cs. *Tetrahedron* **1995**, *51*, 1867.

to access any polyol configuration by proper choice of auxiliary. This sequence also allowed for efficient recovery of the D- and L-auxiliaries in the form of their respective thioglycosides **14** and **16**, which can be recycled back to the starting glucals (cf., ref 4b). It is noteworthy that the iterative homologation protocol described here allows for ready differentiation of the polyol chain termini and internal hydroxyl functions, as would be required for the synthesis of roflamycoin. In this context, the chiral auxiliaries are *multifunctional* in that they may also serve as acid-labile protecting groups during subsequent synthetic operations. The simplicity and generality of this iterative strategy for 1, 3, 5, ... $(2n + 1)$ polyol synthesis suggest an attractive alternative for the synthesis of molecules containing this structural motif.

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Supporting Information Available: Experimental procedures and characterization data for compounds **1**−**16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) General iterative homologation protocol (**6** → **9** or **12**): (1) $NaBH_4$ (0.25 equiv, 0.1 M)/EtOH, 0 °C, 5 min; (2) glucal **2** or **10** (1.5 equiv, 0.2 M), $HBr{\cdot}PPh_3$ (5 mol %)/DCM, RT; flash chromatography; (3) 1 N aqueous NaOH (6 equiv)/1:1 THF-^{i}PrOH; (4) HOTT (1.5 equiv, 0.1 M), Et_3N (3.0 equiv), DMAP (0.1 equiv)/3:1 THF−MeCN, 30 min, rt; (5) add trap **4** (10 equiv), *hν* (sun lamp), <30 min, 0 °C.; concentrate then SiO_2/EtOAc; flash chromatography.

(10) Prepared in 27% overall yield from very inexpensive ($0.08/g) α-D-glucoheptonic γ-lactone via the following nine-step sequence: (1) PhCHO, catalytic HCl; (2) aqueous $NaIO_4$; (3) hot 1 N HCl; (4) MeOH, catalytic NaOMe; (5) Ac_2O, catalytic $HClO_4$; (6) 30 wt % HBr/AcOH; (7) Zn dust, $CuSO_4{\cdot}5H_2O$, buffered aqueous HOAc; (8) excess MeMgCl, THF, 0 °C → rt; (9) NaH, MeI, THF.

(11) Synthetic sequence for **9** → **13** (42% overall yield) and **12** → **15** (35% overall yield): (1) LAH/THF; (2) aqueous $NaIO_4$; (3) $NaBH_4$/MeOH; (4) Ac_2O−pyridine; (5) PhSH, $BF_3{\cdot}OEt_2$ (isolate **14** and/or **16** by flash chromatography, 86−88% yield); (6) DMP, catalytic TsOH.

(12) Rychnovsky, S. D.; Griesgraber, G.; Schlegel, R. *J. Am. Chem. Soc.* **1995**, *117*, 197.