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Development of an Effective Chiral Auxiliary for Hydroxyalkyl Radicals

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The development of an effective chiral auxiliary for hydroxyalkyl radicals is delineated. Both the 2-tetrahydropyranyl (THP) and tri-*O*-benzyl-2-deoxy-α-D-glucopyranosyl (GLU) auxiliaries resulted in diastereoselective radical additions to methyl acrylate at −78 °C (ds = 6/1 and 11/1, respectively). The developing stereochemistry at the radical center was completely under auxiliary control. Correlation experiments showed that the D-GLU auxiliary led to attack on the radical *Si*-face. The selectivity of these radical additions dropped-off considerably when the more reactive 2-nitropropene trap was employed. Computational studies suggested that the observed facial selectivity was due primarily to entropic factors in the transition state but that a smaller temperature-dependent enthalpic contribution was also involved. It was hypothesized that incorporation of a quaternary center at C-6 (THP numbering) would restore the facial selectivity with more reactive radical traps by restricting the orientations available to the incoming alkene. In the event, the *trans*-6-*tert*-butyltetrahydropyranyl (tBu-THP) auxiliary resulted in very good diastereoselection with 2-nitropropene (ds = 35/1 at −78 °C, 15/1 at 0 °C, and 8/1 at RT) as did the tri-*O*-benzyl-6,6-dimethyl-2-α-D-deoxyglucopyranosyl (diMe-GLU) auxiliary during additions to ethyl α-trifluoroacetoxyacrylate (ds = 10/1 at 0 °C). A protocol for recovery of the sugar-derived chiral auxiliaries was also established. This work sets the stage for the development of a novel approach to 1, 3, 5...(2*n* + 1) polyols based on iterative radical homologation as well as the application of these pyranosidic auxiliaries to other synthetically important reactions.

Introduction

Radical-based C−C bond forming reactions offer a powerful alternative to their polar counterparts and, accordingly, occupy an important role in the arsenal of organic synthesis.[1] The different reactivity patterns associated with carbon radicals (versus carbanions and carbocations), especially in terms of functional group compatibility, augurs well for the application of radicals to complex synthetic problems. Furthermore, an improved understanding of radical structure/reactivity now makes the design of successful radical chain processes relatively straightforward. Whereas early work on radical chemistry focused on issues related to chemoselectivity and regioselectivity, attention has now shifted to the control of stereochemistry.[2]

Both substrate derived and auxiliary derived chirality have been used to control the stereochemical course of radical reactions. Most of the auxiliary work to date has focused on chiral equivalents of the carboxylic acid substituted carbon radical, [•CH(R)CO_2H], some notable examples of which (structures **4**−**7**) are depicted in Figure 1. In each of these systems, the preferred orientation of the auxiliary relative to the prochiral carbon radical results from steric and/or electronic factors. The corresponding auxiliary-substituted acrylamides serve as good models that enable one to understand the conformational preferences of these chiral radicals.[3] Upon completion of the radical homologation reaction, the carboxylic acid moiety in **3** can be released by hydrolysis and the chiral auxiliary recycled. Following the developmental path of closed-shell processes such as the Diels−Alder reaction and Lewis acid-mediated carbonyl additions, recent efforts have resulted in enantioselective free radical reactions.[4] Despite these advances, a truely general approach to the control of acyclic stereochemistry during radical reactions still remains an elusive goal. In this context, the development of a readily available and easily recoverable chiral auxiliary for hydroxyalkyl radicals would represent a particularly valuable synthetic advance since it would complement the existing methodology.

(1) (a) Hart, D. J. *Science* **1984**, *223*, 883. (b) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon−Carbon Bonds*; Pergamon Press: New York, 1986. (c) Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541. (d) Curran, D. P. *Synthesis* **1988**, *417*, 489. (e) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237. (f) Renaud, P.; Sibi, M. *Radicals in Organic Synthesis*; Vol. 1, Wiley-VCH: Weinheim, 2001.

(2) (a) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 969. (b) Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296. (c) Smadja, W. *Synlett* **1994**, 1. (d) *Stereochemistry of Radical Reactions: Concepts, Guidelines, and Synthetic Applications*; Curran, D. P.; Porter, N. A.; Giese, B., Eds.; VCH: Weinheim, 1996. (e) Renaud, P.; Gerster, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2563.

(3) Sibi, M. P.; Ji, J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 190.

(4) Sibi, M. P.; Porter, N. A. *Acc. Chem. Res.* **1999**, *32*, 163.

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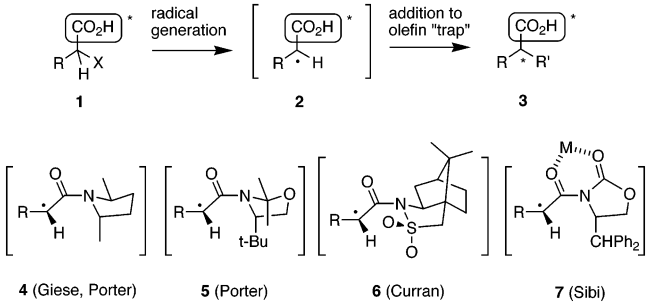


FIGURE 1. Carboxamide/imide-based chiral auxiliaries.

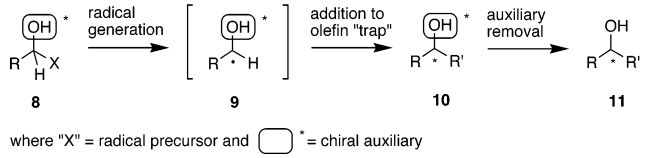


FIGURE 2. Auxiliary-mediated hydroxyalkyl radical homologation.

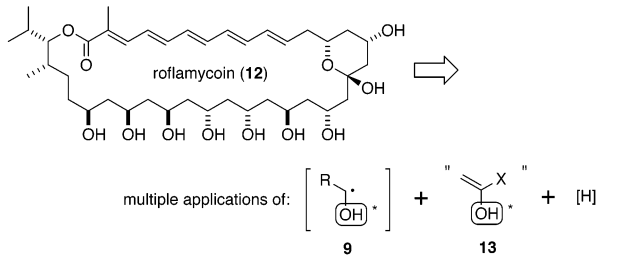


FIGURE 3. Strategy for polyol synthesis via iterative radical homologation.

Although the work cited above allowed control over facial selectivity with prochiral carbon radicals α to carbonyl groups, the development of an analogous chiral hydroxyalkyl radical equivalent has lagged behind. We thus set out to formulate a plan that would accomplish the reaction sequence embodied in Figure 2. Generation of the chiral hydroxylalkyl radical equivalent **9** would be effected via the functionality "X" in the precursor **8**. The radical **9** would then be intercepted in a diastereoselective manner by an appropriate olefinic radical trap (C−C bond formation) eventually leading to the construct **10**. Removal of the auxiliary would, at this stage, reveal a chiral secondary alcohol **11**. While the advantage of synthesizing isolated secondary alcohols in this manner may not be immediately obvious, it must be stated that our long-term goal was to employ a radical trap that embodies the precursor structure (see **9** + **13** in Figure 3). In this case, the process becomes iterative and suggests a novel approach to the synthesis of 1,3,5...(2*n* + 1) polyol systems that constitute a number of macrocyclic antibiotic structures such as roflamycoin (**12**).[5] This strategy presumes that the chiral auxiliary attached to the α-carbon will dominate the stereochemical course of the reaction over any substrate control that might result from the inherent chirality of "R" in the growing chain.

(5) A complimentary radical-based approach to 1,3-diols based on the [1,2]-Wittig rearrangement of *β*-alkoxyalkyl allyl ethers has been reported. This reaction is believed to proceed via an achiral radical anion [$^{-}$O−CH$^{\bullet}$−CH=CH$_2$] See: Schreiber, S. L.; Goulet, M. T. *Tetrahedron Lett.* **1987**, *28*, 1043.

In order for the proposed radical homologation methodology to be useful for asymmetric synthesis, it would have to fulfill the following criteria:

(1) The chiral auxiliary must be readily available and easily introduced.

(2) The chiral auxiliary must exert high and predictable diastereoselection during the radical addition.

(3) Radical generation must be accomplished efficiently under mild conditions from readily available precursors.

(4) The chiral radical equivalent must undergo clean addition (C−C bond formation) to a variety of synthetically useful traps.

(5) The auxiliary should be recoverable and possibly multifunctional.

We now present a full account of our efforts in this area, which have resulted in the development of a practical chiral auxiliary for hydroxyalkyl radicals. While we were completing our initial studies,[6] Curran reported two examples of stereocontrolled selenium transfer to 7-phenylmenthyloxyalkyl radicals.[7] This was, to our knowledge, the first example of a chiral auxiliary for hydroxyalkyl radicals. Although high levels of diastereoselectivity were observed at the selenoacetal center (C−Se bond formation), this auxiliary suffered from the fact that the ether linkage precludes its removal under mild conditions. Furthermore, no examples of C−C bond formation were reported.

Results and Discussion

Design Hypothesis. The success with carbonyl substituted α-carbon radicals stems from the fact that established conformational control elements of enolates (A-strain, chelation) could be used to introduce diastereofacial bias. Furthermore, known transformations of carboxylic acids could be used for both the attachment and removal of the chiral auxiliary. In considering an analogous approach to chiral hydroxyalkyl radical equivalents, it occurred to us that the tetrahydropyran (THP) group might serve as an effective scaffold for the design of a chiral auxiliary. The THP group and its carbohydrate relatives are readily installed and removed from alcohols under mildly acidic conditions.[8] The anomeric carbon is necessarily chiral, its configuration can be controlled, and it provides a structural conduit for transmitting stereochemical information to the prochiral radical center. The nearest analogies that we could find for a THP-based chiral auxiliary for hydroxyalkyl radicals were the chiral *γ*-alkoxyallylboronates of Wuts[9] and Hoffmann[10] as well as the glycosylated dienes of Lubineau[11] and Stoodley.[12] Roush showed that carbohydrates could be used to control *γ*-alkoxyallylstannane additions to aldehydes.[13] More

(6) Garner, P. P.; Cox, P. B.; Klippenstein, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 4183.

(7) Curran, D. P.; Geib, S. J.; Kuo, L. H. *Tetrahedron Lett.* **1994**, *35*, 6235.

(8) For a review of the use of carbohydrates as recoverable chiral auxiliaries, see: Kunz, H.; Rück, K. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 336.

(9) Wuts, P. G. M.; Bigelow, S. S. *Chem. Commun.* **1984**, 736.

(10) Metternich, R.; Hoffmann, R. W. *Tetrahedron Lett.* **1984**, *25*, 4095.

(11) Lubineau, A.; Queneau, Y. *Tetrahedron* **1989**, *45*, 6697, and prior work cited therein.

(12) Beagley, B.; Larsen, D. S.; Pritchard, R. G.; Stoodley, R. J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 3113, and prior work cited therein.

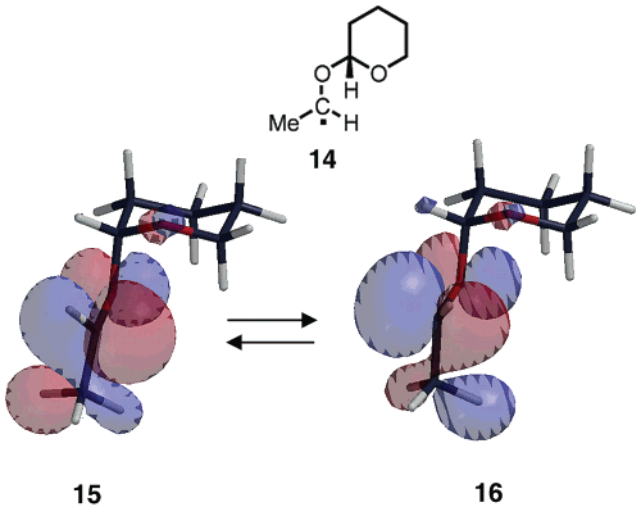


FIGURE 4. Ground state conformation rationale for stereocontrol with a pyranosidic auxiliary. Structures **15** and **16** were generated by performing geometry-optimized ab initio calculations at the UHF/6-31G* level with Spartan 5.1.3.

recently, Tius has reported the use of glucose as well as a camphor derived lactol (with an embedded THP substructure) as chiral auxiliaries for oxygenated allenes.[14]

This line of reasoning led us to consider pyranosidic chiral auxiliaries for hydroxyalkyl radicals having the general structure **14** (Figure 4). In analogy to the known solid-state and solution conformational preferences of α-methyl glycosides,[15] we expected that the C(2)−O(1′) rotamer with a O(1)−C(2)−O(1′)−C(2′) dihedral angle of ∼60° would be preferred since it minimized an unfavorable gauche interaction with C(3) and benefits from the *exo*-anomeric effect. This expectation is supported by ab initio calculations (Figure 4). There is also spectroscopic evidence indicating that oxygen substituted alkyl radicals are slightly pyramidalized due to a stabilizing n → SOMO interaction.[16] Thus, the true structure of radical **14** may best be described as an equilibrium between two pyramidalized radicals **15** and **16** of nearly equal energy. If radical addition proceeds via a relatively early transition state (TS), the reaction diastereoselectivity would be governed (at least in part) by the relative proportions of *Si*-pyramidialized radical **15** and its *Re*-counterpart **16**. An example of such "kinetic quenching" of diastereomeric radicals has been reported by Rychnovsky and coworkers.[17] Of course, the Curtin−Hammett principle would be in effect if the difference in activation energies is greater than the barrier to interconversion between these ground state conformers.[18] In this case, the reaction diastereoselectivity would be dictated primarily by the influence that the chiral auxiliary has on the competing *Si*- and *Re*-transition state energies. This, in fact, turns out to be the case with radicals such as **14** (vide infra).

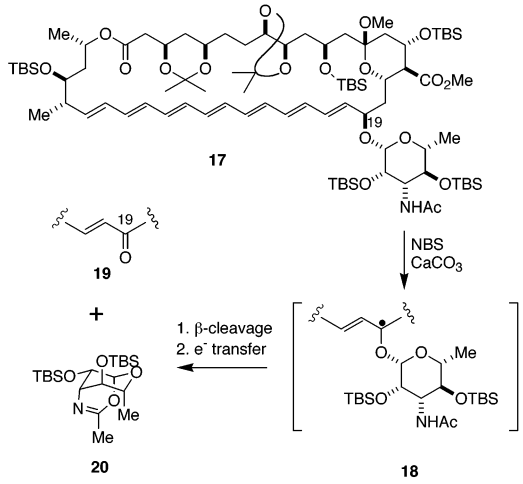


FIGURE 5. Nicolaou's oxidative deglycosylation of amphotericin B.

At this point in our studies, however, it was not at all clear that tetrahydropyranyloxyalkyl radicals such as **14** could even be generated and trapped. Despite the fact that radical fragmentations are relatively rare, we feared that such a reaction could provide a path to a tetrahydropyranyl radical, examples of which are well-known (see ref 2a). In fact, just such a fragmentation was proposed by Nicolaou to explain the oxidative deglycosidation of amphotericin B (**17**) upon exposure to NBS (Figure 5).[19] This concern turned out to be unfounded, at least with the systems we have studied so far.

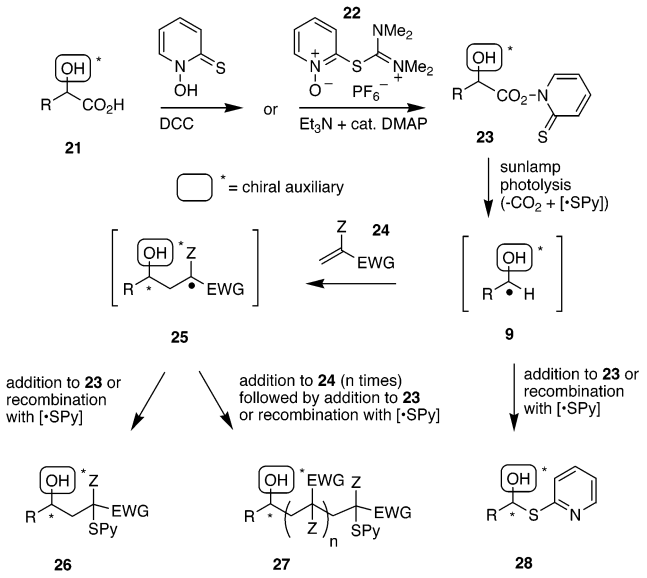
Radical Chemistry

Convenient access to pyranosidylalkyl radicals was to be achieved using chemistry developed by Barton and coworkers (Scheme 1). Thus, α-hydroxyacid derivatives corresponding to **21** were converted to their corresponding Barton esters **23** by one of two methods. In the initial stages of our investigations, we prepared the Barton esters by simply treating the carboxylic acid with 2-mercaptopyridine-*N*-oxide and *N*,*N*′-dicyclohexylcarbodiimide (DCC) in dichloromethane (DCM). However, after encountering difficulty in getting this reaction to go to completion with hindered carboxylic acid substrates (sterically encumbered R or auxiliary groups), we developed the so-called HOTT reagent, *S*-(1-oxido-2-pyridinyl)-1,1,3,3-tetramethylthiouronium hexafluorophosphate (**22**), for the synthesis of "difficult" Barton esters.[20] This reagent eventually became the method of choice for all of our Barton esterifications. Because of their inherent instability toward visible light, the bright yellow Barton esters were not isolated but generated in the dark and used immediately for the next step.

Upon photolysis using a sunlamp in the presence of an excess of electron deficient olefin, the Barton ester **23** undergoes decarboxylation to give the radical **9**. This

(13) Roush, W. R.; VanNieuwenhze, M. S. *J. Am. Chem. Soc.* **1994**, *116*, 8536.
(14) Harrington, P. E.; Tius, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 8509, and prior work cited therein.
(15) (a) Jeffrey, G. A.; Pople, J. A.; Binkley, J. S.; Vishveshwara, S. *J. Am. Chem. Soc.* **1978**, *100*, 373. (b) Wu, T.-C.; Goekjian, P. G.; Kishi, Y. *J. Org. Chem.* **1987**, *52*, 4819. This paper suggests that steric destabilization is more important than exo-anomeric stabilization in determining the conformational preferences of glycosides.
(16) McKelvery, R. D.; Sugawara, T.; Iwamura, H. *Magn. Reson. Chem.* **1985**, *23*, 330.
(17) Buckmelter, A. J.; Powers, J. P.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1998**, *120*, 5589.
(18) Roth, M.; Damm, W.; Giese, B. *Tetrahedron Lett.* **1996**, *37*, 351.
(19) Nicolaou, K. C.; Chakraborty, T.. K.; Ogawa, Y.; Daines, R. A.; Simpkins, N.. S.; Furst, G. T. *J. Am. Chem. Soc.* **1988**, *110*, 4660.
(20) Garner, P.; Anderson, J. T.; Dey, S.; Youngs, W. J.; Galat, K. *J. Org. Chem.* **1998**, *63*, 5732.

SCHEME 1



nucleophilic carbon-centered radical then adds to the electron deficient olefin **24** to give the electron-deficient addend radical **25**, which can either transfer a thiopyridyl group from unreacted **23** or collapse with [•SPy] to give the α-thiopyridyl ether **26**. Possible side reactions include further addition of **25** to the trap **24** (telomerization) leading to species such as **27** as well as "radical decarboxylation" to give the hemithioacetal **28**. The extent that these side reactions compete with the desired intermolecular addition reaction was found to be both trap and auxiliary dependent. For a particular radical-trap pair, the rate of the desired radical addition was found to depend on both electronic (SOMO−LUMO gap) and steric factors. Throughout these studies, we are assuming that the rate of auxiliary loss would be approximately the same for each diastereomer.

Three different radical traps were employed in this auxiliary development study (Figure 6). Methyl acrylate (**29**), 2-nitropropene (**30**), and ethyl α-trifluoroacetoxyacrylate (**31**)[21] have all been used successfully as traps for radicals derived from Barton ester precursors. The latter alkene is particularly interesting in that it possesses a structure that make it functionally equivalent to the hypothetical iterative trap **13**. As will be discussed below, the diastereoselectivity observed with a particular chiral auxiliary also varies as a function of the radical trap. To facilitate comparison, the results of our radical trapping experiments with each of these traps are collected separately in Tables 1−3.

Preliminary Trapping Studies. To test the general validity of our proposal, we prepared the diastereomeric carboxylic acids **32** and **33** (Scheme 2) from the chromatographically separable THP ethers of (*S*)-methyl lactate. Mash had established that the faster eluting ester **33** possessed the (2*S*,1′*S*) configuration whereas the slower eluting ester configuration was (2*S*,1′*R*).[22] These esters were saponified and the resulting carboxylic acids

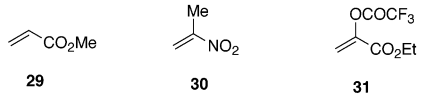


FIGURE 6. Olefinic radical "traps" used in this study.

independently subjected to Barton's radical decarboxylation conditions[23] in the presence of methyl acrylate. Barton esterification was accomplished using DCC. Photolysis of the *diastereomeric* Barton esters **34** and **35** led to the formation of *enantiomeric* radicals **36** and *ent*-**36**, respectively, which could be trapped with methyl acrylate to give the *enantiomeric* addends **37** and *ent*-**37** (X = SPy) in good overall yield along with small amounts of double addition telomer. Telomer formation (see structure **27** in Scheme 1), which results from the further addition of addend radicals such as **25** to the alkene **24**, was generally observed when methyl acrylate was the radical trap. Unfortunately, the lower reactivity of methyl acrylate toward radical **36** made it necessary to use 5 equiv of this trap in these experiments. These represent optimized reaction conditions for this trap. The diastereoselectivity of these radical additions was best determined after reductive cleavage of the 2-thiopyridyl ethers to afford **37** and *ent*-**37** (X = H). The absolute configuration of these adducts was established by subsequent correlation experiments (see below). The diastereoselectivity associated with the formation of **37** mirrored that found for *ent*-**37** under the same reaction conditions. As expected, higher diastereoselectivities were observed at lower reaction temperatures (rxn T, ds: rt, 4/1; −20 °C, 5/1; −78 °C, 6/1; see Supporting Information for details).[24] That the *diastereomeric* relationship between acids **32** and **33** was transformed into an *enantiomeric* relationship in adducts **37** and *ent*-**37** showed that the stereochemical course of these reactions was under auxiliary control and, thus, independent of the starting α-hydroxyester configuration.

Computational Studies

To better understand the interplay of these stereocontrol elements, ab initio calculations were performed on the competing *Re*- and *Si*-transition structures (TSs).[25] Energies and canonical partition functions (employing rigid rotor harmonic oscillator assumptions) were determined for both pyramidalized radicals corresponding to **36** and six transition states (TS) corresponding to the addition of $CH_2{=}CH_2$ to both faces of **36** in three different torsional orientations. The three separate transition structures for addition to the *Si*-face were found to be

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

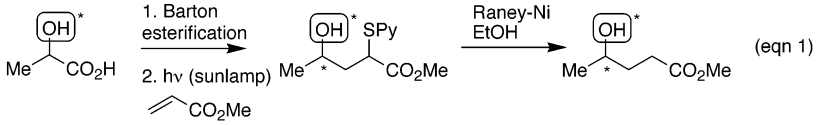
(22) Mash, E. A.; Arterburn, J. B.; Fryling, J. A.; Mitchell, S. H. *J. Org. Chem.* **1991**, *56*, 1088.

(23) Barton, D. H. R.; Crich, D.; Kretzschmar, G. *J. Chem. Soc., Perkin Trans. 1* **1986**, 39.

(24) The diastereomer ratios at −20 and −78 °C differ from those reported in our original Communication (ref 6). We attribute this difference to unintentional diastereomer enrichment during "rough" flash chromatography of the intermediate thiopyridyl ethers as opposed to the desulfurized products.

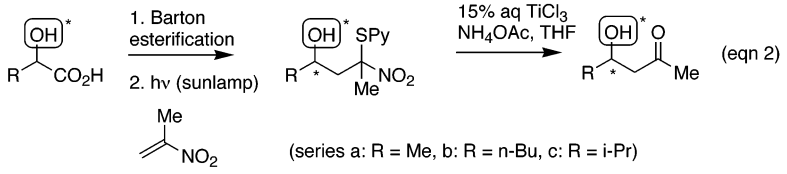
(25) Quantum mechanical calculations were performed at the Hartree−Fock level with a STO-3g basis set using the GAUSSIAN 92 Program Package, Revision A: Frisch, M. J.; Trucks, G. W.; Head-Gordon, M.; Gill, P. M. W.; Wong, M. W.; Foresman, J. B.; Johnson, B. G.; Schlegel, H. B.; Robb, M. A.; Replogle, S.; Gomperts, R.; Andres, J. L.; Raghavachari, K.; Binkley, J. S.; Gonzalez, C.; Martin, R. L.; Fox, D. J.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Pople, J. A. Gaussian Inc., Pittsburgh, PA, 1992.

TABLE 1. Radical Additions to Methyl Acrylate



entry		auxiliary structure	radical addition temperature	major product structure	diastereoselectivity
1.	**32**		room temp		**37**: 4/1
2.	**32**		-20 °C		**37**: 5/1
3.	**32**		-78 °C		**37**: 6/1
4.	**40**		-78 °C		**44**: 11/1
5.	**55**		room temp		**58**: 9/1

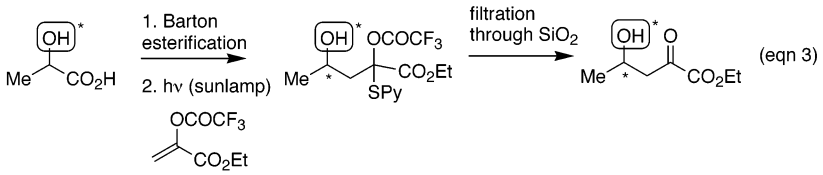
TABLE 2. Radical Additions to 2-Nitropropene



entry		auxiliary structure	radical addition temperature	major product structure	diastereoselectivity
1.	**40a**		-78 °C		**48a**: 5/1
2.	**40a**		-100 °C		**48a**: 6/1
3.	**40b**		-78 °C		**48b**: 7/1
4.	**40b**		-100 °C		**48b**: 8/1
5.	**40c**		-78 °C		**48c**: 8/1
6.	**32**		-78 °C		**49**: 3/1
7.	**55**		room temp		**57**: 8/1
8.	**55**		0 °C		**57**: 15/1
9.	**55**		-78 °C		**57**: 35/1
10.	**59**		-78 °C		**60**: 2/1

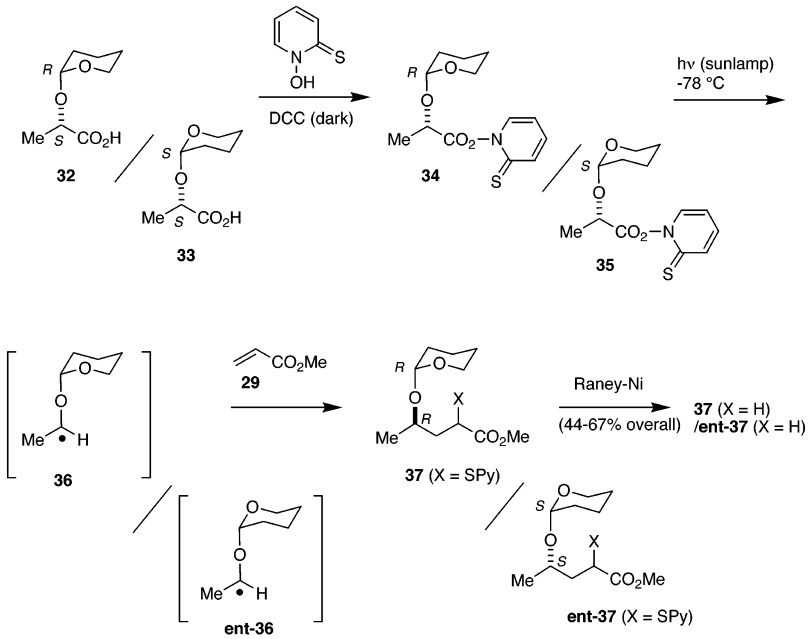
within 0.1 kcal/mol of each other while those for addition to the *Re*-face were 0.2, 0.3, and 1.0 kcal/mol higher in energy than the lowest value for *Si*-addition. Furthermore, the torsional motions in the *Re*-TS are, on average, much more strongly hindered than those associated with the *Si*-TS (Figure 7). As a result, entropic effects strongly

TABLE 3. Radical Additions to Ethyl α-Trifluoroacetoxyacrylate



entry	substrate auxiliary	radical addition temperature	major product structure	diastereoselectivity
1.	**65**	0 °C		**69**: 10/1
		-78 °C		**69**: >20/1
2.	**40**	0 °C		**70**: 2/1

SCHEME 2



favor (i.e., by a factor of 6) *Si*-attack; yielding a net calculated preference of 12/1 for the (*R*,*R*)-diastereomer at room temperature and 17/1 at −78 °C.[26] *These entropic effects are simply indicative of the greater probability of CH_2═CH_2 having an appropriate orientation for Si-attack and suggest caution when attempting to explain kinetic preferences in terms of enthalpic factors alone.*[27]

To visualize the connection between steric hindrance and entropy, one may consider the "cone of acceptance" defined by rotating the incoming alkene about the axis of the newly forming bond. This cone represents all possible (reactive) orientations of the alkene as it approaches the radical center. Auxiliary substituents at C-5 restrict the number of reactive orientations available to the alkene during *Re*-approach. Since no such restriction occurs during *Si*-approach, it is preferred. We stress that this TS model is only meant to be used as a guide for auxiliary design and may not be appropriate for all situations. Since the calculations were performed on a hypothetical reaction (radical + ethylene),

(26) The small values of the energetic differences between the transition states for the *Si*-face and *Re*-face additions suggests that the diastereoselectivity for this reaction should be quite small (ds = 1.9/1) when a prequilibrium between the two radicals and only energetic effects are considered. The barrier for inversion of these pyramidalized radicals through a planar configuration is calculated to be on the order of 2.0 kcal/mol, which is consistent with our observation that the diastereomeric Barton esters led to identical diastereomer ratios. For experimental support of this notion, see: Hoffmann, R.; Rückert, T.; Brückner, R. *Tetrahedron Lett.* **1993**, *34*, 297.

(27) For an alternative approach, see: Damm, W.; Giese, B.; Hartung, J.; Hasskerl, T.; Houk, K. N.; Hüter, O.; Zipse, H. *J. Am. Chem. Soc.* **1992**, *114*, 4067.

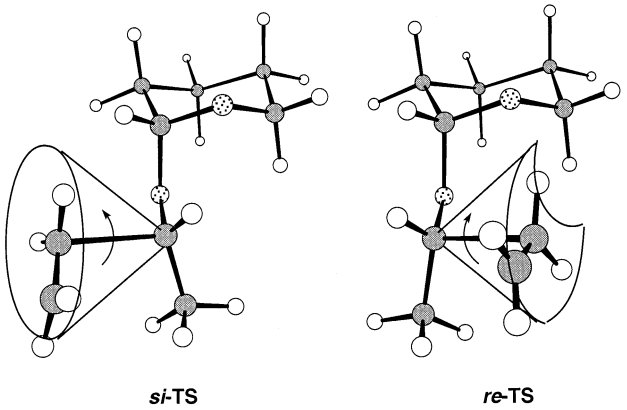


FIGURE 7. Calculated TSs for the *Si*- and *Re*-addition of **36** to ethylene. Only one of three torsional orientations about the developing C−C bond is shown.

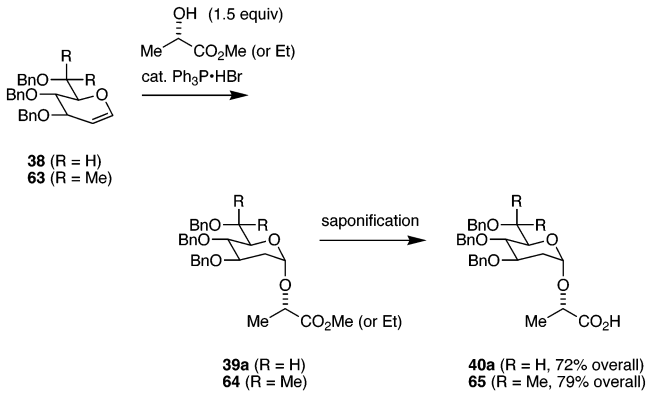
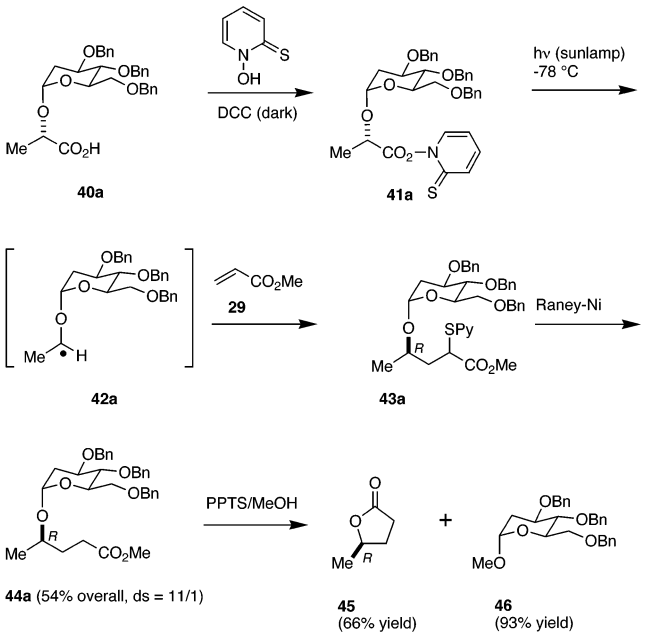


FIGURE 8. Synthesis of 2-deoxyglycosidic substrates.

one cannot expect a quantitative correlation between the theoretical and observed diastereoselectivities (with electron-deficient alkenes). However, trends that are observed can be considered valid. We conclude that the temperature dependence of the reaction diastereoselectivity is primarily due to enthalpic factors but that the (T-independent) preference for *Si*-attack results from entropic effects.

Sugar-Derived Auxiliaries. Next, experiments were conducted to see if acetal mediated acyclic stereocontrol would extend to the use of carbohydrates as *recoverable* chiral auxiliaries. We chose to investigate 2-deoxyglucose based auxiliaries because of their synthetic accessibility. Since our results with the THP auxiliary were consistent with preferential addition to the *Si*-face of radical **36**, we presumed that additional pyranoside substituents at C-3, C-4, and C-5 (carbohydrate numbering) would not interfere with the absolute sense of asymmetric induction. The 2-deoxy-α-glucoside **39** was prepared by the addition of methyl lactate to tri-O-benzyl-D-glucal (**38**) following the procedure of Mioskowski and Falck (Figure 8).[28] The use of Ph_3P•HBr as a catalyst in this reaction is essential in that it leads to the desired α-2-deoxyglycoside without competing Ferrier rearrangement. Saponification of ester **39** gave the carboxylic acid **40** in good overall yield. Because the stereochemical course of the radical additions are under auxiliary control (see above), the configuration of the starting hydroxyester **40** is a moot point and racemic α-hydroxyesters (conveniently available by the cyanohydrin synthesis) may also be used.

SCHEME 3



Subjection of the carboxylic acid **40a** to the Barton chemistry again resulted in the smooth formation of a chiral radical **42a** which could be trapped with methyl acrylate (**29**) (Scheme 3). This reaction afforded the adduct **43a** in 61% yield along with 16% of double addition telomer. The diastereoselectivity of this radical addition at −78 °C was found to be 11/1 after reductive removal of the thiopyridyl group. This diastereomer ratio was determined by careful HPLC analysis of the crude desulfurization reaction mixture obtained from crude **43a**. To unambiguously determine the absolute configuration of the newly formed stereocenter, **44a** was subjected to acidic methanolysis to afford the known (*R*)-γ-lactone **45** and the methyl 2-deoxyglucoside **46** (which could, in theory, be recycled). Synthetic **45** prepared from a 5.8/1 mixture of **44** and its (4*S*)-diastereomer exhibited an $[\alpha]_D$ of +21.3° (*c* 0.25, CH_2Cl_2) [lit.[29] +30.1° (*c* 0.85, CH_2Cl_2)]. A similar reaction on the THP-adduct *ent*-**37** (X = H) produced the antipodal (*S*)-γ-lactone. These correlation experiments confirmed that the empirically observed diastereofacial selectivity of these radical additions was indeed consistent with our computationally derived TS model.

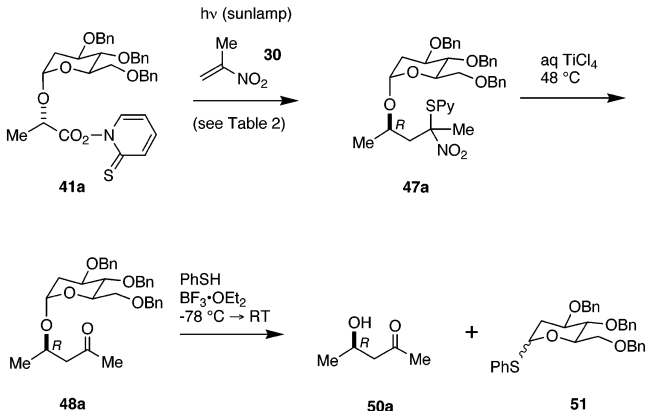
Radical Approach to Aldols. The use of another established radical trap with Barton ester **41** resulted in a conceptually novel approach to asymmetric aldol synthesis (Scheme 4).[30] Thus, photolysis of the Barton ester **41** in the presence of 2-nitropropene (**30**) produced the primary adducts **47** as a mixture of diastereomers. Conversion of the geminal nitro thioether function to a ketone was best accomplished by first filtering the crude reaction mixture through silica gel (to remove the *N*,*N*′-dicyclohexylurea byproduct) then exposing the crude

(28) Bolitt, V.; Mioskowski, C.; Lee, S.-G.; Falck, J. R. *J. Org. Chem.* **1990**, *55*, 5812.

(29) Mori, K. *Tetrahedron* **1975**, *31*, 3011.

(30) Garner, P.; Leslie, R.; Anderson, J. T. *J. Org. Chem.* **1996**, *61*, 6754.

SCHEME 4



adducts to reductive Nef conditions.[31] The protected aldols **48** could be obtained in excellent overall yields from the starting carboxylic acids (better than 90% per step in optimized cases). The kinetic diastereomer ratios were readily determined by comparing the crude ^{1}H NMR spectra with those of deliberately prepared mixtures. The diastereoselectivity observed with trap **30**, while still respectable, was even lower than that observed during analogous additions to methyl acrylate. Only marginal improvements in selectivity were observed when the steric bulk of R was increased, and the reaction temperature was lowered (Table 2, entries 2−5). Note that the diastereoselectivity was even worse when the unsubstituted THP auxiliary was used with this trap (entry 6).

Glycoside cleavage with concomitant production of the free aldol represented a potential difficulty because of the ease with which these aldol products can suffer dehydration. Attempted use of our previously elucidated conditions for auxiliary removal (PPTS/MeOH) failed to give any detectable aldol product. However, exposure of **48** to PhSH + BF_3•OEt_2, according to Danishefsky's precedent,[32] resulted in clean conversion to the free aldols **50** and the 2-deoxythioglycosides **51** (as a mixture of anomers). The negative optical rotations observed for the free aldols indicated that the newly formed stereocenter had the *R*-configuration[33] as was expected from our previous radical addition results with methyl acrylate. Free aldols could be obtained in >90% ee (Mosher ester analysis)[34] starting from protected aldols that had been purified (enriched) by flash chromatography. To complete the auxiliary recovery cycle (Figure 9), the thioglycosides **51** were oxidized with OXONE and the resulting sulfoxides **52** heated to induce sulfenic acid elimination. This two-step procedure afforded the starting tri-*O*-benzyl-D-glucal **38** in very good yield.

Auxiliary Design Revisited. According to our TS model (Figure 7), it is the α-hydrogen substituent at C-6 (THP numbering) that interferes with *Re*-approach of the trap to radical **14** resulting in the observed *Si*-selectivity. We reasoned that the drop-off in diastereoselectivity observed with the more reactive 2-nitropropene trap was

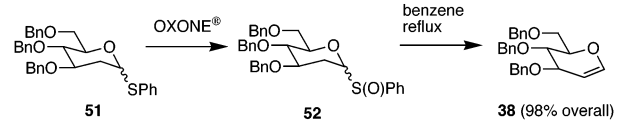


FIGURE 9. Chiral auxiliary reformation.

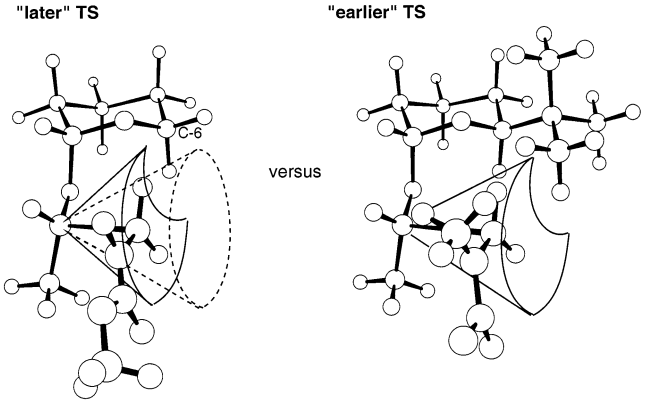


FIGURE 10. Postulated effect of C-6 substitution on the *Re*-TSs of radical additions to methyl acrylate (left) and 2-nitropropene (right).

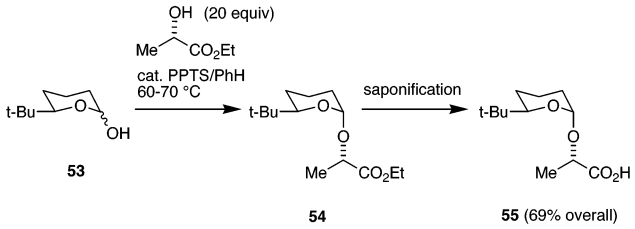


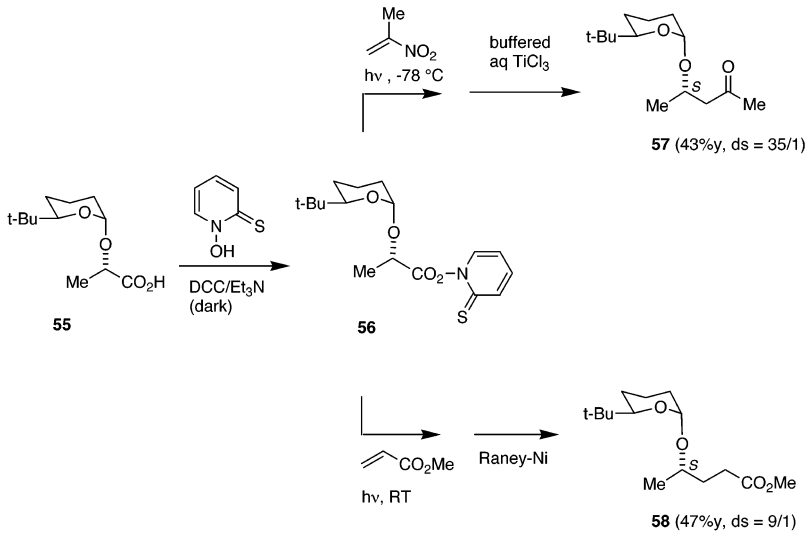
FIGURE 11. Synthesis of tBu-THP auxiliary substrates.

a consequence of an earlier TS, with commitment to bond formation occurring beyond the effect of the Glu and THP C-6 substituents (shown qualitatively in Figure 10). This hypothesis suggested that the incorporation of an α-substituent at C-6 other than H would result in higher diastereoselectivities. Unfortunately, such a substitution would also introduce a 1,3-diaxial interaction and disrupt the preference for the α-anomer or chair conformation as required by our model. The incorporation of a *trans-tert*-butyl group at C-6 of the auxiliary, on the other hand, would hinder *Re*-approach for even the reactive 2-nitropropene trap while maintaining the desired chair conformation. Although one might expect the benzyloxymethyl substituent of the glucose derived auxiliary to be large enough to hinder the *Re*-approach of any trap, this is true for only one of the three available staggered rotamers about the exocyclic C−C bond. No such ambiguity exists with the *tert*-butyl substituent, which necessarily places a methyl group in the path of the incoming trap irrespective of exocyclic C−C bond rotation.

To test this idea, an asymmetric synthesis of the *tert*-butyl substituted lactol **53** was devised building on the work of Crimmins (see Supporting Information for synthesis details).[35] This compound served as an effective auxiliary precursor (Figure 11). Anomeric mixture **53** reacted smoothly with an excess of inexpensive (*S*)-ethyl lactate in the presence of PPTS to give the α-anomer **54** in good yield. These conditions ensured that unreacted lactol would not compete with ethyl lactate for the

(31) McMurry, J. E.; Melton, J. *J. Org. Chem.* **1973**, *38*, 4367.
(32) Halcomb, R. L.; Boyer, S. H.; Wittman, M. D.; Olson, S. H.; Denhart, D. J.; Liu, K. K. C.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 5720.
(33) Cf. Fauve, A.; Veschambre, H. *J. Org. Chem.* **1988**, *53*, 5215.
(34) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

SCHEME 5



oxonium intermediate to give the "lactol dimers" which appeared to be less effective oxonium ion precursors. The *O*-protected lactate ester **54** could then be saponified to give the carboxylic acid **55** which was subjected to Barton esterifiation and photolysis in the presence of either 2-nitropropene or methyl acrylate to give **57** or **58** (40−50% overall yield) after reductive desulfurization or hydrolysis (Scheme 5).

As the results in Scheme 5 and Table 2 (entries 7−9) indicate, the *tert*-butyl substituted auxiliary leads to a dramatic enhancement of the diastereofacial selectivity during addition of the lactate derived radical to 2-nitropropene.[36] Significantly, the ratio of protected aldol diastereomers **57** was 35/1 at −78 °C, which corresponds to a diastereomeric excess (de) of 94%. This represents a 7-fold increase in diastereofacial selectivity over that observed with the glucose derived auxiliary at the same reaction temperature. Considerable stereodifferentiation was observed even when the addition reaction was performed at room temperature, with the diastereoselectivity higher than that observed with the glucose derived auxiliary at −78 °C! The radical addition to methyl acrylate also benefits from the use of this new auxiliary, with adduct **48** being formed with a diastereoselectivity of 9/1 at RT (Table 1, entry 5). As is usual with this trap, 12% of the telomer resulting from radical addition to 2 equiv of acrylate was also isolated. The configuration of the major product was correlated with (*S*)-4-methylbutyrolactone as described above thus confirming that the absolute sense of stereocontrol with this auxiliary conforms to our TS model.

We also investigated the use of the camphor derived "NOE auxiliary" (Table 2, entry 10) since it embodies a *β*-quaternary carbon at a position analogous to C-6 of our THP auxiliary. The starting acid **59** was prepared from the commercially available "NOE-lactol dimer" as described above for the *tert*-butyl-substituted auxiliary.[37] Unfortunately, both the yield and diastereoselectivity of the radical addition reaction were disappointing (42% yield, ds = 2/1) with this auxiliary. We tentatively ascribed this result to the conformational flexibility of the furanoside ring as well as the splay that results from the five- versus six-membered ring. Both of these factors cause the radical center to be further away from the quaternary carbon which is expected to block the approach to one face of the radical.

2nd Generation Sugar Auxiliary. Even though the *tert*-butyl-substituted auxiliary represented an effective solution to the stereocontrol problem, the isolated yields of the products were only moderate. The lowered yields were traced to the noticeable lability of adducts possessing this auxiliary when compared to adducts with the 2-deoxyglucose derived auxiliary. When the reductive hydrolysis was not properly buffered during the radical aldol sequence, the *tert*-butyl auxiliary was eliminated and lactol **53** was isolated in 46% yield. The analogous sequence with the sugar auxiliary could be performed under unbuffered conditions (pH ∼ 1) without any problem. Furthermore, the *tert*-butyl auxiliary protected aldol **57** had to be stored at −20 °C to avoid decomposition whereas the sugar protected aldol **48** could be kept at 5 °C indefinitely without any problem. Clearly, an auxiliary was needed that merged the favorable stability of the 2-deoxyglucose derived auxiliary with the enhanced stereocontrol associated with the *tert*-butyl-substituted THP auxiliary.

A carbohydrate literature search revealed a possible candidate for an auxiliary that could be accessed starting from an inexpensive sugar derivative. The uronate derived glucal **63** could be easily prepared on a large scale starting from commercially available, inexpensive D-glucurono-6,3-lactone (**61**).[38] This compound was considered

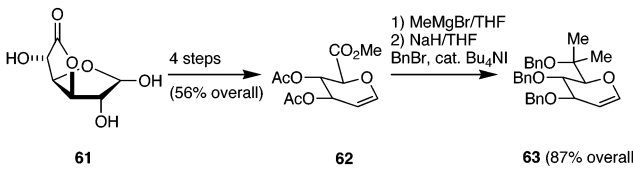
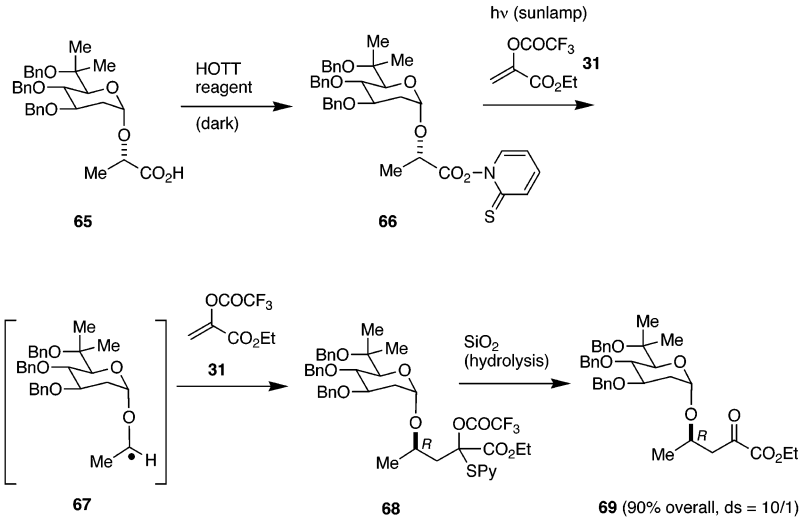


FIGURE 12. Synthesis of 2nd generation sugar (diMe-GLU) auxiliary.

(35) Crimmins, M. T.; Al-awar, R. S.; Vallin, I. M.; Hollis, W. G.; O'Mahony, R.; Lever, J. G.; Bankaitis-Davis, D. M. *J. Am. Chem. Soc.* **1996**, *118*, 7513.
(36) Garner, P.; Anderson, J. T. *Tetrahedron Lett.* **1997**, *38*, 6647.
(37) We thank Mr. Subhakar Dey for preparing this material.

SCHEME 6



to be an ideal auxiliary precursor since C-6 could be converted to a tertiary alcohol by a double Grignard addition to give the auxiliary glucal **63** after *O*-benzylation (Figure 12). This compound could be processed as described for **38** → **40** (Figure 8) to give the ethyl ester **64** and then, after saponification, the carboxylic acid **65**.

When carboxylic acid **65** was subjected to HOTT-mediated Barton esterification and the resulting solution photolyzed at 0 °C for 20−25 min in the presence of ethyl α-trifluoroacetoxyacrylate (**31**), a clean reaction was observed (Scheme 6, Table 3).[39] The auxiliary-protected γ-hydroxy-α-ketoester **69** was isolated in 90% overall yield after silica gel mediated hydrolysis of the hemithioacetal moiety in the initially formed adduct **68** It should be noted that somewhat lower yields were observed when either saturated $NaHCO_3$ or K_2CO_3/EtOH were used for hydrolysis as described by Barton. Control experiments confirmed that adduct **69** was susceptible to base-catalyzed elimination of the auxiliary lactol. The diastereoselectivity of this radical addition reaction was determined to be 10/1, which is very good considering that the reaction was performed at 0 °C. For comparison, same reaction with the unmodified glucal auxiliary gave a 2/1 mixture of the diastereomeric adduct **70** at this same temperature. As expected from our earlier studies, higher diastereoselectivities (>20/1) were observed when the radical homologation of **65** was performed at −78 °C.

Conclusions

The development of an effective recoverable chiral auxiliary for hydroxyalkyl radicals has been achieved. The key breakthrough in the auxiliary design process came as a result of an ab initio modeling of the competing transition states associated with the radical addition reaction. This work sets the stage for the development of a novel approach to 1, 3, 5...(2*n* + 1) polyols based on iterative radical homologation as well as the application of pyranosidic chiral auxiliaries to other synthetically important closed-shelled processes.[40]

Experimental Section

Melting points were determined using a Mel-Temp Capillary melting point apparatus and are not corrected. All moisture-sensitive reactions were performed in an inert, dry atmosphere of Ar or N_2. Reagent grade solvents were used for either chromatography or extraction. The following solvents and reagents were purified beyond commercial reagent grade: THF was distilled under Ar or N_2 from a purple solution of sodium−benzophenone ketyl. Benzene and methylene chloride were distilled over CaH_2 (0−1 mm grain size) under an inert atmosphere (Ar or N_2). Acetonitrile, diisopropylethylamine, pyridine, thiophenol, toluene, and triethylamine were distilled over CaH_2 and stored over activated 4 Å molecular sieves. Analytical thin-layer chromatography (TLC) was performed using either Merck silica gel 60 F-254 plates or JT-Baker Si250F plates (0.25 mm thickness). The plates were visualized first with UV illumination followed by charring with 5% *p*-anisaldehyde in 95:5:1 EtOH−AcOH−H_2SO_4, 2% vanillin in 98:2 EtOH−H_2SO_4, or "Verghn's reagent"[41] (12.5 g of ammonium molybdate and 0.5 g of ceric sulfate dissolved in 250 mL of 10% aq H_2SO_4). Flash chromatography was performed using silica gel (230−400 mesh). The solvent compositions reported for all chromatographic separations are on a volume/volume (v/v) basis.

Synthesis of Carboxylic Acid Substrates. (2*S*,2′*S*)- and (2*S*,2′*R*)-2-(Tetrahydropyran-2-yloxy)propionic Acid (32 and 33). To a 0.4 M stirred solution of the ester in THF was added 4 equiv of 1 N NaOH at 0 °C. After 1 h at this temperature, TLC analysis (3:2 hexanes/EtOAc) revealed that the starting material was consumed. The stirred solution was then acidified at 0 °C by the slow addition of 1 N HCl to pH = 4 (pH paper) and extracted three times with EtOAc. The aqueous phase was then acidified to pH = 3 and extracted three times with EtOAc. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated at reduced pressure to give the carboxylic acid (yield = 53−71%) as a clear oil which was used without further purification. R_f 0.15 (3:2 hexanes/EtOAc).

(2*S*)-[[2-Deoxy-3,4,6-tris-*O*-(phenylmethyl)-α-D-*arabino*-hexopyranosyl]oxy]propanoic Acid, Methyl Ester (39a). To a solution of tri-*O*-benzyl-D-glucal **(38)** (2.45 g, 5.88 mmol) and (*S*)-methyl lactate (0.88 mL, 8.8 mmol) in freshly distilled CH_2Cl_2 (15 mL) was added $Ph_3P{\cdot}HBr$ (100 mg, 0.300 mmol), and the solution was stirred at ambient temperature, under

(38) (a) Fehlhaber, H. W.; Snatzke, G.; Vlahov, I. *Liebigs Ann. Chem.* **1987**, 637. (b) Wyss, P. C.; Kiss, J.; Arnold, W. *Helv. Chim. Acta* **1975**, *58*, 637.

(39) Garner, P.; Anderson, J. T. *Org. Lett.* **1999**, *2*, 1057.

(40) For a recent application of pyranosidic chiral auxiliaries to the Diels−Alder reaction, see: Garner, P.; Anderson, J. T.; Turske, R. A. *Chem. Commun.* **2000**, 1579.

(41) Corey, E. J.; Roberts, B. E. *J. Am. Chem. Soc.* **1997**, *119*, 12425.

Ar, for 2 h. The reaction was then quenched with sat aq $NaHCO_3$ and the resulting suspension extracted with CH_2Cl_2 (3 × 75 mL), the organic layers were combined, dried ($MgSO_4$), and filtered, and the solvent was removed to provide a thick oily residue that was purified by flash chromatography (17% EtOAc−hexanes) to give the pure glucoside **39a** (2.58 g, 83%) as a thick colorless oil. R_f 0.33, 25% EtOAc−hexanes; $[\alpha]^{25}_D$ + 58.9° (*c* 5.05, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.18 (m, 15 H, 3 × Ph), 5.06 (br d, J = 3 Hz, 1 H, H-1′), 4.90 (d, J = 11.1 Hz, 1 H, 0.5 PhCH_2), 4.68 (s, 2 H, PhCH_2), 4.63 (d, J = 12 Hz, 1 H, 0.5 PhCH_2), 4.53 (d, J = 11.1 Hz, 1 H, 0.5 PhCH_2), 4.48 (d, J = 12.0 Hz, 1 H, 0.5 PhCH_2), 4.19 (q, J = 6.8 Hz, 1 H, H-2), 4.04 (ddd, J = 11.7, 9.6, 5.7 Hz, 1 H, H-3′), 3.94 (dt, J = 10.5, 2.1 Hz, 1 H, H-5′), 3.77 (m, 2 H, H-4′, H-6′), 3.67 (s, 3 H, OMe), 3.54 (dd, J = 10.5, 2.1 Hz, 1 H, H-6′), 2.27 (ddd, J = 12.6, 5.7,1.0 Hz, 1 H, H-2′ eq), 1.91 (ddd, J = 12.6, 9.6, 3 Hz, 1 H, H-2′ ax), 1.39 (d, J = 6.7 Hz, 3 H, Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2 (CO), 138.8, 138.7, 138.2 (aromatic C), 128.4, 128.3, 127.90, 127.88, 127.8, 127.7, 127.63, 127.58 (aromatic PhCH), 97.6 (anomeric CH), 78.2, 77.5 (CH), 74.9, 73.5 (CH_2), 72.8 (CH), 72.1 (CH_2), 71.4 (CH), 68.7 (CH_2), 53.0 (CH_3), 35.7 (CH_2), 18.0 (CH_3); IR ($CHCl_3$) 3000, 2940, 2820, 1740, 1440, 1350, 1200, 1090 cm^{-1}; EIMS (*m*/*z*): [M − $PhCH_2$]$^+$ calcd for $C_{24}H_{29}O_7$, 429.1913; found, 429.1899.

General Procedure for the Saponification of Esters 39a−c. The protected α-hydroxy ester **39** was dissolved in MeOH (0.15 M) and vigorously stirred at 0 °C. To the stirring solution was added aq NaOH solution (1.0 M, 7 equiv) over 5 min. The resulting solution was warmed to room temperature and stirred overnight (ca. 13 h) when the reaction was judged to be complete by TLC. The contents were cooled to 0 °C and acidified to pH = 4 by slowly adding aq HCl solution (1.0 M). The acidified mixture was poured onto brine and extracted with EtOAc (3×). The organic layers were combined and washed with brine, dried over $MgSO_4$, filtered through cotton, and then concentrated by rotary evaporation and then vacuum pumped to give the acid **40** as a thick clear oil.

2-[[2-Deoxy-3,4,6-tris-*O*-(phenylmethyl)-α-D-*arabino*-hexopyranosyl]oxy]hexanoic Acid (40b). A 1:1 mixture of diastereomers: ^{1}H NMR (300 MHz, $CDCl_3$) (excluding CO_2H) δ 7.39−7.12 (m, 15 H, Ar), 5.05 (d, J = 2.6 Hz, 0.5 H, H-1′), 5.01 (d, J = 2.7 Hz, 0.5 H, H-1′), 4.92−4.83 (m, 1 H), 4.71−4.39 (5 H), 4.29 (t, J = 6.2 Hz, 0.5 H), 4.21−4.14 (m, 0.5 H), 4.08−3.95 (m, 2 H), 3.82−3.72 (m, 1.5 H), 3.72−3.45 (m, 3.5 H), 2.45 (dd, J = 13.1, 5.1 Hz, 0.5 H), 2.31 (dd, J = 13.2, 4.8 Hz, 0.5 H), 1.86−1.68 (m, 3 H), 1.49−1.34 (m, 5 H), 0.99−0.83 (m, 3 H); ^{13}C NMR (APT) (75 MHz, $CDCl_3$) δ 178.3 (+), 177.9 (+), 138.5 (+), 138.3 (+), 138.0 (+), 128.4 (−), 128.16 (−), 128.13 (−), 128.11 (−), 127.98 (−), 127.95 (−), 127.92 (−), 127.87 (−), 127.86 (−), 127.8 (−), 127.72 (−), 127.69 (−), 127.66 (−), 127.6 (−), 98.8 (−), 96.5 (−), 78.1 (−), 77.3 (−), 75.2 (+), 74.9 (+), 73.45 (+), 73.36 (+), 72.0 (+), 71.7 (−), 68.7 (+), 68.5 (+), 35.5 (+), 32.4 (+), 32.0 (+), 27.5 (+), 27.1 (+), 22.4 (+), 22.3 (+), 13.9 (−), 13.84 (−), 13.83 (−).

2-[[2-Deoxy-3,4,6-tris-*O*-(phenylmethyl)-α-D-*arabino*-hexopyranosyl]oxy]-3-methylbutanoic Acid (40c). Data for more polar diastereomer on TLC (EtOAc−hexanes): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.16 (m, 15 H, Ar), 5.03 (d, J = 2.6 Hz, 1 H, H-1′), 4.89 (d, J = 10.8 Hz, 1 H, 0.5 PhCH_2), 4.72−4.61 (m, 3H, 1.5 PhCH_2), 4.52 (m, 2 H, PhCH_2), 4.14 (d, J = 4.4 Hz, 1 H, H-2), 3.99 (ddd, J = 11.3, 8.8, 4.8 Hz, 1 H, H-3′), 3.78 (m, 2 H), 3.70−3.57 (m, 2 H), 2.44 (dd, J = 12.1, 5.0 Hz, 1 H, H-2′eq), 2.16 (m, 1 H, H-3), 1.77 (m, 1 H, H-2′ ax), 1.01 (d, J = 6.8 Hz, 3 H, *Me*CHMe), 0.96 (d, J = 6.9 Hz, 3 H, MeCH*Me*); ^{13}C NMR (APT) (75 MHz, $CDCl_3$) δ 176.6 (+), 138.54 (+), 138.47 (+), 138.0 (+), 128.33 (−), 128.28 (−), 128.27 (−), 127.98 (−), 127.95 (−), 127.92 (−), 127.89 (−), 127.86 (−), 127.8 (−), 127.70 (−), 127.67 (−), 127.66 (−), 127.6 (−), 127.54 (−), 127.48 (−), 100.0 (−), 83.2 (−), 78.0 (−), 74.8 (+), 73.3 (+), 72.0 (+), 71.9 (−), 68.5 (+), 35.5 (+), 31.3 (−), 18.5 (−), 17.5 (−).

[2*S*-(2α,6*β*)]-2-[[6-(1,1-Dimethylethyl)tetrahydro-2*H*-pyran-2-yl]oxy]propanoic Acid, Ethyl Ester (54). The lactol **53** (425 mg, 2.69 mmol), (*S*)-ethyl lactate (6.36 g, 6.10 mL, 53.8 mmol), and a catalytic amount of PPTS (30 mg) were dissolved in freshly distilled dry benzene (18 mL) and heated to reflux under Ar. The reaction was complete (TLC) after 1 h. The contents were cooled to room temperature and then poured into sat aq $NaHCO_3$ (20 mL) and extracted with EtOAc (3 × 50 mL). The organic layers were combined and washed with brine (20 mL), dried over $MgSO_4$, filtered through cotton, and then concentrated by rotary evaporation. The crude product was purified by column chromatography (SiO_2) using 4% Et_2O−hexanes to give **54** as a clear oil, 69% yield. R_f 0.66, 20% EtOAc−hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.92 (d, J = 2.8 Hz, 1 H, H-2′), 4.38 (q, J = 7.0 Hz, 1 H, H-2), 4.19 (2H, OCH_2CH_3), 3.35 (dd, J = 11.8, 1.9 Hz, 1 H, H-6′), 1.90−1.72 (m, 2 H), 1.66−1.53 (3H), 1.44 (d, J = 7.1 Hz, 3 H, H-3), 1.38−1.22 (m + t, J = 7.1 Hz, 4 H, OCH_2CH_3), 0.89 (s, 9 H, *t*-Bu); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5 (CO), 96.2, 76.5, 68.8, 60.6, 33.6, 29.4, 25.5, 24.9, 18.6, 18.1, 14.1; EIMS (*m*/*z*): [M − H]$^+$ calcd for $C_{14}H_{25}O_4$, 257.1753; found, 257.1765; [M − *t*-Bu]$^+$ calcd for $C_{10}H_{17}O_4$, 201.1127; found, 201.1128.

[2*S*-(2α,6*β*)]-2-[[6-(1,1-Dimethylethyl)tetrahydro-2*H*-pyran-2-yl]oxy]propanoic Acid (55). The protected α-hydroxy ester **54** (472 mg, 1.83 mmol) was dissolved in THF (15 mL) and stirred at 0 °C. To the stirring solution was added 1.0 N NaOH (13 mL) over 5 min. The resulting solution was stirred overnight (ca. 13 h) under Ar at room temperature when TLC showed the reaction to be complete. The contents were cooled to 0 °C and acidified to pH = 4 by slowly adding 1.0 N HCl. The acidified reaction contents were poured onto brine (50 mL) and extracted with EtOAc (3 × 80 mL). The organic layers were combined and washed with brine (50 mL), dried over $MgSO_4$, filtered through cotton, and then concentrated to give **55** as a thick clear oil, quantitative yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.95 (d, J = 2.6 Hz, 1 H, H-2′), 4.43 (q, J = 7.0 Hz, 1 H, H-2), 3.34 (dd, J = 11.5, 1.7 Hz, 1 H, H-6′), 1.90−1.70 (m, 2 H), 1.68−1.54 (m, 3 H), 1.49 (d, J = 7.1 Hz, 3 H, H-3), 1.38−1.24 (m, 1 H), 0.89 (s, 9 H, *t*-Bu); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.1 (CO), 96.6, 76.7, 68.7, 33.7, 29.3, 25.8, 24.9, 18.5, 18.0; EIMS (*m*/*z*): M^+ calcd for $C_{12}H_{22}O_4$, 230.1518; found, 230.1511.

1,5-Anhydro-2,7-dideoxy-6-*C*-methyl-3,4,6-tris-*O*-(phenylmethyl)-D-*arabino*-hept-1-enitol (63). A dry THF (0.44 M) solution of the triester **62** was added to a 0 °C 3.0 M THF solution of MeMgCl (7 equiv) over a period of 5 min under Ar. The resulting solution was allowed to warm to room temperature and stirred for 90 min when TLC (70% EtOAc/hexanes) showed the reaction to be complete. The reaction was quenched at 0 °C by the careful addition of 5 mL of saturated aq NH_4Cl solution. The reaction mixture was poured onto 25 mL of H_2O and extracted 4 × 40 mL EtOAc. The organic layers were combined and washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated. No purification, 87% crude yield. A dry THF solution (30 mL) of this crude triol (4.05 g, 23.2 mmol) was added to a THF suspension (20 mL) of NaH (3.35 g, 139 mmol, rinsed with 3 × 10 mL pentane to remove the oil) under Ar over 10 min. The resulting mixture was stirred for 15 min at RT. To the reaction mixture was added Bu_4NI (0.43 g, 1.2 mmol) followed by benzyl bromide (13.8 mL, 116 mmol) over a 10 min period. The resulting mixture was stirred overnight (15 h) when TLC (15% EtOAc−hexanes) showed that the reaction was complete. The reaction mixture was poured onto ice (75 mL) and extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with brine (75 mL), dried over Na_2SO_4, filtered through cotton, and then concentrated using rotary evaporation and vacuum pumping. The crude yellow product was purified by column chromatography using 4% EtOAc−hexanes to give **63** as a light yellow oil, 87% yield. R_f 0.29, 10% EtOAc−hexanes; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35−7.20 (m, 15 H, 3 × Ph), 6.44 (d, J = 4.6 Hz, 1 H, H-1), 4.91 (m, 1 H, H-2), 4.89 (d, 1 = 11.2 Hz,1 H, 0.5

PhCH_2), 4.74 (d, 1 = 11.0 Hz,1 H, 0.5 PhCH_2), 4.64 (d, 1 = 11.6 Hz,1 H, 0.5 PhCH_2), 4.60−4.52 (m, 3 H, 1.5 PhCH_2), 4.31 (dt, J = 8.6, 1.8 Hz, 1 H, H-3), 3.99 (dd, J = 9.2, 6.7 Hz, 1 H, H-4), 3.84 (d, J = 9.2 Hz, 1 H, H-5), 1.42 (s, 3 H, Me), 1.40 (s, 3 H, Me); ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.2, 139.7, 138.4, 138.3, 128.4, 128.24, 128.17, 128.0, 127.8, 127.6, 127.5, 127.3, 127.0, 100.3, 82.3, 78.3, 76.8, 76.5, 73.9, 70.8, 64.3, 24.6, 23.4; EIMS (m/z): [M − $PhCH_2$]$^+$ calcd for $C_{22}H_{25}O_4$, 353.1753; found, 353.1730.

(2*S*)-2-[[2,7-Dideoxy-6-*C*-methyl-3,4,6-tris-*O*-(phenylmethyl)-α-D-*arabino*-heptopyranosyl]oxy]propanoic Acid, Ethyl Ester (64). (An adaptation of the procedure described above for **39** was employed.) R_f 0.47, 25% EtOAc−hexanes; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34−7.19 (m, 15 H, 3 × Ph), 5.07 (br t, J = 4 Hz, 1 H, H-1′), 4.81−4.58 (m, 6 H, 3 × PhCH_2), 4.27 (q, J = 6.8 Hz, 1 H, CH_3CH), 4.18 (m, 2 H, OCH_2CH_3), 4.00 (ddd, J = 10.3, 5.9, 4.6 Hz, 1 H, H-3′), 3.87−3.79 (m, 2 H, H-4′, H-5′), 2.25 (dt, J = 13.4, 4.3 Hz, 1 H, H-2′ eq), 1.88 (ddd, J = 13.9, 9.6, 4.5 Hz, 1 H, H-2′ ax), 1.40−1.38 (m, 9 H, 2 × Me, CH_3CH), 1.27 (t, J = 7.1 Hz, 3 H, OCH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.4, 140.0, 138.7, 138.6, 128.3, 128.1, 127.8, 127.6, 127.5, 127.2, 127.1, 126.8, 95.7, 78.6, 77.4, 76.7, 76.1, 73.3, 71.8, 71.2, 64.3, 60.8, 34.2, 25.1, 23.1, 17.5, 14.2; EIMS (m/z): calcd [M − $PhCH_2$]$^+$ for $C_{27}H_{35}O_7$, 471.23828; found, 471.23788; calcd [M − $C(CH_3)_2OCH_2Ph$]$^+$ for $C_{24}H_{29}O_6$, 413.1964; found, 413.1962.

(2*S*)-2-[[2,7-Dideoxy-6-*C*-methyl-3,4,6-tris-*O*-(phenylmethyl)-α-D-*arabino*-heptopyranosyl]oxy]propanoic Acid (65). (An adaptation of the procedure described above for **55** was employed.) ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33−7.18 (m, 15 H, 3 × Ph), 5.11 (t, J = 4.3 Hz, 1 H, H-1′), 4.73−4.56 (m, 6 H, 3 × PhCH_2), 4.32 (q, J = 6.9 Hz, 1 H, CH_3CH), 3.94 (ddd, J = 8.4, 5.1, 4.2 Hz, 1 H, H-3′), 3.87−3.77 (m, 2 H, H-4′, H-5′), 2.19 (dt, J = 13.7, 4.0 Hz, 1 H, H-2′ eq), 1.99 (ddd, J = 13.3, 8.2, 5.0 Hz, 1 H, H-2′ ax), 1.43 (d, J = 6.8 Hz, 3 H, CH_3CH), 1.36 (s, 3 H, Me), 1.33 (s, 3 H, Me); ^{13}C NMR (APT) (75 MHz, $CDCl_3$): δ 176.9 (+), 139.8 (+), 138.3 (+), 128.4 (−), 128.2 (−), 128.1 (−), 127.7 (−), 127.4 (−), 127.1 (−), 126.9 (−), 95.9 (−), 77.9 (−), 76.6 (−), 73.1 (+), 71.7 (+), 71.1 (−), 64.4 (+), 33.4 (+), 24.7 (−), 22.9 (−), 17.4 (−); IR (neat): 1745 cm^{-1} (C=O); EIMS (m/z): [M − $PhCH_2$]$^+$ calcd for $C_{25}H_{31}O_7$, 444.2070; found 444.2099.

Barton Esterification Reactions. A. DCC Procedure. To a 0.1 M solution of carboxylic acid and 2-mercaptopyridine-*N*-oxide (1.5 equiv) in freshly distilled CH_2Cl_2 was added DCC (1.5 equiv) under Ar. The mixture was stirred at RT in the dark for ca. 1.5 h or until the reaction was judged to be complete by TLC (50% EtOAc−hexanes).

B. Original HOTT Procedure. A solution of carboxylic acid (0.1 M), Et_3N, or Hünig's base (4.0 equiv), and DMAP (0.1 equiv) in dry THF was added to a two-neck flask containing HOTT (1.5 equiv) in the dark under an Ar atmosphere. This mixture was stirred in the dark until the reaction was judged to be complete by IR spectroscopy. When IR monitoring was not possible (because of overlapping carbonyl bands), the reaction was allowed to proceed for an arbitrary time and presumed to be complete if no starting acid was detected after the trapping step. In general, IR monitoring was performed by injecting 75 μL of the reaction mixture into an IR solution cell (NaCl, 0.1 mm gap) in a very dimly lit room. A second solution cell containing THF was used as a reference. The bright yellow Barton ester solution was then submitted to one of the trapping reactions.

C. Improved HOTT Procedure. A dry THF solution of the acid was added to an aluminum foil-covered flask containing a dry CH_3CN solution of HOTT (1.5 equiv) and DMAP (0.1 equiv) at room temperature under Ar. It was later determined that DMAP was *not* necessary for fast and complete Barton esterification when this mixed solvent system was used. The final concentration of acid was 0.1 M in (3:1) THF−CH_3CN. Et_3N (3 equiv) was added to the mixture and the resulting solution stirred in the dark for 30 min under Ar at room temperature until the reaction was judged to be complete by IR analysis (see above).

Radical Additions to Methyl Acrylate. Methyl acrylate (**29**) (5 equiv) was added to the fluorescent yellow suspension of Barton ester (in most cases, prepared by method A above) and the mixture irradiated using a 275 W sunlamp at −78 °C until the Barton ester had been consumed as evidenced by TLC analysis. The reaction mixture was then filtered through Celite, and the volatiles removed to provide a residue that was either processed as described below to determine the kinetic diastereoselectivity or subjected to flash chromatography to afford the pure adducts.

Raney Nickel Activation. A 20 g amount of Nickel−aluminum alloy was added to 100 mL of 6 N NaOH over 45 min with vigorous stirring at 0 °C under Ar, when the ice bath was removed and the mixture was stirred at room temperature for 4 h. The basic supernatant was then decanted, and the dark solid was washed with water (20 × 300 mL) and MeOH (3 × 300 mL), stirring the mixture for about 1 min for each washing. At the end of this procedure, the catalyst was suspended in 120 mL of MeOH under Ar.

Raney Nickel Reduction. The ester was dissolved in MeOH, the freshly activated suspension of Raney-Ni in MeOH (ca. 20 mL for 100 mg of the starting carboxylic acid) was added at room temperature under argon, and the mixture was vigorously stirred overnight. After TLC analysis indicated that the starting material was consumed, the mixture was filtered through a pad of Celite and concentrated under reduced pressure to give a crude product that was purified by flash chromatography.

Determination of Diastereomer Ratios of Methyl Acrylate Adducts. The diastereoselectivity (ds) of the radical reactions leading to adducts **37**/*ent*-**37**, **44**, and **60** were determined using either NMR or HPLC based analytical techniques. In the case of **37** and *ent*-**37**, the crude 2-thiopyridyl ether mixture was filtered through silica gel collecting all fractions containing material within R_f 0.6 and 0.4 (3/2 hexanes−EtOAc). The resulting mixture was then subjected to Raney-Ni reduction. The desulfurized products were purified by flash chromatography taking care to avoid inadvertent diastereomer enrichment and the diastereoselectivites determined by ^{1}H NMR.

With **44** and **60**, the crude radical reaction mixture was subjected to "rough" flash chromatography, taking care to collect all monoadducts (which had identical R_f values in 25% EtOAc−hexanes). This mixture of primary adducts was subjected to Raney-Ni reduction as described above and the crude product mixtures analyzed by ^{1}H NMR spectroscopy or reverse phase HPLC (C-18 Dynamax column, gradient elution using 90% → 20% H_2O−MeCN at 1% /min, then 20% → 17% over 20 min, flow rate = 1 mL/min).

In the case of radical reactions leading to adduct **58**, the following GC conditions were used to determine the diastereoselectivity: Column: HP-5 (cross-linked 5% PhMe Silicone); 30 m × 0.32 mm × 2.5 μm film thickness; initial oven temperature: 60 °C for 10 min; injector temperature: 250 °C; ramp: 10 °C/min; final oven temperature: 250 °C for 5 min; detector temperature: 250 °C; retention times: major diastereomer: 22.3 min, minor diastereomer 21.8 min.

37 and *ent*-37 (X = SPy): R_f 0.48, 3/1 hexanes−EtOAc; **37** (X = SPy), $[\alpha]^{22}_D$ +21.3° (*c* 1.2, $CHCl_3$); *ent*-**37** (X = SPy), $[\alpha]^{22}_D$ −22.6° (*c* 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (m, 1 H, Py), 7.45 (m, 1 H, Py), 6.95 (m, 1 H, Py), 4.85−4.50 (m, 2 H, H-1′, H-3), 3.9 (m, 2 H, H-1, H-5′), 3.69 (2s, 3 H, CO_2Me), 3.4 (m, 1 H, H-5′), 2.31−1.41 (m, 8 H, H-2′, H-3′, H-4′, H-2), 1.28 (d, 3 H, J = 6.3 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2 (CO), 157.1 (PyC), 149.5, 149.4, 136.23, 136.20, 122.4, 122.3, 120.1, 120.0 (Py CH), 100.6, 99.8 (anomeric CH), 73.2, 72.7 (CH), 62.8 (CH_2), 52.49, 52.45 (CH_3), 43.4, 43.2 (CH), 39.4, 39.3, 31.0, 30.9, 25.49, 25.46 (CH_2), 22.4, 21.9 (CH_3), 20.0, 19.9 (CH_2); IR ($CHCl_3$) 3000, 2940, 1730, 1570, 1410, 1120, 1020

cm^{-1}; HRMS *m/z* calcd for $C_{16}H_{23}NO_4S$ [M]$^+$ 325.1348, obsd 325.1343.

[*R*-(*R*,S)]-4-[(Tetrahydro-2*H*-pyran-2-yl)oxy]pentanoic Acid, Methyl Ester (37, X = H):** R_f 0.59, 4/1 hexanes−EtOAc; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.60 (t, J = 2.7 Hz, 1 H, H-2′), 3.75 (sextet, J = 6.0 Hz, 1 H, H-4), 3.67 (s, 3 H, OMe), 3.49 (m, 1 H, H-6′), 2.37 (t, J = 7.8 Hz, 2 H, H-2), 1.80−1.50 (m, 8 H), 1.24 (d, J = 6.3 Hz, 3 H, H-5); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2 (CO), 99.8 (anomeric CH), 73.3 (CH), 62.9 (CH_2), 51.6 (CH_3) 31.5, 31.0, 30.0, 25.5 (CH_2), 21.5 (CH_3), 20.0 (CH_2); IR (CH_2Cl_2) 2940, 1730, 1430, 1360, 1330, 1190, 1160, 1130, 1060 cm^{-1}; EIMS (*m/z*): [M − H]$^+$ calcd for $C_{11}H_{19}O_4$, 215.1283; found, 215.1279.

THP−Auxiliary Telomer Characterization: R_f 0.14, 3/1 hexanes−EtOAc; MS (EI) *m/z*, 411 (10%, [M]$^+$), 326 (30%, [M − C_5H_9O]$^+$), 310 (100%, [M − $C_5H_9O_2$]$^+$), 301 (<10%, [M − SPy]$^+$), 269 (<10%, [M − $C_8H_{14}O_2$]$^+$); HRMS (EI) *m/z* calcd for $C_{20}H_{29}NO_6S$ [M]$^+$ 411.1716, obsd 411.1717.

(*S*)-4-Methylbutyrolactone (*ent*-45). To a 0.2 M solution of *ent*-**37** (X = H) in MeOH was added a catalytic amount of PPTS, and the stirred mixture was refluxed overnight at which point TLC (4/1 hexanes−EtOAc) analysis revealed that the starting material was consumed. The mixture was poured into a saturated aqueous solution of $NaHCO_3$ and extracted five times with EtOAc. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated by rotary evaporation, keeping the bath at 3 °C because the lactone is volatile. The crude mixture was purified by flash chromatography. The separation was monitored by ^{1}H NMR since the product could not be detected by TLC. Yield = 55%. Starting from *ent*-**37** (X = H) with ds = 6/1, $[\alpha]^{25}_D$ = -21.4° (*c* 0.70, CH_2Cl_2). (Spectral data reported below for compound **45**.)

3,5-Dideoxy-4-*O*-[2-deoxy-3,4,6-tris-*O*-(phenylmethyl)-α-D-*arabino*-hexopyranosyl]-2-*S*-(2-pyridinyl)-2-thiopentanoic Acid, Methyl Ester (43a): R_f 0.65, 2/1 hexanes−EtOAc; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (m, 1 H, Py), 7.48 (m, 1 H, Py), 7.39−7.14 (m, 16 H, Py, 3 × Ph), 7.10 (m, 1H, Py), 5.10 (br d, 1 H, J = 2.7 Hz, H-1′), 4.95−4.48 (m, 7 H, 3 × PhCH_2, H-2), 4.07−3.60 (m, 9 H, H-3′, H-4′, H-5′, H-6′, H-1, CO_2Me), 2.40−1.40 (m, 4 H, H-2′ eq, H-2′ ax, 2 × H-2), 1.28 (d, 3 H, J = 6.0 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 172.9 (CO), 157.0 (PyC), 149.53, 149.47 (CH), 138.86, 138.60, 138.20 (C), 136.33, 136.25 (PyCH), 128.51, 128.46, 128.39, 128.35, 128.13, 128.0, 127.93, 127.89, 127.8, 127.7, 127.6 (ArCH), 122.5, 122.4, 120.2, 120.1 (PyCH), 99.3, 98.6 (anomeric CH), 78.4, 77.7 (CH), 75.1, 75.0 (CH_2), 73.8 (CH), 73.53 (CH_2), 73.50 (CH), 71.8, 71.6 (CH_2), 71.1, 71.0 (CH), 68.99, 68.96 (CH_2), 52.6, 52.5 (CH_3), 43.3, 43.1 (CH), 39.4, 39.3, 35.8, 35.7 (CH_2), 22.0, 21.6 (CH_3); IR ($CHCl_3$) 3000, 2910,1750, 1570, 1450, 1410, 1020 cm^{-1}; EIMS (*m/z*): M$^+$ calcd for $C_{38}H_{43}NO_7S$, 657.2760; found, 657.2742.

Glucal-Auxiliary Telomer Characterization: R_f 0.16, 3/1 hexanes−EtOAc; MS (EI) *m/z*, 411 (40%, [M]$^+$), 328 (100%, [M − $C_{27}H_{29}O_4$ + 2H]$^+$), 326 (<10%, [M − $C_{27}H_{29}O_4$]$^+$), 310 (<10%, [M − $C_{27}H_{29}O_5$]$^+$); HRMS (EI) *m/z* calcd for $C_{42}H_{49}NO_9S$ [M]$^+$ 743.3128, obsd 743.3070.

(4*R*)-4-[[2-Deoxy-3,4,6-tris-*O*-(phenylmethyl)-α-D-*arabino*-hexopyranosyl]oxy]pentanoic Acid, Methyl Ester (44): R_f 0.48, 3/1 hexanes−EtOAc; $[\alpha]^{25}_D$ + 52.1° (*c* 0.83, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.10 (m, 15 H, 3 × Ph), 5.04 (br d, J = 3.0 Hz, 1 H, H-1′), 4.91 (d, J = 10.8 Hz, 1 H, 0.5 PhCH_2), 4.65 (m, 3 H, 1.5 PhCH_2), 4.50 (m, 2 H, PhCH_2), 3.98 (ddd, J = 11.5, 9.4, 5.1 Hz, 1 H, H-3′), 3.90−3.60 (m, 8 H, H-4′, H-5′, 2 × H-6′, H-4, CO_2Me), 2.36 (t, J = 7.6 Hz, 2 H, H-2), 2.25 (dd, J = 13.5, 5.1 Hz, 1 H, H-2′ eq), 1.87−1.67 (m, 3 H, H-3, H-2′ ax), 1.20 (d, J = 6.3 Hz, 3 H, Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1 (CO), 138.8, 138.5, 138.2 (C), 128.4, 128.1, 127.9, 127.7, 127.6 (PhCH), 97.7 (anomeric CH), 78.4, 77.8 (CH), 75.1 (CH_2), 70.9 (CH), 68.9 (CH_2), 51.7 (CH_3), 35.9, 31.5, 30.1 (CH_2), 21.2 (CH_3); IR ($CHCl_3$) 3000, 1725, 1530, 1460, 1430 cm^{-1}; HRMS−FAB (*m*-nitrobenzyl alcohol, *m/z*): M$^+$ calcd for $C_{33}H_{40}O_7$, 548.2774; found, 548.2771.

Auxiliary Removal and γ-Lactone Formation. The glucoside **44** (210 mg, 0.38 mmol) was dissolved in MeOH, a catalytic amount of PPTS added, and the resulting solution was refluxed overnight. The reaction mixture was then quenched with satd $NaHCO_3$ solution, extracted with Et_2O, dried ($MgSO_4$), and filtered and the solvent removed to provide the crude product mixture that was purified by flash chromatography (2/1 petroleum ether−Et_2O) to supply the γ-lactone **45** (25 mg, 66%) and methyl glucoside **46** (160 mg, 93%).

(*R*)-4-Methylbutyrolactone (45). Starting from **44** with ds = 5.8/1, $[\alpha]^{25}_D$ = +21.3° (*c* 0.25, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.56 (sextet, 1 H, J = 6.3 Hz, H-4), 2.55 (m, 2 H, H-2), 2.35 (sextet, 1 H, 6.3 Hz, H-3), 1.84 (m, 1 H, H-3), 1.41 (d, 3 H, J = 6.3 Hz, Me); IR (neat) 2960, 2920, 1780, 1450 cm^{-1}.

Methyl 2-deoxy-3,4,6-tris-*O*-(phenylmethyl)-α-D-*arabino*-hexopyranoside (46): R_f 0.50, 3/1 hexanes−EtOAc; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (15 H, 3 × Ph), 4.92 (d, J = 10.8 Hz, 1H, 0.5 PhCH_2), 4.88 (br d, J = 2.4 Hz, 1H, H-1′), 4.70−4.50 (5H, 2.5 PhCH_2), 4.00 (ddd, J = 11.5, 9.6, 5.7 Hz, 1H, H-3′), 3.80−3.50 (4H, H-4′, H-5′, 2 × H-6′), 3.34 (s, 3H, OCH_3), 2.30 (ddd, J = 12.6, 5.7, 1.0 Hz, 1H, H-2′ eq), 1.85 (ddd, J = 12.6, 9.6, 3.0 Hz, 1H, H-2′ ax); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6, 138.2, 128.5, 128.42, 128.38, 128.1, 128.0, 127.9, 127.81, 127.78, 127.7, 127.6 (PhCH), 98.6 (anomeric CH), 78.3, 77.7, (CH), 75.0, 73.5, 71.8 (CH_2), 70.7 (CH), 69.0 (CH_2), 54.7 (CH_3), 35.5 (CH_2); IR ($CHCl_3$) 3000, 2920, 2840, 1490, 1445, 1355 cm^{-1}; EIMS (*m/z*): M$^+$ calcd for $C_{28}H_{32}O_5$, 448.2250; found, 448.2240.

[2*S*-[2α(*S),6*β*]]-4-[[6-(1,1-Dimethylethyl)tetrahydro-2*H*-pyran-2-yl]oxy]pentanoic Acid Methyl Ester (58):** R_f 0.67, 3/1 hexanes−EtOAc; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.89 (s, 1 H, H-2′), 3.79 (sextet, J = 6.1 Hz, 1 H, H-4), 3.67 (s, 3 H, OMe), 3.42 (dd, J = 12.1, 1.7 Hz, 1 H, H-6′), 2.35 (t, J = 7.7 Hz, 2 H, H-2), 1.84−1.70 (m, 3 H), 1.62−1.52 (m, 4 H), 1.35−1.20 (m + d, J = 6.3 Hz, 4 H, H-5), 0.88 (s, 9 H, *t*-Bu); ^{13}C NMR (APT) (75 MHz, $CDCl_3$) δ 174.1 (+) (CO), 96.5 (−), 75.9 (−), 71.0 (−), 51.5 (−), 33.8 (+), 30.8 (+), 30.1 (+), 29.7 (+), 25.9 (−), 25.1 (+), 20.9 (−), 18.3 (+); EIMS (*m/z*): [M + H]$^+$ calcd for $C_{15}H_{29}O_4$, 273.2064; found, 273.2068; M$^+$ calcd for $C_{15}H_{28}O_4$, 272.1988; found, 272.1835.

2-[(2*S*)-2-[[(2*R*,6*R*)-6-(1,1-Dimethylethyl)tetrahydro-2*H*-pyran-2-yl]oxy]propyl]pentanedioic Acid Dimethyl Ester (*tert*-Butyl-Auxiliary Telomer). Mixture of diastereomers (1:1); R_f 0.40, 4/1 hexanes−EtOAc; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.88 (br d, J = 2.2 Hz, 1 H, H-2′), 4.83 (br d, J = 2.2 Hz, H-2′, 1 H), 3.71 (sextet, J = 5.6 Hz, 1 H, H-6), 3.67 (s, 2 × OMe), 3.41 (dd, J = 11.9, 2.5 Hz, 1 H, H-6′), 2.61−2.42 (m, 1 H), 2.32 (t, J = 7.2 Hz, 2 H), 2.02−1.66 (m, 8 H), 1.66−1.41 (m, 10 H), 1.31−1.19 (m + d, J = 6.4 Hz, 10 H), 0.87 (s), 0.86 (s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.0, 175.7, 173.2, 97.3, 96.6, 77.1, 75.9, 71.1, 70.9, 51.53, 51.48, 41.6, 40.7, 38.8, 38.7, 33.8, 33.7, 31.6, 31.5, 30.2, 30.0, 29.6, 29.3, 27.8, 27.7, 25.9, 25.8, 25.1, 21.44, 21.37, 18.2; EIMS (*m/z*): [M − OCH_3]$^+$ calcd for $C_{18}H_{31}O_5$, 327.2171; found, 327.2176.

Radical Additions to 2-Nitropropene. The reaction flask containing the preformed Barton ester (generally prepared using procedure "A") was cooled to the desired temperature, and 2-nitropropene (3 equiv) was added. The resulting mixture was irradiated with a 275 W sunlamp until the intermediate Barton ester was consumed as judged by TLC. The reaction mixture was then filtered through ca. 1 cm of Celite and the resulting filter cake washed with CH_2Cl_2. The volatiles were removed to give the crude adduct as an orange oil that was filtered through a column of silica gel eluting with 20% EtOAc−hexanes to remove residual dicyclohexylurea and other baseline material.

Buffered Reductive Hydrolysis (Ketone Formation). To a THF solution (ca. 0.4 M) of the primary radical adducts was added freshly prepared 15% aq $TiCl_3$ solution (25−30 equiv) buffered to pH 5−6 using NH_4OAc (6 equiv). The reaction mixture was heated to ca. 48 °C and stirred under

Ar overnight. The reaction was monitored by TLC (40% EtOAc−hexanes) and IR spectroscopy to determine C═O formation (1710 cm^{-1}) and $-NO_2$ disappearance (1550 cm^{-1}). When the reaction was judged complete, the mixture was poured into water and extracted with Et_2O then EtOAc. The combined organic layers were washed with sat aq $NaHCO_3$ and brine, dried with Na_2SO_4, filtered, and concentrated to give the *O*-protected aldol as an oily residue which was purified by flash column chromatography (SiO_2) eluting with EtOAc−hexanes.

(4*R*)-4-[[2-Deoxy-3,4,6-tris-*O*-(phenylmethyl)-α-D-*arabino*-hexopyranosyl]oxy]-2-pentanone (48a): R_f 0.44, 3/2 hexanes−EtOAc; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.15 (m, 15 H, 3 × Ph), 5.1 (br d, J = 2.6 Hz, 1 H, H-1′), 4.9 (d, J = 10.8 Hz, 1 H, 0.5 PhCH_2), 4.68−4.48 (m, 5 H, 2.5 PhCH_2), 4.15 (sextet, J = 6.1 Hz, 1 H, H-4), 3.95 (ddd, J = 13.8, 8.9, 5.1 Hz, 1 H, H-3′), 3.85−3.57 (m, 4 H), 2.70 (dd, J = 16.1, 7.7 Hz, 1H, H-3), 2.40 (dd, J = 16.1, 4.9 Hz, 1H, H-3), 2.18−2.11 (m + s, 4 H, H-2′eq, COCH_3), 1.69 (ddd (apparent td), J = 12.3, 12.3, 3.7 Hz, 1 H, H-2′ ax), 1.20 (d, J = 6.4 Hz, 3 H, CHCH_3); ^{13}C NMR (APT) (75 MHz, $CDCl_3$) δ 207.0 (+, CO), 138.7 (+), 138.5 (+), 138.2 (+), 128.3 (−), 128.0 (−), 127.9 (−), 127.8 (−), 127.70 (−), 127.67 (−), 127.64 (−), 127.61 (−), 127.5 (−), 98.1 (-, anomeric C), 78.3 (−), 77.5 (−), 75.0 (+), 73.5 (+), 71.7 (+), 71.4 (−), 71.1 (−), 68.9 (+), 50.6 (+), 35.9 (+), 31.1 (−), 31.0 (−), 21.6 (−); EIMS (*m*/*z*): M^+ calcd for $C_{32}H_{38}O_6$, 518.2668; found, 518.2767.

(±)-4-[[2-Tetrahydro-2*H*-pyran-2-yl]oxy]-2-pentanone (49). Inseparable (3:1) mixture of diastereomers, data for major diastereomer: R_f 0.45, 3/2 hexanes−EtOAc; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.67 (m, 1 H, H-2′), 4.20 (sextet, J = 6.2 Hz, 1 H, H-4), 3.90 (m, 1 H, H-6′), 3.50 (m, 1 H, H-6′), 2.75 (dd, J = 15.9, 7.6 Hz, H-3), 2.44 (dd, J = 15.9, 5.0 Hz, H-3), 2.16 (s, 3 H, H-1), 1.85−1.62 (m, 2 H), 1.58−1.45 (m, 4 H), 1.27 (d, J = 6.3 Hz, 3 H, H-5); Diagnostic ^{1}H NMR (300 MHz, $CDCl_3$) data for minor diastereomer: δ 2.19 (s, 1 H, H-1), 1.17 (d, J = 6.2 Hz, 1 H, H-5); ^{13}C NMR (APT) (75 MHz, $CDCl_3$): δ 207.3 (+), 99.5 (−), 96.5 (−, minor diastereomer), 70.8 (−), 68.4 (−, minor), 62.8 (+), 62.6 (+, minor), 51.2 (+, minor), 50.6 (+), 31.9 (+), 25.3 (+), 21.9 (−), 19.9 (+), 19.8 (+, minor), 19.7 (−); EIMS (*m*/*z*): M^+ calcd for $C_{10}H_{18}O_3$, 186.1256; found, 186.1245.

(4*R*)-4-[[2-Deoxy-3,4,6-tris-*O*-(phenylmethyl)-α-D-*arabino*-hexopyranosyl]oxy]-2-octanone (48b): R_f 0.47, 3/2 hexanes−EtOAc; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.16 (m, 15 H, 3 × Ph), 5.10 (br d, J = 2.9 Hz, 1 H, H-1′), 4.88 (d, J = 10.8 Hz, 1 H, 0.5 PhCH_2), 4.68−4.48 (m, 5 H, 2.5 PhCH_2), 4.05 (quintet, J = 6.2 Hz, 1 H, H-4), 3.91 (ddd, J = 13.5, 8.7, 4.8 Hz, 1 H, H-3′), 3.87−3.57 (m, 4 H), 2.65 (dd, J = 15.9, 7.5 Hz, 1 H, H-3), 2.46 (dd, J = 15.9, 4.8 Hz, 1 H, H-3), 2.18−2.13 (s + m, 4 H, COCH_3, H-2′eq), 1.70 (ddd (apparent td), J = 12.3, 12.3, 3.8 Hz, 1 H, H-2′ ax), 1.64−1.46 (m, 2 H, 2/9 n-Bu), 1.35−1.20 (m, 4 H, 4/9 n-Bu), 0.90−0.80 (m, 3 H, 3/9 n-Bu); ^{13}C NMR (APT) (75 MHz, $CDCl_3$) δ 207.3 (+, CO), 138.7 (+), 138.4 (+), 138.1 (+), 128.3 (−), 128.1 (−), 128.02 (−), 127.99 (−), 127.96 (−), 127.86 (−), 127.83 (−), 127.81 (−), 127.7 (−), 127.64 (−), 127.61 (−), 127.58 (−), 127.55 (−), 127.5 (−), 97.5 (−, anomeric C), 78.3 (−), 77.5 (−), 75.0 (+), 74.8 (−), 73.4 (+), 71.6 (+), 71.3 (−), 68.8 (+), 47.9 (+), 35.9 (+), 34.9 (+), 31.1 (−), 27.4 (+), 22.6 (+), 13.9 (−); EIMS (*m*/*z*): $[M - H]^+$ calcd for $C_{35}H_{44}O_6$, 559.3060; found, 559.2977.

(4*R*)-4-[[2-Deoxy-3,4,6-tris-*O*-(phenylmethyl)-α-D-*arabino*-hexopyranosyl]oxy]-5-methyl-2-hexanone (48c): R_f 0.47, 3/2 hexanes−EtOAc; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.17 (m, 15 H, 3 × Ph), 5.10 (d, J = 3.2 Hz, 1 H, H-1′), 4.88 (d, J = 10.8 Hz, 1 H, 0.5 PhCH_2), 4.66−4.47 (m, 5 H, 2.5 PhCH_2), 3.93 (m, 1 H, H-4), 3.90−3.74 (m, 3 H), 3.68−3.55 (m, 2 H), 2.60 (dd, J = 16.1, 8.7 Hz, 1 H, H-3), 2.38 (dd, J = 16.1, 3.5 Hz, 1 H, H-3), 2.14 (s + m, 4 H, COCH_3, H-2′eq), 1.99 (m, 1 H, H-5), 1.69 (dt, J = 12.2, 12.2, 3.7 Hz, 1 H, H-2′ ax), 0.88 (d, J = 6.9 Hz, 3 H, *Me*CHMe), 0.82 (d, J = 6.9 Hz, 3 H, MeCH*Me*); ^{13}C NMR (APT) (75 MHz, $CDCl_3$) δ 207.7 (+, CO), 138.7 (+), 138.4 (+), 138.2 (+), 128.3 (−), 128.1 (−), 128.02 (−), 127.99 (−), 127.9 (−), 127.83 (−), 127.80 (−), 127.76 (−), 127.7 (−), 127.63 (−), 127.60 (−), 127.57 (−), 127.5 (−), 98.4 (−, anomeric C), 79.8 (−), 78.4 (−), 77.5 (−), 75.0 (+), 73.4 (+), 71.6 (+), 71.4 (−), 68.9 (+), 43.6 (+), 36.0 (+), 31.7 (−), 18.5 (−), 17.0 (−); EIMS (*m*/*z*): $[M - H]^+$ calcd for $C_{34}H_{42}O_6$, 545.2903; found, 545.2597.

Aldol Deprotection. To a 0.1 M solution of *O*-protected aldol **48a** in dry CH_2Cl_2 at −78 °C were added thiophenol (5 equiv) and BF_3·OEt_2 (1.5 equiv) under Ar. The reaction mixture was stirred for 2 h at −78 °C after which the cooling bath was removed allowing the reaction mixture to warm to room temperature and stirred for 1 h. When the reaction was complete, as judged by TLC, the contents were poured into sat aq $NaHCO_3$ and extracted with CH_2Cl_2. The organic layers were combined and dried with Na_2SO_4, filtered, and then concentrated to an oil which was purified by gradient flash chromatography (10% → 50% → 100% EtOAc−hexanes) to give the thioglycoside **51** and then the deprotected aldol **50a**.

Glucal Reformation. To a 0.02 M solution of **51** in 3:1:1 MeOH−THF−H_2O at 0 °C was added 2 equiv of OXONE with stirring. When judged complete by TLC, the reaction was quenched with 10% $NaHSO_3$ solution and extracted with EtOAc. The organic layers were combined and washed with sat aq $NaHCO_3$ and brine, dried over Na_2SO_4, and then concentrated. The residue was dissolved in dry benzene to make a 0.06 M solution which was heated to reflux until TLC showed depletion of the intermediate sulfoxide **52** after ca. 90 min. The reaction contents were cooled to room temperature and then poured into sat aq $NaHCO_3$ and extracted with EtOAc. The organic layers were combined and washed with brine, dried over Na_2SO_4, and then concentrated. Purification of tri-*O*-benzyl-D-glucal (**38**) was effected by flash chromatography (11% EtOAc−hexanes).

(4*R*)-4-Hydroxy-2-pentanone (50a) (from a 4.8/1 mixture of **48a**/***dia*-48a**): R_f 0.28, 3/2 hexanes−EtOAc; $[\alpha]^{20}_J$ −32° (*c* 0.48, $CHCl_3$) corresponds to 51% ee (3/1 de); lit.[42] $[\alpha]^{25}_J$ −60° (95% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.20 (m, 1 H, H-4), 3.10 (br, 1 H, OH), 2.64 (dd, J = 17.6, 3.3 Hz, 1 H, H-3), 2.55 (dd, J = 17.6, 8.8 Hz, 1 H, H-3), 2.18 (s, 3 H, H-1), 1.20 (d, J = 7.0 Hz, 3 H, CHCH_3); EIMS (*m*/*z*): M^+ calcd for $C_5H_{10}O_2$, 102.0681; found, 102.0667.

(4*R*)-4-Hydroxy-2-octanone (50b) (from >95% pure **48b**): R_f 0.16, 3/1 hexanes−EtOAc; $[\alpha]^{25}_D$ −36° (*c* 0.81, $CHCl_3$) (>90% ee according to Mosher ester study); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.03 (m, 1 H, H-4), 3.00 (br s, 1 H, OH), 2.63 (dd, J = 17.6, 3.1 Hz, 1 H, H-3), 2.54 (dd, J = 17.6, 8.8 Hz, 1 H, H-3), 2.18 (s, 3 H, COCH_3), 1.53−1.26 (m, 6 H, 3 × CH_2), 0.90 (t, J = 7.1 Hz, 3 H); EIMS (*m*/*z*): M^+ calcd for $C_8H_{16}O_2$, 144.1150; found, 144.1136.

Phenyl 2-Deoxy-3,4,6-tris-*O*-(phenylmethyl)-1-thio-D-*arabino*-hexopyranoside (51). A 2/1 mixture of anomers: R_f 0.67, 3/2 hexanes−EtOAc; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54−7.19 (m), 5.68 (d, J = 4.9 Hz), 4.91 (d, J = 10.9 Hz, 0.5 H), 4.90 (d, J = 10.9 Hz, 0.5 H), 4.76−4.43 (m, 0.5 H), 4.30 (dd, J = 7.9, 1.8 Hz, 0.5 H), 3.95 (ddd, J = 13.3, 8.7, 4.8 Hz,), 3.85−3.50 (m, 3 H), 2.49−2.42 (m, 1 H), 2.18−2.08 (m, 1 H), 1.83−1.52 (m, 2 H), 1.30−1.26 (m, 1 H); ^{13}C NMR (APT) (75 MHz, $CDCl_3$) δ 138.43 (+), 138.36 (+), 138.2 (+), 138.1 (+), 135.0 (+), 134.1 (+), 131.4 (−), 131.24 (−), 131.21 (−), 131.18 (−), 131.16 (−), 129.1 (−), 129.01 (−), 128.98 (−), 128.95 (−), 128.92 (−), 128.89 (−), 128.87 (−), 128.7 (−), 128.61 (−), 128.58 (−), 128.55 (−), 128.52 (−), 128.49 (−), 128.46 (−), 128.45 (−), 128.37 (−), 128.35 (−), 128.3 (−), 128.1 (−), 128.04 (−), 128.01 (−), 127.98 (−), 127.92 (−), 127.90 (−), 127.86 (−), 127.8 (−), 127.73 (−), 127.70 (−), 127.49 (−), 127.48 (−), 127.32 (−), 127.30 (−), 127.2 (−), 127.0 (−), 84.0 (−), 82.1 (−), 80.7 (−), 79.3 (−), 78.4 (−), 77.94 (−), 77.90 (−), 77.88 (−), 75.0 (+), 73.4 (+), 71.9 (+), 71.7 (−), 69.5 (+), 68.9 (+), 36.9 (+), 36.3 (+).

[2*S*-[2α(*S),6*β*]]-4-[[6-(1,1-Dimethylethyl)tetrahydro-2*H*-pyran-2-yl]oxy]-2-pentanone (57):** R_f 0.47, 4/1 hex-

(42) See ref 29.

anes−EtOAc, $[\alpha]^{22}_D$ −108.5° (*c* 2.67, $CHCl_3$), $[\alpha]^{22}_J$ −113.4° (*c* 2.67, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.94 (s, 1 H, H-2′), 4.20 (sextet, J = 6.3 Hz, 1 H, H-4), 3.35 (dd, J = 11.5, 1.7 Hz, 1 H, H-6′), 2.71 (dd, J = 15.5, 6.0 Hz, 1 H, H-3), 2.45 (dd, J = 15.5, 6.3 Hz, 1 H, H-3), 2.16 (s, 3 H, H-1), 1.84−1.65 (m, 1 H), 1.63−1.53 (m, 4 H), 1.34−1.20 (m + d, J = 6.3 Hz, 4 H, H-5), 0.88 (s, 9 H, *t*-Bu); ^{13}C NMR (APT) (75 MHz, $CDCl_3$) δ 207.5 (+) (CO), 96.5 (−), 76.0 (−), 68.8 (−), 50.3 (+), 33.8 (+), 31.0 (−), 30.2 (+), 25.9 (−), 25.1 (+), 21.7 (−), 18.2 (+); EIMS (*m*/*z*): $[M - H]^+$ calcd for $C_{14}H_{25}O_3$, 241.1804; found, 241.1809; $[M - t\text{-Bu}]^+$ calcd for $C_{10}H_{18}O_3$, 185.1178; found, 185.1180.

(4*S*)-4-[(1,10,10-Trimethyl-3-oxatricyclo[5.2.1.0^{2,6}]dec-4-yl)oxy]-2-pentanone (60): R_f 0.46 (minor diastereomer), 0.52 (major), 7/3 hexanes−EtOAc; ^{1}H NMR (300 MHz, $CDCl_3$), major diastereomer: δ 5.39 (d, J = 4.9 Hz, 1 H, anomeric-H), 4.25−4.18 (m, 2 H), 2.89 (m, 1 H), 2.72 (dd, J = 15.3, 7.6 Hz, 1 H, H-3), 2.43 (dd, J = 15.3, 5.3 Hz, 1 H, H-3), 2.17 (s, 3 H, H-1), 1.88 (m, 1 H), 1.72−1.49 (m, 4 H), 1.40−1.22 (m, 2 H), 1.17 (d, J = 6.2 Hz, 3H, H-5), 0.97 (s, 3 H, Me), 0.91 (s, 3 H, Me), 0.86 (s, 3 H, Me); ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.5, 106.3, 89.5, 68.4, 52.3, 51.6, 48.7, 47.5, 40.2, 32.9, 26.6, 20.9, 20.6, 20.0, 18.8, 14.8; EIMS (*m*/*z*): M^+ calcd for $C_{17}H_{28}O_3$, 280.2038; found, 280.1980; $[M - CH_3CHOCH_2COCH_3]^+$ calcd for $C_{12}H_{19}O$, 195.1385; found, 195.1387.

Radical Addition to Ethyl α-Trifluoroacetoxyacrylate. To the preformed Barton ester solution (generally prepared from substrates **40** and **66** using procedure "C") was added trap **31** (3−10 equiv) and the resulting solution cooled to 0 °C. The aluminum foil covering was removed and placed directly under the flask to reflect the light from the sunlamp. The stirred reaction mixture was photolyzed for 25−30 min using a 275 W sunlamp. The reaction was monitored by TLC (3/2 hexanes−EtOAc). Upon completion of the photolysis (usually 25 min), irradiation was stopped and the solvent removed via rotary evaporation. To facilitate the determination of diastereomer ratios, the crude product was filtered through a small plug of SiO_2 (3−5 cm high × 1.5−3 cm wide), eluting with 50−100 mL 3/2 hexanes−EtOAc. The crude product was purified by column chromatography using EtOAc−hexanes.

(4*R*)-4-[[2,7-Dideoxy-6-*C*-methyl-3,4,6-tris-*O*-(phenylmethyl)-α-D-*arabino*-heptopyranosyl]oxy]-2-oxopentanoic Acid, Ethyl Ester (69): 90% yield (ds = 10/1). R_f (major diastereomer) 0.32, 3/1 hexanes−EtOAc; R_f (minor diastereomer) 0.38, 25% EtOAc−hexanes; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35−7.19 (m, 15 H, 3 × Ph), 5.12 (t, J = 3.4 Hz, 1 H, H-1′), 4.79 (d, J = 10.7 Hz, 1 H, 0.5 PhCH_2), 4.65−4.55 (m, 5 H, 2.5 PhCH_2), 4.30 (q, J = 7.1 Hz, 2 H, OCH_2CH$_3$), 4.24 (m, 1 H, H-4), 3.90 (ddd, J = 10.4, 6.4, 4.4 Hz, 1 H, H-3′), 3.81−3.70 (m, 2 H, H-4′, H-5′), 3.07 (dd, J = 16.7, 6.7 Hz, 1 H, H-3), 2.92 (dd, J = 16.8, 5.5 Hz, 1 H, H-3), 2.08 (dt, J = 13.2, 4.2 Hz, 1 H, H-2′ eq), 1.79 (ddd, J = 13.9, 9.6, 4.4 Hz, 1 H, H-2′ ax), 1.41−1.33 (m, 9 H, 2 × Me, OCH$_2$CH_3), 1.26 (d, J = 6.3 Hz, 3 H, H-5); ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.7, 168.9, 140.0, 138.5, 128.3, 128.12, 128.05, 127.7, 127.6, 127.4, 127.2, 127.1, 126.8, 96.7, 78.5, 77.3, 76.8, 76.2, 73.4, 71.5, 69.7, 64.4, 62.5, 45.8, 34.2, 25.1, 23.3, 21.7, 13.9; EIMS (*m*/*z*): M^+ calcd for $C_{36}H_{44}O_8$, 604.3036; found, 604.3039.

(4*R*)-4-[[2-Deoxy-3,4,6-tris-*O*-(phenylmethyl)-α-D-*arabino*-hexopyranosyl]oxy]-2-oxopentanoic Acid, Ethyl Ester (70): A 2/1 mixture of diastereomers; R_f 0.59, 3/2 hexanes−EtOAc; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39−7.12 (m, 15 H), 5.13 (d, J = 3.0 Hz, H-1′), 5.09 (d, J = 3.2 Hz, H-1′), 4.88 (d, J = 10.9 Hz), 4.86 (d, J = 10.7 Hz), 4.70−4.43 (m, 6 H), 4.36−4.19 (m, 3 H), 4.00−3.55 (m, 5 H), 3.19 (dd, J = 17.1, 7.3 Hz), 3.09 (dd, J = 17.1, 7.7 Hz), 2.88 (d, 0.5 H), 2.82 (d, 0.5 H), 2.19 (dd, 1 H), 1.82−1.62 (m, 1 H)), 1.35 (t, J = 7.1 Hz), 1.26 (d, J = 6.3 Hz), 1.20 (d, 6.1 Hz); EIMS (*m*/*z*): M^+ calcd for $C_{34}H_{40}O_8$, 576.2723; found, 576.2706.

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Supporting Information Available: Computational details for the radicals in Figure 4 and transition structures in Figure 7; experimental details for synthesis of lactol **53** (the synthesis of compound **62** may be found in the Supporting Information of ref 39), and ^{1}H NMR spectra of compounds **37, 40b**, **40c**, **48a**, **48b**, **48c**, **49**, **53**, **54**, **55**, **57**, **60**, **63**, **64**, **65**, and **69**. This information is available free of charge via the Internet at http://pubs.acs.org.

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