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3-Fluoro-6-*tert*-butyltetrahydropyranosyl Trichloroacetamidates. "Chiral Auxiliary Donors" for Hydroxyalkyl Radicals

Philip Garner* and Özge Şeşenoğlu

Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106-7078

ppg@case.edu

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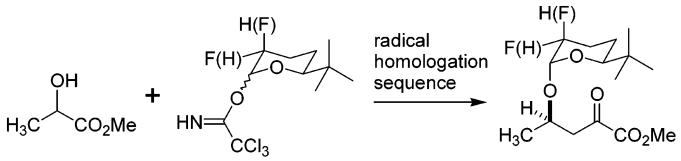
ABSTRACT



An improved THP-based chiral auxiliary for hydroxyalkyl radicals is reported. The key modifications involve introduction of a fluorine substituent at C-3 to make the acetal center more robust and the use of Schmidt's trichloroacetamidate glycosylation methodology for efficient attachment of the auxiliary to the radical precursor. The resulting chiral hydroxyalkyl radical equivalents add to methyl 2-trifluoroacetoxyacrylate with selectivities ranging from 9:1 (0 °C) to 15:1 (–78 °C).

In connection with the development of an iterative approach to 1,3,5···(2*n* + 1) polyol synthesis, we have been engaged in the search for the "perfect" chiral auxiliary for the hydroxyalkyl radicals (Figure 1). Such an auxiliary should

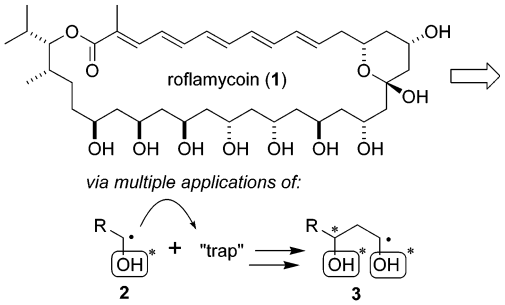


Figure 1. Strategy for polyol synthesis via iterative radical homologation.

(1) be readily available, (2) be readily attached to the hydroxyl group, (3) exert a high level of stereocontrol during the addition step, (4) be compatible with subsequent chemistry, and (5) be efficiently removed with the potential for recovery and reuse. Additional considerations must be taken into account if the use of multiple chiral auxiliaries is being considered. In such a case, the ideal auxiliary would be small (low molecular weight) and every atom contained therein should be essential to its function. Efficiency can be improved further through multitasking wherein the auxiliary would serve more than one function.

It was with these thoughts in mind that we began investigating the development of practical acetal-based chiral auxiliaries for hydroxyalkyl radicals.

Analysis of the transition states associated with addition of the 1-(2-tetrahydropyranosyl)oxyethyl radical to alkenes led to our development of the 6-*tert*-butyltetrahydropyranosyl (tBu-THP) auxiliary (Figure 2, structure **2a**).[1] Indeed, we demonstrated that this chiral auxiliary is capable of exerting significant diastereofacial control during the key radical C−C bond-forming step. The tBu-THP auxiliary design principles appear to be general, as evidenced by their application to the Diels−Alder reaction.[2] Unfortunately, the method that

(1) Garner, P.; Anderson, J. T.; Cox, P. B.; Klippenstein, S.; Leslie, R.; Scardovi, N. *J. Org. Chem.* **2002**, *67*, 6195 and references therein.

(2) Garner, P.; Anderson, J. T.; Turske, R. A. *Chem. Commun.* **2000**, 1579.

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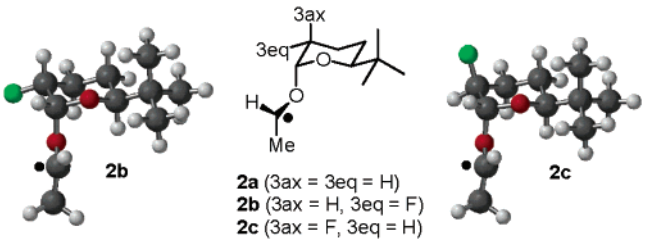
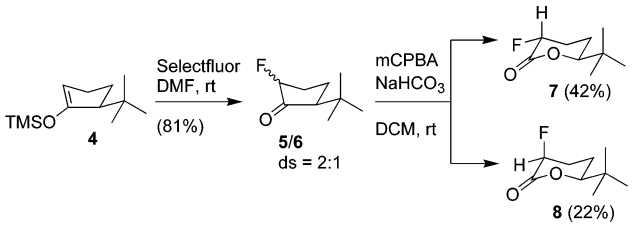


Figure 2. Structures of 6-*tert*-butyltetrahydropyranosyl)oxyethyl radicals.

we originally used to form the mixed acetal radical precursor (dehydrative condensation of a hydroxyester with the lactol) required heating in the presence of a large excess of alcohol. Furthermore, the tBu-THP ether was somewhat prone to acid-catalyzed hydrolytic degradation. Neither of these problems would be amenable to our envisioned polymer-supported strategy. This led us to consider the use of milder glycosylation conditions as well as the introduction of an electronegative fluorine atom at C-3, a well-known tactic that had been used to stabilize analogous 2-deoxyglycosides.[3] We now report the synthesis and use of two new fluorinated "chiral auxiliary donors" for hydroxyalkyl radicals (see **2b** and **2c** in Figure 1).[4]

Our synthesis of the racemic[5] auxiliaries began (Scheme 1) by converting the known 2-*tert*-butylcyclopentanone[6] to

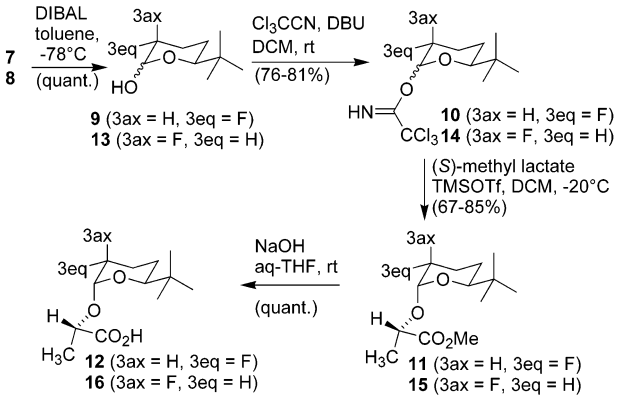
Scheme 1. Synthesis and Separation of Fluorinated Lactones



the less substituted trimethylsilyl enol ether **4** (TMSOTf + Et_3N) followed by exposure to Selectfluor (1-chloromethyl-4-fluoro-1,4-diazabicyclo[2.2.2]octane bis(tetrafluoroborate) or F-TEDA-BF_4) to give a 2:1 mixture of chromatographically inseparable *trans*- and *cis*-2-fluoro-5-*tert*-butylcyclopentanones (**5**/**6**).[7] The ratio of **5** to **6** can be increased to 4:1 by equilibrium using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The 2:1 mixture of fluoroketones was exposed to buffered *m*-chloroperbenzoic acid (*m*-CPBA) to give the chromatographically separable *trans*- and *cis*-6-*tert*-butyl-3-fluorotetrahydrapyran-2-ones (**7**) and (**8**) in 42 and 22% yield, respectively. The stereochemical assignments for **7** and **8** are based on both proton NMR data (H-3 of **7** appears as a ddd with $J = 47.1$, 10.6, and 6.3 Hz, whereas in **8** it is a dt with $J = 47.5$ and 5.8 Hz) and fluorine NMR data (F of **7** appears as a dt with $J = 47.4$ and 11.0 Hz, while in **8** it is a ddd with $J = 47.6$, 20.3, and 11.3 Hz).

At this point, the fluorinated chiral auxiliaries were ready to be attached to our standard radical precursor, (*S*)-methyl lactate (Scheme 2). The sequence began with the low-

Scheme 2. Attachment of Chiral Auxiliaries to the Radical Precursor



temperature DIBAL reduction of the lactones **7** and **8** to give the lactols **9** and **13** in quantitative yield. Lactols **9** and **13** were then transformed into the trichloroacetamidates **10** and **14**, respectively, by application of the standard Schmidt conditions (Cl_3CCN + DBU).[8]

These fluorinated "chiral auxiliary donors" were coupled to (*S*)-methyl lactate (1.1 equiv) in the presence of TMSOTf −20 °C to give good yields of the α-lactates **11** and **15**.[9] None of the corresponding *β*-lactates were detected in these reactions. It should be noted that Schmidt glycosylation has been performed using polymer supported alcohol acceptors.[10] Therefore, this methodology will be applicable to our projected polymer-supported radical homologations. Saponification of these esters proceeded uneventfully to give the corresponding carboxylic acids **12** and **16** quantitatively. These carboxylic acids were relatively stable compounds (no decomposition after 3 months storage in refrigerator) as a consequence of the fluorine substituent's effect on acetal stability.

(3) (a) Withers, S. G.; MacLennan, D. J.; Street, I. P. *Carbohydr. Res.* **1986**, *154*, 127. We thank Prof. David Crich (UIC) for bringing this work to our attention. (b) We were originally inspired by Fried's use of fluorine substitution to stabilize the very labile thromboxane A_2 nucleus. See: Fried, J.; Hallinan, E. A.; Szwedo, M. J. *J. Am. Chem. Soc.* **1984**, *106*, 3871.

(4) We recently reported a camphor-derived chiral auxiliary for hydroxyalkyl radicals that also incorporated an analogous fluorinated THP unit into its structure. However, the diastereofacial selectivity observed with this auxiliary was only modest (ds ≤ 4.5:1 at −78 °C) due to geometrically induced distortion of the THP ring from an ideal chair conformation. See: Garner, P.; Sesenoglu, O.; Burgoon, H. *Tetrahedron: Asymmetry* **2003**, *14*, 2883.

(5) Racemic 2-*tert*-butylcyclopentanone was used in this preliminary feasibility study. The individual enantiomers are available via kinetic resolution: Mori, A.: Yamamoto, H. *J. Org. Chem.* **1985**, *50*, 5446.

(6) (a) Chan, T. H.; Paterson, I.; Pinsonnault, J. *Tetrahedron Lett.* **1977**, 4183. (b) Reetz, M. T.; Maier, W. F. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 48.

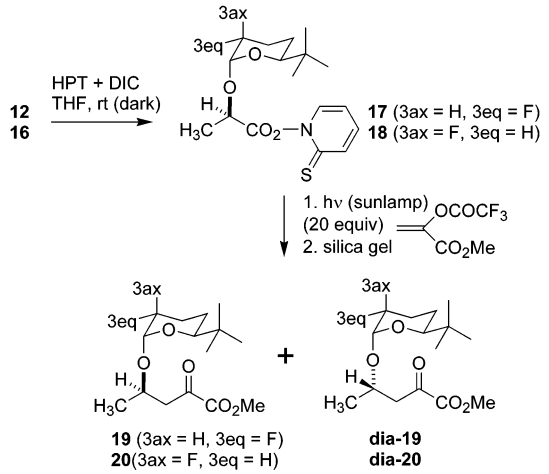
(7) Lal, G. S. *J. Org. Chem.* **1993**, *53*, 2791.

(8) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212.

(9) Albert, M.; Paul, B. J.; Dax, K. *Synlett* **1999**, 1483.

(10) Seeberger, P. H.; Haase, W.-C. *Chem. Rev.* **2000**, *100*, 4349.

Scheme 3. Radical Generation and Homologation



The impact of the fluorinated chiral auxiliaries on radical additions to methyl 2-trifluoroacetoxyacrylate was then examined (Scheme 3, Table 1). In preparation for photolytic radical generation, the carboxylic acids were converted to their corresponding Barton esters[11] by exposure to *N*-hydroxy-2-pyridinethione (HPT) in the presence of diisopropylcarbodiimide (DIC) in the dark. It was not possible to use our usual HOTT reaction conditions for these Barton esterification (see ref 1) because the β-alkoxyketone adducts were unstable to the HOTT reaction milieu (β-elimination). The crude Barton ester mixture was cooled to the appropriate temperature (see Table 1), an excess of radical trap was added, and the reaction vessel was irradiated with a 275 W sunlamp with stirring for 1 h. Workup consisted of filtration through a plug of silica gel followed by flash chromatography to give the chromatographically inseparable adducts **19** (major) + **dia-19** (minor) and **20** (major) + **dia-20** (minor), respectively.

As can be seen from our results, both fluorinated chiral auxiliaries impart high levels of diastereofacial selectivity irrespective of the relative configuration of the fluorine-substituted C-3. The selectivities are somewhat higher when the addition reaction is conducted at −78 °C. Diastereochemical assignments for the adducts are tentatively based on our working TS hypothesis for the facial selectivity of auxiliary controlled radical addition[1] as well as NMR similarities between the adducts and analogous, fully characterized compounds.[12] It should be noted that these reactions were much cleaner than the isolated yields imply, as judged by TLC analysis of the crude product mixtures.

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

Table 1. Results of Auxiliary Controlled Radical Homologation

entry	addition temperature (°C)	major/minor adducts	ds	yield (%)
1	0	**19/dia-19**	9:1	54
2	−78	**19/dia-19**	13:1	45
3	0	**20/dia-20**	11:1	57
4	−78	**20/dia-20**	15:1	49

In conclusion, we have improved on our earlier design of a simple THP-based chiral auxiliary for hydroxyalkyl radicals. The key modifications involve (1) introduction of a fluorine substituent at C-3 to make the acetal center more robust and (2) the use of Schmidt's trichloroacetamidate glycosylation methodology for efficient attachment of the auxiliary. The resulting chiral hydroxyalkyl radical equivalents **2b** and **2c** were shown to add to methyl 2-trifluoroacetoxyacrylate with high diastereofacial selectivity. While the chemical yields of these radical homologations still need to be improved, the work described herein provides an effective solution to the problem of how to attach the chiral auxiliary to a hydroxyl group. Further improvement and application of the fluorinated "chiral auxiliary donor" concept will be reported in due course.

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

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(12) In every system that we have examined thus far, the diastereotopic methylene protons α to the ketone in the major diastereomer resonate upfield of the corresponding signals of the minor diastereomer (see the Supporting Information for details.)