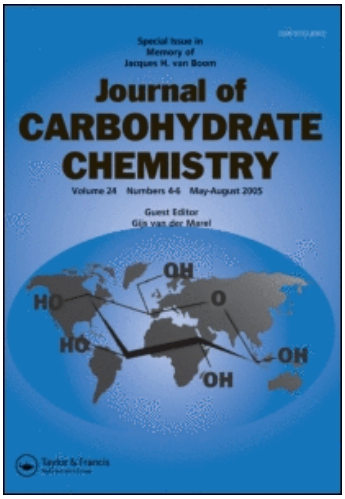

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Carbohydrates to Carbocycles via Radical Aldehyde Cyclizations

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CARBOHYDRATES TO CARBOCYCLES VIA RADICAL ALDEHYDE CYCLIZATIONS

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ABSTRACT

Previous work in this laboratory has shown that radical aldehyde cyclizations provide efficient routes for the preparation of cycloalkanols. This process seems well suited to carbohydrate substrates and could conceivably be developed for novel routes from carbohydrates to carbocycles. Several aldehydic substrates have been prepared with a variety of different radical progenitors. The preliminary conclusions seem to be that α-oxygenated aldehydes are poor substrates, a probable reason being that the intermediate alkoxy radicals are prone to decomposition by β-scission. The formation of the radical intermediates has been demonstrated by trapping experiments with acrylonitrile.

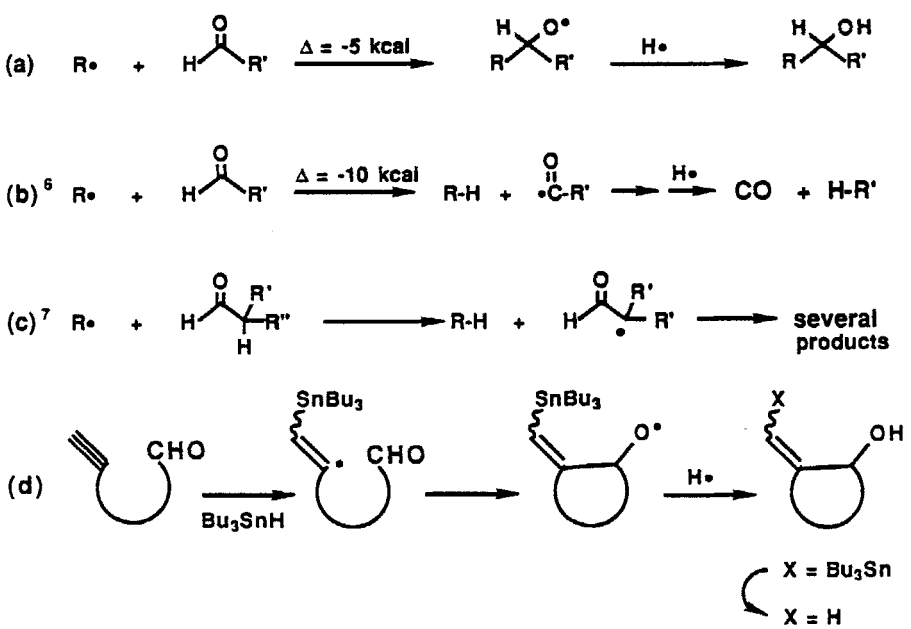
INTRODUCTION

We have recently reported success in accomplishing several efficient carbohydrate-based free radical cyclizations in which *aldehydo* functional groups served as the radical acceptors.[1,2,3] This operationally simple

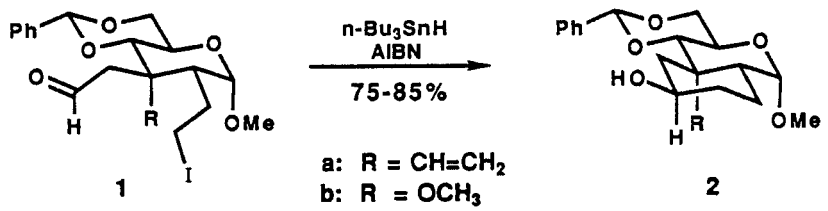
reaction has captured our interest[4,5] and has encouraged us to explore its generality as a versatile route to cycloalkanols. We report herein some of our results which reveal some of the potential, as well as limitations of the process.

The widely held view that the *aldehydo* group is not an ideal radical trap is based on ample precedents which demonstrate that formation of the desired adducts (which are secondary alcohols) is often compromised by competing low-energy side reactions. Thus, although the addition of a carbon radical to an aldehyde (Scheme Ia) is an exothermic process, the results of Walling and Padwa[6] show that an alternate reaction course involving abstraction of the aldehydic proton, followed by loss of carbon monoxide (Scheme Ib) is more exothermic. Furthermore, Maruyama found that products resulting from hydrogen abstraction *alpha* to the carbonyl group (e.g., Scheme Ic) were obtained in the cases of *alpha*-disubstituted aldehydes.[7]

In spite of this murky history, we found that iodoaldehydes **1a**, and **1b** underwent free radical cyclization to give cyclohexanols **2a** and **2b** in good yields (Scheme II).[1,2] Encouraged by these initial observations, we decided to extend our investigation to determine the scope of this methodology. The



Scheme I



1 2

Scheme II[2]

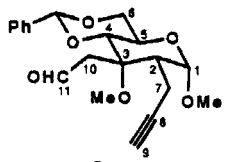
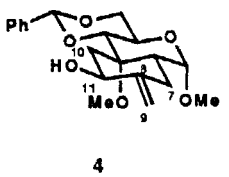
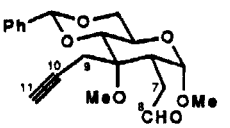
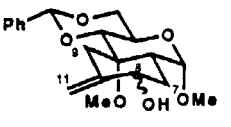
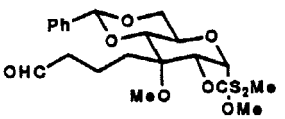
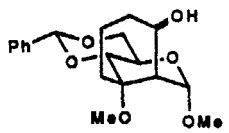
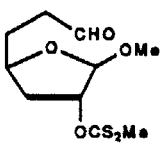
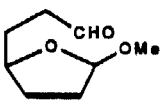
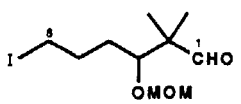
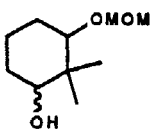
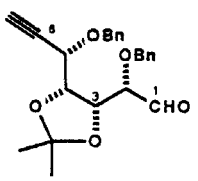
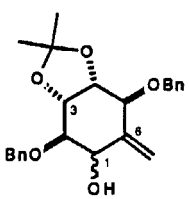
results obtained thus far indicate that radical aldehyde cyclizations are extremely substrate specific.

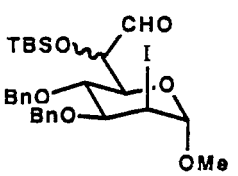
RESULTS AND DISCUSSION

Some of our results are shown in Table I. Entries (i), (ii), and (iii) show the formation of annulated pyranosides[8] which is reminiscent of the result, **1** → **2**, in Scheme II. However, the source of the radicals was different than in **1**. Vinyl radicals were generated by the addition of tri-*n*-butyltin to alkynyl groups,[9] as summarized in Scheme Id. In the cases of **3** and **5** (Table I), cyclization with the aldehyde afforded the alcohols **4** and **6**, respectively. Compound **4** was obtained as a single isomer in 45% yield. However, cyclization of **5** was not stereoselective, compound **6** being obtained in 40% yield as a mixture of epimeric alcohols. In entry (iii), we turned our attention to the generation of a secondary radical from the xanthate ester of a secondary alcohol as described by Barton and McCombie.[10] Giese and co-workers[11] have shown that such radicals can be captured intermolecularly by suitable acceptors. In the case of **7**, cyclohexanol **8** was obtained in only 25% yield. In the case of xanthate ester **9** cyclization was not observed, the only isolated product observed being that of deoxygenation, **10**.

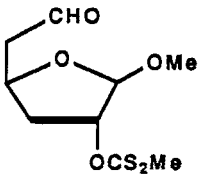
The successes in entries (i)-(iii) and in Scheme II are for substrates where the reacting moieties are anchored to the pyranoside ring. It was therefore of interest to see how acyclic substrates would fare [see entries (v) and (vi)]. Compound **11** yielded 30% of **12**, the poor result being probably related to the highly hindered environment of the aldehyde receptor. The even lower yield of the hexitol **14** will be discussed below. In addition, the

Table I

Entry	Substrate	Product	% Yield
I	 3	 4	45%
II	 5	 6	40%
III	 7	 8	25%
IV	 9	 10	35%
V	 11	 12	30%
VI	 13	 14	10%



15



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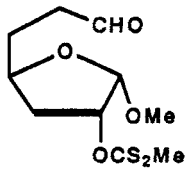
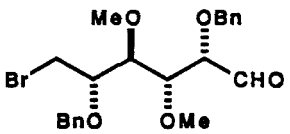
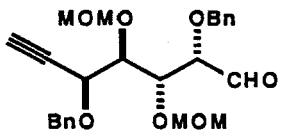


17



18



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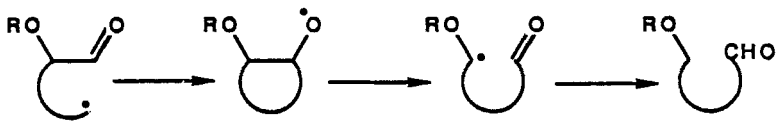
Scheme III
(Unsuccessful cases)

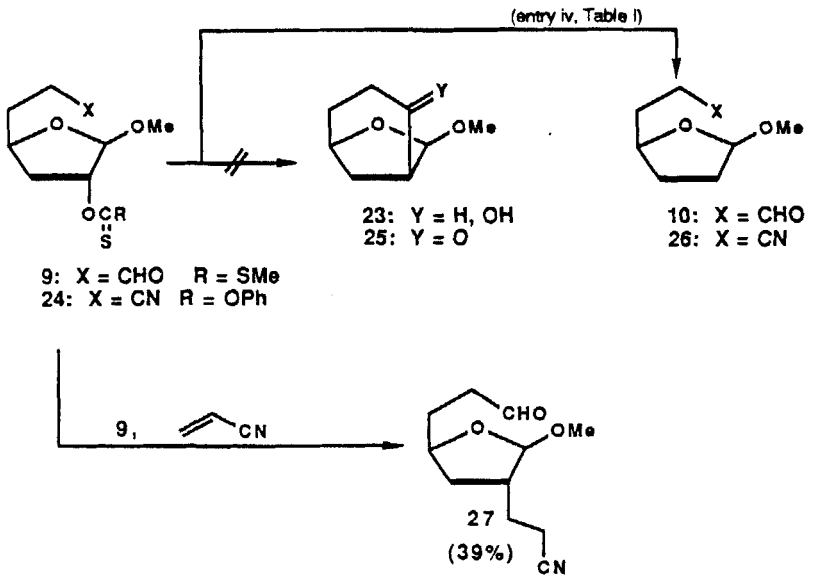


20 21 22

Scheme IV

substrates shown in Scheme III were also tested, but no cycloalkanol formation was observed.

Unlike our initial work in this area,[1-3] the radical aldehyde cyclization attempts reported here represent only a moderate level of success. Undoubtedly, there are several factors that contribute to the efficiency of cycloalkanol formation, and although a more systematic study will be required to identify all of the factors responsible for success or failure, it appears from the failures with substrates **15**, **18**, and **19** (Scheme III) that an oxygen *alpha* to the aldehyde is inhibitory. This effect may have also contributed to the poor yield of **14**. These results are most likely due to the fact that in each case an oxygen-centered radical (e.g., **20**) is produced which is prone to β-scission leading to the highly stabilized intermediate **21** (Scheme IV). This is then reduced to **22** which corresponds to the product of carbonyl translocation. We have observed direct evidence for such carbonyl translocations in other systems as previously reported.[2,3]

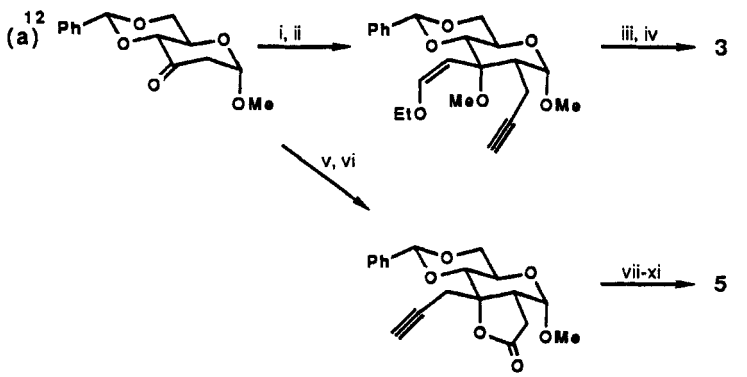


Scheme V

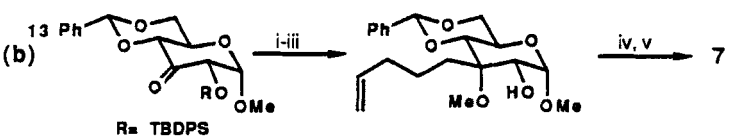
The complete failure with **18**, even in light of the poor result with **13**, gives clear evidence of the pronounced effect that structural changes can have. In the case of substrates **15**, **16**, and **9** cyclization would have given [2.2.2], [2.2.1], and [3.2.1] oxabicycloalkyl systems respectively, and failure to give cyclized products is probably due to the adverse ring strain that would result. Thus, substrate **9** did not afford cyclohexanol **23**. Similarly, the nitrile **24** did not give the cyclohexanone **25**, but the deoxygenated material **26**. However, it is noteworthy that in the case of **9**, the intermediate radical could be trapped to give nitrile **27** (Scheme V).

Consequently, our results indicate that substrates for the radical aldehyde cyclization need to be chosen with caution. Experiments to fine-tune the structural requirements are underway and will be reported in due course.

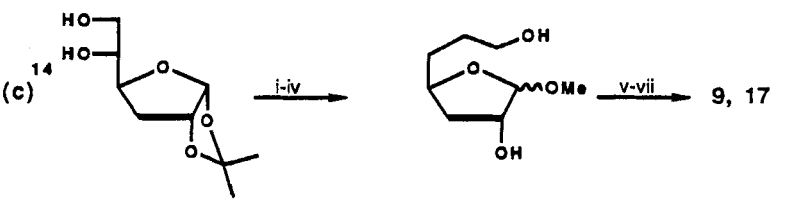
Choice and Synthesis of Substrates. The compounds used in this study were chosen in the hope that they would allow us to test the applicability of the aldehyde cyclization to complex, highly-substituted systems. The importance of factors such as steric effects (with **11**), regiochemical effects (**3** versus **5**) and ring strain (**9**, **15**, and **16**) could be explored. The substrates were prepared by the most expedient routes from well-known starting materials as summarized in Scheme VI.



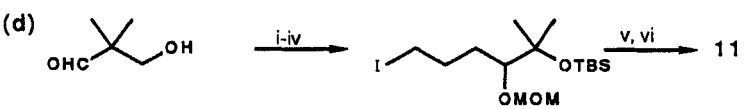
(i) propargyl bromide/LDA; (ii) EtOCH=CHLi; (iii) NaH/MeI; (iv) $HOAc/H_2O$; (v) EtO_2CCH_2Br/LDA; (vi) propargyl bromide/Zn/THF; (vii) LAH; (viii) TBSCl; (ix) NaH/MeI; (x) nBu_4NF; (xi) PCC.



(i) $CH_2=CH(CH_2)_3MgBr$; (ii) NaH/MeI; (iii) nBu_4NF; (iv) NaH/CS_2/MeI; (v) $OsO_4/NaIO_4$.



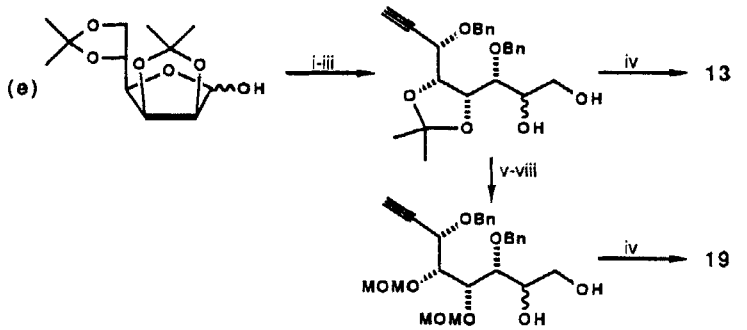
(i) $NaIO_4$; (ii) $Ph_3=CHCO_2Et$; (iii) H_2/Pd then LAH; (iv) $MeOH/H_2SO_4$ (separate anomers);(v) TBSCl; (vi) NaH/CS_2/MeI; (vii) nBu_4NF; (viii) PCC.



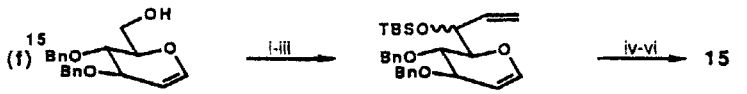
(i) TBSCl; (ii) $CH_2=CHCH_2MgBr$; (iii) MOMCl; (iv) BH_3/I_2; (v) $HOAc/H_2O$; (vi) PCC.

Scheme VI

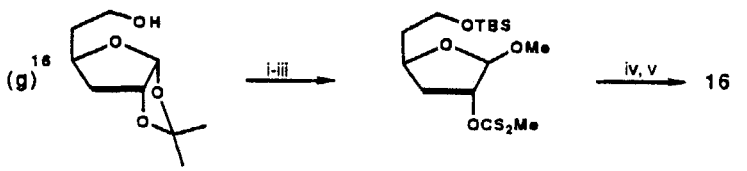
(continued)



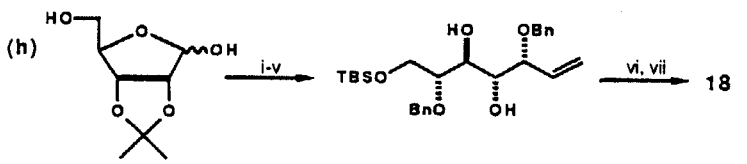
(i) TMSC≡CMgBr; (ii) NaH/BnBr; (iii) HOAc/H_2O; (iv) $NaIO_4$; (v)$COCl_2$; (vi) H_3O^+; (vii) MOMCl; (viii) NaOMe.



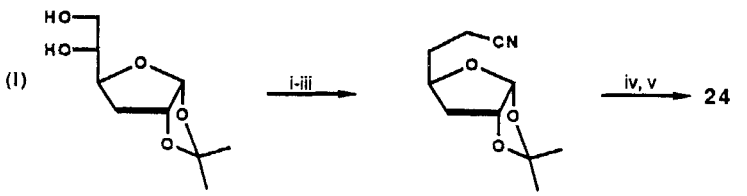
(i) PCC; (ii) CH_2=CHMgBr; (iii) TBSCl; (iv) NIS/MeOH; (v) OsO_4/NMMO; (vi) $Pb(OAc)_4$.



(i) MeOH/HCl (separate anomers); (ii) TBSCl; (iii) NaH/CS_2/MeI; (iv) nBu_4NF; (v) PCC



(i) TBSCl; (ii) CH_2=CHMgBr; (iii) NaH/BnBr; (iv) H_3O^+; (v) TBSCl; (vi) NaH/MeI; (vii) nBu_4NF; (viii) Ph_3P/ CBr_4; (ix) OsO_4/$NaIO_4$.



(i) $NaIO_4$; (ii) $(EtO)_2P(O)CH_2CN$; (iii) H_2/Pd; (iv) MeOH/H_2SO_4 (separate anomers); (v) PhOCSCl.

Scheme VI (contd.)

Intermediates were not fully characterized, but the authenticity of each of the substrates for radical cyclization rests on satisfactory elemental analyses or high resolution mass spectra, and approbatory ^1H NMR spectral data.

Radical Generation. Radicals were generated entirely by the use of tri-*n*-butyltin hydride under standard conditions (see Experimental). Vinyl radicals were prepared as summarized in Scheme Id. Protodestannylation of the product was achieved by stirring with silica gel.[9]

EXPERIMENTAL

General Procedures. Melting points were determined in capillary tubes using a Buchi Model 510 melting point apparatus and are uncorrected. Elemental analyses were performed by M-H-W Laboratories, PO Box 15149, Phoenix, AZ. IR spectra were recorded on a Perkin-Elmer 298. Optical rotations were determined at the sodium D line using a Perkin-Elmer 241 polarimeter. ^1H and ^{13}C NMR spectra were determined on a Varian XL-300 spectrometer. Unless otherwise stated, the solvent used was $CDCl_3$ with internal tetramethylsilane or $CHCl_3$ as the standard and coupling constants are reported in Hz. For the purpose of ^1H NMR interpretation, compound structures have been numbered in Table I. The progress of all reactions was monitored by thin layer chromatography (TLC), which was performed on aluminum plates precoated with silica gel HF-254 (0.2 mm layers) containing a fluorescent indicator (5539, Merck). Detection was first by UV (254 nm), then charring with a solution of ammonium molybdate(VI) tetrahydrate (12.5 g) and cerium(IV) sulfate tetrahydrate (5.0 g) in 10% aqueous sulfuric acid (500 mL). Flash chromatography was performed using Kiesselgel 60 (230-400 mesh, Merck).

Substrates for attempted cyclization.

The starting materials, prepared as outlined in Scheme VI, were authenticated by the parameters shown:

For **3** (syrup). IR (neat) 3310, 2740, 1720 cm^{-1}; $[\alpha]_D^{21}$ + 50.2 ° (c 0.4, $CHCl_3$); ^1H NMR δ 1.98 (t, 1H, $J_{9,7} = J_{9,7'} = 2.7$, H9), 2.30-2.55 (m, 3H), 2.85 (dd, 1H, $J_{10,11} = 2.4$, $J_{10,10'} = 16.2$, H10), 3.30 (dd, 1H, $J_{10,10'} = 16.2$, $J_{10,11} = 1.5$, H10'), 3.40 (s, 3H, OCH_3), 3.55 (s, 3H, OCH_3), 3.70 (t, 1H, $J_{6ax,6eq} = J_{6ax,5} = 9.5$, H6ax), 3.88 (d, 1H, $J_{4,5} = 9.5$, H4), 4.22-4.40 (m, 2H), 4.77 (d, 1H, $J_{1,2} = 4.0$, H1), 5.44 (s, 1H, PhCH), 7.30-7.50 (m, 5H), 9.84 (dd, 1H, $J_{11,10'} = 1.5$, $J_{11,10} = 2.4$, H11).

Anal. Calcd. for $C_{20}H_{24}O_6$: C, 66.67; H, 6.67. Found: C, 66.64; H, 6.63.

For **5** (mp 122 °). IR ($CHCl_3$) 3310, 2750, 1720 cm^{-1}; $[\alpha]_D^{20}$ + 43.5 ° (c 0.4, $CHCl_3$); ^1H NMR δ 2.10 (dd, 1H, $J_{11,9}$ = 2.8, $J_{11,9'}$ = 2.7, H11), 2.40 (dd, 1H, $J_{9,11}$ = 2.8, $J_{9,9'}$ = 16.7, H9), 2.64 (ddd, 1H, $J_{7,2}$ = 3.5, $J_{7,7'}$ = 17.8, $J_{7,8}$ = 1.0, H7), 2.81 (ddd, 1H, $J_{7',8}$ = 1.7, $J_{7',7}$ = 17.8, $J_{7',2}$ = 8.4, H7'), 2.89-2.95 (m, 1H, H2), 3.14 (dd, 1H, $J_{9',9}$ = 16.7, $J_{9',11}$ = 2.7, H9'), 3.37 (s, 3H, OCH_3), 3.49 (s, 3H, $-OCH_3$), 3.74 (t, 1H, $J_{6ax,5} = J_{6ax,6eq}$ = 10.1, H6ax), 3.91(d, 1H, $J_{4,5}$ = 9.5, H4), 4.20-4.30 (m, 1H, H5), 4.34 (dd, 1H, $J_{6eq,6ax}$ = 10.1, $J_{6eq,5}$ = 5.4, H6eq), 4.75 (d, 1H, $J_{1,2}$ = 4.4, H1), 5.49 (s, 1H, PhCH), 7.35-7.52 (m, 5H), 9.83 (dd, 1H, $J_{8,7}$ = 1.0, $J_{8,7'}$ = 1.7, H8).

Anal. Calcd. for $C_{20}H_{24}O_6$: C, 66.70; H, 6.70. Found: C, 66.86; H, 6.83.

For **7**. $[\alpha]_D^{22}$ + 6.0° (c 0.96, $CHCl_3$); ^1H NMR δ 1.60-1.80 (m, 3H), 1.85-2.00 (m, 1H), 2.42 (t, 1H, J = 5.6, H2), 2.60 (s, 3H, SCH_3), 3.41 (s, 3H, OCH_3), 3.54 (s, 3H, OCH_3), 3.62 (d, 1H, $J_{4,5}$ = 8.7, H4), 3.70 (dd, 1H, $J_{5,6ax} = J_{6ax,6eq}$ = 12.1, H6ax), 4.30-4.45 (m, 2H, H5, H6eq), 4.95 (d, 1H, $J_{1,2}$ = 4.4, H1), 5.44 (s, 1H, PhCH), 5.75 (d, 1H, $J_{1,2}$ = 4.4, H2), 7.30-7.50 (m, 5H), 9.70 (s, 1H, CHO). LRMS (CI/C_2H_6O): m/z 501 $(M + C_2H_5O)^+$, 457 $(M + H)^+$.

Anal. Calcd. for $C_{21}H_{28}O_7S_2$: C, 55.24; H, 6.18; S, 14.04. Found: C, 55.14; H, 6.17; S, 14.21.

For **9** (colorless oil). IR (neat) 1720 cm^{-1}; $[\alpha]_D^{20}$ - 16.1 ° (c 1.8, $CHCl_3$); ^1H NMR δ 1.8-2.1 (m, 3H, H3 and CH_2 CH_2 CHO), 2.27 (dd, 1H, J = 14.2 and 6.1, H3), 2.56 (s, 3H, SCH_3), 2.62 (m, 2H, CH_2 CHO): 3.37 (s, 3H, OCH_3), 4.35 (m, 1H, H4), 5.00 (s, 1H, H1), 5.78 (d, 1H, J = 4.9, H2), 9.83 (t, 1H, J = 1.4, CHO).

Anal. Calcd. for $C_{10}H_{16}O_4S_2$: C, 45.44; H, 6.10; S, 24.26. Found: C, 45.49; H, 6.10; S, 24.18.

For **11**. IR (neat) 1725 cm^{-1}; ^1H NMR δ 1.02, 1.06 (s, s, 3H each, CH_3), 1.50-1.72 (m, 2H), 1.80-1.96 (m, 1H), 1.98-2.15 (m, 1H), 3.12 (t, 2H, J = 6.7, CH_2CH_2I), 3.36 (s, 3H, OCH_3), 3.64 (dd, 1H, $J_{3,4}$ = 8.06, $J_{3,4'}$ = 3.5, H3), 4.55-4.70 (m, 2H), 9.56 (s, 1H, CHO).

Anal. Calcd for $C_{10}H_{19}O_3I$: C, 38.20; H, 6.10. Found: C, 38.02; H, 6.20.

For **13**. IR (neat) 3275, 1730 cm^{-1}; $[\alpha]_D^{20}$ - 148.77 ° (c 0.98, $CHCl_3$); ^1H NMR δ 1.40 (s, 3H, $C(CH_3)_2$), 1.55 (s, 3H, $C(CH_3)_2$), 2.59 (d, 1H, $J_{7,5}$ = 1.7, H7), 3.83 (dd, 1H, $J_{2,1}$ = 1.5, $J_{2,3}$ = 3.9, H2), 4.12 (d, 1H, J = 11.9, OCH_2Ph), 4.22-4.48 (m, 5H), 4.72 (d, 1H, J = 10.3, OCH_2Ph), 7.25-7.40 (m, 10H), 9.52 (d, 1H, $J_{1,2}$ = 1.5, H1). LRMS (CI/C_2H_5O): m/z 439 $(M+ C_2H_5O)^+$, 395 $(M + H)^+$.

For **15**. ^1H NMR δ 0.07 (s), 0.10 (s), 0.11 (s), 0.16 (s), 0.97 (s), 0.98 (s), 3.22 (s), 3.33 (s), 3.94-4.08 (m), 4.17 (br s), 4.34-4.66 (m), 4.89 (d), 5.00-5.05 (2d), 7.15-7.38 (m), 9.40 (s), 9.68 (d). LRMS (CI/NH_3): m/z 644 $(M + NH_4)^+$.

Anal. Calcd. for $C_{30}H_{39}O_6I$: C, 53.76; H, 6.12; I. 20.28. Found: C, 53.59; H, 6.33; I, 20.49.

For **16**. $[\alpha]_D^{22}$ - 27.0 ° (c 0.69, $CHCl_3$); ^1H NMR δ 2.08 (ddd, 1H, $J_{3,3'}$ = 14.4, $J_{2,3}$ = 4.9, $J_{3,4}$ = 8.8, H3), 2.44 (dd, 1H, $J_{3',4}$ = 6.5, $J_{3',3}$ = 14.4, H3'), 2.57 (s, 3H, SCH_3), 2.71 (dd, 1H, $J_{5',5}$ = 17.0, $J_{5',4}$ = 5.8, H5'), 2.84 (ddd, 1H, $J_{H5,5'}$ = 17.0, $J_{4,5}$ = 7.5, $J_{5,6}$ = 2.1, H5), 3.37 (s, 3H, OCH_3), 4.77-4.88 (m, 1H, H4), 5.03 (s, 1H, H1), 5.80 (d, 1H, $J_{2,3}$ = 4.9, H2), 9.83 (br s, 1H, H6). LRMS (CI/NH_3): m/z 268 $(M + NH_4)^+$, 251 $(M + H)^+$.

Anal. Calcd. for $C_9H_{14}O_4S_2$: C, 43.17; H, 5.64; S, 25.61. Found: C, 42.97; H, 5.54; S, 25.39.

For **17** (colorless oil). IR (neat) 1720 cm^{-1}; ^1H NMR δ 1.6-2.4 (m, 6H), 2.58 (s, 3H, SCH_3), 3.38 (s, 3H, OCH_3), 4.28 (m, 1H, H4), 5.15 (d, 1H, J = 4.2, H1), 5.68 (m, 1H, H2), 9.80 (t, 1H, J = 1.4, CHO). LRMS (CI/NH_3): m/z 282 $(M + NH_4)^+$, 265 $(M + H)^+$. HRMS Calcd. for $C_{19}H_{13}O_3S_2$ $(M\text{-}OCH_3)^+$: 233.0306. Found: 233.0310.

For **18**. IR (neat) 1730 cm^{-1}; ^1H NMR δ 3.33 (s, 3H, OCH_3), 3.44 (s, 3H, OCH_3), 3.54 (d, 2H, $J_{6,5}$ = 5.8, H6), 3.70-3.80 (m, 2H), 3.93 (dt, 1H, $J_{5,6}$ = 5.8, $J_{5,4}$ = 2.2, H5), 4.08 (dd, 1H, $J_{2,3}$ = 2.3, $J_{2,1}$ = 0.9, H2), 4.65 (s, 2H, OCH_2Ph), 4.73 (s, 1H, OCH_2Ph), 4.75 (s, 1H, OCH_2Ph), 7.25-7.40 (m, 10H), 9.52 (d, 1H, $J_{1,2}$ = 0.9, H1).

For **19** (mp 53-54 °). IR ($CHCl_3$) 3300, 1730 cm^{-1}; $[\alpha]_D^{20}$ - 90.6 ° (c 0.98, $CHCl_3$); ^1H NMR δ 2.56 (d, 1H, $J_{7,5}$ = 2.2, H7), 3.27 (s, 3H, OCH_3), 3.37 (s, 3H, OCH_3), 4.30 (dd, 1H, $J_{4,3}$ = 7.1, $J_{4,5}$ = 3.7, H4), 4.18 (dd, 1H, $J_{2,1}$ = 0.7, $J_{2,3}$ = 2.5, H2), 4.22 (dd, 1H, $J_{3,2}$ = 2.5, $J_{3,4}$ = 7.1, H3), 4.47 (d, 1H, J = 11.6, OCH_2Ph), 4.54 (dd, 1H, $J_{5,7}$ = 2.2, $J_{5,4}$ = 3.7, H5), 4.55-4.86 (m, 7H), 7.25-7.40 (m, 10H), 9.67 (d, 1H, $J_{1,2}$ = 0.7, H1).

For **24** (colorless oil). IR (neat) 2250 cm^{-1}; $[\alpha]_D^{20}$ + 10.1 ° (c 2.6, $CHCl_3$); ^1H NMR δ 1.1-2.6 (m, 6H), 3.40 (s, 3H, OCH_3), 4.4 (m, 1H, H4), 5.11 (s, 1H, H1), 5.54 (d, 1H, J = 4.8, H2), 7.0-7.5 (m, 3H, ArH).

Anal. Calcd. for $C_{15}H_{17}NO_4S$: C, 58.62; H, 5.57; N, 4.56; S, 10.43. Found: C, 58.70; H, 5.64; N, 4.58; S, 10.51.

General procedure for cyclizations. The aldehyde was dissolved in benzene or toluene (0.005-0.02 M) and heated to reflux. A solution of tri-*n*-butyltin hydride (1.0-1.5 eq.) and catalytic AIBN in the same solvent was added slowly *via* syringe (2-22 h). The solvent was removed by use of a rotary evaporator, and ^1H NMR and TLC was used to evaluate the success of the reaction. The products shown in Table I were isolated by flash chromatography, and identified by spectral data. For entries (i), (ii), and (vi), the crude reaction mixtures were stirred with silica gel (5 g/0.1 mmol

substrate) in methylene chloride (15 mL/0.1 mmol substrate) overnight to effect protodestannylation[9] before chromatography.

For **4**. To a solution of **3** (37.6 mg, 0.104 mmol) in benzene (6.2 mL) at reflux under argon was added Bu_3SnH (35 μL, 0.13 mmol) and a catalytic amount of AIBN. The reaction mixture was maintained at reflux for 4.5 h and worked up as indicated in the general procedure. Purification by flash chromatography (10 ---> 40% EtOAc/PE) gave alcohol **4** (17.1 mg, 45%) (R_f 0.27 (30% EtOAc/PE)), as a crystalline solid. (mp 150-151 °). IR ($CHCl_3$) 3600, 3500, 1650 cm^{-1}; $[\alpha]_D^{20}$ + 37.5 ° (c 0.76, $CHCl_3$); ^1H NMR δ 1.13 (dd, 1H, $J_{10ax,10eq}$ = 13.5, $J_{10ax,9}$ = 11.9, H10ax), 1.63 (d, 1H, OH, J = 5.9), 1.82 (ddd, 1H, $J_{2,7ax}$ = 13.5, $J_{2,1}$ = 4.2, $J_{2,7eq}$ = 3.7, H2), 2.15 (dd, 1H, $J_{7eq,7ax}$ = 13.5, $J_{7eq,2}$ = 3.7, H7eq), 2.58 (t, 1H, $J_{7ax,7eq}$ = $J_{7ax,2}$ = 13.5, H7ax), 3.03 (dd, 1H, $J_{10eq,10ax}$ = 13.5, $J_{10eq,9}$ = 4.9, H10eq), 3.40 (s, 3H, OCH_3), 3.50 (d, 1H, $J_{4,5}$ = 9.3, H4), 3.62 (s, 3H, OCH_3), 3.64-3.76 (m, 1H, H6ax), 4.22-4.37 (m, 3H), 4.52 (d, 1H, J = 4.2, H1), 4.88 (d, 1H, J = 1.7, C=CH_2), 5.0 (d, 1H, J = 1.7, C=CH_2), 5.44 (s, 1H, PhCH), 7.33-7.50 (m, 5H).

Anal. Calcd. for $C_{20}H_{26}O_6$: C, 66.30; H, 7.20. Found: C, 66.26; H, 7.13.

For **6**. To a solution of **5** (49 mg, 0.14 mmol) in benzene (7 mL) at reflux under argon was added Bu_3SnH (55 μL, 0.20 mmol) and AIBN (cat.). The reaction mixture was maintained at reflux for 2 h and worked up as indicated in the general procedure. Purification by flash chromatography (20 ---> 50% EtOAc/PE) gave a 3:1 mixture of equatorial:axial alcohols (20 mg, 40%) as crystalline solids: **6a** (axial alcohol, mp 125-126°, R_f=0.24 (50% EtOAc/PE). IR ($CHCl_3$) 3600, 3500 cm^{-1}; $[\alpha]_D^{21}$ + 43.5 ° (c 0.4, $CHCl_3$); ^1H NMR δ 1.62 (dt, 1H, $J_{7eq,7ax}$ = 13.7, $J_{7eq,8}$ = 3.4, H7eq), 2.09 (dt, 1H, $J_{7ax,2}$ = $J_{7ax,7eq}$ = 13.7, $J_{7ax,8}$ = 3.3, H7ax), 2.27 (d, 1H, $J_{10,10'}$ = 14.7, H10), 2.46 (ddd, $J_{2,7ax}$ = 13.7, $J_{2,7eq}$ = 3.4, $J_{2,1}$ = 4.2, H2), 3.12 (d, 1H, $J_{10',10}$ = 14.7, H10'), 3.38 (s, 3H, OCH_3), 3.53 (s, 3H, OCH_3), 3.56-3.80 (m, 2H), 4.20-4.34 (m, 2H), 4.42 (br s, 1H, H8), 4.48 (d, 1H, J = 4.2, H1), 4.90 (br s, 1H, C=CH_2), 5.04 (br s, 1H, C=CH_2), 5.45 (s, 1H, PhCH_2), 7.35-7.52 (m, 5H). HRMS Calcd. for $C_{20}H_{27}O_6$ $(M+H)^+$: 363.1808. Found: 363.1810.

6b (equatorial alcohol, mp 114-115°, R_f=0.17 (50% EtOAc/PE)). IR ($CHCl_3$) 3600, 3500 cm^{-1}; $[\alpha]_D^{21}$ + 88.9 ° (c 0.35, $CHCl_3$); ^1H NMR δ 1.78-1.88 (m, 3H), 1.90-2.00 (m, 1H), 3.30-3.40 (m, 1H), 3.38 (s, 3H, OCH_3), 3.48-3.55 (m, 1H), 3.52 (s, 3H, OCH_3), 3.62-3.75 (m, 1H), 4.00-4.14 (m, 1H), 4.20-4.34 (m, 2H), 4.48 (d, 1H, J = 1.7, H1), 4.90 (d, 1H, J = 1.5, C=CH_2), 5.15 (d, 1H, J = 1.5, C=CH_2), 5.42 (s, 1H, PhCH), 7.32-7.50 (m, 5H).

For **8**. To a solution of **7** (40.4 mg, 0.0885 mmol) in benzene (13 mL) was added catalytic AIBN and Bu_3SnH hydride (40 μL, 0.15 mmol). The

solution was heated at reflux for 1 h. Rotary evaporation and flash chromatography (25 ---> 100% EtOAc/PE) of the residue afforded **8** (8.2 mg, 26%). R_f=0.40 (80% EtOAc/PE). $[\alpha]_D^{22}$ + 39.2 ° (c 0.48, $CHCl_3$); ^1H NMR δ 1.28-1.83 (m, 4H), 1.91 (d, 1H, $J_{2,7}$ = 10.7, H2), 2.04-2.09 (m, 1H), 2.28-2.32 (m, 1H), 3.41 (s, 3H, OCH_3), 3.42 (s, 3H, OCH_3), 3.65-3.80 (m, 3H, H4, H6ax, H7), 4.23-4.46 (m, 2H, H5, H6eq), 4.98 (s, 1H, H1), 5.46 (s, 1H, PhCH), 7.28-7.52 (m, 1H, 5H). LRMS (CI/NH_3) m/z 368 $(M + NH_4)^+$. HRMS (CI/NH_3) Calcd. for $C_{19}H_{27}O_6$ $[M+H]^+$: 351.1808. Found: 351.1819.

For **10**. To a refluxing 6 mM solution of the aldehyde **9** (77 mg, 0.29 mmol), Bu_3SnH (0.5 eq.) and AIBN (cat.) in dry toluene, additional Bu_3SnH (0.9 eq.) and AIBN (cat.) dissolved in 1.3 mL of toluene were added *via* syringe over 75 min. After refluxing for another 15 min, evaporation of the solvent and flash chromatography (silica gel, 30 ---> 50% EtOAc/PE) afforded the reduced product **10** (16 mg, 35%) as a colorless oil. IR (neat) 1720 cm^{-1}; ^1H NMR δ 1.6-2.1 (m, 6H), 2.58 (m, 2H, CH_2CHO), 3.31 (s, 3H, OCH_3), 4.06 (m, 1H, H4), 4.92 (d, 1H, J = 3.9, H1), 9.81 (t, 1H, J = 1.6, 1H, CHO); ^{13}C NMR δ 202.28, 105.06, 79.55, 54.22, 40.89, 33.21, 29.57, and 29.14. HRMS (EI) Calcd. for $C_7H_{11}O_2$ $(M-OCH_3)^+$: 127.0759. Found: 127.0748.

For **12**. A mixture of **11** (37.1 mg, 0.118 mmol), Bu_3SnH (40 μL, 0.18 mmol), and a catalytic amount of AIBN in tetrahydrofuran (12 mL) was maintained at reflux under argon for 40 min and worked up as indicated in the general procedure. Purification by flash chromatography (30% diethyl ether/PE) gave alcohols **12** (8.1 mg, 36%) as a 1:1 mixture of isomers. R_f=0.33 (50% diethyl ether/PE). IR (neat) 3500 cm^{-1}; ^1H NMR δ 0.75-0.95 (m, 1H), 0.95-1.06 (m, 6H, $C(CH_3)_2$, 1.20-1.35 (m, 1H), 1.40-1.80 (m, 6H), 3.25-3.40 (m, 0.5H), 3.38-3.40 (s, 3H total, OCH_3), 3.48-3.78 (m, 0.5H), 4.55-4.75 (m, 2H). HRMS Calcd. for $C_8H_{15}O_2$ $[M-C_2H_5O]^+$: 143.1072. Found 143.1072.

For **14**. To a solution of **13** (46.6 mg, 0.105 mmol) in benzene (6 mL) at reflux was added a mixture of Bu_3SnH (44 μL, 0.16 mmol), and AIBN (3.4 mg, 0.021 mmol) in benzene (0.5 mL) over 5 h. The reaction mixture was maintained at reflux for an additional 5 h and worked up according to the general procedure. Purification by flash chromatography (10% EtOAc/PE) gave **14** (4.7 mg, 11%) as a mixture of epimeric alcohols. **14a**: equatorial alcohol, R_f=0.44 (40% EtOAc/PE). IR (neat) 3450 cm^{-1}; ^1H NMR δ 1.38 (s, 3H, $C(CH_3)_2$), 1.50 (s, 3H, $C(CH_3)_2$), 2.02 (d, 1H, OH), 3.61 (dd, 1H, $J_{2,1}$ = 8.2, $J_{2,3}$ = 6.1, H2), 3.95-4.02 (m, 1H), 4.10-4.15 (m, 1H), 4.24 (t, 1H, $J_{3,4} = J_{3,2}$ = 6.1, H3), 4.37 (dd, 1H, $J_{4,3}$ = 6.1, $J_{4,5}$ = 3.8, H4), 4.66 (d, 1H, J = 12.6, OCH_2Ph), 4.62 (d, 1H, J = 11.5, OCH_2Ph), 4.82 (d, 1H, J = 12.60, OCH_2Ph), 4.88 (d, 1H, J = 11.5, OCH_2Ph), 5.48 (br s, 1H, $C=CH_2$), 5.54 (br s, 1H, $C=CH_2$) 7.25-7.42 (m,

10H). LRMS (CI/C_2H_5O): m/z 441 $(M + C_2H_5O)^+$, 397 $(M + H)^+$. HRMS (CI/NH_3) Calcd. for $C_{24}H_{29}O_5$ $[M+H]^+$: 397.2015. Found: 397.2015.

14b: axial alcohol, R_f=0.33 (40% EtOAc/PE). ^1H NMR δ 1.36 (s, 3H, $C(CH_3)_2$), 1.41 (s, 3H, $C(CH_3)_2$), 2.30 (d, 1H, J = 4.1, OH), 3.65 (dd, 1H, $J_{2,1}$ = 3.3, $J_{2,3}$ = 5.9, H2), 4.33 (t, 1H, $J_{3,2} = J_{3,4}$ = 5.9), 4.42 (dd, 1H, $J_{4,3}$ = 5.9, $J_{4,5}$ = 3.7, H4), 4.45-4.52 (m, 2H), 4.59-4.80 (m, 4H, OCH_2Ph), 5.40 (br s, 1H, $C=CH_2$), 5.50 (br s, 1H, $C=CH_2$), 7.25-7.40 (m, 10H). LRMS (CI/C_2H_5O): m/z 441 $(M + C_2H_4O)^+$, 397 $(M + H)^+$. HRMS (CI/NH_3) Calcd. for $C_{24}H_{29}O_5$: 397.2015. Found: 397.205.

For **26**. To a solution of nitrile **24** (41 mg, 0.13 mmol) in benzene (50 mL) Bu_3SnH (54 μL, 1.5 eq.), and AIBN (cat.) in benzene (6 mL) were added *via* syringe over 9 h. Evaporation of the solvents and flash chromatography afforded the reduced product **26** as a volatile coloress oil (7 mg, 34%). IR (neat) 2250 cm^{-1}; ^1H NMR δ 1.6-2.2 (m, 6H), 2.50 (m, 2H, CH_2CN), 3.32 (s, 3H, OCH_3), 4.14 (m, 1H, H4), 4.95 (dd, 1H, J = 3.9 and 1.2, H1). LRMS (CI/NH_3): m/z 173 $(M + NH_4)^+$.

Anal. Calcd. for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.97; H, 8.66; N, 9.29.

For **27**. A solution of the aldehyde **9** (77 mg, 0.29 mmol), acrylonitrile (0.29 mL, 15 eq.), Bu_3SnH (0.12 mL, 1.5 eq.), and AIBN (cat.) in dry toluene (50 mL) was refluxed for 45 min. Evaporation of the solvents and flash column chromatography (EtOAc/PE) afforded nitrile **27** (24 mg, 39%) as a colorless oil. IR (neat) 2250, 1720 cm^{-1}; ^1H NMR δ 1.5-2.0 (m, 6H), 2.29 (m, 1H, H2), 2.39 (t, 2H, J = 7.3, CH_2CN), 2.60 (m, 2H, CH_2 CHO), 3.33 (s, 3H, OCH_3), 4.15 (m, 1H, H4), 4.65 (d, 1H, J = 1.4, H1), 9.82 (t, 1H, J = 1.4, CHO). HRMS Calcd. for $C_{11}H_{18}NO_3$ $[M+H]^+$: 212.1287. Found: 212.1286.

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