JOC Article

2-Deoxyribose as a Rich Source of Chiral 5-Carbon Building Blocks§

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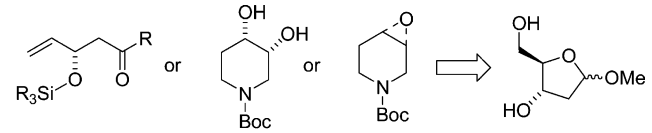
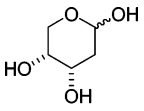


R = H, OH, NMe(OMe)

We have developed concise routes to a number of useful chiral 5-carbon synthetic building blocks using readily available *O*-1-methyl-2-deoxyribose as starting material. Novel transformations include the use of indium triflate to catalyze the oxidation of a methyl furanoside to the corresponding lactone with MCPBA and the Vasella-type fragmentation of a 5-iodo furanoside using chromium(II) chloride when zinc proved ineffective. In addition, 3,4-disubstitued piperidine derivatives were prepared without hydroxyl group protection via a simple reductive amination reaction.

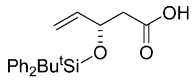
Introduction

2-Deoxyribose (**1**) is unique among deoxysugars in that it is available in commercial quantities at relatively low cost. This reflects the fact that it is manufactured by alkaline degradation of inexpensive glucose. Consequently synthetic organic chemists have utilized 2-deoxyribose as a starting material in the total syntheses of molecules as diverse as brevetoxin B,[1] disparlure,[2] and leukotriene B4.[3] Nevertheless we suggest that, given the availability and highly functional nature of 2-deoxyribose, it remains underutilized in organic synthesis.



1

A case in point is carboxylic acid **2**, a key intermediate in a recent synthesis of (+)-diplodialides B and C.[4] This excellent chiral building block was prepared in 11 steps from 1,3-propanediol via a route involving the Katsuki−Sharpless asymmetric epoxidation and multiple chromatographic purifications. In the current paper we report an alternative synthesis of **2** starting with the commercially available *O*-methyl glycoside of 2-deoxyribose. This improved route affords **2** in four simple steps without the need for chromatography.



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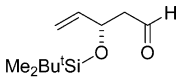

3

The related (*S*)-aldehyde **3** has been utilized in the synthesis of 1α,25-dihydroxy-22-oxavitamin D_3[5] and in a ring-closing metathesis approach to dictyostatin.[6] In both applications, **3** was again prepared by Sharpless AE.[7] Again, we find that use of 2-deoxyribose as ultimate starting material provides greatly simplified access to **3**.

In addition to these acyclic derivatives, 2-deoxyribose based syntheses were also developed for piperidines **4** and **5**. The

§ Dedicated to Prof. Jay K. Kochi on the occasion of his 80th birthday.

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(1) Matsuo, G.; Kawamura, K.; Hori, N.; Matsukura, H.; Nakata, N. *J. Am. Chem. Soc*. **2004**, *126*, 14374.

(2) Kang, S.-K.; Kim, Y.-S.; Lim, J.-S.; Kim, K.-S.; Kim, S.-G. *Tetrahedron Lett.* **1991**, *32*, 363.

(3) Guindon, Y.; Delorme, D.; Lau, C. K.; Zamboni, R. *J. Org. Chem*. **1988**, *53*, 267.

(4) Sharma, G. V. M.; Reddy, K. L. *Tetrahedron*: *Asymmetry* **2006**, *17*, 3197.

(5) Hatakeyama, S.; Okano, T.; Maeyama, J.; Tomoyuki, E.; Hiyamizu, H.; Iwabuchi, Y.; Nakagawa, K.; Ozono, K.; Kawase, A.; Kubodera, N. *Bioorg. Med. Chem.* **2001**, *9*, 403.

(6) Kangani, C. O.; Brueckner, A. M.; Curran, D. P. *Org. Lett.* **2005**, *7*, 379.

(7) The (*R*)-enantiomer of aldehyde **3** has been prepared by a sequence of enzymatic resolution of the *tert*-butyl β-ketoester, chromatographic separation, DIBAL reduction, and silylation. Tan, C.-H.; Holmes, A. B. *Chem. Eur. J.* **2001**, *7*, 1845. See also: Vrielynck, S.; Vandewalle, M.; Garcia, A. M.; Mascarenas, J. L.; Mourino, A. *Tetrahedron Lett.* **1995**, *36*, 9023.

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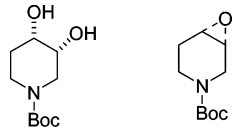
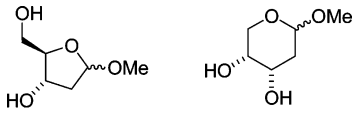


4 **5**

racemate of epoxide **5** is a precursor to the gastrointestinal stimulant cisapride,[8] while racemic **4** has been shown to be an invaluable carbohydrate scaffold for drug discovery in the area of extracellular signaling.[9] Enantiopure (3*R*,4*S*)-**4** and (3*R*,4*S*)-**5** were readily synthesized from 2-deoxyribose. In preparing these piperidine derivatives we took advantage of the reductive amination chemistry developed by Wong and co-workers in connection with the chemoenzymatic synthesis of deoxy aza sugars.[10]

Results and Discussion

For convenience, commercial 1-*O*-methyl-2-deoxy-D-ribose (**6**) was used as starting material throughout these studies. While commercial **6** consists principally of the furanoside form shown, in our experience it contains varying amounts (up to 15%) of the pyranoside isomer **7**. (Furanoside **6** is the kinetic product of acetalization of **1** while **7** is the thermodynamic product. Which of these isomers predominates is a critical function of reaction time and temperature and the nature and concentration of the acid catalyst.[11]) Thus part of any apparent yield loss in the present studies must be attributed to this contaminant. In this regard it is noteworthy that both acetals are now available via improved syntheses, which allow isolation of pure **6**[12] or **7**.[13]

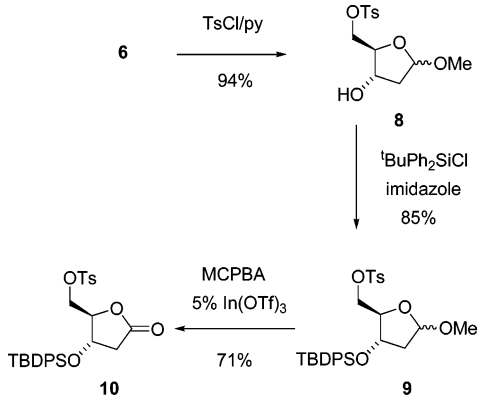


6 **7**

In the case of carboxylic acid **2** we were especially desirous of developing a route that was scaleable and hence chromatography-free. Given the heterogeneous starting material, this seemed to necessitate a route proceeding through a solid intermediate, which could be purified by crystallization. A reasonable candidate seemed to be the lactone **10** (Scheme 1), which we envisioned could be prepared via the Grieco-type oxidation[14] of the corresponding methyl furanoside **9**.

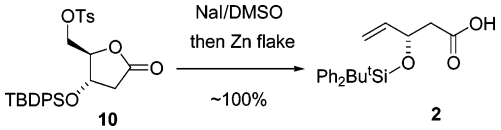
Selective tosylation of **6** on the C5 oxygen is known in the literature.[15] In our experience, use of excess tosyl chloride promotes tosylation at the 2° hydroxyl. For this reason (and recognizing the presence of **7** in the starting material) it is better to utilize a nominally substoichiometric amount of tosyl chloride. Any unreacted **7** is expected to be removed during the course of extractive workup.

SCHEME 1. Preparation of Crystalline Lactone 10

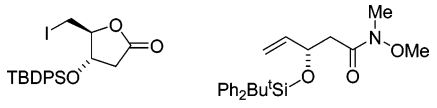


Tosylate **8** so produced was of sufficient purity to be carried on to the subsequent silylation and oxidation steps. Protection as the *tert*-butyldiphenylsilyl ether afforded **9**. However, we were disappointed to find that oxidation under the usual conditions[14] (BF_3 etherate as Lewis acid promoter) afforded only recovered starting material. The reason for this failure is not clear but seems to be associated with the presence of the silyl protecting group. The problem was circumvented by use of indium triflate as an alternative Lewis acid. By using 5% of $In(OTf)_3$, the desired lactone **10** was obtained as a snow-white crystalline solid (mp 102 °C). As we had hoped, **10** was readily purified by crystallization from heptane/ethyl acetate.

A simple one-pot procedure was then developed to convert lactone **10** into the carboxylic acid **2**. A solution of **10** and sodium iodide was heated overnight to convert the tosylate into the corresponding iodide. At this point zinc flakes were added to the solution, which was further stirred for 90 min at room temperature. After extractive workup, **2** was obtained in essentially quantitative yield.



Alternatively, if desired, the intermediate iodide **11** could be separately isolated (see the Supporting Information).



To further enhance the synthetic utility of **2**, we also converted it into the corresponding Weinreb amide, i.e., compound **12**. T3P[16] was used as a coupling reagent and the product was purified by flash chromatography to separate ca. 15% of silanol, which was cleaved under these conditions, affording pure **12** in 77% yield.

(8) Kim, B. J.; Pyun, D. K.; Jung, H. J.; Hyun, J. K.; Kim, J. H.; Kim, E. J.; Jeong, W. J.; Lee, C. H. *Synth. Commun.* **2001**, *31*, 1081.

(9) Tamaruya, Y.; Suzuki, M.; Kamura, G.; Kanai, M.; Hama, K.; Shimizu, K.; Aoki, J.; Arai, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2843.

(10) Kajimoto, T.; Chen, L.; Liu, K. K.-C.; Wong, C.-H. *J. Am. Chem. Soc.* **1991**, *113*, 6678.

(11) Deriaz, R. E.; Overend, W. G.; Stacey, M.; Wiggins, L. F. *J. Chem. Soc.* **1949**, 2836.

(12) For example, Grinstaff and co-workers have reported a protocol that affords **6** in 96% isolated yield. Hashmi, S. A. N.; Hu, X.; Immoos, C. E.; Lee, S. J.; Grinstaff, M. W. *Org. Lett.* **2002**, *4*, 4571.

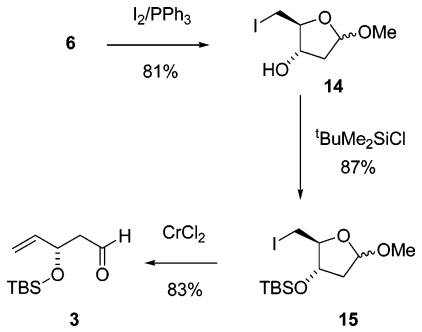
(13) Crotti, P.; Di Bussolo, V.; Favero, L.; Macchia, F.; Pineschi, M. *Tetrahedron*: *Asymmetry* **1996**, *7*, 779.

(14) Grieco, P. A.; Oguri, T.; Yokoyama, Y. *Tetrahedron Lett.* **1978**, *19*, 419.

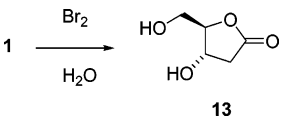
(15) (a) Zamboni, R.; Milette, S.; Rokach, J. *Tetrahedron Lett.* **1984**, *51*, 5835. (b) Aly, Y. L.; Abdel-Megied, A. E.-S.; Pedersen, E. B.; Nielsen, C. *Liebigs Ann. Chem.* **1992**, 127.

(16) T3P is *n*-propylphosphonic acid cyclic anhydride. For a brief review of its chemistry, see: Llanes Garcia, A. L. *Synlett.* **2007**, 1328.

SCHEME 2. Preparation of Aldehyde 3



We note that an alternative route to compound **10** can be imagined based on the well-known oxidation of 2-deoxyribose to 2-deoxyribonolactone **13** using elemental bromine.[17] For small-scale synthesis, this approach would eliminate the need to convert **1** to methyl furanoside **6** and also circumvents the requirement to deal with mixtures of anomers. Indeed, Hollingsworth has reported the synthesis of the C3-unprotected analogue of **2** using such a strategy.[18] Our reason for avoiding this chemistry reflects our interest in a scaleable route: the oxidation of **1** to **13** is carried out in dilute aqueous solution. This requires the distillation of a large amount of water to isolate **13**.

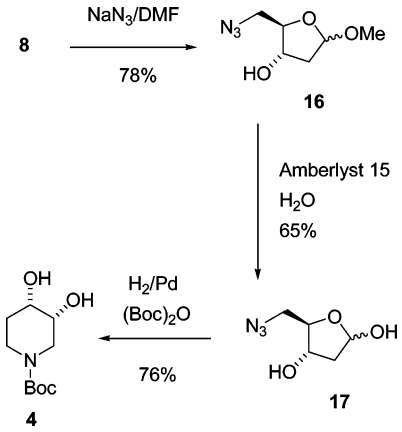


We next turned our attention to the aldehyde building block **3**. The literature indicates that **3** can be prepared via DIBAL reduction of the corresponding ester.[7] However, we wished to avoid unnecessary oxidation−reduction steps, taking advantage of the fact that **6** already exists in the aldehyde oxidation state. For this reason we prepared iodide **14**, which we hoped to open under Vasella-type conditions.[19]

Methyl furanoside **6** was first converted to the primary iodide **14** following the literature procedure[20] as shown in Scheme 2. It was then protected as the *tert*-butyldimethylsilyl ether **15**. Vasella-type reductive opening of **15** was attempted with a variety of zinc sources including zinc dust, zinc flake, zinc amalgam, zinc−copper couple, and diisopropylzinc containing $NiBr_2$ as catalyst. Complete consumption of iodide **15** was generally observed. These procedures afforded the aldehyde **3** in yields ranging from 11% to 50% but none was judged satisfactory.

While disappointing, this was not entirely unexpected. Aldehydes produced via the Vasella reaction often prove unstable under the reaction conditions. Madsen has recently demonstrated an elegant solution to this problem in which the newly released aldehyde species is trapped in situ with a vinyl or propargyl organometallic reagent.[21]In cases where isolation of the aldehyde is required, Fuerstner has pointed out the desirability of carrying these reactions out under anhydrous conditions and has utilized highly active zinc/silver-graphite for this purpose.[19c] As an alternative, we considered the use of chromium(II) chloride[22] as reductant. The mechanistic studies of Kochi on the reduction of vicinal disubstituted compounds (including β-halohydrins) with $CrCl_2$ suggested that this reagent might be suitable for Vasella-type reductions under mild, aprotic conditions.[23] Consistent with these proposals, chromium(II) chloride in THF cleanly reduced **15** to the ring-opened aldehyde **3** in 83% yield after flash chromatography (Scheme 2).

SCHEME 3. Preparation of Dihydroxypiperidine 4



Our approach to the piperidine cis-diol **4** also began with the previously mentioned monotosylate **8**,[24] which was now converted to the corresponding C5 azide **16** without protection following a literature procedure[25] as shown in Scheme 3. Interestingly, conversion of the methyl furanoside moiety of **16** to the free lactol **17** proved the most difficult step of the synthetic sequence. A variety of reagents and conditions have been reported for the selective hydrolysis of methyl furanosides.[26] From the standpoint of operational simplicity, we found that use of strongly acidic Amberlyst 15 resin to catalyze the hydrolysis was advantageous. Hydrolysis was complete after 4 h at room temperature. Polar impurities were removed by passing the product over a bed of silica gel.

The reductive amination of **17** was carried out in ethanol with 5% palladium on carbon as catalyst. The resulting freebase could be isolated (see the Supporting Information) and was shown

(17) Deriaz, R. E.; Overend, W. G.; Stacey, M.; Teece, E. G.; Wiggins, L. F. *J. Chem. Soc.* **1949**, 1879. For updated versions of this reaction, see: Han, S.-Y.; Joullie, M. M.; Petasis, N. A.; Bigorra, J.; Corbera, J.; Font, J.; Ortuno, R. M. *Tetrahedron* **1993**, *49*, 349. Wang, Z.-X.; Wiebe, L. I.; DeClercq, E.; Balzarini, J.; Knaus, E. E. *Can. J. Chem.* **2000**, *78*, 1081.

(18) Song, J.; Hollingsworth, R. I. *Tetrahedron*: *Asymmetry* **2001**, *12*, 387.

(19) (a) Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1979**, *62*, 1990. (b) Nakane, M.; Hutchinson, C. R.; Gollman, H. *Tetrahedron Lett.* **1980**, *21*, 1213. (c) Fuerstner, A.; Jumbam, D.; Teslic, J.; Weidmann, H. *J. Org. Chem.* **1991**, *56*, 2213.

(20) Skaanderup, P. R.; Poulsen, C. S.; Hyldtoft, L.; Jorgensen, M. R.; Madsen, R. *Synthesis* **2002**, 1721.

(21) (a) Madsen, R.; Hyldtoft, L. *J. Am. Chem. Soc.* **2000**, *122*, 8444. (b) Poulsen, C. S.; Madsen, R. *J. Org. Chem.* **2002**, *67*, 4441.

(22) Review: Hanson, J. R. *Synthesis* **1974**, 1.

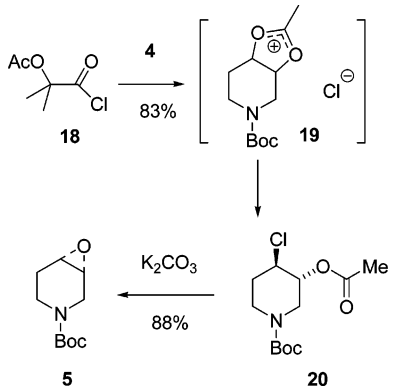
(23) Kochi, J. K.; Singleton, D. M. *J. Am. Chem. Soc.* **1968**, *90*, 1582.

(24) Tosylate **8** used in the preparation of diol **4** was purified by flash chromatography. Unlike the preparation of **2**, there is no crystalline intermediate in the sequence leading to compound **4**. Thus the yields in Scheme 1 are based on crude **8** while those in Scheme 3 are based on chromatographed **8** as starting material.

(25) (a) Tulshian, D. B.; Gundes, A. F.; Czarniecki *Bioorg. Med. Chem. Lett.* **1992**, *2*, 525. (b) Schmidt, L.; Pedersen, E. B.; Nielson, C. *Acta Chim. Scand.* **1994**, *48*, 215. (c) El-Barbary, A. A.; Khodair, A. I.; Pedersen, E. B.; Nielsen, C. *Nucleosides Nucleotides* **1994**, *13*, 707.

(26) For example: (a) HCl/HOAc: Gadikota, R. R.; Keller, A. I.; Callam, C. S.; Lowary, T. L. *Tetrahedron*: *Asymmetry* **2003**, *14*, 737. (b) 80% aqueous HOAc: Vandendriessche, F.; Snoeck, R.; Janssen, G.; Hoogmartens, J.; Van, Aerscshot, A.; De Clercq, E.; Herdewijn, P. *J. Med. Chem.* **1992**, *35*, 1458. (c) 0.5 M formic acid: Moustakis, C.; Viala, J.; Capdevila, J.; Falck, J. R. *J. Am. Chem. Soc.* **1985**, *107*, 5283. (d) BCl_3·Me_2S: Congreve, M. S.; Holmes, A. B.; Hughes, A. B.; Looney, M. G. *J. Am. Chem. Soc.* **1993**, *115*, 5815.

SCHEME 4. Preparation of (3*R*,4*S*)-Epoxide 5



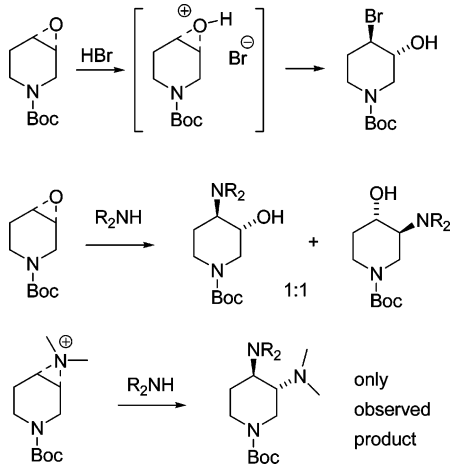
by ^{1}H and ^{13}C NMR to be identical with material produced by the chemoenzymatic procedure of Wong.[10] However, for the preparation of **4**, it was advantageous to treat the filtered product solution in situ with di-*tert*-butyl dicarbonate to afford **4** directly, thus circumventing the isolation step. By using this expedient, the yield of **4** from **17** was 76% despite some loss of hydrophilic product during extractive workup.

For conversion of cis-diol **4** to the epoxide **5**, two reagents can be considered, namely Viehe's salt[27] (dichloromethylenedimethyliminium chloride) and the Moffatt reagent[28] (1-chlorocarbonyl-1-methylethyl acetate, **18**). We initially examined the use of Viehe's salt but found that the vigorous conditions for hydrolysis of the intermediate chloro carbamate were problematic. In contrast, reaction of **4** with the Moffatt reagent (Scheme 4) gives the chloro acetate **20**, which was converted under mild conditions to epoxide **5**. Regioselective formation of **20** as the 4-chloro regioisomer was demonstrated by 2D NMR studies, while chiral HPLC confirmed that the epoxide product **5** was >99% ee.

The highly regioselective formation of chloro acetate **20** is noteworthy.[29] This result is consistent with literature observations[8,30,31] on the nucleophilic opening of related 3,4-disubstituted heterocycles under conditions where the intermediate bears a significant positive charge (Scheme 5).

As shown in Scheme 5, opening of **5** with HBr affords a single β-bromohydrin while opening the same epoxide with dialkylamines gives a 1:1 mixture of regioisomers.[8] The latter reaction also contrasts with the opening of dialkylaziridinium

SCHEME 5. Effect of Charge on Regioselectivity



ions with dialkylamines, which again is completely regiospecific.[30,31] These results suggest that the directing effect of the ring heteroatom in 3,4-disubstituted heterocycles is more pronounced when nucleophilic addition proceeds by way of a cationic intermediate. This is relevant to the selective formation of **20** since the reaction of the Moffatt reagent with cis-diols is proposed[28] to proceed through a cationic intermediate of type **19**.

Conclusion

In the foregoing discussion we have shown that 2-deoxy-D-ribose is readily converted into a series of chiral 5-carbon intermediates of demonstrated synthetic utility. Most of this chemistry should be amenable to larger scale manufacture of these chiral building blocks. The principal limitation in this approach is that **1** is commercially available only as the D-stereoisomer. However, the recent development of straightforward technology to convert **1** to into 2-deoxy-L-ribose[32] may remove this restriction as well. We hope that these procedures will further enhance the attractiveness of 2-deoxyribose as an available, enantiopure, and highly functional starting material.

Experimental Section

2-Deoxy-1-*O*-methyl-3-*O*-*tert*-butyldiphenylsilyl-5-*O*-(*p*-toluenesulfonyl)-D-ribofuranose, 9. Tosylate **8** was first prepared following the literature procedure.[15] Toluenesulfonyl chloride (11.6 g, 60.7 mmol, 0.9 equiv) was added to a solution of **6** (10.0 g, 67.5 mmol) in pyridine (200 mL). The mixture was stirred overnight after which the solvent was removed at reduced pressure. The residue was taken up in ethyl acetate (300 mL) and was washed sequentially with 1 N HCl, saturated $NaHCO_3$ solution, water, and brine (100 mL each). The solution was dried (Na_2SO_4) and the solvent was removed to afford **8** (17.2 g, 94% based on TsCl) for which NMR data were consistent with those in the literature.[15] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (2H, m), 7.32 (2H, m), 4.99 (1H, m), 4.37−4.01 (3H, m), 3.31 (1.5H, s), 3.18 (1.5H, m), 2.90 (0.5H, d, J = 11 Hz), 2.46 (0.5H, d, J = 5.3 Hz), 2.41 (3H, s), 2.22−1.92 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.0, 132.6, 129.9, 127.9, 105.6, 105.3, 84.3, 82.9, 72.6, 72.4, 70.2, 69.4, 55.0, 41.2, 40.9, 21.6.

A solution of **8** (5.30 g, 17.6 mmol) in anhydrous DMF (200 mL) was cooled to 10 °C in an ice bath. To the cold solution was

(27) (a) Sunay, U.; Mootoo, D.; Molino, B.; Fraser-Reid, B. *Tetrahedron Lett.* **1986**, *27*, 4697. (b) Fraser-Reid, B.; Molino, B. F.; Magdzinski, L.; Mootoo, D. R. *J. Org. Chem.* **1987**, *52*, 4505.

(28) Greenberg, S.; Moffatt, J. G. *J. Am. Chem. Soc.* **1973**, *95*, 4016.

(29) Our results using Viehe's salt are not directly comparable since the protecting group on nitrogen was benzyl rather than Boc. Nevertheless, it is noteworthy that this reaction gave a nearly 1:1 mixture of regioisomeric chloro carbamates. This is consistent with the proposal (ref 26) that the positive charge in the case of Viehe's salt is delocalized and resides mainly on the iminium nitrogen.

(30) See also: (a) D'Andrea, S. V.; Michalson, E. T.; Freeman, J. P.; Chidester, C. G.; Szmuszkovicz, J. *J. Org. Chem.* **1991**, *56*, 3133. (b) Zhao, S.; Ghosh, A.; D'Andrea, S. V.; Freeman, J. P.; VonVoigtlander, P. F.; Carter, D. B.; Smith, M. W.; Blinn, J. R.; Szmuszkovicz, J. *Heterocycles* **1994**, *39*, 163. (c) Thomas-Xavier, M.; Appenzeller, J.; Pardo, D. G.; Cossy, J. *Org. Lett.* **2006**, *8*, 3509.

(31) Similarly, Crotti has studied addition of nucleophiles to 3,4-epoxytetrahydropyran (the oxygen analogue of **5**) and finds that selectivity for attack at the 4-position is enhanced by the addition of Lewis acids. These results were rationalized in terms of "chelation effects" but seem to us to reflect the enhanced directing effect of the ring oxygen as binding to the Lewis acid makes the epoxide more electron deficient. Chini, M.; Crotti, P.; Gardelli, C.; Macchia, F. *Tetrahedron* **1994**, *50*, 1261.

(32) Ji, Q.; Pang, M.; Han, J.; Feng, S.; Zhang, X.; Ma, Y.; Meng, J. *Synlett* **2006**, 2498.

added imidazole (1.44 g, 21.1 mmol, 1.2 equiv) after which *tert*-butyldiphenylsilyl chloride (5.4 mL, 22 mmol, 1.2 equiv) was added at once. The mixture was stirred overnight at room temperature. Heptane (100 mL) was added to the mixture, which was washed with water (3 × 100 mL) and brine (100 mL). The organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure affording **9** (9.31 g, 85%) as a pale yellow oil in adequate purity to be carried on in the following step. (Note that under these conditions, excess $^tBuPh_2SiCl$ is converted to the silanol, which is retained as an impurity in **9** but is shed during the crystallization of **10**.) A sample of **9** was purified by flash chromatography as a mixture of α and β anomers for characterization. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.8−7.2 (14H, m), 4.98 (0.5H, m), 4.81 (0.5, m), 4.26−3.61 (4H, m), 3.31 (1.5H, s), 3.12 (1.5H, s), 2.42 (3H, s), 2.04 (1H, m), 1.85 (1H,m), 1.03 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.6, 135.6, 133.6, 130.0, 127.7, 105.6, 104.8, 83.6, 81.8, 73.5, 72.6, 70.4, 69.5, 55.0, 54.8, 41.8, 41.4, 31.99, 26.7, 22.6, 21.5, 19.0, 14.1. Anal. Calcd for $C_{29}H_{36}O_6SSi$: C, 64.41; H, 6.71. Found: C, 64.51; H, 6.65.

2-Deoxy-3-*O*-*tert*-butyldiphenylsilyl-5-*O*-(*p*-toluenesulfonyl)-D-ribonolactone, 10. Commercial 3-chloroperbenzoic acid (MCPBA) contains a significant amount of water that could potentially interfere with the reaction.[33] Consequently commercial MCPBA (6.05 g, 27 mmol, nominal 2 equiv) was dissolved in dichloromethane (300 mL) and the aqueous layer was removed by using a separatory funnel. To the solution were added **9** (7.30 g, 13.5 mmol) and indium(III) trifluoromethanesulfonate (0.38 g, 0.68 mmol, 5%) as catalyst. After being stirred overnight at room temperature, the reaction mixture was washed with 1 N NaOH (3 × 100 mL), water (3 × 100 mL), and brine (100 mL). The resulting solution was dried (Na_2SO_4) and the solvent was removed at reduced pressure. The semisolid residue was crystallized from 80:20 heptane/ethyl acetate to afford **10** (5.05 g, 71%) as a white crystalline solid, mp 102 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62−7.29 (14H, m), 4.37 (1H, m), 4.31 (1H, m), 3.83 (1H, dd, J = 3, 11 Hz), 3.81 (1H, dd, J = 3, 11 Hz), 2.59 (1H, dd, J = 7, 18 Hz), 2.47 (1H, dd, J = 3, 18), 2.41 (3H, s), 1.02 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.2, 144.6, 135.5, 132.6, 130.4, 130.0, 128.1, 127.9, 84.3, 70.0, 67.7, 38.1, 26.7, 21.6, 18.9. Anal. Calcd for $C_{28}H_{32}O_6SSi$: C, 64.09; H, 6.15. Found: C, 64.10; H, 6.27.

(3*S*)-3-*tert*-Butyldiphenylsilyloxypent-4-enoic Acid, 2. A solution of **10** (5.00 g, 9.53 mmol) and sodium iodide (3.57 g, 23.8 mmol, 2.5 equiv) in anhydrous DMSO (45 mL) were heated at 60 °C for 18 h. The mixture was cooled to room temperature whereupon zinc flake (1.71 g, 26.2 mmol, 2.7 equiv) was added and stirring was continued for 1.5 h at room temperature. The mixture was filtered into a flask containing water (100 mL) and 1 N HCl (25 mL) with stirring. The contents of the flask were rinsed into a separatory funnel with dichloromethane (75 mL). The organic layer was separated and washed with water (2 × 50 mL). Removal of solvent at reduced pressure and drying in high vacuum afforded **2** (3.35 g, 99%) as a yellow oil. $[\alpha]^{25}_D$ −11.2 (*c* 1.00, $CHCl_3$) {lit.[4] $[\alpha]^{28}_D$ −10.0 (*c* 0.6, $CHCl_3$)}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71−7.62 (4H, m), 7.48−7.30 (6H, m), 5.83 (1H, ddd, J = 17, 10, 6 Hz), 4.98 (1H, d, J = 17 Hz), 4.94 (1H, d, J = 10 Hz), 4.57 (1H, apparent q, J = 6 Hz), 2.56 (1H, d, J = 7, 3 Hz), 2.42 (1H, d, J = 7, 3 Hz), 1.05 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.4, 139.2, 136.0. 133.6, 130.0, 127.8, 116.0, 71.4, 43.6, 27.3, 19.9. Anal. Calcd for $C_{21}H_{26}O_3Si$: C, 71.14; H, 7.39. Found: C, 69.80; H, 7.44.

(3*S*)-*N*-Methyl-*N*-methoxy-3-*tert*-butyldiphenylsilyloxypent-4-enamide, 12. A flask was charged with **2** (3.35 g, 9.45 g) and (*N*,*O*)-dimethylhydroxylamine hydrochloride (1.84 g, 18.9 mmol, 2 equiv). A solution of triethylamine (3.82 g, 37.8 mmol, 4 equiv) in anhydrous acetonitrile (35 mL) was added. The coupling agent T3P[16] was added as the commercially available 50% solution in ethyl acetate (12.0 g, 18.9 mmol) and the weighing vessel was rinsed in with additional acetonitrile (12 mL). The mixture was stirred for 23 h at room temperature and rinsed into a separatory funnel with water (75 mL) and ethyl acetate (75 mL). The organic layer was separated and washed with 10% citric acid (100 mL) and finally with water (50 mL). After removal of the solvent at reduced pressure, the residue was purified by flash chromatography with 80:20 heptane/diethyl ether as eluant to afford **12** (3.02 g, 77%) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75−7.63 (6H, m), 7.45−7.30 (4H, m), 5.89 (1H, ddd, J = 17, 10, 6 Hz), 5.03 (1H, d, J = 17 Hz), 4.93 (1H, d, J = 10 Hz), 4.74 (1H, m), 3.54 (3H, s), 3.08 (3H, s), 2.79 (1H, m), 2.52 (1H, m), 1.07 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2, 139.9, 135.9, 134.0, 129.5, 127.3, 114.8, 71.5, 61.1, 40.6, 31.8, 26.9. 19.2. Anal. Calcd for $C_{23}H_{31}NO_3Si$: C, 69.48; H, 7.86; N, 3.52. Found: C, 69.56; H, 7.91; N, 3.33.

2,5-Dideoxy-1-*O*-methyl-3-*O*-*tert*-butyldimethylsilyl-5-iodo-D-ribofuranose, 15. The C3-unprotected iodide **14** was first prepared following the procedure of Madsen.[20] A solution of **6** (5.00 g, 33.7 mmol), triphenylphosphine (13.3 g, 50.6 mmol, 1.5 equiv), imidazole (4.60 g, 67.5 mmol, 2 equiv), and iodine (13.0 g, 50.6 mmol, 1.5 equiv) in anhydrous THF (100 mL) was stirred overnight at room temperature. A white precipitate of imidazole hydroiodide was formed, which was filtered off by using a bed of Celite 545. The filtrate was dried on 10 g of silica gel and purified by flash chromatography, using 70:30 hexanes/ethyl acetate as eluant. Evaporation of the solvents afforded **14** (7.1 g, 81%) as a colorless oil. NMR data matched those in the literature for the mixed α and β anomers.[15b] ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.07 (1H, s), 4.39 (0.5H, m), 4.03 (1.5H, m), 3.33 (3H, m), 3.19 (1H, m), 3.14 (1H, m), 2.96 (1H, br), 2.22 (1H, m), 2.05 (0.5H, m), 1.95 (0.5H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 105.6, 105.3, 85.9, 85.7, 75.5, 75.4, 55.2, 54.9, 41.7, 40.8, 7.8, 6.7.

A solution of **14** (6.35 g, 24.6 mmol) in anhydrous DMF (100 mL) was cooled to 10 °C in an ice bath. To the cold solution was added imidazole (2.0 g, 29.5 mmol, 1.2 equiv). A 1.0 M solution of *tert*-butyldimethylsilyl chloride in dichloromethane (24.6 mL, 1.0 equiv) was slowly added to the cold solution with use of a syringe. The reaction mixture was stirred overnight at room temperature. Heptane (100 mL) was added and the mixture was washed with water (3 × 100 mL) and brine (100 mL). The organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure affording **15** (8.0 g, 87%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): 5.01 (0.5H, dd, J = 2, 5 Hz), 4.91 (0.5H, dd, J = 3, 5 Hz), 4.27 (0.5H, m), 3.86 (1H, m), 3.49 (0.5H, m), 3.39 (0.5H, dd, J = 4, 10 Hz), 3.31 (1.5H, s), 3.28 (1.5H, s), 3.22−3.14 (1.5H, overlapping m), 2.38 (0.5 H, m), 2.11 (0.5H, m), 2.00 (0.5H, m), 1.76 (0.5H, m), 0.78 (9H, s), 0.02 (1.5H, s), 0.00 (3H, s), −0.01 (1.5H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 105.2, 104.4, 85.8, 80.5, 75.5, 75.1, 55.2, 42.5, 41.9, 25.7, 17.9, 7.8, 7.7, −4.55, −4.65. Anal. Calcd for $C_{12}H_{25}IO_3Si$: C, 38.71; H, 6.77. Found: C, 38.46; H, 6.59.

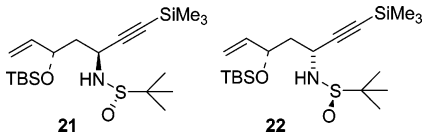
(3*S*)-3-*tert*-Butyldimethylsilyloxy-pent-4-enal, 3. Generation of anhydrous $CrCl_2$ solution was found to be more facile with use of commercial chromium(III) chloride tris(tetrahydrofuran) complex[34] rather than unsolvated $CrCl_3$, which is slow to dissolve and sometimes requires heating. A flask was charged with $CrCl_3$·3THF (4.45 g, 11.9 mmol) and zinc flakes (3.34 g, 51.1 mmol) and was thoroughly flushed with nitrogen. Anhydrous THF (60 mL) was added and the mixture was stirred 30 min during which time the solution changed color from violet to pale blue. A solution of **15** (3.47 g, 9.32 mmol) in THF (10 mL) was gradually added over the course of 10 min with use of a syringe. After 24 h the mixture

(33) Attempting to dry a CH_2Cl_2 solution of commercial MCPBA with 4A molecular sieves results in its conversion to dibenzoyl peroxide. If a greater level of dryness is desired beyond that described in the text, we recommend drying commercial MCPBA in high vacuum at room temperature for a period of 1 to 2 h.

(34) Alternatively, $CrCl_3$·3THF can be prepared by a straightforward literature procedure: Kern, R. J. *J. Inorg. Nucl. Chem.* **1962**, *24*, 1105.

was filtered through a 1 cm bed of Celite into a flask containing a stirred mixture of water (135 mL) and 1 N HCl (15 mL). The product was extracted into hexanes (50 mL) and was washed with water (50 mL) and dried ($MgSO_4$). Removal of the solvent at reduced pressure gave the product, which was purified by flash chromatography affording **3** (1.66 g, 83%) as a colorless liquid. $[\alpha]^{25}_D$ −3.2 (*c* 2.0, $CHCl_3$) {lit.[7] for (3*R*)-enantiomer $[\alpha]^{25}_D$ +3.0 (*c* 2.58, $CHCl_3$)}. ^{1}H NMR (400 MHz, CD_2Cl_2): δ 9.69 (1H, br t, J = 2.4 Hz), 5.82 (1H, ddd, J = 5.7, 10.5, 17.0 Hz), 5.21 (1H, dt, J = 1.3, 17.0 Hz), 5.05 (1H, dt, J = 1.3, 10.5 Hz), 4.60 (1H, br q, J = 5 Hz), 2.57 (1H, ddd, J = 2.6, 6.5, 15.6 Hz), 2.49 (1H, ddd, J = 2.0, 4.9, 15.6 Hz), 0.86 (9H, s), 0.02 (3H, s), 0.01 (3H, s). ^{13}C NMR (100 MHz, CD_2Cl_2): δ 202.3, 140.8, 115.5, 170.1, 51.8, 26.6, 18.7, −4.55, −4.65. Anal. Calcd for $C_{11}H_{22}O_2Si$: C, 61.63; H, 10.34. Found: C, 61.67; H, 10.37.

The optical purity of **3** was further confirmed by separate conversion into the diastereomeric propargylic sulfinamides **21** and **22**, using the Ellman chiral auxiliary[35] and the improved protocol for acetylide addition reported by Hou and co-workers.[36] (See the Supporting Information for details.)



2,5-Dideoxy-1-*O*-methyl-5-azido-D-ribofuranose, 16. Following the literature procedure,[25] sodium azide (5.86 g, 90.2 mmol, 4 equiv) and tetrabutylammonium iodide (0.50 g, 1.4 mmol, 0.06 equiv) were added to a solution of **8**[24] (6.81 g, 22.5 mmol) in anhydrous DMF (50 mL). The mixture was stirred for 36 h at 80 °C and after cooling was added to ethyl acetate (50 mL) and heptane (50 mL). The resulting organic phase was extracted with water (100 mL then 50 mL) and was dried (Na_2SO_4). Removal of the solvent at reduced pressure afforded **16** (3.27 g, 78%) as a 1:1 mixture of α and β anomers, which was purified by flash chromatography in 70:30 hexanes/ethyl acetate. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.07 (0.5H, dd, J = 4, 10 Hz), 5.02 (0.5H, dd, J = 4, 13 Hz), 4.11 (0.5H, m), 4.05 (0.5H, m), 3.91 (0.5H, m), 3.41−3.18 (2H, m), 3.32 (1.5H, s), 3.29 (1.5H, s), 2.97 (1H, br), 2.14 (1H, m), 1.95 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 105.3, 85.3, 84.5, 73.1, 72.6, 55.2, 54.8, 53.6, 52.4, 41.4, 41.1.

(3*R*,4*S*)-1-*tert*-Butoxycarbonyl-3,4-dihydroxypiperidine, 4. Lactol **17** was first released following the general literature precedent.[25a] A mixture of **16** (3.50 g, 20.2 mmol), water[37] (100 mL), and Amberlyst 15 resin (10 g) was stirred 4 h at room temperature. After filtration the mixture was stirred briefly with Amberlyst 21 (5.0 g) to scavenge any traces of acid and was re-filtered. Silica was added to the resulting solution and water was removed at reduced pressure keeping the temperature below 50 °C. The product was then eluted with 92:8 dichloromethane/methanol to afford **17** (2.10 g, 65%) as an amber oil, which was immediately carried on to the next step.

A Fischer−Porter tube was charged with a solution of crude **17** (2.43 g, 15.3 mmol) in anhydrous ethanol (75 mL). After adding 5% palladium on carbon catalyst (1.00 g), the system was flushed with hydrogen and stirred under 60 psi H_2 for 24 h at room temperature. The solution was filtered and a solution of di-*tert*-butyl dicarbonate (3.06 g, 14 mmol) in ethanol (10 mL) was added dropwise with stirring. After 48 h, any excess $(Boc)_2O$ was destroyed by addition of triethylamine (1.01 g, 10 mmol) and taurine (1.25 g, 10 mmol) and the mixture was again stirred overnight. The mixture was filtered to remove some undissolved taurine and the solvent was distilled at reduced pressure. The residue was taken up in dichloromethane (25 mL) and was washed with water (10 mL). Distillation of the solvent afforded **4** (2.53 g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.65−2.97 (8H, overlapping br m), 1.52 (1H, br m), 1.34 (1H, br m), 1.15 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.8, 80.3, 68.8, 68.3, 45.9 (br), 40.6 (br), 29.9, 28.9. Anal. Calcd for $C_{10}H_{19}NO_4$: C, 55.28; H, 8.81; N, 6.45. Found: C, 55.13; H, 8.70; N, 6.38.

(3*R*,4*R*)-1-*tert*-Butoxycarbonyl-3-acetoxy-4-chloropiperidine, 20. A solution of 1-chlorocarbonyl-1-methylethyl acetate (1.05 g, 6.38 mmol, 1.2 equiv) in dichloromethane (5 mL) was added dropwise with stirring to a solution of **4** (1.16 g, 5.34 mmol) in dichloromethane (10 mL). The mixture was stirred an additional 1 h at room temperature whereupon saturated $NaHCO_3$ solution (15 mL) was added and stirring was continued an additional 15 min. The organic layer was separated, washed with water (10 mL), and dried ($MgSO_4$). After removal of the solvent, the residue was purified by flash chromatography to afford **20** (1.23 g, 83%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.80 (1H, m), 4.09 (1H, m), 3.76 (d, J = 13.8 Hz), 3.6−3.4 (3H, overlapping m), 2.23 (1H, m), 2.09 (3H, s), 1.82 (1H, m), 1.47 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 155.0, 80.4, 71.2 (br), 57.0, 44.1 (br), 40.5 (br), 31.5, 28.7, 21.7. To avoid complications from carbamate rotamers, 2D NMR studies were carried out in DMSO-d_6 at 100 °C. (See the Supporting Information.) Anal. Calcd for $C_{12}H_{20}ClNO_4$: C, 51.89; H, 7.26. Found: C, 51.78; H, 7.29.

(3*R*,4*S*)-1-*tert*-Butoxycarbonyl-3,4-epoxypiperidine, 5. A solution of potassium carbonate (1.93 g, 14.0 mmol, 3 equiv) in water (2.5 mL) was added to a solution of **20** (1.30 g, 4.68 mmol) in methanol (25 mL). The heterogeneous mixture was stirred for 2 h at room temperature and was then filtered. The filtrate was diluted with water (75 mL) and the product was extracted into chloroform (2 × 25 mL). The organic phase was washed with water (10 mL) and solvent was distilled at reduced pressure to afford **5** (0.82 g, 4.1 mmol, 88%) as a pale yellow oil. As expected, several NMR resonances are broad (and the C2 and C6 resonances in the ^{13}C spectrum are bifurcate) due to carbamate rotamers. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.00−3.08 (6H, overlapping m), 2.02 (1H, br s), 1.94 (1H, br s), 1.46 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.2, 80.1, 51.0, 50.6 (br), 42.9 and 42.3 (br), 38.0 and 36.9 (br), 28.9, 24.8. Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.41; H, 8.82; N, 6.95.

The enantiomeric excess of the product was shown to be >99% by chiral capillary column gas chromatography (Rt-bDEXsm column, J&W Scientific, 30 m × 0.25 mm i.d., 0.25 μm film, flow rate 40 cm/s, programmed from 110 to 220 °C at 20 deg min^{-1}). Retention times for the enantiomers were established to be 24.3 min for (3*S*,4*R*)-**5** and 25.4 min for (3*R*,4*S*)-**5** by comparison with a sample of authentic racemate prepared by the literature procedure.[30b] Sample chromatograms are given in the Supporting Information.

Acknowledgment. The authors thank Ms. Shirley Wong for chiral gas chromatographic analyses and Ms. Sarah Traeger for 2D NMR studies.

Supporting Information Available: Synthetic details for compounds **11**, **21**, and **22** and freebase of compound **4**, 2D NMR studies on **20**, chiral gas chromatographic analysis of **5**, DTC analysis of **10** and **22**, and ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(37) We find that the use of organic co-solvents diminishes the yield of **17**.