Synthesis of 2′,3′-Didehydro-2′,3′-dideoxynucleosides by Reaction of 5′-*O*-Protected Nucleoside 2′,3′-Dimesylates with Lithium Areneselenolates

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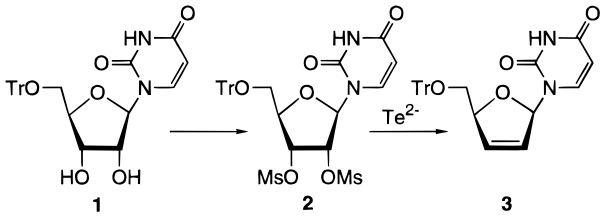
Introduction

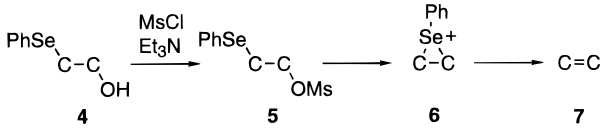
Conversion of nucleosides into their 2′,3′-didehydro-2′,3′-dideoxy derivatives is currently an important topic in medicinal chemistry because the deoxygenated compounds or their hydrogenation products (2′,3′-dideoxynucleosides) have been found, in certain cases, to inhibit the progress of HIV infection.[1] We have recently reported that conversion of 5′-*O*-protected nucleosides into the corresponding 2′,3′-dimesylates, followed by treatment with Te^{2-}, constitutes an effective method for deoxygenation (Scheme 1, **1** → **2** → **3**).[2] During the course of our work, we wondered whether the same transformation could also be accomplished by treating the dimesylates with $ArSe^-$.[3] This possibility was based on the fact that compounds of partial structure **4** afford olefins when the hydroxyl function is converted into a good leaving group (e.g., OMs), as shown in Scheme 2.[4] In principle, the proposed intermediates (**5** and **6**) should also be accessible by displacement of a single mesyloxy group from a vicinal dimesylate (Scheme 3). We have now tested the process summarized by Scheme 3 and describe a number of examples (see Table 1) where it represents a convenient route to olefins of the nucleoside series.

Each of the four nucleoside dimesylates examined (see Table 1) was converted into the corresponding olefin on treatment with $PhSe^-Li^+$ (⩾2 mol per mole of dimesylate) in refluxing THF, the selenide anion being generated from diphenyl diselenide and Et_3BHLi.[5,6] The sugar-

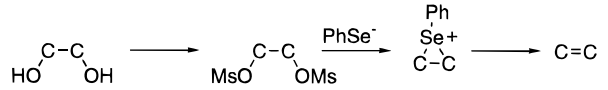
Scheme 1



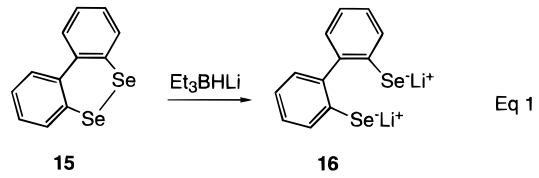
Scheme 2



Scheme 3



derived dimesylate **12a** likewise afforded olefin, but the primary−secondary dimesylates **13a** and **14a** behaved in a different way. The former gave a very low yield (38%)[7] of olefin under our standard conditions with $PhSe^-Li^+$, but reacted efficiently with the aryl selenide dianion **16**, prepared as shown in eq 1. This dianion was



tried in order to determine if a cyclic bis(selenide) would form and then collapse[8] to olefin, but this mode of action was not verified, since **16** did not prove to be a general reagent. In the case of the reaction between **13a** and **16**, 1 mol of the reagent precursor (**15**[9]) was used per mole of dimesylate. The other sugar-derived dimesylate **14a** failed to give olefin with $PhSe^-Li^+$, and when we tried the hindered selenide **17**,[10] both mesyloxy groups of **14a** were displaced by the selenide (^{1}H NMR), with little, if any, of the desired olefin being formed. This last experiment with **17** was done in an attempt to restrict dis-

(1) For a review on AIDS-driven nucleoside chemistry, see: Huryn, D. M.; Okabe, M. *Chem. Rev.* **1992**, *92*, 1745.

(2) Clive, D. L. J.; Wickens, P. L.; Sgarbi, P. W. M. *J. Org. Chem.* **1996**, *61*, 7426.

(3) Simple vicinal dimesylates have been converted into olefins by the action of an iodide ion, but this method does not appear to be useful in the nucleoside series, at least, as judged by a test case we examined (see ref 2).

(4) (a) Reich, H. J.; Chow, F.; Shah, S. K. *J. Am. Chem. Soc.* **1979**, *101*, 6638. (b) Clive, D. L. J.; Russell, C. G.; Suri, S. C. *J. Org. Chem.* **1982**, *47*, 1632. (c) Rémion, J.; Dumont, W.; Krief, A. *Tetrahedron Lett.* **1976**, *17*, 1385. (d) Rémion, J.; Krief, A. *Tetrahedron Lett.* **1976**, *17*, 3743.

(5) We did not establish whether the liberated Et_3B plays any role in the reaction. cf. Dittmer, D. C.; Zhang, Y.; Discordia, R. P. *J. Org. Chem.* **1994**, *59*, 1004.

(6) Gladysz, J. A.; Hornby, J. L.; Garbe, J. E. *J. Org. Chem.* **1978**, *43*, 1204.

(7) A significant byproduct was the result of displacement of both OMs groups by PhSe (see Experimental Section).

(8) For examples of vicinal bis(phenyl selenides) that collapse spontaneously to olefins, see: Piettre, S.; Janousek, Z.; Merenyi, R.; Viehe, H. G. *Tetrahedron* **1985**, *41*, 2527. In the case of 1,2-bis(methylseleno) compounds, chromatography over silica gel causes decomposition to dimethyl diselenide and the corresponding olefin: Hermans, B.; Colard, N.; Hevesi, L. *Tetrahedron Lett.* **1992**, *33*, 4629. cf. Gulliver, D. J.; Hope, E. G.; Levason, W.; Murray, S. G.; Potter, D. M.; Marshall, G. L. *J. Chem. Soc., Perkin Trans. 2* **1984**, 429. Batchelor, R. J.; Einstein, F. W. B.; Gay, I. D.; Gu, J.-H.; Johnston, B. D.; Pinto, B. M. *J. Am. Chem. Soc.* **1989**, *111*, 6582.

(9) Murata, S.; Suzuki, T.; Yanagisawa, A.; Suga, S. *J. Heterocycl. Chem.* **1991**, *28*, 433.

(10) Made from the corresponding diselenide (Kuwajima, I.; Shimizu, M.; Urabe, H. *J. Org. Chem.* **1982**, *47*, 837) by treatment with Et_3BHLi (cf. ref 6).

(11) Generated from the corresponding ditelluride (ref 12) by treatment with $NaBH_4$ in EtOH.

(12) Morgan, G. T.; Kellett, R. E. *J. Chem. Soc.* **1926**, 1080.

(13) Generated from the corresponding ditelluride (ref 14) by treatment with $NaBH_4$ in EtOH.

(14) Morgan, G. T.; Drew, H. D. K. *J. Chem. Soc.* **1925**, 2307.

(15) A THF solution of the selenol acid (Kamiyama, T.; Enomoto, S.; Inoue, M. *Chem. Pharm. Bull.* **1985**, *33*, 5184) was added to a suspension of NaH (2.1 mole of per mol selenol acid). The suspension was stirred for 5 min and was then transferred by cannula into a solution of **13a** (1 mol) in THF. No change was detected (TLC) after 24 h.

(16) Bis[2-(hydroxymethyl)phenyl] diselenide was made by reduction ($LiAlH_4$) of the selenol acid corresponding to **20**, followed by aerial oxidation. The diselenide [FTIR (CH_2Cl_2 cast) 3310 (broad), 747 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.7−7.1 (m, 16 H), 4.70 (s, 4 H), 2.2−1.8 (br s, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 137.0 (s′), 133.4 (d′), 131.3 (d′), 130.1 (d′), 128.0 (d′), 124.5 (s′), 33.4 (t′); exact mass *m*/*z* calcd for $C_{14}H_{14}O_2{}^{80}Se_2$ 373.93243, found 373.93374] was reduced *in situ* (Et_3BHLi).

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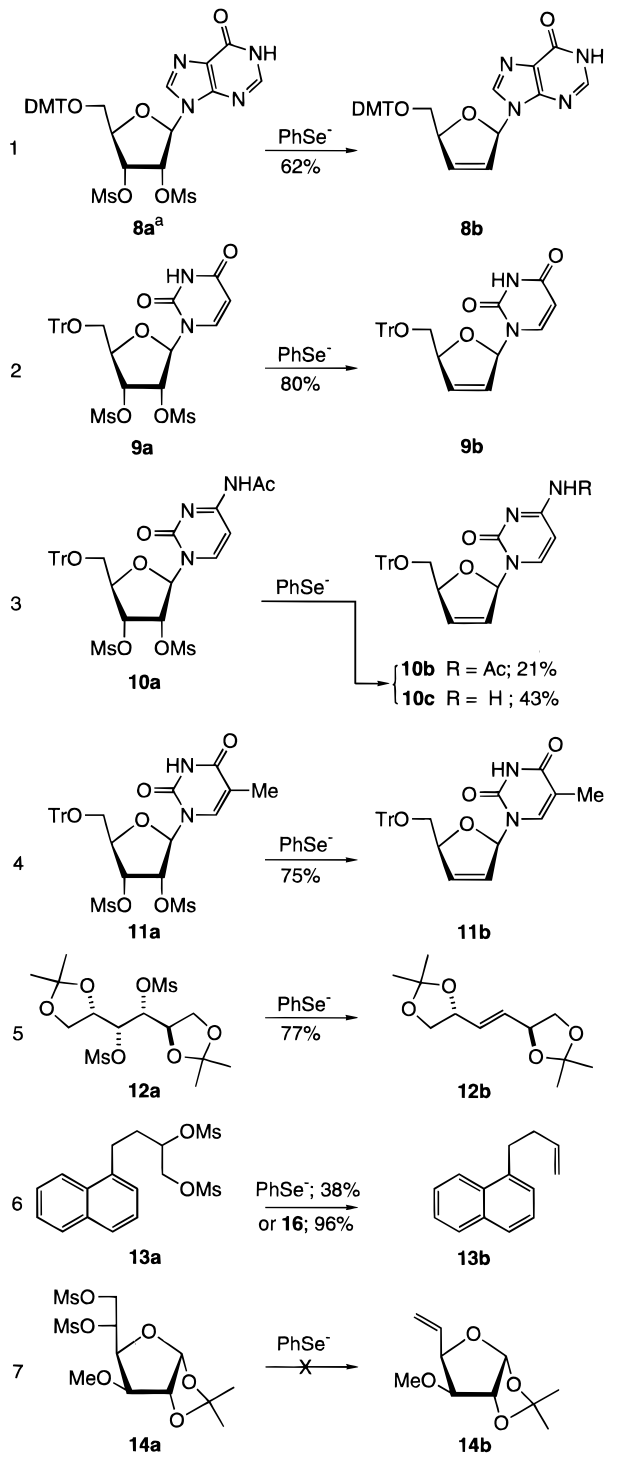
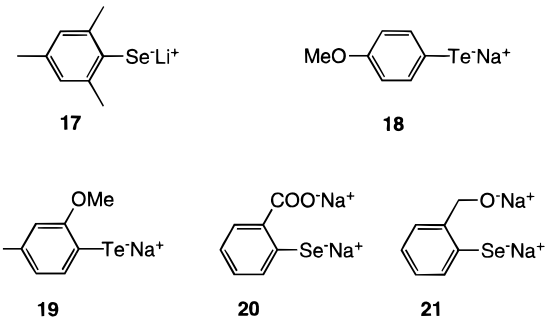
Table 1



[a]DMT = dimethoxytrityl, i.e., bis(4-methoxyphenyl)phenylmethyl

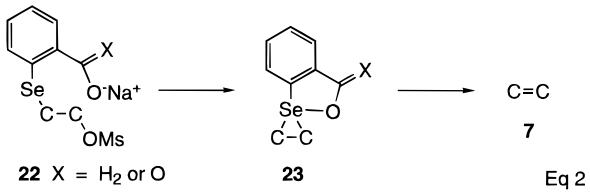
placement to just a single mesyloxy function on the basis of steric factors inherent in the reagent, as opposed to the substrate.[8] It is not clear why the two primary−secondary dimesylates (**13a** and **14a**) behave differently from the others, but all of the secondary−secondary dimesylates are converted into olefins under our standard conditions.

We also examined aryl tellurides **18**[11] and (more extensively) **19**,[13] but found that yields (using dimesylate **9a**, as a test case) were significantly lower than those with the selenium reagent; however, treatment of **13a** with **19** afforded olefin **13b** in 95% yield, and in this case,



use of a catalytic amount of the ditelluride corresponding to **19**, with a stoichiometric amount of $NaBH_4$, also led to olefin in good yield (*ca.* 89%).

Finally, we made a cursory examination of the selenide anions **20**[15] and **21**[16] in order to see if the intramolecular processes **22** → **23** (eq 2) might occur and facilitate the deoxygenation. However, with dimesylate **13a** again as the test case, deoxygenation did not occur, at least to any noticeable extent with either of these reagents.



In summary, $PhSe^-Li^+$ converts secondary−secondary vicinal dimesylates of the nucleoside series into the corresponding dideoxy didehydro derivatives.

Experimental Section

General Procedures. The same general procedures as used previously[2] were followed.

5′-*O*-[Bis(4-methoxyphenyl)phenylmethyl]-2′,3′-didehydro-2′,3′-dideoxyinosine (8b). General Procedure. Et_3BHLi (1 M in THF, 0.52 mL, 0.52 mmol) was added dropwise by syringe to a stirred solution of PhSeSePh (79.7 mg, 0.255 mmol) in THF (1 mL) (Ar atmosphere). At the end of the addition a colorless solution had formed, and then **8a**[2] (72.6 mg, 0.255 mmol) in THF (1.5 mL) was injected, followed by Et_3N (0.5 mL) and HMPA (40 μL). The solution was refluxed and stirred for 20 h, and then it was cooled and evaporated at room temperature. Flash chromatography of the residue over silica gel (1 × 25 cm), using 5% MeOH−CH_2Cl_2, gave **8b**[2] (33.2 mg, 62%), which was identical to an authentic sample and, like that sample,[2] contained slight impurities (^{1}H NMR, 300 MHz).

2′,3′-Didehydro-2′,3′-dideoxy-5′-*O*-(triphenylmethyl)uridine (9b). The general procedure was followed, using Et_3BHLi (1.0 M in THF, 1.1 mL, 1.1 mmol), PhSeSePh (155.5 mg, 0.498 mmol) in THF (2.5 mL), dimesylate **9a**[2] (128.2 mg, 0.200 mmol) in THF (2.5 mL), Et_3N (1.0 mL), HMPA (40 μL), and a reflux period of 12 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 × 15 cm), using 1% MeOH−CH_2Cl_2 and then 2% MeOH−CH_2Cl_2, gave **9b**[2,17] (72.6 mg, 80% yield) as a white solid: mp 190−192 °C (lit.[17] mp 188−191 °C).

***N*-Acetyl-2′,3′-didehydro-2′,3′-dideoxy-5′-*O*-(triphenylmethyl)cytidine (10b) and 2′,3′-Didehydro-2′,3′-dideoxy-5′-*O*-(triphenylmethyl)cytidine (10c).** Et_3BHLi (1.0 M in THF, 0.73 mL, 0.73 mmol) was added dropwise by syringe to a stirred solution of PhSeSePh (114.3 mg, 0.366 mmol) in THF (1 mL) (Ar atmosphere). At the end of the addition a colorless solution had formed. This was taken up into a syringe and added dropwise to a stirred solution of **10a**[2] (104.6 mg, 0.153 mmol) in

(17) Mansuri, M. M.; Starrett, J. E., Jr.; Wos, J. A.; Tortolani, D. R.; Brodfuehrer, P. R.; Howell, H. G.; Martin, J. C. *J. Org. Chem.* **1989**, *54*, 4780.

THF (1.5 mL) (Ar atmosphere). Then Et_3N (0.5 mL) and HMPA (*ca.* 40 μL) were injected, and the solution was stirred and refluxed for 22 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 × 18 cm), using 7.5% MeOH−CH_2Cl_2, gave **10b**[2] (15.7 mg, 21%) along with 2′,3′-dideoxy-2,3-didehydro-5′-*O*-(triphenylmethyl)cytidine (**10c**) (30.0 mg, ca. 43%), which was not obtained pure: FTIR (CH_2Cl_2 cast) 3500−3100 (broad) cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 7.6 (d, J = 7 Hz, 1 H), 7.4−7.1 (m, 16 H), 6.9 (s, 1 H), 6.2 (d, J = 6 Hz, 1 H), 5.8 (d, J = 6 Hz, 1 H), 4.9 (br s, 1 H), 3.4−3.1 (m, 2 H); ^{13}C (CD_2Cl_2, 75.5 MHz) δ 166.31 (s′), 156.39 (s′), 143.90 (s′), 142.38 (d′), 133.53 (d′), 129.08 (d′), 128.28 (d′), 127.73 (d′), 127.59 (d′), 94.85 (d′), 91.01 (d′), 87.43 (s′), 86.03 (d′), 65.48 (t′). The mass spectrum (EI) was uninformative, as the highest mass peak corresponded to Ph_3C.

2′,3′-Didehydro-2′,3′-dideoxy-5-methyl-5′-*O*-(triphenylmethyl)uridine (11b). The general procedure was followed, using Et_3BHLi (1.0 M in THF, 0.49 mL, 0.49 mmol), PhSeSePh (76.9 mg, 0.246 mmol) in THF (1 mL), dimesylate **11a**[2,18] (64.7 mg, 0.0985 mmol) in THF (1.5 mL), Et_3N (0.5 mL), HMPA (*ca.* 20 μL), and a reflux period of 12 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 × 20 cm), using 2% MeOH−CH_2Cl_2, gave **11b**[2,19] (34.5 mg, 75%) as a white solid: mp 105−109 °C (lit.[19] mp 107−111 °C).

(*E*)-3,4-Dideoxy-1,2:5,6-di-*O*-isopropylidene-*erythro*-3(*E*)-hex-3-enitol (12b). The general procedure was followed, using Et_3BHLi (1 M in THF, 0.94 mL, 0.94 mmol), PhSeSePh (143.6 mg, 0.460 mmol) in THF (1.5 mL), dimesylate **12a**[20] (76.9 mg, 0.184 mmol) in THF (1.5 mL), Et_3N (0.92 mL), HMPA (40 μL), and a reflux period of 17 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (2.5 × 20 cm), using 25% EtOAc−hexane, gave **12b**[2,21] (32.3 mg, 77%) as a white solid: mp 69−70 °C (lit.[21] mp 69−71 °C).

1-(3-Butenyl)naphthalene (13b). Use of Diselenin 16. Et_3BHLi (1 M in THF, 0.23 mL, 0.23 mmol) was added dropwise by syringe to a stirred solution of dibenzo[*c*,*e*][1,2]diselenin (**15**)[9] (33.3 mg, 0.107 mmol) in THF (5 mL) (Ar atmosphere). At the end of the addition a colorless solution had formed. Dimesylate **13a**[2] (40.0 mg, 0.1074 mmol) in THF (0.82 mL) was then injected dropwise; the solution was stirred at room temperature for 18 h and then evaporated at room temperature. Flash chromatography of the hexane-soluble portion of the residue over silica gel (2.0 × 15 cm), using hexane, gave **13b**[22] (19.6 mg, 100%), spectroscopically identical with an authentic sample,[22] and allowed recovery of dibenzo[*c*,*e*][1,2]diselenin (30.4 mg, 91%).

1-(3-Butenyl)naphthalene (13b). Use of PhSe$^-$Li$^+$. The general procedure was followed, using Et_3BHLi (1.0 M in THF, 0.2 mL, 0.2 mmol), PhSeSePh (31.2 mg, 0.100 mmol) in THF (1 mL), dimesylate **13a**[2] (37.3 mg, 0.100 mmol) in THF (1.5 mL), Et_3N (0.5 mL), HMPA (40 μL), and a reaction time of 12 h at room temperature. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 × 15 cm), using petroleum ether, gave **13b**[22] (7.0 mg, 38%). The byproduct of this reaction was isolated (59%) and identified as the bis(phenyl selenide) corresponding to displacement of both OMs groups: FTIR (CH_2Cl_2, cast) 3067, 3054, 2925, 1476, 1436, 735, 690 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 8.09 (m, 1 H), 7.88 (m, 1 H), 7.73 (d, J = 7.2 Hz, 1 H), 7.09−7.60 (m, 14 H), 3.5−3.0 (m, 5 H), 2.51 (m, 1 H), 1.99 (m, 1 H); ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 138.01, 135.08, 134.37, 133.56, 132.25, 129.87, 129.51, 129.40, 129.12, 129.05, 128.15, 128.03, 127.41, 127.10, 126.62, 126.20, 125.88, 124.27, 45.01, 35.18, 34.94, 31.33; mass (CI) m/z calcd $C_{26}H_{24}{}^{80}Se_2$ (M + NH_3) 513.0, found 513.4.

1-(3-Butenyl)naphthalene (13b). Use of Tellurium Reagent 19. (a) Stoichiometric Reaction. Bis(2,4-dimethoxyphenyl) ditelluride[14] (0.278 g, 0.525 mmol) was placed in a three-neck round-bottomed flask carrying a side arm addition tube containing $NaBH_4$ (0.182 g, 6.88 mmol). Deoxygenated EtOH (5 mL) was added, and the mixture was stirred and cooled (0 °C). The $NaBH_4$ was added slowly (H_2 evolution) until the orange solution turned clear (Ar atmosphere). After 1 h, the cold bath was removed and stirring was continued for 1 h. Dimesylate **13a**[2] (0.163 g, 0.437 mmol) in THF (2 mL) was then added. After 4 h, CH_2Cl_2 (20 mL) was added, and the solution was evaporated. Addition of CH_2Cl_2 and evaporation was repeated twice more, and the residue was then adsorbed on silica gel (0.5 g) from a little CH_2Cl_2. Flash chromatography over silica gel (3 × 30 cm), using hexane, gave **13b** (0.076 g, 95%), spectroscopically identical to an authentic sample.[22]

(b) Catalytic Reaction. Absolute EtOH (1 mL) was added to bis(2,4-dimethoxyphenyl) ditelluride[14] (0.029 g, 0.056 mmol) in a three-neck round-bottomed flask fitted with a side arm addition tube containing $NaBH_4$ (0.173 g, 4.57 mmol). Dimesylate **13a** (0.161 g, 0.432 mmol) in THF (2 mL) was added, and then the $NaBH_4$ was added over 5−6 h (Ar atmosphere). The mixture was stirred at room temperature for a further 22 h. CH_2Cl_2 (25 mL) was added, and the solvent was evaporated. Addition of CH_2Cl_2 (25 mL) and evaporation was repeated twice more, and the residue was then adsorbed on silica (0.5 g) from a little CH_2Cl_2. Flash chromatography over silica gel (2 × 20 cm), using hexane, gave **13b** (0.070 g, 89%), as a colorless oil, spectroscopically identical to an authentic sample.

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Supporting Information Available: NMR spectra for new compounds that were not analyzed (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(20) Prepared (88% yield) by the reported method (Kuszmann, J.; Sohár, P. *Carbohydr. Res.* **1979**, *74*, 187). The parent diol was prepared (36% yield) according to: Chittenden, G. J. F. *Carbohydr. Res.* **1982**, *108*, 81.

(21) (a) Kuszmann, J.; Sohár, P. *Carbohydr. Res.* **1980**, *83*, 63. (b) Köll, P.; Kopf, J.; Metzger, J. O.; Schwarting, W.; Oelting, M. *Liebigs Ann.* **1987**, 199.

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