6.69 (d, J = 9.8 Hz, 1 H), 6.99 (dm, J_{HF} = 8.6 Hz, 2 H), 7.56 (dm, J_{HF} = 5.4 Hz, 2 H); ^{13}C NMR δ 13.6, 15.0, 19.3, 22.0, 28.5, 28.8, 30.9, 32.9, 35.2, 51.4, 78.0, 96.4, 114.9, 115.1, 123.7, 127.5, 127.6, 131.1, 134.8, 134.9, 160.6, 163.9, 171.5; IR (neat) 2232, 1726 cm^{-1}; mass spectrum m/e (relative intensity) 328 (M^+, 36.5), 269 (61.2), 213 (100), 198 (50.2); exact mass calcd for $C_{21}H_{25}FO_2$ 328.1838, found 328.1849.

Acknowledgment. I thank Dr. Kohei Tamao of Kyoto University for valuable discussion and encouragement and Dr. Yasuhiro Fujiwara of Kyoto Pharmaceutical University for NMR experiments. Also, thanks are due to Sumitomo Chemical Co., Ltd. and Osaka Seiyaku Co., Ltd. for financial support. This research was partially supported by the Scientific Fund of Kyoto Pharmaceutical University.

Registry No. *trans*-**1a**, 52341-32-9; **1a** (Y = CN), 52315-07-8; **1b**, 52918-63-5; **3**, 63142-57-4; **4**, 63142-56-3; **5**, 61976-30-5; **6**, 113830-50-5; **7**, 133575-08-3; **8**, 78479-01-3; **9**, 133472-19-2; **10**, 133472-20-5; 11, 133575-09-4; **12**, 133575-10-7; **13**, 133472-21-6; **14**, 133472-22-7; **15**, 133472-23-8; **16**, 133472-24-9; **17**, 133472-25-0; A, 28557-00-8; B, 89523-62-6; C, 133472-26-1; D, 65960-05-6; E, 133472-27-2; F, 81745-84-8; G, 81745-86-0; $PdCl_2$(dppb), 29964-62-3.

Supplementary Material Available: ^{1}H NMR and ^{13}C NMR spectra for all new compounds (18 pages). Ordering information is given on any current masthead page.

Synthesis of 2,3-*O*-Isopropylidene-D-glyceraldehyde in High Chemical and Optical Purity: Observations on the Development of a Practical Bulk Process

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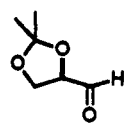
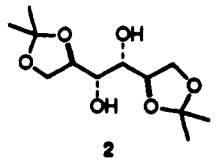
We recently required an expedient, practical synthesis for 2,3-*O*-isopropylidene-D-glyceraldehyde (**1**) that would be readily adaptable to a multiple-kilogram scale. The frequent appearance[1] of this compound in the literature testifies to its importance as a chiral pool material, while the number of reported procedures[2,3] for obtaining this material bear witness to the generally unsatisfactory nature of existing technology for its synthesis. Our involvement with this compound as a starting material in a linear synthesis route required examination and modification of existing chemistries to enable a practical bulk synthesis of this compound. We report here our findings, which represent improvements on existing literature procedures and provide access to **1** of high quality in an efficient and reliable manner.



1

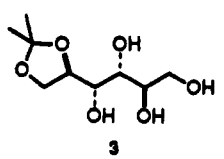


2

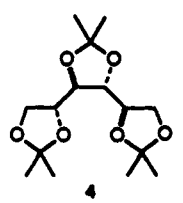
The majority of procedures for obtaining **1** have employed variants of the classic Baer and Fisher preparation dating from the 1930's.[3a] Thus, D-mannitol has been ketalized using a variety of methods[2,3] to provide 1,2:5,6-diisopropylidene-D-mannitol (**2**). The 3,4 glycol linkage of this material was then cleaved, generally with either lead tetraacetate[3a,b] or sodium periodate[3c-j] to provide **1**. Other modifications of this general approach have appeared,[4] as have syntheses of **1** from other source materials;[5] these require additional steps which render them unattractive as candidates for a large-scale process.

Opting for a two-step process from D-mannitol as the most expeditious route to **1**, we examined several of the methods for the synthesis of diacetonide **2**.[2d] We selected the procedure reported by Chittenden, which used catalytic stannous chloride ($SnCl_2$) and 2,2-dimethoxypropane to ketalize D-mannitol in 54–58% recrystallized yield.[2b] The procedure was chosen for its combination of high throughput, low catalyst loads, simple processing, and reproducibility.

Our initial examination of this procedure foreboded several problems for large-scale processing. Attempted recrystallization of the crude **2** from dibutyl ether as per the Chittenden procedure gave gelatinous material requiring large volumes of solvent to enable stirring, thus effectively limiting throughput. Use of other solvents gave similar results. Moreover, the recrystallized material varied in quality and was eventually found to be contaminated with 5–10% of 1,2-monoacetonide **3**,[2c] as determined by ^{1}H NMR (DMSO-d_6). Since the cleavage of **3** would require 3 molar equiv of oxidant to afford **1**, its presence was undesirable. It was found that a simple slurry of the crude reaction material in dichloromethane (CH_2Cl_2), followed by filtration, effectively removed any traces of **3** from the product solution. The other major byproduct, triacetonide **4** (15–20%),[6] did not interfere in the subsequent step and therefore did not require removal.



3



4

In initial experiments, the reaction sometimes failed to go to completion, remaining heterogeneous. It was found that commercial supplies of 1,2-dimethoxyethane (glyme) contained low levels of diphenylamine and isoquinoline, both potentially detrimental to the tin catalyst. Control experiments demonstrated an inhibiting effect for isoquinoline; diphenylamine-spiked reactions showed no aberration. Simple distillation of solvent prior to use,

(1) Review: Jurczak, J.; Pikul, S.; Bauer, T. *Tetrahedron* **1986**, *42*, 447–488.

(2) Syntheses of **2** only: (a) Chittenden, G. J. F. *Carbohydr. Res.* **1980**, *84*, 350–352. (b) *Carbohydr. Res.* **1980**, *87*, 219–226. (c) Debost, J.-L.; Gelas, J.; Horton, D. *J. Org. Chem.* **1983**, *48*, 1381–1382. (d) A comparative study of the methods used in references 2b, 2c, and 3a has appeared: Kuszmann, J.; Tomori, E.; Meerwald, I. *Carbohydr. Res.* **1984**, *128*, 87–99. (e) Kohan, G.; Just, G. *Synthesis* **1974**, 192. (f) Morpain, C.; Nasser, B.; Laude, B.; Latruffe, N. *Org. Prep. Proc. Intl.* **1990**, *22*, 540–543. (g) Tipson, R. S.; Cohen, A. *Carbohydr. Res.* **1968**, *7*, 232–243.

(3) Syntheses of **1** via **2**: (a) Baer, E.; Fisher, H. O. L. *J. Biol. Chem.* **1939**, *128*, 463–473. (b) Kierstead, R. W.; Faraone, A.; Mennona, F.; Mullin, J.; Guthrie, R. W.; Crowley, H.; Simko, B.; Blaber, L. C. *J. Med. Chem.* **1983**, *26*, 1561–1569. (c) LeCocq, J.; Ballou, C. E. *Biochemistry* **1964**, *3*, 976. (d) Golding, B. T.; Ioannou, P. V. *Synthesis* **1977**, 423–424. (e) Baldwin, J. J.; Raab, A. W.; Mensler, K.; Arison, B. H.; McClure, D. E. *J. Org. Chem.* **1978**, *43*, 4876–4878. (f) Eibl, H. *Chem. Phys. Lipids* **1981**, *28*, 1–5. (g) Hirth, G.; Walther, W. *Helv. Chim. Acta* **1985**, *68*, 1863–1871. (h) Takano, S.; Kurotaki, A.; Takahashi, M.; Ogasawara, K. *Synthesis* **1986**, 403–406. (i) Coe, J. W. Ph.D. Thesis, Massachussetts Institute of Technology, 1988. We thank Professor W. R. Roush for providing us with this information. (j) Jackson, D. *Synth. Commun.* **1988**, *18*, 337–341.

(4) Schreiber, S. L.; Satake, K. *Tetrahedron Lett.* **1986**, *27*, 2575–2578.

(5) Mikkilineni, A. B.; Kumar, P.; Abushanab, E. *J. Org. Chem.* **1988**, *53*, 6005–6009.

(6) Kuszmann, J.; Tomori, E. *Carbohydr. Res.* **1982**, *137*, 276–281.

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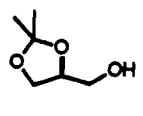
either at atmospheric or reduced pressure, served to remove these impurities.

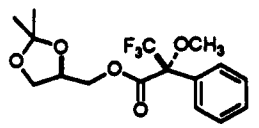
The presence of high levels of residual glyme in the crude diacetonide product was found to be detrimental in the subsequent oxidation step. For small-scale reactions, drying in vacuo was sufficient to reduce glyme to acceptable levels; for large- (1800-L and greater) scale reactions, however, high levels of glyme entrained in product solid proved resistant to removal. It was found that heating the reactor to the point where the solid product mixture liquified (ca. 90 °C) enabled the evaporative removal of glyme to an acceptable level (about equimolar to diacetonide 2).

Attempts at yield improvement from a mean of about 54% proved futile. Adjustments in stoichiometry of the 2,2-dimethoxypropane produced varying amounts of byproducts 3 and 4, but did not affect the overall yield of 2. The distribution of products remained the same for at least 4 h after completion (evidenced by a clear solution); increased levels of triacetonide 4 were observed when the reaction was allowed to proceed for longer periods. Protic acids (methanesulfonic, hydrochloric) catalyzed the reaction, but resulted in formation of substantially higher amounts of triacetonide.

Satisfied with the reproducibility of the modified Chittenden procedure, we turned to the glycol cleavage reaction. From the outset, it was clear that lead tetraacetate oxidation[2a,b] was not viable on large scale; apart from toxicity and waste disposal issues, the process in general was known to proceed in low yield and generated 2 equiv of acetic acid that seriously complicated purification. We examined sodium periodate ($NaIO_4$) as an alternative. While frequently employed to effect the glycol cleavage of 2, the reported reaction conditions did not enable easy isolation of 1 and the crude product was usually reduced in situ to the 2,3-*O*-isopropylidene-D-glycerol (5).[7] We focused on a method recently reported by Jackson that employed heterogeneous sodium periodate (2 equiv) in CH_2Cl_2 containing water (40 wt % relative to 2), which enabled easy isolation of 1 in a reported distilled yield of 91%.[3j]



5



6

Our investigation of the procedure produced several simplifications. It was found that simple filtration of the oxidant and distillation of the filtrate served to adequately dessicate the reaction, eliminating the need for the large amounts of dessicant employed in the original procedure; the small amount of residual water that remained was removed via its azeotrope with CH_2Cl_2. The water employed as cosolvent in the reaction was replaced with an equal volume amount of saturated aqueous sodium bicarbonate when it was determined that formic acid (presumably generated from cleavage of 3) in the distillate was catalyzing polymerization of product. While this effect was pronounced in early runs prior to our discovery of 3 as a contaminant in 2, it persisted even after the slurry removal of 3, suggesting adventitious hydrolysis of 2 (or 4) to 3 under the literature conditions. By use of the bicarbonate modification, formic acid was reduced to an acceptable (<3%) level.

(7) For an example where enantiomeric 1 was extracted and isolated, see: Hubschwerlen, C. *Synthesis* 1986, 962–964.

Attempts to lower the oxidant stoichiometry were also successful. It was found that 2 reacted completely with 1.25 equiv of $NaIO_4$ when the latter was milled and passed through a 140-mesh screen sieve. Optimization studies determined that the highest yield of 1 (72%) could be obtained using 1.4 equiv of oxidant. However, the use of finely milled $NaIO_4$ was unappealing on production scale, and the scale-up of this modification was not attempted. The procedure is included in the Experimental Section.

Yields for the modified oxidation procedure consistently ranged from 66–72% over several orders of magnitude in scale and over the course of numerous laboratory-scale preparations and several multiple hundred kilogram campaigns. Despite the consistency and reliability of this procedure, we have been unsuccessful in duplicating the 91% yield cited in the original paper; by use of these and other modifications, or employing the procedure verbatim, the highest yield to date has been 73%.[17]

Freshly prepared and distilled aldehyde from this procedure exhibited optical rotation values in excess of those reported in the literature; we routinely obtained values in the +73° to +80° range vs a literature range for both enantiomers of 63° to 70°.[8,3a,j] Reduction ($NaBH_4$) of 1 to 5, followed by derivatization as the (*R*)-α-methoxy-α-(trifluoromethyl)-α-phenyl (Mosher)[9] ester 6 showed the material to be enantiomerically pure by ^{19}F NMR within the limits of detection (diastereomer quantification ca. 0.5%, 99% enantiomeric excess (ee)). On large scale, solvent removal and distillation required proportionally longer times than on laboratory scale, typically 12 h from start to finish. Even under these aggressive conditions, material from these runs showed only slight racemization, ranging from >99% to ~93% ee.

The monomeric stability of material from this procedure varied with both distillation and storage conditions. A 5% distillation forerun helped retard the rate of polymerization, as levels of formic acid and other impurities in the product were lowered. The monomer was most stable when it was excluded from moisture and air. Left in the open atmosphere, it polymerized over the course of hours to days; in anhydrous air, the same phenomena was observed over the course of two weeks. Kept under anhydrous nitrogen, the material still polymerized slowly, losing ~30% monomer after 4 weeks. The polymer could be cracked upon redistillation (threshhold temperature ca. 90 °C) to provide monomer in high yield. We were surprised to find that 1 retained its enantiomeric purity under routine laboratory conditions involving repeated distillation and repolymerization; samples distilled from a pot of 1-year-old production material over a 5-week period showed only slight deviation in enantiomeric excess (ee),[10] while redistillation of week-old distillate showed no detectable change in ee. In light of these findings, we at-

(8) De Wilde, H.; De Clercq, P.; Vandewalle, M. *Tetrahedron Lett.* 1987, *28*, 4757–4758.

(9) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* 1969, *34*, 2543–2549. We substituted NaCl with a catalytic amount of DMF in the preparation of this acid chloride and obtained complete and clean reaction within 16 h. Alcohol 6 was derivatized using 1.5 equiv each of the (*S*)-(+)-Mosher acid chloride (>99.6% ee) and pyridine in dichloromethane (2 mL) on a 40-mg scale.

(10) In fact, an *increase* in enantiomeric excess was observed upon repeated distillation! This phenomenon suggests that cracking of oligomer was slow at this temperature (pot temperature ca. 90 °C) relative to distillation of monomer and that the findings in fact represent an archaeological account of the sample's history. Thus, material which polymerized initially during storage (and was thus protected from opportunistic racemization) was distilled last and was mildly enriched relative to free monomer and material obtained from polymer strand termini (distilling first, but representing material most subject to adventitious racemization). The range was from 3.7% enantiomer (first distillation) to 2.8% (final). Initial material was approximately 27% monomeric by weight.

tribute the observed variance in optical rotation to chemical rather than stereochemical considerations. Literature allegations[11] of the compound's stereochemical instability may stem in part from misinterpretation of previous literature[12] or experience with 1 obtained by other methods.[13]

The use of CH_2Cl_2 as solvent in the oxidation step dovetails well with the use of that same solvent in the purification process for the formation of diacetonide. Thus, the slurry can be the final process for diacetonide purification, and the material held as a solution, or the slurry can be incorporated as a pretreatment of diacetonide prior to the oxidation step. For large-scale work, diacetonide 2 has been treated in both fashions.

This chemistry has been scaled to 7500-L equipment, and multiple hundred-kilogram lots of aldehyde have been produced following essentially the procedure delineated previously with the same yield range observed on 5- and 10-g scale. It thus represents a highly reliable procedure for the synthesis of 2 in reasonable overall yield (34–36%).

Experimental Section[14]

1,2:5,6-Diisopropylidene-D-mannitol (2). To a vessel equipped with overhead agitator and reflux condenser was added D-mannitol (75 g, 0.41 mol), glyme (180 mL, freshly distilled), and 2,2-dimethoxypropane (120 mL, 0.98 mol). To this stirred mixture was added $SnCl_2$ (0.075 g, 0.4 mmol) and the mixture heated to reflux (ca. 74 °C) until a clear solution was obtained (ca. 1 h). The reaction was held at that temperature for 30 min then cooled to ambient temperature, and pyridine (0.09 mL, 1.14 mmol) was added. The solvents were removed in vacuo (6–10 mmHg, contents heated to 80–90 °C), and the residual material was cooled. The yield of 2 may be estimated by ^1H NMR (vs CH_2Cl_2, 32K data points, 6-s relaxation delay, 30° pulse) at this point. The crude material was slurried in CH_2Cl_2 (540 mL) at ambient temp for 1 h and then filtered to provide a solution containing 58 g of 2 (54%) as determined by capillary GC analysis (30 M DB-1, 145 °C vs internal standard dimethyl phthalate). A portion was removed, concentrated, and recrystallized (*n*-butyl ether): mp 121.8–123.4 °C (lit.[2a] mp 118–120 °C); $[\alpha]_D$ = +1.9° (*c* = 1.74, CH_3OH) (lit.[15] $[\alpha]_D$ = +1.9° (*c* = 2, CH_3OH)); ^1H NMR ($CDCl_3$) δ 4.22–4.10 (m, 4 H), 3.98 (dd, 2 H, *J* = 8.4, 5.4 Hz), 3.75 (approx. t, 2 H, *J* = 6.2 Hz), 2.70 (d, 2 H, *J* = 6.7 Hz), 1.42 (s, 3 H), 1.36 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 109.39, 76.22, 71.16, 66.74, 26.72, 25.19; IR (KBr) 3400, 3292, 2980, 2933, 2895, 1386, 1372, 1265, 1212, 1070, 859 cm^{-1}. Anal. Calcd for $C_{12}H_{22}O_6$: C, 54.95; H, 8.45. Found: C, 54.80; H, 8.50.

2,3-*O*-(Isopropylidene)-D-glyceraldehyde (1). Method A. To a vessel equipped with overhead agitator and thermometer was added diacetonide 2 (33 g, 0.13 mol) in CH_2Cl_2 (300–350 mL). Saturated aqueous $NaHCO_3$ (11.9 mL) was then added to the flask, maintaining the temperature at or below 25 °C. Solid $NaIO_4$ (52.8 g, 0.25 mol) was then added over a 20-min period with vigorous agitation and the reaction allowed to proceed for 2 h while the temperature was maintained below 30 °C. The solids were removed by filtration[16] and the filtrate was distilled at atmospheric pressure to a temperature of 55 °C. The residual oil was transferred to a smaller vessel and distilled at 30 mmHg; after a brief forerun, 22 g (67%) of 1 was obtained: bp 72–74 °C (30 mmHg); $[\alpha]_D$ = +80.1° (*c* = 1.534, benzene) (lit.[3j] $[\alpha]_D$ = +63.3° (*c* = 1.25, benzene); ^1H NMR ($CDCl_3$) δ 9.55 (d, 1 H, *J* = 1.8 Hz), 4.25 (m, 1 H), 4.05–3.93 (m, 2 H), 1.42 (s, 3 H), 1.36 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 201.38, 110.79, 79.49, 65.11, 25.84, 24.73; IR (neat): 2990, 2940, 2890, 2820, 1730, 1375, 1250, 1215, 1150, 1070, 840 cm^{-1}; exact mass found 131.0710, calcd for $C_6H_{11}O_3$ $(M + H)^+$ 131.0708.

2,3-*O*-(Isopropylidene)-D-glyceraldehyde (1). Method B. To a vessel equipped with overhead agitator and thermometer was added diacetonide 2 (16.5 g, 60 mmol) in CH_2Cl_2 (150–175 mL) and saturated aqueous $NaHCO_3$ (6 mL). $NaIO_4$ (18.9 g, 84 mmol, 1.4 equiv) that had been sifted through a 140-mesh screen was then added in five portions over 20 min, with vigorous agitation, maintaining the temperature below 25 °C. After being stirred for 2 h, the solution was decanted into a second vessel, and the remaining solids were stirred with additional CH_2Cl_2 (53 mL) for 5 min.[16] This rinse was then combined with the CH_2Cl_2 solution and the solvent removed via atmospheric distillation (still-pot temperature <55 °C). The residual oil was then fractionally distilled (still-pot temperature <135 °C) through a Vigreux column. After a brief forerun at 67–72 °C, distillation provided 2 (12.0 g, 92 mmol, 72%) as an oil: bp 72–74 °C (30 mmHg); $[\alpha]_D$ = +73.1° (*c* = 1.34, benzene). Spectral data as in the previous text. Exact mass found 131.0709, calculated for $C_6H_{11}O_3$ $(M + H)^+$ 131.0708.

Acknowledgment. We are grateful to the engineers and technicians in our pilot plants for able assistance in the successful scale-up of these reactions. It is also a pleasure to acknowledge our colleagues and consultants for many fruitful discussions.

Registry No. 1, 15186-48-8; 2, 1707-77-3; D-mannitol, 69-65-8.

Supplementary Material Available: ^1H NMR spectra for compound 2 prepared by both methods (2 pages). Ordering information is given on any current masthead page.

(11) Jaeger, V.; Wehner, V. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 469–470. Leonard, J.; Mohialdin, S.; Swain, P. A. *Synth. Commun.* **1989**, *19*, 3529–3534. A study of the racemization of 1 under Knoevenagel–Doebner condensation conditions has appeared: Lopez Aparicio, F. J.; Izquierdo Cubero, I.; Portal Olea, M. D. *Carbohydr. Res.* **1983**, *115*, 250–253.

(12) Jung, M. E.; Shaw, T. E. *J. Am. Chem. Soc.* **1980**, *102*, 6304–6311.

(13) While this manuscript was being readied for release, we became aware of independent work within Lilly that confirmed these findings. See: Hertel, L. W.; Grossman, C. S.; Kroin, J. S. *Synth. Commun.* **1991**, *21*, in press.

(14) Melting and boiling points are uncorrected. Proton and carbon NMR spectra were obtained at 300 and 75.5 MHz, respectively, and are referenced to residual protonated solvent or internal TMS. HRMS and combustion analyses were performed by Molecular Structure Research at Eli Lilly and Co.

(15) *Aldrich Catalog Handbook of Fine Chemicals, 1990–1991*; Aldrich Chemical Co., Inc.: Milwaukee, WI, 1990; p 487.

(16) The mixed oxidation state iodate/periodate salts recovered from this procedure show instability that increases with scale. We recommend timely decomposition of the salts in aqueous solution using either sodium thiosulfate or sodium bisulfite for reaction scales larger than 1 mol.

(17) **Note Added in Proof:** More recently, repetition of the Jackson procedure afforded an 84% yield, more consistent with the author's findings, when the $MgSO_4/NaIO_4$ filter cake rinse was performed by careful reslurry in dichloromethane followed by filtration. Thus, while the present optimized procedure avoids the use of large excesses (200 mol % relative to 2) of $MgSO_4$ dessicant and is therefore better suited to large scale, small-scale needs may be better served by including the drying protocol.

Preparation of Noncondensed 2-Substituted 1-Methylimidazoles via Ipso Substitution Reaction on 2-Sulfinyl or 2-Sulfonyl Derivatives of 4,5-Disubstituted 1-Methylimidazoles

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Introduction

Heteroaromatic nucleophilic addition–elimination reactions are commonly recognized in many electron-deficient heterocycles. However, literature reports of this reaction with electron-rich imidazoles and condensed imidazoles are uncommon, with few examples of the former.[1] During the course of our continuing research in the de-

(1) (a) Pozharskii, A. F.; Ganovskii, A. D.; Simonov, A. M. *Russ. Chem. Rev.* **1966**, *36*, 122. (b) Schofield, K.; Grimmett, M. R.; Keene, B. R. T. *Heteroaromatic Nitrogen Compounds, The Azoles*; Cambridge Univ. Press: London, 1976. (c) Grimmett, M. R. *Adv. Heterocycl. Chem.* **1970**, *12*, 103. (d) Grimmett, M. R. *Adv. Heterocycl. Chem.* **1980**, *27*, 241. (e) Preston, P. N. *Chem. Rev.* **1974**, *74*, 279.

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