Acknowledgment. We are grateful to the Natural Sciences and Engineering Research Council, and to British Petroleum, for support of this research. We are indebted to Johnson-Matthey for providing a generous loan of rhodium chloride, used to prepare 1.

Registry No. 2, 141046-47-1; CH_2=$CHCO_2Et$, 140-88-5; CH_2=$CHCO_2Bu$-s, 2998-08-5; CH_2=$C(CH_3)CO_2Me$, 80-62-6; (Z)-CH_3CH=$CHCO_2Et$, 6776-19-8; (E)-CH_3CH=$CHCO_2Et$, 623-70-1; $CH_3CH(CHO)CO_2Et$, 27772-62-9; $CH_3CH(CHO)CO_2Bu$-s, 141046-48-2; $OHCC(CH_3)_2CO_2Me$, 13865-20-8; $CH_3CH_2CH(CHO)CO_2Et$, 36873-42-4; $OHC(CH_2)_2CO_2Et$, 10138-10-0; $OHCCH_2CH(CH_3)CO_2Me$, 13865-21-9; $OHCCH(CH_3)CH_2CO_2Et$, 54998-57-1; CH_3C(=CHOH)CO_2Et, 54843-13-9; CH_3C(=CHOH)CO_2Bu-s, 141046-49-3; (COD)Rh(BPh_4) complex, 31974-01-3; α-methylene-δ-butyrolactone, 547-65-9; 3-methyl-2-oxo-3-furancarboxaldehyde, 55341-13-4; dppb, 7688-25-7.

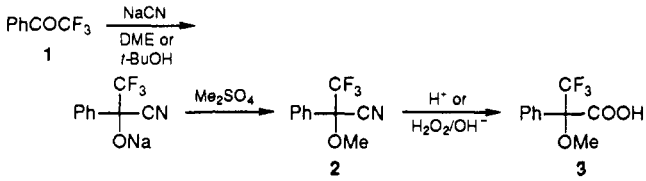
A New and Simple Synthesis of Mosher's Acid

Yuri Goldberg and Howard Alper*

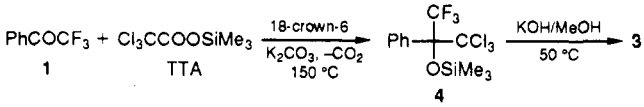
Department of Chemistry, University of Ottawa, Ottawa, Ontario, Canada K1N 6N5

Received January 14, 1992

A frequently used chiral reagent for the determination of enantiomeric purity of chiral alcohols and amines[1] is α-methoxy-α-(trifluoromethyl)phenylacetic acid, also known as Mosher's acid.[2] This compound has been synthesized by reaction of α,α,α-trifluoroacetophenone (1) with sodium cyanide in 1,2-dimethoxyethane (DME) followed by alkylation with dimethyl sulfate to give the nitrile 2 and finally hydrolysis of 2, first to the amide and then to the acid 3.[2] More recently, a modified synthesis of 3[3]



was developed, with minor improvements realized over the original preparation (i.e., use of *tert*-butyl alcohol instead of DME and use of alkaline hydrogen peroxide for the hydrolysis of 2). While these methods afford Mosher's acid in quite good yield, they require the use of toxic sodium cyanide and dimethyl sulfate. We now report a new method for the preparation of Mosher's acid, based on the addition of trimethylsilyl trichloroacetate (TTA) to 1 and subsequent hydrolysis of 4 to 3. This may be done without isolation of 4, thus providing an efficient one-flask procedure for the synthesis of 3.



TTA, a known[4,5] reagent for the trichloromethylation of ketones, has been prepared by silylation of trichloroacetic acid with hexamethyldisilazane,[6] hexamethyldisiloxane,[7] or trimethylchlorosilane.[8] Disadvantages of these methods include concurrent formation of side products[6,7] and long reaction times.[8] We have found that solid–liquid[9] phase transfer catalyzed (PTC) reaction of sodium trichloroacetate with chloromethylsilane is a simple, mild, and convenient route to TTA. When a mixture of CCl_3COONa (0.10 mol), Me_3SiCl (0.12 mol), and 18-crown-6 (5 mmol) in benzene was stirred for 4 h at room temperature, TTA was obtained in 75% yield of pure material. The yield increased to 83% when the reaction was run for 12 h. Other phase-transfer agents, including quaternary ammonium salts, a polymer bound phosphonium salt, poly(ethylene glycol) (PEG-400), and tris(polyoxaheptyl)amine (TDA-1) were much less effective in this regard (Table I). Of these it is noteworthy that polymer-anchored tributylhexylphosphonium bromide can be reused without a loss in activity.

Table I. Phase Transfer Catalyzed Silylation of Sodium Trichloroacetate[a]

phase-transfer agent	reaction time, h	% TTA[b]
18-crown-6	4	75
	12	83
$Bu_4N^+HSO_4^-$	24	2[c]
Adogen 464	24	19
$(n\text{-}C_8H_{17})_4N^+Br^-$	24	48
Ⓟ-$(CH_2)_6PBu_3^+Br^-$	24	45 (47)[d]
PEG-400	24	23
TDA-1	24	26

[a] Molar ratio of $Cl_3CCOONa$:Me_3SiCl:catalyst was 1.0:1.2:0.05, rt in benzene. [b] Isolated yield of pure material. [c] GC yield. [d] Yield after reuse of phase-transfer catalyst.

Treatment of TTA with 1 in the presence of catalytic quantities of 18-crown-6 and K_2CO_3, for 30 min at 150 °C afforded 4 in 83% yield. Dibenzo-18-crown-6 and dicyclohexano-18-crown-6 can be used in place of 18-crown-6 with similar results, and TDA-1 was also useful, but a longer reaction time (3 h) was necessary in this case. Methanolic potassium hydroxide was used to effect simultaneous disilylation, hydrolysis, and methylation, resulting in the conversion of 4 to 3 in 79% yield. This method has been useful for the preparation of α-methoxymandelic acid from phenyl(trichloromethyl)carbinol.[10]

Experimental Section

Trimethylsilyl Trichloroacetate (TTA). To a suspension of sodium trichloroacetate (18.54 g, 0.10 mol) in benzene (30 mL) containing 18-crown-6 (1.32 g, 5.0 mmol) was added chlorotrimethylsilane (12.84 g, 0.118 mmol), and the reaction mixture was stirred at rt for 12 h. The solution was filtered, and benzene and excess Me_3SiCl were removed by rotary evaporation. Vacuum distillation of the residue afforded 19.65 g (83%) of TTA, bp 42–43 °C (1 mmHg) [lit.[10] bp 69 °C (10 mmHg)].

α-Methoxy-α-(trifluoromethyl)phenylacetic Acid (3). A mixture of 1 (1.74 g, 10 mmol), TTA (2.83 g, 12 mmol), 18-crown-6 (0.132 g, 0.5 mmol), and K_2CO_3 was stirred at 150 °C until the evolution of CO_2 was complete (i.e., 30 min). If required, 4 can be isolated by vacuum distillation [2.98 g (82% yield); bp 65–67 °C (0.2 mmHg); ^1H NMR ($CDCl_3$) δ 0.25 (s, 9 H, $SiMe_3$), 7.3–7.8 (m, 5 H, Ph) ppm; MS *m/e* 247 [M − CCl_3]$^+$]. Compound 4, or the reaction mixture above, is dissolved in methanol (15 mL) and warmed to 60 °C. A solution of 5.6 g (0.1 mol) of KOH in methanol (50 mL) was added dropwise, and stirring was continued

(1) Yamaguchi, S. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 1, Chapter 7.
(2) Dull, D. L.; Mosher, H. S. *J. Am. Chem. Soc.* **1967**, *89*, 4230. Dale, J. H.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
(3) Hall, W. E.; Seeholzer, K.; Baumeister, M.; Ugi, I. *Tetrahedron* **1986**, *42*, 547.
(4) Renga, J. M.; Wang, P. C. *Tetrahedron Lett.* **1985**, *26*, 1175.
(5) de Jesus, M. A.; Prieto, J. A.; del Valle, L.; Larson, G. *Synth. Commun.* **1987**, *17*, 1047.
(6) Okada, T.; Okawara, R. *J. Organomet. Chem.* **1972**, *42*, 117.
(7) Matsumoto, H.; Hoshino, Y.; Nakabayashi, S.; Nakano, T.; Nagai, Y. *Chem. Lett.* **1980**, 1475.
(8) Hergott, H. H.; Simchen, G. *Synthesis* **1980**, 626.
(9) Mack, M. P.; Berge, C. T. U.S. Pat. 4,379,766, 1983; *Chem. Abstr.* **1983**, *99*, P5817a.
(10) Reeve, W.; Bianchi, R. J.; McKee, J. R. *J. Org. Chem.* **1975**, *40*, 339.

0022-3263/92/1957-3731$03.00/0

at 60 °C for 6 h. The cooled reaction mixture was diluted with water (65 mL), acidified to pH 1 using 10% HCl, and then extracted with ether (3 × 150 mL). The combined ether extract was dried ($MgSO_4$) and concentrated. Distillation of the residue gave 1.85 g, (79%) of Mosher's acid, bp 90–93 °C (0.3 mmHg) [lit.[3] bp 105–110 °C (1.0 mmHg)]. Spectral data were in accord with that of an authentic sample.

Acknowledgment. We are grateful to the Natural Sciences and Engineering Research Council of Canada for support of this research.

Registry No. 1, 434-45-7; 3, 81655-41-6; 4, 141090-95-1; TTA, 25436-07-1; PEG-400, 25322-68-3; TDA-1, 70384-51-9; Cl_3CCO_2H·Na, 650-51-1; $Bu_4N^+·HSO_4^-$, 32503-27-8; $(n\text{-}C_8H_{17})_4N^+·Br^-$, 14866-33-2; 18-crown-6, 17455-13-9; dibenzo-18-crown-6, 14187-32-7; dicyclohexano-18-crown-6, 16069-36-6.

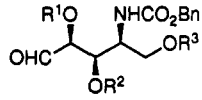
A Convenient Preparation of Terminally Differentiated, Selectively Protected Six-Carbon Synthons from D-Glucosamine

Robert S. Coleman,*[1a] Yong Dong, and Andrew J. Carpenter[1b]

Department of Chemistry and Biochemistry, University of South Carolina, Columbia, South Carolina 29208

Received March 2, 1992

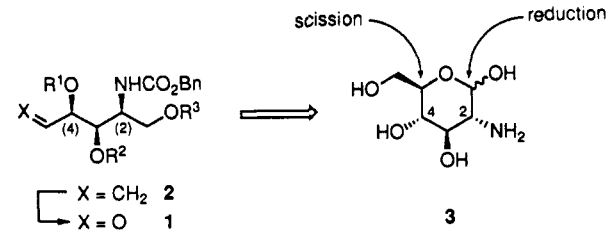
In the course of studies directed toward the total synthesis of the naturally occurring antitumor agents azinomycin A and B,[2] we developed a requirement for five-carbon fragments[3] bearing the absolute stereochemistry and selectively protected functional groups depicted by aldehyde **1**. This requirement was subject to several considerations, including the ability to smoothly unmask a potentially unstable aldehyde, to produce a selectively protected *syn*-1,2-diol ($R^1 \neq R^2$), and to readily access an unprotected primary hydroxyl group in **1** (R^3 = H). Economic considerations dictated that targets such as **1** must be available in homoenantiomeric form. Herein, we detail a high-yielding, effectual synthetic route to variably protected precursors of aldehyde **1**, subject to efficiently satisfying the conditions specified above.



1

The synthesis of systems related to **1** relied on the observation that the three stereogenic centers of aldehyde **1** possess the same absolute configuration as C2, C3, and C4 of D-glucosamine (**3**), a readily available and inexpensive starting material ($20/mol).[3] This strategic observation is outlined in Scheme I. Aldehyde **1** would be available

Scheme I



from olefin **2** by oxidative cleavage, conceptually providing a convertible precursor that in turn can be mapped onto the pyran skeleton of D-glucosamine (**3**). In turn, suitable protection of the C2–C4 amino diol functionality of **3**, pyran ring scission using a Vasella fragmentation,[4] and reduction of C1 to the alcohol oxidation state would provide ready entry into systems depicted by **2**.

Synthesis of the variously protected 6-deoxy-6-iodo-D-glucosamine derivatives **10a–d** is detailed in Scheme II. Reaction of carbamate **4**[5] with *p*-anisaldehyde or benzaldehyde dimethyl acetal (cat. CSA, DMF, 90 °C, 12–48 h)[6] afforded 4,6-*O*-benzylidene acetals **5a** (75%; PMP = *p*-methoxyphenyl) and **6a** (73%). Protection of the remaining C3-hydroxyl group as the corresponding benzyl ether (**5a**; KH, $PhCH_2Br$, cat. $n\text{-}Bu_4NI$, THF, 0 °C, 67%) or silyl ether (**6a**; *t*-$BuMe_2SiOTf$, 2,6-lutidine, CH_2Cl_2, 24 °C, 100%) afforded **5b** and **6b**, respectively. Cleavage of the labile *p*-methoxybenzylidene acetal of **5a** (2% HCl in CH_3OH, 24 °C, 92%) afforded diol **7**. Selective iodination of the primary C6-hydroxyl group of **8** (I_2, Ph_3P, pyridine, toluene, 70 °C, 87%)[7] afforded **8**; acetylation of the remaining C4-hydroxyl group of **9** (Ac_2O, Et_3N, CH_2Cl_2, 24 °C, 100%) afforded 6-deoxy-6-iodo-D-glucosamine derivative **10a**. Alternatively, the benzylidene acetal of **6b** was cleaved using the Hanessian–Hullar protocol[8] (*N*-bromosuccinimide, cat. AIBN, $BaCO_3$, CCl_4, reflux, 72%) to provide the fully protected 6-bromo-6-deoxy-D-glucosamine derivative **9**, which was converted to iodide **10b** (NaI, acetone, reflux, 100%).[9] Symmetrically protected 6-deoxy-6-iodo-D-glucosamine derivatives **10c** and **10d** were prepared from carbamate **4** by selective iodination of the primary C6-hydroxyl group (I_2, Ph_3P, pyridine, toluene, 80 °C, 69%)[7] and either silylation (*t*-$BuMe_2SiOTf$, 2,6-lutidine, CH_2Cl_2, 24 °C, 52%) or acylation (Ac_2O, pyridine, 24 °C, 100%) of the remaining secondary hydroxyl groups.

Scission of the pyran ring system (Scheme III) was achieved by Vasella fragmentation[4a] of iodides **10a–d** (activated Zn, 95% EtOH, 78 °C, 1 h), in a process that cleanly and in high yield afforded the corresponding 5-hexenal derivatives **11a–d** (X = O), with no detectable epimerization of the C2-stereogenic center (^1H NMR). In

(1) (a) Recipient of a Camille and Henry Dreyfus Foundation Distinguished New Faculty Award (1989–1994) and an American Cancer Society Junior Faculty Research Award (1991–1993). (b) Recipient of a U.S. Department of Education graduate fellowship (1991–1992).

(2) (a) Coleman, R. S.; Carpenter, A. J. *J. Org. Chem.* Submitted for publication. (b) Nagaoka, K.; Matsumoto, M.; Oono, J.; Yokoi, K.; Ishizeki, S.; Nakashima, T. *J. Antibiot.* **1986**, *39*, 1527. Yokoi, K.; Nagaoka, K.; Nakashima, T. *Chem. Pharm. Bull.* **1986**, *34*, 4554. Ishizeki, S.; Ohtsuka, M.; Irinoda, K.; Kukita, K.-I.; Nagaoka, K.; Nakashima, T. *J. Antibiot.* **1987**, *40*, 60.

(3) Hanessian, S. *Acc. Chem. Res.* **1979**, *12*, 159. Hanessian, S. *Total Synthesis of Natural Products: The 'Chiron' Approach*; Pergamon Press: Oxford, 1983. Schmidt, R. R.; Maier, M. *Synthesis* **1982**, 747.

(4) (a) Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1984**, *67*, 1328. (b) For a closely related strategy in which tri-*O*-acetyl-D-galactal was converted via a series of functional group manipulations and a Vasella fragmentation into a six-carbon synthon for preparation of the C22–C27 fragment of FK-506, see: Linde, R. G., II; Egbertson, M.; Coleman, R. S.; Jones, A. B.; Danishefsky, S. J. *J. Org. Chem.* **1990**, *55*, 2771.

(5) Readily available from D-glucosamine hydrochloride by N-protection ($ClCO_2Bn$, $NaHCO_3$, dioxane/H_2O, 24 °C) and methyl glycoside formation (2% HCl in CH_3OH, reflux, 24 h). Chargaff, E.; Bovarnick, M. *J. Biol. Chem.* **1937**, *118*, 421. Neuberger, A.; Rivers, R. P. *J. Chem. Soc.* **1939**, 122.

(6) Evans, M. E. In *Methods in Carbohydrate Chemistry*; Whistler, R. L., BeMiller, J. N., Eds.; Academic Press: New York, 1980; Vol. 8, p 313.

(7) Anisuzzaman, A. K. M.; Whistler, R. L. *Carbohydr. Res.* **1978**, *61*, 511.

(8) Hanessian, S.; Plessas, N. R. *J. Org. Chem.* **1969**, *34*, 1035, 1045, 1053. Hullar, T. L.; Siskin, S. B. *J. Org. Chem.* **1970**, *35*, 225.

(9) Bromide **9** failed to smoothly undergo Vasella fragmentation under standard conditions[4a] (activated Zn, 95% EtOH, 78 °C, 1–3 h).

0022-3263/92/1957-3732$03.00/0