JOC*Note*

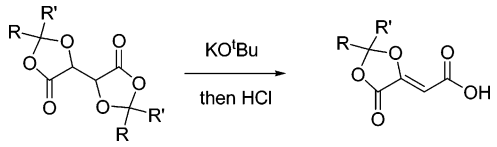
Synthesis of *Z*-5-Carboxymethylene-1,3-dioxolan-4-ones: A Better Way

Keming Zhu, James H. Simpson, Edward J. Delaney, and William A. Nugent*

Bristol-Myers Squibb Company, Process Research and Development Department, P.O. Box 4000, Princeton, New Jersey 08543

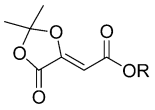
william.nugent@bms.com

Received January 4, 2007

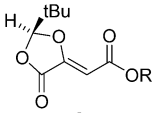


The title compounds were prepared by a straightforward two-step procedure. Tartaric acid was first protected as either a bis(ketal) or a bis(acetal). This intermediate was then treated with potassium *tert*-butoxide at reduced temperature to effect a stereoselective elimination leading to the *Z* diastereomer of the α,*β*-unsaturated acid. This protocol is useful for the laboratory-scale synthesis of these compounds but can also be scaled up to produce kilogram quantities of the material.

Carboxymethylene-1,3-dioxolan-4-ones, as exemplified by structures **1** and **2**, are versatile synthetic intermediates that have found application as pharmaceutical building blocks.



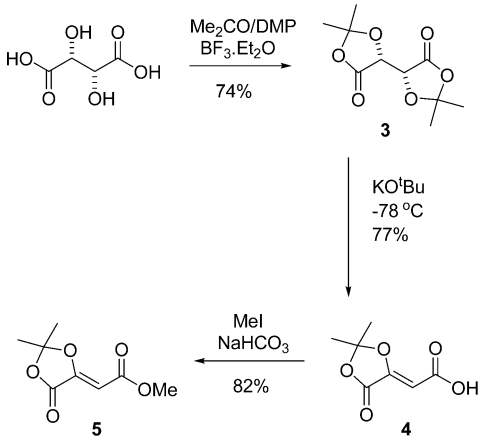
1



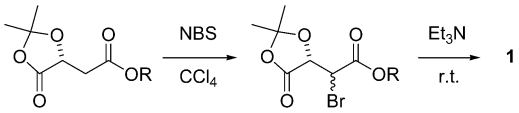
2

Compound **1** (R = H) has been incorporated into several drug candidates ranging from nonsteroidal anti-inflammatories[1] to potent inhibitors of HIV integrase.[2] Mattay and co-workers have shown that the chiral analogues **2** exhibit useful levels of asymmetric induction in radical addition chemistry[3] and as dienophiles in the Diels−Alder reaction.[4] Given their synthetic utility, it is unfortunate that existing synthetic routes to these compounds are somewhat inefficient.[5] We wish to describe a straightforward two-step synthesis of **1** and **2** (R = H) as well as a procedure for converting the carboxylic acids to their methyl esters. Although we report this chemistry in the context of a laboratory synthesis, we have also applied this new protocol to the preparation of compound **1** (R = H) in up to metric ton quantities.

SCHEME 1. Synthesis of Acetonide 5



The conventional route[1,4] to these compounds involves the free-radical bromination of an acetonide-protected malic acid ester, for example



Protection of the C4 carboxylic acid as an ester is required because the carboxylic acid functionality interferes with the bromination.[4] The intermediate bromide is an oil, which precludes purification via crystallization. In essence, this bromination step is required because malic acid is in the wrong oxidation state[6] for the desired elimination. Thus, it seems reasonable that tartaric acid might represent a better starting material than malic acid from the standpoint of synthetic efficiency.[7]

Tartaric acid bis(acetonide) **3** was first reported by Fischer and Taube in 1927.[8] Subsequently, an improved laboratory synthesis of **3** was reported.[9] This involves the treatment of tartaric acid with acetone and 2,2-dimethoxypropane at 0 °C in the presence of boron trifluoride diethyl etherate (Scheme 1).

Under these conditions, the formation of **3** reaches equilibrium with two mono-acetonide intermediates (not shown), and the reaction does not go to completion. For larger-scale reactions, we found it useful to drive the equilibrium by distillation of

* Corresponding author. Phone: (609) 252-3689. Fax: (609) 252-7825.

(1) Schwenker, G.; Stiefvater, K. *Arch. Pharm. (Weinheim, Ger.)* **1991**, *324*, 307.

(2) Walker, M. A.; Johnson, T. D.; Meanwell, N. A.; Banville, J. Preparation of Carbamoyl Keto Acid Tautomers as HIV Integrase Inhibitors for Treatment of AIDS or ORC. World Patent Appl. 2,001,096,283, 2001; *Chem. Abstr.* **2002**, *136*, 53533.

(3) (a) Kneer, G.; Mattay, J. *Tetrahedron Lett.* **1992**, *33*, 8051. (b) Kneer, G.; Mattay, J.; Heidbreder, A. *J. Prakt. Chem* **1995**, *337*, 113.

(4) Kneer, G.; Mattay, J.; Raabe, G.; Krueger, C.; Lauterwein, J. *Synthesis* **1990**, 599.

(5) In addition to the bromination route outlined in eq 1, compounds in this series have also been prepared by condensation of a glyoxylate ester with a stabilized Wittig reagent: Ramage, R.; McCleary, P. P. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1555.

(6) For a thought-provoking discussion regarding the impact of the oxidation state of intermediates on synthetic efficiency, see: Fraunhoffer, K. J.; Bachovchin, D. A.; White, M. C. *Org. Lett.* **2005**, *7*, 223.

(7) For an outstanding review of tartaric and malic acids as chiral building blocks, see: Gawronski, J.; Gawronska, K. *Tartaric and Malic Acids in Synthesis*: *A Source Book of Building Blocks, Ligands, Auxiliaries, and Resolving Agents*; Wiley: New York, 1999.

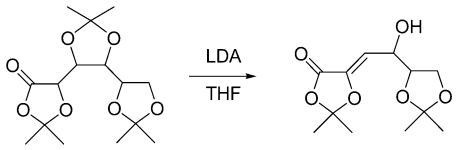
(8) Fischer, H. O. L.; Taube, C. *Chem. Ber.* **1927**, *60*, 485.

(9) Dermer, O. C.; George, C. *Proc. Okla. Acad. Sci.* **1972**, *52*, 66; *Chem. Abstr.* **1973**, *78*, 3643.

10.1021/jo0700171 CCC: $37.00
Published on Web 04/14/2007

methanol or water, providing **3** in up to 74% yield after crystallization. However, for laboratory-scale synthesis, a simple expedient is to concentrate the reaction mixture on a rotary evaporator followed by dilution with ice-cold water. The hydrophobic solid **3** separates, while the mono-acetonides remain in solution. The yield of crystalline **3** is only 30−40% under these conditions, but given the cheap starting material and operational simplicity, the procedure is attractive for producing **3** when only a few grams are needed.

Regarding the elimination reaction required to complete the synthesis, we were encouraged by the report of a similar elimination in which the tris(acetonide) of gluconic acid was treated with LDA.[10]



We were therefore nonplussed to find that when **3** was treated with LDA under the literature conditions, the overwhelming product after extractive workup was the recovered starting material.[11]

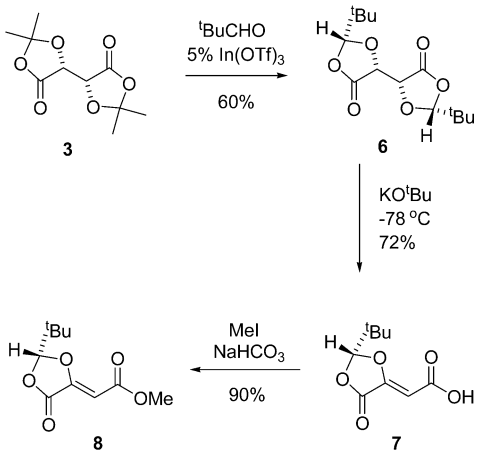
We subsequently found that treatment of **3** with potassium *tert*-butoxide in THF effects the desired elimination to produce (after quenching with anhydrous HCl) *Z*-**4** as shown in Scheme 1. Reduced temperature is required to minimize the formation of isomeric *E*-**4**. At −78 °C, the reaction is complete in 30 min, and the *Z*/*E* selectivity is >95:5. Pure *Z*-**4** is then obtained by a single crystallization from ethyl acetate.

For some applications, the methyl ester **5** rather than acid **4** may be desired. Conversion of **4** to **5** was easily accomplished by treatment with methyl iodide in DMF using sodium bicarbonate as the base.[12] (Use of potassium carbonate in this application resulted in up to 20% decomposition of the acetonide as indicated by free acetone in the reaction mixture.)

We then turned our attention to the optically active analogue **8**. Direct preparation of the requisite bis(acetal) starting material **6** from tartaric acid using lithium perchlorate as a promoter has been reported.[13] However, in the case of sterically bulky trimethylacetaldehyde, we find this reaction to be somewhat sluggish, possibly reflecting the back reaction with water. As an alternative, we found that transacetalization of **3** with trimethylacetaldehyde in the presence of indium triflate[14] (Scheme 2) provided complete conversion overnight at room temperature.

Selectivity to the desired (2*R*,2′*R*,5*R*,5′*R*) versus the undesired (2*S*,2′*R*,5*R*,5′*R*) stereoisomer was 14:1. Moreover, the desired compound is a high melting solid, while the minor isomer is an oil[13] so that **6** could be obtained as a single stereoisomer by simple trituration of the crude product with heptane.

SCHEME 2. Synthesis of Enantiopure Acetal 8



Also shown in Scheme 2, the reaction of bis(acetal) **6** with potassium *tert*-butoxide results in an elimination reaction analogous to that observed with bis(acetonide) **3**. Crystallization of the crude product from hot 1:1 heptane/ethyl acetate afforded analytically pure **7**. Treatment of **7** with methyl iodide and sodium bicarbonate in DMF again resulted in clean methylation. Both the (*R*) and the (*S*) enantiomers of **8** were prepared; chiral HPLC analysis indicated that the ee of these materials was 99 and 98%, respectively.[15]

We have had occasion to scale up the synthesis of **4** to produce kilogram quantities of the material. Details are provided in the Supporting Information. For reasons of practicality, several minor modifications were made to the laboratory-scale synthesis for operations at a kilogram scale: (1) the conversion of tartaric acid to acetonide **3** was conducted at 50 °C. Distillation of methanol at a reduced pressure was used to increase conversion, affording **3** in 74% yield. (2) Instead of the cold water workup, **3** was crystallized from MTBE/heptane. (3) The elimination reaction to produce **4** was conducted at −40 °C rather than −78 °C. The *Z*/*E* ratio diminished slightly to 95:5, but crystallization still effectively removed the undesired *E* diastereomer. (4) Anhydrous HCl was generated in a separate reaction vessel from acetyl chloride and methanol. (5) Heptane was used as an anti-solvent for the crystallization of **4** from ethyl acetate.

In summary, we have developed an improved synthesis of *Z*-5-carboxymethylene-1,3-dioxolan-4-ones such as **1** and **2**, starting from inexpensive tartaric acid. In addition to the shorter synthetic sequence, this approach has several advantages over the conventional bromination route. All of the intermediates are crystalline solids; no chromatography is required. A particular advantage of using tartaric rather than malic acid as a starting material is the ability to improve the final optical purity of chiral derivatives like **8** by crystallization of the diastereomers of a bis(acetal) intermediate such as **6**. Also, this approach provides access to the free carboxylic acids (exemplified by **4** and **7**) that are of particular interest for pharmaceutical synthesis. We expect that this chemistry will lead to further research activity on these interesting synthetic intermediates.

(10) Jarosz, S.; Ciunik, Z. *Pol. J. Chem.* **1998**, *72*, 1182.

(11) Quenching the reaction mixture with DCl resulted in no deuterium incorporation in the recovered **3**. This seems to rule out the possibility that deprotonation occurs but results in a chelation-stabilized carbanion that does not undergo elimination.

(12) For another example utilizing sodium bicarbonate in the alkylation of a base-sensitive carboxylic acid, see: Mobashery, S.; Johnston, M. *J. Org. Chem.* **1986**, *51*, 4723.

(13) Markert, M.; Buchem, I.; Krueger, H.; Mahrwald, R. *Tetrahedron: Asymmetry* **2004**, *15*, 803.

(14) For a somewhat related transformation, see: Smith, B. M.; Graham, A. E. *Tetrahedron Lett.* **2006**, *47*, 9317.

(15) The slightly lower ee for the (*S*)-acetal presumably reflects the somewhat lower optical purity of the unnatural (*S*,*S*)-tartaric acid starting material.

Experimental Section

2,2,2′,2′-Tetramethyl-[4,4′]bis[[1,3]dioxolanyl]-5,5′-dione, 3. A 500 mL round-bottomed flask was charged with L-tartaric acid (20.0 g, 133 mmol). Acetone (200 mL) and 2,2-dimethoxypropane (100 mL) were added, and the mixture was cooled to 0 °C. Boron trifluoride diethyl etherate (2.0 mL, 16 mmol) was added via syringe, and the mixture was stirred for 4 h at 0 °C. The resultant solution was concentrated to ca. 30 mL on a rotary evaporator after which ice-cold water (200 mL) was added with vigorous stirring. The solid product was collected by filtration and dried in vacuum overnight to afford **3** (9.21 g, 30%) as a snow-white powder, mp 102 °C (lit.[8] 102 °C). The material so produced was pure by NMR and elemental analysis but may be crystallized from hot anhydrous ethanol (4 mL/g) to afford **3** as large transparent needles. ^{1}H NMR ($CDCl_3$): δ 1.60 (s, 6H), 1.66 (s, 6H), 4.83 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 26.7, 73.5, 112.2, 169.1. Anal. Calcd for $C_{10}H_{14}O_6$: C, 52.17; H, 6.13 Found: C, 52.25; H, 5.98.

When this precipitation approach to **3** is used, it appears important to promptly dry the product in vacuum. Residual moisture promotes decomposition of **3** to tartaric acid.

***Z*-2,2-Dimethyl-5-carboxymethylene-1,3-dioxolan-4-one, 4.** A 50 mL round-bottomed flask was charged with **3** (0.92 g, 4.00 mmol) and anhydrous tetrahydrofuran (10 mL). The mixture was cooled to −78 °C, and a 1.0 M solution of potassium *tert*-butoxide (4.4 mL, 4.4 mmol) was added via syringe. After stirring for 1 h at −78 °C, a solution of 4 M HCl in dioxane (1.0 mL, 4.0 mmol) was added, and the flask was removed from the bath. After 5 min, the mixture was transferred to a separatory funnel containing 0.1 M HCl (20 mL) and ethyl acetate (50 mL). The organic layer was separated, washed with water (20 mL), and dried ($MgSO_4$). Distillation of the solvent afforded the crude product, which was then crystallized from hot ethyl acetate (5 mL) to afford **4** (0.54 g, 78%) as a fine white needles, mp 204 °C. ^{1}H NMR (DMSO-d_6): δ 1.70 (s, 6H), 5.55 (s, 1H), 12.62 (br s, 1H). ^{13}C NMR (DMSO-d_6): δ 26.0, 95.6, 114.4, 146.9, 161.9, 164.8. Anal. Calcd for $C_7H_8O_5$: C, 48.84; H, 4.68. Found: C, 48.98; H, 4.45.

We were initially somewhat concerned about the storage stability of compound **4** since it contains both acetonide and carboxylic acid functionality. However, a sample stored under air for 3 years showed no degradation. In contrast, a sample of **3** stored under the same conditions showed ca. 15% decomposition by NMR. Somewhat surprisingly, analogous reaction of the bis(acetonide) from *meso*-tartaric acid with potassium *tert*-butoxide (−50 °C) also produced predominantly the *Z*-alkene (diastereomer ratio = 92.5:7.5). One possible interpretation of this result is that epimerization of the *meso*-bis(acetonide) to the DL-diastereomer is faster than elimination.

***Z*-2,2-Dimethyl-5-carboxymethylene-1,3-dioxolan-4-one, Methyl Ester, 5.** A vial was charged with **4** (0.34 g, 2.0 mmol) and sodium bicarbonate (0.34 g, 4.0 mmol). A solution of iodomethane (0.56 g, 4.0 mmol) in anhydrous DMF (6 mL) was added, and the mixture was stirred at room temperature for 24 h. The mixture was transferred to a separatory funnel with ethyl acetate (20 mL), heptane (20 mL), and water (25 mL). The organic phase was separated, further washed with 10% aqueous lithium chloride (20 mL, used to aid in removal of DMF) followed by water (15 mL), and dried ($MgSO_4$). Distillation of the solvent and vacuum drying afforded **5** (0.30 g, 82%) as an analytically pure white solid, mp 102 °C. ^{1}H NMR ($CDCl_3$): δ 1.76 (s, 6H), 3.78 (s, 3H), 5.85 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 26.7, 51.7, 96.1, 114.3, 147.2, 161.8, 164.5. Anal. Calcd for $C_8H_{10}O_5$: C, 51.61; H, 5.41. Found: C, 51.41; H, 5.16.

(2*R*,2′*R*,5*R*,5′*R*)-2,2′-Di-*tert*-butyl-5,5′-bis(1,3-dioxolane-4,4′)-dione, 6. A 100 mL round-bottomed flask was charged with **3** (2.30 g, 10.0 mmol) and indium trifluoromethanesulfonate (0.28 g, 0.5 mmol). A solution of trimethylacetaldehyde (5.4 mL, 50 mmol) in anhydrous dichloromethane (15 mL) was added, and the mixture was stirred 24 h at room temperature. The mixture was transferred to a separatory funnel with 25 mL of saturated aqueous sodium hydrogen carbonate solution, 50 mL of water, and 25 mL of dichloromethane. The organic phase was separated, and the aqueous phase was washed with an additional 25 mL of dichloromethane. The combined organics were washed with water (25 mL) and dried ($MgSO_4$). Distillation of solvent at reduced pressure afforded crude **6** (2.56 g) as a cream solid that by NMR was a 14:1 mixture of diastereomers. This material was suspended in 25 mL of heptane and stirred for 2 h at room temperature. The insoluble material was collected by filtration and dried in vacuum to afford pure **6** (1.72 g, 60%) as a snow-white solid. NMR data were essentially identical to those reported in the literature.[13] ^{1}H NMR ($CDCl_3$): δ 1.01 (s, 18H), 4.72 (s, 2H), 5.23 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 23.2, 34.3, 73.0, 110.1, 169.6. Melting point sample was crystallized from hot 2:1 heptane/ethyl acetate, mp 152 °C (lit.[13] 136−138 °C). Anal. Calcd for $C_{14}H_{22}O_6$: C, 58.73; H, 7.74. Found: 58.91; 7.89.

***Z*-(2*R*)-2-*tert*-Butyl-5-carboxymethylene-1,3-dioxolan-4-one, 7.** A 50 mL round-bottomed flask was charged with **6** (1.14 g, 4.00 mmol) and anhydrous tetrahydrofuran (10 mL). The mixture was cooled to −78 °C, and a 1.0 M solution of potassium *tert*-butoxide (4.4 mL, 4.4 mmol) was added via syringe. After stirring for 1 h at −78 °C, a solution of 4 M HCl in dioxane (1.0 mL, 4.0 mmol) was added, and the flask was removed from the bath. After 5 min, the mixture was transferred to a separatory funnel containing 0.1 M HCl (20 mL) and ethyl acetate (50 mL). The organic layer was separated, washed with water (20 mL), and dried ($MgSO_4$). Distillation of the solvent afforded the crude product, which was then crystallized from hot 1:1 heptane/ethyl acetate (6 mL) to afford **7** as a white solid, mp 197 °C. ^{1}H NMR (DMSO-d_6): δ 0.93 (s, 9H), 5.55 (s, 1H), 5.92 (s, 1H), 12.64 (br s, 1H). ^{13}C NMR (DMSO-d_6): δ 22.3, 35.3, 95.0, 110.7, 147.0, 162.3, 164.7. Anal. Calcd for $C_9H_{12}O_5$: C, 54.00; H, 6.04. Found: C, 53.98; H, 5.73.

***Z*-(2*R*)-2-*tert*-Butyl-5-carboxymethylene-1,3-dioxolan-4-one, Methyl Ester, 8.** A vial was charged with **7** (0.28 g, 1.4 mmol) and sodium bicarbonate (0.24 g, 2.9 mmol). A solution of iodomethane (0.41 g, 2.9 mmol) in anhydrous DMF (5 mL) was added, and the mixture was stirred at room temperature for 14 h. The mixture was transferred to a separatory funnel with ethyl acetate (20 mL), heptane (20 mL), and water (25 mL). The organic phase was separated, further washed with water (4 × 25 mL), and dried ($MgSO_4$). Distillation of the solvent and vacuum drying afforded **8** (0.27 g, 90%) as an analytically pure white solid, mp 89 °C. ^{1}H NMR ($CDCl_3$): δ 1.03 (s, 9H), 3.78 (s, 3H), 5.70 (s, 1H), 5.82 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 22.8, 36.1, 51.7, 95.5, 111.7, 147.1, 161.9, 164.3. Anal. Calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 56.12; H, 6.48. The same synthetic sequence was used to prepare (*2S*)-**8** from (*S*,*S*)-tartaric acid. The enantiomeric excess of the products was determined by chiral HPLC (Chiralcel-OJ-RH column, 15 cm length, 4.6 mm diameter, 5 μm particle size, mobile phase 98:2 heptane/isopropanol, flow rate 1 mL/min, UV detector at 254 nm). Retention times were 6.6 min for (*R*)-**8** and 10.3 min for (*S*)-**8**, and ee was 99.3 and 97.8%, respectively.

Supporting Information Available: General methods, details of kilogram-scale synthesis of **3** and **4**, and copies of ^{1}H and ^{13}C NMR spectra for compounds **3**−**8**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0700171