A Convenient Assay for the Optical Purity of Monomethyl 3-Hydroxypentanedioate

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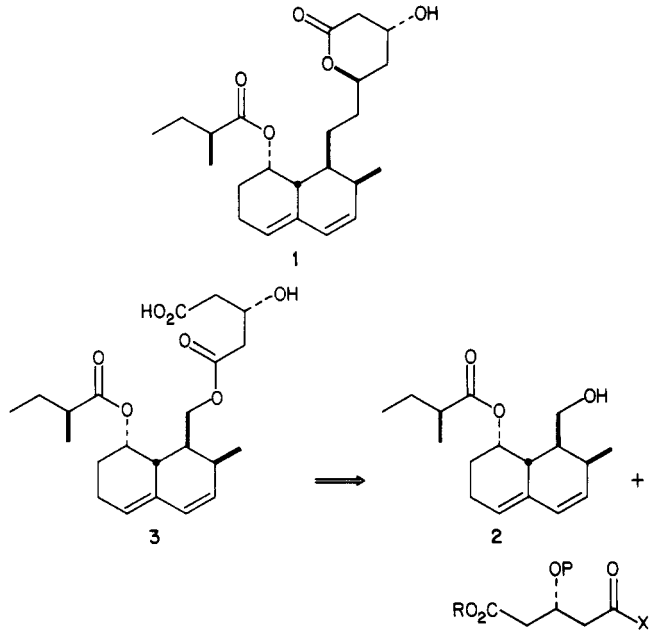
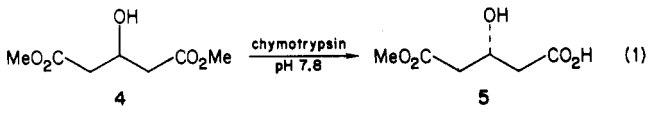
As part of our continuing effort to synthesize and study the biological activity of compounds related to the important hypocholesterolemic agent compactin (1) and other mevinic acids,[1] we desired a readily available synthon possessing high enantiomeric purity which could be used to transform optically pure alcohol **2** to its hydroxyglutarate ester **3**. (*R*)-Monomethyl 3-hydroxypentanedioate (**5**) is particularly attractive for this purpose, since it is obtained easily by chymotrypsin-mediated hydrolysis of the corresponding dimethyl ester (**4**) (eq 1).[2]





(1)

Although enantiomerically enriched **5** is available by this method, decreases in the optical yield of the enzymatic reaction result if the pH of the reaction mixture is not properly controlled. If this process is to be of preparative utility, it is essential that one have available a quantitative and expeditious analytical technique for determination of the degree of assymetric induction. Unfortunately, the only criterion available for assaying the optical purity of **5** is its rather low specific rotation, $[\alpha]^{22}_D$ −1.7° (*c* 12.5% in $CHCl_3$).[2] However, comparison of a specific rotation with a literature value is an unreliable method for evaluating enantiomeric purity. This physical property is sensitive to temperature and substrate concentration, especially in the case of a compound such as **5** which may exhibit several alternative modes of hydrogen bonding depending on the specific environment in which it exists. For example, the specific rotation of an enantiomerically enriched sample of **5** was determined at two different concentrations, and the following results were obtained: $[\alpha]^{23}_D$ −6.1° (*c* 0.64, $CHCl_3$), $[\alpha]^{23}_D$ −1.04° (*c* 12.1, $CHCl_3$). Furthermore, a minor contaminant which has a relatively large specific rotation may give misleading information with respect to the enantiomeric purity of the sample being assayed.

Scheme I

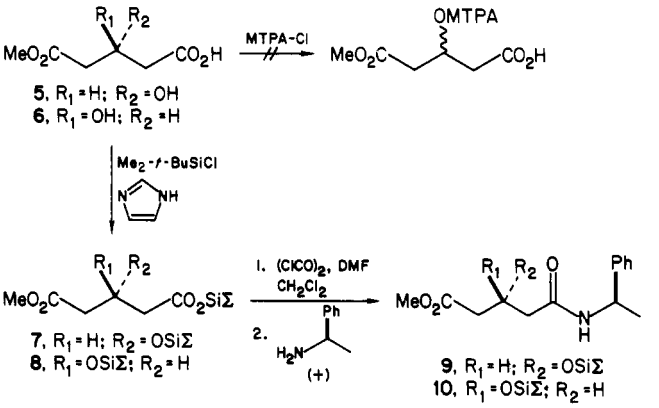


Table I

	9	10
$\delta_{t\text{-Bu}}$ (ppm)	0.86	0.79
δ_{Ome} (ppm)	3.65	3.68
HPLC retention time (3:1 Et_2O/hexanes)	3.6 min	4.8 min

The method of choice in such a situation is to derivatize the reaction product with an optically pure reagent and assay the resulting diastereomeric mixture by an appropriate analytical technique.[3] Treatment of the hydrolysis product with (*S*)-methoxy(trifluoromethyl)phenylacetyl chloride (MTPA-Cl)[4] affords a complex product mixture, presumably due to complications arising from the competition between formation of the mixed anhydride and the desired acylation reaction. To circumvent this problem, the hydroxy acids **5** and **6** are first converted to the corresponding bis-silylated enantiomers **7** and **8** in quantitative yield.[5,6] Treatment of **7** and **8** with oxalyl chloride in the presence of catalytic dimethylformamide[7] gives the corresponding acid chlorides which are converted, without isolation, into diastereomeric amides **9** and **10** in 85–100% yield by excess α-(+)-methylbenzylamine (Scheme I). Useful physical and spectral properties of **9** and **10** are summarized in Table I. Base-line separation of **9** and **10** is achieved easily with HPLC. Hence, HPLC analysis (UV detector, 254 nm) of the crude product mixture provides a rapid and accurate value for the diastereomeric ratio **9**:**10** and an excellent probe for the enantiomeric purity of the chymotrypsin hydrolysis product. The diastereomeric ratio may also be obtained from the relative intensities of the respective *tert*-butyl or methoxy resonances of **9** and **10** in the ^1H NMR spectrum of the mixture. It should also be noted that the amides may be separated by silica gel column chromatography: R_f values (3:2 Et_2O/hexanes): **9**, 0.32; **10**, 0.26.

(1) Heathcock, C. H.; Taschner, M. J.; Rosen, T.; Thomas, J. A.; Hadley, C. R.; Popják, G. *Tetrahedron Lett.* **1982**, *23*, 4747.
(2) Cohen, S. G.; Khedouri, E. *J. Am. Chem. Soc.* **1961**, *83*, 4228.
(3) For a review of methods for the determination of enantiomeric composition, see: Raban, M.; Mislow, K. "Topics in Stereochemistry"; Allinger, N. L., Eliel, E., Eds.; Interscience: New York, Vol. II, p 199.
(4) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
(5) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
(6) The symbol ΣSi is used to represent the (*tert*-butyldimethyl)silyl radical.
(7) Wissner, A.; Grudzinskas, C. V. *J. Org. Chem.* **1978**, *43*, 3972.

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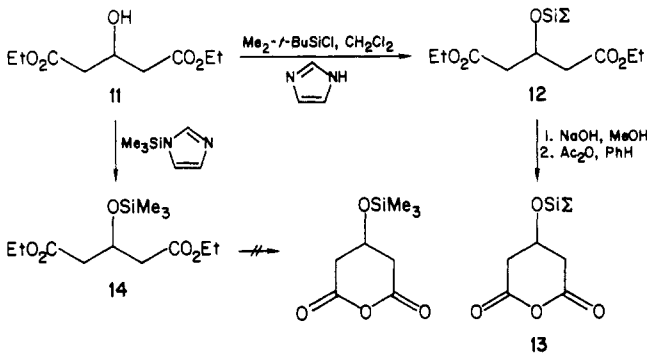
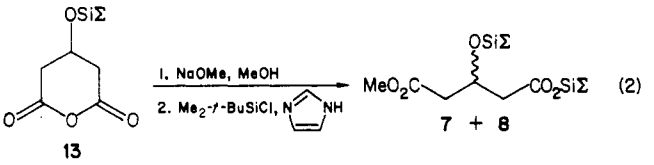
Scheme II



To insure that **9** and **10** possess equal extinction coefficients at the detection wavelength, the α-methylbenzyl amides were prepared from a racemic mixture of **7** and **8**. The racemic material is prepared from anhydride **13** by sequential methanolysis (NaOMe, methanol) and silylation in 89% overall yield (eq 2). The synthesis of 3-[(*tert*-



(2)

butyldimethylsilyl)oxy]glutaric anhydride (**13**), a useful reagent itself, is summarized in Scheme II. Treatment of commercially available diethyl 3-hydroxypentanedioate with *tert*-butylchlorodimethylsilane and imidazole affords silyl ether **12** in 95% yield. Compound **12** is converted to the corresponding dicarboxylate which is cyclized to obtain crystalline **13** in 70% yield for the two-step sequence.[10]

Treatment of **11** with *N*-(trimethylsilyl)imidazole[8] (room temperature, 12.5 h) furnishes analytically pure trimethylsilyl ether **14** in quantitative yield. This material, however, decomposes upon attempted conversion to the corresponding (trimethylsilyl)oxy anhydride.

In summary, compound **5** is a versatile chiral synthon,[9] possessing three differentiated functional groups. We believe our procedure will be of practical interest to researchers engaged in asymmetric synthesis as a simple check for the enantiomeric integrity of this valuable building block.

Experimental Section

General Methods. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Benzene was distilled from sodium. Methylene chloride and acetic anhydride were distilled from phosphorus pentoxide. Oxalyl chloride was distilled and stored at −15 °C. Melting points are uncorrected. Infrared (IR) spectra were determined with a Perkin-Elmer Model 297 infrared recording spectrophotometer. ^{1}H NMR spectra were determined with the UCB 250 spectrometer (a superconducting, FT instrument operating at 250 MHz). All NMR spectra were recorded with deuteriochloroform as the solvent. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. Significant ^{1}H NMR data are tabulated in order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), number of protons, coupling constant(s) in hertz. Thin-layer chromatography (TLC) was performed with Analtech silica gel GF TLC plates (250 μm) and visualization was effected with a 5% solution of 12-molybdophosphoric acid in ethanol. Gravity column chromatography was done with Merck Silica Gel 60 (70–230 mesh ASTM), and flash chromatography[11] was done with MN silica gel 60 (230–400 mesh ASTM). High-performance liquid chromatography (HPLC) was done with a Waters Model ALC-GPC-244 liquid chromatograph using a μ-Porasil column. Elemental analyses were performed by the Microanalytical Laboratory, operated by the College of Chemistry, University of California, Berkeley, CA.

(*R*)-Monomethyl 3-Hydroxypentanedioate (5). This material was prepared as described previously:[2] ^{1}H NMR δ 2.59 (d, 2, J = 6.4), 2.62 (d, 2, J = 6.4), 3.73 (s, 3), 4.48 (quintet, 1, J = 6.3).

(*S*)-Methyl *tert*-Butyldimethylsilyl 3-[(*tert*-Butyldimethylsilyl)oxy]pentanedioate (7). Under a nitrogen atmosphere, into a 100-mL round-bottomed flask equipped with a magnetic stirring bar and a rubber septum was placed 428 mg (2.64 mmol) of **5** in 3 mL of CH_2Cl_2. To the stirring solution was added 735 mg (10.8 mmol) of imidazole followed by 816 mg (5.41 mmol) of *tert*-butylchlorodimethylsilane. The mixture was stirred at room temperature for a period of 18 h and then treated with an additional 220 mg (3.23 mmol) of imidazole and 245 mg (1.62 mmol) of *tert*-butylchlorodimethylsilane. After being stirred for 6 h, the mixture was diluted with ether and washed with saturated aqueous $NaHCO_3$, water, and brine. The combined aqueous washing were extracted with ether. The combined organic fractions were dried over $MgSO_4$, and the solvent was removed with a rotary evaporator to obtain 1.04 g (100%) of crude **7** as a white solid. A small sample was purified by flash chromatography (242 mg of crude **7**, 17 g of silica gel) with 1:4 ether/hexanes as the eluant to obtain 111 mg of analytically pure **7** as a white crystalline solid:[11] mp 44–46 °C; IR ($CHCl_3$); 2950, 2860, 1735, 1720 cm^{-1}; ^{1}H NMR δ 0.06 (s, 3), 0.08 (s, 3), 0.26 (s, 6), 0.84 (s, 9), 0.93 (s, 9), 2.56 (m, 4), 3.67 (s, 3), 4.52 (quintet, 1, J = 6.1). Anal. Calcd for $C_{18}H_{38}O_5Si_2$: C, 55.34; H, 9.80. Found: C, 55.50; H, 9.81.

(3*R*,1′*R*)-*N*-(1′-Phenylethyl)-3-[(*tert*-butyldimethylsilyl)oxy]-4-carbomethoxybutanamide (9). Under an argon atmosphere, into an oven-dried 10-mL round-bottomed flask equipped with a rubber septum and a magnetic stirring bar was placed 22.1 mg (0.057 mmol) of analytically pure **7** in 0.1 mL of a mixture of 1 drop of DMF in 3 mL of CH_2Cl_2. To the stirring solution, at 0 °C, was added 6.5 μL (9.4 mg, 0.074 mmol) of oxalyl chloride dropwise by syringe. The reaction mixture was stirred for 1.5 h at 0 °C and 25 min at room temperature. The system was cooled to 0 °C, and a solution of 31 μL (29.2 mg, 0.23 mmol) of (*R*)-1-phenylethanamine in 0.13 mL of CH_2Cl_2 (0.05 mL rinse) was added to the mixture. The cooling bath was removed and the mixture was stirred for 2 h at room temperature, diluted with 25 mL of ether, and washed with 5 mL of water, 5 mL of 1 M aqueous phosphoric acid, 10 mL of 1 M aqueous phosphoric acid, 5 mL of saturated aqueous $NaHCO_3$, and 5 mL of brine. The ether solution was dried over $MgSO_4$, and the solvent was removed with a rotary evaporator to obtain 28.2 mg of pale yellow oil. The crude product was analyzed by HPLC with the following parameters: solvent: 3:1 ether/hexanes; flow rate, 2.0 mL min^{-1}; pressure, 250–300 psi; detector, UV (254 nm); t_R 3.6 min (**9**), 4.8 min (**10**). The crude material was purified by column chromatography (2.5 g of silica gel with 2:1 ether/hexanes as the eluant to obtain 19.0 mg (88% yield) of amide as a colorless oil.

Compound **9**: IR ($CHCl_3$) 3450, 3370, 2950, 2850, 1730, 1660 cm^{-1}; ^{1}H NMR δ 0.08 (s, 3), 0.10 (s, 3), 0.86 (s, 9), 1.47 (d, 3, J = 7.0), 2.39 (dd, 1, J = 5.2, 15), 2.45 (d, 1, J = 2.4), 2.48 (d, 1, J = 1.8), 2.55 (d, 1, J = 5.1, 15), 3.65 (s, 3), 4.50 (m, 1), 5.12 (m, 1), 6.55 (br d, 1, J = 7.6), 7.35 (m, 5). Anal. Calcd for $C_{20}H_{33}O_4Si$: C, 63.28; H, 8.76, N, 3.83. Found: C, 63.04; H, 8.70; N, 3.83.

Compound **10**: IR ($CHCl_3$) 3950, 3370, 2950, 2860, 1730, 1660 cm^{-1}; ^{1}H NMR δ 0.03 (s, 3), 0.06 (s, 3), 0.79 (s, 9), 1.50 (d, 3, J = 6.9), 2.40 (dd, 1, J = 4.9, 15), 2.55 (dd, 1, J = 5.2, 15), 2.59 (d, 2, J = 6.1), 3.68 (s, 3), 4.52 (m, 1), 5.12 (m, 1), 6.55 (br d, 1, J =

(8) Birkofer, L.; Ritter, A. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 417.
(9) For additional recent examples of the synthetic potential of **5**, see: (a) Morrison, M. A.; Miller, M. J. *J. Org. Chem.* **1983**, *48*, 4421. (b) Brooks, D. W.; Palmer, J. T. *Tetrahedron Lett.* **1983**, *24*, 3059.
(10) On a relatively small scale (less than 5 mmol), the corresponding dipotassium salt has been converted to **13** in greater than 80% yield (**12** → **13**). However, the disodium salt is more convenient for larger scale preparations, because it is pulverized more readily and more soluble in benzene than its potassium counterpart.
(11) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(12) Compound **7** is somewhat unstable to silica gel chromatography, presumably due to silyl ester cleavage.

7.6), 7.35 (m, 5). Anal. Calcd for $C_{20}H_{33}NO_4Si$: C, 63.28; H, 8.76; N, 3.83. Found: C, 63.04; H, 8.85; N, 3.59.

Diethyl 3-[(*tert*-Butyldimethylsilyl)oxy]pentanedioate (12). Under a nitrogen atmosphere, into a 100-mL round-bottomed flask equipped with a rubber septum and a magnetic stirring bar was placed 4.08 g (60.0 mmol) of imidazole in 35 mL of CH_2Cl_2. To this solution was added a solution of 4.50 g (30.0 mmol) of *tert*-butylchlorodimethylsilane in 10 mL of CH_2Cl_2. After the reaction mixture was stirred for 10 min, a solution of 4.08 g (20.0 mmol) of diethyl 3-hydroxypentanedioate (11) in 10 mL of CH_2Cl_2 was added dropwise. The mixture was stirred for 18 h at room temperature and partitioned between 250 mL of ether and 50 mL of water. The layers were separated, the organic phase was washed with 50 mL of brine, and the combined aqueous washings were extracted with 100 mL of ether. After drying the combined organic fractions over $MgSO_4$, the solvent was removed with a rotary evaporator to afford 6.13 g of yellow liquid. The crude material was purified by silica gel column chromatography with 1:8 ether/hexanes as the eluant to obtain 6.07 g (95% yield) of 12 as a colorless liquid: IR (film) 2940, 2865, 1745 cm^{-1}; ^1H NMR δ 0.07 (s, 6), 0.84 (s, 9), 1.26 (t, 6, J = 7.1), 2.54 (d, 4, J = 6.2), 4.12 (q, 2, J = 7.1), 4.13 (q, 2, J = 7.2), 4.55 (quintet, 1, J = 6.2). Anal. Calcd for $C_{15}H_{30}O_5Si$: C, 56.56; H, 9.50. Found: C, 56.71; H, 9.35.

Diethyl 3-[(trimethylsilyl)oxy]pentanedioate (14): IR (film) 2975, 1730, 1370, 1250 cm^{-1}; ^1H NMR δ 0.01 (s, 9), 1.16 (t, 6, J = 7.2), 2.42 (d, 4, J = 6.3), 4.02 (dd, 2, J = 5.4, 7.2), 4.08 (dd, 2, J = 5.4, 7.2), 4.46 (m, 1). Anal. Calcd for $C_{12}H_{24}O_5Si$: C, 52.14; H, 8.75. Found: C, 51.92; H, 8.56.

3-[(*tert*-Butyldimethylsilyl)oxy]pentanedioic Anhydride (13). Under a nitrogen atmosphere, into a 100-mL round-bottomed flask equipped with a rubber septum and a magnetic stirring bar was placed 4.40 g (13.8 mmol) of diester 12 and 1.10 g (27.6 mmol) of NaOH. To the system was added 15 mL of methanol, and the mixture was stirred overnight at room temperature. The solvent was removed with a rotary evaporator, and residual methanol was removed under high vacuum (5 h, 0.9 torr) to obtain a tan solid. The system was equipped with a reflux condenser, charged with 30 mL of benzene and 20 mL of acetic anhydride, and heated at reflux for a period of 1.5 h. After being cooled to room temperature, the reaction mixture was partitioned between 300 mL of $CHCl_3$ and 100 mL of brine, the layers were separated, and the organic phase was washed with three 100-mL portions of aqueous $NaHCO_3$. The $CHCl_3$ solution was dried over $MgSO_4$ and the solvent was removed with a rotary evaporator. The resulting pale brown oil crystallized under high vacuum (4 h, 50 °C, 0.7 torr). The crude material was washed with hexanes and recrystallized from hexanes to obtain 2.36 g (70% yield)[10] of 13 as white plates: mp 80–81 °C; IR ($CHCl_3$) 2925, 2860, 1820, 1765, 1255 cm^{-1}; ^1H NMR δ 0.10 (s, 6), 0.86 (s, 9), 2.72 (dd, 2, J = 2.7, 16), 2.92 (dd, 2, J = 3.8, 16), 4.38 (m, 1). Anal. Calcd for $C_{11}H_{20}O_4Si$: C, 54.08; H, 8.25. Found: C, 53.93; H, 8.27.

Racemic Methyl *tert*-Butyldimethylsilyl 3-[(*tert*-Butyldimethylsilyl)oxy]pentanedioate (7 and 8). Under a nitrogen atmosphere, into a 50-mL round-bottomed flask equipped with a rubber septum and a magnetic stirring bar was placed 6 mL of methanol. To the system was added 176 mg (7.66 mmol) of sodium, and the mixture was stirred at room temperature until all the sodium had reacted (20 min). To the system, at 0 °C, was added a solution of 1.50 g (6.15 mmol) of anhydride 13 in 6 mL of methanol, and the mixture was stirred for 1 h at 0 °C. The solvent was removed with a rotary evaporator, and residual methanol was removed under high vacuum (1 h, 0.4 torr). The resulting oil was partitioned between 30 mL of CH_2Cl_2 and 7 mL of 5% aqueous hydrochloric acid, the layers were separated, and the organic phase was washed with two 10-mL portions of brine. The $CHCl_3$ solution was dried over $MgSO_4$, and the solvent was removed with a rotary evaporator to obtain 1.68 g of crude methyl 3-[(*tert*-butyldimethylsilyl)oxy]pentanedioate, which was silylated without further purification.

Under a nitrogen atmosphere, into a 50-mL round-bottomed flask equipped with a rubber septum and a magnetic stirring bar was placed 868 mg (12.7 mmol) of imidazole in 6 mL of CH_2Cl_2. To the resulting solution was added 960 mg (6.38 mmol) of *tert*-butylchlorodimethylsilane in 1.5 mL of CH_2Cl_2. After 10 min a solution of the foregoing crude silyloxy acid (1.68 g, 6.09 mmol) in 4.5 mL of CH_2Cl_2 was added, and the mixture was stirred for 1 h at room temperature. The reaction mixture was diluted with 40 mL of ether and washed with two 5-mL portions of water, 5 mL of saturated aqueous $NaHCO_3$, and 5 mL of brine. The organic phase was dried over $MgSO_4$, and the bulk of the solvent was removed with a rotary evaporator. The residue was subjected to high vacuum (1 h, 0.4 torr) to obtain 2.13 g (89% yield from 13) of racemic silyl ester; mp 40–41 °C. The ^1H NMR spectrum of the product thus obtained was identical with that of the optically active material (7).

The racemic compound was converted to a 1:1 mixture of diastereomeric amides 9 and 10 by the procedure outlined above. Analysis of the crude product mixture by HPLC indicated a 9:10 ratio of 49.8:50.2.

Registry No. 5, 87118-53-4; 6, 87118-64-7; 7, 91424-35-0; (±)-7, 91465-61-1; 8, 91424-36-1; 9, 91424-37-2; 10, 91424-38-3; 11, 32328-03-3; 12, 91424-39-4; 13, 91424-40-7; 14, 91424-41-8; *tert*-butylchlorodimethylsilane, 18162-48-6.

Convenient Preparation of *N,N*-Dimethylacetamide Dimethyl Acetal

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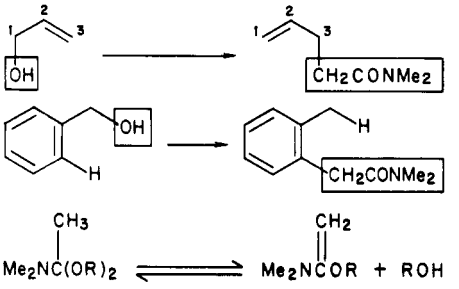
N,N-Dimethylacetamide acetals are valuable reagents for C–C connective syntheses of γ,δ-unsaturated amides[1] from allylic alcohols (eq 1) and (*o*-methylaryl)acetamides[1a] from arene methanols (eq 2) via amide-Claisen rearrangements. These syntheses exploit a facile reversible in situ generation of 1-(dimethylamino)-1-alkoxyethylenes[2] from *N,N*-dimethylacetamide acetals (eq 3).



Previously, *N,N*-dimethylacetamide acetals were prepared from dimethylacetamide by reaction with trialkyloxonium fluoborates followed by sodium alcoholate.[3] We now report experimental details for a different synthesis of *N,N*-dimethylacetamide dimethyl acetal[4] which is patterned after a synthesis of dimethylformamide dimethyl acetal[5] from dimethylformamide–dimethyl sulfate complex.[1d] The present method[6] is more convenient because

(1) (a) Wick, A. E.; Felix, D.; Steen, K.; Eschenmoser, A. *Helv. Chim. Acta* **1964**, *47*, 2425. (b) Hill, R. K.; Soman, R.; Sawada, S. *J. Org. Chem.* **1972**, *37*, 3737. (c) Ziegler, F. E.; Bennett, G. B. *J. Am. Chem. Soc.* **1973**, *95*, 7458. (d) Bredereck, H.; Effenberger, F.; Simchen, G. *Chem. Ber.* **1963**, *96*, 1350. (e) Meerwein, H.; Florian, W.; Schön, N.; Stopp, G. *Liebigs. Ann. Chem.* **1961**, *641*, 1.

(2) Felix, D.; Gschwend-Steen, K.; Wick, A. E.; Eschenmoser, A. *Helv. Chim. Acta* **1969**, *52*, 1030.

(3) Meerwein, H.; Florian, W.; Schön, N.; Stopp, G. *Liebigs Ann. Chem.* **1961**, *641*, 1.

(4) 1,1-Dimethoxy-1-(dimethylamino)ethane.

(5) Bredereck, H.; Simchen, G.; Rebstdat, S.; Kantlehner, W.; Horn, P.; Wahl, R.; Hoffmann, H.; Grieshaber, P. *Chem. Ber.* **1968**, *101*, 41.

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