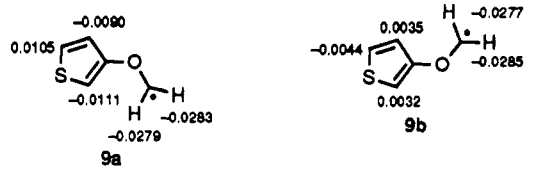
Scheme IV



Ar–O rotation, $\Delta E^{*} = 3.75$ kcal/mol
O–$\dot{C}H_2$ rotation, $\Delta E^{*} = 2.94$ kcal/mol

could be disentangled and are as follows: 0.8 G (2 H), 17.6 G (2 H). The small splitting corresponds to a pair of accidentally equivalent positions in the ring (the third ring splitting being 0) and the large splitting to the pair of OCH_2 hydrogens.

Finally, radical **9** could be obtained from 3-methoxythiophene. Its ESR spectrum at -40 °C is even simpler than that of **2** in that it features a triplet (a_H = 17.5 G) for the pair of the CH_2 hydrogens and a doublet (a_H = 0.85 G) for one of the ring hydrogens. The ab initio calculations (Scheme IV) indicate that **9a** is more stable than **9b** by 1.8 kcal/mol: the observed ring splitting was assigned to position 2. At lower temperatures (below -120 °C) the spectrum of **9** displays two different CH_2 splittings (16.7 and 18.7 G) and this allowed us to determine, by computer line shape simulation, a value of 4.7 ± 0.2 kcal/mol for the O–$\dot{C}H_2$ rotational process. Such a value, as predicted by the calculations, is indeed larger than that determined for **2** (4.15 ± 0.2 kcal/mol). Even more interesting is the observation that in the spectrum of **9**, below -120 °C, two additional lines were also detected (Figure 2). The intensity of each of these lines is about 20–30% that of each line of the main spectrum, and they coalesce in a reversible manner with the corresponding more intense companions. These less intense lines are most likely due to the second conformer, generated by the restricted rotation about the Ar–O bond: according to the ab initio calculations they are part of the spectrum of the less stable conformer **9b**. Owing to the presence of only two visible lines, a complete analysis of the spectrum of the minor conformer could not be carried out. However, the fact that the majority of the spectral lines of the two conformers are superimposed indicates that the two sets of hyperfine splittings are extremely similar. Only the existence of two different *g* factors allowed two spectra for the two conformers to be detected. This lends support to the view that, in the case of **1** and **2** (where symmetry prevents the existence of conformers and hence of different *g* factors), the difference of the H splittings for the ortho positions is too small to be detected. Furthermore, in the ESR spectrum of radical **9** the separation of the ESR lines corresponding to the pair of rotational conformers (0.5 G) is much smaller than that (2.0 G) originated by the restricted O–$\dot{C}H_2$ rotation. The latter coalesce, nonetheless, in the same temperature range of the former ones, thus indicating that the Ar–O rotational barrier of **9** (although not accurately measurable) cannot be smaller (and is most likely larger) than that of the O–$\dot{C}H_2$ barrier, in agreement with the theoretical predictions.

Conclusions

With this final experiment on 3-methoxythiophene we have obtained evidence for the existence of the restricted Ar–O rotation in radicals of the type $ArO\dot{C}H_2$. Such an effect can only rarely be observed owing to similarity of the splittings of the ring hydrogens in positions syn and anti to the CH_2 moiety. On the other hand, the a_H values of the two methylenic hydrogens are sufficiently different that accurate determinations of O–$\dot{C}H_2$ rotational barriers can be made provided appropriate compounds are selected and sufficiently low temperatures reached.

Experimental Section

Materials. 1,3,5-Trimethoxybenzene and 2-methoxyfuran were commercially available and were purified before the use. 2-Methoxythiophene,[21] 3-methoxythiophene,[22] and 2-methylthiofuran[23] were prepared following the literature. 2,5-Dimethoxythiophene was prepared[21] by refluxing for 75 h the commercially available 2,5-dibromothiophene (6 g, 25 mmol) with 2.2 g (27 mmol) of cupric oxide in a flask containing 40 mL of 10% sodium methoxide in methanol (174 mmol). The reaction mixture was cooled, the solid part was filtered off, and the solvent was removed. The residue was poured on water (50 mL) and extracted with Et_2O. After the organic layer was dried and the solvent was eliminated, the crude product was distilled at low pressure: yield 1.6 g (45%); bp (5 mmHg) 92–93 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 3.8 (6 H, s, CH_3), 5.8 (2 H, s, CH); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 60.4 (q, CH_3), 101.1 (d, CH), 154.7 (s, C). Anal. Calcd for $C_6H_8O_2S$: C, 50.0; H, 5.5. Found: C, 49.6; H, 5.8.

ESR Measurements. The spectra were obtained by photolysis of cyclopropane solutions containing di-*tert*-butyl peroxide within the cavity of an ESR spectrometer (Varian E-3). The samples were prepared by condensing the cyclopropane into quartz tubes (containing the appropriate material) connected to a vacuum line. The tubes were then sealed in vacuo. The temperatures were monitored by inserting a thermocouple in the ESR cavity before or after the spectral measurements.

Acknowledgment. We gratefully thank Prof. F. Bernardi (University of Bologna) for helpful comments and stimulating discussions on performing and interpreting the theoretical calculations. Financial support has been received from the Ministry for the Scientific Research (MURST) and from the CNR.

Registry No. **1**, 17374-79-7; **2**, 69305-47-1; **3**, 130410-19-4; **4**, 130410-20-7; **7**, 130410-21-8; **9**, 130410-22-9; $Me_3CO^{\bullet}$, 3141-58-0; 1,3,5-trimethoxybenzene, 621-23-8; 2-methoxyfuran, 25414-22-6; methoxythiophene, 16839-97-7; 3-methoxythiophene, 17573-92-1; 2-methylthiofuran, 13129-38-9; 2,5-dimethoxythiophene, 58386-20-2; 2,5-dibromothiophene, 3141-27-3; di-*tert*-butyl peroxide, 110-05-4.

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A Useful New Enantiomerically Pure Synthon from Malic Acid: Chelation-Controlled Activation as a Route to Regioselectivity

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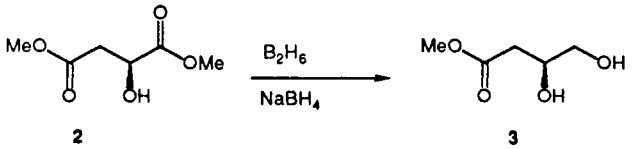
Recently, we had need of aldehyde **1**, which could, in principle, be obtained in optically active form from malic acid. However, no simple methods for achieving the required transformations are presently known. The closest report is that of Saito, who found that reduction of di-



2 **3**

methyl malate (**2**) with diborane and catalytic amounts of

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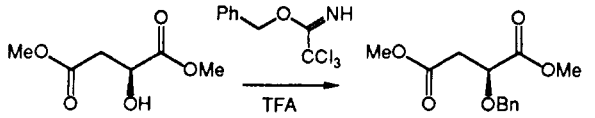
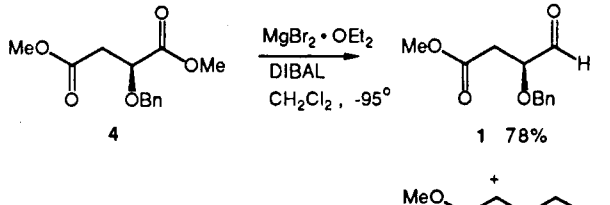
sodium borohydride afforded diol **3** with no detectable reduction at C_4.[1] Unfortunately, this procedure is not applicable to derivatives of dimethylmalate in which the hydroxyl group is protected, as no regioselectivity is observed in such reductions.

It occurred to us that selective activation of the C_1 ester function toward reducing agents could, in principle, be achieved via bidentate complexation of the C_1 carbonyl oxygen and the protected hydroxyl at C_2, provided that a Lewis acid with a marked preference for five-ring (vs six-ring) chelation could be identified. Several observations from these laboratories suggested that Mg^{2+} would be an excellent candidate for such a Lewis acid. In fact, magnesium bromide etherate proves to be highly successful in this regard, and we detail herein the preparation of two new enantiomerically pure synthons derived from the protected dimethyl malate **4**[2] using this simple stratagem, the use of aldehyde **1** in further stereocontrolled elaborations, and application of this procedure to **9**, a homologue of **4**.



2 **4** 68%

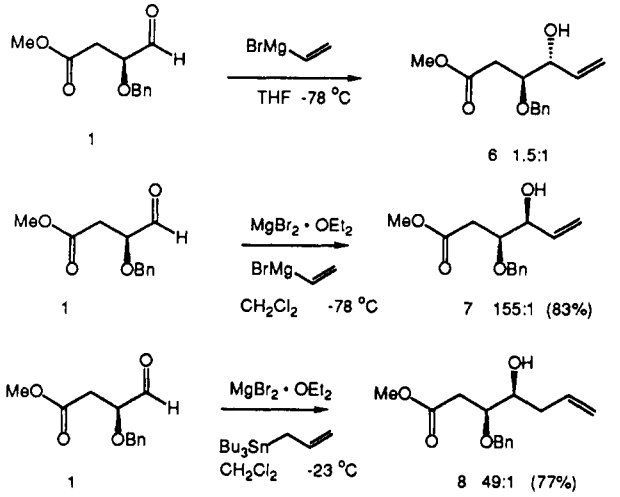
Conversion of **4** to the desired aldehyde **1** was easily achieved by addition of **4** to a stirring suspension of magnesium bromide etherate in methylene chloride at 0 °C, stirring the solution at 0 °C for 1 h to insure complete complexation, cooling the solution to −90 to −95 °C (ether–dry ice bath), and slowly adding 1.0 equiv of diisobutylaluminum hydride. Quenching with methanol and workup with saturated aqueous Rochelle salts then afforded the desired aldehyde **1** with no observed reduction of the C_4 carbonyl function. In several runs on various scales, the only observed byproducts are the alcohol **5** derived from overreduction and unreacted starting material. It should be noted that the use of magnesium bromide is essential to obtain this result; in the absence of magnesium bromide, mixtures containing all possible reduction products are produced.



4 **1** 78% **5**

If alcohol **5** is desired, it can be prepared very cleanly and in high yield by using a simple variation of the process above: addition of 2.0 equiv of diisobutylaluminum hydride to a solution of the magnesium bromide complex of **4** at −40 °C.

The aldehyde **1** has proven to be an especially useful chiral intermediate due to the high levels of diastereofacial selectivity that may be realized upon the addition of various carbon nucleophiles. One case that has been examined quite thoroughly is the addition of vinyl organometallics to **1**. With commercial solutions of vinylmagnesium bromide in THF, using THF as solvent, the Felkin–Anh[3] product **6** is the major observed product, with low (1.5:1) diastereoselectivity; the same results are obtained when vinyllithium is used.[4] The "chelation controlled" product is produced with modest (4:1) selectivity upon addition of vinylmagnesium bromide (as a THF solution) to a solution of **1** in methylene chloride containing 1 equiv of magnesium bromide. Attempts to improve upon the diastereofacial selectivity in the chelation manifold by employing the reagent formed from vinylmagnesium bromide, magnesium bromide etherate, and cuprous iodide in either ether or mixtures of ether and dimethyl sulfide as solvent[5] proved unsuccessful as poor selectivity and low conversions of starting material to product were found in this case. With methylene chloride as solvent, excellent stereoselectivity was observed (40:1), but this procedure was compromised by the reaction of reagent with solvent in competition with addition to the aldehyde, which necessitated that 10 equiv or more of reagent be employed to achieve complete consumption of starting material. By far the best results were obtained by simply removing THF in vacuo from commercial vinylmagnesium bromide in THF, adding methylene chloride, and adding this solution to the complex formed from **1** and 1 equiv of magnesium bromide etherate in methylene chloride, which gave the chelation-controlled product **7** in excellent yield (83%) and with remarkably high (155:1) diastereofacial selectivity.



1 **6** 1.5:1

1 **7** 155:1 (83%)

1 **8** 49:1 (77%)

We have also examined the Lewis acid mediated addition of allyltri-*n*-butylstannane to **1**. As expected, based upon previous work in our laboratories,[6] good diastereofacial selectivity consistent with "chelation control" is readily achieved under mild conditions by employing magnesium bromide etherate as the Lewis acid, which affords **8** in 77% yield and 49:1 stereoselectivity. Finally, the same selective reduction procedure has been applied to the benzyloxy-protected substrate **9**, which affords aldehyde **10** in 70% isolated yield.

Although there are numerous examples in the literature that employ chelation to control the stereochemistry of

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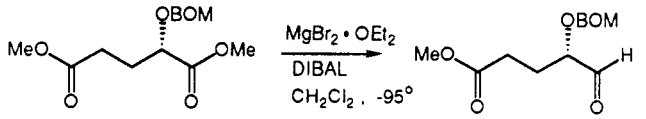

9 10

nucleophilic additions to carbonyl compounds, the concept of using such effects to control regioselectivity by specifically activating one of two identical functional groups is far less common. We expect that this strategy will prove generally useful, particularly with reagents of low nucleophilicity, and further studies to test this premise are in progress.

Experimental Section

General Procedures. All reactions were carried out under an atmosphere of argon or nitrogen. Solvents were purified according to the guidelines in *Purification of Common Laboratory Chemicals* (Perrin, Armarego, and Perrin, Pergamon: Oxford, 1966). Reagent-grade methanol was purchased and used without further purification. Yields were calculated for material judged homogeneous by TLC and NMR. TLC was performed on Merck kieselgel 60 F_{254} plates, visualizing with a 254-nm UV lamp and staining with an ethanol solution of 12-molybdophosphoric acid. Column chromatography was performed with use of W. G. Grace Davisil 62 silica gel, slurry packed in glass columns. MPLC was performed with Altex columns packed with W. G. Grace Davisil 633 silica gel. Solvents were pumped with an FMI lab pump operating between 60 and 100 psi and fractions were collected with Gilson fractionators. Capillary GC analyses were carried out on J and W DB-5 or DX-4 columns 30 m in length with a film thickness of 1 μm (DB-5) and 0.25 μm (DX-4), with He as the carrier gas (80 psi) and flame ionization detection. Optical rotations were obtained at room temperature with a microcell, 1-dm path length. ^{1}H and ^{13}C NMR spectra were acquired at 75 MHz and 300 MHz, respectively. Exact mass values were calculated by peak matching with an internal standard whose mass was within ±10% of the unknown compound. Infrared spectral data are approximate (±5 cm^{-1}).

Dimethyl (*S*)-2-(Phenylmethoxy)butanedioate (4). To a stirring solution of (*S*)-malic acid dimethyl ester (3.7 g, 23 mmol) in 150 mL of cyclohexane and 75 mL of methylene chloride was added freshly prepared *O*-benzyl trichloroacetimidate (17 g, 69 mmol). To the mixture was slowly added trifluoroacetic acid (1.7 g, 15 mmol), and the solution was stirred for 36 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (5 mL) and water (200 mL). The aqueous layer was separated and extracted with 30% EtOAc/hexanes (3 × 200 mL). The combined organic layer was dried with Na_2SO_4 and concentrated. The mixture was diluted with 10% EtOAc/hexanes and gravity filtered to remove the solid trichloroacetamide. The filtrate was concentrated and chromatographed by MPLC through a 100 × 2.5 cm column monitored by UV detection (254 nm), eluting with 20% EtOAc/hexanes. The product-containing fractions were combined and concentrated to yield 3.9 g (68%) of a colorless oil: $[\alpha]_D$ −68.5° (*c* 11.4, $CHCl_3$); R_f 0.48 (35% EtOAc/hexanes); 300-MHz ^{1}H NMR ($CDCl_3$) δ 7.32 (m, 5 H), 4.65 (AB q, $\Delta\delta_{AB}$ = 70.3 Hz, J = 11.4, 2 H), 4.40 (dd, J = 7.4, 7.4 Hz, 1 H), 3.76 (s, 3 H), 3.68 (s, 3 H), 2.81 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 171.7, 170.4, 137.1, 128.3, 128.0, 127.9, 74.4, 73.0, 52.1, 51.9, 37.7; IR (neat) 3025, 2950, 1740, 1495, 1435, 1360, 1275, 1165, 1115, 1020, 740, 695. Anal. Calcd for $C_{13}H_{16}O_5$: C, 61.90; H, 6.36. Found: C, 62.07; H, 6.38.

Methyl (*S*)-4-Oxo-3-(phenylmethoxy)butanoate (1). To a stirring solution of (S)-*O*-benzylmalic acid dimethyl ester (0.45 g, 1.77 mmol) in methylene chloride (25 mL) was added magnesium bromide etherate (0.5 g, 2 mmol). The solution was stirred for 1 h and cooled to −90 °C. To the solution was added a 1.5 M solution of diisobutylaluminum hydride in toluene (1.5 mL, 2.1 mmol) via syringe pump over 90 min. After complete addition and 30 min, methanol (2 mL) was slowly added followed by saturated Rochelle salts (30 mL). The mixture was warmed to room temperature and stirred for 2 h. The layers were separated and the aqueous phase was extracted three times with methylene chloride (30 mL). The combined organic phase was dried with Na_2SO_4 and concentrated. The mixture was separated by MPLC through a 50 × 2.5 cm column monitored by UV detection (254 nm), eluting with 20% EtOAc/hexanes. The product-containing fractions were collected and concentrated to yield 0.32 g (78%) of a colorless oil: $[\alpha]_D$ −56.3° (*c* 0.7 $CHCl_3$); R_f 0.39 (35% EtOAc/hexanes); 300-MHz ^{1}H NMR ($CDCl_3$) δ 9.73 (d, J = 0.7 Hz, 1 H), 7.29 (m, 5 H), 4.70 (s, 2 H), 4.17 (ddd, J = 6.8, 4.8, 0.7 Hz, 1 H), 3.68 (s, 3 H), 2.80 (dd, J = 16.4, 4.8 Hz, 1 H), 2.71 (dd, J = 16.4, 6.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 201.9, 170.4, 136.9, 128.5, 128.1, 128.0, 79.5, 73.0, 52.0, 35.7; IR (neat) 3030, 2950, 2860, 2730, 1740, 1495, 1455, 1440, 1360, 1260, 1190, 1170, 1110, 1025, 890, 740, 695; mass spectrum (CI, isobutane), m/z (rel intensity) (M + 1) 223 (27), 181 (2), 131 (2), 116 (7), 103 (8), 91 (100); HRMS exact mass calcd for $C_{12}H_{15}O_4$ 223.09862, found 223.09703. Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.36; H, 6.55.

Methyl (3*S*,4*S*)-4-Hydroxy-3-(phenylmethoxy)hept-6-enoate (8). To a stirring solution of (*S*)-3-(benzyloxy)-4-oxobutanoic acid methyl ester (0.12 g, 0.54 mmol) in methylene chloride (6 mL) at −23 °C was added magnesium bromide etherate (0.17 g, 0.65 mmol). The solution was stirred for 20 min, and to the solution was slowly added allyltri-*n*-butylstannane (0.21 g, 0.65 mmol) via syringe over 10 min. The solution was stirred for 7 h and allowed to warm to room temperature. The reaction was quenched with saturated aqueous NH_4Cl (2 mL) and water (5 mL). The aqueous layer was separated and extracted three times with methylene chloride (3 × 7 mL). The combined organic phase was dried with Na_2SO_4 and concentrated. The mixture was separated by gravity chromatography with a 10 × 1 cm column, eluting with 15% EtOAc/hexanes. The product-containing fractions were collected and concentrated to yield 0.11 g (77%) of a colorless oil (49:1 mixture of inseparable diastereomers): $[\alpha]_D$ +2.0° (*c* 1.6 $CHCl_3$); R_f 0.36 (35% EtOAc/hexanes); capillary GC (DX-4, 149–250 °C, 3 °C/min) (minor) 20.4 min, (major) 22.2 min; 300-MHz ^{1}H NMR ($CDCl_3$) δ 7.32 (m, 5 H), 5.84 (m, 1 H), 5.16 (m, 2 H), 4.62 (AB q, $\Delta\delta_{AB}$ = 22.3, J = 11.2 Hz, 2 H), 3.91 (ddd, J = 6.5, 6.0, 3.9 Hz, 1 H), 3.69 (s, 3 H), 3.68 (m, 1 H), 2.73 (dd, J = 15.9, 5.8 Hz, 1 H), 2.65 (dd, J = 15.9, 6.6 Hz, 1 H), 2.32 (m, 2 H), 2.19 (d, J = 6.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 172.4, 138.1, 134.8, 128.7, 128.1, 128.1, 117.0, 77.9, 73.2, 72.6, 52.0, 38.2, 36.3; IR (neat) 3480 (br), 3070, 3035, 2955, 2910, 1740, 1645, 1500, 1455, 1440, 1360, 1270, 1195, 1170, 1075, 1025, 990, 915, 735, 695; HRMS exact mass calcd for (M + 1) $C_{15}H_{21}O_4$ 265.14203, found 265.14398. Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.07; H, 7.16.

Methyl (3*S*,4*S*)-4-Hydroxy-3-(phenylmethoxy)hex-5-enoate (7). To a stirring solution of (*S*)-3-(benzyloxy)-4-oxobutanoic acid methyl ester (0.10 g, 0.45 mmol) in methylene chloride (6 mL) was added magnesium bromide etherate (0.14 g, 0.54 mmol). The solution was stirred for 1 h and cooled to −78 °C. A solution of vinylmagnesium bromide in methylene chloride was prepared by three freeze, evaporation, and dilution cycles of the commercially available (Aldrich) 1 M in THF solution of vinylmagnesium bromide. To the aldehyde/magnesium bromide complex was added a 1 M solution of vinylmagnesium bromide in methylene chloride (0.59 mL, 0.59 mmol) slowly via syringe over 15 min. The reaction was stirred for 5 h and allowed to warm to room temperature. The reaction was quenched with saturated aqueous NH_4Cl (2 mL) and water (5 mL). The aqueous layer was separated and extracted with methylene chloride (3 × 10 mL) The combined organic phase was dried with Na_2SO_4 and concentrated. The mixture was separated by gravity chromatography with a 15 × 1.5 cm column eluting with 20% EtOAc/hexanes. The product-containing fractions were collected and concentrated to yield 0.093 g (83%) of a colorless oil (155:1 mixture of inseparable diastereomers): $[\alpha]_D$ −16.8° (*c* 0.41 $CHCl_3$); R_f 0.45 (35% EtOAc/hexanes); capillary GC (DX-4, 149–250 °C, 5 °C/min) (minor) 13.7 min, (major) 15.3 min; 300-MHz ^{1}H NMR ($CDCl_3$) δ 7.30 (m, 5 H), 5.91 (m, 1 H), 5.32 (m, 2 H), 4.63 (AB q, $\Delta\delta_{AB}$ = 40.1 Hz, J = 11.4 Hz, 2 H), 4.15 (m, 1 H), 3.93 (ddd, J = 7.0, 5.3, 5.2 Hz, 1 H), 3.69 (m, 1 H), 3.67 (s, 3 H), 2.66 (dd, J = 15.6, 5.6 Hz, 1 H), 2.60 (dd, J = 15.6, 7.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 172.0, 137.9, 136.9, 128.4, 128.3, 127.9, 117.2, 78.7, 74.2, 73.3, 51.7, 36.2; IR (neat) 3470 (br), 3075, 3035, 2955, 2880, 1735, 1665, 1495, 1455, 1430, 1360, 1250, 1170, 1075, 1025, 990, 925, 735, 695; HRMS exact mass calcd for $C_{14}H_{19}O_4$ 251.12856, found 251.12833. Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 66.51; H, 6.97.

Dimethyl (*S*)-2-((Phenylmethoxy)methoxy)pentanedioate (9). A solution of (*S*)-α-butyrolactone-α-carboxylic acid (5.22 g, 0.0401 mol) and 4 drops of concentrated HCl in 50 mL of dry methanol was heated to reflux overnight. The mixture was cooled to 0 °C, and solid $NaHCO_3$ was added. The solution was filtered, concentrated in vacuo, then taken up in 50 mL of methylene chloride, and dried. Filtration followed by concentration in vacuo gave 7.06 g (100%) of the desired diester. This material was immediately dissolved in 80 mL of methylene chloride and treated with diisopropylethylamine (11.4 g, 88.2 mmol) and chloromethyl benzyl ether (12.6 g, 80.2 mmol). After stirring at room temperature for 48 h, aqueous workup and ether extraction followed by MPLC chromatography (silica gel, 25% EtOAc/hexanes) gave 10.2 g (86%) of the protected diester as a colorless oil: $[\alpha]_D$ -38.6° (*c* 3.94, $CHCl_3$); R_f 0.41 (35% EtOAc/hexanes); 300-MHz ^1H NMR ($CDCl_3$) δ 7.33 (m, 5 H), 4.81 (dd, *J* = 1.2 Hz, 2 H), 4.63 (s, 2 H), 4.26 (dd, *J* = 7.6, 4.9 Hz, 1 H), 3.70 (s, 3 H), 3.66 (s, 3 H), 2.48 (dt, *J* = 3.7, 2.9 Hz, 2 H), 2.12 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 173.1, 172.4, 137.4, 128.4, 127.8, 127.7, 94.3, 74.4, 70.1, 29.5, 27.8; IR (neat, cm^{-1}) 3050, 2900, 1740, 1730. Anal. Calcd for $C_{15}H_{20}O_6$: C, 60.80; H, 6.80. Found: C, 60.92; H, 6.77.

Methyl (*S*)-5-Oxo-4-((phenylmethoxy)methoxy)pentanoate (10). A solution of the protected diester (1.27 g, 4.29 mmol) and magnesium bromide etherate (1.22 g, 4.72 mmol) in 25 mL of methylene chloride was stirred at room temperature for 30 min and then cooled to -95 °C. Diisobutylaluminum hydride (3.1 mL of a 1.5 M solution in toluene, 4.72 mmol) was then added dropwise via syringe pump (one drop every 8-10 s) in such a manner as to allow the solution to run down the side arm of the flask and be thoroughly cooled to -95 °C before entry into the reaction mixture. After addition was complete, 3 mL of anhydrous methanol was added in the same manner, and the reaction mixture was then allowed to warm to room temperature. Saturated aqueous Rochelle salts (10 mL) was added, the solution was stirred for 2 h, and the layers were separated. The aqueous layer was extracted with 2 × 10 mL portions of methylene chloride, and the combined organic layers were dried over sodium sulfate. Concentration in vacuo followed by MPLC chromatography (silica gel, 25% EtOAc/hexanes) gave 0.868 g (76%) of the aldehyde as a colorless oil: $[\alpha]_D$ -50.6° (*c* 1.5, $CHCl_3$); R_f 0.28 (35% EtOAc/hexanes); 300-MHz ^1H NMR ($CDCl_3$) δ 9.75 (d, *J* = 1.1 Hz, 1 H), 7.32 (m, 5 H), 4.80 (d, *J* = 2.0 Hz, 2 H), 4.63 (d, *J* = 2.9, 2 H), 4.25 (dd, *J* = 7.1, 5.1 Hz, 1 H), 3.70 (s, 3 H), 2.59 (m, 2 H), 2.12 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 201.1, 172.4, 137.4, 127.8, 94.3, 74.4, 70.3, 52.1, 34.4, 25.2; IR (neat, cm^{-1}) 2945, 2900, 1740, 1730, 1360. Anal. Calcd for $C_{14}H_{18}O_5$: C 63.10; H 6.81. Found: C, 62.89; H, 6.79.

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Registry No. 1, 129151-77-5; 4, 82130-73-2; 7, 129151-78-6; 8, 129151-79-7; 9, 129151-80-0; 10, 129151-81-1; $Bu_3SnCH_2CH=CH_2$, 24850-33-7; (*S*)-$MeO_2CCH_2CH_2CH(OH)CO_2Me$, 55094-97-8; (*S*)-$MeO_2CCH_2CH(OH)CO_2Me$, 617-55-0; (*S*)-α-butyrolactone-α-carboxylic acid, 21461-84-7.

N-Alkylation of Trifluoroacetamide with 2-Bromo Carboxylic Esters under PTC Conditions: A New Procedure for the Synthesis of α-Amino Acids

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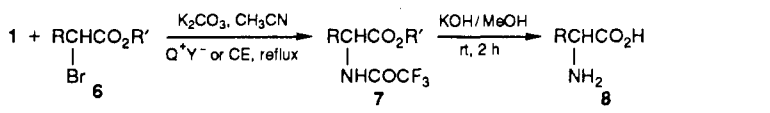
Mono- and bis-N-alkylations of trifluoroacetamide (1) are useful procedures for the synthesis of primary and secondary amines, respectively.[1-3] The intermediate mono- and bis-N-substituted trifluoroacetamides 2 and 3 are either hydrolyzed or reduced by $NaBH_4$ under very mild reaction conditions[4] to the corresponding primary or secondary amines 4 and 5, in almost quantitative yields.[1-3,5,7]

The alkylation reaction is accomplished under homogeneous conditions using the preformed sodium[1] or potassium[2] salt of 1, or better still under solid-liquid phase-transfer catalysis (SL-PTC) conditions starting from 1 and anhydrous potassium carbonate.[8]

Here we report that the SL-PTC procedure can be used for the selective mono-N-alkylation of 1 by alkyl 2-bromo carboxylic esters 6, affording the corresponding *N*-(trifluoroacetyl)-2-amino esters 7. Since, as discussed above,[4] 7 is easily and quantitatively hydrolyzed to 8, the procedure described here represents a new way of synthesis of natural and unnatural α-amino acids 8 (Scheme I).

Scheme I



R = H, alkyl, aryl; R' = Me, Et; Q^+Y^- = $C_6H_5CH_2N^+Et_3Cl^-$, $Bu_4N^+Br^-$, $Bu_4N^+Cl^-$, $hexyl_4N^+Cl^-$, $Bu_4P^+Br^-$; CE = dicyclohexano-18-crown-6.

Table I. *N*-(Trifluoroacetyl)-2-amino Carboxylic Esters 7a-k, 10, Prepared under SL-PTC Conditions[a] at 80 °C from 2-Bromo Carboxylic Esters 6, $RCHBrCO_2R'$

	6					
entry		R	R'	time, h	products	yield,[b] %
1	a	H	Et	0.5	7a	65
2	b	Me	Et	2	7b	72
3	c	$Me(CH_2)_9$	Et	3.5	7c	75
4	d	Ph	Et	0.3	7d	70
5	e	C_6H_4Me-2	Me	0.3	7e	81
6	f	C_6H_4OMe-3	Me	0.3	7f	70
7	g	C_6H_4F-4	Me	0.3	7g	–[c]
8	h	C_6H_4Cl-4	Me	0.3	7h	–[c]
9	i	C_6H_4Br-4	Me	0.3	7i	–[c]
10	j	$PhCH_2$	Et	48[d]	7j	16
					9	60
11	k	$Br(CH_2)_4$	Me[e]	20	7k	11
					10	52

[a] 6 (20 mmol), TEBA (2 mmol), 1 (40 mmol), K_2CO_3 (40 mmol) in CH_3CN (40 mL), at 80 °C. [b] Isolated yields. [c] Not isolated. The crude of N-alkylation was hydrolyzed (see Table II, entries 7-9). [d] At 25 °C. [e] 80 mmol of 1 and K_2CO_3 were used.

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