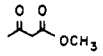
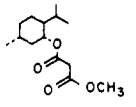
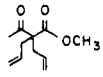
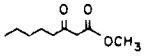
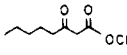
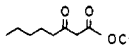
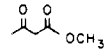
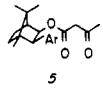
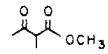
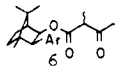
Table I

reaction no.	acetoacetate	alcohol	products	yield, %
1			 3	83
2				*a*
3	 EXCESS ESTER		 4	74
4		 EXCESS ALCOHOL	 4	41
5				*a*
6			 5	71
7			 6	55

[a] No reaction.

4-(dimethylamino)pyridine (4-DMAP), and 6 mL of toluene. The mixture was magnetically stirred until the *l*-menthol and 4-DMAP were in solution, and then 0.62 mL (5.77 mmol, 3.0 equiv) of methyl acetoacetate was added. The mixture was warmed to reflux for 42 h.[8] The reaction mixture was cooled in an ice/water bath and quenched with 20 mL of saturated ammonium chloride solution. Extracting solvent (20 mL) was added, and the two layers were separated. The aqueous layer was extracted three times with extracting solvent (25-mL portions). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was bulb-to-bulb distilled to remove excess methyl acetoacetate (bp_{50} 70 °C). The pot residue was chromatographed on 10 g of silica gel with 3.0% EtOAc/petroleum ether. The first 30 mL was discarded. The next 60 mL was concentrated in vacuo to give 385 mg (1.6 mmol, 83%) of *l*-menthyl acetoacetate **3** as a clear oil: R_f (20% EtOAc/hexane) 0.53; ^{1}H NMR 2.3 (s, 3 H), 3.4 (s, 2 H), 4.7 (dt, J = 4.4, 10.9 Hz, 1 H), 0.7–1.2 (m, 10 H) [which includes 0.91 (d, J = 6.5 Hz, 3 H), 0.89 (d, J = 7.0 Hz, 3 H), 0.77 (d, J = 6.9 Hz, 3 H); ^{13}C NMR 16.2 (q), 20.7 (q), 22.0 (q), 23.3 (t), 26.1 (q), 30.1 (d), 31.4 (d), 34.2 (t), 40.7 (t), 46.9 (d), 50.6 (t), 75.5 (d), 166.7 (s), 198.8 (s); IR 2975, 1728, 1655, 1245, 1155; MS; 240 (200), 138 (100), 123 (550), 95 (170). Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.95; H, 10.07. Found: C, 70.06; H, 10.20.

Preparation of 4: R_f (20% EtOAc/hexane) 0.47; ^{1}H NMR 0.8–1.1 (m, 6 H), 1.2–1.8 (m, 10 H), 2.54 (t, J = 2.3 Hz, 2 h), 3.44 (3, 2 H), 4.13 (t, J = 6.6 Hz, 2 H); ^{13}C NMR 13.6 (q), 13.8 (q), 19.1 (t), 22.4 (t), 23.3 (t), 30.7 (t), 31.3 (t), 43.0 (t), 49.4 (t), 65.2 (t), 167.0 (s), 202.5 (s); IR 2975, 1755, 1730, 1660, 1475, 1240, 1205, 1155; MS, 214 (36), 158 (330), 103 (490), 99 (71), 43 (100).

Preparation of 5: R_f (20% EtOAc/hexane) 0.42; ^{1}H NMR 1.0 (s, 3 H), 1.25 (s, 3 H), 1.29 (s, 3 H), 1.4–2.1 (m, 8 H), 2.6 (s, 3 H), 4.1 (d, J = 8.9 Hz, 1 H), 5.6 (d, J = 8.716 Hz, 1 H), 7.3–7.5 (m, 3 H), 7.6 (d, J = 7.2 Hz, 1 H), 7.7 (d, J = 8.1 Hz, 1 H); 7.8 (d, J = 7.9 Hz, 1 H), 8.04 (d, J = 8.3 Hz, 1 H); IR 2970, 1750, 1725, 1555, 1400, 1245, 1035; MS, 364 (50), 262 (40), 254 (63), 170 (100), 141 (36).

Preparation of 6: R_f (20% EtOAc/hexane) 0.31; ^{1}H NMR 0.45 (d, J = 7.1 Hz, 1.5 H), 0.58 (d, J = 7.1 Hz, 1.5 H), 1.0 (s, 3 H), 1.26–1.4 (m, 12 H), 2.65 (q, J = 7.2 Hz, 0.5 H), 2.74 (q, J = 7.1 Hz, 0.5 H), 4.08 (d, J = 8.8 Hz, 1 H), 5.55 (d, J = 8.9 Hz, 1 H), 7.61 (d, J = 7.5 Hz, 1 H), 7.69 (d, J = 7.9 Hz, 1 H), 7.80 (d, J = 7.9 Hz, 1 H); 8.03 (d, J = 8.2 Hz, 1 H). ^{13}C NMR 14.7, 21.5, 23.8, 27.1, 27.5, 42.5, 48.3, 49.4, 51.3, 53.1, 53.6, 55.4, 80.5, 123.4, 124.5, 125.1, 126.1, 126.7, 127.2, 128.9, 133.2, 133.6, 135.2, 169.4, 202.41; IR 2970, 1745, 1725, 1655, 1400, 1240, 1205, 1035; MS, 378 (17), 279 (45), 262 (43), 254 (54), 170 (100), 167 (62), 149 (87).

(8) Reaction times are reduced if larger quantities of 4-DMAP are used.

Acknowledgment. We thank the National Science Foundation (CHE 8306692) and the National Institutes of Health (GM 32027) for support of this work. D.F.T. thanks ICI Americas for an unrestricted research grant.

Registry No. 1, 105-45-3; 3, 97403-74-2; 4, 97403-75-3; *l*-menthol, 2216-51-5; 4-(dimethylamino)pyridine, 1122-58-3; 4-(methoxycarbonyl)-4-acetyl-1,6-heptadiene, 3666-84-0; methyl 3-oxooctanoate, 22348-95-4; methyl 2-methyl-3-oxobutyrate, 17094-21-2.

A Short Enantiospecific Synthesis of 2-Amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (ADTN)

J. Eric Nordlander,*† Mark J. Payne, F. George Njoroge, Vasanth M. Vishwanath, Gi Rin Han, George D. Laikos, and Michael A. Balk

Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106

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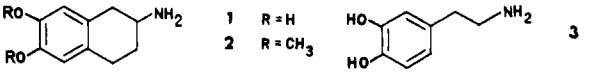
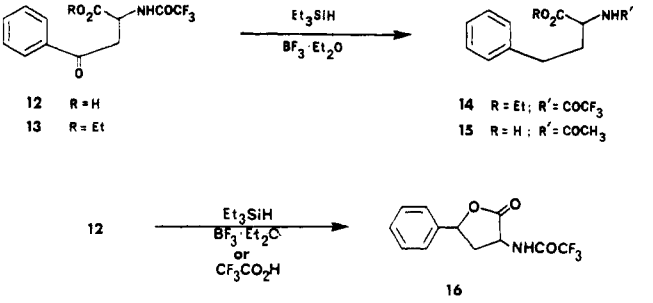
2-Amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (ADTN) (**1**) has received intense neuropharmacological study in recent years as a powerful agonist of dopamine (**3**).[1] Several approaches have been developed for the



synthesis of racemic **1** and related 2-aminotetralins.[2] McDermed and co-workers have obtained the enantiomers of **1** by classical resolution of the bis(methyl ether) **2** followed by demethylation.[3] We report here the first enantiospecific synthesis of ADTN bis(methyl ether), making readily available in high purity either enantiomer of ADTN.

Our route to (*R*)-(+)-ADTN bis(methyl ether) (**10**) was based on (*R*)-*N*-(trifluoroacetyl)aspartic anhydride[4] (**5**) as a chiral synthon[5] (Scheme I). The C,N complement of the product was assembled by Friedel–Crafts acylation of veratrole (**4**) with 1.05 equiv of **5** in the presence of 2.0 equiv of anhydrous $AlCl_3$ in CH_2Cl_2 at room temperature with efficient stirring under N_2.[6,7] A single isomeric ketone **6**, was obtained in 55% yield after conventional workup and recrystallization from EtOAc/hexane.

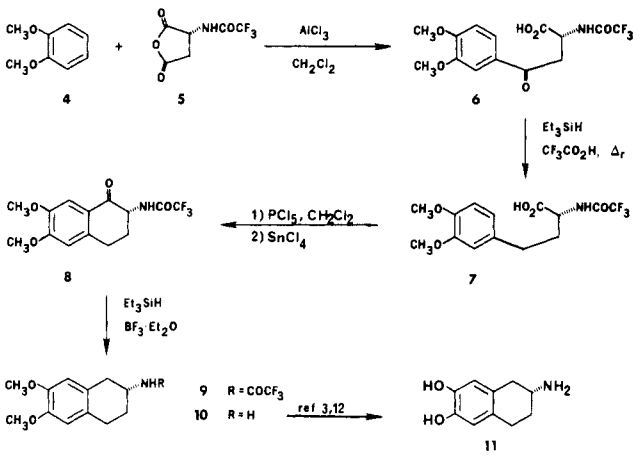
The regiochemistry of the reaction of **4** and **5** was established from the analogous product **12**, from C_6H_6 + (racemic) **5**. Reduction of the ethyl ester **13** with Et_3SiH in $BF_3{\cdot}Et_2O$[8] gave the norketo compound **14**, which was



† Current address: Department of Chemistry, Cleveland State University, Cleveland, Ohio 44115.

0022-3263/85/1950-3619$01.50/0

Scheme I

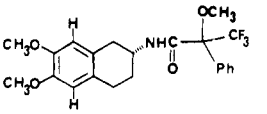


subjected to alkaline hydrolysis and acetylated to furnish **15**. The ^1H NMR spectrum of **15** was identical with that earlier reported for this compound after secure verification of its structure.[7] Attempted direct deketonization of acid **12** with Et_3SiH and either $BF_3{\cdot}Et_2O$ or CF_3CO_2H took place with cyclization to give only lactone **16**. A precedent has been reported by Doyle and co-workers.[8]

Keto acid **6** (Scheme I), in contrast to **12**, was reduced with Et_3SiH in boiling CF_3CO_2H[8] to amido acid **7** in 72% yield. The normal deketonization of **6** is apparently due to the stabilization of an intermediate benzylic carbenium ion by the *p*-methoxy group. Acid **7** was cyclized via the acid chloride to amido ketone **8** in 80% yield; a one-vessel procedure was used with PCl_5 and $SnCl_4$ added sequentially.[9] Deoxygenation of **8** with Et_3SiH in $BF_3{\cdot}Et_2O$[8] at room temperature gave trifluoroacetamide **9** (85%), which was converted by mild alkaline hydrolysis[6] to the end product, **10**, isolated as the HCl salt (46%).

The optical activity measured for free **10** was $[\alpha]^{22}_D$ +86.5° (*c* 1.70, MeOH). McDermed and co-workers have found $[\alpha]^{20}_D$ +80.85° (*c* 2, MeOH) for the corresponding material from optical resolution,[10] which was assayed biologically to have an enantiomeric excess of >90%.[3]

The configurational purity of **10** was determined securely from the 270-MHz ^1H NMR spectrum of its amide, **17**, derived from (−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (Mosher's Acid).[11] The corresponding amide



prepared from the racemic amine (acquired by reductive amination of 6,7-dimethoxy-2-tetralone[2b]) exhibited four separate singlets for the aromatic protons at δ ($CDCl_3$) 6.45, 6.48, 6.49, and 6.52. The two outside peaks were augmented by adding some **17** to this sample, establishing a distinction between the diastereomeric amides. Neat **17** gave rise to the two outside peaks with only a faintly perceptible signal between them. Assuming the Mosher's acid to have been 99% configurationally pure, we estimate that the optical purity of **17** was ≥97% (enantiomeric excess ≥94%). On this basis the comparative optical activities of our synthetic and McDermed's resolved **10** correspond to an enantiomeric excess of ≥90% for the latter, consistent with that group's original estimate.[3]

The didemethylation of **10** to (*R*)-(+)-ADTN (**11**) has been described[3,12] and can be concluded to proceed without configurational alteration.

Experimental Section

General. Capillary melting points are uncorrected. Infrared spectra were recorded on a Beckman IR-8 or IR-10 spectrophotometer. ^1H NMR spectra were obtained at 60 MHz on a Varian EM-360A spectrometer, at 200 MHz on a Varian XL-200 Fourier-transform spectrometer, and at 270 MHz on a Bruker WH 180/270 Fourier-transform spectrometer using $CDCl_3$ as solvent and Me_4Si as internal standard unless otherwise noted; sodium 3-(trimethylsilyl)-1-propanesulfonate was employed as internal standard when the solvent was D_2O. ^{13}C NMR spectra were recorded at 25.4 MHz and ^{19}F NMR spectra at 94.1 MHz on a Varian XL-100-15 spectrometer using acetone-d_6 for internal lock. ^{19}F chemical shifts are reported with respect to α,α,α-trifluorotoluene. Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

(*R*)-(−)-4-(3,4-Dimethoxyphenyl)-4-oxo-2-[(trifluoroacetyl)amino]butanoic Acid (6). Aluminum chloride (11.1 g, 83 mmol) slurried in 50 mL of CH_2Cl_2 was added in portions to a stirred suspension of 7.05 g (33 mmol) of freshly recrystallized *N*-(trifluoroacetyl)-D-aspartic anhydride (**5**),[4] from D-aspartic acid (Aldrich, 99+%), in 100 mL of CH_2Cl_2 containing 6.4 mL (6.92 g, 50 mmol) of freshly distilled veratrole (**4**). The mixture was stirred under N_2 for 80 h. A solid complex was separated by filtration and added in portions to 80 mL of stirred 6 M HCl. After 20 min the supernatant was decanted to leave a brown gum, which crystallized upon the addition of ether with stirring. The solid was collected by vacuum filtration and air-dried to afford crude product. The supernatant HCl layer was extracted with 4 × 50 mL of Et_2O. The original filtrate was poured into a second portion of 6 M HCl in a separatory funnel, and the layers were separated. The aqueous layer was extracted with 4 × 50 mL of Et_2O, and all the organic solutions were combined and dried over $MgSO_4$. Rotary evaporation gave a light brown solid, which crystallized from Et_2O/hexane and was collected by vacuum filtration. These crystals were washed free of veratrole with petroleum ether and were combined with the product isolated above. Recrystallization

(1) (a) Seeman, P. *Pharmacol. Rev.* **1980**, *32*, 229. (b) Maura, G.; Raiteri, M. *Neurochem. Int.* **1982**, *4*, 225. (c) List, S. J.; Wreggett, A.; Seeman, P. *J. Neurosci.* **1982**, *2*, 895. (d) Horn, A. S.; Griever-Kazemier, H.; Dijkstra, D. *J. Med. Chem.* **1982**, *25*, 993. (e) Woodruff, G. N. *Adv. Biosci.* **1982**, *37*, 1.

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(6) For the advantageous use of *N*-(trifluoroacetyl)amino acid chlorides in Friedel–Crafts syntheses, see: Nordlander, J. E.; Payne, M. J.; Njoroge, F. G.; Balk, M. A.; Laikos, G. D.; Vishwanath, V. M. *J. Org. Chem.* **1984**, *49*, 4107.

(7) Aspartic anhydride has been employed in one previous Friedel–Crafts reaction as the *N*-phthaloyl derivative. See: Reifenrath, W. G.; Bertelli, D. J.; Micklus, M. J.; Fries, D. S. *Tetrahedron Lett.* **1976**, 1959.

(8) (a) West, C. T.; Donnelly, S. J.; Kooistra, D. A.; Doyle, M. P. *J. Org. Chem.* **1973**, *38*, 2675. (b) Doyle, M. P.; West, C. T.; Donnelly, S. J.; McOsker, C. C. *J. Organomet. Chem.* **1976**, *117*, 129. (c) Fry, J. L.; Orfanopoulos, M.; Adlington, M. G.; Dittman, W. R., Jr.; Silverman, S. B. *J. Org. Chem.* **1978**, *43*, 374.

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(11) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543. Kalyanam, N.; Lightner, A. *Tetrahedron Lett.* **1979**, 415.

(12) McDermed, J. D.; McKenzie, G. M.; Phillips, A. P. *J. Med. Chem.* **1975**, *18*, 362.

from EtOAc/hexane provided 6.33 g (18 mmol, 55%) of **6** as colorless crystals: mp 148–150 °C; IR (Nujol) 3360, 1725, 1715, 1683, 1275, 1250, 1195, 1165, 1030, 818, 775, 735 cm^{-1}; ^1H NMR (acetone-d_6) δ 3.62 (d, J = 4 Hz, 2 H, CH_2), 3.82 (d, J = 2 Hz, 6 H, CH_3O), 4.85 (br s, 1 H, OH), 4.97 (q, J = 5 Hz, 1 H, NHC*H*), 6.66–7.10, 7.39–7.77 (m, 3 H, Ar), 8.56 (br s, 1 H, NH); ^{19}F NMR (acetone-d_6) δ −13.3 (s, 3 H); $[\alpha]^{20}_D$ −35.28° (*c* 2.65, acetone).

Anal. Calcd for $C_{14}H_{14}F_3NO_6$: C, 48.16; H, 4.04; N, 4.01. Found: C, 47.91; H, 4.01; N, 3.94.

(*R*)-(−)-4-(3,4-Dimethoxyphenyl)-2-[(trifluoroacetyl)amino]butanoic Acid (7). Triethylsilane (1.83 mL, 1.33 g, 11.5 mmol) was added to a magnetically stirred solution of 1.00 g (2.9 mmol) of keto acid **6** in 4.4 mL (6.5 g, 57 mmol) of freshly distilled trifluoroacetic acid.[6,8] This solution was boiled under reflux under N_2 for 2 h and then carefully neutralized to pH 8 with $NaHCO_3$ solution. The aqueous solution was washed twice with Et_2O and acidified (pH <5) by the dropwise addition of concentrated HCl. The product was extracted with 3 × 30 mL of Et_2O, the organic layers were dried over $MgSO_4$, and the ether was removed by rotary evaporation to yield a yellow oil, which solidified on standing. This solid was recrystallized from $CHCl_3/PhCH_3$/hexane to afford 0.7 g (2.1 mmol, 72%) of carboxylic acid **7** as colorless crystals: mp 159–160 °C; IR (Nujol) 3348, 1766, 1715, 1275, 1230, 1188, 1035, 802, 775, 735 cm^{-1}; ^1H NMR (acetone-d_6) δ 2.30 (m, 2 H, $ArCH_2CH_2$), 2.70 (t, 2 H, $ArCH_2$), 3.76 (s, 6 H, CH_3O), 4.21 (s, 1 H, OH), 4.43 (m, 1 H, NHC*H*), 6.75 (s, 3 H, Ar), 8.20 (br s, 1 H, NH); $[\alpha]^{20}_D$ −6.29 (*c* 1.35, MeOH).

Anal. Calcd for $C_{14}H_{16}F_3NO_5$: C, 50.15; H, 4.81; N, 4.18. Found: C, 50.15; H, 4.87; N, 4.11.

(*R*)-(−)-1-Oxo-2-[(trifluoroacetyl)amino]-6,7-dimethoxy-1,2,3,4-tetrahydronaphthalene (8). To an ice-cooled solution of 0.4 g (1.19 mmol) of carboxylic acid **7** in 7 mL of CH_2Cl_2 was added 0.28 g (1.2 mmol) of solid PCl_5. Stirring was continued for 1 h at 0 °C, and 340 μL (0.37 g, 1.42 mmol) of $SnCl_4$ was added.[9] The mixture was stirred for 0.5 h at 0 °C and then allowed to warm to room temperature and stirred for an additional 4 h. The mixture was poured into ice water and vigorously stirred for 10 min. The layers were separated, and the aqueous phase was extracted with three portions of CH_2Cl_2. The CH_2Cl_2 solution was dried over $MgSO_4$ and rotary evaporated to furnish white crystals, which were recrystallized from toluene to afford 0.30 g (0.96 mmol, 80%) of colorless tetralone **8**: mp 198–200 °C; IR (Nujol) 3303, 1708, 1672, 1268, 1192, 1180, 1160, 1140, 1012, 784, 715 cm^{-1}; ^1H NMR δ 1.83–2.46 (m, 2 H, $ArCH_2CH_2$), 2.63–3.40 (m, 2 H, $ArCH_2$), 3.95 (d, J = 2 Hz, 6 H, CH_3O), 4.23–4.83 (m, 1 H, C*H*NH), 6.66, 7.45 (s, 2 H, Ar); $[\alpha]^{20}_D$ −24.64° (*c* 1.75, $CHCl_3$).

Anal. Calcd for $C_{14}H_{14}F_3NO_4$: C, 53.00; H, 4.45; N, 4.42. Found: C, 52.87; H, 4.38; N, 4.26.

(*R*)-(+)-2-[(Trifluoroacetyl)amino]-6,7-dimethoxy-1,2,3,4-tetrahydronaphthalene (9). Triethylsilane (0.30 mL, 0.22 g, 1.9 mmol) was added to a solution of 0.150 g (0.47 mmol) of tetralone **8** in 1.16 mL (1.34 g, 9.5 mmol) of freshly distilled $BF_3{\cdot}Et_2O$,[6,8] and the resulting solution was stirred at room temperature under N_2 for 48 h. After basification of the mixture by addition to saturated $NaHCO_3$, the layers were separated, and the product was extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated on a rotary evaporator to afford a brown solid, which was recrystallized from $PhCH_3$/heptane to give 0.122 g (0.40 mmol, 85%) of 2-[(trifluoroacetyl)amino]-6,7-dimethoxytetralin (**9**) as long, colorless needles: mp 121–122 °C; IR (Nujol) 3314, 1715, 1247, 1199, 1179, 1134, 1009 cm^{-1}; ^1H NMR δ 1.97 (m, 2 H, $ArCH_2CH_2$), 2.89 (m, 4 H, $ArCH_2$), 3.85 (s, 6 H, CH_3O), 4.31 (m, 1 H, C*H*NH), 6.56 (d, J = 3 Hz, 2 H, Ar); $[\alpha]^{20}_D$ +75.4° (*c* 6.25, MeOH).

Anal. Calcd for $C_{14}H_{16}F_3NO_3$: C, 55.45; H, 5.32. Found: C, 55.70; H, 5.41.

(*R*)-(+)-2-Amino-6,7-dimethoxy-1,2,3,4-tetrahydronaphthalene (10). To a stirred suspension of 0.137 g (0.99 mmol) of K_2CO_3 in 2.8 mL of MeOH containing 0.14 mL of H_2O was added 0.105 g (0.35 mmol) of trifluoroacetamide **9**, and the mixture was boiled under reflux for 2 h.[6] The mixture was allowed to cool to room temperature, and the undissolved K_2CO_3 was removed by filtration through a cotton plug. The filtrate was concentrated in vacuo, and the dark residue was diluted with 5 mL of H_2O. The product was extracted with Et_2O (4 × 10 mL), the Et_2O layers were dried (K_2CO_3), and the volatiles were removed by rotary evaporation. The resulting green gum was dissolved in 20 mL of anhydrous ether and filtered through a cotton plug to remove insoluble particles. The filtrate was chilled in an ice–water bath, and anhydrous HCl was passed through the solution. The precipitated HCl salt was collected by vacuum filtration and recrystallized from MeOH/Et_2O to give 0.040 g (0.16 mmol, 46%) of 2-amino-6,7-dimethoxytetralin hydrochloride (**10**·HCl) as beige crystals: mp 212–214 °C (lit.[10] mp 215–217 °C); ^1H NMR (D_2O) δ 1.46–2.17 (m, 3 H, C*H*NH_2, $ArCH_2CH_2$), 2.70–3.16 (m, 4 H, $ArCH_2$), 3.85 (s, 6 H, CH_3O), 6.84 (s, 2 H, Ar); $[\alpha]^{20}_D$ +73.2° (*c* 0.97, MeOH). An aqueous solution of **10**·HCl was basified with 28% ammonia and extracted with $CHCl_3$ to yield, after concentration, free **10** as a yellow oil: ^1H NMR δ 1.53–2.05 (m, 4 H, NH_2, $ArCH_2CH_2$), 2.54–3.00 (m, 5 H, $ArCH_2$, C*H*NH_2), 3.79 (s, 6 H, CH_3O), 6.50 (s, 2 H, Ar); $[\alpha]^{22}_D$ +86.5° (*c* 1.70, MeOH) (lit.[10] $[\alpha]^{20}_D$ + 80.85° (*c* 2, MeOH)).

4-Oxo-4-phenyl-2-[(trifluoroacetyl)amino]butanoic Acid (12). Aluminum chloride (7.98 g, 60 mmol) was added in portions to a stirred mixture of 5.74 g (27 mmol) of racemic **5** in 120 mL of dry benzene, and the resulting suspension was boiled under reflux for 3 h. Standard workup followed by recrystallization ($PhCH_3$) yielded 5.18 g (18 mmol, 66%) of carboxylic acid **12** as colorless crystals: mp 157–160 °C; IR (Nujol) 3410, 3390, 1760, 1756, 1700, 1670, 1175, 1160, 890, 740, 675 cm^{-1}; ^1H NMR (Me_2CO-d_6) δ 3.73 (d, J = 6 Hz, 2 H, CH_2), 4.75 (s, 1 H, OH), 5.02 (q, J = 8 Hz, 1 H, C*H*NH), 7.10–8.10 (m, 5 H, Ar), 8.23–8.77 (br s, 1 H, NH); ^{19}F NMR (Me_2CO-d_6) δ −13.3 (s, 3 H).

Anal. Calcd for $C_{12}H_{10}F_3NO_4$: C, 49.83; H, 3.49; N, 4.84. Found: C, 49.83; H, 3.61; N, 4.82.

Ethyl 4-Oxo-4-phenyl-2-[(trifluoroacetyl)amino]butanoate (13). In a 50-mL round-bottomed flask were placed 2.00 g (6.9 mmol) of carboxylic acid **12**, 0.5 mL (8.7 mmol) of absolute EtOH, 1.57 g (7.6 mmol) of *N,N'*-dicyclohexylcarbodiimide,[13] 0.01 g (0.7 mmol) of 4-pyrrolidinopyridine, and 25 mL of CH_3CN. The solution was stirred at room temperature for 20 h, and the precipitated dicyclohexylurea was removed by vacuum filtration. The filtrate was concentrated by rotary evaporation and diluted with 10 mL of 5% HCl and the product extracted with $CHCl_3$ (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to afford a reddish oil. Purification by flash chromatography (1:3 EtOAc/hexane) followed by recrystallization from $PhCH_3$/hexanes yielded 0.94 g (3.1 mmol, 45%) of ethyl 2-[(trifluoroacetyl)amino]-4-oxo-4-phenylbutanoate (**13**): mp 68–71 °C; ^1H NMR δ 1.23 (t, J = 7 Hz, 3 H, CH_3), 3.60, 3.70 (dd, J = 4 Hz, 2 H, CH_2CO), 4.20 (q, J = 6 Hz, 2 H, CH_3CH_2), 4.87 (m, J = 4 Hz, 1 H, C*H*NH), 7.00–8.00 (m, 6 H, Ar, NH).

Anal. Calcd for $C_{14}H_{14}F_3NO_4$: C, 53.00; H, 4.45; N, 4.42. Found: C, 52.91; H, 4.62; N, 4.45.

2-(Acetylamino)-4-phenylbutanoic Acid (15). Triethylsilane (1.65 mL, 1.20 g, 11 mmol) was added to a stirred solution of 0.94 g (3.0 mmol) of ethyl ester **13** in 7.3 mL (8.42 g, 60 mmol) of freshly distilled $BF_3{\cdot}Et_2O$.[6,8] The solution was stirred at room temperature under N_2 for 48 h and diluted with saturated NaCl solution. The product was extracted with Et_2O (3 × 20 mL), the Et_2O layers were dried over $MgSO_4$, and the volatiles were removed by rotary evaporation. Flash chromatography (CH_2Cl_2) provided 0.20 g (0.7 mmol, 22%) of the desired ethyl 2-[(trifluoroacetyl)amino]-4-phenylbutanoate (**14**) as a yellow oil: ^1H NMR δ 1.30 (t, J = 6 Hz, 3 H, CH_3), 2.20 (q, J = 6 Hz, 2 H, $ArCH_2CH_2$), 2.64 (t, J = 6 Hz, 2 H, $ArCH_2$), 4.20 (q, J = 7 Hz, 2 H, CH_3CH_2), 4.60 (q, J = 6 Hz, 1 H, C*H*NH), 6.84 (br s, 1 H, NH), 7.17 (s, 5 H, Ar).

To a stirred suspension of 0.44 g (1.4 mmol) of $Ba(OH)_2$ in 4 mL of MeOH and 1 mL of H_2O was added 0.14 g (0.46 mmol) of **14**. The mixture was boiled under reflux for 6 h and was allowed to cool to room temperature. The insolubles were removed by filtration, and the volatiles were removed by rotary evaporation. The residue was taken up in 5 mL of H_2O, and CO_2 was bubbled into the solution to precipitate $BaCO_3$. The $BaCO_3$ was filtered and the water removed under reduced pressure to give the crude amino acid, which was dissolved in 5 mL of MeOH. Acetic anhydride (0.44 mL, 0.47 g, 4.6 mmol) was added, and the solution was stirred at room temperture for 10 h. The solution was con-

(13) Hassner, A.; Alexanian, V. *Tetrahedron Lett.* **1978**, 4475.

centrated under reduced pressure and diluted with 5% HCl and the product extracted into $CHCl_3$. The combined organic layers were dried over $MgSO_4$ and concentrated by rotary evaporation. Flash chromatography (CH_2Cl_2) provided 0.06 g (0.28 mmol, 60%) of carboxylic acid **15**, which had a ^1H NMR spectrum identical with that previously reported:[7] ^1H NMR δ 2.03 (s, 3 H, CH_3CO), 2.15 (q, 2 H, $ArCH_2CH_2$), 2.69 (t, J = 6 Hz, 2 H, $ArCH_2$), 3.75 (s, 1 H, OH), 4.68 (q, J = 6 Hz, 1 H, NHC*H*), 7.26 (s, 5 H, Ar), 7.49 (s, 1 H, NH).

α-[(Trifluoroacetyl)amino]-γ-phenyl-γ-butyrolactone (16). Triethylsilane (0.38 mL, 0.28 g, 2.4 mmol) was added to a solution of 0.20 g (0.69 mmol) of keto acid **12** in 1.06 mL (1.57 g, 14 mmol) of freshly distilled trifluoroacetic acid. The solution was heated under reflux for 1 h, allowed to cool, and poured into 5 mL of cold H_2O. The product was extracted with $CHCl_3$ (3 × 10 mL), dried over $MgSO_4$, and evaporated under vacuum to give a white solid, which was recrystallized from $PhCH_3$ to yield 0.094 g (0.35 mmol, 50%) of pure lactone **16**: mp 168–170 °C; IR (Nujol) 3345, 1779, 1722, 1557, 1217, 1185, 1147, 752, 702 cm^{-1}; ^1H NMR (Me_2CO-d_6) δ 2.32–3.36 (m, 2 H, CH_2), 5.11 (m, 1 H, C*H*NH), 5.53, 5.72 (dd, J = 6 Hz, 1 H, ArC*H*), 7.50 (s, 5 H, Ar), 9.17 (br s, 1 H, NH); ^{13}C NMR (Me_2SO-d_6) δ 35.2, 49.6, 77.6, 126.0, 128.4, 138.4, 156.0 (q, CF_3), 172.8, 194.4; ^{19}F NMR (Me_2CO-d_6) δ −13.4.

Anal. Calcd for $C_{12}H_{10}F_3NO_3$: C, 52.76; H, 3.69; N, 5.13. Found: C, 52.78; H, 3.80; N, 5.03.

Diastereomeric Amides from Mosher's Acid and 2-Amino-6,7-dimethoxy-1,2,3,4-tetrahydronaphthalene. To a magnetically stirred solution of 21 mg (0.10 mmol) of crude (*R*)-(+)-ADTN bis(methyl ether) (**10**) in 2 mL of CCl_4 at room temperature under N_2 was added 300 μL of dry pyridine followed by 35 mg (0.14 mmol) of the acid chloride[11] of (−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (Mosher's Acid) (Aldrich, 99+%). After 12 h (at which point the formation of precipitated pyridinium chloride was apparently complete) the solution was diluted with CH_2Cl_2 and washed successively with dilute aqueous HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl. After drying over $MgSO_4$ the solvents were removed by rotary evaporation to yield the carboxamide **17**. The same reaction was carried out with the racemic amine **2**, which was obtained by the reductive amination of 6,7-dimethoxy-2-tetralone (Aldrich) with $NaBH_3CN$ in the presence of NH_4OAc.[2b]

The 1:1 mixture of diastereomeric amides from the racemic amine **2** had the following ^1H NMR (270 MHz): δ 1.65–2.08 (m, 4 H, $ArCH_2CH_2$), 2.52 and 2.98 (2 q_{AB}, J_{gem} = 7 Hz, 4 H, $ArCH_2CHN$), 2.75 (m, 4 H, $ArCH_2CH_2$), 3.38 (s, 6 H, CH_3OCCO), 3.75 (s, 12 H, $Ar(OCH_3)_2$), 4.24 (m, 2 H, NHC*H*), 6.45, 6.48, 6.49, 6.52 (s, 4 H, Ar), 6.76 (2 d, J = 10 Hz, 2 H, NH), 7.11–7.66 (m, 10 H, Ph). As anticipated, the amide from the optically active amine, **10**, had a simpler spectrum under the same conditions: δ 1.65–2.08 (m, 2 H, $ArCH_2CH_2$), 2.55 and 3.00 (q_{AB}, J_{gem} = 7 Hz, 2 H, $ArCH_2CHN$), 2.75 (m, 2 H, $ArCH_2CH_2$), 3.38 (s, 3 H, CH_3OCCO), 3.76 (s, 6 H, $Ar(OCH_3)_2$), 4.24 (m, 1 H, NHC*H*), 6.45 (s, 1 H, ArH_a), 6.52 (s, 1 H, ArH_b), 6.80 (d, J = 10 Hz, 1 H, NH), 7.11–7.76 (m, 5 H, Ar). The best region of the spectra for analysis of the enantiomeric purity of **10** was that of the aromatic protons, δ 6.4–6.6. On this basis, **10** was estimated to have an enantiomeric excess of ≥94%, as described in the text.

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Registry No. (±)-**2**, 97466-04-1; **4**, 91-16-7; **5**, 75403-90-6; (±)-**5**, 97466-03-0; **6**, 97403-64-0; **7**, 97403-65-1; **8**, 97403-66-2; **9**, 97403-67-3; **10**, 97403-68-4; **10**·HCl, 97403-63-9; **11**, 71074-51-6; (±)-**12**, 97403-69-5; (±)-**13**, 97403-70-8; (±)-**14**, 97403-71-9; (±)-**15**, 5440-40-4; (±)-**16**, 97403-72-0; **17**, 97415-81-1; (2*S*)-**17**, 97403-73-1; C_6H_6, 71-43-2; Mosher's acid chloride, 39637-99-5.

Olefin Synthesis by Reaction of Stabilized Carbanions with Carbene Equivalents. 1. Use of (Iodomethyl)tributylstannane for Methylenation of Sulfones

Bruce A. Pearlman,* Sterling R. Putt, and Jeffrey A. Fleming

Chemical Process Research and Development Department, The Upjohn Company, Kalamazoo, Michigan 49001

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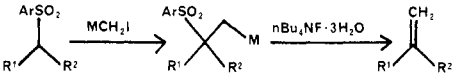
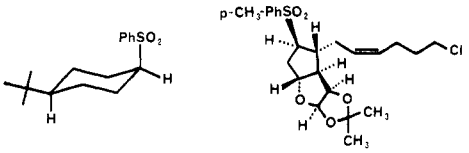
Recently, a novel method for methylenation of *sec*-alkyl aryl sulfones consisting of alkylation with Me_3SiCH_2I followed by fluoride-induced desulfonylsilylation (eq 1, M = Me_3Si) was reported.[1] This method is effective for



1 2 3

methylenation of sterically unhindered sulfones such as 3α-(phenylsulfonyl)cholestane[1] and *cis*-4-*tert*-butylcyclohexyl phenyl sulfone (**1a**).[2] However, it is ineffective for methylenation of moderately hindered sulfones such as **1b**[3] due to the slowness of the alkylation step.[4,5]



1a 1b

The purpose of this paper is to report that not only unhindered sulfones such as **1a** but also moderately hindered sulfones such as **1b** can be methylenated in excellent yield by employing the eq 1 method with either of two tin analogues of the silicon reagent (eq 1, M = *n*-Bu_3Sn or Me_3Sn).[6] Not only does this modification solve the problem of the slowness of the alkylation, but it also results in a tremendous increase in the rate of the *n*-Bu_4NF·$3H_2O$-induced fragmentation.

The operating procedure is straightforward. First, the sulfone is deprotonated, by treatment of a solution in THF at −78 °C with either LDA or *n*-BuLi.[7] Next, the tin

(1) Kocienski, P. J. *Tetrahedron Lett.* **1979**, 2649.

(2) Prepared from 4-*tert*-butylcyclohexanone by successive treatments with 1.00 equiv of LAH (Et_2O, room temperature, 15 min; 100.0%), 1.25 equiv of TsCl (pyr, room temperature, 16 h; 100.0%), 3.4 equiv of PhSH and 3.2 equiv of NaH (THF, Δ, 10 h; 89.9%), and 3.6 equiv of MCPBA (CH_2Cl_2, 0 °C, 40 min; 94.8%): mp 114.5–115.5 °C.

(3) The method of preparation of this compound will be disclosed in a subsequent paper.

(4) (a) Kocienski, P. J. *J. Org. Chem.* **1980**, *45*, 2037. (b) Kocienski, P.; Todd, M. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1777.

(5) (a) Kocienski, P.; Todd, M. *J. Chem. Soc., Chem. Commun.* **1982**, 1078. (b) Kocienski, P.; Todd, M. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1783.

(6) After this work was essentially complete, three papers[6a–c] appeared in which the use of *n*-Bu_3SnCH_2I for methylenation of sulfones was described. However, the yields (46–78%) are inferior to those afforded by the procedure described herein, presumably because a slight excess of *n*-BuLi (1.05[6a]–1.15[6c] equiv) is employed to deprotonate the sulfone.[7] Also, harsher reagents (aryllithiums)[6b] or conditions (xylene, Δ, 7 h, or SiO_2, CH_2Cl_2, Δ, 20 h)[6d] are employed to effect fragmentation. Thus, the procedure described herein is more practical. (a) Ochiai, M.; Tada, S.; Sumi, K.; Fujita, E. *Tetrahedron Lett.* **1982**, *23*, 2205. (b) Ochiai, M.; Sumi, K.; Fujita, E.; Tada, S. *Chem. Pharm. Bull.* **1983**, *31*, 3346. (c) Ochiai, M.; Ukita, T.; Fujita, E.; Tada, S. *Chem. Pharm. Bull.* **1984**, *32*, 1829. (d) Ochiai, M.; Ukita, T.; Fujita, E. *J. Chem. Soc., Chem. Commun.* **1983**, 619.

(7) Use of an excess of *n*-BuLi must be avoided since, as Fujita and co-workers have reported,[6a,c] *n*-BuLi reacts with *n*-Bu_3SnCH_2I to form *n*-BuI, which then alkylates the lithiated sulfone preferentially. Since it is difficult to measure exactly 1.0 equiv, we routinely use 1.1 equiv and then quench the excess with an appropriate amount of *i*-Pr_2NH (0.2 equiv, −78 °C, 8 min).

0022-3263/85/1950-3622$01.50/0