1.33 (t, J = 7.23 Hz, 3 H), 1.31 (s, 3 H).

(7*S*,8*R*)-2-(Acetoxymethyl)-7,8-(isopropylidenedioxy)bicyclo[3.3.0]oct-2-en-*exo*-4-yl *p*-(Benzyloxy)benzoate (11). Method 1. Alcohol **10f** (7.6 mg, 0.028 mmol) was dissolved in dry THF under argon. To the mixture was added triphenylphosphene (14.9 mg, 0.058 mmol) and 4-(benzyloxy)benzoic acid (12.9 mg, 0.058 mmol) against a flow of argon followed by diethyl azodicarboxylate (8.97 μL, 0.058 mmol) via syringe. The deep yellow color from DEAD dissappeared after a few seconds, and TLC analysis indicated that the reaction was complete after 5 min. The mixture was evaporated to dryness under vacuum and the residue chromatographed over 10% deactivated flash silica with hexane–Et_2O (8:1 → 1:1) to obtain 6.4 mg (54.6%) of clear oil which was rechromatographed similarly to remove a slight contaminant from the DEAD reagent to give 6.4 mg (47.2%) of clear benzoate ester **11**: R_f = 0.15, hexane–EtOAc (4:1); $[\alpha]^{25}_D$ = −45.69; IR (neat) 3064, 3033, 2983, 2932, 1744, 1707, 1605, 1455, 1371, 1248, 1167, 1095, 1057, 951, 848, 771, 738, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.97 (ddd, J = 9.01, 2.64, 2.09 Hz, 2 H), 7.44–7.32 (m, 5 H), 6.98 (ddd, J = 9.01, 2.66, 2.14 Hz, 2 H), 5.78 (br s, 1 H), 5.47 (s, 1 H), 5.12 (s, 2 H), 4.82 (ddd, J = 14.8, 1.0, 1.0 Hz, 1 H), 4.71 (ddd, J = 14.9, 1.0, 1.0 Hz, 1 H), 4.66 (dd, J = 4.68, 4.68 Hz, 1 H), 4.55 (d, J = 5.09 Hz, 1 H), 3.38 (br d, J = 6.88 Hz, 1 H), 3.13 (ddd, J = 9.54, 7.74, 7.74 Hz, 1 H), 2.37 (dd, J = 14.78, 8.09 Hz, 1 H), 2.12 (s, 3 H), 1.55 (ddd, J = 14.85, 9.86, 4.84 Hz, 1 H), 1.47 (s, 3 H), 1.31 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 170.52 (C), 166.13 (C), 162.49 (C), 146.30 (C), 136.20 (C), 131.66 (CH, double intensity), 128.66 (CH, double intensity), 128.19 (CH), 127.46 (CH, double intensity), 125.01 (CH), 129.91 (C), 114.42 (CH, double intensity), 110.28 (C), 82.81 (CH), 82.08 (CH), 81.70 (CH), 70.07 (CH_2), 61.39 (CH_2), 58.06 (CH), 47.51 (CH), 35.06 (CH_2), 27.13 (CH_3), 24.76 (CH_3), 20.83 (CH_3); MS (CI, m/e (rel. int.)) 479 (1, M^+), 463 (2), 419 (7), 361 (3), 251 (80), 229 (50), 211 (40), 193 (100), 151 (30), 133 (40), 121 (20), 105 (10), 91 (90); HRMS calcd for $C_{20}H_{34}O_6Si$ 479.2070, found 479.2063.

Specionin Acetate (1a). Acetate **11** (2 mg) was dissolved in methylene chloride and treated with excess *m*-CPBA at room temperature. NMR spectrum of an aliquot after 6 h indicated the presence of epoxy protons at 3.69 and 3.66 ppm corresponding to **12a** and **12b**, respectively. The reaction was quenched with aqueous bicarbonate and extracted with methylene chloride. The crude product was hydrogenated in EtOH over Pd(C) at 40 psi for 8 h to provide the debenzylated derivative **13** as evidenced by the absence of signals corresponding to the acetonide. To the filtrate from the hydrogenation was added sodium periodate and a crystal of *p*-TsOH and the mixture stirred at room temperature overnight, according to the published protocol.[5a] Purification of the crude product by filtration through silica and HPLC (C-18, $MeOH/H_2O$) gave **1a** identical with an authentic sample (vide NMR and HPLC).

Acknowledgment. The authors are grateful to the National Institutes of Health (GM-40648) for support of this work and to professor John Leonard (Salford University, UK) for ^1H NMR spectra and a sample of specionin acetate. Helpful discussions with professor James Tanko and Mr. Carlton Foster of Virginia Tech are appreciated. The authors also thank Dr. Alison Fleming and Dr. Nina Heard for their efforts in the development of the annulation methodology.

Supplementary Material Available: ^1H NMR spectra for compounds **9a–h**, **3a–e**, **8e**, **10a–f**, **11**, and **1a** (28 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Notes

Synthesis of the Chiral 4-Substituted 1-Phenylcyclohexene PD137789 via Intramolecular Wittig Reaction

Stephen J. Johnson,* Suzanne R. Kesten, and Lawrence D. Wise

Department of Chemistry, Parke-Davis Pharmaceutical Research Division, Warner-Lambert Company, 2800 Plymouth Road, Ann Arbor, Michigan 48105

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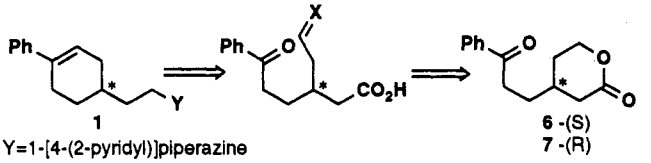
The 4-substituted 1-phenylcyclohexene PD137789 (1) has dopamine agonist properties while its enantiomer appears to be an antagonist.[1] The two enantiomers are extremely difficult to resolve by standard methods and so far have only been separated by chiral HPLC. To provide a supply of PD137789 (1) for evaluation as a potential antipsychotic agent, we sought to develop a practical multigram chiral synthesis. We devised a strategy involving intramolecular cyclization with concomitant double-bond formation since this would generate and maintain the specific relationship between the double bond and the chiral center which is key to maintaining enantiotopic integrity. Such a strategy could exploit elements of existing approaches to chiral 3-substituted γ-butyrolactones as a means of generating the chiral center. Reactions which proceed through symmetric intermediates or isomerize the double bond had to be avoided since they would lead to racemization.



1 Y=1-[4-(2-pyridyl)]piperazine

6 -(S)
7 -(R)

Enzymatic differentiation of otherwise equivalent functional groups in symmetric prochiral compounds is an efficient source of enantiomerically enriched compounds since it is a catalytic process which optimally would convert all starting material to a single enantiomer.[2] In the case in point, the preferred substrate for this type of enantioselection would have the skeletal framework already in place for a subsequent cyclization. The ketal diester **4** fits this criterion.

A three-step synthesis of diester **4** was developed starting from commercially available methyl 3-benzoylpropionate.

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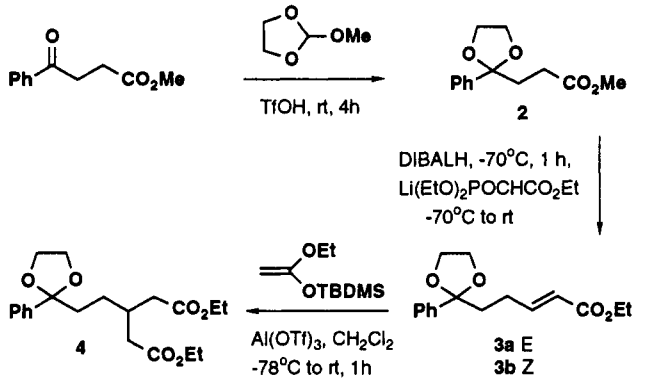
0022-3263/92/1957-4746$03.00/0

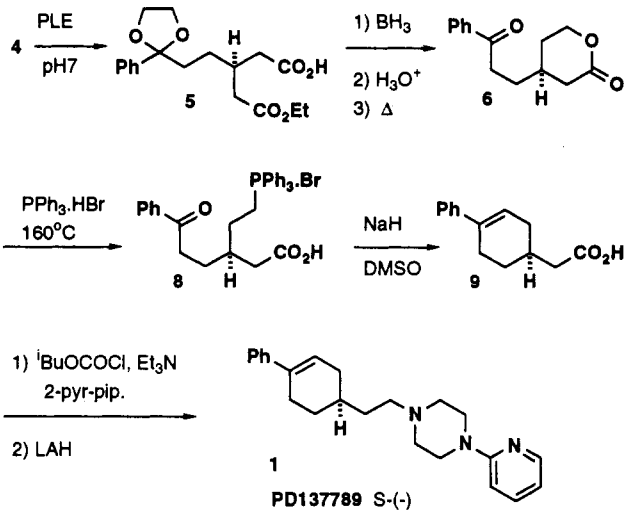
Under standard TsOH, benzene conditions using a Dean-Stark water separator, the protection of the ketone function as the ethylene glycol ketal **2** was difficult to drive to completion and substantial transesterification occurred with the ethylene glycol. Even ketalization employing 2-methoxy-1,3-dioxolane[3] with TsOH or MsOH catalysis did not go to completion, apparently because the acid catalyst was inactivated by esterification. However, changing the catalyst to TfOH gave a rapid reaction to produce ketal **2** in high yield. Ketal **2** was not stable at room temperature for long periods but did crystallize below 18 °C and could be stored as a solid in the cold. The ketal–aldehyde obtainable by partial reduction of the ester in **2** was even less stable, undergoing inter alia rearrangement to the ketone–acetal on standing at room temperature. Consequently, the most practical chain extension employed in situ trapping of the DIBALH partially reduced ester with a Wadsworth–Emmons reagent in a fashion similar to that described by Takacs[4] to afford the unsaturated ester **3** (56% yield) as a 15:1 mixture of the *E* and *Z* isomers **3a** and **3b**. Lewis acid catalyzed Michael addition of an acetate derived ketene acetal[5,6] to ester **3** gave the desired diester **4** in good yield (69%). Both $Al(OTf)_3$[6] and HgI_2[7] were effective catalysts[8] but $Al(OTf)_3$ was preferred because of the toxicity of Hg compounds.



Pig liver esterase (PLE) partial hydrolysis of diester **4** was expected to proceed with good selectivity because of analogy with examples reported by Ohno[9] and by Jones[2] in which compounds with a benzene ring attached by a three-atom spacer to the 3-position of 1,5-pentanedioic acid diesters gave ee's of 86–93%. PLE-catalyzed hydrolysis of diester **4** at pH 7 did proceed at a reasonable rate at room temperature to afford a good yield (70%) of mono acid **5** with a greater than 92% ee as determined by chiral HPLC after conversion to PD137789 (**1**) (enantiomer ratio 96.3:3.7). Since the absolute configuration of the mono acid **5** is predictable and the configuration of cyclohexene **1** was not known at the time, an important feature of the synthetic approach at this stage was that either enantiomeric lactone **6** or **7** could be produced from mono acid **5**. Thus, borane reduction of the carboxylic acid with acid-catalyzed deketalization and thermal lactonization afforded (*S*)-lactone **6** (56% yield).

Alternatively, reduction of the ester with basic lithium borohydride led to (*R*)-lactone **7**. The absolute configuration of the (*R*)-(+)-lactone **7** was confirmed by conversion to the (*R*)-(+)-styryl-lactone ([*R*-(*E*)]-tetrahydro-4-(3-phenyl-2-propenyl)-2*H*-pyran-2-one) reported by Ohno.[9]

With both lactones in hand, we sought an expeditious route to the target cyclohexene. Partial reduction of the lactone carbonyl to a lactol followed by McMurry Ti(0) cyclization[10] provided cyclohexenes in low yields. Variations on this approach in which the lactol was opened to the aldehyde with protection of the alcohol gave higher yields in the McMurry cyclization but required elaborate protection schemes. The direct conversion of lactones to triphenylphosphonium salts with subsequent deprotonation to Wittig reagents, as recently reported by Hamanaka,[11] offered an appealing alternative. Indeed, reaction of (*S*)-lactone **6** with triphenylphosphonium hydrobromide at 160 °C afforded the desired phosphonium salt **8** which cyclized[12] to the (*S*)-cyclohexene acetic acid **9** (65% yield) upon treatment with 2 equiv of base in DMSO.



The acid **9** was coupled with 2-pyridylpiperazine and reduced by standard means to afford (*S*)-(−)-PD137789 (**1**) with a 92% ee in approximately 8% overall yield. Thus, the synthesis proved the absolute configuration of PD137789 and is capable of providing either enantiomer depending on whether lactone isomer **6** or **7** is used. The crystalline product and chiral intermediates were not further enantiomerically enriched by recrystallization. However, there are opportunities to improve the selectivity of the esterase hydrolysis by varying conditions or by employing other enzymes.

The intramolecular Wittig cyclization is a fairly general method for the regiospecific synthesis of functionalized cyclohexenes and cyclopentenes. In the near future, we plan to report a number of other applications of pharmaceutical interest.

Experimental Section

General. Elemental analyses and most spectra were processed by the Analytical Section at Parke-Davis. NMR spectra were

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(12) For a review see: Becker, K. B. *Tetrahedron* **1980**, *36*, 1717. For a recent example see: Kinder, F. R.; Jarosinski, M. A.; Anderson, W. K. *J. Org. Chem.* **1991**, *56*, 6475.

acquired on a Varian XL200, a Bruker AM250, or a Varian XL300. MS (EI and CI) were obtained on a VG TRIO-2A instrument at 70 eV (EI) or with 1% NH_3 in CH_4 (CI). MS (FAB) were obtained on a Finnegan TSQ 70 employing thiogycerol as the matrix solvent. Reactions were run under an atmosphere of N_2.

Materials. Methyl 3-benzoylpropionoate was obtained from Lancaster Synthesis Inc. Porcine liver esterase (EC 3.1.1.1) was obtained from Sigma Chemical Co. Other reagents were obtained from Aldrich Chemical Co. or were prepared according to referenced literature procedures.

Methyl 2-Phenyl-1,3-dioxane-2-propanoate (2). To methyl 3-benzoylpropionoate (153.0 g, 0.80 mol) and 2-methoxy-1,3-dioxolane (171 g, 1.65 mol) cooled on ice–water was added TfOH (2.5 mL) dropwise with stirring. The cooling bath was removed, and the reaction was monitored by GC. If necessary, additional TfOH (2 mL) was added after 1 h. After 3 h at rt, Et_2O (400 mL) and saturated aqueous $NaHCO_3$ (150 mL) were added with vigorous stirring. The ether layer was separated, washed with water (100 mL), dried over $MgSO_4$, and concentrated vacuum to afford the ketal **2** as an oil (181.9 g, 96% yield, >98% pure by GC). The compound was not stable for long periods at rt but formed crystals upon cooling, mp 19.5–22 °C, bp 117–125 °C (0.5 Torr): ^1H NMR (250 MHz, $CDCl_3$) δ 7.30 (s, 5 H), 3.97 (m, 2 H), 3.67 (m, 2 H), 3.55 (s, 3 H), 2.32 (t, 2 H, J = 7 Hz), 2.12 (t, 2 H, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 173.9, 142.1, 128.2 (2 C), 128.1, 125.7 (2 C), 109.5, 64.7 (2 C), 51.6, 35.5, 28.7; IR (KBr) 1739 cm^{-1}; MS (FAB) 237 ($[M + H]^+$, 100).

Ethyl (*E*)-5-(2-Phenyl-1,3-dioxan-2-yl)-2-pentenoate (3a) and *Z*-Isomer 3b. To the ester **2** (15.0 g, 63.6 mmol) in toluene (250 mL) cooled on dry ice/acetone was added DIBALH in toluene (1.5 M, 47 mL, 70.5 mmol) over a 30-min period keeping the internal temperature below –65 °C. The solution was stirred at –76 °C for 1 h. A quenched aliquot was checked for excessive starting material. If necessary, more DIBALH was added. In a separate flask, *n*-BuLi in hexane (1.6 M, 47.5 mL, 76 mmol) was added dropwise to triethyl phosphonoacetate (17.1 g, 76 mmol) in THF (250 mL) with cooling on ice. This phosphorylide solution was stirred an additional 30 min and then added via cannula to the DIBALH-reduced ester solution keeping the internal temperature of the reaction mixture below –60 °C. After 30 min the cooling bath was removed and the reaction mixture warmed to rt over 90 min. "Supersaturated" aqueous Na_2SO_4 (100 mL, freshly prepared from anhydrous Na_2SO_4) was added with vigorous stirring. After 1 h the mixture was filtered with Celite, the filter cake was washed thoroughly with THF, and the combined filtrate was concentrated under vacuum to afford crude product containing an approximately 15:1 mixture of **3a** and **3b** by NMR. Chromatography (SiO_2, hexane/ethyl acetate (3:1)) afforded **3a** and **3b**, 9.8 g (56%), as an oil. Early fractions contained 85% **3b** and late fractions contained pure **3a**. Data for *E*-isomer **3a**: ^1H NMR (200 MHz, $CDCl_3$) δ 7.5–7.2 (m, 5 H), 6.95 (dt, 1 H, J = 15.7, 6.6 Hz), 5.77 (d, 1 H, J = 15.7 Hz), 4.15 (q, 2 H, J = 7.1 Hz), 4.02 (m, 2 H), 3.77 (m, 2 H), 2.28 (m, 2 H), 2.03 (m, 2 H), 1.26 (t, 3 H, J = 7.1 Hz); ^{13}C ($CDCl_3$) δ 166.6, 148.8, 142.2, 128.2 (2 C), 128.0, 125.7 (2 C), 121.1, 109.8, 64.6 (2 C), 60.1, 38.6, 26.6, 14.3; IR (KBr) 1718, 1653 cm^{-1}; MS (FAB) 289 ($[M + H]^+$, 3), 277 ($[M - OH]^+$, 66). Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.55; H, 7.30. Found: C, 69.59; H, 7.30. Data for *Z*-isomer **3b**: ^1H NMR (250 MHz, $CDCl_3$) δ 7.5–7.2 (m, 5 H), 6.21 (dt, 1 H, J = 11.5, 7.4 Hz), 5.71 (dt, 1 H, J = 11.5, 1.7 Hz), 4.14 (q, 2 H, J = 7.1 Hz), 4.02 (m, 2 H), 3.77 (m, 2 H), 2.75 (m, 2 H), 2.03 (t, 2 H, J = 8 Hz), 1.25 (t, 3 H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 166.4, 149.8, 142.5, 128.1 (2 C), 127.9, 125.7 (2 C), 119.6, 110.0, 64.6 (2 C), 59.8, 39.5, 23.7, 14.3; IR (KBR) 1719 cm^{-1}; (EI–MS did not show $M^{+\cdot}$). Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.55; H, 7.30. Found: C, 69.87; H, 7.56.

Diethyl 3-[2-(2-Phenyl-1,3-dioxan-2-yl)ethyl]pentanedioate (4). Triisobutylaluminum in toluene (25% w/v, 3.5 mL, 3.5 mmol) was added dropwise to TfOH (0.93 mL, 1.57 g, 10.5 mmol) in CH_2Cl_2 (30 mL) cooled on ice–water. The mixture was stirred at rt for 30 min and then cooled on dry ice/acetone while a solution of 1-(dimethyl-*tert*-butylsiloxy)-1-ethoxyethene[6] (10.1 g, 50 mmol) and unsaturated ester **3** (9.81 g, 35.5 mmol) in CH_2Cl_2 (100 mL) was added rapidly. After the mixture was stirred in the cold for 5 min the cooling bath was changed to ice–water. After 1 h, 10% aqueous K_2CO_3 (30 mL) was added and the mixture was stirred without cooling for 30 min. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organics were dried ($MgSO_4$) and concentrated under vacuum to afford crude diester **4** (12.5 g) which could be used directly in the following PLE hydrolysis. Chromatography (SiO_2, 4:1 hexane/ethyl acetate) afforded pure diester **4** (9.0 g, 69% yield): ^1H NMR (200 MHz, $CDCl_3$) δ 7.5–7.25 (m, 5 H), 4.08 (q, 4 H, J = 7.2 Hz), 4.00 (m, 2 H), 3.76 (m, 2 H), 2.31 (s, 5 H), 1.91 (m, 2 H), 1.44 (m, 2 H), 1.22 (t, 6 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 172.2, 142.4, 128.9 (2 C), 127.7, 125.5 (2 C), 110.0, 64.4 (2 C), 60.1 (2 C), 38.4 (2 C), 37.4, 32.0, 27.6, 14.1 (2 C); IR (KBr) 1734 cm^{-1}; MS (CI, 1% NH_3 in CH_4) 365 ($[M + H]^+$, 100). Anal. Calcd for $C_{20}H_{28}O_6$: C, 65.92; H, 7.74. Found: C, 65.71; H, 7.70.

Monoethyl (*S*)-3-[2-(2-Phenyl-1,3-dioxan-2-yl)ethyl]pentanedioate (5). To the crude diester **4** (40.3 g, containing approximately 77 mmol) stirred vigorously with 0.1 M pH 7.0 phosphate buffer (500 mL) was added porcine liver esterase (EC 3.3.1.1) suspended in 3.2 M $(NH_4)_2SO_4$ (3,150 units/mL, 12.5 mL, 394 000 units). The mixture was maintained at pH 7.0–7.2 by addition of 1 M NaOH from a syringe pump controlled by a pH meter/controller at rt. After 3 days, 70 mL of 1 M NaOH had been used. The aqueous phase was adjusted to pH 9.0 by addition of 1 M NaOH. The mixture was washed with ether (300 mL × 2) (filtered to break up emulsion) and then acidified to pH 2.5 with 1 M HCl and extracted with ether (600 mL then 300 mL). The ether extract was dried over $MgSO_4$, filtered, concentrated, and stirred under high vacuum to afford pure desired product **5** (18.9 g, approximately 70% yield): $[\alpha]_D$ –0.4° (*c* 2.3, $CHCl_3$); ^1H NMR (250 MHz, DMSO) δ 12.05 (br s, 1 H), 7.34 (m, 5 H), 3.99 (q, 2 H, J = 7.3 Hz), 3.94 (m, 2 H), 3.64 (m, 2 H), 2.4–2.0 (m, 5 H), 1.80 (m, 2 H), 1.28 (m, 2 H), 1.12 (t, 3 H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 178.4, 172.4, 142.4, 128.1 (2 C), 127.8, 125.6 (2 C), 110.1, 64.5 (2 C), 60.2, 38.3, 38.1, 37.4, 31.7, 27.7, 14.1; IR (KBr) 1730, 1700 cm^{-1}; MS (FAB) 337 ($M + H^+$, 100). Anal. Calcd for $C_{18}H_{24}O_6$: C, 64.27; H, 7.19. Found: C, 64.27; H, 7.43.

(*S*)-Tetrahydro-4-(3-oxo-3-phenylpropyl)-2*H*-pyran-2-one (6). To the monoacid **5** (12.3 g, 36.6 mmol) in THF (100 mL) stirred at rt was added borane in THF (1 M, 44 mL, 44 mmol) dropwise. After an initial exotherm with gas evolution, the solution was stirred for 2.5 h, and then water (10 mL) was added, followed by 1 M HCl (50 mL). The solution was heated under reflux for 15 min. The bulk of the THF was removed under vacuum and the residue was extracted with $CHCl_3$ (250 mL then 100 mL). The extract was dried ($MgSO_4$) and concentrated under vacuum to afford an oil which solidified on standing (8.45 g). The solid was recrystallized from ethyl acetate (10 mL)–Et_2O (50 mL) with cooling to 0 °C to afford pure **6** as colorless crystals (4.75 g, 56% yield), mp 80–83 °C: $[\alpha]_D$ –22.4° (*c* 2.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, 2 H, J = 7.3 Hz), 7.57 (t, 1 H, J = 7.3 Hz), 7.46 (t, 2 H, J = 7.3 Hz), 4.42 (m, 1 H), 4.25 (td, 1 H, J = 11.0, 3.4 Hz), 3.02 (t, 2 H, J = 7.3 Hz), 2.73 (dd, 1 H, J = 16, 4 Hz), 2.19 (dd, 1 H, J = 17, 10 Hz), 2.02 (m, 2 H), 1.84 (m, 2 H), 1.57 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 199.1, 170.9, 136.6, 133.2, 128.7 (2 C), 127.9 (2 C), 68.4.36.4, 35.1,31.0, 30.1, 28.8; MS (EI) 233 (1.7, $[M + H]^+$), 105 (100); IR (KBr) 1739, 1680 cm^{-1}. Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.42; H, 6.99.

(*R*)-ε-Oxo-β-[2-(triphenylphosphoranyl)ethyl]benzenehexanoic Acid Bromide (8). The lactone **6** (4.65 g, 20 mmol) and triphenylphosphonium hydrobromide (7.10 g, 20 mmol) were stirred together and heated in an oil bath at 160 °C for 2 h. Upon cooling the phosphonium salt **8** was obtained as a glassy solid (11.7 g) which was used directly in the following reaction: ^1H NMR (200 MHz) δ 7.9–7.2 (m, 20 H), 3.74 (m, 1 H) 3.5 (m, 1 H), 2.9 (m, 3 H), 2.60 (m, 1 H) 2.38 (m, 1 H), 1.75 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 199.9, 173.9, 136.5, 135.2 (3 C), 133.5 (d, 6 C, J_{C-P} = 10 Hz), 133.15, 130.5 (d, 6 C, J_{C-P} = 12 Hz), 128.6 (2 C), 128.0 (2 C), 117.8 (d, 3 C, J_{C-P} = 86 Hz), 39.4, 35.9, 35.7, 27.2, 25.9, 19.0 (d, 1 C, J_{C-P} = 51 Hz). Anal. Calcd for $C_{32}H_{32}BrO_3P$: C, 66.79; H, 5.60. Found: C, 66.71; H, 5.73.

(*S*)-4-Phenyl-3-cyclohexene-1-acetic Acid (9). To the crude phosphonium salt **8** (11.7 g, 20 mmol) stirred in DMSO (100 mL) was added dimsylsodium in DMSO (2 M, 20 mL, 40 mmol, freshly prepared by dissolving NaH in DMSO at 70 °C over 2 h) with cooling to 19–22 °C. After 1.5 h the DMSO was distilled off at 40–70 °C under high vacuum. The residue was dissolved in dilute $NaHCO_3$ (100 mL), washed with EtOAc(30 mL), acidified with 1 M HCl, and extracted into $CHCl_3$ (3 × 40 mL). The extract

was dried ($MgSO_4$) and concentrated under vacuum to afford the acid **9** (2.80 g, 65% yield), mp 101–103 °C: $[\alpha]_D$ −66.0° (*c* 2.6, $CHCl_3$); ^1H NMR δ 11 (br s, 1 H), 7.43–7.2 (m, 5 H), 6.09 (m, 1 H, 2.5 (m, 3 H), 2.40 (d, 2 H, *J* = 6.7 Hz), 2.23 (m, 2 H), 2.0 (m, 2 H), 1.53 (m, 1 H); ^{13}C ($CDCl_3$) δ 178.3, 142.0, 136.3, 128.2, 126.7, 125.0, 123.1, 40.6, 32.0, 30.1, 28.8, 26.9; IR (KBr) 1702 cm^{-1}; MS (EI) 216 (26, $M^{\cdot+}$), 156 (100). Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.40; H, 7.35.

(*S*)-1-[(4-Phenyl-3-cyclohexen-1-yl)acetyl]-4-(2-pyridinyl)piperazine (10). To the acid **9** (4.00 g, 18.5 mmol) in CH_2Cl_2 (65 mL) stirred with cooling on ice–water was added isobutyl chloroformate (2.65 g, 2.52 mL, 19.5 mmol) dropwise. The mixture was stirred at 0 °C for 1 h, and then 1-(2-pyridyl)piperazine (2.84 g, 2.06 mL, 20.3 mmol) was added. After 15 min the cooling bath was removed, and then after 1 h the mixture was diluted with CH_2Cl_2 (100 mL), washed with water (2 × 100 mL), dried ($MgSO_4$), and concentrated under vacuum. The residue (8 g) was chromatographed on silica gel (EtOAc) and recrystallized from hexane (100 mL)/EtOAc (100 mL) to afford pure product **10** (5.78 g, 87%), mp 123–125 °C: $[\alpha]_D$ −46.1° (*c* 2.64, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.21 (m, 1 H), 7.58–7.18 (m's, 6 H), 6.68 (m, 2 H), 6.09 (m, 1 H), 3.80 (m, 2 H), 3.65 (s, 4 H), 3.51 (m, 2 H), 2.58–1.80 (m's, 8 H), 1.50 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 170.8, 159.1, 147.9, 142.0, 137.7, 136.3, 128.2 (2 C), 126.7, 124.9 (2 C), 123.3, 113.9, 107.2, 45.5, 45.4, 41.1, 39.3 (probably 2 C), 32.3, 30.4, 29.2, 26.9; IR (KBr) 1637, 1590 cm^{-1}; MS (EI) 361 (13, $M^{\cdot+}$), 107 (100). Anal. Calcd for $C_{23}H_{27}N_3O$: C, 76.42; H, 7.53; N, 11.55. Found: C, 75.95; H, 7.53; N, 11.55.

(*S*)-1-[2-(4-Phenyl-3-cyclohexen-1-yl)ethyl]-4-(2-pyridinyl)piperazine (1). The amide **9** (5.80 g, 16.0 mmol) in THF (100 mL) and $LiAlH_4$ in Et_2O (1 M, 11 mL, 11 mmol) were mixed and heated under reflux for 4 h. The mixture was cooled and quenched with saturated aqueous Na_2SO_4 (6 mL) and then stirred for 45 min. The mixture was filtered, the residue was washed with THF, and the combined filtrate was concentrated under vacuum. The residue was recrystallized from methyl *tert*-butyl ether to afford pure **1** (4.90 g, 88% yield), mp 113–114 °C: $[\alpha]_D$ −56.7° (*c* 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 8.21 (m, 1 H), 7.5–7.1 (m, 6 H), 6.68 (m, 2 H), 6.09 (m, 1 H), 3.57 (m, 4 H), 2.58 (m, 4 H), 2.43 (m, 4 H), 2.33 (m, 1 H), 2.0–1.4 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 159.6, 147.9, 142.2, 137.4, 136.4, 128.2 (2 C), 126.6, 124.9 (2 C), 123.9, 113.2, 107.0, 56.7, 53.2 (2 C), 45.2 (2 C), 33.4, 32.6, 31.7, 29.4, 27.2. Anal. Calcd for $C_{23}H_{29}N_3$: C, 79.50; H, 8.41; N, 12.09. Found: C, 79.67; H, 8.55; N, 12.23. HPLC on a Chiracel OJ column eluted with 9:1 hexane/2-propanol showed the enantiomer ratio to be 96.3:3.7.

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Aerosol Fluorination of 1-Chloroadamantane, 2-Chloroadamantane, and Methyl 1-Adamantylacetate: A Novel Synthetic Approach to 1- and 2-Substituted Hydryl-, Methyl-, and (Difluoromethyl)-*F*-adamantanes

James L. Adcock,* Huimin Luo, and Sharique S. Zuberi

Department of Chemistry, University of Tennessee, Knoxville, Tennessee 37996-1600

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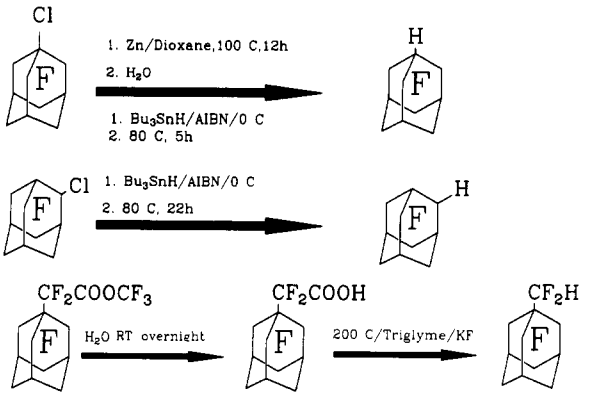
Adamantane has interested chemists for nearly a century. Research based on its unusual chemical and physical properties has led to important advances in several areas of organic chemistry.[1,2] Many adamantane derivatives such as chlorinated adamantanes[3,4] and 1,2-disubstituted adamantanes[5] have been synthesized. However, far fewer highly fluorinated adamantane derivatives are known.[6,7] The synthesis of perfluoroadamantane by aerosol direct fluorination was reported several years ago by our group.[8] However, the extreme stabilities of C–F bonds made it difficult to derivatize. This prompted us to search for a good synthon for other fluorinated adamantane derivatives. Since the application of aerosol direct fluorination to alkyl chlorides has been demonstrated,[9,10] and 1-chloroadamantane and 2-chloroadamantane are commercially available, they were chosen as precursors to make, hopefully, more reactive perfluoroadamantane derivatives. Direct fluorination of carboxylic acid esters has also been shown to produce fluorinated carboxylic acid derivatives.[11] In this paper, we report direct fluorinations of 1-chloroadamantane, 2-chloroadamantane, and methyl 1-adamantylacetate; subsequent syntheses of 1-hydryl-*F*-adamantane, 2-hydryl-*F*-adamantane, 1-methyl-*F*-adamantane, and 2-methyl-*F*-adamantane from the corresponding chloro-*F*-adamantanes and 1-(difluoromethyl)-*F*-adamantane from *F*-1-adamantylacetic acid are also described, proving the utility of our synthons.

Scheme I. Synthesis of 1-Hydryl-*F*-adamantane, 2-Hydryl-*F*-adamantane, and 1-(Difluoromethyl)-*F*-adamantane



Results and Discussion

With the help of spectroscopic techniques (vide infra), the major products (98% by weight) collected from the aerosol direct fluorination of 1-chloroadamantane and 2-chloroadamantane were identified as their corresponding perfluorinated analogues. No chlorine loss or 1,2-chloride shift was observed in either of the compounds. Considering the total rearrangement of tertiary alkyl chlorides in noncyclic systems and partial rearrangements of secondary alkyl chlorides, the lack of a 1,2-chlorine shift is noteworthy if not too surprising. We attribute this lack of a 1,2-chlorine shift to the rigidity of the adamantane skeleton. The percent yields based on the throughput (amounts injected) of 1-chloro-*F*-adamantane and 2-chloro-*F*-adamantane are 59.2% and 50.7%, respectively. The aerosol direct fluorination of methyl 1-adamantyl-

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