Crystallization-Induced Diastereoselection: Asymmetric Synthesis of Substance P Inhibitors

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Abstract: A novel three-component condensation followed by a crystallization-induced asymmetric transformation is used to build this key substance P inhibitor intermediate in a short synthetic sequence.

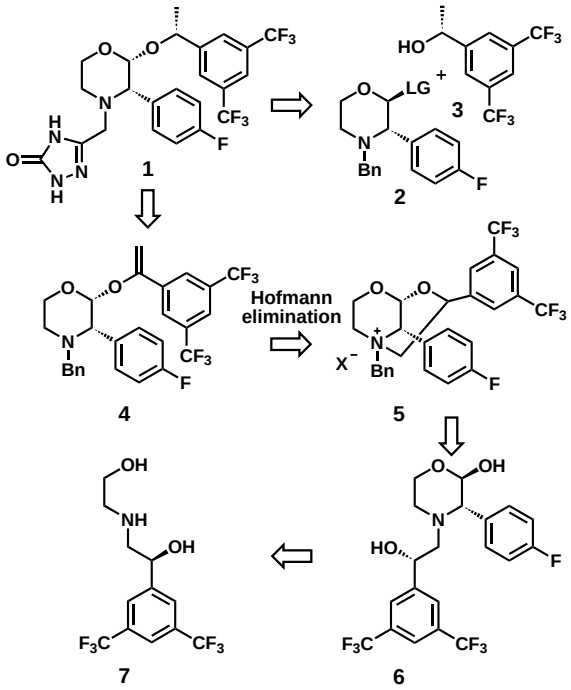
Keywords: asymmetric synthesis · crystallization-driven transformation · dihydroxylation · Mitsunobu reaction · substance P inhibitors

Introduction

Although the neuropeptide substance P was isolated from brain cells as early as 1931,[1] its functional role was not well understood until the advent of orally-available substance P inhibitors.[2] These compounds show great promise for the treatment of chemotherapy-induced emesis, but more excitingly, a recent clinical trial has shown the efficacy of a Merck substance P antagonist as an antidepressant in patients with major depressive disorder. This landmark discovery is even more significant as it demonstrates a novel mode of action for antidepressive therapy.[3]

Results and Discussion

Structurally, the Merck substance P antagonists consist of a C2/C3 *cis*-substituted morpholine acetal core linked to a heterocycle, such as the 3-oxo-1,2,4-triazole moiety in **1**.[4] An initial retrosynthetic analysis of **1** suggested an apparently trivial disconnection at the acetal center (Scheme 1) leading to 3,5-bis(trifluoromethyl)-*sec*-phenethyl alcohol **3** and the activated morpholine **2**. Unfortunately, this glycosidation-type approach failed, as either facile elimination of the leaving group (LG) or substitution from the β-face resulted in the undesired *trans* stereochemistry, presumably due to steric blocking by the adjacent 4-fluorophenyl group. Alternatively, vinyl ether **4** was a desirable intermediate, since diastereoselective hydrogenation of the vinyl ether is known to afford the requisite stereochemistry at the newly formed chiral center.[4] Importantly, **4** is retrosynthetically transformed to the bicyclic quaternary ammonium salt **5** by a regioselective Hofmann elimination. The critical *cis*-stereochemistry in **5** is set by an



Scheme 1. Retrosynthetic analysis of **1**.

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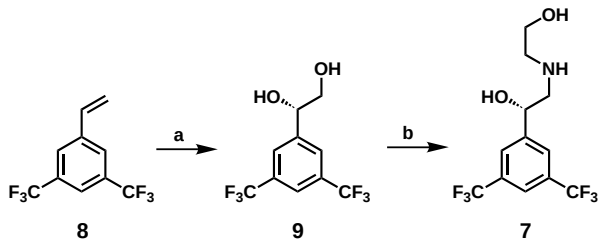
  0947-6539/02/0806-1372 $ 17.50+.50/0

intramolecular displacement of the lactol hydroxyl group of **6**, thus overcoming the bias towards the *trans* arrangement. We envisioned deriving lactol **6** from chiral aminodiol **7** using a new Mannich boronic acid condensation. It was imperative to the success of this strategy that the single stereocenter of aminodiol **7** controls both stereocenters in the morpholine ring of **6**.

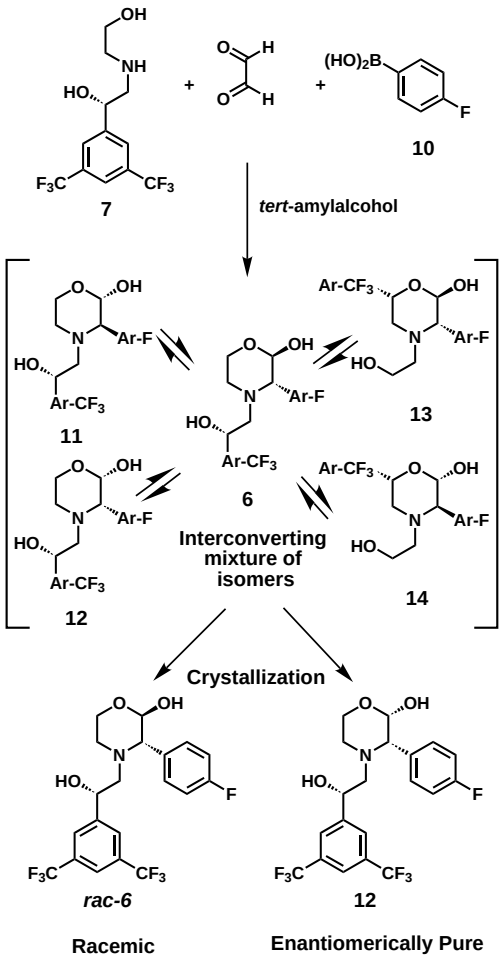
Synthesis of aminodiol **7** in racemic or enantiomerically pure form was readily achieved by using known chemistry. A Sharpless asymmetric dihydroxylation of 3,5-bis(trifluoromethyl)styrene (**8**) set up the necessary absolute stereochemistry, and subsequent selective activation of the primary alcohol as the mesylate followed by displacement with ethanolamine lead cleanly to crystalline **7** (Scheme 2; see also Experimental Section). An ambitious new three-component condensation was then utilized to assemble the core morpholine ring system in one step from **7**.[5]



Scheme 2. Synthesis of aminodiol **7**. a) $(DHQ)_2PHAL$, K_2OsO_4, NMNO, *t*BuOH, water; b) $MeSO_2Cl$, 2,6-lutidine, MeCN.

Heating **7** with 4-fluorophenylboronic acid (**10**) and aqueous glyoxal afforded, in quantitative yield, a mixture of lactol diastereomers: **6**, **11**, and **12** (50:10: <2 area %) and regioisomers **13** and **14** (10 and 20 area %) (Scheme 3). This poor selectivity would severely limit the utility of this morpholine synthesis, if not for the fact that these isomers are interconvertible, presumably through the ring-opened aldehyde/diol. Thus, a chromatographically isolated mixture of **11** and **12** returns to the initially observed isomeric mixture of **6**, **11**, **12**, **13**, and **14** by addition of DBU, catalytic H_3PO_4, or by simple heating. This facile equilibration of the isomers in solution, coupled with a crystallization of the desired diastereomer, could lead to a crystallization-induced transformation that would funnel the complex mixture into a single crystalline isomer.[6] Indeed, this crystallization-induced asymmetric transformation was first demonstrated in the racemic series by seeding the mixture of **6**, **11**, **12**, **13**, and **14** with crystalline *rac*-**6** to afford the desired *rac*-**6** in 65 % yield (90 area %).

Crystal properties of enantiomerically pure compounds are expected to differ from those of the racemate.[7] Thus, the dependence of our synthesis on a crystallization-induced asymmetric transformation gives this often inconsequential issue great significance. Repeating the boronic acid condensation with (*S*)-**7**, we obtained the same expected ratio of isomers in solution. However, attempts to crystallize enantiomerically-pure *trans*-lactol **6** were unsuccessful and resulted in the isolation of a minor component of the reaction mixture, the *cis*-lactol **12**. Pure **12** was obtained in 86 % yield by slow

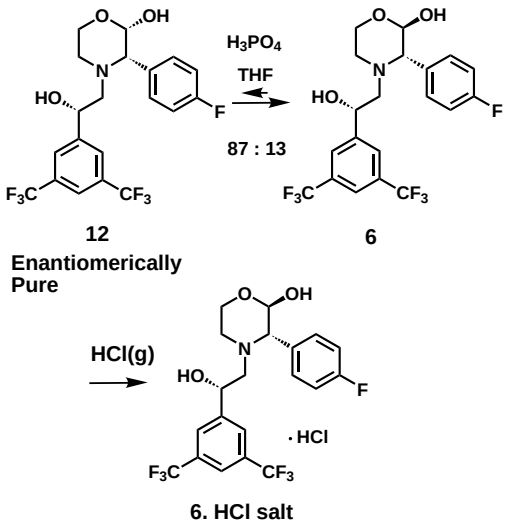


Scheme 3. Interconversion of diastereomers.

crystallization from the reaction mixture with methylcyclohexane. Evidently, the *trans*-lactol **6** is still the thermodynamically preferred species in solution and, consequently, brief exposure of a solution of the *cis*-lactol **12** to a trace amount of H_3PO_4 rapidly establishes a 87:13 equilibrium of *trans*/*cis*-lactols **6** and **12** (Scheme 4). Single-crystal X-ray structures were obtained for *rac*-**6** and enantiomerically pure **12** and show extensive hydrogen-bonding networks for both cases.[8] While the X-ray result confirms the structural assignments, a simple explanation for the forces that stabilize the minor species **12** of a mixture in the crystalline state of the enantiomerically pure product is not readily apparent (see Supporting Information).

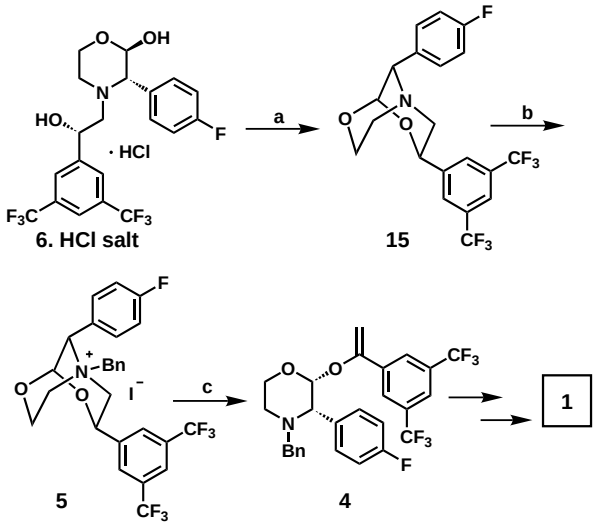
As the subsequent steps required the use of the *trans*-lactol **6** (*vide infra*), **12** was first converted to *trans*-lactol **6**. This was accomplished in 98 % yield by equilibration of a solution of **12** to the 87:13 *trans*/*cis* mixture and slow precipitation of the *trans*-lactol **6** as the HCl salt. A simple conversion to the free base gives a solution of clean *trans*-lactol **6**, which is stable at 20 °C for extended periods of time in the absence of strong bases or acids.

Although a number of the lactol isomers could potentially cyclize to bicyclic acetal **15**, attempts to achieve this transformation under traditional acetal-forming conditions result-



Scheme 4. *cis*–*trans* Isomerization.

ed in complex mixtures. We then focused on the cyclization of *trans*-lactol **6** through selective activation of the lactol hydroxyl group and S_N2 type cyclization with the side chain alcohol from the α-face. The different steric and electronic environment of both alcohols made it likely that a regioselective activation of the lactol hydroxyl would be possible, and the neutral conditions required to prevent the facile elimination of the activated lactol **2** directed us to the Mitsunobu reaction.[9] Treatment of a solution of **6** with tributylphosphine in THF at $-30\,^{\circ}C$ followed by the addition of diisopropyl diazodicarboxylate (DIAD) and warming to ambient temperature led to the formation of crystalline bicyclic acetal **15** in 86% isolated yield from **6**·HCl (Scheme 5).



Scheme 5. a) i) aq. K_2CO_3, EtOAc; ii) Bu_3P, DIAD, THF, $-30\,^{\circ}C$ to $20\,^{\circ}C$, 86%; b) BnI, acetone, $50\,^{\circ}C$, 89%; c) 1.1 equiv NaOH, EtOH, H_2O, 90%.

The bicyclic acetal was quaternized in acetone with benzyl iodide at $50\,^{\circ}C$ to yield 89% of iodide salt **5**. Regioselective Hofmann elimination proceeded as expected by heating **5** in ethanol/water (3:1) with 1.1 equivalents of sodium hydroxide.[10] The choice of iodide counterion for salt **5** allowed the direct isolation of the key vinyl ether **4** in 90% yield with rejection of the sodium iodide byproduct in the liquors.

In conclusion, we have developed a short practical asymmetric synthesis of vinylether intermediate **4**, a key intermediate for the synthesis of substance P inhibitor **1**, in 58% overall yield from readily available starting materials. The morpholine core is assembled rapidly in a novel three-component cyclization, and a subsequent crystallization-induced asymmetric transformation is used to funnel the complex mixture of diastereomers into a single species, thus establishing the morpholine stereochemistry. A diastereoselective formation of the bicyclic acetal **15**, quaternization to **5**, and a subsequent regioselective Hofmann elimination lead to **4**. Notably, all chiral centers in **4** and subsequently in **1** are ultimately derived from the single chiral center in diol (*S*)-**7**, prepared by the Sharpless catalytic asymmetric dihydroxylation.

Experimental Section

General: All reagents were purchased from common commercial sources and used as received. All reactions were performed in a dry nitrogen atmosphere. Column chromatography was performed with EM Science silica gel 60 (230–400 mesh).

Unless otherwise stated all reactions were monitored by HPLC analysis by using a Thermo Separations AS1000 with a Zorbax Rx-C8 reverse phase column. Optical rotations and microanlyses were determined by QTI (Whitehouse, NJ). NMR spectra were obtained on Bruker Avance 600, 500, and 400 MHz spectrometers. Spin–spin coupling constants (J) are reported in hertz.

Preparation of 3,5-bistrifluoromethylstyrene (8): A solution of 3,5-bis(trifluoromethyl)bromobenzene (75 g, 0.256 mol), tetrabutylammonium chloride (71.4 g, 0.256 mol), triethylamine (71.3 mL, 0.97 mol), and palladium(II) acetate (113 mg) in acetonitrile (360 mL) was deoxygenated with a vigorous flow of nitrogen. The reaction was pressurized with ethylene (950 psi) and heated to $80\,^{\circ}C$ for 36 hours. Pentane (400 mL) was added, and, after washing with water (3×200 mL), the organic layer was dried over Na_2SO_4 and the solvent was removed in vacuo to afford **8** as a pale yellow oil (58.2 g, 0.242 mol, 95% yield). ^1H NMR/^{13}C NMR consistent with that purchased from Aldrich.

Preparation of (*S*)-bis-3,5-(trifluoromethyl)phenyl ethyleneglycol (9): Hydroquinine 1,4-phthalazinediyl diether ($(DHQ)_2PHAL$) (13.3 g, 17.0 mmol) was added to a solution of potassium osmate dihydrate (5.68 g, 15.4 mmol) in *tert*-butanol (2.3 L)/water (1.97 L). An aqueous solution of *N*-methylmorpholine *N*-oxide (596 mL, 50 wt.%, 2.88 mol) was then added. After 15 minutes styrene **8** (468 g, 1.95 mol) was added over 3.5 hours, while a temperature of $15\,^{\circ}C$ was maintained. The reaction mixture was warmed to $23\,^{\circ}C$ for 30 minutes and quenched by the addition of 10% aq. Na_2SO_3. After aging for 18 hours, the phases were separated and the aqueous layers extracted with ethyl acetate (1×2 L). The organic layers were combined, washed with 0.4 N H_2SO_4 saturated with Na_2SO_4 (2.4 L). After drying over Na_2SO_4 the solvent was removed in vacuo to afford crude **9** as an off white solid (87% *ee*). Recrystallization from ethyl acetate/hexanes gave **9** as a white solid (395 g, 74%, >99% *ee*). M.p. 142–144 °C; $[\alpha]_{589}^{25} = 19.85^{\circ}$ ($c = 2.833$ in MeOH); ^1H NMR (400.13 MHz, $[D_6]$DMSO): $\delta = 8.02$ (s, 2H), 7.94 (s, 1H), 5.69 (d, $J = 4.8$ Hz, 1H), 4.84 (t, $J = 5.6$ Hz, 1H), 4.77 (q, $J = 5.3$ Hz, 1H), 3.59 (m, 1H), 3.50 (m, 1H); ^{13}C NMR (100.61 MHz, $[D_6]$DMSO): $\delta = 147.7$, 130.1 (q, $J = 32.8$ Hz), 127.5 (q, $J = 3.2$ Hz), 123.9 (q, $J = 273.1$ Hz), 120.8 (septet, $J = 4.0$ Hz), 72.6, 66.8; IR(KBr): $\tilde{\nu} = 3312$, 2896, 1622, 1473 cm^{-1}; elemental analysis calcd (%) for $C_{10}H_8F_6O_2$: C 43.81, H 2.94, F 41.58; found: C 43.45, H 2.77, F 41.93.

Preparation of (*S*)-2-imino[1-(bis-3,5-(trifluoromethyl)phenyl)ethanol]-2′-ethanol (7): Methanesulfonyl chloride (89 mL, 1.26 mol) was added over 1 hour to a solution of diol **9** (300 g, 1.09 mol) in acetonitrile (900 mL)

  0947-6539/02/0806-1374 $ 17.50+.50/0 *Chem. Eur. J.* **2002**, *8*, No. 6

containing 2,6-lutidine (600 mL, 5.2 mol). HPLC analysis indicated complete consumption of diol. After addition of 2-aminoethanol (1 L), the acetonitrile and 2,6-lutidine were removed by reduced pressure distillation at 90 °C over 3 hours. The remaining oil was partitioned between 10% aqueous sodium carbonate (1 L) and ethyl acetate (1.2 L). The organic layer was washed with water (3 × 300 mL) and then with brine (1 × 300 mL). After drying with $MgSO_4$, the solvent was removed to afford an oil. Crystallization from MBTE/heptane afforded 59% of (*S*)-**7** as a white solid (205 g, 0.647 mol). M.p. 80–82 °C; $[\alpha]_{589}^{25} = 34.4°$ ($c = 2.64$ in MeOH); ^{1}H NMR (400.13 MHz, [D$_6$]DMSO): $\delta = 8.03$ (s, 2H), 7.93 (s, 1H), 5.71 (br s, 1H), 4.85 (m, 1H), 4.46 (br s, 1H), 3.43 (t, $J = 5.6$ Hz, 2H), 2.75 (m, 1H), 2.69 (m, 1H), 2.59 (m, 2H), 1.95 (br s, 1H); ^{13}C NMR (100.61 MHz, [D$_6$]DMSO): $\delta = 148.7$, 130.1 (q, $J = 32.0$ Hz), 127.1 (q, $J = 3.2$ Hz), 123.8 (q, $J = 272.3$ Hz), 120.7 (m), 70.8, 60.8, 57.2, 51.8; IR (KBr): $\tilde{\nu} = 2973$, 2868, 1427, 1029 cm^{-1}; elemental analysis calcd (%) for $C_{12}H_{13}F_6NO_2$: C 45.43, H 4.13, F 35.93, N 4.42; found: C 45.15, H 3.77, F 35.89, N 4.12.

Preparation of lactol 12: A 40% aqueous glyoxal solution (0.46 mL, 2 equiv) were added to a solution of aminodiol (*S*)-**7** (632 mg, 2.00 mmol) in *tert*-amylalcohol (10 mL). After a 1 hour, 4-fluorophenylboronic acid (335 mg, 2.54 mmol) was added, and the reaction mixture was heated to 40 °C for 15 hours. The reaction mixture was diluted with cyclohexane (80 mL) and washed with water (3 × 30 mL). Drying ($MgSO_4$) and evaporation gave a glassy solid, consisting of the diastereomeric mixture **6**, **11**, **12**, **13**, and **14** (1.06 g), which partially crystallized on standing. After addition of methylcyclohexane (4 mL) and EtOAc (0.15 mL), the resulting slurry was aged for 18 hours in a 45 °C bath to give the crystalline *cis*-lactol **12** (775 mg, 95 A%, 86% yield). M.p. 130–132 °C; $[\alpha]_{589}^{25} = 1.14°$ ($c = 1.075$ in MeOH); ^{1}H NMR (600.13 MHz, CD_3CN): $\delta = 7.83$ (s, 1H), 7.78 (s, 2H), 7.40 (m, 2H), 7.05 (m, 2H), 4.96 (dd, $J = 9.8$, 3.4 Hz, 1H), 4.80 (dd, $J = 7.9$, 1.9 Hz, 1H), 4.29 (d, $J = 7.9$ Hz, 1H), 4.19 (td, $J = 11.7$, 2.6 Hz, 1H), 3.87 (br s, 1H), 3.63 (m, 1H), 3.59 (d, $J = 1.9$ Hz, 1H), 3.17 (dt, $J = 11.7$, 2.6 Hz, 1H), 2.53 (td, $J = 11.3$, 3.8 Hz, 1H), 2.38 (dd, $J = 12.8$, 9.8 Hz, 1H), 2.21 (dd, $J = 12.8$, 3.4 Hz, 1H); ^{13}C NMR (150.90 MHz, CD_3CN; selected data): $\delta =$ 94.0, 70.5, 68.8, 62.4, 59.8, 52.2; IR (KBr): $\tilde{\nu} = 3395$, 1029, 800 cm^{-1}; elemental analysis calcd (%) for $C_{20}H_{18}F_7NO_3$: C 52.99, H 4.00, F 29.33, N 3.09; found: C 52.62, H 3.91, F 29.25, N 3.03.

Preparation of 6·HCl salt: A solution of the *cis*-lactol **12** (705 mg, 1.57 mmol) in EtOAc (10 mL) was heated to reflux. After cooling to room temperature, the solution was saturated with HCl gas. To the clear solution of the salt, methylcyclohexane (10 mL) was added. The slow crystallization was allowed to take place over 18 hours, hen the slurry was concentrated to about half its volume and filtered to give the desired **6·HCl** salt (747 mg, 94 A%, 98% yield). M.p. 176–178 °C; $[\alpha]_{589}^{25} = 77°$ ($c = 4.7$ in MeOH); ^{1}H NMR (600.13 MHz, CD_3CN): $\delta = 12.01$ (br s, 1H), 7.89 (s, 1H), 7.86 (s, 2H), 7.80 (br m, 2H), 7.21(m, 2H), 6.26 (br, 1H), 5.39 (d, $J = 10.2$ Hz, 1H), 5.26 (d, $J = 7.9$ Hz, 1H), 5.08 (br, 1H), 4.63 (t, $J = 12.5$ Hz, 1H), 4.21 (dd, $J = 13.2$, 2.6 Hz, 1H), 3.98 (d, $J = 12.5$ Hz, 1H), 3.89 (d, $J = 7.9$ Hz, 1H), 3.32 (m, 1H), 3.12 (d, $J = 13.2$ Hz, 1H), 2.98 (dd, $J = 13.2$, 10.2 Hz, 1H); ^{13}C NMR (150.90 MHz, CD_3CN): $\delta = 164.4$ (d, $J = 247.8$ Hz), 143.5, 133.2 (br), 132.0 (q, $J = 33.6$ Hz), 127.8 (q, $J = 3.1$ Hz), 124.5 (q, $J = 271.6$ Hz), 122.8 (m), 117.0 (d, $J = 22.0$ Hz), 95.4, 72.6, 66.1, 64.3, 61.8, 53.4; IR (KBr): $\tilde{\nu} = 3278$, 3059, 1098, 959 cm^{-1}; elemental analysis calcd (%) for $C_{20}H_{19}ClF_7NO_3$: C 49.04, H 3.91, Cl 7.24, F 27.15, N 2.86; found: C 48.65, H 3.77, Cl 7.36, F 26.9, N 2.81.

Preparation of bicyclic acetal 15: A slurry of lactol HCl salt **6** (4.25 g, 8.68 mmol) in ethyl acetate (50 mL) was washed with dilute aqueous potassium carbonate (0.7 g in 70 mL water). The organic layer was further washed with water and dried over $MgSO_4$. The solvent was switched into THF (40 mL), and the solution cooled to −30 °C. Tributylphosphine (2.65 mL, 10.4 mmol) was added followed by the addition of DIAD (2.0 mL, 9.98 mmol) over 30 minutes, while a temperature below −25 °C was maintained. After the addition, the reaction was allowed to warm to 15 °C over 3 hours, and the solvent was removed in vacuo. The residue was filtered through a short silica gel column (20% ethylacetate in hexane) and recrystallized from EtOH/water (1:1) to afford bicyclic acetal **15** as a white solid (3.23 g, 7.43 mmol, 86% yield). M.p. 99–101 °C; $[\alpha]_{589}^{25} = 23.5°$ ($c =$ 1.36 in MeOH); ^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta = 7.72$ (s, 1H), 7.58 (m, 4H), 7.11 (m, 2H), 5.61 (s, 1H), 5.58 (dd, $J = 10.3$, 6.4 Hz, 1H), 4.46 (ddd, $J = 11.9$, 10.0, 6.0 Hz, 1H), 4.22 (s, 1H), 3.98 (ddd, $J = 11.9$, 7.0, 3.4 Hz, 1H), 3.91 (ddd, $J = 13.9$, 10.0, 7.0 Hz, 1H), 3.47 (ddd, $J = 13.9$, 6.0, 3.4 Hz, 1H), 2.90 (m, 2H); ^{13}C NMR (125.77 MHz, $CDCl_3$): $\delta = 161.1$ (d, $J = 247.2$ Hz), 143.9, 132.9 (d, $J = 3.1$ Hz), 131.7 (q, $J = 33.2$ Hz), 129.4 (d, $J = 8.0$ Hz), 126.0 (q, $J = 2.5$ Hz), 123.1 (q, $J = 272.6$ Hz), 121.6 (m), 115.4 (d, $J =$ 20.9 Hz), 89.0, 71.5, 61.2, 56.8, 52.7, 52.6; IR (KBr): $\tilde{\nu} = 3073$, 2976, 1016, 935 cm^{-1}; elemental analysis calcd (%) for $C_{20}H_{16}F_7NO_2$: C 55.18, H 3.70, F 30.55, N 3.22; found: C 55.10, H 3.60, F 30.66, N 3.20.

Preparation of bicyclic acetal quaternary ammonium iodide 5: Benzyl chloride (0.7 mL, 6.08 mmol) was added to a solution of sodium iodide (880 mg, 587 mmol) in acetone (10 mL), and the reaction mixture stirred in the dark for 18 hours. The resulting slurry was filtered, bicyclic acetal (**15**) (2.00 g, 4.60 mmol) was added, and the resulting solution was heated at 50 °C for 8 hours. The solvent was switched into cyclohexane (10 mL), and the product was removed by filtration to afford quaternary salt **5** as a pale yellow solid (2.76 g, 89%). M.p. 169–171 °C; $[\alpha]_{589}^{25} = -0.86°$ ($c = 2.05$ in MeOH); ^{1}H NMR (500.13 MHz, CD_3CN): $\delta = 8.25$ (m, 2H), 8.15 (s, 2H), 8.09 (s, 1H), 7.55 (m, 2H), 7.51 (m, 1H), 7.44 (m 2H), 7.32 (m, 2H), 6.03 (s, 1H), 5.91 (dd, $J = 11.9$, 3.6 Hz, 1H), 5.77 (s, 1H), 5.62 (d, $J = 12.3$ Hz,), 4.82 (m, 1H), 4.70 (m, 1H), 4.45 (m, 1H), 3.75 (d, $J = 12.3$ Hz, 1H), 3.68 (m, 2H), 3.57 (t, $J \approx 12$ Hz, 1H); ^{13}C NMR (125.77 MHz, CD_3CN): $\delta = 165.3$ (q, $J = 249.8$ Hz), 140.1, 136.5 (v br), 134.6, 132.6 (q, $J = 33.8$ Hz), 131.7, 130.0, 128.3 (q, $J = 3.7$ Hz), 126.8, 124.8 (d, $J = 3.7$ Hz), 124.4 (q, $J = 272.0$ Hz), 124.0 (m), 117.2 (d, $J = 22.1$ Hz), 94.7, 69.3, 67.1, 65.0, 60.2, 58.2, 57.8; IR (KBr): $\tilde{\nu} = 3278$, 3059, 1098, 959 cm^{-1}.

Preparation of *cis*-vinyl ether 4: A slurry of quaternary salt **5** (2.00 g, 2.98 mmol) in ethanol (3 mL) was heated at 40 °C. Sodium hydroxide (2 N, 1.64 mL, 3.28 mmol) was added and heating was continued until dissolution occurred. After 20 minutes the reaction was seeded with **4** (20 mg). After 40 minutes at 40 °C precipitation of **4** occurred. The reaction was heated at 75 °C for a further 4 hours and then allowed to cool. An ethanol/water mixture (4:3, 7 mL) was added over 45 minutes. After 1 hour the product **4** was isolated by filtration and washed twice with 1:1 ethanol/water. After drying 1.46 g **4** was obtained as a white powder (90%). Supercritical-fluid chromatographic analysis (OD column, 3% MeOH isocratic) indicated $\gg$99% *ee* of the desired enantiomer. M.p. 101–103 °C; $[\alpha]_{589}^{25} = 114.1°$ ($c = 1.18$ in MeOH); IR (KBr): $\tilde{\nu} = 3028$, 2882, 1466, 753 cm^{-1}; elemental analysis calcd (%) for $C_{27}H_{22}F_7NO_2$: C 61.72, H 4.22, F 25.31, N 2.67; found: C 61.22, H 4.13, F 25.09, N 2.61.

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[10] Products from alternative fragmentation pathways were not observed.

Received: January 4, 2002 [F3779]

  0947-6539/02/0806-1376 $ 17.50+.50/0