An Efficient Protocol for the Preparation of Primary Alcohols Bearing a β-Chiral Center via an Oxazolidinone Auxiliary Mediated Resolution, and Application to the Synthesis of 4,4-Disubstituted Piperidine Substance P Antagonists

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The role of the neuropeptide substance P in the physiological responses associated with the transmission of pain, and the induction of inflammation as a result of noxious stimuli, has received considerable attention in recent years.[1,2] It has been suggested that suitable substance P receptor antagonists may be of significant clinical utility in the treatment of a range of clinical conditions, including arthritis,[3] migraine,[4] and in controlling the emesis induced by a variety of cytotoxic agents.[5] Furthermore, recent clinical findings suggest significant potential as a novel treatment for depression.[6] As a result of extensive interest in this field, a number of structurally diverse classes of substance P receptor antagonists are now known, including a class of 4,4-disubstituted piperidines developed in these laboratories.[7]

As a consequence of our interest in this structural class, we required access to significant quantities of an advanced intermediate (**1**). This necessitated development of an expedient route to the preparation, in homochiral form, of a bis(trifluoromethyl)benzyl ether bearing a pendant hydroxymethyl substituent at the benzylic position, from alcohol **2** (Figure 1). At the onset of this work we were not aware of which enantiomer was required and so chose to pursue a resolution strategy which could provide access to either enantiomer at will. In this paper we describe an expedient route for preparation of homochiral **1** on a multigram scale.

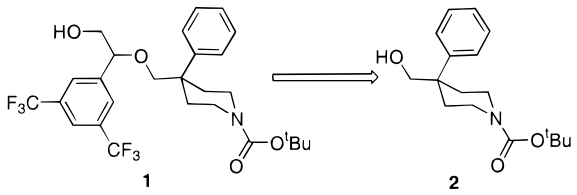
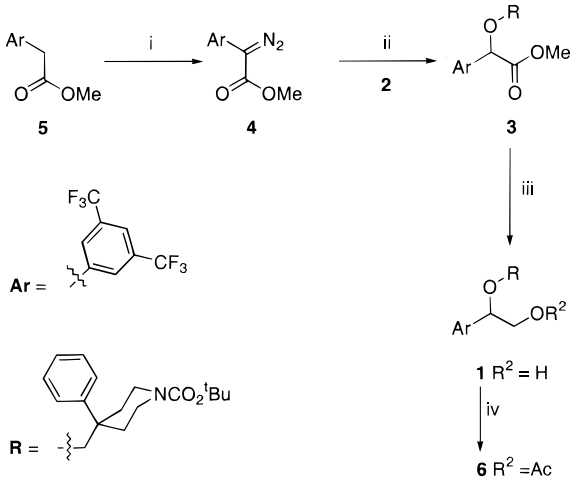


Figure 1.

Scheme 1[a]



[a] Reagents: (i) *p*-$NO_2PhSO_2N_3$, DBU, CH_3CN, −5 °C; (ii) **2**, $Rh_2(OAc)_4$, PhH, 80 °C; (iii) $LiBH_4$, MeOH; (iv) Ac_2O, Py.

An attractive option appeared to be construction of the ether linkage via transition metal catalyzed carbene insertion into the readily available[7] alcohol **2**, followed by reduction of the resulting ester **3** and subsequent resolution by derivatization of the primary alcohol. The required α-diazo ester **4**, a stable crystalline solid, was prepared in 92% yield, on multigram scale, by diazo-transfer from *p*-nitrophenylsulfonyl azide, mediated by DBU (Scheme 1).[7b] *p*-Nitrophenylsulfonyl azide was found to be superior to other reagents such as trisyl azide, in that it is readily purified by crystallization, and the sulfonamide byproduct of diazo-transfer is easily removed due to the greater polarity and hence enhanced aqueous solubility of its sodium salt. Upon slow addition of the α-diazo ester **4** to 1.75 equiv of alcohol **2** in benzene at reflux in the presence of catalytic rhodium acetate, a smooth insertion reaction occurred to afford desired ether **3** in 70−85% yield, isolated from the recoverable excess of alcohol by a simple chromatographic separation. Borohydride reduction of the ester of **3** proceeded cleanly to afford the desired racemic alcohol (±)-**1**. This route

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(4) Shepheard, S. L.; Williamson, D. J.; Williams, J.; Hill, R. G.; Hargreaves, R. J. *Neuropharmacology* **1995**, *34*, 255.
(5) Tattersall, F. D.; Rycroft, W.; Francis, B.; Pearce, D.; Merchant, K.; MacLeod, A. M.; Ladduwahetty, T.; Keown, L.; Swain, C.; Baker, R.; Cascieri, M.; Ber, E.; Metzger, J.; MacIntyre, D. E.; Hill, R. G.; Hargreaves, R. J. *Neuropharmacology* **1996**, *35* , 1121.
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(7) (a) Stevenson, G. I.; MacLeod, A. M.; Huscroft, I.; Cascieri, M. A.; Sadowski, S.; Baker, R. *J. Med. Chem.* **1995**, *38*, 1264. For additional examples, see Patent Appl. WO 95/19344. (b) Taber, D.; Gleave, D. M.; Herr, R. J.; Moody, K.; Hennessy, M., *J. Org. Chem.* **1995**, *60*, 2283. While we have experienced no difficulties with the preparation or subsequent reaction of diazo compound **4** on the scale reported, and **4** appears to be stable to prolonged storage at −18 °C (5 years), the usual precautions against explosion when handling organic azides and organic diazo compounds should be observed. For preparation of diazo-transfer reagents, including an excellent discussion of the hazards and safety considerations in their handling and usage, see Bollinger, F. W.; Tuma, L. D. *Synlett* **1996**, 407. Diazo compound **4** has been subjected to differential scan calorimetry which indicates that the compound melts in the region of 48−50 °C, with a heat of fusion of 66.53 J/g, which is not especially large. TGA analysis indicates a moderate rate of decomposition above the melting point, presumably by loss of nitrogen, with a 7.6% weight loss. Diazo compounds flanked by two electron-withdrawing π-systems are generally observed to be relatively stable entities.

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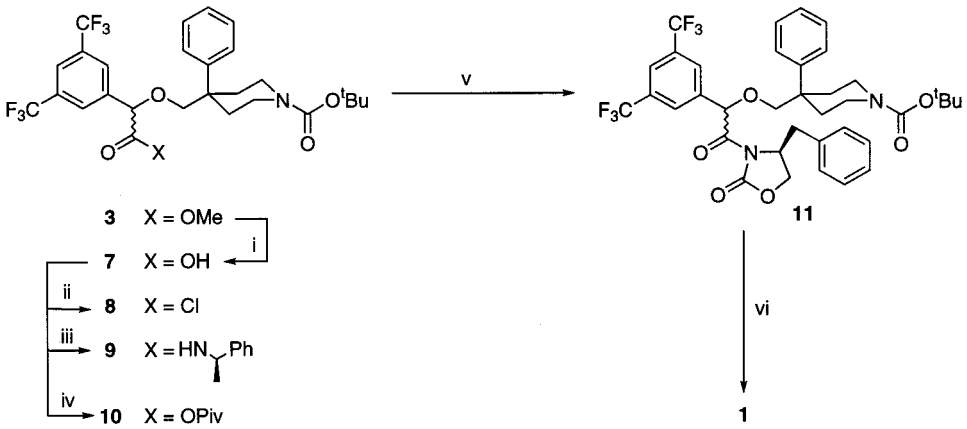
Scheme 2[a]



[a] Reagents: (i) KOH, MeOH:H_2O (60:1), 0 °C; (ii) $(COCl)_2$, DCM, cat. DMF; (iii) EDC, HOBT, (+)-α-methylbenzylamine; (iv) Me_3CCOCl, Et_3N, DCM; (v) (a) THF, ^{n}BuLi, (*S*)-(−)-4-benzyl-2-oxazolidinone, −78 °C, (b) **8**, PhMe; (vi) $LiBH_4$, THF, H_2O.

proved to be amenable to the rapid preparation of 100 g batches of **3**.

With a reliable route to alcohol (±)-**1** in hand, attention was focused upon the resolution strategy. A number of potential approaches to the resolution of a primary alcohol bearing a *β*-chiral center were considered worthy of exploration. A variety of derivatizing agents for the chromatographic resolution of alcohols have been reported in the literature; however, many are most effective for secondary alcohols.[8] Attempts to resolve the primary alcohol (±)-**1** by coupling it with a variety of chiral auxiliaries failed to provide a practical means of separation of the resulting diastereoisomers. Furthermore, ^{1}H NMR (360 MHz) also failed to show resolved spectra of the mixture of diastereoisomers. The derived acetate **6**, after cleavage of the N-Boc protecting group, was resolved enzymatically by iterative treatment with porcine pancreatic lipase,[9] and subsequent reprotection afforded (+)-**1** in high enantiomeric excess (98% ee), but only 10 mg of the homochiral alcohol was obtained from 850 mg of the racemic mixture. Although this route was not viable for the large-scale synthesis of (+)-**1**, it did allow us to establish that the biological activity resided principally with compounds which were derived from the (+)-enantiomer of **1**.

Derivatization of the acid **7** was then examined as an alternative approach; it was found that the menthyl ester offered resolved ^{1}H NMR spectra of the diastereoisomers, but separation by chromatography under a variety of conditions was not feasible. In contrast, the α-methyl benzamide diastereoisomers **9** were readily separable by chromatography, but conversion to homochiral alcohol **1** under mild conditions was not achievable. Reasoning that the notable R_f difference between the diastereoisomeric amides may be due to the more conformationally constrained nature of the amide bond as compared with the ester, other chiral auxiliaries that confer a similar degree of torsional rigidity were examined. Diastereoisomeric imides derived from chiral oxazolidinones have previously been suggested as being easily separable by chromatography.[10] It is also well documented that oxazolidinone imides can be reduced to the corresponding primary alcohols without loss of stereochemical integrity.[11] The acid **7** was converted to (*S*)-(−)-4-benzyl-2-oxazolidinone derivative **11** via the action of the lithio salt of the oxazolidinone on acid chloride **8** in 54% overall yield from methyl ester **3**. Preparation of the imides using the pivalic anhydride[12] intermediate **10** resulted in far lower yields. The R_f difference between the two resulting diastereoisomers **11A** and **11B** was sufficient to make them readily separable on ca. 20 g scale. Reduction with lithium borohydride to yield alcohol **1** was significantly improved upon the addition of 1 equiv of water.[14] Reduction of the more polar imide (diastereoisomer **11B**) derived from (*S*)−(−)- 4-benzyl oxazolidinone gave (−)**1** in 97% ee and 88% yield, whereas reduction of the less polar imide (diastereoisomer **11A**) gave (+)-**1** in only 88% ee. Hence the (*R*)-(+)-benzyl oxazolidinone was chosen as the preferred auxiliary for the synthesis of the desired (+)-enantiomer, since in this case it would be derived from the more polar imide and therefore retain a higher degree of stereochemical integrity during the reduction, to afford (+)-**1** in 97% ee[15] as assessed by HPLC.[16] Removal of the Boc protecting group with methanolic HCl allows crystallization of the amine hydrochloride salt.

To improve the efficiency of the route, racemization of the undesired diastereoisomer **11A** to provide more of the desired diastereoisomer **11B** was examined. The two flanking electron-withdrawing groups should render the chiral center prone to epimerization. A range of bases were screened for their ability to induce racemization of diastereomer **11A**. Strong bases such as LDA apparently caused decomposition of the starting material. Conditions used by Evans et al. for the generation of the boron enolates[13] from similar imides, however, resulted in a clean racemization to a 1:1 mixture of diastereoisomers

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(15) After installation of the desired N-substituent (see ref 7), a single crystallization typically raised the ee of the product above 99.5%.

(16) Enantiomeric purity was determined on a Diacel Chiralpak AD column, eluent 3% ethanol in hexane @ 1.5 mL min^{-1} @ 40 °C, monitored at 210 nM.

11. Furthermore, it was observed that the action of triethylamine alone, in DCM at room temperature, resulted in a 1.8:1 ratio of **11B** to **11A**, presumably reflecting thermodynamic control. Hence, iterative treatment of the undesired diastereomer with triethylamine resulted in almost complete conversion of the material to the desired diastereoisomer.[17]

In summary we have described a practical and high-yielding route to multigram quantities of **1**, relying on a diazo-insertion strategy which permits a highly convergent synthesis, followed by an effective resolution protocol which exploits the acyloxazolidinone moiety as a surrogate for a primary alcohol.

Experimental Section

General Proceedures. NMR spectra were recorded at 300 K. Flash column chromatography was carried out on silica gel (E. Merck Art 7734). "Petroleum ether" refers to petroleum ether with bp 60−80 °C. Reagents and dry solvents were purchased from Fluka or Aldrich and used without further purification. Glassware was dried at 130−150 °C prior to use, and reactions were performed under an atmosphere of dry nitrogen unless otherwise specified. Organic solvents were evaporated on a rotary evaporator at reduced pressure. Elemental analyses were determined by Butterworth Laboratories Ltd., Teddington, England.

Methyl 2-Diazo-2-(3,5-bis(trifluoromethyl)phenyl)acetate (4). To a solution of methyl 3,5-bis(trifluoromethyl)-phenylacetate (**5**) (53.0 g, 184 mmol) and 4-nitrobenzenesulfonyl azide (42 g, 184 mmol) in dry acetonitrile (250 mL), cooled to −10 °C, was added DBU (30.0 g, 196 mmol) dropwise over 30 min with stirring, and the mixture was stirred at −10 °C for a further 0.5 h. The solvents were evaporated at reduced pressure, and the residue was partitioned between ether and water. The organic layer was washed with sat. $NaHCO_3$ aq, dried (Na_2SO_4), and evaporated, and residue was chromatographed on silica gel (eluent 2.5% Et_2O/ hexane) to afford **4** (52.8 g, 92%) as yellow prisms (significant exotherm when oil crystallizes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (2H, s), 7.65 (1H, s), 3.91 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 132.3(q, J_{C-F} 33 Hz), 129.1, 123.1(q, J_{C-F} 271 Hz), 123.0(m), 119.1(m), 52.4. ^{19}F NMR (376.36 MHz, $CDCl_3$) δ −63.55. *m/e* (ES^+) 284 ($M - N_2$). IR (film, NaCl) 1740, 2140 cm^{-1}. HPLC purity > 99.2% by two systems (TSKgel Super ODS 100 × 4.6 mm column [supplied by Fisher Scientific], eluent 40% H_2O/ CH_3CN @ 1 mL/min; Supelco Discovery 150 × 4.6 mm column [supplied by Supelco U.K.], eluent 35% H_2O/ CH_3CN @ 1 mL/min monitored at 210 nM).

Methyl 2-[(*N*-*tert*-Butoxycarbonyl-4-phenylpiperidin-4-yl)methoxy]-2-(3,5-bis(trifluoromethyl)phenyl)acetate (3). Slow addition (over 60 h via syringe pump) of the α-diazo ester **4** (49.26 g) as a solution in benzene (50 mL) to alcohol **2**[7] (80 g, 1.75 equiv) in benzene (150 mL) at reflux under nitrogen, in the presence of catalytic rhodium acetate (100 mg, 0.15 mol %), afforded, after evaporation and chromatography of the residue on silica gel (eluent 25% to 40% Et_2O/ hexane), ester **3** (62.5 g, 70%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (1H, s), 7.70 (2H, s), 7.35 (4H, m), 7.25 (1H, m), 4.67 (1H, s), 3.79 (2H, m), 3.69 (3H, s), 3.67 (1H, d, J = 9 Hz), 3.37 (1H, d, J = 9 Hz), 3.04 (2H, m), 2.31 (1H, m), 2.19 (1H, m), 1.91 (2H, m), 1.44 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.87, 154.97, 141.79, 138.97, 131.73(q, J_{C-F} = 33 Hz), 128.58, 127.17, 126.96 (m), 126.66, 123.14 (q, J_{C-F} = 273 Hz), 122.37 (m), 79.96, 79.53, 79.39, 52.60, 41.72, 40 (br m, CH_2N), 31.88, 31.4, 28.4. ^{19}F NMR (376.36 MHz, $CDCl_3$) δ −63.29. *m/e* (ES^+) 576 (MH^+), 520 ($MH^+ - (CH_3)_2CCH_2$)), 476 (MH^+ − Boc). HPLC purity > 97.8% by two systems (TSKgel Super ODS 100 × 4.6 mm column [supplied by Fisher Scientific], eluent 70% CH_3CN/0.1% aqueous trifluoroacetic acid @ 1 mL/min; ACE 3C18 150 × 4.6 mm column eluent 80% CH_3CN/0.1% aqueous trifluoroacetic acid @ 1 mL/min monitored at 210 nM).

***N*-{2-[(*N*-*tert*-Butoxycarbonyl-4-phenylpiperidin-4-yl)-methoxy]-2-(3,5-bis(trifluoromethyl)phenyl)acetyl}-4(*R*)-benzyl-2-oxazolidinone (11).** To a solution of methyl ester **3** (11 g, 0.019 mol) in methanol (100 mL) at 0 °C was added KOH (3.2 g, 0.057 mol), followed by water (3 mL). The homogeneous solution was stirred at 0 °C for 1 h. The methanol was removed in vacuo and pH 4 buffer (100 mL) added to the residue. The product was extracted into Et_2O, dried ($MgSO_4$), and evaporated in vacuo. The resulting white foam (10.6 g) was dissolved in anhydrous DCM (50 mL). DMF (0.5 mL) was added followed by oxalyl chloride (2.23 mL, 25.7 mmol) dropwise. After stirring at 25 °C for 0.5 h, the solvent was removed in vacuo. The resulting residue was azeotroped with toluene (50 mL) and then, as a solution in anhydrous toluene (40 mL), added at −78 °C to the lithium anion of (4*R*)-4-benzyl-2-oxazolidinone (generated by adding n-BuLi (11.8 mL, 1.6 M, 18.8 mmol) to a solution of (4*R*)-(+)-4-benzyl-2-oxazolidinone (3.34 g, 18.8 mmol) in THF (100 mL) at −78 °C and stirring for 0.5 h). The resulting colorless solution was stirred at −78 °C for a further 0.75 h and quenched by addition of Et_2O (400 mL), and sat. NH_4Cl aq (30 mL). The organic layer was dried ($MgSO_4$). The clear oil obtained after removal of solvent in vacuo was chromatographed on silica gel (eluent 20% ethyl acetate/hexane to obtain diastereomer **11A** (3.4 g, 25%), and then 30% ethyl acetate/hexane to obtain diastereomer **11B** (4.0 g, 29%), as colorless foams.

Diastereoisomer 11A. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (1H, s), 7.70 (2H, s), 7.34−7.19 (10H, m), 5.94 (1H, s), 4.58 (1H, m), 4.17 (2H, m), 3.77 (2H, m), 3.67 (1H, d, J = 9 Hz), 3.31 (1H, d, J = 9 Hz), 3.28 (1H, m), 3.02 (2H, m), 2.79 (1H, m), 2.19 (2H, m), 1.90 (2H, m) 1.43 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.91, 154.97, 152.82, 141.81, 138.38, 134.69, 131.74 (q, J_{C-F} = 33 Hz), 129.41, 129.06, 128.56, 128.50, 127.58, 127.15, 126.63, 123.08 (q, J_{C-F} = 273 Hz), 122.81 (m), 79.37, 79.21, 78.20, 66.69, 55.45, 41.63, 40 (br m, CH_2N), 37.74, 31.84 (br m), 31.37 (br m), 28.42. ^{19}F NMR (376.36 MHz, $CDCl_3$) δ −63.14. *m/e* (ES^+) 721 (MH^+), 665 ($MH^+ - (CH_3)_2CCH_2$)), 621(MH^+ − Boc). Anal. Calcd for $C_{37}H_{38}F_6N_2O_6$: C, 61.66; H, 5.31; N, 3.88%. Found: C, 61.97; H, 5.28; N, 3.88%.

Diastereoisomer 11B. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (1H, s), 7.77 (2H, s), 7.34−7.16 (8H, m), 6.95 (2H, m), 5.93 (1H, s), 4.69 (1H, m), 4.25 (1H, m), 4.17 (1H, m), 3.77 (2H, m), 3.61 (1H, d, J = 8.7 Hz), 3.29 (1H, d, J = 8.7 Hz), 3.04 (3H, m), 2.62 (1H, m), 2.17 (2H, m), 1.89 (2H, m) 1.43 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.97, 154.95, 152.86, 141.78, 138.43, 134.28, 131.81 (q, J_{C-F} = 33 Hz), 129.21, 128.88, 128.52, 127.49, 127.17, 126.61, 123.09 (q, J_{C-F} = 273 Hz), 122.78 (m), 79.37, 79.27, 78.24, 66.77, 55.11, 41.63, 40 (br m, CH_2N), 37.31, 31.80 (br m), 31.39 (br m), 28.42. ^{19}F NMR (376.36 MHz, $CDCl_3$) δ −63.14. *m/e* (ES^+) 721 (MH^+), 665 ($MH^+ - (CH_3)_2CCH_2$)), 621 (MH^+ − Boc). Anal. Calcd for $C_{37}H_{38}F_6N_2O_6$: C, 61.66; H, 5.31; N, 3.88%. Found: C, 61.57; H, 5.32; N, 3.75%.

Diastereomer **11A** (3.0 g) and dry triethylamine (5 mL) in DCM (50 mL) was allowed to stand at 25 °C for 16 h. The solvents were evaporated, and the mixture was separated by chromatography as described above to obtain diastereomer **11B** (1.85 g). Diastereomer **11A** (1.0 g) was also recovered.

(+)-2-[(*N*-*tert*-Butoxycarbonyl-4-phenylpiperidin-4-yl)-methoxy]-2-(3,5-bis(trifluoromethyl)phenyl)ethanol (+1). Diastereomer **11B** (1.8 g, 2.5 mmol) was dissolved in diethyl ether (50 mL) and cooled to 0 °C under a nitrogen atmosphere. Water (0.05 mL, 2.75 mmol) was added, followed by lithium borohydride (0.054 g, 2.5 mmol). The reaction was stirred at 0 °C for 0.75 h and quenched by addition of 1 N NaOH (50 mL). The mixture was extracted with ethyl acetate, and the organic solutions were washed with brine, dried ($MgSO_4$), filtered and evaporated in vacuo. The residue was purified by chromatography on silica gel eluting with 20% ethyl acetate/hexane to obtain (+)-**1** (1.2 g, 88%, 97% ee) as a white foam: α_D +31.1° (c = 1; CH_2Cl_2), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (1H, s), 7.52 (2H, s), 7.40−7.32 (4H, m), 7.27 (1H, m), 4.29 (1H, m), 3.76 (2H, m), 3.50 (2H, m), 3.41 (1H, d, J = 8.8 Hz), 3.34 (1H, d, J = 8.8 Hz), 3.04 (2H, m), 2.24 (2H, m), 1.83 (3H, m), 1.44 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.94, 142.03, 141.53, 131.88 (q, J_{C-F} = 33 Hz), 128.70, 126.95, 126.78, 126.68 (m), 123.13 (q, J_{C-F} =

(17) As yet we have been unable to prepare crystalline derivatives of **11** or **1** suitable for X-ray structural determination of the absolute configuration.

273 Hz), 122.06 (m), 82.30, 79.49, 79.06, 66.82, 41.71, 40 (br m, CH_2N), 31.92 (br m), 28.42 ppm. ^{19}F NMR (376.36 MHz, $CDCl_3$) δ −63.26. *m/e* (ES^+) 548 (MH^+), 492 ($MH^+ - (CH_3)_2CCH_2$)), 448 (MH^+ − Boc). HPLC purity > 99.5% by two systems (Hypersil Hypurity 150 × 4.6 mm column, eluent 62% CH_3CN/H_2O @ 1 mL/min; Supelco Discovery 150 × 4.6 mm column, eluent 50% CH_3CN/H_2O @ 1 mL/min monitored at 210 nM). Anal. Calcd for $C_{27}H_{31}F_6N_1O_4$: C, 59.23; H, 5.71; N, 2.56%. Found: C, 59.32; H, 5.80; N, 2.46%.

Acknowledgment. We thank Mr. James McCabe for his valuable assistance with obtaining differential scan calorimetric measurements on diazo compound **4.**

Supporting Information Available: ^1H and ^{13}C NMR spectra for **1**, **3**, **4**, **11A**, and **11B**. This material is available free of charge via the Internet at http://pubs.acs.org.

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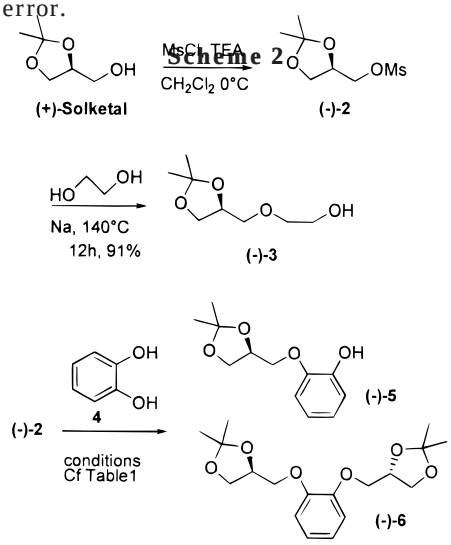
Additions and Corrections

Vol. 64, 1999

Yvan Le Huérou, Julien Doyon, and René L. Grée*. Stereocontrolled Synthesis of Key Advanced Intermediates toward Simplified Acetogenin Analogues.

Page 6784, Scheme 2. (+)-Solketal and subsequent derivatives have been represented with the configuration opposite to that of the optical rotation shown. The experimental section which describes the synthesis of both enantiomers is, however, correct. Scheme 2 and all subsequent pictorial material should be corrected as shown below. We thank Dr. R. E. Dardis for bringing this mistake to our attention and we apologize to the readers for this error.

Scheme 2



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