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A New and Convergent Synthesis of (2*S*)-7-(4,4′-Bipiperidinylcarbonyl)-2,3,4,5-tetrahydro-4-methyl-3-oxo-1*H*-1,4-benzodiazepine-2-acetic Acid Using a Palladium-Catalysed Aminocarbonylation Reaction

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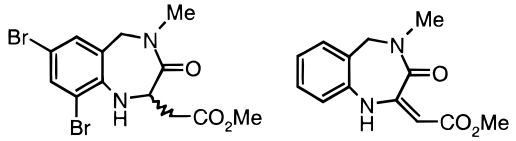
Abstract:

Palladium-catalysed aminocarbonylation of a 7-bromo- or 7-iodo-1,4-benzodiazepine with *N*-Cbz-4,4′-bipiperidine hydrochloride efficiently introduced the 7-(4,4′-bipiperidinylcarbonyl) moiety of (2*S*)-7-(4,4′-bipiperidinylcarbonyl)-2,3,4,5-tetrahydro-4-methyl-3-oxo-1*H*-1,4-benzodiazepine-2-acetic acid.

SB-214857 is a potent GP IIb/IIIa antagonist and, as a consequence, inhibits platelet aggregation.[1] It has been proposed for clinical trials for the prevention of secondary thrombotic events such as heart attack and stroke. Initial supplies of SB-214857 for toxicological testing were made using the medicinal chemistry route[2] which is summarised in Scheme 1. A number of problems were encountered using this chemistry, in particular during the intramolecular fluoride displacement reaction. To obtain satisfactory and consistent yields of cyclized product SB-218093, anhydrous conditions were required. The reaction was therefore performed in the presence of a large quantity of molecular sieves, and this caused serious difficulties with stirring. Even under these optimized conditions, unacceptable levels of racemization (ca. 5%) occurred on a 50 kg scale.[3] We did not consider this route suitable for further scale-up.

A program of research was therefore initiated to discover if more efficient and practical routes to SB-214857 could be developed. Exploratory studies related to methods for producing the basic ring structure for **8** led to an efficient route to the benzodiazepine **1**.[4] Based upon this structure, we decided to explore the feasibility of preparing benzodiazepines **2** and **3** with a view to subsequent aminocarbonylation with bipiperidine **6** (Scheme 2). We anticipated that this strategic conversion would be difficult since carbonylations to prepare acyclic amides are not well developed[5] and, as substrates, 1,4-benzodiazepines are unknown and electron-rich aromatics are rare.

The electrophilic halogenation of **1** was initially discouraging due to its intrinsic properties. For example, bromination of the electron-rich aromatic ring using bromine or *N*-bromosuccinimide in dichloromethane led to formation of unacceptable levels (ca. 10%) of the dibromide **4**. Use of standard reagents for the iodination of substituted anilines such as iodine in the presence of copper(II) salts,[6] benzyltrimethylammonium dichloroiodate,[7] *N*-iodosuccinimide, or iodine monochloride[8] resulted in significant oxidation, where **5** was formed as a major byproduct. Clearly, electrophilic



4 **5**

iodination at either enolizable position followed by elimination was a major competing pathway. However, using nonstandard reagents and conditions, we eventually overcame these liabilities. The bromide **2** was prepared in 95% yield by bromination of **1** with tetrabutylammonium tribromide in dichloromethane, and the iodide **3** was also eventually prepared in 95% yield, by iodination of **1** with iodine monochloride−pyridine complex[9] in dichloromethane:water ca. 2:1.

Having overcome the problems in the production of benzodiazepines **2** and **3**, initial attempts to aminocarbonylate benzodiazepine **2** using conditions employed by Heck[10] (ArBr; Ar′NH_2, *n*-Bu_3N, $PdBr_2(Ph_3P)_2$, 1.5 mol %; CO, 1 atm; 100 °C) were unsuccessful. However, it was noted that, when extra triphenylphosphine was added and a large excess of a different palladium catalyst, palladium(0) tetrakistriphenylphosphine (20 mol %), was used, some of the desired aminocarbonylated product **7** was formed in variable yield. This result encouraged us to search for more cost-effective, reliable, and robust conditions since we had now shown that the required transformation could be accomplished in the presence of palladium(0) and carbon monoxide.

We examined a number of interacting parameters. *N*-Methylpyrrolidinone is a surprisingly useful solvent for the

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(2) (a) Bondinell, W. E.; Callahan, J. F.; Huffman, W. F.; Keenan, R. M.; Ku, T. W.; Newlander, K. A.; Samanen, J. M.; Uzinskas, I. N. Patent WO 9414776, 7 July 1994; CAN 123:112082. (b) Miller, W. H.; Ku, T. W.; Ali, F. E.; Bondinell, W. E.; Calvo, R. R.; Davis, L. D.; Erhard, K. F.; Hall, L. B.; Huffman, W. F.; Keenan, R. M.; Kwon, C.; Newlander, K. A.; Ross, S. T.; Samanen, J. M.; Takata, D. T. and Yuan, C.-K. *Tetrahedron Lett*. **1995**, *36*, 9433.

(3) An alternative route using an intermolecular fluoride displacement reaction where no racemization is detected has recently been disclosed: Thomas, W. K.; Fadia, E. A.; Bondinell, W. E.; Erhard, K. F.; Huffman, W. F.; Venslavsky, J. W.; Yuan, C.-C.-K. *Tetrahedron Lett.* **1997**, *38*, 3131.

(4) Unpublished results.

(5) Colquhoun, H. M.; Thompson, D. J.; Twigg, M. V. *Carbonylation*; Plenum Press: New York, p 145.

(6) Horiuchi, C. A.; Satoh, J. Y. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2691.

(7) Kajigaeshi, S.; Kakinami, T.; Yamasaki, H.; Fujisaki, S.; Okamoto, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 600.

(8) Zembower, D. E.; Ames, M. M. *Synthesis* **1994**, 1433.

(9) Muathen, H. A. *J. Chem. Res.* **1994**, 405.

(10) Schoenberg, A.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3327.

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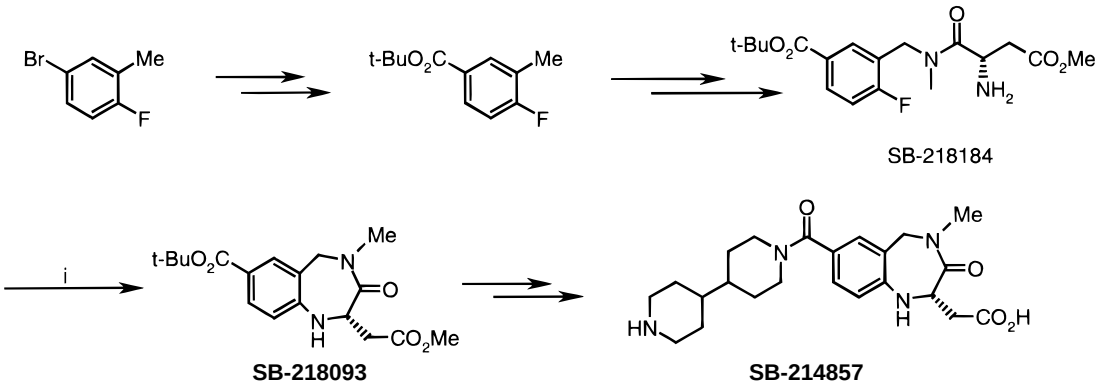
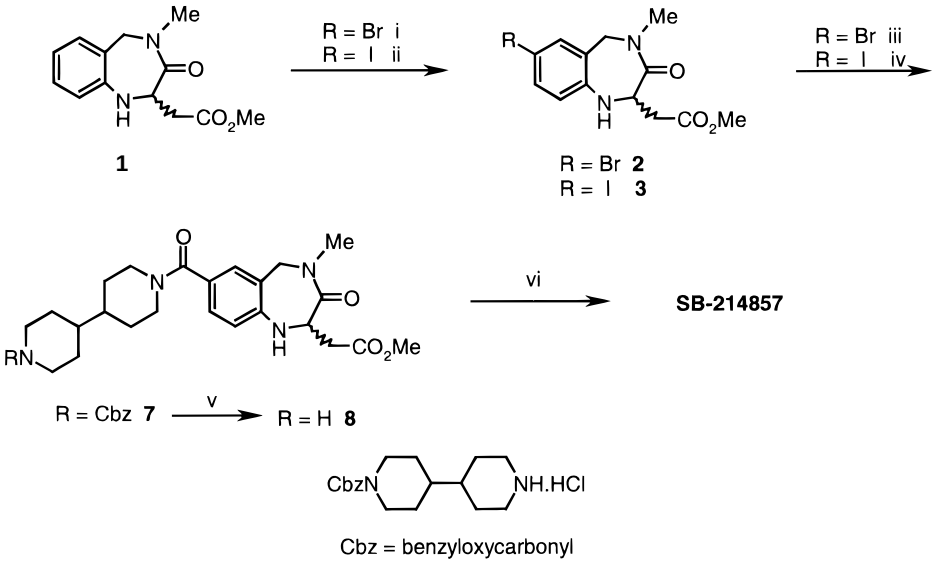
Scheme 1[a]



[a] Reagents and conditions: (i) DMSO, toluene, 3-Å molecular sieves, 5 kg/kg of SB-218184, 128−130 °C, 22 h, 40%.

Scheme 2[a]



[a] Reagents and conditions: (i) Bu_4NBr_3, 1.00 equiv, CH_2Cl_2, room temperature, 95%; (ii) ICl·pyridine, 1.10 equiv, CH_2Cl_2, H_2O, room temperature, 95%; (iii) $Pd(OAc)_2$, 0.02 equiv, PPh_3, 0.2 equiv, **6**, 1.4 equiv, CO (atmospheric pressure), NMP, Hünig's base, 9.7 equiv, HCO_2NH_4, 0.24 equiv, H_2O, 7.2 equiv, 100 °C, 75%; (iv) $PdCl_2(PPh_3)_2$, 0.02 equiv, **6**, 1.15 equiv, NMP, Hünig's base, 3.0 equiv, H_2O, 2.2 equiv, CO, 6−15 psi, 95 °C, 85%; (v) HCO_2NH_4, 2.0 equiv, 10% Pd−C, MeOH, reflux, 85%; (vi) resolution.[13]

conversion, especially when the reaction is run at 100 °C. The nature of the palladium ligand was found to be essential. *N*,*N*,*N*′,*N*′-Tetramethylethylenediamine and triethyl phosphite gave stable complexes, but they were inert. Tris(2-furyl)-phosphine did not provide enough stabilization, and the metal precipitated. Consequently, using these ligands, no aminocarbonylation occurred. However, triphenylphosphine was very effective, as it both solubilised and stabilised palladium(0) to give an active complex.

A major breakthrough occurred when it was discovered that a less expensive and more stable source of palladium catalyst [$Pd(OAc)_2$, 2 mol %] was effective if an aqueous solution of ammonium formate was added periodically during the reaction. The ammonium formate functioned to reduce palladium(II) to palladium(0) to maintain a supply of active catalyst. This combination of palladium(II) acetate, triphenylphosphine, and a reducing agent to generate an active catalyst[11] for the aminocarbonylation reaction is, to the best of our knowledge, unprecedented. These conditions were sufficiently robust that **2** could be converted reproducibly to the amide **7** in 75% isolated yield (Scheme 2).

Our attention then turned to aminocarbonylation of iodide **3**. It was run efficiently in *N*-methylpyrrolidinone at 95 °C under an atmosphere of carbon monoxide. A variety of palladium(II) catalysts were screened, e.g., $Pd(NH_3)_4Cl_2·H_2O$, (*cis*,*cis*-1,5-cyclooctadiene)palladium(II) chloride, dichloro-(*N*,*N*,*N*′,*N*′-tetramethylethylenediamine)palladium(II), $Pd(OAc)_2$, $PdCl_2$, $PdBr_2$, $PdNa_2Cl_4$, or $PdCl_2(Ph_3P)_2$; surprisingly, all were successful, and there was negligible variation in yield. In the case of the iodide **3**, nitrogen- and phosphorus-based ligands and the counterion do not play an important role in the reaction. Under the reaction conditions, palladium(II) is reduced to a soluble form of palladium(0), and at the end of the reaction the metal precipitates as palladium black. Addition of water, however, was important since the reaction proceeded very slowly (50% conversion

(11) For a discussion concerning the likely active catalytic species, see: Colquhoun, H. M.; Thompson, D. J.; Twigg, M. V. *Carbonylation*; Plenum Press: New York, 1991; pp 16−18.

after 24 h) under anhydrous conditions. Efficient stirring was required in order to maintain a sufficient concentration of carbon monoxide in solution to obtain an acceptable reaction rate. When higher pressures of carbon monoxide (5−40 psi) were used, the rate increased further to the extent that the reaction was complete within 2−3 h. Suitable conditions are illustrated (Scheme 2), and the product **7** was isolated after a simple workup in 85% yield.

Catalytic transfer hydrogenation[12] of pure **7** using ammonium formate and 10% palladium on charcoal in methanol resulted in facile removal of the Cbz protecting group to give **8** in 85% yield. Finally, resolution[13] of the ester **8** gave the final drug substance SB-214857 in high yield and stereochemical purity.

In conclusion, the 4,4′-bipiperidinylcarbonyl moiety of SB-214857 was introduced in a highly convergent manner using a surprisingly efficient palladium-catalysed aminocarbonylation process. Bromobenzodiazepine **2** and the corresponding iodide **3** differed significantly in their reactivities, and careful choice of ligand and addition of a reducing agent to maintain palladium(0) levels was necessary for bromide **2** to drive the reaction to completion. This gave us additional variables to control when considering scale-up. We therefore chose to scale up aminocarbonylation of the iodide **3**, and the resultant process has been run routinely in standard pilot plant equipment to produce several hundreds of kilograms of **7**, a late-stage intermediate to SB-214857.

Experimental Section

IR spectra were recorded on a Perkin-Elmer 781 spectrophotometer. ^{1}H (400 MHz) NMR specra were recorded on a Joel GSX FT spectrometer. Chemical shifts are reported as parts per million downfield from tetramethylsilane as internal standard. Accurate mass measurements were performed on a Micromass 70 SEQ double-focusing mass spectrometer. HPLC chromatography was performed using a HICHROM S5ODS columm. Eluant A: 0.1% trifluoroacetic acid in water. Eluant B: 0.1% trifluoroacetic acid in acetonitrile. Gradient: 100% A → 100% B over 20 min; 100% B → 100% A over 10 min. UV detection at 254 nm. Product purity was deturmined by HPLC assay against a primary reference standard.

Methyl (2*RS*)-7-Bromo-2,3,4,5-tetrahydro-4-methyl-3-oxo-1*H*-1,4-benzodiazepine-2-acetate (2). Methyl 2,3,4,5-tetrahydro-4-methyl-3-oxo-1*H*-1,4-benzodiazepine-2-acetate (**1**) (23.65 g, 95 mmol) was dissolved in dichloromethane (250 mL). *n*-Bu_4NBr_3 (46 g, 95 mmol) was added in small portions, maintaining the temperature at ca. 25 °C. After the addition, the reaction was stirred at ambient temperature for 1 h. The reaction had gone to completion according to HPLC. The reaction mixture was washed with a 10% aqueous solution of $NaHCO_3$ (250 mL) and water (250 mL) and was then dried (Na_2SO_4). The bulk of the solvent was removed in vacuo, and the residue was chromatographed on silica gel using ethyl acetate as eluant. Hence, the title compound (28.90 g, 92%) was obtained as a white solid. ^{1}H NMR ($CDCl_3$): δ 2.65 (dd, AMX, 1H), 3.00 (dd, AMX, 1H), 3.10 (s, 3H), 3.70 (d, 1H), 3.75 (s, 3H), 5.00 (t, AMX, 1H), 5.40 (d, 1H), 6.45 (d, 1H), 7.05 (d, 1H), and 7.20 (dd, 1H).

Methyl (2*RS*)-7-(4,4′-Bipiperidinylcarbonyl)-2,3,4,5-tetrahydro-4-methyl-3-oxo-1*H*-1,4-benzodiazepine-2-acetate (7) from Bromide 2. A 250-mL three-neck flask was charged with bromobenzodiazepine **2** (5.00 g, 15.3 mmol), triphenylphosphine (810 mg, 3.09 mmol), palladium(II) acetate (70 mg, 0.31 mmol), diisopropylethylamine (26 mL, 150 mmol), *N*-methylpyrrolidinone (40 mL), and bipiperidine **6** (7.25 g, 21.4 mmol). Carbon monoxide gas was passed through the resultant solution for 10 min, after which time it was heated to 100−110 °C and stirred vigorously under an atmosphere of carbon monoxide. After 1 h, ammonium formate (60 mg in 0.5 mL water) was added, and the same quantity was added at hourly intervals over the next 3 h. The reaction was monitored by HPLC and had gone to completion within 5 h. The reaction mixture was then concentrated in vacuo to remove as much diisopropylethylamine as possible, and the remaining solution was diluted with dichloromethane (30 mL). This solution was washed with water (2 × 30 mL) and was then concentrated in vacuo to leave a brown viscous oil. The oil was dissolved in ethyl acetate (80 mL), and within 15 min a precipitate had formed. This was stirred at room temperature for 1 h and then at 0 °C for 1 h. The precipitate was filtered and washed with ethyl acetate (4 × 20 mL) and dried in the open air for 3 h at ambient temperature. The title compound (6.52 g, 74%) was thus obtained as a pale yellow powder (found M^+ 576.2940; $C_{33}H_{40}N_4O_6$ requires *m*/*z* 576.2948). ^{1}H NMR ($CDCl_3$): δ 1.05−1.40 (m, 2H), 1.60−1.80 (m, 8H), 2.60 (dd, 1H), 2.65 (br s, 4H), 3.00 (dd, 1H), 3.10 (s, 3H), 3.70 (d, 1H), 3.75 (s, 3H), 4.20 (br s, 4H), 4.40 (d, 1H), 5.05 (ddd, 1H), 5.15 (s, 2H), 5.45 (d, 1H), 6.50 (d, 1H), 7.10 (s, 1H), 7.15 (d, 1H), and 7.30−7.40 (m, 5H). IR (Nujol): 3300, 2920, 1740, 1690, 1650, 1590, and 1370 cm^{-1}.

Methyl (2*RS*)-7-Iodo-2,3,4,5-tetrahydro-4-methyl-3-oxo-1*H*-1,4-benzodiazepine-2-acetate 3. Benzodiazepine **1** (97.6 kg at 95.3%, 374.6 mol) was added to dichloromethane (961 L) and the mixture heated to 38 °C to obtain a solution. The solution was cooled to 35 °C and demineralised water (428 L) added. Pyridine iodine monochloride (99.4 kg at 100%, 411.7 mol) was then added. The mixture was stirred at 28 °C for 1 h. HPLC analysis indicated that the reaction had gone to completion within 1 h.

The mixture was heated to 35 °C, dichloromethane (488 L) added, and the temperature adjusted to 36 °C. The mixture was stirred for 5 min, and the phases were allowed to separate for 50 min. The organic phase was added to dilute sodium metabisulphite, prepared from sodium metabisulphite (6.5 kg) in demineralised water (490 L). The mixture was stirred at 33 °C for 5 min, and the phases were allowed to separate for 55 min. The aqueous phase was discarded, and the organic phase was washed with dilute sodium bicarbonate solution (538.0 kg), taken from a solution of sodium bicarbonate (150.0 kg) in demineralised water (1500 L), maintaining the temperature at 35 °C, and then was washed

(12) Johnstone, R. A. W.; Wilby, A. H.; Entwhistle, I. D. *Chem. Rev.* **1985**, *85*, 129.
(13) Patent WO 9829561; *Chem. Abstr.* **1998**, *129*, 121708.

with demineralised water (490 L). Solvent (1028 L) was distilled off at atmospheric pressure, and 60−80 petroleum ether (695.0 kg) was then added. The mixture was stirred at 40 °C for 30 min. The mixture was cooled to 10 °C over 2 h. The product crystallised after 5 min. Stirring was continued for 2 h, maintaining the temperature between 4 and 10 °C. The product was isolated in the centrifuge and washed with 60−80 petroleum ether (281 L). The wet cake (159.3 kg) was dried at 35−40 °C under vacuum over 31 h to give the title compound (129.4 kg at 94.6% (87%)).

Methyl (2*RS*)-7-(4,4′-Bipiperidinylcarbonyl)-2,3,4,5-tetrahydro-4-methyl-3-oxo-1*H*-1,4-benzodiazepine-2-acetate (7) from Iodide 3. *N*-Methyl-2-pyrrolidinone (400 L), diisopropylethylamine (103.5 kg, 800.8 mol), palladium(II) chloride bistriphenylphosphine (3.8 kg, 5.4 mol), bipiperidine **6** (104.3 kg, 308 mol), benzodiazepine **3** (100.0 kg at 94.6%, 252.8 mol), and demineralised water (10.5 kg, 585.3 mol) were charged to a reactor. The vessel was purged four times with nitrogen and three times with carbon monixide and sealed. The mixture was heated to 95 °C and stirred at 95−99 °C, maintaining a constant carbon monoxide pressure of 10−12 psi for 4 h and 10 min. A sample was taken after 3 h and 45 min, and the reaction had gone to completion according to HPLC.

The solution was cooled to 55 °C, and a mixture of diisopropylethylamine and solvent was distilled off under vacuum (volume of distillate = 58 L) to a maximum temperature of 109 °C. The resulting concentrate was cooled to 30 °C and dichloromethane (910 L) added. Celite (5.0 kg) was charged and the slurry filtered to a second reactor, washing the filters and lines through with dichloromethane (60.0 kg). The filtrate was washed with demineralised water (2 × 800 L), maintaining the temperature at 25−30 °C during the separation. Solvent (656 L) was distilled off at atmospheric pressure and methanol (950 L) added. The distillation was continued to a base temperature of 64 °C, the volume being maintained by the addition of methanol until 200 L of solvent had been removed and 200 L of methanol had been added. The product precipitated from solution during the "put and take". The slurry was coooled to 3 °C and stirred at 0−5 °C for 3 h. The product was isolated in the centrifuge in two spins, washing each spin three times with methanol (3 × 360.0 kg/spin). The wet cake from spin 1 (104.1 kg) was dried at 35−40 °C under vacuum over 48 h and 40 min to give **7**, 66.4 kg at 97.7%, 112.5 mol. The wet cake from spin 2 (102.0 kg) was dried at 35−40 °C under vacuum over 66 h and 50 min to give 60.5 kg at 97.6%, 102.3 mol. The combined yield was 123.9 kg (85%).

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