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A Practical Synthesis of a Potent δ-Opioid Antagonist: Use of a Modified Knorr Pyrrole Synthesis

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Abstract:

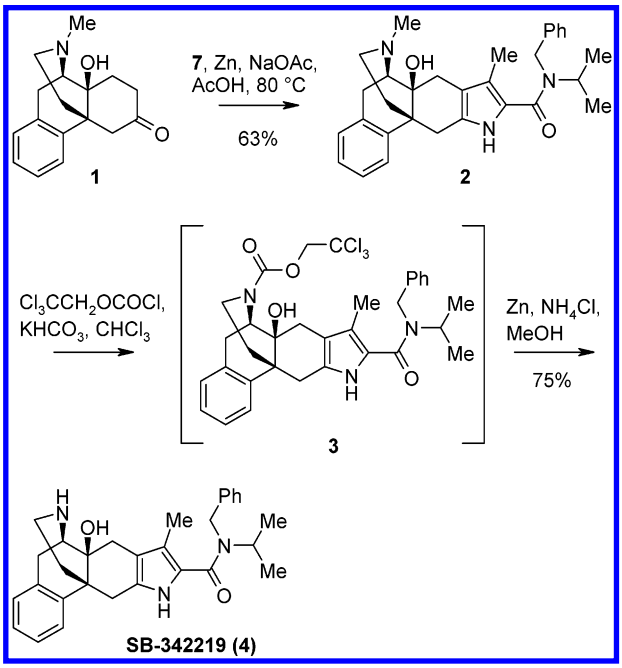
A modified Knorr pyrrole reaction is described which may have practical benefits for the large-scale synthesis of SB-342219. The use of zinc to reduce a phenylhydrazone is replaced by the hydrogenation of the corresponding oxime to provide a common aminoketone intermediate. The modifications have practical benefit with respect to carrying out the reaction and isolating the product. A modified N-demethylation procedure is also described. The use of zinc to reduce an intermediate trichloroethylcarbamate is replaced with the aqueous hydrolysis of the corresponding 1-chloroethylcarbamate.

SB-342219 (**4**) is a selective δ-opioid receptor agonist and as such has undergone preclinical evaluation for the potential treatment of neuropathic pain.[1] In this report we describe some technical improvements to the synthesis of SB-342219 (**4**) that are applicable to a large-scale synthesis. The medicinal chemistry route[2] is summarized in Scheme 1. The advanced intermediate ketone **1** was obtained from oxycodone in accordance with the published procedures.[3] The tetra-substituted pyrrole **2** was prepared using the Knorr pyrrole synthesis[4] where the α-aminoketone is formed in situ, by reduction of the phenylhydrazone **7** (Scheme 2). N-Demethylation of **2** was achieved via the intermediate trichloroethylcarbamate **3**, and then cleavage of the carbamate with zinc gives the target compound SB-342219 (**4**).

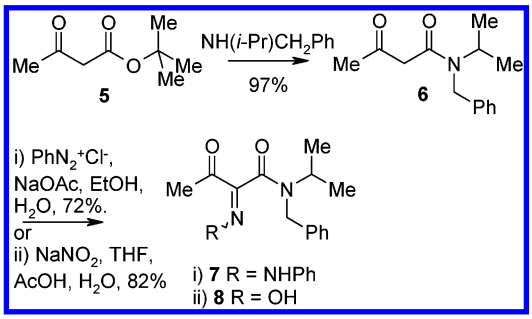
Although the Knorr pyrrole reaction was highly regioselective (none of the alternate regioisomer was observed) and high yielding, there were aspects of the process that we felt would cause problems for scale-up, which were mainly associated with the use of zinc. There was a need to add the finely divided zinc powder in portions to the hot, flammable solvent to maintain a low concentration of the intermediate α-aminoketone, formed by reduction of the phenylhydrazone **7**. The crude product **2** also required extensive purification by chromatography primarily to remove the by-product aniline. The problems associated with the N-demethylation procedure were the following: (1) the use of chloroform for the formation of the intermediate carbamate, (2) the addition of zinc powder to a hot, flammable solvent for the cleavage of the carbamate, and (3) the requirement for chromatography to ensure pure SB-342219 (**4**).

To alleviate some of the problems associated with the Knorr pyrrole reaction using phenylhydrazone **7**, the use of the corresponding oxime **8** was investigated as the α-ami-

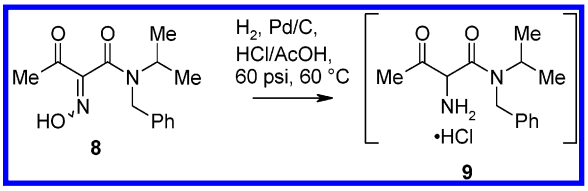
Scheme 1



Scheme 2



Scheme 3



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(1) Dondio, G.; Ronzoni, S.; Farina, C.; Graziani, D.; Parini, C.; Petrillo, P.; Giardina, G. A. M. *Farmaco* **2001**, *56*, 117−119.

(2) Clarke, S. E.; Dondio, G.; Raveglia, L. G.; Ronzoni, S. WO 00/63210, 2000.

(3) Preparation of 14-Hydroxy-17-methylmorphinan-6-one **1**. (a) Schmidhammer, H.; Jacobson, A. E.; Atwell, L.; Brossi, A. *Helv. Chim. Acta* **1981**, *64*, 2540−2543. (b) Brossi, A.; Atwell, L.; Jacobson, A. E.; Rozwadowska, M. D.; Schmidhammer, H.; Flippen-Anderson, J. L.; Gilardi, R. *Helv. Chim. Acta* **1982**, *65*, 2394−2404.

(4) Joule, J. A.; Mills. K. *Heterocyclic Chemistry*, 4th ed.; Blackwell Sciences Ltd: Oxford, 2000.

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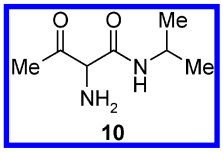

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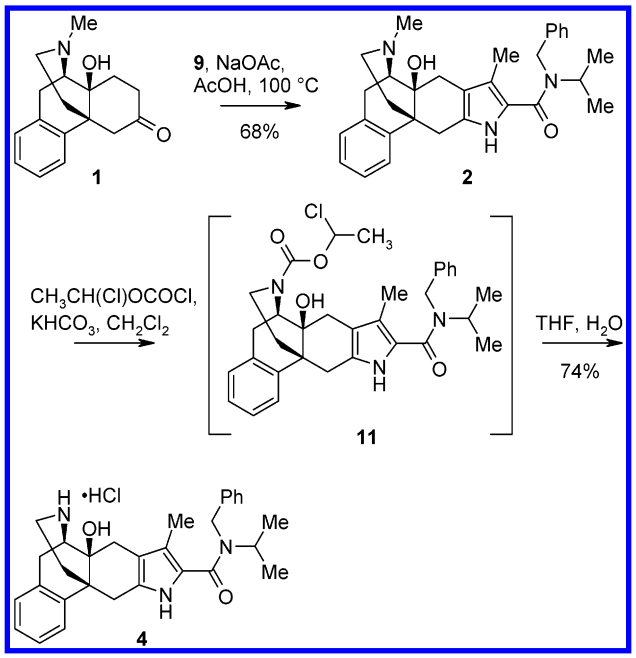
Figure 1.

Scheme 4



noketone **9** precursor. The preparation of oxime **8** is shown in Scheme 2. Condensation of *tert*-butyl acetoacetate **5** with *N*-isopropylbenzylamine gave the amide **6** in 97% yield which was then converted to the oxime **8** in 82% yield by treatment with sodium nitrite in aqueous acetic acid.[5]

Although the in situ reduction of oxime **8** to α-aminoketone **9** for the Knorr pyrrole reaction could not be achieved, a very workable two-step procedure was developed. Catalytic hydrogenation of oxime **8** over palladium on charcoal in acetic acid, in the presence of 2.0 equiv of anhydrous HCl, could be achieved at 60 °C and 60 psi of hydrogen pressure, Scheme 3. The hydrogenation reaction could be performed at lower hydrogen pressures by using 2.0 equiv of methanesulphonic acid; however, this resulted in the formation of elevated levels of des-benzyl impurity **10**, Figure 1. It was feared that impurities derived from the reaction of **10** would be very difficult to remove from subsequent products. Likewise the use of concentrated hydrochloric acid in place of anhydrous HCl also led to elevated levels of **10** being formed. Although α-aminoketone **9** could not be isolated as a solid, the reduction was clean and efficient. The filtered acetic acid solution of **9** was stable and was used directly in the modified Knorr pyrrole reaction.

The Knorr pyrrole reaction was carried out by the slow addition of the acetic acid solution of **9** to a solution of ketone **1** and sodium acetate in acetic acid at 100 °C, Scheme 4. Between 2.5 and 3.0 equiv of α-aminoketone **9** was required to ensure complete consumption of the valuable ketone **1**.

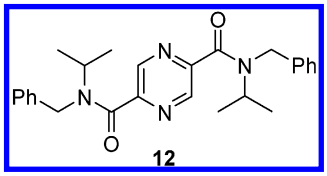


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Figure 2.

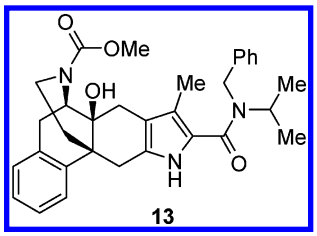

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Figure 3.

The absence of aniline from the reaction mixture made the work-up and isolation of product pyrrole **2** simpler. The product could be extracted into aqueous citric acid, and the nonbasic pyrazine by-product **12**, Figure 2, formed from α-aminoketone **9** by dimerisation and subsequent oxidation, could be removed by washing with toluene. Pyrrole **2** could then be isolated by crystallisation from toluene/heptane and then recrystallised from *i*-PrOH in 68% overall yield if a further up-grade in purity was required.

Alternative methods for the cleavage of trichloroethylcarbamate **3** to SB-342219 (**4**) were evaluated; however, none proved suitable for scale-up. A number of alternative chloroformates (e.g., benzyl, allyl, and 1-chloroethyl) have been reported for N-demethylation. Of these the use of 1-chloroethyl chloroformate appeared attractive since cleavage of the intermediate carbamate is reported to proceed with methanol.[6] Complete, clean formation of the 1-chloroethylcarbamate **11** only proceeded in a satisfactory manner in chlorinated solvents; dichloromethane was the most appropriate solvent. Attempts to replace the heterogeneous inorganic base, potassium hydrogen carbonate, with an organic base (e.g. imidazole, DBU or pyridine) were not successful. The intermediate 1-chloroethylcarbamate **11** was not isolated, but used directly in the hydrolysis reaction. Treatment of the crude carbamate **11** with methanol resulted in the formation of product **4**, but contamination with methylcarbamate **13** was noted (Figure 3). Hydrolysis of carbamate **11** was shown to be possible using wet, water-miscible solvents, and THF was found to work particularly well. By minimising the amount of water used, it was possible to isolate pure SB-342219 (**4**), as the hydrochloride salt, in 74% yield, directly from the reaction mixture and thus avoid the use of chromatography. This modified demethylation procedure overcomes all the main problems associated with the original procedure along with the additional benefit that 1-chloroethyl chloroformate is considerably cheaper than the corresponding trichloroethyl variant.

In conclusion we have developed an alternative procedure for the Knorr pyrrole reaction that does not use zinc metal in the preparation of the α-aminoketone **9**. Likewise we have

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(6) Hengeveld, J. E.; Gupta, A. K.; Kemp, A. H.; Thomas, A. V. *Tetrahedron Lett.* **1999**, *40*, 2497−2500.

developed a very mild method for N-demethylation; both of these procedures worked efficiently and cleanly, and we believe they would be suitable for the large-scale preparation of a potential pharmaceutical ingredient.

Experimental Section

***N*-(1-Methylethyl)-3-oxo-*N*-(phenylmethyl)butanamide 6.** To *N*-isopropylbenzylamine (25.00 g, 168 mmol) at 100 °C was added *tert*-butyl acetoacetate (24.76 g, 157 mmol) over 10 min, maintaining the temperature at 100 °C. The reaction was heated to 115 °C and a vacuum cautiously applied (100 mmHg). Once the collection of distillate had stopped, the reaction was cooled to 30 °C and EtOAc (75 mL) added. The solution was washed with 0.6 M aqueous HCl (25 mL), brine (25 mL), saturated aqueous $NaHCO_3$ (25 mL), brine (25 mL), and then the solvent was removed by vacuum distillation to leave acetoacetamide **6** (35.47 g, 97%) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.04−1.09 (m, 6 H), 1.80 (s, 0.4 H), 1.95 (s, 0.3 H), 2.09 (s, 0.9 H), 2.21 (s, 1.4 H), 3.32 (s, 0.4 H), 3.42 (s, 0.6 H), 3.78 (s, 1.0 H), 4.03 (hept, J = 6.6 Hz, 0.5 H), 4.38 (m, 0.1 H), 4.47 (s, 1.4 H), 4.52−4.74 (m, 0.8 H), 5.11 (s, 0.1 H), 5.58 (s, 0.1 H), 7.16−7.41 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.1, 20.1, 20.3, 21.2, 21.4, 21.4, 21.9, 30.2, 30.4, 43.5, 43.9, 44.8, 45.7, 46.1, 46.5, 49.9, 50.3, 50.5, 86.9, 88.3, 125.7, 125.9, 126.6, 126.7, 126.8, 127.0, 127.3, 128.3, 128.6, 128.8, 138.0, 138.3, 139.0, 166.6, 167.6, 175.1, 202.5, 202.6; IR (neat, cm^{-1}) 1721, 1631; LRMS (CI +ve) *m*/*z* 234 (M^+ + H).

(2*EZ*)-2-(Hydroxyimino)-*N*-(1-methylethyl)-3-oxo-*N*-(phenylmethyl)butanamide 8. To a solution of acetoacetamide **6** (15.0 g, 64.3 mmol) and acetic acid (15 mL) in THF (30 mL) at 15 °C was added a solution of sodium nitrite (6.21 g, 90 mmol) in water (9.3 mL) over 2 h, maintaining the temperature <20 °C. The reaction mixture was then stirred at 20 °C for a further 1 h before being added to water (150 mL). The resulting slurry was stirred at 20 °C for a further 30 min before the solid was isolated by filtration. The wet solid was dissolved in methanol (50 mL) and then heated to reflux. Water (50 mL) was added, maintaining the solution at reflux. The resulting slurry was cooled to 10 °C and then aged at 10 °C for 30 min prior to isolation by filtration. The filtercake was washed with water (3.75 mL) and then dried under vacuum at 80 °C to give oxime **8** (13.8 g, 82%) as a white solid: mp = 158−160 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (d, J = 6.5 Hz, 4.5 H), 1.22 (d, J = 6.8 Hz, 1.5 H), 2.17 (s, 0.75 H), 2.44 (s, 2.25 H), 3.70 (hept, J = 6.5 Hz, 0.75 H), 4.27 (s, 0.5 H), 4.55 (hept, J = 6.7 Hz, 0.25 H), 4.72 (s, 1.5 H), 7.19−7.41 (m, 5 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 19.7, 20.9, 21.4, 25.2, 25.4, 40.1, 42.3, 46.6, 48.0, 49.9, 126.3, 126.5, 127.1, 127.6, 127.9, 128.2, 137.9, 138.8, 153.4, 162.6, 163.0, 194.3, 194.9; IR (neat, cm^{-1}) 1682, 1591 and 1582; HRMS (CI +ve) *m*/*z* Calcd for $C_{14}H_{18}N_2O_3Na$: (M^+ + Na): 285.1209. Found: 285.1208; Anal. Calcd for $C_{14}H_{18}N_2O_3$: C, 64.1; H, 6.9; N, 10.7. Found: C, 64.15; H, 6.9; N, 10.8.

(6*R*,6a*S*,11a*R*) 5,6,6a,7,10,11-Hexahydro-6a-hydroxy-8,14-dimethyl-*N*-(1-methylethyl)-*N*-(phenylmethyl)-6,11a-(iminoethano)-11aH-naphth[2,1-*f*]indole-9-carboxamide 2. To a suitable pressure vessel were charged oxime **8** (16.0 g, 61.0 mmol), 10% palladium on charcoal (4.0 g, Johnson Matthey type 87L, 50% water wet), and acetic acid (80 mL). The system was purged with nitrogen, then HCl gas (5.0 g, 137 mmol) added, and the solution stirred for 5 min. The vessel was purged with hydrogen and pressurised to 60 psi with hydrogen. The stirrer was started, and the vessel was heated to 60 °C. After 90 min the vessel was cooled, depressurised, and then purged with nitrogen. The palladium on charcoal was removed by filtration through Celite, and the filtercake was washed with acetic acid (20 mL) to leave a solution of α-aminoketone **9** as the hydrochloride salt in 100 mL of acetic acid.

To a solution of morphinanone **1** (6.21 g, 22.9 mmol) and sodium acetate (14.1 g, 172 mmol) in acetic acid (55 mL) at 100 °C was added the acetic acid solution of α-aminoketone **9** (61 mmol, 100 mL) over 2 h, maintaining the temperature at 100 °C. Once the reaction was complete, the acetic acid was removed by distillation under reduced pressure. Toluene (120 mL) was added and the solvent removed by distillation under reduced pressure. Toluene (145 mL) was added followed by water (120 mL) and the pH adjusted to pH = 9 by the addition of 14.8 M ammonia (40 mL). The layers were separated, and the aqueous layer was discarded. The toluene solution was extracted with 5% v/v aqueous citric acid (140 mL) and the toluene discarded. Toluene 145 (mL) was added and the pH adjusted to pH = 6.8 by the addition of 14.8 M ammonia (8 mL). The layers were separated, and the aqueous phase was discarded. The toluene solution was washed with water (25 mL) and then concentrated by vacuum distillation to leave a residual volume of 35 mL. The solution was warmed to 45−50 °C to induce crystallisation. Once nucleation had occurred, a mixture of toluene (12 mL) and heptane (12 mL) was added at 50 °C. The slurry was aged at 50 °C for 1 h then at 0 °C for 30 min prior to isolation by filtration. The filtercake was washed with a mixture of toluene (12 mL) and heptane (6 mL) and then partially dried under under vacuum. The crude **2** was then recrystallised from refluxing *i*-PrOH (60 mL). The resulting slurry was cooled to 0 °C and then isolated by filtration. The filtercake was washed with *i*-PrOH (12 mL) and then dried under vacuum at 50 °C to afford pyrrole **2** (7.53 g, 68%) as a white solid: mp = 232−233 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (d, J = 6.4 Hz, 3 H), 1.17 (d, J = 6.6 Hz, 3 H), 1.19−1.27 (m, 1 H), 1.93 (s, 3 H), 2.08−2.23 (m, 2 H), 2.40 (s, 3 H), 2.32−2.46 (m, 3 H), 2.85−2.93 (m, 2 H), 2.96−3.05 (m, 1 H), 3.12 (d, J = 16.2 Hz, 1 H), 3.24 (d, J = 18.6 Hz, 1 H), 4.32 (d, J = 15.5 Hz, 1 H), 4.43 (hept, J = 6.5 Hz, 1 H), 4.58 (s, 1 H), 4.77 (d, J = 15.4 Hz, 1 H), 7.01−7.12 (m, 3 H), 7.12−7.28 (m, 6 H), 8.26 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.5, 20.9, 21.0, 24.5, 28.5, 29.4, 36.7, 40.4, 42.5, 44.5, 45.1, 50.2, 62.0, 69.8, 114.1, 118.4, 120.8, 124.4, 125.4, 125.9, 126.1, 126.8, 126.8, 127.2, 127.8, 135.3, 139.4, 139.6, 166.5; IR (neat, cm^{-1}) 1614 and 1324; HRMS (CI +ve) *m*/*z* Calcd for $C_{31}H_{38}N_3O_2$ (M^+ + H): 484.2959. Found: 484.2954; Anal. Calcd for $C_{31}H_{37}N_3O_2$: C, 77.0; H, 7.7; N, 8.7. Found: C, 77.0; H, 7.7; N, 8.75.

(6*R*,6a*S*,11a*R*)-5,6,6a,7,10,11-Hexahydro-6a-hydroxy-8-methyl-*N*-(1-methylethyl)-*N*-(phenylmethyl)-6,11a-(iminoethano)-11aH-naphth[2,1-*f*]indole-9-carboxamide monohydrochloride 4. To a solution of *N*-methylamine **2** (3.65 g, 7.55 mmol) in CH_2Cl_2 (55 mL) at room temperature was added potassium hydrogen carbonate (9.07 g, 90.6 mmol) and then 1-chloroethyl chloroformate (4.85 g, 33.9 mmol). Once the addition was complete, the reaction was heated at 40 °C for 16 h. The reaction mixture was cooled to room temperature, the inorganic salts were removed by filtration, and the filtercake was washed with CH_2Cl_2 (20 mL). The combined filtrate was concentrated by vacuum distillation to leave a residual volume = 10 mL. THF (73 mL) was added and a further 15 mL of distillate collected by vacuum distillation. Water (3.6 mL) was added and the reaction mixture heated at 50 °C for 5 h. The resulting slurry was then cooled to 20 °C and then aged for 1 h prior to isolation by filtration. The filtercake was washed with THF (20 mL) and then dried under vacuum at 50 °C to afford amine hydrochloride **4** (2.83 g, 74%) as a white solid: mp > 250 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 1.15 (d, J = 6.6 Hz, 6 H), 1.46 (d, J = 13.0 Hz, 1 H), 1.87 (s, 3 H), 2.42−2.58 (m, 3 H), 2.81 (td, J = 13.7, 3.2 Hz, 1 H), 2.94 (d, J = 16.5 Hz, 1 H), 3.09 (dd, J = 13.0, 3.9 Hz, 1 H), 3.24 (d, J = 19.3 Hz, 1 H), 3.40 (d, J = 16.4 Hz, 1 H), 3.64−3.78 (m, 2 H), 4.37 (hept, J = 6.9 Hz, 1 H), 4.59 (d, J = 16.6 Hz, 1 H), 4.62 (d, J = 16.6 Hz, 1 H), 7.13−7.24 (m, 8 H), 7.37 (d, J = 7.4 Hz, 1 H); ^{13}C NMR (100 MHz, CD_3OD) δ 8.3, 19.5, 27.4, 28.8, 29.5, 32.4, 36.0, 39.9, 49.7, 55.7, 67.7, 111.9, 118.0, 120.4, 124.5, 125.8, 126.0, 126.3, 126.6, 127.2, 127.4, 132.7, 137.7, 138.6, 167.1; IR (neat, cm^{-1}) 1714 and 1573; HRMS (CI +ve) *m*/*z* Calcd for $C_{30}H_{36}N_3O_2$ (M^+ + H): 470.2802. Found: 470.2798; Anal. Calcd for $C_{30}H_{35}N_3O_2$.HCl: C, 71.2; H, 7.2; N, 8.3. Found: C, 71.1; H, 7.15; N, 8.4.

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