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Synthesis of novel spirocyclic cocaine analogs using the Suzuki coupling

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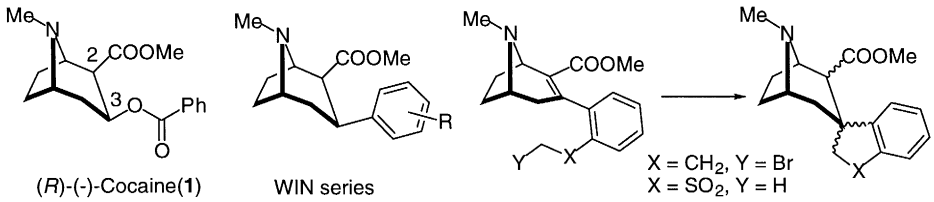
Abstract

Novel spirocyclic cocaine analogs were synthesized by employing the Suzuki coupling of *ortho*-substituted arylboronic acids and an enol triflate derived from cocaine.

Cocaine (**1**) is a major drug of abuse whose devastating effects have captured the attention of health officials and policy makers. Its reinforcing and stimulant properties have been associated with its ability to bind to monoamine transporter systems, particularly the dopamine transporter (DAT).[1] A number of highly potent cocaine analogs together with information concerning their structure–activity relationships (SAR) at the DAT have been reported.[2] However, the precise details of the binding interactions between these analogs and the DAT are still a matter of much discussion.[2–4]



Previously it has been shown that replacement of the C-3 benzoate by phenyl leads to higher potency cocaine analogs referred to as the 'WIN series'. With respect to the 3-position of these WIN analogs, SAR studies have focused primarily on the steric and electronic effects of substituents located at the *para* position of the phenyl ring, replacement of the phenyl group by other aromatic moieties, and additionally on the orientation (α versus β) of the aryl substituent.[3a,4] In continuation of our efforts to identify ligands of possible use in the treatment of cocaine abuse, we chose to explore the effects of rigidifying the orientation of the 3-aryl substituent by making it part of a spirocyclic system with or

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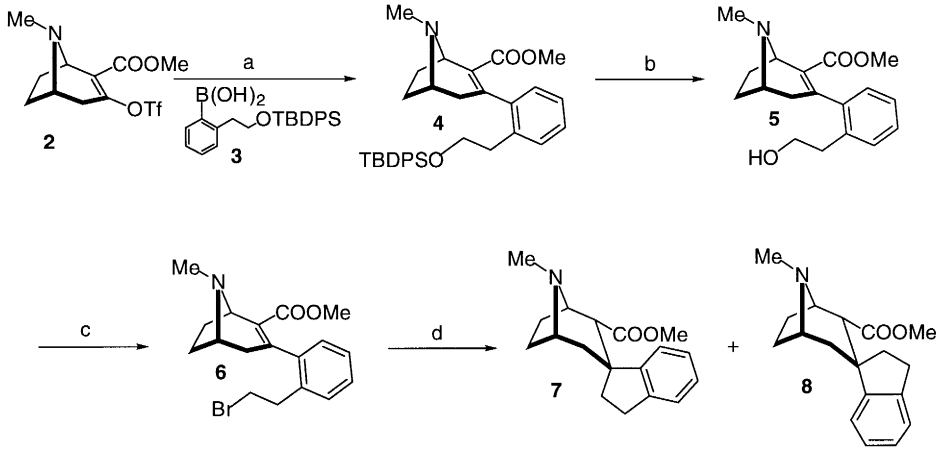
without a heteroatom. To our knowledge, the synthesis of such spiro compounds has not been reported previously.

The synthetic route employed in the present study (Scheme 1) exploits the Pd-catalyzed Suzuki coupling of *ortho*-substituted arylboronic acids and an enol triflate prepared from cocaine, and the subsequent formation of the spiro compound using a radical cyclization or intramolecular Michael addition. The synthesis commences with the preparation of (*R*)-2-(methoxycarbonyl)-3-tropinone from (−)-cocaine by benzoate hydrolysis[5] followed by Swern oxidation of the resulting alcohol. The ketone was then converted to the enol triflate **2** in 75% yield by reaction with *N*-phenyltrifluoromethanesulfonimide and sodium bis(trimethylsilyl)amide in THF as previously described by Carroll et al.[6] The enol triflate **2** was then coupled with the arylboronic acid **3** (prepared by treatment of the aryl bromide with *n*-BuLi and triisopropyl borate in THF, followed by hydrolysis of the resulting alkoxyborane with 1N HCl) using Suzuki's method.[7] The reaction of *ortho*-substituted arylboronic acids with enol triflates proved troublesome in some cases and the low yields of these reactions can be attributed to the steric hindrance exerted by the *ortho*-substituent.[7] After careful experimentation with the known literature variants of the Suzuki coupling, we found that treatment of arylboronic acid **3** with the enol triflate **2** in diethoxymethane in the presence of lithium bromide, tris(dibenzylideneacetone)dipalladium(0) catalyst, and 2M aqueous sodium carbonate under reflux conditions followed by chromatographic purification gave the desired product **4** in 72% yield.[6]



Scheme 1. Reagents and conditions: (a) Pd_2dba_3, LiBr, aq. Na_2CO_3, diethoxymethane, reflux; (b) TBAF, THF, rt; (c) PPh_3, CBr_4, CH_2Cl_2, rt; (d) AIBN, Bu_3SnH, benzene, 80°C

The *t*-butyldiphenylsilyl group was removed using *n*-Bu_4NF in THF at room temperature to give the alcohol **5** in 81% yield. The alcohol was converted to the bromo compound **6** by reaction with triphenylphosphine and carbon tetrabromide in CH_2Cl_2 at room temperature in 87% yield. The radical cyclization was carried out in 74% yield with an excess of tributyltin hydride and an equimolar amount of AIBN in benzene at 80°C using a syringe pump for slow addition. Two isomers **7** and **8** were formed in a 3:2 ratio, and these were separated by careful flash chromatography.[8] The orientation of the ester group was established by X-ray analysis (Fig. 1)[9] as α in both compounds, a consequence of trapping the radical formed after the cyclization step from the sterically less hindered *exo* face of the tropane ring.

The C-3 spirocyclic cocaine analog containing sulfur as a heteroatom was synthesized as described in Scheme 2. Suzuki coupling of the enol triflate **2** with the boronic acid **9** gave compound **10** in 82% yield. The oxidation of the sulfide **10** was carried out using Oxone® in a 2:1 mixture of MeOH and H_2O at room temperature for 4 h to give the sulfone **11** in 91% yield.[10] The presence of the sulfone function

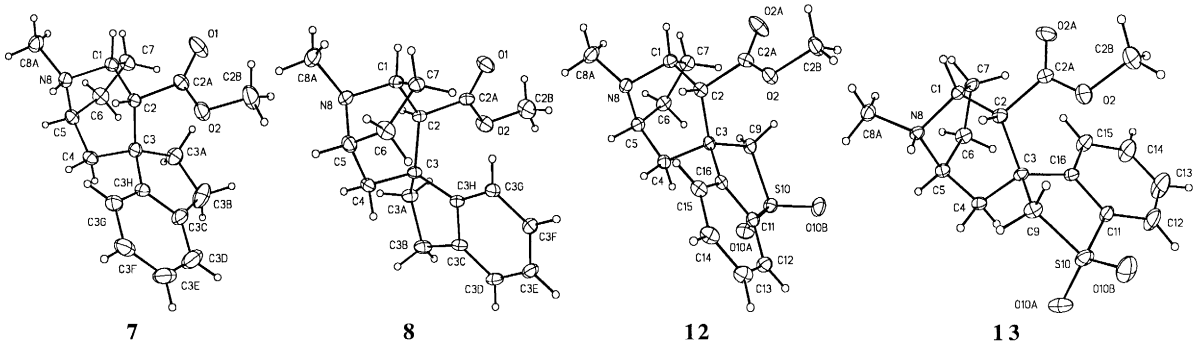
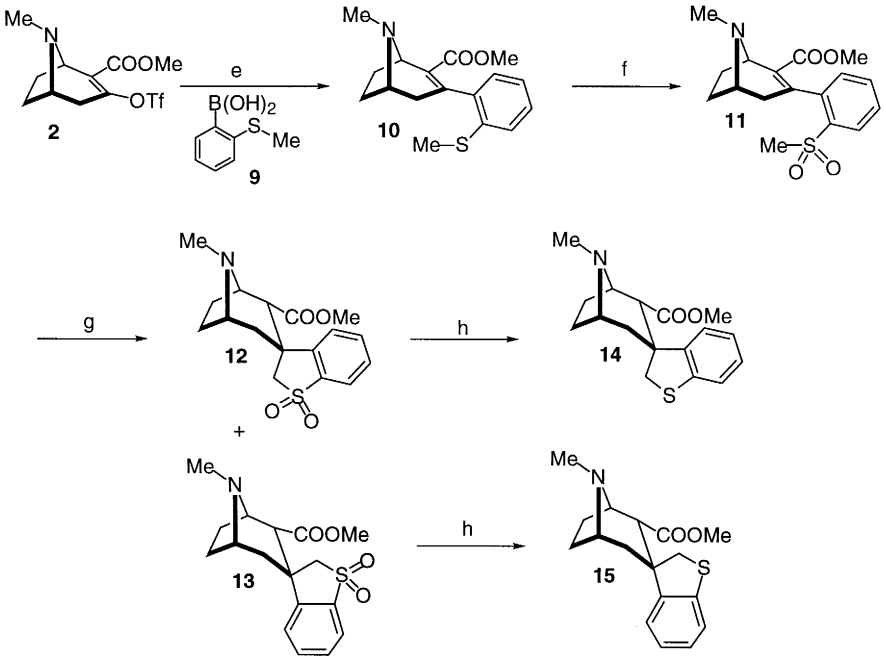


Fig. 1. ORTEP drawings of compounds **7**, **8**, **12** and **13**

was confirmed by a strong IR absorption at 1310 cm^{-1}. Sulfone **11** was subjected to an intramolecular Michael addition by employing LDA as a base at −78°C for 2 h, then quenching with aq. NH_4Cl solution at the same temperature to obtain a 3:1 mixture of two spiro sulfones **12** and **13** in 72% yield. X-Ray crystal structure analysis demonstrated again that the C-2 ester groups possess the α-orientation in both products (Fig. 1).[9] Reduction of sulfones **12** and **13** to sulfides **14** and **15**[8] was carried out with SmI_2 in THF/HMPA at 65°C in good yield.[11]



Scheme 2. Reagents and conditions: (e) Pd_2dba_3, LiBr, aq. Na_2CO_3, diethoxymethane, reflux; (f) Oxone®, $MeOH/H_2O$, rt; (g) LDA, THF, −78°C; (h) SmI_2, THF, HMPA, 65°C

In conclusion, the synthesis of a novel class of spirocyclic cocaine analogs has been accomplished by means of the Suzuki coupling in combination with a radical cyclization or intramolecular Michael addition. To our surprise, pharmacological studies show that compound **8** has reasonable potency at the NET (K_i=143±29 nM) while it is relatively inactive at the DAT (K_i=2.09±0.38 μM).[12] Some of the present compounds are being investigated for their effects in animal behavioral models, and these results will be reported elsewhere.

Acknowledgements

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8. Compound **7**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.33 (d, *J*=7.3 Hz, 1H), 7.25–7.15 (m, 3H), 3.46–3.34 (m, 5H), 3.25 (narrow m, 1H), 3.00–2.76 (m, 2H), 2.42–2.20 (m, 5H), 2.17–2.07 (m, 2H), 1.98–1.88 (m, 1H), 1.80–1.71 (m, 3H). Compound **8**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37 (d, *J*=5.9 Hz, 1H), 7.19–7.09 (m, 3H), 3.47 (t, *J*=4.7 Hz, 1H), 3.33 (s, 3H), 3.31 (d, *J*=3.9 Hz, 1H), 3.21 (narrow m, 1H), 2.92–2.71 (m, 3H), 2.68–2.58 (m, 1H), 2.41 (s, 3H), 2.34–2.18 (m, 2H), 2.11–1.99 (m, 2H), 1.88 (dd, *J*=1.7 Hz, 13.9 Hz, 1H), 1.82–1.72 (m, 1H). Compound **14**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40 (dd, *J*=2.4 Hz, 6.1 Hz, 1H), 7.16–7.08 (m, 3H), 3.68 (d, *J*=11.4 Hz, 1H), 3.49–3.40 (m, 6H), 3.28–3.20 (m, 1H), 2.40 (s, 3H), 2.33–2.13 (m, 4H), 2.07–1.98 (m, 1H), 1.92–1.89 (m, 1H). Compound **15**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40–7.32 (m, 1H), 7.16–7.08 (m, 3H), 3.66 (d, *J*=11.5 Hz, 1H), 3.58–3.41 (m, 6H), 3.35 (narrow m, 1H), 2.46 (s, 3H), 2.38 (narrow m, 1H), 2.26–2.14 (m, 3H), 1.96–1.63 (m, 2H).
9. Atomic coordinates for all four structures have been deposited with the Cambridge Crystallographic Data Base, 12 Union Road, Cambridge CB2 1EZ, UK (deposit@ccdc.cam.ac.uk).
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12. We thank Dr. Kenneth M. Johnson for providing the uptake data.