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Synthesis of C-3 alkyl analogs of cocaine

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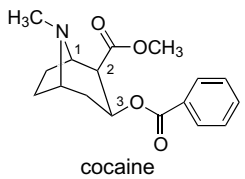
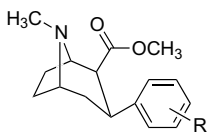
Abstract—The first general stereocontrolled approach to C-3 alkyl analogs of cocaine is described. The route utilized versatile intermediates 2β-hydroxymethyl-3α-cyanotropane and 2β-hydroxymethyl-3β-cyanotropane.

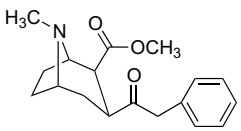
No specific treatment exists for cocaine addiction or overdose.[1] Cocaine acts by blocking a neurotransmitter reuptake transporter that normally removes dopamine from a synapse in the reward pathway of the central nervous system.[2] Cocaine amplifies neurotransmission in this pathway resulting in reinforcement of antecedent behavior (i.e. cocaine self-administration). Small molecule antagonists of cocaine have proven elusive, perhaps because of the difficulties inherent in blocking a blocker. In the course of exploring novel transition-state analogs through which to elicit catalytic antibodies that hydrolyze cocaine at its benzoyl ester,[3] we required access to the C-3 analog of cocaine **1**. Herein, we report the first general approach to the synthesis of a C-3 alkyl analog of cocaine, achieved through preparation of 2β-hydroxymethyl-3β-cyanotropane **2** (Scheme 1).



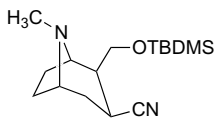
cocaine



WIN series



C-3 alkyl analog **1**



3β-cyano intermediate **2**

Myriad cocaine analogs have been synthesized for structure–activity studies,[5] but no C-3 alkyl analogs are among them. Carbon–carbon bond formation at C-3 is sterically hindered and the relative stereochemistry at C-2 and C-3 is difficult to control. The only reported cocaine analogs with a carbon substituent at C-3 are the 'WIN' series[5] with a phenyl group or other aromatic moiety at this position. Most WIN compounds are synthesized through Michael addition of arylmagnesium bromides to dehydroecgonine methyl ester,[6] but our attempts to expand this method to alkyl nucleophiles were unsuccessful.

As a simple, alternative approach to C-3 analogs we considered S_N2 substitution of the mesylate of a previously reported alloecgonine methyl ester **3**.[7] Literature precedents[4] and our own initial trials indicated an unavoidable elimination of the mesylate of **3** if the methyl ester was unprotected. Thus, alloecgonine methyl ester **3** was reduced to diol **4** by $LiAlH_4$ in 87% yield, and the primary alcohol of **4** selectively protected with *t*-butyldimethylsilyl chloride to provide **5** in 91% yield. Mesylation of alcohol **5** proceeded in 88% yield and reflux of **6** in $EtOH/H_2O$ in the presence of KCN provided the bisaxial α-nitrile **8** in 74% yield. Retention of configuration at C-3 of **8** was unexpected, but could be attributed to the participation of the tropane nitrogen (intermediate **7**). Fortunately, the α-nitrile epimerized with $NaNH_2$ to the desired β-isomer **2** in 83% yield. The configuration of the two nitriles was clearly established through the comparison of their ^1H NMR spectra with the corresponding isomers of cocaine. Specifically, the C-3 proton in **8** showed the same coupling pattern and constants as allococaine (doublet at 2.90 ppm with a coupling constant $J=5.3$ Hz), whereas the C-3 proton in **2** showed a pattern and coupling

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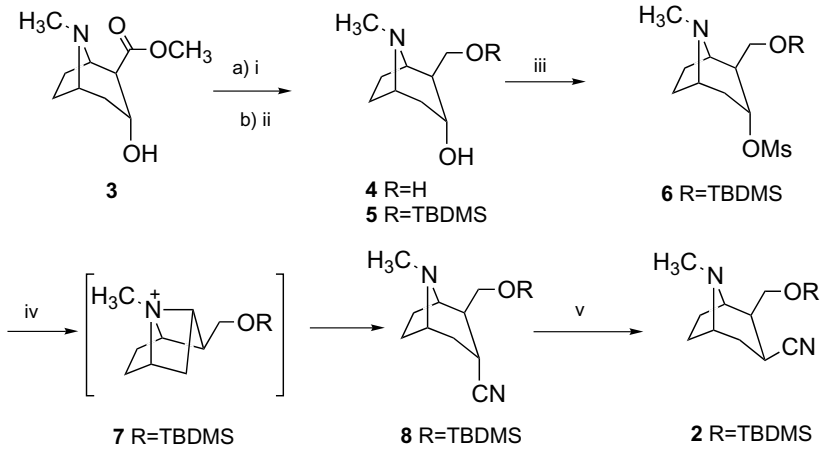
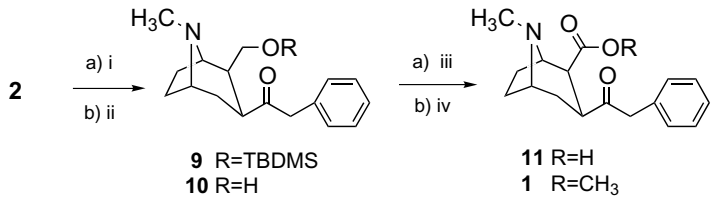


Scheme 1. *Reagents and conditions*: (i) $LiAlH_4$/THF, 3 h; (ii) TBDMSCl/imidazole, CH_2Cl_2; (iii) $MsCl/Et_3N$, CH_2Cl_2; (iv) $KCN/EtOH:H_2O$ (10:3), reflux, 4 h; (v) $NaNH_2$, C_6H_6, reflux, 24 h.



Scheme 2. *Reagents and conditions*: (i) $PhCH_2Li$, ether, 3 h; (ii) t-Bu_4NF, THF; (iii) (a) Swern oxidation, (b) $NaClO_2$, i-BuOH, H_2O; (iv) CH_2N_2.

constants comparable to those of cocaine (a five line 1:2:2:2:1 multiplet at 2.85 ppm with $J_{H2\alpha\text{-}H3\alpha} = J_{H3\alpha\text{-}H4\alpha} = 6$ Hz, $J_{H3\alpha\text{-}H4\beta} = 12$ Hz).[7,9]

Nitrile **2** is readily transformed to C-3 alkyl analogs of cocaine, and nitrile **8** provides the corresponding analogs of allococaine. As an illustration, we transformed **2** into the desired transposed-carbonyl analog of cocaine **1**. Thus, nitrile **2** was treated with an ethereal solution of benzyl lithium (prepared from tribenzyltin chloride with methyllithium)[8] to yield ketone **9** in 73% yield (Scheme 2). Acidic deprotection of the primary hydroxyl group of **9**, followed by two-step oxidation (Swern and $NaClO_2$) gave the acid **11** and methylation with CH_2N_2 provided analog **1** (50% yield for two steps from **10**).

In conclusion, the versatile C-3 tropane nitriles **2** and **8** provide the first practical routes to C-3 alkyl analogs of cocaine and allococaine, respectively. Binding studies of analog **1** with our current anti-cocaine catalytic antibodies[3] and cocaine aptamers[10] are in progress.

Acknowledgements

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9. Compound **8**: mp: 73°C; ^1H NMR ($CDCl_3$, 300 MHz) δ: 3.95 (dd, 1H, $J=2$, 12 Hz), 3.70 (dd, 1H, $J=3$, 12 Hz), 3.35 (s, broad, 1H), 3.25 (s, broad, 1H), 2.90 (d, 1H,

$J=10$ Hz, H at C-3), 2.25 (m, 1H), 2.20 (s, 3H), 2.20–2.00 (m, 5H), 1.90 (m, 2H), 0.90 (s, 9H), 0.00 (s, 6H); MS for $C_{16}H_{30}N_2OSi$ cald. 294, found 295 (M+1). Compound **2**: mp: 77°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 4.05 (dd, 1H, $J=5$, 12 Hz), 3.85 (dd, 1H, $J=7$, 12 Hz), 3.30 (broad, 1H), 3.10 (broad, 1H), 2.85 (dt, 1H, $J=6$, 12 Hz, H at C-3), 2.10 (s, 3H), 2.0–1.5 (m, 7H), 0.85 (s, 9H), 0.00 (s, 6H); MS for $C_{16}H_{30}N_2OSi$ cald. 294, found 295 (M+1). Compound **1**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.25 (m, 5H), 3.86 (d, 1H, $J=17$ Hz), 3.68 (s, 3H), 3.65 (d, 1H, $J=17$ Hz), 3.25 (s, broad, 1H), 3.10 (s, broad, 1H), 2.68 (dt, 1H, $J=6$, 12 Hz, H at C-3), 2.57 (m, 1H), 2.20 (s, 3H), 1.95 (m, 4H), 1.30 (m, 3H).

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