Synthesis of the isomers of (1*R*)-3-(phenylthio)tropane-2-carboxylic acid methyl ester. A new class of ligands for the dopamine transporter

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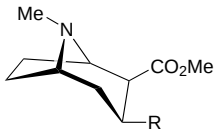
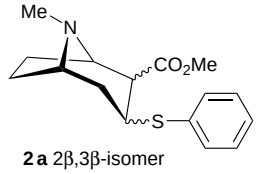
The syntheses of all four isomers of (1*R*)-3-(phenylthio)tropane-2-carboxylic acid methyl ester are described; the 2β,3β-isomer shows high affinity for the cocaine binding site on the dopamine transporter.

The behavioural and reinforcing properties of (−)-cocaine **1a** are attributed to its inhibition of dopamine (DA) reuptake.[1,2] We and others have reported that analogues of 3β-(phenyl)tropane-2β-carboxylic acid methyl ester **1b** (WIN 35,065-2) were more potent than cocaine in inhibiting radioligand binding to the cocaine binding site on the dopamine transporter (DAT).[3] However, to the best of our knowledge cocaine analogues possessing a sulfur substituent directly attached to the C-3 position on the tropane ring have not been reported.



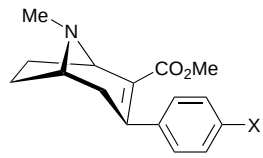
1a R = OC(O)Ph
b WIN 35,065-2: R = Ph



2 a 2β,3β-isomer
b 2α,3β-isomer
c 2β,3α-isomer
d 2α,3α-isomer

Here we describe the synthesis of the four possible isomers of (1*R*)-3-(phenylthio)tropane-2-carboxylic acid methyl ester **2a**–**d**. Compound **2a** has the same stereochemistry as **1b** and differs from **1b** by having a sulfur atom between the 3β-phenyl group and the tropane ring system.

We recently reported that samarium iodide reduction of tropene **3** provided a new synthesis of **4**.[4] This result suggested that the synthesis of (1*R*)-3-(phenylthio)trop-2-ene-2-carboxylic acid methyl ester **5** followed by its reduction with samarium iodide[4,5] might afford the 2β,3β isomer **2a**. We found that treatment of (1*R*)-3-(trifluoromethylsulfonyloxy)trop-2-ene-2-carboxylic acid methyl ester **6**[4] with the sodium salt of thiophenol in THF gave **5** in 86% yield (Scheme 1).† We also found that the sodium salt of benzenesulfinic acid displaced the trifluoromethylsulfonyloxy substituent from **6** to afford the 3-(phenylsulfonyl)trop-2-ene-2-carboxylic acid methyl ester **7** in 78% yield.[6] At −78 °C, slow syringe-pump addition of a methanolic solution of **5** to samarium iodide in THF gave 85%



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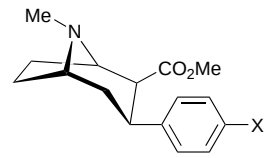

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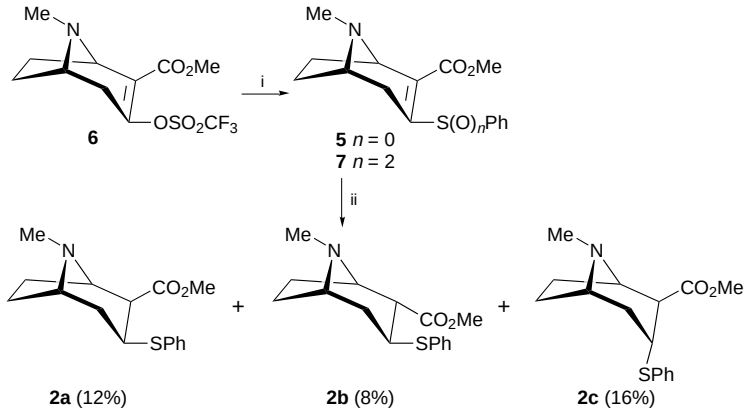
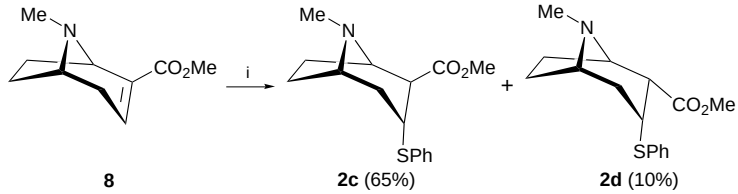


Scheme 1 *Reagents and conditions*: i, for **5**: NaSPh, THF (86%); for **7**: benzenesulfinic acid sodium salt, DMF (78%); ii, SmI_2, inverse addition, MeOH −78 °C



Scheme 2 *Reagents*: i, PhSH, Et_3N

of a 15 : 3 : 1 ratio of **2a**, **2b** and **2c**, respectively. None of the 2α,3α isomer **2d** was produced. Silica gel flash column chromatography[7] [Et_3N–Et_2O–hexanes (1 : 9 : 10)] was used to separate **2b** (R_f 0.25, 8%) from **2a** and **2c** (R_f 0.35). The **2a** and **2c** isomers were separated by HPLC on a silica gel column using Et_3N–Pr^iOH–hexanes (1 : 99 : 1900) as the eluent system to afford individual isomers **2a** and **2c** in 12 and 16% yields, respectively. The 2β,3β isomer **2a** had mp 55–57 °C (fusion) and $[\alpha]_D$ −83.19 (*c* 0.47, MeOH) for its (+)-tartrate salt. The (+)-tartrate salt of compound **2b** had mp 143–144 °C and $[\alpha]_D$ +49.9 (*c* 0.22, MeOH), and **2c** (+)-tartrate had mp 53–58 °C (fusion) and $[\alpha]_D$ of −37.17 (*c* 0.955, MeOH).

The 2α,3α isomer **2d** was prepared as shown in Scheme 2. Nucleophilic addition of thiophenol to anhydroecgonine methyl ester **8**[8] in the presence of Et_3N gave, after 24 h, the 2β,3α isomer **2c** and 2α,3α isomer **2d**. Silica gel flash chromatography using Et_3N–Et_2O (1 : 4) gave **2c** (R_f 0.91, 65%) and **2d** (R_f 0.29, 10%), respectively. Compound **2d** had mp 179–180 °C and an $[\alpha]_D$ +60.4 (*c* 0.106, MeOH) for its hydrochloride salt. Reaction times of several days afforded, after purification, a 1.2:1 ratio of **2c** and **2d** in 75% overall yield. In either case, the nucleophile shows complete preference for an α-face attack on **8**, possibly due to steric hindrance provided by the *N*-methyl group. The formation of two products may be a consequence of complete facial bias during protonation of the intermediate enol ester to give **2c** followed by partial base-catalysed epimerization of H-2 to afford **2d**. Again, the base-catalysed epimerization of **2c** at C-2 could be forced by an unfavourable steric repulsion between the *N*-methyl and the 2-methoxycarbonyl group. Basic conditions encourage facile elimination of thiophenol from **2d** to give **8**. Neither of the isomers **2a** or **2b** were observed in the above reaction when the sodium salt of thiophenol was replaced by the lithium or magnesium salts.

Two dimensional NMR experiments (COSY and HETCOR) aided in chemical shift assignments, while the *J* values and NOESY experiments were used to decipher the stereochemical relationship of the C-2 and C-3 substituents in the **2a**–**d** isomers. For example, **2b** has a large $J_{2,3}$ value of 12.0 Hz, expected for their *anti* disposition. On the contrary, $J_{2,3}$ for **2a**, **2c** and **2d**, were 5.2, 1.1 and 6.9 Hz, respectively. Most importantly, H-2 in **2b** showed an NOE with N-Me and H-4_{ax}, while H-3 showed an NOE with H-6_{ax} and H-7_{ax}. The observed NOE results are possible *only if* **2b** exists in a chair conformation with H-2 and H-3 in diaxial positions (Fig. 1). Using similar arguments, **2a**, **2c** and **2d** were shown to possess the relative stereochemistry and conformation as displayed in their corresponding structures. It was also interesting to note that the proton spectra patterns of **2a**–**d** resemble those of the corresponding cocaine isomers.[9]

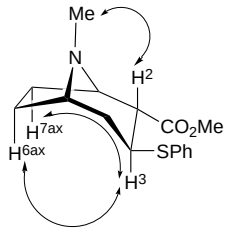


Fig. 1 Structure of **2b** with selected NOE effects

Binding data on **2a**–**d** revealed that the 2β,3β isomer **2a** was the most potent (IC_{50} 14.3 nm dm^{-3}) at the cocaine binding site of the dopamine transporter. The other isomers **2c** (IC_{50} 183 nm dm^{-3}), **2d** (IC_{50} 222 nm dm^{-3}) and **2b** (IC_{50} 613 nm dm^{-3}) were only moderately potent. It is interesting to note that **2a** is slightly more potent than the lead compound, WIN 35065-2 (IC_{50} 23 nm dm^{-3}). Since substitution of the phenyl group of the WIN 35,065-2 series was found to increase potency,[3] substituted phenyl analogues of **2a**, and even **2c**–**d**, may be more potent. Studies along this line are underway, and results will be reported in due course.

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Footnote

† All new compounds showed satisfactory elemental analyses.

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