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Synthesis of the 2β,3β-, 2α,3β-, 2β,3α- and 2α,3α- isomers of 6β-hydroxy-3-(*p*-tolyl)tropane-2-carboxylic acid methyl ester

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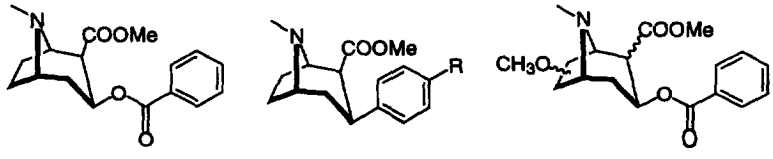
Abstract

6-Hydroxytropanone (**8**) was synthesized by a Mannich type condensation between acetonedicarboxylic acid, methylamine hydrochloride, and the hydrolysis product of 2,5-dimethoxydihydrofuran and was used as the key intermediate for the synthesis of the four racemic isomers of 6β-hydroxy-2-(methoxycarbonyl)-3-(*p*-tolyl)tropane.

The abuse of cocaine (**1**) is one of the greatest concerns of the public today and has therefore become a focus of medical, social, and political leaders.[1,2] Cocaine is a potent stimulant of the mammalian central nervous system. Its reinforcing and stimulant properties have been associated with its propensity to bind to monoamine transporter systems, particularly the dopamine transporter (DAT).[3] Extensive structure–activity relationship studies of cocaine have identified structural features required for potency in the inhibition of radioligand binding at the DAT. These include an aromatic ring attached directly (the WIN series) or through a short space to the 3-position,[4] the possible presence of a heteroatom (nitrogen or oxygen)[5] in the one-carbon bridge, and rather diverse substitutents including ester, ketone, alkyl, alkenyl, aryl, and heteroaryl groups at the 2-position. The WIN analogs of cocaine (the 3β-aryl-2β-(methoxycarbonyl)-8-azabicyclo[3.2.1]octanes, (**2**) have, in particular, served as important lead compounds in this area of drug design (Fig. 1).[6]



(-)-cocaine (1) WIN analog (2) 3

Figure 1.

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In the present study, we have expanded our investigation of the effect of introducing substituents on the two-carbon bridge of the tropane ring. In 1993, we had first demonstrated that the methoxylation of cocaines in the 6- and 7- positions (**3**) led to compounds of pharmacological interest,[7] at least one of these methoxylated analogs was found to be capable of countering, to a minor extent, the effects of cocaine on dopamine reuptake. This finding along with others supports the idea that it may be possible to design a functional antagonist of cocaine through appropriate structural modifications of cocaine.[8]

In continuation of our efforts to identify ligands of possible use in the treatment of cocaine abuse, we chose to explore the effect of introducing a 6β-hydroxyl group into a WIN series compound. While a variety of 6- and 7-substituted WIN analogs have been made to date,[9] many of these have proven to be poorly active, with the exception of compounds bearing relatively small groups such as fluorine. Additionally, for the present study we wished to have access to all four isomers possessing either an α or β configuration at positions 2 and 3 in order to develop a more comprehensive SAR. Herein, we report the synthesis of these four compounds **4a–4d** in racemic form (Fig. 2).

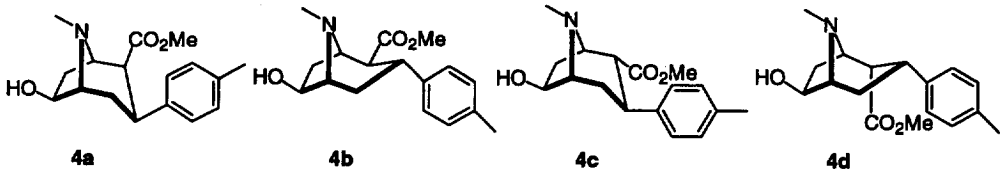
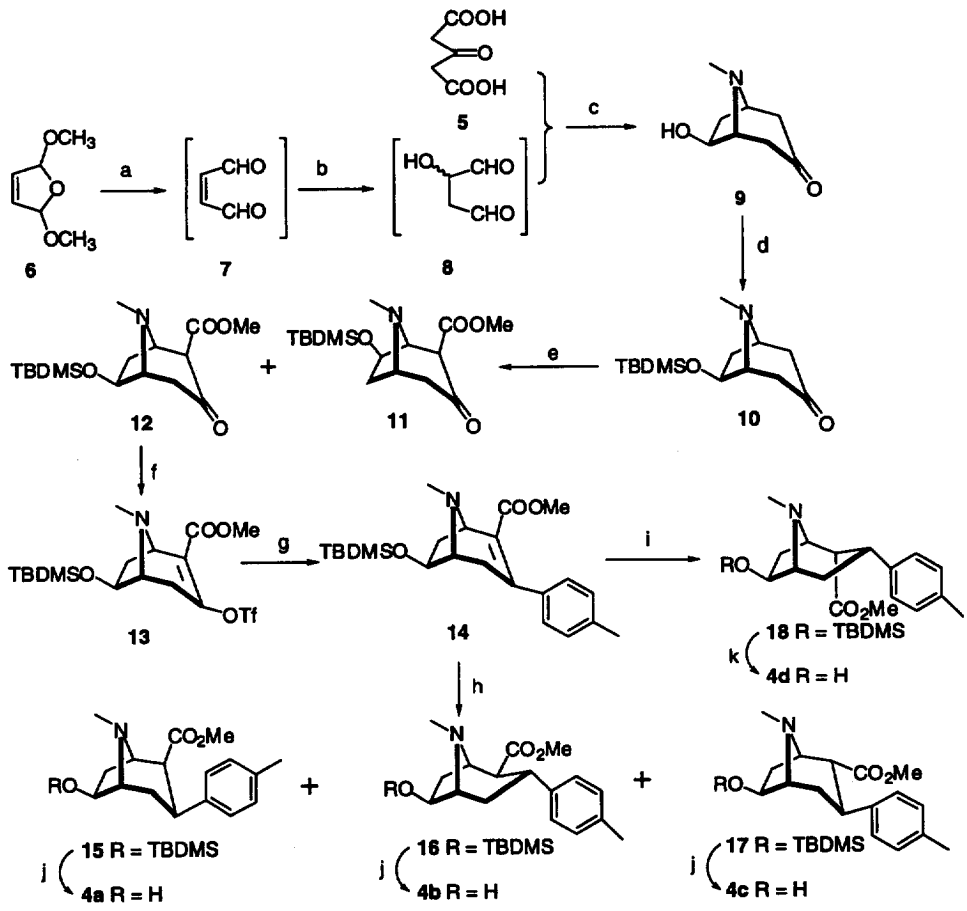


Figure 2.

The synthesis of racemic 6β-hydroxytropinone was based upon a Mannich type condensation reaction (Scheme 1).[10] A solution of 2,5-dimethoxydihydrofuran (**6**) in 3 N HCl was stirred overnight at room temperature and then neutralized by the addition of 6 N NaOH. This mixture was then added to a solution of acetonedicarboxylic acid (**5**), methylamine hydrochloride, and sodium acetate in water (pH~4.3). The crude product was recrystallized from isopropanol, and pure 6β-hydroxytropinone (**9**) was obtained as white solid in 42% yield. This compound was protected as its *t*-butyldimethylsilyl ether, and intermediate **10** was then deprotonated with LDA in the same manner as described by Majewski for tropinone.[11] The resulting enolate was reacted with methyl cyanoformate to give in 64% yield the corresponding methoxycarbonylated derivatives **11** and **12** in a ratio of 9:7. The two isomers can be separated by careful flash column chromatography, and their structures were assigned by X-ray after the TBDMS group was removed. Next, ketone **12** was converted into the enol triflate **13** in 62% yield by reaction with *N*-phenyltrifluoro-methanesulfonimide and sodium bis(trimethylsilyl)amide in THF at −78°C to rt. The enol triflate **13** was then coupled with preformed *p*-tolyl-boronic acid[12] according to the Suzuki protocol in 1,2-dimethoxyethane in the presence of sodium carbonate, lithium chloride, and tris(dibenzylideneacetone)dipalladium(0) to provide the alkene **14** in 97% yield.

Reduction of **14** with samarium iodide at −78°C using methanol as the proton source gave the saturated tropane analogs **15** (38%), **16** (48%), and **17** (5.2%). Intermediate **15** was converted to compound **17** in high yield by treatment with sodium methoxide in methanol. Hydrogenation of **14** with 10% Pd/C as catalyst provides the 2α,3α-substituted isomer **18** exclusively. Finally, the TBDMS group of each of the compounds **15**, **16**, and **17** was removed in high yield (>90%) with *n*-Bu_4NF in THF at room temperature to give corresponding hydroxytropanes **4a**, **4b**, and **4c**.[13] As the exposure of **18** to *n*-Bu_4NF led to its conversion to **4b**, compound **18** was instead deprotected with 48% HF to afford 6β-hydroxy-2α-(methoxycarbonyl)-3-(*p*-tolyl)tropane (**4d**) in 92% yield.[14]

These four hydroxylated tropanes were tested for their ability to inhibit mazindol binding at the dopamine transporter (DAT). As is apparent from the data in Table 1, the most potent compound is **4a** which is approximately twofold more active than cocaine (K_i (cocaine)=170 nM), taking into account



Scheme 1. Synthetic route to the 6β-hydroxylated WIN analogs. Reagents and conditions: (a) 3N HCl, rt, 12 h; (b) neutralization with 6N NaOH; (c) NaOAc, CH_3NH_2·HCl, rt, 2 d; (d) TBDMSCl, imidazole, DMF, rt, 12 h; (e) LDA, NC-COOMe, THF −78°C, 1 h; (f) $NaN(TMS)_2$, $PhNTf_2$, THF, −78°C to rt, overnight; (g) *p*-tolylboronic acid, Pd_2dba_3, Na_2CO_3, LiCl, DME, 1 h; (h) SmI_2, MeOH, THF, −78°C, 1 h; (i) H_2 (30 psi), 10% Pd/C, MeOH, 12 h; (j) *n*-Bu_4NF, THF, rt, 12 h; (k) 48% HF, CH_3CN, rt, overnight

Table 1
IC_{50} and K_i values for the inhibition of mazindol binding at DAT

compound	IC_{50}	K_i
cocaine	288 nM	170 nM
4a	214.9 nM	143.2 nM
4b	930.3 nM	620.2 nM
4c	15.31 μM	10.21 μM
4d	7.86 μM	5.07 μM

the fact that **4a** is racemic. The boat tropane **4b** is the next most active compound, while the two isomers having an α-oriented ester group show only micromolar binding activity.

In conclusion, the present work details a route to all four isomers of 6β-hydroxy-2-(methoxycarbonyl)-3-(*p*-tolyl)tropane. Some of these compounds are being investigated for their effects in animal behavioral models, and these results will be reported elsewhere.

Acknowledgements

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13. Compound **4a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.12 (d, *J*=8.4 Hz, 2H), 7.08 (d, *J*=8.4 Hz, 2H), 4.47 (dd, *J*=3.9, 6.0 Hz, 1H), 3.83 (br s, 1H), 3.50 (s, 3H), 3.31 (br s, 1H), 2.83 (m, 1H), 2.75 (m, 1H), 2.58 (s, 3H), 2.51 (dd, *J*=3.3, 12.6 Hz, 1H), 2.30 (s, 3H), 2.27 (m, 2H), 1.86 (br s, 1H), 1.78 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 21.18, 30.94, 38.94, 42.77, 51.39, 51.67, 66.46, 70.79, 77.54, 127.15 (2C), 128.93 (2C), 135.58, 139.68, 172.26. Compound **4b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.09 (br s, 4H), 4.25 (br s, 1H), 3.64 (m, 1H), 3.61 (s, 3H), 3.45 (m, 1H), 3.20 (d, *J*=9.0 Hz, 1H), 2.68 (s, 3H), 2.47 (d, *J*=9.0 Hz, 1H), 2.35 (m, 1H), 2.18 (m, 2H), 1.98 (br s, 1H), 1.39 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 21.17, 33.26, 35.92, 40.81, 42.40, 52.03, 54.50, 62.22, 67.48, 80.12, 127.59 (2C), 129.33 (2C), 136.03, 141.28, 175.37. Compound **4c**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.13 (d, *J*=8.1 Hz, 2H), 7.09 (d, *J*=8.1 Hz, 2H), 4.34 (br d, *J*=6.0 Hz, 1H), 3.58 (br d, *J*=6.9 Hz, 1H), 3.52 (s, 3H), 3.14 (m, 2H), 2.93 (ddd, *J*=6.0, 12.0, 12.6 Hz, 1H), 2.70 (s, 3H), 2.52 (dd, *J*=7.2, 14.1 Hz, 1H), 2.30 (s, 3H), 2.18 (br s, 1H), 1.87 (m, 2H), 1.55 (ddd, *J*=2.1, 6.0, 13.8 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 21.23, 30.19, 35.60, 37.37, 37.78, 44.85, 51.80, 62.55, 68.04, 75.76, 127.48 (2C), 129.44 (2C), 136.36, 140.78, 173.89.
14. Compound **4d**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.09 (d, *J*=8.4 Hz, 2H), 7.05 (d, *J*=8.4 Hz, 2H), 4.09 (dd, *J*=3.0, 7.2 Hz, 1H), 3.74 (m, 1H), 3.63 (m, 1H), 3.48 (s, 3H), 3.46 (m, 1H), 3.17 (m, 1H), 2.68 (s, 3H), 3.63 (dd, *J*=6.9, 14.4 Hz, 1H), 2.46 (m, 1H), 2.32 (br s, 1H), 2.00 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 21.06, 30.64, 35.03, 37.30, 38.75, 44.81, 51.54, 61.07, 68.31, 77.43, 127.59 (2C), 128.97 (2C), 135.64, 140.15, 174.09.