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Synthesis of the 2β,3α- and 2β,3β-Isomers of 3-(*p*-Substituted phenyl)tropane-2-carboxylic Acid Methyl Esters

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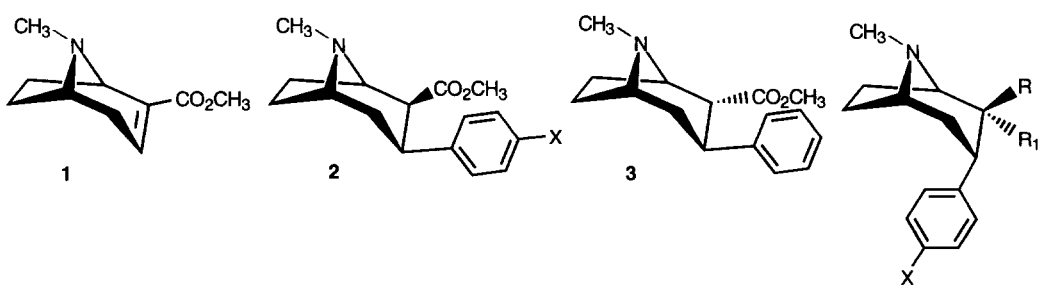
Abstract: The synthesis of 3-(*p*-substituted phenyl)trop-2-ene-2-carboxylic acid methyl ester **8** and its reduction with samarium iodide provide a new synthesis of 3β-(4'-substituted phenyl)tropane-2β-carboxylic acid methyl ester (**2**) and, in addition, give the first synthesis of the 2β,3α-diastereoisomer **4**.

In 1973, Clarke and coworkers[1] reported that the addition of phenyl magnesium bromide to anhydroecognine methyl ester (**1**) gave a 1:3 mixture of 3β-phenyltropane-2β-carboxylic acid methyl ester (**2**, X = H) and its 2α-isomer **3**. The same authors also reported the synthesis of the 3β-(*p*-fluorophenyl)- and 3β-(*p*-methoxyphenyl)- analogs, **2** (X = F and CH_3O, respectively), using the same methodology. In addition, the synthetic method developed by Clarke[1] was utilized to prepare many 3β-(substituted phenyl)tropane-2β-carboxylic acid methyl esters (**2**),[2-4] and these compounds have proven to be extremely valuable for the characterization of the cocaine binding site on the dopamine and serotonin transporters.[2-4] To our knowledge, the synthesis of the 2β,3α- and 2α,3α-isomers, **4** and **5** respectively, of this class of compounds has not been reported. In this report, we describe the synthesis of **4** and a new synthesis of **2**, where X = F, C_2H_5, and $C(CH_3)_3$.



In the process of preparing 3β-(4'-alkylsubstituted phenyl)tropane analogs of **2**, we found that whereas the addition of 4-methylphenyl magnesium bromide to **1** provided **2** (X = CH_3) in good yield,[5] the addition of 4-ethylphenyl magnesium bromide gave only a 10 % yield of **2** (X = C_2H_5).[6] Moreover, we were unable to prepare the 4-*tert*-butyl analog **2** [X = $(CH_3)_3C$] following the Clarke method.[1] Consequently, investigation of alternative methods for the synthesis of **2** was undertaken. Since triflates were reported to couple with

aryltrimethyltin derivatives or arylboronic acids to give arylolefins,[7] the route shown in Scheme 1 was examined.

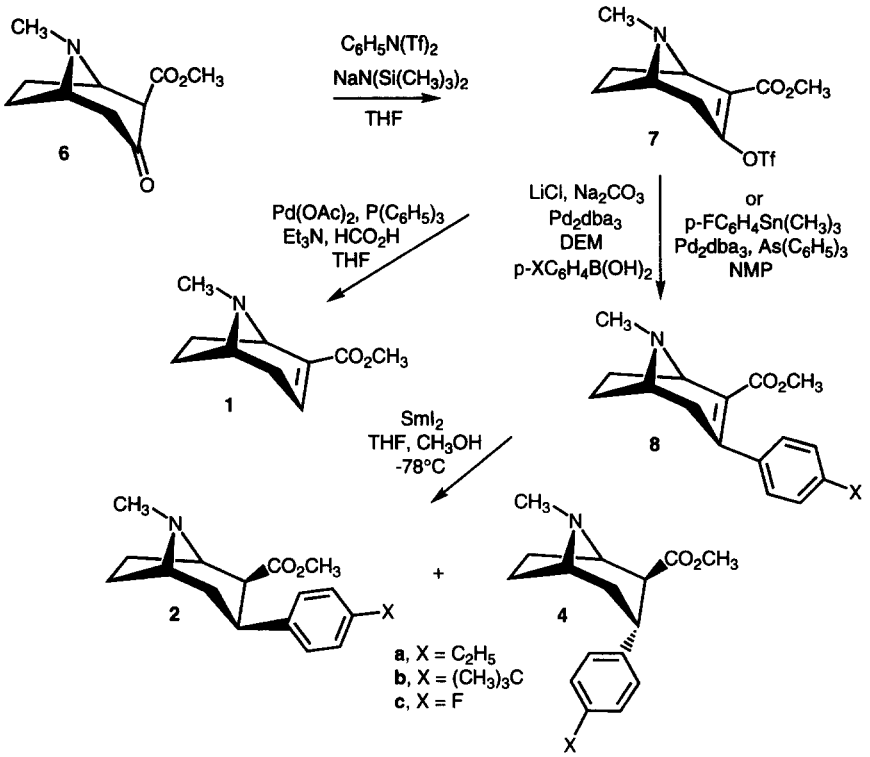
Synthesis of the triflate **7**[8] was easily accomplished in high yields (80–90%) by the addition of triflimide to a tetrahydrofuran solution of (R)-(+)-2-carbomethoxy-3-tropinone (**6**)[1] containing sodium bis(trimethylsilyl)amide. Reaction of **7** with *p*-ethyl-, *p-tert*-butyl-, and *p*-fluorophenylboronic acid[9] in refluxing diethoxymethane using either tris(dibenzylideneacetone)dipalladium(0) or tetrakis(triphenylphosphine)palladium(0) as catalyst,[10] followed by chromatographic purification, gave *p*-ethylphenyl- and *p-tert*-butylphenyltropenes **8a** and **8c** as solids (86% yield) and the *p*-fluorophenyltropene as an oil (85% yield).[11] The tropene **8c** could also be obtained in 31.4% yield by coupling of the triflate **7** with *p*-fluorophenyl trimethyltin. Reduction of the triflate **7** using formic acid, triethylamine, and triphenylphosphine in the presence of palladium acetate afforded anhydroecgonine methyl ester **1**, providing a new synthesis of this compound.

Reduction of **8a-c** with samarium iodide[12] at –78 °C using methanol as the proton source, followed by quenching with trifluoroacetic acid at –78 °C, gave a mixture of 3α-(*p*-substituted phenyl)tropane-2β-carboxylic acid methyl ester (**4**) and 3β-(*p*-substituted phenyl)tropane-2β-carboxylic acid methyl ester (**2**) which were separated by column chromatography. The yields from the reduction and the physical properties of the products are listed in the table. The structures of 2β,3β-isomers **2a** and **2c** were established by comparison with authentic samples.[1,6] The structure of the *p-tert*-butylphenyl isomer **2b** was determined from analysis of the ^{1}H NMR spectrum which showed chemical shift and coupling constant values of the C-2 and C-3 protons to be almost identical to those found for **2a** and **2c**. The 2β,3α stereochemistry of **4c** was established by direct comparison to a sample of **4c** prepared by the method shown in Scheme 2.[13] The addition of *p*-fluorophenyl lithium to 2-(3'-methyl-1',2',4'-oxadiazol-5'-yl)-8-methyl-8-azabicyclo[3.2.1]oct-2-ene followed by treatment with sodium methoxide in methanol gave 3α-(*p*-fluorophenyl)-2β-(3'-methyl-1',2',4'-oxadiazol-5'-yl)tropane (**10**, X = F). The non-aromatic region of the ^{1}H NMR spectrum of **10** (X = F) was essentially identical to that of 3α-(phenyl)-2β-(3'-methyl-1',2',4'-oxadiazol-5'-yl)tropane (**10**, X = H) whose stereochemistry had been previously established.[13-15] Catalytic hydrogenation of **10** (X = F) using palladium on carbon catalyst in methanol gave **4c** which was identical to the sample prepared in Scheme 1. The almost identical values for the chemical shifts and coupling constants of the C-2 and C-3 protons of **4a** and **4b** and those of **4c** shows that **4a** and **4b** also possess 2β,3α stereochemistry.

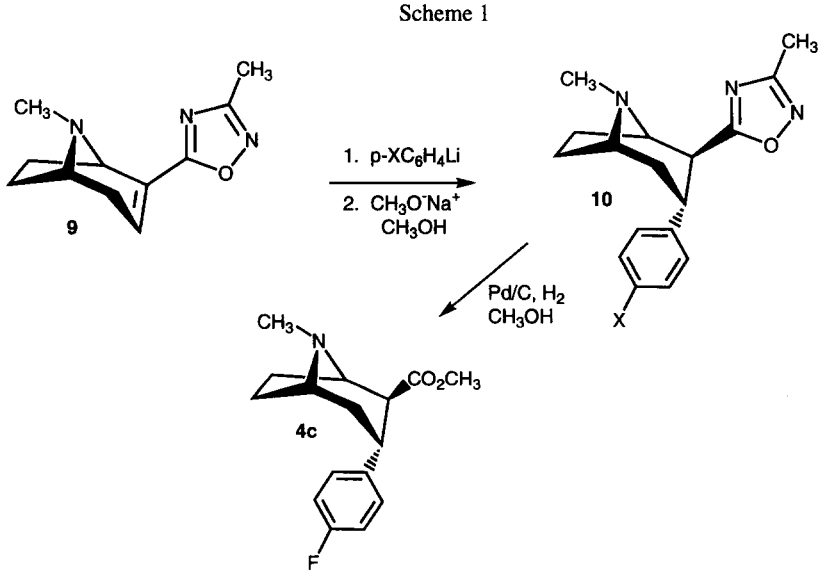
Table. Physical Properties and percent yields of tropanes **2** and **4**

compound	% Yield	molecular formula[a,b]	mp °C	$[\alpha]_D$ (c) CH_3OH
2a	31.1	$C_{22}H_{31}NO_8 \cdot 0.25\ H_2O$[c]	103 dec	–89.6° (0.52)
2b	27.2	$C_{24}H_{35}NO_8 \cdot 0.25\ H_2O$	172–174	–89.8° (0.52)
2c	48.9	$C_{20}H_{26}FNO_8 \cdot 0.5H_2O$	108 dec	–85.6° (1.01)
4a	42.0	$C_{22}H_{31}NO_8 \cdot 1.25\ H_2O$	68 dec	–48.5° (0.52)
4b	39.6	$C_{24}H_{35}NO_8 \cdot 1.0\ H_2O$	62–66 dec	–46.6° (0.52)
4c	39.0	$C_{20}H_{26}FNO_8 \cdot 0.5H_2O$	65 dec	–34.4° (0.54)

[a] C, H, and N analyses were within 0.4% of the theoretical values. [b] Compounds were characterized as their tartrate salts. [c] Lit. ref. 4. for $C_{22}H_{31}NO_8 \cdot 0.5\ H_2O$; mp 112–113°C, $[\alpha]_D$ –93.7° (c 0.205, CH_3OH).



Scheme 1



Scheme 2

In summary, a new method for the synthesis of the 3α- and 3β-(4'-substituted phenyl)tropane-2β-carboxylic acid methyl esters (**4** and **2**, respectively) has been developed. Studies are currently in progress to synthesize other analogs unobtainable by the Clarke[1] method and to improve the selectivity of the reduction of the tropenes **8**.

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