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SYNTHESIS AND TRANSPORTER BINDING PROPERTIES OF (*R*)-2β,3β- AND (*R*)-2α,3α-DIARYLTROPANES

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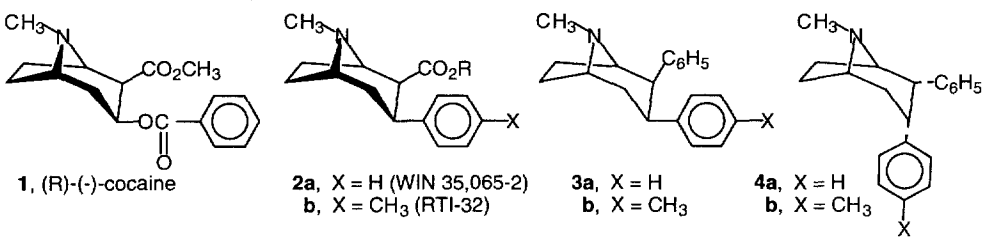
Abstract: (*R*)-2-Aryl-2-tropinone (**9**) was synthesized from (*R*)-2-carbomethoxy-3-tropinone (**5**) and was used as the key intermediate for the synthesis of (*R*)-2β,3β- and (*R*)-2α,3α-diaryltropanes. Inhibition of radioligand binding studies at the dopamine, serotonin, and norepinephrine transporters showed that the (*R*)-3β-(4-methylphenyl)-2β-phenyltropane (**3b**, RTI-422) possessed an IC_{50} value of 1.96 nM at the dopamine transporter and was highly selective for this transporter relative to the serotonin and norepinephrine transporters.

The dopamine transporter (DAT) is responsible for uptake of dopamine (DA).[1] It is well known that (*R*)-cocaine (**1**) interacts with the DAT and inhibits the uptake of DA. A number of pharmacological findings suggest that this inhibition of DA uptake may be responsible for the reinforcing and locomotor properties of cocaine.[2–6] These findings prompted extensive studies aimed at a better understanding of the structural requirements required for potent and selective binding at the DAT.[7] Extensive structure activity relationship (SAR) studies of the 3β-phenyl-8-methyl-8-azabicyclo[3.2.1]octane-2β-carboxylic acid methyl ester [3β-phenyltropane-2-carboxylic acid methyl ester, **2a** (WIN 35,065-2)] class of inhibitors have identified structural features required for potent and selective inhibition of radioligand binding at the DAT.[7] As part of these studies, we recently described the synthesis of racemic (*R,S*)-2β,3β- and (*R,S*)-2α,3α-diphenyltropane [(*R,S*)-**3a** and (*R,S*)-**4a**, respectively] and reported that (*R,S*)-**3a** and WIN 35,065-2 possessed essentially the same affinity for the DAT, while the 2α,3α-isomer (*R,S*)-**4a** showed much weaker affinity.[8] In this report, we describe the synthesis of (*R*)-**3a** and (*R*)-**4a** as well as analogs (*R*)-**3b** and (*R*)-**4b**, which possess the same absolute stereochemistry as (*R*)-cocaine and WIN 35,065-2. We also compare the monoamine transporter binding properties of these optical isomers to WIN 35,065-2 and 3β-(4-methylphenyl)tropane-2-carboxylic acid methyl ester (**2b**).



1, (R)-(-)-cocaine

2a, X = H (WIN 35,065-2)
b, X = CH_3 (RTI-32)

3a, X = H
b, X = CH_3

4a, X = H
b, X = CH_3

Chemistry

Based on our reported synthesis of (*R,S*)-**3a** and (*R,S*)-**4a**, we envisioned that the (*R*)-isomers of **3a** and **3b** and **4a** and **4b** could be prepared from (*R*)-3-phenyl- and (*R*)-3-(4-methylphenyl)-2-tropinone (**9a** and **9b**, respectively). These key intermediates were synthesized from (*R*)-2-carbomethoxy-3-tropinone (**5**)[9,10] by the route shown in Scheme 1. The addition of N-phenyltrifluoromethanesulfonamide to a tetrahydrofuran solution of **5** containing sodium bis(trimethylsilyl)amide afforded the triflate **6**. Reaction of **6** with phenyl- or

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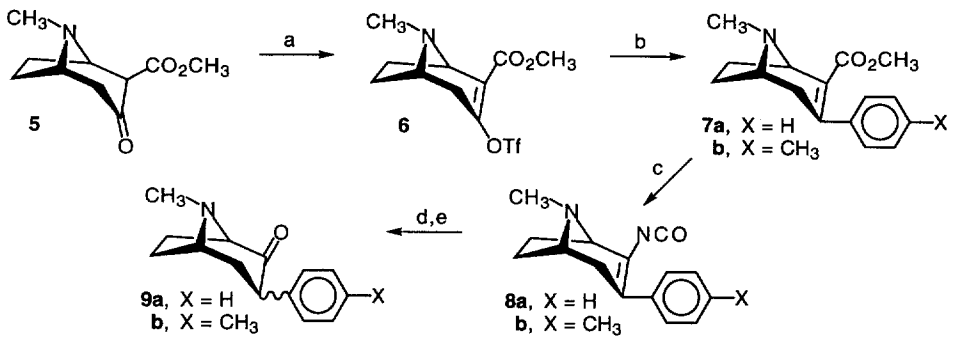
4-methylphenylboronic acid[11] in refluxing diethoxymethane (DEM) using tetrakis(triphenylphosphine)-palladium(0) as catalyst[12] followed by chromatographic purification gave 3-phenyl- or 3-(4-methylphenyl)-2-tropene **7a** or **7b** in 88% and 89% yields, respectively. Hydrolysis of **7a** or **7b** with 0.5 N potassium hydroxide solution followed by acidification to pH 6 gave the corresponding carboxylic acid which was treated with diphenylphosphoryl azide in toluene containing triethylamine. The resulting intermediate isocyanate **8a** or **8b** was refluxed in ethanol to afford the corresponding urethane which was hydrolyzed with 19% hydrochloride acid to give the desired (*R*)-2-tropinone **9a** or **9b** in 62% and 55% yields, respectively, from **5**.

Scheme 1



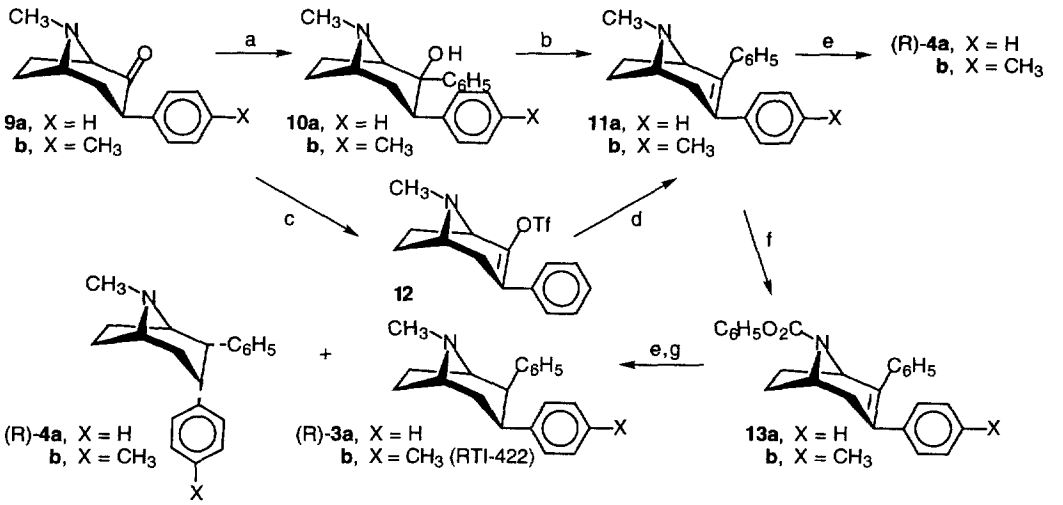
Reagents: (a) $(CF_3SO_2)_2NC_6H_4$, $NaN[Si(CH_3)_3]_2$, THF; (b) *p*-$XC_6H_4B(OH)_2$, $Pd[P(C_6H_5)_3]_4$, CsF, DEM; (c) (i) 0.5N KOH followed by 1 N HCl, (ii) $(C_6H_5O)_2PON_3$, $(C_2H_5)_3N$, toluene; (d) C_2H_5OH, reflux 8 h; (e) reflux with 19% HCl for 1 h

Compounds (*R*)-**3a** and (*R*)-**3b** and (*R*)-**4a** and (*R*)-**4b** were synthesized from the appropriate 3-aryl-2-tropanone (**9**) by the route shown in Scheme 2. Addition of the appropriate aryl magnesium bromide to **9a** or **9b** gives the addition product **10a** or **10b**, which was dehydrated with concentrated hydrobromic acid to yield the 2,3-diaryltropenes **11a** and **11b**. Tropane **11a** was also prepared by converting **9a** to triflate **12** using N-phenyl-trifluoromethanesulfonamide and sodium bis(trimethylsilyl)amide. Reaction of **12** with phenylboronic acid in diethoxymethane using tetrakis(triphenylphosphine)palladium(0) gave the desired tropene **11a**. Catalytic reduction of **11a** or **11b** in methanol using 5% palladium on carbon gave exclusively the 2α,3α-isomers (*R*)-**4a** or (*R*)-**4b**. No reduction conditions were found that would directly convert (*R*)-**11a** or (*R*)-**11b** to (*R*)-**3a** or (*R*)-**3b**. However, we found that catalytic reduction of N-phenoxycarbonyl-protected analogs **13a** and **13b**, followed by lithium aluminum hydride reduction to convert the carbamate to the N-methyl group, gave a mixture of the (*R*)-2β,3β-**3** and (*R*)-2α,3α-**4** isomers, which could be separated by chromatography. The carbamates **13a** and **13b** were obtained by N-demethylation of **11a** and **11b** with phenyl chloroformate. The relative stereochemistry of each compound was determined by a direct comparison to the previously reported R,S-isomers.[8]

Biology

The IC_{50} values for the inhibition of radioligand binding at the dopamine, serotonin, and norepinephrine transporters by the (*R*)-**3a** and (*R*)-**3b** and (*R*)-**4a** and (*R*)-**4b** are listed in the Table. For comparison, the previously reported IC_{50} values for the (*R,S*)-**3a** and (*R,S*)-**4a** as well as values for cocaine (**1**), **2a** (WIN 35,065-2), and **2b** (RTI-32) are also listed. The binding affinities at the dopamine, serotonin, and norepinephrine transporters were determined via competitive binding assays using previously reported procedures.[13,14]

Scheme 2



Reagents: (a) C_6H_5MgBr, $(C_2H_5)_2O$; (b) conc. HBr, reflux, 15 min; (c) $(CF_3SO_2)_2NC_6H_4$, $NaN[Si(CH_3)_3]_2$, THF; (d) $C_6H_5B(OH)_2$, $Pd[P(C_6H_5)_3]_4$, CsF, DEM; (e) CH_3OH, H_2, 5% Pd/C; (f) C_6H_5OCOCl, CH_2Cl_2, $NaHCO_3$; (g) $LiAlH_4$, $(C_2H_5)_2O$

Table. Comparison of Monoamine Transporter Binding Potencies for the Stereoisomers **3** and **4**

Compd	IC_{50} (nM)		
	[^{3}H]WIN 35,428 (DAT)	[^{3}H]Paroxetine (5-HTT)	[^{3}H]Nisoxetine (NET)
cocaine (**1**)[a]	89 ± 4.8	1050 ± 89	3300 ± 290
WIN 35,065-2 (**2a**)[a]	23 ± 5	1960 ± 61	920 ± 73
RTI-32 (**2b**)[a]	1.71 ± 0.3	240 ± 27	60 ± 0.53
(*R*)-**3a**	12.6 ± 1.86	21,100 ± 3320	917 ± 149
(*R,S*)-**3a**[b]	28 ± 1.9	34,700 ± 3950	2670 ± 6270
(*R*)-**4a**	690 ± 37	41,300 ± 5300	1040 ± 41
(*R,S*)-**4a**[b]	1270 ± 120	18,600 ± 1880	2770 ± 280
RTI-422 [(*R*)-**3b**]	1.96 ± 0.08	11,000 ± 83	479 ± 86
(*R*)-**4b**	429 ± 59	15,800 ± 3740	4850 ± 72

[a]IC_{50} values taken from ref 14. [b]Taken from ref 8.

Discussion

The results for the inhibition of binding at the DAT listed in the Table provide additional support that a phenyl ring can replace the 2β-carbomethoxy group in WIN 35,065-2 without loss in binding affinity. We previously reported that (*R,S*)-**3a** with an IC_{50} value of 28 nM was quite similar to the 23 nM IC_{50} value of WIN 35,065-2.[8] Since the binding affinity of (*S*)-(+)-cocaine and WIN 35,065-3, which is the (*S*)-enantiomer of WIN 35,065-2, is much lower than natural (*R*)-(-)-cocaine and WIN 35,065-2, respectively, we expected that (*R*)-**3a** would be more potent than the (*R,S*)-**3a**. We found that (*R*)-**3a** possessed an IC_{50} value of 12.6 nM, making it a little more than twice as potent as (*R,S*)-**3a**. Since the addition of a *p*-methyl group to WIN 35,065-2

(**2a**) to give RTI-32 (**2b**) resulted in a 14-fold (23 nM vs. 1.71 nM) increase in potency at the DAT, we hoped that the addition of the *p*-methyl group to (*R*)-**3a** to give (*R*)-**3b** would also give a large increase in potency. The data in the Table shows that (*R*)-**3b** is six times more potent than (*R*)-**3a** and that (*R*)-**3b** has essentially the same affinity for the DAT as RTI-32 (**2b**) (1.96 nM vs. 1.71 nM). Importantly, both (*R*)-**3a** and (*R*)-**3b** show much greater selectivity for the DAT relative to the 5-HTT and NET than WIN 35,065-2 (**2a**) and RTI-32 (**2b**). The higher potency of the 2β,3β-isomer (*R*)-**3a** and (*R*)-**3b** relative to the 2α,3α-isomers (*R*)-**4a** and (*R*)-**4b**, respectively, is consistent with the results obtained with cocaine isomers.[15]

Conclusions

We have developed a general synthetic method to prepare the 2β,3β- and 2α,3α-isomers of (*R*)-2,3-diaryltropanes. We used the method to prepare (*R*)-3β-(4-methylphenyl)-2β-phenyltropane (**3b**) and found that **3b** is a potent and selective ligand for the DAT. The synthesis of other (*R*)-3β-(substituted phenyl)-2β-phenyltropanes would be expected to provide additional analogs with greater potency at the DAT. Also, the addition of substituents to the 2β-phenyl ring might alter both potency and selectivity. Studies along these lines are planned and will be reported in due course.

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