

Synthesis of 3-(4-heteroaryl-phenyl)-8-oxabicyclo[3.2.1]octane-2-carboxylic acid methyl esters

Lokman Torun,^a Shanghao Liu,^a Bertha K. Madras^b and Peter C. Meltzer^{a,*}

^aOrganix Inc., 240 Salem Street, Woburn, MA 02801, USA

^bNew England Regional Primate Research Center, Southborough, MA 01772, USA

Received 28 September 2005; revised 25 October 2005; accepted 25 October 2005

Available online 1 December 2005

Abstract—Cross coupling protocols were applied for the synthesis of 3-(4-heteroaryl-phenyl)-8-oxabicyclo[3.2.1]oct-2-ene-2-carboxylic acid methyl esters. Stille conditions produced the corresponding products in reasonable yields. Samarium iodide reduction of the resulting coupling products produced the 2 β -carbomethoxy-3 α -aryl-8-oxabicyclo[3.2.1]octane diastereoisomers as the major, and the 2 β -carbomethoxy-3 β -aryl-8-oxabicyclo[3.2.1]octane diastereoisomer as the minor products. Both diastereoisomers manifested inhibition of the dopamine (DAT) and serotonin (SERT) transporters, with some selectivity for SERT inhibition.

© 2005 Elsevier Ltd. All rights reserved.

The discovery and development of potential medications for cocaine abuse has focused to a large extent on the diverse family of bicyclo[3.2.1]octanes.^{1–3} These compounds bind potently to monoamine uptake mechanisms in the mammalian system (dopamine (DAT), serotonin (SERT) and norepinephrine (NET) transporters) and these systems have been implicated in the pharmacology of addiction caused by cocaine, itself a bicyclo[3.2.1]octane. In particular, the stimulatory and addictive properties of cocaine have been thought to be largely due to its ability to inhibit the DAT,^{4–9} although the SERT has also been implicated.^{10–13}

In an extensive investigation aimed at developing medications for cocaine abuse, we have shown that the DAT and SERT inhibitory potency of the bicyclo[3.2.1]octane system is not limited by the nature of the heteroatom at the 8-position. While cocaine and its potent 3-aryl congeners **1** (Fig. 1) are 8-azabicyclo[3.2.1]octanes, we have demonstrated that 8-carba,¹⁴ 8-oxa¹⁴ and 8-thia¹⁵ bicyclo[3.2.1]octanes (**2–4**) have significant potency in inhibition of monoamine transport and are often equipotent to their 8-aza counterparts.¹ In our search for SERT selective uptake inhibitors we have now explored the introduction of heteroaryl moieties on the 3-aryl ring

within the 8-oxabicyclooctane series. In this regard, Davies et al.¹⁶ and Fu et al.¹⁷ have reported the synthesis and biological effects of 3-heterobiaryl systems in the 8-azabicyclo[3.2.1]octane series. They found that the introduction of 4-(2-pyrrolyl)phenyl¹⁶ and 4-(2-thiophenyl)phenyl¹⁷ caused these molecules to increase binding potency at SERT and decrease binding potency at DAT, thus providing compounds in which the DAT vs. SERT selectivity of the monoaryl compounds had been reversed. We now present the synthesis of a series of 3-(4-heteroarylphenyl)-8-oxa-2-carbomethoxybicyclo[3.2.1]octanes.

The synthesis of 8-oxabicyclooctanes such as **3** has been described in detail previously.¹⁸ The route that we had developed utilized a Suzuki coupling of the vinyltriflate **24** (Scheme 2) with appropriate arylboronic acids. The 4-bromophenyl compound (Scheme 1) **5** was available via this route, so we initially planned to utilize **5** in a second Suzuki coupling to obtain **10–12**. To our surprise, Suzuki conditions (Pd(PPh₃)₄, LiCl, Na₂CO₃, CH₂Cl₂) did not produce any product with 2-furanboronic acid, **6**. Furthermore, only a low yield (36%) of **11** was obtained with **7** under these conditions. However, Stille coupling of **5** with both **8** and **9** proved successful (56–61%).

A more general synthesis of the bicyclooctanes **10–13** was developed and is shown in Scheme 2. Since **24**¹⁸ is readily available in our laboratories, we elected to use

Keywords: Oxatropanes; Cocaine antagonist; Suzuki coupling; Stille coupling; SmI₂.

* Corresponding author. Tel.: +1 781 932 4142; fax: +1 781 933 6695; e-mail: Meltzer@organixinc.com

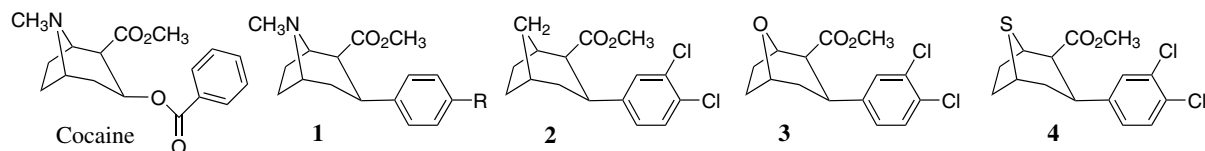
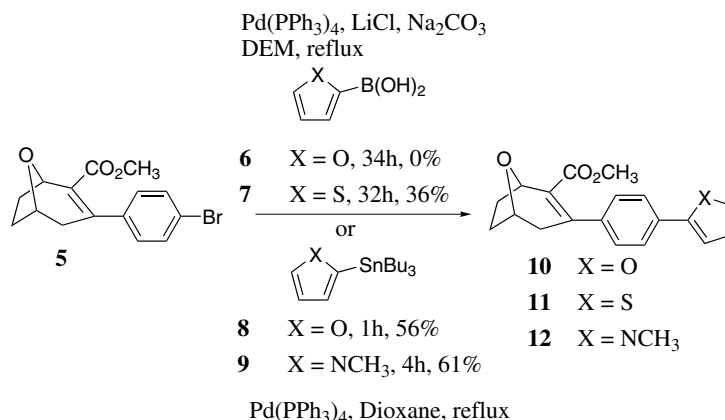
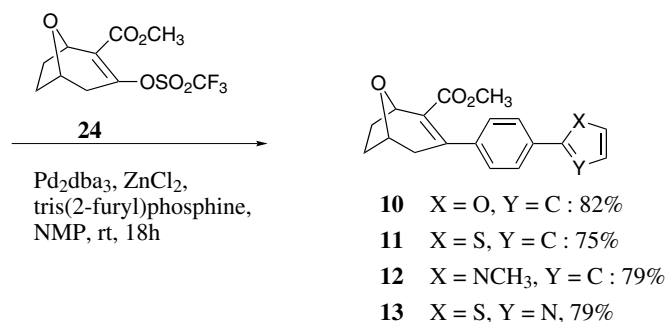
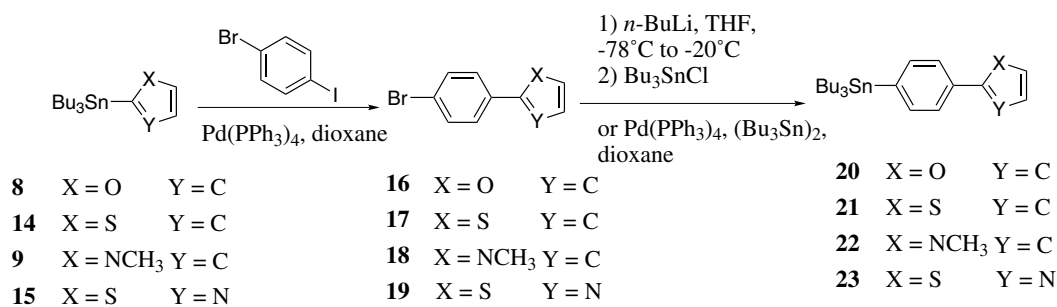


Figure 1.



Scheme 1. Application of Suzuki and Stille protocols to the synthesis of 10–12.



Scheme 2. Synthesis of biaryl-8-oxatropenes 10–13.

Stille coupling with appropriate stannanes to obtain the target compounds. Thus coupling of the arylstannanes **8**, **9**, **14**, **15** with 1-bromo-4-iodobenzene, with Pd(PPh₃)₄ as catalyst, provided the biaryl compounds **16–19**, which were purified by column chromatography (40–87%). Treatment with *n*-BuLi at –70 °C in THF for 1 h, followed by addition of tributyltin chloride then provided the tributylstannyl compounds **20–23**. Attempts to purify these stannyl compounds resulted

in substantial decomposition. Consequently they were used in the following reactions without purification.

The bicyclooxatropenes **10–13** were then obtained by a second Stille coupling. Thus cross coupling of the triflate **24**¹⁸ with the arylstannane building blocks **20–23** was carried out at room temperature in 1-methyl-2-pyrrolidinone (NMP) in the presence of Pd₂dba₃, tris-(2-furyl)phosphine and ZnCl₂. Treatment of the crude

reaction mixture with 10% aq KF greatly simplified the removal of tin byproduct by transforming it into insoluble tributyltin fluoride, which can be removed by filtration. The products were obtained in high yields (75–82%) after flash column chromatography on silica gel with ethyl acetate/hexane (1:9) as the eluent. When necessary, products were further purified by recrystallization. Characterization was performed by ^1H NMR spectroscopy, mass spectrometry and elemental analysis. The ^1H NMR spectra of these compounds are diagnostic (Table 1). In particular the H_1 proton appears as a doublet between δ 4.96–5.02 while H_5 is a multiplet at δ 4.64–4.68. Furthermore, $\text{H}_{4\beta}$ appears as a doublet at δ 2.95–3.08 with the $\text{H}_{4\alpha}$ proton as a doublet at δ 2.14–2.28.

Earlier structure–activity relationship studies have pointed conclusively to the fact that the biologically interesting isomers within the broad class of bicyclo[3.2.1]octanes have certain stereospecific requirements.^{1,18,19} In particular, the 2 β -carbomethoxy-3 β -aryl (chair) configured compounds generally manifested potency at both DAT and SERT. In contrast, the 2 β -carbomethoxy-3 α -aryl (boat) compounds were generally far less potent at SERT. This lesser potency at SERT was also the case in the 2,3-unsaturated class of compounds to which **10–13** belong.²⁰ For these reasons we were particularly interested in obtaining the 2 β -carbomethoxy-3 β -aryl (chair) configured compounds. We anticipated that these would be inherently more potent at inhibition of the SERT, and in this new class of compounds that potency at SERT may be further enhanced by the presence of the new heteroaryl substituent. Reduction of the 2,3-unsaturated compounds **10–13** can be affected

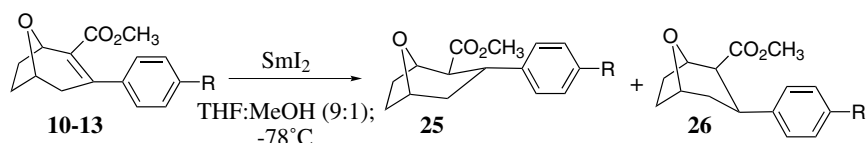
in many ways. However, methods such as catalytic hydrogenation result in reduction occurring from the β -face, thus resulting in 2 α ,3 α -configured compounds. The most effective manner in which to obtain both the boat and chair 2 β -carbomethoxy configured compounds has proved to be by the use of the single electron transfer reducing agent SmI_2 ^{21–23} in a solvent such as methanol.^{18,24} Thus, samarium iodide reduction of **10–13** in 10% methanol in tetrahydrofuran at -78°C provided the 2 β -carbomethoxy-3 α -aryl (boat) compounds in reasonable yield with the exception of **25d** for which only a 9% yield was achieved (Scheme 3). The 2 β -carbomethoxy-3 β -aryl (chair) diastereomers were obtained in substantially lower yields for **26a** and **26c** while **26b** and **26d** were not obtained. In the latter case, the major product proved to be the 2 α - COOCH_3 , 3 α -aryl boat configured compound. Unfortunately the 2 α - COOCH_3 diastereomers are often biologically uninteresting since they generally bind poorly at monoamine uptake systems.^{1,19} Separation was achieved by column chromatography on silica gel using 10% ethyl acetate in hexane. Yields are given in Table 2. Again, ^1H NMR spectroscopy was diagnostic for these compounds. The stereochemistry at the 2- and the 3-positions was established by the characteristic coupling constants and chemical shifts of the corresponding protons (Table 1). These are in good agreement with published work from our group.¹⁸ Specifically, 3 α -aryl compounds manifest a double doublet for $\text{H}_{4\alpha}$ at about δ 1.4 whereas 3 β -aryl compounds present a multiplet at δ 1.9 for this proton. The proton at H_2 is also diagnostic in that 3 α -aryl compounds manifest a double doublet at about δ 2.6 whereas 3 β -aryl compounds have doublet at about δ 2.8.

Table 1. Physical and spectral data^a

Compd	Melting point ($^\circ\text{C}$)	Yield (%)	^1H NMR (δ ppm) diagnostic peaks (J Hz)				
2,3-Enes			H_1 (d)	H_5 (m)		$\text{H}_{4\alpha}$ (dd)	$\text{H}_{4\beta}$ (d)
10	107–108	82	5.01	4.64		2.15	2.95
11	111–112	75	5.02	4.65		2.14	2.96
12	Oil	79	5.01	4.67		2.17	2.96
13	Oil	79	4.96	4.68		2.28	3.08
3- α -Aryl			$\text{H}_{1,5}$ (m)	H_2 (dd)	H_3 (dt)	$\text{H}_{4\alpha}$ (ddd)	$\text{H}_{4\beta}$
25a	130–131	53	4.4–4.5	2.55	3.27	1.41	2.40
25b	136–138	79	4.4–4.5	2.56 (10.1, 2.2)	3.28	1.41	2.40
25c	Oil	54	4.5–4.6	2.58 (10.2, 2.2)	3.29	1.44	2.45
25d	112–114	9	4.5–4.6	2.57 (10.1, 2.4)	3.32	1.44	2.45
3- β -Aryl			$\text{H}_{1,5}$ (m)	H_2 (d)	H_3 (dt)	$\text{H}_{4\alpha}$ (m)	$\text{H}_{4\beta}$ (dt)
26a	140–142	21	4.6–4.7	2.85 (5.2)	3.23	1.9	2.79
26c	Oil	22	4.6–4.7	2.87 (5.2)	3.24	1.9	2.80

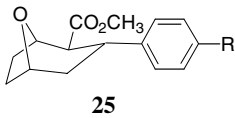
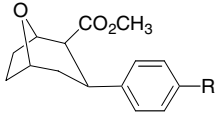








Doublet (d), multiplet (m), double doublet (dd), double double doublet (ddd).

^a Spectra measured in CDCl_3 .



Scheme 3. SmI_2 reduction of 3-biaryl-2-carbomethoxybicyclo[3.2.1]oct-2-enes.

Table 2. Distribution of diastereomers obtained from samarium iodide reduction

 25			 26		
Compound	R	Yield (%)	Compound	R	Yield (%)
25a		53	26a		21
25b		79	26b		Not obtained
25c		54	26c		22
25d		9	26d		Not obtained ^a

^a The 2 α -COOCH₃-3 α -aryl boat configured compound was the major product (25%).

It is noteworthy that within the series of 8-oxabicyclo[3.2.1]octanes, the 3 α -aryl compounds are generally formed in higher yields than the 3 β -aryl compounds.¹⁸ Indeed, in the case of the reduction of **11** and **13**, the 3 β -aryl compound **26b** and **26d** were not isolated at all. Only the 3 α -aryl **25b** was obtained (79%), while **13** yielded a major product in which the 2-COOCH₃ was isomerized to the 2 α -configuration. The reasons for the general dominance of the 3 α -aryl over the 3 β -aryl are unclear. Possibly, a preference for 3 α -aryl reduced products might be dominated by an intermediate species in which the samarium is coordinated to the bridge oxygen, and probably to the C2-carbomethoxy group. It may then be surmised that proton transfer occurs preferentially from the β -face of the molecule to provide, predominantly, the 3 α -aryl substituent.

The IC₅₀ values for inhibition of the dopamine transporter (DAT) and the serotonin transporter (SERT) are shown in Table 3). It is noteworthy that the reduced compounds **25** and **26** were generally more potent inhib-

itors of the SERT. However, in contrast to the parent 8-oxatropanes,¹⁸ both the boat and chair compounds manifested some selectivity versus inhibition of the DAT.

A series of (*R,S*) 3-(4-heteroarylphenyl)-8-oxabicyclo[3.2.1]carboxylic acid methyl esters were synthesized via Stille coupling. Samarium iodide reduction of the bicyclooctenes produced the 3 α -aryl diastereomer predominantly over the 3 β -aryl diastereomer. Both 3 α -aryl and the 3 β -aryl diastereomers manifest a preferential inhibition of the serotonin transporter compared with their inhibition of the dopamine transporter.

Acknowledgement

We thank the National Institute on Drug Abuse for financial support (DA 11542, DA 7-8825, DA 06303).

Supplementary data

The supplementary data, including full experimental details, are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.10.170.

References and notes

- Meltzer, P. C.; Blundell, P.; Madras, B. K. *Med. Chem. Res.* **1998**, *8*, 12–34.
- Singh, S. *Chem. Rev.* **2000**, *100*, 925–1024.
- Carroll, F. I. *J. Med. Chem.* **2003**, *46*, 1775–1794.
- Kennedy, L. T.; Hanbauer, I. *J. Neurochem.* **1983**, *34*, 1137–1144.
- Schoemaker, H.; Pimoule, C.; Arbilla, S.; Scatton, B.; Javoy-Agid, F.; Langer, S. Z. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1985**, *329*, 227–235.

Table 3. Inhibition of [³H]WIN 35,428 binding to the human dopamine transporter (hDAT) and [³H]citalopram binding to the human serotonin transporter (hSERT)^a

Compound	DAT IC ₅₀ (nM)	SERT IC ₅₀ (nM)	DAT/SERT ^b
10	102	248	0.4
11	272	242	1.1
12	>10,000	>10,000	1
13	>5,000	>14,000	1
25a	139	32	4.3
25b	356	35	10.2
25c	1000	395	2.5
25d	1770	128	13.8
26a	64	30	2.1
26c	12,400	566	21.9

^a Compounds are racemic. Each value is the mean of two or more independent experiments, each conducted in triplicate.

^b Ratio of SERT inhibition to DAT inhibition.

6. Reith, M. E. A.; Meisler, B. E.; Sershen, H.; Lajtha, A. *Biochem. Pharmacol.* **1986**, *35*, 1123–1129.
7. Ritz, M. C.; Lamb, R. J.; Goldberg, S. R.; Kuhar, M. J. *Science* **1987**, *237*, 1219–1223.
8. Madras, B. K.; Fahey, M. A.; Bergman, J.; Canfield, D. R.; Spealman, R. D. *J. Pharmacol. Exp. Ther.* **1989**, *251*, 131–141.
9. Canfield, D. R.; Spealman, R. D.; Kaufman, M. J.; Madras, B. K. *Synapse* **1990**, *6*, 189–195.
10. Spealman, R. D. *Psychopharmacology* **1993**, *112*, 93–99.
11. Howell, L. L.; Byrd, L. D. *J. Pharmacol. Exp. Ther.* **1996**, *276*, 1551–1559.
12. Kimmel, H. L.; Carroll, F. I.; Kuhar, M. J. *Drug Alcohol Dependence* **2001**, *65*, 25–36.
13. Czoty, P. W.; Ginsburg, B. C.; Howell, L. L. *J. Pharmacol. Exp. Ther.* **2002**, *300*, 831–837.
14. Meltzer, P. C.; Blundell, P.; Yong, Y. F.; Chen, Z.; George, C.; Gonzalez, M. D.; Madras, B. K. *J. Med. Chem.* **2000**, *43*, 2982–2991.
15. Meltzer, P. C.; Pham-Huu, D.-P.; Madras, B. K. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 6007–6010.
16. Davies, H. M. L.; Ren, P.; Kong, N.; Sexton, T.; Childers, S. R. *Bioorg. Med. Chem. Lett.* **2001**, *11*.
17. Fu, X.; Baldwin, R. M.; Kula, N. S.; Baldessarini, R. J.; Innis, R. B.; Tamagnan, G. Synthesis and Monoamine Transporter Binding Affinities of 2 β -Carbomethoxy-3 β -(4-Aromatic Substituted Phenyl) Tropanes. In *222nd ACS National Meeting, Med. Chem. Div.*, 2001; pp Abstracts #219.
18. Meltzer, P. C.; Liang, A. Y.; Blundell, P.; Gonzalez, M. D.; Chen, Z.; George, C.; Madras, B. K. *J. Med. Chem.* **1997**, *40*, 2661–2673.
19. Meltzer, P. C.; Wang, B.; Chen, Z.; Blundell, P.; Jayaraman, M.; Gonzalez, M. D.; George, C.; Madras, B. K. *J. Med. Chem.* **2001**, *44*, 2619–2635.
20. Meltzer, P. C.; Blundell, P.; Huang, H.; Liu, S.; Yong, Y. F.; Madras, B. K. *Bioorg. Med. Chem.* **2000**, *8*, 581–590.
21. Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693–2698.
22. Molander, G. A.; Kenny, C. *J. Am. Chem. Soc.* **1989**, *111*, 8236–8246.
23. Keck, G. E.; Wager, C. A.; Sell, T.; Wager, T. T. *J. Org. Chem.* **1999**, *64*, 2172–2173.
24. Keverline, K. I.; Abraham, P.; Lewin, A. H.; Carroll, F. I. *Tetrahedron Lett.* **1995**, *36*, 3099–3102.