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Synthesis of 6- or 7- Hydroxy and 6- or 7- Methoxy Tropanes

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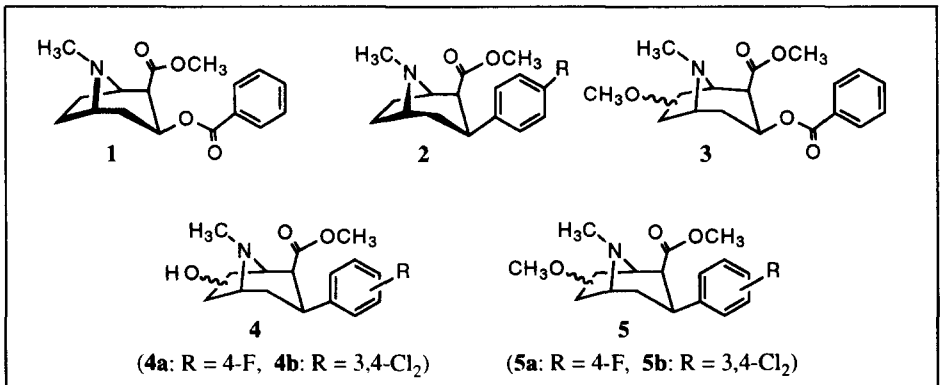
Abstract: A novel Mannich type condensation between the monomethyl ester of acetonedicarboxylic acid, methylamine hydrochloride, and hydrolyzed dimethoxydihydrofuran gave 6- or 7- functionalized β-keto ester tropanes **12 - 15**. Further elaboration afforded a series of 6- or 7- hydroxy and 6- or 7-methoxy 2β-methoxycarbonyl-3-aryltropanes. © 1997, Elsevier Science Ltd. All rights reserved.

Cocaine abuse presents a considerable drug problem throughout the world.[1,2] The stimulant and reinforcing properties of cocaine (**1**) have been related to its ability to bind to monoamine transporter systems, particularly to the dopamine transporter (DAT).[3] Cocaine analogs such as the 3-aryltropanes (2-carbomethoxy-3-aryl-8-azabicyclo[3.2.1]octanes) (**2**)[4] are highly potent and selective ligands for these monoamine uptake proteins in mammalian caudate-putamen. Although much information concerning the structure-activity relationships (SAR)[5-9] of these compounds has been reported, the nature of the binding interaction between cocaine and its analogs to the DAT is still a matter of conjecture and considerable doubt has been cast on current models of this interaction.[7,10,11]

Tropanes, such as **2**, possess an 8-amine which can provide a binding point to the dopamine transporter, specifically to an aspartic acid residue (Asp^{79}).[12] The basicity of this nitrogen presumably effects the strength of the subsequent hydrogen bonding interaction. However, it has been argued that strong basicity may not necessarily be a prerequisite for tight binding.[11] Moreover, methoxy substitution at the 6- and 7- position of cocaine itself (as in **3**) did not eliminate binding to the transporter.[13,14]



1 **2** **3**

4 (**4a**: R = 4-F, **4b**: R = 3,4-Cl_2)

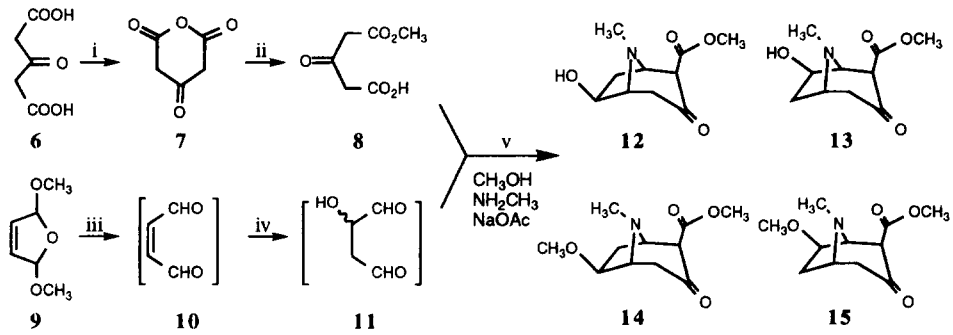
5 (**5a**: R = 4-F, **5b**: R = 3,4-Cl_2)

In a research program directed toward the elucidation of the structural requirements for tropane binding and efficacy at cocaine binding sites of specific biogenic amines (serotonin, dopamine and norepinephrine), we chose to explore the ramifications of introduction of a 6- or 7- hydroxyl or methoxyl group, specifically in the β-

orientation, as in 3-aryltropane analogs **4** and **5**. These compounds were designed to evaluate the importance of the tropane nitrogen basicity since such a β-oriented hydroxyl group can undergo intramolecular hydrogen bonding to the 8-amino function and thereby reduce the basicity of this nitrogen.

Our synthesis of a family of racemic 6- and 7- oxygenated tropanes was based upon a Mannich type condensation reaction.[15-17] Thus, a solution of dimethoxydihydrofuran, **9**, in 3N HCl was stirred for 12 h at room temperature and then neutralized by addition of aqueous sodium hydroxide. To this mixture, methylamine hydrochloride in water, and acetonedicarboxylic acid anhydride, **7**, in methanol were added. The pH of the reaction was maintained at about 4.5 by the addition of sodium acetate (Scheme 1). This biomimetic reaction gave, after careful column chromatography, a mixture of 6- and 7- hydroxy β-keto esters **12** and **13** in a total yield of 48% and a ratio of 3 to 1.[18] The exo (β) stereochemistry of the hydroxyl group at C6 (**12**), or C7 (**13**), was confirmed by detailed NMR studies.[19] Most importantly, a coupling constant of J = 0 Hz between H-5 and H-6 (δ = 4.05 ppm) in the case of **12**, and between H-1 and H-7 (δ = 4.1 ppm) in the case of **13**, confirmed a dihedral angle of 90° for both compounds. Such a dihedral angle can only be obtained between a 6- or 7-α-oriented proton and the relevant bridgehead proton at C1 or C5 respectively thus confirming the β-orientation of the hydroxy moieties in **12** and **13**. Indeed, no significant amounts of α-hydroxy isomers could be isolated.

Scheme 1



Reagents and Conditions: i) Acetic Anhydride. Acetic Acid. ii) Methanol. iii) 3N HCl, 12 h. iv) 3N NaOH. v) 24 h

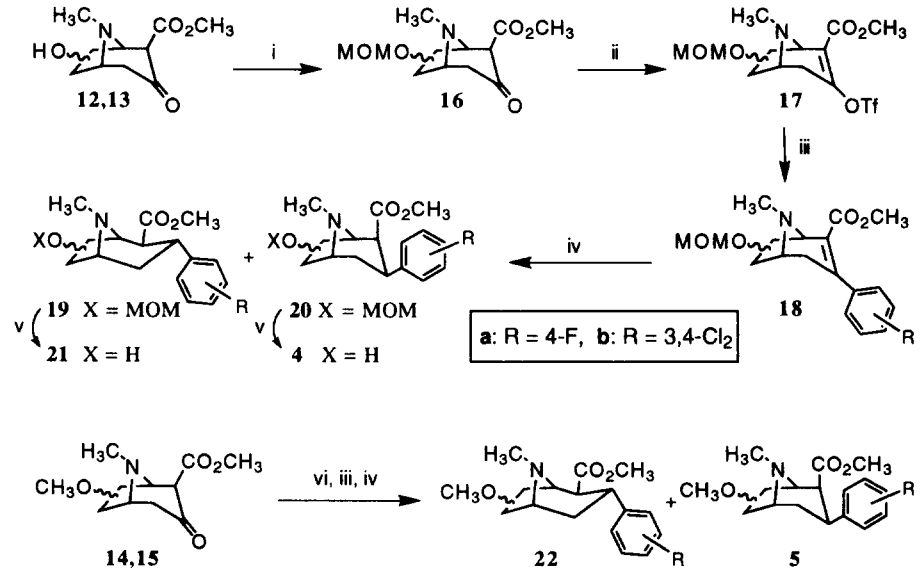
In addition to **12** and **13**, less polar tropanes were also obtained from the reaction. Chromatographic separation of these provided compounds **14** and **15** in 12% yield in a ratio of 1:3. The formation of these methoxy β-keto esters is likely due to the presence of methanol in the reaction of **8** and **11**. This methanol is thought to react with residual amounts of intermediate **10** to form a methoxylated succindialdehyde which could then condense with methylamine hydrochloride and the monomethyl ester of acetonedicarboxylic acid to provide the methoxy products **14** and **15**.

The 6- and 7- hydroxy β-keto esters **12** and **13** were each methoxymethylated with dimethoxymethane in dichloromethane with *p*-toluenesulfonic acid as catalyst, in about 60 % yield. Subsequent conversion[20,21] to the vinyl enoltriflate **17** was then achieved with sodium bistrimethylsilyl amide and phenyl triflimide at low

temperature (Scheme 2). The alkenes **18**, were then obtained in about 85% yield by Suzuki coupling of the triflates with the corresponding preformed boronic acids. Reduction of **18** with samarium iodide at -78°C, with methanol as the proton source, and subsequent chromatography, then afforded the saturated tropane analogs, **19** (ca. 61%) and **20** (ca. 20%).[22] Compound **19** was shown by ^{1}H NMR to exit in a twist-boat conformation, while **20** assumed a twist-chair conformation. Finally, the MOM group of each of **19** and **20** was removed in high yield (ca. 85%) with trimethylsilyl bromide in dichloromethane at 0° C to give the corresponding hydroxy tropanes **21** and **4**.[19]

The 6- and 7- methoxy β-keto esters **14** and **15** were transformed into their enoltriflates with trifluoromethanesulfonic anhydride and triethylamine in methylene chloride.[23] Analogous transformations then provided the methoxy tropanes **5** and **22** in a ratio of 1:2 (Scheme 2: step iv).[19]

Scheme 2



Reagents and Conditions: i) $(CH_3O)_2CH_2$, pTSA. ii) $Na(TMS)_2N$, $Ph(Tf)_2N$, -78°C . iii) $ArB(OH)_2$, Pd_2dba_3 Na_2CO_3, LiCl. iv) SmI_2, Methanol, -78°C. v) TMSBr, CH_2Cl_2, 0°C. vi) $(CF_3SO_2)_2O$, Et_3N, CH_2Cl_2, O°C.

In this manuscript we report the first synthesis of 6- and 7- hydroxy and 6- and 7-methoxy 2β-methoxycarbonyl-3-aryl-tropanes. The pharmacological evaluation of these compounds is currently under investigation.

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References and Notes

1. Blaine, J. D.; Ling, W. *Psychopharmacol. Bull.* **1992**, *28*, 11.
2. Adams, E. H.; Gfoerer, J. C. *Psychiatr. Ann.* **1988**, *18*, 325.
3. Ritz, M. C.; Lamb, R. J.; Goldberg, S. R.; Kuhar, M. J. *Science* **1987**, *237*, 1219.
4. Clarke, R. L.; Daum, S. J.; Gambino, A. J.; Aceto, M. D.; Pearl, J.; Levitt, M.; Cumiskey, W. R.; Bogado, E. F. *J. Med. Chem.* **1973**, *16*, 1260.
5. Carroll, F. I.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. *J. Med. Chem.* **1992**, *35*, 969.
6. Meltzer, P. C.; Liang, A. Y.; Brownell, A.-L.; Elmaleh, D. R.; Madras, B. K. *J. Med. Chem.* **1993**, *36*, 855.
7. Meltzer, P. C.; Liang, A. Y.; Madras, B. K. *J. Med. Chem.* **1994**, *37*, 2001.
8. Carroll, F. I.; Mascarella, S. W.; Kuzemko, M. A.; Gao, Y.; Abraham, P.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. *J. Med. Chem.* **1994**, *37*, 2865.
9. Meltzer, P. C.; Liang, A. Y.; Madras, B. K. *J. Med. Chem.* **1996**, *39*, 371.
10. Davies, H. M. L.; Saikali, E.; Sexton, T.; Childers, S. R. *Eur. J. Pharmacol. Mol. Pharm.* **1993**, *244*, 93.
11. Kozikowski, A. P.; Saiah, M. K. E.; Bergmann, J. S.; Johnson, K. M. *J. Med. Chem.* **1994**, *37*, 3440.
12. Kitayama, S.; Shimada, S.; Xu, H.; Markham, L.; Donovan, D. H.; Uhl, G. R. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *89*, 7782.
13. Kozikowski, A. P.; Simoni, D.; Malredini, S.; Roberti, M.; Stoelwinder, J. *Tetrahedron Lett.* **1996**, *37*, 5333.
14. Simoni, D.; Stoelwinder, J.; Kozikowski, A. P.; Johnson, K. M.; Bergmann, J. S.; Ball, R. G. *J. Med. Chem.* **1993**, *36*, 3975.
15. Robinson, R. *J. Chem. Soc.* **1917**, *111*, 762.
16. Nedenskov, P.; Clauson-Kaas, N. *Acta Chem. Scand.* **1957**, *22*, 1385.
17. Sheehan, J. C.; Bloom, B. M. *J. Am. Chem. Soc.* **1952**, *74*, 3825.
18. The separation of compounds **12** and **13** by flash chromatography is laborious. These compounds could be easily separated as their triflates, **17**. ^{1}H NMR decoupling of **17** confirmed the position of the MOM group.
19. Selected ^{1}H NMR data (400 MHz, $CDCl_3$): (**4b**, 7β-OH) δ 7.31 (d, J = 8.5 Hz, 1H, *Ph*), 7.27 (d, J = 1.8 Hz, 1H, *Ph*), 7.05 (dd, J = 8.5, 1.8 Hz, 1H, *Ph*), 4.52 (dd, J = 6.8, 3.1 Hz, 1H, $H_{7\alpha}$), 3.58 (br s, 1H, H_5), 3.52 (br s, 1H, H_1), 3.51 (s, 3H, CO_2Me), 2.99 (dd, J = 4.6, 4.2 Hz, 1H, $H_{2\alpha}$), 2.64 (ddd, J = 11.3, 5.8, 4.6 Hz, 1H, $H_{3\alpha}$), 2.53 (s, 3H, *NMe*), 2.44 (ddd, J = 12.4, 11.3, 2.4 Hz, 1H, $H_{4\beta}$), 2.17 (ddd, J = 14.1, 6.7, 3.4 Hz, 1H, $H_{6\beta}$), 2.10 (dd, J = 14.0, 6.8 Hz, 1H, $H_{6\alpha}$), 1.55 (m, 1H, $H_{4\alpha}$). (**5b**, 7β-OCH_3) δ 7.31 (d, J = 8.5 Hz, 1H, *Ph*), 7.28 (d, J = 1.8 Hz, 1H, *Ph*), 7.07 (dd, J = 8.5, 1.8 Hz, 1H, *Ph*), 3.96 (dd, J = 7.3, 3.0 Hz, 1H, $H_{7\alpha}$), 3.61 (br s, 1H, H_1), 3.52 (br s, 1H, H_5), 3.51 (s, 3H, CO_2Me), 3.34 (s, 3H, *OMe*), 2.95 (dd, J = 4.6, 3.7 Hz, 1H, $H_{2\alpha}$), 2.64 (ddd, J = 9.8, 6.4, 4.6 Hz, 1H, $H_{3\alpha}$), 2.47 (m, 1H, $H_{4\beta}$), 2.43 (s, 3H, *NMe*), 2.18 (ddd, J = 14.1, 6.7, 3.0 Hz, 1H, $H_{6\beta}$), 2.10 (dd, J = 14.0, 7.3 Hz, 1H, $H_{6\alpha}$), 1.55 (m, 1H, $H_{4\alpha}$).
20. Keverline, K. I.; Abraham, P.; Lewin, A. H.; Carroll, F. I. *Tetrahedron Lett.* **1995**, *36*, 3099.
21. Carroll, F. I. *Personal Communication* **1995**,
22. The reaction is currently being optimized. With trifluoroacetic acid (see ref 20) as quenching agent the ratio of **21** to **4** (MOM protecting group was lost) was about 1:1. Hydrogenation of **18b** (H_2, PtO_2) provides the α-substituted conformer exclusively with concommitant loss of chlorine.
23. Chen, Z.; Izenwasser, S.; Katz, J. L.; Zhu, N.; Klein, C. L.; Trudell, M. L. *J. Med. Chem.* **1996**, *39*, 4744.

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