Synthesis and Nicotinic Acetylcholine Receptor Affinity of Bivalent Tropane-3-Carboxylates

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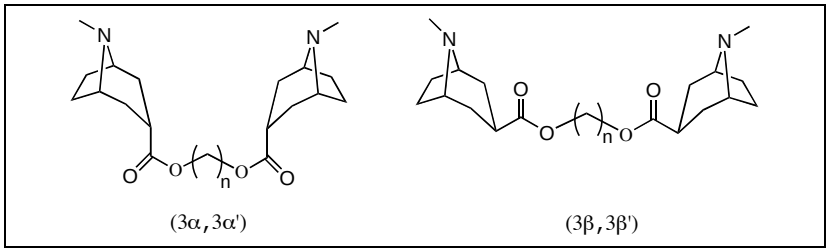
Received February 1, 2007



A series of diol di-(tropane-3α-carboxylate) esters and diol di-(tropane-3β-carboxylate) esters were synthesized from 3-tropene-3-carboxylic acid and tropane-3β-carboxylic acid, respectively. The bivalent tropane-3-carboxylates were evaluated for their ability to inhibit [^{3}H]cytisine binding at rat brain nicotinic acetylcholine receptors (nAChRs). In general the (3β,3β')-isomers were more potent than (3α,3α')-isomer and the (3β,3β')-decyl derivative (n = 10, K_i = 145 nM) exhibited the most potent affinity for nAChRs of the series.

J. Heterocyclic Chem., **44**, 1425 (2007).

INTRODUCTION

Neuronal nicotinic acetylcholine receptors (nAChRs) have long been the target for the development of therapeutic agents for tobacco addiction, smoking cessation, muscle relaxation and antihypertension [1,2]. Recently, nAChRs have been identified as potential targets for the development of new therapeutic agents for the treatment of a number of other central nervous system (CNS) diseases and disorders which include Alzheimer's Disease, Parkinson's Disease, Tourette syndrome, anxiety and depression [2-4]. Unfortunately, to date there are few neuronal nAChR agents in which the therapeutic value of the drug significantly overwhelms the side effects. Side effects such as cardiovascular and gastrointestinal dysfunction, addiction, neuromuscular effects and seizures have limited the use of nAChR agents in drug therapies. Therefore, the search for potent and selective nAChR agents is an extremely important endeavor that will provide pharmacological tools for the study of nAChR function and lead to new therapeutic agents and medications for the treatment of a variety of neurological diseases.

The use of bivalent compounds has been proven to be a successful approach for the development of compounds with improved potency and selectivity for a variety of receptors in the CNS [5-7]. However, there have been few reports of bivalent compounds exhibiting neuronal nAChR affinity [8,9]. Of the bivalent systems that have been reported, the bivalent ligand typically exhibited significantly diminished potency relative to the monomeric congener. Bivalent epibatidine derivatives **1**, were reported to exhibited a 40-350-fold decrease in affinity relative to epibatidine [8,9]. The paucity of bivalent compounds that bind to neuronal nAChRs with high affinity, led us to consider neuromuscular nAChR ligands as lead compounds for delevopment of a new bivalent ligand system. Recently, Gyermek and coworkers reported the bisquaternary ammonium tropine diester (**2**) as a new class of neuromuscular blocking (NMB) agents with modest side effects [10]. Bivalent tropane compounds such as **2**, have been extensively studied as NMB agents at neuromuscular nAChRs [11]. Therefore it was envisaged that a bis-tropane scaffold would be a useful starting point for the development of novel bivalent neuronal nAChR ligands.

Neuromuscular nAChRs have been well characterized and differ significantly from neuronal nAChRs in structure and function [2,12]. As a result, ligand structures can be quite different for these two classes of receptors. However despite these differences, at the onset of this study the focus was to design a new series of bivalent neuronal nAChR ligands using a bis-tropane scaffold. To this end, we envisaged two structural modifications of **2** that were necessary to achieve the goal of neuronal nAChR affinity. As part of our design rationale it was necessary to develop lipophilic congeners that would

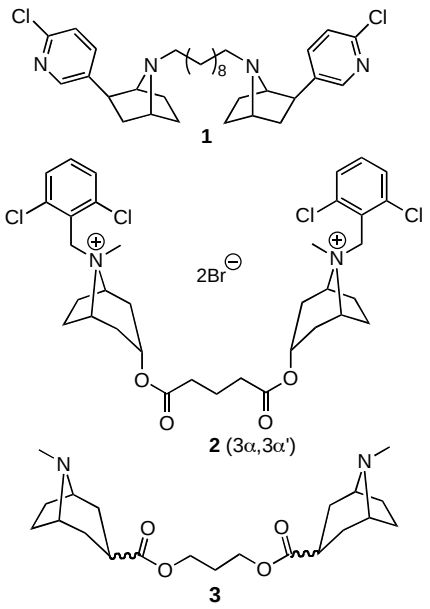


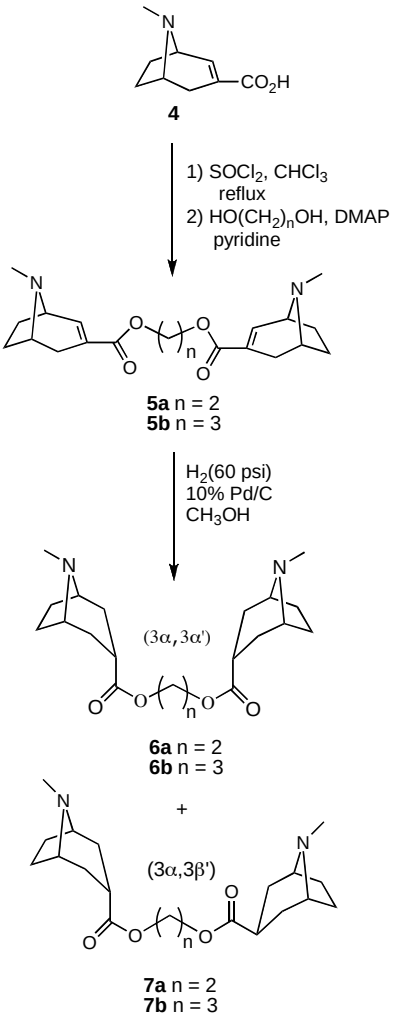
Figure 1

penetrate into the brain. The quaternary ammonium nitrogen atom of **2** was not consistent with the goal of a CNS active compound. Therefore, the tertiary nitrogen atom of tropane was deemed an ideal moiety to meet the criteria of blood brain barrier permeability. Secondly, of the reported tropane analogues that bind to nicotinic acetycholine ion channel complexes, the acetoxy derivatives of 2-, 3- and 6-tropine have been shown to be generally more selective for neuronal muscarinic receptors [13]. However, the constitutional isomers, the corresponding carbomethoxy derivatives have been reported to be more selective for neuronal ($\alpha4\beta2$) nicotinic receptors [13]. In lieu of these results, it was of interest to alter the connectivity of the ester attachment in **2** and explore the structure-activity relationships of simple tethered tropane-3-carboxylate derivatives. To this end, a series of 3,3'-diol di-(tropane-3-carboxylate) derivatives **3** were identified as targets for synthesis. Herein we describe the synthesis and neuronal nAChR affinity of a series 3,3'-diol di-(tropane-3-carboxylate) derivatives.

RESULTS AND DISCUSSION

The 3α,3α'-diol tropane-3-carboxylates **6a** and **6b** were selected as the initial targets due to the structural and stereochemical similarity to **2**. Previous attempts at direct esterification of 3α-tropane-3-carboxylic acid resulted in complex product mixtures due to the propensity of the 3α-carboxylate to epimerize and furnish the more stable 3β-tropane-3-carboxylic acid [14]. Therefore, as illustrated in Scheme 1, a 3α,3α'-diol tropane-3-carboxylates **6a** and **6b** were prepared *via* an indirect method from the 2-tropene-3-carboxylic acid (**4**). The acid **4** was readily prepared from 2-tropinone using procedures previously developed in our laboratory [14]. Conversion of **4** into the corresponding acid chloride with thionyl chloride followed by esterification with the appropriate diol furnished the corresponding diesters **5a** and **5b**. Subsequent hydrogenation of diesters **5a** and **5b** afforded the desired 3α,3α'-sterochemistry of **6a** and **6b** in good overall yields. The ethylene derivative the (3α,3β')-ethylene glycol di-(tropane-3-carboxylate) (**7a**) was also obtained as a side product in 17 % yield, while the propylene congener **7b** was not present in sufficient quantities to isolate in pure form. Overall, this indirect route for formation of the 3α,3α'-isomers was found to minimize formation of mixed 3,3'-stereoisomers.

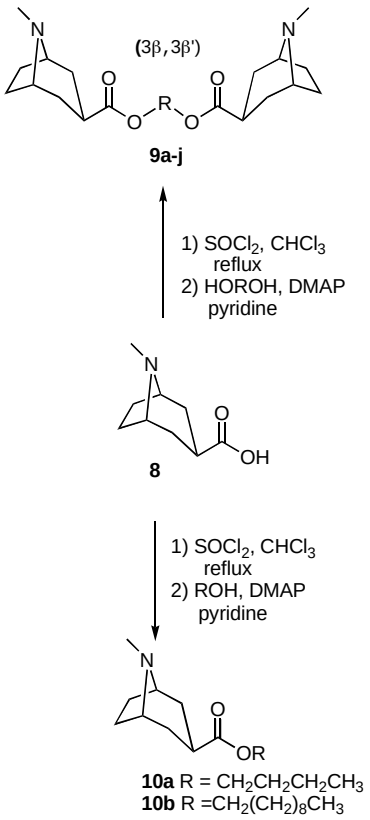
Scheme 1



The corresponding (3β,3β')-diol di-(tropane-3-carboxylate) congeners **9a** and **9b** were prepared from 3β-tropane-3-carboxylic acid (**8**) [14]. Treatment of **8** with thionyl chloride and concomitant diesterification with the

corresponding diol in pyridine with 10% 4-dimethyl-aminopyridine (DMAP) furnished **9a** (71%) and **9b** (60%) in good yields. Under these conditions no mixed 3,3'-stereoisomers (*e.g.* **7a,b**) were observed.

Scheme 2



The binding affinities of the diol di-(tropane-3-carboxylate) esters summarized in Table 1, were determined by the inhibition of [^{3}H]cytisine binding in homogenates of rat striatum [15]. There are a variety of nAChRs subtypes that exist in the central nervous system; however, the α4β2-subtype are the predominant nAChR subtypes in rat striatum tissue and [^{3}H]cytisine is selective for this subtype [16]. Therefore, the data presented in Table 1 principally represents the compounds affinity at α4β2-subtype receptors. Surprisingly the 3α,3α'-isomers **6a** and **6b** exhibited low affinity for nAChRs. Compounds **6a** and **6b** did not fully inhibit [^{3}H]cytisine binding at the highest dose tested (100 μM), hence the binding affinities are reported as the percent inhibition at 100 μM. Alternatively, 3β-stereochemistry at one or both tropane residues (**7a**, **9a** and **9b**) increased nAChR affinity significantly. In addition, it was noted that increasing the tether length by one methylene unit decreased the binding affinity of the (3α,3α')-isomer **6a** while the binding affinity of the (3β,3β')-isomer **9b** was increased four-fold over **9a**. This prompted further investigation of the effects of the tether length on the binding affinity of the 3β,3β'-diol di-(tropane-3-carboxylate) derivatives.

Table 1

Inhibition of [^{3}H]cytisine binding.

Cmpd [a]	R	K_i (nM)[b]
6a	-$(CH_2)_2$-	43%[c]
6b	-$(CH_2)_3$-	24%[c]
7a	-$(CH_2)_2$-	2,570 ± 630
9a	-$(CH_2)_2$-	3,430 ± 1,500
9b	-$(CH_2)_3$-	835 ± 100
9c	-$(CH_2)_4$-	247 ± 24
9d	*t*-CH_2CH=$CHCH_2$-	1,090 ± 110
9e	-$(CH_2)_5$-	575 ± 63
9f	-$(CH_2)_6$-	560 ± 35
9g	-$(CH_2)_7$-	546 ± 27
9h	-$(CH_2)_8$-	621 ± 70
9i	-$(CH_2)_9$-	259 ± 28
9j	-$(CH_2)_{10}$-	145 ± 2
10a	-$(CH_2)_3CH_3$	477 ± 24
10b	-$(CH_2)_9CH_3$	2254 ± 470

[a]Tested as the oxalate salt. [b]All values are the mean ±SEM of three experiments, each performed in triplicate. [c]Percent inhibition at highest dose tested (100 μM).

The 3β, 3β'-diol di-(tropane-3-carboxylate) derivatives **9c-j** were prepared using the procedure described above from **8** and the corresponding commercially available diols (Scheme 2). The effect of tether length on the binding affinity of the bis-tropane esters was quite striking. The (3β,3β')-decyl diester **9j** was found to be the most potent compound of the series and was 24-fold more potent than the ethylene diol congener **9a**.

Within the class of the 3β,3β'-congeners the binding affinities of were not incrementally proportional to the tether length. The decyl (**9j**) and butyl (**9c**) analogues exhibited the most potent affinity. Intermediate tether lengths (C5-C8) afforded compounds that were less favorable for binding and compounds with shortened tethers (C2-C3) exhibited some of the lowest potency of the series. The binding affinities of **9a-j** corresponded to the tether length in the following order: C10>C4≈C9>C5≈C6≈C7≈C8>C3>C2. In addition it appears that the more rigid tether of **9d** (K_i = 1,090 nM) was not as readily accommodated by the nAChR ion complex as was the more flexible saturated analogue **9c** (K_i = 259 nM). These results suggest that the length of the tether may not only be important for maintaining the proper distance between the tropane residues but may also be important for obtaining a conformation with molecular topology favorable for interaction at binding sites at neuronal nAChR ion channels. The high affinity of the decyl analogue **9j** relative to the other congeners is consistent with conformational activity relationships described for several classes of NMB agents [17]. However, this is in contrast to the structure-activity

relationships of bivalent epibatidine analogues in which the decyl analogues exhibited the lowest affinity for α4β2 subtype nAChRs [8]. Presumably this difference results from the diffenent connectivity of the tethering units to the bicyclic amine moieties. For the epibatidine derivatives **1**, the tether is directly connected to the nitrogen atoms, which results in a linear separation of the nitrogen atoms and closely approximates the separation of the binding sites on the ion channel. However for the tropanes, the tether is five atoms removed from the nitrogen atom. As such the relative orientation of the two nitrogen atoms can be quite varied. It is believed that the longer tethers offer greater conformational freedom and facilitate orientation of bulky tropane units into a conformation that is favorable for interaction at nAChRs.

To confirm that the potency of the bivalent ligands was impart due to tethering of the tropane residues, the mono esters **10** were prepared (Scheme 2) and evaluated at nAChRs. The butyl ester **10a** (K_i = 477 nM) was only 2-fold less potent than the bivalent congener **9c,** while the decyl ester **10b** (K_i = 2254 nM) exhibited a 16-fold decrease in affinity relative to the bivalent ester **9j**. Although these data indicated that there is little difference between the mono and bivalent ligands **10a** and **9c**, the effect of tethering the tropane residues appears to be significant for the decyl analogues and suggests that the decyl tether is optimum for this series for molecular recognition of a bis-tropane scaffold at neuronal nAChRs.

In summary, we have synthesized and identified a new class of bivalent neuronal nAChR ligands and have demonstrated that a ten-carbon tether between two tropane-3β-carboxylate residues afforded a compound with nanomolar affinity for nAChRs. These novel bivalent compounds will undoubtedly be useful as lead compounds and pharmacological probes to explore the structure-activity relationships of nAChR ion channel complexes. Further evaluation of these and other bivalent nAChR ligands is under investigation and will be reported in due course.

EXPERIMENTAL

All new compounds were characterized as the free base by ^{1}H nmr and ^{13}C nmr. The nmr spectra were recorded on a Varian-400 MHz spectrometer at ambient temperature in deuterio-chloroform with tetraamethylsilane as an internal standard. The oxalate salts were characterized by elemental analysis. C, H, N analysis were determined by Atlantic Microlabs, Inc., Norcross, GA. Melting points were recorded on a Hoover Mel-Temp apparatus and are uncorrected

General Procedure for the Preparation of Oxalate Salts. To a stirred solution of the bis-tropane (1 equiv.) in a tetrahydrofuran (10 ml) was added a solution of oxalic acid (2.2 equiv.) in tetrahydrofuran. The mixture was then cooled to 0 °C and allowed to stand for several hours. The white solid was filtered under vacuum and rinsed with several portions of ether. The amorphous solids were then dried thoroughly under reduced pressure (0.1 mm Hg) at 65°C.

Ethylene glycol bis-(trop-2-ene-3-carboxylate) (5a). To finely powdered (**4**) [14] (1.0 g, 6.0 mmol) in a 50 ml round bottom flask were added chloroform (10 ml) and thionyl chloride (1.8 ml, 24 mmol). The reaction was refluxed for 3 h under nitrogen. The solvent was removed under reduced pressure and the residue was flashed twice with benzene to afford the acid chloride. Without further purification, the crude acid chloride was added slowly to a vigorously stirred solution of diol (2.4 mmol) and anhydrous pyridine (3 ml). After complete addition, the mixture was heated to 110 ℃ under nitrogen for 16 h. The mixture was cooled to room temperature and water (10 ml) and dichloromethane (10 ml) were added to dissolve the mixture. The organic layer was separated and the aqueous phase was extracted with dichloromethane (3 × 10 ml). The organic layers were combined, dried (sodium sulfate) and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel-dichloromethane: methanol: triethylamine, 80:2:1, v/v). to afford 760 mg of **5a** (88%) as a white solid. mp 76-78 ℃; ir: 1715 (C=O), 1639 (C=C) cm^{-1}; ^{1}H nmr: δ 7.0 (d, 2H J = 5.6 Hz), 4.35 (s, 4H), 3.45 (t, 2H, J = 5.6 Hz), 3.36 (t, 2H, J = 5.6 Hz), 2.67 (dd, 2H, J = 18, 4.0 Hz), 2.36 (s, 6H), 2.29-2.15 (m, 2H), 2.14-2.07 (m, 2H), 1.95 (d, 2H, J = 18 Hz), 1.87 (td, 2H, J = 11, 2.4 Hz), 1.56-1.51 (m, 2H); ^{13}C nmr: δ 166.2 (2), 142.4(2), 125.9(2) 61.9(2), 58.8(2), 57.0(2), 36.2(2), 33.0(2), 30.3(2), 29.5 (2). *Anal*. Calcd for $C_{20}H_{28}N_2O_4$: C, 66.64; H, 7.83; N, 7.77. Found: C, 66.42; H, 7.96; N, 7.87.

1,3-Propanediol bis-(trop-2-ene-3-carboxylate) (5b). To finely powdered (**4**)[14] (3.1 g, 18.5 mmol) in a 100 ml round bottom flask were added chloroform (300 ml) and thionyl chloride (6 ml, 80 mmol). The reaction was refluxed for 3 h under nitrogen. The solvent was removed under reduced pressure and the residue was flashed twice with toluene to afford the acid chloride. Without further purification, the crude acid chloride was added together with 4-dimethylaminopyridine (30 mg) to a vigorously stirred solution of 1,3-propanediol (0.53 ml, 7.4 mmol) and anhydrous pyridine (10 ml). After complete addition, the mixture was stirred under nitrogen at room temperature for 24 h. Water (20 ml) and dichloromethane (20 ml) were added to dissolve the mixture. The organic layer was separated and the aqueous phase was extracted with dichloro-methane (3 × 20 ml). The organic layers were combined, dried (sodium sulfate) and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel-dichloromethane: methanol: triethylamine, 80:2:1, v/v) to afford 1.9 g of **5b** (71%) as a light brown oil. ^{1}H nmr: δ 7.01 (d, 2H, J = 5.6), 4.21 (t, 4H, J = 12.4 Hz), 3.41 (t, 2H, J = 5.6 Hz), 3.35 (t, 2H, J = 5.6 Hz), 2.64 (d, 2H, J = 18 Hz), 2.35 (s, 6H), 2.19-2.03 (m, 8H), 1.95-1.90 (m, 2H), 1.54 (m, 2H); ^{13}C nmr: δ 166.6, 141.8, 126.3, 61.0 (2), 58.9(2), 57.1(2), 36.1(2), 33.1(2), 30.4(2), 29.5(2), 28.0. Anal. Calcd for $C_{21}H_{30}N_2O_4$: C, 67.35; H, 8.07; N, 7.48. Found: C, 67.46; H, 8.08; N, 7.50.

General Procedure for the Synthesis of Diol bis(tropane-3α-carboxylate) (6). A suspension of (**5**) (1.0 g) and 10 % palladium on carbon (150 mg) in methanol (10 ml) was hydrogenated (60 psi) at room temperature for 3 days. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel-dichloromethane:methanol: triethylamine, 80:2:1, v/v). The ir and nmr spectra were recorded

for the freebase. The freebase was converted into the oxalate salt for analysis.

Ethylene glycol bis(tropane-3α-carboxylate) (6a). This compound was isolated as a colorless liquid (72%) and converted into the oxalate salt. Ir: 1727 (C=O) cm^{-1}; ^1H nmr: δ 4.34 (s, 4H), 3.07 (t, 4H, J = 3.4 Hz), 2.55 (tt, 2H, J = 8.4, 1Hz), 2.23 (s, 6H), 2.21 (ddd, 4H, J = 14.0, 2.0, 1 Hz), 1.95 (ddd, 4H, J = 14, 8, 3.2 Hz), 1.93-1.86 (m, 4H), 1.57-1.52 (m, 4H); ^{13}C nmr: δ 175.9 (2), 62.6 (4), 60.3 (2), 40.4 (2), 33.3 (2), 31.5 (4), 24.7 (4). *Anal.* Calcd for $C_{20}H_{32}N_2O_4 \bullet 2C_2H_2O_4 \cdot H_2O$: C, 51.24; H, 6.81; N, 4.98. Found: C, 51.16; H, 6.91; N, 5.02.

1,3-Propanediol bis(tropane-3α-carboxylate) (6b). This compound was isolated as a light brown oil (35%) and converted into the oxalate salt. ir: 1727 (C=O) cm^{-1}; ^1H nmr: δ 4.20 (t, 4H, J = 12.8 Hz), 3.07 (brs, 4H), 2.54 (t, 2H, J=12.8 Hz), 2.23 (s, 6H), 2.18 (brs, 2H), 2.05-2.00 (m, 8H), 1.93-1.89 (m, 4H), 1.56-1.54 (m, 4H); ^{13}C nmr: δ 175.8(2), 61.3(2), 60.2(4), 40.1(2), 33.1(4), 31.2(2), 27.9, 24.5(4). *Anal.* Calcd for $C_{21}H_{34}N_2O_4 \bullet 2C_2H_2O_4$: C, 53.76; H, 6.86; N, 5.03. Found: C, 54.18; H, 7.03; N, 5.12.

3α,3β´-Ethylene glycol bis(tropane-3-carboxylate) (7a). This compound was isolated as a colorless liquid (17%) and converted into the oxalate salt. ir: 1729 (C=O) cm^{-1}. ^1H nmr: δ 4.26 (brs, 4H), 3.16 (t, 2H, J = 3.2 Hz), 3.07 (t, 2H, J = 3.2 Hz), 2.60-2.51 (m, 2H), 2.25 (s, 3H), 2.23 (s, 3H), 2.20 (dd, 1H, J = 15, 2 Hz), 2.07-2.0 (m, 4H), 1.90-1.83 (m, 4H), 1.63 (ddd, 2H, J = 13, 6.0, 3.5 Hz), 1.57-1.51 (m, 4H); ^{13}C nmr: δ 176.0, 175.4, 62.6 (2), 62.3(2), 60.6, 60.3, 40.5, 40.0, 34.5, 33.4, 33.3(2), 31.5(2), 26.4(2), 24.8(2). *Anal.* Calcd for $C_{20}H_{32}N_2O_4 \bullet 2C_2H_2O_4 \bullet 2H_2O$: C, 49.65; H, 6.94; N, 4.82. Found: C, 49.93; H, 7.23; N, 4.77.

Ethylene glycol bis(tropane-3β-carboxylate) (9a). To finely powdered (**8**) [14] (1.0 g, 6.0 mmol) in a 50 ml round bottom flask were added chloroform (10 ml) and thionyl chloride (1.8 ml, 24 mmol). The reaction was refluxed for 3 h under nitrogen. The solvent was removed under reduced pressure and the residue was flashed twice with benzene to afford the acid chloride. Without further purification, the crude product was added slowly to a vigorously stirred solution of diol (2.4 mmol) and anhydrous pyridine (3 ml). After complete addition, the mixture was heated to 110 ℃ under nitrogen for 16 h. The mixture was cooled to room temperature and water (10 ml) and dichloromethane (10 ml) were added to dissolve any solids in the mixture. The organic layer was separated and the water phase was extracted with dichloromethane (3 × 10 ml). The organic layers were combined, dried (sodium sulfate) and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel-dichloromethane: methanol: triethylamine, 80:2:1, v/v) to afford 620 mg of **9a** (71%) as a white solid. mp 96-98 ℃; ir: 1732 (C=O) cm^{-1}; ^1H nmr δ 4.21 (s, 4H), 3.17 (t, 4H, J = 3.2Hz), 2.58 (tt, 2H, J = 13, 5.6 Hz), 2.27 (s, 6H), 2.05-2.01 (m, 4H), 1.88 (td, 4H, J = 13, 2.4 Hz), 1.63 (ddd, 4H, J = 13, 5.4, 3.2 Hz), 1.57-1.52 (m, 4H); ^{13}C nmr: δ 175.3(2), 62.3(4), 60.6(2), 40.0(2), 34.6(2), 33.4(4), 26.4(4). This compound was converted into the oxalate salt. Anal. Calcd for $C_{20}H_{32}N_2O_4 \bullet 2C_2H_2O_4$: C, 52.94; H, 6.66; N, 5.14. Found: C, 52.82; H, 6.84; N, 4.82.

General Procedure for the Synthesis of Diol bis(tropane-3β-carboxylate) (9b-j). To finely powdered (**8**) [14] (1 equiv.) in a round bottom flask were added chloroform (52 equiv.) and thionyl chloride (4 equiv.). The reaction was heated at reflux for 3 h under nitrogen. The solvent was removed under reduced pressure and the residue was flashed twice with toluene to afford the acid chloride. Without further purification, the crude acid chloride was added together with 4-dimethylaminopyridine (10%) to a vigorously stirred solution of diol (0.4 equiv.) and anhydrous pyridine (10 equiv.). After complete addition, the mixture was stirred and heated to dissolve any remaining solids. Heating and stirring were continued under nitrogen for 24 h to maintain a homogeneous mixture. The mixture was allowed to cool to room temperature, then water and dichloromethane were added to dissolve any solids present in the mixture. The organic layer was separated and the aqueous phase was extracted with dichloromethane. The organic layers were combined, dried (sodium sulfate) and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel-dichloromethane: methanol: triethylamine, 80:2:1, v/v) to afford **9b-j** as an oil. The ir and nmr spectra were recorded for the freebase. The freebase was converted into the oxalate salt for analysis.

1,3-Propanediol bis(tropane-3β-carboxylate) (9b). This compound was isolated as a light brown oil (60%) and converted into the oxalate salt ^1H nmr: δ 4.11 (t, 4H, J = 12.4 Hz), 3.27 (brs, 4H), 2.63-2.57 (m, 2H), 2.35 (s, 6H), 2.10-1.89 (m, 12H), 1.71-1.59 (m, 6H); ^{13}C nmr: δ 175.4(2), 60.8(2), 60.4(4), 39.8(2), 34.4(4), 33.1(2), 27.9, 26.1(4). *Anal.* Calcd for $C_{21}H_{34}N_2O_4 \bullet 2C_2H_2O_4$: C, 53.76; H, 6.86; N, 5.03. Found: C, 53.11; H, 7.03; N, 4.94.

1,4-Butanediol bis(tropane-3β-carboxylate) (9c). This compound was isolated as a light brown oil (66%) and converted into the oxalate salt. ^1H nmr: δ 4.07 (brs, 4H), 3.32 (brs, 4H), 2.65-2.56 (m, 2H), 2.38 (s, 6H), 2.12-2.10 (m, 4H), 2.05-1.97 (m, 4H), 1.73-1.64 (m, 12H); ^{13}C nmr: δ 174.7(2), 63.7(4), 60.5(2), 39.2(2), 33.8(4), 32.4(2), 25.6(4), 25.0(2). *Anal.* Calcd for $C_{22}H_{36}N_2O_4 \bullet 2C_2H_2O_4 \bullet H_2O$: C, 52.88; H, 7.17; N, 4.74. Found: C, 52.92; H, 7.21; N, 4.94.**2-Butene-1, 4-diol bis(tropane-3β-carboxylate) (9d).** This compound was isolated as a light brown oil (73%) and converted into the oxalate salt. ^1H nmr: δ 5.70 (t, 2H, J = 8.4Hz), 4.64 (d, 4H, J = 4.8 Hz), 3.20 (brs, 4H), 2.64-2.55 (m, 2H), 2.29 (s, 6H), 2.06-2.03 (m, 4H), 1.94-1.87 (m, 4H), 1.67-1.62 (m, 4H), 1.59-1.53 (m, 4H); ^{13}C nmr: δ 175.0(2), 128.0(2), 60.3(4), 59.8(2), 39.7(2), 34.2(4), 32.9(2), 26.1(4). *Anal.* Calcd for $C_{22}H_{34}N_2O_4 \bullet 2C_2H_2O_4 \bullet H_2O$: C, 53.06; H, 7.19; N, 4.76. Found: C, 54.86; H, 7.23; N, 5.00.

1,5-Pentanediol bis(tropane-3β-carboxylate) (9e). This compound was isolated as a light brown oil (63%) and converted into the oxalate salt. ^1H nmr: δ 4.04 (t, 4H, J = 13.2 Hz), 3.19 (brs, 4H), 2.63-2.54 (m, 2H), 2.29 (s, 6H), 2.06-2.04 (m, 4H), 1.94-1.84 (m, 4H), 1.66-1.54 (m, 12H), 1.42-1.34 (m, 2H); ^{13}C nmr: δ 175.5(2), 64.1(2), 60.4(4), 39.8(2), 34.4(4), 33.2(2), 28.2(2), 26.1(4), 22.4. *Anal.* Calcd for $C_{23}H_{38}N_2O_4 \bullet 2C_2H_2O_4 \bullet 1/2H_2O$: C, 54.45; H, 7.28; N, 4.70. Found: C, 54.60; H, 7.23; N, 4.80.

1,6-Hexanediol bis(tropane-3β-carboxylate) (9f). This compound was isolated as a light brown oil (68%) and converted into the oxalate salt. ^1H nmr: δ 4.04 (t, 4H, J = 13.2), 3.19 (brs, 4H), 2.62-2.54 (m, 2H), 2.29 (s, 6H), 2.06-2.03 (m, 4H), 1.94-1.87 (m, 4H), 1.67-1.54 (m, 12H), 1.39-1.33 (m, 4H); ^{13}C nmr: δ 175.5(2), 64.2(2), 60.4(4), 39.8(2), 34.4(4), 33.1(2), 28.5(2), 26.1(4), 25.5(2). *Anal.* Calcd for $C_{24}H_{40}N_2O_4 \bullet 2C_2H_2O_4 \bullet H_2O$: C, 54.39; H, 7.50; N, 4.53. Found: C, 54.60; H, 7.81; N, 4.56.

1,7-Heptanediol bis(tropane-3β-carboxylate) (9g). This compound was isolated as a light brown oil (70%) and converted into the oxalate salt. ^1H nmr: δ 4.04 (t, 4H, J = 13.2 Hz), 3.19 (brs, 4H), 2.62-2.54 (m, 2H), 2.29 (s, 6H), 2.05-2.02 (m, 4H), 1.93-1.87 (m, 4H), 1.67-1.54 (m, 12H), 1.34-1.32 (m, 6H); ^{13}C

nmr: δ 175.5(2), 64.3(2), 60.4(4), 39.8(2), 34.4(4), 33.1(2), 28.8, 28.5(2), 26.1(4), 25.7(2). *Anal.* Calcd for $C_{25}H_{42}N_2O_4 \cdot 2C_2H_2O_4 \cdot 1/2H_2O$: C, 55.84; H, 7.60; N, 4.49. Found: C, 55.79; H, 7.61; N, 4.56.

1,8-Octanediol bis(tropane-3β-carboxylate) (9h). This compound was isolated as a light brown oil (52%) and converted into the oxalate salt. ^{1}H nmr: δ 4.04 (t, 4H, J = 13.2 Hz), 3.19 (brs, 4H), 2.62-2.54 (m, 2H), 2.29 (s, 6H), 2.05-2.03 (m, 4H), 1.94-1.87 (m, 4H), 1.67-1.54 (m, 12H), 1.30-1.26 (m, 8H); ^{13}C nmr: δ 175.6(2), 64.4(2), 60.4(4), 39.8(2), 34.4(4), 33.2(2), 29.1(2), 28.6(2), 26.1(4) 25.8(2). *Anal.* Calcd for $C_{26}H_{44}N_2O_4 \cdot 2C_2H_2O_4$: C, 57.31; H, 7.70; N, 4.45. Found: C, 57.75; H, 7.67; N, 4.49.

1,9-Nonanediol bis(tropane-3β-carboxylate) (9i). This compound was isolated as a light brown oil (86%) and converted into the oxalate salt. ^{1}H nmr: δ 4.04 (t, 4H, J = 14.0 Hz), 3.24 (brs, 4H), 2.62-2.55 (m, 2H), 2.33 (s, 6H), 2.08-2.06 (m, 4H), 1.98-1.92 (m, 4H), 1.69-1.56 (m, 12H), 1.29 (brs, 10H); ^{13}C nmr: δ 175.2(2), 64.3(2), 60.4(4), 39.5(2), 34.1(4), 32.8(2), 29.1, 28.9(2), 28.4(2), 25.9(1), 25.6(2). *Anal.* Calcd for $C_{27}H_{46}N_2O_4 \cdot 2C_2H_2O_4$: C, 57.93; H, 7.84; N, 4.36. Found: C, 57.95; H, 7.81; N, 4.51.

1,10-Decanediol bis(tropane-3β-carboxylate) (9j). This compound was isolated as a light brown oil (74%) and converted into the oxalate salt. ^{1}H nmr: δ 4.04 (t, 4H, J = 13.6 Hz), 3.19 (brs, 4H), 2.62-2.53 (m, 2H), 2.29 (s, 6H), 2.06-2.02 (m, 4H), 1.94-1.87 (m, 4H), 1.68-1.54 (m, 12H), 1.28-1.27 (m, 12H); ^{13}C nmr: δ 175.6(2), 64.4(2), 60.4(4), 39.8(2), 34.4(4), 33.2(2), 29.4(2), 29.2(2), 28.6(2), 26.1(4), 25.8(2). *Anal.* Calcd for $C_{28}H_{48}N_2O_4 \cdot 2C_2H_2O_4 \cdot 1/2H_2O$: C, 57.31; H, 7.70; N, 4.45. Found: C, 57.75; H, 7.67; N, 4.49.

General Procedure for the Synthesis of tropane-3β-carboxylate esters. To finely powdered (**8**) [14] (1 equiv.) in a round bottom flask were added chloroform (52 equiv.) and thionyl chloride (4 equiv.). The reaction was heated at reflux for 3 h under nitrogen. The solvent was removed under reduced pressure and the residue was flashed twice with toluene to afford the acid chloride. Without further purification, the crude acid chloride was added together with 4-dimethylaminopyridine (10%) to a vigorously stirred solution of alcohol (1.2 equiv.) and anhydrous pyridine (10 equiv.). After complete addition, the mixture was stirred and heated to dissolve any remaining solids. Heating and stirring were continued under nitrogen for 24 h to maintain a homogeneous mixture. The mixture was allowed to cool to room temperature, then water and dichloromethane were added to dissolve any solids present in the mixture. The organic layer was separated and the aqueous phase was extracted with dichloromethane. The organic layers were combined, dried (sodium sulfate) and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel-dichloromethane: methanol: triethylamine, 80:2:1, v/v) to afford **10a-b** as an oil. The ir and nmr spectra were recorded for the freebase. The freebase was converted into the oxalate salt for analysis.

***n*-Butyl 8-methyl-8-azabicyclo[3.2.1]octan-3β-carboxylic acid ester (10a).** This compound was isolated as a colorless oil (73%) and converted into the oxalate salt. ^{1}H nmr: δ 4.05 (t, 2H, J = 13.2Hz), 3.19(brs, 2H), 2.63-2.54(m, 1H), 2.30(s, 3H), 2.05-2.03(m, 2H), 1.94-1.88(m, 2H), 1.67-1.56(m, 6H), 1.41-1.34(m, 2H), 0.92(t, 3H, J=15.2Hz); ^{13}C nmr: δ 175.6, 64.2, 60.4(2), 39.7, 34.4(2), 33.1, 30.6, 26.1(2), 19.1, 13.6. *Anal.* Calcd for $C_{13}H_{23}NO_2 \cdot C_2H_2O_4 \cdot 1/2\,H_2O$: C, 55.53; H, 8.08; N, 4.32. Found: C, 55.21; H, 8.08; N, 4.21.

***n*-Decyl 8-methyl-8-azabicyclo[3,2,1]octan-3β-carboxylic acid ester (10b).** This compound was isolated as a colorless oil (74%) and converted into the oxalate salt. ^{1}H nmr: δ 4.03 (t, 2H, J = 13.2Hz), 3.20-3.19(m, 2H), 2.62-2.54(m, 1H), 2.30(s, 3H), 2.06-2.02(m, 2H), 1.95-1.88(m, 2H), 1.67-1.54(m, 6H), 1.26(brs, 14H), 0.88(t, 3H, J=13.6Hz); ^{13}C nmr: δ 175.6, 64.5, 60.4(2), 39.7, 34.4(2), 33.1, 31.8, 29.3, 29.2(2), 28.6, 26.1(2), 25.9, 22.6, 15.9, 14.1. *Anal.* Calcd for $C_{19}H_{35}NO_2 \cdot 2HCl \cdot 1/2H_2O$: C, 64.27; H, 10.50; N, 3.95. Found: C, 63.81; H, 10.47; N, 3.90.

Acknowledgment. The authors are grateful to the National Institute on Drug Abuse for the financial support of this research.

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