JOC*Note*

Stereoselective Syntheses of the Three Isomers of Ethylene Glycol Bis(tropane-3-carboxylate)

Jie Cheng, Zakhia Moore, Edwin D. Stevens, and Mark L. Trudell*

Department of Chemistry, University of New Orleans, New Orleans, Louisiana 70148

mtrudell@uno.edu

Received March 11, 2002

Abstract: Three epimers of ethylene glycol bis(tropane-3-carboxylate) (3α,3α′-, 3α,3*β*′-, 3*β*,3*β*′-) have been synthesized by starting from 3-tropinone. 3-Tropinone was converted into the corresponding enol triflate and then subjected to palladium-catalyzed alkoxycarbonylation to provide the key intermediate methyl trop-2-ene-3-carboxylate in good yield. Stereoselective routes were developed to afford the three stereoisomers of ethylene glycol bis(tropane-3-carboxylate).

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.[1−4] 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, Tourettes syndrome, anxiety, and depression.[1−4] 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 therapy. Therefore, the search for potent and selective nAChR agents is an extremely important endeavor that will provide pharmacological tools for the study of nAChR functions as well as to provide therapeutic agents and medications for the treatment of a variety of neurological diseases.

Recently, Gyermek and co-workers reported bisquaternary ammonium tropinyl diesters (**1**; Figure 1) as a new class of neuromuscular blocking (NMB) agents with modest side effects.[5] However, to our knowledge, there have been no reports of ditropane carboxylate derivatives as potential nAChR ligands. This prompted an investigation of the synthetic scope and biological activities of a series of ditropane derivatives. Herein, we report the synthesis of the three ethylene glycol bis(tropane-3-carboxylate) epimers (**2**).

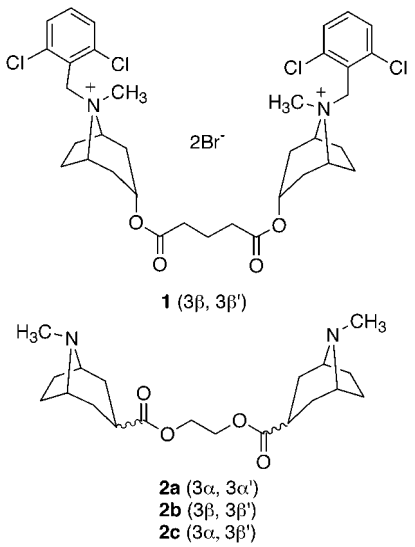


FIGURE 1. Ethylene glycol bis(tropane-3-carboxylate) stereoisomers.

The synthesis of the desired stereoisomers of ethylene glycol bis(tropane-3-carboxylate) first required the preparation of the two stereoisomeric intermediates, *endo*- and *exo*-tropane-3-carboxylic acids. It was envisaged that the stereoselective synthesis of ditropanecarboxylate derivatives would proceed efficiently from the corresponding tropane-3-caboxylic acid and avoid the potentially difficult separation of isomeric ditropane carboxylates. To date, there have been very few efficient synthetic methods that stereoselectively afford *endo*- and *exo*-tropane-3-carboxylic acids.[6,7] As illustrated in Scheme 1, the preparation of the tropane-3-carboxylic acids was achieved via a convenient approach starting from commercially available 3-tropinone (**3**). Tropinone (**3**) was converted into the corresponding enol triflate (**4**) with sodium bis(trimethylsilyl)amide and *N*-phenyltrifluoromethanesulfonimide in THF at −78 °C in 90% yield. Palladium-catalyzed methoxycarbonylation[8−13] of **4** was then envisaged to furnish the methyl trop-2-ene-3-carboxylate (**5**).[6]

As summarized in Table 1, it was determined after a survey of several reaction conditions/Pd-ligand systems that an optimum yield of **5** could be achieved under a

(1) Arneric, S. P., Brioni, J. D., Eds. *Neuronal Nicotinic Receptors: Pharmacology and Therapeutic Opportunities*; John Wiley & Sons Inc.: New York, 1999 and references therein.
(2) Lloyd, G. K.; Williams, M. *J. Pharmacol. Exp. Ther.* **2000**, *292*, 461−467.
(3) Holladay, M. W.; Dart, M. J.; Lynch, J. K. *J. Med. Chem.* **1997**, *40*, 4169−4194.
(4) McDonald, I. A.; Cosford, N.; Vernier, J.-M. *Annu. Rep. Med. Chem.* **1995**, *30*, 41−49.
(5) Gyermek, L.; Lee, C.; Nguyen, N. *Acta Anaesthesiol. Scand.* **1999**, *43*, 651−657.
(6) Zirkle, C. L.; Geissman, T. A.; Bloom, M.; Craig, P. N.; Gerns, F. R.; Indik, Z. K.; Pavloff, A. M. *J. Org. Chem.* **1962**, *27*, 1269−1279.
(7) Willstatter, R. *Ber. Dtsch. Chem. Ges.* **1896**, *29*, 1575, 2216.
(8) For a review, see: Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry: A Guide for the Synthetic Chemist*; Elsevier Science: Amsterdam, 2000, and references therein.
(9) Tsuji, J. *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*; John Wiley & Sons. Inc.: New York, 1996; pp 188−209 and references therein.
(10) Ganjee, A.; Zeng, Y.; McGuire, J. J.; Kisliuk, R. L. *J. Med. Chem.* **2002**, *45*, 1942−1948.
(11) Song, J. J.; Yee, N. K. *J. Org. Chem.* **2001**, *66*, 605−608.
(12) Cacchi, S.; Ciattini, G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1986**, *27*, 3931−3934.
(13) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1985**, *26*, 1109−1112.

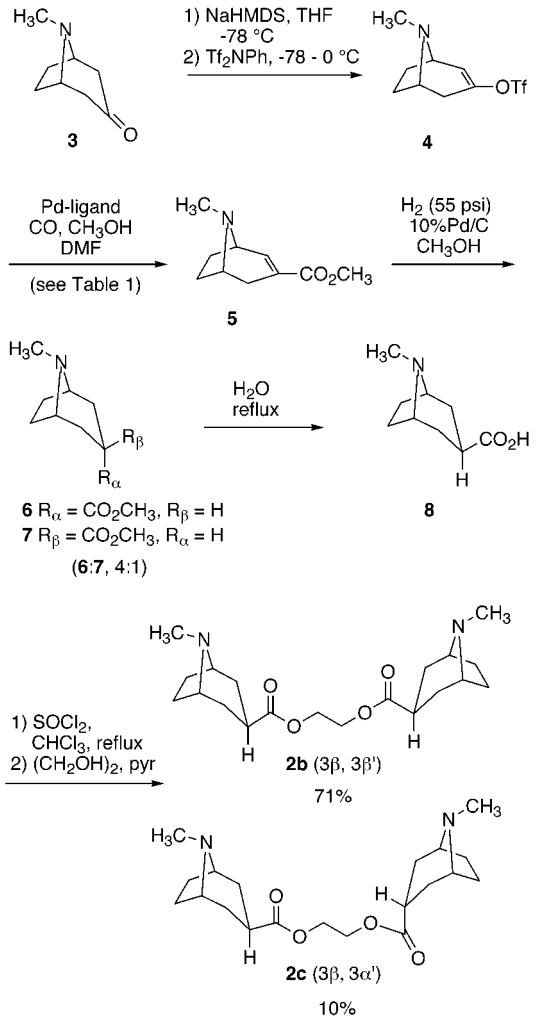
10.1021/jo020170p CCC: $22.00
Published on Web 06/28/2002

TABLE 1. Pd−Ligand-Catalyzed Methoxycarbonylation of 4[a]

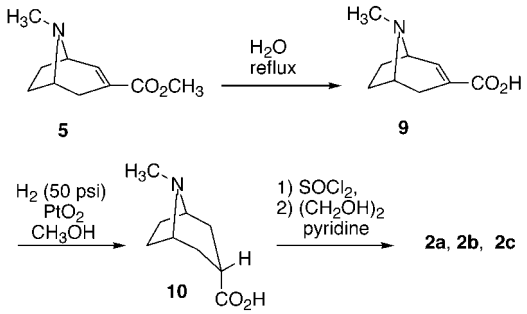
entry	Pd−ligand	base	*T* (°C)	solvent	time (h)[b]	yield (%)[c]
1	$Pd(OAc)_2/PPh_3$	Et_3N	rt	CH_3OH, DMF	10	51
2	$Pd(OAc)_2$/dppp	Et_3N	80	CH_3OH, DMF	20	3.8
3	$Pd(OAc)_2$/BINAP	Et_3N	80	CH_3OH, DMF	18	22
4	$Pd(OAc)_2$/dppf	Et_3N	rt	CH_3OH, DMF	18	65
5	$Pd(OAc)_2$/dppf	Et_3N	rt	CH_3OH, DMSO	18	25
6	$Pd(OAc)_2$/dppf	KOAc[d]	50	CH_3OH, DMSO	18	16

[a] Typical reaction conditions: Pd (3 mol %); ligand (6 mol %); **4** (2 mmol); base (4 mmol); CH_3OH (3 mL); DMF (2 mL). [b] The enol triflate **4** was completely consumed while monitored by TLC. [c] Isolated yields. [d] A 3 equiv amount of KOAc was added.

SCHEME 1



SCHEME 2



CO(g) atmosphere (1 atm) in methanol/DMF, with $Pd(OAc)_2$ (3 mol %) and 1,2′-bis(diphenylphosphino)ferrocene (dppf, 6 mol %) (entry 4). These conditions furnished **5** in 65% yield after workup and bulb-to-bulb distillation.

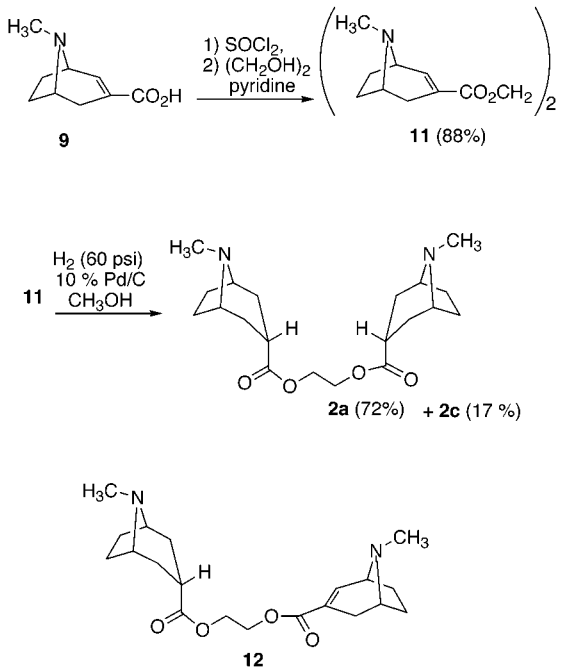
One limitation of the reaction was found to be the concentration of methanol necessary for complete conversion. Generally, a 30-fold excess of methanol was required for high yields of **5**. This suggested that high boiling or highly functionalized alcohols would be of limited use in this system.

Hydrogenation (55 psi) of the tropene ester **5** over 10% Pd/C gave a mixture of *endo*- and *exo*-methyl tropane-3-carboxylate (4:1 *endo*-**6**−*exo*-**7**). Hydrolysis of the epimeric mixture afforded the *exo*-tropane-3-carboxylic acid (**8**) as a single isomer in 95% yield over two steps.[6] Treatment of **8** with thionyl chloride in refluxing chloroform furnished the corresponding acid chloride, and without purification the acid chloride was added slowly to a solution of ethylene glycol in pyridine. This furnished the desired ethylene glycol bis(tropane-3β-carboxylate) (**2b**) in 71% yield. In addition a 10% yield of the 3β,3α'-ethylene glycol bis(tropane-3-carboxylate) (**2c**) was formed resulting from the acid-catalyzed epimerization of the 3β-carbonyl group of **2b** or **8**. Reaction yields were found to be higher in concentrated solution (2 M). Higher dilutions of the acid chloride in pyridine led to lower yields of the ethylene glycol bis(tropane-3-carboxylates). The stereochemical assignment of **2b,c** was confirmed by one-dimensional ^1H and ^{13}C NMR spectroscopy, selective proton decoupling, and two-dimensional COSY and NOESY spectroscopic techniques. In addition, the structure of **2b** was unequivocally established by X-ray crystallography.

The synthesis of the ethylene glycol bis(tropane-3α-carboxylate) (**2a)** was initially envisaged to proceed in a fashion similar to **2b**. As illustrated in Scheme 2, the methyl ester **5** was hydrolyzed in refluxing distilled water to give the trop-2-ene-3-carboxylic acid (**9**) in nearly quantitative yield. Direct preparation of **9** via carbonylation of **4** [$Pd(OAc)_2$, KOAc, CO(g), DMF] was also attempted. However, the an intractable mixture was obtained. Hydrogenation (50 psi) of **9** over Adam's catalyst in methanol provided the *endo*-tropane-3-carboxylic acid (**10**) in 98% yield.[6] Attempted direct esterification of **10** with DCC/DMAP and ethylene glycol in DMF resulted in low yields (<10%) of the desired ester **2a**. In addition, conversion of **10** into the acid chloride and concomitant esterification afforded a mixture of the epimeric dimers **2a**−**c**.

As an alternative route to avoid epimerization of **10**, hydrogenation of the ethylene glycol bis(trop-2-ene-3-carboxylate) (**11**), was envisaged to afford the 3α,3α'-diester **2a**. Initially, the synthesis of **11** was attempted from the enol triflate **4** and ethylene glycol using the palladium alkoxycarbonylation chemistry developed for

SCHEME 3



the methyl ester **5**. However, the required stoichiometry of the enol triflate **4** and ethylene glycol (2:1) was not compatible with the reaction conditions and only very low yields of **11** were obtained.

The ethylene glycol bis(trop-2-ene-3-carboxylate) (**11**) was then indirectly prepared from the tropene carboxylic acid **9** using the thionyl chloride/ethylene glycol−pyridine procedure (Scheme 3). The ethylene glycol bis(trop-2-ene-3-carboxylate) (**11**) was obtained in 88% yield as the sole product. Subsequent hydrogenation (60 psi) of **11** over 10% Pd/C in methanol for 3 days provided the desired 3α,3α′-diester **2a** in 72% yield. In addition, the 3*β*, 3α′-diester epimer **2c** was obtained in 17% yield and trace amounts (<10%) of the methyl tropane-3-carboxylates **6** and **7** that resulted from transesterification were identified. Alternatively, treatment of **11** with samarium iodide[14] proved to be less effective and only afforded a 20% yield of compound **2a** and an 18% yield of the partially reduced diester **12**.

In conclusion, an efficient procedure was developed for the facile synthesis of trop-2-ene-3-carboxylic acid derivatives from 3-tropinone. Furthermore, the trop-2-ene-3-carboxylic acid derivatives were stereoselectively converted into the tropane-3-carboxylic acids **8** and **10** as well as the ethylene glycol bis(tropane-3-carboxylate) epimers **2a,b** in good overall yields. The biological activity of **2a**−**c** at nAChRs is currently under investigation and will be reported elsewhere in due course.

Experimental Section

The spectral data for all compounds are reported for the free base. The free base of **2a**−**c** was then converted into the oxalate salt to give a hygroscopic solid used for microanalysis and biological testing. Melting points are uncorrected. Microanalyses for C, H, and N were performed by Atlantic Microlabs Inc., Norcross, GA.

Trop-2-ene-3-trifluoromethylsulfonate (4). Tropinone (**3**) (7.0 g, 50 mmol) was dissolved in anhydrous THF (30 mL) under N_2. After the solution was cooled to −78 °C, sodium bis-(trimethylsilyl)amide (1.0 M solution in THF, 63 mL, 63 mmol) was added dropwise via syringe. After the mixture was stirred for 3 h, *N*-phenyltrifluoromethanesulfonamide (22 g, 63 mmol) was added under nitrogen. The reaction was stirred for 30 min at −78 °C, and then warmed to 0 °C. The reaction was allowed to warm slowly to room temperature and stirred overnight. The solvent was removed from the reaction, and the residue was purified by flash chromatography (EtOAc) to furnish **4** as a yellow oil (12 g, 90%): R_f = 0.18 (EtOAc); ^{1}H NMR(400 MHz, $CDCl_3$) δ 5.85 (d, J = 5.6 Hz, 1H), 3.47 (t, J = 5.6 Hz, 1H), 3.44−3.42 (m, 1H), 2.82 (dd, J = 17.2, 3.2 Hz, 1H), 2.41 (s, 3H), 2.24−2.16 (m, 1H), 2.12−2.02 (m, 1H), 1.97−1.91 (m, 2H), 1.67−1.61 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 145.8, 129.4, 120.1, 58.5, 57.8, 35.1, 34.0, 33.2, 29.5; IR ($CHCl_3$) 1678 cm^{-1}; MS (EI) *m*/*z* 271 (M^+, 13), 110 (100).

Methyl trop-2-ene-3-carboxylate (5).[6] A mixture of **4** (540 mg, 2.0 mmol), $Pd(OAc)_2$ (13 mg, 0.06 mmol), dppf (6.5 mg, 0.12 mmol), Et_3N (560 μL, 4 mmol), and CH_3OH (3.0 mL, 74 mmol) in DMF (2 mL) was purged with CO(g) for 5 min and stirred under a CO(g) balloon at room temperature for 18 h. The mixture was concentrated, and the residue was dissolved in Et_2O (10 mL) and saturated aqueous Na_2CO_3 (10 mL). The aqueous layer was separated, and the organic layer was washed with water (2 × 10 mL). Each aqueous layer was extracted with ether (3 × 10 mL). The organic layers were combined, washed with brine and dried over Na_2SO_4. The solvent was removed under vacuum, and the resulting liquid was purified by vacuum bulb-to-bulb distillation (Kugelrohr) at 70−75 °C, 0.30 mmHg (lit.[6] bp 131−134 °C, 15 mmHg). This afforded **5** as a colorless liquid (235 mg, 65%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (d, J = 5.2 Hz, 1H), 3.69 (s, 3H), 3.38 (t, J = 5.2 Hz, 1H), 3.30 (t, J = 5.6 Hz, 1H), 2.63 (dd, J = 18, 4.0 Hz, 1H), 2.32 (s, 3H), 2.20−2.11 (m, 1H), 2.10−2.01 (m, 1H), 1.92 (d, J = 18 Hz, 1H), 1.84 (dt, J = 11, 2.8 Hz, 1H), 1.52−1.46 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 167.1, 144.8, 126.1, 58.8, 57.0, 51.5, 36.1, 33.2, 30.3, 29.7; IR ($CHCl_3$) 1715, 1639 cm^{-1}; MS (EI) *m*/*z* 181 (M^+, 42), 152 (100).

Tropane-3*β*-carboxylic Acid (8).[6] A suspension of **5** (1.0 g, 5.5 mmol) and 10% Pd/C (100 mg) in methanol (10 mL) was hydrogenated (55 psi) at room temperature for 18 h. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure to give the crude saturated product methyl tropane-3-carboxylate (1.0 g) (4:1 *endo*-**6**−*exo*-**7**, by ^{1}H NMR). The mixture was dissolved in H_2O (30 mL), and the solution was refluxed for 3 h. The water was evaporated under vacuum to dryness, and the white solid was dried further under vacuum at 50 °C over P_2O_5 for 24 h. This afforded crude **8** (1.0 g, 98%), which without further purification was used in the next step. An analytical sample was obtained by recrystallization from EtOH: mp 220−222 °C (lit.[6] mp 219−220 °C); ^{1}H NMR (400 MHz, D_2O) (*N*-invertomers, 6:1) δ 3.78 (brs, 1.72H), 3.70 (s, 0.28H), 2.67−2.61 (m, 1H), 2.60 (s, 2.58H), 2.57 (s, 0.42H), 2.19−2.14 (m, 2H), 1.94−1.89 (m, 4H), 1.86−1.85 (m, 2H); ^{13}C NMR (75.5 MHz, D_2O) δ 180.5, 63.6, 60.0, 38.5, 33.7, 32.3, 32.9, 25.6, 25.5, 23.6; IR (film) 3427, 2530, 1664 cm^{-1}. Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.93; N, 8.28. Found: C, 63.56; H, 9.04; N, 8.31.

Ethylene Glycol Bis(tropane-3*β*-carboxylate) (2b). To finely powered **8** (1.0 g, 6.0 mmol) in a 50 mL round-bottom flask were added $CHCl_3$ (10 mL) and $SOCl_2$ (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 ethylene glycol (130 μL, 2.4 mmol) and dried pyridine (3 mL). After complete addition, the mixture was heated to 110 °C under nitrogen for 16 h. The mixture was cooled to room temperature, and H_2O (10 mL) and CH_2Cl_2 (10 mL) were added to dissolve the mixture. The organic layer was separated, and the water phase was extracted with CH_2Cl_2 (3 × 10 mL).

(14) Keverline-Frantz, K. I.; Boja, J. W.; Kuhar, M. J.; Abraham, P.; Burgess, J. P.; Lewin, A. H.; Carroll, F. I. *J. Med. Chem*. **1998**, *41*, 247−257.

The organic layers were combined, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (80:2:1 CH_2Cl_2−CH_3OH−Et_3N) to give **2b** as a white solid (612 mg, 71%): mp 96−98 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 (s, 4H), 3.17 (t, J = 3.2 Hz, 4H), 2.58 (tt, J = 13, 5.6 Hz 2H), 2.27 (s, 6H), 2.05−2.01 (m, 4H), 1.88 (td, J = 13, 2.4 Hz, 4H), 1.63 (ddd, J = 13, 5.4, 3.2 Hz, 4H), 1.57−1.52 (m, 4H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 175.3 (2), 62.3 (4), 60.6 (2), 40.0 (2), 34.6 (2), 33.4 (4), 26.4 (4); IR ($CHCl_3$) 1732 cm^{-1}. Anal. Calcd for $C_{20}H_{32}N_2O_4$: C, 65.91; H, 8.85; N, 7.69. Found: C, 65.82; H, 8.84; N, 7.82.

3*β*, 3α′-Ethylene glycol bis(tropane-3-carboxylate) (2c) formed as a colorless liquid (83 mg, 10%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.26 (brs, 4H), 3.16 (t, J = 3.2 Hz, 2H), 3.07 (t, J = 3.2 Hz, 2H), 2.60−2.51 (m, 2H), 2.25 (s, 3H), 2.23 (s, 3H), 2.20 (dd, J = 15, 2 Hz, 1H), 2.07−2.0 (m, 4H), 1.90−1.83 (m, 4H), 1.63 (ddd, J = 13, 6.0, 3.5 Hz, 2H), 1.57−1.51 (m, 4H); ^{13}C NMR (75.5 MHz, $CDCl_3$) 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); IR ($CHCl_3$) 1729 cm^{-1}. Anal. Calcd for $C_{20}H_{32}N_2O_4 \cdot 2C_2H_2O_4 \cdot 2H_2O$: C, 49.65; H, 6.94; N, 4.82. Found: C, 49.93; H, 7.23; N, 4.77.

Trop-2-ene-3-carboxylic Acid (9).[6] A solution of **5** (3.6 g, 20 mmol) in distilled water (30 mL) was refluxed for 3 h. The water was evaporated under vacuum to dryness, and the white solid was further dried over P_2O_5 under vacuum at 50 °C for 24 h. This afforded the crude acid **9** (3.1 g, 93%) with >98% purity, which without further purification was used in the next step. An analytical sample was obtained by recrystallization from CH_3OH: mp > 350 °C (lit.[6] mp > 350 °C); ^{1}H NMR (400 MHz, D_2O) (rotomers, 2:1) δ 6.55 (d, J = 6.0 Hz, 0.67H), 6.44 (d, J = 5.6 Hz, 0.33H), 4.06 (t, J = 5.6 Hz, 0.33H), 3.99 (t, J = 5.2 Hz, 0.67H), 3.92−3.85(m, 1H), 2.84 (dd, J = 18, 3.6 Hz, 1H), 2.69 (s, 0.99H), 2.66 (s, 2.01H), 2.34−2.08 (m, 4H), 1.83−1.76 (m, 1H); ^{13}C NMR (75.5 MHz, D_2O) δ 173.5, 132.7, 132.5, 132.4, 128.4, 62.3, 61.5, 60.1, 58.8, 38.0, 34.7, 32.2 (2), 29.9, 29.6, 27.6, 25.5; IR (film) 3445, 2539, 1651, 1563 cm^{-1}. Anal. Calcd for $C_9H_{15}NO_2 \cdot H_2O$: C, 58.36; H, 8.16; N, 7.56. Found: C, 57.98; H, 8.02; N, 7.43.

8-Methyl-8-azabicyclo[3.2.1]octane-3α-carboxylic Acid (10).[6] A suspension of **9** (300 mg, 1.8 mmol) and PtO_2 (21 mg) in CH_3OH (8 mL) was hydrogenated (50 psi) at room temperature for 18 h. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure to give the saturated crude product **10** (300 mg, 98%) with >98% purity. An analytical sample was obtained by recrystallization from CH_3OH: mp 244−246 °C (lit.[6] mp 233 °C); ^{1}H NMR δ (400 MHz, D_2O) (rotomers, 9:1) 3.64 (s, 1.8H) 3.61 (s, 0.2H) 2.52 (s, 2.7H) 2.51 (s, 0.3H), 2.37 (d, J = 15 Hz, 2H), 2.29 (tt, J = 7.6, 1.2 Hz, 1H), 2.04−1.96 (m, 4H), 1.91 (d, J = 12 Hz, 2H); ^{13}C NMR (75.5 MHz, D_2O) δ 181.6, 63.2, 59.3, 38.3, 33.2, 32.6, 30.9, 24.4, 23.6, 22.4; IR (film) 3419, 2527, 1650 cm^{-1}. Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.93; N, 8.28. Found: C, 63.96; H, 8.85; N, 8.04.

Ethylene Glycol Bis(trop-2-ene-3-carboxylate) (11). To finely powered **9** (1.0 g, 6.0 mmol) in a 50 mL round-bottom flask were added $CHCl_3$ (10 mL) and $SOCl_2$ (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 ethylene glycol (130 μL, 2.4 mmol) and pyridine (3 mL). After complete addition, the mixture was heated to 110 °C under nitrogen for 16 h. The mixture was cooled to room temperature, and H_2O (10 mL) and CH_2Cl_2 (10 mL) were added to dissolve the mixture. The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography to afford **11** (760 mg, 88%) as a white solid: mp 76−78 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.0 (d, J = 5.6 Hz, 2H), 4.35 (s, 4H), 3.45 (t, J = 5.6 Hz, 2H), 3.36 (t, J = 5.6 Hz, 2H), 2.67 (dd, J = 18, 4.0 Hz, 2H), 2.36 (s, 6H), 2.29−2.15 (m, 2H), 2.14−2.07 (m, 2H), 1.95 (d, J = 18 Hz, 2H), 1.87 (td, J = 11, 2.4 Hz, 2H), 1.56−1.51 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) 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); IR ($CHCl_3$) 1715, 1639 cm^{-1}. 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.

Ethylene Glycol Bis(tropane-3α-carboxylate) (2a). Method A. A suspension of **11** (1.0 g, 2.8 mmol) and 10% Pd/C (150 mg) in CH_3OH (10 mL) was hydrogenated (50 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 (80:2:1 CH_2Cl_2−CH_3OH−Et_3N). This furnished **2a** as a colorless liquid (625 mg, 72%): ^{1}H NMR ($CDCl_3$) δ 4.34 (s, 4H), 3.07 (t, J = 3.4 Hz, 4H), 2.55 (tt, J = 8.4, 1 Hz, 2H), 2.23 (s, 6H), 2.21 (ddd, J = 14.0, 2.0, 1 Hz, 4H), 1.95 (ddd, J = 14, 8, 3.2 Hz, 4H), 1.93−1.86 (m, 4H), 1.57−1.52 (m, 4H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 175.9 (2), 62.6 (4), 60.3 (2), 40.4 (2), 33.3 (2), 31.5 (4), 24.7 (4); IR ($CHCl_3$) 1727 cm^{-1}. Anal. Calcd for $C_{20}H_{32}N_2O_4 \cdot 2C_2H_2O_4 \cdot H_2O$: C, 51.24; H, 6.81; N, 4.98. Found: C, 51.16; H, 6.91; N, 5.02.

Method B. To a solution of **11** (0.70 g, 1.9 mmol) in THF (5 mL) at −30 °C under argon was added dropwise a solution of SmI_2 (0.1 M in THF, 78 mL, 7.8 mmol). After the mixture was stirred for 30 min, CH_3OH (anhydrous, 10 mL) was added and the new mixture was stirred for 4 h. TLC analysis indicated the starting material had been consumed. The mixture was quenched with TFA (2 mL) and H_2O (37 mL). After being warmed to room temperature, the mixture was adjusted to pH = 11 with NH_4OH and filtered through Celite. Et_2O and saturated Na_2CO_3 were added to the filtrate, and the layers were separated. The aqueous layer was extracted with Et_2O. The organic layers were combined, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (80:8:4 CH_2Cl_2−CH_3OH−Et_3N) to furnish **2a** (141 mg, 20%) and **12** as a colorless oil (127 mg, 18%). **12:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (d, J = 5.2 Hz, 1H), 4.28 (s, 4H), 3.35 (t, J = 5.6 Hz, 1H), 3.27 (t, J = 5.8 Hz, 1H), 2.99 (t, J = 3.2 Hz, 2H), 2.59 (dd, J = 18, 4 Hz, 1H), 2.49 (t, J = 8.4 Hz, 1H), 2.28 (s, 3H), 2.16 (s, 3H), 2.14 (dd, J = 16, 1.2 Hz, 2H), 2.06−1.93 (m, 4H), 1.88−1.83 (m, 3H), 1.79 (td, J = 11, 2.4 Hz, 1H), 1.53−1.39 (m, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 175.8, 166.4, 142.7, 126.0, 62.5, 62.2, 60.2 (2), 59.0, 57.1, 40.3, 36.3, 33.2, 31.3 (2), 31.4, 30.4, 29.8, 24.6 (2); IR ($CHCl_3$) 1719, 1639 cm^{-1}; MS (EI) m/z 362 (M^+, 6), 138 (100).

Acknowledgment. We thank the National Institute on Drug Abuse (Grant DA12703) for the financial support of this research.

Supporting Information Available: The 2D COSY and NOESY NMR spectra for **2a,b** as well as the X-ray crystallographic data (tables and a figure) for **2b**. This information is available free of charge via the Internet at http://pubs.acs.org.

JO020170P