N-Demethylation of (±)-6β-Acetoxy-3-Tropinone. Synthesis of (±)-6β-Acetoxynortropane [1]

Xiao-Shu He and Arnold Brossi*

Natural Products Section, Laboratory of Structural Biology,
NIDDK, National Institutes of Health,
Bethesda, Maryland 20892, USA

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Nortropinone **5**, prepared from **3** by *N*-demethylation with trichloroethyl chloroformate, followed by deprotection of carbamate **4** with zinc in acetic acid, served as a starting material to prepare the *N*-protected 6-acetoxy ketones **7** and **9-12**, and alcohols **6** and **8**. Nortropane **16** was prepared from **3** by decarbonylation *via* dithioketal **13** followed by *N*-demethylation, and from **10** by decarbonylation *via* dithioketal **14**. When ethanol was used in the desulfurization of **14** instead of tetrahydrofuran, substantial amounts of the *N*-ethylated amine **17** were produced.

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The alkaloid baogongteng A from *Erycibe obtusifola* Benth. [2] is, unlike atropine and scopolamine which are medically used as anticholinergics, a nortropane alkaloid [3]. It was reported that baogongteng A has potentially useful cholinergic properties [4-6], which stimulated interest in its synthesis. The first total synthesis of racemic baogongteng A was accomplished from tropinone **3** [7], which is readily available from **1** by acetylation [8]. In the Chinese synthesis the *N*-demethylation step is executed at a late stage, after the hydroxy group at C(2) has been put in place, and after the removal of the carbonyl oxygen. We were interested in changing the sequence of these reactions, and to effect the *N*-demethylation of **3** followed by proper *N*-protection early on. The results of this investigation which led to an effective route to prepare nor-compounds and their *N*-protected analogs are reported here. Since alcohol **1** has been resolved into its optical isomers **1a,b** [9], achieved here with camphorsulfonic acids, the chemistry described can well be executed with the optical isomers of these compounds.

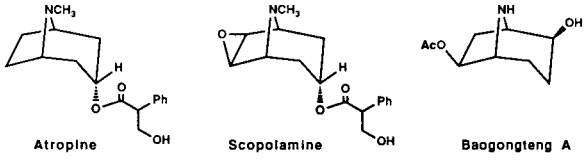

Figure 1

N-Demethylation of **3** with trichloroethyl chloroformate, reported to be the reagent of choice for tropane demethylation [10], when carried out in refluxing toluene afforded **4**, and nortropinone **5** after treatment of **4** with zinc in acetic acid in 60% overall yield. The addition of sodium bicarbonate in the carbamoylation reaction was found to be disadvantageous, producing undesired by-product [11]. Routine alkylation of **5** with di-*tert*-butyldicarbonate, benzyl chloroformate, ethyl chloroformate, and benzyl chloride, afforded ketones **9**, **11**, **12** and **10** respectively, and *N*-acetylation afforded ketone **7**. Hydrolysis of **7** and **9** with aqueous hydrochloric acid afforded alcohols **8** and **6** respectively (Figure 2).

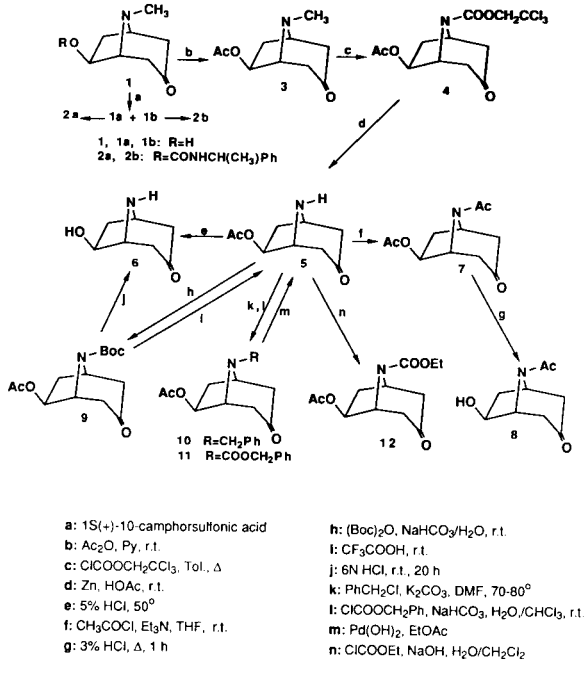

Figure 2

Decarbonylation of ketones **3** and **10** followed protocol already used by the Chinese scientists in their total synthesis [7]. For this purpose both ketones were reacted with 1,2-ethanedithiol or 1,3-propanedithiol in the presence of boron trifluoride etherate to afford dithioketals **13** and **14** respectively. Whereas desulfurization of **13** leading to tropane **15** could be accomplished with Raney Nickel in refluxing ethanol without difficulties, similar reaction with the benzylamine **14** afforded the *N*-ethylamine **17**, instead of the expected nor-compound **16**. The desired nortropane **16** was obtained from tropane **15** by *N*-demethylation with

trichloroethyl chloroformate followed by treatment of the carbamate (not isolated) with zinc in acetic acid, and by perfecting the desulfurization of dithioketal **14** with Raney Nickel in tetrahydrofuran.

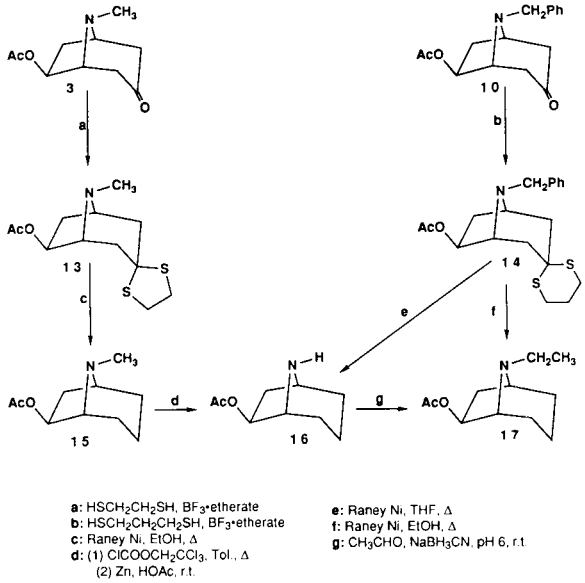

Figure 3

Reductive *N*-alkylation of amines with alcohol in the presence of metal catalysts is not uncommon [12], and probably proceeds by formation of the aldehyde by metal-catalyzed-dehydrogenation which then forms a Schiff-base with the amine ultimately resulting in *N*-alkylated substitution. Most of the compounds described here were characterized as crystalline salts and their uniformity is attested by the appearance of single spot on tlc chromatograms.

EXPERIMENTAL

Melting points are uncorrected and determined on a Fisher-Johns apparatus. Other data were collected as follows: optical rotation ($[\alpha]_D$) on a Perkin-Elmer-241MC automatic polarimeter; ir spectra in cm^{-1} on a Beckman-IR-4230 instrument and ^1H nmr (δ) on a Varian XL-300 spectrometer. The ms (m/e) for electron-impact (EI ms) were obtained on a V. G. Micromass 7070F mass spectrometer while ms (m/e) for chemical ionization (CI ms) were obtained on a Finnigan-1015D mass spectrometer and gc on a Hewlett-Packard 5890 instrument. Thin-layer chromatography plates (silica gel), Analtech Inc., Newark, NJ were used. For column chromatography (GHLF), Merck 60 (230-400 mesh) was employed. Solvent systems used for tlc were (A) chloroform-methanol (96:4) and (B) chloroform-methanol-ammonium hydroxide (90:9:1). Either phosphomolybdic acid (PMA) or iodine was used to visualize tlc plates.

Optical Resolution of (±)-**1**.

(±)-6β-Hydroxy-3-tropinone (**1**) 502 mg (3.24 mmoles) and (1*S*)-(+)-10-camphorsulfonic acid 752.6 mg (3.24 mmoles) were dissolved in methanol and the solvent was evaporated to give an oil. On standing at room temperature for several days, a white solid appeared. The solid was collected and recrystallized from 2-propanol three times to give white crystals 132 mg, mp 189°; $[\alpha]_D$ +3.80° (c 1.08, water).

Anal. Calcd. for $C_8H_{13}NO_2 \cdot C_{10}H_{16}SO_4$ (387.481): C, 55.79; H, 7.54; N, 3.61; S, 8.27. Found: C, 55.86; H, 7.57; N, 3.61; S, 8.18.

The salt (100 mg) was dissolved in water (2 ml), adjusted with concentrated ammonium hydroxide to *p*H 9. The solution was saturated with sodium chloride and extracted with chloroform (10 x 30 ml). The chloroform layer was dried (sodium sulfate) and evaporated *in vacuo*. The residue was recrystallized from 2-propanol/isooctane (1:3) to give 27.4 mg of crystals of **1a**, mp 130°; $[\alpha]_D$ −27.56° (c 1.06, water) [lit [9] mp 129-130°; $[\alpha]_D^{20}$ −22.8° ±2° (water)].

Anal. Calcd. for $C_8H_{13}NO_2$ (155.187): C, 61.91; H, 8.44; N, 9.03. Found: C, 61.99; H, 8.46; N, 9.08.

The first mother liquid was evaporated *in vacuo*. To the residue was added with water (15 ml) and potassium hydroxide (4.5 g) under ice cooling. The basic solution was extracted with chloroform (15 x 30 ml). The chloroform layer was washed with brine (2 x 15 ml), dried (sodium sulfate) and evaporated *in vacuo* to give crystals 249.4 mg. The crystals 249.4 mg (1.6 mmoles) and (1*R*)-(−)-10-camphorsulfonic acid 373.8 mg (1.6 mmoles) were dissolved in 2-propanol. After recrystallization from 2-propanol three times, 99 mg of crystals were obtained, mp 189°; $[\alpha]_D$ −4.40° (c 1.03, water).

Anal. Calcd. for $C_8H_{13}NO_2 \cdot C_{10}H_{16}SO_4$ (387.481): C, 55.79; H, 7.54; N, 3.61; S, 8.27. Found: C, 55.57; H, 7.42; N, 3.65; S, 8.12.

The salt (80 mg) was dissolved in water (2 ml) and adjusted with concentrated ammonium hydroxide to *p*H 9. The solution was saturated with sodium chloride and extracted with chloroform (10 x 30 ml). The chloroform layer was dried (sodium sulfate) and evaporated *in vacuo*. The residue was recrystallized from 2-propanol/isooctane (1:3) to give 20.1 mg of crystals of **1b**, mp 129-130°; $[\alpha]_D$ +23.64° (c 1.05, water) [lit [9] mp 121-123°; $[\alpha]_D^{20}$ +48.6° ±2° (water)].

Anal. Calcd. for $C_8H_{13}NO_2$ (155.187): C, 61.91; H, 8.44; N, 9.03. Found: C, 61.87; H, 8.46; N, 9.03.

Analyses of Optical Purity of **1a** and **1b**.

Reactions of (±)-**1**, **1a** and **1b** with (*R*)-(+)-1-Phenylethyl Isocyanate.

Formation of Diastereoisomers of **2a** and **2b**.

To a solution of 28 mg (0.18 mmoles) of the appropriate crystalline base in 2 ml of chloroform (hydrocarbon stabilized) was added a solution of 48 mg (0.33 mmole) of optically pure (*R*)-(+)-1-phenylethyl isocyanate in 1 ml of chloroform. The reaction mixture was refluxed for 1 hour, cooled and evaporated *in vacuo*. The residue was passed through a preparative thin layer chromatography system [chloroform:methanol (100:4)] to give a colorless oil which was utilized for the nmr analysis. Resonances for the *N*-methyl singlet of **2a** and **2b** were centered at δ 2.57 and 2.62 ppm respectively, or for the *N*-methyl doublet of (±)-**2** at δ 2.62 and 2.64 ppm.

6β-Acetoxy-3-tropinone Oxalate (**3**•$C_2H_2O_4$).

A mixture of compound **1** (12.5 g, 80 mmoles), pyridine (75 ml) and acetic anhydride (50 ml) was stirred at room temperature overnight, then evaporated to dryness *in vacuo* [13]. The residue was dissolved in chloroform, washed with 10% aqueous potassium carbonate solution and brine, dried (sodium sulfate) and concentrated *in vacuo* to give a slightly brown oil which was converted into the oxalate salt with a 10% oxalic acid solution (in acetone) to give 22.1 g (96%) of **3**•oxalate, mp 121-122°; ir (chloroform): ν 1739, 1727, 1220 cm^{-1}; ms: CI (m/e) 198 (MH^+); ^1H nmr (deuteriochloroform): δ 2.02 (s, 3H, $COCH_3$), 1.97-2.70 (m, 6H, 2,4,7-H), 2.60 (s, 3H, NCH_3), 3.47 (d, 1H, 5-H), 3.60 (m, 1H, 1-H), 4.87-4.91 (dd, 1H, 6-H) ppm.

Anal. Calcd. for $C_{10}H_{15}NO_3$•$C_2H_2O_4$ (287.27): C, 50.17; H, 5.97; N, 4.88. Found: C, 50.08; H, 6.00; N, 4.89.

6β-Acetoxy-*N*-demethyl-*N*-(2′,2′,2′-trichloroethoxycarbonyl)-3-tropinone (**4**).

The oxalate of **3** (2.9 g, 10 mmoles) was dissolved in water (containing excess ammonium hydroxide), then extracted with chloroform. The chloroform layer was washed (brine), dried (sodium sulfate), and evaporated *in vacuo* to give oil **3** (free base). The oil was refluxed in toluene (60 ml) and about 20 ml of toluene was distilled out. 2,2,2-Trichloroethyl chloroformate (3 ml, 22.2 mmoles) was added. The mixture was refluxed overnight under nitrogen, cooled and then filtered. The filter cake (0.34 g) was the hydrochloride salt of **3**. The filtrate was washed with 5% aqueous hydrochloric acid solution, brine, and evaporated *in vacuo*. The residue was purified by passage through a short column of silica gel (decreased pressure), eluted with dichloromethane to remove unreacted chloroformate and a by-product [10], then with ethyl acetate to give 3.08 g of **4** as an oil (gc analysis 95%, yield 86%) which crystallized on standing, mp 81-83°; ir (chloroform): ν 1745, 1735, 1722, 1422, 1200, 1120 cm^{-1}; ms: EI (m/e) 357 (M^+); ^1H nmr (deuteriochloroform): δ 2.05-2.06 (d, 3H, $COCH_3$), 2.11-2.77 (m, 6H, 2,4,7-H), 4.56-5.02 (m, 5H, 1,5,6-H, $-CH_2CCl_3$) ppm.

Anal. Calcd. for $C_{12}H_{14}Cl_3NO_5$ (358.61): C, 40.19; H, 3.93; N, 3.91; Cl, 29.66. Found: C, 40.25; H, 3.92; N, 3.83; Cl, 29.75.

6β-Acetoxy-3-nortropinone Oxalate (**5**•$C_2H_2O_4$).

The carbamate **4** (1.5 g, 4.2 mmoles) was dissolved in acetic acid (30 ml). Zinc powder (1 g) was added portionwise over 10 minutes. The mixture was stirred vigorously at room temperature overnight, then filtered on celite 535. The filtrate was evaporated *in vacuo*. The residue was dissolved in water, adjusted to *p*H 6 with concentrated ammonium hydroxide, and extracted with ether (2 x 15 ml). The *p*H was adjusted to **9**, and the basified solution was extracted with chloroform (3 x 50 ml). The chloroform layer was washed with brine, dried (sodium sulfate) and evaporated *in vacuo* to give an oil (0.64 g) which was converted into the oxalate salt with oxalic acid (0.32 g, in 2-propanol) to give 0.82 g of **5**•oxalate (71%); mp 164-166° dec; ms: CI (m/e) 184 (MH^+); ^1H nmr (dimethyl sulfoxide-d_6): δ 2.04 (s, 3H, $COCH_3$), 2.08-2.94 (m, 6H, 2,4,7-H), 4.21-4.30 (m, 2H, 1,5-H), 5.04 (dd, 1H, 6-H) ppm.

Anal. Calcd. for $C_9H_{13}NO_3$•$C_2H_2O_4$ (273.24): C, 48.35; H, 5.53; N, 5.13. Found: C, 48.28; H, 5.57; N, 5.11.

6β-Hydroxy-3-nortropinone Hydrochloride (**6**•HCl).

Method A.

Nortropinone **5** (294 mg of free base, 1.6 mmoles) was dissolved in 5% aqueous hydrochloric acid solution (5 ml), refluxed for 50 minutes, cooled and evaporated *in vacuo* to give light brown crystals which were decolorized by treatment with charcoal-water to give 230 mg (81%) of colorless crystals of **6**•HCl, mp 188-192° dec; ms: CI (m/e) 142 (MH^+); ^1H nmr (dimethyl sulfoxide-d_6): δ 1.93-2.98 (m, 6H, 2,4,7-H), 3.96-3.97 (d, 1H, 5-H), 4.23-4.28 (m, 1H, 1-H), 5.64-5.65 (d, 1H, 6-H) ppm.

Anal. Calcd. for $C_7H_{11}NO_2$•HCl•¼H_2O (177.63): C, 46.16; H, 6.92; N, 7.69; Cl, 19.47. Found: C, 46.33; H, 6.90; N, 7.74; Cl, 19.56.

Method B.

Carbamate **9** (52 mg, 0.18 mmole) was dissolved in 6*N* hydrochloric acid (1 ml). The mixture was stirred at room temperature for 17 hours, cooled and evaporated *in vauco* to give the hydrochloride salt of **6** quantitatively.

6β-Acetoxy-*N*-demethyl-*N*-acetyl-3-tropinone (**7**).

Nortropinone oxalate (**5**•$C_2H_2O_4$) 500 mg (1.83 mmoles) was dissolved in water (containing excess of ammonium hydroxide) and then extracted with chloroform. The free base and triethyl amine 570 mg (5.6 mmoles) were dissolved in tetrahydrofuran (20 ml). Acetyl chloride 0.15 ml (2.1 mmoles) was added to the solution at room temperature while stirring. It was stirred for 30 minutes, then filtered. The filtrate was evaporated *in vacuo*. The residue was subjected to preparative thin layer chromatography [chloroform:methanol:ammonium hydroxide (95:4.5:0.5)] to give **7** as a colorless oil which became silky crystals after standing at room temperature for several months (400 mg, 97%), mp 100-101°; ir (chloroform): ν 1740, 1720, 1644, 1420, 1204 cm^{-1}; ms: CI (m/e) 226 (MH^+); ^1H nmr (deuteriochloroform): δ 2.28-2.31 (d, 3H, $OCOCH_3$), 2.41-2.47 (d, 3H, $NCOCH_3$), 2.32-3.04 (m, 6H, 2,4,7-H), 4.59-5.32 (m, 3H, 1,5,6-H) ppm.

Anal. Calcd. for $C_{11}H_{15}NO_4$ (225.237): C, 58.65; H, 6.71; N, 6.22. Found: C, 58.71; H, 6.73; N, 6.21.

6β-Hydroxy-*N*-demethyl-*N*-acetyl-3-tropinone (**8**).

Compound **7** (660 mg, 2.9 mmoles) was dissolved in ethanol (1 ml). To this solution was added 3% aqueous hydrochloric acid solution (9 ml). The resulting solution refluxed for 1 hour, cooled, and evaporated *in vacuo* to give a pale brown oil. The oil was dissolved in water 2 ml, adjusted to *p*H 9 with concentrated ammonium hydroxide and extracted with chloroform. The aqueous layer was adjusted to *p*H 2 by dropwise addition of concentrated hydrochloric acid and the acidified solution was saturated with sodium chloride, and extracted with chloroform (6 x 50 ml) again. The chloroform layer was dried (sodium sulfate) and evaporated *in vacuo* to give a solid (176 mg) which was recrystallized from hexane to afford **8** as white crystals (122 mg), mp 130-131°; ms: CI (m/e) 184 (MH^+); ^1H nmr (deuteriochloroform): δ 2.20-2.22 (d, 3H, $COCH_3$), 1.62-2.76 (m, 6H, 2,4,7-H), 4.27-5.04 (m, 3H, 1,5,6-H) ppm.

Anal. Calcd. for $C_9H_{13}NO_3$ (183.197): C, 59.00; H, 7.15; N, 7.65. Found: C, 58.86; H, 7.11; N, 7.63.

6β-Acetoxy-*N*-demethyl-*N*-(*tert*-butoxycarbonyl)-3-tropinone (**9**).

A mixture of compound **5** (1.29 g, free base, 7 mmoles), sodium bicarbonate (1.77 g, 21 mmoles), water (30 ml) and di-*tert*-butyl dicarbonate (1.9 g, 8.7 mmoles) was stirred at room temperature

for 24 hours, then extracted with chloroform. The chloroform layer was washed with 5% aqueous hydrochloric acid solution (cooled to 0-4°) followed by brine, dried (sodium sulfate), and evaporated *in vacuo* to give **9** as an oil (1.94 g, 98%); ir (chloroform): ν 1735, 1714, 1692, 1386, 1200 cm^{-1}; ms: CI (m/e) 284 (MH^+), 184; ^1H nmr (deuteriochloroform): δ 1.40 (s, 9H, $COOC(CH_3)_3$), 1.95 (s, 3H, $COCH_3$), 2.04-2.63 (m, 6H, 2,4,7-H), 4.28-4.56 (q, 2H, 1,5-H), 4.83 (t, 1H, 6-H) ppm.

Anal. Calcd. for $C_{14}H_{21}NO_5$ (283.317): C, 59.35; H, 7.47; N, 4.94. Found: C, 59.25; H, 7.50; N, 4.91.

Compound **9** (48 mg, 0.17 mmole) was dissolved in chloroform (2 ml, free of ethanol), then trifluoroacetic acid (0.5 ml) was added. After stirring at room temperature for 1 hour, the solvent was evaporated *in vacuo* to give **5** quantitatively.

6β-Acetoxy-*N*-demethyl-*N*-benzyl-3-tropinone Hydrobromide (**10**·HBr).

A mixture of **5**·oxalate (355 mg, 1.3 mmoles) in *N,N*-dimethylformamide (15 ml), potassium carbonate (400 mg, 2.9 mmoles) and benzyl chloride (230 mg, 1.8 mmoles) was stirred at 70-80° overnight, then cooled, poured into ether/water (50 ml/30 ml). The ether layer was separated, washed with brine, dried (sodium sulfate) and evaporated *in vacuo*. The residue was purified by chromatography on silica gel [chloroform:methanol (98:2)] to give **10** as an oil (316 mg, 89%) [ms: EI (m/e) 274 (MH^+)] which was converted to the hydrobromide salt with 48% aqueous hydrobromic acid solution (in 2-propanol), mp 206-208° dec; ms: CI (m/e) 274 (MH^+); ^1H nmr (dimethyl sulfoxide-d_6): δ 2.12 (s, 3H, $COCH_3$), 2.51-3.09 (m, 6H, 2,4,7-H), 4.13-4.28 (d, 2H, 1,5-H), 4.52 (s, 2H, $-CH_2Ph$), 5.11 (t, 1H, 6-H), 7.51-7.63 (m, 5H, phenyl-H) ppm.

Anal. Calcd. for $C_{16}H_{19}NO_3$·HBr (354.236): C, 54.25; H, 5.69; N, 3.95; Br, 22.56. Found: C, 54.35; H, 5.70; N, 3.89; Br, 22.48.

The free base of **10** can be converted to the hydroiodide salt in ethyl acetate by dropwise addition of 57% aqueous hydroiodic acid solution to *p*H 3, mp 197-199° dec.

Anal. Calcd. for $C_{16}H_{19}NO_3$·HI (401.227): C, 47.89; H, 5.02; N, 3.49; I, 31.63. Found: C, 47.83; H, 5.04; N, 3.50; I, 31.52.

A mixture of compound **10** (122 mg, 0.5 mmole) and palladous hydroxide (40 mg) in ethyl acetate (20 ml) was stirred at room temperature under hydrogen. Progress of the reaction was followed by tlc (system A) until it was completed. The reaction mixture was filtered through celite 535 and evaporated *in vacuo* to give compound **5**. The oxalate salt was found to be identical with a sample prepared differently.

6β-Acetoxy-*N*-demethyl-*N*-(benzyloxycarbonyl)-3-tropinone (**11**).

Compound **5** (330 mg of free base, 1.8 mmoles), sodium bicarbonate (455 mg, 5.4 mmoles) and benzyl chloroformate (0.4 ml, 2.8 mmoles) were dissolved in water/chloroform (5 ml/5ml) and the reaction mixture was stirred at room temperature for 24 hours, then extracted with chloroform. The chloroform layer was washed with 5% aqueous hydrochloric acid solution, brine, dried (sodium sulfate) and evaporated *in vacuo*. The residue was purified by flash chromatography on a short silica gel column using dichloromethane followed by ethyl acetate as eluants to give **11** as an oil (530 mg, 93%), ms: CI (m/e) 318 (MH^+), 335 (MNH_4^+); ^1H nmr (deuteriochloroform): δ 1.99-2.03 (d, 3H, $COCH_3$), 2.16-2.73 (m, 6H, 2,4,7-H), 4.52-4.74 (m, 2H, 1,5-H), 4.96 (t, 1H, 6-H), 5.21 (s, 2H, CH_2Ph), 7.37 (s, 5H, phenyl-H) ppm.

Anal. Calcd. for $C_{17}H_{19}NO_5$ (317.327): C, 64.34; H, 6.03; N, 4.41. Found: C, 64.38; H, 6.03; N, 4.46.

Compound **11** could be converted back into **5** by catalytic debenzylation under conditions similar to those used for the conversion of **10** to **5**.

6β-Acetoxy-*N*-demethyl-*N*-(ethoxycarbonyl)-3-tropinone (**12**).

To a vigorously stirred solution of **5**·oxalate (500 mg, 1.83 mmoles) in dichloromethane/water (4 ml/4 ml) was added 10% aqueous sodium hydroxide solution to *p*H 7. Ethyl chloroformate (230 mg, 2.1 mmoles) in dichloromethane (2 ml) was added during 10 minutes at 8-10°. The solution was stirred at room temperature for 5 hours and kept alkaline by the periodic addition of 10% aqueous sodium hydroxide solution. The dichloromethane layer was diluted, separated, washed with 5% aqueous hydrochloric acid solution followed by brine, dried (sodium sulfate) and evaporated *in vacuo*. The residue was subjected to preparative thin layer chromatography on silica gel [chloroform:methanol (98:2)] to give **12** as a colorless oil (280 mg, 60%): ir (chloroform): ν 1734, 1700, 1422, 1200 cm^{-1}; ms: CI (m/e) 256 (MH^+); ^1H nmr (deuteriochloroform): δ 1.56 (t, 3H, $OCCH_3$), 2.30 (s, 3H, $COCH_3$), 2.42-2.95 (m, 6H, 2,4,7-H), 4.48 (q, 2H, OCH_2Me), 4.73-4.95 (m, 2H, 1,5-H), 5.21 (t, 1H, 6-H) ppm.

Anal. Calcd. for $C_{12}H_{17}NO_5$ (255.267): C, 56.46; H, 6.71; N, 5.49. Found: C, 56.35; H, 6.73; N, 5.45.

6β-Acetoxy-3-(1′,2′-ethylenedithiano)tropane Hydroiodide (**13**·HI).

Compound **3** (3.26 g of free base, 16.5 mmoles) was dissolved in 1,2-ethanedithiol (10 ml). Boron trifluoride etherate (5 ml) was added. After stirring overnight at room temperature under nitrogen, the reaction mixture was poured into water, extracted with ether to remove 1,2-ethanedithiol. The aqueous layer was adjusted to *p*H 9 with concentrated ammonium hydroxide (ice-bath), and extracted with chloroform. The chloroform layer was washed (brine), dried (sodium sulfate) and evaporated *in vacuo* to give a colorless oil which was converted to hydroiodide salt of **13** in ethyl acetate by dropwise addition of 57% aqueous hydroiodic acid solution to *p*H 3 (5.65 g, 81%), mp 229-233°; ms: CI (m/e) 274 (MH^+); ^1H nmr (dimethyl sulfoxide-d_6): δ 2.05 (s, 3H, $COCH_3$), 2.42-2.92 (m, 6H, 2,4,7-H), 2.87-2.88 (d, 3H, NCH_3), 3.23-3.54 (dm, 4H, SCH_2CH_2S), 4.08-4.17 (m, 2H, 1,5-H), 5.71-5.75 (dd, 1H, 6-H) ppm.

Anal. Calcd. for $C_{12}H_{19}NS_2O_2$·HI (401.307): C, 35.91; H, 5.02; N, 3.49; S, 15.98; I, 31.62. Found: C, 36.00; H, 5.00; N, 3.51; S, 16.06; I, 31.72.

6β-Acetoxy-*N*-demethyl-*N*-benzyl-3-(1′,3′-propylenedithiano)tropane (**14**).

Compound **10** as the free base, from its hydrobromide salt (1 g, 2.8 mmoles) was dissolved in 1,3-propanedithiol (4 ml). Boron trifluoride etherate (3 ml) was added. After stirring overnight at room temperature under nitrogen, the reaction mixture was poured into water, extracted with ether. Then, the aqueous layer was adjusted to *p*H 9 with concentrated ammonium hydroxide (ice-bath), extracted with chloroform. The chloroform layer was washed (brine), dried (sodium sulfate) and evaporated *in vacuo* to afford an oil which was purified by a preparative thin layer chromatography on silica gel [chloroform:methanol (100:1)] to give a colorless oil. The oil was crystallized in ethanol to give **14** as white crystals (660 mg, 65%), mp 74-76°; ms: CI (m/e) 364 (MH^+);

hrms: Calcd. for $C_{19}H_{25}NS_2O_2$ (363.1310); Found: 363.1293; ^1H nmr (deuteriochloroform): δ 2.06 (s, 3H, $COCH_3$), 1.57-3.04 (m, 12H, methylene-H), 3.24-3.89 (m, 3H, 1,5,6-H), 5.63 (s, 2H, CH_2Ph), 7.26 (s, 5H, phenyl-H) ppm.

Anal. Calcd. for $C_{19}H_{25}NS_2O_2$ (363.131): C, 62.77; H, 6.93; N, 3.85; S, 17.64. Found: C, 62.67; H, 6.91; N, 3.85; S, 17.56.

6β-Acetoxytropane Hydrochloride (**15**•HCl) [14].

Dithioketal **13** as the free base prepared from its hydroiodide salt (1.48 g, 3.7 mmoles) was dissolved in ethanol (30 ml) (or tetrahydrofuran). Raney Nickel (3 g) was added. The reaction mixture was refluxed under hydrogen until all the starting material had disappeared. The reaction mixture was cooled and filtered (on celite 535). The filter cake was washed with a large amount of ethanol followed by chloroform. The filtrate was evaporated *in vacuo*. The residue was dissolved in chloroform and filtered again. The filtrate was evaporated *in vacuo* to give **15**•HCl as a solid (400 mg, 49%) which was recrystallized with acetone to give white crystals, mp 196-198°; ms: CI (m/e) 184 (MH^+); ^1H nmr (deuteriochloroform): δ 2.11 (s, 3H, $COCH_3$), 1.43-2.74 (m, 8H, methylene-H), 3.00 (s, 3H, NCH_3), 3.69 (s, 1H, 5-H), 3.92-3.95 (m, 1H, 1-H), 5.23-5.27 (dd, 1H, 6-H) ppm.

Anal. Calcd. for $C_{10}H_{17}NO_2$•HCl (219.7): C, 54.67; H, 8.26; N, 6.38. Found: C, 54.67; H, 8.21; N, 6.66.

6β-Acetoxynortropane Oxalate (**16**•$C_2H_2O_4$).

Method A.

Compound **15**•HCl (152 mg, 0.69 mmole) was dissolved in toluene (12 ml). After distilling 5 ml of toluene, potassium carbonate (95 mg, 0.69 mmole) and 2,2,2-trichloroethyl chloroformate (0.3 ml, 2.2 mmoles) were added. The reaction mixture was refluxed under nitrogen overnight, cooled and diluted with toluene. The toluene solution was washed with 5% aqueous hydrochloric acid solution followed by brine, dried (sodium sulfate) and evaporated *in vacuo* to give an oil. This was purified by passage through a short column of silica gel (decreased pressure), first eluting with dichloromethane to remove unreacted chloroformate and by-product, then with ethyl acetate to give trichloroethyl carbamate as a colorless oil. The oil was dissolved in acetic acid (5 ml), and zinc powder (0.2 g) added. The reaction mixture was stirred vigorously at room temperature overnight and filtered (on celite 535). The filtrate was evaporated *in vacuo* and the residue was dissolved in water (5 ml), and extracted with ether. The aqueous layer was adjusted to *p*H 9 with concentrated ammonium hydroxide, and extracted with chloroform. The chloroform layer was washed with brine, dried (sodium sulfate) and evaporated *in vacuo* to give **16** as a colorless oil (110 mg) which was converted to oxalate salt with oxalic acid (60 mg, in 2-propanol) to give **16**•oxalate as white crystals (126 mg, 72%), mp 179-180°; ms: CI (m/e) 170 (MH^+); ^1H nmr (dimethyl sulfoxide-d_6): δ 2.04 (s, 3H, $COCH_3$), 1.54-2.42 (m, 8H, 2,3,4,7-H), 4.00 (s, 1H, 5-H), 4.03-4.06 (d, 1H, 1-H), 5.10-5.14 (dd, 1H, 6-H) ppm.

Anal. Calcd. for $C_9H_{15}NO_2$•$C_2H_2O_4$ (259.257): C, 50.96; H, 6.61; N, 5.40. Found: C, 50.99; H, 6.65; N, 5.36.

Method B.

Dithioketal **14** (300 mg, 0.8 mmole) was dissolved in tetrahydrofuran (25 ml). Raney Nickel (3 g) was added. The reaction mixture was refluxed under hydrogen until all the starting material had disappeared. After cooling and filtration through celite 535, the filter cake was washed with a large amount of tetrahydrofuran followed by chloroform. The filtrate was evaporated *in vacuo* to give an oil which was dissolved in 5% aqueous oxalic acid solution (5 ml), and washed with ether. The aqueous layer was adjusted to *p*H 9 with concentrated ammonium hydroxide, extracted with chloroform. The chloroform layer was washed with brine, dried (sodium sulfate) and evaporated *in vacuo* to give **16** as a colorless oil (100 mg). This base was converted with oxalic acid (50 mg, in 2-propanol) to oxalate salt (75 mg, 34%) as white crystals; tlc, mp, CI ms and ^1H nmr were identical with that prepared by method A.

6β-Acetoxy-*N*-demethyl-*N*-ethyltropane (**17**).

Method A.

Dithioketal **14** (200 mg, 0.55 mmole) was dissolved in ethanol (20 ml), Raney Nickel (2 g) was added. The reaction mixture was refluxed under hydrogen until all starting material had disappeared. After cooling, it was filtered through celite 535. The filter cake was washed with ethanol followed by chloroform. The solvent was evaporated *in vacuo* to give **17** as an oil (70 mg, 64%), ms: CI (m/e) 198 (MH^+); ^1H nmr (deuteriochloroform): δ 1.37 (t, 3H, N-C-CH_3, J = 7 Hz), 1.96 (s, 3H, $COCH_3$), 1.41-2.52 (m, 8H, 2,3,4,7-H), 3.09 (m, 2H, N-CH_2Me, J = 7 Hz), 3.72 (s, 1H, 5-H), 3.98 (d, 1H, 1-H), 5.08 (dd, 1H, 6-H) ppm.

Anal. Calcd. for $C_{11}H_{19}NO_2$ (197.267): C, 66.97; H, 9.71; N, 7.10. Found: C, 66.71; H, 9.76; N, 6.94.

Method B.

The oxalate of **16** (71 mg, 0.27 mmole) was converted to free base (oil). The oil was dissolved in methanol (2 ml), and rendered acidic (*p*H 4) with methanolic hydrogen chloride solution. Acetaldehyde (50 μl) was then added. After 15 minutes, sodium cyanoborohydride (67 mg) was added. The reaction mixture was stirred at room temperature under nitrogen for 19 hours and during this time, kept at *p*H 6 with methanolic hydrogen chloride solution. The reaction mixture was evaporated *in vacuo*. To the residue, saturated sodium carbonate solution (5 ml) was added and the base extracted with chloroform. The chloroform layer was washed with brine, dried (sodium sulfate) and evaporated *in vacuo* to give **17** as an oil (49 mg, 90%) which was identical with that obtained by method A by tlc, CI ms and ^1H nmr.

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[1] All compounds described here, except compounds **1a**, **1b**, **2a** and **2b**, are racemic mixtures.

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