

CHEMISTRY OF N-CHLORONORTROPINE DERIVATIVES: SYNTHESIS OF A  
BRIDGED AZIRIDINE COMPOUND AND NEW TROPANE DERIVATIVES

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**Abstract**—An unsymmetrical bridged aziridine compound was obtained from N-chloronortropinone. This compound was found to react with acyl halides, acid anhydrides, and other reagents, including a Michael acceptor, dimethyl acetylenedicarboxylate (DMAD), giving new tropane bases with a ketone functional group at the bridged ethylene moiety. In the case of Michael-type addition, the retention of the aziridine ring system was observed in some solvents.

In the course of studying the chemistry of N-chloronortropine derivatives we found that under basic conditions N-chloronortropinone (2) gave a new compound, the bridged aziridine compound (3), which might be a useful synthetic intermediate to produce new tropan derivatives. It has been indicated by some workers that it is difficult to convert tropin-type bases (tropine, tropinone, atropine, cocaine, etc.) to scopolamine, tropanediol, telodine, and their esters (scopolamine, etc.) which bear an oxygen function(s) at the ethylene bridge.<sup>1</sup> In this paper, a new synthetic procedure for tropane derivatives, the precursors of scopolamines, from an unsymmetrical bridged aziridine compound is introduced. The starting material was prepared as follows. N-Chloronortropinone (2) was obtained in quantitative yield from nortropinone<sup>2</sup> (1) with equimolar amounts of t-butyl hypochlorite and sodium bicarbonate. The treatment of N-chloronortropinone (2) with sodium methoxide in anhydrous methanol at room temperature (20 °C) gave the bridged aziridine (3). This aziridine (3) was also obtained quantitatively by passing an ether solution of 2 through a basic aluminium oxide column. The molecular structure was determined to be as shown in Chart 1 from the high-resolution mass spectrum (m/z 123.0672), infrared (ir), and <sup>13</sup>C-nmr spectra. The large J<sub>CH</sub> value (180 Hz) in-

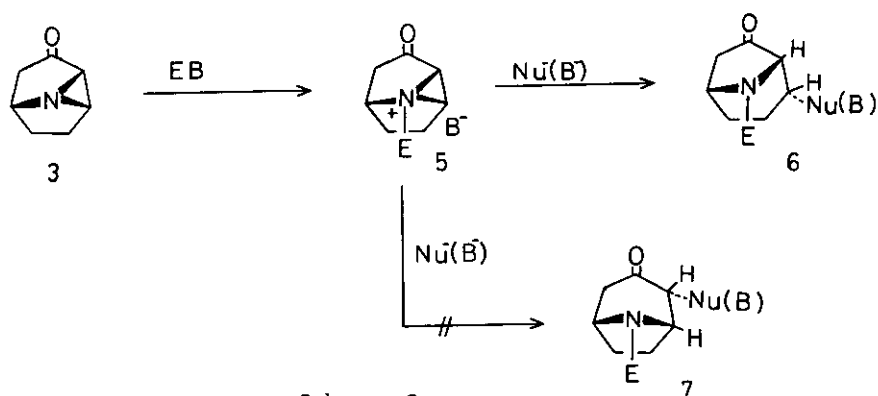
indicates the existence of a three-membered ring system, that is, an aziridine ring. This is a new compound, because although the symmetric bridged aziridine compound (4) has been reported <sup>3,4</sup>, no unsymmetrical derivative has been described.

Chart 1

We studied the ring opening-reaction of the aziridine with the aim of synthesizing new tropane derivatives. It was found that the aziridine 3 reacted with acyl halides, acid anhydrides and other reagents ( $\text{ClCOOEt}$ ,  $\text{BrCN}$ ,  $\text{Cl}_2$ , etc.) to give 6 in methylene chloride at room temperature. But it did not react with phenol or hydrogen cyanide. In an acetic anhydride-acetic acid system, 6b was the major product. The quaternary ammonium salt 5 was obtained when 3 was allowed to react with methyl iodide ( $\text{E} = \text{Me}$ ) and trifluoroacetic acid ( $\text{E} = \text{H}$ ). These salts were converted into 6g and 6h by treatment with basic aluminum oxide ( $\text{Al}_2\text{O}_3$ ) and by heating with methanol, respectively. Most of these reactions gave good yields as shown in Table I. However, compound 7 could not be obtained. The structures of the products were supported by the nmr spectra; for example, in the spectrum of 6g the signal of the methine proton on the carbon substituted with the hydroxyl group appeared as a doublet of triplets ( $J = 5 \text{ Hz}, 5 \text{ Hz}, 11 \text{ Hz}$ ), so that it must have three neighboring protons, which supports the structure 6g. The above results show that the nucleophilic attack occurred predominantly at the  $\text{C}_1$  carbon atom of the aziridine molecule (Scheme I). The large  $J$  value ( $J = 11 \text{ Hz}$ ) indicates that the methine proton is situated in the axial position.

Table I. Synthesis of N-acyl or alkyl-2 $\alpha$ -substituted nortropan-7-ones

| 6 | E     | Nu  |                   | mp (° C) | yield |
|---|-------|-----|-------------------|----------|-------|
| a | Ac    | OAc | colorless needles | 89-90    | 66%   |
| b | Ac    | OH  | colorless prisms  | 175-177  | 32%   |
| c | Ac    | Cl  | colorless needles | 126-127  | 62%   |
| d | CN    | Br  | colorless plates  | 124-125  | 71%   |
| e | Ms    | Cl  | colorless flakes  | 95-96    | 58%   |
| f | COOEt | Cl  | syrup             | -----    | 66%   |
| g | Me    | OH  | syrup             | -----    | 16%   |
| h | H     | OMe | syrup             | -----    | 23%   |
| i | Cl    | Cl  | amorphous         | -----    | 80%   |
| j | Ts    | Cl  | colorless prisms  | 185-186  | 36%   |



Thus, the nucleophile should be substituted on the  $C_1$  carbon atom of 6 in the  $\alpha$  configuration. The structures of 6a-f, h-i were similarly assigned. Moreover, we found that the aziridine (3) reacted with dimethyl acetylenedicarboxylate (DMAD); Michael-type addition to DMAD affords different products depending upon the solvent employed. As shown in Scheme II, when there was no proton source except 3 itself, that is, when methylene chloride was used as the solvent, 9 was the only product. The molecular formula of 9 was determined as  $C_{13}H_{15}NO_5$  by mass spectroscopy. The  $^{13}C$ -nmr spectrum of 9 showed large coupling constant ( $J = 169$  Hz), indicating that the aziridine ring system is retained. The  $^1H$ -nmr spectrum revealed that 9 contains an unsaturated carbonyl group, two double bonds and two esters. These data are consistent with the indicated structure. The two carboxylate esters may be (*Z*)-form rich according to Dolfini.<sup>5</sup> On the other hand, the reaction of the aziridine (3) and DMAD in aprotic solvents ( $CH_2Cl_2$ , AcOEt) containing adequate amounts of proton sources (1.5-10.0 moles) at  $0^\circ C$  gave 11 in good yields. These results are summarized in Table II. In the case of 11c, the proton  $H_f$  ( $\delta$  4.55-4.79) showed multiplet signals. This suggests that nucleophilic attack occurred at the  $\beta$  carbon atom in  $\alpha$  configuration with respect to carbonyl group. Other products (11a, b, d) were assigned in a similar manner. The configuration of the two carboxylate esters was assigned to be (*Z*)-form because the  $H_a$  proton signal appears at  $\delta$  4.83 to  $\delta$  4.90 in 11a, b, c, d.<sup>5,6</sup> The mechanism of the reaction of 3 with DMAD producing 9 and 11 is assumed to be as shown in Chart 2. In the absence of a proton source, the intermediate (13) would be expected to undergo stereospecific collapse via intramolecular protonation, leading to the (*Z*)-form of the esters; in the presence of a proton source, protonation

by BH could become the favored path to give 11. It is already established that many aziridine compounds undergo Michael-type addition with yne-carboxylates.<sup>7</sup> However, reactions which can introduce many nucleophiles onto carbon atoms are rare,<sup>8</sup> and we believe that the method described here, will be a unique and useful one for the synthesis of new tropane derivatives.

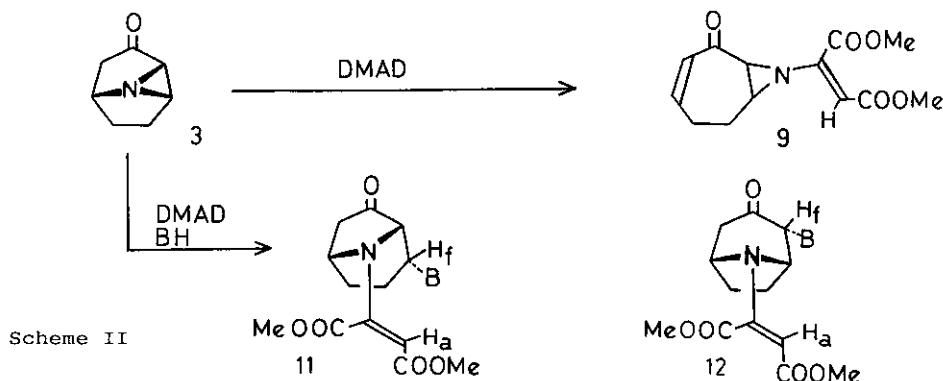
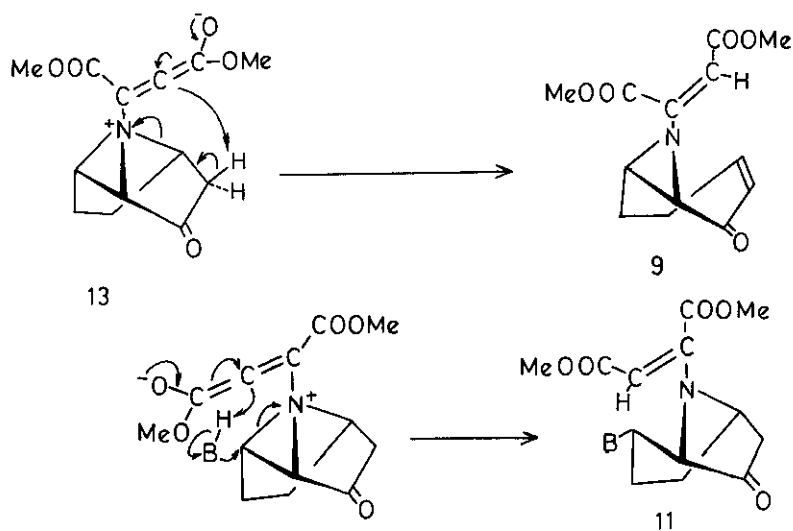


Table II. Dimethyl (2 $\alpha$ -substituted 7-oxonortrop-N-yl)maleates

| <u>11</u> | BH               | B-     | mp ( $^{\circ}$ C) | yield |
|-----------|------------------|--------|--------------------|-------|
| a         | MeOH             | MeO-   | 91-92              | 63%   |
| b         | H <sub>2</sub> O | HO-    | *                  | 44%   |
| c         | COMe             | HCCOMe | 195-197            | 30%   |
|           | CH <sub>2</sub>  | OCMe   |                    |       |
| d         | PhOH             | PhO-   | *                  | 43%   |

\* colorless syrup



## EXPERIMENTAL

Chromatographic materials were from Merck: silica gel (Kieselgel 60, and for PTLC Camag DF-5) and alumina (Art.1097 and neutral alumina, and for PTLC Camag Aluminum oxide D-5 and Art. 1094) were used. Infrared (ir) spectra were recorded with a Nippon Bunko DS-402G spectrophotometer and mass spectra (ms) were determined on JEOL JM-S01SG-2 spectrometer. Nuclear magnetic resonances ( $^1\text{H}$ -nmr and  $^{13}\text{C}$ -nmr) were obtained on a JEOL JNM-FX100 spectrometer. Analytical gas-liquid chromatography (GLC) was performed on a JEOL FGC-20K.

Preparation of the bridged aziridine (3) from nortropinone (1)--t-Butyl hypochlorite (1.94 g, 18 mmol) was added dropwise to an absolute ether solution of nortropinone (1) (2.9 g, 18 mmol) in the presence of sodium bicarbonate (1.7 g) at 10 °C over a period of 45 min in the dark. After the addition was complete, the mixture was stirred for a further 4 h at this temperature. The remaining precipitate was filtered off and carefully concentrated in vacuo to give a colorless ether solution of 2, which was used in the following reaction without further purification. Either method A or method B was used to prepare compound 3 from 2.

A) A solution of sodium methoxide (0.94 g, 17.4 mmol) in methanol (50ml) was added to a solution of 2 (2.5 g, 16 mmol) in anhydrous methanol (50 ml) at room temperature. The mixture was stirred for 1 h. The solvent was carefully evaporated off in vacuo to give the residue, which was chromatographed on  $\text{Al}_2\text{O}_3$  using  $\text{CH}_2\text{Cl}_2$  as the eluent to afford pure 3 (0.7 g, 36%) as a red volatile liquid at room temperature (colorless prisms in hexane- $\text{CH}_2\text{Cl}_2$  solution at -10°C ).

B) An ether solution of N-chloronortropinone (2) (15.1 g, 95 mmol) was passed through basic aluminum oxide ( $\text{Al}_2\text{O}_3$ ; Merck Art. 1097, 500 g) using  $\text{CH}_2\text{Cl}_2$  as the eluent to furnish 3 (10.5 g, 90%) as a red volatile liquid. High-resolution ms: Found 123.0672. Calcd for  $\text{C}_7\text{H}_9\text{NO}$  ( $\text{M}^+$ ) 123.0685. Ir (cap):  $1735\text{ cm}^{-1}$ ,  $^1\text{H}$ -nmr ( $\text{CDCl}_3/\text{TMS}$ )  $\delta$ : 3.90-4.30 (1H, q-like,  $J=9\text{ Hz}$ ,  $J=5\text{ Hz}$ ), 1.50-3.20 (8H, m).  $^{13}\text{C}$ -Nmr ( $\text{CDCl}_3/\text{TMS}$ )  $\delta$ : 210.2 (s, ketone), 61.4 (d, -CH-,  $J=155\text{ Hz}$ ), 53.6 (d, -CH-,  $J=180\text{ Hz}$ ), 49.5 (d, -CH-,  $J=180\text{ Hz}$ ), 45.9 (t, - $\text{CH}_2$ -,  $J=129\text{ Hz}$ ), 39.5 (t, - $\text{CH}_2$ -,  $J=137\text{ Hz}$ ), 22.7 (t, - $\text{CH}_2$ -,  $J=137\text{ Hz}$ ).

N-Acetyl-2 $\alpha$ -acetoxynortropan-7-one (6a)--Acetic anhydride (0.63 g, 1.03 eq) was added to a solution of 3 (0.74 g, 6 mmol) in  $\text{CH}_2\text{Cl}_2$  (100 ml) at room temperature.

The reaction mixture was stirred for 2 h, then concentrated to dryness in vacuo and the residue was purified by column chromatography on  $\text{Al}_2\text{O}_3$  using  $\text{CH}_2\text{Cl}_2$  as the eluent to give 6a (0.87 g, 64%) as colorless needles, mp 89-90°C. Anal. Calcd for  $\text{C}_{11}\text{H}_{15}\text{NO}_4$ : C, 58.65; H, 6.71; N, 6.22. Found: C, 58.59; H, 6.71; N, 6.45.  $^1\text{H-Nmr}$  ( $\text{CDCl}_3/\text{TMS}$ )  $\delta$ : 2.12 (3H, s), 2.14 (3H, s), 2.26 (1H, d,  $J=18$  Hz), 2.63 (1H, d&d,  $J=18$  Hz, 7 Hz), 4.38 (1H, d,  $J=4$  Hz), 4.60-4.90 (1H, m), 5.04 (1H, d,  $J=7$  Hz). Ir (KBr): 1762, 1738, 1645  $\text{cm}^{-1}$ . Ms  $m/z$ : 225 ( $\text{M}^+$ ).

N-Acetyl-2 $\alpha$ -chloronortropan-7-one (6c)--Acetyl chloride (0.224 g, 2.85 mmol) was carefully added to a solution of 3 (0.125 g, 1 mmol) in  $\text{CH}_2\text{Cl}_2$  (30 ml) at room temperature. The mixture was stirred for 5 h and concentrated to dryness in vacuo. The residue was purified by recrystallization from ether to afford pure 6c (0.127 g, 62%) as colorless needles, mp 126-127°C. Anal. Calcd for  $\text{C}_9\text{H}_{12}\text{ClNO}_2$ : C, 53.61; H, 6.00; N, 6.95. Found: C, 53.79; H, 5.98; N, 6.79. Ir (KBr): 1770, 1640, 1450, 1430  $\text{cm}^{-1}$ . Ms  $m/z$ : 201, 203 ( $\text{M}^+$ ).

N-Cyano-2 $\alpha$ -bromonortropan-7-one (6d)--A solution of cyanogen bromide (0.180 g, 1.6 eq) in  $\text{CH}_2\text{Cl}_2$  (10 ml) was added to a solution of 3 (0.132 g, 1 mmol) in  $\text{CH}_2\text{Cl}_2$  (20 ml) at room temperature. The mixture was refluxed for 2 h, then concentrated in vacuo, and the residue was purified by column chromatography on silica gel using  $\text{CH}_2\text{Cl}_2$  as the eluent to give 6d (0.175 g, 71%) as colorless needles, mp 124-125°C. Anal. Calcd for  $\text{C}_8\text{H}_9\text{BrN}_2\text{O}$ : C, 42.33; H, 3.98; N, 11.80. Found: C, 41.95; H, 3.96; N, 2.23.  $^1\text{H-Nmr}$  ( $\text{CDCl}_3/\text{TMS}$ )  $\delta$ : 2.34 (1H, d,  $J=18$  Hz), 2.80 (1H, d&d,  $J=7$  Hz, 18 Hz), 3.88 (1H, d,  $J=3$  Hz), 4.33 (1H, d,  $J=7$  Hz), 4.54-4.40 (1H, m). Ms  $m/z$ : 228, 230 ( $\text{M}^+$ ). Ir (KBr) 2210, 1763  $\text{cm}^{-1}$ .  $^{13}\text{C-Nmr}$  ( $\text{CDCl}_3/\text{TMS}$ )  $\delta$ : 29.1 (t), 29.5 (t), 40.9 (t), 42.4 (d), 57.2 (d), 65.7 (d), 113.3 (s), 203.3 (s).

N-Acetyl-2 $\alpha$ -hydroxynortropan-7-one (6b) (hydrolysis of 6a)--A solution of saturated potassium carbonate (2 g) in water (10 ml) was added to a solution of 6a (0.36 g, 1.6 mmol) in methanol (10 ml) at room temperature. The mixture was stirred for 1.5 h and concentrated to dryness in vacuo, and the residue was purified by column chromatography on silica gel using  $\text{CH}_2\text{Cl}_2$  as the eluent to give pure 6b (0.153 g, 52%), colorless prisms, mp 175-177°C. A part of the 6a (0.078 g, 22%) was recovered. 6b: Anal. Calcd for  $\text{C}_9\text{H}_{13}\text{NO}_3$ : C, 59.00; H, 7.15; N, 7.65. Found: C, 58.77; H, 7.11; N, 7.53.  $^1\text{H-Nmr}$  ( $\text{CDCl}_3/\text{TMS}$ )  $\delta$ : 2.08 (3H, s), 2.25 (1H, d,  $J=18$

Hz), 2.75 (1H, d&d, J=18 Hz, 8 Hz), 3.70-4.00 (1H, m), 4.36 (2H, d, J=4 Hz), 4.62 (1H, d, J=8 Hz).

N-Mesyl-2 $\alpha$ -chloronortropan-7-one (6e)--Mesyl chloride (0.6 g, 3.4 eq) was added to a solution of 3 (0.15 g, 1.2 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (30 ml) at room temperature. The mixture was refluxed for 2 h. The solvent was evaporated off in vacuo and the residue was recrystallized from ether to give 6e (0.19 g, 58%) as colorless flakes mp 95-96°C. Anal. Calcd for C<sub>8</sub>H<sub>12</sub>ClO<sub>3</sub>S: C, 40.72; H, 5.05; N, 5.65. Found: C, 40.42; H, 5.09; N, 5.89. <sup>1</sup>H-Nmr (CDCl<sub>3</sub>/TMS)  $\delta$ : 3.03 (3H, s), 2.30 (1H, d, J=19 Hz), 2.79 (1H, d&d, J=8 Hz, 19 Hz), 4.09 (1H, d, J=4 Hz), 4.10-4.40 (1H, m), 4.66 (1H, d, J=8 Hz). Ms m/z: 223, 225 (M<sup>+</sup>). Ir (Cap.): 1758, 1340, 1150 cm<sup>-1</sup>.

N-Ethoxycarbonyl-2 $\alpha$ -chloronortropan-7-one (6f)--Ethyl chloroformate (1.2 g, 10 eq) was added to a solution of 3 (0.138 g, 1.1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (30 ml). The mixture was refluxed for 2 h, then evaporated in vacuo, and the residue was chromatographed on silica gel using CH<sub>2</sub>Cl<sub>2</sub> as the eluent to afford 6f (0.17 g, 66%) as a colorless syrup. <sup>1</sup>H-Nmr (CDCl<sub>3</sub>/TMS)  $\delta$ : 1.30 (3H, t, J=6 Hz), 2.27 (1H, d, J=6 Hz), 2.76 (1H, d&d, J=7 Hz, 18 Hz), 4.22 (2H, q, J=6 Hz), 4.66 (1H, d, J=7 Hz). Ir (Cap.): 1768, 1705, 1422 cm<sup>-1</sup>. <sup>13</sup>C-Nmr (CDCl<sub>3</sub>/TMS)  $\delta$ : 14.6 (q), 29.0 (t), 29.5 (t), 42.3 (t), 51.2 (d), 54.0 (d), 61.8 (t), 63.7 (d), 153.1 (s), 206.9 (s). Ms m/z: 231, 233 (M<sup>+</sup>).

N-Methyl-2 $\alpha$ -hydroxynortropan-7-one (6g)--Methyl iodide (1 ml) was added to a solution of 3 (0.20 g, 1.6 mmol) in benzene (50 ml). The mixture was stirred for 20 h at room temperature. After removal of the precipitate, the filtrate was passed through an aluminum oxide column (50 g) eluting with CH<sub>2</sub>Cl<sub>2</sub>-hexane (1:1) to give 6g (0.04 g, 16%) as a red syrup. Ms m/z: 155 (M<sup>+</sup>), ir (CHCl<sub>3</sub>): 1740 cm<sup>-1</sup>. <sup>1</sup>H-Nmr (CD<sub>3</sub>OD/TMS)  $\delta$ : 2.59 (1H, d, J=19 Hz), 2.95 (3H, s), 3.07 (1H, d&d, J=8 Hz, J=19 Hz), 3.73 (1H, J=4 Hz), 4.23 (1H, d&t, J=5 Hz, 5 Hz, 11 Hz), 4.34 (1H, d, J=8 Hz).

2 $\alpha$ -Methoxynortropan-7-one (6h)--Compound 3 (0.14 g, 1.2 mmol) was added to a solution of borontrifluoride etherate (1.0 g, 7 mmol) in absolute methanol (30 ml) at room temperature with stirring. After 30 min, aqueous 5% potassium carbonate solution (20 ml) was added to the mixture. The reaction mixture was concentrated

under reduced pressure to half of its original volume. Extraction with  $\text{CH}_2\text{Cl}_2$  (3x50 ml) followed by drying and evaporation of the combined organic layers afforded the residue, which was purified by column chromatography on  $\text{Al}_2\text{O}_3$  using  $\text{CH}_2\text{Cl}_2$ -MeOH (50:1) as the eluent to give 6h (0.04 g, 23%) as a pale yellow syrup.  $^1\text{H-Nmr}$  ( $\text{CDCl}_3/\text{TMS}$ )  $\delta$ : 2.14 (1H, d,  $J=18$  Hz), 2.50 (1H, d&d,  $J=8$  Hz, 18 Hz), 3.46 (3H, s), 3.84 (1H, d,  $J=8$  Hz).

Synthesis of compound (9); Michael addition of 3 to DMAD--Dimethyl acetylenedicarboxylate (DMAD) (0.168 g, 1.2 mmol) was added dropwise to a solution of 3 (0.145 g, 1.2 mmol) in absolute  $\text{CH}_2\text{Cl}_2$  (30 ml) at  $0^\circ\text{C}$ . The mixture was stirred for 3 h at this temperature. The solvent was evaporated off in vacuo to give the residue, which was chromatographed on silica gel using ethyl acetate-hexane (1:1) as the eluent to furnish 9 (0.209 g, 67%) as a colorless liquid.  $\text{Ms m/z}$ : 265 ( $\text{M}^+$ ).  $^1\text{H-Nmr}$  ( $\text{CDCl}_3/\text{TMS}$ )  $\delta$ : 2.96 (2H, br s), 3.71 (3H, s), 3.89 (3H, s), 5.46 (1H, s), 5.95 (1H, d,  $J=12$  Hz), 6.54 (1H, m,  $J=12$  Hz, 3 Hz, 6 Hz).  $^{13}\text{C-Nmr}$  ( $\text{CDCl}_3/\text{TMS}$ )  $\delta$ : 24.7 (t,  $J=128$  Hz), 27.2 (t,  $J=128$  Hz), 43.7 (d,  $J=169$  Hz), 49.3 (d,  $J=169$  Hz), 51.5 (q,  $J=147$  Hz), 52.7 (q,  $J=149$  Hz), 104.9 (d,  $J=163$  Hz), 129.1 (d,  $J=159$  Hz), 146.7 (d,  $J=152$  Hz), 155.7 (s), 164.8 (s), 165.4 (s), 196.4 (s).  $\text{Ir (Cap)}$ : 1745, 1720, 1660, 1625, 1150  $\text{cm}^{-1}$ .  $\text{Uv nm } (\epsilon)$ : 235 (8900).

Dimethyl (2 $\alpha$ -methoxy-7-oxonortropan-1-yl)maleate (11a)--DMAD (0.164 g, 1.2 mmol) was added dropwise to a solution of 3 (0.12 g, 1 mmol) in absolute  $\text{CH}_2\text{Cl}_2$  (30 ml) containing absolute methanol (0.05 g, 1.56 mmol) with external cooling (at  $0^\circ\text{C}$ ). The mixture was stirred for 3 h at  $0^\circ\text{C}$  and then evaporated in vacuo to give the residue, which was purified by chromatography on silica gel using ethyl acetate-hexane (1:1) as the eluent and recrystallized from ether to furnish 11a (0.188 g, 63%) as colorless flakes, mp  $91-92^\circ\text{C}$ . Anal. Calcd for  $\text{C}_{14}\text{H}_{19}\text{NO}$ : C, 56.56; H, 6.44; N, 4.71. Found: C, 56.44; H, 6.61; N, 4.75.  $\text{Ms m/z}$ : 297 ( $\text{M}^+$ ).  $^1\text{H-Nmr}$  ( $\text{CDCl}_3/\text{TMS}$ )  $\delta$ : 2.29 (1H, d,  $J=17$  Hz), 2.76 (1H, d&d,  $J=17$  Hz, 8 Hz), 3.44 (3H, s), 3.69 (3H, s), 3.97 (3H, s), 4.23 (1H, d,  $J=8$  Hz), 4.89 (1H, s).  $^{13}\text{C-Nmr}$  ( $\text{CDCl}_3/\text{TMS}$ )  $\delta$ : 24.7 (t,  $J=130$  Hz), 26.4 (t,  $J=130$  Hz), 42.0 (t,  $J=138$  Hz), 50.9 (q,  $J=145$  Hz), 53.06 (q,  $J=150$  Hz), 54.1 (d,  $J=155$  Hz), 56.5 (q,  $J=145$  Hz), 63.0 (d,  $J=150$  Hz), 75.2 (d,  $J=147$  Hz), 86.7 (d,  $J=164$  Hz), 149.2 (s), 164.6 (s), 167.0 (s), 206.3 (s).  $\text{Uv nm } (\epsilon)$ : 277 (25900), 226 (29700).



Dimethyl (2 $\alpha$ -hydroxy-7-oxonortropan-1-yl)maleate (11b)--A solution of H<sub>2</sub>O (0.03 g, 1.7 mmol) in tetrahydrofuran (5 ml) was added to a solution of 3 (0.05 g, 0.42 mmol) in ethyl acetate (30 ml) at room temperature. The mixture was kept at 0°C with external cooling. To this mixture, DMAD (0.05 g, 0.4 mmol) was added dropwise. After stirring for 6 h at 0°C, the reaction mixture was concentrated in vacuo to give the residue, which was purified by PTLC using ethyl acetate-hexane (1:1) as the eluent to give pure 11b (0.05 g, 44%) as a pale yellow syrup. <sup>1</sup>H-Nmr (CDCl<sub>3</sub>/TMS)  $\delta$ : 2.22 (1H, d, J=16 Hz), 2.72 (1H, d&d, J=16 Hz, 7 Hz), 3.56 (3H, s), 3.55-4.06 (2H, m), 3.83 (3H, s), 4.11 (1H, m), 4.83 (1H, s), 5.22 (1H, s).

Dimethyl [2 $\alpha$ -(2-oxo-3-penten-4-oxy)-7-oxonortropan-1-yl]maleate (11c)--Acetyl acetone (0.25 g, 40 mmol) was added to a solution of 3 (0.05 g, 0.42 mmol) in ethyl acetate (30 ml), and the mixture was kept at 0°C with external cooling. To this mixture, DMAD (0.13 g, 0.9 mmol) was added dropwise at 0°C. After stirring for 4 h at 0°C, the reaction mixture was concentrated in vacuo to give the residue, which was recrystallized from ether to furnish 11c (0.045 g, 30%) as a colorless powder, mp 195-197°C. Ms m/z: 365 (M<sup>+</sup>). Ir (KBr): 1770, 1735, 1690, 1635, 1570, 1155 cm<sup>-1</sup>. <sup>1</sup>H-Nmr (CDCl<sub>3</sub>/TMS)  $\delta$ : 2.07 (3H, s), 2.31 (3H, s), 2.36 (1H, d, J=18 Hz), 2.75 (1H, d&d, J=18 Hz, 7 Hz), 3.67 (3H, s), 3.76 (1H, d, J=4 Hz), 3.95 (3H, s), 4.27 (1H, d, J=7 Hz), 4.55-4.79 (1H, m), 4.90 (1H, s), 5.18 (1H, s).

Dimethyl (2 $\alpha$ -phenoxy-7-oxonortropan-1-yl)maleate (11d)--Phenol (0.40 g, 10 eq) was added to a solution of 3 (0.05 g, 0.42 mmol) in ethyl acetate (30 ml) at room temperature. DMAD (0.10 g, 1.8 eq) was then added, and the mixture was stirred for 3 h at this temperature then concentrated in vacuo to give the residue, which was purified by column chromatography on silica gel using CH<sub>2</sub>Cl<sub>2</sub> as the eluent to afford 11d (0.064 g, 44%) as a colorless syrup. Ms m/z: 359 (M<sup>+</sup>). <sup>1</sup>H-Nmr (CDCl<sub>3</sub>/TMS)  $\delta$ : 3.67 (3H, s), 3.85 (3H, s), 4.25 (1H, d, J=6 Hz), 4.44-4.74 (1H, m), 4.86 (1H, s), 6.80-7.44 (5H, m). Ir (KBr): 1765, 1740, 1690, 1670, 1650, 1580 cm<sup>-1</sup>.

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