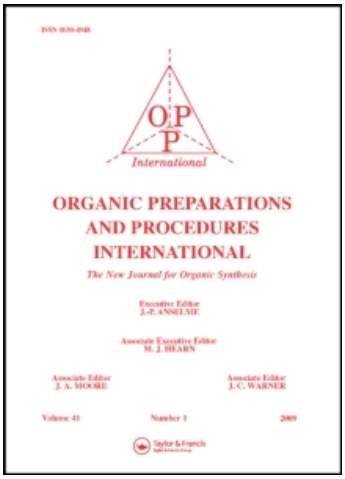

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SYNTHESIS OF 3-QUINUCLIDINYL BENZILATE DERIVATIVES

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The same procedure was used to hydrolyze 3,4-bis(dibromomethyl)benzophenone; 5- and 6- benzoylphthalides were separated from the crude product by silica gel chromatography using benzene as eluent.

Anal. Calcd. $C_{15}H_{10}O_3$ (for 2b): C, 75.62; H, 4.23. Found: C, 75.40; H, 4.19

Anal. Calcd. $C_{15}H_{10}O_3$ (for 3b): C, 75.62; H, 4.23. Found: C, 75.55; H, 4.16

The yields and the physical constants of compounds (2a,b and 3a,b) are listed in Table I.

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SYNTHESIS OF 3-QUINUCLIDINYL BENZILATE DERIVATIVES

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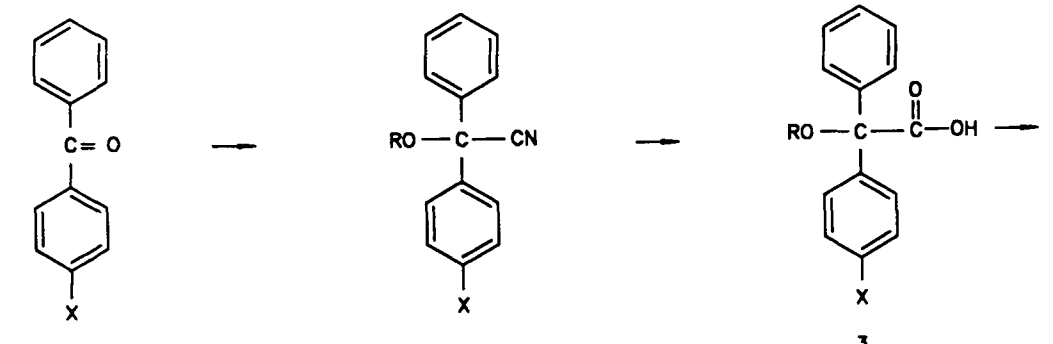
3-Quinuclidinyl benzilate (QNB) has been shown to be an effective muscarinic antagonist.[1] Radioiodinated analogs of QNB have been used effectively for myocardial imaging.[2] Generally, the radioiodinated QNB derivatives are obtained in low yield, by direct electrophilic iodination of 3-quinuclidinyl benzilate[3] or by halogen exchange reactions.[4] We have developed effective routes to 4-bromo- and 4-iodo analogs of QNB. These agents can be used to prepare the

corresponding radiolabeled agents via halogen-halogen exchange or metallation-halogenation sequences. We also prepared the boronic acid derivative of QNB (6). Boronic acid derivatives of a number of physiologically active compounds have been used as precursors to a variety of high specific activity radiopharmaceuticals. Preliminary studies indicate that the boronic acid 6 is easily converted to the iodinated QNB derivative 5 using conditions suitable for radioiodination.[5]



1

a- X=Br

b- X=I

2

a- X=Br R=Si(CH$_3$)$_3$

b- X=I R=Si(CH$_3$)$_3$

c- X=Br R=CH$_2$OCH$_3$

d- X=I R=CH$_2$OCH$_3$

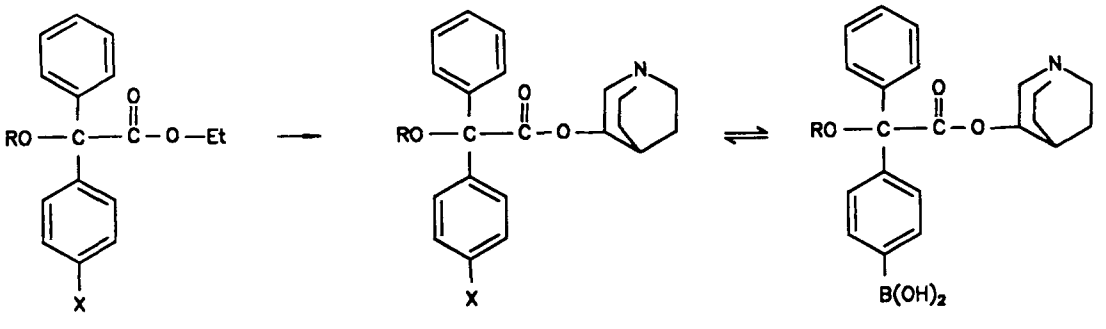
3

a- X=Br R=OH

b- X=I R=OH

c- X=Br R=CH$_2$OCH$_3$

d- X=I R=CH$_2$OCH$_3$



4

a- X=Br R=H

b- X=I R=H

c- X=Br R=CH$_2$OCH$_3$

d- X=I R=CH$_2$OCH$_3$

5

a- X=Br R=H

b- X=I R=H

c- X=Br R=CH$_2$OCH$_3$

d- X=I R=CH$_2$OCH$_3$

6

a- R=OH

b- R=CH$_2$OCH$_3$

Commercially available 4-halobenzophenones (1a, 1b)[6] were converted to the corresponding trimethylsiloxynitriles (2a, 2b) by treatment with trimethylsilyl cyanide. The nitriles thus obtained were hydrolyzed to the corresponding acids (3). The acids (3) were then converted under basic conditions to the ethyl esters (4) which were purified by column chromatography.

The transesterification of the ethyl esters (4) to the corresponding 3-quinuclidinyl esters (5) was performed by heating 4 with a mixture of 3-quinuclidinol, benzene and sodium.

The methoxymethyl ether derivatives (2c and 2d) were also prepared by reaction of 2a and 2b with chloromethoxymethyl ether/P_2O_5/$CHCl_3$.[7] The nitriles (2c and 2d) thus obtained were hydrolyzed under basic conditions to give 3c and 3d. The ethyl esters (4c and 4d) were obtained under basic conditions and converted to the 3-quinuclidinyl esters 5c and 5d. The boronic acid (6) was prepared using a lithium exchange reaction (5b, 5d) with n-BuLi followed by addition of methyl borate.

EXPERIMENTAL SECTION

The ^1H and ^{13}C NMR spectra were obtained on a Jeol-FX90Q spectrometer using TMS as an internal standard. The melting points were recorded using a Fisher-Jones melting point apparatus and are uncorrected. Elemental analyses were carried out at Galbraith Laboratories, Knoxville, TN. Mass spectra were determined on ZAB-EQ.

α-Trimethylsiloxy-α-(4-bromophenyl)-α-phenylacetonitrile (2a).- A 250 ml round bottom flask equipped with a septum inlet, magnetic stirring bar and a gas outlet (mercury bubbler) was assembled hot, then flushed with argon (or nitrogen) while being flame dried. After cooling to room temperature in a stream of argon, 4-bromobenzophenone (1a) (10.5 g, 40 mmol) was introduced into the flask under a stream of argon, along with anhyd. ZnI_2 (540 mg, catalyst). Anhydrous methylene chloride (40 ml) was added with stirring. Trimethylsilyl cyanide (10 ml, 80 mmol) was then introduced dropwise via a syringe and the mixture stirred at room temperature for 72 hrs; then CH_2Cl_2 (100 ml) was added and the solution transferred to a separatory funnel. After washing with saturated aqueous $NaHCO_3$ (5 x 25 ml) and water, the organic layer was dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the residue purified by column chromatography (150 g of silica gel, 200 ml of hexane), to yield 11.3 g (95%) of a pale yellow oil, bp. 135-140°/0.11 mm Hg. ^1H-NMR (DMSO-d_6): δ 0.017 (s, 9H, $(CH_3)_3Si$), 7.34-7.49 (m, Ar-H). ^{13}C NMR (DMSO-d_6): δ 75.55 (-C-CN), 120.03 (-C≡N), 122.30 (Ar-C-Br) and 125.33-140.94 (Other Ar-C).

Anal. Calcd. for $C_{17}H_{18}BrNOSi$: C, 56.66; H, 5.03. Found: C, 56.59; H, 4.98

α-Trimethylsiloxy-α-(4-iodophenyl)-α-phenylacetonitrile (2b) was obtained as described above in 98% yield as a viscous oil which was used directly to prepare 3b. ^1H NMR ($CDCl_3$): δ 7.05-7.59 (m, Ar-H); 0.026 (s, 9H, $(CH_3)_3Si$). ^{13}C NMR ($CDCl_3$): δ 76.02 (-C-CN), 94.71 (C-I), 120.22 (CN), 125.83, 127.75, 128.73, 128.94, 137.72, 141.35, 142.0 (Ar-C). MS: Calcd. for $C_{17}H_{18}INOSi$: 407 (M^+). Found: 407.

α-Hydroxy-α-(4-bromophenyl)-α-phenylacetic Acid (3a).- Compound 2a (12.0 g, 41.6 mmol) was heated at 80-85° for 48 hrs in 150 ml of a mixture of H_2O-CH_3COOH-conc. HCl (1:3:3). After cooling, the solvent was evaporated and the residue dissolved in 200 ml of saturated Na_2CO_3 aqueous solution. The solution was washed with ether (5 x 30 ml); the aqueous layer was cooled in an ice-bath, acidified with 6N HCl and extracted with ether (5 x 50 ml); the

combined organic layer was washed with water, dried and the solvent evaporated to give 4.0 g (32%) of 3a, mp. 124-126°. ^{1}H NMR (DMSO-d_6): δ 2.51 (s, 1H, -C-OH) and 7.36-7.68 (m, Ar-H). ^{13}C NMR (DMSO-d_6): δ 79.94 (HO-C-COOH), 120.57 (Ar-C-Br), 126.93-143.32 (Ar-C) and 174.29 COOH).

Anal. Calcd. for $C_{14}H_{11}BrO_3$: C, 54.74; H, 3.61. Found: C, 54.82; H, 3.89

α-Hydroxy-α-(4-iodophenyl)-α-phenylacetic Acid (3b) was obtained as described above. A viscous oil was obtained in 52% yield which was used directly to prepare 4b. ^{1}H NMR ($CDCl_3$): δ 7.16-7.72 (m, Ar-H). ^{13}C NMR ($CDCl_3$): δ 80.92 (-C-COOH), 94.71 (-C-I), 127.27, 128.78, 129.46, 137.45, 140.78 (Ar-C), 178.60 (-COOH).

Ethyl α-Hydroxy-α-(4-bromophenyl)-α-phenylacetate (4a).- A suspension of K_2CO_3 (0.96 g, 9.6 mmol), 18-crown-6 (100 mg) and 3a (1.59 g, 6.45 mmol) in 50 ml of dry (molecular sieves) acetonitrile was stirred at room temperature for 30 min. Ethyl bromide (2.3 ml, 32.2 mmol) was added dropwise and the mixture stirred at room temperature for 96 hrs. The precipitate was collected and washed with more acetonitrile (30 ml); the combined filtrate was concentrated under vacuum and the residue was charged on a silica gel column (20 g) and eluted successively with hexane (200 ml), hexane-benzene (4:1) (200 ml), hexane-benzene (1:1) (250 ml). Evaporation of the solvent from the last fraction gave 1.53 g of a colorless oil (71%) which solidified on standing, mp. 38-40°. ^{1}H NMR (DMSO-d_6): δ 1.2 (t, 3H, -CH_2CH_3), 4.2 (q, 2H, -CH_2CH_3) and 7-7.6 (m, Ar-H). ^{13}C NMR (DMSO-d_6): δ 13.98 (-O-CH_2-CH_3), 61.71 (-O-CH_2-CH_3), 80.50 (HO-C-C-O-), 121.11 (Ar-C-Br), 127.07-143.16 (Ar-C) and 172.93 (-$COOC_2H_5$).

Anal. Calcd. for $C_{16}H_{15}BrO_3$: C, 57.33; H, 4.51. Found: C, 57.20; H, 4.67

Ethyl α-Hydroxy-α-(4-iodophenyl)-α-phenylacetate (4b) was obtained as described above in 75% yield, mp. 40-42°. ^{1}H NMR ($CDCl_3$): δ 1.26 (t, 3H, CH_3), 4.31 (q, 2H, CH_2O), 7.16-7.71 (m, 9H, Ar-H). ^{13}C NMR ($CDCl_3$): δ 14.07 (CH_3), 63.15 (CH_2O), 80.65 (-C-$COOC_2H_5$), 94.11 (C-I), 127.24, 128.27, 129.54, 137.18, 141.78 (Ar-carbons), 173.94 (-$COOC_2H_5$). EI-MS: Calcd. for $C_{16}H_{15}IO_3$: 382.0065965. Found: 382.0048.

(R,S)-1-Azabicyclo[2.2.2]oct-3-yl (R,S)-α-Hydroxy-α-(4-bromophenyl)-α-phenylacetate (5a).- A solution of (R,S)-3-quinuclidinol (1.9 g, 15 mmol) in 30 ml of dry benzene was refluxed and 15 ml of benzene was distilled off using a Dean-Stark trap. A clean piece of sodium (150 mg) was added and the suspension refluxed for 1 hr. A solution of 4a (1.1 g, 3 mmol) in 30 ml of dry benzene was also refluxed and 15 ml of benzene distilled off. The solution of 4a was added, by means of a syringe, to the 3-quinuclidinol solution and the mixture refluxed for 24 hrs. The solvent was evaporated, H_2O added (50 ml) and the mixture extracted with ethyl acetate (5 x 50 ml). The combined organic layer was washed repeatedly with water to remove the excess 3-quinuclidinol and the solution dried over anhyd. $MgSO_4$. Evaporation of the solvent yielded a white residue which was recrystallized from acetonitrile to yield 0.99 g (83%) of the product, mp. 172-173°. ^{1}H NMR (DMSO-d_6): δ 1.12-3.24 (m, 12H, quinuclidinyl protons) and 7-7.6

(m, 9H, Ar-H). ^{13}C NMR (DMSO-d_6): δ 18.5, 22.8, 24.0, 45.2, 46.5, 54.0, 72.5 (quinuclidinyl carbons), 80.0 (OH-C-COO3Q), 120.0 (Ar-C-Br), 125-142 (Ar-C) and 172.50 (-COO3Q).

Anal. Calcd. for $C_{21}H_{22}BrNO_3$: C, 60.58; H, 5.32; N, 3.36

Found: C, 60.49; H, 5.51; N, 3.48

(R,S)-1-Azabicyclo[2.2.2]oct-3-yl (R,S)-α-Hydroxy-α-(4-iodophenyl)-α-phenylacetate (5b) was obtained as described above. The yield was 78%, mp. 142-144°. ^1H NMR ($CDCl_3$): δ 1.28-3.26 (m, 12H, quinuclidinyl protons), 4.91 (s, br, 1H, OH), 7.0-7.71 (m, 9H, Ar-H). ^{13}C NMR ($CDCl_3$): δ 19.30, 24.17, 25.12, 46.14, 47.01, 54.84, 74.23 (quinuclidinyl carbons), 80.73 (-C-COOQ), 94.0 (C-I), 127.27, 128.24, 129.51, 137.10, 142.03 (Ar carbons), 176.69 (-COO 3Q). HRMS: Calcd. for $C_{21}H_{22}INO_3$: 463.0645 (M^+). Found: 463. 0604.

α-(Methoxymethyl)-α-(4-bromophenyl)-α-phenylacetonitrile (2c).- To a stirred solution of 2a (1.44 g, 5 mmol) in chloroform (10 ml, dried over P_2O_5) were added phosphorus pentoxide (1.2 g) and chloromethyl methyl ether (1.06 ml, 15 mmol) [Caution: carcinogen]; the reaction mixture was stirred for 4 hrs and then poured into an ice cooled aqueous solution of sodium carbonate. The thick oily material remaining in the reaction flask was washed with additional Na_2CO_3 solution and the combined basic solution was extracted with ether (6 x 25 ml). The combined ethereal layer was washed with brine, dried over anhyd. $MgSO_4$ and evaporated to give an oil. This product was purified by passing through a column of silica gel (20 g) and eluted with hexane (125 ml), hexane-benzene (4:1) (150 ml), hexane-benzene (1:1) (150 ml). The last fraction collected contained 1.04 g (63%) of the product. ^1H NMR (DMSO-d_6): δ 3.43 (s, 3H, -OCH_3), 4.81 (s, 2H, -O-CH_2-O-) and 7-8 (Ar-H); ^{13}C NMR (DMSO-d_6): δ 56.37 (-OCH_3), 78.09 (-O-C-CN), 93.80 (-OCH_2O-), 118.94 (-CN), 122.90 (Ar-C-Br) and 126.34-138.34 (Ar-C).

Anal. Calcd. for $C_{16}H_{14}BrNO_2$: C, 57.84; H, 4.24; N, 4.21; Br, 24.05

Found: C, 58.14; H, 4.27; N, 3.75; Br, 24.33

α-(Methoxymethyl)-α-(4-iodophenyl)-α-phenylacetonitrile (2d) was obtained as described above. The product was an oil obtained in 56% yield which was used directly to prepare 3d. ^1H NMR ($CDCl_3$): δ 3.46 (d, 3H, CH_3O), 4.78 (d, 2H, CH_2O), 7.21-7.73 (m, 9H, Ar-H). ^{13}C NMR ($CDCl_3$): δ 56.73 (CH$_3$O), 78.86 (-C-CN), 94.35 (CH$_2$O), 95.14 (C-I), 118.54 (CN), 126.72, 128.32, 128.51, 128.86, 129.32, 137.97, 138.56, 139.35 (Ar carbons).

Anal. Calcd. for $C_{16}H_{14}INO_2$: C, 50.68; H, 3.72; N, 3.69. Found: C, 50.39; H, 3.81; N, 3.66

α-(Methoxymethyl)-α-(4-bromophenyl)-α-phenylacetic Acid (3c).- Compound 2c (3.6 g, 10.8 mmol) was dissolved in ethylene glycol (75 ml) and aq. sodium hydroxide (20 ml, 35%) was added. The mixture was heated at 135-140° for 24 hrs; the solution was then cooled to room temperature and water (700 ml) added. The mixture was washed with ether (5 x 30 ml) and then cooled in an ice bath. Dilute HCl was added (pH ~ 4) and the product extracted into ether (5 x

50 ml). The combined organic layer was washed with brine, dried and the solvent evaporated to yield 2.77 g (72%) of a viscous oil. ^{1}H NMR (DMSO-d_6): δ 3.20 (s, 3H, -OC<u>H</u>$_3$), 4.65 (s, 2H, -O-C<u>H</u>$_2$-O-) and 7-8 (Ar-<u>H</u>). ^{13}C NMR (DMSO-d_6): δ 55.75 (-O-<u>C</u>H$_3$), 84.81 (-O-<u>C</u>-COOH), 92.75 (-O<u>C</u>H$_2$O-), 121.30 (Ar-<u>C</u>-Br), 128.10-140.83 (Ar-<u>C</u>) and 172.28 (-<u>C</u>OOH). The product was used directly to prepare <u>4c</u>.

<u>α-(Methoxymethyl)-α-(4-iodophenyl)-α-phenylacetic Acid</u> (<u>3d</u>) was obtained as described above. The reaction yielded an oil (71%) which was used directly to prepare <u>4d</u>. ^{1}H NMR ($CDCl_3$): δ 3.31 (s, 3H, C<u>H</u>$_3$O), 4.65 (s, 2H, C<u>H</u>$_2$O), 10.58 (s, br, 1H, -COO<u>H</u>). ^{13}C NMR ($CDCl_3$): δ 56.43 (<u>C</u>H$_3$O), 85.50 (-<u>C</u>-COOH), 93.30 (CH$_3$O<u>C</u>H$_2$O-), 94.22 (C-I), 175.0 (-<u>C</u>OOH).

<u>Ethyl α-(Methoxymethyl)-α-(4-bromophenyl)-α-phenylacetate</u> (<u>4c</u>).- The reaction was carried out as described for compound <u>4a</u> using the following quantities: <u>3c</u> (2.87 g, 8 mmol) in dry CH_3CN (30 ml), K_2CO_3 (1.22 g, 12 mmol), crown ether (120 mg) and ethyl bromide (3.0 ml, 40 mmol). The oily product was purified by column chromatography (silica gel, 20 g) and eluted successively with hexane (250 ml), hexane-benzene (1:1) (300 ml) and finally benzene (150 ml). The second fraction yielded 1.73 g (57%) of a colorless oil, bp. 175-180°/0.02 mm Hg. ^{1}H NMR (DMSO-d_6): δ 1.3 (t, 3H, -OCH$_2$C<u>H</u>$_3$), 3.2 (s, -OC<u>H</u>$_3$), 4.2 (q, 2H, OC<u>H</u>$_2$CH$_3$), 4.7 (s, -OC<u>H</u>$_2$-) and 7-7.6 (Ar-<u>H</u>). ^{13}C NMR (DMSO-d_6): δ 13.90 (-OCH$_2$<u>C</u>H$_3$), 55.99 (-O-<u>C</u>H$_3$), 61.84 (O<u>C</u>H$_2$CH$_3$), 84.89 (-O-<u>C</u>-C-), 92.94 (-O<u>C</u>H$_2$O-), 121.62 (Ar-<u>C</u>-Br), 128-140.37 (Ar-<u>C</u>) and 170.84 (-<u>C</u>OOH).

<u>Anal</u>. Calcd. for $C_{18}H_{19}BrO_4$: C, 57.00; H, 5.04; Br, 21.06
Found: C, 57.05; H, 5.09; Br, 21.44

<u>Ethyl α-(Methoxymethyl)-α-(4-iodophenyl)-α-phenylacetate</u> (<u>4d</u>) was obtained in 88% yield as a solid, mp. 47-49°, in a fashion analogous to <u>4c</u>. ^{1}H NMR ($CDCl_3$): δ 1.22 (t, 3H, C<u>H</u>$_3$), 3.34 (s, 3H, C<u>H</u>$_3$O), 4.24 (q, 2H, C<u>H</u>$_2$O), 4.69 (s, 2H, OC<u>H</u>$_2$O), 7.10-7.70 (m, 9H, Ar-H). ^{13}C NMR ($CDCl_3$): δ 14.02 (<u>C</u>H$_3$), 56.43 (<u>C</u>H$_3$O), 61.88 (O<u>C</u>H$_2$), 85.50 (-<u>C</u>-COOC$_2$H$_5$), 93.30 (O<u>C</u>H$_2$O), 94.22 (C-I), 128.0, 128.32, 128.51, 130.08, 130.38, 140.13, 140.92 (Ar carbons), 171.36 (-C-<u>C</u>OOC$_2$H$_5$).

<u>Anal</u>. Calcd. for $C_{18}H_{19}IO_4$: C, 50.72; H, 4.49; N, 29.77
Found: C, 50.62; H, 4.49; N, 29.83

<u>(R,S)-1-Azabicyclo[2.2.2]oct-3-yl (R,S)-α-(Methoxymethyl)-α-(4-bromophenyl)-α-phenylacetate</u> (<u>5c</u>).- The reaction was carried out as described earlier (<u>5a</u>) using the following quantities: 1.3 g (3.4 mmol) of <u>4c</u> and 3-quinuclidinol (2.16 g, 17.0 mmol) in benzene (30 ml). The product was purified by column chromatography (silica gel, 20 g) using CH_2Cl_2 (100 ml) followed by CH_2Cl_2-CH_3OH (20:1) (150 ml). The fraction eluted with CH_2Cl_2-CH_3OH (20:1) contained 0.68 g (44.1%) of the product, mp. 158-160°. ^{1}H NMR (DMSO-d_6): δ 3.24 (s, 3H, -OC<u>H</u>$_3$), 4.70 (s, 2H, -OC<u>H</u>$_2$-) and 7-8 (m, Ar-H). ^{13}C NMR (DMSO-d_6): δ 19.13, 23.87, 24.81, 45.81, 46.70, 54.64, 73.08 (Quinuclidinyl carbons), 55.83 (-O<u>C</u>H$_3$), 84.95 (-O-<u>C</u>-C-),

92.78 (-O<u>C</u>H_2O-), 121.57 (Ar-<u>C</u>-Br), 127.04-140.26 (Ar-<u>C</u>) and 170.30 (-<u>C</u>OO3Q).
<u>Anal</u>. Calcd. for $C_{23}H_{26}BrNO_4$: C, 60.00; H, 5.69. Found: C, 60.41; H, 5.32
<u>(R,S)-1-Azabicyclo[2.2.2]oct-3-yl (R,S)-α-(Methoxymethyl)-α-(4-iodophenyl)-α-phenylacetate</u> (<u>5d</u>) was prepared, as described for <u>5a</u>, in 77% yield. ^{1}H NMR ($CDCl_3$): δ 1.30-3.17 (m, 12H, quinuclidinyl protons), 3.31 (d, 3H, C<u>H</u>$_3$O), 4.70 (s, 2H, OC<u>H</u>$_2$O), 7.34-7.69 (m, 9H, Ar-H). ^{13}C NMR ($CDCl_3$): δ 19.32, 24.17, 25.12, 46.38, 47.22, 54.97, 72.87 (quinuclidinyl carbons), 56.43 (<u>C</u>H_3O), 85.74 (-<u>C</u>-COOQ), 93.43 (O<u>C</u>H_2O), 94.33 (<u>C</u>-I), 127.94, 128.11, 130.49, 137.04, 140.19, 140.81 (Ar carbons), 171.04 (-COOH). HRMS: Calcd. for $C_{23}H_{26}INO_4$: 508.0985 (M^++1). Found: 508.0986.
<u>1-Azabicyclo[2.2.2]oct-3-yl (R,S,)-α-Hydroxy-α-(4-phenylboronic acid)-α-phenylacetate</u> (<u>6a</u>).- A flame-dried, nitrogen flushed, septum capped, round-bottom flask was cooled to -78° and then compound <u>5b</u> (926 mg, 2 mmol), in a mixture of 9 ml of dry THF and 45 ml of dry ether, was added <u>via</u> a syringe. <u>n</u>-BuLi (1.6 M solution in hexane, 2.8 ml, 4.4 mmol) was then added and the mixture stirred for 20 min at -78°. Methyl borate (2.1 ml, 20 mmol) was added and the mixture was stirred for an additional 1 hr at -78° and, finally, 3 hrs at room temperature. The resulting suspension was poured into water, stirred for 15 min., extracted with ethyl acetate and dried over $MgSO_4$. The solvent was evaporated to yield a semi-solid which was triturated with ether to yield a solid which was washed repeatedly with ethyl acetate to yield 0.39 g (51%) of QNB boronic acid (<u>6a</u>), mp. 244-246°. ^{1}H NMR (CD_3OD): δ 1.13-3.31 (quinuclidinyl protons), 4.83 (s, 2H, $B(OH)_2$), 6.97-7.62 (m, 9H, Ar protons). ^{13}C NMR (CD_3OD): δ 19.61, 24.08, 25.92, 46.78, 47.67, 55.26, 73.38 (quinuclidinyl carbons), 82.75 (<u>C</u>-I) 127.53, 128.64, 128.91, 134.32, 144.10, 144.59 (Ar carbons), 174.79 (-<u>C</u>OOQ). ^{11}B NMR (CD_3OD): δ 18.60. FAB-MS (using glycerol as the matrix) produced the boronic ester <u>via</u> reaction of the boronic acid and glycerol: Calcd. for $C_{24}H_{28}BNO_6$: 438.2088 $(M+H)^+$. Found: 438.1792.
<u>1-Azabicyclo[2.2.2]oct-3-yl (R,S)-α-(Methoxymethyl)-α-(4-phenylboronic acid)- α-phenylacetate</u> (<u>6b</u>), mp. 241-243°, was obtained from <u>5d</u> as described above in 40% yield. ^{1}H NMR (CD_3OD): δ 1.15-2.91 (m, 12H, quinuclidinyl protons), 3.30 (s, 3H, CH_3O), 4.71 (s, 2H, OCH_2O), 4.88 (s, 2H, $B(OH)_2$), 7.38-7.64 (m, 9H, Ar-H). ^{13}C NMR (CD_3OD): δ 19.45, 23.70, 25.73, 46.81, 47.70, 55.09, 72.62 (quinuclidinyl carbons), 56.75 (CH_3O), 87.40 (-<u>C</u>-OOQ), 94.29 (OCH_2O), 126.63, 128.96, 129.72, 134.30, 141.99 (Ar carbons), 172.82 (-<u>C</u>OOQ). ^{11}B NMR (CD_3OD): δ 18.26. FAB-MS (using glycerol as the matrix) produced the boronic ester <u>via</u> reaction of the boronic acid and glycerol: Calcd. for $C_{26}H_{32}BNO_7$: 482.2350 $(M + 1)^+$. Found: 482.2474.
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AN EFFICIENT SYNTHESIS OF α,β-UNSATURATED CARBOXYLIC ACIDS AND NITRILES

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The preparation of α,β-unsaturated carboxylic acids and nitriles is of importance because of their usefulness in organic synthesis. Condensation of aldehydes with malonic acid or cyanoacetic acid at elevated temperature in the presence of nitrogen bases (Knoevenagel reaction) is commonly employed.[1,2] With aromatic aldehydes, the reaction gives the desired products although the yields vary depending upon the reaction conditions. However, the method does not appear to be suitable with aliphatic aldehydes, especially those of low bp because of poor yield and formation of side-products such as β,γ-unsaturated carboxylic acids. In addition, the long reaction time also seems deleterious.[3-5] Our attempts to reproduce the reported yield of crotonic acid from the reaction of acetaldehyde with malonic acid were not successful.[6] The preparation of α,β-unsaturated nitriles appears to be quite troublesome because of incomplete decarboxylation. Even with aromatic aldehydes the yields of cinnamonitriles are generally low.[7]