# Convenient preparation of aryl-substituted nortropanes by Suzuki–Miyaura methodology[1]

**Shyamali Ghosh, William A. Kinney, Diane A. Gauthier, Edward C. Lawson, Tomas Hudlicky, and Bruce E. Maryanoff**

**Abstract:** The synthesis of a new bicyclic vinyl boronate (**5**) was accomplished from N-Boc-nortropinone (**6**) in two steps. The Suzuki–Miyaura coupling of **5** to a variety of aryl bromides and triflates afforded 3-aryl-8-azabicyclo[3.2.1]oct-2-enes in good yields by adjusting the substrate and (or) reaction conditions. Reduction to the 3-aryl-8-azabicyclo[3.2.1]octanes was achieved by hydrogenation. Interestingly, the coupling was also successful with benzyl bromides, providing entry into another group of intermediates.

*Key words:* nortropane, Suzuki–Miyaura, boronate, piperidine, GPCR, benzyl bromide.

**Résumé :** La synthèse d'un nouveau boronate de vinyle cyclique (**5**) a été réalisée en deux étapes à partir de la N-Boc-tropinone (**6**). Le couplage du composé **5** avec des bromures et des triflates d'aryles en faisant appel à la méthode de Suzuki–Miyaura et en ajustant le substrat et les conditions réactionnelles conduit à la formation de 3-aryl-8-azabicyclo[3.2.1]oct-2-ènes avec de bons rendements. La réduction des 3-aryl-8-azabicyclo[3.2.1]octanes a été réalisée par hydrogénation. Il est intéressant de noter que la réaction de couplage a été réalisée avec succès avec des bromures de benzyle, ce qui permet d'accéder à un autre groupe d'intermédiaires.

*Mots clés :* nortropane, Suzuki–Miyaura, boronate, pipéridine, GPCR, bromure de benzyle.

[Traduit par la Rédaction]

## Introduction

Phenyl piperidines have proven to be valuable templates for the construction of modulators of G-protein coupled receptors (GPCRs), which are the target of the largest group of marketed drugs (~50%). Of the 38 GPCR-targeted drugs on the market, listed in a recent review (1), five are aryl piperidines (Allegra, Claritin, Duragesic, Risperdal) or aryl-substituted bicyclic piperidines (Atrovent, Combivent). Several others are aryl piperazines or morphine-related polycyclic aryl piperidines. To illustrate the structural diversity of piperidine-containing GPCR ligands, some examples are illustrated in the following: μ-opioid agonist loperamide (**1**) (2), selective δ-opioid agonist **2** (3), urotensin-II receptor antagonist palosuran (**3**) (4), and nonpeptidyl growth hormone secretagogue **4** (5). These compounds demonstrate the importance of aryl piperidines and how selectivity can be altered by making changes in the aryl piperidine architecture and pendant groups. We were interested in preparing aryl-substituted 8-azabicyclo[3.2.1]octane (nortropane) systems related to **2** and **4** in pursuit of novel GPCR ligands.

We envisioned accessing aryl nortropanes by a Suzuki–Miyaura (6) coupling of bicyclic vinyl boronate (**5**) with various aryl halides (Scheme 1). This approach was useful in the preparation of a variety of 4-phenyl tetrahydropyridines from an N-Boc-piperid-3-en-4-yl boronate (7*b*). The palladium/copper(I)-catalyzed Negishi coupling of 4-piperidinylzinc iodide with aryl halides and the piperid-3-en-4-ol phosphate coupling with aryl boronic acids are also noteworthy methods to prepare 4-arylpiperidines (8, 9). Recently, a Stille coupling of a bicyclic vinyl tin reagent provided access to phenyl-substituted 8-azabicyclo[3.2.1]oct-2-enes (nortropene) and nortropanes (5). The coupling of a bicyclic vinyl boronate with aryl halides might provide a less toxic alternative to a variety of interesting nortropenes and nortropanes. Besides investigating an alternative approach, we also wanted to determine whether a greater variety of aryl and benzyl halide coupling partners could be used in combination with **5** than had been demonstrated with the Suzuki couplings of the N-Boc-piperid-3-en-4-yl boronate (7*b*).

## Results and discussion

The synthesis of **5** was accomplished by the methods outlined for the preparation of other pinacolato boronates (7).

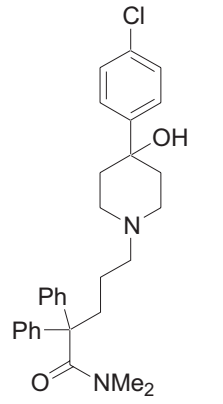
Received 16 September 2005. Published on the NRC Research Press Web site at http://canjchem.nrc.ca on 5 May 2006.

*Dedicated to Professor Walter Szarek on the occasion of his 65th birthday.*

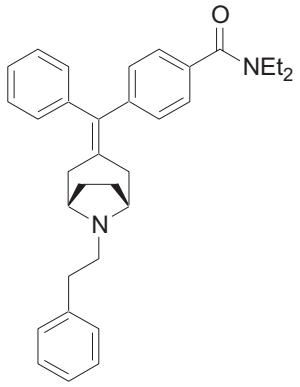
**S. Ghosh, W.A. Kinney,[2] D.A. Gauthier, E.C. Lawson, and B.E. Maryanoff.** Johnson & Johnson P.R.D., L.L.C., Spring House, PA 19477, USA.
**T. Hudlicky.** Brock University, St. Catharines, ON L2S 3A1, Canada.

[1]This article is part of a Special Issue dedicated to Professor Walter Szarek.
[2]Corresponding author (e-mail: wkinney1@prdus.jnj.com).

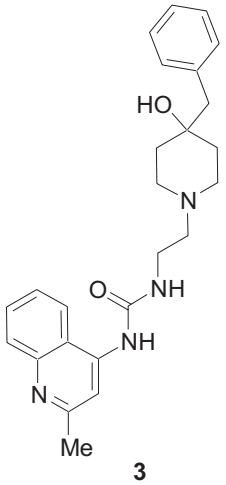
 doi:10.1139/V06-045 



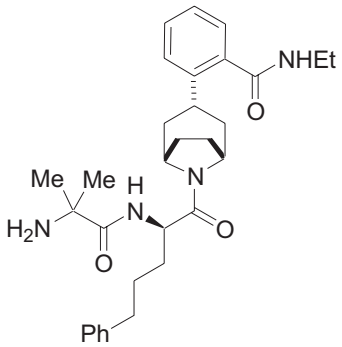

**1**




**2**




**3**

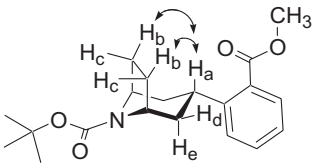



**4**

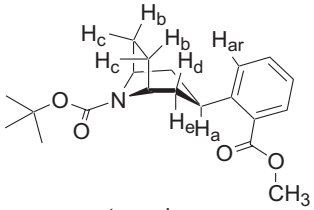
N-Boc-nortropinone (**6**) was deprotonated with potassium-hexamethyldisilazide at low temperature and reacted with Comins' reagent (2-(*N*,*N*-bistriflouromethanesulfonyl)amino-5-chloropyridine) to yield the vinyl triflate **7** in 92% yield. The triflate **7** was coupled with bis(pinacolato)diboron, using [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) dichloromethane complex ($PdCl_2$-dppf, 2 mol%) as the catalyst, to afford bicyclic boronate (**5**) in good yield (77%–84%). This optimized yield was obtained by using only 1 equiv. of the diboron reagent and by carefully monitoring the reaction progress by $^1$H NMR (vinyl proton of **5** vs. **7**).

The coupling of bicyclic boronate (**5**) with a variety of substituted benzene derivatives (**8**) was initially investigated (Table 1). Reaction of 1-bromo-4-methoxybenzene (**8a**) with **5** using $PdCl_2$-dppf as the catalyst (10 mol%) and potassium carbonate as the base (Method A) gave a low yield of the desired coupling. This poor result was overcome by instead utilizing triflate **8b**, which gave a quantitative yield of **9a**. In other cases the aryl bromides performed satisfactorily. For example, 1-bromo-4-methylbenzene (**8c**) and 2-bromobenzoic acid methyl ester (**8d**) gave a reasonable yield of the coupled products **9c** and **9d** (65% in each case). The example of 2-bromobenzoic acid ethyl ester (**8e**) was added to provide a direct comparison to the Stille approach, which gave a low yield (42%) of **9e** (5). In contrast, coupling of **8e** with **5** afforded **9e** more efficiently (72%). When an additional chlorine substituent was added to the aryl ring (**8f**, **8g**), the triflate (10) was a much better substrate than the bromo derivative, giving an excellent yield of **9f**. The nitro substituent in **8h** did not significantly affect the coupling yield with the arylbromide. The disubstituted nitro ester (**9h**) is a useful intermediate for adding a variety of groups at the 2- and 4-phenyl positions.

The fully reduced 3-aryl-8-azabicyclo[3.2.1]octanes (**10**, Scheme 1) could be achieved by reduction of the double bond in **9**. For example, **9d** was treated with hydrogen and 10% palladium on carbon to afford a quantitative yield of **10d** as a mixture of isomers. The same two isomers of **10d** were obtained when **9f** was reduced because of the additional reduction of the chlorine substituent. The isomers of **10d** (from **9f**) were separated by column chromatography and analyzed by 1D and 2D NMR to assign protons and distinguish the two isomers. For example, an expected NOE was observed between the $H_a$ and $H_b$ protons in the cis isomer (vide infra). The cis isomer is defined as having the aryl and the amine on the same side of the bicycle. Once the two isomers were distinguished, the $^1$H NMR spectrum on the product **10d** derived from **9d** was analyzed to determine the ratio of isomers. There was a predominance of the cis isomer (cis:trans, 1.65:1), as determined by ratios of the $H_a$ and $CH_3O$- integrations of the two isomers, which are clearly separated (e.g., $H_a$-cis δ 4.10 ppm, $H_a$-trans δ 3.29 ppm).




cis isomer
of **10d**




trans isomer
of **10d**

The nitrophenyl olefin (**9h**) was also efficiently (91%) reduced under the above conditions to yield the aminophenyl nortorpane (**10h**). In this case, the ratio of isomers was reversed (trans:cis, 1.27:1) based on the same comparison of $H_a$ and $CH_3O$- integrations. Chlorophenyl tropane (**10f**) was available, albeit in low yield (29%, unoptimized), by a Sandmeyer reaction (11) with **10h**.

A variety of aryl and benzyl halides were evaluated as coupling partners for bicyclic boronate (**5**) (Table 1). The electron-deficient aryl bromide, 2-bromopyridine (**11**), coupled in good yield with **5** to give 2-pyridyl nortropene (**9i**). Electron-rich 3-bromoindole (**12**) did not couple efficiently under the usual conditions (Method A), but **9j** was obtained in good yield by using the same catalyst with aqueous sodium carbonate and dimethoxyethane (Method B) (12). While the reaction of benzyl bromides with aryl boronic acids has been seen in recent years (13), their reaction with vinyl boronic acids is less common (13*d*, 13*e*). Although the yield was only moderate (47%), boronate **5** coupled successfully with **13** using tetrakis(triphenylphoshine)palladium(0) as the catalyst (13*b*) to give benzyl-substituted 8-azabicyclo[3.2.1]oct-2-ene (**9k**). In the case of benzyl bromide (**14**), the coupling product **9l** and its isomer **15l** were isolated (**9l**:**15l**, 77:23) in similar yield to **9k**. The exocyclic

**Scheme 1.**

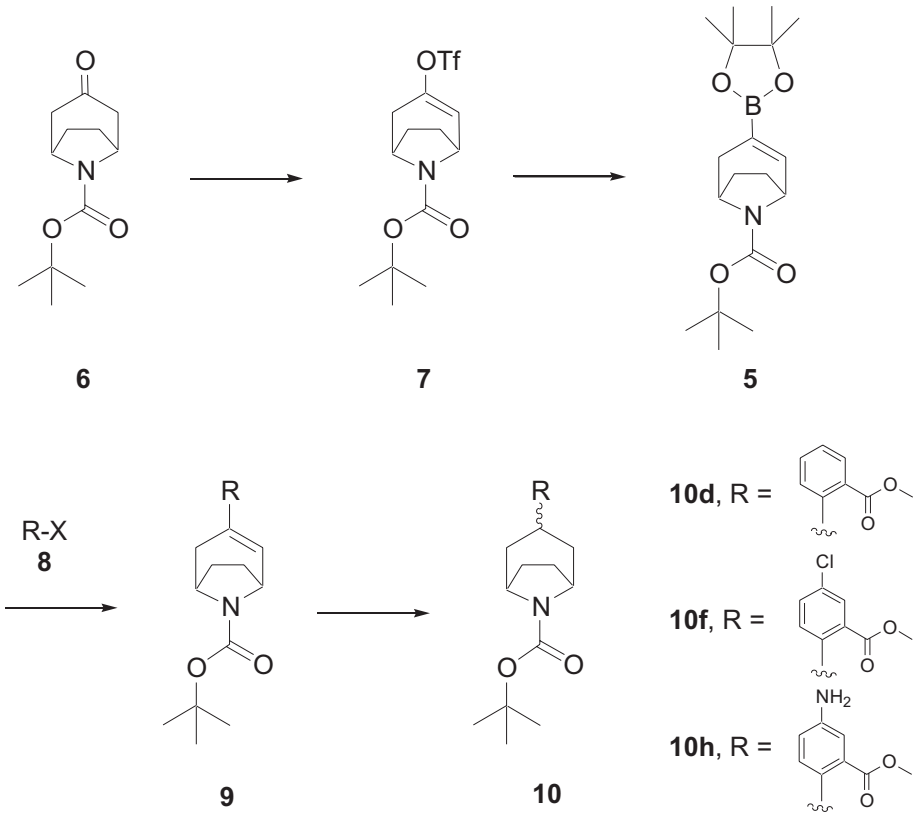
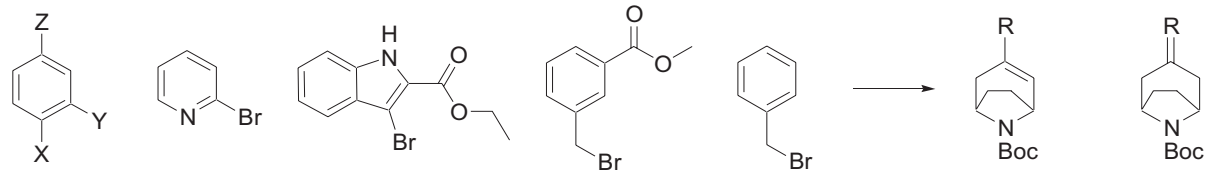



**Table 1.** Examples of coupling of **5** with aryl and benzyl groups.




**8** **11** **12** **13** **14** **9** **15**

| Ar-X | X, Y, Z | Isolated yield (%) | Product | Ar-X or Bz-X | X, Y, Z | Isolated yield (%) | Product |
|---|---|---|---|---|---|---|---|
| **8a** | Br, H, OMe | 31[a] | **9a** | **8g** | OTf, $CO_2Me$, Cl | 96[a] | **9f** |
| **8b** | OTf, H, OMe | 100[a] | **9a** | **8h** | Br, $CO_2Me$, $NO_2$ | 63[a] | **9h** |
| **8c** | Br, H, Me | 65[a] | **9c** | **11** | | 65[a] | **9i** |
| **8d** | Br, $CO_2Me$, H | 65[a] | **9d** | **12** | | 16[a], 83[b] | **9j** |
| **8e** | Br, $CO_2Et$, H | 72[a] | **9e** | **13** | | 47[c] | **9k** |
| **8f** | Br, $CO_2Me$, Cl | 35[a] | **9f** | **14** | | 54[c] | **9l**, **15l** (77:23) |

[a]Method A: Isolated yield using 0.1 equiv. $PdCl_2$-dppf, 3 equiv. $K_2CO_3$, DMF–EtOH (4:1), 100 °C, 3–16 h.
[b]Method B: Isolated yield using 0.1 equiv. $PdCl_2$-dppf, 4 equiv. 2 mol/L $Na_2CO_3$, DME, 100 °C, 10 h.
[c]Method C: Isolated yield using 0.1 equiv. $[Pd(PPh)_3]_4$, 2 equiv. 2 mol/L $Na_2CO_3$, DME, 100 °C, 16 h.

double bond product **15k** was also observed in the crude NMR spectrum of **9k** (**9k**:**15k**, 85:15), but it was not isolated.

In summary, the synthesis of new bicyclic boronate **5** was accomplished from N-Boc-nortropinone in two steps. The Suzuki–Miyaura coupling of **5** to a variety of aryl bromides and triflates afforded 3-aryl-8-azabicyclo[3.2.1]oct-2-enes in good yields by adjusting the substrate and (or) reaction conditions. Reduction to the 3-aryl-8-azabicyclo[3.2.1]octanes was achieved in good yields in cases in which the substrate had compatible functionality. Interestingly, the coupling of **5** also was successful with benzyl bromides, providing entry into another group of intermediates. The methodology described by Eastwood (7*b*) has been extended to an elaborated piperidine fragment, as well as to a greater variety of coupling partners. The chemistry demonstrated in this report should be applicable to other piperidine and bicyclic piperidine systems.

## Experimental

$^1$H NMR spectra were acquired at 300 MHz on a Bruker Avance-300 spectrometer in $CDCl_3$ unless indicated otherwise, using $Me_4Si$ as an internal standard. Normal-phase preparative chromatography was performed on an Isco Combiflash separation system Sg 100c equipped with a Redisep normal-phase disposable columns for flash chromatography containing 12 g of silica gel (optimal flow rate 30 mL/min, column volume 16.8 mL, normal-phase silica part no. 68-2203-026) with detection at 254 nm. Reverse-phase preparative chromatography was performed on a Gilson HPLC with a reversed-phase Kromasil column (10 μ, 100 Å, C18, column size 250 mm × 50 mm). Electrospray (ES) mass spectra were obtained on a Micromass platform LC single quadruple mass spectrometer in the positive mode. LC–MS analyses were performed on a Hewlett Packard series 1100 HPLC instrument eluting with a gradient of water/MeCN/$CF_3COOH$ (10:90:0.2 to 90:10:0.2) over 6 min with a flow rate of 0.75mL/min on a Supelco ABZ + PLUS column (50 mm × 2.1 mm; 3.0 μ particle size) at 32 °C. Accurate mass measurements were performed using a Micromass (Manchester, UK) Autospec E OA-TOF high-resolution magnetic sector mass spectrometer tuned to a resolution of 6000 using the 10% valley definition. The ions were produced in a fast atom bombardment ion source at an accelerating voltage of 8 kV. Linear voltage scans at 33 Da/s were collected to include the protonated sample ion and two polyethylene glycol ions which were used as internal reference standards. The molecular mass was calculated using a linear extrapolation method. Reported mass values are averages over 100 s. Elemental analyses were determined by Quantitative Technologies, Inc., Whitehouse, New Jersey.

### 3-Trifluoromethanesulfonyloxy-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylic acid *tert*-butyl ester (7)

A solution of N-Boc-nortropinone (**6**, 15.0 g, 67 mmol) in THF (80 mL) was added over 30 min to a cooled (–78 °C) 0.5 mol/L solution of potassium hexamethyldisilazide (162 mL, 81 mmol) in toluene under argon. More THF (20 mL) was added to the reaction mixture, which was stirred for 3.5 h and then treated with 2-(*N*,*N*-bistrifluoromethanesulfonyl)amino-5-chloropyridine (32.0 g, 81 mmol). The reaction mixture was stirred at –78 °C for 4 h and then allowed to warm to room temperature (rt) overnight (final temp: –30 °C). The reaction mixture was adsorbed onto silica gel (40 g) and purified by careful flash chromatography (elution with 10% ethyl acetate in pentane) to provide triflate **7** as a waxy solid (22 g, 92%). $^1$H NMR ($CDCl_3$, 300 MHz) δ: 5.89 (br s, 1H), 4.25 (br m, 2H), 2.86 (br m, 1H), 2.15–1.59 (m, 5H), 1.30 (s, 9H).

### 3-(4,4,5,5-Tetramethyl[1,3,2]dioxaborolan-2-yl)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylic acid *tert*-butyl ester (5)

The triflate **7** (20.5 g, 57 mmol) was dissolved in dioxane (200 mL) and potassium acetate (16.8 g, 171 mmol), bis(pinacolato)diboron (15.0 g, 59 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) dichloromethane complex ($PdCl_2$-dppf, 1.0 g, 1.2 mmol), and 1,1′-bis(diphenylphosphino)ferrocene (0.7 g, mmol, 1.3 mmol) were added and the mixture was degassed with argon for 20 min. The reddish mixture was heated with stirring at 80 °C for 8–10 h, with the color turning a dark brown within the first 2 h. The product to starting material ratio was monitored by removing aliquots, evaporating the solvent, and examining the sample by $^1$H NMR spectroscopy (ratio of vinyl H of the boronate **5** vs. the triflate **7**). The reaction mixture was cooled, filtered through Celite®, and adsorbed on silica gel (40 g). Chromatography (gradient elution with 5%–10% ethyl acetate in pentane) yielded the pure boronate **5** as a white solid (14.7 g, 77%, mp 98 °C). The fractions that showed an integration ratio of at least 10:14 (Boc-group : pinacol-group Hs) were combined to afford pure **5**. Crude boronate **5** of 41% purity (3.1 g, 7%), contaminated with diboron byproducts, was also obtained as a waxy solid. The purity of crude **5** was determined by coupling this crude material with **8b** affording a 41% yield of **9a** vs. 100% yield with pure **5** (1). $^1$H NMR ($CDCl_3$, 300 MHz) δ: 6.71 (br s, 1H), 4.31–4.23 (m, 2H), 2.76–2.71 (m, 1H), 2.08 (m, 1H), 1.90–1.84 (m, 2H), 1.63–1.55 (m, 2H), 1.40 (s, 9H), 1.20 (s, 12H). HRMS ($EI^+$) *m*/*z* calcd. for $C_{18}H_{30}BNO_4$: 335.2268; found: 335.2278. Anal. calcd. for $C_{18}H_{30}BNO_4$: C 64.49, H 9.02; found: C 64.46, H 9.00.

### Method A (ref. 7*b*): 3-(4-Methoxyphenyl)-8-azabicyclo-[3.2.1]oct-2-ene-8-carboxylic acid *tert*-butyl ester (9a)

To a mixture of 4-methoxy phenyl triflate (**8b**) (80 mg, 0.31 mmol), the bicyclic boronate **5** (100 mg, 0.30 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) dichloromethane complex ($PdCl_2$-dppf, 24 mg, 0.03 mmol), and $K_2CO_3$ (123 mg, 0.89 mmol) in a sealable tube (thick walled) was added DMF and EtOH (4:1, 2.5 mL). The mixture was stirred under argon at rt for 5–10 min and the tube was then sealed and heated at 100 °C for 3 h (3–16 h). The mixture was cooled to rt then filtered thru a pad of Celite®, washing with EtOAc. The combined organic layer was concentrated and purified by flash chromatography using a gradient system of 5%–50% ethyl acetate (0.1% TEA) in heptane. The desired product **9a** was isolated as a white solid (0.11 g, 100%). $^1$H NMR ($CDCl_3$, 300 MHz) δ: 7.29 (d, *J* = 9 Hz, 2H), 6.85 (d, *J* = 9 Hz, 2H), 6.33 (br s, 1H), 4.6–4.4 (m, 2H), 3.80 (s, 3H), 3.1 (m, 1H), 2.3–1.6 (m, 5H), 1.45 (s, 9H). MS ($ES^+$, M – Boc + 1) *m*/*z*: 216.1. Anal. calcd. for $C_{19}H_{25}NO_3$: C 72.35, H 7.99, N 4.44; found: C 72.56, H 7.96, N 4.36.

### 3-*p*-Tolyl-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylic acid *tert*-butyl ester (9c)

Aryl bromide **8c** was combined with **5** by Method A to yield **9c** as an oil (65%). $^1$H NMR ($CDCl_3$, 300 MHz) δ: 7.25 (d, *J* = 8 Hz, 2H), 7.11 (d, *J* = 8 Hz, 2H), 6.39 (br s, 1H), 4.6–4.4 (m, 2H), 3.2–3.0 (m, 1H), 2.33 (s, 3H), 2.3–1.6 (m, 5H), 1.44 (s, 9H). MS ($ES^+$, M – Boc + 1) *m*/*z*: 200.1. HRMS ($FAB^+$) *m*/*z* calcd. for $C_{19}H_{25}NO_2$: 299.1885; found: 299.1893.

### 3-(2-Methoxycarbonylphenyl)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylic acid *tert*-butyl ester (9d)

Aryl bromide **8d** was combined with **5** by Method A to yield **9d** as an oil (65%). $^1$H NMR ($CDCl_3$, 300 MHz) δ: 7.76 (d of d, *J* = 7.7, 1.3 Hz, 1H), 7.42 (m, 1H), 7.30 (m, 1H), 7.12 (d, *J* = 7.5 Hz, 1H), 5.83 (br s, 1H), 4.5–4.3 (m,

2H), 3.85 (s, 3H), 3.1–2.8 (m, 1H), 2.3–1.9 (m, 5H), 1.49 (s, 9H). MS ($ES^+$, M – Boc + 1) *m/z*: 244.2. HRMS ($FAB^+$) *m/z* calcd. for $C_{20}H_{25}NO_4$: 343.1784; found: 343.1788.

**3-(2-Ethoxycarbonylphenyl)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylic acid *tert*-butyl ester (9e)**

Aryl bromide **8e** was combined with **5** by Method A to yield **9e** as an oil (72%). $^1H$ NMR ($CDCl_3$, 300 MHz) δ: 7.74 (d, *J* = 7.6 Hz, 1H), 7.41 (m, 1H), 7.30 (m, 1H), 7.12 (d of d, *J* = 7.5, 0.8 Hz, 1H), 5.83 (br s, 1H), 4.6–4.2 (m, 4H), 3.1–2.8 (m, 1H), 2.3–1.9 (m, 5H), 1.49 (s, 9H), 1.36 (t, *J* = 7 Hz, 3H). MS ($ES^+$, M – Boc + 1) *m/z*: 258.1. HRMS ($FAB^+$) *m/z* calcd. for $C_{21}H_{27}NO_4$: 357.1940; found: 357.1935.

**3-(4-Chloro-2-methoxycarbonylphenyl)-8-azabicyclo-[3.2.1]oct-2-ene-8-carboxylic acid *tert*-butyl ester (9f)**

Aryl triflate **8g** (10), prepared from the corresponding phenol, was combined with **5** by Method A to yield **9f** as an oil (96%). $^1H$ NMR ($CDCl_3$, 300 MHz) δ: 7.75 (d, *J* = 2.2 Hz, 1H), 7.38 (d of d, *J* = 8.2, 2.2 Hz, 1H), 7.05 (d, *J* = 8.2 Hz, 1H), 5.83 (br s, 1H), 4.5–4.3 (m, 2H), 3.86 (s, 3H), 3.0–2.8 (m, 1H), 2.3–1.9 (m, 5H), 1.49 (s, 9H). MS ($ES^+$, M – Boc + 1) *m/z*: 278.1.

**3-(2-Methoxycarbonyl-4-nitro-phenyl)-8-azabicyclo-[3.2.1]oct-2-ene-8-carboxylic acid *tert*-butyl ester (9h)**

Aryl bromide **8h** was combined with **5** by Method A to yield **9h** as an oil (63%). $^1H$ NMR ($CDCl_3$, 300 MHz) δ: 8.63 (d, *J* = 2.4 Hz, 1H), 8.26 (d of d, *J* = 8.4, 2.4 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 5.91 (br s, 1H), 4.5–4.3 (m, 2H), 3.92 (s, 3H), 3.1–2.8 (m, 1H), 2.3–1.9 (m, 5H), 1.50 (s, 9H). MS (ES, M + Na) *m/z*: 411.1. HRMS ($FAB^+$) *m/z* calcd. for $C_{20}H_{24}N_2O_6$ + H: 389.1713; found: 389.1706.

**3-Pyridin-2-yl-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylic acid *tert*-butyl ester (9i)**

2-Bromopyridine (**11**) was combined with **5** by Method A, but purified by reverse-phase HPLC (10%–90% MeCN–$H_2O$ containing 0.2% TFA), to yield the TFA salt of **9i** as an oil (65%). $^1H$ NMR ($CDCl_3$, 300 MHz) δ: 8.9 (m, 1H), 8.1 (m, 1H), 7.6 (m, 2H), 7.04 (br m, 1H), 4.7–4.5 (m, 2H), 3.5–1.7 (m, 5H), 1.45 (s, 9H). MS ($ES^+$, M + 1) *m/z*: 287.3. HRMS ($FAB^+$) *m/z* calcd. for $C_{17}H_{22}N_2O_2$ + H: 287.1760; found: 287.1760.

**Method B (ref. 12): 3-(8-*tert*-Butoxycarbonyl-8-azabicyclo[3.2.1]oct-2-en-3-yl)-1*H*-indole-2-carboxylic acid ethyl ester (9j)**

To a mixture of the 3-bromoindole (**12**, 80 mg, 0.30 mmol), compound **5** (100 mg, 0.30 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) dichloromethane complex ($PdCl_2$-dppf, 30 mg, 0.04 mmol), and 2 mol/L aq. $Na_2CO_3$ (0.6 mL, 1.2 mmol) in a sealable tube (thick walled) was added DME (3 mL). After stirring under argon for 5 min, the tube was sealed and heated at 100 °C for 10 h. The reaction mixture was cooled to rt and then filtered through a pad of Celite®, washing with EtOAc. The organic layer was concentrated and purified by flash chromatography using a gradient system of 5%–50% ethyl acetate (0.1% TEA) in heptane. The desired product **9j** was isolated as a white solid (113 mg, 83%). $^1H$ NMR ($CDCl_3$, 300 MHz) δ: 8.78 (br s, NH), 7.61 (m, 1H), 7.4–7.2 (m, 2H), 7.13 (m, 1H), 6.09 (br s, 1H), 4.6–4.4 (m, 2H), 4.41 (q, *J* = 7 Hz, 2H), 3.6–3.4 (m, 1H), 3.2–2.9 (m, 1H), 2.4–2.0 (m, 4H), 1.50 (s, 9H), 1.42 (t, *J* = 7 Hz, 3H). MS ($ES^+$, M + Na) *m/z*: 419.2. Anal. calcd. for $C_{23}H_{28}N_2O_4$: C 69.67, H 7.12, N 7.07; found: C 69.86, H 7.25, N 6.90.

**Method C (ref. 13*b*): 3-(3-Methoxycarbonyl-benzyl)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylic acid *tert*-butyl ester (9k)**

To a mixture of benzyl bromide (**13**) (72 mg, 0.31 mmol), boronate **5** (100 mg, 0.30 mmol), tetrakis(triphenylphoshine)palladium(0) (34 mg, 0.03 mmol), and 2 mol/L $Na_2CO_3$ (0.30 mL, 0.60 mmol) in a sealable tube (thick walled) was added DME (3 mL). The mixture was stirred under argon for 5 min. The tube was then sealed and the reaction mixture was heated at 100 °C for 16 h. The reaction mixture was cooled to rt and then filtered through a pad of Celite®, washing with ethyl acetate. The filtrate was diluted with water and extracted with ethyl acetate. The organic layer was separated, dried (sodium sulfate), concentrated, and purified by flash chromatography using a gradient system of 5%–50% ethyl acetate (0.1% TEA) in heptane. Desired product **9k** was isolated as a white solid (53 mg, 47%). $^1H$ NMR ($CDCl_3$, 300 MHz) δ: 7.9–7.8 (m, 2H), 7.3 (m, 2H), 5.8 (br d, 1H), 4.4–4.1 (m, 2H), 3.91 (s, 3H), 3.24 (AB q, 2H), 2.8–1.8 (m, 4H), 1.6–1.3 (m, 2H), 1.4 (br s, 9H). MS ($ES^+$, M + Na) *m/z*: 380.1. HRMS ($FAB^+$) *m/z* calcd. for $C_{21}H_{27}NO_4$ + H: 358.2018; found: 358.2005.

**3-Benzyl-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylic acid *tert*-butyl ester (9l) and 3-benzylidene-8-azabicyclo-[3.2.1]octane-8-carboxylic acid *tert*-butyl ester (15l)**

Benzyl bromide (**14**) was combined with **5** according to Method C to yield a mixture of **9l** and **15l** as a colorless oil (54%, **9l**:**15l**, 77:23, the exocyclic double bond isomer). $^1H$ NMR ($CDCl_3$, 300 MHz) δ: 7.39–7.15 (m, 5H), 6.45 (br s, 0.23H), 5.84 (br d, 0.77H), 4.4–4.1 (m, 2H), 3.5–2.5 (m, 4H), 2.2–1.5 (m, 4H), 1.40 (m, 9H). MS ($ES^+$, M + Na) *m/z*: 321.9. HRMS ($FAB^+$) *m/z* calcd. for $C_{19}H_{25}NO_2$ – H: 298.1807; found: 298.1799.

**3-(2-Methoxycarbonylphenyl)-8-azabicyclo[3.2.1]octane-8-carboxylic acid *tert*-butyl ester (10d)**

Compound **9d** (40 mg, 0.12 mmol), MeOH (15 mL), and 10% Pd-C (15 mg) were shaken in a Parr apparatus (40 psig of hydrogen, 3.7 atm) for 16 h. The reaction mixture was filtered through Celite® and concentrated to give **10d** as an oil (41 mg, mixture of two isomers, 100%). The ratio of isomers in the reaction mixture was determined to be 1.65:1 cis:trans. The isomers of **10d** were initially formed in the hydrogenation of **9f** and separated by flash chromatography using a gradient system of 5%–25% ethyl acetate (0.1% TEA) in heptane over 20 min (flow rate 40 mL/min) and their structures were determined. Analysis by $^1H$, $^{13}C$, and 2-D NMR determined that the faster eluting, major isomer was the cis isomer. Analysis of **10d** mixture from **9d**: $^1H$ NMR ($CDCl_3$, 300 MHz) δ: 7.78 (m, 0.62H), 7.65 (m, 0.38H), 7.44 (m, 1H), 7.34 (m, 1H), 7.24 (m, 1H), 4.4–4.2 (m, 2H), 4.10 (m, $0.62H_{a\text{-}cis}$), 3.91 (s, $1.9H_{cis}$), 3.87 (s, $1.1H_{trans}$), 3.29

(m, 0.38$H_{a\text{-}trans}$), 2.54 (m, 1H), 2.1–1.3 (m, 7H), 1.51 (s, 9H). MS ($ES^+$, M + Na) *m/z*: 368.0. HRMS (FAB+) *m/z* calcd. for $C_{20}H_{27}NO_4$: 345.1940; found: 345.1940.[3]

**3-(4-Chloro-2-methoxycarbonylphenyl)-8-azabicyclo-[3.2.1]octane-8-carboxylic acid *tert*-butyl ester (10f)**

To a stirred mixture (11) of copper(II) chloride (58 mg, 0.43 mmol) in dry acetonitrile (1.5 mL) was added *tert*-butyl nitrite (0.064 mL, 0.54 mmol) via syringe at rt under a nitrogen atmosphere. The resulting dark green suspension was then heated (65 °C) with vigorous stirring. To the warm reaction mixture was added a solution of **10h** (130 mg, 0.36 mmol) in dry acetonitrile (4 mL) via syringe (5 min). The resulting black solution was stirred at 65 °C for 1 h then allowed to cool to rt. The reaction was diluted with ether (10 mL), washed with aq. 1 N HCl (10 mL), washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude mixture was purified by flash chromatography using a gradient system of 5%–50% ethyl acetate (0.1% TEA) in heptane. The desired product **10f** was isolated as a clear colorless oil (40 mg, 29%) with the same mixture of isomers as **10h** (trans:cis, 1.3:1). $^1$H NMR ($CDCl_3$, 300 MHz) δ: 7.77 (d, *J* = 2.3 Hz, 0.44H), 7.64 (d, *J* = 2.3 Hz, 0.56H), 7.38 (m, 1H), 7.3–7.2 (m, 1H), 4.4–4.2 (m, 2H), 4.09 (m, 0.44H), 3.91 (s, 1.3H), 3.88 (s, 1.7H), 3.26 (m, 0.56H), 2.5 (m, 1H), 2.1–1.3 (m, 7H), 1.51 (s, 9H), 1.36 (m, 2H). MS ($ES^+$, M + 1) *m/z*: 380.0.

**3-(4-Amino-2-methoxycarbonylphenyl)-8-azabicyclo-[3.2.1]octane-8-carboxylic acid *tert*-butyl ester (10h)**

Compound **9h** (180 mg, 0.46 mmol), MeOH (30 mL), and 10% Pd-C (60 mg) were shaken in a Parr apparatus (40 psig of hydrogen) for 16 h. The reaction mixture was filtered through Celite®, concentrated and purified by reverse-phase HPLC (20%–90% MeCN–$H_2O$ containing 0.2% TFA). The TFA salt of compound **10h** was isolated as a white solid (200 mg, mixture of two isomers, 91%, ratio 1.27:1 of trans:cis by $^1$H NMR) after lyophylization. $^1$H NMR ($CDCl_3$, 300 MHz) δ: 7.39 (br s, 0.44H), 7.3–7.2 (m, 1.56H), 7.04 (m, 1H), 4.3–4.2 (m, 2H), 4.04 (m, 0.44H), 3.90 (s, 1.3H), 3.85 (s, 1.7H), 3.21 (m, 0.56H), 2.44 (m, 1H), 2.2–1.2 (m, 7H), 1.55 (s, 9H). MS ($ES^+$, M + 1) *m/z*: 361.2. HRMS ($FAB^+$) *m/z* calcd. for $C_{20}H_{29}N_2O_4$ + H: 361.2127; found: 361.2111.

## Acknowledgements

This project was performed as a collaboration between Johnson & Johnson Pharmaceutical Research and Development, L.L.C. and TDC Research Inc., Department of Chemistry, Brock University, St. Catharines, Ontario. The authors thank William Jones for obtaining extensive accurate mass data, and Hank Breslin and Mark McDonnell for important scientific discussions.

## References

1. P. Nambi and N. Aiyar. Assay Drug Dev. Technol. **1**, 305 (2003).
2. F. Awouters, A. Megens, M. Verlinden, J. Schuurkes, C. Niemegeers, and P.A. Janssen. Dig. Dis. Sci. **38**, 977 (1993).
3. J.R. Carson, S.J. Coats, E.E. Codd, S.L. Dax, J. Lee, R.P. Martinez, L.A. McKown, L.A. Neilson, P.M. Pitis, W.-N. Wu, and S.-P. Zhang. Bioorg. Med. Chem. Lett. **14**, 2113 (2004).
4. M. Clozel, C. Binkert, M. Birker-Robaczewska, C. Boukhadra, S.-S. Ding, W. Fischli, P. Hess, B. Mathys, K. Morrison, C. Mueller, C. Mueller, O. Nayler, C. Qiu, M. Rey, M.W. Scherz, J. Velker, T. Weller, J.-F. Xi, and P. Ziltener. J. Pharmacol. Exp. Ther. **311**, 204 (2004).
5. Z. Lu, J.R. Tata, K. Cheng, L. Wei, W.W.-S. Chan, B. Butler, K.D. Schleim, T.M. Jacks, G. Hickey, and A.A. Patchett. Bioorg. Med. Chem. Lett. **13**, 1817 (2003).
6. (*a*) N. Miyaura, T. Yanagi, and A. Suzuki. Synth. Commun. **11**, 513 (1981); (*b*) N. Miyaura and A. Suzuki. Chem. Rev. **95**, 2457 (1995).
7. (*a*) T. Ishiyama, Y. Itoh, T. Kitano, and N. Miyaura. Tetrahedron Lett. **38**, 3447 (1997); (*b*) P.R. Eastwood. Tetrahedron Lett. **41**, 3705 (2000).
8. E.G. Corley, K. Conrad, J.A. Murry, C. Savarin, J. Holko, and G. Boice. J. Org. Chem. **69**, 5120 (2004).
9. U.S. Larsen, L. Martiny, and M. Begtrup. Tetrahedron Lett. **46**, 4261 (2005).
10. D.E. Frantz, D.G. Weaver, J.P. Carey, M.H. Kress, and U.H. Dolling. Org. Lett. **4**, 4717 (2002).
11. L.E. Burgess. Synth. Commun. **27**, 2181 (1997).
12. W.W.K.R. Mederski, M. Lefort, M. Germann, and D. Kux. Tetrahedron, **55**, 12757 (1999).
13. (*a*) M.J. Sharp and V. Snieckus. Tetrahedron Lett. **26**, 5997 (1985); (*b*) G.J. Pernía, J.D. Kilburn, J.W. Essex, R.J. Mortishire-Smith, and M. Rowley. J. Am. Chem. Soc. **118**, 10220 (1996); (*c*) S. Chowdhury and P.E. Georghiou. Tetrahedron Lett. **40**, 7599 (1999); (*d*) C.H. Oh and Y.M. Lim. Bull. Korean Chem. Soc. **23**, 663 (2002); (*e*) S. Langle, M. Abarbri, and A. Duchêne. Tetrahedron Lett. **44**, 9255 (2003); (*f*) L. Chahen, H. Doucet, and M. Santelli. Synlett, 1668 (2003).

[3] Supplementary data (the $^1$H NMR structural assignments and NOE data for the cis and trans isomers of **10d**) for this article are available on the journal Web site (http://canjchem.nrc.ca) or may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0R6, Canada. DUD 5023. For more information on obtaining material refer to http://cisti-icist.nrc-cnrc.gc.ca/irm/unpub_e.shtml.