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ARTICLE *in* THE JOURNAL OF ORGANIC CHEMISTRY · FEBRUARY 2002

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Preparation of 8-Substituted Xanthine CVT-124 Precursor by Late Stage Pyrimidine Ring Closure

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Received July 13, 2001

To develop a novel route for the scaleable synthesis of the chiral xanthine CVT-124 (**1**, aka. BG9719), a method for the late stage pyrimidine ring closure of the nitrogen-protected endo 2-norbornenyl imidazole **3** was developed. The three-component coupling of benzylamine, 2-cyanoglycine ethyl ester (**4**), and methyl 5-norbornene-2-carboximidate hydrochloride (**5**) was demonstrated to achieve **3** in 23−46% isolated yields. The imidazole **3** was then elaborated to construct the *N*-benzyl xanthine **2** as a 1:1 mixture of exo and endo isomers, which were separable at this stage by chromatography. The nitrogen-protected endo xanthine **2** is a key intermediate in the synthesis of CVT-124.

Introduction

The chiral xanthine CVT-124 (**1**, aka. BG9719) is a potent and selective adenosine A1 receptor antagonist that recently entered Phase II clinical trials by a collaborative effort between CV Therapeutics, Inc., and Biogen, Inc. This target has previously been made by two different research groups[1,2] and was constructed using the classical methods of xanthine synthesis, i.e., ring closures to form the imidazole ring in the final steps (Scheme 1).

As part of a program to develop a novel and scaleable route for the chiral synthesis of xanthine **1**, one plan was to devise a method for the late stage ring closure of endo 2-norbornyl imidazole **3** to the corresponding nitrogen-protected xanthine **2** (Scheme 2). This imidazole was envisioned to arise from the three-component coupling of benzylamine, 2-cyanoglycine derivative **4**, and the endo norbornenyl imidate hydrochloride **5**. This route was to be developed in such a way that the arrangement of substituents around the heterocyclic ring of **3** would be unambiguous and was partially based on a recently reported synthesis.[3]

Results and Discussion

Development of New Chemistry: The Model Scaffold. In order to investigate this new chemistry, a model study was undertaken using an isopropyl moiety in place of the norbornenyl ring. Thus, ethyl cyanoglyoxylate-2-oxime (**6**) was reduced according to literature precedent[4] to 2-cyanoglycine ethyl ester (**4**) in yields comparable to those of known procedures (Scheme 3).[3−5] Amine **4** was then condensed with methyl 2-methylpropionimidate hydrochloride (**7**)[6] in refluxing chloroform. The resulting slurry was filtered, and the filtrate was subjected to a second condensation reaction with benzylamine in refluxing chlororform.[3] After purification by flash column chromatography and recrystallization, the desired 2-isopropyl imidazole **8** was isolated in 43% yield. By achieving the synthesis in this fashion, the *N*-benzyl protecting group resides on the N-1 imidazole nitrogen unambiguously. It should be noted that the use of chloroform, while

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† Present address: Telik, Inc., 750 Gateway Blvd., South San Francisco, CA 94080.

(1) (a) Moore, A. G.; Schow, S. R.; Lum, R. T.; Nelson, M. G.; Melville, C. R. *Synthesis* **1999**, *7*, 1123. (b) Pfister, J. R.; Belardinelli, L.; Lee, G.; Lum, R. T.; Milner, P.; Stanley, W. C.; Linden, J.; Baker, S. P.; Schreiner, G. *J. Med. Chem.* **1997**, *40*, 1773.

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(3) (a) Ahn, H.-S.; Bercovici, A.; Boykow, G.; Bronnenkant, A.; Chackalamannil, S.; Chow, J.; Cleven, R.; Cook, J.; Czarniecki, M.; Domalski, C.; Fawzi, A.; Green, M.; Gündes, A.; Ho, G.; Laudicina, M.; Lindo, N.; Ma, K.; Manna, M.; McKittrick, B.; Mirzai, B.; Nechuta, T.; Neustadt, B.; Puchalski, C.; Pula, K.; Silverman, L.; Smith, E.; Stamford, A.; Tedesco, R. P.; Tsai, H.; Tulshian, D.; Vaccaro, H.; Watkins, R. W.; Weng, X.; Witkowski, J. T.; Xia, Y.; Zhang, H. *J. Med. Chem.* **1997**, *40*, 2196. (b) See also: Mackenzie, G.; Wilson, H. A.; Shaw, G.; Ewing, D. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2541.

(4) De Meester, J. W. G.; van der Plas, H. C.; Middelhoven, W. J. *J. Heterocycl. Chem.* **1987**, *24*, 441.

(5) (a) Brown, T.; Shaw, G. *J. Chem. Soc.* **1980**, 2310. (b) Shaw, G.; Wilson, D. V. *J. Chem. Soc.* **1962**, 2937. (c) Hosmane, R. S.; Lim, B. B. *Tetrahedron Lett.* **1985**, *26*, 1915.

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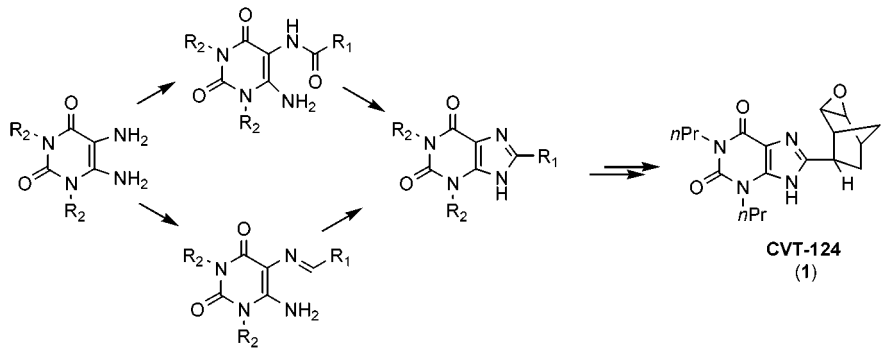
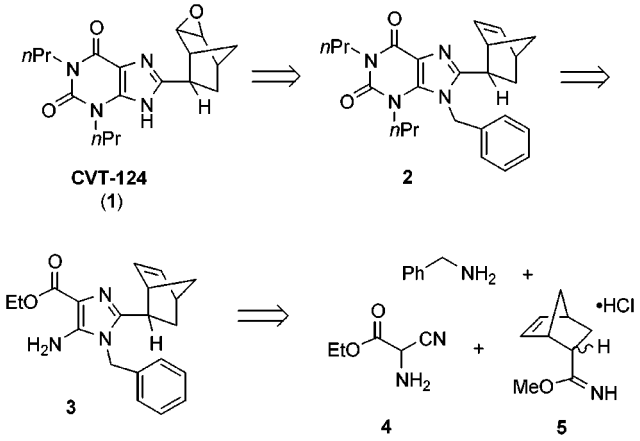
10.1021/jo015925r CCC: $22.00
Published on Web 12/07/2001

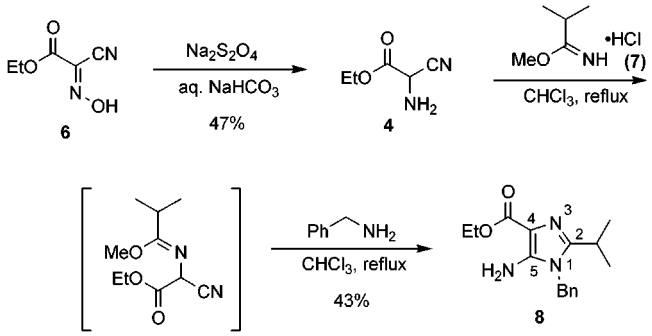
Scheme 1



Scheme 2



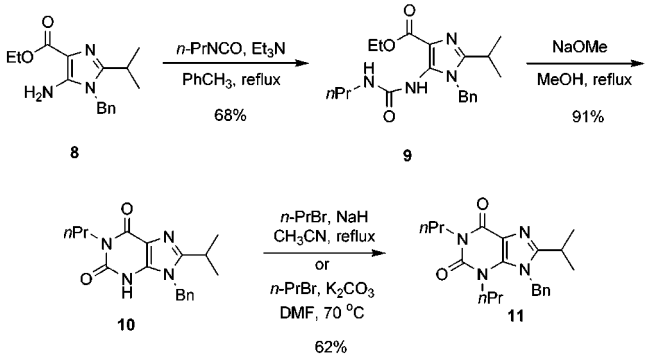
Scheme 3



not a solvent of choice for commercial-scale production, could be replaced with isopropyl acetate to furnish **8** in a somewhat diminished overall yield (24%).

Literature precedent demonstrated that pyrimidines may be constructed from the ring closure of 4(5)-amino-5(4)-carboxy imidazoles (Scheme 4).[7] Thus, to build the model xanthine ring system **11**, imidazole **8** was coupled with *n*-propyl isocyanate to produce unsymmetrical urea **9** in 68% isolated yield. This was followed by the equilibrium deprotonation of the *N*-propyl urea nitrogen of **9** by treatment with sodium methoxide in refluxing methanol to provide xanthine **10** in 91% isolated yield. Finally, N-alkylation of xanthine **10** with sodium hydride and 1-bromopropane proceeded to afford bis-propyl model compound **11** in 62% isolated yield. Alkylation of xanthine **10** with 1-bromopropane was also achieved with

Scheme 4



potassium carbonate at 70 °C in DMF to produce **11** in a comparable yield.[8]

Application of New Chemistry: Construction of the *endo*-Norbornenyl System. This synthetic route was then applied toward the construction of the CVT-124 core **2**, with the initial emphasis on building the 2-norbornenyl imidazole **3**. First, methyl imidate hydrochloride **5** was prepared via the Pinner reaction[9] between 5-norbornene-2-carbonitrile (**12**) and methanol in ethereal HCl in 82% yield (Scheme 5). Use of the commercially available starting material **12** (a 1:1 mixture of endo and exo isomers) resulted in a 1:1 mixture of methyl imidate epimers from the Pinner reaction. Following the chemistry developed for the model system, we treated imidate **5** with cyanoglycine ester **4** in chloroform and filtered the mixture after it was stirred for 1 h at reflux. The filtrate, containing the intermediate cyanoglycine imidate **13**, was treated with benzylamine and refluxed for an additional 17 h. The solution was then cooled, concentrated, and purified by flash chromatography to produce *N*-1-benzyl imidazole **3** in 46% isolated yield.

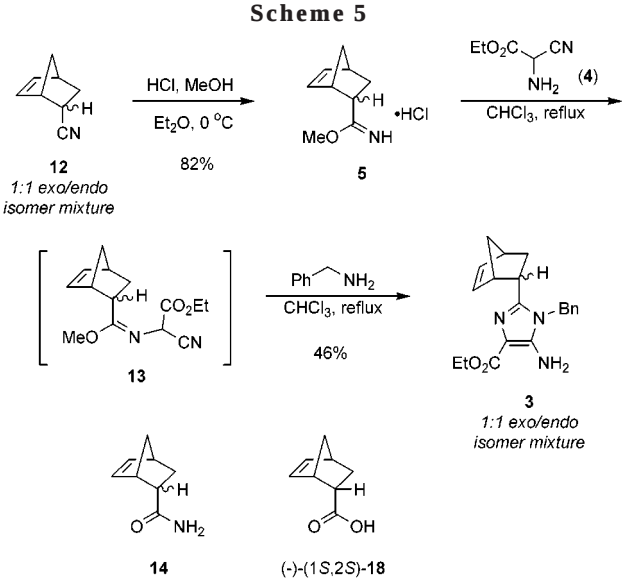
On a small scale, it was also found that a practical purification of **3** could be achieved without a lengthy chromatography. When a small amount of the crude reaction mixture (about 2 g) from the bis-condensation was filtered through a short plug of silica gel, eluting with methanol/methylene chloride (5:95), fairly clean imidazole was isolated upon concentration of the filtrate. When this residue was dissolved in 2 N HCl solution, washed repeatedly with ether, and then made basic with 2 N

(7) (a) Bridson, P. K.; Wang, X. *Synthesis* **1995**, 855. (b) Edenhofer, A. *Helv. Chim. Acta*. **1975**, *58*, 2192. (c) See also: Shaw, G. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Ed.; Elsevier Science, Ltd.: Exeter, 1996; Vol. 7, Chapter 7.11, p 397.

(8) Sakai, R.; Konno, K.; Yamamoto, Y.; Sanae, F.; Takagi, K.; Hasegawa, T.; Iwasaki, N.; Kakiuchi, M.; Kato, H.; Miyamoto, K. *J. Med. Chem*. **1992**, *35*, 4039.

(9) (a) Pinner, A.; Klein, F. *Ber*. **1877**, *10*, 1889. (b) Moreau, R. C.; Reynaud, P. *Bull. Soc. Chim. Fr*. **1964**, 2997. (c) Cooper, F. C.; Partridge, M. W. *J. Chem. Soc*. **1952**, 5036.

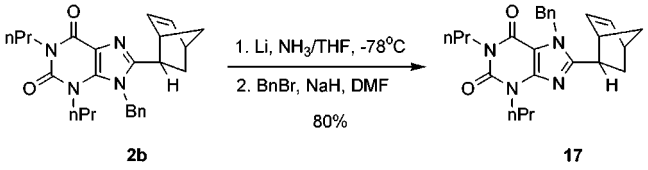
Scheme 5



NaOH solution, the clean imidazole **3** could be collected by vacuum filtration as a white solid. The ratio of exo/endo isomers was unchanged from **12** (1:1, as confirmed by ^{1}H NMR analyses), even after chromatography or acid/base extraction purifications. Interestingly, the major byproduct from the condensation reaction was found to be amide **14** (Scheme 5), which was formed by the hydrolysis of imidate **5**. This compound was found to be insoluble in cold chloroform, which allowed for its quick removal from the crude reaction mixture and simplified the chromatographic purification process.

The 1:1 epimeric mixture of imidates **3** was elaborated to xanthine scaffold **2** on the basis of the chemistry developed in the model system (Scheme 6). Imidazole **3** was treated with *n*-propyl isocyanate and triethylamine in refluxing toluene overnight to produce the unsymmetrical urea **15** in 61% isolated yield. While a chromatographic purification allowed for a greater isolated yield of urea **15**, it was found that treatment of the crude reaction residue with cold ether was sufficient to provide consistent amounts of clean **15** by simple precipitation. Cyclization of **15** to xanthine **16** with sodium methoxide was achieved in less than 2 h in refluxing methanol. In this case, the crude reaction residue was diluted with aqueous HCl solution and extracted with methylene chloride to ultimately provide **16** as a colorless oil in 96% isolated yield. Xanthine **16** was N-alkylated under the standard conditions[8] with 1-bromopropane and potassium carbonate at 70 °C in DMF to produce a 1:1 epimeric mixture of 2-norbornenyl xanthines **2a** and **2b**. It was found that the two isomers could be separated at this stage by chromatography to produce roughly equal amounts of the exo isomer **2a** (in 50% isolated yield) and the requisite endo isomer **2b** (in 43% isolated yield).

Interestingly, the ^{1}H NMR spectrum of the endo *N*-1-benzyl isomer **2b** was similar, but not identical to the ^{1}H NMR spectrum of endo *N*-3-benzyl xanthine **17**, which was prepared by dissolving metal deprotection of **2b** followed by direct N-alkylation with benzyl bromide and sodium hydride in DMF. In this case, the regiochemistry of the alkylation is such that the benzyl group approaches from the least hindered side of pyrimidine to provide the N-3 positional isomer **17** selectively, as expected.[3,10] Comparison of the spectral data of **2b** and **17** helped to prove the structural assignments unambiguously.



Conclusions

To develop a novel and scaleable route for the synthesis of the endo xanthine CVT-124 (**1**, aka. BG9719), a method was devised for the late stage pyrimidine ring closure of 2-norbornenyl imidazole **3** to the 8-substituted nitrogen-protected xanthine precursor **2**. The imidazole scaffold **3** was in turn prepared by a three-component coupling of methyl 5-norbornene-2-carboximidate hydrochloride (**5**), 2-cyanoglycine ethyl ester (**4**), and benzylamine. Imidazole **3** was then elaborated to construct xanthine **2** as a 1:1 mixture of exo and endo isomers, which were separable by flash chromatography. The *N*-benzyl endo compound **2b** is a key component in the synthesis of CVT-124 (**1**), and this process should therefore be amenable to the preparation of chiral **1** from the requisite chiral endo imidate **5**. Precursor **5** is accessible from known (−)-(1*S*,2*S*)-5-norbornene-2-carboxylic acid (**18**, Scheme 5)[11] by straightforward chemistry via primary amide **14**.[12,13] It should be mentioned that work was developed to provide an alternative route to the preparation of **1**, which is currently prepared by a more classical route similar to the chemistry described in Scheme 1.[14]

Experimental Section

General Procedures. All nonaqueous reactions were performed under a dry atmosphere of nitrogen. Reagents purchased from commercial sources were used as received, unless noted otherwise. Anhydrous solvents were obtained from commercial sources and used as received. The ^{1}H NMR spectrum of endo *N*-3-benzyl derivative **17** (made independently) was supplied for comparison by CV Therapeutics, Inc.. Proton magnetic resonance spectra were obtained on a Bruker AC 300 MHz NMR instrument, using either tetramethylsilane or chloroform as an internal reference. Thin-layer chromatography was performed using 1″ × 3″ in. Analtech GF 350 silica gel plates with a fluorescent indicator. Visualization of TLC plates was realized by observation under a UV lamp, in iodine

(10) For other recent examples of regioselective N-3 alkylation of similar xanthines, see: (a) Akguen, H.; Balkan, A.; Guenay, S.; Erol, K.; Boydag, S. *Eur. J. Med. Chem.* **1997**, *32*, 175. (b) Avasthi, K.; Chandra, T.; Rawat, D. S.; Bhakuni, D. S. *Indian J. Chem., Sect. B* **1996**, *35*, 437. (c) Del Guidice, M. R.; Borioni, A.; Mustazza, C.; Gatta, F.; Dionisotti, S.; Zocchi, C.; Ongini, E. *Eur. J. Med. Chem.* **1996**, *31*, 59. (d) Mueller, C. E.; Sandoval-Ramirez, J. *Synthesis* **1995**, 1295.

(11) For current large-scale synthesis of the chiral endo 5-norbornene-2-carboxylic acid **18**, see: (a) Poll, T.; Sobczak, A.; Hartmann, H.; Helmchen, G. *Tetrahedron Lett.* **1985**, *26*, 3095. (b) Chang, H. X.; Zhou, L.; McCargar, R. D.; Mahmud, T.; Hirst, I. *Org. Proc. Res. Dev.* **1999**, *3*, 289 and references therein.

(12) For recent examples of aliphatic carboxylic acid to primary amide conversions, see: (a) Josse, O.; Labar, D.; Marchand-Brynaert, J. *Synthesis* **1999**, 404. (b) Wang, W.; McMurray, J. S. *Tetrahedron Lett.* **1999**, *40*, 2501. (c) Muller, G. W.; Shire, M. G.; Wong, L. M.; Corral, L. G.; Patterson, R. T.; Chen, Y.; Stirling, D. I. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2669. (d) Boeckman, R. K., Jr.; Connell, B. T. *J. Am. Chem. Soc.* **1995**, *117*, 12369. (e) Fernandez, F.; Lopez, C.; Hergueta, A. R. *Tetrahedron* **1995**, *51*, 10317.

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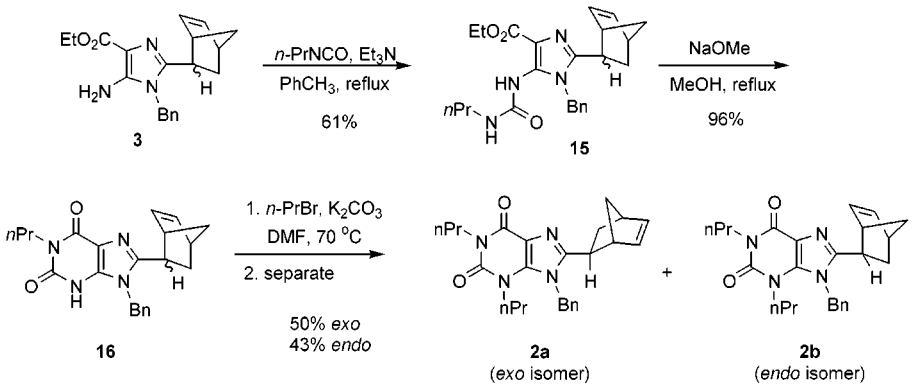
(14) (a) Dowling, J. E.; Kumaravel, G.; Petter, R. C. U.S. Pat. Appl. WO 01/34604 A2 (2000). (b) Kiesman, W. F.; Dowling, J. E.; Ensinger, C. L.; Kumaravel, G.; Petter, R. C.; Chang, H. X.; Lin, K. C. U.S. Pat. Appl. WO 01/34610 A1 (2000).

Scheme 6



vapors, or by dipping in commercial phosphomolybdic acid solution, followed by warming. Infrared spectra were obtained as KBr pellets and obtained on a Perkin-Elmer Spectrum 1000 FT-Infrared Spectrophotometer. CI Mass spectroscopic analyses were performed on a Shimadzu QP-5000 GC/Mass Spectrometer (methane) by direct injection. Melting points were obtained either by differential scanning calorimetry (DSC) using a Perkin-Elmer model DSC-4 instrument or by using an electrothermal instrument and are uncorrected. Elemental analyses were performed by Quantitative Technologies, Inc., Whitehouse, NJ.

Ethyl 5-Amino-2-(2-methylethyl)-1-benzyl-1*H*-imidazole-4-carboxylate (8). A mixture of 2-cyanoglycine ethyl ester (**4**,[3−5] 2.66 g, 21 mmol) and methyl 2-methylpropionimidate hydrochloride (**7**,[6] 2.60 g, 18 mmol) in anhydrous chloroform (10 mL) was heated at reflux under nitrogen and stirred for 60 min. The mixture was cooled to room temperature and filtered through a short plug of Celite (10 g), rinsing the solid support with chloroform (30 mL). The filtrate was charged with benzylamine (2.3 mL, 21 mmol), and the mixture was heated to reflux for 17 h. The reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure to produce a red oil. This residue was purified by flash column chromatography on silica gel, eluting with methanol/methylene chloride (2:98), to produce the partially purified imidazole as a yellow solid (1.81 g). Recrystallization of this solid with ethyl acetate/hexanes produced the purified product **8** (0.495 g, 10% yield). A second impure fraction from the flash column chromatography was also recrystallized with ethyl acetate/hexanes to yield additional **8** (0.849 g, 16% yield). The mother liquors from the two recrystallizations were combined, and the solvents were removed under reduced pressure. The resulting residue was then purified by flash column chromatography on silica gel, eluting with methanol/methylene chloride (1:99), to produce additional **8** (0.860 g, 17% yield). The total amount of isolated product **8** was 2.20 g (43% yield): ^{1}H NMR ($CDCl_3$) δ 1.32 (d, 6H, J = 6.9 Hz), 1.40 (t, 3H, J = 2.4 Hz), 2.92 (m, 1H), 4.43 (q, 2H, J = 3.3 Hz), 4.65 (br s, 2H), 5.02 (s, 3H), 7.06 (m, 2H), 7.39 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 165.0, 147.6, 145.7, 134.8, 129.3, 128.5, 110.5, 59.9, 45.6, 26.4, 21.4, 14.7; CI MS m/z 288 $(M + H)^+$.

Ethyl 5-[[(*n*-Propylamino)carbonyl]amino]-2-(2-methylethyl)-1-benzyl-1*H*-imidazole-4-carboxylate (9). *n*-Propyl isocyanate (0.20 mL, 2.1 mmol) was added to a mixture of **8** (0.200 g, 0.70 mmol) and triethylamine (0.29 mL, 2.08 mmol) in anhydrous toluene (4 mL) at room temperature under nitrogen, and the reaction mixture was heated at reflux to stir for 14.5 h. The mixture was cooled to room temperature; the solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/hexanes (1:1), to produce **9** as a white solid (0.175 g, 68% yield): ^{1}H NMR ($CDCl_3$) δ 0.86 (t, 3H, J = 8.9 Hz), 1.27 (q, 3H, J = 7.2 Hz), 1.39 (m, 6H), 2.97 (m, 1H), 3.11 (m, 3H), 4.15 (q, 2H, J = 10.5 Hz), 4.30 (q, 2H, J = 9.1 Hz), 5.00 (s, 2H), 6.63 (br s, 2H), 7.16 (m, 2H), 7.35 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 161.6, 154.5, 153.7, 135.2, 130.1, 129.0, 128.3, 127.0, 60.6, 47.0, 42.2, 27.1, 22.7, 21.3, 14.2, 11.2; IR (KBr) 3377, 3969, 1711, 1661, 1508 cm^{-1}; CI MS m/z 373 $(M + H)^+$.

1-*n*-Propyl-3,9-dihydro-9-benzyl-8-(2-methylethyl)-1*H*-purine-2,6-dione (10). Sodium methoxide (0.20 mL, 0.53 mmol, 25% in methanol) was added to a solution of **9** (0.098 g, 0.26 mmol) in anhydrous methanol (2 mL) at room temperature under nitrogen, and the mixture was heated at reflux to stir for 80 min. The mixture was cooled to room temperature, and the solvent was removed under reduced pressure. The foamy residue was diluted with 10% HCl solution (3 mL) and extracted with chloroform (3 × 20 mL). The combined organic extracts were washed with brine and dried ($MgSO_4$), and the solvent was removed under reduced pressure to produce **10** as a white solid (0.078 g, 91% yield): mp 255−260 °C; TLC R_f (50% ethyl acetate/hexanes) = 0.50; ^{1}H NMR ($CDCl_3$) δ 0.86 (t, 3H, J = 10.5 Hz), 1.27 (d, 6H, J = 7.1 Hz), 1.56 (m, 2H), 2.91 (m, 1H), 3.87 (m, 2H), 5.31 (m, 2H), 7.01 (m, 2H), 7.33 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 157.2, 153.7, 153.2, 138.4, 134.5, 129.1, 128.3, 125.6, 114.9, 46.2, 42.4, 29.7, 26.4, 21.4, 21.1, 11.3; IR (KBr) 2967, 1717, 1663, 1577, 1453 cm^{-1}; CI MS m/z 327 $(M + H)^+$, 145.

1,3-Dipropyl-3,9-dihydro-9-benzyl-8-(2-methylethyl)-1*H*-purine-2,6-dione (11). Method A. Sodium hydride (0.020 g, 0.46 mmol, 60% dispersion in oil) was added to a solution of **10** (0.150 g, 0.46 mmol) in anhydrous acetonitrile (5 mL) at room temperature under nitrogen, after which the suspension was charged with 1-bromopropane (0.10 mL, 0.92 mmol) and *N*,*N*-dimethylformamide (2 mL). The reaction mixture was stirred at room temperature for 3 h, after which it was heated at reflux to stir for 3.5 h. The mixture was cooled to room temperature and diluted with water (20 mL). The aqueous mixture was extracted with ethyl acetate (3 × 20 mL), and the combined organic extracts were washed with brine and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/hexanes (1:1), to produce **11** as a clear oil (0.105 g, 62% yield): mp 95−105 °C; TLC R_f (50% ethyl acetate/hexanes) = 0.30; ^{1}H NMR ($CDCl_3$) δ 0.92 (t, 3H, J = 6.0 Hz), 1.06 (t, 3H, J = 10.8 Hz), 1.27 (d, 6H, J = 4.0 Hz), 1.65−1.85 (m, 4H), 2.94 (m, 1H), 4.09 (m, 2H), 4.34 (t, 2H, J = 6.0 Hz), 5.23 (s, 2H), 7.14 (m, 2H), 7.34 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 157.2, 155.4, 154.8, 147.9, 136.7, 129.1, 128.1, 127.0, 118.1, 70.6, 45.6, 43.2, 27.2, 22.2, 22.1, 21.7, 11.6, 10.8; IR (KBr) 2967, 1699, 1559, 1531, 1487 cm^{-1}; CI MS m/z 369 $(M + H)^+$, 279, 229.

Method B. A mixture of **10** (0.148 g, 0.45 mmol), potassium carbonate (0.075 g, 0.54 mmol), and 1-bromopropane (0.10 mL, 0.66 mmol) in anhydrous *N*,*N*-dimethylformamide (3 mL) was heated at reflux under nitrogen to stir for 1 h. The mixture was cooled to room temperature and diluted with ether. This organic solution was washed with water (6 × 10 mL) and dried ($MgSO_4$). The solvents were removed under reduced pressure to produce **11** as a colorless oil, which solidified upon standing (0.103 g, 62%). The ^{1}H NMR and IR spectra, TLC, and CI MS analyses were identical to the data obtained from Method A.

Methyl 5-Norbornene-2-carboximidate Hydrochloride (5, 1:1 Exo/Endo Mixture). Hydrogen chloride gas (about 3 equiv, by weight) was introduced into a solution of 5-norbornene-2-carbonitrile (**12**, 55 g, 462 mmol) and anhydrous methanol (19 mL, 462 mmol) in anhydrous diethyl ether (300 mL) at 0 °C over a 1 h period through a gas inlet tube below the surface of the reaction mixture. The gas flow was terminated, and the reaction mixture was stirred for 1 h, after which the mixture was placed in the freezer for 3 days. The precipitate was collected by vacuum filtration and washed with anhydrous diethyl ether (100 mL). The solids were dried overnight (30 mmHg vacuum, 50 °C) to produce **5** as an off-white solid (71.4 g, 82% yield): mp (DSC) 181 °C; ^{1}H NMR ($CDCl_3$) δ 6.31 (dd, 1H, J = 3.1, 5.8 Hz), 6.20 (t, 2H, J = 3.5 Hz), 5.91 (dd, 1H, J = 2.5, 5.8 Hz), 4.32 (s, 3H), 4.23 (s, 3H), 3.53 (s, 1H), 3.16 (s, 1H), 3.03 (s, 1H), 2.87−2.84 (m, 1H), 2.13−2.06 (m, 1H), 1.66−1.60 (m, 3H), 1.54−1.43 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 182.7, 181.7, 178.5, 177.2, 139.8, 138.6, 138.5, 138.1, 136.1, 132.4, 131.2, 61.0, 60.7, 50.3, 48.2, 48.1, 47.3, 46.8, 46.6, 46.4, 44.6, 44.3, 43.2, 42.9, 42.8, 42.6, 42.1, 41.8, 37.6, 31.3, 30.8, 30.1, 30.0; IR (KBr) 3378, 3194, 2974, 1655, 1405 cm^{-1}; CI MS m/z 275 (M + H)$^+$, 152, 138. The ^{1}H NMR spectrum was consistent with a 1:1 mixture of the exo and endo structures.

Ethyl 5-Amino-2-[2-norborn-5-enyl]-1-benzyl-1*H*-imidazole-4-carboxylate (3, 1:1 Exo/Endo Mixture). A mixture of 2-cyanoglycine ethyl ester (**4**,[3−5] 11.8 g, 92 mmol) and **5** (1:1 exo/endo mixture, 19.1 g, 101 mmol) in anhydrous chloroform (150 mL) under nitrogen was heated at reflux to stir for 1.5 h. The mixture was cooled to room temperature and filtered through a short plug of Celite, rinsing the solid support with chloroform (200 mL). The filtrate was partially concentrated to a final volume of about 150 mL and charged with benzylamine (11.1 mL, 101 mmol), and the mixture was heated at reflux to stir for 21 h. The mixture was cooled to room temperature; the solvent was removed under reduced pressure to produce an orange solid, which was purified by flash column chromatography on silica gel, eluting with methanol/methylene chloride (1:99), to produce **3** as a yellow solid (14.3 g, 46% yield): mp (DSC) 249 °C; TLC R_f (5% methanol/chloroform) = 0.66, 0.60; ^{1}H NMR ($CDCl_3$) δ 7.45−7.30 (m, 6H), 7.13−7.05 (m, 4H), 6.27−6.23 (m, 1H), 6.13−6.07 (m, 2H), 5.92−5.85 (m, 1H), 5.15−5.03 (m, 4H), 4.71 (s, 2H), 4.62 (s, 2H), 4.42−4.28 (m, 4H), 3.23−3.18 (m, 1H), 3.10 (s, 1H), 3.02−2.85 (m, 2H), 2.53−2.47 (m, 1H), 2.40−2.33 (m, 1H), 2.13−2.00 (m, 1H), 1.83−1.78 (m, 1H), 1.70 (br s, 2H), 1.52−1.34 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 165.2, 146.4, 146.0, 138.6, 137.6, 135.9, 135.1, 135.0, 132.4, 129.6, 128.5, 126.2, 125.9, 60.0, 49.9, 47.6, 46.9, 46.4, 45.9, 42.6, 42.1, 36.7, 36.6, 31.2, 30.8, 15.0, 14.9; IR (KBr) 3413, 2977, 1670, 1455 cm^{-1}; CI MS m/z 338 (M + H)$^+$, 292, 272. The ^{1}H NMR spectrum was consistent with a 1:1 mixture of the exo and endo structures.

An alternative, nonchromatographic method for purification was carried out on a small scale. A 1 g sample of the crude reaction residue (after removal of the reaction solvent) was filtered through a plug of silica gel, eluting with methanol/methylene chloride (1:19, 150 mL). The solvent was removed under reduced pressure, and the residue was dissolved in 2 N HCl solution (100 mL). This acid solution was washed with ether (2 × 100 mL), and the aqueous layer was made basic with 2 N NaOH solution (110 mL). The precipitate was collected by vacuum filtration, washed with water (50 mL), and dried overnight (30 mmHg vacuum, 60 °C) to produce **3** as a white powder. The ^{1}H NMR spectrum was identical to the spectrum obtained from the chromatographic purification.

Ethyl 5-[[(*n*-Propylamino)carbonyl]amino]-2-[2-norborn-5-enyl]-1-benzyl-1*H*-imidazole-4-carboxylate (15, 1:1 Exo/Endo Mixture). *n*-Propyl isocyanate (5.4 mL, 58 mmol) was added to a solution of **3** (1:1 exo/endo mixture, 6.5 g, 19 mmol) and triethylamine (8.1 mL, 58 mmol) in anhydrous toluene (80 mL) under nitrogen, and the reaction mixture was heated at reflux to stir for 18 h. The mixture was cooled to room temperature, and the solvent was removed under reduced pressure. The residue was charged with ether (100 mL), and the precipitate was collected by vacuum filtration and washed with ether (30 mL). The filtrate solution was concentrated to a volume of about 50 mL and cooled at 0 °C to stand for 1 h. The resulting precipitate was collected by vacuum filtration and washed with cold ether (10 mL). The two crops of solids were combined and dried overnight (30 mmHg vacuum, 50 °C) to produce **15** as an off-white powder (5.0 g, 61% yield): mp 168−170 °C; TLC R_f (50% ethyl acetate/hexanes) = 0.51; ^{1}H NMR ($CDCl_3$) δ 7.37−7.31 (m, 6H), 7.13−7.08 (m, 4H), 6.31−6.27 (m, 1H), 6.20−6.05 (m, 2H), 5.95−5.90 (m, 1H), 5.15−4.90 (m, 4H), 4.32−4.18 (m, 4H), 3.40−3.30 (m, 1H), 3.25−3.20 (m, 1H), 3.20−3.10 (m, 4H), 3.10−2.95 (m, 2H), 2.95−2.80 (m, 2H), 2.70−2.60 (m, 1H), 2.40−2.30 (m, 1H), 1.95−1.85 (m, 2H), 1.55−1.40 (m, 4H), 1.40−1.35 (m, 4H), 1.35−1.20 (m, 6H), 0.95−0.75 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 161.9, 154.9, 154.7, 154.5, 152.4, 151.2, 138.8, 137.7, 136.1, 135.5, 132.3, 129.2, 128.5, 127.6, 127.3, 60.8, 60.7, 50.0, 47.8, 47.4, 46.9, 46.4, 42.8, 42.5, 42.2, 37.3, 31.8, 31.1, 23.0, 22.9, 14.5, 11.5, 11.4; IR (KBr) 3356, 2967, 2875, 1718, 1665, 1508 cm^{-1}; CI MS m/z 423 (M + H)$^+$, 364. The ^{1}H NMR spectrum was consistent with a 1:1 mixture of the exo and endo structures.

1-*n*-Propyl-3,9-dihydro-9-benzyl-8-[2-norborn-5-enyl]-1*H*-purine-2,6-dione (16, 1:1 Exo/Endo Mixture). Sodium methoxide (8.7 mL, 40 mmol, 25% in methanol) was added to a solution of **15** (1:1 exo/endo mixture, 3.4 g, 8.0 mmol) in anhydrous methanol (80 mL) at room temperature under nitrogen, and the reaction mixture was heated at reflux to stir for 1.5 h. The mixture was cooled to room temperature, and the solvent was removed under reduced pressure. The residue was charged with 2 N HCl solution (50 mL) and extracted with methylene chloride (2 × 100 mL). The combined organic extracts were washed with brine (1 × 100 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure to produce a colorless oil, which crystallized upon standing to produce **16** as an off-white solid (2.9 g, 96% yield): mp (DSC) 235 °C; TLC R_f (5% methanol/chloroform) = 0.56; ^{1}H NMR ($CDCl_3$) δ 7.40−7.30 (m, 6H), 7.10−6.95 (m, 4H), 6.30−6.25 (m, 1H), 6.20−6.05 (m, 2H), 5.85−5.80 (m, 1H), 5.35 (s, 2H), 5.28 (d, 2H, J = 8.8 Hz), 3.90−3.80 (q, 4H, J = 7.3 Hz), 3.66 (s, 4H), 3.23−3.10 (m, 2H), 3.10−2.90 (m, 2H), 2.73 (s, 1H), 2.55−2.45 (m, 1H), 2.31−2.25 (m, 1H), 2.09−1.99 (m, 1H), 1.95−1.78 (m, 1H), 1.65−1.45 (m, 2H), 1.45−1.28 (m, 2H), 0.92 (t, 3H, J = 7.2 Hz), 0.86 (t, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 138.7, 137.6, 135.6, 132.0, 129.2, 128.5, 126.1, 125.6, 49.8, 47.6, 46.7, 46.5, 46.1, 42.5, 42.0, 36.6, 36.4, 31.7, 31.0, 21.1, 11.3; IR (KBr) 3448, 2923, 2851, 2364, 1718, 1648, 1458 cm^{-1}; CI MS m/z 377 (M + H)$^+$, 329, 311. The ^{1}H NMR spectrum was consistent with a 1:1 mixture of the exo and endo structures.

1,3-Dipropyl-3,9-dihydro-9-benzyl-8-*exo*-[2-norborn-5-enyl]-1*H*-purine-2,6-dione (2a) and 1,3-Dipropyl-3,9-dihydro-9-benzyl-8-*endo*-[2-norborn-5-enyl]-1*H*-purine-2,6-dione (2b). A mixture of 1-bromopropane (1.4 mL, 15 mmol), potassium carbonate (2.1 g, 15 mmol), and **16** (1:1 exo/endo mixture, 2.9 g, 7.7 mmol) in anhydrous *N*,*N*-dimethylformamide (50 mL) was heated at 70 °C under nitrogen and stirred for 2.5 h. The mixture was cooled to room temperature and diluted with ether (300 mL). This solution was washed with water (2 × 100 mL) and brine (1 × 100 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure to produce crude **2** as a yellow oil. The NMR spectrum of this crude residue was consistent with the proposed structures as a 1:1 mixture of exo and endo 2-norbornenyl epimers. This oil was then purified by flash column chromatography on silica gel, eluting with ethyl acetate/hexanes (4:6), to first produce the exo isomer **2a** as a colorless oil, which crystallized to a white solid upon standing (1.6 g, 50% yield): mp (DSC) 119 °C; TLC R_f (50% ethyl acetate/hexanes) = 0.64; ^{1}H NMR ($CDCl_3$) δ 7.33−7.29 (m, 3H), 7.18−7.15 (m, 2H), 6.15−6.13 (m, 1H), 6.12−6.01 (m, 1H), 5.25 (q, 2H, J = 22.9 Hz), 4.36 (t, 2H, J = 6.5 Hz), 4.08 (t, 2H, J = 9.1 Hz), 2.93 (s, 1H), 2.65 (s, 1H), 2.58−2.54 (m, 1H), 2.36−2.29 (m, 1H), 1.93 (d, 1H, J = 8.5 Hz), 1.82 (q, 2H, J = 7.2 Hz), 1.71 (q, 2H, J = 7.5 Hz), 1.41−1.30 (m, 2H), 1.04 (t, 3H, J = 7.5 Hz), 0.96 (t, 3H, J = 7.5 Hz);

^{13}C NMR ($CDCl_3$) δ 157.5, 154.5, 153.7, 138.4, 136.5, 135.8, 128.7 (2), 127.8, 127.1 (2), 70.3, 47.5, 46.0, 45.4, 42.8, 41.8, 36.8, 31.4, 21.9, 21.7, 11.210.3; IR (KBr) 2968, 1701, 1555, 1483 cm^{-1}; CI MS *m*/*z* 419 $(M + H)^+$, 381, 353. Anal. Calcd for $C_{25}H_{30}N_4O_2$: C, 71.74; H, 7.22; N, 13.39. Found: C, 71.72; H, 7.20; N, 13.20. This was followed by the endo isomer **2b** as a colorless oil, which crystallized to a white solid upon standing (1.4 g, 43% yield): mp (DSC) 110 °C; TLC R_f (50% ethyl acetate/hexanes) = 0.46; ^{1}H NMR ($CDCl_3$) δ 7.33−7.28 (m, 3H), 7.14−7.12 (m, 2H), 6.22−6.20 (m, 1H), 5.84−5.82 (m, 1H), 5.33 (s, 2H), 4.32 (t, 2H, J = 6.5 Hz), 4.05 (t, 2H, J = 8.0 Hz), 3.21−3.19 (m, 1H), 3.07 (s, 1H), 2.90 (s, 1H), 2.04−2.02 (m, 1H), 1.84−1.75 (m, 2H), 1.73−1.66 (m, 2H), 1.44−1.42 (m, 1H), 1.31−1.25 (m, 1H), 1.01 (t, 3H, J = 7.4 Hz), 0.95 (t, 3H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 156.7, 152.0, 147.8, 137.2, 136.5, 132.2, 128.7 (2), 127.7, 126.5 (2), 70.2, 49.8, 46.4, 45.4, 42.8, 42.4, 37.3, 31.2, 21.8, 21.6, 11.4, 10.3; IR (KBr) 2967, 1701, 1554, 1485 cm^{-1}; CI MS *m*/*z* 419 $(M + H)^+$, 381, 352. Anal. Calcd for $C_{25}H_{30}N_4O_2$: C, 71.74; H, 7.22; N, 13.39. Found: C, 71.60; H, 7.17; N, 13.28.

1,3-Dipropyl-3,7-dihydro-7-benzyl-8-*endo*-[2-norborn-5-enyl]-1*H*-purine-2,6-dione (17). Ammonia was condensed into a solution of **2a** (0.300 g, 7.0 mmol) in anhydrous tetrahydrofuran (50 mL) at −78 °C under nitrogen to a total volume of 100 mL. This was followed by the portionwise addition of lithium metal (0.050 g, excess) to the point at which the solution maintained a deep blue color for 5 min. The mixture was diluted with methanol (20 mL), cooled to room temperature, and diluted with saturated ammonium chloride solution (100 mL). The mixture was then extracted with ethyl acetate (2 × 100 mL), and the combined organic extracts were dried ($MgSO_4$). The solvents were removed under reduced pressure to produce the crude xanthine as a yellow oil, which was dissolved in anhydrous *N*,*N*-dimethylformamide (10 mL) at room temperature under nitrogen and treated with sodium hydride (0.035 g, 0.8 mmol, 60% dispersion in mineral oil). The suspension was stirred at room temperature for 15 min after which benzylamine (0.1 mL, 0.8 mmol) was added and the mixture was stirred at room temperature for 22 h. The mixture was diluted with water (50 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$), and the solvents were removed under reduced pressure. The resulting amber oil was purified by flash column chromatography on silica gel, eluting with ethyl acetate/hexanes (1:3), to produce the endo *N*-3-benzyl positional isomer **17** as a colorless oil, which crystallized to a white solid upon standing (0.240 g, 80% yield over two steps). The ^{1}H NMR spectrum ($CDCl_3$) was identical to the known material provided by CV Therapeutics, Inc.: CI MS *m*/*z* 419 $(M + H)^+$.

Acknowledgment. The authors acknowledge and thank Marek G. Nelson, Ph.D., of Protein Design Labs (formerly of CV Therapeutics, Inc.) for copies of spectral data for compound **17** and for many helpful discussions and Biogen, Inc., for permission to publish this body of work. This work constitutes a six-month research effort by Albany Molecular Research, Inc., on behalf of CV Therapeutics, Inc., and Biogen, Inc.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra for all new compounds reported in this manuscript. This material is available free of charge via the Internet at http://pubs.acs.org.

JO015925R