New Process for the Synthesis of UP 269-6, a 1,2,4-Triazolo[1,5-*c*]pyrimidine Derivative as a Potent Orally Active Angiotensin II Antagonist

T. Boyer, L. Fournel, E. Nicolaï* and J. M. Teulon

Laboratoires UPSA, 128 rue Danton,
92500 Rueil Malmaison, France
Received January 25, 1996

A new synthetic route to prepare the 2-hydroxy-5-methyl-7-*n*-propyl-8-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-[1,2,4]triazolo[1,5-*c*]pyrimidine (**UP 269-6**, Ripisartan) is described. **UP 269-6** is a non-peptide angiotensin II antagonist currently in phase II clinical trials for the treatment of hypertension and chronic heart failure. Its development needed a suitable process for industrial production. The laboratory scale synthesis was optimized and particularly two key steps: 4-hydrazinopyrimidine formation without isolation of the 4-chloro intermediate and its cyclization into triazolo[1,5-*c*]pyrimidine derivative without isolation of the triazolo[4,3-*c*]pyrimidine isomer using urea in *N*-methylpyrrolidone at 160°C. This cyclization process affords a new and efficient way to prepare directly 2-hydroxytriazolo[1,5-*c*]pyrimidine without isolation of the corresponding triazolo[4,3-*c*]pyrimidine.

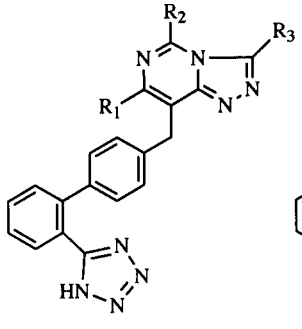
J. Heterocyclic Chem., **33**, 1307 (1996).

Introduction.

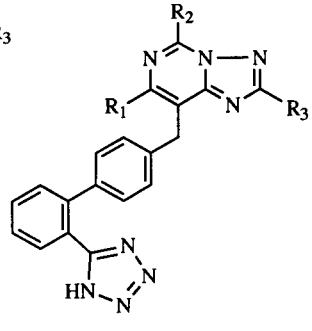
As a part of our research program to discover new non-peptide angiotensin II antagonists we have developed a series of C-linked triazolopyrimidines [Ia-b] of formula I and II (Chart I). From this series, the 2-hydroxy-5-methyl 7-*n*-propyl-8-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-[1,2,4]triazolo[1,5-*c*]pyrimidine (**UP 269-6**, Ripisartan, Chart II) [2a-c] was selected as the lead compound and is currently in phase II clinical trials for the treatment of hypertension.

Chart I

Structures of Derivatives of Formula **I** and **II**



Formula **I**.
Triazolo[4,3-*c*]pyrimidine

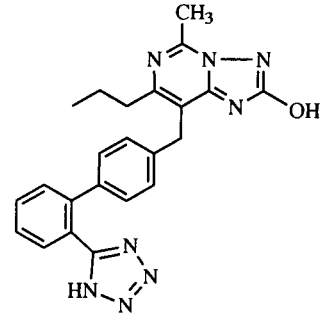


Formula **II**.
Triazolo[1,5-*c*]pyrimidine

The original synthesis of **UP 269-6** carried out on the laboratory scale involved 7 steps as depicted in Scheme I, the overall yield was 11%. The scale up of the process needed improved yields, simpler procedures, cheaper starting materials and increased purity. We would like to describe here a new process suitable for the industrial synthesis of **UP 269-6** and offering a new and efficient way for the synthesis of 2-hydroxytriazolo[1,5-*c*]pyrimidine without isolation of the [4,3-*c*] isomer.

Chart II

Structure of **UP 269-6**



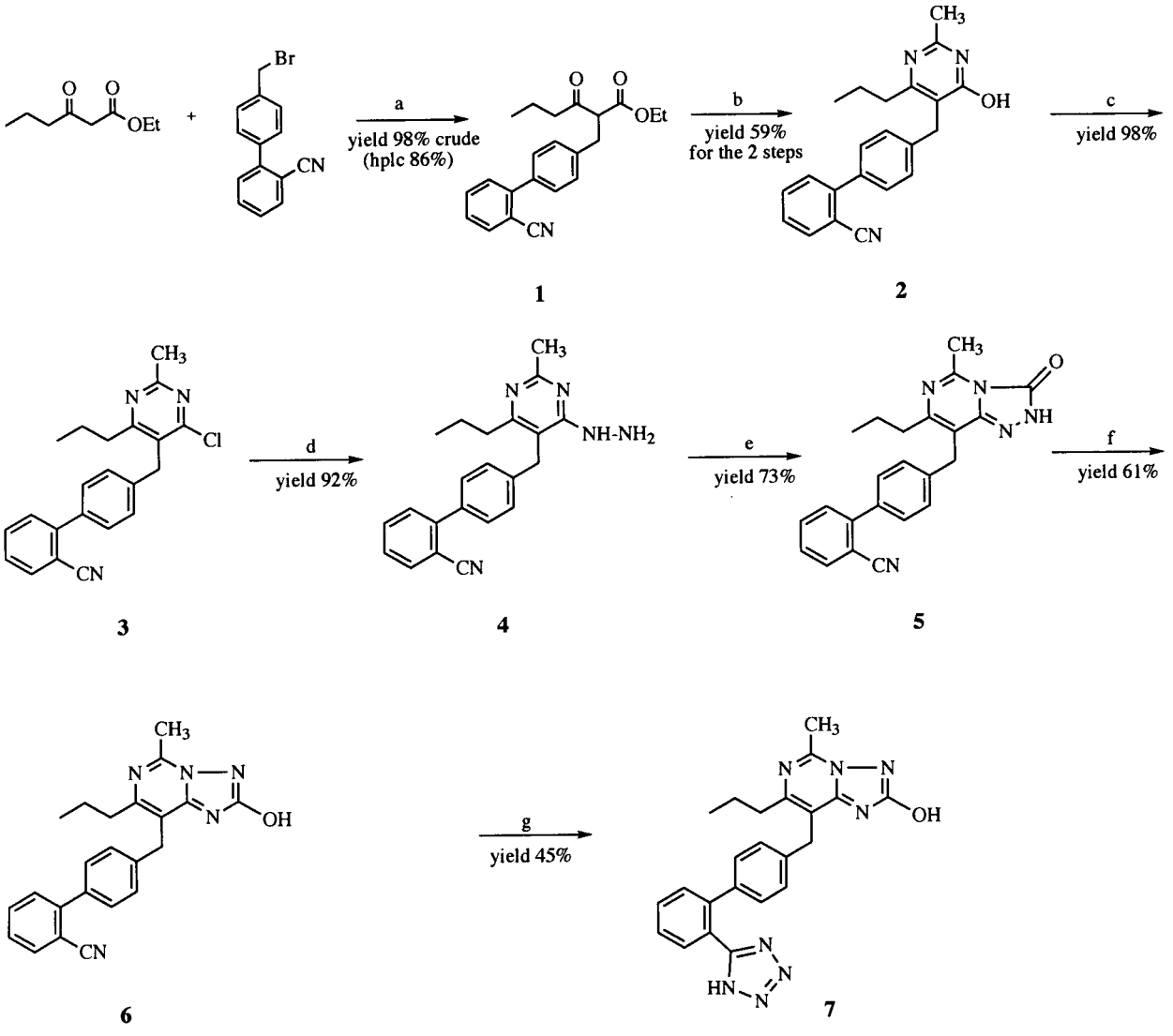
UP 269-6

Chemistry.

The new synthesis of **UP 269-6** was achieved in a 6-step procedure without purification of **1** and **3** intermediates (see Scheme II). The first four steps were the same as those of the original procedure but used new experimental conditions. Ethyl butyrylacetate was alkylated with 4-bromomethyl-2′-cyanobiphenyl [1b] in tetrahydrofuran at reflux 15 hours in presence of lithium chloride and *N,N*-diisopropylamine according to Sung-Eun *et al* [3] method (Scheme III) in order to avoid dialkylation. The keto-ester **1** was used crude after elimination of the excess

Scheme I

Original Synthesis of **UP 269-6** (laboratory scale)



[a] LiCl, $(i\text{-Pr})_2$NEt, THF, reflux 15 hours; [b] NaOMe, MeOH, acetamide hydrochloride, r-t, 20 hours, reflux 3 hours; [c] $POCl_3$, 100°C, 6 hours; [d] N_2H_4, EtOH, reflux, 2 hours; [e] CDI, THF, reflux , 1.5 hours; [f] 3N KOH, EtOH, 60°C, 4 hours; [g] Me_3SnN_3, toluene, reflux 24 hours.

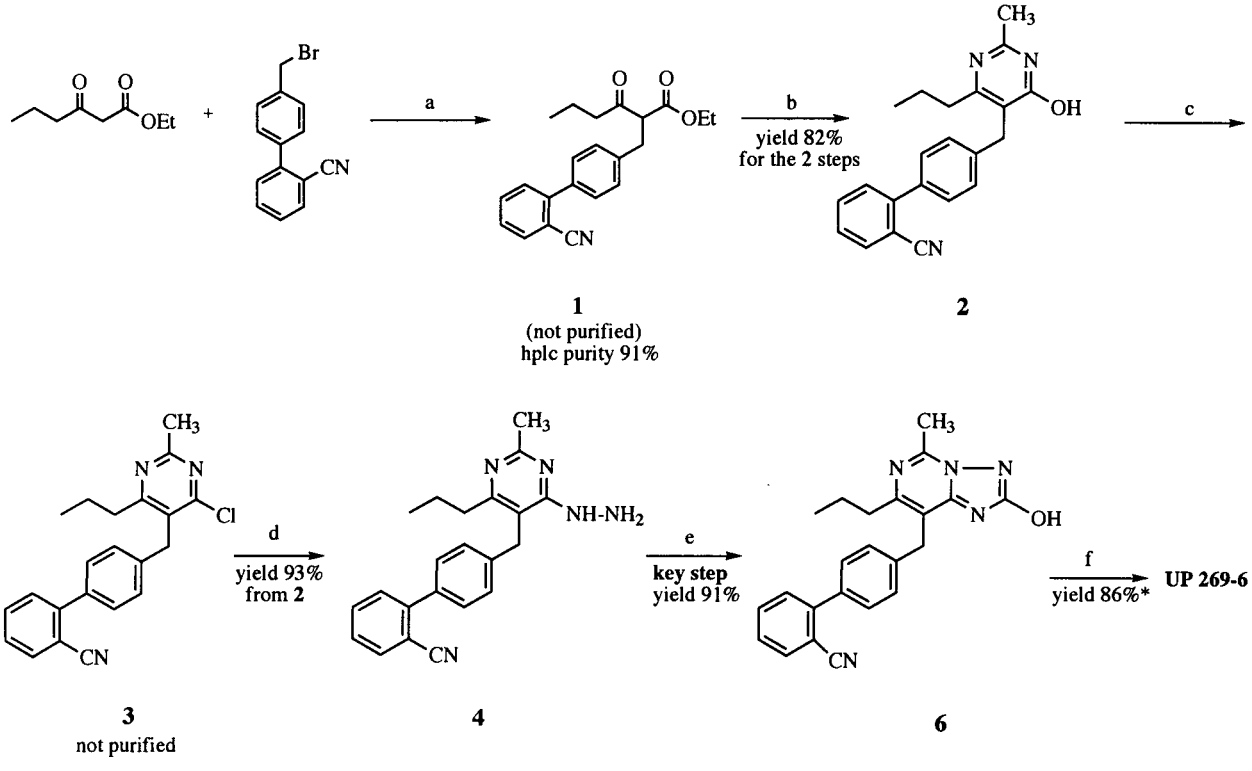
of ethyl butyrylacetate by distillation in presence of *N*-methylpyrrolidone. The cyclization of **1** was achieved by reaction with 2.5 equivalents of acetamidine hydrochloride in presence of 2.65 equivalents of sodium methoxide in methanol, 20 hours at room temperature and 2 hours at reflux. The first key step of the synthesis was the formation of the 4-hydrazinopyrimidine **4**. The treatment of **2** with 5.8 equivalents of phosphorus oxychloride in toluene for 8 hours at reflux led to the 4-chloropyrimidine **3** which was taken into ethanol after elimination of toluene and phosphorus oxychloride. The treatment of this ethanolic suspension of **3** with 11.2 equivalents (from **2**) of hydrazine hydrate at reflux for 2 hours afforded the 4-hydrazinopyrimidine **4**. The second key step was the cyclization of **4** into the 2-hydroxytriazolo[1,5-*c*]pyrimidine **6** without isolation of the [4,3-*c*] isomer **5** (Scheme I). Treatment of **4** with 2.7 equivalents of urea in *N*-methylpyrrolidone at 160-165°C for 2 hours allowed to obtain directly the [1,5-*c*] isomer **6** in 91% yield. The formation of the tetrazole (**UP 269-6**) was achieved by treatment of **6** with 1.9 equivalents of trimethylstannyl azide in xylene at 115°C for 24 hours.

Discussion.

The first step led to a mixture of the ketoester **1** and ethyl butyrylacetate used in excess, it was important to

Scheme II

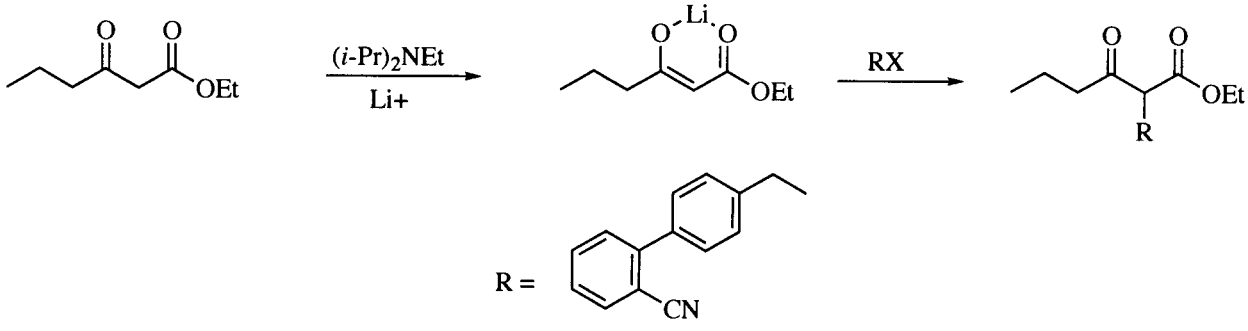
Industrial Process for the Synthesis of **UP 269-6**



[a] LiCl, $(i\text{-Pr})_2NEt$, THF, reflux 15 hours; [b] NaOMe 30% in MeOH, acetamide hydrochloride, r-t, 20 hours, reflux 2 hours; [c] $POCl_3$, toluene, reflux 8 hours; [d] N_2H_4, EtOH, reflux, 2 hours; [e] urea, *N*-methylpyrrolidone, 160-165°C, 2 hours; [f] Me_3SnN_3, xylene, 115°C, 24 hours; *[f] is not the industrial process; Industrial production: 91% of pure **UP 269-6** with a different process.

Scheme III

Monoalkylation of the Ketoester According to Sung-Eun Yoo



eliminate this excess starting material in order to avoid the excessive consumption of acetamidine hydrochloride in the second step and the formation of 4-hydroxy-2-methyl-6-*n*-propylpyrimidine as a side product. A distillation of the oily residue after addition of *N*-methylpyrrolidone allowed us to eliminate almost entirely the excess reagent. The yield of the two first steps was sensibly improved by optimization of experimental conditions (previous yield 59%, optimal yield 82% for the two steps). The formation of 4-hydrazinopyrimidine **4** from 4-hydroxy derivative **2** was subjected to some modifications. The chlorination of **2** was achieved in toluene with subsequent addition of phosphorus oxychloride at 80°C. This allowed us to improve safety conditions and better

control of the exothermic effect. In order to simplify the process, it was decided to use directly the 4-chloro derivative **3** without isolation, after elimination of the excess of phosphorus oxychloride and subsequent suspension of the residue in ethanol. This ethanolic suspension was rapidly added (to avoid the formation of 4-ethoxy derivative) to a solution of 11.2 equivalents of hydrazine hydrate in ethanol. This procedure allowed us to reduce manipulation time and avoided the handling and the degradation of the irritant 4-chloro intermediate **3**.

In the original synthesis the formation of 2-hydroxytriazolo[1,5-*c*]pyrimidine **6** from hydrazinopyrimidine **4** (Scheme 1) proceeded in 2 steps. The first step used expensive reagent *N,N'*-carbonyldiimidazole and led to the [4,3-*c*] isomer **5** in 73% yield. The latter was transformed into the [1,5-*c*] isomer **6** by a Dimroth type rearrangement using drastic alkaline conditions involving the use of 3*N* potassium hydroxide in ethanol, the yield was only 61% and an important amount of amide derivative was obtained as a side product resulting from the hydrolysis of the nitrile group. In the industrial process we used a cheaper cyclization reagent, urea. Moreover using *N*-methylpyrrolidone at reflux as the solvent, the Dimroth rearrangement was achieved thermically without isolation of **5** and under these conditions the formation of the amide impurity was never detected. Finally the yield of this one step procedure was 91% (45% in the original synthesis in two steps). This process affords a new and efficient alternative to the previous literature reports [4a-b] for the synthesis of 2-hydroxytriazolo[1,5-*c*]pyrimidines and avoid isolation of the [4,3-*c*] isomer and its rearrangement under alkaline conditions, so that alkaline sensitive groups such as nitriles or esters for example are not hydrolyzed.

Conclusion.

The process described herein allowed to improve sensibly the overall yield of the synthesis of **UP 269-6** (from 11% to 60%). The key step of the new synthesis was the cyclization of the 4-hydrazinopyrimidine **4** into the 2-hydroxytriazolo[1,5-*c*]pyrimidine **6** without formation of the [4,3-*c*] isomer **5**. Used more widely, this process would provide a new efficient and simple way to obtain directly 2-hydroxytriazolo[1,5-*c*]pyrimidines from 4-hydrazinopyrimidines in good yields and using cheap reagents.

EXPERIMENTAL

The ^{1}H nmr spectra were measured at 200 MHz on a Bruker AC 200 spectrometer and recorded in deuteriochloroform or DMSO-d_6. Chemical shifts were reported in δ (ppm) units relative to internal reference tetramethylsilane. Melting points were recorded on an Electrothermal digital capillary melting point apparatus and are uncorrected. Elemental analyses were obtained by using a Carlo Erba Model-106 elemental analyser. The hplc experiments were performed on a Varian liquid chromatograph with uv detector (λ = 260 nm) and suitable integration system (C8 lichrosorb column). Starting materials were commercially available or their preparation can be found in references [1a,b].

Ethyl 2-(2'-Cyanobiphenyl-4-yl)methyl-3-oxohexanoate (**1**).

A mixture of 154.5 g (0.568 mole) of 4-bromomethyl-2'-cyanobiphenyl, 39 g (0.92 mole) of lithium chloride, 197 ml (1.13 moles) of *N,N*-diisopropylethylamine and 144 g (0.910 mole) of ethyl butyrylacetate in 600 ml of dry tetrahydrofuran was refluxed for 15 hours. The mixture was concentrated under vacuum until it became pasty and 1 l of chloroform was added, the solution was allowed to return to room temperature and 350 ml of water were added. After stirring for 30 minutes the mixture was separated and the organic layer was washed with a solution of 40 ml of concentrated hydrochloric acid (30%) in 350 ml of water (*p*H = 1) and 3 times with 350 ml of water. The solution was dried over sodium sulfate, treated with charcoal, filtered off and concentrated under vacuum. To the oily residue was added 140 ml of *N*-methylpyrrolidone and distillation under 4 mm of Hg at a temperature below 108°C allowed us to eliminate the excess ethyl butyrylacetate. The crude oily residue weighed 196.6 g and was used without further purification in the next step; ^{1}H nmr (deuteriochloroform): 0.86 (t, J = 7.4 Hz, 3H) 1.22 (t, J = 7.5 Hz, 3H), 1.57 (sext, J = 7.4 Hz, 2H), 2.29-2.65 (m, 2H), 3.22 (d, J = 7.5 Hz, 2H), 3.84 (t, J = 7.5 Hz, 1H), 4.16 (q, J = 7 Hz, 2H), 7.30 (d, J = 8 Hz, 2H), 7.39-7.49 (m, 4H), 7.63 (t, J = 8 Hz, 1H), 7.75 (d, J = 8 Hz, 1H); hplc purity: 90.9%.

5-[(2'-Cyanobiphenyl-4-yl)methyl]-4-hydroxy-2-methyl-6-propylpyrimidine (**2**).

To a solution of 135 g (1.43 moles) of acetamidine hydrochloride in 900 ml of methanol was added 269.1 ml (1.49 moles) of 30% sodium methylate in methanol then a solution of crude **1** (196.6 g, 0.563 mole) in 85 ml of methanol. The mixture was stirred at room temperature for 20 hours and refluxed for 2 hours before evaporation of the methanol under vacuum. After cooling, 1 l of chloroform, 825 ml of water and 33 ml of acetic acid were successively added under stirring (*p*H = 5.6). The stirring was continued for 2 hours and the mixture was allowed to stand at room temperature for 4 hours. The organic layer was washed twice with 800 ml of water, dried over sodium sulfate and concentrated under vacuum. To the residue was added 600 ml of 2-methoxyethanol and 150 ml of the solvent were eliminated by distillation at atmospheric pressure at 112-114°C. The solution was allowed to stand at room temperature for 12 hours. After cooling to 10°C, the solid material was collected and washed with 18 ml of 2-methoxyethanol then twice with 43 ml of water to give 159.6 g (82% from 4'-bromomethyl-2-cyanobiphenyl) of **2**, mp 207°C; ^{1}H nmr (deuteriochloroform): 0.94 (t, J = 7.5 Hz, 3H), 1.62 (sext, J = 7.5 Hz, 2H), 2.40 (s, 3H), 2.60 (t, J = 7.5 Hz, 2H), 3.97 (s, 2H), 7.44-7.35 (m, 6H), 7.58 (t, J = 7.6 Hz, 1H), 7.74 (d, J = 7.6 Hz, 1H); hplc purity: 99.70%.

Anal. Calcd. for $C_{22}H_{21}N_3O$: C, 76.94; H, 6.16; N, 12.24. Found: C, 76.75; H, 6.14; N, 12.10.

4-Chloro-5-[(2'-cyanobiphenyl-4-yl)methyl]-2-methyl-6-propylpyrimidine (**3**).

A suspension of 150 g (0.38 mole) of **2** in 900 ml of toluene

was heated at 80°C and 397 g (2.54 moles) of phosphorus oxychloride were added dropwise in the course of 1 hour. The mixture was heated to reflux for 8 hours. The solvent and the excess of phosphorus oxychloride were evaporated off under vacuum, then 725 ml of toluene were added and distilled off under vacuum in order to eliminate the residual phosphorus oxychloride. The residue was taken up into 1 l of chloroform and 450 ml of water were added with cooling. The organic layer was washed 4 times with 450 ml of water and dried over sodium sulfate. The chloroform was evaporated off under vacuum, 150 ml of ethanol were rapidly added at 45°C, the resulting suspension was cooled to 20°C and used directly in the next step without further purification.

5-[(2′-Cyanobiphenyl-4-yl)methyl]-4-hydrazino-2-methyl-6-propylpyrimidine (**4**).

The above ethanolic suspension of **3** was added in 1 hour to a refluxed solution of 246 g (4.92 moles) of hydrazine hydrate in 150 ml of ethanol. A slightly exothermic effect maintained the reflux during a few minutes without heating. When the exothermic effect was completed, the reflux was continued for 2 hours. The mixture was allowed to return to room temperature and after 12 hours was cooled with iced water bath, filtered off, washed twice with 60 ml of water and dried under vacuum to give 145.7 g (93% overall yield from **2**), mp 159°C; ^{1}H nmr (deuteriochloroform): 0.98 (t, J = 7.5 Hz, 3H), 1.69 (sext, J = 7.5 Hz, 2H), 2.57 (s, 3H), 2.68 (t, J = 7.5 Hz, 2H), 3.90 (s, 2H), 3.98 (br s, 2H), 5.77 (s,1H), 7.20 (d, J = 8 Hz, 2H), 7.51-7.44 (m, 4H), 7.65 (t, J = 7.8 Hz, 1H), 7.76 (d, J = 7.8 Hz, 1H); hplc purity: 99.8%.

Anal. Calcd. for $C_{22}H_{23}N_5$: C, 73.92; H, 6.49; N, 19.59. Found: C, 74.10; H, 6.61; N, 19.59.

8-[2′-Cyanobiphenyl-4-yl)methyl]-2-hydroxy-5-methyl-7-propyl-1,2,4-triazolo[1,5-*c*]pyrimidine (**6**).

A solution of 145.7 g (0.41 mole) of **4** and 65.8 g (2.72 moles) of urea in 146 ml of freshly distilled *N*-methylpyrrolidone was slowly heated to reach 160-165°C during 2 hours. After 6 hours at this temperature, the mixture was cooled to 80°C and poured dropwise into a solution of 17.5 g (0.44 mole) of sodium hydroxide in 730 ml of cold water at such a rate to keep the temperature below 20°C. To this mixture was added 1100 ml of ethyl acetate and the biphasic mixture was filtered and separated. The aqueous layer was washed 3 times with 120 ml of ethyl acetate, passed over charcoal and filtered. Then 71.6 ml of acetic acid were added and the solution was stirred for 1 hour. The solid material was collected by filtration and taken up into 1200 ml of water, filtered off, washed with 250 ml of water and dried at 60°C for 30 hours to give 141.7 g (91%) of **6**, mp 225°C, ^{1}H nmr (deuteriochloroform): 0.96 (t, J = 7 Hz, 3H), 1.69 (sext, J = 7 Hz, 2H), 2.81 (t, J = 7 Hz, 2H), 2.87 (s, 3H), 4.30 (s, 2H), 7.49-7.30 (m, 6H), 7.61 (d, J = 7.5 Hz, 1H), 7.74 (d, J = 7.5 Hz, 1H); hplc purity: 99.7%.

Anal. Calcd. for: $C_{23}H_{21}N_5O$: C, 72.04; H, 5.52; N, 18.27. Found: C, 72.40; H, 5.62; N, 18.33.

2-Hydroxy-5-methyl-7-propyl-8-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1,2,4-triazolo[1,5-*c*]pyrimidine (**UP 269-6**).

A mixture of 5.1 g (24.7 mmoles) of trimethyltin azide and 4.98 g (13 mmoles) of **6** was heated to 115°C for 24 hours in 50 ml of xylene. The temperature was then allowed to return to 80°C and the precipitate was filtered off, washed with hot xylene, and suspended in 75 ml of tetrahydrofuran. Hydrogen chloride gas was bubbled into this suspension until complete dissolution and then again during 20 minutes. A white precipitate was filtered off after stirring for 1 hour, washed twice with tetrahydrofuran and recrystallized in 6 volumes from acetic acid. The crystals which formed after 16 hours at room temperature were filtered and washed twice with 0.6 volume of acetic acid then taken up into 6 volumes of ethanol and refluxed for 4 hours. The mixture was allowed to return to room temperature, stirred for 16 hours and the crystals filtered off and dried to give 4.76 g (86%) of **UP 269-6**, mp 234-235°C, ^{1}H nmr (DMSO-d_6): 0.84 (t, J = 7.5 Hz, 3H), 1.53 (sext, J = 7.5 Hz, 2H), 2.65 (t, J = 7.5 Hz, 2H), 2.71 (s, 3H), 4.16 (s, 2H), 6.99 (d, J = 8 Hz, 2H), 7.15 (d, J = 8 Hz, 2H), 7.67-7.49 (m, 4H); hplc purity: 99.9%.

Anal. Calcd. for $C_{23}H_{22}N_8O$: C, 64.77; H, 5.20; N, 26.28. Found: C, 64.92; H, 5.30; N, 26.09.

Acknowledgment.

We thank M. L. Forgue, B. Gazal, J. Goyard, S. Malessan and T. Pham for technical assistance, Anne Gourvil and Catherine Gouedard for elemental analysis and hplc data and Marie-France De Oliveira for secretarial assistance.

REFERENCES AND NOTES

* Author to whom correspondence should be addressed.

[1a] E. Nicolaï, G. Curé, J. Goyard, M. Kirchner, J. M. Teulon, A. Versigny, M. Cazes, F. Caussade, A. Virone-Oddos and A. Cloarec, *J. Med. Chem.*, **37**, 2371 (1994); [b] N. Bru-Magniez, E. Nicolaï and J. M. Teulon, US Patent 5,217,973 (1993).

[2a] F. Caussade, A. Virone-Oddos, C. Delchambre, M. Cazes, A. Versigny and A. Cloarec, *Fundam. Clin. Pharmacol.*, **9**, 119 (1995); [b] M. Mcintyre, R.J. McFadyen, P.A. Meredith, J. Menard, H.R. Brunner, J. Insuasty and J. L. Reid, *J. Cardiovasc. Pharmacol.*, **25**, 994 (1995); [c] N. Inglessis, J. Nussberger, M. Hagmann, O. Hiesse-Provot, J. Insuasty, J. Reid, J. Menard and H.R. Brunner, *J. Cardiovasc. Pharmacol.*, **25**, 986 (1995).

[3] Y. Sung-Eun and Y .Y. Kyu, *Bull. Korean Chem. Soc.*, **10** 112 (1989).

[4a] G. W. Miller, F. L. Rose, *J. Chem. Soc.*, 5642 (1963); [b] G. W. Miller and F. L. Rose, *J. Chem. Soc.*, 3357 (1965).