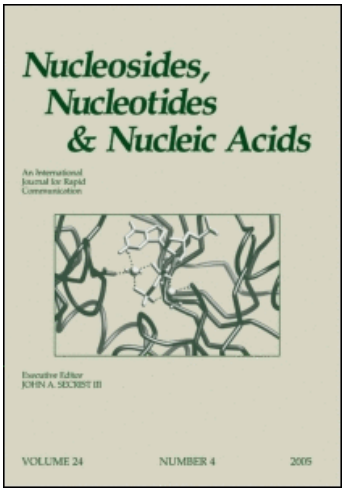


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

An Expeditious Synthesis of Homochiral (R) 2-(9-Purinyl)butane-1, 4-Diols from (S) Butane-1, 2, 4-Triol

Michel Perbost[a]; Marc Lucas[a]; Claude Chavis[a]; Jean-Louis Imbach[a]
[a] Université de Montpellier II, Sciences et Techniques du Languedoc, Laboratoire de Chimie Bio-Organique, Montpellier Cedex 5, France

To cite this Article Perbost, Michel , Lucas, Marc , Chavis, Claude and Imbach, Jean-Louis(1992) 'An Expeditious Synthesis of Homochiral (R) 2-(9-Purinyl)butane-1, 4-Diols from (S) Butane-1, 2, 4-Triol', Nucleosides, Nucleotides and Nucleic Acids, 11: 8, 1529 — 1537
To link to this Article: DOI: 10.1080/07328319208021193
URL: http://dx.doi.org/10.1080/07328319208021193

NUCLEOSIDES & NUCLEOTIDES, 11(8), 1529-1537 (1992)

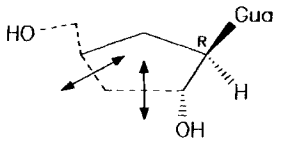
AN EXPEDITIOUS SYNTHESIS OF HOMOCHIRAL (R) 2-(9-PURINYL)BUTANE-1, 4-DIOLS FROM (S) BUTANE-1, 2, 4-TRIOL

Michel Perbost, Marc Lucas, Claude Chavis and Jean-Louis Imbach*

Université de Montpellier II, Sciences et Techniques du Languedoc,
Laboratoire de Chimie Bio-Organique, Associé au CNRS n°488, case 008,
34095 Montpellier Cedex 5 (France)

Abstract: The synthesis of (R) 2-(9-adenyl) and (R) 2-(9-guanyl)butane-1, 4-diols are described *via* an alkylation reaction of 6-chloropurine and $\underline{N}^2$-acetyl-$\underline{O}^6$-diphenylcarbamoyl guanine by (S) 1, 4-di-*tert*-butyldiphenylsilyloxybutane-2-ol under Mitsunobu conditions.

The chemistry and biology of nucleoside analogues have been the subject of intensive work during the past decades. Among the different families studied (acyclic,[1] carbocyclic[2], carboacyclic[1] and dideoxy nucleosides), various molecules *i.e.* 3'-azido-3'-deoxythymidine (AZT),[3] 2',3'-didehydro-2',3'-dideoxycytidine (ddC),[4] 2',3'-didehydro-2',3'-dideoxyinosine (ddI),[5] carbocyclic oxetanocin guanine analogue (COXT-G),[6] oxetanocin (OXT-A),[7] acyclovir (ACV)[8] emerged with potent activity against *herpes simplex* and/or human immunodeficiency viruses. The search for new molecules which exhibit high therapeutic indexes is today of great interest for antiviral research.



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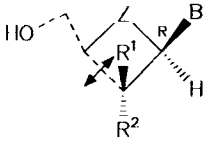
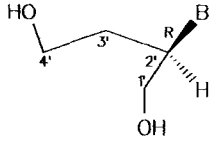
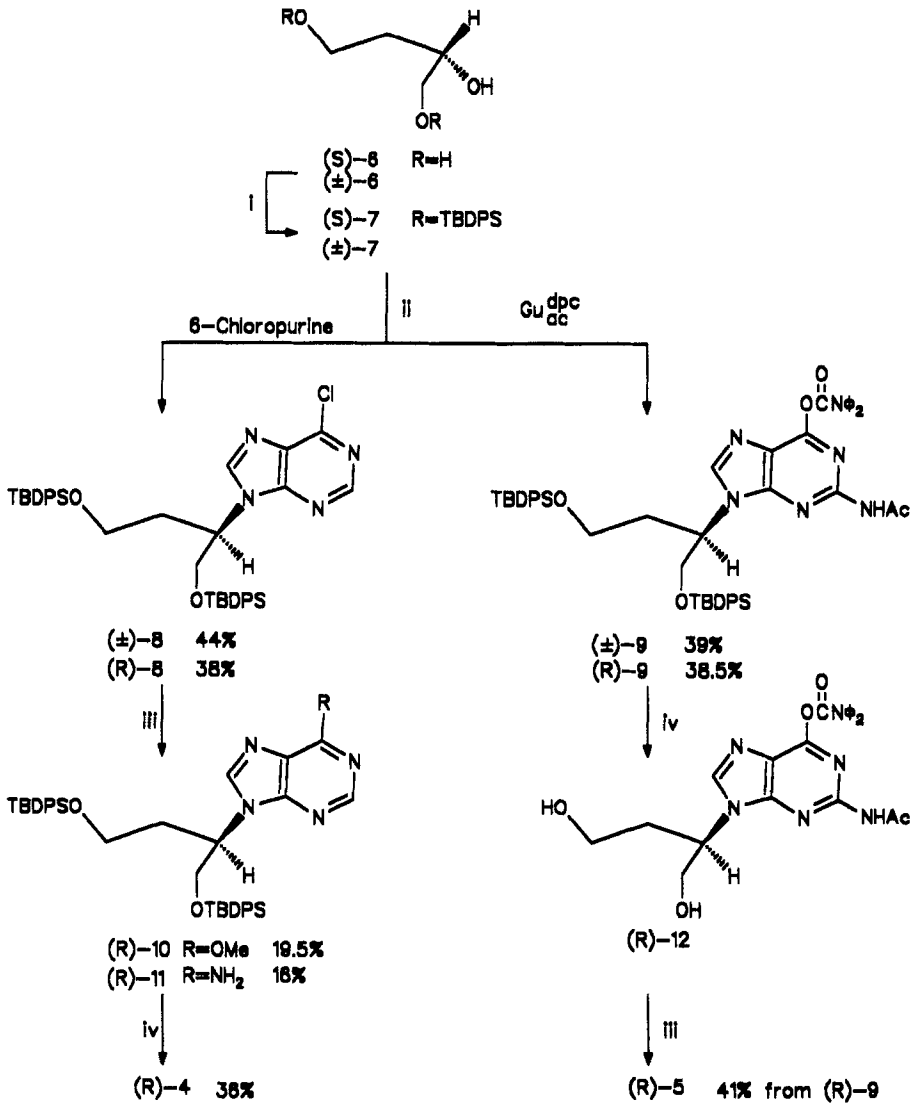


	R^1	R^2	Z	B
2	H	OH	CH_2	Gua
3	OH	H	O	Ade



4 B=Ade
5 B=Gua

Scheme 1



Scheme 2. i: TBDPSCl, pyridine, RT, 98% yield; ii: $Ø_3P$, DEAD, THF, 0°C to RT; iii: NH_3/MeOH, 50°C; iv: TBAF/THF, RT.

This paper deals with the synthesis of homochiral carboacyclic nucleoside analogues **4** and **5** (scheme 1) which formally mimic, after C-C bonds cleavage and deletion of exo-methylene, the structure of biologically active parent molecules such as carbocyclic 3'-deoxyguanosine[9] **1**, *nor*oxetanocin guanine analogue[10] **2** (both moderately active against HSV-1 and HSV-2) and *epinor*oxetanocin[11] **3** (significantly active against HIV-1). As it has been shown[12] for various modified nucleoside analogues that the biological properties of enantiomers were not additive when compared with the corresponding racemate and that this later was usually less active than one of the two enantiomers (often the stereoisomer related to the natural configuration of nucleosides), we undertook the unequivocal synthesis of (R) 2-(9-adenyl) and (R) 2-(9-guanyl)butane-1, 4-diols **4** and **5** from (S) butane-1, 2, 4-triol **6** in order to evaluate their antiviral properties for comparison with those of the corresponding racemic mixtures.

As the racemic compounds **4** and **5** can be obtained[13] *via* a conjugate addition of adenine and protected guanine on diethyl maleate (followed by the reduction of the ester functions and removal of the protecting groups), we firstly performed asymmetric Michael-type additions on optically pure (-)-dimenthyl maleate and fumarate (from (-)-menthol): the lack of asymmetric induction in the formation of diastereomeric adducts led us to investigate the alkylation of heterocyclic base precursors of adenine and guanine residues by the diether alcohol **7** derived from (S) butane-1, 2, 4-triol **6** under Mitsunobu conditions[14] (scheme 2).

It is worth noting that few examples[15-16] of Mitsunobu-type reactions have been reported between modified or protected nucleobases and *pseudo*-sugars. For our purpose, we devised the sequence of reactions which started with the silylation of the two primary hydroxyl functions of butanetriol (S)-**6** by *tert*-butyldiphenylchlorosilane in pyridine at room temperature in a nearly quantitative yield. The disilyl ether (S)-**7** was then subjected to an alkylation reaction by 6-chloropurine or $\underline{N}^2$-acetyl-$\underline{O}^6$-diphenylcarbamoyl guanine[17] in the presence of triphenylphosphine and DEAD in THF (0°C to room temperature). The resulting compounds (R)-**8** and (R)-**9** were obtained with inverted configuration[14] at C-2', but in yields not exceeding 39%. Some assays done with racemic **7** did not led to compounds (±)-**8** and (±)-**9** with enhanced yields. In similar conditions 3-benzylthymine[18] did not afford the expected bisalkylated thymine.

Treatment of the 6-chloropurine derivative (R)-**8** by methanolic ammonia afforded the expected adenine derivative **11** (16% yield) accompanied by the formation of the corresponding 6-methoxy derivative **10** (19.5%). Then, the TBDPS groups of compound **11** were removed with TBAF in THF to give **4** in 36% yield.

In the case of alkylated guanine (R)-**9**, the alcohol functions were first liberated with TBAF in THF to give the diol **12** which was, without further purification, fully deprotected with methanolic ammonia to afford (R)-**5** in 41% overall yield from **9**. The regioisomerism (N-9 *versus* N-7) was confirmed by U.V. spectroscopy in different media.

All the compounds were fully characterized by ^{1}H-NMR, mass and U.V. spectroscopy and by their elemental analyses.

The biological evaluations of carboacyclic purinyl nucleosides (R)-**4** and (R)-**5** are in progress.

Experimental

M.p.s were obtained with a Büchi (capillary) apparatus and were uncorrected. UV spectra were determined on an Uvikon-810 spectrophotometer. Elemental analyses were performed by the 'Service de Microanalyse du CNRS, Division de Vernaison'. ^{1}H NMR spectra were determined on a Brüker AC250 or AM300 spectrometer. Mass spectra were obtained with a Jeol JMS-DX300 by the FAB ionization method.

*(±)-1, 4-(*Tert-*butyldiphenylsilyloxy)butane-2-ol* **7**

To a solution of (±)-butane-1, 2, 4-triol **6** (2.02 g, 19 mmol) in anhydrous pyridine (15 mL) was added *tert*-butyldiphenylchlorosilane (12.37 g, 45.6 mmol) at -10°C. After being stirred for 3 h, the solution was hydrolysed with water (50 mL) and extracted twice with diethyl ether (200 mL). The ethereal extracts were washed once with 10% aqueous $NaHCO_3$ then with brine and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residual yellow oil was chromatographed on a silica gel column with pentane-dichloromethane 75:25 as the eluting system to afford **7** (11 g, 99% yield) as an oil. R_f 0.72 (dichloromethane). δ_H (300 MHz, DMSO-d_6) 0.97 (s, 9H, tBu), 0.98 (s, 9H, tBu), 1.52 (m, 1H, H-3"), 1.91 (m, 1H, H-3'), 3.44 (dd, $J_{4"-3}$ = 6.64 Hz, $J_{4"-4'}$ = 9.84 Hz, 1H, H-4"), 3.58 (dd, $J_{4'-3}$ = 5.17 Hz, $J_{4"-4'}$ = 9.84 Hz, 1H, H-4'), 3.8 (m, 3H, H-1", H-1', H-2'), 4.63 (d, J_{HO-CH_2} = 5.3 Hz, 1H, OH), 7.42 (m, 12H, aromatic) and 7.62 (m, 8H, aromatic).

*(S)-1, 4-(*Tert-*butyldiphenylsilyloxy)butane-2-ol* **7**

To a solution of (S)-butane-1, 2, 4-triol **6** (3 g, 28.27 mmol) in anhydrous pyridine (15 mL) was added *tert*-butyldiphenylchlorosilane (18.66 g, 67.85 mmol) at -10°C. After a similar treatment as for the racemic compound, **7** was isolated as an oil (16.15 g, 98% yield). It had the same spectral data as compound (±)-**7**; $[\alpha]_D^{22}$ -8.18°

(c 1.1 in methanol), $[\alpha]_D^{22}$ -4.76° (c 1.05 in chloroform); Anal. Calcd for $C_{36}H_{46}O_3Si_2$: C, 74.38; H, 8.17. Found: C, 74.17; H, 7.95.

*(±)-1, 4-(*Tert*-butyldiphenylsilyloxy)-2-[9-(6-chloro)purinyl]butane* **8**

To a solution of (±)-**7** (0.94 g, 1.62 mmol) in THF (16 mL) were added 6-chloropurine (0.25 g, 1.62 mmol), triphenylphosphine (0.42 g, 1.62 mmol) and diethyl azodicarboxylate (0.25 mL, 1.62 mmol) at -10°C. After being stirred 12 h, the solution became homogeneous and the solvent was evaporated under reduced pressure. The residual yellow oil was chromatographed on a silica gel column with dichloromethane (methanol from 0 to 2%) to afford **8** (0.5 g, 44.3% yield) as white crystals, m.p. 126-128°C, R_f 0.41 (dichloromethane), UV (EtOH, 95%) λ_{max} 265.5 nm, UV (0.1 M HCl) λ_{max} 265.5 nm, UV (0.1 M KOH) λ_{max} 265.5 nm, δ_H (300 MHz, $CDCl_3$) 0.95 (s, 9H, tBu), 0.99 (s, 9H, tBu), 2.17 (m, 1H, H-3"), 2.38 (m, 1H, H-3'), 3.41 (m, 1H, H-4"), 3.65 (m, 1H, H-4'), 3.95 (dd, $J_{1"-2'}$ = 3.53 Hz, $J_{1"-1'}$ = 10.92 Hz, 1H, H-1"), 4.04 (dd, $J_{1'-2'}$ = 6.16 Hz, $J_{1"-1'}$ = 10.92 Hz, 1H, H-1'), 4.99 (m, 1H, H-2'), 7.35 (m, 20H, aromatic), 8.05 (s, 1H, 2-H) and 8.55 (s, 1H, 8-H); m/z 719 $[M+H]^+$ and 154 $[B+2H]^+$.

*(R)-1, 4-(*Tert*-butyldiphenylsilyloxy)-2-[9-(6-chloro)purinyl]butane* **8**

To a solution of (S)-**7** (3.77 g, 6.47 mmol) in THF (65 mL) was added 6-chloropurine (1.2 g, 7.76 mmol), triphenylphosphine (1.7 g, 6.47 mmol) and diethyl azodicarboxylate (1.02 mL, 6.47 mmol) at -10°C. After a similar treatment as for the previous compound, (R)-**8** was isolated (2.15 g, 38% yield) as a solid, m.p. 144.5-145.5°C, $[\alpha]_D^{22}$ -8.18° (c 1.1 in methanol), $[\alpha]_D^{22}$ -10.89° (c 1.01 in chloroform). It had the same spectral data as compound (±)-**8**; m/z 719 $[M+H]^+$ and 154 $[B+2H]^+$; Anal. Calcd for $C_{41}H_{47}N_4O_2ClSi_2$: C, 68.44; H, 6.38; N, 7.79. Found: C, 68.68; H, 6.62; N, 7.82.

*(±)-1, 4-(*Tert*-butyldiphenylsilyloxy)-2-[9-(N²-acetyl-O⁶-diphenylcarbamoyl)guanyl] butane* **9**

To a solution of (±)-**7** (0.94 g, 1.62 mmol) in THF (16 mL) was added $\underline{N}^2$-acetyl-$\underline{O}^6$-diphenylcarbamoyl guanine (0.63 g, 1.62 mmol), triphenylphosphine (0.42 g, 1.62 mmol) and diethyl azodicarboxylate (0.25 mL, 1.62 mmol) at -10°C. After a similar treatment as for (±)-**8**, compound (±)-**9** was isolated as an oil (0.6 g, 39.4% yield), R_f 0.29 (dichloromethane). UV (EtOH, 95%) λ_{max} 280 nm, UV (0.1 M HCl) λ_{max} 280 nm, UV (0.1 M KOH) λ_{max} 280 nm. δ_H (300 MHz, $CDCl_3$) 0.94 (s, 9H, tBu), 0.99 (s, 9H, tBu), 1.9 (m, 1H, H-3"), 2.05 (m, 1H, H-3'), 2.36 (s,

3H, 2-NCOMe), 3.4 (m, 1H, H-4"), 3.61 (m, 1H, H-4'), 3.95 (m, 2H, H-1", H-1'), 4.72 (m, 1H, H-2'), 7.35 (m, 30H, aromatic), 7.84 (s, 1H, 8-H) and 8.8 (s, 1H, 2-NH); m/z 953 $[M+H]^+$.

*(R)-1, 4-(*Tert*-butyldiphenylsilyloxy)-2-[9-(*$\underline{N}^2$*-acetyl-*$\underline{O}^6$*-diphenylcarbamoyl)guanyl] butane* **9**

To a solution of (S)-**7** (3.77 g, 6.47 mmol) in THF (65 mL) was added $\underline{N}^2$-acetyl-$\underline{O}^6$-diphenylcarbamoyl guanine (3.01 g, 7.66 mmol), triphenylphosphine (1.7 g, 6.47 mmol) and diethyl azodicarboxylate (1.02 mL, 6.47 mmol) at -10°C. After a similar treatment as for (±)-**8**, compound (R)-**9** was isolated as an oil (2.87 g, 39% yield), $[\alpha]_D^{22}$ -8.18° (c 1.1 in methanol); $[\alpha]_D^{22}$ -18.6° (c 1.1 in chloroform); m/z 953 $[M+H]^+$.

(R)-2-(9-guanyl)butane-1, 4-diol **5**

To (R)-**9** (1.6 g, 1.68 mmol) dissolved in THF (55 mL) was added a solution (6.72 mL, 6.72 mmol) of tetrabutylammonium fluoride (1 M in THF) and the reaction was stirred for 24 h at room temperature. The solvent was evaporated under reduced pressure. Methanolic ammonia (6 mL) was added and the solution was stirred for 7 d. The solvent was evaporated under reduced pressure and the crude product was chromatographed by HPLC on silica gel (reverse phase C2) using water as the eluent to afford **5** (0.164 g, 41% yield) as a solid, m.p. 228-230°C, R_f 0.31 (isopropanol/ammonium hydroxyde/water 10:2:1), UV (EtOH, 95%) λ_{max} 253 (ϵ 12500), sh 268 nm (ϵ 8820), UV (0.1 M HCl) λ_{max} 256 nm, UV (0.1 M KOH) λ_{max} 257 nm, δ_H (300 MHz, DMSO-d_6) 1.96 (m, 2H, H-3', H-3"), 3.18 (m, 1H, H-4"), 3.31 (m, 1H,H-4'), 3.6 (dd, $J_{1"-2'}$ = 4.35 Hz, $J_{1'-1"}$ = 11.33 Hz, 1H, H-1"), 3.75 (dd, $J_{1'-2'}$ = 7 Hz, $J_{1'-1"}$ = 11.33 Hz, 1H, H-1'), 4.41 (m, 1H, OH), 4.53 (m, 1H, H-2'), 4.99 (m, 1H, OH), 6.43 (s, 2H, NH_2), 7.65 (s, 1H, 8-H) and 10.62 (s, 1H, 1-NH); m/z 240 $[MH]^+$ and 136 $[BH_2]^+$; Anal. Calcd for $C_9H_{13}N_5O_3$: C, 45.2; H, 5.48; N, 29.29. Found: C, 44.98; H, 5.37; N, 29.02. $[\alpha]_D^{18}$ +34.7° (c 0.95 in water).

*(R)-1, 4-(*Tert*-butyldiphenylsilyloxy)-2-(9-adenyl)butane* **11**

To (R)-**8** (0.9 g, 1.25 mmol) dissolved in dichloromethane (50 mL) was added methanolic ammonia (55 mL) and the reaction was stirred 7 d. at 53°C. Solvents were evaporated under reduced pressure and the residual oil was chromatographed on a silica gel column with dichloromethane (methanol from 0 to 2%) to afford **11** as a solid (0.15 g, 16% yield), R_f 0.12 (dichloromethane-methanol 98:2), m.p. 57-59°C,

UV (EtOH, 95%) λ_{max} 260 nm (ϵ 13500), UV (0.1 M KOH) λ_{max} 260 nm, UV (0.1 M HCl) λ_{max} 260 nm, δ_H (250 MHz, DMSO-d_6) 0.81 (s, 9H, tBu), 0.86 (s, 9H, tBu), 2.25 (m, 1H, H-3"), 2.45 (m, 1H, H-3'), 3.47 (m, 1H, H-4"), 3.6 (m, 1H, H-4'), 3.95 (dd, $J_{1"\text{-}2'}$ = 4.26 Hz, $J_{1"\text{-}1'}$ = 10.23 Hz, 1H, H-1"), 4.02 (dd, $J_{1'\text{-}2'}$ = 7.02 Hz, $J_{1"\text{-}1'}$ = 10.23 Hz, 1H, H-1'), 4.97 (m, 1H, H-2'), 7.35 (m, 20H, aromatic), 8.1 (s, 1H, 2-H) and 8.15 (s, 1H, 8-H); m/z 701 $[M+H]^+$ and 136 $[B+2H]^+$.

A second compound (R)-**10** was isolated as an oil (0.19 g, 19.5%), R_f 0.54 (dichloromethane-methanol 98:2), m.p. 57-59°C, UV (EtOH, 95%) λ_{max} 253 nm (ϵ 10200), UV (0.1 M KOH) λ_{max} 253 nm, UV (0.1 M HCl) λ_{max} 253 nm, δ_H (250 MHz, DMSO-d_6) 0.78 (s, 9H, tBu), 0.83 (s, 9H, tBu), 2.22 (m, 1H, H-3"), 2.4 (m, 1H, H-3'), 3.47 (m, 1H,H-4"), 3.57 (m, 1H, H-4'), 4 (m, 2H, H-1", H-1'), 4.1 (s, 3H, OMe), 5.05 (m, 1H, H-2'), 7.35 (m, 20H, aromatic), 8.37 (s, 1H, 2-H) and 8.43 (s, 1H, 8-H); m/z 716 $[M+H]^+$ and 151 $[B+2H]^+$.

(R)-2-(9-adenyl)butane-1, 4-diol **4**

To (R)-**11** (0.33 g, 0.46 mmol) dissolved in THF (10 mL) was added a solution (1.2 mL, 1.2 mmol) of tetrabutylammonium fluoride (1 M in THF). The reaction was stirred at room temperature for 5 h. The solvent was evaporated under reduced pressure and the residue extracted with dichloromethane. The aqueous phase was chromatographed by HPLC on silica gel (reverse phase C2) using water as the eluent to afford **4** as a solid, m.p. 173-174°C, R_f 0.31 (isopropanol/ ammonium hydroxyde/ water 10:2:1), UV (EtOH, 95%) λ_{max} 260 nm (ϵ 13700), UV (0.1 M KOH) λ_{max} 260 nm, UV (0.1 M HCl) λ_{max} 260 nm, δ_H (250 MHz, DMSO-d_6) 2.08 (m, 2H, H-3', H-3"), 3.21 (m, 1H, H-4"), 3.32 (m, 1H, H-4'), 3.7 (1H, m, H-1"), 3.86 (m, 1H, H-1'), 4.57 (t, $J_{HO\text{-}CH_2}$ = 4.93 Hz, 1H, OH), 4.6 (m, 1H, H-2'), 5.03 (t, $J_{HO\text{-}CH_2}$ = 5.17 Hz, 1H, OH), 7.18 (s, 2H, NH_2) and 8.1 (s, 2H, 2-H, 8-H); m/z 224 $[MH]^+$ and 136 $[BH_2]^+$; Anal. Calcd for $C_9H_{13}N_5O_2$: C, 48.42; H, 5.86; N, 31.37. Found: C, 48.57; H, 6.13; N, 31.14. $[\alpha]_D^{18}$ +34.8° (c 1 in water).

ACKNOWLEDGMENTS: The authors are deeply grateful to the "Ligue Nationale contre le Cancer" for a grant (to M.P.) and to A. N. R. S. (Agence Nationale de Recherche contre le Sida) for generous support.

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Received 2/25/92
Accepted 6/17/92