

A Synthesis of (+)-Cyclaradine, Carbocyclic Analogue of 9- β -D-Arabinofuranosyladenine

Kin-ichi TADANO,* Hiroshi KIMURA, and Seiichiro OGAWA

Department of Applied Chemistry, Faculty of Science and Technology, Keio University,
Hiyoshi, Kohoku-ku, Yokohama 223

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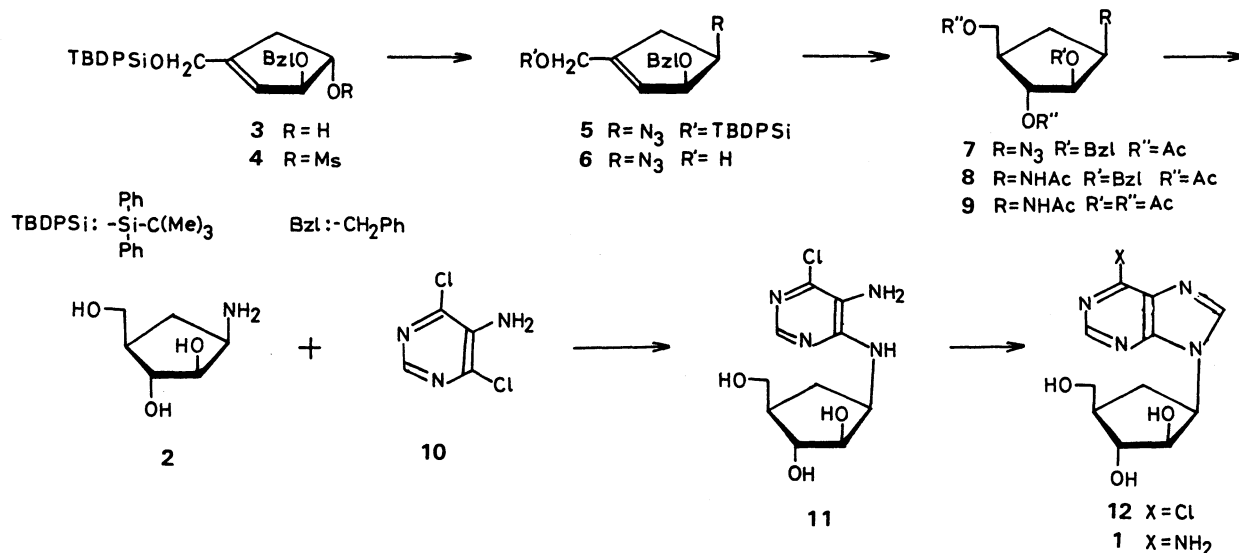
Synopsis. The title compound, a promising antiviral carbocyclic nucleoside analogue, was synthesized enantio-specifically. The present synthesis involves a coupling reaction of 5-amino-4,6-dichloropyrimidine and (1*R*,2*R*,3*R*,4*R*)-2,3-dihydroxy-4-(hydroxymethyl)cyclopentanamine which was in turn prepared from *D*-xylose.

Aristeromycin¹⁾ and neplanocin A²⁾ known as antimicrobial and antitumor agents are representatives of carbocyclic analogue of nucleosides. Sugar moieties of nucleosides are replaced by (hydroxymethyl)cyclopentanepolyol or (hydroxymethyl)-1-cyclopentenepolyol in their structures. The synthesis and biological evaluation of the carbocyclic analogues of nucleosides are current concerns from a pharmacological viewpoint.³⁾ In 1977, Vince and Daluge reported a synthesis of racemic carbocyclic analogue of arabinosyladenine.⁴⁾ This synthetic carbocyclic analogue (**1**) of nucleoside, simply called cyclaradine, arouses much attention owing to its remarkable cytotoxicity against P-388 mouse lymphoid leukemia cells ($LD_{50}=1 \times 10^{-5}$ M[†]). Compound **1** was completely resistant to deamination by adenosine deaminase under the conditions in which the antiviral nucleoside 9- β -D-arabinosyladenine was completely deaminated.⁴⁾ Furthermore, the racemic **1** inhibits the replication of herpes simplex virus types 1 and 2.⁵⁾ This inhibition effect may regard **1** as a candidate for antiherpes agent. We describe herein an enantiospecific synthesis of (+)-cyclaradine (**1**).

Recently, we have reported the synthesis of (3*S*,4*S*)-3-(benzyloxy)-1-[[*(t*-butyldiphenylsilyl)oxy]methyl]-4-hydroxy-1-cyclopentene (**3**) from *D*-xylose.⁶⁾ Our syn-

thesis of **1** commenced with **3**. Mesylation of **3** gave **4** in 96% yield. The mesyloxy group in **4** was displaced by azido group with inversion of configuration at C-4 by treatment with NaN₃ in hot DMF in 81% yield. The silyl protecting group in the resultant azide **5** was then removed with tetrabutylammonium fluoride to give **6** quantitatively. Hydroboration of **6** with borane-THF complex in THF at 0°C and successive treatment of the product with H₂O₂ in an alkaline solution followed by acetylation provided **7** as a sole product in 79% yield. This highly stereoselective hydroboration with the preferential attack of borane from the less hindered α -side was similar to our previous result obtained by employing the structurally resembling model.⁶⁾ Treatment of **7** with H₂S in aqueous pyridine followed by acetylation gave **8** in 98% yield. Debenzylation of **8** according to the Hanessian's procedure⁷⁾ followed by acetylation provided the fully acetylated derivative (**9**) of (1*R*,2*R*,3*R*,4*R*)-2,3-dihydroxy-4-(hydroxymethyl)cyclopentanamine (**2**) in 93% yield. Hydrolysis of **9** with aqueous HCl gave **2** in 81% yield after purification by passage through Amberlite CG-120 column.

Coupling of **2** and 5-amino-4,6-dichloropyrimidine (**10**)⁸⁾ in boiling 1-butanol in the presence of triethylamine gave a carbocyclic analogue of pyrimidine nucleoside **11**. Cyclization of **11** to a purine derivative **12** was achieved by treatment with triethyl orthoformate in the presence of *p*-toluenesulfonic acid at 60°C under reduced pressure. Finally, desired **1** was obtained by heating a solution of **12** in saturated methanolic ammonia at 60°C in an autoclave. The conversion of **2** into **1** was achieved in an overall yield



[†] 1 M=1 mol dm⁻³.

of approximately 50% (compounds **11** and **12** were not purified to obtain analytical samples). The synthetic **1** was fully characterized by spectral means.

The IC_{50} of the synthetic **1** for P-388 mouse lymphoid leukemia cells (in vitro) was $4.25 \mu\text{g ml}^{-1}$.

Experimental

General procedure was described in the previous paper.⁶⁾

(3S,4S)-3-(Benzyloxy)-4-[(methylsulfonyl)oxy]-1-[(*t*-butyldiphenylsilyl)oxy]methyl-1-cyclopentene (4). A solution of **3** (1.01 g, 2.2 mmol) and methanesulfonyl chloride (0.51 ml, 6.6 mmol) in pyridine (10 ml) was stirred at room temperature for 1 h. The reaction mixture was diluted with CH_2Cl_2 (200 ml) and washed with water (100 ml). The aqueous layer was extracted with CH_2Cl_2 (200 ml $\times$ 3). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed on silica gel (AcOEt/hexane 1:10) to give **4** (1.13 g, 96%) as a colorless oil: TLC R_f 0.60 (AcOEt/hexane 1:3); $[\alpha]_D^{25} + 38.7^\circ$ (c 0.86, CHCl_3); IR $\nu_{\text{max}}^{\text{neat}}$ 3090, 2875, 1670, 1185 cm^{-1} ; $^1\text{H NMR}$ (90 MHz, CDCl_3) δ =1.05 (9H, s, Me_3CSi), 2.0–2.2 (2H, m, H-5,5'), 2.94 (3H, s, MeSO_2O), 4.16 (2H, br s, $\text{CH}_2\text{OTBDPSi}$), 4.59 (2H, s, $\text{OCH}_2\text{C}_6\text{H}_5$), 4.5–4.8 (1H, m, H-3), 5.13 (1H, dt, J =5 and 9 Hz, H-4), 5.69 (1H, br s, H-2), 7.2–8.0 (15H, m, $3\times\text{C}_6\text{H}_5$). Found: C, 67.43; H, 6.76%. Calcd for $\text{C}_{30}\text{H}_{36}\text{O}_5\text{SSi}$: C, 67.13; H, 6.76%.

(3S,4R)-4-Azido-3-(benzyloxy)-1-[(*t*-butyldiphenylsilyl)oxy]methyl-1-cyclopentene (5). A mixture of **4** (1.12 g, 2.1 mmol) and sodium azide (814 mg, 12.5 mmol) in DMF (60 ml) was heated at 130°C with stirring for 7 h. The mixture was diluted with AcOEt (400 ml) and washed with water (100 ml $\times$ 3). The combined aqueous phases were extracted with CH_2Cl_2 (200 ml $\times$ 3). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed on silica gel (AcOEt/hexane 1:100) to give **5** (822 mg, 81%) as a colorless oil [42.5 mg (4%) of **4** was recovered]; TLC R_f 0.88 (AcOEt/hexane 1:10); $[\alpha]_D^{25} + 37.4^\circ$ (c 0.71, CHCl_3); IR $\nu_{\text{max}}^{\text{neat}}$ 3075, 2860, 2100, 1590, 1430 cm^{-1} ; $^1\text{H NMR}$ (90 MHz, CDCl_3) δ =1.03 (9H, s, Me_3CSi), 2.49, 2.56 (each 1H, each br s, H-5,5'), 3.85 (1H, dd, J =6 and 12 Hz, H-4), 4.22 (2H, br s, $\text{CH}_2\text{OTBDPSi}$), 4.4–4.7 (1H, m, H-3), 4.65 (2H, d, J =4.5 Hz, $\text{OCH}_2\text{C}_6\text{H}_5$), 5.82 (1H, br s, H-2), 7.3–7.9 (15H, m, $3\times\text{C}_6\text{H}_5$). Found: C, 72.02; H, 6.81; N, 8.61%. Calcd for $\text{C}_{29}\text{H}_{33}\text{N}_3\text{O}_5\text{Si}$: C, 72.02; H, 6.88; N, 8.69%.

(3S,4R)-4-Azido-3-(benzyloxy)-1-cyclopentene-1-methanol (6). A solution of **5** (797 mg, 1.65 mmol) in THF (20 ml) was stirred in the presence of tetrabutylammonium fluoride (1 M in THF, 2.5 ml, 2.5 mmol) at room temperature for 30 min. The solution was concentrated in vacuo. The residue was chromatographed on silica gel (AcOEt/hexane 1:7) to give **6** (401 mg, 99%) as a colorless oil: TLC R_f 0.57 (AcOEt/hexane 1:1); $[\alpha]_D^{29} + 43.4^\circ$ (c 0.67, CHCl_3); IR $\nu_{\text{max}}^{\text{neat}}$ 3610, 2100, 1420 cm^{-1} ; $^1\text{H NMR}$ (90 MHz, CDCl_3) δ =2.37 (1H, br s, OH), 2.51, 2.57 (each 1H, each br s, H-5,5'), 3.87 (1H, dd, J =6 and 12 Hz, H-4), 4.13 (2H, br s, CH_2OH), 4.49 (1H, br s, H-3), 4.55, 4.74 (each 1H, each d, J =12 Hz, $\text{OCH}_2\text{C}_6\text{H}_5$), 5.75 (1H, m, H-2), 7.37 (5H, s, $\text{OCH}_2\text{C}_6\text{H}_5$).

(1R,2R,3R,4R)-2-Acetoxy-1-(acetoxymethyl)-4-azido-3-(benzyloxy)cyclopentane (7). To a solution of **6** (400 mg, 1.6 mmol) in THF (30 ml) was added BH_3 -THF (1 M in THF, 13.0 ml, 13.0 mmol) at 0°C under an argon atmosphere. The mixture was stirred at 0°C for 2 h, and to it were added water (15 ml), 3 M aqueous NaOH (18 ml), and 35% aqueous H_2O_2 (20 ml) successively. The mixture was then stirred at room temperature for 4 h. To it was added saturated aqueous NaSO_3 (20 ml). This was extracted with CH_2Cl_2 (300 ml $\times$ 4) and AcOEt (300 ml $\times$ 2). The combined

organic phases were dried (Na_2SO_4) and concentrated in vacuo. The residue was acetylated with acetic anhydride (3 ml) in pyridine (3 ml) for 2 h. The mixture was concentrated in vacuo. The residue was chromatographed on silica gel (AcOEt/hexane 1:14) to give **7** (446 mg, 79%) as a colorless oil: TLC R_f 0.60 (AcOEt/hexane 1:3); $[\alpha]_D^{29} - 12.8^\circ$ (c 0.80, CHCl_3); IR $\nu_{\text{max}}^{\text{neat}}$ 3020, 2110, 1730, 1450, 1360 cm^{-1} ; $^1\text{H NMR}$ (90 MHz, CDCl_3) δ =1.5–2.5 (3H, m, H-1,5,5'), 2.02 (6H, s, $2\times\text{OAc}$), 3.5–3.9 (2H, m, H-3,4), 4.09 (2H, dd, J =4.5 and 6 Hz, CH_2OAc), 4.68 (2H, s, $\text{OCH}_2\text{C}_6\text{H}_5$), 4.99 (1H, t, J =4.5 Hz, H-2), 7.32 (5H, s, $\text{OCH}_2\text{C}_6\text{H}_5$). Found: C, 58.47; H, 5.99; N, 11.81%. Calcd for $\text{C}_{17}\text{H}_{21}\text{N}_3\text{O}_5$: C, 58.78; H, 6.09; N, 12.10%.

(1R,2R,3R,4R)-1-Acetamido-3-acetoxy-4-(acetoxymethyl)-2-(benzyloxy)cyclopentane (8). To a solution of **7** (440 mg, 1.3 mmol) in a mixture of water and pyridine (1:4, 50 ml) was bubbled H_2S at room temperature for 2 h. This solution was stirred more 24 h, and then concentrated in vacuo. The residue was acetylated with acetic anhydride (4 ml) in pyridine (4 ml) for 1 h. The mixture was concentrated in vacuo. The residue was chromatographed on silica gel (PhCH_3 , then AcOEt/hexane 1:1) to give **8** (452 mg, 98%) as a colorless oil: TLC R_f 0.56 (EtOH/ PhCH_3 1:5); $[\alpha]_D^{26} + 41.5^\circ$ (c 1.42, CHCl_3); IR $\nu_{\text{max}}^{\text{neat}}$ 3300, 2925, 1730, 1650, 1535, 1360, 1230 cm^{-1} ; $^1\text{H NMR}$ (90 MHz, CDCl_3) δ =1.4–2.5 (3H, m, H-4, 5, 5'), 1.93 (3H, s, NCOCH_3), 2.04, 2.06 (each 3H, each s, $2\times\text{OCOCH}_3$), 3.71 (1H, d, J =5 Hz, H-2), 4.1–4.5 (3H, m, H-1, CH_2OAc), 4.51, 4.81 (each d, each 1H, J =12 Hz, $\text{OCH}_2\text{C}_6\text{H}_5$), 4.99 (1H, dd, J =1 and 3.5 Hz, H-2), 5.90 (1H, d, J =8 Hz, NH), 7.3–7.4 (5H, m, $\text{OCH}_2\text{C}_6\text{H}_5$); high-resolution mass spectrum, Calcd for $\text{C}_{19}\text{H}_{25}\text{NO}_6$: M, 363.1680, Found: m/z 363.1680.

(1R,2R,3R,4R)-1-Acetamido-2,3-diacetoxy-4-(acetoxymethyl)cyclopentane (9). A solution of **8** (443 mg, 1.2 mmol) in a mixture of cyclohexene (10 ml) and EtOH (6 ml) in the presence of 20% $\text{Pd}(\text{OH})_2$ on charcoal (600 mg) was refluxed for 2 h. The catalyst was removed through a Celite pad, and the filtrate was concentrated in vacuo. The residue was acetylated with acetic anhydride (4 ml) in pyridine (4 ml) for 2 h. The reaction mixture was concentrated in vacuo. The residue was chromatographed on silica gel (EtOH/ PhCH_3 1:20) to give **9** (356 mg, 93%) as colorless needles, mp 125.5 – 126.5°C : TLC R_f 0.36 (EtOH/ PhCH_3 1:5); $[\alpha]_D^{31} + 28.8^\circ$ (c 0.86, CHCl_3); IR $\nu_{\text{max}}^{\text{neat}}$ 3300, 1745, 1660, 1545, 1440, 1375 cm^{-1} ; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ =1.40–1.48 (1H, m, H-5), 1.99 (3H, s, NCOCH_3), 2.07, 2.13 (6H, 3H, each s, $3\times\text{OCOCH}_3$), 2.25–2.40 (2H, m, H-4, 5'), 4.07–4.19 (2H, m, CH_2OAc), 4.55–4.63 (1H, m, H-1), 4.92 (1H, dd, J =2.4 and 4.9 Hz, H-3), 5.08 (1H, dd, J =2.4 and 5.4 Hz, H-2), 5.62 (1H, d, J =8.8 Hz, NH); high-resolution mass spectrum, Calcd for $\text{C}_{14}\text{H}_{22}\text{NO}_7$: M+H, 316.1394. Found: m/z 316.1387. Found: C, 53.14; H, 6.49; N, 4.47%. Calcd for $\text{C}_{14}\text{H}_{21}\text{NO}_7$: C, 53.33; H, 6.71; N, 4.44%.

(1R,2R,3R,4R)-2,3-Dihydroxy-4-(hydroxymethyl)cyclopentanamine (2). A solution of **9** (32 mg, 0.1 mmol) in 2 M aqueous HCl (2 ml) was heated at 70°C for 2 h, and then concentrated in vacuo. The residue was dissolved in water (2 ml) and the aqueous solution was neutralized by addition of Amberlite IRA-400 (OH^-). The resin was removed, and the filtrate was concentrated in vacuo. The residue in a small amount of water was applied on a column of Amberlite CG-120 (H^+). The column was eluted with 0.1 M aqueous NH_4OH to give **2** (12 mg, 81%) as a colorless oil: TLC R_f 0.43 (MeOH/water 1:2); $[\alpha]_D^{22} - 125.8^\circ$ (c 0.56, H_2O); $^1\text{H NMR}$ (90 MHz, CD_3OD) δ =1.1–2.4 (4H, m, H-1, 4, 5, 5'), 3.50, 3.56 (2H, each s, CH_2OH), 3.4–4.0 (2H, m, H-2, 3); $^{13}\text{C NMR}$ (100 MHz, CD_3OD) δ =33.69, 47.24, 53.55, 64.79, 79.74, 79.86; high-resolution mass spectrum, Calcd for $\text{C}_6\text{H}_{13}\text{NO}_3$: M, 147.0894. Found: m/z 147.0886.

9-[(1R,2R,3R,4R)-2,3-Dihydroxy-4-(hydroxymethyl)cyclopentyl]adenine, (+)-Cyclaradine (I). Compound **9** (216 mg) was hydrolyzed as described above. After neutralization of the reaction solution with Amberlite IRA-400, the filtrate was concentrated to give **2** (141 mg) which was used without further purification. A mixture of **2** and 5-amino-4,6-dichloropyrimidine (674 mg, 4.1 mmol) in 1-butanol (45 ml) was refluxed for 22 h in the presence of triethylamine (0.96 ml, 6.9 mmol). The reaction mixture was then concentrated in vacuo. The residue was dissolved in water (100 ml), and this was washed with CHCl_3 (20 ml $\times$ 5). The combined organic phases were extracted with water (100 ml $\times$ 2). The combined aqueous phases were concentrated, and the residual yellow crystals were dissolved in water (3 ml), then this aqueous solution was heated with active carbon. This was filtered, and the filtrate was concentrated in vacuo. The resultant white solids were chromatographed on silica gel (EtOH/ PhCH_3 1:9) to give 5-amino-4-chloro-6-[(1R,2R,3R,4R)-2,3-dihydroxy-4-(hydroxymethyl)cyclopentyl]aminopyrimidine (**11**) (140 mg) as white powders: IR $\nu_{\text{max}}^{\text{KBr}}$ 3340, 2920, 1570, 1410 cm^{-1} ; ^1H NMR (90 MHz, CD_3OD) δ =1.3—2.6 (3H, m, H-4, 5, 5' of the cyclopentane ring), 3.59, 3.65 (each 1H, each s, CH_2OH), 3.7—3.9, 3.9—4.1 (each 1H, each m, H-2, 3 of the cyclopentane ring), 7.74 (1H, s, H-2 of the pyrimidine ring).

A solution of **11** (115 mg) in a mixture of DMF (12 ml) and triethyl orthoformate (0.7 ml) was heated at 60 °C under 13 mmHg †† in the presence of *p*-TsOH (80 mg). After 1 h, *p*-TsOH (10 mg) was added and the mixture was heated for total 2 h. The reaction mixture was neutralized with Amberlite IRA 400 (OH^-), and the resin was removed. The filtrate was concentrated in vacuo. The residue in a small amount of water was applied on a column of Amberlite CG-120 (H^+). The column was eluted with water to give 6-chloro-9-[(1R,2R,3R,4R)-2,3-dihydroxy-4-(hydroxymethyl)cyclopentyl]-purine (**12**) (89 mg) as white powders: IR $\nu_{\text{max}}^{\text{KBr}}$ 3380, 2920, 1595, 1560, 1490 cm^{-1} ; ^1H NMR (90 MHz, CD_3OD) δ =1.9—2.6 (3H, m, H-4, 5, 5' of the cyclopentane ring), 3.65, 3.70 (each 1H, each s, CH_2OH), 3.88 (1H, t, J =3 Hz, H-2 or 3 of the cyclopentane ring), 4.01 (1H, dd, J =3 and 6 Hz, H-3 or 2 of the cyclopentane ring), 5.0—5.3 (1H, m, H-1 of the cyclopentane ring), 8.49, 8.53 (each 1H, each s, H-2 and 8 of purine ring).

A solution of **12** (40 mg) in saturated methanolic ammonia (20 ml) was heated at 60 °C in an autoclave for 15 h. The reaction solution was concentrated in vacuo, and the residue was purified by repeated PTLC (EtOH/ PhCH_3 1:1, four times development) to give **1** (39 mg) as white powders, mp 235—245 °C (decomp): TLC R_f 0.15 (EtOH/ PhCH_3 1:1); $[\alpha]_D^{22} +48^\circ$ (*c* 1.50, MeOH): IR $\nu_{\text{max}}^{\text{KBr}}$ 3300, 2920, 2840, 1630,

1250 cm^{-1} ; ^1H NMR (400 MHz, CD_3OD) δ =2.13—2.21, 2.40—2.47 (2H, 1H, each m, H-4, 5, 5' of the cyclopentane ring), 3.71—3.81 (2H, m, CH_2OH), 3.97 (1H, dd, J =2.7 and 4.2 Hz, H-2 or 3 of the cyclopentane ring), 4.10 (1H, dd, J =2.7 and 5.2 Hz, H-3 or 2 of the cyclopentane ring), 5.08—5.14 (1H, m, H-1 of the cyclopentane ring), 8.19, 8.28 (each 1H, each s, H-2 and 8 of adenine ring); ^{13}C NMR (100 MHz, CD_3OD) δ =31.51, 47.52, 56.83, 64.58, 78.22, 80.02, 119.70, 142.54, 151.01, 153.45, 157.13; high-resolution mass spectrum, Calcd for $\text{C}_{11}\text{H}_{16}\text{N}_5\text{O}_3$: M^+H , 266.1251, Found: m/z 266.1251.

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References

- 1) Isolation: a) T. Kusaka, H. Yamamoto, M. Shibata, M. Muroi, T. Kishi, and K. Mizuno, *J. Antibiot.*, **21**, 255 (1968); b) T. Kishi, M. Muroi, T. Kusaka, M. Nishikawa, K. Kamiya, and K. Mizuno, *Chem. Pharm. Bull.*, **20**, 940 (1972). Total synthesis: c) Y. F. Shealy and J. D. Clayton, *J. Am. Chem. Soc.*, **88**, 3885 (1966); d) M. Arita, K. Adachi, Y. Ito, H. Sawai, and M. Ohno, *ibid.*, **105**, 4049, (1983); e) A. K. Saksena, *Tetrahedron Lett.*, **21**, 133 (1980); f) G. V. B. Madhavan and J. C. Martin, *J. Org. Chem.*, **51**, 1287 (1986).
- 2) Isolation: a) S. Yaginuma, N. Muto, M. Tsujino, Y. Sudate, M. Hayashi, and M. Otani, *J. Antibiot.*, **34**, 359 (1981); b) M. Hayashi, S. Yaginuma, H. Yoshioka, and K. Nakatsu, *ibid.*, **34**, 675 (1981). Total synthesis: c) M. Jung, G. Offenbacher, and J. Retey, *Helv. Chim. Acta*, **66**, 1915 (1983); d) M.-I. Lim and V. E. Marquez, *Tetrahedron Lett.*, **24**, 4051 and 5559 (1983). See also Ref. 1d.
- 3) A leading review for this area: V. E. Marquez and M.-I. Lim, *Med. Res. Rev.*, **6**, 1 (1986).
- 4) S. Daluge and R. Vince, *J. Med. Chem.*, **20**, 612 (1977).
- 5) R. Vince, S. Daluge, H. Lee, W. M. Shannon, G. Arnett, T. W. Schafer, T. L. Nagabhushan, P. Reichert, and H. Tsai, *Science*, **221**, 1405 (1983); W. M. Shannon, L. Westbrook, G. Arnett, S. Daluge, H. Lee, and R. Vince, *Antimicrob. Agents Chemother.*, **24**, 538 (1983).
- 6) K. Tadano, H. Kimura, M. Hoshino, S. Ogawa, and T. Suami, *Bull. Chem. Soc. Jpn.*, **60**, 3673 (1987).
- 7) S. Hanessian, T. J. Liak, and B. Vanasse, *Synthesis*, **1981**, 396.
- 8) Commercially available from Aldrich Chemical Co., Inc. For related coupling reactions: A. B. Cheikh, L. E. Craine, S. G. Recher, and J. Zemlicka, *J. Org. Chem.*, **53**, 929 (1988), and also see Refs. 1d, 1f, and 2d.

†† 1 mmHg=133.322 Pa.