5′-Homoneplanocin A Inhibits Hepatitis B and Hepatitis C

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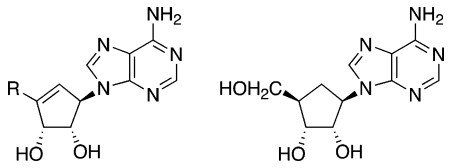
As an outgrowth of our program to develop an efficient synthesis of 5′-homoneplanocin A, its antiviral potential was explored beyond that already in the literature. From that, this compound was found to have meaningful activity toward hepatitis B and hepatitis C, which represents an example of one agent effective toward both viruses. These data and an improved preparation of 5′-homoneplanocin A are reported.

Introduction

Nucleosides have provided a plentiful source of new structural leads in antiviral drug development.[1] Included in this class of compounds are the carbocyclic nucleosides,[2] which, because of the presence of a cyclopentyl moiety, offer sites for modification not possible with the typical ribofuranosyl nucleosides. One of the most promising of this group has been the naturally occurring neplanocin A (**1**).[3] Its antiviral effects have been attributed to inhibition of *S*-adenosyl-L-homocysteine (AdoHcy) hydrolase, which in turn affects viral mRNA capping methylation.[4]



1, R=CH_2OH
3, R=H
4, R=CH_2CH_2OH

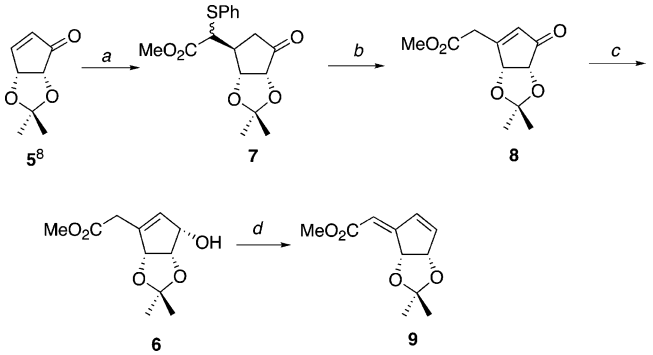
2

As with its saturated carbocyclic partner aristeromycin (**2**), neplanocin A is susceptible to 5′-nucleotide formation that renders it unacceptable for antiviral therapeutic development.[3a] Borchardt and others[5,6] have addressed this by investigating the truncated derivative **3**, which cannot serve as a substrate for nucleotide formation. In considering other neplanocin candidates, we were attracted to the work of Shuto,[7] who found 5′-homoneplanocin (**4**) to have significant antiviral activity with no interfering cytotoxicity. To explore the antiviral potential of **4** more thoroughly required us to develop a practical synthesis of it. Once that was accomplished, the effects of **4** on viruses other than those previously evaluated[7] were undertaken. The results of this study are described here.

Chemistry

The plan to **4** was designed to convert the conveniently available cyclopentenone **5**[8] (Scheme 1) into the cyclopentenol **6** for the purposes of subjecting it to a Mitsunobu procedure[9] with 6-chloropurine or adenine. In that direction, **5** underwent a regioselective and stereoselective 1,4-addition[10] of methyl phenylthioacetate to yield **7**. Oxidation of **7** with *m*-chloroperoxybenzoic acid (*m*-CPBA) followed by dehydrosulfenylation[11] in refluxing toluene in the presence of a small amount of calcium carbonate yielded, after double bond migration into the ring, enone **8**.[12] Luche reduction[13] of **8** cleanly afforded **6**. Subjecting **6** to Mitsunubo reaction conditions with 6-chloropurine gave the elimination product **9** instead of the desired coupled product.

Scheme 1[a]



[a] Reaction conditions: (a) $PhSCH_2CO_2Me$, *n*-BuLi, DIPA, HMPA/THF, 90%; (b) (i) *m*-CPBA, CH_2Cl_2; (ii) $CaCO_3$, toluene, 83% (two steps); (c) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 100%; (d) 6-chloropurine, Ph_3P, DIAD, THF, 81%.

This unexpected result forced us to seek a strategy different from that for **4** that would avoid the potential to form the extended conjugated system **9**. Thus, reduction of the ketone and ester functionalities in **8** with diisobutylaluminum hydride (DIBAL) yielded diol **10** (Scheme 2). Selective primary alcohol protection of **10** with *tert*-butyldimethylsilyl chloride (TBDMSCl) afforded the coupling precursor **11**, which was subjected to Mitsunubo reaction conditions with adenine to afford **12**. The final product **4** was obtained by deprotection of **12** with hydrochloric acid.

This synthetic method to **4** has three advantages over the existing route:[7] (1) fewer steps from enone (**5** in this case, *ent*-**5** in the literature[7] procedure); (2) higher overall yield (27% versus 9.5%[7]); (3) avoidance of the use of an expensive palladium reagent that is necessary for a 1,3-shift in the Shuto[7] process.

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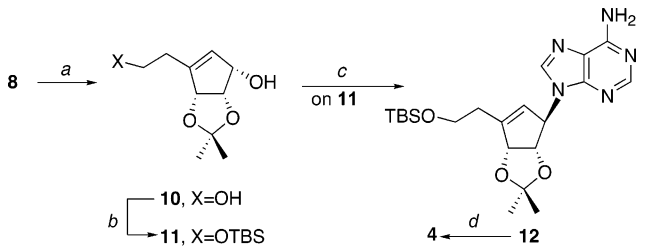
Scheme 2[a]



[a] Reaction conditions: (a) DIBAL, CH_2Cl_2, 87%; (b) TBDMSCl, imidazole, CH_2Cl_2, 88%; (c) adenine, Ph_3P, DIAD, THF, 43%; (d) HCl, MeOH, 90%.

Antiviral Results

Compound **4** was evaluated against a wide variety of DNA viruses and RNA viruses. In addition to those previously reported[7] the following viruses were evaluated: cowpox, influenza A (H1N1 and H3N2), influenza B, pichinde, Venezuelan equine encephalitis, yellow fever, West Nile, hepatitis B (HBV), and hepatitis C (HCV). The most noteworthy observation from this analysis was the ability of **4** to show activity against HBV[14] and HCV[15] (Tables 1 and 2). It is true that while **4** is not as effective as the standard reference agents used in the assays, it does offer a basis for analogue development of one agent to treat both infections. It also provides a very significant compound for exploring the biochemical basis for coeffectiveness with the potential of uncovering a common, exploitable metabolic feature for HBV and HCV. These possibilities are under intense pursuit in our laboratories.

Compound **4** affected none of the other new viruses assayed.[16]

Experimental Section

All melting points were recorded on a Meltemp II melting point apparatus, and the values were uncorrected. The combustion analyses were performed at Atlantic Microlab, Norcross, GA. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AC 250 spectrometer (operated at 250 and 62.9 MHz, respectively) or Bruker AV 400 spectrometer (operated at 400 and 100 MHz, respectively), all referenced to internal tetramethylsilane (TMS) at 0.0 ppm. The reactions were monitored by thin-layer chromatography (TLC) using 0.25 mm Whatman Diamond silica gel 60-F_{254} precoated plates with visualization by irradiation with a Mineralight UVGL-25 lamp. Column chromatography was performed on Whatman silica, 230−400 mesh, 60 Å, and elution was done with the indicated solvent system. Yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) homogeneous materials.

Methyl 2-((3a*R*,6*S*,6a*R*)-Tetrahydro-2,2-dimethyl-4-oxo-3a*H*-cyclopenta[*d*][1,3]dioxol-6-yl)-2-(phenylthio)-acetate (7). To a solution of diisopropylamine (0.85 mL, 6.1 mmol) in THF (15 mL) was added dropwise *n*-BuLi (2.60 mL, 2.5 M in hexanes, 6.50 mmol) at 0 °C. The solution was stirred at the same temperature for 30 min before it was cooled to −70 °C. Methyl phenylthioacetate (1.00 g, 5.50 mmol) was then added dropwise using a syringe. After the resulting pale-yellow solution was stirred at the same temperature for 1 h, hexamethylphosphoramide (HMPA) (3.0 mL) was added followed by the dropwise addition of **5**[8] (0.77 g, 5.0 mmol) in THF (5.0 mL). This mixture was kept at −70 °C for 1 h, and saturated NH_4Cl solution (10 mL) was added to quench the reaction. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic phase was dried (anhydrous $MgSO_4$), and the solvent was removed. The residue was purified by column chromatography to afford **7** as a colorless liquid mixture of two diastereoisomers (1.50 g, 90%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.47 (m, 4H), 7.34 (m, 6H), 4.85 (d, J = 5.8 Hz, 1H), 4.80 (d, J = 5.7 Hz, 1H), 4.45 (d, J = 5.7 Hz, 1H), 4.39 (d, J = 5.8 Hz, 1H), 3.76 (d, J = 5.1 Hz, 1H), 3.75 (d, J = 6.8 Hz, 1H), 3.69 (s, 3H), 3.68 (s, 3H), 2.86 (m, 4H), 2.35 (m, 2H), 1.42 (s, 6H), 1.34 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 211.9, 211.8, 171.3, 171.1, 133.1, 133.0, 132.5, 129.3, 128.6, 128.5, 111.9, 80.1, 78.8, 53.8, 52.5, 40.2, 39.9, 38.5, 38.4, 26.6, 24.6, 24.5. Anal. ($C_{17}H_{20}O_5S$) C, H, S.

Methyl 2-((3a*R*,6a*R*)-4,6a-Dihydro-2,2-dimethyl-4-oxo-3a*H*-cyclopenta[*d*][1,3]dioxol-6-yl)acetate (8). To a solution of **7** (3.23 g, 9.60 mmol) in CH_2Cl_2 (100 mL) at −78 °C was added a solution of *m*-CPBA (2.50 g, 77%, 11.1 mmol) in CH_2Cl_2 (40 mL). The mixture was gradually warmed to −40 °C and stirred at this temperature for 2.5 h. Sodium bisulfite solution (0.75 g in 30 mL of H_2O) was added to quench the reaction. The organic layer was separated, washed with saturated Na_2CO_3 (2 × 30 mL), and dried (anhydrous Na_2SO_4). The solvent was removed to afford the intermediate sulfoxide as a white foam. This white foam was dissolved in toluene (120 mL), and calcium carbonate (1.00 g, 10 mmol) was added. The mixture was brought to reflux for 12 h. The solvent was removed and the residue was purified by column chromatography to afford **8** as colorless liquid (1.80 g, 83%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.13 (s, 1H), 5.23 (dd, J = 5.7, 0.6 Hz, 1H), 4.51 (d, J = 5.7 Hz, 1H), 3.76 (s, 3H), 3.55 (qq, J = 17.6, 17.6, 0.8 Hz, 2H), 1.44 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 201.7, 168.6, 168.5, 131.6, 115.5, 80.0, 77.7, 52.5, 35.6, 27.4, 26.3. Anal. ($C_{11}H_{14}O_5$) C, H.

Table 2. Activity of **4** against HCV Replication in AVA5 Cell Cultures[a]

treatment	CC_{50} (μM)	EC_{50} (μM)	EC_{90} (μM)	SI (CC_{50}/EC_{50})
IFN-α	>10000[b,c]	1.6 ± 0.2	8.7 ± 0.8	>6250
ribavirin	71 ± 1.2	>100[c]	>100[c]	
4	216 ± 2.0	7.3 ± 0.8	31 ± 2.8	30

[a] Values presented (±standard deviations) were calculated by linear regression analysis using data combined from all treated cultures. EC_{50} and EC_{90} are drug concentrations at which a 2-fold and a 10-fold depression of HCV RNA (relative to the average levels in untreated cultures), respectively, was observed. CC_{50} is the drug concentration at which a 2-fold lower level of neutral red dye uptake (relative to the average levels in untreated cultures) was observed. [b] Concentrations for IFN-α are expressed as "IU/mL". [c] No cytotoxic or antiviral effect at the highest indicated concentration.

Table 1. Relative Potency of **4** against HBV Replication in 2.2.15 Cells[a]

		extracellular virion DNA		intracellular RI		SI (CC_{50}/EC_{90})	
compd	CC_{50} (μM)	EC_{50} (μM)	EC_{90} (μM)	EC_{50} (μM)	EC_{90} (μM)	virion	RI
lamivudine	2675 ± 94	0.06 ± 0.007	0.17 ± 0.02	0.23 ± 0.02	0.69 ± 0.07	11630	3877
4	1213 ± 78	0.53 ± 0.06	7.7 ± 0.6	6.1 ± 0.7	27 ± 2.8	158	45

[a] Values presented (±standard deviations) were calculated by linear regression analysis (two to four experiments, four to six replicates per concentration). EC_{50} and EC_{90} are drug concentrations at which a 2-fold and a 10-fold depression of HBV DNA (relative to the average levels in untreated cultures), respectively, was observed. CC_{50} is the drug concentration at which a 2-fold depression of neutral red dye uptake (relative to the average levels in untreated cultures) was observed. The EC_{90} values were used for the calculation of the selectivity indexes (SI) because at least a 3-fold depression of HBV RI levels is typically required to achieve statistical significance in this assay system.[17] RI is the HBV DNA replication of intermediates.

Methyl 2-((3a*S*,4*S*,6a*R*)-4,6a-Dihydro-4-hydroxy-2,2-dimethyl-3a*H*-cyclopenta[*d*][1,3]dioxol-6-yl)acetate (6). To a solution of **8** (0.63 g, 2.8 mmol) and $CeCl_3 \cdot 7H_2O$ (0.89 g, 2.4 mmol) in MeOH (15 mL) at 0 °C was added portionwise $NaBH_4$ (0.15 g, 3.9 mmol). The mixture was stirred at the same temperature for 1.5 h before the reaction was quenched with H_2O (10 mL). Methylene chloride (30 mL) was added to the mixture, and the organic phase was separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic phases were washed with brine and dried (anhydrous Na_2SO_4). Evaporation of the solvent afforded **6** as a clean product (0.64 g, 100%) as determined by NMR with no further purification necessary: ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.69 (s, 1H), 5.01 (d, J = 5.4 Hz, 1H), 4.77 (t, J = 5.4 Hz, 1H), 4.58 (m, 1H), 3.70 (s, 3H), 3.23 (s, 2H), 2.80 (br, 1H), 1.41 (s, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 171.0, 138.3, 133.3, 112.6, 84.3, 78.0, 73.5, 52.1, 33.4, 27.7, 26.8. Anal. ($C_{11}H_{16}O_5$) C, H.

(2*Z*)-Methyl 2-((3a*S*,6a*R*)-2,2-Dimethyl-3a*H*-cyclopenta-[*d*][1,3]dioxol-6(6a*H*)-ylidene)acetate (9). To a suspension of **6** (0.64 g, 2.8 mmol), Ph_3P (1.08 g, 4.2 mmol), and 6-chloropurine (0.65 g, 4.2 mmol) in THF (20 mL) at 0 °C was added a solution of diisopropyl azodicarboxylate (DIAD) (0.85 g, 4.2 mmol) in THF (10 mL). The mixture was warmed to room temperature and then stirred for 2 h. The solvent was removed and the residue was purified by column chromatography to afford **9** as a colorless liquid (0.48 g, 81%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.35 (d, J = 5.8, 1H), 6.50 (dt, J = 5.8, 1.9 Hz, 1H), 5.95 (s, 1H), 5.15 (dd, J = 5.6, 1.9 Hz, 1H), 5.00 (d, J = 5.6 Hz, 1H), 3.74 (s, 3H), 1.41 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 167.5, 158.9, 143.8, 133.0, 114.1, 112.9, 81.9, 79.9, 51.5, 27.6, 26.4.

(3a*S*,4*S*,6a*R*)-4,6a-Dihydro-6-(2-hydroxyethyl)-2,2-dimethyl-3a*H*-cyclopenta[*d*][1,3]dioxol-4-ol (10). To a solution of **8** (1.18 g, 5.22 mmol) in anhydrous CH_2Cl_2 (50 mL) at −50 °C was added diisobutylaluminum hydride (DIBAL) (20.0 mL, 1 M in CH_2Cl_2, 20.0 mmol) dropwise. The mixture was stirred at the same temperature for 4 h before the reaction was quenched with MeOH (5 mL). Tartrate solution (20 mL) was added, and the mixture was warmed to room temperature and then stirred for 1 h. The organic phase was separated, and the aqueous solution was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried (anhydrous Na_2SO_4). The solvent was removed under vacuum to cleanly afford **10** as a colorless liquid (0.90 g, 87%) of sufficient purity (NMR) for use in the next step: ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.61 (s, 1H), 4.88 (d, J = 5.5 Hz, 1H), 4.77 (t, J = 5.6 Hz, 1H), 4.54 (m, 1H), 3.76 (m, 2H), 2.79 (m, 2H), 2.44 (m, 2H), 1.45 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 142.8, 131.5, 112.3, 84.6, 77.6, 73.1, 60.6, 31.9, 27.4, 26.3. Anal. ($C_{10}H_{16}O_4$) C, H.

(3a*S*,4*S*,6a*R*)-6-[2-(*tert*-Butyldimethylsilanyloxy)ethyl]-4,6a-dihydro-2,2-dimethyl-3a*H*-cyclopenta[*d*][1,3]dioxol-4-ol (11). To an ice-chilled solution of **10** (0.90 g, 4.5 mmol) in CH_2Cl_2 (40 mL) was added imidazole (0.48 g, 7.1 mmol) and *tert*-butyldimethylsilyl chloride (TBDMSCl) (0.76 g, 5.0 mmol). The mixture was stirred at room temperature for 12 h. The resulting precipitate was removed by filtration, and the filtrate was evaporated. The residue was purified by column chromatography (EtOAc/hexanes = 1:4) to afford **11** as a colorless oil (1.24 g, 88%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.53 (s, 1H), 4.84 (d, J = 5.5 Hz, 1H), 4.70 (t, J = 5.5 Hz, 1H), 4.51 (m, 1H), 3.76 (m, 2H), 2.68 (d, J = 10 Hz, 1H, OH), 2.37 (m, 2H), 1.39 (s, 3H), 1.38 (s, 3H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 143.2, 130.7, 112.4, 85.2, 77.8, 73.7, 61.4, 31.6, 27.9, 27.0, 26.1, 18.4, −5.1. Anal. ($C_{16}H_{30}O_4Si$) C, H.

(3a*S*,4*S*,6a*R*)-9-{6-[2-(*tert*-Butyldimethylsilanyloxy)-ethyl]-2,2-dimethyl-4,6a-dihydro-3a*H*-cyclopenta[*d*][1,3]-dioxol-4-yl}-9*H*-purin-6-ylamine (12). To a suspension of **11** (1.10 g, 3.50 mmol), Ph_3P (0.99 g, 3.8 mmol), and adenine (0.54 g, 4.0 mmol) in dry THF (40 mL) at 0 °C was added dropwise a solution of DIAD (0.77 mL, 3.8 mmol) in THF (5 mL). The mixture was stirred at room temperature for 12 h and then at 50 °C for 8 h. The solvent was removed and the residue was purified by column chromatography (EtOAc/hexanes = 4:1) to give **12** as a white solid (0.63 g, 43%): mp 121−122 °C (lit.[7] 133−134 °C); ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.69 (s, 1H), 6.34 (br, 2H), 5.63 (d, J = 12.4 Hz, 2H), 5.29 (d, J = 5.5 Hz, 1H), 4.62 (d, J = 5.5 Hz, 1H), 3.90 (m, 2H), 2.55 (m, 2H), 1.47 (s, 3H), 1.37 (s, 3H), 0.90 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 155.9, 153.4, 150.4, 150.0, 138.5, 123.0, 120.3, 112.6, 85.6, 84.4, 64.5, 60.7, 32.2, 27.6, 26.3, 26.1, 18.4, −5.1. Anal. ($C_{21}H_{33}N_5O_3Si$) C, H, N.

(3*Z*)(1*S*,2*R*,5*R*)-5-(6-Aminopurin-9-yl)-3-(2-hydroxyethyl)cyclopent-3-ene-1,2-diol (4). Compound **12** (0.40 g, 0.93 mmol) was dissolved in a mixture of MeOH (10 mL) and 1 N HCl (10 mL), and the resulting solution was stirred at room temperature for 5 h. Basic resin (Amberlite IR 67) was added to neutralize the solution, which was followed by filtration. The filtrate was removed under vacuum and the residue was purified by column chromatography (EtOAc/MeOH/NH_4OH = 6:2:1) to provide **4** as a white solid (0.23 g, 90%): mp 181−182 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.15 (s, 1H), 8.08 (s, 1H), 7.34 (br, 2H), 5.62 (s, 1H), 5.33 (s, 1H), 4.44 (d, J = 5.4 Hz, 1H), 4.23 (t, J = 5.2 Hz, 1H), 3.62 (t, J = 6.8 Hz, 2H), 2.35 (t, J = 6.8 Hz, 2H); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 155.7, 152.0, 149.6, 147.5, 139.6, 125.0, 119.2, 76.4, 74.6, 64.6, 59.0, 32.6.[7]

HBV Antiviral Analysis. HBV antiviral analyses were conducted as previously described.[17] In brief, confluent cultures of 2.2.15 cells were maintained on 96-well flat-bottomed tissue culture plates in RPMI1640 medium with 2% fetal bovine serum.[17] Cultures (six for each test concentration on two replicate plates) were treated with nine consecutive daily doses of the test compounds. Medium was changed daily with fresh test compounds. HBV DNA levels were assessed 24 h after the last treatment by quantitative blot hybridization.[17] Uptake of neutral red dye by semiquantitative analysis of the absorbance of internalized dye at 510 nM (A_{510}) was used to determine the relative level of toxicity 24 h following the last treatment (three cultures per test concentration).[17] For these analyses, cultures of 2.2.15 cells were maintained on 96-well plates seeded at the same time with the identical pool of stock cells used for the antiviral analyses and maintained in an identical manner.

HCV Antiviral Analysis. AVA5 cells (Huh 7 cells containing the subgenomic HCV replicon BB7)[18] were used for these studies as previously described.[19] Stock cultures were maintained in a subconfluent state in this culture medium with 1 mg/mL G418 (Invitrogen, Inc.).[18] Cells for antiviral analysis were seeded into 24-well tissue culture plates (Nunc, Inc.) and grown for 3 days in the presence of G418. G418 was then removed for the duration of the antiviral treatments to eliminate potential loss of cells due to the reduction of HCV replicon (and G418 resistance) copy number. Cultures (rapidly dividing, three cultures per concentration) were treated for 3 consecutive days with the test compounds. Medium was replaced daily with fresh test compounds. Analysis of HCV RNA was performed 24 h following the last addition of test compounds by quantitative blot hybridization.[18] Toxicity analyses in AVA5 cells were performed as described above. The interferon-α (IFN-α) was purchased from PBL Biomedical Laboratories.

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Supporting Information Available: Results from elemental analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Confirmation of the regioselectivity and stereoselectivity of this reaction became available with the conversion of **7** to the known[7] **4**.

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