Studies towards the Synthesis of the Hypermodified Nucleoside of Rat Liver Phenylalanine Transfer Ribonucleic Acid: Improved Synthesis of the Base β-Hydroxywybutine

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Received March 6, 1998; accepted April 14, 1998

An improved synthesis of the key intermediates (3 and 8) for the synthesis of β-hydroxywybutines [[*R*-(*R,S*)]- and [*S*-(*R**,*R**)]-4], the most probable structures for the minor base from rat liver tRNA^{Phe}, has been achieved by the Wittig reaction between 1-benzyl-7-formylwye (1) and the phosphorane derived from (*R*)-2-[(methoxycarbonyl)amino]-3-(triphenylphosphonio)propanoate (10), followed by methylation, OsO_4 oxidation, and cyclocondensation with $COCl_2$ in the presence of pyridine. The racemic forms of β-hydroxywybutines [(*R**,*S**)- and (*R**,*R**)-4], which were required for the determination of the optical purity of [*R*-(*R**,*S**)]- and [*S*-(*R**,*R**)]-4 by means of chiral HPLC, were conveniently prepared through pyrolysis of the cyclic carbonate 3 followed by $NaBH_4$ reduction and catalytic hydrogenolysis. The samples of [*R*-(*R**,*S**)]- and [*S*-(*R**,*R**)]-4 were thus shown to be optically pure.**

Key words tRNA hypermodified base; β-hydroxywybutine chiral synthesis; Wittig reaction; cyclic carbonate hydrogenolysis; cyclic carbonate pyrolysis; chiral HPLC

β-Hydroxywybutines [[*R*-(*R**,*S**)]- and [*S*-(*R**,*R**)]-**4**], the most probable structures for the minor base from rat liver tRNA^{Phe}, have been synthesized by us through dihydroxylation of the olefin **5** followed by cyclocondensation with $(COCl)_2$ and subsequent hydrogenolysis.[1] The key intermediate **5** was in turn prepared by either the Wittig reaction between the aldehyde **1** and the phosphonium chloride **9**[2] or palladium-catalyzed arylation of (*S*)-*N*-(methoxycarbonyl)vinylglycine with the iodide **6**[3] (Chart 1). The latter method was applicable to the nucleoside level. Thus, 3-β-D-ribofuranosylwybutine (**11**), the most probable structure for the minor nucleoside from yeast tRNA^{Phe}, was synthesized through the olefin **13** by successive catalytic hydrogenation, chromatographic separation, methylation, and deprotection.[3] Unfortunately, **13** was formed together with its diastereomer, and we obtained too small an amount of **13** by means of HPLC[3b] to utilize it as an intermediate for the synthesis of the target nucleoside **12**. In the present work, we intended to improve the synthesis of **4** so that we may achieve the synthesis of **12**[4] by applying the same method.

Results and Discussion

Wittig Reaction with the Inner Salt 10 Both methods of synthesizing **5** described above have drawbacks: the Wittig reaction employing the phosphonium chloride **9** followed by methylation gave crude **5** in only 16% maximum yield with unsatisfactory reproducibility[2]; the Heck reaction of **6** with *N*-(methoxycarbonyl)vinylglycine in $HCONMe_2$ was accompanied by partial racemization.[3] Recently, we found that the Heck reaction of (*S*)-*N*-(benzyloxycarbonyl)vinylglycine with 4-iodoanisole smoothly proceeded in H_2O, giving a product of high optical purity.[5] We then carried out the reaction of **6** with

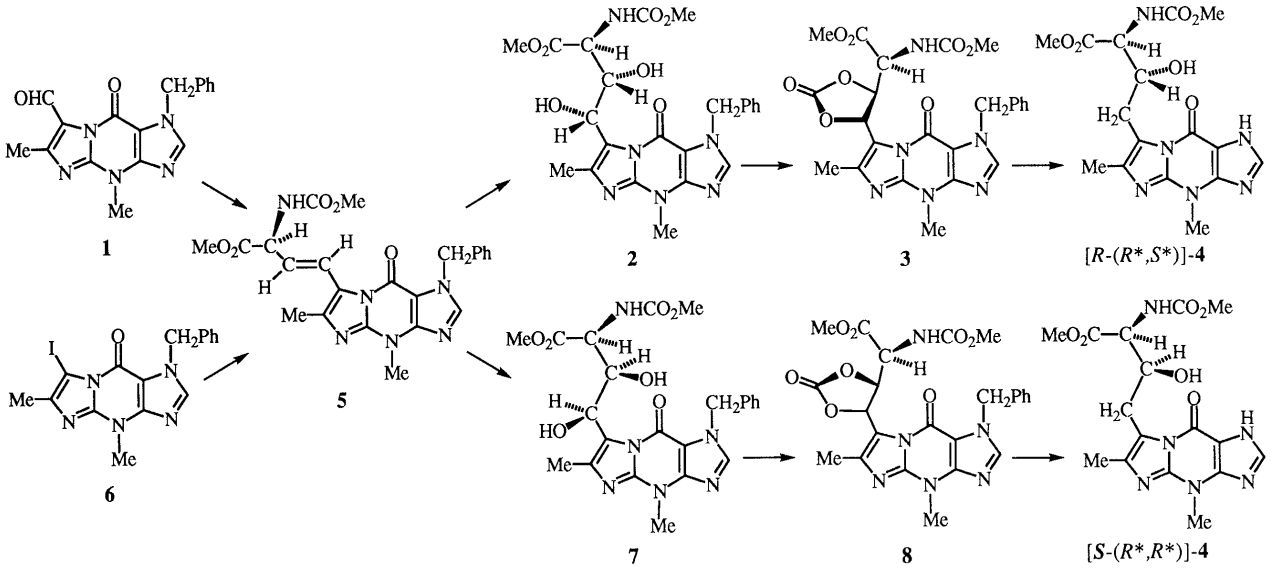

Chart 1

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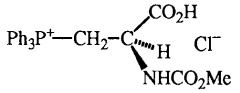

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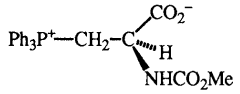

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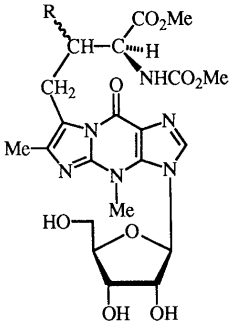
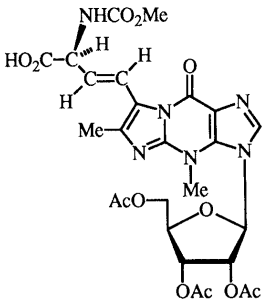


11: R = H
12: R = OH



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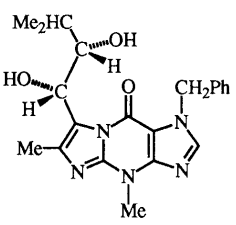
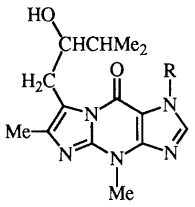
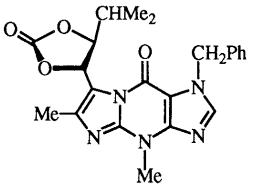


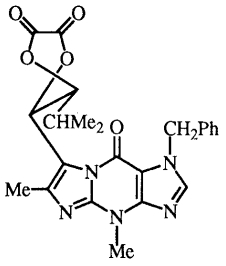
(±)-14



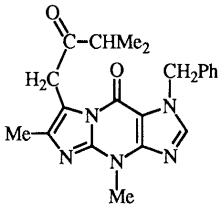
15: R = H
16: R = $PhCH_2$



(±)-17



(±)-18



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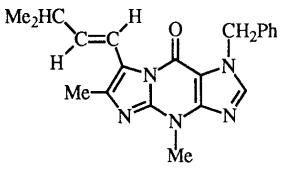

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N-(methoxycarbonyl)vinylglycine replacing the solvent $HCONMe_2$ by H_2O; however, we found that the reaction did not take place in this case at all.

It is noteworthy that the synthesis of enantiomerically pure protected 4-oxo-α-amino acids was achieved by Jackson's group through palladium-catalyzed acylation of the organozinc reagent.[6] We attempted to apply this method to the reaction between the organozinc reagent derived from methyl (*R*)-3-iodo-2-[(methoxycarbonyl)-amino]propanoate,[2b] and 1-benzyl-7-(chlorocarbonyl)-wye, which was prepared *in situ* from 1-benzyl-7-carboxywye.[7] However, we obtained no desired product.

These unfruitful results forced us to investigate again the Wittig reaction with **1**. We have reported that the inner salt **10** is superior to the chloride **9** for the Wittig reaction with benzaldehyde.[8] We found in the present study that this was also the case for the reaction with **1**, and **5** was obtained, after methylation with Me_3SiCHN_2–MeOH, in 26% yield.

Dihydroxylation of 5 The procedure for the transformation of **5** to **4** (Chart 1)[1b] was not sufficiently efficient for our purposes. We desired to convert the olefin **5** into the monohydroxy compound (**27** or **28**) through hydroboration and boron-zinc exchange reaction according to the recently reported procedure,[9] but hydroboration of **5** with Et_2BH disappointingly proceeded only sluggishly.

Dihydroxy compounds (**2** and **7**) were previously obtained in 69% and 24% yields, respectively, by OsO_4 oxidation of **5** in acetone–0.5 M phosphate buffer (pH 6) (2.7 : 1, v/v) in the presence of *N*-methylmorpholine *N*-oxide at room temperature for 4 h.[1b] In the present study, **2** and **7** were obtained in 56% and 37% yields, respectively, by changing the solvent to acetone–0.5 M phosphate buffer (pH 6) (1 : 1, v/v).

Attempted deoxygenation of **2** by catalytic hydrogenolysis over Raney Ni at 40 °C and atmospheric pressure resulted in complete recovery of **2**. The reaction of **2** with $NaCNBH_3$–ZnI_2 according to the reported procedure[10] took place only slowly to give a complex mixture, a result similar to an earlier experience[1b] of deoxygenation. Thus, our next task was to find an efficient deoxygenation using the model compound (±)-**14**.[11]

Cyclic Oxalate of (±)-14 Although (±)-**14** afforded the cyclic carbonate (±)-**17** as the major product on treatment with $(COCl)_2$ in the presence of NEt_3,[1b] we have disclosed that treatment of *threo*-1,2-diols with $(COCl)_2$ in the presence of pyridine instead of NEt_3 exclusively provides their cyclic oxalates.[12] Indeed the reaction of (±)-**14** with $(COCl)_2$ rapidly proceeded in tetrahydrofuran (THF) at 0 °C in the presence of pyridine, producing no trace of the cyclic carbonate (±)-**17**. The putative cyclic oxalate (±)-**18** thus formed, was unstable in the reaction mixture at room temperature; it completely decomposed to the olefin **20**[11] and other unidentified products within 45 h. It also decomposed on silica gel to a mixture of compounds, three of which were the ketone **19**,[1b] the olefin **20**, and the diol (±)-**14**. When, without purification, a THF solution of (±)-**18** was treated with $NaBH_4$, the reaction proceeded slowly at room temperature to give a complex mixture of products which did not contain the desired product **16**. Similar treatment of a THF solution of (±)-**18** with *n*-Bu_3SnH[13] in the presence or absence of azobisisobutyronitrile followed by alkaline hydrolysis also did not provide **16**. Interestingly, when a THF solution of (±)-**18** was shaken under H_2 in the presence of Pd–C at room temperature for 1.5 h, **20** was obtained in 77% yield, together with (±)-**14** (7% yield). The mechanism for such facile elimination reaction of (±)-**18** in the presence of Pd–C is not clear. Under these conditions, the catalyst might be poisoned by pyridine, leaving the olefin **20** intact.

Deoxygenation through Cyclic Carbonates The cyclic carbonate (±)-**17** was previously prepared in 63% yield by treatment of (±)-**14** with $(COCl)_2$ in THF in the presence of Et_3N; the use of $COCl_2$ or diphosgene instead

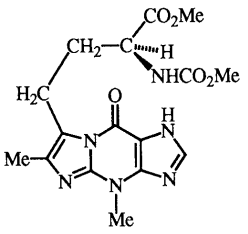
of $(COCl)_2$ markedly reduced the yield of (±)-**17**.[1b] As we have found that Et_3N rapidly consumes $COCl_2$ in THF,[7] (±)-**14** was treated in the present work with $COCl_2$ in THF in the presence of pyridine to produce (±)-**17** in 82% yield. The yield of (±)-**17** reached 93% by replacing the solvent with CH_2Cl_2.[14] The use of 2,4,6-collidine instead of pyridine significantly retarded the reaction. When the diol **2** was treated with $COCl_2$ in CH_2Cl_2 in the presence of pyridine, the carbonate **3** was obtained in 70% yield. Similar treatment of the diastereomer **7** afforded the carbonate **8** in 55% yield with 23% recovery of **7**.

Compound (±)-**17** had a melting point of 213—215 °C with evolution of a gas, and a clean reaction was suggested to occur by means of TLC. The decarboxylated product, thus obtained in 89% yield, was the ketone **19**.[1b] Reduction of **19** with $NaBH_4$ should provide **16**, completing the model experiment. However, this route is obviously unsuitable for chiral synthesis of **4**, because the ketone (*S*)-**26** to be formed must be configurationally unstable (*vide infra*).

Compounds [*R*-(*R**,*S**)]- and [*S*-(*R**,*R**)]-**4** have been prepared by hydrogenolysis of **3** and **8** over Pd–C in 44—48% yields, together with the dideoxy compound **21** (28—41% yields).[1b] Similar treatment of (±)-**17** provided **15** (46% yield) and the dideoxy compound **22** (28% yield).[1b] Although the mechanism for the formation of the dideoxy compounds is not clear, we intended in the present work to minimize dideoxygenation. Palladium-catalyzed hydrogenolysis of carbonates with ammonium formate[15] did not work for (±)-**17**, resulting in complete recovery of (±)-**17**. Table 1 summarizes the results of hydrogenolysis of (±)-**17** with H_2 using Raney Ni or Pt instead of Pd–C, showing that the use of Raney Ni gave a considerable amount of the undesired compound **23**[11] and the use of Pt afforded other undesired 1-cyclohexylmethyl compounds (**24** and **25**) besides **23**. From these results it is clear that Pd–C is the best of these three catalysts for the synthesis of **4**, but Pt might be quite useful for hydrogenolysis of substrates bearing no benzyl group in view of its higher selectivity for monodeoxygenation.

Determination of Optical Purity of 4 In our previous work[1b] we estimated the optical purities of [*R*-(*R**,*S**)]- and [*S*-(*R**,*R**)]-**4**, which were obtained by hydrogenolysis of the cyclic carbonates (**3** and **8**), on the basis of the optical purity of the by-product **21**, because neither of their enantiomers nor racemic modifications were available. As mentioned above, the cyclic carbonate **17** easily provided the ketone **19**. This rearrangement supplies a convenient route to (*R**,*S**)- and (*R**,*R**)-**4** from the cyclic carbonate (**3** or **8**). Thus, the ketone **26** was obtained in 27% yield by heating **3** at 200—210 °C for 1—2 min. Reduction of **26** with $NaBH_4$ in MeOH at room temperature afforded (±)-**27** and (±)-**28** in 23% and 51% yields, respectively. Catalytic hydrogenolysis of these compounds over Pearlman's catalyst afforded (*R**,*S**)- and (*R**,*R**)-**4**, respectively. Both compounds were cleanly resolved by means of HPLC using a chiral column. According to this HPLC analysis, the samples of [*R*-(*R**,*S**)]- and [*S*-(*R**,*R**)]-**4**[1b] were confirmed to be optically pure.

In conclusion, we have established a basis for the synthesis of 3-(β-D-ribofuranosyl)-β-hydroxywybutines (**12**)[4] by improving individual steps of the reaction sequence from **1** leading to the precursors (**3** and **8**) of **4**. The information obtained with **17** on the selectivity of hydro-



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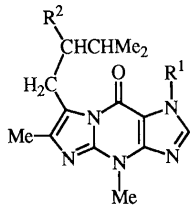


22: $R^1 = R^2 = H$

23: $R^1 = PhCH_2$; $R^2 = H$

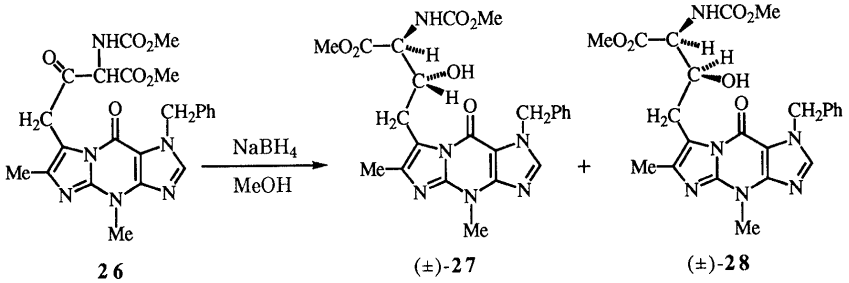
24: R^1 = cyclohexylmethyl; $R^2 = H$

25: R^1 = cyclohexylmethyl; $R^2 = OH$

Table 1. Catalytic Hydrogenolysis of (±)-**17**

Catalyst	Reaction conditions		Yield (%)					
	Temperature	Time (h)	**15**	**22**	**16**	**23**	**25**	**24**
Pd–C	*ca.* 60 °C	10.5	46[a,b]	28[a,b]	—	—	—	—
Raney Ni	Room temperature	2	—	—	11[c,d]	85[c,d]	—	—
Pt	*ca.* 60 °C	9	—	—	49[c]	12[c]	25[c]	6[c]

a) Taken from ref. 1*b*. *b*) Isolated yield. *c*) Determined by ^{1}H-NMR spectroscopy. *d*) With 3% recovery of (±)-**17**.



26 (±)-**27** (±)-**28**

Chart 2

genolysis of the cyclic carbonate should also help toward the efficient synthesis of **12**. Furthermore, the present method for the determination of the optical purity of **4** will be useful for determining the diastereomeric purity of **12** when it is synthesized.

Experimental

General Notes All melting points were determined by using a Yamato MP-1 or a Büchi model 530 capillary melting point apparatus and are corrected. Spectra reported herein were recorded on a Hitachi M-80 mass spectrometer, a Hitachi model 320 UV spectrophotometer (in solutions of 95% aqueous ethanol), a Shimadzu FTIR-8100 IR spectrophotometer, JEOL JNM-GSX-500 or a JEOL JNM-EX-270 NMR spectrometer (recorded at 25 °C in $CDCl_3$ with Me_4Si as an internal standard). The HPLC system employed consisted of a Waters 6000A pump, a U6K injector, and a model 440 absorbance detector (operated at 254 nm). Elemental analyses and MS measurements were performed by Mr. Y. Itatani and his associates at Kanazawa University. Flash chromatography was performed according to the reported procedure.[16] The following abbreviations are used: br = broad, d = doublet, dd = doublet-of-doublets, m = multiplet, s = singlet, sh = shoulder.

[*S*-(*E*)]-4-(1-Benzyl-4,6-dimethyl-9-oxo-4,9-dihydro-1*H*-imidazo[1,2-*a*]purin-7-yl)-2-[(methoxycarbonyl)amino]-3-butenoic Acid Methyl Ester (5) The phosphonium salt **10**[8] (1.5 g) was dried three times by coevaporation with a mixture of $CHCl_3$ (20 ml each time) and benzene (20 ml each time). The residue was dried over P_2O_5 at 2 mmHg and 80 °C for 18 h. A portion (1.23 g, 3.02 mmol) of dried **10** was dissolved in a mixture of $(Me_2N)_3PO$ (18 ml) and THF (50 ml) under N_2. A 1.57 M solution of *n*-BuLi (3.8 ml, 5.97 mmol) in hexane was added dropwise over a period of 10 min to the stirred solution of **10**, which had been cooled to −70 °C (bath temperature), and stirring was continued for a further 20 min. Finely pulverized **1** (970 mg, 3.02 mmol) was then added, and the mixture was stirred for 1 h at that temperature and then allowed to warm to 0 °C with stirring. The resulting mixture was neutralized with 10% aqueous H_3PO_4 and concentrated *in vacuo*. The residue was brought to pH 3 with 10% aqueous H_3PO_4 after addition of H_2O (100 ml), and the mixture was extracted with $CHCl_3$ (3 × 30 ml). The organic layers were combined and extracted with saturated aqueous $NaHCO_3$ (5 × 30 ml). The aqueous layers were combined, brought to pH 3 with 10% aqueous H_3PO_4, and extracted with $CHCl_3$ (4 × 50 ml). The $CHCl_3$ extracts were combined, dried ($MgSO_4$), and concentrated *in vacuo* to leave a reddish oil. This was dissolved in a mixture of MeOH (3 ml) and benzene (12 ml), and 2 M Me_3SiCHN_2–hexane (1.5 ml) was added. AcOH (0.5 ml) was then added to the resulting solution, and the mixture was concentrated *in vacuo*. The oily residue was subjected to flash chromatography [hexane–AcOEt–EtOH (1 : 15 : 2, v/v)] to afford a semisolid (2 g). This was washed with AcOEt (30 ml) to give **5** (124 mg), mp 165—178 °C. The AcOEt washings were washed with H_2O (3 × 50 ml), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was triturated with MeOH and dried to give a second crop of **5** (243 mg; the total yield was 26%), mp 160—173 °C. These samples of **5** were identical (by comparison of the IR spectrum and TLC mobility) with an authentic specimen.[2b] Recrystallization of crude **5** from MeOH provided **5** (254 mg, 18%) as colorless needles, mp 178.5—181 °C.

Dihydroxylation of 5 A stock solution of OsO_4 (2.5 w/v% in *tert*-BuOH) (1.5 ml) was added to a suspension of **5** (660 mg, 1.42 mmol) in a mixture of acetone (100 ml), *N*-methylmorpholine *N*-oxide monohydrate (240 mg, 1.78 mmol), and 0.5 M phosphate buffer (pH 6) (100 ml), and the resulting mixture was stirred at room temperature for 3 h. $Na_2S_2O_5$ (415 mg, 2.18 mmol) was added to the mixture, and the whole was stirred at room temperature for 10 min. The resulting mixture was concentrated *in vacuo* to a volume of *ca.* 100 ml and extracted with $CHCl_3$ (3 × 100 ml). The organic layers were combined, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was triturated with MeOH (1 ml). The resulting solid was collected by filtration and dried to afford **2**[1b] (277 mg), mp 192—195 °C (dec.). The filtrate was concentrated, and the residue was subjected to repeated flash chromatography [1,2-dichloroethane–EtOH (7 : 1, v/v)] to afford a second crop of **2** (90 mg) and **7**[1b] (174 mg) as a colorless glass. Further purification of a mixture of **2** and **7** by repeated preparative TLC [silica gel, benzene–EtOH (6 : 1, v/v)] afforded **2** (28 mg; the total yield was 395 mg, 56%) and **7** (88 mg; the total yield was 262 mg, 37%).

***trans*-(±)-1-Benzyl-7-(5-isopropyl-2-oxo-1,3-dioxolan-4-yl)-4,6-dimethyl-1,4-dihydro-9*H*-imidazo[1,2-*a*]purin-9-one [(±)-17]** A 2 M solution of $COCl_2$ in toluene (0.28 ml, 0.56 mmol) was diluted with CH_2Cl_2 (2 ml) and added to a stirred solution of (±)-**14**[11] (99 mg, 0.25 mmol) and pyridine (0.19 ml) in CH_2Cl_2 (4 ml) in an ice bath over a period of 5 min. The resulting mixture was stirred at 0 °C for a further 15 min, washed successively with H_2O (10 ml), 5% aqueous citric acid (10 ml), and saturated aqueous $NaHCO_3$ (10 ml), dried ($MgSO_4$), and concentrated *in vacuo* to leave (±)-**17** (99 mg, 93%), mp 212—214 °C (dec.), which was identical (by comparison of the IR spectrum and TLC mobility) with an authentic specimen.[1b]

[4*S*-[4α(*R),5β]]-5-[1-Benzyl-4,6-dimethyl-9-oxo-4,9-dihydro-1*H*-imidazo[1,2-*a*]purin-7-yl]-α-[(methoxycarbonyl)amino]-2-oxo-1,3-dioxolane-4-acetic Acid Methyl Ester (3)** A solution of 2 M $COCl_2$–toluene (0.12 ml, 0.24 mmol) in CH_2Cl_2 (1 ml) was added dropwise to a stirred solution of **2** (50 mg, 0.1 mmol) and pyridine (0.08 ml) in CH_2Cl_2 (2 ml) in an ice bath over a period of 1 min. The mixture was stirred for a further 15 min and concentrated *in vacuo*. The resulting solid residue was subjected to flash chromatography [$CHCl_3$–MeOH (30 : 1, v/v)] to afford **3** (37 mg, 70%), mp 190—191.5 °C (dec.), which was identical (by comparison of the IR spectrum and TLC mobility) with an authentic specimen.[1b]

[4*R*-[4α(*S),5β]]-5-[1-Benzyl-4,6-dimethyl-9-oxo-4,9-dihydro-1*H*-imidazo[1,2-*a*]purin-7-yl]-α-[(methoxycarbonyl)amino]-2-oxo-1,3-dioxolane-4-acetic Acid Methyl Ester (8)** A solution of 2 M $COCl_2$–toluene (0.6 ml, 1.2 mmol) in CH_2Cl_2 (7 ml) was added dropwise to a stirred solution of **7** (260 mg, 0.522 mmol) and pyridine (0.4 ml) in CH_2Cl_2 (10 ml) in an ice bath over a period of 20 min. The mixture was stirred for a further 10 min and extracted with H_2O (2 × 20 ml). The organic layer was washed successively with 5% aqueous citric acid (2 × 20 ml), H_2O (20 ml), and saturated aqueous $NaHCO_3$ (10 ml), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was recrystallized from EtOH to give **8** (131 mg) [mp 162—165 °C (dec.)], which was identical (by comparison of the IR spectrum and TLC mobility) with an authentic specimen.[1b] The ethanolic filtrate was concentrated, and the residue was purified by preparative TLC [silica gel, benzene–EtOH (6 : 1, v/v)] to give a second crop of **8** (19 mg; the total yield was 55%), mp 161.5—163.5 °C (dec.).

The H_2O extracts (40 ml) of the reaction mixture were extracted with CH_2Cl_2 (2 × 20 ml). The CH_2Cl_2 layers were combined, washed successively with 5% aqueous citric acid (2 × 20 ml), H_2O (10 ml), and saturated aqueous $NaHCO_3$ (10 ml), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was subjected to flash chromatography [$CHCl_3$–MeOH (20 : 1, v/v)] to give **7** (61 mg, 23% recovery).

Hydrogenolysis of (±)-17 i) Catalyzed by Raney Ni: A mixture of (±)-**17** (30 mg, 0.071 mmol), Raney Ni W-2 (0.1 ml), and EtOH (20 ml) was shaken under H_2 at atmospheric pressure and room temperature for 2 h. The catalyst was filtered off and washed with hot EtOH (100 ml). The filtrate and washings were combined and concentrated *in vacuo* to leave a colorless solid (27 mg). This was a mixture of (±)-1-benzyl-7-(2-hydroxy-3-methylbutyl)-4,6-dimethyl-1,4-dihydro-9*H*-imidazo[1,2-*a*]-purin-9-one (**16**) (11%), **23**[11] (85%), and (±)-**17** (3%) on the basis of its ^{1}H-NMR spectrum [the yields were determined from the peak areas of the C(2)-H signals]. A portion (21 mg) of the mixture was subjected to preparative TLC [silica gel, CH_2Cl_2–MeOH (30 : 1, v/v)] to afford **16** (2 mg) and a mixture of **23** and (±)-**17** (17 mg). Compound **16** was obtained as a colorless solid, ^{1}H-NMR δ: 1.04 (6H, d, J = 6.6 Hz, $\underline{Me}_2CH$), 1.79 (1H, m, $Me_2C\underline{H}$), 2.27 [3H, s, C(6)-Me], 3.23 (3H, m, $C\underline{H}_2CHO\underline{H}$), 3.54 (1H, m, $CH_2C\underline{H}OH$), 3.91 (3H, s, NMe), 5.57 and 5.61 (1H each, d, J = 15 Hz, $PhC\underline{H}_2$), 7.35 (5H, m, $\underline{Ph}CH_2$), 7.63 [1H, s, C(2)-H].

ii) Catalyzed by Pt: A mixture of (±)-**17** (30 mg, 0.071 mmol), PtO_2 (30 mg), and EtOH (20 ml) was shaken under H_2 at *ca.* 60 °C and atmospheric pressure for 9 h. The catalyst was filtered off and washed with hot EtOH (100 ml). The filtrate and washings were combined and concentrated *in vacuo* to leave a colorless solid (28 mg). A portion (22 mg) of this material was subjected to preparative TLC [silica gel, 1,2-dichloroethane–EtOH (10 : 1, v/v)] to afford two mixtures as colorless solids. One of them (4 mg) was a mixture of **23**[11] (12%) and 1-(cyclohexylmethyl)-4,6-dimethyl-7-(3-methylbutyl)-1,4-dihydro-9*H*-imidazo[1,2-*a*]purin-9-one (**24**) (6%) on the basis of its MS and ^{1}H-NMR spectra [for **24**, MS *m/z*: 369 (M^+), 312; ^{1}H-NMR δ: 4.22 (2H, d, J = 7.3 Hz, $C_6H_{11}C\underline{H}_2$), 7.56 [1H, s, C(2)-H]]. The other (16 mg) was a mixture of **16** (49%) and (±)-1-(cyclohexylmethyl)-7-(2-hydroxy-3-methylbutyl)-4,6-dimethyl-1,4-dihydro-9*H*-imidazo[1,2-*a*]purin-9-one

(**25**) (25%) on the basis of its MS and ^{1}H-NMR spectra [for **25**, MS *m/z*: 385 (M^+), 312; ^{1}H-NMR δ: 4.19 (2H, m, $C_6H_{11}C\underline{H}_2$), 7.59 [1H, s, C(2)-H]]. The yields of these compounds were determined by comparison of the peak areas of the signals arising from C(2)-H.

1-Benzyl-4,6-dimethyl-7-(3-methyl-2-oxobutyl)-1,4-dihydro-9*H*-imidazo[1,2-*a*]purin-9-one (19) Compound (±)-**17** (126 mg, 0.299 mmol) was heated at 220—230 °C (bath temperature) for 1—2 min and cooled to room temperature to give a colorless solid, mp 183—190 °C. This was recrystallized from EtOH to give **19** (78 mg), mp 189—191 °C. The mother liquor was concentrated *in vacuo*, and the residue was subjected to flash chromatography [AcOEt–EtOH (10 : 1, v/v)] to afford a second crop of **19** (23 mg; the total yield was 89%), mp 183—187 °C. Recrystallization of **19** from EtOH afforded an analytical sample as colorless needles, mp 190—192 °C; MS *m/z*: 377 (M^+); UV $\lambda_{max}^{95\%\ EtOH}$ 240 nm (ε 30600), 259 (sh) (6600), 319 (5700); IR ν_{max}^{Nujol} cm^{-1}: 1711, 1684 (C=O); ^{1}H-NMR δ: 1.18 (6H, d, J=7 Hz, $\underline{Me}_2CH$), 2.22 [3H, s, C(6)-Me], 2.85 (1H, septet, J=7 Hz, $Me_2C\underline{H}$), 3.89 (3H, s, NMe), 4.20 [2H, s, C(7)-CH_2], 5.53 (2H, s, PhC$\underline{H}_2$), 7.34 (5H, m, $\underline{Ph}CH_2$), 7.59 [1H, s, C(2)-H]. *Anal.* Calcd for $C_{21}H_{23}N_5O_2$: C, 66.83; H, 6.14; N, 18.55. Found: C, 66.68; H, 6.20; N, 18.50.

(±)-1-Benzyl-α-[(methoxycarbonyl)amino]-β-oxo-4,6-dimethyl-9-oxo-4,9-dihydro-1*H*-imidazo[1,2-*a*]purine-7-butanoic Acid Methyl Ester (26) Compound **3** (80 mg, 0.15 mmol) was heated at 200—210 °C (bath temperature) for 1—2 min, and the product was subjected to flash chromatography [AcOEt–EtOH (10 : 1, v/v)]. Crude **26** (30 mg) thus obtained, was recrystallized from MeOH to provide **26**·2H_2O (21 mg, 27%), mp 183—187.5 °C. Further recrystallization of this sample from MeOH afforded an analytical sample of **26**·2H_2O as colorless needles, mp 188—190 °C; MS *m/z*: 480 (M^+); UV $\lambda_{max}^{95\%\ EtOH}$ 241 nm (ε 32100), 257 (sh) (7400), 318 (6100); IR ν_{max}^{Nujol} cm^{-1}: 3350, 3101 (NH and H_2O), 1751, 1732, 1724, 1693 (C=O); ^{1}H-NMR δ: 2.23 [3H, s, C(6)-Me], 3.72 and 3.81 (3H each, s, two OMe's), 3.89 (3H, s, NMe), 4.33 and 4.41 [1H each, d, J=18 Hz, C(γ)-H_2], 5.35 [a total of 1H with a small broad signal at 5.24, d, J=7 Hz, C(α)-H], 5.47 and 5.51 (1H each, d, J=15 Hz, PhC$\underline{H}_2$), 6.07 (a total of 1H with a small broad signal at 5.89, br d, J=7 Hz, NH), 7.34 (5H, m, $\underline{Ph}CH_2$), 7.62 [1H, s, C(2)-H]. *Anal.* Calcd for $C_{23}H_{24}N_6O_6\cdot 2H_2O$: C, 53.48; H, 5.46; N, 16.27. Found: C, 53.76; H, 5.27; N, 16.32.

$NaBH_4$ Reduction of 26 A mixture of **26**·2H_2O (23 mg, 0.045 mmol), $NaBH_4$ (5 mg, 0.1 mmol), and MeOH (4 ml) was stirred at room temperature for 40 min. Acetone (0.5 ml) was added to the mixture, and stirring was continued for a further 10 min. The mixture was concentrated *in vacuo*, and the residue was partitioned between H_2O (10 ml) and CH_2Cl_2 (10 ml). The aqueous layer was extracted with CH_2Cl_2 (10 ml). The CH_2Cl_2 layers were combined, washed with H_2O (10 ml), dried ($MgSO_4$), and concentrated *in vacuo*. The residue (19 mg) was subjected to preparative TLC [silica gel, $CHCl_3$–MeOH (30 : 1, v/v)] to afford (*R**,*S**)-1-benzyl-β-hydroxy-α-[(methoxycarbonyl)amino]-4,6-dimethyl-9-oxo-4,9-dihydro-1*H*-imidazo[1,2-*a*]purine-7-butanoic acid methyl ester [(±)-**27**] (5 mg, 23%) as a colorless glass [^{1}H-NMR δ: 2.27 [3H, s, C(6)-Me], 3.22 (dd, J=15, 3.5 Hz) and 3.46 (dd, J=15, 8.5 Hz) [1H each, C(γ)-H_2], 3.74 and 3.77 (3H each, s, two OMe's), 3.92 (3H, s, NMe), 4.15 (1H, br, OH), 4.37 [1H, m, C(β)-H], 4.49 [a total of 1H with a small broad signal at 4.30, dd, J=2, 9 Hz, C(α)-H], 5.57 and 5.60 (1H each, d, J=15 Hz, PhC$\underline{H}_2$), 5.65 (a total of 1H with a small broad signal at 5.35, d, J=9 Hz, NH), 7.35 (5H, m, $\underline{Ph}CH_2$), 7.66 [1H, s, C(2)-H]] and (*R**,*R**)-1-benzyl-β-hydroxy-α-[(methoxycarbonyl)-amino]-4,6-dimethyl-9-oxo-4,9-dihydro-1*H*-imidazo[1,2-*a*]purine-7-butanoic acid methyl ester [(±)-**28**] (11 mg, 51%) as a colorless glass [^{1}H-NMR δ: 2.26 [3H, s, C(6)-Me], 3.36 (dd, J=15, 8.5 Hz) and 3.41 (dd, J=15, 4.5 Hz) [1H each, C(γ)-H_2], 3.72 and 3.73 (3H each, s, two OMe's), 3.80 (1H, br, OH), 3.90 (3H, s, NMe), 4.15 [1H, br, C(β)-H], 4.52 [a total of 1H with a small broad signal at 4.05, br, C(α)-H], 5.55 and 5.60 (1H each, d, J=15 Hz, PhC$\underline{H}_2$), 5.90 (a total of 1H with a small broad signal at 5.35, br d, J=8 Hz, NH), 7.35 (5H, m, $\underline{Ph}CH_2$), 7.66 [1H, s, C(2)-H]].

(*R,*S**)-β-Hydroxy-α-[(methoxycarbonyl)amino]-4,6-dimethyl-9-oxo-4,9-dihydro-1*H*-imidazo[1,2-*a*]purine-7-butanoic Acid Methyl Ester [(*R**,*S**)-4]** A solution of (±)-**27** (4 mg) in MeOH (4 ml) was shaken under H_2 over $Pd(OH)_2$–C (4 mg) at *ca.* 60 °C and atmospheric pressure for 6 h. The catalyst was filtered off and extracted with MeOH using a Soxhlet extractor. The methanolic filtrate and extracts were combined and concentrated *in vacuo*. The residue was subjected to preparative TLC [silica gel, CH_2Cl_2–MeOH (10 : 1, v/v)] to afford (*R**,*S**)-**4** (2 mg) as a colorless solid [mp 226—228.5 °C (dec.)], whose ^{1}H-NMR spectrum and TLC mobility were identical with those of [*R*-(*R**,*S**)]-**4**.[1b]

(*R,*R**)-β-Hydroxy-α-[(methoxycarbonyl)amino]-4,6-dimethyl-9-oxo-4,9-dihydro-1*H*-imidazo[1,2-*a*]purine-7-butanoic Acid Methyl Ester [(*R**,*R**)-4]** This compound (5 mg) was obtained as a colorless solid from (±)-**28** (10 mg) in a manner similar to that described above for the preparation of (*R**,*S**)-**4**. Recrystallization of the crude product from MeOH afforded (*R**,*R**)-**4** as colorless needles [mp 234—236 °C (dec.)], which showed identical ^{1}H-NMR spectrum and TLC mobility with those of [*S*-(*R**,*R**)]-**4**.[1b]

Evaluation of Optical Purities of [*R*-(*R,*S**)]- and [*S*-(*R**,*R**)]-4** Compound (*R**,*S**)-**4** was cleanly resolved on a Sumichiral OA-3200 column to give [*S*-(*R**,*S**)]-**4** (retention time, 32.0 min) and [*R*-(*R**,*S**)]-**4** (retention time, 33.7 min) by elution with hexane–AcOEt–MeOH–CF_3CO_2H (50 : 40 : 7 : 0.4) at a flow rate of 0.7 ml per min at room temperature. Complete resolution was also realized with (*R**,*R**)-**4**, and [*R*-(*R**,*R**)]- and [*S*-(*R**,*R**)]-**4** showed their retention times at 33.8 and 35.8 min, respectively, under these conditions. According to this HPLC analysis, the samples of [*R*-(*R**,*S**)]- and [*S*-(*R**,*R**)]-**4**[1b] were both free of their antipodes.

Acknowledgment This work was supported by a grant from the Japan Research Foundation for Optically Active Compounds and Grants-in-Aid for Scientific Research (Nos. 07557289 and 09672140) from the Ministry of Education, Science, Sports and Culture, Japan.

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