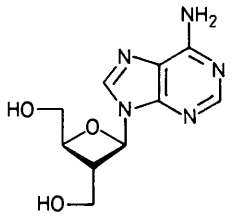
Enantio- and Diastereo-selective Synthesis of Carbocyclic Oxetanocin Analogues

Yuh-ichiro Ichikawa,*[a] Aya Narita,[a] Akira Shiozawa,[a] Yujiro Hayashi,[b] and Koichi Narasaka[b]

[a] *Research Laboratories, Nippon Kayaku Co., Ltd., 31-12, Shimo 3-Chome, Kita-ku, Tokyo 115, Japan*
[b] *Department of Chemistry, Faculty of Science, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113, Japan*

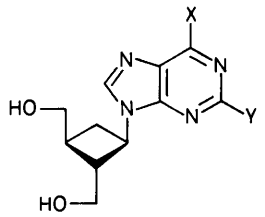
Carbocyclic oxetanocin-A (COXT-A) (**2a**) and -G (COXT-G) (**2b**) were synthesized enantio- and diastereo-selectively; these compounds exhibited potent antiviral activities.

Oxetanocin A (**1**), a novel nucleoside antibiotic having an oxetanosyl-*N*-glycoside linkage, exhibits antiviral and antitumour activity.[1] Since it was isolated in 1986, continuous studies have been made in our laboratories concerning the chemistry[2,3] and biological activity[3,4] of this unique 4-membered ring containing a nucleoside and its synthetic congeners. As part of these studies, we were interested in the carbocyclic analogues of oxetanocins (COXTs). We planned synthesizing carbocyclic oxetanocin-A (**2a**) and -G (**2b**) in optically pure forms, because the biological activities of carbocyclic nucleo-



oxetanocin A

(1)



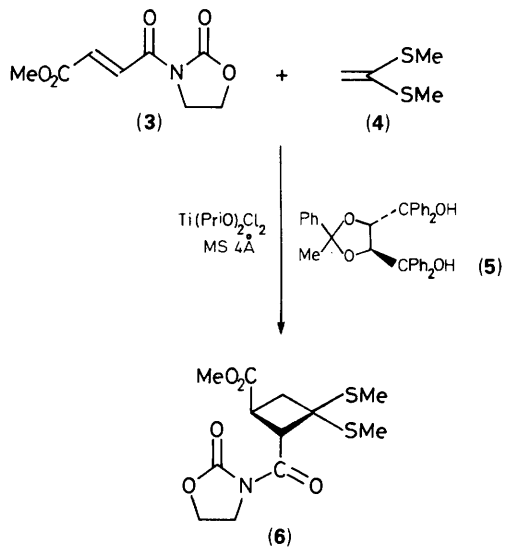
(2) a; X = NH_2, Y = H

b; X = OH, Y = NH_2

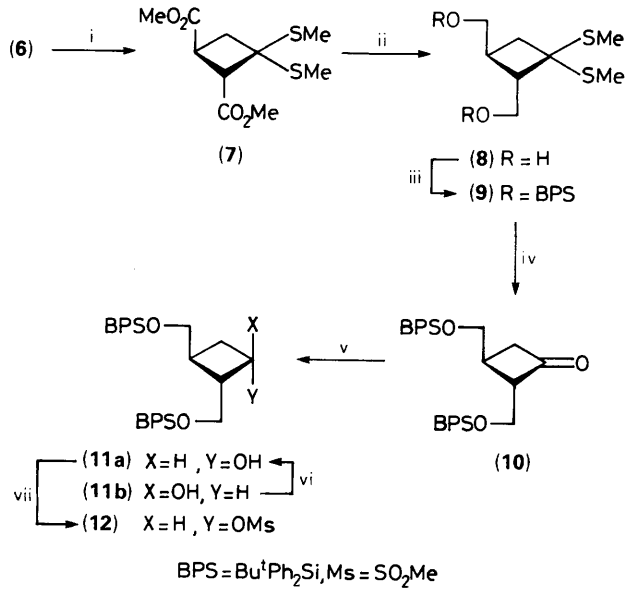
sides now have been shown to reside mainly in the 'natural' enantiomer.[5] Recently, Honjo independently reported the synthesis of a carbocyclic analogue of oxetanocin A as a racemate in an almost non-stereoselective manner, but any antiviral activity was not mentioned.[6] Here, we wish to report the enantio- and diastereo-selective synthesis of homochiral COXT-A (**2a**) and COXT-G (**2b**) and their antiviral activities. The key feature of our synthetic route is the stereoselective and asymmetric [2 + 2] formation of a cyclobutane ring using a catalytic amount of a chiral titanium reagent.[7]

The chiral titanium reagent was prepared *in situ* by mixing dichlorodi-isopropoxytitanium and (2*S*,3*S*)-2,3-*O*-(1-phenylethylidene)-1,1,4,4-tetraphenylbutane-1,2,3,4-tetraol (**5**) derived from (−)-tartaric acid. The reaction of 3-[3-(methoxycarbonyl)acryloyl]-1,3-oxazolidin-2-one (**3**) and 1,1-bis(methylthio)ethylene (**4**) in the presence of 10 mol% of the above chiral titanium catalyst and molecular sieves 4Å in toluene–hexane at 0 °C gave (2*S*,3*S*)-3-methoxycarbonyl-1,1-bis(methylthio)-2-(2-oxo-oxazolidin-3-yl)carbonylcyclobutane (**6**) {$[\alpha]_D$ −11.1° (*c* 1.15, CH_2Cl_2)} in 83% yield and in >98% enantiomeric excess (Scheme 1).†‡

The cyclobutane thus obtained was converted to the diester (**7**) (96% yield) by treatment with dimethoxymagnesium in methanol. Lithium aluminum hydride reduction of the diester (**7**) afforded the diol (**8**) (99% yield).‡ Recrystallization of this compound from ethyl acetate–hexane gave the optically pure diol (**8**)‡ {$[\alpha]_D$ −32.0° (*c* 1.03, CH_2Cl_2)} in 94% yield, which was then converted to the corresponding silylether (**9**), using t-butyldiphenylsilyl chloride, in quantitative yield. Treatment of compound (**9**) with *N*-chlorosuccinimide (NCS)–silver nitrate according to the literature method[8] generated the cyclobutanone (**10**) in 93% yield. The treatment of (**10**) with lithium tri(t-butoxy)aluminum hydride in tetrahydrofuran (THF) at −78 °C to room temperature afforded the 1,2-*cis*-



Scheme 1. MS = molecular sieves.



Scheme 2. *Reagents and conditions*; i, $(MeO)_2Mg$/MeOH, 0 °C, 96%; ii, $LiAlH_4$/ether, 0 °C, 99%; iii, Bu^tPh_2SiCl, Et_3N, 4-dimethylaminopyridine/CH_2Cl_2, 100%; iv, NCS–$AgNO_3$/MeCN–H_2O, 93%; v, DIBAL/toluene, −78 °C, 82% (**11a**), 17% (**11b**); vi, benzoic acid, diethyl azodicarboxylate, Ph_3P/benzene, 97%, then DIBAL/toluene, −78 °C, 95%; vii, $MeSO_2Cl$, Et_3N/CH_2Cl_2, 100%.

(**11a**) and the 1,2-*trans*-cyclobutanol (**11b**)§ in 8.6% and 88% yields, respectively. However, the desired 1,2-*cis*-cyclobutanol (**11a**) was obtained diastereoselectively (82% isolated

† The [2 + 2] reaction using (2*R*,3*R*)-2,3-*O*-(1-phenylethylidene)-1,1,4,4-tetraphenylbutane-1,2,3,4-tetraol as a catalyst ligand gave (2*R*,3*R*)-3-methoxycarbonyl-1,1-bis(methylthio)-2-(2-oxo-oxazolidin-3-yl)carbonylcyclobutane (**6′**).[7] The physical data of the compound (**6**), except for the sign of the optical rotation, were identical with those of the compound (**6′**).

‡ The optical purity was determined by the 400 or 500 MHz ^{1}H NMR analysis of the bis-(*R*)-MTPA [MTPA = α-methoxy-α-(trifluoromethyl)phenylacetyl] ester of compound (**8**).[7] Two sets of the two singlet signals of thiomethyl groups were observed in the spectrum of the compound derived from the racemate. A pair of very small signals (<1%) originating from the antipode of the compound (**8**) was observed in the case of the chromatographically isolated product. The MTPA ester of the recrystallized compound (**8**) showed no signals originating from the antipode.

§ The configurations of these diastereoisomers were determined by comparison of the COSY and NOESY ^{1}H NMR spectra (400 MHz) of the corresponding benzoates. The 1,2-*trans*-cyclobutanol (**11b**) could readily be converted to the 1,2-*cis*-cyclobutanol (**11a**) by inversion of the C-1 hydroxy group, namely, by the Mitsunobu reaction[9] (97%) followed by reductive removal of the resulting benzoyl group with DIBAL (95%).

yield) by di-isobutylaluminium hydride (DIBAL) reduction. Treatment of the 1,2-*cis*-cyclobutanol (**11a**) with methanesulphonyl chloride and triethylamine gave the mesylate (**12**) in quantitative yield (Scheme 2).

The mesylate (**12**) was coupled with adenine with the aid of sodium hydride in *N,N*-dimethylformamide (DMF) at 140 °C to give the *N*-9 substituted adenine in 46% yield. Finally, deprotection (HCl/MeOH) of the adenine derivative furnished the optically pure carbocyclic oxetanocin A (**2a**)¶ {$[\alpha]_D$ −45.7° (*c* 1.00, pyridine)} in 74% yield.

Coupling of the mesylate (**12**) with 2-amino-6-(2-methoxy)ethoxypurine using lithium hydride in DMF (30% yield) followed by deprotection [HCl/MeOH at room temperature, then HCl (2 M) reflux] gave the pure carbocyclic oxetanocin G (**2b**)†† {$[\alpha]_D$ +25.4° [c 1.01 NaOH (0.1 M)]} in 79% yield.‡‡

Thus we accomplished the enantio- and diastereo-selective synthesis of carbocyclic oxetanocins (A and G) with configuration analogous to the natural oxetanocin A. Fifty per cent inhibitory concentrations (IC_{50}) against herpes simplex virus (HSV) types 1 and 2, human cytomegalovirus (HCMV),[4c] hepatitis B virus (HBV),[4b] and human immunodeficiency virus (HIV)[4a] in cell cultures were 1.6, 1.6, 12, 0.024, and 0.03 μg ml^{-1} for COXT-A (**2a**), and 0.047, 0.08, 0.4, 0.86, and 0.3 μg ml^{-1} for COXT-G (**2b**), respectively. These results indicate that COXT-A shows much higher (×350) activity against HBV than adenosine arabinoside and one tenth of the activity of azidothymidine as an anti-HIV. COXT-G is 2—3 times more active than acyclovir against HSVs and has comparative activity with gancyclovir against HCMV.

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¶ Recrystallized from MeOH–ether. UV λ_{max} (H_2O) nm: pH 1, 259; pH 7, 259; pH 13, 259. Fast atom bombardment FAB MS: calcd. for $[C_{11}H_{15}N_5O_2 + H]^+$: 250.1304. Found: 250.1305.

†† Recrystallized from water. UV λ_{max} (H_2O) nm: pH 1, 253, 277sh; pH 7, 253, 268sh; pH 13, 256sh. FAB MS: calcd. for $[C_{11}H_{15}N_5O_3 + H]^+$: 266.1253. Found: 266.1251.

‡‡ All compounds gave satisfactory analytical and/or spectral data. All indicated yields are isolated yields by column chromatography on silica gel and/or recrystallization. All of the reactions described in this paper were performed on a 1—50 g scale.

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