HIGHLY STEREOSELECTIVE SYNTHESIS OF CARBOCYCLIC ANALOGUES OF OXETANOCIN[1,2]

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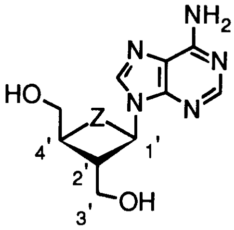
A highly stereoselective synthetic method of trans,trans-2,3-dihydroxymethylcyclobutylamine, a versatile precursor for carbocyclic oxetanosyl-N-glycosides, from 4-hydroxymethyl-2-pyridone has been elaborated. The method is applicable to the synthesis of either a variety of the carbocyclic oxetanosyl-N-glycosides or their cis,cis-isomers with complete stereoselection.

KEYWORDS carbocyclic oxetanocin; oxetanosyl-N-glycoside, 4-hydroxymethyl-2-pyridone; photopyridone; 2-azabicyclo[2.2.0]hexan-3-one; β-lactam cleavage; 2,3-dihydroxymethylcyclobutylamine

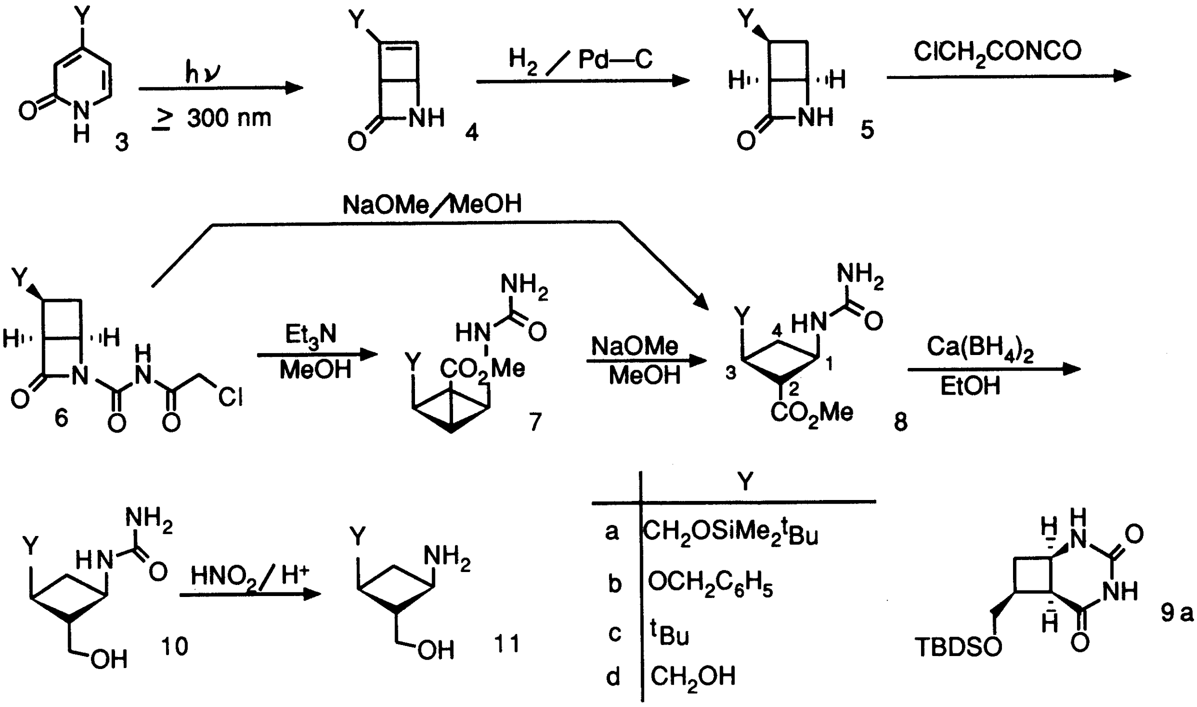
Oxetanocin (**1**: a novel oxetanosyl-N-glycoside) produced by a strain of *Bacillus megaterium*[3,4] is antiviral, antitumor, and antibacterial activities.[5] Since aristeromycin[6] and neplanocin[7] (the carbocyclic analogues of ribofuranosyl nucleosides) have shown significant biological activity, much attention has been focussed on the synthesis of carbocyclic analogues of this nucleoside. This paper reports the highly stereoselective synthesis of the carbocyclic oxetanocin (**2**) from 4-hydroxymethyl-2-pyridone[8] (**3d**), which is applicable to the synthesis not only of **2** and its derivatives but also of the so-far unknown pyrimidine counterparts.



1: Z=O
2: Z=CH2

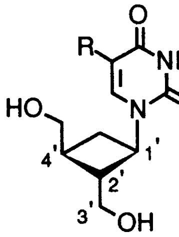
When 4-(*tert*-butyldimethylsilyloxymethyl)-2-pyridone[9] (**3a**) was irradiated by high-pressure mercury lamp (Pyrex filter), the photopyridone[10] (**4a**) was obtained in a satisfactory yield. Catalytic hydrogenation of **4a** with Pd-C occurred at the less hindered side (*exo*-side) to give the dihydro derivative (**5a**) as a sole product in quantitative yield. Treatment of the dihydro derivative (**5a**) with chloroacetyl isocyanate in benzene afforded the *N*-chloroacetylcarbamoyl derivative (**6a**), which in turn was treated with sodium methoxide in methanol[11] at 25°C for 16 h to give the ring-opened product[12] (**8a**) as the major product, together with a small amount of **9a** which was obviously formed before the inversion of the methoxycarbonyl group of the initially formed all *cis*-isomer (**7a**) (Table I). Reduction of **8a** with calcium borohydride in ethanol then afforded the *trans,trans*-cyclobutane (**10a**). Treatment of **10a** with nitrous acid in an acidic medium afforded the unprotected amine [**11d**: isolated as the triacetate (oil) in 42% yield].

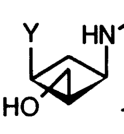
The products (**10a** and **11d**) thus obtained act as versatile intermediates for the synthesis of carbocyclic oxetanocin and other oxetanosyl-N-glycosides, as stated below. Thus, the elaboration of the 9-adenyl substituent of **11a** is accomplished by a known two step sequence[13] (the reaction of alkylamines with 5-amino-4,6-dichloropyrimidine,



	Y
a	$CH_2OSiMe_2{}^tBu$
b	$OCH_2C_6H_5$
c	${}^tBu$
d	CH_2OH

followed by treatment with triethyl orthoformate). Actually, Honjo *et al.*[14] have recently succeeded in synthesizing of **2** from appropriately protected **11d**. Further, since ureas are nice building blocks for a variety of uracils, as demonstrated in our recent work,[15] **10a** would serve as a precursor of carbocyclic oxetanosyl pyrimidine-type nucleosides (**12**).


12 R = H, CH$_3$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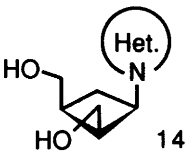
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Table I. Conversion of 2-Pyridones (**3**) to trans,trans-1,2,3-Trisubstituted Cyclobutanes (**10**) via **4**, **5**, **6**, and **8** [Mps in °C and Yields in (%)].

Compd.	**4**	**5**	**6**	**8**[a]	**10**
a	---	48-50 (50)[b]	oil (98)	74-76 (62)[c]	142-143 (90)
b	122-124[16] (96)	105-107 (89)[16]	70-71 (98)	123-125 (98)	125-127 (98)
c	62-64 (98)	58-60 (88)	70-72 (95)	126-127 (22)[d]	141-143 (66)

a) The yields correspond to those obtained when **6** was treated by NaOMe/MeOH at room temperature.
b) The overall yield from 4-(tert-butyldimethylsilyloxymethyl)-2-pyridone (**3a**).
c) The by-product (**9a**) was obtained in 24% yield.
d) Though the isomerization of **7** to **8** was completed within 1 d in **a** and **b**, the same inversion was much slower in **7c** and the latter was obtained in 48% yield under the same condition.

Added to high stereoselection which is superior to the previously reported method for **2**,$^{14)}$ the present method is applicable to the synthesis not only of **2**- and **12**-type compounds having a variety of substituents at the 4'-position (line 1), but also of the related N-glycosides having all the substituents on the cyclobutane ring in the cis-relationship: **13** and **14** (line 2). In the study along line 1, we have already assured that, when two other 2-pyridones (**3b**$^{16)}$ and **3c**$^{17)}$) were used as the starting materials, the corresponding all trans-cyclobutylamines (**10b** and **10c**) were obtained as the sole products, respectively. The result so far obtained is summarized in Table I.

As for the work along line 2, it is enough to mention that all cis-cyclobutylamine (e.g. **7b**: mp 138-140°C) was obtained as a sole product when **6b** was treated with triethylamine in methanol. As expected, by treatment of **7b** with sodium methoxide in methanol, **8b** was obtained as the sole product in almost quantitative yield. Reduction with calcium borohydride of **7b** afforded the corresponding all cis-isomer (**13b**).

The biological evaluation of the newly synthesized carbocyclic oxetanocin (**2**), the corresponding pyrimidine nucleosides (**12**), and their stereoisomers (e.g. **14**) will be reported separately in due course.

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9) Compound (**3a**: mp 126-127°C) was prepared from 4-hydroxymethyl-2-pyridone (**3d**) by treatment with tert-butyldimethylsilyl chloride and imidazole in DMF and used for the irradiation reaction (0.01M solution in acetonitrile with ice-salt cooling).
10) All new compounds were identified by either elemental analysis or by high-resolution mass spectra and the structures were supported by acceptable spectral data.
11) Removal of the chloroacetyl group in the related compounds under mild basic conditions has been reported recently: N. Katagiri, M. Muto, and C. Kaneko, Nucleic Acids Res., Symp. Ser., No. 21, 75 (1989).
12) The stereochemistries of **7** and **8** were differentiated from each other by the ^{1}H-NMR signals: the long-range coupling constants between H-2 and H-4 in **7** are ca. 4 Hz, while those of **8** are 0 Hz. The significant coupling in **7** is attributed to the W-configuration of these two protons of the puckered cyclobutane ring.
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