Tetrahedron Letters, Vol. 34, No. 47, pp. 7639-7640, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Zirconium-Mediated Ring Contraction: An Efficient Synthesis of Enantiomerically Pure Key Intermediate of Carbocyclic Oxetanocin

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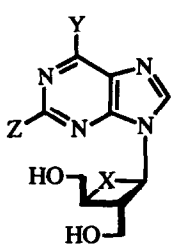
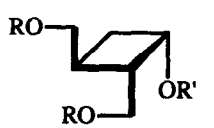
Abstract: *A key intermediate **3b** of carbocyclic oxetanocin analogues (COXTs) **2** was prepared from 4-vinylfuranoside derivative by zirconium-mediated ring contraction.*

Carbocyclic oxetanocin analogues (COXTs) **2** which have a cyclobutane moiety instead of an oxetane sugar portion of oxetanocin (**1**) has attracted much attention because of their potent antiviral activities.[1] For the syntheses of COXTs, preparation of the optically active cyclobutane derivative as a key intermediate through chiral synthesis, optical resolution, and/or enzymatic method has been reported.[1,2]



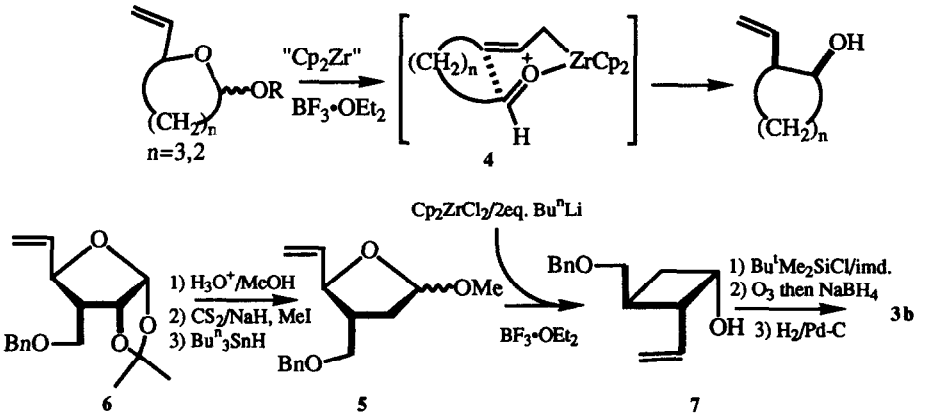
1 X=O, Y=NH_2, Z=H (Oxetanocin)
2 X=CH_2, Y=NH_2, Z=H (COXT-A)
X=CH_2, Y=OH, Z=OH (COXT-G)



3 **a** R=Bu^tPh_2Si, R'=H
b R=H, R'=Bu^tMe_2Si
c R=COPh, R'=H

During our studies on the chemistry of organozirconium compounds, we found that an efficient ring contraction of 5-vinylpyranoside or 4-vinylfuranoside derivatives by treating with zirconocene ("Cp_2Zr") equivalent in the presence of BF_3•OEt_2 proceeds stereoselectively through an intramolecular addition of (Z)-allylic zirconium of a cyclic oxocarbenium ion **4** to yield 1,2-cis-vinylcyclopentanol or 1,2-cis-vinylcyclobutanol derivatives in an optically pure form (Scheme 1).[3] In these transformations, an efficient formation of the 1,2-cis-vinylcyclobutanol derivative from 4-vinylfuranoside prompted us to examine a preparation of **3b** since the relative stereochemistry of the ring contraction product is ideally suited to the preparation of **3**. We describe herein an efficient synthesis of an optically pure **3c** by the zirconium-mediated ring contraction which we developed.

Scheme 1



2-Deoxy-4-vinylfuranoside **5** for the zirconium-mediated ring contraction can easily be prepared from the known furanose derivative **6**[4] in three steps (60 % from **6**); i) H_3O^+/MeOH, ii) CS_2/NaH, MeI, Et_2O reflux, iii) nBu_3SnH/toluene reflux. Reaction of **5** in the presence of BF_3•OEt_2 with "Cp_2Zr",[5] which was generated *in situ* from Cp_2ZrCl_2 and nBuLi (2 equimolar) in toluene at -78 °C~ambient temperature, gave a (1*S*,2*R*,3*S*)-2-vinyl-3-(benzyloxymethyl)cyclobutanol (**7**) in 64 % yield as we expected[6,7] [^{1}H-NMR ring protons ($CDCl_3$) δ; 4.39 (ddd, J=6.8, 6.5, 4.4 Hz, 1H), 2.95 (ddd, J=7.5, 6.8, 6.3 Hz, 1H), 2.60 (m, 1H), 2.17 (ddd, J=12.4, 6.8, 6.5 Hz, 1H), 2.01 (ddd, J=12.4, 9.3, 4.4 Hz, 1H), $[\alpha]_D$ +82.6° (c 1.31, $CHCl_3$)]. The subsequent conversion of **7** to **3b** was accomplished without any difficulties in three steps; i) TBDMSCl/imidazole/DMF (86 %), ii) O_3/CH_2Cl_2-2.5 % Py at -78 °C follwed by $NaBH_4$ reduction (66 %), iii) H_2/Pd-C in MeOH (97 %). Although all of the cyclobutanol derivatives were characterized by spectral data, the final confirmation was attained by converting **3b** to the known dibenzoate **3c**[8] and by comparing the ^{1}H-NMR spectral data and the specific rotation values. Thus we accomplished an efficient synthesis of the optically pure intermediate **3** of carbocyclic oxetanocin **2**. Further applications of the zirconium-mediated ring contraction to other vinyl sugar derivatives for the synthesis of biologically important compounds are being undertaken, which will be reported in due course.

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5) a) Negishi, E.; Cederbaum, F. K.; Takahashi, T. *Tetrahedron Lett.* **1986**, *27*, 2829-2832. b) Swanson, D. R.; Negishi, E. *Organometallics* **1991**, *10*, 825-826.
6) The structures of the new compounds were fully characterized by IR, NMR (^{1}H and ^{13}C) and HRMS.
7) The *R*-configuration of 3-benzyloxymethyl group of **5** is very important for the preparation of "natural" COXT in the zirconium-mediated ring contraction, because the relative stereochemistry between the newly formed chiral centers and the benzyloxymethyl group in the product **7** becomes trans . See also ref.3.
8) Bisacchi, G. S.; Braitman, A.; Cianci, C. W.; Clark, J. M.; Field, A. K.; Hagen, M. E.; Hockstein, D. R.; Malley, M. F.; Mitt, T.; Slusarchyk, W. A.; Sundeen, J. E.; Terry, B. J.; Tuomari, A. V.; Weaver, E. R.; Young, M. G.; Zahler, R. *J. Med. Chem.* **1991**, *34*, 1415-1421.

(Received in Japan 5 August 1993)