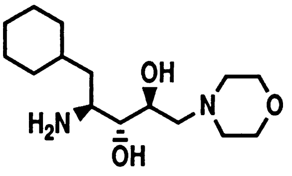
CHEMISTRY LETTERS, pp. 1709-1710, 1990.

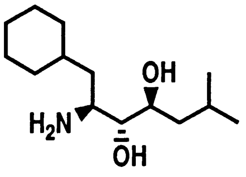
Novel Synthesis of (*2S, 3R, 4S*)-4-Amino-5-cyclohexyl-1-morpholino-2,3-pentanediol and (*2S, 3R, 4S*)-2-Amino-1-cyclohexyl-6-methyl-3,4-heptanediol, the C-Terminal Components of Renin Inhibitors

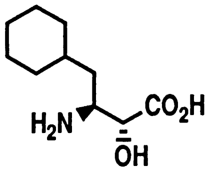
Yuko KOBAYASHI, Kazuhiko NAKATANI, Yoshio ITO,† and Shiro TERASHIMA*
Sagami Chemical Research Center, Nishi-Ohnuma, Sagamihara, Kanagawa 229

The title synthesis could be accomplished in a highly stereo-and regioselective manner by employing epoxide formation with inversion of configuration followed by epoxide opening with a nucleophile.

The renin inhibitors currently being developed as promising antihypertensive agents involve the title 1,2,3-aminodiols (**1** and **2**) as their C-terminal components.1,2) Previously, it was reported from this labolatory that the addition reaction of cyclohexylmethylmagnesium bromide with the imine (**5**) prepared from unnatural (*2S, 3S*)-tartaric acid *via* 4-O-benzyl-2,3-isopropylidene-D-threose (**4**), proceeded highly stereoselectively in the presence of cerium(III) chloride, affording the amine (**6**) as a sole product.3) The addition product (**6**) could be derived to (*2R, 3S*)-3-amino-4-cyclohexyl-2-hydroxybutyric acid (cyclohexylnorstatine) (**3**), the C-terminal component of another renin inhibitor, by removing the terminal one carbon unit. 3) We wish to report here that the same addition product (**6**) could be also elaborated to **1** and **2** in a highly stereo- and regioselective manner by employing epoxide formation with inversion of configuration followed by epoxide opening with a nucleophile.


1

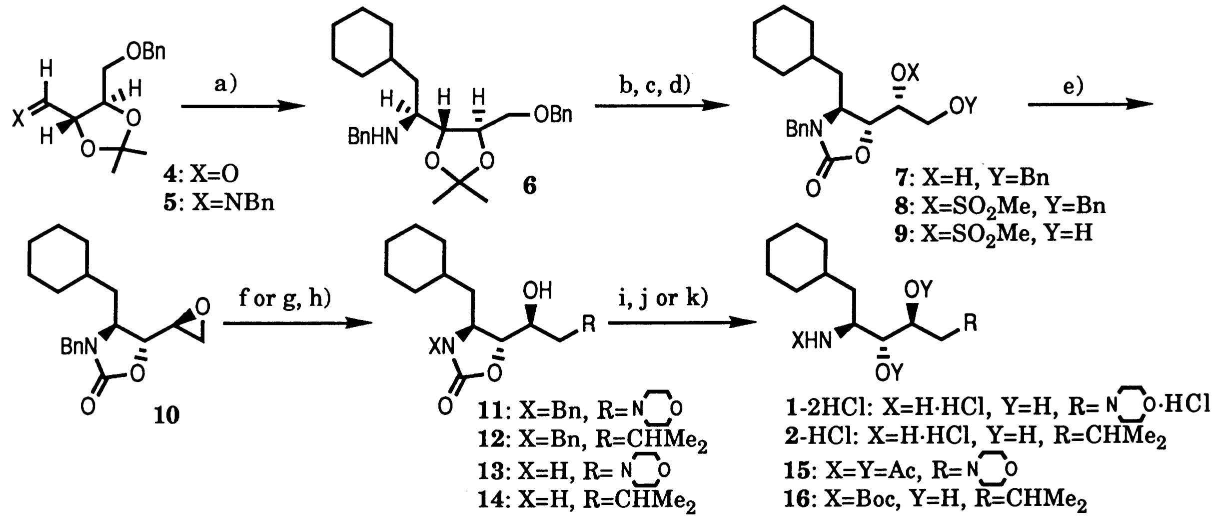

2


3

Thus, the oxazolidin-2-one (**7**), $[\alpha]_D^{20}$ -29.7° (c 1.25, $CHCl_3$), could be prepared from **4** *via* **5** and **6** in the same manner as previously reported.3) Mesylation of **7** followed by hydrogenolysis of the mesylate (**8**) gave the alcohol (**9**) as a colorless oil. Treatment of **9** with sodium methoxide afforded the oily epoxide (**10**) as a sole product, $[\alpha]_D^{20}$ -7.6° (c 0.706, $CHCl_3$). That the epoxide formation underwent in a highly stereoselective manner with inversion of configuration could be definitely established by the successful syntheses of **1** and **2** from **10** (*vide infra*). Reaction of **10** with morpholine effected the highly regioselective epoxide opening, giving rise to the alcohol (**11**) as a sole product, caramel, $[\alpha]_D^{20}$ -55.2° (c 0.782, $CHCl_3$). Similar highly regioselective epoxide opening could be also achieved by the reaction of **10** with isopropylmagnesium chloride in the presence of copper(I) iodide, giving the alcohol (**12**), caramel, $[\alpha]_D^{20}$ -35.0° (c 0.982, $CHCl_3$). Reductive removal of the N-benzyl groups present in **11** and **12** produced the unprotected oxazolidin-2-one derivatives (**13** and **14**), **13**: mp 173-174 °C and $[\alpha]_D^{20}$ -79.8° (c 0.694,

---

† Present address: Department of Chemistry, Faculty of Sciences, Kyushu University, Fukuoka 812.



a) c-$C_6H_{11}CH_2MgBr$ (5.0 equiv.)-$CeCl_3$ (5.0 equiv.) in Et_2O-THF, -30 °C, 2 h, then, rt, 12 h, 75% (see Ref. 3). b) i) $ClCO_2Me$-anhyd. K_2CO_3 in THF, 0 °C, 7 h ii) 80% aq. AcOH, 80 °C, 5 h iii) 10% KOH in MeOH, rt, 3.5 h, 90% (**7**) from **6**. c) $MeSO_2Cl$ (1.3 equiv.) in pyridine, 0 °C, 3 h, 96%. d) H_2 (1 atm)-20% $Pd(OH)_2/C$ in MeOH, rt, 2 d, 98%. e) NaOMe (8.3 equiv.) in THF, 0 °C, 0.5 h, 94%. f) morpholine (2.1 equiv.) in MeOH, rt, 1 d, 94% (**11**) from **10**. g) $Me_2CHMgCl$ (3.0 equiv.)-CuI (0.16 equiv.) in Et_2O, 0 °C, 1.5 h, 62% (**12**) from **10**. h) Na in Liq. NH_3, -78 °C, 2 h, 78% (**13**) from **11** or 51% (**14**) from **12**. i) 37% HCl, reflux, 3 d, quantitative yield (**1**-2HCl or **2**-HCl) from **13** or **14**. j) Ac_2O-pyridine, rt, 6.5 h, 99% (**15**) from **13** *via* **1**-2HCl. k) t-Boc_2O (2.0 equiv.)-Et_3N (3.0 equiv.) in $CHCl_3$, rt, 2 h, 84% (**16**) from **14** *via* **2**-HCl.

$CHCl_3$), and **14**: mp 162-162.5 °C and $[\alpha]_D^{20}$ -81.2° (c 0.739, $CHCl_3$). Subsequent acidic hydrolyses of **13** and **14** furnished **1** and **2** as their hydrochlorides (**1**-2HCl[4] and **2**-HCl). These hydrochlorides (**1**-2HCl and **2**-HCl) obtained both as a hydroscopic caramel were rigorously identified as their derivatives. Thus, acetylation of **1**-2HCl gave the corresponding triacetate (**15**) as a pale yellow caramel,[5] $[\alpha]_D^{20}$ -48.7° (c 0.986, $CHCl_3$). The N-t-butoxycarbonyl derivative (**16**) could be prepared from **2**-HCl by treating with di-t-butyl dicarbonate, mp 134-135 °C and $[\alpha]_D^{20}$ -67.4° (c 1.17, $CHCl_3$) [lit.,[2] mp 130-131 °C and $[\alpha]_D^{20}$ -64.91° (c 2.20, $CHCl_3$)]. Successful syntheses of **1**-2HCl and **2**-HCl from **10** definitely established the steric course of epoxide formation and the regiochemistries of epoxide opening.

The explored synthetic routes may further amplify the usefulness of the addition reaction of a Grignard reagent with an imine in the presence of cerium(III) chloride for the syntheses of renin inhibitor key intermediates.

References

1) **1**: M. Nakano, S. Atsuumi, Y. Koike, S. Tanaka, H. Funabashi, J. Hashimoto, and H. Morishima, *Tetrahedron Lett.*, **31**, 1569 (1990) and references therein.
2) **2**: J. R. Luly, C-N. Hsiao, N. BaMaung, and J. J. Plattner, *J. Org. Chem.*, **53**, 6109 (1988) and references therein.
3) T. Matsumoto, Y. Kobayashi, Y. Takemoto, Y. Ito, T. Kamijo, H. Harada, and S. Terashima, *Tetrahedron Lett.*, accepted for publication.
4) ^{13}C-NMR (D_2O) δ: 28.27, 28.31, 28.65, 35.17, 35.25, 35.63, 39.80, 51.93, 53.80, 56.24, 62.13, 66.28 (2xC), 67.98, 72.99. This spectrum was found to be very similar to that of **1** (free base) reported.[1]
5) ^1H-NMR ($CDCl_3$): 0.8-1.8 (13H, m, $C_6H_{11}CH_2$), 1.96, 2.05, 2.10 (3Hx3, 3s, $COCH_3$x3), 2.46 (1H, dd, J=13.2, 6.5 Hz, CHCHHN), 2.46 (4H, m, CH_2NCH_2), 2.60 (1H, dd, J=13.2, 5.8 Hz, CHCHHN), 3.65 (4H, 2t, J=each 4.6 Hz, CH_2OCH_2), 4.52 (1H, m, CHNHAc), 5.11 (1H, dd, J=6.0, 3.2 Hz, CHOAc), 5.34 (1H, d, J=10.1 Hz, NH). MS: m/z: 413 ($[M+1]^+$), 369, 293, 184, 100. IR ($CHCl_3$): 2940, 2860, 1740, 1680, 1372, 1116 cm^{-1}.

(Received July 6, 1990)