Pergamon

Tetrahedron: Asymmetry Vol. 5, No. 9, pp. 1649-1652, 1994
Elsevier Science Ltd
Printed in Great Britain
0957-4166/94 $7.00+0.00

0957-4166(94)00236-3

An Asymmetric Synthesis of (–)-Carbovir

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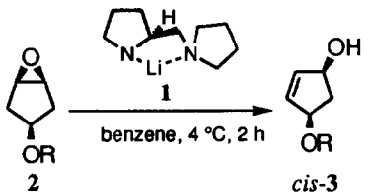
Abstract: Enantioselective deprotonation of *trans*-4-*t*-butyldimethylsiloxymethyl-1,2-epoxycyclopentane (*trans*-**4**) by a chiral lithium amide, lithium (*S*)-2-(pyrrolidin-1-ylmethyl)pyrrolidide (**1**), afforded (1*S*,4*S*)-*trans*-4-*t*-butyldimethylsiloxymethyl-2-cyclopenten-1-ol (*trans*-**7**) in 83 %ee. Alcohol *trans*-**7** was easily transformed to (–)-carbovir, an anti-HIV carbocyclic nucleoside.

We have been studying an enantioselective deprotonation of *meso*-epoxides by the use of a chiral lithium amide, lithium (*S*)-2-(pyrrolidin-1-ylmethyl)pyrrolidide (**1**),[1,2] and applied the reaction to the highly enantioselective synthesis of (1*S*,4*R*)-*cis*-4-*t*-butyldimethylsiloxy-2-cyclopenten-1-ol (*cis*-**3a**), (1*S*,4*R*)-*cis*-4-tetrahydropyranyloxy-2-cyclopenten-1-ol (*cis*-**3b**) and the corresponding *trans* isomers, useful synthetic intermediates for the synthesis of various cyclopentanoids.[2,3] In line with this work, we have started

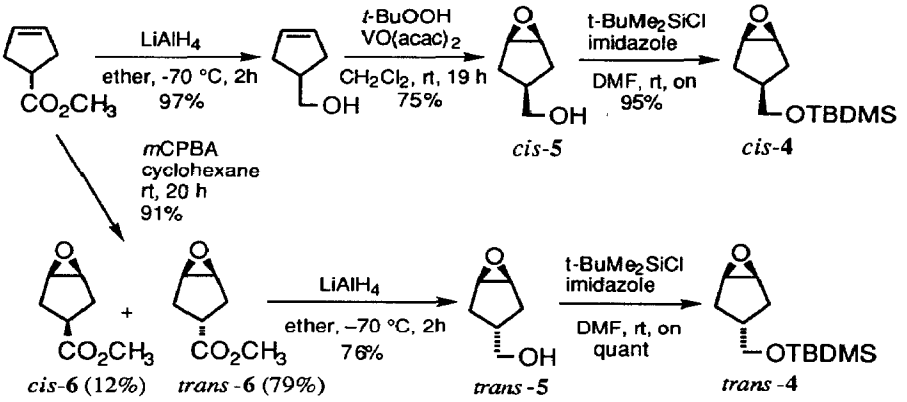


2 *cis*-**3**

a (R=TBDMS) 90% ee (92%)
b (R=THP) 89% ee (78%)

investigating an enantioselective deprotonation of *cis*- and *trans*-4-*t*-butyldimethylsiloxymethyl-1,2-epoxycyclopentane (**4**) and its synthetic application since the resulting alcohols seemed to be useful chiral synthetic intermediates. Recently an enantioselective transformation of *cis*-4-hydroxymethyl-1,2-epoxycyclopentane (*cis*-**5**) to chiral *cis*-4-hydroxymethyl-2-cyclopenten-1-ol by a chiral lithium amide was reported,[4] which prompted us to report our own results obtained by the reaction of both *cis*- and *trans*-**4** with **1** in this communication.[5]

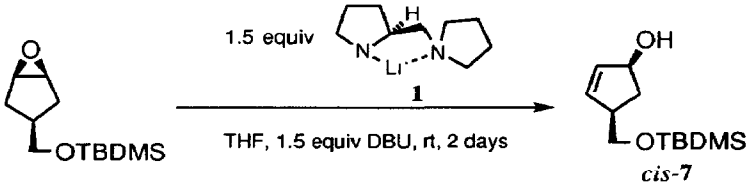
Preparations of *cis*- and *trans*-**4** were summarized in Scheme 1. Epoxide *cis*-**4**[6] was obtained by *t*-butyldimethylsilylation (*t*-butyldimethylchlorosilane (TBDMSCl), imidazole, DMF, rt, overnight, 95%) of *cis*-epoxy alcohol **5**, obtained by a similar method reported by others.[4] On the other hand, methyl *trans*-3,4-epoxycyclopentanecarboxylate (*trans*-**6**) was obtained predominantly by the epoxidation of methyl 3-cyclopentenecarboxylate with *m*-chloroperbenzoic acid (*m*CPBA) in cyclohexane (rt, 20 h, 91%, *trans* : *cis* = 87 : 13) and separated from the stereoisomer *cis*-**6** by silica gel column chromatography.[7] Ester *trans*-**6** was



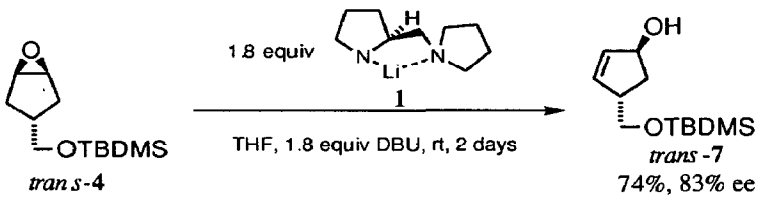
Scheme 1

reduced to alcohol *trans*-**5** ($LiAlH_4$, ether, −70 °C, 2 h, 76%) which was converted to *trans*-**4**[6] quantitatively (TBDMSCl, imidazole, DMF, rt, overnight).[8]

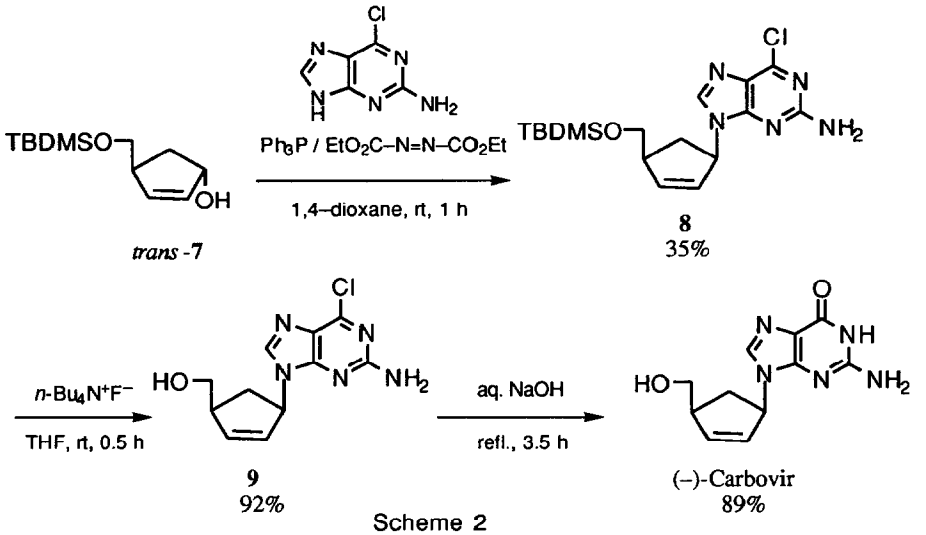
In the first place we examined the reaction of *cis*-**4** by using **1** because *cis*-4-*t*-butyldimethylsiloxy-1,2-epoxycyclopentane (**2a**) was found to give higher selectivity than the corresponding *trans* isomer.[2b] Alcohol *cis*-**7** was not obtained when the reaction was carried out in benzene, which was the best solvent in the transformation of **2** with **1**, even under higher reaction temperature (refluxing benzene). Alcohol *cis*-**7**[6] was obtained in 28% yield using 1.5 equiv of **1** when the reaction was carried out in THF for 2 days in the presence of 1,8-diazabicyclo[4.3.0]undec-7-en (DBU) (1.5 equiv). The ee of alcohol *cis*-**7** was 72% as determined after deriving to (*S*)-MTPA ester. It is interesting that *cis*-**7** was obtained by the reaction of *cis*-**4** and **1** although protected forms of *cis*-**5** were unreactive to LDA or other chiral lithium amide.[4]



Because steric hindrance of the substituent of epoxide *cis*-**4** was considered to be responsible for the low yield, we examined the reaction of *trans*-**4** with **1**, which was carried out by using 1.5 equiv of **1** in THF at room temperature for 2 days to yield *trans*-**7**[6] in 26% yield (11% recovery of *trans*-**4**) and 50% ee . The yield and selectivity were improved by using 1.8 equiv of **1** and 1.8 equiv of DBU as additive (74%, 83% ee). The ee of *trans*-**7** was determined after deriving to (*S*)-MTPA ester.



The hydroxyl group of alcohol *trans*-**7** was then replaced by 2-amino-6-chloropurine using triphenylphosphine and diethyl azodicarboxylate[9] in 1,4-dioxane to yield (–)-carbovir precursor **8**[6,10] (35%). (–)-Carbovir[6] was obtained by desilylation of **8** with tetrabutylammounium fluoride in THF (**9**,[6] 92%) followed by the treatment of **9** with aqueous sodium hydroxide (89%).[11] (Scheme 2)



Scheme 2

In addition to our previous results,[2] it has become apparent that the enantioselective deprotonation of *meso*-cyclopentene oxide derivatives by chiral lithium amide **1** is a useful method for the preparation of chiral substituted 2-cyclopenten-1-ol derivatives. Other applications of this method for the synthesis of chiral natural compounds are now under way in this laboratory.

Acknowledgment: Authors wish to express their thanks to Professor T. Tsunoda of Tokushima Bunri University for a kind gift of *N,N,N',N'*-tetramethylazodicarboxamide and valuable suggestion. One of the authors (M. A.) appreciates financial support from Ito Science Foundation and Kanagawa Academy of Science and Technology.

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3. The high selectivities of the reactions were fully confirmed by specific rotations of the series of the compounds,[2] ^{1}H-NMR measurements of the derivatives in the presence of Eu(hfbc)$_3$,[2] and ^{1}H-NMR measurements of the corresponding (*S*)-MTPA esters[12] although others reported lower selectivities.[13]
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6. The physical properties and spectroscopic data of *cis*-**4**, *trans*-**4**, *cis*-**7**, *trans*-**7**, **8**, **9**, and (–)-carbovir are as follows.

   cis-**4**: colorless oil. IR (neat) ν: 2900, 1470, 1260, 1000, 950, 840, 780 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.01 (s, 6H), 0.86 (s, 9H), 1.65–1.90 (m, 4H), 2.10–2.30 (m, 1H), 3.36 (d, 2H, J=7.9 Hz), 3.43 (s, 2H).

   trans-**4**[14] : colorless oil. IR (neat) ν: 2950, 1470, 1120, 1090, 1000, 840, 780 cm^{-1}. ^{1}H NMR (270

MHz, $CDCl_3$) δ: 0.01 (s, 6H), 0.86 (s, 9H), 1.45 (dd, 2H, J=8.9, 13.2 Hz), 1.84–2.10 (m, 1H), 2.04 (dd, 2H, J=7.2, 13.2 Hz), 3.44 (s, 2H), 3.52 (d, 2H, J=5.3 Hz).

cis-**7**: colorless oil. $[\alpha]_D^{23}$ +33.2 (*c* 0.78, $CHCl_3$). IR (neat) ν: 3400, 2950, 1480, 1280, 1090, 840, 780 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ: 0.01 (s, 6H), 0.84 (s, 9H), 1.48 (d, 2H, J=15.3 Hz), 2.10 –2.35 (m, 1H), 2.60–2.85 (m, 1H), 3.40–3.70 (m, 1H), 4.40–4.65 (m, 1H), 5.65–5.75 (m, 1H), 5.85–5.95 (m, 1H).

trans-**7**: colorless oil. $[\alpha]_D^{25}$ –134.8 (*c* 2.02, $CHCl_3$) (for 83% ee). IR (neat) ν: 3300, 2900, 1470, 1250, 1100, 830, 770 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ: 0.01 (s, 6H), 0.86 (s, 9H), 1.77 (ddd, 1H, J=14.1, 7.8, 3.3 Hz), 1.91 (ddd, 1H, J=14.1, 7.3, 4.6 Hz), 2.29 (br s, 1H), 2.85–3.10 (m, 1H), 3.46 (ddd, 2H, J=24.3, 9.6, 6.5 Hz), 4.78–4.92 (m, 1H), 5.85 (dt, 1H, J=5.6, 2.0 Hz), 5.94 (dd, 1H, J=5.6, 1.6 Hz). ^{13}C NMR (67.94 MHz, $CDCl_3$) δ: 136.9, 134.2, 76.9, 66.7, 47.3, 36.8, 25.8, 18.2, –5.4.

8: mp 124–127 °C. $[\alpha]_D^{22}$ –77.0 (*c* 1.01, $CHCl_3$). IR (KBr) ν: 3375, 3340, 3215, 2960, 2940, 2900, 2870, 1650, 1610, 1565, 1475, 1125, 840, 785 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ: 0.01 (s, 6H), 0.84 (s, 9H), 1.63 (dt, 1H, J=13.9, 6.3 Hz), 2.71 (dt, 1H, J=13.9, 8.7 Hz), 2.85–3.05 (m, 1H), 3.57 (dd, 1H, J=10.1, 5.4 Hz), 3.67 (dd, 1H, J=10.1, 5.0 Hz), 5.35 (br s, 2H), 5.45–5.60 (m, 1H), 5.78 (dt, 1H, J=5.6, 2.0 Hz), 6.12 (dt, 1H, J=5.6, 2.0 Hz), 7.82 (s, 1H). ^{13}C NMR (67.94 MHz, $CDCl_3$) δ: 159.0, 153.4, 151.0, 140.8, 139.3, 129.1, 125.4, 65.4, 59.3, 47.8, 34.4, 25.9, 18.4, –5.4.

9: mp 150–153 °C (lit.[15] 145-147 °C). $[\alpha]_D^{23}$ –83.8 (*c* 0.41, CH_3OH) (lit.[11c] $[\alpha]_D^{24}$ –75 (*c* 0.9, CH_3OH)). IR (KBr) ν: 3450, 3330, 3215, 3090, 1635, 1615, 1580, 1465, 1410, 1210, 1055, 925, 785 cm^{-1}. ^1H NMR (270 MHz, DMSO-d_6) δ: 1.64 (dt, 1H, J=13.9, 5.4 Hz), 2.63 (dt, 1H, J=13.9, 8.7 Hz), 2.80–2.97 (m, 1H), 3.45 (t, 2H, J=5.4 Hz), 4.73 (t, 1H, J=5.3 Hz), 5.35–5.55 (m, 1H), 5.91 (dt, 1H, J=5.6, 2.1 Hz), 6.15 (dt, 1H, J=5.6, 2.0 Hz), 6.91 (br s, 2H), 8.04 (s, 1H).

(–)-Carbovir: mp >235 °C (decomp.) (lit.[11b] mp 278-283 °C (decomp)). $[\alpha]_D^{21}$ –54.6 (*c* 0.22, CH_3OH) (lit.[11b] $[\alpha]_D^{23}$ –67 (*c* 1.0, CH_3OH)). IR (KBr) ν: 3320, 3220, 2950, 2880, 1690, 1630, 1600, 1535, 1485, 1410, 1380, 1180, 1035, 780 cm^{-1}. ^1H NMR (270 MHz, DMSO-d_6) δ: 1.56 (dt, 1H, J=14.0, 5.8 Hz), 2.58 (dt, 1H, J=13.4, 8.8 Hz), 2.78–2.95 (m, 1H), 3.43 (t, 2H, J=5.5 Hz), 4.73 (t, 1H, J=5.5 Hz), 5.25–5.50 (m, 1H), 5.80–5.95 (m, 1H), 6.05–6.20 (m, 1H), 6.44 (br s, 2H), 7.58 (s, 1H), 10.54 (br s, 1H).

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(*Received in Japan* 1 *July* 1994; *accepted* 1 *August* 1994)