February 1998 *Chem. Pharm. Bull.* **46**(2) 335—336 (1998)

Enantioselective [2,3] Sigmatropic Rearrangement of α-Propargyloxyacetic Acids Mediated by BuLi–(−)-Sparteine Complex

Shino MANABE[1]

Faculty of Pharmaceutical Sciences, University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113, Japan.
Received July 14, 1997; accepted October 22, 1997

The [2,3] sigmatropic rearrangement of α-propargyloxyacetic acids was achieved by the use of BuLi–(−)-sparteine complex in toluene. BuLi–chiral ligand complexes are stronger bases than lithium amides, so they are expected to be good mediators of this reaction.

Key words BuLi–(−)-sparteine complex; chiral allenylalcohol; α-propargyloxy acetic acid; enantioselective [2,3]-sigmatropic rearrangement

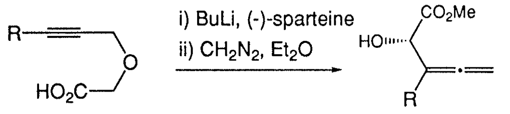
The [2,3] sigmatropic rearrangement is a highly useful reaction in synthetic organic chemistry, not only because it gives highly functionalized derivatives, which are expected to be key intermediates in the synthesis of natural products, but also because it is a powerful tool to control the stereochemistry of acyclic molecules.[2] Diastereoselective [2,3] sigmatropic rearrangements of substrates containing chiral substituents have been extensively investigated.[3] However, there are only a few reports of enantioselective versions of this reaction.

In 1988, Marshall and Lebreton reported the first example of the enantioselective reaction of a 13-membered cyclic propargyl ether with chiral lithium amide, and the product, which is a precursor of cembranoid, was obtained in 70% ee.[4] But in the same report, they noted that the enantioselective reaction of acyclic molecules was completely unsuccessful with the same lithium amide. In 1992, Marshall and Wang reported the enantioselective rearrangement of acyclic α-propargyloxyacetic acids induced by the same chiral lithium amide.[5] However, the use of lithium amides for this reaction may not be appropriate, because they are insufficiently basic, especially in the case of substrates such as alkenyl benzyl ethers, bis (alkenyl) ethers, and bis (propargyl) ethers, which are typical substrates of this reaction.[6] So it is necessary to develop a chiral strong base to achieve the enantioselective reaction.

It is expected that organolithium–chiral ligand complex, which is a stronger base than lithium amide, would be a suitable mediator of this reaction. Actually, *sec*-BuLi–(−)-sparteine complex has been reported by Hoppe *et al.* and Kerrick and Beak independently to be a good chiral base to make dipole-stabilized carbanions.[7] Here, the author shows that the enantioselective [2,3] sigmatropic rearrangement of α-propargyloxyacetic acids is also possible with BuLi–(−)-sparteine complex.

Representative results are shown in Table 1. Enantiomeric excess (ee) values and absolute configurations of products were determined by optical rotation measurements.[5] It was found that a proper choice of solvent, *i.e.* toluene, is important for realizing enantioselectivity (run 1). In tetrahydrofuran (THF) and ether, the ee of the products were low (runs 2, 4). The BuLi–(−)-sparteine complex was not soluble in hexane at −78 °C, so the yield

Table 1. Results of the Reaction

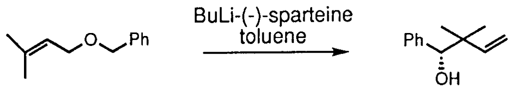


1a-1c
a = n-C_7H_{15}
b = iso-Bu
c = iso-Pr

2a-2c
a = n-C_7H_{15}
b = iso-Bu
c = iso-Pr

Run	Substrate	R	Solvent	Temp.	Yield (%)	ee (%)	Recovery of **1**[a]
1	**1a**	n-C_7H_{15}	Toluene	−78 °C	34	42	31
2	**1a**	n-C_2H_{15}	Ether	−78 °C	19	14	35
3	**1a**	n-C_7H_{15}	Hexane	−78 °C	25	14	32
4	**1a**	n-C_7H_{15}	THF	−78 °C	50	5	38
5	**1a**	n-C_7H_{15}	Toluene	−40 °C	40	34	23
6	**1a**	n-C_7H_{15}	Toluene	−20 °C	37	28	29
7	**1a**	n-C_7H_{15}	Toluene[b]	−78 °C	48	35	14
8	**1a**	n-C_7H_{15}	Toluene[c]	−78 °C	36	27	23
9	**1a**	n-C_7H_{15}	Toluene[d]	−78 °C	35	48	38
10	**1b**	iso-Bu	Toluene	−78 °C	36	40	63
11	**1c**	iso-Pr	Toluene	−78 °C	44	42	24

a) **1** was recovered as the methyl ester. *b*) 4.5 eq of (−)-sparteine was used. *c*) *sec*-BuLi was used. *d*) 35 ml of toluene was used.



3

4

70%, 19%ee

Chart 1

and ee were low (run 3). The reactions stopped after *ca.* 50% of the starting materials had been consumed for some unknown reason. Yields were not improved, when the reactions were carried out at higher temperature (runs 5, 6). The starting materials were recovered as the corresponding methyl esters. Interestingly, *sec*-BuLi–(−)-sparteine complex gave a lower ee in this case (run 8). In a diluted condition, the highest ee was observed (run 9). The nature of the substituent of the triple bond did not affect the ee of the products (runs 10, 11).

The mechanism of the asymmetric induction is not clear at this point. The two limiting mechanisms which could account for the observed enantioselectivities are as follows: 1) the BuLi–chiral ligand complex removes the prochiral proton, and the chirality of the generated sp^3 carbanion is transferred to the new chiral center (deprotonation mechanism). 2) (−)-sparteine coordinates to the Li atom of the enolate of the carboxylic acid, and asymmetric induction occurs by differentiation of sp^2 plane of the enolate (enolate mechanism).

In conclusion, BuLi–(−)-sparteine complex is effective in the enantioselective [2,3] sigmatropic rearrangement of α-propargyloxyacetic acids. BuLi–chiral ligand systems are expected to be applicable to a variety of reactions as a chiral base.[8]

Experimental

Spectra reported herein were recorded on a JASCO Report-100 infrared spectrometer, a JEOL JNM-EX-270 FT NMR system with tetramethylsilane as an internal standard, a JEOL JMS-01 SG-Z, DX-303, and a SX-102 mass spectrometer. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. Silica gel (Fuji Davison BW-200) was used for column chromatography.

Methyl (*S*)-2-Hydroxy-3-heptyl-3,4-pentadienoate [(*S*)-2a] (Run 1) (−)-Sparteine (516 mg, 2.20 mmol) in toluene (1 ml) was added dropwise to a solution of BuLi (1.4 ml, 1.60 N hexane, 2.2 mmol) in toluene (2 ml) at −78 °C under an Ar atmosphere. The flask was rinsed with toluene (1 ml). After 10 min, the acid **1a** (212 mg, 1.0 mmol) in toluene (1 ml) was added to the resulting pale yellow solution at −78 °C. The flask was rinsed with toluene (1 ml). The mixture was stirred at −78 °C for 5 h. The reaction was quenched with aqueous 10% HCl, and the aqueous layer was extracted with CH_2Cl_2. The combined layer was dried over Na_2SO_4, and the solvent was removed *in vacuo*. The crude residue was dissolved in ether, and excess CH_2N_2 in ether was added at 0 °C. The mixture was stirred until TLC showed no trace of the acids. The excess CH_2N_2 was decomposed by adding acetic acid. After evaporation, the crude mixture was purified by silica gel column chromatography (hexane : ether 4 : 1) to afford **2a** (77.0 mg, 34%) as a colorless oil. ^{1}H-NMR (in $CDCl_3$): δ 4.90—4.87 (m, 2H), 4.58 (d, J=7.6 Hz, 1H), 3.78 (s, 3H), 2.88 (d, J=7.6 Hz, 1H, D_2O-exchangeable), 2.1—1.9 (m, 2H), 1.4—1.2 (m, 10H), 0.86 (t, J=6.8 Hz, 3H). IR (neat): 3500, 2950—2850, 1950, 1740. $[\alpha]_{\mathrm{D}}^{25}$ +28° (c=1.72, $CHCl_3$).[5]

Methyl (2-Decynyloxy)acetate Recovery of starting material as the methyl ester. ^{1}H-NMR (in $CDCl_3$): δ 4.29 (t, J=2.0 Hz, 2H), 4.20 (s, 2H), 3.77 (d, 3H), 2.3—2.1 (m, 2H), 1.6—1.2 (m, 10H), 0.89 (t, J=6.9 Hz, 3H). IR (neat): 2950—2850, 1750.

Methyl (*S*)-2-Hydroxy-3-(2-methylpropyl)-3,4-pentadienoate [(*S*)-2b] (Run 10) By means of the above procedure, the alcohol **2b** (71.0 mg, 36%) was obtained as a colorless oil. ^{1}H-NMR (in $CDCl_3$): δ 4.88 (m, 2H), 4.56 (d, J=7.7 Hz, 1H), 3.77 (s, 3H), 2.86 (d, J=7.7 Hz, 1H, D_2O-exchangeable), 1.95—1.83 (m, 2H), 1.8—1.7 (m, 1H), 0.90 (d, J=6.5 Hz, 3H), 0.89 (d, J=6.5 Hz, 3H). IR (neat): 3500, 1950, 1740. $[\alpha]_{\mathrm{D}}^{25}$ +28° (c=0.98, $CHCl_3$).[5]

Methyl (*S*)-2-Hydroxy-3-isopropyl-3,4-pentadienoate [(*S*)-2c](Run 11) By means of the above procedure, the alcohol **2c** (74.9 mg, 44%) was obtained as a colorless oil. ^{1}H-NMR (in $CDCl_3$): δ 4.91 (m, 2H), 4.63 (d, J=8.1 Hz, 1H), 3.77 (s, 3H), 2.83 (d, J=8.1 Hz, 1H, D_2O-exchangeable), 2.32 (m, 1H), 1.06 (d, J=6.6 Hz, 3H), 1.04 (d, J=6.6 Hz, 3H). IR (neat): 3500, 1960, 1740. $[\alpha]_{\mathrm{D}}^{25}$ +21° (c=1.09, $CHCl_3$).[5]

Acknowledgements The author would like to thank Professor Kenji Koga for helpful discussions.

References and Notes

1) Present address: *The Institute of Physical and Chemical Research (RIKEN), Hirosawa, Wako-shi, Saitama 351-01, Japan.*
2) For recent reviews; *a*) Nakai T., Mikami K., "Organic Reactions," Vol. 46, John & Wiley and Sons, Inc.; New York, 1994, pp. 105—210; *b*) Marshall J. A., "Comprehensive Organic Synthesis," Vol. 3, ed. by Trost B. M., Fleming I., Pergamon, London, 1991, pp. 975—1014; *c*) Brückner R., "Comprehensive Organic Synthesis," Vol. 6, ed. by Trost B. M.; Fleming, I., Pergamon, London, 1991, pp. 873—908.
3) *a*) Mikami K., Takahashi O., Kasuga T., Nakai, T., *Chem. Lett.*, **1985**, 1729—1732; Mikami K., Fujimoto K., Kasuga T., Nakai T., *Tetrahedron Lett.*, **25**, 6011—6014 (1984); Takahashi O., Mikami K., Nakai T., *Chem. Lett.*, **1987**, 69—72; *b*) Enders D., Backhaus D., Runsink J., *Angew. Chem. Int. Ed. Engl.*, **33**, 2098—2100 (1994); Enders D., Backhaus D., *Synlett*, **1995**, 631—632.
4) Marshall J. A., Lebreton J., *J. Am. Chem. Soc.*, **110**, 2925—2931 (1988).
5) Marshall J. A., Wang X., *J. Org. Chem.*, **57**, 2747—2750 (1992).
6) The [2,3] sigmatropic rearrangement of the benzyl prenyl ether **3** mediated by lithiated bis[(*S*,*S*)-1-phenylethylamine] did not proceed in THF at −78 °C. The starting material **3** was recovered in 92% yield. The same reaction proceeded at 0 °C in 81% yield, but the ee of the product was 0%.
7) *a*) Kerrick S. T., Beak P., *J. Am. Chem. Soc.*, **113**, 9708—9710 (1991); *b*) Hoppe D., Carstens A., Krämer T., *Angew. Chem. Int. Ed. Engl.*, **29**, 1424—1425 (1990).
8) *a*) The [2,3] sigmatropic rearrangement of benzyl prenyl ether **3** mediated by BuLi–(−)-sparteine complex in toluene at −78 °C gave the corresponding product **4** in 70% yield, 19% ee (Chart 1); *b*) Application of BuLi–chiral ligand complex to enantioselective [2,3] sigmatropic rearrangement; Manabe S., *Chem. Commun.*, 737—738 (1997).