Pergamon

Tetrahedron Letters, Vol. 37, No. 49, pp. 8895-8898, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)02077-1

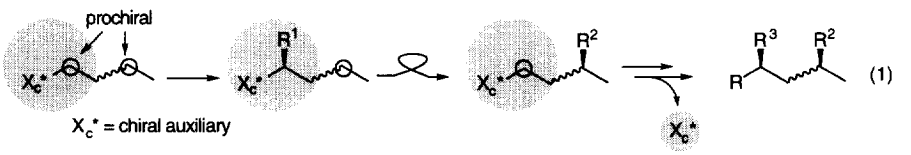
Chiral Dienolate Chemistry in Remote Asymmetric Induction: The Allylation / Cope Rearrangement Sequence Leading to γ-Chiral α,β-Unsaturated Acid Derivatives

Katsuhiko Tomooka, Atsushi Nagasawa, Shih-Yi Wei, and Takeshi Nakai*

Department of Chemical Technology, Tokyo Institute of Technology, Meguro-ku, Tokyo 152, Japan

Abstract: *The allylation of the dienolate derived from the chiral α, β- or β, γ-unsaturated imide followed by the Cope rearrangement is shown to effect the net remote asymmetric induction to create a new chirality of either configuration at the γ-position in high % de. The utility of this approach is shown in the asymmetric synthesis of the C6 side chain of zaragozic acid A.* Copyright © 1996 Elsevier Science Ltd

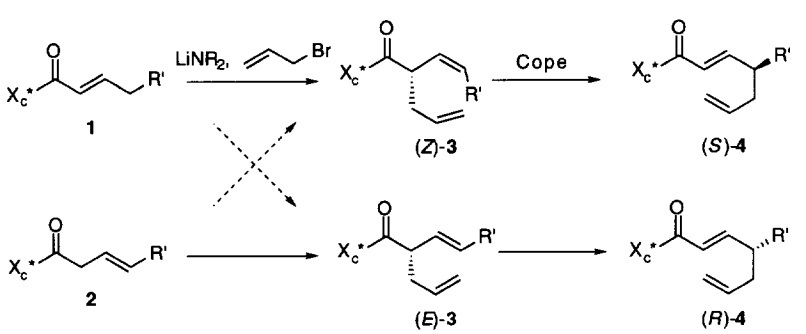
While the chiral auxiliary-based asymmetric induction constitutes the underlying principle most often utilized for asymmetric synthesis,[1] the asymmetric induction at a position beyond the asymmetric environment imparted by the chiral auxiliary is, of course, extremely difficult. Conceptually, however, this problem could be solved by the proper combination in tandem of an asymmetric induction process within the asymmetric environment with an asymmetric transmission process to effect the net remote asymmetric induction (eq 1).



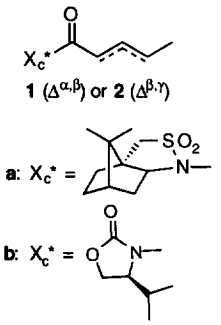
(1)

To realize this concept, we designed a general synthetic approach which relies upon the chiral dienolate chemistry for the asymmetric induction followed by the sigmatropic process for the asymmetric transmission. Disclosed herein is the realization of such approach in which the asymmetric allylation of the dienolate derived from the chiral α,β- (**1**) or β,γ-unsaturated imide (**2**) is combined with the Cope rearrangement, thus creating a new chiral center at the γ-position (Scheme 1).[2] The key to the success is the efficient cooperation of the high % de and the high *E* or *Z* selectivity in the initial process, and the efficient asymmetric transmission in the subsequent process. A particularly notable feature of this approach is that either configuration can be created at the γ-position from the same auxiliary by virtue of the *E* / *Z* control in the dienolate reaction.

Scheme 1



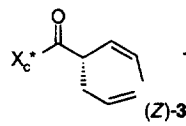
Inspired by the pioneering works of Krebs[3a] and Kende[3b] on the chemistry of dienolates derived from the α,β-unsaturated ethyl esters, we first examined the diastereoselectivity and *E*/*Z* selectivity in the allylation of the chiral dienolates derived from the chiral (*E*)-α,β- (**1**) and (*E*)-β,γ-unsaturated imides (**2**)[4] with various chiral auxiliaries (eq 2). Significantly enough, the allylation of the lithium dienolate derived from **1a** (with Oppolzer's chiral auxiliary[1b]) was found to provide a synthetically useful level of *Z* selectivity along with an extremely high % de to give (*Z*)-**3a**[5] as the main product. In contrast, a similar reaction of **2a** afforded (*E*)-**3a**[5] with complete retention of the *E* geometry and in a comparably high % de. The senses of geometrical selection thus observed are consistent with those reported for the achiral dienolates,[3] although the mechanistic origins are still unclear. Unfortunately, similar reactions of **1b** and **2b** (with Evans' chiral auxiliary[1a]) resulted in considerably lowered % de's, while the *E* or *Z* selectivity was comparably high.[6]



1 ($\Delta^{\alpha,\beta}$) or 2 ($\Delta^{\beta,\gamma}$)

LHMDS, 

THF, HMPA, -78 °C



(*Z*)-3 + (*E*)-3 (2)

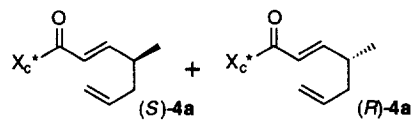
a: X_c^* =

b: X_c^* =

Imide	Yield (%)	(*Z*)-3 : (*E*)-3	% de of major product
1a	98	78 : 22 (88 : 12)[a]	>99
1b	85	86 : 14	49
2a	87	<1 : >99	>99
2b	85	1 : 99	48

[a]After recrystallization from hexane.

With the two stereoisomers (*Z*)- and (*E*)-**3a** in hand, our effort was directed to the asymmetric transmission via the Cope rearrangements (eq 3). The thermolysis of (*Z*)-**3a** (88% *Z*) in naphthalene at 220 ℃ was found to afford a mixture of (*S*)-and (*R*)-**4a** in the ratio of 85 : 15, respectively.[7] In contrast, the thermolysis of (*E*)-**3a** (>99% *E*) under the same conditions afforded (*R*)-**4a** as the sole product.[7] The observed senses of the asymmetric transmission might be visualized by the chair-like transition states $\mathbf{T}_1$ and $\mathbf{T}_2$ where the bulky imide moiety occupies preferentially in the sterically more favorable pseudo-equatorial orientation to end up the exclusive formation of the *E* geometry in **4a**. Overall, the asymmetric allylation / Cope sequence of (*E*)-**1a** or (*E*)-**2a** permits easy access to either γ-(*S*)- or -(*R*)-configurated α,β-unsaturated acid derivatives, a type of compound which is often found in natural products but is otherwise difficult to obtain in enantio-enriched forms.

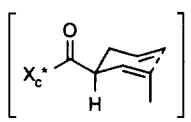
(*Z*)- or (*E*)-**3a** $\xrightarrow{\Delta}$  (3)

(*S*)-**4a** (*R*)-**4a**

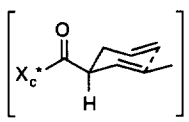
(*Z*)-**3a** (>99% de, 88% *Z*) 85 : 15 (96 : 4)[a] (94%)

(*E*)-**3a** (>99% de, >99% *E*) <1 : >99 (83%)

[a]After recrystallization from cyclohexane.



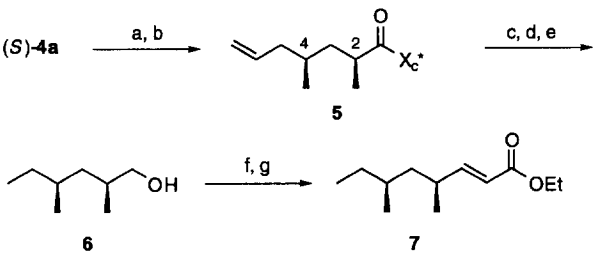
$\mathbf{T}_1 \rightarrow$ (*S*)-**4a**



$\mathbf{T}_2 \rightarrow$ (*R*)-**4a**

As can be imagined by eq 1, the present approach can be extended to a methodology for 1,3-remote stereocontrol,[8] since the resulting γ-chiral product is well suited for introducing another chiral center at the α-position. In order to demonstrate the potential of this methodology, we carried out the asymmetric synthesis of the C6 side chain of zaragozic acid A (**7**)[9] from (*S*)-**4a** obtained above (Scheme 2). Thus, (*S*)-**4a** (92% de after recrystallization) was subjected to the hydride reduction on the α,β-double bond with L-selectride followed by methylation of the chiral enolate of the resulting amide which gave the α,γ-dimethyl imide **5** in 92% de.[10] The stereochemistry of (2*S*, 4*S*)-**5** was confirmed by X-ray crystallography.[11] The standard three-step sequence of **5** afforded (2*S*, 4*S*)-dimethylhexan-1-ol (**6**).[12] Oxidation of **6** to the aldehyde followed by the Horner-Wittig reaction furnished the desired side chain **7** in 96% *syn* and >99% ee.[13] The overall sequence outlined here should represent a general approach to 1,3-remote stereocontrol.

Scheme 2



(a) L-Selectride, THF, -78 °C; (b) LHMDS, MeI, THF, -78 °C (two steps 68%); (c) O_3, MeOH / $NaBH_4$, -78 °C→rt; (d) Ts_2O, Et_3N, DMAP, CH_2Cl_2, rt (two steps 76%); (e) $LiBEt_3H$, THF, -78 °C (85%); (f) TPAP, NMO, MS 4A, CH_2Cl_2, rt; (g) $(EtO)_2POCH_2CO_2Et$, NaH, THF, rt (two steps 94%).

In summary, we have developed a general synthetic approach to the remote asymmetric induction which involves the asymmetric allylation of the chiral dienolates of the α,β- or β,γ-unsaturated imides and the Cope rearrangement to afford the γ-chiral-α,β-unsaturated acid derivatives in a highly stereocontrolled fashion. The applicability of the present approach to 1,3-remote stereocontrol has been demonstrated by the asymmetric synthesis of the C6 side chain of zaragozic acid A. Further works along the synthetic concept presented in this study is in progress.[14]

Acknowledgment: This work is partially supported by a Grant-in Aid for Scientific Research (Type B) from the Ministry of Education, Science, and Culture, Japan.

References and Notes

1. Reviews: (a) Evans, D. A.; Takacs, J. M.; McGee, L. R.; Ennis, M. D.; Mathre, D. J.; Bartroli, J. *Pure Appl. Chem.* **1981**, *53*, 1109-1127. Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 23-32. (b) Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969-2004.
2. This work was presented at the 69th Annual Meeting of the Chemical Society of Japan, Kyoto, 1995, 1H101. After the completion of this work, a conceptually similar but operationally different work has recently been reported by the Merck Frosst group: Black, W. C.; Giroux, A.; Greidanus, G. *Tetrahedron Lett.* **1996**, *37*, 4471-4474.
3. (a) Krebs, E.-P. *Helv. Chim. Acta* **1981**, *64*, 1023-1025. (b) Kende, A. S.; Toder, B. H. *J. Org. Chem.* **1982**, *47*, 163-167. (c) Cameron, D. W.; Looney, M. G.; Pattermann, J. A. *Tetrahedron Lett.* **1995**, *36*, 7555-7558. For mechanistic discussion: (d) Galatsis, P.; Manwell, J. J.; Millan, S. D. *Tetrahedron Lett.* **1996**, *37*, 5261-5264.

4. Imides **1** and **2** were prepared from (*E*)-2- and (*E*)-3-pentenoyl chloride, respectively, via reactions with (2*S*)-bornane-10,2-sultam or (4*S*)-isopropyl-2-oxazolidinone according to the reported procedures: Oppolzer, W.; Blagg, J.; Rodriguez, I.; Walther, E. *J. Am. Chem. Soc.* **1990**, *112*, 2767-2772; Gage, J. R.; Evans, D. A. *Org. Synth. Coll.* **1993**, *VIII*, 339-343.
5. The geometric and diastereomeric purity of **3a** were determined by ^{1}H NMR ($CDCl_3$): the δ value (ppm) of α-CH, 3.70-3.80 (m) for (*E*, *S*)-**3a**, 4.08 (dddd, *J*=9.3, 8.4, 6.0, 0.9 Hz) for (*Z*, *R*)-**3a**, and 4.13 (dddd, *J*=9.3, 7.1, 7.1, 0.9 Hz) for (*Z*, *S*)-**3a**.
6. The geometric and diastereomeric purity were determined by capillary GC (PEG 20M, 25m).
7. The diastereomers of **4a** are distinguishable by ^{13}C NMR ($CDCl_3$): the δ value (ppm) of γ-CH_3, 18.57 for (*S*)-**4a** and 18.72 for (*R*)-**4a**.
8. Selected recent examples of 1,3-remote stereocontrol: (a) Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1996**, *37*, 1081-1084. (b) White, J. D.; Johnson, A. T. *J. Org. Chem.* **1994**, *59*, 3347-3358. (c) Ishiwata, H.; Sone, H.; Kigoshi, H.; Yamada, K. *J. Org. Chem.* **1994**, *59*, 4712-4713. (d) Nagao, Y.; Inoue, T.; Hashimoto, K.; Hagiwara, Y.; Ochiai, M.; Fujita, E. *J. Chem. Soc., Chem. Commun.* **1985**, 1419-1420.
9. Total synthesis of zaragozic acid A: Nicolaou, K. C.; Nadin, A.; Leresche, J. E.; Yue, E. W.; Greca, S. L. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2190-2191. For the synthesis of the C6 side chain of zaragozic acid A: (a) Nicolaou, K. C.; Yue, E. D.; Naniwa, Y.; Riccardis, F. D.; Nadin, A.; Leresche, J. E.; Greca, S. L.; Yang, Z. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2184-2187. (b) Shlessinger, R. H.; Gillman, K. W. *Tetrahedron Lett.* **1996**, *37*, 1331-1334.
10. The diastereomers of **5** are distinguishable by ^{1}H NMR ($CDCl_3$): the δ value (ppm) of γ-CH_3, 0.86 for (2*S*, 4*R*)-**5** and 0.90 for (2*S*, 4*S*)-**5**.
11. Crystal data for (2*S*, 4*S*)-**5** ($C_{19}H_{31}NO_3S$): orthorhombic, $P2_12_12_1$ (#19), a=11.280(2) Å, b=22.627(2) Å, c=7.797(2) Å, V= 1990.0(5) Å^3, Z=4. A total of 2638 reflections ($h,k,\pm l$) were collected in the range 6° < 2θ < 55° with 1247 having I > 3.00σ(I) being used in the structural refinement by full-matrix least-squares techniques (337 variables) using the TEXSAN crystallographic package from Molecular Structures Corporation. Final *R*=0.038, R_w=0.049 (Fig.1).

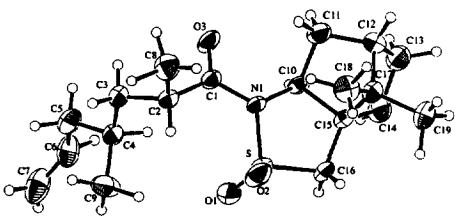


Fig. 1 ORTEP representation of **5**

12. The specific rotation of **6**; $[\alpha]_D^{27}$ -4.5° (c 1.60, $CHCl_3$). The literature value for the optically pure (2*R*, 4*R*)-isomer : $[\alpha]_D^{22}$ +3.7° (c 1.67, $CHCl_3$).[8b]
13. Data for **7**: ^{1}H NMR ($CDCl_3$) δ 0.80-1.00 (m, 6H), 1.03 (d, *J*=6.7 Hz, 3H), 1.05-1.20 (m, 2H), 1.20-1.45 (m, 6H), 2.30-2.50 (m, 1H), 4.18 (q, *J*=7.1 Hz, 2H), 5.77 (dd, *J*=15.7, 1.1 Hz, 1H), 6.80 (dd, *J*=15.7, 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 11.24, 14.35, 18.91, 20.46, 29.87, 31.90, 34.30, 43.43, 60.16, 119.52, 154.62, 166.82. The diastereomers of **7** are distinguishable by ^{1}H NMR ($CDCl_3$): the δ value (ppm) of β-CH, 6.80 for (4*S*, 6*S*)-**7** and 6.87 for (4*S*, 6*R*)-**7**.
14. Tomooka, K.; Nagasawa, A.; Wei, S.-Y.; Nakai, T., the following paper.

(*Received in Japan* 24 *September* 1996; *accepted* 21 *October* 1996)