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Asymmetric transformation of the second kind of racemic naproxen

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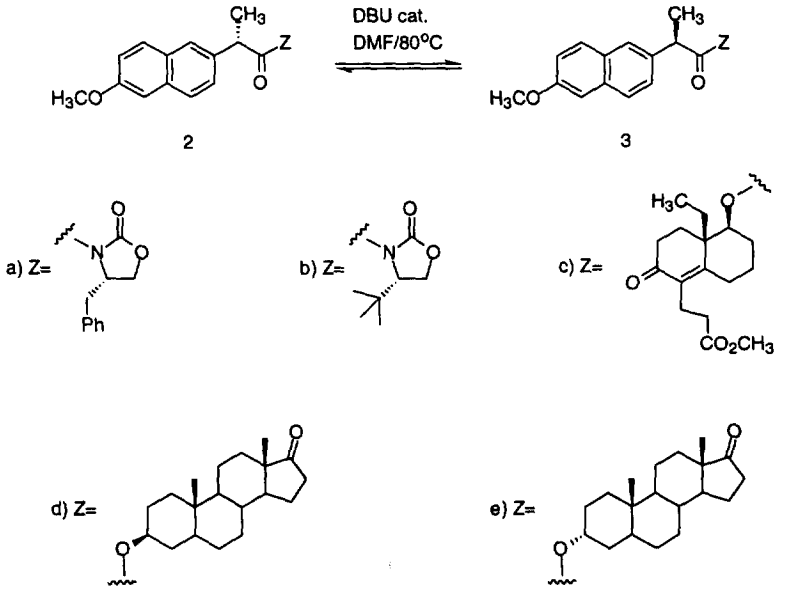
Abstract: Several chiral derivatives of racemic naproxen were subjected to asymmetric transformations. Notably, asymmetric transformation of the second kind of a mixture of **2b** and **3b** gave a diastereomeric excess (d.e.) over 90% in favor of **2b**. This d.e. was increased to over 99% after recrystallization. © 1997 Elsevier Science Ltd

2-Arylpropionic acids belong to a class of non-steroidal anti-inflammatory drugs of great therapeutic importance.[1] These compounds have a similar pathway of action: by inhibiting cyclooxygenase they hinder the arachidonic acid biotransformation to prostaglandins and thromboxane A_2, which are responsible for the inflammatory mechanism.[2]

The higher biological activity is usually exhibited by one enantiomer. Naproxen (**1**) is one of best tolerated pharmaceuticals of this family. The *S*-enantiomer exceeds by a factor of 28 the *R*-enantiomer in biological activity.[3]



Scheme 1.

A number of different asymmetric approaches to (*S*)-(+)-naproxen have been reported in literature.[4]

One possible route to effectively obtain one enantiomer from the racemic mixture could be through an asymmetric transformation.[5,6] Thus a chiral auxiliary would be attached to racemic naproxen, and the resulting mixture of epimers **2** and **3** (Scheme 1) would be subjected to an equilibrium between each other to cause enrichment of one based on its different physical properties.

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Table 1. Equilibrium between **2** and **3** under homogeneous conditions[1]

Run	Chiral Auxiliary	Ratio at Equilibrium (HPLC)	
		2	**3**
1	a	4.0	6.0
2	b	3.0	7.0
3	c	5.1	4.9
4	d	5.7	4.3
5	e	4.1	5.9

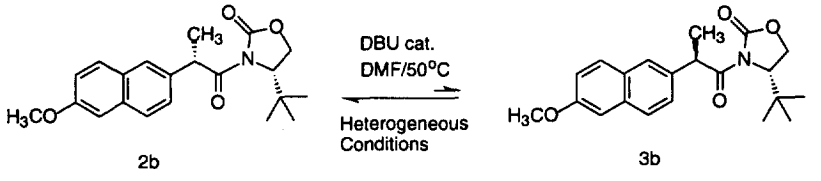
Note 1. DBU (0.25 equiv), DMF (1:10 w/v) at 80°C until equilibrium was reached by HPLC.

In this report, we would like to disclose a very efficient transformation of diastereomer **3** into **2** from a 1:1 mixture of them. First, we attempted an asymmetric transformation of the first kind, i.e. interconversion between **2** and **3** in an homogeneous solution. Thus, a ca 1:1 mixture of a number of different diastereomers **2** and **3** was prepared from racemic naproxen[7] and treated with catalytic 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in DMF at 80°C (Scheme 1).

The equilibrium is promoted by the action of the base DBU through a deprotonation–protonation at the benzylic position.[8,9] Clearly, the enrichment of one epimer would be the result of its major thermodynamic stability under the reaction conditions. Table 1 presents the results.

Unfortunately, no case from Table 1 gave the desired epimer **2** in major proportion. The greater difference between the epimers was obtained when a mixture of **2b** and **3b** (**b** denotes the chiral auxiliary) was used, although in favor of the wrong **3b** in a 7:3 ratio (run 2).

However, it was found that derivative **2b** is much less soluble in DMF than **3b**.[10] When a mixture of **2b** and **3b** was subjected to the same conditions except now using minimum DMF, completely different results were obtained. The desired **2b** now became the main component (Scheme 2). Interconversion under these heterogeneous conditions is known as asymmetric transformation of the second kind,[5] and the enrichment of **2b** is the result of its precipitation under the reaction conditions.[11,12] Table 2 presents the results.



Scheme 2.

A ratio over 95:5 (i.e., over 90% d.e.) could be obtained (runs 2–4). The role of the volume of DMF was critical, any increase of this solvent reduced the ratio (cf. runs 1 and 2).

Isolation of product, which involved filtration only, increased the ratio to 98.6:1.4 (97.2% d.e.) for run 4.[13–15] Furthermore, recrystallization (dichloromethane/methyl alcohol) enlarged further the ratio to 99.97:0.03 (99.94% d.e.). The overall yield was 78.3% from racemic naproxen.

Finally, removal of the chiral auxiliary of **2b** gave naproxen with 99.90% ee.[13]

Table 2. Interconversion between **2b** and **3b** under heterogeneous conditions[1]

Run	Scale (g)	DMF (mL)	DBU (mL)	Ratio at Equilibrium (HPLC)[2]	
				2b	**3b**
1	0.05	0.125	0.006	88.2	11.8
2	0.05	0.075	0.006	97.2	2.8
3	0.5	0.16	0.051	96.4	3.6
4	10.0	0.5	1.19	95.4	4.6[3]

Note 1: 1) At 50°C until no change was obsreved by HPLC (ca. 25 h).
2) From reaction mixture, prior to work up (filtration).
3) A 98.6:1.4 ratio was obtained after filtration.

References

1. Lambardino, J. G. *Nonsteroidal Antiinflammatory Drugs*. Wiley Interscience, John Wiley & Sons, New York, 1985.
2. Vane, J. R. *Nature (New Biol.)* **1971**, *231*, 232.
3. (a) Tsuchichashi, G. *Tetrahedron* **1982**, 5427; (b) Shen, T. Y. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 460; (c) Harrison, J. T.; Lewis, B.; Nelson, O.; Rocks, W.; Roszkowski, A.; Tomalonis, A.; Fried, J. H. *J. Med. Chem.* **1970**, *13*, 203.
4. For some recent asymmetric synthesis, see the following: (a) Wan, K. T.; Davis, M. E. *J. Catal.* **1995**, *152*, 25; (b) Zhao, H.; Wu, Y. L. *Chin. Chem. Lett.*. **1994**, *5*, 461; (c) Mashima, K.; Kusano, K.; Sato, N.; Matsumura, Y.; Nozaki, K.; Kumobayashi, H.; Sayo, N.; Hori, Y.; Ishizaki, T. *J. Org. Chem.*. **1994**, *59*, 3064; (d) Del Campo, C.; García, M.; Gradillas, A.; Llama, E. F.; Salazar, L.; Sánchez-Montero, J. M.; Sinisterra, J. V. *J. Mol. Catal.* **1993**, *84*, 399; (e) Ahn, K. H.; Jin, Cj. S.; Kang, D. H.; Shin, Y. S.; Kim, J. S.; Han, D. S.; Kim, D. H. *J. Heterocycl. Chem.* **1993**, *30*, 825; (f) García, H.; Del Campo, C.; Llama, E. F.; Sánchez-Montero, J. M.; Sinisterra, V. *Tetrahedron* **1993**, *49*, 8433; (g) Chan, A. S. C.; Lareman, S. A.; Miller, R. E.; *ACS Symp. Ser.* **1993**, *517*, 27; (h) Brown, J. D. *Tetrahedron: Asymmetry* **1992**, *3*, 1551; (i) Saburi, Masahiko; Ohnuki, M.; Ogasawara, M.; Takahashi, T.; Uchida, Y. *Tetrahedron Lett.* **1992** *33*, 5783; (j) Fadel, A. *Synlett* **1992**, 48; (k) González, A. *Synth. Commun.* **1991**, *21*, 1353; (l) Kumar, A.; Salunkhe, R. V.; Rave, R. A.; Dike, S. *J. Chem. Soc., Chem. Commun.* **1991**, 485.
5. (a) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*. John Wiley & Sons, New York, 1994, pp. 364–374; (b) Morrison, J. D. In *Asymmetric Synthesis*, ed. J. D. Morrison. Academic Press, New York, 1983, Vol. I, Chapter 1; (c) Jacques, J.; Collet, A.; Wiley, S. H. *Enantiomers, Racemates and Resolutions*. John Wiley & Sons, New York, 1981, Chapter 6.
6. Two patent references have appeared in which one enantiomer is enriched: (a) Arai, K.; Obara, Y.; Takahashi, Y.; Takakuwa, Y. *Jen. Kokai Tokkyo Koho JP 61238 734*, Oct. 24, 1986; *Chem. Abstr*: 1987, *106*, 196063x; (b) Piselli, F. L. *Eur. Patent Appl.* EP 298 395, Jan. 11, 1989; *Chem. Abstr.* 1989, *111*, 7085a.
7. Matthews, G. J.; Arnold, R. A. *Ger. Offen.* 2 805 488, Aug. 17, 1978; *Chem. Abstr*: 1979, *90*, 6106u.
8. For other epimerizations promoted by DBU, see: (a) Atsuro, T.; Yasumichi, F. *Jpn. Kokai Tokkio Koho JP 05255 245*, Oct. 5, 1993; *Chem. Abstr*: 1994, *120*, 134282y; (b) Masaji, K.; Motomichi, K.; Kunikatsu, S. *J. Org. Chem.* **1989**, *54*, 5908; (c) Jones, D. W.; Thompson, A. M. *J. Chem. Soc., Chem. Commun.* **1989**, 1370; (d) Hermkens, P. H. H.; Plate, R.; Ottenheijm, H. C. J. *Tetrahedron* **1988**, *44*, 1991.
9. For non-equilibrium enrichment of one epimer (or enantiomer) through a deprotonation–protonation sequence, namely, stereoselective kinetic protonation, see: (a) Mohrig, J. R.; Rosenberg, R. E.; Apostol, J. W.; Bastienaansen, M.; Evans, J. W.; Franklin, S. J.; Frisbie, C. D.; Fu, S. S.; Hamm, M. L.; Hirose, C. B.; Hunstad, D. A.; James, T. L.; King, R. W.; Larson, C. J.; Latham, H. A.; Owen, D. A.; Stein, K. A.; Warnet R. *J. Am. Chem. Soc.* **1997**, *119*, 479 and references therein; (b) Fehr, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2567; (c) Duhamel, P. *Bull. Soc. Chim. Fr.* **1996**, *133*, 457.
10. **3b** is soluble in DMF in a 1:1 w/v ratio, whereas **2b** in a 1:13 w/v ratio.
11. Use of a mixture of **2a** and **3a**, i.e., (*S*)-4-benzyloxazolidinone as chiral auxiliary, did not give good results because both **2a** and **3a** are quite soluble in DMF.
12. For similar asymmetric transformations of the second kind, see: (a) Feringa, B. L.; De Jong, J. C. *J. Org. Chem.* **1988**, *53*, 1125; (b) Cooper, J.; Humber, D. C.; Long, A. G. *Synth. Commun.* **1986**, *16*, 1469; (c) Hagmann, W. K. *Ibid.* **1986**, *16*, 437.
13. Experimental description. To a fine suspension of racemic 2-(6-methoxy-2-naphtyl)propionic acid (racemic naproxen)[7] (8.85 g, 38.4 mmol) in dichloromethane (200 mL) was added oxalyl chloride (7.1 mL, 81.4 mmol). After 2 h at 20–25°C, the reaction mixture was concentrated to dryness.

Additional dichoromethane (50 mL) was added and the whole was again taken to dryness. Dry THF (160 mL) was added and the resulting solution was cooled to about −72°C, when a fresh solution of lithium (*S*)-4-*tert*-butyl-2-oxazolidinone[14] in THF (213 mL, 38.4 mmol, 0.18 M in 2.5:1 v/v THF/hexane) was added. After 30 min at about −72°C, the mixture was allowed to reach 20–25°C. Saturated ammonium chloride (75 mL) was added, and the solvent was removed *in vacuo*. The product was extracted with dichloromethane (3×80 mL) and the resulting organic solution was washed with 1 N sodium hydroxide (100 mL), 1 N ammonium choride (2×100 mL), dried ($MgSO_4$), filtered and concentrated to dryness to give crude **2b** and **3b** (14.8 g, HPLC ratio: 44:56, respectively). To a suspension of crude **2b** and **3b** (10.0 g, 28.2 mmol) in DMF (0.5 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 1.19 mL, 7.96 mmol). The mixture was heated at 50–55°C for 28 h. After cooling to 0–5°C, cold methanol (0–5°C, 20 mL) was added and the mixture was maintained for 20 min at 0–5°C. Product was filtered and dried. Crude **2b** [7.53 g, d.e. 97.2% (HPLC)] was crystallized from dichoromethane/methyl alcohol to obtain pure **2b** (7.24 g, d.e. 99.94%, 78.3% overall yield from racemic naproxen): colorless solid; mp 184–185°C; $[\alpha]_D^{25}$ +119 (c 0.27, $CHCl_3$); IR (KBr) 1768, 1709, 1230, 1209, 1188; ^1H NMR (200 MHz, $CDCl_3$) δ 1.00 (s, 9H), 1.65 (d, 3H, *J*=7.05 Hz), 3.95 (s, 3H), 4.08 (dd, 2H, *J*=9.1, 7.5 Hz), 4.25 (dd, 1H, *J*=9.1, 1.3 Hz), 4.45 (dd, 1H, *J*=7.5, 1.3 Hz), 5.33 (q, 1H, *J*=7.05 Hz), 7.1–7.8 (m, 6H); LSIMS m/z 356 $[MH]^+$; HR-LSIMS calcd for $C_{21}H_{26}NO_4$ $[MH]^+$ 356.1862, found 356.1865; anal. calcd for $C_{21}H_{25}NO_4$: C, 70.97; H, 7.09; N, 3.94. Found: C, 70.99; H, 7.04; N, 4.12. To a solution of **2b** (7.17 g, 20.2 mmol) in THF (100 mL) were added water (5 mL) and 30% aqueous hydrogen peroxide (9.1 mL, 80.8 mmol) slowly at 8–10°C.[15] A solution of lithium hydroxide monohydrate (1.36 g, 32.3 mmol) in water (40 mL) was added, and the mixture was stirred at 25–30°C for 1 h. 1.4 M sodium bisulfite (60 mL) was added, and after 10 min, 1.2 N $NaHCO_3$ (100 mL). THF was removed *in vacuo*, and recovered oxazolidinone was extracted with dichloromethane (2×100 mL). Acidification of aqueous phase with 1:1 HCl to pH 1 followed by extraction with dichloromethane (2×100 mL), water wash, and concentration to dryness gave pure (*S*)-naproxen [3.97 g, ee 99.90% (HPLC on chiral AGP column), 85.4% yield]: mp 155–156°C (lit.[3c] mp 152–154°C), $[\alpha]_D^{25}$ +67.5 (c 1.0, $CHCl_3$) ($[\alpha]_D^{25}$ lit.[3c] +66 (c 1.0, $CHCl_3$)).

14. Evans, D. A.; Chapman, K. T.; Tan Hong, D.; Kawaguchi, A. T. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1184.
15. Gage, J. R.; Evans, D. A. *Org. Synth.* **1989**, *68*, 83.

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