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Supplementary Material Available: Figures of the Nomarski microscopy, the double crystal X-ray diffraction, and the RBS channeling experiments (6 pages). Ordering information is given on any current masthead page.

α-Hydroxy Esters as Chiral Reagents: Asymmetric Synthesis of 2-Arylpropionic Acids

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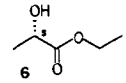
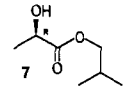
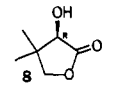
The 2-arylpropionic acids are a class of non-steroidal antiinflammatory agents that have remained an area of intense study.[1] Often only one enantiomer is biologically active. Therefore, the asymmetric synthesis of this class of compounds has received considerable attention. While many approaches have been developed, the majority lack simplicity and high stereoselectivity.[2] We wish to report an exciting find in the asymmetric transformation[3] of racemic 2-arylpropionic acids to either their *S* or *R* enantiomers by tertiary amine mediated addition of the chiral alcohols, (*S*)-ethyl lactate (**6**), (*R*)-isobutyl lactate (**7**), or the α-hydroxylactone, (*R*)-pantolactone (**8**), to the respective arylmethylketenes providing 2-arylpropionate esters in 94–99% diastereomeric excesses (de's). This communication describes the unprecedented use of simple, readily available chiral alcohols for highly diastereoselective protonations.

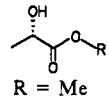
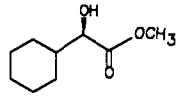
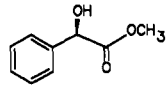
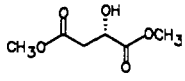
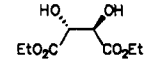
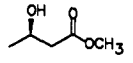
Addition of a chiral alcohol or amine to a ketene was reported as early as 1919 (de < 35%).[4] Recent advances by Ruechardt[5] and Bellucci[6] brought diastereomeric excesses above 80% but required alcohols of limited availability. Naturally occurring α-hydroxy esters and lactones are a readily available source of chirality. They have received little attention as chiral reagents,[7]

Table I[a]

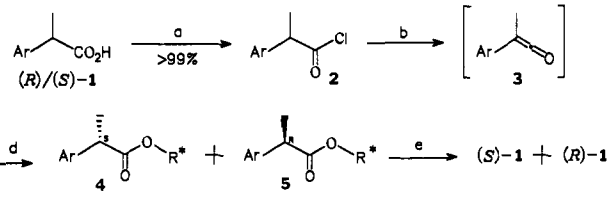
R*OH	ratio of diastereomers	% yield (4 + 5)	ratio of enantiomers (*S*)-1/(*R*)-1	% overall yield (*S*)-1 + (*R*)-1
 6	97:3 *S,S/R,S*	92	94.5:5.5	89
 7	97:3 *R,R/S,R*	96	5.5:94.5	83
 8	>99:1 *R,R/S,R*	90	0.5:99.5	86

[a] Ar = *p*-isobutylphenyl.

Table II

entry	alcohol	ratio of diastereomers	ratio of enantiomers *S/R*
			
1	R = Me	95:5	93.5:6.5
2	R = Et	95:5	93:7
3	R = *i*-Pr	95:5	93:7
4	R = benzyl	95:5	91.5:8.5
5			5:95
6			0.5:99.5
7			34:66
8			80:20
9			11:89
10		67:33	34:66
11			46:54

Scheme I[a]



[a] (a) $SOCl_2$ (110 mol %), DMF (5 mol %), heptane or toluene, 50–55 °C; (b) trimethylamine or dimethylethylamine (300 mol %), 25 °C; (c) R*OH (120 mol %), same solvent (0.2 M) as (a), −78 °C; (d) 3-(dimethylamino)propylamine (5–10 mol %), 25 °C or acetic acid–H_2O, 70 °C; (e) acetic acid–2 N HCl, 85 °C, or LiOH, heptane–acetonitrile–water, 5 °C.

(1) Rieu, J.-P.; Boucherle, A.; Cousse, H.; Mouzin, G. *Tetrahedron* **1986**, *42*, 4095.

(2) (a) Lubell, W. D.; Rapoport, H. *J. Am. Chem. Soc.* **1988**, *110*, 7447. (b) Castaldi, G.; Cavicchioli, S.; Giordano, C.; Uggeri, F. *J. Org. Chem.* **1987**, *52*, 3018. (c) Honda, Y.; Ori, A.; Tsuchihashi, G. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1027. (d) Ando, A.; Shioiri, T. *J. Chem. Soc., Chem. Commun.* **1987**, 656. (e) Rieu, J.-P.; Boucherle, A.; Cousse, H.; Mouzin, G. *Tetrahedron* **1986**, *42*, 4095. (f) Piccolo, O.; Spreafico, F.; Visentin, G. *J. Org. Chem.* **1985**, *50*, 3945 and references therein.

(3) Asymmetric transformation of a racemic compound into its optically active form is becoming an increasingly viable approach to asymmetric synthesis. For examples, see: (a) Kagan, H. B.; Fiaud, J. C. New Approaches in Asymmetric Synthesis. In *Topics in Stereochemistry*; Eliel, E. L., Allinger, N. L., Eds.; Vol. 10, pp 175–286. (b) Boyle, W. J.; Sifniades, S.; Van Peppen, J. F. *J. Org. Chem.* **1979**, *26*, 4841. (c) Shibata, S.; Matsushita, H.; Kaneko, H.; Noguchi, M.; Saburi, M.; Yoshikawa, S. *Heterocycles* **1981**, *16*, 1901. (d) Hongo, C.; Yamada, S.; Chibata, I. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3286 and 3291. (e) Shibata, S.; Matsushita, H. K.; Noguchi, M.; Saburi, M.; Yoshikawa, S. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3546. (f) Shibata, S.; Matsushita, H.; Kaneko, H.; Noguchi, M.; Saburi, M.; Yoshikawa, S. *Chem. Lett.* **1982**, 1983. (g) Shibata, S.; Matsushita, H.; Kaneko, H.; Noguchi, M.; Sakurai, T.; Saburi, M.; Yoshikawa, S. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 3531. (h) Hongo, C.; Tohyama, M.; Yoshioka, R.; Yamada, S.; Chibata, I. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 433. (i) Hagmann, W. K. *Synth. Commun.* **1986**, *16*, 437. (j) Reider, P. J.; Davis, P.; Hughes, D. L.; Grabowski, E. J. J. *J. Org. Chem.* **1987**, *52*, 955. For a recent example of asymmetric transformation by enantioselective protonation, see: Fehr, C.; Galindo, J. *J. Am. Chem. Soc.* **1988**, *110*, 6909 and references therein.

(4) For examples of asymmetric ketene additions before 1981, see: (a) McKenzie, A.; Christie, E. W. *J. Chem. Soc.* **1934**, 1070. (b) Pracejus, H. *Liebigs Ann. Chem.* **1960**, *634*, 9 and 23. (c) Pracejus, H.; Tille, A. *Chem. Ber.* **1963**, *96*, 854. (d) Anders, E.; Ruch, E.; Ugi, I. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 25. (e) Seikaly, H. R.; Tidwell, T. T. *Tetrahedron* **1986**, *42*, 2587. (f) Stoutamire, D. W. U.S. Patent, 1986, patent number: 4,570,017. (b) Morrison, J. D.; Mosher, H. S. *Asymmetric Organic Reactions*; American Chemical Society: Washington, D.C., 1980.

(5) (a) Salz, U.; Ruechardt, C. *Tetrahedron Lett.* **1982**, *23*, 4017. (b) Jaehme, J.; Ruechardt, C. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 885.

(6) Bellucci, G.; Berti, G.; Bianchini, R.; Vecchiani, S. *Gazz. Chim. Ital.* **1988**, *118*, 451.

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finding instead utility in asymmetric synthesis as building blocks.[8]

Reaction of the ketene (**3**) derived from racemic ibuprofen (**1**) (Scheme I, Ar = *p*-isobutylphenyl) with chiral α-hydroxy esters gave the 2-arylpropionate esters **4** or **5** in de's of 94–99%.[9] (*S*)-Ethyl lactate provided the *S* stereochemistry and (*R*)-isobutyl lactate the *R* stereochemistry at the benzylic carbon.[10,11] The diastereoselectivity was not affected by the electronics of the aryl ring: phenyl-, 4-methoxyphenyl-, and 4-nitrophenylmethylketenes all showed high selectivity. Substitution of the methyl group with ethyl gave no decrease in selectivity. The naproxen ester [Ar = 2-(6-methoxynaphthyl)] was obtained with a de of 80%.

The reaction of *S*-ethyl lactate with ibuprofen ketene (**3**) was highly dependent on solvent: while more polar solvents lowered the diastereoselectivity, hexanes and heptane were found to be most effective. In cases where the substrate [e.g., naproxen, Ar = 2-(6-methoxynaphthyl)] or the chiral alcohol were insoluble in heptane, toluene was a suitable substitute. Less sterically hindered amines provided higher de's as well as more efficient generation of the ketene. Trimethylamine, dimethylethylamine, and *N*-methylpyrrolidine provided the highest de's (94–99%), while triethylamine (90% de) and diisopropylethylamine (80% de) proved inferior. In the absence of amine the de decreased to 60%. Reaction temperature was not a major factor with only a 7% decrease in de seen in going from −78 °C to room temperature. Optimum conditions with (*S*)-ethyl lactate (**6**) were as follows: −78 °C, 0.02 M; (98.6:1.4 *S,S*/*R,S*); increasing concentration to 1.0 M gave slightly lower selectvity (95:5). The reaction is third order (first order with respect to the ketene, alcohol, and amine) and possesses a pronounced deuterium isotope effect ($k_H/k_D \sim 4$).

A study of the structural effects of the alcohol was carried out to determine the controlling features of the chiral reagent (Table II).[12] This led to the discovery of the completely diastereoselective reagent, (*R*)-pantolactone. Variation of the ester alkyl group did not affect the diastereoselectivity (entries 1–4). However, increased steric bulk adjacent to the hydroxy group had a marked positive effect [cf. (*S*)-ethyl lactate, methyl (*R*)-hexahydromandelate, and (*R*)-pantolactone (entries 1, 5, and 6, respectively)]. The most important feature of the chiral reagent was the proximity of the hydroxyl group to a hydrogen bonding moiety, preferably a carbonyl.[15] If no such group was present, as with an aliphatic alcohol (entry 11), the diastereoselectivity was low. Displacement of the hydroxyl group from the carbonyl by one methylene unit (entry 10) caused a tremendous drop in the diastereoselectivity. The α-hydrogen bonding group can be an ester, amide,[16] or phenyl group as with *sec*-phenethyl alcohol.[5] Alternative sites for hydrogen bonding weaken the key interaction of the α-hydroxyl group and the carbonyl, reducing selectivity (entries 7–9). In all cases the (*S*)- and (*R*)-hydroxy esters provided predominantly the *S* and *R* stereochemistry, respectively. Maximum diastereoselectivity in the ketene addition can be obtaned by the proper grouping of three structural features: a chiral hydroxyl group (1) which is α to a carbonyl group (2) and adjacent to a tertiary alkyl group (3) containing no hydrogen bonding moieties. (*R*)-Pantolactone (entry 6) fits all these criteria and gives remarkable selectivity!

This work provides a practical chiral synthesis of 2-arylaliphatic acids: either enantiomer can be prepared easily with readily available chiral alcohols. The utility of the method is evidenced by the chiral syntheses of ibuprofen and naproxen. The relationship of hydrogen bonding to high diastereoselectivity shown here is far from obvious. Studies toward elucidation of the mechanism of this diastereoselective addition and determination of the scope of α-hydroxy esters as chiral reagents are in progress.

(7) (a) Poll, T.; Helmchen, G.; Bauer, B. *Tetrahedron Lett.* **1984**, *25*, 2191. (b) Poll, T.; Sobczak, A.; Hartmann, H.; Helmchen, G. *Tetrahedron Lett.* **1985**, *26*, 3095. (c) Helmchen, G.; Karge, R.; Weetman, J. *Modern Synthetic Methods* **1986**, *4*, 261. (d) Bianchi, G.; Achilli, F.; Gamba, A.; Vercesi, D. *J. Chem. Soc., Perkin Trans. 1* **1988**, 417.

(8) (a) Kelly, T. R.; Kaul, P. N. *J. Org. Chem.* **1983**, *48*, 2775. (b) Reference 2f. (c) Yanagiya, M.; Shirahama, H.; Matsumoto, T. *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu* **1986**, *28*, 325 and references therein. (d) Overberger, C. G.; Chang, J. Y. *Tetrahedron Lett.* **1989**, *30*, 51.

(9) The generation of the ketene with 300 mol % of amine was followed by infrared spectroscopy. The acid chloride peak of **2** at 1790 cm^{-1} disappeared as the ketene peak of **3** at 2100 cm^{-1} intensified. The chiral reagent was then added neat at −78 °C. The ratio of the diastereomers was easily observed by HPLC: Microsorb C-8 4.6 mm × 150 mm; acetonitrile–water–phosphoric acid 60:40:0.1; 1.5 mL/min; 230 nm.

(10) Optical purity of commercial lactate esters was assayed by HPLC after conversion to the α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) esters (1.1 equiv of triethylamine, 4-(dimethylamino)pyridine, and (*R*)- or (*S*)-MTPA, each, in methylene chloride). Microsorb C-8; acetonitrile–water–trifluoroacetic acid 55:45:0.1, 1.5 mL/min; 230 nm. Cf: (a) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org Chem.* **1969**, *34*, 2543. (b) Reference 2c.

(11) After the ketene had completely reacted, anhydride (2–5%) generated from extraneous water was selectively cleaved with 3-(dimethylamino)-propylamine (ref 10a) or acetic acid–water (4:1; 70 °C). The esters were either hydrolyzed in acetic acid–2 N aqueous hydrochloric acid (5:2, 85 °C) or with LiOH in acetonitrile–water at 5 °C. For a discussion of the saponification of epimerizable acyl derivatives, see: (a) Evans, D. A.; Ellman, J. A.; Dorow, R. L. *Tetrahedron Lett.* **1987**, *28*, 1123. (b) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141. Isolated ibuprofen is assayed for chirality by conversion to the benzamides (i. carbonyl diimidazole, isopropyl acetate; ii. benzylamine), and the enantiomers are separated on a chiral Pirkle L-Phenylglycine Covalent column; 97:3 hexanes–isopropy alcohol. For additional discussion on the chiral assay of α-methylarylacetic acids, see: (c) Wainer, I. W.; Doyle, T D. *J. Chromatogr.* **1984**, *284*, 117.

(12) Comparisons were carried out on ketene **3** (derived from ibuprofen) in toluene since many of the chiral alcohols were not soluble in hexanes or heptane at −78 °C.

(13) Benzyl lactate (bp 128 °C, 0.07 mm) was prepared by formation of potassium (*S*)-lactate (potassium hydroxide, 1% aqueous ethanol) and benzylation of the isolated salt (benzyl bromide, DMF, 100 °C).

(14) Methyl (*R*)-hexahydromandelate was prepared by heating a solution of (*R*)-hexahydromandelic acid in methanol-concentrated sulfuric acid (99:1) at reflux.

(15) (a) Aaron, H. S. Conformational Analysis of Intramolecular-Hydrogen-Bonded Compounds in Dilute Solution by Infrared Spectroscopy. In *Topics in Stereochemistry*; Allinger, N. L., Eliel, E. L., Eds.; John Wiley & Sons: New York, 1979; Vol. 11, pp 1–52. (b) Mori, N.; Omura, S.; Yamamoto, O.; Suzuki, T.; Tsuzuki, Y. *Bull. Chem. Soc. Jpn.* **1963**, *36*, 1401. (c) Mori, N.; Omura, S.; Kobayashi, N.; Tsuzuki, Y. *Bull. Chem. Soc. Jpn.* **1965**, *38*, 2149. (d) Mori, N.; Asano, Y.; Tsuzuki, Y. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 1871.

(16) (*S*)-Dimethyllactamide (ref 2c) similarly provides high diastereoselectivity. This will be discussed in forthcoming publications.

1,2-Dithiete Is More Stable Than 1,2-Dithioglyoxal As Evidenced by a Combined Experimental and Theoretical IR Spectroscopic Approach

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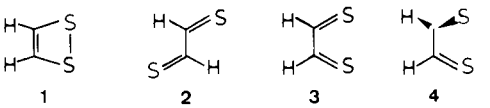
A photoelectron (PE) spectroscopic study on the pyrolysis of 1,3-dithiol-2-one provided evidence that 1,2-dithiete (**1**) is more stable than its valence isomers *trans*-(**2**)-, *cis*-(**3**)-, or *gauche*-(**4**)-dithioglyoxal.[1] This result was further backed by a microwave



1 2 3 4

(1) Schulz, R.; Schweig, A.; Hartke, K.; Köster, J. *J. Am. Chem. Soc.* **1983**, *105*, 4519.

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