equiv) was added dropwise (2 min). The mixture was stirred for 20 min, diluted with aqueous $NaHSO_3$, and extracted thoroughly with ether. The organic phase was washed once with H_2O and then extracted with 10 mL of 1.25 N NaOH and 10 mL of H_2O. The aqueous extract was washed once with ether, acidified with 10 mL of 2 N HCl, and extracted with ether. The dried ($MgSO_4$) extract was concentrated (≤30 °C) and the residue was taken up in hexane (2 × 5 mL). The hexane solution was filtered through a pad of Na_2SO_4 and concentrated (≤30 °C), producing the liquid acid. Conversion to the acid halide was affected at room temperature with an ethereal solution of $SOCl_2$ (88 μL, 1.2 mmol) and DMF (10 μL, 0.12 mmol).[10b] After 4 h the mixture was concentrated (≤30 °C), and the residue was added dropwise as an etheral solution (1–2 mL) to a cooled solution of (*R*)-(+)-1-(1-naphthyl)ethylamine (0.5 g) in 5 mL of anhydrous ether. The chiral amine had been purchased from K and K Laboratories and was purified as a bitartrate by using (*S*)-tartaric acid. The bitartrate was recrystallized from 50% aqueous MeOH until the amide formed from (*R*)-**6** showed no further improvement in diastereomer composition. The amine was taken to be 100% *R* and the determined enantiomeric purity of **6** was thereby minimized. The amide preparation, which was quite clean judged by TLC and high-performance LC, was worked up in the usual manner and analyzed directly to avoid fractionation. The yield of amide was 211 mg (66%). Analysis by high-performance LC was done with the analytical column already described and 10% ethyl acetate–hexane (H_2O saturated) at 4 mL/min with UV detection (254 nm). The (*R*)-(+)-dienal **6** was judged to be ≥99%, and the (*S*)-(−)-isomer was ≥96.5%. The amide derivatives were collected by high-performance LC and showed the following spectral characteristics: IR (CCl_4) 3450 (amide NH), 1675 cm^{-1} (amide C=O); NMR (*R,R* diastereomer) 1.40, 1.48 (s, 6 H, CH_3C=), 1.51 (d, 3 H, J = 7 Hz, CH_3CH), 2.14 (d, 2 H, J = 7, $CHCH_2C$=O), 4.53, 4.58 (d, 4 H, H_2C=), 5.73 (m, 1 H, NH), 7–8 (m, 7 H, aryl H).

(*R*)-(+)-3,9-Dimethyl-6-(1-methylethenyl)-3,9-decadien-1-ol (Pentagonal) Propanoate (1, X = $OCCH_2CH_3$). Method A (Conventional Multiple Wittig Reaction Employing Ethylene Oxide). Ethylidenetriphenylphosphorane was prepared in the usual manner from the phosphonium bromide (19.7 g, 53 mmol) and 1 equiv of butyllithium in 100 mL of THF (N_2). The solution was chilled to −5 °C and ethylene oxide (2.65 mL, 53 mmol) was injected from a precooled syringe.

The temperature of the mixture rose to 25 °C. The mixture was stirred in an ice–MeOH bath for 0.5 h after which time another 53 mmol of butyllithium was added. The (*R*)-(+)-dienal **6** (4.4 g, 26.5 mmol) was added. The mixture was stirred for 0.25 h without cooling and was then worked up in the usual fashion (hexane extraction). A sample of the alcohol was purified by passage through a column of silica gel (5% loading) and eluted with 20% ether–hexane. GLC on OV-101 indicated a 70:30 ratio of *Z:E*. Preparative high-performance LC with 20% ether–hexane at 10 mL/min with refractive index (RI) detection resulted in collection of the *R,Z* and *R,E* alcohols: NMR (*R,Z*) δ 0.74, 1.80, 1.82 (s, 9 H, CH_3C=), 3.81 (t, 2 H, H_2COH), 4.90 (m, 4 H, H_2C=C), 5.4 (m, 1 H, HC=); NMR (*R,E*) was the same except that the allylic methyl signals were δ 1.74, 1.76, and 1.82 (s, 9 H, CH_3C=).

The propionate ester were prepared from the crude alcohol product above (presuming 26.5 mmol of alcohol) by using triethylamine (5.7 mL, 40 mmol) and proionyl chloride (3.5 mL, 40 mmol) in 125 mL of anhydrous ether in the usual fashion (ice-bath cooling while adding acid halide to the amine–alcohol solution). The crude product was purified by passage through silica gel (25 g), eluting with 5% ethyl acetate–hexane. Preparative high-performance LC with 3% ether–hexane at 10 mL/min with RI detection provided the *R,Z* propionate (3.95 g, 67%): $[\alpha]^{25}_D$ +7.10 (*c* 10, $CHCl_3$); IR (film) 1740 (ester C=O), 880 cm^{-1} (H_2C=CR_2); NMR δ 1.16 (s,CH_3), 1.74, 1.80, 1.82 (s, 9 H, CH_3C=), 4.28 (t, 2 H, CH_2O), 4.98 (m, 4 H, H_2C=), 5.55 (m, 1 H, HC=). *R,E* propionate: $[\alpha]^{25}_D$ +7.62 (*c* 10, $CHCl_2$); NMR was the same excepting δ 1.74, 1.74, 1.82, (s, 9 H, CH_3C=); chemical-ionization mass spectrum (isobutane), *m/e* (relative intensity) 270 (P + 1, 2), 205 (P + 1 − $C_2H_5CO_2H$, 100).

Anal. Calcd for $C_{18}H_{30}O_2$: C, 77.65; H, 10.86. Found: C, 77.81; H, 10.98.

Method B (Directed Wittig Reaction To Prepare the *R,E* Alcohol). The triphenylphosphonium salt of the tetrahydropyranyl ether of 3-iodo-1-propanol was obtained (as an oil) in the usual manner. The salt (7.3 g, 15 mmol) was dissolved in 75 mL of THF (N_2) and converted to the ylide with 1 equiv of butyllithium at 0 °C. The temperature was lowered to −75 °C, and the (*R*)-(+)-dienal **6** (2.28 g, 15 mmol) was added. Another equivalent of butyllithium (−75 °C) was added to the decolorized solution and, after 0.5 h, the temperature was allowed to rise to −5 °C. Methyl iodide (1.25 mL, 20 mmol) was added, and (after 0.5 h at 0 °C) the decolorized mixture was worked up in the usual fashion. Purification of the alcohol by chromatography on silica gel as described above gave 1.17 g (35%). GLC analysis of the alcohol or its propionate indicated ≥97% *E*.

Method C (Directed Wittig Reaction To Prepare the *R,Z* Alcohol). The procedure was identical with that of method B except that the phosphonium salt employed was ethyltriphenylphosphonium bromide (6.3 g, 15 mmol) and ethylene oxide (1 mL, 20 mmol) was used instead of methyl iodide. The chromatographically purified alcohol weighed 0.50 g (15%) and was ≥98% *Z*.[11]

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Registry No. (*R,Z*)-1 (X = H), 73770-42-0; (*R,E*)-1 (X = H), 73770-43-1; (*R,E*)-1 (X = $OCCH_2CH_3$), 73770-44-2; (*R,Z*)-1 (X = $OCCH_2CH_3$), 73416-54-3; (*R*)-**5**, 73770-45-3; (*S*)-**5**, 73770-46-4; (*R*)-**6**, 73770-47-5; (*R*)-**6** (*R*)-1-(1-naphthyl)ethylamide, 73770-48-6; (*R*)-limonene, 5989-27-5; (*S*)-limonene, 5989-54-8; methylenetriphenylphosphorane, 3487-44-3; (*R*)-6-methyl-3-(1-methylethenyl)-6-hepten-1-one dimethyl acetal, 73770-49-7; ethylidenetriphenylphosphorane, 1754-88-7; ethylene oxide, 75-21-8; propionyl chloride, 79-03-8; 3-iodo-1-propanol THP ether triphenylphosphonium salt, 52103-13-6; ethyltriphenylphosphonium bromide, 1530-32-1.

(11) Mention of a commercial or proprietary product in this paper does not constitute an endorsement of that product by the USDA.

Resolution of α-Substituted Mandelic Acids via Chiral Oxazolines Using Pressurized Chromatography

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The advent of novel methods of asymmetric syntheses has led to many exciting new developments in the past few years. However, with the wide range of chiral products prepared arose the concurrent problem of determining enantiomeric purity. We have previously described,[1] along with others,[2] the separation of diastereomeric precursors, using medium- and high-pressure liquid chromatography,

(1) A. I. Meyers, J. Slade, R. K. Smith, E. D. Mihelich, F. M. Hershenson, and C. D. Liang, *J. Org. Chem.*, **44**, 2247 (1979).

(2) W. H. Pirkle and P. E. Adams, *J. Org. Chem.*, **43**, 378 (1978); W. H. Pirkle and P. L. Rinaldi, *ibid.*, **43**, 3803 (1978); G. Helmchen, H. Volter, and W. Schule, *Tetrahedron Lett.*, 1417 (1977); I. S. Krull, *Adv. Chromatogr. (N.Y.)*, **16**, 175 (1978).

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Table I. Medium-Pressure Liquid Chromatography of Diastereomers 2 at 25 °C and 90 psi

	R in 2	column load, g[a]	acetone/hexane, % by volume	pure diastereomer 2[c] grams recovd	mp, °C[d]	$[\alpha]^{22}_D$, deg (c, solvent)
2a	Me	3.85[b]	25/75	1.96	92-94	−22.4 (10.2, $CHCl_3$)
b	Et	1.73[b]	10/90	0.48	oil	−9.23 (1.3, $CHCl_3$)
c	*n*-propyl	1.62	10/90	0.32	oil	−20.8 (1.3, EtOH)
d	isopropyl	0.97	6/94	0.07	76-78	−0.45 (2.2, $CHCl_3$)
e	isobutyl	0.91	6/94	0.20	wax	−9.04 (2.1, $CHCl_3$)
f	*p*-tolyl	0.91	12/88	0.27	wax	+12.1 (2.8, $CHCl_3$)
g	*p*-anisyl	1.17	14/86	0.51	69-71	+18.3 (2.4, $CHCl_3$)
h	α-naphthyl	1.02	12/88	0.48	oil	−40.8 (1.3, $CHCl_3$)
i	2-thienyl	0.89	16/84	0.45	120-122	−6.3 (8.7, $CHCl_3$)

[a] A 15 × 1000 cm glass column packed with silica gel 60 was used except where noted. [b] A 25 × 1000 cm glass column packed with silica gel 60 was used. [c] Purity was confirmed by high-pressure liquid chromatography; see Table II. [d] All the pure oxazolines 2 showed characteristic infrared frequencies (mineral oil) at 1650-1670 (C=N) and 3275-3450 cm^{-1} (OH). Complete spectral data for 2 and 3 can be found in the Ph.D. thesis of J. Slade, Colorado State University, 1979.

Table II. High-Pressure Liquid Chromatography Data for Determining Diastereomeric Purity of 2

R in 2	column	elution solvent(s)	flow rate, mL/min	retention time, min[b] major	minor
Me	μ-Porasil	10% acetone/hexane	3.0	6.0	7.0
Et	μ-Porasil	10% acetone/hexane	2.0	4.4	5.0
n-propyl	μ-Porasil	10% acetone/hexane	1.0	8.1	9.1
isopropyl	μ-Porasil	10% acetone/hexane	1.0	5.7	6.0
isobutyl	μ-Porasil	10% acetone/hexane	1.0	6.6	6.9
p-tolyl	μ-Bondpak[a]	acetonitrile	1.5	5.0	5.3
p-anisyl	μ-Bondpak[a]	methanol	1.5	4.3	4.5
α-naphthyl	μ-Bondpak[a]	acetonitrile	1.5	4.8	5.5
2-thienyl	μ-Porasil	20% acetone/hexane	2.0	2.5	2.8

[a] Two reverse-phase columns (3.9 mm × 30 cm) in series were employed. [b] Monitored at 254 nm.

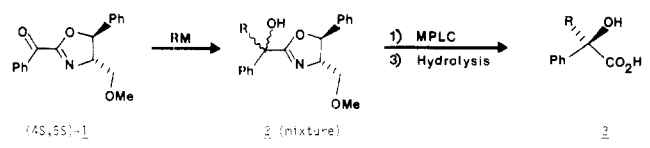
Table III. α-Hydroxy Acids 3 from Diastereomerically Pure Oxazolines 2

R in 3	mp, °C	$[\alpha]^{25}_D$, deg (c, EtOH)	config	anal. calcd C	calcd H	found C	found H
Me	114-116[a]	+36.3 (2.7)	*S*[f]				
Et	124-125[b]	+33.3 (0.87)	*S*[f]				
n-propyl	97-99	+21.6 (2.5)	*S*[f]	74.34	7.37[c]	74.43	7.23
isopropyl	103-105	+32.5 (2.0)	*S*[f]	68.04	7.22	68.32	7.18
isobutyl	118-120	+20.0 (2.0)	*S*[f]	69.23	7.69	68.62	7.76[d]
p-tolyl	122-123[e]	−2.4 (5.0)[g]	*S*[f]				
p-anisyl	137-139	−4.2 (1.3)	*S*	69.77	5.43	69.69	5.60
α-naphthyl	83-86	−4.0 (4.0)	*S*[f]	79.43	5.91[c]	79.15	5.92
2-thienyl	109-111	−20.0 (2.0)	*S*	61.54	4.27	61.38	4.35

[a] R. Barnes and B. Juliano, *J. Am. Chem. Soc.*, 81, 6462 (1959), report a melting point of 116-117 °C. [b] S. Mitsui et al., *Chem. Ind. (London)*, 233 (1964), report a melting point of 126 °C. [c] Analyses performed on corresponding oxazoline 2. [d] Contained trace of solvent which could not be removed. [e] A. McKenzie and E. W. Christie, *Biochem. Z.*, 277, 426 (1935), report a melting point of 125 °C. [f] Absolute configurations are known for these enantiomers: A. I. Meyers and J. Slade, *J. Org. Chem.*, companion paper in this issue. [g] Rotation at 546 nm.

to reach pure enantiomers which may serve as standards for asymmetric syntheses.

In this report we describe the resolution of α-substituted mandelic acids 3 by hydrolysis of 2 after separation on a previously described medium-pressure LC unit.[1] We have already described[3] the asymmetric alkylation of the benzoyloxazoline 1 with organolithium and Grignard reagents



(4S,5S)-1 2 (mixture) 3

furnishing the α-phenyl-α-hydroxy adducts 2 enriched (30–87%) in one diastereomer. Although H^1 NMR techniques were utilized in some instances to determine the diastereomeric ratio[3] of 2, the resulting α-hydroxy acids obtained after hydrolysis were in the main unknown with regard to their specific rotations. For the evaluation of the efficiency of the asymmetric alkylation of 1 to 2 and ultimately to 3, it was necessary to have enantiomerically pure hydroxy acids for comparison. This was routinely performed by resolution of 2 using medium-pressure LC to obtain diastereomerically pure materials which were hydrolyzed[3] to the enantiomerically pure acids 3. Although separations were done on a gram scale (Table I), it was also necessary to monitor these separations by using the highly efficient analytical tool, high-pressure liquid chromatography. Thus, crude diastereomeric mixtures of 2 were subjected to high-pressure LC analysis (Table II), and both diastereomers were visible as two distinct peaks with a UV detector. When the preparative separations were carried out, only those fractions which showed the complete ab-

(3) A. I. Meyers and J. Slade, *J. Org. Chem.*, companion paper in this issue.

sence of the minor diastereomer were hydrolyzed to the α-hydroxy acids (Table III). In this fashion, preparatively useful and enantiomerically pure acids **3** were obtained and characterized. The specific rotations of the acids are listed in Table III and may be assumed to represent at least 99% optical purity. As a check on the resolution efficiency, the α-methyl and the α-ethyl hydroxy acids previously described[4] gave $[\alpha]_D$ values in excellent agreement with those found in this work. The absolute configurations presented in Table III were all previously reported for the enantiomers presented except for the two cases of the *p*-anisyl and 2-thienyl acids. However, CD curves for all the acids in Table III were examined and gave the same general sense (negative) for the plot. Due to the low (215–220 nm) maxima, peaks and, therefore, molecular ellipticity (Θ) could not be ascertained. Since it is generally true[5] that compounds in a homologous series will exhibit the same sign for $\Delta\epsilon$ if they have the same absolute configuration at the chiral centers, this behavior provides further support to the assigned configuration for the *p*-anisyl and 2-thienyl derivatives.

In summary, diastereomers resulting from addition of organometallics to the benzoyloxazoline not only provide asymmetrically prepared α-hydroxy acids but may also be resolved with pressurized chromatography to enantiomerically pure products. It should be noted that no separation of diastereomers was possible by fractional crystallization (except for **2**, R = Me, previously reported[6]) or repeated elutions on preparative thin-layer plates.

Experimental Section

Medium-pressure liquid chromatography was performed on a home-built unit described in detail elsewhere.[1] The solvent system chosen for elution in Table I was based on obtaining an R_f of 0.1–0.15 on silica gel TLC plates (0.5 mm). Empirically this was found to be useful for achieving optimum separation and recovery of material. Samples of mixtures of **2** were introduced as 25–50% (by volume) solutions in the chosen eluting solvent and then chromatographed at a median pressure of 50 psi (extremes were 10–90 psi during the pump cycle) and at a flow rate of 15–20 mL/min. Fractions (5, 10, or 15 mL) were collected, and the presence of eluted materials was monitored by thin-layer chromatography (Merck, silica gel PF254, visualized by ultraviolet light). All the fractions possessing identical material and showing only a single spot were combined and the solvents evaporated to give pure material as indicated in Table I.

High-pressure liquid chromatography was performed on a Waters Associates instrument comprised of the following units: a Model 440 absorbance detector (UV); a Model R401 differential refractometer; a Model 6000A solvent delivery system; a Model U6K universal injector; a μ-Porasil No. 27477 3.9 mm × 30 cm column or a reverse-phase μ-Bondapak C_{18}, No. 27324, 3.9 mm × 30 cm column; a Houston Instrument Omniscribe Series B-5000 recorder. Samples of 0.5–2.0 μL were introduced as 5% (by volume) solutions in the appropriate eluting solvent and were chromatographed at pressures of 500–3000 psi at flow rates of 1–3 mL/min. Retention times and other parameters are given in Table II.

α-Substituted Madelic Acids 3. The fractions of **2** collected by medium-pressure LC which indicated the absence of any diastereomeric material were, after combination and concentration, subjected to the hydrolysis conditions reported in the accompanying paper.[3] The residue remaining, on concentration, gave analytically pure acids whose specific rotations are given in Table III.

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Registry No. 2a isomer 1, 63007-16-9; **2a** isomer 2, 63007-17-0; **2b** isomer 1, 69766-02-5; **2b** isomer 2, 69766-03-6; **2c** isomer 1, 73697-92-4; **2c** isomer 2, 73697-93-5; **2d** isomer 1, 73712-27-3; **2d** isomer 2, 73697-94-6; **2e** isomer 1, 73697-95-7; **2e** isomer 2, 73697-96-8; **2f** isomer 1, 73697-97-9; **2f** isomer 2, 73697-98-0; **2g** isomer 1, 73697-99-1; **2g** isomer 2, 73698-00-7; **2h** isomer 1, 73698-01-8; **2h** isomer 2, 73698-02-9; **2i** isomer 1, 73698-03-0; **2i** isomer 2, 73698-04-1; **3a**, 13113-71-8; **3b**, 24256-91-5; **3c**, 73698-05-2; **3d**, 73746-01-7; **3e**, 73698-06-3; **3f**, 52166-05-9; **3g**, 73698-07-4; **3h**, 73698-08-5; **3i**, 64471-38-1.

(4) R. Barnes and B. Juliano, *J. Am. Chem. Soc.*, 81, 6462 (1959), report $[\alpha]_D$ +35.3° for (*S*)-(+)-atrolactic acid. S. Mitsui, *Chem. Ind. (London)*, 223 (1954), reports $[\alpha]_D$ +33.7° for (*S*)-(+)-α-ethylmandelic acid.

(5) P. Crabbe, "Optical Rotary Dispersion and Circular Dichroism in Organic Chemistry", Holden-Day, San Francisco, 1965.

(6) A. I. Meyers and J. Slade, *Synth. Commun.*, 6, 601 (1976).

Reactivity of Phenoxide Ion with Aryl Radicals[1]

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The $S_{RN}1$ mechanism of aromatic substitution has been proved to operate on different kinds of aromatic compounds and nucleophiles. Several types of carbanions, phosphanions, and amide ions have been found to participate as nucleophiles by this mechanism.[2] Among these nucleophiles those having an element belonging to the 6A group of elements with general structure $Ph-Z^-$ have especially been objects of our attention.

Arenethiolate ions are known to react satisfactorily at saturated carbon sites,[3] at the 4-position of the isoquinoline system,[4] and at benzene ring sites by the $S_{RN}1$ mechanism.[2]

Recently we reported that phenyl selenide and phenyl telluride ions were two new nucleophiles probably operating by this mechanism.[5] These nucleophiles gave substitution products in photostimulated reactions in liquid ammonia, in yields that go from moderate to good, depending on the aromatic moiety and the leaving group of the substrate. These nucleophiles are supposed to follow the standard $S_{RN}1$ mechanism as sketched in Scheme I.[2]

Scheme I

$$ArX + \text{electron donor} \rightarrow (ArX)^{-}\cdot \quad (1)$$

$$(ArX)^{-}\cdot \rightarrow Ar\cdot + X^- \quad (2)$$

$$Ar\cdot + Ph-Z^- \rightarrow (Ar-Z-Ph)^{-}\cdot \quad (3)$$

$$(Ar-Z-Ph)^{-}\cdot + ArX \rightarrow (ArX)^{-}\cdot + Ar-Z-Ph \quad (4)$$

$$Z = S, Se, Te$$

Steps 2–4 are the chain-propagation cycle of the proposed mechanism. The radical anion formed in step 3 transfers its extra electron to the substrate to give the substitution product. This has been the main reaction pathway with PhS^- and $PhSe^-$ ions. $PhTe^-$ ion gave not only the substitution product but also products coming from the decomposition of the intermediate radical anion.[5] The relative reactivity of $PhS^-/PhSe^-$ is about 20 as determined in preliminary experiments.

Phenoxide ion instead is totally unreactive toward phenyl radicals in reactions stimulated by alkali metals,[6]

(1) This research was supported in part by the Consejo Nacional de Investigaciones Científicas y Técnicas, Argentina.

(2) Bunnett, J. F. *Acc. Chem. Res.* **1978**, *11*, 413.

(3) Kornblum, N. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 734.

(4) Zoltewicz, J. A.; Oestreich, T. M. *J. Am. Chem. Soc.* **1973**, *95*, 6863.

(5) Pierini, A. B.; Rossi, R. A. *J. Org. Chem.* **1979**, *44*, 4667.

(6) Rossi, R. A.; Bunnett, J. F. *J. Org. Chem.* **1973**, *38*, 3020.

0022-3263/80/1945-2914$01.00/0