(30 mL) and added, over a period of 8 h, to a solution of 4-(dimethylamino)pyridine (28 mg, 0.231 mmol) in benzene (50 mL) heated at 80 °C. After complete addition, the solution refluxed for 15 h. The reaction mixture was washed with 5% hydrochloric acid solution, water, 5% sodium bicarbonate solution, and brine. The organic layer was dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography (hexane:ether = 2:1) to yield pure solid lactone **19** (20 mg, 60%). Mp = 169-170 °C (hexane-ether). $[\alpha]_D$ = +97.7° (c = 1.2, $CHCl_3$). IR: 1710, 1600, 1160, 1090. ^1H NMR: 6.56 (d, 1 H, Ar, J = 2.2 Hz); 6.44 (d, 1 H, C=C, J = 16.4 Hz); 6.35 (d, 1 H, Ar, J = 2.2 Hz); 6.33 (dt, 1 H, J = 16.4 and 4.1 Hz); 5.20 (m, 1 H, CHOCO); 3.82, 3.79 (2 s, 6 H, OCH_3); 2.80 (m, 4 H, CH_2S), 2.50-1.50 (m, 14 H, CH_2); 1.36 (d, 3 H, CH_3, J = 6.3 Hz). ^{13}C NMR: 168.2 (CO); 161.0, 157.4 (C-2, C-3); 136 (C-6); 133.0, 125.7 (2 CH=); 116.7 (C-1); 101.2 (C-5); 97.4 (C-3); 70.9 (CHO); 55.9, 55.4, 52.7 (2 OCH_3, SCS); 36.4 35.4, 35.0, 29.7, 26.1 (2 C), 25.7, 21.1, 20.1, 18.3 (9 CH_2, CH_3). MS m/z: 436 (M^+, 53), 361 (27), 330 (23); 234 (21), 217 (36), 215 (20), 205 (47), 203 (50), 189 (100), 145 (56), 107 (21).

(+)-(S)-Dimethylzearalenone (1b). To a stirred solution of lactone **19** (9 mg, 0.02 mmol) in aqueous 80% acetonitrile (1 mL) were successively added calcium carbonate (2.5 mg) and iodomethane (9 mL, 0.1 mmol). The mixture was maintained at room temperature, and additional portions (3 × 0.1 mmol) of iodomethane were added (4 days; TLC, hexane:ethyl acetate = 1:1). Dichloromethane addition and filtration by a short silica gel column to retain sulfonium salts yielded pure **1b** (6 mg, 84%) as a white solid. Mp = 110-111 °C (hexane-ether). $[\alpha]_D$ = +23.7° (c = 0.35, MeOH) [lit.[2a] mp = 108-110 °C; $[\alpha]_D$ = +25 (MeOH)]. IR: 1720, 1710, 1600, 1580, 1270, 1210, 1160. ^1H NMR: 6.60 (d, 1 H, Ar, J = 2.1 Hz); 6.39 (dd, 1 H, C=C, J = 15.5 and 1.9 Hz); 6.38 (d, 1 H, Ar, J = 2.1 Hz); 5.99 (ddd, 1 H, C=C, J = 15.5, 4.4 and 10.0 Hz); 5.32 (m, 1 H, HCOCO); 3.83, 3.80 (2 s, 6 H, OCH_3); 2.85-1.45 (m, 12 H, CH_2); 1.34 (d, 3 H, CH_3, J = 6.3 Hz). MS m/z: 346 (M^+, 22), 235 (19), 217 (100), 207 (31), 204 (30), 189 (86), 151 (37).[2e]

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Supplementary Material Available: ^1H NMR spectra of **1b**, **3-19**, ^{13}C NMR spectra of **3-7** and **9-19**, and mass spectra of **1b**, **3-5**, and **7-19** (59 pages). Ordering information is given on any current masthead page.

Optically Active Amines. 36.[1] Application of the Benzene Chirality Rule to Ring-Substituted Mandelic Acids

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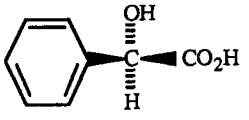
The positive sign of the ^1L_b Cotton effects (CEs) from about 250 to 270 nm in the circular dichroism (CD) spectrum of (R)-mandelic acid and its sodium salt is determined by vibronic borrowing from allowed transitions at shorter wavelength. On ring substitution, transition moments are induced in the benzene ring bonds adjacent to the attachment bond of the chiral group, resulting in enhanced coupling of the ^1L_b transition with the chiral group. The sign of the ^1L_b CEs for a ring-substituted (R)-mandelic acid may be the same or opposite to that of (R)-mandelic acid, but the sign of its ^1L_b CEs can often be correlated with its absolute configuration provided the ring position of the substituent and its spectroscopic moment is taken into account.

Among the many structural variations that have been examined to obtain β-lactam antibiotics with higher levels and wider breadth of antimicrobial activity have been those involving the acylamino side chain.[2] Some studies have focused on semisynthetic penicillins[2] and cephalosporins[3,4] and totally synthetic 1-oxacephens[5] and tricyclic β-lactams[6] in which the acyl group on the side chain was derived from mandelic acid (**1a**). For the cephalosporins,



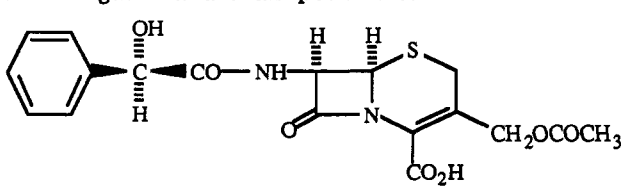
(R)-**1a**

also included were studies of the in vitro and in vivo activity of benzene ring-substituted derivatives of (7R)-7-((R)-mandelamido)cephalosporanic acid (**2**) against Gram-negative and Gram-positive bacteria.[3] Since **2** is

Table I. Mandelic Acids Used

compd	name	$[\alpha]^{23-25}_D$,[a] deg	% ee
(R)-**1a**	(R)-mandelic acid	-152[b]	99[c]
(S)-**1b**	(S)-p-methylmandelic acid	+145[b]	95[d]
(S)-**1f**	(S)-m-methylmandelic acid	+137[e]	95[d]
(R)-**1g**	(R)-m-chloromandelic acid	-113[e]	97[d]
(R)-**1h**	(R)-m-fluoromandelic acid	-119[f]	92[g]
(R)-**1i**	(R)-o-methylmandelic acid	-171[e]	98[d]
(R)-**3c**	(R)-p-(aminomethyl)mandelic acid	-116[h]	94[d]

[a] c 0.333-4.40 g/100 mL of solvent. [b] Methanol as solvent. [c] On the basis that the rotatory power of this compound in ref 8 corresponds to 100% ee. [d] On the basis that the rotatory power of this compound or its enantiomer in ref 3 corresponds to 100% ee. [e] Ethanol as solvent. [f] Acetone as solvent. [g] On the basis that the rotory power of this compound in ref 9 corresponds to 100% ee. [h] 1 N hydrochloric acid as solvent.



2

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(2) Nayler, J. H. C. *Adv. Drug Res.* **1973**, *7*, 1-105.
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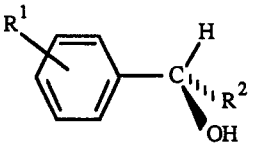
0022-3263/91/1956-2322$02.50/0

Table II. Spectral Data for Mandelic Acids in Methanol

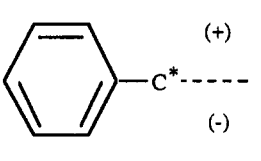


		^1L_b band origin			
		$R^2 = CO_2H$ ((*R*)-1)		$R^2 = CO_2^-$ ((*R*)-3[a])	
code	R^1	EA λ_{max}, nm (ϵ^c)	CD[b] λ_{max}, nm ($\Delta\epsilon^d$)	EA λ_{max}, nm (ϵ^c)	CD[b] λ_{max}, nm ($\Delta\epsilon^d$)
		No Additional Ring Substituent			
a	H	267 (79)	269 (+0.067)	268 (75)	268 (+0.024)
		Para Substituted			
b	CH_3[e]	273 (160)	273 (–0.18)	273 (240)	274 (–0.27)
c	$^+NH_3CH_2$[f]			270 (160)	271 (+0.094)
d	$ClNH_3CH_2$[g]	270 (160)	271 (+0.11)		
e	NH_2CH_2			271 (140)	273 (–0.082)
		Meta Substituted			
f	CH_3[e]	272 (340)	274 (+0.14)	273 (290)	274 (+0.20)
g	Cl	275 (260)	275 (+0.19)	275 (240)	276 (+0.25)
h	F	269 (980)	270 (+0.11)	269 (980)	270 (+0.25)
		Ortho Substituted			
i	CH_3	273 (280)	275 (–0.036)	273 (250)	273 (+0.045)

[a] Except for (*R*)-**3c**, formed in situ by the addition of 2 drops of 10% KOH to the sample cell. [b] Corrected to 100% ee. [c] Molar absorptivity. [d] Molar dichroic absorption. $\Delta\epsilon = [\theta]/3300$ where $[\theta]$ is the molecular ellipicity. [e] Enantiomer used. [f] Water as solvent. [g] Formed in situ by the addition of 2 drops of 10% hydrochloric acid to the sample cell containing (*R*)-**3c**.

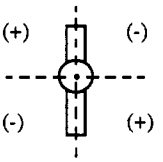
substantially more active in vitro against both types of bacteria than is its (*S*)-mandelamido diastereomer, biological evaluation was done with the ring-substituted (*R*)-mandelic acid derivatives. The absolute configurations of some of these ring-substituted mandelic acids were established earlier, but for others, only the racemic form had previously been characterized. The absolute configurations of the latter mandeloyl groups were established on the basis of the proton nuclear magnetic resonance (^1H NMR) spectra of the chephalosporins themselves,[3] the N–H doublet for the (*R*)-mandelamido group of the cephalosporin appearing at lower field (δ 8.54) than that for the (*S*)-mandelamido group (δ 8.38). The absolute configurations of the monosubstituted mandelic acids, however, are more easily established by an interpretation of the circular dichroism (CD) spectra of the ring-substituted mandelic acids using the benzene chirality rule.[7]

The CD spectra of chiral benzene compounds such as (*R*)-mandelic acid ((*R*)-**1a**) and other enantiopure (100% ee), ring-substituted mandelic acids (Table I) show a number of Cotton effects (CEs) from about 255 to 270 nm (Figure 1). These CEs are associated with electronic transitions from the lowest energy vibrational mode in the ground state to vibrational modes in the ^1L_b electronically excited state of the benzene chromophore.[10-12] For benzene compounds without additional ring substituents, earlier work[13,14] indicates that the sign of the ^1L_b CEs is determined by vibronic borrowing[15,16] from benzene transitions at shorter wavelength, and an empirical sector rule has been established[1] to correlate this sign with the absolute configuration of a chiral center contiguous to the benzene ring. For a particular absolute configuration, the sign can be predicted on assessment of the preferred conformation of the chiral group about its attachment bond to the benzene ring and with the use of quadrant projection I. The signs in the latter give the CD contributions to the ^1L_b CEs by groups lying in the four quadrants. The sum of these contributions gives the sign to the ^1L_b CEs associated with transitions from the lowest energy vibrational mode of the ground state to totally symmetrical vibrational modes in the first electronically excited state of the benzene chromophore.[10,11] The lowest energy of these CEs is the ^1L_b band origin. For a few enantiopure benzene compounds, additional, weak CD maxima are observed within the ^1L_b band with a sign opposite to that of the ^1L_b band origin. These latter CD maxima are associated with transitions to nontotally symmetric vibrational modes in the electronically excited state.[10]



near quadrants

Ia



all quadrants

Ib

Since the rotatory contributions of a carboxyl group and a carboxylate group are larger than that of an hydroxyl group,[1] and the preferred conformation of both (*R*)-mandelic acid[17] ((*R*)-**1a**) and its potassium salt ((*R*)-**3a**) is

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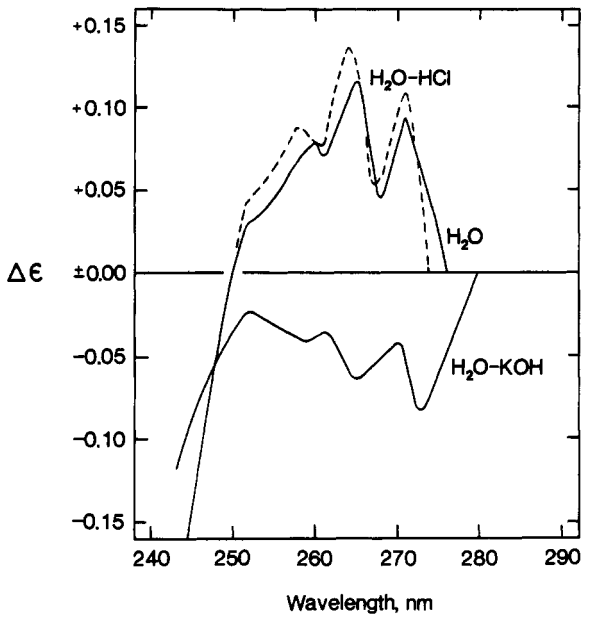


Figure 1. Circular dichroism spectra of *p*-(aminomethyl)mandelic acid ((*R*)-**3c**) in water (H_2O) and with added excess hydrochloric acid (H_2O–HCl) to give (*R*)-**1d** and aqueous potassium hydroxide (H_2O–KOH) to give (*R*)-**3e**.

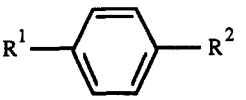
such that the hydrogen atom at the chiral center nearly eclipses the benzene ring plane (Table II),[18] both (*R*)-**1a** and (*R*)-**3a** show positive ^1L_b CEs, as indicated by the sign of the respective ^1L_b band origins (Table II).

On additional ring substitution of a chiral benzene compound, transition moments are induced in the benzene ring bonds adjacent to the attachment bond of the chiral group.[13] These induced bond transition moments result in enhanced coupling of the ^1L_b transition with the chiral group, and the sign of the ^1L_b CEs may be the same or different from that of the unsubstituted parent.[9,12-14,19-23] Since on additional ring substitution there is no significant change in the preferred conformation of the chiral group about its attachment bond to the benzene ring,[7,18,22] a reversal of sign of the ^1L_b CEs may be viewed as the overshadowing of the vibronic contribution to the ^1L_b CEs by an induced contribution of opposite sign. This latter contribution depends on both the ring position and spectroscopic moment[24] of the additional substituent. These considerations can be used to correlate the absolute configurations of a chiral center contiguous to a substituted benzene ring with the sign of its ^1L_b CEs, the details for the application of this method being called the benzene chirality rule.[7] The rule is now applied to the interpretation of the ^1L_b CEs of ring-substituted mandelic acids for establishment of their absolute configurations.

Results and Discussion

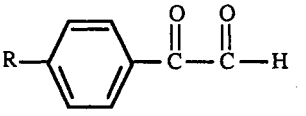
As seen in Table II, the sign of the ^1L_b CEs for (−)-*p*-methylmandelic acid[25] ((−)-**1b**) is negative and opposite to that of those for (*R*)-mandelic acid ((*R*)-**1a**). The spectroscopic moment of a methyl group is positive,[24] and for a group with a positive spectroscopic moment in the para position, the induced contribution to the ^1L_b CEs is opposite to that of the vibronic contribution.[7] Since all enantiopure mandelic acids of established absolute configuration and para-substituted with an atom or group with a positive spectroscopic moment so far reported[9,19] show ^1L_b CEs with a sign opposite to that of the unsubstituted parent, (−)-**1b** can be assigned the *R* configuration. The same assignment can be inferred from the report[26] that both phenylglyoxal (**4a**) and *p*-tolylglyoxal (**4b**) on digestion with fresh carp muscle tissue gave (−)-**1a** and (−)-**1b**, respectively, by way of an asymmetric enzymic synthesis, both with the same *R* absolute configuration.

Table III. Electronic Absorption Data for Substituted Benzenes in Methanol



compd	R^1	R^2	^1L_b band origin λ_{max}, nm (ϵ^a)
5a	CH_3	CH_2NH_3Cl	271 (130)
5b	H	CH_2NH_3Cl	267 (120)
5c	H	CH_3	268 (230)
5d	H	CH_2NH_2[b]	268 (100)
5e	CH_3	CH_2NH_2[b]	273 (310)

[a] Molar absorptivity. [b] Formed in situ from its purified hydrochloride salt by addition of 1 drop of 10% KOH to the sample cell.



4a, R = H

b, R = CH_3

In water, (−)-*p*-(aminomethyl)mandelic acid ((*R*)-**3c**) exists as a zwitterion, and on the basis of a negative spectroscopic moment for the *p*-ammoniomethyl group, the sign of the ^1L_b CEs is positive as predicted (Figure 1). The sign of the ^1L_b CEs of (*R*)-**3c** is the same sign as that of (*R*)-**3a** because both the vibronic and induced contributions have the same sign when a group with a negative spectroscopic moment is substituted in the para position.[7] That the spectroscopic moment for the ammoniomethyl group is negative is seen in the electronic absorption (EA) data in Table III. The ^1L_b band origin molar absorptivity (ϵ) for (*p*-methylbenzyl)ammonium chloride (**5a**) is slightly larger than that for benzylammonium chloride (**5b**) and substantially smaller than that for toluene (**5c**), the negative spectroscopic moment for the ammoniomethyl group in **5a** partially canceling the positive spectroscopic of the methyl group.[27]

Treatment of (*R*)-**3c** with hydrochloric acid protonates the carboxylate group to give (*R*)-**1d**, and as expected the sign of the ^1L_b CEs remains unchanged (Figure 1). Treatment of (*R*)-**3c** with potassium hydroxide gives potassium *p*-(aminomethyl)mandelate ((*R*)-**3e**), and the ^1L_b CEs are now negative (Figure 1). The negative CEs are the result of a negative induced rotatory contribution of the *p*-aminomethyl group. It should be noted that the spectroscopic moment of this latter group was given earlier as negative,[28] but the data in Table III clearly show it to

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(19) Korver, O. *Tetrahedron* **1970**, *26*, 5507–5518.
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(25) In Table II, the sign of the ^1L_b band origin is given for the *R* configuration regardless of which enantiomer was actually used.
(26) Fujise, S.; Iwakiri, M. *Biochem. Z.* **1936**, *283*, 298–300.
(27) Matsen, F. A. In *Chemical Applications of Spectroscopy*; West, W., Ed.; Interscience: New York, 1956; Chapter V, Part 2.

be positive.[27] As seen in the table, the spectroscopic moment of the aminomethyl group in **5d** augments that of the positive methyl group in **5e**, and thus the spectroscopic moment of both groups is positive.

When a group with a positive spectroscopic moment is in the meta position, the vibronic and the induced contribution have the same sign. Thus, (−)-**1f**, (−)-**1g**, and (−)-**1h**, all showing positive ^1L_b CEs, are assigned the *R* configuration. This configuration was assigned earlier to (−)-**1f** on the basis of the ^1H NMR spectrum of its cephalosporanic acid derivative[3] and to (−)-**1g** and (−)-**1h** on observation of the ^1H NMR spectra of their methyl esters in (+)-α-(1-naphthyl)ethylamine.[9] The configurational assignment for (+)-**1g** as *S* was confirmed by its reductive dehalogenation to (*S*)-**1a**,[19] and that for (−)-**1h** as *R* by comparison of its CD spectrum with that of (*R*)-**1g**,[19] both (−)-**1h** and (*R*)-**1g** showing positive ^1L_b CEs.[19] More recently, however, the enantiomer of **1h** showing negative ^1L_b CEs in methanol was reassigned the *R* configuration,[21] contrary to the prediction here by the benzene chirality rule.[7] We now find, however, that the earlier configurational assignment was correct in that the potassium salt of (−)-*m*-fluoromandelic acid on hydrogenolysis over Raney nickel in aqueous ethanol gave (*R*)-mandelic acid. Thus, both (*R*)-**1h** and (*R*)-**3h** show, as predicted,[7] positive ^1L_b CEs.

Finally (−)-*o*-methylmandelic acid ((−)-**1i**) was assigned the *R* configuration on the basis of the ^1H NMR spectrum of its 7-aminocephalosporanic acid derivative.[3] This same configurational assignment can also be made by using the benzene chirality rule.[7] Thus, a methyl group with a positive spectroscopic moment when ortho to the attachment bond of the chiral group induces a positive contribution to the ^1L_b CEs, which overshadows the negative vibronic contribution, and the sign of the ^1L_b CE is opposite to that of the unsubstituted parent.[22] Treatment of (*R*)-**1i** with potassium hydroxide gives the carboxylate salt (*R*)-**3i**, and the sign of the ^1L_b CEs is reversed from that of (*R*)-**1i**. The positive vibrational contribution in (*R*)-**3i** is not overshadowed by the negative induced contribution, and the sign of the ^1L_b CEs is the same as the unsubstituted parent (*R*)-**3a**.

The CD observations with (*R*)-*o*-methylmandelic acid ((*R*)-**1i**) and its potassium salt ((*R*)-**3i**) underscores the point made earlier[7] in connection with the benzene chirality rule. When the vibronic and induced contributions to the ^1L_b CEs are of opposite signs, a prediction as to the sign of the ^1L_b CEs shown by a particular enantiomer is somewhat ambiguous. However, for all previously reported enantiopure (phenylalkyl)carbinols,[7] (phenylalkyl)carbinamines,[7,13] mandelic acids,[9,19,21] methyl mandelates,[19] and β-hydroxy-β-phenylpropionic acids,[20] ortho or para substituted with an atom or group with a positive spectroscopic moment[24] (CH_3, F, Cl, Br, OCH_3), ^1L_b CEs with a sign opposite to that of their unsubstituted parents are seen. For the corresponding enantiopure, ortho- or para-substituted mandelic acid salts, only the CD spectra of those shown in Table II have been reported, and of these, only potassium (*R*)-*o*-methylmandelate ((*R*)-**3i**) has ^1L_b CEs of the same sign as that of potassium (*R*)-mandelate ((*R*)-**3a**) itself. For other ortho- or para-substituted mandelic acids, it is not known if the sign of the ^1L_b CEs is reversed on formation of the corresponding salt from that shown by the corresponding mandelic acid.

When both the vibronic and induced contributions have the same sign, there is no ambiguity as to the prediction of the sign of the ^1L_b CEs for a particular enantiomer.[7] Thus, the enantiopure mandelic acids (*R*)-**1d,f–h** and their salts (*R*)-**3c,f–h** in Table II, para substituted with a group with a negative spectroscopic moment[24] ($^+NH_3CH_2$), or meta substituted with a group or an atom with a positive spectroscopic moment[24] (CH_3, Cl, F), are unambiguously predicted to show ^1L_b CEs of the same sign as their respective unsubstituted parents, (*R*)-mandelic acid ((*R*)-**1a**) and potassium (*R*)-mandelate ((*R*)-**3a**).

Experimental Section

Melting points were taken in open capillary tubes and are corrected. Rotatory powers at the sodium D line were measured in a 1-dm sample tube. Electronic absorption spectra were measured with a Cary Model 14 spectrometer with matched 1-cm cells and the normal variable slit. Circular dichroism spectra were obtained at 24–28 °C with a Cary Model 60 spectropolarimeter with a CD Model 6001 accessory. The sample cell was 1 cm, and the slit was programmed for a spectral band width of 1.5 nm. Spectral measurements began at 300 nm, and the molecular ellipicity ($[\theta]$) values are corrected to 100% enantiomeric excess (ee). The EA and CD spectra of the mandelic acid salts were usually determined by addition of 2 drops of 10% aqueous potassium hydroxide or 10% hydrochloric acid to the sample cell (3 mL) containing the mandelic acid. For the few samples where a different dilution was used for the spectral measurement of the salt, enough acid or base was added to ensure complete conversion to the salt. Concentrations given with the CD spectra are for grams of acid or zwitterion per 100 mL of solvent. *p*-Methylbenzylamine hydrochloride (**5a**) and benzylamine hydrochloride (**5b**) were recrystallized from ethanol. After their EA spectra were measured, 1 drop of 10% aqueous potassium hydroxide was added to the sample cells (3 mL) and the EA spectra of the amines were measured.

(*R*)-Mandelic acid ((*R*)-1a): mp 129–132 °C, $[\alpha]^{24}_D$ −152° (*c* 2.52 CH_3OH) [lit.[8] mp 133 °C, $[\alpha]^{18}_D$ −154° (*c* 1.47, absolute CH_3CH_2OH)]; 99% ee; EA max (CH_3OH) 267 nm (ε 79) (sh), 264 (160), 258 (200), 252 (180), 246 (160) (sh); (CH_3OH–KOH) 268 (75) (sh), 265 (140), 258 (190), 253 (160), 248 (120), 216 (5200) (sh); CD (CH_3OH, *c* 0.0552) $[\theta]_{273}$ ±0, $[\theta]_{269}$ +220, $[\theta]_{266}$ +30, $[\theta]_{263}$ +290, $[\theta]_{260}$ +40, $[\theta]_{257}$ +190, $[\theta]_{254}$ ±0; (CH_3OH, *c* 0.005 52) $[\theta]_{254}$ ±0, $[\theta]_{223}$ −7500, $[\theta]_{221}$ −7200; (CH_3OH–KOH, *c* 0.114) $[\theta]_{280}$ ±0, $[\theta]_{274}$ −20,[29] $[\theta]_{271}$ ±0, $[\theta]_{268}$ +80, $[\theta]_{266}$ +40, $[\theta]_{264}$ +110, $[\theta]_{262}$ +90, $[\theta]_{258}$ +110, $[\theta]_{255}$ +40, $[\theta]_{253}$ +60, $[\theta]_{250}$ ±0; (CH_3OH–KOH, *c* 0.003 83) $[\theta]_{250}$ ±0, $[\theta]_{220}$ −23 000, $[\theta]_{217}$ −21 000.

(*S*)-*p*-Methylmandelic Acid ((*S*)-1b). The racemic acid was prepared in 60% yield from tolualdehyde by the phase-transfer method of Merz.[30] After recrystallization from toluene, (±)-**1b** had mp 143–145 °C (lit.[30] mp 144 °C) and was resolved by fractional recrystallization of the (−)-α-phenylethylamine salts from methanol (2×). The less soluble salt (48%) had mp 189–200 °C and $[\alpha]^{28}_D$ +47° (*c* 1.25, CH_3OH) and was decomposed in 3 N hydrochloric acid. The mandelic acid was extracted (3×) into ether, and the ethereal solution was dried (Na_2SO_4). Evaporation of the ether and recrystallization of the residue from toluene gave (*S*)-**1b** (90%): mp 128–133 °C, $[\alpha]^{28}_D$ +145° (*c* 1.09, CH_3OH) [lit.[3] mp 132–134 °C, $[\alpha]^{25}_D$ −153° (*c* 0.3, CH_3CH_2OH) for the *R* enantiomer]; 95% ee; EA max (CH_3OH) 273 nm (ε 160), 268 (180), 264 (250), 257 (190), 252 (170), 220 (6900); (CH_3OH–KOH) 273 (240), 267 (250) (sh), 265 (300), 259 (240), 253 (180) (sh), 222 (8100); CD (CH_3OH, *c* 0.0288) $[\theta]_{278}$ ±0, $[\theta]_{273}$ +580, $[\theta]_{270}$ +280, $[\theta]_{266}$ +580, $[\theta]_{262}$ +440, $[\theta]_{259}$ +470 $[\theta]_{255}$ +400; (CH_3OH, *c* 0.002 88) $[\theta]_{255}$ +400, $[\theta]_{226}$ +36 000, $[\theta]_{222}$ +33 000; (CH_3OH–KOH, *c* 0.0274) $[\theta]_{280}$ ±0, $[\theta]_{274}$ +890, $[\theta]_{272}$ +400, $[\theta]_{268}$ +840, $[\theta]_{263}$ +530, $[\theta]_{261}$ +580, $[\theta]_{257}$ +350 (sh), $[\theta]_{249}$ +190, $[\theta]_{239}$ +1200.

(*S*)-*m*-Methylmandelic Acid ((*S*)-1f). The racemic acid was prepared from *m*-tolualdehyde using the phase-transfer method of Merz.[30] After recrystallization from toluene, (±)-**1f** had mp 91–93 °C (lit.[31] mp 93–94 °C). The racemic acid was resolved by

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(29) This CD maximum is assumed not to be associated with the ^1L_b origin.

(30) Merz, A. *Synthesis* **1974**, 724–725.

(31) Papa, D.; Schwenk, E.; Ginsberg, H. F. *J. Org. Chem.* **1949**, *14*, 723–731.

fractional recrystallization (4×) of the (-)-α-phenylethylamine salts from isopropyl alcohol. The less soluble salt (24%) had mp 154-157 °C and $[\alpha]^{25}_D$ +46° (c 1.0, CH_3CH_2OH). The mandelic acid (S)-**1f** was isolated as outline above for (S)-**1b** and recrystallized from toluene: mp 108-110 °C, $[\alpha]^{25}_D$ +137° (c 0.333, CH_3CH_2OH) [lit.[3] mp 109-112 °C, $[\alpha]^{25}_D$ -144° (c 0.3, CH_3CH_2OH) for the R enantiomer]; 95% ee; EA max (CH_3OH) 272 nm (ε 340), 265 (380), 258 (340) (sh); (CH_3OH-KOH) 273 (290), 265 (350), 258 (300) (sh); CD (CH_3OH, c 0.0251) $[\theta]_{277}$ ±0, $[\theta]_{274}$ -470, $[\theta]_{270}$ -130, $[\theta]_{267}$ -450, $[\theta]_{264}$ -200, $[\theta]_{261}$ -210, $[\theta]_{254}$ ±0; (c 0.00100) $[\theta]_{254}$ ±0, $[\theta]_{226}$ +1700, $[\theta]_{206}$ ±0; (CH_3OH-KOH, c 0.0500) $[\theta]_{280}$ ±0, $[\theta]_{274}$ -670, $[\theta]_{271}$ -280, $[\theta]_{266}$ -470, $[\theta]_{263}$ -300, $[\theta]_{261}$ -340, $[\theta]_{246}$ ±0, $[\theta]_{240}$ +670.

(R)-m-Chloromandelic acid[32] **((R)-1g)**: mp 103-105 °C, $[\alpha]^{23}_D$ -113° (c 4.40, CH_3CH_2OH) [lit.[3] mp 103-105 °C, $[\alpha]^{25}_D$ -116° (c 4, C_2H_5OH)]; 97% ee; EA max (CH_3OH) 275 nm (ε 260), 267 (310), 261 (270), 253 (390) (sh); (CH_3OH-KOH) 275 (240), 267 (310), 261 (250), 254 (220); CD (CH_3OH, c 0.0358) $[\theta]_{278}$ ±0, $[\theta]_{275}$ +620, $[\theta]_{272}$ +280, $[\theta]_{267}$ +650, $[\theta]_{264}$ +340, $[\theta]_{261}$ +370, $[\theta]_{256}$ +32 (sh), $[\theta]_{252}$ ±0, $[\theta]_{243}$ -1400; (CH_3OH-KOH, c 0.0358) $[\theta]_{281}$ ±0, $[\theta]_{276}$ +810, $[\theta]_{273}$ +400, $[\theta]_{268}$ +850, $[\theta]_{264}$ +420, $[\theta]_{262}$ +530, $[\theta]_{255}$ +260 (sh), $[\theta]_{247}$ ±0, $[\theta]_{243}$ -830.

(R)-m-Fluoromandelic Acid ((R)-1h). The racemic acid was prepared in 28% yield from m-fluorobenzaldehyde by way of the corresponding cyanohydrin.[33] Recrystallization from benzene gave a somewhat impure (±)-**1h**: mp 80-85 °C [lit.[9] mp 97 °C]. The acid was resolved by fractional crystallization of its (-)-ephedrine salt from 95% ethanol (2×). The less soluble salt (28%) had $[\alpha]^{25}_D$ -59° (c 4.33, CH_3OH). The mandelic acid (R)-**1h** was isolated as outlined above for the isolation of (S)-**1b** from its salt and recrystallized from benzene: mp 115-117 °C, $[\alpha]^{24}_D$ -119° (c 2.83, acetone) [lit.[9] mp 121 °C, $[\alpha]^{25}_{578}$ -129° (c 1, acetone)]; 92% ee; ^1H NMR (300 MHz, CD_3SOCD_3) δ 5.07 (s, 1, CHOH), 6.0 (v br s, 2), 7.07 (dt, 1, J = 2.2 and 8.4 Hz, ArH), 7.24 (m, 2, ArH), 7.36 (m, 1, ArH); EA max 269 nm (ε 980), 262 (1000), 257 (670), 251 (390), (CH_3OH-KOH) 269 (980), 263 (970), 257 (640), 252 (390); CD (CH_3OH, c 0.0325) $[\theta]_{273}$ ±0, $[\theta]_{270}$ +370, $[\theta]_{267}$ +90, $[\theta]_{263}$ +320, $[\theta]_{258}$ +200 (sh), $[\theta]_{252}$ ±0, $[\theta]_{243}$ -2700, (CH_3OH-KOH, c 0.0325) $[\theta]_{275}$ ±0, $[\theta]_{270}$ +840, $[\theta]_{267}$ +410, $[\theta]_{263}$ +880, $[\theta]_{259}$ +580, $[\theta]_{257}$ +610, $[\theta]_{252}$ +280 (sh), $[\theta]_{245}$ ±0, $[\theta]_{235}$ -3000.

(R)-o-Methylmandelic acid[32] **((R)-1i)**: mp 61-63 °C, $[\alpha]^{24}_D$ -171° (c 2.66, CH_3CH_2OH) [lit.[3] mp 61-63 °C, $[\alpha]^{25}_D$ -175° (c 2, CH_3CH_2OH)]; 98% ee; EA max (CH_3OH) 273 nm (ε 280), 265 (330), 261 (300); (CH_3OH-KOH) 273 (250), 264 (310); CD (CH_3OH, c 0.0537) $[\theta]_{280}$ ±0 $[\theta]_{275}$ -120, $[\theta]_{273}$ -20, $[\theta]_{269}$ -110, $[\theta]_{265}$ -20, $[\theta]_{263}$ -60, $[\theta]_{255}$ -20, $[\theta]_{245}$ -1100; (CH_3OH-KOH, c 0.0537) $[\theta]_{277}$ ±0, $[\theta]_{276}$ -30,[29] $[\theta]_{275}$ ±0, $[\theta]_{273}$ +150, $[\theta]_{269}$ +50, $[\theta]_{265}$ +120, $[\theta]_{263}$ +90, $[\theta]_{257}$ +100, $[\theta]_{247}$ ±0, $[\theta]_{238}$ -1000.

(R)-p-(Aminomethyl)mandelic acid[32] **((R)-3c)**: mp >260 °C, $[\alpha]^{23}_D$ -116° (c 1.5, 1 N HCl) [lit.[3] mp >200 °C, $[\alpha]^{25}_D$ -124° (c 1.5, 1 N HCl)]; 94% ee; EA max (H_2O) 270 nm (ε 160), 265 (250), 260 (280), 255 (230); (H_2O-HCl) 270 (160), 265 (240), 260 (240), 255 (180); (H_2O-KOH) 271 (140) (sh), 267 (200) (sh), 262 (250), 256 (230), 253 (190) (sh); CD (H_2O, c 0.0400) $[\theta]_{276}$ ±0, $[\theta]_{271}$ +310, $[\theta]_{268}$ +150, $[\theta]_{265}$ +380, $[\theta]_{261}$ +230, $[\theta]_{260}$ +260, $[\theta]_{253}$ +120 (sh), $[\theta]_{250}$ ±0, $[\theta]_{238}$ -2100; (H_2O-HCl, c 0.0400) $[\theta]_{274}$ ±0, $[\theta]_{271}$ +360, $[\theta]_{267}$ +170, $[\theta]_{264}$ +450, $[\theta]_{261}$ +250, $[\theta]_{258}$ +290, $[\theta]_{254}$ +150 (sh), $[\theta]_{250}$ ±0, $[\theta]_{249}$ -100; (H_2O-KOH, c 0.0400) $[\theta]_{280}$ ±0, $[\theta]_{273}$ -270, $[\theta]_{271}$ -140, $[\theta]_{265}$ -210, $[\theta]_{261}$ -120, $[\theta]_{259}$ -140, $[\theta]_{252}$ -75, $[\theta]_{243}$ -390.

p-Methylbenzylamine hydrochloride (5a): EA max (CH_3OH) 271 nm (ε 130), 266 (160), 262 (230), 255 (180), 251 (130) (sh), (CH_3OH-KOH) 273 (310), 267 (290), 264 (320), 259 (250), 252 (160) (sh).

Benzylamine hydrochloride (5b): EA max (CH_3OH) 267 nm (ε 120), 263 (170), 261 (170), 256 (210), 251 (150), 246 (110) (sh), 242 (72) (sh), (CH_3OH-KOH) 268 (100), 264 (140), 261 (150) (sh), 258 (190), 252 (150), 247 (110) (sh), 242 (70) (sh).

Toluene (5c): EA max (CH_3OH) 268 nm (ε 230), 265 (170), 262 (250), 260 (210), 255 (190), 249 (120) (sh), 243 (75) (sh).

Hydrogenolysis of (R)-m-Fluoromandelic Acid ((R)-1h). A mixture of (R)-**1h**, $[\alpha]^{24}_D$ -119° (c 2.83, acetone) (0.30 g, 1.8 mmol), potassium hydroxide (1.12 g, 19.9 mmol), 90% aqueous ethanol (50 mL), and Raney nickel (2.0 g, wet) was stirred under an atmosphere of hydrogen (680 mmHg, 25 °C). An equivalent amount of hydrogen (47 mL, 1.7 mmol) was consumed in 1.5 h, and the catalyst was removed by filtration. The filtrate was acidified (pH <2) and evaporated to about 15 mL, and water (30 mL) was added. The solution was extracted with ether (2 × 25 mL). The dried ($MgSO_4$) ethereal solution was evaporated at reduced pressure. Recrystallization of the solid residue from benzene gave (R)-mandelic acid ((R)-**1a**) (90 mg, 34%): mp 122-124 °C, $[\alpha]^{25}_D$ -139° (c 1.14, H_2O) [lit.[17] $[\alpha]^{26}_D$ -130° (c 3.24, H_2O)]; ^1H NMR (300 MHz, CD_3SOCD_3) δ 5.02 (s, 1, CHOH), 7.30 (m, 3, ArH), 7.42 (m, 2, ArH). This ^1H NMR spectrum was different from that of (R)-**1h** but identical with that of (R)-**1a** under the same conditions of observation.

(32) Purchased from Niels Clauson-Kaas A/S Chemical Research Laboratory, Rugmarken 28, DK-3520 Farum, Denmark.

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Pentacovalent Oxaphosphorane Chemistry in Organic Synthesis. 2. Total Syntheses of (±)-*trans*- and (±)-*cis*-Neocnidilides

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Both (±)-*trans*- and (±)-*cis*-neocnidilides (1 and 2) have been synthesized via the route illustrated in Scheme III. The condensation of the 1,2λ⁵-oxaphospholene **5b** with valeraldehyde produced the highly substituted phosphonates **12s** and **12a**, which were transformed via an intramolecular Wadsworth-Horner-Emmons olefination reaction to the title compounds.

The carbon analogue[1] of the Ramirez carbonyl condensation reaction forms the basis of the syntheses of both (±)-*trans*- and (±)-*cis*-neocnidilides (1 and 2). These compounds are major constituents of the volatile oil of most representatives of *Apium graveleues* L (Umbelliferae) and have been found to inhibit both the growth and the toxin production of mycotoxin-producing fungi.[2] The structure of *trans*-neocnidilide, isolated from *Cnidium officinale*, was reported by Mitsuhashi and Muramatsu in

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(2) Suzuki, H.; Tanaka, A.; Yamashita, K. *Agric. Biol. Chem.* **1987**, *51*, 3369.

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