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HIGHLY ENANTIOSELECTIVE SYNTHESES OF α-HYDROXYACIDS USING N-BENZYL-4,4,7α-TRIMETHYL-TRANS-OCTAHYDRO-1,3-BENZOXAZINE AS A CHIRAL ADJUVANT+

XU-CHANG HE and ERNEST L. ELIEL*

W.R. Kenan, Jr. Laboratories, University of North Carolina
Chapel Hill, NC 27514 USA

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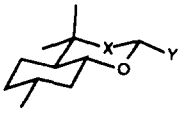
Addition of Grignard and organolithium reagents to as well as hydride reduction of 2α-benzoyl-N-benzyl-4,4,7α-trimethyl-trans-octahydro-1,3-benzoxazine (2, Y = C_6H_5CO) and addition of phenylmagnesium bromide to the corresponding 2-acetyl analog (11) proceed in highly diastereoselective fashion to produce virtually exclusively the diastereomer predicted on the basis of Cram's chelate rule if chelation involves the ring oxygen atom. Mild acid hydrolysis of the adducts followed by selective oxidation produces highly enantiomerically pure α-hydroxyacids with clean recovery of the chiral adjuvant.

In previous publications[1-3] we have described the use of 4,4,7 -trimethyl-trans-hexahydro-1,3-benzoxathiane (1) as a chiral adjuvant for the synthesis of α-hydroxyacids in high enantiomeric purity. The method involves preparation of the 2α-acyl derivatives of 1, followed by



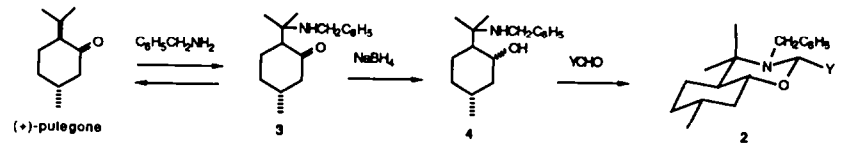
1 X = S, Y = H
2 X = $NCH_2C_6H_5$

addition of a Grignard reagent (highly stereoselective) or hydride reduction (fairly highly stereoselective) followed by N-chlorosuccinimide - silver nitrate cleavage to an α-hydroxy-aldehyde, oxidized to the α-hydroxyacid by sodium chlorite. The by-product of cleavage is a sultine which can be readily reconverted to the original 1,3-oxathiane 1.

In the present paper, we report the preparation of the nitrogen analog 2 (Y = H) (with a benzylamino group in place of sulfur) and its 2-acyl derivatives (2, Y = RC=O) and the stereochemistry of reaction of the latter with Grignard reagents and with hydrides. Some of the results were quite surprising - notably the fact that reactions with 2 (Y = RC=O) are generally even more stereoselective than those with the 2-acyl derivatives of 1.

Compound 2, like 1, was prepared from commercially available (+)-pulegone as shown in Scheme 1. The first step, 1,4-additon of benzylamine[4] is reversible and was therefore immediately followed by sodium borohydride reduction to convert the intermediate aminoketone 3 to the aminoalcohol 4 and its diastereomers; however, 3 can be characterized in the form of its picrate. 1,4-Addition to pulegone is apparently attended with some retro-aldol reaction followed by Schiff base formation, since a by-product in the reduction of 3 was N-(3-methylcyclohexyl)benzylamine.[5] Formation of this by-product could be minimized by carrying out the sodium borohydride reduction in a partially aqueous medium (~80% ethanol). Aminoalcohol 4 was purified as its crystalline benzoate or p-toluate and was obtained in diastereomerically pure form (as evidenced by ^1H and ^{13}C

+Dedicated to Hans Wynberg on the occasion of his sixty-fifth birthday

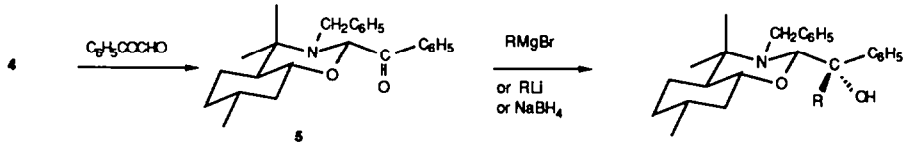


Scheme 1

nmr spectra) in about 35% yield. Subsequent condensation with formaldehyde[6] gave the tetrahydro-1,3-oxazine 2 (Y = H) in high yield; the overall yield of 2 (Y = H) from pulegone is thus comparable to that of 1.[7]

Since, unlike 1, 2 (Y = H) cannot readily be acylated in the 2-position, the benzoyl derivative 5 (equivalent to 2, R = $C_6H_5C{=}O$) was prepared, in good yield, by condensing 4 with phenylglyoxal C_6H_5COCHO.

Addition of Grignard reagents to 5 (Scheme 2) proceeded in good yield and high diastereomer excess even at temperatures as high as 20°C. As shown in Scheme 2, methyl, ethyl, α-naphthyl and



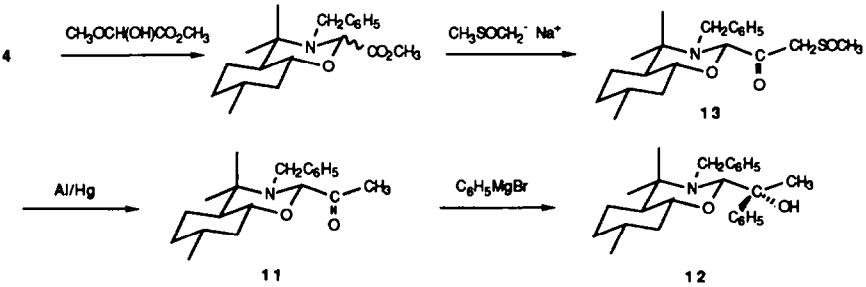
RMgBr: R = CH3 (6), C2H5 (7), α-naphthyl (8), HC≡C (9)
RLi: R = CH3 (6)
$NaBH_4$: R = H (10)

Scheme 2

ethynyl Grignard reagents were so added. In the case of 6, proton and ^{13}C nmr signals of the diastereomer 12 (vide infra) were completely absent and the diastereomeric purity of this material is therefore 100% within experimental error (estimated as 2%). In the case of 7-10, the diastereomers were not available, but the absence of characteristic nmr peaks for H(2), C(2) and C(α) of the diastereomer suggest that these compounds were also highly diastereomerically pure. In the case of 7, 9 and 10, this also follows from the high enantiomeric purity of the hydrolysis/oxidation products, as explained in the sequel.

Methyllithium, CH_3Li, which had shown diminished stereoselectivity in addition to 1,3-oxathianes,[8] nonetheless also added highly stereoselectively to 5, yielding the same diastereomer as CH_3MgBr. This suggests that the ring oxygen atom in 5 chelates very much better than the benzylamino moiety not only with Grignard reagents but also with organolithiums. In view of the ability of the latter to coordinate well with bifunctional amines, such as tetramethylethylenediamine,[9] this finding came as somewhat of a surprise.

In order to make sure that the configurational homogeneity of products 6 from 5 and CH_3MrBr or CH_3Li, suggested by the simplicity of their ^1H and ^{13}C nmr spectra was real and not due to an accidental, if unusual, complete coincidence of the proton and ^{13}C nmr signals of 6 and its diastereomer, the methyl ketone 11 was synthesized as shown in Scheme 3 and was treated with phenylmagnesium bromide (Scheme 3). The proton and ^{13}C nmr spectra of the product 12 were substantially different from those of 6, proving that the two compounds had opposite configuration



Scheme 3

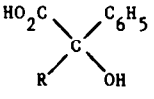
at the carbinol carbon. Moreover, whereas addition of the phenyl Grignard reagent to the methyl ketone derived from 1 proceeds with high stereoselectivity only at low temperature (-78°C), formation of 12 from 11 was highly stereoselective even at 5°C.

Unlike in the reduction of acyl derivatives of 1, sodium borohydride reduction of 5 also proceeded with nearly 100% diastereoselectivity to yield carbinol 10. Reduction with diisobutylaluminum hydride (DIBAL®) and a fortiori lithium triethylborohydride ("Super-Hydride®") was slightly less selective and less clean chemically but produced the same major diastereomer as $NaBH_4$. In the case of DIBAL this was unexpected since, in the reduction of the acyl derivatives of 1, DIBAL and hydride reductants give opposite results,[10] with hydrides giving the product expected on the basis of Cram's chelate rule and DIBAL giving the opposite diastereomer, perhaps because the Cornforth rule operates here.

The tetrahydro-1,3-oxazines 6-10 were readily converted into α-hydroxyacids by treatment with dilute (~1%) aqueous alcoholic hydrochloric acid followed by oxidation with sodium chlorite.[11] The

Table 1

Synthesis of



R	Reagent	Temp. °C[a]	Product[b] Yield%[c]	config.	e.e.%[d]	Ref.
CH_3	CH_3MgBr	20	44	S	98	e
CH_3	CH_3MgBr	-70		S	98	
CH_3	CH_3Li	-70	47	S	95	
C_2H_5	C_2H_5MgBr	5	77	S	~100	f
HC≡C	HC≡CMgBr	20	63	S	97±1	g
α-Naphthyl	$C_{10}H_7MgBr$	20	23	R	82±1	h
H	$NaBH_4$	5	48	S	80	i

[a]Temperature of addition. [b]α-hydroxyacid; in some instances, yield is based on chromatographically purified methyl esters. [c]Overall yield of α-hydroxyacid from 5. [d]Enantiomeric excess. [e]A.I. Meyers and J. Slade, Syn.Commun. 6, 601 (1976). [f]S. Mitsui, S. Imaizumi, S. Y. Senda, and K. Konno, Chem.& Ind. (London) 1964, 233. [g]I. Iwai and Y. Yura, J.Pharm.Soc.Japan 80, 1193 (1960). [h]A.I. Meyers and J. Slade, J.Org.Chem. 45, 2912 (1980). [i]H.M. Peters, D.M. Feigl and H.S. Mosher, J.Org.Chem. 33, 4245 (1968).

enantiomeric excess (e.e.) of the products (Table I) was determined by converting the tertiary hydroxyacids to their methyl esters with diazomethane and then ascertaining the e.e. of the latter by proton nmr spectroscopy in the presence of $Eu(hfc)_3$.[12a] Mandelic acid was reduced to the corresponding glycol whose e.e. was determined as previously described.[12b] Racemic mandelic and atrolactic acids, for calibration purposes, were available commercially; the remaining methyl esters of racemic α-hydroxyacids (7-9) were prepared, albeit in low yield, by addition of the appropriate Grignard reagent to methyl benzoylformate, $C_6H_5COCO_2CH_3$.[13] The configuration of all the acids was established by comparison of the sign of their rotation with that reported in the literature,[14] as indicated in Table 1. In all cases the sign of rotation corresponded to that expected on the assumption that the initial nucleophilic addition to ketones 4 and 11 proceeded in accordance with Cram's chelate rule,[2b,15] chelation involving the ring oxygen. Enantiomeric purity of the products was generally high (>95%) except in the cases of mandelic and α-naphthylmandelic acids (Table 1, last two entries). The latter acid, being of the diarylcarbinol, ArAr'C(OH)X, type is probably subject to facile racemization in acid through formation of a diarylcarbinyl carbocation, $ArAr'CX^+$. Mandelic acid may have been partially racemized at the aldehyde stage since its precursor 10 appeared to be diastereomerically pure. The chiral adjuvant 4 was recovered from the acid hydrolysis mixture of the tetrahydrooxazines (after extraction of the acid formed), by

acid-base work-up and extraction, in high yield and undiminished enantiomeric and diastereomeric purity.

Extension of the method by alkylation of β-ketosulfoxide 13 to produce a variety of higher alkyl ketone analogs of 11[16] is presently under study. In comparison with the previously described[1-3] synthesis of nearly enantiomerically pure α-hydroxyacids via 1, the present method has the advantage of proceeding with generally higher stereoselectivity in the 5-20°C temperature range, even in sodium borohydride reduction, and of greater ease of cleavage of the intermediate tetrahydrooxazine derivatives 6-10, with easier recovery of the chiral adjuvant. Synthesis of chiral adjuvant 4 is slightly simpler than synthesis of 1; overall yields from (+)-pulegone are about the same. Against this must be weighed the more complex synthesis of ketones such as 11, since there is no obvious method of alkylating 2 (R = H) in the 2-position. However, phenyl ketone 5 is readily prepared from commercially available phenylglyoxal.

In addition to its significance in highly enantioselective synthesis, the present method has led to at least two interesting observations. One of these is the highly stereoselective addition of methyllithium to 5, another the fact that $NaBH_4$ and DIBAL produce the same stereoisomer of 10. The causes for this behavior are under further study.

EXPERIMENTAL SECTION

Proton and carbon-13 nmr spectra were recorded on a Bruker AC-200 (200 MHz or 50.3 MHz) spectrometer. Chemical shifts are expressed as parts per million (ppm) downfield from internal Me_4Si; coupling patterns are designated s (singlet), d (doublet), t (triplet), q (quartet) or m (multiplet).

IR spectra were obtained on a Beckman Model 4250 spectrophotometer calibrated with the 1601^{-1} band of polystyrene. Intensities are reported as s (strong), m (medium), w (weak) and br (broad).

Optical rotations were measured on a Perkin-Elmer Model 141 Polarimeter equipped with a sodium lamp in a 1-dm thermostated cell; reported temperatures are uncorrected.

Melting points were observed on an Electrothermal melting point apparatus and are uncorrected.

5c-Methyl-2t[1-methyl-1-(benzylamino)ethyl]cyclohexan-1r-ol (4)

To 15.2 g (0.1 mole) of (+)-pulegone 15.2 ml of benzylamine was added dropwise with shaking. The mixture was allowed to stand at room temperature for 20 h to produce 3, then dissolved in 200 ml 95% EtOH and 20 ml H_2O and cooled to 5°C with an ice bath. Solid sodium borohydride (3.4 g) was added to the mixture over 2 h which was then stirred overnight with ice bath cooling. Water (50 ml) was added to the mixture and, after 1 h stirring 350 ml of a half-saturated aqueous sodium chloride solution and 200 ml of petroleum ether was added and the mixture transferred to a separatory funnel. The basic water phase was extracted with additional portions of petroleum ether (2x150 ml and 100 ml).

The combined petroleum ether layers were washed once with water (100 ml) and then extracted 3 times (2x100 ml, 50 ml) with 5% aqueous hydrochloric acid. The combined acidic water layer was neutralized with saturated aqueous Na_2CO_3 to pH 12 and extracted 3 times with 200 ml each of ethyl acetate-hexanes (1:1). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated at reduced pressure to yield 21.8g (83.5%) crude aminoalcohol 3.

To 10.2 g of benzoic acid dissolved in 100 ml of ethyl acetate, a solution of 21.8 g of the above crude aminoalcohol in 50 ml of ethyl acetate was added with stirring. The mixture was then cooled in an ice-bath and allowed to stand overnight near 5°C. The crystals formed were collected and washed with a small quantity of cold ethyl acetate to yield 13.48 g (35.2%) of the benzoate salt of aminoalcohol 4, mp 138-40°C. The analytic sample was recrystallized from ethyl acetate, mp 139-141°C.

^1H NMR ($CDCl_3$): δ 0.9 (d, J=6.5 Hz, 3H), 1.33 (s, 3H), 1.38 (s, 3H), 3.6 (d of t, J = 10.5 Hz, 4 Hz, 1H), 4.0 (AB, J = 12 Hz), 7.2-7.6 (m, 8H), 7.9-8.2 (m, 2H).

^{13}C NMR ($CDCl_3$): δ 19.7, 21.8, 23.7, 25.6, 31.2, 34.3, 44.2, 44.7, 48.2, 60.9, 72.3, 127.6, 128.3, 128.8, 129.1, 129.4, 130.6, 134.4, 136.1, 172.1.

$[\alpha]_D^{21}$ -26.3° (CH_2Cl_2, c = 0.602).

Decomposition of the benzoate salt of amino-alcohol 4. The above pure salt dissolved in methylene chloride and about 1.5 equivalents of aqueous Na_2CO_3 were placed in a separatory funnel and shaken until there was no solid phase. The basic water layer was separated and extracted once with methylene chloride. The combined methylene chloride phase was washed with a half-saturated aqueous sodium chloride solution, dried over Na_2SO_4 and concentrated at reduced pressure to afford pure aminoalcohol 4, mp 93-95°C, in almost quantitative yield. The analytical sample was recrystallized from hexanes, mp 95-96°C.

^{1}H NMR ($CDCl_3$): δ 0.92 (d, J = 6.4 Hz, 3H), 1.18 (s, 3H), 1.22 (s, 3H), 3.66 (d of t, J = 10.2 Hz, 4.2 Hz, 1H), 3.77 (AB, J = 11.7 Hz, 2H), 7.1-7.3 (m, 5H).

^{13}C NMR ($CDCl_3$) δ 21.6, 22.1, 25.6, 26.4, 31.0, 35.0, 44.5, 45.9, 49.9, 57.0, 77.6, 127.2, 128.4, 128.6, 139.6.

IR (CCl_4) cm^{-1}: 3200 (br), 3010 (m), 1185 (m), 1165 (m), 690 (s).

$[\alpha]_D^{22}$: -31.5° (hexanes, c = 0.6565).

Anal. Calc'd. for $C_{17}H_{27}ON$: C, 78.11; H, 10.41. Found: C, 78.27; H, 10.38.

p-Toluate salt of aminoalcohol 4: mp, 176-8°C.

^{1}H NMR ($CDCl_3$): δ 0.90 (d, J = 6.4 Hz, 3H), 1.30 (s, 3H), 1.34 (s, 3H), 2.40 (s, 3H), 3.67 (d of t, J = 10.3 Hz, 4.2 Hz), 1H), 3.92 (AB, J = 12.2 Hz), 7.1-8.1 (m, 9H).

^{13}C NMR ($CDCl_3$): δ 20.0, 21.5, 21.9, 24.4, 25.8, 31.4, 34.5, 44.4, 45.0, 49.1, 60.3, 75.5, 128.1, 128.5, 128.8, 129.7, 132.0, 135.5, 141.4, 170.0.

$[\alpha]_D^{21}$ -28.2° (CH_2Cl_2, C = 0.879).

5t-Methyl-2-[1-methyl-1-(benzylamino)ethyl]cyclohexanone (3) picrate.

The picrate was prepared from crude 3 described above according to standard procedure[17] and recrystallized from aqueous ethanol to produce yellow crystals, mp 129-31°C.

^{1}H NMR ($CDCl_3$): δ 1.06 (d, J = 6.1 Hz, 3H), 1.55 (s, 3H), 1.62 (s, 3H), 3.0 (dd, J = 5.5 Hz, 1H), 4.15 (br.t, 2H), 7.23 (m, 5H), 8.75 (s, 2H).

^{13}C NMR ($CDCl_3$): δ 19.5, 21.6, 22.1, 27.5, 33.0, 34.5, 45.0, 50.4, 53.9, 61.7, 126.2, 127.9, 128.7, 129.2, 129.3, 130.8, 141.4, 161.6, 214.9.

IR (CCl_4) cm^{-1}: 3090 (w), 1740 (s), 1690 (m), 1630 (s), 1610 (s), 1155 (m), 1070 (w), 1040 (w).

$[\alpha]_D^{22}$: -8.8° (95% EtOH, c, 0.622).

N-Benzyl-4,4,7α-trimethyl-trans-octahydro-1,3-benzoxazine (2, Y = H) To 261 mg (1 mmole) of aminoalcohol 4 dissolved in 3 ml of anhydrous ethyl alcohol 0.6 g of anhydrous K_2CO_3 was added, followed by dropwise addition of 0.6 ml of formaldehyde solution (37% containing 10% methyl alcohol) with stirring, which was continued overnight at room temperature. Then 30 ml of water was added, the aqueous phase was extracted with hexanes (20 ml x 4), the combined hexane layers were washed with water, dried over Na_2SO_4 and concentrated to yield 290 mg of crude product. From this, 250 mg (91.6%) of pure product (2, Y = H) was obtained by silica gel column chromatography (elution with 2% ethyl acetate in hexanes). The analytical sample was distilled in a Kugelrohr, bp 145-150°C/1mm Hg.

^{1}H NMR ($CDCl_2$): δ 0.93 (d, J = 6.5 Hz, 3H), 1.17 (s, 3H), 1.20 (s, 3H), 3.42 (dt, J = 10.5 Hz, 4.1 Hz, 1H), 3.82 (AB, J = 14.2 Hz), 4.28 (AB, J = 10.6 Hz), 7.1-7.6 (m, 5H).

^{13}C NMR ($CDCl_3$): δ 18.1, 22.3, 25.1, 27.1, 31.3, 35.0, 41.4, 47.5, 49.3, 55.3, 75.6, 77.9, 126.5, 128.1, 128.3, 140.9.

IR (film) cm^{-1}: 3040 (w), 3025 (m), 3010 (s), 1605 (w), 1495 (s), 1190 (s), 1020 (s), 725 (s), 690 (s).

$[\alpha]_D^{21}$ -74.6° (EtOAc, c = 2.126).

Anal.Calc'd. for $C_{18}H_{27}ON$: C, 79.07; H, 9.95. Found: C, 79.46; H, 9.95

2α-Benzoyl-N-benzyl-4,4,7α-trimethyl-trans-octahydro-1,3-benzoxazine (5). To 1.31 g (5 mmole) of aminoalcohol 4 dissolved in 100 ml benzene, 1.34 g (10 mmole) of freshly distilled anhydrous phenylglyoxal[18] was added. The mixture was heated at reflux overnight with water being separated by a Dean-Stark trap.

After cooling, 20 ml water was added, the mixture stirred for 2 h and the water phase extracted once with ethyl acetate. The combined organic layer was washed with water (20 ml x 2), dried over Na_2SO_4 and concentrated at reduced pressure to produce crude product from which pure 5 was obtained by recrystallization from ethyl acetate-hexanes, yield 1.08 g, mp 143.5-145°C. The mother liquor was concentrated and chromatographed with silica gel (elution with 5% ethyl acetate-hexanes) to afford an additional 0.37 g mp. 143-5°. Combined yield 77%, analytical sample, mp 144.5-6°C.

^{1}H NMR ($CDCl_3$): δ 0.97 (d, J = 6.3 Hz, 3H), 1.07 (s, 3H), 1.50 (s, 3H), 3.68 (dt, J = 10.4 Hz, 4.0 Hz, 1H, 3.93 (AB, J = 17.2 Hz), 5.97 (s, 1H), 6.92 (s, 5H), 7.2-8.0 (m, 5H).

^{13}C NMR ($CDCl_3$): δ 20.8, 22.2, 25.0, 27.2, 31.4, 35.0, 41.3, 45.5, 48.0, 58.3, 76.7, 88.0, 125.7, 127.48, 127.54, 127.8, 129.2, 132.8, 135.0, 141.4, 195.1.

IR (CCl_4) cm^{-1}: 3030 (w), 3010 (w), 1700 (s), 1680 (m), 1445 (m), 1160 (m), 680 (s).

$[\alpha]_D^{22}$: -10.8° (EtOAc, c 0.73).

Anal.Calc'd. for $C_{25}H_{31}O_2N$: C, 79.54; H, 8.28. Found: C, 79.29; H, 8.06.

Carbinol 6 from Addition of Methylmagnesium bromide to Ketone 5. To a stirred solution of 38 mg (0.1 mmole) of ketone 5 in 8 ml of anhydrous ethyl ether, 0.6 ml of 2.9M ethereal methylmagnesium bromide (Aldrich) was added dropwise under a nitrogen atmosphere at such a rate that the reaction temperature was maintained near room temperature. Stirring was continued for 1 hr when TLC showed that the starting ketone had disappeared.

The mixture was quenched with saturated aqueous NH_4Cl with cooling, then 20 ml of ethyl acetate and 5 ml of brine were added. The layers were separated and the water layer was further extracted with ethyl acetate (20 ml x 2). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated at reduced pressure to yield 47 mg of crude oily carbinol 6, characterized by NMR spectroscopy.

^{1}H NMR ($CDCl_3$): δ 0.57 (s, 3H), 0.90 (d, J = 6.4 Hz, 3H), 1.19 (s, 3H), 1.50 (s, 3H), 3.55 (d, J = 17.6 Hz, 1H), 3.61 (dt, J = 10.4 Hz, 4.0 Hz, 1H), 4.36 (d, J = 17.6 Hz, 1H), 4.96 (s, 1H), 6.2-6.4 (m, 2H), 6.8-7.4 (m, 8H).

^{13}C NMR ($CDCl_3$): δ 22.3, 22.5, 24.8, 27.2, 29.7 (minor impurity), 31.5, 33.1, 35.2, 41.5, 43.7, 46.7, 58.0, 75.7, 77.8, 90.6, 124.6, 125.4, 125.9, 126.2, 127.1, 127.7, 144.0, 144.5.

IR (film) cm^{-1}: 3550 (br), 3040 (w), 3025 (m), 3010 (m), 1605 (m), 1495 (s), 1085 (s), 1020 (s), 690 (s).

Carbinol 7 from Addition of Ethylmagnesium Bromide ketone 5. The preparation was analogous to that of 6; ethylmagnesium bromide was prepared as described.[19] The produce was an oil, characterized by nmr spectroscopy.

^{1}H NMR ($CDCl_3$): δ 0.54 (s, 3H), 0.90 (d, J = 6.4 Hz, 3H), 1.19 (s, 3H), 3.55 (d, J = 17.5 Hz, 1H), 3.60 (dt, J = 10.5, 4.0 Hz, 1H), 4.67 (d, J = 17.5, 1H), 4.95 (s, 1H), 6.2-6.4 (m, 2H), 6.7-7.5 (m, 8H).

^{13}C NMR ($CDCl_3$): δ 6.6, 21.7, 22.0, 24.2, 26.7, 30.9, 34.5, 36.6, 40.9, 43.0, 46.5, 57.3, 75.7, 77.1, 90.3, 123.1, 125.5, 126.4, 126.8, 128.5, 140.9, 144.0 (and other small peaks).

Carbinol 8 from α-Naphthylmagnesium Bromide and Ketone 5. α-Naphthylmagnesium bromide was prepared as described[20] and was added to ketone 5 as described above for 6. The product was partially purified by chromatography on silica gel.

^{1}H NMR ($CDCl_3$): δ 0.62 (s, 3H), 0.86 (d, J = 6.4 Hz, 3H), 1.28 (s, 3H), 3.74 (d, J = 18.0, 1H), 3.84 (dt, 1H), 5.0 (d, J = 18.0 Hz, 1H), 5.87 (s, 1H), 6.3-8.5 (m, 17H).

^{13}C NMR ($CDCl_3$): δ 22.2, 23.0, 25.0, 27.2, 31.5, 35.2, 41.2, 43.5, 47.2, 59.1, 77.5, 81.2, 88.4, 123.1, 124.1, 124.7, 124.8, 124.9, 125.8, 126.5, 126.6, 127.1, 127.8, 128.1, 128.3, 128.9, 131.7, 135.1, 141.8, 143.0, 144.5.

Carbinol 9 from Ethynylmagnesium Bromide and Ketone 5. Ethynylmagnesium bromide was prepared as described in the literature[21] and was added to ketone 5 as described above for 6.

^{1}H NMR ($CDCl_3$): δ 0.90 (s, 3H), 0.94 (d, J = 6.4 Hz, 3H), 1.27 (s, 3H), 2.54 (s, 1H), 3.50 (dt, J = 10.4 Hz, 3.9 Hz, 1H), 3.83 (d, J = 18.1 Hz, 1H), 4.92 (s, 1H), 4.96 (d, J = 18.1, 1H), 6.9-7.6 (m, 10H).

^{13}C NMR ($CDCl_3$): δ 22.1, 22.7, 24.8, 26.8, 31.4, 35.0, 41.1, 44.5, 46.1, 58.8, 72.1, 73.3, 78.4, 86.7, 91.2, 125.6, 125.9, 126.4, 127.3, 127.8, 127.9, 142.0, 143.4.

Reduction of Ketone 5 with $NaBH_4$. To 38 mg (0.1 mmol) of 5 dissolved in 5 ml of 95% ethanol and cooled in an ice bath, 20 mg of $NaBH_4$ was added with magnetic stirring. After 2 h stirring an additional 20 mg of $NaBH_4$ was added and the mixture was further stirred for 3 h at 5°C. Then 15 ml of H_2O was added, the mixture was stirred for 0.5 h and was then concentrated by means of a water aspirator to remove as much ethanol as possible at room temperature. The remaining water layer was saturated with a solid NaCl and extracted with ethyl acetate (20 ml x 3). The combined organic layers were washed with brine (10 ml x 2), dried over Na_2SO_4 and concentrated at reduced pressure to give 46 mg of crude product.

^{1}H NMR ($CDCl_3$): δ 0.87 (d, J = 6.4 Hz, 3H), 1.19 (s, 3H), 1.35 (s, 3H), 3.32 (dt, J = 10.5, 3.6 Hz, 1H), 4.15 (AB, J = 17.6 Hz), 4.55 (AB, J = 8.4 Hz), 7.0-7.6 (m, 10H).

^{13}C NMR ($CDCl_3$): δ 22.1, 22.6, 25.0, 27.4, 31.3, 35.0, 41.0, 45.5, 45.6, 57.6, 71.9, 77.2, 90.7, 126.6, 127.2, 127.3, 127.7, 128.3, 128.7, 140.8, 143.1.

IR (film) cm^{-1}: 3470 (br), 3040 (w), 3030 (m), 3010 (m), 1605 (m), 1490 (s), 1165 (s), 1050 (s), 1025 (s), 750 (s), 705 (s), 685 (s).

Hydrolysis of Carbinol 6 and Oxidation. Crude 6, 47 mg, was dissolved in 8 ml of ethyl alcohol and 4 ml of 2% HCl was added under a nitrogen atmosphere The mixture was heated to reflux for 4 h, cooled and concentrated by aspirator to remove most of the ethanol. To the residue, dissolved in 6 ml of acetone, 1 ml of 2-methyl-2-butene (as chlorine scavenger) and then 6 ml of a freshly prepared solution of 0.91 g KH_2PO_4 and 0.81 g $NaClO_2$ in 15 ml of H_2O was added dropwise. The mixture was stirred at room temperature for 45 min and then concentrated to remove acetone. To this residue, 15 ml of 5% aqueous Na_2CO_3 was added. The basic water layer was extracted with ether (20 ml x 3) and then acidified with 5% HCl until pH 1.

The acidic water layer was saturated with saturated aqueous sodium chloride and extracted with ethyl acetate (20 ml x 3). The combined ethyl acetate layer was washed once with brine, dried over Na_2SO_4 and concentrated to yield crude atrolactic acid, 15 mg.

^{1}H NMR ($CDCl_3$): δ 1.84 (s, 3H), 7.2-7.8 (m, 5H) and 1.1-1.3 containing minor impurity peaks.

TLC showed the major component to be identical in R_f with atrolactic acid (Aldrich) (developed with acetone:methylene chloride 1:3).

Other carbinols (7-9) were hydrolyzed similarly. In the case of 8, a longer hydrolysis time with more concentrated hydrochloric acid was required. Hydrolysis of 10 required only 1 h.

Recovery of Chiral Adjuvant 4. The above ether extract was washed once with brine and extracted with 5% aqueous hydrochloric acid (10 ml x 3). The combined acidic water layer was made basic with solid $NaCO_3.H_2O$ to pH 12 and extracted with hexanes (20 ml x 3). The combined hexane layers were washed with brine (until pH 7) dried over Na_2SO_4 and concentrated to yield 25 mg of pure amino alcohol (>95% recovery).

Determination of Enantiomeric Excess of α-Hydroxyacids with the Chiral Shift Reagent $Eu(hfc)_3$. The tertiary α-hydroxyacids were treated with diazomethane to yield the corresponding methyl esters whose enantiomeric excess was determined by adding $Eu(hfc)_3$ to a deuteriochloroform solution observing the proton NMR spectra and integrating the $CO_2\underline{Me}$ signals. The methyl ester signal was doubled in all cases, as evidenced by calibration experiments on racemic material; in the case of the ethynyl compound better resolution was attained for the ethynyl ($C\equiv\underline{CH}$) protons. The sensitivity of the measurements were checked by adding racemic material to the resolved compounds and repeating the measurement of enantiomeric excess.

The enantiomeric purity of mandelic acid was determined by reducing the acid to the corresponding glycol by means of lithium aluminum hydride in ether (standard procedure), isolating the glycol, converting it, by means of benzaldehyde and acid, to a cis-trans mixture of 2,4-diphenyl-1,3-dioxolans and determining the enantiomeric purity of the latter by means of proton nmr in the presence of $Eu(hfc)_3$.[12b]

(±)-Methyl α-(1-Naphthyl)mandelate.[13]

Ethereal α-naphthylmagnesium bromide[20] (in slight excess) was added to methyl benzoylformate in ether at 5°C. After the usual work-up, the product was obtained in 64.8% yield, mp 152-154°C.

^{1}H NMR ($CDCl_3$): δ 3.77 (s, 3H), 7.0-8.2 (m, 12H).

^{13}C NMR ($CDCl_3$): δ 53.5, 82.0, 124.2, 125.5, 126.0, 126.1, 126.5, 127.0, 128.1, 128.2, 128.8, 129.7, 131.3, 134.6, 137.5, 141.4, 175.8.

The addition of ethylmagnesium bromide and ethynylmagnesium bromide to methyl benzoylformate proceeded best at -70°C. Even at this temperature, the yields were lower than for the α-naphthyl compound.

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References and Footnotes

1 E.L. Eliel, J.K. Koskimies and B. Lohri, J.Am.Chem.Soc. 100, 1614 (1978); J.E. Lynch and E.L. Eliel, J.Am.Chem.Soc. 106, 2943 (1984).

2 Reviews: (a) E.L. Eliel, J.K. Koskimies, B. Lohri, W.J. Frazee, S. Morris-Natschke, J.E. Lynch and K. Soai in "Asymmetric Reactions and Processes in Chemistry", E.L. Eliel and S. Otsuka eds. ACS Symposium Series No. 185; Washington, DC 1982, 37; (b) E.L. Eliel in "Asymmetric Synthesis", J.E. Morrison ed., Academic Press, Inc. New York, 1983, 125; (c) E.L. Eliel, Phosphorus and Sulfur, 24, 73 (1985).

3 Applications: T. Kogure and E.L. Eliel, J.Org.Chem. 49, 576 (1984); S.V. Frye and E.L. Eliel, J.Org.Chem. 50, 3402 (1985); S.V. Frye and E.L. Eliel, Tetrahedron Lett. 26, 3907 (1985); S.V. Frye and E.L. Eliel, Croatica Chemica Acta 58, 674 (1985); S.V. Frye and E.L. Eliel, Tetrahedron Lett. 27, 3223 (1986); M. Ohwa, T. Kogure and E.L. Eliel, J.Org.Chem. 51, 2599 (1986); E.L. Eliel, M.T. Alvarez and J.E. Lynch, Nouveau J.Chem. 10, 749 (1986); K.-Y. Ko and E.L. Eliel, J.Org.Chem. 51, 5353 (1986); M. Ohwa and E.L. Eliel, Chem.Lett. 1987, 41.

4 cf. (a) N.H. Cromwell, Chem.Revs. 38, 83 (1946); (b) R. Baltzly, E. Lorz, P.B. Russell and F.M. Smith, J.Am.Chem.Soc. 77, 624 (1955).

5 J.E. Wrobol and B. Ganem, Tetrahedron Lett. 22 3447 (1981); B. Ganem, personal communication.

6 cf. Z. Eckstein and T. Urbanski in "Advances in Heterocyclic Chemistry", Academic Press, New York, 2, 311 (1963); ibid. 23, 1 (1978).

7 E.L. Eliel, S.V. Frye, J.E. Lynch and K. Kume, Org.Syntheses, in press.

8 E.L. Eliel and S. Morris-Natschke, J.Am.Chem.Soc. 106, 2937 (1984).

9 cf. A.W. Langer, ed., "Polyamine Chelated Alkali Metal Compounds" Adv.in Chem.Ser. No. 130, Am.Chem.Soc., 1974.

10 K.-Y. Ko, W.J. Frazee and E.L. Eliel, Tetrahedron 40, 1333 (1984).

11 (a) B.O. Lindgren and T. Nilsson, Acta Chem.Scand. 27, 888 (1973); (b) G.A. Kraus and B. Roth, J.Org.Chem. 45, 4825 (1980).

12 (a) R.R. Fraser in "Asymmetric Synthesis", J.D. Morrison ed., Academic Press, New York, Vol.1, 1983, 173; (b) E.L. Eliel and K.-Y. Ko, Tetrahedron Lett. 24, 3547 (1983).

13 cf. V. Grignard, Ann.Chim. [7] 27, 556 (1902) (corresponding ethyl esters).

14 cf. J. Jacques, C. Gros and S. Bourcier, "Stereochemistry, Fundamentals and Methods", Vol. 4, H.B. Kagan, ed., Georg Thieme Verlag, Stuttgart, FRG, 1977; see also footnotes to Table 1.

15 D.J. Cram and K.R. Kopecky, J.Am.Chem.Soc. 81, 2748 (1959); see also ref. 2b.

16 H.O. House, "Modern Synthetic Reactions" W.A. Benjamin, Inc. Menlo Park, California, 2nd ed. 1972, 519, 725.

17 D.D. Perrin, W.L.F. Armarego and D.R. Perrin, "Purification of Laboratory Chemicals" Pergamon Press, Oxford, UK, 2nd ed. 1980, 68.

18 Prepared from the commerically available hydrate by the procedure of A.I. Vogel, "A Textbook of Practical Organic Chemistry" Longmans Green & Co., London, UK 3rd ed., 1956, 866. When the hydrate was used, K_2CO_3 was required as a catalyst and the yield was diminished.

19 W.W. Moyer and C.S. Marvel, Org.Syntheses Coll.Vol.II, 1943, 602.

20 H. Gilman, N.B. St. John and F. Schulze, Org.Syntheses Coll.Vol. II, 1943, 425.

21 L. Skatebøl, E.R.H. Jones and M.C. Whiting, Org.Syntheses Coll.Vol.IV, 1963, 792.