N, 6.68.

4-(4-Methylphenyl)-1,8-naphthyridin-2-one (19). A mixture of 2.06 g (5 mmol) of **18**, 10 mL of dioxane and 10 mL of 3 N HCl was warmed at reflux for 3 days. The mixture was then poured into water and neutralized with K_2CO_3, and the resulting solid was filtered, thoroughly washed with water, and recrystallized from acetonitrile to give 0.99 g (84%) of **19** as colorless needles: mp 233–5 °C; NMR (200 MHz) 8.51 (dd, J = 1.5, 5, 1 H, H-8), 7.78 (dd, J = 1.5, 8, 1 H, H-6), 7.33 (s, 4 H), 7.17 (dd, J = 5, 8, 1 H, H-7), 6.43 (s, 1 H, H-3), 2.36 (s, 3 H, CH_3); IR 1687 cm^{-1}. Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.01; H, 5.38; N, 11.84.

3-Methyl-1,8-naphthyridin-2-one (21). To a solution of 18 mmol of LDA in 25 mL of THF prepared at −78 °C by the general procedure described above was slowly added a solution of 2.34 g (18 mmol) of *tert*-butyl propanoate in 3 mL of THF. After stirring at −78 °C for 15 min a solution of 1.75 g (8.5 mmol) of **2a** in 5 mL of THF was added, and the resulting bright yellow mixture was stirred at −78 °C for 15 min and then allowed to warm to room temperature. The mixture was poured into aqueous NH_4Cl and extracted twice with methylene chloride, and the combined organic layers were dried over $MgSO_4$ and evaporated to dryness to leave a yellow gum. TLC of this material showed two materials, presumably a mixture of diastereomeric alcohols **20**.

The mixture of alcohols prepared above was warmed at reflux in a solution of 5 mL of dioxane and 20 mL of 3 N HCl for 24 h. The resulting solution was cooled, poured into water, and neutralized with K_2CO_3 to precipitate a tan solid. The solid was filtered, thoroughly washed with water, and dried to leave 1.08 g (79%) of **21** which was pure by TLC and NMR analysis. Recrystallization of a sample of this material from acetonitrile gave colorless crystalline **21**: mp 234–6 °C; NMR (200 MHz, DMSO-d_6) 8.42 (dd, J = 1.5, 5, 1 H, H-7), 7.98 (dd, J = 1.5, 8, 1 H, H-5), 7.74 (br s, 1 H, H-4), 7.18 (dd, J = 5, 8, 1 H, H-6), 2.07 (br s, 3 H, CH_3); IR 1663 cm^{-1}. Anal. Calcd for $C_9H_8N_2O$: C, 67.48; H, 5.03; N, 17.49. Found: C, 67.29; H, 4.96; N, 17.37.

2,2-Dimethyl-*N*-(4-chloro-2-formylphenyl)propanamide (23). A solution of 10.58 g (50 mmol) of **22**[17] in 100 mL of THF was treated at −78 °C with 125 mmol of *n*-butyllithium in the usual fashion. The resulting solution was stirred at 0 °C for 2 h when a solution of 7.3 g (100 mmol) of DMF in 10 mL of THF was slowly added. After stirring at 0 °C for 1 h, the mixture was poured into 1 N HCl, stirred for 15 min, and then extracted with two portions of ether. The combined organic layers were washed with saturated NaCl, dried over $MgSO_4$, and evaporated. The residue was purified by preparative HPLC, eluting with 9:1 hexane/ethyl acetate, to give 9.24 g (77%) of **23** as a colorless solid. The solid was recrystallized from hexane to give colorless needles of **23**: mp 92–4 °C; NMR 10.12 (s, 1 H, CHO), 8.99 (d, J = 9, 1 H, H-6), 7.84–7.63 (m, 2 H, H-3 and H-5), 1.37 (s, 9 H, *tert*-butyl); IR 3320 (br), 2985, 1680 (br, strong) cm^{-1}. Anal. Calcd for $C_{12}H_{14}ClNO_2$: C, 60.13; H, 5.89; N, 5.84. Found: C, 60.28; H, 6.06; N, 6.08.

5-Chloro-2-[(2,2-dimethyl-1-oxopropyl)amino]-β-hydroxybenzenepropanoic Acid, 1,1-Dimethylethyl Ester (24). Reaction of 7.19 g (30 mmol) of **23** and 63 mmol of *tert*-butyl lithioacetate as described above followed by a standard workup left a colorless oil which was crystallized from hexane to give 10.06 g (94%) of **24** as colorless crystals: mp 89–91 °C; NMR 9.67 (br, 1 H, NH), 8.29 (d, J = 9, 1 H, H-6), 7.49–7.23 (m, 2 H, H-4 and H-5), 5.17 (m, sharpens to dd, J = 5, 9 with D_2O, 1 H, C*H*OH), 4.44 (br, exch with D_2O, 1 H, OH), 2.93 (dd, J = 9, 17, 1 H), 2.63 (dd, J = 5, 17, 1 H), 1.49 (s, 9 H, *tert*-butyl), 1.33 (s, 9 H, *tert*-butyl); IR 3540, 3345, 2910, 1732, 1660 cm^{-1}. Anal. Calcd for $C_{18}H_{26}ClNO_4$: C, 60.75; H, 7.37; N, 3.94. Found: C, 61.06; H, 7.56; N, 3.94.

6-Chloroquinolin-2-one (25). A mixture of 5.33 g (15 mmol) of **24**, 25 mL of dioxane, and 25 mL of 3 N HCl was warmed at reflux for a period of 4 h. The mixture was cooled and poured into water, and the resulting precipitate was collected by filtration, dried, and then recrystallized from ethanol to give 2.36 g (88%) of **25** as colorless crystals: mp 265–7 °C (lit.[18] mp 265–6 °C); NMR (200 MHz, DMSO-d_6) 7.84 (d, J = 9, 1 H, H-4), 7.73 (d, J = 2, 1 H, H-5), 7.49 (dd, J = 2, 8.5, 1 H, H-7), 7.28 (d, J = 8.5, 1 H, H-8), 6.54 (d, J = 9, 1 H, H-3). Anal. Calcd for C_9H_6ClNO: C, 60.18; H, 3.37; N, 7.80. Found: C, 59.92; H, 3.49; N, 7.90.

Synthesis of (2*S*,3*R*)-3-Amino-2-hydroxy-5-methylhexanoic Acid: Bridging Effect of KF

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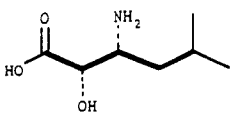
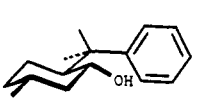
Natural (2*S*,3*R*)-3-amino-2-hydroxy-5-methylhexanoic acid is synthesized in 53–55% yield (referred to (−)-8-phenylmenthol used as chiral auxiliary) by condensation of 1-nitro-3-methylbutane on (−)-8-phenylmenthol glyoxylate hydrate using KF as a mild base. With a large excess of KF in THF it has been possible to increase the diastereoselectivity of the nitro aldol condensation (up to **I**/**II**/**III**/**IV** = 77/13/10/0).

(2*S*,3*R*)-3-Amino-2-hydroxy-5-methylhexanoic acid (**8a**) is the N-terminal amino acid of amastatine,[1] a tetrapeptide which has been found to inhibit leucine aminopeptidase and aminopeptidase A.[2] Recently it has been shown[3] that an antihypertensive drug, KRI 1230, containing the 2*R*,3*S* isomer of this acid is a human renin inhibitor as potent as the corresponding compound containing (3*S*,4*S*)-statine which drew new attention to this acid.

Amino hydroxy acid **8** has been synthesized from D-leucine[4,5] as a mixture of 2*S*,3*R* and 2*R*,3*R* diastereomers



(2S,3R)-8



(−)-8-phenylmenthol [29]

in a 70/30 ratio, respectively, and a total yield for the mixture of about 45% or from L-leucine[6] as a mixture of 2*R*,3*S* and 2*S* 3*S* in a 23/77 ratio, respectively, and a total yield for the mixture of about 45%.[7] Amino hydroxy acid,

(1) Tobe, H.; Morishima, H.; Naganawa, H.; Takita, T.; Aoyagi, T.; Umezawa, H. *Agr. Biol. Chem.* **1979**, *43*, 591.
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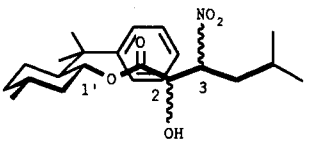
0022-3263/90/1955-4750$02.50/0

Table I. Nitro Aldol Condensation 2 + 3 = 4

	base	solvent	t, °C	react time, h	yield, %	diasteromer mixture 4I/II/III/IV
1	KF (6)	iPrOH	rt	12	80	45/45/5/5
2	KF (6)	iPrOH	rt	24	85	50/35/9/6
3	KF (6)	iPrPH	0	8	0	
4	KF (6)	THF	rt	48	90	68/16/13/3
5	KF (12)	THF	rt	18	90	70/15/11/4
6	KF (12)	THF	0	72	90	77/13/10/0
7	KF (6)/18-C-6	THF	rt	0, 5	90	35/35/15/15
8	TBAF[a] (0, 5)	THF	0	0, 5	90	27/27/23/23

[a] Tetrabutylammonium fluoride.

Table II. ^{1}H NMR Data for the Four Isomers of Compound 4



	H-1′, δ (ppm)	J_{aa}, Hz	J_{ae}, Hz	H-2, δ (ppm)	$J_{2,3}$, Hz	H-3, δ (ppm)	$J_{3,4}$, Hz
4I	4.95	10	4	d, 3.05	3.5	ddd, 4.22	5.5, 8.5
4II	4.95	10	4	d, 3.35	3.5	dt, 4.32	3.5, 10.5
4III	4.95	10	4	d, 3.72	3.5	ddd, 4.55	6.5, 8
4IV	4.95	10	4	d, 3.96	3.5	dt, 4.66	3.5, 10

(2S,3R)-8, 90% optically pure, has also been obtained in 50% yield through asymmetric epoxidation of the corresponding allylic alcohol.[8]

Recent work in our laboratory has focused on the use of nitroalkanes in diastereo- and enantioselective synthesis[9,10] as a route to bioactive compounds.

The two most extensively used bases in nitro-aldol reaction are NaOH[11,12] and BuLi;[13,14] however, when the substrate contains an ester function (as in glyoxylic esters) the less commonly used fluorine salts[13,15,16] are the best suitable bases.[10]

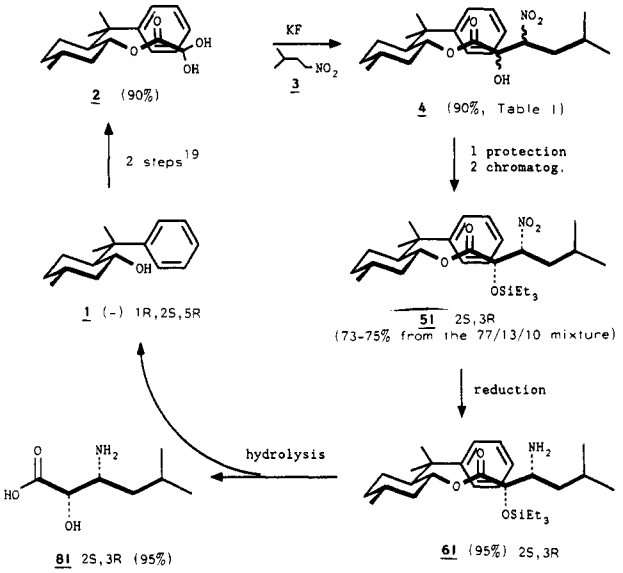
This paper reports the synthesis of pure (2S,3R)-3-amino-2-hydroxy-5-methylhexanoic acid in 53–55% total yield by addition of 1-nitro-3-methylbutane to (−)-8-phenylmenthyl glyoxylate hydrate[17] promoted by fluoride ion.

Results

Synthesis. As shown in Scheme I, the key material in this synthesis is (−)-8-phenylmenthyl glyoxylate hydrate **2**, which is a stable colorless oil easily prepared in 90% yield either in three steps using Jurczack's method[18] or in two steps by double-bond oxidation of 8-phenylmenthyl acrylate.[19]

In the key step 1-nitro-3-methylbutane **3** in the presence of fluoride salts adds smoothly to (−)-8-phenylmenthyl glyoxylate monohydrate **2** (90% yield) to give compound

Scheme I



4 as a mixture of the four possible diastereomers (Table I). The diastereomer ratio depends on reaction conditions (vide infra for comments) and is determined by 200-MHz ^{1}H NMR spectroscopy of crude products of the reactions.

When triethylsilyl chloride/DMF/imidazole at room temperature was used for the protection of the hydroxyl group, modification of diastereomer ratio was observed. A 68/16/13/3 mixture of **4**, under these conditions, was converted into a 33/27/27/13 mixture of **5**. To avoid equilibration at C-2 and epimerization at C-3, protection was performed at 0 °C with triethylsilyl triflate (1.5 equiv) followed by addition of NEt_3 (2 equiv). A 70/15/11/4 mixture of **4** was then converted to a 72/14/12/2 mixture of **5**. After protection, achieved under the above conditions, diastereomer **5I** (from experiments 1 and 6, Table I) and diastereomer **5II** (from experiment 1, Table I) were isolated, 90–95% yields, by flash chromatography[20] on silica gel 60 pretreated with 1% NEt_3.

(7) Inversion of diastereoselectivity comes from differences in mechanisms.
(8) Chong, J. M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1563.
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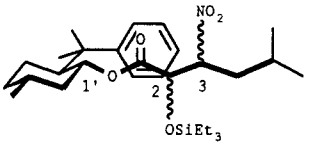
(17) For the use of 8-phenylmenthyl glyoxylate as chiral substrate, see: Whitesell, J. K.; Allen, D. E. *J. Am. Chem. Soc.* **1988**, *110*, 3585 and references therein.
(18) Jurczak, J.; Zamojski, A. *Ann. Soc. Chim. Polonorum* **1977**, *44*, 2257.
(19) Khair, N. Thesis, Strasbourg, December 1989.
(20) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

Table III. ^{1}H NMR Data for the Four Isomers of Compounds 5



	H-1', δ (ppm)	J_{aa}, Hz	J_{ae}, Hz	H-2, δ (ppm)	$J_{2,3}$, Hz	H-3, δ (ppm)	$J_{3,4}$, Hz
5I	4.9	10.5	4	d, 3.6	4	dt, 4.36	4, 9.5
5II	4.9	10.5	4	d, 4.1	4	dt, 4.15	3, 11
5III	4.9	10.5	4	d, 4.0	4	ddd, 4.65	2.5, 11.5
5IV	4.9	10.5	4	d, 4.24	5.5	*a*	

[a] Lost in the noise, δ = 4.5 ppm.

After Raney Ni/EtOH reduction of **5I** and/or **5II**, deprotection and hydrolysis were achieved in 6 N HCl. Further treatment with excess epoxypropane in anhydrous ethanol afforded the amino hydroxy acid **8I** and/or **8II** as white powders (vide infra for isomer identification).

When the best reaction conditions are used (experiment 6, Table I), 3-amino-2-hydroxy-5-methylhexanoic acid **8I** (corresponding to the major diastereomer **4I**, 77%, formed in step 3) can be obtained in 53–55% overall yield based on (−)-8-phenylmenthol, and it will be shown below that **8I** is the desired 2*S*,3*R* amino hydroxy acid.

Furthermore, the chiral auxiliary (−)-8-phenylmenthol is recovered in about 60% yield, and can thus be used again.[21]

Proton NMR. Assignment and determination of diastereomer ratios in compounds **4** and **5** have been made using H-1′, H-2, and H-3 signals. The relevant NMR data are given in Tables II and III. In each of the four diastereomers of compound **4**, the H-1′ signal is a doublet of triplet (one $^3J_{ae}$ = 4 Hz and two $^3J_{aa}$ = 10 Hz). Having but slightly different chemical shifts the four H-1′ signals overlap and lead, when the diastereomer populations have similar values, to a jumbled multiplet centered at 4.95 ppm. The H-2 signal is, as expected, a doublet (when $^3J_{2,OH}$ = 0 Hz) and the H-3 signal is a doublet of doublet of doublet (ddd) or a doublet of triplet (dt) according to the value of the coupling constants.

The diastereomer ratio has easily been determined from the four H-2 well-resolved doublets and checked on the H-3 multiplets.

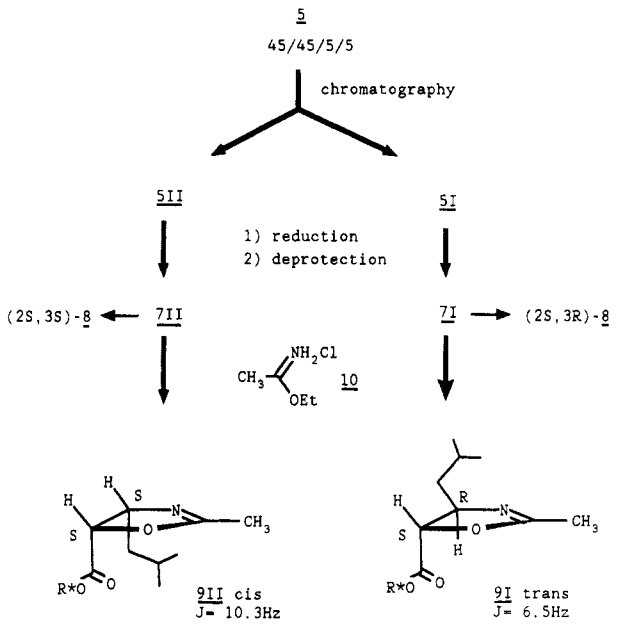
In compound **5**, the H-1′ signals of the four diasteromers are doublet of triplets and overlap. In diastereomer **5II**, protons H-2 and H-3 lead to an AB part of an ABX_2. The diastereomer ratio has also been determined from the four H-2 doublets, but less easily than in compound **4**. Correlation between **4I** and **5I** has been done comparing the spectra of the 70/15/11/4 mixture of **4** and of the 72/14/12/2 mixture of **5** obtained through the nonracemizing method of protection (see above).

According to our previous result[10] concerning the synthesis of (−)-(*S*)-isoserine from the same chiral auxiliary (−)-8-phenylmenthol, we postulate that the configuration at C-2 is *S* in the major diastereomer **I**. However, from the NMR data it is not possible to decide whether **5I** (and/or **4I**) is 2*S*,3*R* or 2*S*,3*S*.

The literature values of $[\alpha]_D$ for (2*S*,3*R*)-**8** and (2*S*,3*S*)-**8** being to similar, respectively −28° (or −29°) and −30.6°, the value −28° obtained for **8I** (see the Experimental Section) does not allow assignment of the configuration.

Therefore, amino alcohols **7I** and **7II** have been synthesized by deprotection of pure **5I** and pure **5II**, using

Scheme II



methylammonium fluoride (MAF),[22] and then converted to oxazolines **9I** and **9II** by treatment with ethyl iminoacetate hydrochloride **10**.[23,24]

The trans and cis configurations are assigned respectively to oxazoline **9I** and **9II** on the basis of the $^3J_{2,3}$ coupling constant. In the *trans*-oxazoline the dihedral angle H-2–C-2–C-3–H-3 is, according to molecular models, close to 120° while in the *cis*-oxazoline this dihedral angle is close to 0°; therefore, in accord with the Karplus–Conroy curve, one expects $^3J_{trans}$ to be smaller than $^3J_{cis}$. Oxazoline **9I** with $^3J_{2,3}$ = 6.5 Hz was thus attributed the trans structure and oxazoline **9II** with $^3J_{2,3}$ = 10.3 Hz the cis structure.

Therefore, as shown on Scheme II, diastereomer **5I** (R_f = 0.28, ether/hexane, 5/95) leads to the *trans*-oxazoline **9I** and diastereomer **5II** (R_f = 0.35, ether/hexane, 5/95) leads to the *cis*-oxazoline **9II**.

Considering our previous results on isoserine[10] and the above results, diastereomer **5I** is assigned the 2*S*,3*R* configuration while **5II** has the 2*S*,3*S* configuration.

This is in accord with the hydrolysis of **7I** to the known (2*S*,3*R*)-**8**.

Improvement of the Asymmetric Induction: A Bridging Effect of KF. The changes in diastereomer

(21) (−)-8-Phenylmenthol is recovered during hydrolysis (step 6, Scheme I) through ether extraction of the acidic aqueous phase.

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Table IV. Asymmetric Induction at C-2 and C-3 in Reaction 2 + 3 = 4 (Experiments 1–8, Table I)

	1	2	3	4	5	6	7	8
C-2[a]	90/10	85/15	–	84/16	85/15	90/10	70/30	54/46
C-3[b]	50/50	56/44	–	70/30	74/26	77/23	50/50	50/50

[a] Induction at C-2: I + II/III + IV (taken from values given in Table I). [b] Induction at C-3: I + IV/II + III (taken from values given in Table I).

ratio with the reaction conditions are given in Table I. With catalytic amounts of KF in iPrOH, the usual conditions used by Wollenberg[15] for the synthesis of nitroalkane, the reaction is too slow. We found that with larger amounts of KF the reaction proceeds at a reasonable speed in iPrOH and also in THF. We also noticed that KF must not be too dry, probably because traces of water favor dissolution of KF in the reaction mixture.

Consistent with this is the fact that with tetrabutylammonium fluoride (TBAF) as a base,[25] or on addition of 1 equiv of 18-crown-6,[26] the rate of the reaction increases (entries 7 and 8).

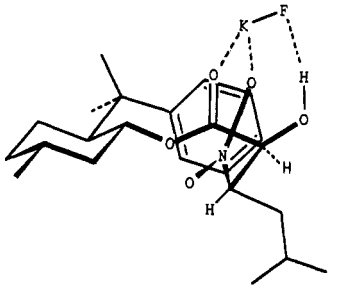
Interestingly, changing the solvent from iPrOH (entries 1 and 2) to THF (entry 4) increases the asymmetric induction, and diastereomer **I** becomes substantially more populated (68%) than the three others. When the amount of KF is increased (12 equiv) and the reaction temperature lowered, diastereomer **I** reached 77%, the highest ratio we were able to attain.

It has been established that **4I** and **4II** have respectively 2*S*,3*R* and 2*S*,3*S* configurations. Since the pattern of H-3 signals are similar in **4I** and **4III** (ddd) and in **4II** and **4IV** (td), one can postulate that **4III** and **4IV** have respectively the 2*R*,3*S* and 2*R*,3*R* configurations. With these assignments the asymmetric induction at C-2 and C-3 can be calculated, and the results are given in Table IV.

The asymmetric induction at C-2, 85/15 to 90/10, is slightly smaller than in the case of isoserine, 95/5 (10), and it does not change much with reaction conditions. On the other hand, asymmetric induction at C-3 varies with the reaction conditions from 50–56/50–44 in iPrOH to 70–77/30–23 in THF and also with increasing amounts of KF.

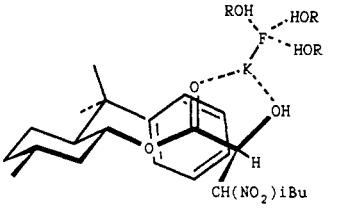
This later trend could be explained through chelate-enforced chirality transfer[27] if, remembering that we are dealing with an equilibrated reaction, one postulates an H-bond-promoted formation of a complex between KF and substrate **4** which is more stable in the case of the 2*S*,3*R* configuration, model 1.[28]

Model 1



One can understand from this model that increasing the amount of KF (in THF) increases the concentration in the bridged species and consequently the concentration in 2*S*,3*R* isomer, on quenching with cold water. In iPrOH, competition between the solvent proton and the C-2 hydroxyl proton for the fluoride ion tends to break the intramolecular H bond. The potassium ion remains alone for bridging and probably leads to a new complex which could well be model 2 and would explain why the asymmetric induction remains almost constant at C-2 (because of the K bridge) but decreases at C-3 (because the CH(NO_2)iBu fragment is freed).

Model 2



On addition of 18-crown-6 (Table I, entry 7) because of the large formation constant between 18-crown-6 and K^+ (log K_S = 6.1 in MeOH), the potassium ion is largely withdrawn from the substrate. The KF bridge is broken, which can explain the decreases in asymmetric induction at C-2 (70/30 instead of 90/10) and at C-3 (50/50 instead of 70/30). When TBAF, where no bridging is possible with the ammonium ion, is used as a base (Table I, entry 8), the asymmetric induction at C-2 and C-3 drops, as expected from the proposed model, to 0%.

Conclusion

When 1-nitro-3-methylbutane (**3**) was condensed with (–)-8-phenylmenthyl glyoxylate hydrate (**2**) in the presence of KF in THF, diastereomers **4I**, of the condensation product **4**, was obtained in 77% as a mixture of three diastereomers (77/13/10, Table I). After purification, protection, hydrogenation, and hydrolysis (Scheme I), (2*S*,3*R*)-3-amino-2-hydroxy-5-methylhexanoic acid was obtained in an overall yield of 53–55%. The (–)-8-phenylmenthol, used as chiral auxiliary, is recovered and can be used again.

Experimental Section

All starting materials were commercially available research-grade chemicals and used without further purification. All reactions were run under argon. Solvents were dried before use (THF is refluxed over $LiAlH_4$; iPrOH is refluxed over CaO, distilled and stored on molecular sieves; 4A); KF from Fluka is used as received. (–)-8-Phenylmenthol (optically pure and free from the other isomer, $[\alpha]_D$ = –26.2° (*c* 2, EtOH)) has been prepared from (+)-pulegone and purified according to a modified Corey's method.[29,30] 1-Nitro-3-methylbutane has been prepared (60% yield after distillation, bp 34° (15mmHg)) by *m*-chloroperbenzoic acid (mCPBA) oxidation of isoamylamine.[31]

^1H NMR and ^{13}C NMR spectra were obtained on a Bruker WP 200 SY instrument. IR spectra were recorded on a Perkin-Elmer 1310 instrument. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Melting points were taken on a Reichert microscope (and uncorrected). Hydrogenations have been conducted in a Roth autoclave. Merck TLC plates silica gel 60 F_{254} (0.25 mm) pretreated with 1% NEt_3 have been used, and the spots were detected using UV and phosphomolybdic acid.

Nitro Aldol Condensation. To a well-stirred solution of **2** (5.9 mmol) and **3** (12 mmol) in 20 mL of the desired solvent were added 6–72 mmol of KF at once. The reaction mixture was stirred

(25) It is also known that in TBAF/THF, F^- can be considered more naked than in KF hydrates, which makes it a stronger base.

(26) 18-Crown-6, especially suited to complex potassium ions, increases the solubility of KF and the reactivity of the anion F^-, see: *Synthetic Multidentate Macrocyclic Compounds*; Izatt, R. M., Christensen, J. J., Eds.; Academic Press: San Francisco, 1978; p 111.

(27) *Asymmetric Synthesis*; Morrison, J. D., Eds.; Academic Press: New York, 1984; Vol 3, p 80 (D. A. Evans).

(28) In complex KF-**4I** the small H atom points toward the phenyl ring and the isobutyl group is away from the menthyl ring.

(29) Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908.
(30) Vedejs, E. *Organic Synthesis INC.* **1987**, *65*, 203.
(31) Gilbert, K. E.; Borden, W. T. *J. Org. Chem.* **1979**, *44*, 659.

at the desired temperature until no starting material remained as shown by TLC. The mixture was then poured into 40 mL of cold water. After extraction with hexane (6 × 10 mL), the organic layers were dried ($MgSO_4$) and concentrated under vacuum (without heating). The colorless viscous liquid **4** (80–90% yield according to the choosen conditions) was studied by NMR prior to purification.

Protection. To a solution of nitro alcohol **4** (2.9 mmol) in CH_2Cl_2 (6 mL) at 0 °C were added dropwise and rapidly 1.5 equiv of triethylsilyl triflate (4.4 mmol) and then 1.7 equiv of NEt_3 in the same way. When the reaction was over (5–10 min) the mixture was poured into 50 mL of cold water, the organic layer was separated, the aqueous layer was extracted with ether (4 × 20 mL), and the organic layers were joined and dried ($MgSO_4$). After concentration, the colorless liquid **5** (about 90–95% yield) was studied by NMR spectroscopy.

Chromatographic Separation or Purification. The 70/15/11/4 mixture of **4** (1.3 g) was purified on a silica gel 60 (230–400 mesh) column (diameter = 30 mm, h = 150 mm) pretreated with 1% NEt_3, using ether/hexane (5/95) which gives 0.84 g of pure **5I**.

Hydrogenation. Raney Ni (200 mg, washed with water until pH = 5.7) was added to a solution of compound **5** (1.5 mmol) in EtOH (50 mL). The mixture was stirred and heated at 50 °C under 40 atm of H_2 for 16 h in an autoclave. After filtration over Celite and evaporation of the solvent, a colorless viscous liquid **6** was obtained (85–95% yield).

Deprotection. Deprotection was done with methylammonium fluoride (MAF) in CH_3CN/THF. This reagent has been developed to avoid water workup and is described (*Synth. Commun.* **1989**, *21*, 1335).

Oxazoline. To a solution of amino alcohol **7I** or **7II** (0.5 mmol) in CH_2Cl_2 (4 mL) at 0 °C was added (in one fraction) 1.2 equiv (0.6 mmol) of imino ether **10**. The mixture was stirred at 0 °C for 6 h and then poured into 10 mL of cold water. After separation the aqueous layer was extracted twice with 10 mL of CH_2Cl_2. The organic layers were joined, dried ($MgSO_4$), and concentrated under vacuum. The colorless oil obtained (94%) was studied by NMR, prior to purification.

(−)-8-Phenylmenthyl 2-Hydroxy-5-methyl-3-nitrohexanoate (4). Diastereomer mixture **4**: **I/II/III/IV** = 68/16/13/3; IR ($CHCl_3$) 4470 (γ_{OH}), 1715 ($\gamma_{C=O}$), 1545 and 1370 cm^{-1} (γ_{NO_2} (sym and asym)); ^1H NMR (200 MHz, $CDCl_3$/TMS) δ 7.25 (4 H, b s, H_{Ar}), 7.15 (1 H, m, H_{Ar}), 2.25–0.95 (26 H, among which 1.3, s, Me-8′ or -9′ in **4I** and 1.2, s, Me-9′ or -8′ in **4I**); for protons H-1′, H-2, and H-3, see Table II. Anal. Calcd for $C_{23}H_{35}O_5N$: C, 68.11; H, 8.7; N, 3.4. Found: C, 68.25; H, 8.98; N, 3.32.

(−)-8-Phenylmenthyl 5-Methyl-3-nitro-2-((triethylsilyl)oxy)hexanoate (5). Diastereomer **5I** (fraction 2, R_f = 0.28, ether/hexane, 5/95): 2*S*,3*R*; IR (film) 1750 ($\gamma_{C=O}$), 1555 and 1370 cm^{-1} (γ_{NO_2}); ^1H NMR (200 MHz, $CDCl_3$/TMS) δ 7.3 (4 H, b s, H_{Ar}), 7.15 (1 H, m, H_{Ar}), 2.25–0.4 (41 H among which 1.35, s, 3 H, Me-8′ or -9′; 1.2, s, 3 H, Me-9′ or -8′; 0.6 m, 6 H, $SiCH_2$), for protons H-1′, H-2, and H-3 see Table III; ^{13}C NMR (50.3 MHz, $CDCl_3$/TMS) δ 169.7 (C1), 152.7 (C10′), 128.8 (C_{meta}), 126 (C_{ortho}), 125.9 (C_{para}), 88.4 (C3), 77.7 (C1′), 40.4 (C11′), 51, 32.1, 29, 25.8, 25.4, 23.6, 22.4 (3 CH and 5 CH_3 chain and ring), 41.8, 38.6, 35.4, 27.4 (4 CH_2, chain and ring), 7.2 (3 CH_3, $OSi(CH_2CH_3)_3$), 5.6 (3 CH_2, $OSi(CH_2CH_3)_3$). Anal. Calcd for $C_{29}H_{49}O_5NSi$: C, 67.26; H, 9.15; N, 2.7. Found: C, 67.25; H, 9.36; N, 2.7.

Diastereomer **5II** (fraction 1, R_f = 0.35, ether/hexane, 5/95): 2*S*,3*S*; same NMR spectrum but for protons H-1′, H-2, and H-3 (see Table III).

(−)-8-Phenylmenthyl 3-Amino-5-methyl-2-((triethylsilyl)oxy)hexanoate (6). Diastereomer **6I** (from **5I**): 2*S*,3*R*; IR (film) 3345 (broad γ_{NH_2}), 1730 cm^{-1} ($\gamma_{C=O}$); $[\alpha]_D$ = −18.8° (*c* 2, EtOH); ^1H NMR (200 MHz, $CDCl_3$/TMS) δ 7.29 (4 H, b s, H_{Ar}), 7.15 (1 H, m, H_{Ar}), 4.8 (1 H, td, $^3J_{aa}$ = 10 Hz, $^3J_{ae}$ = 4 Hz, H-1′), 3.9 (1 H, d, $^3J_{2,3}$ = 2 Hz, H-2), 2.65 (1 H, ddd, $^3J_{3,2}$ = 2 Hz, $^3J_{3,4}$ = 3 and 4 Hz, H-3), 2.1–0.4 (41 H among which 1.3, s, Me-8′ or -9′; 1.2, s, Me-9′ or -8′; 0.65, m, 6 H, $SiCH_2$); ^{13}C NMR (50.3 MHz, $CDCl_3$/TMS) δ 172.1 (C1), 161.9 (C10′), 127.9 (C_{meta}), 125.2 (C_{ortho}), 125 (C_{para}), 75.3 (C2), 75.2 (C1′), 52.6 (C3), 39.5 (C11′), 24.7, 23.3, 22.1, 21.6, 50.2, 31.3, 27.8 (5 CH_3 and 3 CH, chain and ring), 43.5, 41.5, 34.6, 26.6 (4 CH_2 chain and ring), 7.1 (3 CH_3, $OSi(CH_2CH_3)_3$), 5.6 (3 CH_2, $OSi(CH_2CH_3)_3$). Anal. Calcd for $C_{29}H_{51}O_3NSi$: C, 71.4; H, 10.12; N, 2.79. Found: C, 71.16; H, 10.37; N, 2.79.

Diastereomer **6II** (from **5II**): 2*S*,3*S*; IR (film) 3345 (broad γ_{NH_2}), 1740 cm^{-1} ($\gamma_{C=O}$); ^1H NMR (200 MHz, $CDCl_3$/TMS) δ 7.3 (4 H, b s, H_{Ar}), 7.15 (1 H, m, H_{Ar}), 4.75 (1 H, td, $^3J_{aa}$ = 10.5 Hz, $^3J_{ae}$ = 4 Hz, H-1′), 3.5 (1 H, d, $^3J_{2,3}$ = 4 Hz, H-2), 2.6 (1 H, td, $^3J_{3,2}$ = 4 Hz, $^3J_{3,4}$ = 10 and 4 Hz, H-3), 2.1–0.4 (41 H).

(−)-8-Phenylmenthyl 3-Amino-2-hydroxy-5-methylhexanoate (7). Diastereomer **7I** (from **6I**): 2*S*,3*R*; colorless crystals, mp 97–8 °C; IR ($CHCl_3$) 3400 (broad γ_{OH} and γ_{NH_2}), 1715 cm^{-1} ($\gamma_{C=O}$); $[\alpha]_D$ = −6.5° (*c* 1.6, EtOH); ^1H NMR (200 MHz, $CDCl_3$/TMS) δ 7.3 (4 H, b s, H_{Ar}), 7.15 (1 H, m, H_{Ar}), 4.9 (1 H, td, $^3J_{aa}$ = 10.5 Hz, $^3J_{Ae}$ = 4.5 Hz, H-1′), 2.98 (1 H, d, $^3J_{2,3}$ = 2.2 Hz, H-2), 2.66 (1 H, td, $^3J_{3,2}$ = 2.2 Hz, $^3J_{3,4}$ = 7 and 2.2 Hz, H-3), 2.2–0.9 (28 H); ^{13}C NMR (50.3 MHz, $CDCl_3$/TMS) δ 173.5 (C1), 151.6 (C10′), 127.9 (C_{meta}), 125.2 (C_{ortho}), 125 (C_{para}), 75.6 (C2), 72.7 (C1′), 39.4 (C11′), 51.2 (C3), 50.3, 31.2, 29.4, 24.5, 23, 22.2, 21.6 (3 CH and 5 CH_3, chain and ring), 43, 41.5, 34.4, 26.2 (4 CH_2, chain and ring). Anal. Calcd for $C_{23}H_{37}O_3N$: C, 73.54; H, 9.95; N, 3.73. Found: C, 73.61; H, 9.86; N, 3.74.

Diastereomer **7II** (from **6II**): 2*S*,3*S*; IR ($CHCl_3$) 3400 (broad γ_{OH} and γ_{NH_2}), 1715 cm^{-1} ($\gamma_{C=O}$); ^1H NMR (200 MHz, $CDCl_3$/TMS) δ 7.3 (4 H, b s, H_{Ar}), 7.15 (1 H, m, H_{Ar}), 4.9 (1 H, td, $^3J_{aa}$ = 11 Hz, $^3J_{ae}$ = 4.3 Hz, H-1′), 3.17 (1 H, d, $^3J_{2,3}$ = 3.2 Hz, H-2), 2.63 (1 H, td, $^3J_{3,2}$ = 3.2 Hz, $^3J_{3,4}$ = 10 and 3.2 Hz, H-3), 2.1–1 (28 H).

3-Amino-2-hydroxy-5-methylhexanoic Acid (8). Diastereomer **8I** (from **7I**): 2*S*,3*R*; white solid, mp 186–8 °C (lit. 188–9 °C[1] and 213–4 °C[8]; $[\alpha]_D$ = −28° (*c* 0.5, AcOH) [lit. −28° (*c* 0.5, AcOH) and −29° (*c* 0.6, AcOH)[8]]; IR (KBr) 3400 and 3200 (broad γ_{OH} and $\gamma_{NH_3^+}$), 1610 (band I of amino acids), 1570, 1410 cm^{-1} (band II of amino acids); ^1H NMR (200 MHz, D_2O positioned at 4.65 ppm): δ 3.92 (1 H, d, $^3J_{2,3}$ = 3.5 Hz, H-2), 3.3 (1 H, dt, $^3J_{3,2}$ = 3.5 Hz, $^3J_{3,4}$ = 9 and 3.5 Hz, H-3), 1.45 (3 H, m, H-4 and H-5), 0.76 (3 H, d, ^3J = 6.5 Hz, Me-6 or -7), 0.75 (3 H, d, ^3J = 6.5 Hz, Me-7 or -6).

Diastereomer **8II** (from **7II**): 2*S*,3*S*; white solid, mp 225–30 °C (lit. 2*S*,3*S*, 280–2 °C; 2*R*,3*R*, 195–7 °C[1]); IR (KBr) 3400 and 3050 (broad γ_{OH} and $\gamma_{NH_3^+}$), 1630 (band I of amino acids), 1590, 1520, 1490 cm^{-1} (band II of amino acids); ^1H NMR (200 MHz, D_2O positioned at 4.65 ppm) δ 4.05 (1 H, d, $^3J_{2,3}$ = 3.5 Hz, H-2), 3.5 (1 H, dt, $^3J_{3,2}$ = 3.5 Hz, $^3J_{3,4}$ = 9 and 3.5 Hz, H-3), 1.4 (2 H, m, H-4), 1.15 (1 H, m, H-5), 0.76 (3 H, d, ^3J = 6.5 Hz, Me-6 or -7), 0.72 (3 H, d, ^3J = 6.5 Hz, Me-7 or -6).

***trans*-Oxazoline 9I (from 7I):** IR ($CHCl_3$) 1730 ($\gamma_{C=O}$), 1675 cm^{-1} ($\gamma_{C=N}$); ^1H NMR (200 MHz, $CDCl_3$/TMS) δ 7.4 (4 H, b s, H_{Ar}), 7.15 (1 H, m, H_{Ar}), 4.9 (1 H, td, $^3J_{aa}$ = 10.8 Hz, $^3J_{ae}$ = 4 Hz, H-1′), 3.75 (1 H, qq, $^3J_{3,2}$ = 6.5 Hz, $^3J_{3,4}$ = 6.5 and 6.5 Hz, $^5J_{3,Me}$ = 1.5 Hz, H-3), 3.3 (1 H, d, $^3J_{2,3}$ = 6.5 Hz, H-2), 2.2–0.75 (29 H among which 2, 3 H, d, $^5J_{Me,3}$ = 1.5 Hz, MeC=).

***cis*-Oxazoline 9II (from 7II):** IR ($CHCl_3$) 1730 ($\gamma_{C=O}$), 1675 cm^{-1} ($\gamma_{C=N}$); $[\alpha]_D$ = −29° (*c* 3.6, $CHCl_3$); R_f = 0.18 (Et_2O/hexane, 40/60); ^1H NMR (200 MHz, $CDCl_3$/TMS) δ 7.35 (4 H, b s, H_{Ar}), 7.15 (1 H, m, H_{Ar}), 4.95 (1 H, td, $^3J_{aa}$ = 10.5 Hz, $^3J_{ae}$ = 4 Hz, H-1′), 4 (1 H, tdq, $^3J_{3,2}$ = 10.2 Hz, $^3J_{3,4}$ = 4 and 4 Hz, $^5J_{3,Me}$ = 1.5 Hz, H-3), 3.65 (1 H, d, $^3J_{2,3}$ = 10.2 Hz, H-2), 2.2–0.75 (29 H among which 2, 3 H, d, $^5J_{Me,3}$ = 1.5 Hz, MeC=).

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