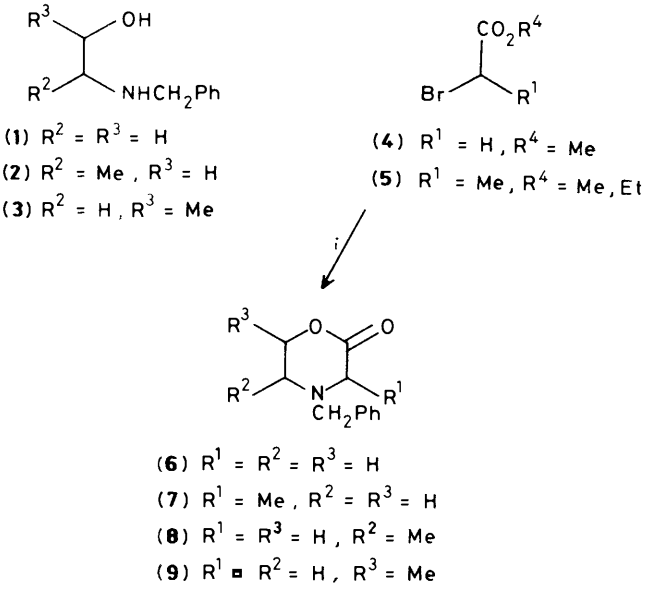
Synthesis and Reaction of Optically Active Morpholinones

Choji Kashima * **and Kazuo Harada**
Department of Chemistry, University of Tsukuba, Tsukuba, Ibaraki 305, Japan

The reactions of variously substituted chiral morpholin-2- and -3-ones chemoselectively synthesized from chiral amino acids and lactic acid as the chiral source are described.

Many biologically important compounds possessing a δ-lactone and δ-lactam structure are known. Chiral morpholin-2- and -3-ones, which are essentially δ-lactones and δ-lactams, respectively, have received some recent interest. Morpholin-2-ones, which can be synthesized from chiral 2-amino alcohols, have been studied as an amino acid analogue,[1] whilst morpholin-3-ones have been studied as an optically active hydroxy acid analogue,[2] and as a chiral building block for pharmaceutically interesting compounds.[3] Based on our previous studies on the alkylation[4] and acylation of 2-amino alcohols, we carried out the synthesis of chiral morpholin-2- and -3-ones by the reaction of 2-amino alcohols with two-carbon units, such as 2-bromo esters and 2-halogeno acid halides. We also describe a new synthesis of morpholin-2-ones from chiral amino acids, which were extremely difficult to obtain by previous methods. Furthermore, both the optical purities of the resulting morpholin-2- and -3-ones were determined, and their behaviour under nucleophilic attack examined.

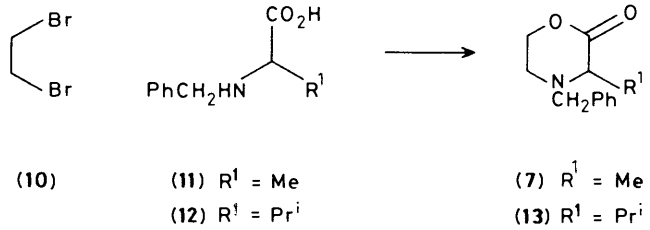
Synthesis of Chiral Morpholin-2-ones.—The synthesis of chiral morpholin-2-ones, substituted at all possible 3-, 5-, and 6-positions, was attempted. First, according to the method of Benet,[5] the reaction of chiral *N*-benzyl-2-amino alcohols with bromo esters was carried out (Scheme 1). The reaction of



Scheme 1. *Reagents:* i, Et_3N–benzene

(*S*)-2-benzylaminopropanol *S*-(**2**), derived from (*S*)-alanine, with methyl bromoacetate (**4**) yielded (*S*)-4-benzyl-5-methylmorpholin-2-one *S*-(**8**). Similarly, the reaction of (*S*)-1-benzylaminopropan-2-ol *S*-(**3**) derived from (*S*)-lactic acid, with methyl bromoacetate yielded (*S*)-4-benzyl-6-methylmorpholin-2-one *S*-(**8**). In the attempt to synthesize optically active 3-substituted morpholin-2-ones, the reaction of benzylaminoethanol with methyl (*S*)-2-bromopropionate *S*-(**5**) was carried out in the presence of DABCO (1,4-diazabicyclo-[2.2.2]octane). However, the resulting (*R*)-4-benzyl-3-methylmorpholin-2-one *R*-(**7**) showed a low optical purity, probably owing to the very harsh reaction conditions used. Since compound (**7**) can be considered as an amino acid analogue, its synthesis from a chiral amino acid was attempted.

It has been reported that amino acids react with epoxides or 2-chloroethanol to yield morpholin-2-ones,[6] although, in very poor yields. We also carried out the reaction of *N*-benzyl-(*S*)-valine (**13**) with bromoethanol, to yield the corresponding morpholin-2-one in a very low yield. However, since amino acids can generally be esterified by treatment with the appropriate alkyl halide in the presence of a base,[7] *N*-benzyl-(*S*)-amino acid was expected to yield chiral morpholin-2-ones. When *N*-benzyl-(*S*)-alanine (**11**), ethylene bromide, and potassium carbonate were heated at 80 °C for 12 h in DMF (dimethylformamide), *S*-(**7**) was obtained in 44% yield. This reaction was applied to other amino acids (Scheme 2), the yields



Scheme 2. *Reagents:* i, K_2CO_3–DMF

and physical properties of the morpholin-2-ones so formed being listed in Table 1. However, the reaction of (*S*)-proline, possessing a secondary amino group, with ethylene bromide under similar conditions yielded a complex mixture of products.

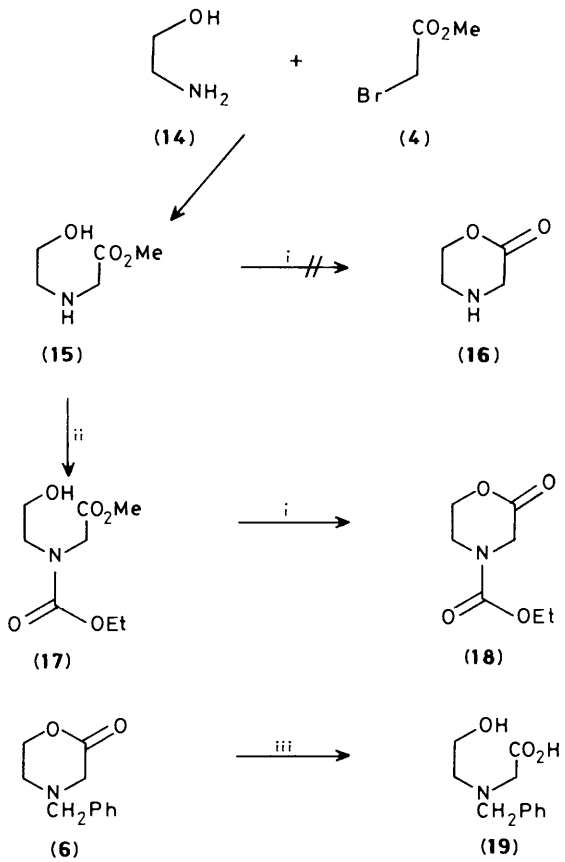
The synthesis of an *N*-unsubstituted morpholin-2-one was also attempted (Scheme 3). Although the aminoethanol (**14**) when treated with methyl bromoacetate (**4**) as described above gave the corresponding hydroxy ester (**15**), heating this in the presence of toluene-*p*-sulphonic acid failed to give the morpholin-2-one (**16**). *N*-Protection by ethyl chloroformate and cyclization using toluene-*p*-sulphonic acid yielded *N*-ethoxycarbonylmorpholin-2-one (**18**), however, in a very poor yield. Therefore, further deprotection was not attempted. Hydrogenolysis of *N*-benzylmorpholin-2-one (**6**) gave the *N*-benzyl hydroxy acid (**19**). These results indicate that the *N*-unsubstituted morpholin-2-ones are apt to undergo nucleophilic attack by the free amino group, and that they are easily hydrolysed.

In this way, we synthesized the chiral morpholin-2-ones substituted in all three possible positions. Further, a variety of

Table 1. Physical properties of substituted morpholin-2-ones

Compound	Method*	Yield (%)	$[\alpha]_D$†	Found (%) C	H	N	Formula	Requires (%) C	H	N
(**6**)	A	89		69.15	6.85	7.35	$C_{11}H_{13}NO_3$	69.09	6.85	7.32
S- and *R*-(**7**)	A	32		70.4	7.35	6.8	$C_{12}H_{15}NO_2$	70.22	7.36	6.82
S-(**7**)	B	44	+47.79	70.2	7.35	6.8	$C_{12}H_{15}NO_2$	70.22	7.36	6.82
R-(**7**)	B	39	−51.26	70.1	7.4	6.8	$C_{12}H_{15}NO_2$	70.22	7.36	6.82
S- and *R*-(**8**)	A	44		70.05	7.4	6.65	$C_{12}H_{15}NO_2$	70.22	7.36	6.82
S-(**8**)	A	69	+68.95	70.3	7.35	6.7	$C_{12}H_{15}NO_2$	70.22	7.36	6.82
S- and *R*-(**9**)	A	47		70.05	7.4	6.8	$C_{12}H_{15}NO_2$	70.22	7.36	6.22
S-(**9**)	A	39	+0.60	70.1	7.4	6.8	$C_{12}H_{15}NO_3$	70.22	7.36	6.22
S-(**13**)	B	74	−32.50	71.45	8.15	5.9	$C_{14}H_{19}NO_2$	72.07	8.20	6.00

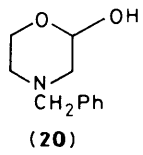
* A, from amino alcohol; B, from amino acid. † All solvents listed in the Experimental section.



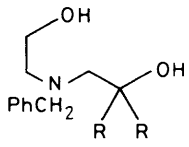
Scheme 3. *Reagents:* i, TsOH; ii, $ClCO_2Et$–Et_3N; iii, H_2–Pd–C

3- and 5-substituted morpholin-2-ones were prepared by the use of various amino acids.

Reaction of Morpholin-2-ones with Nucleophiles.—In order to investigate the reactivity of morpholin-2-ones to nucleophilic attack, compound (**6**) was treated with lithium aluminium hydride to give the hemiacetal (**20**) and the diethanolamine (**21**) in 20 and 30% yields, respectively. Similarly, reduction with lithium borohydride yielded (**20**) and (**21**) in 55 and 30% yields, respectively. There have been a number of reports on the reduction of lactones to cyclic ethers, and in this case, reduction was expected to yield the corresponding morpholine. Petit's method[8] with (±)-(**9**) using sodium borohydride and boron trifluoride–ether complex, however, proved unsuccessful. Similarly, Edward's method[9] (catalytic hydrogenation using platinum oxide in acetic acid) was unsuccessful. In fact, reactions with primary amines, benzylamine, methyl glycinate and a secondary amine, pyrrolidine, all resulted in the formation

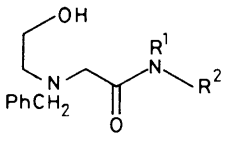


(**20**)



(**21**) R = H

(**22**) R = Me



(**23**) R^1 = $PhCH_2$, R^2 = H

(**24**) R^1 = CH_2CO_2Me, R^2 = H

(**25**) R^1, R^2 = $-(CH_2)_4-$

of the corresponding hydroxy amides (**23**), (**24**), and (**25**) in 65, 58, and 85% yields, respectively. Reaction with methylmagnesium iodide yielded the corresponding diethanolamine (**22**) in 94% yield. These results show that nucleophilic reagents give rise to opening of the morpholin-2-one ring.

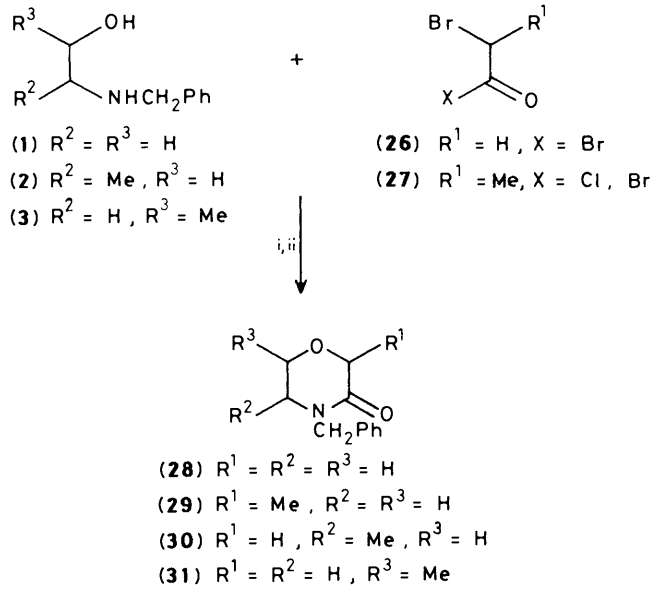
Synthesis of Chiral Morpholin-3-ones.—First, chiral morpholin-3-ones were synthesized by a literature procedure (Scheme 4).[10] The reaction of *S*-(**2**) with bromoacetyl bromide (**26**) in the presence of triethylamine, followed by cyclization of the resulting hydroxy bromide with sodium hydride in tetrahydrofuran yielded (*S*)-4-benzyl-5-methylmorpholin-3-one *S*-(**30**). Similarly, the reaction of (*S*)-1-benzylaminopropan-2-ol *S*-(**3**) resulted in the formation of (*S*)-4-benzyl-6-methylmorpholin-3-one *S*-(**31**). The reaction of 2-benzylaminoethanol with (*S*)-2-bromopropionyl chloride (**30**), derived from (*S*)-alanine, gave (*R*)-4-benzyl-2-methylmorpholin-3-one *R*-(**29**). Cyclization using sodium hydride at room temperature, gave *R*-(**29**) with an optical purity of *ca.* 70%, as determined by a europium shift reagent. However, by cooling the reaction mixture to 0 °C or below, the reaction proceeded with complete inversion to yield optically pure *R*-(**29**). The yields and physical properties of the morpholin-3-ones are listed in Table 2.

Reaction of Chiral Morpholin-3-ones with Nucleophiles.—Although morpholin-3-ones failed to react with amines, with organo-magnesium and -lithium reagents they gave, unlike the corresponding δ-lactams,[10] complex reaction mixtures.

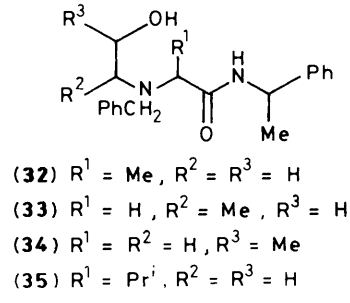
Table 2. Physical properties of substituted morpholin-3-ones

Compound	Yield (%)*	$[\alpha]_D$†	Found (%) C	H	N	Formula	Requires (%) C	H	N
(**28**)	89		69.0	6.9	7.35	$C_{11}H_{13}NO_2$	69.09	6.85	7.32
S- and *R*-(**29**)	59		70.1	7.4	6.85	$C_{12}H_{15}NO_2$	70.22	7.36	6.82
R-(**29**)	37	+71.81	70.05	7.45	6.7	$C_{12}H_{15}NO_2$	70.22	7.36	6.82
S- and *R*-(**30**)	44		70.0	7.45	6.8	$C_{12}H_{15}NO_2$	70.22	7.36	6.82
S-(**30**)	57	−85.82	70.15	7.45	6.7	$C_{12}H_{15}NO_2$	70.22	7.36	6.82
S- and *R*-(**31**)	87		70.2	7.45	6.8	$C_{12}H_{15}NO_2$	70.22	7.36	6.82
S-(**31**)	25	+62.94	70.05	7.4	6.8	$C_{12}H_{15}NO_2$	70.22	7.36	6.82

* All yields from the amino alcohol except for *R*-(**32**) from the 2-bromo acid. † All solvents listed in the Experimental section.



Scheme 4. *Reagents*: i, Et_3N–CH_2Cl_2; ii, NaH–THF



However, as expected, lithium aluminium hydride reduction of 4-benzylmorpholin-3-one (**28**) yielded the corresponding 4-benzylmorpholine (**32**) in a 91% yield. The lithium aluminium hydride reductions of the variously substituted morpholin-3-ones was also carried out and the results are shown in Table 3. It is noteworthy that both stereoisomers of 4-benzyl-2-methylmorpholine (**33**) can be synthesized from the naturally occurring (*S*)-amino acids or hydroxy acids.

Optical Purities of Chiral Morpholin-2- and -3-ones.—The optical purities of morpholin-2-ones *S*-(**7**), *R*-(**7**), *S*-(**8**), and *S*-(**13**) were found to be greater than 98% by reaction with (*S*)- or (*R*)-α-phenylethylamine, and separation of the resulting diastereoisomeric hydroxy amides by capillary gas chromatography. When the (*S*)-morpholinone was used, the (*S,R*)-isomer was always eluted first, and showed the separability factors (α) listed in Table 4. It is well known that the amide NH group is very important in the gas chromatographic separation of diastereoisomers *via* hydrogen bonding.[11] Therefore, as expected, a decrease in the sparability of the two diastereoisomers was observed as the distance between the amide NH group and the chiral centre became greater. As a result, in the case of compound (**8**), no separation of diastereoisomers was observed, and the optical purity could not be determined.

Table 3. Lithium aluminium hydride reduction of morpholin-3-ones

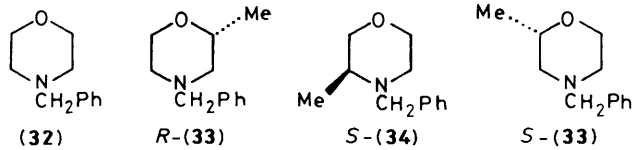
Morpholinone	Morpholine	Yield (%)
(**28**)	(**32**)	91
R-(**29**)	*R*-(**33**)	84
S-(**30**)	*S*-(**34**)	82[14]
S-(**31**)	*S*-(**33**)	67

Table 4. Gas chromatographic separations of diastereoisomeric hydroxy amides

Morpholin-2-one	Hydroxy amide	Yield (%)	α*
(**7**)	(**32**)	99	1.09
(**8**)	(**33**)	66	1.04
(**9**)	(**34**)	75	1.00
(**13**)	(**35**)	66	1.11

* The (*S,S*)- or (*R,R*)-form eluted first. α Represents the ratio of the retention time of the two peaks.

The optical purity of *R*-(**29**) was found to be greater than 95% by ^1H n.m.r. using a chiral europium shift reagent [Eu(tfc)$_3$]. The 3-methyl doublet peak of racemic compound (**29**) split into two doublet peaks and the (*S*)-enantiomer showed a larger downfield shift [$\Delta\delta_{S-R}$ = 18 Hz per equivalent of Eu(tfc)$_3$]. ^1H N.m.r. separations of the enantiomers of morpholin-2-ones and morpholin-3-ones (**30**) and (**31**) were unsuccessful using Eu(tfc)$_3$. However, the optical purity of (**30**) was determined as



almost 100% by reduction with lithium aluminium hydride to the corresponding (*S*)-morpholine (**34**) and comparison of the specific rotation with the literature value.[12] Morpholin-3-one (**31**) was also found to be enantiomerically pure (>95%) as determined by lithium aluminium hydride reduction to *S*-(**33**) and comparison with *R*-(**33**) obtained from optically pure compound (**31**). From these results, compound (**8**) was assumed

to be optically pure based on the fact that (**31**), which was synthesized from the same (*S*)-amino alcohol (**3**), was optically pure, and that no racemization seemed to occur under the subsequent reaction conditions employed.

Experimental

M.p.s were measured on a Yanagimoto micro melting point apparatus, and uncorrected. The i.r. spectra were measured on a Jasco IRA-1 i.r. spectrometer. ^1H and ^{13}C N.m.r. spectra were recorded using a Hitachi R-24 and a JEOL-100 spectrophotometer, respectively, using tetramethylsilane as an internal standard. Gas chromatography was performed on a Shimadzu GC-12A gas chromatograph using a capillary column (CBP-M25-025). Elemental analysis was performed on a Perkin-Elmer Model 240 elemental analyser. The specific rotations were measured on a Jasco DIP-360 digital polarimeter.

2-Benzylaminoethanol, (*RS*)-2-benzylaminopropanol, and (*RS*)-1-benzylaminopropan-2-ol were synthesized from the corresponding amino alcohols by a method similar to that reported by Saavedra.[12] *N*-Benzyl-(*R*)- and -(*S*)-amino acids were synthesized as described by Quitt.[13] (*S*)-2-Benzylaminopropanol, and (*S*)-2-benzylamino-4-methylpentanol were synthesized by *N*-benzylation of the corresponding amino alcohols, or by lithium aluminium hydride reduction of the corresponding *N*-benzylamino acids. (*S*)-1-Benzylaminopropan-2-ol was prepared from (*S*)-lactic acid by formation of an amide with benzylamine, and reduction using lithium aluminium hydride. Methyl (*S*)-2-bromopropionate was prepared from (*S*)-bromopropionic acid {$[\alpha]_D$ −28.79° [*c* 1.88, $CHCl_3$], lit.,[14] $[\alpha]_D$ −27.2°}. (*S*)-2-Bromopropionyl chloride was also prepared from (*S*)-2-bromopropionic acid using thionyl chloride.

General Procedure for the Synthesis of N-*Benzylmorpholin-2-ones from* 2-*Benzylamino Alcohols.*—The appropriate 2-bromo ester was added dropwise to a solution of the 2-benzylamino alcohol (10 mmol), triethylamine (10 mmol), and benzene (10 ml), at room temperature and the mixture stirred for 12 h in the case of methyl 2-bromoacetate, or heated at reflux for up to 3 days in the case of ethyl 2-bromopropionate. The reaction mixture was washed with dilute aqueous hydrochloric acid, dried ($MgSO_4$), and evaporated under reduced pressure to yield the corresponding hydroxy ester and morpholin-2-one. The hydroxy ester was converted into the morpholin-2-one when heated in refluxing benzene in the presence of a small amount of toluene-*p*-sulphonic acid for up to a day. The crude product was purified by silica gel column chromatography using benzene–ethyl acetate (5:1 or 15:1) as the eluant.

4-*Benzylmorpholin-2-one* (**6**). B.p. 140 °C/5 mmHg; $\nu_{max.}$($CHCl_3$) 1 750 cm^{-1}; δ_H($CDCl_3$) 2.63 (t, 2 H, *J* 5 Hz, 5-H), 3.27 (s, 2 H, 3-H), 3.53 (s, 2 H, CH_2Ph), 4.32 (t, 2 H, *J* 5 Hz, 6-H), and 7.28 (s, 5 H, Ph); δ_C($CDCl_3$) 48.5 (t, C-5), 55.6 (t, C-3), 61.5 (t, CH_2Ph), 68.7 (t, C-6), 127.6 (d, Ph), 128.4 (d, Ph), 128.9 (d, Ph), 136.2 (s, Ph), and 167.3 p.p.m. (s, C-2).

(S)- *and* (R)-4-*Benzyl-3-methylmorpholin-2-one* S- *and* R-(**7**). B.p. 155 °C/5 mmHg; $\nu_{max.}$($CHCl_3$) 1 725 cm^{-1}; δ_H($CDCl_3$) 1.53 (d, 3 H, *J* 7 Hz, 3-Me), 2.3—3.0 (m, 2 H, 5-H), 3.31 (d, 1 H, *J* 14 Hz, CH_2Ph), 3.36 (q, 1 H, *J* 7 Hz, 3-H), 3.95 (d, 1 H, *J* 14 Hz, CH_2Ph), 4.1—4.4 (m, 2 H, 6-H), and 7.30 (s, 5 H, Ph); δ_C($CDCl_3$) 16.3 (q, 3-Me), 46.3 (t, C-5), 58.3 (t, CH_2Ph), 60.1 (d, C-3), 68.2 (t, C-6), 127.5 (d, Ph), 128.4 (d, Ph), 128.8 (d, Ph), 137.3 (s, Ph), and 171.0 p.p.m. (s, C-2).

(S)- *and* (R)-4-*Benzyl-5-methylmorpholin-2-one* S- *and* R-(**8**). B.p. 160 °C/5 mmHg. (S)-4-*Benzyl-5-methylmorpholin-2-one* S-(**8**). B.p. 180 °C/5 mmHg; $[\alpha]_D^{27}$ +68.95° (*c* 1.78, $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 735 cm^{-1}; δ_H($CDCl_3$) 1.11 (d, 3 H, *J* 7 Hz, 5-Me), 2.6—3.0 (m, 1 H, 5-H), 3.05 (d, 1 H, *J* 18 Hz, 3-H), 3.25 (d, 1 H, *J* 13 Hz, CH_2Ph), 3.41 (d, 1 H, *J* 18 Hz, 3-H), 3.88 (d, 1 H, *J* 13 Hz, CH_2Ph), 4.0—4.4 (m, 2 H, 6-H), and 7.28 (s, 5 H, Ph); δ_C($CDCl_3$) 12.4 (q, 3-Me), 51.1 (d, C-5), 52.4 (t, C-3), 57.5 (t, CH_2Ph), 73.5 (t, C-6), 127.5 (d, Ph), 128.4 (d, Ph), 128.8 (d, Ph), 136.9 (s, Ph), and 167.9 p.p.m. (s, C-2).

(S)- *and* (R)-4-*Benzyl-6-methylmorpholin-2-one* S- *and* R-(**8**). B.p. 160 °C/5 mmHg. (S)-4-*Benzyl-6-methylmorpholin-2-one* S-(**8**). B.p. 160 °C/5 mmHg; $[\alpha]_D$ −0.64° (*c* 2.18, $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 735 cm^{-1}; δ_H($CDCl_3$) 1.31 (d, 3 H, *J* 7 Hz, 6-Me), 2.1—2.2 (m, 1 H, 5-H), 2.7—2.9 (m, 1 H, 5-H), 3.01 (d, 1 H, *J* 17 Hz, 3-H), 3.49 (d, 1 H, *J* 17 Hz, 3-H), 3.52 (s, 2 H, CH_2Ph), 4.4—4.7 (m, 1 H, 6-H), and 7.29 (s, 5 H, Ph); δ_C($CDCl_3$) 19.1 (q, 6-Me), 54.9 (t, C-3), 54.9 (t, C-5), 61.4 (t, CH_2Ph), 75.9 (d, C-6), 127.6 (d, Ph), 128.5 (d, Ph), 128.9 (d, Ph), 136.4 (s, Ph), and 167.8 p.p.m. (s, C-2).

4-*Ethoxycarbonylmorpholin-2-one* (**18**). B.p. 170 °C/30 mmHg; δ_H($CDCl_3$) 1.28 (t, 3 H, *J* 7 Hz, OCH_2CH_3), 3.69 (t, 2 H, *J* 5 Hz, 5-H), 4.23 (q, 2 H, *J* 7 Hz, OCH_2CH_3), 4.26 (s, 2 H, 3-H), and 4.45 (t, 2 H, *J* 5 Hz, 6-H).

N-*Benzyl*-N-(2-*hydroxyethyl*)*glycine* (**19**).—A mixture of *N*-benzylmorpholin-2-one (1 mmol) and 5% Pd–C (20 mg) in acetic acid (5 ml) was stirred overnight at room temperature under a hydrogen atmosphere. The Pd–C was filtered off, and the acetic acid was evaporated under reduced pressure to yield white crystals. The crude product was recrystallized to yield the pure hydroxy acid, m.p. 193—194 °C (from methanol–hexane) (Found: C, 63.0; H, 7.25; N, 6.6. $C_{11}H_{15}NO_3$ requires C, 63.14; H, 7.22; N, 6.69%); δ_H(D_2O, DSS) 3.42 (t, 2 H, *J* 5 Hz), 3.81 (s, 2 H), 4.01 (t, 2 H, *J* 5 Hz), 4.48 (s, 2 H), and 7.60 (s, 5 H).

Synthesis of 3-*Substituted Morpholin-2-ones from* N-*Benzylamino Acids.*—A suspension of the *N*-benzylamino acid (10 mmol), potassium carbonate (20 mmol), and 1,2-dibromoethane (50 mmol) in dimethylformamide (20 ml) was stirred for 1—4 h at 100 °C. The reaction mixture was diluted with dichloromethane and washed several times with water. The excess of 1,2-dibromoethane was distilled off under reduced pressure, and the crude product was purified as described previously.

(S)-4-*Benzyl-3-methylmorpholin-2-one* S-(**7**). B.p. 155 °C/5 mmHg; $[\alpha]_D^{22}$ +47.79° (*c* 1.95, $CHCl_3$).

(R)-4-*Benzyl-3-methylmorpholin-2-one* R-(**7**). B.p. 155 °C/5 mmHg; $[\alpha]_D^{26}$ −51.26° (*c* 2.02, $CHCl_3$).

(S)-4-*Benzyl-3-isopropylmorpholin-2-one* S-(**13**). B.p. 180 °C/5 mmHg; $[\alpha]_D^{24}$ −32.50° (*c* 2.38, $CHCl_3$); δ_H($CDCl_3$) 1.15 [d, 3 H, *J* 7 Hz, $CH(CH_3)_2$], 1.08 [d, 3 H, *J* 7 Hz, $CH(CH_3)_2$], 2.0—2.2 [m, 1 H, $CH(CH_3)_2$], 2.3—2.9 (m, 2 H, 5-H), 3.22 (d, 1 H, *J* 4 Hz, 3-H), 3.42 (d, 1 H, *J* 13 Hz, CH_2Ph), 3.90 (d, 1 H, *J* 13 Hz, CH_2Ph), 4.1—4.4 (m, 2 H, 6-H), and 7.29 (s, 5 H); δ_C($CDCl_3$) 18.0 [q, $CH(CH_3)_2$], 19.6 [q, $CH(CH_3)_2$], 32.1 [d, $CH(CH_3)_2$], 46.6 (t, C-5), 60.1 (t, CH_2Ph), 67.1 (d, C-3), 70.1 (t, C-6), 127.1 (d, Ph), 128.2 (d, Ph), 128.3 (d, Ph), 137.5 (s, Ph), and 169.6 p.p.m. (s, C-2).

Reaction of Morpholin-2-one (**6**) *with Nucleophiles.*—The reaction of compound (**6**) (1 mmol) with lithium aluminium hydride (1 mmol) in dry ether (10 ml) for 2 h at room temperature under an argon atmosphere followed by work-up resulted in the formation of the hemiacetal (**20**) (20% yield); δ_H($CDCl_3$) 2.2—2.8 (m, 4 H), 3.47 (s, 2 H), 3.5—4.2 (m, 4 H), 4.25 (br s, 1 H), 4.8—5.0 (m, 1 H), and 7.29 (s, 5 H); and the diethanolamine (**21**) (30% yield); δ_H($CDCl_3$) 2.70 (t, 4 H, *J* 5 Hz), 3.41 (s, 2 H), 3.61 (t, 4 H, *J* 5 Hz), 3.70 (s, 2 H), and 7.35 p.p.m. (s, 5 H). Compound (**6**) (2 mmol) was treated with lithium borohydride (2 mmol) in dry ether (20 ml) for 2 h at room temperature under argon atmosphere, diluted with dichloromethane, washed with water, dried ($MgSO_4$), and evaporated under reduced pressure. The crude mixture was applied to silica

gel column chromatography, to yield the hemiacetal (**20**) and diethanolamine (**21**) in 55 and 30% yields, respectively. Compound (**6**) (1 mmol) was treated with pyrrolidine (2.5 ml) at 80 °C for 12 h to give, after removal of the excess of amine by acidic extraction, and purification by silica gel chromatography (eluant chloroform–acetone–ethanol, 100:5:1) the hydroxy amide (**25**) (85% yield); $\nu_{max.}(CHCl_3)$ 3 340 and 1 625 cm^{-1}; $\delta_H(CDCl_3)$ 1.5—2.1 (m, 4 H), 2.88 (t, 2 H, *J* 5 Hz), 3.20 (s, 2 H), 3.0—3.7 (m, 4 H), 3.64 (t, 2 H, *J* 5 Hz), 3.87 (s, 2 H), 4.11 (s, 1 H), and 7.35 (s, 5 H). Reaction of compound (**6**) with benzylamine and methyl glycinate was also carried out in a similar manner to yield hydroxy amide (**23**) (65%); $\delta_H(CDCl_3)$ 1.36 (d, 3 H, *J* 7 Hz), 2.74 (t, 2 H, *J* 5 Hz), 3.18 (s, 2 H), 3.69 (t, 2 H, *J* 5 Hz), 3.75 (s, 3 H), 4.85 (dq, 1 H, *J* 7 Hz), 7.35 (s, 5 H), and 8.04 (d, 1 H, *J* 7 Hz); and (**24**) (58%); $\nu_{max.}(CHCl_3)$ 3 320 and 1 650 cm^{-1}; $\delta_H(CDCl_3)$ 2.55 (br s, 2 H), 2.65 (t, 2 H, *J* 6 Hz), 3.17 (s, 2 H), 3.60 (t, 2 H, *J* 6 Hz), 3.73 (s, 2 H), 4.37 (d, 2 H, *J* 6 Hz), and 7.23 p.p.m. (s, 5 H). A mixture of compound (**6**) (2 mmol) and methylmagnesium iodide (10 mmol) in ether at room temperature was stirred for 12 h at room temperature and then worked up. Purification of the residue by silica gel column chromatography (eluant chloroform–acetone–ethanol, 100:40:8) yielded the diethanolamine (**22**) in a 94% yield; $\delta_H(CDCl_3)$ 1.14 (s, 6 H), 2.71 (t, 2 H, *J* 5 Hz), 3.55 (t, 2 H, *J* 5 Hz), 3.78 (s, 2 H), 4.00 (br s, 2 H), and 7.31 (s, 5 H).

General Procedure for the Synthesis of Substituted Morpholin-3-ones.- A solution of the *N*-benzylamino alcohol (10 mmol) and triethylamine (10 mmol) in dichloromethane (10 ml) was cooled in an ice–methanol bath, and a mixture of the 2-bromoacid halide in dichloromethane was added dropwise over a period of 10—20 min under an argon atmosphere. The bath was removed and the reaction mixture was stirred for a further 1—12 h. It has been reported that slight racemization occurs during this process, and that care should be taken by dilution and lowering of temperature.[15] The resulting solution was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure. No *O*-acylation was observed during this process, and the crude hydroxy amide in tetrahydrofuran (10 ml) was added dropwise to a suspension of sodium hydride (11 mmol) in tetrahydrofuran at room temperature under an argon atmosphere, and stirred for up to 12 h. The reaction was quenched with a small amount of water and tetrahydrofuran was removed under reduced pressure. The resulting oil was diluted with dichloromethane and washed with water. The crude product was purified by silica gel column chromatography (eluant chloroform–acetone–ethanol, 100:5:1).

4-*Benzylmorpholin*-3-*one* (**28**). B.p. 100 °C/5 mmHg; $\nu_{max.}(CHCl_3)$ 1 630 cm^{-1}; $\delta_H(CDCl_3)$ 3.19 (t, 2 H, *J* 6 Hz, 5-H), 3.76 (t, 2 H, *J* 6 Hz, 6-H), 4.17 (s, 2 H, CH_2Ph), 4.57 (s, 2 H, 2-H), and 7.26 (s, 5 H, Ph); $\delta_C(CDCl_3)$ 45.4 (t, CH_2Ph), 49.2 (t, C-5), 63.7 (t, C-6), 68.0 (t, C-2), 127.5 (d, Ph), 128.1 (d, Ph), 128.6 (d, Ph), 136.2 (s, Ph), and 166.5 p.p.m. (s, C-3).

(S)- *and* (R)-4-*Benzyl*-2-*methylmorpholin*-3-*one* S- *and* R-(**29**). B.p. 130 °C 5 mmHg; $\nu_{max.}(CHCl_3)$ 1 625 cm^{-1}; $\delta_H(CDCl_3)$ 1.51 (d, 3 H, *J* 7 Hz, 2-Me), 2.9—4.0 (m, 4 H), 4.26 (q, 1 H, *J* 7 Hz), 2-H), 4.45 (d, 1 H, *J* 15 Hz, CH_2Ph), 4.72 (d, 1 H, *J* 15 Hz, CH_2Ph), and 7.28 (s, 5 H, Ph); $\delta_C(CDCl_3)$ 18.0 (q, 2-Me), 46.2 (t, CH_2Ph), 49.7 (t, C-5), 62.5 (t, C-6), 74.3 (d, C-2), 127.6 (d, Ph), 128.1 (d, Ph). 128.7 (d, Ph), 136.5 (s, Ph), and 169.8 p.p.m. (s, C-3).

(R)-4-*Benzyl*-2-*methylmorpholin*-3-*one* R-(**29**). B.p. 160 °C/5 mmHg; $[\alpha]_D^{25}$ +71.8° (*c* 2.12, $CHCl_3$).

(S)- *and* (R)-4-*Benzyl*-5-*methylmorpholin*-3-*one* S- *and* R-(**30**). B.p. 140 °C/5 mmHg.

(S)-4-*Benzyl*-5-*methylmorpholin*-3-*one* S-(**29**). B.p. 160 °C/5 mmHg; $[\alpha]_D^{28}$ −85.8° (*c* 2.23, MeOH); $\nu_{max.}(CHCl_3)$ 1 630 cm^{-1}; $\delta_H(CDCl_3)$ 1.24 (d, 3 H, *J* 6 Hz, 5-Me), 3.2—3.5 (m, 1 H, 5-H), 3.5—3.8 (m, 2 H, 6-H), 3.95 (d, 1 H, *J* 15 Hz, 2-H), 4.21 (s, 2 H, CH_2Ph), 5.31 (d, 1 H, *J* 15 Hz, 2-H), and 7.27 (s, 5 H, Ph); $\delta_C(CDCl_3)$ 16.6 (q, 5-Me), 46.4 (t, CH_2Ph), 49.9 (d, C-5), 67.9 (t, C-6), 69.3 (t, C-2), 126.8 (d, Ph), 127.9 (d, Ph), 128.7 (d, Ph), 136.7 (s, Ph), and 167.0 p.p.m. (s, C-3).

(S)- *and* (R)-4-*Benzyl*-6-*methylmorpholin*-3-*one* S- *and* R-(**31**). B.p. 140 °C/5 mmHg.

(S)-4-*Benzyl*-6-*methylmorpholin*-3-*one* S-(**31**). B.p. 160 °C/5 mmHg; $[\alpha]_D^{29}$ +62.9° (*c* 2.86, MeOH); $\nu_{max.}(CHCl_3)$ 1 635 cm^{-1}; $\delta_H(CDCl_3)$ 1.19 (d, 3 H, *J* 6 Hz, 6-Me), 3.0—3.3 (m, 2 H, 5-H), 3.6—4.0 (m, 1 H, 6-H), 4.16 (d, 1 H, *J* 17 Hz, CH_2Ph), 4.35 (d, 1 H, *J* 17 Hz, CH_2Ph), 4.45 (d, 1 H, *J* 15 Hz, 2-H), 4.72 (d, 1 H, *J* 15 Hz, 2-H), and 7.29 (s, 5 H, Ph); $\delta_C(CDCl_3)$ 18.2 (q, 6-Me), 49.4 (t, C-5), 51.7 (t, CH_2Ph), 67.7 (t, C-2), 69.6 (d, C-6), 127.6 (d, Ph), 128.2 (d, Ph), 128.7 (d, Ph), 136.1 (s, Ph), and 166.6 p.p.m. (s, C-3).

Lithium Aluminium Hydride Reductions of Substituted Morpholin-3-ones.—The morpholin-3-one (1 mmol) in tetrahydrofuran (5 ml) was added dropwise to a suspension of lithium aluminium hydride (2 mmol) in tetrahydrofuran (20 ml) at room temperature and the mixture then heated at reflux for 24 h. Work-up and purification by silica gel column chromatography (eluant chloroform–acetone–ethanol, 100:20:4) yielded the pure morpholine.

(S)-4-*Benzyl*-2-*methylmorpholine* S-(**33**). B.p. 160 °C/5 mmHg; $[\alpha]_D^{26}$ −13.4° (*c* 2.53, $CHCl_3$); $\delta_H(CDCl_3)$ 1.10 (d, 3 H), 1.4—2.3 (m, 2 H), 2.4—2.8 (m, 2 H), 3.46 (s, 2 H), 3.3—3.9 (m, 3 H), and 7.28 (s, 5 H).

(R)-4-*Benzyl*-2-*methylmorpholine* R-(**33**). B.p. 120 °C/5 mmHg; $[\alpha]_D^{26}$ +13.0° (*c* 3.21, $CHCl_3$).

(S)-4-*Benzyl*-3-*methylmorpholine* S-(**34**). B.p. 160 °C/5 mmHg; $[\alpha]_D^{28}$ +72.0° (*c* 0.754, $CHCl_3$) [lit.[3c] (*R*)-form: $[\alpha]_D$ −73.4° (EtOH)].

Gas Chromatographic Separations of Diastereoisomeric Hydroxy Amides.—Morpholin-2-ones (**7**)—(**8**) and (**13**) were treated with DL-phenylethylamine (10 mol equiv.) at 100 °C for 24 h and worked up as described previously to yield the pure hydroxy amides (**39**)—(**42**), respectively. (**39**), 99% yield; $\delta_H(CDCl_3)$ 1.22 (d, 3 H, *J* 7 Hz), 1.42 (d, 3 H, *J* 7 Hz), 2.5—2.8 (m, 2 H), 2.9—3.2 (m, 1 H), 3.31 (d, 1 H, *J* 6 Hz), 3.68 (s, 2 H), 3.5—3.8 (m, 2 H), 4.8—5.3 (m, 1 H), 7.38 (s, 10 H), and 8.83 (d, 1 H, *J* 7 Hz); (**40**), 66% yield; $\delta_H(CDCl_3)$ 0.92 (d, 3 H, *J* 7 Hz), 1.35 (d, 3 H, *J* 7 Hz), 3.09 (s, 2 H), 3.0—3.7 (m, 3 H), 4.01 (br s, 2 H), 4.7—5.2 (m, 1 H), 7.20 (s, 5 H), and 8.26 (d, 1 H, *J* 7 Hz); (**41**), 75% yield; $\delta_H(CDCl_3)$ 1.06 (d, 3 H, *J* 6 Hz), 1.40 (d, 3 H, *J* 7 Hz), 2.3—2.6 (m, 2 H), 2.86 (br s, 1 H), 3.07 (s, 2 H), 3.70 (d, 2 H), 3.6—4.0 (m, 1 H), 4.7—5.2 (m, 1 H), and 7.21 (s, 10 H); (**42**), 66% yield; $\delta_H(CDCl_3)$ 0.95 (d, 6 H, *J* 6 Hz), 1.34 (d, 3 H, *J* 6 Hz), 1.93 (br s, 1 H), 1.8—2.2 (m, 1 H), 2.72 (t, 2 H, *J* 5 Hz), 3.04 (d, 1 H, *J* 5 Hz), 3.71 (d, 2 H, *J* 5 Hz), 4.20 (t, 2 H, *J* 5 Hz), and 7.30 (s, 10 H).

References

1 R. M. Williams, D. Zhai, and P. J. Sinclair, *J. Org. Chem.*, 1986, **51**, 5021.
2 J. W. Ludwig, M. Newcomb, and O. E. Bergbreister, *Tetrahedron Lett.*, 1986, 2731.
3 (*a*) G. R. Brown, A. J. Foubister, and B. Wright, *J. Chem. Soc., Perkin Trans. 1*, 1985, 2577; (*b*) R. E. TenBrick, *J. Org. Chem.*, 1987, **57**, 418; (*c*) G. Bettoni, C. Cellucci, S. Ferorelli, R. Perrone, and V. Tortorella, *Tetrahedron*, 1986, **42**, 2117.
4 C. Kashima, K. Harada, and Y. Omote, *Can. J. Chem.*, 1985, **63**, 288.
5 M. Benet, *C.R. Seances Acad. Sci., Ser. C*, 1979, 288, 299.
6 K. Yankowski and C. Berse, *Can. J. Chem.*, 1968, **46**, 1939.
7 G. C. Stelakatos and N. Argyropoulos, *J. Chem. Soc. C*, 1970, 964.
8 G. R. Pettit and D. M. Piatak, *J. Org. Chem.*, 1962, **27**, 2127.
9 J. T. Edward and J. M. Ferland, *Chem. Ind.*, 1964, 975.
10 N. J. Leonard and F. P. Hauck, Jr., *J. Am. Chem. Soc.*, 1957, **79**, 5279.

11 V. Schurig in 'Asymmetric Synthesis,' J. D. Morrison (ed.), Academic Press, 1983, vol. 1, p. 59.
12 J. E. Saavedra, *J. Org. Chem.*, 1985, **50**, 2271.
13 P. Quitt, J. Hellerbach, and K. Vogler, *Helv. Chim. Acta*, 1963, **46**, 327.
14 S.-c. J. Fu, S. M. Birnbaum, and J. P. Greenstein, *J. Am. Chem. Soc.*, 1954, **76**, 6054.
15 K. Watabe, S.-C. Chang, E. Gil-Av, and B. Koppenhoefer, *Synthesis*, 1987, 225.

Received 2*nd July* 1987; *Paper* 7/1177