Thanos, *J. Am. Chem. Soc.*, **98**, 3267 (1976), studied amine quaternization rates in *exo*- and *endo*-2-dimethylaminonorborane, the endo amine quaternized 20 times slower than the exo. However, Menger considered this to be a small factor, which is to say that the *endo*-dimethylamino group is not subjected to unusual steric effects within the endo cavity. The ^{13}C data obtained on **7a,b** and **8a,b** indirectly support Menger's observations because the steric substituent effect, as well as the other chemical shift values for the norbornyl carbons, is about the same in both **7** and **8**. However, a greater "freedom of motion" is observed in the exo case, owing to its greater ability to achieve minimum strain since there is some freedom of motion with respect to the *exo*-norbornyl skeleton. On the other hand, for the endo there is less freedom of motion (its cavity is smaller); hence, the hydrogen on the *endo*-α-*N*-alkyl carbon is more rigidly held in a specific orientation, thereby giving it a larger steric compression shift. Of course, the difference in steric shift of the endo (11.6 ppm) vs. exo (10.0 ppm) is quite moderate.

Synthesis of the 2,3-Dihydro-6*H*-1,4-oxazin-2-ones Chiral at C(3) and Asymmetric Induction in Hydrogenation of the Azomethine Bond

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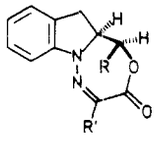
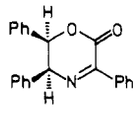
The 2,3-dihydro-6*H*-1,4-oxazin-2-ones **17–26** chiral at C(3) have been prepared, starting from various α-halomethyl aryl ketones and N-protected α-amino acids via intermediary α-(O-α′-N′-protected aminoacyl) hydroxy ketones **1–8** and corresponding hydrobromides **9–16**. 1,3-Asymmetric induction in hydrogeneration of the azomethine bond in **17–24** led to 1,3-disubstituted tetrahydrooxazin-2-ones **27–34**. Their diastereomeric purity was estimated as >98%, based on the analysis of their LIS–NMR spectra, whereas their "3,5-cis" relative configuration was proposed on the grounds of the direction taken by the hydrogenation, based on the conformational analysis of the starting 2,3-dihydro derivatives **17–24**. Heterogeneously catalyzed hydrogenation of the chiral six-membered azomethine derivatives, investigated for the short series of ligands (Me, *i*-Pr, Bz) at the original chiral center, revealed that conformational rigidity around an azomethine bond ensures high diastereoselectivity of the process regardless of the spatial requirements of the larger group on the first center.

Hydrogenation of the azomethine double bond with concurrent asymmetric induction is the most widely used method for preparing chiral compounds with an amino group attached to an asymmetric carbon atom. Knowledge of the greatest significance in this field came mostly from studies by Hiskey and Northrop,[1-3] Harada,[4-6] and Corey.[7,8] Conformational rigidity of the substrate, usually much higher in cyclic than in open-chain azomethine derivatives, significantly enhances the diastereoselectivity of hydrogenation. Thus, reductions of the six- and seven-membered substrates I and II, as carried



I R
a H
b CH_3

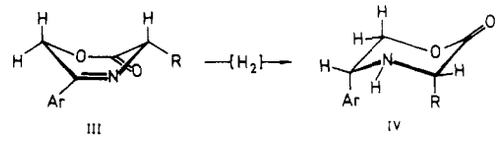


II

out by Corey[6,7] and Kagan,[9] respectively, resulted in nearly 100% stereoselectivity. A recent report[10] of another highly diastereoselective hydrogenation of 2-propyl-5-methyl-$\Delta^{1,2}$-octahydroquinolin in the last step of *d,l*-pumiliotoxin synthesis is also relevant.

Obviously, the high nonequivalence of the diastereotopic faces about the azomethine bond is largely accentuated in cyclic substrates like I and II, which enables a highly stereoselective approach of the reducing agent (diastereoface differentiating reaction[11]). As a part of a wider synthetic program encompassing the preparation of various chiral compounds by diastereoselective azomethine double-bond hydrogenation, we have embarked upon a more detailed study of the diastereoselectivity in 1,3-asymmetric induction obtained with cyclic, six-membered azomethine substrates. Results from this study are the subject of this report.

Scheme I



III IV

Asymmetric hydrogenation of the compounds characterized by the general formulas III, i.e., derivatives of 2,3-dihydro-6*H*-1,4-oxazin-2-ones, has been chosen as an appropriate model reaction (Scheme I).

The envisaged route leading to the azomethine substrates III is shown in Scheme II.

It consists of three steps and starts from easily available prochiral compounds, α-halomethyl ketones, and their equally available chiral counterparts, α-amino acids. This route should lead to C(3)-chiral derivatives III possessing various groups at the inducing chiral center. This, in turn, should allow a study on the dependence of the diastereoselectivity of hydrogenation on the steric requirements of the larger groups R′ on the C(3) atom.

Results and Discussion

To start the synthesis of III according to Scheme II, α-halomethyl ketones and potassium salts of N-protected α-

Scheme II

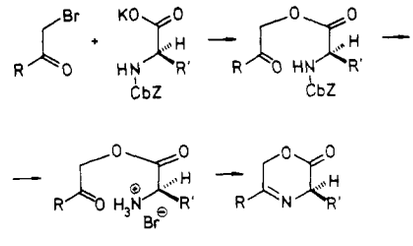


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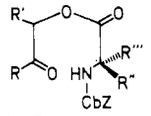
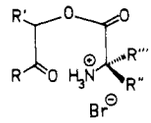
Table I. Esters Prepared from α-Halomethyl Ketones and *N*-Protected α-Amino Acids



Registry no.	Compd	R	R′	R″	R‴	Recrystn solvent	Mp, °C	Yield,[a] %	Analyzed for[b]
6479-48-7	1[c]	Ph	H	H	*i*-Pr	Cyclohexane	103–104	79.5	$C_{21}H_{23}NO_5$
6599-33-3	2	Ph	H	H	Bz	MeOH	92–94	74.0	$C_{25}H_{23}NO_5$
64975-99-1	3	*p*-FPh	H	H	*i*-Pr	Cyclohexane	78–80	74.5	$C_{21}H_{22}FNO_5$
64976-00-7	4	2,5-Di-OMePh	H	H	*i*-Pr	96% EtOH	99–102	100	$C_{23}H_{27}NO_7$
64976-01-8	5	*p*-Biphenylyl	H	H	*i*-Pr	EtOH	107–108	76.8	$C_{27}H_{27}NO_5$
64976-02-9	6	*p*-Biphenylyl	H	H	Me	EtOAc	181–183	87.0	$C_{25}H_{23}NO_5$
64976-03-0	7	*p*-Biphenylyl	H	H	Bz	*i*-PrOH	142–144	84.0	$C_{31}H_{27}NO_5$
64976-04-1	8	2′-Naphthyl	H	H	*i*-Pr	MeOH	98–99	78.9	$C_{25}H_{25}NO_5$

[a] Yields relate to the recrystallized substances. [b] Satisfactory analytical data (±0.3% for C, H, N) were obtained for all compounds listed in the table. [c] N Protected with a *tert*-butoxy group (Boc.)

Table II. Preparation and Physical Properties of Various α-(*O*-Aminoacyl) Hydroxy Ketone Hydrobromides



Registry no.	Compd	R	R′	R″	R‴	Recrystn solvent	Mp, °C	Yield,[a] %	Analyzed for[b]	$[\alpha]_D$	*c* (in MeOH)
6479-54-5	9	Ph	H	H	*i*-Pr	*i*-PrOH	182–184	95.9	$C_{13}H_{18}BrNO_3$	+12.5°	2.00
6479-55-6	10	Ph	H	H	Bz	Acetone–ether	159–162	90.0	$C_{17}H_{18}BrNO_3$	+5.3°	1.42
64976-05-2	11	p-FPh	H	H	*i*-Pr	*i*-PrOH	160–161	81.3	$C_{13}H_{17}BrFNO_3$	+11.5°	2.06
64976-06-3	12	2,5-Di-OMePh	H	H	*i*-Pr	*i*-PrOH	161–163	82.0	$C_{15}H_{22}BrNO_5$	+12.5°	2.07
64976-07-4	13	*p*-Biphenylyl	H	H	*i*-Pr	MeOH	208–210	97.3	$C_{19}H_{22}BrNO_3$	−6.5°	1.02[c]
64976-08-5	14	*p*-Biphenylyl	H	H	Me	MeOH	217–219	89.0	$C_{17}H_{18}BrNO_3$	−10.3°	1.50[c]
64976-09-6	15	*p*-Biphenylyl	H	H	Bz	MeOH–ether (1:1)	172–174	80.1	$C_{23}H_{22}BrNO_3$	+2.0°	1.15
64976-10-9	16	2′-Naphthyl	H	H	*i*-Pr	EtOH	188–190	98.9	$C_{17}H_{20}BrNO_3$	+20.8°	2.02

[a] Yields are given for crude products. [b] Satisfactory analytical data (±0.3% for C, H, N) were obtained for all compounds listed in the table. [c] Determined in dimethylformamide.

amino acids were condensed in solution at room temperature. DMF was the most favorable solvent. Intermediate esters **1–8** (Table I) have been isolated in yields usually above 90%. (See, however, paragraph concerning supplementary material at the end of the paper.) The Cbz-protecting group was cleaved using 33% hydrobromic acid in acetic acid, as attempted hydrogenolytic cleavage of **1** (10% Pd/C in acetone–MeOH, 1:1, bubbling hydrogen) led, within a few minutes, to hydrogenolysis of the ester group. One of the products was acetophenone in nearly quantitative yield.

The hydrobromides **9–16,** obtained from **1–8,** were isolated in 80–100% yields. Melting points, specific rotations, and other pertinent data of these compounds are summarized in Table II.

A number of trials was necessary to get acceptable yields of the oxazinones **17–24** in the cyclization step. The use of basic or acidic conditions, or of some organic solvents, led to extensive hydrolysis, whereby α-hydroxyl ketones were formed, and concomitant precipitation of the free α-amino acids occurred. Careful reaction control revealed that, on dissolution in water or methanol, the cyclization of some hydrobromides proceeded, indeed, in a clean fashion but was followed by a pH drop from 5 to about 2. This low pH caused extensive hydrolysis and slowed down the cyclization. Therefore, cyclization in acetate buffer at pH 5.0, at room temperature, led clearly to the formation of compounds **17–24** in 65–90% yields (Table III).[12]

On the basis of analysis of Dreiding models for compounds **17–24** conformational equilibria, according to Scheme III, may be proposed.

Two quasi-boat conformations should correspond to the discrete energy minima. In these conformations the bulky R group should markedly inhibit the approach of the reducing agent toward the "α face" of these molecules. This inhibition occurs because of the conically symmetric free-rotation space around the axis of local symmetry of the isopropyl, benzyl, and methyl groups in these compounds. Consequently, coplanar approach toward the "β face", i.e., from above in Scheme III, should be encouraged and a proton on the new chiral center at C(5) should be "1,3-cis" with respect to protons on the C(3) center.[13]

Hydrogenation of dihydrooxazinones was preferably performed by passing hydrogen through methanolic solutions and using 10% Pd/C as a catalyst. Some data characteristic of the compounds **27–34** are given in Table IV. Conditions and reagents used in other attempts at hydrogenation are briefly described in the Experimental Section.

Crude hydrogenation products **27–34** were purified by rapid filtration through silica gel to avoid their decomposition and to retain the original diastereomeric ratio. These samples, and those obtained by recrystallization to a constant rotation value

Scheme III

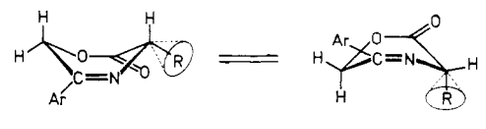
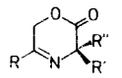


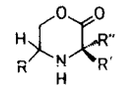
Table III. Preparation and Physical Properties of 2,3-Dihydro-6*H*-1,4-oxazin-2-ones 17–26



Registry no.	Compd	R	R′	R″	Recrystn solvent	Mp, °C	Yield, %	$[\alpha]_D/c$ ($CHCl_3$)	Analyzed for[a]	NMR (in $CDCl_3$)	IR, cm^{-1}
64976-11-0	**17**	Ph	H	*i*-Pr	Light petroleum	72 74	67.8	−51.6°/5.00	$C_{13}H_{15}NO_2$	1.07 (dd, 6 H), 2.50 (m, 1 H), 3.99 (m, 1 H), 5.23 (ds, 2 H), 7.3–7.8 (m, 5 H)	1738, 1655, 1390, 1370, 690
65085-99-6	**18**	Ph	H	Bz	MeOH–H_2O (3:1)[2]	58–60	66.2	+26.0°/2.00	$C_{17}H_{15}NO_2$	3.37 (d, 2 H), 4.0–5.15 (m, 2 + 1 H), 7.15–7.55 (m, 10 H)	1755, 1650, 1595, 700
64976-12-1	**19**	*p*-FPh	H	*i*-Pr	Cyclohexane	75–76	71.1	−45.8°/2.08	$C_{13}H_{14}FNO_2$	1.05 (dd, 6 H), 2.50 (m, 1 H), 4.13 (m, 1 H), 5.29 (ds, 2 H), 7.10 (dd, 2 H), 7.78 (dd, 2 H)	1745, 1665, 1610, 1520, 850
64976-13-2	**20**	2,5-di-OMePh	H	*i*-Pr	MeOH–H_2O (1:1)[2]	95–97	81.4	−113.2°/ 2.43	$C_{15}H_{19}NO_4$	1.12 (dd, 6 H), 2.50 (ds, 2 H), 3.7 and 3.8 (ss, 2 + 3 H), 4.10 (m, 1 H), 5.22 (ds, 2 H), 6.87 (d, 2 H), 7.21 (d, 1 H)	1752, 1622, 1608, 1500, 826
64976-14-3	**21**	p-Biphenylyl	H	*i*-Pr	*i*-PrOH	130–132	83.0	−14.6°/1.97	$C_{19}H_{19}NO_2$	1.03 (dd, 6 H), 2.47 (m, 1 H), 4.15 (m, 1 H), 5.30 (ds, 2 H), 7.28–7.9 (m, 9 H)	1740, 1625, 1605, 765, 690
64976-15-4	**22**	p-Biphenylyl	H	Me			72.3	+20.5°/1.87	$C_{17}H_{15}NO_2$	1.69 (d, 3 H), 4.30 (q, 1 H), 3.32 (m, 2 H), 7.3–8.1 (m, 9 H)	1760, 1630, 1605, 1485, 840, 830, 725, 690
64976-16-5	**23**	p-Biphenylyl	H	Bz	96% EtOH	160–162	92.5	+273.7°/ 1.37	$C_{23}H_{19}NO_2$	3.38 (d, 2 H), 4.30 (m, 1 H), 4.85 (s, 2 H), 7.2–7.7 (m, 14 H)	1740, 1630, 1605, 760, 698
64976-17-6	**24**	2′-Naphthyl	H	*i*-Pr	MeOH	91–92	88.2	−49.5°/2.06	$C_{17}H_{17}NO_2$	1.10 (dd, 6 H), 2.57 (m, 1 H), 4.20 (m, 1 H), 5.39 (m, 2 H), 7.4–8.05 (m, 7 H)	1735, 1645, 825, 740
64976-18-7	**25**	Ph	Ph	H	96% EtOH	116–118	88.4	−9.0°/1.12	$C_{16}H_{13}NO_2$	5.37 (s, 2 H), 5.63 (s, 1 H), 7.3–8.1 (m, 10 H)	1735, ($\nu_{C=O}$), 1655, ($\nu_{C=N}$), 1600, 1580, 1499, 698
64975-85-5	**26**	*p*-BrPh	Ph	H	Cyclohexane	122–124	89.1	−0.4°/2.64	$C_{16}H_{12}BrNO_2$	5.32 (ds, 2 H), 5.62 (d, 1 H), 7.3–7.9 (m, 9 H)	1745, 1658, 1589, 826

[a] Satisfactory analytical data (±0.3% for C, H, N) were obtained for compounds listed in the table.

Table IV. Preparation and Physical Properties of Tetrahydro-1,4-oxazin-2-ones 27–34



Registry no.	Compd	R	R′	R″	Recrystn solvent	Mp, °C	Yield,[a] %	$[\alpha]_D/c$ ($CHCl_3$) Chromatographed	$[\alpha]_D/c$ ($CHCl_3$) Recrystallized	Analyzed for[b]	NMR (in $CDCl_3$)	IR, cm^{-1}
64975-86-6	**27**	Ph	H	*i*-Pr	MeOH	68–70	61.4	−75.3°/ 2.02[c]	−75.3°/ 2.02[c]	$C_{13}H_{17}NO_2$	1.02 and 1.06 (dd, 6 H), 1.84 (br s, 1 H), 2.4 (m, 1 H), 3.03 (d, 1 H), 4.15 (s, 2 + 1 H), 7.2–7.55 (m, 5 H)	3340 (δ_{NH}), 1730 ($\nu_{C=O}$), 1385, 1370 (*gem*-dimethyl), 710, 700
64975-87-7	**28**	Ph	H	Bz	*n*-Hexane	76–78	45.0	−157.9°/ 2.09	−169.0°/ 2.28	$C_{17}H_{17}NO_2$	2.83 (br s, 1 H), 2.75, 4.35 (m, 6 H), 7.25–7.45 (m, 10 H)	3325 (δ_{NH}), 1730 ($\nu_{C=O}$), 1605 ($\nu_{C=C}$), 700
64975-88-8	**29**	*p*-FPh	H	*i*-Pr		Oil	34.7	−65.0°/ 1.56[c]		$C_{13}H_{16}FNO_2$	1.05 and 1.09 (dd, 6 H), 1.92 (br s, 1 H), 2.4 (m, 1 H), 3.75 (d, 1 H), 4.20 (s, 2 + 1 H), 6.9–7.55 (m, 4 H)	(neat) 3350 (δ_{NH}), 1740 ($\nu_{C=O}$), 1380 (*gem*-dimethyl), 840
64975-89-9	**30**	2,5-di-OMePh	H	*i*-Pr	MeOH	125–126	45.0	−75.5°/ 1.50[c]	−76.3°/ 1.51[c]	$C_{15}H_{21}NO_4$	1.06 and 1.08 (dd, 6 H), 1.80 (br, s, 1 H), 2.5 (m, 1 H), 3.78 and 3.80 (ds, 6 H), 4.05–4.75 (m, 1 + 1 + 2 H), 6.80 (d, 2 H), 7.10 (m, 1 H)	3340 (δ_{NH}), 298–2850 (ν_{CH_3}), 1735 ($\nu_{C=O}$), 1605, 1500, 860, 820
64975-90-2	**31**	*p*-Biphenylyl	H	*i*-Pr	MeOH	142–143	68.9	−83.9°/ 1.65	−84.3°/ 1.90	$C_{19}H_{21}NO_2$	1.05 and 1.10 (dd, 6 H), 2.00 (brs, 1 H), 2.45 (m, 1 H), 3.77 (d, 1 H), 4.22 (s, 2 + 1 H), 7.25–7.7 (m, 9 H)	3350 (δ_{NH}), 1740 ($\nu_{C=O}$), 845, 765, 700
64975-91-3	**32**	*p*-Biphenylyl	H	Me	96% EtOH	164–166	30.6	−56.0°/ 1.39	−81.1°/ 2.00	$C_{17}H_{17}NO_2$	1.52 (d, 3 H), 1.92 (br s, 1 H), 3.88 (q, 1 H), 4.30 (s, 2 + 1 H), 7.2–7.7 (m, 9 H)	3300 (δ_{NH}), 1740 ($\nu_{C=O}$), 1600, 1490, 853, 730, 690
64975-92-4	**33**	*p*-Biphenylyl	H	Bz	96% EtOH	158–160	80.1	−173.8°/ 1.11	−187.7°/ 1.06	$C_{23}H_{21}NO_2$	1.82 (br s, 1 H), 2.75–4.30 (m, 6 H), 7.2–7.7 (m, 14 H)	3320 (δ_{NH}), 1730 ($\nu_{C=O}$), 1600, 760, 700
64975-93-5	**34**	2′-Naphthyl	H	*i*-Pr	MeOH	78–80	50.6	−91.0°/ 1.18	−109.6°/ 1.25	$C_{17}H_{19}NO_2$	1.03 and 1.06 (dd, 6 H), 1.89 (br s, 1 H), 2.45 (m, 1 H), 3.83 (d, 1 H), 4.31 (m, 2 + 1 H), 7.35–7.95 (m, 7 H)	33300 (δ_{NH}), 1730 ($\nu_{C=O}$), 1365, 1368 (*gem*-dimethyl), 1605, 825, 740, 695

[a] Yields are given for chromatographically pure products. [b] Satisfactory analytical data (±0.3% for C, H, N) were obtained for all compounds listed in the table. [c] Determined in methanol.

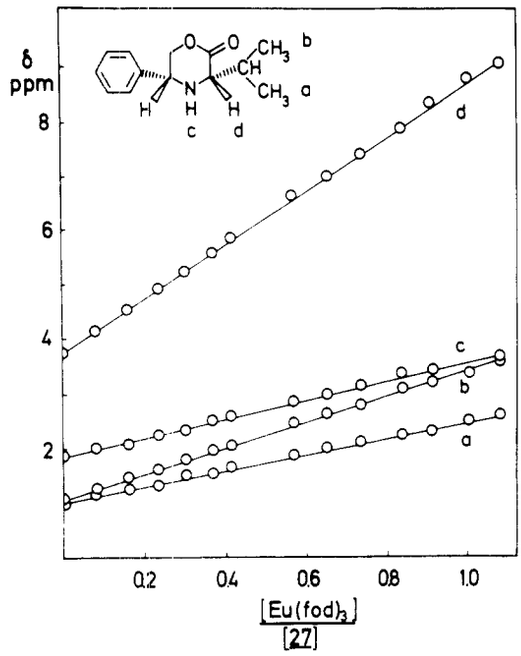


Figure 1. Dependence of the LSR induced shifts on the reagent/substrate ratio for various groups of protons in compound **27**.

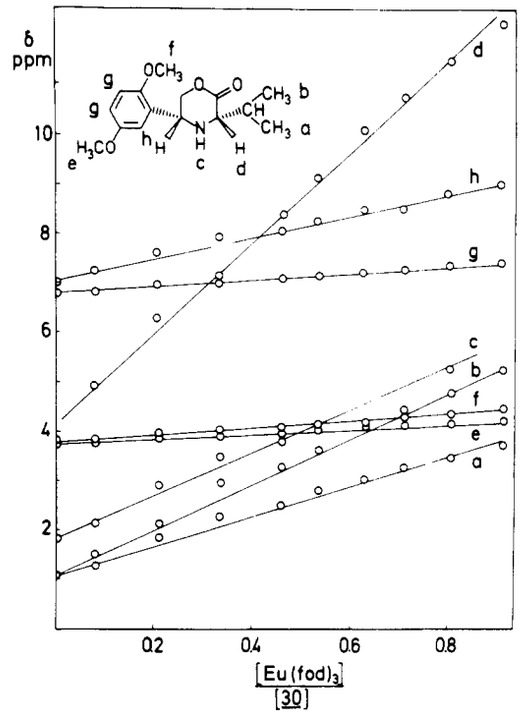


Figure 2. Dependence of the LSR induced shifts on the reagent/substrate ratio for various groups of protons in compound **30**.

(only one recrystallization was usually required), were carefully checked for diastereomeric composition using the LIS method.[14,15] Generally, only one diastereomer was detected using $Eu(fod)_3$ as an achiral reagent. In some cases, signals due to traces of the other diastereomer could be distinguished from the noise of the baseline, but integration of such signals was not possible. We concluded, therefore, that in all cases investigated asymmetric induction led to at least a 98–99% excess of one diastereomer, regardless of the group present on the C(3) chiral center.

Two typical examples of the plot of δ_{meas} vs. lanthanide/substrate concentration ratio for the compounds **27** and **30** are given in Figures 1 and 2.

In all compounds investigated, the proton on C(3) and a proton of the two methyl groups turned out to be the nuclei most sensitive to the addition of LSR. This indicated that the coordination center for the shift reagent is probably the carbonyl oxygen of the lactone group but not the most basic center, i.e., the N(4) atom. Coordination of the lanthanide reagent to the weaker electron-donating center is caused entirely by steric conditions. Two bulky groups (Ar and R) flank the N(4) atom so that an approach of the lanthanide reagent is precluded.

Such selective coordination of the polyfunctional organic molecules, favoring a less nucleophilic center because of the sterical hindrances at the stronger one, was repeatedly observed.[16,17]

In conclusion, it may be stated that high diastereoselectivity of heterogeneously catalyzed hydrogenation of the azomethine double bond, as in compounds **17–24**, was achieved. In these substrates, substituents of different bulkiness were present at the chiral center C(3) (methyl, benzyl, isopropyl). The diastereoselectivity achieved in hydrogenation indicates that in order to obtain high asymmetric induction it is of prime importance to ensure conformational rigidity of the substrate. A substanital difference in the spatial requirements of the ligands on the inducing chiral center is less important.

Experimental Section

Melting points were determined on a Mettler 51 melting point apparatus. Infrared spectra were recorded on Perkin-Elmer M-257 and M-720 spectrometers and are for KBr pellets, unless stated otherwise. A Perkin-Elmer R 12 spectrometer was used to obtain ^1H NMR spectra. All ligand-induced shift (LIS) measurements were performed in $CDCl_3$ solution using Merck $Eu(fod)_3$ Uvasol grade without further purification. Usually, the investigated range of LSR/substrate concentration ratios was from 0.05 to 0.5. Optical rotations were measured on a Perkin-Elmer 141 polarimeter. Thin-layer chromatography (TLC) was performed on aluminum or glass plates precoated with Merck's silica gel 60F 254. Column chromatography was run over granular silica gel, 0.05–0.2 mm (Merck).

General Procedure for Preparation of Esters 1–8. N-Protected α-amino acid (50.0 mmol) was dissolved in methanol (50.0 mL), and a solution of potassium hydroxide (2.80 g, 50.0 mmol) in methanol (50.0 mL) was added. Then the solvent was evaporated in vacuo, and the residual potassium salt was dissolved in dimethylformamide (100 mL). To this solution the desired α-halomethyl aryl (or alkyl) ketone (50 mmol) was added, and the reaction mixture was stirred at room temperature. The reaction was followed up by TLC using chloroform–ether (9:1) as the eluant and was usually found to be completed within 20 h. After completion, the dimethylformamide was evaporated in vacuo at 80 °C, the residue was slurried in water (100 mL), and undissolved crude esters were collected by suction, washed with water, and recrystallized from the solvents stated in Table I. The spectroscopic properties are briefly listed below.

Infrared spectra of all compounds exhibited the following characteristic bands (cm^{-1}): 3340–3370 (δ_{NH}), 1740–1755 ($\nu_{COCH_2OC=O}$), 1695–1710 ($\nu_{PHC=O}$), 1680–1690 ($\nu_{HNC=O}$), 1510–1540 (ν_{NH}).

NMR spectra of all compounds (except **2**) exhibited singlets at 5.05–5.15 ppm (2 H) for benzylic protons within the N-Cbz group. All compounds exhibited double singlets between 5.20 and 5.60 ppm (which sometimes collapsed into one singlet) for geminal protons $COCH_2O$. All spectra were recorded in $CDCl_3$ except those for **1**, which were recorded in acetone-d_6.

General Procedure for the Preparation of Compounds 9–16. Compounds **1–8** (30 mmol) were dissolved in 33% hydrogen bromide in acetic acid (100 mL) and stirred until evolution of the gas ceased (0.5–1 h). The resulting solution was diluted by the addition of ether (200 mL), and light petroleum (100 mL) was added to precipitate products. The pasty (sometimes oily) products were brought to crystallization by extended scratching. Crude hydrobromides were collected by suction, washed with ether, and recrystallized from the solvents specified in Table II.

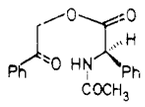
Infrared spectra of all compounds exhibited the following characteristic bands (cm^{-1}): 3000–3100, 2500–2800, 1900–2100 ($-NH_3^+$), 1740–1765 ($\nu_{COCH_2C=O}$), and a Ph*C*=*O* band between 1690 and 1705 cm^{-1}.

NMR spectra were generally recorded in MeOH-d_4, but those of compounds **9** and **13** were recorded in D_2O and those of **13** and **14** in

Me_2SO-d_6. The *S*-alanyl derivative **14** exhibited a characteristic doublet-quartet pattern ($CH_3CHCNCO$) centered between 1.60 and 1.73 ppm, and 4.2 and 4.38 ppm, respectively. The *S*-phenylalanyl derivatives **10** and **15** exhibited a simple pattern consisting of a doublet at 3.45 ppm (1 H) and a multiplet centered at 4.5 ppm (2 H). The *S*-valyl derivatives **9, 11, 12,** and **13** exhibited a characteristic doublet due to protons from the two superimposed diastereotopic methylenic groups, at 1.15–1.22 ppm (6 H), and a multiplet for the $(CH_3)_2CH$ proton at 2.30–2.50 ppm.

General Procedure for the Preparation of 3,5-Disubstituted 2,3-Dihydro-6*H*-1,4-oxazin-2-ones 17–26. The hydrobromides **9–16** (10 mmol) were dissolved in 0.2 M acetate buffer (100 mL, prepared from 70 parts of 0.2 M aqueous sodium acetate and 30 parts of 0.2 M acetic acid). The resulting solution was stirred for periods ranging from 2 to 24 h at room temperature, and completeness of the reaction was checked by TLC using chloroform–ether (9:1) or ether–acetone (3:1) as eluting systems. During the reaction, cyclic products precipitated and were separated by suction. Only compound **24** was cyclized for 48 h and, since it did not separate within this period, it was isolated by extraction of the aqueous buffer solution with chloroform (3 × 30 mL). Extracts were combined, dried (Na_2SO_4), and concentrated for crystallization. After recrystallization from the solvents listed in Table III, pure compounds **17–26** were obtained. Their spectroscopic and other characteristic data are given in Table III.

Attempts at Hydrogenation of the C=N Bond in the 2,3-Dihydro-6*H*-1,4-oxazin-2-ones. Various reducing agents or hydrogenation catalysts, or both, were tried to find optimum conditions for the hydrogenation of the C=N bond in compounds **17–26,** e.g., sodium borohydride, diborane, Raney Ni, Pd/$BaSO_4$, and Pd/C (5 and 10%, respectively, from Fluka). The following solvents were used: dioxane, ethyl acetate, acetic anhydride, and methanol. Catalytic hydrogenation by a flow of hydrogen gave rise to a much less hydrogenolytic decomposition than a batch system under otherwise identical reaction conditions (10% Pd/C, methanol). Catalytic hydrogenation proved to be of no use with the C(3) phenyl derivatives **25** and **26,** however, since concomitant hydrogenolysis was inevitable. An attempt to quench the reduced product as the *N*-acetyl derivative, starting from 503 mg (2 mmol) of **25** and using acetic anhydride as the solvent (10.0 mL) and 10% Pd/C catalyst (100 mg), led to compound **35** (508 mg, 81.7%).



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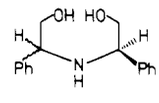

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α-(*R*)-*N*-Acetylphenylglycyloxyacetophenone (35): Recrystallized from CCl_4; mp 131–133°C; NMR ($CDCl_3$) δ 1.93 (s, 3 H), 5.26 (s, 2 H), 5.75 (d, 1 H, degenerated into a singlet on addition of D_2O), 6.67 (d, 1 H, disappeared on addition of D_2O), 7.2–7.9 (m, 10 H); IR 3325 (δ_{NH}), 1748 (ν_{CO}, ester), 1715 (ν_{CO}, ketone), 1650 (ν_{CO}, amine), 1551, 698, 690 cm^{-1}; $[\alpha]^{24}D$ +1.0° (*c* 2.02 in $CHCl_3$).

Anal. Calcd for $C_{18}H_{17}NO_4$ (311.34): C, 69.44; H, 5.50; N, 4.50. Found: C, 69.67; H, 5.30; N, 4.64.

When $NaBH_4$ was used to reduce **25** and **26,** extensive hydrolytic decomposition took place, whereas the use of diborane led to nonselective reduction of both functionalities in **25** to give the diol **36.**

1,1′-Diphenyldiethanolamine (36). The solution of freshly recrystallized sodium brohydride (182 mg, 4.8 mmol) in diglyme (6.0 mL, carefully dried over CaH_2, and freshly distilled from $LiAlH_4$) was added dropwise, during 1 h, to the solution of BF_3·Et_2O (1.2 mL, 9.6 mmol, freshly distilled from CaH_2) in dry diglyme (2.0 mL). Using an apparatus similar to the one described in the literature,[18] a stream of nitrogen was introduced, which carried diborane into a flask containing dihydrooxazin-2-one, **25** (503 mg, 2.0 mmol), dissolved in THF (5.0 mL, dried by a 3-Å molecular sieve). After stirring for 1 h at room temperature, the reaction mixture was heated for another hour at 70–80 °C. Then it was cooled and water (2 mL) and acetic acid (0.5 mL) were added. After subsequent dilution with more water(20 mL), the mixture was extracted with ether (3 × 10 mL). The combined extracts were dried (Na_2SO_4) and evaporated. The oily residue was purified on a column [15 g of silica gel, ether–light petroleum (1:1) as the eluant] to give 248 mg (49%) of oily **36,** which decomposed on attempted metal-block distillation. A pure sample was obtained by repeated chromatography and was dried for 24 h at 0.01 mmHg over P_2O_5: NMR ($CDCl_3$) δ 2.77 (s, 2 H, disappeared on addition of D_2O), 3.70 (m, 2 H), 4.35 (s, 4 H), 4.5–4.8 (m, 2 H), 7.2–7.5 (m, 10 H).

Anal. Calcd for $C_{16}H_{19}NO_2$ (257.33): C, 74.68; H, 5.74; N, 5.44. Found: C, 74.39; H, 6.02; N, 5.33.

General Procedure for the Catalytic Hydrogenation of Compounds 17–24. All compounds (5.0 mmol) were dissolved in methanol (50.0 mL), to which ethyl acetate was sometimes added in order to improve the solubility. Subsequentialy, 100–150 mg of 10% Pd/C was added and the reaction mixture was vigorously stirred while hydrogen was very slowly bubbled through the suspension. The hydrogenation was followed up by TLC using ether–light petroleum (1:1) as the eluant. The reduced products **27–34** appeared as new spots having somewhat smaller R_f values, but exhibiting a much weaker fluorescence under the UV-254 lamp, so that their location with iodine vapors was sometimes required. Reactions were usually completed within 1–3 h, after which the catalyst was filtered off, the filtrate was evaporated, and the crude products were purified, first by chromatography [25 g of silica gel, ether–light petroleum (1:1) as the eluant] and then by crystallization from the solvents listed in Table IV.

Both the chromatographically purified samples of compounds **27–34** and those recrystallized to constant rotations and melting points (usually two crystallizations were sufficient) were analyzed for diastereomeric composition using the LIS method in NMR, as described in the introductory section of this paper.

Note Added in Proof. After this manuscript was accepted for publication, a paper appeared [G. Schulz and W. Steglich, *Chem. Ber.,* **110,** 3615 (1977)] where some of the title compounds were described. The authors explained the reactivity of C(5)-alkyl-1,4-oxazin-2-ones as well.

Registry No.—35, 6495-94-6; **36,** 64975-95-7; *N*-Cbz-*S*-Val, 1149-26-4; *N*-Cbz-*S*-Phe, 1161-13-3; *N*-Cbz-*S*-Ala, 1142-20-7; $PhCOCH_2Br$, 70-11-1; p-$FC_6H_4COCH_2Br$, 403-29-2; 2,5-di-MeO-$C_6H_3COCH_2Br$, 1204-21-3; p-$PhC_6H_4COCH_2Br$, 135-73-9; 2-bromo-1-(2-naphthalenyl)ethanone, 613-54-7; $PhCOCH_2O$-$COCH(Ph)NH_2$·HBr, 64975-77-5; $PhCOCH_2OCOCH(Ph)NH$·Cbz, 64975-96-8; $HO_2CCH(Ph)NH$·Cbz, 17609-52-8; p-BrC_6H_4CO-$CH_2OCOCH(Ph)NH_2$·HBr, 64975-79-7; p-$BrC_6H_4COCH_2O$-$COCH(Ph)NH$·Cbz, 64975-97-9; p-$BrC_6H_4COCH_2Br$, 99-73-0.

Supplementary Material Available. Full spectroscopic (IR, NMR) and analytical data for other intermediary compounds prepared during this work (5 pages). Ordering information is given on any current masthead page.

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(12) Note: All compounds in Table III possess a C(5)-aryl group, but no dihydrooxazin-2-one derivatives bearing a C(5)-alkyl group could be isolated from corresponding reaction mixtures. (See paragraph on supplementary material at the end of the paper). Attempts to bring about cyclizations of such compounds failed, even when weak ion-exchange resins or 3-Å molecular sieves were used as cyclization promotors, as well as when using conditions according to Vigneron et al.[9] (dry benzene, presence of silver nitrate).
Failures of cyclization of C(5)-alkyl 2,3-dihydro-6*H*-1,4-oxazin-2-ones presumably reflect lower reactivity of the carbonyl group and higher vulnerability of the resulting ring system. This system seems to be stabilized enough in the derivatives **17–24** by the conjugative interaction of the endocyclic azomethine double bond, so that these derivatives could be isolated.
(13) This implies an *S* absolute configuration of the new chiral center C(5), if the inducing center C(3) possesses an *S* configuration. Detailed analysis of the CD spectra of these compounds will be published separately.
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