Synthesis and Stereoselective Reactions of 2-(Pyrrol-1-yl)alkanals and 2-(Pyrrol-1-yl)alkan-1-ones

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2-(2,5-Dimethylpyrrol-1-yl)alkanals, 2-(pyrrol-1-yl)alkanals, and 2-(2,5-dimethylpyrrol-1-yl)alkan-1-ones were prepared. The reactions of these compounds with Grignard and hydride reagents proceeded stereoselectively to give the corresponding 2-(pyrrol-1-yl)alcohols, which were converted into 2-amino alcohols, such as norephedrine and ephedrine, by cleavage of the pyrrole ring.

2-Aminoalkanals were known to be extremely important intermediates in the synthesis of diastereoisomeric 1,2-disubstituted 2-amino-ethanols.[1,2] 2-Aminoethanols of this class include pharmacologically important compounds such as ephedrine, where receptor centres for these drugs are very stereoselective. Another important 2-aminoethanol of this class, the dipeptide analogue statine, was recently synthesized by alkylation of the corresponding 2-aminoalkanal.[3a,4] These 2-aminoethanol derivatives were found to play a key role as protease inhibitors. 2-Aminoalkanals can easily be prepared by oxidation of 2-amino alcohols,[3] or by reduction of α-amino acids, where the amino group was usually protected by acylation. However, these 2-aminoalkanals are known to racemize quite rapidly, and are difficult to obtain in the optically active form. Racemization of 2-aminoalkanals has been reported to be retarded by using a 9-phenylfluoren-9-yl group as an amino-protecting group.[5] This has been attributed to the ability of the bulky 9-phenylfluorenyl group to prevent enolization by preventing removal of the α-proton.

Alkylation of 2-aminoalkanals usually gives the *threo*-form with low stereoselectivity. For example, the reaction of 2-(*N*,*N*-dialkylamino)alkanals with Grignard reagents has been reported to yield the corresponding *threo*-1,2-disubstituted 2-aminoethanols, except in the case of extremely bulky amino substituents.[6]

On the other hand, 2-aminoalkan-1-ones are also regarded as being important intermediates in the synthesis of diastereoisomeric 2-amino alcohols.[1] 2-Aminoalkan-1-ones protected with alkyl or acyl groups were reduced with hydride reagents to yield the corresponding 1,2-disubstituted 2-aminoethanols, and gave 1,1,2-trisubstituted 2-aminoethanols by treatment with organometallic reagents such as Grignard reagents. For example, treatment of 2-(benzyloxycarbonylamino)alkan-1-ones with triethylsilane and trifluoroacetic acid gave the corresponding 1,2-disubstituted 2-aminoethanols in optically pure form. In this case, the *erythro*-isomer was obtained preferentially.[7] From these facts, the amino substituents of 2-aminoalkanals and alkan-1-ones could influence the stereoselectivities of the formation of the resulting 2-amino alcohols.

Our previous paper reported that the pyrrole ring was a useful protecting group of primary amines and did not cause any racemization.[8] That is, treatment of hexane-2,5-dione or 2,5-dimethoxytetrahydrofuran with primary amines easily afforded the *N*-substituted pyrroles, which regenerated the primary amines on ozonolysis or reaction with hydroxylamine hydrochloride. Also, the pyrrole ring, especially in 2,5-dimethylpyrrole, was demonstrated to be a bulky group.[9] Therefore it was assumed that racemization of 2-aminoalkanals would be retarded by the use of the pyrrole ring as an amino-protecting group. Further it was expected that the formation of the *erythro*-form in the reaction of 2-aminoalkanals with organometallic compounds would be increased by the use of the bulky 2,5-dimethylpyrrole ring, while the *threo*-isomer would be predominantly formed in the hydride reduction of 2-aminoalkan-1-ones. Since the *erythro*-form of ephedrine-type compounds and the *threo*-form of statines exhibit potent biological activity, a stereoselective method to obtain 2-amino alcohols in the optically pure form would be of great synthetic importance.

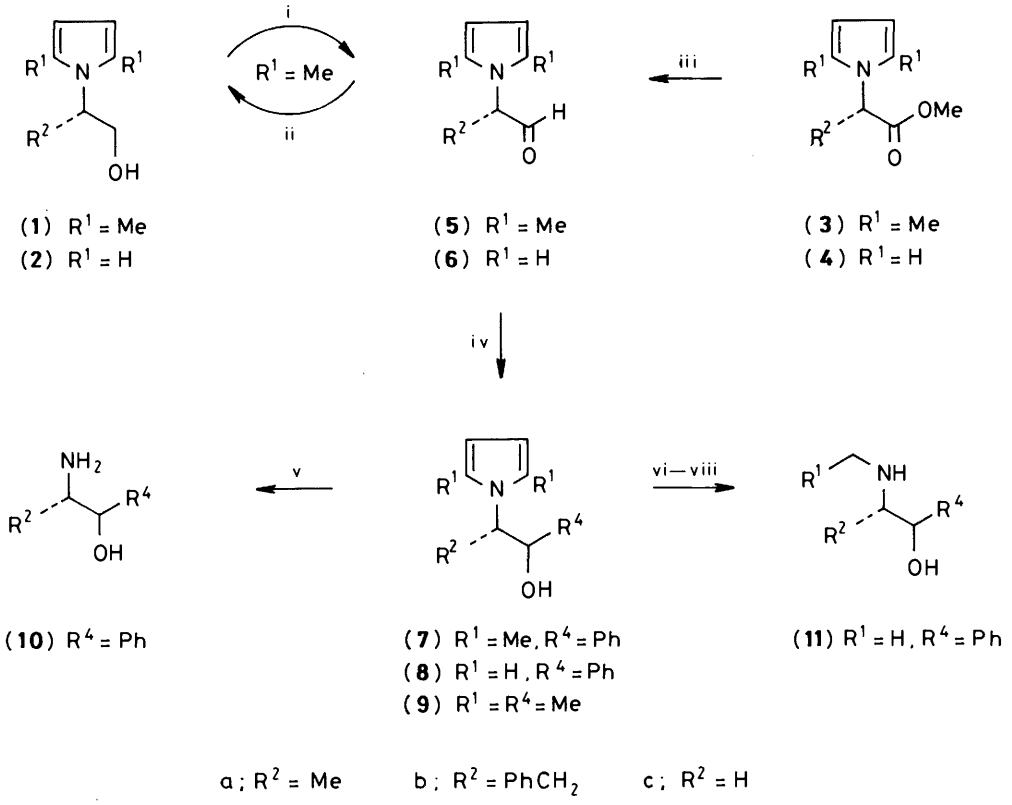
Results and Discussion

First, the synthesis of various 2-(pyrrol-1-yl)alkanals was carried out by the oxidation of 2-(pyrrol-1-yl) alcohols. The oxidizing agent was optimized in the reaction of 2-(2,5-dimethylpyrrol-1-yl)-3-phenylpropan-1-ol (**1b**) and 3-phenyl-2-(pyrrol-1-yl)propan-1-ol (**2b**). When (**1b**) was oxidized by Collins' reagent,[10] the aldehyde could not be obtained presumably due to oxidation of the pyrrole ring. However, oxidation of (**1b**) with dimethyl sulphoxide and *N*,*N*′-dicyclohexylcarbodi-imide (DMSO–DCC)[11] yielded the aldehyde (**5b**) in moderate (36%) yield. Similarly, various 2-(2,5-dimethylpyrrol-1-yl)alkanals (**5**) were obtained, as listed in Table 1. Even using DMSO–DCC oxidation, the unsubstituted pyrrole compound (**2b**), however, could not give the required aldehyde (**6b**). Therefore, the preparation of 2-(pyrrol-1-yl)alkanals (**5**) by an oxidative route can only be achieved in the case of 2-(2,5-dimethylpyrrol-1-yl) alcohols (**1**).

Second, the preparation of aldehydes from the corresponding esters was attempted by di-isobutylaluminium hydride (DIBAL) reduction.[12] Methyl 2-(2,5-dimethylpyrrol-1-yl)alkanoates (**3**) were treated with DIBAL in ether at −78 °C to yield the corresponding 2-(2,5-dimethylpyrrol-1-yl)alkanals (**5**) in better yields than the oxidative method (Table 1). Also, methyl 2-(pyrrol-1-yl)alkanoates (**4**) were treated with DIBAL to yield the desired 2-(pyrrol-1-yl)alkanals (**6**) in good yields (Table 1), though the synthesis of compounds (**6**) was not achieved by the oxidative method. These results showed that the DIBAL reduction of esters (**3**) and (**4**) was more favourable for the synthesis of 2-(pyrrol-1-yl)alkanals (**5**) and (**6**) than was the DMSO–DCC oxidation of the alcohols (**1**) (Scheme 1).

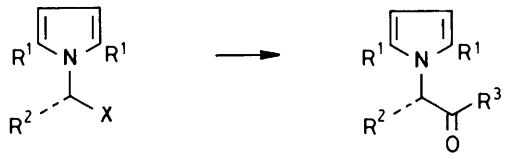
Since ketones can be synthesized from amide compounds using organometallic reagents,[13] the synthesis of ketones using 2-(pyrrol-1-yl)alkanamides was performed. *N*,*N*-Dimethyl-2-(2,5-dimethylpyrrol-1-yl)propanamide (**12a**) was treated with phenyl-lithium in ether to give the desired ketone (**14a**) in 80% yield. Similar reactions were carried out using methyl-lithium. The results are listed in Table 1.

In order to compare the rates of racemization of the resulting aldehydes (**5**) and (**6**) with those of 2-aminoalkanals protected



Scheme 1. *Reagents:* i, DMSO–DCC; ii, $LiAlH_4$ or $NaBH_4$; iii, DIBAL; iv, R^4MgX; v, O_3 or NH_2OH; vi, O_3; vii, $NaBH_4$; vii, $LiAlH_4$

Table 1. Yield of 2-(pyrrol-1-yl)-alkanals and -alkan-1-ones



	Reactant				Product	Yield
	R^1	R^2	X	Reagent	R^3	(%)
(**1a**)	Me	Me	CH_2OH	DMSO–DCC	(**5a**) H	28
(**1b**)	Me	$PhCH_2$	CH_2OH	DMSO–DCC	(**5b**) H	36
(**1c**)	Me	H	CH_2OH	DMSO–DCC	(**5c**) H	31
(**2b**)	H	$PhCH_2$	CH_2OH	DMSI–DCC		0
(**3a**)	Me	Me	CO_2Me	DIBAL	(**5a**) H	71
(**3b**)	Me	$PhCH_2$	CO_2Me	DIBAL	(**5b**) H	68
	Me	Pr^i	CO_2Me	DIBAL	H	0
(**4a**)	H	Me	CO_2Me	DIBAL	(**6a**) H	80
(**4b**)	H	$PhCH_2$	CO_2Me	DIBAL	(**6b**) H	85
(**12a**)	Me	Me	$CONMe_2$	PhLi	(**14a**) Ph	80
(**13a**)	Me	Me	$CONC_4H_8$	PhLi	(**14a**) Ph	74
(**13b**)	Me	$PhCH_2$	$CONC_4H_8$	PhLi	(**14b**) Ph	29
(**12a**)	Me	Me	$CONMe_2$	MeLi	(**15a**) Me	65

Table 2. Racemization (%) of *N*-protected 2-aminoalkanals at room temperature for 15 h in THF

Protecting group	$MeCHNH_2CHO$	$PhCH_2CHNH_2CHO$
2,5-Dimethylpyrrol-1-yl	24	9
Pyrrol-1-yl	40	28
Benzyloxycarbonyl	50	37
t-Butoxycarbonyl	10	21

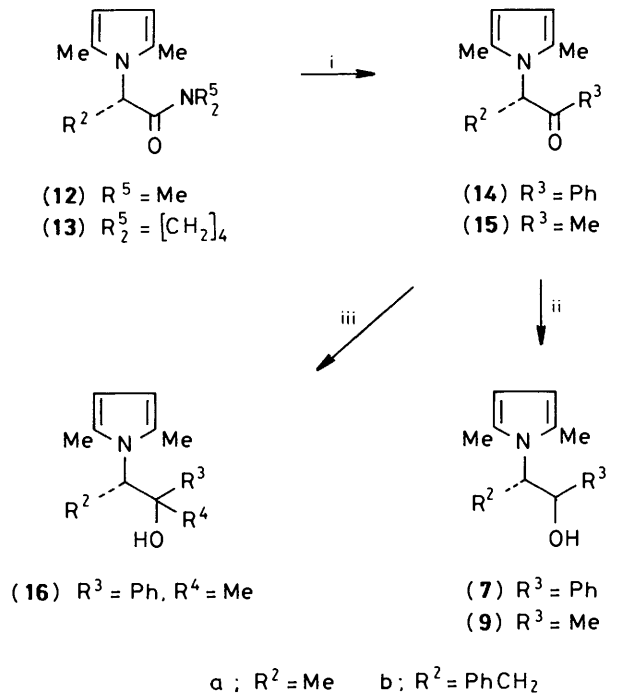
by conventional amino-protecting groups such as benzyloxycarbonyl (Z) and t-butoxycarbonyl (Boc), the rates of racemization of (**5a** and **b**) and (**6a** and **b**) were determined by comparing the specific rotations before and after stirring at room temperature in tetrahydrofuran (THF) for 15 h, and the results are summarized in Table 2. Here, the 2,5-dimethylpyrrole derivatives (**5**) were more stable than the Boc-derivatives towards racemization. Furthermore, the fact that

Table 3. Grignard reaction of 2-(pyrrol-1-yl)-alkanals and -alkan-1-ones

Reactant				Product		Yield	*threo*:
	R^1	R^2	R^3		R^4	(%)	*erythro*
(5a)	Me	Me	H	**(7a)**	Ph	99	33:67
(5a)	Me	Me	H	**(9a)**	Me	92	12:88
(5b)	Me	$PhCH_2$	H	**(7b)**	Ph	99	21:79
(6a)	H	Me	H	**(8a)**	Ph	94	25:75
(6b)	H	$PhCH_2$	H	**(8b)**	Ph	93	20:80
(14a)	Me	Me	Ph	**(16a)**	Me	56	93:7
(15a)	Me	Me	Me	**(16a)**	Ph	76	15:85

Table 4. Hydride reduction of 2-(pyrrol-1-yl)-alkanals and -alkan-1-ones

Reactant					Product		
	R^1	R^2	R^3	Hydride		Yield (%)	*threo*: *erythro*
(5a)	Me	Me	H	$LiAlH_4$	**(1a)**	92	
(5a)	Me	Me	H	$NaBH_4$	**(1a)**	77	
(14a)	Me	Me	Ph	$LiAlH_4$	**(7a)**	78	95:5
(14a)	Me	Me	Ph	DIBAL	**(7a)**	75	92:8
(14a)	Me	Me	Ph	$NaBH_4$	**(7a)**	56	88:12
(14b)	Me	$PhCH_2$	Ph	$LiAlH_4$	**(7b)**	89	100:0
(15a)	Me	Me	Me	$LiAlH_4$	**(9a)**	78	97:3



Scheme 2. *Reagents:* i, R^3Li; ii, $LiAlH_4$; iii, R^4MgX

aldehydes (**5**) showed slower rates of racemization than the parent aldehydes (**6**) can be explained by the steric hindrance of the two methyl groups on the pyrrole ring of compounds (**5**) preventing attack on the α-carbon. When methyl 2-(2,5-dimethylpyrrol-1-yl)propanoate (**3a**) was treated with DIBAL at −78 °C in ether, and the resulting aldehyde (**5a**) was treated with lithium aluminium hydride without isolation, the corresponding alcohol (**1a**) was obtained in the optically pure form. This fact indicated that the racemization of aldehyde (**5a**) hardly occurred at −78 °C. In addition, the rate of racemization of (**5a**) was accelerated in the presence of triethylamine as a base and silica gel as an acid, respectively. In the case of 2-(2,5-dimethylpyrrol-1-yl)-1-phenylpropan-1-one (**14a**), no racemization was observed after 4 days at room temperature.

When 2-(2,5-dimethylpyrrol-1-yl)propanal (**5a**) was treated with phenylmagnesium bromide in ether at room temperature, 2-(2,5-dimethylpyrrol-1-yl)-1-phenylpropan-1-ol (**7a**) was obtained in good yield. By reaction of compound (**7a**) with hydroxylamine hydrochloride, the desired norephedrine (**10a**) was obtained in 89% yield. The ratio between the *erythro*-form and the *threo*-form was determined to be 2:1 by means of ^1H n.m.r. spectroscopy of either (**7a**) or the resulting product (**10a**). When the freshly prepared aldehyde (**5a**) was treated with phenylmagnesium bromide at −78 °C in ether, the *erythro*-enriched alcohol (**7a**) was obtained in 63% yield with the ratio 3:1. After separation using h.p.l.c., the *erythro*-isomer was treated with hydroxylamine hydrochloride to give the desired *erythro*-isomer of norephedrine (**10a**). By comparison of the specific rotation of the obtained *erythro*-isomer with those in the literature,[14] the optical purity of the (1*S*,2*R*-)-*erythro*-norephedrine (**10a**) was found to be 72%.

Similarly the reaction of 2-(2,5-dimethylpyrrol-1-yl)- (**5**) and 2-(pyrrol-1-yl)-alkanals (**6**) with phenyl- and methyl-magnesium halides was performed at room temperature in ether to give the corresponding 2-(pyrrol-1-yl) alcohols (**7**)—(**9**). The results are summarized in Table 3, from which it can be seen that the *erythro*-form was predominantly obtained, while the *threo*-form was preferentially formed by use of conventional amino-protecting groups. Furthermore, the pyrrole ring of compounds (**7**), (**8**), and (**9**) was decomposed to yield the desired 1,2-disubstituted 2-amino alcohols in moderate yields by treatment with hydroxylamine hydrochloride or by ozonolysis followed by hydrolysis. In the case of 2-(2,5-dimethylpyrrol-1-yl)alkan-1-ones (**14**) and (**15**), the Grignard reaction proceeded more stereoselectively to afford corresponding alcohols (**16**). By treatment with hydroxylamine hydrochloride, compound (**16**) gave the desired 1,1,2-trisubstituted 2-aminoethanol.

On treatment with ozone at −78 °C in methanol followed by decomposition of the resulting ozonide with sodium borohydride without isolation, the corresponding 2-formaminoethanol was obtained from compound (**8a**). Further reduction with lithium aluminium hydride in THF gave the corresponding 2-methylaminoethanol, ephedrine (**11a**), in 44% yield.

When 2-(2,5-dimethylpyrrol-1-yl)alkan-1-ones (**14**) and (**15**) were treated with lithium aluminium hydride at room temperature in THF the *threo*-pyrrol-2-yl alcohols (**7**) and (**9**) were obtained in good yield with high stereoselectivity (see Scheme 2). By the use of sodium borohydride and DIBAL, ketone (**14a**) gave alcohol (**7a**) predominantly in the *threo*-form. Results are given in Table 4.

The stereoselectivity of these reactions was explained by Cram's rule, where the pyrrole ring acts as the largest substituent group. On the other hand, a conventionally protected amino group is the second bulkiest group. Therefore, addition reactions on the carbonyl group of 2-amino-alkanals and -alkan-1-ones gave very different results with respect to stereoselectivity from those of the reaction using conventional amino protecting groups.

In conclusion, the pyrrole ring was found to be an excellent amino protecting group for 2-aminoalkanals, which yielded the *erythro*-forms of the corresponding 1,2-disubstituted 2-(pyrrol-1-yl)ethanols in high yield with moderate stereoselectivity on reaction with Grignard reagents. In the case of hydride reduction 2-aminoalkan-1-ones protected with a 2,5-dimethylpyrrole ring, the *threo*-form of 1,2-disubstituted 2-(pyrrol-1-yl)ethanols was obtained with high stereoselectivity in good yield. Furthermore, the pyrrole ring of these 2-(pyrrol-1-yl)ethanols was easily cleaved by treatment with hydroxylamine

hydrochloride or by ozonolysis to give 1,2-disubstituted 2-aminoethanols and 1,2-disubstituted 2-(*N*-alkylamino)ethanols in moderate yields. The ability of the pyrrole ring to prevent racemization of 2-aminoalkanals was found to be similar or sometimes higher than that of the conventionally employed Boc-group.

Experimental

M.p.s were measured on a Yanagimoto micro melting point apparatus, and are uncorrected. I.r. spectra were measured on a Jasco IRA-1 infrared spectrophotometer. ^1H and ^{13}C N.m.r. spectra were measured on a Hitachi R-24 (60 MHz) spectrometer, a JEOL FX-100 (100 MHz) spectrometer, or a JEOL FX-90Q (90 MHz) spectrometer with tetramethylsilane as internal standard. Specific rotations were measured on a Jasco DIP-360 digital polarimeter. Elemental analysis was performed on a Perkin-Elmer Model 240 elemental analyser. According to the method reported in our previous paper,[8] 2-(pyrrol-1-yl)-alkanaotes (**3**) and (**4**) and -alkanamides (**12**) and (**13**) were prepared from α-amino acids. 2-(Pyrrol-1-yl)alcohols (**1**) and (**2**) were prepared from the corresponding esters (**3**) and (**4**) by $LiAlH_4$ reduction.

Synthesis of 2-(2,5-*Dimethylpyrrol*-1-*yl*)*alkanals* (**5**) *by DMSO–DCC Oxidation.*—A solution of DCC (3 mmol) in DMSO (5 ml) was added to a solution of a 2-(2,5-dimethylpyrrol-1-yl)alcohol (**1**) and phosphoric acid (0.5 mmol) in DMSO (5 ml), and the solution was stirred for 10 h at room temperature. The reaction mixture was diluted with water, and extracted with dichloromethane. The extract was washed with water, dried over anhydrous magnesium sulphate, and evaporated. The crude product was purified by column chromatography on silica gel with hexane–benzene mixtures to yield liquid alkanals (**5**).

Synthesis of 2-(*Pyrrol*-1-*yl*)*alkanals* (**5**) *and* (**6**) *by DIBAL Reduction.*—A solution of a methyl 2-(2,5-dimethylpyrrol-1-yl)alkanoate (**3**) or methyl 2-(pyrrol-1-yl)alkanoate (**4**) (10 mmol) in ether (30 ml) was cooled to −78 °C under argon. To this solution was added dropwise DIBAL (1 mol l^{-1} hexane solution) (10—20 mmol) *via* a syringe. The solution was stirred for 2 h at −78 °C. The reaction was quenched by the addition of methanol (5 ml), and the solution was warmed to room temperature. 1M-Aqueous sodium potassium tartrate (20 ml) was added to this solution, and the mixture was stirred for 2 h. The organic layer was washed with water, dried over anhydrous magnesium sulphate, and evaporated. The crude product was purified as described previously.

2-(2,5-*Dimethylpyrrol*-1-*yl*)*propanal* (**5a**). B.p. 80—90 °C/4 mmHg; 28% yield (oxidation), 71% yield (reduction); $\delta_H(CDCl_3)$ 1.50 (3 H, d, *J* 7.3 Hz), 2.16 (6 H, s), 4.61 (1 H, q, *J* 7.3 Hz), 5.83 (2 H, s), and 9.74 (1 H, s); $\delta_C(CDCl_3)$ 13.0 (q), 14.7 (q), 59.6 (d), 107.2 (d), 127.7 (s), and 199.6 (d) (Found: C, 71.0; H, 8.6; N, 9.2. $C_9H_{13}NO$ requires C, 71.48; H, 8.66; N, 9.26%).

2-(2,5-*Dimethylpyrrol*-1-*yl*)-3-*phenylpropanal* (**5b**). B.p. 130—135 °C/4 mmHg; 36% yield (oxidation), 68% yield (reduction); $\nu_{max.}(CHCl_3)$ 1 730 cm^{-1}; $\delta_H(CDCl_3)$ 1.89 (6 H, s), 3.22 (2 H, ABX, *J* 3.9, 9.8, and 14.2 Hz), 4.56 (1 H, dd, *J* 3.9 and 9.8 Hz), 5.78 (2 H, s), 6.79—7.29 (5 H, m), and 9.78 (1 H, s); $\delta_C(CDCl_3)$ 12.9 (q), 35.5 (t), 66.2 (d), 107.2 (d), 126.8 (d), 128.1 (s), 128.5 (d), 129.2 (d), 137.1 (s) and 198.7 (d) (Found: C, 79.2; H, 7.6; N, 6.1. $C_{15}H_{17}NO$ requires C, 79.26; H, 7.53; N, 6.16%).

2-(2,5-*Dimethylpyrrol*-1-*yl*)*ethanal* (**5c**). B.p. 100—120 °C/25 mmHg; 31% yield (oxidation); $\nu_{max.}(CHCl_3)$ 1 750 cm^{-1}; $\delta_H(CDCl_3)$ 2.13 (6 H, s), 4.50 (2 H, d, *J* 1.0 Hz), 5.83 (2 H, s), and 9.58 (1 H, t, *J* 1.0 Hz); $\delta_C(CDCl_3)$ 12.4 (q), 53.4 (t), 106.2 (d), 127.8 (s), and 197.4 (d) (Found: C, 69.55; H, 8.15; N, 10.0. $C_8H_{11}NO$ requires C, 70.04; H, 8.08; N, 10.21%).

2-(*Pyrrol*-1-*yl*)*propanal* (**6a**). B.p. 75—80 °C/5 mmHg; 80% yield (reduction); $\nu_{max.}(CHCl_3)$ 1 735 cm^{-1}; $\delta_H(CDCl_3)$ 1.61 (3 H, d, *J* 7.3 Hz), 4.56 (1 H, q, *J* 7.3 Hz), 6.26 (2 H, t, *J* 2.0 Hz), 6.70 (2 H, t, *J* 2.0 Hz), and 9.57 (1 H, d, *J* 1.0 Hz); $\delta_C(CDCl_3)$ 15.1 (q), 62.8 (d), 109.6 (d), 119.5 (d), and 198.5 (d) (Found: M^+, 123.0686. C_7H_9NO requires *M*, 123.0684).

3-*Phenyl*-2-(*pyrrol*-1-*yl*)*propanal* (**6b**). B.p. 120—125 °C/4 mmHg; 85% yield (reduction); $\delta_H(CDCl_3)$ 3.22 (2 H, ABX, *J* 4.9, 9.8, and 14.2 Hz), 4.58 (1 H, dd, *J* 4.9 and 9.8 Hz), 6.20 (2 H, t, *J* 2.0 Hz), 6.56 (2 H, t, *J* 2.0 Hz), 6.75—7.27 (5 H, m), and 9.69 (1 H, s); $\delta_C(CDCl_3)$ 36.5 (t), 69.2 (d), 109.7 (d), 120.0 (d), 126.9 (d), 128.6 (d), 128.8 (d), 136.4 (s), and 197.4 (d) (Found: C, 78.2; H, 6.6; N, 7.0. $C_{13}H_{13}NO$ requires C, 78.36; H, 6.57; N, 7.02%).

Synthesis of Amide Compounds (**12**) *and* (**13**) *from* 2-(*Pyrrol*-1-*yl*)*alkanoic Acids using DCC.*—To a solution of a 2-(2,5-dimethylpyrrol-1-yl)alkanoic acid (1 mmol) in dichloromethane (10 ml) was added a solution of DCC (1 mmol) in dichloromethane (10 ml), and the mixture was stirred for 10 min at 0 °C. An excess of amine, was added, and the mixture was stirred for 2 h at 0 °C, allowed to warm to room temperature, and stirred overnight. The reaction mixture was filtered, washed successively with dil. hydrochloric acid, aqueous sodium hydrogencarbonate, and water. The organic layer was dried over anhydrous magnesium sulphate, and evaporated. The crude product was purified by column chromatography on silica gel with benzene–ethyl acetate mixtures to yield the amides as needles.

2-(2,5-*Dimethylpyrrol*-1-*yl*)-N,N-*dimethylpropionamide* (**12a**). M.p. 101—102 °C; 60% yield; $\delta_H(CDCl_3)$ 1.51 (3 H, d, *J* 6.8 Hz), 2.17 (6 H, s), 2.59 (3 H, s), 2.98 (3 H, s), 4.81 (1 H, q, *J* 6.8 Hz), and 5.76 (2 H, s); $\delta_C(CDCl_3)$ 12.9 (q), 18.4 (q), 36.0 (q), 36.7 (q), 52.2 (d), 106.6 (d), 127.3 (s), and 170.2 (s) (Found: C, 68.1; H, 9.5; N, 14.4. $C_{11}H_{18}N_2O$ requires C, 68.01; H, 9.34; N, 14.42%).

2-(2,5-*Dimethylpyrrol*-1-*yl*)-N,N-*tetramethylenepropionamide* (**13a**). M.p. 126—127 °C; 69% yield; $\delta_H(CDCl_3)$ 1.52 (3 H, d, *J* 6.8 Hz), 1.6—2.0 (4 H, m), 2.17 (6 H, s), 2.2—2.5 (1 H, m), 3.0—3.3 (1 H, m), 3.3—3.7 (2 H, m), 4.74 (1 H, q, *J* 6.8 Hz), and 5.74 (2 H, s); $\delta_C(CDCl_3)$ 13.0 (q), 17.9 (q), 23.8 (t), 26.4 (t), 45.2 (t), 46.9 (t), 53.2 (d), 106.3 (d), 127.5 (s), and 168.7 (s) (Found: C, 70.9; H, 9.35; N, 12.7. $C_{13}H_{20}N_2O$ requires C, 70.87; H, 9.15; N, 12.72%).

2-(2,5-*Dimethylpyrrol*-1-*yl*)-3-*phenyl*-N,N-*tetramethylenepropionamide* (**6b**). M.p. 77—78 °C; 78% yield; $\delta_H(CDCl_3)$ 1.6—1.9 (4 H, m), 1.88 (6 H, s), 2.0—2.5 (1 H, m), 3.09 (1 H, dd, *J* 13.7 and 9.8 Hz), 3.0—3.2 (1 H, m), 3.4—3.6 (1 H, m), 3.58 (1 H, dd, *J* 13.7 and 4.9 Hz), 4.65 (1 H, dd, *J* 9.8 and 4.9 Hz), 5.69 (2 H, s), 6.8—7.0 (2 H, m), and 7.0—7.3 (3 H, m); $\delta_C(CDCl_3)$ 12.9 (q), 23.7 (t), 26.4 (t), 38.4 (t), 45.4 (t), 53.4 (t), 59.6 (d), 106.4 (d), 126.4 (s), 126.4 (d), 128.2 (d), 129.7 (d), 138.2 (s), and 168.1 (s) (Found: C, 77.0; H, 8.3; N, 9.4. $C_{19}H_{24}N_2O$ requires C, 76.99; H, 8.16; N, 9.45%).

Synthesis of 2-(2,5-*Dimethylpyrrol*-1-*yl*)*alkan*-1-*ones using Organolithium Reagents.*—To a suspension of lithium (24 mmol) in ether (10 ml) at 0 °C was added dropwise a solution of alkyl halide (12 mmol) in ether (20 ml), and the solution was stirred for 2 h at 0 °C. To this solution was added dropwise a solution of 2-(2,5-dimethylpyrrol-1-yl)alkanoic acid amide (**12**) or (**13**) in a mixture of ether (15 ml) and THF (15 ml), and the solution was stirred for 1 h at 0 °C, and for another 4 h at room temperature. To the reaction mixture was added saturated aqueous ammonium chloride (20 ml), and the mixture was stirred for 30 min at room temperature. The water layer was extracted with ether, and the extract was combined with the organic mother liquor. The organic layer was washed

successively with dil. hydrochloric acid and water, dried over anhydrous magnesium sulphate, and evaporated. The crude product was purified by column chromatography on silica gel with hexane–benzene mixtures to yield the ketones (**14**) or (**15**) as needles or liquids.

2-(2,5-*Dimethylpyrrol*-1-*yl*)-1-*phenylpropan*-1-*one* (**14a**). M.p. 64.0—65.0 °C; 80% yield [from (**12a**)], 74% yield [from (**13a**)]; $\nu_{max.}$($CHCl_3$) 1 685 cm^{-1}; δ_H($CDCl_3$) 1.62 (3 H, d, *J* 6.8 Hz), 2.17 (6 H, s), 5.32 (1 H, q, *J* 6.8 Hz), 5.76 (2 H, s), and 7.23—7.64 (5 H, m); δ_C($CDCl_3$) 13.2 (q), 17.0 (q), 56.7 (d), 107.2 (d), 127.1 (s), 128.4 (d), 128.6 (d), 133.1 (d), 135.8 (s), and 197.4 (s) (Found: C, 79.3; H, 7.5; N, 6.1. $C_{15}H_{17}NO$ requires C, 79.26; H, 7.53; N, 6.16%).

2-(2,5-*Dimethylpyrrol*-1-*yl*)-1,3-*diphenylpropan*-1-*one* (**14b**). M.p. 71—72 °C; 29% yield; δ_H($CDCl_3$) 1.90 (6 H, s), 3.41 (2 H, ABX, *J* 14.0, 9.5, and 4.9 Hz), 5.26 (1 H, dd, *J* 9.5 and 4.9 Hz), 5.70 (2 H, s), and 6.8—7.7 (10 H, m); δ_C($CDCl_3$) 13.1 (q), 37.3 (t), 63.0 (d), 107.3 (d), 126.6 (d), 127.7 (d), 128.0 (d), 128.3 (d), 128.4 (d), 128.6 (d), 129.6 (d), 133.1 (d), 135.8 (s), 137.9 (s), and 196.7 (s) (Found: C, 83.0; H, 7.0; N, 4.5. $C_{21}H_{21}NO$ requires C, 83.13; H, 6.98; N, 4.62%).

3-(2,5-*Dimethylpyrrol*-1-*yl*)*butan*-2-*one* (**15a**). B.p. 80—85 °C/5 mmHg; 65% yield; $\nu_{max.}$($CHCl_3$) 1 720 cm^{-1}; δ_H($CDCl_3$) 1.53 (3 H, d, *J* 7.3 Hz), 1.92 (3 H, s), 2.16 (6 H, s), 4.60 (1 H, q, *J* 7.3 Hz), and 5.82 (2 H, s); δ_C($CDCl_3$) 13.1 (q), 15.4 (q), 26.4 (q), 59.7 (d), 107.1 (d), 127.6 (s), and 206.5 (s) (Found: M^+, 165.1145. $C_{10}H_{15}NO$ requires *M*, 165.1154).

Measurements of the Rate of Racemization of N-*Protected* 2-*Aminoalkanals*.—A solution of the aldehyde in THF was stirred for 15 h at room temperature. The resulting aldehyde was purified by distillation under reduced pressure, and the extent of racemization was determined by comparison of the specific rotation of the aldehyde before and after reaction.

Grignard Reaction of 2-(*Pyrrol*-1-*yl*)-*alkanals and* -*alkan*-1-*ones*.—To a solution of phenylmagnesium bromide (5 mmol) in ether (4 ml) was added a solution of a 2-(2,5-dimethylpyrrol-1-yl)alkanal (**5**) or 2-(pyrrol-1-yl)alkanal (**6**) (2 mmol) in ether (5 ml), and the solution was stirred for 12 h at room temperature. In the case of aldehyde (**5a**), the reaction was also carried out at −78 °C, and by addition of phenylmagnesium bromide to the aldehyde freshly prepared by DIBAL reduction of ester (**3a**), without purification, at −78 °C. The reaction was quenched by the addition of methanol followed by water, and the mixture was diluted with water, and extracted with ether. The extract was washed with dil. hydrochloric acid, dried over anhydrous magnesium sulphate, and evaporated. The crude product was purified by column chromatography on silica gel with benzene–ethyl acetate mixtures to yield the corresponding alcohol (**7**)—(**9**) and (**16**).

Hydride Reduction of 2-(2,5-*Dimethylpyrrol*-1-*yl*)*alkan*-1-*ones*.—A solution of a 2-(2,5-dimethylpyrrol-1-yl)alkan-1-one (**14**) or (**15**) (1 mmol) in THF (5 ml) was added to a suspension of lithium aluminium hydride, DIBAL, or sodium borohydride (1 mmol) in THF (5 ml) at 0 °C, and the solution was stirred for 1 h at 0 °C, and for another 4 h at room temperature. The reaction mixture was quenched with ethyl acetate followed by water, filtered over Celite, diluted with water, and extracted with dichloromethane. The extract was dried over anhydrous magnesium sulphate, and evaporated. The crude product was purified by distillation under reduced pressure or by recrystallization from hexane–benzene mixtures to yield the product alcohol as a liquid or needles.

2-(2,5-*Dimethylpyrrol*-1-*yl*)-1-*phenylpropan*-1-*ol* (**7a**). *erythro–threo*-Mixture: m.p. 108.0—109.0 °C; 99% yield (Found: C, 78.6; H, 8.4; N, 6.1. $C_{15}H_{19}NO$ requires C, 78.56; H, 8.35; N, 6.10%).

erythro: M.p. 122.0—124.0 °C [(1*R*,2*S*) form]; $[\alpha]_D^{28}$ +34.2° (*c* 0.25 in $CHCl_3$) [(*S*,*R*) form]; δ_H($CDCl_3$) 1.60 (3 H, d, *J* 6.8 Hz), 2.08 (6 H, s), 2.32 (1 H, br s), 4.07—4.37 (1 H, m), 4.90 (1 H, d, *J* 8.3 Hz), 5.60 (2 H, s), and 6.99—7.25 (5 H, m); δ_C($CDCl_3$) 14.4 (q), 16.4 (q), 57.6 (d), 76.2 (d), 106.4 (d), 125.7 (d), 127.8 (d), 128.1 (s), 128.1 (d), and 141.9 (s).

threo: $[\alpha]_D^{27}$ +58.9° (*c* 0.4 in $CHCl_3$) [(1*S*,2*S*) form]; δ_H($CDCl_3$) 1.22 (3 H, d, *J* 7.3 Hz), 2.01—2.14 (1 H, m), 2.28 (3 H, s), 2.40 (3 H, s), 4.11—4.43 (1 H, m), 4.86 (1 H, d, *J* 9.8 Hz), 5.80 (2 H, s), and 7.10—7.43 (5 H, m); δ_C($CDCl_3$) 13.5 (q), 15.2 (q), 16.7 (q), 58.3 (d), 77.1 (d), 105.8 (d), 108.4 (d), 127.0 (d), 128.0 (s), 128.2 (d), 128.5 (d), and 141.1 (s).

2-(2,5-*Dimethylpyrrol*-1-*yl*)-1,3-*diphenylpropan*-1-*ol* (**7b**). *erythro–threo*-Mixture: m.p. 77—78 °C; 99% yield [from (**5b**)]; 89% yield [from (**14b**)] (Found: C, 82.5; H, 7.4; N, 4.3. $C_{21}H_{23}NO$ requires C, 82.58; H, 7.59; N, 4.58%).

erythro: δ_H($CDCl_3$) 1.27 (3 H, s), 1.89 (1 H, s), 2.54 (3 H, s), 3.0—3.6 (2 H, m), 4.1—4.4 (1 H, m), 5.10 (1 H, d, *J* 9.3 Hz), 5.29 (1 H, d, *J* 2.9 Hz), 5.69 (1 H, d, *J* 3.4 Hz), and 6.8—7.5 (10 H, m); δ_C($CDCl_3$) 12.5 (q), 16.0 (q), 36.6 (t), 64.4 (d), 75.0 (d), 104.5 (d), 108.3 (d), 125.8—128.9 (Ar), 129.9 (s), 139.1 (s), and 142.0 (s).

threo: δ_H($CDCl_3$) 1.71 (3 H, s), 2.26 (1 H, br s), 2.56 (3 H, s), 2.5—3.2 (2 H, m), 4.1—4.4 (1 H, m), 5.13 (1 H, d, *J* 7.3 Hz), 5.60 (1 H, d, *J* 2.9 Hz), 5.85 (1 H, d, *J* 2.4 Hz), 6.5—6.7 (2 H, m), 6.9—7.2 (3 H, m), and 7.2—7.5 (5 H, m); δ_C($CDCl_3$) 13.0 (q), 15.4 (q), 36.4 (t), 65.6 (d), 75.8 (d), 105.5 (d), 109.0 (d), 126.3 (d), 127.2 (d), 128.1 (d), 128.5 (d), 128.6 (d), 128.7 (d), 131.5 (s), 138.2 (s), and 141.2 (s).

3-(2,5-*Dimethylpyrrol*-1-*yl*)*butan*-2-*ol* (**9a**). *erythro–threo*-Mixture: b.p. 95—100 °C/5 mmHg; 92% yield [from (**5a**)], 78% yield [from (**15a**)] (Found: C, 71.8; H, 10.2; N, 8.35. $C_{10}H_{17}NO$ requires C, 71.81; H, 10.25; N, 8.37%).

erythro: δ_H($CDCl_3$) 0.98 (3 H, d, *J* 5.8 Hz), 1.55 (3 H, d, *J* 6.9 Hz), 1.95 (1 H, br s), 2.25 (6 H, s), 3.7—4.3 (2 H, m), and 5.74 (2 H, s); δ_C($CDCl_3$) 14.4 (q), 17.0 (q), 20.7 (q), 57.6 (d), 70.8 d), 106.6 (d), and 127.9 (s).

threo: δ_H($CDCl_3$) 1.23 (3 H, d, *J* 5.4 Hz), 1.40 (3 H, d, *J* 6.8 Hz), 2.11 (1 H, br s), 2.24 (6 H, s), 3.7—4.2 (2 H, m), and 5.70 (2 H, s); δ_C($CDCl_3$) 14.2 (q), 17.1 (q), 20.0 (q), 58.7 (d), 69.9 (d), 106.8 (d), and 128.5 (s).

1-*Phenyl*-2-(*pyrrol*-1-*yl*)*propan*-1-*ol* (**8a**). *erythro–threo*- Mixture: b.p. 165—170 °C/5 mmHg; 94% yield (Found: C, 77.5; H, 7.6; N, 6.9. $C_{19}H_{19}NO$ requires C, 77.58; H, 7.51; N, 6.96%).

erythro: δ_H($CDCl_3$) 1.42 (3 H, d, *J* 6.8 Hz), 2.27 (1 H, br s), 4.0—4.4 (1 H, m), 4.7—4.8 (1 H, m), 6.08 (2 H, t, *J* 2.0 Hz), 6.62 (2 H, t, *J* 2.0 Hz), and 6.9—7.6 (5 H, m); δ_C($CDCl_3$) 14.8 (q), 60.7 (d), 77.8 (d), 107.8 (d), 119.4 (d), 126.0—129.5 (Ar), and 140.7 (s).

threo: δ_H($CDCl_3$) 1.26 (3 H, d, *J* 6.8 Hz), 2.27 (1 H, br s), 4.0—4.4 (1 H, m), 4.61 (1 H, d, *J* 7.3 Hz), 6.18 (2 H, t, *J* 2.0 Hz), 6.74 (2 H, t, *J* 2.0 Hz), and 6.9—7.6 (5 H, m); δ_C($CDCl_3$) 17.7 (q), 61.5 (d), 79.0 (d), 108.3 (d), 120.5 (d), 126.0—129.5 (Ar), and 140.4 (s).

1,3-*Diphenyl*-2-(*pyrrol*-1-*yl*)*propan*-1-*ol* (**8b**). *erythro–threo*-Mixture: b.p. 135—140 °C/5 mmHg; 93% yield (Found: C, 82.05; H, 6.8; N, 4.7. $C_{15}H_{19}NO$ requires C, 82.28; H, 6.90; N, 5.05%).

erythro: δ_H($CDCl_3$) 2.28 (1 H, d, *J* 3.4 Hz), 2.9—3.3 (2 H, m), 4.0—4.3 (1 H, m), 4.8—5.0 (1 H, m), 5.99 (2 H, t, *J* 2.0 Hz), 6.52 (2 H, t, *J* 2.0 Hz), and 6.71—7.50 (10 H, m); δ_C($CDCl_3$) 36.1 (t), 67.6 (d), 77.0 (d), 107.8 (d), 119.8 (d), 125.8—129.6 (Ar), 138.3 (s), and 140.9 (s).

threo: δ_H($CDCl_3$) 2.16 (1 H, d, *J* 2.4 Hz), 2.9—3.3 (2 H, m), 4.0—4.3 (1 H, m), 4.8—5.0 (1 H, m), 6.10 (2 H, t, *J* 2.0 Hz), 6.61 (2 H, t, *J* 2.0 Hz), and 6.7—7.5 (10 H, m); δ_C($CDCl_3$) 38.4 (t), 68.3 (d), 76.7 (d), 108.2 (d), 120.1 (d), 125.8—129.6 (Ar), 137.9 (s), and 140.6 (s).

3-(2,5-*Dimethylpyrrol*-1-*yl*)-2-*phenylbutan*-2-*ol* (**6a**). *erythro–threo*-Mixture: m.p. 71—72 °C; 56% yield (Found: C, 78.9; H, 8.9; N, 5.7. $C_{16}H_{21}NO$ requires C, 78.97; H, 8.69; N, 5.75%).

erythro: $\delta_H(CDCl_3)$ 1.32 (3 H, s), 1.35 (3 H, d, *J* 7.3 Hz), 1.79 (1 H, br s), 2.33 (3 H, s), 2.36 (3 H, s), 4.40 (1 H, q, *J* 7.3 Hz), 5.79 (2 H, s), and 7.14—7.63 (5 H, m); $\delta_C(CDCl_3)$ 14.2 (q), 14.4 (q), 15.6 (q), 28.3 (q), 60.2 (d), 78.4 (s), 105.7 (d), 108.1 (d), 125.0 (d), 126.9 (d), 128.3 (d), 129.3 (s), 129.9 (s), and 146.3 (s).

threo: M.p. 74.0—75.0 °C; $\delta_H(CDCl_3)$ 1.49 (3 H, d, *J* 7.3 Hz), 1.68 (3 H, s), 1.88 (1 H, br s), 1.94 (3 H, s), 2.34 (3 H, s), 4.30 (1 H, q, *J* 7.3 Hz), 5.62 (1 H, d, *J* 2.9 Hz), 5.75 (1 H, d, *J* 2.9 Hz), and 7.13—7.41 (5 H, m); $\delta_C(CDCl_3)$ 13.7 (q), 15.8 (q), 16.0 (q), 25.4 (q), 60.9 (d), 77.9 (s), 105.4 (d), 108.3 (d), 125.8 (d), 127.3 (d), 128.0 (d), 128.8 (s), 130.9 (s), and 145.5 (s).

Reaction of 2-(2,5-*Dimethylpyrrol*-1-*yl*) *Alcohols* (**7**) *with Hydroxylamine Hydrochloride.*—A solution of hydroxylamine hydrochloride (20 ml), potassium hydroxide (10 ml), and a 2-(2,5-dimethylpyrrol-1-yl) alcohol (**7**) (1 mmol) in (3:1) methanol–water (20 ml) was refluxed for 48 h. The reaction mixture was diluted with water, acidified with hydrochloric acid, washed with dichloromethane, basified with aqueous sodium hydroxide, and extracted with dichloromethane. The extract was washed with dil. aqueous sodium hydroxide, dried over anhydrous magnesium sulphate, and evaporated. From alcohols (**7a**) and (**7b**) the corresponding 2-amino alcohols, (**10a**) and (**10b**), were obtained in 89 and 83% yield, respectively.

Ozonolysis and Hydrolysis of 2-(*Pyrrol*-1-*yl*) *Alcohols* (**8**).—A 2-(pyrrol-1-yl) alcohol (**8**) (1 mmol) was treated with ozone at −78 °C in methanol (20 ml), and argon was bubbled through the solution. To this solution at 0 °C was added sodium borohydride (5 mmol). The mixture was stirred for 15 min at 0 °C, and evaporated. The mixture was dissolved in 0.5M-methanolic hydrochloric acid (10 ml), refluxed for 1 h, and evaporated. The residue was diluted with water, acidified with hydrochloric acid, washed with dichloromethane, basified with aqueous sodium hydroxide solution, and extracted with dichloromethane. The extract was washed with dil. aqueous sodium hydroxide, dried over anhydrous magnesium sulphate, and evaporated. From alcohols (**8a**) and (**8b**) the corresponding 2-amino alcohols, (**10a**) and (**10b**), were obtained in 79 and 62% yield, respectively.

Ozonolysis and Lithium Aluminium Hydride Reduction of Compound (**7a**).—The 2-(pyrrol-1-yl) alcohol (**7a**) (1 mmol) was treated with ozone at −78 °C in methanol (20 ml), and argon was bubbled through the solution. To this solution at 0 °C was added sodium borohydride (5 mmol). The mixture was stirred for 15 min at 0 °C, and evaporated. The residue was dissolved in THF (10 ml), and to this solution at 0 °C was added a suspension of lithium aluminium hydride (1.5 mmol) in THF (5 ml). The solution was stirred for 1 h at 0 °C, allowed to warm to room temperature, and refluxed for another 4 h. The reaction was quenched by the addition of ethyl acetate followed by water, and the mixture was filtered over Celite, diluted with water, and extracted with dichloromethane. The extract was in turn extracted with hydrochloric acid. The water layer was basified with aqueous sodium hydroxide, and extracted with dichloromethane. This extract was dried over anhydrous magnesium sulphate, and evaporated to afford ephedrine (**11a**) in 44% yield, identical with an authentic sample.

Determination of Stereoselectivities.—The stereoselectivity of the reaction of 2-(pyrrol-1-yl)-alkanals (**5**) and (**6**) and -alkan-1-ones (**14**) and (**15**) could be determined by the ^1H n.m.r. spectroscopy of the resulting alcohols (**7**)—(**9**) and (**16**). The selectivity ratios were found by ^1H n.m.r. analysis of the 1,2-disubstituted 2-aminoethanols which were regenerated from alcohols (**7**) and (**8**) by cleavage of the pyrrole ring using the reaction with hydroxylamine hydrochloride or ozonolysis.

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