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Origins of Diastereoselectivity in the Alkylation of N-Substituted Lactams and Amides derived from Optically Active Aminoalcohols.

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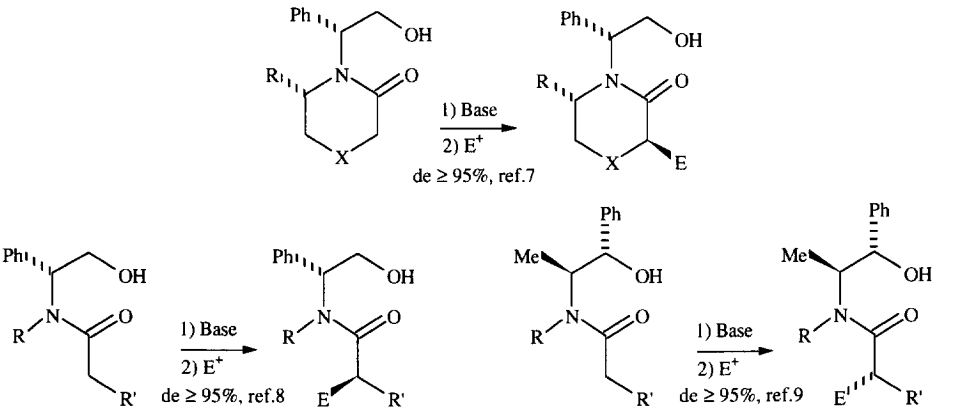
Abstract: The origins of diastereoselectivity in the alkylation of lactams **1a** and **1b** and amides **6a** and **6b** are discussed. A rigid intermediate in which the pyramidalized amide nitrogen chelated the alkoxide lithium cation is invoked. Further experiments conducted with different substrates are in agreement with the proposed model. Furthermore this model can explain the differences observed previously between ephedrine and pseudoephedrine amide alkylation.

The asymmetric alkylation of amide enolates has been studied intensively for over 15 years.[1] Since the pioneering work by Larchevêque[2], Evans[3] and Sonnet[4], numerous chiral auxiliaries have been examined for their capacity to influence asymmetric induction.[5] In this context, imides derived from chiral 2-oxazolidiones have proven to be particularly versatile auxiliaries for diastereoselective enolate alkylations.[6]

Recently we described a general method for the diastereoselective alkylation of lactam[7] and amide[8] enolates wherein phenylglycinol is employed as the chiral inductor (Scheme 1).

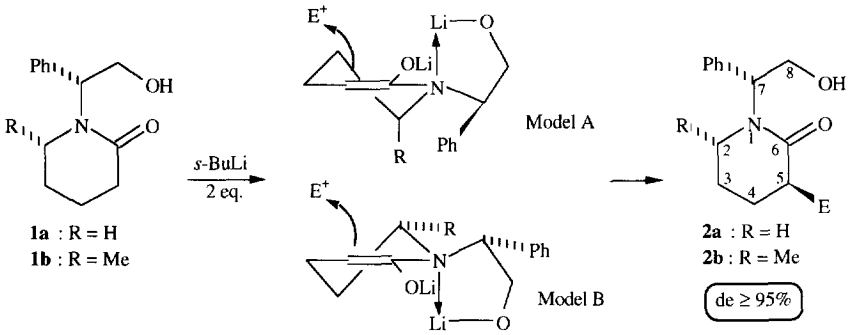


Scheme 1

Simultaneously, results on the related reaction of amides derived from pseudoephedrine were reported by Myers and coll.[9] In both studies total diastereoselectivity was observed and the configuration of the newly created stereogenic centers were determined unambiguously by X-ray crystallography. In order to clarify the origins of this diastereoselectively, we decided to investigate the alkylation of amides and lactams derived from different β and γ substituted chiral aminoalcohols under a variety of conditions (solvent, additive, temperature).

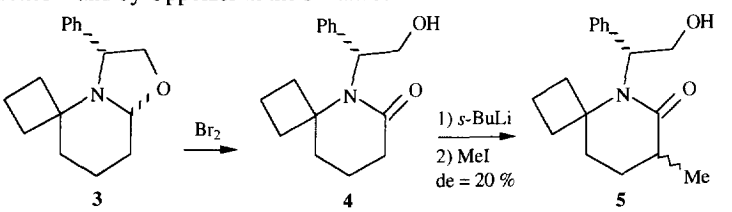
Our first experiments were conducted on lactams **1a** and **1b** (scheme 2) prepared from (*R*)-(-)-phenylglycinol.[7a,c] Very high de's were observed when the enolate anions of **1a,b** were reacted with MeI, $PhCH_2Br$, $CH_2{=}CHCH_2Br$ and Br_2.[7] This diastereoselectivity can best be explained by one or the other of the chelation controlled processes indicated in scheme 2. In both models (A and B) the pyramidalized amide nitrogen[10] and the alkoxide oxygen atom chelate strongly to a lithium cation. Consistent with this picture is

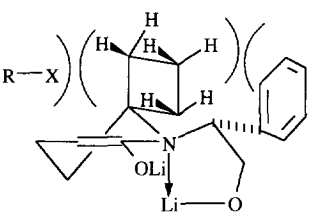
the observed lower reactivity and the loss of diastereoselectivity in reactions where O-protected derivatives (O-silyl and O-alkyl) were alkylated with the above series of electrophiles. Basically, the essential differences between models A and B involve the configuration of the stereogenic nitrogen and the conformation of the product immediately following alkylation which would be chair-like in model A and boat-like in model B. Indeed, the six membered ring can adopt two conformations with different interactions. In model A (scheme 2), a 1,3-diaxial interaction can occur if R is a large substituent. In model B, the interaction between R and phenyl ring seemed to be the most important. Further experiments indicated that our initially proposed model A[7a] could not explain some of the observed results. For instance, when lactam **1b** was alkylated, derivatives **2b** were obtained in good yield with high de (≥ 95 %), but compound **4**, obtained by oxidation[11] of oxazolidine **3**,[12] led to product **5** as an inseparable mixture of diastereomers with markedly lower diastereoselectivity (de = 20 %), (scheme 3).



Scheme 2

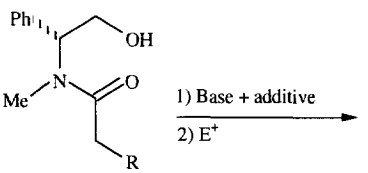
These results are difficult to reconcile with model A where the same 1,3-diaxial interactions occurs in each case. However, by evoking model B one can see that steric interactions between the aromatic ring, the cyclobutyl ring and the electrophile can explain the poor diastereoselectivity observed during the synthesis of **5**. At this stage of our study we considered that a species reminiscent to that depicted in model B is probably involved in the enolate alkylation reactions. This would imply *the approach of the electrophile anti to the chelated nitrogen lone pair* (Scheme 2). A similar geometry has been postulated by Meyers to explain the diastereoselective alkylation of non-racemic bicyclic lactams[13], by Seebach for the alkylation of chiral imidazolidinones[14] and by Oppolzer in the sultam series.[15]





Scheme 3

In order to interpret the results observed with amides, the model proposed in the cyclic series was extrapolated to acyclic systems. It was particularly interesting to see how such a model could be useful to explain our results with N-methylphenylglycinol (de > 95 %),[8] and the different reports from the literature wherein pseudoephedrine (de > 95 %)[9] and ephedrine (70 %)[2] have been employed as chiral inductors. The lower selectivity observed for the latter auxiliary has been claimed to be a consequence of differences in experimental conditions between Larchevêque and Myers's works.[16] Larchevêque effected deprotonation of amides with LDA in THF/HMPA, while Myers employed LDA with LiCl as an additive. Lithium enolate aggregates or mixed solvates/aggregates between HMPA and LDA may react differently, explaining the observed differences although Myers reported that the diastereoselectivty during the alkylation of ephedrine propionamide was not influenced by experimental conditions.[9a] In order to clarify this problem we studied the alkylation of N-methylphenylglycinol amides **6** to **7** under different conditions (table). All the experiments were conducted in THF and, unlike Larchevêque and Myers, *s*-BuLi was used as the base. With N-alkylphenylglycinol as auxiliaries, the use of LDA led to low yields of the alkylated product. This difference in reactivity between phenylglycinol amides and other amides is far from clear and is a subject of current investigation.



6a : R = Et
6b : R = Ph

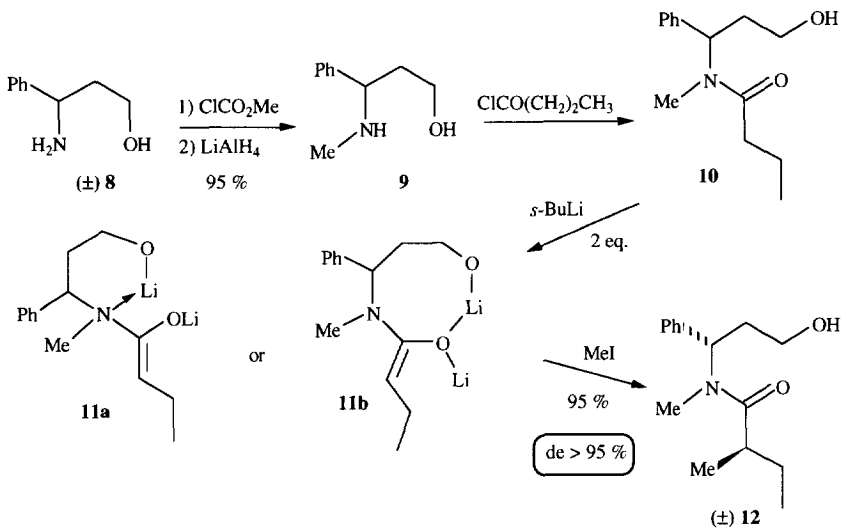
7aa : R = Et, E = Me
7ab : R = Et, E = CH_2Ph
7ba : R = Ph, E = Me
7bb : R = Ph, E = CH_2Ph

However the results clearly show that diastereoselectivity was not greatly influenced by the nature of additives since only a slight difference in reactivity was observed when LiCl was used in place of HMPA (Table). It is interesting to note that the reaction can be conducted at -23°C without loss of diastereoselectivity (entries 2, 4 and 8).

Table. Alkylation of amides **6a** and **6b** in THF with s-BuLi.

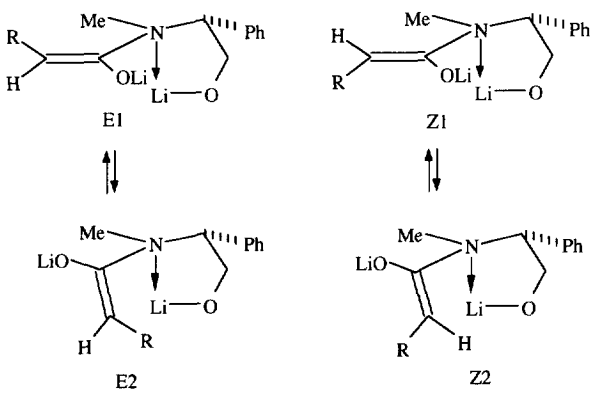
Entry	Amide	E^+	additive	temp. (in °C)	**7** Yield (%)	de (%)
1	**6a**	MeI	HMPA (5 eq.)	-78	66, **7aa**	> 98
2	**6a**	MeI	LiCl (6 eq)	-23	94, **7aa**	> 98
3	**6a**	$PhCH_2Br$	HMPA (5 eq.)	-78	75, **7ab**	> 95
4	**6a**	$PhCH_2Br$	LiCl (6 eq)	-23	78, **7ab**	> 95
5	**6b**	MeI	none	-78	66, **7ba**	80
6	**6b**	MeI	HMPA (5eq.)	-78	90, **7ba**	80
7	**6b**	MeI	LiBr (1 eq)	-78	93, **7ba**	84
8	**6b**	MeI	LiCl (6 eq)	-23	93, **7ba**	86
9	**6b**	$PhCH_2Br$	HMPA (5eq.)	-78	60, **7bb**	> 95
10	**6b**	$PhCH_2Br$	LiCl (6 eq)	-78 to -20	64, **7bb**	> 95

To provide evidence to support our N-chelated model, amide **10** (prepared from (±)-3-amino-3-phenylpropanol **8**) was alkylated with MeI (scheme 4). In this reaction chelation between nitrogen and the lithium alcoholate will lead to a favoured rigid 6 membered ring intermediate **11a**. In contrast, it is less obvious that good diastereoselectivity would be observed in the reaction of an "Evans" type intermediate **11b** in which chelation between the enolate oxygen and lithium alcoholate would lead to an unlikely non rigid 8 membered species. As expected in this experiment, only one isomer **12** was obtained from **10** in 95 % yield. This result establishes the validity of our model and confirms that nitrogen is involved in the chelation process.



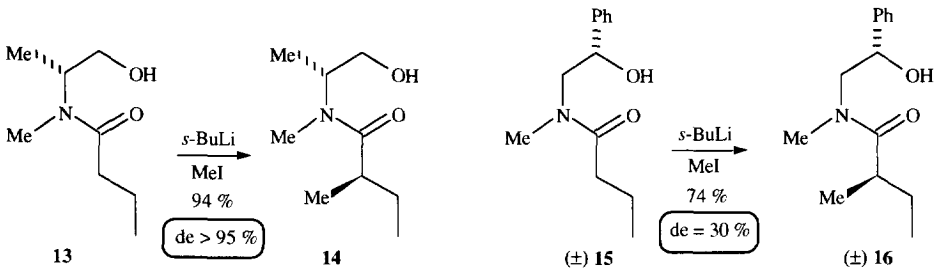
Scheme 4

Applying the model to the acyclic series, four intermediates can be postulated (scheme 5). It is known from the work by Evans that enolates generally adopt a Z configuration.[3] On the other hand, it is also well accepted that $A^{1,3}$ allylic strain favours intermediate Z-1 compared to Z-2.[17] For these reasons we consider Z-1 to be the more stable species. An approach of the electrophile from the topside of this enolate (anti to the N-Li bond) as described in the lactam series is in agreement with the observed configuration of the newly created stereogenic center.[8]



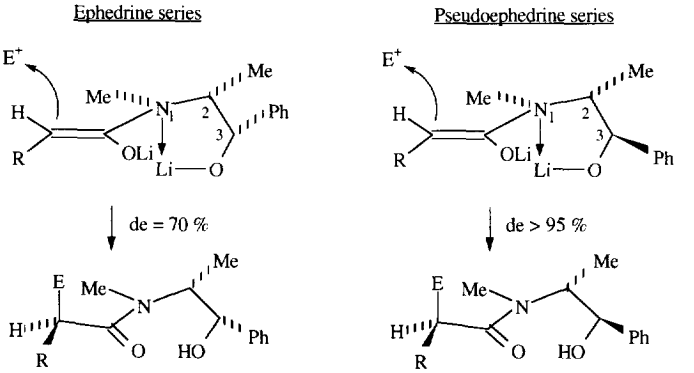
Scheme 5

We then tried to use this model to explain the difference in diastereoselectivity between the ephedrine and pseudoephedrine series. In order to study the influence of each stereogenic center on the selectivity of alkylations, we prepared amides **13** and **15** from (R)-alaninol and (±)-2-amino-1-phenylethanol respectively. Compound **13** was methylated in 95% de whereas poor diastereoselectivity was observed in the alkylation of **15** (scheme 6)



Scheme 6

These experiments suggest that the stereogenic center β to the nitrogen does not have a strong influence on stereoselectivity and that the lower de's in the ephedrine series cannot be explained by a "mismatch" induction between the two stereogenic centers. In the N-chelated model, the use of pseudoephedrine would lead to the formation of a 5 membered ring with 3 substituents in a 1-2 cis, 2-3 trans relationship (scheme 7). In the ephedrine series, the 3 substituents are all cis providing a less stable intermediate.



Scheme 7

In conclusion, the high diastereoselectivity observed in the alkylation of lactams or amides with chiral substituted β or γ-amino-alcohols as chiral inductors can be explained by the formation of a 5 membered intermediate with approach of the electrophile anti to the chelated nitrogen lone pair. In the ephedrine or pseudoephedrine series, the asymmetric induction is mainly due to the center α to the nitrogen. Although the influence of the second lithium atom has not been evoked in our hypothesis, our original model can explain not only the diastereoselectivity and the configuration of the newly created asymmetric center, but also the differences observed in the ephedrine and pseuoephedrine series. Recently, a similar model has been independently proposed by Myers,[18] to explain the opposite π-facial selectivity observed during the alkylation of pseudoephedrine amide enolates with epoxides. Further synthetic applications in both the lactam and amide series are under investigation in our laboratory and others[19] and will be reported in due course.

EXPERIMENTAL SECTION

^1H NMR and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz respectively on a Bruker AC 300 spectrometer. Optical rotations were measured at room temperature (20°C) with a Perkin-Elmer 241 automatic polarimeter. Product purification was performed by flash chromatography on Silica Gel (Merck 60). Optical purities were determined by chromatographic analyses (HPLC) performed on a Millipore Waters 717 instrument equipped with a Chiracel® OD column, (Heptane/EtOH : 95/5). All reactions involving air sensitive materials were carried out under a N_2 atmosphere. For the amide products in solution, two rotamers are generally present.In NMR spectra they are identified as "M" and "m" for the major and the minor forms respectively.

(R)-N-(2-Hydroxy-1-phenylethyl)-N-methyl-butanamide 6a. R-(-)-N-Methyl-phenylglycinol (1.3g, 8.6 mmol) was dissolved in CH_2Cl_2 (30 mL). Butyryl chloride (1 mL, 10.4 mmol), then aq. solution of NaOH (0.42g in H_2O, 8 mL) were slowly added. After stirring for 1h, the reacting mixture was diluted with water (30 mL), then extracted with CH_2Cl_2 (3x 20 mL). Organic layers were washed with water, then dried over MgSO4 and evaporated to afford a residue from which **6a** (1.52g, 80% yield) was obtained after flash-chromatography (CH_2Cl_2/MeOH : 95/5). $[\alpha]_D$: -120 (c = 0.67, $CHCl_3$), ^1H NMR ($CDCl_3$) δ : 0.92 (m, $3H^M$ + $3H^m$), 1.65 (m, $2H^M$ + $2H^m$), 2.32 (t, J = 7.5 Hz, $2H^m$), 2.50 (m, $2H^M$), 2.62 (s, $3H^m$), 2.66 (s, $3H^M$), 3.72 (br.s, OH^M), 3.80-4.16 (m, $2H^M$ + $2H^m$), 4.42 (br.s, OH^m), 5.12 (dd, J = 9.2, 4.8 Hz, $1H^m$), 5.85 (dd, J = 9.2, 5.1, $1H^M$), 7.12-7.38 (m, $5H^M$ + $5H^m$). ^{13}C NMR ($CDCl_3$) δ: 13.8 (M), 13.9 (m), 18.4 (M), 18.8 (m), 28.1 (m), 30.5 (M), 35.4 (m), 35.8 (M), 57.3 (M), 60.9 (M), 61.1 (m), 61.3 (m), 126.7, 127.4, 127.5, 128.4, 128.7, 137.2 (m), 137.5 (M), 174.7 (M + m). IR ($CHCl_3$) : 3395, 1622, 1451. MS (CI) : 222 (MH^+).

(R)-N-(2-Hydroxy-1-phenylethyl)-N-methyl-benzeneacetamide 6b. The same procedure using phenyl acetic acid (1.1 eq) furnished amide **6b** in 90% yield. m.p. 75-77°C (AcOEt/cyclohexane). $[\alpha]_D$: -117 (c = 1.25, $CHCl_3$). ^1H NMR ($CDCl_3$) δ : 2.70 (s, $3H^m$), 2.80 (s, $3H^M$), 3.90-4.30 (m, $4H^M$ + $4H^m$), 5.30 (m, $1H^m$), 6.00 (m, $1H^M$), 7.20-7.50 (m, $10H^M$ + $10H^m$). ^{13}C NMR ($CDCl_3$) δ : 28.4(m), 31.6 (M), 41.6 (m), 41.8 (M), 58.7 (M + m), 61.5 (m), 61.9 (M), 127.0, 127.7, 127.9, 128.8, 129.1, 137.4, 173.2 (M + m). IR ($CHCl_3$) : 1631, 1490. MS (CI) : 270 (MH^+).

General procedure for the alkylation of amides : 6a, 6b, 10, 13 and 15.

Preparation of **7aa** is typical : to a solution of amide **6a** (321 mg, 1.45 mmol) in THF (17 ml) and HMPA (0,6 ml) *s*-BuLi (1.3 M, 2.5 eq.) was added at -78°C under nitrogen atmosphere. The mixture was stirred for 20 min and iodomethane (271 µl, 3 eq.) was added dropwise. After stirring for 3 hours at -78°C, the mixture was treated with saturated NH_4Cl, extracted with ethyl acetate, washed with brine, dried over $MgSO_4$ and solvent was evaporated. The crude product was purified by flash chromatography (ethyl acetate) to give a white solid which was crystallized from ethyle acetate/cyclohexane 90/10 (226 mg, 66% yield).

(R,R)-N-(2-Hydroxy-1-phenylethyl)-N,2-dimethyl-butanamide 7aa. m.p. = 108°C (ethyle acetate/cyclohexane 90/10). $[\alpha]_D$ = -125 (c = 1.06 in $CHCl_3$) ; ^1H NMR ($CDCl_3$) : δ = 0.83 (t, *J* = 5.9 Hz, $3H^m$),0.91 (t, *J* = 5.9 Hz, $3H^M$), 1.12 (d, *J* = 6.5 Hz, $3H^M$), 1.18 (d, *J* = 6.5 Hz, $3H^m$), 1.43 (m, $1H^M$ + $1H^m$), 1.72 (m, $1H^M$ + $1H^m$), 2.12 (br. s, OH^m), 2.63 (m, $1H^M$), 2.72 (s, $3H^m$), 2.77 (s, $3H^M$) 2.80 (m, $1H^m$) 3.57 (br. s, $1H^M$), 3.98 (m, $1H^M$ + $1H^m$), 4.13 (m, $1H^M$ + $1H^m$), 5.18 (dd, *J* = 9.4, 5.3 Hz, $1H^m$), 5.91 (dd, *J* = 9.4, 5.3 Hz, $1H^M$), 7.12-7.36 (m, $5H^M$ + $5H^m$). ^{13}C NMR ($CDCl_3$) : δ = 12.1 (M); 12.3 (m), 17.3 (M), 18.0 (m), 27.1 (M), 27.6 (m), 28.6 (m), 30.7 (M), 37.6 (m), 38.1 (M), 57.6 (M + m), 61.3 (M), 61.5 (m), 126.8, 127.6, 128.7, 128.8 (C ar.^{M}, C ar.^{m}), 137.6 (M + m), 178.7 (M + m). IR (film) : 3100, 1618 cm^{-1}. MS (CI) : 236 (MH^+).Anal. Calcd for $C_{14}H_{21}NO_2$: 71.46 (C) ; 8.99 (H) ; 5.95 (N) found : 71.33 (C) ; 8.83 (H) ; 5.76 (N).

(αS,1R)-α-Ethyl-N-(2-hydroxy-1-phenylethyl)-N-methyl-benzene-propanamide 7ab. Amorphous ; $[\alpha]_D$ -2 (c = 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$) : δ = 0.72 (t, *J* = 7.4 Hz, $3H^m$), 1.00 (t, J = 7.4 Hz, $3H^M$), 1.52 (m, $1H^M + 1H^m$), 1.73 (m, $1H^M + 1H^m$), 2.48 (s, $3H^m + 3H^M$), 2.70-3.01 (m, $3H^m + 3H^M$), 3.91 (t, *J* = 10.2 Hz, $1H^m + 1H^M$), 4.12 (dd, *J* = 10.3, 5.0 Hz, $1H^m + 1H^M$), 4.92 (dd, *J* = 9.8, 5.1 Hz, $1H^m$), 5.90 (dd, *J* = 9.8, 5.0, $1H^M$), 6.72 (m, $1H^m + 1H^M$, OH), 7.1-7.35 ($10H^m + 10H^M$). ^{13}C NMR ($CDCl_3$) : δ = 12.1 (m + M), 25.8 (m), 26.9 (M), 28.1 (m), 31.0 (M), 39.6 (M + m), 45.7 (m), 46.2 (M), 57.6 (M + m), 61.5 (M), 62.1 (m), 126.2, 127.3, 127.6, 128.5, 129.1, 129.4 (C ar), 137.0 (M + m), 140.0 (M + m), 177.4 (M + m). IR (film) : 3018, 1619 cm^{-1}. MS (CI) : 312 (MH^+). Anal. Calcd for $C_{20}H_{25}NO_2$: 77.13 (C); 8.09 (H) ; 4.49 (N) ; found : 76.98 (C) ; 8.16 (H) ; 4.31 (N).

(R,R)-N-(2-hydroxy-1-phenylethyl)-N,α-dimethyl-benzeneacetamide 7ba. m.p. = 91-93°C. $[\alpha]_D$ -140 (c = 0.79, $CHCl_3$); ^1H NMR ($CDCl_3$) : δ = 1.45 (d, *J* = 6.4 Hz, $3H^m$), 1.55 (d, *J* = 6.4 Hz, $3H^M$), 2.52 (s, $3H^m$), 2.65 (s, $3H^M$), 3.90-4.15 (m, $3H^M + 3H^m$), 5.25 (m, $1H^m$), 5.90 (m, $1H^M$), 6.4 (d, *J* = 8.0 Hz, $1H^M + 1H^m$, OH^M, OH^m), 7.0-7.30 (m, $10H^M + 10H^m$). ^{13}C NMR ($CDCl_3$): δ = 20.7 (M), 21.1 (m), 28.3 (M), 31.0 (m), 43.3 (M), 44.0 (m), 58.7 (M), 60.4 (m), 60.7 (M), 61.5 (m), 126.9, 127.3, 127.7, 128.4, 128.7, 129.0, 129.1 (C ar.^{M}, C ar.^{m}), 136.4, 137.2, 141.5, 142.7 (M + m), 175.6 (M + m). IR (film) : 1635, 1450 cm^{-1}. MS (CI) : 284 (MH^+).Anal. Calcd for $C_{18}H_{21}NO_2$: 76.29 (C) ; 7.47 (H) ; 4.94 (N) found : 76.41 (C) ; 7.51 (H) ; 4.99 (N).

(R,R)-N-(2-Hydroxy-1-phenylethyl)-N-methyl-α-phenyl-benzenepropanamide 7bb. m.p. : 134-136°C (AcOEt/cyclohexane). $[\alpha]_D$ -122 (c = 2.59, $CHCl_3$); ^1H NMR (DMSO, 135°C) : δ = 2.64 (s, 3H), 2.95 (dd, J = 13.8, 6.3 Hz, 1H), 3.42 (dd, J = 13.8, 8.2 Hz, 1H), 3.80 (dd, J = 12.5, 7.0 Hz, 1H), 3.90 (dd, J = 12.0, 7.0 Hz, 1H), 5.50 (dd, J = 8.2, 6.3 Hz, 1H), 5.52 (t, J = 7.0 Hz, 1H), 7.10-7.40 (m, 10H). ^{13}C NMR (DMSO, rt , 2 rotamers in a 1/1 ratio) : δ = 28.2, 31.2, 41.8, 42.0, 50.9, 51.8, 58.1, 60.5, 60.6, 61.7, 125.0- 129.2, 137.0, 140.1, 175.0. IR (film) : 3014, 1647, 1449. MS (CI) : 360 (MH^+). .Anal. Calcd for $C_{24}H_{25}NO_2$: 80.19 (C) ; 7.01 (H) ; 3.89 (N) found : 79.91 (C) ; 7.15 (H) ; 3.80 (N).

(±)-N-(3-Hydroxy-1-phenylpropyl)-N-methyl-butanamide 10. Compound **10** was prepared from 3-N-methyl-3-phenyl-propanol (0.8 g) in 43 % yield as described for **6a**. Oil; ^1H NMR ($CDCl_3$) : δ = 0.95 (m, $3H^M + 3H^m$), 1.71-2.13 (m, $3H^M + 3H^m$), 2.35 (t, *J* = 7.2 Hz, $2H^M + 2H^m$), 2.53 (s, $3H^M$), 2.61 (s, $3H^m$), 3.42 (td, *J* = 11.7, 3.4 Hz, $1H^M + 1H^m$), 3.69 (ddd, *J* = 11.7, 5.3, 2.5 Hz, $1H^M + 1H^m$), 3.90 (br. s., $1H^M$, OH^M), 5.27 (dd, *J* = 9.9, 5.1 Hz, $1H^m$), 6.00 (dd, *J* = 12.2, 3.5 Hz, $1H^M$), 7.13-7.43 (m, $5H^M + 5H^m$). ^{13}C NMR ($CDCl_3$): δ = 13.9 (M), 14.0 (m), 18.6 (M), 18.7 (m), 27.8 (m), 29.9 (M), 31.3 (M), 33.4 (m), 35.0 (m), 35.6 (M), 51.7 (M + m), 55.4 (m), 58.3 (M), 126.7, 127.1, 127.4, 127.5, 127.8, 128.5 (C ar.^{m}, C ar.^{M}), 139.0 (M + m), 175.0 (M + m). IR (film) : 3415, 2962, 1621 cm^{-1}. MS (CI) : 236. HRMS Calcd for 235.1572, found : 235.1579.

(±)-N-(3-Hydroxy-1-phenylpropyl)-N,2-dimethyl-butanamide(±)-12 ^1H NMR ($CDCl_3$, TMS) : δ = 0.89 (m, 3H), 1.13 (d, *J* = 7.7 Hz, 3H), 1.42 (m, 1H), 1.73 (m, 1H), 1.88 (m, 1H), 2.15 (m, 1H), 2.53 (s, 3H), 2.63 (m, 1H), 3.42 (m, 1H), 3.67 (br. s., 1H, OH), 3.90 (m, 1H), 6.05 (m, 1H), 7.12-7.38 (m, 5H) ^{13}C NMR ($CDCl_3$) δ = 12,2, 17,5, 27,0, 30,0, 31,1, 38,1, 51,7, 58,3, 127,6, 127,8, 128,7, 139,2, 179,0. IR (film) : 2960, 1614 cm^{-1}. HRMS Calcd for 249.1729, found : 249.1741.

(R)-N-(2-Hydroxy-1-methylethyl)-N-methyl-butanamide 13. Compound **13** was prepared from (R)-N-methyl-alaninol (380 mg, 4.2 mmol) in 35 % yield as described for **6a**. Oil. $[\alpha]_D$: +39 (c = 0.26, $CHCl_3$).^1H NMR ($CDCl_3$) : δ = 1.03 (m, $3H^M + 3H^m$), 1.08 (d, J = 7.0 Hz, $3H^M$), 1.11 (d, J = 6.8 Hz, $3H^m$), 1.67 (m, $2H^M + 2H^m$), 2.29 (t, J = 7.2 Hz, $2H^M$), 2.34 (t, J = 7.4 Hz, 2H), 2.80 (s, $3H^m$), 2.87 (s, $3H^M$), 3.43-3.62 (m, $2H^M + 2H^m$), 3.74 (dd, J = 7.4, 4.4 Hz, $1H^M$), 4.12 (m, $1H^m$), 4.21 (dd, J = 7.3, 4.9 Hz,

$1H^m$), 4.66 (m, $1H^M$). ^{13}C NMR ($CDCl_3$) : δ = 13.9 (M+m), 18.5 (M), 18.9 (m), 26.0 (m), 29.8 (M), 35.6 (m), 36.1 (M), 51.1 (M), 54.2 (m), 63.4 (m), 64.1 (M), 174.3 (m), 174.6 (M). IR (film) : 1614 cm^{-1}. MS (CI) : 177 ($MH^+ + NH_3$), 160 (MH^+).

(R,R)-N-(2-Hydroxy-1-methylethyl)-N,2-dimethyl-butanamide 14. $[\alpha]_D$ = -4.5 (c = 0.32 in $CHCl_3$) ^1H NMR ($CDCl_3$, TMS) : δ = 0.83 (m, $3H^M + 3H^m$), 1.11 (d, *J* = 6.7 Hz, $3H^M + 3H^m$), 1.13 (d, *J* = 3.5 Hz, $3H^m$), 1.17 (d, *J* = 3.6 Hz, $3H^M$), 1.42 (m, $1H^M + 1H^m$), 1.67 (m, $1H^M + 1H^m$), 2.63 (m, $1H^M + 1H^m$), 2.76 (s, $3H^m$), 2.91 (s, $3H^M$), 3.38-3.68 (m, $2H^M + 2H^m$), 4.15 (m, $1H^m$), 4.69 (m, $1H^M$). ^{13}C NMR ($CDCl_3$): δ = 12.0, 13.8, 15.2, 17.2 (M), 17.6 (m), 26.4 (m), 27.2 (M), 27.6 (m), 30.0 (M), 37.3 (m), 38.1 (M), 51.6 (M), 54.0 (m), 63.6 (m), 64.5 (M), 178.2 (m), 178.4 (M). IR (film) : 3388, 2966, 1614, 1467 cm^{-1}. HRMS Calcd for 174.1494 (M+1), found : 174.1494.

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