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ASYMMETRIC ALKYLATION OF CHIRAL *N,N*-DISUBSTITUTED AMIDES *

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Summary

Chiral *N,N*-disubstituted amides may be readily synthesized by reacting an anhydride with *l*- or *d*-ephedrine.

The alkylation of the carbanions derived from these amides affords α-substituted chiral ketones and acids after cleavage. A study of the reaction characteristics indicates that the nature of the counter ion (Li or Mg) is the critical factor in the asymmetric synthesis.

In this way, (*S*)-(+)-4-methyl-3-heptanone, an alarm pheromone of "Atta Texana", was synthesized in 81% enantiomeric excess.

In recent years, there have been a large number of reported attempts to generate optically active compounds via asymmetric synthesis [1,2]. Nevertheless preparatively useful reactions are rare enough and rarest among efficient asymmetric synthesis is carbon—carbon bond formation with the simultaneous creation of a new chiral center.

Recently the use of carbanions derived from chiral molecules has provided a new methodology to effect such reactions. The utilisation of oxazolines has allowed synthesis of chiral acids and lactones [3]; chiral imines were also used to achieve the preparation of chiral substituted aldehydes, ketones [4,5,6] and α-aminoacids [7]. Chiral hydrazones offer an alternative route to these compounds [8].

However, preparation of these chiral intermediates often necessitates the use of sophisticated chiral compounds. We were interested in using chiral inducers which are easier to obtain.

The requirements for an efficient asymmetric synthesis have been reviewed by Eliel [9] and it is especially important that the inducer may be readily separated from the chiral product, and recovered in good yield. Moreover it is of

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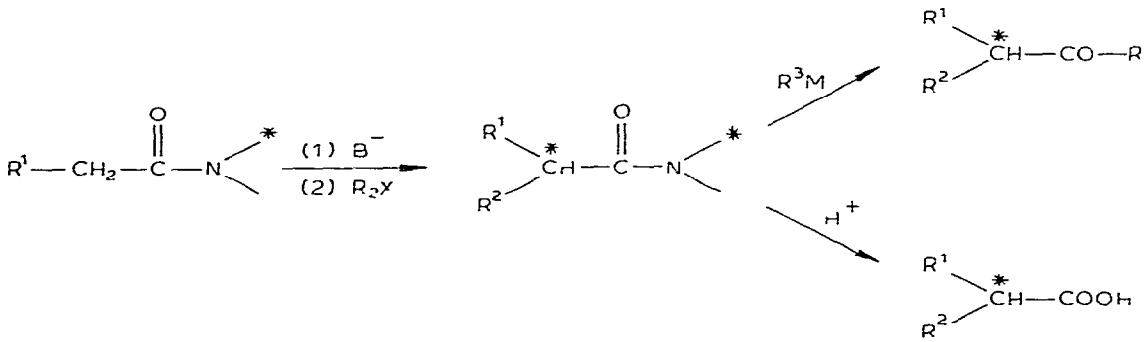
* Dedicated to Prof. Henri Normant on the occasion of his 72nd birthday, June 25th, 1979.

prime importance that the inducer possesses a function susceptible to favouring chelation with carbanions Therefore we thought of employing *N,N*-disubstituted amides, the carbanions of which are easy enough to obtain and to alkylate [10] Moreover, the secondary amines required to prepare them may be recovered after cleavage of the amide

We now report in some detail the results of a study (preliminary communication [11]) which leads to chiral α-substituted alkanoic acids and ketones according to the following scheme:



Chiral reagents

To obtain *N,N*-substituted amides, we have utilized *l*- or *d*-ephedrine (and related compounds) as the chiral inducer This product is interesting because it is commercially available, cheap, and optically pure. Besides, it bears a hydroxyl function, the presence of which is suspected of playing an important role during the induction However this compound is not very stable, and is easily transformed into pseudoephedrine by heating in an acidic medium [12] Moreover it is capable of yielding deoxyephedrine upon dehydration

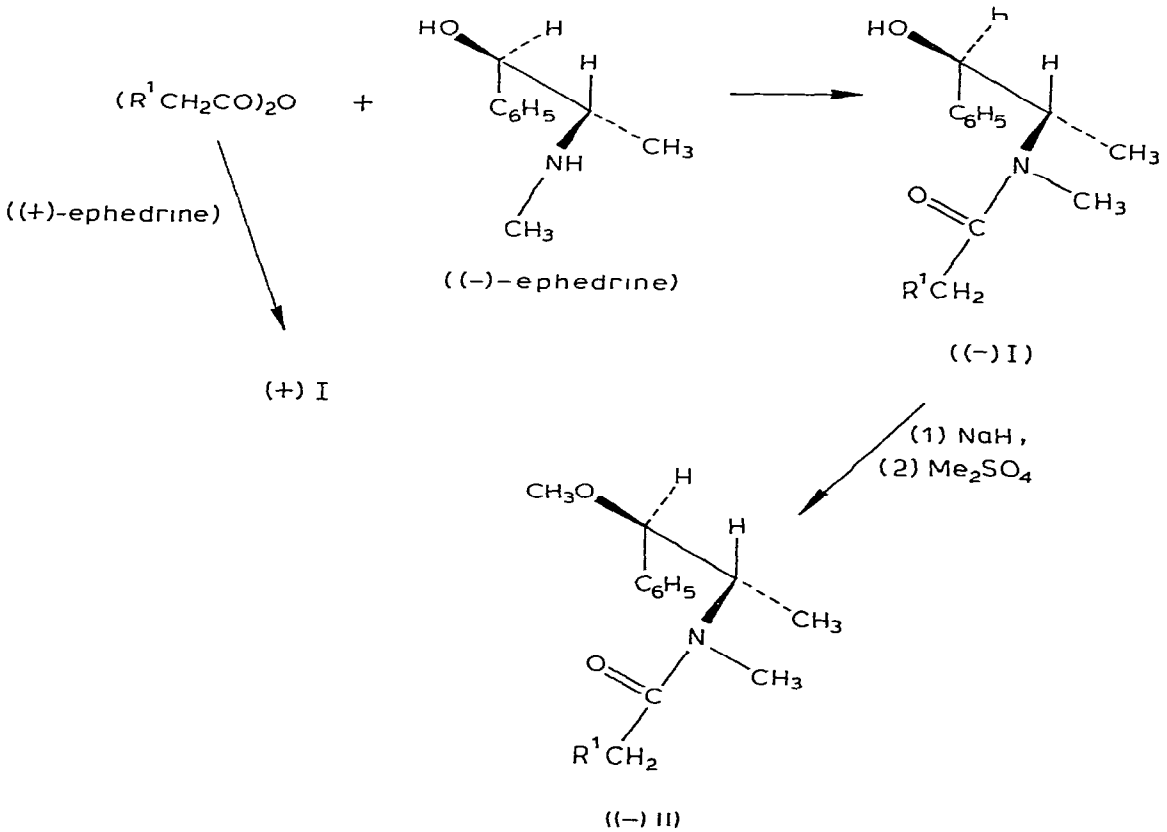
Acetylation of ephedrine was previously described by Mitchell [13]. By operating under well defined conditions, he succeeded in obtaining *N*-acetylated *l*-ephedrine without epimerisation We have extended Mitchell's procedure to other chiral amides, the reaction is performed by heating a mixture of *l*- or *d*-ephedrine with an excess of the relevant anhydride for ten minutes at 65°C In fact, the exothermicity of the reaction is often sufficient to sustain the reaction without heating. Results are summarized in Table 1

TABLE 1

SYNTHESIS OF AMIDES I

	R^1	Chiral inducer	Yield (%)	Melting point (°C)	$[\alpha]_D^{20}$
1	CH_3	(—)-ephedrine	95	71	—104 0° ($CHCl_3$ *c* 3 2)
2	CH_3	(+)-ephedrine	95	71	+ 95 5° ($CHCl_3$ *c* 3 67)
3	C_2H_5	(—)-ephedrine	93	40	—100 0° ($CHCl_3$ *c* 3 17)
4	n-C_4H_9	(—)-ephedrine	98	-	— 86 3° ($CHCl_3$ *c* 3 44)

It is noteworthy that the reaction may also be routinely performed by heating ephedrine with an acid chloride in the presence of a tertiary amine However yields are poorer than by using the anhydride method (yield ~75%) because of the small difference in basicity between the ephedrine and the tertiary amine, which is used to trap the hydrochloric acid *O*-Alkylated compounds (II) cannot be prepared in the same way because the *O*-alkylated ephedrine is not accessible The reaction of ephedrine with sodium hydride followed by alkylation with methyl sulfate gives a complex mixture of *O*- and *N*-alkylated products Besides, the usual hydroxyl protecting methods lead to a partial epimerisation of ephedrine It is possible after acylation to alkylate the alcoholate derived from ephedrine and to synthetize II in excellent yield The reaction is almost quantitative when using sodium hydride followed by addition of a slight excess of methyl sulfate



Metalation and alkylation of chiral amides

Since hydrogen atoms in α position to an amide are only very weakly acid, it is necessary to utilize very powerful bases in order to create anions α to *N*,*N*-disubstituted amides quantitatively [10] Lithium amides (diisopropyl or cyclohexylisopropyl) in ether were generally used.

In the beginning, we used the *O*-substituted amides II in order to limit the

difficulties due to presence of a free hydroxyl function. Metalation is difficult enough, it being necessary, in THF, to wait about 2 h at room temperature to ensure complete reaction. Alkylation is then performed by addition of a halide. Iodides are sufficiently reactive to give substitution in THF, but alkyl bromides give low yield unless they are added with HMPT, the reaction is then achieved in a few hours (3 to 5) at −40°C.

In the same manner, we succeeded in alkylating amides I (the hydroxyl group of which is free) by using two equivalents of base. Yields are quasi-quantitative.

A detailed study was carried out using various metalation and alkylation temperatures, the effect of changing the nature of the Z groups attached to the oxygen was also investigated.

However, the solvent influence was not studied because of the presence of HMPT, which is frequently necessary to obtain good yields in alkylation reactions.

This study was realised by ^{13}C NMR. By recording spectra of the crude mixture isolated after alkylation, it is possible to observe the two diastereoisomers IVA and IVB and to measure the diastereomeric ratio of alkylation. Thus, the amides (−) I and (−) II were alkylated with ethyl iodide under various conditions. Results are summarized in Table 2.

The diastereomeric ratio determination is rather difficult when products are dissolved in deuterochloroform. Indeed, we observed two rotation isomers in this solvent (each peak gives a doublet). By operating in warm deuterated DMSO, it is possible to observe the coalescence of these peaks (the temperature required is about 170°C). By this method it is also possible to measure the diastereomeric ratio for more substituted compounds, but the identification of the

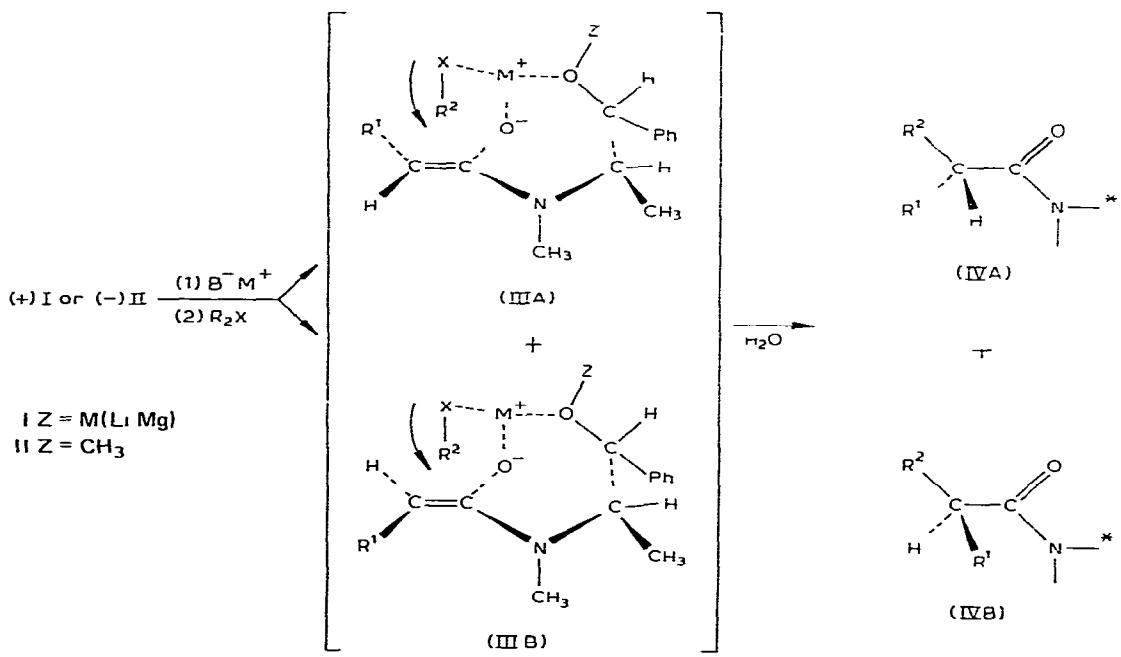


TABLE 2

ALKYLATION OF AMIDES I AND II (R^1 = Me) WITH ETHYL IODIDE [a]

Metalation temperature (°C)	Alkylation temperature (°C)	Yield (%)	Z	IVA/IVB [b]
−50	−30	70	Li	80/20
0	−30	70	Li	80,20
0	+10	95	Li	76/24
0	−40	98	CH_3	65/35
0	+15	100	CH_3	55/45

[a] Reaction was achieved with lithium diisopropylamine (LDA) in THF. [b] The addition of HMPT had little effect on isymmetric inductions

two diastereoisomers is sometimes difficult As shown in Table 2, variation of metalation temperature has no effect However we observed a slight modification of the diastereomeric ratio with alkylation temperature For Z = Li, it is not very significant, but it is notable for Z = CH_3 The more interesting result is given by the variation of the diastereomeric ratio with the nature of the group Z It must be emphasised that this result is not in agreement with Meyer's results which showed a better induction with a methoxy ligand than with a free alcohol

Thus, in order to ameliorate our optical yields we have increased the size of Z by using magnesium as counter-ion The use of magnesium is not possible by direct metalation because Grignard reagents are too weak bases (even in HMPT) to abstract a proton from *N,N*-disubstituted amides

Although magnesium carbanions can be readily obtained by metal exchange the anion of the amide is prepared as previously by reaction with LDA in ether; magnesium dibromide in ether is then added to give the transmetalation The new anion may be alkylated, but its reactivity is appreciably decreased and it is necessary to use a solution of an alkyl iodide in HMPT in order to do this When operating at room temperature, the reaction is complete in about 10 h Although the alkylation temperature is high, we observed in this case a diastereomeric ratio frequently greater than 95% (in fact, we were sometimes unable to observe the second diastereoisomer by ^{13}C NMR) The main results are summarized in Table 3

It is of noteworthy that alkylation with ethyl iodide gives only a medium chemical yield This result is due to the reaction of the iodide with diisopropylamine generated from lithium amide, this being favoured by the high tem-

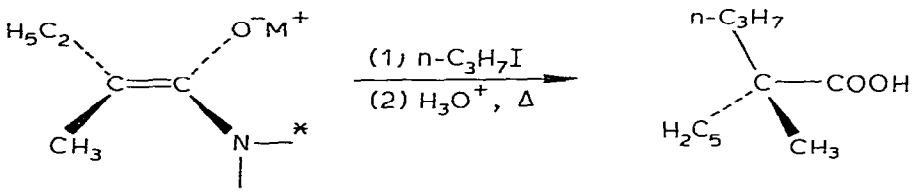
TABLE 3

ALKYLATION OF I IN THE PRESENCE OF $MgBr_2$

R^1	R^2X	Yield (%)	IVA/IVB (^{13}C NMR)
Me	Et I	75	90/10
Me	$(Et)_2SO_4$	95	90/10
Me	n-BuI	95	>95/ 5
Et	n-BuI	93	95/ 5
Et	Benzyl chloride	95	~100/ 0

perature of alkylation In this case the reaction is preferably performed using ethyl sulfate which affords C-alkylation exclusively

The use of magnesium salts does not allow a second alkylation in order to synthesize trisubstituted compounds Acid VI can only be obtained from alkylation of VA VB does not react with n-propyl iodide (even with HMPT) Optical purity is then very poor (23%).



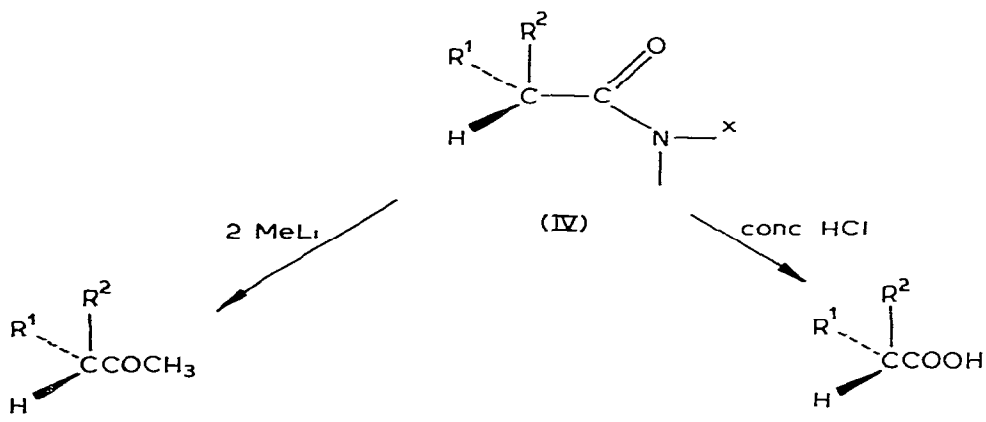
(VA . M = Li,
VB M = Mg)

(VI)

Synthesis of chiral ketones and acids

N,N-Disubstituted amides are interesting because they allow synthesis of substituted ketones by reaction with an organometallic compound Moreover, they may also be hydrolysed to substituted acids

It is of a great importance to find reactions which limit the racemization of



(IV)

(VII)

(VIII)

the asymmetric carbon atom. It is easy enough to obtain chiral acids with good optical yields because racemization is sufficiently slow in acidic media. By heating to reflux with concentrated hydrochloric acid, amides IV give acids VIII in good yield. Results are summarized in Table 4.

Ketones are more difficult to isolate because they are prepared by addition of an organometallic compound and it is well known that basic media favour racemisation (by enolisation of the carbonyl).

TABLE 4

SYNTHESIS OF CHIRAL SUBSTITUTED KETONES AND ACIDS

Entry	Compound	R^1	R^2X	IV A – B Chem yield (%)	VII or VIII Chem yield [a] (%)	$[\alpha]_D^{20}$ (c solvent)	e.e. (%)	Configuration
1	(—) I	Me	EtI	75	VII 53	—10.9° (0.81 $CHCl_3$)	44	*R*
2	(—) I	Me	Et_2SO_4	95	VII 68	—11.1° (0.90 $CHCl_3$)	45	*R*
3	(—) I	Me	n-BuI	95	VII 63	—15.9° (3.2 $CHCl_3$)	65 [b]	*R*
4	(+) I	Me	n-BuI	95	VII 65	+14.8° (3.2 $CHCl_3$)	61 [b]	*S*
5	(—) I	Et	n-BuI	93	VII 72	— 1.9° (5.2 EtOH)	55 [b]	*R*
6	(—) I	Et	Benzyl chloride	89	VII 66	—30.3° (8.56 C_6H_6)	74	*R*
7	(—) I	Me	n-BuI	95	VIII 68	—14.5° (neat)	78	*R*
8	(—) I	Me	i-hexI	90	VIII 55	—12.8° (5.1, $CHCl_3$)	77	*R*
9	(—) I	nBu	Et_2SO_4	98	VIII 71	+3.2° (3.31 $CHCl_3$)	81	*S*
10	(—) I	Et	n-BuI	96	VIII 69	—3.0° (3.25 $CHCl_3$)	79	*R*

[a] From amide I. [b] Determined by 250 MHz NMR with a chiral shift reagent $Eu(hfpc)_3$.

Grignard compounds are inert towards amides IV. Even upon warming, the amide is recovered after hydrolysis.

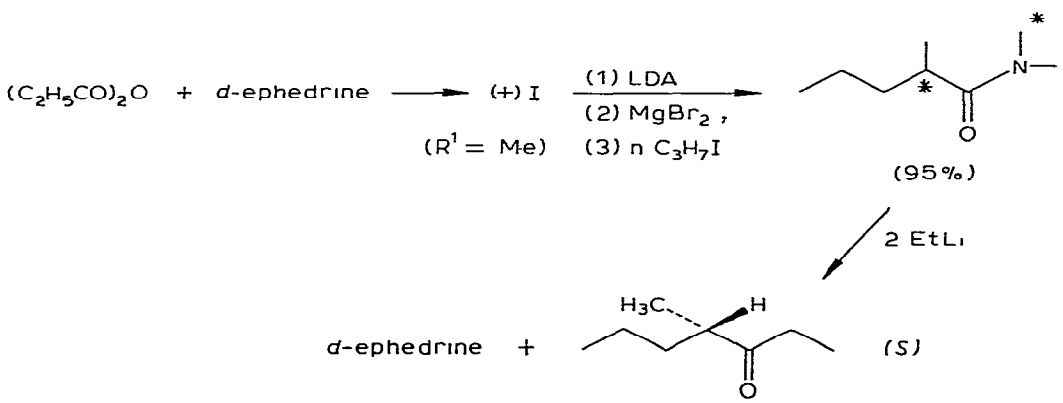
Organolithium compounds give better results and the reaction of two equivalents of such a compound causes the cleavage. After acid hydrolysis, ketones VII are then isolated in moderate chemical yields but in good optical yields. It is also possible to recover the chiral inducer from the aqueous phase.

We tried to limit the racemisation by using milder conditions. Triethyl oxonium fluoroborate was employed in order to generate an imidate salt [14]. These compounds are known to be very reactive towards nucleophiles (H_2O, RM, etc) and we thought that it would be possible to prepare ketones or acids under mild conditions in this way.

In fact all these experiments were negative and we did not succeed in preparing the salts derived from amides I or II (with protected hydroxyl).

Synthesis of (S)-(+)-4-methyl-3-heptanone

This compound is the principal alarm pheromone of "Atta Texana", a leaf-cutting ant. The synthesis of this chiral ketone was interesting because the (+)-enantiomer is about 400 times more active than the (—)-enantiomer [15].



In order to obtain the correct configuration we prepared amide I (R^1 = methyl) derived from *d*-ephedrine The alkylation with n-propyl iodide affords the alkylated amide in 95% yield This amide is then treated with equivalents of ethyllithium to provide, after acid hydrolysis the *S* ketone ($[\alpha]_D^{20}$ +17 9°) in 55% chemical yield and in 81% enantiomeric excess This attractive and efficient route illustrates the interest provided by the use of chiral amides

Discussion

It is of noteworthy from Table 4 that it is possible to prepare either the *R* or the *S* enantiomer in a series from a single chiral substrate. since compounds are formed in comparable enantiomeric purity with opposite configuration when the alkyl group introduction is reversed (entries 9 and 10)

On the other hand, study of the results summarized in Table 2 shows that the diastereomeric ratio is unchanged on variation of the metalation temperature The influence of the alkylation temperature is more perceptible but still not diamatic. However it seems probable that the metalation step determines the yield of the asymmetric synthesis Indeed removal of the pro *R* or pro *S* proton in I determines the *E*/*Z* ratio of the enolates IIIA and IIIB and by studying a space filling model of the compound, we can rationalise that the presence of a methyl group bound to the nitrogen atom greatly favours the formation of enolate IIIA from amide (—) I

A similar result was previously established by Meyers for oxazolines [3]

The small variation of enantiomeric excess with alkylation temperature is consistent with the fact that the electrophile reacts with anion III according to a preferential path

In fact, we can assume that the alkylating agent approaches the molecule from above according to the arrow. This would be the favoured approach because of steric hindrance from below and because of the possible chelation which may be established between the negative pole of the electrophile and the metallic cation (it must be emphasised that results are unchanged by alkylating the anion III with a sulfate)

It is more difficult to explain why optical yields are better with compounds I (the hydroxyl of which is free) than with compounds II (the hydroxyl of which is protected as a methoxy group). An explanation may be found if we suppose that the alcoholate is not free but forms an almost covalent bond with the metal (at least with magnesium) Moreover it is inserted in a tight pair or in a solvent separated pair and the size of such an association ought to influence greatly the stereochemistry of the reaction.

However the small variation of enantiomeric excess with experimental conditions (temperature, solvent, alkylating agent) limits the possibilities for a valuable determination of the mechanism.

Understanding of this reaction is still incomplete and undoubtedly the direct observation of enolates by the NMR technique would be desirable, it would thus be possible to determine that the metalation is definitely the controlling step of the reaction.

From a synthetic point of view, this method allows the use of common compounds to synthesize chiral substituted ketones and acids of predictable

configuration with good optical yields under very mild conditions It must also be emphasised that all the steps are achieved at room temperature

Experimental

General

Lithium diisopropylamide was routinely prepared by adding 1 0 equiv of n-butyllithium to 1 05 equiv of dry isopropylamine at 0°C Magnesium dibromide was prepared by adding 1 0 mol of dibromoethane to 1 0 g-atom of magnesium in ether (120 cm^3) The metal was consumed in about 2 h at 30°C VPC analysis of amides was carried out on a column packed with 6% PS 410 (Alltech) on Chromosorb W AW 80—100 mesh at 240°C Optical rotations were measured on a Perkin—Elmer polarimeter 141 Infrared spectra were recorded on a Perkin—Elmer 457 and PMR spectra on a Bruker WP 80 spectrometer (80 MHz) in CCl_4 Chemical shifts are given in ppm with TMS as internal standard, ^{13}C NMR spectra were recorded on a Jeol FX 60 Q and determination of enantiomeric excess was achieved at 250 MHz (Cameca, TSN 250) with tris[(3-heptafluoropropylhydroxymethylene)-*d*-camphorato]-europium(III) *l*- and *d*-ephedrine were obtained from Aldrich Co

Chiral amides (Table 1)

Amides I 0 1 mol of ephedrine (*l*- or *d*-) is heated with 0 15 mol of anhydride at 65°C for ten minutes The mixture is poured into a cold sodium hydroxide solution (2 *N*) and stirred for one hour in order to eliminate the excess of anhydride After extraction, the product is dissolved in 40 cm^3 of warm benzene and 40 cm^3 of 30—65°C petroleum ether is gradually added After crystallisation, the product is filtered and dried under vacuum IR (film) 3400 cm^{-1} (OH), 1620 cm^{-1} (C=O)

1 and 2 M p 71°C PMR δ 2 20, q, 2H (CH_3—CH_2); 2 75, s, 3H (N—CH_3), 4 3, m, 1H (*CH*OH), 7 3, s, 5H (C_6H_5) 1 $[\alpha]_D^{20}$ —101 0° ($CHCl_3$, *c* 3.2), 2 $[\alpha]_D^{20}$ +95 5° ($CHCl_3$, *c* 3 67)

3· M p 40°C PMR δ 2 25, t, 2H (CH_2—CO), 2 73, s, 3H (N—CH_3), 4 3, m, 1H (*CH*OH). 7.2, s, 5H (C_6H_5) $[\alpha]_D^{20}$ —100 0° ($CHCl_3$, *c* 3 17)

4 PMR δ 2 18, t, 2H (CH_2—CO), 2 69, s, 3H (N—CH_3), 4 2, m, 1H (*CH*OH), 7 2, s, 5H (C_6H_5). $[\alpha]_D^{20}$ —86.3° ($CHCl_3$, *c* 3 44)

Amides II 0 05 mol of amide I (R^1 = Me) in THF (25 cm^3) is slowly added to a suspension of sodium hydride (0 05 mol) in THF After stirring for one hour, 0 06 mol of dimethyl sulfate is added and the mixture is heated for thirty minutes at 40°C After hydrolysis the product is extracted and distilled B p. 105°C/0 1 mmHg PMR δ 2 22, q, 2H (CH_3—CH_2); 2.77, s, 3H (N—CH_3); 3.29, s, 3H (O—CH_3), 4 25, m, 1H (*CH*-OCH_3), 7 3, s, 5H (C_6H_5) $[\alpha]_D^{20}$ —54 3° ($CHCl_3$, *c* 3.53).

Alkylation of amides. 0 025 mol of amide dissolved in 20 cm^3 of THF is slowly added at 0°C (ice bath) to a solution of 0 05 mol of lithium diisopropylamide in ether The mixture is allowed to stir for 2 h 0 05 mol of $MgBr_2$ in 50 cm^3 of ether is then added and stirred for thirty minutes After addition of a solution of alkyl iodide (0.08 mol) in 20 cm^3 of HMPT, the mixture is stirred for 12 h at room temperature and quenched by pouring into a saturated solu-

tion of ammonium chloride After extraction, the solution is washed with sodium thiosulfate and dried

The same procedure is utilized with methyl and ethyl sulfate or with benzyl chloride in this case, the excess of chloride is removed by filtration on a short column of silica gel (hexane/ether 80/20)

The crude product is analyzed by ^{13}C NMR or cleaved in ketone or in acid Amide IV (R^1 = Me, R^2 = Et). ^{13}C NMR (deuterated DMSO 170°C) δ (ppm) (TMS). 9 2 (CH_3—CH_2), 13 2 (CH_3—CH), 26 4 (CH_3—CH_2), 31 4 (CH_3—N), 56 8 (CH—N); 75 5 (CH—O), 130 7, 131 2 and 132 0 (phenyl), 144 2 (phenyl) 173.4 (C=O).

Spectra of amides derived from amide II possess an additional band at δ 54 8 ppm (O—CH_3).

Synthesis of R and S ketones

Crude substituted amides IV are dissolved in ether and a solution of 2 equiv of MeLi in ether is slowly added at —10°C After stirring for 45 minutes, the mixture is poured into hydrochloric acid (~5 *N*) at 0°C and extracted with pentane. After distillation or chromatography on silica gel (hexane and hexane/ethylacetate, 95/5) pure ketones are isolated.

R-(—)-3-Methyl-2-pentanone B p 115°C IR 1715 cm^{-1} (C=O) PMR δ (ppm) 0 95, t, 3H (CH_3—CH_2); 1 02, d, 3H (CH_3—CH), 2 05, s, 3H (CH_3—CO) $[\alpha]_D^{20}$ —10 9° ($CHCl_3$, *c* 0 81); lit [16], $[\alpha]_D^{20}$ —24 9°

R-(—)-3-Methyl-2-heptanone. B.p. 57°C/18 mmHg IR 1715 cm^{-1} (C=O) PMR· δ (ppm) 0.98, t, 3H (CH_3—CH_2), 1 0, d, 3H (CH_3—CH); 2 1, s, 3H (CH_3—CO). $[\alpha]_D^{20}$ —15.9° ($CHCl_3$, *c* 3.2)

S-(+)-3-Methyl-2-heptanone As for the *R*-enantiomer, but $[\alpha]_D^{20}$ + 14 8° ($CHCl_3$, *c* 3 2) The enantiomeric excess was measured by dedoubling the singlet of CH_3—CO (addition of a chiral shift reagent)

R-(—)-3-Ethyl-2-heptanone IR 1710 cm^{-1} (C=O) PMR δ (ppm) 0 99 and 1.02, 2t, 6H (CH_3—CH_2), 2 03, s, 3H (CH_3—CO) $[\alpha]_D^{20}$ —1 9° (EtOH, *c* 5 2), lit [17] $[\alpha]_D^{20}$ —0 7°).

R-(—)-2-Ethyl-1-phenyl-3-butanone IR· 1715 cm^{-1} (C=O) PMR· δ (ppm) 0.95, t, 3H (CH_3—CH_2), 2 05, s, 3H (CH_3—CO); 2 35, d, 2H (CH_2—C_6H_5) $[\alpha]_D^{20}$ —33.7° (EtOH abs, *c* 2.52) (lit [18], $[\alpha]_D^{20}$ —45 5°)

Synthesis of S-(+)-4-methyl-3-heptanone

The ketone is synthesized as previously described. 0 045 mol of EtLi is added to 0.025 mol of the crude amide III between —15 and —10°C IR 1710 cm^{-1} (C=O). PMR: δ (ppm) 0.98 and 1 02, 2t and 1d, 9H (CH_3—CH_2 and CH_3—CH); 2.31, q, 2H (CH_2—CO) $[\alpha]_D^{20}$ + 17 9° (hexane, *c* 1 1)(lit [15] $[\alpha]_D^{27}$ + 22 0°).

Synthesis of R and S acids

0.025 mol of the alkylated amide is refluxed with conc HCl for 20—30 h After cooling, the mixture is extracted and washed with cold sodium hydroxide (5 *N*). The aqueous phase is then quickly acidified and extracted with pentane The pure acid is isolated as a colorless oil after removal of solvents.

(R)-(—)-2-Methylhexanoic acid IR: 3400 cm^{-1} (OH); 1725 cm^{-1} (C=O)

PMR δ (ppm) 0.95, t, 3H (CH_3—CH_2), 1 07, d, 3H (CH_3—CH) $[\alpha]_D^{20}$ —14 5° (neat), lit [19], $[\alpha]_D^{20}$ +18 7°

(R)-(—)-2,6-Dimethylheptanoic acid IR 3400 cm^{-1} (OH), 1720 cm^{-1} (C=O) PMR δ (ppm) 0 92, d, 6H ((CH_3)$_2$—CH), 1 02, d, 3H (CH_3—CH) $[\alpha]_D^{20}$ —12°8 ($CHCl_3$, *c* 5 1) (lit [20] $[\alpha]_D^{25}$ —16 6°)

(R)-(—)-2-Ethylhexanoic acid IR 3420 cm^{-1} (OH), 1720 cm^{-1}(C=O) PMR δ (ppm) 0 95 and 1 0, 2t, 6H (CH_3—CH_2) $[\alpha]_D^{20}$ —3 0° ($CHCl_3$, *c* 3 3)(lit [21] $[\alpha]_D^{20}$ —3.94°)

(S)-(+)-2-Ethylhexanoic acid As for R-enantiomer but $[\alpha]_D^{20}$ +3 2° ($CHCl_3$, C = 3 3)

(R)-(—)-2-Ethyl-2-methylpentanoic acid The first alkylation is achieved as usual with $(Et)_2SO_4$ as the alkylating agent, the second is achieved without adding $MgBr_2$ with n-PrI as the alkylating agent After cleavage with conc HCl, the pure acid is isolated by silica gel chromatography (hexane/ethyl acetate, 92/8) IR 2400 cm^{-1} (OH) and 1725 cm^{-1} (C=O) PMR δ (ppm) 0 98, s, 3H (CH_3—C), 1 0, 2t, 6H (CH_3—CH_2) $[\alpha]_D^{20}$ —4 5° (EtOH 95, *c* 3 6) (lit [22] $[\alpha]_D^{20}$ +19 7°)

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References

1 H B Kagan and J C Fiaud Top Stereochem , 10 (1978) 175
2 D Valentine Jr and J W Scott Synthesis (1978) 329
3 A I Meyers, Accounts, 11 (1978) 375
4 D Mea-Jachet and A Horeau Bull Soc Chim Fr (1968) 4751 M Kitomoto K Hiroi S Terashima and S Yamada Chem Pharm Bull 22 (1974) 459 J K Whitesell and M A Whitesell J Org Chem 42 (1977) 377 S Hashimoto and K Koga Tetrahedron Lett (1978) 573
5 A I Meyers D R Williams and M Druelinger J Amer Chem Soc 98 (1976) 3032 D R Williams and A I Meyers J Org Chem 43 (1978) 3245 A I Meyers G S Poindexter and Z Brich J Org Chem 43 (1978) 892
6 S Hashimoto S Yamada and K Koga J Amer Chem Soc 98 (1976) 7450 S Hashimoto N Komeshima S Yamada and K Koga Tetrahedron Lett (1978) 2907
7 S Yamada T Ogun and T Shioiri J Chem Soc Chem Commun (1976) 136
8 D Enders and H Eichenauer Angew Chem Int Ed Engl 15 (1976) 549 Tetrahedron Lett (1977) 191 H Eichenauer E Friedrich W Lutz and D Enders Angew Chem Int Ed Engl , 17 (1978) 206
9 E L Eliel Tetrahedron 30 (1974) 1503
10 T Cuvigny and H Normant C R Acad Sci Paris Ser C 268 (1969) 1380 P Deslongchamps V O Cheriyan and D R Patterson Can J Chem 53 (1975) 1682 P Hullot T Cuvigny M Larcheveque and H Normant Can J Chem 54 (1976) 1098 55 (1977) 266
11 M Larcheveque E Ignatova and T Cuvigny Tetrahedron Lett (1978) 3961
12 E Spath and P Gohring Monatsh , 41 (1920) 319
13 W Mitchell J Chem Soc (1940) 1153
14 H Bredereck W Kantlehner and D Schweizer Chem Ber 104 (1971) 3475
15 R G Riley and R M Silverstein, Tetrahedron 30 (1974) 1171
16 C Djerassi and L E Geller J Amer Chem Soc 81 (1959) 2789
17 J Kenyon and D P Young J Chem Soc , (1941) 266
18 T Kashiwagi K Fujihori S Kozuka and S Oae Tetrahedron 26 (1970) 3647
19 P A Levene and R E Marker, J Biol Chem , 98 (1932) 1
20 Ka Kong Chan and G Saucy, J Org Chem 42 (1977) 3828
21 J Kenyon and B C Platt J Chem Soc (1939) 633
22 W Bleazard and E Rochstein J Chem Soc (1958) 3789