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2-HYDROXY-3-PINANONE AS CHIRAL AUXILIARY IN THE ASYMMETRIC SYNTHESIS OF α-AMINO ACIDS

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Summary: *The reactivity of lithiated chiral Schiff bases 2 with carbonyl compounds is studied. They do not react with ketones but with aldehydes good chemical yields are obtained in the presence of cosolvents. On the other hand, the reaction with unsaturated carbonyl compounds (ethylenic, acetylenic, allenic) is very rapid and affords a variety of amino esters with good chemical and optical yields. With the lactone 7, prepared by cyclisation of the ester of glycine with 2-hydroxy 3-pinanone, the first results obtained with alkyl halides, aldehydes and epoxide show excellent stereoselectivity and good chemical yields.*

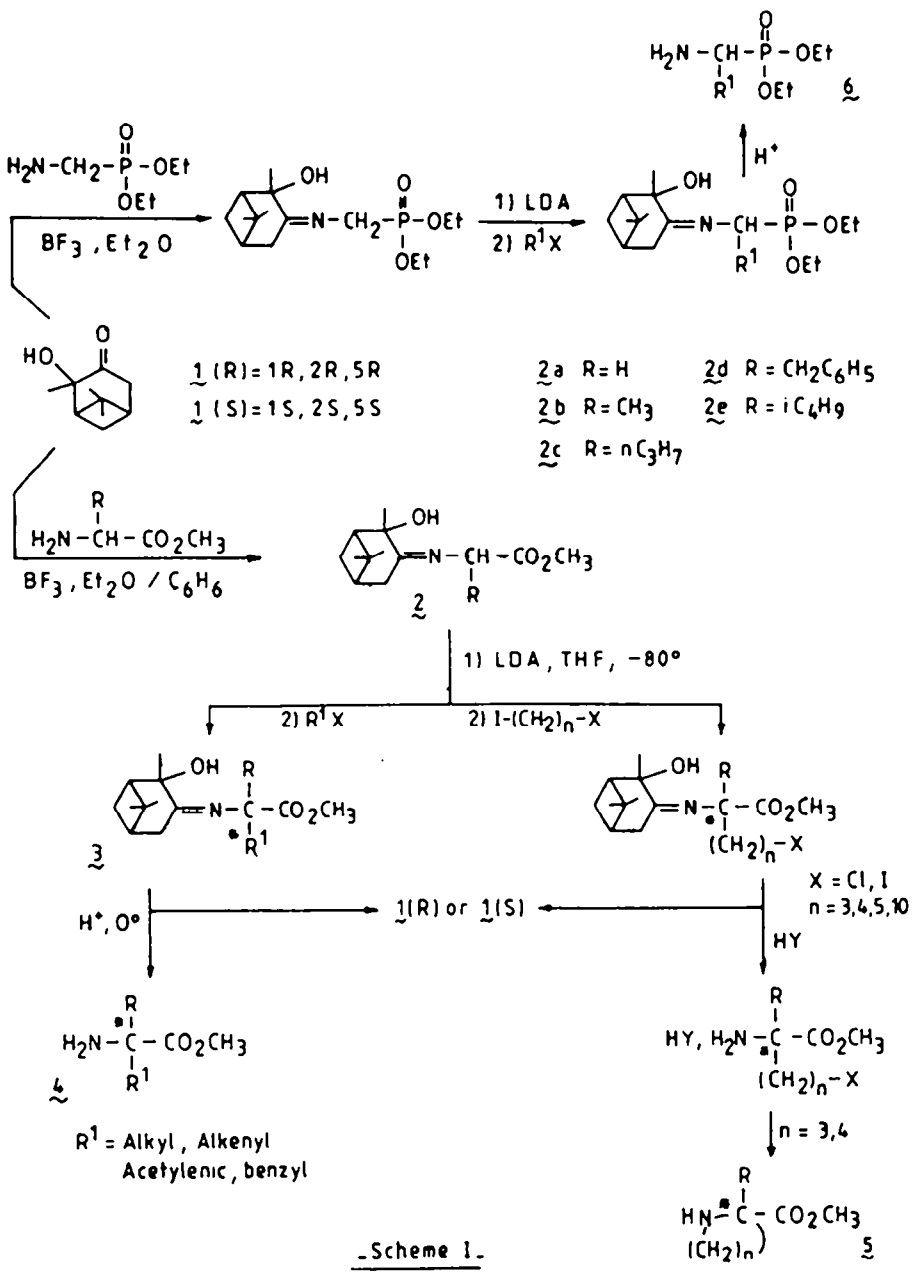
INTRODUCTION

The wide spectrum of the applications of amino acids and the economic impact of such products has led to the development of a variety of procedures for their extraction from natural sources and for their chemical synthesis[1]. Most aminoacids are biologically active in one enantiomeric form, therefore the difficult task for the organic chemist is to synthesize enantiomerically pure compounds. Several methods are now available for the preparation of amino acids of high enantiomeric purity using asymmetric hydrogenation[2], chiral enolates[3], electrophilic glycinates[4] and asymmetric amination[5].

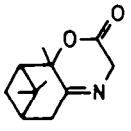
Because of our interest in the synthesis of a great variety of optically pure amino acids we have developed methods which permit the easy access to such products.

Two strategies have been explored : modification of enantiomerically pure α-amino acids derivatives without loss of the optical purity or creation of the asymmetric centre and formation of one C-C bond to the α-carbon. Thus a general method[6] of synthesis of α-amino esters was elaborated by reaction of organocuprates with tosyl and halogeno derivatives of L-serine and L-homoserine. We[7] have also prepared optically pure proline derivatives using the Hofmann-Loeffler-Freytag reaction carried out by irradiation of N-chloro L-amino acids in sulphuric acid.

Next we have developed a general and efficient method by diastereoselective alkylation of chiral Schiff bases. YAMADA[8] described the asymmetric synthesis of four monosubstituted D-α-aminoacid derivatives (66%<ee<83%) by alkylation of the Schiff base prepared from the glycine t-butyl ester and (1S,2S,5S) 2-hydroxy 3-pinanone.This chiral auxiliary and its enantiomer are very attractive, because they were easily obtained by



- Scheme I -



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- Scheme II -

permanganate oxidation of (+) or (-)α-pinene[9] which are commercial inexpensive products. Schiff bases were prepared with good yields in refluxing benzene containing boron trifluoride etherate.

We have studied thoroughly this method and have been able to introduce primary and secondary alkyl, unsaturated (ethylenic, acetylenic, aromatic), halogenated substituents at the α-carbon of the Schiff bases of glycine, alanine, phenylalanine, leucine, valine, norvaline amino esters. Furthermore we have shown[10] that diastereoisomeric Schiff bases were sufficiently stable to be separated by column chromatography (or flash chromatography), the stability could be ascribed to the intramolecular hydrogen bond between the hydroxyl group and the nitrogen. So we can obtain enantiomerically pure compounds, even with an incomplete stereoselectivity of the reaction. This method was also used for the asymmetric synthesis of disubstituted amino acids[11] 4, imino acids[12] 5, aminophosphonic[13] 6 and aminophosphinic acids[14]. These different results are summarized in Scheme I.

From the Schiff bases of glycine and alanine methyl esters this process fullfills the requirements necessary for an asymmetric synthesis : good to excellent chemical yields, enantiomeric excesses in the range 50 to >95%, the chiral auxiliary is recoverable and the absolute configuration of the reaction products is easily predictable. Starting from (1R,2R,5R) 2-hydroxy 3-pinanone S amino esters were obtained, whereas (1S,2S,5S) 2-hydroxy 3-pinanone gave R aminoesters.

With the other Schiff bases possessing bulky substituents, the numerous results we have obtained[15] showed clearly that the chemical and optical yields were dependent on the substituent R present on the Schiff base before alkylation. Recently we have reported[16] that chirality of the starting imine is also important ;with the Schiff base of valine methyl ester and (1R,2R,5R) 2-hydroxy 3-pinanone, after metalation with LDA, only the diastereomer RRR,S gave a reaction with electrophiles like D_2O or CH_3I. This study was extended to Schiff bases of leucine, phenylalanine and norvaline methyl esters. Diastereoisomers RRR,S do not epimerise in presence of LDA and were alkylated by methyl iodide with retention of configuration. The reactivity of diastereoisomers RRR,R was dependent on the substituent R present on the Schiff base before alkylation. Identical results were obtained with (1S,2S,5S) 2-hydroxy 3-pinanone.

This article deals first with the reactivity of the Schiff bases with saturated and unsaturated carbonyl compounds. Next we report our first results obtained with the rigid system formed by the lactone 7 (R) or 7 (S) prepared from the ester of glycine with 1 (R) or 1 (S).

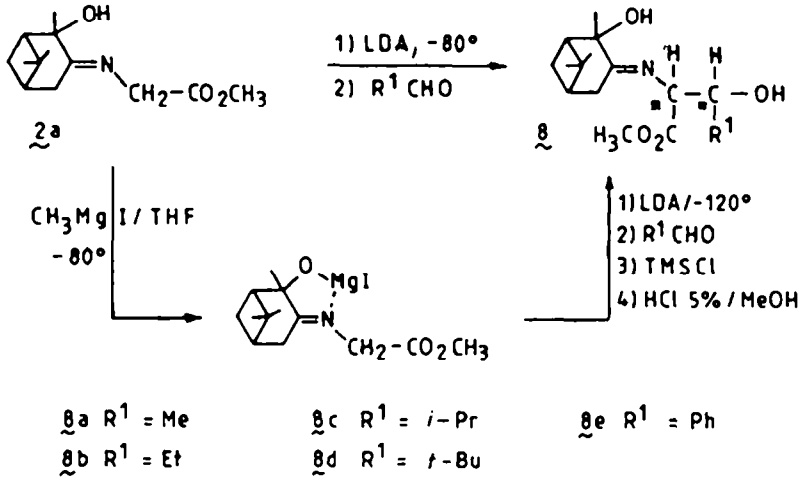
RESULTS

a) Reactivity of lithiated Schiff bases with saturated carbonyl compounds

To delineate the scope and limitations of the method it was of interest to examine the reactivity of the lithiated Schiff bases 2 with carbonyl compounds. At -80°C in THF the dianion prepared from methyl glycinate with two equivalents of LDA did not react with ketones such as dimethyl ketone but did react with aldehydes. The results are summarized in Table I.Two chiral centres are created and four diastereoisomers can be formed. As shown in Table I two or three of them were detected by ^{1}H-NMR or thin layer chromatography, but they are difficult to separate by column chromatography. The chemical yields were low, despite the experimental conditions employed. For example, changing the temperature (-100° to +20°) or the reaction time did not modify the yield, the starting Schiff base being recovered. We have examined the influence of solvent polarity : it has been well established[17] that lithium enolates exist as aggregates depending on the solvent.

Table I

R_1	Schiff bases	Yield	Number of stereoisomers	Relative proportions
CH_3	8a	20	2	60 / 40
CH_2-CH_3	8b	40	3	50 / 32.5 / 17.5
$CH(CH_3)_2$	8c	32	3	90.5 / 6 / 3.5
$C(CH_3)_3$	8d	28	2	55 / 45
Ph	8e	28	2	55 / 45



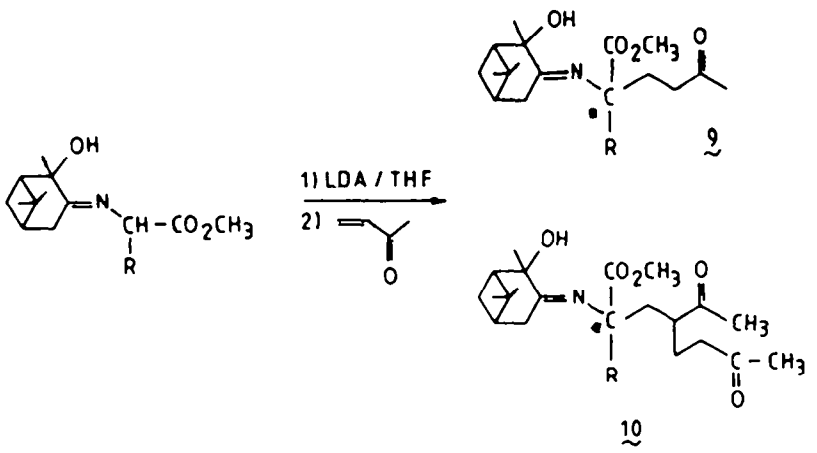
8a R^1 = Me 8c R^1 = *i*-Pr 8e R^1 = Ph
8b R^1 = Et 8d R^1 = *t*-Bu

- Scheme III -

In DME the chemical yield of the reaction of the lithiated Schiff base of methyl glycinate with acetaldehyde was enhanced (40%) but the stereoselectivity did not change. Two cosolvents have been employed, HMPA and TMEDA, and in these two cases, the aldol products were obtained with 90% yield and always with a low stereoselectivity. We have tried to prepare a more chelated intermediate by using methylmagnesium iodide as outlined in Scheme III ; in addition we could expect the magnesium to provide an electrophilic assistance to the carbonyl approach. In this case, starting from acetaldehyde and benzaldehyde, the aldol products 8a and 8e were prepared with 35 and 47% yield respectively. In both cases two diastereoisomers are formed in the proportions 60/40. Much better yield and diastereoselection was obtained by replacement of Li by Ti. The lithiated Schiff base treated by $Ti(OiPr)_3Cl$ led to the titanium intermediate which reacted with acetaldehyde to give the aldol product with 75% yield, two diastereomers were formed (70/30). It remains to study the influence of the ligands located on Ti on the stereoselectivity.

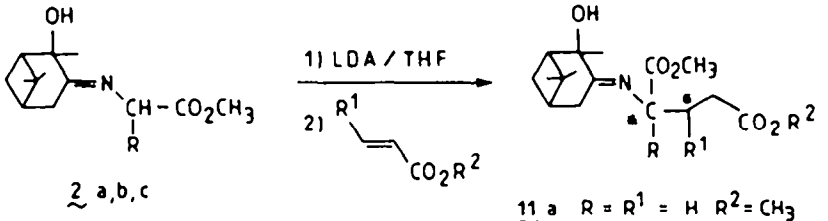
b) Unsaturated carbonyl compounds

Three Schiff bases have been studied : glycine methyl ester 2a, alanine methyl ester 2b and norvaline methyl ester 2c. With methyl vinyl ketone, 2a in the presence of two equivalents of LDA at -80°C gave a mixture of the desired 1,4 addition product 9 (10% yield) and a compound 10 arising from the reaction of the intermediate anion on another molecule of methyl vinyl ketone (33% yield).



Scheme IV.

With methyl acrylate, 2a gave the addition product 11a in 50% yield (de=48%); the two diastereomers could be separated. Starting from (R) 2-hydroxy 3-pinanone 1, the configuration of the major isomer, following hydrolysis, was S, as in the alkylation reactions.



11 a R = R¹ = H R²=CH3
b R = CH3 R¹=H R²=CH3

12 a R = H R¹=CH3 R²=Et
b R = CH3 R¹=CH3 R²=Et
c R=n-C3H7 R¹=CH3 R²=Et

Scheme V.

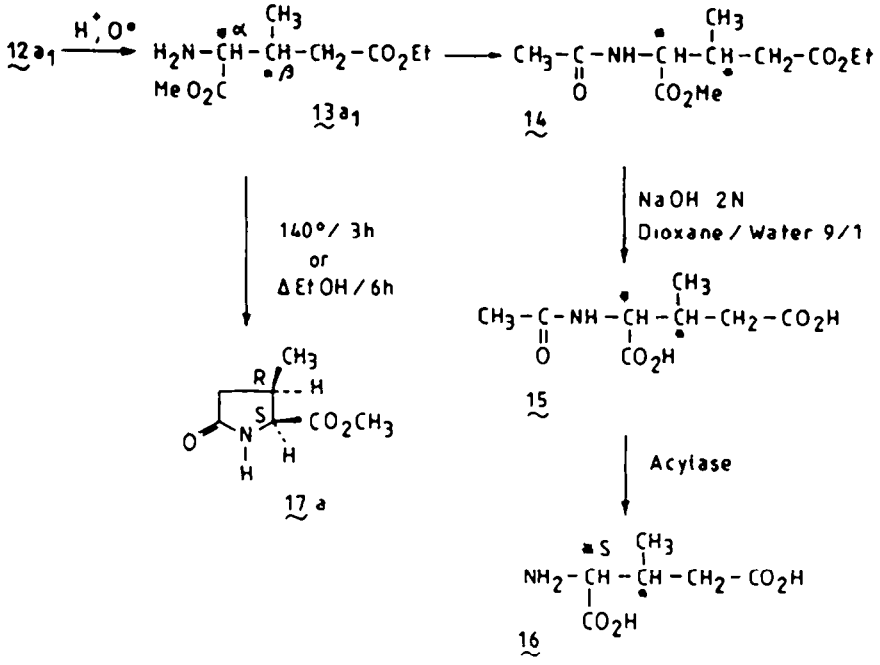
Table II

Schiff bases	Total Yield	Number of Diastereoisomers	Pure Isomer	Mixture	(Proportions)
12a	74	4	32	42	(55/18/27)
12b	90	1	90		
12c	80	1	80		

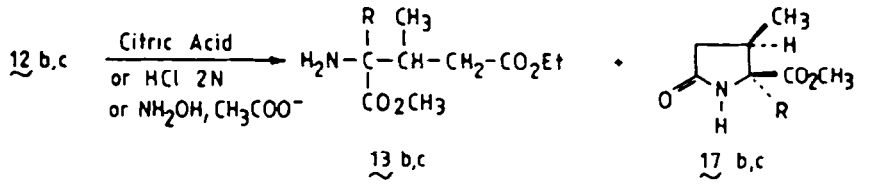
Similarly, starting from Schiff base 2b, two diastereoisomers 11b were formed in 52% yield (de = 71%). With ethyl crotonate, two chiral centres were created and therefore four diastereomers were possible. The results are summarized in Table II. The optical yield was highly dependent on the starting Schiff base.The major isomer of 12a, 12a1 could be separated by column chromatography. Cleavage of the imines was performed with 15% citric acid or 2N HCl . When the acidic hydrolysis proceeded slowly or sluggishly, the cleavage was carried out with hydroxylamine acetate.

The configuration of the Cα carbon of 13a1 obtained after hydrolysis of 12a1 was determined by an enzymatic method. Compound 13a1 was transformed into the N-acetyl

derivative 14 which was saponified (2N NaOH) to give the N-acetyl diacid 15. 15 was treated with acylase during 40 h at ambient temperature to give the diacid 16, indicating the configuration S for the α carbon.. Indeed, in this case also, (R)-2-hydroxy 3-pinanone induced the S configuration, The small differences in coupling constants values $J_{H\alpha H\beta}$ (4.5 and 6 Hz) observed for 13a₁ and its minor isomers did not allow its use for assignment of relative configuration. Therefore we have cyclised 13a₁ into pyrrolidinone 17a. According to INUI'S[18] results, the value of the coupling constant (9Hz) allows the assignment of structure 17a.



Scheme VI



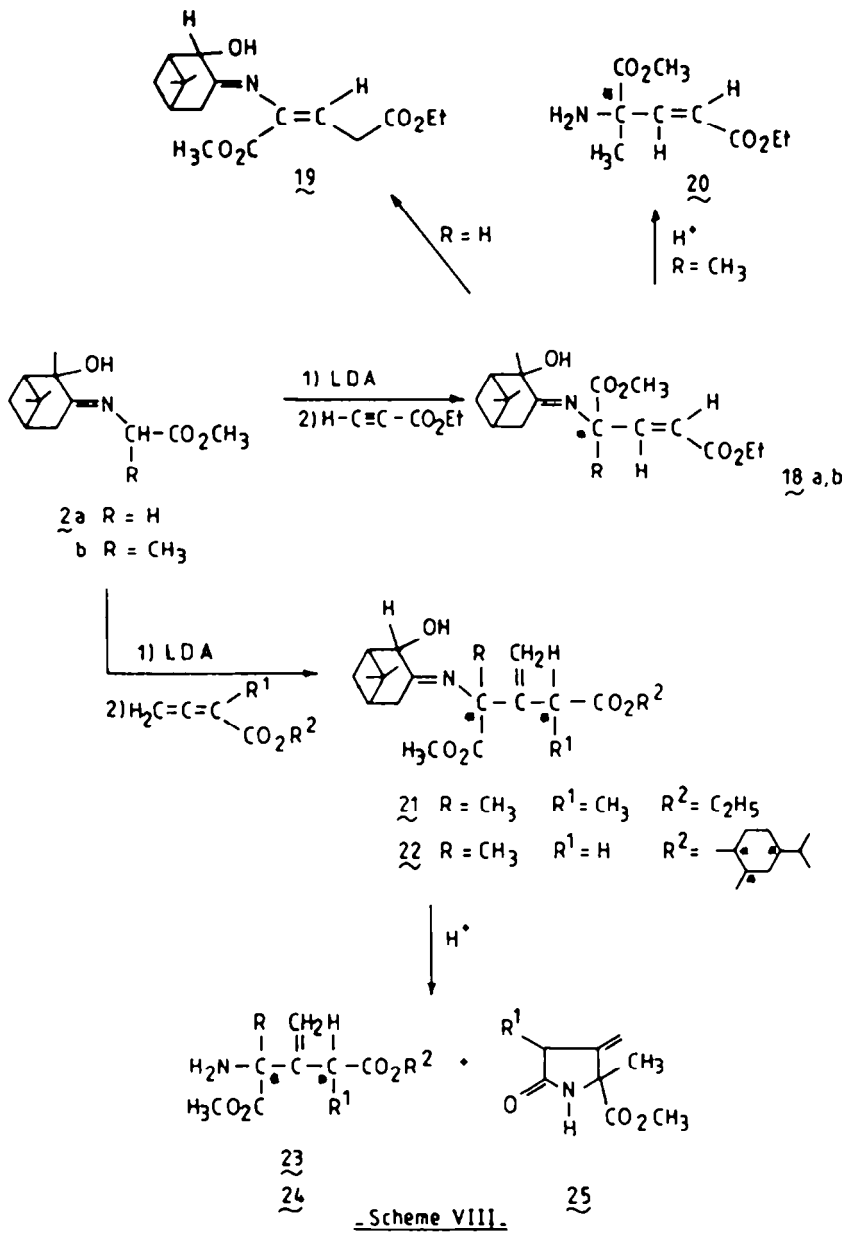
Scheme VII

Hydrolysis of 12b by 15% citric acid led to the amino ester 13b with 51% yield (ee>95%). By analogy we have assigned the configuration S to the α carbon and R to the β carbon. When hydrolysis was performed with 2N HCl at 20°C, 17b was the main product. Cleavage of 13c needed hydroxylamine acetate and the pyrrolidinone 17c was obtained directly (61%,ee>95%).

The condensation of 2a with ethyl propiolate was also very rapid at -80°C. In 20 min it gave the compound 19 (64% yield) resulting from the migration of the double bond in 18a.

The lithiated Schiff base from 2b reacted with ethyl propiolate to give 18b 40% yield Z/E : 35/65. Acidic cleavage with 2N HCl led to 20 (59% yield; ee>95%).

To avoid the migration of the double bond, the condensation of allenic compounds was carried out only with 2b (R=CH_3). The adducts 21 (35% yield) and 22 (74%) were obtained and were cleaved by 2N HCl to give the amino esters 23 and 24 and the pyrrolidinone 25 (ee>95%).



Scheme VIII.

c) Lactone 7 as chiral auxiliary

In order to know the role of the acidic hydrogen in the reactions of lithiated Schiff bases we thought first to prepare a derivative without this group. We could use the corresponding methoxy derivative, but MUKAIYAMA[19] et al. working with optically active 3-hydroxy-3-phenylbutan-2-one as chiral auxiliary, reported that the hydroxyl group was essential to gain high optical yield ; when O-methylated or O-methoxymethylated imines were used in place of an hydroxyimine, the optical purity was very low (5 - 10% ee).

For this reason, we decided to synthesize the lactone 7 which had two advantages : first it was a rigid system with a diastereoface shielded by three methyl groups. After deprotonation we could expect the electrophile to enter the other face ; thus the asymmetric induction should be excellent, secondly, after acid hydrolysis we should obtain amino acids directly.

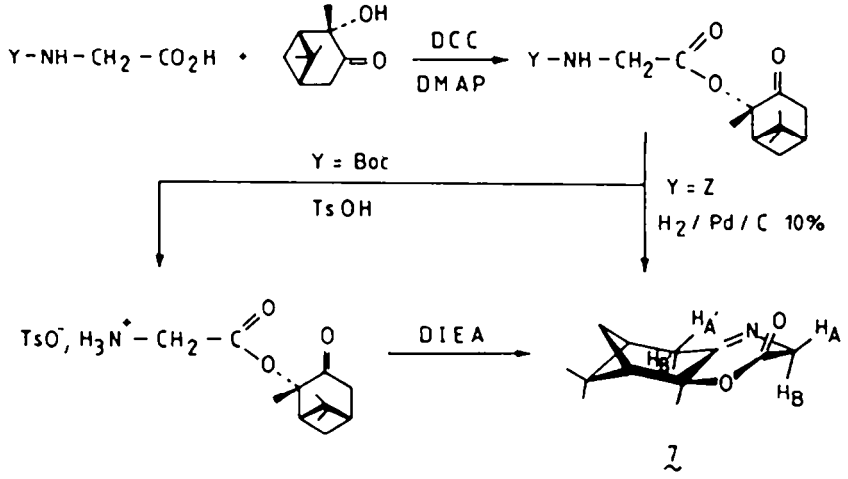
Compound 7 could not be prepared in a good yield starting from glycine methyl ester Schiff base. Several attempts have been performed using acidic (p-toluene sulfonic acid,

oxalic acid, SiO_2 in C_6H_6) or basic media (OH^-, imidazole), they were unsuccessful. Only one method permitted the preparation of 7 with 15% yield : 2a was left during ten days on a Kieselgel containing column and 7 was eluted with the starting Schiff base. The difficulties encountered could be assigned to the stereochemistry of 2a which can exist with two configurations : Z or E. Both the ^{13}C NMR and the 250 MHz ^1H-NMR were consistent only with the presence of one diastereomer which had the configuration E. Therefore 7 was obtained by the other strategy outlined in Scheme X

2 E 2 Z

Scheme IX

The ester was prepared starting from Boc or Z glycine and 2-hydroxy-3-pinanone using dicyclohexylcarbodiimide (DCC) and dimethylaminopyridine (DMAP). After cleavage of the protecting group, the lactone 7 was obtained (55% overall yield). ^1H-NMR spectrum of 7 is typical. The two protons of the AB system centered at 4.4 ppm don't present the same couplings : H_A is only coupled with H_B (J_{HAHB} = 19.8 Hz) and H_B is coupled in addition with $H_{A'}$ and $H_{B'}$ located on the C_4 carbon of the pinane nucleus ($J_{HBHB'}$ = 4.2 Hz, $J_{HBHA'}$ = 2.6 Hz). These attributions have been accomplished using molecular models and according to ATKINSON's[20] work on homoallylic couplings.



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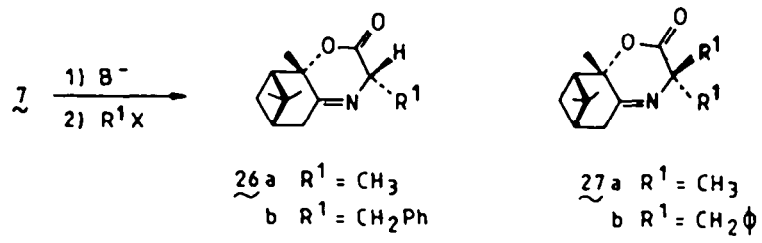
Scheme X

All the reactions studied have been performed in THF, at -80°C, two bases have been systematically used t-BuOK and LDA and, as discussed below, the best results were obtained with t-BuOK.

The lactone reacted with methyl iodide in the presence of t-BuOK to give 26a (60% yield, de >95%) and a small amount of the dialkylated product 27a (14% yield). 26a and 27a were easily separated on column chromatography. With LDA, even after 18 h of reaction, 26a was obtained in only 5 % yield, starting material 7 was recovered.



Scheme XI

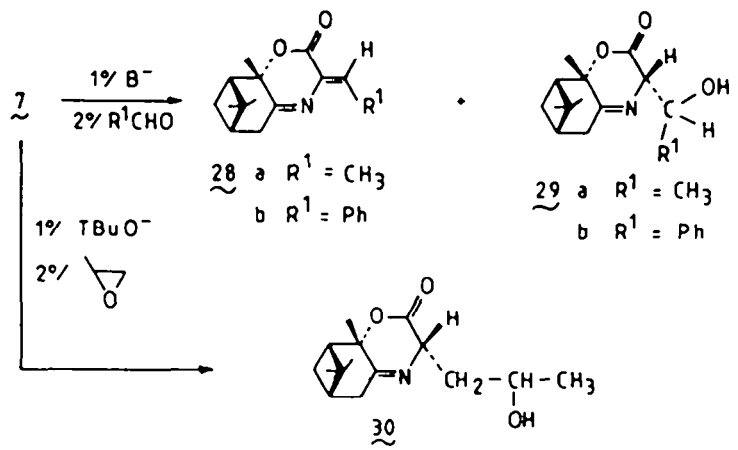
In the ^{1}H-NMR spectrum, the splitting of the proton α to the methyl group demonstrates that the electrophile entered the opposite face to the gem dimethyl group since this proton shows homoallylic coupling. This fact was confirmed after acidic cleavage (2N HCl, 0°C, 18 h); starting from the (S) lactone optically pure S alanine was prepared. With benzyl bromide, several bases and cosolvents have been used. The monoalkylated product 26b was never obtained, only the dialkylated one 27b was prepared in some cases. The results are summarized in Table III

Table III

Base	Experimental Conditions	Yield 7	Yield 27b
TBuOK	24 h (-80° to -45°C)	90	-
TBuOK	48 h (-70° to 0°C)	40	41
TBuOK/HMPA (2 eq)	24 h (-70° to -18°C)	40	40
LDA	48 h (-70° to +18°C)	45*	-
LDA/HMPA (5 eq)	24 h (-70° to - 2°C)	37	45
L.T.M.P.[a]	7 h (-70° to -40°C)	50*	
L.D.E.A.[b]	24 h (-90° to +18°C)	60*	

a:lithium tetramethylpiperidide; b:lithium diethylamide
* non identified products were isolated

The lactone 7, in the presence of t-BuOK, reacted with acetaldehyde very rapidly (15 min at -80°C) to furnish the dehydro compound 28a in 85% yield, the corresponding alcohol 29a could not be isolated.

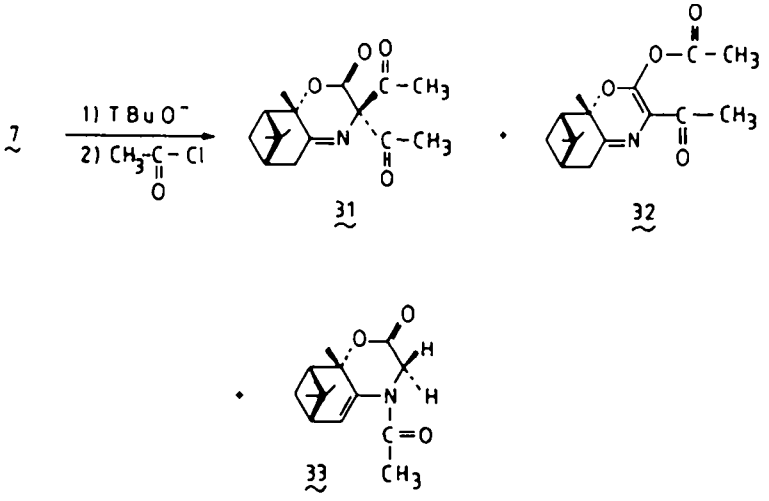


Scheme XII

In the same conditions benzaldehyde gave a mixture of the two products 28b (52% yield) and 29b (32% yield) separated by column chromatography ; 28a and 28b were obtained with a single configuration for the double bond. Starting from the (R)-lactone, compound 29b was a mixture of two isomers syn and anti (66/34), the carbon α to the C=O group having R configuration (in ^{1}H-NMR spectrum the proton linked to this carbon shows homoallylic coupling). With unsaturated carbonyl compounds (methyl vinyl ketone, ethyl crotonate) preliminary attempts in the presence of t-BuOK or LDA were unsuccessfull, the starting products were recovered.

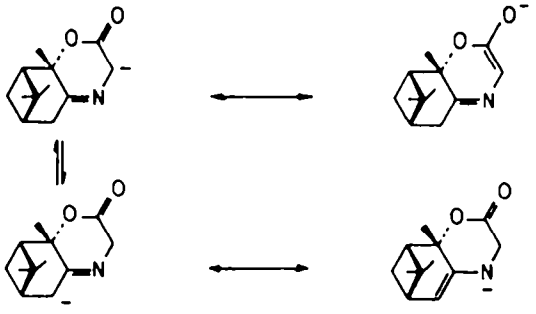
As expected, 7 treated with t-BuOK reacted with methyl oxirane in the presence of $BF_3.Et_2O$ to give 30 in 60% yield. As we have previously noted, the ^{1}H-NMR spectrum showed that the electrophile entered the less shielded face from the side opposite to the gem dimethyl group.

Suprising results were obtained with acetyl chloride, 7 in the presence of t-BuOK at -80°C led to a mixture of three products 31, 32, 33 separated by column chromatography ; with LDA only 33 was obtained and the starting lactone was recovered. Structures have been assigned using IR, NMR and Mass spectra.



- Scheme XIII -

This last reaction pointed out for the first time with these structures the equilibrium between two resonance-stabilized carbanions. The reactivty of the acid chloride allowed isolation of three of the four possible isomeric products.



- Scheme XIV -

CONCLUSION

The results we have described demonstrate the important role of the electrophile as well as the chiral auxiliary. With Schiff bases 2, lithium diisopropylamide can be considered as a good working base but with the lactone 7 t-BuOK is better. The role of aggregates is to be determined and work is in progress with different solvents and bases.

If, with alkyl halides reactions worked well starting from Schiff bases or from lactone, it is not the case for the carbonyl compounds. With saturated carbonyl compounds, the reactions with lithiated Schiff bases gave good yields only in the presence of cosolvents but the lactone 7 reacted well. However the reverse was obtained with unsaturated carbonyl compounds: the reactivity was better with Schiff bases.

As demonstrated this route provides nearly access to natural and unnatural α amino acids of predictable chirality. Efforts to further expand the scope and utility of these methodologies and to explain the reasons of the differences of reactivity are presently under active investigation.

EXPERIMENTAL

Melting points are uncorrected. Reagents and solvents were purified in the usual way. All reactions involving lithium derivatives were carried out under anhydrous conditions in a nitrogen atmosphere. LDA was prepared from BuLi in ether. Spectra were recorded with the following instruments. IR : Perkin-Elmer spectrophotometer 298. ^{1}H-NMR : Varian EM-360 and Varian XL 100. Mass Spectra : Jeol JMS DX 100 and DX 300. Optical rotations were determined with a Perkin-Elmer Model 141 polarimeter. Routine analyses agree with calculated values within ± 0.3%. Enantiomeric purity was checked by ^{1}H-NMR spectroscopy on the amino ester (0.15-0.2 M CCl_4/TMS solution in the presence of 0.2-0.6 mole equivalent of d-Eu(hfc)$_3$).

General procedure for reactions of Schiff bases with carbonyl compounds

The Schiff base (1mmol) was added under nitrogen, at- 80°C to a stirred suspension of LDA (2.3 mmol) in dry THF (20ml), the mixture was stirred for 30 min more. After the addition of the carbonyl compound, the mixture was stirred at -80°C and the reaction was followed by T.L.C. (Kieselgel Merck 60 F_{254}). If necessary, the temperature was allowed to warm to 30°C (saturated carbonyl coumpounds). The mixture was poured into a solution of NH_4Cl (7ml), the aqueous phase extracted with ether (3 x 70 ml), the organic layer was dried (Na_2SO_4), evaporated (t<50°C), and the residue chromatographed over silicagel (30 parts).

8a: two diastereoisomers ^{1}H-NMR (CCl_4) δ : 0.80(s,3H); 0.85(s,3H); 1.12 (d,6H,J=6Hz); 1.30(s,3H); 1.35(s,3H); 1.40(s,3H); 1.45(s,3H); 1.60(d,2H,J=12Hz); 1.82-3(m,14H); 3.71(s,3H); 3.79(s,3H); 3.95(d,1H,J=6.75Hz); 4.13(d,1H,J=6Hz); 4.14(m,2H). MS EI M$^+$: 283.

8c: mp= 88°C ^{1}H-NMR (CCl_4) δ : 0.83(d,6H,J=7.5Hz); 0.84(s,3H); 1.02(d,1H,J=7.5Hz); 1.37(s,3H); 1.45(s,3H); 1.62(d,1H,J=10Hz); 2.00(m,2H); 2.30(m,1H); 2.57(m,2H); 3.28(m,2H); 3.77(s,3H); 3.78(m,1H); 4.17(d,1H,J=7.5Hz). MS EI M$^+$:311. Anal. Calcd for $C_{17}H_{29}NO_4$: C.65.59; H.9.32; N.4.50. Found : C.65.71; H.9.21; N.4.65.

11a: two isomers separated by column chromatography (Ether-hexane 5/1) Rf: 0.93. ^{1}H-NMR δ (CCl_4) : 0.85(s,3H); 1.33(s,3H); 1.40(s,3H); 1.50-3.00(m,11H); 3.66(s,3H); 3.70(s,3H); 4.23(t,1H,J=7Hz). Rf: 0.70. ^{1}H-NMR (CCl_4) δ : 0.82(s,3H); 1.33(s,3H); 1.43(s,3H); 1.50-3.00(m,11H); 3.63(s,3H); 3.71(s,3H); 4.25(t,1H,J=7.5Hz). MS EI M$^+$: 325.

12a$_1$: Rf: 0.69 (Ether-hexane 2/1). ^{1}H-NMR ($CDCl_3$) δ : 0.90(s,3H); 1.10(d,3H,J=6.5Hz);

1.32(t,3H,J=7.5Hz); 1.33(m,1H); 1.37(s,3H); 1.5(s,3H); 1.59(d,1H,J=10,5Hz); 1.7-3(m,8H); 3.75(s,3H); 4.13(q,2H,J=7.5Hz); 4.24(d,1H,J=4.5Hz). MS EI M$^+$: 353.

12b: Rf: 0.59 (Ether-hexane 4/1). ^{1}H-NMR (CCl_4) δ : 0.87(s,3H); 0.90(d,3H,J=7Hz); 1.23(t,3H,J=7.5Hz); 1.30(s,3H); 1.33(s,3H); 1.40(s,3H); 1.5(d,1H,J=9Hz); 1.70-3,00(m,9H); 3.67(s,3H); 4.07(q,2H,J=7.5Hz).

Hydrolysis of condensed Schiff bases

a) With acid

The purified Schiff base (1 mmol) was dissolved in THF (7 ml) and hydrolysed at 0° or 25°C with 15% citric acid (6 ml) during 80 h or 2 N HCl during 24 h, depending on the structure of the starting product. The solvent was evaporated at ambient temperature and the aqueous layer extracted with benzene ; the benzene layer containing the ketol was extracted with 15% aqueous citric acid. The combined aqueous layer was basified with sodium carbonate and extracted with diethyl ether. The ethereal extracts were dried (Na_2SO_4), concentrated and the residue purified by column chromatography on silica gel.

b) With hydroxylamine acetate

To a cold solution of NaOH (4,6 mmol) in methanol (50 ml) was added hydroxylamine hydrochloride (4.6 mmol) and acetic acid (4.6 mmol). A solution of Schiff base (4.5 mmol) in methanol (20 ml) was added and the mixture was stirred at ambient temperature for 20 h. The solution was concentrated, diluted with 10% hydrochloric acid, extracted with ether and the extracts were dried, the solvent evaporated and 2-hydroxy 3-pinanone oxime was obtained. The aqueous layer was basified and extracted with ether, the extracts dried and concentrated to give the aminoesters.

13a$_1$:$[\alpha]_D$= -22.4°(c=1.82, $CHCl_3$). ^{1}H-NMR(CCl_4) δ : 0.77(d,3H,J=6Hz); 1.40(t,3H,J=7Hz); 1.44(s,3H); 2.16(m,1H); 2.46(d,2H,J=10.5Hz); 3.50(d,1H,J=4Hz) ; 3.78(s,3H); 4.15 (q,2H,J=7Hz). Anal. Calcd. for $C_9H_{17}NO_4$: C,53.21; H,8.37; N,6.89. Found C,53.24; H,8.36; N,6.90.

13b: $[\alpha]_D$= -23.4°(c=2.13, $CHCl_3$). ^{1}H-NMR (CCl_4) δ : 0.80(d,3H,J=7Hz); 1.15(s,3H); 1.10(t,3H,J=7.5Hz); 1.30(s,2H); 1.67-2.50(m,3H); 3.60(m,3H); 4,00(q,2H,J=7.5Hz). MS. EI M$^+$: 217.

24: $[\alpha]_D$ = -36.5°(c=1.15,$CHCl_3$). ^{1}H-NMR (CCl_4) δ : 0.47(s,3H); 0.93(s,3H); 1.40(s,6H); 1.1-2.67(m,9H); 2.23(s,2H); 3.00(m,2H); 3.34(s,3H); 4.6(m,1H); 5.07(m,1H); 5.25(m,1H).

Synthesis of the lactone 7

To a cold solution of Boc-glycine (4.4 mmol), 4-dimethylaminopyridine (22mmol), and 2-hydroxy-3-pinanone (5 mmol) in CH_2Cl_2 (16 ml), was added N,N,dicylohexylcarbodiimide (4.8 mmol); the mixture was stirred at 0°C during 2 h and at ambient temperature during 12 h. The solvent was evaporated the residue treated by ethyl acetate to precipitate dicyclohexylurea which was filtered. The filtrate was washed with a saturated bicarbonate solution and water. The organic layer was dried (Na_2SO_4) and the solvent evaporated to furnish the ester (62%). ^{1}H-NMR (CCl_4) δ : 0.87(s,3H); 1.37(s,3H); 1.43(s,9H); 1.6(s,3H); 1.77-3.5(m,3H); 3.47(d,2H, J=5,5 Hz); 4.97(m,1H).

To this ester (5.1 mmol) dissolved in ether (2.6 ml) and cooled to -10°C, was added dropwise during 30 min a solution of paratoluene sulfonic acid (5.1 mmol) in ethanol (6 ml). The mixture was stirred at ambient temperature during 3 h. The solvent was evaporated

to furnish an oily residue which was dissolved in ethyl acetate and neutralised (pH = 7.2) with diisopropyl ethylamine to give the lactone (66%): mp = 130°C; $[\alpha]_D$ = +220° for (R) and -220° for (S) (c=2,00 $CHCl_3$). MS EI. M$^+$: 207.
^{1}H-NMR ($CDCl_3$) δ : 1.08(s,3H); 1.22(d,1H, J=12.5Hz); 1.43(s,3H); 1.64(s,3H); 2.19(m,2H); 2.4(m,1H); 2.83 (A'B' system, 2H, J=17.5Hz); 4.4(AB system, 2H , J=19.8Hz).
^{13}C-NMR ($CDCl_3$) δ : 22.25; 22.96; 27.50; 27.66; 36.96; 39.46; 39.75; 50.46; 51.67; 85.07; 170.09; 173.53. IR : 1750, 1660 cm^{-1}.

Reactions of the lactone

They were performed using the general procedure described for the Schiff bases, in this case only one equivalent of base (t-BuOK or LDA) was necessary.

26a: (60%). mp=72°C. ^{1}H-NMR ($CDCl_3$) δ : 1.06(s,3H); 1.20(d,1H,J=12,5Hz); 1.40(s,3H); 1.66(s,3H); 1.79(d,3H,J=7.5Hz); 2.18(m,2H); 2.82 (AB system, J=18Hz); 4.15(m,1H); MS EI M$^+$: 221.

27a: (14%). mp = 98°C. ^{1}H-NMR ($CDCl_3$) δ : 1.67(s,3H); 1.28(d,1H,J=12Hz) ; 1.48(s,3H); 1.63(s,3H); 1.73(s,3H); 1.78(s,3H); 2.2(m,2H); 2.53(m,1H); 3.02(AB system, J=18Hz). MS EI M$^+$:235. Anal. Calcd. for $C_{14}H_{21}NO_2$: C,71.11; H,8.99; N,5.73. Found: C,71.22; H,9.19; N,5.51.

27b:(45%). ^{1}H-NMR (CCl_4) δ : 0.38(s,3H); 0.83(s,3H); 1.17(s,3H); 0.61-1.9(m,4H); 2.60(m,2H); 3.28(m,2H); 3.32(m,2H); 7.23(s,5H); 7.33(s,5H). MS EI M$^+$: 387.

28a: (85%). mp= 59°C. ^{1}H-NMR (CCl_4) δ : 1.10(s,3H); 1.23(d,1H,J=12Hz); 1.43(s,3H); 1.5(s,3H); 2.01(d,3H,J=7.5Hz); 2.1-3.2(m,5H); 6.70(q,1H,J=7.5Hz). MS EI M$^+$: 233.

28b: (52%). mp= 92°C. ^{1}H-NMR (CCl_4) δ : 1.1(s,3H); 1.3(d,1H,J=12Hz); 1.4(s,3H); 1.55(s,3H); 2.00-3.20(m,5H); 7.27(s,1H); 7.30-8.30(m,5H). MS EI M$^+$: 295.

29b: (32%). ^{1}H-NMR (CCl_4) δ :for SYN 1,00(s,3H); 1.10(d,1H,J=12Hz); 1.35(s,3H); 1.5(s,3H); 1.70-3.10(m,5H); 3.70(m,1H); 4.16(m,1H); 5.35(d,1H,J=3Hz); 7.10-7.70(m,5H) and for ANTI 0.96(s,3H); 1.10(d,1H,J=12 Hz); 1.35(s,3H); 1.53(s,3H); 1.79-3.10(m,5H); 3.70(m,1H); 4.13(m,1H); 5.10(d,1H, J=7.5Hz); 7.10-7.70(m,5H). MS EI M$^+$: 313.

30: (60%). ^{1}H-NMR (CCl_4) δ : 1.13(s,3H); 1.33(m,6H); 1.45(s,3H); 1.20-2.80(m,5H); 2.20(m,2H); 3.21(m,2H); 3.51(m,1H); 4.31(m,1H); MS EI M$^+$: 265.

31: (25%). ^{1}H-NMR (CCl_4) δ : 1.04(s,3H); 1.38(s,3H); 1.53(s,3H); 2.18(s,6H); 1.8-2.60(m,4H); 2.83(m,2H).

32: (14%). ^{1}H-NMR (CCl_4) δ : 1.07(s,3H); 1.4(s,3H); 1.53(s,3H); 2.2(s,3H); 2.38(s,3H); 1.91-2.60(m,4H); 2.83(m,2H). IR : 1750, 1710, 1640 cm^{-1} . MS EI M$^+$: 291.

33: (53%). mp= 76°C. ^{1}H-NMR (CCl_4) δ : 1.13(s,3H); 1.5(s,3H); 1.55(s,3H); 1.01-2.15(m,2H); 2.19(s,3H); 2.50(s,3H); 4.37 (AB System, J=20 Hz); 6.43(m,1H);. IR : 3020, 1730, 1650. MS FAB (M+H$^+$): 250.

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