

Tetrahedron 55 (1999) 7601-7612

TETRAHEDRON

# Study of the Reaction of Imines Derived from (R)-Glyceraldehyde with Danishefsky's Diene.

Ramón Badorrey, Carlos Cativiela, María D. Díaz-de-Villegas and José A. Gálvez

Departamento de Química Orgánica, Facultad de Ciencias-Instituto de Ciencia de Materiales de Aragón, Universidad de Zaragoza-CSIC, E-50009 Zaragoza, Spain.

Received 21 January 1999; revised 1 April 1999; accepted 22 April 1999

#### Abstract

*N*-Benzylimines derived from conveniently protected (*R*)-glyceraldehyde underwent diastereoselective tandem Mannich-Michael reaction with Danishefsky's diene in the presence of Lewis acids. The temperature, catalyst and solvent dependence of the product ratio is described. Under zinc iodide-catalysed conditions in acetonitrile at -20 °C, double stereodifferentiation using (*R*)-2,3-di-O-benzylglyceraldehyde (*S*)-*N*- $\alpha$ -(methylbenzyl)imine as starting material was successful and the reaction occurred with good yield and complete diastereoselectivity. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Asymmetric synthesis, alkaloids, Diels-Alder reactions, nitrogen heterocycles.

#### Introduction

Nitrogen-containing heterocycles are abundant in nature and exhibit diverse and important biological properties [1–4]. One of the parent systems, the piperidine ring, is contained in numerous physiologically active compounds [5]. Accordingly, novel strategies for the stereoselective synthesis of enantiopure piperidines continue to receive considerable attention in the field of synthetic organic chemistry [6–8]. The hetero Diels–Alder reaction [9,10] of C–N double bonds with carbon dienes is probably the most efficient route to substituted piperidine derivatives reported to date. This reaction potentially allows the rapid construction of quite complex piperidines, functionalised or derivatised at various positions.

The development of methods to effect the hetero Diels-Alder reaction asymmetrically was, for a long time, restricted to only a few attempts. However, during the last decade this field has been the subject of intense research activity. The diastereoselectivity of this reaction has been investigated with chiral C-acylimines [11-15], chiral alkoxy imines [16-19], imines derived from chiral amino sugars [20,21], chiral amino esters [22,23] or chiral amino alcohols [24],

Corresponding author e-mail: loladiaz@posta.unizar.es, jagl@posta.unizar.es

chiral tricarbonylchromium complexes of substituted benzaldehyde imines [25,26], chiral 1,3butadienes [27,28] and chiral Lewis acids [29,30]. In some of these cases a cycloaddition pathway was suggested, while in others an addition-cyclization pathway (tandem Mannich-Michael reaction) was postulated.

Our recent work [31-35] has been directed towards the synthesis of highly functionalised amino acids from chiral imines derived from conveniently protected (R)-glyceraldehyde, a useful starting material from the chiral pool. As a result of that work we reported the asymmetric hetero Diels-Alder reaction of (R)-2,3-di-O-benzylglyceraldehyde N-benzylimine with Danishefsky's diene as a new approach to homochiral piperidine building blocks and its application to the synthesis of (R)-4-oxopipecolic acid [36]. We have now completed a more detailed study of that topic, including double induction using imines derived from (R)-2,3-di-Obenzylglyceraldehyde and a chiral amine, (R) or (S)- $\alpha$ -methylbenzylamine, as a starting material.

#### **Results and discussion**

As previously reported, imine 1, obtained from crude (R)-2,3-di-O-benzylglyceraldehyde and benzylamine, reacts in dichloromethane with 1-methoxy-3-trimethylsilyloxy-buta-1,3-diene (Danishefsky's diene) in the presence of 1.1 eq. of a Lewis acid catalyst to give the cyclic enaminones 2a and 2b. The yields of these reactions are low to acceptable depending on the Lewis acid and reaction temperature used. In general, good stereoselectivity is observed in favour of the diastereomer of R configuration as determined by correlation of the major diastereomer 2a with (R)-4-oxopipecolic acid [36] (Scheme 1, Table 1). From this study we concluded that the best catalyst system in dichloromethane is ZnI<sub>2</sub> at -40 °C (Table 1, entry 10).



#### Scheme 1

It is interesting to note that the sense of induction was not affected by the complexing properties of the Lewis acid employed [24,37]: both the chelating zinc salt and the aluminum or boron catalysts, which usually prefer tetracoordination, gave the same diastereomer 2a in excess. The stereochemical course of the reaction with non-chelating Lewis acids can be explained by assuming that the catalyst coordinates to the imine nitrogen and that the glyceraldehyde moiety preferentially adopts an anti-Felkin–Anh conformation A [38], in which the  $\alpha$ -C–OBn bond is oriented perpendicular to the imine group. The silyloxydiene should now preferentially attack from the *re*-side and give the observed major product. On the other hand,

the alkoxy imine 1 can behave as a bifunctional ligand towards chelating Lewis acids, such as  $ZnI_2$ , and if we assume that the Zn(II) coordinates with the nitrogen of the imine group and the adjacent oxygen to form a 5-membered ring intermediate **B** [39], this chelate should also be preferentially attacked from the *re*-side (Figure 1). These hypothetical models should be regarded as working hypotheses only, because the situation could be even more complicated due to the possibility of the imine undergoing *E* to *Z* isomerization [37,40].



#### Figure 1

#### Table 1.

Entry	Lewis acid	Temp. (°C)	Time (h)	Yield (%)	d.r.*
1	MgBr <sub>2</sub>	r.t.	24	_ b	-
2	Eu(fod)3	r.t.	24	- <sup>b</sup>	-
3	SnCl <sub>4</sub>	r.t.	0.25	- <sup>c</sup>	-
4	TiCl <sub>4</sub>	r.t.	0.25	- <sup>c</sup>	-
5	Et <sub>2</sub> AlCl	r.t.	0.25	16	82/18
6	BF <sub>3</sub> .Et <sub>2</sub> O	r.t.	0.25	15	80/20
7	$ZnI_2$	r.t.	0.25	16	85/15
8	Et <sub>2</sub> AlCl	-40	4	53	84/16
9	BF3.Et2O	-40	4	35	86/14
10	$ZnI_2$	40	4	67	91/9
11	Et <sub>2</sub> AICI	-78	10	52	82/18
12	BF3.Et2O	78	10	34	85/25
13	ZnI <sub>2</sub>	-78	10	67	90/10
14	SnCl <sub>4</sub>	-78	0.25	- <sup>c</sup>	-
15	TiCl <sub>4</sub>	-78	0.25	- <sup>c</sup>	-

Lewis acid and temperature influence on the reaction of 1 with Danishefsky's diene

<sup>a</sup> Determined from the spectra of the crude reaction mixture by integration of the <sup>1</sup>H-NMR absorptions of one of the ethylenic protons [major:  $\delta = 6.90$  (dd), minor:  $\delta = 7.02$  (dd)]. <sup>b</sup> A complex mixture of products was obtained. <sup>c</sup> Rapid decomposition was observed.

It has been reported that the diastereofacial selectivities of intermolecular hetero Diels-Alder reactions with alkoxy imines can be modified by the polarity of the reaction solvent [41]. We have therefore studied the influence of this variable on the stereochemical course of the reaction between (R)-2,3-di-O-benzylglyceraldehyde N-benzylimine and Danishefsky's diene catalysed by  $ZnI_2$  at -40 °C (Table 2).

#### Table 2.

Solvent influence on the reaction of 1 with Danishefsky's diene.

Entry	Solvent	catalyst (eq)	Yield (%) <sup>a</sup>	d.r. <sup>b</sup>
1	toluene	1.1	65	75/25
2	diethyl ether	1.1	30	76/24
3	tetrahydrofuran	1.1	63	80/20
4	dichloromethane	1.1	67	91/9
5	nitroethane	1.1	65	95/5
6	nitroethane	0.2	59	95/5
7	acetonitrile	1.1	88	95/5
8	acetonitrile	0.2	70	95/5
	h			

<sup>a</sup> Reaction time 4 h. <sup>b</sup> Determined from the spectra of the crude reaction mixture by integration of the <sup>1</sup>H-NMR absorptions of one of the ethylenic protons [major:  $\delta = 6.90$  (dd), minor:  $\delta = 7.02$  (dd)].

We observed that, with aprotic solvents, an increase in the solvent polarity led to an improvement in the diastereoselectivity of the reaction. The reasons for this phenomenon are not clear, although it may result from stabilisation of the chelated intermediate by polar solvents [41]. The best results were obtained when the reaction was carried out in nitroethane or acetonitrile (Table 2, entries 5, 6, 7 and 8). It is worth noting that the same yield and diastereoselectivity was obtained when a less than stoichiometric amount of  $ZnI_2$  (0.2 eq.) in nitroethane or acetonitrile was used as catalyst (Table 2, entries 6 and 8).

Although the asymmetric induction was high, removal of the undesired diastereomer 2b was difficult, and homochiral product 2a was hard to obtain. As an alternative, we therefore tested the reaction between the imine 3 – obtained from benzylamine and (R)-2,3-di-O-isopropylideneglyceraldehyde, previously purified by distillation [42] – and Danishefsky's diene under the experimental conditions described above. In this case we observed the formation of the corresponding diastereomeric enaminones 4a and 4b in excellent yield (93%) but, unfortunately, with very low stereoselectivity (d.r. 69/31). (Scheme 2). Due to this disappointing result we did not continue our studies on this starting compound.



Scheme 2

Finally, we studied the possibility of the use of imines, derived from chiral amines, as starting compounds to perform a double asymmetric induction process. With this aim in mind, crude (R)-2,3-di-O-benzylglyceraldehyde was treated with (S)- or (R)- $\alpha$ -methylbenzylamine to give the corresponding two imines 5 and 8 bearing two chiral centres. These imines were treated with Danishefsky's diene under the optimal reaction conditions previously developed; i.e. using acetonitrile as solvent in the presence of ZnI<sub>2</sub> as the Lewis acid. These imines proved to be less reactive than imine 1 and the processes had to be carried out at -20 rather than -40 °C in order to obtain acceptable yields. Cyclic enaminone 7 and a mixture of enaminones 9a and 9b were obtained in 75 and 73% yield from imines 5 and 8, respectively, after 4 h (Scheme 3). With the imine derived from (R)- $\alpha$ -methylbenzylamine, only modest asymmetric induction was observed (d.r. 64/36), however, with the imine derived from (S)- $\alpha$ -methylbenzylamine only a single diastereomer 7 could be detected by NMR.



The diastereoselectivities of these processes reflect the net directing effect of both stereogenic units present in the starting imines 5 and 8, i.e. 1,2-induction from the group at C-2 plus (matched pair) or minus (mismatched pair) 1,3-induction from the respective  $N-\alpha$ -methylbenzyl moiety.

The diastereomeric ratio of compounds 9a and 9b was determined from the spectra of the reaction mixture by integration of the <sup>1</sup>H-NMR absorptions of the methyl protons of the *N*- $\alpha$ -methylbenzyl moiety. The absolute configuration at the newly formed stereogenic carbon (C2) of compounds 7 and 9a was determined by conversion of these products to the known compound 15, which is an intermediate product in our previously reported [36] synthetic route to naturally occurring (*R*)-4-oxopipecolic acid, according to Scheme 4. Selective reduction of enaminone 7 or the mixture of 9a and 9b, with L-selectride<sup>®</sup> in THF at -78 °C gave, respectively, the 4-piperidinone 10 or a mixture of piperidones 12a and 12b from which the major compound 12a was isolated by column chromatography. The carbonyl groups of these compounds were protected with ethylene glycol in the presence of boron trifluoride diethyl etherate to obtain the corresponding ketals 11 and 13. Both compounds were separately converted into the *N*-BOC derivative 14 by selective hydrogenolytic debenzylation, followed

by protection of the piperidine ring nitrogen with di-*tert*-butyldicarbonate. Finally, removal of the O-benzyl groups by hydrogenolysis using palladium hydroxide as a catalyst gave the desired diol 15, whose absolute configuration had been previously correlated with that of (R)-4-oxopipecolic acid. Comparison of the specific rotation of compound 15,  $[\alpha]_D^{25} = +45.0$  (c = 1, CHCl3), with the known value<sup>#</sup> allowed us to unambiguously assign the R configuration to the newly formed stereogenic centre.



#### Scheme 4

The stereochemistry of the reaction between imine 7 (matched pair) and Danishefsky's diene in the presence of ZnI<sub>2</sub> as the Lewis acid can be understood in terms of the rational model C involving a 5-membered compacting chelate ( $\alpha$ -chelate) with the Zn atom (Figure 2). This model is similar to that proposed by Jäger *et al.* [43] to explain the stereochemical course of the addition of Grignard reagents to related imines. The N- $\alpha$ -methylbenzyl group is depicted in the conformation that is known to be preferred in related systems due to allylic 1,3-strain [44,45]. In the intermediate complex, both the benzyloxymethyl group in the chiral (R)-glyceraldehyde moiety and the phenyl group in the chiral amine would effectively block the *si*-face of the (E)imine 7<sup>1</sup> complexed with ZnI<sub>2</sub> and the diene would approach the *re*-face.

The mechanism of the reaction between imines and electron-rich dienes, like Danishefsky's diene, in the presence of a Lewis acid is a matter of debate and may vary with the structure of the reagents. This reaction is usually denoted as a [4+2] cycloaddition, but Kunz *et al.* [20]

<sup>&</sup>lt;sup>#</sup> For the same compound, correlated with (R)-oxopipecolic acid according to reference 14,  $[\alpha]D^{25} = +45.0$  (c=1, CHCl<sub>3</sub>)

<sup>&</sup>lt;sup>1</sup> The preferred E geometry of 7 could clearly be demonstrated by <sup>1</sup>H-NMR analysis and NOE experiments.

postulated a stepwise tandem Mannich-Michael process. In the reaction of imine 5 with Danishefsky's diene the intermediate compound 6 (Scheme 3), which resulted from addition of the silyl enol ether moiety of the diene, was detected. This Mannich intermediate was then treated with 1N HCl and Michael addition followed by elimination of methanol to afford the cyclic enaminone 7 occurred immediately. Moreover, when dilute HCl was used for the work-up prior to chromatographic separation, only enaminone 7 was detected. From these results we infer that a tandem Mannich-Michael sequence occurred when N-benzylimines derived from conveniently protected (R)-glyceraldehyde were used as reagents in the reaction with Danishefsky's diene.



#### Conclusion

In summary: the optimal conditions to carry out the reaction between N-benzylimines derived from (R)-2,3-di-O-benzylglyceraldehyde and Danishefsky's diene are to work at low temperature, use acetonitrile as solvent and ZnI<sub>2</sub> as Lewis acid. Under these conditions, double stereodifferentiation using (S)- $\alpha$ -methylbenzylamine as chiral auxiliary occurs and the reaction takes place with complete control of stereochemistry. The resulting enaminone provides a potential scaffold for other useful synthetic transformations [6] that can presumably be used to prepare analogues of a wide variety of alkaloids containing the piperidine ring as well as cyclic amino acid derivatives. Research into this area is underway and will be reported in due course.

#### Experimental

General. All reagents were purchased from the Aldrich Chemical Co. and used as received. (R)-2,3-di-O-benzylglyceraldehyde N-benzylimine (R)-2,3-di-O-isopropylidene (1), glyceraldehyde N-benzylimine (3), (R)-2,3-di-O-benzylglyceräldehyde (S)-αmethylbenzylimine (5) and (R)-2,3-di-O-benzylglyceraldehyde (R)- $\alpha$ -methylbenzylimine (8) were obtained according to our previously described procedure for the synthesis of imine 1 [32]. Melting points were determined with a Büchi 510 capillary melting point apparatus and are uncorrected. IR spectra were recorded using a Perkin-Elmer 1600 FT-IR infrared spectrophotometer. <sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectra were recorded on a Varian Unity-300 or a Bruker ARX-300 spectrometer in deuterochloroform using the residual solvent signal as the internal standard; chemical shifts ( $\delta$ ) are given in parts per million and the coupling constants (J) in Hertz. The <sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectra of N-BOC protected compounds were not conclusive at room temperature due to the presence of a dynamic equilibrium between rotamers caused by the restricted rotation of the nitrogen-carbon bond of the urethane group. In order to

overcome this problem NMR spectra of these compounds were run at 333 K. Optical rotations were measured on a Perkin–Elmer 241-C polarimeter at 25 °C. Elemental analyses were performed using a Perkin–Elmer 200 C,H,N,S elemental analyser. Mass spectra (MS) were determined on a high resolution VG-autospec spectrometer. TLC was performed on Merck 60  $F_{240}$  precoated silica gel polyester plates and products were visualised by UV light (254 nm) and anisaldehyde/sulphuric acid/ethanol (2:1:100). Column chromatography was performed using silica gel (Kiesegel 60).

## General procedure for Lewis-Acid Catalysed reaction of imines 1 and 3 with Danishefsky's diene

To a cooled suspension of the Lewis acid (3.3 mmol) in the selected dry solvent (35 ml) under argon at the corresponding temperature was added a solution of the imine 1 or 3 (3 mmol) in the same dry solvent (15 ml) and the mixture was stirred for 5 min. Commercial Danishefsky's diene (95%) (652 mg, 3.6 mmol) was added in one portion *via* syringe. After completion of the reaction, the dark yellow solution was poured into saturated aqueous NaHCO<sub>3</sub> and extracted with dichloromethane. The combined organic phases were washed with HCl 1N and brine, dried over MgSO<sub>4</sub> and the solvent evaporated *in vacuo*. The resulting dark-coloured oil was purified by silica gel column chromatography (1st ether, 2nd ethyl acetate as eluents) to afford the corresponding adducts as a mixture of diastereomers. For yields and stereoselectivities see Tables 1 and 2, as well as the text corresponding to Scheme 2.

(R)-N-Benzyl-2-[(S)-1,2-dibenzyloxyethyl]-5,6-dihydro-4-pyridone (2a)

From a 95/5 mixture of diastereomers: Yellowish oil, IR (neat) 1635, 1585 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  2.17 (bd, 1H, J = 16.8 Hz); 2.66 (dd, 1H, J = 7.2 Hz, J = 16.8 Hz); 3.47 (dd, 1H, J = 3.6 Hz, J = 11.1 Hz); 3.67 (dd, 1H, J = 2.7 Hz, J = 11.1 Hz); 3.72–3.80 (m, 1H); 4.11 (ddd, 1H, J = 2.7 Hz, J = 3.6 Hz, J = 8.4 Hz); 4.32 (d, 1H, J = 15.3 Hz); 4.46 (d, 1H, J = 11.7 Hz); 4.49 (s, 2H); 4.62 (d, 1H, J = 15.3 Hz); 4.67 (d, 1H, J = 11.7 Hz); 4.85 (bd, 1H, J = 7.2 Hz); 6.90 (dd, 1H, J = 1.2 Hz, J = 7.2 Hz); 7.15–7.37 (m, 15H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  37.3; 56.7; 60.4; 68.1; 72.6; 73.5; 75.8; 97.0; 127.4; 127.7; 127.8; 128.0; 128.0; 128.2; 128.4; 128.4; 128.9; 137.3; 137.7; 137.8; 152.7; 190.0; HRMS (EI): m/z = 427.2155 (M<sup>+</sup> calcd. for C<sub>28</sub>H<sub>29</sub>NO<sub>3</sub>: 427.2147).

(R)-N-Benzyl-2-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]-5,6-dihydro-4-pyridone (4a)

From a 69/31 mixture of diastereomers 4a/4b: Yellowish oil, <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  1.32 (s, 3H); 1.42 (s, 3H); 1.95 (ddd, 1H, J = 1.3 Hz, J = 1.3 Hz, J = 17.0 Hz); 2.75 (dd, 1H, J = 7.3 Hz, J = 17.0 Hz); 3.36–3.43 (m, 1H); 3.48 (dd, 1H, J = 6.6 Hz, J = 8.6 Hz); 4.04 (dd, 1H, J = 6.6 Hz, J = 8.6 Hz); 4.49 (d, 1H, J = 15.1 Hz); 4.69 (ddd, 1H, J = 4.5 Hz, J = 6.0 Hz, J = 7.5 Hz); 4.76 (d, 1H, J = 15.1 Hz); 4.94 (bd, 1H, J = 7.5 Hz); 7.11 (dd, 1H, J = 1.1 Hz, J = 7.5 Hz); 7.25–7.40 (m, 5H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  25.3; 26.7; 37.3; 58.9; 60.0; 66.7; 73.4; 96.9; 109.9; 127.6; 128.2; 129.0; 136.9; 152.9; 189.0; HRMS of the 69/31 mixture of diastereomers (EI): m/z = 287.1516 (M<sup>+</sup> calcd. for C<sub>17</sub>H<sub>21</sub>NO<sub>3</sub>: 287.1521).

(S)-N-Benzyl-2-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]-5,6-dihydro-4-pyridone (4b)

From a 69/31 mixture of diastereomers 4a/4b: Yellowish oil ,<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  1.31 (s, 3H); 1.39 (s, 3H); 2.38 (ddd, 1H, J = 0.9 Hz, J = 2.5 Hz, J = 16.8 Hz); 2.68 (dd, 1H, J =

8.2 Hz, J = 16.8 Hz); 3.63–3.70 (m, 1H); 3.73 (dd, 1H, J = 7.5 Hz, J = 8.5 Hz); 4.01 (dd, 1H, J = 6.0 Hz, J = 8.5 Hz); 4.22 (ddd, 1H, J = 4.5 Hz, J = 6.0 Hz, J = 7.5 Hz); 4.47 (d, 1H, J = 15.3 Hz); 4.57 (d, 1H, J = 15.3 Hz); 4.94 (bd, 1H, J = 7.5 Hz); 7.13 (dd, 1H, J = 0.9 Hz, J = 7.5 Hz); 7.25–7.40 (m, 5H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  25.3; 26.3; 36.3; 59.2; 60.4; 66.0; 73.4; 98.0; 109.0; 127.3; 128.3; 129.1; 136.6; 153.5; 189.7; HRMS of the 69/31 mixture of diastereomers (EI): m/z = 287.1516 (M<sup>+</sup> calcd. for C<sub>17</sub>H<sub>21</sub>NO<sub>3</sub>: 287.1521).

### General procedure for Lewis-Acid Catalysed reaction of imines 5 and 8 with Danishefsky's diene

To a suspension of ZnI<sub>2</sub> (1.05 g, 3.3 mmol) in dry acetonitrile (35 ml), cooled under argon at -20 °C, was added a solution of the crude imine 5 or 8 (1.12 g, 3 mmol) in dry acetonitrile (15 ml) and the mixture was stirred for 5 min. Commercial Danishefsky's diene (95%) (652 mg, 3.6 mmol) was added in one portion *via* syringe. After 4 hours at -20 °C, the dark yellow solution was poured into saturated aqueous NaHCO<sub>3</sub> and extracted with dichloromethane. The combined organic phases were washed with 1N HCl and brine, dried over MgSO<sub>4</sub> and the solvent evaporated *in vacuo*. The resulting dark-coloured oil was purified by silica gel column chromatography (1st ether, 2nd ethyl acetate as eluents) to yield 0.99 g (75% yield) of 7 or 0.96 g (73% yield) of **9a** and **9b** as a 64/36 mixture of diastereomers, respectively.

(R)-N-[(S)- $\alpha$ -Methylbenzyl]-2-[(S)-1,2-dibenzyloxyethyl]-5,6-dihydro-4-pyridone (7)

Yellowish oil;  $[\alpha]_D^{20}$ = +84.0 (*c* = 1 in CHCl<sub>3</sub>); IR (neat) 1639, 1581 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  1.57 (d, 3H, *J* = 6.8 Hz); 2.36 (bd, 1H, *J* = 16.9 Hz); 2.73 (dd, 1H, *J* = 6.4 Hz, *J* = 16.9 Hz); 3.51 (dd, 1H, *J* = 3.1 Hz, *J* = 11.1 Hz); 3.73 (dd, 1H, *J* = 1.9 Hz, *J* = 11.1 Hz); 3.96–4.10 (m, 2H); 4.47 (d, 1H, *J* = 11.7 Hz); 4.48 (d, 1H, *J* = 12 Hz); 4.54 (d, 1H, *J* = 12 Hz); 4.65 (d, 1H, *J* = 11.7 Hz); 4.70 (q, 1H, *J* = 6.8 Hz); 4.78 (d, 1H, *J* = 7.4 Hz); 6.71 (d, 1H, *J* = 7.4 Hz); 7.20–7.40 (m, 15H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  20.2; 37.3; 56.7; 62.7; 67.7; 72.2; 73.5; 76.4; 97.5; 127.8; 127.8; 127.9; 128.0; 128.3; 128.4; 128.8; 137.8; 138.0; 139.2; 149.8; 190.4; HRMS (EI): *m/z* = 441.2306 (M<sup>+</sup> calcd. for C<sub>29</sub>H<sub>31</sub>NO<sub>3</sub>: 441.2304).

(R)- $N-[(R)-\alpha$ -Methylbenzyl]-2-[(S)-1,2-dibenzyloxyethyl]-5,6-dihydro-4-pyridone (**9a**)

From a 64/36 mixture of diastereomers **9a/9b**: Yellowish oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) from the 64/36 mixture of diastereomers  $\delta$  1.40 (d, 3H, J = 6.9 Hz); 2.12 (bd, 1H, J = 17.2 Hz); 2.57 (dd, 1H, J = 7 Hz, J = 17.2 Hz); 3.44 (dd, 1H, J = 3.6 Hz, J = 11.1 Hz); 3.60–3.70 (m, 2H); 4.05–4.12 (m, 1H); 4.46 (d, 1H, J = 11.7 Hz); 4.48 (s, 2H); 4.64 (d, 1H, J = 11.7 Hz); 4.76 (q, 1H, J = 6.9 Hz); 4.98 (d, 1H, J = 7.5 Hz); 6.74 (d, 1H, J = 7.5 Hz); 7.15–7.45 (m, 15H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  21.2; 36.8; 57.7; 63.3; 67.9; 72.7; 73.4; 76.0; 96.5; 125.7; 127.6; 127.6; 127.7; 127.8; 128.0; 128.3; 128.4; 128.8; 137.7; 137.8; 143.4; 147.3; 190.1; HRMS (EI): m/z = 441.2312 (M<sup>+</sup> calcd. for C<sub>29</sub>H<sub>31</sub>NO<sub>3</sub>: 441.2304).

General procedure for reduction of (R)-N-[(S)- $\alpha$ -methylbenzyl]-2-[(S)-1,2-dibenzyloxyethyl]-5,6-dihydro-4-pyridone (7) or the mixture of (R) and (S)-N-[(R)- $\alpha$ -methylbenzyl]-2-[(S)-1,2dibenzyloxyethyl]-5,6-dihydro-4-pyridones (**9a**) and (**9b**)

To a solution of enantiomerically pure compound 7 or to a solution of a diastereomeric mixture (d.r. 64/36) of **9a** and **9b** (0.88 g, 2 mmol) in dry THF (30 ml) was added dropwise L-selectride<sup>®</sup> 1M (2.2 ml, 2.2 mmol) at -78 °C under an argon atmosphere. After being stirred for

72 h at that temperature, the reaction mixture was quenched with saturated aqueous NH4Cl and extracted with ether. The combined organic phases were washed with brine, dried over MgSO4 and the solvent was evaporated *in vacuo*. The crude product was purified by silica gel column chromatography (ether/hexane 1/2 as eluent) to give 0.75 g (85% yield) of 10 or 0.50 g (57% yield) of 12a.

### (R)-N-[(S)- $\alpha$ -Methylbenzyl]-2-[(S)-1,2-dibenzyloxyethyl]-4-pyridone (10)

Colourless oil;  $[\alpha]_D^{20} = +0.8$  (c = 1 in CHCl<sub>3</sub>); IR (neat) 1712 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  1.35 (d, 3H, J = 6.6 Hz); 2.12–2.21 (m, 2H); 2.32 (ddd, 1H, J = 6 Hz, J = 9.9 Hz, J = 16.6 Hz); 2.60 (dd, 1H, J = 6.6 Hz, J = 15 Hz); 3.04–3.20 (m, 1H); 3.22–3.30 (m, 1H); 3.34 (ddd, 1H, J = 4.2 Hz, J = 9.9 Hz, J = 13.8 Hz); 3.53–3.61 (m, 1H); 3.62–3.72 (m, 2H); 4.00 (q, 1H, J = 6.6 Hz); 4.45 (d, 1H, J = 12.3 Hz); 4.50 (d, 1H, J = 12.3 Hz); 4.55 (d, 1H, J = 11.4 Hz); 4.63 (d, 1H, J = 11.4 Hz); 7.10–7.40 (m, 15H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  19.2; 38.8; 40.0; 43.3; 58.5; 58.6; 71.8; 73.3; 73.5; 81.2; 127.1; 127.4; 127.5; 127.6; 128.1; 128.2; 128.3; 128.4; 138.2; 138.3; 145.1; 209.0; HRMS (FAB+): m/z = 443.2453 (M<sup>+</sup> calcd. for C<sub>29</sub>H<sub>33</sub>NO<sub>3</sub>: 443.2460).

(R)-N-[(R)- $\alpha$ -Methylbenzyl]-2-[(S)-1,2-dibenzyloxyethyl]-4-pyridone (12a)

Colourless oil; IR (neat) 1708 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  1.34 (d, 3H, *J* = 6.6 Hz); 1.98 (bd, 1H, *J* = 15.5 Hz); 2.19 (bd, 1H, *J* = 15 Hz); 2.33 (ddd, 1H, *J* = 6.6 Hz, *J* = 10.8 Hz, *J* = 15.5 Hz); 2.50 (dd, 1H, *J* = 6.9 Hz, *J* = 15 Hz); 2.68–2.78 (m, 1H); 3.30 (ddd, 1H, *J* = 3.9 Hz, *J* = 10.8 Hz, *J* = 14.7 Hz); 3.70–3.74 (m, 2H); 3.76–3.81 (m, 1H); 3.88 (dd, 1H, *J* = 4.8 Hz, *J* = 8.7 Hz); 4.01 (q, 1H, *J* = 6.6 Hz); 4.56 (s, 4H); 7.10–7.50 (m, 15H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  20.5; 39.1; 39.4; 43.8; 57.8; 59.6; 70.6; 72.6; 73.4; 78.4; 127.1; 127.5; 127.6; 127.7; 127.8; 128.2; 128.3; 128.4; 128.5; 138.1; 138.2; 145.3; 209.6; HRMS (FAB+): *m*/*z* = 443.2451 (M+ calcd. for C<sub>29</sub>H<sub>33</sub>NO<sub>3</sub>: 443.2460).

General procedure for the synthesis of (R)-N- $[(S)-\alpha$ -methylbenzyl]-2-[(S)-1,2-dibenzyloxyethyl]-4-(1,3-dioxolane-2-yl)piperidine (11) and (R)-N- $[(R)-\alpha$ -methylbenzyl]-2-[(S)-1,2-dibenzyloxyethyl]-4-(1,3-dioxolane-2-yl)piperidine (13)

A solution of 10 or 12a (443 mg, 1 mmol) in dry chloroform (10 ml) and ethylene glycol (2 ml) was cooled to -10 °C. To this solution, boron trifluoride etherate (0.5 ml) was added slowly *via* a syringe. The reaction mixture was allowed to stir for 3 h at room temperature, poured into water (10 ml), and extracted with dichloromethane. The organic layer was successively washed with 10% sodium bicarbonate, water and saturated brine solution. After drying over MgSO4, the solvent was removed *in vacuo*. The crude product was purified by silica gel column (ether/hexane 1/2) to yield 400 mg (82% yield) of 11 or 415 mg (85% yield) of 13.

(*R*)-*N*-[(*S*)- $\alpha$ -Methylbenzyl]-2-[(*S*)-1,2-dibenzyloxyethyl]-4-(1,3-dioxolane-2-yl)piperidine (11) Colourless oil; IR (neat) 950 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  1.23 (d, 3H, *J* = 6.6 Hz); 1.40–1.53 (m, 2H); 2.00–2.10 (m, 1H); 2.29–2.51 (m, 2H); 3.07 (ddd, 1H, *J* = 3.0 Hz, *J* = 5.1 Hz, *J* = 10.8 Hz); 3.63 (dd, 1H, *J* = 7.2 Hz, *J* = 10.5 Hz); 3.81–3.93 (m, 5H); 3.99 (dd, 1H, *J* = 1.5 Hz, *J* = 10.8 Hz); 4.08–4.19 (m, 2H); 4.49 (d, 1H, *J* = 12.1 Hz); 4.56 (d, 1H, *J* = 12.1 Hz); 4.71 (d, 1H, *J* = 12 Hz); 4.78 (d, 1H, *J* = 12 Hz); 7.10–7.42 (m, 15H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  10.2; 35.1; 42.3; 54.8; 56.6; 64.2; 71.3; 72.7; 73.7; 77.8; 108.0; 126.4; 127.4; 127.5; 127.7; 127.8; 128.0; 128.2; 128.3; 138.7; 139.3; 144.4; HRMS (FAB+): m/z = 488.2821 (MH+ calcd. for C<sub>31</sub>H<sub>38</sub>NO<sub>4</sub>: 488.2800).

(*R*)-*N*-[(*R*)- $\alpha$ -Methylbenzyl]-2-[(*S*)-1,2-dibenzyloxyethyl]-4-(1,3-dioxolane-2-yl)piperidine (**13**) Colourless oil; IR (neat) 952 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  1.30 (d, 3H, *J* = 6.9 Hz); 1.45–1.70 (m, 2H); 1.87–1.97 (m, 1H); 2.10–2.24 (m, 1H); 2.85–3.00 (m, 2H); 3.51 (dd, 1H, *J* = 6.7 Hz, *J* = 10.6 Hz); 3.75–3.93 (m, 6H); 4.00 (dd, 1H, *J* = 6.6 Hz, *J* = 13.5 Hz); 4.25–4.35 (m, 1H); 4.57 (s, 2H); 4.73 (s, 2H); 7.00–7.55 (m, 15H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  20.1; 33.8; 34.0; 42.7; 55.8; 56.4; 64.0; 64.1; 70.9; 72.3; 73.4; 77.4; 107.6; 126.8; 127.4; 127.5; 127.7; 127.8; 127.9; 128.0; 128.2; 128.3; 138.6; 139.1; 141.2; HRMS (FAB+): *m*/*z* = 488.2809 (MH+ calcd. for C<sub>31</sub>H<sub>38</sub>NO4: 488.2800).

(R)-N-tert-Butoxycarbonyl-2-[(S)-1,2-dibenzyloxyethyl]-4-(1,3-dioxolane-2-yl)piperidine (14) To a stirred suspension of 20% Pd(OH)<sub>2</sub>/C (100 mg) in absolute ethanol (10 ml) under H<sub>2</sub> at 1 atm, was added a solution of 11 or 13 (487 mg, 1 mmol) in absolute ethanol (10 ml). The reaction was stirred for 3 h at room temperature, filtered and the solvent evaporated *in vacuo*. The resulting N-debenzylated product, diisopropylethylamine (13 mg, 0,1 mmol) and di-tertbutyl dicarbonate (546 mg, 2.5 mmol) were dissolved in dry THF (25 ml). After being stirred at 50 °C for 20 h the reaction mixture was treated with ether (25 ml), washed with 1M aqueous KHSO4, dried over anhydrous MgSO4, filtered and concentrated *in vacuo* to afford a crude product which was purified by flash chromatography (ether/hexane 1/1) to give compound 14 (338 mg, 70% from 11 or 318 mg, 66% from 13) as a colourless oil.

Oil; IR (nujol) 1691, 946 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  1.40 (s, 9H); 1.50–1.80 (m, 4H); 2.73 (ddd, 1H, *J* = 3.6 Hz, *J* = 12.3 Hz, *J* = 13.8 Hz); 3.55 (dd, 1H, *J* = 4.3 Hz, *J* = 11 Hz); 3.60–3.85 (m, 7H); 4.03 (ddd, 1H, *J* = 2.7 Hz, *J* = 4.1 Hz, *J* = 9.9 Hz); 4.47 (d, 1H, *J* = 11.7 Hz); 4.48 (d, 1H, *J* = 12.3 Hz); 4.63 (d, 1H, *J* = 12.3 Hz); 4.69 (d, 1H, *J* = 11.7 Hz); 7.10–7.45 (m, 10H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  28.4; 34.5; 34.8; 39.8; 52.0; 64.0; 64.5; 70.1; 72.3; 73.3; 75.8; 79.4; 107.3; 127.3; 127.5; 127.8; 127.9; 128.1; 128.3; 138.4; 138.9; 155.2; HRMS (FAB+): *m/z* = 484.2705 (MH<sup>+</sup> calcd. for C<sub>28</sub>H<sub>38</sub>NO<sub>6</sub>: 484.2699).

(R)-N-tert-Butoxycarbonyl-2-[(S)-1,2-dihydroxyethyl]-4-(1,3-dioxolane-2-yl)piperidine (15) A solution of 14 (241 mg, 0.5 mmol) in ethanol (15 ml) was hydrogenated with 20%  $Pd(OH)_2/C$  (80 mg) as a catalyst at room temperature and atmospheric pressure for 24 h. When the reaction was complete the catalyst was removed by filtration and the filtrate evaporate to dryness. The resulting crude material was purified by flash chromatography (ethyl acetate) to afford 139 mg (92% yield) of 15 as a white solid.

M. p. = 117 °C;  $[\alpha]_D^{20}$  = +45.0 (*c* = 1 in CHCl<sub>3</sub>); IR (nujol) 1717 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  1.43 (s, 9H); 1.60–1.71 (m, 2H); 1.77 (bd, 1H, *J* = 14.2 Hz); 3.87 (dd, 1H, *J* = 7.3 Hz, *J* = 14.2 Hz); 3.18–3.37 (m, 1H); 3.45–3.60 (m, 3H); 3.80–4.10 (m, 7H); 4.30–4.45 (m, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  28.3; 34.4; 36.1; 39.4; 51.6; 63.7; 64.2; 64.8; 74.0; 80.6; 107.1; 156.3; HRMS (EI): m/z = 242.1385 (M<sup>+</sup>-C<sub>2</sub>H<sub>5</sub>O<sub>2</sub> calcd. for C<sub>12</sub>H<sub>20</sub>NO<sub>4</sub>: 242.1392). Anal Calc. for C<sub>14</sub>H<sub>25</sub>NO<sub>6</sub>: C, 55.43; H, 8.31; N, 4.52. Found: C, 55.47; H, 8.25; N, 4.47.

Acknowledgement: This work was made possible by the generous financial support of the Dirección General de Investigación Científica y Técnica, project number PB94-0098. R. B. would like to express his gratitude to the Ministerio de Educación y Cultura for a grant.

#### References

- [1] Strunz, G.M.; Findlay, J.A., in "The Alkaloids", Academic Press, New York, 1986, Vol. 26, pg. 89.
- [2] Numata, A.; Ibuka, T.; In "The Alkaloids", Academic Press, New York, 1987, Vol. 31, pg. 193.
- [3] Daly, J.W.; Garaffo, H.M.; Spande, T.F. in "The Alkaloids", Academic Press, San Diego, 1993, Vol. 43, pg. 185.
- [4] Pinder, A.R. Nat. Prod. Rep. 1993, 10, 491.
- [5] Southon, I.W.; Buckingham, J., "Dictionary of Alkaloids", Chapman and Hall, London 1989.
- [6] Comins, D.L.; Joseph, S.P.; Goehring, R.R. J. Am. Chem. Soc. 1994, 116, 4719-4728.
- [7] Laschat, S. Liebigs Ann. 1997, 1-11.
- [8] Bailey, P.D.; Millwood, P.A.; Smith, P.D. Chem. Commun. 1998, 633-640.
- [9] Waldmann, H. Synthesis 1994, 535-551.
- [10] Tietze, L.F., Kettschau, G. Top. Curr. Chem. 1997, 189, 1-120.
- [11] Hamley, P.; Helmchen, G.; Holmes, A.B.; Marshall, D.R.; Mackinnon, J.W.M.; Smith, D.F.; Ziller, J.W. J. Chem. Soc., Chem. Commun. 1992, 786-788.
- [12] Abraham H.; Stella, L. Tetrahedron 1992, 48, 9707–9718.
- [13] MacFarlane, A.K.; Thomas, G.; Whiting, A. Tetrahedron Lett. 1993, 34, 2379-2382.
- [14] Bailey, P.D.; Londesbrough, D.J.; Hancox, T.C.; Heffernan, J.D.; Holmes, A.B. J. Chem. Soc., Chem. Commun. 1994, 2543– 2344
- [15] Ager, D.; Cooper, N.; Cox, G.G.; Garro-Helion, F.; Harwood, L.M. Tetrahedron: Asymmetry 1996, 7, 2563–2566.
- [16] Midland, M.M.; Koops, R.W. J. Org. Chem. 1992, 57, 1158-1161 and references herein.
- [17] Ishimaru, K.; Yamamoto, Y.; Akiba, K. Tetrahedron 1997, 53, 5423-5432 and references herein.
- [18] Herczegh, P.; Kovacs, I.; Erdösi, G.; Varga, T.; Agócs, A.; Szilágyi, L.; Sztaricskai, F.; Bereceibar, A.; Lukacs, G.; Olesker, A. Pure Appl. Chem. 1997, 69, 519–524 and references herein.
- [19] Yu, L.; Li, J.; Ramirez, J.; Chem, D.; Wang, P.G. J. Org. Chem. 1997, 62, 903-907.
- [20] Kunz, H.; Pfrengle, W. Angew. Chem. Int. Ed. Engl. 1989, 28, 1067-1069.
- [21] Weymann, W.; Pfrengle, W.; Schollmeyer, D.; Kunz, H. Synthesis 1997, 1151-1160.
- [22] Larsen, S.D.; Grieco, P.A. J. Am. Chem. Soc. 1985, 107, 1768-1769.
- [23] Waldmann, H. Synlett 1995, 133-141. and references therein.
- [24] Devine, P.N.; Reilly, M.; Oh, T. Tetrahedron Lett. 1993, 34, 5827-5830.
- [25] Baldoli, C.; Del Buttero, P.; Di Ciolo, M.; Maiorana, S.; Papagni, A. Synlett 1996, 258-260.
- [26] Kündig, E.P.; Xu, L.H.; Romaens, P.; Bernardinelli, G. Synlett 1996, 270-272.
- [27] Hamada, T.; Zenkoh, T.; Sato, H.; Yonemitsu, O. Tetrahedron Lett. 1991, 32, 1649-1652.
- [28] Barluenga, J.; Aznar, F.; Ribas, C.; Valdés, C.; Fernandez, M.; Cabal, M.P.; Trujillo, J. Chem. Eur. J. 1996, 2, 805-811.
- [29] Ishihara, K.; Miyata, M.; Hattori, K.; Tada, T.; Yamamoto, H. J. Am. chem. Soc. 1994, 116, 10520-10524 and references therein.
- [30] Kobayashi, S.; Komiyama, S.; Ishitami, H. Angew. Chem. Int. Ed. 1998, 37, 979–989.
- [31] Cativiela, C.; Díaz-de-Villegas, M.D.; Gálvez, J.A. Tetrahedron Lett. 1995, 36, 2859-2860.
- [32] Cativiela, C.; Díaz-de-Villegas, M.D.; Gálvez, J.A. Tetrahedron: Asymmetry 1996, 7, 529-536.
- [33] Cativiela, C.; Díaz-de-Villegas, M.D.; Gálvez, J.A.; García, J.I. Tetrahedron 1996, 52, 9563-9574.
- [34] Badorrey, R.; Cativiela, C.; Díaz-de-Villegas, M.D.; Gálvez, J.A. Tetrahedron 1997, 53, 1411-1416.
- [35] Badorrey, R.; Cativiela, C.; Díaz-de-Villegas, M.D.; Gálvez, J.A. Synthesis 1997, 747-749.
- [36] Badorrey, R.; Cativiela, C.; Díaz-de-Villegas, M.D.; Gálvez, J.A. Tetrahedron Lett. 1997, 38, 2547-2550.
- [37] Waldmann, H.; Braun, M. J. Org. Chem. 1992, 57, 4444-4451.
- [38] Anh, N.T. Top. Curr. Chem. 1980, 88, 145.
- [39] Reetz, M.T. Acc. Chem. Res. 1993, 26, 462-468.
- [40] see ref 17 in Alvaro, G.; Savoia, D.; Valentinetti, M.R. Tetrahedron 1996, 52, 12571-12586.
- [41] Ishimaru, K; Watanabe, K.; Yamamoto, Y.; Akiba, K. Synlett 1994, 495-498.
- [42] Schmid, C.R.; Bryant, J.D.; Dowlatzedah, M.; Phillips, J.L.; Prather, D.E.; Schantz, R.D.; Sear, N.L.; Vianco, C.S. J. Org. Chem 1991, 56, 4056–4058.
- [43] Veith, V.; Leurs, S.; Jäger, V. Chem. Commun. 1996, 329-330.
- [44] Klein, M.; Wingen, V.; Buss, V. J. Am. Chem. Soc. 1987, 109, 6486-6492.
- [45] Hoffmann R.W. Chem. Rev. 1989, 89, 1841-1860.