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## N-Boc 2-Acyloxazolidines: Useful Precursors to Enantiopure 1,2-Diols via Highly Diastereoselective Nucleophilic Additions

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Abstract: N-Boc 2-Acyloxazolidines were synthesized from norephedrine and phenylglycinol. This preparation involves: (i) a transformation of the above  $\beta$ -amino alcohols into N-Boc 2-ethoxycarbonyloxazolidines, (ii) the formation of the corresponding Weinreb amides and, (iii) a reaction between these amides and organometallic reagents. Such diastereomerically pure heterocycles react cleanly with various nucleophilic reagents (Grignard reagents, sodium borohydride and allylsilane) to afford the corresponding alcohols. Treatment of these hydroxyoxazolidines with trifluoro acetic acid, followed by hydrolysis and reduction of the intermediate a-hydroxy aldehydes afforded 1,2-diols. The overall transformation exhibited in most cases a complete diastereoselectivity which can be explained by a chelated model for the nucleophilic addition.

Chiral heterocycles have attracted substantial interest as auxiliaries for asymmetric induction in nucleophilic additions onto carbonyl moieties. This was initiated by the pioneering work of Eliel who made use in the early 1970s of 1,3-oxathianes derived from (+)-pulegone.<sup>1</sup> Since then, other chiral adjuvants have been reported: proline-derived diamines,<sup>2</sup> prolinol,<sup>3</sup> 1,3-diols,<sup>4</sup> as well as 1,2-diols<sup>5</sup> and 1,2-diamines<sup>6</sup> having a C<sub>2</sub> axis of symmetry. They are exploited to control the creation of a new stereogenic center from an connected prochiral C=O or C=N moiety.

Likewise, 1,2-amino alcohols, specially those derived from ephedrine and its analogs, have emerged as very convenient chiral auxiliaries due to their commercial availability under both enantiomeric forms. Condensation of these reagents with aldehydic moieties lead easily to oxazolidines and this reaction exhibits a high degree of stereocontrol.<sup>7</sup> In order to prevent an untimely hydrolysis to occur it soon appeared necessary to protect the heterocyclic nitrogen atom and this problem was solved by the use of an *N*-tosyl or an *N*-Cbz substituent.<sup>8,9</sup> However it should be noted that the above problem was then transferred at the auxiliary removal stage which therefore requires either a treatment with 1,2-ethanedithiol and BF<sub>3</sub>-Et<sub>2</sub>O as suggested by Scolastico<sup>10</sup> or an electrochemical procedure which was very recently proposed by Hoppe<sup>11</sup>.

We wish to present here a full account<sup>12</sup> of our work in which N-Boc oxazolidines are used as chiral inductors.<sup>13</sup> Actually the N-tert-butoxycarbonyl protective group is very popular since it is both easily introduced and removed. Its use in the present case has required the development of a method in order to control the creation of the C-2 oxazolidine stereogenic center. The framework of this method is resumed in Scheme 1.



Scheme 1

The second part of this strategy includes a Weinreb amide intermediate<sup>14</sup> which provides a simple access to various acyloxazolidines. Owing to the Boc substituent which will interact with the reagent during a subsequent addition step, the carbonyl diastereofaces are now well differentiated with respect to nucleophilic attack.

#### A. SYNTHESIS OF N-BOC 2-ACYL OXAZOLIDINES

The most simple way to get such heterocycles should be a direct condensation of the  $\beta$ -amino alcohol with the required substituted glyoxal. However this method, in our hand, was shown to be efficient in the only case of (1R,2S)-norephedrine 1 and phenylglyoxal 2 (eq. 1). This condensation, followed by treatment with di-*tert*butyldicarbonate (Boc<sub>2</sub>O), furnished the *cis* acyloxazolidine 3 (in this paper the *cis* and *trans* descriptors refer to the relative geometry of the carbon substituents on the heterocycle). Actually other reported similar condensations of substituted glyoxals with the proline-derived chiral auxiliaries<sup>2,3</sup> suffer from the same limitation since they have been restricted to non-enolisable aldehydes.



In contrast to the above reaction which has a very limited scope, the method depicted in Scheme 1 is much more versatile. Its first step consists in condensing either (1R,2S)-ephedrine 1 or (R)-phenylglycinol 4 with ethyl glyoxylate and treating the resulting intermediate oxazolidine with Boc<sub>2</sub>O. Without any special precaution, these amino alcohols led respectively to their corresponding 2-ethoxycarbonyl oxazolidines. Heterocycle 5 was thus obtained as the only *cis* stereoisomer whereas the norephedrine-derived oxazolidine was constituted by a near 1:1 mixture of the two epimers 6 and 7.



In order to get oxazolidine  $\mathbf{6}$  in a diastereometrically pure form, it was necessary to add Boc<sub>2</sub>O at a very slow rate. It was therefore possible to obtain the pure *cis* epimer  $\mathbf{6}$ . This result can be explained by a higher reactivity of intermediate *cis*  $\mathbf{8}$  than *trans* intermediate  $\mathbf{9}$  towards Boc fixation. Since  $\mathbf{8}$  and  $\mathbf{9}$  are likely to exist as an equilibrium mixture, the slow introduction of Boc<sub>2</sub>O drives this equilibrium towards the production of  $\mathbf{8}$ . The higher reactivity of  $\mathbf{8}$  can be ascribed to the lesser crowding of its nitrogen lone pair. The same effect should also be operative in the case of phenylglycinol derivatives but here the difference of reactivity inherent to the intermediates corresponding to  $\mathbf{8}$  and  $\mathbf{9}$  is still higher than in the norephedrine case. It was checked that there is no equilibrium between *N*-Boc oxazolidines  $\mathbf{6}$  and  $\mathbf{7}$  under these experimental conditions.



Oxazolidines 5 and 6 were transformed into Weinreb<sup>14</sup> derivatives 12 et 13 either directly or via the corresponding carboxylic acids 10 and 11 (Scheme 3). Amides 12 and 13 were reacted with organometallic reagents and vielded 2-acyloxazolidines 14-21 (Grignard reagents for ketones 14-20 and butyllithium for 21).



Reagents and conditions: (a) LiOH, EtOH/THF/H<sub>2</sub>O, 84% (10) and 73%(11); (b) DCC, Me(OMe)NH<sub>2</sub>+Cl<sup>-</sup>, 72% (12) and 64% (13); (c) see text; (d) Me(OMe)NH<sub>2</sub>+Cl<sup>-</sup>, Et<sub>3</sub>Al, CH<sub>2</sub>Cl<sub>2</sub>, 78%.

This method is very simple to perform and furnishes 2-acyloxazolidines from both (1R,2S)-norephedrine and (R)-phenylglycinol in fair to good overall yields of isolated products. It should be noted however that these ketones are unstable and must be utilized as soon as possible.

#### **B. ADDITION OF ORGANOMETALLIC REAGENTS**

Addition of Grignard reagents and trimethylsilane-TiCl<sub>4</sub> to ketones 14-21 occurs with moderate to excellent diastereoselectivity (Table 1) except for the allylmagnesium bromide which afforded both epimers in ca.1:1 ratio.<sup>15</sup> Diastereomeric excesses were determined by examination of the hydroxyoxazolidines <sup>1</sup>H NMR spectra: the methine hydrogen at C-2 appears as a sharp singlet at 5.1-5.3 ppm and allowed a clear analysis of the reaction product. Furthermore, compounds 26-29 (R = Ph, R': see Table) showed a remarkable shielding effect by the phenyl substituent (R) on the methyl group at C-4 which thus resonated at ca. -0.20 ppm. Compound 30 (R = Me, R' = Ph) is epimeric of 28 (R = Ph, R' = Me) at the new stereogenic center: the corresponding signal of the methyl group in this compound appeared at 0.89 ppm. In the case of the products resulting from the addition of the allyl Grignard reagent, two doublets were present at -0.18 and 0.92 ppm.

The produced alcohols result from a nucleophilic attack onto the Re diastereoface of the carbonyl group in the phenylglycinol derivatives 14-17 or onto the *Si* face in the case of norephedrine-derived oxazolidines 3 and 18-21. The determination of the configuration of the new stereogenic center results from the knowledge of the absolute configuration of the ensuing homochiral 1,2-diols (*vide infra*) and, in the particular case of hydroxyoxazolidine 28, from an X-ray structural determination (Fig. 1).



Table 1. Addition of Organometallic Reagents on 2-Acyloxazolidines 3 and 14-21.

Substrate	Organometallic	Conditions	Product	de	Yield
	R'M			%	%
14	PhMgBr	Et <sub>2</sub> O, 0°C	22	56	97
15	MeMgI	Et <sub>2</sub> O, 0°C	23	84	77
16	MeMgI	Et <sub>2</sub> O, 0°C→20°C	24	>95	65
17	MeMgI	Et <sub>2</sub> O,-50°C→10°C	25	>95	52
3	CH <sub>2</sub> =CHMgCl	THF. 0°C	26	>95	69
"	EtMgBr	THF. 0°C	27	>95	53
"	MeMgI	Et <sub>2</sub> O, 0°C	28	>95	70
"	CH <sub>2</sub> =CH-CH <sub>2</sub> MgBr	Et <sub>2</sub> O, 20°C	29	2	54
н	CH <sub>2</sub> =CH-CH <sub>2</sub> SiMe <sub>3</sub>	TiCl <sub>4</sub> , CH <sub>2</sub> Cl <sub>2</sub> , -70°C	29	>95	97
18	PhMgBr	Et <sub>2</sub> O, 20°C	30	>95	53
19	MeMgI	Et <sub>2</sub> O, 20°C	31	68	78
20	MeMgI	Et2O -50°C→10°C	32	>95	98
21	MeMgI	Et <sub>2</sub> O, 20°C	33	>95	91

Not only does this X-ray structure provide information about the configuration of the *cis* hydroxy oxazolidine (i.e. the C-2 center and the hydroxyl-bearing carbon are respectively S and R) but it also shows two interesting details. First, a hydrogen bond is apparent between the hydroxyl and the carbonyl group of the carbamate moiety (dO(2)-O(3) = 2.63 Å, cf. Fig.1). This H bond locks the urethane conformation; as a consequence, the <sup>1</sup>H NMR spectra of the related compounds exhibit sharp and well-resolved signals, thus facilitating the analysis.



Figure 1. X-Ray structure of hydroxy oxazolidine 28 (crystallographic numbering)

On the other hand, the methyl substituent borne by the ring is hemmed in between the two phenyl group (cf. C(11) in Fig.1) and there is a shielding effect which explains the low value of the corresponding chemical shift (vide supra).

We also decided to examine another nucleophilic reagent than the organometallic ones; to this end, 2-acyl oxazolidine 3 was reacted with sodium borohydride. This reaction was performed with and without added cerium chloride.<sup>17</sup> In both cases, the yields are nearly quantitative but diastereoselectivity was complete (de > 95%) only when CeCl<sub>3</sub> was present: otherwise diastereomeric excess was limited to 80%. In this case too, the created stereogenic center was R (eq.2) this means that the stereoselectivity of a nucleophilic attack onto the carbonyl group of a norephedrine-derived acyloxazolidine is the same as with organometallics. During the course of this work, an analogous reduction of compound 3 (reagents: NaBH<sub>4</sub>, LiI) has been described by Colombo *et al.*<sup>18</sup> and these published results are in complete agreement with ours.



The stereoselectivity which was observed for the above additions can be rationalized by chelation of the metal cation by both urethane and carbonyl moieties.<sup>19,20</sup> Examination of molecular models reveals that this chelation generates a severe crowding of the Re face of the carbonyl in norephedrine-derived acyloxazolidines **3** and **18-21**. The addition was thus directed onto the *Si* diastereoface (Fig.2). In the case of phenylglycinol-derived acyloxazolidines **14-17**, the addition is now directed onto the Re face (Fig.3) but now the presence of only one substituent (the phenyl group) on the oxazolidine ring explains that the steric control is less pronounced, specially with substrates **14** and **15** (see Table) in which the R group is not large enough. The role of cerium chloride during the reduction process strengthens the hypothesis that the steric requirements of the chelated transition state are responsible of the observed diastereoselectivity: cerium cation is a well-known complexing agent.<sup>21</sup>



Figure 2: Si face attack onto the acyl group of oxazolidines 3 and 18-21

Figure 3: *Re* face attack onto the acyl group of oxazolidines 14-17

The produced crude hydroxyoxazolidines 23, 24, 26-29 and 33 were transformed into the corresponding 1,2-diols 35-41 by a three-step sequence: (i) removal of the Boc group by treatment with trifluoroacetic acid, (ii) hydrolysis of the obtained triflate salts and, (iii) reduction of the released  $\alpha$ -hydroxy aldehydes (eq.3). The yields of the overall transformation from acyloxazolidines 15, 16, 3 and 21 to the above diols range from 42 to 61%.



The absolute configurations of these diols were deduced by comparison with literature values (see experimental section): the stereogenic centers of phenylglycinol and norephedrine-derived diols are respectively S and R. Their enantiomeric excesses were determined from examination of the <sup>1</sup>H NMR spectra of the Mosher derivatives.

This novel synthetic route offers a convenient entry to 2-acyloxazolidines, provides a highly stereoselective process for the formation of enantiopure 1,2-diols and continues to expand the scope of the still growing oxazolidine use in asymmetric synthesis. The most significant point of this study is the marked benefit supplied by the Boc protecting group which can be easily introduced and removed and which allows a high level diastereoselectivity during the organometallic as well as the hydride addition.

#### **EXPERIMENTAL SECTION**

#### General comments

<sup>1</sup>H and <sup>13</sup>C spectra (CDCl<sub>3</sub> solution unless otherwise stated) were respectively carried out on a Bruker AC 200 spectrometer at 200 and 50 MHz; chemical shifts are reported in ppm from TMS. Optical rotations were determined with a Perkin Elmer 141 instrument. Melting points were obtained with a Reichert apparatus (hot stage provided with a microscope) and are uncorrected. Mass spectra were performed on ZAB HSQ (Fisons) apparatus. All reactions were carried out under nitrogen except those performed in aqueous solution. Column chromatography was performed on silica gel, 230-400 mesh by using various mixtures of diethyl ether (E) and petroleum ether (PE). TLCs were run on silica gel 60  $F_{254}$  plates (Merck). Ether and THF were distilled from sodium/benzophenone ketyl. Mention of "usual workup" means: (i) decantation of the organic layer, (ii) extraction of the aqueous layer with ether, (iii) drying of the combined organic phases over MgSO4, (iv) solvent evaporation under reduced pressure. Compositions of stereoisomeric mixtures were determined by NMR analysis on crude products before any purification.

#### (2S,4S,5R)-4-Methyl-2-(1-oxo-1-phenyl)methyl-5-phenyl-3-tert-butoxycarbonyloxazolidine 3

To a solution of (1R,2S)-norephedrine (4 g, 26.4 mmol) in THF (100 ml) were added successively a solution of phenylglyoxal monohydrate (4 g, 26.4 mmol) in THF (50 ml) and anhydrous magnesium sulfate (50 g). The suspension was stirred at rt for 0.5 h and filtered over a pad of Celite. Evaporation of the solvent under reduced pressure gave an oily residue which was dissolved in ethyl acetate (200 ml). To this solution was added in one portion di-*tert*-butyldicarbonate (5.7 g, 26.4 mmol) and the mixture was refluxed for 0.5 h. Usual workup gave a crude solid which was washed with small portions of petroleum ether. Compound **3** was obtained as a light yellow solid (7.4 g, 76 %): mp 104°C;  $[\alpha]_{D}^{20}$ : -111.6 (c 1.6, CHCl<sub>3</sub>); <sup>1</sup>H NMR: 0.92 (d, J = 5.6 Hz, 3H), 1.36 and 1.54 (two s, 9H), 4.4 (m, 1H), 5.4 (d, J = 5.6 Hz, 1H), 6.24 and 6.36 (two s, 1H), 7.3-7.6 (m, 8H), 8.18 (d, J = 7.3 Hz, 2H); <sup>13</sup>C NMR: 14.7, 26.4, 55.5, 80.8, 83.5, 85.9, 126.2, 128.0, 128.3, 128.7, 129.2, 133.6, 134.9, 135.7, 160.2, 193.1; IR (CHCl<sub>3</sub>): 1700, 1685 cm<sup>-1</sup>. Anal. Calcd for C<sub>22</sub>H<sub>25</sub>NO<sub>4</sub>: C, 71.91; H, 6.86; N, 3.81. Found : C, 71.64; H, 6.89; N, 3.67.

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## (2R,4R)-2-Ethoxycarbonyl-4-phenyl-3-tert-butoxycarbonyloxazolidine 5

A solution of (*R*)-phenylglycinol (7 g, 51 mmol) and freshly prepared ethyl glyoxylate (5.7 g, 55.9 mmol) in toluene (200 ml) was refluxed in a Dean-Stark apparatus for 0.5 h. The solution was cooled to rt and di-*tert*-butyldicarbonate was added. The solution was then refluxed for 3h and cooled to rt. Addition of water followed by usual workup gave crude ester 5 as an oil (17.7 g, 99 %):  $[\alpha]_{D}$ : +48.2 (c 0.8, CHCl<sub>3</sub>); <sup>1</sup>H NMR: 1.13 (bs, 9H), 1.26 (t, J = 7.2 Hz, 3H), 4.03 (t, J = 8.3 Hz, 1H), 4.22 (q, J = 7.2 Hz, 2H), 4.39 (dd, J = 7.2 and 8.7 Hz, 1H), 4.8 (bs, 1H), 5.50 (bs, 1H), 7.21-7.33 (m, 3H), 7.43 (dd, J = 1.8 and 8.2 Hz, 2H); <sup>13</sup>C NMR: 14.0, 28.0, 60.7, 61.6, 75.4, 81.1, 86.5, 126.9, 127.6, 128.3, 139, 152.7, 169.0; IR (CHCl<sub>3</sub>) 1740 cm<sup>-1</sup>.

## (2S, 4S, 5R)-2-Ethoxycarbonyl-4-methyl-5-phenyl-3-tert-butoxycarbonyloxazolidine 6

A solution of (1R,2S)-*no*rephedrine (4 g, 26.4 mmol) and freshly prepared ethyl glyoxylate (3 g, 29.4 mmol) in toluene (200 ml) was refluxed in a Dean-Stark apparatus for 0.5 h. The solvent was then evaporated under reduced pressure and the residue was dissolved in ethyl acetate (200 ml). To this solution was added dropwise overnight a solution of di-*tert*-butyldicarbonate (5.8 g, 26.4 mmol) in ethyl acetate (200 ml) at 50°C and the solution was heated at this temperature for an additional 4 h. Evaporation of the solvent under reduced pressure gave a residue which was subjected to flash chromatography (E/PE : 20/80). Compound **6** was obtained as a clear oil (8.2 g, 98 %):  $[\alpha]_{D}^{20}$ : -118.7 (*c* 2.4, CHCl<sub>3</sub>); <sup>1</sup>H NMR : 0.91 (d, J = 6.7 Hz, 3H), 1.35 (t, J=7 Hz, 3H), 1.47 (bs, 9H), 4.30 (q, J = 7Hz overlap with bs, 3H), 5.23 (d, J = 5.6 Hz, 1H), 5.40 (bs, 1H), 7.25-7.35 (m, 5H); RMN <sup>13</sup>C : 14.0, 14.7, 28.3, 55.4, 61.6, 80.9, 83.1, 85.2, 126.1, 127.9, 128.2, 135.5, 168.3; IR (CHCl<sub>3</sub>) : 1740, 1700, 1685 cm<sup>-1</sup>. Anal. Calcd for C<sub>18</sub>H<sub>25</sub>NO<sub>5</sub> : C, 64.46; H, 7.51; N, 4.19. Found : C, 64.09; H, 7.39; N, 4.11.

## (2R, 4R)-2-Carboxy-4-phenyl-3-tert-butoxycarbonyloxazolidine 10

The procedure described thereafter for the preparation of acid **11** using crude ester **5** (17.7 g) gave acid **10** as a solid (12.8 g, 84 %): mp 143-145°C;  $[\alpha]_D$ : +54 (*c* 1.1, CHCl<sub>3</sub>); <sup>1</sup>H NMR: 1.22 (bs, 9H), 4.13 (t, J = 8.7 Hz, 1H), 4.50 (t, J = 8.7 Hz, 1H), 4.8-4.9 (m, 1H), 5.64 (s, 1H), 7.28-7.35 (m, 5H), 9.81 (bs, 1H); <sup>13</sup>C NMR: 27.9, 60.8, 75.5, 83.0, 85.8, 126.7, 128.8, 128.6, 136.0, 156.0, 171.2; IR (CHCl<sub>3</sub>) 3500, 1775, 1700, 1650 cm<sup>-1</sup>; m/z 248, 220 (M<sup>+</sup>- O-t-Bu), 192, 148; exact mass calc. for M<sup>+</sup>- O-t-Bu: 220.06098, found: 220.06106.

## (2S,4S,5R)-2-Carboxy-4-methyl-5-phenyl-3-tert-butoxycarbonyloxazolidine 11

To a solution of crude ester **6** (8.2 g, 25.8 mmol) in THF/EtOH/H<sub>2</sub>O : 2/2/1 (350 ml) was added portionwise at 0°C lithium hydroxyde monohydrate (10.7 g, 260 mmol). The suspension was stirred for 1 h at rt, concentrated under reduced pressure to a volume of *ca*.100 ml and diluted with water (150 ml). This solution was washed with ether (2X50 ml), acidified to pH 1 with 2N HCl and extracted with ether (3X100ml). Drying on MgSO<sub>4</sub> of the etheral extracts and evaporation of the solvent gave acid **11** as an oil that crystallised on standing (5.8 g, 73%): mp 108°C;  $[\alpha]_D^{(2)}$ : -119 (*c* 2.6, CHCl<sub>3</sub>); <sup>1</sup>H NMR : 0.88 (bs, 3H), 1.49 (bs, 9H), 4.31 (bs, 1H), 5.27 (d, J = 5.6 Hz, 1H), 5.47 (bs, 1H), 7.25-7.35 (m, 5H), 11.36 (bs, 1H); <sup>13</sup>C NMR : 14.8, 29.4, 55.4, 82, 83.1, 84.9, 126.3, 128.2, 128.4, 135.5, 171.1, 173.6; m/z 262, 234 (M<sup>+-</sup> O-t-Bu), 206, 162; exact mass calc. for M<sup>+-</sup> O-t-Bu: 234.07663, found: 234, 07669.

## (2R,4R)-2-(N-Methoxy-N-methyl) carbamoyl-4-phenyl-3-tert-butoxy carbonylox azolidine 12

The procedure described thereafter for the preparation of amide 13 from acid 11 was used starting with acid 10 (2 g, 6.82 mmol). Amide 12 was obtained as an oil (1.6 g, 72 %):  $[\alpha]_D^{(2)}$ : +30.4 (c 0.7, CHCl<sub>3</sub>); <sup>1</sup>H NMR: 1.07 and 1.32 (two bs, 9H), 3.22 (s, 3H), 3.76 (s, 3H), 4.03-4.08 (bm, 1H), 4.33 (dd, J = 6.8 and 8.6 Hz, 1H), 4.70-4.75 (bm, 1H), 6.02 (bs, 1H), 7.17-7.31 (m, 3H), 7.63 (dd, J = 1.7 and 8.4 Hz, 2H); <sup>13</sup>C NMR: 28.0, 32.2, 61.3, 61.9, 75.5, 80.6, 83.5, 127.5, 128.2, 139.1, 153.0, 168.7; IR (CHCl<sub>3</sub>) 1675, 1685 cm<sup>-1</sup>; m/z 263 (M<sup>+</sup>- O-t-Bu), 248, 192, 148; exact mass calc. for M<sup>+</sup>- O-t-Bu: 263.10318, found: 263.10309.

### (2S,4S,5R)-2-(N-Methoxy-N-methyl)-carbamoyl-4-methyl-5-phenyl-3-tert-butoxycarbonyloxazolidine 13

From acid 11. To a solution of acid 11 (3.7 g, 12 mmol) in dichloromethane (80 ml) was added successively 1, 3-dicyclohexylcabodiimide (2.77 g, 13.5 mmol), N,O-dimethylhydroxylamine hydrochloride (1,33 g, 13.5 mmol) and pyridine (3.1 g, 40 mmol). The suspension was stirred at rt for 1 h and was then filtrated on Celite. The organic layer was washed successively with 1N HCl, a saturated aqueous solution of sodium hydrogenocarbonate and brine. Drying on MgSO<sub>4</sub> followed by evaporation of the solvent gave a residue which was flash chromatographied (E/PE : 30/70). Amide 13 was obtained as a white solid (2.95 g 70 %): mp 78°C;  $[\alpha]_{D}^{20}$ : -99.8 (c 0.6, CHCl<sub>3</sub>); <sup>1</sup>H NMR : 0.91 (d, J = 6.5 Hz, 3H), 1.43 and 1.47 (two bs, 9H), 3.29 (s, 3H), 3.82 (s, 3H), 4.2- 4.3 (m, 1H), 5.24 (bs, 1H), 5.88 and 5.97 (two bs, 1H), 7.25-7.36 (m, 5H); <sup>13</sup>C NMR : 14.7, 28.4, 32.4, 55.2, 62.1, 80.5, 82.4, 83.2, 126.3, 127.9, 128.2, 135.7; IR (CHCl<sub>3</sub>): 1685 cm<sup>-1</sup>. Anal. Calcd for C<sub>18</sub>H<sub>26</sub>N<sub>2</sub>O<sub>5</sub> : C, 61.69; H, 7.48; N, 7.99. Found : C, 62.07; H, 7.45; N, 7.82.

From ester 6: To a solution of N, O-dimethylhydroxylamine hydrochloride (1,5 g, 15.4 mmol) in dichloromethane (35 ml) cooled at -20°C was added dropwise a 1N solution of triethylaluminium in hexane (15.4 ml, 15.4 mmol). The solution was allowed to reach rt and was stirred for 1 h. The mixture was then cooled at -30°C and a solution of ester 6 (1.7 g, 5.1 mmol) in dichloromethane (35 ml) was added dropwise. The solution was allowed to reach rt and stirred for 3 h. A 1N aqueous solution of tartaric acid (35 ml) was then cautiously added and the mixture was stirred for an additional hour. Usual workup gave a residue which was purified as above (1.4 g, 78%).

#### General procedure for the preparation of 2-acyl oxazolidines 14-21 from the Weinreb amides 12 and 13

To a solution of the Weinreb amide (3.2 mmol) in THF or ether (20 ml) cooled at  $0^{\circ}$ C or  $-78^{\circ}$ C was added dropwise a solution (etheral solutions for Grignard reagents, hexane solution for butyllithium) of the organometallic reagent (6 mmol). The reaction was monitored by TLC and was stirred at  $0^{\circ}$ C until completion. Hydrolysis with a saturated aqueous solution of NH<sub>4</sub>Cl followed by usual workup gave crude acyl oxazolidines 14-21 which were purified by flash chromatography.

#### (2R,4R)-4-Phenyl-2-(1-oxoethyl)-3-tert-butoxycarbonyloxazolidine 14

Conditions: 10 mn at 0°C in ether. Compound 14 was obtained as an oil (844 mg, 91 %):  $[\alpha]_D^{20}$ : +25.7 (c 3.6, CHCl<sub>3</sub>); <sup>1</sup>H NMR: 1.28 and 1.33 (two bs, 9H), 2.29 (s, 3H), 3.96 (t J = 8.4 Hz, 1H), 4.37 (dd, J = 7.5 and 8.9 Hz, 1H), 4.85 (bs, 1H), 5.47 (bs, 1H), 7.23-7.37 (m, 5H); <sup>13</sup>C NMR: 26.0, 28.0, 60.7, 74.7, 81.2, 89.8, 126.8, 127.6, 128.4, 139.1, 153.4, 203.2; IR (CHCl<sub>3</sub>): 1690, 1725 cm<sup>-1</sup>.

#### (2R,4R)-2-(1-Oxo-1phenyl)methyl-4-phenyl-3-tert-butoxycarbonyloxazolidine 15

Conditions: 10 mn at 0°C in THF. Compound **15** was obtained as a solid (1.13 g, 95%): mp 122°C;  $[\alpha]_D^{20}$ : +28.2 (c 3.5, CHCl<sub>3</sub>); <sup>1</sup>H NMR: 1.24 and 1.33 (two bs, 9H), 3.97 (t, J = 8.5 Hz, 1H), 4.46 (dd, J = 7 and 8.8 Hz, 1H), 4.94 (bs, 1H), 6.34 and 6.49 (two bs, 1H), 7.25-7.70 (m, 8H), 8.17 (d, J = 8.2 Hz, 2H); <sup>13</sup>C NMR: 27.9, 61.0, 75.1, 80.8, 87.1, 127.0, 127.5, 128.3, 128.5, 129.0, 133.5, 134.5, 139.0, 193.3; IR (CHCl<sub>3</sub>): 1695 cm<sup>-1</sup>; m/z 268 (M<sup>+</sup>- O-t-Bu), 248, 206, 192; exact mass calc. for M<sup>+</sup>-O-t-Bu: 268.09737, found: 268.09749.

#### (2R,4R)-2-(1-Oxo-2-phenyl)ethyl-4-phenyl-3-tert-butoxycarbonyloxazolidine 16

Conditions: 0.5 h at 0°C in THF. Compound **16** was obtained as an oil (748 mg, 64 %):  $[\alpha]_D^{20}$ : +33.7 (c 3.7, CHCl<sub>3</sub>); <sup>1</sup>H NMR: 1.33 ( bs, 9H), 3.9-4.1 (m, 3H), 4.44 (dd, J = 7 and 8.9 Hz, 1H), 4.92 (bs, 1H), 5.72 (bs, 1H), 7.25-7.43 (m, 10H); <sup>13</sup>C NMR: 28.1, 45.4, 60.9, 74.9, 81.3, 89.3, 126.9, 127.0, 127.7, 128.5, 128.6, 129.7, 133.3, 139.0, 153.5, 202.6; IR (CHCl<sub>3</sub>): 1690, 1720 cm<sup>-1</sup>.

### (2R.4R)-2-(5-Methyl-1-oxo)hex-5-envl-4-phenyl-3-tert-butoxycarbonyloxazolidine 17

Conditions : 0.5 h at 0°C in THF. Compound 17 was obtained as an oil (1.27 g, 68 %):  $[\alpha]_D^{20}$ : +22.9 (c 3.2, CHCl<sub>3</sub>); <sup>1</sup>H NMR: 1.28 (bs, 9H), 1.71 (s, 3H), 1.77-1.88 (m, 2H), 2.06 (t, J = 7.4 Hz, 2H), 2.67 (t, J = 7.1Hz, 2H), 3.99 (t, J = 8.5 Hz, 1H), 4.39 (dd, J = 7 and 8.8 Hz, 1H), 4.65 (s, 1H), 4.73 (s, 1H), 4.87 (bs, 1H), 5.50 (bs, 1H), 7.25-7.45 (m, 5H); <sup>13</sup>C NMR: 20.9, 22.1, 28.0, 37.0, 38.1, 60.8, 74.8, 81.1, 89.6, 110.6, 126.9, 127.6, 128.4, 139.2, 144.7, 153.3, 205.4; IR (CHCl<sub>3</sub>): 1680, 1710, 1730 cm-1.

#### (2S,4S,5R)-4-Methyl-2-(1-oxo)ethyl-5-phenyl-3-tert-butoxycarbonyloxazolidine 18

Conditions: 10 mn at 0°C in ether. Compound 18 was obtained as a solid (910 mg, 93 %): mp 56°C;  $[\alpha]_{1}^{20}$ : 68.2 (c 1.7, CHCl<sub>3</sub>); <sup>1</sup>H NMR; 0.80 (d, J = 6.8 Hz, 3H), 1.39 (s, 9H), 2.25 (bs, 3H), 4.25 (bs, 1H), 5.08 (bs. 1H), 5.16 (d, J = 5.8 Hz, 1H), 7.25-7.35 (m, 5H); <sup>13</sup>C NMR; 15.6, 28.2, 55.5, 81.3, 82.8, 88.8, 125.9, 128.0, 135.3, 154.1, 203.1; IR (CHCl<sub>3</sub>): 1805, 1780, 1700 cm-<sup>1</sup>.

## (2S,4S,5R)-4-Methyl-2-(1-oxo-2-phenyl)ethyl-5-phenyl-3-tert-butoxycarbonyloxazolidine 19

Conditions: 10 mn at 0°C in ether. Compound **19** was obtained as an oil (613 mg, 51 %):  $[\alpha]_{D}^{20}$ : -79.2 (c 6.1,  $CHCl_3$ ; <sup>1</sup>H NMR: 0.92 (bd, J = 5.8 Hz, 3H), 1.45 (bs, 9H), 4.04 (s, 2H), 4.3-4.4 (bm, 1H), 5.26 (d, J = 5.8 Hz, 3H), 1.45 (bs, 9H), 4.04 (s, 2H), 4.3-4.4 (bm, 1H), 5.26 (d, J = 5.8 Hz, 3H), 5.26 (d, J = 5.8 Hz), 5.26 (d, J = Hz, 1H), 5.3-5.5 (m, 1H), 7.28-7.45 (m, 10H); <sup>13</sup>C NMR: 15.5, 28.2, 43.5, 55.5, 81.1, 82.8, 88.4, 125.9, 127.9, 128.2, 128.4, 129.6, 133.4, 135.4, 152.0, 201.1; IR (CHCl<sub>3</sub>): 1710 cm-<sup>1</sup>.

## (2S,4S,5R)-4-Methyl-2-[(5-methyl-1-oxo)hex-5-enyl]-5-phenyl-3-tert-butoxycarbonyloxazolidine\_20

Conditions : 0.5 h at 0°C in THF. Compound 20 was obtained as an oil (885 mg, 75%);  $[\alpha]_{D}^{(2)}$ : -75.6 (c 1, CHCl<sub>3</sub>); <sup>1</sup>H NMR: 0.82 (d, J = 6.5 Hz, 3H), 1.42 (bs, 9H), 1.69 (s, 3H), 1.75-1.86 (m, 2H), 2.05 (t, J = 7.3 Hz, 2H), 2.64 (t, J = 7.1 Hz, 2H), 4.28 (bs, 1H), 4.65 (s, 1H), 4.69 (s, 1H), 5.17 (d, J = 5.3 Hz, 1H), 5.3 (bs, 1H), 7.23-7.37 (m, 5H); <sup>13</sup>C NMR: 15.4, 20.9, 22.1, 28.2, 36.2, 36.9, 55.5, 81, 82.8, 88.6, 110.5, 126.0, 127.9, 128.2, 135.5, 144.8, 152.2, 204.1; IR (CHCl<sub>3</sub>): 1680, 1710, 1730 cm-<sup>1</sup>; m/z 341, 298, 262, 250, 206,

#### (2S,4S,5R)-4-Methyl-2-(1-oxo)pentyl-5-phenyl-3-tert-butoxycarbonyloxazolidine 21

Conditions: -78°C to 0°C in THF. Compound 21 was obtained as an oil (687 mg, 55 %):  $[\alpha]_{D}^{20}$ : -75.2 (c 4.9, CHCl<sub>3</sub>); <sup>1</sup>H NMR: 0.78 (d, J = 6.4 Hz, 3H), 0.85 (t, J = 7.3 Hz, 3H), 1.2-1.4 (m, 11H), 1.50-1.65 (m, 2H). 2.59 (t, J = 7.1 Hz, 2H), 4.21 (bs, 1H), 5.12 (d, J = 5.7 Hz, 1H), 5.25 (bs, 1H), 7.15-7.30 (m, 5H);  $;^{13}C$ NMR: 13.8, 15.4, 22.2, 25.2, 28.2, 36.3, 55.5, 81.0, 82.7, 88.6, 125.9, 127.9, 128.2, 135.5, 153.2, 204.2; IR (CHCl<sub>3</sub>): 1710, 1785, 1805 cm-<sup>1</sup>; m/z 277, 206, 177, 144.

## General procedure for the addition of Grignard reagents on 2-acyl oxazolidines 3 and 14-21: preparation of oxazolidines 22-33

To a solution of 2-acyl oxazolidine (1 to 3 mmol) in THF or ether (10 ml / mmol) cooled at 0°C was added dropwise a solution of the organometallic reagent (3 equiv of etheral solutions for Grignard reagents). The reaction was monitored by TLC and was stirred at rt until completion. Hydrolysis with a saturated aqueous solution of NH4Cl followed by usual workup gave crude oxazolidines 22-33 which were purified by flash chromatography.

## (2R,4R)-2-(1S)- and (2R,4R)-2-(1R)-(1-Hydroxy-1-phenyl)ethyl-4-phenyl-3-tert-butoxy-carbonyloxazolidine 22 and 23

From addition of phenyl magnesium bromide on ketone 14. Conditions: 10 mn at 0°C. After flash chromatography, an oily mixture of 22 and 23 was obtained in a respective ratio of 22/78 (495 mg, 97 %)

From addition of methylmagnesium iodide on ketone 15. Conditions: 3h at 0°C. After flash chromatography, an oily mixture of 22 and 23 was obtained in a respective ratio of 8/92 (386 mg, 77 %); <sup>1</sup>H NMR (signals belonging to compound 23 are italicized): 1.32 et 1.44 (two s, 9H), 1.64 and 1.82 (two s, 3H), 4.1-4.3 (m, 2H), 4.80 and 5.05 (two t, 1H), 5.25 et 5.35 (two s, 1H), 6.3 and 6.4 (two s, 1H), 7.1-7.8 (m, 10H); <sup>13</sup>C NMR : 23.4, 26.8, 27.8, 28.0, 61.2, 61.8, 72.5, 73.3, 75.9, 76.2, 82.0, 82.3, 96.2, 97.1, 125.3, 126.1, 126.5, 126.6, 126.8, 127.0, 127.5, 127.7, 127.9, 128.3, 129.3, 139.6, 139.9, 144.1, 145.3, 156.3, 156.8; IR (CHCl<sub>3</sub>) : 3285, 1665, 1400 cm<sup>-1</sup>.

## (2R,4R)-2-(1S)-(1-Hydroxy-1-methyl-2-phenyl)ethyl-4-phenyl-3-tert-butoxycarbonyloxazolidine 24 Conditions: 10 mn at 0°C. After flash chromatography 24 is obtained as a solid (500 mg, 65 %); mp 100-109°C; $[\alpha]_D^{(2)}$ : -9.5 (c 0.6, CHCl<sub>3</sub>); <sup>1</sup>H NMR : 1.18 (s, 3H), 1.41 (s, 9H), 2.77 and 2.96 (AB J=13.2Hz, 2H), 4.36 (d, J=6.3Hz, 2H), 5.08 (t, J = 6.3Hz, 1H), 5.20 (s, 1H), 7.24-7.49 (m, 11H); IR (CHCl<sub>3</sub>): 1705, 1360 cm<sup>-1</sup>; m/z 310 (M<sup>+</sup>- O-t-Bu) 292, 248, 206, 192; exact mass calc. for M<sup>+</sup>- O-t-Bu: 310.144316, found: 310.144247.

(2R,4R)-2-(1S)-(1,5 Dimethyl-1-hydroxy)hex-5-enyl-4-phenyl-3-tert-butoxycarbonyloxazolidine 25 Conditions: -50 to 0°C, 1h in ether. After flash chromatography **25** is obtained as an oil (457 mg, 52 %):  $[\alpha]_{D}^{-1}$ : -11.8 (c 2.1, CHCl<sub>3</sub>); <sup>1</sup>H NMR : 1.25 (s, 3H), 1.35 (s, 9H), 1.48 (s, 3H,), 1.67 (s, 4H), 1.99 (t, J=6.1 Hz, 2H), 4.15-4.25 (m, 2H), 4.61 (s, 1H), 4.65 (s, 1H), 4.97 (t, J = 5.7 Hz, 1H), 5.05 (s, 1H), 7.24-7.39 (m, 5H); <sup>13</sup>C NMR : 20.9, 22.0, 23.5, 28.0, 36.4, 38.2, 61.2, 72.8, 74.2, 81.6, 96.5, 110.0, 126.6, 127.3, 128.2, 140.5, 145.6, 155.9; IR (CHCl<sub>3</sub>) : 3320, 1705-1650 cm<sup>-1</sup>; m/z 302 (M<sup>+</sup>- O-t-Bu) 276, 248, 192; exact mass calc. for M<sup>+</sup>- O-t-Bu: 302.17562, found: 302.17562.

# (2S,4S,5R)-2-[(1R)-(1-Hydroxy-1-phenyl)prop-2-enyl]-4-methyl-5-phenyl-3-tert-butoxycarbonyloxazolidine 26

Conditions: 10 mn in THF. Compound **26** was obtained as a solid (368 mg, 69 %): mp 170°C;  $[\alpha]_D^{20}$ : -77.4 (*c* 0.5, CHCl<sub>3</sub>); <sup>1</sup>H NMR: -0.25 (d, J = 6.7 Hz, 3H), 1.44 (s, 9H), 3.92 (m, 1H), 4.92 (d, J = 5.9 Hz, 1H), 5.17 (s, 1H), 5.31 (dd, J = 2 and 10.6 Hz, 1H), 5.73 (dd, J = 2 and 16.8 Hz, 1H), 6.75 (dd, J = 10.6 and 16.8 Hz, 1H), 7.1-7.35 (m, 8H), 7.45 (s, 1H) 7.60 (d, J = 8.6 Hz, 2H); <sup>13</sup>C NMR: 14.0, 28.3, 56.4, 77.7, 80.9, 81.9, 95.0, 115.4, 126.1, 127.4, 127.5, 127.9, 128.3, 135.5, 139.6, 142.1, 155.9; IR (CHCl<sub>3</sub>): 1405, 1660, 3280 cm-<sup>1</sup>; Anal. Calcd for C<sub>24</sub>H<sub>29</sub>NO<sub>4</sub> : C, 72.88; H, 7.39; N, 3.54. Found : C, 72.75; H, 7.34; N, 3.54.

## (2S,4S,5R)-2-(1R)-(1-Hydroxy-1-phenyl)propyl-4-methyl-5-phenyl-3-tert-butoxy-carbonyloxazqlidine 27

Conditions: 1 h in THF. Compound **27** was obtained as a solid (287 mg, 53 %): mp 119°C;  $[\alpha]_{D}^{20}$ : -81.2 (*c* 0.9, CHCl<sub>3</sub>); <sup>1</sup>H NMR: -0.22 (d, J = 6.7 Hz, 3H), 0.99 (t, J = 7.3 Hz, 3H), 1.46 (s, 9H), 2.0-2.5 (m, 2H), 3.95 (m, 1H), 5.01 (d, J = 5.9 Hz, 1H), 5.29 (s, 1H), 7.2-7.4 (m, 9H), 7.59 (d, J = 8.6 Hz, 2H); <sup>13</sup>C NMR: 7.6, 13.8, 28.3, 30.5, 56.5, 78.3, 80.8, 81.7, 94.4, 126.2, 126.8, 127.4, 127.7, 127.9, 128.3, 135.7, 142.2, 155.7; IR (CHCl<sub>3</sub>): 1400, 1660, 3280 cm<sup>-1</sup>; m/z 324 (M<sup>+</sup>- O-t-Bu), 294, 262, 206, 162; exact mass calc. for M<sup>+</sup>- O-t-Bu: 324.15997, found: 324.15977.

## (2S,4S,5R)-2-(1R)-(1-Hydroxy-1-phenyl)ethyl-4-methyl-5-phenyl-3-tert-butoxy-carbonyloxazolidine<sub>0</sub>28 Conditions: 0.5 h in THF. Compound **28** was obtained as a solid (359 mg, 70 %): mp 160°C; $[\alpha]_D$ : -79.9 (c 0.6, CHCl<sub>3</sub>); <sup>1</sup>H NMR: -0.22 (d, J = 6.7 Hz, 3H), 1.50 (s, 9H), 1.82 (s, 3H), 3.92-4.0 (m, 1H), 5.01 (d, J = 5.9 Hz, 1H), 5.28 (s, 1H), 7.2-7.4 (m, 9H), 7.59 (d, J = 8.6 Hz, 2H) ; <sup>13</sup>C NMR: 13.9, 25.6, 28.3, 56.5, 76.1, 80.7, 81.6, 95.0, 126.1, 126.9, 127.1, 127.3, 127.8, 128.2, 135.6, 143.6, 157.0; IR (CHCl<sub>3</sub>): 1405, 3290 cm<sup>-1</sup>; Anal. Calcd for C<sub>23</sub>H<sub>29</sub>NO<sub>4</sub> : C, 72.03; H, 7.62; N, 3.65. Found : C, 72.03; H, 7.52; N, 3.64.

Crystal data.  $C_{23}H_{29}NO_4$ , M = 383.5, orthorhombic, space group P  $2_12_12_1$ , a = 9.214(1), b = 13.526(1), c = 17.488(9) Å, V = 2179 Å<sup>3</sup>, D<sub>c</sub> = 1.17 g.cm<sup>-3</sup>, Z = 4,  $\mu$ (Mo-K $\alpha$ ) = 0.74 cm<sup>-1</sup>. Data were collected at room temperature on a Philips PW 1100 diffractometer. The structure was solved by use of SHELXS86 program, G.M. Sheldrick, Program for Crystal Structure Solution, University of Göttingen, 1986, and refined by least-squares analysis using anisotropic thermal parameters except for the phenyl rings. H atoms were put in the refinement in calculated positions and re-calculated after each refinement cycle. Of 2179 observed reflections, 1206 with I>3 $\sigma$ (I) were used to solve and refine the structure to R = 0.069 and R<sub>w</sub> = 0.065 (unit weights, 194 least-squares parameters). The program used was CRYSTALS for refinements and CAMERON for views. Atomic coordinates, bond lengths, angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

# $(2S,4S,5R)-2-[(1RS)-(1-Hydroxy-1-phenyl)but-3-enyl]-4-methyl-5-phenyl-3-tert-butoxycarbonyloxazolidine (1RS) \ 29$

Conditions (from allylmagnesium bromide): 1 day at rt in ether. A mixture of epimers in a ratio 49/51 was obtained as an oil (300 mg, 54 %): <sup>1</sup>H NMR : -0.18 et 0.92 (two d, J = 6.7 Hz, 3H), 1.52 et 1.60 (two s, 9H), 2.65-2.75 (m, 0.5H) 2.95-3.20 (m, 1.5 H), 4.00-4.36 (m, 1H), 4.98-5.30 (m, 3H), 5.20 and 5.36 (two s, 1H), 5.75-6.15 (m, 1H), 6.52 (s, 0.5H), 7.2-7.5 (m, 8.5H), 7.78 and 7.64 (two d, J = 7.2Hz, 2H); <sup>13</sup>C NMR: (signals italicized belong to the above compound **29**): *13.8*, 16.1, *28.3*, 28.4, 39.3, *42.4*, 56.5, 57.0, 76.9, 77.7, 80.5, 80.8, 81.7, 82.1, 94.0, 94.6, 117.7, 125.9, 126.1, 127.0, 127.3, 127.6, 127.8, 128.3, 134.0, 134.1, 135.7, 135.8, 142.2, 142.6, 155.7, 156.2; IR (CHCl<sub>3</sub>): 3280, 1705, 1660, 1400cm<sup>-1</sup>.

(2S,4S,5R)-2-[(1R)-(1-Hydroxy-1-phenyl)but-3-enyl]-4-methyl-5-phenyl-3-tert-butoxycarbonyloxazolidine 29To a solution of TiCl<sub>4</sub> (258 mg, 1.36 mmol) in dichloromethane (15 ml) cooled at -78°C was added dropwise successively a solution of ketone 3 (0.5 g, 1.36 mmol) in dichloromethane (5 ml) and allyltrimethylsilane (309 mg, 2.7 mmol). The solution was allowed to reach -20°C and hydrolyzed at this temperature by addition of water (10 ml). After filtration on Celite, usual workup followed by flash chromatography yielded 29 as an oil (538 mg, 97 %): [ $\alpha$ ]<sub>D</sub>: -80.2 (c 1.3, CHCl<sub>3</sub>); <sup>1</sup>H NMR : -0.20 (d, J = 6.7 Hz, 3H), 1.50 (s, 9H), 2.9-3.2 (m, 2H), 3.97 (m, 1H), 4.98 (d, J = 5.9Hz, 1H), 5.10 (dd, J = 1.7 Hz, Jcis = 10.2Hz, 1H), 5.23 (dd, J=1.7Hz, Jtrans = 17.3Hz, 1H), 5.33 (s, 1H), 5.9-6.15 (m, 1H), 7.15-7.41 (m, 8H), 7.51 (s, 1H), 7.62 (d, J= 7.2Hz, 2H); m/z 336 (M<sup>+</sup>- O-t-Bu), 312, 268, 262, 206; exact mass calc. for M<sup>+</sup>- O-t-Bu: 336.159966, found: 336.16015.

(2*S*, 4*S*, 5*R*)-2-(1*S*)-(1-Hydroxy-1-phenyl)ethyl-4-methyl-5-phenyl-3-tert-butoxycarbonyloxazolidine **30** Conditions: 0.5 h in ether. Compound **30** was obtained as a solid (274 mg, 53 %): mp 124°C;  $[\alpha]_D^{20}$ : -112.2 (c 0.5, CHCl<sub>3</sub>); <sup>1</sup>H NMR : 0.89 (d, J = 6.7 Hz, 3H), 1.58 (s, 9H), 1.70 (s, 3H), 4.33 (m, 1H), 4.99 (d, J = 7.1 Hz, 1H), 5.21 (s, 1H), 7.0-7.35 (m, 9H), 7.63 (d, J = 8.1Hz, 2H); <sup>13</sup>C NMR : 16.1, 22.8, 28.3, 56.8, 75.2, 80.4, 82.0, 94.5, 115.4, 119.7, 125.8, 126.8, 127.0, 127.3, 127.7, 128.2, 129.3, 135.8, 144.9, 156.2; IR (CHCl<sub>3</sub>): 3280, 1660, 1400 cm<sup>-1</sup>.

# (2S,4S,5R)-2-(1R)-(1-Hydroxy-1-methyl-2-phenyl)ethyl-4-methyl-5-phenyl-3-tert-butoxycarbonyloxazolidine 31

Conditions: 1 day at rt in ether. Compound **31** was obtained as an oil (420 mg, 78 %). An amount of 16 % of the (15) diastereoisomer was detected by NMR:  $[\alpha]_D^{20}$ : -74.6 (c 1.3, CHCl<sub>3</sub>); <sup>1</sup>H NMR : (Signals of the major diasteroisomer): 0.74 (d, J = 6.7 Hz, 3H), 1.06 (s, 3H), 1.44 (s, 9H), 2.65 and 2.75 (AB, J = 12 Hz, 2H), 4.15-4.25 (m, 1H), 5.04 (d, J = 6.0 Hz, 1H), 5.07 (s, 1H), 5.9 (bs, 1H), 7.10-7.34 (m, 10H); IR (CHCl<sub>3</sub>): 3310, 1695, 1665, 1400cm<sup>-1</sup>.

(2S,4S,5R)-2-[(1R)-(1,5-Dimethyl-1-hydroxy)hex-5-enyl]-4-methyl-5-phenyl-3-tert-butoxycarbonyloxazolidine 32

Conditions: 0.5 h in ether. Compound 32 was obtained as a solid (1.06 g, 99 %): mp 108°C;  $[\alpha]_D^{20}$ : -85.7 (*c* 0.98, CHCl<sub>3</sub>); <sup>1</sup>H NMR : 0.68 (d, J=6.6 Hz, 3H,), 1.23 (s, 3H,), 1.42 (s, 12H), 1.64 (d, J = 0.9 Hz, 4H), 1.97 (t, J = 7.2 Hz, 2H), 4.10-4.25 (m, 1H), 4.60 (s, 2H), 4.98 (s, 1H), 5.01 (d, J = 5.6 Hz, 1H), 7.18-7.30 (m, 5H); <sup>13</sup>C NMR : 15.9, 20.9, 22.3, 23.6, 28.5, 35.5, 38.6, 56.8, 73.1, 80.4, 81.6, 95.8, 110.0, 126.1, 128.0, 128.4, 136.1, 146.1, 155.4; IR (CHCl<sub>3</sub>): 3320, 1665, 1600 cm<sup>-1</sup>; m/z 324, 294, 262, 206, 162.

(25, 45, 5R)-2-(1R)-(1-Hydroxy-1-methyl)pentyl-4-methyl-5-phenyl-3-tert-butoxycarbonyloxazolidine 33 Conditions: 0.5 h in ether. Compound 33 was obtained as an oil (450 mg, 91%):  $[\alpha]_D^{(2)}$ : -82.7 (c 1.5, CHCl<sub>3</sub>); <sup>1</sup>H NMR : 0.68 (d, J = 6.7 Hz, 3H), 0.84 (t, J = 7 Hz, 3H), 1.2-1.5 (m, 18H), 4.1-4.2 (m, 1H), 4.95 (s, 1H), 4.97 (d, J = 5.6 Hz, 1H), 7.2-7.45 (m, 5H); <sup>13</sup>C NMR : 13.8, 15.5, 23.1, 24.9, 28.0, 35.5, 56.4, 73.0, 80.1, 81.4, 95.4, 125.7, 127.6, 128.1, 135.6, 155.2; IR (CHCl<sub>3</sub>): 3250, 1660, 1410 cm<sup>-1</sup>.

#### (2S,4S,5R)-2-(1R)-(1-Hydroxy-1-phenyl)methyl-4-methyl-5-phenyl-3-tert-butoxycarbonyloxazolidine 34

To a solution of ketone 3 (500 mg, 1.36 mmol) and cerium chloride heptahydrate (507 mg, 1.36 mmol) in methanol (25 ml) was added portionwise sodium borohydride (59 mg 1.56 mmol) at rt. The mixture was stirred for 1.5 h and hydrolysed by addition of an aqueous saturated solution of ammonium chloride. Usual workup yielded 34 as a white solid (465 mg, 93%): mp 144°C;  $[\alpha]_{D}^{20}$ : -91.4 (*c* 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR : -0.15 (d, J = 5.8 Hz, 3H), 1.54 (s, 9H), 3.98 (m, 1H), 5.06 (d, J = 5.8 Hz, 1H), 5.15 (d, J = 9.1 Hz, 1H), 5.57 (s, 1H), 6.33 (d, J = 9.1 Hz, 1H), 7.23-7.50 (m, 10H); <sup>13</sup>C NMR : 14.1, 28.4, 56.1, 75.0, 81.1, 81.4, 91.6, 126.1, 127.6, 127.8, 128.2, 135.6, 139.9, 157.5; IR (CHCl<sub>3</sub>) : 3310, 1710 cm<sup>-1</sup>; Anal. Calcd for C<sub>22</sub>H<sub>27</sub>NO<sub>4</sub> : C, 71.52; H, 7.37; N, 3.79. Found : C, 71.48; H, 7.37; N, 3.73.

#### General procedure for the synthesis of 1,2-diols 35-41 from oxazolidines 23, 24, 26-29 and 33

To a solution of crude oxazolidine (1 to 3 mmol) in dichloromethane (10 ml / mmol) cooled at 0°C was added trifluoroacetic acid (2 ml / mmol). The solution was stirred at 0°C for 3 h and concentrated under reduced pressure. The residue was taken up three times in dichloromethane (5 ml/ mmol) and evaporated under reduced pressure. The final oily residue was then diluted in 1/1 THF/water (10 ml / mmol) and stirred at rt for 2 h. THF was evaporated under reduced pressure and the remaining aqueous layer was saturated with brine, extracted with ether (3 X 20 ml). Drying of the extracts on MgSO<sub>4</sub> and concentration gave an oil that was dissolved in ethanol (10 ml / mmol). To this solution was added sodium borohydride (2 mmol / mmol of starting oxazolidine) and the mixture was stirred at rt for 1 h.The reaction was quenched by addition of an aqueous saturated solution of ammonium chloride ( 10 ml / mmol) and the ethanol was evaporated under reduced pressure. The remaining aqueous suspension was saturated with brine. Usual workup gave crude diols **34-40** which were purified by flash chromatography. The yields described thereafter are based on the starting 2-acyl oxazolidine.

#### General procedure for the synthesis of the Mosher esters of 1,2-diols 35-41

To a solution of 1,2 diol (0.5 mmol), triethylamine (140 mg, 1 mmol) and 4-dimethylaminopyridine (12 mg, 0.1 mmol) in THF (5 ml) was added (+)-MTPACl (2 ml of a 0.5 M solution in THF, 1 mmol). The mixture was refluxed for one night and it was chequed by TLC that all the starting 1.2-diol was consumed. Addition of water (10 ml) and ether (10 ml) followed by usual workup gave crude Mosher ester that was rapidly filtrated over silica gel and analysed by <sup>1</sup>H NMR.

#### (2S)-2-Phenylpropane-1,2-diol 35

After flash chromatography (E/PE : 70/30), 35 was obtained as an oil (112mg, 54%);  $[\alpha]_D^{20}$ : +7.4 (c 9.6, Et<sub>2</sub>O), lit.<sup>22</sup>: +8.9 (c 6.8, Et<sub>2</sub>O); Mosher ester : <sup>1</sup>H NMR (major diasteroisomer): 1.44 (s, 3H), 3.28 (d, J=1.0 Hz, 3H), (minor diastereoisomer) : 1.59 (s, 3H), 3.32 (d, J=1.0 Hz, 3H). These two compounds appear in a 92/8 ratio.

#### (2S)-2-Benzylpropane-1,2-diol 36

After flash chromatography (E/PE : 90/10), **36** was obtained as a solid (95mg, 42%): mp 65°C (lit.<sup>23</sup>: 67-68°C);  $[\alpha]_{D}^{20}$ : -24.0 (c 1.0, H<sub>2</sub>O), lit.<sup>23</sup>: -23.8 (c 3.1, H<sub>2</sub>O); <sup>1</sup>H NMR : 1.14 (s, 3H), 2.2 and 2.6 (two bs, 2H), 2.78 and 2.86 (AB, J=13.3 Hz, 2H), 3.42 and 3.50 (AB, J=11.0 Hz, 2H), 7.20-7.36 (m, 5H); <sup>13</sup>C NMR: 23.4, 44.6, 69.1, 73.0, 126.5, 128.2, 130.4, 136.9; Mosher ester <sup>1</sup>H NMR : 1.21 (s, 3H), 3.60 (s, 3H) only one diastereoisomer can be detected.

## (2R)-1,2-Dihydroxy-2-phenylbut-3-ene 37

After flash chromatography ( E/PE : 60/40), diol 37 was obtained as an oil (123mg, 61%):  $[\alpha]_D^{20}$ : +47.3 (c 1.2, EtOH), lit.<sup>2</sup>: -39.9 (c 1.0, EtOH) for *ent*-37; <sup>1</sup>H NMR : 2.8 et 3.3 (two bs, 2H), 3.76 (s, 2H), 5.28 (dd, 1.3Hz, Jcis = 10.7 Hz, 1H), 5.38 (dd, J = 1.3Hz, Jtrans = 17.4 Hz, 1H), 6.14 (dd, J = 10.7 and 17.4 Hz, 1H), 7.2-7.5 (m, 5H); <sup>13</sup>C NMR : 69.0, 76.1, 115.1, 125.4, 127.1, 128.1, 140.3, 142.2; IR (CHCl<sub>3</sub>) : 3570, 3410, 1600 cm<sup>-1</sup>; Mosher ester: <sup>1</sup>H NMR: 3.46 (s, 3H) only one diastereoisomer can be detected.

## (2R)-1,2-Dihydroxy-2-phenylbutane 38

After flash chromatography (E/PE : 55/45), diol **38** was obtained as an oil (125mg, 55%):  $[\alpha]_{D}^{20}$ : +7.3 (c 0.7, EtOH), lit.<sup>2</sup>: -11.4 (c 3.7, EtOH) for *ent*-**38**; <sup>1</sup>H NMR : 0.64 (t J = 7.4 Hz, 3H), 1.6-1.8 (m, 2H), 2.94 (bs, 2H), 3.53 and 3.67 (AB, J = 11.2 Hz, 2H), 7.1-7.3 (m, 5H); <sup>13</sup>C NMR : 7.7, 31.4, 70.4, 77.8, 125.9, 127.2, 128.5, 143.5; IR (CHCl<sub>3</sub>) : 3570, 3420, 1600 cm<sup>-1</sup>; Mosher ester: <sup>1</sup>H NMR: 0.7 (t, J = 7.4 Hz, 3H) 3.31 (s, 3H) only one diastereoisomer can be detected.

## (2R)-1,2-Dihydroxy-2-phenylpropane 39

After flash chromatography (E/PE: 80/20), **39** was obtained as an oil (117mg, 57%):  $[\alpha]_D^{20}$ : -8.4 (c 3.7, Et<sub>2</sub>O), lit.<sup>22</sup>: +8.9 (c 6.8, Et<sub>2</sub>O) for *ent*-**39**; <sup>1</sup>H NMR : 1.50 (s, 3H), 2.81 and 3.24 (two bs, 2H), 3.57 and 3.73 (AB, J=11.2 Hz, 2H), 7.23-7.46 (m, 5H); <sup>13</sup>C NMR : 26.0, 71.0, 74.9, 125.1, 127.1, 128.4, 145.1; IR (CHCl<sub>3</sub>): 3595, 3430, 1605, 1380 cm<sup>-1</sup>; Mosher ester: <sup>1</sup>H NMR : 1.59 (s, 3H), 3.44 (s, 3H) only one diastereoisomer can be detected.

## (2R)-1,2-Dihydroxy-2-phenylpent-4-ene 40

After flash chromatography (E/PE : 40/60), diol 40 was obtained as an oil (0.12g, 51%):  $[\alpha]_D^{20}$ : +43.4 (c 1.2, CHCl<sub>3</sub>), lit.<sup>24</sup>: +49.5 (c 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR : 2.62 (d, J=7.4 Hz, 2H), 3.09 (s, 2H), 3.64 and 3.73 (AB, J=11.4 Hz, 2H), 5.08 (d, Jcis=9.8 Hz, 1H), 5.10 (d, Jtrans=18.4Hz, 1H), 5.4-5.6 (m, 1H), 7.2-7.45 (m, 5H); <sup>13</sup>C NMR : 43.0, 69.7, 76.3, 119.1, 125.5, 127.0, 128.3, 133.0, 143.4; IR (CHCl<sub>3</sub>) : 3550, 3410, 1635, 1595, 1380, 1345 cm<sup>-1</sup>; Mosher ester <sup>1</sup>H NMR : 3.43 (s, 3H) only one diastereoisomer can be detected.

## (2R)-1,2-Dihydroxy-2-methylhexane 41

After flash chromatography (E/PE: 100/0), diol **41** was obtained as an oil (94mg, 52%):  $[\alpha]_D^{20}$ : +1.92 (c 0.8, CHCl<sub>3</sub>), lit.<sup>25</sup>: +4.4 (c 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR: 0.84 (t, J=6.5 Hz, 3H), 1.07 (s, 3H), 1.17-1.44 (m, 6H), 3.00 (bs, 2H), 3.31 and 3.39 (AB, J=11.1 Hz, 2H); <sup>13</sup>C NMR: 14.2, 23.2, 23.5, 26.1, 38.6, 69.8, 73.3; IR (CHCl<sub>3</sub>): 3590, 3450, 1380 cm<sup>-1</sup>; ; Mosher ester <sup>1</sup>H NMR : 1.11 (s, 3H), 3.49 (s, 3H) only one diastereoisomer can be detected.

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