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Grignard Reactions to Chiral Oxazolidine Aldehydes

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Abstract: Modest to high levels of asymmetric induction are observed with Grignard additions to Garner type aldehydes. The resultant secondary alcohols are important precursors of chiral building blocks for asymmetric synthesis and we have demonstrated that they can be readily converted into their respective γ-hydroxy-β-amino alcohols and β-hydroxyamino acids. Additionally, aryloxy ethers, important components of many natural products, can be obtained from these precursors. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

γ-Hydroxy−β−amino alcohols and their respective amino acids constitute important classes of substances. They are often found as components of more complex structures which possess interesting biological properties, e.g. the sphingosines[1,2] and many natural peptide antibiotics[3]. In addition they are synthetically useful intermediates towards β-lactams.[4] Direct routes to these chiral building blocks[5] have relied on stereoselective additions to chiral serine aldehyde[6,7] or glycine equivalents[8] or reductions of α-amino ketones[9].

Our interest in the synthesis of these building blocks stems from their presence in cyclopeptide alkaloids.[10,11] Although over 200 of these natural products have been isolated and their structures determined little is known of their biological significance. Though plants containing these alkaloids were reported to have therapeutic value,[11] few of these natural products have been tested for their biological activity, due to the lack of large quantities of the pure compounds. Hence, efficient synthetic strategies are required to produce significant amounts of these natural products. We have completed the total synthesis of nummularine F (**Fig. 1**)[12,13] which contains β-hydroxyproline.

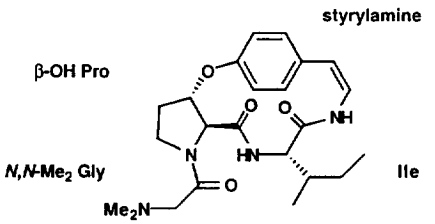
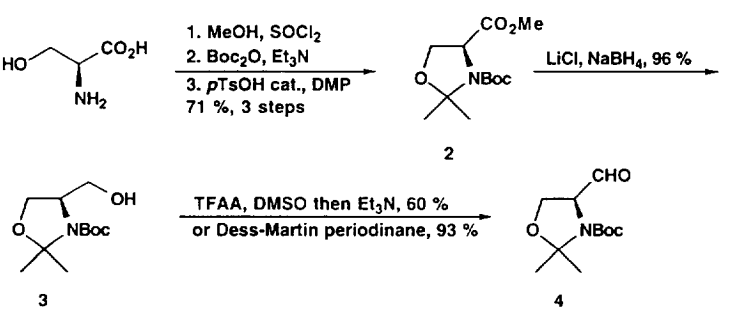


Fig. 1. Nummularine F.

One of the most challenging steps of the synthesis is the formation of the alkyl-aryl ether with the desired configuration (usually *trans*). The phenoxyproline residue contained in nummularine F was obtained *via* Mitsunobu reaction of a suitably protected *cis*-2-(hydroxymethyl)-3-pyrrolidinol with an appropriately functionalized aromatic residue.[14] As a continuation of these investigations, we aim to develop methodology for the synthesis of other aryloxy ethers present in cyclopeptide alkaloids.

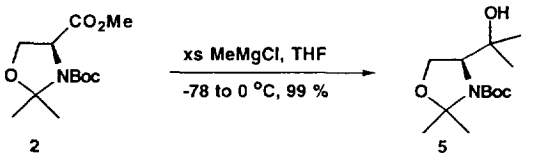
RESULTS AND DISCUSSION

Initial investigations focused on the stereoselective synthesis of the β-hydroxyamino acid components. To this end we required a general route which would allow for the synthesis of multigram quantities of the desired amino acids.[15] The Garner aldehyde **4**[7] appeared suited for our purposes as a chiral serine aldehyde equivalent bearing protecting groups which are readily cleaved. Our synthesis of **4** is a slightly modified approach to that previously reported.[16] *L*-Serine was used as a source of chirality and was suitably protected to afford oxazolidine ester **2** (**Scheme 1**). Reduction of **2** to the Garner aldehyde with DIBAL is often problematic.[17,18] In our hands, the aldehyde suffered from over-reduction unless freshly purchased DIBAL was used for this transformation. A far more convenient route, particularly on a large scale involved a two-step reduction-oxidation sequence. Reduction was effected with sodium borohydride in the presence of LiCl and the alcohol oxidized with either the Dess-Martin periodinane[19] or on a gram scale under Swern conditions to afford the aldehyde in good yield.



Scheme 1

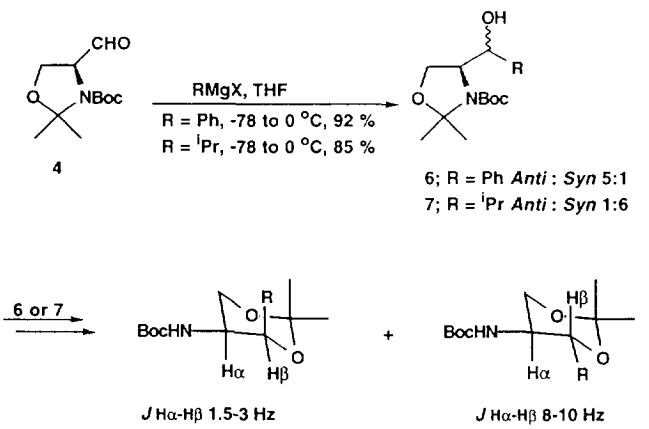
The desired β-hydroxyvaline precursor **5** required for the synthesis of hymenocardine[20,21] was synthesized by addition of an excess of methylmagnesium chloride to ester **2**. The resultant alcohol was obtained in essentially quantitative yield (**Scheme 2**).



Scheme 2

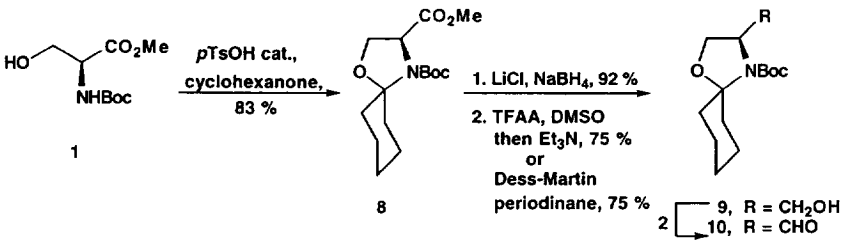
Since the respective β-hydroxyleucine and phenylserine derivatives are synthetically useful precursors for cyclopeptide alkaloids of the frangulanine and integerrine classes respectively,[11] the Garner aldehyde **4** was treated with the appropriate Grignard reagents to afford these compounds. Reaction of the Garner aldehyde with phenylmagnesium bromide under conditions of non-chelation control, proceeded at -78 °C to yield the phenylserine precursor **6** as a diastereomeric mixture in a ratio of 5:1 in favor of the *anti* diastereoisomer (**Scheme 3**). Recrystallization afforded a 77 % yield of pure *anti*-**6**. The absolute stereochemistry was established by converting a diastereomeric mixture of **6** into its respective 1,3-dioxolanes (*op. cit.*). Radunz *et al.* obtained the the *anti*-diastereomer as the major adduct in a ratio of 73:27.[22]

In contrast with these results, when **4** was treated with isopropylmagnesium chloride under identical conditions a reversal in selectivity was observed and the corresponding *syn* diastereomer was isolated as the major adduct in a ratio of 6:1 (**Scheme 3**). Recrystallization gave pure *syn*-**7** in a yield of 73 %. Assignment of absolute stereochemistry was afforded by X-ray analysis[23] of the major adduct from the corresponding reaction with the Garner aldehyde derived from *D*-serine, and again by conversion of the diastereomeric mixture into its respective 1,3-dioxolanes. The Garner aldehyde derived from *D*-serine was also reported to react with isopropylmagnesium chloride to give the corresponding *syn*-diastereomer as the major product.[24]



Scheme 3

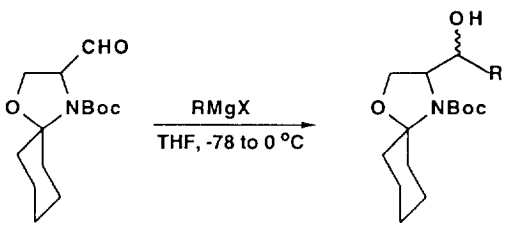
In an effort to improve the level of asymmetric induction, we opted to increase the steric bulk of the substituents on the oxazolidine ring of the Garner aldehyde. Replacement of the dimethyl substituents with a cyclohexyl ring afforded aldehyde **10** by treatment of *N*-Boc serine methyl ester with cyclohexanone in the presence of an acid catalyst and subsequent reduction-oxidation of **8** (*vide supra*) (**Scheme 4**).



Scheme 4

Results for the addition of a range of Grignard reagents to **10** are shown in **Table 1**. Increasing the steric bulk on the oxazolidine ring does indeed lead to an increase in diastereoselection as shown by entries **11** and **16**. In the case of the addition of isopropylmagnesium chloride the ratio of diastereomers (*anti* : *syn*) increased from 1:6 to 1:9 and in the case of phenylmagnesium bromide from 5:1 to 8:1. Entry **11** afforded the *anti* -diastereomer as the major adduct in a ratio of 2:1 and this stereoselectivity compares favorably to results obtained by Beaulieu where no stereoselectivity was observed for the addition of methylmagnesium bromide to the Cbz-protected derivative of the Garner aldehyde **4**.[25]

Additions to α-amino aldehydes derived from *L*-amino acids and therefore to the Garner aldehyde **4** derived from *L*-serine would be expected to occur as a non-chelation controlled Felkin-Ahn attack on the *re* face (**Fig. 1**).[26] Therefore, the observed reversal in selectivity for isopropylmagnesium chloride was of some concern and other Grignard reagents were investigated under identical conditions (**Table 1**).



Entry	R Substituent	Diastereomeric Ratio *Anti* / *Syn*	Yield %
11	Me	2 : 1[a,b]	96
12	Et	1 : 9[b,c]	57
13	^{i}Pr	1 : 9[a,b,c]	73
14	^{t}Bu	1 : 13[c]	15
15	C_6H_{11}	1 : 15[b,c]	74
16	Ph	8 : 1[b,c]	72

[a] ratio determined by 500 MHz ^{1}H nmr [b] major diastereomer assigned by X-ray analysis [c] ratio determined by 500 MHz ^{1}H nmr of the corresponding 1,3-dioxolanes.

Table 1. 1, 2-Asymmetric Induction of a Modified Garner Aldehyde

As predicted by the Felkin-Anh model (**Fig. 2**) the *anti*-diastereomer was obtained as the major adduct in the additions of methylmagnesium chloride and phenylmagnesium bromide to **10**. However, other Grignard reagents afforded the *syn* adduct as the major product. This reversal in selectivity could occur *via* a chelated intermediate as proposed in **Fig. 3**. Chelation is anticipated to occur with the urethane carbonyl as opposed to the electron deficient nitrogen.

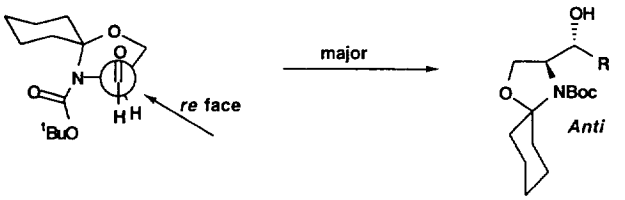


Fig. 2. Felkin-Anh Model Illustrating Attack from the Least Encumbered Face.

Indeed X-ray analysis of the major products show a strong intramolecular hydrogen bond between the hydroxyl group and the urethane carbonyl for both alcohols **13** and **15**. The same hydrogen bond was also shown to exist in solution (*vide infra*). Moreover a change in the geometry about the amide bond in the urethane protecting group must occur for complexation to arise with the urethane carbonyl, and the ORTEP representations shown in **Figs. 4** and **5** of products arising from a chelated and a non-chelated intermediate indicate that this may have occurred. This observation suggests the urethane carbonyl as the site for metal coordination in the transition state, thus giving rise to the *syn*-diastereomer as the predominant adduct.

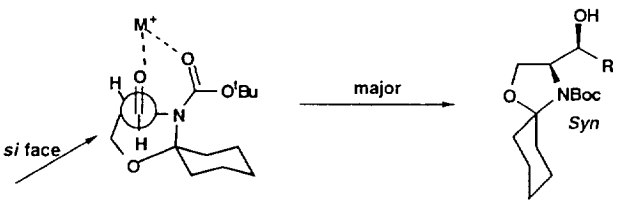


Fig. 3. Cram Chelation Model Resulting in *syn* Selectivity.

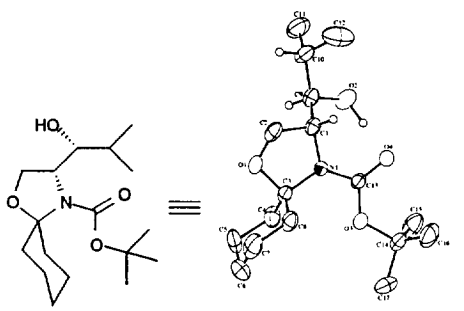


Fig. 4. ORTEP Representation of **13** (Derived from D-Serine) Illustrating the *trans* Geometry of the Amide Bond.

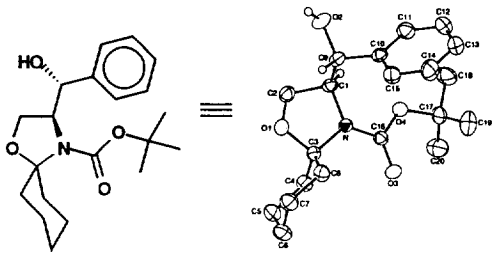


Fig. 5. ORTEP Representation of **16** (Derived from L-Serine) Illustrating the *cis* Geometry of the Amide Bond.

Table 1 shows that increasing stereoselectivity is observed with increasing steric bulk of the incoming nucleophile. However, simultaneously an increase in the undesirable competing reduction of aldehyde **10** was also observed. In most cases, reactions involving a Grignard reagent with β-hydrogen atoms were accompanied by only 2-5 % reduction to give alcohol **9** as a minor by-product. However, the reaction of **10** with *tert*-butylmagnesium bromide suffered in particular from this undesirable pathway and even saturation of the Grignard reagent solution with magnesium bromide prior to addition[27] failed to alleviate this problem. No reduction was observed in the reactions of **10** with methylmagnesium chloride and phenylmagnesium bromide, which both lack hydrogen atoms at the β-position.

The results in **Table 1** can be rationalized in terms of the reactivity of the Grignard reagent. We observed that the most reactive reagents were the methyl and phenyl Grignard reagents which gave rise to products *via* a proposed non-chelation pathway (**Fig. 2**). Thereafter the order of reactivity decreased with the steric bulk of the reagent to afford increasing amounts of products derived *via* a suggested chelated intermediate (**Fig. 3**). It is presumed that reaction with either methyl or phenyl Grignard reagents is kinetically faster, and can occur before chelation takes place. Reactions of the Garner aldehyde **4** with vinylmagnesium bromide, a reagent similar in reactivity to phenylmagnesium bromide, also afforded a product through a non-chelation pathway under similar reaction conditions.[28,29] Coleman also showed the reaction to be non-stereoselective with diethyl ether as solvent in the presence of a Lewis acid. Under these conditions the potential for chelation is greater and an equal competition for a non-chelation pathway and a pathway involving apparent chelation explains the lack of selectivity (**Fig. 6**).[29] Coleman favors a coordinated delivery pathway to explain the lack of chelation control with vinyllithium in contrast to the high levels of apparent chelation with vinylzinc chloride (path B in preference to path A). However, we disfavor the pathway arising through a coordinated intermediate for steric reasons, particularly in the case of **13-16**, where a transition state involving chelation would be less prone to steric considerations.

Confirmation that the pathway involving non-chelation could be influenced by the solvent was achieved by reaction of **10** with phenylmagnesium bromide in diethyl ether, a solvent more likely to favor chelation. A diastereomeric mixture of secondary alcohols **16** was afforded in a reduced ratio of 2:1, as opposed to 8:1 in

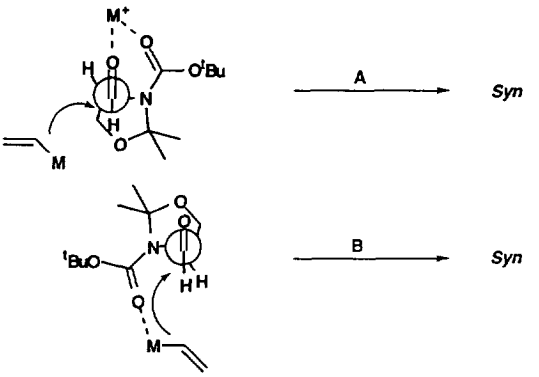
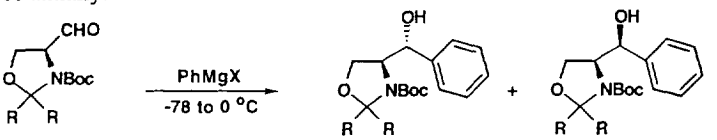


Fig. 6. A: Chelated Transition State; B: Coordinated Delivery.

THF, in favor of the *anti*-diastereomer (**Table 2**). Koskinen also showed that reaction of the Garner aldehyde **4** with diethyl ether as solvent, produced the *syn* diastereomer as the major adduct in a ratio of 3:2,[30] suggesting that these reactions proceeded with a higher degree of chelation. In addition, it has been reported that the diastereoselectivity of the reaction between the Garner aldehyde and isopropylmagnesium chloride can be increased in the presence of $TiCl_4$ to yield the *syn*-adduct by chelation control, although the overall yield is lowered substantially.[24]



4 or 10 *anti*-16 *syn*-16

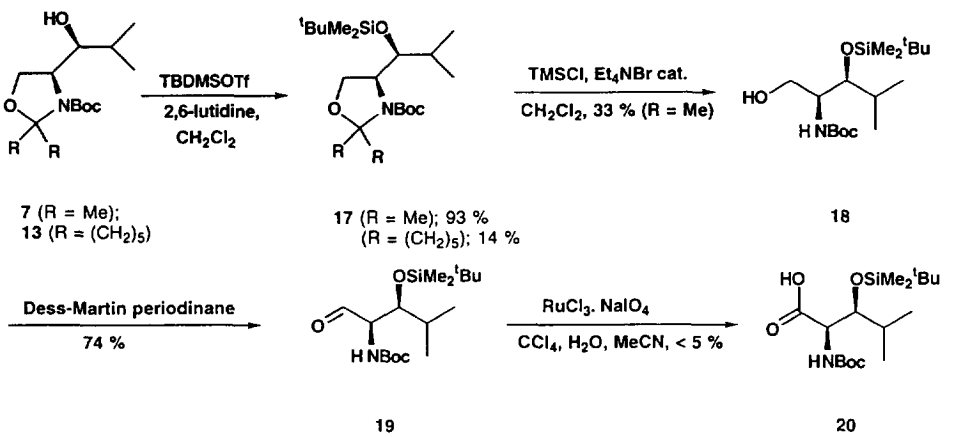
R	Solvent		
$(CH_2)_5$	Et_2O	2	1
$(CH_2)_5$	THF	8	1
Me	Et_2O	2	3
Me	THF	5	1

Table 2. Effect of Solvents on Presumed Chelation Control.

β-Hydroxyleucine, in addition to being a constituent of the frangulanine class of cyclopeptide alkaloids, is present in many natural products[3] and there have been several syntheses of this amino acid to date.[31-35] The major strategy utilized for its synthesis has generally involved the use of Sharpless asymmetric dihydroxylation/epoxidation methodology.

Our investigations toward the synthesis of β-hydroxyleucine utilized precursors **7** and **13** as key intermediates. Although these precursors possess the opposite stereochemistry to that desired for the synthesis of cyclopeptide alkaloids of the frangulanine class, it was opted to perform model studies with these materials which are derived from the more affordable *L*-serine. However, preliminary investigations were unsuccessful.

We had anticipated that protection of the secondary alcohol followed by hydrolytic cleavage of the acetonide, oxidation and removal of protecting groups would yield the desired amino acid. Unfortunately yields for derivatization of the secondary alcohols (OMOM, OMPM, OBn, OMe, OTs, OMs) were uniformly poor presumably because of the existence of an intramolecular hydrogen bond. Consideration of the X-ray structures of both **7** and **13** (and also **15**) led us to verify the existence of an intramolecular hydrogen bond between the urethane carbonyl and the secondary hydroxyl group (CO···H bond distances for **7** and **13** were 1.90 and 1.66 Å; OH···O bond angles were 158.0° and 172.7° respectively). This intramolecular hydrogen bond was also shown to exist in solution; bands at 3569 and 3571 cm^{-1} remaining unchanged with dilution in non-polar solvents in the infrared spectra of these compounds. These secondary alcohols could be derivatized as the corresponding silyl ethers **17** by treatment with TBDMSOTf (**Scheme 5**). Presumably this transformation could be achieved because of the higher affinity that oxygen possesses for silicon, though the yield for the alcohol with the stronger intramolecular hydrogen bond, **17** (R = $(CH_2)_5$), was poor.

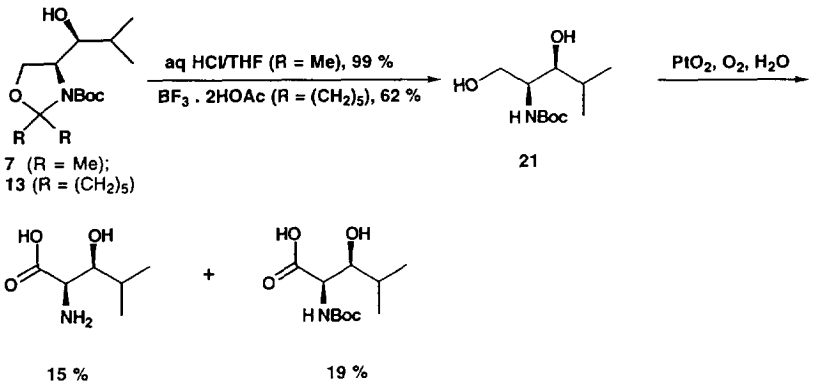


Scheme 5

The silyl ether proved to be incompatible with other protecting groups in **17** and the acetonide could not be selectively cleaved in high yield. TMSBr, formed *in situ*, proved to be the most effective reagent for transformation of **17** into **18** (CSA, *p*TsOH and ion-exchange resin were largely ineffective). Oxidation of **18** to the corresponding diprotected β-hydroxyleucine could only be achieved *via* a two-step protocol. Direct oxidations with pyridinium dichromate and potassium permanganate were unsuccessful. Troublesome oxidations of derivatives of serine aldehydes have previously been noted.[6] A two-step sequence involving oxidation with the Dess-Martin periodinane and then ruthenium trichloride/sodium *meta*-periodate yielded only trace amounts of the desired acid.

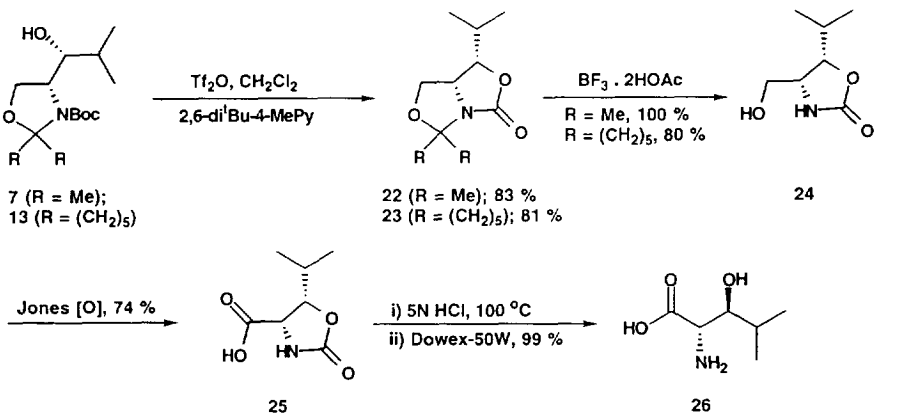
As an alternative we chose to cleave the acetonide of **17** and then attempt to perform a selective oxidation of the corresponding diol. The most efficient method of cleavage depended upon the type of acetonide. Hydrolysis with aqueous HCl in THF afforded the corresponding γ-hydroxy-β-aminodiol **21** in essentially quantitative yield with the oxazolidine ring bearing dimethyl substituents (**Scheme 6**). However, when precursor **13** was treated under identical conditions, the corresponding 1,3-dioxolane was isolated as the major product. The desired transformation was accomplished by treating such substrates with boron

trifluoride-acetic acid complex. Selective oxidation of the primary alcohol of **21** with Adam's catalyst afforded a mixture of *N*-Boc-β-hydroxyleucine as well as the deprotected amino acid both in low yields.



Scheme 6

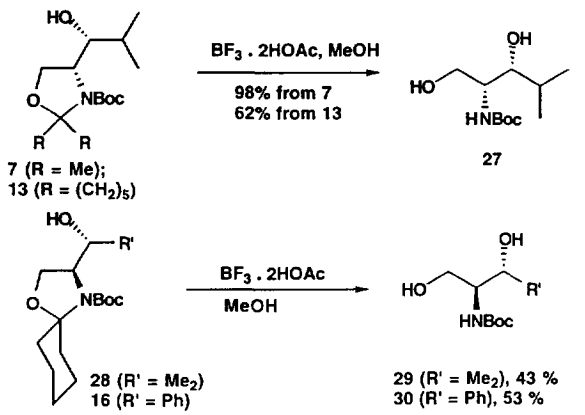
We sought an alternative and more efficient pathway to β-hydroxyleucine and a successful route to the (2*S*, 3*S*)-stereoisomer **26** is shown in **Scheme 7.** Treatment of alcohols **7** and **13** with triflic anhydride furnished the bicyclic compounds **22** and **23** in good yield.[36] Although there is a precedent for this type of intramolecular cyclization, most are performed under harsh conditions.[37-40] This methodology utilizes milder conditions and has also been used for the synthesis of other β-hydroxyamino acids.[41] Hydrolysis of the bicyclic compounds was achieved with boron trifluoride-acetic acid complex to afford oxazolidinone **24.** Subsequent Jones oxidation yielded the oxazolidinone carboxylic acid **25** which was subjected to hydrolysis. Liberation of the amino acid from its hydrochloride salt was then achieved with an ion exchange resin to furnish (2*S*, 3*S*)-β-hydroxyleucine in high yield, whose spectral data proved identical to that previously reported.[35]



Scheme 7

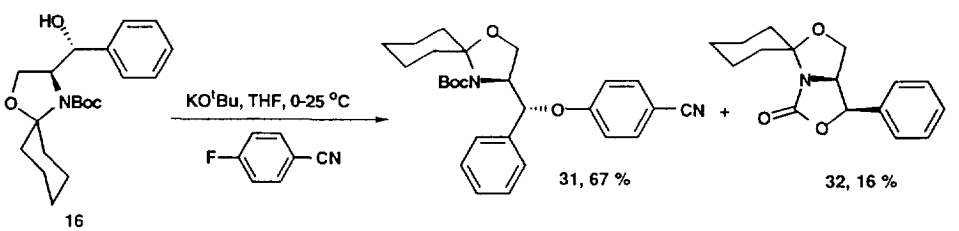
Since γ-hydroxy-β-amino alcohols are also useful building blocks,[42] we were able to demonstrate that the β-hydroxyamino acid precursors **13, 16** and **28** (derived from the reaction of **8** with excess methylmagnesium chloride) could readily be deprotected to afford these compounds. Hydrolysis was

performed with boron trifluoride-acetic acid to afford the desired alcohols in moderate yields due to partial decomposition of the products on silica gel (**Scheme 8**).



Scheme 8

In order to test the significance of these building blocks as intermediates towards the synthesis of cyclopeptide alkaloids, we considered their transformation into the aryloxy ethers present in the respective natural products. Concerning the integerrine class of alkaloids the alkyl-aryl ether would need to be formed with retention of configuration at the 3-position of substrate **16**. A nucleophilic aromatic substitution was effected by reaction of the corresponding anion of **16** with 4-fluorobenzonitrile to afford the desired phenoxyphenylalanine precursor **31** in good yield (**Scheme 9**). The reaction was also accompanied by intramolecular cyclization of the urethane carbonyl to the 3-position, displacing cyanophenolate and giving rise to spirobicyclic **32**. It was initially assumed that **32** was formed *via* an S_N2 pathway and it was envisioned that the cyclization could be driven to completion at higher temperatures. However, heating **31** in chloroform at reflux afforded none of the cyclized product.



Scheme 9

Evidence that the formation of **32** from **31** occurs with retention of configuration was obtained by consideration of the coupling constant between $H_{7'}$ and $H_{7'a}$ in **32** ($J_{7'\text{-}7'a}$ 8.5 Hz)[36,43,44] and also *via* nÖe experiments (**Fig. 7**). None of the *threo* product was observed indicating that there is a kinetic preference for formation of only the *erythro* product *via* an S_N1 pathway. Treatment of **16** with base alone affords none of the cyclized adduct.

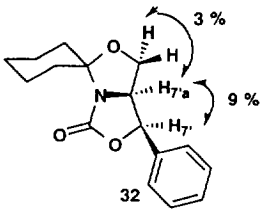
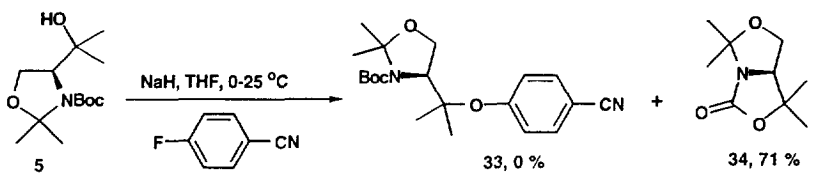


Fig. 7. Nuclear Överhauser Enhancements of Spirobicycle **32**.

To investigate whether the phenoxyvaline unit required for the synthesis of the cyclopeptide alkaloid hymenocardine, could be obtained *via* the same pathway, the corresponding anion of the β-hydroxyvaline precursor **5** was treated with 4-fluorobenzonitrile under similar conditions (**Scheme 10**). None of the desired aryloxy ether **33** was isolated. Instead, an intramolecular cyclization occurred to yield bicyclic **34** in high yield.



Scheme 10

CONCLUSION

In conclusion, we have demonstrated that levels of asymmetric induction of Grignard additions to chiral serine aldehyde equivalents are increased with the modified Garner aldehyde **10**. The stereochemical outcome of additions to such aldehydes is difficult to predict,[2,6,22,24,30,36] and no models are as yet in existence which take into consideration the influence of temperature and solvent on diastereoselectivity for 1,2-asymmetric induction.[45] We have attempted to rationalize the unexpected selectivity detected in some cases based on the observed reactivity of the organomagnesium species, though this issue is obviously a more complex one and aggregation in solution may also play a role in determining the mechanistic pathway.

A number of important chiral building blocks have been synthesized including a valuable aryloxy ether, phenoxyphenylalanine, which is a major component in the integerrine class of cyclopeptide alkaloids.

ACKNOWLEDGEMENTS

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EXPERIMENTAL

^{13}C NMR spectra were recorded at 125 MHz unless otherwise noted. Mass spectra were recorded with electron impact (EI) or chemical ionization (CI) using methane or ammonia. All manipulations were routinely carried out under an inert atmosphere of Ar. With the exception of cyclohexylmagnesium bromide which was freshly prepared, all Grignard reagents were purchased from Aldrich as stock solutions in THF and were titrated prior to use according to standard procedure[46]. Where necessary, solvents and reagents were dried and purified according to recommended methods. Petroleum ether refers to the fraction boiling in the range 40-60 °C. Optical rotations (in degrees, °) were recorded on a Perkin-Elmer Model 241 or 341 polarimeter at the sodium D line. Gas chromatograms were obtained on a Hewlett Packard 5890 GC incorporating a HP-1 Crosslinked Methyl Silicone Gum capillary column. Elemental analyses were performed at the University of Pennsylvania, Chemistry Department Elemental Analysis facility.

(2*R*)-2-*tert*-Butoxycarbonylamino-3-hydroxypropionic acid methyl ester (1).[7] Freshly distilled thionyl chloride (22.0 mL, 0.30 mol) was added dropwise with stirring to a cooled suspension of *D*-serine (31.7 g, 0.30 mol) in anhydrous methanol (370 mL). The mixture was stirred at room temperature for 2 h and then refluxed for 8 h. The solvent was removed under reduced pressure and methanol (3 x 50 mL) was added and then removed under reduced pressure. The white residue remaining was triturated with anhydrous diethyl ether to afford a crude product. To this product in methylene chloride (800 mL) were added triethylamine (92.0 mL, 0.91 mol) and di-*tert*-butyl dicarbonate (72.5g, 0.33 mol) at room temperature with cooling. The reaction mixture was stirred at that temperature for 8 h, and the solution then washed with 1N $KHSO_4$ (250 mL), 5 % $NaHCO_3$ (250 mL), 10 % citric acid (250 mL), and saturated NaCl solution (250 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to afford the product as a colorless, sticky foam (63.8 g, 94 % yield for 2 steps). The crude product was used without further purification; R_f 0.25 (CH_3OH : CH_2Cl_2, 5 %, v/v); ^1H NMR (250 MHz, $CDCl_3$) δ 5.61 (d, J = 7.7 Hz, 1H), 4.35-4.44 (m, 1H), 4.00-3.85 (m, 2H), 3.78 (s, 3H), 3.00 (s, 1H), 1.46 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 171.4, 156.8, 80.2, 63.2, 55.6, 52.5, 28.2; IR ($CHCl_3$) 3600 (m), 3450 (s), 3040 (w), 2990 (s), 2960 (s), 2905 (s), 2880 (w), 1750 (s), 1700 (s), 1500 (s), 1440 (m), 1370 (m), 1240 (m), 1170 (m), 1060 (m), 930 (w), 845 (w), 800 (w) cm^{-1}; HRMS calcd for $C_9H_{18}NO_5$: 220.1185, found 220.1193; $[\alpha]_D^{20}$ -9.37° (c = 3.18, $CHCl_3$); Found: C, 48.82; H, 7.75; N, 6.20. $C_9H_{17}NO_5$ requires C, 49.29; H, 7.76; N, 6.39. The antipode **1** was also synthesized from L-serine; $[\alpha]_D^{20}$ -9.40° (c = 3.10, $CHCl_3$), Lit[47] $[\alpha]_D^{20}$ -18.9° (c = 5.0, MeOH).

2,2-Dimethyloxazolidine-(4*R*)-3,4-dicarboxylic acid 3-*tert*-butyl ester 4-methyl ester (2).[7] A solution of (2*R*)-2-*tert*-butoxycarbonylamino-3-hydroxypropionic acid methyl ester (18.5 g, 84.5 mmol), 2,2-dimethoxypropane (DMP, 18 mL, 172 mmol), and $TsOH{\cdot}H_2O$ (0.24 g, 1.3 mmol) in benzene (270 mL) was heated at reflux for 30 min and slowly distilled until a volume of 250 mL of solvent had been collected. Additional DMP (5.4 mL) and benzene (95 mL) were added, and the procedure was repeated to collect 95 mL of distillate. The cooled solution was diluted with diethyl ether (450 mL) and washed with saturated $NaHCO_3$ solution (2x70 mL), and saturated NaCl solution (70 mL). The organic layer was dried over Na_2SO_4 and the drying agent removed by filtration. Concentration of the filtrate yielded a product, which was purified by column chromatography to afford the product as a pale yellow oil (16.4 g, 75 % yield); R_f 0.75 (CH_3OH : CH_2Cl_2, 5 %, v/v); ^1H NMR (250 MHz, $CDCl_3$) δ 4.50-4.36 (m, 1H), 4.01-4.19 (m, 2H), 3.76 (s, 3H), 1.73-1.41 (m, 15H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 173.7, 151.2, 95.0, 80.3, 66.2 and 66.0 (rotamer), 59.2, 53.3,

28.3, 26.0 and 25.1 (rotamer), 24.9 and 24.3 (rotamer); IR ($CHCl_3$) 3040 (m), 2980 (s), 2880 (m), 1760 (s), 1710 (s), 1440 (w), 1400 (s), 1370 (s), 1240 (m), 1170 (m), 1100 (m), 1055 (m), 845 (s), 800 (w) cm^{-1}; HRMS $C_{12}H_{22}NO_5$ requires 260.1498, found 260.1484; $[\alpha]_D^{20}$ +49.8° (*c* = 1.04, $CHCl_3$);. Found: C, 55.56; H, 8.39; N, 5.71. $C_{12}H_{21}NO_5$ requires C, 55.60; H, 8.11; N, 5.41. The antipode **2** was also synthesized by the above route from the starting material derived from L-serine; $[\alpha]_D^{20}$ -48.8° (*c* = 1.00, $CHCl_3$), Lit[7]. $[\alpha]_D^{20}$ -57° (*c* = 1.3, $CHCl_3$).

(4*S*)-4-Hydroxymethyl-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (3).[7] To a suspension of lithium chloride (5.20 g, 124 mmol) and sodium borohydride (4.7 g, 124 mmol) in ethanol (90 mL), at 0 °C under nitrogen, a solution of 2,2-dimethyloxazolidine-(4*R*)-3,4-dicarboxylic acid 3-*tert*-butyl ester 4-methyl ester (16.0 g, 62 mmol) in dry THF (62 mL) was added dropwise. The mixture was stirred at room temperature for 4 h and the precipitate formed was removed by filtration and washed with ethanol (40 mL). The filtrate and washings were then concentrated to a white residue which was extracted with ethyl acetate. The organic layer was washed with saturated NaCl solution (250 mL) and dried over Na_2SO_4. Concentration followed by chromatography of the crude material on silica gel afforded the product (13.6 g, 96 % yield) as a colorless oil; R_f 0.27 (CH_3OH : CH_2Cl_2, 10 %, v/v); ^1H NMR (250 MHz, $CDCl_3$) δ 4.10-3.95 (m, 3H), 3.86-3.70 (m, 2H), 3.62-3.50 (m, 1H), 1.65-1.40 (m, 15H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 156.6, 94.0, 80.3, 65.2, 64.8, 59.4, 28.3, 27.0, 24.5; IR ($CHCl_3$) 3450 (bs), 2990 (s), 2960 (s), 2890 (s), 1720 (m), 1700 (s), 1480 (m), 1460 (s), 1400 (s), 1370 (s), 1260 (m), 1170 (s), 1110 (m), 1070 (s), 845 (m), 830 (m) cm^{-1}; HRMS $C_{11}H_{21}NO_4$ requires 232.1548, found 232.1542; $[\alpha]_D^{20}$ +17.9° (*c* = 2.13, $CHCl_3$), Lit.[7] $[\alpha]_D^{20}$+23.6° (*c* = 1.44, $CHCl_3$); Found: C, 57.28; H, 9.21; N, 5.74. $C_{11}H_{21}NO_4$ requires C, 57.10; H, 9.09; N, 6.06. The antipode **3** was also synthesized by the above route from the starting material derived from L-serine; $[\alpha]_D^{20}$ -19.8° (*c* = 1.00, $CHCl_3$)

(4*R*)-4-Formyl-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (4).[7] To a precooled solution of methylene chloride (68 mL) and dimethylsulfoxide (8.4 mL, 118 mmol) at -78 °C was added dropwise trifluoroacetic anhydride (12.6 mL, 89 mmol). After 1 h, (4*S*)-4-hydroxymethyl-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (13.6 g, 59.3 mmol) in methylene chloride (44 mL) was added over a period of 15 min. The reaction mixture was stirred at -78 °C for 1 h, at which time triethylamine (24.2 mL, 178 mmol) was added. The resulting solution was warmed to 25 °C, quenched with saturated aqueous NaCl solution (50 mL) and extracted with diethyl ether (2x100 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to afford a crude oil. The oil was purified by column chromatography to yield the aldehyde as a colorless oil (8.16 g, 60 % yield); R_f 0.24 (EtOAc : petroleum ether 20 %, v/v); ^1H NMR (250 MHz, $CDCl_3$) δ 9.47 (d, *J* = 8.0 Hz, 1H), 3.90-4.30 m (3H), 1.30-1.70 m (15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.5, 156.0, 94.9, 80.9, 64.6, 63.8, 28.1, 25.6, 23.7; IR ($CHCl_3$) 3040 (w), 2990 (s), 2960 (s), 2905 (s), 2870 (m), 2810 (m), 1700 (s), 1620 (s), 1400 (m), 1365 (m), 1260 (m), 1250 (m), 1170 (s), 1090 (s), 1060 (s), 845 (m) cm^{-1}; $[\alpha]_D^{20}$ +83.8° (*c* = 1.00, $CHCl_3$), Lit. [7]. $[\alpha]_D^{20}$ +95.0° (*c* = 1.34, $CHCl_3$); Found: C, 57.29; H, 8.47; N, 6.24. $C_{11}H_{19}NO_4$ requires C, 57.64; H, 8.30; N, 6.11. The antipode **4** was also synthesized by the same route from the starting material derived from L-serine; $[\alpha]_D^{20}$ -87.2° (*c* = 1.00, $CHCl_3$), Lit[7]. $[\alpha]_D^{20}$ -91.7° (*c* = 1.04, $CHCl_3$).

(4*S*)-4-(1-Hydroxy-1-methylethyl)-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (5). To 2,2-dimethyloxazolidine-(4*S*)-3,4-dicarboxylic acid 3-*tert*-butyl ester 4-methyl ester (1.0 g, 4.4 mmol) in dry THF (25 mL) at -78 °C under nitrogen, was added dropwise methylmagnesium chloride (4.4 mL of a 3.0 M solution

in THF, 13.1 mmol). After stirring at -78 °C for 1h, the reaction mixture was diluted with diethyl ether (150 mL) and quenched with saturated NH_4Cl solution. The organic layer was washed with saturated NaCl, dried over Na_2SO_4, filtered, and the filtrate concentrated to afford an off-white solid. Purification by column chromatography on silica gel and recrystallization (EtOAc : petroleum ether) afforded **5** as a white crystalline solid (1.1 g, 99 % yield) ; mp 39-41 °C; R_f 0.40 (EtOAc: petroleum ether, 20 %, v/v); ^1H NMR (500 MHz, $CDCl_3$) δ 5.29 (bs, 1H), 4.02 (m, 1H), 3.84 (m, 1H), 1.59 (s, 3H), 1.53 (s, 3H), 1.20 (s, 3H), 1.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.8, 94.6, 79.2, 72.8, 66.4, 65.1, 29.8, 28.4 and 28.3 (rotamer), 28.2 and 28.1 (rotamer), 27.8, 26.1, 24.5, 24.4; IR (film) 3395 br (m), 2978 (m), 1698 (s) cm^{-1}; HRMS $C_{13}H_{26}NO_4$ requires 260.1862, found 260.1866; *m/z* (CI, NH_3) 260 (MH^+, 21), 204 (100), 186 (53), 160 (10), 144 (66); $[\alpha]_D^{20}$ -27.5° (*c* = 5.3, $CHCl_3$).

(4*S*)-4-[(1*S*)-1-Hydroxyphenylmethyl]-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (6).[22]To a precooled solution of THF (25 mL) and (4*S*)-4-formyl-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (1.0 g, 4.4 mmol) at -78 °C under nitrogen, was added dropwise a 0.69 M solution of phenylmagnesium bromide (19 mL, 13.1 mmol) in THF over 30 min. The resultant yellow solution was stirred for an additional 2 h at -78 °C, and then warmed to 0 °C. The reaction mixture was then diluted with diethyl ether (150 mL) and quenched with saturated NH_4Cl solution. The organic layer was washed with saturated NaCl, dried over Na_2SO_4, filtered, and the filtrate concentrated to afford an off-white solid. Purification by column chromatography on silica gel and recrystallization (EtOAc: petroleum ether) yielded pure **6** (1.03 g, 77 % yield) as a white solid; mp 99-100 °C; R_f 0.75 (EtOAc: petroleum ether, 20 %, v/v); ^1H NMR (500 MHz, $CDCl_3$) δ 7.36-7.22 (m, 5H), 5.05 (s, 1H), 4.73-4.71 (m, 1H), 4.28-4.23 (m, 2H), 4.10-4.01 (m, 1H), 1.67-1.16 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8 and 151.9 (rotamer), 94.4, 80.8 and 80.1 (rotamer), 77.7, 74.5 and 73.3 (rotamer), 64.5 and 64.0 (rotamer), 63.3 and 62. 8 (rotamer), 28.2, 26.3 and 25.8 (rotamer). 24.2 and 22.7 (rotamer); IR (film) 3458 (m), 2977 (m), 1693 (s), 1454 (m), 1388 (s), 1249 (m), 1166 (m), 1096 (m) cm^{-1};.HRMS $C_{17}H_{26}NO_4$ requires 308.1861, found 308.1869; *m/z* (CI, NH_3)308 (MH^+, 15), 252 (60), 234 (50), 200 (100), 194 (40), 144 (35), 107 (38);$[\alpha]_D^{20}$ -8.0° (*c* = 1.25, $CHCl_3$). Found: C, 65.98; H, 8.06; N, 4.21 $C_{17}H_{25}NO_4$ requires C, 66.41; H, 8.20; N, 4.56.

(4*R*)-4-[(1*R*)-1-Hydroxy-2-methylpropyl]-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (7). To a precooled solution of THF (160 mL) and (4*S*)-4-formyl-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (5.50 g, 24.2 mmol) at -78 °C under nitrogen, was added dropwise a 2 M solution of isopropylmagnesium chloride (40.0 mL, 79.9 mmol) in THF over 30 min. The resultant yellow solution was stirred for an additional 2 h at -78 °C, and then warmed to 0 °C. The reaction mixture was then diluted with diethyl ether (150 mL) and quenched with saturated NH_4Cl solution. The organic layer was washed with saturated NaCl, dried over Na_2SO_4, filtered, and concentrated to afford a crude oil. Purification by column chromatography on silica gel and recrystallization (EtOAc : petroleum ether) afforded the pure alcohol (4.79 g, 73 yield %) as a white solid; mp 78-80° C; R_f 0.48 (EtOAc : petroleum ether, 20%, v/v); ^1H NMR (500 MHz, $CDCl_3$) δ 4.05 (bs, 2H), 3.95-3.87 (m, 1H), 3.80-3.74 (m, 1H), 3.53-3.43 (m, 1H), 1.72-1.61 (m, 1H), 1.60-1.41 (m, 15H), 1.01 and 0.94 (rotamer) (d, *J* = 6.9 Hz, 3H), 0.91 and 0.89 (rotamer) (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.4, 94.2, 81.3, 79.3, 65.3, 61.4, 30.9, 28.3, 27.2, 24.4, 20.3, 14.2; IR ($CHCl_3$) 3569 (w), 3450 (s), 3030 (m), 2960 (s), 2905 (s), 1700 (s), 1655 (s), 1450 (m), 1400 (m), 1380 (m), 1370 (m), 1240 (m), 1170 (m), 1105 (m), 1050 (m), 1020 (m), 860 (m), 845 (m) cm^{-1}; HRMS calcd $C_{14}H_{28}NO_4$ requires 274.2018, found 274.2023; $[\alpha]_D^{20}$ +55.3° (*c* = 1.15, $CHCl_3$); $C_{14}H_{28}NO_4$ requires C,

61.54; H, 9.90; N, 5.13. Found: C, 61.33; H, 9.97; N, 5.27. The antipode **7** was also synthesized by the same route from the starting material derived from L-serine; $[\alpha]_D^{20}$ -54.3° (*c* = 1.48, $CHCl_3$).

1-Oxa-4-azaspiro[4.5]decane-(3*R*)-3,4-dicarboxylic acid 4-*tert*-butyl ester 3-methyl ester (8). A solution of (2*R*)-2-*tert*-Butoxycarbonylamino-3-hydroxypropionic acid methyl ester (4.38 g, 20 mmol), cyclohexanone (19.6 g, 200 mmol) and $TsOH.H_2O$ (0.057 g, 0.3 mmol) in dry benzene (400 mL) was heated under reflux in a Soxhlet apparatus with 4Å molecular sieves (*ca.* 40 g) for 36 h. The solvent was removed *in vacuo*, the mixture diluted with diethyl ether (200 mL) and the organic layer washed successively with saturated $NaHCO_3$ solution (50 mL) and brine (3 x 50 mL) before being dried over $MgSO_4$. Filtration and concentration of the mixture yielded the crude product which was purified by column chromatography on silica gel to afford the product (4.99 g, 83 yield %) as a colorless liquid; R_f 0.31 (EtOAc : petroleum ether, 20 %, v/v); ^1H NMR (500 MHz, $CDCl_3$) δ 4.50-4.30 (m, 1H), 4.11-3.90 (m, 2H), 3.66 (s, 3H), 2.41-1.47 (m, 9H), 1.32 and1.40 (s, 9H), 1.00-1.25 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 150.6, 96.0, 80.2, 66.0, 58.6, 52.1, 32.8, 32.0, 28.2, 24.2, 23.5, 23.4; IR (CH_2Cl_2) 2960 (s), 2880 (m), 1760 (s), 1700 (s), 1450 (m), 1440 (m), 1400 (s), 1370(s), 1290(m), 1240 (m), 1180 (s), 1140 (m), 1090 (m), 910 (m) cm^{-1}; HRMS (CI, NH_3) calcd for $C_{15}H_{25}NO_5$ requires 299.1733, found 299.1742; *m/z* 299 (M^+, 12), 244 (8), 226 (12), 199 (43), 170 (23), 156 (100), 140 (8); $[\alpha]_D^{20}$ +39.8° (*c* = 3.40, $CHCl_3$); $C_{15}H_{25}NO_5$: C, 60.17; H, 8.42; N, 4.68. Found: C, 59.94; H, 8.58; N, 4.49. The antipode **8** was also synthesized by the same route from the starting material derived from L-serine; $[\alpha]_D^{20}$ -38.0° (*c* = 3.00, $CHCl_3$).

(3*S*)-3-Hydroxymethyl-1-oxa-4-azaspiro[4.5]decane-4-carboxylic acid *tert*-butyl ester (9). Treatment of 1-oxa-4-azaspiro[4.5]decane-(3*S*)-3,4-dicarboxylic acid 4-*tert*-butyl ester 3-methyl ester (4.10 g, 13.71 mmol) with lithium chloride (1.16 g, 27.42 mmol) and sodium borohydride (1.04 g, 27.42 mmol) according to the procedure outlined earlier afforded **9** as a white solid after purification by column chromatography on silica gel (3.42 g, 92 % yield); mp 99 °C; R_f 0.41 (EtOAc : petroleum ether, 30 %, v/v); ^1H NMR (500 MHz, $CDCl_3$) δ 4.15-3.45 (m, 5H), 3.20-2.70 (s, 1H), 2.55-1.92 (m, 2H), 1.80-0.95 (m, 17H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.0, 95.6, 80.1, 65.8, 65.3, 59.6, 35.8, 31.8, 28.6, 25.1, 23.6, 23.5; IR (KBr) 3440 (m), 2940 (s), 1690 (s), 1490 (m), 1450 (w), 1390 (s), 1360 (m), 1160 (s), 900 (w) cm^{-1}; HRMS calcd for $C_{14}H_{26}NO_4$ requires 272.1862, found 272.1858; *m/z* (CI, NH_3) 272 (MH^+, 100), 216 (35), 172 (58); $[\alpha]_D^{20}$ +21.9° (*c* = 0.80, $CHCl_3$); Found: C, 61.58; H, 9.54; N, 4.91. $C_{14}H_{25}NO_4$ requires C, 61.95; H, 9.29; N, 5.16. The antipode **9** was also synthesized by the same route from the starting material derived from L-serine; $[\alpha]_D^{20}$ -18.8° (*c* = 1.00, $CHCl_3$).

(3*R*)-3-Formyl-1-oxo-4-azaspiro[4.5]decane-4-carboxylic acid *tert*-butyl ester (10). Dess-Martin periodinane (3 g, 7.1 mmol) was added to (3*R*)-3-hydroxymethyl-1-oxa-4-azaspiro[4.5]decane-4-carboxylic acid *tert*-butyl ester (1.5 g, 5.5 mmol) in dichloromethane (50 mL) and the reaction stirred until tlc indicated complete consumption of starting material (usually 1 h). Diethyl ether (100 mL) was then added to the reaction mixture and the mixture poured into saturated $NaHCO_3$ solution and an excess of $Na_2S_2O_3$ solution. The organic layer was washed with 0.5 M NaOH (50 mL) and saturated NaCl solution (50 mL) before being dried and concentrated to yield the product as a colorless oil (1.1 g, 75 % yield); mp 99 °C; R_f 0.26 (EtOAc : petroleum, 7 %, v/v); ^1H NMR (500 MHz, $CDCl_3$) δ 9.50 (d, *J* = 18 Hz, 1H), 4.35-3.92 (m, 3H), 2.55-1.95 (m, 2H), 1.78-1.01 (m, 17H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.5 151.3, 99.8, 96.3, 81.0, 64.6, 63.9, 41.9, 34.0, 31.3, 28.2, 27.0, 24.5, 23.2; IR ($CHCl_3$) 2970 (m), 2930 (s), 2860 (w), 1720 (m), 1700 (s), 1450 (w), 1390 (s), 1370 (s), 1170 (m), 1120 (m), 1070 (m) cm^{-1}; HRMS calcd for $C_{14}H_{23}NO_4$ requires 269.1627,

found 269.1621; *m/z* (CI, NH_3) 270 (MH^+, 14), 269 (26), 240 (30), 214 (74), 196 (25), 169 (53), 140 (100); $[\alpha]_D^{20}$ +66.0° (*c* = 1.57, $CHCl_3$); Found: C, 62.00; H, 9.08; N, 4.49. $C_{14}H_{23}NO_4$ requires C, 62.42; H, 8.61; N, 5.20. The antipode **10** was also synthesized by the same route from the starting material derived from L-serine; $[\alpha]_D^{20}$ -66.4° (*c* = 1.51, $CHCl_3$).

(3*S*)-3-[1-(1*R*)-Hydroxyethyl]-1-oxa-4-azaspiro[4.5]decane-4-carboxylic acid *tert*-butyl ester (11). Aldehyde **10** (0.57 g, 2.10 mmol) was treated with methylmagnesium chloride (2.35 mL of a 3.0 M solution in THF, 7.0 mmol) according to the procedure outlined earlier to afford a crude oil which was purified by column chromatography and then recrystallized (EtOAc: petroleum ether) to give **11** as a white solid (0.38 g, 64 % yield); mp 102 °C; R_f 0.51 (EtOAc : petroleum ether, 20 %, v/v); ^1H NMR (500 MHz, $CDCl_3$) δ 4.03 (m, 1H), 3.90 (m, 2H), 3.77 (m, 1H), 2.22 (m, 1H), 2.03 (m, 1H), 1.78-1.53 (m, 7H), 1.51 (s, 9H), 1.26-1.00 (m and d, *J* = 6.3 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.1, 95.7, 80.9, 69.5, 64.4, 62.2, 34.8, 31.0, 29.0, 28.4, 23.4 and 23.2 (rotamer), 19.0, 18.4; IR (film) 3395 br (m), 2970 (s), 1680 (s) cm^{-1}; HRMS calcd for $C_{15}H_{28}NO_4$: 286.2018, found 286.2027; *m/z* (CI, NH_3) 286 (100), 247 (32), 230 (57), 186 (38); $[\alpha]_D^{20}$ 17.0° (*c* = 0.98, $CHCl_3$); Found: C, 62.96; H, 9.66; N, 5.13. $C_{15}H_{27}NO_4$ requires C, 63.13; H, 9.54; N, 4.91.

(3*S*)-3-[(1*S*)-1-Hydroxypropyl]-1-oxa-4-azaspiro[4.5]decane-4-carboxylic acid *tert*-butyl ester (12). Aldehyde **10** (1.0 g, 3.72 mmol) was treated with ethylmagnesium bromide (14.7 mL of a 0.76 M solution in THF, 11.15 mmol) according to the procedure outlined above to afford a crude product which was purified by column chromatography on silica gel to yield **12** as a colorless oil (0.53 g, 51 % yield); R_f 0.30 (EtOAc : petroleum ether, 10 %, v/v); ^1H NMR (500 MHz, $CDCl_3$) δ 4.00 (bm, 1H), 3.91 (m, 1H), 3.85 (dd, *J* = 9.7, 6.0 Hz, 1H), 3.77 (m, 1H), 3.65-3.58 (m, 1H), 2.24 (m, 1H), 2.10 (m, 1H), 1.68-1.40 (m, 17H), 1.35 (m, 1H), 1.16 (m, 1H), 0.98 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.1, 95.6, 81.4, 74.4, 64.7, 45.8, 35.8, 34.9, 31.2, 28.6, 28.4, 25.9, 24.9, 23.4, 23.2, 10.6; IR (film) 3569 (w), 3453 (m), 2971 (m), 2930 (s), 1698 (s) cm^{-1}; HRMS calcd for $C_{16}H_{30}NO_4$: 300.2174, found 300.2180; *m/z* (CI, NH_3) 300 (MH^+, 100), 244 (18), 200 (70); $[\alpha]_D^{20}$ -20.6° (*c* = 1.0, $CHCl_3$).

(3*R*)-3-[(1*R*)-1-Hydroxy-2-methylpropyl]-1-oxa-4-azaspiro[4.5]-decane-4-carboxylic acid *tert*-butyl ester (13). (3*R*)-3-Formyl-1-oxo-4-azaspiro[4.5]decane-4-carboxylic acid *tert*-butyl ester (1.26 g, 4.68 mmol) was treated with isopropylmagnesium chloride (1.47 g, 14.3 mmol) according to the procedure outlined earlier to afford a crude oil which was purified by column chromatography and then recrystallized (EtOAc : petroleum ether) to give the alcohol as white needles (0.96 g, 66 % yield); mp 130° C; R_f 0.54 (EtOAc : petroleum ether, 13 %, v/v); ^1H NMR (500 MHz, $CDCl_3$) δ 5.30 (d, *J* = 15 Hz, 1H), 4.10-3.30 (m, 4H), 2.80-2.02 (m, 2H), 1.75-1.25 (m, 16H), 1.20-0.75 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5, 99.0, 79.2, 76.1, 64.9, 45.5, 35.8, 31.0, 29.2, 28.4, 28.3, 27.0, 24.9, 23.4, 22.5, 20.4, 14.2; IR ($CHCl_3$) 3400 (m), 2970 (s), 2920 (s), 1700 (m), 1650 (s), 1480 (w), 1450 (w), 1400 (s), 1360 (m), 1170 (m), 1130 (m), 1090 (w), 1000 (w), 900 (w) cm^{-1}; HRMS calcd for $C_{17}H_{31}NO_4$: 313.2253, found 313.2246; *m/z* (CI, NH_3) 313 (23) 259 (12), 258 (68), 241 (26), 214 (38), (213 (56), 170 (100), (140 (98), 123 (20); $[\alpha]_D^{20}$ +48.7° (*c* = 1.43, $CHCl_3$); Found: C, 64.73; H, 10.27; N, 4.30. $C_{17}H_{31}NO_4$ requires C, 65.13; H, 9.97; N, 4.47. The antipode **13** was also synthesized by the same route from the starting material derived from L-serine; $[\alpha]_D^{20}$ -49.0° (*c* = 1.00, $CHCl_3$).

(3*S*)-3-[(1*R*)-1-Hydroxy-2,2-dimethylpropyl)-1-oxa-4-azaspiro[4.5]decane-4-carboxylic acid *tert*-butyl ester (14). Aldehyde **10** (1.0 g, 3.72 mmol) was treated with *tert*butylmagnesium bromide (14.3 mL of a 0.78 M solution in THF, 11.15 mmol) according to the procedure outlined above to afford a crude product which was purified by column chromatography on silica gel to yield **14** as a colorless oil (0.17 g, 14 % yield); R_f

0.54 (EtOAc : petroleum ether, 10 %, v/v); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.02 (m, 1H), 3.87 (dd, J = 9.0, 5.1 Hz, 1H), 3.70 (d, J = 9.0 Hz, 1H), 3.17 (t, J = 9.1 Hz, 1H), 2.30-2.11 (m, 2H), 2.10-1.79 (m, 2H), 1.78-1.38 (m, 15H), 1.14 (m, 1H), 0.95 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.6, 94.9, 81.0, 80.4, 67.7, 57.9, 35.5, 30.9, 28.5, 26.8, 26.2, 26.0, 24.9, 23.5, 23.4; IR (film) 3550 (w), 3477 (m), 2972 (m), 2932 (s), 2862 (m), 1697 (s) cm^{-1}; HRMS calcd for $C_{18}H_{34}NO_4$: 328.2487, found 328.2485; *m/z* (CI, NH_3) 328 (MH^+, 100), 272 (22), 246 (15), 228 (84); $[\alpha]_D^{20}$ -27.5° (c = 0.67, $CHCl_3$).

(3*S*)-3-[(1*S*)-1-Cyclohexylhydroxymethyl]-1-oxa-4-azaspiro[4.5]decane-4-carboxylic acid *tert*-butyl ester (15). A 1.12 M solution of cyclohexylmagnesium bromide (10 mL) (freshly prepared form cyclohexyl bromide and magnesium turnings) was added to aldehyde **10** (1.0 g, 3.72 mmol) at -78 °C in dry THF (10 mL). The reaction mixture was warmed slowly to 0 °C and when tlc indicated complete consumption of starting material, the reaction mixture was diluted with diethyl ether (50 mL) and quenched with saturated NH_4Cl solution. The organic layer was washed with saturated NaCl, dried over $MgSO_4$, filtered, and the filtrate concentrated under reduced pressure to afford a white solid. The crude material was purified by column chromatography on silica gel and recrystallized (EtOAc : petroleum ether) to yield pure **15** (0.82 g, 62 % yield) as a white solid; mp 117-118° C; R_f 0.75 (EtOAc : petroleum ether, 20 %, v/v); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.06 (bm, 1H), 3.83 (dd, J = 9.2, 5.7 Hz, 1H), 3.71 (d, J = 9.2 Hz, 1H), 3.45-3.38 (m, 1H), 2.32-2.10 (m, 2H), 2.05 (m, 1H), 1.92 (m, 1H), 1.78 (m, 2H), 1.74-1.33 (m, 17H), 1.32-1.01 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.0, 95.8, 81.2, 78.5, 70.5, 66.0 and 65.1 (rotamer), 59.7, 55.1, 41.6, 35.8 and 34.1 (rotamer), 32.1 and 31.0 (rotamer), 30.5 and 29.9 (rotamer), 28.4, 27.6, 26.7 and 26.4 (rotamer), 26.1 and 25.8 (rotamer), 25.2 and 25.0 (rotamer), 24.9, 23.4, 22.9 and 22.7 (rotamer); IR (CCl_4) 3571 (w), 3436 (m), 2971 (m), 2931 (s), 2856 (s), 1705 (m), 1660 (s) cm^{-1}; HRMS calcd for $C_{20}H_{36}NO_4$: 354.2644, found 354.2633; *m/z* (CI, NH_3) 354 (MH^+, 94), 298 (76), 254 (100); $[\alpha]_D^{20}$ -42.8° (c = 1.0, $CHCl_3$).

(3*S*)-3-[(1*S*)-1-Hydroxyphenylmethyl]-1-oxa-4-azaspiro[4.5]decane-4-carboxylic acid *tert*-butyl ester (16). Aldehyde **10** (0.48 g, 1.80 mmol) was treated with phenylmagnesium bromide (5.9 mL of a 0.7 M solution in THF, 4.1 mmol) according to the procedure outlined above to afford a white solid which was purified by recrystallization (EtOAc : petroleum ether) to give **16** as a white crystalline solid (0.40 g, 64 % yield); mp 140 °C; R_f 0.61 (EtOAc : petroleum ether, 20 %, v/v); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, J = 7.4 Hz, 1H), 7.31 (m, 2H), 7.22 (d, J = 7.4 Hz, 1H), 5.05 (s, 1H), 4.25 (bs, 1H), 4.10-3.88 (m, 2H), 3.77 (m, 1H), 2.54 (m, 1H), 2.22 (m, 1H), 2.01 (m, 1H), 1.73-1.35 (m, 14H), 1.26-0.95 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.0 and 152.1 (rotamer), 141.1, 128.4 and 128.2 (rotamer), 127.3, 125.9, 95.9, 80.9 and 80.4 (rotamer), 74.7 and 73.6 (rotamer), 63.6, 62.9, 35.0 and 34.6 (rotamer), 31.0, 29.4, 28.4, 24.8, 23.4, 23.2; IR (film) 3370 br (s), 3010 (w), 2970 (s), 1680 (s) cm^{-1}; HRMS calcd for $C_{20}H_{30}NO_4$: 348.2175, found 348.2189; *m/z* (CI, NH_3) 348 (MH^+, 11), 292 (33), 274 (25), 240 (71), 140 (100); $[\alpha]_D^{20}$ -3.6° (c = 1.0, $CDCl_3$).

(4*R*, 5*S*)-1-Isopropyl-5,5-dimethyldihydrooxazolo[3,4-c]oxazol-3-one (22). Triflic anhydride (237 µL, 1.41 mmol) was added to (4*R*)-4-[(1*R*)-1-hydroxy-2-methylpropyl]-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (0.3 g, 1.17 mmol) and 2,6-di-*tert*butyl 4-methylpyridine (0.57 g, 2.79 mmol) in CH_2Cl_2 (12 mL) at 0 °C. After stirring for 1 min the resultant white precipitate was filtered and the organics washed with a 5 % aqueous solution of $NaHCO_3$ before being dried and concentrated to yield **22** as a white solid (188 mg, 81 % yield); mp 39 °C; R_f 0.60 (EtOAc : petroleum ether, 20 %, v/v); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.25 (m, 1H), 4.15 (dd, J = 10.4, 7.8 Hz, 1H), 3.96 (dd, J = 8.2, 6.0 Hz, 1H), 3.64 (m, 1H), 1.85 (m, 1H), 1.72 (s, 3H), 1.46 (s, 3H), 1.08 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.2, 98.9, 79.7, 63.7, 61.0, 29.6, 23.5,

19.8, 18.0; IR (film) 2962 (m), 1746 (s) cm^{-1}; HRMS calcd for $C_{10}H_{18}NO_3$: 200.1286, found 200.1283; *m/z* (CI, NH_3) 200 (MH^+, 100), 177 (20), 160 (44); $[\alpha]_D^{20}$ -72.0° (*c* = 1.0, $CHCl_3$).

(7'*S*, 7'a*R*)-Dihydro-7'-isopropylspiro[cyclohexane-1,3'-[1*H*, 3*H*, 5*H*]oxazolo-[3,4-*c*]oxazol]-5'-one (23). Treatment of (3*R*)-3-[(1*R*)-1-hydroxy-2-methylpropyl]-1-oxa-4-azaspiro[4.5]-decane-4-carboxylic acid *tert*-butyl ester (31 mg, 0.10 mmol) with triflic anhydride (20 µL, 0.12 mmol) and 2,6-di-*tert*butyl 4-methylpyridine (50 mg, 0.24 mmol) in CH_2Cl_2 (1 mL) at 0 °C according to the procedure outlined above afforded **23** as a white solid (11 mg, 83 % yield); mp 98 °C; R_f 0.57 (EtOAc : petroleum ether, 20 %, v/v); ^1H NMR (500 MHz, $CDCl_3$) δ 4.25 (m, 1H), 4.15 (dd, *J* = 10.4, 7.8 Hz, 1H), 3.93 (dd, *J* = 8.1, 6.6 Hz, 1H), 3.65 (m, 1H), 2.43 (m, 1H), 1.90-1.41 (m, 9H), 1.31 (m, 1H), 1.08 (d, *J* = 6.7 Hz, 3H), 0.85 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.2, 96.5, 79.9, 63.1, 60.6, 37.6, 31.9, 29.5, 24.9, 23.6, 23.1, 19.8, 18.0; IR (film) 2960 (m), 1738 (s) cm^{-1}; HRMS calcd for $C_{13}H_{22}NO_3$: 240.1599, found 240.1606; *m/z* (CI, NH_3) 257 ($M+NH_4^+$, 5), 240 (MH^+, 100), 196 (5), 152 (5); $[\alpha]_D^{20}$+36.0° (*c* = 0.5, $CHCl_3$); Found: C, 65.14; H, 8.78; N, 5.90. $C_{13}H_{21}NO_3$ requires C, 65.25; H, 8.84; N, 5.85.

4-(4*S*)-Hydroxymethyl-5-5(*R*)-isopropyloxazolidin-2-one (24).[44]Method A : Bicyclic derivative **22** (0.16 g, 0.8 mmol) was treated with boron trifluoride-acetic acid (1.2 mL, 8.60 mmol) in methanol (5 mL) for 3 h at room temperature followed by a basic work-up to give **24** as a white solid (0.13 g, 98 % yield); mp 82 °C; R_f 0.52 (MeOH : CH_2Cl_2, 10 %, v/v); ^1H NMR (500 MHz, $CDCl_3$) δ 6.48 (s, 1H), 4.16 (dd, *J* = 10.6, 6.8 Hz, 2H), 3.75 (m, 3H), 3.55 (bm, 1H), 2.03 (m, 1H), 1.06 (d, *J* = 6.4 Hz, 3H), 0.92 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.8, 85.1, 60.6, 56.6, 27.4, 19.8, 18.7; IR (film) 3378 br (s), 2962 (m), 1749 (s) cm^{-1}; HRMS calcd for $C_7H_{19}N_2O_3$: 177.1239, found 177.1247; *m/z* (CI, NH_3) 177 ($M+NH_4^+$, 90), 160 (MH^+, 100); $[\alpha]_D^{20}$ +95.6° (*c* = 1.0, $CHCl_3$), Lit.[44]. $[\alpha]_D^{20}$ +51.2° (*c* = 0.78, MeOH).

Method B : Treatment of spiro derivative **23** (85 mg, 0.36 mmol) with boron trifluoride-acetic acid (0.6 mL, 3.9 mmol) according to the procedure outlined above afforded **24** as a white solid (45 mg, 80 % yield); data as above.

5-(5*R*)-Isopropyl-2-oxo-oxazolidine-4(*R*)-carboxylic acid (25).[44]Jones reagent (2.5 eq.) was added to compound **24** (100 mg, 0.63 mmol) in acetone (6 mL) at 0 °C and the reaction warmed to room temperature and stirred for 0.5 h. Propan-2-ol was then added to quench excess Jones reagent and the mixture decanted. The solid residue was dissolved in brine and washed with $CHCl_3$. The organics were combined, dried and concentrated *in vacuo* to yield the carboxylic acid as a white solid (80 mg, 74 % yield); mp 164 °C; R_f 0.42 (BuOH : AcOH : H_2O 4:1:1); ^1H NMR (500 MHz, D_2O) δ 4.54 (m, 1H), 4.31 (d, *J* = 8.5 Hz, 2H), 1.94 (m, 1H), 0.94 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR (125 MHz, D_2O) δ 175.0, 162.7, 85.8, 59.4, 29.7, 19.3, 18.2; IR (CCl_4) 3420 br (s), 2960 (m), 1750 (m), 1649 (m) cm^{-1}; HRMS calcd for $C_7H_{15}N2O_4$: 191.1032, found 191.1036; *m/z* (CI, NH_3) 191 ($M+NH_4^+$, 100), 174 (MH^+, 7), 161 (18), 145 (70), 128 (52); $[\alpha]_D^{20}$ +13.4° (*c* = 0.5, H_2O), Lit.[44] $[\alpha]_D^{20}$ +16.94° (*c* = 1.95, MeOH).

(2*S*, 3*S*)-3-Hydroxyleucine (26).[35] 5-(5*R*)-Isopropyl-2-oxo-oxazolidine-4(*R*)-carboxylic acid **25** (140 mg, 0.81 mmol) was dissolved in 5 M aq. HCl (5 mL) and heated at 100 °C for 8h. The solution was then concentrated *in vacuo* and the residue passed through a Dowex-50W (mesh 200-400) column, eluting with 1 M aq. NH_4OH to yield **26** as a white solid (119 mg, 99 % yield); R_f 0.40 (nBuOH : HOAc : H_2O : py, 5:1:4:5); $[\alpha]_D^{25}$ +35.0° (*c* = 1.00, H_2O), Lit[35]. $[\alpha]_D^{25}$ +37.0° (*c* = 1.00, H_2O).

[(2*R*)-2-(Hydroxy-(1*R*)-1-hydroxymethyl-3-methylbutyl]-carbamic acid *tert*-butyl ester (27). Method A: Alcohol **7** (0.5 g, 1.95 mmol) was treated with a 0.5 M aqueous solution HCl (2.5 mL) in THF (80 mL) and

stirred for 12 h. The reaction mixture was then dried over $MgSO_4$, filtered and the filtrate concentrated to yield amino diol **27** as a hygroscopic colorless oil (0.45 g, 99 % yield); R_f 0.42 (EtOAc : petroleum ether, 50 %, v/v); ^1H NMR (500 MHz, $CDCl_3$) δ 5.23 (bs, 1H), 3.75 (bs, 2H), 3.46 (m, 1H), 3.05-2.87 (bs, 2H), 1.71 (m, 1H), 1.41 (s, 9H), 0.97 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.9, 79.9, 78.0, 65.6, 52.1, 31.0, 28.3, 19.0, 18.7; IR (film) 3396 br (m), 2963 (m), 1686 (s), 1508 (m) cm^{-1}; HRMS calcd for $C_{11}H_{24}NO_4$: 234.1705, found 234.1701; *m/z* (CI, NH_3) 234 (MH^+, 100), 178 (37), 134 (40); $[\alpha]_D^{20}$ -8.1° (*c* = 1.3, $CHCl_3$).

Method B : Treatment of alcohol **7** (2.23 g, 8.16mmol) with boron trifluoride-acetic acid (0.17.0 mL, 122 mmol) in methanol (71mL) for 2.5 h at 0 °C, followed by a basic work-up afforded a crude product which was purified by column chromatography on silica gel to give **27** as a colorless oil (1.87 g, 98 % yield); data as above.

(3*S*)-3-(1-Hydroxy-1-methylethyl)-1-oxa-4-azaspiro[4.5]decane-4-carboxylic acid *tert*-butyl ester (28). Methyl ester **8** (1.0 g, 3.3 mmol) was treated with methylmagnesium chloride (7.4 mL of a 3.0 M solution in THF, 22.0 mmol) according to the procedure outlined earlier to afford a solid which was recrystallized (EtOAc : petroleum ether) to yield **28** as a white crystalline solid (0.53 g, 53 % yield); mp 124 °C; R_f 0.55 (EtOAc : petroleum ether, 20 %, v/v); ^1H NMR (500 MHz, $CDCl_3$) δ 5.15 (bs, 1H), 4.08-3.96 (m, 1H), 3.95-3.83 (m, 1H), 3.82-3.65 (m, 1H), 2.46-2.16 (m, 2H), 2.15-2.00 (m, 2H), 1.91-1.40 (m, 15H), 1.16 (s, 3H), 1.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.9, 96.1, 81.4, 73.0, 66.2, 64.7, 34.5, 30.9, 28.3 and 28.0 (rotamer), 25.0, 24.5, 23.5 and 23.3 (rotamer); IR (film) 3350 (m), 2974 (m), 2940 (m), 1651 (s), 1398 (s), 1368 (m) cm^{-1}; HRMS calcd for $C_{16}H_{30}NO_4$: 300.2175, found 300.2172; *m/z* (CI, NH_3) 300 (MH^+, 10), 244 (42), 226 (13), 184 (14), 156 (28), 140 (100); $[\alpha]_D^{20}$ -21.3° (*c* = 1.0, $CHCl_3$) and [2-2(*S*)-hydroxy-1-hydroxymethyl-2-methylpropyl]-carbamic acid *tert*-butyl ester **29** (0.12 g, 16 % yield) as a white solid (data below).

[(2*S*)-2-Hydroxy-1-hydroxymethyl-2-methylpropyl]-carbamic acid *tert*-butyl ester (29). Treatment of alcohol **28** (86 mg, 0.29 mmol) with boron trifluoride-acetic acid (0.44 mL, 3.20 mmol) in methanol (2.2 mL) for 3 h at room temperature followed by a basic work-up afforded **29** as a hygroscopic pale yellow oil after chromatography on silica gel (27 mg, 43 % yield); R_f 0.61 (MeOH : CH_2Cl_2, 10 %, v/v); ^1H NMR (500 MHz, $CDCl_3$) δ 5.54-5.25 (bs, 1H), 3.98 (dd, *J* = 11.2, 3.0 Hz, 1H), 3.76 (dd, *J* = 11.2, 3.0 Hz, 1H), 3.50-3.40 (bs, 1H), 3.05-2.75 (bs, 2H), 1.41 (s, 9H), 1.32 (s, 3H), 1.21 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.4, 79.6, 73.7, 63.4, 57.7, 28.4, 27.5, 27.4; IR (neat) 3386 br (s), 2977 (m), 1691 (s), 1510 (m) cm^{-1}; HRMS calcd for $C_{10}H_{22}NO_4$: 220.1549, found 220.1543; *m/z* (CI, NH_3) 220 (MH^+, 60), 164 (100), 146 (45), 120 (15); $[\alpha]_D^{20}$ +16.5° (*c* = 1.0, $CHCl_3$).

(2*S*)-2-[(1*S*)-1-(Hydroxyphenylmethyl)-ethyl]-carbamic acid *tert*-butyl ester (30). Treatment of alcohol **16** (0.32 g, 0.9 mmol) with boron trifluoride-acetic acid (1.4 mL, 10 mmol) in methanol (7 mL) for 3 h at room temperature followed by a basic work-up afforded **30** as a hygroscopic pale yellow oil after chromatography on silica gel (0.13 g, 53 % yield); R_f 0.61 (MeOH : CH_2Cl_2, 10 %, v/v); ^1H NMR (500 MHz, $CDCl_3$) δ 7.45-7.25 (m, 5H), 5.40-5.30 (bs, 1H), 5.03 (s, 1H), 3.78 (dd, *J* = 12.0, 3.5 Hz, 2H), 3.60 (m, 1H), 3.08 (bs, 1H), 2.45 (s, 1H), 1.44 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.1, 141.0, 128.5, 127.8, 125.8, 79.9, 76.3, 61.9, 56.4, 28.4; IR (film) 3374 br (s), 2976 (m), 1689 (s), 1505 (m) cm^{-1}; HRMS calcd for $C_{14}H_{22}NO_4$: 268.1549, found 268.1559; *m/z* (CI, NH_3) 268 (MH^+, 70), 229 (50), 212 (100), 194 (48), 178 (18); $[\alpha]_D^{20}$ -3.6° (*c* = 1.0, $CHCl_3$).

3-(3*S*)-[1-(1*S*)-(4-Cyanophenoxy)phenylmethyl]-1-oxa-4-azaspiro[4.5]decane-4-carboxylic acid *tert*-butyl ester (31). Alcohol **16** (37 mg, 0.11 mmol) in anhydrous THF (1 mL) was treated with a 1.0 M solution of potassium *tert*-butoxide (0.13 mL, 0.13 mmol) at 0 °C and stirred for 20 min. To this solution was added 4-fluorobenzonitrile (15 mg, 0.13 mmol) and the reaction stirred for 16h at room temperature. The reaction mixture was then diluted with diethyl ether (5 mL) and a saturated aqueous solution of NH_4Cl (1 mL) added. The organic layer was then separated and the aqueous layer back extracted with diethyl ether (2x10 mL). The organics were combined and dried before being concentrated and the residue purified by chromatography on silica gel to yield **31** as a colorless oil (32 mg, 67 % yield); R_f 0.63 (EtOAc : petroleum ether, 20 %, v/v); ^1H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, J = 7.8 Hz, 2H), 7.39-7.25 (m, 5H), 6.86 (m, 2H), 5.74 and 5.40 (rotamer) (m, 1H), 4.29 and 4.19 (rotamer) (m, 1H), 4.13 (dd, J = 7.5, 1.9 Hz, 1H), 3.78 (m, 1H), 2.44-2.28 (m, 1H), 2.16-1.99 (m, 1H), 1.80-1.50 (m, 7H), 1.39 and 1.30 (rotamer) (s, 9H), 1.25 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.0, 137.3, 134.7, 134.6, 133.9, 129.1, 129.0, 128.9,128.8, 126.1, 126.0, 116.9, 116.8, 116.4, 79.2, 78.1, 64.0, 62.5, 35.1, 31.9, 29.8, 28.3, 24.9, 23.5; IR (film) 3015 (w), 2931 (s), 2863 (w), 2225 (m), 1699 (s), 1604 (m) cm^{-1}; HRMS calcd for $C_{27}H_{33}N_2O_4$: 449.2440, found 449.2431; *m/z* (CI, NH_3) 449 (MH^+, 33), 393 (34), 348 (18), 305 (52), 274 (98), 240 (100), 208 (61), 184 (48), 140 (100); $[\alpha]_D^{20}$ +3.2° (*c* = 1.0, $CHCl_3$) and

(7'*S*, 7'a*S*)-dihydro-7'-phenylspiro[cyclohexane-1,3'-[1*H*, 3*H*, 5*H*]oxazolo-[3,4-*c*]oxazol]-5'-one (32) as a colorless oil (5 mg, 16 %); R_f 0.46 (EtOAc : petroleum ether, 20 %, v/v); ^1H NMR (500 MHz, $CDCl_3$) δ 7.39-7.24 (m, 5H), 5.73 (d, J = 8.5 Hz, 1H), 4.62 (m, 1H), 3.56 (dd, J = 8.8, 6.5 Hz, 1H), 3.09 (m, 1H), 2.45 (m, 1H), 1.85-1.75 (m, 1H), 1.74-1.62 (m, 2H), 1.60-1.46 (m, 5H), 1.31 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.9, 135.4, 128.9, 128.6, 124.8, 96.8, 75.2, 64.5, 62.0, 37.0, 31.7, 24.8, 23.4, 23.0; IR (film) 3020 (w), 2933 (m), 1760 (s) cm^{-1}; HRMS calcd for $C_{16}H_{20}NO_3$: 274.1443, found 274.1457; *m/z* (CI, NH_3) 274 (MH^+, 86), 273 (100), 230 (33), 186 (74), 140 (48); $[\alpha]_D^{20}$ -62.2° (*c* = 0.5, $CHCl_3$).

(5*S*)-1,1,5,5-Tetramethyldihydrooxazolo[3,4-c]oxazol-3-one (34). Alcohol **5** (0.109 mg, 0.42 mmol) in dry THF (3 mL) was added to sodium hydride (20 mg of a 60% dispersion in mineral oil, washed twice with petroleum ether; 0.51 mmol) at 0 °C and stirred at this temperature for 20 min. To this solution was added 4-flurobenzonitrile (61 mg, 0.51 mmol) and the reaction stirred for 16h at room temperature. The reaction mixture was then diluted with diethyl ether (5 mL) and a saturated aqueous solution of NH_4Cl (1 mL) added. The organic layer was then separated and the aqueous layer back extracted with diethyl ether (2x10 mL). The organics were combined and dried before being concentrated and the residue purified by chromatography on silica gel to yield **34** as a white solid (55 mg, 71 % yield); mp 89-90 °C; R_f 0.51 (EtOAc : petroleum ether, 50 %, v/v); ^1H NMR (500 MHz, $CDCl_3$) δ 3.96 (dd, J = 8.6, 6.5 Hz, 1H), 3.88 (dd, J = 8.6, 6.5 Hz, 1H), 3.67 (t, J = 8.6 Hz, 1H), 1.65 (s, 3H), 1.46 (s, 3H), 1.37 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.1, 94.4, 78.9, 67.3, 64.2, 28.6, 27.4, 23.4, 22.8; IR (film) 2989 (m), 2938 (m), 2883 (w), 1733 (s), 1459 (w) cm^{-1}; HRMS calcd for $C_9H_{16}NO_3$: 186.1130, found 186.1136; *m/z* (CI, NH_3) 186 (MH^+, 100), 170 (89), 155 (12), 126 (59); $[\alpha]_D^{20}$ -45.5° (*c* = 1.0, $CHCl_3$).

REFERENCES

1. Herold, P. *Helv. Chim. Acta* **1988**, *71*, 354-363 and references therein.
2. Nimkar, S.; Menaldino, D.; Merrill, A. H.; Liotta, D. *Tetrahedron Lett.* **1988**, *29*, 3037-3040 and references therein.
3. Hale, K. J.; Manaviazar, S.; Delisser, V. M. *Tetrahedron* **1994**, *50*, 9181-9188.
4. Ageno, G.; Banfi, L.; Cascio, G.; Guanti, G.; Manghisi, E.; Riva, R.; Rocca, V. *Tetrahedron* **1995**, *51*, 8121-8134.
5. Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1531.
6. Blaskovich, M. A.; Lajoie, G. A. *J. Am. Chem. Soc.* **1993**, *115*, 5021-5030 and references therein.
7. Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361-2364.
8. Blaser, D.; Seebach, D. *Liebigs Ann. Chem.* **1991**, 1067-1078 and references therein.
9. Roemmele, R. C.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 1866.
10. Schmidt, U.; Haslinger, E. *The Alkaloids, Vol. 26*; Academic Press: New York, **1985**, Chapter 6, 299.
11. Joullié, M. M.; Nutt, R. F. *Alkaloids: Chemical and Biological Perspectives, Vol. 3*; Wiley: New York, **1985**, Vol. 3, 113-168.
12. Heffner, R. J.; Jiang, J.; Joullié, M. M. *J. Am. Chem. Soc.* **1992**, *114*, 10181-10189.
13. Tschesche, R.; Elgamal, G.; Miana, G. A.; Eckhardt, G. *Tetrahedron* **1975**, *31*, 2944.
14. Heffner, R. J.; Joullié, M. M. In *Presented at the 200th ACS National Meeting*, Washington, D. C., **1990**, ORGN 175.
15. Jiang, J.; Zhang, Z.; Williams, L.; Joullié, M. M. In *Presented at the 208th ACS National Meeting*; Washington, DC, **1994**, ORGN 029.
16. Garner, P.; Park, J. M. *Org. Synth.* **1991**, *70*, 18-28.
17. Roush, W. R.; Hunt, J. A. *J. Org. Chem.* **1995**, *60*, 798-806.
18. Meffre, P.; Durand, P.; Branquet, E.; Le Goffic, F. *Synth. Comm.* **1994**, *24*, 2147-2152.
19. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
20. Païs, M.; Marchand, J.; Ratle, G.; Jarreau, F.-X. *Bull. Soc. Chim. Fr.* **1968**, 2979-2984.
21. Païs, M.; Marchand, J.; Monseur, X.; Jarreau, F.-X.; Goutarel, R. *C. R. Acad. Sci. Ser. C.* **1967**, *264*, 1409-1411.
22. Radunz, H.-E.; Devant, R. M.; Eiermann, V. *Liebigs Ann. Chem.* **1988**, 1103-1105.
23. All X-ray data included in this paper has been deposited in the Cambridge Crystallographic Data Centre.
24. Han, B. H.; Kim, Y. C.; Park, M. K.; Park, J. H. *Heterocycles* **1995**, *41*, 1909-1914.
25. Beaulieu, P. L. *Tetrahedron Lett.* **1991**, *32*, 1031-1034.
26. Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149-164.
27. Kharasch, M. S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*; Prentice-Hall Inc.: New York, **1954**, 147-166.
28. Garner, P.; Park, J. M. *J. Org. Chem.* **1988**, *53*, 2979-2984.
29. Coleman, R. S.; Carpenter, A. J. *Tetrahedron Lett.* **1992**, *33*, 1697-1700.
30. Koskinen, A. M. P.; Hassila, H.; Myllymäki, V. T.; Rissanen, K. *Tetrahedron Lett.* **1995**, *36*, 5619-5622.
31. Caldwell, C. G.; Bondy, S. S. *Synthesis* **1990**, 34-36.

32. Corey, E. J.; Lee, D.-H.; Choi, S. *Tetrahedron Lett.* **1992**, *33*, 6735-6738.
33. Jung, M. E.; Jung, Y. H. *Tetrahedron Lett.* **1989**, *30*, 6637-6640.
34. Kanemasa, S.; Mori, T.; Tatsukawa, A. *Tetrahedron Lett.* **1993**, *34*, 8293-8296.
35. Sunazuka, T.; Nagamitsu, T.; Tanaka, H.; Omura, S.; Sprengeler, P. A.; Smith III, A. B. *Tetrahedron Lett.* **1993**, *34*, 4447-4448.
36. Williams, L.; Zhang, Z.; Ding, X.; Joullie´, M. M. *Tetrahedron Lett.* **1995**, *36*, 7031-7034.
37. Attenburrow, J.; Elliott, D. F.; Penny, G. F. *J. Chem. Soc.* **1948**, 310-318.
38. Agami, C.; Couty, F.; Hamon, L.; Venier, O. *Tetrahedron Lett.* **1993**, *34*, 4509-4512.
39. Agami, C.; Couty, F.; Hamon, L.; Venier, O. *Bull. Soc. Chim. Fr.* **1995**, *132*, 808-814.
40. Curran, T. P.; Pollastri, M. P.; Abelleira, S. M.; Messier, R. J.; McCollum, T. A.; Rowe, C. G. *Tetrahedron Lett.* **1994**, *35*, 5409-5412.
41. Williams, L.; Hauze, D.; Joullié, M. M. *Heterocycl. Commun.* **1996**, *2*, 55-56.
42. Katsumura, S.; Yamamoto, N.; Morita, M.; Han, Q. *Tetrahedron: Asymmetry* **1994**, *5*, 161-164.
43. Futagawa, S.; Inui, T.; Shiba, T. *Bull.Chem .Soc. Jpn.* **1973**, *46*, 3308-3310.
44. Schmidt, U.; Respondek, R.; Lieberknecht, A.; Werner, J.; Fischer, P. *Synthesis* **1989**, 256-261.
45. Cainelli, G.; Giacomini, D.; Walzl, M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2150-2152.
46. Lin, H.-S.; Paquette, L. A. *Synth. Commun.* **1994**, *24*, 2503-2506.
47. McKillop, A.; Taylor, R. J. K.; Watson, R. J.; Lewis, N. *Synthesis* **1994**, 31-33.

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