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Grignard Reactions to Chiral Oxazolidine Aldehydes

Lorenzo Williams, Zhongda Zhang, Feng Shao, Patrick J. Carroll and Madeleine M. Joullié*

Department of Chemistry, University of Pennsylvania Philadelphia, PA 19104-6323, U.S.A.

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 antibiotics³. In addition they are synthetically useful intermediates towards β -lactams.⁴ Direct routes to these chiral building blocks⁵ have relied on stereoselective additions to chiral serine aldehyde^{6.7} or glycine equivalents⁸ or reductions of α -amino ketones⁹.

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 4⁷ 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 periodinane¹⁹ or on a gram scale under Swern conditions to afford the aldehyde in good yield.



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).



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 analysis²³ 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



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).





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 <i>Anti / Syn</i>	Yield %
11	Me	2 : 1 ^{a,b}	96
12	Et	1 : 9b,c	57
13	iPr	1 : 9a,b,c	73
14	^t Bu	1 : 13°	15
15	C ₆ H ₁₁	1:15 ^{b,c}	74
16	Ph	8:1 ^{b,c}	72

^a ratio determined by 500 MHz ¹H nmr ^b major diastereomer assigned by X-ray

analysis ^c ratio determined by 500 MHz ¹H 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 addition²⁷ 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 TiCl₄ to yield the *syn*-adduct by chelation control, although the overall yield is lowered substantially.²⁴



R	Solvent		
(CH ₂)5	Et ₂ O	2	1
(CH ₂)5	THF	8	1
Me	Et ₂ O	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 products³ 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.

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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 = (CH₂)₅), was poor.



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.



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



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).





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.



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 $(J_{7'-7'a} 8.5 \text{ Hz})^{36,43,44}$ 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.



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.

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EXPERIMENTAL

¹³C 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 procedure⁴⁶. 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.

(2R)-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 KHSO₄ (250 mL), 5 % NaHCO₃ (250 mL), 10 % citric acid (250 mL), and saturated NaCl solution (250 mL). The organic layer was dried over Na₂SO₄, 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: Rf 0.25 (CH₃OH : CH_2Cl_2 , 5%, v/v); ¹H NMR (250 MHz, CDCl₃) 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); ¹³C NMR (62.5 MHz, CDCl₃) δ 171.4, 156.8, 80.2, 63.2, 55.6, 52.5. 28.2: IR (CHCl₃) 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 C₉H₁₈NO₅: 220.1185, found 220.1193; $[\alpha_{10}^{20}, -9.37^{\circ}]$ (c = 3.18, CHCl₃); Found: C, 48.82; H, 7.75; N, 6.20. C₉H₁₇NO₅ 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, CHCl₃), Lit⁴⁷ $[\alpha]_D^{20}$ -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-H₂O (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 NaHCO₃ solution (2x70 mL), and saturated NaCl solution (70 mL). The organic layer was dried over Na₂SO₄ 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 (CH₃OH : CH₂Cl₂, 5 %, v/v); ¹H NMR (250 MHz, CDCl₃) δ 4.50-4.36 (m, 1H), 4.01-4.19 (m, 2H), 3.76 (s, 3H), 1.73-1.41 (m, 15H); ¹³C NMR (62.5 MHz, CDCl₃) 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 (CHCl₃) 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 C₁₂H₂₂NO₅ requires 260.1498, found 260.1484; $[\alpha]_D^{20}$ +49.8° (c = 1.04, CHCl₃); Found: C, 55.56; H, 8.39; N, 5.71. C₁₂H₂₁NO₅ 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, CHCl₃), Lit⁷. $[\alpha]_D^{20}$ -57° (c = 1.3, CHCl₃).

(4S)-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-(4R)-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 Na₂SO₄. Concentration followed by chromatography of the crude material on silica gel afforded the product (13.6 g, 96 % yield) as a colorless oil; Rf 0.27 (CH₃OH : CH₂Cl₂, 10 %, v/v); ¹H NMR (250 MHz, CDCl₃) 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); ¹³C NMR (62.5 MHz, CDCl₃) δ 156.6, 94.0, 80.3, 65.2, 64.8, 59.4, 28.3, 27.0, 24.5; IR (CHCl₃) 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; $\left[\alpha_{12}^{20}+17.9^{\circ}(c=2.13, \text{CHCl}_3), \text{Lit.}^7\left[\alpha\right]_{12}^{20}+23.6^{\circ}(c=1.44, 1.5)\right]$ CHCl₃); Found: C, 57.28; H, 9.21; N, 5.74. C₁₁H₂₁NO₄ 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; $[\alpha]_{10}^{20}$ -19.8° (c = 1.00, CHCl₃)

(4R)-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, (4S)-4-hydroxymethyl-2,2-dimethyloxazolidine-3carboxylic 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, guenched with saturated aqueous NaCl solution (50 mL) and extracted with diethyl ether (2x100 mL). The organic layer was dried over Na₂SO₄, 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); Rf 0.24 (EtOAc : petroleum ether 20 %, v/v); ¹H NMR (250 MHz, CDCl₃) δ 9.47 (d, J = 8.0 Hz, 1H), 3.90-4.30 m (3H), 1.30-1.70 m (15H); ¹³C NMR (125 MHz, CDCl₃) δ 200.5, 156.0, 94.9, 80.9, 64.6, 63.8, 28.1, 25.6, 23.7; IR (CHCl₃) 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, CHCl₃), Lit. ⁷. $[\alpha]_D^{20}$ +95.0° (c = 1.34, CHCl₃); Found: C, 57.29; H, 8.47; N, 6.24. C11H 19NO4 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; $[\alpha]_{20}^{20}$ -87.2° (c = 1.00, CHCl₃), Lit⁷. $[\alpha]_{20}^{20}$ -91.7° (c = 1.04, CHCl₃).

(4S)-4-(1-Hydroxy-1-methylethyl)-2,2-dimethyloxazolidine-3-carboxylic acid tert-butyl ester (5). To 2,2dimethyloxazolidine-(4S)-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 NH₄Cl solution. The organic layer was washed with saturated NaCl, dried over Na₂SO₄, 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, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₁₃H₂₆NO₄ requires 260.1862, found 260.1866; *m/z* (CI, NH₃) 260 (MH⁺, 21), 204 (100), 186 (53), 160 (10), 144 (66); [α] ²⁰_D -27.5° (*c* = 5.3, CHCl₃).

(4S)-4-[(1S)-1-Hydroxyphenylmethyl]-2,2-dimethyloxazolidine-3-carboxylic acid tert-butyl ester (6).²²To a precooled solution of THF (25 mL) and (4S)-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 vellow 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 NH₄Cl solution. The organic layer was washed with saturated NaCl, dried over Na2SO4, 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; Rf 0.75 (EtOAc: petroleum ether, 20 %, v/v); ¹H NMR (500 MHz, CDCl3) & 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₁₇H₂₆NO₄ requires 308.1861, found 308.1869; *m/z* (CI, NH₃)308 (MH⁺, 15), 252 (60), 234 (50), 200 (100), 194 (40), 144 (35), 107 (38); $[\alpha_{10}^{20} - 8.0^{\circ} (c = 1.25, CHCl_3)]$. Found: C, 65.98; H, 8.06; N, 4.21 C17H25NO4 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 NH₄Cl solution. The organic layer was washed with saturated NaCl, dried over Na₂SO₄, 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, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 (CHCl₃) 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 C₁₄H₂₈NO₄ requires 274.2018, found 274.2023; [α]²⁰/₂ +55.3° (*c* = 1.15, CHCl₃); C₁₄H₂₈NO₄ 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, CHCl₃).

1-Oxa-4-azaspiro[4.5]decane-(3R)-3.4-dicarboxvlic acid 4-tert-butvl ester 3-methyl ester (8). A solution of (2R)-2-tert-Butoxycarbonylamino-3-hydroxypropionic acid methyl ester (4.38 g, 20 mmol), cyclohexanone (19.6 g. 200 mmol) and TsOH.H₂O (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 NaHCO3 solution (50 mL) and brine (3 x 50 mL) before being dried over MgSO4. 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; Rf 0.31 (EtOAc : petroleum ether, 20 %, y/y): ¹H NMR (500 MHz, CDCl₃) 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 and 1.40 (s, 9H), 1.00-1.25 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) 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 (CH₂Cl₂) 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, NH₃) calcd for C15H25NO5 requires 299.1733, found 299.1742; n/z 299 (M+, 12), 244 (8), 226 (12), 199 (43), 170 (23), 156 (100), 140 (8); $[\alpha]_{D}^{20}$ +39.8° (*c* = 3.40, CHCl₃); C₁₅H₂₅NO₅: 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, CHCl₃).

(3*S*)-3-Hydroxymethyl-1-oxa-4-azaspiro[4.5]decane-4-carboxylic acid *tert*-butyl ester (9). Treatment of 1oxa-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, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₁₄H₂₆NO4 requires 272.1862, found 272.1858; *m/z* (CI, NH₃) 272 (MH⁺, 100), 216 (35), 172 (58); [α]²⁰_D +21.9° (*c* = 0.80, CHCl₃); Found: C, 61.58; H, 9.54; N, 4.91. C₁₄H₂₅NO4 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; [α]²⁰_D -18.8° (*c* = 1.00, CHCl₃).

(3R)-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 NaHCO₃ solution and an excess of Na₂S₂O₃ 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, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 (CHCl₃) 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 C₁₄H₂₃NO₄ requires 269.1627,

found 269.1621; m/z (CI, NH₃) 270 (MH⁺, 14), 269 (26), 240 (30), 214 (74), 196 (25), 169 (53), 140 (100); $[\alpha]_D^{20}$ +66.0° (c = 1.57, CHCl₃); Found: C, 62.00; H, 9.08; N, 4.49. C₁₄H₂₃NO₄ 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, CHCl₃).

(35)-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, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₁₅H₂₈NO₄: 286.2018, found 286.2027; *m/z* (CI, NH₃) 286 (100), 247 (32), 230 (57), 186 (38); [α]_D²⁰ 17.0° (*c* = 0.98, CHCl₃); Found: C, 62.96; H, 9.66; N, 5.13. C₁₅H₂₇NO₄ 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, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₁₆H₃₀NO4: 300.2174, found 300.2180; *m/z* (CI, NH₃) 300 (MH⁺, 100), 244 (18), 200 (70); [α]²_D⁰-20.6° (*c* = 1.0, CHCl₃).

(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, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 (CHCl₃) 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 C₁₇H₃₁NO₄: 313.2253, found 313.2246; *m/z* (CI, NH₃) 313 (23) 259 (12), 258 (68), 241 (26), 214 (38), (213 (56), 170 (100), (140 (98), 123 (20); [α_{10}^{20} +48.7° (*c* = 1.43, CHCl₃); Found: C, 64.73; H, 10.27; N, 4.30. C₁₇H₃₁NO₄ 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; [α]²⁰₂ -49.0° (*c* = 1.00, CHCl₃).

(3S)-3-[(1R)-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); Rf

0.54 (EtOAc : petroleum ether, 10 %, v/v); ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₁₈H₃₄NO₄: 328.2487, found 328.2485; *m*/z (CI, NH₃) 328 (MH⁺, 100), 272 (22), 246 (15), 228 (84); [α]²⁰₂₀ -27.5° (*c* = 0.67, CHCl₃).

(3S)-3-[(1S)-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 the indicated complete consumption of starting material, the reaction mixture was diluted with diethyl ether (50 mL) and quenched with saturated NH4Cl solution. The organic layer was washed with saturated NaCl, dried over MgSO4, 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; Rf 0.75 (EtOAc : petroleum ether, 20 %, y/y); ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) & 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 (CCl₄) 3571 (w), 3436 (m), 2971 (m), 2931 (s), 2856 (s), 1705 (m), 1660 (s) cm⁻¹; HRMS calcd for C₂₀H₃₆NO₄; 354,2644, found 354,2633. $n\nu/z$ (CI, NH₃) 354 (MH⁺, 94), 298 (76), 254 (100); [α]_D²⁰ -42.8° (c = 1.0, CHCl₃).

(3S)-3-[(1S)-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; Rf 0.61 (EtOAc : petroleum ether, 20 %, v/v); ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₂₀H₃₀NO₄: 348.2175, found 348.2189; m/z (CI, NH₃) 348 (MH⁺, 11), 292 (33), 274 (25), 240 (71), 140 (100); $[\alpha]_D^{20}$ -3.6° (c = 1.0, CDCl₃). (4R, 5S)-1-Isopropyl-5,5-dimethyldihydrooxazolo[3,4-c]oxazol-3-one (22). Triflic anhydride (237 µL, 1.41 mmol) was added to (4R)-4-[(1R)-1-hydroxy-2-methylpropyl]-2,2-dimethyloxazolidine-3-carboxylic acid tertbutyl ester (0.3 g, 1.17 mmol) and 2,6-di-tert butyl 4-methylpyridine (0.57 g, 2.79 mmol) in CH₂Cl₂ (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 NaHCO3 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); ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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, NH₃) 200 (MH⁺, 100), 177 (20), 160 (44); [α] $_D^{20}$ -72.0° (*c* = 1.0, CHCl₃).

(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 (3R)-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 CH₂Cl₂ (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, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₁₃H₂₂NO₃: 240.1599, found 240.1606; *m/z* (CI, NH₃) 257 (M+NH₄+, 5), 240 (MH⁺, 100), 196 (5), 152 (5); [α]²⁰_D+36.0° (*c* = 0.5, CHCl₃); Found: C, 65.14; H, 8.78; N, 5.90. C₁₃H₂₁NO₃ requires C, 65.25; H, 8.84; N, 5.85.

4-(4*S*)-Hydroxymethyl-5-5(*R*)-isopropyloxazolidin-2-one (24).⁴⁴Method 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 : CH₂Cl₂, 10 %, v/v); ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₇H₁₉N₂O₃: 177.1239, found 177.1247; *m*/z (CI, NH₃) 177 (M+NH₄⁺, 90), 160 (MH⁺, 100); $[\alpha]_{D}^{20}$ +95.6° (*c* = 1.0, CHCl₃), 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).⁴⁴Jones 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 CHCl₃. 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 : H₂O 4:1:1); ¹H NMR (500 MHz, D₂O) 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); ¹³C NMR (125 MHz, D₂O) δ 175.0, 162.7, 85.8, 59.4, 29.7, 19.3, 18.2; IR (CCl₄) 3420 br (s), 2960 (m), 1750 (m), 1649 (m) cm⁻¹; HRMS calcd for C₇H₁₅N2O₄: 191.1032, found 191.1036; *m*/z (CI, NH₃) 191 (M+NH₄⁺, 100), 174 (MH⁺, 7), 161 (18), 145 (70), 128 (52); [α]²⁰_D+13.4° (*c* = 0.5, H₂O), Lit.⁴⁴[α]²⁰_D+16.94° (*c* = 1.95, MeOH).

(2S, 3S)-3-Hydroxyleucine (26).³⁵ 5-(5R)-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. NH₄OH to yield 26 as a white solid (119 mg, 99 % yield); R_f 0.40 (nBuOH : HOAc : H₂O : py, 5:1:4:5); $[\alpha]_D^{25}$ +35.0° (c = 1.00, H₂O), Lit³⁵. $[\alpha]_D^{25}$ +37.0° (c = 1.00, H₂O).

[(2R)-2-(Hydroxy-(1R)-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 MgSO₄, 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, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₁₁H₂₄NO₄: 234.1705, found 234.1701; *m*/z (CI, NH₃) 234 (MH⁺, 100), 178 (37), 134 (40); $[\alpha]_{12}^{20}$ -8.1° (*c* = 1.3, CHCl₃).

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 $^{\circ}$ 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, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₁₆H₃₀NO₄: 300.2175, found 300.2172; *m*/z (CI, NH₃) 300 (MH⁺, 10), 244 (42), 226 (13), 184 (14), 156 (28), 140 (100); [$\alpha \frac{20}{D}$ -21.3° (*c* = 1.0, CHCl₃) 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 : CH₂Cl₂, 10 %, v/v); ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₁₀H₂₂NO₄: 220.1549, found 220.1543; *m/z* (CI, NH₃) 220 (MH⁺, 60), 164 (100), 146 (45), 120 (15); [α]_D²⁰ +16.5° (*c* = 1.0, CHCl₃).

(2S)-2-[(1S)-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 : CH₂Cl₂, 10 %, v/v); ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₁₄H₂₂NO₄: 268.1549, found 268.1559; *m/z* (CI, NH₃) 268 (MH⁺, 70), 229 (50), 212 (100), 194 (48), 178 (18); [α]²⁰_D -3.6° (*c* = 1.0, CHCl₃).

3-(3S)-[1-(1S)-(4-Cvanophenoxy)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 4fluorobenzonitrile (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 NH4Cl (1 mL) added. The organic laver 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); Rf 0.63 (EtOAc : petroleum ether, 20 %, v/v); ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) & 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 C₂₇H₃₃N₂O₄: 449.2440, found 449.2431; m/z (CI, NH₃) 449 (MH⁺, 33), 393 (34), 348 (18), 305 (52), 274 (98), 240 (100), 208 (61), 184 (48), 140 (100); $[\alpha_D^{20} + 3.2^\circ (c = 1.0, CHCl_3)]$ and (7'S, 7'aS)-dihydro-7'-phenylspiro[cyclohexane-1,3'-[1H, 3H, 5H]oxazolo-[3,4-c]oxazol]-5'-one (32) as a colorless oil (5 mg, 16 %); Rf 0.46 (EtOAc : petroleum ether, 20 %, v/v); ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₁₆H₂₀NO₃: 274.1443, found 274.1457; *m/z* (CI, NH₃) 274 (MH⁺, 86), 273 (100), 230 (33), 186 (74), 140 (48); $[\alpha]_D^{20}$ -62.2° (*c* = 0.5, CHCl₃).

(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 NH₄Cl (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, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C9H₁₆NO₃: 186.1130, found 186.1136; *m*/z (CI, NH₃) 186 (MH⁺, 100), 170 (89), 155 (12), 126 (59); [α]²⁰₂-45.5° (*c* = 1.0, CHCl₃).

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