DOI: 10.1002/ejoc.200800208

Preparation and Transmetallation of Enantioenriched α-Aminoorganostannanes Derived from *N*-Boc Phenylglycinol: Application to the Synthesis of Alafosfalin

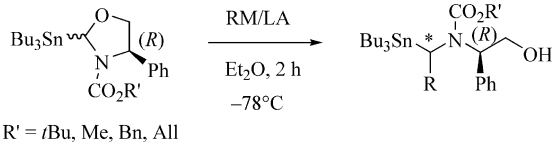
Vincent Coeffard,[a,b] Isabelle Beaudet,[a,b] Michel Evain,[c,d] Erwan Le Grognec,*[a,b] and Jean-Paul Quintard*[a,b]

Keywords: Asymmetric synthesis / Amino acids / Lithium / Tin / Transmetallation

Enantioenriched tributylstannylated α-amino alcohols were synthesised by an improved procedure based on ring opening of 2-tributylstannyloxazolidines. Corresponding α-amino organolithiums were generated from *O*-silylated tributylstannylated α-amino alcohols and trapped with retention of configuration. Thereby, this methodology was used to synthesise the antibacterial α-aminophosphonic acid alafosfalin.

Introduction

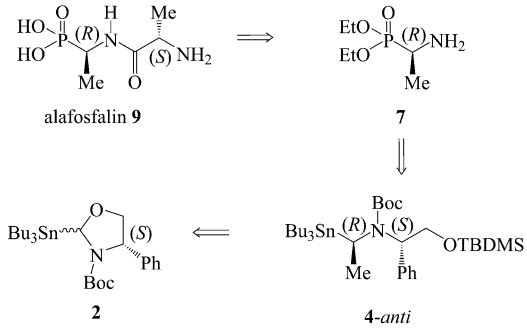
The use of α-aminoorganostannanes is an efficient route to reach the corresponding α-aminoanions through a Sn–Li transmetallation reaction.[1] Starting from enantioenriched α-aminoorganostannanes, enantioenriched α-aminoanions can be similarly obtained.[2] The preparations of these precursors were, however, restricted to enantioselective deprotonation/stannylation sequences,[3] Mitsunobu-type reactions on chiral α-stannylalcohols,[4] resolution of diastereomeric mixtures[5] or addition of tributylstannyllithium to *N*-*tert*-butanesulfinimines.[6] In the course of a study devoted to the preparation of α-aminoorganostannanes, we recently reported a diastereoselective synthesis of chiral α-aminoorganotributyltin derivatives by ring opening of 2-tributylstannyl-1,3-oxazolidines (Scheme 1).[7] Lewis acid assisted ring opening of these heterocycles with soft nucleophiles like lithium diorganocuprates, allyltributyltin or higher-order magnesium dialkylcyanocuprates afforded tributylstannyl α-amino alcohols with diastereoselectivities up to 93:7 in favour of the *anti* isomer [(*S*,*R*) configuration].[7b]



Scheme 1. Diastereoselective ring opening of 2-tributylstannyl-1,3-oxazolidines by organometallic reagents.

Herein, we report both improvement and application of this methodology to the preparation of enantioenriched chiral α-amino anions, which has enabled us to synthesise the antibacterial agent alafosfalin. This relevant α-aminophosphonic acid was prepared through an unprecedented electrophilic phosphorylation reaction, which thus opens a new route for generating optically active α-aminophosphonic acid derivatives whose number of syntheses has been escalating rapidly due to the importance of such compounds in medicinal chemistry and pharmaceutical sciences.[8–10]

A retrosynthetic analysis reveals that alafosfalin (**9**) can be obtained by peptide coupling of chiral α-amino phosphonate derivative **7** and commercially available *N*-Boc-L-Ala (Scheme 2).[11] We anticipated that silylated derivative



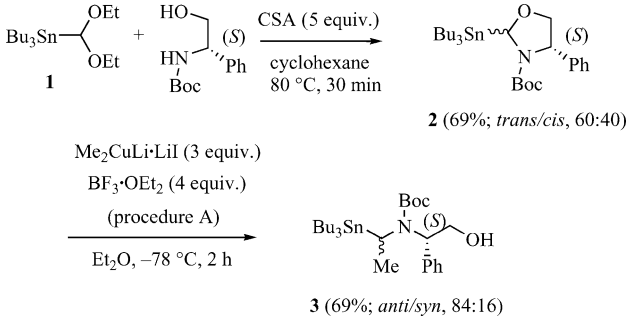
Scheme 2. Retrosynthesis of alafosfalin.

[a] Université de Nantes, CEISAM, Chimie Et Interdisciplinarité: Synthèse, Analyse, Modélisation, UFR des Sciences et des Techniques,
2, rue de la Houssinière, B. P. 92208, 44322 Nantes Cedex 3, France
Fax: +33-2-51-12-54-02
E-mail: erwan.legrognec@univ-nantes.fr
jean-paul.quintard@univ-nantes.fr
[b] CNRS, UMR CNRS 6230,
2 rue de la Houssinière, B. P. 92208, 44322 Nantes Cedex 3, France
[c] Université de Nantes, IMN, Institut des Matériaux de Nantes, UFR des Sciences et des Techniques,
2, rue de la Houssinière, B. P. 92208, 44322 Nantes Cedex 3, France
[d] CNRS, UMR 6502,
2 rue de la Houssinière, B. P. 32229, 44322, Nantes Cedex 3, France

4-*anti* should lead to **7** through a transmetallation/trapping sequence followed by both cleavage of the *tert*-butyloxycarbonyl and phenylglycinol moieties. In order to obtain the (*R*) enantiomer of **7**, we needed to prepare 2-tributylstannyl-1,3-oxazolidine **2** derived from *N*-protected (*S*)-phenylglycinol. The *tert*-butyloxycarbonyl group was chosen as a nitrogen protecting group because it is known to stabilise the resultant organolithiums produced during Sn–Li transmetallation.[4a] Furthermore, we considered that this protecting group usually deprotected by trifluoroacetic acid would be compatible with our synthesis.[12]

Results and Discussion

The synthetic route started from *N*-Boc (*S*)-phenylglycinol as shown in Scheme 3. According to our previous work,[13] transacetalisation of readily available diethoxymethyltributylstannane (**1**)[14] with *N*-Boc (*S*)-phenylglycinol in the presence of camphorsulfonic acid (CSA) afforded a diastereomeric mixture of two oxazolidines **2** in 69% yield (**2**-*trans*/**2**-*cis*, 60:40).[15]



Scheme 3. Synthesis of tributylstannylated α-amino alcohols **3** via oxazolidines **2**.

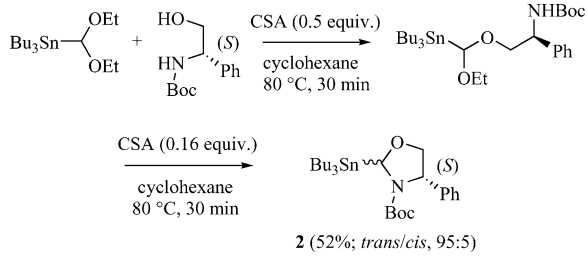
Ring opening of these heterocycles by $Me_2CuLi{\cdot}LiI$ in the presence of $BF_3{\cdot}OEt_2$ gave rise to a mixture of tributylstannylated α-amino alcohols **3**-*anti* and **3**-*syn* in 69% yield as previously reported (**3**-*anti*/**3**-*syn*, 84:16).[7a] Unfortunately, the diastereomeric ratio observed in this reaction appeared to be variable and was often shifted to 50:50 instead of 84:16 (procedure A, see Table 1). These observations prompted us to optimise the reaction conditions in order to improve both reproducibility and selectivity of this ring-opening step. Our investigations are listed in Table 1.

Table 1. Optimisation of ring-opening conditions of oxazolidines **2** by $Me_2CuLi{\cdot}LiI/BF_3{\cdot}OEt_2$.

Entry	Oxazolidine	$BF_3{\cdot}OEt_2$ [equiv.]	Yield [%]	*dr* (**3** *anti*/*syn*)[a]
1	**2**-*trans*	4[b]	65	50:50
2	**2**-*cis*	4[b]	62	48:52
3	**2**-*trans*	4[c]	65	78:22
4	**2**-*trans*	1[c]	75	87:13
5	**2**-*trans*	0[c]	0	–
6	**2**-*cis*	1[c]	42	26:74

[a] Determined by HPLC analysis of the crude. [b] Procedure A: $Me_2CuLi{\cdot}LiI$ (3 equiv.) and $BF_3{\cdot}OEt_2$ (4 equiv.) were stirred at –78 °C for 15 min before oxazolidine **2** was added. [c] Procedure B: Oxazolidine **2** and $Me_2CuLi{\cdot}LiI$ (3 equiv.) were stirred for 30 min at –78 °C before $BF_3{\cdot}OEt_2$ was added.

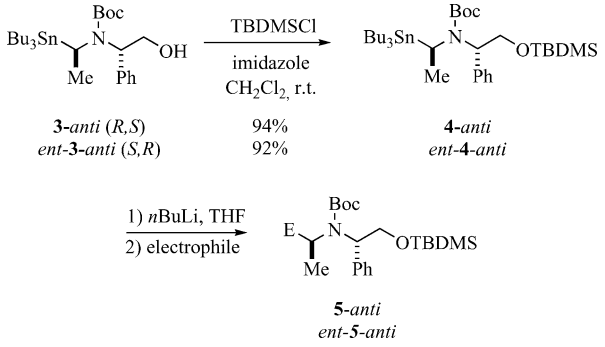
Regardless of the configuration of starting oxazolidines **2**, a mixture of both diastereomers **3**-*anti*/**3**-*syn* was obtained during the ring-opening reaction following the previously reported procedure A (Table 1, Entries 1 & 2). In order to improve the diastereoselectivities, we decided to change the order of events. By stirring a mixture of oxazolidine **2**-*trans* and $Me_2CuLi{\cdot}LiI$ at –78 °C for 30 min before the addition of $BF_3{\cdot}OEt_2$ (procedure B), we were pleased to observe that higher selectivities were obtained. Indeed, by using 4 equiv. of $BF_3{\cdot}OEt_2$, tributylstannylated α-amino alcohol **3** was obtained in 65% yield with a good diastereoselectivity (Table 1, Entry 3; **3**-*anti*/**3**-*syn*, 78:22). A decrease in the number of equivalents of $BF_3{\cdot}OEt_2$ improved both yield and selectivity in favour of the *anti* isomer (Table 1, Entry 4; yield: 75%, **3**-*anti*/**3**-*syn*, 87:13). At this juncture, we confirmed that the presence of $BF_3{\cdot}OEt_2$ was essential, as no reaction occurred in its absence (Table 1, Entry 5). It is worth to note that starting from oxazolidine **2**-*cis*, ring opening according to procedure B led to **3** in moderate yield with inverse diastereoselectivity (Table 1, Entry 6; **3**-*anti*/**3**-*syn*, 26:74). These results confirm a mechanism involving an iminium intermediate for Entries 1 and 2, as proposed for this type of reaction on organic oxazolidine, and a concerted mechanism for Entries 3–6, which is consistent with previous studies on cyclic α-stannyl acetals.[16] Investigations of the ring-opening reaction showed that the best results were obtained starting from oxazolidine **2**-*trans* (Table 1, Entry 4). Therefore, we set out to improve the diastereoselectivity of the transacetalisation reaction in favour of the *trans* isomer. Indeed, in the initial procedure, oxazolidine **2** was obtained as a mixture of both diastereomers (**2**-*trans*/**2**-*cis*, 60:40; Scheme 3).[13] After numerous attempts, we found that addition of CSA in two separate portions gave the best results in terms of diastereoselectivity. By using 0.5 equiv. of CSA, the total conversion of **1** into the monoexchanged derivative was observed by HPLC after 30 min of reaction (Scheme 4).[17]



Scheme 4. Optimised synthesis of oxazolidines **2**-*trans*.

Then, a further amount of CSA (0.16 equiv.) led to the conversion of the monotransacetalised derivative into oxazolidine **2** after 30 min of reaction. By following this procedure, the *trans* isomer, which is the kinetic product,[13] was obtained predominantly in 52% yield (*trans*/*cis*, 95:5 determined by ^1H NMR analysis of the crude). With these two improved steps, we were able to prepare **3** in a reproducible fashion with good diastereoselectivities and to ob-

tain **3**-*anti* as a pure compound after chromatography on silica gel. Similar results were obtained by starting from (*R*)-phenylglycinol to prepare *ent*-**3**-*anti* via oxazolidines *ent*-**2**. The key step involving Sn–Li transmetallation was then considered. In order to prevent cyclisation into oxazolidinones during the transmetallation step,[18] amino alcohol **3**-*anti* and *ent*-**3**-*anti* were protected by the use of TBDMSCl in the presence of imidazole to provide **4**-*anti* and *ent*-**4**-*anti* in high yields (Scheme 5).



Scheme 5. Transmetallation reaction.

We decided to use a procedure similar to those described by Chong: transmetallation of **4**-*anti* or *ent*-**4**-*anti* with 1.6 equiv. of *n*BuLi at –78 °C in THF.[4] Under these conditions, we first evaluated the reactivity of the α-aminoorganolithium species towards electrophiles like cyclohexanone, Me_3SnCl or CO_2 (Table 2). With cyclohexanone, a mixture of *ent*-**5a**-*anti* and *ent*-**5a**-*syn* adducts was observed by ^1H NMR spectroscopic analysis (*ent*-**5a**-*anti*/*ent*-**5a**-*syn*, 92:8), which indicates that a slight epimerisation occurred during the transmetallation reaction (Table 2, Entry 1).

Table 2. Transmetallation of *ent*-**4**-*anti* and reactions with electrophiles.[a]

Entry	Electrophile	Compound	Yield [%]	*dr* (*anti*/*syn*)[b]
1	cyclohexanone	*ent*-**5a**	60	92:8
2	Me_3SnCl	*ent*-**5b**	69	>95:5
3	CO_2	*ent*-**5c**	77	95:5
4	$ClP(O)(OEt)_2$	*ent*-**5d**	75	85:15[c]

[a] *n*BuLi (1.6 equiv.) was added to a solution of *ent*-**4**-*anti* in THF (0.1 M) at –78 °C; and the reaction mixture was stirred for 20 min before the electrophile (2 equiv.) was added. After 20 min at –78 °C, the reaction was quenched with aqueous NH_4Cl. [b] Determined by ^1H NMR spectroscopic analysis of the crude product. For the determination of the *anti*/*syn* geometries, see text. [c] The *anti*/*syn* geometries were firmly established after full characterisation of alafosfalin (vide infra).

After separation by chromatography, suitable crystals of both diastereomers of *ent*-**5a** were obtained from a saturated acetonitrile solution at room temperature. The radiocrystallographic structure pointed to an *anti* configuration for the major isomer (Figure 1), which indicates that the transmetallation/trapping sequence takes place with retention of configuration at the carbon centre. This result is consistent with previous studies dealing with transmetallation of α-aminoorganostannanes.[3a,7a] Similarly, the absolute configuration of the *syn* isomer was unambiguously established by an X-ray diffraction study (Figure 2). Both compounds *ent*-**5a**-*anti* and *ent*-**5a**-*syn* exhibit a noticeable planar nitrogen (ΣN_α = 359.07 and 359.72°, respectively), as it was observed for trimethylstannyl desilylated *ent*-**5b**-*anti* (ΣN_α = 359.72°).[7a] In addition, it is worth noting that a strong hydrogen bond is observed between the oxygen atom of the carbamate and the hydrogen atom of the hydroxy functionality in both structures (1.889 Å for *ent*-**5a**-*anti* and 1.865 Å for *ent*-**5a**-*syn*).

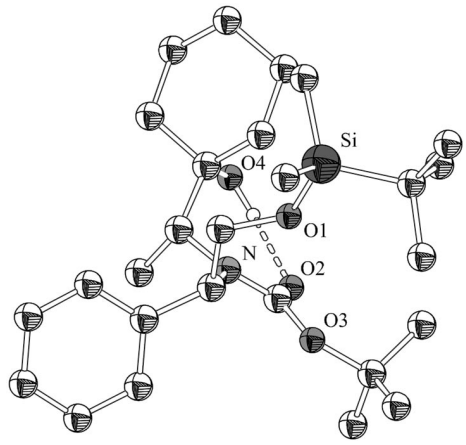


Figure 1. Molecular structure of compound *ent*-**5a**-*anti* (hydrogen atoms are omitted for clarity).

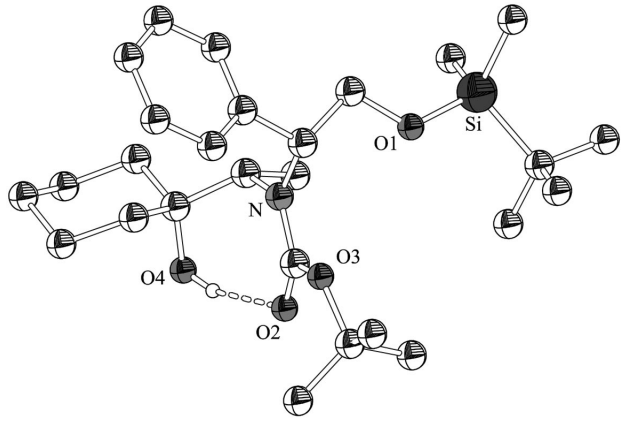
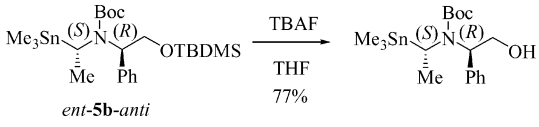


Figure 2. Molecular structure of *ent*-**5a**-*syn* (hydrogen atoms are omitted for clarity).

With Me_3SnCl, derivative *ent*-**5b** was obtained in 69% yield with a high diastereoselectivity (*anti*/*syn*, >95:5), as no *syn* derivative was detected by ^1H NMR spectroscopy (Table 2, Entry 2). The *anti* configuration was confirmed by comparison to ^1H and ^{13}C NMR spectra of *ent*-**5a**-*anti*. In addition, after treatment of *ent*-**5b**-*anti* with tetrabutylammonium fluoride (TBAF) in THF, the obtained desilylated trimethylstannyl α-amino alcohol exhibits NMR spectroscopic data in full agreement with the *anti* diastereomer previously described and firmly identified on the basis of its radiocrystallographic structure (Scheme 6).[7a]



Scheme 6. Deprotection of the alcohol functionality of *ent*-**5b**-*anti*.

By using CO_2 as an electrophile, derivative *ent*-**5c** was obtained in 77% yield with a high diastereoselectivity (*anti*/*syn*, 95:5). The geometry of the major isomer was determined to be *anti* by comparison to the ^1H and ^{13}C NMR spectra of *ent*-**5a**-*anti* and *ent*-**5b**-*anti*.

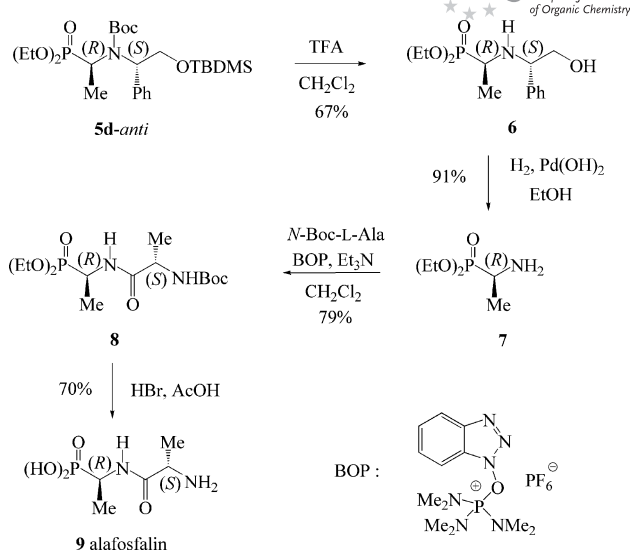
The retention of configuration observed during the transmetallation/carboxylation sequence of *ent*-**4**-*anti* is in full agreement with previous results obtained on similar compounds.[4a] Finally, by using diethyl chlorophosphate as an electrophile, we obtained *ent*-**5d** in 75% yield but with a lower diastereoselectivity (*ent*-**5d**-*anti*/*ent*-**5d**-*syn*, 85:15; vide infra for the determination of *anti*/*syn* geometries). In order to complete the synthesis of alafosfalin, we then focused our work on the use of (*S*)-phenylglycinol derivatives. Under similar transmetallation conditions, we also observed complete conversion of **4**-*anti*, and ^1H NMR spectroscopic analysis revealed a *dr* = 84:16 (**5d**-*anti*/**5d**-*syn*). In order to increase the *dr* of this reaction step, we investigated the importance of the reaction temperature (Table 3).

Table 3. Influence of the temperature on the transmetallation reaction of **4**-*anti*.[a]

Entry	*T* [°C]	Conversion[b] (yield, %)	**5d**-*anti*/**5d**-*syn*[b]
1	–78	100 (77)	84:16
2	–85	90 (73)	93:7
3	–95	27 (nd)[c]	96:4

[a] *n*BuLi (1.6 equiv.) was added to a solution of **4**-*anti* in THF (0.1 M) at the indicated temperature, and the reaction mixture was stirred for 15 min before $ClP(O)(OEt)_2$ (2 equiv.) was added. After 30 min at the same temperature, the reaction was quenched with aqueous NH_4Cl. [b] Determined by NMR spectroscopic analysis of the crude product. [c] Not determined.

By carrying out this transmetallation reaction at –95 °C, a 96:4 (**5d**-*anti*/**5d**-*syn*) diastereoselectivity was obtained (Table 3, Entry 3). However, the conversion determined by ^1H NMR spectroscopic analysis of the crude did not exceed 27%. The best results were obtained by treatment of **4**-*anti* with *n*BuLi over 15 min at –85 °C, followed by addition of diethyl chlorophosphate (2 equiv.) (Table 3, Entry 2). Under this set of conditions, desired compound **5d**-*anti* was obtained in good yield with high diastereoselectivity (**5d**-*anti*/**5d**-*syn*, 93:7). After purification by liquid chromatography on silica gel, **5d**-*anti* was treated with an excess amount of trifluoroacetic acid in dichloromethane over 3 h at room temperature. The simultaneous deprotection of the amine and the alcohol occurred to afford **6** in 67% yield as a colourless oil after purification on silica gel (Scheme 7).[19] Hydrogenolysis of the chiral directing group in **6** with catalytic palladium hydroxide on carbon in absolute ethanol (25 °C, 20 h) afforded α-amino phosphonodiester **7** in 91% yield after flash chromatography (Scheme 7).



Scheme 7. Synthesis of alafosfalin.

Compound **7** was isolated as a colourless oil and proved to be quite stable towards air and moisture but was found to be volatile. A subsequent peptide coupling between *N*-Boc-L-alanine and **7** in the presence of BOP (Scheme 7) and Et_3N in CH_2Cl_2 gave **8** in 79% yield after purification by chromatography. Targeted alafosfalin (**9**) was finally obtained in 70% yield after treatment of **8** with an excess amount of HBr in acetic acid. The comparison of the optical rotation value measured, $[\alpha]_D^{20} = -48.0$ (c = 0.2, H_2O), with that reported in the literature, $[\alpha]_D^{20} = -45.0$ (c = 0.2, H_2O),[20] confirmed the stereochemistry of **9** and, consequently, the retention of configuration during the transmetallation/trapping sequence performed with diethyl chlorophosphate (vide supra).

Conclusions

We developed a route to reach highly enantioenriched α-aminoorganostannanes through diastereoselective ring opening of 2-tributylstannyl-1,3-oxazolidines by lithium dimethylcuprate in the presence of boron trifluoride. The subsequent Sn–Li transmetallation/trapping sequence of the obtained *O*-silylated chiral α-aminoorganostannanes was shown to occur with retention of configuration, which thus opens interesting possibilities for the synthesis of bioactive molecules. An illustration of this methodology is given by the synthesis of alafosfalin from *N*-Boc-(*S*)-phenylglycinol through an electrophilic phosphorylation of the chiral α-amino anion. Work is currently in progress to reach organotin precursors in an enantiopure fashion (avoiding liquid chromatography purification) and to extend the use of enantiopure chiral α-amino anions for the synthesis of other classes of compounds exhibiting relevant biological properties.

Experimental Section

General Method: ^{1}H, ^{13}C, ^{119}Sn and ^{31}P spectra were recorded with Bruker Avance 300 or Bruker ARX 400 instruments. Chemical shifts are given in ppm as δ values related to tetramethylsilane (^{1}H, ^{13}C), tetramethylstannane (^{119}Sn) or external 85% phosphoric acid (^{31}P) and coupling constants are given in Hz. Mass spectra were obtained either in ESI mode with a Bruker Esquive 3000+ spectrometer or in EI mode (70 eV) with a HP apparatus (Engine 5989A) in direct introduction mode. Organostannyl fragments are given for ^{120}Sn, which means that the given abundance is broadly one third of the overall abundance of the organostannyl fragment when compared to organic ones. HRMS analyses were carried out either at the University Claude Bernard Lyon 1 or at the CRMPO in Rennes (Centre Régional de Mesures Physiques de l'Ouest). IR spectra were recorded with a Bruker IFS Vector 22 apparatus. Optical rotations were measured by using a Perkin–Elmer 341 apparatus, and melting points were obtained with a Tottoli SMP3 Stuart apparatus. Diethyl ether and THF were distilled from sodium–benzophenone prior to use. Cyclohexane and CH_2Cl_2 were dried with CaH_2 prior to use, and EtOH was dried with magnesium ethoxide and distilled before use. TLC analyses were conducted on silica-coated plates (Merck Kieselgel $60F_{254}$). Diethoxymethyltributylstannane (**1**) was obtained by treatment of tributylstannylmagnesium chloride with diethylphenylorthoformate according to previous reports.[14] Tributylstannylmagnesium chloride was prepared by using tributyltin hydride, which was a Chemtura (Bergkamen) product. Palladium hydroxide on carbon used for the debenzylation of **6** was purchased from Aldrich (20 wt.-% loading, matrix carbon, wet support).

(4*S*)-3-(*tert*-Butoxycarbonyl)-4-phenyl-2-tributylstannyl-1,3-oxazolidine (2): *N*-Boc (*S*)-phenylglycinol (1.53 mmol, 362 mg), CSA (0.64 mmol, 148 mg) and cyclohexane (35 mL) were placed successively in a 100-mL round-bottom flask. The reaction mixture was warmed at 80 °C and diethoxymethyltributylstannane (**1**; 1.27 mmol, 500 mg) was added. After about 30 min, further CSA (0.21 mmol, 50 mg) was added, and the reaction mixture was still heated for 30 min. At the end of the reaction, K_2CO_3 (s) was added to the solution. Then, the reaction mixture was filtered at room temperature through neutral alumina with diethyl ether as eluent. The reaction mixture was concentrated under reduced pressure, and the crude residue was purified by chromatography on silica gel (hexanes/diethyl ether, 95:5) to afford pure **2**-*trans* and pure **2**-*cis* as colourless oils (358 mg, 52%; **2**-*trans*/**2**-*cis*, 95:5). **2**-*trans*: $[\alpha]_D^{20}$ = +132.1 (*c* = 1.2, $CHCl_3$) [ref.[13] *ent*-**2**-*trans*: $[\alpha]_D^{20}$ = –144.1 (*c* = 1.1, $CHCl_3$)]. All the physical and spectroscopic data for **2**-*trans* and **2**-*cis* were in complete agreement with those reported for *ent*-**2**-*trans* and *ent*-**2**-*cis*.[13]

***tert*-Butyl [1-(Tributylstannyl)ethyl][(1*S*)-2-hydroxy-1-phenylethyl]-carbamate (3)**

Procedure A: Diethyl ether (25 mL) was added to CuI (3 mmol) placed in a Schlenk tube, and the mixture was cooled to –78 °C. The organometallic reagent (MeLi, 6 mmol) was added dropwise, and the mixture was stirred for 30 min at –78 °C and then warmed to –50 °C. The Schlenk tube was then cooled to –78 °C and $BF_3{\cdot}OEt_2$ (4 mmol) was added dropwise. After stirring for 15 min, a solution of **2** (1 mmol) in diethyl ether (5 mL) was added, and the mixture was stirred for 2 h at –78 °C. The reaction was monitored by TLC (hexanes/diethyl ether, 80:20). When complete, the reaction was quenched with saturated aqueous NH_4Cl, and the crude was filtered through a pad of Celite. The crude product was extracted with diethyl ether, and the combined organic extracts were dried ($MgSO_4$) and filtered. The solvent was evaporated under vacuum. The residue was purified by flash chromatography on silica gel (hexanes/diethyl ether, 80:20) to give pure **3**-*anti* and pure **3**-*syn* as oils.

Procedure B: Diethyl ether (25 mL) was added to CuI (3 mmol) placed in a Schlenk tube, and the mixture was cooled to –78 °C. The organometallic reagent (MeLi, 6 mmol) was added dropwise, and the mixture was stirred for 30 min at –78 °C and then warmed to –50 °C. The Schlenk tube was then cooled to –78 °C and a solution of **2** (1 mmol) in diethyl ether (5 mL) was added dropwise. After stirring for 30 min, $BF_3{\cdot}OEt_2$ (0, 1 or 4 mmol) was added, and the mixture was stirred for 2 h at –78 °C. The reaction was monitored by TLC (hexanes/diethyl ether, 80:20). When finished, the reaction was quenched with saturated aqueous NH_4Cl, and the crude was filtered through a pad of Celite. The crude product was extracted with diethyl ether, and the combined organic extract was dried ($MgSO_4$) and filtered. The solvent was evaporated under vacuum. The residue was purified by flash chromatography on silica gel (hexanes/diethyl ether, 80:20) to give pure **3**-*anti* and pure **3**-*syn* as oils.

All the spectroscopic data for **3**-*anti* and **3**-*syn* were in complete agreement with those reported for *ent*-**3**-*anti* and *ent*-**3**-*syn*.[7]

***tert*-Butyl [(1*R*)-1-(Tributylstannyl)ethyl][(1*S*)-(2-*tert*-butyldimethylsiloxy)-1-phenylethyl]carbamate (4-*anti*):** *tert*-Butyldimethylsilyl chloride (184 mg, 1.22 mmol) and imidazole (168 mg, 2.46 mmol) were added to a solution of **3**-*anti* (225 mg, 0.41 mmol) in CH_2Cl_2 (5.5 mL). The reaction mixture was stirred overnight at room temperature. After addition of H_2O (7 mL), the aqueous layer was extracted with CH_2Cl_2 (2 × 6 mL), and the combined organic extract was dried ($MgSO_4$) and filtered. The solvents were evaporated in vacuo. The residue was purified by flash chromatography on silica gel (hexanes/diethyl ether, 98:2) to afford pure **4**-*anti* (255 mg, 94%) as a colourless oil. $[\alpha]_D^{20}$ = +36.4 (*c* = 1.05, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 300 K, Me_4Si): δ = 0.03 (s, 3 H, SiCH_3), 0.04 (s, 3 H, SiCH_3), 0.70–0.90 (m, 15 H, H_{Bu}), 0.85 [s, 9 H, SiC(CH_3)$_3$], 0.95 (d, ^{3}J = 7.2 Hz, 3 H, CH_3CHSn), 1.20–1.55 (m, 12 H, H_{Bu}), 1.42 [s, 9 H, OC(CH_3)$_3$], 2.85 (q, ^{3}J = 7.2 Hz, $^{2}J_{Sn,H}$ = 47 Hz, 1 H, CH_3CHSn), 3.95 (dd, ^{2}J = 10.2 Hz, ^{3}J = 6.4 Hz, 1 H, CH_2OSi), 4.06 (dd, ^{2}J = 10.2 Hz, ^{3}J = 8.1 Hz, 1 H, CH_2OSi), 4.99 (dd, ^{3}J = 8.1 Hz, ^{3}J = 6.4 Hz, 1 H, CHPh), 7.18–7.40 (m, 5 H, C_6H_5) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 300 K, Me_4Si): δ = –5.2 [2 C, Si(CH_3)$_2$], 10.6 ($^{1}J_{Sn,C}$ = 310–320 Hz, 3 C), 13.9 (3 C), 18.5 [1 C, SiC(CH_3)$_3$], 18.6 (1 C, $CHCH_3$), 26.1 [3 C, SiC(CH_3)$_3$], 27.5 ($^{3}J_{Sn,C}$ = 56 Hz, 3 C), 28.7 [3 C, OC(CH_3)$_3$], 29.4 (3 C), 41.0 ($^{1}J_{Sn,C}$ = 376–386 Hz, 1 C, CHSn), 62.9 (1 C, CHPh), 63.5 (1 C, CH_2OSi), 79.5 [1 C, OC(CH_3)$_3$], 127.3–128.3 (5 C, C_6H_5), 139.7 (1 C, C_6H_5), 155.4 (1 C, C=O) ppm. ^{119}Sn NMR (112 MHz, $CDCl_3$, 300 K, Me_4Sn): δ = –25.4 ppm. MS (EI): *m*/*z* (%) = 612 (2), 556 (1), 424 (1), 291 (2), 235 (9), 179 (12) organostannyl fragments; 278 (100), 192 (13), 148 (8), 73 (12), 57 (20), 41 (8) organic fragments. HRMS (ESI): calcd. for $C_{33}H_{63}NO_3SiNa^{120}Sn$ $[M + Na]^+$ 692.3497; found 692.3484.

***tert*-Butyl [(1*R*)-1-(Tributylstannyl)ethyl][(1*S*)-(2-*tert*-butyldimethylsiloxy)-1-phenylethyl]carbamate (*ent*-4-*anti*):** By following the procedure described for **4**-*anti*, *ent*-**4**-*anti* was obtained in 92% yield. All the spectroscopic data were in agreement with those reported for **4**-*anti*. $[\alpha]_D^{20}$ = –38.1 (*c* = 1.02, $CHCl_3$).

General Procedure for the Transmetallation Reaction: α-Aminoorganostannane **4**-*anti* or *ent*-**4**-*anti* (1 mmol) was placed into a Schlenk tube. The oil was dissolved in THF (10 mL), and the solution was cooled to the desired temperature (Tables 2 and 3) whilst under an argon atmosphere. *n*-Butyllithium (1.4 M, 1.6 mmol) was added dropwise slowly to the solution, which acquired a light-yel-

low colour. Once this addition was complete, the solution was stirred for 20 min (or 15 min) at the same temperature. Then, electrophile (2 mmol) was added, and the reaction mixture was quenched at the same temperature after 20 min (or 30 min) by the addition of saturated aqueous NH_4Cl. The aqueous phase was extracted with diethyl ether (3 × 10 mL). The combined organic extract was dried ($MgSO_4$) and filtered, and the solvents were evaporated in vacuo. Purification by chromatography on silica gel afforded the desired products.

***tert*-Butyl [(1*R*)-(2-*tert*-Butyldimethylsiloxy)-1-phenylethyl][1-(1-hydroxycyclohexyl)ethyl]carbamate (*ent*-5a):** The crude product was analysed by ^1H NMR spectroscopy and found to be a mixture of *ent*-**5a**-*anti*/*ent*-**5a**-*syn* in a 92:8 ratio. Purification by chromatography on silica gel (gradient elution, hexanes/diethyl ether, 100:0→95:5). Yield: 60%. IR (neat): $\tilde{\nu}$ = 3379, 2931, 2856, 1661, 1438, 1343, 1170, 838, 775 cm^{-1}. MS (CI): *m*/*z* = 478 $[M + H]^+$. HRMS (ESI): calcd. for $C_{27}H_{47}NO_4NaSi$ $[M + Na]^+$ 500.3172; found 500.3165.

Diastereomer *ent*-5a-*anti*: White crystals., m.p. 91 °C (CH_3CN). $[\alpha]_D^{20}$ = +17.2 (*c* = 1.0, $CHCl_3$). ^1H NMR (300 MHz, C_6D_6, 300 K, Me_4Si): δ = 0.10 (s, 3 H, SiCH_3), 0.14 (s, 3 H, SiCH_3), 0.95 [s, 9 H, SiC(CH_3)$_3$], 1.10 (d, ^3J = 7.4 Hz, 3 H, CH_3CHN), 1.38 [s, 9 H, OC(CH_3)$_3$], 1.35–2.20 [m, 10 H, (CH_2)$_5$], 3.88 (dd, ^2J = 9.4 Hz, ^3J = 4.9 Hz, 1 H, CH_2OSi), 4.05 (m, 1 H, O*H*), 4.24 (q, ^3J = 7.4 Hz, 1 H, CH$_3$C*H*N), 5.08 (dd, ^3J = 10.7 Hz, ^3J = 4.9 Hz, 1 H, C*H*Ph), 5.31 (dd, ^3J = 10.7 Hz, ^2J = 9.4 Hz, 1 H, CH_2OSi), 7.00–7.45 (m, 5 H, C_6H_5) ppm. ^{13}C NMR (75 MHz, C_6D_6, 300 K, Me_4Si): δ = –5.2 [2 C, Si(*C*H$_3$)$_2$], 13.2 (1 C, *C*H$_3$CHN), 18.5 [1 C, Si*C*(CH$_3$)$_3$], 22.5 (1 C, *C*H$_2$), 26.1 [4 C, *C*H$_2$ + SiC(*C*H$_3$)$_3$], 28.5 [3 C, OC(*C*H$_3$)$_3$], 34.5 (1 C, *C*H$_2$), 36.3 (1 C, *C*H$_2$), 37.0 (1 C, *C*H$_2$), 59.7 (1 C, CH$_3$*C*HN), 61.7 (1 C, *C*HPh), 66.9 (1 C, *C*H$_2$OSi), 74.4 (1 C, *C*OH), 79.2 [1 C, O*C*(CH$_3$)$_3$], 127.1–128.9 (5 C, C_6H_5), 141.4 (1 C, C_6H_5), 156.9 (1 C, *C*=O) ppm.

Diastereomer *ent*-5a-*syn*: White crystals, m.p. 110 °C (CH_3CN). ^1H NMR (400 MHz, C_6D_6, 320 K, Me_4Si): δ = 0.04 (s, 3 H, SiCH_3), 0.05 (s, 3 H, SiCH_3), 0.70–2.10 [m, 10 H, (CH_2)$_5$], 0.94 [s, 9 H, SiC(CH_3)$_3$], 1.43 [s, 9 H, OC(CH_3)$_3$], 1.50 (d, ^3J = 6.2 Hz, 3 H, CH_3CHN), 3.05 (m, 1 H, CH$_3$C*H*N), 3.97–4.12 (m, 2 H, CH_2OSi), 5.21 (br. t, ^3J = 7.2 Hz, 1 H, C*H*Ph), 7.00–7.30 (m, 5 H, C_6H_5) ppm. ^{13}C NMR (75 MHz, C_6D_6, 300 K, Me_4Si): δ = –5.7 [2 C, Si(*C*H$_3$)$_2$], 13.2 (1 C, *C*H$_3$CHN), 18.3 [1 C, Si*C*(CH$_3$)$_3$], 22.2 (1 C, *C*H$_2$), 25.9 [3 C, SiC(*C*H$_3$)$_3$], 26.5 (1 C, *C*H$_2$), 28.5 [3 C, OC(*C*H$_3$)$_3$], 35.6 (2 C, *C*H$_2$), 37.8 (1 C, *C*H$_2$), 61.8 (1 C, CH$_3$*C*HN), 62.9 (1 C, *C*H$_2$OSi), 63.6 (1 C, *C*HPh), 71.8 (1 C, *C*OH), 80.5 [1 C, O*C*(CH$_3$)$_3$], 127.7–128.9 (5 C, C_6H_5), 139.0 (1 C, C_6H_5), 157.1 (1 C, *C*=O) ppm.

***tert*-Butyl [(1*R*)-2-(*tert*-Butyldimethylsiloxy)-1-phenylethyl][(1*S*)-1-(trimethylstannyl)ethyl]carbamate (*ent*-5b-*anti*):** Purification by chromatography on silica gel (gradient elution, hexanes/diethyl ether, 100:0→90:10) gave *ent*-**5b**-*anti* as a colourless oil (69%). $[\alpha]_D^{20}$ = –51.5 (*c* = 1.0, $CHCl_3$). ^1H NMR (300 MHz, C_6D_6, 300 K, Me_4Si): δ = 0.06 [s, 3 H, Si(CH_3)$_2$], 0.08 [s, 3 H, Si(CH_3)$_2$], 0.31 [s, $^2J_{Sn,H}$ = 51 Hz, 9 H, (CH_3)$_3$Sn], 0.93 [s, 9 H, SiC(CH_3)$_3$], 1.18 (d, ^3J = 7.4 Hz, 3 H, CH_3CHN), 1.40 [s, 9 H, OC(CH_3)$_3$], 2.89 (q, ^3J = 7.4 Hz, $^2J_{Sn,H}$ = 53 Hz, 1 H, CH$_3$C*H*N), 4.12 (d, ^3J = 7.2 Hz, 2 H, CH_2OSi), 5.21 (br. t, ^3J = 7.2 Hz, 1 H, C*H*Ph), 7.00–7.50 (m, 5 H, C_6H_5) ppm. ^{13}C NMR (75 MHz, C_6D_6, 300 K, Me_4Si): δ = –7.8 [3 C, (*C*H$_3$)$_3$Sn], –5.4 [2 C, Si(*C*H$_3$)$_2$], 18.2 (1 C, *C*H$_3$CHN), 18.6 [1 C, Si*C*(CH$_3$)$_3$], 26.1 [3 C, SiC(*C*H$_3$)$_3$], 29.6 [3 C, OC(*C*H$_3$)$_3$], 52.4 (1 C, CH$_3$*C*HN), 63.0 (1 C, *C*HPh), 63.7 (1 C, *C*H$_2$OSi), 79.7 [1 C, O*C*(CH$_3$)$_3$], 128.0–128.4 (5 C, C_6H_5), 140.0 (1 C, C_6H_5), 155.9 (1 C, *C*=O) ppm. ^{119}Sn NMR (112 MHz, C_6D_6, 300 K, Me_4Sn): δ = –10.9 ppm. IR (neat): $\tilde{\nu}$ = 2956, 2928, 2857, 1670, 1421, 1366, 1171, 1104, 836, 775, 699 cm^{-1}. MS (CI): *m*/*z* = 544 $[M + H]^+$. HRMS (ESI): calcd. for $C_{24}H_{45}NO_3NaSi^{120}Sn$ $[M + Na]^+$ 566.2088; found 566.2108.

2-{(*tert*-Butoxycarbonyl)[(1*R*)-2-(*tert*-butyldimethylsiloxy)-1-phenylethyl]amino}propanoic Acid (*ent*-5c): The crude product was analysed by ^1H NMR spectroscopy and found to be a mixture of *ent*-**5c**-*anti*/*ent*-**5c**-*syn* in a 95:5 ratio. Purification by chromatography on silica gel (gradient elution, hexanes/diethyl ether, 100:0→CH_2Cl_2/MeOH, 90:10) gave *ent*-**5c**-*anti* and *ent*-**5c**-*syn* as colourless oils (77%). IR (neat): $\tilde{\nu}$ = 3378, 3064, 2955, 2928, 2856, 1700, 1419, 1165, 837, 774, 699 cm^{-1}. MS (CI): *m*/*z* = 424 $[M + H]^+$.

Diastereomer *ent*-5c-*anti*: $[\alpha]_D^{20}$ = –36.7 (*c* = 1.0, $CHCl_3$). ^1H NMR (300 MHz, C_6D_6, 300 K, Me_4Si): δ = 0.05 [s, 6 H, Si(CH_3)$_2$], 0.92 [s, 9 H, SiC(CH_3)$_3$], 1.14 (d, ^3J = 6.8 Hz, 3 H, CH_3CHN), 1.46 [s, 9 H, OC(CH_3)$_3$], 3.48 (q, ^3J = 6.8 Hz, 1 H, CH$_3$C*H*N), 3.78–4.02 (m, 2 H, CH_2OSi), 5.76 (m, 1 H, C*H*Ph), 6.90–7.25 (m, 5 H, C_6H_5), 9.22 (br. s, 1 H, CO_2H) ppm. ^{13}C NMR (75 MHz, C_6D_6, 300 K, Me_4Si): δ = –5.7 [2 C, Si(*C*H$_3$)$_2$], 16.2 (1 C, *C*H$_3$CHN), 18.4 [1 C, Si*C*(CH$_3$)$_3$], 26.0 [3 C, SiC(*C*H$_3$)$_3$], 28.2 [3 C, OC(*C*H$_3$)$_3$], 52.4 (1 C, CH$_3$*C*HN), 58.1 (1 C, *C*HPh), 61.4 (1 C, *C*H$_2$OSi), 81.6 [1 C, O*C*(CH$_3$)$_3$], 127.7–128.8 (5 C, C_6H_5), 137.2 (1 C, C_6H_5), 155.1 (1 C, *C*=O carbamate), 173.4 (1 C, *C*=O acid) ppm.

Diastereomer *ent*-5c-*syn*: ^1H NMR (300 MHz, C_6D_6, 300 K, Me_4Si): δ = 0.11 [s, 3 H, Si(CH_3)$_2$], 0.13 [s, 3 H, Si(CH_3)$_2$], 0.98 [s, 9 H, SiC(CH_3)$_3$], 1.50 [s, 9 H, OC(CH_3)$_3$], 1.64 (d, ^3J = 6.9 Hz, 3 H, CH_3CHN), 3.78 (br. q, ^3J = 6.9 Hz, 1 H, CH$_3$C*H*N), 4.08–4.21 (m, 2 H, CH_2OSi), 5.35 (m, 1 H, C*H*Ph), 7.11–7.50 (m, 5 H, C_6H_5), 8.60 (br. s, 1 H, CO_2H) ppm. ^{13}C NMR (75 MHz, C_6D_6, 300 K, Me_4Si): δ = –5.4 [2 C, Si(*C*H$_3$)$_2$], 17.1 (1 C, *C*H$_3$CHN), 18.3 [1 C, Si*C*(CH$_3$)$_3$], 26.0 [3 C, SiC(*C*H$_3$)$_3$], 28.4 [3 C, OC(*C*H$_3$)$_3$], 53.7 (1 C, CH$_3$*C*HN), 61.4 (1 C, *C*HPh), 62.9 (1 C, *C*H$_2$OSi), 80.8 [1 C, O*C*(CH$_3$)$_3$], 126.2–130.8 (5 C, C_6H_5), 138.1 (1 C, C_6H_5), 154.9 (1 C, *C*=O carbamate), 177.6 (1 C, *C*=O acid) ppm.

***tert*-Butyl [1-(Diethoxyphosphoryl)ethyl][(1*R*)-2-(*tert*-butyldimethylsiloxy)-1-phenylethyl]carbamate (*ent*-5d):** The crude product was analysed by ^1H NMR spectroscopy and found to be a mixture of *ent*-**5d**-*anti*/*ent*-**5d**-*syn* in a 85:15 ratio. After flash chromatography on silica gel (gradient elution, hexanes/diethyl ether, 95:5→20:80), pure diastereomers *ent*-**5d**-*anti* and *ent*-**5d**-*syn* (230 mg, 75%) were obtained as colourless oils. IR (neat): $\tilde{\nu}$ = 2977, 2956, 2930, 2857, 1695, 1422, 1387, 1252, 1053, 1024, 838, 777 cm^{-1}. MS (ESI): *m*/*z* = 516 $[M + H]^+$. HRMS (ESI): calcd. for $C_{25}H_{46}NO_6PSiNa$ $[M + Na]^+$ 538.2730; found 538.2734.

Diastereomer *ent*-5d-*anti*: R_f = 0.42 (hexanes/diethyl ether, 30:70). $[\alpha]_D^{20}$ = +30.8 (*c* = 0.96, $CHCl_3$). ^1H NMR (300 MHz, [D$_8$]THF, 300 K, Me_4Si): δ = 0.06 [s, 6 H, Si(CH_3)$_2$], 0.88 [s, 9 H, SiC(CH_3)$_3$], 1.18 (dd, $^3J_{H,P}$ = 15.3 Hz, ^3J = 6.5 Hz, 1 H, CH_3CHP), 1.26 (t, ^3J = 7 Hz, 3 H, OCH$_2$CH_3), 1.27 (t, ^3J = 7 Hz, 3 H, OCH$_2$CH_3), 1.38 [s, 9 H, OC(CH_3)$_3$], 4.04–4.20 (m, 6 H, CH$_3$C*H*P, OCH_2CH$_3$, CH_2OSi), 4.32 (m, 1 H, CH_2OSi), 4.82 (m, 1 H, C*H*Ph), 7.2–7.5 (m, 5 H, C_6H_5) ppm. ^{13}C NMR (75 MHz, [D$_8$]THF, 300 K, Me_4Si): δ = –5.2 [1 C, Si(*C*H$_3$)$_2$], –5.0 [1 C, Si(*C*H$_3$)$_2$], 14.4 (d, $^2J_{P,C}$ = 5 Hz, 1 C, CH*C*H$_3$), 17.0 (2 C, OCH$_2$*C*H$_3$), 19.0 [1 C, Si*C*(CH$_3$)$_3$], 26.5 [3 C, SiC(*C*H$_3$)$_3$], 28.7 [3 C, OC(*C*H$_3$)$_3$], 49.8 (d, $^1J_{P,C}$ = 156 Hz, 1 C, *C*HP), 61.5 (1 C, *C*HC$_6$H$_5$), 62.0 (1 C, *C*H$_2$CH$_3$), 62.7 (1 C, *C*H$_2$CH$_3$), 66.9 (1 C, *C*H$_2$OSi), 80.9 [1 C, O*C*(CH$_3$)$_3$], 127.6 (1 C, C_6H_5), 128.7 (4 C, C_6H_5), 142.1 (1 C, C_6H_5), 155.6 (1 C, *C*=O) ppm. ^{31}P NMR (121 MHz, [D$_8$]THF, 300 K, H_3PO_4): δ = 26.9 ppm.

Diastereomer *ent*-5d-*syn*: R_f = 0.35 (hexanes/diethyl ether, 30:70). ^{1}H NMR (400 MHz, C_6D_6, 340 K, Me_4Si): δ = 0.05 [s, 6 H, Si(CH_3)$_2$], 0.92 (m, 3 H, OCH$_2$CH_3), 0.94 [s, 9 H, SiC(CH_3)$_3$], 1.08 (m, 3 H, OCH$_2$CH_3), 1.42 [s, OC(CH_3)$_3$], 1.65 (dd, $^2J_{H,P}$ = 15.7 Hz, ^3J = 7.3 Hz, 3 H, PCHCH_3), 3.55–3.75 (m, 2 H, OCH_2CH$_3$), 3.87–4.02 (m, 2 H, OCH_2CH$_3$), 4.16 (m, 2 H, CH_2OSi), 4.43 (m, 1 H, PCHCH$_3$), 5.13 (m, 1 H, CHPh), 7.08 (br. t, ^3J = 7.5 Hz, 1 H, C$_6H_5$), 7.21 (br. t, ^3J = 7.5 Hz, 2 H, C$_6H_5$), 7.70 (br. d, ^3J = 7.5 Hz, 2 H, C$_6H_5$) ppm. ^{13}C NMR (100 MHz, C_6D_6, 340 K, Me_4Si): δ = –5.2 [2 C, Si(CH_3)$_2$], 15.2 (d, $^2J_{P,C}$ = 3 Hz, 1 C, PCHCH$_3$), 16.3 (d, $^3J_{P,C}$ = 6 Hz, 1 C, OCH$_2$$CH_3$), 16.5 (d, $^3J_{P,C}$ = 6 Hz, 1 C, OCH$_2$$CH_3$), 18.5 [1 C, Si$C$(CH$_3$)$_3$], 26.2 [3 C, SiC(C$H_3$)$_3$], 28.6 [3 C, OC(C$H_3$)$_3$], 49.6 (d, $^1J_{P,C}$ = 158 Hz, 1 C, PCHCH$_3$), 61.2 (d, $^2J_{P,C}$ = 7 Hz, 1 C, OCH$_2$CH$_3$), 61.9 (1 C, CHC$_6$H$_5$), 63.3 (d, $^2J_{P,C}$ = 6 Hz, 1 C, OCH$_2$CH$_3$), 65.5 (1 C, CH$_2$OSi), 80.4 [1 C, OC(CH$_3$)$_3$], 127.1 (1 C, C$_6$H$_5$), 128.1 (2 C, C$_6$H$_5$), 129.0 (2 C, C$_6$H$_5$), 140.4 (1 C, C$_6$H$_5$), 155.4 (1 C, C=O) ppm. ^{31}P NMR (121 MHz, [D$_8$]THF, 300 K, H_3PO_4): δ = 26.7 ppm.

***tert*-Butyl [1-(Diethoxyphosphoryl)ethyl][(1*S*)-2-(*tert*-butyldimethylsiloxy)-1-phenylethyl]carbamate (5d):** By working at –85 °C and after purification by chromatography on silica gel (gradient elution, hexanes/diethyl ether, 95:5→20:80), pure diastereomers **5d**-*anti* and **5d**-*syn* (225 mg, 73%) were obtained. All spectroscopic data were in full agreement with those corresponding to *ent*-**5d**-*anti* {**5d**-*anti*: $[\alpha]_D^{20}$ = –33.7 (*c* = 0.89, CHCl$_3$)} and *ent*-**5d**-*syn*.

Diethyl (1*R*)-1{[(1*S*)-2-Hydroxy-1-phenylethyl]amino}ethylphosphonate (6): In a 25-mL single-necked, round-bottom flask equipped with a magnetic stirring bar, rubber septum and argon balloon was placed **5d**-*anti* (79 mg, 0.15 mmol) in CH_2Cl_2 (6 mL). To the solution was added TFA (683 μL, 9.2 mmol) at room temperature, and the reaction mixture was stirred for 3 h. At this time, saturated aqueous $NaHCO_3$ was added until pH 9, and the solution was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phase was washed with brine (3 mL), dried with $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (gradient elution, CH_2Cl_2/MeOH, 95:5→90:10) to afford **6** (31 mg, 67%) as a colourless oil. R_f = 0.51 (CH_2Cl_2/MeOH, 94:6). $[\alpha]_D^{20}$ = +46.0 (*c* = 1.0, CHCl$_3$). ^{1}H NMR (300 MHz, CDCl$_3$, 300 K, Me_4Si): δ = 1.22 (t, ^3J = 7 Hz, 3 H, OCH$_2$CH_3), 1.22 (dd, $^3J_{H,P}$ = 18 Hz, ^3J = 6.5 Hz, 3 H, PCHCH_3), 1.25 (t, ^3J = 7 Hz, 3 H, OCH$_2$CH_3), 2.80 (dq, $^2J_{H,P}$ = 17 Hz, ^3J = 6.5 Hz, 1 H, PCHCH$_3$), 3.50 (dd, ^2J = 11 Hz, ^3J = 8 Hz, 1 H, CH_2OH), 3.61 (dd, ^2J = 11 Hz, ^3J = 4 Hz, 1 H, CH_2OH), 3.90 (dd, ^3J = 8 Hz, ^3J = 4 Hz, 1 H, CHPh), 3.99 (q, ^3J = 7 Hz, 2 H, CH$_3$CH_2O), 4.05 (dq, ^2J = 10 Hz, ^3J = 7 Hz, 1 H, CH$_3$CH_2O), 4.11 (dq, ^2J = 10 Hz, ^3J = 7 Hz, 1 H, CH$_3$CH_2O), 7.18–7.27 (m, 5 H, C$_6H_5$) ppm. ^{13}C NMR (75 MHz, CDCl$_3$; 300 K, Me_4Si): δ = 14.0 (1 C, CHCH$_3$), 16.5 (2 C, CH$_3$CH$_2$), 46.8 (d, $^1J_{P,C}$ = 160 Hz, 1 C, PCHCH$_3$), 61.5 (d, $^3J_{P,C}$ = 16 Hz, 1 C, CHPh), 62.1 (d, $^2J_{P,C}$ = 6 Hz, 1 C, CH$_3$$CH_2$O), 62.7 (d, $^2J_{P,C}$ = 7 Hz, 1 C, CH$_3$$CH_2$O), 67.2 (1 C, CH$_2$OH), 127.7 (4 C, C$_6H_5$), 128.6 (1 C, C$_6H_5$), 139.9 (1 C, C$_6H_5$) ppm. ^{31}P NMR (121 MHz, CDCl$_3$, 300 K, H_3PO_4): δ = 29.3 ppm. IR (neat): $\tilde{\nu}$ = 3378, 2980, 2931, 2908, 2869, 1453, 1221, 1027, 966, 703 cm^{-1}. MS (ESI): *m*/*z* = 302 [M + H]$^+$. HRMS (ESI): calcd. for $C_{14}H_{24}NO_4PNa$ [M + Na]$^+$ 324.1341; found 324.1343.

Diethyl [(1*R*)-1-Aminoethyl]phosphonate (7): Compound **6** (78 mg, 0.26 mmol) was dissolved in absolute ethanol (11 mL), and 20% palladium hydroxide on carbon (110 mg) was added. Then, the flask was connected to a balloon of hydrogen. The mixture was thoroughly degassed at aspirator pressure and back-filled with hydrogen (3 times). The mixture was stirred under an atmosphere of hydrogen at room temperature for 20 h and then degassed at aspirator pressure. After filtration through Celite, washing with EtOH (3 × 10 mL) and concentration, flash chromatography (AcOEt) afforded **7** (43 mg, 91%) as a colourless oil. R_f = 0.21 (AcOEt). $[\alpha]_D^{20}$ = –5.0 (*c* = 1.8, CHCl$_3$) {$[\alpha]_D^{20}$ = –5.4 (*c* = 1.8, CHCl$_3$)[9c]}. ^{1}H NMR (300 MHz, CDCl$_3$, 300 K, Me_4Si): δ = 1.31 (m, 9 H, CH_3CH$_2$O and CH$_3$CHP), 1.59 (br. s, 2 H, NH_2), 3.08 (m, 1 H, PCHCH$_3$), 4.12 (m, 4 H, CH$_3$CH_2O) ppm. All other physical and spectroscopic data for **7** were in complete agreement with the reported ones.[9c]

Diethyl (1*R*)-1-({(2*S*)-2-[(*tert*-Butoxycarbonyl)amino]propanoyl}amino)ethylphosphonate (8): In a 5-mL, single-necked, round-bottomed flask was placed **7** (38 mg, 0.21 mmol) in CH_2Cl_2 (0.3 mL) under an atmosphere of argon. To this solution was successively added Et_3N (30 μL, 0.21 mmol) in CH_2Cl_2 (0.2 mL), BOP (93 mg, 0.21 mmol) in CH_2Cl_2 (0.2 mL) and *N*-Boc-L-Ala (40 mg, 0.21 mmol) in CH_2Cl_2 (0.4 mL) at room temperature. A slightly basic pH was maintained by gradual addition of Et_3N. After 45 min stirring, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and then successively washed with aqueous solutions of HCl (1 M, 3 × 10 mL), saturated solution of NaCl (10 mL), saturated aqueous solutions of $NaHCO_3$ (3 × 10 mL) and saturated solution of NaCl (10 mL). The organic phase was dried with $MgSO_4$, filtered and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (AcOEt) to afford **8** (58 mg, 79%) as a colourless oil. R_f = 0.25 (AcOEt). $[\alpha]_D^{20}$ = –38.6 (*c* = 0.5, CHCl$_3$). ^{1}H NMR (300 MHz, CDCl$_3$, 300 K, Me_4Si): δ = 1.25–1.40 [m, 12 H, OCH$_2$CH_3 and PCHCH_3 and CH_3CHC(O)], 1.42 [s, 9 H, (CH_3)$_3$CO], 4.05–4.25 [m, 5 H, OCH_2CH$_3$ and CH$_3$CHC(O)], 4.44 (m, $^2J_{H,P}$ = 17.6 Hz, ^3J = 8.6 Hz, ^3J = 7.5 Hz, 1 H, PCHCH$_3$), 5.16 (d, ^3J = 6 Hz, 1 H, NH), 6.75 (d, ^3J = 8.6 Hz, 1 H, NH) ppm. ^{13}C NMR (75 MHz, CDCl$_3$, 300 K, Me_4Si): δ = 15.7 (1 C, PCHCH$_3$), 16.5 (2 C, CH$_3$CH$_2$O), 18.6 [1 C, CH$_3$CH(O)], 28.4 [3 C, (CH_3)$_3$CO], 40.9 (d, $^1J_{P,C}$ = 158 Hz, 1 C, PCHCH$_3$), 50.3 [1 C, CH$_3$$C$HC(O)], 62.7 (2 C, CH$_3$$CH_2$O), 80.1 [1 C, (CH$_3$)$_3$$C$O], 155.4 (1 C, C=O carbamate), 172.4 (1 C, C=O amide) ppm. ^{31}P NMR (121 MHz, CDCl$_3$, 300 K, H_3PO_4): δ = 25.6 ppm. MS (ESI): *m*/*z* = 375 [M + Na]$^+$. HRMS (ESI): calcd. for $C_{14}H_{29}N_2O_6PNa$ [M + Na]$^+$ 375.1661; found 324.1663.

Alafosfalin (9): In a 5-mL, single-necked, round-bottomed flask, phosphonodipeptide **8** (26 mg, 0.07 mmol) was dissolved in HBr (33% in glacial acetic acid, 2 mL) and left overnight. Then, anhydrous diethyl ether (15 mL) was added. The mixture was stirred for 10 min, and the upper phase was then decanted. The residue was evaporated, and the remaining gum was dissolved in methanol (1.5 mL) and treated with an excess amount of propylene oxide. The precipitated material was filtered off and crystallised from water/ethanol to give pure alafosfalin (**9**) as white crystals (10 mg, 70%). $[\alpha]_D^{20}$ = –48.0 (*c* = 0.2, H_2O) {ref.[20] $[\alpha]_D^{20}$ = –45.0 (*c* = 0.2, H_2O)}. ^{1}H NMR (400 MHz, D_2O, 300 K, Me_4Si): δ = 1.34 (dd, $^3J_{H,P}$ = 15 Hz, ^3J = 6.9 Hz, 3 H, PCHCH_3), 1.34 (d, ^3J = 5.9 Hz, 3 H, CH_3CHNH$_2$), 4.09 (m, 2 H, PCHCH$_3$ and CH$_3$CHNH$_2$) ppm. ^{31}P NMR (300 MHz, D_2O, 300 K, H_3PO_4): δ = 19.3 ppm. MS (ESI): *m*/*z* = 197 [M + H]$^+$. All other physical data are in complete agreement with the reported ones.[10e]

Single-Crystal X-ray Structure Determination

Crystal Structure Data for *ent*-5a-*anti*: $C_{27}H_{47}NO_4Si$, M_w = 477.8, colourless block, 0.6 × 0.3 × 0.2 mm^3, monoclinic, $P2_1$, *a* = 11.0541(9) Å, *b* = 11.9272(9) Å, *c* = 12.1419(12) Å, β = 113.101(6)°, *V* = 1472.5(2) Å^3, *Z* = 2, D_x = 1.077 g cm^{-3}, μ = 0.109 mm^{-1}. 38329 reflections were measured with a Nonius-Kappa CCD dif-

fractometer (graphite monochromator, $\lambda = 0.71073$ Å) up to a resolution of $(\sin\theta/\lambda)_{max} = 0.70$ Å^{-1} at a temperature of 120 K. 11990 reflections were unique ($R_{int} = 0.047$). The structure was solved by direct methods[21] and refined with JANA2006 program[22] against F^2 for all reflections. Non-hydrogen atoms were refined with anisotropic displacement parameters. All H atoms were introduced in geometrically optimised positions and refined with a riding model, except the H atom of the OH group, which was refined. 300 parameters were refined with no restraints. R_1/wR_2 [$I \geq 2\sigma(I)$] = 0.0549/0.1207. R_1/wR_2 [all reflections] = 0.0807/0.1362, $S = 1.84$. Residual electron density is between –0.29 and 0.29 e$^-$Å^{-3}.

Crystal Structure Data for *ent*-5a-*syn*: $C_{27}H_{47}NO_4Si$, $M_w = 477.8$, colourless block, $0.5 \times 0.45 \times 0.4$ mm^3, orthorhombic, $P2_12_12_1$, $a = 10.8481(11)$ Å, $b = 11.4274(7)$ Å, $c = 23.891(3)$ Å, $V = 2961.7(5)$ Å^3, $Z = 4$, $D_x = 1.071$ g cm^{-3}, $\mu = 0.108$ mm^{-1}. 53491 reflections were measured with a Nonius-Kappa CCD diffractometer (graphite monochromator, $\lambda = 0.71073$ Å) up to a resolution of $(\sin\theta/\lambda)_{max} = 0.70$ Å^{-1} at a temperature of 150 K. 11676 reflections were unique ($R_{int} = 0.030$). The structure was solved by direct methods[21] and refined with JANA2006 program[22] against F^2 for all reflections. Non-hydrogen atoms were refined with anisotropic displacement parameters. All H atoms were introduced in geometrically optimised positions and refined with a riding model, except the H atom of the OH group, which was refined. 301 parameters were refined with no restraints. R_1/wR_2 [$I \geq 2\sigma(I)$] = 0.0530/0.1278. R_1/wR_2 [all reflections] = 0.0762/0.1421, $S = 2.17$. Residual electron density is between –0.2 and 0.35 e$^-$Å^{-3}.

CCDC-662569 (for *ent*-**5a**-*anti*) and -662570 (for *ent*-**5a**-*syn*) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgments

We are grateful to Centre National de la Recherche Scientifique (CNRS) and to Ministère de l'Enseignement Supérieur et de la Recherche (MESR) for financial support and for a doctoral fellowship (V. C.). We wish also to acknowledge Chemtura (Bergkamen) for a gift of tributyltin hydride.

[1] a) D. J. Peterson, *J. Organomet. Chem.* **1970**, *21*, P63–P64; b) D. J. Peterson, J. F. Ward, *J. Organomet. Chem.* **1974**, *66*, 209–217; c) J.-P. Quintard, B. Elissondo, B. Jousseaume, *Synthesis* **1984**, 495–498; d) B. Elissondo, J.-B. Verlhac, J.-P. Quintard, M. Pereyre, *J. Organomet. Chem.* **1988**, *339*, 267–275.

[2] R. E. Gawley, I. Coldham in *The Chemistry of Organolithium Compounds* (Eds.: Z. Rappoport, I. Marek), Wiley, Chichester, **2004**, pp 997–1053.

[3] a) S. T. Kerrick, P. Beak, *J. Am. Chem. Soc.* **1991**, *113*, 9708–9710; b) S. Wu, S. Lee, P. Beak, *J. Am. Chem. Soc.* **1996**, *118*, 715–721; c) G. A. Weisenburger, P. Beak, *J. Org. Chem.* **1996**, *118*, 12218–12219.

[4] a) J. M. Chong, S. B. Park, *J. Org. Chem.* **1992**, *57*, 2220–2222; b) A. F. Burchat, J. M. Chong, S. B. Park, *Tetrahedron Lett.* **1993**, *34*, 51–54.

[5] A. Ncube, S. B. Park, J. M. Chong, *J. Org. Chem.* **2002**, *67*, 3625–3636.

[6] K. W. Kells, J. M. Chong, *Org. Lett.* **2003**, *5*, 4215–4218.

[7] a) J.-C. Cintrat, V. Léat, J.-L. Parrain, E. Le Grognec, I. Beaudet, L. Toupet, J.-P. Quintard, *Organometallics* **2004**, *23*, 943–945; b) V. Coeffard, J.-C. Cintrat, E. Le Grognec, I. Beaudet, J.-P. Quintard, *J. Organomet. Chem.* **2006**, *691*, 1488–1497.

[8] a) A. P. Kaplan, P. A. Bartlett, *Biochemistry* **1991**, *30*, 8165–8170; b) P. Kafarski, B. Lejczak, *Phosphorus Sulfur Silicon Relat. Elem.* **1991**, *63*, 193–215; c) J. Hiratake, J. Oda, *Biosci. Biotechnol. Biochem.* **1997**, *61*, 211–218; d) V. P. Kukhar, H. R. Hudson (Eds.), *Aminophosphonic and Aminophosphinic Acids*; John Wiley & Sons, New York, **2000**.

[9] For auxiliary-based synthesis of chiral α-amino phosphonic acid derivatives, see: a) B. Dhawan, D. Redmore, *Phosphorus Sulfur Relat. Elem.* **1987**, *32*, 119–144; b) V. A. Kukhar, V. H. Soloshonok, V. A. Solodenko, *Phosphorus Sulfur Silicon Relat. Elem.* **1994**, *92*, 239–264; c) A. B. Smith III, K. M. Yager, C. M. Taylor, *J. Am. Chem. Soc.* **1995**, *117*, 10879–10888; d) K. Moonen, I. Laureyn, C. V. Stevens, *Chem. Rev.* **2004**, *104*, 6177–6215. For recent reviews on catalytic asymmetric synthesis of α-amino phosphonic acid derivatives, see: e) H. Gröger, B. Hammer, *Chem. Eur. J.* **2000**, *6*, 943–948; f) J.-A. Ma, *Chem. Soc. Rev.* **2006**, *35*, 630–636.

[10] a) J. G. Allen, F. R. Atherton, M. J. Hall, C. H. Hassal, S. W. Holmes, R. W. Lambert, L. J. Nisbet, P. S. Ringrose, *Nature* **1978**, *272*, 56–58; b) J. G. Allen, F. R. Atherton, M. J. Hall, C. H. Hassall, S. W. Holmes, R. W. Lambert, L. J. Nisbet, P. S. Ringrose, *Antimicrob. Agents Chemother.* **1979**, *15*, 684–695; c) F. R. Atherton, M. J. Hall, C. H. Hassall, R. W. Lambert, W. J. Llyod, P. S. Ringrose, *Antimicrob. Agents Chemother.* **1979**, *15*, 696–705; d) H. B. Maruyama, M. Arisawa, T. Sawada, *Antimicrob. Agents Chemother.* **1979**, *16*, 444–451; e) F. R. Atherton, C. H. Hassall, R. W. Lambert, *J. Med. Chem.* **1986**, *29*, 29–40; f) J. Neumann, M. Bruch, S. Gebauer, M. Brandsch, *Eur. J. Biochem.* **2004**, *271*, 2012–2017.

[11] This coupling has already been reported by using **7** in racemic form, see: a) P. Coutrot, C. Grison, C. Charbonnier-Gérardin, *Tetrahedron* **1992**, *48*, 9841–9868; b) C. Grison, C. Comoy, P. Coutrot, *L'Actualité Chimique* **2001**, *10*, 38–48.

[12] T. W. Greene, P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 3rd ed., Wiley Interscience, New York, **1999**.

[13] J.-C. Cintrat, V. Léat-Crest, J.-L. Parrain, E. Le Grognec, I. Beaudet, J.-P. Quintard, *Eur. J. Org. Chem.* **2004**, 4251–4267.

[14] a) J.-P. Quintard, B. Elissondo, D. Mouko-Mpegna, *J. Organomet. Chem.* **1983**, *251*, 175–187; b) J. L. Parrain, I. Beaudet, J.-C. Cintrat, A. Duchêne, J.-P. Quintard, *Bull. Soc. Chim. Fr.* **1994**, *131*, 304–312.

[15] The *cis* and *trans* isomers were defined by the relative position of the Bu_3Sn moiety and the phenyl group on the oxazolidine cycle. See J.-C. Cintrat, V. Léat-Crest, J.-L. Parrain, E. Le Grognec, I. Beaudet, L. Toupet, J.-P. Quintard, *Eur. J. Org. Chem.* **2004**, 4268–4279.

[16] J.-C. Cintrat, E. Blart, J.-L. Parrain, J.-P. Quintard, *Tetrahedron* **1997**, *53*, 7615–7628.

[17] The monoexchanged compound has already been isolated and fully characterized, see ref.[13]

[18] V. Coeffard, E. Le Grognec, I. Beaudet, M. Lepeltier, V. Léat-Crest, J.-P. Quintard, *Synthesis* **2006**, *24*, 4151–4158.

[19] F. Cavelier, C. Enjalbal, *Tetrahedron Lett.* **1996**, *37*, 5131–5134.

[20] a) V. A. Solodenko, V. P. Kukhar, *Tetrahedron Lett.* **1989**, *30*, 6917–6918; b) V. A. Solodenko, T. Kasheva, V. P. Kukhar, *Synth. Commun.* **1991**, *21*, 1631–1641.

[21] M. C. Burla, R. Caliandro, M. Camalli, B. Carrozzini, G. L. Cascarano, L. De Caro, C. Giacovazzo, G. Polidori, R. Spagna, *J. Appl. Crystallogr.* **2005**, *38*, 381–388.

[22] V. Petricek, M. Dusek, L. Palatinus, *JANA2006: The Crystallographic Computing System*, Institute of Physics, Praha, Czech Republic, **2006**.

Received: February 24, 2008
Published Online: May 21, 2008

