Synthesis of an (*R*)-Garner-type Aldehyde from L-Serine: Useful Building Block for a (+)-Furanomycin Derivative

Giuseppe Bartoli,[a] Giustino Di Antonio,[b] Roberto Fiocchi,[c] Sandra Giuli,*[c] Enrico Marcantoni,*[c] Mauro Marcolini[c]

[a] Department of Organic Chemistry 'A. Mangini', University of Bologna, Viale Risorgimento 4, 40136 Bologna, Italy

[b] Chemistry Research Centre, Boehringer-Ingelheim S.p.A., via Lorenzini 8, 20139 Milano, Italy

[c] Department of Chemical Sciences, University of Camerino, via S. Agostino 1, 62032 Camerino (MC), Italy
Fax +39(737)402297; E-mail: enrico.marcantoni@unicam.it

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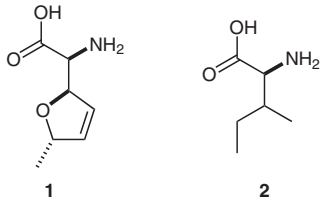
Abstract: (+)-Furanomycin is an antibiotic that substitutes for L-isoleucine in bacterial protein translation. We propose here a new short synthesis of a useful intermediate, a 1,2-diprotected 2-amino-pent-4-ene-1,3-diol, starting from the inexpensive natural amino acid L-serine, and via a Garner-type aldehyde. The (*R*)-α-amino aldehyde was obtained by the construction of an oxazoline ring between the N-protected amino group and the hydroxy group that resulted from reduction of the carboxylic acid functionality of L-serine.

Key words: amino acids, diastereoselectivity, lanthanides, natural products, protecting groups, Wittig reactions

The increasing need for creating novel compounds that contain functional and structural diversity continues to give impetus to method development in synthetic chemistry. In this regard, our research interest has been focused on the total synthesis of small biologically active molecules and of useful building blocks for the synthesis of antibiotics and natural products.[1] Recently we have become interested in the synthesis of olefinic 1,2-amino alcohols[2] that are important intermediates for the preparation of amino acid analogues such as (+)-furanomycin (**1**) (Figure 1). First isolated in 1967 by Katagiri and co-workers[3] from the fermentation broth of *Streptomyces threomyceticus*, it is one of very few natural amino acid antibiotics containing a dihydrofuranyl ring system.[4] This non-proteinogenic α-amino acid is one of the smallest antibacterial natural products reported. (+)-Furanomycin (**1**) is accepted as a substrate by isoleucyl aminoacyl-tRNA synthetase, and its antibacterial activity results from substitution for L-isoleucine (**2**) (Figure 1) during bacterial protein translation.[5] Several syntheses of (+)-furanomycin (**1**) and derivatives have been disclosed, due to the interest in its activity and its moderate chemical complexity.

The first total synthesis of a racemic mixture of (±)-furanomycin (**1**) was published by Masamune and Ono in 1975.[6] The first enantioselective synthesis of **1** appeared five years later when Joullié and co-workers reported a nine-step synthesis starting from D-glucose.[7] In 1998, Kang et al. proposed a 20-step synthesis, whereby the *trans*-2,5-disubstituted dihydrofuran ring was obtained by



1 2

Figure 1

a mercury-cation-promoted cyclization.[8] These methods involve the use of sugars, or similar hydroxy compounds,[9] as the chiral pool.[10] Two years later, however, Standaert reported an alternative approach starting from the well-studied and commercially available (*R*)-Garner aldehyde as the chiral building block.[11] Garner's aldehyde represents an ideal chiral building block for the preparation of many potentially useful chiral molecules in enantiomerically pure form.[12] The major drawback of Standaert's synthesis lies in the use of the unnatural and expensive amino acid D-serine as the starting material. However, although the (*S*)-Garner aldehyde could be easily prepared from L-serine, a unique method to synthesize the (*R*)-Garner aldehyde from a substantially cheaper and more readily available natural amino acid was developed by Datta using (*S*)-methionine.[13] To the best of our knowledge, the synthesis of an (*R*)-Garner-type aldehyde starting from L-serine is unprecedented, and it constitutes an attractive source of chiral nonracemic starting material for many asymmetric syntheses.[14] In this paper, we describe a new method for the synthesis of the (*R*)-Garner-type aldehyde **13**, and for the subsequent addition of a vinyl organocerium compound to provide intermediate *syn*-**14** for (+)-furanomycin synthesis.

Our investigations and studies for a convenient total synthesis of **1** led us to the choice of natural amino acid L-serine (Scheme 1) as an appropriate starting material for the synthesis of the dihydrofuranylglycine ring system present in our antibiotic target. Our retrosynthetic analysis (Scheme 1) shows that the key step to build the 2,5-disubstituted dihydrofuran ring consists of ring-closing metathesis (RCM)[15] of **3**. The formation of dihydrofuran rings by RCM is a known procedure, and it is used to build unsaturated five- or six-membered cyclic ethers.[16] Hence, our initial investigations focused on the stereoselective synthesis of intermediate *syn*-**14** by vinylation of the corresponding α-amino aldehyde **13**. To this end, we required

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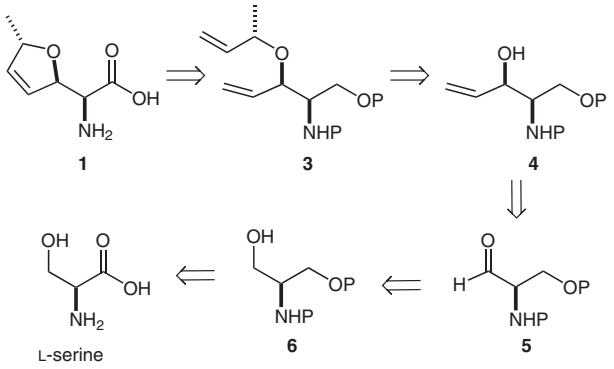
a general route that would lead to the synthetic equivalent of **4** and the desired (*R*)-aldehyde **5** (Scheme 1).



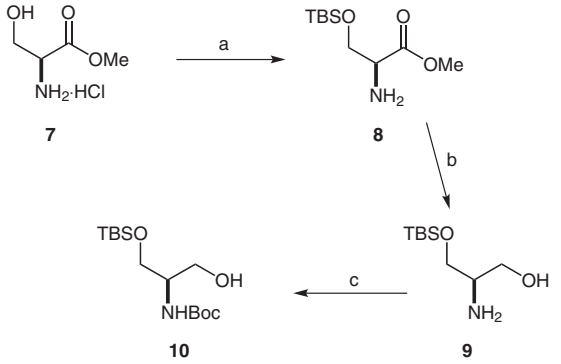
Scheme 1

The retrosynthetic idea presented in Scheme 1 prompted us to explore the methodology for obtaining the N,O-protected amino aldehyde **13**, derived from L-serine, as the source of chirality. In this strategy, the *S*-configuration at the C2 position of L-serine is opposite to that required for (+)-furanomycin (**1**). Thus, we formed an oxazoline ring of the Garner-type aldehyde starting from compound **10** (see Scheme 2) by a cyclization involving the N-Boc-protected amino group and the hydroxy group resulting from the reduced carboxylic moiety (see Scheme 3). Subsequent oxidation of the C3 hydroxy group of L-serine yielded the aldehyde with the desired *R*-configuration, as required for total synthesis of **1**. The preparation of **10** involved protection of the hydroxy group of L-serine as the silyl ether **8** by treatment with *tert*-butyldimethylsilyl chloride (Scheme 2). This protecting group was chosen for its ease of introduction, and for the nonchelating nature of the resulting silyl ether. In addition, by replacing L-serine with the commercially available L-serine methyl ester hydrochloride as starting material, protection of the acid moiety of L-serine could be avoided. Reduction of **8** to the corresponding amino alcohol **9** was easily achieved with sodium borohydride (Scheme 2).[17] N-Boc protection of this amino alcohol afforded the desired intermediate **10** in high yield.[18]

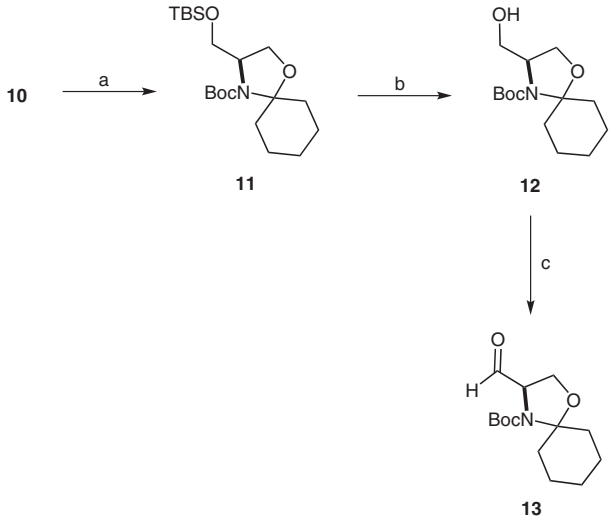
To form the oxazolidine ring from the resulting amino alcohol **10** (Scheme 3), compound **10** was then subjected to reaction with 2,2-dimethoxypropane in acetone at room temperature, with boron trifluoride–diethyl ether used as the catalyst in the absence of solvent.[19] However, subsequent attempts at oxidizing the thus formed N,O-oxazolidine of **10** by treatment with oxidizing agents such as pyridinium chlorochromate and the Dess–Martin periodinane and by following the Parikh–Doering procedure proved unsuccessful due to racemization of the aldehyde product to various extents. Troublesome oxidations of derivatives of serine have previously been noted.[20]

The alternative protection of the amino group of **9** (see Scheme 2) as the *N*-(9-phenylfluoren-9-yl) derivative, which is known to prevent racemization during the synthesis of the corresponding aldehyde,[21] was also unsuccessful because of instability of the resulting aldehyde. Therefore, in an effort to improve the stereochemical stability of the target (*R*)-Garner-type aldehyde, we looked at increasing the steric bulk of the substituents on the oxazolidine ring. We thus chose to cyclize compound **10** (see Scheme 3) using a ketone more bulky than acetone, and 4-*tert*-butylcyclohexanone was initially chosen based on the known preference of a 4-*tert*-butyl group for the equatorial position. Oxidation by the sulfur trioxide–pyridine–dimethyl sulfoxide complex[22] resulted in a racemization-free, but low-yielding procedure. The yield was, however, satisfactory when cyclohexanone was used in the cyclization of precursor **10** to afford **11** (Scheme 3).

Cleavage of the silyl ether moiety in **11** by tetrabutylammonium fluoride led to alcohol **12** (Scheme 3). In contrast, with our cerium(III) chloride heptahydrate–sodium iodide system for the deprotection of alkyl silyl ethers[23] a long reaction time was required and the N-Boc protecting group was also removed.[24] The subsequent oxidation of **12**, carried out according to the Pfitzner–Moffatt proce-



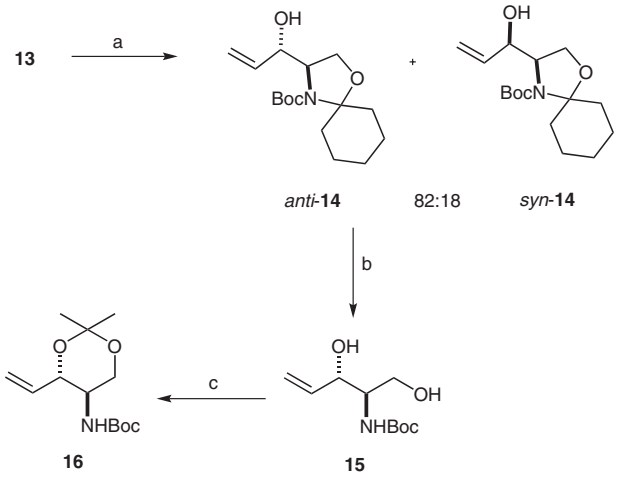
Scheme 2 *Reagents and conditions*: (a) TBSCl, imidazole, CH_2Cl_2, r.t., 48 h; (b) $NaBH_4$, EtOH, 35 °C, 5 h; (c) Boc_2O, dioxane, 5 °C, 30 min, then r.t., 3.5 h.



Scheme 3 *Reagents and conditions*: (a) cyclohexanone, PTSA, benzene, reflux, 24 h; (b) TBAF, THF, r.t., 2 h; (c) Et_3N, DMSO, CH_2Cl_2, SO_3·py, 0 °C, 15 min, then r.t., 2.5 h.

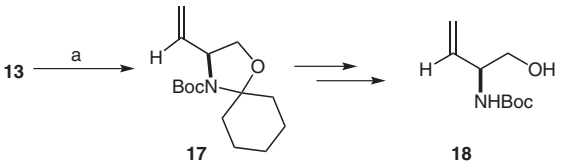
dure, afforded the desired stable aldehyde **13** in good yield (Scheme 3), and its optical rotation matched that found by Joullié.[25] The ^{1}H NMR spectrum of aldehyde **13** at room temperature in chloroform-*d* solution displayed two broad but well-resolved singlets at 9.53 and 9.58 ppm (ratio 4:3) for the CHO group, while the ^{13}C NMR spectrum consisted of two sets of resonances for the rotameric mixture. Similar spectroscopic features have been described for *N*-(*tert*-butoxycarbonyl)-(*S*)-propinal by Pettit and co-workers.[26] Attempts at improving the yield by using either pyridinium chlorochromate or the Dess–Martin reagent were again not successful.

The interest in this (*R*)-Garner-type aldehyde **13** as a building block is due to its possible conversion into other intermediates that are useful in the synthesis of numerous compounds of biological interest.[27] For instance, the addition of vinylmetal reagents to carbonyl compounds is recognized as a fundamental reaction for the preparation of allylic alcohols. In view of this, we tried the addition of a vinylcerium reagent, prepared from the corresponding vinyl Grignard reagent and anhydrous cerium(III) chloride,[28] to aldehyde **13** (Scheme 4). The ability of cerium(III) chloride to mediate high-yielding and highly diastereoselective transfer of carbon frameworks to aldehydes having base-epimerizable centers adjacent to a carbonyl group is well known.[29] As illustrated in Scheme 4, we obtained a mixture of allylic alcohols *anti*-**14** and *syn*-**14**, both widely used as building blocks in the syntheses of naturally occurring and pharmacologically interesting compounds.[30] The *anti* configuration of the major product, allylic alcohol *anti*-**14** (*anti*-**14**/*syn*-**14**, 82:18), is in complete agreement with the Felkin–Anh model that predicts the attack at the *Si* face.[31] The *anti* diastereoselectivity was verified by conversion of *anti*-**14** into 1,3-dioxane **16** (Scheme 4), for which the H4–H5 coupling constant ($J_{H4–H5}$ = 10 Hz) confirmed a *trans* relationship for these two protons and, indirectly, the *anti* stereochemistry of adduct *anti*-**14**.[32]



Scheme 4 *Reagents and conditions*: (a) H_2C=CHMgCl, $CeCl_3$, THF, –78 °C, 2 h, then –30 °C, 1 h; (b) BF_3·OEt_2, AcOH, MeOH, r.t., 3 h; (c) $(MeO)_2CMe_2$, PPTS, CH_2Cl_2, r.t., 48 h.

The two diastereomers *anti*-**14** and *syn*-**14** were easily separable by column chromatography, but because *syn*-**14** is necessary for the synthesis of (+)-furanomycin, we were prompted to further investigate the diastereoselective addition of the vinyl nucleophile to aldehyde **1**. The allylic alcohol *anti*-**14** has interesting applications in organic synthesis,[33] and the (*R*)-Garner-type aldehyde **13** is a versatile reagent. For example, we found that a Wittig reaction of aldehyde **13** in the presence of a strong base such as *n*-butyllithium affords vinyl derivative **17** without epimerization at the stereogenic center (Scheme 5). It is known that Garner's aldehyde can be methylenated without epimerization only when Wittig–Horner conditions are used.[34] Our approach via aldehyde **13** thus provides an alternative to the latter method in the preparation vinylglycinol **18**, a useful chiral building block,[35] whose potential has thus far been limited by its relative inaccessibility.



Scheme 5 *Reagents and conditions*: (a) $[Ph_3PMe]Br$, *n*-BuLi, THF, –78 °C, 30 min, then 25 °C, 4 h.

In conclusion, we have presented an improved useful procedure for obtaining (*R*)-Garner-type aldehyde **13**, an intermediate in a known synthesis of (+)-furanomycin (**1**). We arrive at the correct absolute configuration without use of the unnatural D-serine. The stereochemical stability of our (*R*)-Garner-type aldehyde allowed us to effect its methylenation to vinylglycinol derivative **17** without epimerization by use of a classical Wittig reaction with *n*-butyllithium as strong base. Thus, aldehyde **13** can be used as a building block in the design of new complex molecules with biological activity. Further studies aimed at improving the diastereoselectivity of nucleophilic additions to aldehyde **13** are underway.

Most solvents and reagents were used without purification unless mentioned otherwise. Solvents (EtOAc and hexane) for flash chromatography were distilled. Anhyd THF and Et_2O were prepared by distillation from sodium/benzophenone under a N_2 atmosphere immediately before use, while CH_2Cl_2 was freshly distilled from CaH_2. Et_3N was distilled over CaH_2 and stored under N_2 until used. Commercial L-serine was used as received. Melting points are uncorrected. Reactions of compounds sensitive to air or moisture were performed under N_2. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 400 spectrometer and are referenced to the solvent as internal standard. Mass spectra were recorded on a Hewlett-Packard 6890N gas chromatograph with a mass-selective detector MSD HP 5973N, utilizing electron ionization at an ionizing energy of 70 eV. Microanalyses were performed on a Perkin-Elmer Analyzer 2400 CHN. IR spectra were recorded on a Perkin-Elmer FTIR Paragon 500 spectrometer using thin films on NaCl plates. Only the characteristic peaks are quoted. Analytical GC was performed with a capillary-fused silica column (0.32 mm × 25 m), with stationary phase OV1 (film thickness 0.40–0.45 μm). Solns were evaporated under reduced pressure with a rotary evaporator and the residue was

chromatographed on a Baker silica gel (230–400 mesh) column using EtOAc–hexanes mixtures as eluent. Analytical TLC was performed using precoated glass-backed plates (Merck Kieselgel 60 F254) and visualized by UV, Von's reagent, $KMnO_4$, or I_2 stain.

(*R*)-2-Amino-3-(*tert*-butyldimethylsiloxy)propan-1-ol (9)

Imidazole (15.2 g, 0.22 mol) was added portionwise to a cooled soln (0 °C) of L-(+)-serine methyl ester (**7**; 10 g, 0.064 mmol) and TBSCl (20.34 g, 0.135 mol) in CH_2Cl_2 (75 mL) in a three-necked round-bottomed flask under N_2. Then the cooling bath was removed and the mixture was stirred at r.t. for 48 h. After disappearance of the starting material, a soln of 2 N HCl was added to the mixture until the pH was 5. The product was extracted from the aqueous soln with CH_2Cl_2 (6 × 100 mL). The combined organic layer was washed with brine (2 × 40 mL) and dried (Na_2SO_4) and the solvent was removed in vacuo; this gave **8** as a white solid; yield: 12.99 g (87%). The compound was used without further purification.

The silyl serine methyl ester **8** (2 g, 8.58 mmol) was dissolved in absolute EtOH (34 mL), and $NaBH_4$ (1.30 g, 34.28 mmol) was added at once. The mixture was warmed to 35 °C, and the reduction was complete after 5 h. Then the mixture was treated with a pH 3 phosphate buffer and the hydrolysis was monitored by GC-MS. After 1.5 h, the mixture was concentrated and the silyl amino alcohol **9** was extracted with $CHCl_3$ (3 × 50 mL). Purification by chromatography (silica gel, $CHCl_3$–MeOH, 9:1) gave product **9**.

Yield: 2.59 g (79%); colorless oil; $[\alpha]_D^{25}$ +3.4 (*c* 1.60, $CHCl_3$).

IR (neat): 3449, 3352, 1648, 1389, 1361 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 6 H), 0.90 (s, 9 H), 2.27 (br s, 3 H), 2.99 (t, *J* = 4.9 Hz, 1 H), 3.53 (dd, *J* = 10.7, 6.0 Hz, 1 H), 3.58–3.68 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.7, 19.2, 24.3, 54.2, 64.2, 65.

MS (EI, 70 eV): *m*/*z* = 205 [M^+], 174, 158, 148, 131, 119, 101, 75 (100), 60.

Anal. Calcd for $C_9H_{23}NO_2Si$: C, 52.63; H, 11.29; N, 6.82. Found: C, 52.58; H, 11.28; N, 6.80.

***tert*-Butyl *N*-[(1*R*)-2-(*tert*-Butyldimethylsiloxy)-1-(hydroxymethyl)ethyl]carbamate (10)**

A soln of $(Boc)_2O$ (1.76 g, 8.06 mmol) in dioxane (6.5 mL) was added dropwise to an ice-cold, magnetically stirred soln of **9** in 1 N aq NaOH (14 mL). The mixture (two-phase) was stirred at 5 °C for 30 min, then allowed to warm to r.t., and stirred overnight. The mixture was concentrated to half its original volume by rotary evaporation. It was then cooled in an ice–water bath, acidified to pH 2–3 by the slow addition of 1 N aq $KHSO_4$, and then extracted with EtOAc (4 × 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated; this gave amino alcohol **10**. The product was used without further purification.

Yield: 3.45 g (93%); colorless oil.

IR (neat): 3449, 3360, 1714, 1694 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.07 (s, 6 H), 0.89 (t, *J* = 2.7 Hz, 9 H), 1.45 (s, 9 H), 2.80 (br s, 1 H, OH), 3.51–3.71 (m, 2 H), 3.75–3.85 (m, 3 H), 5.30 (br s, 1 H, NH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.8, 19.0, 25.7, 28.6, 54.0, 64.3, 79.0, 154.9.

MS (EI, 70 eV): *m*/*z* = 274, 232, 218, 192, 174, 148, 131, 116, 100, 75, 57 (100), 41.

Anal. Calcd for $C_{14}H_{31}NO_4Si$: C, 55.04; H, 10.23; N, 4.59. Found: C, 54.99; H, 10.20; N, 4.55.

***tert*-Butyl (3*S*)-3-(Hydroxymethyl)-1-oxa-4-azaspiro[4.5]decane-4-carboxylate (12)**

A soln of **10** (2.00 g, 6.55 mmol) in anhyd benzene (60 mL), freshly distilled cyclohexanone (65.5 mmol, 6.79 mL), and PTSA·H_2O (0.018 g, 0.098 mmol) were added to a three-necked, round-bottomed flask, equipped with a magnetic stirring bar, Dean–Stark trap, thermometer, and a reflux condenser with a $CaSO_4$-filled drying tube. The mixture was heated at reflux for 24 h. After evaporation of the benzene, the cooled amber soln was partitioned between sat. $NaHCO_3$ soln (75 mL) and Et_2O (3 × 150 mL). Then the organic layer was washed with brine (2 × 30 mL) and dried ($MgSO_4$), filtered, and concentrated to give the crude product. The crude was purified by chromatography (silica gel, cyclohexene–EtOAc, 9:1) to give **11**; yield: 1.79 g (71%).

A 1.0 M soln of TBAF in THF (4.67 mL, 4.67 mmol) was added to a soln of **11** (1.50 g, 3.89 mmol) in anhyd THF (95 mL). After 2 h, the resulting mixture was partitioned between H_2O (2 × 50 mL) and EtOAc (4 × 60 mL), and the phases were separated. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, cyclohexane–EtOAc, 7:3) to give compound **12**.

Yield: 0.89 g (86%); white crystals; mp 104 °C.

IR (neat): 3477, 1667, 1376, 1295, 1276 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.00–1.80 (m, 17 H), 1.85–2.45 (m, 2 H), 2.74 (br s, OH, 1 H), 3.45–4.15 (m, 5 H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.6, 23.6, 25.7, 28.6, 31.8, 35.8, 45.0, 63.3, 65.8, 95.7, 98.6, 155.0.

Anal. Calcd for $C_{14}H_{25}NO_4$: C, 61.97; H, 9.29; N, 5.16. Found: C, 61.95; H, 9.28; N, 5.10.

***tert*-Butyl (3*R*)-3-Formyl-1-oxa-4-azaspiro[4.5]decane-4-carboxylate (13)**

Freshly distilled Et_3N (1.84 mL, 13.24 mmol) was added to a soln of alcohol **12** (0.50 g) in freshly distilled DMSO (1.85 mL) and CH_2Cl_2 (15 mL) and the soln was stirred under argon at 0 °C. SO_3·py complex (1.184 g, 7.44 mmol) was added portionwise and the reaction mixture was stirred at the same temperature for 15 min. Then the mixture was allowed to warm to r.t., stirred for 2.5 h, diluted with CH_2Cl_2 (100 mL), and poured into ice water (100 mL). The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (4 × 60 mL). The combined organic soln was washed with H_2O (2 × 35 mL) and brine (2 × 20 mL), dried ($MgSO_4$), and concentrated. This gave aldehyde **13** virtually pure [GC-MS showed 1.67% of the (methylsulfanyl)methyl ether formed by a Pummerer rearrangement], pure enough to be used in the following step.

Yield: 0.427g (86%); colorless oil; $[\alpha]_D^{25}$ +65.6 (*c* 1.57, $CHCl_3$).

IR (neat): 2863, 1738, 1709, 1452, 1365 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.01–1.78 (m, 17 H), 1.95–2.55 (m, 2 H) 3.92–4.35 (m, 3 H), 9.53 (s, 1 H), 9.58 (s, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.4, 24.7, 25.1, 28.5, 31.6, 32.4, 34.3, 35.3, 63.6, 64.1, 64.9, 81.3, 96.3, 151.3, 200.2.

MS (EI, 70 eV): *m*/*z* = 269 [M^+], 240, 213, 196, 184, 140, 126, 96, 57 (100), 41, 29.

Anal. Calcd for $C_{14}H_{23}NO_4$: C, 62.43; H, 8.61; N, 5.20. Found: C, 62.42; H, 8.58; N, 5.18.

***tert*-Butyl (3*R*)-3-[(1*R*)-1-Hydroxyallyl]-1-oxa-4-azaspiro[4.5]decane-4-carboxylate (*syn*-14) and *tert*-Butyl (3*R*)-3-[(1*S*)-1-Hydroxyallyl]-1-oxa-4-azaspiro[4.5]decane-4-carboxylate (*anti*-14)**

$CeCl_3·7H_2O$ (0.16 g, 0.43 mmol) was quickly and finely ground to a powder in a mortar and placed in a 100-mL three-necked flask.

The flask was immersed in an oil bath and heated gradually to 135–140 °C under vacuum (<0.5 Torr). The powder was heated without stirring for 1 h, and then the $CeCl_3$ was stirred at the same temperature for another 1 h to be dried completely. While the flask was still hot, N_2 was introduced, and the powder was cooled in an ice bath. Freshly distilled THF (10 mL) was added all at once with vigorous stirring. The ice bath was removed and the suspension was well stirred overnight under N_2 at r.t. The flask was cooled at –78 °C and a freshly prepared 0.87 M soln of vinylmagnesium bromide in THF (0.49 mL, 0.43 mmol) was added slowly. The mixture was stirred at –30 °C for 1 h, and then cooled at –78 °C while a soln of aldehyde **13** (0.40 g, 0.148 mmol) in THF (5 mL) was added dropwise to the mixture. The reaction mixture was stirred for 2 h at –78 °C and for 1 h at –30 °C. The reaction was monitored by TLC and GC-MS. To the mixture was added a sat. soln of NH_4Cl (15 mL) and the flask was allowed to warm to r.t. Then the aqueous phase was extracted with Et_2O (4 × 40 mL) and the combined organic extract was washed with sat. $NaHCO_3$ soln (20 mL) and brine (20 mL) and dried ($MgSO_4$). The crude mixture of diastereomers **14** was purified by chromatography (silica gel, cyclohexane–EtOAc, 8:2).

Yield: 0.10 g (86%); *anti*-**14**/*syn*-**14** (82:18).

IR (neat): 3418, 3078, 1694, 1455, 1392 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ (*anti*-**14**) = 0.95–1.70 (m, 17 H), 1.82–2.45 (m, 2 H), 3.65–4.25 (m, 4 H), 5.17 (dt, *J* = 10.4, 1.65 Hz, 1 H), 5.33 (d, *J* = 17.2 Hz, 1 H), 5.76–5.90 (m, 1 H).

^1H NMR (400 MHz, $CDCl_3$): δ (*syn*-**14**) = 0.95–1.75 (m, 17 H), 1.85–2.65 (s, 2 H), 3.65–4.42 (m, 4 H), 5.20 (d, *J* = 10.4 Hz, 1 H), 5.31 (d, *J* = 17.1 Hz, 1 H), 5.72–5.84 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (*anti*-**14**) = 23.5, 25.1, 28.5, 29.8, 31.5, 34.9, 61.7, 64.5, 74.3, 81.4, 96.0, 116.3, 137.1, 154.4.

^{13}C NMR (100 MHz, $CDCl_3$): δ (*syn*-**14**) = 23.6, 25.1, 28.5, 29.9, 31.2, 35.7, 61.7, 64.2, 75.7, 81.8, 96.0, 118.0, 137.6, 152.3.

MS (EI, 70 eV): *m*/*z* = 297 [M^+], 240, 184, 154, 140, 123, 96, 81, 69, 57(100), 41, 29.

Anal. Calcd for $C_{16}H_{27}NO_4$: C, 64.62; H, 9.15; N, 4.71. Found: C, 64.55; H, 9.08; N, 4.70.

tert-Butyl *N*-[(4*S*,5*R*)-2,2-Dimethyl-4-vinyl-1,3-dioxan-5-yl]carbamate (16)

$BF_3{\cdot}OEt_2$ (0.43 mL, 3.53 mmol) and AcOH (0.40 mL) were added to a soln of *anti*-**14** (0.095 g, 0.32 mmol) in MeOH (2.5 mL). The soln was stirred for 3 h at r.t., and then a sat. $NaHCO_3$ soln (5 mL) was added and the mixture was extracted with CH_2Cl_2 (4 × 30 mL). The crude product **15** was used for the next step without further purification. PPTS (0.080 g, 0.32 mmol) was added to a soln of **15** (0.069 g, 0.32 mmol) and $(MeO)_2CMe_2$ (0.78 mL, 6.4 mmol) in CH_2Cl_2 (5 mL), and the mixture was stirred at r.t. for 48 h. The volatiles were removed by evaporation in vacuo and the residue was characterized without further purification.

Yield: 0.063 g (77%); colorless oil.

IR (neat): 3079, 1703, 1368, 1160, 1066 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.43 (s, 9 H), 1.49 (s, 6 H) 3.45–3.70 (m, 2 H), 3.96 (dd, *J* = 10.3, 4.9 Hz, 1 H), 4.04–4.12 (m, 1 H), 4.36 (br s, 1 H), 5.22 (dd, *J* = 16.5, 10.2 Hz, 2 H), 5.86 (ddd, *J* = 17.2, 10.3, 6.9 Hz, 1 H).

Anal. Calcd for $C_{13}H_{23}NO_4$: C, 60.68; H, 9.01; N, 5.44. Found: C, 60.66; H, 8.96; N, 5.40.

tert-Butyl (3*S*)-3-Vinyl-1-oxa-4-azaspiro[4.5]decane-4-carboxylate (17)

The $[Ph_3PMe]Br$ (0.273 g, 0.765 mmol) was suspended in anhyd THF (7 mL) in a three-necked flask under a N_2 atmosphere. The suspension was cooled to –78 °C, and 1.6 M *n*-BuLi in THF (0.38 mL, 0.61 mmol) was added dropwise. The mixture was stirred for 0.5 h, allowing the temperature to reach 0 °C, at which point it was stirred for an additional 1 h. The resulting dark red soln was used for the Wittig reaction with aldehyde **13**. The soln was cooled (–78 °C) and compound **13** (0.165 g, 0.612 mmol) in THF (5 mL) was added dropwise over 10 min. The reaction mixture was stirred under N_2; the temperature was allowed to reach 25 °C and then the mixture was stirred for 4 h. After the reaction was quenched by the addition of sat. aq NH_4Cl (30 mL), the THF was evaporated under reduced pressure and the residue was extracted with EtOAc (4 × 40 mL). The combined organic phases were washed with H_2O (25 mL) and brine (15 mL) and dried ($MgSO_4$). After evaporation of the solvent under reduced pressure, the residue was purified by flash chromatography (cyclohexane–EtOAc, 9:1).

Yield: 0.115 g (75%); colorless oil; $[\alpha]_D$ –10.9 (*c* 1.46, $CHCl_3$).

^1H NMR (400 MHz, $CDCl_3$): δ = 0.80–1.85 (m, 17 H), 2.00–2.57 (m, 2 H), 3.72 (dd, *J* = 8.8, 2.0 Hz, 1 H), 3.98 (dd, *J* = 8.8, 5.9 Hz, 1 H), 4.18–4.45 (m, 1 H), 5.05–5.30 (m, 1 H), 5.69–5.90 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.6, 24.8, 28.6, 30.9, 35.1, 59.8, 68.1, 79.9, 95.6, 115.8, 137.8, 152.8.

MS (EI, 70 eV): *m*/*z* = 267 [M^+], 211, 168, 124, 111, 70, 57 (100), 41.

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