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Synthesis of (*S*)-*N*-*tert*-Butoxycarbonyl-*N*,*O*-isopropylidene-α-methylserinal: A Potential Building Block for the Asymmetric Synthesis of Non-natural Amino Acids.

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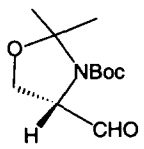
Abstract

The title compound (*S*)-α-methylserinal acetonide has been efficiently prepared from (*S*)-α-methylserine, which is readily available in enantiomerically pure form by Curtius rearrangement of α,α-dialkyl 2-cyanoesters obtained by diastereoselective alkylation of (1*S*,2*R*,4*R*)-10-dicyclohexylsulfamoylisobornyl 2-cyanopropanoate using methoxymethyl iodide or paraformaldehyde as electrophiles by an extension of our recently developed methodology for the synthesis of α,α-dialkylamino acids. © 1998 Elsevier Science Ltd. All rights reserved.

Keywords: Amino acids and derivatives; asymmetric synthesis.

N-*tert*-Butoxycarbonyl-*N*,*O*-isopropylidene serinal (**1**), known as Garner aldehyde, is one of the most widely used chiral building blocks in contemporary organic synthesis [1-7]. In recent years the synthesis of this aldehyde in both of its enantiomerically pure forms has been intensively investigated [8-13] because the development of a simple and practical gram scale procedure is crucial to its extensive application in synthesis.



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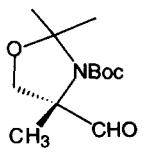

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Figure 1

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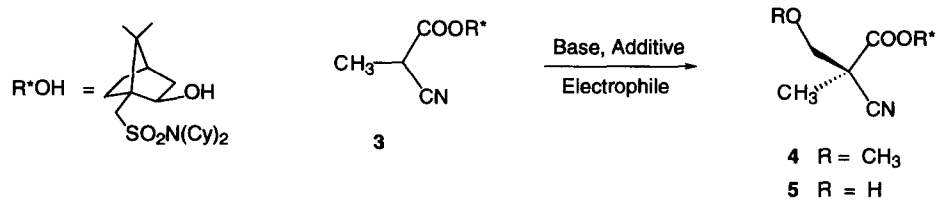
As a part of our research project directed towards the design and synthesis of novel constrained amino acids, we became interested in the stereoselective synthesis of the as yet unknown homolog of **1**, the α-methyl derivative **2**, which can be regarded as an ideal precursor for the synthesis of α-methylamino acids (Figure 1).

In the original procedure [8], and in most of the subsequent modifications, for the synthesis of both the (*S*)- and (*R*)-forms of Garner aldehyde, (*S*)- or (*R*)-serine have been used as starting materials. Due to this fact, our first goal was to obtain (*S*)-α-methylserine to be used as the starting compound.

Although there are several reports dealing with the asymmetric synthesis of α-methylserine and its derivatives [14,15], we preferred to obtain this compound by an extension of our recently developed methodology for the asymmetric synthesis of α,α-dialkylamino acids [16-21] and, in this way, to prove the applicability of this method to the synthesis of α,α-dialkylamino acids with functional groups on the side chain.

The starting material in our general strategy, the (1*S*,2*R*,4*R*)-10-dicyclohexylsulfamoylisobornyl 2-cyanopropanoate (**3**), was easily obtained by esterification of 2-cyanopropanoic acid with (1*S*,2*R*,4*R*)-10-dicyclohexylsulfamoylisoborneol [22]. Firstly, we attempted to alkylate the carbanion of **3** with methoxymethyl iodide under a variety of conditions (Scheme 1). As shown in Table 1, when the reaction was performed with LDA as base we obtained a high yield of the alkylated compound **4** as an almost equimolecular mixture of diastereoisomers. The addition of an external lithium complexing agent, hexamethylphosphoramide (HMPA), or an inorganic salt, LiCl, together with the electrophile in order to avoid the formation of aggregates [23] perceptibly improved the diastereoselectivity of the alkylation process (d.r. = 75/25). Replacement of LDA by other bases such as lithium, sodium and potassium hexamethyldisilazanes was not wholly satisfactory and, although the chemical yields were high, with the lithium or potassium enolates the diastereoselectivity drastically diminished.

As an alternative, we tested the alkylation reaction of **3** with the cheapest and less harmful electrophile, paraformaldehyde. When LDA was used as the base we obtained the desired alkylated compound **5** in high yields with a slightly better diastereoselectivity in the presence of HMPA (d.r. = 78/22) than in the absence of HMPA (d.r. = 72/28).



Scheme 1

We had recently observed that the alkylation reaction of the cyanoester **3** with reactive electrophiles, such as allyl halides [24] or α-halocarbonyl compounds [25], can be conveniently performed at room temperature using potassium carbonate instead of the very strong, moisture and air-sensitive base LDA. Therefore, a solution of (1*S*,2*R*,4*R*)-10-dicyclohexylsulfamoylisobornyl 2-cyanopropanoate (**3**) in acetone was treated with potassium

carbonate in the presence of methoxymethyl iodide or paraformaldehyde. However, in both cases we only recovered the unreacted starting material.

Table 1.

Results obtained in the alkylation of compound **3**.

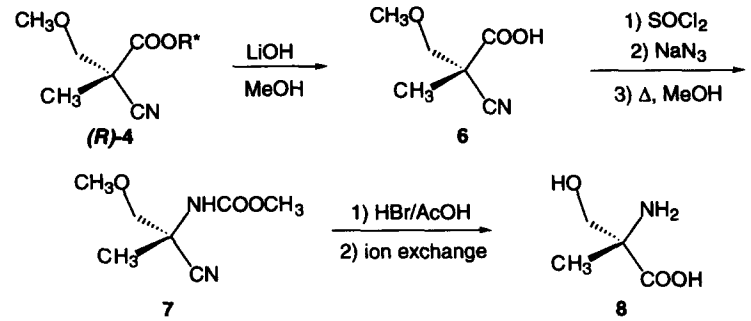
Entry	Electrophile	Base	Additive	Compound	Yield %	d. r.[a]
1	CH_3OCH_2I	LDA	---	**4**	97	55/45
2	CH_3OCH_2I	LDA	HMPA	**4**	95	75/25
3	CH_3OCH_2I	LDA	LiCl	**4**	93	75/25
4	CH_3OCH_2I	LiHMDS	---	**4**	90	52/48
5	CH_3OCH_2I	NaHMDS	---	**4**	90	70/30
6	CH_3OCH_2I	KHMDS	---	**4**	90	53/47
7	CH_3OCH_2I	K_2CO_3	---	**4**	0	---
8	$(CH_2O)_n$	LDA	---	**5**	85	72/28
9	$(CH_2O)_n$	LDA	HMPA	**5**	87	78/22
10	$(CH_2O)_n$	K_2CO_3	---	**5**	0	---

[a] Determined from the spectra of the crude reaction mixture by integration of the ^{1}H-NMR absorptions of the methylene protons of the methoxymethyl group for alkylated compound **4** and by integration of the ^{1}H-NMR absorptions of the methine proton of the ester group for alkylated compound **5**.

The major diastereoisomers formed in the alkylation reactions with methoxymethyl iodide and paraformaldehyde were easily isolated in diastereomerically pure form by chromatography (SiO_2, diethyl ether/hexane = 1:2) and the absolute configurations of the newly-formed stereogenic centre at C(2) were unambiguously assigned as *R* by single crystal X-ray analysis in both cases. This assignment clearly demonstrates that the attack of the electrophile occurs from the Cα-Re side of the *Z*-enolate intermediate, opposite to the 10-dicyclohexylsulfamoyl group which is in accordance with our previously proposed model [26].

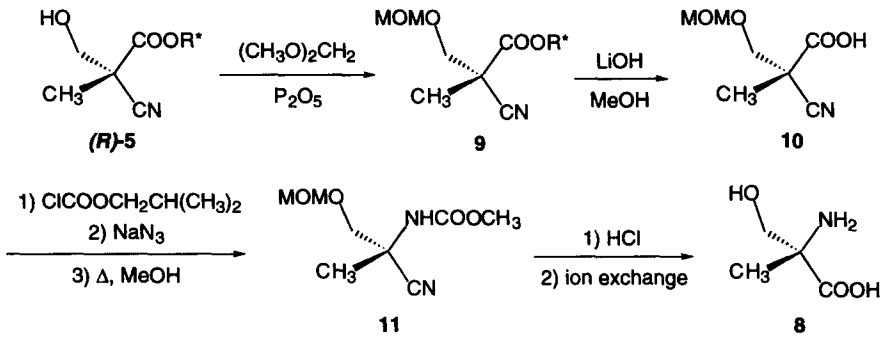
We subsequently attempted the synthesis of (*S*)-α-methylserine from the diastereomerically pure precursors (1*S*,2*R*,4*R*)-10-dicyclohexylsulfamoylisobornyl (*R*)-2-cyano-2-(methoxymethyl)propanoate [(***R***)**-4**] and (1*S*,2*R*,4*R*)-10-dicyclohexylsulfamoylisobornyl (*R*)-2-cyano-2-(hydroxymethyl)propanoate [(***R***)**-5**].

To this end, compound (***R***)**-4** was hydrolysed with 2M lithium hydroxide in methanol to give the corresponding (*R*)-2-cyano-2-(methoxymethyl)propanoate (**6**) in 92% yield, and this compound underwent a Curtius-type rearrangement to afford (*R*)-2-methoxycarbonylamino-2-(methoxymethyl)propanenitrile (**7**) in 95% yield. The cyanourethane **7** was deprotected with concomitant hydrolysis of the cyano group by treatment with a mixture of hydrobromic acid/acetic acid (5:1) to afford (*S*)-α-methylserine hydrobromide, from which enantiomerically pure (*S*)-α-methylserine (**8**) was obtained by ion exchange chromatography in 90% overall yield for the two steps (Scheme 2).



Scheme 2

In contrast, basic hydrolysis of the ester group in (1*S*,2*R*,4*R*)-10-dicyclohexylsulfamoylisobornyl (*R*)-2-cyano-2-(hydroxymethyl)propanoate [(***R***)-**5**] required prior protection of the hydroxy group under mild conditions. For this reason, (***R***)-**5** was treated with dimethoxymethane in the presence of phosphorus pentoxide to afford, by an acid-catalysed acetal exchange reaction [27], the *O*-methoxymethyl derivative **9** in nearly quantitative yield. Compound **9** was then satisfactorily hydrolysed with 2N lithium hydroxide in methanol to give the corresponding 2-cyano-2-(methoxymethoxymethyl)propanoic acid (**10**) in 98% yield. For the final step in the synthesis of (*S*)-α-methylserine we attempted the Curtius rearrangement. All attempts to obtain the corresponding acid chloride by treatment of compound **10** with thionyl chloride were unsuccessful as the compound arising from the migration of the methoxymethyl protecting group from the hydroxy to the carboxylic acid group was the main product of the reaction. As an alternative the acylazide was obtained from compound **10** by reaction with isobutyl chloroformate and in situ trapping of the mixed anhydride with sodium azide. The acylazide obtained in this way was subjected to a Curtius rearrangement, without being isolated, by heating in a mixture of toluene/methanol. The resulting urethane **11**, obtained in 55% yield, was hydrolyzed in an acidic medium to release the hydrochloride of (*S*)-α-methylserine and the free amino acid **8** was easily obtained from this compound in 93% overall yield by ion exchange chromatography (Scheme 3).

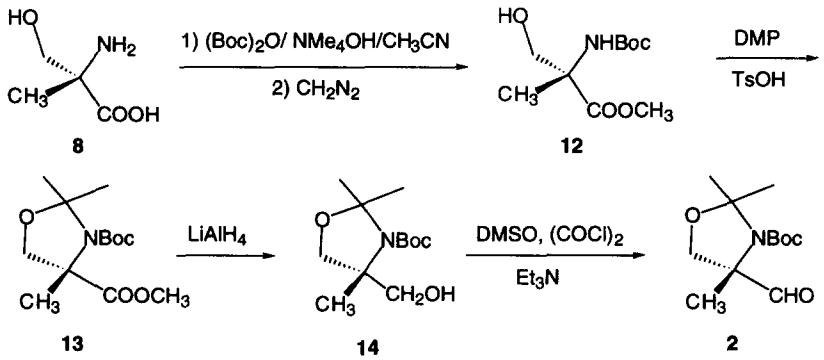


Scheme 3

Having obtained (*S*)-α-methylserine, we investigated the direct conversion of this amino acid to the (*S*)-α-methylserinal derivative **2**. Treatment of the free amino acid with di-*tert*-

butyldicarbonate under standard conditions (sodium hydroxide as base and a mixture of dioxane/water as solvent) afforded the *N*-Boc protected amino acid in only 50% yield after long reaction times and the use of a large excess of reagent. For this reason we tried the reaction using a modification recently reported by Johnson et al. [28] for the *N*-Boc protection of sterically hindered amino acids. This method consists of the use of the lipophilic base tetramethylammonium hydroxide to solubilize the zwitterionic amino acid in acetonitrile. By following this procedure *N-tert*-butoxycarbonyl (*S*)-α-methylserine was obtained in 72% yield after a reaction period of 24 h. Esterification of the crude product with diazomethane afforded compound **12** in 75% yield after purification by column chromatography. The slow distillation of a solution comprising of **12**, 2,2-dimethoxypropane, and a catalytic amount of *p*-toluensulfonic acid in benzene resulted in the clean formation of oxazolidine **13**, which was isolated in 90% yield.

Reduction of **13** to the corresponding aldehyde with DIBAL is often problematic. A far more convenient route, particularly on a large scale, involves a two step reduction-oxidation sequence. Reduction was effected with lithium aluminium hydride in THF at room temperature and the alcohol **14** was oxidised under Swern conditions to afford the desired protected aldehyde **2** in about 70% yield for the last two steps (Scheme 4). The enantiomeric integrity of compound **2** was confirmed by means of a chiral lanthanide shift reagent (CLSR) [Eu(hfc)$_3$] in a ^{1}H-NMR study. With a CLSR/substrate ratio suitable for causing the splitting of the diastereotopic signals, we only observed the peaks arising from one enantiomer.[1]



Scheme 4

In summary, our methodology for the synthesis of α,α-dialkylamino acids based on the diastereoselective alkylation of chiral 2-cyano esters can be successfully applied to the preparation of enantiomerically pure (*S*)-α-methylserine by using (1*S*,2*R*,4*R*)-10-dicyclohexylsulfamoylisobornyl 2-cyanopropanoate as starting material and methoxymethyl iodide or paraformaldehyde as the electrophile. This non-proteinogenic amino acid has been efficiently converted into the valuable chiral building block (*S*)-*N-tert*-butoxycarbonyl-*N*,*O*-isopropyliden-α-methylserinal (**2**). Application of this aldehyde in several asymmetric reactions is currently under investigation.

[1] The experiment was run at room temperature as at the coalescence temperature splitting on racemic compound was not observed.

Experimental

General. All reagents were purchased from the Aldrich Chemical Co. and used as received. (1*S*,2*R*,4*R*)-10-Dicyclohexylsulfamoylisobornyl 2-cyanopropanoate (**3**) was obtained according to our previously described procedure [22] by esterification of 2-cyanopropanoic acid with (1*S*,2*R*,4*R*)-10-dicyclohexylsulfamoylisoborneol. Melting points were determined with a Büchi 510 capillary melting point apparatus and are uncorrected. IR spectra were recorded using a Perkin-Elmer 1600 FT-IR infrared spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian Unity-300 or a Bruker ARX-300 spectrometer in deuterochloroform using the residual solvent signal as the internal standard; chemical shifts (δ) are given in parts per million and the coupling constants (J) in Hertz. The ^{1}H-NMR and ^{13}C-NMR spectra of *N*-Boc protected compounds were not conclusive at room temperature due to the presence of a dynamic equilibrium between rotamers caused by the restricted rotation of the nitrogen-carbon bond of the urethane group. In order to overcome this problem NMR spectra of these compounds were run at 333 K. Optical rotations were measured on a Perkin-Elmer 241-C polarimeter at 25 °C. Elemental analyses were performed using a Perkin-Elmer 200 C,H,N,S elemental analyser. Mass spectra (MS) were determined on a high resolution VG-autospec spectrometer. TLC was performed on Merck 60 F_{240} precoated silica gel polyester plates and products were visualised by UV light (254 nm) and ninhydrin or anisaldehyde/sulphuric acid/ethanol (2:1:100). Column chromatography was performed using silica gel (Kiesegel 60).

General procedure for the enolate alkylation of compound **3**

A solution of (1*S*,2*R*,4*R*)-10-dicyclohexylsulfamoylisobornyl 2-cyanopropanoate (**3**) (478 mg, 1 mmol) in dry THF (5 ml) was added to a THF solution (20 ml) of base (1.1 mmol), under argon at –78 °C. After 1 h a mixture of the corresponding electrophile [methoxymethyl iodide (344 mg, 2 mmol) or paraformaldehyde (300 mg)] and, when necessary, the additive [HMPA (270 mg, 1.5 mmol) or LiCl (424 mg, 10 mmol)] in dry THF (10 ml) was added. The reaction mixture was allowed to warm up to room temperature and stirring was continued for 12 h. The resulting mixture was then quenched with a saturated aqueous NH_4Cl solution (20 ml). Ether extraction, washing with water, drying over $MgSO_4$ and concentration *in vacuo* yielded the corresponding alkylated compound **4** or **5** as a mixture of diastereoisomers (see Table 1). In both cases the major compound was isolated from the diastereomeric mixture by column chromatography (eluent ether/hexane, 1:2) as a white solid.

(1S,2R,4R)-10-Dicyclohexylsulfamoylisobornyl (R)-2-cyano-2-(methoxymethyl)propanoate [(***R***)-**4**]

Mp 174 °C; $[\alpha]_D^{20}$ = –54.2 (c = 0.5 in $CHCl_3$); IR (Nujol) 2248, 1741 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.86 (s, 3H); 1.08 (s, 3H); 1.56 (s, 3H); 1.05–2.0 (m, 27H); 2.61 (d, 1H, J = 13.3 Hz); 3.25–3.37 (m, 2H); 3.38 (s, 3H); 3.41 (d, 1H, J = 13.3 Hz); 3.52 (d, 1H, J = 9 Hz); 3.70 (d, 1H, J = 9 Hz); 4.95–4.98 (dd, 1H, J = 7.8 Hz, J = 3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.5, 19.9, 20.3, 25.2, 26.2, 26.4, 27.0, 30.6, 32.3, 33.3, 39.2, 44.4, 44.9, 49.4, 49.7, 53.7, 57.5, 59.6, 80.7, 119.5, 167.0; Anal. Calcd. for $C_{28}H_{46}N_2O_5S$: C, 64.34; H, 8.87; N, 5.36; S, 6.13. Found: C, 64.56; H, 8.94; N, 5.42; S, 6.17.

(1S,2R,4R)-10-Dicyclohexylsulfamoylisobornyl (R)-2-cyano-2-(hydroxymethyl)propanoate [(***R***)-**5**]

Mp 159 °C; $[\alpha]_D^{20} = -53.4$ (c = 1 in $CHCl_3$); IR (Nujol) 2248, 1745 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.86 (s, 3H); 1.05 (s, 3H); 1.57 (s, 3H); 1.0–2.1 (m, 27H); 2.62 (d, 1H, J = 13.2 Hz); 2.63 (t, 1H, J = 9.9 Hz); 3.15–3.37 (m, 2H); 3.35 (d, 1H, J = 13.2 Hz); 3.86 (dd, 1H, J = 29.1 Hz, J = 9.9 Hz); 3.88 (dd, 1H, J = 29.1 Hz, J = 9.9 Hz); 4.9–5.05 (dd, 1H, J = 7.8 Hz, J = 3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.0, 19.9, 20.3, 25.1, 26.3, 26.4, 27.0, 30.8, 32.3, 33.3, 39.4, 44.4, 46.8, 49.4, 49.7, 53.9, 57.6, 67.5, 80.9, 119.3, 167.3; Anal. Calcd. for $C_{27}H_{44}N_2O_5S$: C, 63.75; H, 8.72; N, 5.51; S, 6.30. Found: C, 63.59; H, 8.84; N, 5.42; S, 6.27.

(R)-2-Cyano-2-(methoxymethyl)propanoic acid (**6**)

(1*S*,2*R*,4*R*)-10-Dicyclohexylsulfamoylisobornyl (*R*)-2-cyano-2-(methoxymethyl)propanoate [(***R***)-**4**] (520 mg, 1 mmol) was added to a 2N solution of LiOH in methanol (30 ml) and the reaction mixture was stirred at room temperature for 3 h. The resulting solution was evaporated *in vacuo* and the residue partitioned between ether and water and the aqueous layer was extracted with ether in order to remove and recover the chiral auxiliary. The aqueous layer was then acidified with 20% hydrochloric acid and extracted with ether. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford (*R*)-2-cyano-2-(methoxymethyl)propanoic acid (**5**) as an oil in 92% yield.

Oil; $[\alpha]_D^{20} = -8.2$ (c = 0.5 in $CHCl_3$); IR (Nujol) 2254, 1745 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.6 (s, 3H); 3.43 (s, 3H); 3.6 (d, 1H, J = 9 Hz); 3.7 (d, 1H, J = 9 Hz); 5.03 (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.7, 45.0, 59.7, 75.5, 118.4, 172.2; HRMS (EI): m/z = 144.0655 (MH^+ calcd. for $C_6H_{10}NO_3$ 144.0660).

(R)-2-Methoxycarbonylamino-2-(methoxymethyl)propanenitrile (**7**)

Thionyl chloride (5 ml) was added to (*R*)-2-cyano-2-(methoxymethyl)propanoic acid (**6**) (143 mg, 1 mmol) and the reaction mixture was stirred at 80 °C for 2 h. The excess thionyl chloride was removed under reduced pressure and the oily residue was dissolved in acetone (3 ml). A solution of sodium azide (130 mg, 2 mmol) in water (1 ml) was added and stirring was continued for 1 h. The acetone was removed *in vacuo* and the aqueous layer was extracted with ether. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was dissolved in a mixture of toluene (20 ml) and methanol (10 ml) and the resulting solution was heated under reflux for 3 h. The solvents were evaporated *in vacuo* and the crude product was purified by flash chromatography (eluent ether/hexane, 1:3) to afford (*R*)-2-methoxycarbonylamino-2-(methoxymethyl)-propanenitrile (**7**) as an oil in 95% yield.

Oil; $[\alpha]_D^{20} = -38.3$ (c = 0.3 in $CHCl_3$); IR (Nujol) 3331, 2242, 1734 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.68 (s, 3H); 3.45 (s, 3H); 3.52 (d, 1H, J = 9.5 Hz); 3.62 (d, 1H, J = 9.5 Hz); 3.71 (s, 3H); 5.3 (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.2, 50.7, 52.5, 59.5, 75.9, 119.3, 155.3; HRMS (EI): m/z = 172.0840 (M^+ calcd. for $C_7H_{12}N_2O_3$ 172.0847).

(S)-α-Methylserine (**8**)

(*R*)-2-Methoxycarbonylamino-2-(methoxymethyl)propanenitrile (**7**) (172 mg, 1 mmol) was hydrolysed by refluxing for 12 h with a mixture of hydrobromic acid/acetic acid (20 ml). After the reaction was complete, the hydrobromic and acetic acids were removed *in vacuo*. The residue was dissolved in water (20 ml), washed with ether, applied to a Dowex 50W x 8 column (H^+ form, 50 ml) and eluted with 5% aqueous ammonia. The fractions containing the amino acid were combined and evaporated *in vacuo* to afford (*S*)-α-methylserine (**8**) as a white solid in 90% yield.

Mp 252–257 °C dec., lit. [29] mp 245–250 °C dec.; $[\alpha]_D^{20}$ = +6.0 (*c* = 1 in H_2O), lit. [29] $[\alpha]_D^{20}$ = +6.1 (*c* = 1 in H_2O); IR (Nujol) 3500–2500, 1605 cm^{-1}; ^1H NMR (D_2O, 300 MHz) δ 1.28 (s, 3H); 3.52 (d, 1H, *J* = 12 Hz); 3.76 (d, 1H, *J* = 12 Hz); ^{13}C NMR (D_2O, 75 MHz) δ 17.0, 61.1, 63.3, 174.0.

(1S,2R,4R)-10-Dicyclohexylsulfamoylisobornyl (R)-2-cyano-2-(methoxymethoxymethyl) propanoate (**9**)

To a stirred solution of (1*S*,2*R*,4*R*)-10-dicyclohexylsulfamoylisobornyl (*R*)-2-cyano-2-(hydroxymethyl)propanoate [(***R***)-**5**] (508 mg, 1 mmol) in dry chloroform (5 ml) was added dimethoxymethane (5 ml, a large excess) and phosphorus pentoxide (2.5 g). After completion of the reaction, usually in 15 min, the mixture was poured into an ice-cooled solution of sodium carbonate and the mixture was extracted with ether. The ethereal layer was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. The crude product was purified by flash chromatography (eluent ether/hexane, 1:2) to afford (1*S*,2*R*,4*R*)-10-dicyclohexylsulfamoylisobornyl (*R*)-2-cyano-2-(methoxymethoxymethyl)propanoate (**9**) as a white solid in 99% yield.

Mp 134 °C; $[\alpha]_D^{20}$ = –49.4 (*c* = 1 in $CHCl_3$); IR (Nujol) 2241, 1745 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.86 (s, 3H); 1.08 (s, 3H): 1.57 (s, 3H); 0.96–2.0 (m, 27H); 2.6 (d, 1H, *J* = 13.2 Hz); 3.16–3.38 (m, 2H); 3.33 (s, 3H); 3.41 (d, 1H, *J* = 13.2 Hz); 3.64 (d, 1H, *J* = 9.3 Hz); 3.84 (d, 1H, *J* = 9.3 Hz); 4.60 (s, 2H); 4.9–5.05 (dd, 1H, *J* = 7.8 Hz, *J* = 3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.6, 19.9, 20.3, 25.2, 26.2, 26.4, 27.0, 30.6, 32.3, 33.3, 39.1, 44.4, 44.7, 49.4, 49.7, 53.7, 55.6, 57.5, 71.4, 80.7, 96.3, 119.5, 167.0; Anal. Calcd. for $C_{29}H_{48}N_2O_6S$: C, 63.14; H, 8.75; N, 5.07; S, 5.80. Found: C, 62.87; H, 8.91; N, 5.17; S, 5.99.

(R)-2-Cyano-2-(methoxymethoxymethyl)propanoic acid (**10**)

The saponification of compound (1*S*,2*R*,4*R*)-10-dicyclohexylsulfamoylisobornyl (*R*)-2-cyano-2-(methoxymethoxymethyl)propanoate (**9**) (552 mg, 1 mmol) according to the previously described procedure for (***R***)-**4** afforded (*R*)-2-cyano-2-(methoxymethoxymethyl)propanoic acid (**10**) as an oil in 98% yield.

Oil; $[\alpha]_D^{20}$ = –0.6 (*c* = 1 in $CHCl_3$); IR (Nujol) 2252, 1747 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.63 (s, 3H); 3.39 (s, 3H); 3.77 (d, 1H, *J* = 9.5 Hz); 3.88 (d, 1H, *J* = 9.5 Hz); 4.67 (s, 2H); 6.6 (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.8, 45.0, 55.7, 70.6, 96.4, 118.6, 171.4; HRMS (EI): *m/z* = 142.0504 (M^+- CH_3O calcd. for $C_6H_8NO_3$ 142.0540).

(R)-2-Methoxycarbonylamino-2-(methoxymethoxymethyl)propanenitrile (**11**)
N-Methylmorpholine (112 mg, 1.1 mmol) and isobutyl chloroformate (150 mg, 1.1 mmol) were added successively to a solution of (*R*)-2-cyano-2-(methoxymethoxymethyl)propanoic acid (**10**) (173 mg, 1 mmol) in dry THF (10 ml) at –15 °C and the reaction was stirred for 30 min. The resulting mixture was allowed to warm up to 0 °C, solution of sodium azide (130 mg, 2 mmol) in water (1 ml) was then added and stirring was continued for 1 h. The THF was removed *in vacuo* and the aqueous layer was extracted with ether. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was dissolved in a mixture of toluene (20 ml) and methanol (10 ml) and the resulting solution was heated under reflux for 3 h. The solvents were evaporated *in vacuo* and the crude product was purified by flash chromatography (eluent ether) to afford (*R*)-2-methoxycarbonylamino-2-(methoxymethoxymethyl)propanenitrile (**11**) as an oil in 55% yield.
Oil; $[\alpha]_D^{20} = -64.8$ (c = 1 in $CHCl_3$); IR (Nujol) 3336, 2248, 1747 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.68 (s, 3H); 3.39 (s, 3H); 3.65 (d, 1H, J = 10.2 Hz); 3.70 (s, 3H); 3.78 (d, 1H, J = 10.2 Hz); 4.67 (s, 2H); 5.48 (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.2, 50.9, 52.5, 55.9, 71.6, 96.8, 119.2, 155.2; HRMS (EI): m/z = 202.0961 (M^+ calcd. for $C_8H_{14}N_2O_4$ 202.0953).

(S)-α-Methylserine (**8**)
(*R*)-2-Methoxycarbonylamino-2-(methoxymethoxymethyl)propanenitrile (**11**) (202 mg, 1 mmol) was hydrolysed by refluxing for 12 h with 20% hydrochloric acid (40 ml). After the reaction was complete the hydrochloric acid was evaporated *in vacuo*. The residue was dissolved in water (20 ml), washed with ether, applied to a Dowex 50W x 8 column (H^+ form, 50 ml) and eluted with 5% aqueous ammonia. The fractions containing the amino acid were combined and evaporated *in vacuo* to afford (*S*)-α-methylserine (**8**) as a white solid in 93% yield. $[\alpha]_D^{20} = +5.9$ (c = 0.98 in H_2O), lit. [29] $[\alpha]_D^{20} = +6.1$ (c = 1 in H_2O)

(S)-N-(tert-Butoxycarbonyl)-α-methylserine methyl ester (**12**)
(*S*)-α-Methylserine (119 mg, 1 mmol) and tetramethylammonium hydroxide pentahydrate (180 mg, 1 mmol) were added to freshly distilled acetonitrile (5 ml). The mixture was stirred at room temperature until a solution had formed and Boc_2O (325 mg, 1.5 mmol) was then added and stirring was continued for 17 h. A further portion of Boc_2O (110 mg, 0,5 mmol) was added and the mixture was stirred for an additional 8 h. The solvent was removed *in vacuo* and the residue was partitioned between water and ether. The aqueous layer was washed with an additional portion of ether and then acidified with solid citric acid to pH 3–4. The aqueous solution was extracted three times with ethyl acetate and the combined organic extracts were washed with water, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give (*S*)-*N*-Boc-α-methylserine as a colourless oil. This material was dissolved in ether (5 ml), cooled in an ice-bath, and treated with ethereal diazomethane. After 30 min at 0 °C, excess diazomethane was destroyed with anhydrous calcium chloride and the resulting solution was filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (eluent hexane/ethyl acetate 1:1) to afford (*S*)-*N*-(*tert*-butoxycarbonyl)-α-methylserine methyl ester (**12**) as an oil in 54% overall yield.

Oil; $[\alpha]_D^{20}$ = +0.25 (*c* = 1 in $CHCl_3$); IR (neat) 3520, 3315, 1733, 1715 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, 333 K) δ 1.42 (s, 9H); 1.44 (s, 3H); 3.25 (brs, 1H); 3.72–3.78 (m, 1H); 3.75 (s, 3H); 3.96 (dd, 1H, *J* = 5.4 Hz, *J* = 11.4 Hz); 5.26 (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz, 333 K) δ 20.7, 28.2, 52.4, 61.1, 66.9, 80.2, 155.3, 173.8; HRMS (EI): *m/z* = 233.1254 (M^+ calcd. for $C_{10}H_{19}NO_5$ 233.1262).

(S)-N-(tert-Butoxycarbonyl)-4-methoxycarbonyl-2,2,4-trimethyl-3-oxazolidine (**13**)
A solution of (*S*)-*N*-(*tert*-butoxycarbonyl)-α-methylserine methyl ester (**12**) (233 mg, 1 mmol), 2,2-dimethoxypropane (210 mg, 2 mmol), and *p*-toluenesulfonic acid monohydrate (2.8 mg, 0.015 mmol) in benzene (10 ml) was heated under reflux for 2 h with continuous azeotropic removal of water with a Dean-Stark apparatus. A further portion of 2,2-dimethoxypropane (52 mg, 0.5 mmol) in benzene (2 ml) was added and azeotropic removal of water was continued for an additional 12 h. The mixture was concentrated *in vacuo* and the residue partitioned between saturated $NaHCO_3$ solution and ether. The organic layer was washed successively with saturated $NaHCO_3$ solution and brine, then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (eluent hexane/ethyl acetate 8:2) to afford (*S*)-*N*-(*tert*-butoxycarbonyl)-4-methoxycarbonyl-2,2,4-trimethyl-3-oxazolidine (**13**) as an oil in 90% yield.
Oil; $[\alpha]_D^{20}$ = –15.05 (*c* = 1 in $CHCl_3$); IR (neat) 1747, 1704 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, 333 K) δ 1.40 (s, 3H); 1.43 (s, 9H); 1.56 (s, 6H); 3.72 (s, 3H); 3.76 (d, 1H, *J* = 8.7 Hz); 4.07 (d, 1H, *J* = 8.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz, 333 K) δ 22.1, 23.6, 26.4, 28.4, 52.2, 65.5, 74.1, 80.4, 96.5, 151.0, 172.9; HRMS (EI): *m/z* = 274.1648 (MH^+ calcd. for $C_{13}H_{24}NO_5$ 274.1654).

(S)-N-(tert-Butoxycarbonyl)-4-hydroxymethyl-2,2,4-trimethyl-3-oxazolidine (**14**)
To a suspension of $LiAlH_4$ (81 mg, 2.1 mmol) in ether (10 ml) was added dropwise with vigorous stirring, a solution of (*S*)-*N*-(*tert*-butoxycarbonyl)-4-methoxycarbonyl-2,2,4-trimethyl-3-oxazolidine (**13**) (275 mg, 1 mmol) in ether (10 ml). Stirring was continued for an additional 2 h and after completion of the reaction (TLC, hexane/ethyl acetate 3/2) the mixture was cooled to 0 °C and quenched carefully by the addition of water (0.1 ml), 1N NaOH solution (0.5 ml) and water (0.5 ml). After stirring at room temperature for 3 h the white precipitate was filtered off and washed thoroughly with ether. The filtrate was concentrated *in vacuo* and the residue purified by flash chromatography (eluent hexane/ethyl acetate 3:2) to afford (*S*)-*N*-(*tert*-butoxycarbonyl)-4-hydroxymethyl-2,2,4-trimethyl-3-oxazolidine (**14**) as a white solid in 75% yield.
Mp 59–62 °C; $[\alpha]_D^{20}$ = –5.2 (*c* = 1 in $CHCl_3$); IR (Nujol) 3423, 1694, 1673 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, 333 K) δ 1.37 (s, 3H); 1.46 (s, 9H); 1.48 (s, 3H); 1.54 (s, 3H); 3.61–3.64 (m, 4H); 3.81 (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz, 333 K) δ 19.6, 25.6, 27.1, 28.4, 64.6, 67.9, 72.1, 81.0, 95.3, 153.5; Anal. Calcd. for $C_{12}H_{23}NO_4$: C, 58.75; H, 9.45; N, 5.71. Found: C, 58.63; H, 9.63; N, 5.34; HRMS (EI): *m/z* = 246.1699 (MH^+ calcd. for $C_{12}H_{24}NO_4$ 246.1705).

(S)-N-(tert-Butoxycarbonyl)-4-formyl-2,2,4-trimethyl-3-oxazolidine (**2**)
To a stirred solution of oxalyl chloride (160 mg, 1.25 mmol) in methylene chloride (5 ml) at –78 °C under argon was added dropwise DMSO (0.15 ml, 2 mmol) *via* a cannula. After

stirring for 5 min a solution of (*S*)-*N*-(*tert*-butoxycarbonyl)-4-hydroxymethyl-2,2,4-trimethyl-3-oxazolidine (**14**) (245 mg, 1 mmol) in methylene chloride (3 ml) was added and stirring was continued for 15 min. Triethylamine (0.6 ml, 4.5 mmol) was then added and stirring was continued for an additional 1 h. The mixture was warmed to –50 °C and after stirring for 3 h the mixture was partitioned between saturated aqueous $NaHCO_3$ and ether. The organic layer was washed twice with 1M $NaHSO_4$ and saturated aqueous $NaHCO_3$, dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (eluent hexane/ethyl acetate 3:2) to afford (*S*)-*N*-(*tert*-butoxycarbonyl)-4-formyl-2,2,4-trimethyl-3-oxazolidine (**2**) as a white solid in 92% yield.

Mp 53–56 °C; $[\alpha]_D^{20} = -23.79$ (c = 0.66 in $CHCl_3$); IR (Nujol) 1473, 1698 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, 333 K) δ 1.43 (s, 9H); 1.48 (s, 3H); 1.58 (s, 3H); 1.60 (s, 3H); 3.63 (dd, 1H, J = 9 Hz); 3.89 (dd, 1H, J = 9 Hz); 9.41 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz, 333 K) δ 18.1, 24.8, 26.2, 28.4, 68.8, 69.9, 81.3, 96.3, 151.0, 198.0; Anal. Calcd. for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.58; H, 8.53; N, 5.33; HRMS (EI): m/z = 214.1440 (M^+-CHO calcd. for $C_{11}H_{20}NO_3$ 214.1443).

Single crystal X-ray diffraction analysis of (***R***)-**4**[2]

Crystallographic measurements were carried out at ambient temperature on a 4-circle Siemens P4 diffractometer using graphite monochromated molybdenum $K\alpha$ X-radiation (λ = 0.71069 Å). One equivalent set of data was collected in the range 4 ° < 2θ < 50 ° using ω/2θ scans. No significant variation was observed in the intensity of the three standard reflections. The structure was solved by direct methods using SIR92 [30] and was refined by full-matrix least squares (based on F^2) using SHELXL-93 [31] which used all data for refinement. The weighting scheme was $\omega = [\sigma^2(F_0^2) + (1.7166P)^2 + 0.7368P]^{-1}$ where $P = (F_0^2 + 2F_c^2)/3$. All non-hydrogen atoms were refined with anisotropic thermal parameters. All hydrogen atoms were constrained to predicted positions.

$C_{28}H_{46}N_2O_5S$, 0.54 x 0.38 x 0.22 mm, M_t = 522.73, orthorhombic, space group $P2_12_12_1$, a = 13.339(5), b = 14.785(5), c = 15.061(5) Å, V = 2970.3(18) $Å^3$, Z = 4, ρ_{calc} = 1.169 g cm^{-3}, $F(000)$ = 1136, μ = 1.46 cm^{-1}. 5221 independent reflections measured. Final R = 0.1079, ωR = 0.1441 for all independent reflections, R = 0.0618, ωR = 0.1239 for 3435 observed reflections with $F_0 > 4\sigma F_0$.

Single crystal X-ray diffraction analysis of (***R***)-**9**[2]

Crystallographic measurements were carried out at ambient temperature on a 4-circle Siemens P4 diffractometer using graphite monochromated molybdenum $K\alpha$ X-radiation (λ = 0.71069 Å). One equivalent set of data was collected in the range 4 ° < 2θ < 50 ° using ω/2θ scans. No significant variation was observed in the intensity of the three standard reflections. The structure was solved by direct methods using SIR92 [30] and was refined by full-matrix least squares (based on F^2) using SHELXL-93 [31] which used all data for refinement. The weighting scheme was $w = [\sigma^2(F_0^2) + (0.1343P)^2 + 0.00P]^{-1}$ where $P = (F_0^2 + 2F_c^2)/3$. All non-hydrogen atoms were refined with anisotropic thermal parameters. All hydrogen atoms were constrained to predicted positions.

[2] Crystals of compounds (***R***)-**4** and (***R***)-**9** suitable for X-ray crystallographic studies were obtained by slow evaporation from methanol solutions. Supplementary data for X-ray crystagraphic studies on (***R***)-**4** and (***R***)-**9** including tables of bond lengths and angles have been deposited with Cambridge Crystallographic Data Centre and are available on request.

$C_{29}H_{48}N_2O_6S$, 0.5 x 0.22 x 0.18 mm, M_t = 552,75, hexagonal, space group $P6_1$, a = 22.677(5), b = 22.677(5), c = 10.834(5) Å, V = 4825(3) Å^3, Z = 6, ρ_{calc} = 1.141 g cm^{-3}, $F(000)$ = 1800, μ = 1,41 cm^{-1}. 3308 independent reflections measured. Final R = 0.1652, ωR = 0.2454 for all independent reflections, R = 0.0838, ωR = 0.2065 for 1754 observed reflections with $F_0 > 4\sigma F_0$.

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