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α-Methylserinals as an access to α-methyl-β-hydroxyamino acids: application in the synthesis of all stereoisomers of α-methylthreonine

Alberto Avenoza,* Jesús H. Busto, Francisco Corzana, Jesús M. Peregrina,* David Sucunza and María M. Zurbano

Departamento de Química, Universidad de La Rioja, Grupo de Síntesis Química de La Rioja, U.A.-C.S.I.C., E-26006 Logroño, Spain

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Abstract—The asymmetric synthesis of all stereoisomers of α-methylthreonine using a stereodivergent synthetic route starting from (*S*)- and (*R*)-*N*-Boc-*N*,*O*-isopropylidene-α-methylserinals is reported. The key step involves the asymmetric addition of methylmagnesium bromide to these aldehydes with a high level of asymmetric induction being observed. This methodology represents a powerful tool for the synthesis of different β-substituted α-methylserines.

1. Introduction

The incorporation of conformationally constrained amino acids into biologically active peptides has emerged as an important route for preparing peptide-based drug molecules.[1–5] The resulting peptidomimetics have increased potency and selectivity, fewer side effects, improved oral bioavailability and also minimize enzymatic degradation.[6] Among the conformationally restricted amino acids, the α,β-disubstituted systems can severely restrict the conformations of the peptide backbone[7] and provide key information concerning the conformation responsible for biological recognition.[6] On the other hand, serine and threonine are unique residues because the hydroxyl groups on their side chains are crucial for the linkages in glycopeptides. It has been shown that O-glycosilation of serine and threonine in peptides not only influences the physical properties and conformations, but also protects these conjugates against proteolitic attack.[8] As a consequence, new and versatile synthetic methodologies for the synthesis of β-substituted serines have become an important goal for organic chemists.[9,10]

In an effort to combine the two aforementioned processes, and in connection with our research into the asymmetric synthesis of conformationally restricted amino acids,[11] we focused our attention on β-substituted α-methylserines. In this field, we have previously reported the synthesis of α-methyl-β-phenylserines,[12] α,β,β-trimethylserines[13] and α-methyl-β,β-diphenylserine derivatives[13] using Grignard additions to the chiral building blocks (*S*)- and (*R*)-**1a** or (*S*)- and (*R*)-**1b**, which can be readily obtained from α-methylserine.[14]

Herein we report the application of this methodology to the asymmetric synthesis of α-methylthreonines **2** (Fig. 1) and demonstrate that our method is a powerful tool for the synthesis of β-substituted α-methylserines.

To the best of our knowledge there are only three methods in the literature for the synthesis of enantiomerically pure **2**. Seebach and co-workers[15] described how the enolization of two oxazolines, both prepared from L-threonine, followed by the electrophilic attack of iodomethane and further transformations, provided (2*S*,3*S*)- and (2*R*,3*R*)-**2**. Ohfune and Moon[16] obtained four stereoisomers of amino acid **2** using an intramolecular version of an asymmetric Strecker synthesis. More recently, Goodman and co-workers[7,17] reported the enantioselective synthesis of all stereoisomers of compound **2** using the Sharpless asymmetric dihydroxylation reaction to generate the stereogenic centre in one step.

* Corresponding authors. Tel./fax: +34-941-299655; e-mail addresses: alberto.avenoza@dq.unirioja.es; jesusmanuel.peregrina@dq.unirioja.es

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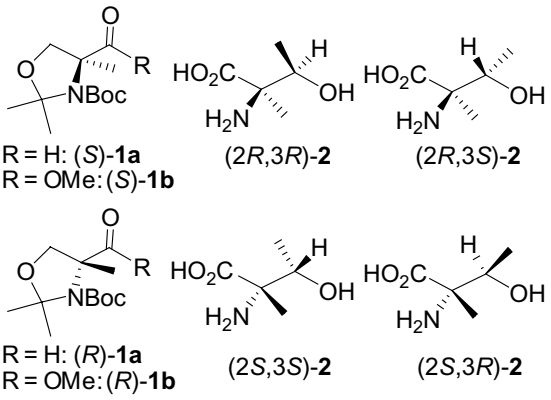


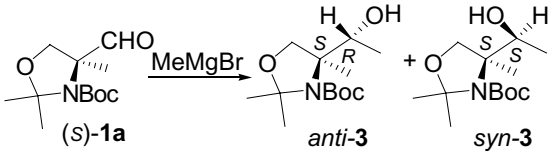
Figure 1. Chiral building blocks **1a**,**b** and α-methylthreonines **2**.

2. Results and discussion

In our methodology, the oxazolidine ring of α-methylserinal derivative **1a** contributes the chiral amino acid moiety with the new stereogenic centre at the β-carbon being created by a nucleophilic attack by an organometallic compound on the aldehyde group.

In the synthesis of α-methylthreonines **2**, we assessed the reaction between oxazolidine (*S*)-**1a** and MeMgBr under different conditions of temperature and solvents (Table 1). The best result in terms of diastereoselectivity in favour of *anti*-**3** was obtained when the reaction was carried out at −78 °C in THF (Table 1, entry 2). Under these conditions the yield of the reaction was 87%. As one would expect, the use of diethyl ether, a solvent more likely to favour chelation, led to a significant decrease in the diastereoselectivity[12] (Table 1, entry 3). It is important to underline that the use of MeLi gave lower yields in all cases.

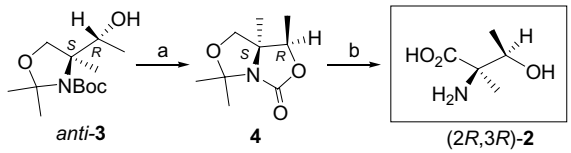
Table 1. MeMgBr additions to α-methylserinal **1**



Entry	Solvent	*T* (°C)	*anti*/*syn*[a]
1	THF	−50	87/13
2	THF	−78	95/5
3	Et_2O	−78	65/35

[a] Determined by integration of the CH signals of products *anti*-**3** and *syn*-**3** in the ^1H NMR spectrum.

Starting from enantiomerically pure *anti*-**3**, we synthesized (2*R*,3*R*)-**2** with an overall yield of 46% (Scheme 1) in four steps: (1) intramolecular cyclization of compound *anti*-**3** to give compound **4**, promoted by the propensity of the *N*-Boc group to react intramolecularly with nucleophiles,[18] therefore compound **4** was obtained by attack of the alkoxide ion on the carbonyl carbon of the Boc group; (2) selective deprotection of the acetonide moiety by hydrochloric acid; (3) subsequent Jones

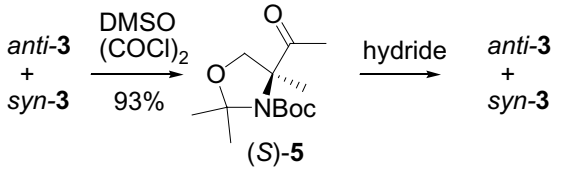


Scheme 1. Reagents and conditions: (a) NaH, DMF, 0 °C, 6 h, 88%; (b) (i) 4 M HCl/THF (1:1), 25 °C, 2 h; (ii) Jones reagent, acetone, 1 h, 0 °C and another 4 h, 25 °C; (iii) 6 M HCl reflux, 48 h; (iv) propylene oxide/EtOH (1:3), reflux, 2 h (52% from **4**).

oxidation and (4) acid hydrolysis using hydrochloric acid under reflux. Liberation of amino acid **2** from its hydrochloride salt was achieved by heating the salt under reflux with propylene oxide in ethanol. The spectroscopic data of this compound are identical to those previously reported in the literature.[15]

In an effort to synthesize (2*R*,3*S*)-**2**, and bearing in mind that it was not possible to obtain *syn*-**3** as the major diastereomer in the addition reaction, we focused our attention on the stereoselective reduction of ketone (*S*)-**5**. This compound was obtained in 93% yield by treating the mixture of *anti*-**3** and *syn*-**3** with DMSO and oxalyl chloride at −78 °C in THF. Unfortunately, as can be seen in Table 2, none of the reducing agents used gave *syn*-**3** with high selectivity.

Table 2. Diastereoselective reduction of ketone **5**



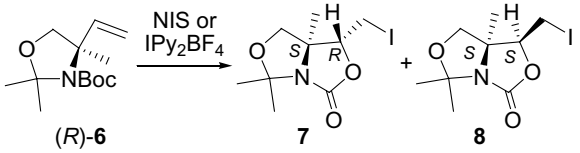
Entry[a]	Hydride	Solvent	*anti*/*syn*
1	n-Bu_4NBH_4	MeOH	35/65
2	$LiBH_4$	MeOH	45/55
3	$NaBH_4$	MeOH	60/40
4	L-Selectride®	THF	70/30
5	DIBAL-H	THF	75/25

[a] All the reactions were carried out at −78 °C.

These results forced us to turn our attention to compound (*R*)-**6**, the synthesis of which was previously reported by our group.[19] The selective iodocyclization[20,21] of this allylic carbamate with NIS or IPy_2BF_4[22,23] gave a mixture of compounds **7** and **8** (Table 3), which could not be separated by column chromatography. The best diastereoselectivity in favour of **7** was achieved when the reaction was carried out with IPy_2BF_4 in CH_3CN at −40 °C (Table 3, entry 5).

In order to obtain amino acid (2*R*,3*S*)-**2**, we proposed the retrosynthetic route shown in Scheme 2. However, treatment of the mixture of compounds **7** and **8** (Table 3, entry 5) with a variety of different reagents, such as Mg, Bu_3SnH-AIBN, *n*-BuLi, $LiAlH_4$ or $LiBH_4$, gave derivative **9** in very low yield, after column chromatography. Indeed, the highest yield (30%) was obtained when the

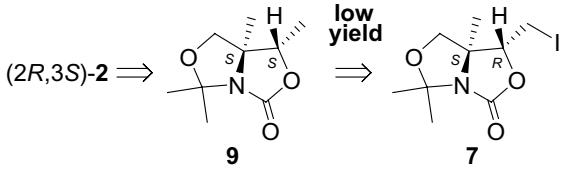
Table 3. Regio- and diastereoselective iodocyclization of the allylic carbamate (*R*)-**6**



(*R*)-**6** **7** **8**

Entry	Reagent	Solvent	*T* (°C)	Yield (%)	**7**/**8**[a]
1	NIS	CH_2Cl_2	25	40	84/16
2	IPy_2BF_4	Dioxane	10	70	92/8
3	IPy_2BF_4	CH_2Cl_2	−50	65	89/11
4	IPy_2BF_4	THF	−78	68	90/10
5	IPy_2BF_4	CH_3CN	−40	70	95/5

[a] Determined by integration of the CH signals of products **7** and **8** in the ^{1}H NMR spectrum.



9 **7**

Scheme 2. Retrosynthetic route to obtain (2*R*,3*S*)-**2** from compound **7**.

reaction was carried out with $LiAlH_4$ in THF at 25 °C. The structure of this compound was determined by X-ray analysis of a monocrystal obtained by crystallization from chloroform/hexane (Fig. 2).[†]

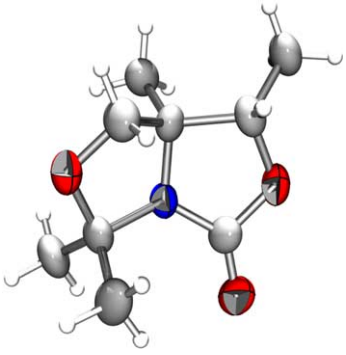
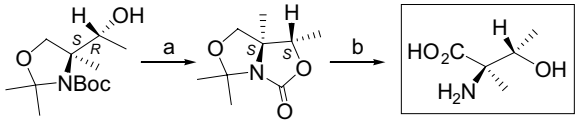


Figure 2. ORTEP drawing of the molecular structure of compound **9**.

[†] Crystal data: (a) $C_9H_{15}N_1O_3$, $M_w = 185.22$, colourless prism of $0.7\times0.37\times0.2$ mm, $T = 223$ K, orthorhombic, space group $P2_12_12_1$, $Z = 4$, $a = 6.8080(4)$ Å, $b = 9.0645(5)$ Å, $c = 15.8652(9)$ Å, $V = 979.06(10)$ Å^3, $d_{calcd} = 1.257$ g cm^{-3}, $F(000) = 400$, $\lambda = 0.71073$ Å (Mo, Kα), $\mu = 0.089$ mm^{-1}, Nonius kappa CCD diffractometer, θ range 1.28–27.87°, 4359 collected reflections, 2190 unique, full-matrix least-squares (SHELXL97[24]), $R_1 = 0.0735$, $wR_2 = 0.1802$, ($R_1 = 0.1082$, $wR_2 = 0.2127$ all data), goodness of fit = 1.039, residual electron density between 0.283 and −0.261 e Å^{-3}. Hydrogen atoms were located from mixed methods (electron-density maps and theoretical positions). Further details on the crystal structure are available on request from Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, UK on quoting the depository number 221220.

It is important to note that the heterocyclic intermediate **7** is suitable for conversion into polyfunctionalized structures and could be a valuable precursor for biologically active compounds. Work in this area is currently in progress and will be reported in due course.

In an effort to obtain compound **9** in high yield, we focused our attention on derivative *anti*-**3**. The intramolecular cyclization of *anti*-**3**, in this case with triflic anhydride, gave bicyclic compound **9** in 88% yield by nucleophilic attack of the carbamate group on the activated alcohol with total inversion at the stereogenic centre.[18] The same strategy used to prepare amino acid (2*R*,3*R*)-**2** from **4**, was used with amino acid (2*R*,3*S*)-**2**, obtained from compound **9** in 52% yield. The spectroscopic data of this amino acid were identical to those previously reported (Scheme 3).[7,16]



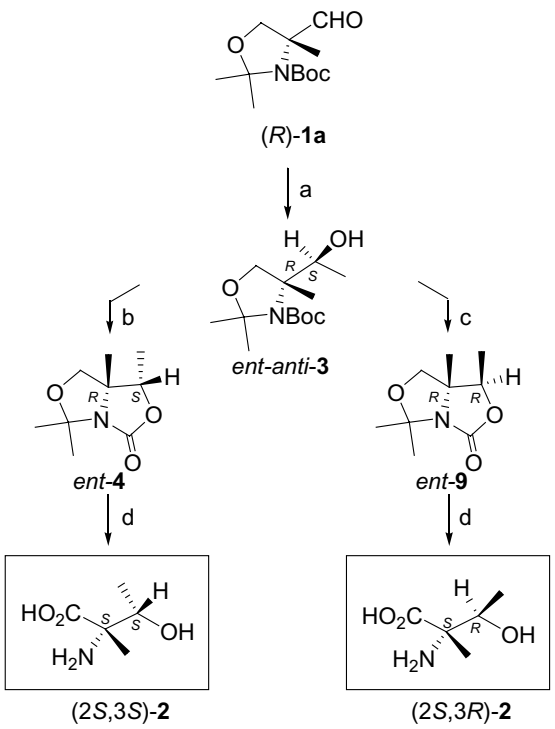
anti-**3** **9** (2*R*,3*S*)-**2**

Scheme 3. Reagents and conditions: (a) Tf_2O, 2,6-di-*tert*-butyl-4-methylpyridine, CH_2Cl_2, 0 °C, 5 min, 88%; (b) (i) 4 M HCl/THF (1:1), 25 °C, 2 h; (ii) Jones reagent, acetone, 3 h, 0 °C and another 3 h, 25 °C; (iii) 6 M HCl reflux, 48 h; (iv) propylene oxide/EtOH (1:3), reflux, 2 h (52% from **9**).

The other enantiomers of α-methylthreonine [(2*S*,3*S*)-**2** and (2*S*,3*R*)-**2**] were obtained using the same strategy as described above but starting from (*R*)-**1a** (Scheme 4). The spectroscopic data of these amino acids were identical to those of the enantiomers (2*R*,3*R*)-**2** and (2*R*,3*S*)-**2**, except that their specific rotations were opposite in sign (Scheme 4).

3. Conclusions

In summary, we have developed a stereoselective synthesis for all the stereoisomers of α-methylthreonine **2**.



Scheme 4. Reagents and conditions: (a) MeMgBr, THF, −78 °C, 4 h, 87%; (b) NaH, DMF, 25 °C, 6 h, 88%; (c) Tf_2O, 2,6-di-*tert*-butyl-4-methylpyridine, CH_2Cl_2, 0 °C, 5 min, 88%; (d) (i) 4 M HCl/THF (1:1), 25 °C, 2 h; (ii) Jones reagent, acetone, 3 h, 0 °C and another 3 h, 25 °C; (iii) 6 M HCl reflux, 48 h; (iv) propylene oxide/EtOH (1:3), reflux, 48 h (52% from *ent*-**4** or *ent*-**9**).

The route involves the asymmetric addition of methylmagnesium bromide to the chiral building blocks (*S*)-**1a** and (*R*)-**1a**. This methodology can be easily applied to the asymmetric synthesis of β-substituted α-methylserines by simply changing the organometallic reagent. Moreover, the heterocyclic intermediate **7** described herein is suitable for conversion into polyfunctionalized structures and could therefore be used as a precursor for biologically active compounds.

4. Experimental

4.1. General procedures

Solvents were purified according to standard procedures. Analytical TLC was performed using Polychrom SI F_{254} plates. Column chromatography was performed using Silica gel 60 (230–400 mesh). ^1H and ^{13}C NMR spectra were recorded on a Bruker ARX-300 spectrometer. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ with TMS as the internal standard and in D_2O with TMS as the external standard using a coaxial microtube (chemical shifts are reported in ppm on the δ scale, coupling constants in Hz). The assignment of all separate signals in the ^1H NMR spectra was made on the basis of coupling constants, selective proton–proton homonuclear decoupling experiments, proton–proton COSY experiments and proton–carbon HETCOR experiments. Melting points were determined on a Büchi SMP-20 melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin–Elmer 341 polarimeter in 1.0 and 0.5 dm cells of 1.0 and 3.4 mL capacity, respectively. Microanalyses were carried out on a CE Instruments EA-1110 analyser and are in good agreement with the calculated values.

4.2. (4*S*,1′*R*)-*N*-(*tert*-Butoxycarbonyl)-4-(1′-hydroxyethyl)-2,2,4-trimethyloxazolidine *anti*-3

To a pre-cooled solution of (*S*)-**1a** (0.90 g, 3.70 mmol) in THF (25 mL) at −78 °C was added dropwise a 3 M solution of phenylmagnesium bromide (2.5 mL, 7.40 mmol) in THF over 5 min. The resulting yellow solution was stirred for an additional 4 h at −78 °C and then warmed to 0 °C over 10 min. The reaction mixture was diluted with diethyl ether (30 mL) and quenched with saturated NH_4Cl solution (30 mL). The organic layer was washed with brine (30 mL), dried over Na_2SO_4 and concentrated to give a pale yellow oil, which was purified by column chromatography (hexane/ethyl acetate, 4/1) to give *anti*-**3** as a colourless oil (0.83 g, 3.20 mmol); yield: 87%. $[\alpha]_D^{25} = -11.1$ (*c* 0.91, MeOH); ^1H NMR ($CDCl_3$): δ 1.16 (d, 3H, $J = 6.3$ Hz, $CHOHCH_3$), 1.40–1.60 [m, 18H, $(CH_3)_2C$, $C(CH_3)N$, $(CH_3)_3CO$], 3.66–3.77 (m, 3H, CH_2, $CHOHCH_3$), 4.60–4.80 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$): δ 18.6 ($CHOHCH_3$), 21.2, 25.5, 26.6 [$(CH_3)_2C$, $C(CH_3)N$], 28.3 [$(CH_3)_3CO$], 67.4 [$C(CH_3)N$], 70.7, 72.7 (CH_2, $CHOHCH_3$), 80.9 [$(CH_3)_3CO$], 95.5 [$(CH_3)_2C$], 153.5 (CO); ESI^+ $(m/z) = 260$. Anal. Calcd for $C_{13}H_{25}NO_4$: C, 60.21; H, 9.72; N, 5.40. Found: C, 60.05; H, 9.61; N, 5.30.

4.3. (1*R*,7a*S*)-1,5,5,7a-Tetramethyl-2,6-dioxa-4-azapentalen-3-one 4

To a solution of *anti*-**3** (0.35 g, 1.35 mmol) in DMF (10 mL) at 0 °C was added NaH (65 mg, 1.62 mmol). The resulting suspension was stirred at 0 °C for 6 h and then quenched at 0 °C with H_2O (10 mL). The resulting mixture was concentrated to obtain a pale yellow solid, which was washed with ethyl acetate (3 × 15 mL). This solution was dried over Na_2SO_4, evaporated and the crude residue purified by column chromatography (hexane/ethyl acetate, 7/3) to give **4** (0.22 g, 1.19 mmol) as a white solid; yield: 88%. Mp: 48 °C. $[\alpha]_D^{25} = +25.5$ (*c* 1.00, MeOH); ^1H NMR ($CDCl_3$): δ 1.27 (d, 3H, $J = 6.6$ Hz, $CHOCH_3$), 1.45, 1.46, 1.59 [3s, 9H, $(CH_3)_2C$, $C(CH_3)N$], 3.58 (d, 1H, $J = 9.0$ Hz, CH_2), 3.81 (d, 1H, $J = 9.0$ Hz, CH_2), 4.29 (q, 1H, $J = 6.6$ Hz, $CHOCH_3$); ^{13}C NMR ($CDCl_3$): δ 16.4 ($CHOC_3$), 23.7, 26.3, 28.4 [$(CH_3)_2C$, $C(CH_3)N$], 69.0 (CH_2), 73.8 [$C(CH_3)N$], 78.4 ($CHOCH_3$), 94.7 [$(CH_3)_2C$], 156.3 (CO); ESI^+ $(m/z) = 186$. Anal. Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.44; H, 7.99; N, 7.63.

4.4. (2*R*,3*R*)-α-Methylthreonine 2

To a solution of **4** (0.20 g, 1.04 mmol) in THF (7 mL) was added aqueous 4 M HCl (7 mL). The mixture was

stirred at 25 °C for 2 h and the solvent removed to give (4*S*,5*R*)-4-(hydroxymethyl)-4,5-dimethyloxazolidin-2-one (0.13 g, 0.90 mmol) as a white solid after purification by column chromatography (CH_2Cl_2/MeOH, 9.5/0.5); yield: 80%. Mp: 58 °C. $[\alpha]_D^{25} = +0.3$ (*c* 0.95, MeOH); ^{1}H NMR ($CDCl_3$): δ 1.21 [s, 3H, C(CH_3)N], 1.40 (d, 3H, $J = 6.9$ Hz, CHOCH_3), 3.47 (d, 1H, $J = 12.0$ Hz, CH_2), 3.63 (d, 1H, $J = 12.0$ Hz, CH_2), 4.25 (br s, 1H, OH), 4.38 (q, 1H, $J = 6.9$ Hz, C*H*OCH$_3$), 6.78 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 13.2 (CHOCH_3), 21.3 [C(CH_3)N], 61.4 [C(CH_3)N], 64.9 (CH_2), 82.2 (*C*HOCH$_3$), 160.4 (CO); ESI$^+$ (m/z) = 146. Anal. Calcd for $C_6H_{11}NO_3$: C, 49.65; H, 7.64; N, 9.65. Found: C, 49.58; H, 7.48; N, 9.74. To a solution of (4*S*,5*R*)-4-(hydroxymethyl)-4,5-dimethyloxazolidin-2-one (0.10 g, 0.69 mmol) in acetone (10 mL) at 0 °C was added a 1.5-fold excess of Jones reagent dropwise over 5 min. The mixture was stirred at 0 °C for 1 h and then at 25 °C for 4 h. The excess Jones reagent was then destroyed with 2-propanol. The mixture was partitioned between brine (10 mL) and ethyl acetate (20 mL). The aqueous phase was extracted several times with ethyl acetate (4 × 15 mL). The organic phases were combined, dried over Na_2SO_4 and concentrated. The resulting white solid was dissolved in aqueous 6 M HCl (5 mL) and heated at 100 °C for 48 h. The solution was concentrated to give 2-amino-3-hydroxy-2-methylbutanoic acid hydrochloride as a white solid. This compound was dissolved in 4 mL of EtOH/propylene oxide (3/1) and the mixture then heated under reflux for 2 h. After this time, the amino acid precipitated as a white solid (60 mg, 0.45 mmol); yield: 65%. $[\alpha]_D^{25} = -11.6$ (*c* 0.85, H_2O); ^{1}H NMR (D_2O): δ 1.22 (d, 3H, $J = 6.6$ Hz, CHOCH_3), 1.51 [s, 3H, C(CH_3)N], 4.06 (q, 1H, $J = 6.6$ Hz, C*H*OCH$_3$); ^{13}C NMR (D_2O): δ 16.9, 20.0 [CHOCH_3, C(CH_3)N], 65.2 [C(CH_3)N], 69.3 (*C*HOCH$_3$), 175.0 (CO); ESI$^+$ (m/z) = 134. Anal. Calcd for $C_5H_{11}NO_3$: C, 45.10; H, 8.33; N, 10.52. Found: C, 45.33; H, 8.46; N, 10.40.

4.5. (*S*)-*N*-(*tert*-Butoxycarbonyl)-4-acetyl-2,2,4-trimethyloxazolidine 5

DMSO (0.16 g, 2.08 mmol) was added to a cooled (−78 °C) solution of oxalyl chloride (0.16 g, 1.25 mmol) in CH_2Cl_2 (10 mL). The resulting solution was stirred for 5 min at −78 °C and a solution of *anti*-**3** and *syn*-**3** (0.27 g, 1.04 mmol) in CH_2Cl_2 (5 mL) added. The resulting mixture was stirred for 15 min at −78 °C and Et_3N (0.42 g, 4.17 mmol) added. The solution was allowed to warm up to 25 °C and then quenched by the addition of saturated $NaHCO_3$ (20 mL) and then diluted with Et_2O (20 mL). The phases were separated and the organic phase washed with aqueous 1 M $KHSO_4$ solution (15 mL), saturated $NaHCO_3$ (15 mL) and brine (15 mL). The organic phase was dried, filtered and concentrated. The crude product was purified by column chromatography (hexane/ethyl acetate, 9/1) to give **5** (0.25 g, 0.97 mmol) as a colourless oil; yield: 93%. $[\alpha]_D^{25} = -18.0$ (*c* 1.45, MeOH); ^{1}H NMR ($CDCl_3$): δ 1.35–1.68 [m, 18H, (CH_3)$_3$CO, CH_3, (CH_3)$_2$C], 2.19 (s, 3H, COCH_3), 3.69–3.73 (m, 1H, CH_2O), 3.92 (d, 1H, $J = 9.3$ Hz, CH_2O); ^{13}C NMR ($CDCl_3$): δ 19.5, 20.7 (CH_3), 24.4 (CO*C*H$_3$), 24.8, 25.4, 25.7, 26.5 [(*C*H$_3$)$_2$C], 28.2 [(*C*H$_3$)$_3$CO], 69.9, 70.3 [*C*(CH_3)N], 71.8, 72.1 (CH_2O), 80.9 [(CH$_3$)$_3$*C*O], 95.1, 96.1 [(CH$_3$)$_2$*C*], 150.7, 151.4 (NCO), 207.0 (*C*OCH$_3$); ESI$^+$ (m/z) = 258. Anal. Calcd for $C_{13}H_{23}NO_4$: C, 60.68; H, 9.01; N, 5.44. Found: C, 60.52; H, 9.09; N, 5.61.

4.6. (1*R*,7a*S*)-1-Iodomethyl-5,5,7a-trimethyl-2,6-dioxa-4-azapentalen-3-one 7

To a solution of olefin **6** (0.43 g, 1.78 mmol) in CH_3CN (10 mL) was added IPy_2BF_4 (0.86 g, 2.32 mmol) at −40 °C. The mixture was stirred for 12 h at −40 °C and the reaction then quenched by the addition of 0.5 M HCl (15 mL) and CH_2Cl_2 (15 mL). The phases were separated and the organic phase was washed with 0.5 M HCl (15 mL), saturated $NaHCO_3$ (15 mL), 0.1 M Na_2SO_3 (15 mL) and brine (15 mL). The organic phase was dried, filtered and concentrated. The crude product was purified by column chromatography (hexane/ethyl acetate, 4/1) to give a mixture of **7** and **8** in a ratio 95/5 in favour of **7** as a yellow solid (0.39 g, 1.25 mmol); yield: 70%. Compound **7**: ^{1}H NMR ($CDCl_3$): δ 1.48, 1.50, 1.60 (3s, 9H, 3CH_3), 3.16 ('t', 1H, $J = 10.2$ Hz, CH_2I), 3.39 (dd, 1H, $J = 4.8$ Hz, $J = 10.2$ Hz, CH_2I), 3.88 (s, 2H, CH_2O), 4.57 (dd, 1H, $J = 4.8$ Hz, $J = 10.2$ Hz, CHO); ^{13}C NMR ($CDCl_3$): δ −1.9 (CH_2I), 18.4, 23.6, 27.8 [(*C*H$_3$)$_2$C, C(*C*H$_3$)N], 68.2 [*C*(CH_3)N], 74.0 (CH_2O), 83.4 (CHO), 93.7 [(CH$_3$)$_2$*C*], 153.6 (CO); ESI$^+$ (m/z) = 312. Anal. Calcd for $C_9H_{14}INO_3$: C, 34.74; H, 4.54; N, 4.50. Found: C, 34.56; H, 4.69; N, 4.58. Spectroscopic data of the minor compound **8**, extracted from the mixture of compounds **7** and **8**: ^{1}H NMR ($CDCl_3$): δ 1.48, 1.50, 1.60 (3s, 9H, 3CH_3), 3.07 ('t', 1H, $J = 10.2$ Hz, CH_2I), 3.31 (dd, 1H, $J = 4.8$ Hz, $J = 10.2$ Hz, CH_2I), 3.92 (s, 2H, CH_2O), 4.43 (dd, 1H, $J = 4.8$ Hz, $J = 10.2$ Hz, CHO).

4.7. (1*S*,7a*S*)-1,5,5,7a-Tetramethyl-2,6-dioxa-4-azapentalen-3-one 9

Triflic anhydride (215 μL, 1.25 mmol) was added to a solution of *anti*-**3** (0.27 g, 1.04 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (0.52 g, 2.50 mmol) in CH_2Cl_2 (20 mL) at 0 °C. The mixture was stirred for 5 min at 0 °C and the resultant white solid filtered off. The organic phases were washed with 5% aqueous $NaHCO_3$ (10 mL), dried over Na_2SO_4 and concentrated to give a yellow oil, which was purified by column chromatography (hexane/ethyl acetate, 7/3) to give **9** (0.17 g, 0.92 mmol) as a white solid; yield: 88%. Mp: 44 °C. $[\alpha]_D^{25} = -18.0$ (*c* 1.05, MeOH); ^{1}H NMR ($CDCl_3$): δ 1.30–1.35 (m, 6H, CHOCH_3, CH_3), 1.47 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 3.69 (d, 1H, $J = 8.7$ Hz, CH_2), 3.74 (d, 1H, $J = 8.7$ Hz, CH_2), 4.45 (q, 1H, $J = 6.6$ Hz, C*H*OCH$_3$); ^{13}C NMR ($CDCl_3$): δ 15.0, 20.0, 23.7, 27.9 [CHO*C*H$_3$ (*C*H$_3$)$_2$C, C(*C*H$_3$)N], 68.6 [*C*(CH_3)N], 73.8 (CH_2), 79.9 (*C*HOCH$_3$), 94.3 [(CH$_3$)$_2$*C*], 156.0 (CO); ESI$^+$ (m/z) = 186. Anal. Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.49; H, 8.20; N, 7.63.

4.8. (2*R*,3*S*)-α-Methylthreonine 2

In a similar way to that described for its diastereomer (2*R*,3*R*)-**2**, compound (2*R*,3*S*)-**2** (42 mg, 52%) was obtained from compound **9** (112 mg, 0.61 mmol). $[\alpha]_D^{25} = +13.4$ (*c* 0.75, H_2O); ^1H NMR (D_2O): δ 1.25 (d, 3H, $J = 6.3$ Hz, $CHOCH_3$), 1.40 [s, 3H, $C(CH_3)N$], 4.19 (q, 1H, $J = 6.3$ Hz, $CHOCH_3$); ^{13}C NMR (D_2O): δ 16.2, 17.2 [$CHOCH_3$, $C(CH_3)N$], 65.3 [$C(CH_3)N$], 69.1 ($CHOCH_3$), 175.8 (CO); ESI^+ (m/z) = 134. Anal. Calcd for $C_5H_{11}NO_3$: C, 45.10; H, 8.33; N, 10.52. Found: C, 45.22; H, 8.20; N, 10.40.

4.9. (4*R*,1′*S*)-*N*-(*tert*-Butoxycarbonyl)-4-(1′-hydroxyethyl)-2,2,4-trimethyloxazolidine *ent-anti*-3

In a similar way to that described for its enantiomer *anti*-**3**, compound *ent-anti*-**3** (0.68 g, 87%) was obtained from aldehyde (*R*)-**1a** (0.73 g, 3.0 mmol). $[\alpha]_D^{25} = +11.7$ (*c* 0.90, MeOH); Anal. Calcd for $C_{13}H_{25}NO_4$: C, 60.21; H, 9.72; N, 5.40. Found: C, 60.02; H, 9.55; N, 5.38.

4.10. (1*S*,7a*R*)-1,5,5,7a-Tetramethyl-2,6-dioxa-4-aza-pentalen-3-one *ent*-4

In a similar way to that described for its enantiomer **4**, compound *ent*-**4** (0.22 g, 88%) was obtained from *ent-anti*-**3** (0.35 g, 1.35 mmol). $[\alpha]_D^{25} = -25.8$ (*c* 1.02, MeOH); Anal. Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.42; H, 8.01; N, 7.69.

4.11. (2*S*,3*S*)-α-Methylthreonine 2

In a similar way to that described for its enantiomer (2*R*,3*R*)-**2**, compound (2*S*,3*S*)-**2** (48 mg, 46%) was obtained from compound ent-**4** (144 mg, 0.78 mmol). $[\alpha]_D^{25} = +11.4$ (*c* 0.80, H_2O); Anal. Calcd for $C_5H_{11}NO_3$: C, 45.10; H, 8.33; N, 10.52. Found: C, 45.30; H, 8.44; N, 10.39.

4.12. (1*R*,7a*R*)-1,5,5,7a-Tetramethyl-2,6-dioxa-4-aza-pentalen-3-one *ent*-9

In a similar way to that described for its enantiomer **9**, compound *ent*-**9** (0.17 g, 88%) was obtained from *ent-anti*-**3** (0.27 g, 1.04 mmol). $[\alpha]_D^{25} = +18.1$ (*c* 1.15, MeOH); Anal. Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.46; H, 8.19; N, 7.68.

4.13. (2*S*,3*R*)-α-Methylthreonine 2

In a similar way to that described for its enantiomer (2*R*,3*S*)-**2**, compound (2*S*,3*R*)-**2** (36 mg, 46%) was obtained from compound ent-**9** (109 mg, 0.59 mmol). $[\alpha]_D^{25} = -13.6$ (*c* 0.70, H_2O); Anal. Calcd for $C_5H_{11}NO_3$: C, 45.10; H, 8.33; N, 10.52. Found: C, 45.22; H, 8.20; N, 10.40.

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