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Asymmetric Synthesis of *N*-Protected *syn* and *anti* (*E*)-3-amino-2-hydroxy-4-hexenoate: A Practical Method for The C-α Epimerization of *anti* β-Amino-α-hydroxy acids

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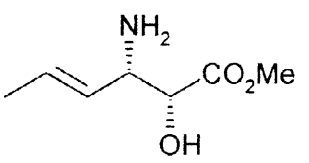
Abstract: A practical method to convert *anti* β-amino-α-hydroxy acids into the corresponding *syn* esters *via* the DCC/DMAP·HCl mediated esterification was devised, and methyl (2*R*,3*S*)-(*E*)-3-*t*-butoxycarbonylamino-2-hydroxy-4-hexenoate **15** was synthesised from the corresponding (2*S*,3*S*)-isomer **9** using the epimerization procedure developed. The α- and β-stereogenic centres of **9** were constructed by the Michael addition of a homochiral lithium amide to *t*-butyl sorbate and subsequent oxidation of the enolate intermediate in one pot.

Introduction

β-Amino-α-hydroxy acids are important components in a variety of biologically active compounds such as alkaloids, peptides and pseudopeptides.[1-4] For instance, the taxol C-13 side chain is one of the most significant β-amino-α-hydroxy acid derivatives of current interest.[5-11] Allophenylnorstatine is another example which has been identified as the most effective hydroxymethylcarbonyl isostere in the kynostatin class of HIV-1 protease inhibitors designed by Kiso and co-workers.[4,12,13] The configuration of the two stereogenic centres often has a profound effect, and change of the stereochemistry frequently leads to a significant loss in activity.[4,12,13] In this respect, considerable efforts have been devoted to the diastereo- and enantioselective synthesis of these substances.[5-11,14,15]

During the course of a development program to synthesise a range of β-amino-α-hydroxy acids, we needed to prepare methyl (2*R*,3*S*)-3-amino-2-hydroxy-4-hexenoate **1** in an appropriately protected form. Previously, we had developed a methodology for the asymmetric synthesis of β-amino acid derivatives using the highly diastereoselective Michael addition of lithium amides to α,β-unsaturated esters and amides.[16,17] This methodology was further extended to the synthesis of β-amino-α-hydroxy acids and related compounds *via* hydroxylation of the β-amino enolates using homochiral (camphorsulfonyl)oxaziridine.[18-20]

Recently, we have reported the synthesis of **2** in the *N*-Boc protected form using these procedures.[21] For the synthesis of the corresponding *syn* isomer **1**, however, development of a method for efficient C-α epimerization was necessary since the aminohydroxylation sequence is highly *anti* selective. Herein, we wish to report a convenient method to convert *anti* β-amino-α-hydroxy acids into the corresponding *syn* ester and its application to the synthesis of a protected derivative of the β-amino-α-hydroxy ester **1**.



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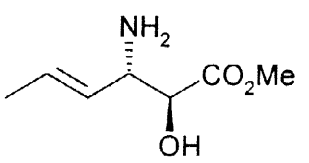

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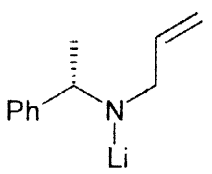

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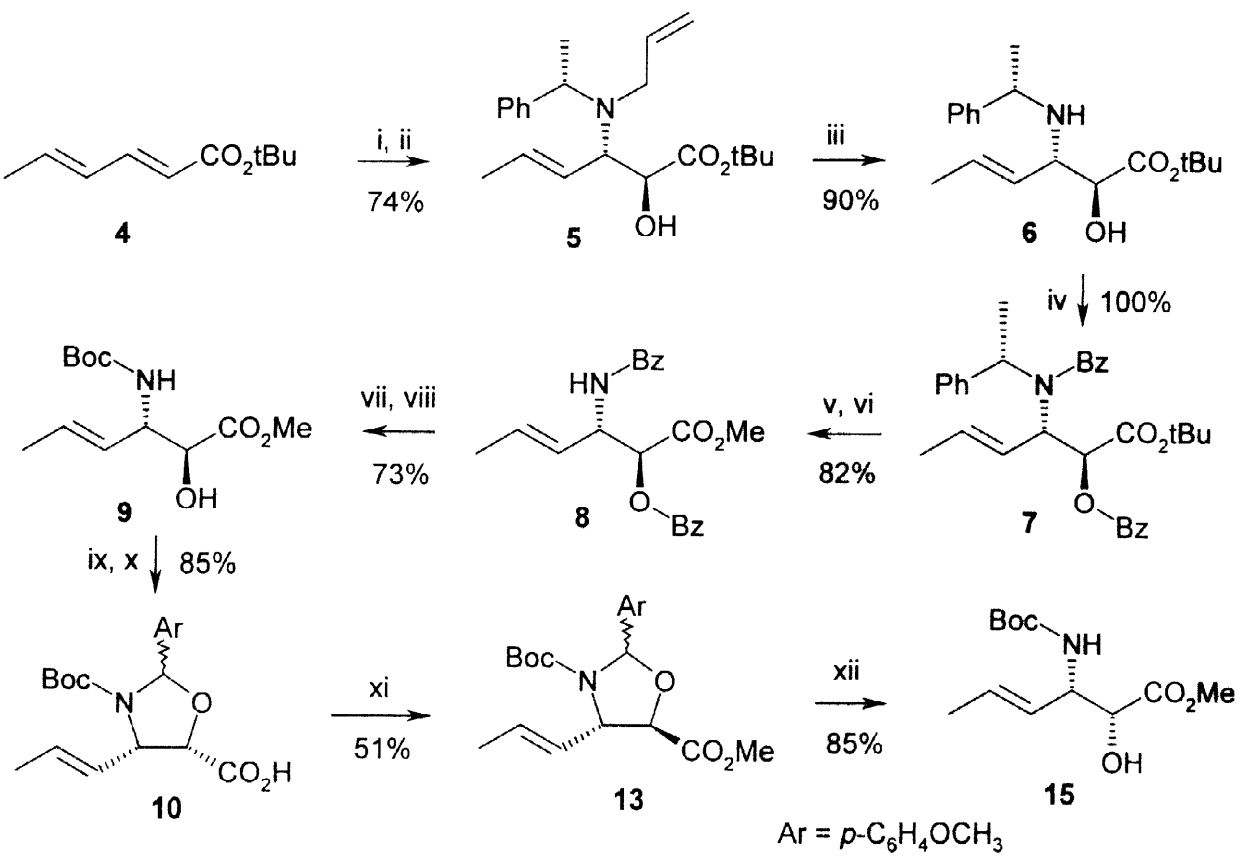
Results and Discussion

The *anti* β-amino-α-hydroxy ester **5** was prepared by the sequential treatment of *t*-butyl sorbate with the lithium amide (*S*)-**3** and (+)-(camphorsulfonyl)oxaziridine in 63% yield with 96% de.[21] The allyl substituent attached to the β-amino nitrogen was removed by palladium catalysed deallylation reaction using *N,N'*-dimethylbarbituric acid as the allyl cation scavenger. The resulting β-amino-α-hydroxyester **6** was dibenzoylated to give **7**. Cleavage of the α-methylbenzyl group of **7** was effected by treatment with formic acid at 50°C and esterification of the resulting acid gave the methyl ester **8**. The *anti* ester **9** could be obtained by Boc protection of the β-amino group followed by alcoholysis of the two benzoyl groups.

Initially, it was anticipated that inversion of configuration at C-α could be effected by the intramolecular Mitsunobu inversion sequence *via* a dihydrooxazole intermediate starting from the *N*-benzoyl analogue of **9**.[20] However, the method could not be used as extensive decomposition occurred during hydrolysis of the dihydrooxazole under strongly acidic conditions. The standard intermolecular Mitsunobu reaction of **9** by treatment with diethyl azodicarboxylate, triphenylphosphine, and acetic acid led to recovery of the starting materials. Attempted replacement of the C-α mesylate of **9** by acetate anion was also unsuccessful. As a result, we focused our attention on the *p*-methoxybenzylidene protected compound **10**. It has been reported by Greene that DCC/DMAP mediated coupling of the "wrong" isomer of the protected taxol C-13 side chain, similar to **10**, with a derivative of 10-deacetyl baccatin III occurs with efficient C-α epimerization.[22] However, when the DCC/DMAP esterification of **10** with methanol was attempted under their conditions at 70°C in toluene, virtually no epimerization was observed (Table 1, entry 1). Substituting the alcohol by the bulkier *t*-butanol led to some, but incomplete epimerization (entry 2). Very little epimerization was observed at room temperature (entry 3). In these experiments, esterification was effected by addition of DCC to the mixture of the acid, DMAP and the alcohol (*Method A*).



Reagents: i) (*S*)-**3**, ii) (+)-camphorsulfonyloxaziridine, iii) $Pd(PPh_3)_4$, *N,N'*-dimethylbarbituric acid, iv) benzoyl chloride, triethylamine, DMAP, v) HCOOH, 50°C, vi) $SOCl_2$, MeOH, vii) $(Boc)_2O$, viii) NaOMe, MeOH, ix) *p*-methoxybenzaldehyde dimethylacetal, PTSA, x) LiOH, MeOH, water, xi) DCC, DMAP·HCl, MeOH, xii) HCl, MeOH

Greene reported that his *cis* ester was stable to epimerization under the reaction conditions.[22] We confirmed this by heating **11** in the presence of DMAP in toluene at 70°C. Formation of **13** could not be detected under these conditions. Therefore, it appears that the epimerization proceeds *via* the activated intermediate **16**. The rapid inversion of the stereochemistry to give **17** is explained by intramolecular deprotonation of the α-hydrogen by the highly basic imino nitrogen of the intermediate.[23] This implied that if **16** is left in the absence of the alcohol until the *cis-trans* equilibrium is reached, a much higher extent of the epimerization to the more stable *trans* isomer **17** could be achieved. Indeed, treatment of **10** with DCC and DMAP in dichloromethane at room temperature for 30 min, followed by addition of alcohols methanol or *t*-butanol (*Method B*) resulted in almost complete conversion into the *trans* isomers **13** and **14** (entries 4 and 5). However, the yields of the isomerized esters were disappointing due to extensive formation of the *N*-acylurea **18**. During their investigation of the DCC/DMAP mediated macrolactonization, Keck and Boden found that DMAP·HCl was highly effective in preventing the formation of the *N*-acylurea side product.[24] Indeed, use of DMAP·HCl as the additive (*Method C*) significantly decreased the rate of the *N*-acylurea formation. Although the rate of epimerization was also decreased slightly, **10** could be converted into the *trans* esters **13** and **14** in good yield with the high *trans/cis* ratio (entry 6-8). The isomers **11** and **13** were readily separated by silica gel chromatography. Finally, removal of the benzylidene protection of **13** furnished the *syn* β-amino-α-hydroxy ester **15** in 85% yield.

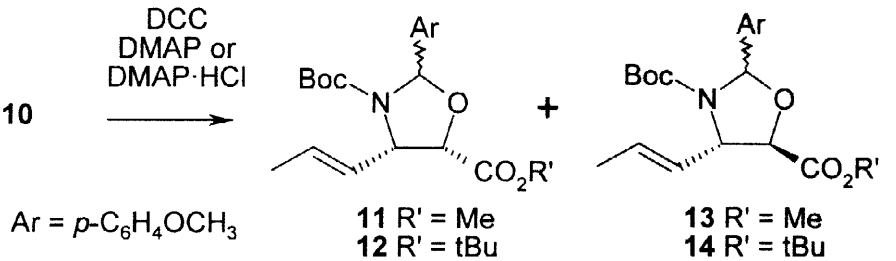


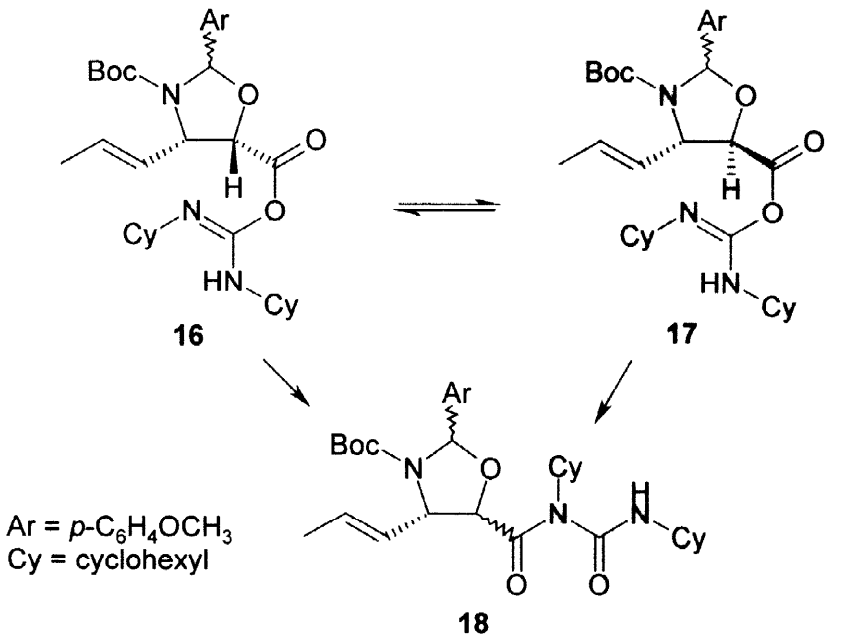
Table 1 C-α epimerization of **10** by DCC/DMAP·HCl esterification

entry	alcohol	solvent	temp (°C)	method[c] (epimerization time)	*trans*: *cis*[b]	yield[a] (%)
1	MeOH	toluene	70	A	1:>50	51
2	*t*-BuOH	toluene	70	A	1.8:1	90
3	*t*-BuOH	DCM	rt	A	1:19	74
4	MeOH	DCM	rt	B (30 min)	37:1	6
5	*t*-BuOH	DCM	rt	B (30 min)	>50:1	4
6	*t*-BuOH	DCM	rt	C (10 min)	7.3:1	95
7	MeOH	DCM	rt	C (30 min)	32:1	51
8	*t*-BuOH	DCM	rt	C (60 min)	>50:1	40

a Yield of the mixture of *cis* and *trans* isomers after chromatography.
b Determined by ^{1}H nmr spectroscopic analysis of the crude reaction mixture
c See experimental section for detail

In summary, the *syn* (2*R*,3*S*)-(*E*)-3-*t*-butoxycarbonylamino-2-hydroxy-4-hexenoate **15** was synthesised *via* the asymmetric aminohydroxylation of *t*-butyl sorbate using the lithium amide (*S*)-**3** and (+)-(camphorsulfonyl)oxaziridine. During the synthesis, a practical method for the C-α epimerization of the *p*-methoxybenzylidene protected β-amino-α-hydroxy acid **10** by the DCC/DMAP·HCl esterification procedure was devised. As a variety of *anti* β-amino-α-hydroxy acid derivatives in homochiral form can be readily

accessed using the aminohydroxylation of α,β-unsaturated carbonyl compounds, this epimerization method provides a convenient tool for the synthesis of the corresponding *syn* isomers.



Experimental

General

All reactions involving organometallic or other moisture sensitive reagents were performed under an atmosphere of dry nitrogen. All reagents were used as supplied. Column chromatography was performed on Kieselgel 60 silica gel (Merck). Nmr spectra were recorded either using a Bruker AM 360 (^{1}H; 360.13 MHz and ^{13}C 90.59 MHz), WH 300 (^{1}H; 300.13 MHz), AM 200 (^{1}H; 200 MHz and ^{13}C; 50.3 MHz) spectrometers. All spectra were recorded using $CDCl_3$ as solvent and internally referenced to residual $CHCl_3$ (δ_H 7.27 and δ_C 77.0). ^{13}C Nmr were obtained with DEPT editing. All chemical shifts are given in parts per million relative to tetramethylsilane (δ_H 0.00) and coupling constants (*J*) are given in Hertz. Mass spectra were obtained using either chemical ionisation (CI) on VG MASSLAB VG 20-250 or electrospray (ES+) using MicroMass Platform instruments. High resolution mass spectra were recorded using chemical ionisation (CI) on a VG-AutoSpec instrument. Infra-red spectra were obtained using Perkin-Elmer 1750 or 983 spectrophotometer. Elemental analysis was carried out by the Dyson Perrins analytical department using a Carla Erba 1106 analyser. Melting points were recorded using a Gallenkamp hot stage apparatus and are uncorrected. Optical rotations were recorded using a Perkin-Elmer 241 or 141 porlarimeters which has a thermally jacketed 10 cm cell and are given in units of 10^{-1}deg cm^{2}g^{-1}.

tert-Butyl (2*S*,3*S*,4*E*)-3-allyl[(1*R*)-1-phenylethyl]amino-2-hydroxy-4-hexenoate, (5)

To a solution of (*S*)-(α-methylbenzyl)allylamine (147 g, 0.64 mol) in THF (800 mL) was added n-butyllithium (0.59 mol, 1.6 M solution in hexanes) at -78°C. After stirring for 1 h, a solution of *t*-butyl sorbate (90 g, 0.54 mol) in THF (370 mL) was added dropwise *via* canula and the mixture stirred for 1 h at -78°C. Solid (+)-(camphorsulfonyl)oxaziridine (142 g, 0.62 mol) was added and the reaction was stirred at -78°C for 6 h, then allowed to warm to ambient temperature and quenched by addition of saturated ammonium chloride solution. The mixture was cooled to 0°C and the solid precipitated was filtered off. Concentration and addition of a small amount of *t*-butyl methyl ether caused precipitation of more solid. After removal of the solid by

filtration, the filtrate was washed successively with sat. aq. citric acid, sat. aq. $NaHCO_3$ and dried over $MgSO_4$. Removal of the solvent gave the crude product as a pale brown solid. The diastereoslelectivity was shown to be 49:1 (96% de) by ^1H nmr analysis. This residue was purified by chromatography on silica gel [EtOAc/40-60 petrol (1:19)] to give the title compound **5** (96% de) as a colourless oil (116 g, 63%); $[\alpha]_D^{22}$ +50.4 (c 1.99, $CHCl_3$); (Found: C, 73.32; H, 9.24; N 4.11. $C_{21}H_{31}NO_3$ requires C, 73.01; H, 9.04; N, 4.05); ν_{max}(film)/cm^{-1} 3505bm (OH), 2977s, 1724s (C=O), 1641m (C=C); δ_H (300MHz) 7.48-7.19 (5H, m), 5.83 (1H, dddd, *J* 17.2, 10.0, 7.5, 5.0), 5.70-5.53 (2H, m), 5.12 (1H, dq, *J* 17.2, 1.4), 5.04 (1H, dq, *J* 10.0, 1.1), 4.26 (1H, q, *J* 6.8), 4.11 (1H, d, *J* 3.3), 3.57 (1H, dd, *J* 8.2, 3.3), 3.37 (1H, ddt, *J* 15.1, 5.0, 1.8), 3.20 (1H, dd, *J* 15.1, 7.5), 3.09 (1H, br s), 1.71(3H, d, *J* 4.9), 1.42 (9H, s), 1.35 (3H, d, *J* 6.8); δ_C (50MHz) 172.7, 144.6, 138.9, 129.9, 128.2, 128.0, 126.8, 116.1, 81.8, 73.5, 63.7, 56.8, 50.3, 27.9, 17.9, 14.6; *m/z* (CI, NH_3) 346 (MH^+, 100%).

tert-Butyl (2*S*,3*S*,4*E*)-2-hydroxy-3-[(1*R*)-1-phenylethyl]amino-4-hexenoate, (6)

A solution of tetrakis(triphenylphosphine)palladium(0) (2.0 g, 1.7 mmol), *N,N'*-dimethylbarbituric acid (80 g, 513 mmol) and **5** (59 g, 171 mmol) in deoxygenated dichloromethane (1 L) was stirred under nitrogen at ambient temperature overnight. Dichloromethane was removed under reduced pressure and the residue was dissolved in *t*-butyl methyl ether (500 mL). The organic solution was washed with $NaHCO_3$ aq. and removal of the solvent gave the crude product as a pale brown solid (75.5 g). This material was combined with the second batch of **6** (75.0 g) obtained from **5** (57 g) using the same procedures. The combined solid (150.5 g) was suspended in 1N HCl (1.5 L), washed with *t*-butyl methyl ether (3 x 200 mL), basified to pH 10-11 with NaOH aq., extracted with dichloromethane (4 x 200 mL) and dried over $MgSO_4$. Filtration and removal of the solvent gave the desired product **6** as a viscous yellow oil (95 g, 93%); $[\alpha]_D^{22}$ -32.7 (c 1.75, $CHCl_3$); (Found: C, 70.46; H, 8.93; N, 4.53. $C_{18}H_{27}NO_3$ requires C, 70.79; H, 8.91; N, 4.59); ν_{max}(film)/cm^{-1} 3500bm (OH), 2975s, 1728s (C=O); δ_H (300MHz) 7.38-7.22 (5H, m), 5.56 (1H, dq, *J* 15.3, 6.5), 5.28 (1H, ddq, *J* 15.3, 8.6, 1.7), 4.25 (1H, d, *J* 3.3), 3.87 (1H, q, *J* 6.5), 3.33 (1H, dd, *J* 8.6, 3.3), 3.22 (1H, br s), 1.77 (1H, br s), 1.66 (3H, dd, *J* 6.5, 1.4), 1.42 (9H, s), 1.33 (3H, d, *J* 6.5); δ_C (50MHz) 172.8, 145.9, 129.5, 128.6, 126.9, 127.8, 127.1, 82.3, 71.8, 60.1, 54.2, 27.9, 23.3, 17.7; *m/z* (CI, NH_3) 306 (MH^+, 100%).

tert-Butyl (2*S*,3*S*,4*E*)-2-(benzoyloxy)-3-benzoyl[(1*R*)-1-phenylethyl]amino-4-hexenoate, (7)

To a solution of **6** (78 g, 256 mmol) and triethylamine (140 g, 1.39 mol) in THF (1.5 L) was added benzoyl chloride (179 g, 1.27 mol) dropwise at 0°C. The reaction mixture was stirred at ambient temperature for 1 h, then heated at refulx overnight. After cooling, the solid precipitated was filtered off and the filtrate washed successively with dilute HCl aq. and saturated $NaHCO_3$ aq. The organic solution was dried over $MgSO_4$ and removal of the solvent gave the title compound **7** as a very viscous oil (201 g); δ_H (360MHz) 8.15-7.06 (15H, m), 6.07 (1H, m), 5.73 (1H, dq, *J* 15.1, 6.6), 5.38 (1H, d, *J* 2.4), 5.03 (1H, q, *J* 6.6), 4.86 (1H, br s), 1.78 (3H, d, *J* 6.6), 1.72 (3H, d, *J* 6.6), 1.27 (9H, s). This material was used for the next step without further purification.

Methyl (2*S*,3*S*,4*E*)-3-(benzoylamino)-2-(benzoyloxy)-4-hexenoate, (8)

A solution of the crude **7** (200 g), obtained from the previous step, in 98% formic acid (500 mL) was heated at 60°C for 3 h. Formic acid was removed under reduced pressure and the residue dissolved in methanol (1.5 L). To the methanolic solution was added triethylamine (65 g, 0.64 mol) then thionyl chloride (60.9 g, 0.51 mol) dropwise with cooling (ice-water bath). After heating at reflux for 2.5 h, the solvent and excess thionyl chloride were removed under reduced pressure to give a viscous oil, which was purified by chromatography on silica gel [hexane/EtOAc (1:1)] to give the methyl ester **8** (78.0 g, 86% from **6** over three steps); δ_H (360MHz) 8.14-7.40 (10H, m), 6.54 (1H, br d, *J* 7.6), 5.92 (1H, dq, *J* 14.2, 6.5), 5.63 (1H, ddq, *J* 14.2, 6.5, 1.4), 5.52 (1H, d, *J* 3.8), 5.37 (1H, m), 3.82 (3H, s), 1.78 (3H, dd, *J* 6.6, 1.4). This material was used for the next step without further purification.

tert-Butyl (2*S*,3*S*,4*E*)-3-[(_tert_-butoxycarbonyl)amino]-2-hydroxy-4-hexenoate, (9)

To a solution of **8** (77 g, 182 mmol) in dichloromethane (100 mL) was added di-*t*-butyl dicarbonate (119 g, 545 mmol) and triethylamine (36.8 g, 364 mmol) and the mixture was cooled to 0°C. 4-Dimethylaminopyridine

(33.4 g, 276 mmol) was added in small portions during a period of 20 min. The cooling bath was removed and stirring was continued at ambient temperature for 2 days. The reaction mixture was filtered through silica gel and the filtrate was concentrated under vacuum to give a brown oil. To the residue was added di-*t*-butyl dicarbonate (79 g, 362 mmol), triethylamine (27.6 g, 273 mmol) and 4-dimethylaminopyridine (1.0 g, 8.2 mmol), and the mixture was stirred at ambient temperature for 5 h. The reaction mixture was again placed under vacuum and most of the volatiles were removed. To the residue was added a small amount of dichloromethane, di-*t*-butyl dicarbonate (10 g, 46 mmol) and triethylamine (9.5 g, 94 mmol) and the mixture was stirred at ambient temperature overnight. The reaction mixture was filtered through silica gel and the filtrate concentrated under vacuum to give a brown oil. The residue was dissolved in methanol (1 L), cooled to 0°C and sodium methoxide (21.6 g, 400 mmol) was added with stirring. After stirring for 45 min at 0°C solid ammonium chloride (30 g) was added and the volume of the mixture was reduced to about 800 mL under vacuum. Brine (1 L) was added and the mixture was extracted with *t*-butyl methyl ether (3 x 300 mL) and dried over $MgSO_4$. Filtration and removal of the solvent under reduced pressure gave a brown oil which was purified by chromatography on silica gel [hexane/EtOAc (1:1)] to give the title compound **9** as a pale yellow solid (43.6g 77%); m.p. 74-76.5°C. The spectroscopic data for this material were in excellent agreement with those reported previously.[21]

3-(*tert*-Butyl) 5-methyl (4*S*,5*S*)-2-(4-methoxyphenyl)-4-[(*E*)-1-propenyl]-1,3-oxazolane-3,5-dicarboxylate, (11)

To a solution of **9** (21.0 g, 81.1 mmol) and anisaldehyde dimethylacetal (15.5 g, 85.2 mmol) in toluene (200 mL) was added pyridinium *p*-toluenesulfonate (2.0 g, 8.0 mmol) and the mixture heated at 80°C for 4 h, during which period methanol formed was constantly removed by means of distillation under reduced pressure. The reaction was quenched by addition of a small amount of solid potassium carbonate and the mixture was filtered through a plug of silica gel. The filtrate was concentrated and the residue purified by chromatography on silica gel [cyclohexane:EtOAc (9:1 to 4:1)] to give the methyl ester **11** (29.1 g, 95%) as an inseparable mixture (6:1) of the C-2 epimers; HRMS (CI) calcd. for $C_{20}H_{28}NO_6$ (MH^+) 378.1917, found 378.1923; ν_{max}(film)/cm^{-1} 2975m, 1766s, 1741s, 1702s, 1612m, 1514s, 1392s, 1367s, 1348s, 1296s, 1250s, 1214s, 1173s, 833m. For the major C-2 epimer; δ_H (360MHz) 7.44 (2H, d, *J* 9.5), 6.91 (2H, d, *J* 9.5), 5.92 (1H, br s), 5.80 (1H, dq, *J* 13.2, 6.4), 5.53 (1H, dd, *J* 13.2, 7.6), 4.83-4.66 (2H, m), 3.82 (3H, s), 3.76 (3H, s), 1.72 (3H, dd, *J* 6.4, 1.2), 1.33 (9H, s).

(4*S*,5*S*)-3-(*tert*-Butoxycarbonyl)-2-(4-methoxyphenyl)-4-[(*E*)-1-propenyl]-1,3-oxazolane-5-carboxylic acid, (10)

To a solution of **11** (21.5 g, 56.9 mmol) in methanol-water (4:1, 200 mL) was added lithium hydroxide (9.55 g, 228 mmol) and the mixture was stirred at ambient temperature for 30 min. The solution was diluted with water and the pH of the solution was adjusted to 3 to 4 by addition of 5% HCl aq. The aqueous solution was extracted with ethyl acetate and dried over $MgSO_4$. Filtration and removal of the solvent under reduced pressure gave the title compound **10** as a white hygroscopic foam (19.6 g, 95%). This inseparable mixture (6:1) of the C-2 epimers was used for the epimerization experiments without further purification. For the major C-2 epimer; δ_H (360MHz), 7.43 (2H, d, *J* 8.7), 6.90 (2H, d, *J* 8.7), 5.94 (1H, br s), 5.92-5.80 (1H, m), 5.63-5.42 (1H, m), 4.85-4.71 (2H, m), 3.82 (3H, s), 1.73 (3H, d, *J* 6.4), 1.33 (9H, s).

General procedure for the epimerization

Method A: The acid **10** (1 eq), alcohol (3 eq), and DMAP (0.3 to 0.8 eq) were dissolved in dry solvent (10 mL / 1 mmol of **10**), and DCC (1.1 eq) was added. After stirring overnight at the specified temperature, the reaction mixture was filtered to remove the solid precipitated during the reaction period. The filtrate was concentrated under reduced pressure and the *cis* and *trans* isomers (**11**, **12**, **13** and **14**) were separated by flash silica gel chromatography [hexane/EtOAc (10:1 to 5:1)].

Method B: The acid **10** (1 eq), DCC (1.1 eq), DMAP (0.8 eq) were dissolved in dry solvent (10 mL / 1 mmol of **10**), and the mixture was stirred at room temperature for a specified period. The alcohol (3 eq) was added and after overnight stirring, the reaction was worked up as in Method A.

Method C: The epimerization-esterification was performed as in Method B, except that a mixture of DMAP (1 eq), and DMAP·2HCl (0.6 eq) was used instead of DMAP (0.8 eq).

Di(*tert*-butyl) (4*S*,5*S*)-2-(4-methoxyphenyl)-4-[(*E*)-1-propenyl]-1,3-oxazolane-3,5-dicarboxylate, (12)

Obtained as an inseparable mixture (5:1) of the C-2 epimers; HRMS (CI) calcd. for $C_{23}H_{34}NO_6$ (MH^+) 420.2386, found 420.2390; ν_{max}(film)/cm^{-1} 2976m, 2934m, 1754s, 1701s, 1612m, 1513s, 1390s, 1368s, 1303s, 1251s, 1167s, 1101s, 1067s, 1035s, 831m. For the major C-2 epimer; δ_H (360MHz) 7.46 (2H, d, *J* 9.5), 6.88 (2H, d, *J* 9.5), 5.87 (1H, br s), 5.56 (1H, dd, *J* 15.2, 9.5), 5.28 (1H, brs), 4.75-4.73 (2H, m), 3.82 (3H, s), 1.72, (3H, dd, *J* 6.5, 1.2), 1.47 (9H, s), 1.32 (9H, s).

3-(*tert*-Butyl) 5-methyl (4*S*,5*R*)-2-(4-methoxyphenyl)-4-[(*E*)-1-propenyl]-1,3-oxazolane-3,5-dicarboxylate, (13)

Obtained as an inseparable mixture (6:1) of the C-2 epimers; HRMS (CI) calcd. for $C_{20}H_{28}NO_6$ (MH^+) 378.1917, found 378.1911; ν_{max}(film)/cm^{-1} 2975m, 2934m, 1753s, 1701s, 1612m, 1513s, 1392s, 1366s, 1249s, 1173s, 1134s, 1098s, 830m. For the major C-2 epimer; δ_H (360MHz) 7.39 (2H, d, *J* 8.7), 6.90 (2H, d, *J* 8.7), 6.30 (1H, br s), 5.82 (1H, dq, *J* 15.1, 1.4), 5.55 (1H, dd, *J* 15.1, 6.8), 4.65 (1H, br s), 4.48 (1H, d, *J* 3.4), 3.82 (3H, s), 3.81 (3H, s), 1.74 (3H, dd, *J* 6.5, 1.4), 1.36 (9H, s).

Di(*tert*-butyl) (4*S*,5*R*)-2-(4-methoxyphenyl)-4-[(*E*)-1-propenyl]-1,3-oxazolane-3,5-dicarboxylate, (14)

Obtained as an inseparable mixture (5:1) of the C-2 epimers; HRMS (CI) calcd. for $C_{23}H_{34}NO_6$ (MH^+) 420.2386, found 420.2392; ν_{max}(film)/cm^{-1} 2977m, 2933m, 1745s, 1703s, 1612m, 1513s, 1392s, 1368s, 1249s, 1169s, 830m. For the major C-2 epimer; δ_H (360MHz), 7.39 (2H, d, *J* 8.7), 6.89 (2H, d, *J* 8.7), 6.32 (1H, br s), 5.77 (1H, dq, *J* 14.6, 6.6), 5.52 (1H, ddq, *J* 15.1, 7.5, 1.4), 4.58 (1H, br s), 4.33 (1H, d, *J* 3.7), 3.82 (3H, s), 1.73 (3H, dd, *J* 6.4, 1.2), 1.50 (9H, s), 1.38 (9H, s).

Methyl (2*R*,3*S*,4*E*)-3-[(*tert*-butoxycarbonyl)amino]-2-hydroxy-4-hexenoate, (15)

Acetyl chloride (140 μL) was added to dry methanol (20 mL) and the mixture was stirred at ambient temperature for 1 h prior to the addition of **13** (310 mg, 0.82 mmol). After stirring for further 1 h, the reaction was quenched by addition of solid sodium bicarbonate (1.5 g) and the crude product purified by chromatography on silica gel [hexane:EtOAc (5:1)] to give the title compound **15** as a viscous oil (182 mg, 85%); $[\alpha]_D^{25}$ -51.3 (*c* 1.05, $CHCl_3$); (Found: C, 55.96; H, 8.16; N 5.30. $C_{12}H_{21}NO_5$ requires C, 55.58; H, 8.16; N, 5.40); ν_{max} (ATR)/cm^{-1} 3360s (OH), 1741s, 1716s, 1698s, 1512s; δ_H (360MHz), 5.73 (1H, dq, *J* 15.3, 6.6), 5.51 (1H, dd, *J* 15.3, 5.1), 4.88 (1H, br s, D_2O exchange), 4.55 (1H, br s), 4.23 (1H, dd, *J* 4.8, 2.2), 3.81 (3H, s), 3.14 (1H, br s, D_2O exchange), 1.72 (3H, dq, *J* 6.5, 1.1), 1.42 (9H, s); *m/z* (ES+) 260 [$(M+H)^+$, 100%], 204 (36%).

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