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Tetrahedron 61 (2005) 4971–4981

Stereoselective synthesis of new modified conformationally constrained L-tyrosine analogue with potential applications to SH2 domain ligands

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Received 23 December 2004; revised 7 March 2005; accepted 10 March 2005

Available online 7 April 2005

Abstract—This paper reports the stereoselective synthesis of a modified tricyclic tyrosine analogue **3**, whose conformation is constrained by the covalent bonds and designed on the basis of X-ray and solution structures of SH2 domain and its natural peptide ligand. A Michael addition followed by an alkylation in high stereoselections, a Friedel–Crafts and a Mannich reaction-based cyclization served as the key steps in the synthesis.
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1. Introduction

In recent years, developments of new ligands of the SH2 (Src homology 2) domains have drawn more and more attention in drug design[1] because of its tight relationships with a variety of human cancers. As a general principle, constrained conformation has often benefited the ligand's binding with the protein, such as alanine analogues[2] and tyrosine analogues.[1,3] The previous X-ray and solution structure of liganded SH2 domain have provided a clear skeleton of the relevant ligands,[4] which plays the key role in the design of conformationally constrained tyrosine analogues. Based on these knowledge and principles, ligands or ligand platforms **1**, **2**, **3** and **4** were designed (Fig. 1). Burke and colleagues firstly reported the design and synthetic routes of racemic amino acid **1**[5] and **2**.[6] In our recent works, we reported the enantioselective syntheses of both D-**2**[7] and L-**2**.[8] However, these studies[6] showed that more modifications on the structure **2** are required to enhance the binding affinity with SH2 domain. Therefore, addition of one more carboxyl group on **2** (amino acid **3**) provides one practical possibility for such a purpose through more hydrogen-bonding generation, because this provides a site to introduce proper amino acid side chains. In this paper, we report our recent achievement on the enantiososelective synthesis of amino acid **3**.

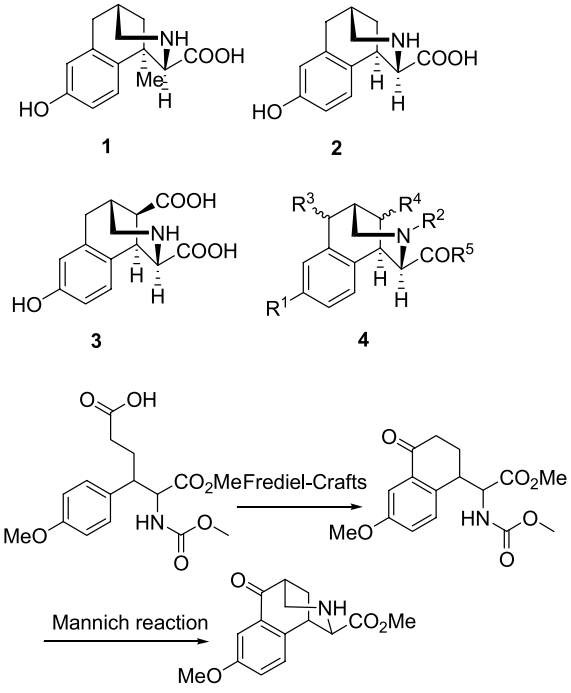

Figure 1. Structures of conformation-constrained tyrosine analogues **1**–**4**, and representation of construction of the tricylclo-skeleton.

2. Synthesis

A method for the construction of the tricyclo-skeleton of these ligands has been established during our previous

Keywords: Src homology 2; L-Tyrosine; Mannich reaction.
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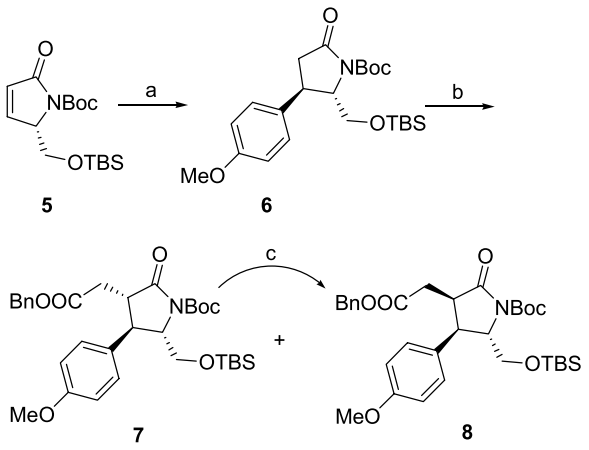
0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.03.042

synthesis of the analogue D-**2**[7] and L-**2**,[8] which featured a Friedel–Crafts reaction followed by a Mannich reaction (Fig. 1). Accordingly, for the synthesis of L-tyrosine analogue **3**, our first task was to prepare the precursor of the Friedel–Crafts reaction, compound **10**.

Our first synthetic strategy of the precursor acid **10** is based on a Michael addition followed by an alkylation. Unsaturated lactam **5** was prepared from L-Glu over six steps in 68% overall yield.[9] The aryl group was introduced smoothly in high yield using THF as the solvent and only one isomer was obtained.[10] However, if methyl sulfide was used as the co-solvent (1:1 with tetrahydrofuran) in this step, a tandem-Michael-addition product was detected as the major product[11] (Scheme 1).



Scheme 1. Reagents and conditions: (a) CuBr·Me_2S, 4-MeOPhMgBr, THF, −78 to 0 °C, 90%; (b) LiHMDS, $BrCH_2COOBn$, THF, −78 to 0 °C, 98% (c) (1) LDA, THF, −78 °C, 30 min; (2) AcOH, −78 to 0 °C, 70%.

Alkylation of the lactam **6** with benzyl bromoacetate gave two isomers, **7** and **8** (ratio 1.5:1), in 98% total yield, and the 3,4-*trans*-isomer could be converted to the *cis* one completely when being treated with LHMDS (sodium bis(trimethylsilyl) amide) followed by acetic acid. Oxidation and deprotection of compound **8** afforded the precursor **10**[12] for the Friedel–Crafts reaction. Ketone **11** was obtained smoothly according to our reported method,[7,8] and the *tert*-butoxoyl carbonyl group was cleaved at the same time. The stereochemistry of **11** was confirmed by the X-ray analysis (Fig. 2).[13] Now it came to the expected Mannich reaction. No Mannich product was deducted, when ketone **11** was treated directly with formaldehyde. Reprotection and ring opening of **11** gave diester **13**, which

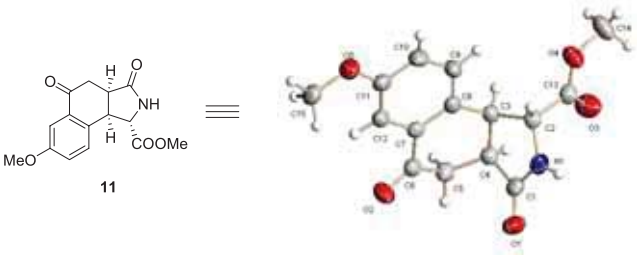
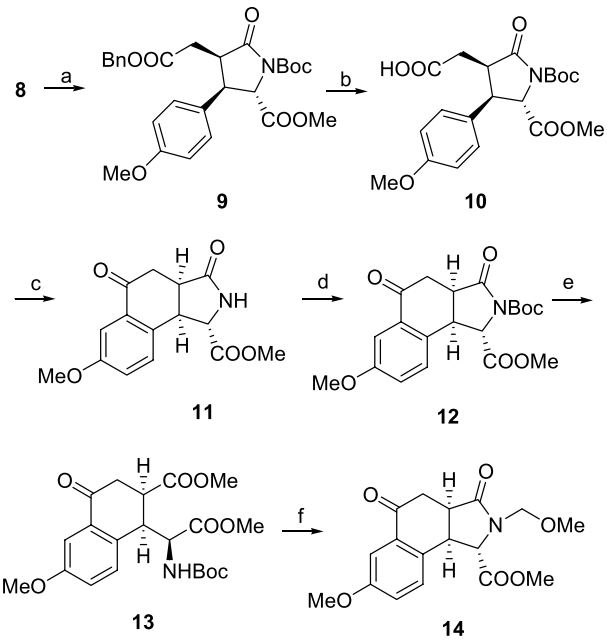


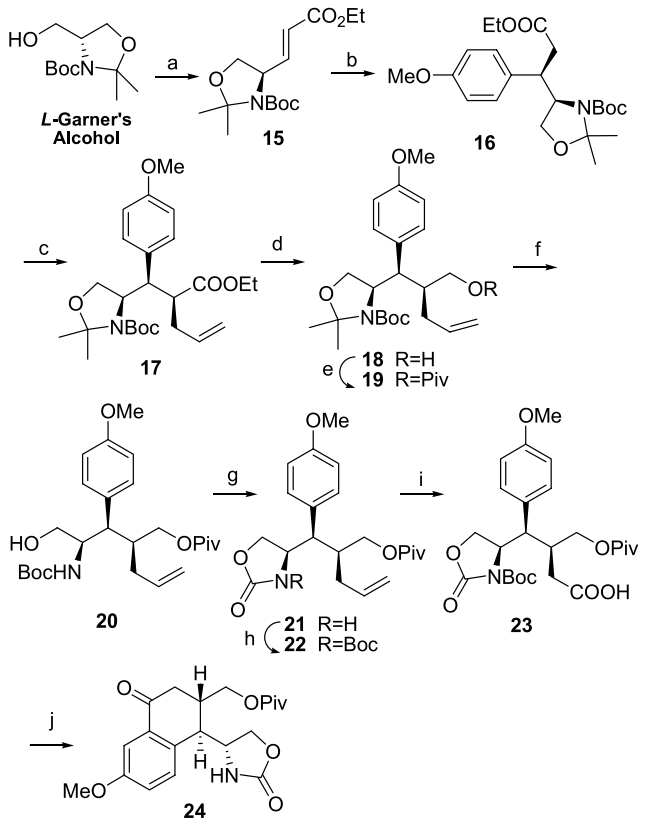
Figure 2. ORTEP drawing of ketone **11** based on the X-ray analysis.[13]

was then treated with trifluoroacetic acid followed by formaldehyde in hope of getting the Mannich product. Unfortunately, **14** was provided as the only product. It was believed that formation of the kinetically and thermodynamically favored lactam retarded the expected Mannich reaction. Attempt to reduce the diester in **13** to corresponding diol was not successful due to the formation of a five-membered lactol (Scheme 2). So we had to prepare an alternative precursor for this Mannich reaction.



Scheme 2. Reagents and conditions: (a) (1) Jones reagent, acetone, 0 °C, 4 h; (2) CH_2N_2, Et_2O, rt, 10 min, 55% for two steps; (b) 1 atm H_2, Pd/C (10%) (cat), EtOAc, rt, 3 h, 68%; (c) (1) $(COCl)_2$, DMF (cat), CS_2/CH_2Cl_2, rt, 2 h; (2) $AlCl_3$, CH_2Cl_2, rt, overnight, 74%; (d) $(Boc)_2O$, DMAP (cat), CH_3CN, rt, 2 h, 81%; (e) K_2CO_3, MeOH, rt, 45 min, 100% (conv%: 60%); (f) (1) TFA, CH_2Cl_2, rt, 60 min; (2) HCHO, ROH, reflux, 12 h, 75%.

Synthesis of **23**, the alternative Mannich reaction substrate, commenced with acyclic unsaturated ester **15**, which was prepared form L-Garner's alcohol through Swern oxidation followed by a Wittig olefination (Scheme 3). It is noteworthy that the Wittig reagent used in this step should be free of sodium hydroxide, otherwise recemization would happen.[14] Michael addition of *p*-methoxylphenylmagnesium bromide to unsaturated ester **15** in the presence of CuI gave ester **16** as the only isomer, whose stereochemistry was confirmed by the X-ray of the corresponding alcohol **25** (Fig. 3).[13] Allylation of ester **16** also afforded one isomer **17** in nearly quantitative yield. Reduction of ester **17** with lithium aluminum hydride, protection of the resulting hydroxyl group as trimethyl acetate and cleavage of the ketal with *p*-toluenesulphonic acid gave alcohol **20**, which was converted to oxazolidone **21** after being treated with sodium hydride in DMF. Protection of the amide group with di-*tert*-butyl dicarbonate and oxidation of the terminal double bond followed by further oxidation with sodium chlorite afforded acid **23**. The subsequent Mannich reaction proceeded uneventfully and ketone **24** was afforded in 74% yield under the previously



Scheme 3. Reagents and conditions: (a) (1) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 2 h; (2) $Ph_3P{=}CHCOOEt$, PhH, rt, overnight, 81%; (b) *p*-methoxylphenylmagnesium bromide, CuI, THF, −78 to 0 °C, 100%; (c) (1) LDA, HMPA, THF, −78 °C, 30 min; (2) allyl bromide, −78 °C–rt, 100%; (d) LAH, THF, 0 °C, 60 min, 95%; (e) PivCl, Et_3N, DMAP (cat), CH_2Cl_2, 0 °C—rt, overnight, 100%; (f) PTSA, MeOH, rt, overnight, 84%; (g) NaH, DMF, 0 °C, 60 min, 76%; (h) $(Boc)_2O$, Et_3N, DMAP (cat), CH_2Cl_2, 0 °C—rt, overnight, 93%; (i) (1) O_3, CH_2Cl_2/MeOH, −78 °C, 1 h; (2) Me_2S, −78 to 0 °C; (3) $NaClO_2$, KH_2PO_3, 2-methyl-2-butane, ^{t}BuOH/H_2O, 84%; (j) (1) $(COCl)_2$, DMF (cat), CS_2/CH_2Cl_2, rt, 2 h; (2) $AlCl_3$, CH_2Cl_2, 0 °C—rt, overnight, 74%.

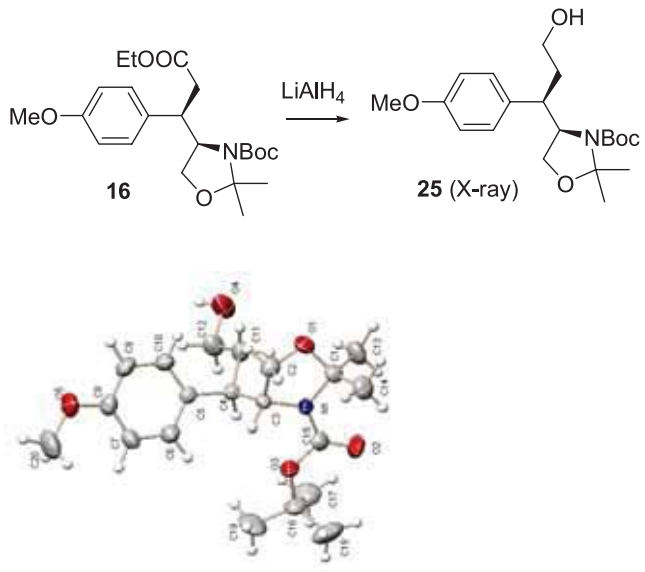
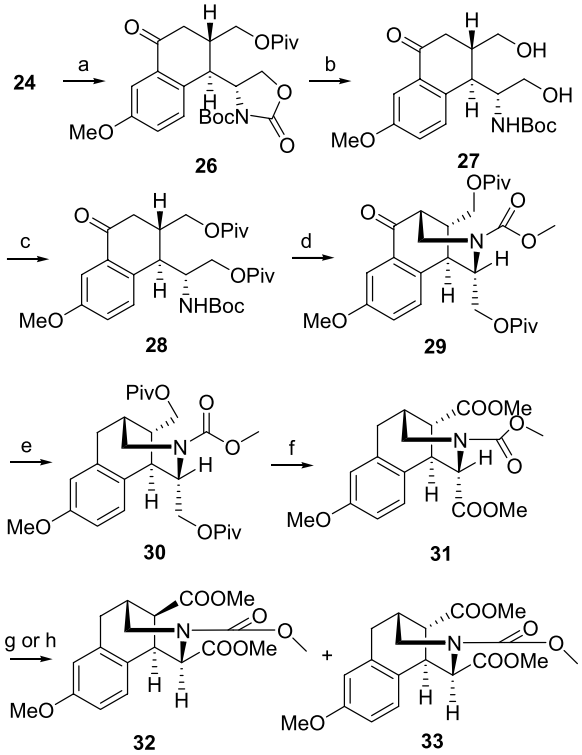


Figure 3. ORTEP drawing of alcohol **25** based on the X-ray analysis.[13]

reported conditions.[8] Again, the *N*-*tert*-butoxyl carbonyl group was cleaved in this step (Scheme 3).

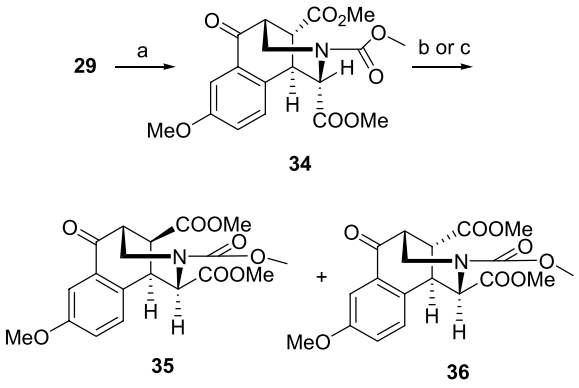
Protection of the amide group of ketone **24** with di-*tert*-butyl dicarbonate again and treatment with cesium carbonate in methanol afforded diol **27**, and the two hydroxyl groups were both protected with trimethylacetyl chloride. Cleavage of the *tert*-butoxyol carbonyl followed by refluxing with formaldehyde in ethanol, and reprotection of the newly formed amino group with methyl chloroformate gave tricyclo ketone **29** in nearly quantitative yield over three steps. Attempt to reduce the carbonyl of **29** to methylene by dithioacetal/Raney-nickel was failed because the prerequisite dithioacetal cannot be formed presumably due to the steric hindrance; yet reduction with sodium borohydride smoothly gave the corresponding alcohol, which could be reduced further to compound **30** by Barton–McCombie method. Reductive cleavage of the trimethyl acetyl groups followed by oxidation gave diester **31** in total 63% yield over four steps. To get the correct stereochemistry, diester **31** was treated with sodium methoxide in methanol firstly, and **32** was separated in quantitative yield; treatment with LDA followed by acetic acid gave both **32** and **33** in about 1:1 ratio (based on ^{1}H NMR spectrum), but they cannot be separated by the



Scheme 4. Reagents and conditions: (a) $(Boc)_2O$, Et_3N, DMAP (cat), CH_2Cl_2, 0 °C–rt, 2 h, 95%; (b) Cs_2CO_3, MeOH, rt, overnight, 86%; (c) PivCl, Et_3N, DMAP (cat), CH_2Cl_2, 0 °C—rt, overnight, 76%; (d) (1) TFA, CH_2Cl_2, rt, 2 h; (2) HCHO (36% aq), EtOH, refluxed, 2 h; (3) ClCOOMe, $NaHCO_3$, dioxane/H_2O, rt, 60 min, 100%; (e) (1) $NaBH_4$, MeOH, rt, 20 min; (2) (i) NaH (60%), THF, 0 °C, 30 min; (ii) CS_2, 0 °C—rt, 1.5 h; (iii) MeI, rt, 2 h, 86% for two steps; (3) *n*-Bu_3SnH, AIBN, toluene, refluxed, 3 h, 100%; (f) (1) DIBAL-H, CH_2Cl_2, −78 °C, 40 min; (2) DMP, CH_2Cl_2, rt, 60 min; (3) $NaClO_2$, KH_2PO_3, 2-methyl-2-butene, ^{t}BuOH/H_2O, rt; (4) CH_2N_2, Et_2O, rt, 20 min, 63% for four steps; (g) NaOMe, MeOH, 0 °C, 20 min, 100%; (h) (1) LDA, HMPA, −78 °C, 30 min; (2) AcOH, −78 °C, 10 min.

column chromatography (Scheme 4). The stereochemistry of **32** was elucidated by chemical relation (see below).

Reductive cleavage of the trimethyl acetyl group of ketone **29** with DIBAL-H (the ketone carbonyl group was reduced to the corresponding hydroxyl group) followed by oxidation and etherification gave diester **34** (the hydroxyl group was oxidized back to the carbonyl group), in 50% total yield over four steps. Similar as diester **31**, if **34** was treated with sodium methoxide in methanol, only **36** was generated; and treatment with LDA followed by acetic acid gave both **35** and **36** in about 1:1 ratio, fortunately both of them could be easily separated by column chromatography (Scheme 5). The stereochemistry of compound **34**, **35** and **36** were all confirmed by the NOESY studies (Fig. 4).



Scheme 5. Reagents and conditions: (a) (1) DIBAL-H, CH_2Cl_2, −78 °C, 40 min; (2) DMP, CH_2Cl_2, rt, 60 min; (3) $NaClO_2$, KH_2PO_3, 2-methyl-2-butene, $^tBuOH/H_2O$, rt; 4. CH_2N_2, Et_2O, rt, 20 min, 50% for four steps; (b) NaOMe, MeOH, 0 °C, 20 min, 80% (for **36**); (c) (1) LDA, HMPA, −78 °C, 30 min; (2) AcOH, −78 °C, 10 min, 36% (for **35**) and 36% (for **36**).

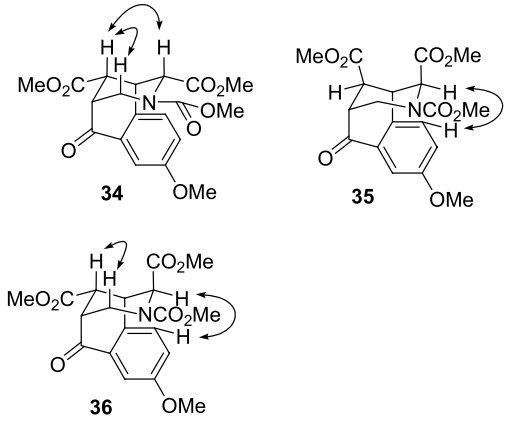
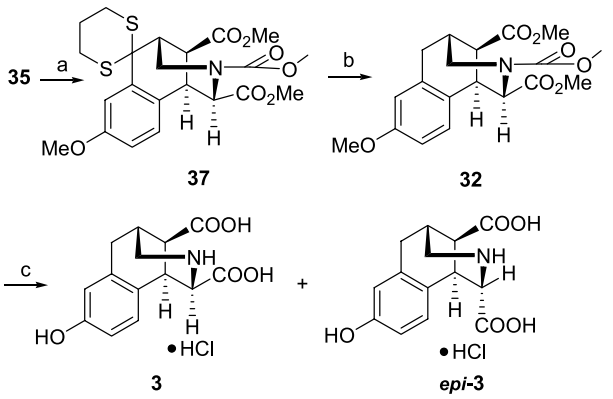


Figure 4. NOESY studies of compounds **34**, **35** and **36**.

Protection of the ketone **35** with 1,3-propandithol followed by reduction with Raney-nickel gave ester **32**. Refluxing of ester **32** with 6 N HCl for 4 days afforded amino acid **3** and its isomer *epi*-**3** (about 1:1 based on the ^1H NMR spectrum) (Scheme 6). Because the stereochemistry of α-carbon (in *R* configuration) of *epi*-**3** could be converted to the *S* one (**3**) automatically under basic conditions or during amide formation reactions,[5,8] both **3** and *epi*-**3** (as well as their mixture) are good for use in the further application to synthesis of new SH2 domain ligands.



Scheme 6. Reagents and conditions: (a) 1,3-propanedithiol, $BF_3 \cdot Et_2O$, CH_2Cl_2, rt, 48 h; (b) Raney-nickel, EtOH, rt, 30 min, 74% for two steps; (c) 6 N HCl, reflux, 4 days, 85%.

3. Summary

In conclusion, an enantioselective synthetic route of new tricyclic amino acid analogue **3** was developed efficiently, utilizing Michael addition followed by allyllation, intramolecular Friedel–Crafts cyclization and intramolecular Mannich cyclization as the key steps. All the stereochemistries in this route were well controlled and the key reactions were optimized and well repeated in good yields. This would give a good starting point to develop the new SH2 domain ligands based on the conformationconstrained tyrosine analogue **3** as a scaffold. The chemical diversity studies on **3** and related biochemical experiments are in progress in this laboratory.

4. Experimental

4.1. General methods

All reactions were carried out under argon or nitrogen in oven-dried glassware using standard gastight syringes, cannulas, and septa. Solvents and reagents were purified and dried by standard methods prior to use; optical rotations were measured at rt. IR spectra were recorded on an FT-IR instrument. ^1H NMR spectra were recorded at 300 MHz and reported in parts per million (δ) downfield relative to TMS as internal standard, and ^{13}C NMR spectra were recorded at 75 MHz and assigned in parts per million (δ). Flash column chromatography was performed on silica gel (10–40 μm) using a mixture of petroleum ether and ethyl acetate as the eluent.

4.1.1. (2*S*,3*R*)-2-(*tert*-Butyl-dimethyl-silanyloxymethyl)-3-(4-methoxy-phenyl)-5-oxo-pyrrolidine-1-carboxylic acid *tert*-butyl ester (6). To a suspension of $CuBr \cdot Me_2S$ (12.6 g, 61.3 mmol) in dry THF (40 mL) at −40 °C, was added fresh prepared *p*-anisolemagesium bromide (0.5 M in THF, 122 mL, 61.0 mmol). After 30 min the mixture was cooled to −78 °C. A mixture solution of unsaturated amide **5** (2.00 g, 6.10 mmol) and TMSCl (1.50 mL, 11.9 mmol) in dry THF (30 mL) was added to the above suspension, the reaction mixture was stirred at −78 °C for 30 min and slowly warmed to rt. Satd NH_4Cl was added and the mixture was extracted with ether, the combined ether extracts were

washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography to give **6** as a pale yellow solid (2.40 g) in 90% yield. Mp: 58–59 °C. $[\alpha]_D^{20}=-29.5$ (*c* 1.6, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.12 (d, $J=8.7$ Hz, 2H), 6.87 (d, $J=8.7$ Hz, 2H), 4.07–4.02 (m, 1H), 3.99 (dd, $J=10.2$, 3.6 Hz, 1H), 3.84–3.78 (m, 1H), 3.80 (s, 3H), 3.43 (dt, $J=9.6$, 2.1 Hz, 1H), 3.15 (dd, $J=17.4$, 9.6 Hz, 1H), 2.50 (dd, $J=17.4$, 2.7 Hz, 1H), 1.55 (s, 9H), 0.94 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.3, 158.5, 149.8, 136.3, 127.3, 114.3, 82.9, 66.9, 63.5, 55.2, 40.1, 37.9, 28.0, 25.8, 18.1, −5.58 ppm. EIMS (*m/z*, %): 336 [$(MH-100)^+$, 4.47], 322[$(MH_2-115)^+$, 59.3]. ESIMS (*m/z*, %): 474.3 $(M+K)^+$, 458.3 $(M+Na)^+$, 336.2 $(MH-100)^+$. IR (KBr): 2956, 1774, 1290, 1164, 774, 538 cm^{-1}. Anal. for $C_{23}H_{37}NO_5Si$. Calcd: C, 63.41; H, 8.56; N, 3.22. Found: C, 63.67; H, 8.64; N 3.20. ee%=96.8% (measured by HPLC).

4.1.2. (3*S*,4*R*,5*S*)-3-Benzyloxycarbonylmethyl-5-(*tert*-butyldimethyl-silanyloxymethyl)-4-(4-methoxy-phenyl)-2-oxo-pyrrolidine-1-carboxylic acid *tert*-butyl ester [7 (3*S*) and 8 (3*R*)]. To a solution of **6** (2.05 g, 4.71 mmol) in dry THF (30 mL) at −78 °C, was added fresh LHMDS (0.5 M in THF, 20 mL, 10. 0 mmol); the mixture was stirred for 30 min and $BrCH_2COOBn$ (2.20 g, 9.61 mmol) was added, then the mixture was slowly warmed to rt after another 30 min. Sat. NH_4Cl was added and the mixture was extracted with ether. The combined ether extracts were washed with brine, dried over Na_2SO_4 and concentrated in vacuo, the residue was purified by flash column chromatography to give **7** (1.50 g) and **8** (1.00 g) in 98% total yield, both as pale yellow oil. Date for **7**: $[\alpha]_D^{20}=-10.5$ (*c* 2.7, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.30–7.26 (m, 3H), 7.21–7.17 (m, 2H), 7.10 (d, $J=8.6$ Hz, 2H), 6.82 (d, $J=8.6$ Hz, 2H), 4.94 (AB, $J_{AB}=12.4$ Hz, 1H), 4.83 (AB, $J_{AB}=12.4$ Hz, 1H), 4.13 (dd, $J=10.8$, 3.1 Hz, 1H), 3.94 3.91 (m, 1H), 3.76 (s, 3H), 3.49 (dd, $J=10.8$, 1.5 Hz, 1H), 3.17 3.11 (m, 2H), 2.83 (dd, $J=15.9$, 5.9 Hz, 1H), 2.50 (dd, $J=15.9$, 7.3 Hz, 1H), 1.52 (s, 9H), 0.85 (s, 9H), 0.01 (s, 3H), 0.00 (s, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.6, 171.1, 158.9, 150.1, 135.6, 132.1, 128.8, 128.4, 128.1, 114.3, 83.1, 66.4, 64.9, 60.0, 55.2, 47.3, 43.9, 34.8, 29.6, 28.1, 25.8, 18.2, −5.5 ppm. EIMS (*m/z*, %): 483 [$(M-100)^+$, 0.60]. ESIMS (*m/z*, %): 606.3 [$(M+Na)^+$, 30.0], 584.3 [$(M+H)^+$, 8.0], 484.2 [$(MH-100)^+$, 100]. IR(film): 2932, 1716, 1253, 837, 830 cm^{-1}. Anal. for $C_{32}H_{45}NO_7Si$. Calcd: C, 65.84; H, 7.77; N, 2.40. Found: C, 66.19; H, 7.77; N, 2.17.

Date for **8**: $[\alpha]_D^{20}=-31.0$ (*c* 1.6, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.30–7.15 (m, 5H), 6.80 (dd, $J=8.6$ Hz, 2H), 6.65 (dd, $J=8.6$ Hz, 2H), 5.03 (AB, $J_{AB}=12.3$ Hz, 1H), 4.93 (AB, $J_{AB}=12.3$ Hz, 1H), 4.13–4.10 (m, 1H), 3.95 (dd, $J=10.6$, 4.1 Hz, 1H), 3.77 (dd, $J=10.6$, 2.3 Hz, 1H), 3.70–3.60 (m, 4H), 3.52 (d, $J=9.0$ Hz, 1H), 2.65 (dd, $J=17.7$, 4.2 Hz, 1H), 1.81 (dd, $J=17.7$, 10.3 Hz, 1H), 1.48 (s, 9H), 0.83 (s, 9H), 0.01 (s, 3H), 0.00 (s, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.7, 171.7, 158.8, 150.0, 135.8, 132.3, 128.5, 128.3, 128.2, 114.3, 83.2, 66.3, 64.9, 63.7, 55.2, 44.1, 42.9, 31.5, 28.1, 25.8, 18.2, −5.50 ppm. EIMS (*m/z*, %): 483 [$(M-100)^+$, 0.77], 468 [$(M-115)^+$, 7.33]. ESIMS (*m/z*, %): 606.3 [$(M+Na)^+$, 11.0], 484.2 [$(MH-100)^+$, 100]. IR (film): 2932, 1741, 1254, 838, 699 cm^{-1}. Anal. for $C_{32}H_{45}NO_7Si$. Calcd: C, 65.84; H, 7.77; N, 2.40. Found: C, 66.22; H, 8.03; N, 2.30.

4.1.3. (3*R*,4*R*,5*S*)-3-Benzyloxycarbonylmethyl-5-(*tert*-butyldimethyl-silanyloxymethyl)-4-(4-methoxy-phenyl)-2-oxo-pyrrolidine-1-carboxylic acid *tert*-butyl ester (8). To a solution of **7** (0.81 mg, 1.39 mmol) in dry THF (30 mL) at −78 °C, was added fresh LHMDS (0.67 M in THF, 6.3 mL, 4.22 mmol), the mixture was stirred at −78 °C for 40 min and AcOH (0.27 mL, 4.29 mmol) was added dropwise. Satd NH_4Cl was added after additional 10 min, the mixture was warmed to rt and extracted with Et_2O. The combined Et_2O extracts were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography to give a pale yellow oil (596 mg) in 73% yield. (The physical data has been shown in the preparation of compound **7** and **8**).

4.1.4. (2*S*,3*R*,4*R*)-4-Benzyloxycarbonylmethyl-3-(4-methoxy-phenyl)-5-oxo-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (9). To a solution of **8** (1.46 g, 2.50 mmol) in acetone (40 mL) at 0 °C, was added dropwise Jone's reagent (2.67 M, 2.40 mL, 6.41 mmol); the mixture was warmed to rt and stirred for 4 h. *iso*-propanol (15 mL) was added, and the mixture was filtered through a celite after being stirred for 30 min, the filtrate was basified with sat. $NaHCO_3$, and acetone was removed in vacuo; the residue aqueous phase was extracted with ether two times, then acidified to pH 3–4, and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were washed by brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was dissolved in Et_2O (20 mL) and treated with CH_2N_2 in Et_2O; after 10 min, excess CH_2N_2 was destroyed by AcOH and the mixture was concentrated in vacuo, The residue was purified by flash column chromatography to give a pale yellow oil (664 mg) in 54% yield. $[\alpha]_D^{20}=-2.2$ (*c* 1.3, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.40–7.32 (m, 3H), 7.28–7.22 (m, 2H), 6.90 (d, $J=8.7$ Hz, 2H), 6.75 (d, $J=8.7$ Hz, 2H), 5.10 (AB, $J_{AB}=12.0$ Hz, 1H), 4.99 (AB, $J_{AB}=12.0$ Hz, 1H), 4.67 (s, 1H), 3.83 (s, 3H), 3.77 (s, 3H), 3.67 (d, $J=9.0$ Hz, 1H), 3.55–3.45 (m, 1H), 2.81 (dd, $J=18.0$, 3.9 Hz, 1H), 1.92 (dd, $J=18.0$, 10.8 Hz, 1H), 1.52 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.1, 171.4, 170.6, 159.1, 149.1, 135.5, 130.0, 128.4, 128.3, 128.2, 114.4, 84.0, 66.5, 64.2, 55.2, 52.8, 43.4, 42.6, 30.9, 27.8 ppm. EIMS (*m/z*, %): 497 (M^+, 3.99), 397 [$(M-100)^+$, 7.78]. IR (film): 2981, 1794, 1751, 1255, 836, 531 cm^{-1}. Anal. for $C_{27}H_{31}NO_8$. Calcd: C, 65.18; H, 6.28; N, 2.82. Found: C, 65.33; H, 6.15; N, 2.80.

4.1.5. (2*S*,3*R*,4*R*)-4-Carboxymethyl-3-(4-methoxy-phenyl)-5-oxo-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (10). To a solution of **9** (250 mg, 0.50 mmol) in ethyl acetate (5 mL), was added Pd/C (10%, 25 mg), and the mixture was stirred at rt for 3 h under 1 atm hydrogen. Pd/C was filtered off and the filtrate was concentrated in vacuo, the residue was purified by flash column chromatography directly to give a pale yellow oil (140 mg) in 68% yield. $[\alpha]_D^{20}=-2.1$ (*c* 0.7, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.00 (d, $J=8.4$ Hz, 2H), 6.86 (d, $J=8.1$ Hz, 2H), 4.70 (s, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.67 (d, $J=8.7$ Hz, 1H), 3.47 (m, 1H), 2.79 (dd, $J=12.3$, 3.9 Hz, 1H), 1.98 (dd, $J=12.3$, 9.9 Hz, 1H), 1.53 (s, 9H)

ppm. EIMS (*m/z*, %): 307 [$(M-100)^+$, 7.89]. IR (film): 3226, 2950, 1751, 1255, 838, 550 cm^{-1}. HR-MALDI for $(C_{20}H_{25}NO_8+Na)^+$. Calcd: 430.1478. Found 430.1472.

4.1.6. 7-Methoxy-3,5-dioxo-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-benzo[*e*]isoindole-1*S*-carboxylic acid methyl ester (11). To a solution of acid **10** (100 mg, 0.245 mmol) in dry CH_2Cl_2 (4.0 mL) and CS_2 (10.0 mL) at 0 °C, was added $(COCl)^2$ (87 μL, 1.02 mmol), followed by the slow addition of dry DMF (6 μL, 0.077 mmol). The mixture was warmed to rt and stirred for 2 h, the solvent was removed to give a yellow oil. To the solution of this oil in dry CH_2Cl_2 (20 mL) at 0 °C, was added $AlCl_3$ (160 mg, 1.20 mmol) in one portion. The reaction mixture was warmed to rt and stirred overnight. Crashed ice was added and the reaction mixture was extracted with CH_2Cl_2, the CH_2Cl_2 extracts were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography to give ketone **11** (54 mg) as a white solid in 76% yield. Mp: 178–180 °C. $[\alpha]_D^{20}=-8.7$ (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.44 (d, $J=2.9$ Hz, 1H), 7.40 (d, $J=8.7$ Hz, 1H), 7.18 (dd, $J=8.7$, 2.9 Hz, 1H), 7.15 (br s, 1H), 4.25 (s, 1H), 4.02 (dd, $J=7.8$, 1.8 Hz, 1H), 3.87 (s, 3H), 3.82 (s, 3H), 3.25–3.19 (m, 1H), 3.10 (dd, $J=16.9$, 4.1 Hz, 1H), 2.72 (dd, $J=16.9$, 7.1 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.0, 177.0, 171.5, 159.2, 133.8, 133.3, 130.0, 123.0, 108.7, 62.6, 55.6, 52.9, 40.5, 38.0, 34.7 ppm. EIMS (*m/z*, %): 289 (M^+, 29.73). IR (KBr): 3396, 1693, 1198, 839, 548 cm^{-1}.

4.1.7. 7-Methoxy-3,5-dioxo-1,3,3*a*,4,5,9*b*-hexahydro-benzo[*e*] isoindole-1*S*,2-dicarboxylic acid 2-*tert*-butyl ester 1-methyl ester (12). To a solution of ketone **11** (53 mg, 0.183 mmol) in dry CH_3CN (10 mL) at rt, was added Boc_2O (84 mg, 0.385 mmol) and DMAP (2 mg, 0.016 mmol) successively. After being stirred for 1.5 h, the mixture was diluted with CH_2Cl_2, washed by water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo, the residue was purified by flash column chromatography to give ketone **12** (58 mg) as a colorless oil in 81% yield. $[\alpha]_D^{20}=+33.5$ (*c* 1.6, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.49 (d, $J=2.7$ Hz, 1H), 7.45 (d, $J=8.7$ Hz, 1H), 7.23 (dd, $J=8.7$, 2.7 Hz, 1H), 4.75 (s, 1H), 3.90 (s, 3H), 3.85 (s, 3H), 3.83 (d, $J=6.9$ Hz, 1H), 3.42 (dt, $J=6.9$, 3.0 Hz, 1H), 3.25 (dd, $J=17.1$, 3.0 Hz, 1H), 2.73 (dd, $J=17.1$, 6.9 Hz, 1H), 1.46 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.4, 172.3, 170.9, 160.0, 150.0, 134.2, 132.6, 130.1, 123.7, 109.2, 84.6, 65.6, 56.0, 53.4, 40.5, 37.3, 34.7, 28.2 ppm. EIMS (*m/z*, %): 389 (M^+, 24.0). ESIMS (*m/z*, %): 428.2 [$(M+K)^+$, 13.0], 412.2 [$(M+Na)^+$, 25.0]. IR (film): 2981, 1793, 1753, 1304, 732, 538 cm^{-1}. HR-MALDI for $(C_{20}H_{23}NO_7+Na)^+$. Calcd: 412.1372. Found: 412.1361.

4.1.8. (1*R*,2*R*)-1-(*tert*-Butoxycarbonylaminomethoxycarbonyl-methyl)-6-methoxy-4-oxo-1,2,3,4-tetrahydro-naphthalene-2-carboxylic acid methyl ester (13). To a solution of ketone **12** (58 mg, 0.149 mmol) in methanol (5.0 mL), was added K_2CO_3 (31 mg, 0.225 mmol), and the mixture was stirred at rt for 30 min. Water was added and the resulted mixture was extracted with ethyl acetate (50 mL×3); the organic layer was washed by brine, dried over anhydrous Na_2SO_4, filtered and concentrated, the residue was purified by flash column chromatography to give diester **13** as a colorless oil (32 mg) in 74% yield, and recovered material as a colorless oil (15 mg). $[\alpha]_D^{20}=+101.0$ (*c* 0.9, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.54 (s, 1H), 7.06 (s, 2H), 5.10 (d, $J=9.9$ Hz, 1H), 4.56 (t, $J=9.9$ Hz, 1H), 3.85–3.75 (m, 7H), 3.47 (s, 3H), 3.36–3.10 (m, 2H), 2.95 (dd, $J=18.3$, 3.0 Hz, 1H), 1.43 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.5, 172.2, 159.5, 133.7, 133.1, 129.1, 121.5, 110.2, 80.6, 55.5, 52.2, 52.1, 43.3, 42.0, 35.5, 28.2, 14.2 ppm. ESIMS (*m/z*, %):460.3 [$(M+K)^+$, 3.0], 444.3 [$(M+Na)^+$, 100], 422.3 [$(MH)^+$, 3.0]. IR (film): 3387, 2850, 1730, 1212, 828, 563 cm^{-1}. HR-MALDI for $(C_{21}H_{27}NO_8+Na)^+$. Calcd: 444.1634. Found: 444.1633.

4.1.9. (1*S*,4*R*)-7-Methoxy-2-methoxymethyl-3,5-dioxo-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-benzo[*e*]isoindole-1-carboxylic acid methyl ester (14). To a solution of ester **13** (10 mg, 0.024 mmol) in DCM (3.0 mL) was added TFA (3.0 mL), and the mixture was stirred at rt for 2 h. Solvent was removed in vacuo, and the residue was redissolved in methanol (10 mL), HCHO (30% aq, 0.30 mL, 3.00 mmol) was added to the above solution. The mixture was refluxed for 2 h and concentrated; the residue was purified by flash column chromatography directly to give a colorless oil (6.0 mg) in 75% yield. ^1H NMR (300 MHz, $CDCl_3$): δ 7.49 (d, $J=3.0$ Hz, 1H), 7.43 (d, $J=8.7$ Hz, 1H), 7.21 (dd, $J=8.7$, 3.0 Hz, 1H), 4.81 (AB, $J_{AB}=11.1$ Hz, 1H), 4.53 (AB, $J_{AB}=11.4$ Hz, 1H), 4.37 (s, 1H), 3.99 (d, $J=7.5$ Hz, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 3.42–3.36 (m, 1H), 3.26 (dd, $J=17.1$, 2.4 Hz, 1H), 2.80 (s, 3H), 2.75 (dd, $J=17.1$, 6.9 Hz, 1H) ppm. EIMS (*m/z*, %): 333 (M^+, 4.93), 302 [$(M-31)^+$, 20.15]. ESIMS (*m/z*, %): 351.1 [$(M+NH_4)^+$, 25.0], 334.1 [$(M+H)^+$, 38.0], 302.1 [$(M-OMe)^+$, 100]. IR (film): 2927, 1716, 1283, 1228, 757, 496 cm^{-1}. HR-EIMS for $C_{17}H_{19}NO_6^+$. Calcd: 333.1212. Found: 333.1232.

4.1.10. (4*R*)-4-(2-Ethoxycarbonyl-vinyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (15). To a solution of $(COCl)_2$ (5.7 mL, 67.3 mmol) in dry DCM (250 mL) at −78 °C, was added a solution of DMSO (9.3 mL, 0.131 mol) in dry DCM (40 mL) during 15 min. Garner's alcohol (10.0 g, 43.2 mmol) in dry DCM (40 mL) was added dropwise to the above solution. The mixture was stirred at −78 °C for 2 h before Et_3N (50.0 mL, 356 mmol) was added, then warmed to rt. Satd NH_4Cl was added and the resulted mixture was extracted with DCM, the organic layer was washed by brine, dried over anhydrous Na_2SO_4, filtered and concentrated; the residue was redissolved in ether (100 mL), filter through a celite to remove the $Et_3N\cdot HCl$. Ether was removed in vacuo and the residue was used directly for the next step. To a solution of the above residue in benzene (150 mL) at 0 °C, was added $Ph_3P{=}CHCOOEt$ (18.4 g, 52.5 mmol), and the mixture was stirred at rt overnight. Most of the benzene was removed and ether (150 mL) was added, filtered and concentrated, the residue was purified by flash column chromatography directly to give a pale yellow oil (10.7 g) in 83% yield. $[\alpha]_D^{20}=-61.4$ (*c* 0.95, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 6.95–6.78 (m, 1H), 6.02–5.85 (m, 1H), 4.62–4.50 (m, 0.4H), 4.50–4.38 (m, 0.6H), 4.30–4.15 (m, 2H), 4.15–4.05 (m, 1H), 3.85–3.78 (m, 1H), 1.65–1.25 (m, 18H) ppm. ee%=97.3% (measured by HPLC).

4.1.11. (1*R*,4*R*)-4-[2-Ethoxycarbonyl-1-(4-methoxy-phenyl)-ethyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (16). To the suspension of CuI (16.0 g, 84.0 mmol) in dry THF (100 mL) at −78 °C, was added fresh prepared *p*-methoxylphenylmagnesium bromide (0.5 M, 0.34 L, 0.17 mol) dropwise, the mixture was slowly warmed to −20 °C during 60 min. The mixture was cooled back to −78 °C, then a solution of TMSCl (25.4 mL, 0.20 mol) and ester **15** (5.0 g, 16.7 mmol) in dry THF (30 mL) was added. The mixture was stirred at −78 °C for 60 min and warmed to 0 °C during 2 h. Satd NH_4Cl was added and the resulted mixture was extracted with ether, the organic layer was washed by Satd $Na_2S_2O_3$ and brine, dried over anhydrous Na_2SO_4, concentrated, the residue was purified by flash column chromatography to give a colorless oil (6.98 g) in 100% yield. $[\alpha]_D^{20}=+38.5$ (*c* 2.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.26–7.10 (m, 2H), 6.88–6.80 (m, 2H), 4.10–3.65 (m, 9H), 2.85–2.70 (m, 2H), 1.60–1.30 (m, 15H), 1.25–1.05 (m, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.4, 158.3, 152.7/152.3$_{(conformer)}$, 132.1, 129.0, 128.6, 113.9, 113.6, 94.6/94.0, 80.1, 63.8/63.4, 61.8/61.5, 60.1, 55.0, 42.0, 33.7/32.5, 28.3, 26.6/25.9, 23.7/22.2, 13.9 ppm. EIMS (*m*/*z*, %): 407 (M^+, 0.43). IR (film): 2980, 1700, 1252, 1178, 854, 541 cm^{-1}. Anal. for $C_{22}H_{33}NO_6$. Calcd: C, 64.84; H, 8.16; N, 3.44. Found: C, 65.10; H, 8.29; N, 3.37. ee% > 96.4% (measured by HPLC).

4.1.12. (1*R*,2*S*,4*R*)-4-[2-Ethoxycarbonyl-1-(4-methoxy-phenyl)-pent-4-enyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (17). To a solution of $(i\text{-Pr})_2NH$ (7.6 mL, 54.3 mmol) in dry THF (250 mL) at 0 °C, was added *n*-BuLi (1.6 M in hexane, 30.0 mL, 48.0 mmol) dropwise, the mixture was stirred for 15 min and cooled to −78 °C. HMPA (11.5 mL, 63.4 mmol) was added to the above solution, and the mixture was stirred for 30 min before ester **16** (13.0 g, 31.9 mmol) in dry THF (40 mL) was added. Allylic bromide (4.1 mL, 48.4 mmol) was added after another 30 min. The mixture was stirred at −78 °C for 30 min and warmed to rt during 60 min, satd NH_4Cl was added and the resulted mixture was extracted with ether. The organic layer was washed by brine, dried over Na_2SO_4, filtered and concentrated; the residue was purified by flash column chromatography to give a pale yellow oil (14.5 g) in 100% yield. $[\alpha]_D^{20}=-62.8$ (*c* 1.3, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.10 (d, $J=8.4$ Hz, 2H), 6.82 (d, $J=8.4$ Hz, 2H), 5.68–5.52 (m, 1H), 4.92–4.79 (m, 2H), 4.25–4.10 (m, 3H), 4.03–3.90 (m, 2H), 3.80 (s, 3H), 3.40–3.10 (m, 2H), 2.17–1.95 (m, 2H), 1.60–1.45 (m, 15H), 0.80 (m, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.4, 134.5, 131.0, 116.8, 113.3, 69.5, 60.3, 60.0, 55.2, 52.0, 48.5, 35.7, 28.3, 25.3, 24.4, 14.3 ppm. EIMS (*m*/*z*, %): 447 (M^+, 0.35). IR (film): 2980, 1697, 1391, 1180, 1037, 840, 566 cm^{-1}. Anal. for $C_{25}H_{37}NO_6$. Calcd: C, 67.09; H, 8.33; N, 3.13. Found: C, 67.35; H, 8.35; N, 3.05.

4.1.13. (1*R*,2*S*,4*R*)-4-[2-Hydroxymethyl-1-(4-methoxy-phenyl)-pent-4-enyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (18). To suspension of $LiAlH_4$ (1.83 g, 46.0 mmol) in dry THF (250 mL) at 0 °C, was added a solution of ester **17** (20.5 g, 46.0 mmol) in dry THF, the mixture was stirred at 0 °C for 1.5 h. Water (5.0 mL) was added dropwise to the reaction mixture, and the mixture was stirred vigorously until becoming white. The mixture was dried with anhydrous Na_2SO_4, filtered and concentrated; the residue was purified by flash column chromatography to give a colorless oil (17.3 g) in 93% yield. $[\alpha]_D^{20}=-70.1$ (*c* 1.7, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.09 (d, $J=8.4$ Hz, 2H), 6.79 (d, $J=8.4$ Hz, 2H), 5.76–5.70 (m, 1H), 4.98–4.84 (m, 2H), 4.60–4.43 (m, 1H), 4.08 (m, 1H), 3.99–3.90 (m, 1H), 3.80 (s, 3H), 3.80–3.72 (m, 1H), 3.60–3.50 (m, 1H), 3.40–3.28 (m, 1H), 2.86 (m, 1H), 2.28 (m, 1H), 2.05 (m, 1H), 1.68 (m, 1H), 1.50–1.30 (m, 12H), 0.90 (m, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.2, 136.6, 131.9, 131.0, 116.4, 113.2, 94.4, 80.2, 68.9, 64.0, 58.3, 55.1, 42.8, 34.8, 28.3, 25.4, 24.5 ppm. EIMS (*m*/*z*, %): 407 (0.48), 308 (0.63). IR (film): 3462, 2978, 1694, 1513, 1249, 1178, 1040, 842, 563 cm^{-1}. Anal. for $C_{23}H_{35}NO_5$. Calcd: C, 68.12; H, 8.70; N, 3.45. Found: C, 68.07; H, 8.88; N, 3.33.

4.1.14. (1*R*,2*S*,4*R*)-4-[2-(2,2-Dimethyl-propionyloxy-methyl)-1-(4-methoxy-phenyl)-pent-4-enyl]-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (19). To a solution of alcohol **18** (6.50 g, 16.0 mmol) in dry DCM (100 mL) at 0 °C was added Et_3N (13.5 mL, 96.0 mmol), DMAP (195 mg, 1.60 mmol) and PivCl (7.9 mL, 64.0 mmol), then the mixture was warmed to rt and stirred overnight. The reaction mixture was diluted with DCM, washed by water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated; the resulted residue was purified by flash column chromatography to give a pale yellow oil (8.16 g) in 100% yield. $[\alpha]_D^{20}=-42.1$ (*c* 2.2, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.08 (d, $J=8.7$ Hz, 2H), 6.80 (d, $J=8.7$ Hz, 2H), 5.70 (m, 1H), 5.00–4.90 (m, 2H), 4.45 (m, 1H), 4.30 (m, 1H), 4.05–3.84 (m, 3H), 3.80 (s, 3H), 2.98 (m, 1H), 2.38 (m, 1H), 2.17 (m, 1H), 1.73 (m, 1H), 1.60–1.00 (m, 24H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.3, 158.3, 153.1, 136.1, 131.3/130.9, 130.7, 116.8, 113.0, 94.0, 79.7, 68.5, 64.0, 58.1, 55.1, 50.7, 40.0, 38.9, 33.5, 28.2, 27.2, 26.0, 24.6 ppm. EIMS (*m*/*z*, %): 491 (0.20), 490 (MH^+, 0.61). IR (film): 2977, 1695, 1366, 1163, 838, 561 cm^{-1}. HR-MALDI for $(C_{28}H_{43}NO_6+Na)^+$. Calcd: 512.2988. Found: 512.2957.

4.1.15. 2,2-Dimethyl-propionic acid 2*S*-[2*R*-*tert*-butoxy-carbonylamino-3-hydroxy-1*R*-(4-methoxyphenyl)-propyl]-pent-4-enyl ester (20). To a solution of **19** (7.33 g, 15.0 mmol) in methanol (800 mL), was added PTSA·H_2O (86 mg, 0.45 mmol), and the mixture was stirred at rt overnight. Satd $NaHCO_3$ (20 mL) was added to the reaction mixture, then methanol was removed in vacuo, and the residue mixture was extracted with EtOAc; the organic phase was washed by brine, dried over anhydrous Na_2SO_4, filtered and concentrated, the residue was purified by flash column chromatography to give a pale yellow oil (5.68) in 84% yield. $[\alpha]_D^{20}=-51.8$ (*c* 1.7, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.08 (d, $J=8.7$ Hz, 2H), 6.80 (d, $J=8.7$ Hz, 2H), 5.72–5.58 (m, 1H), 5.00–4.82 (m, 2H), 4.40–4.25 (m, 1H), 4.20–4.00 (m, 2H), 3.80 (s, 3H), 3.48–3.25 (m, 2H), 3.00 (m, 1H), 2.30–2.10 (m, 2H), 2.10–1.95 (m, 2H), 1.78 (m, 1H), 1.50–1.18 (m, 18H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.3, 158.6, 156.2, 135.9, 130.2, 129.7, 117.0, 113.9, 79.6, 64.3, 63.4, 55.2, 52.0, 45.3, 38.9, 38.0, 32.8, 28.3, 27.2 ppm. EIMS (*m*/*z*, %): 350 (1.31). IR (KBr film): 3437, 2978, 1725, 1168, 1036, 838, 539 cm^{-1}. HR-MALDI for $(C_{25}H_{39}NO_6+Na)^+$. Calcd: 472.2675. Found: 472.2697.

4.1.16. 2,2-Dimethyl-propionic acid 2*S*-[*R*-(4-methoxy-phenyl)-*R*-(2-oxo-oxazolidin-4-yl)-methyl]-pent-4-enyl ester (21). To a suspension of NaH (60%, 1.10 g, 27.3 mmol) in dry DMF (50) at 0 °C, was added the solution of alcohol **20** (4.9 g, 10.9 mmol) in dry DMF (50 mL) dropwise, and the mixture was stirred for 30 min. Satd NH_4Cl (20 mL) was added to the reaction mixture, then DMF was removed in vacuo, and the residue mixture was extracted with EtOAc; the organic phase was washed by brine, dried over anhydrous Na_2SO_4, filtered and concentrated, the residue was purified by flash column chromatography to give a colorless oil (3.10 g) in 76% yield. $[\alpha]_D^{20}=+3.91$ (*c* 1.2, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.10 (d, $J=8.4$ Hz, 2H), 6.90 (d, $J=8.4$ Hz, 2H), 5.70–5.60 (m, 2H), 5.10–4.90 (m, 2H), 4.50 (t, $J=8.4$ Hz, 1H), 4.40–4.33 (m, 1H), 4.11–4.00 (m, 2H), 3.93 (dd, $J=12.0$, 6.3 Hz, 1H), 3.80 (s, 3H), 2.80–2.76 (m, 1H), 2.15–2.00 (m, 2H), 1.77–1.70 (m, 1H), 1.25 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.3, 159.0, 135.0, 130.1, 128.5, 117.7, 114.3, 68.8, 64.0, 55.2, 53.5, 49.9, 38.9, 32.8 27.2 ppm. EIMS (*m*/*z*, %): 291 (3.33), 290 (17.04), 289 (8.13). IR (film): 3280, 2974, 1751, 1162, 1034, 769, 553 cm^{-1}.

4.1.17. 4*R*-[2*S*-(2,2-Dimethyl-propionyloxymethyl)-1*R*-(4-methoxy-phenyl)-pent-4-enyl]-2-oxo-oxazolidine-3-carboxylic acid *tert*-butyl ester (22). To a solution of **21** (6.3 g, 16.8 mmol) in dry DCM (300 mL) at 0 °C, was added Et_3N (8.2 mL, 58.5 mmol), DMAP (100 mg, 0.82 mmol) and $(Boc)_2O$ (10.8 g, 49.5 mmol), the mixture was warmed to rt and stirred overnight. The reaction mixture was washed by water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated; the residue was purified by flash column chromatography to give a colorless oil (7.40 g) in 93% yield. $[\alpha]_D^{20}=-99.9$ (*c* 2.4, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.01 (d, $J=8.4$ Hz, 2H), 6.80 (d, $J=8.1$ Hz, 2H), 5.60 (m, 1H), 5.00–4.75 (m, 3H), 4.54 (dd, $J=11.1$, 3.9 Hz, 1H), 4.30 (m, 1H), 4.15 (m, 1H), 4.02 (m, 1H), 3.75 (s, 3H), 2.70 (dd, $J=10.8$, 2.7 Hz, 1H), 2.30 (m, 1H), 1.94 (m, 1H), 1.75 (m, 1H), 1.52 (s, 9H), 1.20 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.3, 159.0, 151.8, 150.2, 135.2, 130.3, 127.4, 117.4, 114.1, 84.1, 67.2, 62.9, 55.0, 54.6, 51.1, 38.9, 38.6, 33.7, 27.8, 27.2 ppm. ESIMS (*m*/*z*, %): 498.2 $[(M+Na)^+$, 10], 376.2 $[(MH-100)^+$, 40]. IR (KBr film): 2978, 1819, 1154, 1062, 776, 566 cm^{-1}. Anal. for $C_{26}H_{37}NO_7$. Calcd: C, 65.66; H, 7.84; N, 2.95. Found: C, 65.69; H, 7.64; N, 2.88.

4.1.18. 4*R*-[3-Carboxy-2*S*-(2,2-dimethyl-propionyloxy-methyl)-1*R*-(4-methoxy-phenyl)-propyl]-2-oxo-oxazolidine-3-carboxylic acid *tert*-butyl ester (23). O_3 was bulbed through the solution of **22** (1.50 g, 3.15 mmol) in DCM (40 mL) and methanol (10 mL) at −78 °C until pale blue (about 2 h), then Me_2S (10 mL) was added; the mixture was warmed to rt during 2 h and concentrated to a colorless oil which was used directly. To the solution of the above residue in ^tBuOH (50 mL) and H_2O (10 mL) at 0 °C, was added KH_2PO_4 (643 mg, 4.73 mmol) and 2-methyl-2-butene (1.34 mL, 12.6 mmol), $NaClO_2$ (860 mg, 9.46 mmol, in three portions); the mixture was warmed to rt and stirred overnight. Satd $Na_2S_2O_3$ (20 mL) was added to the reaction mixture and ^tBuOH was removed in vacuo, the residue aqueous was acidified to pH 3–4 and extracted by DCM, the organic layer was washed by brine, dried over anhydrous Na_2SO_4, filtered and concentrated, the residue was purified by flash column chromatography to give a white wax (1.30 g) in 84% yield. $[\alpha]_D^{20}=-80.3$ (*c* 2.4, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.04 (m, 2H), 6.80 (m, 2H), 4.84 (d, $J=8.4$ Hz, 1H), 4.63 (dd, $J=11.7$, 4.5 Hz, 1H), 4.35 (t, $J=8.6$ Hz, 1H), 4.27 (dd, $J=12.0$, 3.0 Hz, 1H), 4.03 (dd, $J=12.0$, 1.8 Hz, 1H), 3.78 (s, 3H), 2.84 (m, 1H), 2.74 (dd, $J=11.6$, 2.0 Hz, 1H), 2.15 (m, 2H), 1.56 (s, 9H), 1.23 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.4, 177.8, 159.4, 151.8, 150.2, 130.3, 126.6, 114.5, 84.5, 67.1, 63.8, 55.1, 54.2, 51.0, 39.0, 35.9, 34.5, 27.9, 27.2 ppm. ESIMS (*m*/*z*, %): 516.3 $[(M+Na)^+$, 10], 394.2 $[(MH-100)^+$, 50]. IR (film): 3224, 2979, 1813, 1726, 1156, 913, 734, 648 cm^{-1}. Anal. for $C_{25}H_{35}NO_9$. Calcd: C, 60.84; H, 7.15; N, 2.84. Found: C, 60.89; H, 7.22; N, 2.78.

4.1.19. 2,2-Dimethyl-propionic acid 6-methoxy-4-oxo-1*R*-(2-oxo-oxazolidin-4*R*-yl)-1*R*,2*R*,3,4-tetrahydro-naphthalen-2-ylmethyl ester (24). To a solution of acid **23** (1.25 g, 2.54 mmol) in DCM (5.0 mL) and CS_2 (30 mL) at rt, was added $(COCl)_2$ (0.67 mL, 7.61 mmol) and DMF (60 μL, 0.76 mmol), and the mixture was stirred at rt for 2 h. The solvent was removed in vacuo and the residue was redissovled in dry DCM (60 mL) and protected under N_2 as soon as possible, the solution was cooled to 0 °C before $AlCl_3$ (1.19 g, 8.89 mmol) was added, the reaction mixture was warmed to rt and stirred overnight. The mixture was poured into a mixture was ice and water and extracted with DCM, the organic phase was washed by brine, dried over anhydrous Na_2SO_4, filtered and concentrated, the residue was purified by flash column chromatography to give a white wax (0.70 g) in 74% yield. $[\alpha]_D^{20}=+62.4$ (*c* 1.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.41 (d, $J=2.7$ Hz, 1H), 7.15 (d, $J=8.4$ Hz, 1H), 7.04 (dd, $J=8.4$, 2.7 Hz, 1H), 5.85 (s, 1H), 4.52 (t, $J=8.4$ Hz, 1H), 4.17 (dd, $J=9.0$, 6.0 Hz, 1H), 4.00 (m, 1H), 3.89 (m, 2H), 3.75 (s, 3H), 2.87 (d, $J=9.0$ Hz, 1H), 2.80 (dd, $J=19.2$, 6.0 Hz, 1H), 2.55 (d, $J=19.2$ Hz, 1H), 2.42 (m, 1H), 1.06 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.6, 178.0, 159.4, 158.9, 132.5, 131.7, 121.8, 110.2, 69.1, 65.7, 55.4, 55.3, 44.6, 38.6, 35.5, 34.0, 26.9 ppm. EIMS (*m*/*z*, %): 375 (M^+, 0.62). IR (film): 3334, 2970, 1683, 1284, 1156, 1033, 769, 532 cm^{-1}. Anal. for $C_{20}H_{25}NO_6$. Calcd: C, 63.99; H, 6.71; N, 3.73. Found: C, 64.43; H, 7.03; N, 3.58. ee%=99.13% (measured by HPLC).

4.1.20. 4*R*-[2*R*-(2,2-Dimethyl-propionyloxymethyl)-6-methoxy-4-oxo-1*R*,2*R*,3,4-tetrahydro-naphthalen-1-yl]-2-oxooxazolidine-3-carboxylic acid *tert*-butyl ester (26). To a solution of ketone **24** (1.00 g, 2.66 mmol) in dry DCM (30 mL) at 0 °C, was added Et_3N (1.2 mL, 8.56 mmol), DMAP (5 mg, 0.041 mmol) and $(Boc)_2O$ (0.70 g, 3.21 mmol), the mixture was warmed to rt and stirred overnight. The reaction mixture was washed by water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated; the residue was purified by flash column chromatography to give a colorless oil (1.20 g) in 95% yield. $[\alpha]_D^{20}=+27.2$ (*c* 1.1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.55 (d, $J=2.7$ Hz, 1H), 7.18–7.10 (m, 2H), 4.59–4.53 (m, 1H), 4.39–4.33 (m, 1H), 4.16–4.10 (m, 1H), 4.05–3.90 (m, 2H), 3.84 (s, 3H), 3.23 (d, $J=8.7$ Hz, 1H), 2.92 (dd, $J=18.6$, 5.7 Hz, 1H), 2.69 (d, $J=18.3$ Hz, 1H), 2.58–2.51 (m, 1H), 1.24 (s, 9H), 1.11 (s, 9H) ppm. ^{13}C NMR (75 MHz,

$CDCl_3$): δ 194.7, 178.1, 159.6, 151.8, 148.4, 133.2, 131.9, 131.0, 122.2, 110.0, 84.1, 66.6, 66.0, 56.9, 55.6, 41.9, 38.7, 35.9, 34.0, 27.5, 27.0 ppm. ESIMS (*m/z*, %): 498.2 [$(M+Na)^+$, 15], 476.2 [$(MH)^+$, 100]. IR (film): 2978, 1816, 1728, 1284, 1156, 732, 550 cm^{-1}. Anal. for $C_{25}H_{33}NO_8$. Calcd: C, 63.14; H, 6.99; N, 2.95. Found: C, 63.23; H, 7.02; N, 2.88.

4.1.21. [2-Hydroxy-1*R*-(2*R*-hydroxymethyl-6-methoxy-4-oxo-1*R*,2*R*,3,4-tetrahydro-naphthalen-1-yl)-ethyl]-carbamic acid *tert*-butyl ester (27). To a solution of ketone **26** (1.10 g, 2.31 mmol) in methanol (50 mL), was added Cs_2CO_3 (1.65 g, 5.05 mmol), the mixture was stirred at rt overnight. Satd NaCl (30 mL) was added to the reaction mixture, and methanol was removed in vacuo, the residue was extracted with DCM; the organic layer was washed by water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated, the residue was purified by flash column chromatography to give a white wax (0.75 g) in 86% yield. $[\alpha]_D^{20}=+54.1$ (*c* 1.2, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.48 (d, *J*=2.7 Hz, 1H), 7.20 (d, *J*=8.4 Hz, 1H), 7.05 (dd, *J*=8.4, 2.7 Hz, 1H), 4.85 (d, *J*=9.6 Hz, 1H), 4.00–3.60 (m, 7H), 3.55–3.30 (m, 3H), 3.05–2.80 (m, 2H), 2.50 (m, 2H), 1.26 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.0, 158.9, 155.8, 133.4, 133.3, 132.4, 121.5, 109.4, 79.9, 64.8, 63.0, 55.5, 39.3, 38.6, 36.4, 29.6, 28.2 ppm. EIMS (*m/z*, %): 310 (1.10), 292 (3.39), 266 (1.09). ESIMS (*m/z*, %): 753 [$(2M+Na)^+$, 25], 731.4 [$(2M+H)^+$, 35], 310 [$(MH_2-C_4H_9)^+$, 100], 266 [$(MH-100)^+$, 8]. IR (film): 3360, 2927, 1683, 1035, 875, 533 cm^{-1}.

4.1.22. 2,2-Dimethyl-propionic acid 2*R*-*tert*-butoxycarbonylamino-2*R*-[2-(2,2-dimethylpropionyloxymethyl)-6-methoxy-4-oxo-1*R*,2*R*,3,4-tetrahydronaphthalen-1-yl]-ethyl ester (28). To a solution of diol **27** (0.66 g, 1.80 mmol) in dry DCM (30 mL) at 0 °C was added Et_3N (2.50 mL, 18.0 mmol), DMAP (5 mg, 0.041 mmol) and PivCl (1.80 mL, 14.5 mmol), then the mixture was warmed to rt and stirred overnight. The reaction mixture was diluted with DCM, washed by water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated; the resulted residue was purified by flash column chromatography to give a pale yellow oil (0.74 g) in 76% yield. $[\alpha]_D^{20}=+21.3$ (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.45 (s, 1H), 7.01 (m, 2H), 4.32–4.00 (m, 2H), 4.15–3.95 (m, 2H), 3.83 (d, *J*=6.9 Hz, 2H), 3.77 (s, 3H), 3.00–2.90 (m, 2H), 2.70–2.62 (m, 1H), 2.49 (m, 1H), 1.25 (s, 9H), 1.15 (s, 9H), 1.05 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.0, 177.7, 177.5, 158.7, 154.6, 133.4, 131.1, 131.0, 121.1, 109.2, 79.4, 66.4, 63.8, 59.8, 54.9, 53.1, 40.4, 38.3, 38.1, 36.2, 35.6, 27.6, 26.6, 26.5, 20.5, 13.6 ppm. ESIMS (*m/z*, %): 556.3 $(M+Na)^+$. IR (film): 3363, 2977, 1731, 1284, 1154, 1035, 877, 771, 537 cm^{-1}. HR-ESIMS for $(C_{29}H_{43}NO_8+Na)^+$. Calcd: 556.2886. Found: 556.2878.

4.1.23. (1*R*, 9*S*,12*R*, 13*R*)-12,13-Bis-(2,2-dimethylpropionyloxymethyl)-5-methoxy-8-oxo-11-azatricyclo[7.3.1.02,7]trideca-2(7),3,5-triene-11-carboxylic acid methyl ester (29). To a solution of **28** (0.66 g, 1.24 mmol) in DCM (10 mL), was added TFA (10 mL); after 2 h at rt, the mixture was concentrated to a pale yellow oil. To the solution of the above yellow oil in ethanol (30 mL), was added HCHO (36%, 0.50 mL, 6.00 mmol) and the mixture was refluxed for 2 h. The solvent was removed in vacuo and the residue was redissolved in dioxane (10 mL), water (5.0 mL) and sat. $NaHCO_3$ (5.0 mL), ClCOOMe (0.12 mL, 1.55 mmol) was added and the mixture was stirred at rt for 2 h. Dioxane was removed in vacuo and the residue was extracted with EtOAc, the organic layer was washed by water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The resulted residue was purified by flash column chromatography to give a colorless oil (0.72 g) in 100% yield. $[\alpha]_D^{20}=+51.2$ (*c* 1.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.50 (d, *J*=2.7 Hz, 1H), 7.19 (d, *J*=8.7 Hz, 1H), 7.14 (dd, *J*=8.7, 2.7 Hz, 1H), 4.64–4.55 (m, 2H), 4.47 (dd, *J*=12.0, 9.6 Hz, 1H), 3.96–3.80 (m, 5H), 3.70 (ddd, *J*=9.6, 4.5, 1.5 Hz, 1H), 3.26 (s, 3H), 3.21 (m, 2H), 2.67 (m, 1H), 2.60 (m, 1H), 1.27 (s, 9H), 1.15 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.7, 178.4, 178.3, 159.9, 155.8, 134.9, 132.0, 131.1, 122.6, 109.5, 64.8, 63.0, 62.1, 55.9, 52.7, 50.7, 45.4, 45.2, 39.2, 38.8, 31.9, 27.5, 27.3, 23.0 ppm. ESIMS (*m/z*, %): 526.4 $(M+Na)^+$, 542.4 $(M+K)^+$. IR (film): 2974, 1730, 1284, 1159, 764, 532 cm^{-1}. HR-ESIMS for $(C_{27}H_{37}NO_8+Na)^+$. Calcd: 526.2417. Found: 526.2412.

4.1.24. (1*R*,9*S*,12*R*,13*S*)-12,13-Bis-(2,2-dimethylpropionyloxymethyl)-5-methoxy-11-azatricyclo[7.3.1.02,7]trideca-2(7),3,5-triene-11-carboxylic acid methyl ester (30). To a solution of ketone **29** (0.70 g, 1.39 mmol) in methanol (20 mL) at 0 °C, was added $NaBH_4$ (53 mg, 1.39 mmol); satd NH_4Cl was added after 10 min and the mixture was extracted with EtOAc; the organic layer was washed by brine, dried over anhydrous Na_2SO_4, filtered and concentrated, the resulting residue was purified by flash column chromatography to give a white wax (642 mg) (contaminated by inseparable material). To a suspension of NaH (60%, 253 mg, 6.33 mmol) in dry THF (15.0 mL) at 0 °C, was added the solution of the above white wax in dry THF (5 mL), CS_2 (0.77 mL, 12.7 mmol) was added after 30 min. The mixture was warmed to rt and stirred for 60 min before MeI (0.79 mL, 12.7 mmol) was added, then stirred for another 2 h. Satd NH_4Cl was added and the mixture was extracted with ether. The organic layer was washed by brine, dried over anhydrous Na_2SO_4, filtered and concentrated, the residue was purified by flash column chromatography to give white wax (553 mg) and ketone **29** (154 mg), in 86% modified yield for two steps, and 78% conversion for the first step.

To the solution of the above product (553 mg) in dry toluene (30 mL), was added AIBN (30 mg, 0.19 mmol) and *n*-Bu_3SnH (0.50 mL, 1.86 mmol) under N_2, the mixture was refluxed for 3 h. Solvent was removed in vacuo and the residue was purified by flash column chromatography directly to give a white wax (450 mg) in 100% yield. $[\alpha]_D^{20}=-4.50$ (*c* 1.2, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 6.93 (d, *J*=8.7 Hz, 1H), 6.68 (dd, *J*=8.7, 2.7 Hz, 1H), 6.60 (d, *J*=2.4 Hz, 1H), 4.37 (dd, *J*=11.4, 5.7 Hz, 1H), 4.29 (dd, *J*=11.4, 9.0 Hz, 1H), 4.20 (dd, *J*=13.5, 3.0 Hz, 1H), 3.90 (dd, *J*=11.1, 7.2 Hz, 1H), 3.81 (dd, *J*=11.1, 8.1 Hz, 1H), 3.75 (s, 3H), 3.62 (m, 1H), 3.30–3.22 (m, 4H), 3.00 (s, 1H), 2.90–2.80 (m, 2H), 2.30 (m, 1H), 2.17 (m, 1H), 1.23 (s. 9H), 1.18 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.0, 138.0, 133.3, 130.3, 128.9, 128.5, 128.3, 127.3, 72.3, 60.8, 56.6, 55.2, 26.0, 22.4, 22.1, 20.6 ppm. EIMS (*m/z*, %): 489 (M^+, 2.17). IR (film): 2974, 1729, 1160,

1037, 733, 454 cm^{-1}. HR-MALDI for $(C_{27}H_{39}NO_7+Na)^+$. Calcd: 512.2624. Found: 512.2604.

4.1.25. (1*R*,9*S*,12*R*,13*S*)-5-Methoxy-11-azatricyclo-[7.3.1.02,7]trideca-2(7),3,5-triene-11,12,13-tricarboxylic acid trimethyl ester (31). The procedure was the same as the preparation of compound **34**. From material **30** (125 mg), **31** (61 mg) was obtained in 3% yield for four steps. $[\alpha]_D^{20}=+72.6$ (*c* 1.4, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.02 (d, $J=8.5$ Hz, 1H), 6.65 (dd, $J=8.5$, 2.6 Hz, 1H), 6.55 (d, $J=2.5$ Hz, 1H), 4.50 (d, $J=6.2$ Hz, 1H), 4.00 (br s, 1H), 3.87 (d, $J=6.0$ Hz, 1H), 3.80 (s, 3H), 3.67–3.50 (m, 9H), 3.45 (m, 1H), 3.05 (dd, $J=17.5$, 5.0 Hz, 1H), 2.87 (m, 1H), 2.80 (m, 1H), 2.67 (d, $J=17.6$ Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.2, 170.2, 158.9, 135.7, 131.4, 125.4, 113.6, 112.3, 62.2, 55.1, 52.9, 52.0, 51.6, 42.7, 35.6, 31.8, 29.7, 28.2 ppm. EIMS (*m*/*z*, %): 378 (MH^+, 3.41), 3.77 (M^+, 20.30), 318 [$(M-59)^+$, 100]. IR (film): 2954, 1734, 1709, 1257, 1198, 778, 531 cm^{-1}.

4.1.26. (1*R*,9*S*,12*S*,13*S*)5-Methoxy-11-azatricyclo-[7.3.1.02,7]trideca-2(7),3,5-triene-11,12,13-tricarboxylic acid trimethyl ester (33). To a solution of diester **31** (5 mg) in methanol (5.0 mL) at rt, was added NaOMe (3 mg); sat. NH_4Cl was added after 10 min. The mixture was extracted with EtOAc, the organic layer was washed by brine, dried over anhydrous Na_2SO_4, filtered and concentrated, the residue was purified by flash column chromatography to give a colorless oil (5 mg) in 100% yield. $[\alpha]_D^{20}=+14.1$ (*c* 0.4, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.10 (m, 1H), 6.68 (m, 1H), 6.53 (m, 1H), 4.75 (d, $J=3.0$ Hz, 0.5H), 4.61 (d, $J=2.1$ Hz, 0.5H), 4.25 (dd, $J=13.5$, 1.5 Hz, 0.5H), 4.10 (dd, $J=13.5$, 1.5 Hz, 0.5H), 3.90 (d, $J=1.2$ Hz, 0.5H), 3.86 (d, $J=1.2$ Hz, 0.5H), 3.80 (s, 3H), 3.75 (s, 3H), 3.64–3.35 (m, 7H), 3.20 (m, 1H), 2.78–2.55 (m, 3H) ppm.

4.1.27. (1*R*,9*S*,12*R*,13*R*)-5-Methoxy-8-oxo-11-azatricyclo-[7.3.1.02,7]trideca-2(7),3,5-triene-11,12,13-tricarboxylic acid trimethyl ester (34). To a solution of ketone **29** (250 mg, 0.50 mmol) in dry DCM (20 mL) at −78 °C, was added DIBAL-H (1.0 in cyclohexane, 7.5 mL, 7.5 mmol), 1 N HCl (20 mL) was added after 60 min. The mixture was extracted with DCM, washed by brine, dried over anhydrous Na_2SO_4, filtered and concentrated, the residue was used directly. To a solution of the above residue in DCM (20 mL), was added Dess–Martin Periodinane (2.50 g, 5.91 mmol), and the mixture was stirred at rt for 30 min before sat. $Na_2S_2O_3$ and sat. $NaHCO_3$ were added. The reaction mixture was extracted with DCM, the organic layer was washed by brine, dried over Na_2SO_4, filtered and concentrated to a residue which was redissoved in ^{t}BuOH (5.0 mL) and H_2O (1.0 mL); to this solution was added KH_2PO_4 (408 mg, 3.00 mmol), 2-methyl-2-butane (0.85 mL, 8.00 mmol) and $NaClO_2$ (543 mg, 6.00 mmol), the mixture was stirred at rt for 60 min before sat. $Na_2S_2O_3$ was added. The solvent was removed in vacuo, the residue was redissoved in $CHCl_3$ and dried over Na_2SO_4, filtered and concentrated. The residue was redissolved in Et_2O (30 mL) and excess CH_2N_2 (in ether) was added at 0 °C, the mixture was stirred at rt for 30 min and concentrated. The residue was purified by flash column chromatography directly to give a colorless oil (100 mg) in 50% yield for four steps. $[\alpha]_D^{20}=+51.2$ (*c* 1.3, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.45 (d, $J=2.8$ Hz, 1H), 7.26 (d, $J=8.5$ Hz, 1H), 7.05 (dd, $J=8.5$, 2.8 Hz, 1H), 4.35 (dd, $J=12.3$, 2.6 Hz, 1H), 4.25 (d, $J=3.7$ Hz, 1H), 4.00 (s, 1H), 3.80 (s, 3H), 3.55 (s, 3H), 3.52 (s, 3H), 3.50–3.38 (m, 4H), 3.20–3.09 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.1, 171.4, 169.0, 159.7, 157.2, 133.1, 131.7, 131.0, 122.0, 108.7, 61.9, 55.4, 53.1, 52.5, 51.9, 48.0, 47.6, 42.8, 38.3 ppm. EIMS (*m*/*z*, %): 392 (MH^+, 2.81), 391 (M^+, 11.19), 332 [$(M-89)^+$, 100]. IR (film): 2955, 1713, 1234, 1037 cm^{-1}. HR-MALDI for $(C_{19}H_{21}NO_8+Na)^+$. Calcd: 414.1159. Found: 414.1112.

4.1.28. (1*R*,9*S*,12*S*,13*R*)5-Methoxy-8-oxo-11-azatricyclo-[7.3.1.02,7]trideca-2(7),3,5-triene-11,12,13-tricarboxylic acid trimethyl ester (36). The procedure was similar to the preparation of compound **33**. From material **34** (25 mg), **36** was obtained (20 mg) in 80% yield. (The physical data are shown in the preparation of **35** and **36**).

4.1.29. (1*R*,9*S*,12*S*,13*S*/*R*)-5-Methoxy-8-oxo-11-azatricyclo[7.3.1.02,7]trideca-2(7),3,5-triene-11,12,13-tricarboxylic acid trimethyl ester [35(13*S*) and 36(13*R*)]. To a solution of LDA (2.0 M in THF, 1.05 mL, 2.10 mmol) in dry THF (5.0 mL) at −78 °C, was added HMPA (0.6 mL, 3.31 mmol), after 30 min the solution of ketone **34** (55 mg, 0.14 mmol) in THF (5.0 mL) was added dropwise. The mixture was stirred at −78 °C for additional 30 min before acetic acid (0.14 mL, 2.10 mmol) was added, then warmed to rt and quenched by satd NH_4Cl. The reaction mixture was extracted by ether, the organic layer was washed by brine, dried over anhydrous Na_2SO_4, filtered and concentrated, the residue was purified by flash column chromatography to give **35** as a colorless oil (20 mg) in 36% yield, and **36** as a pale yellow oil (20 mg) in 36% yield. Date for **35**: $[\alpha]_D^{20}=+48.4$ (*c* 0.3, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.45 (m, 1H), 7.35 (m, 1H), 7.12 (m, 1H), 4.60 (s, 0.6H), 4.50 (s, 0.4H), 4.30–4.05 (m, 2H), 3.90–3.70 (m, 10H), 3.60–3.45 (m, 3H), 3.25–3.10 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.5, 170.8, 170.7, 159.5, 157.1/156.5, 137.0, 133.4/133.2, 129.1/128.8, 123.0/122.8, 109.5/109.4, 58.0, 57.2, 55.6, 53.2/53.1, 52.5/52.4, 42.7, 42.1, 41.9/41.6, 37.4/37.3 ppm. EIMS (*m*/*z*, %): 391 (M^+, 1.57), [332 $(M-59)^+$, 100]. ESIMS (*m*/*z*, %): 392.2 (MH^+). IR (film): 2957, 1740, 1710, 1447, 1234, 1025, 778, 531 cm^{-1}. HR-MALDI for $(C_{19}H_{21}NO_8+Na)^+$. Calcd: 414.1159. Found: 414.1153. Date for **36**: $[\alpha]_D^{20}=+36.3$ (*c* 0.7, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.45 (m, 1H), 7.30 (m, 1H), 7.10 (m, 1H), 4.86 (d, $J=2.0$ Hz, 0.7H), 4.72 (d, $J=2.0$ Hz, 0.3H), 4.45 (dd, $J=13.4$, 2.0 Hz, 0.3H), 4.35 (dd, $J=13.4$, 3.1 Hz, 0.7H), 4.12–4.04 (m, 1H), 3.85–3.55 (m, 6H), 3.55–3.45 (m, 7H), 3.13–3.00 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.7/196.1, 171.8/171.7, 170.3, 159.5/159.4, 156.9/156.3, 133.5/133.3, 133.1, 129.7/129.4, 122.8, 108.9/108.8, 60.5/59.8, 55.5, 53.2/53.1, 52.9, 52.4, 45.4/45.1, 44.1/44.0, 42.8/42.7, 38.1 ppm. EIMS (*m*/*z*, %): 392 (MH^+, 2.15), 391 (M^+, 9.47), [332 $(M-59)^+$, 100]. IR (film): 1739, 1224, 1031, 771, 530 cm^{-1}.

4.1.30. (1*R*,9*S*,12*S*,13*R*)-5-Methoxy-11-azatricyclo-[7.3.1.02,7]trideca-2(7),3,5-triene-11,12,13-tricarboxylic acid trimethyl ester (32). To a solution of **35** (20 mg, 0.051 mmol) in dry CH_2Cl_2 (5.0 mL) at 0 °C, was added $BF_3\cdot Et_2O$ (20 μL, 0.16 mmol) and 1,3-propanedithiol

(40 μL, 0.40 mmol). After stirring at rt for 48 h, the reaction was quenched with sat. $NaHCO_3$ and the mixture was extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography to give the sulfer-ketal as a colorless oil (20 mg). To a solution of sulfer-ketal (20 mg) in EtOH (15 mL), was added Raney-nickel (about 0.5 g). After 40 min, Raney-Nickel was filtered through a pad of celite and the filtrate was concentrated. The residue was redissoved in EtOAc and washed with water and brine. The organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography to give a colorless oil (14 mg) in 73% yield for two steps. $[\alpha]_D^{20} = +3.13$ (*c* 0.4, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.17–7.12 (m, 1H), 6.74–6.70 (m, 1H), 6.61 (s, 1H), 4.56 (s, 0.5H), 4.43 (s, 0.5H), 4.10 (m, 0.5H), 3.95–3.90 (m, 2H), 3.80–3.70 (m, 9.5H), 3.60–3.40 (m, 3H), 3.20 (m, 1H), 2.98–2.82 (m, 1H), 2.80 (s, 1H), 2.68 (m, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.6, 171.2/171.1, 158.6, 156.8, 137.3/136.9, 130.5, 128.9/128.6, 113.0, 112.6/112.1, 59.4, 59.0, 55.2, 52.9/52.8, 52.2/52.0, 45.2/44.9, 41.2/41.1, 36.9/36.7, 35.2/35.1, 27.8/27.7 ppm. EIMS (*m/z*, %): 378 (MH^+, 1.12), 377 (M^+, 5.36), 318 [$(M-59)^+$, 100]. ESIMS (*m/z*, %): 400.10 $(M+Na)^+$, 378.10 $(M+H)^+$, 318 $(M-59)^+$. IR (KBr film): 2956, 1741, 1706, 1226, 1120, 776, 530 cm^{-1}.

4.1.31. (1*R*,9*S*,12*S*,13*R*)-5-hydroxy-11-azatricyclo-[7.3.1.02,7]trideca-2(7),3,5-triene-12,13-dicarboxylic acid hydrochloride salt (3). Compound **32** (14 mg, 0.037 mmol) was refluxed with HCl (6 N, 10 mL) for 4 days. The mixture was concentrated in vacuo to give **3** and *epi*-**3** as a white solid (10 mg) in 85% yield. $[\alpha]_D^{20} = +30.5$ (*c* 0.3, H_2O). ^1H NMR (300 MHz, $CDCl_3$): δ 7.00 (d, $J=7.8$ Hz, 0.6H), 6.80 (d, $J=8.1$ Hz, 0.4H), 6.60–6.43 (m, 2H), 4.10 (m, 1H), 3.95–3.68 (m, 1.4H), 3.45 (d, $J=12.6$ Hz, 0.6H), 3.23–3.00 (m, 2H), 2.95–2.50 (m, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.9, 177.4, 172.9, 172.1, 158.2, 157.8, 143.0, 140.5, 139.2, 133.3, 133.1, 129.3, 127.5, 117.9, 117.6, 116.8, 63.7, 60.3, 51.0, 49.2, 44.4, 41.6, 37.7, 37.5, 36.4, 32.0, 29.3, 28.9 ppm. ESIMS (*m/z*, %): 278.1 $(M+H)^+$. IR (KBr): 3375, 3131, 1720, 1403, 1214, 824 cm^{-1}. HR-ESIMS for $(C_{14}H_{15}NO_5+H)^+$. Calcd: 278.1028. Found: 278.1021.

Acknowledgements

This project is financially supported by NSFC (20425205 and 20321202), MOST of China (G2000077502) and Chinese Academy of Sciences.

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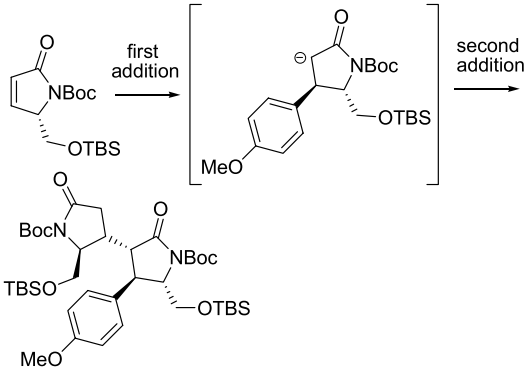
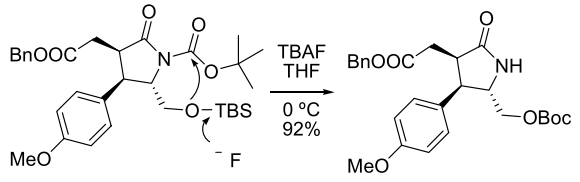
11. Formation of the two-time Michael addition product:



12. If **8** was treated with TBAF, Boc immigration occurred in high conversion.



13. CCDC 264692 & 264693 contain the supplementary crystallographic data for compounds **25** and **11**, respectively, in this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.
14. The Wittig reagent was prepared by treating the corresponding phosphonium salt with aq. NaOH solution. If the excess NaOH was not washed off completely, the olefin product of the Witting reaction maybe partly racemize because of the base.