Tetrahedron 70 (2014) 7185–7191

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of the unusual α-amino acid component of some novel histone deacetylase inhibiting cyclic peptides

Amit K. Pahari, Jyoti Prasad Mukherjee, Shital K. Chattopadhyay *

Department of Chemistry, University of Kalyani, Kalyani 741235, West Bengal, India

ARTICLE INFO

Article history:
Received 6 April 2014
Received in revised form 1 July 2014
Accepted 9 July 2014
Available online 15 July 2014

This work is respectfully dedicated to fond memories of my mentor Late Professor A. McKillop

Keywords:
α-Amino acid
Cyclic peptides
Cross-metathesis
Histone deacetylase inhibitor
Chiral pool

ABSTRACT

A flexible protocol for the synthesis of three lipophilic α-amino acid components of some novel cyclic peptides having important histone deacetylase inhibiting properties has been developed from a common source, which featured a cross-metathesis reaction between two unhindered terminal olefins as the key step.

1. Introduction

Several members of an interesting family[1] of cyclic tetrapeptides contain a lipophilic amino acid, such as 2-amino-8-oxodecanoic acid (Aoda) or (2*S*,9*S*)-2-amino-8-oxo-9,10-epoxydecanoic acid (Aoe) as an unusual component of their structure. Typical examples include apicidines[2] (**1**, **2**), microsporin[3] (**3**), trapoxin[4] (**4**), HC-toxin[5] (**5**) etc. (Fig. 1), which display useful levels of histone deacetylase inhibition activity and a great deal of attention is currently being expended on the discovery of new inhibitor (HDACi) designs.[6] In the quest for more selective HDACi, hybrid structures accommodating structural features of different subclasses, e.g., CHAP 31 (**6**) have also been targeted.[7] It has been suggested[8] that the terminal carbonyl group in members of this family functionally mimics the C-8 keto group of the acetylated lysine residue (**7**) of histones and additional substituents, such as epoxide (as in Aoe) or an alkyl group (as in Aoda) control the reversibility/irreversibility of inhibition. Because of the fascinating biological activity associated with the molecules, many elegant reports on the synthesis of the individual members of the family of natural products[3,9] and/or the unusual amino acid component[10] have emerged. However, a common synthetic entry into Aoe or Aoda with additional opportunity of incorporation of skeletal diversity remains important. Herein, we report the synthesis of Aoe, Aoda and a related α-amino acid from a common source.

2. Results and discussion

We argued that a successful cross-metathesis (CM) reaction[11] between two suitably substituted C-6 olefins would install the 10-carbon framework of Aoe, Aoda and related amino acids.[9f] Thus, we identified the glutamic acid-derived terminal olefin **11** (Scheme 1) as one such C-6 olefin with which cross metathesis of either of the other C-6 olefins **14**, **16** or **22** would deliver the desired amino acids. We therefore focused on the preparation of these sub-units.

Thus, the known[12] glutamic acid-derived aldehyde **8** on Wittig methylenation followed by one-pot conversion of the oxazolidine unit in the resulting olefin **9** into an α-amino-carboxylic acid unit involving deprotection–oxidation sequence produced the carboxylic acid **10** in good yield. Esterification of the latter with methyl iodide under conventional conditions led quick access to the desired C6 fragment **11** in an overall yield of 38.6% over three steps. The CM partner **14** was prepared by allylation of propionaldehyde (**12**) with allylzinc bromide [prepared in situ by treatment of allyl bromide with zinc powder].

* Corresponding author. Fax: +91 33 25828282; e-mail address: skchatto@yahoo.com (S.K. Chattopadhyay).

http://dx.doi.org/10.1016/j.tet.2014.07.045
0040-4020/

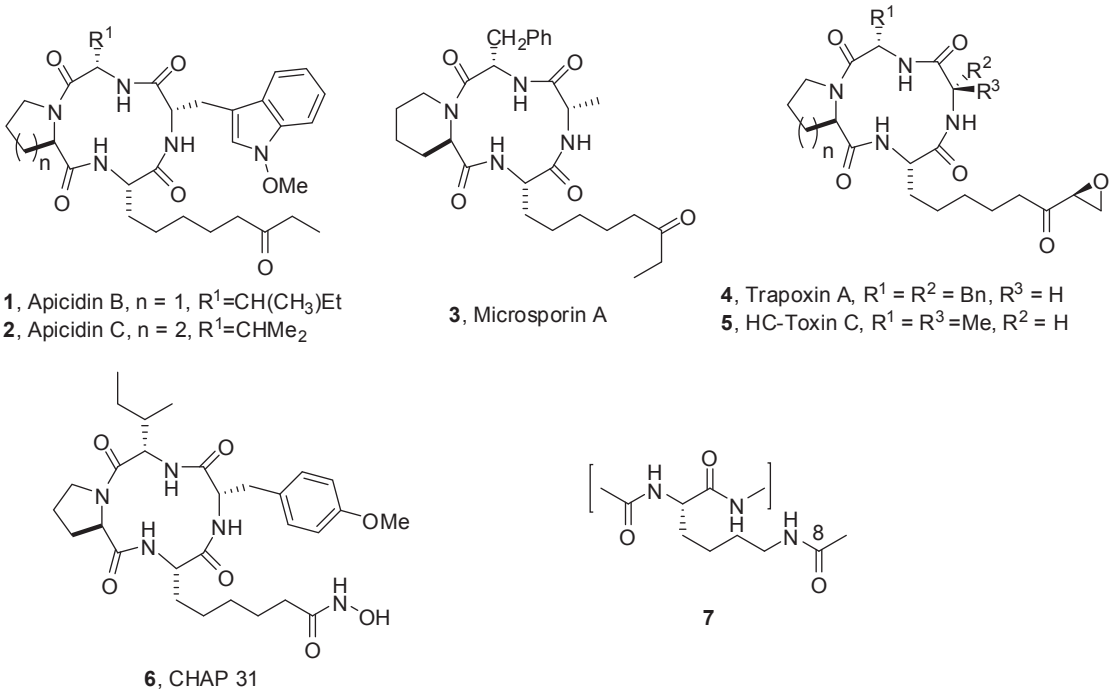
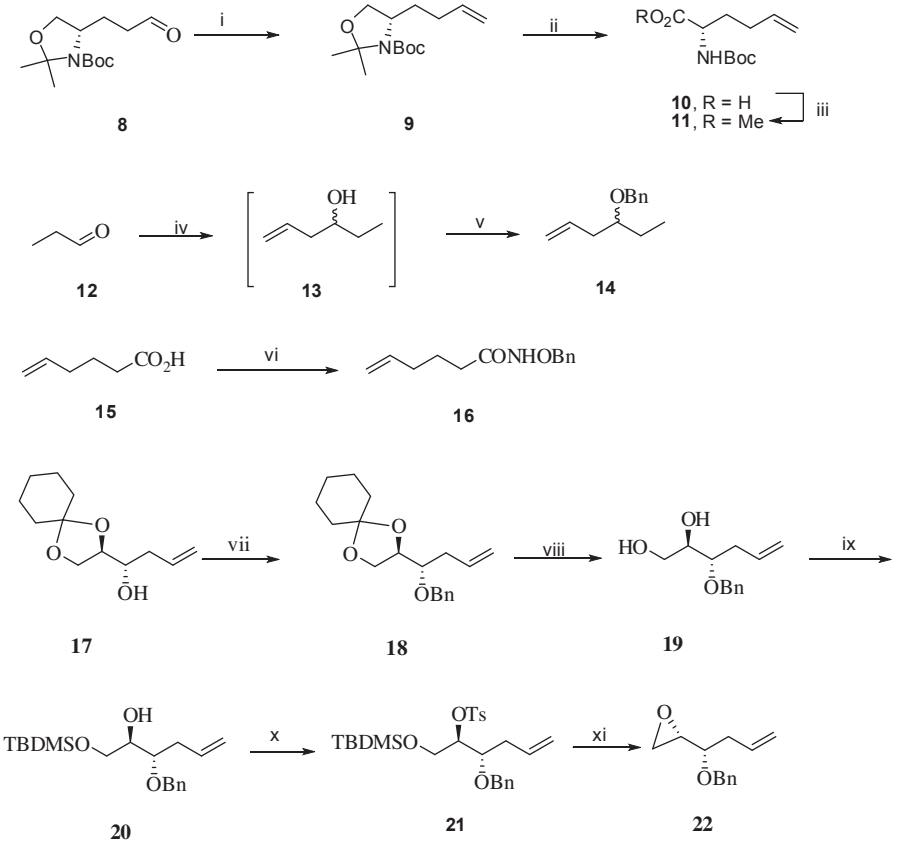


Fig. 1. Structures of some naturally occurring histone deacetylase inhibitors.



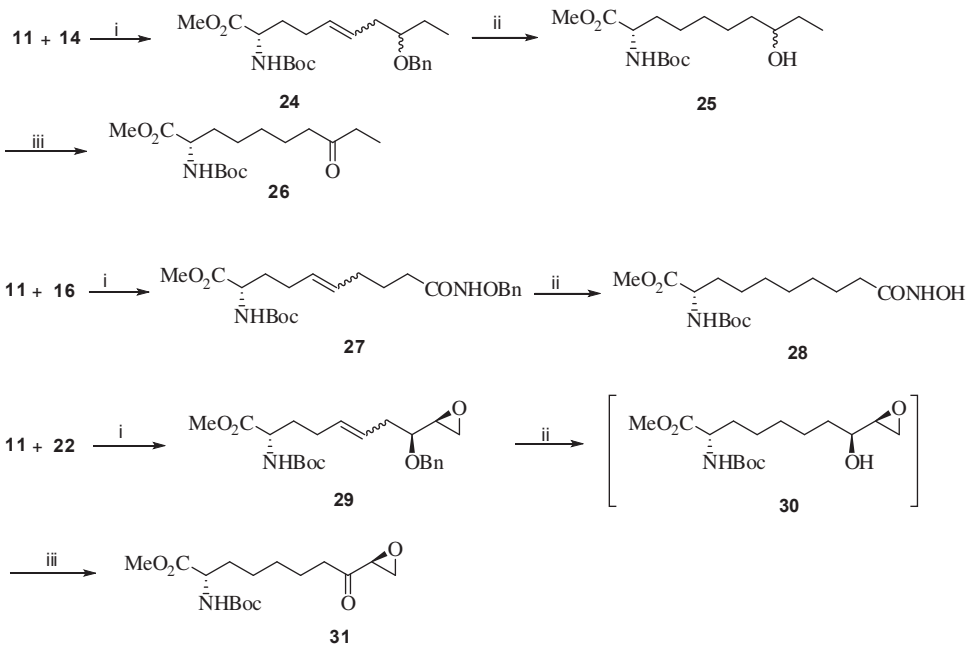
Scheme 1. Reagents: (i) $MePh_3PBr$, *n*-BuLi, THF, 0 °C, 3 h, 83%; (ii) chromic acid, acetone, 2 h, 64%; (iii) Cs_2CO_3, CH_3I, DMF, 12 h, 75%; (iv) Zn-dust, allyl bromide, NH_4Cl; (v) NaH, BnBr, 45% over two steps; (vi) $NH_2OBn{\cdot}HCl$, NMM, HOBt, EDC, 94%; (vii) NaH, benzyl bromide, 91%; (viii) 6(N) HCl, THF, 79%; (ix) imidazole, DMAP, TBDMSCl, DCM, 8 h, 84%; (vi) DMAP, *p*-TSCl, pyridine, 24 h, 86%; (vii) TBAF, THF, 1 h, 74%.

The resulting secondary alcohol **13** was used without purification in the subsequent benzylation reaction. The *O*-benzyl ether **14** was obtained in a yield of 45% over two steps.

Conversion of 5-hexenoic acid (**15**) into its hydroxamate **16** was achieved by treatment of the former with *O*-benzylhydroxylamine in the presence of DCC & HOBt using *N*-methylmorpholine as a base. The remaining CM partner **22** was prepared from the known[13] homoallyl alcohol **18** derived from (*R*)-2,3-*O*-cyclohexylidene-glyceraldehyde. Thus, benzylation of the secondary alcohol **17** leading to **18** followed by cleavage of the dioxolane moiety

in the latter resulted in the formation of the diol **19**. The latter was selectively silylated at the primary hydroxyl function leading to **20** and subsequently the secondary-OH was *O*-tosylated to get the triply protected triol derivative **21**. Removal of the TBDMS group using TBAF resulted in the concomitant formation of the epoxide ring perhaps involving intramolecular displacement of the OTs-group by the in situ generated alkoxy anion. The five step sequence proceeded in an overall yield of 38%.

concomitant removal of the *O*-benzyl group to provide the desired product **28** in an overall yield of 55% over two steps. Analogously, cross metathesis of **11** with the epoxy-olefin **22** provided the CM product **29**, also as a mixture of geometric isomers. This was then hydrogenated into the epoxy alcohol **30**. The latter was used as such in the subsequent oxidation reaction leading to the desired Aoe derivative **31** in an overall yield of 32% over three steps.



Scheme 2. Reagents and conditions: (i) Grubbs' catalyst **23** (5 mol %), CuI (10 mol %), CH_2Cl_2, reflux, 4 h, 54% (**24**), 62% (**27**), 52% (**29**). (ii) H_2, $Pd(OH)_2$, THF/MeOH, 2 h, 85% (**25**), 88% (**28**), 79% (**30**). (iii) Dess–Martin periodinane, CH_2Cl_2, 1 h, 78% (**26**), 62% (**31**).

Having all four CM ingredients (**11**, **14**, **16**, **22**) in hand, we then focused on their union. Cross-metathesis of terminal and unhindered olefins (i.e., not having a bulky functionality on the allylic carbon) [Category 'A' according to Grubbs' classification[14]] is known to be statistical in nature and several methodological developments have emerged for yield improvement.[15] We tried some of these most successful conditions for the CM between the olefins **11** and **14** using Grubbs' first and second generation catalysts. However, the desired conversion to **24** (Scheme 2) was obtained in <20% yield in most of the cases. Pleasingly, the yield of **24** could be improved up to 54% when Grubbs' second-generation catalyst[16] benzylidene[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro-(tricyclohexylphosphine)ruthenium (**23**) was used in the presence of CuI as an additive.[17] However, several attempts to improve the yield further were fruitless. Since the product was an epimeric mixture, it could not be ascertained whether it also consisted of geometric isomers. However, geometric isomerism was not considered important since the isomeric identity will be lost in the subsequent hydrogenation step. The CM-product **24** on hydrogenation led to saturation of the double bond with concomitant deprotection of the OBn-group as expected. The resulting 2°-alcohol **25** was then oxidized with Dess–Martin periodinane to obtain the Aoda derivative **26**. Similarly, CM between the olefins **11** & **16** under the developed conditions provided the product olefin **27** in slightly better yield (62%) and as one isomer. However, the nature of the geometric isomer formed could not be ascertained since the two olefinic protons appeared together in the ^1H NMR spectrum. Hydrogenation of the CM product **27** proceeded smoothly with

3. Conclusion

In brief, we have developed a general synthetic entry into three lipophilic α-amino acids (**26**, **28**, **31**) from easily available starting materials and using amino acid and carbohydrate derivatives as source of chirality. The key step of the synthesis is a CM reaction between two terminal olefins having remote functionality. Although the yield of the CM reaction is somewhat modest, it allows diversity creation. The prepared amino acids may prove to be biologically relevant for analogue design and the protocol may prove to be adaptable for the synthesis of related amino acids. It may thus complement to the existing procedures for the synthesis of such type of compounds.[3,9]

4. Experimental

4.1. General

Optical rotations were recorded in spectroscopic grade chloroform on a Rudolph Autopol polarimeter, $[\alpha]_D$ values are recorded in units of 10^{-1} deg cm^2 g^{-1}. Infrared spectra were recorded on a Perkin–Elmer Spectrum-1 spectrophotometer purchased through a DST-FIST grant. Proton and carbon NMR spectra were recorded on a Bruker DRX-400 spectrometer and the chemical shifts are recorded relative to residual solvent or TMS as standard. Data for the rotamers are given in parentheses. Mass spectra were recorded on a JEOL-JMS 600 instrument from I. I. C. B., Kolkata or IACS, Kolkata. Petroleum ether refers to the fraction boiling in the

range 60–80 °C. Silica gel (120–200 mesh) for column chromatography was purchased from Spectrochem, India.

*4.1.1. (S)-tert-Butyl 4-(but-3-enyl)-2,2-dimethyloxazolidine-3-carboxylate (**9**).* *n*-BuLi (2 M in hexane, 0.5 ml) was added dropwise over 10 min to a stirred suspension of the Wittig salt ($MePh_3P^+Br^-$) (416 mg, 1.16 mmol) in dry THF (8 ml) at 0 °C under argon atmosphere and the resulting solution was allowed to come to room temperature over 30 min when the solution turned deep yellow. It was cooled back to 0 °C and then a solution of the aldehyde **8** (200 mg, 0.78 mmol) in THF (8 ml) was added dropwise over 15 min while stirring. It was stirred for 30 min and then allowed to come to room temperature and stirring was continued for 3 h. The reaction mixture was then quenched with aqueous NH_4Cl solution (10 ml) and extracted with ethyl acetate (2×25 ml). The combined organic extract was washed successively with water (1×25 ml) and brine (1×25 ml), and then dried over $MgSO_4$. It was then filtered and the filtrate was concentrated in vacuo to leave the crude product, which was purified by flash chromatography over silica gel using a mixture of ethyl acetate/hexane (1:10) to give the product **9** as a colourless oil (168 mg, 83%). $[\alpha]_D^{25}$ +5.6 (*c* 0.28 in $CHCl_3$). IR (neat): 2980, 1698, 1389, 1366, 1176, 1095 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.83–5.79 (1H, m), 5.05 (1H, dd, *J*=1.6, 17.2 Hz), 4.98 (1H, d, *J*=9.2 Hz), 3.93–3.90 (1H, m), 3.79–3.68 (2H, m), 2.06–2.01 (2H, m), 1.59 (2H, d, *J*=1.8 Hz), 1.47 (9H, s), 1.33 (3H, s), 1.21 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.1, 137.8, 115.0 (114.9), 93.6 (93.1), 79.9 (79.4), 66.8 (66.6), 57.2 (56.8), 32.6 (31.9), 30.5, 28.4, 27.5 (26.7), 24.5 (23.2). *m*/*z* (TOF MS ES$^+$) 278 ([M+Na]$^+$). Elemental analyses: C, 65.77%; H, 9.75%; N, 5.58%; $C_{14}H_{25}NO_3$ requires C, 65.85%; H, 9.87%; N, 5.49%.

*4.1.2. (S)-2-(tert-Butoxycarbonylamino)hex-5-enoic acid (**10**).* An aqueous solution of chromic acid (3 ml, 8 equiv) was added dropwise to a vigorously stirred solution of **9** (200 mg, 0.76 mmol) in acetone (8 ml) and stirring was continued for 2 h at room temperature. The reaction mixture was then partitioned between water (25 ml) and ether (25 ml). The organic layer was washed successively with water (3×20 ml), brine (20 ml) and then dried over $MgSO_4$. It was filtered and the filtrate was concentrated to leave the crude product as a yellowish oil, which on chromatography over silica using a mixture of petroleum ether/ethyl acetate (1:1) as eluent afforded the product **10** as a colourless oil (112 mg, 64%). $[\alpha]_D^{25}$ +17.4 (*c* 0.57 in $CHCl_3$). IR (neat): 3370, 2925, 1694, 1367, 1168 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.85–5.77 (1H, m), 5.16–5.00 (3H, m), 4.33 (1H, br s), 4.02–4.01 (1H, m), 2.23–2.14 (2H, m), 1.97 (1H, br s), 1.79–1.73 (1H, m), 1.45 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.3 (177.0), 156.0 (155.6), 136.8, 115.8, 80.2 (54.0), 53.0, 31.6, 29.4, 28.3. HRMS (TOF MS ES$^+$) calcd for $C_{11}H_{19}NO_4$ ([M+Na]$^+$) 252.1212, found 252.1210.

*4.1.3. (S)-Methyl 2-(tert-butoxycarbonylamino)hex-5-enoate (**11**).* Methyl iodide (0.08 ml, 1.3 mmol) was added dropwise to a stirred solution of **10** (100 mg, 0.43 mmol) in dry DMF (4 ml) at 0 °C under nitrogen atmosphere in the presence of anhydrous Cs_2CO_3 (275 mg, 0.84 mmol) and stirring continued for 12 h at room temperature. It was then diluted with water (25 ml) and extracted with ethyl acetate (2×25 ml). The combined organic layer was washed successively with water (2×25 ml) and brine (25 ml). The organic extract was then dried over anhydrous $MgSO_4$, filtered and the filtrate was concentrated in vacuo to leave a crude product, which was purified by column chromatography on silica gel using ethyl acetate in petroleum ether (1:9) solvent to provide the compound **11** as a liquid (80 mg, 75%). $[\alpha]_D^{25}$ +13.8 (*c* 0.98 in $CHCl_3$). IR (neat): 3370, 2979, 1744, 1716, 1367, 1164 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.82–5.75 (1H, m), 5.07–4.99 (3H, m), 4.33 (1H, d, *J*=4.8 Hz), 3.74 (3H, s), 2.14–2.09 (2H, m), 1.93–1.88 (1H, m), 1.76–1.67 (1H, m), 1.44 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.3, 155.3, 136.9, 115.6, 79.8, 52.9, 52.2, 31.9, 29.4, 28.2. *m*/*z* (TOF MS ES$^+$) 266 ([M+Na]$^+$). Elemental analyses: C, 59.13%; H, 8.50%; N, 5.89%; $C_{12}H_{21}NO_4$ requires C, 59.24%; H, 8.70%; N, 5.76%.

*4.1.4. 3-Benzyloxy-hex-5-ene (**14**).* Zn-dust (1.79 g, 27.4 mmol) followed by allyl bromide (2.2 ml, 26 mmol) were added to a cold (~10 °C) and well-stirred solution of propionaldehyde (1 ml, 13.7 mmol), in tetrahydrofuran (5 ml) and then a saturated aqueous solution of NH_4Cl (10 ml) was added dropwise over a period of 30 min. The reaction mixture was then stirred at ambient temperature for 5 h until the aldehyde was totally consumed. The mixture was then filtered and the precipitate was washed thoroughly with ether. The combined filtrate was then diluted with water (10 ml) and extracted with ether (2×20 ml). The combined organic layer was washed successively with HCl (5%, 10 ml), water (2×10 ml) and brine (10 ml). It was then dried ($MgSO_4$), filtered and the filtrate was reduced to ~2 ml and the resulting solution of the crude allyl alcohol **13** was cooled to 0 °C under nitrogen. NaH (672 mg, 28 mmol) was added portionwise to it and then benzyl bromide (1.7 ml, 14 mmol) was added dropwise over 15 min. The reaction mixture was stirred at the same temperature for 12 h. It was quenched with saturated NH_4Cl solution (10 ml) at 0 °C and then diluted with ether (1×25 ml). The organic phase was washed with water (20 ml) and brine (20 ml), and then dried over $MgSO_4$. It was then filtered and the filtrate was concentrated at reduced pressure to leave a crude product, which on chromatography over silica gel using ethyl acetate/hexane mixture (1:49) afforded the benzyl ether **14** as a colourless liquid (1.2 g, 45% over two steps). IR (neat): 2933, 1093, 1067, 735 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.36–7.25 (5H, m), 5.91–5.80 (1H, m), 5.11–5.04 (2H, m), 4.55 (1H, d, *J*=11.9 Hz), 4.51 (1H, d, *J*=12.0 Hz), 3.38 (1H, quin., *J*=6.0 Hz), 2.36–2.28 (2H, m), 1.60–1.53 (2H, m), 0.95 (3H, t, *J*=7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.9, 135.1, 128.3, 127.7, 127.4, 116.8, 79.8, 70.9, 37.9, 26.3, 9.6. *m*/*z* (TOF MS ES$^+$) 213 ([M+Na]$^+$). Elemental analyses: C, 82.27%; H, 9.69%. $C_{13}H_{18}O$ requires C, 82.06%; H, 9.53%.

*4.1.5. N-(Benzyloxy)hex-5-enamide (**16**).* *N*-Methylmorpholine (230 μl, 2.0 mmol) was dropwise added to a stirred solution of *O*-benzylhydroxylamine hydrochloride (160 mg, 1.0 mmol) in anhydrous CH_2Cl_2 (12 ml) at 0 °C under N_2 atmosphere. The resulting mixture was stirred for 10 min and then hexenoic acid **15** (115 mg, 1.0 mmol) and HOBt (135 mg, 1.0 mmol) were added sequentially and stirring was continued for another 15 min at the same temperature. EDC·HCl (230 mg, 1.2 mmol) was then added in one portion and the reaction mixture was stirred for 45 min more before being allowed to come to room temperature over 2 h. It was then diluted with CH_2Cl_2 (20 ml) and the combined organic solution was washed sequentially with saturated aqueous solution of $NaHCO_3$ (20 ml), HCl (3%, 20 ml), H_2O (25 ml) and brine (25 ml). It was then dried over $MgSO_4$, filtered and the filtrate was concentrated in vacuo to leave the crude product as a light yellow liquid, which was purified by column chromatography over silica gel using petroleum ether/ethyl acetate (6:4) as eluent to provide the product **16** as a colourless viscous liquid (206 mg, 94%). IR (neat): 3199, 3032, 2935, 1655, 1498, 1456 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.4 (1H, s), 7.44–7.38 (5H, m), 5.77–5.71 (1H, m), 5.00–4.96 (2H, m), 4.90 (2H, s), 2.07–2.05 (4H, m), 1.72 (2H, t, *J*=7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 137.8, 135.5, 129.1, 128.5, 128.4, 115.3, 78.0, 33.0, 32.3, 24.6. HRMS (TOF MS ES$^+$) calcd for $C_{13}H_{17}NO_2$ ([M+Na]$^+$) 242.1157, found 242.1157.

*4.1.6. (R)-2-((S)-1-(Benzyloxy)but-3-enyl)-1,4-dioxaspiro[4.5]decane (**18**).* NaH (60%, 306 mg, 7.7 mmol) was added portionwise to a solution of the compound **17** (810 mg, 3.8 mmol) in DMF (6 ml) at 0 °C during 10 min. Benzyl bromide (0.81 ml, 6.8 mmol) was then

added dropwise and the resulting mixture was stirred for 12 h. It was then slowly quenched with saturated aqueous NH_4Cl solution (10 ml) at 0 °C and then diluted with ether (2×50 ml). The combined organic phase was washed with water (2×25 ml) and brine (2×25 ml), dried over $MgSO_4$ and concentrated at reduced pressure to leave a residue, which was purified by chromatography over silica gel using ethyl acetate/hexane mixture (2:98) to afford **18** as colourless liquid (1.04 g, 91%). $[\alpha]_D^{25}$ +26.2 (*c* 0.92 in $CHCl_3$). IR (neat): 2935, 2862, 1449, 1164, 1101 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.33–7.25 (5H, m), 5.95–5.84 (1H, m), 5.16–5.08 (2H, m), 4.66 (1H, d, *J*=11.2 Hz), 4.58 (1H, d, *J*=11.2 Hz), 4.08 (1H, q, *J*=6 Hz), 4.03–4.01 (1H, m), 3.89 (1H, dd, *J*=6, 8 Hz), 3.59 (1H, q, *J*=5.2 Hz), 2.47–2.32 (2H, m), 1.62–1.55 (8H, m), 1.39 (2H, br s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.4, 134.3, 128.3, 127.8, 127.6, 117.5, 109.6, 79.0, 77.3, 72.5, 66.1, 36.3, 35.7, 34.9, 25.2, 24.0, 23.8. *m*/*z* (TOF MS ES^+) 325 ($[M+Na]^+$). Elemental analyses: C, 75.59%; H, 8.50%. $C_{19}H_{26}O_3$ requires C, 75.46%; H, 8.67%.

*4.1.7. (2R,3S)-3-(Benzyloxy)hex-5-ene-1,2-diol (**19**).* HCl (6 N, 10 ml) was added dropwise to a solution of the acetal **18** (1.0 g, 3.31 mmol) in THF (10 ml) at 0 °C while stirring and the resulting mixture was stirred for 3 h before being diluted with water (50 ml) and then carefully neutralized with $NaHCO_3$. It was then extracted with CH_2Cl_2 (2×50 ml) and the combined organic extract was washed successively with water (2×50 ml), brine (1×50 ml), and dried over $MgSO_4$. It was then filtered and the filtrate was concentrated in vacuo to leave a pale yellow mass, which was purified by chromatography over silica gel using ethyl acetate/hexane mixture (60:40) to provide **19** (583 mg, 79%) as a colourless liquid. $[\alpha]_D^{25}$ +31.9 (*c* 0.66 in $CHCl_3$). IR (neat): 3401, 2928, 1641, 1454, 1089, 1073 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.37–7.25 (5H, m), 5.92–5.82 (1H, m), 5.18–5.09 (2H, m), 4.68 (1H, d, *J*=11.2 Hz), 4.51 (1H, d, *J*=11.2 Hz), 3.79–3.70 (3H, m), 3.65 (1H, q, *J*=5.6 Hz), 2.50 (1H, br s), 2.47–2.43 (2H, m), 2.20 (1H, br s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.9, 134.2, 128.5, 127.9, 127.8, 117.8, 80.4, 72.5, 72.3, 63.3, 35.0. *m*/*z* (TOF MS ES^+) 245 ($[M+Na]^+$). Elemental analyses: C, 70.36%; H, 8.01%. $C_{13}H_{18}O_3$ requires C, 70.24%; H, 8.16%.

*4.1.8. (2R,3S)-3-(Benzyloxy)-1-(tert-butyldimethylsilyloxy)hex-5-en-2-ol (**20**).* Imidazole (244 mg, 3.58 mmol), 4-dimethylaminopyridine (29 mg, 0.23 mmol) and *tert*-butyldimethylsilyl chloride (197 mg, 1.30 mmol) were sequentially added to a stirred solution of the diol **19** (265 mg, 1.19 mmol) in anhydrous CH_2Cl_2 (5 ml) under nitrogen at room temperature. Stirring was continued for 8 h, and then the solution was diluted with ether (25 ml). The combined organic extract was washed with 1(N) HCl (1×20 ml), water (1×20 ml), brine (1×20 ml), and then dried over anhydrous $MgSO_4$. It was then filtered and the filtrate was concentrated in vacuo. The residue was purified by silica gel chromatography using a mixture of ethyl acetate/hexane (4:96) to yield the silyl ether **20** as a colourless liquid (342 mg, 84%). $[\alpha]_D^{25}$ +25.0 (*c* 2.33 in $CHCl_3$). IR (neat): 3470, 2929, 2858, 1254, 1096, 836 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.27–7.18 (5H, m), 5.89–5.80 (1H, m), 5.11–5.01 (2H, m), 4.57 (1H, d, *J*=11.6 Hz), 4.45 (1H, d, *J*=11.2 Hz) 3.70–3.66 (1H, m), 3.63–3.57 (2H, m), 3.44 (1H, dd, *J*=10.4, 6.0 Hz), 2.46–2.31 (3H, m), 0.83 (9H, s), −0.001 (6H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.4, 134.8, 128.4, 127.9, 127.7, 117.3, 78.8, 72.5, 72.1, 63.8, 34.7, 25.9, 18.3, −5.3. HRMS (TOF MS ES^+) calcd for $C_{19}H_{32}O_3Si$ ($[M+Na]^+$) 359.2018, found 359.2016.

*4.1.9. (2R,3S)-3-(Benzyloxy)-1-(tert-butyldimethylsilyloxy)hex-5-en-2-yl 4-methylbenzenesulfonate (**21**).* DMAP (ca. 19 mg) followed by tosyl chloride (295 mg, 1.54 mmol) was added to a stirred solution of the alcohol **20** (260 mg, 0.77 mmol) in pyridine (5 ml) and the resulting solution was stirred for 24 h at room temperature. It was then diluted with ether (25 ml), washed successively with 6(N) HCl (1×20 ml), water (1×25 ml) and brine (1×25 ml) and then dried over anhydrous $MgSO_4$. It was filtered and the filtrate was concentrated in vacuo to get a residue, which was purified by silica gel chromatography using a mixture of ethyl acetate/hexane (3:97) to yield the corresponding tosylate **21** as a colourless viscous liquid (325 mg, 86%). $[\alpha]_D^{25}$ −4.8 (*c* 3.57 in $CHCl_3$). IR (neat): 2857, 2929, 1363, 1189, 1177, 1097 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.79–7.77 (2H, d, *J*=8.4 Hz), 7.33–7.25 (7H, m), 5.80–5.69 (1H, m), 5.08–5.03 (2H, m), 4.59–4.46 (3H, m) 3.90–3.76 (3H, m), 2.40 (3H, s), 2.33–2.22 (2H, m), 0.84 (9H, s), −0.001 (6H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.6, 138.0, 134.2, 134.1, 129.7, 128.3, 128.0, 127.8, 127.7, 117.7, 83.2, 77.5, 72.7, 61.2,35.2, 25.9, 21.6, 18.3, −5.4, −5.5. HRMS (TOF MS ES^+) calcd for $C_{26}H_{38}O_5SSi$ ($[M+Na]^+$) 513.2107, found 513.2106.

*4.1.10. (S)-2-((S)-1-(Benzyloxy)but-3-enyl)oxirane (**22**).* A solution of *n*-tetrabutylammonium fluoride (346 mg, 1.32 mmol) in anhydrous THF (2 ml) was added in one portion to a cooled stirred solution of the silyl ether **21** (325 mg, 0.66 mmol) in anhydrous THF (8 ml) and stirring was continued for 1 h at room temperature. The reaction was quenched by adding a solution of NH_4Cl (200 mg in 20 ml water) with continuous stirring and then diluted with ether (25 ml). The combined organic extract was washed with brine (25 ml) and then dried over anhydrous $MgSO_4$. It was filtered and the filtrate was concentrated in vacuo to leave a crude mass, which was purified by silica gel chromatography using a mixture ethyl acetate/hexane mixture (2:98) to yield the corresponding epoxide **22** as a colourless liquid (100 mg, 74%). $[\alpha]_D^{25}$ −26.4 (*c* 0.47 in $CHCl_3$). IR (neat): 2926, 1641, 1454, 1094, 1071 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.35–7.25 (5H, m), 5.96–5.85(1H, m), 5.17–5.09 (2H, m), 4.64 (1H, d, *J*=12.0 Hz), 4.54 (1H, d, *J*=12.0 Hz), 3.36–3.31(1H, m), 2.98–2.95 (1H, m), 2.78 (1H, dd, *J*=4.0, 5.2 Hz), 2.72 (1H, dd, *J*=2.8, 5.2 Hz), 2.50–2.37 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.9, 133.4, 127.8, 127.1, 127.1, 116.9, 77.2, 71.6, 52.6, 45.1, 36.7. HRMS (TOF MS ES^+) calcd for $C_{13}H_{16}O_2$ ($[M+Na]^+$) 227.1048, found 227.1047.

4.1.11. General procedure for cross metathesis. Grubbs' second-generation catalyst **23** (14 mg, 0.016 mmol) was added to a stirred suspension of CuI (6 mg, 0.032 mmol) in a solution of the olefin **11** (80 mg, 0.328 mmol) and appropriate second olefin **14**/**16**/**22** (0.328 mmol) in dry DCM (6.0 ml) under argon atmosphere and the resulting mixture was stirred at room temperature for 15 min before being heated to reflux for 4 h. The reaction mixture was allowed to cool to room temperature, a few drops of DMSO was added and stirred for overnight. It was then concentrated in vacuo and the residue was purified by column chromatography over silica gel using appropriate mixture of ethyl acetate in petroleum ether (15:85) to provide the coupled product.

*4.1.12. (S)-Methyl 8-(benzyloxy)-2-(tert-butoxycarbonylamino)dec-5-enoate (**24**).* Eluent: ethyl acetate in petroleum ether (15:85). Yield: 72 mg, 54%. $[\alpha]_D^{25}$ +14.8 (*c* 0.88 in $CHCl_3$). IR (neat): 3369, 2931, 1745, 1717, 1366, 1168 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.34–7.24 (5.13H, m), 7.28–7.24 (2.63H, m), 5.51–5.37 (1.54H, m), 4.99 (1H, m), 4.55–4.47 (2.59H, m), 4.35–4.29 (1.18H, m), 3.74–3.71 (3.78H, m), 3.36–3.30 (1.18H, m), 2.28–2.24 (2.76H, m), 2.13–2.03 (1.84H, m), 1.88–1.83 (1H, m), 1.70–1.64 (1.03H, m), 1.56–1.51 (5.3H, m), 1.44–1.41 (12.2H, overlapping singlets), 0.94–0.87 (4H, t, *J*=7.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.3, 155.3, 139.0, 130.7, 128.3, 127.8, 127.7, 127.4, 80.0, 79.8, 70.8, 53.1, 52.2, 36.5, 35.7, 32.5, 32.4, 31.3, 28.5, 28.3, 26.5, 26.3, 23.3, 9.9, 9.7. HRMS (TOF MS ES^+) calcd for $C_{23}H_{35}NO_5$ ($[M+Na]^+$) 428.2413, found 428.2386.

*4.1.13. (S)-Methyl 2-(tert-butoxycarbonylamino)-10-(benzyloxyamino)-10-oxodec-5-enoate (**27**).* Eluent: ethyl acetate/petroleum ether (4:6). Yield: 88 mg (62%). $[\alpha]_D^{25}$ +10.1 (*c* 1.85 in $CHCl_3$). IR

(neat): 3262, 2977, 2931, 1742, 1691, 1517, 1454, 1367 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 10.94 (1H, s), 7.42–7.32 (5H, m), 7.26 (1H, d, J=8.0 Hz), 5.36–5.34 (2H, m), 4.77 (2H, s), 4.27 (1H, s), 3.61–3.60 (1H, m), 3.49 (3H, s), 1.98–1.88 (6H, m), 1.64–1.62 (2H, m), 1.52 (2H, t, J=7.2 Hz), 1.37 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.5, 170.8, 155.5, 135.5, 131.5, 129.4, 129.1, 128.5, 80.2, 78.0, 52.3, 52.1, 32.2, 31.6, 31.3, 28.3, 28.1, 24.6. HRMS (TOF MS ES$^+$) calcd for $C_{23}H_{34}N_2O_6$ ([M+Na]$^+$) 457.2315, found 457.2311.

*4.1.14. (2S,8S)-Methyl 8-(benzyloxy)-2-(tert-butoxycarbonylamino)-8-((S)-oxiran-2-yl)oct-5-enoate (**29**).* Eluent: ethyl acetate/petroleum ether (15:85). Yield: 71 mg (52%). $[\alpha]_D^{25}$ −7.4 (c 1.01 in $CHCl_3$). IR (neat): 3362, 2929, 1745, 1716, 1366, 1166 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.35–7.26 (7.4H, m, including peak for $CHCl_3$), 5.60–5.39 (2.43H, m), 5.0 (1H, br s), 4.82–4.79 (0.85H, m), 4.65–4.52 (1.85H, m), 4.30 (1H, br s), 3.73–3.72 (3.8H, overlapping singlets), 3.30–3.26 (0.34H, m), 3.10–2.94 (2H, m), 2.78–2.70 (1.64H, m), 2.52–2.49 (1.2H, m), 2.45–2.27 (2.73H, m), 2.18–2.06 (2H, m), 1.87–1.84 (1H, m), 1.44–1.43 (12H, overlapping singlets). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.3, 155.3, 138.5, 131.4, 128.3, 128.3, 127.7, 127.6, 127.5, 126.7, 80.2, 79.9, 77.9, 72.1, 71.6, 54.6, 53.1, 53.0, 52.2, 45.6, 43.4, 38.4, 36.0, 35.8, 32.5, 30.4, 28.5, 28.3, 23.4. HRMS (TOF MS ES$^+$) calcd for $C_{23}H_{33}NO_6$ ([M+Na]$^+$) 442.2206, found 442.2207.

4.1.15. General procedure for hydrogenation. Appropriate CM product (0.14 mmol) was taken in a mixture of THF and MeOH (1:1, 4 ml) containing 1 drop of TFA. Then $Pd(OH)_2$ (10 mg) was added and the solution was degassed several times. Hydrogen gas was let in and the resulting heterogeneous mixture was vigorously stirred at atmospheric pressure for 2 h. It was filtered through Celite®, the filter cake was washed with methanol (5 ml) and the combined filtrate was concentrated in vacuo. The crude product thus obtained was purified by chromatography over silica gel using appropriate mixture of ethyl acetate and petroleum ether as eluent.

*4.1.16. (S)-Methyl 2-(tert-butoxycarbonylamino)-8-hydroxydecanoate (**25**).* Eluent: ethyl acetate and petroleum ether (1:3). Yield: 38 mg (85%). IR (neat): 3371, 2854, 2925, 1740, 1718, 1366, 1164 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.01 (1H, s), 4.30 (1H, s), 3.73 (3.7H, s), 3.51 (1.3H, s), 1.79 (1H, br s), 1.44–1.25 (27H, m), 0.94 (3.64H, t, J=7.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.5, 155.4, 79.8, 73.1, 73.07, 73.0, 53.3, 52.1, 36.7, 36.5, 32.7, 32.6, 30.1, 29.15, 29.1, 28.3, 25.4, 25.2, 9.9, 9.8. HRMS (TOF MS ES$^+$) calcd for $C_{16}H_{31}NO_5$ ([M+Na]$^+$) 318.2280, found 318.2248.

*4.1.17. (S)-Methyl 2-(tert-butoxycarbonylamino)-10-(hydroxyamino)-10-oxodecanoate (**28**).* Eluent: ethyl acetate/petroleum ether (1:1). Yield: 42 mg (88%). $[\alpha]_D^{25}$ +5.4 (c 0.7 in $CHCl_3$). IR (neat): 3339, 2927, 2856, 1741, 1712, 1667, 1519 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.98 (1H, d, J=6.8 Hz), 4.22 (1H, br s), 3.66 (3H, s), 2.07 (2H, br s), 1.68 (2H, br s), 1.56–1.49 (7H, m), 1.36 (9H, s), 1.29–1.15 (7H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.6, 171.6, 155.6, 80.0, 53.3, 52.3, 32.63, 29.7, 28.6, 28.5, 28.3, 25.0. HRMS (TOF MS ES$^+$) calcd for $C_{16}H_{30}N_2O_6$ ([M+K]$^+$) 385.1741, found 385.1751.

4.1.18. General procedure for Dess–Martin oxidation. Dess–Martin periodinane (67 mg, 0.15 mmol) was added in one portion to a solution of the appropriate secondary alcohol (0.12 mmol) in CH_2Cl_2 (1 ml) and the reaction mixture was stirred at room temperature for 1 h. It was then diluted with CH_2Cl_2 (10 ml) and then quenched with saturated aqueous solution of $Na_2S_2O_3$ (2 ml) and saturated aqueous solution of $NaHCO_3$ (2 ml). The aqueous phase was extracted with CH_2Cl_2 (10 ml). The combined organic extract was dried over anhydrous $MgSO_4$, filtered and the filtrate was concentrated in vacuo. The crude product thus obtained was purified by chromatography over silica gel using appropriate mixture of ethyl acetate in petroleum ether solvent to give the desired α-amino acid.

*4.1.19. (S)-Methyl 2-(tert-butoxycarbonylamino)-8-oxodecanoate (**26**).* Eluent: ethyl acetate in petroleum ether (2:8). Yield: 30 mg (78%). $[\alpha]_D^{25}$ +8.5 (c 0.56 in $CHCl_3$). IR (neat): 3374, 2977, 1744, 1717, 1366, 1165 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.01 (1H, s), 4.29 (1H, d, J=5.2 Hz), 3.75 (3H, s), 2.43–2.37 (4H, m), 1.78 (1H, br s), 1.59–1.55 (3H, m), 1.44 (9H, s), 1.36–1.25 (4H, m), 1.06 (3H, t, J=7.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 211.6, 173.4, 155.3, 79.8, 53.3, 52.2, 42.1, 35.9, 32.6, 28.7, 28.3, 25.0, 23.5, 7.8. HRMS (TOF MS ES$^+$) calcd for $C_{16}H_{29}NO_5$ ([M+Na]$^+$) 338.1943, found 338.1951.

*4.1.20. (S)-Methyl 2-(tert-butoxycarbonylamino)-8-((S)-oxiran-2-yl)-8-oxooctanoate (**31**).* Yield: 28 mg (62% over two steps). $[\alpha]_D^{25}$ +36.2 (c 0.71 in $CHCl_3$). IR (neat): 3434, 2929, 1741, 1713, 1367, 1164 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.01 (1H, br s), 4.29 (1H, s), 3.73 (3H, s), 3.43 (1H, dd, J=2.4, 4.4 Hz), 3.01 (1H, t, J=5.2 Hz), 2.87 (1H, dd, J=2.4, 5.6 Hz), 2.46–2.41 (1H, m), 2.32–2.29 (1H, m), 1.79–1.77 (2H, m), 1.66–1.53 (4H, m), 1.44 (9H, s), 1.39–1.25 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.7, 173.4, 155.4, 79.9, 53.4, 53.3, 52.3, 46.1, 36.3, 32.5, 28.6, 28.3, 25.0, 22.5. HRMS (TOF MS ES$^+$) calcd for $C_{16}H_{27}NO_6$ ([M+Na]$^+$) 352.1736, found 352.1738.

Acknowledgements

We are thankful to Department of Science and Technology, New Delhi, for funds (Grant No. SR/S1/OC-92/2012) and Council of Scientific and Industrial Research (Grant No. 02/0164/13/EMR-II), New Delhi, for fellowships. Partial financial supports from DST-PURSE programme, and University of Kalyani is also gratefully acknowledged.

Supplementary data

^1H NMR and ^{13}C NMR spectra of all new compounds are provided. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.07.045.

References and notes

1. (a) Bolden, J. E.; Peart, M. J.; Johnstone, R. W. *Nat. Rev. Drug Discovery* **2006**, *5*, 769; (b) Newkirk, T. L.; Bowers, A. A.; Williams, R. M. *Nat. Prod. Rep.* **2009**, *26*, 1293.
2. Singh, S.; Zink, D.; Polishook, J.; Dombrowski, A.; Darkin-Rattray, S.; Schmatz, D.; Goetz, M. *Tetrahedron Lett.* **1996**, *37*, 8077.
3. Gu, W.; Cueto, M.; Jensen, P.; Fenical, W.; Silverman, R. *Tetrahedron* **2007**, *63*, 6535.
4. Taunton, J.; Hassig, C.; Schreiber, S. *Science* **1996**, *272*, 408.
5. Pringle, R. *Plant Physiol.* **1970**, *46*, 45.
6. (a) Ilies, M.; Dowling, D. P.; Lombardi, P. M.; Christianson, D. W. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 5854; (b) Dandapani, S.; Lowe, J. T.; Comer, E.; Marcaurelle, L. A. *J. Org. Chem.* **2011**, *76*, 8042; (c) Olsen, C. A.; Reza Ghadiri, M. *J. Med. Chem.* **2009**, *52*, 7836; (d) Bieliauskas, A. V.; Pflum, M. K. *Chem. Soc. Rev.* **2008**, *37*, 1402; (e) Cole, P. A. *Nat. Chem. Biol.* **2008**, *4*, 590.
7. Komatsu, Y.; Tomizaki, K.-Y.; Tsukamoto, M.; Kato, T.; Nishino, N.; Sato, S.; Yamori, T.; Tsuruo, T.; Furumai, R.; Yoshida, M.; Horinouchi, S.; Hayashi, H. *Cancer Res.* **2001**, *61*, 4459.
8. Pazin, M. J.; Kadonaga, J. T. *Cell* **1997**, *89*, 325.
9. (a) Schreiber, S. *ACS Med. Chem. Lett.* **2012**, *3*, 112; (b) Vickers, C. J.; Olsen, C. A.; Leman, L. J.; Ghadiri, M. R. *ACS Med. Chem. Lett.* **2012**, *3*, 505; (c) Oyelere, A. K. *Curr. Top. Med. Chem.* **2010**, *10*, 1359; (d) Quirin, C.; Kazmaier, U. *Eur. J. Org. Chem.* **2009**, 371; (e) Wen, S.; Carey, K.; Nakao, Y.; Fusetani, N.; Packham, G.; Ganesan, A. *Org. Lett.* **2007**, *9*, 1105; (f) Xie, W.; Zou, B.; Pei, D.; Ma, D. *Org. Lett.* **2005**, *7*, 2775; (g) Rodriguez, M.; Terracciano, S.; Cini, E.; Settembrini, G.; Bruno, I.; Bifulco, G.; Taddei, M.; Gomez-Paloma, L. *Angew. Chem., Int. Ed.* **2006**, *45*, 423; (h) Yurek-George, A.; Habens, F.; Brimmmell, M.; Packham, G.; Ganessan, A. *J. Am. Chem. Soc.* **2004**, *126*, 1030; (i) Singh, S.; Zink, D.; Liesch, J.; Mosley, R.; Dombrowski, A.; Bills, G.; Darkin-rattray, S.; Schmatz, S.; Goetz, M. *J. Org. Chem.* **2002**, *67*, 815; (j) Taunton, J.; Collins, J. L.; Schreiber, S. *J. Am. Chem. Soc.* **1996**, *118*, 10412.
10. (a) Rodriguez, M.; Bruno, I.; Cini, E.; Marchett, M.; Taddei, M.; Gomez-Paloma, L. *J. Org. Chem.* **2006**, *71*, 103; (b) Izzo, N.; Maulucci, N.; Bifulco, G.; De Riccardis, F. *Angew. Chem., Int. Ed.* **2006**, *45*, 7557; (c) Baldwin, J. E.; Adlington, R. M.;

Godfrey, C. R. A.; Patel, V. K. *Tetrahedron* **1993**, *49*, 7837; (d) Ikegami, S.; Uchiyama, H.; Hayama, T.; Katsuki, T.; Yamaguchi, M. *Tetrahedron* **1988**, *44*, 5333; (e) Schmidt, U.; Leibernecht, A.; Griesser, H.; Bartkowiak, F. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 318; (f) Rich, D. H.; Singh, J.; Gardner, J. H. *J. Org. Chem.* **1983**, *48*, 432.

11. *Metathesis in Natural Product Synthesis*; Arseniyadis, J. S., Meyer, C., Eds.; Wiley-VCH: Weinheim, Germany, 2010; p 287.
12. Chattopadhyay, S. K.; Sarkar, K.; Karmakar, S. *Synlett* **2005**, 2083 and the references cited therein.
13. Biswas, T.; Biswas, T.; Chattopadhyay, S. K. *Tetrahedron: Asymmetry* **2010**, *21*, 232.
14. Chatterjee, A. K.; Choi, T. L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.
15. For some assorted reports on cross metathesis-mediated synthesis of α-amino acids, see: (a) Enholm, J. E.; Low, T.; Cooper, D.; Ghivirija, I. *Tetrahedron* **2012**, *68*, 6920; (b) Tosatti, P.; Campbell, A. J.; House, D.; Nelson, A.; Marsden, S. P. *J. Org. Chem.* **2011**, *76*, 5495; (c) Drummond, L. J.; Sutherland, A. *Tetrahedron* **2010**, *66*, 5349; (d) Fustero, S.; Sánchez-Roselló, M.; Aceña, J. L.; Fernández, B.; Asensio, A.; Sanz-Cervera, J. F.; Del Pozo, C. *J. Org. Chem.* **2009**, *74*, 3413; (e) Enholm, E.; Low, T. *J. Org. Chem.* **2006**, *71*, 2272; (f) Elaridi, J.; Patel, J.; Jackson, W. R.; Robinson, A. J. *J. Org. Chem.* **2006**, *71*, 7538; (g) Chowdhury, A. R.; Boons, G.-J. *Tetrahedron Lett.* **2005**, *46*, 1675; (h) Dondoni, A.; Giovannini, P. P.; Perrone, D. *J. Org. Chem.* **2005**, *70*, 5508; (i) Boyle, T. P.; Bremner, J. B.; Coates, J. A.; Keller, P. A.; Pyne, S. G. *Tetrahedron* **2005**, *61*, 7271; (j) Biswas, K.; Coltart, D. M.; Danishefsky, S. J. *Tetrahedron Lett.* **2002**, *43*, 6107; (k) Biagini, S. C. G.; Gibson, S. E.; Keen, S. P. *J. Chem. Soc.; Perkin Trans. 1* **1998**, 2495.
16. Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100.
17. Roy, S.; Spilling, C. D. *Org. Lett.* **2010**, *12*, 5326.