Tetrahedron 69 (2013) 3565–3570

Contents lists available at SciVerse ScienceDirect

Tetrahedron

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

An efficient synthesis of L-3,4,5-trioxygenated phenylalanine compounds from L-tyrosine

Ruijiao Chen [a,†], Hao Liu [a,†], Xiubing Liu [a], Xiaochuan Chen [a,b,*]

[a] Key Laboratory of Green Chemistry & Technology of Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, PR China
[b] State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, PR China

ARTICLE INFO

Article history:
Received 10 December 2012
Received in revised form 12 February 2013
Accepted 22 February 2013
Available online 27 February 2013

Keywords:
Trioxygenated phenylalanine
L-Tyrosine
Asymmetric synthesis
Aryl dilithium
Bis-phenol

ABSTRACT

A new strategy for the synthesis of L-3,4,5-trioxygenated phenylalanine derivatives from L-tyrosine is developed for the first time. The approach, featuring the transformation of aryl diiodide to bis-phenol via a one-pot procedure including lithiation, boronation, and oxidation, is highly practical. By this robust protocol, *N*-protected L-3,5-bis(*tert*-butyldimethylsilyloxy)-4-methoxy-phenylalanine and L-3,4,5-trimethoxy-phenylalanine derivatives were obtained from L-tyrosine in 9 steps with 36–40% overall yields.

1. Introduction

L-3,4,5-Trioxygenated phenylalanines **1** are an important class of nonproteinogenic amino acids, which are frequently found in biologically active molecules as privileged structural fragments. For example (Fig. 1), TMC-2 compounds, produced by *Aspergillus oryzae* A374, are potent dipeptidyl peptidase IV inhibitors with high selectivity.[1] Natural bicyclic hexapeptide RA-XVIII (**3**) and the dimmer show a strong antitumor activity.[2] As a novel series of proteasome inhibitors, peptide **4** and their derivatives are opening a potential new approach in cancer therapy.[3] The tunichromes, a kind of reducing blood pigments from Sea Squirts, harbored in cells that take part in a variety of physiological responses.[4] Moreover, protected L-3,4,5-trioxygenated phenylalanine **6** and its corresponding aldehyde derivative **7** (Fig. 2) are key coupling partners in the asymmetric syntheses of marine tetrahydroisoquinoline alkaloids and analogues, such as ecteinascidin 743 (Et 743, **8**), phthalascidin 650 (Pt 650, **9**), and saframycin A (**10**).[5] These alkaloids possess remarkable antitumor and antimicrobial activity:[6] Et 743 is approved by the European Commission as an anticancer agent for the patient with advanced soft-tissue sarcomas.[7] Pt 650, a structurally simplified synthetic analogue of Et 743, was found to display a comparable antitumor activity to Et 743 and may be a more economical therapeutic agent.[5b,8]

Therefore the development of methods for the synthesis of L-3,4,5-trioxygenated phenylalanine compounds has attracted the attention of organic chemists. In 1996, Corey et al. described the first approach to this kind of L-amino acid derivatives via a chiral rhodium-catalyzed asymmetric hydrogenation of benzylic enamine as key

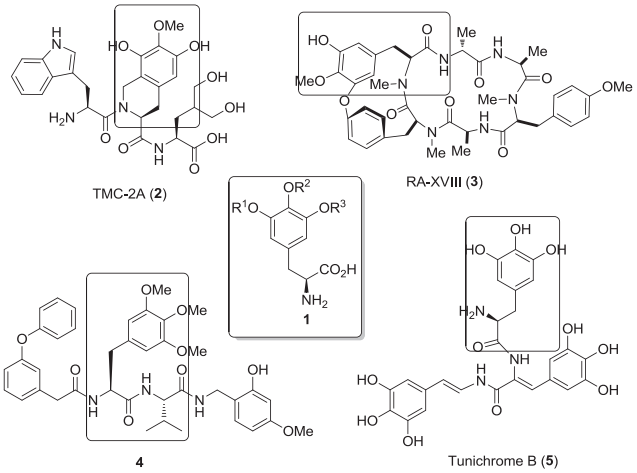


Fig. 1. L-3,4,5-Trioxygenated phenylalanines and representative related bioactive compounds.

* Corresponding author. Tel.: +86 28 85412095; fax: +86 28 85413712; e-mail address: chenxc@scu.edu.cn (X. Chen).
† These individuals contributed equally to this work.

0040-4020/$ – see front matter
http://dx.doi.org/10.1016/j.tet.2013.02.079

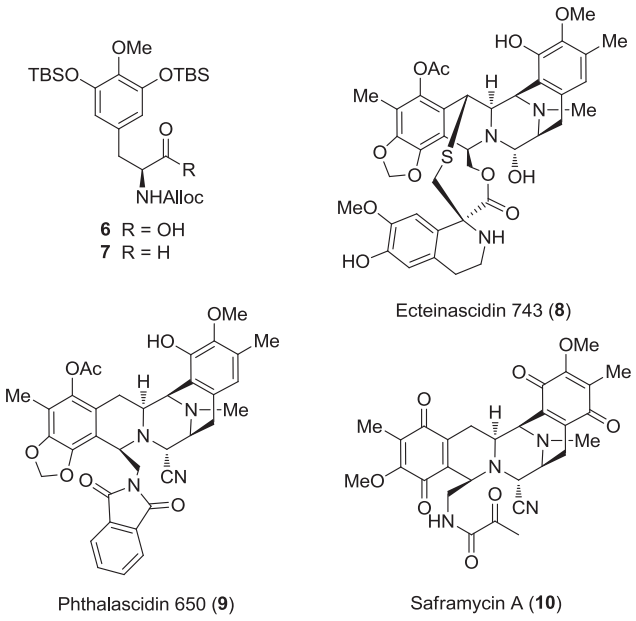
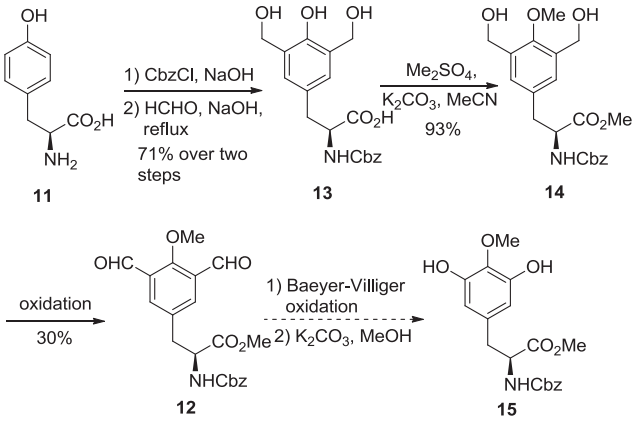


Fig. 2. Synthetic segments for several tetrahydroisoquinoline alkaloids.

step, by which **6** was synthesized in 10 steps from methyl 3,5-dihydroxy-4-methoxybenzoate.[5a] Jackson and co-workers synthesized L-3,4,5-trimethoxy-phenylalanine ester derivative by a palladium catalyzed coupling reaction between serine-derived organozinc reagent and 3,4,5-trimethoxyiodobenzene.[9] Laumen et al. prepared *N*-acetyl protected L-3,4,5-trimethoxy-phenylalanine by way of enzymatic resolution hydrolysis of the corresponding racemic amino acid esters.[10] Although these elegant strategies for the enantioselective synthesis of L-3,4,5-trioxygenated phenylalanine compounds have been developed successfully, exploitation of new synthetic route with lower cost and simpler procedure is still very significant. As a cheap natural amino acid, L-tyrosine (**11**), was employed to synthesize nonproteinogenic amino acids like L-3-hydroxy-4-methoxy-5-methylphenylalanine and phenylalanol by us[11] and other groups.[12] However, to the best of our knowledge, the synthesis of L-3,4,5-trioxygenated phenylalanine compounds from L-tyrosine has not been described in the literature. Herein we report the concise transformation of L-tyrosine to these unnatural amino acid derivatives.

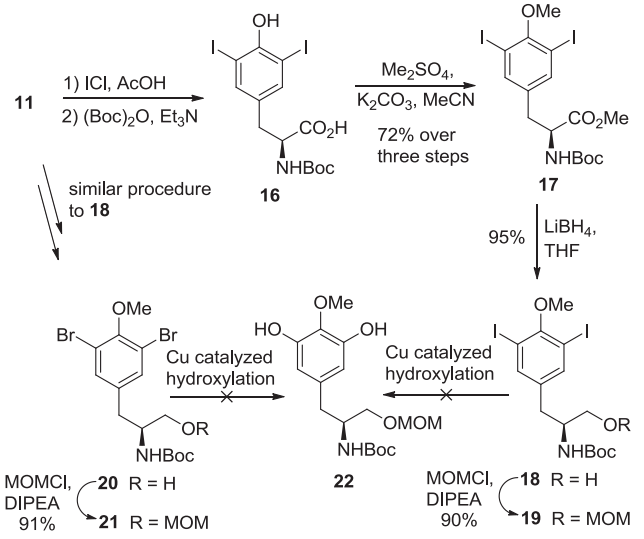
2. Results and discussion

Our initially attempted strategy was based on key Baeyer–Villiger oxidation of the substituted isophthalaldehyde derivative **12** (Scheme 1). *N*-protection of L-tyrosine as Cbz group followed by a base-catalyzed phenolic aldol reaction with excessive formaldehyde furnished the known bishydroxymethylated compound **13**[13] in 71% yield. Esterification of the carboxylic acid and etherification of the phenol proceeded in one-pot by treatment of **13** with Me_2SO_4 to give **14**. Oxidation of diol **14** to the corresponding dicarbaldehyde **12** was then investigated. However, the substituted isophthalaldehyde **12** was obtained at most in 30% yield under the attempted conditions including Dess–Martin periodinane, IBX, PCC, MnO_2, and Swern oxidation protocols,[14] even though diol **14** was consumed thoroughly. Furthermore, the subsequent conversion of **12** to bis-phenol **15** by a sequence involving Baeyer–Villiger oxidation and hydrolysis of formyl group was also disappointed. Treatment of **12** with various Baeyer–Villiger oxidation conditions[15] always lead to a complex mixture, which is stirred in aqueous methanol in the presence of K_2CO_3 to just yield a trace amount of the desired **15**. Because of the poor yield in the last stage this short route lost its value in practical synthesis.



Scheme 1. The initial strategy on the synthesis of **15** via a key Baeyer–Villiger oxidation of **12**.

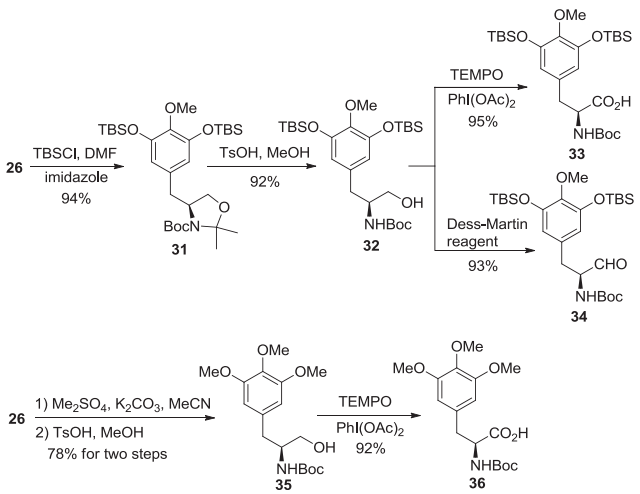
Intrigued by the reported methods on transformation of aryl halides to the phenols via a copper-mediated hydroxylation process,[16] we intended to utilize aryl dihalide intermediates to synthesize L-3,4,5-trioxygenated phenylalanine compounds (Scheme 2). Iodination of L-tyrosine with ICl[17] followed by protection of amino group smoothly gave L-*N*-Boc-3,5-diiodo-tyrosine **16**, which was subjected to the esterification and the etherification in one-pot leading to **17** in 72% overall yield for three steps. Methyl ester **17** also could be obtained from L-tyrosine in four steps with 48% overall yield according to Sanda's procedure.[18] The methyl ester group in **17** was reduced with lithium borohydride to provide alcohol **18**. Protection of hydroxyl group as MOM ether gave **19**. Similarly, 3,5-dibromo analogue **21** also prepared from **11** or the known L-3,5-dibromo-tyrosine[19] by the same procedure. According to literature, copper-catalyzed hydroxylation of **19** and **21** was next attempted. Unfortunately, the reaction conditions (refluxing in aqueous hydroxide solution) are too harsh for the sensitive substrates, such as **19** and **21**. *t*-Butyloxy carbomate (Boc) as amine protecting group, which is stable to usual alkalic conditions, was cleaved in the reaction under these conditions. Only small amount of monohydroxylated product with free amino group was detected, and di-hydroxylated compound **22** was not produced.



Scheme 2. The preparation of dihalides **19** and **21** from L-tyrosine.

Thus, we adopted an alternative protocol for the transformation of aryl halides to phenols by oxidation of the formed borate intermediate,[20] although dihalide substrates employed in this transformation are rare and simple.[21] The one-pot procedure involved three reaction stage including lithiation, boronation, and oxidation at two positions on the aryl ring. The investigation results showed that diiodide **19** was more easier converted to the aryl dilithium species than dibromide **21** at lithiation stage (Scheme 3). When the dibromide substrate **21** was applied, considerable material still remained in aryl monolithiation stage in the metalation even the *n*-butyllithium was improved to 5 equiv. After treatment of **19** with 3.2 equiv *n*-butyllithium, the iodine atoms could be exchanged thoroughly to produce the resultant aryl dilithium. However, the subsequent reaction of the aryl dilithium with trimethyl bromate proceeded so difficultly that the desirable bis-phenol **22** was obtained as a minor product only in 18% yield from **19** together with mono-phenol compound **23** as major product (53% yield) after oxidation. Presumably, the lithiation of the acidic amide NH group may disturb the boronation. To avoid the above situation, protection of the vicinal O–H and CON–H functionalities in **18** and **20** as oxazolidine ring with 2,2-dimethoxypropane (2,2-DMP) furnished **25** and **29**, respectively. To our delight, following the similar procedure the desired bis-phenol **26** was obtained from diiodide **25** in 80% yield along with a small amount of inseparable monohydroxylated mixture **27** and **28**, the ratio of which is judged by integration of the peaks in ^{1}H NMR spectrum. In contrast, when dibromide **29** is recruited as material to prepare **26**, the result is still unsatisfactory because the formation of the same dianion from **29** is much harder than from **25**.

With bis-phenol **26** in hand, the subsequent transformation becomes easy to achieve (Scheme 4). Protection of the two phenol groups in **26** with TBSCl gave silyl ether **31**. Selective hydrolysis of oxazolidine in the presence of a catalytic amount of TsOH furnished the desired alcohol **32**. Oxidation of primary hydroxy to carboxylic acid using TEMPO (0.2 equiv) and [bis(acetoxy)-iodo]benzene (BAIB) as co-oxidant[22] proceeded smoothly to afford the desired amino acid **33** in 95% yield. On the other hand, **32** was converted *N*-protected amino aldehyde **34** by Dess–Martin periodinane or Swern oxidation protocol with high yield. O-Methylation of bis-phenol **26** then followed by the similar procedures afforded another useful trioxygenated phenylalanine derivative **36**.



Scheme 4. Conversion of bis-phenol **26** to L-3,4,5-trioxygenated phenylalanine derivative **33**, **34**, and **36**.

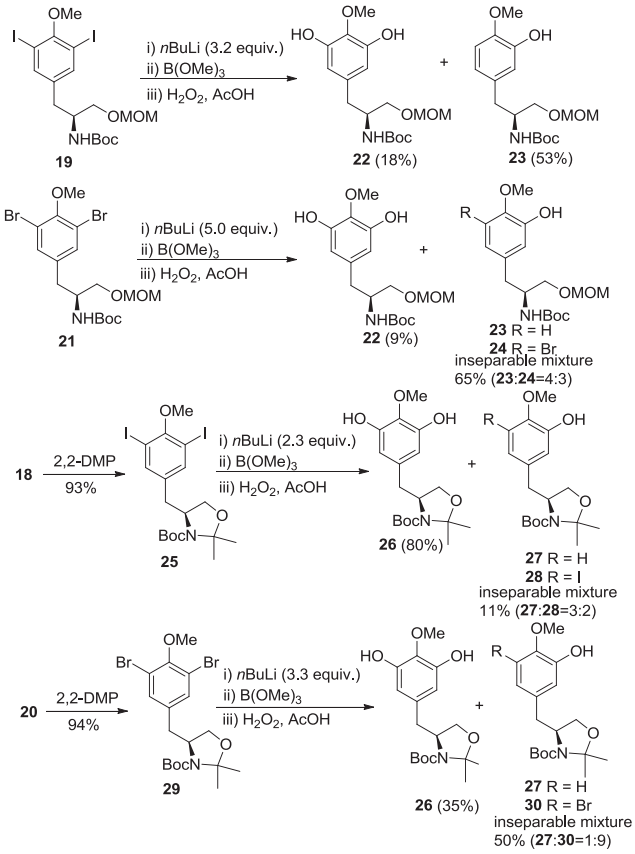
3. Conclusions

In summary, we developed a new approach to the synthesis of protected L-3,4,5-trioxygenated phenylalanine derivatives from commercial and cheap L-tyrosine. Bishydroxylation of the diiodide, such as **25** was employed as a key step. Through this approach, three L-3,4,5-trioxygenated phenylalanine derivatives **33**, **34**, and **36** were obtained in nine steps with 36–40% overall yield. Our approach has several advantages: (1) Reagents and materials, which are expensive or need additionally be prepared are seldom involved. (2) High yields are achieved in the whole synthesis. (3) The employed reactions are easy to operate and be scaled up. (4) It is conveniently extended to the synthesis of other L-3,4,5-trioxygenated phenylalanine derivatives by selectively manipulating the hydroxyl-protective groups on the phenols. The robust preparation procedure of L-3,4,5-trioxygenated phenylalanine derivatives would greatly improve the ease of synthesis and the overall yield of many structurally related bioactive compounds.

4. Experimental

4.1. General

Solvents for reaction were distilled prior to use: Ether and tetrahydrofuran were distilled from Na/benzophenone, CH_2Cl_2, anhydrous CH_3CN from CaH_2. All reagents were obtained from commercial suppliers unless otherwise stated. IR spectra were recorded on a commercial spectrophotometer. Optical rotations were reported as follows: $[\alpha]_D^T$ (*c* *g*/100 mL, in solvent). ^{1}H NMR spectra were recorded on commercial instruments (400 or 600 MHz) with TMS as the internal standard. Data are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, m=multiplet, br=broad), coupling constants (Hertz),



Scheme 3. Investigation on the bishydroxylation of several aryl dihalides by oxidation of the borate intermediate.

integration. ^{13}C NMR data were collected on commercial instruments (100 or 150 MHz) with complete proton decoupling. Chemical shifts are reported in parts per million from the tetramethylsilane with the solvent resonance as internal standard. HRMS spectra were recorded using a commercial apparatus and methanol or Dichloromethane was used to dissolve the sample.

4.2. (*S*)-Methyl-2-(*tert*-butoxycarbonylamino)-3-(3,5-diiodo-4-methoxyphenyl)propanoate 17

L-Tyrosine **11** (5.14 g, 28.4 mmol) was dissolved in 73 mL of glacial AcOH and heated to 40 °C. Then 3.2 mL of ICl in 23 mL of glacial AcOH was added dropwise to the reaction. The mixture was heated at 80 °C for 8 h. Then the solvent was evaporated and the residue was dissolved in MeOH/H_2O (2:1, 87 mL), and $NaHCO_3$ (8.3 g, 99.3 mmol), Boc_2O (7.3 mL, 34.1 mmol) were added. The resulting mixture was stirred overnight at room temperature. The solvent was evaporated and the residue was diluted with H_2O (60 mL), extracted with ethyl acetate (3×80 mL). The combined organic layer was dried with Na_2SO_4, filtered, and the solvent evaporated in vacuo. The crude was taken up in dry CH_3CN (142 mL) were added $(CH_3)_2SO_4$ (8.1 mL, 85.2 mmol) and anhydrous K_2CO_3 (11.8 g, 85.2 mmol), and the resulting mixture was stirred at 60 °C for 5 h. The solvent removed in vacuo, and the water (150 mL) was added. The mixture was extracted with ethyl acetate (3×100 mL). The combined organic layer was dried with Na_2SO_4 and concentrated. This crude product was purified over silica gel column chromatography to give the compound **17** as a pale yellow powder (11.5 g, 72% over three steps). Mp 73–75 °C, $[\alpha]_D^{26}$ +71 (*c* 1.1, in $CHCl_3$); IR(neat) ν_{max}: 3370, 2975, 1712, 1504, 1462, 1362, 1250, 1166, 1057, 996, 706 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.47 (s, 2H), 5.19 (d, *J*=8 Hz, 1H), 4.42 (m, 1H), 3.74 (s, 3H), 3.67 (s, 3H), 2.98 (dd, *J*=5.4, 13.8 Hz, 1H), 2.81 (dd, *J*=6.7, 13.7 Hz, 1H), 1.35 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 171.6, 157.6, 154.8, 140.4, 136.2, 90.3, 79.9, 60.5, 54.1, 52.4, 36.3, 28.2; HRMS (ESI^+): *m*/*z* $[M+Na]^+$ calcd for $C_{16}H_{21}I_2NO_5Na$: 583.9407; found: 583.9411.

4.3. (*S*)-*tert*-Butyl-1-(3,5-diiodo-4-methoxyphenyl)-3-hydroxypropan-2-ylcarbamate 18

To a solution of the compound **17** (8.3 g, 14.8 mmol) in anhydrous THF (74 mL), and $LiBH_4$ (11.1 mL, 22.2 mmol) was added under argon atmosphere. The resulting mixture was stirred overnight at rt, and methanol (1 mL)was added. Then the solvent was evaporated and the residue was diluted with H_2O (50 mL), extracted with ethyl acetate (3×30 mL), and dried (Na_2SO_4). After concentration and column chromatography, the amino alcohol **18** (7.50 g, 95%) was isolated as a white gel; $[\alpha]_D^{26}$ −2 (*c* 1.0, in $CHCl_3$); IR (neat) ν_{max}: 3345, 2974, 2933, 1686, 1528, 1462, 1366, 1250, 1168, 999, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.62 (s, 2H), 4.88 (d, *J*=5.5 Hz, 1H), 3.82 (s, 3H), 3.75 (m, 1H), 3.64 (m, 1H), 3.54 (m, 1H), 2.73 (d, *J*=6.9 Hz, 2H), 2.67 (br s, 1H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 157.4, 156.0, 140.6, 138.3, 90.5, 79.9, 63.6, 60.8, 53.5, 35.6, 28.5; HRMS (ESI^+): *m*/*z* $[M+Na]^+$ calcd for $C_{15}H_{21}I_2NO_4Na$: 555.9458; found: 555.9450.

4.4. (*S*)-*tert*-Butyl-1-(3,5-dibromo-4-methoxyphenyl)-3-hydroxypropan-2-ylcarbamate 20

Compound **20** was synthesized from L-tyrosine with the similar procedure to **18**. $[\alpha]_D^{26}$ −36 (*c* 1.2, in $CHCl_3$); IR (neat) ν_{max}: 3342, 2976, 1680, 1529, 1467, 1366, 1253, 1167, 1005, 706 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.34 (s, 2H), 5.09 (d, *J*=8 Hz, 1H), 3.81 (s, 3H), 3.74 (m, 1H), 3.59 (m, 2H), 3.42 (br s, 1 H), 2.74 (m, 2H), 1.35 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 156.0, 152.5, 137.1, 133.4, 117.9, 79.8, 63.4, 60.6, 53.4, 36.1, 28.4; HRMS (ESI^+): *m*/*z* $[M+Na]^+$ calcd for $C_{15}H_{21}Br_2NO_4Na$: 459.9735; found: 459.9740.

4.5. (*S*)-*tert*-Butyl-1-(3,5-diiodo-4-methoxyphenyl)-3-(methoxymethoxy) propan-2-ylcarbamate 19

To an ice-cooled solution of compound **18** (7.1 g, 13.3 mmol) in dry CH_2Cl_2 (67 mL), DIPEA (3.9 mL, 33.3 mmol) was added at 0 °C under argon atmosphere. After 2 min. MOMCl (1.8 mL, 23.9 mmol) was added and the reaction mixture was allowed to stir at room temperature for 10 h. After completion of the reaction, water was added, organic layer was separated and aqueous phase was extracted with CH_2Cl_2 (3×50 mL). The combined organic layer was washed with brine (50 mL), dried with anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure to obtain reddish crude product. This crude product was purified over silica gel column chromatography to give the pure compound **19** as a pale yellow oil (6.9 g, 90%). IR (neat) ν_{max}: 3355, 2931, 2822, 1701, 1514, 1461, 1249, 1169, 1038, 997, 705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.59 (s, 2H), 4.93 (d, *J*=8.4 Hz, 1H), 4.59 (m, 2H), 3.83 (m, 1H), 3.78 (s, 3H), 3.45 (dd, *J*=3.6, 10.0 Hz, 1H), 3.41 (dd, *J*=4.0, 10.0 Hz, 1H), 3.36 (s, 3 H), 2.70 (m, 2H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 157.3, 155.2, 140.6, 138.2, 96.9, 90.4, 79.5, 68.2, 60.7, 55.6, 51.3, 36.1, 28.4; HRMS (ESI^+): *m*/*z* $[M+Na]^+$ calcd for $C_{17}H_{25}I_2NO_5Na$: 599.9720; found: 599.9716.

4.6. (*S*)-*tert*-Butyl(1-(3,5-dibromo-4-methoxyphenyl)-3-(methoxymethoxy)propan-2-yl)carbamate 21

Compound **21** was prepared from **20** with the similar procedure to **19**. Yield: 91%; IR (neat) ν_{max}: 3351, 2931, 1709, 1540, 1470, 1259, 1169, 1039, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.34 (s, 2H), 4.93 (d, *J*=8.3 Hz, 1H), 4.60 (m, 2H), 3.85 (m, 1H), 3.82 (s, 3H), 3.47 (dd, *J*=3.6, 10.0 Hz, 1H), 3.42 (dd, *J*=4.1, 10.0 Hz, 1H), 3.36 (s, 3H), 2.72 (m, 2H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 155.3, 152.6, 137.1, 133.5, 117.9, 96.9, 79.6, 68.3, 60.6, 55.6, 51.4, 36.7, 28.4; HRMS (ESI^+): *m*/*z* $[M+Na]^+$ calcd for $C_{17}H_{25}Br_2NO_5Na$: 503.9997; found: 503.9994.

4.7. (*S*)-*tert*-Butyl 4-(3,5-diiodo-4-methoxybenzyl)-2,2-dimethyloxazolidine-3-carboxylate 25

2-Methoxypropene (5.9 mL, 48.0 mmol) was added to a solution of the compound **18** (5.2 g, 9.6 mmol) in acetone (20 mL). To a stirred solution was added TsOH monohydrate (17 mg, 0.096 mmol). The reaction mixture was refluxed for 3 h. When the reaction was complete, by TLC analysis, the solution was evaporated in vacuo. The residue was dissolved in ethyl acetate (75 mL) and washed with aqueous $NaHCO_3$ (2×30 mL). The organic layer was dried with anhydrous Na_2SO_4 and evaporated in vacuo and the residue purified by column chromatography to afford the compound **25** as a pale yellow oil (5.12 g, 93%). $[\alpha]_D^{26}$ +34 (*c* 1.8, in $CHCl_3$); IR (neat) ν_{max}: 2977, 2935, 2875, 1697, 1463, 1389, 1254, 997, 847, 706 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.63 (s, 1H), 7.57 (s, 1H), 4.08–3.86 (m, 1H), 3.80 (s, 3H), 3.78 (d, *J*=5.7 Hz, 1H), 3.68 (d, *J*=9.1 Hz, 1H), 3.06–2.89 (m, 1H), 2.59–2.50 (m, 1H), 1.60–1.40 (m, 6H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 152.8, 152.7, 152.1, 151.5, 137.3, 137.2, 133.5, 133.3, 118.2, 118.0, 94.2, 93.7, 80.4, 79.9, 66.1, 65.7, 60.6, 58.7, 38.5, 37.2, 28.5, 28.4, 27.4, 26.9, 24.4, 23.2; HRMS (ESI^+): *m*/*z* $[M+H]^+$ calcd for $C_{18}H_{26}I_2NO_4$: 573.9951; found: 573.9954.

4.8. (*S*)-*tert*-Butyl-4-(3,5-dibromo-4-methoxybenzyl)-2,2-dimethyloxazolid-ine-3-carboxylate 29

Compound **29** was prepared from **20** with the similar procedure to **25**. Yield: 94%; $[\alpha]_D^{26}$ −26 (*c* 0.9, in $CHCl_3$); IR (neat) ν_{max}: 2977, 2933, 2872, 1698, 1473, 1387, 1260, 999, 848, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.36 (s, 1H), 7.29 (s, 1H), 4.02–3.89 (m, 1H), 3.82 (s, 3H), 3.79 (m, 1H), 3.67 (d, *J*=9.2 Hz, 1H), 3.06–2.89 (m, 1H), 2.61–2.52 (m, 1H), 1.58 (s, 1.5H), 1.48 (s, 12H), 1.42 (s, 1.5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 157.6, 157.5, 152.2, 151.5, 140.7, 140.5, 138.6, 138.4, 94.3, 93.7, 90.7, 90.5, 80.5, 80.0, 66.2, 65.7, 60.8, 58.8, 38.1, 36.7, 28.6, 28.5, 27.5, 26.9, 24.5, 23.3; HRMS (ESI^+): *m*/*z* $[M+Na]^+$ calcd for $C_{18}H_{25}Br_2NO_4Na$: 500.0048; found: 500.0046.

4.9. (*S*)-*tert*-Butyl-4-(3,5-dihydroxy-4-methoxybenzyl)-2,2-dimethyloxazoli-dine-3-carboxylate 26

To a solution of compound **25** (1.3 g, 2.3 mmol) in dry ether (23 mL) at −78 °C, *n*-BuLi (2.6 mL, 2.0 M solution in hexane, 5.2 mmol) was added dropwise under argon atmosphere. After 2 h, $B(OMe)_3$ (2.5 mL, 23.0 mmol) was added to the mixture all at once. The solution was allowed to warm to 35 °C, stirred for overnight and then cooled to 0 °C. The reaction mixture was treated with AcOH (1.3 mL, 23.0 mmol) and 30% H_2O_2 (2.3 mL, 23.0 mmol), and further stirred overnight. The reaction was quenched with NH_4Cl aq and worked up. The organic layer was dried with anhydrous Na_2SO_4, evaporated in vacuo and the residue purified by silica gel column chromatography to afford compound **26** (0.65 g, 80%) as a colorless oil. $[\alpha]_D^{27}$ −45 (*c* 1.0, in $CHCl_3$); IR (neat) ν_{max}: 3376, 2979, 2936, 2877, 1695, 1596, 1395, 1251, 1100, 1062, 850 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.43 (s, 1H), 6.34 (s, 1H), 6.13 (br s, 2H), 4.00 (m, 1H), 3.87 (s, 1H), 3.76 (m, 2H), 3.05 (dd, *J*=2.5, 13.2 Hz, 0.5H), 2.97 (dd, *J*=2.8, 12.8 Hz, 0.5H), 2.45 (dd, *J*=12.2, 23.4 Hz, 1H), 1.63 (s, 1.5H), 1.57 (s, 1.5H), 1.52 (s, 4.5H), 1.50 (s, 4.5H), 1.49 (s, 1.5H), 1.47 (s, 1.5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 152.4, 151.8, 149.4, 149.3, 135.0, 134.7, 133.4, 133.3, 109.0, 108.8, 94.1, 93.8, 80.9, 80.0, 66.1, 65.7, 60.9, 60.8, 59.0, 58.9, 39.3, 38.1, 28.5, 28.4, 27.6, 26.9, 24.5, 23.3; HRMS (ESI^+): *m*/*z* $[M+Na]^+$ calcd for $C_{18}H_{27}NO_6Na$: 376.1736; found: 376.1732.

4.10. (*S*)-*tert*-Butyl-4-(3,5-bis((*tert*-butyldimethylsilyl)oxy)-4-methoxybenzyl)-2,2-dimethyloxazolidine-3-carboxylate 31

To a solution of compound **26** (0.49 g, 1.4 mmol) in DMF (2.8 mL) was added imidazole (0.21 g, 3.1 mmol) and *tert*-butyldimethylsilyl chloride (0.45 g, 3.1 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 5 h and then diluted with ethyl acetate (100 mL) and water (50 mL). Layers were separated and the aqueous phase was extracted with ethyl acetate (20 mL). The combined organic phases were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and the residue purified by silica gel column chromatography to afford compound **31** (0.76 g, 94%) as a colorless oil. $[\alpha]_D^{27}$ −28 (*c* 1.7, in CH_2Cl_2); IR (neat) ν_{max}: 2932, 2858, 1719, 1577, 1495, 1254, 1092, 1010, 834 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.35 (s, 2H), 3.96 (m, 1H), 3.76 (m, 2H), 3.69 (s, 3H), 3.02 (m, 1H), 2.44 (m, 1H), 1.64 (s, 1.5H), 1.58 (s, 1.5H), 1.53 (s, 9H), 1.49 (s, 1.5H), 1.46 (s, 1.5H), 0.99 (s, 18H), 0.15 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 152.2, 151.7, 149.8, 149.6, 141.6, 140.6, 137.1, 133.8, 116.0, 115.8, 94.1, 93.3, 80.1, 79.7, 66.1, 65.8, 60.1, 60.0, 59.5, 58.9, 39.3, 38.0, 28.7, 28.5, 27.0, 26.5, 26.1, 25.8, 24.7, 23.3, 18.4, −3.2, −4.6; HRMS (ESI^+): *m*/*z* $[M+Na]^+$ calcd for $C_{30}H_{55}NO_6Si_2Na$: 604.3466; found: 604.3460.

4.11. (*S*)-*tert*-Butyl(1-(3,5-bis((*tert*-butyldimethylsilyl)oxy)-4-methoxyphenyl)-3-hydroxypropan-2-yl)carbamate 32

To a solution of compound **31** (0.40 g, 0.69 mmol) in methanol (15 mL) was added PTSA hydrate (3 mg, 0.014 mmol) at room temperature. The reaction mixture was stirred overnight, and saturated aqueous solution of $NaHCO_3$ (5 mL) was used to quench the reaction. Methanol was removed under reduced pressure and the aqueous residue was extracted with ethyl acetate (3×30 mL). The combined organic phases were washed with brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel to give compound **32** (0.34 g, 92%) as a colorless oil. $[\alpha]_D^{27}$ −6 (*c* 1.6, in CH_2Cl_2); IR (neat) ν_{max}: 3439, 2932, 2859, 1695, 1576, 1495, 1433, 1253, 1173, 1093, 834 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.34 (s, 2H), 4.70 (d, *J*=7.2 Hz, 1H), 3.78 (br s, 1H), 3.69 (s, 3H), 3.63 (m, 1H), 3.53 (m, 1H), 2.65 (m, 2H), 1.42 (s, 9H), 0.99 (s, 18H), 0.16 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 156.2, 149.7, 141.6, 132.8, 115.6, 79.6, 64.6, 59.9, 53.4, 36.9, 28.4, 25.7, 18.3, −4.6; HRMS (ESI^+): *m*/*z* $[M+H]^+$ calcd for $C_{27}H_{52}NO_6Si_2$: 542.3333; found: 542.3329.

4.12. (*S*)-3-(3,5-Bis((*tert*-butyldimethylsilyl)oxy)-4-methoxyphenyl)-2-((*tert*-butoxycarbonyl)amino) propanoic acid 33

To a solution of compound **32** (66 mg, 0.12 mmol) in CH_3CN/H_2O (1:1, 1.6 mL) was added TEMPO (3.8 mg, 0.024 mmol) and phenyliodonium diacetate (85 mg, 0.26 mmol) at room temperature. After stirring for 5 h, the mixture was filtered through a short pad of Celite and then concentrated in vacuo. The residue was diluted with ethyl acetate (200 mL) and washed with brine (50 mL), dried over anhydrous Na_2SO_4. The combined filtrates were concentrated in vacuo and the residue was purified by flash chromatography on silica gel to give the compound **33** (63 mg, 95%) as a colorless oil. $[\alpha]_D^{27}$ +11 (*c* 1.6, in CH_2Cl_2); IR (neat) ν_{max}: 3383, 2933, 2860, 1700, 1576, 1433, 1388, 1255, 1174, 1099, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 10.80 (br s, 1H), 6.53 (m, 0.3H), 6.36 (s, 0.5H), 6.32 (s, 1.5H), 4.94 (d, *J*=8.1 Hz, 0.7H), 4.53 (m, 0.7H), 4.32 (m, 0.3H), 3.69 (s, 3H), 3.01 (dd, *J*=5.2, 14.0 Hz, 1H), 2.89 (dd, *J*=6.4, 13.9 Hz, 0.7H), 2.73 (dd, *J*=9.3, 13.4 Hz, 0.3H), 1.41 (s, 6H), 1.35 (s, 3H), 0.99 (s, 18H), 0.15 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 176.7, 176.4, 156.5, 155.4, 149.8, 142.1, 141.9, 131.7, 130.9, 115.8, 81.5, 80.2, 60.0, 56.2, 54.2, 38.9, 37.3, 32.0, 28.4, 28.2, 25.8, 18.4, −4.5; HRMS (ESI^+): *m*/*z* $[M+Na]^+$ calcd for $C_{27}H_{49}NO_7Si_2Na$: 578.2945; found: 578.2950.

4.13. (*S*)-*tert*-Butyl(1-(3,5-bis((*tert*-butyldimethylsilyl)oxy)-4-methoxyphenyl)-3-oxopropan-2-yl)carbamate 34

To a solution of the compound **32** (60 mg, 0.11 mmol) in DCM (2 mL), Dess–Martin periodinane (DMP, 51 mg, 0.12 mmol) was added at room temperature. The reaction mixture was stirred for 3 h and then added with saturated aqueous sodium bicarbonate solution ($NaHCO_3$, 5 mL). Layers were separated, and the aqueous layer was extracted with DCM (2×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography on silica gel to provide **34** (55 mg, 93%) as an oil. $[\alpha]_D^{27}$ +7 (*c* 0.96, in $CHCl_3$); IR (neat) ν_{max}: 3433, 2930, 2857, 1714, 1576, 1432, 1360, 1254, 1167, 1093, 834 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.59 (s, 1H), 6.29 (s, 2H), 5.01 (d, *J*=5.8 Hz, 1H), 4.31 (m, 1H), 3.69 (s, 3H), 3.67 (m, 1H), 2.95 (m, 1H), 1.44 (s, 9H), 0.99 (s, 18H), 0.15 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 199.7, 155.5, 150.0, 142.1, 130.8, 115.8, 80.3, 60.6, 60.1, 35.1, 28.4, 25.8, 18.4, −4.5; HRMS

(ESI$^+$): m/z $[M+Na]^+$ calcd for $C_{27}H_{49}NO_6Si_2Na$: 562.2996; found: 562.2999.

4.14. (*S*)-*tert*-Butyl (1-hydroxy-3-(3,4,5-trimethoxyphenyl) propan-2-yl)carbamate 35

To a solution of **26** (0.18 g, 0.51 mmol) in dry CH_3CN (5.1 mL) were added $(CH_3)_2SO_4$ (0.15 mL, 1.6 mmol) and anhydrous K_2CO_3 (0.22 g, 1.6 mmol), and the resulting mixture was stirred at 60 °C for 5 h. The solvent removed in vacuo, and the water (40 mL) was added. The mixture was extracted with ethyl acetate (3×25 mL). The combined organic layer was dried with Na_2SO_4, filtered, and the solvent evaporated in vacuo. The residue was taken up in methanol (15 mL) was added PTSA hydrate (4.5 mg, 0.021 mmol) at room temperature. The reaction mixture was stirred overnight, and saturated aqueous solution of $NaHCO_3$ (5 mL) was used to quench the reaction. Methanol was removed under reduced pressure and the aqueous residue was extracted with ethyl acetate (3×30 mL). The combined organic phases were washed with brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel to give compound **35** (0.14 g, 78% over two steps) $[\alpha]_D^{15}$ −14 (*c* 0.5, in CH_2Cl_2); IR(neat) ν_{max}: 3357, 2936, 1685, 1592, 1509, 1458, 1422, 1367, 1242, 1168, 1127, 1051, 780 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.43 (s, 2H), 4.85 (d, J=5.0 Hz, 1H), 3.85 (s, 6H), 3.85 (m, 1H), 3.82 (s, 3H), 3.68 (br d, J=10.5 Hz, 1H), 3.59 (dd, J=4.5, 10.4 Hz, 1H), 2.79 (m, 2H), 2.62 (br s, 1H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 156.1, 153.2, 136.5, 133.6, 106.1, 79.7, 64.2, 60.9, 56.0, 53.5, 37.7, 28.4; HRMS (ESI$^+$): m/z $[M+H]^+$ calcd for $C_{17}H_{28}NO_6$: 342.1917; found: 342.1912.

4.15. (*S*)-2-((*tert*-Butoxycarbonyl)amino)-3-(3,4,5-trimethoxy-phenyl)propanoic acid 36

To a solution of compound **35** (53 mg, 0.14 mmol) in CH_3CN/H_2O (1:1, 1.6 mL) was added TEMPO (4.4 mg, 0.028 mmol) and phenyliodonium diacetate (100 mg, 0.31 mmol) at room temperature. After stirring for 5 h, the mixture was filtered through a short pad of Celite and then concentrated in vacuo. The residue was diluted with ethyl acetate (200 mL) and washed with brine (50 mL), dried over anhydrous Na_2SO_4. The combined filtrates were concentrated in vacuo and the residue was purified by flash chromatography on silica gel to give the compound **36** (50 mg, 92%). $[\alpha]_D^{15}$ +13 (*c* 0.4, in MeOH); IR(neat) ν_{max}: 3350, 2930, 1712, 1592, 1508, 1459, 1423, 1244, 1165, 1128, 1012, 780 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.40 (s, 2H), 6.39 (d, 0.3H), 5.00 (d, J=7.7 Hz, 0.7H), 4.60 (m, 0.7H), 4.38 (m, 0.3H), 3.83 (s, 9H), 3.17 (dd, J=4.8, 13.9 Hz, 1H), 3.06 (dd, J=6.8, 13.9 Hz, 0.7H), 2.87 (m, 0.3H), 1.43 (s, 6.3H), 1.26 (s, 2.7H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 176.0, 155.4, 153.2, 137.0, 131.5, 106.4, 106.2, 80.4, 60.8, 56.1, 54.3, 38.1, 28.3, 28.0; HRMS (ESI$^+$): m/z $[M+Na]^+$ calcd for $C_{17}H_{25}NO_7Na$: 378.1529; found: 378.1535.

Acknowledgements

We thank Sichuan University Analytical and Testing Center as well as Prof. Xiaoming Feng group for NMR determination. This work was supported by grants from the National Natural Science Foundation of China (20802045, 21172153 and J1103315/J0104), the National Basic Research Program of China (973 Program, No. 2012CB833200).

Supplementary data

Copies of ^{1}H and ^{13}C NMR spectra. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.02.079.

References and notes

1. (a) Nonaka, N.; Asai, Y.; Nishio, M.; Takahashi, K.; Okuda, T.; Tanaka, S.; Sugita, T.; Ohnuki, T.; Komatsubara, S. *J. Antibiot.* **1997**, *50*, 646–652; (b) Asai, Y.; Nonaka, N.; Nishio, M.; Okamura, K.; Date, T.; Sugita, T.; Ohnuki, T.; Komatsubara, S. *J. Antibiot.* **1997**, *50*, 653–658.
2. (a) Lee, J.-E.; Hitotsuyanagi, Y.; Kim, I.-H.; Hasuda, T.; Takeya, K. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 808–811; (b) Hitotsuyanagi, Y.; Aihara, T.; Takeya, K. *Tetrahedron Lett.* **2001**, *41*, 6127–6130.
3. Furet, P.; Imbach, P.; Noorani, M.; Koeppler, J.; Laumen, K.; Lang, M.; Guagnano, V.; Fuerst, P.; Roesel, J.; Zimmermann, J.; Garcia-Echeverria, C. *J. Med. Chem.* **2004**, *47*, 4810–4813.
4. (a) Oltz, E. M.; Bruening, R. C.; Smith, M. J.; Kustin, K.; Nakanishi, K. *J. Am. Chem. Soc.* **1988**, *110*, 6162–6172; (b) Bruening, R. C.; Oltz, E. M.; Furukawa, J.; Nakanishi, K.; Kustin, K. *J. Nat. Prod.* **1986**, *49*, 193–204.
5. (a) Corey, E. J.; Gin, D. Y.; Kania, R. S. *J. Am. Chem. Soc.* **1996**, *118*, 9202–9203; (b) Martinez, E. J.; Owa, T.; Schreiber, S. L.; Corey, E. J. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 3496–3501; (c) Martinez, E. J.; Corey, E. J. *Org. Lett.* **1999**, *1*, 75–77; (d) Martinez, E. J.; Corey, E. J. *Org. Lett.* **2000**, *2*, 993–996.
6. (a) Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669–1730; (b) Aune, G. J.; Furuta, T.; Pommier, Y. *Anticancer Drugs* **2002**, *13*, 545–555; (c) Xing, C.; LaPorte, J. R.; Barbay, J. K.; Myers, A. G. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5862–5866; (d) Siengalewicz, P.; Rinner, U.; Mulzer, J. *Chem. Soc. Rev.* **2008**, *37*, 2676–2690.
7. (a) Cuevas, C.; Francesch, A. *Nat. Prod. Rep.* **2009**, *26*, 322–337; (b) Molinski, T. F.; Dalisay, D. S.; Lievens, S. L.; Saludes, J. P. *Nat. Rev. Drug Discovery* **2009**, *8*, 69–85.
8. (a) Martinez, E. J.; Corey, E. J.; Owa, T. *Chem. Biol.* **2001**, *8*, 1151–1160; (b) Ortìn, I.; Gonzáles, J. F.; de la Cuesta, E.; Manguan-Garcia, C.; Perona, R.; Avendaño, C. *Bioorg. Med. Chem.* **2008**, *16*, 9065–9078.
9. Deboves, H. J. C.; Montalbetti, C. A. G. N.; Jackson, R. F. W. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1876–1884.
10. Laumen, K.; Ghisalba, O. *Eng. Life Sci.* **2006**, *6*, 193–194.
11. Chen, R.; Zhu, D.; Hu, Z.; Zheng, Z.; Chen, X. *Tetrahedron: Asymmetry* **2002**, *21*, 39–42.
12. (a) Schmidt, E. W.; Nelson, J. T.; Fillmore, J. P. *Tetrahedron Lett.* **2004**, *45*, 3921–3924; (b) Demoulin, N.; Zhu, J. *Synlett* **2009**, 466–468; (c) Liao, X. W.; Dong, W. F.; Liu, W.; Guan, B. H.; Liu, Z. Z. *J. Heterocycl. Chem.* **2010**, *47*, 50–53.
13. (a) Atkinson, M.; Hartley, D.; Lunts, L. H. C.; Ritchie, A. C. *J. Med. Chem.* **1974**, *17*, 248–249; (b) Bew, S. P.; Hughes, D. L.; Sharma, S. V. *J. Org. Chem.* **2006**, *71*, 7881–7884.
14. (a) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651–1660; (b) Manusco, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480–2482.
15. (a) Guzman, J. A.; Mendoza, V.; Garcia, E.; Garibay, C. F.; Olivares, L. Z.; Maldonado, L. A. *Synth. Commun.* **1995**, *25*, 2121–2133; (b) Chen, C.; Zhu, Y.-F.; Wilcoxen, K. *J. Org. Chem.* **2000**, *65*, 2574–2576; (c) Bovicelli, P.; Antonioletti, R.; Barontini, M.; Borioni, G.; Bernini, R.; Mincione, E. *Tetrahedron Lett.* **2005**, *46*, 1255–1257.
16. (a) Marshall, L. J.; Cableb, K. M.; Botting, N. P. *Org. Biomol. Chem.* **2009**, *7*, 785–788; (b) Tlili, A.; Xia, N.; Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 8725–8728; (c) Zhao, D. B.; Wu, N. J.; Zhang, S.; Xi, P. H.; Su, X. Y.; Lan, J. B.; You, Y. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 8729–8732; (d) Maurer, S.; Liu, W.; Zhang, X.; Jiang, Y.; Ma, D. *Synlett* **2010**, 976–978; (e) Yang, D.; Fu, H. *Chem.—Eur. J.* **2010**, *16*, 2366–2370; (g) Jing, L.; Wei, J.; Zhou, L.; Huang, Z.; Li, Z.; Zhou, X. *Chem. Commun.* **2010**, 4767–4769.
17. Faul, M. M.; Winneroski, L. L.; York, J. S.; Reinhard, M. R.; Hoying, R. C.; Gritton, W. H.; Dominianni, S. J. *Heterocycles* **2001**, *55*, 689–704.
18. Liu, R.; Sogawa, H.; Shiotsuki, M.; Masuda, T.; Sanda, F. *Polymer* **2010**, *51*, 2255–2263.
19. (a) Verschueren, K.; Toth, G.; Tourwe, D.; Lebl, M.; Van Binst, G.; Hruby, V. *Synthesis* **1992**, 458–460; (b) Ding, W.; Zhang, J.; Yao, Z.; Lu, R.; Wu, D.; Li, G.; Shen, Z.; Sun, Y.; Lin, G.; Wang, C.; Zhao, M.; Peng, S. *Bioorg. Med. Chem.* **2004**, *12*, 4989–4994; (c) Liu, C.; Thomas, J. B.; Brieaddy, L.; Berrang, B.; Carroll, F. I. *Synthesis* **2008**, *6*, 856–858.
20. (a) Demerseman, P.; Einhorn, J.; Royer, R.; Gourvest, J.-F. *J. Heterocycl. Chem.* **1985**, *22*, 39–43; (b) Endo, A.; Yanagisawa, A.; Abe, M.; Tohma, S.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 6552–6554; (c) Chen, J.; Chen, X.; Bois-Choussy, M.; Zhu, J. *J. Am. Chem. Soc.* **2006**, *128*, 87–89; (d) Kim, B. G.; Kim, H.-J.; Jang, J. H.; Cho, E. A.; Henkensmeier, D.; Kim, S.-K.; Oh, I.-H.; Hong, S.-A.; Lim, T.-H. *Polym. Int.* **2011**, *60*, 685–691.
21. (a) Green, K. *J. Org. Chem.* **1991**, *56*, 4326–4329; (b) Alberico, D.; Lautens, M. *Synlett* **2006**, 2969–2972; (c) Alberico, D.; Rudolph, A.; Lautens, M. *J. Org. Chem.* **2007**, *72*, 775–781.
22. (a) Epp, J. B.; Widlanski, T. S. *J. Org. Chem.* **1999**, *64*, 293–295; (b) Jin, Y.; Liu, Y.; Wang, Z.; Kwong, S.; Xu, Z.; Ye, T. *Org. Lett.* **2010**, *12*, 1100–1103.