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A Concise and Practical Semi-synthesis of Ecteinascidin 743 and (-)-Jorumycin

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Abstract: Ecteinascidin 743 is an antitumor drug used to treat specific soft tissue sarcomas (STS). Herein, a concise and practical semi-synthesis of Ecteinascidin 743 starting from Safracin B is presented by the strategy of directly converting an aliphatic amino group to the acetoxyl group. Through this strategy, Ecteinascidin 743 was synthesized via 14 steps with 1.5% overall yield. The synthetic approach also provided access to other tetrahydro-isoquinoline alkaloids, such as (-)-Jorumycin (a promising anticancer candidate). (-)-Jorumycin was prepared in six steps and 24.1% overall yield from Safracin B.

Introduction

Ecteinascidin 743 and (-)-Jorumycin

Ecteinascidin 743 (Trabectedin, compound **1**, Figure 1), a tetrahydro-isoquinoline alkaloid, is a marine-derived antitumor drug isolated by Rinehart and co-workers[1, 2]. (-)-Jorumycin (compound **2**, an analogue of **1**, Figure 1) is a promising candidate for new anticancer drugs that was isolated from *Jorunna funebris* in 2000[3]. Both of **1** and **2** displayed significantly cytotoxic[2-6]. In 2015, **1** was approved for the treatment of specific soft tissue sarcomas (STS).

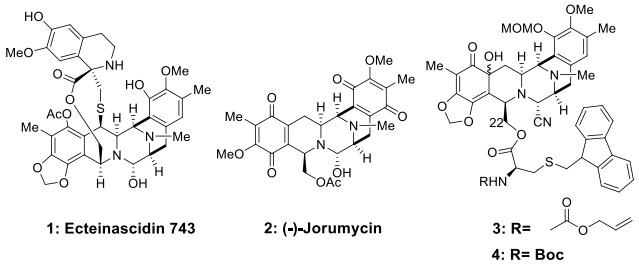

Figure 1. The structures of Ecteinascidin 743 (**1**), (-)-Jorumycin (**2**), and compounds **3** and **4**

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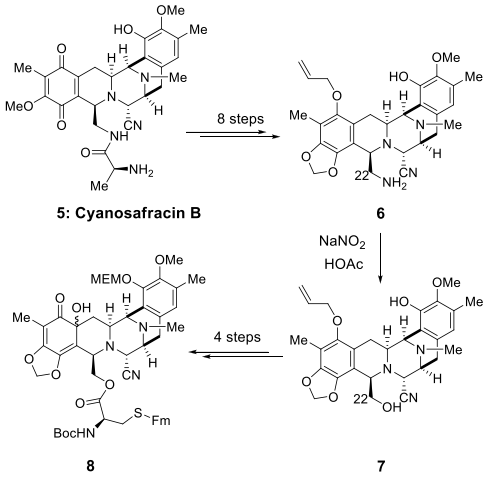
Electronic Supplementary Information (ESI) available: analytical data for the reported compounds

Because of the unique structures and the remarkable biological activities, **1** and **2** are attractive synthetic targets for chemists. Four total syntheses [7-10] and one semi-synthesis[6] of **2** had been reported. For **1**, Corey's group initially published a total synthesis involving 36 steps with an overall yield of 0.72%[11].Then Fukuyama[12, 13] and Zhu[14], respectively, reported its synthetic routes. Meanwhile, other groups[15, 16] studied its formal total synthesis. In 2000, based on Corey's synthesis, a semi-synthetic process for **1** starting from Cyanosafracin B (compound **5**) was developed as an industrial route, which took 21 steps in 1.0% overall yield reported by Cuevas and co-workers[17].

Compound **3** was a key intermediate in Corey's synthetic route (Figure 1)[11]. Cuevas et al. reported several routes to prepare **3** and its derivatives[17-21]. The essential issue for the semi-synthesis of **3** and its derivatives was how to convert the aliphatic amino group at C22 to the hydroxyl group. Four different strategies were developed for this issue[17-21], and the best strategy is outlined in Scheme 1. In this strategy, intermediate **8** (a derivative of **3**) was achieved in 13 steps and 5.7% overall yield from **5** [20].

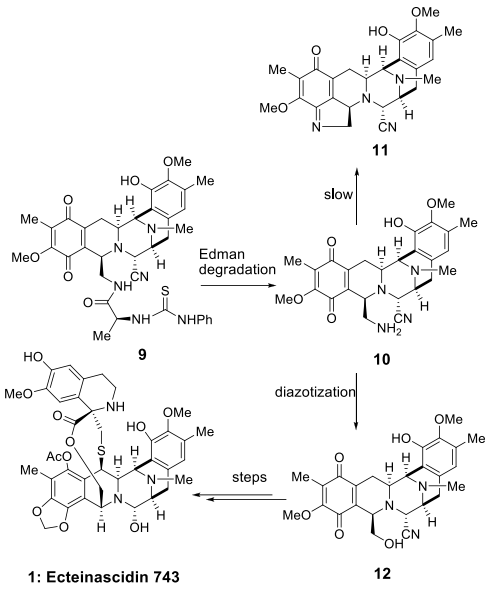


Scheme 1. The semi-synthesis of intermediate **8**[20]

Although wonderful work were accomplished by Cuevas and co-workers, there are still some drawbacks needed to be resolved for the semi-synthesis of **8**, such as long steps (13 steps), many protective groups and the use of poisonous reagent (n-Bu_3SnH). Based on the work of Cuevas et al. we developed a more concise and practical synthesis of **4** (a derivative of **8**) in 9 steps with 9.1% overall yield, by directly converting an aliphatic amino group to an ester group. Moreover, this synthetic approach also provided access to (-)-Jorumycin.

Finally, we prepared Ecteinascidin 743 in 14 steps and synthesized (-)-Jorumycin through the new route in six steps.

Retrosynthetic analysis

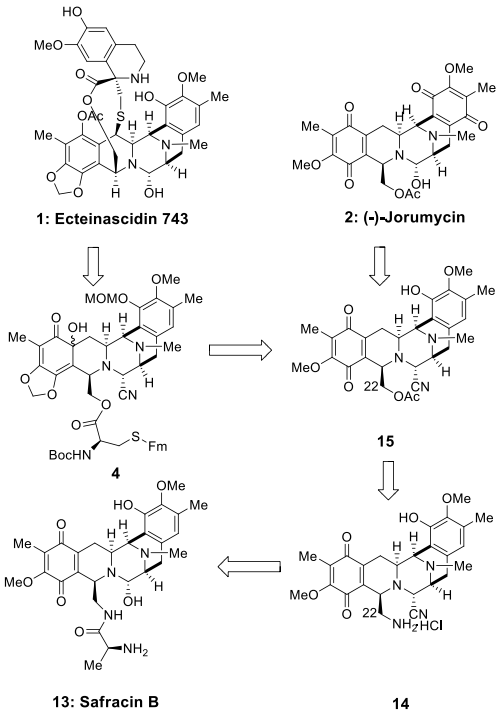


Scheme 2. The synthetic strategy for **1** via compound **12**

For the synthesis of **1**, we considered shifting the Edman degradation and diazotization to the earlier steps to optimize the route (Scheme 2). However, two synthetic challenges appeared: 1) It was difficult to selectively protect the phenol group of **12** (Scheme 2), because the reactivity of the phenol group and the hydroxyl group was very similar; and 2) the intermediate **10** was unstable and would slowly convert to a stable intermediate (compound **11**, Scheme 2)[19, 22].

Interestingly, a salt of **10** (amine hydrochloride **14**) was obtained after Edman degradation in our experiment. And amine hydrochloride **14** was stable. Then we optimized our strategy, which is outlined in Scheme 3. Inspired by the method of directly converting an aliphatic amino group to an ester group by diazotization[23-25], compound **15** (an analogue of **12**) was designed as an appropriate intermediate for the synthesis of **4** (Scheme 3), since the hydroxyl group of **15** had been protected and the protection of phenol group would not be affected.

There are several advantages for this strategy, listed as follows: 1) We shifted the primary amine's diazotization from the ninth step to the fourth step, making the route more economical, because the yield of primary amine's diazotization was low[17-21]; 2) the conversion of the amino group to the ester group was carried out in one step, and the ester group could be deprotected when the methoxy-p-quinone was hydrolyzed under basic condition, so none of steps would be increased for the hydroxyl group's protection and deprotection at C22 (Scheme 3); and 3) (-)-Jorumycin could be synthesized from **15** (Scheme 3).

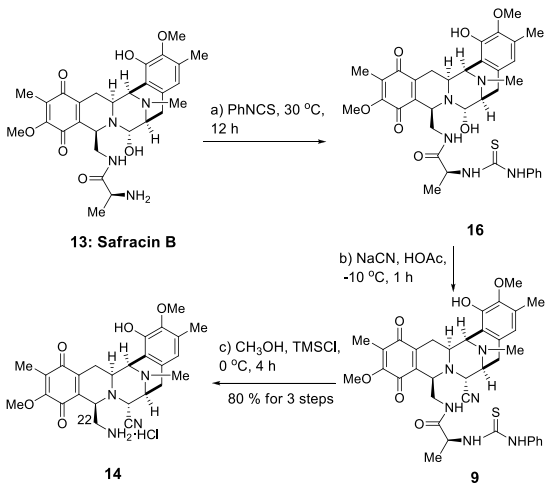


Scheme 3. The retrosynthetic analysis of **1** and **2**

Results and Discussion

The synthesis of key intermediate 15

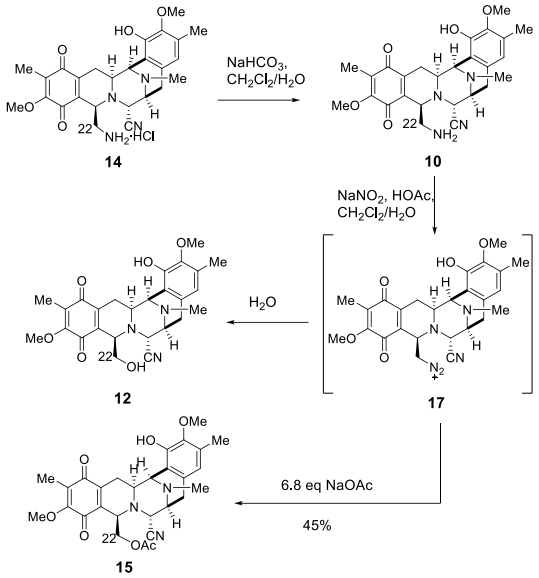
Our synthesis started from Safracin B (**13**, Scheme 4). Compound **13** is an antibiotic of bacterial origin, which is available through fermentation of the bacteria *Pseudomonas fluorescence* and can be obtained in kilogram scale[26, 27]. The synthesis of **15** from amine **13** is outlined in Schemes 4 and 5.



Scheme 4. The synthesis of intermediate **14**

The amino group of Safracin B was reacted with phenyl isothiocyanate to give the thiourea **16**[21, 28]. Then the hydroxyl group of **16** was substituted by the cyano group (NaCN, CH_3COOH) [7], followed by Edman degradation[21] (TMSCl, MeOH) to furnish the amine hydrochloride **14** in 80% overall yield for the three steps without column chromatography. The amine

hydrochloride **14** was directly precipitated from the reaction solution. Its free base (intermediate **10**, Scheme 5) would slowly convert to compound **11** （Scheme 2）, which was previously reported[19], but amine hydrochloride **14** was stable at 0 °C for long-term storage.

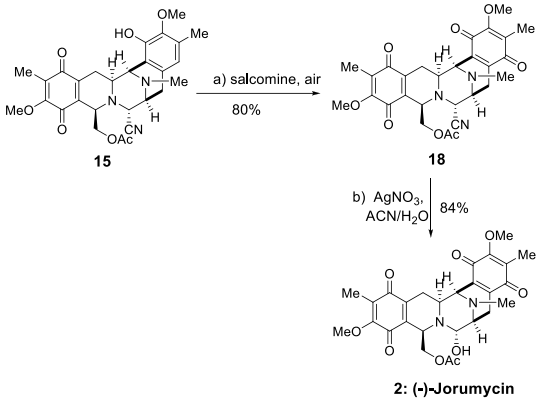


Scheme 5. The synthesis of intermediate **15**

With the stable intermediate **14** in hand, we considered converting the amino group at C22 to the acetoxyl group (Scheme 5). Firstly, the amine hydrochloride **14** was treated with $NaHCO_3$ in CH_2Cl_2/H_2O at 0 °C to give its free base (**10**'s methylene chloride solution), since the chloride ion in intermediate **14** was a good nucleophile and it would react with **17** to produce by-product. Then, to convert amino group at C22 to the acetoxyl group, a great amount of NaOAc (6.8 eq) was added as a competitive nucleophile of water for the selective synthesis of **15** (Scheme 5). Finally, **10** was treated with $NaNO_2$ and NaOAc under acidic condition in CH_2Cl_2/H_2O at -5 °C to give **15** (45% yield). Although **15** was obtained, we wondered why the diazotization was not affected in our experimental condition. We concluded that this was due to the following reasons: 1) the acetic acid was massive (60 eq) in the condition of diazotization, and **10** was converted into a salt which was unfavourable for the formation of **11** under acidic condition; 2) the reaction was carried out in a two-phase solution (CH_2Cl_2/H_2O) which contained a large amount of water, making the dehydration of **10** more difficult[29]; and 3) the temperature of the reaction was low (-5~0°C).

The synthesis of (-)-Jorumycin from intermediate 15

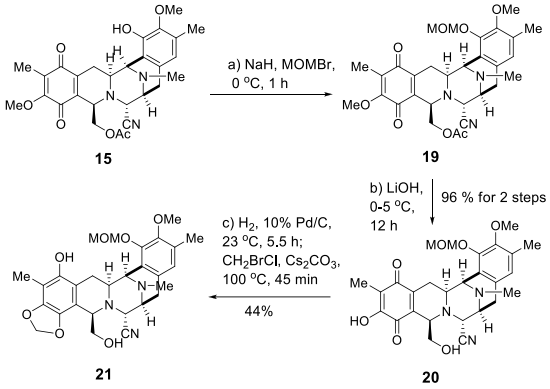
To synthesize (-)-Jorumycin, intermediate **15** was oxidized by salcomine in air[9, 30] and the cyano group was substituted by a hydroxyl group ($AgNO_3$, ACN/H_2O) to obtain (-)-Jorumycin (**2**, Scheme 6).



Scheme 6. The synthesis of (-)-Jorumycin

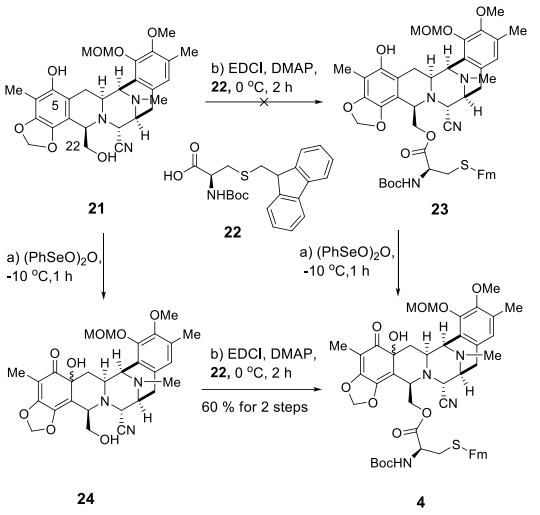
The synthesis of Ecteinascidin 743 from intermediate 15

To synthesize Ecteinascidin 743, intermediate **15** was protected with MOM (MOMBr, NaH). Then the methoxy-p-quinone and the ester group were hydrolyzed with LiOH in H_2O/THF in one pot to give **20** (96% yield for the two steps without column chromatography, Scheme 7)[21]. Intermediate **20** was reduced by 10% Pd/C, then immediately treated with CH_2BrCl /Cs_2CO_3 in DMF to form a five-member cycle to obtain **21** (44% yield)[17].



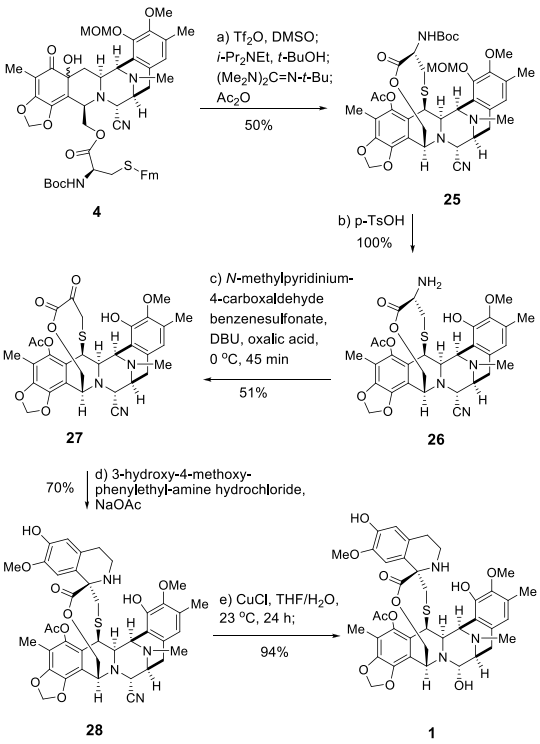
Scheme 7. The synthesis of intermediate **21**

With **21** in hand, we conceived ester condensation of **21** with **22** to gain **23**, and then oxidized **23** with $(PhSeO)_2O$ to obtain **4** (Scheme 8). During the synthesis of **23**, the major product was a by-product. The by-product was monitored by mass spectrometry, and the results showed that **21** was reacted with 2 eq of **22**. And Jia[31] reported the phenol group at C5 was more active than the hydroxyl at C22 for esterification (Scheme 8). So we proposed another method to prepare **4**. Directly oxidizing the phenol group of **21** with $(PhSeO)_2O$ in THF, followed by ester condensation (EDCI, DMAP) with **22** to give **4** in 60% overall yield for the two steps (Scheme 8)[11].



Scheme 8. The synthesis of intermediate **4**

Then we adopted a five-step chemical reaction to get the final product (Ecteinascidin 743) according to Corey's protocol (Scheme 9). The ten-member sulfide **25** was formed by Swern oxidization (DMSO, Tf_2O, -40 °C; *i*-Pr_2NEt, 0 °C), deprotection of sulfide ($(Me_2N)_2$=N-*t*-Bu, 23 °C), Micheal addition and ester condensation (Ac_2O, 23 °C) successively[11]. Then the amino and



Scheme 9. The synthesis of Ecteinascidin 743

phenol groups of **25** were deprotected to give amine **26** (100% yield without column chromatography)[18]. The amino group of compound **26** was converted to a ketone using Rapoport's salt (*N*-methylpyridinium-4-carboxaldehyde benzenesulfonate, DBU, oxalic acid, 0 °C) to give **27** (51% yield without column chromatography)[11, 17]. Compound **27** was reacted with 3-hydroxy-4-methoxyphenylethyl-amine hydrochloride (NaOAc, EtOH, 23°C) through Pictet-Spengler reaction to form a tetrahydroisoquinoline derivative **28** (70% yield)[11-14]. Finally, the cyano group was substituted by hydroxyl group to afford the aim compound **1** (94% yield)[11, 18].

Conclusions

In summary, we accomplished the semi-synthesis of Ecteinascidin 743 and (-)-Jorumycin. The key step was directly converting the aliphatic amino group at C22 to the acetoxyl group. We made several improvements to Ceuvas et al.'s method, which are listed as follows: 1) an alternative route was provided, and four steps were saved in the semi-synthesis of Ecteinascidin 743 starting from a different compound (safracin B); 2) we needed five times less column chromatography in this alternative route, while Cuevas et al. needed 16 times more column chromatography; and 3) the allylic protecting group wasn't used to protect the phenol group, so we did not need to use the highly toxic reagent (n-Bu_3SnH) for the deprotection of the allylic protecting group. Finally, a concise route was provided for the semi-synthesis of Ecteinascidin 743 in 14 steps and 1.5% overall yield from Safracin B. Our synthetic approach also provides access to other tetrahydro-isoquinoline alkaloids, such as (-)-Jorumycin. And (-)-Jorumycin was prepared in six steps and 24.1% overall yield from Safracin B.

Experimental Section

General

All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Diethyl ether and tetrahydrofuran were distilled immediately before use from sodium-benzophenoneketyl. Methylene chloride, DMF, dimethyl sulfoxide, and *N*, *N*-diisopropylethylamine, were distilled from calcium hydride and stored under an argon atmosphere. Methanol was distilled from magnesium and stored under an argon atmosphere. Acetone was dried over drierite and distilled before use. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Solvents were used for chromatography which were supplied by Sinopharm Chemicals. Reactions were monitored by thin layer chromatography (TLC) which were carried out on S-2 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and aqueous ammonium cerium nitrate/ammonium molybdate or basic aqueous potassium permanganate as developing agent. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin layer chromatography separations were carried out on 0.25 or 0.50 mm E. Merck silica gel plates (60F-254). ^1H and ^{13}C NMR spectra were recorded on a Bruker 400 MHz

spectrometer. The solvents used for NMR spectroscopy were $CDCl_3$ and DMSO-d_6, and TMS was used as the internal reference. IR spectra were recorded on a Thermo Nicolet Nexus 670 FTIR spectrometer. HRMS spectra were obtained on Bruker maXis 4G. Method of ionization was ESI (Elektron Spray Ionization).

Compound 16: To a solution of **13** (Safracin B) (30.0 g, 55.5 mmol) in CH_2Cl_2 (180 mL), phenyl isothiocyanate (27.8 g, 24.4 mL, 204 mmol) was added at 30 °C. The solution was stirred for 12 h. Then the solvent was removed under reduced pressure to afford compound **16** that was directly used in next step without further purification. $[\alpha]_D^{25}$ -121.0 (c 1.0, DMSO), ^{1}H NMR (400 MHz，DMSO-d_6): δ = 9.94（s, 1 H），8.66（s, 1 H）7.46-7.40 (m, 3 H), 7.36 (t, *J* = 8 Hz, 3 H), 7.15 (t, *J* = 7.6 Hz, 1 H), 6.20 (s, 1 H), 4.47 (s, 1 H), 4.36 (t, *J* = 7.2 Hz, 1 H), 3.99-3.63 (m, 5 H), 3.52 (s, 1 H), 3.33 (s, 3 H), 2.99 (d, *J* = 2.8 Hz, 1 H), 2.96-2.73 (m, 4 H), 2.16 (s, 3 H), 1.98 (s, 3 H), 1.84 (s, 3 H),1.59 (m, 1 H), 1.15 (d, *J* = 6.1 Hz, 2 H), 0.46 (d, *J* = 2.8 Hz, 3 H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 185.9, 181.4, 178.7, 171.4, 155.6, 147.5, 142.9, 139.1, 135.5, 131.2, 128.8, 127.2, 124.4, 123.0, 120.0, 118.4, 117.1, 60.7, 59.8, 58.3, 57.3, 55.3, 54.7, 54.4, 52.0, 41.3, 38.1, 24.9, 24.0, 18.3, 15.2, 8.7; IR (KBr): 3497, 3386, 2929, 2838, 1665, 1657, 1613, 1517, 1450, 1319, 1236, 1187, 1159, 1102, 1062, 1002, 837 cm^{-1}; HRMS (ESI): *m*/*z* [M + H - H_2O]$^+$ calcd for $C_{35}H_{40}N_5O_6S$: 658.2694; found: 658.2813.

Compound 9: To a stirred solution of **16** in THF (120 mL), HOAc (35.7 g, 34.0 mL, 595 mmol) was added at −10 °C. Then an aqueous solution of NaCN (40.0 mL, 138.7 mmol, 17% (w/v)) was portion wise added. The reaction mixture was stirred at this temperature for 1 h. It was basified with an aqueous solution of Na_2CO_3 (pH = 9), and extracted with CH_2Cl_2 (100 mL). The organic phase was washed with water twice, dried with Na_2SO_4, filtered and concentrated under reduced pressure. The residue was stirred in petroleum ether (200 mL) for 2 h. Then the solid was isolated by filtration and directly used in next step without further purification. $[\alpha]_D^{25}$ -115.0 (c 0.5, DMSO), ^{1}H NMR (400 MHz，DMSO-d_6): δ = 9.87 （s, 1 H），8.56 （s, 1 H），7.45-7.43 (m, 3 H), 7.36-7.32 (m, 2 H), 7.15-7.05 (m, 2 H), 6.22 (s, 1 H), 4.88 (d, *J* = 5.2 Hz 1 H), 4.42-4.41 (m, 1 H), 4.40-4.39 (m, 1 H), 4.30-4.28 (m, 1 H), 4.13 (s, 1 H), 3.89 (s, 3 H), 3.87-3.72 (m, 1 H), 3.53 (s, 3 H), 3.11-2.97 (m, 3 H), 2.85-2.55 (m, 2 H), 2.11 (s, 3 H), 2.02 (s, 3 H), 1.82 (s, 3 H), 1.70-1.52 (m, 1 H), 0.55 (d, *J* = 6.8 Hz, 3 H) ppm; ^{13}C NMR (100 MHZ，DMSO-d_6): δ = 186.1, 181.6, 178.9, 171.3, 155.6, 147.4, 143.0, 142.9, 139.2, 137.3, 131.2, 128.8, 128.6, 127.2, 124.3, 122.9, 120.1, 117.4, 81.8, 60.6, 59.8, 57.7, 55.6, 52.8, 52.1, 50.8, 41.3, 25.1, 23.9, 18.4, 15.4, 8.7; IR (KBr): 3475, 3347, 3265, 2935, 2849, 2360, 2339, 1655, 1620, 1520, 1497, 1449, 1416, 1374, 1344, 1320, 1237, 1191, 1156, 1105, 1076, 1059, 1046, 1024, 1002, 965, 924, 896, 876, 838, 802 cm^{-1}; HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{36}H_{40}N_6O_6SNa$: 707.2628; found: 707.2626.

Compound 14: To a solution of **9** in MeOH (120 mL), Me_3SiCl (80.5 mL, 635.0 mmol) was added at 0 °C. The solution was stirred for 3 h. Then the reaction mixture was filtered to give a yellow solid. The solid was washed with CH_2Cl_2 twice and dried under reduced pressure to give **14** (22.8 g, 80% yield for the three steps from compound **13**). $[\alpha]_D^{25}$ -72.0 (c 0.5, DMSO), ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.54 (s, 3 H), 6.53 (s, 1 H), 5.07 (s, 1 H), 4.54 (s, 1 H), 4.14 (m, 2 H), 3.97 (m, 5 H), 3.64 (s, 3 H), 3.29 (s, 1 H), 3.19-2.84 (m, 5H), 2.20 (s, 3 H), 1.84 (s, 3 H), 1.74 (dt, *J* = 23.8, 11.9 Hz, 1 H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 185.6, 181.3, 156.1, 148.1, 144.4, 142.4, 134.5, 131.5, 129.0, 127.2, 120.5, 61.2, 60.6, 60.4, 57.0, 56.6, 54.5, 53.3, 26.1, 24.3, 16.2, 15.9, 9.3, 9.1 ppm; IR (KBr): 3200, 2950, 2884, 2550, 2361, 1661, 1642, 1623, 1468, 1451, 1423, 1415, 1381, 1319, 1301, 1280, 1257, 1241, 1174, 1189, 1141, 1092, 1063, 1035, 979, 962 cm^{-1}; HRMS (ESI): *m*/*z* [M - Cl]$^+$ calcd for $C_{26}H_{31}N_4O_5$: 479.2289; found: 479.2290.

Compound 15: To a mixture of 10% $NaHCO_3$ (100 mL) and CH_2Cl_2 (100 mL), intermediate **14** (10.0 g, 19.4 mmol) was portion wise added at 0 °C. Then the aqueous phase was extracted with dichloromethane (30 mL × 2). The combined organic phase was added to a solution of water (160 mL), HOAc (73.5 g, 70 ml, 1.25 mol) and NaOAc (10.0 g, 121.9 mmol) at −5 °C under N_2 atmosphere. Then an aqueous solution of $NaNO_2$ (80 ml, 38.8 mmol, 3.3% (w/v)) was portion wise added. The reaction mixture was stirred for 0.5 h. Then the organic phase was basified with $NaHCO_3$ (pH = 8) and dried by anhydrous Na_2SO_4. Solvent was removed under reduced pressure. The residue was purified by flash column chromatography (ethyl acetate/ petroleum ether gradient from 1:5 to 1:4) to obtain **15** (4.6 g, 45%). $[\alpha]_D^{25}$ -95.0 (c 0.5, DMSO), ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.48 (s, 1 H), 4.72 (dd, *J* = 11.5, 3.1 Hz, 1 H), 4.21 (d, *J* = 8.0 Hz, 1 H), 4.13 (s, 1 H), 3.95 (s, 3 H), 3.94 (s, 1 H), 3.76 (s, 3 H), 3.70-3.66 (m, 1 H), 3.48-3.46(m, 1H), 3.21-2.99 (m, 3 H), 2.57 (d, *J* = 18.1 Hz, 1 H), 2.35 (s, 3 H), 2.23 (s, 3 H), 1.94 (s, 3 H), 1.65-1.64 (m, 1 H), 1.37 (s, 3 H) ppm ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.0, 181.2, 170.1, 155.5, 146.5, 142.9, 142.8, 135.4, 130.8, 129.1, 128.8, 121.3, 117.4, 115.5, 68.4, 61.9, 61.1, 60.8, 59.1, 56.0, 55.2, 55.1, 41.6, 25.2, 24.7, 22.9, 19.9, 15.6, 8.8 ppm; IR (KBr): 3432, 2935, 1741, 1656, 1499, 1456, 1418, 1375, 1321, 1234, 1190, 1158, 1105, 1057, 1005, 838 cm^{-1}; HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{28}H_{31}N_3O_7Na$: 544.2060; found: 544.2063.

Compound 19: To a solution of NaH (0.88 g, 60.0% (w/w), 22.0 mmol) in THF (30 mL), bromomethylmethyl ether (1.8 mL, 22.0 mmol) was added at 0 °C. Then a mixture of **15** (4.6 g, 8.8 mmol) in THF (30 mL) was portion wise added. The reaction mixture was stirred for 1 h at this temperature and quenched by 3.0% water in THF (30 mL). The solution was partitioned between CH_2Cl_2 (100 ml) and water (40 mL). Organic phase was washed with saturated aqueous sodium chloride solution (100 mL), dried with sodium sulfate, filtered and concentrated under reduced pressure to obtain **19** that was directly used in next step without further purification. $[\alpha]_D^{25}$ -10.0 (c 0.5, DMSO), ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.73 (s, 1 H), 5.16 (q, *J* = 6.0 Hz, 2 H), 4.67 (dd, *J* = 11.5, 3.0 Hz, 1 H), 4.42 (d, *J* = 2.3 Hz, 1 H), 4.19 (s, 1 H), 4.01 (s, 3 H), 3.96 (d, *J* = 1.9 Hz, 1 H), 3.77-3.69 (m, 4 H), 3.67 (dd, *J* = 7.4, 5.0 Hz, 2 H), 3.59 (s, 3 H), 3.35-3.22 (m, 1 H), 3.19-3.01 (m, 2 H), 2.69 (d, *J* = 18.2 Hz, 1 H), 2.45 (s, 3 H), 2.24 (d, *J* = 8.4 Hz, 3 H), 1.97 (s, 3 H), 1.47-1.38 (m, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.8, 181.1, 169.9, 155.5, 148.4, 148.3, 142.4, 135.3, 131.7, 129.8, 128.7, 125.5, 121.6, 116.9, 99.3, 62.1, 61.0, 59.9, 58.8, 57.7, 56.6, 55.8, 54.8, 41.0, 31.5, 25.7, 24.4, 19.9, 15.6, 8.7 ppm; IR (KBr): 3432, 2935, 1741, 1636, 1458, 1383, 1234, 1163, 1105, 1039, 924 cm^{-1}; HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{30}H_{35}N_3O_6Na$: 588.2322; found: 588.2326.

Compound 20: A mixture of LiOH (2.6 g, 61.7 mmol) in water (123 mL) and THF (63 mL) was cooled to 0 °C. Then a solution of **19** in THF (60 mL) was portion wise added. The reaction mixture was stirred for 12 h at this temperature. Then it was slowly added to a buffer solution (300 ml, 0.043 g Na_2HPO_4: 0.059 g citric acid per ml of H_2O), and extracted with CH_2Cl_2 (100 mL × 2). Organic phase was washed with saturated aqueous sodium chloride solution (100 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to obtain **20** (4.3 g, 95% yield for the two steps from compound **19**). $[\alpha]_D^{25}$ -74.0 (c 0.5, DMSO), ^{1}H NMR (400 MHz,

$CDCl_3$): δ = 6.72 (s, 1 H), 5.16 (s, 2 H), 4.31 (d, *J* = 2.0 Hz, 1 H), 4.07 (d, *J* = 2.4 Hz, 1 H), 3.85 (s, 1 H), 3.73-3.66 (m, 4 H), 3.60 (s, 3 H), 3.48 (dd, *J* = 11.6, 1.4 Hz, 1 H), 3.42 (d, *J* = 7.0 Hz, 1 H), 3.28 (m, 1 H), 3.18-3.11 (m, 2 H), 2.50 (d, *J* = 18.1 Hz, 1 H), 2.38 (s, 3 H), 2.22 (s, 3 H), 1.92 (s, 3 H), 1.63-1.60 (m , 1 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.2, 181.2, 151.1, 148.7, 144.9, 133.6, 131.7, 129.3, 125.1, 123.0, 117.2, 99.2, 62.3, 60.0, 59.2, 57.7, 57.0, 56.4, 55.0, 41.6, 31.6, 25.6, 24.8, 22.6, 15.8, 14.1, 8.0 ppm; IR (KBr) 3432, 2932, 1637, 1383, 1164 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{27}H_{32}N_3O_7$: 510.2240; found: 510.2242.

Compound 21: To a suspension of **20** (3.1 g, 6.0 mmol) in DMF (30.0 ml), 10% Pd/C (0.62 g) was added. The reaction was stirred under H_2 (1 MPa pressure) for 5.5 h. Then it was cooled to 0 °C and filtered under N_2 atmosphere. The filtrate was added to a flask containing Cs_2CO_3 (1.9 g, 5.9 mmol) and CH_2BrCl (6.0 mL, 92.5 mmol) under N_2 atmosphere. The solution was stirred for 45 min at 100 °C and cooled to room temperature. The reaction mixture was filtered. Then water (100 mL) and ethyl acetate (100 mL) was added to the filtrate. The organic layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (ethyl acetate/ petroleum ether gradient from 0:1 to 1:1) to obtain **21** (1.4 g, 44%). $[\alpha]_D^{25}$ -11.0 (c 0.1, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.71 (s, 1 H), 5.91 (d, *J* = 1.3 Hz, 1 H), 5.84 (d, *J* = 1.3 Hz, 1 H), 5.42 (d, *J* = 16.6 Hz, 1 H), 5.33-5.31 (m, 1 H), 5.20 (t, *J* = 6.5 Hz, 1 H), 4.28 (d, *J* = 2.3 Hz, 1 H), 4.10 (d, *J* = 2.5 Hz, 1 H), 4.05-3.98 (m, 1 H), 3.72-3.67 (m, 5 H), 3.56 (m, 2 H), 3.44-3.36 (m, 2 H), 3.18-3.07 (m, 2 H), 2.54 (d, *J* =2.0 Hz, 1 H), 2.37 (d, *J* = 5.7 Hz, 3 H), 2.23 (d, *J* = 11.3 Hz, 3 H), 2.10 (s, 3 H), 1.87-1.81 (m, 1 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.1, 147.9, 145.5, 144.6, 136.2, 131.3, 129.8, 125.0, 122.9, 117.6, 112.8, 112.2, 106.3, 100.8, 99.8, 63.2, 59.8, 58.1, 57.7, 56.8, 56.0, 55.3, 41.7, 25.9, 25.7, 15.8, 8.8 ppm; IR (KBr): 3456, 2930, 2850, 1658, 1639, 1635, 1483, 1441, 1401, 1339, 1234, 1156, 1102, 1060, 958, 926, 887, 736 cm^{-1}; HRMS (ESI): *m/z* $[M + H - H_2O]^+$ calcd for $C_{28}H_{32}N_3O_6$: 524.2391; found: 524.2395.

Compound 24: To a stirred solution of benzeneseleninic anhydride (0.82g, 2.3 mmol) in THF (60 mL), a suspension of **21** (1.2g, 2.3 mmol) in THF (60 mL) was portion wise added at −10 °C. The reaction mixture was stirred at this temperature for 20 min. Then it was filtered. Then water (80 mL) and CH_2Cl_2 (80 mL) were added to the filtrate. Organic layer was washed with water (30 mL) and dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to obtain **24** (mixture of isomer) that was directly used in next step without further purification. **Isomer 1:** $[\alpha]_D^{25}$ 235.0 (c 0.1, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.65 (s, 1 H), 5.86 (s, 1 H), 5.74 (s, 1 H), 5.05-5.01 (m, 2 H), 4.32-4.27 (m, 1 H), 4.10- 4.04(m, 3 H), 3.80-3.75 (m, 1 H), 3.63 (s, 3 H), 3.51 (s, 3 H), 3.41 (d, *J* = 8.6 Hz, 1 H), 3.11 (d, *J* = 30.0 Hz, 1 H), 3.04-2.97 (m, 1 H), 2.56 (d, *J* = 17.9 Hz, 1 H), 2.41-2.33 (m, 1 H), 2.25 (s, 3 H), 2.20 (s, 3 H), 2.15-2.11 (m, 1 H), 1.79 (s, 3 H) ppm;^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.5, 159.9, 148.7, 148.2, 137.7, 130.7, 130.2, 125.1, 124.01, 116.7, 113.6, 104.9, 100.9, 99.1, 72.2, 59.9, 58.6, 57.7, 57.4, 56.8, 56.6, 56.1, 55.2, 41.3, 25.5, 15.9, 7.1 ppm. IR (KBr): 3835, 3733, 3434, 2922, 2847, 2360, 2339, 2228, 2075, 1711, 1679, 1629, 1538, 1483, 1444, 1416, 1380, 1304, 1233, 1205, 1141, 1087, 1046, 1019, 996, 971, 927, 891, 852, 811 cm^{-1}; **Isomer 2:** $[\alpha]_D^{25}$ 120.0 (c 0.1, CH_3Cl), ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.74 (s, 1 H), 5.87-5.81 (m, 2 H), 5.18-5.12 (m, 2 H), 4.12 (d, *J* = 2.5 Hz, 2 H), 3.95 (d, *J* = 4.6 Hz, 2 H), 3.89-3.78 (m, 1 H), 3.70 (s, 3 H), 3.54 (s, 3 H), 3.36-3.34 (m, 2 H), 3.08-3.02 (m, 1 H), 2.64 (s, 1 H), 2.58 (d, *J* = 17.9 Hz, 1 H), 2.33 (s, 3 H), 2.27-2.17 (m, 4 H), 2.03 (dd, *J* = 15.3, 8.1 Hz, 1 H), 1.83 (s, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.7, 159.0, 148.8, 148.4, 140.5, 131.4, 130.3, 125.5, 123.0, 117.0, 111.0, 104.3, 101.6, 99.4, 70.3, 61.7, 60.5, 58.5, 58.1, 57.7, 57.2, 55.2, 41.6, 36.3, 25.6, 15.8, 7.3 ppm. IR (KBr): 3708, 3672, 3648, 3443, 2922, 2851, 2360, 2339, 1717, 1646, 1575, 1558, 1524, 1484, 1446, 1417, 1379, 1345, 1234, 1205, 1157, 1133, 1089, 1059, 1037, 994, 971, 953, 926, 887, 807 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{34}N_3O_8$:540.2340; found: 540.2335.

Compound 4: To a stirred solution of **24** in CH_2Cl_2 (60 mL), 4-dimethylaminopyridine (0.80 g, 6.9 mmol), **22** (1.40 g, 3.50 mmol) and EDCI (1.30 g, 6.90 mmol) was added at 0 °C. The reaction mixture was stirred for 2 h and neutralized by water (80 mL). Organic phase was washed with an aqueous of 0.2 M NaH_2PO_4 (30 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (ethyl acetate/ petroleum ether gradient from 0:1 to 1:1) to obtain **4** (mixture of isomer, 1.30 g, 60% yield for the two steps from compound **24**). **Isomer 1:** $[\alpha]_D^{25}$ 93.0 (c 0.1, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 7.5 Hz, 2 H), 7.69 (d, *J* = 7.4 Hz, 2 H), 7.42-7.39 (m, 2 H), 7.38-7.32 (m, 2 H), 6.57 (s, 1 H), 5.74 (s, 1 H), 5.65 (s, 1 H), 5.35 (d, J = 8.1 Hz, 1 H), 5.03 (q, *J* = 6.0 Hz, 2 H), 4.68 (d, *J* = 11.9 Hz, 1 H), 4.54 (d, *J* = 7.0 Hz, 1 H), 4.47-4.35 (m, 1 H), 4.14 (t, *J* = 6.3 Hz, 1 H), 4.07 (d, *J* = 4.0 Hz, 1 H), 4.02 (d, *J* = 4.0 Hz, 1 H), 3.92-3.90 (m, 1 H), 3.88-3.76 (m, 1 H), 3.64 (s, 3 H), 3.52 (s, 3 H), 3.32 (d, *J* = 8.4 Hz, 1 H), 3.19-3.17 (m, 1 H), 2.99-2.92 (m, 2 H), 2.44 (d, *J* = 17.9 Hz, 1 H), 2.32-2.25 (m, 1 H), 2.23 (s, 3 H), 2.19 (s, 3 H), 2.12 (d, *J* = 2.7 Hz, 1 H), 2.09 (d, *J* = 2.6 Hz, 1 H), 1.79 (s, 3H), 1.46 (s, 9 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.4, 170.9, 160.1, 155.3, 148.7, 148.2, 145.7, 145.6, 141.1, 138.5, 130.7, 130.1, 127.7, 127.6, 127.1, 125.0, 124.9, 124.8, 124.0, 119.9, 116.9, 111.7, 104.8, 101.0, 99.2, 80.3, 72.4, 59.8, 58.2, 57.7, 56.6, 56.5, 56.1, 55.2, 53.6, 46.9, 41.9, 41.3, 37.2, 35.3, 28.3, 25.5, 15.9, 7.1 ppm. IR (KBr): 3747, 3734, 3706, 3689, 3673, 3647, 3423, 2923, 2851, 2360, 2339, 1744, 1713, 1635, 1557, 1484, 1449, 1416, 1345, 1232, 1157, 1087, 1050, 1020, 997, 925, 894, 810 cm^{-1}; **Isomer 2:** $[\alpha]_D^{25}$ 89.0 (c 0.1, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 7.5 Hz, 2 H), 7.65 (t, *J* = 6.7 Hz, 2 H), 7.40 (t, *J* = 7.4 Hz, 2 H), 7.32 (t, *J* = 7.4 Hz, 2 H), 6.65 (s, 1 H), 5.74 (d, *J* = 8.7 Hz, 2 H), 5.33 (d, *J* = 6.9 Hz, 1 H), 5.13-5.09 (m, 2 H), 4.48 (d, *J* = 6.0 Hz, 1 H), 4.23 (dd, *J* = 11.2, 6.1 Hz, 1 H), 4.17-4.15 (m, 1 H), 4.09 (t, *J* = 6.4 Hz, 1 H), 4.05-4.03 (m, 2 H), 3.96 (t, *J* = 6.1 Hz, 1 H), 3.86 (s, 3 H), 3.52 (s, 3 H), 3.26 (d, *J* = 7.7 Hz, 1 H), 3.10-3.02 (m, 3 H), 2.98 (dd, *J* = 18.0, 7.7 Hz, 2 H), 2.92 (dd, *J* = 13.9, 5.5 Hz, 1 H), 2.48 (d, *J* = 17.9 Hz, 1 H), 2.41 (dd, *J* = 12.3, 8.4 Hz, 2 H), 2.28 (s, 3 H), 2.23 (s, 3 H), 1.90-1.82 (m, 1 H), 1.80 (d, *J* = 5.3 Hz, 3 H), 1.45 (d, *J* = 5.7 Hz, 9 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.6, 170.7, 158.2, 155.1, 148.7, 148.6, 145.7, 145.6, 142.3, 141.0, 131.2, 129.9, 127.7, 127.1, 125.1, 124.8, 119.9, 117.3, 108.3, 104.6, 101.5, 99.3, 80.4, 70.6, 66.7, 60.9, 60.3, 57.6, 56.8, 56.4, 55.7, 55.3, 53.6, 46.9, 41.5, 37.1, 36.9, 28.3, 25.7, 15.8, 7.4 ppm. IR (KBr): 3747, 3733, 3688, 3672, 3648, 3564, 3420, 2923, 2851, 2360, 2339, 1919, 1867, 1844, 1827, 1744, 1714, 1648, 1574, 1557, 1504, 1486, 1450, 1417, 1345, 1234, 1160, 1090, 1057, 1028, 995, 954, 927, 887, 808 cm^{-1}; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{50}H_{56}N_4O_{11}SNa$: 943.3559; found: 943.3554.

Compound 25: To a solution of triflic anhydride (8.18 g, 4.90 ml, 29.0 mmol) in CH_2Cl_2 (130 mL), DMSO (5.10 mL, 72.5 mmol) was portion wise added at −78 °C. The solution was stirred at this temperature for 30 min. Then a solution of **4** (13.4 g, 14.5 mmol) in CH_2Cl_2 (130 mL) at −78 °C was added portion wise.

During the addition, the temperature was kept at −78 °C. The reaction mixture was stirred at −40 °C for 45 min. After this, *i*-Pr_2NEt (13.83 g, 18.7 mL, 113.1 mmol) in anhydrous CH_2Cl_2 (18 mL) was slowly added and the reaction mixture was kept at 0 ºC for 45 minutes. Then *t*-BuOH (5.5 mL, 58 mmol) in anhydrous CH_2Cl_2 (10 mL) was added and stirred for 15 min. 2-*t*-Butyl-1, 1, 3, 3-tetramethylguanidine (17.4 g, 101.5 mmol) was slowly added and the mixture was stirred at 23 °C for 40 min. Then acetic anhydride (14.8 g, 145 mmol) was added and the reaction mixture was kept at 23 °C for 15 min. The mixture was washed with aqueous saturated solution of NH_4Cl (50 mL × 3). And the organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (ethyl acetate/hexane gradient from 0:1 to 1:4) to obtain compound **25** (5.60 g, 50%). $[\alpha]_D^{25}$ -12.0 (c 0.1, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.80 (s, 1 H), 6.09 (s, 1 H), 5.99 (s, 1 H), 5.20 (d, *J* = 5.4 Hz, 1 H), 5.14 (d, *J* = 5.5 Hz, 1 H), 5.01 (d, *J* = 11.7 Hz, 1 H), 4.63 (d, *J* =9.3 Hz, 1 H), 4.50 (s, 1 H), 4.33 (d, *J* = 4.7 Hz, 1 H), 4.28-4.25 (m, 2 H), 4.19 (s, 1 H), 4.14 (d, *J* = 11.6 Hz, 1 H), 3.78 (s, 3 H), 3.57 (s, 3 H), 3.45-3.41 (m, 2 H), 2.97-2.92 (m, 2 H), 2.80 (s, 1 H), 2.31 (s, 3 H), 2.29 (s, 3 H), 2.23-2.20 (m, 4 H), 2.07-2.02 (m, 4 H), 1.46 (s, 9 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6, 168.5, 155.1, 149.5, 148.4, 145.8, 141.0, 140.4, 131.5, 130.4, 125.2, 124.9, 124.8, 120.4, 118.0, 113.5, 113.3, 102.0, 99.2, 79.7, 61.4, 60.2, 59.6, 59.1, 58.9, 57.4, 54.8, 54.6, 53.8, 41.8, 41.4, 38.6, 28.5, 28.3, 28.2, 20.3, 15.8, 9.6 ppm; IR (KBr): 3802, 3748, 3734, 3673, 3648, 3564, 3431, 2922, 2850, 2360, 2340, 1868, 1827, 1760, 1716, 1670, 1649, 1557, 1539, 1502, 1455, 1433, 1370, 1339, 1237, 1194, 1162, 1088, 1055, 998, 969, 929, 896, 861 cm^{-1}; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{38}H_{48}N_4O_{11}S$: 767.2945; found: 767.2957.

Compound 26: A mixture of **25** (5.0 g, 6.50 mmol) and *p*-TsOH (7.10 g, 41.4 mmol) in CH_2Cl_2 (50 mL) was stirred at 23 °C for 7 h. Then it was basified with $NaHCO_3$. Organic phase was washed with saturated aqueous sodium chloride solution, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to obtain **26** (4.10 g, 100%). $[\alpha]_D^{25}$ -16.0 (c 0.1, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.52 (s, 1 H), 6.08 (s, 1 H), 5.98 (s, 1 H), 5.00 (d, *J* = 11.6 Hz, 1 H), 4.52 (s, 1 H), 4.25 (s, 2 H), 4.18 (s, 1 H), 4.13 (d, *J* = 11.7 Hz, 2 H), 3.77 (s, 3 H), 3.42-3.41 (m, 2 H), 3.30 (t, *J* =2.9 Hz, 2 H), 2.91-2.90 (m, 2 H), 2.30 (s, 3 H) , 2.28 (s, 3 H), 2.21 (m, 2 H), 2.18 (s, 3 H), 2.03 (s, 4 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.1, 168.7, 148.0, 145.6, 143.0, 141.0, 140.3, 130.5, 129.4, 120.8, 120.4, 118.3, 118.2, 113.7, 113.3, 101.9, 61.4, 61.2, 60.1, 59.3, 59.1, 54.7, 54.6, 53.9, 41.7, 41.5, 38.6, 34.2, 23.8, 20.6, 15.7, 9.6 ppm; IR (KBr): 3444, 2925, 2360, 2339, 1749, 1717, 1699, 1650, 1557, 1540, 1505, 1457, 1383, 1307, 1236, 1193, 1087, 1062, 912, 806 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{31}H_{35}N_4O_8S$: 623.2163; found: 623.2170.

Compound 27: To a solution of *N*-methyl pyridine-4-carboxaldehyde benzenesulfonate (9.30 g, 33.6 mmol) in anhydrous DMF (300 mL) and CH_2Cl_2 (300 ml), **26** (3.0 g, 4.80 mmol) was added. The solution was stirred for 3.5 h. Then it was cooled to 0 ºC, and DBU (1.72 g, 1.70 mL, 11.5 mmol) in CH_2Cl_2 (100 mL) was slowly added. After 25 min, a freshly saturated aqueous solution of oxalic acid (180 mL) was added to the reaction mixture at this temperature. The mixture was stirred for 45 min at 23 ºC. Then the reaction mixture was extracted with ethyl acetate. The combined organic layers was washed with saturated aqueous sodium chloride solution and dried over sodium sulphate. The solvent was removed under reduced pressure to obtain **27** (1.50 g, 51%). $[\alpha]_D^{25}$ 133.0 (c 0.1, $CHCl_3$), ^{1}H NMR (400MHz, $CDCl_3$): δ = 6.50 (s, 1 H), 6.10 (s, 1 H), 6.01 (s, 1 H), 5.88 (s, 1 H), 5.08 (d, *J* = 11.4 Hz, 1 H), 4.67 (s, 1 H), 4.39 (s, 1 H), 4.28 (d, *J* = 4.6 Hz, 1 H), 4.21 (d, *J* = 11.4 Hz, 1 H), 4.17 (s, 1 H), 3.75 (s, 3 H), 3.55 (d, *J* = 4.6 Hz, 1 H), 3.43 (d, *J* = 9.0 Hz, 1 H), 2.92-2.58 (m, 3 H), 2.32 (s, 3 H), 2.23 (s, 3 H), 2.14 (s, 3 H), 2.04 (s, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.7, 168.6, 160.5, 147.2, 146.4, 143.0, 141.6, 140.7, 130.4, 129.8, 121.6, 120.1, 117.9, 117.2, 113.5, 113.3, 102.2, 61.8, 61.4, 60.2, 59.8, 58.9, 54.6, 43.2, 41.6, 36.9, 24.1, 20.3, 15.8, 9.6 ppm; IR (KBr): 3448, 2933, 2653, 2360, 2339, 1761, 1728, 1622, 1557, 1540, 1502, 1457, 1433, 1371, 1305, 1270, 1235, 1194, 1144, 1106, 1086, 1062, 1029, 1001, 960, 912, 860 cm^{-1}; HRMS (ESI): m/z $[M +H]^+$ calcd for $C_{31}H_{33}N_3O_9S$: 622.1854; found: 622.1853.

Compound 28: A mixture of **27** (1.50 g, 2.40 mmol), 3-hydroxy-4-methoxyphenylethyl-amine (4.90 g, 24.0 mmol) and NaOAc (2.20 g, 26.4 mmol) in anhydrous EtOH (50 mL) was stirred at 23 °C for 5 h. The solvent was removed under reduced pressure to obtain a yellow solid. Ethyl acetate (100 mL) was added and stirred for 0.5 h. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (ethyl acetate/ petroleum ether gradient from 1:4 to 1:1) to obtain **28** (1.30 g, 70%). $[\alpha]_D^{25}$ -65.0 (c 0.1, $CHCl_3$), ^{1}H NMR (400 MHz,$CDCl_3$): δ = 6.61 (s, 1 H), 6.48 (s, 1 H), 6.45 (s, 1 H), 6.06 (s, 1 H), 5.99 (s, 1 H), 5.86 (s, 1 H), 5.02 (d, *J* = 11.5 Hz, 1 H), 4.58 (s, 1 H), 4.34 (s, 1 H), 4.29 (d, *J* = 4.5 Hz, 1 H), 4.20 (s, 1 H), 4.14 (d, *J* = 11.3 Hz, 1 H), 3.80 (s, 3 H), 3.62 (s, 3 H), 3.52 (d, *J* = 4.4 Hz, 1 H), 3.43 (s, 1 H), 3.15-3.11 (m, 1 H), 2.97-2.95 (m, 2 H), 2.83-2.81 (m, 1 H), 2.68-2.63 (m, 1 H), 2.51-2.46 (m, 1 H), 2.40-2.38 (m, 1 H), 2.34 (s, 3 H), 2.28 (s, 3 H), 2.21 (s, 3 H), 2.17-2.12 (m, 1 H), 2.06 (s, 3 H) ppm ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.4, 168.2, 147.9, 145.3, 144.7, 144.4, 143.1, 141.4, 140.1, 130.8, 129.5, 129.0, 125.4, 121.1, 120.7, 118.2, 118.1, 114.2, 114.0, 113.4, 109.8, 101.9, 64.7, 61.1, 60.4, 60.1, 59.7, 59.6, 55.2, 54.6, 42.0, 41.9, 41.6, 39.7, 29.7, 24.2, 20.4, 15.8, 9.7 ppm; IR (KBr): 3440, 2929, 2853 2360, 2338, 2251, 1744, 1665, 1621, 1590, 1557, 1510, 1457, 1370, 1326, 1261, 1236, 1105, 1087, 1056, 1027, 975, 958, 912, 862, 802 cm^{-1}; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{40}H_{44}N_4O_{10}S$: 771.2768; found: 771.2678.

Ecteinascidin 743 (1): To a solution of **28** (1.30 g, 1.70 mmol) in THF (40 mL) and H_2O (10 mL), CuCl (1.70 g, 17.0 mmol) was added at 23 °C. The solution was stirred for 24 h in darkness. Then the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl, diluted with ethyl acetate, and washed with saturated aqueous solutions of $NaHCO_3$. The aqueous layer was extracted with ethyl acetate and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford Ecteinascidin 743 (1.20 g, 94%). $[\alpha]_D^{25}$ -81.0 (c 0.1, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.63 (s, 1 H), 6.49 (s, 1 H), 6.46 (s, 1 H), 6.04 (s, 1 H), 5.96 (s, 1 H), 5.73 (s, 1 H), 5.16 (d, *J* = 11.2 Hz, 1 H), 4.84 (s, 1 H), 4.51-4.47 (m, 2 H), 4.19 (d, *J* = 3.7 Hz, 1 H), 4.05 (d, *J* = 11.4, 1 H), 3.81 (s, 3 H), 3.62-3.60 (m, 4 H), 3.25-3.23 (m, 1 H), 3.17-3.16 (m, 1 H), 2.90-2.88 (m, 3 H), 2.67-2.61 (m, 1 H), 2.51-2.47 (m, 1 H), 2.39-2.34 (m, 4 H), 2.28 (s, 3 H), 2.20-2.16 (m, 4 H), 2.05 (s, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.5, 168.4, 147.7, 145.1, 144.5, 144.3, 143.0, 141.3, 140.5, 134.3, 132.5, 131.5, 129.2, 129.1, 128.8, 127.7, 126.0, 121.8, 120.9, 118.0, 115.9, 114.1, 112.5, 109.9, 101.6, 82.1, 68.2, 64.7, 61.4, 60.3, 57.8, 57.7, 56.0, 55.1, 54.9, 42.2, 41.4, 39.7, 38.7, 31.9, 28.9, 28.8, 24.1, 23.7, 23.0, 20.4, 15.8, 14.0, 9.7 ppm; IR (KBr): 3429, 2926, 2853, 2360, 2339, 1764, 1742, 1651, 1621, 1590, 1557, 1511, 1457, 1431,1369, 1325, 1234, 1194,1107, 1087, 1051, 1028, 967, 915, 860, 800 cm^{-1}; HRMS (ESI): m/z $[M + H - H_2O]^+$ calcd for $C_{39}H_{42}N_3O_{10}S$: 744.2585; found: 744.2580.

Compound 18: A mixture of **15** (0.30 g, 0.48 mmol) and salcomine (0.15 g, 0.48 mmol) in anhydrous ACN (12 mL) was stirred at 23 °C in air for 5 h. Then the reaction mixture was filtered through a short silica gel column and the silica gel column was carefully washed with ethyl acetate. Then the solvent was removed under reduced pressure and the residue was purified by flash column chromatography (ethyl acetate/ petroleum ether gradient from 1:5 to 1:4) to afford **18** (0.25 g, 80%). $[\alpha]_D^{25}$ -127.0 (c 0.1, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.45 (d, *J* = 9.2 Hz, 1 H), 4.08-3.95 (m, 9 H), 3.82 (t, *J* = 14.7 Hz, 1 H), 3.38 (d, *J* = 6.5 Hz, 1 H), 3.11 (d, *J* = 11.2 Hz, 1 H), 2.95 (d, *J* = 16.9 Hz, 1 H), 2.79-2.72 (m, 1 H), 2.35 (s, 1 H), 2.31 (s, 3 H), 1.96 (s, 6 H), 1.86-1.67 (m, 3 H), 1.34-1.27 (m, 1 H) ppm.^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.3, 185.5, 182.6, 181.1, 170.0, 155.6, 155.3, 142.4, 142.0, 135.6, 135.0, 128.9, 128.8, 117.1, 63.7, 61.2, 59.1, 55.9, 54.7, 54.6, 53.5, 41.6, 25.4, 21.3, 20.6, 8.9, 8.7 ppm; IR (KBr): 3447, 2942, 1741, 1654, 1617, 1456, 1374, 1313, 1278, 1234, 1189, 1149, 1080, 1043, 964, 877, 840 cm^{-1}; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{28}H_{30}N_3O_8$: 536.2027; found: 536.2027.

(-)-Jorumycin (2): To a solution of **18** (0.17 g, 0.32 mmol) in ACN (3 mL) and H_2O (2 mL), $AgNO_3$ (0.54 g, 3.2 mmol) was added at 23 °C under argon atmosphere. The solution was stirred for 4 h at 45 °C in darkness. Then it was quenched with a saturated aqueous solution of NaCl, diluted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (ethyl acetate/ petroleum ether gradient from 1:2 to 1:0) to give **2** (0.14 g, 84%). $[\alpha]_D^{25}$ -72.0 (c 0.1, $CHCl_3$),^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.43 (dd, *J* = 10.9, 2.7 Hz, 2 H), 4.36 (dd, *J* = 24.5, 3.4 Hz, 1 H), 4.01 (s, 3 H), 3.99 (s, 3 H), 3.96-3.83 (m, 2 H), 3.81 (dt, *J* = 16.0, 8.0 Hz, 1 H), 3.19-3.15 (m, 2 H), 2.86 (d, *J* = 16.2 Hz, 1 H), 2.65 (dd, *J* = 21.0, 7.5 Hz, 1 H), 2.35-2.21 (m, 3 H), 1.96 (s, 3 H), 1.94 (s, 3 H), 1.80-1.72 (m, 3 H), 1.30-1.24 (m, 1 H) ppm.^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.5, 185.8, 182.6, 181.3, 170.0, 155.6, 155.2, 141.9, 141.8, 137.3, 134.5, 128.7, 128.3, 83.0, 64.2, 61.0, 60.9, 57.4, 54.2, 52.7, 51.0, 42.0, 41.4, 27.0, 25.6, 20.5, 20.4, 14.2, 8.7, 8.6 ppm; IR (KBr): 3446, 2937, 2853, 1741, 1654, 1616, 1522, 1449, 1375, 1311, 1234, 1189, 1148, 1100, 1081, 1039, 991, 900, 873, 840 cm^{-1}; HRMS (ESI): m/z $[M + H - H_2O]^+$ calcd for $C_{27}H_{29}N_2O_8$: 509.1918; found: 509.1918.

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Keywords: Ecteinascidin 743 • (-)-Jorumycin • Safracin B • Concise • Practical

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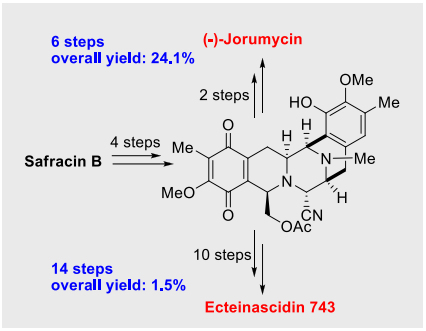
FULL PAPER

Ecteinascidin 743 (an anticancer drug) was synthesized from Safracin B via 14 steps with 1.5% overall yield by the strategy of directly converting an aliphatic amino group to the acetoxyl group. The synthetic approach was also used to synthesis of (-)-Jorumycin (a promising anticancer candidate). And (-)-Jorumycin was prepared in six steps from Safracin B and 24.1% overall yield.



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A Concise and Practical Semi-synthesis of Ecteinascidin 743 and (-)-Jorumycin

* Semi-synthesis