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Synthetic studies on ecteinascidin 743: asymmetric synthesis of the versatile amino acid component

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Abstract—The asymmetric synthesis of the modified tyrosine derivative as a basic building block for the ecteinascidin and safracin family of antitumor alkaloids has been achieved in nine steps and 39% overall yield.

Ecteinascidin (ET)-743 (**1**), is a natural product isolated from the marine tunicate *Ecteinascidia turbinata*,[1] and has been demonstrated to be a highly promising, exceedingly potent antitumor agent currently in phase II/III clinical trials.[2] The novel structure of ET-743 combined with its meagre availability from natural sources, and the unique mechanism of action[3] have made this drug a very attractive synthetic target. The first total synthesis of ET-743 was accomplished by Corey and co-workers.[4] Later Corey, Schreiber and co-workers prepared a synthetic analogue of ET-743 (phthalascidin, Pt-650) that has virtually the same cytotoxicity as the natural product.[5] In 2000, a semi-synthesis of Et-743 from cyanosfracin B was described.[6] Very recently, another total synthesis of ET-743 was reported by Fukuyama and co-workers.[7]

In addition to Et-743 (Fig. 1), the structurally related safracins,[8] saframycins[9] and renieramycins[10] are also potent antitumor antibiotics that contain structurally related amino acid components. We report here, a potentially general method to synthesize a highly functionalized tyrosine derivative that represents the 'eastern' sector of Et-743 that may be of potential use for the asymmetric total synthesis of several members of this family of natural products and congeners.[11] Our approach is based on the use of the optically pure oxazinone **12** as template.[12,13] Our retrosynthetic strategy for Et-743 is illustrated in Scheme 1.

As shown in Scheme 1, the key amino acid **9** was envisioned to arise via the coupling of the sodium enolate of optically active (>99:1 er) oxazinone **12**[12,13] with the benzyl bromide derivative of aldehyde **11** to furnish the alkylation product **10**. Further manipulation would involve *N*-methylation of the amine group and the phenol protecting group to give amino acid **9**. We have reported separately, the construction of optically pure β-lactams corresponding to **8** which has been converted into a pentacyclic intermediate such as **7**.[14]

The synthesis commenced with 3-(benzyloxy)-4-methoxy-5-methylbenzaldehyde (**13**),[15] which could be conveniently made in ~10 gram scale batches from

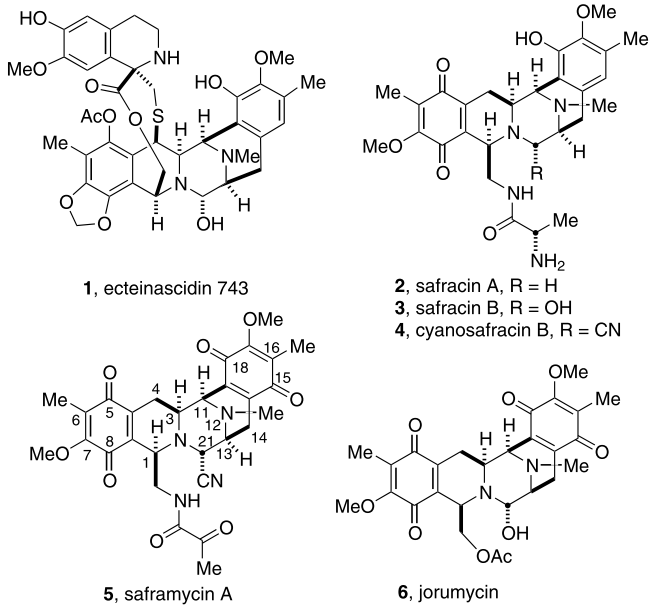

Figure 1.

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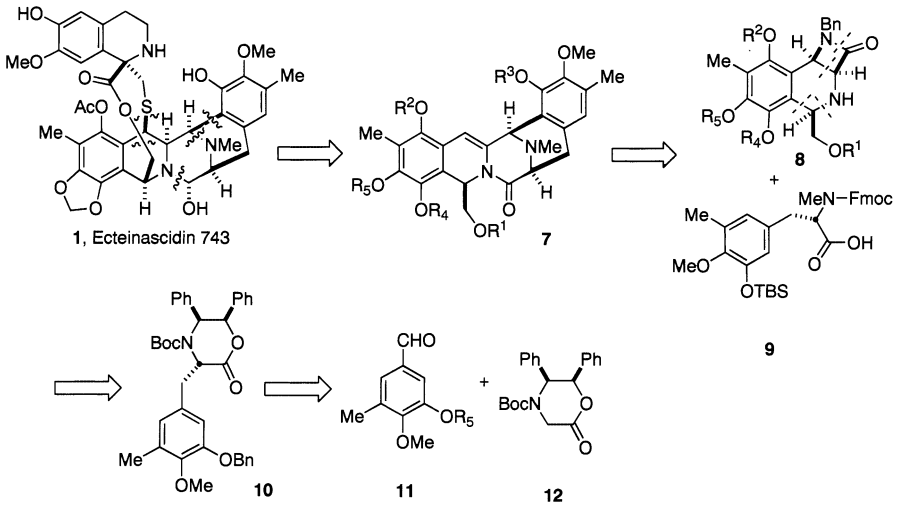
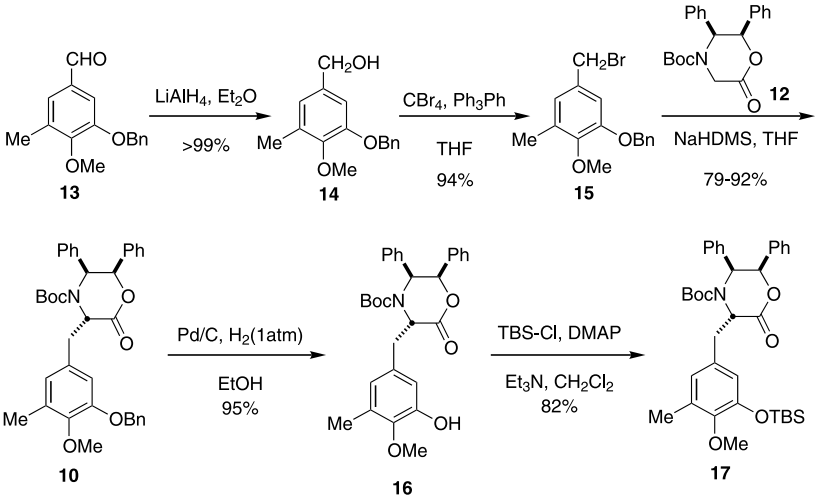


Scheme 1.

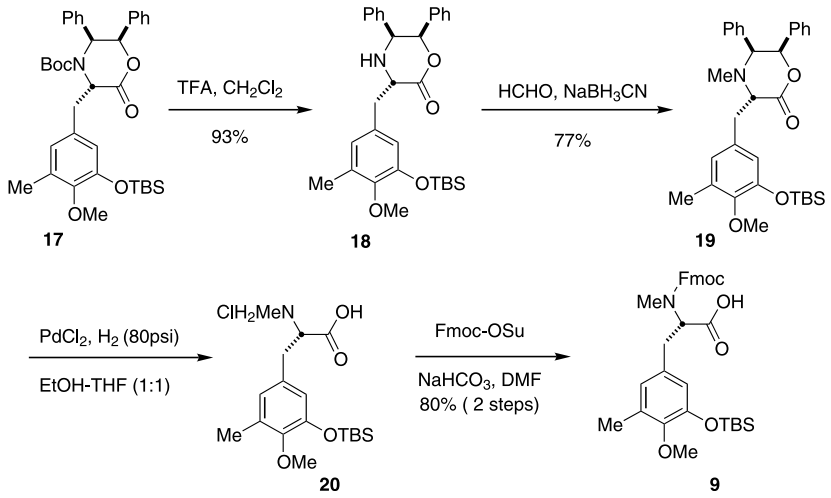
vanillin in seven steps: (i) HCHO, Me_2NH, ethanol (94%); (ii) Ac_2O; conc. HCl; $SnCl_2$ (78%); (iii) $AlCl_3$, pyridine, CH_2Cl_2 90%; (iv) TIPS-Cl, Et_3N, DMF (82%); (v) Me_2SO_4, K_2CO_3, acetone (88%); (vi) TBAF, THF (82%); (vii) BnBr, K_2CO_3, acetone (86%). As shown in Scheme 2, the aldehyde of **13** was reduced to the corresponding alcohol (**14**) by treatment with LAH in quantitative yield. Alcohol **14** was converted into benzyl bromide derivative **15** through the agency of CBr_4, Ph_3P in 94% yield. Next, **15** was condensed with the sodium enolate (NaHMDS, THF, −78°C) of oxazinone **12** to afford the alkylation product **10** in 79–92% yield. The *O*-benzyl group of **10** was removed by catalytic hydrogenation to give the corresponding phenol **16** in 95% yield, followed by protection as the *O*-TBS ether under standard conditions providing **17** in 82% yield.

The final conversion of **17** into **9** is illustrated in Scheme 3. The *N*-*t*-Boc group of compound **17** was removed by treatment with TFA in 93% yield affording the secondary amine **18**. In practice, we found it quite difficult to effect the efficient *N*-methylation of **18** and after extensive studies, it was found that the best conditions for this transformation was via reductive amination using formaldehyde furnishing **19** ($NaBH_3CN$, HCHO, CH_3CN, 77% yield). The chiral auxiliary of **19** was removed by catalytic hydrogenation to provide the amino acid hydrochloride salt **20**.[16] Finally, the secondary amine was protected as the corresponding Fmoc derivative furnishing **9** in 80% yield for the two steps.[17]

Compound **9** should prove to be a versatile amino acid, which contains the requisite functionality and desired absolute stereochemistry, for the synthesis of the ecteinascidins and related alkaloids. Efforts to utilize this intermediate for the concise asymmetric synthesis of the ecteinascidin, saframycin as well as safracin family are currently under study in these laboratories.



Scheme 2.



Scheme 3.

Acknowledgements

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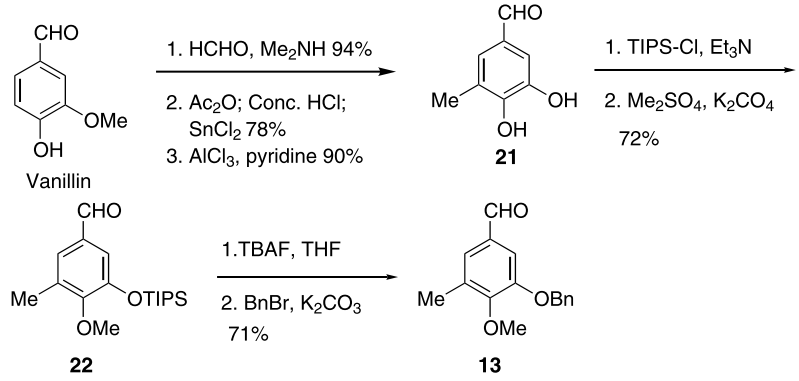
15. (a) Synthesis of this aldehyde could also be achieved in four steps for small scale (1∼2 g) from commercial available isovanillin: (i) NaH, DMF; MOM-Br 95%; (ii) *n*BuLi, *N*-methylpiperazine, THF; *n*BuLi; MeI 40%; (iii) MsOH, CH_2Cl_2/H_2O; (iv) BnBr, K_2CO_3, acetone 81% for two steps; (b) Sinhababu, A. K.; Borchardt, R. T. *Synth. Commun*. **1983**, *13*, 677–683. The synthesis of **13** as described in the text is prepared according to the following scheme.



16. This amino acid salt is soluble in ether, and it thus proved expedient to take the crude salt on directly for the next step without further purification.
17. All new compounds gave satisfactory spectroscopic and analytical data consistent with the assigned structures.
Alcohol **14**: ^{1}H NMR (300 MHz) δ $CDCl_3$: 1.95 (1H, s), 2.32 (3H, s), 3.88 (3H, s), 4.60 (2H, s), 5.15 (2H, s), 6.82 (1H, s), 6.89–6.90 (1H, d, J=1.8 Hz), 7.37–7.52 (5H, m). ^{13}C NMR (75 Hz) δ $CDCl_3$: 16.1, 60.4, 65.3, 70.7, 110.7, 121.8, 127.3, 127.9, 128.6, 132.1, 136.4, 137.1, 147.1, 151.8. IR (NaCl, neat) 3396, 2932, 2872, 2827, 1591, 1495, 1433, 1325, 1230, 1143, 1089, 1008, 737, 697 cm^{-1}. HRMS (FAB$^+$) calcd for $C_{16}H_{18}O_3$: 258.1256; found: 258.1249.
Bromide **15**: ^{1}H NMR (300 MHz) δ $CDCl_3$: 2.33 (3H, s), 3.91 (3H, s), 4.49 (2H, s), 5.17 (2H, s), 6.89–6.90 (1H, d, J=2.1 Hz), 6.92–6.93 (1H, d, J=2.4 Hz), 7.39–7.54 (5H, m). ^{13}C NMR δ $CDCl_3$: 15.1, 33.3, 59.3, 69.8, 111.7, 123.0, 126.4, 127.0, 127.6, 131.4, 131.9, 135.9, 147.0, 150.77. IR (NaCl, neat): 3031, 2932, 2828, 1589, 1493, 1434, 1333, 1287, 1211, 1150, 1090, 1008, 738, 698 cm^{-1}. HRMS (FAB$^+$) calcd for $C_{16}H_{17}O_2Br$: 320.0419; found: 320.0418.
Compound **10**: ^{1}H NMR (400 MHz) (DMSO-d_6, 373 K) δ DMSO: 1.16–1.41 (9H, broad), 2.23 (3H, s), 3.27–3.30 (3H, d, J=16 Hz), 3.41–3.46 (1H, m), 3.77 (3H, s), 5.04 (1H, broad), 5.14 (3H, s), 5.4 (1H, broad), 6.59–6.61 (2H, d, J=7.2 Hz), 6.78 (1H, s), 6.86–6.87 (2H, d, J=5.6 Hz), 6.93 (1H, s), 7.09–7.49 (9H, m). ^{13}C NMR (100 MHz) (DMSO-d_6, 373 K) δ DMSO: 13.5, 15.0, 27.2, 57.9, 59.2, 59.7, 70.3, 77.5, 80.0, 113.9, 123.8, 125.8, 126.7, 126.9, 127.2, 127.3, 127.6, 127.8, 130.8, 131.2, 134.2, 136.7, 146.1, 151.0, 167.8, 169.5. IR (NaCl, neat): 3032, 2931, 1754, 1697, 1588, 1494, 1453, 1382, 1331, 1233, 1161, 1085, 1010, 738, 702 cm^{-1}. HRMS (FAB$^+$) calcd for $C_{37}H_{39}NO_6$: 593.2777; found: 593.2781. $[\alpha]_D^{25}$ +22.5 (*c* 0.71, CH_2Cl_2).
Compound **16**: ^{1}H NMR (400 MHz) (DMSO-d_6, 373 K) δ DMSO: 1.08–1.47 (9H, broad), 2.20 (3H, s), 3.16–3.19 (1H, broad), 3.34–3.39 (1H, m), 3.47–3.51 (1H, m), 3.73 (3H, s), 5.01 (1H, broad), 5.08 (1H, broad), 5.38 (1H, broad), 6.56–6.59 (3H, m), 6.69 (1H, s), 6.85–6.86 (2H, d, J=6.4 Hz), 7.08–7.26 (6H, m). ^{13}C NMR (100 MHz) (DMSO-d_6, 373 K) δ DMSO: 15.0, 17.8, 27.2, 55.6, 58.8, 59.6, 77.4, 80.0, 115.3, 115.4, 121.8, 125.7, 126.7, 126.9, 127.2, 127.6, 130.4, 131.0, 134.2, 145.1, 149.4, 167.9. IR (NaCl, neat): 3399, 2977, 2933, 1754, 1697, 1590, 1497, 1454, 1386, 1357, 1301, 1161, 1119, 1060, 1003, 736, 702 cm^{-1}. HRMS (FAB$^+$) calcd for $C_{30}H_{33}NO_6$: 503.2308, found: 503.2307. $[\alpha]_D^{25}$ +37.8 (*c* 1.27, CH_2Cl_2).
Compound **17**: ^{1}H NMR (400 MHz) (DMSO-d_6, 373 K) δ DMSO: 0.17–0.18 (6H, s), 1.00 (9H, s), 1.05–1.50 (9H, broad), 2.22 (3H, s), 3.19–3.22 (1H, broad), 3.37–3.42 (1H, broad), 3.73 (3H, s), 4.99 (1H, broad), 5.08 (1H, broad), 5.30 (1H, broad), 6.56–6.58 (2H, d, J=6.8 Hz), 6.66 (1H, s), 6.73 (1H, s), 6.83–6.84 (2H, d, J=4.8 Hz), 7.10–7.25 (6H, m). ^{13}C NMR (100 MHz) (DMSO-d_6, 373 K) δ DMSO: −5.2, 15.1, 17.4, 25.1, 27.2, 58.9, 77.5, 80.1, 119.4, 119.5, 124.2, 125.7, 126.8, 127.0, 127.3, 127.7, 131.3, 134.1, 147.7, 148.2, 167.82. IR (NaCl, neat): 3032, 2927, 2856, 1757, 1702, 1585, 488, 1454, 1380, 1357, 1254, 1162, 1116, 1067, 1011, 838, 784, 701 cm^{-1}. HRMS (FAB$^+$) calcd for $C_{36}H_{47}NO_6Si$: 617.3173; found: 617.3169. $[\alpha]_D^{25}$ +22.1 (*c* 1.09, CH_2Cl_2).
Compound **18**: ^{1}H NMR (400 MHz) δ $CDCl_3$: −0.01 (3H, s), 0.02 (3H, s), 0.90 (9H, s), 1.23 (1H, broad), 2.15 (3H, s), 3.12–3.17 (2H, m), 3.68 (3H, s), 4.15–4.18 (1H, dd, J=4.0 Hz, 9.2 Hz), 4.60 (1H, d, J=3.6 Hz), 5.55–5.56 (1H, d, J=3.6 Hz), 6.49–6.50 (1H, d, J=2.0 Hz), 6.62 (1H, d, J=1.6 Hz), 6.85–6.88 (4H, m), 7.11–7.23 (6H, m). ^{13}C NMR (100 MHz) δ $CDCl_3$: −4.6, 16.1, 18.3, 25.8, 29.8, 38.5, 56.7, 58.3, 59.9, 85.3, 120.0, 124.6, 127.3, 127.7, 127.8, 128.2, 128.4, 132.4, 132.9, 135.1, 136.8, 148.8, 149.0, 170.6. IR (NaCl, neat): 3325, 2955, 2929,

2857, 1738, 1584, 1489, 1336, 1253, 1226, 1180, 1070, 1012, 838, 783, 699 cm^{-1}. HRMS (FAB^+) calcd for $C_{31}H_{40}NO_4Si$: 518.2727; found: 518.2719. $[\alpha]_D^{25}$ +55.4 (*c* 0.70, CH_2Cl_2).

Compound **19**: ^1H NMR (400 MHz) δ $CDCl_3$: 0.18 (3H, s), 0.20 (3H, s), 1.03 (9H, s), 2.27 (3H, s), 2.39 (3H, s), 3.03–3.23 (2H, dd, $J=4.0$ Hz, 13.2 Hz), 3.76 (3H, s), 3.97–4.01 (2H, m), 5.06 (1H, s), 6.71 (1H, s) 6.74 (1H, s), 6.78–6.79 (2H, d, $J=7.2$ Hz), 6.86–6.87 (2H, d, $J=5.2$ Hz), 7.10–7.19 (6H, m). ^{13}C NMR (100 MHz) δ $CDCl_3$: –4.5, –4.4, 16.2, 18.4, 25.9, 29.8, 37.4, 39.7, 60.0, 64.7, 67.4, 81.7, 121.0, 125.5, 126.1, 127.8, 127.9, 128.0, 128.2, 129.4, 132.0, 132.6, 134.3, 135.9, 148.4, 148.8, 171.7. IR (NaCl, neat): 2930, 2857, 1744, 1585, 1489, 1351, 1315, 1254, 1176, 1146, 1070, 1012, 839, 783, 712, 697 cm^{-1}. HRMS (FAB^+) calcd for $C_{32}H_{42}NO_4Si$: 532.2883; found: 532.2861. $[\alpha]_D^{25}$ –40.5 (*c* 1.11, CH_2Cl_2).

Compound **9**: ^1H NMR (300 Hz) δ $CDCl_3$ 0.14 (6H, s), 0.99 (9H, s), 2.18 (3H, s), 2.87 (3H, s), 2.6–3.3 (4H, m), 3.66 (3H, s), 4.14–4.37 (3H, m), 4.64–4.93 (1H, m), 6.48 (1H, s), 6.59–6.64 (1H, s), 7.25–7.54 (6H, m), 7.72–7.76 (2H, dd, $J=3.0$ Hz, 7.5 Hz), 8.04 (1H, s); ^{13}C NMR (75 MHz) δ –4.3, 16.3, 18.5, 25.9, 31.9, 32.6, 34.4, 36.9, 47.3, 59.9, 60.9, 68.1, 119.3, 120.0, 124.0, 124.9, 125.1, 127.1, 127.7, 132.3, 132.4, 141.3, 144.0, 148.6, 163.0, 174.8; IR (neat, film): 2954, 2929, 2857, 1682, 1598, 1451, 1322, 1142, 839 cm^{-1}; HRMS calcd for $C_{33}H_{41}NO_6Si$: 575.2703, found: 575.2697. $[\alpha]_D$ –40.8 (*c* 0.5, CH_2Cl_2).