A Short Enantioselective Synthesis of Protected L-3-Hydroxy-4-methoxy-5-methyl Phenylalanine and its Corresponding Aldehyde – A Common Subunit of Ecteinascidin-743, Safracin and Congeners

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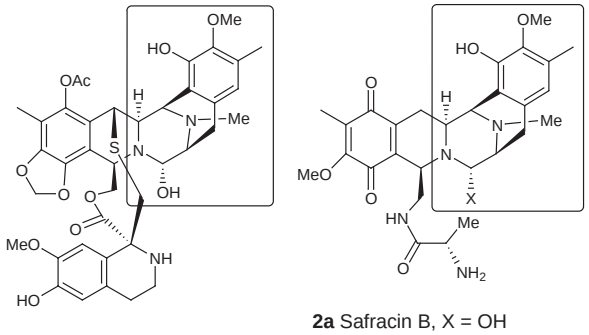
Abstract: An asymmetric synthesis of appropriately protected L-3-hydroxy-4-methoxy-5-methyl phenylalanine from 3-methyl-catechol is described featuring a key enantioselective alkylation step.

Key words: amino acid, Ecteinascidin 743, phase transfer catalyst, glycine template, L-DOPA derivative.

Ecteinascidin 743 (Et 743, **1**, Figure 1), which has been isolated from the Caribbean tunicate *Ecteinascidia turbinate*, possesses potent cytotoxic activity against a variety of tumor cell lines in vitro and against several rodent tumors and human tumor xenografts in vivo.[1] It is currently in phase II/III clinicals trials as an anticancer agent. Whilst the Et 743 is structurally related to the safracin (**2a**, **2b**) class of antibiotics,[2] the presence of a 1,4-bridged 10-membered macrolactone in **1** made its synthesis even more challenging.[3] To date, two total syntheses of Et 743 (**1**) have been accomplished by Corey,[4] Fukuyama,[5] and a semi synthesis from cyanosafracin B (**2b**) has been realized by Cuevas et al.[6] Other original contributions have been reported from the group of Kubo,[7] Danishefsky,[8] and Williams.[9]

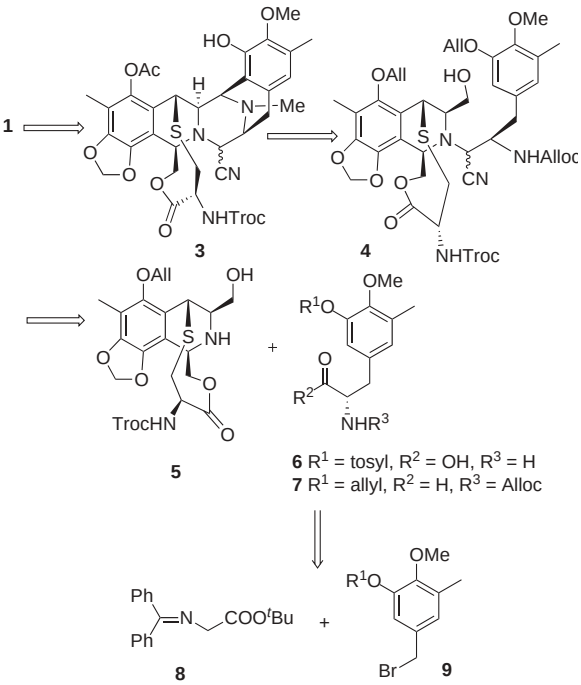


1 Ecteinascidin 743

2a Safracin B, X = OH
2b Cyanosafracin B, X = CN

Figure 1

Our group is working on a convergent synthetic approach in which the tetrahydroisoquinoline with a 1,4-bridged 10-membered macrocycle **5** and amino acid **6**/or amino aldehyde **7** are projected to be the key intermediates. We have already described a concise synthesis of enantiomerically pure macrolactone **5** from sesamol.[10] Reported herein is an asymmetric synthesis of L-amino acid **6** and amino aldehyde **7**. The key step of this synthesis is the enantioselective alkylation of *N*-(diphenylmethylene) glycine *tert*-butyl ester **8** by 3-tolylsulfonyloxy-4-methoxy-5-methyl benzyl bromide **9** under phase transfer catalytic conditions.[11–13] A synthesis of this amino acid wherein the key operation is a diastereoselective alkylation of chiral oxazinone has very recently been communicated by the group of Williams.[9a] Besides being enantioselective, our synthesis started from 3-methyl catechol, instead of vanillin, that considerably shortened the synthesis of the substituted benzyl bromide **9**.



Scheme 1 Retrosynthesis of Et 743 (**1**)

The synthesis of substituted benzyl bromide **9** is described in Scheme 2. Regioselective mono-protection of 3-methyl catechol (**10**) with tosyl chloride[5b] followed by methylation provided compound **12**. The tosylation was conducted at lower temperature with a slight default in tosyl chloride to avoid bis-tosylation. Formylation of **12** with

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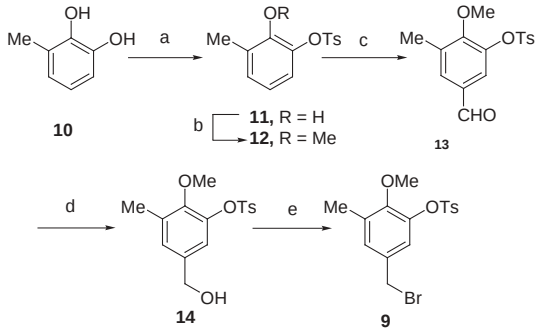
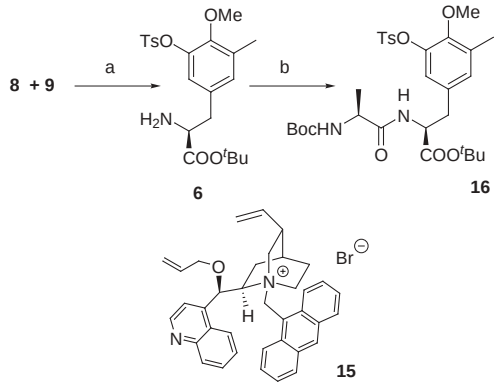


Scheme 2 *Reagents and conditions*: a) TsCl, Et_3N, CH_2Cl_2, –70 °C; b) MeI, K_2CO_3, acetone, 55 °C, 84% for two steps; c) $TiCl_4$ in CH_2Cl_2, Cl_2CHOCH_3, 0 °C → r.t., 85%; d) $NaBH_4$, MeOH–THF–H_2O (1:1:0.1), 0 °C, quantitative; e) PBr_3, toluene–CH_2Cl_2, (4:1), 0 °C → r.t., 96%

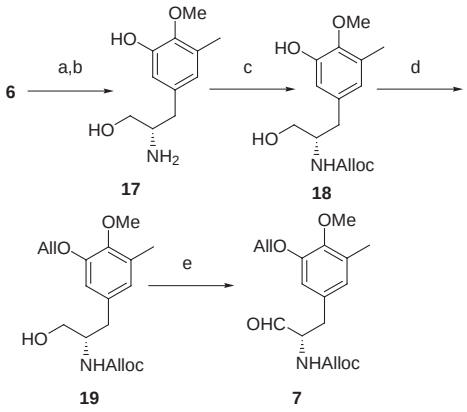
α,α-dichloromethyl methyl ether in the presence of titanium chloride (1 M in CH_2Cl_2) provided **13** in 85% yield as the only isolable regioisomer.[14] The presence of a tosyloxy function at C-3 might account for the observed high regioselectivity. Reduction of aldehyde **13** to alcohol **14** ($NaBH_4$, MeOH–THF–H_2O) followed by bromination (PBr_3, toluene–CH_2Cl_2 = 4:1) furnished **9** in 96% overall yield. This 5-step synthesis of **9** compared favorably to the previous 9-step synthesis starting from vanillin.[9a]



Scheme 3 *Reagents and conditions*: a) **15** (10%), $CsOH·H_2O$, CH_2Cl_2, –78 °C then after work up THF–H_2O–AcOH (1:1:1), 85%; b) *N*-Boc-D-Ala, EDCI, HOBt, DMF, r.t., 87%, dr = 10:1.

Following Corey's procedure, alkylation of *N*-(diphenylmethylene) glycine *tert*-butyl ester **8** with **9** in the presence of a catalytic amount of *O*-9-allyl-*N*-(9′-anthracenylmethyl)cinchonidium bromide **15** (0.1 equiv) afforded, after chemoselective hydrolysis of the imine function (THF–H_2O–AcOH), the amino ester **6** in 85% overall yield. The enantiomeric purity of this compound was determined to be higher than 90% by its transformation to the dipeptide **16**.

While compound **6** is ready to couple with macrolactone **5** to advance the total synthesis, an alternative coupling partner for **5** would be the amino aldehyde **7**. The transformation of **6** to **7** is shown in the Scheme 4. Reduction



Scheme 4 *Reagents and conditions*: a) $LiBH_4$, MeOH, Et_2O, r.t.; b) aq 2 N NaOH, EtOH, reflux; c) AllocCl, sat. aq $NaHCO_3$, CH_2Cl_2, r.t. then K_2CO_3, MeOH–H_2O (10:1), r.t.; d) Allyl bromide, K_2CO_3, acetone, reflux; 60–65% overall yield from **6**; e) Swern oxidation, 92%.

of ester to alcohol followed by *N*-protection as allyl carbamate afforded amino alcohol **18**. Selective allylation of phenol followed by Swern oxidation of the remaining primary alcohol provided then the expected amino aldehyde **7**.[15] The overall yield of this 5-step sequence is about 55%. Both amino ester **6** and amino aldehyde **7** could be considered as versatile building blocks in the synthesis of ecteinascidin and safracin family alkaloids.

The (*S*) configuration of amino ester **6** was assigned by taking the Corey-Lygo empiric model in account. To further prove this assignment, both (*S*)- and (*R*)-*O*-methylmandelic amide **20** and **21** were synthesized (Figure 2). The calculated chemical shift differences [$\delta_{ArCH2\ (\mathbf{20}–\mathbf{21})}$ = –0.08 ppm; $\delta_{TBDMSOCH2\ (\mathbf{20}–\mathbf{21})}$ = 0.09 ppm] are in accord with the *S* configuration of the amino alcohol, hence that of the amino ester **6**.[16] In addition, analysis of ^{1}H NMR spectra of compounds **21** and **22** indicated that the de of **20** and **21**, and hence the ee of their precursor **6**, is higher than 90%.

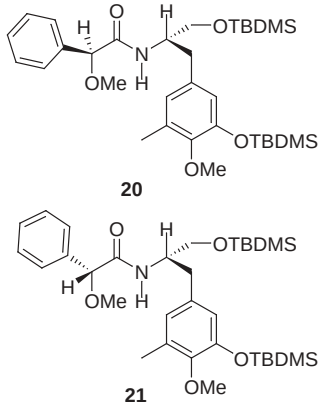


Figure 2

In conclusion, we have developed a short asymmetric synthesis of a protected L-3-hydroxy-4-methoxy-5-methyl phenylalanine (**6**) and the corresponding aldehyde (**7**). Key steps are: a) the regioselective tosylation of catechol,

which ensures the regioselective formylation of the aromatic ring and, b) the efficient enantioselective alkylation under phase transfer conditions. We are pursuing the total synthesis of Et 743 and related natural products using the advanced intermediates **5** and **7**.

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(15) Compound **6**. $[\alpha]_D^{23}$ +13 (*c* = 0.8, $CHCl_3$). IR ($CHCl_3$): 3382, 3034, 2981, 2938, 1725, 1598, 1495, 1370, 1293, 1218, 1178 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$, 293 K): δ = 7.76 (d, *J* = 7.6 Hz, 2 H), 7.32 (d, *J* = 7.5 Hz, 2 H), 6.90 (br s, 1 H), 6.79 (br s, 1 H), 3.67 (s, 3 H), 3.48 (dd, *J* = 7.3, 5.5 Hz, 1 H), 2.88 (dd, *J* = 13.7, 5.5 Hz, 1 H), 2.67 (dd, *J* = 13.7, 7.3 Hz, 1 H), 2.44 (s, 3 H), 2.19 (s, 3 H), 1.42 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$, 293 K): 174.0, 149.3, 145.1, 142.2, 133.1, 132.8, 130.4, 129.5, 129.2, 128.5, 128.4, 121.8, 81.2, 60.5, 56.0, 40.2, 28.1, 27.9, 21.6, 15.9. MS (ESI^+): *m*/*z* = 436.2 [M + H]$^+$, 458.3 [M + Na]$^+$, 474.2 [M + K]$^+$. HRMS (ESI^+): *m*/*z* [M + H$^+$] calcd for $C_{22}H_{30}O_6S$: 436.1794; found: 436.1789. Compound **7**. $[\alpha]_D^{23}$ +22 (*c* = 1, $CHCl_3$). IR ($CHCl_3$): 3426, 3024, 2933, 2830, 1716, 1590, 1496, 1343, 1232, 1087, 1007 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 293 K): 9.52 (s, 1 H), 6.56 (m, 2 H), 5.96 (ddd, *J* = 17.7, 12.5, 7.2 Hz, 1 H), 5.82 (m, 1 H), 5.33 (ddt, *J* = 16.8, 1.7, 1.6 Hz, 1 H), 5.17 (m, 4 H), 4.47 (m, 4 H), 4.46 (m, 1 H), 3.80 (s, 3 H), 2.98 (dd, *J* = 14.0, 6.5 Hz, 1 H), 2.89 (dd, *J* = 14.0, 6.8 Hz, 1 H), 2.21 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$, 293 K): 199.2, 155.8, 151.6, 146.7, 133.2, 132.5, 132.3, 130.6, 123.8, 118.0, 117.5, 112.7, 69.4, 65.9, 60.9, 60.1, 35.2, 15.9. MS (ESI^+): *m*/*z* = 334.2 [M + H]$^+$.

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