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Synthetic studies towards (±)-phthalascidin 650: synthesis of a fully functionalized N-protected-α-amino-aldehyde

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Abstract—An efficient synthesis of fully functionalized N-protected α-amino-aldehyde (±)-**13** as synthetic precursor of the tetrahydroisoquinoline alkaloid phthalascidin 650 is reported. Starting from sesamol **6**, 11 steps are required to give rise to the desired N-protected α-amino-aldehyde (±)-**13** in 25% overall yield. This synthetic strategy involves the elaboration of fully functionalized aromatic aldehyde **7** and its transformation into an α-amino-alcohol through a Knoevenagel condensation. The phthalimidomethyl derivative (±)-**11** was then synthesised from **8** by a Bischler–Napieralski reaction, a diastereoselective hydrogenation of the resultant dihydroisoquinoline and transformed into the corresponding N-protected α-amino-aldehyde (±)-**13**.

Phthalascidin 650 (Pt 650, **1**) is a modified structural synthetic analogue of ecteinascidin 743 (Et 743, **2**) and displayed a similar antitumor activity than those described for Et 743 (Fig. 1).[1] The tetrahydroisoquinoline family member, Et 743, was isolated from the Caribbean tunicate *Ecteinascidia turbinate*[2] and displayed highly potent cytotoxic activity against a variety of tumor cancer cells in vitro and is currently undergoing phase II/III clinical trials.[3]

Until now, only three total syntheses of **2** have been reported by Corey et al.,[4] Fukuyama and co-workers,[5] and Zhu and co-workers.[6] The synthesis and biological profile of Pt 650 was first reported by Corey. A semisynthesis achieved by Cuevas et al.[7] has also been reported starting from cyanosafracin B, an antibiotic of bacterial origin, available through fermentation of the bacteria *Pseudomonas fluorescens*.[8] However, since the discovery of Pt 650, several research groups were involved in the research of potentially more active structures, bearing a piperazine system.[9] The most impressive results were reported by Myers, with the discovery of a quinaldic acid derivative (QAD, **3**), exhibiting excellent antitumoral activity against a range of cancer cell lines in vitro.[9a,c] This group also described the synthesis of a wide range of synthetic analogues using the solid supported chemistry.[9a,b] Spencer et al.,[9d] Ong et al.,[9e]

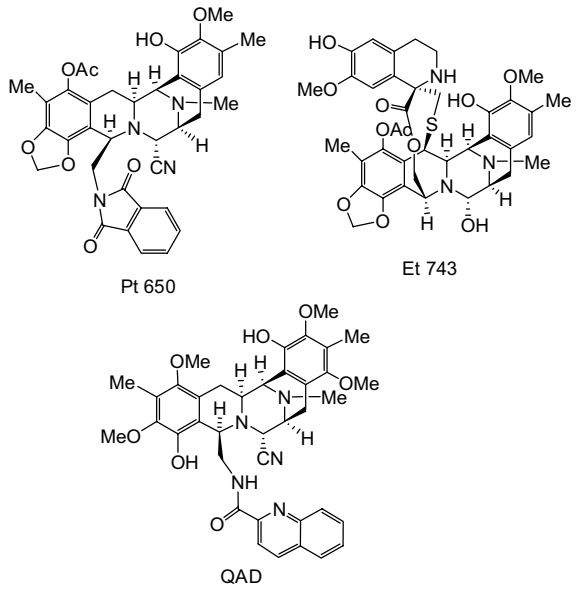

Figure 1. Phthalascidin 650 (Pt 650, **1**), ecteinascidin 743 (Et 743, **2**), quinaldic acid derivative (QAD, **3**).

Keywords: Tetrahydroisoquinoline; Bischler–Napieralski; α-Amino-aldehyde; Phthalascidin 650.
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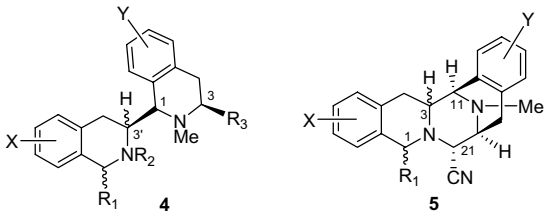
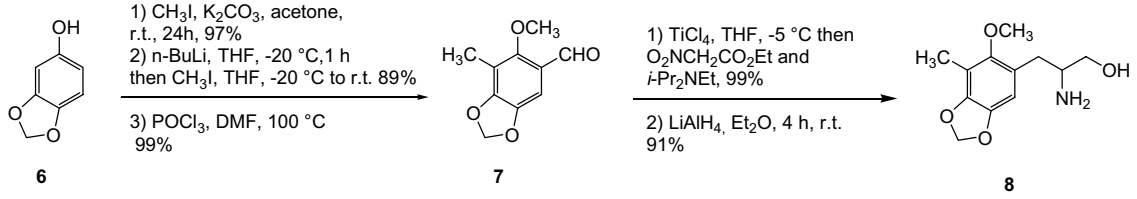


Figure 2. (1,3′)-Bis-tetrahydroisoquinolines of type **4** and pentacyclic piperazine systems of type **5**.

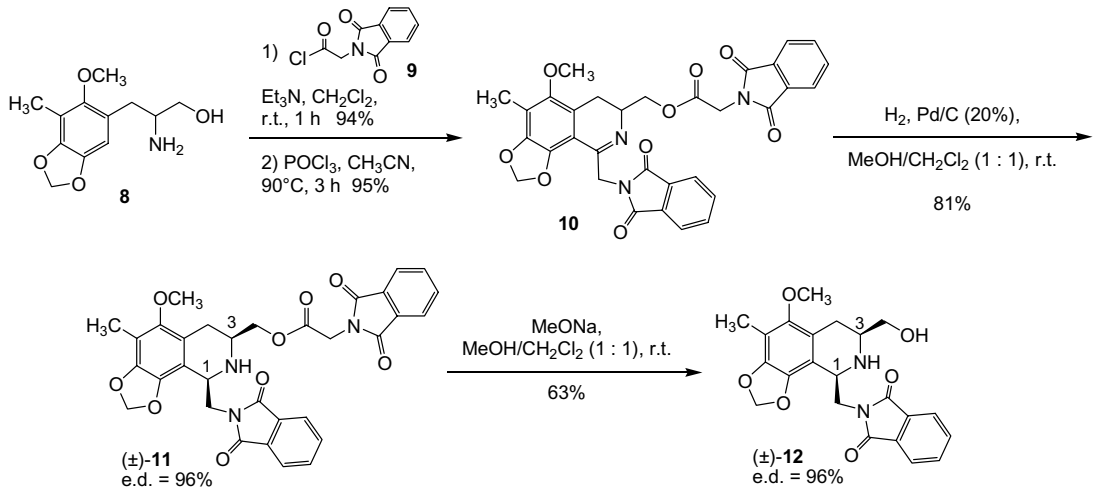
Williams and co-workers,[9f,g] Liu and co-workers,[9h,i] Avendaño and co-workers,[9j,k] Echavarren,[9m] Kubo and co-workers,[9m,n] and Grieco[9p] were also involved in the synthesis and biological evaluation of simpler Et 743 synthetic analogues and obtained promising results.

In our previous Letters, we reported the synthesis and inhibition of cancer cell proliferation of (1,3′)-bis-tetrahydroisoquinolines and pentacyclic piperazine systems of types **4** and **5**, respectively (Fig. 2).[10] These results encouraged us to focus on the total synthesis of (±)-Pt 650 by a new strategy and shorter synthetic sequence. Herein, we report an efficient synthesis of a fully functionalized α-amino-aldehyde as synthetic precursor for the construction of the tetrahydroisoquinoline alkaloid (±)-phthalascidin 650. A new synthetic approach involving a Bischler–Napieralski reaction was considered to obtain a fully functionalized N-protected α-amino-aldehyde bearing phthalimidomethyl function as synthetic precursor of (±)-Pt 650 and related to the synthesis of (*R*)-praziquantel (see Schemes 1 and 2).

Starting from the commercially available sesamol **6**, methylation of the hydroxyl group by MeI in a mixture of acetone and K_2CO_3, followed by a selective *ortho*-lithiation in THF using *n*-BuLi at −20 °C, and an addition of MeI, allowed the formation of the corresponding methylated intermediate in 86% yield over two steps. The Vilsmeier–Haack formylation of this derivative with $POCl_3$ in DMF at 100 °C, gave rise to aldehyde **7**, which was purified by recrystallization in 99% yield.[11] Aldehyde **7** was then engaged in a Knoevenagel condensation with ethyl nitroacetate in THF, in the presence of $TiCl_4$ and *i*-Pr_2NEt, to afford the corresponding nitroalkene in 99% yield as a 1:1 mixture of *E*/*Z* isomers.[12] Then, the simultaneous reduction of the alkene, ester, and nitro functions was accomplished by $LiAlH_4$ in Et_2O in 91% yield, giving the racemic α-amino-alcohol **8** without further purification. Compound **8** was obtained in five steps with an overall yield of 77%. α-Amino-alcohol **8** was then transformed in a diphthalimido methyl derivative. This compound was prepared by acylation of the alcohol and amine functions with phthaloyl glycine chloride **9** in CH_2Cl_2, in the presence of NEt_3, providing the diprotected compound in 94% yield. This derivative was then converted the corresponding dihydroisoquinoline **10** through a Bischler–Napieralski reaction with $POCl_3$ in DMF and proceeded in 95% yield.[13]



Scheme 1. Synthesis of α-amino-alcohol **8**.

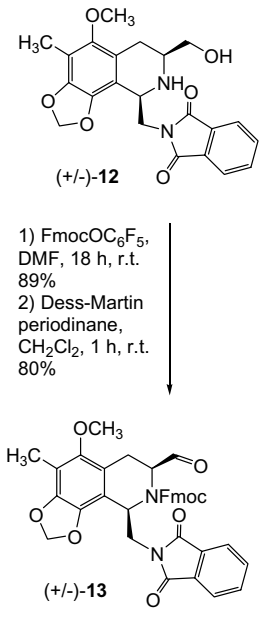


Scheme 2. Synthesis of phthalimidomethyl derivative (±)-**12**.

From compound **10**, the possibility to conduct a highly diastereoselective hydrogenation of dihydroisoquinoline was evident. Indeed, the reduction of the imine function by H_2 in the presence of 20% Pd/C in a 1:1 mixture of $MeOH/CH_2Cl_2$ proceeded smoothly, to give racemic α-amino-ester *syn*-**11** in 81% yield with a diastereoisomeric excess of 96%, determined by ^1H NMR of the crude reaction mixture. The α-amino-ester *syn*-**11** was then transesterified in a 1:1 mixture of $MeOH/CH_2Cl_2$ in the presence of MeONa, providing the α-amino-alcohol *syn*-**12** in 63% yield. The *syn*-configuration of **12** was determined on the basis of the 500 MHz NOESY spectrum analysis from the correlation analysis of the cross-peak protons between H-1 and H-3.

In view of the encountered difficulties in our preliminary studies (epimerization and mixture of isomers),[10] fitting of our synthetic conditions was considered. Indeed, 9-fluorenylmethoxycarbonyl as a protecting group of the amine function was used, due to exceptional precedent results concerning the epimerization of optically instable α-amino-aldehyde using different oxidizing agents.[14] The amine function of (±)-**12** was consequently protected in the presence of 9-fluorenylmethyl pentafluorophenyl carbonate in DMF, affording the corresponding N-protected α-amino-alcohol in 89% yield and separated from the diastereoisomer mixture. Subsequent oxidation of alcohol function of this derivative in the presence of Dess–Martin periodinane reagent[15] in CH_2Cl_2 gave rise to the formation of the chemically and optically stable aldehyde (±)-**13** in 80% yield (see Scheme 3).[16]

In fact, after 10 days, the ^1H NMR spectrum of (±)-**13** was identical and did not display distinctive signals of aldehyde H-3 stereocenter epimerization and consequently appearance of a new diastereoisomer. Moreover, two rotamers were characterized for each α-amino-alcohol and α-amino-aldehyde compound. Indeed, ^1H NMR



Scheme 3. Synthesis of N-protected-α-amino-aldehyde **13**.

experiment in DMSO-d_6 at 80 °C suppressed the presence of rotamers to give a well defined spectrum.

To conclude, an efficient synthesis of N-protected-α-amino-aldehyde (±)-**13** bearing a phthalimido methyl function in C-1 position, which constitutes one of the two tetrahydroisoquinoline fragments of (±)-Pt 650, has been synthesized in 11 steps from sesamol **6** with an overall yield of 25%. We hope that our new synthetic approach will give rise to the synthesis and biological evaluation of (±)-Pt 650 and its analogues. An adaptation of this strategy for the synthesis and biological evaluation of ecteinascidin analogues from α-amino-alcohol **8**, with our recently published work using the oxidative nucleophilic substitution (S_NOx), could be considered.[17]

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16. *Data for compound* (±)-**13**: A 15% weight solution of Dess–Martin periodinane (670 mg, 0.237 mmol) in CH_2Cl_2 was added to a solution of the *N*-Fmoc α-amino-alcohol (±)-**12** (100 mg, 0.158 mmol) in CH_2Cl_2 (1 mL) at 0 °C. After stirring for 30 min at room temperature, the mixture was diluted with Et_2O (10 mL), and saturated solutions of $Na_2S_2O_3$ (5 mL) and $NaHCO_3$ (5 mL) were added. The resulting biphasic mixture was then stirred for 30 min, by which time both layers had become clear and colourless. After 20 min under stirring, the mixture was diluted with Et_2O (10 mL), and the organic layer separated, washed successively with $NaHCO_3$ (10 mL), H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, evaporated and purified by flash column chromatography (SiO_2, cyclohexane/AcOEt = 80/20) to yield (±)-**13** as a white solid (79.7 mg, 80%), mp = 114 °C, $R_f = 0.6$ (cyclohexane/AcOEt = 50/50). ^{1}H NMR (500 MHz, DMSO-d_6, 80 °C) $\delta = 9.57$ (s, 1H, C*H*O), 7.84 (s, 6H, 6Ar*H*), 7.60 (br s, 1H, 1Ar*H*), 7.51 (d, 1H, $J = 7.6$ Hz, 1Ar*H*), 7.41–7.37 (m, 2H, 2Ar*H*), 7.31–7.27 (m, 2H, 2Ar*H*), 5.91 (s, 1H, OCH_AH_BO), 5.64 (t, 1H, $J = 7.$ 2 Hz, C*H*CH_2N), 5.44 (s, 1H, OCH_AH_BO), 4.24 (m, 2H, OCH_AH_BCH and OCH_AH_BCH), 4.16 (m, 1H, OCH_2CH), 4.05 (m, 1H, C*H*CHO), 3.93 (m, 1H, $CHCH_AH_BN$), 3.87 (m, 1H, $CHCH_AH_BN$), 3.66 (s, 3H, OCH_3), 3.14 (m, 1H, $J = 5.6$, 15.4 Hz, CH_AH_BCHN), 2.86 (dd, 1H, $J = 11.7$, 15.4 Hz, CH_AH_BCHN), 2.09 (s, 3H, CH_3). ^{13}C NMR (125 MHz, DMSO-d_6, 80 °C) $\delta = 199.5$ (*C*HO), 167.0 (3C, 3NCO), 155.3 (ArCO), 149.9 (Ar*C*O), 144.2 (Ar*C*O), 143.2 (Ar*C*), 140.3 (2Ar*C*), 138.7 (Ar*C*), 134.1 (2Ar*C*H), 131.1 (2Ar*C*), 127.3 (2Ar*C*H), 126.7 (2Ar*C*H), 124.4 (2Ar*C*H), 122.6 (2Ar*C*H), 119.6 (2Ar*C*H), 117.0 (Ar*C*), 112.5 (Ar*C*), 112.1 (Ar*C*), 100.9 (OCH_2O), 66.2 (CH_2), 60.4 (CH and OCH_3), 48.1 (CH), 46.3 (CH), 41.5 (CH_2), 20.7 (CH_2), 8.5 (CH_3). ESI-MS: m/z (%) = 653 $[M+Na]^+$ (33), 631 $[M+H]^+$ (69), 453 $[M+H-C_{13}H_9CH_2]^+$ (41), 409 $[M+H-C_{13}H_9CH_2-CO_2]^+$ (100), 391 $[M+H-C_{13}H_9CH_2-CO_2-H_2O]^+$ (100). HRMS (ESI) calcd for $C_{37}H_{30}N_2NaO_8$ $[M+Na]^+$ 653.1900, found 653.1901.
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