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Synthetic Studies of Et-743, Preparation of A Racemic Amino Alcohol Precursor

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Abstract: A mild two-step method was used to cleave the lactam ring of the tricyclic intermediate **1**. A key racemic amino alcohol precursor **5** for the construction of Et-743 skeleton was synthesized from **1** through four steps in total yield of 47%.

Keywords: Et-743, lactam, cleavage.

Et-743 is an exceedingly potent anti-neoplastic marine isoquinoline alkaloid isolated from the *Carribean Ecteinascidia Turbinata*. It is being tested against cancer in the US at Phase Ⅱ clinically trial stage[1]. In order to synthesize Et-743 and its analogs, we designed and investigated a synthetic route on the basis of related literatures[2]. In our previous articles[3], we reported some preliminary results of our research. Now we present the establishment of an efficient route of synthesizing the key racemic amino alcohol precursor **5**.

Hydrolysis of lactams such as **1** remained a problem and the classical methods such as acidic or basic hydrolysis were unsuitable, because of the incomplete transformation or possible racemization. A mild two-step method [4] was employed to cleave the lactam ring in **1**. Thus **1** first reacted with $(t\text{-Boc})_2O$ to give N-*t*-Boc protected compound **2**. Methanolysis of **2** with sodium methoxide regioselectively opened the lactam ring to give methyl ester **3** almost quantitatively. However, when **2** was attempted to be reduced with $NaBH_4$ (H^- ion as the nucleophilic regent), it failed to open the lactam ring and give the desired alcohol **4** (**Scheme 1**).

In order to remove the *t*-Boc group in **3**, we used the standard acidic conditions such as HCl/CH_3OH, CF_3COOH/CH_2Cl_2, CH_3SO_3H/EtOAc *etc*[5]. To our surprise, lactam **1** was obtained almost quantitatively, which indicated that **1** was a rather stable compound despite of the seemingly high rigidity of the tricyclic lactam skeleton of **1**. The structure of **5** was confirmed through analysis of its ^{1}H-NMR, ^{13}C-NMR, FAB-MS, IR spectra .

The strategy we adopted to solve this problem was as follows: the methyl ester

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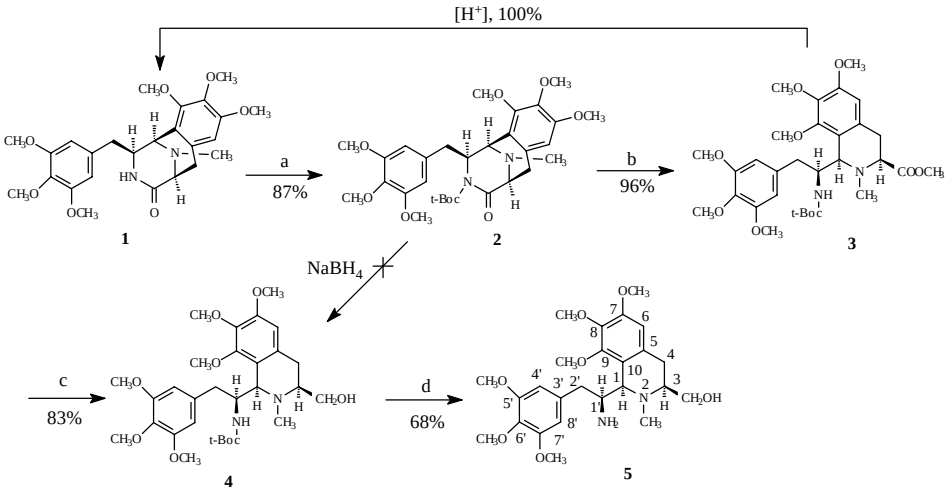
Scheme 1



Regents and conditions: a. $(t\text{-Boc})_2O$, DMAP, THF, reflux; b. CH_3ONa, CH_3OH-DMF, r.t.; c. $LiAlH_4$, THF, 0℃; d. HCl-CH_3OH

group was first reduced with $LiAlH_4$ in THF to give the N-*t*-Boc alcohol **4** in a yield of 83%. **4** was then deprotected with HCl/MeOH to give the amino alcohol **5** in a yield of 68%. This strategy avoided the undesired formation of the stable tricyclic lactam **1**.

In conclusion, an efficient method was established for the cleavage of the lactam ring of the tricyclic intermediate **1** and the synthesis of the racemic amino alcohol precursor **5**. Construction of the skeleton of Et-743 and its analogs is in progress.

References and Notes

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6. Data of compound **3**: colorless oil, ^{1}H-NMR (300HMz, $CDCl_3$): δ ppm 6.51 (s,3H,Ar-H), 4.62(d,1H,J=10.2Hz,H-1), 4.1(m,1H,H-3), 3.96(s,3H,$COOCH_3$), 3.7-3.9(s,18H,6xOCH_3), 3.2 (m,3H,H-1´,H-2´), 2.85(m,1H,H-4), 2.7(m,1H,H-4), 2.6(s,3H,N-CH_3), 1.2(s,9H,-C$(CH_3)_3$); IR (KBr, cm^{-1}): 3392(NH), 1739(ester C=O), 1712(Boc-, C=O), 1589, 1506; FAB-MS: *m/z* 605 (M^++1), 549, 294,
7. Data of compound **4**: colorless oil, ^{1}H-NMR (300HMz, $CDCl_3$): δ ppm 6.48(s,1H,Ar-H), 6.45(s,2H,Ar-H), 4.5(d,1H,J=10.2Hz,H-1), 4.0(m,1H,H-1´), 3.7-3.9(s,19H,6xOCH_3,CHOH), 3.5(dd,1H,J=10.2,3.5Hz,CHOH), 3.2(d,J=13.2Hz,1H,H-4), 3.05(m,1H,H-2´), 2.6(t,J=13.2Hz, 1H,H-4), 2.5(m,5H,N-CH_3,H-3,H-2´), 1.15(s,9H,-C$(CH_3)_3$); IR (Film, cm^{-1}): 3417(NH,OH), 1699(Boc-,C=O), 1589, 1504; FAB-MS: *m/z* 577 (M^++1), 521, 266,
8. Data of compound **5**: yellowish needles, ^{1}H-NMR (300HMz, $CDCl_3$): δ ppm 6.50 (s,1H,H-6), 6.44(s,2H,H-4´,H-8´), 3.91(s,3H,OCH_3), 3.85(s,6H,2OCH_3), 3.82(s,6H,2OCH_3), 3.80(s, 3H, OCH_3), 3.7-3.8 (m,2H,CHOH,H-1), 3.45 (d,1H,J=10.2Hz,CHOH), 3.23(d,1H, J=13.2Hz, H-4), 3.01(dd,J=13.2,3.6Hz,1H,H-2´), 2.91(dd,1H,J=13.2,3.6Hz,H-1´), 2.55(s,3H,N-CH_3), 2.50 (d,

2H,J=13.2Hz,H-2´), 2.42(m,1H,H-3), 2.40(dd,1H,J=10.2,13.2Hz,H-1´), 2.5-2.1(br,3H,NH_2, OH); ^{13}C-NMR ($CDCl_3$): δ ppm 153.4(C-5´,C-7´), 152.7(C-9), 151.5(C-7), 140.4(C-6´), 136.5(C-8), 135.7(C-3´), 132.5(C-5), 121.1(C-10), 107.0(C-6), 106.2(C-4´,C-8´), 64.6(C-1), 63.5(CH_2OH), 63.2(C-3), 61.3(OCH_3), 61.0(2xOCH_3), 58.9(C-1´), 56.3(2xOCH_3), 56.2 (N-CH_3), 40.9(C-4), 32.1(C-2´); IR (KBr, cm^{-1}): 3435(br,N-H,O-H), 1600, 1587(benzene ring); FAB-MS: *m/z* 633 (M^++1), 591, 547, 306, 264, 220; HRMS(FAB): Calcd. $C_{35}H_{40}N_2O_9$ 632.273381, Found 632.273351.

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