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Study on the Total Synthesis of Et 743 and its Analogues: Synthesis of a Tricyclic Intermediate and its 11-Epimer

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Abstracts: The tricyclic compound **1**, a key intermediate of the pentacyclic core of Et 743 and its analogues, was synthesized. Its 11-epimer was found as the product of racemization when BOP was used as the coupling agent, but not when BOP-Cl used in the same reaction. The stereochemistry of both isomers was confirmed on basis of the ^{1}H NMR and NOE-difference spectra.

Keywords: Et 743, tricyclic compound, synthesis, stereochemistry.

In the previous paper[1], we reported a novel synthetic route to construct the pentacyclic core of antitumor marine natural product Et 743 and its analogue phthalascidin[2-3]. However, this route was simplified by using the readily available L-dopa as the starting material and ignoring introduction of appropriate substitutes on the 1-position of 1,2,3,4-tetrahydroisoquinoline moiety. Therefore, the further study of this program was concentrated on improving the applicability of this route to our underlying targets by introducing a methyl group into the 1-position. In this paper, we successfully synthesized a tricyclic compound **1**, employing the synthetic route we have established, although sometimes compound **2**, the 11-epimer of compound **1**, was produced as a co-product. The stereochemistry of both isomers was confirmed on basis of the ^{1}H NMR and NOE-difference spectra.

As seen in **Scheme 1**, compound **1** was synthesized according to the synthetic process previously reported by us[1]. Thus, the amino component methyl (1S,3S)-1-methyl-6,7-dimethoxyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate **3** was coupled with carboxyl component **4** through the action of coupling agent to afford the dipeptide **5**. At first, benzotriazol-1-yloxytris(dimethylamino) phosphonium hexafluorophosphate (BOP) was used in this coupling reaction. However, treatment of compound **5** with CF_3COOH in CH_2Cl_2 afforded the desired product **1** in 49% yield along with its 11-epimer **2** in 19% yield. This result suggested that the carboxyl component **4** was partially racemized during the coupling step, which is possibly due to the huge steric hindrance around the amino group induced by introduction of a methyl

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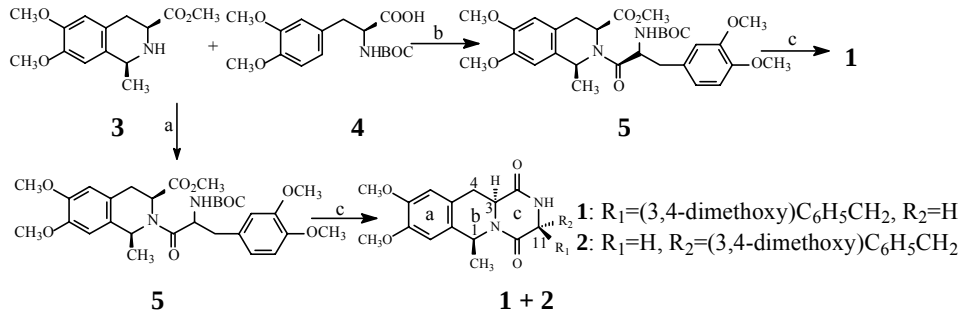
group into the 1-position. Although the desired compound **1** was produced as the major product and could be separated from its 11-epimer **2** by column chromatograph, the racemization was desirable to be avoided as possible as it could be. This problem was resolved by using another coupling agent, N,N-bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl), in the reaction. Compound **1** was produced as the sole product in 60% overall yield and no obvious racemization was observed.

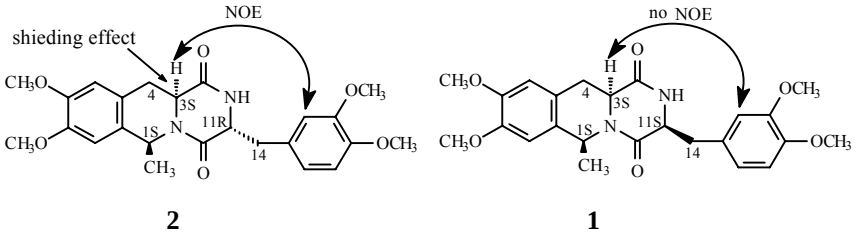
Scheme 1



Reagents and conditions: a: BOP, Et_3N, DMF, r.t., 6h, 60%; b: BOP-Cl, Et_3N, CH_2Cl_2, r.t., 2h, 78%; c: CF_3COOH, CH_2Cl_2, r.t., 2h.

The stereochemistry of both isomers **1** and **2** was mainly determined by analysis of their NOE-difference and ^1H NMR spectra[4]. For compound **2**, irradiation of H-3 proton led to an enhancement of the aromatic hydrogen proton signal, which suggested that the 11-benzyl group is closed to the 3-H in the space. Thus, the 3-11 *trans* arrangement is to be assigned to compound **2**, whereas compound **1** was believed to be the desired 3-11 *cis* product. This conclusion can be confirmed further by comparison of the chemical shift of H-3 proton in both isomers **1** and **2**. In $CDCl_3$, the H-3 proton of **2** (δ 3.16 ppm) resonated at higher field than the corresponding proton (δ 4.13 ppm) of **1**, because of the shielding effect induced by the aromatic ring (**Scheme 2**). Similar spectral phenomena were also observed in some other cyclic dipeptides[5].

Scheme 2



In summary, we successfully synthesized the tricyclic compound **1** as the key intermediate of the pentacyclic core of Et 743. It shows that the synthetic route established by us is still efficient when introducing a substitute into the 1-position, which

makes it a promising process to the total synthesis of Et 743 and its analogues. Further study on this program is still in progress.

References and Notes

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4. Spectral data: compound **1**, colorless foam solid, mp: 90-92℃, $[\alpha]_D^{20}$ –81.4 (c 0.95, $CHCl_3$). IR (KBr): 1685, 1660cm^{-1}; ^1H NMR (300MHz, $CDCl_3$, δ ppm): 1.37 (d, 3H, J=6.6 Hz, CH_3), 2.84 (dd, 1H, J=10.2, 14.4 Hz, H-4), 3.02 (dd, 1H, J=12.6, 15.6 Hz, H-14), 3.28 (dd, 1H, J=3.6, 15.6 Hz, H-14), 3.60 (dd, 1H, J=3.6, 14.4Hz, H-4), 4.00 (dd, 1H, J=3.6, 12.6 Hz, H-13), 4.13 (dd, 1H, J=3.6, 10.2 Hz, H-3), 5.37 (q, 1H, J=6.6 Hz, H-1), 5.78 (brs, 1H, NH), 6.69 (s, 1H, ArH), 6.74 (s, 1H, ArH), 6.76 (s, 1H, ArH), 6.79 (d, 1H, J=7.8 Hz, ArH), 6.85 (d, 1H, J=7.8 Hz, ArH); ^{13}C NMR (300MHz, $CDCl_3$, δ ppm): 24.41, 29.55, 36.62, 52.33, 54.75, 55.80, 55.83, 55.87, 55.94, 56.01, 109.29, 111.03, 111.53, 111.86, 121.28, 124.90, 128.03, 129.93, 148.00, 148.25, 148.39, 149.44, 165.89, 166.60; FABMS (*m/z*): 441 (M+H). compound **2,** colorless foam solid, mp: 92-94℃, $[\alpha]_D^{20}$ +27.7 (c 0.95, $CHCl_3$). ^1H NMR (300MHz, $CDCl_3$, δ ppm): 1.20 (d, 3H, J=6.9 Hz, CH_3), 2.90 (dd, 1H, J=13.0, 17.8 Hz, H-4), 3.02 (dd, dd, 2H, J=3.0, 7.8, 12.0 Hz, H-14), 3.16 (dd, 1H, J=6.0, 13.0 Hz, H-3), 3.22 (dd, 1H, J=6.0, 17.8Hz, H-4), 3.87 (s, 12H, 4×CH_3O), 4.23 (dd, 1H, J=3.0, 7.8 Hz, H-13), 5.26 (q, 1H, J=6.9 Hz, H-1), 6.18 (brs, 1H, NH), 6.69-6.65 (m, 5H, 5×ArH); FABMS (*m/z*): 441 (M+H).
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