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Preparation of AChE Inhibitors From Jujubogenin

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Abstract: A dammarane derivative dihydrojujubogenin-2-en-1-one, which possesses a skeleton and pharmacophore partially similar to those of Territrem B, a potent AChE inhibitor, was synthesized *via* three different paths. The anti-AChE activity of this compound and related analogue was measured.

Keywords: Alzheimer disease (AD), acetylcholinesterase (AChE) inhibitor, pharmaceutical chemistry, jujubogenin, Territrem B analogues.

The advanced medical technology has lengthened the life expectancy of human beings. This makes some previously ignored diseases prominent, such as Alzheimer disease (AD). The low level of acetylcholine (ACh) in brain is considered to be one of main reasons for suffering such memory loss disease. Thereby, how to elevate ACh level in brain and enhance the cognition has become a main issue [1,2]. One of the approaches is to investigate acetylcholinesterase (AChE) inhibitors, which can prevent the hydrolysis of ACh in brain. Territrem B has been demonstrated to be a potent AChE inhibitor (IC_{50} 47 nM) and the 2-en-1-one structural moiety was found to be a pharmacophore [3,4]. However, the supply of this metabolite, is limited since the yield from cell cultures of *Aspergillus terrus* is very poor. This restricts our further investigation of this type of AChE inhibitors, such as constructing a QSAR concept. So we utilized naturally abundant ingredients having similar skeleton and stereochemistry at A and B ring to Territrem B as starting material and tried to build up 2-en-1-one pharmacophore and assayed their anti-AChE activity. Based on this design, the method of preparation of a jujubogenin-2-en-1-one analog **1** from the triterpenoid jujubogenin glycosides, present in the subtropical plant *Colubrina asiatica* was investigated [5,6].

The *n*-BuOH extract from the aerial part of *Colubrina asiatica* which contained jujubogenin glycosides was oxidatively cleaved under a strong alkaline condition (O_2,NaOBu, BuOH, 90°C, overnight) [7] to afford the common aglycone – jujubogenin **2** [5] in 0.1% overall yield. Catalytic hydrogenation of **2** yielded dihydrojujubogenin **3**, ESI-MS *m/z* 475 $[M+H]^+$, ^{1}H NMR δ ($CDCl_3$) 3.91 (m, 1H, H-23), 0.85 (d, *J*=6.5 Hz, 3H) and 0.85 (d, *J*=6.6 Hz, 3H) for Me-26 and Me-27. This procedure was aimed to avoid any interference caused by Δ^{24} in the following reactions. Selective O-mesylation at the

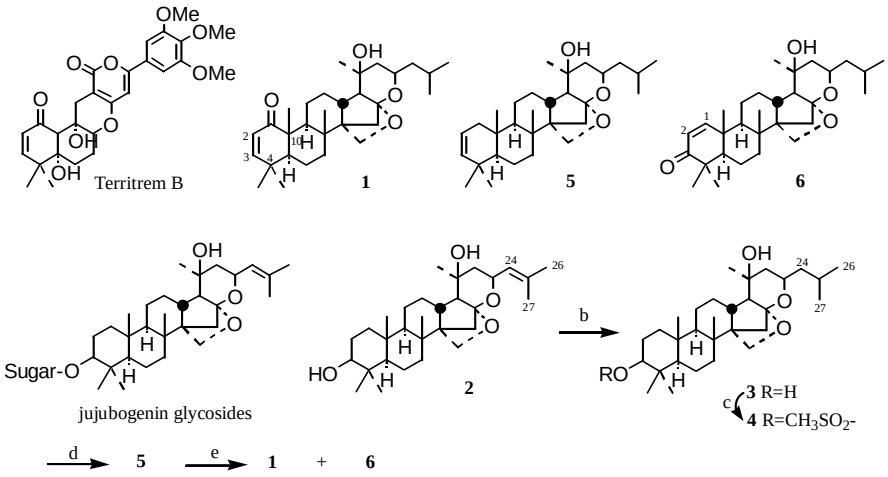
3-OH, using much excess of mesyl chloride due to the steric hindrance caused by 4,4-dimethyl groups, afforded **4** [8]. ESI-MS *m/z* 553 $[M+H]^+$, ^1H NMR ($CDCl_3$) δ 4.27 (dd, 1H, *J*=11.5, 5.2 Hz, H-3) and 2.98 (s, 3H, SO_2Me)]. Treatment of **4** with DBU afforded the 2-ene product **5** in a 65% yield [8]. The ESI-MS of **5** showed $[M+H]^+$ at *m/z* 457 and the ^1H NMR spectrum ($CDCl_3$) showed characteristic signals for H-2 (δ 5.38, ddd, 1H, *J*=10.1, 5.1, 1.0 Hz) and H-3 (δ 5.33, dd, 1H, *J*=10.1, 2.1 Hz). Allylic oxidation on C-1 of **5**, however, suffered a lot of problems, attributable to the steric hindrance of the 10-methyl group. Finally, we found that reaction of **5** with chromic trioxide in acetic acid will afford the highest yield of 24% of **1** and 22% of **6** [9]. The ESI-MS of **1** showed $[M+H]^+$ at *m/z* 471 and its ^1H NMR spectrum ($CDCl_3$) showed a characteristic AX system for H-2 (δ 5.62, d) and H-3 (δ 6.26, d), J_{ax}=10.1 Hz. The EIMS spectrum of **6** showed $[M]^+$ at *m/z* 470 and its ^1H NMR spectrum ($CDCl_3$) showed a characteristic AX system for H-1 (δ 7.07 d) and H-2 (δ 5.79, d), J_{ax}=10.2 Hz. The structure for **1** and **6** were distinguished by NOE difference experiments. Irradiation at the doublet of the downfield olefinic proton (H-3, δ 6.26) in **1** enhanced two methyl singlets at δ 1.07 (4β-Me) and 1.03 (4α-Me), supporting the structure for **1**. These two methyl signals were distinguished by another NOE difference experiment which enhanced the signals of 10-Me singlet (δ1.17) and H-3 upon irradiation at the methyl singlet at δ 1.07.

Another synthetic route as depicted in **Scheme 2** was explored to improve the low yield problem as discussed above (**Scheme 1**). Jujubogenin **2** was first oxidized by PDC in DMF to a 3-one product **7**, followed by hydrogenation of the 23,24-double bond to afford **8**, ESI-MS $[M+H]^+$ at *m/z* 473, ^{13}C NMR δ ($CDCl_3$) 217.7 (s) for C-3 [10]. Treatment of the 3-one **8** with LDA and phenylselenium bromide, and then $NaIO_4$ oxidation, afford the Δ^1,3-one product **6** [11,12]. Epoxidation of the 1,2-double bond in **6** by hydrogen peroxide in an ice bath afforded **9**, ESI-MS $[M+H]^+$ at *m/z* 487, ^1H NMR δ ($CDCl_3$) 3.33 (d, 1H, *J*=4.7 Hz) and 3.54 (d, 1H, *J*=4.7 Hz) for H-1 and H-2 [13]. Wharton rearrangement [13,14] of the epoxide **9** led to the production of the allylic alcohol **10**, ESI-MS $[M+H]^+$ at *m/z* 473, ^1H NMR δ ($CDCl_3$) 3.59 (d, 1H, *J*=5.8 Hz, H-1), 5.68 (dd, 1H, *J*=9.9, 5.8 Hz, H-2), 5.51 (d, 1H, *J*=9.9 Hz, H-3). PDC oxidation of **10** led to the expected product **1** in a high yield (82%).

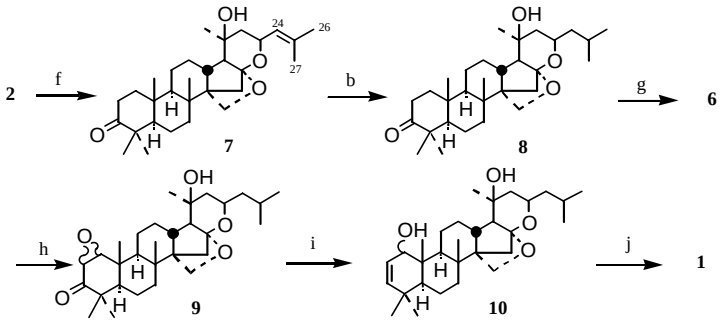
In another procedure, the 2-ene product **5** was first epoxidized by MPCBA (*meta*-perchlorobenzoic acid) to form an epoxide **11**, which was further cleavaged by the phenylselenide anion and followed by an oxidation by 30% hydrogen peroxide to allow the consequent elimination of a PhSeOH. This produced an allylic alcohol **12** [15], which could easily be consequently oxidized to enone **6** (**Scheme 3**). NOE difference experiment disclosed that the epoxide of **11** adopted an α-orientation. Furthermore, the mechanism of this base-induced rearrangement belong to a cyclic syn elimination mechanism [16], which led the C-1 a syn product of the 2α, 3α-epoxy, therefore the 3-hydroxy group of the allylic alcohol **12** should also be an axial one (3α-OH).

The enone products, 2-en-1-one **1**, **6**, and **5** were assayed against eel AChE [17]. The preliminary results showed that the IC_{50} of compounds **1** and **5** was about 50 μM, at such concentration **6** inhibited AChE only about 10%. This study demonstrated at least 2-en or 2-en-1-one moiety to be essential for the anti-AChE activity.

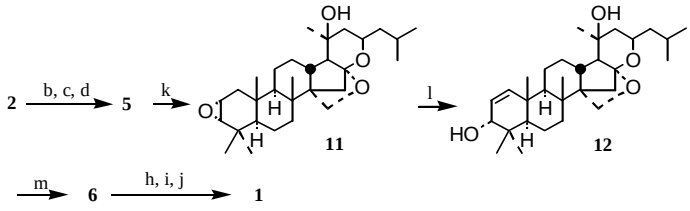
Scheme 1



Scheme 2



Scheme 3



a. NaOBu^n, O_2, *n*-BuOH, 90^{o}C, 24 hr; b. Pd-C, H_2, rt, 48 hr (91%); c. MsCl, py, 0^{o}C, 1 hr (82%); d. DBU, toluene, reflux, 34 hr (65%); e.CrO_3, HOAc, 80^{o}C, 24 hr (**1**, 24%; **6**, 22%); f. PDC, DMF, 0^{o}C, 10 hr (92%); g. (i) LDA, PhSeBr, THF, -78^{o}C, 0.5 hr (ii). $NaIO_4$, MeOH-H_2O (1:1), 12 hr (50% in two steps); h. 30% H_2O_2, 10% NaOH, MeOH, 0^{o}C, 4 hr (78%); i. $N_2H_4{\cdot}H_2O$, MeOH, AcOH, 0^{o}C to reflux (0.5 hr + 13 hr) (40%); j. PDC, DMF, reflux 60 hr (82%); k. MCPBA, CH_2Cl_2,0^{o}C, 10 hr (80%); l. (i)PhSeSePh, $NaBH_4$, EtOH, rt, 2.5 hr (ii) excess H_2O_2, 0^{o}C - rt, 8 hr(78% in two steps); m. MnO_2, Na_2CO_3, CH_2Cl_2, 0^{o}C, 3 hr (90%).

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