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Synthesis of 2-En-1-one-ebelactonyl Benzoates of Territrem B Analogues from Jujubogenin

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Abstract: Two series of territrem B analogues (**10a**-**10c** and **18**) have been designed and synthesized from jujubogenin **5a** which was prepared from jujubogenin glycosides **5b** obtained from the leaves of *Zizyphus jujuba*. The structures of the new compounds were confirmed by ^{1}H-, ^{13}C-NMR and MS data. Compounds **10c** and **18** showed weak inhibitory effect on AChE at 10^{-4} mol/L.

Keywords: Territrem B analogues, acetylcholinesterase (AChE) inhibitor, jujubogenin.

AChE inhibitors are important target on drug discovery for the treatment of Alzheimer disease. Tacrine **1**, E2020 **2** as well as huperzine A **3** are the few distinguished successful leading compounds in this aspect[1~3]. Recently, the potential activity of territrem B (**Figure 1**) on AChE inhibition (IC_{50} =7.8 nmol/L) led to a wide interest. Furthermore, its inhibitory mechanism is totally different from the known AChE inhibitors[3~5]. The interest in synthesis of new leading compounds was limited by the scarcity of territrem B from natural source. This prompted us to study the analogues of territrem B. Moreover, according to the preliminary SAR investigation on territrem B derivatives, the 2-en-1-one moiety and aromatic E ring should be essential for their inhibitory activity on AChE[6,7].

According to the chocking hypothesis, Chen and Luo proposed that territrem B binding to the AChE channel could block Ach, interring to the catalytic center of AChE, so that the substrate (ACh) was prevented from being hydrolyzed and the concentration of ACh in brain was improved[8]. In order to chock the channel entrance, an appropriate spatial position between the two pharmacophores olefine ketone and aromatic ring in territrem B analogues might be necessary. Therefore, we designed and synthesized 2-en-1-one-20-ebelactonyl benzoate **10** and 2-en-1-one-13-ebelactonylbenzoate **18** from the natural abundant herbal resource.

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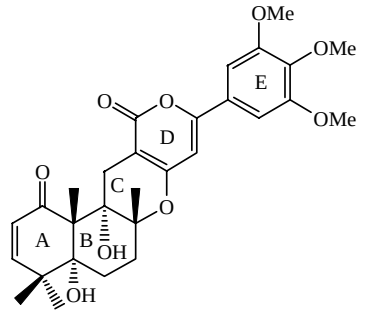
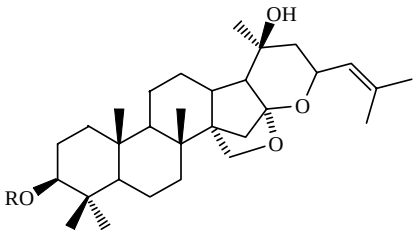
Figure 1



4 Territrem B

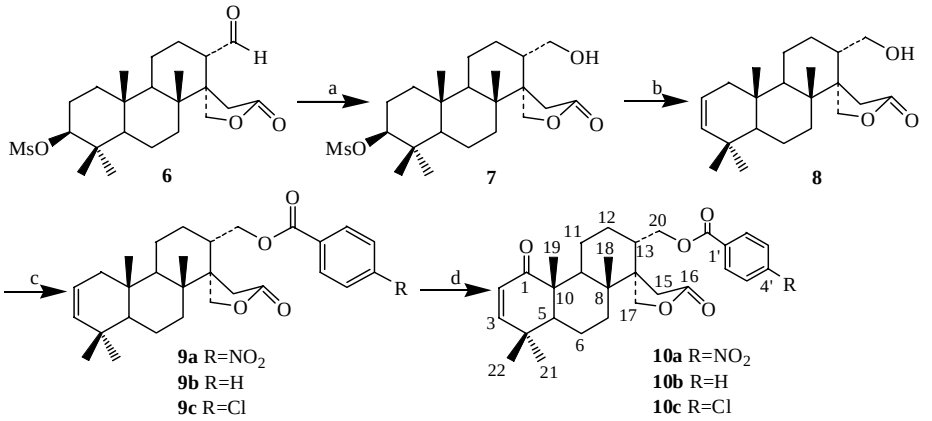


5a R=H
5b R=Sugar

Compound msebehyde **6** (**Scheme 1**) was prepared from jujubogenin **5a** (**Figure 1**) according to the literature[7], and **5a** was obtained from jujubogenin glycosides **5b** extracted from the leaves of *Zizyphus jujuba*[7]. Reduction of **6** with sodium borohydride in methanol gave alcohol **7**, which could be used directly in the next step without purification to provide 2-en-20-ebelactonol **8** in total yield of 52%. 2-En-20-ebelactonyl-(4-nitro)-benzoate **9a** could be obtained from **8** utilizing modified Mitsunobu reaction in 20% yield[9]. However, when the group R was replaced by hydrogen or chlorine, the relative derivatives **9b** or **9c** could not be obtained by this method. Therefore, **8** was treated with benzoic anhydride or *p*-chlorobenzoic anhydride in the presence of 4-dimethyl-aminopyridine (DMAP) to give corresponding benzoates **9b** and **9c** in the yield of 60% and 28%, respectively[10]. Target compounds **10a**, **10b** or **10c** could be prepared by oxidation of **9a**, **9b** or **9c** with chromium trioxide in acetic acid in the yield of 37.2%, 33.5% and 10.9%, respectively[7].

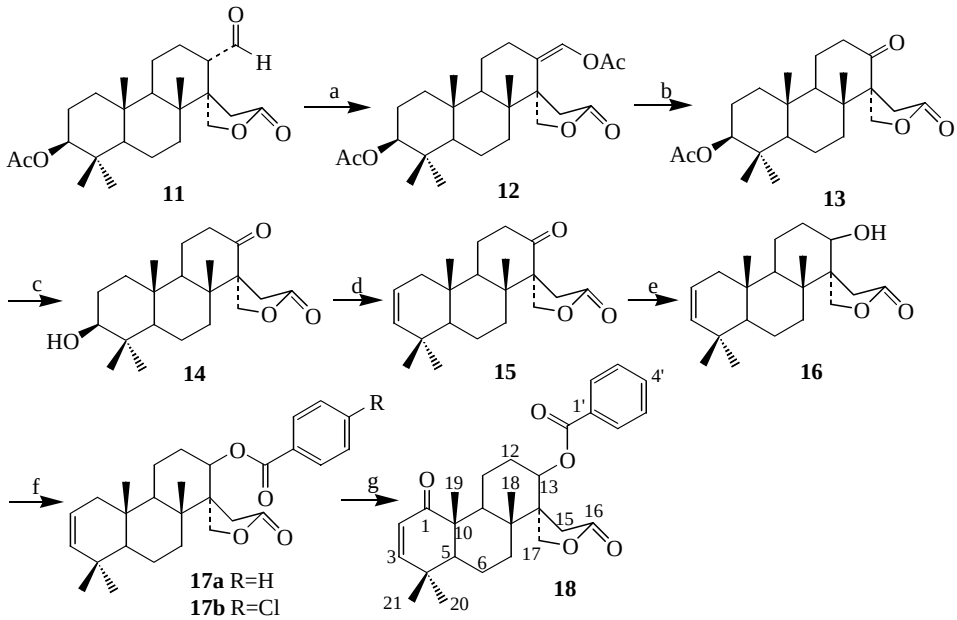
Compound **11** was prepared by the similar method of preparing **6** from jujubogenin **5a** (**Scheme 2**)[7]. The acetylated ebehyde **11** was treated with acetic anhydride in the presence of sodium acetate under reflux for 6 h to give enolic acetate **12**, which could be ozonized directly followed by reduction with dimethyl sulfide to afford ketone **13** in a total yield of 63.2%[11,12]. The ketone **13** was hydrolyzed with potassium carbonate in methanol at room temperature to afford **14** in 50% yield. Compound **14** was then treated with methylsulfonyl chloride in pyridine at 0^{o}C to afford a 3β-mesylate which could be dehydrated by lithium carbonate on the mesylate in refluxing dimethyl-acetamide (DMAC) to give **15** in the overall yield of 50.6%[13]. Compound **15** could be further reduced by sodium borohydride to give **16** which was reacted with benzoic anhydride or *p*-chlorobenzoic anhydride to afford 2-en-13-ebelactonyl benzoate derivatives **17a** and **17b** in the yield of 14.3% and 10.2%, respectively[10]. Oxidation of **17a** with chromium trioxide in acetic acid afforded target compound **18** in the yield of 20%. The structures of **10** and **18** as well as of all the intermediates involved in **Scheme 1** and **Scheme 2** were confirmed by ^{1}H-, ^{13}C-NMR and MS spectral data.

Scheme 1



Reagents and conditions: a) $NaBH_4/CH_3OH$, 0℃, 2 h; b) Li_2CO_3/DMAC, reflux for 0.5 h; c) RPhCOOH, DEAD, PPh_3, benzene, 40℃, 4 h or $(RPhCO)_2O$/DMAP, Et_3N, 80℃, 24 h; d) CrO_3/AcOH, 80 ℃, 0.5 h.

Scheme 2



Reagents and conditions: a) Ac_2O, NaOAc, reflux, 6 h; b) O_3/O_2, -78℃, 1 h; Me_2S, -10℃, 1 h; 0-20℃, 1 h, 63.2% (based on **11**); c) K_2CO_3, MeOH, rt, 2 h, 50%; d) MsCl/Py, 0℃, 8 h; Li_2CO_3/DMAC, reflux, 0.5 h, 50.6%; e) $NaBH_4/CH_3OH$, 0℃, 2 h, 88%; f) $(RPhCO)_2O$/DMAP, Et_3N, 80℃, 24 h; g) CrO_3 in acetic acid, 80℃, 1 h, 20%.

Both of the target compounds (**10** and **18**) were subjected to AChE inhibitory assay. Compound **10c** showed a 26% inhibition, while **18** exhibited a ratio of 32% on AChE

inhibition at 100 μmol/L concentration. This implies that the other structural factors influencing the inhibition ratio among the territrem B analogues remain unclear. More derivatives of **10** and **18** possessing different substituents on the aromatic rings will be synthesized in our on-going work.

Acknowledgments

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14. Selected data of compounds: **10a.** Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm), 1.09 (s, 3H, Me-22), 1.11 (s, 3H, Me-19), 1.22 (s, 3H, Me-21), 1.26 (s, 3H, Me-18), 2.41 (d, 1H, *J*=18.4 Hz, H-15′), 2.73 (d, 1H, *J* =18.4 Hz, H-15), 4.33 (m, 3H, *J* =10.4 Hz, H-17, H-20), 4.38 (d, 1H, *J* =10.4 Hz, H-17′); 5.69 (d, 1H, *J* =10.0 Hz, H-2), 6.34 (d, 1H, *J* =10.0 Hz, H-3), 8.21 (d, 2H, *J* =8.8 Hz, H-3′, 5′), 8.30 (d, 2H, *J* =8.8 Hz, H-2′, 6′); EIMS *m/z* 509 (M^+). **10b.** Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.10 (s, 3H, Me-22), 1.12 (s, 3H, Me-19), 1.21 (s, 3H, Me-21), 1.27 (s, 3H, Me-18), 2.54 (d, 1H, *J*=18.4 Hz, H-15′), 2.69 (d, 1H, *J* =18.4 Hz, H-15), 4.26 (dd, 1H, *J* =6.0, 11.6 Hz, H-20), 4.34 (m, 2H, H-17, H-20′), 4.40 (d, 1H, *J* =10.8 Hz, H-17′); 5.70 (d, 1H, *J* =10.4 Hz, H-2), 6.34 (d, 1H, *J* =10.4 Hz, H-3), 7.45 (t, 2H, *J* =7.8 Hz, H-3′, H-5′), 7.58 (t, 1H, *J* =7.8 Hz, H-4′), 8.06 (t, 2H, *J* =7.8 Hz, H-2′, H-6′); EIMS *m/z* 464 (M^+). **18.** Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.06 (s, 3H, Me-22), 1.10 (s, 3H, Me-19), 1.21 (s, 3H, Me-21), 1.27 (s, 3H, Me-18), 2.46 (d, 1H, *J* =18.4 Hz, H-15), 2.66 (d, 1H, *J* =18.4 Hz, H-15′), 4.12 (d, 1H, *J* =10.4 Hz, H-17), 4.63 (d, 1H, *J* =10.4 Hz, H-17′), 5.72 (d, 1H, *J* =10.4 Hz, H-2), 6.36 (d, 1H, *J* =10.4 Hz, H-3), 7.48 (t, 2H, *J* =7.6 Hz, H-3′, H-5′), 7.60 (t, 1H, *J* =7.6 Hz, H-4′), 8.05 (t, 2H, *J* =7.6 Hz, H-2′, H-6′); EIMS *m/z* 450 (M^+).

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