

Mimetic Preparation of Analogues of Territrem B, A Potent Acetylcholinesterase Inhibitor

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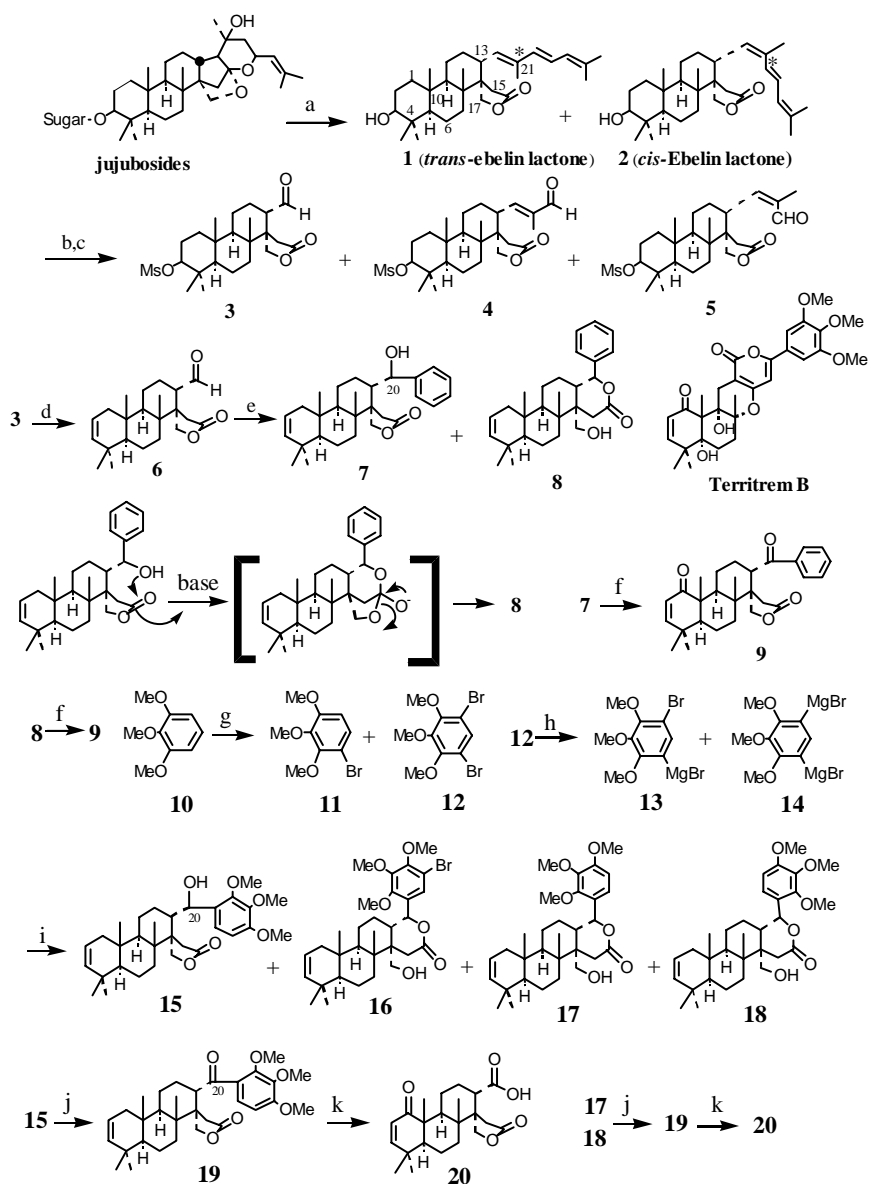
Abstract: A mimetic synthesis of a potent acetylcholinesterase inhibitor, Territrem B, was carried out from the naturally occurring jujubosides. The anti-AChE activity of the product, which possesses the 2-en-1-one pharmacophore and the aromatic ring, was measured. The aromatic ring moiety seemed to be less influencing when comparing with the 2-en-1-one moiety.

Keywords: Acetylcholinesterase inhibitor, Territrem B analogues, jujubosides.

One of the strategies of bettering Alzheimer's Disease is focused on cholinergic compound based on the cholinergic hypothesis¹. An important approach to cholinergic augmentation is administration of cholinesterase inhibitors such as Huperzine A². Territrem B is a potent AChE inhibitor (IC₅₀ 47 nM, *H. Zea* AChE)³, and its inhibitory mechanism is totally different with the known AChE inhibitors⁴. In the last report we have described three routes of synthesizing Territrem B analogues, which possess the same A/B ring stereochemistry and 2-en-1-one moiety, which is identified to be the pharmacophore of the anti-AChE activity, with those of Territrem B^{5,6}.

To further mimetic Territrem B by constructing the aromatic moiety in the molecular, which is possibly present to be another pharmacophore, jujubosides are utilized to form this type of analogues. After acidic hydrolysis, the glycosides were not only hydrolyzed, but also cleaved on the acidic-sensitive ketal group and afforded a pair of epimer of trans-ebelin lactone **1** and cis-ebelin lactone **2**^{7,8}. The mixture of **1** and **2** was mesylated and subjected to ozonolysis, which formed three aldehydes as totally ozone-oxidized product, **3**, as well as a pair of partial ozone-oxidized aldehydes, **4** and **5**⁹. The formation of the unexpected aldehydes **4** and **5** are possibly due to the steric hinderance of C-21 as well as the nonuniformity of the electric density of the conjugated triene. DBU treatment of **3** afforded 2-en-ebeyde **6**¹⁰, which is consequently reacted with a Grignard reagent, benzomagnesium bromide, under kinetic control. The expected alcohol **7** was obtained in 28% yield as well as a rearranged alcohol **8** was isolated in 23% yield, apart from the 16 percents of the unreacted aldehyde **6**. The formation of the unexpected alcohol **8** is assumed to be due to the neighboring group participate reaction, for the oxygen anion in a basic environment would attack the five-membered lactone and,

after a



(a) HCl:EtOH:H₂O (1:3:3, v/v/v), 80°C, 4-6 hr, **1:2** in a 45:55 ratio for totally yield of 4.5% of the crude extract; (b) MsCl, Py, 0°C, 10 hr, 83%; (c) 1. O₃, MeOH, -78°C, <1 hr; 2. thiourea, 0°C - rt, 6 hr; (d) DBU, toluene, reflux, 10 hr, 54%; (e) 0.8 equiv. of C₆H₅MgBr, CH₂Cl₂, -78°C, 20 min, 28% of **7**, 23% of **8**, 16% of unreacted **6**; (f) CrO₃, HOAc, 80°C, 2hr, 71%; (g) Br₂, pyridine, 0-80°C, 1.5 hr, **11:12** in a 1:1 ratio for total yield of 86%; (h) 1 equiv. of Mg, THF, rt, 15 min.; (i) 0.8 equiv. of **13** & **14**, CH₂Cl₂, -78°C, 20 min, 12% of **15**, 16% of **16**, 12% of **17** and 8% of **18**, 18% of unreacted **6**; (j) CrO₃, HOAc, 80°C, 2 hr, 84%; (k) excess of CrO₃ in HOAc, reflux 12 hr, 56%.

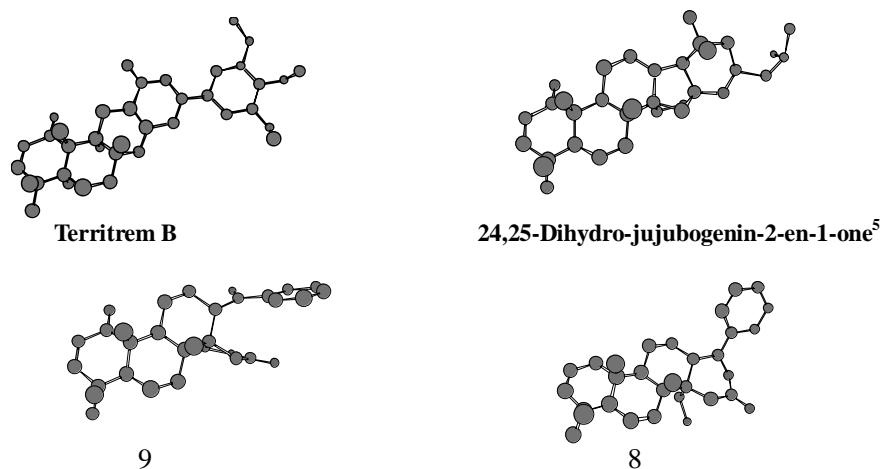
rearrangement, gave a six-membered lactone ring as well as a primary alcohol. Though this side reaction consumed the expected product **7**, it could be seen that the structure of **8** possesses more structural similarity of Territrem B (see **Figure 1**, which shows the minimized-energy configuration of Territrem B and the synthetic analogues). Unfortunately, further oxidation of **8** by chromic trioxide or pyridinium dichromate could only afford **9**, which is rightly the oxidative product of **7** in the same condition¹¹.

Now that the benzene ring moiety was successfully constructed, a trimethoxy benzyl side chain was also attempted, to combine on the 2-en-ebeyde **6**. During preparation of the trimethoxy benzyl Grignard reagent from 1,2,3-trimethoxybenzene **10**, the monobromide **11** and dibromide **12** were formed in a 1:1 ratio. The dibromide **12** was further prepared to Grignard reagents **13** and **14**, which reacted directly with 2-en-ebeyde **6**. Four products were purified after work-up, the sole expected alcohol **15** was obtained in 12% yield, while three other rearranged alcohols were achieved, for **16** in 16% yield, **17** in 12% yield and **18** in 8% yield. Furthermore, 18% of the unreacted 2-en-ebeyde was recovered in this kinetic control Grignard reaction.

In the final step chromic trioxide was applied to oxidize the C-1 of **17** to form a 2-en-1-one moiety. Both of the expected alcohol **15** and the rearranged alcohols of **17** and **18** could be easily oxidized to the mono-ketone product **19**¹¹. However, treatment of **19** with much excess of chromic trioxide would only afford compound **20**, which possesses the 2-en-1-one moiety but loss the aromatic ring, possibly arose from that the over-crowded trimethoxy benzoic part is fragile under this oxidative condition.

The anti-AChE activity of **9**, which contains both a 2-en-1-one pharmacophore and an aromatic ring moiety, showed only a little bit stronger inhibitory value (IC_{50} about 10 μ M) than that of the previously reported Territrem B analogue 24,25-Dihydrojujubogenin-2-en-1-one⁵. This suggested that the aromatic ring present in the Territrem B is perhaps not the major factor of its anti-AChE activity. Therefore further investigation of preparing Territrem B analogues possessing both 5 α -OH and 9 α -OH and 2-en-1-one moiety will be designed.

Figure 1. Minimized-Energy Configurations of Territrem B and the Synthetic Analogues



Acknowledgment

This work is financially supported by National Science Council, China (Taipei) under grant NSC 87-2314-002-005. One of us (Y. Zhao) would like to express his thankfulness to NSC for offering the postdoctoral research fellowship and to National Taiwan University for affording the visiting professor employment.

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Received 12 May 2000