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Synthesis of the C5-C10 Segment of Taurospongin A

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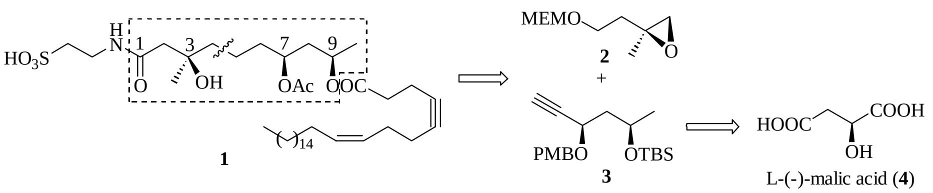
Abstract: Stereoselective synthesis of C5-C10 segment **3** of taurospongin A (**1**) has been developed successfully from L-(-)-malic acid.

Keywords: Stereoselective synthesis, taurospongin A, L-(-)-malic acid.

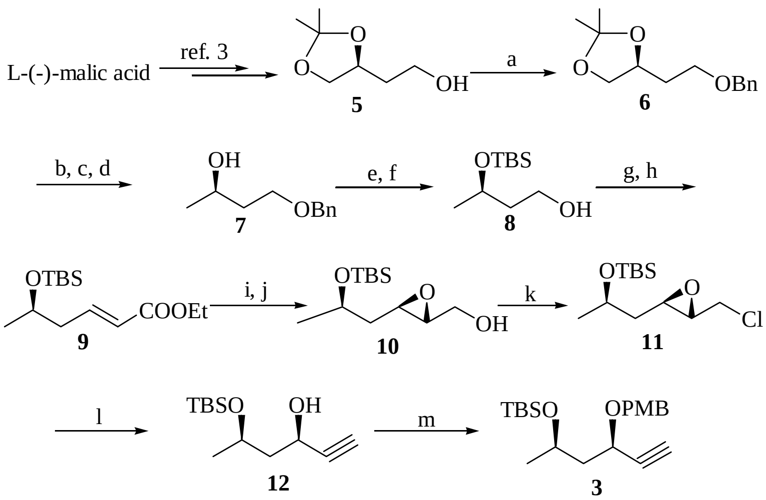
Taurospongin A (**1**), isolated from the Okinawan marine sponge *Hippospongia* sp., have proved to exhibit potent inhibitory activity against DNA polymerase β and HIV reverse transcriptase[1]. Its structure was determined to be an unprecedented class of marine natural products consisting of taurine, trihydroxy fatty acid, and unsaturated fatty acid residues. Attracted by its interesting structure, a total synthesis has been recently reported[2]. Due to the unique structure and interesting biological activities, we have been interested in developing an efficient method for total synthesis of Taurospongin A. Here we describe the stereoselective synthesis of the C5-C10 segment **3**.

Scheme 1



Based on the retrosynthetic analysis in **Scheme 1**, the intermediate **3** could be synthesize from natural L-(-)-malic acid (**4**). Accordingly, as shown in **scheme 2**, (S)-1,2-diisoacetonide-1,2,4-butanetriol (**5**) was prepared from L-malic acid by the published method[3]. Protection of the hydroxy group in **5** afforded a benzyl ether **6**. Removal of the acetonide group in **6** and then selective tosylation of the primary hydroxy group[4] followed by $LiAlH_4$ reduction generated **7**. TBS protection of **7** and subsequent removal of the benzyl group afforded **8**. Conversion of **8** into **9** was achieved by Dess-Martin oxidation[5] and subsequent Wittig-Honer olefination. After reduction of **9** with DIBAL, Sharpless asymmetric epoxidation[6] of the corresponding allyl alcohol with (-)-diethyl tartrate afforded **10** with 98% de (HPLC determined). **10** was smoothly transformed to chloride **11** with PPh_3/CCl_4[7]. Treatment of 11 with nBuLi gave terminal alkyne **12**[7], which was protected with PMB to afford the C5-C10 segment **3**[8].

Scheme 2



Reagents and conditions: a) NaH, BnBr, DMF, THF, rt, 76%; b) PTSA, MeOH, rt; c) pTsCl, pyridine, -20°C, 74% (two steps); d) $LiAlH_4$, THF, 0°C, 94%; e) TBSCl, imidazole, DMF, rt, 93%; f) 10% Pd/C, EtOH, rt, 24h, 94%; g) DMP, CH_2Cl_2, rt, 2h; h) $(EtO)_2P(O)CH_2COOEt$, NaH, THF, 86% (two steps); i) DIBAL, CH_2Cl_2, -78°C; j) (-)-DIPT, $Ti(O\text{-}iPr)_4$, TBHP, CH_2Cl_2, -20°C, 92% (two steps); k) PPh_3, CCl_4, reflux, 24h, 88%; l) nBuLi, THF, -33°C, 92%; m) $PMBOC(NH)CCl_3$, CSA, CH_2Cl_2, 97%.

Thus the synthesis of the C5-C10 segment **3** of taurospongin A (**1**) has been completed. The synthesis of other segments and total synthesis of taurospongin A are under investigation.

References and notes

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8. Selected data of compound **3** : $[\alpha]_D$ = 45.3 (c 0.95 in CH_3Cl); IR (neat) 3307, 2950, 2930, 2850, 2100, 1612, 1513, 1247, 1072, 835cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ: 7.25 (d, 2H, J = 8.5Hz), 6.85 (d, 2H, J = 8.5Hz), 4.72, 4.43 (AB, 2H), 4.16 (m, 1H), 4.02 (m, 1H), 3.79 (s, 3H), 2.45 (d, 1H, J = 2.2Hz), 1.92 (m, 1H), 1.75 (m, 1H), 1.14 (d, 3H, J = 6.0Hz), 0.81 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); EIMS (*m/z*) 347 (M^+-1), 121; Anal Cald for $C_{20}H_{32}O_3Si$: C, 68.92; H, 9.25. Found: C, 69.06; H, 9.14.

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