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Synthetic Study towards Taurospongin A: Wittig Olefination Approach to the Core Structure

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Abstract: An efficient, convergent and enantioselective synthetic approach to the trihydroxy core structure **2** of Taurospongin A **1** is described. The featured step is a classic Wittig coupling reaction between C1-C4 aldehyde segment **4** and C5-C10 phosphate salt segment (**5**).

Keywords: Taurospongin A, Wittig olefination, enantioselective synthesis.

Taurospongin A (**1**), isolated from the Okinawan marine sponge *Hippospongia* sp. in 1997, has proved to exhibit potent inhibitory activity against DNA polymerase β (IC_{50} 7.0 μM) and HIV reverse transcriptase (IC_{50} 6.5 μM)[1]. Its structure was determined to be an unprecedented class of marine natural products consisting of taurine, trihydroxy fatty acid, and long chain unsaturated fatty acid residues. The interesting biological activities of **1**, combined with its unique structure, has led to a synthetic study in our group. During our synthetic work, the group of Jacobsen[2] reported the synthesis of **1**. In their synthesis, a hydrolytic kinetic resolution, a coupling reaction between lithium acetylide derivative and Weinreb amide derivative, and a Noyori reduction were used as the key steps to construct the core structure[2]. In this communication we wish to report a convenient Wittig olefination approach to synthesize the core structure **2** of Taurospongin A.

According to the retrosynthesis analysis in **Scheme 1**, the core segment **2** could be obtained by Wittg coupling reaction between the C1-C4 **4** and C5-C10 **5** segments. Segment **4** and **5** could be derived from commercially available 3-methylbut-3-en-1-ol **6** and methyl (*R*)-3-hydroxybutylate **7**, respectively .

The C1-C4 segment **4** was obtained in 78% overall yield starting with the chiral diol **8**[3] (>95% *ee*) which was derived from **6** through Sharpless asymmetric dihydroxylation[4] (**Scheme 2**). The primary hydroxyl group in **8** was selectively acetylated with Ac_2O/Py (96%) and then the sterically tertiary hydroxyl group was protected as a MOM ether in 87% yield on treatment with MOMCl, diisopropyl-ethylamine and sodium iodide in refluxing 2-dimethoxyethane[5]. The acetyl group was then smoothly removed using K_2CO_3/MeOH to afford the primary alcohol **9** in 95% yield. Dess-Martin oxidation[6] of **9** furnished the aldehyde **4** in 99% yield, corresponding to C1-C4 segment.

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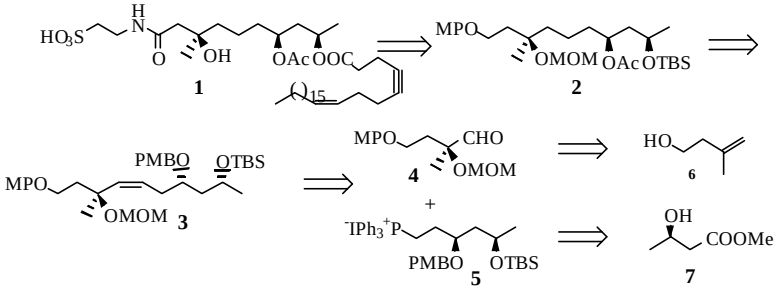
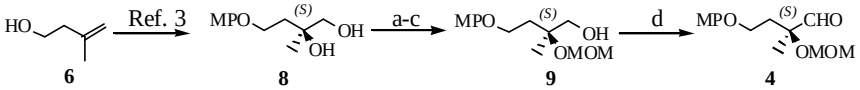
Scheme 1



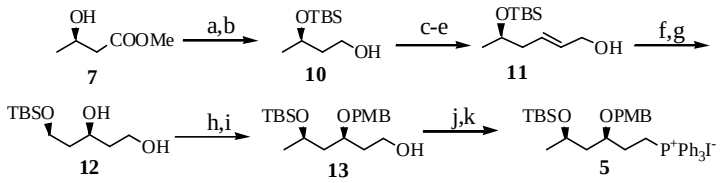
Scheme 2



Reagents and conditions: (a) Ac_2O, Py, rt, 96%; (b) MOMCl, NaI, DIPEA, DME, reflux, 87%; (c) K_2CO_3, MeOH, 0°C, 95%; (d) Dess-Martin Periodinane (2.0 eq.), CH_2Cl_2, rt, 1h, 99%.

The Wittig phosphonium salt **5** was constructed from **7**, which was obtained from poly [(*R*)-3-hydroxybutyric acid] (PHB)[7] (**Scheme 3**). Protection of the secondary hydroxyl group of **7** with TBS (97%) followed by DIBAL-H reduction afforded the primary alcohol **10** in 98% yield. Oxidation of **10** using Dess-Martin periodinane followed by Wittig-Horner olefination with diethyl ethoxycarbonyl- methylphosphonate gave the corresponding *E*-α, β-unsaturated ester in 86% yield, which was subsequently reduced with DIBAL-H giving the trans allylic alcohol **11** in quantitative yield. Sharpless asymmetric epoxidation[8] of **11** using (-)-DIPT as the chiral auxiliary gave the corresponding 2, 3-epoxy alcohol (98% de, determined by HPLC) in 92% yield, which was selectively cleaved of the oxirane ring with Red-Al leading to the exclusive formation of the 1, 3-diol **12** in 76% yield[9]. Protection of **12** as *p*-methoxybenzylidene acetal was followed without purification by DIBAL-H mediated acetal cleavage, resulting 100:1 mixture of regioisomers (90%) in which the desired product **13** predominated (separated by silica gel column).

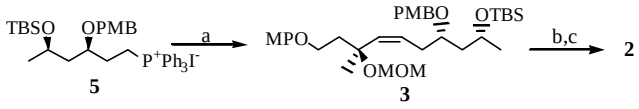
Scheme 3



Reagents and conditions: (a) TBSCl, imidazole, DMF, rt, 97%; (b) DIBAL-H, toluene, 0°C, 98%; (c) Dess-Martin Periodinane (1.3 eq.), CH_2Cl_2, rt, 2 h; (d) $(EtO)_2P(O)CH_2COOEt$, NaH, THF, 0°C, 86% (for two steps); (e) DIBAL-H, CH_2Cl_2, -78°C, 100%; (f) (-)-DIPT, Ti(O-*i*Pr)$_4$, TBHP, CH_2Cl_2, -20°C, 92%; (g) Red-Al, THF, 0°C, 76%; (h) *p*-$CH_3OC_6H_4CH(OCH_3)_2$, PPTS, benzene, rt, 4 h; (i) DIBAL-H, CH_2Cl_2, -78°C, 90% (for two steps); (j) PPh_3, imidazole, I_2, THF/CH_3CN (3:1), rt, 2 h, 90%; (k) PPh_3 (3eq.), CH_3CN, reflux, 24 h, 100%.

Treatment **13** with PPh_3/I_2/imidazole system[10] to give the corresponding iodide in 90% yield, which was reacted with excess PPh_3 in CH_3CN to afford the desired phosphonium salt **5** in quantitative yield. Generation of the ylide from phosphonium salt **5** using *n*-BuLi in HMPA/THF followed by addition aldehyde **4** resulted in the formation of the *Z*-olefin **3** as a single stereoisomer in 91% yield (**Scheme 4**). Catalytic hydrogenation of the double bond and meanwhile removal of the PMB protective group in **3** using 10% Pd/C , then acetylation with Ac_2O/Py afforded the core structure **2**[11] in 91% yield.

Scheme 4



Reagents and conditions: (a) n-BuLi, THF/HMPA, -78°C, 0.5h, then **4**, THF, -78°C-rt, 91%; (b) 10% Pd/C, H_2, EtOH, rt, 16h; c) Ac_2O, Py., rt, 91% in two steps.

In summary, we have developed a route for the synthesis of the core structure of taurospongin A. It' s a convergent route and all the steps in the route are conventional and high yields.

Acknowledgments

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11. Satisfactory spectral and analytical data were obtained for all new compounds. Selected spectral data of **2**: $[\alpha]_D^{25}$ –1.8 (c 1.5 in $CHCl_3$); IR (film): 2955, 2930, 2850, 1736, 1510, 1464, 1375, 1234, 1144, 1040, 930, 827, 775 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$, δ ppm): 6.82 (s, 4H), 4.97 (m, 1H), 4.70 (s, 2H), 4.02 (t, 2H, J=6.8Hz), 3.82 (m, 1H), 3.78 (s, 3H), 3.39 (s, 3H), 2.01 (s, 3H), 1.99 (m, 1H), 1.81 (m, 1H), 1.65-1.32 (m, 8H), 1.25 (s, 3H), 1.16 (d, 3H,

J=6.1Hz), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 170.57, 153.72, 153.05, 115.34, 114.62, 90.80, 77.20, 71.63, 65.65, 64.60, 55.69, 55.36, 44.28, 39.67, 38.47, 34.99, 25.82, 23.90, 23.44, 21.16, 19.48, 18.07, -4.44, -4.83; EIMS (*m/z*): 526 (M^+), 419, 377, 365, 121; HREIMS (*m/z*): calcd. for $C_{28}H_{50}SiO_7$ 526.3329; found 526.3306.

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