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A formal synthesis of (+)-didemniserinolipid B employing a Pd-mediated 6-*endo* selective alkynediol cycloisomerization

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ABSTRACT

Herein, we describe a concise assembly of central 6,8-dioxabicyclo[3,2,1]octane core of didemniserinolipid by employing a Pd-mediated alkynediol cycloisomerization and a formal total synthesis of didemniserinolipid B.

The construction of bridged bicyclic ketal units through cycloisomerization of alkynediols[1] has gained attention recently due to the isolation of several new natural products integrated with bridged bicyclic ketal units and the diverse biological activities documented for them.[2–4] Various metals like palladium, silver, gold, platinum, and iridium have been explored as catalysts for the alkynediol cycloisomerization reaction.[1,5] The key issue of the cycloisomerization reactions is the mode of cyclization, that is, *exo*-dig versus *endo*-dig.[6] Recently, we reported a systematic investigation dealing with the influence of electronic and steric factors over alkynol cycloisomerization reactions mediated by the $Pd[CH_3CN]_2Cl_2$ complex. This study has revealed that the nucleophile prefer selectively the β-carbon of alkyne with respect to the –I group. Based on these findings, herein we document an exclusive 6-*endo* cyclization of an ω-alkyne-1,2,3-triol forming the central 6,8-dioxabicyclo[3,2,1]octane core of didemniserinolipids and a formal synthesis of didemniserinolipid B (**1**).

Didemniserinolipids A–C were isolated from the methanol extract of marine tunicate *Didemnum* sp., by González et al. in 1999 as the first examples of serinolipids with a unique 6,8-dioxabicyclo[3,2,1]octane core.[7] Subsequent to the isolation of cyclodidemniserinol trisulfate, a related serinolipid with promising HIV-integrase inhibition by Faulkner and co-workers,[8] these serinolipids have attracted considerable synthetic interest.[9,10] The assigned constitution and the relative stereochemistry of the didemniserinolipid B has been cross-checked by chemical

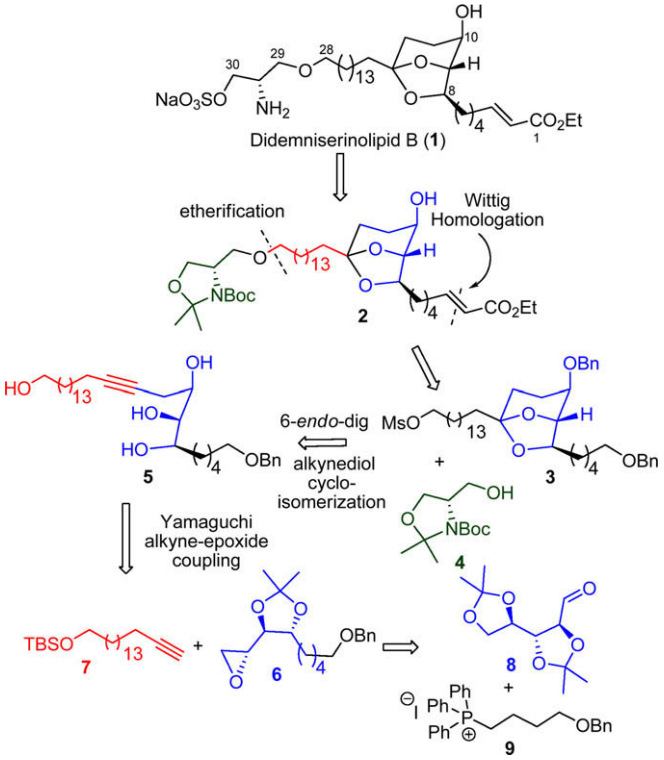

Figure 1. Structure of didemniserinolipid and key retrosynthetic disconnections.

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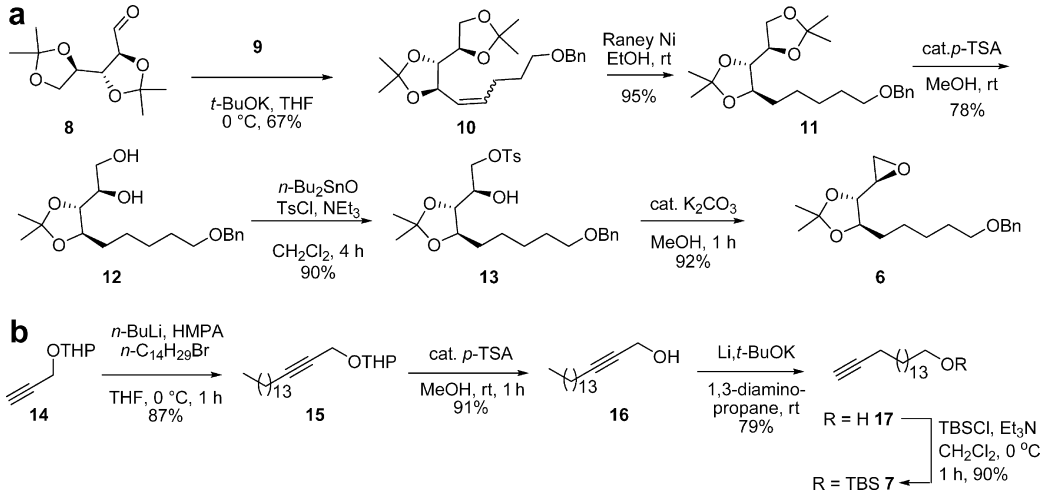
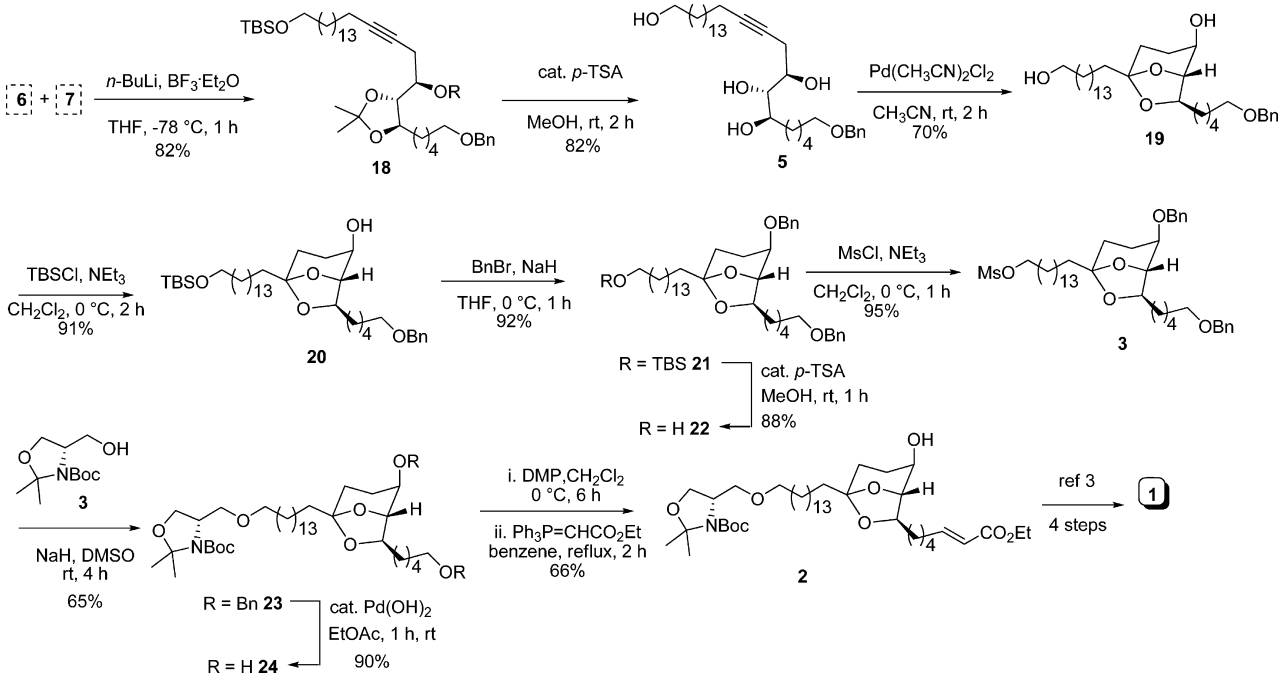
synthesis providing its absolute stereochemistry (**1**, Fig. 1) and a revision in the constitution, by Ley and co-workers.[9] Recently, Burke and co-workers reported the second total synthesis of **1** employing an indigenous 'intermolecular ketalization followed by ring-closing metathesis' (K/RCM) strategy.[10]

As outlined in Figure 1, our synthesis of the bridged bicyclic ketal core relied upon the palladium mediated cycloisomerization of the ω-alkyne-1,2,3-triol **5**. Though several possibilities exist, the major concern is the competitive 5-*exo*-dig versus 6-*endo*-dig mode of addition of the central hydroxyl group, the latter being anticipated from our observations. The synthesis of **2**, an advanced intermediate reported in Burke's total synthesis of didemniserinolipid B was planned by etherification of the **3** with the D-serinol unit **4** followed by a two carbon Wittig homologation at C(3). The synthesis of the key ω-alkyne-1,2,3-triol **5** was intended through the coupling of epoxide **6** and C_{17}-alkynol **7** following the Yamaguchi protocol.[11] The easily available D-arabinose derivative **8** was identified as the starting point for the synthesis of epoxide **6** after stereochemical comparison. An alkyne zipper reaction[12] of a suitable propargyl alcohol for accessing **7** was planned.

As planned, our synthesis started with the Wittig reaction of the arabinose diacetonide **8** (prepared in 3 steps from D-mannitol)[13] and 4-carbon ylide generated from the known phosphonium salt **9**[14] (Scheme 1) to afford *E*/*Z* mixture of **10**. The hydrogenation of **10** with Raney Ni proceeded by acetonide hydrolysis using PPTS in MeOH resulted in diol **12**. Diol **12** was transformed into oxirane **6** by selective primary OH tosylation using TsCl, Bu_2SnO, and triethylamine in dichloromethane followed by cyclization using K_2CO_3 in methanol.[15] The requisite C_{17}-alkynol **7** was prepared from commercially available propargyl alcohol THP ether **14** by a sequence of 4 steps (Scheme 1b). Thus, the alkylation of **14** with *n*-tetradecyl bromide followed by deprotection of the THP group gave the substituted propargyl alcohol **16**. After considerable experimentation, the acetylenic zipper reaction of **16** could be



Scheme 1. Synthesis of coupling partners (a) epoxide **6** and (b) alkynol **7**.



Scheme 2. Key Pd-mediated cycloisomerization of the ω-alkyne-1,2,3-triol **5** and the formal synthesis of didemniserinolipid B (**1**).

effected successfully with Li/*t*-BuOK[16] in 1,3-diaminopropane as solvent at rt. The resulting alkynol **17** was protected as its TBS ether to procure the key coupling fragment **7**.

After having an easy access to epoxide **6** and alkyne **7**, we next focused our efforts on the synthesis of key cycloisomerization substrate **5**. The coupling of **6** with lithiated alkyne **7** in the presence of $BF_3{\cdot}Et_2O$ delivered alkynol **18** in excellent yields (Scheme 2).[11] Finally, the deprotection of acetonide and the TBS protecting groups of **18** gave tetrol **5**.[17] The next concern was the key cycloisomerization of **5**. The treatment of **5** with $Pd[CH_3CN]_2Cl_2$ (10 mol %) in acetonitrile at room temperature under an argon atmosphere for 2 h gave exclusively **19** in 70% yield. The structure of **19** was established on the basis of spectral and analytical data.[18] The presence of a 6,8-dioxabicyclo[3,2,1]octane moiety in **19** was supported by the existence of three characteristic methine signals in the ^{13}C NMR spectrum at 66.3, 77.9, and 82.4 ppm corresponding to C(8)–C(10) and a quaternary signal corresponding to ketal carbon at 109.5 ppm which are in agreement with the data reported for similar derivatives.

After executing the synthesis of the central bicyclic core with the requisite stereochemical information, the remaining portion of the synthesis required installation of a serinol unit followed by two carbon elongations at the C(3) end. Simple protective-group manipulations and mesylation proceeded smoothly to give the key intermediate **3** in 69% yield, over four steps from diol **19**. The serinol fragment **4** was synthesized according to the reported procedures.[19] By optimizing the conditions reported by Burke and co-workers, the coupling of **3** and **4** was carried out successfully by the slow addition of mesylate **3** to a solution of serinol **4** and NaH in DMSO maintaining the internal temperature at 0 °C. The coupling product **23** was obtained in 65% yield. Removal of the benzyl ethers in **23** under hydrogenolysis followed by selective 1°-OH oxidation of resulting diol **24** with Dess–Martin periodinane (DMP) and two carbon Wittig homologation completed the synthesis of **2** (Scheme 2). The spectral and analytical data of compound **2** were in agreement with the data reported by Burke and co-workers.[20]

In conclusion, a formal synthesis of didemniserinolipid B is documented. Rapid accesses to the key carbon skeleton and a 6-*endo*-selective Pd-mediated cycloisomerization protocol for the central bicyclic core of the didemniserinolipids highlight the accomplished synthesis.

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15. *Spectral data of epoxide* **6:** colorless oil. $[\alpha]_D^{25}$ +4.5 (*c* 1.2, $CHCl_3$). IR ($CHCl_3$): *v* 2937, 2861, 1455, 1371, 1217, 1099, 876, 756, 698 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.33 (s, 6H), 1.33–1.43 (m, 4H), 1.50–1.65 (m, 4H), 2.58 (dd, *J* = 2.6, 5.1 Hz, 1H), 2.75 (dd, *J* = 3.9, 5.1 Hz, 1H), 2.88 (ddd, *J* = 2.6, 3.9, 6.3 Hz, 1H), 3.22 (dd, *J* = 6.3, 7.8 Hz, 1H), 3.40 (t, *J* = 6.5 Hz, 2H), 3.89 (br dt, *J* = 4.7, 7.8 Hz, 1H), 4.43 (s, 2H), 7.18–7.27 (m, 5H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ 25.6 (t), 26.1 (t), 26.6 (q), 27.2 (q), 29.5 (t), 33.1 (t), 45.1 (t), 51.6 (d), 70.2 (t), 72.7 (t), 79.6 (d), 81.1 (d), 109.0 (s), 127.4 (d), 127.5 (d, 2C), 128.2 (d, 2C), 138.6 (s) ppm.ESI-MS: *m/z* 343.3 (100%, $[M+Na]^+$). Anal. Calcd for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 71.40; H, 8.93.
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17. *Spectral data of tetrol* **5:** white solid. $[\alpha]_D^{25}$ −3.2 (*c* 0.5, MeOH). IR (Nujol): *v* 3438, 2923, 1462, 1377, 1111, 1058, 737, 648 cm^{-1}. ^1H NMR (methanol-d_4, 200 MHz): δ 1.22 (m, 18H), 1.35–1.59 (m, 16H), 2.10–2.16 (m, 2H), 2.38 (ddt, *J* = 2.5, 5.8, 16.8 Hz, 1H), 2.54 (ddt, *J* = 2.5, 4.7, 16.9 Hz, 1H), 3.32 (dt, *J* = 1.6, 7.1 Hz, 1H), 3.48 (t, *J* = 6.6 Hz, 2H), 3.52 (t, *J* = 6.4 Hz, 2H), 3.70 (ddd, *J* = 4.7, 6.3, 10.5 Hz, 1H), 3.74–3.80 (m, 1H), 4.43 (s, 2H), 7.22–7.28 (m, 5H) ppm. ^{13}C NMR (methanol-d_4, 50 MHz): δ 19.1 (t), 21.5 (t), 24.3 (t), 26.0 (t), 26.1 (t), 26.5 (t), 29.3 (t), 29.4 (t), 29.5 (t), 29.8 (t), 29.9 (t), 30.0 (t, 6C), 32.7 (t), 33.7 (t), 62.8 (t), 70.5 (d), 70.8 (t), 71.6 (d), 73.3 (t), 74.3 (s), 76.4 (d), 83.0 (s), 128.0 (d), 128.1 (d, 2C), 128.7 (d, 2C), 138.6 (s) ppm. ESI-MS: *m/z* 555.4 (100%, $[M+Na]^+$). Anal. Calcd for $C_{33}H_{56}O_5$: C, 74.39; H, 10.59. Found: C, 74.17; H, 10.44.
18. *Spectral data of bicyclic ketal* **19:** colorless syrup. $[\alpha]_D^{25}$ +14.4 (*c* 1.0, $CHCl_3$). IR ($CHCl_3$): *v* 3437, 2929, 1639, 1560, 1416, 1216, 757, 668 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 1.24–1.32 (m, 23H), 1.35–1.44 (m, 5H), 1.49–1.58 (m, 4H), 1.60–1.69 (m, 6H), 1.77 (dt, *J* = 5.5, 12.3 Hz, 1H), 1.92–2.01 (m, 1H), 3.45 (t, *J* = 6.5 Hz, 2H), 3.57–3.59 (m, 1H), 3.62 (t, *J* = 6.8 Hz, 2H), 3.87 (dd, *J* = 5.3, 7.1 Hz, 1H), 4.04 (br s, 1H), 4.48 (s, 2H), 7.26–7.35 (m, 5H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.9 (t), 25.0 (t), 25.3 (t), 25.7 (t), 26.0 (t, 2C), 26.1 (t), 29.4 (t), 29.5 (t), 29.6 (t, 6C), 29.8 (t), 30.1 (t), 32.9 (t), 35.2 (t), 37.5 (t), 63.0 (t), 66.3 (d), 70.3 (t), 72.9 (t), 77.9 (d), 82.4 (d), 109.5 (s), 127.5 (d), 127.6 (d, 2C), 128.3 (d, 2C), 138.6 (s) ppm. ESI-MS: *m/z* 555.7 (100%, $[M+Na]^+$). Anal. Calcd for $C_{33}H_{56}O_5$: C, 74.39; H, 10.59. Found: C, 74.20; H, 10.46.
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20. *Spectral data of compound* **2:** colorless oil. $[\alpha]_D^{25}$ +24. 6 (*c* 0.5, $CHCl_3$) $^{lit}[\alpha]_D^{25}$ +37.6 (*c* 0.98, $CHCl_3$).[10a] IR ($CHCl_3$): *v* 3451, 2928, 1732, 1693, 1465, 1393, 1247, 1046, 758, 667 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.24–1.70 (m, 54H), 1.78 (dt, *J* = 5.4, 12.4 Hz, 1H), 1.92–2.05 (m, 1H), 2.20 (q, *J* = 6.8 Hz, 2H), 2.30–2.44 (m, 1H), 3.26–3.60 (m, 5H), 3.60 (br s, 1H), 3.86–3.92 (m, 2H), 3.97–3.99 (m, 1H), 4.05 (br s, 1H), 4.11, 4.17 (2q, *J* = 7.2 Hz, 2H), 5.80 (br d, *J* = 15.6 Hz, 1H), 6.94 (dt, *J* = 7.0, 15.6 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3 (q), 22.7 (t), 23.0 (t), 23.1, 24.4 (2q, 1C), 25.0 (t), 25.1 (t), 26.1 (t), 26.7, 27.5 (2q, 1C), 27.8 (t), 28.4, 28.5 (2q, 3C), 29.3 (t), 29.5 (t), 29.7 (t, 8C), 29.8 (t), 30.1 (t), 31.9 (t), 35.0 (t), 37.5 (t), 56.3, 56.5 (2d, 1C), 60.2 (t), 65.4, 65.7 (2t, 1C), 66.2 (d), 69.3, 70.0 (2t, 1C), 71.4 (t), 77.7 (d), 79.7, 80.2 (2s, 1C), 82.4 (d), 93.2, 93.7 (2s, 1C), 109.6 (s), 121.5 (d), 148.9 (d), 166.7 (s) ppm. ESI-MS: *m/z* 746.8 (100%, $[M+Na]^+$). Anal. Calcd for $C_{41}H_{73}NO_9$: C, 68.01; H, 10.16; N, 1.93. Found: C, 67.90; H, 10.03; N, 1.72.