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Stereoselective synthesis of aminocyclitol moieties of trehazolin and trehalostatin via enyne metathesis protocol

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ABSTRACT

Stereoselective and efficient synthesis of respective aminocyclitol moieties **1a** and **2a** of trehazolin and trehalostatin as hexaacetates **1b** and **2b** using ring-closing enyne metathesis as the key reaction is described.

Trehalose is the characteristic blood sugar and reserve carbohydrate of many insects and trehalase plays an important role in the metabolism of trehalose in insects and fungi.[1] In this way specific inhibitors of trehalase may find applications in regulating the trehalose metabolism and thus pave way for the discovery of new insecticides. A diverse collection of naturally occurring trehalase inhibitors is known, most often many of which contain an aminocyclopentitol unit. Trehazolin and trehalostatin come under this collection (Fig. 1). Therefore, it is not surprising that their total synthesis[2] and the elucidation of SARs[3] have received much interest. Trehazolin, isolated by Ando et al. from the culture broth of *Micromonospora* strain SANK 62390, has been shown to be a powerful inhibitor of trehalase in vitro (IC_{50} 0.016 μg/mL for silkworm trehalase).[4] Aminocyclopentitol moiety **1a** of trehazolin is known as trehazolamine. Trehalostatin was isolated by Murao et al. from the culture broth of *Amycolatopsis trehalostatica*.[5] Interestingly, both the aminocyclopentitols of trehazolin **1a** (trehazolamine) and trehalostatin **2a** (*epi*-trehazolamine) share C-2 epimeric relationship with each other. Structurally, both **1a** and **2a** are densely functionalized with contiguous chiral groups; while the C1 carbon bears a chiral tertiary hydroxy group and a hydroxy methyl group, the C2, C3, and C4 carbon atoms are endowed with the hydroxy groups and the C5 is decorated with an amino functionality. Due to the above cited reasons, these two aminocyclopentitols are attractive synthetic targets.[2] Herein we describe the synthesis of both trehazolamine and *epi*-trehazolamine as their derivatives by enyne metathesis protocol.

Enyne metathesis[6,7] has emerged as a powerful tool for the construction of carbocylic ring systems. In continuation of our interest on the total synthesis of bioactive aminocyclitols containing natural products,[7] herein we report the synthesis of trehazolamine and *epi*-trehazolamine as their hexacetates. The retrosynthetic analysis of our approach is shown in Scheme 1. Thus, the targets **1b** and **2b** could be readily assembled by elaboration of precursor **3** using Sharpless epoxidation followed by the epoxide ring-opening reaction with sodium acetate followed by acetylation and the latter could be obtained by the substrate directed dihydroxylation reaction and acetylation. Allylic alcohol **3** in turn was envisioned from 1-vinyl cyclopentene **4** wherein we presumed that the vinylic double bond would serve as the masked 'hydroxymethyl side chain' that could be generated by a sequential regioselective dihydroxylation-oxidative cleavage-reduction reaction set. While diene **4** was accessed from the enyne **5** via the crucial enyne metathesis reaction, the enyne system **5** was realized from Garner's aldehyde **6**.[7]

Thus, the known precursor[7] **7** (Scheme 2) on Swern oxidation ($(COCl)_2/CH_2Cl_2/Et_3N/-78$ °C/1 h) and Wittig olefination ($Ph_3P{=}CH_2/KO^tBu$/THF/0 °C to rt/3 h) furnished olefin **8** (65%). Next the olefin **8** on acetonide deprotection ($CuCl_2{\cdot}2H_2O/CH_3CN$/0 °C/10 min) afforded primary alcohol **9** (95%). Alcohol **9** was oxidized to aldehyde under Swern conditions and the aldehyde thus obtained was converted into vinyl dibromide (CBr_4/TPP/$Et_3N/CH_2Cl_2/-10$ °C/2 h) which under Grignard conditions (EtMgBr/THF/0 °C/10 min) was transformed into a acetylenic compound enyne **5** (88% over three steps). Enyne **5** underwent a facile metathesis reaction

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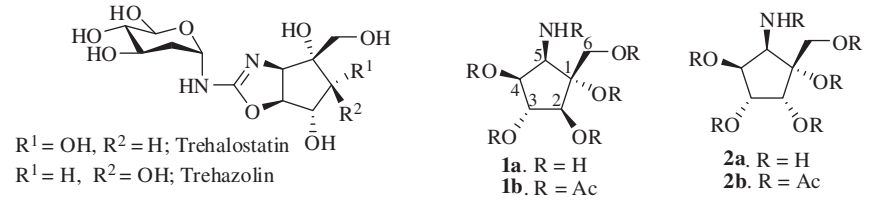
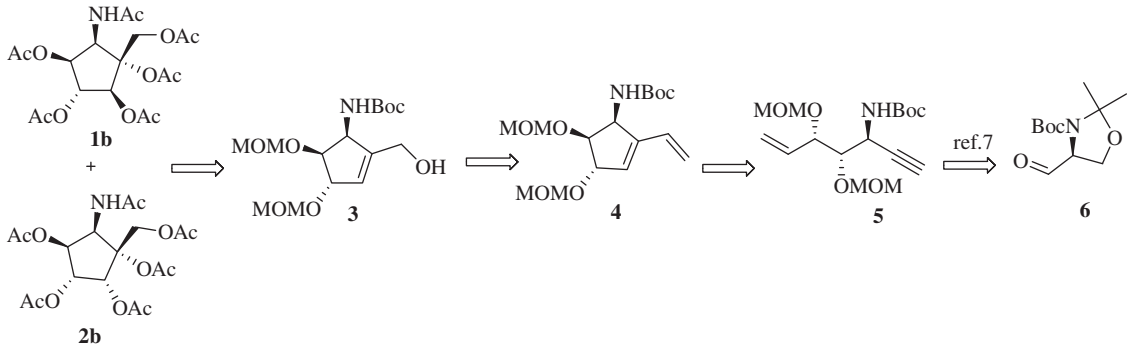
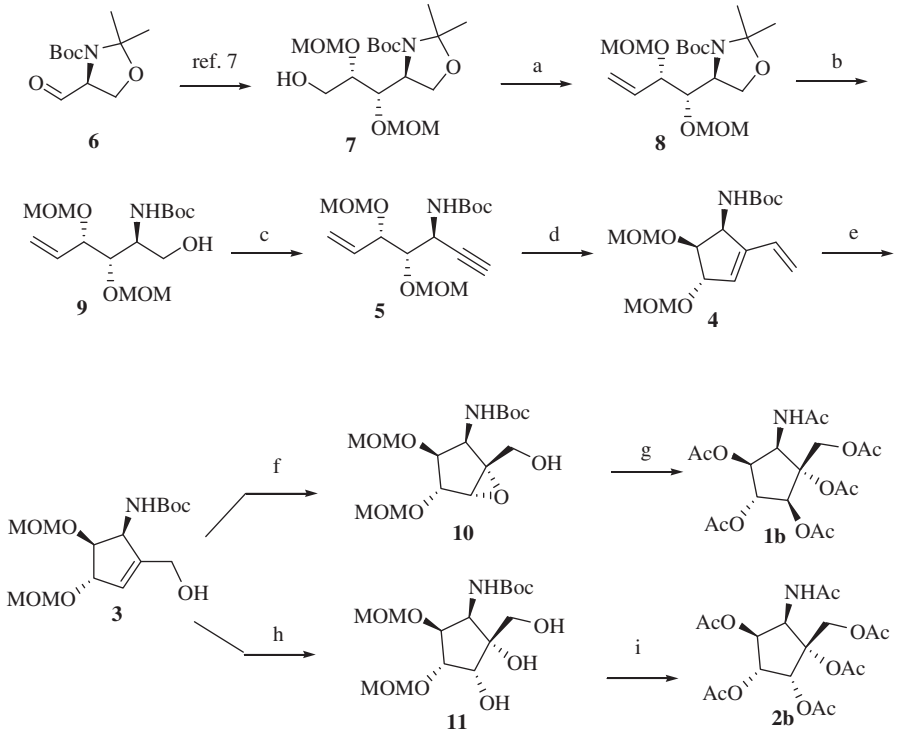


Figure 1.



Scheme 1. Retrosynthetic analysis.



Scheme 2. Reagents and conditions: (a) (i) DMSO, $(COCl)_2$, CH_2Cl_2, Et_3N, −78 °C, 1 h; (ii) $Ph_3P{=}CH_2$, KO^{t}Bu, THF, 0 °C to rt, 3 h, 65% (over two steps); (b) $CuCl_2{\cdot}2H_2O$, CH_3CN, 0 °C, 10 min, 95%; (c) (i) DMSO, $(COCl)_2$, CH_2Cl_2, Et_3N, −78 °C, 1 h; (ii) CBr_4, TPP, Et_3N, CH_2Cl_2, 0 °C, 2 h; (iii) EtMgBr, THF, 0 °C, 10 min, 88% (over three steps); (d) G-II (10 mol %), toluene, 110 °C, 10 h, 91%; (e) (i) OsO_4, NMO, acetone/H_2O (4:1), rt, 2 h; (ii) $NaIO_4$, MeOH/H_2O (9:1), 5 min, rt; (iii) $NaBH_4$, MeOH, 0 °C, 5 min, 73% (over three steps); (f) (−)-DIPT, Ti(O^{i}Pr)$_4$, TBHP, CH_2Cl_2, −20 °C, 24 h, 60%; (g) (i) NaOAc, H_2O/DMF (1:1), 120 °C, 24 h; (ii) TFA, CH_2Cl_2, 0 °C, 8 h; (iii) Ac_2O, Py, DMAP, 24 h, rt, 70% (over three steps); (h) OsO_4, NMO, acetone/H_2O (4:1), 4 h, 80%; (i) (i) TFA, CH_2Cl_2, 0 °C, 8 h; (ii) Ac_2O, Py, DMAP, rt, 24 h, 75% (over two steps).

{G-II (10 mol %)/toluene/110 °C/10 h} to afford the 1-vinylcyclopentene system **4** (91%). Compound **4** was identified from its spectral data. The ^{1}H NMR spectrum of **4** indicated the absence of acetylenic proton whilse displaying the characteristic olefinic protons at δ = 6.30 ppm as a double doublet (J = 17.5, 11.7 Hz), at δ = 5.76 ppm as a singlet, at δ = 5.49 ppm as a doublet (J = 17.5 Hz) and at δ = 5.22 ppm as a doublet (J = 10.9 Hz). The HRMS spectrum displayed the $[M+Na]^+$ 352.1727, calculated 352.1736 for the molecular formula $C_{16}H_{27}NO_6Na$.

According to the envisaged plan, the next task was to differentiate between the two olefins and functionalize selectively the vinylic olefin into the hydroxymethyl side chain. Hence, a

sequential dihydroxylation-oxidative cleavage-reduction protocol was invoked. Thus, the terminal olefinic bond of the conjugated diene **4** on regioselective dihydroxylation {OsO_4/NMO/acetone:H_2O (4:1)/rt/2 h} furnished the corresponding diol which on oxidative cleavage ($NaIO_4$/MeOH/rt/5 min) and reduction of the in situ generated aldehyde ($NaBH_4$/MeOH/rt/5 min) gave the crucial allylic alcohol **3** (73% over three steps). Allylic alcohol **3** underwent Sharpless epoxidation[8] {(−)-DIPT/Ti(O^iPr)$_4$/TBHP/−20 °C/24 h} to give chiral epoxide **10** (60%) which on ring-opening reaction with the acetate ion {NaOAc/DMF:H_2O(1:1)/120 °C/24 h}, one-pot deprotection (TFA/CH_2Cl_2/0 °C/8 h) of MOM and Boc groups followed by acetylation (Ac_2O/py/DMAP/rt/24 h) afforded compound **1b** (70%). Compound **1b** was identical in all respects to hexaacetate of trehazolamine ($[\alpha]_D^{25}$ +5.9 (*c* 0.4, $CHCl_3$)).[2h,j]

Likewise allylic alcohol **3** on dihydroxylation[9] (OsO_4/NMO/acetone:H_2O/rt/4 h) gave the corresponding triol **11** (80%) as the major diastereomer (8:2). The requisite major isomer on global deprotection (TFA/CH_2Cl_2/0 °C/8 h) followed by acetylation (Ac_2O/py/DMAP/rt/24 h) afforded hexaacetate of *epi*-trehazolamine **2b** (75%), {$[\alpha]_D^{25}$ −8.5 (*c* 0.4, $CHCl_3$)}.[10] The HRMS spectrum displayed the $[M+Na]^+$ 454.1338, calculated 454.1325 for the molecular formula $C_{18}H_{25}NO_{11}Na$.

In summary, we have achieved the stereoselective synthesis of trehazolamine and *epi*-trehazolamine as their hexacetates **1b** and **2b**, respectively, using enyne metathesis as the key step.[10] The strategy described could be adopted for the synthesis of similar targets.

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10. *Spectral data of selected compounds*: *Compound* **5**: colorless liquid; $[\alpha]_D^{25}$ +88.6 (*c* 1.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 5.76 (p, *J* = 8.0 Hz, 1H), 5.61 (d, *J* = 8.7 Hz, 1H), 5.47–5.31 (m, 2H), 4.82–4.72 (m, 2H), 4.68 (d, *J* = 6.5 Hz, 1H), 4.61–4.51 (m, 2H), 4.34 (t, *J* = 8.0 Hz, 1H), 3.61 (dd, *J* = 6.5, 3.6 Hz, 1H), 3.44 (s, 3H), 3.37 (s, 3H), 2.25 (s, 1H), 1.44 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.6, 133.8, 120.6, 97.9, 96.1, 93.9, 81.3, 78.3, 77.1, 72.5, 71.3, 55.5, 44.1, 28.3; IR (neat): 3304, 2928, 2852, 1714, 1496, 1161, 1026 cm^{-1}; ESIMS: *m*/*z* 330 $[M+H]^+$, 352 $[M+Na]^+$, HRMS *m*/*z*: Calcd for $C_{16}H_{27}NO_6Na$: 352.1736. Found: 352.1732. *Compound* **4**: yellow color liquid; $[\alpha]_D^{25}$ +134.5 (*c* 1.05, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 6.30 (dd, *J* = 17.5, 11.7 Hz, 1H), 5.76 (s, 1H), 5.49 (d, *J* = 17.5 Hz, 1H), 5.22 (d, *J* = 10.9 Hz, 1H), 4.98 (t, *J* = 8.0 Hz, 1H), 4.74–4.56 (m, 5H), 4.42 (d, *J* = 10.2 Hz, 1H), 4.12 (t, *J* = 5.1 Hz, 1H), 3.37 (s, 3H), 3.36 (s, 3H), 1.43 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.7, 143.5, 130.5, 130.1, 118.4, 96.5, 96.0, 84.1, 80.3, 62.0, 55.6, 55.3, 55.1, 28.2; IR (neat): 3347, 2925, 2855, 1710, 1513, 1158, 1045 cm^{-1}; ESIMS: *m*/*z* 330 $[M+H]^+$, 352 $[M+Na]^+$, HRMS *m*/*z*: Calcd for $C_{16}H_{27}NO_6Na$: 352.1736. Found: 352.1727. *Compound* **3**: colorless syrup; $[\alpha]_D^{25}$ +160.9 (*c* 0.7, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.67 (s, 1H), 5.16 (d, *J* = 7.5 Hz, 1H), 4.80–4.71 (m, 2H), 4.68 (q, *J* = 7.3 Hz, 3H), 4.52 (s, 1H), 4.2 (dd, *J* = 3.02, 6.7 Hz, 1H), 4.09 (s, 2H), 3.39 (s, 3H), 3.35 (s, 3H), 1.45 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.7, 126.4, 125.9, 96.9, 96.1, 84.6, 84.4, 80.2, 59.5, 56.1, 55.4, 54,2, 28.7; IR (neat): 3446, 2928, 2854, 1701, 1514, 1156, 1040 cm^{-1}; ESIMS: *m*/*z* 334 $[M+H]^+$, 356 $[M+Na]^+$, HRMS *m*/*z*: Calcd for $C_{15}H_{27}NO_7Na$: 356.1685. Found: 356.1683. *Compound* **10**: light yellow color sirup; $[\alpha]_D^{25}$ −16.6 (*c* 0.5, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 5.12 (d, *J* = 8.2 Hz, 1H), 4.60 (t, *J* = 6.8 Hz, 2H), 4.53 (dd, *J* = 6.8, 15.6 Hz, 2H), 4.46 (t, *J* = 8.2 Hz, 1H), 4.01 (s, 1H), 3.87 (d, *J* = 7.8 Hz, 1H), 3.80 (d, *J* = 12.6 Hz, 1H), 3.4 (d, *J* = 13.1 Hz, 1H), 3.33 (d, *J* = 19.5 Hz, 1H), 3.28 (s, 6H), 1.36 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.5, 97.1, 94.6, 79.2, 75.1, 63.0, 64.1, 61.5, 55.8, 55.5, 55.4, 49.3, 28.2; IR (neat): 3450, 2830, 1690, 1410, 1157, 1036 cm^{-1}; ESIMS: *m*/*z* 372 $[M+Na]^+$. *Compound* **11**: colorless sirup; $[\alpha]_D^{25}$ +18.5 (*c* 1.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.32 (d, *J* = 7.3 Hz, 1H), 4.78–4.63 (m, 6H), 4.09–43.9 (m, 2H), 3.91 (dd, *J* = 6.4, 1.5 Hz, 1H), 3.76 (d, *J* = 6.4 Hz, 1H), 3.43 (s, 3H), 3.37 (s, 3H), 1.45 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.9, 96.8, 96.4, 90.1, 80.3, 79.7, 79.5, 78.9, 75.1, 63.0, 55.8, 51.1, 28.2; IR (neat): 3440, 2930, 1690, 1510, 1157, 1036 cm^{-1}; ESIMS: *m*/*z* 368 $[M+H]^+$, 390 $[M+Na]^+$, HRMS *m*/*z*: Calcd for $C_{15}H_{29}NO_9Na$: 390.1740. Found: 390.1736. *Compound* **1b**: colorless liquid; $[\alpha]_D^{25}$ +5.9 (*c* 0.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.90 (d, *J* = 9.6 Hz, 1H), 5.77 (d, *J* = 5.6 Hz, 1H), 5.34 (dd, *J* = 7.6, 4.8 Hz, 1H), 5.29 (dd, *J* = 9.2, 8.2 Hz, 1H), 5.21 (t, *J* = 5.2 Hz, 1H), 4.58 and 4.52 (ABq, *J* = 12 Hz, 2H), 2.10 (s, 3H), 2.08 (s, 3H), 2.05 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1, 170.4, 169.9, 169.7, 169.5, 168.9, 86.6, 78.9, 76.4, 73.3, 59.5, 52.7, 23.1, 21.6, 20.9, 20.7, 20.6, 20.5; IR (neat): 3375, 2923, 2790, 1757, 1670, 1226 cm^{-1}; ESIMS: *m*/*z* 432 $[M+H]^+$, 454 $[M+Na]^+$, HRMS *m*/*z*: Calcd for $C_{18}H_{25}NO_{11}Na$: 454.1325. Found: 454.1337. *Compound* **2b**: colorless liquid; $[\alpha]_D^{25}$ −8.5 (*c* 0.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 6.45 (d, *J* = 9.8 Hz, 1H), 5.33 (d, *J* = 7.1 Hz, 1H), 5.24 (dd, *J* = 7.1, 2.2 Hz, 1H), 5.16 (dd, *J* = 7.1, 2.6 Hz, 1H), 4.90 (dd, *J* = 7.1, 8.6 Hz, 1H), 4.51 (d, *J* = 12.0 Hz, 1H), 4.40 (d, *J* = 11.7 Hz, 1H), 2.15 (s, 3H), 2.10 (s, 3H), 2.09 (s, 3H), 2.07 (s, 3H), 2.07 (s, 3H), 1.98 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9, 170.7, 170.4, 170.1, 170.0, 169.8, 79.6, 75.1, 74.6, 74.0, 59.3, 50.5, 25.0, 23.7, 22.6, 20.7, 20.6, 19.7; IR (neat): 3375, 2923, 2853, 1747, 1670, 1226 cm^{-1}; ESIMS: *m*/*z* 432 $[M+H]^+$, 454 $[M+Na]^+$, HRMS *m*/*z*: Calcd for $C_{18}H_{25}NO_{11}Na$: 454.1325. Found: 454.1338.