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Sequential Baylis–Hillman/RCM protocol for the stereoselective synthesis of (+)-MK7607 and (+)-streptol

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ABSTRACT

Sequential Baylis–Hillman/ring-closing metathesis (RCM) approach toward the total synthesis of (+)-MK7607 and (+)-streptol starting from (*R*,*R*)-tartaric acid is reported.

MK7607 (**1**), an unsaturated carbapyranose, commonly referred to as cyclitol, was isolated from *Curvularia eragrostidis* D2452.[1] Compound **1** is considered a natural mimic since it bears a close resemblance to α-galactose that plays an important role in many biological processes.[2] Another structurally similar cyclitol derivative, a C4 epimer of **1** known as streptol (**2**), was isolated from the culture filtrate of an unidentified *Streptomyces* sp. that inhibited the germination of lettuce seedlings.[3] The first total synthesis of **1** was reported by Mehta et al.[4a] using a novel fragmentation sequence of the norbornane system to provide a cyclohexenoid building block that was extrapolated to the target compound. Later, Kim and co-workers[4b] have relied on the stereospecific PBr_3-mediated allylic-transposed bromination followed by its conversion to corresponding hydroxyl group. Additionally, some synthetic analogs of **1** were also reported.[4c–e] However, to the best of our knowledge, so far only one synthesis of **2** was reported.[5] Our recent work encompassing Baylis–Hillman reaction[6] led to different diastereomeric adducts which when involved in an RCM reaction led to diverse scaffolds/building blocks.[7] Herein, we report the synthesis of two cyclitol derivatives **1** and **2** involving a Baylis–Hillman/RCM as the key reaction to construct the diastereomeric cyclohexenoids that were independently extrapolated to target compounds.

The retrosynthetic analysis of (+)-**1** and (+)-**2** is shown in Scheme 1. Accordingly, a common synthetic strategy was envisaged for accessing cyclitols (+)-**1** and (+)-**2** from the Baylis–Hillman adduct **3**,[8] identified as the common intermediate, through an RCM reaction followed by the ester reduction and global deprotection. Adduct **3** in turn could be obtained from allylic alcohol **4** on oxidation followed by the Baylis–Hillman reaction in the presence of ethyl acrylate. While allylic alcohol **4** could be realized from its corresponding epoxide **5** (Scheme 2), conversion to chloro epoxide, and metal-induced ring-opening reaction, the epoxide **5** itself maybe readily obtained from the mono-protected (+)-2,3-*O*-isopropylidene-L-threitol that could eventually be made from commercially available (*R*,*R*)-tartaric acid using the reported procedure.[9]

Thus, the synthesis of these cyclitols (**1** and **2**) commenced (Scheme 2) from the known[9] epoxide **5** that was derived from (*R*,*R*)-tartaric acid according to the reported procedure. Thus, the epoxide **5** was transformed into allylic alcohol **6** through the sodium-induced ring-opening reaction (Na/anhydrous Et_2O/0 °C to rt/12 h/85%) of the corresponding epoxy chloride obtained in excellent yields under conventional methods (TPP/CCl_4/cat.NaHCO_3/reflux/3 h/93%). Hydroxy functionality in **6** was protected as its MOM–ether (MOMCl/DIPEA/CH_2Cl_2/0 °C to rt) which on selective deprotection of benzyl group (DDQ/CH_2Cl_2:H_2O, 19:1)/reflux/3 h/75%) provided the primary alcohol **4**. Swern oxidation of **4** followed by the Baylis–Hillman reaction (ethyl acrylate/DABCO/DMF/24 h/80%/30%de) furnished adduct **3** as an inseparable mixture.[8] The diastereomeric ratio was evaluated based on the relative integration of the separable protons. For instance, ^{1}H NMR of adduct **3** displayed one of the disubstituted olefinic protons at δ 6.31 ppm as

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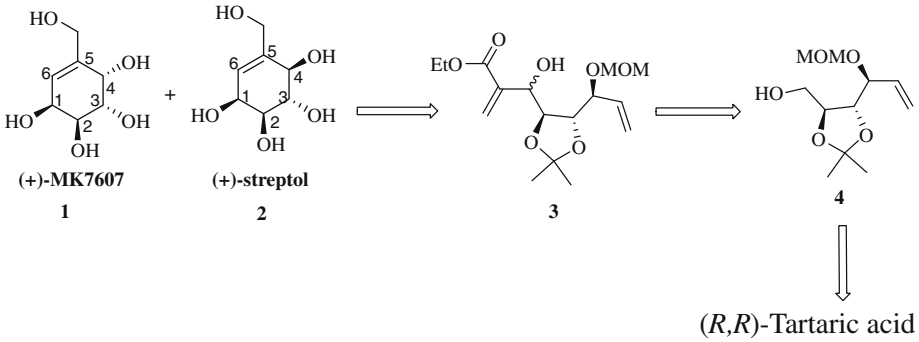
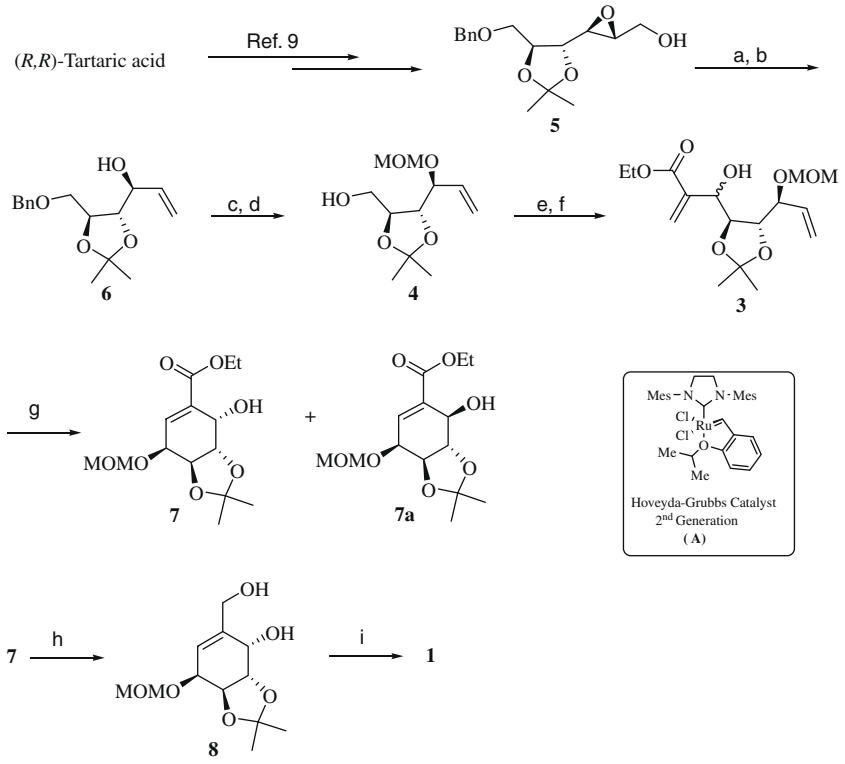


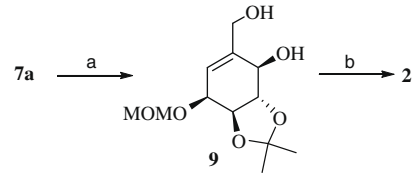
Scheme 1. Retrosynthetic analysis.



Scheme 2. Reagents and conditions: (a) Ph_3P, CCl_4, cat.$NaHCO_3$, reflux, 3 h, 93%; (b) Na, anhydrous Et_2O, 0 °C to rt, 12 h, 85%; (c) MOM–Cl, DIPEA, CH_2Cl_2, 12 h, 0 °C, 90%, (d) DDQ, CH_2Cl_2/H_2O (19:1), reflux, 3 h, 75%; (e) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, 1.5 h, 87%; (f) DABCO, ethyl acrylate, DMF, 24 h, 80%, 30% de; (g) **A** (10 mol %), toluene, 24 h, reflux, 83%; (h) DIBAL-H, −10 °C, THF, 3 h, 99%; (i) DOWEX, MeOH, 70 °C, 2 h, 90%.

a singlet for the major isomer while the same proton resonated at δ 6.20 ppm also as a singlet with the relative integration of 0.65:0.35. The other olefinic proton resonated at δ 5.93 ppm for the major isomer while the same proton of the minor isomer showed at δ 5.91 ppm. Likewise, the characteristic methine proton attached to newly created chiral stereogenic center resonated at δ 4.69 ppm as a doublet (J = 6.7 Hz) for the minor isomer, while the same proton resonated at δ 4.66 ppm as a doublet (J = 6.7 Hz) with the same integral ratio as mentioned above. Also, the MOM–CH_3 protons resonated differently at δ 3.35 ppm and at δ 3.32 ppm as singlets for the major and minor isomers, respectively. The absolute stereochemistry of the major isomer was assigned as '*S*' based on our earlier work.[8] The bisolefin of adduct **3** on ring-closing metathesis (RCM) employing Hoveyda–Grubbs second generation catalyst[10] {**A** (10 mol %)/toluene/110 °C/24 h/combined yield 83%} afforded cyclic compounds **7** (65%) and **7a** (35%) as chromatographically separable entities. Compound **7** was characterized by its spectral data. Thus, ^{1}H NMR spectrum of **7** revealed the lone olefinic proton resonating at δ 6.94 ppm as a doublet (J = 6.0 Hz) and one of the two allylic protons appeared at δ 4.91 ppm as a doublet (J = 3.7 Hz), while the other one resonated at δ 4.54 ppm as a double doublet (J = 3.7, 5.6 Hz) with the rest of the protons at their expected chemical shifts. Further, the HRMS spectrum displayed the $[M+Na]^+$ 325.1263, calculated 325.1267 for the molecular formula $C_{14}H_{22}O_7Na$.

Initially, the major product **7** was taken up for the rest of the synthetic sequence. Thus, ester group in the major product **7** was reduced with DIBAL-H in THF to give the alcohol **8** in quantitative yield. Since the final step of our synthetic endeavor comprises a global deprotection of both acetal and MOM–ether, the same was achieved with the acidic ion-exchange resin DOWEX[4d] (MeOH/70 °C/2 h) to furnish the target **1** (90%). The physical and spectroscopic data of synthetic **1** are consistent with the reported values.[4a,b,11] The HRMS spectrum displayed the $[M+Na]^+$



Scheme 3. Reagents and conditions: (a) DIBAL-H, −10 °C, THF, 3 h, 98%; (b) DOWEX, MeOH, 70 °C, 2 h, 90%.

199.0582, calculated 199.0590 for the molecular formula $C_7H_{12}O_5Na$.

Likewise, the minor isomer **7a** (Scheme 3) when subjected to same set of reactions as applied earlier afforded **9** (98%) which was subsequently transformed into **2** (90%).[5,11] In essence, both the isomers obtained during the Baylis–Hillman reaction were effectively converted into two target compounds through the common synthetic methodology.

In summary, we achieved the synthesis of cyclitols, (+)-MK7607 (**1**), and its C4 epimer, (+)-streptol (**2**) by a hitherto less explored sequential Baylis–Hillman/RCM reaction as the synthetic route to build the cyclohexenoid derivatives that were independently transformed into the target molecules. This report may renew the interest in exploring Baylis–Hillman reaction-based strategies for such natural product synthesis.

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11. *Spectral data for selected compounds. Compound* ***4***: Colorless syrup. $[\alpha]_D^{25}$ +127.0 (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.79–5.68 (m, 1H, olefinic), 5.36–5.31 (m, 2H, olefinic), 4.69 (d, 1H, *J* = 6.7 Hz, $-OCH_2$), 4.52 (d, 1H, *J* = 6.7 Hz, $-OCH_2$), 4.10 (t, 1H, *J* = 6.6 Hz, allylic), 4.04–3.98 (m, 1H, methine), 3.85 (dd, 1H, *J* = 6.0, 7.9 Hz, methine), 3.75–3.64 (m, 2H, $-OCH_2$), 3.36 (s, 3H, $-OCH_3$), 1.40 (br s, 6H, 2 × CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 132.6, 118.1, 107.2, 94.4, 92.0, 75.2, 74.8, 61.2, 54.0, 25.4, 25.2; IR (neat): 3500, 1210 cm^{-1}; ESIMS: *m*/*z* 255 $(M+Na)^+$, HRMS *m*/*z*: Calcd for $C_{11}H_{20}O_5Na$: 255.1210. Found; 255.1208. *Compound* ***3***: Colorless syrup. $[\alpha]_D^{25}$ +52.0 (*c* 0.3, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 6.31 (s, 0.65H, olefinic), 6.20 (s, 0.35H, olefinic), 5.93 (s, 0.65H, olefinic), 5.91 (s, 0.35H, olefinic), 5.84–5.17 (m, 1H, olefinic), 5.39–5.20 (m, 2H, olefinic), 4.69 (d, 0.35H, *J* = 6.7 Hz, methine), 4.64 (d, 0.65H, *J* = 6.7 Hz, methine), 4.57–4.48 (m, 2H, $-OCH_2$), 4.29–4.19 (m, 3H), 4.14–3.94 (m, 2H, $-OCH_2$), 3.35 (s, 1.95H, $-OCH_3$), 3.32 (s, 1.05H, $-OCH_3$), 1.42–1.2 (m, 9H, 3 × CH_3); IR (neat): 3400, 1735, 1610 cm^{-1}; ESIMS: *m*/*z* 353 $(M+Na)^+$, HRMS *m*/*z*: Calcd for $C_{16}H_{26}O_7Na$: 353.1563, Found: 353.1576. *Compound* ***7***: Colorless syrup. $[\alpha]_D^{25}$ +221.0 (*c* 0.37 $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 6.94 (d, 1H, *J* = 6.0 Hz, olefinic), 4.91 (d, 1H, *J* = 3.7 Hz, allylic), 4.84 (d, 1H, *J* = 6.7 Hz, $-OCH_2$), 4.62 (d, 1H, *J* = 6.7 Hz, $-OCH_2$), 4.54 (dd, 1H, *J* = 3.7, 5.6 Hz, allylic), 4.30–4.21 (q, 2H, *J* = 7.1 Hz, $-OCH_2$), 4.02 (dd, 1H, *J* = 3.7, 10.1 Hz, methine), 3.90 (dd, 1H, *J* = 3.7, 10.1 Hz, methine), 3.46 (s, 3H, $-OCH_3$), 1.46 (br s, 6H, 2 × CH_3), 1.34 (t, 3H, *J* = 6.7 Hz, CH_3); ^{13}C NMR (75 MHz,$CDCl_3$): δ 165.4, 135.2, 138, 110.9, 96.7, 96.1, 73.8, 72.8, 67.8, 63.8, 61.1, 55.4, 26.8, 26.7; IR (neat): 3403, 1750, 1620 cm^{-1}; ESIMS: *m*/*z* 325 $(M+Na)^+$, HRMS *m*/*z*: Calcd for $C_{14}H_{22}O_7Na$: 325.1267. Found: 325.1263. *Compound* ***8***: Colorless syrup. $[\alpha]_D^{25}$ +125.8 (*c* 0.5, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 5.88 (d, 1H, *J* = 5.2 Hz, olefinic), 4.84 (d, 1H, *J* = 6.4 Hz, $-OCH_2$), 4.62 (d, 1H, *J* = 6.7 Hz, $-OCH_2$), 4.40 (br s, 1H, allylic), 4.43 (d, 2H, *J* = 5.2 Hz, allylic), 4.27–4.15 (m, 2H), 3.95 (s, 2H, $-OCH_2$), 3.36 (s, 3H, $-OCH_3$), 1.46 (br s, 6H, 2 × CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.8, 124.8, 96.6, 73.8, 73.4, 70.3, 68.3, 65.7, 65.1, 55.5, 26.8, 26.7; ESIMS: *m*/*z* 283 $(M+Na)^+$, HRMS *m*/*z*: Calcd for $C_{12}H_{20}O_6Na$: 283.1149. Found: 283.1157. *Compound* ***1***: White solid: mp 157–159 °C. $[\alpha]_D^{25}$ +201.3 (*c* 0.4, H_2O); ^1H NMR (500 MHz, D_2O): δ 5.71 (d, 1H, *J* = 4.6 Hz, olefinic), 4.18 (t, 1H, *J* = 3.8 Hz, allylic), 4.11 (d, 1H, *J* = 3.1 Hz, allylic), 4.00 (s, 2H, $-OCH_2$), 3.74–3.69 (m, 2H); ^{13}C NMR (75 MHz, D_2O): δ 141.2, 124.9, 69.5, 69.2, 67.6, 66.9, 62.9; IR (neat): 3372, 2955, 1634 cm^{-1}; ESIMS: *m*/*z* 199 $(M+Na)^+$; HRMS *m*/*z*: Calcd for $C_7H_{12}O_5Na$: 199.0590. Found: 199.0582. *Compound* ***7a***: Colorless syrup. $[\alpha]_D^{25}$ +178.9 (*c* 0.85, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 6.88 (d, 1H, *J* = 5.2 Hz, olefinic), 4.84 (d, 1H, *J* = 6.7 Hz, $-OCH_2$), 4.64 (d, 1H, *J* = 6.7 Hz, $-OCH_2$), 4.53 (d, 1H, *J* = 8.3 Hz, allylic), 4.48 (dd, 1H, *J* = 2.2, 3.7 Hz, allylic), 4.25 (q, 2H, *J* = 7.5 Hz, $-OCH_2$), 4.06 (dd, 1H, *J* = 1.8, 6.3 Hz, methine), 3.71 (d, 1H, *J* = 1.5 Hz, –OH), 3.43 (dd, 1H, *J* = 3.4, 6.7 Hz, methine), 3.39 (s, 3H, $-OCH_3$), 1.50 (br s, 6H, 2 × CH_3), 1.34 (t, 3H, *J* = 6.7 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.0, 136.0, 135.0, 111.0, 96.7, 96.2, 76.0, 75.8, 70.8, 68.0, 61.4, 55.5, 27.2, 26.6; IR (neat): 3390, 1750, 1630 cm^{-1}; ESIMS: *m*/*z* 325 $(M+Na)^+$, HRMS *m*/*z*: Calcd for: $C_{14}H_{22}O_7Na$: 325.1267. Found: 325.1263. *Compound* ***2***: $[\alpha]_D^{25}$ +88.1 (*c* 0.3, H_2O); ^1H NMR (300 MHz, D_2O): δ 5.70 (d, 1H, *J* = 4.9 Hz, olefinic), 4.15 (dd, 1H, *J* = 4.3, 5.1 Hz, allylic), 4.10 (d, 1H, *J* = 15.4 Hz, $-CH_2$), 4.00 (d, 1H, *J* = 14.9 Hz, $-CH_2$), 3.90 (dd, 1H, *J* = 7.6, 0.8 Hz, allylic), 3.61 (dd, 1H, *J* = 8.0, 11.0 Hz, methine), 3.47 (dd, 1H, *J* = 3.9, 11 Hz, methine); ^{13}C NMR (75 MHz, D_2O): δ 144.7, 124.9, 75.3, 75.0, 73.6, 68.6, 63.9; IR (neat): 3372, 2955, 1634 cm^{-1}; ESIMS: *m*/*z* 199 $(M+Na)^+$; HRMS *m*/*z*: Calcd for $C_7H_{12}O_5Na$: 199.0580. Found: 199.0570.