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First stereoselective total synthesis of helicascolides A and C

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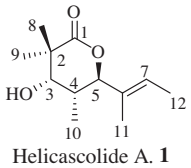
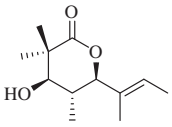
ABSTRACT

The first total synthesis of helicascolides A and C is reported via acid catalyzed acetonide deprotection followed by intramolecular lactonization in one-pot as the key step.

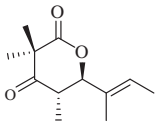
Helicascolides A (**1**) and B (**2**) are the isomeric δ-lactones isolated from the marine fungus *Helicascus kamaloanus* (ATCC 18591)[1] with no significant antifungal activity. Recently, structurally similar helicascolide C (**3**), isolated from marine alga *Gracilaria* sp. SGR-1, showed antifungal activity against phytopathogenic fungus from *Cladosporium cucumerinum*.[2] As a part of our interest in the total synthesis of lactone ring-containing bioactive natural products,[3] herein we report stereoselective total synthesis of helicascolides A and C by acid catalyzed acetonide deprotection followed by lactonization in one-pot. Helicascolides are architecturally unique in the sense that the lactone rings are highly substituted, endowed with gem-dimethyl group next to ketone functionality, chiral groups at C3 (ketone in case of compound **3**), C4, and at C5 make them synthetically attractive targets.



Helicascolide A. **1**



Helicascolide B. **2**



Helicascolide C. **3**

Accordingly, the envisaged retrosynthetic strategy for helicascolides A and C is delineated in Scheme 1. Linear strategy was invoked wherein acid **4** was conceived as the ideal precursor to **1**. Accordingly, acid **4** on exposure to acid (HCl) would lead to the helicascolide A (**1**) via the deprotection of acetonide group followed by an intramolecular lactonization in one-pot. Compound **1** on oxidation would result in helicascolide C (**3**). While acid **4** in turn could be accessed from **5** by the functional group transformations like vinylation on the right-hand side of the fragment followed by a deprotection-double oxidation reaction set of the PMB ether group next to gem-dimethyl carbon on the other side. Compound **5** was envisioned through the Gilman reaction of the corresponding epoxide, while the epoxide itself was obtained from commercially available neopentyl glycol.

Thus, the synthesis (Scheme 2) began with the commercially available neopentyl glycol and its transformation into known[4] conjugate ester **6** which upon treatment with DIBAL-H in CH_2Cl_2 gave allylic alcohol **7** in high yield. Allylic alcohol **7** was converted into chiral epoxy alcohol **8** using Sharpless[5] conditions {(−)-DIPT/Ti(O^iPr)$_4$/ TBHP/CH_2Cl_2/−20 °C/92%}. Later epoxide **8** was treated with Gilman's reagent[6] (Me_2CuLi) followed by the oxidative cleavage of the minor 1,2-diol with $NaIO_4$ in THF/H_2O (4:1) to afford the desired 1,3-diol **5** (75%) as the major isomer. Next, primary alcohol of 1,3-diol was protected as its benzoate ester **9** (Bz-Cl/Et_3N/rt/2 h) and the secondary alcohol as its MOM-ether (MOMCl/DIPEA/CH_2Cl_2/rt) to furnish the all protected intermediate **10** which on reductive cleavage of benzoate ester gave primary alcohol **11**. Later **11** was oxidized under Swern conditions {$(COCl)_2$/DMSO/Et_3N/CH_2Cl_2/−78 °C} to afford the corresponding chiral aldehyde which was subjected to Grignard reaction with (*E*)-1-methyl-2-propenylmagnesiumbromide to afford the olefinic compound **12** (68%) as a 3:1 diastereomeric ratio (as determined from ^{1}H NMR). Hence, the inseparable mixture **12** was treated with 3 N HCl to afford the

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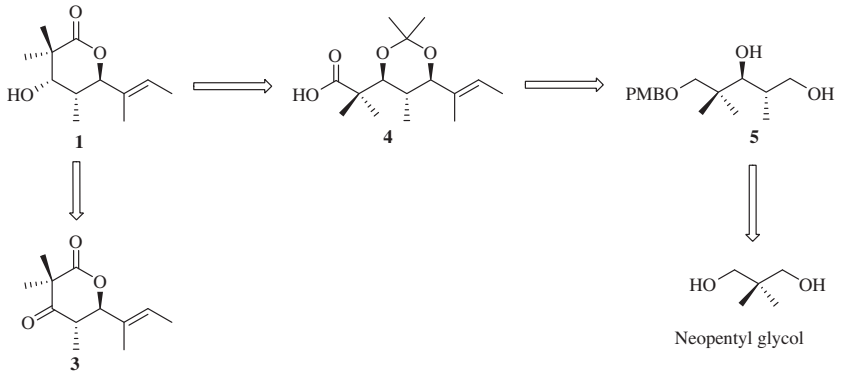
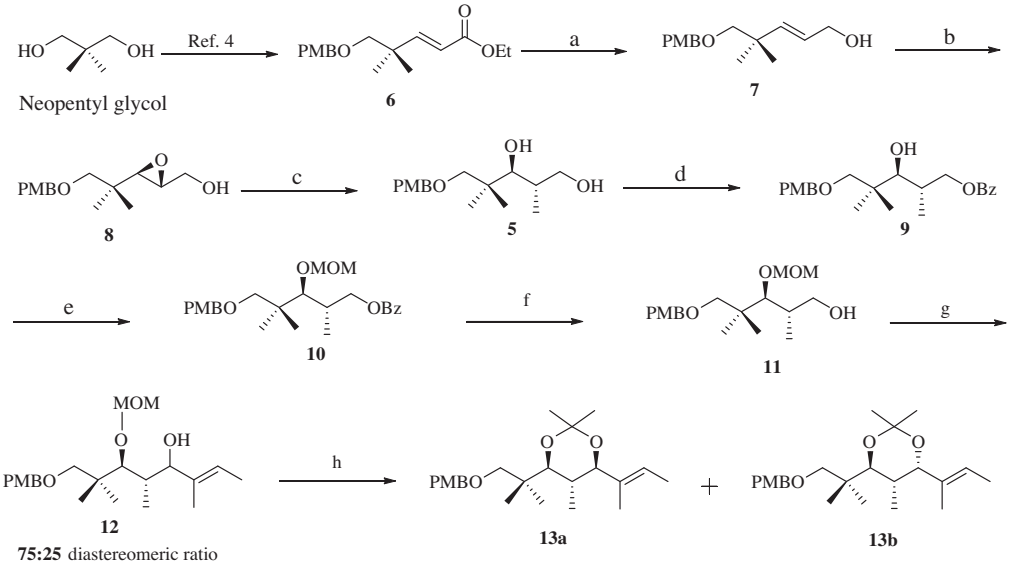


Scheme 1. Reterosynthetic analysis.



Scheme 2. Reagents and conditions: (a) DIBAL-H, CH_2Cl_2, 0 °C, 0.5 h, 98%; (b) (−)-DIPT, Ti(O*i*Pr)$_4$, TBHP, CH_2Cl_2, −20 °C, 8 h, 92%; (c) (i) $(CH_3)_2CuLi$, dry ether, −20 °C, 2 h (ii) $NaIO_4$, THF/H_2O (4:1), (over two steps 75%); (d) BzCl, Et_3N, CH_2Cl_2, 0 °C–rt, 2 h, 95%; (e) MOMCl, DIPEA, CH_2Cl_2, 0 °C–rt, 3 h, 94%; (f) K_2CO_3, MeOH, 0 °C–rt, 4 h, 85%; (g) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, (ii) (*E*)-1-methyl-2-propenylmagnesiumbromide, THF, −40 °C, (over two steps 68%); (h) (i) 3 N HCl, CH_2Cl_2, 0 °C–rt 0.5 h, 65%; (ii) 2,2-DMP, PTSA, CH_2Cl_2, 0 °C, 12 h, 90%.

corresponding free 1,3-diol which was then protected as its acetonide to afford the separable major diastereomer **13a** (75%).

The 1,3-*syn* stereochemistry of the major isomer **13a** was proved by the Rychnovsky's analogy.[7] For instance, the ^{13}C NMR of **13a** revealed the carbon atoms due to the acetonide methyls at δ 19.4 and at δ 30.1 ppm characteristic of the acetonide of a *syn*-1,3-diol moiety. The 1,3-diaxial interactions in *syn*-diol (**13a**), which assumes a chair-conformation, between one of the acetonide methyl groups and proton prompt the two methyl carbons resonate differently unlike *anti*-diol (**13b**), which due to its twisted-boat conformation induces chemical shifts of both the methyl groups of the acetonide group appear at the near same ppm (Fig. 1).

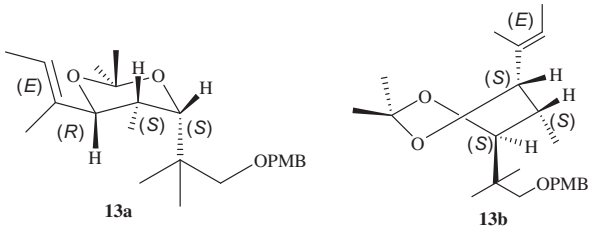
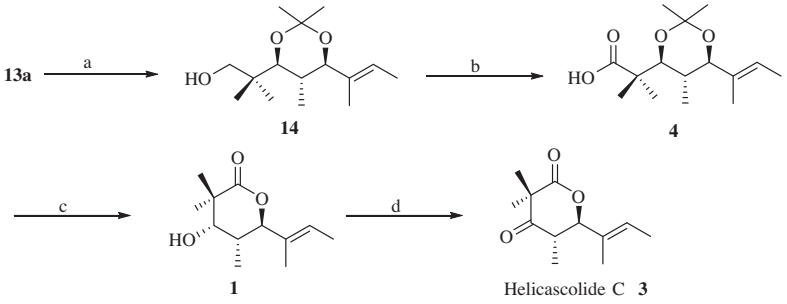


Figure 1. Conformers of *syn*-diol and *anti*-diol.

Cleavage (DDQ/CH_2Cl_2/H_2O/rt/0.5 h) of ether linkage in **13a** afforded the primary alcohol **14** (85%, Scheme 3). The alcohol **14** was oxidized to carboxylic acid **4** under TEMPO/BIAB[8] and acid catalyzed lactonization[9] of **4** to result in helicascolide A (**1**). Finally, **1** was oxidized using Dess-Martin periodinane (DMP/CH_2Cl_2/0 °C/92%) to furnish 6-membered keto lactone (helicascolide C) **3**. The physical and spectroscopic data of **1** and **3** are in consistent with the reported values.[1,2,10]

In summary, the first total synthesis of helicascolide A (8.15% overall yield) and helicascolide C (7.5% overall yield) is reported via acid catalyzed acetonide deprotection followed by lactonization in one-pot as the key step. It is pertinent to mention that helicascolide B could be accessed by the same methodology *albeit* using an appropriate precursor.



Scheme 3. Reagents and conditions: (a) DDQ, CH_2Cl_2/H_2O (19:1), 0 °C–rt, 1.5 h, 85%; (b) TEMPO/BIAB, CH_2Cl_2/H_2O (19:5), 0 °C–rt, 1.5 h, 90%; (c) 5 N HCl, THF, reflux, 0.5 h, 78%; (d) DMP, CH_2Cl_2, 0 °C–rt, 92%.

Acknowledgements

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10. *Spectral data for selected compounds. Compound* **7**: Pale yellow oil; $[\alpha]_D^{25}$ −5.73 (*c* 0.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.26 (d, 2H, *J* = 9.4 Hz), 6.87 (d, 2H, *J* = 9.4 Hz), 5.76–5.59 (m, 2H), 4.47 (s, 2H), 4.08 (d, 2H, *J* = 4.5 Hz), 3.80 (s, 3H), 3.16 (s, 2H), 1.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.1, 139.9, 129.0, 126.2, 113.6, 78.9, 72.9, 63.8, 55.2, 37.2, 24.5; HRMS *m*/*z*: calcd for $C_{15}H_{22}O_3Na$ $[M+Na]^+$ 273.1466. found: 273.1460. *Compound* **8**: Pale yellow oil; $[\alpha]_D^{25}$ +18.6 (*c* 0.65, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.25 (d, 2H, *J* = 8.4 Hz), 6.86 (d, 2H, *J* = 8.4 Hz), 4.43 (s, 2H), 3.85 (dd, 1H, *J* = 12.4, 2.2 Hz), 3.80 (s, 3H), 3.59 (dd, 1H, *J* = 12.2, 4.4 Hz), 3.25 (m, 1H), 3.10–3.07 (m, 1H), 2.90 (d, 1H, *J* = 2.0 Hz), 0.91 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.9, 130.4, 128.8, 113.6, 76.5, 72.8, 62.1, 60.9, 55.3, 55.1, 34.9, 20.9, 20.5; HRMS *m*/*z*: calcd for $C_{15}H_{22}O_4Na$ $[M+Na]^+$ 289.1415. found: 289.1413. *Compound* **9**: colorless oil; $[\alpha]_D^{25}$ −34.36 (*c* 0.6, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 8.05 (m, 2H), 7.55 (m, 1H), 7.40 (m, 2H), 7.22 (d, 2H, *J* = 8.2 Hz), 6.86 (d, 2H, *J* = 8.0 Hz), 4.66 (dd, 1H, *J* = 11.4, 4.4 Hz), 4.44 (s, 2H), 4.15 (dd, 1H, *J* = 11.4, 8.0 Hz), 3.78 (s, 3H), 3.49–3.44 (m, 2H), 3.27 (d, 1H, *J* = 9.1 Hz), 2.21–2.15 (m, 1H), 1.68–1.48 (m, 1H), 1.18 (d, 3H, *J* = 6.86 Hz), 1.00 (d, 6H, *J* = 9.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.8, 159.2, 132.7, 129.4, 129.2, 128.2, 113.8, 82.2, 80.2, 73.2, 67.3, 55.2, 38.9, 34.4, 23.4, 20.5, 18.6; HRMS *m*/*z*: calcd for $C_{23}H_{30}O_5Na$ $[M+Na]^+$ 409.1974 found: 409.1975. *Compound* **10**: Colorless oil; $[\alpha]_D^{25}$ −59.35 (*c* 0.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 8.05 (m, 2H), 7.55 (m, 1H), 7.40 (m, 2H), 7.22 (d, 2H, *J* = 8.6 Hz), 6.84 (d, 2H, *J* = 8.4 Hz), 4.63–4.60 (m, 2H), 4.44–4.35 (m, 2H), 4.13–4.00 (m, 1H), 3.78 (s, 3H), 3.44–3.41 (m, 5H), 3.31 (d, 1H, *J* = 8.7 Hz), 3.14 (d, 1H, *J* = 8.7 Hz), 2.27 (m, 1H), 1.2 (d, 3H, *J* = 6.86 Hz), 0.98 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.6, 158.9, 132.7, 129.4, 129.0, 128.2, 113.6, 99.2, 87.3, 76.8, 72.2, 67.9, 56.2, 55.1, 40.2, 33.0, 29.6, 21.9, 20.8, 19.0; HRMS *m*/*z*: calcd for $C_{25}H_{34}O_6$ Na $[M+Na]^+$ 453.2236 found: 453.2239. *Compound* **5**: Colorless oil; $[\alpha]_D^{25}$ −10. 03 (*c* 0.8, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.21 (d, 2H, *J* = 8.6 Hz), 6.87 (d, 2H, *J* = 8.4 Hz), 4.44 (s, 2H), 4.1 (br. s, 1H), 3.80 (s, 3H), 3.77–3.66 (m, 1H), 3.65–3,57 (m, 1H), 3.53 (d, 1H, *J* = 4.5 Hz), 3.32 (s, 2H), 1.93 (m, 1H), 1.62 (d, 3H, *J* = 1.7 Hz), 1.08–1.07 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.2, 129.2, 113.7, 83.97, 80.8, 73.4, 66.4, 54.9, 35.4, 22.5, 19.0, 17.8; HRMS *m*/*z*: calcd for $C_{16}H_{26}O_4Na$ $[M+Na]^+$ 305.1726. found: 305.1723. *Compound* **11**: Colorless oil; $[\alpha]_D^{25}$ −2.45 (*c* 0.25, $CHCl_3$) : ^1H NMR (300 MHz, $CDCl_3$): δ 7.25 (d, 2H, *J* = 8.3 Hz), 6.89 (d, 2H, *J* = 8.0 Hz), 4.69–4.64 (m, 2H), 4.43–4.40 (m, 2H), 3.80 (s, 3H), 3.70–3.51 (m, 2H), 3.40 (s, 3H), 3.26 (m, 1H), 3.07 (d, 1H, *J* = 9.06 Hz), 2.04–1.92 (m, 1H), 1.49–0.91 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 129.1, 113.6, 99.7, 88.8, 76.7, 72.7, 66.0, 55.2, 36.2, 21.8, 20.5, 18.1; HRMS *m*/*z*: calcd for $C_{18}H_{30}O_5Na$ $[M+Na]^+$ 3491992. found: 349.1990. *Compound* **13a**: Colorless oil; $[\alpha]_D^{25}$ +13.20 (*c* 0.25, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.25 (d, 2H, *J* = 8.6 Hz), 6.86 (d, 2H, *J* = 8.6 Hz), 5.55–5.46 (m, 1H) 4.47–4.35 (m, 3H), 3.80 (s, 3H), 3.58 (d, 1H, *J* = 9.8 Hz), 3.38 (d, 1H, *J* = 8.6 Hz), 3.11(d, 1H, *J* = 8.1 Hz), 1.76–1.60 (m, 4H), 1.56 (s, 3H), 1.44–1.39 (m, 6H), 1.01–0.93 (m, 6H), 0.74 (d, 3H, *J* = 6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 128.8, 124.7, 113.5, 77.7, 77.1, 72.8, 72.1, 55.2, 32.3, 30.1, 23.7, 20.9, 19.4, 18.0, 13.3, 13.2; HRMS *m*/*z*: calcd for $C_{23}H_{36}O_4Na$ $[M+Na]^+$ 399.2514. found: 399.2511. *Compound* **14**: Colorless oil; $[\alpha]_D^{25}$ −5.55 (*c* 0.15, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.51 (q, 1H, *J* = 6.4 Hz), 4.45 (d, 1H, *J* = 10.1 Hz), 3.89–3.77 (m, 1H), 3.63–3.51 (m, 1 H), 3.42 (d, 1H, *J* = 4.5 Hz), 3.07–2.90 (m, 1H), 1.88–1.56 (m, 7H), 1.51–1.26 (m, 6H), 0.99 (s, 6H), 0.77 (d, 3H, *J* = 6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 126.9, 125.1, 97.8, 82.4, 72.8, 72.0, 41.4, 30.1, 24.8, 19.6, 19.4, 17.9, 13.8, 13.2; HRMS *m*/*z*: calcd for $C_{15}H_{28}O_3Na$ $[M+Na]^+$ 279.1934. found: 279.1930. *Compound* **4**: white solid; mp 125–126 °C. $[\alpha]_D^{25}$ −10.56 (*c* 0.25, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.49 (q, 1H, *J* = 6.6 Hz), 4.47 (d, 1H, *J* = 10.1 Hz), 4.01–3.88 (m, 1H), 1.78–1.68 (m, 7H), 1.50–1.46 (m, 3H), 1.43–1.31 (m, 3H), 1.29–1.18 (m, 6H), 0.67 (d, 3H, *J* = 6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 183.0, 133.3, 124.8, 98.4, 71.9, 45.9, 33.7, 30.1, 23.4, 19.5, 19.2, 17.9, 13.2, 11.4; HRMS *m*/*z*: calcd for $C_{15}H_{26}O_4Na$ $[M+Na]^+$ 293.1523. found: 293.1520. *Helicascolide* **A (1)**: white solid; mp 99–100 °C. $[\alpha]_D^{25}$ −33.1 (*c* 0.15, CH_3OH), lit.[2] value $[\alpha]_D^{25}$ −35.2 (*c* 0.14, CH_3OH); ^1H NMR (300 MHz, CD_3OD): δ 5.58 (qq, 1H, *J* = 6.7, 1.3 Hz), 4.64 (d, 1H, *J* = 11.1 Hz), 3.45 (d, 1H, *J* = 1.8 Hz), 2.34–2.32 (m, 1H), 1.68–1.63 (m, 6H), 1.29–1.27 (m, 6H), 0.90 (d, 3H, *J* = 6.7 Hz); ^{13}C NMR (75 MHz, CD_3OD): δ 180.6, 133.4, 127.2, 90.1, 77.4, 45.6, 32.4, 26.9, 23.3, 14.2, 13.3, 10.4; HRMS *m*/*z*: calcd for $C_{12}H_{20}O_3Na$ $[M+Na]^+$ 235.1416. found: 235.1415. *Helicascolide* **C (3)**: white solid; mp 87–88 °C. $[\alpha]_D^{25}$ +20.8 (*c* 0.15, CH_3OH), lit.[2] value $[\alpha]_D^{25}$ +21.2 (*c* 0.34, CH_3OH); ^1H NMR (300 MHz, CD_3OD): δ 5.72–5.70 (m, 1H), 4.69 (d, 1H, *J* = 11.5 Hz), 2.94–2.92 (m, 1H), 1.72–1.69 (m, 6H), 1.40–1.38 (m, 6H), 0.95 (d, 3H, *J* = 6.7 Hz), ^{13}C NMR (75 MHz, CD_3OD): δ 177, 132.3, 129.1, 86.4, 52.6, 44.5, 23.9, 23.8, 13.3, 10.2, 9.7; HRMS *m*/*z*: calcd for $C_{12}H_{18}O_3Na$ $[M+Na]^+$ 233.1145. found: 233.1148.