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Enantioselective syntheses of bioactive epoxyquinone natural products (+)-harveynone and (−)-asperpentyn

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ABSTRACT

Stereo- and enantioselective syntheses of (+)-harveynone and (−)-asperpentyn are reported.

Natural products based on epoxyquinone motif **1** are well known for their occurrence among diverse sources like bacteria, fungi, higher plants, and marine sources.[1] Epoxyquinone class of natural products also exhibit remarkable variation in terms of structural complexity, functional group density, and distribution. While phyllostine **2**,[2a] ambuic acid **3**[2b], and cycloepoxydone **4**[2c] represent mono and bicyclic variants with relatively modest complexity, heptacyclic torreyanic acid **5**[2d] and nonacyclic pestaloquinol A **6**[2e] are among the more complex members of this family, Figure 1. Epoxyquinone natural products exhibit wide-ranging bio-

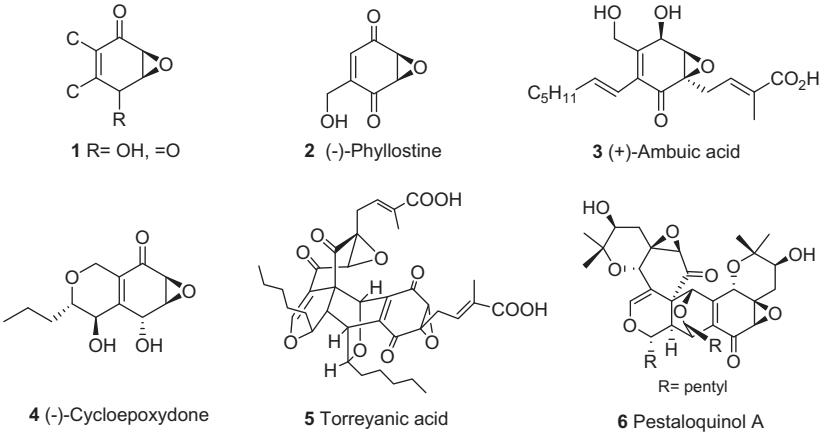

Figure 1. Representative epoxyquinone natural products.

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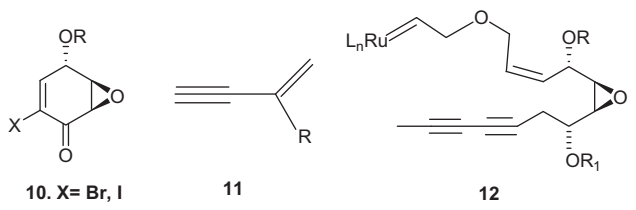
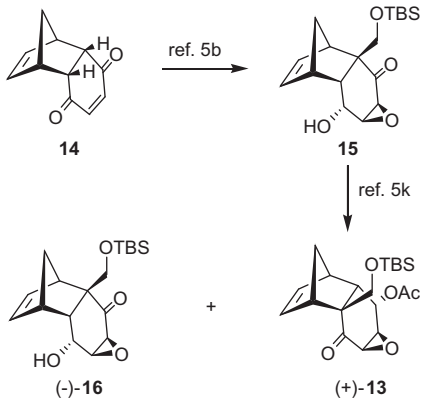


Scheme 1. Approaches to harveynone and asperpentyn.



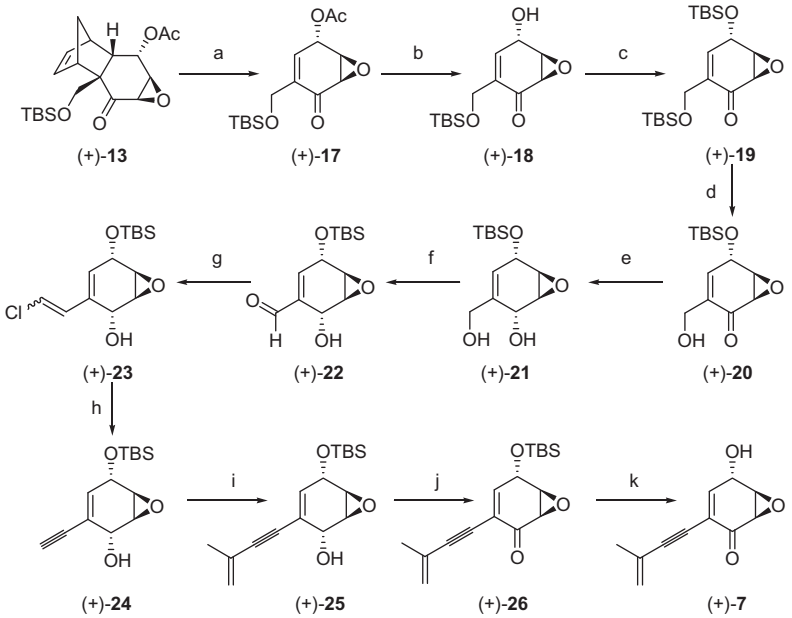
Scheme 2. Preparation of the chiral synthon (+)-**13**.

activity profile that includes phytotoxic, anti-fungal, anti-bacterial, anti-tumor, and specific enzyme inhibitory activity. For these reasons, epoxyquinone natural products have been objects of sustained interest from synthetic chemists world-wide[1,3,4] and our group[5] has also been active in this arena.

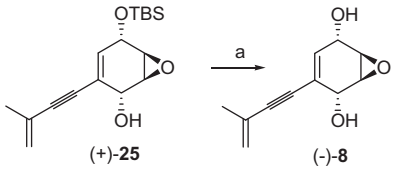
(+)-Harveynone **7** from the tea gray blight fungus *Pestalotiopsis theae*[6a] and its antipode (−)-harveynone from *Curvularia harveyi*,[6b] (−)-asperpentyn **8** from *Aspergillus duricaulis*[7a] and more recently[7b] from *Pestalotiopsis* sp. PSU-MA69, and tricholomenyn A **9** from *Tricholoma acerbum*[8] are among the epoxyquinone natural products that embody an intriguing diene-enyne functionality. Among them, (+)- and (−)-harveynone have been shown to arrest mitosis by inhibiting spindle formation in sea-urchin eggs.[6b] Over the years, natural products **7–9** have emerged as commonly pursued targets for total synthesis both as a testing bed for new tactics and as end objectives in their own right.[4] As an extension and adaptation of our norbornyl based general approach[4] to epoxyquinone natural products, we report here a synthesis of (+)-harveynone and (−)-asperpentyn from a common precursor.

Earlier synthetic approaches[4] to harveynone **7** and asperpentyn **8**, with one notable exception,[4j] have involved Sonogashira or Stille coupling between a 2-halocyclohexenone **10** and an appropriate 1,3-enyne partner **11**, Scheme 1. The exception being an interesting tandem enyne metathesis-metallotropic [1,3]-shift based strategy on **12** which incorporates a disposable tether, Scheme 1.[4j] Our approach to **7** and **8** reported here is a new variant involving Sonogashira coupling between 2-alkynylcyclohexenol and a vinyl halide.

Our synthesis of (+)-**7** and (−)-**8** emanated from tricyclic chiron (+)-**13**, readily available from the Diels–Alder adduct **14** of cyclopentadiene and *p*-benzoquinone via an embellished intermediate **15** reported earlier by us.[5b] A lipase mediated enzymatic resolution protocol on **15** delivered (+)-**13** (∼99% ee) and (−)-**16** (∼99% ee), Scheme 2.[9] Retro-Diels–Alder reaction in (+)-**13** was smooth and led to the functionalized epoxyquinone derivative **(+)-17**, Scheme 3. Controlled base hydrolysis in **(+)-17** delivered the hydroxyl derivative **(+)-18**.[9] Since, the free secondary hydroxyl group in **(+)-18** already had the requisite stereochemical disposition present in the target natural products, it needed to be protected in a more robust and compatible manner along with the deprotection of the TBS-protected primary hydroxyl group for further maneuvers. This proved to be somewhat tricky to execute but could be implemented by smooth conversion to the *bis*-TBS derivative **19** and selective deprotection of the primary TBS protection to yield the requisite mono-protected **(+)-20**,[9] Scheme 3. Stereoselective carbonyl reduction in **(+)-20** by DIBAL-H was mediated through the coordination of aluminum in the reducing reagent with epoxide oxygen on the β-face and hydride delivery from the same face to furnish **(+)-21**.[9] Regioselective oxidation of the allylic primary



Scheme 3. Reagents and conditions: (a) Ph_2O, 230 °C, 20 min, 83%; (b) LiOH, MeOH, 0 °C, 1 h; (c) TBSOTf, 2,6-lutidine, 0 °C, 10 min, 88%; (d) PPTS, MeOH, 25 °C, 2 h, 75%; (e) DIBAL-H (under N_2), −78 °C, 25 min, 73%; (f) MnO_2, CH_2Cl_2, 25 °C, 4 h, 93%; (g) $ClCH_2PPh_3Cl$, *n*-BuLi, THF-HMPA, 0–25 °C, 1.5 h, 72%; (h) *n*-BuLi, THF, −78 °C, 4 h, 77%; (i) 2-bromopropene, $PdCl_2(PPh_3)_2$, *i*-Pr_2NH, CuI, THF, 25 °C, 3 h, 41%; (j) DMP, CH_2Cl_2, 25 °C, 2 h, 90%; (k) 40%HF, CH_3CN, 25 °C, 2 h, 92%.



Scheme 4. Reagents and conditions: (a) 20% HF, CH_3CN, rt, 2 h, 95%.

hydroxyl group in **(+)-21** was uneventful and delivered the aldehyde **(+)-22** in high yield, Scheme 3. Wittig olefination in **(+)-22** with the ylide derived from chloromethyl(triphenyl)phosphorane hydrochloride furnished a mixture of *E*-, *Z*-chloroolefins **23** which was subjected to dehydrohalogenation to eventuate in the alkyne **(+)-24**. Pd^{+2} mediated Sonogashira coupling between **(+)-24** and 2-bromopropene generated **(+)-25** with the key ene-enyne bearing a side arm in place, Scheme 3. Dess–Martin periodinane oxidation in **(+)-25** led to the enone **(+)-26** and further TBS deprotection delivered the natural product (+)-**7** whose spectral data were found to be identical with those reported in the literature,[4] Scheme 3.

Lastly, TBS deprotection in **(+)-25** was carried out routinely with aq. HF to furnish asperpentyn (−)-**8**, Scheme 4, whose spectral data were found to be identical with those reported[4] for the natural product.

In summary, we have outlined enantio- and stereoselective syntheses of epoxyquinone natural products (+)-harveynone and (−)-asperpentyn bearing a diene-enyne functionality, thereby further demonstrating the efficacy and utility of our general norbornyl based strategy for the synthesis of this class of compounds.

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9. All new compounds were characterized on the basis of their spectroscopic data (IR, ^1H, ^{13}C, MS). Spectral data for some of the key compounds are as follows: **19:** $[\alpha]_D^{25}$: (+)-94.3 (*c* 2.97, $CHCl_3$); IR (neat): υ_{max} 1683, 1257, 1093, 838 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.62–6.60 (m, 1H), 4.74–4.72 (m, 1H), 4.47 (dd, 1H, *J* = 1.2, 15.5 Hz), 4.24 (dd, 1H, *J* = 1.8, 15.9 Hz), 3.68–3.65 (m, 1H), 3.46 (dd, 1H, *J* = 0.6, 3.3 Hz), 0.92 (s, 9H), 0.91 (s, 9H), 0.18 (s, 3H), 0.15 (s, 3H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.1, 137.7, 135.8, 63.8, 59.2, 58.5, 53.5, 25.8, 25.7, 18.2, −4.4, −4.6, −5.5; HRMS (ES): *m/z* for $C_{19}H_{36}NaO_4Si_2$ [M^++Na], calcd 407·2050, found 407.2058. **20:** $[\alpha]_D^{25}$: (+)-219.4 (*c* 0.72, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 6.51 (s, 1H), 4.72 (d, 1H, *J* = 4.5 Hz), 4.37 (d, 1H, *J* = 14.4 Hz), 4.26 (d, 1H, *J* = 14.7 Hz), 3.67 (s, 1H), 3.48 (d, 1H, *J* = 3.9 Hz), 0.93 (s, 9H), 0.19 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.0, 139.4, 135.3, 63.7, 60.7, 58.5, 53.4, 25.7, 18.2, −4.4, −4.6; HRMS (ES): *m/z* for $C_{13}H_{22}NaO_4Si$ [M^++Na], calcd 293·1185· found 293.1177. **21**: $[\alpha]_D^{24}$: (+)-43.1 (*c* 1.67, $CHCl_3$); IR (neat): υ_{max} 3400, 1471, 1255, 1075 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.57 (dd, 1H, *J* = 3.3, 1.5 Hz), 4.48 (d, 1H, *J* = 3.9 Hz), 4.32 (d, 1H, *J* = 8.1 Hz), 4.18–4.07 (m, 2H), 3.45 (br s, 1H), 3.35 (t, 1H, *J* = 1.5 Hz), 3.18 (d, 1H, *J* = 1.2 Hz), 0.90 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.0, 121.4, 64.3, 63.7, 63.0, 53.2, 52.7, 25.8, 18.2, −4.7, −4.9; HRMS (ES): *m/z* for $C_{13}H_{24}NaO_4Si$ [M^++Na], calcd 295.1342, found 295.1358. **22**: $[\alpha]_D^{25}$: (+)-98.5 (*c* 1.23, $CHCl_3$); IR (neat): υ_{max} 3457, 1696, 1257, 1082 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.53 (s, 1H), 6.48 (dd, 1H, *J* = 1.5, 3.0 Hz), 4.84 (s, 1H), 4.70–4.68 (m, 1H), 3.45 (d, 1H, *J* = 3.0 Hz), 3.29 (d, 1H, *J* = 0.9 Hz), 2.91 (br s, 1H), 0.92 (s, 9H), 0.18 (s, 3H), 0.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.3, 144.8, 137.4, 63.4, 59.8, 53.1, 53.0, 25.6, 18.1, −4.6, −4.7; HRMS (ES): *m/z* for $C_{13}H_{22}NaO_4Si$ [M^++Na], calcd 293.1185, found 293.1195. **24:** $[\alpha]_D^{24}$: (+)-21.4 (*c* 0.70, $CHCl_3$); IR (neat): υ_{max} 3272, 2929, 1251, 1055 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.02 (dd, 1H, *J* = 1.5, 4.9 Hz), 4.54 (d, 1H, *J* = 3.6 Hz), 4.41 (d, 1H, *J* = 8.4 Hz), 3.42 (t, 1H, *J* = 1.8 Hz), 3.22 (dd, 1H, *J* = 0.9, 1.9 Hz), 2.97 (s, 1H), 2.36 (d, 1H, *J* = 8.4 Hz), 0.92 (s, 9H), 0.16 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 133.5, 121.3, 82.3, 78.6, 65.4, 63.4, 52.5, 52.0, 25.8, 18.2, −4.6, −4.8; HRMS (ES): *m/z* for $C_{14}H_{22}NaO_3Si$ [M^++Na], calcd 289·1236, found 289·1237. **25:** $[\alpha]_D^{24}$: (+)-22.7 (*c* 0.44, $CHCl_3$); IR (neat): υ_{max} 3434, 2929, 1472, 1256 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.93 (dd, 1H, *J* = 1.8, 5.1 Hz), 5.35 (dd, 1H, *J* = 1.2, 1.8 Hz), 5.29 (t, 1H, J=1.8 Hz), 4.56-4.54 (m, 1H), 4.41 (d, 1H, *J* = 8.4 Hz), 3.44–3.42 (m, 1H), 3.23–3.22 (m, 1H), 2.28 (d, 1H, *J* = 15.0 Hz), 1.92 (t, 3H, *J* = 1.2 Hz), 0.92 (s, 9H), 0.16 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 131.7, 126.3, 122.9, 122.3, 91.8, 86.9, 65.7, 63.6, 52.5, 51.9, 25.8, 23.3, 18.2, −4.5, −4.8; HRMS (ES): *m/z* for $C_{17}H_{26}NaO_3Si$ [M^++Na], calcd 329.1549, found 329.1534. **(+)-7:** mp 78.3–78.7 °C; IR (neat) υ_{max} 1701 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 6.85 (dd, 1H, *J* = 2.7, 5.1 Hz), 5.43 (dd, 1H, *J* = 0.6, 1.8 Hz), 5.35 (t, 1H, *J* = 1.5 Hz), 4.78 (t, 1H, *J* = 6.0 Hz), 3.83–3.81 (m, 1H), 3.58 (dd, 1H, *J* = 1.2, 3.6 Hz), 2.26 (d, 1H, *J* = 6.9 Hz), 1.94 (t, 3H, *J* = 0.6 Hz); ^{13}C NMR (75 MHz ,$CDCl_3$) δ 190.3, 145.0, 125.9, 124.1, 123.2, 95.9, 81.2, 63.3, 57.3, 53.4, 23.0; HRMS (ES) *m/z* (M+Na)$^+$ 213.0530.