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# A total synthesis of the epoxyquinone based antifungal natural product (±)-ambuic acid

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**Abstract**—A total synthesis of the recently isolated polyketide natural product (±)-ambuic acid has been accomplished from the readily available Diels–Alder adduct of cyclopentadiene and 2-allyl-*p*-benzoquinone through a simple sequence with sound stereocontrol.


*Pestalotiopsis* spp. and *Monochaetia* spp. are two fungal genera, generally encountered as endophytic fungi, associated with many economically important rain forest plant species in different parts of the world.[1] From the culture extracts of these fungi, Strobel and co-workers in a collaborative study in 2001, reported[2] the isolation and structure determination of a novel, polyketide derived epoxyquinone natural product, (+)-ambuic acid **1**. The structure of **1** was deduced on the basis of incisive 2D-NMR analysis and further confirmed from more recent solid state NMR studies[3] and total synthesis[4] which also secured the absolute configuration of the natural product. Ambuic acid **1** was found to be active against several plant pathogenic fungi and it has been speculated that such activity symbiotically protects the host plant.[2]

The complex structural attributes of **1** makes it an attractive synthetic target and the group of Porco[4] has reported the first synthesis of (+)-ambuic acid through reduction of the quinone **3**, an advanced intermediate in their total synthesis of the related dimeric natural product torreyanic acid **2**, to furnish **4** (48%) and its diastereomer **5** (39%).[4] Ester deprotection in **4** led to (+)-ambuic acid **1**, Scheme 1. As part of our ongoing[5] interest in the total synthesis of epoxyquinone natural products, we were drawn to **1** and disclose here a synthesis of this natural product which is notable for its simplicity, flexibility and good stereocontrol.

Highly functionalized epoxycyclohexenone **6**, readily obtainable from the *endo*-Diels–Alder adduct **7** of cyclopentadiene and 2-allyl-*p*-benzoquinone as described recently by us,[6] was chosen as the starting point for the projected synthesis of ambuic acid **1**. The foremost initial concern in our projected synthesis was to set the correct hydroxyl stereochemistry at C7[7] in the evolution of **6** towards the natural product. Gratifyingly, it was found that $NaBH_4$ reduction in **6** was stereoselective with hydride addition from the face opposite to the epoxide ring and furnished β-hydroxy compound **8** (7:1)[8] as the major product along with the minor epimer. The structure of **8** was fully secured on the basis of X-ray crystal structure determination.[9] The 1,3-diol moiety in **8** was smoothly protected as the acetonide **9** and the key C7 hydroxyl group was protected as its TBS derivative to furnish **10**, Scheme 2.[8] Acetonide deprotection of **10** led to **11** and the primary hydroxyl group was chemoselectively oxidized in $O_2$–TEMPO–CuCl milieu[10] to deliver hydroxyaldehyde **12**.[8] In preparation for the introduction of the alkenyl side chain present in the natural product, the C10 hydroxyl group in **12** was further protected to give acetate **13**, Scheme 2.[8]

The aldehyde functionality in the fully protected acetate **13** was suitably poised for effecting the Wittig olefination to introduce the hexenyl side arm. Reaction of **13** with the ylide derived from *n*-hexyltriphenylphosphonium bromide delivered **14** as an *E*:*Z* mixture (1:2.2), Scheme 3.[8] It was not considered necessary to separate the stereoisomers at this stage as it was planned to address this issue at a later stage in the synthesis through photochemical isomerization in the presence of a better

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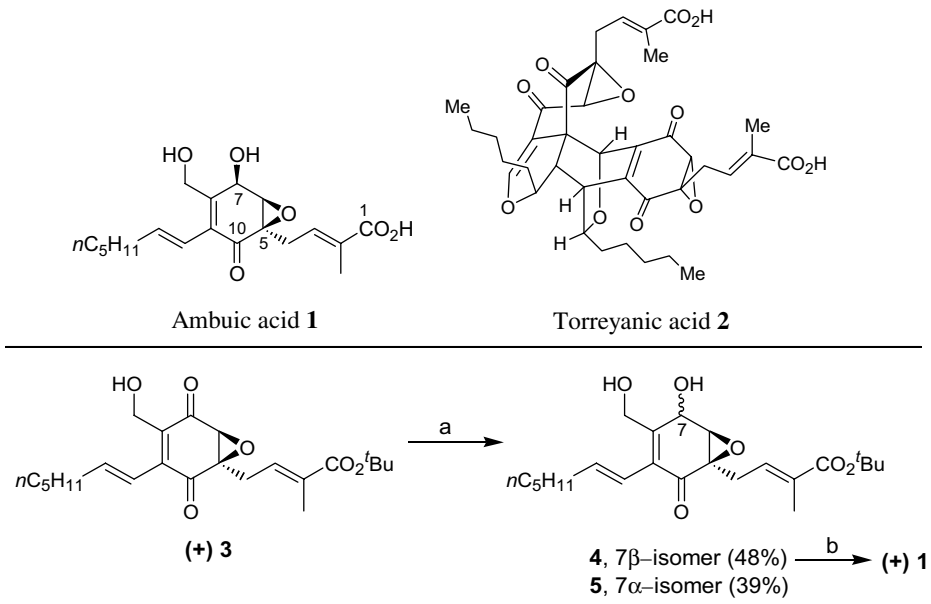
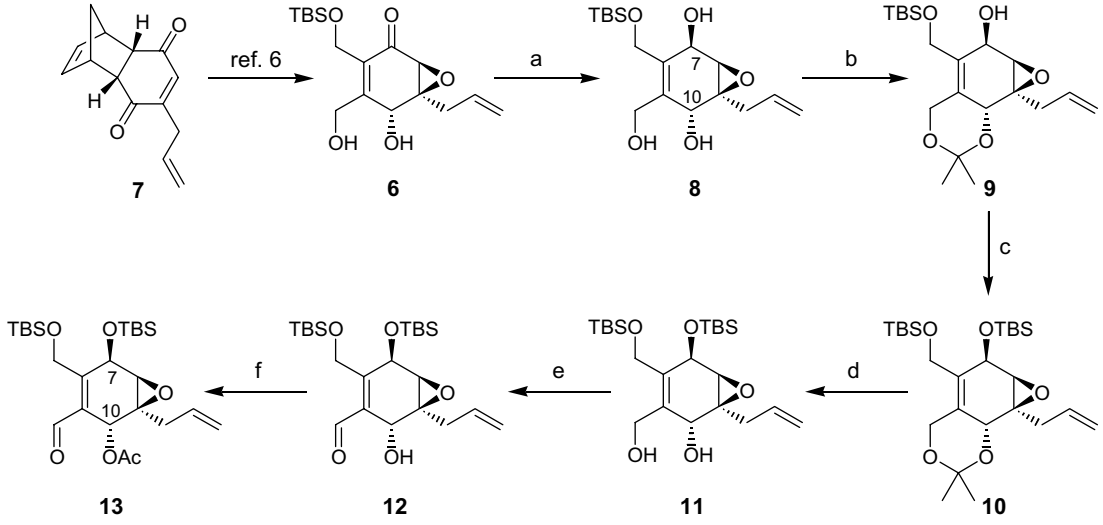



**Scheme 1.** Reagents and conditions: (a) $MeOBEt_2$, $NaBH_4$, −78 °C; (b) 48% HF, $CH_3CN$.

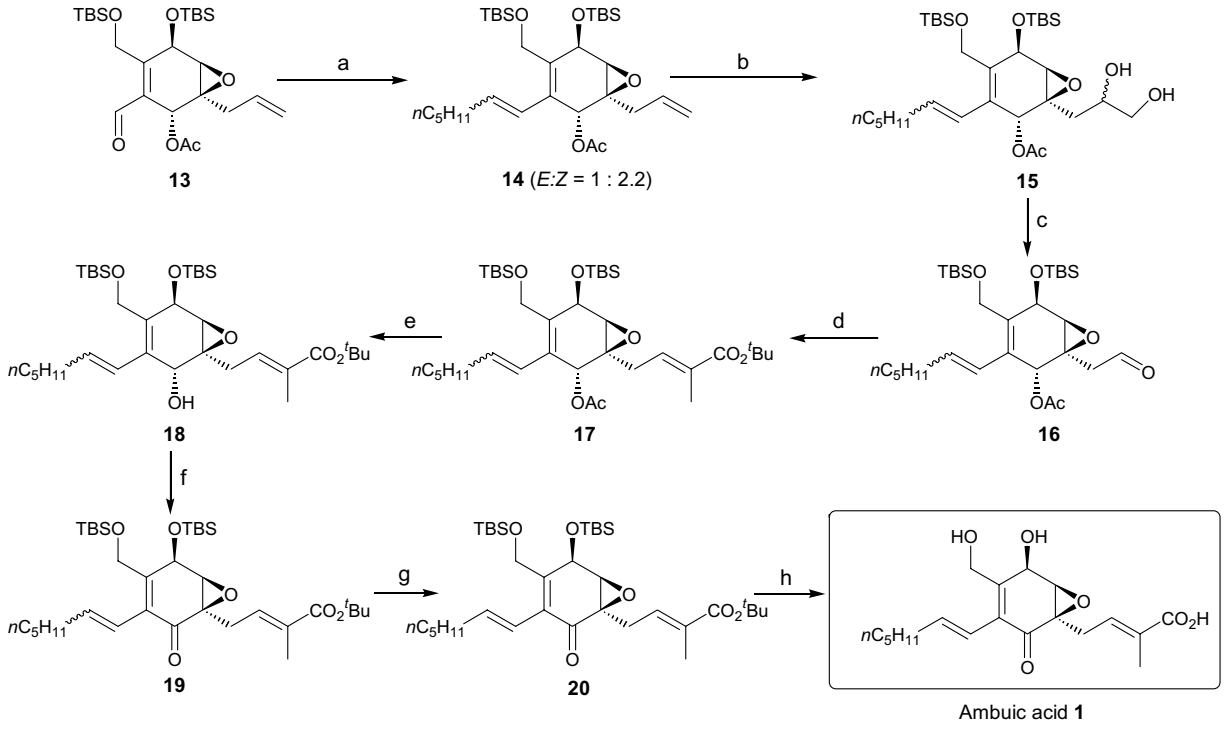



**Scheme 2.** Reagents and conditions: (a) $NaBH_4$, MeOH, −5 °C, 10 min, 75%; (b) PPTS (2 equiv), 2,2-dimethoxypropane, rt, 5 h, 92%; (c) TBSOTf, 2,6-lutidine, DCM, 0 °C, 15 min, 95%; (d) PPTS (0.4 equiv), MeOH, rt, 2 h, 78%; (e) TEMPO, $O_2$, CuCl, DMF, rt, 3 h, 90%; (f) $Ac_2O$, pyridine, DMAP, DCM, 0 °C, 2.5 h, 98%.

chromophoric group (vide infra). Thus, **14** as an *E*:*Z* mixture was carried forward for the elaboration of the key C5 side chain. Regioselective catalytic $OsO_4$ dihydroxylation of **14** gave diol **15** which was directly cleaved with $Pb(OAc)_4$ to furnish aldehyde **16**.[8] Wittig olefination of **16** with (1-*t*-butoxycarbonylethylidene)triphenylphosphorane duly installed the *E*-olefinic arm and gave **17**, Scheme 3.

At this stage, the C10 acetate functionality in **17** was carefully hydrolyzed to give **18** and the resulting hydroxyl group was further oxidized with tetra-*n*-propylammoniumperruthenate (TPAP) to deliver the dienone **19** which was still a mixture of *E*:*Z* isomers as carried forward from **14**. The dienone chromophore in **19** was now appropriately positioned to effect the photochemically mediated thermodynamic *E*:*Z* equilibration and the outcome of this reaction, as expected, was very rewarding. Irradiation of the *E*:*Z* mixture of **19** with a 450 W Hannovia Hg-lamp in the presence of a catalytic amount of iodine resulted in complete conversion to the desired *E*-isomer **20**.[8] The hydroxyl and carboxylic acid protecting groups in **20** were deprotected in a single operation in the presence of HF to deliver ambuic acid **1**. The spectral data ($^1H$ and $^{13}C$ NMR ) of our synthetic **1** were found to be identical with those of natural ambuic acid[2] and of the synthetic product reported by Porco.[4]

In summary, we have achieved a total synthesis of the complex polyketide derived natural product ambuic acid




**Scheme 3.** Reagents and conditions: (a) $n$-$C_6H_{13}PPh_3Br$, $^t$BuOk, ether, 0 °C, 75%; (b) $OsO_4$, NMMO, acetone–water, −25 °C, 3 h, 40% (90% br s m); (c) $Pb(OAc)_4$, THF, 0 °C, 1.5 h, 95%; (d) $Ph_3P{=}C(Me)CO_2{}^tBu$, DCM, −78 °C to −5 °C over 9 h, 65%; (e) LiOH, MeOH, 0 °C, 4 h, 65%; (f) TPAP, NMMO, mol sieves 4 Å, rt, 3 h, 85%; (g) *hv*, 450 W (Hannovia), $I_2$, $CDCl_3$, 10 h, 80%; (h) 40% HF, $CH_3CN$, rt, 3 h, 75%.

**1** from the readily available Diels–Alder adduct of 2-allyl-*p*-benzoquinone and cyclopentadiene through a short, simple sequence. The methodology described here in the context of ambuic acid is amenable to ready adaptation to access many analogues of the natural product.

## Acknowledgements

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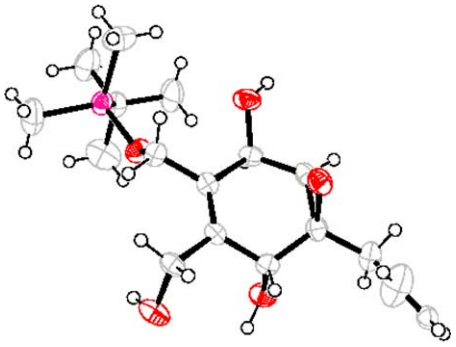
7. Numbering system assigned to the natural product as shown in structure **1** has been followed throughout the manuscript.
8. All new compounds were fully characterized on the basis of IR, $^1$H NMR, $^{13}$C NMR and mass data. Spectral data of selected compounds: **8**: $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 5.91–5.77 (m, 1H), 5.16–5.07 (m, 2H), 4.57 (s, 1H), 4.38–4.27 (m, 4H), 4.09 (d, 1H, $J$ = 12.6 Hz), 3.29–3.26 (m, 1H), 2.83 (dd, 1H, $J$ = 6.9, 14.4 Hz), 2.30 (dd, 1H, $J$ = 7.2, 14.7 Hz), 0.87 (s, 9H), 0.06 (s, 6H); $^{13}$C NMR (75 MHz, $CD_3OD$) $\delta$ 135.6, 134.4, 133.7, 119.0, 67.3, 66.3, 62.8, 61.3, 60.1, 59.2, 37.1, 26.4, 19.2, −5.2, −5.3; HRMS (ES) *m/z* calcd for $C_{17}H_{30}O_5SiK$ $[M+K]^+$: 381.1500. Found: 381.1524. Compound **11**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 5.96–5.83 (m, 1H), 5.25–5.15 (m, 2H), 4.76 (s, 1H), 4.57 (d, 1H, $J$ = 12.0 Hz), 4.47 (s, 1H), 4.39–4.27 (m, 2H), 3.95 (d, 1H, $J$ = 12.0 Hz), 3.24 (d, 1H, $J$ = 2.7 Hz), 3.07 (s, 1H), 2.90 (dd, 1H, $J$ = 7.5, 14.7 Hz), 2.71 (s, 1H), 2.34 (dd, 1H, $J$ = 6.9, 15.0 Hz), 0.93 (s, 9H), 0.90 (s, 9H), 0.17 (s, 6H), 0.11 (s, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 134.8, 134.6, 132.3, 118.8, 69.6, 67.4, 63.1, 61.4, 59.4, 59.1, 35.7, 25.9, 25.8, 18.2, 18.1, −4.0, −4.8, −5.2, −5.3; HRMS (ES) *m/z* calcd for $C_{23}H_{44}O_5Si_2Na$ $[M+Na]^+$: 479.2625. Found: 479.2641. Compound **13**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 10.30 (s, 1H), 6.09 (s, 1H), 5.83–5.69 (m, 1H), 5.17–5.11 (m, 2H), 4.97 (s, 1H), 4.86 (d, 1H, $J$ = 14.1 Hz), 4.54 (d, 1H, $J$ = 14.1 Hz), 3.27 (s, 1H), 2.58 (dd, 1H, $J$ = 6.0, 15.0 Hz), 2.35 (dd, 1H, $J$ = 8.1, 15.0 Hz), 2.00 (s, 3H), 0.95 (s, 9H), 0.87 (s, 9H), 0.21 (s, 6H), 0.07 (s, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 190.5, 169.3, 154.8, 131.0, 130.4, 119.0, 68.1, 65.3, 58.5, 58.4, 35.1, 25.6, 22.0, 20.8, 18.0,

−4.3, −5.0, −5.3, −5.4; HRMS (ES) *m/z* calcd for $C_{25}H_{44}O_6Si_2Na$ $[M+Na]^+$: 519.2574. Found: 519.2598. Compound **20**: $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 6.52 (t, 1H, $J$ = 7.5 Hz), 6.12 (d, 1H, $J$ = 16.2 Hz), 5.81–5.73 (m, 1H), 4.88 (s, 1H), 4.58 (d, 1H, $J$ = 11.7 Hz), 4.39 (d, 1H, $J$ = 11.7 Hz), 3.57 (d, 1H, $J$ = 3.0 Hz), 2.89 (dd, 1H, $J$ = 8.4, 16.5 Hz), 2.71 (dd, 1H, $J$ = 6.3, 16.2 Hz), 2.16 (q, 2H, $J$ = 6.3 Hz), 1.84 (s, 3H), 1.47 (s, 9H), 1.32–1.25 (m, 6H), 0.96 (s, 9H), 0.88 (s, 3H), 0.87 (s, 9H), 0.21 (s, 6H), 0.03 (s, 6H);$^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 194.4, 166.9, 148.9, 139.7, 133.0, 132.5, 131.0, 121.3, 80.3, 65.1, 59.9, 59.7, 59.6, 33.4, 31.4, 28.8, 28.1, 27.4, 25.9, 25.8, 22.5, 18.3, 18.3, 14.0, 12.8, −4.4, −4.7, −5.1, −5.2; HRMS (ES) *m/z* calcd for $C_{35}H_{62}O_6Si_2Na$ $[M+Na]^+$: 657.3983. Found: 657.3992. Compound **1**: $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 6.69 (t, 1H, $J$ = 6.8 Hz), 6.13 (d, 1H, $J$ = 16.0 Hz), 5.83 (m, 1H), 4.83 (s, 1H), 4.51 (d, 1H, $J$ = 12.8 Hz), 4.40 (d, 1H, $J$ = 12.8 Hz), 3.75 (d, 1H, $J$ = 2.8 Hz), 2.78 (dq, 2H, $J$ = 7.6, 15.6 Hz), 2.15 (q, 2H, $J$ = 6.8 Hz), 1.86 (s, 3H), 1.44 (m, 2H), 1.31 (m, 4H), 0.91 (t, 3H, $J$ = 6.8 Hz); $^{13}C$ NMR (100 MHz, $CD_3OD$) $\delta$ 196.0, 171.2, 150.7, 140.2, 136.5, 132.0, 122.7, 65.9, 61.2, 61.1, 60.4, 34.4, 32.5, 29.9, 28.7, 23.5, 14.3, 12.8; HRMS (ES) *m/z* calcd for $C_{19}H_{26}O_6Na$ $[M+Na]^+$: 373.1627. Found: 373.1638.

9. Crystal data: X-ray data were collected at 293 K on a SMART CCD–BRUKER diffractometer with graphite monochromated MoK$\alpha$ radiation ($\lambda$ = 0.7103 Å). The structures were solved by direct methods (SIR92). Refinement was by full-matrix least-squares procedures on $F^2$ using SHELXL-97. Compound **8**: $C_{17}H_{30}O_5Si$, MW = 342.5, crystal system: monoclinic, space group: *C*2/*c*, cell parameters: $a$ = 27.66 (2) Å, $b$ = 9.137 (5) Å, $c$ = 15.098 (9) Å, $\beta$ = 99.50 (1)°, $V$ = 3764.3 (7) Å$^3$, $Z$ = 8, $D_c$ = 1.209 g cm$^{-3}$, $F(000)$ = 1488.0, $\mu$ = 0.15 mm$^{-1}$. *R1* = 0.0684 for 2666 $F_o > 4\sigma(F_o)$ and 0.0835 for all 3305 data. GOF = 1.247. Restrained GOF = 1.113 for all data, CCDC 254042. An ORTEP diagram of compound **8** with 50% ellipsoidal probability level is shown below.



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