The First Synthesis of (−)-Asperpentyn and Efficient Syntheses of
(+)-Harveynone, (+)-Epiepoformin and (−)-Theobroxide

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Abstract: A generally applicable strategy for the synthesis of a range of polyoxygenated cyclohexane natural products has been developed. The enantioselective syntheses of (−)-theobroxide, a polyoxygenated cyclohexane natural compound with potent growth inducing properties in potato microtubers has been achieved via a 1,2 O-silyl migration between trans-hydroxyl groups and a remote hydroxyl directed epoxidation of an enone derived from quinic acid. A thus derived α-iodoenone was subjected to Stille coupling with tetramethylstannane to afford the first title compound. A similar strategy enabled a route to the complete asymmetric synthesis of the acetylenic phytotoxin (+)-harveynone. By selective reduction of (−)-theobroxide, (−)-epiepoformin was also prepared in enantiopure form and similarly, stereoselective reduction of (−)-harveynone completed the first enantioselective synthesis of (−)-asperpentyn, another natural compound with antimicrobial activity.

Keywords: asymmetric synthesis · C–C coupling · natural products · palladium

Introduction

(+)-Harveynone (1), (−)-asperpentyn (2), (+)-epiepoformin (3) and (−)-theobroxide (4) belong to a family of highly oxygenated cyclohexane-based metabolites, mainly epoxides, that have been isolated from bacteria, fungi, higher plants and molluscs. These compounds have stimulated several synthetic efforts[2,5,7,19] due to their biological activities, which range from antifungal to antibacterial, antitumor, phytotoxic and enzyme inhibition.[1,19]

(+)-Harveynone (1) has been isolated from the tea-leaf bight fungus Pestalotia theae and shown to be a phytotoxin.[5] Related compound (−)-asperpentyn (2) has been isolated from the antimicrobial extracts of Aspergillus duricaulis.[5] These natural compounds both contain an acetylenic side chain, which is a characteristic feature of many members of the polyoxygenated cyclohexane family. (+)-Epiepoformin (3) has been isolated from the culture filtrate of an unidentified fungus of the deceased leaf of grape myrtle Lagerstroemia indica,[6] and (−)-theobroxide (4) has been isolated from Lasiodiplodia theobromae and shows exceptional activity as a potato microtuber inducing substance.[4] The rarity and diverse biological activities of these compounds has prompted us to devise a strategy which should be generally applicable to their synthesis, and the synthesis of derivatives, in an enantiopure form and eventually their preparation in useful quantities for biological testing.

(+)-Harveynone has been asymmetrically synthesised by Johnson and co-workers[24] and, in a racemic form, by Taylor and co-workers.[26] There is also only one synthesis of theobroxide described in the literature so far,[5] and two syntheses[5,7] of epiepoformin, one of them racemic,[7] the other relied upon a retro-Diels-Alder reaction for the liberation of the unsaturated product.[5] To our knowledge, (−)-asperpentyn has not been previously synthesised and our synthesis confirms the structure proposed after its isolation.[5]

(−)-Quinic acid (5), an abundant natural substance has, besides a cyclohexane skeleton, a masked 1,4-oxygen functionality suitable for synthesis of the necessary hydroxyl and
carbonyl groups in these positions of the target compounds. This characteristic 1,4-substitution is present in all compounds, for which the synthesis is described herein, and in many other members of the polyoxygenated cyclohexane metabolite family. (−)-Quinic acid also contains hydroxyl functions which are ideally situated for the sequential generation of the necessary enones. Its structure can be transformed selectively in diverse ways and has permitted its use in many other syntheses.16, 9, 11-13 Other advantages are the accessibility and relatively low cost of (−)-quinic acid.

**Results and Discussion**

Our strategy was based on two sequential β-eliminations which allowed the formation of two enone systems, one necessary for the introduction of the epoxide group and the other to remain in the final structure of our target compounds. In Scheme 1 the initial common steps for these syntheses are depicted.

β-Hydroxyketone 6 was obtained in three steps from (−)-quinic acid (5) in excellent yields, as previously described in the literature.16 Silylation of 6 afforded the protected compound 7 in 98% yield, which upon treatment with 0.5NaOH16 furnished a mixture of two compounds later identified as the anticipated product enone 8 and the isomeric enone 9, in approximately 1:1 ratio. The NMR spectra of 8 and 9 were very similar as would be expected. They were identified by treating each separately with acetic anhydride whereupon the less polar isomer becomes aromatic to form compound 15; this indicates that indeed β-hydroxyketone 9 was formed. The acetate 13 was obtained from the other isomer 8 after epoxidation and elimination. The enone 9 clearly resulted from an unusual silyl migration between the trans diequatorial hydroxyl groups which was promoted by the alkoxy formed during elimination. Attempts to transform all of compound 8 into 9 in one reaction with a base failed,19 which indicated that an equilibrium was established between the two products. The separation of these isomers permitted a recycling of isomer 8 with a base, and an increase in the overall yield. Thus, treatment of isomer 8 with a catalytic quantity of hydroxide in THF afforded again a 1:1 mixture of these isomers in quantitative yield. After one recycle about 75% of the required 9 could be obtained. The formation of enone 9 in this way was not predictable but nevertheless turned out to be a key compound.

Epoxidation of the mixture of enones 8 and 9 with 30% hydrogen peroxide in the presence of Triton B afforded an inseparable mixture of only the two epoxides 10 and 11 (Scheme 1). In accordance with our previous observations10 the attack of the epoxidising agent upon the double bond was directed by the free hydroxyl group in the molecule. Thus, the hydroxyl group of enone 8, being below the plane of the molecule, as drawn in Scheme 1, directed the peroxide to the lower face of the enone system with subsequent formation of the epoxide 10. A similar directing effect was observed for the epoxidation of 9 which gave the epoxide 11, where both the hydroxyl and the epoxide groups were cis and above the plane of the molecule as drawn. The importance of the free hydroxyl group in these oxidations was demonstrated by the epoxidation of the acetate 14, obtained by treatment of 8 with acetic anhydride and DMAP in pyridine at 0°C. This epoxidation, employing the bulky βBuOOH, afforded a 1:1 mixture of the two diastereoisomers 13 and 16 (Scheme 2). Thus the absence of the free hydroxyl group drastically reduced the selectivity of the epoxidation reaction.

**Abstract in Portuguese:** Uma estratégia geral para a síntese de produtos naturais com estrutura de ciclohexano polioxigenado foi desenvolvida. A síntese do (−)-teobroxido, um composto natural com potentes propriedades na indução do crescimento dos microtubículos de batatas, foi efetuada via uma migração 1,2 O-sílio entre grupos hidroxilos trans e uma epoxidação, orientada remotamente por um hidroxilo, de uma enona derivada do ácido químico. A α-idoenona obtida foi submetida a um acoplamento de Stille com tetrametilenosilano, para originar o produto referido. Uma estratégia similar permitiu a síntese asimétrica completa da fitoxina acetilênica (−)-harveinona. Através da redução selectiva do (−)-teobroxido, a (−)-epiepiformina foi igualmente preparada na forma enantiotípura e, da mesma maneira, a redução estereoselectiva da (−)-harveinona completou a primeira síntese enantioselectiva da (−)-asperentina, outro composto natural com atividade antimicrobiana.
Elimination of water in compound 11 was carried out by acetylation of a 1:1 mixture of 10 and 11 which led to enone 12 and the acetylated product 13 (Scheme 1). These two products were easily separable by simple chromatography which afforded 12 (44%) \([\alpha]_D^{20} = +331.5 \ (c = 1.22, \text{anhydrous CHCl}_3)\)[20b] *ent*-12: \([\alpha]_D^{20} = -333.3 \ (c = 1.32, \text{anhydrous CHCl}_3)\], and 13 (42%).

\[\alpha\text{-iodination of enone 12 afforded iodoenone 17} (\text{Scheme 3}) \text{ in excellent yields (93%),} \ [\alpha]_D^{20} = +108.6 \ (c = 1.19, \text{anhydrous CHCl}_3)\][20b] *ent*-17: \([\alpha]_D^{20} = -109.7 \ (c = 1.29, \text{anhydrous CHCl}_3)\].

CHCl₃). With the Stille cross-coupling reaction the acetylenic side chain could be introduced in 98% yield. Johnson[22] used a Sonogashira coupling reaction instead of the Stille methodology to perform the same reaction but only in 52% yield. Desilylation of the coupled product 18 with 40% wt HF in H₂O afforded (+)-harveynone (1) in 92% yield (42% overall from 6).[23] \([\alpha]_D^{20} = 206.6 \ (c = 0.38, \text{MeOH})\)[24] *ent*-1: \([\alpha]_D^{20} = -208 \ (c = 0.45, \text{MeOH})\]. The spectroscopic data for our synthetic product is in accordance with those reported in the literature.[26]

In order to synthesise (−)-aspertepent (2) we required a selective method for the reduction of the carbonyl group of enone 18 (Scheme 4). DIBAL-H in THF at −78 °C afforded both possible diastereoisomers with an unsatisfying dr of only 1:1. By performing the same reaction with sodium borohydride and cerium(IV) chloride we were able to increase the diastereoselectivity to 2:7:1 19:20. Deprotection of both alcohols afforded (−)-aspertepent (2) \([\alpha]_D^{20} = -171 \ (c = 0.28, \text{acetone})\).[21]
and 15% yields, respectively. (+)-Iodoxone (26), [α]D20 = +94.8° (c = 0.61, anhydrous acetone).12 [α]D20 = +96.1° (c = 0.95, acetone), an analogue of the natural compound (+)-bromoxone10 was also obtained after cleavage of the silyl ether of α-iodoxone 17 (47% overall yield from 6) (Scheme 5).

**Conclusion**

In summary, an efficient methodology was developed to synthesize four related natural compounds with high enantio-purity. The use of common intermediates readily derived from quinic acid combined with a Stille coupling reaction should permit the synthesis of a wide range of cyclohexene based natural products. This methodology should also be applicable to the synthesis of more complex members of the polyoxygentated cyclohexane family. From compound 13, the anti-biotic LL-C10037α and several members of the manumycin family of antibiotics12 may also be accessible using a little usedaza Stille cross-coupling reaction to introduce the amide side chain. Our studies in this promising area are currently under way.

**Experimental Section**

**General methods** Melting points were determined with a capillary apparatus and are uncorrected. 1H NMR spectra were obtained at 300 MHz in CDCl3 with chemical shift values (δ) in ppm downfield from tetramethylsilane, and 13C NMR spectra were obtained at 100.61 MHz in CDCl3. DEPT was used to aid the structure elucidation and carbon assignments but the data are not reported here. Microanalyses were performed by the I.S. analytical services using a combustion apparatus. IR (ν, cm–1) measured on a FTIR spectrophotometer. Medium pressure preparative column chromatography: silica gel Merck 60H. Preparative TLC: silica gel Merck 60 GF254. Analytical TLC: Aluminum-backed silica gel Merck 60 F254. Specific rotations ([α]) were measured on an automatic polarimeter. Reagents and solvents were purified and dried according to ref.23. All the reactions were carried out in an inert atmosphere (argon), unless otherwise indicated.

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(2R,3S,4S)-1-(tert-Butylmethylsilyloxy)-2,3-epoxy-6-(3-methylbutyl-3-en-1-ynyl)-5-cyclohexen-1-one (17): 1 (0.390 g, 1.56 mmol) in pyridine/CCL₃ (1 mL:1 mL) and a catalytic amount of DMAP were added at 0°C to a solution of enone 12 (0.150 g, 0.62 mmol in pyridine/CCL₃ (1 mL:1 mL). The reaction mixture was stirred at RT for 1 h, and then 20% aqueous Na₂SO₄ solution (4 mL) was added. The mixture was extracted with diethyl ether (3 × 10 mL) and the organic extracts were washed with water (2 × 5 mL), dried over Na₂SO₄ and concentrated to afford a liquid residue which was purified by preparative TLC. Elution with AcOEt/hexane 1:9 furnished 17 (0.213 g, 93%) as a colourless liquid. [α]D° = +108.6 (c = 1.19, anhydrous CHCl₃) [lit-17]: [α]D° = +109.7 (c = 1.29, CHCl₃). [1H NMR (300 MHz, CDCl₃, 300 K, TMS): δ = 7.29 (dd, 2H, JHH = 5.1 Hz, JHH = 2.4 Hz, 1H, H-5), 4.60 (dddd, 2H, JHH = 4.8 Hz, JHH = 1.2 Hz, JHH = 1.2 Hz, 1H, H-3), 3.67 (m, 1H, H-4), 3.43 (m, 1H, H-2 or H-3), 2.93 (s, 3H, CH₃), 0.19, (0.19, 2 × 3H, 2 × SiCH₃)); FT-IR (film): ν = 1697 (C=O, α,β-unsaturated ketone); HR-MS (EI+): calc. for C₂₁H₂₂O₂Si [M + C₂H₅O] –: 328.140846; found: 328.140857.

(2R,3S,4S)-1-(tert-Butylmethylsilyloxy)-2,3-epoxy-6-(3-methylbutyl-3-en-1-ynyl)-5-cyclohexen-1-one (18): Pd(PPh₃)₄Cl₂ (0.0092 g, 5 mol %), (3-methylbutyl-3-en-1-ynyl)tributyltin (0.120 g, 0.34 mmol) and Cu (0.0049 g, 10 mol %) were added to a solution of 17 (0.096 g, 0.26 mmol) in THF (2 mL). After stirring the reaction mixture was added at RT for 3 h, 10% aqueous Na₂SO₄ solution (5 mL) was added to the suspension. The reaction mixture was washed with 10% aqueous KF solution (4 mL) and extracted with diethyl ether (3 × 8 mL). The combined organic layers were dried (MgSO₄) and the solvent evaporated to give a dark residue. Purification by preparative TLC (AcOEt/hexane 1:9) afforded 18 (0.080 g, 98%) as a colourless oil. [α]D° = +13.5 (c = 0.15, CHCl₃); [1H NMR (300 MHz, CDCl₃, 300 K, TMS): δ = 6.65 (dd, 2H, JHH = 5.1 Hz, JHH = 2.7 Hz, 1H, H-5), 5.44 (s, 1H, C=CH₃), 3.55 (t, 1H, JHH = 1.5 Hz, C=CH₃), 4.77 (d, JHH = 4.5 Hz, 1H, H-4), 3.82–3.79 (m, 1H, H-3), 3.58 (dd, JHH = 3.6 Hz, JHH = 0.9 Hz, 1H, H-2), 1.94 (s, 3H, CH₃), 0.92 (s, 3H, Si(CH₃)₂), 0.19, 0.16 (2 × 3H, 2 × SiCH₃)); FT-IR (film): ν = 1697 (C=O, α,β-unsaturated ketone); HR-MS (EI+): calc. for C₂₃H₂₄O₂Si [M + C₂H₅O] –: 354.149473; found: 354.149487.

(2R,3S,4S)-2,3-Epoxy-4-hydroxy-6-(3-methylbut-3-1-en-1-ynyl)-5-cyclohexen-1-one (1): (+)-Harveyone: 40% wt HF in water (0.0072 mL/0.19 mmol) was added at RT to a solution of 18 (0.045 g, 0.15 mmol) in acetonitrile (1 mL). The reaction mixture was stirred until all starting material had been consumed. Saturated aqueous NaHCO₃ solution (2 mL) was added and the mixture was extracted with CHCl₃ (3 × 6 mL). The combined organic phases were dried (MgSO₄) and concentrated to yield a residue which was purified by preparative TLC (AcOEt/hexane 3:7). (+)-Harveyone (0.026 g, 92%) was obtained as a colourless oil. [α]D° = +206.6 (c = 0.38, anhydrous MeOH) [lit-1]: [α]D° = –208 (c = 0.45, MeOH); [1H NMR (300 MHz, CDCl₃, 300 K, TMS): δ = 6.85 (dd, 2H, JHH = 5.1 Hz, JHH = 2.7 Hz, 1H, H-5), 5.44 (s, 1H, C=CH₃), 3.55 (t, 1H, JHH = 1.5 Hz, 1H, C=CH₃), 4.77 (d, JHH = 4.5 Hz, 1H, H-4), 3.82–3.79 (m, 1H, H-3), 3.58 (dd, JHH = 3.6 Hz, JHH = 0.9 Hz, 1H, H-2), 1.94 (s, 3H, CH₃), 0.92 (s, 3H, Si(CH₃)₂), 0.17, 0.15 (2 × 3H, 2 × SiCH₃)); FT-IR (film): ν = 1683 (C=O, α,β-unsaturated ketone); HR-MS (EI+): calc. for C₂₃H₂₄O₂Si [M + C₂H₅O] –: 354.149473; found: 354.149487.

(2R,3S,4S)-1-(tert-Butylmethylsilyloxy)-2,3-epoxy-6-(3-methylbutyl-3-en-1-ynyl)-5-cyclohexen-1-one (22): AsPh₃ (0.0109 g, 10 mol %), Pd(dba)₂·CHCl₃ (0.0095 g, 5 mol % of Pd) and Cu (0.0068 g, 10 mol%) were added to a solution of 17 (0.136 g, 0.37 mmol) in THF (2 mL). The mixture was stirred for 10 min and then MeSn (0.194 g, 1.11 mmol in THF) (0.5 mL) was added. After stirring at 80°C for 30 h, the suspension was cooled and 10% aqueous Na₂SO₃ solution (5 mL) was added. The reaction mixture was washed with 10% aqueous KF solution (4 mL) and extracted with diethyl ether (3 × 8 mL). The combined organic layers were dried (MgSO₄) and the solvent evaporated to give an orange residue. Purification by preparative TLC (AcOEt/hexane 1:9) afforded 22 (0.086 g, 91%) as a colourless oil. [α]D° = +251.3 (c = 1.40, anhydrous CHCl₃) [lit-1]: [α]D° = +250.72 (c = 1.17, CHCl₃); [1H NMR (300 MHz, CDCl₃, 300 K, TMS): δ = 6.30–6.27 (1H, H-5), 4.64 (dd, JHH = 5.7 Hz, 1H, H-5), 1.22 (H, H-2, H-3), 3.65–3.62 (2m, 1H, H-3), 3.48 (dd, JHH = 3.6 Hz, JHH = 0.9 Hz, 1H, H-2), 1.84 (3H, CH₃), 0.92 (s, 3H, Si(CH₃)₂), 0.17, 0.15 (2 × 3H, 2 × SiCH₃)); FT-IR (film): ν = 1683 (C=O, α,β-unsaturated ketone); HR-MS (EI+): calc. for C₂₁H₂₂O₂Si [M + C₂H₅O] –: 329.110491; found: 329.110491.
5 mol% of Pd) were added to a solution of 17 (0.150 g, 0.041 mmol) in THF (2.5 mL). The mixture was stirred for 10 min and then diethylamine (0.129 mL, 1.24 mmol) and Me3Sn (0.214 g, 1.24 mmol) in THF (0.7 mL) were added. After stirring at 80 °C for 24 h, the suspension was cooled and 10% aqueous Na2SO4 solution (5 mL) was added. The mixture was washed with 10% aqueous KF solution (5 mL) and extracted with diethyl ether (3 x 10 mL). The combined organic layers were dried (MgSO4) and the solvent evaporated to give an orange residue. Purification by preparative TLC (AcOEt:hexane = 1:9) afforded 22 (0.105 g, quantitative) as a colourless oil. The spectral data are described in the previous experiment.

(2R,3S,4S)-2,3-Epoxy-4-hydroxy-6-methyl-5-cyclohexen-1-one (3): 3-epi-epofopein in 40% wt HF in water (0.0085 mL, 0.22 mmol) was added at RT to a solution of 22 (0.045 g, 0.18 mmol) in acetonitrile (1 mL). The reaction mixture was stirred until all starting material had been consumed. Saturated aqueous NaHCO3 solution (2 mL) was added and the mixture was extracted with CH2Cl2 (3 x 6 mL). All the combined organic phases were dried (MgSO4) and concentrated to yield a residue which was purified by preparative TLC (AcOEt:hexane = 3:7). 3-epi-Epofopein (0.025 g, 99%) was obtained as a colourless oil. 1H NMR (300 MHz, CDCl3, 300 K, TMS): δ = 6.86–6.44 (m, 1 H, H-5), 4.67 (d, 3J(H,H) = 6.0 Hz, 1 H, H-4), 3.80–3.77 (m, 1 H, H-3), 3.52 (dd, 3J(H,H) = 3.6 Hz, 3J(H,H) = 12 Hz, 1 H, H-2), 1.36 (s, 3H, CH3); FT-IR (film): ν = 1763 cm⁻¹, 1730 cm⁻¹, 1725 cm⁻¹ (C=O, ester, ketone). 19F NMR (CDCl3): δ = +9.61 (e = 0.95, acetoxy); 1H NMR (300 MHz, CDCl3, 300 K, TMS): δ = 7.46 (dl, 3J(H,H) = 5.1 Hz, 3J(H,H) = 2.7 Hz, 1 H, H-5), 4.64 (dl, 3J(H,H) = 3.0 Hz, 1 H, H-4), 3.85–3.83 (m, 1 H, H-2 or H-3), 3.67–3.65 (m, 1 H, H-2 or H-3); FT-IR (KBr): ν = 3360 (O–H), 1678 (C=O, ester, ketone). 1594 (C=O); HR-MS (EI+): calcd for C18H14O4 [M]+: 251.0918; found: 251.09203.

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21. The overall yields were determined assuming one recycle of the silyld ether 8 to the required isomer 9 but were not adjusted for recovered 8.

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