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ScienceDirect
Tetrahedron 62 (2006) 9892–9901
Tetrahedron

Total synthesis of the epoxyquinol dimer (+)-panepophenanthrin: application of a diastereospecific biomimetic Diels–Alder dimerisation

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Received 23 June 2006; accepted 3 August 2006
Available online 1 September 2006

Abstract—An asymmetric total synthesis of the novel and structurally complex epoxyquinol natural product (+)-panepophenanthrin has been accomplished, in which a biomimetic Diels–Alder dimerisation is a key step. The key monomeric precursor was assembled by an efficient Stille cross coupling of two readily available building blocks that upon standing underwent a diastereospecific dimerisation cascade in excellent yield.

1. Introduction

In 2002 Sekizawa et al. reported the isolation of (+)-panepophenanthrin (**1**), from the culture broth of the mushroom strain *Panus rudis* IF08994.[1] Until the recent isolation of Himeic acid A, by Tsukamoto et al. in 2005 from *Aspergillus* sp.,[2] (+)-(**1**) was the only known natural product inhibitor of the ubiquitin activating enzyme E1.[3] The fascinating molecular architecture assigned to (+)-**1** was fully elucidated by complementary spectroscopic and X-ray crystallographic techniques, revealing a complex, densely functionalised core consisting of a highly oxygenated tricyclic ABC ring system, containing 11 contiguous stereocentres and a *trans*-fused lactol functionality (Fig. 1). Although (+)-**1** displayed no significant inhibitory effect in whole cells, the in vitro activity alone make **1** a promising tool for investigating ubiquitin functions linked to serious disease and serve as a platform for future drug development.[4]

Structurally, (+)-**1** belongs to a family of related epoxyquinoid natural products, which have been isolated from terrestrial and marine systems as phylogenetically diverse as fungi, bacteria and worms. The degree of structural complexity displayed by this family ranges from the lower order epoxyquinols, including (+)-epiepoformin (**2**), (+)-isoepoxydon (**3**)[5] and (+)-bromoxone (**4**) and its acetylated derivative (+)-**5**.[6] Increasing in structural complexity belong the natural products (−)-jesterone (**6**), a biologically active antifungal isolated from *Panus jesteri*,[7] and (−)-manumycin A (**7**), isolated from *Streptomyces* sp.,[8] and identified as a novel Ras farnesyltransferase inhibitor.[9] Structurally higher order members of the epoxyquinoid family include (+)-torreyanic acid (**8**), a metabolite isolated from the endophytic fungus *Pestalotiopsis microspora*,[10] and epoxyquinols (+)-A (**9**) and (+)-B (**10**), metabolites isolated from an uncharacterised fungus (Fig. 1).[11] Biosynthetically, compounds **8**, **9** and **10** are believed to arise from Diels–Alder *pseudo*-dimerisation pathways of monomeric epoxyquinol units. Experimental evidence to support the proposed biosynthetic dimerisations has been provided through several elegant synthetic studies.[12,13] Related prenylated epoxyquinols are also known, including enantiomers (+)-harveynone (**11**) and (−)-harveynone (**12**), isolated from *Pestalotiopsis thea*[14] and *Curvularia harveyi*,[15] respectively.

In a previous report,[16] we described a highly efficient synthesis of racemic (±)-panepophenanthrin (**1**), demonstrating the feasibility of a key biomimetic Diels–Alder dimerisation cascade. Herein, we report a full account of our studies on the total synthesis of (+)-**1** and provide a discussion supported by molecular modelling to explain the mechanisms controlling the biomimetic reaction.

Keywords: Total synthesis; Biomimetic synthesis; Stille coupling; Dimerisation cascade; Epoxyquinol; Ubiquitin activating enzyme E1.
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doi:10.1016/j.tet.2006.08.010

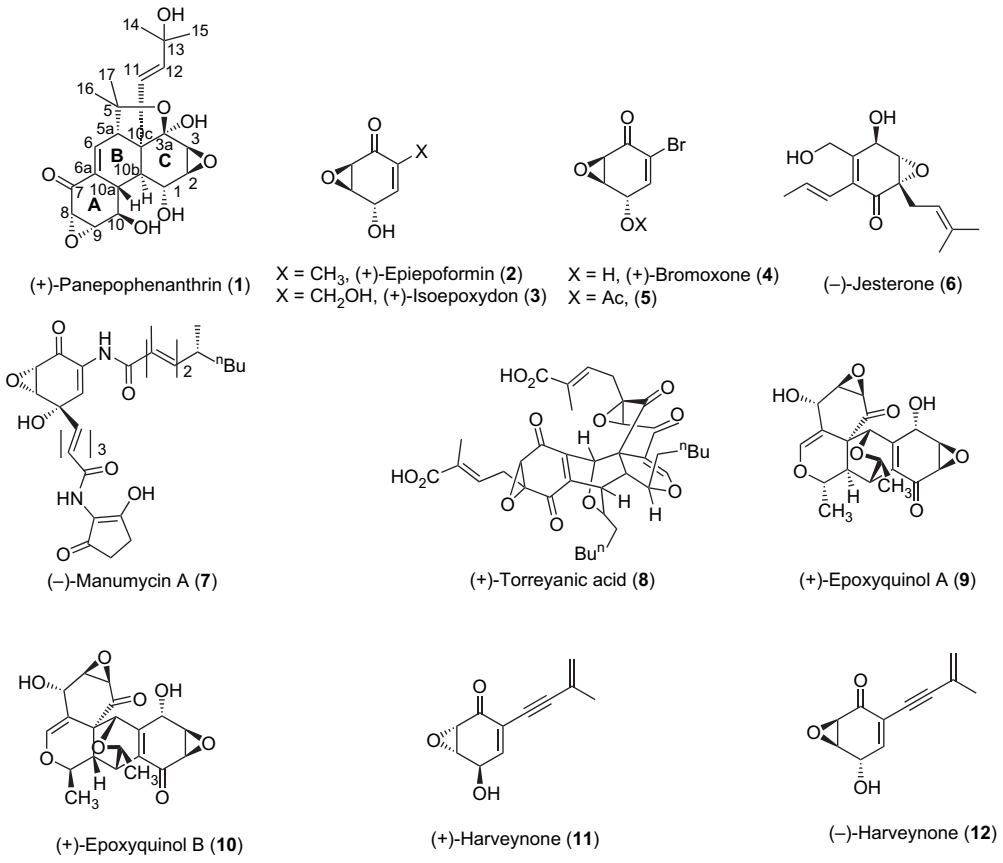


Figure 1. Members of the epoxyquinoid family of natural products.

1.1. Synthetic plan

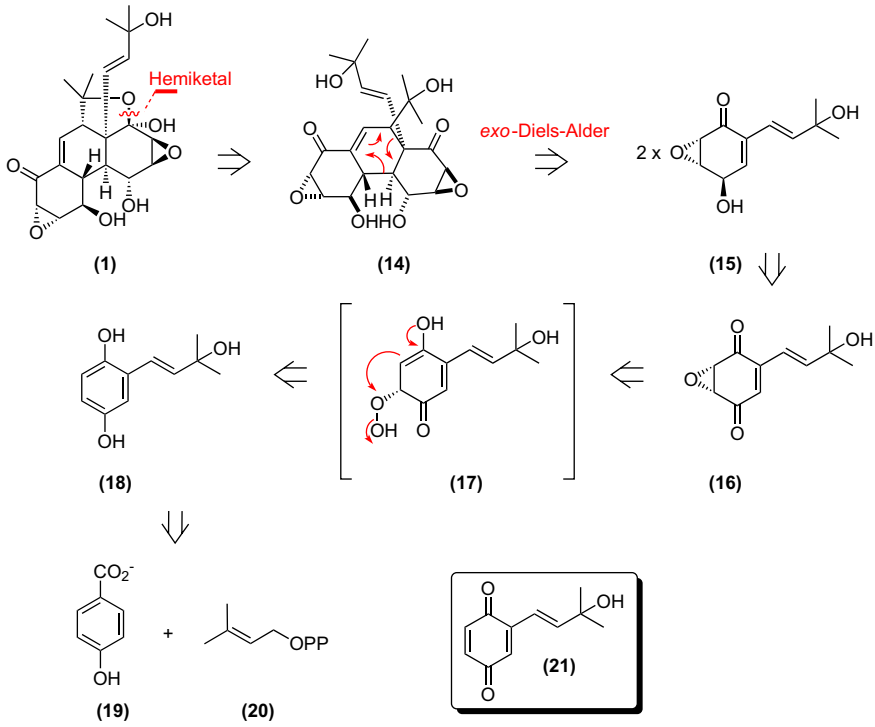
As part of our ongoing studies towards the biomimetic synthesis of complex natural products, we became interested in (+)-**1** for its unique molecular architecture and biological profile. Our biomimetic-retrosynthesis towards the target compound is depicted in Scheme 1. Dimer (+)-**1** was thought as arising through an unusual *exo*-[4+2] Diels–Alder cycloaddition of two monomeric counterparts **15** (the carbonyl group of the dienophile is used to define *exo*/*endo*).

A key assumption in this biomimetic approach was that the molecular framework of **1** arises in nature, through an intrinsically favourable chemical pathway.[17] Thus, if monomer **15** could be realised, then a 'pre-disposed' dimerisation might proceed unaided to yield the target dimer. Thus, (+)-**1** may be thought of having occurred through hemiketal formation of the corresponding hydroxy ketone dimer **14**. It is known that epoxyquinoid derivatives form both hydrates and hemiketals by reaction of water and alcohols with the electrophilic carbonyl group.[18] The open-form precursor of **14** may be derived from an *exo*-Diels–Alder dimerisation of the epoxyquinol monomer **15**.[19] Alternatively, hemiketal formation followed by Diels–Alder cycloaddition was considered as another possibility.[16] The *endo*-Diels–Alder is thought to be disfavoured due to steric factors.

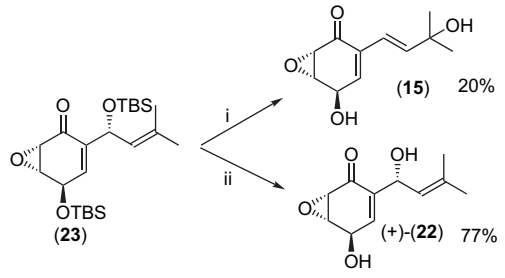
The complexity of the primary synthetic target, although reduced to that of the lower order epoxyquinol monomer **15**, itself posed a relatively complex challenge. Compound **15** belongs to the prenylated epoxyquinol family of natural products, which include the afore mentioned compounds **11** and **12** (Fig. 1). Biosynthetically, monomer **15** can be thought of as arising through a biochemical reduction of epoxyquinone **16**, itself derived from a facially selective enzyme catalysed epoxidation of prenylated hydroxyquinone **18**, through intermediate **17**.[20] Compound **18**, itself having been isolated along with its oxidised counterpart **21** from the fungus *Acremoniu*,[21] may arise from the coupling of 4-hydroxybenzoate (**19**) and DMAPP (dimethylallyl pyrophosphate) (**20**).

Monomer **15** had been reported by Wood and co-workers, as an undesirable side product isolated during their synthetic studies towards (+)-panepoxydone (**22**). Compound **15** was formed through an acid catalysed rearrangement, during the attempted desilylation of TBS-protected panepoxydone (**23**) (Scheme 2).[22] However, no comment regarding the stability of **15** or any noted dimerisation/decomposition pathways was reported. Interestingly, both (+)-**1**[1] and (+)-**22**[23] have been isolated from the common producing fungal species *P. rudis* indicating a probable common biosynthetic pathway.

Synthetic approaches towards such prenylated epoxyquinoids often involve late stage *pseudo*-prenylation of a fully elaborated epoxyquinoid nucleus. For example, Taylor et al. have reported an efficient synthesis of racemic harveynone, employing a palladium/copper catalysed coupling of an alkynylstannane and fully elaborated epoxyiodoenone.[24] Attracted by this logical strategy, and based upon analogous studies,[25–27] we chose to adopt a Stille cross coupling

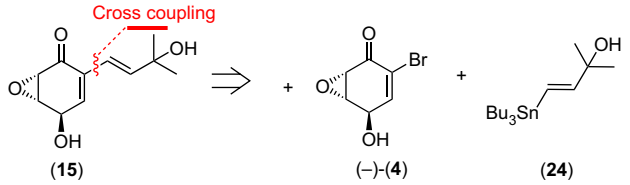


Scheme 1. Proposed biosynthesis of (+)-panepophenanthrin (**1**).



Scheme 2. (i) H_2SiF_6; (ii) TREAT/HF.

approach towards **15**. Thus, further retrosynthetic planning led us to the known building blocks (−)-bromoxone **4**[28] and vinylstannane **24**,[29] as suitable coupling partners (Scheme 3).



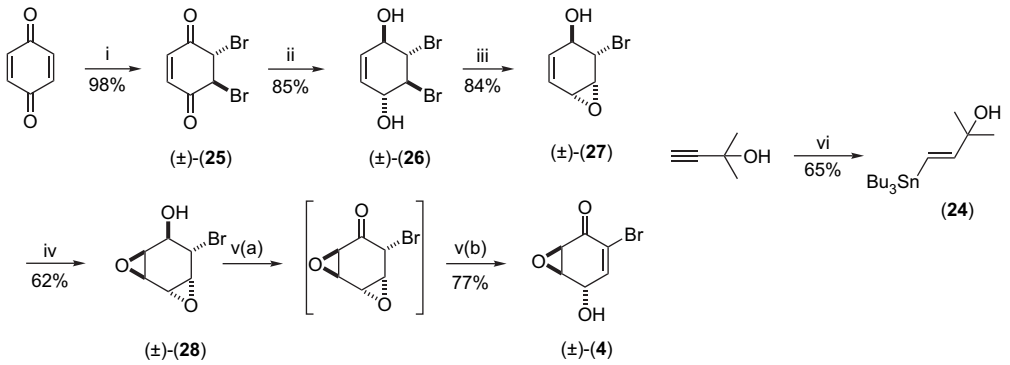
Scheme 3. Retrosynthetic analysis of epoxyquinol monomer **15**.

2. Results and discussion

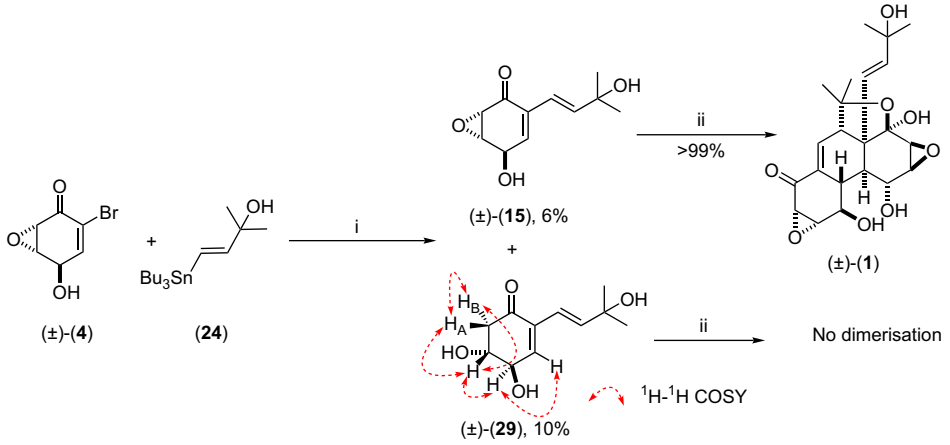
2.1. Feasibility study for *exo*-Diels–Alder dimerisation

Racemic bromoxone (±)-(**4**) was chosen in order to investigate optimum coupling conditions and to evaluate the validity of the proposed dimerisation. A previously reported synthesis of **4** by Altenbach et al. was conveniently chosen, since this was amenable to large scale production.[30] The synthesis began with the bromination of *p*-benzoquinone to (±)-bromoquinone (**25**) in near quantitative yield, followed by reduction with $NaBH_4$ to (±)-diol (**26**) as the only isolated diastereoisomer. Internal substitution (S_Ni) of a single bromo group gave (±)-epoxide (**27**), followed by directed epoxidation with *m*-CPBA to give (±)-bis-epoxide (**28**). The synthesis was completed upon oxidation with DMP and subsequent basic workup to give (±)-bromoxone (**4**) in good overall yield (Scheme 4). Synthesis of the corresponding vinylstannane fragment **24** was achieved following the protocol of Guibé et al. with efficient hydrostannation of commercially available 2-methylbut-3-yn-1-ol with $^nBu_3SnH$ and a catalytic quantity of $PdCl_2(PPh_3)_2$ in THF.[29] This afforded the desired (*E*)-vinylstannane (**24**) in good yield and as the only observed diastereoisomer (Scheme 4).

Our initial attempt at the Stille cross coupling of (±)-**4** and vinylstannane **24** was performed using 7 mol % of Pd_2dba_3 and 22 mol % of $AsPh_3$ in toluene at 110 °C. The reaction was monitored by TLC analysis, which indicated rapid consumption of the (±)-bromoxone (**4**) starting material and formation of several new products. Purification of the crude reaction mixture by flash silica gel chromatography yielded a small quantity (6%) of the desired epoxyquinol monomer (±)-**15**, along with approximately 10% of the reduced side product (±)-**29** (Scheme 5). Upon standing at room temperature overnight, monomer (±)-**15** was completely transformed into racemic (±)-panepophenanthrin (**1**) as the only observable product. The spontaneous conversion of (±)-**15** into target (±)-panepophenanthrin (**1**) provided solid evidence to support our biosynthetic proposal and completed

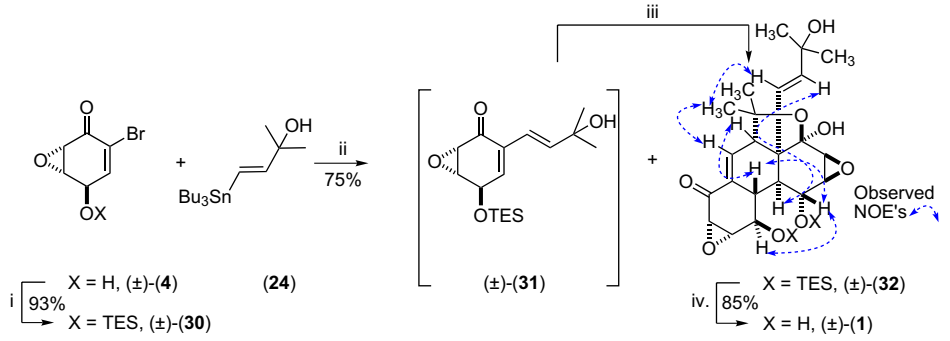


Scheme 4. Synthesis of (±)-bromoxone **4** and vinylstannane **24**: (i) Br_2, $CHCl_3$, 0 °C; (ii) $NaBH_4$ (aq), Et_2O, 0 °C; (iii) LiOH, Et_2O/MeOH (3:1); (iv) *m*-CPBA, CH_2Cl_2, 0 °C; (v) (a) DMP, CH_2Cl_2, 0 °C, (b) $NaHCO_3$, $Na_2S_2O_3$, rt; (vi) 2 mol % $PdCl_2(PPh_3)_2$, Bu_3SnH, THF, rt.



Scheme 5. (i) Pd_2dba_3 (7 mol %), $AsPh_3$ (22 mol %), 1 h, 110 °C, toluene; (ii) neat, rt, overnight.

the target synthesis, albeit in low overall yield (Scheme 5). Although such complexity generating cascade reactions are often a signature of biomimetic strategies,[17] the remarkable diasterospecific nature of the dimerisation cascade was somewhat unexpected.[12c] Improved yields in coupling reactions with protected epoxyquinols had been reported, thus offering a potential solution towards monomer synthesis **15**.[26] Triethyl silane (±)-**30** was chosen as a suitable substrate, since desilylation could be facilitated under mild conditions, without detriment to the sensitive epoxyquinol.[31] Compound (±)-**30** was obtained in 93% yield by action of chlorotriethylsilane and 2,6-lutidine in CH_2Cl_2 at 0 °C, followed by purification of the delicate substrate by flash-Florisil mediated chromatography. Gratifyingly, coupling of the TES-protected bromoxone (±)-**30** with vinylstannane **24** proved successful, furnishing the TES-protected monomer (±)-**31** along with a small quantity of TES-protected dimer (±)-**32**, in a combined yield of 75%. As with the unprotected monomer, compound (±)-**31** dimerised completely upon standing to yield (±)-**32** as a single diastereoisomer. Smooth deprotection of silyl protected (±)-**32** by NH_4F in methanol cleanly generated racemic (±)-**1** in good yield (85%) (Scheme 6). The remarkable diastereospecificity observed in the reaction sequence resulted from an exclusive homochiral dimerisation process. The absence of any observable diastereoisomeric products was suprising and indicative of some important stereochemical control elements in the reaction cascade.



Scheme 6. (i) $SiEt_3Cl$, 2,6-lutidine, CH_2Cl_2, 0 °C; (ii) 10 mol % Pd_2dba_3, 30 mol % $AsPh_3$, toluene, 110 °C, 1 h; (iii) neat, rt, overnight; (iv) NH_4F, MeOH, rt.

2.2. Asymmetric synthesis of (+)-panepophenanthrin (1)

Our racemic synthesis was shortly complemented by an asymmetric synthesis of (+)-**1** by Porco et al.[32] and more recently by Mehta et al.[33]

From the outset of our studies, we had appreciated that enantiomerically pure bromoxone (−)-(**4**) was readily accessible, prepared in an analogous manner to the racemic counterpart with the addition of a kinetic resolution of (±)-diacetate **33**.[30] Thus, upon enzyme catalysed hydrolysis of (±)-**33** by *pig pancreas lipase* (PPL), (+)-diacetate **33** and (+)-diol **26** were recovered, after recrystallisation in 35% yield [>99% ee (by HPLC)] and 39% yield [>99% ee (by HPLC)], respectively. Furnishing the total synthesis of (+)-**1** with enantiomerically pure building blocks yielded 1.73 g of the target compound (Scheme 7). All spectral data (^{1}H and ^{13}C NMR) and specific rotation ($[\alpha]_D^{25}$ +146.0 (*c* 1.0, MeOH), lit.[1] $[\alpha]_D^{26}$ +149.8 (*c* 1.0, MeOH)) for synthetic (+)-**1** were found to be in good agreement with naturally occurring (+)-**1**. Furthermore, slow crystallisation of compound (+)-**1** from a mixture of dichloromethane and methanol (1:1) resulted in the X-ray crystal structure, thus corroborating our success (Fig. 2).[34]

The pre-disposed nature of the dimerisation sequence enabled the formation of an extremely complex structure from relatively simple building blocks. Moreover, the observed diastereospecificity of the reaction indicated that there were some very important stereocontrol elements inherent in the process. Intrigued by these results, we sought to develop a greater understanding of the dynamics of the dimerisation cascade.

Our initial rationalisation for the dimerisation evolved because it provided an explanation for the high degree of diastereospecificity observed in the racemic synthesis. Originally, we had considered that initial, reversible hemiketal formation between two monomer units to give complex **34**, followed by an intramolecular inverse electron demand Diels–Alder reaction may lead to compound (+)-**1**.[16] It

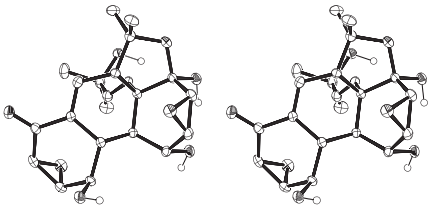
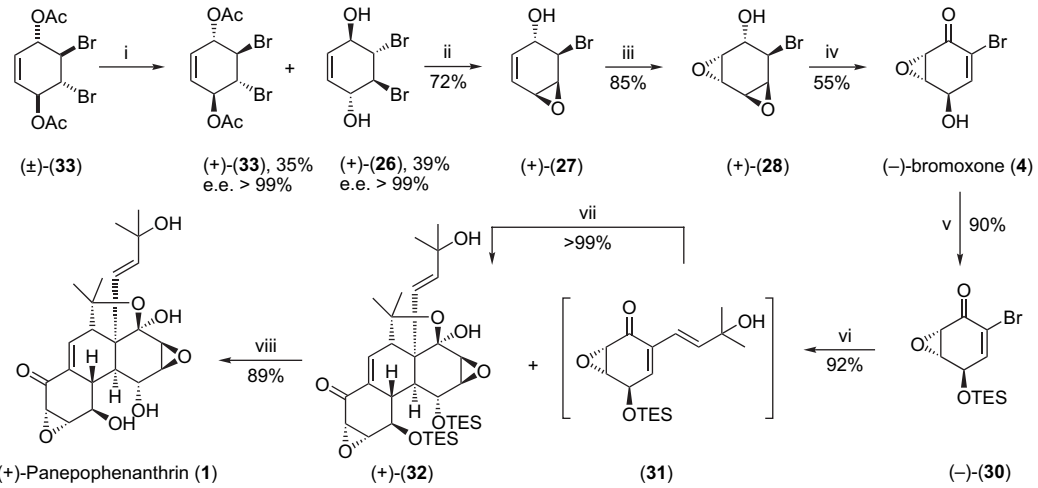


Figure 2. Stereo-representation of the crystal structure of synthetic (+)-panepophenanthrin (**1**).

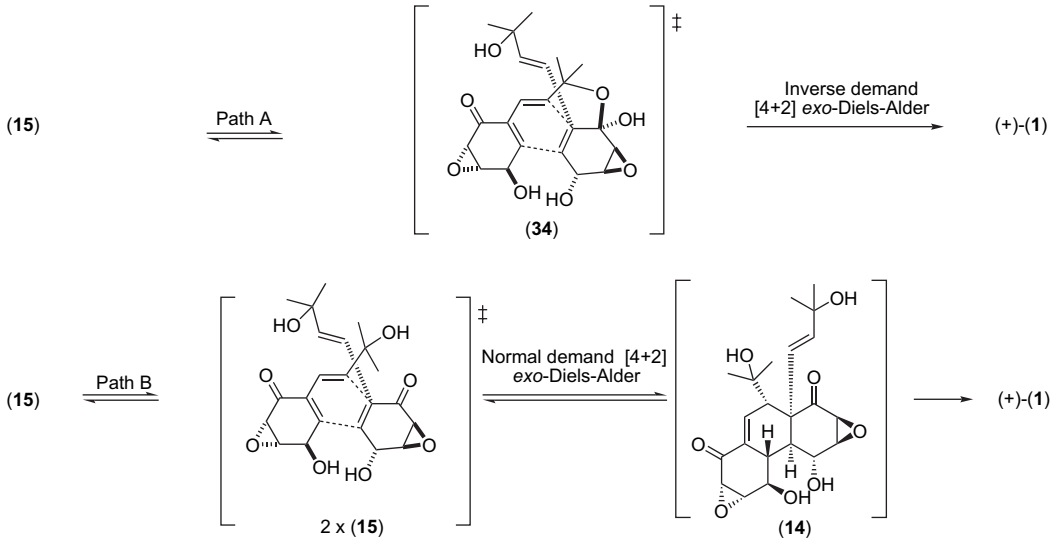
was reasoned that such reversible tethering would result in a highly organised transition state favouring homochiral dimerisation (Scheme 8, Path A). An alternative suggested mechanism[32,33] involves normal mode Diels–Alder cycloaddition to give intermediate **14**, followed by subsequent ring closure to form the five-membered ring hemiketal leading to (+)-(**1**) (Scheme 8, Path B). The latter pathway is supported by dimerisation studies with monomers lacking tertiary hydroxyl residues.[32]

The dimerisation cascade was also found to be sensitive to the stereochemistry of the peripheral functional groups. For example, the presence of the TES-protecting group attached to the hydroxyl moiety of the epoxyquinoid nucleus had no influence on the dimerisation process. This was further demonstrated by synthesising the bulky TBS-protected analogue (±)-**35**, which underwent dimerisation in an identical diastereospecific fashion to yield (±)-**36** (Scheme 9).

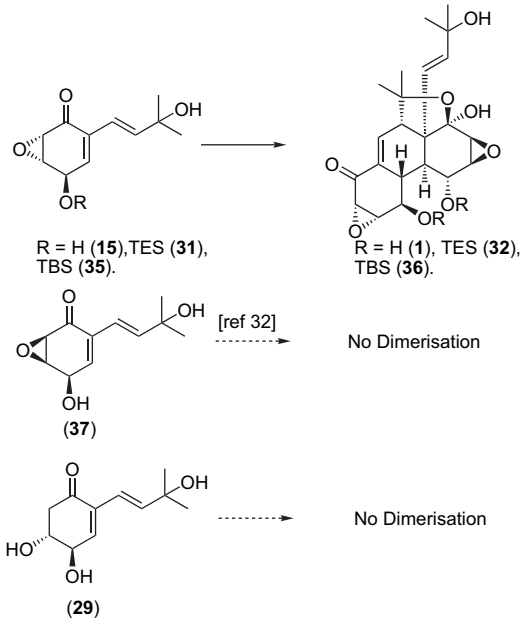
These observations ruled out any hydrogen bonding effects, which may have arisen from the free secondary hydroxyl. On the other hand, it had been demonstrated that the relative stereochemistry of the secondary hydroxyl group to be a very important factor in the dimerisation process.[32] Preparation of the related *syn*-epoxyquinol monomer **37** yielded no dimerisation product under the same conditions as those applied to the corresponding *anti*-isomer. The epoxide motif itself was also found to be essential for dimerisation, since reduced diol side product **29** did not undergo any observable



Scheme 7. (i) *Pig pancreas lipase*, pH 7.0 phosphate buffer, 3 days, rt; (ii) LiOH, Et_2O/MeOH (3:1), 0 °C to rt; (iii) *m*-CPBA, CH_2Cl_2, 0 °C; (iv) (a) DMP, CH_2Cl_2, 0 °C, (b) $NaHCO_3$, $Na_2S_2O_3$; (v) $SiEt_3Cl$, 2,6-lutidine, CH_2Cl_2, 0 °C; (vi) 10 mol % Pd_2dba_3, 30 mol % $AsPh_3$, **24**, toluene, 110 °C, 1 h; (vii) neat, rt, overnight; (viii) NH_4F, MeOH, rt.



Scheme 8. Proposed mechanisms for the biomimetic dimerisation.



Scheme 9. Factors affecting the biomimetic dimerisation.

reaction under similar conditions. These results clearly indicate that both steric and stereoelectronic effects are controlling factors in the dimerisation process.

2.3. Transition state analysis of dimerisation cascade

To further understand the biomimetic dimerisation and explain the observed diastereospecificity of the reaction, a series of theoretical calculations were undertaken. These simulations were performed by disconnecting (+)-**1** in a retro-[4+2] fashion. Each of the structures on the proposed reaction pathways were minimised at the B3LYP/6-31+G* level of theory.[35] Transition state searches were performed by moving the molecules along the reaction co-ordinate, at the HF/STO-3G level of theory, until an energy maximum was identified. All stationary points were characterised via analysis of vibrational modes. For all pathways except (+)–(+) the stationary points were minimised at the HF/6-31+G* level of theory before single point energy calculations were performed at the B3LYP/6-31+G* level.[36]

The results of our simulations are broadly in agreement with those of Lei et al.[32] favouring the reaction pathway that proceeds by a Diels–Alder reaction followed by cyclisation to form the five-membered hemiketal ring (Fig. 3). In the proposed alternative mechanism, the intermediate that would result from initial hemiketal formation (**34**, Scheme 8) is found to have an energy of 11.92 kcal mol^{-1} relative to the energy of the starting materials, whereas that of intermediate **14** is −4.99 kcal mol^{-1}. The transition state search that was performed for both possible pathways also supports the proposal of an initial Diels–Alder reaction followed by an intramolecular hemiketal formation. In the alternative pathway proceeding via initial hemiketal formation, no transition state could be identified.

These results provide some explanation for the observed diastereospecificity resulting from the cascade reaction. It is considered that the second-stage hemiketal formation is essentially irreversible under the given conditions, which would then effectively render the (potentially reversible) first-stage Diels–Alder cycloaddition irreversible, by 'locking' the core structure in place. The alignment required to facilitate such hemi-ketal bridging is provided by intermediate **14**, itself resulting from a homochiral *exo*-Diels–Alder cycloaddition (Scheme 8). The crystal structure of (+)-**1**[1] reveals the close proximity of the tertiary hydroxyl group and ketone, which should substantially favour the formation of the hemiketal bridge (Fig. 2). Whether diastereoisomers resulting from *endo*-heterochiral, *endo*-homochiral or from *exo*-heterochiral Diels–Alder cycloadditions are feasible reaction products is uncertain. However, steric or conformational constraints would seem to disfavour their hemiketal formation, thereby driving the overall equilibrium in favour of conformationally 'locked' **1**.

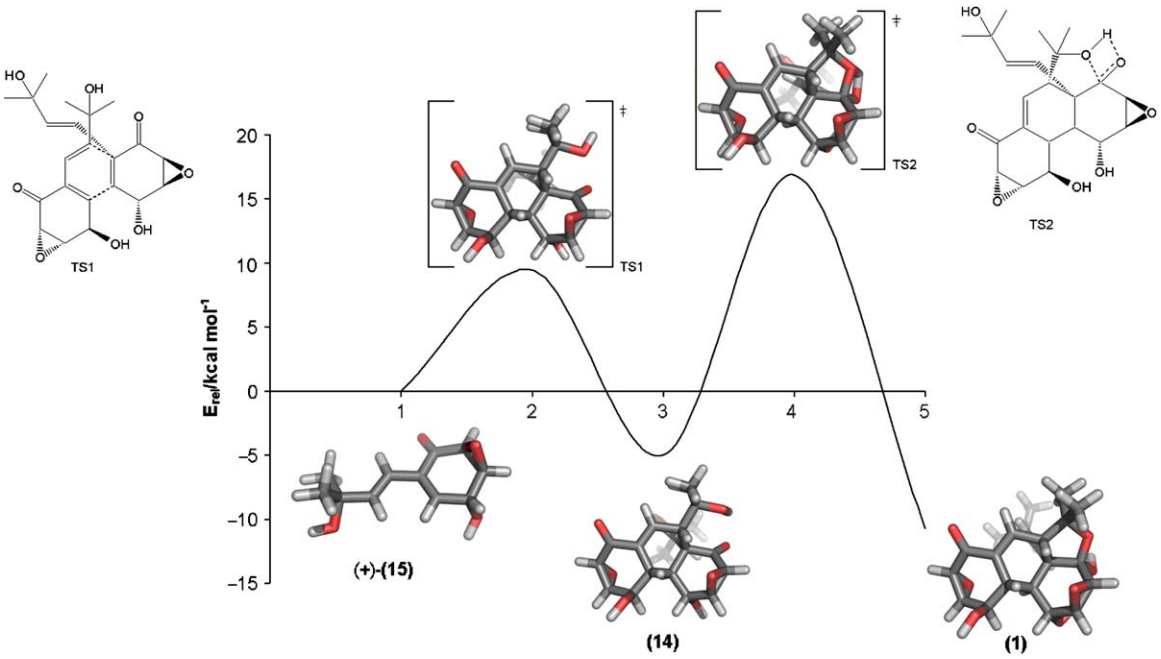


Figure 3. Reaction profile for formation of (+)-panepophenanthrin (**1**).

3. Conclusion

We have achieved a concise and efficient asymmetric synthesis of (+)-panepophenanthrin (**1**) employing a biomimetic dimerisation of an epoxyquinol monomer (+)-**15**. A key feature of our racemic synthesis was the observed diastereospecificity of the reaction sequence, which resulted from exclusive homochiral dimerisation. Our choice of building blocks allowed ready access to enantiomerically pure (+)-(**1**), through an enzyme mediated kinetic resolution of diacetate (±)-**33**, which is amenable to large-scale synthesis. Computational analysis assisted our interpretation of the dimerisation process.

4. Experimental

4.1. General experimental

All reagents were used as obtained from commercial sources unless otherwise stated. Measurement of pH was carried out using Prolabo Rota™ pH 1–10 paper. Infrared (IR) spectra were recorded on Perkin–Elmer Paragon Fourier Transform spectrometer. Proton magnetic resonance spectra (^{1}H NMR) were recorded on Brüker DPX400 (400 MHz), Brüker DRX500 (500 MHz) and Brüker AMX500 (500 MHz) spectrometers at ambient temperatures. Chemical shifts (δ_H) are quoted in parts per million (ppm) and are referenced to the residual solvent peak. *J* values are given in hertz. Carbon magnetic resonance spectra (^{13}C NMR) were recorded on Brüker DPX400 (100.6 MHz), Brüker DRX500 (125.8 MHz) and Brüker AMX500 (125.8 MHz) spectrometers at ambient temperature. Chemical shifts (δ_C) are quoted in parts per million (ppm) and are referenced to $CDCl_3$ unless otherwise stated. Carbon spectral assignments are supported by DEPT analysis and ^{1}H–^{13}C correlations where necessary. HMQC analysis was used in selected cases to aid assignment. Low-resolution mass spectra (*m/z*) were recorded using a V.G.TRIO (GC/MS) spectrometer, a Micromass Platform (APCI) spectrometer, Micromass Autospec spectrometer (CI^+) and a Micromass ZAB spectrometer (CI^+, ESI). Only molecular ions (M^+) and other major fragments are reported, with intensities quoted as percentages of the base peak. High resolution mass spectra were recorded on a VG Autospec spectrometer by chemical ionisation or on a Micromass LCT electro spray ionisation mass spectrometer operating at a resolution of 5000 full width half height. The quoted masses are accurate to ±5 ppm. All reagents were used as obtained from commercial sources unless otherwise stated. Melting points (mp) were obtained using a Buchi 510 Cambridge instruments Gallen™ III hot stage melting point apparatus.

4.1.1. Additional supporting data for known compounds. Compounds (±)-**27**, mp 81–82 °C (lit.[30c] mp 79 °C); (+)-**27** mp 113–115 °C (from $CHCl_3$/hexane) (lit.[37] mp 114–115 °C), $[\alpha]_D^{22}$ +168 (*c* 1.0, $CHCl_3$) (lit.[37] $[\alpha]_D^{25}$ +174 (*c* 1.0, $CHCl_3$)); (±)-**28** mp 92–94 °C; (+)-**28** mp 137–138 °C (from CCl_4/$CHCl_3$), $[\alpha]_D^{22}$ +198 (*c* 1.0, acetone); (±)-bromoxone (**4**) mp 95–97 °C (from CCl_4); (−)-bromoxone (**4**) mp 135–136 °C (from CCl_4/$CHCl_3$) (lit.[28] mp 137–139 °C), $[\alpha]_D^{22}$ −189 (*c* 1.0, acetone) (lit.[28] $[\alpha]_D^{22}$ −188 (*c* 1.85, acetone)); (+)-**33** mp 108–109 °C (lit.[30a] mp 107–109 °C), $[\alpha]_D^{25}$ +12.6 (*c* 1.00, CH_2Cl_2) (lit.[30a] $[\alpha]_D^{25}$ +11.3 (*c* 5.1, CH_2Cl_2)), ee >99% (chiral HPLC: heptane/2-propanol (90:10), flow 0.8 mL min^{-1}) *t*=9.06 min and (+)-**26** mp 164–165 °C (lit.[30a] mp 164–165 °C), $[\alpha]_D^{25}$ +51.3 (*c* 1.00, acetone) (lit.[30a] $[\alpha]_D^{25}$ +49.5 (*c* 1.22, acetone)), ee >99% (chiral HPLC: heptane/2-propanol (90:10), flow 0.8 mL min^{-1}) *t*=10.15 min were prepared according to the procedure of Altenbach et al.[30a] The spectral data (^{1}H and ^{13}C NMR) for these compounds were in agreement with those reported.[30]

4.1.2. (±)-(1*S,5*R**,6*R**)-5-Hydroxy-3-(3-hydroxy-3-methylbut-1-enyl)-7-oxa-bicyclo[4.1.0]hept-3-en-2-one (15), (±)-(4*R**,5*S**)-4,5-dihydroxy-2-(3-hydroxy-3-methylbut-1-enyl)cyclohex-2-enone (29) and (±)-panepophenanthrin (1).** (±)-Bromoxone (**4**) (0.50 g, 2.44 mmol) was dissolved in degassed toluene (10 cm^3) with stirring. Vinylstannane **24** (1.13 g, 3.01 mmol) was added and the mixture heated to 110 °C. In a separate flask, Pd_2dba_3 (160 mg, 0.17 mmol) and $AsPh_3$ (165 mg, 0.54 mmol) were stirred in degassed toluene (5 cm^3) for 20 min. The catalyst solution was added to the above reaction drop-wise over 10 min and the reaction mixture was stirred for an additional 1 h at 110 °C. The solvent was removed under reduced pressure. TLC analysis of the crude mixture indicated several minor products, which upon silica gel chromatography (1:99, MeOH/$CHCl_3$) yielded two clear oils: monomer (±)-**15** (31.00 mg, 6%) and diol (±)-**29** (51.0 mg, 10%). Compound (±)-**15** was found to be unstable and dimerised completely to give (±)-panepophenanthrin (**1**) (30.7 mg, 6%). Compound (±)-**29**: ν_{max}/cm^{-1} (film) 3435 (br, OH), 3100, 2980, 1690 (s, CO), 1600; δ_H (500 MHz, MeOD) 1.30 (6H, s, 2×CH_3), 2.47 (1H, dd, *J* 16.0 and 11.5, CH_2 (H_A)), 2.74 (1H, dd, *J* 16.0 and 4.5, CH_2 (H_B)), 3.83 (1H, ddd, *J* 11.5, 7.5 and 4.5, CH_2CHOH), 4.30 (1H, dd, *J* 7.5 and 2.5, *CH*OH), 6.34 (1H, d, *J* 16.0, C=C*HC*$(CH_3)_2OH$), 6.40 (1H, d, *J* 16.0, *H*C=CHC$(CH_3)_2OH$), 6.83 (1H, br d, *J* 2.5, =C*H*CHOH)); δ_C (125.7 MHz, MeOD) 29.7 (2×*C*H_3), 46.1 (*C*H_2), 71.4 (*C*$(CH_3)_2OH$), 73.2 (CH_2*C*HOH), 73.6 (*C*HOH), 120.3 (=*C*HC$(CH_3)_2OH$), 136.6 (C(O)*C*=), 142.3 (*C*=CHC$(CH_3)_2OH$), 146.5 (=*C*HCHOH), 198.5 (*C*=O); HRMS (ESI) *m/e* calcd for $C_{11}H_{15}O_4$ ($M-H^-$): 211.0970. Found: 211.0969; compound (±)-**15**: ν_{max}/cm^{-1} (film) 3435 (br, OH), 3105, 2982, 1685 (s, CO), 1602; δ_H (400 MHz, MeOD) 1.32 (6H, s, 2×CH_3), 3.48 (1H, br dd, *J* 3.5 and 1.0, *C*(O)C*H*), 3.75–3.77 (1H, m, *J* 3.5 and 2.5, –OC*H*CHOH), 4.64 (1H, br d, *J* 5.0, C*H*OH), 6.31 (1H, d, *J* 16.0, C=C*HC*$(CH_3)_2OH$), 6.45 (1H, d, *J* 16.0, *H*C=CHC$(CH_3)_2OH$), 6.66 (1H, dd, *J* 5.0 and 2.5, =C*H*); δ_C (100.6 MHz, MeOD) 29.7 (2×*C*H_3), 55.2 (C(O)*C*H), 58.7 (–O*C*HCHOH), 64.1 (*C*HOH), 71.4 (*C*$(CH_3)_2OH$), 120.7 (=*C*HC$(CH_3)_2OH$)), 134.3 (C(O)*C*=), 139.7 (=*C*H), 143.4 (*C*=CHC$(CH_3)_2OH$), 195.2 (*C*O); compound (±)-**1**: experimental data given below.

4.1.3. (±)-(1*S,5*R**,6*R**)-3-Bromo-5-triethylsilanyloxy-7-oxabicyclo[4.1.0]hept-3-en-2-one (30).[16]** To a solution of (±)-bromoxone (**4**) (200 mg, 0.98 mmol) in CH_2Cl_2 (10 cm^3) at 0 °C was added 2,6-lutidine (170 μL, 1.46 mmol) with stirring. After 5 min chlorotriethylsilane (220 mg, 1.46 mmol) was added and the mixture was allowed to stir for 30 min. EtOAc was added (20 cm^3) and the mixture was washed with NH_4Cl (30 cm^3) and brine (30 cm^3). Drying of the mixture followed by removal of the solvent under reduced pressure gave a crude brown solid, which could be purified by flash chromatography on Florisil (60–100 mesh) (4:1, 30–40 PE/EtOAc), to give compound (±)-**30** as a pale yellow oil (290 mg, 93%); ν_{max}/cm^{-1} (film) 2957, 2878 (s, C–H), 1705 (s, C=O), 1611 (m, C=C); δ_H (400 MHz, $CDCl_3$) 0.69 (6H, q, *J* 8.0, Si–CH_2), 0.99 (9H, t, *J* 8.0, Si–CH_2CH_3), 3.65 (1H, dd, *J* 3.5 and 1.0, *C*(O)C*H*), 3.68–3.70 (1H, m, –OC*H*CHOH), 4.70 (1H, br d, *J* 5.0, C*H*–$OSiEt_3$), 6.96 (1H, dd, *J* 5.0 and 2.5, =C*H*); δ_C (101.6 MHz, $CDCl_3$) 4.9 (Si–*C*H_2), 6.8 (SiCH_2*C*H_3), 53.6 (*C*(O)*C*H), 58.3 (–O*C*HCHOH), 65.4 (*C*H–$OSiEt_3$), 123.0 (=*C*Br), 144.7 (=*C*H), 186.5 (*C*O); MS (ESI) *m/z*=338/336 $(MNH_4)^+$, (100), 210 (50), 91 (19).

4.1.4. (±)-(1*S,5*R**,6*R**)-3-(3-Hydroxy-3-methylbut-1-enyl)-5-triethylsilanyloxy-7-oxabicyclo[4.1.0]hept-3-enone (31) and (±)-TES-protected panepophenanthrin (32).[16]** TES-protected bromoxone (±)-**30** (1.10 g, 3.40 mmol) was dissolved in degassed toluene (20 cm^3) with stirring. Vinylstannane **24** (1.65 g, 4.40 mmol) was added and the mixture was heated to 110 °C. In a separate flask, Pd_2dba_3 (320 mg, 0.35 mmol) and $AsPh_3$ (330 mg, 1.08 mmol) were stirred in degassed toluene (10 cm^3) for 20 min. The catalyst solution was then added to the above reaction drop-wise over 10 min and the reaction mixture stirred for an additional 1 h at 110 °C. The solvent was removed by rotary evaporation and the crude mixture subjected to flash silica gel chromatography (1:99, MeOH/$CHCl_3$) to afford two products: monomer (±)-**31** and dimer (±)-**32**. Overnight, (±)-**31** was completely transformed into (±)-**32**. Finally (±)-**32** was obtained as a white powder (827 mg, 75%). Compound (±)-**31**: δ_H (MeOD, 400 MHz) 0.63 (6H, q, *J* 8.0, Si*C*H_2), 0.98 (9H, t, *J* 8.0, $SiCH_2CH_3$), 1.30 (3H, br s, CH_3), 1.31 (3H, br s, CH_3), 3.49 (1H, br dd, *J* 4.0 and 1.0, C(O)C*H*), 3.74 (1H, m, –OC*H*CHOH), 4.62 (1H, br d, *J* 5.0, C*H*–$OSiEt_3$), 6.32 (1H, d, *J* 16.0, C=C*H*C$(CH_3)_2OH$), 6.44 (1H, d, *J* 16.0, *H*C=CHC$(CH_3)_2OH$), 6.63 (1H, br dd, *J* 5.0 and 2.5, =C*H*); δ_C (100.6 MHz, MeOD) 4.8 (Si*C*H_2), 6.9 ($SiCH_2CH_3$), 29.7 (2×*C*H_3), 55.2 (C(O)*C*H), 58.7 (–O*C*H-CHOH), 64.1 (*C*H–$OSiEt_3$), 71.4 (*C*$(CH_3)_2OH$), 120.7 (C=*C*HC$(CH_3)_2OH$), 134.3 (C(O)*C*=), 139.7 (=*C*H), 143.4 (*C*=CHC$(CH_3)_2OH$), 195.2 (*C*-2); compound (±)-(**32**) (see Fig. 1 for numbering): mp 89–91 °C; ν_{max}/cm^{-1} (KBr) 3435, 1691 (s, C=O), 1599; δ_H (500 MHz, $CDCl_3$) 0.68 (12H, q, *J* 8.0, Si–CH_2CH_3), 1.0 (18H, m, *J* 8.0 and 8.0, Si–CH_2CH_3), 1.21 (3H, s, *H*-14), 1.24 (3H, s, *H*-15), 1.39 (3H, s, *H*-17), 1.46 (3H, s, *H*-16), 2.11 (1H, d, *J* 11.5, *H*-10b), 2.54 (1H, br d, *J* 11.5, *H*-10a), 3.42–3.47 (3H, m, *H*-2, 3, 5a), 3.49 (1H, d, *J* 4.5, *H*-8), 3.74 (1H, br t, *J* 4.5, *H*-9), 4.53 (1H, d, *J* 3.5, *H*-1), 4.59 (1H, d, *J* 3.5, *H*-10), 5.69 (1H, d, *J* 16.5, *H*-12), 6.14 (1H, d, *J* 16.5, *H*-11), 6.82 (1H, dd, *J* 5.5 and 2.5, *H*-6); δ_C (125.7 MHz, $CDCl_3$) 4.7 (Si–CH_2CH_3), 6.6 (Si–CH_2CH_3), 25.2 (*C*-16), 29.3 (*C*-14), 29.9 (*C*-15), 31.9 (*C*-17), 48.0 (*C*-10b), 49.4 (*C*-10a), 54.2 (*C*-8), 55.0 (*C*-10c), 55.2 (*C*-2), 55.7 (*C*-3), 55.9 (*C*-5a), 59.3 (*C*-9), 65.4 (*C*-10), 68.4 (*C*-1), 71.1 (*C*-13), 78.4 (*C*-5), 101.1 (C-3a), 129.3 (*C*-11), 138.2 (*C*-6a), 138.5 (*C*-6), 141.6 (*C*-12), 194.6 (CO); HRMS (ESI) calcd for $C_{34}H_{55}O_8Si_2$ ($M-H^-$): 647.3436. Found: 647.3457.

4.1.5. (±)-Panepophenanthrin (1).[16] To a round-bottomed flask containing methanol (5 cm^3) was added (±)-**32** (199 mg, 0.31 mmol) followed by stirring for 5 min. NH_4F (45.5 mg, 1.23 mmol) was then added and the mixture was allowed to stir until the reaction had completed as indicated by TLC analysis (approx 2 h). The solvent was removed under reduced pressure and the crude mixture subjected to silica gel chromatography (97:3, $CHCl_3$/MeOH) to give the title compound as a white solid (110 mg, 85%) (see Fig. 1 for numbering);[1] R_f=0.3 (9:1, $CHCl_3$/MeOH); mp 81 °C (from CH_3Cl); ν_{max}/cm^{-1} (KBr) 3435, 1672 (s, CO), 1600 (m, C=C); δ_H (500 MHz, MeOH) 1.23 (3H, s, *H*-14), 1.26

(3H, s, *H*-15), 1.41 (3H, s, *H*-17), 1.51 (3H, s, *H*-16), 2.10 (1H, br d, *J* 10.0, *H*-10b), 2.40 (1H, br d, *J* 10.0, *H*-10a), 3.39 (1H, d, *J* 4.0, *H*-3), 3.41 (1H, dd, *J* 5.0 and 2.0, *H*-5a), 3.49 (1H, d, *J* 4.0, H-8), 3.56 (1H, br t, *J* 3.5, *H*-2), 3.90 (1H, br t, *J* 3.5, *H*-9), 4.41 (1H, br t, *J* 2.0, *H*-1), 4.61 (1H, br t, *J* 2.0, H-10), 5.75 (1H, d, *J* 16.0, *H*-12), 6.05 (1H, d, *J* 16.0, H-11), 6.88 (1H, dd, *J* 5.0 and 3.0, *H*-6); δ_C (125.7 MHz, MeOD) 26.3 (*C*-16), 29.6 (*C*-14), 30.5 (*C*-15), 32.5 (*C*-17), 50.2 (*C*-10b), 51.3 (*C*-10a), 55.2 (*C*-8), 55.8 (*C*-10c), 57.3 (*C*-2), 57.4 (*C*-3), 57.5 (*C*-5a), 60.8 (*C*-9), 66.4 (*C*-10), 69.2 (*C*-1), 71.9 (*C*-13), 79.3 (*C*-5), 102.8 (*C*-3a), 129.4 (*C*-11), 138.9 (*C*-6a), 140.1 (*C*-6), 143.2 (*C*-12), 196.4 (*C*-7); HRMS (ESI) calcd for $C_{22}H_{27}O_8$ ($M-H^-$): 419.1704. Found: 419.1706.

4.1.6. (±)-5-(1*S,5*R**,6*R**)-(*tert*-Butyldimethylsilanoxy)-3-(3-hydroxy-3-methylbut-1-enyl)-7-oxabicyclo[4.1.0]-hept-3-en-2-one (35) and (±)-TBS-protected panepophenanthrin (36).** To a round-bottomed flask was added TBS-protected bromoxone (1.08 g, 3.38 mmol) and was dissolved in degassed toluene (20 cm^3). Vinylstannane **24** (1.65 g, 4.39 mmol) was added and the mixture was heated to 110 °C. In a separate flask, Pd_2dba_3 (320 mg, 0.35 mmol) and $AsPh_3$ (330 mg, 1.07 mmol) were stirred in degassed toluene (10 cm^3) for 20 min. The catalyst solution was then added to the above reaction drop-wise over 10 min and the reaction mixture was stirred for an additional 1 h at 110 °C. The solvent was removed by rotary evaporation and the crude product subjected to silica gel chromatography (1:99, MeOH/CH_2Cl_2) to afford two products: monomer (±)-**35** and dimer (±)-**36**. Upon standing overnight monomer (±)-**35** was completely transformed into the dimer. Finally (±)-**36** was obtained in 66% yield (728 mg) as an off yellow powder. Compound (±)-**35**: δ_H ($CDCl_3$, 400 MHz) 0.65 (6H, q, *J* 8.0, SiC*H*$_2$), 0.13 (3H, s, SiC*H*$_3$), 0.16 (3H, s, SiC*H*$_3$), 0.90 (9H, s, SiC(C*H*$_3$)$_3$), 1.33 (3H, s, C*H*$_3$), 1.35 (3H, s, C*H*$_3$), 3.51 (1H, br d, *J* 4.0 and 1.0, C(O)C*H*), 3.63 (1H, m, *J* 4.0 and 2.5, –OC*H*CHOH), 4.71 (1H, br d, *J* 5.0, C*H*–OTBS), 6.27 (1H, d, *J* 16.0, C=C*H*C(CH$_3$)$_2$OH), 6.36–6.40 (1H, m, =C*H*), 6.41 (1H, d, *J* 16.0, *H*C=CHC(CH$_3$)$_2$OH); δ_C ($CDCl_3$, 100.6 MHz) −4.7, −4.5 (Si*C*H$_3$), 18.0 (Si–*C*), 25.6 (SiC–(*C*H$_3$)$_3$), 29.6 (2×*C*H$_3$), 54.1 (C(O)*C*H), 57.9 (–O*C*HCHOH), 64.1 (C*H*–OTBS), 70.9 (*C*(CH$_3$)$_2$OH), 119.7 (=*C*HC(CH$_3$)$_2$OH), 132.8 (C(O)*C*=), 137.9 (=*CH*), 142.3 (*C*=CHC(CH$_3$)$_2$OH), 193.2 (*C*O); compound (±)-**36**: mp 169–170 °C (from CH_2Cl_2); ν_{max}/cm^{-1} (KBr) 3454 (br, OH), 2930, 2858, 1687 (s, C=O); δ_H (400 MHz, MeOD) 0.18 (12H, br s, Si–C*H*$_3$), 0.87 (18H, br s, Si–C(C*H*$_3$)$_3$), 1.09 (3H, s, *H*-14), 1.16 (3H, s, *H*-15), 1.31 (3H, s, *H*-17), 1.43 (3H, s, *H*-16), 2.09 (1H, d, *J* 11.5, *H*-10b), 2.37 (1H, br d, *J* 11.5, *H*-10a), 3.29–3.48 (4H, m, *H*-2, 3, 5a, 8), 3.87 (1H, br t, *J* 3.5, *H*-9), 4.52 (1H, d, *J* 3.5, H-1), 4.66 (1H, d, *J* 3.5, *H*-10), 5.64 (1H, d, *J* 16.0, *H*-12), 6.01 (1H, d, *J* 16.0, *H*-11), 6.73 (1H, dd, *J* 5.5 and 3.0, *H*-6); δ_C ($CDCl_3$, 125.7 MHz) −4.7, −4.5 (Si*C*H$_3$), 17.9 (Si–*C*), 24.9 (*C*-16), 25.1 (Si–*C*), 28.9 (*C*-14), 29.2 (*C*-15), 31.5 (*C*-17), 48.5 (*C*-10b), 48.6 (*C*-10a), 49.0 (*C*-8), 49.4 (*C*-10c), 54.3 (*C*-2), 55.6 (*C*-3), 56.0 (*C*-5a), 59.5 (*C*-9), 66.4 (*C*-10), 68.8 (*C*-1), 70.8 (*C*-13), 77.8 (*C*-5), 102.1 (*C*-3a), 128.6 (*C*-11), 138.2 (*C*-6a), 138.5 (*C*-6–*C*), 141.9 (*C*-12), 194.6 (*C*O); HRMS (ESI) calcd for $C_{34}H_{55}O_8Si_2$ ($M-H^-$): 647.3436. Found: 647.3448.

4.1.7. (−)-(4*R*,5*S*,6*S*)-2-Bromo-4-triethylsilanoxy-5,6-epoxy-2-cyclohexen-1-one (30). To a solution of (−)-bromoxone (**4**) (4.00 g, 19.51 mmol) in CH_2Cl_2 (100 cm^3) at 0 °C was added 2,6-lutidine (3.40 cm^3, 29.26 mmol) with stirring. After 5 min chlorotriethylsilane (4.40 g, 29.26 mmol) was added and the mixture was allowed to stir for 30 min. EtOAc was added (100 cm^3) and the mixture was washed with NH_4Cl (2×100 cm^3) and brine (2×100 cm^3). Drying of the mixture followed by removal of the solvent under reduced pressure gave a crude brown solid, which could be purified by flash chromatography on Florisil (60–100 mesh) (4:1, 30–40 PE/EtOAc) to give compound (−)-**30** as a clear oil (5.61 g, 90%); $[\alpha]_D^{22}$ −145 (*c* 1.0, acetone). The spectral data (^1H and ^{13}C NMR) for (−)-**30** were in agreement with racemic (±)-**30**.

4.1.8. (+)-TES-protected panepophenanthrin (32). TES-protected bromoxone (−)-**30** (3.50 g, 10.96 mmol) was dissolved in degassed toluene (60 cm^3) with stirring. Vinylstannane **24** (5.32 g, 14.17 mmol) was added and the mixture was heated to 110 °C. In a separate flask, Pd_2dba_3 (1.03 g, 1.13 mmol) and $AsPh_3$ (1.06 mg, 3.48 mmol) were stirred in degassed toluene (30 cm^3) for 20 min. The catalyst solution was then added to the above reaction drop-wise over 10 min and the reaction mixture stirred for an additional 1 h at 110 °C. The solvent was removed by rotary evaporation and the crude mixture left to stand overnight. Purification of the crude oil by flash silica gel chromatography (1:99, MeOH/$CHCl_3$) afforded compound (+)-**32** as an off-white powder (3.27 g, 92%); $[\alpha]_D^{22}$ +182 (*c* 1.0, $CHCl_3$). The spectral data (^1H and ^{13}C NMR) for (+)-**32** were in agreement with racemic (±)-**32**.

4.1.9. (+)-Panepophenanthrin (1). To a round-bottomed flask containing methanol (100 cm^3) was added (+)-**32** (3.00 g, 4.63 mmol) followed by stirring for 5 min. NH_4F (685 mg, 18.50 mmol) was then added and the mixture was allowed to stir until the reaction had gone to completion as indicated by TLC analysis (approx 2–3 h). The solvent was removed under reduced pressure and the crude mixture subjected to silica gel chromatography (97:3, $CHCl_3$/MeOH) to give the title compound as a white solid (1.73 g, 89%); mp 145–148 °C ($CHCl_3$) (lit.[1] mp 144–146 °C); $[\alpha]_D^{22}$ +146 (*c* 1.0, MeOH) (lit.[1] $[\alpha]_D^{26}$ +149.8 (*c* 1.0, MeOH); ν_{max}/cm^{-1} (KBr) 2988, 1672 (s, CO), 1600 (m, C=C); δ_H (500 MHz, MeOH) (see Fig. 1 for numbering)[1] 1.17 (3H, s, *H*-14), 1.21 (3H, s, *H*-15), 1.36 (3H, s, *H*-17), 1.45 (3H, s, *H*-16), 2.04 (1H, br d, *J* 10.0, *H*-10b), 2.32 (1H, br d, *J* 10.0, *H*-10a), 3.31 (1H, d, *J* 4.0, *H*-3), 3.35 (1H, dd, *J* 5.0 and 2.0, *H*-5a), 3.42 (1H, d, *J* 4.0, H-8), 3.50 (1H, br t, *J* 3.5, *H*-2), 3.84 (1H, br t, *J* 3.5, *H*-9), 4.35 (1H, br t, *J* 2.0, *H*-1), 4.55 (1H, br t, *J* 2.0, H-10), 5.69 (1H, d, *J* 16.0, *H*-12), 5.99 (1H, d, *J* 16.0, *H*-11), 6.81 (1H, dd, *J* 5.0 and 3.0, *H*-6); δ_C (125.7 MHz, MeOD) 26.1 (*C*-16), 29.4 (*C*-14), 30.4 (*C*-15), 32.3 (*C*-17), 50.1 (*C*-10b), 51.2 (*C*-10a), 55.2 (*C*-8), 55.6 (*C*-10c), 57.1 (*C*-2), 57.2 (*C*-3), 57.5 (*C*-5a), 60.8 (*C*-9), 66.2 (*C*-10), 69.0 (*C*-1), 71.9 (*C*-13), 79.2 (*C*-5), 102.6 (*C*-3a), 129.2 (*C*-11), 138.9 (*C*-6a), 139.9 (*C*-6), 143.1 (*C*-12), 196.2 (*C*-7); HRMS [(EI)$^-$] calcd for $C_{22}H_{27}O_8$ [(M−H)$^-$]: 419.1704. Found: 419.1706. *Crystal Data for* **1**: $C_{22}H_{30}O_9$, *M*=438.47, monoclinic, *a*=8.9012(2), *b*=22.7413(5), *c*=10.3797(3) Å, *U*=2100.82(9) Å^3, *T*=150 K, space group $P2_1$, *Z*=2,

μ(Mo Kα)=0.107 mm^{-1}, 17,072 reflections measured, 4871 unique (R_{int}=0.053), which were used in calculations. The final *wR* was 0.0442. CCDC no. 247818.

Acknowledgements

We thank the EPSRC for funding J.E.M. and Roche for funding Laurent Commeiras. We thank Dr. B. Odell for NMR assistance.

References and notes

1. Sekizawa, R.; Ikeno, S.; Nakamura, H.; Naganawa, H.; Matsui, S.; Iinuma, H.; Takeuchi, T. *J. Nat. Prod.* **2002**, *65*, 1491.
2. Tsukamoto, S.; Hirota, H.; Imachi, M.; Fujimuro, M.; Onuki, H.; Ohta, T.; Yokosawa, H. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 191.
3. For an overview of the ubiquitination pathway, see: Hershko, A.; Ciechanover, A. *Annu. Rev. Biochem.* **1998**, *67*, 425.
4. For a discussion of E1 as a potential drug target, see: Swinney, D. C. *Drug Discov. Today* **2001**, *6*, 244.
5. Nagasawa, H.; Suzuki, A.; Tamura, S. *Agric. Biol. Chem.* **1978**, *42*, 1303.
6. Higa, T.; Okuda, R. K.; Severns, R. M.; Scheur, P. J.; He, C.-H.; Changfu, X.; Clardy, J. *Tetrahedron* **1987**, *43*, 1063.
7. Li, J. Y.; Strobel, G. A. *Phytochemistry* **2001**, *57*, 261.
8. Buzzetti, F.; Gaumann, E.; Hutter, R.; Keller-Schierlein, W.; Neipp, L.; Prelog, V.; Zahner, H. *Pharm. Acta Helv.* **1963**, *38*, 871.
9. (a) Hara, M.; Akasaka, K.; Akinaga, S.; Okabe, M.; Nakano, H.; Gomez, R.; Wood, D.; Uh, M.; Tamanoi, F. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 2281; (b) Hara, M.; Han, M. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 3333.
10. (a) Lee, J. C.; Yang, X.; Schwartz, M.; Strobel, G. A.; Clardy, J. *Chem. Biol.* **1995**, *2*, 721; (b) Lee, J. C.; Strobel, G. A.; Lobkovsky, E.; Clardy, J. *J. Org. Chem.* **1996**, *61*, 3232.
11. (a) Kakeya, H.; Onose, R.; Koshino, H.; Yoshida, A.; Kobayashi, K.; Kageyama, S.-I.; Osada, H. *J. Am. Chem. Soc.* **2002**, *124*, 3496; (b) Kakeya, H.; Onose, R.; Yoshida, A.; Koshino, H.; Osada, H. *J. Antibiot.* **2002**, *55*, 829.
12. (a) Li, C.; Porco, J. A., Jr. *J. Org. Chem.* **2005**, *70*, 6053; (b) Liang, M.-C.; Bardhan, S.; Li, C.; Pace, E. A.; Porco, J. A., Jr.; Gilmore, T. D. *Mol. Pharmacol.* **2003**, *64*, 123; (c) Li, C.; Johnson, R. P.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 5095; (d) Li, C.; Bardhan, S.; Pace, E. A.; Liang, M.-C.; Gilmore, T. D.; Porco, J. A., Jr. *Org. Lett.* **2002**, *4*, 3267; (e) Hu, Y.; Li, C.; Kulkarni, B. A.; Strobel, G.; Lobkovsky, E.; Torczynski, R. M.; Porco, J. A., Jr. *Org. Lett.* **2001**, *3*, 1649; (f) Li, C.; Lobkovsky, E.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2000**, *122*, 10484.
13. (a) Shoji, M.; Kishida, S.; Kodera, Y.; Shiina, I.; Kakeya, H.; Osada, H.; Hayashi, Y. *Tetrahedron Lett.* **2003**, *44*, 7205; (b) Shoji, M.; Imai, H.; Shiina, I.; Kakeya, H.; Osada, H.; Hayashi, Y. *J. Org. Chem.* **2004**, *69*, 1548.
14. Nagata, T.; Ando, Y.; Hirota, H. *Biosci. Biotechnol. Biochem.* **1992**, *56*, 810.
15. (a) Kawazi, K.; Kobayashi, A.; Oe, K. JP 03 41 075; *Chem. Abstr.* **1991**, *115*, 181517k; (b) Kobayashi, A.; Ooe, K.; Yata, S.; Kawazu, K. Symposiumof papers, the 31st Symposium on the Chemistry of Natural Products, Nagoya, October 1989, 388.
16. Moses, J. E.; Commeiras, L.; Baldwin, J. E.; Adlington, R. M. *Org. Lett.* **2003**, *5*, 2987.
17. (a) Heathcock, C. H. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 14323; (b) Moses, J. E.; Adlington, R. M. *Chem. Commun.* **2005**, 5945.
18. Wipf, P.; Jeger, P.; Kim, Y. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 351.
19. For Diels–Alder dimerisation reactions of 2-vinylcyclohexenones and related dienes, see: Spino, C.; Pesant, M.; Dory, Y. *Angew. Chem., Int. Ed.* **1998**, *37*, 3262.
20. For example, see: (a) Whittle, Y. G.; Gould, S. J. *J. Am. Chem. Soc.* **1987**, *109*, 5043; (b) Gould, S. J.; Shen, B.; Whittle, Y. G. *J. Am. Chem. Soc.* **1989**, *111*, 7932.
21. Lindsey, C. C.; Gómez-Díaz, C.; Villalba, J. M.; Pettus, T. R. R. *Tetrahedron* **2002**, *58*, 4559.
22. Shotwell, J. B.; Hu, S.; Medina, E.; Abe, M.; Cole, R.; Crews, C. M.; Wood, J. L. *Tetrahedron Lett.* **2000**, *41*, 9639.
23. (a) Kis, V. Z.; Closse, A.; Sigg, H.; Hruban, L.; Snatzke, G. *Helv. Chim. Acta* **1970**, *53*, 1577; (b) Erkel, G.; Anke, T.; Sterner, O. *Biochem. Biophys. Res. Commun.* **1996**, *226*, 214.
24. Graham, A. E.; McKerrecher, D.; Davies, D. H.; Taylor, R. J. K. *Tetrahedron Lett.* **1996**, *37*, 7445.
25. Graham, A. E.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1087.
26. Miller, M. W.; Johnson, C. R. *J. Org. Chem.* **1997**, *62*, 1582.
27. Kamikubo, T.; Ogasawara, K. *Chem. Commun.* **1996**, 1679.
28. Johnson, C. R.; Miller, M. W. *J. Org. Chem.* **1995**, *60*, 6674.
29. Zhang, H. X.; Guibé, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857.
30. (a) Block, O.; Klein, G.; Altenbach, H.-J.; Brauer, D. J. *J. Org. Chem.* **2000**, *65*, 716; (b) Adelt, S.; Plettenburg, O.; Stricker, R.; Reiser, G.; Altenbach, H.-J.; Vogel, G. *J. Med. Chem.* **1999**, *42*, 1262; (c) Altenbach, H.-J.; Stegelmeir, H.; Vogel, G. *Tetrahedron Lett.* **1978**, *31*, 3333.
31. Kienzle, F.; Stadlwieser, J.; Rank, W.; Mergelsberg, I. *Tetrahedron Lett.* **1988**, *29*, 6479.
32. Lei, X.; Johnson, R. P.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2003**, *42*, 3913.
33. (a) Mehta, G.; Ramesh, S. S. *Tetrahedron Lett.* **2004**, *45*, 1985; (b) Mehta, G.; Islam, K. *Tetrahedron Lett.* **2004**, *45*, 7683.
34. Crystallographic data (excluding structure factors) for the structure in this paper has been deposited at the Cambridge Crystallographic Data Centre as supplementary publication. CCDC no. 247818. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
35. The optical rotation of monomer **15** was not obtained. The (+) and (−) notation has therefore been arbitrarily assigned for our discussion.
36. All calculations were performed using: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98 (Revision A.7)*; Gaussian: Pittsburgh, PA, 1998.
37. Kohrt, J. T.; Gu, J.-X.; Johnson, C. R. *J. Org. Chem.* **1998**, *63*, 5088.