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Schweinfurthins A–Q: isolation, synthesis, and biochemical properties

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Stilbene analogues have shown remarkable structural diversity constituting simple or tangled structures, which have attracted the synthetic as well as the medicinal chemistry communities. Schweinfurthins are a family of prenylated/geranylated/farnesylated stilbenes that are isolated from an African plant belonging to the *Macaranga* species. These compounds have displayed potency towards central nervous system, renal and breast cancer cell lines. Specifically, these compounds have been found to be potent and selective inhibitors of cell growth in the National Cancer Institute's 60 cell-line screen. In this review article, we described the isolation, synthesis, and biochemical properties of schweinfurthins.

1. Introduction

The role of natural products in drug discovery has been phenomenal. The search for new lead compounds displaying potency and selectivity with the fewest adverse side effects has led to the synthesis of more and more new candidates for the treatment of various diseases. Natural products have been a significant resource of drug leads in the field of medicinal chemistry, and despite an upsurge in the use of combinatorial chemistry as a part of the lead development process, they still play a pivotal role owing to their diverse biochemical properties.[1–4]

Privileged structures have been widely used as effective templates in drug discovery. Stilbenes as such are a simple class of naturally occurring compounds that have a widespread distribution in nature (Fig. 1). Although their molecular backbone is made up of only a 1,2-diphenylethylene moiety, which exists as a *trans*- or *cis*-isomer, stilbenes have shown an immense array of different structural units. The stilbene moiety has been utilised as a starting source for the synthesis of new complex molecules.[5,6]

Resveratrol is a major constituent of the stilbene family that has received significant attention due to its anticancer activity.[7–12] However, there are numerous analogues (naturally occurring, synthetic and semisynthetic) in this family with significant properties and applications.[13–20] Additionally, several stilbene-based scaffolds have been approved for clinical use. For example, diethylstilboestrol and tamoxifen are used for the treatment of prostate cancer and metastatic breast cancer, respectively.[21–25]

Schweinfurthins are prenylated/geranylated/farnesylated stilbenes that are isolated from numerous species of the plant genus *Macaranga* (Euphorbiaceae). There has been an increased interest in the schweinfurthin family because of their selective anti-proliferative activity against human cancer cells. The scarcity of natural schweinfurthins has enticed the evolution of the synthetic approach towards their total synthesis. This review provides details on the isolation, synthesis, and bioactivities of schweinfurthins. The difficulties overcome, along with the successful modification of synthetic strategies, are discussed in this review.

2. Isolation

Macaranga is a genus of tropical trees that belongs to the Euphorbiaceae family and is the only genus in the subtribe Macaranginae. It is one of the largest genera of the Euphorbiaceae, comprising approximately 300 different species generally found in Africa, Australasia, Asia, and various islands in the Indian and Pacific oceans.[26] Until now, 17 naturally occurring schweinfurthins (A–Q) have been isolated from the *Macaranga* genus (Table 1). In addition, one of the closely related congeners, vedelianin, along with two synthetic schweinfurthin analogues, is discussed.

In the past few years, the most common species of the *Macaranga* genus, *M. vedeliana*, *M. pleiostemona*, *M. indica*, *M. tanarius* and *M. schweinfurthii* have been thoroughly studied. A number of different classes of compounds such as prenylated stilbenes, geranylated flavonols, prenylated flavanones, chromenoflavones and diterpenes have been isolated from this species.[33–36]

Schweinfurthins A–D were first isolated by Beutler *et al.* as yellowish solids from a mixed CH_2Cl_2–MeOH extract of *M. schweinfurthii*.[27,28] Another unexplored species of the *Macaranga*

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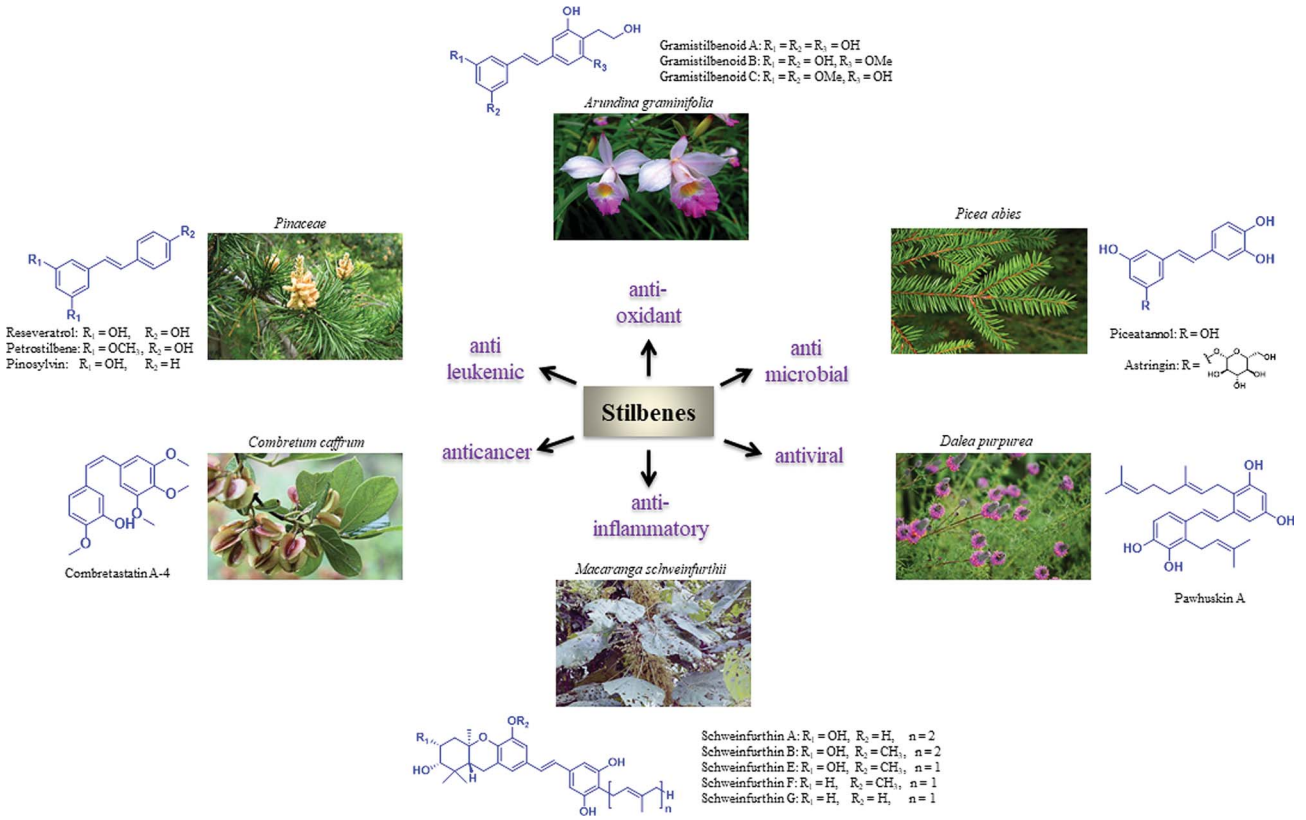


Fig. 1 Bioactive natural products with stilbene moiety.

genus, *M. alnifolia*, was highlighted by Yoder *et al.*, who isolated four new prenylated stilbenes, schweinfurthins E–H, as pale yellow solids from an ethanolic extract of the fruit of *M. alnifolia*.[29] Schweinfurthin H possesses a 2,2-dimethyldihydropyranol moiety, which was first observed in the schweinfurthin family. Klausmeyer *et al.* isolated two prenylated stilbenes, schweinfurthins I and J as yellow oils from the leaf of the *M. schweinfurthii*.[30] Initially, Thoison *et al.* isolated vedelianin in 1991 from the leaves of *M. vedeliana*, which is closely related to the schweinfurthins.[32] Later, Yoder *et al.* also isolated vedelianin along with schweinfurthins E-H from another *Macaranga* species, *M. alnifolia*.[29]

Recently, Péresse *et al.* isolated seven more schweinfurthins, K–Q, from *M. tanarius*. Among these seven newly reported natural products, only schweinfurthin Q has a hexahydroxanthene tricyclic core. Schweinfurthins K, L, and M possess a 2,2-dimethyldihydropyranol moiety. All of the compounds were isolated as orange oils from an ethanolic extract of the dried fruits of *M. tanarius*.[31]

3. Synthesis

Natural schweinfurthins possess a stilbene backbone with prenylated/geranylated/farnesylated moieties on any of the rings. Generally, the stilbene skeleton is synthesized using a Wittig or modified Wittig olefination, Heck, Suzuki, Stille or Sonogashira coupling reactions. In the case of the schweinfurthins, Horner–Wadsworth–Emmons (HWE) olefination has been utilised to selectively construct the *trans*-stilbene skeleton.

3.1. Synthesis of hexahydroxanthene

Hexahydroxanthene, a tricyclic moiety, is present in many schweinfurthins whose stereochemistry was not completely elucidated and hence, its synthesis was of the utmost important (Fig. 2). Previously, Mechoulam and Yagen have reported the cyclisation of geranyl olivetol under harsh reaction conditions using concentrated H_2SO_4 in nitromethane.[37] In addition, an attempt was made to synthesize the hexahydroxanthene core from geranylated phenols by constructing A- and B-rings on the aromatic C-ring in a single step, which resulted in a poor yield, along with byproducts.[38,39]

3.1.1 The Treadwell *et al.* approach (2002). Treadwell *et al.* developed a convenient route for the synthesis of hexahydroxanthene.[40] The presence of phenylthio and phenylselenyl groups at the alpha position, adjacent to the terminal cation on the geranyl chain, might provide substantial stability to the emerging carbocation.[41,42] Based on previous studies, **29** was viewed as a key intermediate for constructing hexahydroxanthene.[43,44]

The synthesis commenced with vanillin (**21**) to give benzaldehyde analogue **23**.[45] The reduction of aldehyde **23** to alcohol **24** followed by protection with triethylsilyl ether afforded **25**,

Table 1 Structures of all schweinfurthins isolated from *Macaranga* species

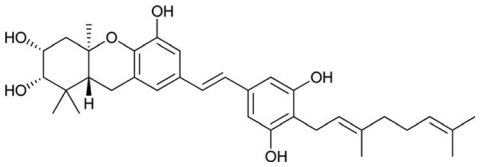
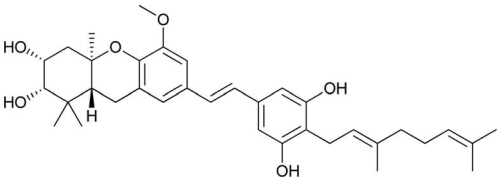
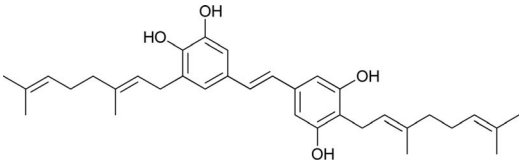
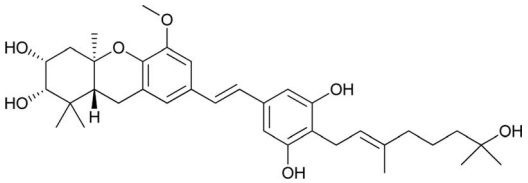
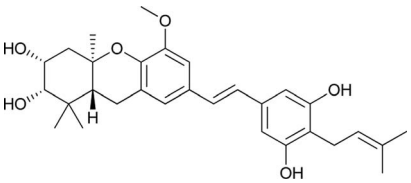
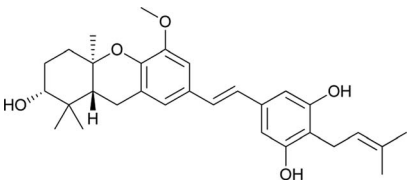
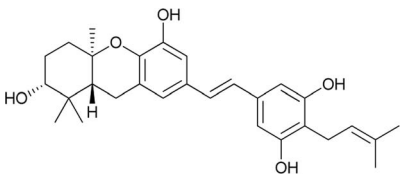
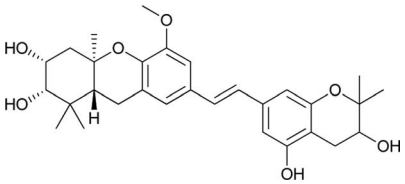
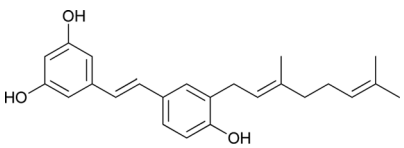
Comp	Name	Structure	Natural source	References
1	Schweinfurthin A		*M. schweinfurthii*	27
2	Schweinfurthin B		*M. schweinfurthii*	27
3	Schweinfurthin C		*M. schweinfurthii*	27
4	Schweinfurthin D		*M. schweinfurthii*	28
5	Schweinfurthin E		*M. alnifolia*	29
6a	Schweinfurthin F		*M. alnifolia*	29
7	Schweinfurthin G		*M. alnifolia*	29
8	Schweinfurthin H		*M. alnifolia*	29
9	Schweinfurthin I		*M. schweinfurthii*	30

Table 1 (*Contd.*)

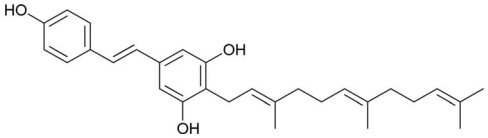
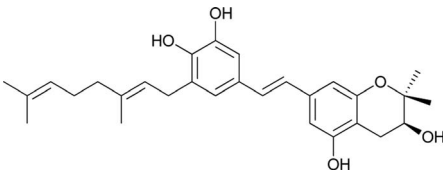
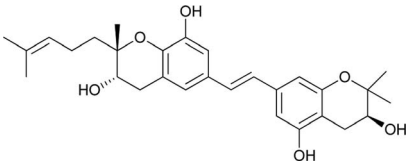
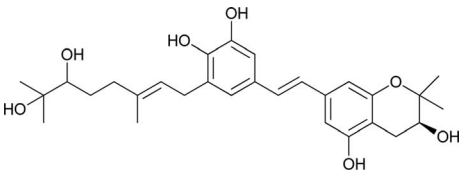
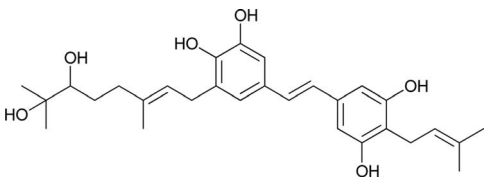
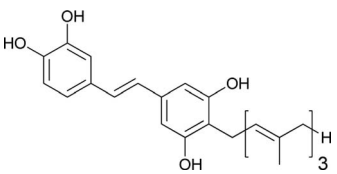
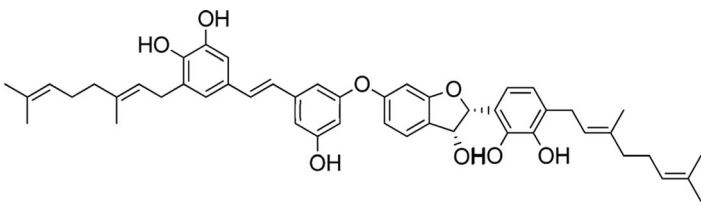
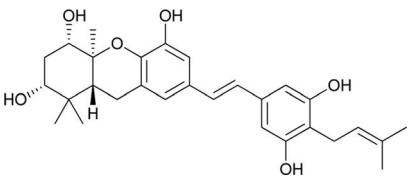
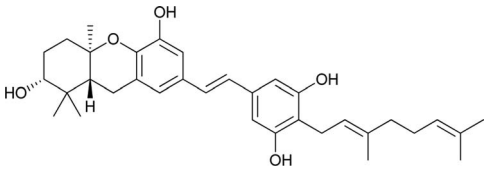
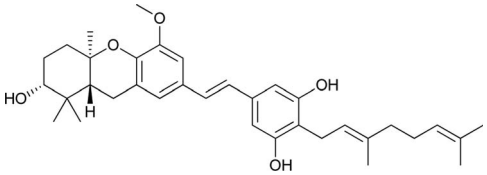
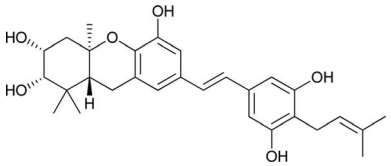
Comp	Name	Structure	Natural source	References
10	Schweinfurthin J		*M. schweinfurthii*	30
11	Schweinfurthin K		*M. tanarius*	31
12	Schweinfurthin L		*M. tanarius*	31
13	Schweinfurthin M		*M. tanarius*	31
14	Schweinfurthin N		*M. tanarius*	31
15	Schweinfurthin O		*M. tanarius*	31
16	Schweinfurthin P		*M. tanarius*	31
17	Schweinfurthin Q		*M. tanarius*	31
18	3-Deoxyschweinfurthin A (3dSA)		—	—

Table 1 (*Contd.*)

Comp	Name	Structure	Natural source	References
19	3-Deoxyschweinfurthin B (3dSB)		—	—
20	(+)-Vedelianin		*M. vedeliana*, *M. alnifolia*	29 and 32

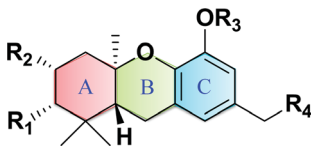
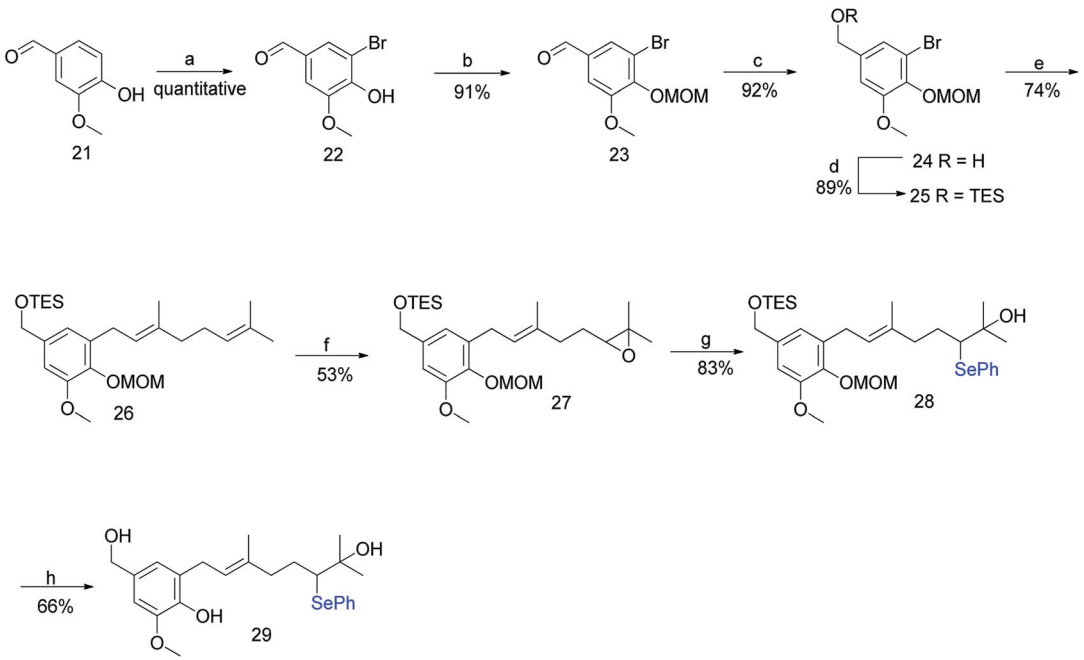


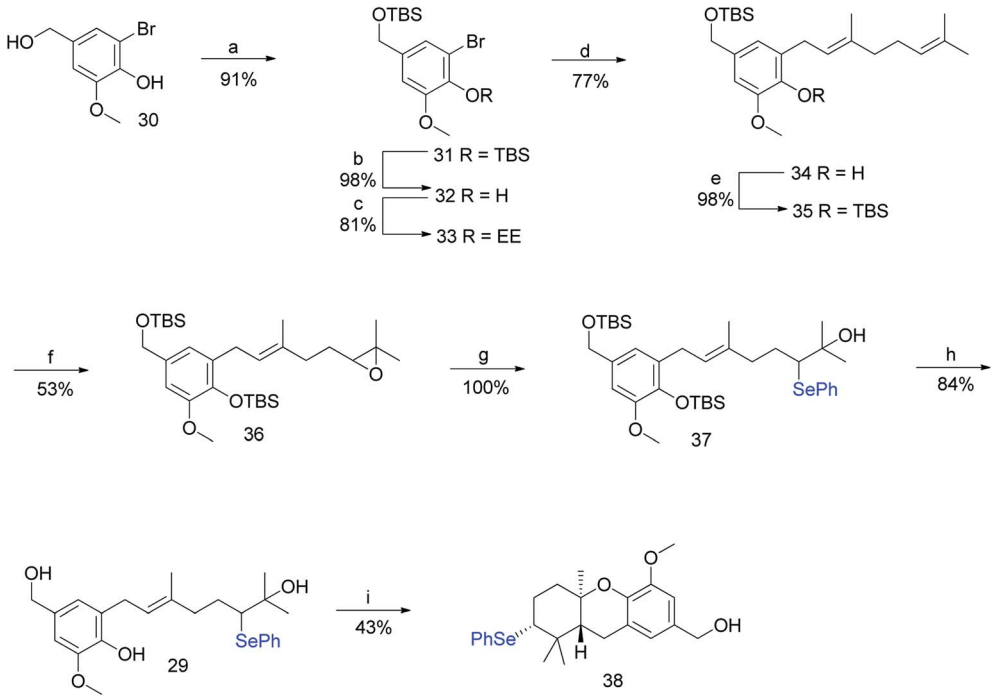
Fig. 2 Hexahydroxanthene moiety.

which upon reacting with geranyl bromide in the presence of *n*-BuLi furnished compound **26** in 74% yield. The *m*-CPBA epoxidation of compound **26** yielded the desired 6,7-epoxide **27** in 53% yield along with traces of 2,3-epoxide. Compound **27** reacted smoothly with a phenyl selenide anion to afford **28**, which upon treatment with 0.5 M HCl (for the deprotection of the silyl ether) and subsequently with 1 M HCl (for the deprotection of MOM) gave hydroxyselenide **29** in 66% yield. The deprotection of both groups in a single step was unsuccessful, resulting in either incomplete deprotection or lower yields along with byproducts (Scheme 1).

To address the deprotection issue, Treadwell *et al.* developed an alternative synthetic route, as shown in Scheme 2. Compound **30** obtained from vanillin was protected with TBS and selectively cleaved to obtain free phenol **32** using TBAF. Compound **32** was protected with ethyl vinyl ether (because silyl group migration from the phenolic oxygen to the adjacent *ortho*-carbon was observed) to give the fully protected compound **33**. The geranylation of **33**, followed by an acidic workup yielded



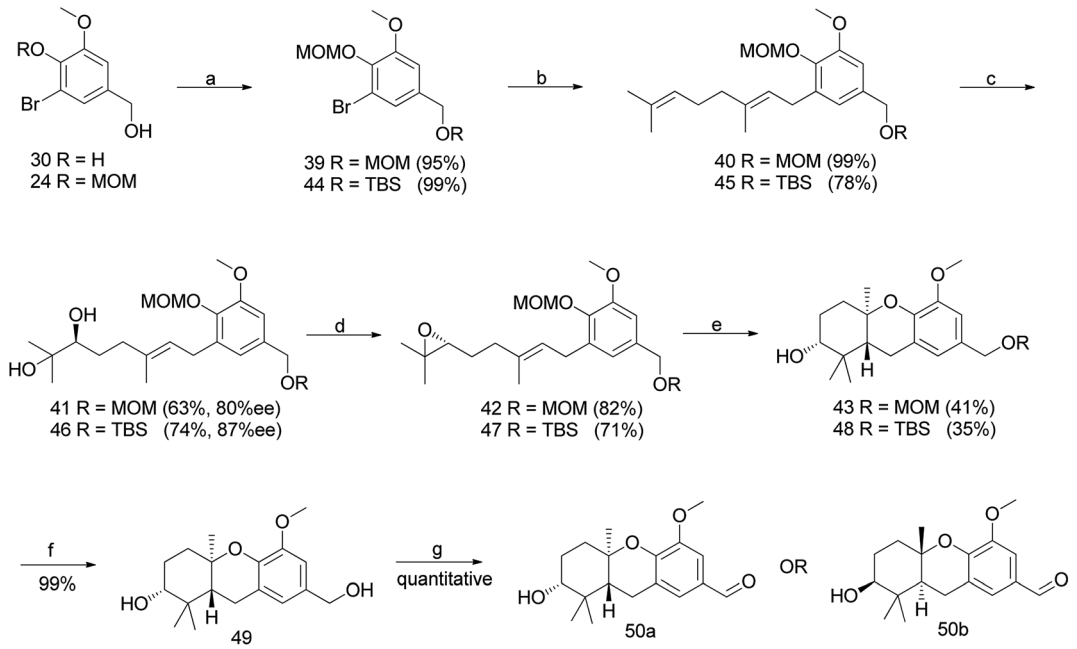
Scheme 1 Synthesis of cyclisation precursor hydroxyselenide (**29**). Reagents and conditions: (a) Br_2, CH_3CO_2H, 25 °C 0.5 h; (b) MOMCl, TBAI, NaH, DMF; (c) LAH, THF, 0 °C, 11 min; (d) TESCl, imidazole, CH_2Cl_2; (e) *n*-BuLi, geranyl bromide, THF, −78 °C; (f) *m*-CPBA, CH_2Cl_2, −30 °C, 30 min; (g) $NaBH_4$, $(PhSe)_2$, EtOH; (h) 0.5 M or 1 M HCl, MeOH, reflux.



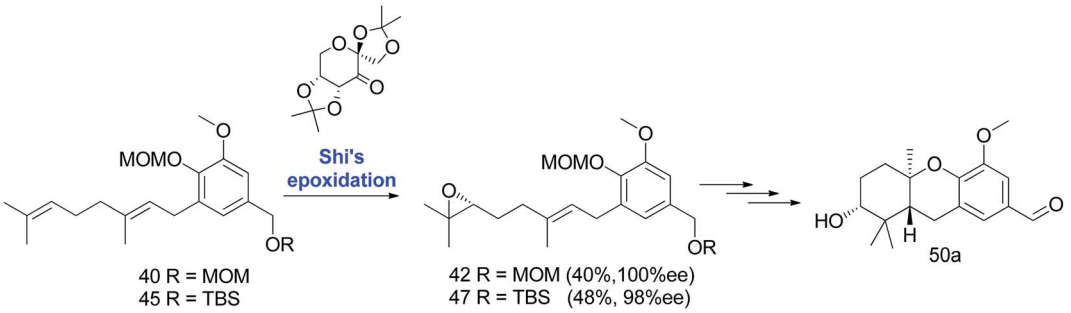
Scheme 2 Synthesis of hexahydroxanthene (**38**). Reagents and conditions: (a) TBSCl, CH_2Cl_2, 18 h; (b) TBAF, THF, 1 h; (c) pyridinium *p*-toluenesulphonate (PPTS), ethyl vinyl ether, CH_2Cl_2, 40 h; (d) *n*-BuLi, geranyl bromide, THF, −78 °C; (e) TBSCl, CH_2Cl_2, 24 h; (f) *m*-CPBA, CH_2Cl_2, −30 °C, 30 min; (g) $NaBH_4$, $(PhSe)_2$, EtOH, 48 h; (h) TBAF, THF, 3 days; (i) TFA, CH_2Cl_2, 24 h.

compound **34**, which was again protected with a silyl ether to afford **35** in 98% yield. A synthetic route similar to Scheme 1 was followed to generate the cyclisation precursor α-hydroxyselenide **29** from **35**. The TFA-induced cyclisation of **29** afforded the tricyclic hexahydroxanthene core (**38**) in 43% yield. The formation of a single diastereomer was confirmed from NMR spectroscopy studies (Scheme 2).

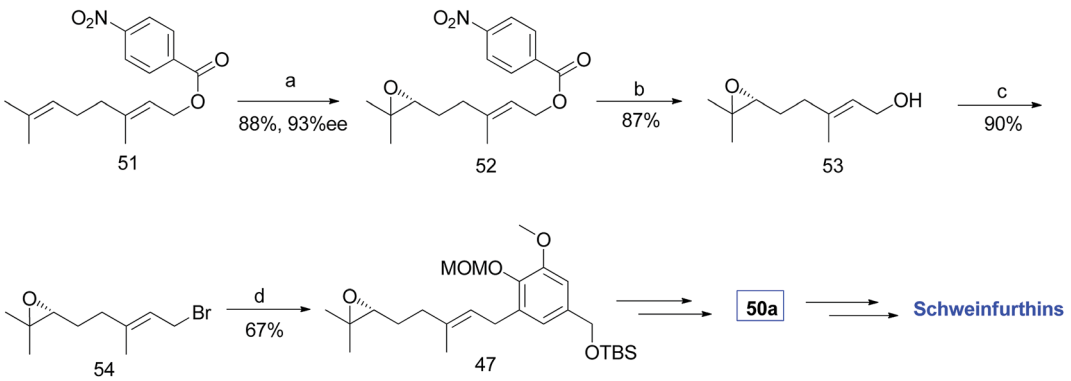
3.1.2 The Neighbors *et al.* approach (2008). The first-generation synthesis of hexahydroxanthene **50a**, involving a cascade cyclisation and asymmetric dihydroxylation, was low



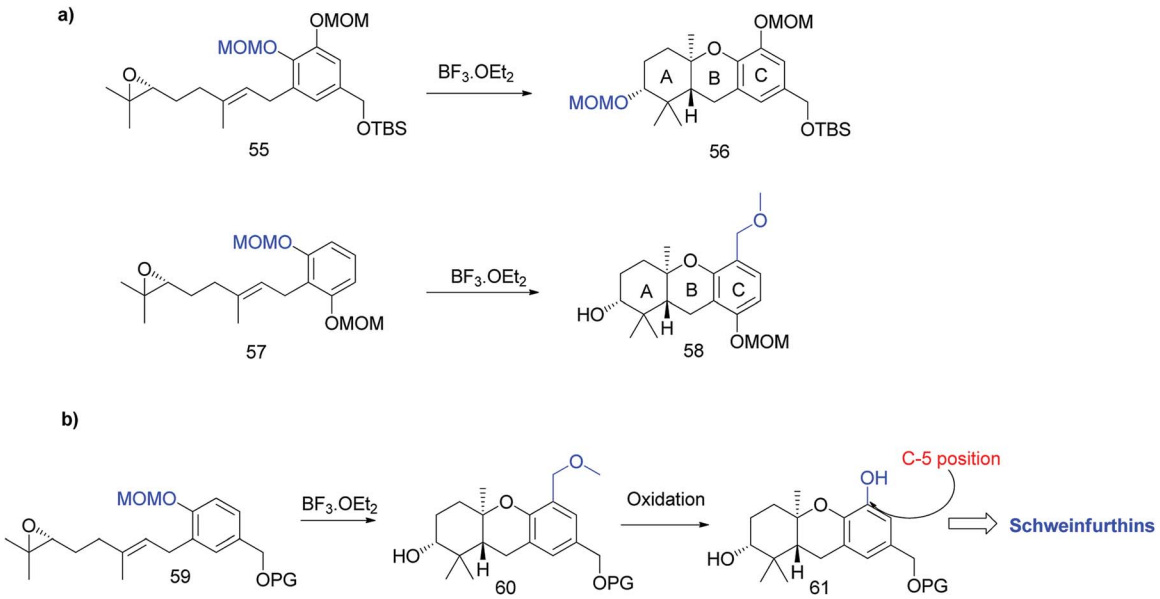
Scheme 3 Synthesis of hexahydroxanthene aldehyde (**50a**) *via* Sharpless dihydroxylation. Reagents and conditions: (a) MOMCl, DIPEA, CH_2Cl_2, 10 h OR TBSCl, imidazole, CH_2Cl_2, 16 h; (b) geranyl bromide, *n*-BuLi, THF, −78 °C; (c) AD-mix-α for **50a** OR AD-mix-β for **50b**, $K_2Os_2O_7$ in H_2O/*t*-BuOH, $CH_3SO_2NH_2$, 4 h; (d) (1) MsCl, NEt_3, CH_2Cl_2, 2 h, (2) K_2CO_3, MeOH, 20 h; (e) TFA, CH_2Cl_2, 1.5 h; (f) TBAF, THF, 1.5 h; (g) MnO_2, CH_2Cl_2.



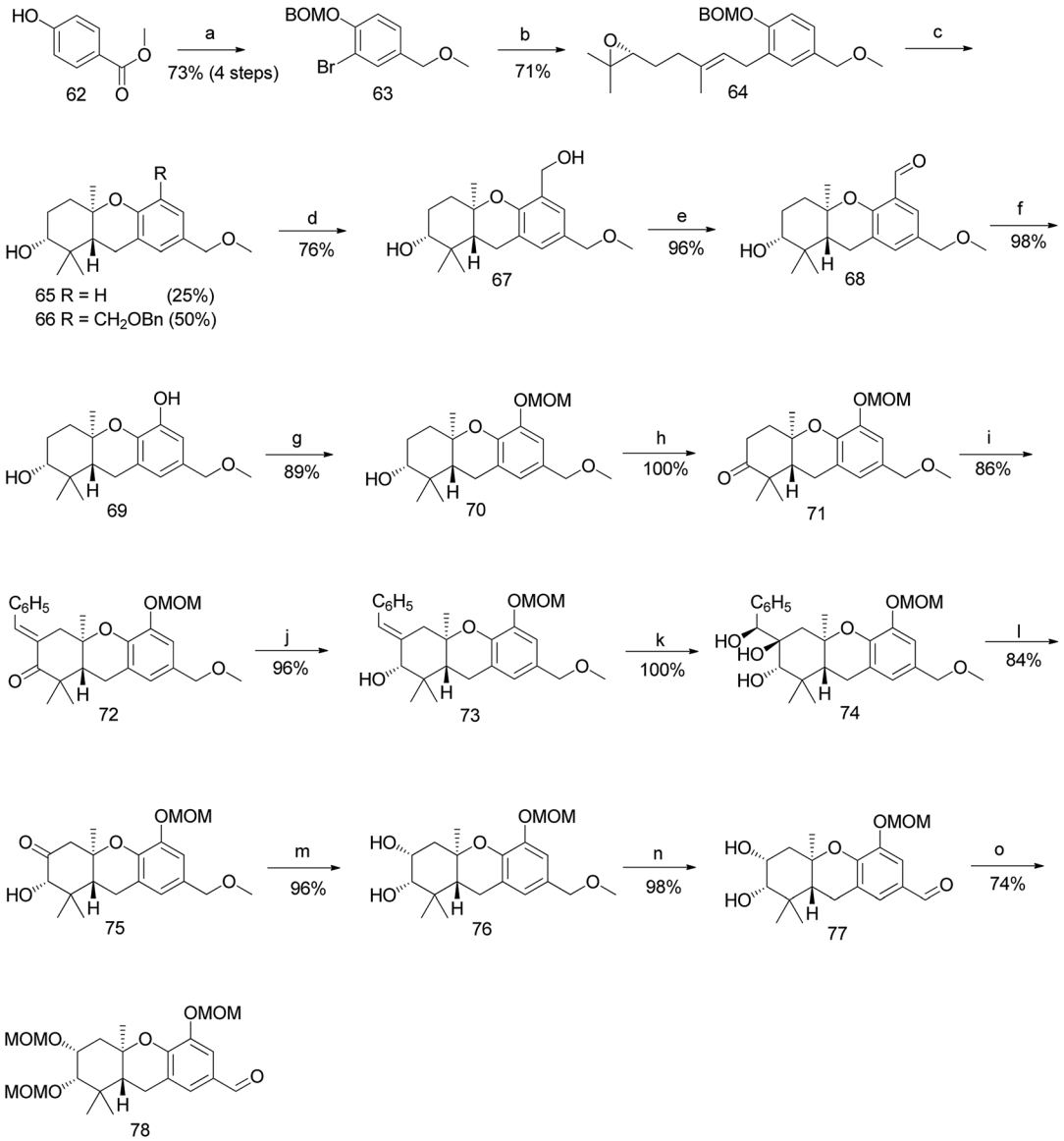
Scheme 4 Synthesis of hexahydroxanthene aldehyde (**50a**) *via* Shi's epoxidation. Reagents and conditions: Shi epoxidation diketal catalyst, buffer solution (2 M K_2CO_3, 0.4 mM EDTA), H_2O_2, CH_3CN:CH_2Cl_2:EtOH.



Scheme 5 Synthesis of *R*-(6,7)-epoxygeranyl bromide (**54**) *via* Shi's epoxidation. Reagents and conditions: (a) Shi epoxidation diketal catalyst, buffer solution (2 M K_2CO_3, 0.4 mM EDTA), H_2O_2, CH_3CN:CH_2Cl_2:EtOH, 3 days; (b) NaOMe, TBAI, MeOH, 2.5 h; (c) (1) MsCl, NEt_3, CH_2Cl_2, 0.5 h; (2) LiBr in THF, 2.5 h; (d) *n*-BuLi, **44**, CuCN, THF, −78 °C.



Scheme 6 Introduction of –OH on aromatic C-ring *via* tandem cascade cyclisation/aromatic substitution. (a) Migration of the MOM group on the A- and C-rings during the $BF_3{\cdot}OEt_2$-mediated cyclisation step; (b) predicted route to introduce –OH onto the C-ring *via* tandem cascade cyclisation/aromatic substitution.



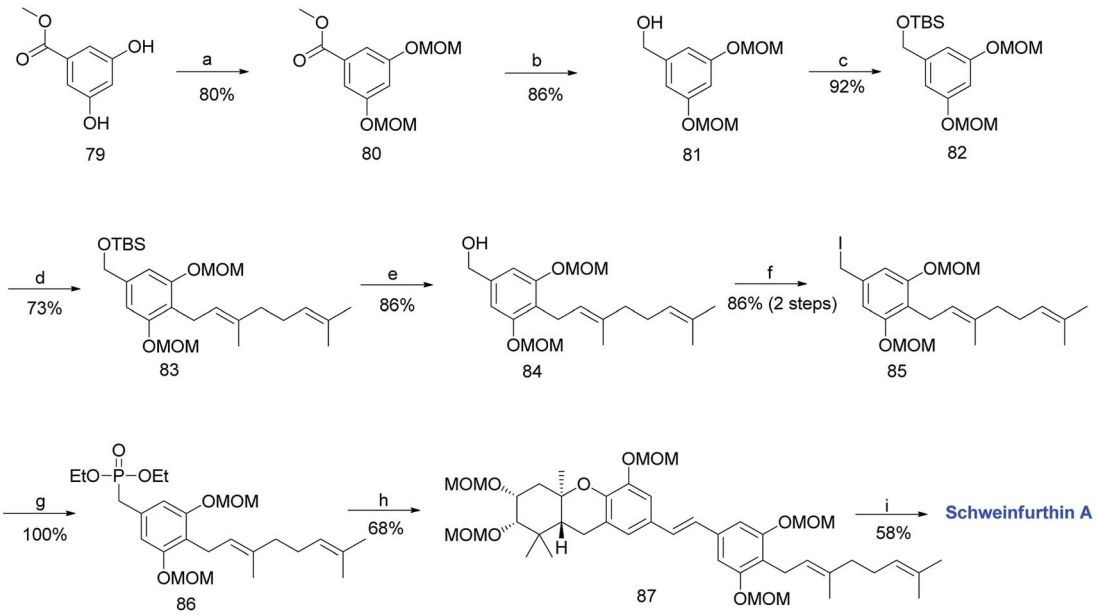
Scheme 7 Synthesis of hexahydroxanthene aldehyde (**78**) by Topczewski *et al.*[50] Reagents and conditions: (a) (1) Br_2, CH_2Cl_2; (2) BOMCl, DIPEA, CH_2Cl_2; (3) $LiBH_4$, ether; (4) MeI, NaH, THF, 5 h; (b) TMEDA, *n*-BuLi, CuI, (*R*)-6,7-epoxy-geranyl bromide **54**, Et_2O, −8 °C; (c) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C, 8 min; (d) H_2, 10% Pd/C, MeOH, 23 h; (e) $MnO_2{\cdot}CH_2Cl_2$, 20 h; (f) (1) *m*-CPBA, CH_2Cl_2, 2 h; (2) K_2CO_3, 20 h; (g) MOMCl, DIPEA, CH_2Cl_2; 2 h; (h) catalytic TPAP, NMO, CH_2Cl_2, 26 h; (i) PhCHO, KOH, EtOH, 25 min; (j) $CeCl_3{\cdot}7H_2O$, $NaBH_4$, MeOH, 2 h; (k) OsO_4, *t*-BuOH, NMO, dioxane:H_2O, 17 h; (l) $NaIO_4$, CH_2Cl_2:H_2O, 24 h; (m) $NaBH_4$, MeOH:THF, 15 min; (n) DDQ, CH_2Cl_2:H_2O, 15 min; (o) MOMCl, DIPEA, CH_2Cl_2, 5 h.

in yield, with 16 steps required from vanillin (10% overall yield).[46] Considering the productivity, Neighbors *et al.* developed efficient synthetic routes for the preparation of a geranyl epoxide ring.[47]

3.1.2.1 A change in protective group strategy. The sharpless dihydroxylation of a MOM-protected compound **40** gave diol **41**, which was transformed to epoxide **42** using a previously developed protocol.[46] Acid catalysed cyclisation using TFA afforded compound **43**; however, the deprotection of an intransigent benzylic MOM group was not observed as anticipated. Hence, the reaction sequence was repeated using TBS as a protecting group to obtain compound **48.** Furthermore, the deprotection of TBS using TBAF gave benzyl alcohol **49**, which upon benzylic oxidation using MnO_2 cleanly afforded aldehyde **50a** in 9% overall yield from vanillin (enantiomer **50b** was synthesized *via* the same route using AD-mix-β) (Scheme 3).[47]

3.1.2.2. Epoxide generation via Shi epoxidation. In addition, Neighbors *et al.* used a conventional synthetic protocol to install the epoxide stereocenter. There has been a successful attempt of enantioselective epoxidation on the aromatic esters of isoprenoids. Owing to the previous work, the epoxidation of **40** and **45** using Shi epoxidation[48,49] yielded **42** and **47** in 40% and 48% yield (>98% ee), respectively. Shi epoxidation was found to be advantageous for reducing the number of required steps with an improved overall yield (Scheme 4).[47]

3.1.2.3 Synthesis of R-(6,7)-epoxygeranyl bromide via Shi epoxidation. Neighbors *et al.* also developed an alternative route by eliminating the epoxidation step in the primary synthetic



Scheme 8 Synthesis of schweinfurthin A by Topczewski *et al.*[50] Reagents and conditions: (a) MOMCl, NaH, DMF, 4 h; (b) LAH, THF, 30 min; (c) TBSCl, imidazole, CH_2Cl_2, 12 h; (d) *n*-BuLi, TMEDA, CuCN, geranyl bromide, THF, −78 °C; (e) TBAF, THF, 3 h; (f) (1) MsCl, NEt_3, CH_2Cl_2, 1 h; (2) NaI, acetone, 22 h; (g) $P(OEt)_3$, reflux, 2.5 h; (h) (1) DIPEA, *n*-BuLi, aldehyde **78**, THF, 2 h (little progress in reaction); (2) KHMDS, 2 h; (i) *p*-TsOH, MeOH.

route and synthesized *R*-(6,7)-epoxygeranyl bromide **54** by Shi epoxidation. The treatment of epoxybromide **54** with aryl bromide **44** using lithium–halogen exchange gave **47** in 67% yield, which could be converted to aldehyde **50a** (Scheme 5).[47]

3.2. Synthesis of schweinfurthin A (2011)

Topczewski *et al.* reported the total synthesis of schweinfurthin A (**1**), which is a potent compound in this family.[50] Previous studies have reported the migration of the MOM group to the hydroxyl group of the A-ring during cascade cyclization (**56**). In addition, an electrophilic aromatic substitution occurs forming a new carbon–carbon bond by migration of the MOM group to an adjacent aromatic C-ring (**58**) (Scheme 6a).[51] Hence, it was envisaged that the boron trifluoride etherate ($BF_3 \cdot OEt_2$)-mediated cyclisation[52] on MOM-protected epoxide **59** may afford hexahydroxanthene **60** with the MOM group moving to the C-5 position, from which intermediate **61** with a phenolic functionality could be obtained by oxidation (Scheme 6b).

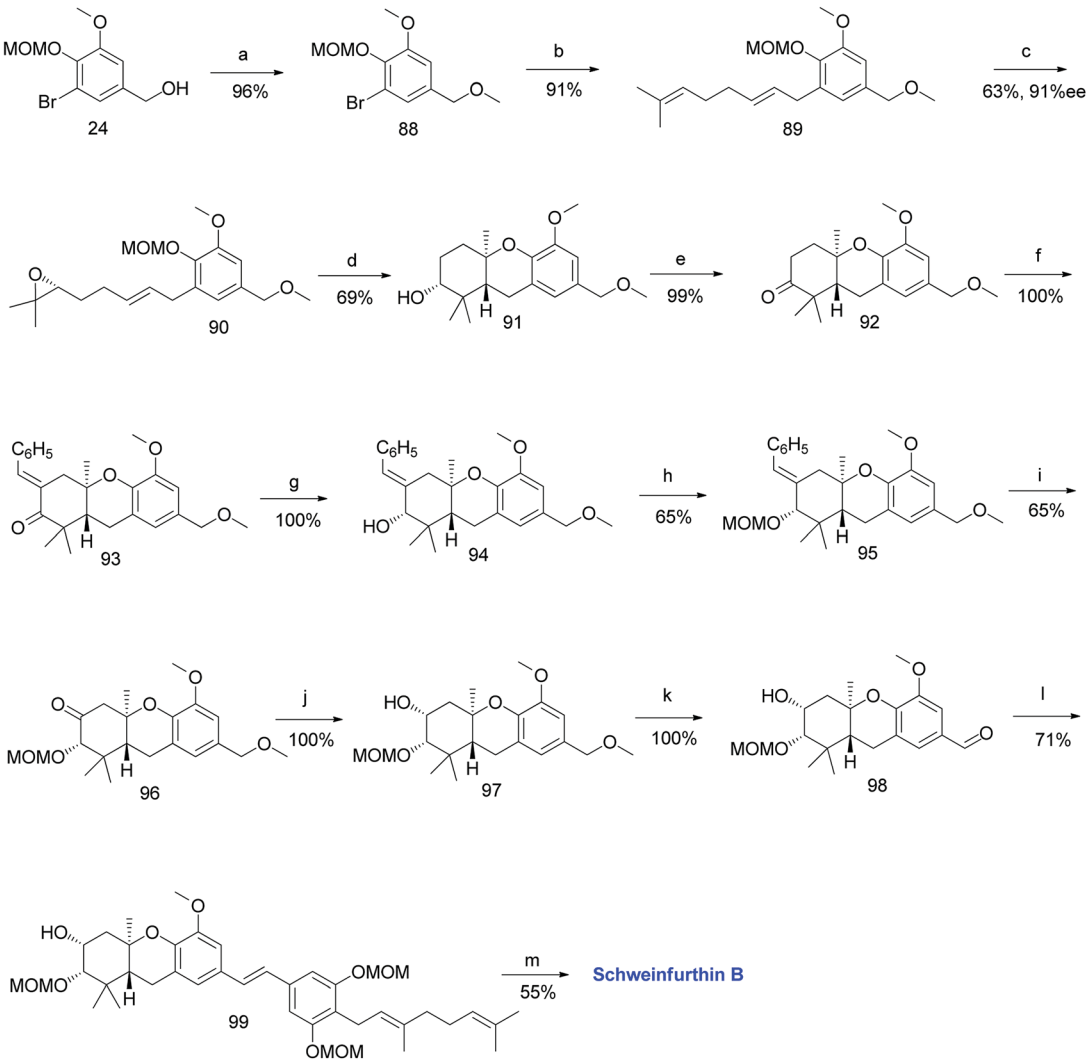
Accordingly, a compound possessing an (*R*)-6,7-epoxygeranyl chain (**64**) was synthesized from 4-hydroxybenzoate (**62**) in 5 steps (93% ee). The $BF_3 \cdot OEt_2$-mediated cascade cyclisation gave an inseparable mixture of **65** and **66** in 25% and 50% yield, respectively. A BOM acetal was chosen as the protecting group because it could be selectively deprotected by hydrogenolysis after being transferred to the C-5 position of the aromatic C-ring. Compounds **65** and **66** were separated by selective hydrogenolysis to afford benzylic alcohol **67** in 76% yield. Furthermore, the chemo-selective benzylic oxidation of **67** gave the corresponding aldehyde **68**, which upon subsequent Baeyer–Villiger oxidation with *m*-CPBA and hydrolysis of formate yielded compound **69** in 98% yield. The –OH functionality was successfully introduced at the C-5 position of the aromatic C-ring, and protection with MOM gave **70** in 89% yield (Scheme 7).

The oxidation of hexahydroxanthene **70** under Ley's conditions gave ketone **71**, which was subjected to aldol condensation with benzaldehyde to give enone **72**, followed by Luche reduction to afford alcohol **73**. Compound **73** was subjected to Upjohn dihydroxylation to give triol **74**, which upon glycolytic cleavage in the presence of $NaIO_4$ yielded ketone **75**. The diastereoselective reduction of **75** using $NaBH_4$ gave diol **76**, and subsequent DDQ oxidation of the methyl ether on the aromatic C-ring gave the intermediate aldehyde **77**. The obtained aldehyde was protected with the MOM group to give aldehyde **78** in 74% yield (Scheme 7).

The required phosphonate ester **86** was synthesized, as depicted in Scheme 8.[53,59] The synthesis began with the MOM-protection of commercially available phenolic ester **79** to obtain compound **80**, followed by reduction to give benzyl alcohol **81**. Furthermore, compound **81** was protected with a TBS group to afford **82**. The metalation of **82** with *n*-BuLi and TMEDA in the presence of copper cyanide (CuCN), followed by a subsequent reaction with geranyl bromide gave **83**. The TBS deprotection of compound **83** using TBAF yielded benzylic alcohol **84** in 86% yield, which was sequentially converted to phosphonate ester **86** by treatment with methanesulfonyl chloride (MsCl), followed by iodination, and subjecting it to the Arbuzov reaction with $P(OEt)_3$. The phosphonate ester **86** was condensed with MOM-protected aldehyde **78** using an HWE olefination in the presence of KHMDS as a base to give protected (*E*)-stilbene **87**. Finally, deprotection of the MOM groups under acidic conditions afforded schweinfurthin A (**1**) in 58% yield (Scheme 8).

3.3. Synthesis of schweinfurthin B (2009)

Topczewski *et al.* reported the synthesis of schweinfurthin B (**2**) by eliminating the established desilylation/oxidation



Scheme 9 Synthesis of schweinfurthin B by Topczewski *et al.*[54] Reagents and conditions: (a) NaH, MeI, THF, 3 h; (b) *n*-BuLi, geranyl bromide, THF, −78 °C; (c) Shi epoxidation diketal catalyst, buffer solution (2 M K_2CO_3, 0.4 mM EDTA), H_2O_2, CH_3CN:CH_2Cl_2:EtOH, 10 h; (d) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C, 7 min; (e) NMO, TPAP, CH_2Cl_2, 18.5 h; (f) benzaldehyde, KOH, EtOH, 2 h. (g) $CeCl_3{\cdot}7H_2O$, $NaBH_4$, CH_3OH, 20 min; (h) MOMCl, DIPEA, CH_2Cl_2, 15 h; (i) $KMnO_4$, $NaHCO_3$, acetone, 20 h; (j) $NaBH_4$, CH_3OH, 10 min; (k) DDQ, CH_2Cl_2:H_2O, 80 min; (l) NaH, phosphonate ester **86**, 15-crown-5, THF; (m) *p*-TsOH, MeOH.

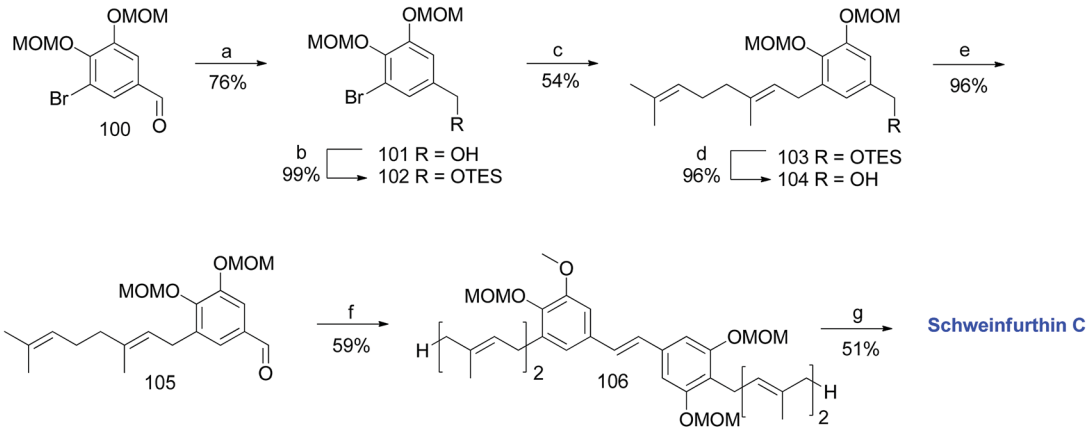
sequence.[54] Benzyl alcohol **24** was protected with a benzyl methyl ether and converted to tricyclic compound **91** *via* Shi epoxidation followed by a $BF_3{\cdot}OEt_2$-mediated cascade cyclisation. The oxidation of compound **91** under Ley's conditions afforded ketone **92**. The aldol condensation of compound **92** with benzaldehyde gave enone **93**, which upon treatment with $OsO_4/NaIO_4$ resulted in an undesirable acetal compound; however, the reduction under Luche conditions afforded the required alcohol **94**. The configuration was evident from NOESY correlations. The oxidation of MOM-protected compound **95** using excess $KMnO_4$ gave ketone **96**, and subsequent $NaBH_4$ reduction yielded secondary alcohol **97**, which upon DDQ oxidation of the methyl ether gave aldehyde **98** in excellent yield. The HWE olefination of phosphonate ester **86** with aldehyde **98** yielded (*E*)-stilbene **99**, which upon deprotection of the MOM groups gave schweinfurthin B (**2**) in 55% yield (Scheme 9).[54]

3.4. Synthesis of schweinfurthin C (1999)

The first total synthesis of schweinfurthin C (**3**) was reported in 1999 by Treadwell *et al.*[53] TES-protected benzylic alcohol **102** was synthesized from the known aldehyde **100**, readily prepared from vanillin.[55–57] Furthermore, a geranyl moiety was installed *via* lithium–halogen exchange using *n*-BuLi and geranyl bromide to give **103**, which upon deprotection followed by PDC oxidation afforded aldehyde **105** in 96% yield. The HWE olefination of phosphonate ester **86** with aldehyde **105** selectively gave (*E*)-stilbene **106**, and deprotection of the MOM groups afforded schweinfurthin C (**3**) in 51% yield (Scheme 10).

3.5. Synthesis of schweinfurthin E (2009)

Topczewski *et al.* reported the synthesis of schweinfurthin E (**5**) using the same synthetic route as schweinfurthin B.[54] A phosphonate ester **108** was synthesized using the reported method.[58,59] A prenyl group was introduced by directed *ortho*-



Scheme 10 Synthesis of schweinfurthin C by Treadwell *et al.*[53] Reagents and conditions: (a) LAH, Et_2O, 0 °C, 10 min; (b) TESCl, CH_2Cl_2, 22 h; (c) *n*-BuLi, geranyl bromide, Et_2O, −78 °C; (d) TBAF, THF, 5 h; (e) PDC, CH_2Cl_2, 2.5 h; (f) phosphonate ester **86**, NaH, THF, 30 min; (g) 3 M HCl, MeOH, reflux, 24 min.

metalation on the known benzylic alcohol **81** to afford compound **107**. Compound **107** was sequentially converted to the desired phosphonate ester **108**, as depicted in Scheme 11. Phosphonate ester **108** and aldehyde **98** were condensed using HWE olefination to give protected (*E*)-stilbene **109**, which was then deprotected under acidic conditions to obtain schweinfurthin E (**5**) in 81% yield (Scheme 11).

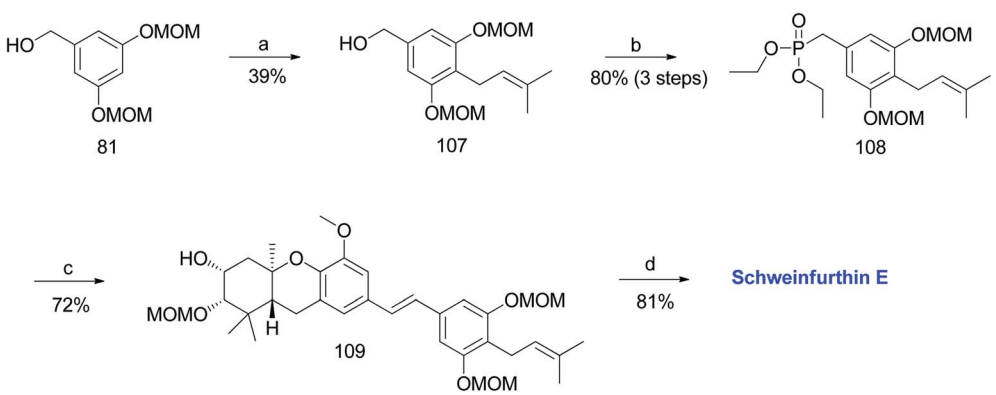
3.6. Synthesis of schweinfurthin F (2007)

Mente *et al.* reported the synthesis of two enantiomers of schweinfurthin F in 2007.[58] Having established the synthetic route for aldehydes **50a,b** and phosphonate ester **108**, HWE olefination followed by the acid-catalysed removal of the MOM groups afforded both the enantiomers schweinfurthin F [(*R*,*R*,*R*)-enantiomer **6a** (69% yield) and (*S*,*S*,*S*)-enantiomer **6b** (53% yield)]. Optical rotations and bioassay results indicated the formation of the **6a** enantiomer, which is the natural form of schweinfurthin F (Scheme 12).

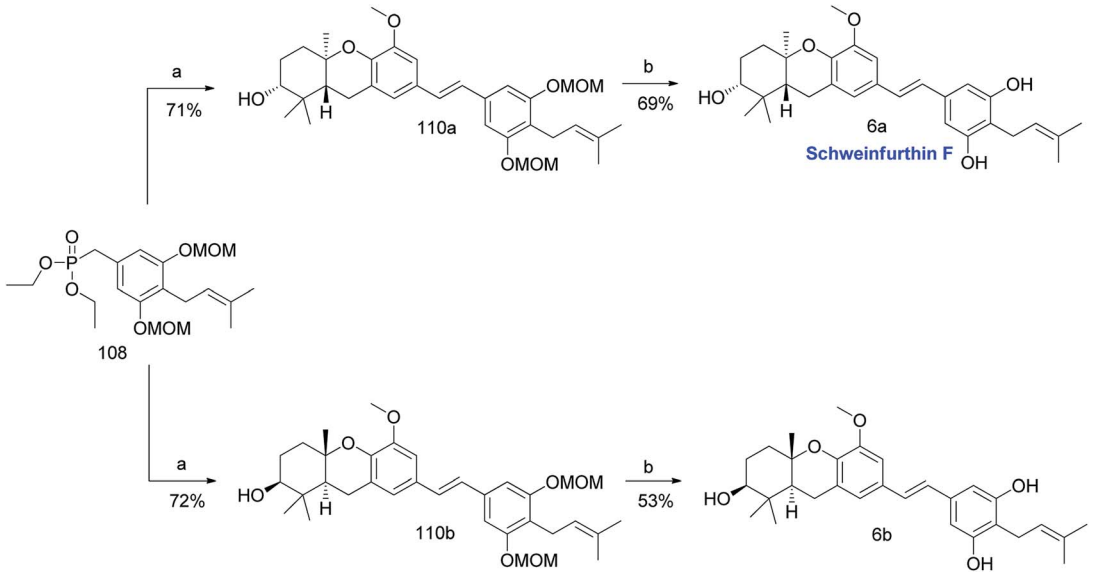
3.7. Synthesis of schweinfurthin G (2008)

Mente *et al.* reported the synthesis of schweinfurthin G (**7**) *via* an efficient cascade cyclisation using $BF_3 \cdot Et_2O$ as a Lewis acid.[52] Initially, several Lewis acids were examined to cyclize epoxide **47**, such as $Ti(OiPr)_4$, $TiCl_4$, $SnCl_4$, $MeAlCl_2$, $In(OTf)_3$ and $BF_3 \cdot Et_2O$. The best result was obtained with the use of $BF_3 \cdot Et_2O$, and the cascade cyclisation was convenient and productive at larger scales. Using this approach, hexahydroxanthene was obtained in excellent yield (~75%) compared with the protic acid-catalysed cyclisation (30–40%).[60–64]

The MOM-protected aldehyde **100** was sequentially converted to epoxide **55** *via* Shi epoxidation. The cascade cyclisation was achieved by reacting with $BF_3 \cdot Et_2O$ to give hexahydroxanthenes **113** and **56** in 52% and 30% yield, respectively. The formation of the A-ring MOM ether **56** was observed due to the reaction of the $CH_3OCH_2^+$ cation with the nucleophilic oxygen of the C-2 hydroxyl group during cyclisation. The deprotection of TBS using TBAF gave compound **114**, which upon benzylic



Scheme 11 Synthesis of schweinfurthin E by Topczewski *et al.*[54] Reagents and conditions: (a) *n*-BuLi, TMEDA, CuBr.DMS, prenyl bromide, −20 °C, 4 h, THF; (b) (1) NEt_3, MsCl, CH_2Cl_2, 4.5 h; (2) NaI, acetone, 13.5 h; (3) $P(OEt)_3$, 100 °C, 4 h; (c) NaH, aldehyde **98**, 15-crown-5, THF; (d) *p*-TsOH, MeOH.



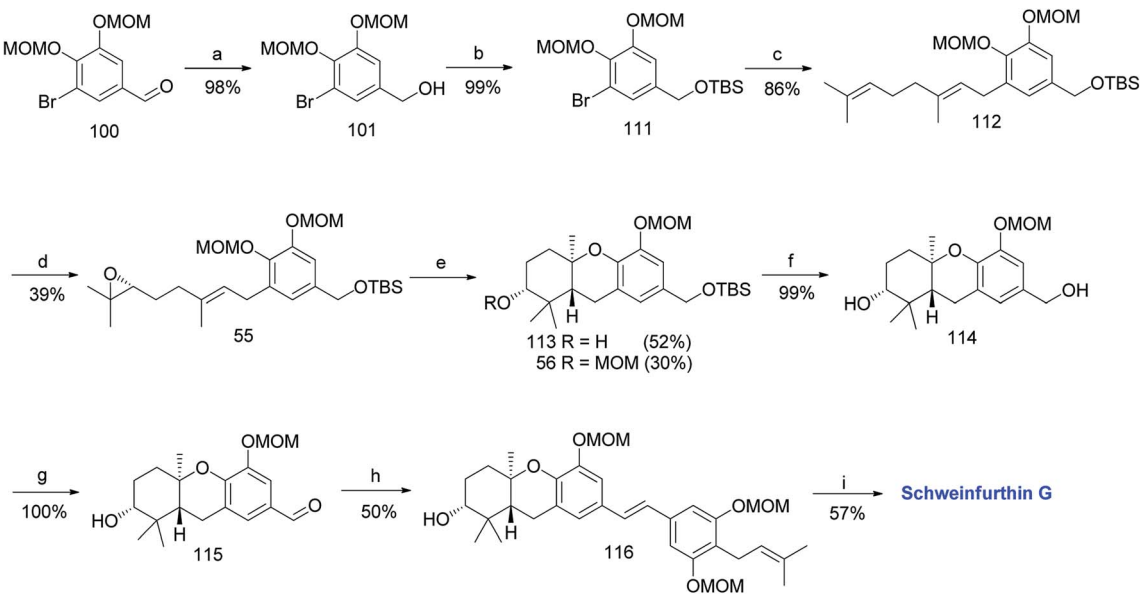
Scheme 12 Synthesis of schweinfurthin F by Mente *et al.*[58] Reagents and conditions: (a) **50a** or **50b**, NaH, 15-crown-5, THF, 0 °C to rt, 24 h; (b) CSA, MeOH, rt for 16 h, 55 °C for 3.5 h.

oxidation using MnO_2 furnished aldehyde **115** in excellent yield. The HWE olefination of phosphonate ester **108** with aldehyde **115** yielded (*E*)-stilbene **116**, which upon MOM-deprotection gave schweinfurthin G (**7**) in 57% yield (Scheme 13).

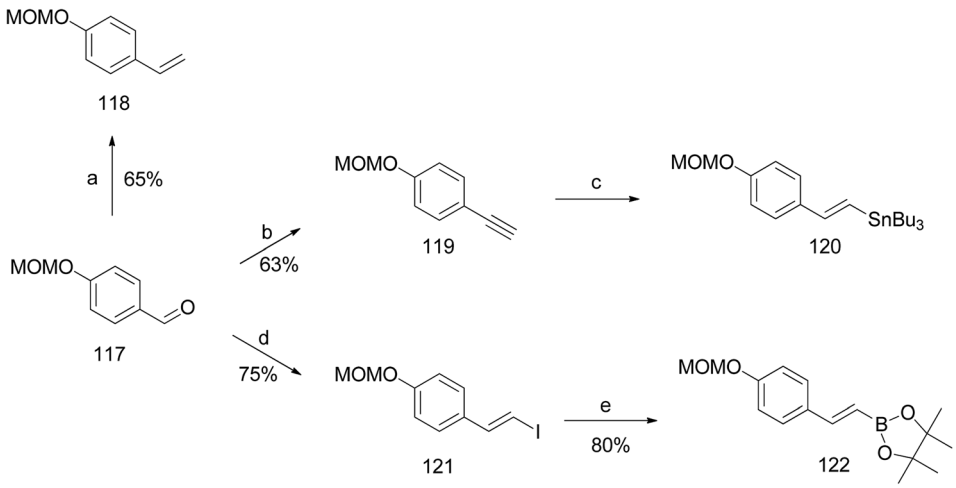
3.8. Synthesis of schweinfurthin J (2012)

Argade *et al.* reported the synthesis of farnesylated stilbene schweinfurthin J (**10**).[65] The required coupling partners for Heck (**118**), Stille (**120**), Suzuki (**122**), and Sonogashira (**119**) coupling reactions were synthesized from aldehyde **117**, as outlined in Scheme 14. A standard Wittig reaction with MOM-protected aldehyde **117** gave alkene **118** in 65% yield. The treatment of aldehyde **117** with the Bestmann–Ohira reagent gave **119**, and followed by radical hydrostannation yielded stannane **120**. Additionally, Takai olefination of aldehyde **117** afforded vinyl iodide **121**, which was subsequently converted to pinacolborane **122** in 80% yield (Scheme 14).

The phenolic compound **123** was alkylated using farnesyl bromide to give **124**, followed by Claisen rearrangement to give *p*-farnesylated compound **125**. The free phenolic group was



Scheme 13 Synthesis of schweinfurthin G by Mente *et al.*[52] Reagents and conditions: (a) $NaBH_4$, THF; (b) TBSCl, imidazole, CH_2Cl_2, 15 h; (c) *n*-BuLi, geranyl bromide, Et_2O, −78 °C, 16 h; (d) Shi epoxidation diketal catalyst, buffer solution (2 M K_2CO_3, 0.4 mM EDTA), H_2O_2, CH_3CN:CH_2Cl_2:EtOH, 22 h; (e) $BF_3 \cdot Et_2O$, CH_2Cl_2, 3.5 min; (f) TBAF, THF; (g) MnO_2, CH_2Cl_2, 16.5 h; (h) NaH, phosphonate ester **108**, 15-crown-5, THF; (i) *p*-TsOH, MeOH.



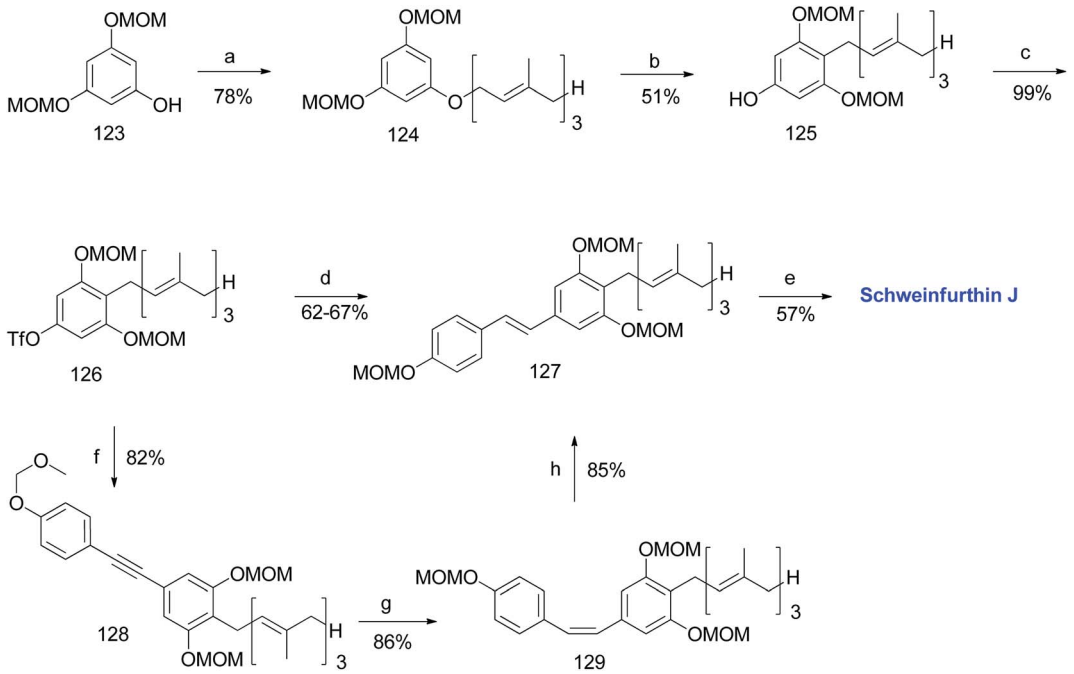
Scheme 14 Synthesis of intermediates **118–120** and **122**. Reagents and conditions: (a) *n*-BuLi, $MePPh_3I$, THF, 24 h; (b) Bestmann–Ohira reagent, K_2CO_3, MeOH, 24 h; (c) *n*-Bu_3SnH, AIBN, 80 °C, 12 h; (d) $CrCl_2$, CHI_3, dioxane:THF, 0 °C, 2 h; (e) *t*-BuLi, boronate, THF, −78 °C, 2 h.

converted to a triflyloxy-leaving group, resulting in the formation of intermediate **126** in modest yield, which underwent Heck, Stille, or Suzuki coupling reactions with the respective coupling partners to yield protected (*E*)-stilbene **127** (62–67% yield). Finally, the acid-catalysed deprotection of **127** afforded schweinfurthin J (**10**) in 57% yield. Alternatively, the Sonogashira coupling of **119** and triflate **126** yielded alkyne **128**, which upon reduction gave *cis*-stilbene **129** using $Pd(OAc)_2$ in the presence of KOH in dimethylformamide (DMF). The isomerization of *cis*-stilbene **129** to *trans*-stilbene **127** (85% yield) was achieved using $Pd(MeCN)_2Cl_2$ as a catalyst (Scheme 15).

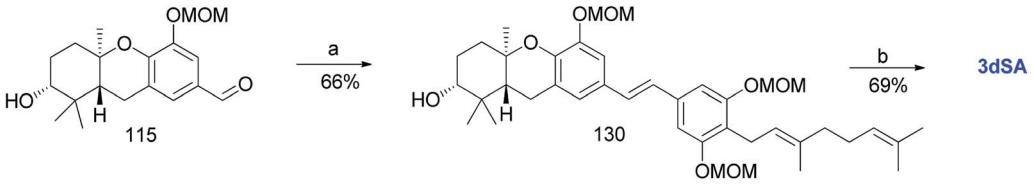
3.9. Synthesis of 3-deoxyschweinfurthin A (3dSA) (2008)

Mente *et al.* reported the synthesis of 3dSA (**18**) from aldehyde **115** and phosphonate ester **86**, similar to that of schweinfurthin G (Scheme 16).[52]

Additionally, Mente *et al.* utilised the byproduct compound **56** and transformed it into the phosphonate ester **132**. The MOM-protected geranyl aldehyde **133** was synthesized by according to a reported procedure[66] and was condensed with phosphonate ester **132** using an HWE reaction to give (*E*)-stilbene **134**. Finally, deprotection of the MOM groups under acidic conditions gave 3dSA (**18**) in 52% yield (Scheme 17).[52]



Scheme 15 Synthesis of schweinfurthin J by Argade *et al.*[65] Reagents and conditions: (a) K_2CO_3, farnesyl bromide, DMF, 12 h; (b) DMA, 200 °C, 3 h; (c) Tf_2O, pyridine, CH_2Cl_2, −20 °C, 2 h; (d) (1) Heck coupling: **118**, $Pd(OAc)_2$, Ph_3P, Et_3N, MeCN, 85 °C, 24 h, 63%; (2) Stille coupling: **120**, $Pd(PPh_3)_4$, LiCl, DMF, 120 °C, 8 h, 67%; (3) Suzuki coupling: **122**, $Pd(PPh_3)_4$, Na_2CO_3, dioxane:H_2O, 90 °C, 8 h, 66%; (e) CSA, MeOH; 12 h; (f) Sonogashira coupling: **119**, $PdCl_2(PPh_3)_2$, CuI, TBAI, DMF:Et_3N, 70 °C, 1.5 h; (g) $Pd(OAc)_2$, KOH, DMF; (h) $Pd(MeCN)_2Cl_2$, CH_2Cl_2, 25 °C, 12 h.



Scheme 16 Synthesis of 3-deoxyschweinfurthin A (3dSA) by Mente *et al.*[52] Reagents and conditions: (a) NaH, phosphonate ester **86**, 15-crown-5, THF; (b) *p*-TsOH, MeOH.

3.10. Synthesis of 3-deoxyschweinfurthin B (3dSB)

3.10.1 The Neighbors *et al.* approach (2005). Neighbors *et al.* reported the first synthesis of 3dSB (**19**) while targeting the synthesis of a natural product, schweinfurthin B.[46] The regioselective dihydroxylation on the terminal olefin of compound **35** *via* Sharpless dihydroxylation gave the desired diol **135** in 68% yield with 83% ee. The (*S*) configuration was assigned to the new asymmetric centre in diol **135**, which was confirmed by treating it with the (*S*)- and (*R*)-enantiomers of *O*-methylmandelic acid under standard mixed anhydride coupling conditions, followed by spectroscopic studies. The diol **135** was transformed to non-racemic epoxide **136**, as depicted in Scheme 18, in 75% yield, followed by deprotection of TBS using TBAF to afford **137**. Furthermore, acid-catalysed cyclisation gave the expected tricyclic core **49** in 38% yield, which upon benzylic oxidation using MnO_2 gave aldehyde **50a**. The HWE olefination reaction between phosphonate ester **86** and aldehyde **50a** yielded protected (*E*)-stilbene **138** and deprotection with camphorsulfonic acid (CSA) afforded 3dSB (**19**) in 77% yield (Scheme 18).

3.10.2 Mente *et al.* approach (2008). Mente *et al.* synthesized 3dSB (**19**) using an alternative route similar to that of 3dSA (Scheme 18).[52] Phosphonate ester **132** and MOM-protected geranyl aldehyde **133** were condensed using an HWE olefination to give (*E*)-stilbene **139**, which was deprotected under acidic conditions to yield 3dSB (**19**) in 81% yield (Scheme 19).

3.11. Synthesis of (+)-vedelianin (2011)

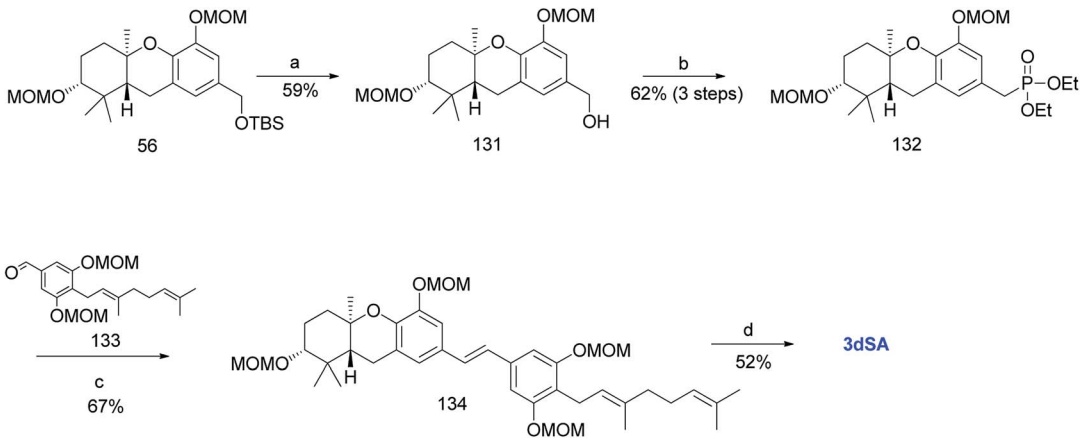
Topczewski *et al.* reported the synthesis of (+)-vedelianin (**20**) using a synthetic route similar to that of schweinfurthin A. A MOM-protected aldehyde **78** was synthesized from **101** *via* Shi epoxidation and a $BF_3 \cdot OEt_2$-mediated cyclisation. The HWE olefination of phosphonate ester **108** with aldehyde **78** selectively yielded (*E*)-stilbene **141**, which upon MOM-deprotection afforded (+)-vedelianin (**20**) (Scheme 20).[67]

4. Biological activities

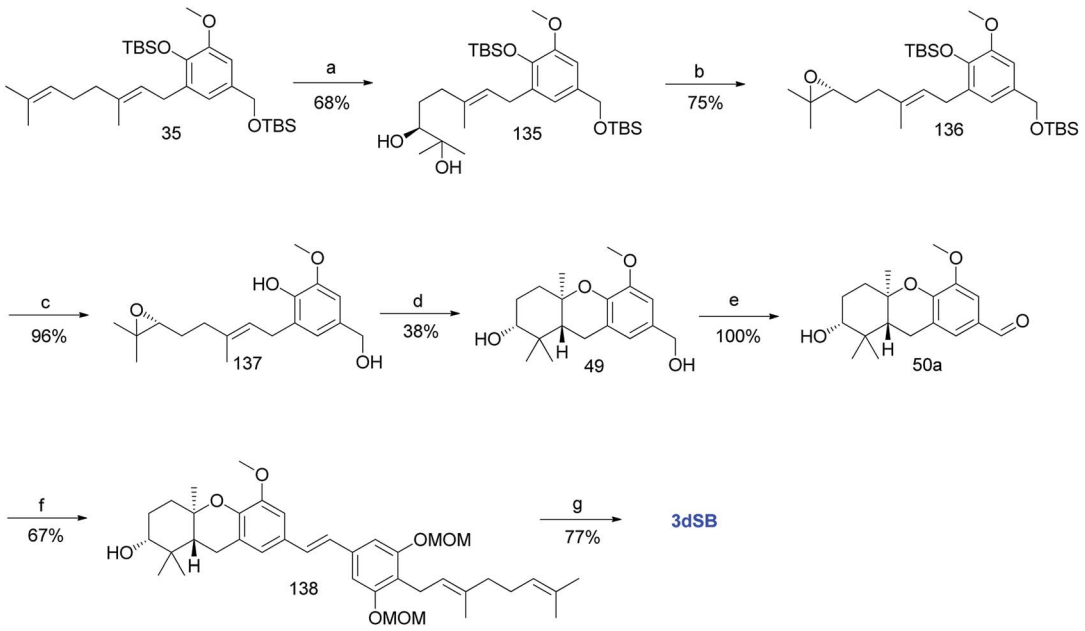
Schweinfurthins have shown a wide range of bioactivities, such as anticancer, antimicrobial, cytotoxicity and radical scavenging effects. However, the focus has always been on their anticancer properties, since they have displayed excellent inhibition of the growth of human cancer cell lines in the National Cancer Institute's 60-cell line screen (NCI-60).

4.1. Anticancer activity

The cytotoxicity of schweinfurthins towards cancer cell lines was first reported by Beutler *et al.* when they isolated three novel geranyl stilbenes, schweinfurthins A (**1**), B (**2**), and C (**3**).[27] Schweinfurthins A (**1**) and B (**2**) were evaluated in an *in vitro* experiment using the lung cancer-derived A549 and glioblastoma multiforme (GBM)-derived SF295 cell lines. A 1 hour



Scheme 17 Synthesis of 3-deoxyschweinfurthin A (3dSA) by Mente *et al.*[52] Reagents and conditions: (a) TBAF, THF, 4 h; (b) (1) MsCl, NEt_3, CH_2Cl_2; (2) NaI, acetone, 15 h; (3) $P(OEt)_3$, 80 °C, 7 h; (c) NaH, geranyl aldehyde **133**, 15-crown-5, THF, 16 h; (d) *p*-TsOH, MeOH.



Scheme 18 Synthesis of 3-deoxyschweinfurthin B (3dSB) by Neighbors *et al.*[46] Reagents and conditions: (a) AD-mix-α in H_2O/*t*-BuOH, $CH_3SO_2NH_2$, 6 °C, 15 h; (b) (1) MsCl, NEt_3, CH_2Cl_2, 2 h; (2) K_2CO_3, MeOH, 20 h; (c) TBAF, THF, 1.5 h; (d) TFA, CH_2Cl_2, 2 h; (e) MnO_2, CH_2Cl_2; (f) phosphonate ester **86**, NaH, THF, 18 h; (g) CSA, MeOH, 5 h.

treatment led to negligible cytotoxicity, whereas evaluation at 48 hours showed modest cytotoxicity for each compound (Table 2). However, schweinfurthin C was found to be biologically inactive.

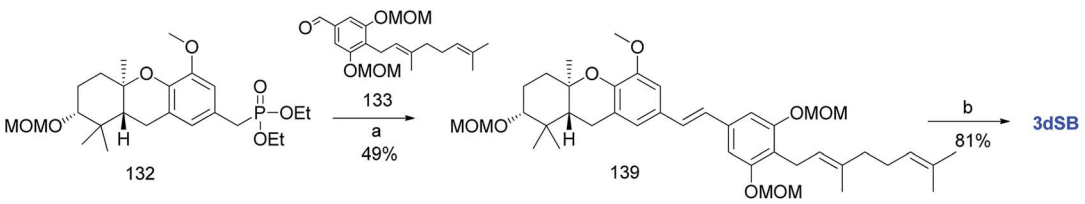
The SF295 cell line was found to be the most sensitive for compound **1**, with a growth inhibition (GI_{50}) of 11 nM and total growth inhibition (TGI) of 52 nM.[27] Schweinfurthin A is a potent member of this family that inhibits the SF295 line at a low nanomolar concentration and displays 1000-fold selectivity compared to that of the A549 cell line; however, its mechanism of action has not been fully elucidated.

GBM is the most common, deadly brain tumor in adults, which is highly infiltrative, resistant to chemotherapy and incurable. Previous studies have shown that neurofibromatosis type 1 (NF1), an autosomal dominant genetic disorder, plays a role in GBM tumorigenesis.[68,69] Turbyville *et al.* studied the mode of action of schweinfurthin A and observed that it inhibited SF295 and KR158 cell lines in a dose-dependent manner with no effect on A549, indicating that schweinfurthin A acts *via* a cytotoxic mechanism rather than a cytostatic one. Further findings have indicated that schweinfurthin A does not act at the level of Ras inhibition, but selectively inhibits proliferation and Rho signalling in the glioma and NF1 tumor cells in an NF1-GRD-dependent manner.[70]

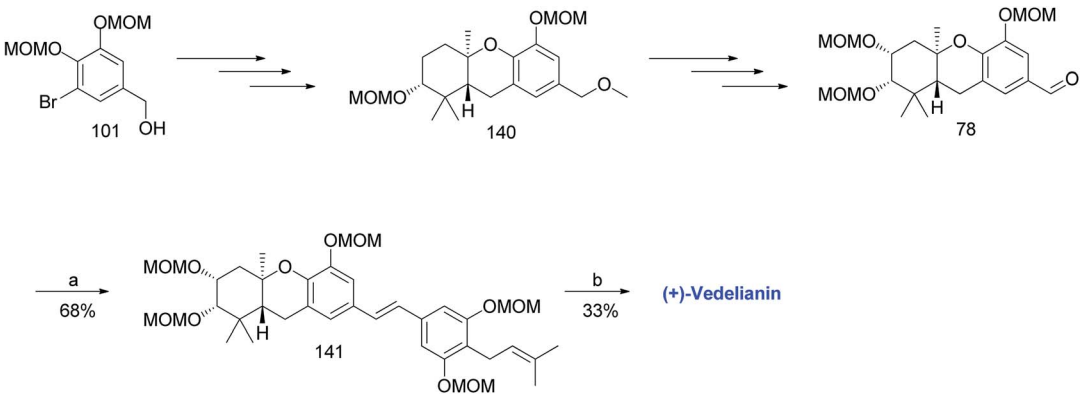
Beutler *et al.* performed a 2 day cytotoxicity assay on schweinfurthin D (**4**) using two cell lines, SF295 and A549. Schweinfurthin D (**4**) (IC_{50} 3.44 nM) was found to be equipotent to schweinfurthin B (**2**) (IC_{50} 5.33 nM) for the SF295 line whereas, for the A549 cell line, the IC_{50} for compounds **4** and **2** were 4.82 μM and 9.77 μM, respectively.[28]

Mente *et al.* tested both the enantiomers of schweinfurthin F (**6a** and **6b**) for growth inhibition in RPMI-8226 human-derived myeloma cells using a 3H-thymidine incorporation assay of DNA synthesis.[58] The enantiomers **6a** and **6b** exhibited an IC_{50} of 0.58 μM and 3.40 μM, respectively (Table 3). In a glioma-derived SNB 75 cell line, a large divergence of bioactivity was observed, where compound **6a** displayed a GI_{50} of 10 nM and its enantiomer **6b** had a GI_{50} of 1.7 μM. The activity pattern was reversed in the malignant glioblastoma-derived human cell line U251, where **6b** showed very high activity with a GI_{50} of <10 nM, while **6a** had a GI_{50} of 13 μM (Table 3).[58]

Yoder *et al.* evaluated the cytotoxicity of schweinfurthins E–H and a congener vedelianin against the A2780 ovarian cancer cell line (Table 4).[29] Vedelianin (**20**) was found to be the most potent



Scheme 19 Synthesis of 3-deoxyschweinfurthin B (3dSB) by Mente *et al.*[52] Reagents and conditions: (a) NaH, geranyl aldehyde, **133**, 15-crown-5, THF, 16 h; (b) *p*-TsOH, MeOH.



Scheme 20 Synthesis of (+)-vedelianin (2011) by Topczewski *et al.*[67] Reagents and conditions: (a) KHMDS, phosphonate ester **108**, THF, 30 min; (b) *p*-TsOH, MeOH, 48 h.

Table 2 Cytotoxicity of schweinfurthins A (**1**) and B (**2**) on SF295 and A549 cell lines

Compound	**1**, IC_{50} (μM)		**2**, IC_{50} (μM)	
Protocol	A549	SF295	A549	SF295
1 h	78.3	85.6	>170	>170
1 h washout	36.4	0.109	142.1	5.1
48 h	6.7	<0.00002	12.6	0.016

compound with an IC_{50} of 0.13 μM. In a comparison of their cytotoxicity, vedelianin (**20**) was found to be twice as potent as schweinfurthin E (**5**) (IC_{50} 0.26 μM) and three times as potent as schweinfurthin G (**7**) (IC_{50} 0.39 μM).

Péresse *et al.* evaluated the cytotoxicity of schweinfurthins G, K–Q, and vedelianin against GBM-derived U87 and lung cancer-derived A549 cells (Table 5).[31] All of the compounds showed good to moderate cytotoxicity on the U87 cell line, except for schweinfurthin P (**16**). As expected, schweinfurthins G (**7**), Q (**17**), and vedelianin (**20**) containing the hexahydroxanthene moiety, were found to be highly cytotoxic with an EC_{50} of 0.04, 0.05, and 0.03 μM, respectively on the U87 cell line. However, on the A549 cell line, only schweinfurthins G (**7**), K (**11**), and L (**12**) and vedelianin (**20**) were found to be active, exhibiting cytotoxicity in the sub-micromolar range.[31]

The schweinfurthin family has been found to strongly inhibit the growth of human cancer cell lines when evaluated in the NCI 60-cell line screen. The mean GI_{50} values of the schweinfurthins are shown in Table 6. Schweinfurthin A (**1**), one of the potent compounds in this family, displayed a mean GI_{50} of 0.36 μM, whereas schweinfurthin B (**2**) was found to have a mean GI_{50} of 0.81 μM.[27] Schweinfurthin E (**5**) was found to be slightly more potent than compounds **1** and **2**, with a mean GI_{50} of 0.19 μM.[29] The two enantiomers of schweinfurthin F, **6a** and **6b** were found to have a mean GI_{50} of 0.41 and 0.13 μM, respectively (Table 6).[58]

Schweinfurthin I (**9**) was observed to be the least potent compound with a mean GI_{50} of 10 μM, whereas schweinfurthin J (**10**) exhibited moderate growth inhibitory activity with a mean GI_{50} of 2.8 μM.[30] The synthetic analogue of schweinfurthin B, 3dSB (**19**) was found to have a mean GI_{50} of 0.21 μM.[46] Vedelianin (**20**) was the most potent compound, which exhibited a mean GI_{50} of 0.08 μM (Table 6).[58,67] The results suggest that the presence of dihydroxy groups on the A-ring of the tricyclic hexahydroxanthene core [schweinfurthins A (**1**), B (**2**), and E (**5**) and vedelianin (**20**)] may be critical for inhibitory activity. Additionally, the mean GI_{50} values of schweinfurthin E (**5**) and vedelianin (**20**) indicated that a shorter prenyl side chain could enhance the inhibitory activity (Table 6).

Table 3 Cytotoxicity of schweinfurthin F (**6a**) and its enantiomer (**6b**) on RPMI-8226, SNB 75, and U251 cell lines

	Compounds	
Cell line	**6a**	**6b**
RPMI-8226	IC_{50} = 0.58 μM	IC_{50} = 3.40 μM
SNB 75	GI_{50} = 10 nM	GI_{50} = 1.7 μM
U251	GI_{50} = 13 μM	GI_{50} < 10 nM

4.2. Free radical scavenging activity

A high level of free radicals in living systems causes adverse effects that can lead to tissue damage, neural disorders, skin irritation, inflammation, cell death or various diseases, including cancer.[71] The harmful effects caused by free radicals are counteracted by antioxidants, either from natural sources in the form of food or synthetic antioxidants.[72–74] Petrova *et al.* evaluated the free radical scavenging activity of schweinfurthins A (**1**) and B (**2**) against DPPH radicals, but they were found to be less active than other extracted lignans (Table 7).[75]

4.3. Antimicrobial activity

Natural products have particularly shown a protective role against microbial invasion. Petrova *et al.* tested schweinfurthins A (**1**) and B (**2**) for antibacterial activity against *Staphylococcus aureus*, and both **1** and **2** demonstrated antimicrobial activity, as shown in Table 8. However, they were not active against *Candida albicans* and *Escherichia coli*.[75]

Table 4 Cytotoxicity of schweinfurthins E–H and vedelianin on A2780 cells

Compound	IC_{50} (μM)
5	0.26
6a	5.0
7	0.39
8	4.5
20	0.13

4.4. Pleiotropic effects of 3-deoxyschweinfurthin on isoprenoid homeostasis

Holstein *et al.* studied the pleiotropic effects of a synthetic schweinfurthin, 3dSB (**18**), on isoprenoid homeostasis to determine whether 3dSB-induced cytotoxicity could be prevented by co-incubation with an isoprenoid species. MTT assays to assess cell metabolic activity were performed by treating human multiple myeloma cell lines (RPMI-8226 and U266) with 3dSB and/or lovastatin in the presence or absence of mevalonate, farnesyl pyrophosphate (FPP) or geranylgeranyl pyrophosphate (GGPP). Cytotoxicity assays demonstrated that 3dSB had a synergistic interaction with lovastatin but not with other isoprenoid biosynthetic pathway (IBP) inhibitors in diverse human cancer cell lines. 3dSB enhanced the lovastatin-induced decrease in protein prenylation. Additionally, intracellular FPP and GGPP levels were decreased in both established cell lines and primary cells. Holstein *et al.* reported that 3dSB alters isoprenoid levels and controls IBP and sterol homeostasis by disrupting multiple aspects of the regulatory elements.[76]

Table 5 Cytotoxicity of schweinfurthins G, K–Q, and vedelianin on the GBM (U87) and lung cancer (A549) cell lines

Compound	U87, EC_{50} (μM)	A549, EC_{50} (μM)
11	0.25 ± 0.08	0.73 ± 0.01
12	0.45 ± 0.03	0.24 ± 0.12
13	0.50 ± 0.04	>10
14	0.10 ± 0.01	>10
15	0.025 ± 0.006	>10
16	>10	>10
17	0.050 ± 0.003	>10
7	0.045 ± 0.005	0.80 ± 0.04
20	0.030 ± 0.009	0.190 ± 0.002
Monomethyl auristatin E	0.00020 ± 0.00003	0.00050 ± 0.00005

Table 6 Growth inhibition activity of schweinfurthins in the NCI 60-cell line screen

Compounds	Mean GI_{50} (μM)	References
1	0.36	27
2	0.81	27
5	0.19	29
6a	0.41	58
6b	0.13	58
9	10	30
10	2.8	30
19	0.21	46
20	0.08	58 and 67

Table 7 Free radical scavenging activity of schweinfurthins A (**1**) and B (**2**)

Compound	DPPH[a] free radical scavenging activity, % inhibition[b]
1	25.4 ± 0.7
2	15.6 ± 0.4
Caffeic acid[c]	65.5 ± 0.1

[a] DPPH solution 0.02% in EtOH. [b] Mean value of three measurements ± S.D. [c] Solution 0.21 mg ml^{-1} in ethanol.

Table 8 Antimicrobial activity of schweinfurthins A (**1**) and B (**2**) against *S. aureus* (at 400 μg in the cup)[a]

Compound	Zone of inhibition (mm)
1	19 ± 1
2	19 ± 1
Streptomycin[b]	30 ± 1

[a] Tests were done in triplicate, values are mean ± S.D. [b] 100 μg in the cup.

5. Conclusion

Schweinfurthins display multiple biological and pharmacological activities. In particular, schweinfurthins possessing hexahydroxanthene have exhibited potent growth inhibitory activity in NCI 60-cell cancer screening. The synthesis of hexahydroxanthene has smoothed the path towards exploring these natural products and carrying out diverse structure–activity relationship studies. Further investment in optimization by preparing new synthetic schweinfurthin analogues that are metabolically stable, potent and specific may enhance the drug discovery process. The *Macaranga* species will continue to be investigated in the future due to the anticancer activity of the schweinfurthins and their congeners. In the present review, we have mainly focused on the synthesis and biological activities of the schweinfurthins. We expect that the information provided in this review might be helpful for the synthesis of schweinfurthin analogues and may offer a platform upon which to develop useful therapeutic candidates.

Conflicts of interest

There are no conflicts to declare.

Abbreviations

TBAI Tetrabutylammonium iodide
m-CPBA *m*-Chloroperoxybenzoic acid

MOM	Methoxymethyl
TBS	*tert*-Butyldimethylsilyl
TBAF	Tetrabutylammonium fluoride
TFA	Trifluoroacetic acid
NMR	Nuclear magnetic resonance
TMEDA	Tetramethylethylenediamine
BOM	Benzyloxymethyl
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
KHMDS	Potassium bis(trimethylsilyl)amide
NOESY	Nuclear Overhauser effect spectroscopy
PDC	Pyridinium dichromate
NCI60	National Cancer Institute; 60 human tumor cell line
GI_{50}	Concentration of compound required to inhibit growth by 50%
TGI	Concentration of compound required for the total inhibition of growth
IC_{50}	Concentration of compound required to inhibit by 50%
EC_{50}	Concentration of a compound expected to produce an effect in 50% of test organisms
DPPH	2,2-diphenyl-1-picrylhydrazyl

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References

1 M. S. Butler, *J. Nat. Prod.*, 2004, **67**, 2141.
2 M. S. Butler, *Nat. Prod. Rep.*, 2005, **22**, 162.
3 B. Shen, *Cell*, 2015, **163**, 1297.
4 M. Dong, B. Pfeiffer and K. Altmann, *Drug Discovery Today*, 2017, **22**, 585.
5 T. Shen, X. Wang and H. Lou, *Nat. Prod. Rep.*, 2009, **26**, 916.
6 Z. I. Chrząścik, *Crit. Rev. Anal. Chem.*, 2009, **39**, 70.
7 S. Fulda, *Drug Discovery Today*, 2010, **15**, 757.
8 L. Carter, J. D'Orazio and K. J. Pearson, *Endocr.-Relat. Cancer*, 2014, **21**, R209.
9 B. Aggarwal, A. Bhardwaj, R. Aggarwal, N. Seeram, S. Shishodia and Y. Takada, *Anticancer Res.*, 2004, **24**, 2783.
10 Z. A. Bishayee, *Cancer Prev. Res.*, 2009, **2**, 409.
11 M. Jang, L. Cai, G. Udeani, K. Slowing, C. Thomas, C. Beecher, H. Fong, N. Farnsworth, A. Kinghorn, R. Mehta, R. Moon and J. M. Pezzuto, *Science*, 1997, **275**, 218.
12 L. Stivala, M. Savio, F. Carafoli, P. Perucca, L. Bianchi, G. Maga, L. Forti, U. Pagnoni, A. Albini, E. Prosperi and V. Vannini, *J. Biol. Chem.*, 2001, **276**, 22586.
13 H. Piotrowska, M. Kucinska and M. Murias, *Mutat. Res.*, 2012, **750**, 60.
14 M. Nalli, G. Ortar, A. Moriello, E. Morera, V. Marzo and L. Petrocellis, *Bioorg. Med. Chem. Lett.*, 2016, **26**, 899.
15 R. Mikstacka, T. Stefański and J. Różański, *Cell. Mol. Biol. Lett.*, 2013, **18**, 368.
16 J. Sirerol, M. Rodríguez, S. Mena, M. Asensi and A. Ortega, *Oxid. Med. Cell. Longevity*, 2016, 3128951.
17 R. Mikstacka, A. Rimando, K. Szalaty, K. Stasik and W. Dubowska, *Xenobiotica*, 2006, **36**, 269.
18 G. Belofsky, A. French, D. Wallace and S. Dodson, *J. Nat. Prod.*, 2004, **67**, 26.
19 M. Liu, Y. Han, D. Xing, Y. Shi, L. Xu, L. Du and Y. Ding, *J. Asian Nat. Prod. Res.*, 2004, **6**, 229.
20 Q. Hu, B. Zhou, Y. Ye, Z. Jiang, X. Huang, Y. Li, G. Du, G. Yang and X. M. Gao, *J. Nat. Prod.*, 2013, **76**, 1854.
21 J. Ingle, D. Ahmann, S. Green, J. Edmonson, H. Bisel, L. Kvols, W. Nichols, E. Creagan, R. Hahn, J. Rubin and S. Frytak, *N. Engl. J. Med.*, 1981, **304**, 16.
22 Z. A. Herbst, H. Ulfelder and D. Poskanzer, *N. Engl. J. Med.*, 1971, **284**, 878.
23 V. Jordan, *Br. J. Pharmacol.*, 2006, **147**, S269.
24 Z. A. Howell, J. Cuzick, M. Baum, A. Buzdar, M. Dowsett, J. Forbes, G. Hoctin-Boes, J. Houghton, G. Locker and J. Tobias, *Lancet*, 2005, **365**, 60.
25 E. Bommel, T. Hendriksz, A. Huiskes and A. G. Zeegers, *Ann. Intern. Med.*, 2006, **144**, 101.
26 G. Webster, *Ann. Mo. Bot. Gard.*, 1994, **81**, 33.
27 J. Beutler, R. Shoemaker, T. Johnson and M. Boyd, *J. Nat. Prod.*, 1998, **61**, 1509.
28 J. Beutler, J. Jato, G. Cragg and M. Boyd, *Nat. Prod. Lett.*, 2000, **14**, 399.
29 B. Yoder, S. Cao, A. Norris, J. Miller, F. Ratovoson, J. Razafitsalama, R. Andriantsiferana, V. Rasamison and D. Kingston, *J. Nat. Prod.*, 2007, **70**, 342.
30 P. Klausmeyer, Q. Van, J. Jato, T. McCloud and J. Beutler, *J. Nat. Prod.*, 2010, **73**, 479.
31 T. Péresse, G. Jézéquel, P. Allard, V. Pham, D. Huong, F. Blanchard, J. Bignon, H. Lévaique, J. Wolfender, M. Litaudon and F. Roussi, *J. Nat. Prod.*, 2017, **80**, 2684.
32 O. Thoison, E. Hnawia, F. Gueritte-voegelein and T. Sevenet, *Phytochemistry*, 1992, **31**, 1439.
33 E. Hnawia, O. Thoison, F. Guéritte-Voegelein, D. Bourret and T. Sévenet, *Phytochemistry*, 1990, **29**, 2367.
34 B. Schutz, A. Wright, T. Rali and O. Sticher, *Phytochemistry*, 1995, **40**, 1273.
35 S. Sultana and M. Ilyas, *Phytochemistry*, 1986, **25**, 953.
36 W. Hui, K. Ng, N. Fukamiya, M. Koreeda and K. Nakanishi, *Phytochemistry*, 1971, **10**, 1617.
37 R. Mechoulam and B. Yagen, *Tetrahedron Lett.*, 1969, **10**, 5349.
38 G. Manners, L. Jurd and K. Stevens, *Tetrahedron*, 1972, **28**, 2949.
39 G. Trammell, *Tetrahedron Lett.*, 1978, **19**, 1525.
40 E. Treadwell, J. Neighbors and D. Wiemer, *Org. Lett.*, 2002, **4**, 3639.
41 B. Branchaud and H. Blanchette, *Tetrahedron Lett.*, 2002, **43**, 351.
42 Z. A. Toshimitsu, C. Hirosawa and K. Tamao, *Synlett*, 1996, 465.
43 T. Kametani, K. Suzuki, H. Kurobe and H. Nemoto, *J. Chem. Soc., Chem. Commun.*, 1979, 1128.

44 T. Kametani, H. Kurobe, H. Nemoto and K. Fukumoto, *J. Chem. Soc., Perkin Trans. 1*, 1982, 1085.
45 D. Boger and I. Jacobson, *J. Org. Chem.*, 1991, **56**, 2115.
46 J. Neighbors, J. Beutler and D. Wiemer, *J. Org. Chem.*, 2005, **70**, 925.
47 J. Neighbors, N. Mente, K. Boss, D. Zehnder and D. Wiemer, *Tetrahedron Lett.*, 2008, **49**, 516.
48 Z. Wang and Y. Shi, *J. Org. Chem.*, 1998, **63**, 3099.
49 L. Shu and Y. Shi, *Tetrahedron Lett.*, 1999, **40**, 8721.
50 J. Topczewski, J. Kodet and D. Wiemer, *J. Org. Chem.*, 2011, **76**, 909.
51 J. Topczewski, M. Callahan, J. Neighbors and D. Wiemer, *J. Am. Chem. Soc.*, 2009, **131**, 14630.
52 N. Mente, J. Neighbors and D. Wiemer, *J. Org. Chem.*, 2008, **73**, 7963.
53 E. Treadwell, S. Cermak and D. Wiemer, *J. Org. Chem.*, 1999, **64**, 8718.
54 J. Topczewski, J. Neighbors and D. Wiemer, *J. Org. Chem.*, 2009, **74**, 6965.
55 J. Stafford and N. Valvano, *J. Org. Chem.*, 1994, **59**, 4346.
56 P. Manchand, P. Belica and H. S. Wong, *Synth. Commun.*, 1990, **20**, 2659.
57 R. Lange, *J. Org. Chem.*, 1962, **27**, 2037.
58 N. Mente, A. Wiemer, J. Neighbors, J. Beutler, R. Hohl and D. Wiemer, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 911.
59 J. Neighbors, M. Salnikova and D. Wiemer, *Tetrahedron Lett.*, 2005, **46**, 1321.
60 N. Yee and R. Coates, *J. Org. Chem.*, 1992, **57**, 4598.
61 E. Corey and K. Liu, *J. Am. Chem. Soc.*, 1997, **119**, 9929.
62 E. Corey and M. Sodeoka, *Tetrahedron Lett.*, 1991, **32**, 7005.
63 J. Zhang and E. Corey, *Org. Lett.*, 2001, **3**, 3215.
64 S. Taylor, M. Ivanovic, L. Simons and M. Davis, *Tetrahedron: Asymmetry*, 2003, **14**, 743.
65 M. Singh and N. P. Argade, *Synthesis*, 2012, **44**, 2895.
66 B. Wang, Y. Zhang, J. Chen, W. Zhang, J. Song, B. Del, L. Brown and G. Miller, PCT Int. Appl., CODEN: PIXXD2 WO 2003009807 A220030206 CAN 138:153318 AN 2003:97274, 2003.
67 J. Topczewski and D. Wiemer, *Tetrahedron Lett.*, 2011, **52**, 1628.
68 K. Reilly, D. Loisel, R. Bronson, M. McLaughlin and T. Jacks, *Nat. Genet.*, 2000, **26**, 109.
69 Y. Zhu, F. Guignard, D. Zhao, L. Liu, D. Burns, R. Mason, A. Messing and L. Parada, *Cancer Cell*, 2005, **8**, 119.
70 T. Turbyville, D. Gürsel, R. Tuskan, J. Walrath, C. Lipschultz, S. Lockett, D. Wiemer, J. Beutler and K. Reilly, *Mol. Cancer Ther.*, 2010, **9**, 1234.
71 I. Gulcin, *Chem.-Biol. Interact.*, 2009, **179**, 71.
72 S. Kedare and R. Singh, *J. Food Sci. Technol.*, 2011, **48**, 412.
73 E. Koksal and I. Gulcin, *Turk. J. Agric. For.*, 2008, **32**, 65.
74 T. Kulisic, A. Radonic, V. Katalinic and M. Milos, *Food Chem.*, 2004, **85**, 633.
75 Z. A. Petrova, M. Popova, C. Kuzmanova, I. Tsvetkova, H. Naydenski, E. Muli and V. Bankova, *Fitoterapia*, 2010, **81**, 509.
76 S. Holstein, C. Kuder, H. Tong and R. Hohl, *Lipids*, 2011, **46**, 907.