ChemComm

Synthesis and Biological Study of the Phomopsolide and Phomopsolidone Natural Products

Journal:	*ChemComm*
Manuscript ID	CC-FEA-06-2020-004069.R1
Article Type:	Feature Article

COMMUNICATION

Synthesis and Biological Study of the Phomopsolide and Phomopsolidone Natural Products.

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Alhanouf Z. Aljahdali, [‡a] Kathryn A. Foster, [‡a] and George O'Doherty* [a]

The complete history of the syntheses and biological activities of the phomopsolide and phomopsolidone classes of natural products is reviewed. These efforts include the successful synthesis of four of the five phomopsolide natural products, two of the four phomopsolidone natural products and two analogues of phomopsolide E, including the 7-oxa and 7-aza analogues. In addition, the utility of these synthetic efforts to enable the initial structure activity relationship studies for these classes of natural products is also covered.

1. Introduction

The history of the phomopsolide and phomopsolidone natural products begins with the search for natural remedies for agricultural diseases caused by fungal infections.[1,2,5] The phomopsolides were initially discovered by Grove[1] and Stierle[2] as part of an effort to find biologically active natural products from trees such as the pacific yew. In particular, Grove was looking for compounds with antiboring/antifeeding properties that would prevent the elm bark beetle from spreading Dutch elm disease, a devastating infection affecting ecosystems containing American elm trees. Despite its name, Dutch elm disease primarily affects the American elm tree. The elm disease is spread by the fungi *Hylurgopinus rufipes* and *Ophiostoma ulmi*.[3,4] The American elm tree was once the most popular in North America, particularly along tree-lined streets in many midwestern cities, due to its adaptability to a range of climates. Once infected, a well-established American elm can be killed within two weeks.[Error! Bookmark not defined.] An infestation is capable of decimating 90% of a city's trees within a 10-year time frame.[Error! Bookmark not defined.] A decade later, a phomopsolide and the structurally related phomopsolidones were found in fungi associated with the grape disease esca. The isolation and structural determination of both natural product classes inspired over 25 years of synthetic efforts. Ultimately, these extensive efforts led medicinal chemists to investigate both classes of compounds for antibacterial and anticancer properties (vide infra).

The phomopsolides and the phomopsolidones are two classes of natural products that share a regioisomeric relationship (*e.g.*, **2** and **8**). They are made up of oxidized decanoic acid lactones that all share a tiglate ester at the *C*-4 or *C*-5 position. The phomopsolides consist of a group of five dihydropyranone containing structures with a *C*-4 tiglate ester in the *(S)*-configuration (Fig. 1).[1,2] All five phomopsolide pyranones are substituted with a *C*-5 pentyl or pent-1-enyl side chain with oxidation at the *C*-8 (ketone or (*S*)-alcohol) and *C*-9 ((*S*)-alcohol) positions.[1,2]

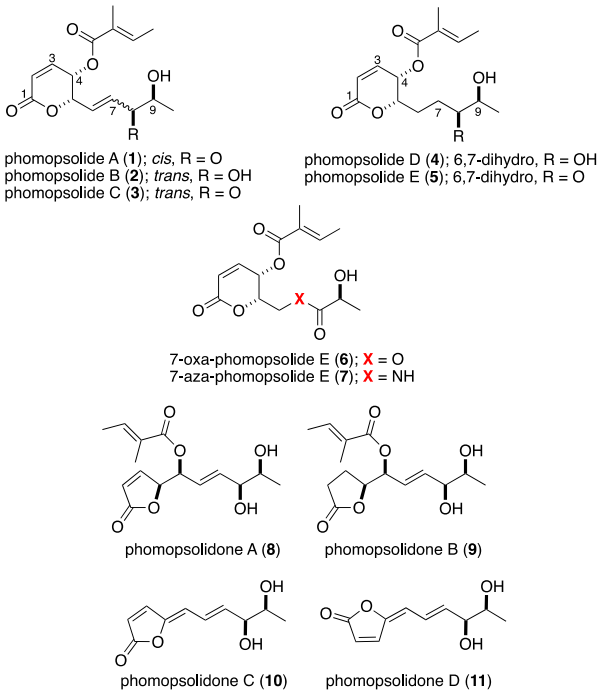


Fig. 1 The phomopsolide and phomopsolidone natural products and analogues.

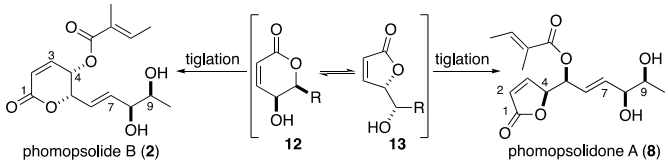
In 2014, Abou-Mansour and his co-workers isolated related furanones, phomopsolidones A-D.[5] Phomopsolidone A is a substituted furanone with a *C*-4 hex-2-enyl side chain with a tigloyloxy group at *C*-5, and two hydroxy groups at *C*-8 and *C*-9 (Fig. 1). Phomopsolidone B is a saturated version of phomopsolidone A with the butanolide double bond being

[a] *Dept. of Chemistry and Chem. Bio., Northeastern Univ. Boston, MA 02115.*
E-mail: g.odoherty@neu.edu
‡ Co-first authors, the order is alphabetical.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

reduced. In contrast, the *E*-*Z*-alkene isomeric phomopsolidones C and D are the result of a *syn*- and *anti*- elimination of tiglic acid from phomopsolidone A.

The structural connection between the two classes of natural products can be seen in the regioisomeric relationship between phomopsolidone A (**8**) and phomopsolide B (**2**), which can be viewed as tiglated products from a mixture of equilibrating hydroxy-lactones (*e.g.*, *C*-5 hydroxybutenolide **12** and *C*-4 hydroxypentenolide **13**, Scheme 1). Not-surprisingly, phomopsolidone A and phomopsolide B appear coincidently in nature.[5]

In addition to the interesting structural and biosynthetic aspects of the phomopsolides and the phomopsolidones, these natural products also possess interesting biological activity. The five phomopsolides (A-E) were found to exhibit antimicrobial activity (e.g., S. aureus).[1] Phomopsolide B and the structurally related phomopsolidones were found in fungi associated with the grape disease esca. Phomopsolidones A and B showed weaker antibacterial activity than their co-metabolite phomopsolide B. In 2015, Gray *et al*., re-isolated phomopsolides A and C and found them to have anti-mycobacterial activity (*Mycobacterium tuberculosis* H37Ra, Table 3).[6] Phomopsolide B was also found in three strains of the fungus (Phomopsis spp.) associated with the disease esca.[3]



Scheme 1 Proposed biosynthesis of phomopsolide B and phomopsolidone A.

2. Synthesis of phomopsolides

As a result of their unique structures and biological activity, the phomopsolides and phomopsolidones have garnered a fair amount of attention from the synthetic community. This includes four syntheses of phomopsolide B, two syntheses of phomopsolide C, one synthesis of phomopsolide D, one synthesis of phomopsolide E, and two syntheses of analogues of phomopsolide E. In addition, there has been two syntheses of phomopsolidone A and one synthesis of phomopsolidone B. These approaches and related biological studies are reviewed.

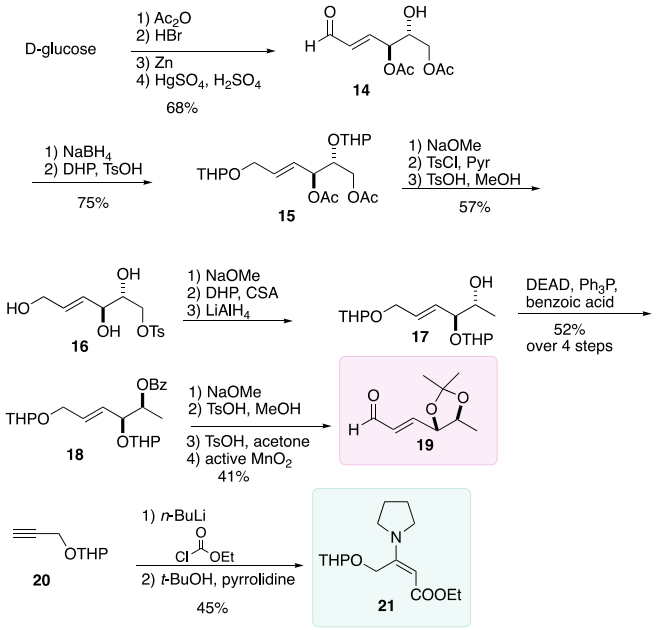
The first synthesis of phomopsolide B was by Noshita in 1994.[7] This was followed by later syntheses of phomopsolide B by Prasad, Atmakur, and Sabitha in 2012, 2014 and 2015, respectively.[8,9,10] The first synthesis of phomopsolide C was in 2002 by O'Doherty,[11] which was followed three years later by a synthesis by Blechert.[12] The first synthesis of phomopsolide D was achieved in 2004 by the O'Doherty group[13] who later accomplished the first synthesis of phomopsolide E in 2019.[14] In addition, several syntheses of phomopsolide analogues have been accomplished. These include the synthesis of 7-oxa-phomopsolide E,[15] 7-aza-phomopsolide E[16] and related *C*-4/*C*-5 stereoisomers. In 2016, the first total syntheses of phomopsolidones A and B were reported by Sabitha.[17,18] Herein we review the total syntheses of the phomopsolide and phomopsolidone natural products, as well as the approaches to various analogues.

2.1. Phomopsolide A

There have been no successful syntheses reported for phomopsolide A. This can be attributed to its instability with respect to the other phomopsolides. Specifically, the *C*-6/7 *cis*-enone portion of phomopsolide A is readily isomerized to the *trans*-enone of phomopsolide B.

2.2. Phomopsolide B

There have been three reported syntheses of phomopsolide B and one reported synthesis of a related diastereomer. The first synthesis of a phomopsolide was of phomopsolide B by Noshita in 1994.[7] The second synthesis was in 2012 by Prasad,[8] which was followed two years later by Atmakur's synthesis of *epi*-phomopsolide B.[9] Finally, the fourth synthesis of phomopsolide B was by Sabitha in 2015.[10]



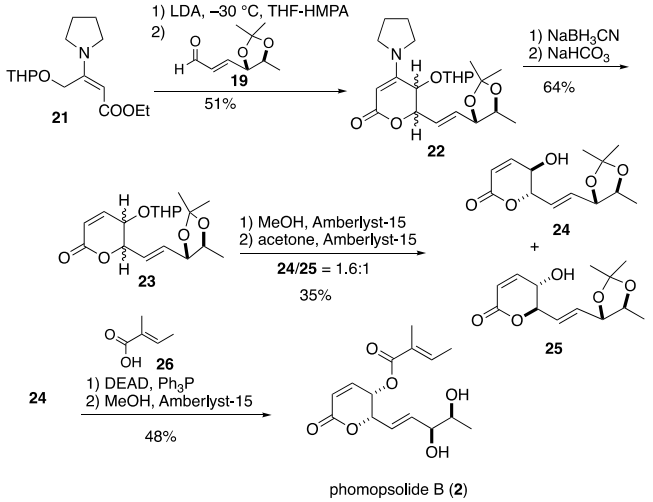
Scheme 2 Synthesis of the phomopsolide B fragments.

2.2.1. Noshita's synthesis of phomopsolide B (1994)

Noshita[7] described his synthesis starting from chiral aldehyde **14**, which can be made in four steps from D-glucose (Scheme 2).[19] A $NaBH_4$ reduction followed by bis THP-ether protection was used to convert **14** into alkene **15**. Base catalyzed methanolysis of two the acetoxy groups in **15** followed by tosylation of the terminal alcohol and deprotection of the THP-groups gave triol **16**. A base-promoted epoxide ring closure was followed by reprotection with two THP-groups and a $LiAlH_4$ reductive ring opening to give **17**. A Mitsunobu invertive esterification at *C*-5 was used to yield **18**. A combination of basic and acidic methanolysis protocols were then followed by

acetonide formation and oxidation of the allylic alcohol with active MnO_2 to provide the key aldehyde fragment **19**. Starting with the protected propargyl ether **20**, a lithium acetylide reaction with ethyl chloroformate followed by base-catalyzed pyrrolidine conjugate addition was used to synthesize the key vinylogous enamine fragment **21**.

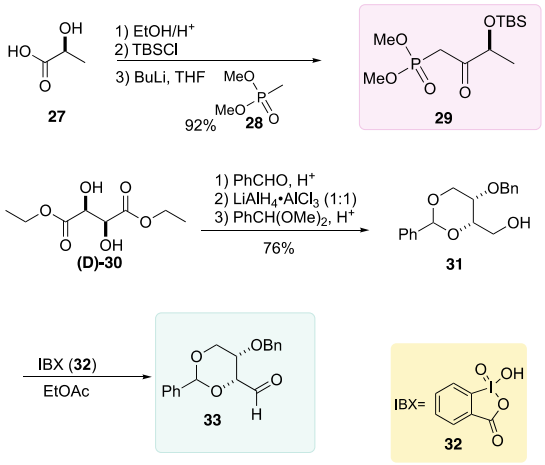
The two key fragments were brought together to assemble phomopsolide B (**2**) (Scheme 3). The stereochemically unselective vinylogous aldol reaction, which commenced with the deprotonation of **21** with LDA followed by addition of the resulting anion across aldehyde **19**, produced pyranone **22** as a rather complex mixture of diastereomers at both the *C*-5 and *C*-6 positions of the pyranone ring and the anomeric position of the THP-group. The *C*-3 pyrrolidine was removed by a conjugate reduction with $NaBH_3CN$ and subsequent elimination upon treatment with $NaHCO_3$ to give **23** as a similarly complex mixture of diastereomers. An acid catalyzed deprotection in methanol removed the THP-group, which was followed by re-installation of the acetonide to provide a 1.6:1 mixture of diastereomers (5*R*/6*S*)-**24** and (5*S*/6*R*)-**25**. An invertive Mitsunobu type esterification[20] was used to install the tiglic acid **26** on the major diastereomer **24**, which was then followed by an acid catalyzed deprotection of the acetonide to afford phomopsolide B (**2**) (Scheme 3). The synthesis of phomopsolide B was accomplished in a total of 25 steps with the longest linear route requiring 17 steps.



Scheme 3 The Noshita synthesis of phomopsolide B.

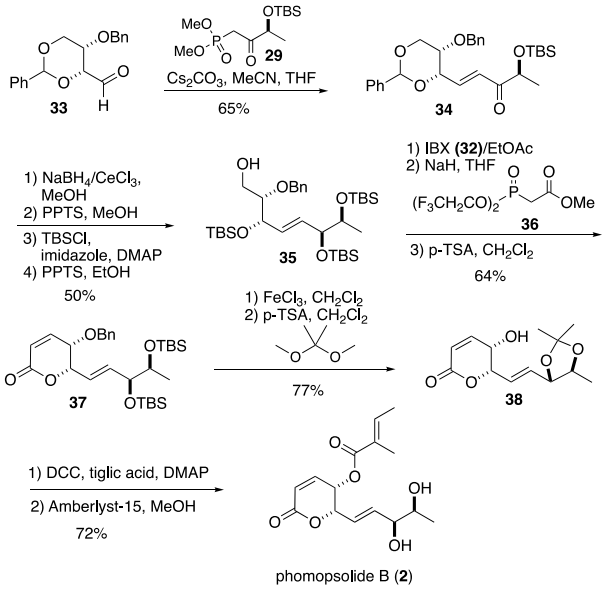
2.2.2. Prasad's synthesis of phomopsolide B (2012)

In 2012, Prasad[8] reported a convergent synthesis of phomopsolide B from two chiral synthons **29** and **33**,[21] which were prepared from lactic acid **27** and tartaric acid **30** respectively (Scheme 4). The synthesis of the keto-phosphonate **29** was accomplished in three steps from lactic acid. This started with the conversion of lactic acid to its ethyl ester followed by TBS-protection. Finally, a condensation of the TBS-protected ester with BuLi/**28** gave the keto-phosphonate **29**. The synthesis of aldehyde **33** was accomplished in four steps from the ethyl ester of D-tartaric acid. This involved a benzylidene protection of the 2,3-diol and a chloroallane reduction to a 2-benzyl-protected 1,2,3,4-tetraol, which was then benzylidene protected to give primary alcohol **31**. Finally, an IBX oxidation[22] of the primary alcohol gave aldehyde **33**.



Scheme 4 Synthesis of the phomopsolide B fragments.

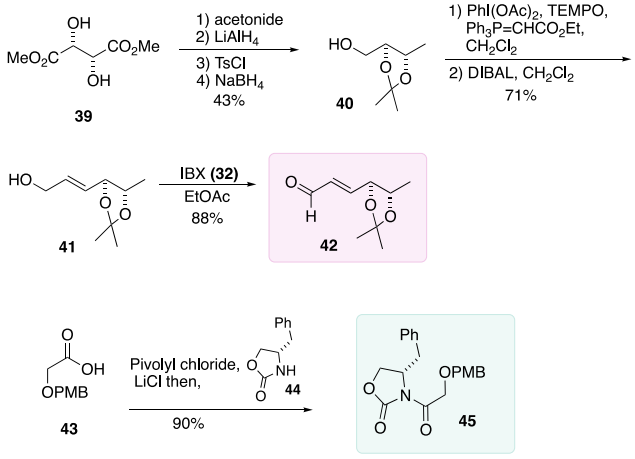
The synthesis of phomopsolide B from **29** and **33** was accomplished in a 12-step procedure (Scheme 5). The coupling commenced in the presence of Cs_2CO_3 in acetonitrile to give enone **34**. A Felkin-Ahn type diastereoselective 1,2-reduction of **34** was accomplished with $NaBH_4$ and $CeCl_3$ followed by deprotection to a mono-Bn-protected tetraol. The resulting triol was per-TBS protected and then selectively deprotected to give primary alcohol **35**. The pyranone was introduced by a three-step sequence of IBX oxidation of the primary alcohol, *cis*-selective olefination with the Still-Gennari reagent **36** and selective TBS-deprotection and lactonization to give **37**. An iron trichloride de-benzylation and acetonide formation converted **37** to acetonide **38**, which was converted into a tiglic ester and deprotected to give phomopsolide B (**2**). The Prasad convergent synthesis of phomopsolide B was accomplished in 19 total steps with 12 longest linear synthesis.



Scheme 5 The Prasad synthesis of phomopsolide B.

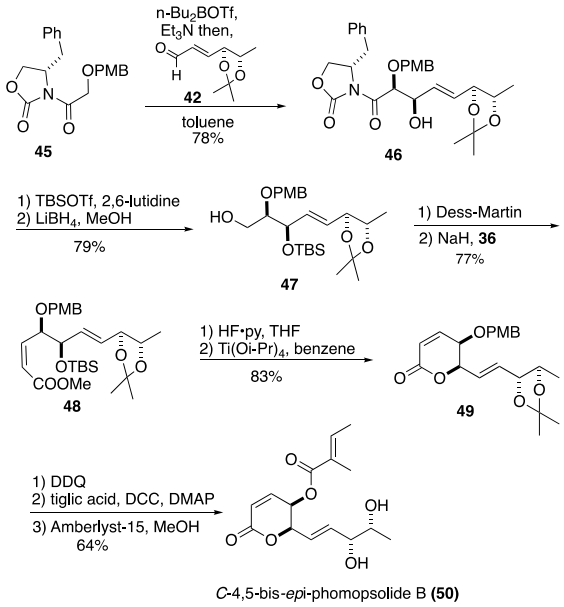
2.2.3. Atmakur's synthesis of bis-*epi*-phomopsolide B (2014)

In 2014, Atmakur[9] reported an alternative approach to the phomopsolides with a synthesis of the *C*-4/5 bis-epimer of phomopsolide B (**50**). The synthesis was a convergent approach from fragments **42** and **45**. Like the Prasad synthesis, the Atmakur synthesis prepared one of the fragments from a tartrate (Scheme 6). This time, the synthesis used dimethyl L-tartrate to establish the *C*-8 and *C*-9 stereocenters. Specifically, dimethyl L-tartrate was protected as an acetonide then reduced to a C_2-symmetric diol. The symmetry of the diol was broken by a mono-tosylation and reductive displacement with $NaBH_4$ to give alcohol **40**.[23] A TEMPO oxidation and *in situ* Wittig olefination,[24] followed by DIBAL reduction was used to prepare allylic alcohol **41**. Finally, an IBX oxidation was used to prepare enal **42**. The other chiral reagent **45** was prepared by acylation of the Evans auxiliary **44** with a PMB-protected glycolic acid **43**.



Scheme 6 Synthesis of the *C*-4,5-bis-*epi*-phomopsolide B fragments.

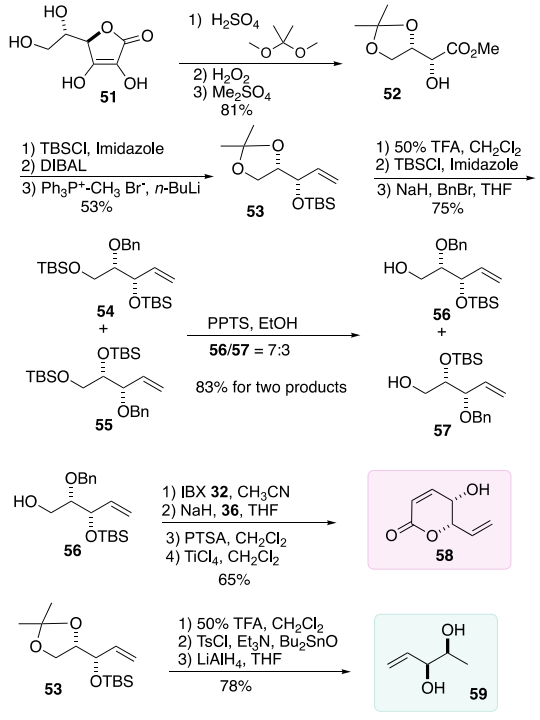
The two fragments were brought together to give **46** by a boron enolate aldol reaction between **45** and **42**. A TBS-protection of the aldol product **46** and reductive removal of the chiral auxiliary gave primary alcohol **47**. A Dess-Martin oxidation[25] and Still-Gennari olefination[26] gave *cis*-enoate **48**. A TBS-deprotection with HF•Py and a titanium tetraisopropoxide promoted lactonization gave pyranone **49**. The PMB group was oxidatively removed with DDQ and a tiglic ester was installed at the *C*-4 position to give the acetonide protected target compound. Finally, the acetonide protecting group was removed with Amberlyst-15 in MeOH to give the *C*-4/5 bis-epimer of phomopsolide B (**50**). The synthesis was accomplished in 18 total steps with a 10 step longest linear route.



Scheme 7 The Atmakur synthesis of bis-*epi*-phomopsolide B.

2.2.4. Sabitha's synthesis of phomopsolide B (2015)

In 2015, Sabitha[10] also reported a convergent synthesis of phomopsolide B. Retrosynthetically, the target molecule was conceived as being derived from two chiral fragments, pyranone **58** and diol **59** (Scheme 8). In the Sabitha synthesis, both fragments were prepared from L-ascorbic acid **51**, which was used to control the *C*-4/5 and *C*-8/9 stereochemistry of alkenol **53** and alkene **56**, respectively.



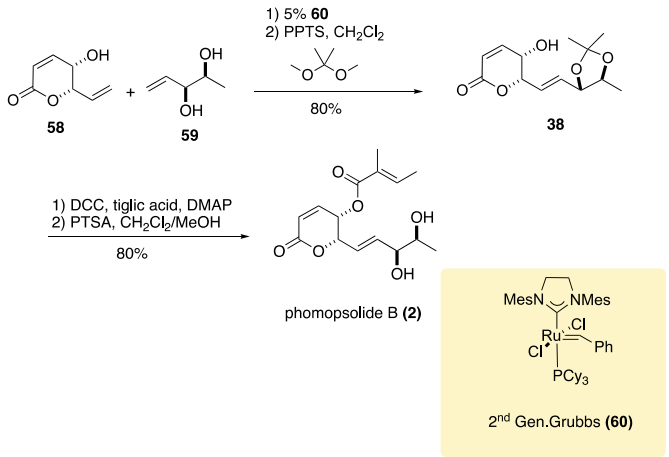
Scheme 8 Synthesis of the phomopsolide B fragments.

The Sabitha synthesis commenced with the acetonide protection of L-ascorbic acid, which was oxidatively cleaved to

a four-carbon acid with hydrogen peroxide. Methylation of the carboxylic acid gave hydroxy-ester **52**. TBS-protection of the alcohol in **52** was followed by selective DIBAL reduction to an aldehyde, which was then treated with the Wittig reagent to form alkene **53**. Acetonide deprotection with aqueous TFA gave a diol of which the primary alcohol was TBS-protected. A base promoted benzyl-ether protection (BnBr/NaH) gave an inseparable mixture of regioisomeric alkenes **54** and **55**. Selective deprotection of the primary TBS-group with PPTS in EtOH produced a similar mixture of two primary alcohols **56** and **57** in a 7:3 ratio that were separated by silica gel column chromatography.

The major alcohol isomer **56** was oxidized with IBX in CH_3CN followed by Still-Gennari olefination to form a *cis*-α,β-unsaturated ester (Scheme 8). The TBS-group was removed along with concomitant lactonization with TsOH and then the benzyl ether was removed with $TiCl_4$ to give pyranone **58**. Returning to alkene **53**, the TBS and acetonide groups were deprotected with aqueous TFA. The resulting triol was selectively sulfonylated at the primary alcohol and the tosylate group was reductively removed with $LiAlH_4$ to give diol **59**.

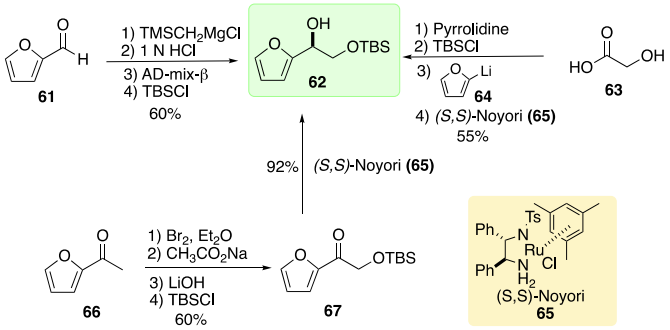
With the two key fragments in hand, Sabitha turned to an olefin cross-metathesis reaction to join the two fragments (Scheme 9). Thus, exposure of a mixture of pyranone **58** and diol **59** to the 2nd generation Grubbs catalyst (**60**)[27] produced a 1:2 mixture of three products. The mixture consisted of the desired hetero-dimer product along with lesser amounts of the two homo-dimers. After acetonide protection, the major isomer **38** was isolated. Esterification of the free alcohol with tiglic acid/DCC followed by deprotection of acetonide with PTSA and MeOH gave phomopsolide B (**2**). The Sabitha synthesis of phomopsolide B was accomplished in 21 total steps with a 14 step longest linear route.



Scheme 9 The Sabitha synthesis of phomopsolide B.

2.3. Phomopsolide C

There have been two syntheses of phomopsolide C (Schemes 10-14). The first synthesis of phomopsolide C was reported in 2002 by O'Doherty *et al*. and the second by Blechert in 2005.[11,12] The two approaches were thematically quite different. While both prepared the *C*-8-10 portion of the molecule from lactic acid, the two approaches used different coupling strategies and chemistry to prepare the pyranone ring system. The O'Doherty synthesis was unique from all other approaches to the phomopsolides in that it used asymmetric catalysis to stereoselectively install the pyranone.

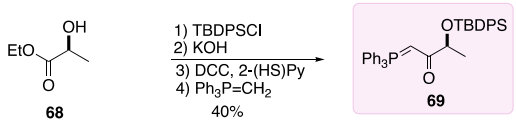


Scheme 10 Asymmetric synthesis of furan alcohol **62**.

2.3.1 O'Doherty's synthesis of phomopsolide C (2002)

The phomopsolide C synthesized by the O'Doherty group[11] was prepared in a convergent fashion from furan alcohol **62** and the stabilized Wittig reagent **69**. The chiral furan alcohol **62** has served as a linchpin molecule for the synthesis of several carbohydrates,[28] alkaloid[29] and polyketide-base[30] products. As a result of the value of enantiomerically enriched material, the group has developed several asymmetric approaches to alcohol **62** (Scheme 10). The initial route involved the conversion of furfural **61** into a diol via a Sharpless dihydroxylation of 2-vinylfuran, which was prepared by an *in situ* Petersen olefination. The resulting diol can be selectively protected with a TBS-group. Alternatively, furan alcohol **62** can be prepared in either enantiomeric form by a Noyori asymmetric hydrogen transfer reaction[31] of **67** to give **62** in excellent enantiopurity. The key achiral ketone **67** can be prepared by two routes. The first approach began with glycolic acid **63**, which was converted into a pyrrolidine amide and TBS-ether. Addition of 2-lithiofuran **64** was yielded into acylfuran **67**. Alternatively, commercially available 2-acetylfuran **66** can be selectively brominated and displaced with sodium acetate. The resulting acetate can be hydrolyzed and protected as a TBS-ether to give **67**.

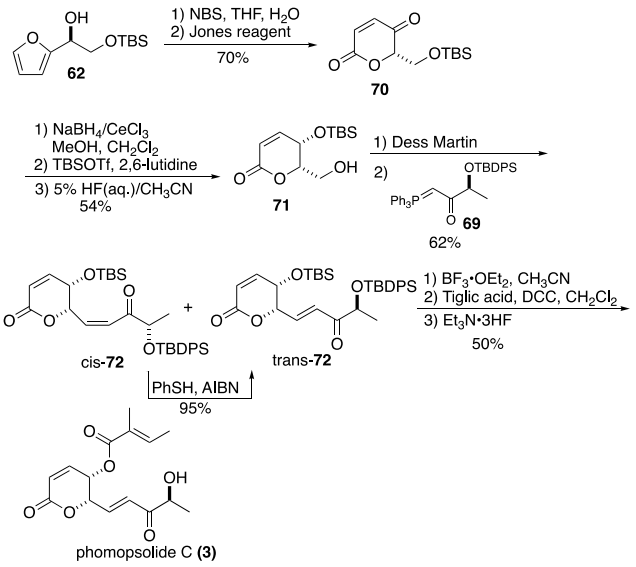
The O'Doherty second fragment **69** was prepared from the ethyl ester of lactic acid **68** (Scheme 11). The route involved a TBDPS-protection and ester hydrolysis with KOH. A DCC-coupling of the resulting acid with 2-thiopyridine gave a thioester which was reacted with the Wittig reagent to give the stabilized Wittig reagent **69**.[32]



Scheme 11 Synthesis of the C-7-10 fragment of phomopsolide C.

The synthesis of the pyranone portion of the phomopsolides commenced with furan alcohol **62** (Scheme 12). Oxidation of furan alcohol **62** with aqueous NBS induced an Achmatowicz rearrangement[33] to a 6-hydroxypyran-3-one intermediate. The hydroxypyranone was further oxidized with Jones reagent to give keto lactone **70** which can be isolated by crystallization, however it is

unstable to silica gel column chromatography. Instead, the crude product **70** can be selectively reduced with $NaBH_4$ under Luche conditions.[34] The resulting pyranone *C*-4 alcohol can be TBS-protected and the *C*-6 alcohol can be selectively deprotected to give **71**. Dess-Martin oxidation of the primary alcohol gave an unstable aldehyde intermediate. When the crude aldehyde was exposed to the Wittig reagent **69** it was transformed into a mixture of enones *trans*-**72** and *cis*-**72**.

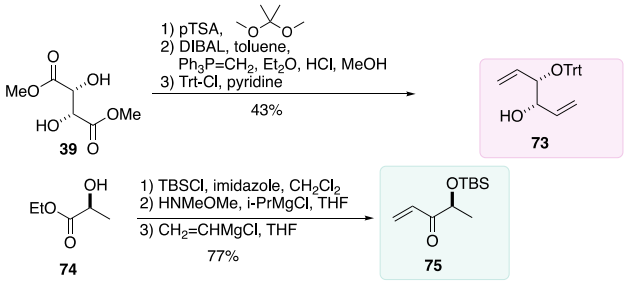


Scheme 12 The O'Doherty synthesis of phomopsolide C.

The less stable *cis*-enone could be readily isomerized (thiophenol/AIBN) to the more stable *trans*-isomer. Selective deprotection of the *C*-4 TBS group in *trans*-**72** gave an alcohol, which was then tiglated. Selective deprotection of the TBDPS group gave phomopsolide C (**3**). Unfortunately, when *cis*-**72** was exposed to a similar three step procedure only the *trans*-isomer was observed. The synthesis as described prepared phomopsolide C (**3**) in 18 total steps and in 14 longest linear steps.

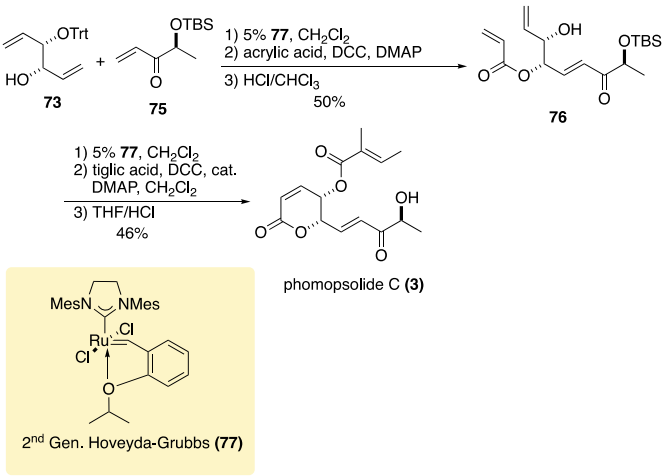
2.3.2 Blechert's synthesis of phomopsolide C (2005)

The Blechert group[12] also developed an approach to phomopsolide C (Schemes 13 and 14). In their convergent approach they also derived the *C*-4/5 stereochemistry from tartaric acid. In practice, the dimethyl ester of *L*-tartaric acid was protected as an acetonide and reduced with DIBAL. The resulting dialdehyde was exposed to excess Wittig reagent to form a dihydroxydiene, which when mono-protected formed trityl-ether **73**. The second coupling fragment **75** was prepared from lactic acid via its ethyl ester **74**. After the alcohol was TBS-protected, the ester was converted into a Weinreb amide. Exposure of the amide to vinyl-Grignard resulted in the formation of enone **75**.



Scheme 13 Synthesis of the phomopsolide C fragments.

With the two key fragments intact, the Blechert group continued their synthesis (Scheme 14) using an olefin cross metathesis reaction between **73** and **75** to form a diene product. DCC coupling with acrylic acid followed by removal of the trityl protecting group led to triene **76**. Once again, they turned to the Grubbs/Hoveyda metathesis catalyst **77**,[35] which induced a ring closing metathesis to form a pyranone ring. The pyranone was coupled with tiglic acid using DCC/DMAP and the TBS-group was removed to produce phomopsolide C (**3**). The synthesis as described prepared phomopsolide C (**3**) in 12 total steps and in 6 longest linear steps.



Scheme 14 The Blechert synthesis of phomopsolide C.

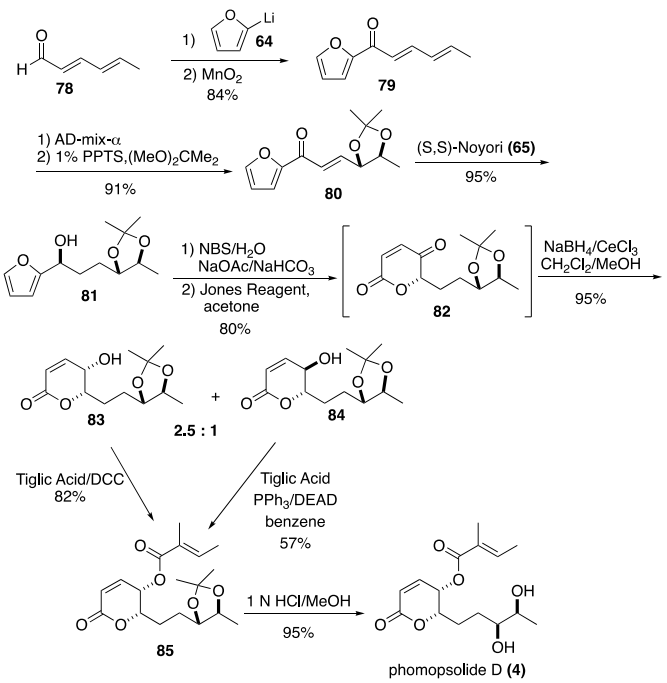
2.4. Phomopsolide D

The only synthesis of phomopsolide D (**4**) thus far was an asymmetric synthesis by the O'Doherty group (Scheme 15).[13] In addition to being the only synthesis of phomopsolide D, this synthesis was the only phomopsolide synthesis to introduce all the chiral centers via asymmetric catalysis. Like their synthesis of phomopsolide C, their approach to phomopsolide D used a combination of Noyori asymmetric reduction and Achmatowicz chemistry to install the pyranone *C*-4/5 stereochemistry. However, in contrast to all the other approaches to the phomopsolides, this approach uniquely installed the *C*-8/9 diol stereochemistry by a Sharpless asymmetric dihydroxylation.[36]

2.4.1 O'Doherty's synthesis of phomopsolide D (2004)

In 2004, the O'Doherty group[13] returned to the phomopsolide structural motif with a synthesis of phomopsolide D (Scheme

15). Retrosynthetically, their asymmetric synthesis was envisioned from achiral dienone **79**, which contained the *C*-1 to *C*-10 carbons of the phomopsolides. The synthesis of dienone **79** was accomplished by a two-step addition of 2-lithiofuran **64** to commercially available sorbal **78** and MnO_2 oxidation. A highly regio- and enantio-selective dihydroxylation of the most electron rich alkene in **79** lead to furan/enone **80** after acetonide protection. The Noyori reduction of the acylfuran **80** with the (*S,S*)-Noyori reagent **65** occurred along with the 1,4-reduction of the enone to give furan alcohol **81** as a single diastereomer. A sequential oxidation of the furan alcohol with first an Achmatowicz rearrangement (NBS/H_2O) and then a Jones oxidation was used to convert furan alcohol **81** to keto lactone **82**. As is generally true for this ring system, keto lactone **82** was unstable to silica gel chromatography and, as a result, the crude material was reduced under Luche conditions ($NaBH_4/CeCl_3$) to give a 2.5:1 ratio of diastereomeric pyranones **83** and **84**. Fortunately, both diastereomers **83** and **84** could be used for the synthesis of phomopsolide D. The major diastereomer **83** was acylated with tiglic acid/DCC in a retentive fashion to form **85**. Using Mitsunobu chemistry (tiglic acid/PPh_3/DEAD), the minor diastereomer was converted into **85** via an invertive acylation reaction. Finally, an acetonide deprotection (HCl/MeOH) gave the natural product phomopsolide D (**4**) in excellent yield. This unique linear synthesis prepared phomopsolide D in 11 total steps and 10 longest linear steps. Thus, using the metric of total steps, one can see some of the advantages of a truly linear approach.



Scheme 15 The O'Doherty synthesis of phomopsolide D.

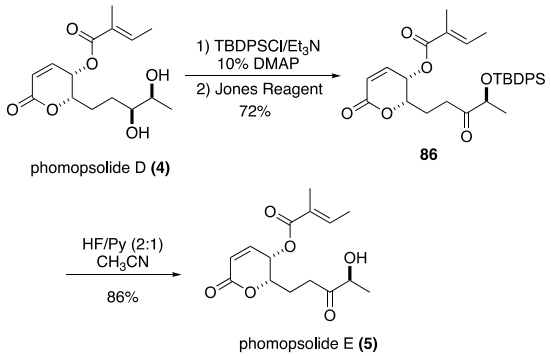
2.5. Phomopsolide E

There has also been only one synthesis of phomopsolide E (**5**), which again was an asymmetric variety by the O'Doherty group.[14] The approach builds upon the approach they developed for phomopsolide D and, in fact, uses phomopsolide D as its starting material (Scheme 16).

2.5.1. O'Doherty's synthesis of phomopsolide E (2019)

After a long hiatus, the O'Doherty group[14] returned to the phomopsolides with a report of a synthesis of phomopsolide E in 2019. The synthesis builds upon their successful synthesis of phomopsolide D in that is uses phomopsolide D as the starting material for their oxidative approach. Interestingly, their initial efforts began by exploring a selective reduction of phomopsolide C and a protected variant. Unfortunately, both materials proved to be too base sensitive.

The O'Doherty group's approach to phomopsolide E began with the regioselective protection of synthetically derived phomopsolide D (**4**) with TBDPSCl. The protected compound was oxidized with Jones reagent to yield the TBDPS-protected phomopsolide D **86**. Exposure of the TBDPS-ether **86** to HF•Py cleanly gave the natural product phomopsolide E (**5**). The synthesis was accomplished in 3 total steps from phomopsolide D (**4**), but also constitutes a 14 total steps/13 longest linear steps asymmetric synthesis from commercially available sorbal **78**. Because the synthesis was from synthetic material with known stereochemical providence, the synthesis of phomopsolide E from D established its absolute and relative stereochemistry.

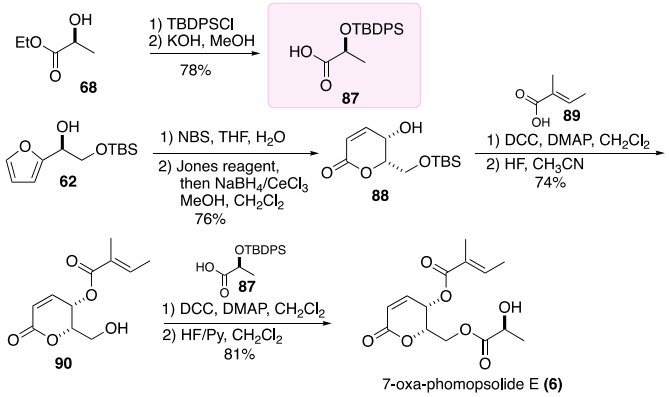


Scheme 16 The O'Doherty synthesis of phomopsolide E.

2.6. O'Doherty's synthesis of 7-oxa-phomopsolide E (2004)

The O'Doherty group's[15] synthetic interest in the phomopsolides extends beyond total synthesis and structural determination. Their interest is also focused on the biological activity of the phomopsolides, where synthetic interest puts a high priority on synthetic efficiency. This effort began with the synthesis of a 7-oxa-analogue of phomopsolide E (**6**) (Scheme 17). Their convergent approach began with the synthesis of TBDPS-protected lactic acid **87**, which was accomplished in two steps from ethyl lactate **68** via TBDPS-protection and ester hydrolysis. Once again, the pyranone portion of the analogue was prepared from furan alcohol **62** by means of an Achmatowicz rearrangement, Jones oxidation and subsequent reduction to give pyranone **88** with a free *C*-4 alcohol. A DCC promoted tiglic acid coupling of the alcohol and HF promoted TBS-deprotection gave the *C*-6 alcohol **90**. A second DCC coupling was used to bring the two components **87** and **90**

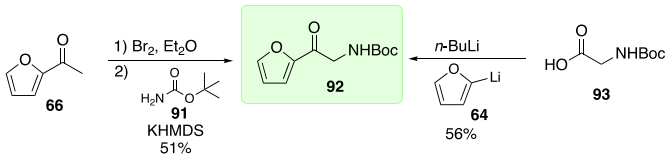
together, which after a TBDPS-deprotection gave the desired analogue 7-oxa-phomopsolide E (**6**). The approach to the oxa-analogue **6** was accomplished in 12 total steps and 6 longest linear steps.



Scheme 17 The O'Doherty synthesis of 7-oxa-phomopsolide E.

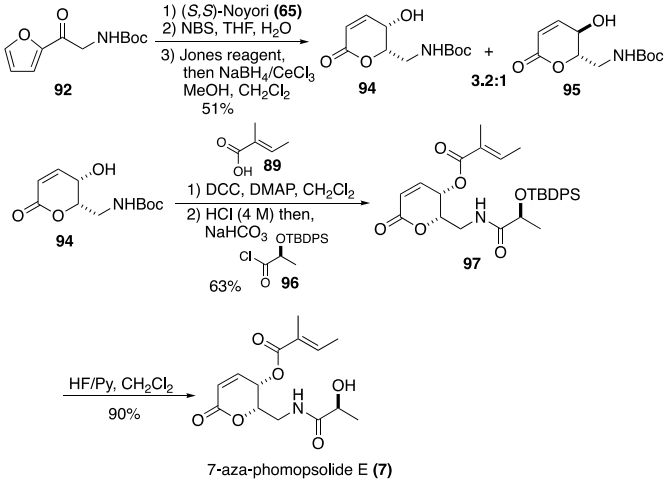
2.7. O'Doherty's synthesis of 7-aza-phomopsolide E (2018)

In addition to the synthesis of the 7-oxa-analogue (**6**), the O'Doherty group[16] also pursued the synthesis of a related 7-aza-analogue (**7**) (Scheme 18). Their synthesis of 7-aza-phomopsolide E (**7**) was a related convergent synthesis using a protected lactic acid chloride **96** and an amino-variant of the *C*-6 alcohol **94**, which was protected as an *N*-Boc amide because it is prone to rearrangement. The synthesis began with the synthesis of the key acylfuran **92**, which the group developed two different approaches to. The first approach involved the α-bromination of 2-acetylfuran **65** and the base promoted displacement with *t*-butyl carbamate **91**. The second and more direct approach involved the addition of excess of 2-lithiofuran **64** to *N*-Boc protected glycine **93** to give **92**.



Scheme 18 Syntheses of *N*-Boc-protected α-amino-acetylfuran 92.

The synthesis continued with a Noyori asymmetric reduction of acylfuran **92** (Scheme 19), which was followed by a three-step double oxidation and Luche reduction sequence to give a 3.2:1 mixture of pyranones **94** and **95**. The major isomer **94** was taken forward with a DCC coupling with tiglic acid followed by a two-step deprotection of the *N*-Boc group and immediate coupling with acid chloride **96** to give the protected analogue **97**. An HF•Py promoted deprotection of the TBDPS-group in **97** gave the desired 7-aza-phomopsolide E (**7**). The approach to the aza-analogue **7** was accomplished in 7 total steps and 3 longest linear steps.



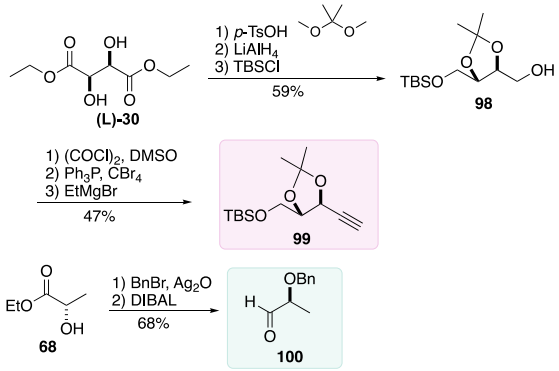
Scheme 19 The O'Doherty synthesis of 7-aza-phomopsolide E.

3. Synthesis of phomopsolidones

In addition to the phomopsolides, there have been synthetic approaches to the isomeric natural products, phomopsolidones A (**8**) and B (**9**). Both of these syntheses were accomplished by the Sabitha group (Schemes 20-22).[17,18] As with the majority of the phomopsolide syntheses, these were convergent syntheses that derived their asymmetry from the two naturally occurring chiral building blocks tartaric acid and lactic acid.

3.1. Sabitha's syntheses of phomopsolidone A (2016)

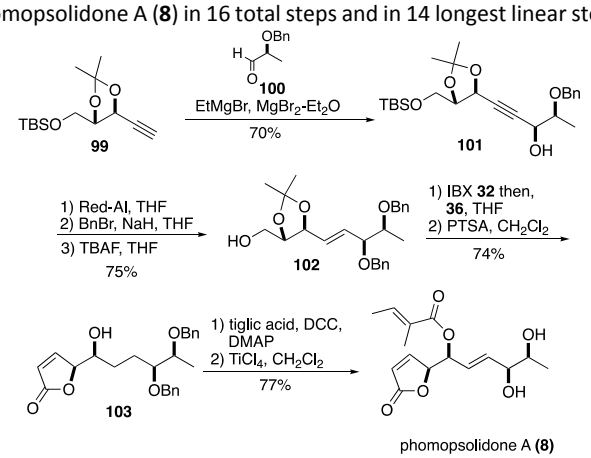
The Sabitha group[17] developed two syntheses of phomopsolidone A (**8**). Their first synthesis of phomopsolidone A (**8**) was accomplish in 2016 by Sabitha *et al.* (Scheme 20). The convergent synthesis began with the syntheses of two chiral components, alkyne **99** and aldehyde **100**. The synthesis of alkyne **99** began with the acetonide protection of diethyl tartrate **30**, which was followed by reduction with $LiAlH_4$ and mono-TBS protection to provide primary alcohol **98**. A Swern oxidation[37] followed by an ethyl Grignard variant of the Corey-Fuchs reaction[38] was used to convert **98** into the desired alkyne **99**. The desired aldehyde **100** was prepared from ethyl lactate **66** by a benzyl protection and DIBAL reduction.



Scheme 20 Fragment synthesis for phomopsolidone A by Sabitha.

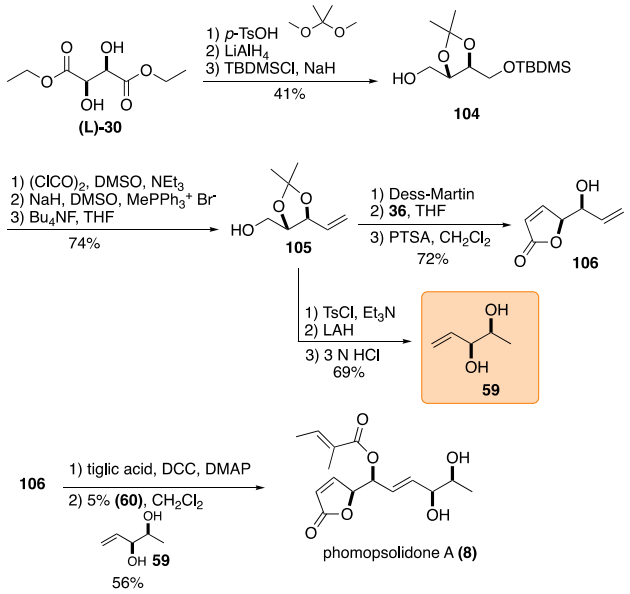
The Sabitha convergent synthesis continued with the addition of metalated **99** to aldehyde **100** via a chelate controlled addition to

diastereoselectively give propargyl alcohol **101** (Scheme 21). A diastereoselective Red-Al reduction of the propargylic alcohol followed by a benzyl-ether protection and TBS-deprotection was used to form primary alcohol **102**. An IBX oxidation to an aldehyde, Still-Gennari *cis*-olefination, acid catalyzed acetonide removal and lactonization led to butenolide **103**. Finally, a DCC/tiglic acid esterification and bis-benzyl ether deprotection gave the natural product phomopsolidone A (**8**). The synthesis as described prepared phomopsolidone A (**8**) in 16 total steps and in 14 longest linear steps.



Scheme 21 The first Sabitha synthesis of phomopsolidone A.

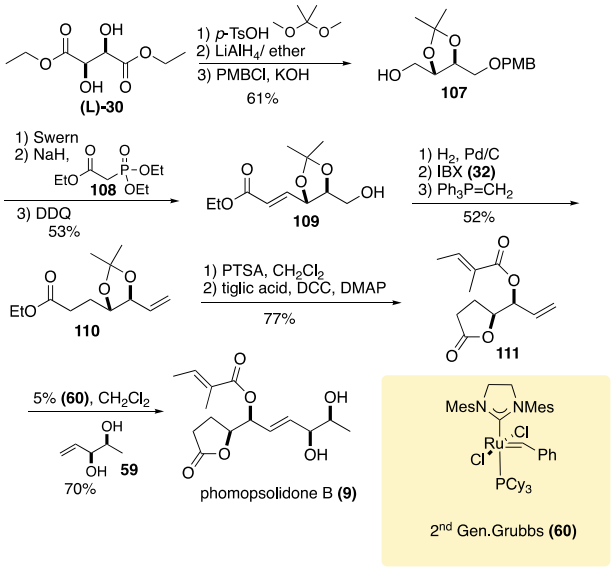
Later that same year, the Sabitha group[18] reported a second-generation synthesis of phomopsolidone A (**8**) (Scheme 22). The synthesis also began with the acetonide protection, $LiAlH_4$ reduction and mono-TBS-protection of diethyl tartrate **29** to form primary alcohol **104**. A Swern oxidation, Wittig olefination and TBS deprotection was used to give primary alcohol **105**.[39] A Dess-Martin oxidation to an aldehyde followed by a Still-Gennari *cis*-olefination, acid catalyzed acetonide removal and lactonization led to butenolide **106**. A tiglic acid/DCC coupling was used to install the *C*-5 tiglic ester, which was followed by a cross metathesis reaction with diol **59**[40] to give phomopsolidone A (**8**). The second-generation synthesis was accomplished in 14 total steps and in 11 longest linear steps.



Scheme 22 The second Sabitha synthesis of phomopsolidone A.

3.2. Sabitha's synthesis of phomopsolidone B (2016)

Using a related approach to their phomopsolidone A (**8**) synthesis, the Sabitha group[18] developed a synthesis of phomopsolidone B (**9**) (Scheme 23). Once again, the synthesis was convergent and derived its asymmetry for both portions from diethyl tartrate **29**. As with the previous approach, the synthesis began with an acetonide protection, $LiAlH_4$ reduction and PMB protection to give primary alcohol **107**. A Swern oxidation, HWE-olefination reagent **108** and DDQ promoted PMB-group deprotection was used to give ω-hydroxy enoate **109**. An alkene hydrogenation, IBX oxidation of the primary alcohol and Wittig olefination was used to form alkene **110**.[41] A concomitant acid catalyzed acetonide removal and lactonization followed by DCC promoted tiglation gave γ **111**. Finally, a cross metathesis reaction between **111** and **59** gave phomopsolidone B (**9**). This synthesis was accomplished in 21 total steps and in 12 longest linear steps.



Scheme 23 The Sabitha synthesis of phomopsolidone B.

4. Biological activity of the phomopsolides and phomopsolidones

The initial biological evaluation of the phomopsolides and the phomopsolidones was centered upon their presumed evolved role in protecting plants (*e.g.*, pacific yew and grapevine) as an antifeeding and/or antimicrobial agent. Of the phomopsolides (A-E), phomopsolide A had the highest antifeeding/boring activity while phomopsolide B had slightly lower activity.[42] In a comparison of phomopsolide B with the phomopsolidones (A-D) (*i.e.*, the grapevine extracts), phomopsolide B was the only one to induce necrosis in grapevine leaves and to inhibit callus growth on the grapevine plant.[42] All five had moderate larvicidal activity, with phomopsolide B, phomopsolidone A and phomopsolidone B slowing larvae development times.[42]

Table 1 Antibacterial activity against *Staphylococcus Aureus.*

Compound	*Staphylococcus aureus*	
	Concentration (μg)	Zone of inhibition (mm)
phomopsolide A (**1**)	25	22
phomopsolide B (**2**)	25	20
phomopsolide C (**3**)	25	22
phomopsolide D (**4**)	100	10
phomopsolide E (**5**)	50	9

In addition, the phomopsolides (A-E) were evaluated for their antibacterial activity against several organisms. In a zone of inhibition study, phomopsolide B showed activity against *Shigella dysenteria* (50 μg, 1.2 cm).[43] Phomopsolides A-E were shown to have slightly better activity against *Staphylococcus aureus* (Table 1). In these zone of inhibition assays, phomopsolides A-C were slightly more active with antibacterial activity evident at 25 μg/mL, whereas higher concentrations were needed for phomopsolides D and E at 100 μg/mL and 50 μg/mL, respectively. Antibacterial activities against *Bacillus subtilis* were also found for phomopsolide B and phomopsolidones A and B.[5] The anti-*B. subtilis* activity was dependent upon the stereochemistry of the pyranone ring, as the *C*-4/5 bis-epimer **50** had significantly reduced activity compared to phomopsoilde B, phomopsolidones A and B (Table 2). [9]

Table 2 Antibacterial activity against *Bacillus subtilis.*

Compound	MIC
phomopsolide B (**2**)	0.1 ng[a]
Epi-phomopsolide B (**50**)	21.1 μM
phomopsolidone A (**8**)	0.1 ng[a]
phomopsolidone B (**9**)	0.1 ng[a]

[a] activity measured via a bioautography method directly from the material on a thin-layer chromatography.

Although modest, phomopsolide A was found to have activity against *Mycobacterium tuberculosis* (Table 3)[5] and less activity for phomopsolide C. No activity was found for phomopsolide B against *Escherichia coli.*, *Candida albicans*, *Saccharomyces cerevisiae*, and *Penicillium avellaneum* (UC-4376).[43]

Table 3 Antibacterial activity against *Mycobacterium tuberculosis* H37Ra.

Compound	MIC (μM)	IC_{50} (μM)
phomopsolide A (**1**)	170	24.4
phomopsolide C (**3**)	680	34.3

The phomopsolides also showed a modicum of anticancer activity against both HeLa and UMUC3 cells with activities in the low μM range for phomopsolides A-C and E (Table 4).[44,43,9] Similar degrees of anticancer activity were found for HEK 293 cells (phomopsolide A, 6.7 μM), Y79 cells (phomopsolide C, 1.4 μM), and H3255 cells (phomopsolide C, 2.6 μM). Not surprisingly, a degree of variability in cancer cell cytotoxicity found was dependent upon the method used, with phomopsolides B and E showing no activity against HeLa or UMUC3 cells in the Alamar Blue viability assay.[44]

Table 4 Anticancer activity against HeLa and UMUC3.

Compound	IC_{50} (μM) against HeLa	IC_{50} (μM) against UMUC3
phomopsolide A (**1**)	6.3,[a] 5.0,[b]	6.5,[a] 4.8[b]
phomopsolide B (**2**)	19.2[c]	6.1[b]
phomopsolide C (**3**)	3.6,[a] 2.7[b]	2.2,[a] 1.4[b]
phomopsolide E (**5**)	7.3[b]	6.6[b]

[a] Alamar Blue Viability Assay was applied; [b] Nuclei Count Proliferation Assay was applied; [c] 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay was applied

The 4,5-bis-epimer of phomopsolide B (**50**) was also screened for anticancer activity (Table 5).[9] In contrast to the antibacterial activity, the anticancer activity was not affected by changes in pyranone stereochemistry. For example, the level of activity was retained for the 4,5-bis-epimers of phomopsolide B (**50**), which showed low μM cytotoxicities for four cell lines (Table 5). These cytotoxicities were on the same order as the cytotoxicity found for the other phomopsolides (Tables 4, 6-7).

Table 5 Cancer cell cytotoxicities of *C*-4/5-bis-*epi*-phomopsolide B (**50**).

Cell Line	IC_{50} (μM)
A549 (non-small cell lung)	10.1 ± 0.22
HeLa (uterus)	6.2 ± 0.12
DU145 (prostate)	15.4 ± 0.16
HepG2 (liver)	12.1 ± 0.21

In addition to confirming the absolute and relative stereochemistry of the phomopsolides, the O'Doherty group also evaluated some of the more readily available synthetic materials as anticancer agents (Tables 6-7).[16] Thus, both synthetic phomopsolides D and E, as well as the oxa- and aza-analogues of phomopsolide E, were screened for cytotoxicity against the NCI panel of 60 cancer cell lines. Depending upon the cell line, the cytotoxicity varied as much as 10-fold (Table 6). For example, phomopsolide D was most active against the renal cell line 786-0 (1.23 μM) and least active against the ovarian cancer cell line SK-OV-3 (11.9 μM); whereas, phomopsolide E was most active against the colon cell line HCT-116 (2.3 μM) and least active against the leukemia cell line MOLT-4 (23.3 μM). Interestingly, the 7-oxa- and 7-aza-phomopsolide E analogues **6** and **7** were also most active against 786-0 (1.9 and 11.3 μM, respectively).[16]

Table 6 Cytotoxicities for phomopsolide D/E and 7-oxa- and aza-analogues.

Compound	Most sensitive cell line	IC_{50} (μM)	Least sensitive cell line	IC_{50} (μM)
phomopsolide D (**4**)	786-0 (renal)	1.23	SK-OV-3 (ovarian)	11.9
phomopsolide E (**5**)	HCT-116 (colon)	2.3	MOLT-4 (leukemia)	23.3
7-oxa-phomopsolide E (**6**)	786-0 (renal)	1.9	CAKI-1 (renal)	10
7-aza-phomopsolide E (**7**)	786-0 (renal)	11.3	DU-145 (prostate)	31.6

When the average cancer cell cytotoxicities for **4**-**7** are looked at by tissue types, most of the average activities range in the 10 to 30 μM range. Interestingly, the leukemia cell lines were a slight outlier to this trend, showing significantly lower average cytotoxicities for phomopsolide D (**4**, 4 μM) and 7-oxa-phomopsolide E (**6**, 8 μM).

Table 7 Tissue specific average cytotoxicities for phomopsolides **4, 5**, **6** and **7**.

Cancer Type	4 IC_{50} (μM)	5 IC_{50} (μM)	6 IC_{50} (μM)	7 IC_{50} (μM)
melanoma	15 ± 4	24 ± 7	13 ± 3	28 ± 9
CNS	17 ± 5	26 ± 11	16 ± 5	29 ± 15
breast	11 ± 3	20 ± 6	12 ± 2	26 ± 10
prostate	18 ± 9	23 ± 15	16 ± 7	25 ± 18
renal	13 ± 4	25 ± 8	15 ± 4	30 ± 11
ovarian	18 ± 6	24 ± 10	16 ± 6	28 ± 14
leukemia	4 ± 3	16 ± 9	8 ± 5	30 ± 14
non-small cell lung	18 ± 6	26 ± 8	19 ± 5	27 ± 9

In addition to trends for the various tissue types, trends in the anticancer activities could be seen for the different analogues in the data across the NCI-60 cell line panel. The average cytotoxicities for each compound across all the cell lines are graphically presented in Fig. 2 and displayed in Table 8. While there is clearly overlapping activity, as there was a broad range of activity depending on the cell lines tested, a general trend of phomopsolide D (**4**) being slightly more active than phomopsolide E (**5**) and 7-oxa-phomopsolide E (**6**) being more active than 7-aza-phomopsolide E (**7**) emerged. This general trend appeared to hold true when the cell lines were divided up by tissue type.

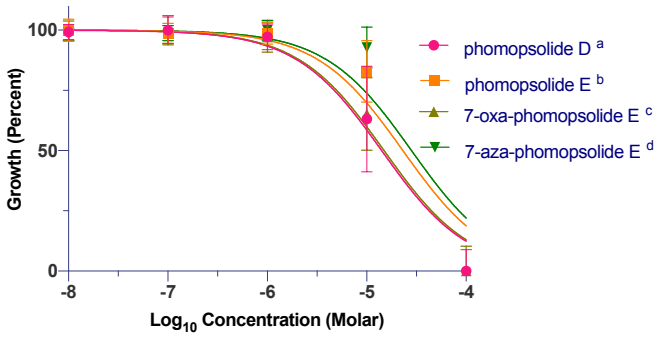


Fig. 2 Average phomopsolide (**4-7**) cytotoxicity curves against the NCI cell lines.

[a] Includes data from 53 of the 60 cell lines tested; [b] Includes data from 57 of the 60 cell lines tested; [c] Includes data from 58 of the 60 cell lines tested; [d] Includes data from 38 of the 60 cell lines tested

Table 8 Average NCI 60 cell-line cytotoxicities for phomopsolides **4, 5**, **6** and **7**.

Compound	Average IC_{50} (μM)
phomopsolide D (**4**)[a]	14 ± 14
phomopsolide E (**5**)[b]	23 ± 16
7-oxa-phomopsolide E (**6**)[c]	15 ± 16
7-aza-phomopsolide E (**7**)[d]	28 ± 18

[a] Includes data from 53 of the 60 cell lines tested; [b] Includes data from 57 of the 60 cell lines tested; [c] Includes data from 58 of the 60 cell lines tested; [d] Includes data from 38 of the 60 cell lines tested

In conclusion, the isolation history of and synthetic efforts toward four of the five phomopsolide natural products (B-E) and two of the four phomopsolidone natural products (A and B) were reviewed. A novel mechanistic interconversion for the biosynthesis of these two classes of natural products was proposed (Scheme 1). In addition, the syntheses of three phomopsolide analogues, including a 7-oxa-, a 7-aza- and a diastereomeric isomer, were covered, which suggest a continuing future of scientific discovery for these novel classes of natural products. In total, the various synthetic approaches comprised thirteen unique synthetic efforts that ranged in synthetic efficiency from a maximum of 25 total steps for the synthesis of phomopsolide B by Noshita to as little as 11 total steps for the synthesis of phomopsolide D by O'Doherty. Of the thirteen syntheses, there were four routes to phomopsolide B (from 18 total steps to 25), two syntheses of phomopsolide C (from 12 total steps to 18), one synthesis of phomopsolide D (11 total steps), one synthesis of phomopsolide E (14 total steps), and two syntheses of analogues of phomopsolide E (7 and 12 steps). In addition, there have been two syntheses of phomopsolidone A (16 and 14 total steps) and one synthesis of phomopsolidone B (21 total steps). Taken in total, the syntheses of the phomopsolide, phomopsolidones and related analogues have enabled the initial structure activity relationship studies of this interesting class of polyketide natural products as both antimicrobial and anticancer agents, which one can imagine as leading to future medicinal chemistry studies.

Keywords: • total synthesis • asymmetric synthesis approach • phomopsolide • phomopsolidone

Conflicts of interest

"There are no conflicts to declare".

Acknowledgements

This work was supported by the National Science Foundation (CHE-1565788) and the National Institutes of Health (AI146485, AI144196 and AI142040). AZA would like to thank King Abdullah Scholarship Program for a graduate fellowship.

1 J. F. Grove, *J. Chem. Soc., Perkin Trans*., 1985, **1**, 865-869.
2 D. B. Stierle, A. A. Stierle and B. Ganser, *J. Nat. Prod*., 1997, **60**, 1207-1209.
3 H. Becker, *Agricultural Research,* 1996, **44**, 4-8.
4 F. S. Santamour and S. E. Bentz, *J. of Arboriculture,* 1995, **21**, 122-131.
5 M. -L. Goddard, N. Mottier, J. Jeanneret-Gris, D. Christen, R. Tabacchi and E. Abou-Mansour, *J.* Agric. *Food Chem.,* 2014, **62**, 8602–8607.
6 T. N. Clark, K. T. Ellsworth, S. Jean, D. Webster, G. A. Robichaud, J. A. Johnson and C. A. Gray, *Nat. Prod. Commun*, 2015, **10**, 1647-1648.
7 T. Noshita, T. Sugiyama, K. Yamashita and T. Oritani, *Biosci. Biotech. Biochem*., 1994, **58**, 740-744; T. Noshita, T. Sugiyama and K. Yamashita, *Agric. Biol. Chem.,* 1991, **55**, 1207–1209.
8 K. R. Prasad and P. Gutala, *Tetrahedron,* 2012, ***68,*** 7489-7493.
9 N. R. Emmadi, C. Bingi, C. G. Kumar, P. Yedla and K. Atmakur, *Synthesis,* 2014, **46**, 2945–2950.
10 D. V. Reddy, G. Sabitha and J. S. Yadav, *Tetrahedron Lett.,* 2015, **56**, 4112-4114.
11 J. M. Harris and G. A. O'Doherty, *Tetrahedron Lett.,* 2002, **43**, 8195-8199.
12 S. Michaelis and S. Blechert, *Org. Lett.,* 2005, **7**, 5513-5516.
13 M. Li and G. A. O'Doherty, *Tetrahedron Lett.,* 2004, **45**, 6407-6411.
14 J. M. Harris, M. Li and G. A. O'Doherty, *Heterocycles*, 2019, **99**, 1217-1225.
15 M. Li, J. G. Scott and G. A. O'Doherty, *Tetrahedron Lett.,* 2004, **45**, 1005-1009.
16 A. Z. Aljahdali, S. A. Freedman, M. Li and G. A. O'Doherty, *Tetrahedron*, 2018, **74**, 7121-7126.
17 K. Shiva Raju, A. Raju and G. Sabitha, *Tetrahedron Lett*., 2016, **57**, 2109–2111.
18 K. Shiva Raju and G. Sabitha, *Tetrahedron: Asymmetry,* 2016, **27**, 639-642.
19 F. Gonzalez, S. Lesage and A. S. Perlin, *Carbohydr. Res*., 1975, **42**, 267-274.
20 O. Mitsunobu, *Synthesis*, 1981, 1-28.
21 E. Lee, C. M. Park and J. S. Yun, *J. Am. Chem. Soc*., 1995, **117**, 8017.
22 K. C. Nicolaou, T. Montagnon, P. S. Baran and Y. -L. Zhong, *J. Am. Chem. Soc*., 2002, **124**, 2245–2258.
23 S. Valverde, B. Herradon, R. M. Rabanal and M. M. Lomas, *Can. J. Chem*., 1987, **65**, 332.
24 V. Loukas, T. Markidis and G. Kokotos, *Molecules,* 2002, **7**, 767-776.
25 D. B. Dess and J. C. Martin, *J. Am. Chem. Soc.,* 1991, **113**, 7277-7287.
26 W. C. Still and C. Gennari, *Tetrahedron Lett.,* 1983, **24**, 4405.
27 M. Scholl, T. M. Trnka, J. P. Morgan and R. H. Grubbs, *Tetrahedron Lett*., 1999, **40**, 2247–2250; J. -K. Huang, E. D. Stevens, S. P. Nolan and J. L. Petersen, *J. Am. Chem. Soc*., 1999, **121**, 2674–2678.

References

28 J. M. Harris, M. D. Keranen and G. A. O'Doherty, *J. Org. Chem.,* 1999, **64**, 2982-2983; J. M. Harris, M. D. Keranen, H. Nguyen, V. G. Young and G. A. O'Doherty, *Carbohydr. Res*., 2000, **328**, 17-36; H. Guo and G. A. O'Doherty, *Org. Let.,* 2005, **7**, 3921-3924; S. R. Guppi, M. Zhou and G. A. O'Doherty, *Org. Lett.,* 2006, **8**, 293-296; M. Zhou and G. A. O'Doherty, *Org. Lett.,* 2006, **8**, 4339-4342; M. Shan and G. A. O'Doherty, *Org. Lett.,* 2006, **8**, 5149-5152; H. Guo and G. A. O'Doherty, *Angew. Chem. Int. Ed.,* 2007, **46**, 5206-5208; X. Yu and G. A. O'Doherty, *Org. Lett*., 2008, **10**, 4529-4532.

29 Y. Ma and G. A. O'Doherty, *Org. Lett*., 2015, **17**, 5280-5283; J. A. Coral, H. Guo, M. Shan and G. A. O'Doherty, *Heterocycles*, 2009, **79**, 521-529; J. N. Abrams, R. S. Babu, H. Guo, D. Le, J. Le, J. M. Osbourn and G. A. O'Doherty, *J. Org. Chem*., 2008, **73**, 1935-1940; H. Guo and G. A. O'Doherty, *Tetrahedron*, 2008, **64**, 304-313; H. Guo and G. A. O'Doherty, *Org. Lett*., 2006, **8**, 1609 – 1612; M. H. Haukaas and G. A. O'Doherty, *Org. Lett*., 2001, **3**, 401-404.

30 J. M. Harris and G. A. O'Doherty, *Tetrahedron,* 2001, **57**, 5161-5171; J. M. Harris and G. A. O'Doherty, *Org. Lett*., 2000, **2**, 2983-2986; J. M. Harris and G. A. O'Doherty, *Tetrahedron Lett*., 2000, **41**, 183-187.

31 R. Noyori and T. Ohkuma, *Angew. Chem. Int. Ed.,* 2001, **40**, 40; R. Noyori, M. Yamakawa and S. Hashiguchi, *J. Org. Chem.,* 2001, **66**, 7931.

32 M. Ferrero, M. Galobardes, R. Martin, T. Montes, R. Romea, R. Rovira, F. Urpi and J. Vilarrasa, *Synthesis*, 2000, **11**, 1608–1614; M. L. Fein and E. M. Filachione, *J. Am. Chem. Soc.,* 1953, **75**, 2097–2099.

33 O. Achmatowicz and R. Bielski, *Carbohydr. Res*., 1977, **55**, 165–176.

34 J. -L. Luche, *J. Am. Chem. Soc.*, 1978, **110**, 2226–2227.

35 K. M. Engle, G. Lu, S. -X. Luo, L. M. Henling, M. K. Takase, P. Liu, K. N. Houk and R. H. Grubbs, *J. Am. Chem. Soc*., 2015, **137**, 5782-5792.

36 K. B. Sharpless, W. Amberg, Y. L. Bennani, G. A. Crispino, J. Hartung, K. S. Jeong, H. L. Kwong, K. Morikawa, Z. M. Wang, D. Xu and X. L. Zhang, *J. Org. Chem.,* 1992, **57**, 2768; H. C. Kolb, M. S. VanNieuwenhze and K. B. Sharpless, *Chem. Rev.,* 1994, **94**, 2483; G. Guo, M. S. Mortensen and G. A. O'Doherty, *Org. Lett.,* 2008, **10**, 3149; M. Li and G. A. O'Doherty, *Org. Lett.,* 2006, **8**, 6087; Y. Zhang and G. A. O'Doherty, *Tetrahedron,* 2005, **61**, 6337–6351.

37 A. J. Mancuso, D. S. Brownfain and D. Swern, *J. Org. Chem*., 1979, **44**, 4148–4150.

38 E. J. Corey and P. L. Fuchs, *Tetrahedron Lett*., 1972, **13**, 3769–3772.

39 V. Andre, H. Lahrache, S. Robin and G. Rousseau, *Tetrahedron*, 2007, **63**, 10059–10066.

40 S. K. Chang, S. M. So, S. M. Lee, M. K. Kim, K. M. Seol, S. M. Kim, J. S. Kang, D. J. Choo, J. Y. Lee and B. M. Kim, *Bull. Korean Chem. Soc*., 2012, **33**, 2213–2218.

41 J. S. Yadav, K. A. Lakshmi, N. M. Reddy, N. Swapnil, A. R. Prasad, *Tetrahedron: Asymmetry,* 2012, **23**, 1155–1160

42 N. Claydon, J. F. Grove and M. Pople, *Phytochemistry*, 1985, **24**, 937-943.

43 L. Yuan, X. Lin, P. -J. Zhao, J. Ma, Y. -J. Huang and Y. -M. Shen, *Helv. Chim. Acta*, 2009, **92**, 1184-1190

44 D. B. Stierle, A. A. Stierle and B. Ganser, *J. Nat. Prod.*, 1997, **60**, 1207-1209.

Table of Content:

A review of the discovery, synthesis and medicinal chemistry of the phomopsolide and phomopsolidone classes of regioisomeric polyketides is presented.