Pergamon

Tetrahedron Letters 43 (2002) 8195–8199

TETRAHEDRON LETTERS

An enantioselective total synthesis of phomopsolide C

Joel M. Harris and George A. O'Doherty*

Department of Chemistry, West Virginia University, Morgantown, WV 26506, USA

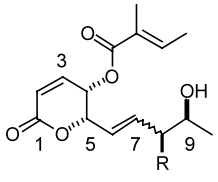
Received 12 July 2002; accepted 31 July 2002

Abstract—A flexible enantioselective route to highly functionalized α,β-unsaturated δ-lactones, has allowed for the synthesis of phomopsolide C. This approach derives its asymmetry from (*S*)-lactic acid and by applying the Sharpless catalytic asymmetric dihydroxylation to vinylfuran. The resulting diols are produced in high enantioexcess and can be stereoselectively transformed into α,β-unsaturated-δ-lactones via a short highly diastereoselective oxidation and reduction sequence. A Wittig olefination reaction was used to introduce the side chain in either *cis* or *trans* form that was further elaborated into phomopsolide C. © 2002 Published by Elsevier Science Ltd.

1. Introduction

Because American elm trees thrive on a wide range of soils and can endure root disturbance, drought and extreme cold, they became the most widely-planted street tree in North America over the past century.[1] Unfortunately, a completely healthy 100-year-old American elm can be killed in as little as two weeks if attacked by Dutch elm disease.[2] Since the arrival of this pandemic to North America, over 40 million elm trees in the United States have been killed.[3] It was not uncommon for a city to lose 90% of its elms in as little as ten years.[4] For instance, Des Moines, Iowa, lost a quarter of a million trees in 6 years.[4] The fungus responsible for Dutch elm disease would be quite innocuous if it were not for its association with the elm bark beetle (Scolytid beetle). Therefore, protecting the trees from the elm bark beetle should prove to be an effective strategy for fighting this suburban pandemic.

In search of natural compounds that have an effective antiboring/antifeeding activity, Grove,[5] and later Stierle,[6] found a series of related 6-substituted 5,6-dihydro-5-hydroxypyran-2-ones, the phomopsolides, with the desired deterrent activity for Scolytid beetles. In 1985, Grove isolated phomopsolide A and B from the fungus *Phomopsis oblonga*, which co-habitate with the elm tree. In 1997, Stierle re-isolated phomopsolide A and B in addition to three new phomopsolides (C–E) from fungi lying in the bark of the Pacific yew (*Taxus brevifolia*) and found them to have potent antimicrobial activity against *S. aureus*.



1a: cis, R = O; **Phomopsolide A**
1b: trans, R = OH; **Phomopsolide B**
1c: trans, R = O; **Phomopsolide C**
1d: 6,7-dihydro, R = OH; **Phomopsolide D**
1e: 6,7-dihydro, R = O; **Phomopsolide E**

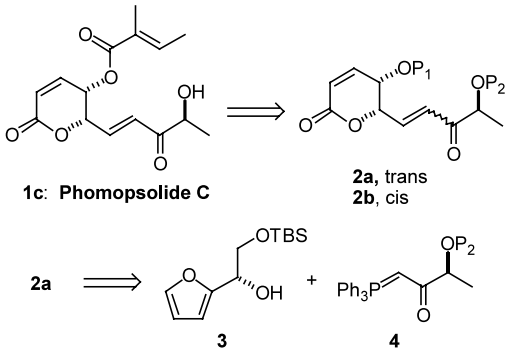
Figure 1.

Inspired by the potent biological activity, in addition to the synthetic challenges the structure offers, we set out to synthesize this class of substituted pyranone using our furan diol chemistry.[7] To date only one phomopsolide has succumbed to total synthesis, that being phomopsolide B by Noshita[8] who synthesized it from glucose in 24 steps. While Noshita's route is significant in that it established the relative and absolute stereochemistry of phomopsolide B, because of its length and poor stereocontrol, we deemed the approach to be too inefficient to provide sufficient quantities of material for further study. Thus, we desired a more expedient route to the phomopsolides, which has better relative stereocontrol in addition to being amenable to the synthesis of the many possible phomopsolides. Herein we report our successful endeavors toward the first synthesis of the densely functionalized pyranone natural product phomopsolide C (**1c**), in enatiomerically pure form (Fig. 1).

Previously, we have had success at enantioselectively synthesizing various biologically important pyranones

* Corresponding author.

0040-4039/02/$ - see front matter © 2002 Published by Elsevier Science Ltd.
PII: S0040-4039(02)01866-X

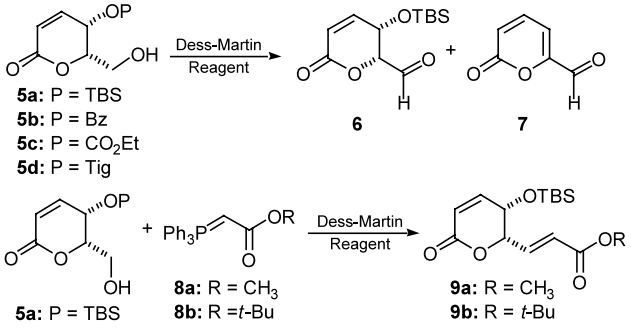


Scheme 1.

from dienoates[9] and furan alcohols.[7,10] The furyl alcohols were enantioselectively prepared from the Sharpless asymmetric dihydroxylation of vinylfuran.[11] At the outset, we targeted a selective synthesis of the *trans* phomopsolide isomers **1b** and **1c** from enone **2a** (Scheme 1), as we felt that *trans* isomer **2a** could provide phomopsolide C.[12] Incorporation of chemoselective and stereoselective enone reductions should produce the other phomopsolides (A, B, D and E) from **2a** or its *cis*-double bond isomer **2b**. We opted for a degree of convergence by deriving the C-9 stereochemistry from lactic acid where as the C-4/C-5 stereochemistry would come from our furan to pyranone oxidation strategy.[7,10]

Our approach to this class of natural products was inspired by our recent synthesis of several altholactones.[7] During those studies we found the use of an in situ Dess–Martin oxidation/Wittig olefination reaction allowed for good yields of olefination products via an unstable aldehyde **6** (Scheme 2). Thus, we planned to use this approach for the production of the *trans* double bond isomers of enone **2**. Initially we planned to install the C-4 tigilate group before the oxidation/Wittig sequence, however we found that the corresponding aldehydes generated from **5b**, **5c**, and **5d** underwent rapid elimination reactions to pyranone **7**. This base sensitivity proved to be problematic throughout the synthesis (vide infra).

We initially investigated the Wittig olefination reaction with more readily available reagents **8a** and **8b**. In practice, we found that a mixture of double bond isomers (*cis* and *trans*-**9a**) were produced when a 1:4



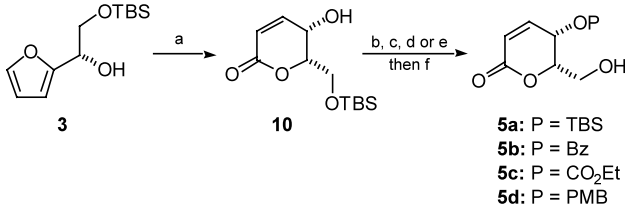
Scheme 2.

mixture of alcohol **5a** and phosphorane **8a** were treated with excess Dess–Martin's reagent (60% yield). Similar results were obtained with the *t*-butyl phosphorane **8b** (75% yield) which exclusively gave the *trans* isomer **9b**. As expected, the more stable *trans* double bond isomer **9a** was easily obtained by a photochemical isomerization ($I_2/h\nu$, >95%). As with the Dess–Martin oxidation of **5**, the in situ oxidation/Wittig reaction of **5** was only compatible with C-4 ether substitution. Hence, exposure of benzoate **5b** and carbonate **5c** to the same reaction sequence provided good yields of the alkene **9c**, which presumably occurs via a base catalyzed elimination of the desired product.

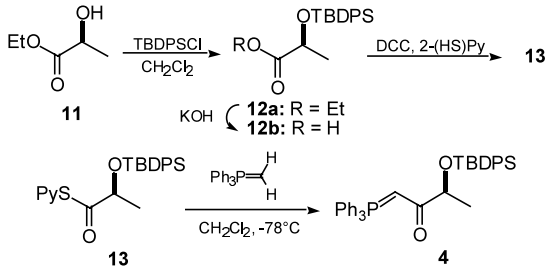
Previously, we have prepared in either enantiomerically pure form the four pyranones **5a** through **5d** prepared from furfural in six steps and good overall yields.[10] Key to this transformation is the efficient production of pyranone **10** from furyl alcohol **3** (Scheme 3). Treatment of furyl alcohol **3** with NBS[13] in aqueous THF (Achmatowicz reaction),[14] then Jones reagent gave a ketolactone intermediate, which was taken on without purification to a Luche reduction[15] with $NaBH_4$ and $CeCl_3$ in MeOH, to give δ-lactone **10**[16] in 70% yield from **3** and >92% ee.[17] The C-4 hydroxyl group of **10** was readily protected as either a TBS ether (85%), benzoyl ester (96%), PMB ether (85%), or ethoxycarbonate (92%). In each case, the primary TBS groups were selectively deprotected with 5% HF in CH_3CN to give primary alcohols **5a** through **5d** (91, 96, 61, 96% yield, respectively). Unfortunately, due to an ensuing elimination reaction only the C-4 TBS and PMB ethers could be carried forward.

Following a protocol developed by Thomas[18] the desired ylide **4** was prepared from (*S*)-ethyl lactate **11** in 4 steps and 40% overall yield (Scheme 3). The hydroxyl group of (*S*)-ethyl lactate **11** was protected with TBDPSCl to give **12a** followed by ester hydrolysis to form the acid **12b** (75%). The carboxylic acid **12b** was converted into the thioester **13** with 2-thiopyridine and DCC (70%), which in turn reacted with the Wittig reagent to give ylide **4** in good yield (70%). Ylide **4** was remarkably stable to silica gel chromatography, but not to long term storage (Scheme 4).

Treatment of aldehyde **6** generated from Dess–Martin oxidation of lactone **5a** with the ylide **4** in CH_2Cl_2 at rt gave a mixture of *trans*- and *cis*-alkenes **2a** and **2b** in



Scheme 3. (a) i. NBS, $NaHCO_3$, NaOAc, THF, H_2O, 0°C; ii. Jones reagent, acetone, 0°C, then $NaBH_4$/CeCl3, MeOH/CH_2Cl_2, −78°C; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2; (c) BzCl, Pyr; (d) PNBO(NH)CCl_3, $BF_3{\cdot}OEt_2$, CH_2Cl_2; (e) $ClCO_2Et$, Pyr; (f) 5% HF(aq.)/AN.

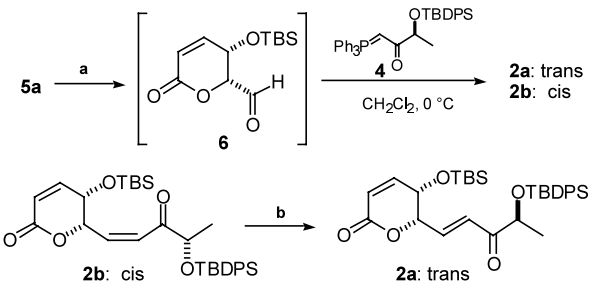


Scheme 4.

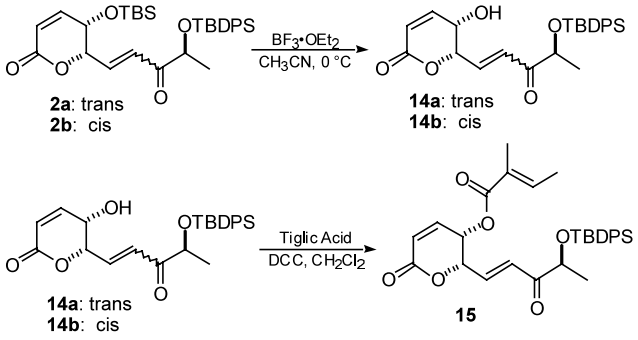
60% yield as a 3:1 mixture in favor of the *trans* alkene (Scheme 5).[19] The double bond isomers were easily separated by silica gel chromatography. The minor isomer δ-lactone **2b** was isomerized to the *trans* isomer **2a** in a >95% yield using AIBN and PhSH in refluxing benzene. A much higher yielding olefination procedure for the *trans* isomer **2a** resulted from an initial florisil purification of aldehyde **6** before exposure to Wittig reagent **4** in refluxing benzene, yielding **2a** and **2b** as a 9:1 ratio and 80% yield.

The two silylethers of **2a** and **2b** were easily differentiated by a selective deprotection with $BF_3{\cdot}OEt_2$ in CH_3CN at 0°C (Scheme 6). The *trans*-allylic alcohol **14a** was isolated in a 91% yield were as the *cis*-allylic alcohol **14b** was isolated in a 78% yield. In the *trans* series, the C-4 tigilate of the phomopsolides was introduced by a DCC coupling of **14a** and tiglic acid, providing **15** in a good yield (75%). Unfortunately in the *cis* series, when the *cis*-enone **14b** was subjected to the same DCC coupling procedure only the *trans* acylated product **15** was detected.

The enone **15** was too base sensitive for TBAF mediated deprotection of the TBDPS group (Scheme 7). For example, exposure of **15** to 1 equiv. of TBAF in CH_2Cl_2 gave exclusively the elimination product **16**. Modifying the basicity of TBAF with acetic acid led to no reaction. Finally resorting to excess $Et_3N{\cdot}3HF$ in CH_2Cl_2 at room temperature for 1-day lead to good yields of phomopsolide C, the *trans*-enone natural product **1c**. While phomopsolide C was unstable to silica gel it could be purified by chromatography on florisil, providing 73% yield of a white solid with spectral data that matched that of the isolated natural product (R_f, optical rotation, IR, ^1H NMR, and ^{13}C NMR).

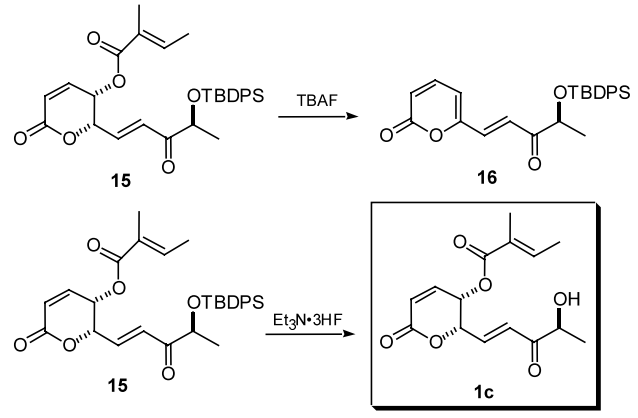


Scheme 5. (a) Dess–Martin periodinane, CH_2Cl_2, $NaHCO_3$, rt; (b) PhSH, 5 mol% AIBN, PhH, reflux.



Scheme 6.

In conclusion, this highly enantio- and diastereocontrolled route to phomopsolide C (**1c**) was completed in 11 steps (longest linear sequence) and 15% overall yield. Unfortunately, due to double bond isomerization we were unable to prepare phomopsolide A. Future work in this area will involve efforts to solve this double bond isomerization problem and broadening this route to include the stereoselective preparation of phomopsolide B, D and E.



Scheme 7.

2. Experimental section

2.1. (5*S*)-5-[*tert*-Butyldimethylsilanyloxy)-(6*S*)-6-[(4*S*)-4-(*tert*-butyldiphenylsilanyloxy)-3-oxo-pent-1(*E*)-enyl]-5,6-dihydropyran-2-one (2a)

The crude aldehyde 6 (237 mg, 0.924 mmol) was dissolved in 10 mL of benzene and phosphorane **4** (813 mg, 1.4 mmol) was added to the solution. The reaction was heated to reflux and stirred for 4 h. The reaction was concentrated and the crude product was purified silica gel chromatography eluting with (30% EtOAc/hexanes) to give a 9:1 ratio of compounds **2a** (378 mg, 0.669 mmol) and **2b** (42 mg, 0.074 mmol) in an 80% overall yield. Major *trans* isomer 2a: R_f (30% EtOAc/hexanes) = 0.15; $[\alpha]_D^{21} = +40.1$ (*c* 2.82, CH_2Cl_2); IR (thin film, cm^{-1}) 3071, 2956, 2931, 2893, 2858, 1736, 1702, 1638, 1472, 1428, 1363, 1248, 1112, 1058; ^1H NMR (500 MHz, $CDCl_3$) δ 7.66 (dd, $J = 7.5$, 1.5 Hz, 2H), 7.62

(dd, $J=8.0$, 1.5 Hz, 2H), 7.45-7.33 (m, 6H), 7.04 (dd, $J=15.5$, 2.0, Hz, 1H), 6.89 (dd, $J=15.5$, 4.0 Hz, 1H), 6.80 (dd, $J=10.0$, 5.0 Hz, 1H), 6.06 (d, $J=10.0$ Hz, 1H), 5.00 (ddd, $J=4.0$, 4.0, 2.0 Hz, 1H), 4.42 (dd, $J=4.5$, 4.5 Hz, 1H), 4.31 (q, $J=7.0$ Hz, 1H), 1.23 (d, $J=6.5$ Hz, 3H), 1.11 (s, 9H), 0.84 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.7, 162.0, 145.0, 139.3, 135.7, 135.6 (2C), 133.4, 132.8, 129.8, 127.62, 127.58, 126.0, 121.8, 79.4, 74.9, 63.4, 26.8, 25.4, 20.5, 19.1, 17.9, −4.6, −5.0; FAB HRMS Calcd for $[C_{32}H_{44}O_5Si_2+Na]^+$: 587.2625, Found: 587.2636.

2.2. (6*S*)-6-[(4*S*)-4-(*tert*-Butyldiphenylsilanyloxy)-3-oxo-pent-1(*E*)-enyl]-(5*S*)-5-hydroxy-5,6-dihydro-pyran-2-one (14a)

Compound **2a** (66 mg, 0.117 mmol) was dissolved in 1 mL of CH_3CN and BF_3OEt_2 (15 uL, 0.12 mmol) was added to the solution at 0°C. The reaction was stirred for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$, extracted (3×25 mL) with Et_2O, and dried (Na_2SO_4). The crude product was purified by silica gel flash chromatography eluting with 100% Et_2O to yield 48 mg (0.106 mmol, 91%) of 15a: R_f (100% Et_2O) = 0.15; $[\alpha]_D^{21}=+28.3$ (*c* 0.4, CH_2Cl_2); IR (thin film, cm^{-1}) 3442, 2957, 2928, 2857, 1731, 1714, 1634, 1470, 1463, 1428, 1384, 1247, 1111; ^{1}H NMR (300 MHz, C_6D_6) δ 7.78–7.71 (m, 4H), 7.25–7.20 (m, 6H), 7.12 (dd, $J=15.9$, 2.1, Hz, 1H), 6.80 (dd, $J=15.6$, 3.9 Hz, 1H), 5.90 (dd, $J=9.9$, 5.4 Hz, 1H), 5.62 (d, $J=9.9$ Hz, 1H), 4.43 (q, $J=6.9$ Hz, 1H), 4.11 (ddd, $J=3.6$, 3.3, 2.1 Hz, 1H), 3.20 (dd, $J=5.4$, 3.0 Hz, 1H), 1.23 (s, 9H), 1.18 (d, $J=6.6$, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 199.5, 161.8, 143.8, 139.5, 136.7, 136.5, 130.6, 128.5, 127.0, 122.9, 79.4, 75.8, 62.5, 27.6, 20.9, 19.9; FAB HRMS Calcd for $[C_{26}H_{30}O_5Si+H]^+$: 473.1760, Found: 473.1759.

2.3. 2-Methylbut-2-enoic acid (2*S*)-2-[(4*S*)-4-(*tert*-butyl-diphenylsilanyloxy)-3-oxo-pent-1(*E*)-enyl]-6-oxo-3,6-dihydro-2*H*-pyran-(3*S*)-3-yl ester (15)

Alcohol **14a** (45 mg, 0.10 mmol), 1.5 mL of CH_2Cl_2, DCC (41 mg, 0.2 mmol), DMAP catalytic amount, and tiglic acid (20 mg, 0.2 mmol) were added to a round bottom flask and stirred at room temperature for 6 h. The reaction was filtered through a pad of celite and concentrated. The crude product was purified by silica gel flash chromatography eluting with 50% Et_2O/hexanes to yield 40 mg (0.075 mmol, 75%) of **15a**: R_f (50% Et_2O/hexanes) = 0.15; $[\alpha]_D^{21}=+71.6$ (*c* 0.25, CH_2Cl_2); IR (thin film, cm^{-1}) 2956, 2926, 2855, 1738, 1716, 1463, 1429, 1245, 1112, 1086; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65–7.59 (m, 4H), 7.44–7.33 (m, 6H), 7.07 (dd, $J=$ 15.5, 1.5, Hz, 1H), 6.84 (m, 1H), 6.78 (dd, $J=16.0$, 4.5 Hz, 1H), 6.24 (d, $J=9.5$ Hz, 1H), 5.36 (dd, $J=5.5$, 3.5 Hz, 1H), 5.21 (ddd, $J=4.0$, 3.5, 2.0 Hz, 1H), 4.30 (q, $J=7.0$ Hz, 1H), 1.76 (dd, $J=6.0$, 1.0 Hz, 3H), 1.25 (s, 3H), 1.22 (d, $J=7.0$ Hz, 3H), 1.10 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.9, 166.5, 164.5, 140.9, 139.9, 137.5, 135.8, 135.7, 130.0, 127.8, 126.7, 125.5, 124.6, 77.6, 74.9, 63.2, 26.9, 20.6, 19.2, 14.5, 11.9; FAB HRMS Calcd for $[C_{31}H_{36}O_6Si+Na]^+$: 555.2179, Found: 555.2184.

2.4. Phomopsolide C (1c)

Ester **15** (3.0 mg, 5.6 μmol), 0.15 mL of THF, and triethylamine trihydrofluoride (10 μL, 5.6 μmol) were added to a plastic vial and stirred at room temperature for 24 h. The reaction was quenched with saturated $NaHCO_3$, the aqueous layer was extracted with ether, and the organic layer was dried ($MgSO_4$). The crude product was purified by silica gel flash chromatography eluting with Et_2O to yield 1.2 mg (4.1 μmol, 73%) of phomopsolide C **1c**: R_f (100% Et_2O) = 0.15; $[\alpha]_D^{21}=+175$ (*c* 0.05, CH_2Cl_2); IR (thin film, cm^{-1}) 3500, 2975, 2926, 1730, 1710, 1643, 1429, 1245, 1112; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.05 (dd, $J=9.5$, 5.5, Hz, 1H), 6.93 (dd, $J=16.0$, 4.0 Hz, 1H), 6.83 (m, 1H), 6.72 (dd, $J=15.5$, 2.0 Hz, 1H), 6.24 (d, $J=10.0$ Hz, 1H), 5.50 (dd, $J=5.5$, 3.5 Hz, 1H), 5.31 (ddd, $J=3.5$, 3.5, 2.0 Hz, 1H), 4.30 (m, 1H), 1.77 (m, 6H), 1.39 (d, $J=7.0$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.0, 166.9, 161.9, 141.3, 140.6, 139.4, 127.6, 126.3, 125.0, 77.6, 72.4, 63.0, 20.2, 15.0. 12.3.

Acknowledgements

We thank the Arnold and Mabel Beckman Foundation for their generous support of our program.

References

1. Becker, H. *Agri. Res.* **1996**, *44*, 4–8.
2. Santamour, F. S.; Bentz, S. E. *J. Arboricult.* **1995**, *21*, 122–131.
3. Sinclair, W. A.; Lyon, H. H.; Johnson, W. T. *Diseases of Trees and Shrubs*; Cornell University Press: Ithaca, NY, 1987; p. 574.
4. (a) Smalley, E. B.; Guries, R. P. *Annu. Rev. Phytopathol.* **1993**, *31*, 325–353; (b) Stipes, R. J.; Campana, R. J. *Compendium of Elm Diseases*; American Phytopathological Society Press: St. Paul, MN, 1981; p. 96.
5. Grove, J. F. *J. Chem. Soc., Perkin Trans. 1* **1985**, 865–869.
6. Stierle, D. B.; Stierle, A. A.; Ganser, B. *J. Nat. Prod.* **1997**, *60*, 1207–1209.
7. For the application of this approach toward several styryllactone natural products see: (a) Harris, J. M.; O'Doherty, G. A. *Tetrahedron* **2001**, *57*, 5161–5171; (b) Harris, J. M.; O'Doherty, G. A. *Org. Lett.* **2000**, *2*, 2983–2986.
8. (a) Noshita, T.; Sugiyama, T.; Yamashita, K. *Agric. Biol. Chem.* **1991**, *55*, 1207–1209; (b) Noshita, T.; Sugiyama, T.; Yamashita, K.; Oritani, T. *Biosci. Biotech. Biochem.* **1994**, *58*, 740–744.
9. For the synthesis of cryptocarya diacetate see: Hunter, T. J.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 2777–2780.
10. Harris, J. M.; O'Doherty, G. A. *Tetrahedron Lett.* **2000**, *41*, 183–187.

11. (a) Harris, J. M.; Keranen, M. D.; O'Doherty, G. A. *J. Org. Chem.* **1999**, *64*, 2982–2983; (b) Harris, J. M.; Keranen, M. D.; Nguyen, H.; Young, V. G.; O'Doherty, G. A. *Carbohydr. Res.* **2000**, *328*, 17–36.
12. Stierle proposed the names *E*-phomopsolide A, 6,7-dihydro-phomopsolide B and 6,7-dihydrophomopsolide B for compounds **1c**, **1d**, **1e** respectively, see Ref. 6. For simplicity sake, we have chosen to use the names phompsolide C, D, and E for the natural products **1c**, **1d**, **1e** respectively.
13. (a) Grapsas, I. K.; Couladouros, E. A.; Georgiadis, M. P. *Pol. J. Chem.* **1990**, *64*, 823–826; (b) Georgiadis, M. P.; Couladoros, E. A. *J. Org. Chem.* **1986**, *51*, 2725–2727.
14. (a) An Achmatowicz reaction is the oxidative rearrangement of furfuryl alcohols to 2-substituted 6-hydroxy-2H-pyran-3(6H)-ones, see: Ref. 13; (b) Achmatowicz, O.; Bielski, R. *Carbohydr. Res.* **1977**, *55*, 165–176. For its use in carbohydrate synthesis see: Ref. 12; (c) Balachari, D.; O'Doherty, G. A. *Org. Lett.* **2000**, *2*, 863–866; (d) Balachari, D.; O'Doherty, G. A. *Org. Lett.* **2000**, *2*, 4033–4036.
15. Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *110*, 2226–2227.
16. All new compounds were identified and characterized by ^{1}H NMR, ^{13}C NMR, FTIR, HRMS, and/or EA analysis.
17. Enantiomeric excesses were determined by ^{1}H NMR and ^{19}F NMR of the Mosher ester derivatives, see: (a) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143–2147; (b) Yamaguchi, S.; Yasuhara, F.; Kabuto, K. T. *Tetrahedron* **1976**, *32*, 1363–1367.
18. Savage, I.; Thomas, E. J.; Wilson, P. D. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3291–3303.
19. Barrett, A. G. M.; Hamprecht, D.; Ohkubo, M. *J. Org. Chem.* **1997**, *62*, 9376–9378.