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A Total Synthesis of Galbonolide B

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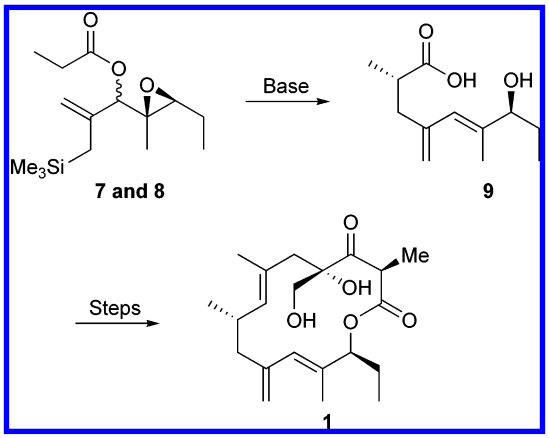
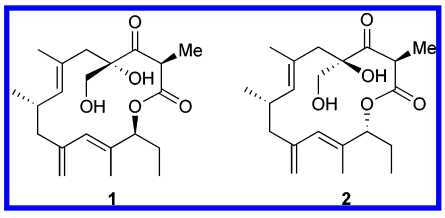


An ester enolate rearrangement/silicon mediated fragmentation cascade was used to convert **7** and **8** into the alcohol **9**. The alcohol **9** was converted into the allylic alcohol **12** and then to the ester **14**. A further ester enolate rearrangement furnished the stereochemical identity of galbonolide B **1**. Base mediated macrocyclization of the acetate ester **16** followed by base mediated alkylation and acetal deprotection gave galbonolide B **1**.

The isolation and structural identification of the galbonolide family of macrocycles were reported by two independent groups led by Achenbach[1] and Otake[2] in 1985. The structure of galbonolide B was initially incorrectly assigned as **2**,[3] but a total synthesis of galbonolide B by Tse[4] demonstrated that structure **1** was correct.



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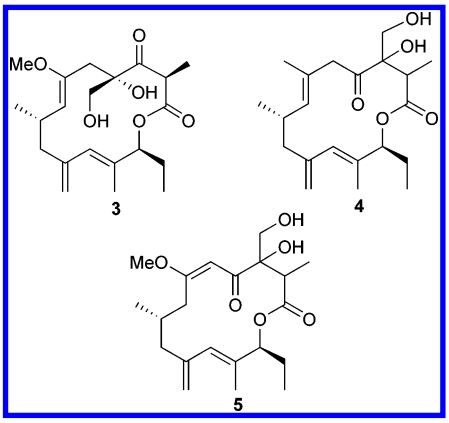
The biological activity of the galbonolide family of macrocycles is of great interest because galbonolides A **3** and B **1** showed good activity against *Deuteromycota* organisms.[5] Two of these, *Candida albicans* and *Rhodotorula rubra*, are pathogenic in man, and *Botrytis cinerea* and *Rhizoctonia solani* are of concern in agriculture.[5] Galbonolide B **1** was shown to be less active than galbonolide A **3** in all organisms tested.[5] In spite of this, the greater stability of galbonolide B **1** over galbonolide A **3** could enhance its commercial value as an antifungal agent.



Galbonolide C **4** was found to have comparable biological activity to galbonolide B **1**, and galbonolide D **5** was inactive. Recent studies have shown that galbonolide derivatives can act as IPC synthase inhibitors.[6]

Thomas et al.[7] have reported an elegant route to the galbonolides, but hitherto only one total synthesis of galbonolide B has been reported.[4] We now report a total synthesis of galbonolide B **1** which relies on an ester enolate rearrangement/silicon mediated fragmentation sequence to set up the required remote stereocenters[8] and the correct diene geometry for the southern moiety of galbonolide B **1** ($C_7 \rightarrow C_{13}$). A further modified ester enolate mediated rearrangement[9] was used to furnish galbonolide B **1** (Figure 1).

Disconnection between C_2 and C_3 in galbonolide B **1** led to the acyclic precursor **16** which has been reported by Tse et al.[4]

(1) Achenbach, H.; Muhlenfeld, A.; Fauth U.; Zahner, H. *Tetrahedron Lett.* **1985**, *26* (50), 6167.
(2) Takatsu, T.; Nakayama, H.; Shimazu, A.; Furihata, K.; Ikeda, K.; Furihata, K.; Seto, H.; Otake, N. *J. Antibiot.* **1985**, *38*, 1806.
(3) Achenbach, H.; Muhlenfeld, A.; Fauth U.; Zahner, H. *Ann. N.Y. Acad. Sci.* **1988**, *544*, 128.
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(5) Fauth, U.; Zahner, H.; Muhlenfeld A.; Achenbach, H. *J. Antibiot.* **1986**, *39*, 1760.
(6) Sakoh, H.; Sugimoto, Y.; Imamura, H.; Sakabura, S.; Jona, H.; Bamba-Nagano, R.; Yamada, K.; Hashizume T.; Morishima, H. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 143.
(7) Smith, P. M.; Thomas, E. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3541.
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(9) (a) Viseux, E. M. E.; Parsons, P. J.; Pavey, J. B. J.; Carter, C. M.; Pinto, I. *Synlett* **2003**, (12), 1856. (b) Ireland, R. E.; Wipf, P.; Armstrong, J. D. *J. Org. Chem.* **1991**, *56* (2), 650. (c) Ireland, R. E.; Daub, J. P. *J. Org.* Chem., **1981**, *46* (3), 479. (d) Ireland, R. E.; Thaisrivongs, S.; Vanier, N.; Wilcox, C. S.; Daub, J. P. *J. Org. Chem.* **1980** *45* (3), 48. (d) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.

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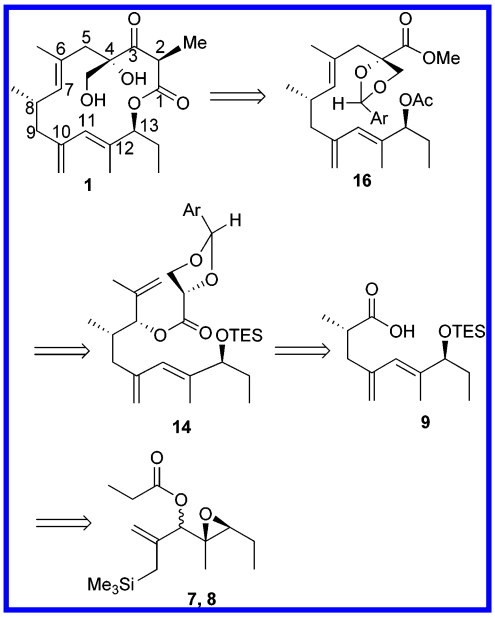
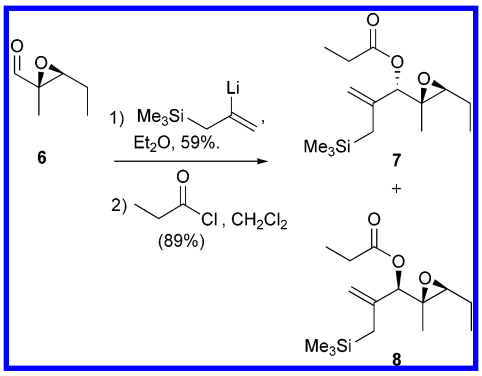
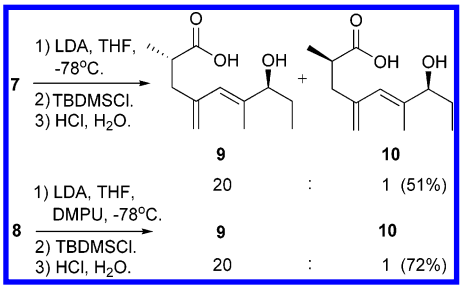


FIGURE 1. Retrosynthetic analysis of galbonolide B **1**.

SCHEME 1. Synthesis of the First Ireland-Claisen Precursor



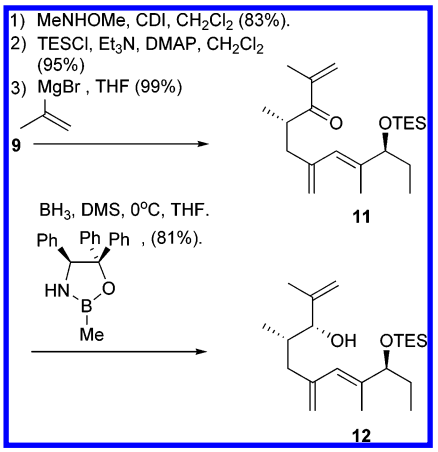
SCHEME 2. Tandem Ester Enolate Rearrangement/Silicon Mediated Fragmentation



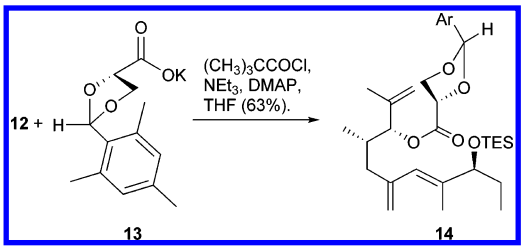
We envisaged that the ketal **16** could be derived from the ester **14** by a base mediated rearrangement of the Ireland Claisen type. The ester **14** could in turn be synthesized from the carboxylic acid **9** which could be prepared from the propionate esters **7** and **8**. Reaction of 1-trimethylsilyl-2-propenyllithium[10] with the epoxyaldehyde **6**[8] gave a mixture of allylic alcohols which were separated and then converted into their respective propionate esters (Scheme 1).

(10) Lawler, D. M.; Simpkins, N. S. *Tetrahedron Lett.* **1998**, *29* (10), 1207.

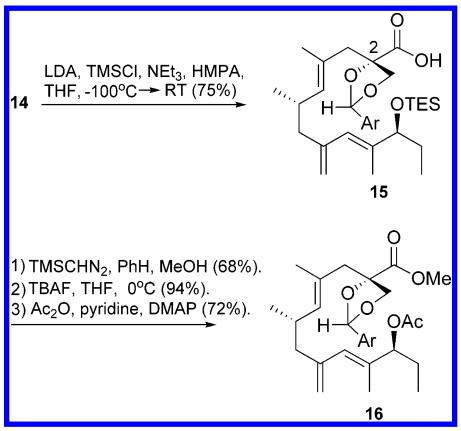
SCHEME 3. Chiral Reduction of Enone 11



SCHEME 4. Synthesis of the Second Ireland-Claisen Precursor



SCHEME 5. Synthesis of the Dieckmann Cyclization Precursor 16

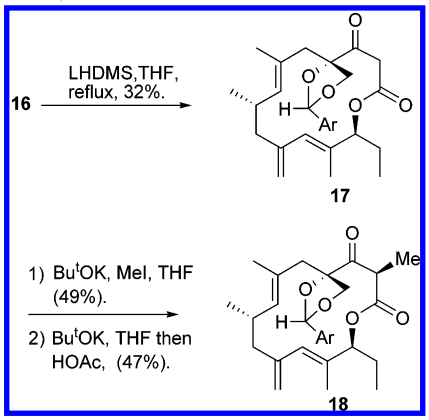


The propionate esters **7** and **8** were formed in a 1.0:1.2 ratio, respectively. Treatment of the ester **7** with lithium diisopropylamide (LDA) and then *tert*-butyldimethylsilyl chloride gave the *E*-silylketene acetal which, after rearrangement and acid workup, gave carboxylic acid **9**. The ester **8** when treated with LDA in the presence of DMPU gave the *Z*-silylketene acetal. This also furnished the carboxylic acid **9** upon workup, together with the minor isomeric alcohol **10**[8] (Scheme 2).

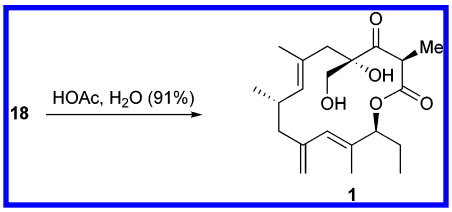
To our delight, the desired carboxylic acid **9** was formed in good yield and as the major isomer. This was confirmed by forming the methyl ester of carboxylic acid **9** and then by X-ray analysis of its 3,5-dinitrobenzoate ester. The carboxylic acid **9** was converted into the key allylic alcohol **12** as shown in Scheme 3.

Conversion of the carboxylic acid **9** into its Weinreb amide[11] followed by protection of the remaining secondary alcohol as a triethylsilyl ether[12] and then reaction of the resulting silyl ether

SCHEME 6. Synthesis of Protected Galbonolide B 18



SCHEME 7. Synthesis of Galbonolide B 1



with 2-propenylmagnesium bromide gave the enone **11**[13] in high (99%) yield. A borane mediated reduction of the enone **11** under the conditions reported by Berenguer et al.[14] gave the homochiral allylic alcohol **12**. The allylic alcohol **12** was coupled with the carboxylate **13**[15] to afford the ester **14** (Scheme 4).

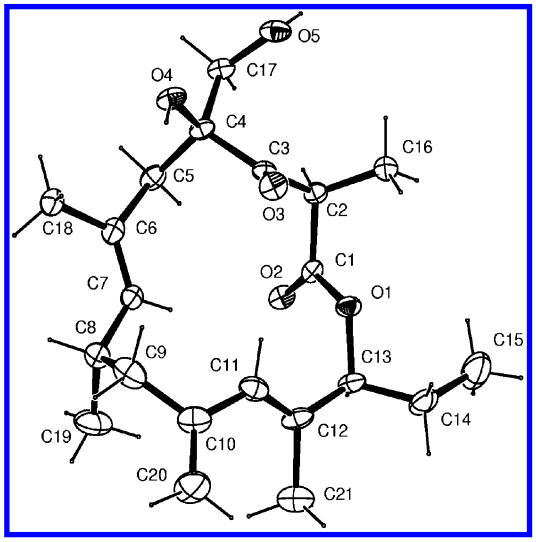
With the ester **14** in hand, experiments were conducted to induce an ester enolate rearrangement such that the diol present at C_4 of galbonolide B **1** could be introduced in one synthetic operation. It was eventually found that when the ester **14** was treated with LDA in the presence of trimethylsilyl chloride and hexamethylphosphoric triamide in THF at −100 °C,[16] the desired rearrangement took place to afford the carboxylic acids **15** and **15′** in 75% yield and a 1:1 ratio. Carboxylic acid **15** and its C_2 epimer, **15′**, were separated by flash column chromatography. Methylation of the carboxylic acid **15** with trimethylsilyldiazomethane[17] followed by removal of the silicon protecting group and acetylation gave the ester **16** (Scheme 5).

Treatment of the ester **16** with lithium hexamethyldisilazide in boiling THF afforded the macrocycle **17** in 32% yield (Scheme 6).

Stereoselective methylation at C_2 was achieved with potassium tertiary butoxide and iodomethane using the procedure of Tse et al.[4] Inversion of the methyl group at C_2 was achieved using potassium tertiary butoxide followed by careful addition of acetic acid to afford the macrocyclic lactone **18** in 47% yield. The macrocyclic lactone **18** was converted into galbonolide B using aqueous acetic acid (91%, Scheme 7).

The macrocycle obtained from acetal cleavage of **18** had identical spectral data in every respect to that published. In addition, X-ray analysis confirmed the structure of galbonolide B **1**.

In summary, we report an efficient total synthesis of the antifungal agent galbonolide B **1**.



Experimental Section

(2*S*,4*S*)-4-((2*E*,7*E*)-(4*S*,9*S*)-2,4,8-Trimethyl-6-methylene-9-triethylsilanyloxy-undeca-2,7-dienyl)-2-(2,4,6-trimethyl-phenyl)-1,3-dioxolane-4-carboxylic Acid (15) and (2*S*,4*R*)-4-((2*E*,7*E*)-(4*S*,9*S*)-2,4,8-Trimethyl-6-methylene-9-triethylsilanyloxy-undeca-2,7-dienyl)-2-(2,4,6-trimethyl-phenyl)-1,3-dioxolane-4-carboxylic Acid (15′). To a solution of $^{i}Pr_2NH$ (230 μL, 2.70 mmol) in THF (9 mL) at 0 °C was added $^{n}BuLi$ (1.15 mL, 2.70 mmol, 2.35 M in hexanes) and stirred for 10 min. The yellow solution was cooled to −100 °C, and HMPA (2 mL) was added. A mixture of TMSCl (454 μL, 3.59 mmol) and Et_3N (250 μL, 1.80 mmol) in THF (1 mL) was filtered and added to the reaction mixture at −100 °C quickly followed by the dropwise addition of ester **14** (530 mg, 0.90 mmol) in THF (6 mL). The resultant pale yellow solution was stirred for 1 h at −100 °C and then allowed to warm slowly to room temperature before being warmed to 40 °C for 10 h. The reaction mixture was cooled to room temperature and quenched with a saturated aqueous solution of NH_4Cl (20 mL), and the phases separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic extracts were washed brine (20 mL). The organic phase was then dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with a gradient of 60% Et_2O/petrol to 100% Et_2O, to afford the title compound **15** as a yellow gum (209 mg, 39%) and **15′** as a yellow gum (190 mg, 36%).

TLC, (90% diethyl ether/petrol) (**15**) $R_f = 0.53$; (**15′**) $R_f = 0.38$; ν_{max} (film/cm^{-1}) 2956 (s), 2876 (s), 1725 (m), 1613 (w), 1454 (m), 1376 (w), 1249 (m), 1067 (s), 1006 (m), 965 (w), 848 (s), 743 (m); δ_H (300 MHz, C_6D_6) (**15**) 7.25 (1H, bs), 6.68 (2H, s), 6.21 (1H, s), 5.81 (1H, s), 5.17 (1H, d, $J = 9.1$ Hz), 5.07 (1H, s), 4.97 (1H, s), 4.64 (1H, d, $J_{AX} = 8.7$ Hz), 3.93 (1H, t, $J = 6.2$ Hz), 3.69 (1H, d, $J = 8.7$ Hz), 2.71−2.47 (3H, m), 2.45 (6H, s), 2.23−2.13 (1H, m), 2.07−1.99 (1H, m), 2.06 (3H, s), 1.80 (3H, s), 1.78 (3H, s), 1.65−1.54 (2H, m), 1.01 (9H, t, $J = 7.9$ Hz), 0.97 (3H, d, $J = 9.1$ Hz), 0.88 (3H, t, $J = 7.2$ Hz), 0.62 (6H, q, $J = 7.9$ Hz); (**15′**) 10.11 (1H, bs), 6.68 (2H, s), 6.45 (1H, s), 5.79 (1H, s), 5.24 (1H, d, $J = 8.8$ Hz), 5.04 (1H, s), 4.93 (1H, s), 4.35 (1H, d, $J_{AX} = 8.3$ Hz), 3.92 (1H, t, $J = 6.2$ Hz), 3.85 (1H, d, $J_{AX} = 8.3$ Hz), 2.71 (1H, d, $J_{AB} = 13.8$ Hz), 2.65−2.54 (1H, m), 2.54−2.48 (1H, m),

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(16) Ireland, R. E.; Norbeck, D. W. *J. Am. Chem. Soc.* **1985**, *107* (11), 3279.
(17) Tripp, J. C.; Schiesser, C. H.; Curran, D. P. *J. Am. Chem. Soc.* **2005**, *127*, (15), 5518.

2.46 (6H, s), 2.24−2.14 (1H, m), 2.10−2.00 (1H, m), 2.06 (3H, s), 1.82 (3H, s), 1.79 (3H, s), 1.62−1.50 (2H, m), 1.01 (3H, d, J = 5.8 Hz), 0.99 (9H, t, J = 6.7 Hz), 0.86 (3H, t, J = 7.6 Hz), 0.61 (6H, q, J = 6.7 Hz); δ_C (75.5 MHz, C_6D_6) (**15**) 175.7, 144.1, 140.9, 139.1, 138.5, 137.3, 130.5, 130.4, 126.4, 115.5, 103.4, 84.3, 80.2, 73.7, 46.1, 45.6, 31.7, 29.7, 20.9, 20.4, 20.3, 17.6, 13.4, 10.3, 7.2, 5.3; (**15′**) 178.8, 144.2, 140.9, 138.9, 138.5, 136.5, 130.4, 129.4, 126.5, 115.2, 103.9, 85.4, 80.2, 73.4, 46.1, 46.1, 31.6, 30.2, 20.9, 20.6, 20.4, 17.4, 13.3, 10.4, 7.2, 5.3; *m*/*z* (EI) 571 (MH+, 1%), 542 (2), 447 (27), 350 (14), 254 (54), 147 (100), 121 (36), 103 (56), 87 (68), 41 (55); HRMS (ESI): calcd. for $C_{34}H_{54}O_5SiNa$ [M + Na]$^+$ 593.3633, found 593.3625.

Acknowledgment. We gratefully acknowledge the EPSRC and AstraZeneca for funding this work. We would like to dedicate this paper to Professor R. C. Cookson FRS on the occasion of his 85th birthday.

Supporting Information Available: General experimental procedures and spectroscopic data for the compounds **1** and **6**−**18**, copies of ^{1}H and ^{13}C NMR spectra and a crystallographic information file for **1** are provided. This material is available free of charge via the Internet at http://pubs.acs.org

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