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Model studies for the synthesis of galbonolide B†‡

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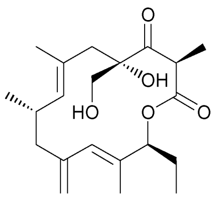
The construction of the fourteen membered ring present in galbonolide B **1** is reported. The 10,11-diene system present in the southern portion of **1** has been constructed using an ester enolate rearrangement/silicon mediated fragmentation cascade, whilst the macrocycle has been synthesised following a Johnson rearrangement/mercury assisted ring closure protocol.

Introduction

The isolation and structural elucidation of members of the galbonolide family of macrocycles was reported in 1985 by two independent groups led by Achenbach[1] and Õtake.[2] The structure of galbonolide B was initially incorrectly assigned as **2**[3] but a total synthesis of galbonolide B by Tse[4] proved the structure to be epimeric at C_4 and C_{13} and hence structure **1** was assigned to galbonolide B.



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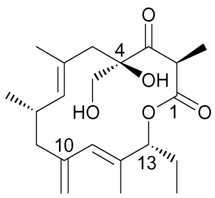

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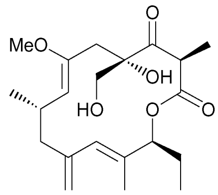

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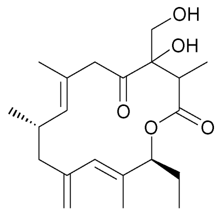

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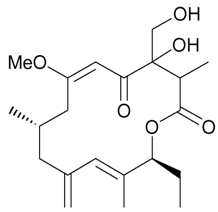

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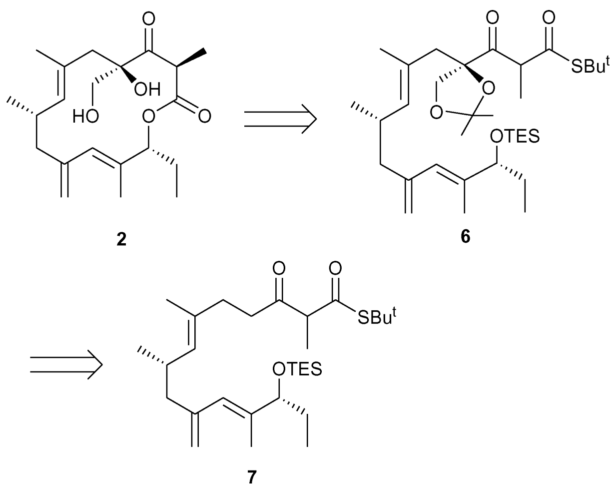
Results and discussion

The galbonolide family of macrocycles has an interesting array of biological properties. Galbonolides A and B (**3** and **1** respectively) showed good activity against a significant proportion of *Deuteromycota* organisms.[5] Among these are fungi that are pathogenic towards man, such as *Candida albicans* and *Rhodotorula rubra*, as well as fungi which are harmful in agriculture, such as *Botrytis cinerea* and *Rhizoctonia solani*.[5]

Although galbonolide A **3** was found to be significantly more active than galbonolide B **1** against every organism tested,[5] its instability over galbonolide B **1** could enhance the profile of galbonolide B **1** as a potent antifungal agent. Galbonolide C **4** was found to be almost as active as galbonolide B **1** and galbonolide D **5** was inactive; recently novel galbonolide derivatives have been prepared as IPC synthase inhibitors.[6]

We wished to develop a novel and flexible route to galbonolides A, B, C and D, which would also allow the construction of more stable analogues with the biological profile of galbonolides A, B and C remaining intact. Smith and Thomas[7] have reported an elegant approach to galbonolide B, which features a Wittig reaction to furnish the southern half of the molecule in question.

Our synthetic approach to galbonolide B, outlined in Scheme 1, was designed to offer a route which could be tailored to analogue preparation. Although the structure of galbonolide B **1** has been revised, we have synthesised a parallel series of compounds that are epimeric at C_{13} in order to establish absolute proof of structure in the family of galbonolides.



Scheme 1

We envisaged that the thioester **7** could be either ring closed at an early stage, or initially converted into the ketal **6**, followed

† This paper is dedicated to the memory of Dr Robert Giles of GlaxoSmithKline (Tonbridge) who was tireless in his support of UK chemistry.
‡ Electronic supplementary information (ESI) available: experimental details. See http://dx.doi.org/10.1039/b505378a

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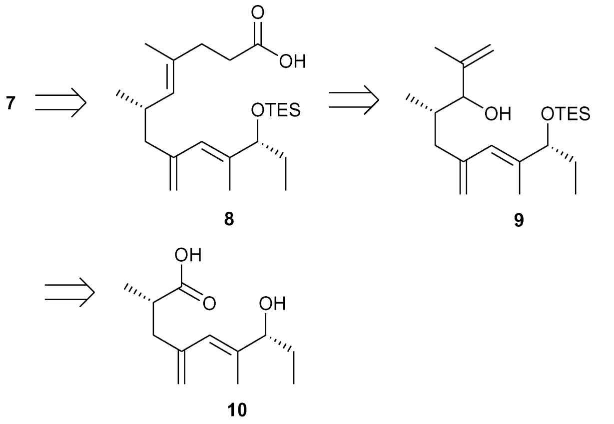
by macrocyclisation according to the procedure of Masamune *et al.*[8]

In order to construct the thioester **7** we required an efficient synthesis of the carboxylic acid **8**, which could in turn be prepared from the carboxylic acid **10** as shown in Scheme 2.



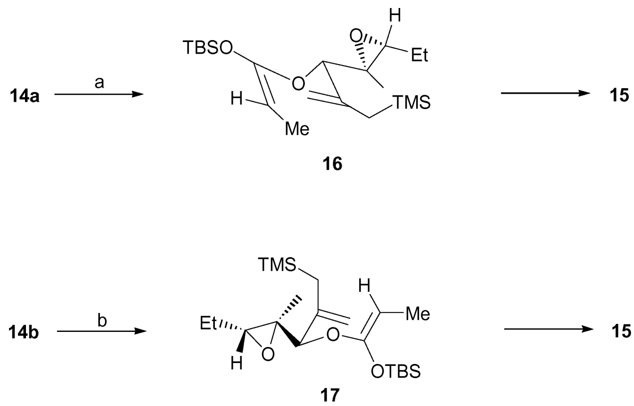
Scheme 2

The carboxylic acid **10** was made using a method that we have previously reported (Scheme 3 and Scheme 4).[9]

Epoxidation of the allylic alcohol **11** using a Sharpless oxidation,[10] followed by treatment of the resulting epoxyalcohol **11a** with the sulfur trioxide–pyridine complex in dimethyl sulfoxide[11] gave the aldehyde **12**. Reaction of **12** with 1-trimethylsilylprop-2-enylmagnesium bromide gave the allylic alcohols **13a** and **13b** as a 1.0 to 1.5 ratio of diastereoisomers, which were easily separated by column chromatography. Conversion of each of the allylic alcohols into their respective propionate esters proceeded in high yield.

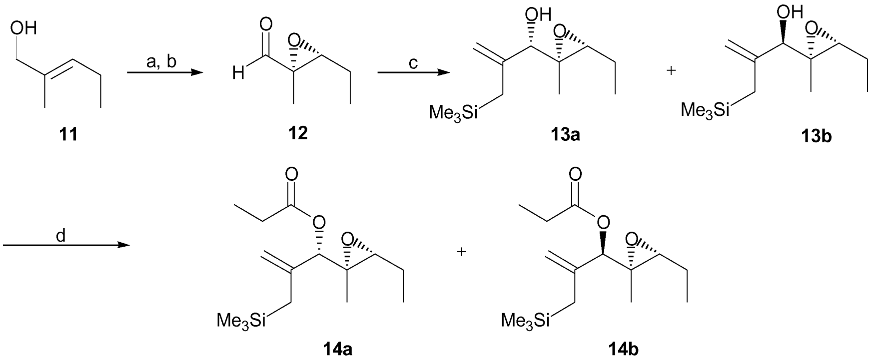
Treatment of the propionate esters **14a** and **14b** with LDA and LDA–DMPU, respectively, gave the desired allylic silanes for fragmentation to furnish the C_7 to C_{13} portion of galbonolide B epimeric at C_{13} (Scheme 4).

Deprotonation of **14a** with LDA followed by the addition of TBSCl gave the *E*-silylketene acetal **16**, which rearranged to give the allylsilane **15**.[12] Deprotonation of **14b** with LDA in the presence of DMPU, followed by addition of TBSCl gave the *Z*-ketene acetal **17**, which also rearranged to give the allylsilane **15** (Scheme 5).

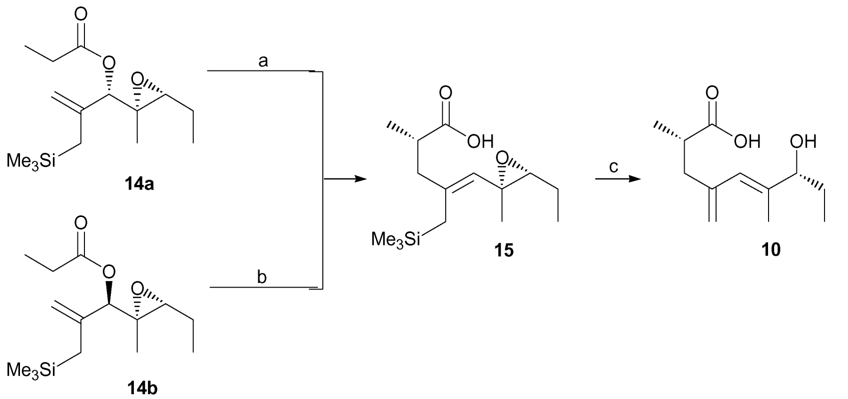


Scheme 5 *Reagents and conditions*: (a) LDA, THF, −78 °C, then TBSCl, DMPU; (b) LDA, THF, DMPU, −78 °C, then TBSCl.

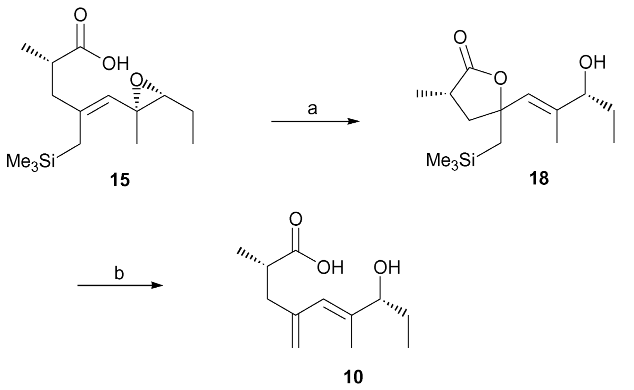
As shown in Scheme 4, we found that treatment of the allylsilane **15** with ammonium chloride, followed by the addition of 2 M hydrochloric acid gave the desired diene **10**. It is interesting to note that reaction of the allylsilane **15** with aqueous ammonium chloride gave the lactone **18**, which underwent ring opening in the presence of mineral acid to give **10** (Scheme 6).



Scheme 3 *Reagents and conditions*: (a) Ti(OPr^i)$_4$, L-(−)-DET, Bu^{t}OOH, DCM, −25 °C, 4 Å molecular sieves, 74%; (b) SO_3–pyridine, Et_3N, DMSO, DCM, 0 °C, 70%; (c) MgBr / SiMe$_3$; (d) $(CH_3CH_2CO)_2O$, DMAP, Et_3N, DCM, 0 °C, 96%.



Scheme 4 *Reagents and conditions*: (a) LDA, THF, −78 °C, then TBSCl, DMPU; (b) LDA, THF, DMPU, −78 °C, then TBSCl; (c) NH_4Cl, H_2O, then HCl (2 M), 90%.



Scheme 6 *Reagents and conditions*: (a) NH_4Cl, H_2O; (b) HCl (2 M).

Although the lactone **18** was not isolated due to its instability, its formation proved to be crucial for the generation of the *E*-double bond in **10**. With the carboxylic acid **10** in hand, the allylic alcohol **9** was synthesised as shown in Scheme 7.

The allylic alcohol **9** proved to be a very versatile intermediate in our synthesis. Reaction of **9** with triethyl orthoacetate in the presence of hexanoic acid followed by solvolysis of the ester gave the acid **23b** in high yield (Scheme 8).

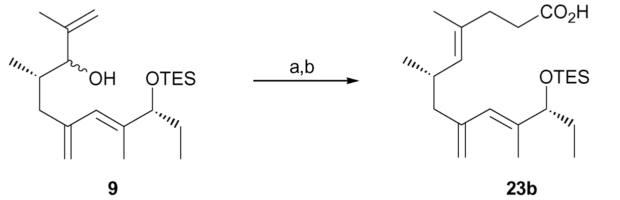
In view of the successful preparation of the carboxylic acid **23b**, which contains a range of relatively labile functionalities, we decided to elaborate the acid **23b** into the thioester **7** using a method described by Masamune *et al.*[8] and designed for the acylation of carboxylic acids under almost neutral conditions. To our delight, the desired coupling occurred in quantitative yield (Scheme 9).

After extensive research, it was found that aqueous acetic acid in tetrahydrofuran removed the triethylsilyl group in moderate to good yield. Treatment of **7** with aqueous acetic acid gave the alcohol **24** in 70% yield and, after further experiments, the alcohol **24** was converted into the desired macrocyclic lactone **25** in quantitative yield, using mercuric acetate in tetrahydrofuran (Scheme 10).

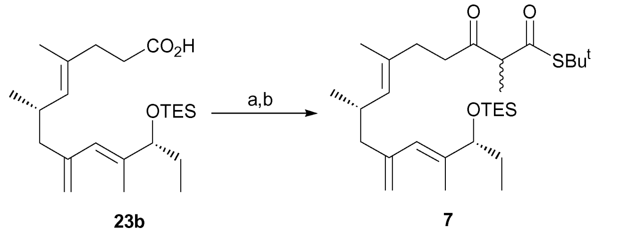
When the lactones **25** were exposed to DBU in dichloromethane, gradual epimerisation at C_2 occurred giving a 2 : 1 mixture in favour of the correct diastereoisomer (Scheme 11).

Experimentation was continued on the series epimeric at C_{13} in order to introduce the desired diol present in galbonolide B. Attempted formation of the dianion derived from **25** resulted in an interesting ring contraction reaction. Treatment of **25** with an excess of LDA in THF, followed by the addition of formaldehyde gave the ring contracted lactone **28** as the sole reaction product (Scheme 12).

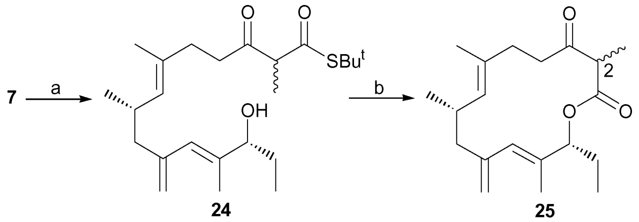
A possible explanation for the formation of the lactone **28** arises from an intermolecular aldol reaction, followed by an intramolecular acylative ring contraction and then dehydration (Scheme 13).



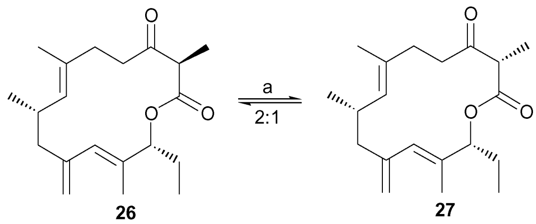
Scheme 8 *Reagents and conditions*: (a) $MeC(OEt)_3$, $C_5H_{11}CO_2H$, Δ; (b) KOH–EtOH–H_2O, then HCl (0.1 M) 88%.



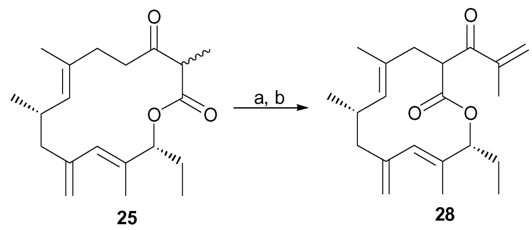
Scheme 9 *Reagents and conditions*: (a) CDI; (b) $(Bu^tSCOCH(CH_3)CO_2)_2Mg$, THF, 97%.



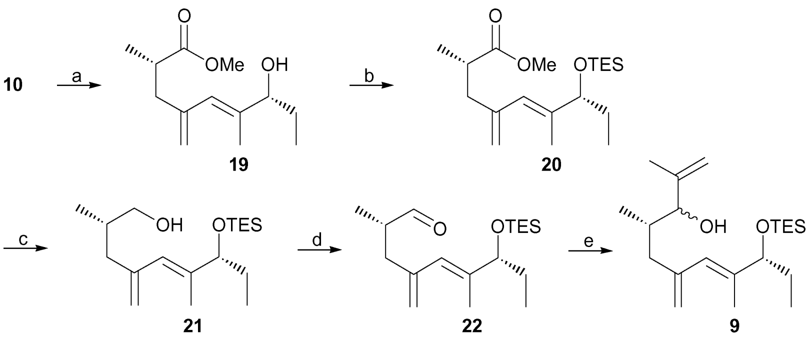
Scheme 10 *Reagents and conditions*: (a) HOAc–H_2O–THF, 2 : 2 : 1, 70%; (b) $Hg(OAc)_2$, Pr^iNEt_2, THF, 99%.

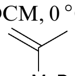


Scheme 11 *Reagents and conditions*: (a) DBU, DCM.



Scheme 12 *Reagents and conditions*: (a) LDA (10 eq.), THF, DMPU; (b) $H_2C{=}O$, THF, 39%.



Scheme 7 *Reagents and conditions*: (a) MeI, DBU, DCM, 0 °C, 75%; (b) TESCl, DMAP, Et_3N, DCM, 0 °C, 99%; (c) DIBAL-H, DCM, 0 °C, 100%; (d) SO_3–pyridine, Et_3N, DMSO, DCM, 0 °C, 76%; (e)  MgBr, THF, 0 °C, 76%.

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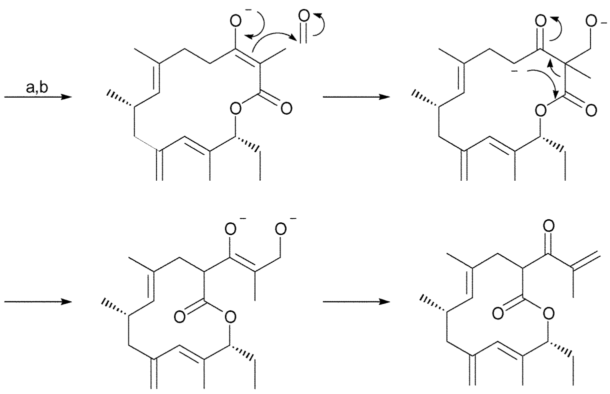

Scheme 13 *Reagents and conditions*: (a) LDA (10 eq.), THF, DMPU; (b) $H_2C{=}O$, THF, 39%.

Conclusions

We have developed an efficient route to the macrocyclic skeleton present in the galbonolides. We are currently making a series of compounds with the *S*-configuration of C_{13}. The ring contraction step shown in Scheme 12 has now been circumvented by the use of an ester enolate rearrangement in order to furnish the requisite diol functionality at C_4 in galbonolide B. The total synthesis of galbonolide B and its analogues will be the subject of a further publication. Experimental details can be found in the electronic supplementary information.‡[13–16]

Acknowledgements

We wish to thank Drs Clive Penkett, Adrian Murray, Mike Urquhart and Eddy Viseux for their interest in this work and the EPSRC, AstraZeneca and Tocris Cookson for research funding. Technical assistance from Drs Avent, Hitchcock and Abdul-Sada is gratefully acknowledged.

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