The Construction of 1,3-Dienes Containing an *E*-Double Bond and an *exo*-Methylene Group

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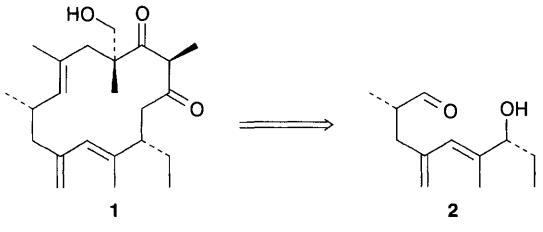
The use of a tandem Ireland Claisen rearrangement followed by an *in situ* silicon mediated epoxide fragmentation provides an efficient entry into 1,3-dienes containing an *E*-double bond and an *exo*-methylene group; initial results regarding remote chirality control are reported.

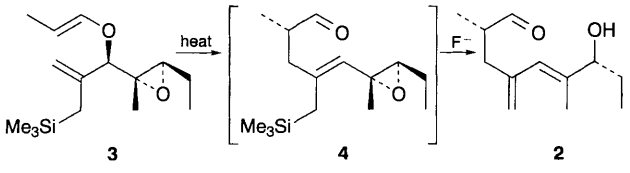
The stereoselective formation of conjugated dienes is of considerable importance, due to their presence in many nautral products as well as their utilization in reactions such as the Diels–Alder reaction. In recent years transition metal mediated cross-coupling methodology has found extensive use in the stereocontrolled formation of dienes.[1] We have recently been concerned with the synthesis of Galbonolide B[2] **1** which has an interesting diene containing an *exo*-methylene group, a structural unit seen in many natural products such as amphidinolide K[3] and the periplanones.[4] Our retrosynthetic analysis to the Galbonolides required the synthesis of the aldehyde **2**, Scheme 1.

We were thus interested in devising a strategy which would not only provide an efficient synthesis of the diene but would also allow control over the two remote chiral centres. To this end we proposed that the aldehyde **2** could be obtained in a one-pot operation from the alkenyl ether **3** by utilising a Claisen rearrangement,[5] followed by an *in situ* silicon mediated epoxide fragmentation, Scheme 2.



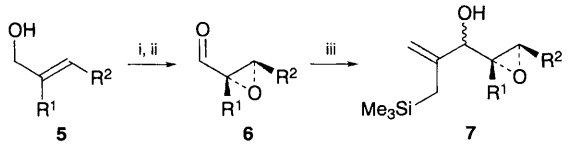
1 **2**

Scheme 1



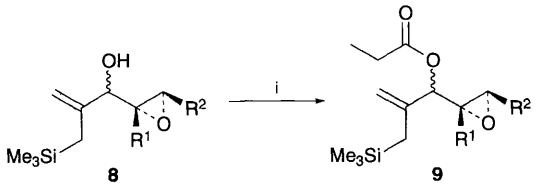
3 **4** **2**

Scheme 2



5 **6** **7**

Scheme 3 *Reagents*: i, *tert*-butyl hydroperoxide, $Ti(OPr^i)_4$, (−)-diethyl tartrate (55–90%) or MCPBA (52–74%); ii, CrO_3.pyr (52–64%); iii, 1-trimethylsilylprop-2-enyl magnesium bromide, THF (41–67%)

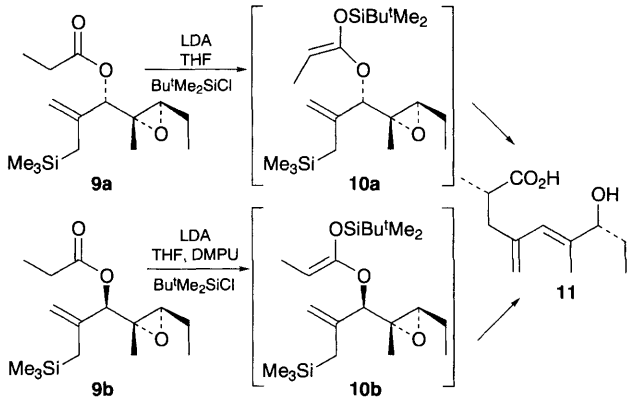


8 **9**

Scheme 4 *Reagents*: i, Propionyl chloride, pyridine (80–100%)

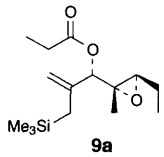
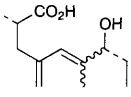
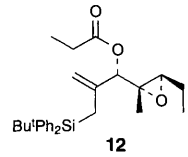
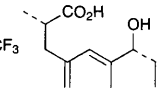
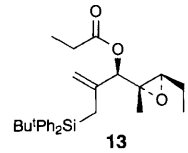
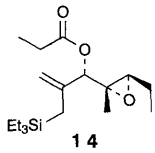
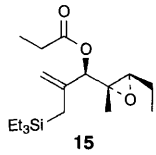
The requisite allylic alcohols **7** were made as shown in Scheme 3.

Attempted formation of the required alkenyl ether **3**, however, resulted in a mixture of double bond isomers, and



Scheme 5 DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone

Table 1

Propanoate	Conditions	Diene	Yield
 **9a**	i, LDA, THF ii, $Bu^tMe_2SiOSO_2CF_3$ iii, $HCl_{(aq)}$	 **11**	90% d.r. 10:1 *E* : *Z* 10:1 to 1:5
 **12**	i, LDA, THF ii, $Bu^tMe_2SiOSO_2CF_3$ iii, $HCl_{(aq)}$ iv, Bu_4NF	 **11**	10–50% d.r. 5.5:1
 **13**	i, LDA, THF, DMPU ii, $Bu^tMe_2SiOSO_2CF_3$ iii, $HCl_{(aq)}$ iv, Bu_4NF	**11**	19% d.r. 2.2:1
 **14**	i, LDA, THF ii, Bu^tMe_2SiCl, DMPU iii, $NH_4Cl_{(aq)}$ iv, $HCl_{(aq)}$	**11**	91% d.r. 3.4:1
 **15**	i, LDA, THF, DMPU ii, Bu^tMe_2SiCl iii, $NH_4Cl_{(aq)}$ iv, $HCl_{(aq)}$	**11**	71% d.r. 1.7:1

[a] d.r = diastereoisomeric ratio.

hence in loss of stereocontrol in **4**. The propanoates **9** were formed (Scheme 4) to facilitate the use of Ireland's Claisen rearrangement methodology.[6]

Deprotonation of the propanoate esters **9** under coordinating or non-coordinating conditions allows control over the silyl ketene acetal geometry, and thus over the remote methyl group stereochemistry. The methodology thereby potentially gives access to the desired isomer **11** from either propanoate diastereoisomer (**9a** or **9b**), Scheme 5.

A series of propanoates were synthesized to test the methodology, and the results are summarised in Table 1.

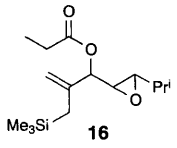
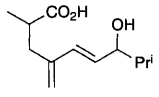
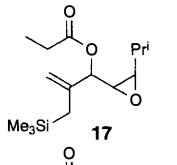
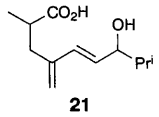
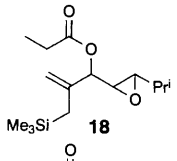
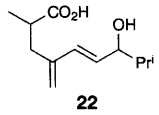
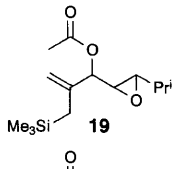
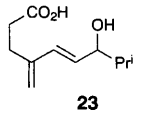
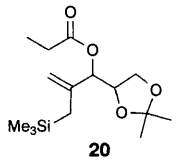
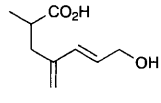
Treatment of propanoate **9a** with LDA in THF, and enolate quench with *tert*-butyldimethylsilyl triflate at −78 °C, followed by acidic workup at room temp., gave high yields of the desired diene **11**. However, exclusive formation of the required *E*-double bond could not be obtained with *E* : *Z* ratios varying from 10 : 1 to 1 : 5. The diastereoisomeric ratio obtained for the remote methyl group was encouragingly high. In order to improve the *E* : *Z* double bond ratio we changed the functionality on silicon, Table 1. The *tert*-butyldiphenylsilyl group gave rise exclusively to the desired *E*-double bond, but in general yields of the dienes were reduced. The best results were obtained using the triethylsilyl group which gave high yields of the required diene **11** together with some diastereocontrol of the remote methyl group. Optimisation of the Ireland Claisen rearrangement will possibly provide improved levels of diastereoselectivity,[7] so further increasing the utility of this reaction.

This methodology has been used on a further series of racemic esters demonstrating the general nature of this diene synthesis as shown in Table 2 [reagents: i, LDA, THF; ii, $Bu^tMe_2SiOSO_2CF_3$; iii, $HCl_{(aq)}$].

Simple 1,2-disubstituted epoxides gave rise exclusively to *E*-double bond products after rearrangement and fragmentation (entries 1–4).

In an extension of the methodology, the ketal **20** also underwent efficient fragmentation to give allyl alcohol **24**.

Table 2

Entry	Propanoate	Diene	Yield (%)
1	 **16**	 **21**	67
2	 **17**	 **21**	41
3	 **18**	 **22**	77
4	 **19**	 **23**	25
5	 **20**	 **24**	60

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References

1 R. F. Heck, *Palladium Reagents in Organic Synthesis*, Academic, London, 1985; E. Negishi, T. Takahashi, S. Baba, D. E. Van Horn and N. Okukado, *J. Am. Chem. Soc.*, 1987, **109**, 2293; J. K. Stille, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 508; A. Suzuki, *Pure Appl. Chem.*, 1991, **63**, 419; W. Cabri and I. Candiani, *Acc. Chem. Res.*, 1995, **28**, 2; A. Duchene, M. Abarbri, J-L. Parrain, M. Kitamura and R. Noyori, *Synlett*, 1994, 524.

2 H. Achenbach, A. Muhlenfeld, U. Fauth and H. Zahner, *Ann. N.Y. Acad. Sci.*, 1988, **544**, 128; H. Nakayama, T. Takatsu, Y. Abe, A. Shimazu, K. Furihata, K. Ikeda, K. Furihata, H. Seto and N. Otake, *Agric. Biol. Chem.*, 1987, **51** (3), 853.

3 J. Kobayashi and M. Ishibashi, *Chem. Rev.*, 1993, **93**, 1753.

4 T. W. Goodwin, *Aspects of Terpenoid Chemistry and Biochemistry*, Academic, London, 1971.

5 W. H. Watanabe and L. E. Conlon, *J. Am. Chem. Soc.*, 1957, **79**, 2828.

6 R. E. Ireland and R. H. Mueller, *J. Am. Chem. Soc.*, 1972, **94**, 5897; R. E. Ireland, R. H. Mueller and A. K. Willard, *J. Am. Chem. Soc.*, 1976, **98**, 2868; R. E. Ireland, S. Thaisrivongs, N. Vanier and C. S. Wilcox, *J. Org. Chem.*, 1980, **45**, 48; R. E. Ireland and J. P. Daub, *J. Org. Chem.*, 1981, **46**, 479.

7 R. E. Ireland, P. Wipf and J. D. Armstrong III, *J. Org. Chem.*, 1991, **56**, 650; M. J. Munchhof and C. H. Heathcock, *Tetrahedron Lett.*, 1992, **33**, 8005; J. Otera, Y. Fujita and S. Fukuzumi, *Synlett*, 1994, 213; K. Hattori and H. Yamamoto, *Tetrahedron*, 1994, **50**, 3009; M. Nagatsuma, F. Shirai, N. Sayo and T. Nakai, *Chem. Lett.*, 1984, 1393; D. A. Oare and C. H. Heathcock, *J. Org. Chem.*, 1990, **55**, 157.