Diastereoselective Synthesis of Vinylcyclopropanes from Dienes and Sulfur Ylides

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Abstract: The reaction of aryl- and vinyl-stabilized sulfonium ylides with electron-poor dienes has been investigated. Clean cyclopropanation to 2-aryl- and 2-vinyl-substituted vinylcyclopropanes, with high regio- and stereocontrol, was observed. This new diastereoselective strategy was applied to formal synthesis of lamoxirene and dictyopterene B.

Key words: vinylcyclopropane, diene, stereoselective synthesis, sulfur, ylides

Vinylcyclopropanes are important compounds which serve as versatile intermediates in the synthesis of many biologically active compounds (Figure 1).[1] This structural motif is also present in numerous natural products.[2] As a result, several strategies have been devised for the synthesis of such structures.[3] The vast majority of these approaches is, however, restricted to the preparation of 2-vinylcyclopropane (di)carboxylic esters,[4,5] with the synthesis of aryl- and vinyl-substituted vinylcyclopropanes remaining a challenge. Indeed, despite the great interest to the latter compounds, their preparation involves generally indirect multistep syntheses.[6,7] We report herein our results on the development of a diastereoselective one-step strategy to aryl- and vinyl-substituted vinylcyclopropanes from dienes and sulfur ylides, and the application of this methodology to the formal synthesis of some natural products.

Several strategies have been developed for the synthesis of cyclopropanes.[1,3] Among these, the sulfur ylide mediated cyclopropanation has emerged as a powerful method: addition of substituted sulfonium ylides to acrylate derivatives leads to cyclopropanes in good yields and generally high diastereoselectivity.[8,9] Recently, Aggarwal, Dai, and others have also developed an efficient asymmetric version of this methodology using chiral sulfonium salts.[10] This prompted us to consider the possibility of applying this methodology to diene esters for the synthesis of substituted vinylcyclopropanes. However, the presence of two electrophilic double bonds in the diene raised the issue of regioselectivity[11] as well as the possibility of double addition.

Thus, we first assessed the feasibility of our strategy by investigating the reaction of diene **1** with the ylide formed by deprotonation of sulfonium salt **2a**.[12] After optimization of base, solvent, and order of addition, we were pleased to find that addition of LiHMDS to a solution of the diene and the salt **2a**, in CH_2Cl_2 at –78 °C, leads cleanly to vinylcyclopropane **3a** in excellent yield (Scheme 1). Diastereoselectivity was determined by ^{1}H NMR and GC of the crude mixture. The *trans* diastereomer of **3a** was obtained with a good diastereoselectivity (93:7). No product arising from a second addition (**5a**) could be detected in ^{1}H NMR whereas the undesired regioisomer **4a** was present in 12% yield in the crude mixture. Regioselectiv-

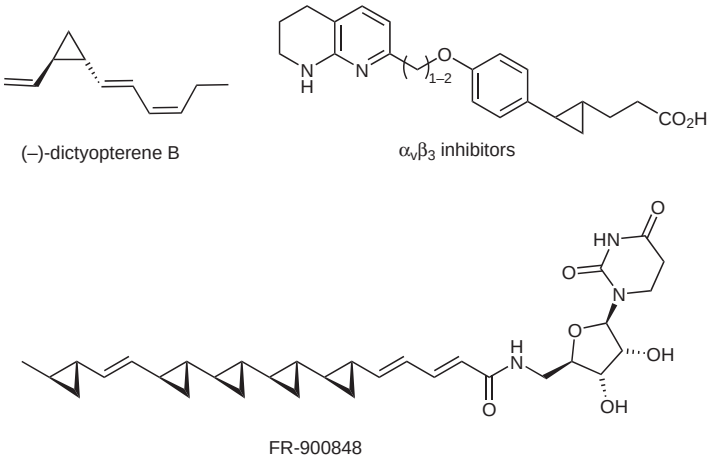

Figure 1 Biologically active cyclopropanes

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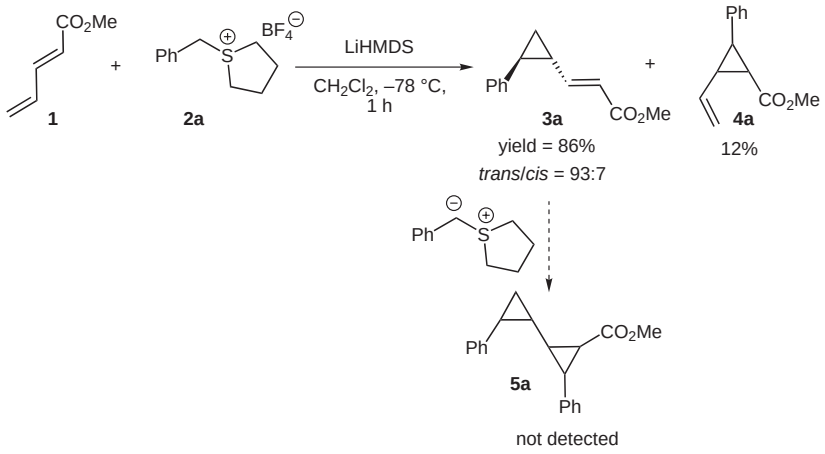
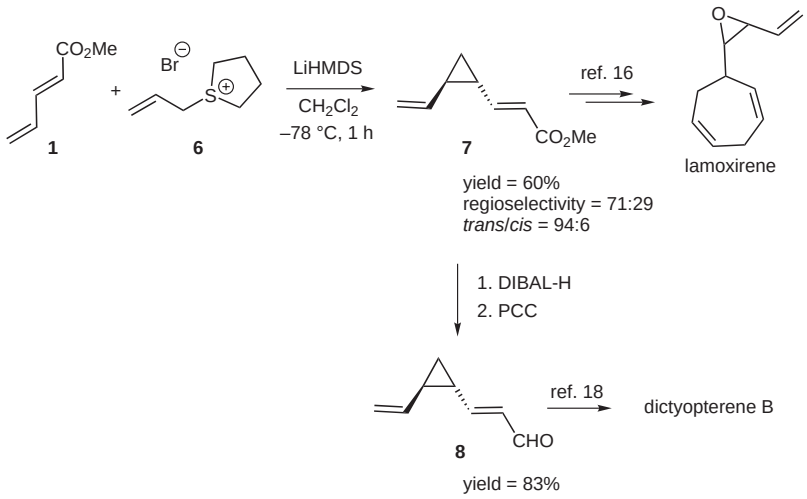


Scheme 1



Scheme 2 Application to formal synthesis of natural products

ity could be improved (>98:2) by the use of KHMDS as a base but a low decrease of diastereoselectivity was then observed (dr = 88:12).

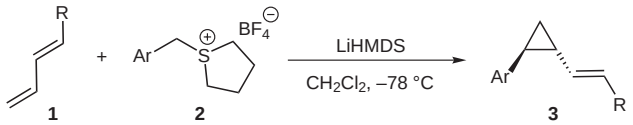
These conditions were then applied to a variety of aryl-stabilized ylides. The corresponding *trans*-aryl-vinylcyclopropanes were obtained in good to excellent yields (Table 1, entries 1–9). Electronic properties of the aryl group (electron-rich or electron-poor) have very little effect on regio- and diastereoselectivities. Steric hindrance, on the other hand, appeared to have a significant influence. Indeed, sterically hindered *ortho*-substituted ylides showed an increased regioselectivity (entries 8 and 9).

Phosphonic groups are often used as bioisosteric replacements of carboxylic functions,[13] we also tried the reaction with 1-(diethylphosphono)butadiene[14] (Table 1, entry10). Reaction of this latter with **2a** gave the corresponding substituted vinylcyclopropane with a good yield and an excellent regioselectivity (no regioisomer was detected in ^{1}H NMR). The observed high regioselectivity can most probably be accounted for by the bulkiness of the phosphonate groups disfavoring 1,4-addition. Diastereoselectivities, on the contrary, are slightly lower than with diene **1**. The presence of this new functional group (phosphonate) increases the possibilities for further transformations.

Finally, the general utility of this new process was further demonstrated by extending its scope to the synthesis of divinylcyclopropane **7**, which represents a formal synthesis of lamoxirene. The synthesis of this natural compound which has an important role in the reproductive cycle of marine brown algae[15] has been described by Boland.[16] In this synthesis, intermediate **7** was obtained by a three-step procedure.[17] Application of our strategy to allylic sulfonium salt **6** enables the expedient preparation of divinylcyclopropane **7** with a moderate yield and a good diastereoselectivity (Scheme 2). Further, transformation of this ester into the corresponding aldehyde constitutes a new diastereoselective access to **8** which is a known intermediate in the synthesis of the gamete attractant dictyopterene B.[18]

In summary, we have developed a practical and general synthesis of substituted vinylcyclopropanes from sulfonium ylides and electron-poor dienes. We have demonstrated that this reaction proceeds with a good regiocontrol and is highly *trans* diastereoselective. The reaction is applicable to a range of substrates with a variety

Table 1 Synthesis of Vinylcyclopropanes



1 **2** **3**

Entry	R	Ar	Yield (%)[a]	Regioselectivity[b]	*trans*/*cis*[b]
1	CO_2Me	Ph	98	88:12	93:7
2		4-$MeOC_6H_4$	94	88:12	85:15
3		4-$CO_2MeC_6H_4$	77	91:9	89:11
4		4-MeC_6H_4	98	88:12	94:6
5		4-FC_6H_4	99	86:14	90:10
6		2-ClC_6H_4	99	89:11	95:5
7		2-$MeOC_6H_4$	99	87:13	93:7
8		3-MeC_6H_4	99	97:3	94:6
9		3-FC_6H_4	88	96:4	92:8
10	$PO(OEt)_2$	Ph	70[c]	>95:5	72:28

[a] Global yield.
[b] Ratio was determined by ^{1}H NMR and/or GC analysis, and relative stereochemistry was determined by ^{1}H NMR (500 MHz).
[c] Reaction carried out at –5 °C.

of functional groups. The efficiency of this method has been demonstrated by the short synthesis of key intermediates in the synthesis of lamoxirene and dictyopterene B. We are currently exploring the use of chiral sulfonium salts to develop an asymmetric version of this strategy.

Typical Procedure for the Cyclopropanation Reaction
LiHMDS (2.2 mmol; 1 M solution in THF) was added dropwise, at –78 °C, to a solution of sulfonium salt (2 mmol) and diene (2.2 mmol) in CH_2Cl_2 (7 mL) The reaction mixture was stirred at this temperature for 1–6 h. The cold bath was then removed, allowing the solution to warm to r.t. The reaction was quenched with HCl (1 N). The organic extract was concentrated under reduced pressure and redissolved in Et_2O. This solution was washed with HCl (1 N), H_2O, and brine before being dried over $MgSO_4$ and concentrated under vacuum to yield the desired substituted cyclopropane. The *cis*- and *trans*-isomers can be separated by column chromatography on silica gel.

Characterization of 3 with Ar = 4-$MeOC_6H_4$ and R = CO_2Me
Major (*trans*) isomer: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.19 (ddd, 1 H, *J* = 9.0, 5.3, 5.2 Hz, *H*CH), 1.32 (ddd, 1 H, *J* = 8.4, 6.2, 5.3 Hz, *H*CH), 1.67 (m, 1 H, *H*CCH_2=CH_2), 2.07 (ddd, 1 H, *J* = 9.0, 6.2, 4.2 Hz, HCAr), 3.65 (s, 3 H, OCH_3), 3.71 (s, 3 H, OCH_3), 5.82 (d, 1 H, *J* = 15.4 Hz, $CHCO_2Me$), 6.52 (dd, 1 H, *J* = 15.4, 9.9 Hz, C*H*=$CHCO_2Me$), 6.75 (d, 2 H, *J* = 8.7 Hz, ArH), 6.94 (d, 2 H, *J* = 8.7 Hz, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.4 (CH_2), 25.3 (CHAr), 25.4 (*C*HCH_2=CH_2), 50.4 (OCH_3), 54.3 (OCH_3), 112.8 (*C*HCOMe), 117.1 (*C*HCO_2Me), 126.0 (*C*HC-cyclopropyl), 128.4 (C-cyclopropyl), 151.2 (CH-cyclopropyl), 157.2 (COMe), 166.1 (CO_2Me). GC (MN OPTIMAS-5; 150 °C for 10 min and then 290 °C, 7 °C/min): 22.3 min. MS (APCI): *m/z* = 233 $[M + 1]^+$, 201 $[M + 1 – MeOH]^+$, 173 $[M + 1 – HCO_2Me]^+$.

Minor (*cis*) isomer: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.32 (m, 1 H, *H*CH), 1.36 (m, 1 H, *H*CH), 1.65 (m, 1 H, *H*CCH_2=CH_2), 2.43 (m, 1 H, HCAr), 3.67 (s, 3 H, OCH_3), 3.73 (5.83 (s, 3 H, OCH_3), 5.84 (d, 1 H, *J* = 15.4 Hz, $CHCO_2Me$), 6.16 (dd, 1 H, *J* = 15.4, 10.5 Hz, C*H*=$CHCO_2Me$), 6.75 (m, 2 H, ArH), 7.06 (d, 2 H, *J* = 8.6 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.8 (CH_2), 16.4 (CHAr), 23.8 (*C*HCH_2=CH_2), 50.2 (OCH_3), 54.2 (OCH_3), 112.8 (*C*HCOMe), 118.4 (*C*HCO_2Me), 129.0 (*C*HC-cyclopropyl), 129.4 (C-cyclopropyl), 149.6 (CH-cyclopropyl), 158.1 (COMe), 165.7 (CO_2Me). GC (MN OPTIMAS-5; 150 °C for 10 min and then 290 °C, 7 °C/min): 20.7 min.

Characterization of 4 with Ar = 4-$MeOC_6H_4$ and R = CO_2Me
^{1}H NMR (500 MHz; $CDCl_3$): δ = 2.15 (dd, 1 H, *J* = 5.4, 4.8 Hz, HCAr), 2.43 (ddd, 1 H, *J* = 9.6, 8.7, 4.8 Hz, *H*CH=CH_2), 2.90 (dd, 1 H, *J* = 9.6, 5.4 Hz, $HCCO_2Me$), 3.76 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 5.01 (dd, 1 H, *J* = 9.9, 2.1 Hz, *cis*-*H*CH=CH), 5.17 (ddd, 1 H, *J* = 17.1, 9.9, 8.7 Hz, C*H*=CH_2), 5.26 (dd, 1 H, *J* = 17.1, 2.1 Hz, *trans*-*H*CH=CH), 6.85 (d, 2 H, *J* = 8.7 Hz, Ar), 7.13 (d, 1 H, *J* = 8.7 Hz, Ar). GC (MN OPTIMAS-5; 150 °C for 10 min and then 290 °C, 7 °C/min): 18.3 min.

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