Stereoselective Synthesis of Substituted 1,3,5-Hexatrienes from Diallylic Sulfones

Xiao-Ping Cao, Tze-Lock Chan,* Hak-Fun Chow* and Jingren Tu

Department of Chemistry, The Chinese University of Hong Kong, Shatin, N.T., Hong Kong

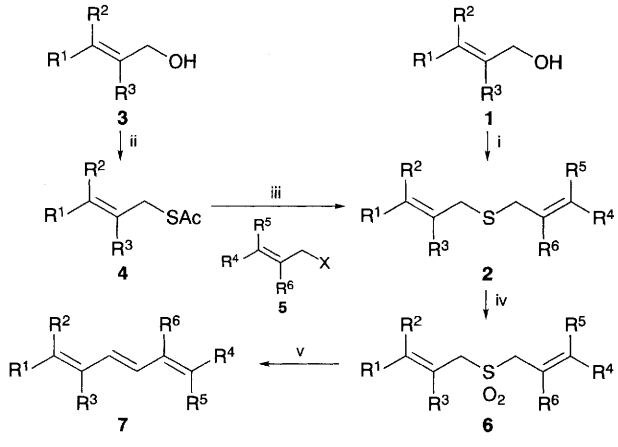
Substituted 1,3,5-hexatrienes **7** can be prepared in excellent yields and with good stereoselectivity from diallylic sulfones **6** employing a modified Ramberg–Bäcklund reaction.

Conjugated 1,3,5-hexatriene is an important structural unit in a wide variety of natural products such as phytoene, vitamins D_2 and D_3, leukotrienes B_4 and C_4, asukamycin and mocimycin.[1] It has also been shown that conjugated polyenes are potentially useful compounds for non-linear optical materials.[2] Most of the established synthetic methods for the construction of conjugated hexatrienes have relied on the Hofmann elimination of hexadienyl quaternary ammonium salts,[3] the Wittig olefination,[4] the Heck reaction of vinyl bromides with conjugated dienes,[5] the Stille coupling between vinyl iodides and 1-trimethylstannylbuta-1,3-dienes,[6] and palladium-catalysed coupling of alkenes to fumaryl chloride and to 5-substituted penta-2,4-dienoyl chloride.[7] While some of these reactions are capable of producing the all (*E*)-conjugated trienes as the major products, stereorandomization of the configurations in the pre-existing double bonds and/or those under construction appears to be quite common in most of them. The recent works of Alami and coworkers[8] provide a solution to the stereoselective formation of (*Z*,*Z*,*Z*)- and (*Z*,*E*,*Z*)-conjugated trienes *via* (palladium and copper)-catalysed coupling of terminal acetylenes to (*Z*)- or (*E*)=1,2-dichloroethene followed by *syn* reduction of the triple bond moieties. We disclose herein a new approach to the stereocontrolled synthesis of conjugated trienes by employing the one-flask Ramberg–Bäcklund reaction recently reported by us.[9]

The idea of utilizing the Ramberg–Bäcklund reaction as a method for assembling the 1,3,5-triene unit from diallyl sulfones was first put to the test by Büchi and Freidinger.[10] However, at a time when a convenient procedure for the conversion of diallyl sulfides into the corresponding sulfones was yet to be discovered, these authors had to resort to a cumbersome route entailing the reaction of 2 mol equiv. of an allylic alcohol with a sulfur transfer reagent to generate first the allyl allylsulfinate (presumably by way of the elusive diallyl sulfoxylate) which was then subjected to a thermal [2,3]sigmatropic rearrangement to arrive at the requisite sulfone. Ramberg–Bäcklund reaction of these diallyl sulfones using the Meyers' protocol[11] led to a mixture of geometric isomers of the conjugated trienes.[10] In the intervening years, several other similar studies on the application of the Ramberg–Bäcklund reaction for the construction of conjugated trienes have appeared,[12] but again the levels of stereocontrol attainable in these works were at best marginal.

Our previous finding that dibenzylic sulfones were smoothly transformed into *trans*-stilbenes in excellent yields and with high stereoselectivity on treatment with CBr_2F_2 in the presence of alumina-supported KOH[9] prompted us to examine the behaviour of diallylic sulfones which are now conveniently prepared by selective oxidation of diallylic sulfides with oxone.[13] What emerges from this investigation is the highly stereoselective generation of a new (*E*)-double bond with the retention of the configurations of the pre-existing ones on the allylic moieties, thus making available an efficient route to the stereocontrolled synthesis of the (*E*,*E*,*E*)-, (*Z*,*E*,*Z*)- and (*E*,*E*,*Z*)-1,3,5-triene units.

The starting materials are the stereochemically pure allyl halides **1** (X = Cl, Br) (Scheme 1). Reactions of **1** with sodium sulfide in methanol afford the symmetrical sulfides **2** ($R^1 = R^4$, $R^2 = R^5$, $R^3 = R^6$, entries 1–3, 8 and 10) in good yields (Table 1). On the other hand, the allyl alcohols **3** can be converted to thiol acetates **4** *via* the Mitsunobu reaction with thioacetic acid



Scheme 1 *Reagents and conditions*: i, Na_2S, MeOH; ii, PPh_3, MeCOSH, diisopropyl azodicarboxylate; iii, KOH, MeOH; iv, oxone, CH_2Cl_2; v, CF_2Br_2, CH_2Cl_2, KOH on Al_2O_3

Table 1 Yields of sulfides, sulfones and trienes

Entry	R^1	R^2	R^3	R^4	R^5	R^6	sulfide **2**	sulfone **6**	triene **7**	(*E*:*Z* ratio of internal C=C)
1	Me	H	H	Me	H	H	89	82	84	(>95:<5)
2	H	H	Me	H	H	Me	97	90	90	(>95:<5)
3	Me	Me	H	Me	Me	H	88	84	82	(75:25)
4	Ph	H	H	H	H	H	93	86	86	(>95:<5)
5	Ph	H	H	Me	H	H	93	89	88	(>95:<5)
6	Ph	H	H	H	H	Me	87	90	92	(>95:<5)
7	Ph	H	H	Me	Me	H	91	95	87	(87:13)
8	Ph	H	H	Ph	H	H	84	89[a]	89[b]	(>95:<5)
9	Ph	H	H	H	Ph	H	80	80[c]	90	(>95:<5)
10	H	Ph	H	H	Ph	H	93	98[d]	54[e]	(91:9)[f]
11	Ph	H	H	Me_3Si	H	H	87	89	84	(>95:<5)
12	H	Ph	H	Me_3Si	H	H	84	90	89	(90:10)[g]

[a] mp 205–206 °C. [b] mp 203–204 °C (lit.[4a] mp 203 °C). [c] mp 125–128 °C. [d] mp 95–96 °C. [e] mp 110 °C. [f] Reaction was coducted at −78 °C in Bu^tOH–CBr_2F_2 (1:1) solution. [g] Reaction was conducted at 0 °C in *tert*-butyl alcohol solution.

in the presence of triphenylphosphine and diisopropyl azodicarboxylate. *In situ* cleavage of **4** with potassium hydroxide in methanol followed by allylation of the resulting thiolates with stereodefined allyl halides **5** (X = Br, Cl) provides the unsymmetrical sulfides **2**. It is noteworthy that the stereochemistry of the double bonds is retained during these transformations. Thus, coupling of (*E*)-cinammyl chloride **1** (R^1 = Ph, R^2 = R^3 = H, X = Cl) with sodium sulfide affords the symmetrical di-(*E*)-cinammyl sulfide **2** (R^1 = R^4 = Ph, R^2 = R^3 = R^5 = R^6 = H, entry 8) in 84% yield (J_{trans} = 15.4 Hz). Similarly, the symmetrical di-(*Z*)-cinammyl sulfide **2** (R^2 = R^5 = Ph, R^1 = R^3 = R^4 = R^6 = H, entry 10) can be obtained in 93% yield (J_{cis} = 11.2 Hz). On the other hand, reaction of (*Z*)-cinammyl chloride **5** (R^5 = Ph, R^4 = R^6 = H, X = Cl) with the thiolate of (*E*)-cinammylthiol acetate **4** (R^1 = Ph, R^2 = R^3 = H) gives the (*E*,*Z*)-sulfide **2** (R^1 = R^5 = Ph, R^2 = R^3 = R^4 = R^6 = H, entry 9) with retention of double-bond geometries at both ends (J_{cis} = 11.5, J_{trans} = 15.1 Hz). Both the symmetrical and unsymmetrical sulfides can be converted into the corresponding sulfones **6** with retention of double-bond geometries by oxone[13] in dichloromethane solution in excellent yields. Treatment of the sulfones **6** with dibromodifluoromethane in the presence of KOH–Al_2O_3[9] in dichloromethane at 0 °C gives the geometrically defined trienes **7** in good yields.

The issue of stereochemistry in the resulting trienes was resolved in the following manner. For the symmetrically substituted 1,3,5-hexatrienes **7** (entries 1–3, 8 and 10), the coupling constants between the two alkenic protons of the central C=C double bond cannot be determined because of their chemical shift equivalence. However, apart from entry 3, we only identified one single hexatriene (^{1}H and ^{13}C NMR) from the crude reaction mixture. The spectroscopic and physical properties of these trienes are consistent with the literature values reported for the respective known geometrical isomers (Table 2) having a central double bond with an (*E*)-configuration. For 2,7-dimethylocta-2,4,6-triene (entry 3), we were unable to find previous literature data. To our surprise, a 3 : 1 mixture of isomers was formed in this case. Based on the preferential formation of the (*E*)-isomers in all cases studied, we therefore tentatively assign as the major isomer the one having the (*E*)-configuration at the central double bond.

For the unsymmetrical trienes, the (*E*)-configuration of the newly formed C=C double bond in each case is readily diagnosed by the discrete ^{1}H NMR coupling constants between the pertinent alkenic protons. The observed $^3J_{HC=CH}$ values vary from 14.9 to 18.2 Hz, indicating (*E*)-stereochemistry. The other two double bonds again retain their stereochemical integrity during the transformation, in spite of the possible role of an allylic anion in the course of the Ramberg–Bäcklund reaction.

Table 2 Alkenic coupling constants ($^3J_{HC=CH}$) of 1,3,5-hexatrienes **7**

Entry	Central C=C bond	Terminal C=C bonds	Ref.
1	—	[a]	14
2	—	—	15
3	—	—	—
4	[a]	9.2, 15.2, 15.6	16
5	15.0	14.9, 15.6	17
6	15.1	15.6	—
7	14.7	15.5	18
8	—	15.6, 15.6	4*b*, 19
9	15.5	11.5, 15.5	4*b*
10	—	11.0, 11.0	—
11	14.7	15.5, 18.2	—
12	14.7	11.5, 18.1	—

[a] Coupling constant cannot be resolved (500 MHz NMR) due to overlapping signals.

It is important to point out, however, that the stereoselectivity of the modified Ramberg–Bäcklund reaction is dependent upon the reaction conditions. Thus, the di-(*Z*)-cinammyl sulfone gave a 65 : 35 mixture of diphenylhexa-(1*Z*,3*E*,5*Z*)-triene and diphenylhexa-(1*Z*,3*Z*,5*Z*)-trienes in dichloromethane solution at 0 °C. When the reaction was conducted in *tert*-butyl alcohol, the stereoselectivity improved to 71 : 29. However, when methanol was employed as the reaction solvent, only the (1*E*,3*E*,5*E*)-triene was obtained, indicating a substantial loss of stereointegrity of the terminal double bonds. It was gratifying that the (*Z*,*E*,*Z*)-triene isomer could be isolated in 91 : 9 ratio in favour of the (*Z*,*Z*,*Z*)-isomer when the reaction was conducted at −78 °C in Bu^tOH–CBr_2F_2 (1 : 1) solution. It is therefore possible to maintain a high level of stereocontrol in the formation of these trienes by judicious choice of solvent and temperature for the Ramberg–Bäcklund reaction.

In summary, we have presented a rapid route to stereochemically defined (*E*,*E*,*E*)-, (*Z*,*E*,*Z*)- and (*E*,*E*,*Z*)-conjugated 1,3,5-trienes. The synthetic transformation utilizes readily available (*E*)- or (*Z*)-allylic halides as starting materials. The synthesis of the requisite sulfones is facile and the reactions can be performed in molar scales. Most importantly, we have now presented an unambiguous proof that the double bonds of stereochemically defined diallyl sulfones retain their stereochemistry and that the newly formed central double bond has an (*E*)-configuration in our modified Ramberg–Bäcklund procedure. This is similar to the case of dibenzyl sulfones which we reported earlier.[9]

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