An 1,2-Elimination Approach to the Enantioselective Synthesis of 1,3-Disubstituted Linear Allenes

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Abstract: The construction of 1,3-disubstituted allene skeleton, which is present in many natural allenes, via an *i*-PrMgBr-mediated elimination of optically active 3-acetoxy-2-iodo-prop-1-ene dervivatives is exemplified through the enantioselective total synthesis of two bioactive natural allenes.

Key words: alkynes, carbanions, elimination, halides, natural products

In contrast to the plentiful choices of approaches to the synthesis of tetrahedral stereogenic carbon centers, the available access to optically active allenes is still rather limited. Up to now all known enantioselective syntheses rely essentially on the S_N2' reaction or Claisen rearrangement of the corresponding propargylic alcohol derivatives.[1] As such reactions do not always proceed in high enantioselectivity and in many cases (e.g., when a 1,3-disubstituted allenic axis is the only chiral element in the molecule) removal of the undesired allenic isomers from the products on preparative scales is practically impossible, efforts to develop new approaches are apparently warranted.

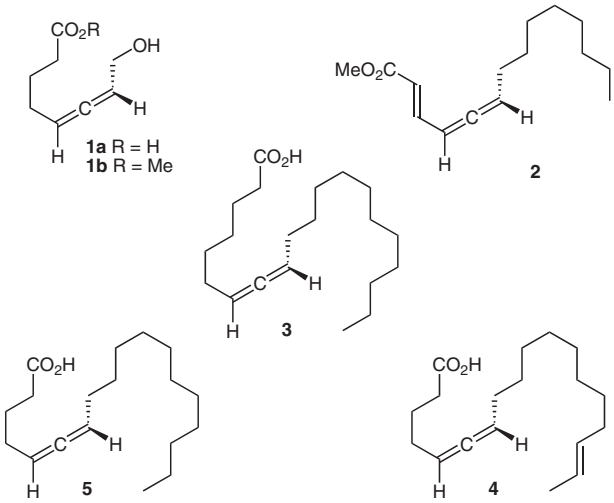
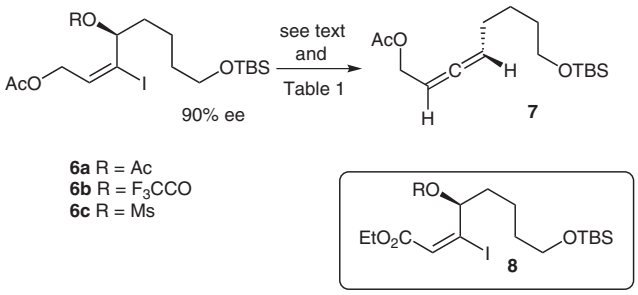


Figure 1

Many naturally occurring 1,3-disubstituted allenes (e.g., compounds **1**–**5**, Figure 1) are biologically active.[2] During our synthetic studies into this type of compounds, we became interested in exploring the possibility of using 1,2-elimination of alkenyl iodides that carry a leaving group at the allylic position to enantioselectively install a chiral allene unit. Such reactions were long known,[3] but in most cases only racemic compounds were involved. Protocols[4] that led to optically active allenes are scant, and, to the best of our knowledge, none of them utilized alkenyl halides as the precursors. This prompted us to perform the work described below.

As our efforts in methodology studies along this line are targeted at eventual synthesis of bioactive natural allenes such as **1**, optically active alkenyl idodides **6**[5] appear to be suitable substrates for the examination of the stereochemical course of the 1,2-elimination reaction leading to **7** (Scheme 1). To facilitate screening of potentially applicable reagents/conditions, diagnostic trials were first performed on a more readily accessible substrate (**8**). The tested reagents included Zn[6] or Mg[7] powder, *t*-BuLi,[8] *i*-PrMgBr,[9] and SmI_2. Among them, only Mg powder, *t*-BuLi, and *i*-PrMgBr seemed to be promising and thus deserved further examinations.



Scheme 1

More careful examination was then performed with **6a**–**c** as the substrates. As expected, without the strong interference from the side reactions associated with the ester group conjugated to the C–C double bond (such as in **8**), the reaction became cleaner, and the results are summarized in Table 1.

The elimination of **6a** was first attempted with Mg activated[10] with LiCl. At ambient temperature, essentially no reactions took place after 24 hours (entry 1). Raising

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the temperature to 70 °C led to the desired compound **7** in 39% yield, but the degree of chirality transfer from the chiral center to the chiral axis was about 69% (entry 2). Changing the leaving group from OAc to $OCOCF_3$ (**6b**), which was expected to be a better leaving group, did result in a higher yield (59%) under the same conditions. However, the stereoselectivity dropped drastically (entry 3). The corresponding mesylate (**6c**), a substrate with even better leaving group ability, gave a complex mixture (entry 4).

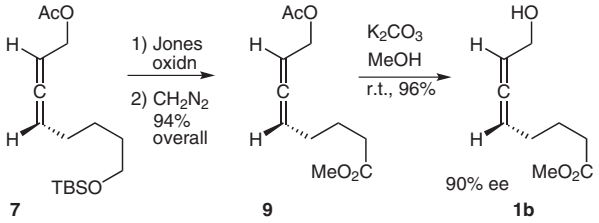
In the absence of the added LiCl, **6a** led to **7** in lower yield (17%), but the enantioselectivity was slightly improved (entry 5). Extension of the reaction time from two to nine hours raised the yield to 30% without causing any apparent adverse effects on the enantioselectivity (entry 6). Under comparable conditions, **6b** gave higher yield of **7** but with lower enantioselectivity (entry 7).

Table 1 Conversion of **6** (90% ee) into **7**[a]

Entry	Substrate	Conditions	Yield of **7** (%)	Eff. (%)[b]
1	**6a**	Mg, LiCl, r.t., 24 h	0[c]	0
2	**6a**	Mg, LiCl, 70 °C, 2 h	39[d]	69
3	**6b**	Mg, LiCl, 70 °C, 2 h	59[e]	11
4	**6c**	Mg, 70 °C, 2 h	mixture	–
5	**6a**	Mg, 70 °C, 2 h	17[f]	79
6	**6a**	Mg, 70 °C, 9 h	30[g]	78
7	**6b**	Mg, 70 °C, 2.5 h	23[h]	20
8	**6a**	*i*-PrMgBr, –78 °C	93	>99
9	**6b**	*i*-PrMgBr, –78 °C	92	>95
10	**6c**	*i*-PrMgBr, LiCl, –78 °C	59	69
11	**6a**	*t*-BuLi, –78 °C	80[i]	>99[j]

[a] All reactions were performed in THF.
[b] Efficiency of the chirality transfer from the allylic stereogenic center to the allene axis, defined as **7** (ee)/**6** (ee)
[c] No reaction occurred.
[d] Along with 54% of recovered **6a**.
[e] Along with 16% of recovered **6b**.
[f] Along with 83% of recovered **6a**.
[g] Along with 59% of recovered **6a**.
[h] Along with 52% of recovered **6a**.
[i] Yield for the deacetylated **7**.
[j] The deacetylated product in this case was transformed into **7** by treatment with Ac_2O.

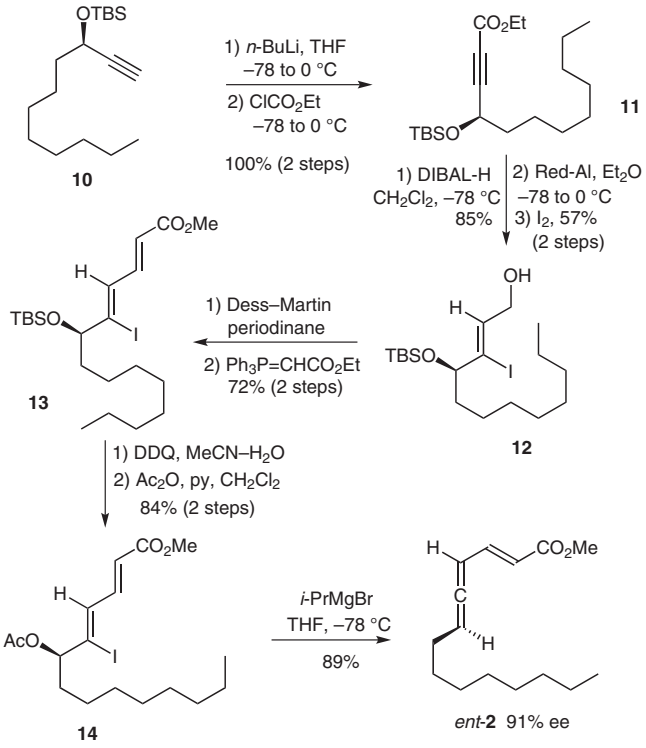
The results with *i*-PrMgBr were much better. By using **6a** as the substrate, the yield and enantioselectivity were 93% and >99%, respectively (entry 8). The other two substrates, **6b** and **6c**, could also be transformed into **7** in high yields and enantioselectivity, though slightly lower than that observed with **6a** (entries 9 and 10). The enantioselectivity observed with *t*-BuLi was also rather good (entry 11) as far as the elimination was concerned. However, as the yield was substantially lower than those using *i*-PrMgBr,[11] the latter protocol was employed in the subsequent studies.



Scheme 2

The allene **7** thus obtained was treated with Jones reagent followed by diazomethane, giving methyl ester **9** in 82% overall yield (Scheme 2). On further exposure to K_2CO_3 in MeOH at ambient temperature, the natural product **1a** (the antifungal constituent of *Sapium japonicum*), was obtained in 96% yield.

Among the linear natural allenes, compound **2**, a sex attractant of male dried bean beetle, is remarkably different from the remainder, containing an extra C–C double bond between an ester group and the allene bonds. To examine if the above conditions are also applicable to substrates with extended double bond(s) systems, we next tested the elimination directly leading to the antipode of **2** (Scheme 3).



Scheme 3

The precursor needed for the key elimination was synthesized from the known[12] optically active propargylic alcohol derivative **10**. Introduction of an ester group was

achieved by treatment of **10** with *n*-BuLi followed by $ClCO_2Et$. Conversion of alkyne to iodoalkene was first attempted under the conditions of Ma and Lu[13] as in the synthesis of **6**. However, in this case we found that it was difficult to separate the desired product from other undesirable side products. To circumvent this problem, an alternative approach was adopted. The ester group was first reduced with DIBAL-H to the corresponding alcohol. The intermediate propargyl alcohol was then treated[14] with Red-Al followed by I_2 to give **12** without complications. Oxidation with Dess–Martin periodinane and Wittig reaction with $Ph_3P{=}CHCO_2Me$ afforded diene **13**. The TBS protecting group was replaced with an acetyl group, providing the desired precursor **14**.[15] The key elimination was then performed under the optimal conditions established in the conversion of **6a** to **7**. With an additional C–C double bond and an ester functionality in conjugation with the iodoalkene functionality, the 1,2-elimination occurred at a much faster rate, affording the desired product *ent*-**2** in 91% yield.

In brief, a new elimination approach to the enantioselective synthesis of 1,3-disubtituted allenes from 3-acetoxy-2-iodo-prop-1-ene derviatives has been developed. The results show experimentally for the first time that the elimination of the alkenyl iodides may proceed with a high level of stereoselectivity and in good product yield in the presence of *i*-PrMgBr as the reagent. The iodoalkenyl functionality in the substrates can be either isolated or in conjugation with another C–C double bond. Compared with the alkenyl sulfoxides,[4b] silanes,[3j] and stannanes[3k,4a] used in the previous elimination protocols, the iodo substrates are synthetically more readily accessible, less toxic and of better atom/chirality[16] economy. All these make the present protocol a good complement to the existing methods for the enantioselective construction of 1,3-disubstituted allenes.[17]

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

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(11) Lower level of functional-group tolerance is also a major concern here, although the simultaneous cleavage of the terminal Ac protecting group is beneficial in this synthesis.

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(15) All attempts to separate the enantiomers of **14** by chiral HPLC failed.
(16) Unlike sulfoxides, there is no stereogenic center in iodide. No loss of stereogenic centers occurred with the elimination of the halides.
(17) **Representative Procedures**

Conversion of 6a into 7

A solution of **6a** (150 mg, 0.30 mmol) in dry THF (2 mL) was added dropwise via a syringe to a solution of *i*-PrMgBr (2 M, in Et_2O, 0.9 mL, 1.8 mmol) in dry THF (5 mL) stirred at –78 °C under argon. After completion of the addition, the stirring was continued at –60 °C for 2.5 h. Aqueous sat. NH_4Cl was added. The mixture was extracted with Et_2O (50 mL), washed with H_2O and brine before being dried over anhyd Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (PE–EtOAc, 100:1) on silica gel gave allene **7** as a colorless oil (84 mg, 0.28 mmol, 93%) along with recovered **6a** (6 mg, 0.012 mmol, 4%).

Data for 7

$[\alpha]_D^{27}$ –33.7 (*c* 0.9, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.28–5.20 (m, 2 H), 4.54 (dd, *J* = 5.8, 2.8 Hz, 2 H), 3.62 (t, *J* = 6.4 Hz, 2 H), 2.07 (s, 3 H), 2.10–2.02 (m, 2 H), 1.54 (quint, *J* = 7.3 Hz, 2 H), 1.48 (quint, *J* = 7.1 Hz, 2 H), 0.90 (s, 9 H), 0.05 (s, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.4, 170.8, 92.8, 86.9, 62.90, 62.87, 32.1, 28.1, 25.9, 25.3, 21.0, 18.3, –5.3. FT-IR (film): 2955, 2930, 2858, 1963, 1744, 1227, 1103 cm^{-1}. ESI-MS: *m/z* = 321.1 $[M + Na]^+$. HRMS (MALDI): *m/z* calcd for $C_{16}H_{30}SiO_3Na$ $[M + Na]^+$: 321.1856; found: 321.1863.