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Preparation of the conjugated polyene chains with the 1,4-dimethyl substitution

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Abstract—Allylic sulfones undergo the conjugate addition to diethyl chloroisopropylidenemalonate, followed by intramolecular cyclopropanation. DBU-promoted ring opening and subsequent desulfonation reactions of the resulting adduct produce the conjugated polyene chains with the 1,4-dimethyl substitution.
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Carotenoids, which are classified as isoprenoids according to their biogenetic origin, have the general structural feature of the conjugated polyene chain.[1] These carotenoids are enzymatically synthesized in biological systems by the coupling reactions of isopentenyl pyrophosphate (IPP) or dimethylallyl pyrophosphate (DMAP),[2] which gives rise to the basic repeating unit of the C_5 prenyl group (Fig. 1a). There are four different ways of connecting the prenyl group: head–head (h–h), head–tail (h–t), tail–head (t–h), and tail–tail (t–t) attachments (Fig. 1b). The t–t combination generates the 1,6-dimethyl substitution pattern, which is mainly found in the center of carotenoid compounds such as β-carotene, lycopene, and astaxanthin etc. The 1,5-dimethyl substitution is the general substitution pattern of carotenoids and retinoids, which is generated from the t–h or the h–t combinations. The h–h combination, producing the 1,4-dimethyl substitution, is not uncommon but present in some natural products from the marine origin or from the gliding bacteria such as immunosuppressant (−)-pateamine,[3] antibiotic haliangicin,[4] and myxopyronin[5] (Fig. 1c) as well as some carotenoid compounds of isomethylpseudoionone, 3-hydroxy-8′-apo-β,ψ-caroten-8′-al, and isocrocetin. There have been intensive synthetic efforts for (−)-pateamine, myxopyronin, and isomethylpseudoionone where the installation of the 1,4-dimethyl substituted polyene chain was the key issue. While the Stille coupling has been the main repertoire for (−)-pateamine,[3] aldol condensation was used for the synthesis of myxopyronin[5a] and isomethylpseudoionone.[6]

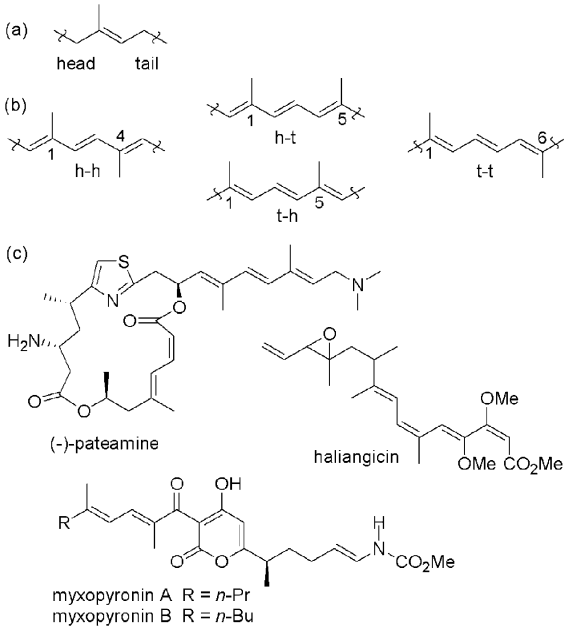

Figure 1. (a) The prenyl group; (b) the attachment patterns of two prenyl groups in the polyene chains and (c) some representative natural products containing the 1,4-dimethyl substituted polyene chain.

We have reported the general and systematic synthetic methods of the 1,5- and the 1,6-dimethyl substituted

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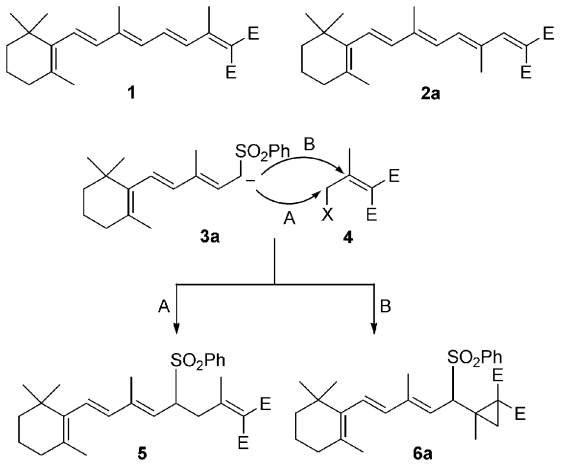


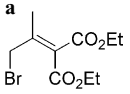
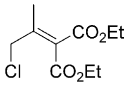
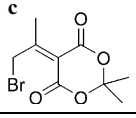
Figure 2. The retinoid **1** and its isomethyl derivative **2a**, and the coupling pathways of the C_{15} allylic sulfone **3a** and the allylic halides **4** with diesters (E) in conjugation.

polyene chains, and thus completed the total syntheses of retinoid and carotenoid compounds.[7] In the synthetic study toward the retinoic acid and its various derivatives **1**, we have developed a new and efficient way of producing the polyene chain **2a**, and generalized this approach to the synthesis of the polyene chains with the 1,4-dimethyl substitution (Fig. 2). We herein report the details of this study.

The C_{15} allylic sulfone **3a** has been efficiently utilized in the synthesis of retinoid compounds by the Julia olefination reaction with the proper C_5 allylic halides.[8] It was envisioned that the reaction of the C_{15} allylic sulfone **3a** and the allylic halides **4** containing two electron-withdrawing ester groups (E) might follow either the allylic coupling pathway (route A) to give **5** or the conjugate addition and subsequent intramolecular cyclopropanation pathway (route B) to give **6a** (Fig. 2), that would generate the conjugated polyene compound **1** with the 1,5-dimethyl substitution or the conjugated polyene compound **2a** with the 1,4-dimethyl substitution, respectively, after base-promoted dehydrosulfonation reaction.

The coupling reaction of the C_{15} allylic sulfone **3a** with three different allylic halides **4a–c** has been extensively studied, and the results were summarized in Table 1.

Table 1. The yields and the conditions of the reactions in Figure 2

Entry	4	Condition	5 (%)	6a (%)
1	**a**	*n*-BuLi/THF	75	9
2		*t*-BuOK/DMF	60	8
3	**b**	*n*-BuLi/THF	—	83
4		*t*-BuOK/DMF	20	36
5	**c**	*n*-BuLi/THF	—	75
6		*t*-BuOK/DMF	—	54

Two different coupling conditions of *n*-BuLi in THF and *t*-BuOK in DMF were utilized for each allylic halide. The allylic coupling of **3a** was observed as the major pathway (A) for the reactive allylic bromide **4a** [9] with acyclic diester substituents to give **5** (entries 1 and 2). A small amount of **6a**, which arose from the pathway B was also obtained in both coupling conditions. With the less reactive allylic chloride **4b**[10] with acyclic diester substituents, on the other hand, the coupling reaction of **3a** followed the pathway B to give **6a**[11] (83% yield) exclusively under the condition utilizing *n*-BuLi (entry 3). The coupling reaction of **3a** and **4b** under *t*-BuOK was less effective since a somewhat low-yield mixture of **5** and **6a** was obtained (entry 4). It was surprising that only the pathway B was observed for the coupling reaction of **3a** and the allylic bromide **4c**[12] with cyclic dilactone substituents (entries 5 and 6). It seemed that the unsaturated cyclic diester group activated **4c** toward the conjugate addition of **3a** even in the presence of the reactive allylic bromide moiety. The conditions using *n*-BuLi were better than those using *t*-BuOK in providing high yields of the coupling products and good selectivities between the two reaction pathways.

The coupled product **6a** then reacted with DBU in benzene at the reflux temperature to give the fully conjugated polyene chain compound **2a**[13] with the 1,4-dimethyl substitution in 92% yield. This reaction proceeded through the initial generation of carbanion at the α carbon to the benzenesulfonyl group of **6a**, followed by the opening reaction of the cyclopropane ring containing diester substituents to give the stabilized carbanionic intermediate structure **C**. After the double bond migration to give the structure **D**, the desulfonation reaction via the allylic E1cb mechanism produced all-(*E*)-**2a** (Fig. 3). This reaction was highly stereoselective to produce (*E*)-configurations of the carbon–carbon double bonds.

The general applicability of this two-step sequence to the synthesis of the conjugated polyene chains **2** with the 1,4-dimethyl substitution has been tested for three other allylic sulfones **3b–d** and the allylic chloride **4b** (Fig. 4 and Table 2). The coupling condition of *n*-BuLi in THF was used, in which no product derived from the direct allylic coupling (the pathway A in Fig. 2) was obtained. Comparable yields of 82% and 81% to **6a** were obtained for **6b** and **6c**, respectively. A somewhat lower yield of 68% for **6d** was attributed to the instability of the allylic sulfone compound **3d** containing the acyclic conjugated triene unit. DBU-promoted dehydrosulfonation reactions of **6b–d** proceeded efficiently to produce

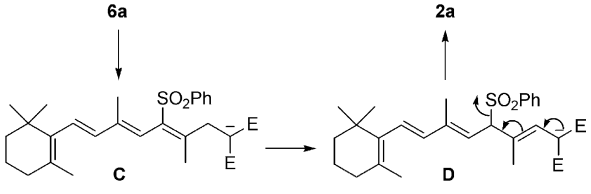


Figure 3. The mechanism of the reaction from **6a** to the conjugated polyene compound **2a** with the 1,4-dimethyl substitution.

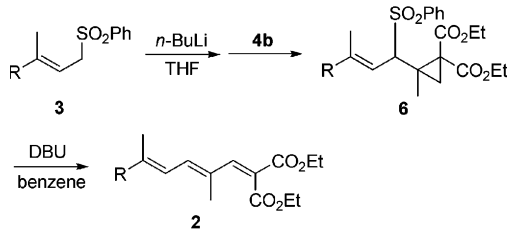
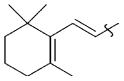
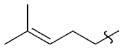
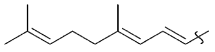


Figure 4. A general synthetic method of the conjugated polyene chains with the 1,4-dimethyl substitution.

Table 2. Structures of the substrates and the yields of the reactions in Figure 4

Entry	Suffix	Structure of R	**6** (%)	**2** (%)
1	**a**		83	92
2	**b**	CH_3	82	52
3	**c**		81	62
4	**d**		68	52

the conjugated polyene chains **2b–d** with the 1,4-dimethyl substitution pattern. Once again, the instability of the acyclic conjugated triene unit in **2b–d** might explain a little lower yields of 52–62%.

In conclusion, we have developed an efficient synthetic method of the conjugated polyene chains with the 1,4-dimethyl substitution, in which (i) the chemoselective conjugate addition of allylic sulfones to the allylic halides with conjugated diesters followed by cyclopropanation and (ii) DBU-promoted dehydrosulfonation of the resulting β-cyclopropylidenesulfone have been demonstrated for the first time. We have proven the generality of this method, which can be usefully applied to the syntheses of various isoprenoid natural products containing the polyene chains with the 1,4-dimethyl substitution.

Acknowledgements

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11. The representative experimental procedure for **6a**: To a stirred solution of the C_{15} allylic sulfone **3a** (1.00 g, 2.90 mmol) in THF (30 mL) at −78 °C under Ar atmosphere was added a 1.6 M solution of *n*-BuLi (2.0 mL, 3.20 mmol). The mixture was stirred for 30 min at that temperature, and a solution of **4b** (0.89 g, 3.77 mmol) in THF (5 mL) was added. The resulting mixture was stirred at −78 °C for 30 min and then at room temperature for 1.5 h. The reaction mixture was quenched with 1 M HCl solution (50 mL), extracted with ether (20 mL × 3), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography to give **6a** (1.30 g, 2.39 mmol) in 83% yield. Data for **6a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (3H, s), 0.98 (3H, s), 1.11 (3H, s), 1.26 (1H, A of ABq, J = 5.1 Hz), 1.34 (1H, B of ABq, J = 5.1 Hz), 1.37 (3H, t, J = 7.2 Hz), 1.38 (3H, t, J = 7.2 Hz), 1.42–1.51 (2H, m), 1.49 (3H, s), 1.57–1.66 (2H, m), 1.68 (3H, s), 2.00 (2H, br t, J = 6.0 Hz), 4.23–4.43 (4H, m), 4.97 (1H, d, J = 11.1 Hz), 5.71 (1H, d, J = 11.1 Hz), 5.97 (1H, A of ABq, J = 16.2 Hz), 6.04 (1H, B of ABq, J = 16.2 Hz), 7.42–7.56 (3H, m), 7.72–7.74 (2H, m) ppm; ^{13}C NMR (75.5 MHz,

$CDCl_3$) δ 11.9, 14.0, 14.1, 17.8, 19.1, 21.5, 26.2, 28.8, 28.8, 30.8, 32.8, 34.1, 39.4, 40.2, 61.5, 62.0, 62.2, 118.5, 128.6, 128.7, 128.9, 129.5, 133.1, 136.0, 137.2, 139.0, 142.4, 168.0, 170.5 ppm; IR (KBr) 2931, 1716, 1447, 1370, 1307, 1149 cm^{-1}; HRMS (FAB^+) calcd for $C_{25}H_{37}O_4$ 401.2692, found 401.2687.

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13. The representative experimental procedure for **2a**: The mixture of **6a** (0.80 g, 1.50 mmol) and DBU (1.14 mL, 7.5 mmol) in benzene (20 mL) was heated at reflux for 4 h. The reaction mixture was then cooled to room temperature, and quenched with 1 M HCl (10 mL). The mixture was extracted with ether (20 mL × 3), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography to give **2a** (0.56 g, 1.39 mmol) in 92% yield. Data for **2a**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.04 (6H, s), 1.30 (3H, t, J = 7.2 Hz), 1.35 (3H, t, J = 7.1 Hz), 1.44–1.50 (2H, m), 1.57–1.67 (2H, m), 1.73 (3H, s), 1.92 (3H, s), 2.02 (3H, s), 2.00–2.07 (2H, m), 4.25 (2H, q, J = 7.1 Hz), 4.32 (2H, q, J = 7.2 Hz), 6.22 (1H, A of ABq, J = 15.2 Hz), 6.34 (1H, d, J = 12.1 Hz), 6.38 (1H, B of ABq, J = 15.2 Hz), 6.91 (1H, d, J = 12.1 Hz), 7.36 (1H, s) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.9, 13.1, 14.0, 14.2, 19.2, 21.8, 28.9, 28.9, 33.1, 34.2, 39.6, 61.2, 61.4, 122.0, 125.3, 130.0, 130.5, 131.4, 137.4, 137.6, 138.5, 142.4, 146.5, 165.0, 167.5 ppm; IR (KBr) 2930, 1732, 1716, 1567, 1253, 1223, 1200 cm^{-1}; HRMS (FAB^+) calcd for $C_{25}H_{36}O_4$ 400.2614, found 400.2613.