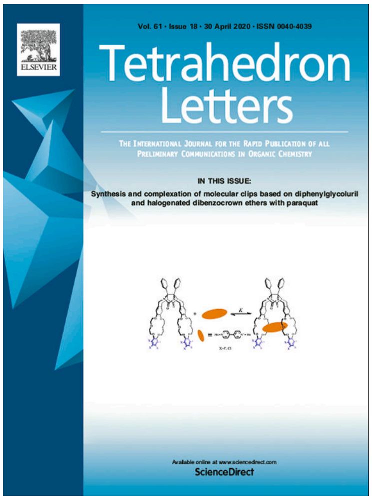

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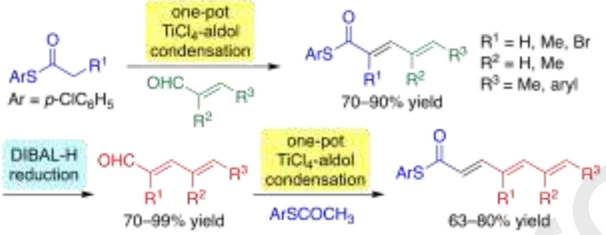

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Synthesis of conjugated multiunsaturated thioesters *via* one-pot $TiCl_4$-promoted aldol condensation

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ABSTRACT

$TiCl_4$-promoted aldol condensations of *S*-4-chlorophenyl thioesters with enals or dienals led to the production of dienyl or trienyl thioesters in good yields. Due to good crystallinity, products with high *E*/*Z* ratios were obtained by simple filtration in many cases. Reduction of the thioester moiety by DIBAL-H afforded the corresponding unsaturated aldehydes while suppressing the *E*/*Z*-isomerization and overreduction. The method was applied to the preparation of simple synthetic intermediates of natural products such as spectinabilin and aureothin.

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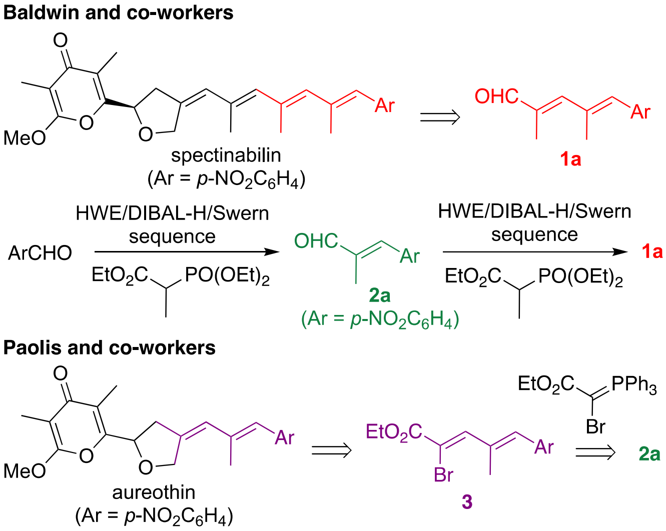
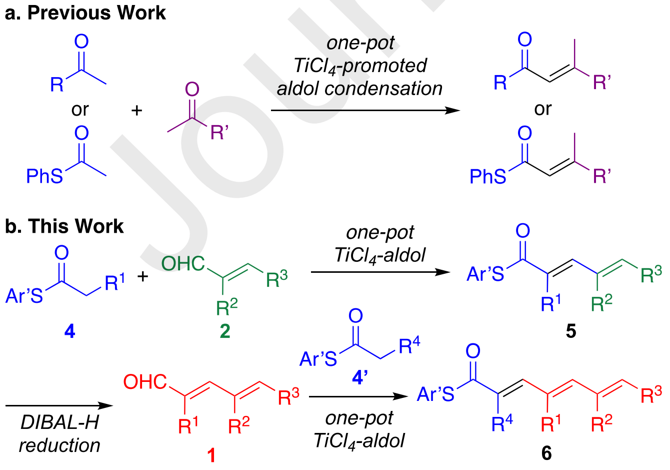
Conjugated polyene structures are found in natural products and are often synthesized from polyenyl carbonyl compounds [1,2]. For example, the total synthesis of spectinablin by Baldwin and co-workers was achieved starting from dienal **1a** (Fig. 1) [3]. Dienal **1a** was prepared from *p*-nitrobenzaldehyde through an iterative Horner-Wadsworth-Emmons reaction/DIBAL-H reduction/Swern oxidation sequence. The recent synthesis of aureothin by Paolis and co-workers used α-bromodienoate **3** prepared by the Wittig reaction of enal **2a** [4].



Scheme 1. Examples of polyene natural product synthesis from polyenyl carbonyl compounds.

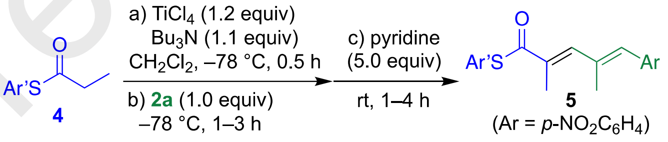
Recently, we reported the one-pot synthesis of β,β-disubstituted α,β-unsaturated ketones or thioesters *via* the TiCl$_4$-promoted aldol condensation between simple ketones or between ketones and *S*-phenyl thioacetate (Scheme 2a) [5]. Herein, we report that dienyl and trienyl thioesters **5** and **6** can be prepared *via* the TiCl$_4$-promoted aldol condensation between *S*-aryl thioester **4** and enal **2** or between dienal **1** and thioester **4'**, respectively (Scheme 2b) [6]. Thioesters **5** and **6** with high *E*/*Z* ratios were obtained by simple filtration in many cases. DIBAL-H reduction of **5** and **6** gave the corresponding conjugated aldehydes such as dienal **1** while maintaining the *E*/*Z* ratio.



Scheme 2. TiCl$_4$-promoted aldol condensation for the synthesis of unsaturated carbonyl compounds.

A starting material, enal **2a** was prepared in high yield by aldol condensation between propionaldehyde and *p*-nitrobenzaldehyde using Bu$_4$NOH as the catalyst [7]. However, further aldol condensation between propionaldehyde and **2a** under the same conditions did not afford dienal **1a**. The self-condensation of propionaldehyde was predominant in this case, indicating that enal **2a** is less electrophilic than propionaldehyde. Therefore, a one-pot TiCl$_4$-promoted aldol condensation [5] was applied between enal **2a** and *S*-phenyl propanethioate (**4a**). Thioester **4a** in dichloromethane was treated successively with TiCl$_4$ and Bu$_3$N at –78 °C. After 30 min at that temperature, solid enal **2a** was added in one portion to the resulting deep purple solution (the aldol step). After 1 h at –78 °C, pyridine (5 equiv) was added to promote the elimination step. The cooling bath was then removed from the experimental set-up and the mixture was stirred at rt. After stirring for more than 1 h, Celite® and Et$_2$O were successively added to promote precipitation of the ammonium (pyridinium) and titanium residue. After filtration and concentration, the crude product was treated with MeOH/H$_2$O to crystalize the desired product. Pure (*2E,4E*)-thioester **5a** was obtained by filtration in good yield (Table 1, entry 1). The residue after crystallization was further purified by column chromatography to give a mixture of (*2E,4E*)- and (*2Z,4E*)-**5a**. The yield and *2E/2Z* ratio obtained by chromatography are given in parenthesis in Table 1.

Table 1. TiCl$_4$-promoted aldol condensation of various thioester **4** with enal **2a**.



Entry	4	Ar'	5	Yield (%)[a]	*2E/2Z*[b]
1	**4a**	Ph	**5a**	74 (13)	100:0 (63:37)
2	**4b**	2,5-Me$_2$C$_6$H$_3$	**5b**	– (89)	– (94:6)
3	**4c**	4-ClC$_6$H$_4$	**5c**	86 (8)	100:0 (92:8)
4	**4d**	4-BrC$_6$H$_4$	**5d**	83 (–)	100:0 (–)
5	**4e**	4-NO$_2$C$_6$H$_4$	**5e**	69 (–)	100:0 (–)
6	**4f**	4-MeOC$_6$H$_4$	**5f**	74 (–)	98:2 (–)

[a] Yields of **5** obtained by crystallization. The data after column chromatography of the crystallization residue are given in parenthesis.

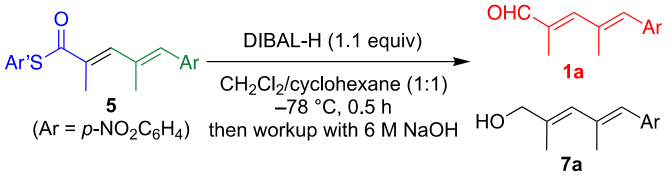
[b] The *2E/2Z* ratio of **5** obtained by crystallization. The data after column chromatography of the crystallization residue are given in parenthesis.

According to the above procedure, the effect of the aryl group (Ar') of thioester **4** was examined (Table 1, Entries 2–6). The reaction tolerated both electron-poor and -rich Ar' groups (Entries 2–6). Among Ar' groups tested, 4-chlorophenyl group gave the best result (Entry 3). The corresponding dienyl thioester (*2E,4E*)-**5c** was obtained as yellow crystals in geometrically pure form. Bulky *S*-2,5-dimethylphenyl thioester **4b** provided a good yield, however product **5b** was difficult to purify by crystallization (Entry 2).

The reduction of thioester **5a–f** to dienal **1a** was next investigated (Table 2). A solution of **5** in dichloromethane/cyclohexane (1:1) was treated with DIBAL-H at

–78 quench the reaction. Use of the strong base was important to suppress the *E*/*Z* isomerization. Among **5a–f**, *S*-4-chlorophenyl thioester **5c** gave the best result in terms of the total yield of **1a** (Entry 3). The over-reduced product **7a** was not obtained in this case. In all cases, dienal (*2E*,*4E*)-**1a** was obtained, confirming the (*2E*,*4E*)-geometry of thioesters **5a–f**. The reaction of strongly electron-withdrawing 4-nitrophenyl derivative **5e** resulted in a low yield of **1a** (Entry 5). We speculate that coordination of the carbonyl oxygen to the aluminum atom of DIBAL-H, which triggers the reduction, is insufficient due to the low Lewis basicity of **5e**. Considering the results in Tables 1 and 2, good crystallinity, and the commercial availability, *p*-chlorophenyl thioesters were selected for further examination.

Table 2. DIBAL-H reduction of thioesters **5**.



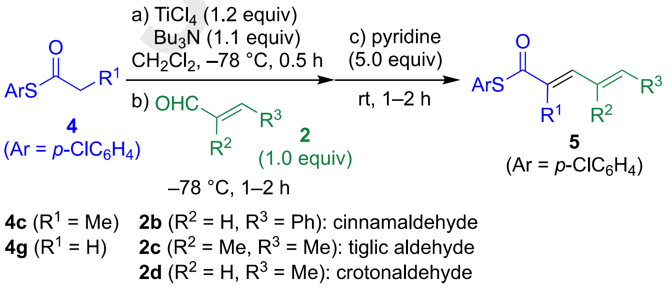
Entry	5	Ar'	Yield **1a** (%)[a]	*2E/2Z*[b]
1	**5a**	Ph	45 (31) [4]	99:1 (74:26)
2	**5b**	2,5-Me$_2$C$_6$H$_3$	– (67) [17]	– (77:30)
3	**5c**	4-ClC$_6$H$_4$	47 (52) [0]	100:0 (88:12)
4	**5d**	4-BrC$_6$H$_4$	34 (51) [4]	100:0 (93:7)
5	**5e**	4-NO$_2$C$_6$H$_4$	12 (21) [13]	100:0 (81:19)
6	**5f**	4-MeOC$_6$H$_4$	66 (28) [6]	100:0 (82:18)

[a] Yield of **1a** obtained by crystallization. The data after column chromatography of the crystallization residue are given in parenthesis. Yields of alcohol **7a** are given in square brackets.

[b] The *2E/2Z* ratio of **1a** obtained by crystallization. The data after column chromatography of the crystallization residue are given in parenthesis.

With *S*-4-chlorophenyl thioesters **4c** (R^1 = Me) or **4g** (R^1 = H), the TiCl$_4$-aldol condensation with various α,β-unsaturated aldehydes were next investigated (Table 3). Like enal **2a**, cinnamaldehyde, tiglic aldehyde, and crotonaldehyde also afforded the desired dienyl thioesters **5g–k** in good yields with high 2*E*/2*Z* ratios (Entries 1–5). The geometry of thioesters **5g–k** was determined by NOESY analysis or the coupling constants in ^{1}H NMR analysis (see ESI).

Table 3. TiCl$_4$-promoted aldol condensation of thioester **4c** or **4g** with various enals **2**.

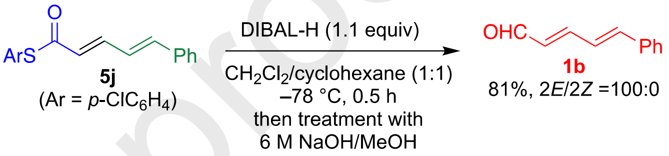


Entry	4	2	5	R^1	R^2	R^3	Yield (%)[a]	*2E/2Z*[b]
1	**4c**	**2b**	**5g**	Me	H	Ph	71	99:1 (–)
2	**4c**	**2c**	**5h**	Me	Me	Me	– (90)	– (91:9)
3	**4c**	**2d**	**5i**	Me	H	Me	– (85)	– (100:0)
4	**4g**	**2b**	**5j**	H	H	Ph	83 (–)	100:0 (–)
5	**4g**	**2d**	**5k**	H	H	Me	– (76)	– (100:0)

[a] Yield of **5** obtained by crystallization. The data after column chromatography of the crystallization residue are given in parenthesis.

[b] The *2E/2Z* ratio of **5** obtained by crystallization. The data after column chromatography of the crystallization residue are given in parenthesis.

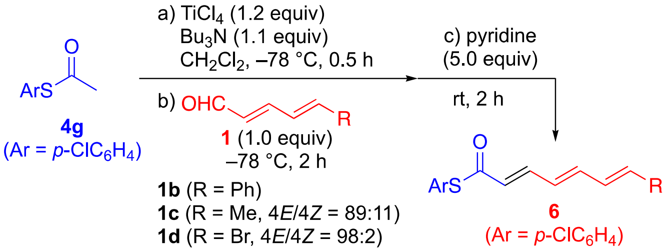
DIBAL-H reduction of dienyl thioester **5j** under the conditions shown in Table 2 gave the corresponding dienal **1b** in good yield (Scheme 3) [8].



Scheme 3. DIBAL-H reduction of dienyl thioester **5j** to dienal **1b**.

The reaction sequence was further extended to the synthesis of trienyl thioesters (Table 4). The TiCl$_4$-promotated condensation between thioester **4g** and dienals **1b–d** [9] afforded trienyl thioesters **6a–c**, respectively (Entries 1–3). These products were obtained by simple filtration due to their good crystallinity. Although a commercially available, geometrical mixture of 2,4-hexadienal (**1d**) (*4E/4Z* = 89:11) was used, a high *E*/*Z* ratio was observed for crystallized product **6b** (Entry 2). Brominated product **6c** would be synthetically useful because of transformability of the alkenyl bromide moiety (Entry 3) [10]. In fact, Suzuki-Miyaura coupling between thioester **6c** and (*E*)-styrylboronic acid was effectively catalyzed by Pd(OAc)$_2$/S-Phos [10e] to give tetraenyl thioester **8** without destroying the thioester moiety (Scheme 4).

Table 4. Synthesis of trienyl thioesters **6**.

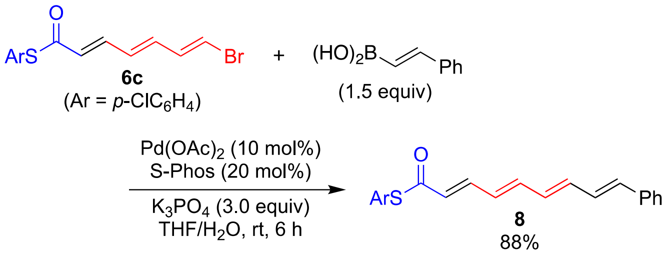


Entry	1	6	R	Yield (%)[a]	dr[b]
1	**1b**	**6a**	Ph	80 (–)	100:0 (–)
2	**1c**	**6b**	Me	45 (18)	97:3 (72:28)
3	**1d**	**6c**	Br	75 (–)	100:0 (–)

[a] Yield of **6** obtained by crystallization. The data after column chromatography of the crystallization residue are given in parenthesis.

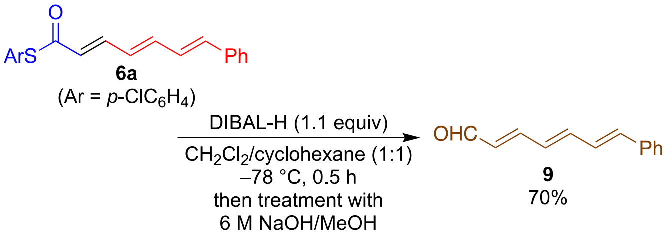
[b] T

by crystallization. The data after column chromatography of the crystallization residue are given in parenthesis.



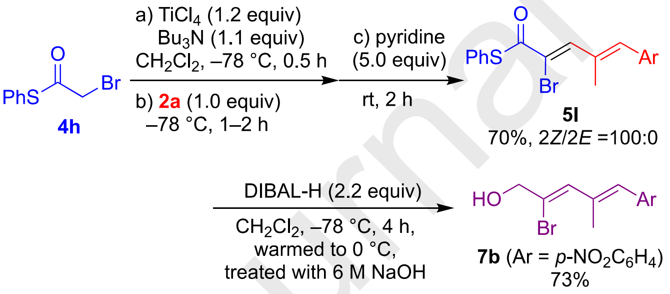
Scheme 4. Synthesis of tetraenyl thioester **8** *via* cross-coupling between bromotrienyl thioester **6c** and styrylboronic acid.

Like the synthesis of **1a** and **1b**, DIBAL-H reduction of thioester **6a** gave the corresponding trienal **9** in a good yield (Scheme 5) [8].



Scheme 5. DIBAL-H reduction of trienyl thioester **6a** to dienal **9**.

The $TiCl_4$-promoted aldol condensation of α-bromothioacetate **4h** [11] with enal **2a** proceeded well under the same conditions to give α-bromodienyl thioester **5l** as crystals with high 2*Z*/2*E* ratio (Scheme 6). Reduction of **5l** with excess DIBAL-H furnished dienol (2*Z*/4*E*)-**7b**, which is a synthetic intermediate of aureothin reported by Paolis and co-workers [4].



Scheme 6. Preparation of α-bromo dienyl thioester **5l** and dienol **7b**, a synthetic intermediate of aureothin.

Conclusion

It has been demonstrated from this work that dienyl or trienyl thioesters can be synthesized *via* the one-pot $TiCl_4$-promoted aldol condensations of *S*-aryl (especially *S*-4-chlorophenyl) thioesters with enals or dienals. Due to good crystallinity, products with high *E*/*Z* ratios were obtained by simple filtration in many cases. Reduction of the thioester moiety by DIBAL-H afforded the corresponding aldehydes while suppressing the *E*/*Z*-isomerization and overreduction. The method was applied to preparation of simple synthetic intermediates of natural products. Further investigations to extend the synthetic utility are underway.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://...

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1. C [illegible]
2. Access to alkenyl bromides applicable to coupling reactions
3. Reduction of *S*-aryl thioesters to aldehydes with less risk of over-reduction
4. Application to preparation of synthetic intermediates of polyene natural products