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A Highly *E*-Stereoselective Approach to *β*-Iodo Morita–Baylis–Hillman Esters: Synthesis of Secokotomolide A

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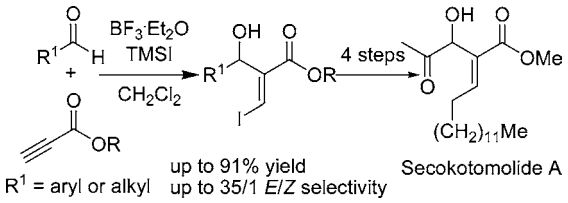
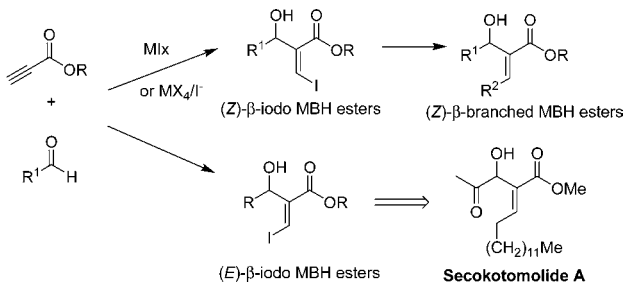
ABSTRACT



A geometric-selective synthesis of (*E*)-*β*-iodo Morita–Baylis–Hillman esters has been developed through a three-component aldol-type reaction using BF_3·Et_2O and TMS-I. The synthetic utility of the (*E*)-*β*-iodo Morita–Baylis–Hillman esters was demonstrated in the first reported short synthesis of secokotomolide A.

β-Branched Morita−Baylis−Hillman (MBH) esters[1] are useful precursors for the synthesis of various biologically active molecules and natural products. However, these esters are not easily accessible by general MBH catalysis.[1a] Usually they are prepared from the reactions of α-metalated acrylates with aldehydes.[2] Another efficient route to various *β*-branched MBH esters is a palladium coupling[3] or organocuprate reaction[4] of *β*-iodo MBH esters. Since these reactions are known to proceed without changing the olefinic geometry, the stereoselective synthesis of *β*-iodo MBH esters is essential to provide *E*/*Z*-controlled *β*-branched MBH esters (Scheme 1). Synthetic approaches to (*Z*)-*β*-iodo MBH esters

Scheme 1



are well established by using $TiCl_4$/(n-Bu)$_4$NI,[5] $ZrCl_4$/(n-Bu)$_4$NI,[6] Et_2AlI,[7] and MgI_2.[8] These methods are mainly based

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(5) Taniguchi, M.; Hino, T.; Kishi, Y. *Tetrahedron Lett.* **1986**, *39*, 4767.
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(7) Wei, H.-X.; Gao, J. J.; Li, G.; Paré, P. W. *Tetrahedron Lett.* **2002**, *43*, 5677.

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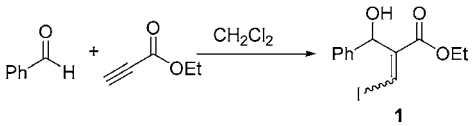
on the multicomponent couplings of α,β-acetylenic esters with aldehydes as acceptors. Recently we disclosed that AlI_3 promoted highly (*Z*)-selective synthetic methods[9] and extended the scope of this reaction by using various ketones as acceptors. However, there are no convenient synthetic methods to synthesize (*E*)-β-iodo MBH esters with alkyl propiolate in one step. Here, we report the first highly (*E*)-stereoselective approach to β-iodo MBH esters by using BF_3·Et_2O and trimethylsilyl iodide as an iodide source. The resultant highly functionalized alkenes can be transformed into (*E*)-β-branched MBH esters, which are useful intermediates of natural products. Indeed, the utility of this methodology is illustrated by the expedient synthesis of secokotomolide A (Scheme 1).

We first examined the reaction between ethylpropiolate and benzaldehyde with various Lewis acids and iodide anions. To our surprise, only the reaction with BF_3·Et_2O and trimethylsilyl iodide as the iodide source afforded (*E*)-major isomer of **1**, while all other reaction conditions[5−9] provided the (*Z*)-major isomer of **1** (Table 1). This is likely due to

Table 1. Results of the Three-Component Aldol-Type Reaction



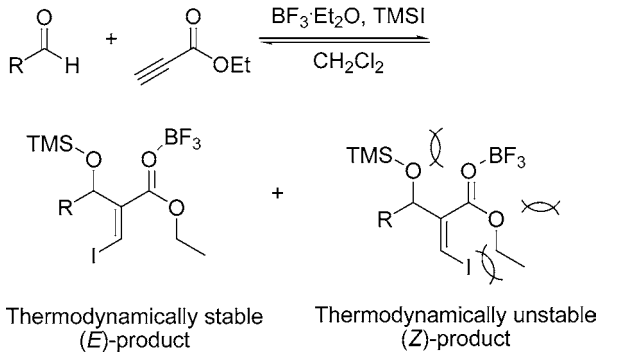
1

entry	iodide source	Lewis acid (equiv)	yield[d] (%)	*E*/*Z* [e]
1[a]	–	MgI_2	85	7/93
2[b]	–	AlI_3	88	1/>99
3[a]	Bu_4NI	MgI_2	49	7/93
4[a]	Bu_4NI	BF_3·Et_2O (1.2)	26	6/94
5[c]	TMS−I	BF_3·Et_2O (1.2)	75	83/17
6[c]	TMS−I	BF_3·Et_2O (1.2)	87	91/9
7[c]	TMS−I	BF_3·Et_2O (0.2)	14	99/1
8[c]	TMS−I	BF_3·Et_2O (0.7)	47	99/1

[a] Reaction temperature is 0 °C. [b] Reaction temperature is −78 °C. [c] Reaction temperature is −40 °C. [d] Yields after column chromatography. [e] Determined by gas chromatography analysis using HP-5 trace analysis column.

the multicoordinating Lewis acids (MgI_2, AlI_3, $TiCl_4$) preferring the chairlike transition state to give the kinetically favorable (*Z*)-product of **1**.[5,8,9] On the other hand, in the present system the (*E*)-selectivity of β-iodo MBH ester seems to be directed by thermodynamic control (Scheme 2). When the reaction was performed for a longer time (5 days) at −40 °C, higher (*E*)-selectivity was observed compared to 2 days (Table 1, entries 5, 6). Interestingly, the chemical yield is closely related to the amount of BF_3·Et_2O (Table 1, entries 6−8). Although the yields were lower, the (*E*)-selectivities were excellent as 99:1 (Table 1, entries 7,8).

Scheme 2



Dichloromethane provided the best results in terms of yield and *E*/*Z* selectivity of product compared to toluene, THF, or acetonitrile. The resulting *Z*,*E* isomers of **1** could be easily separated by silica gel column chromatography. (*E*)-Configuration was unambiguously determined by NOESY 2D NMR and ^1H NMR spectral analysis.

To evaluate the substrate scope of this methodology, we investigated the (*E*)-stereoselective reaction of various aldehydes as aldol receptors under optimized conditions. The optimal reaction conditions are as follows. In a dry reaction round-bottom flask are added 1.3 mmol of ethyl propiolate and 4.0 mL of dry dichloromethane at ambient temperature under N_2 conditions. The solution is cooled to −45 °C, and 1.2 mmol of BF_3·Et_2O, 2.4 mmol of trimethylsilyl iodide, and 1.0 mmol of the aldehyde are added quickly. After stirring for 30 min at this temperature, the mixture is placed in a freezer (−40 °C or −23 °C) for the times indicated in Table 2. The results are summarized in Table 2.

For aromatic aldehydes, substitution by an electron-donating group increased the reaction rate and yield (Table 2, entries 2, 3). Conversely, substitution by an electron-withdrawing group retarded the reaction but provided the higher *E*/*Z*-selectivity (Table 2, entries 5−9). Aliphatic aldehydes[10] can be employed as electrophilic acceptors in this reaction although they show slightly lower yields (Table 2, entries 10,11).

The synthetic utility of the present reaction was further demonstrated by the first synthesis of secokotomolide A,[11] which was isolated from cinnamomum kotoense. Secokotomolide A was found to induce significant cell death in the human HeLa cell line by apoptotic-related DNA damage.[11a] Secobutanolides including secokotomolide have (*E*)-β-long-chain branched MBH methyl ester structures.

Thus. we utilized β-iodo MBH methyl ester for the synthesis, which was envisioned as a suitable precursor for the preparation of secokotomolide A and its various derivatives.

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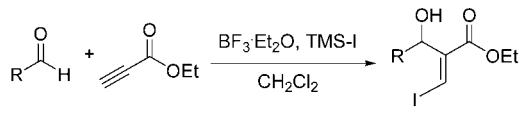
(9) Lee, S. I.; Hwang, G.-S.; Ryu, D. H. *Synlett* **2007**, *1*, 59.

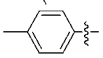
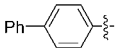
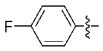
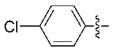
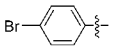
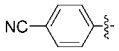
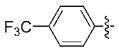
(10) For more sterically hindered aliphatic aldehydes, such as pivalaldehyde and isobutyraldehyde, the *E*/*Z* ratio was ∼1.5/1 because of severe allylic 1,3-interaction between iodine and the alkyl group.

(11) (a) Chen, C.-H.; Lo, W.-L.; Liu, Y.-C.; Chen, C.-Y. J. *Nat. Prod.* **2006**, *69*, 927. (b) Cheng, M.-J.; Jayaprakasam, B.; Ishikawa, T.; Tsai, I.-L.; Wang, J.-J.; Chen, I.-S. *Helv. Chim. Acta* **2003**, *85*, 1909. (c) Cheng, M.-J.; Tsai, I.-L.; Lee, S.-J.; Jayaprakasam, B.; Chen, I.-S. *Phytochemistry* **2005**, *66*, 1180.

Table 2. Results of the Synthesis of Various (*E*)-Selective *β*-iodo MBH Esters



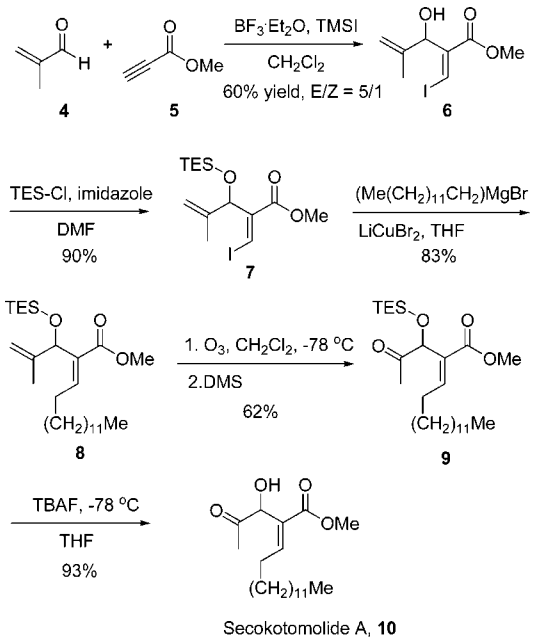
2 MBH esters **3**

entry	product	R	temp (℃)	time (d)	yield (%)[a]	E/Z[b]
1	**3a**		-40	5	87	91/9
2	**3b**		-40	1	91	90/10
3	**3c**		-40	3	91	90/10
4	**3d**		-40	5	85	89/11
5	**3e**		-40	8	83	94/6
6	**3f**		-40	8	84	93/7
7	**3g**		-40	8	86	95/5
8	**3h**		-23	5	77	95/5
9	**3i**		-23	7	76	92/8
10[c]	**3j**	$^{n}C_6H_{13}$	-23	1	63	97/3[d]
11	**3k**		-40	3	60	93/7[d]

[a] Yields after column chromatography. [b] Determined by gas chromatography analysis using HP-5 trace analysis and cyclosil B column. [c] 2.5 equiv of ethyl propiolate and 4.0 equiv of TMS-I was used. [d] Determined by column chromatography separation.

The three-component coupling of methacrolein and methylpropiolate under similar conditions of ethyl propiolate produced the adduct **6** in 60% yield and 84:16 *E*/*Z*-selectivity. After protection of the alcohol group with a triethylsilyl group, the *β*-iodo MBH ester **7** was subjected to a cross-coupling with magnesium bromide in the presence of lithium−copper bromide. The resulting (*E*)-*β*-long-chain branched MBH methyl ester **8** was obtained in high yield of 83% without changing the (*E*)-geometry. Selective ozonolysis of **8** in dichloromethane afforded the ketone **9** in 62% yield. Finally, deprotection of the triethylsilyl group with TBAF furnished racemic secokotomolide A, which was identical in its spectral properties to those of the naturally occurring secokotomolide A (Scheme 3).[11a]

Scheme 3 Total Synthesis of Secokotomolide A



In conclusion, an efficient synthetic method for (*E*)-*β*-iodo Morita−Baylis−Hillman esters has been developed. The new protocol utilizes boron trifluoride diethyl etherate as the Lewis acid promoter and trimethylsilyl iodide as the iodide source. This methodology was successfully applied to the short synthesis of secokotomolide A in five steps, starting from methacrolein and methyl propiolate. The asymmetric synthesis and application of this chemistry to other bioactive compounds are currently in progress.

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Supporting Information Available: Experimental details and characterization data for the products. This material is available via the Internet at http://pubs.acs.org.

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