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Diastereoselective Synthesis of Cephalotaxus Esters via Asymmetric Mukaiyama Aldol Reaction

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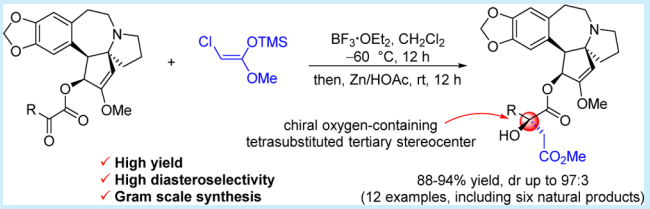
Supporting Information

ABSTRACT: We report a protocol for efficient stereoselective installation of the chiral oxygen-containing tetrasubstituted tertiary carbon stereocenter of the side chain of cephalotaxus esters by means of highly diastereoselective Mukaiyama aldol reactions between α-keto esters (**2**) and a (*Z*)-α-chloro ketene silyl acetal. This protocol permitted synthesis of cephalotaxus esters including six natural products in good to excellent yields (up to 94%) with high diastereoselectivities (dr up to 97:3) and could be performed on a multigram scale.



Cephalotaxus esters **1** (R ≠ H), a group of alkaloids isolated as minor components from conifers of the *Cephalotaxus* genus,[1] have received considerable synthetic attention owing to their potent antileukemia activity and their unique pentacyclic ring structure with a side chain bearing an oxygen-containing chiral carbon center (Figure 1). Recently,

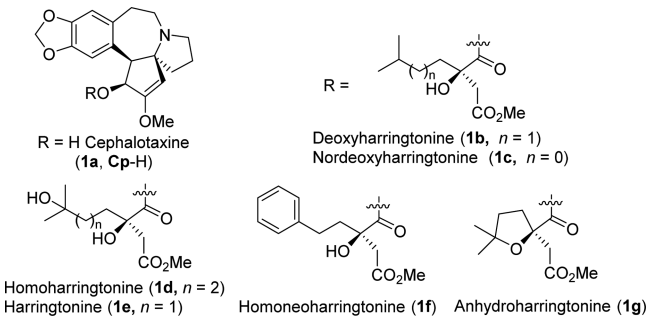


Figure 1. Structures of *Cephalotaxus* esters.

one member of the group, homoharringtonine (**1d**), was approved for the treatment of adults with chronic- or accelerated-phase chronic myeloid leukemia that is resistant or tolerant to at least two tyrosine kinase inhibitors,[2] and this drug may be useful as a new frontline treatment for low- and intermediate-risk patients with acute myeloid leukemia.[3] This biological activity highlights the importance of synthetic studies of cephalotaxus esters. However, most of the reported studies have involved the development of efficient methods for construction of the pentacyclic diterpenoid skeleton, cephalotaxine (**1a**), and relatively little effort has been devoted to enantioselective installation of side chains with a chiral oxygen-containing tetrasubstituted tertiary carbon center.[4]

The chiral side chains, which are nonracemic monoacids, are generally synthesized based upon Seebach's procedure for the alkylation of D-malic acid derivative[5a] or from the corresponding nonracemic chiral epoxides prepared from commercially available monomethyl itaconate,[5b] and the side chains are subsequently joined with cephalotaxine (**1a**) to yield the corresponding cephalotaxus esters (**1**, R ≠ H). However, owing to the formidable steric bulk of both the pentacyclic diterpenoid skeleton and the α-tetrasubstituted monoacids,[6] only a cyclic monoacid, such as a tetrahydropyran[7] or a lactone,[8] can smoothly couple with **1a** to afford the desired product in good to high yields (Scheme 1). For example, chiral cyclic monoacids synthesized from readily available chiral materials such as D-malic acid[9] or generated by chiral resolving reagents such as (−)-quinine[10] have been used for cephalotaxus ester synthesis. In addition, parent alkaloid **1a** has been used as a chiral auxiliary for the enantioselective construction of the chiral oxygen-containing carbon stereocenter by means of a Reformatsky reaction or a related 1,2-addition reaction of the α-keto ester derived from **1a**.[11] However, in most cases, the diastereoselectivities of these reactions are rather low. For example, Mikolajczak reported that the addition of methoxycarbonylmethyllithium ($LiCH_2CO_2Me$) to an α-keto ester derived from **1a** yielded deoxyharringtonine (**1b**) in only 6% yield, along with *epi*-deoxyharringtonine (*epi*-**1b**) in 9% yield.[11b] Reformatsky reaction of the α,ε-diketoester of **1a** gave the addition product in excellent yield (90.5%), but reaction of the addition product with methyllithium afforded homoharringtonine (**1d**) in only 10% yield.[7] These results indicate that the enantioselective construction of the chiral

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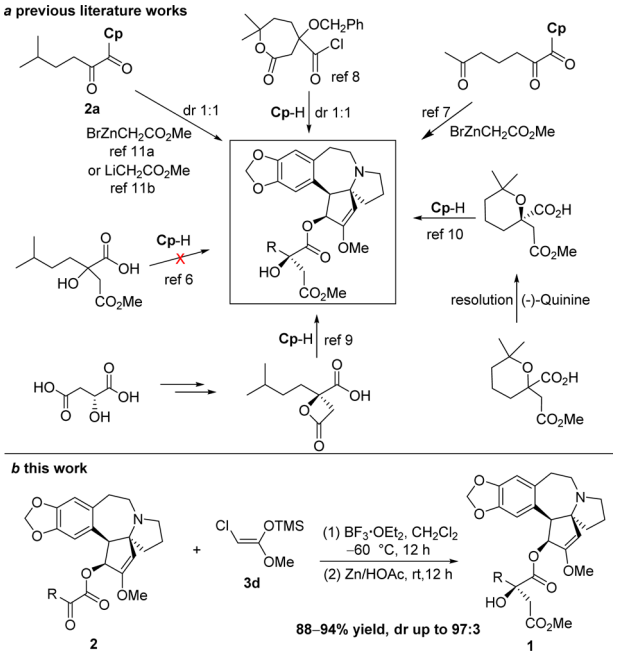
Scheme 1. Diastereoselective Synthesis of Cephalotaxus Esters



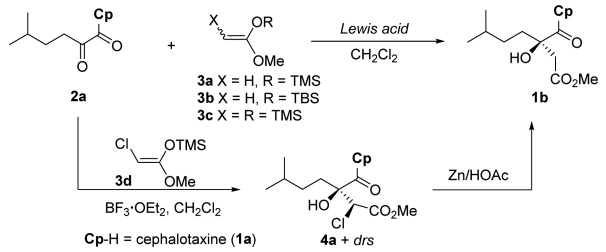
oxygen-containing tetrasubstituted tertiary carbon stereocenter of the side chains of cephalotaxus esters remains a challenge.

To address this challenge, we investigated the use of chiral auxiliary-induced asymmetric Mukaiyama aldol reaction of α-ketoesters, a reaction that has been studied by various research groups.[12] For example, using optically active bulky 8-phenylmenthol or cyclitol as a chiral auxiliary, Chen and Fang[12a] and Akiyama et al.[12b] synthesized a series of chiral α-hydroxyl esters with a chiral tetrasubstituted tertiary carbon stereocenter with good to excellent diastereoselectivities by reactions of the corresponding α-ketoesters with ketene silyl acetals. These reactions represent the only two reported examples of asymmetric Mukaiyama aldol reaction of α-ketoesters with chiral auxiliaries on the ester groups, but these examples suggested to us that this method was promising for the installation of the chiral oxygen-containing tetrasubstituted tertiary carbon stereocenter of the cephalotaxus esters.

In this study, we found that although cephalotaxine (**1a**) was not an efficient chiral auxiliary for reactions of simple ketene silyl acetals, introduction of a halide atom at the α-position of the ketene silyl acetal markedly improved the diastereoselectivity of the reaction.[13] Specifically, we report herein that asymmetric Mukaiyama aldol reactions of α-ketoesters **2** derived from **1a** with (*Z*)-α-chloro-substituted ketene silyl acetal **3d**[13a] followed by dechlorination with zinc/HOAc afforded the corresponding cephalotaxus esters **1** (R ≠ H) or their analogues with high yields (up to 94%) and diastereoselectivities (dr up to 97:3) (Scheme 1). To the best of our knowledge, this is the first report of highly stereoselective installation of the chiral oxygen-containing tetrasubstituted tertiary carbon stereocenter of the side chains of cephalotaxus esters.

Initially, we selected α-ketoester **2a**, which has an isopentyl moiety and is a precursor to deoxyharringtonine (**1b**), as a model substrate. α-Ketoester **2a** was allowed to react with various ketene silyl acetals in the presence of $BF_3{\cdot}Et_2O$ (2.2 equiv) as a Lewis acid catalyst in CH_2Cl_2 at −20 °C. After reaction with **3a** or **3b** for 12 h, we obtained **1b**[14] in good yields and low to moderate diastereoselectivities (Table 1, entries 1 and 2). When the amount of $BF_3{\cdot}Et_2O$ was less than 1 equiv, no identifiable product was obtained (see the Supporting Information), whereas conversion of **2a** was complete when the amount of $BF_3{\cdot}Et_2O$ exceeded 2 equiv. Ketene silyl acetal **3b**, which has a bulky TBS group, gave a higher yield (80%) and higher diastereoselectivity (75:25) than **3a**. Lowering the reaction temperature from −20 to −60 °C (entries 3 and 4) dramatically increased the yield (95%) but did not significantly improve the diastereoselectivity (80:20). Other Lewis acids, including $TiCl_4$, $SnCl_4$, and $ZnBr_2$, were evaluated (entries 5−7) and found to exhibit low catalytic activities. Furthermore, when the results were compared to those achieved with $BF_3{\cdot}Et_2O$, inverse selectivities were observed (entries 5 and 6). Because the bulky TBS group of **3b** resulted in high diastereoselectivity, we also evaluated **3c**, which has an α-TMS group. Owing to the low reactivity of **3c**, the reactions were performed at higher temperatures (0 and −20 °C). Compound **1b** was obtained with excellent diastereoselectivity (>99:1) but in low yields (entries 8 and 9). Next, we evaluated α-chloride ketene silyl acetal **3d** instead of **3c**, knowing that the chlorine atom in the resulting product **4a** could be easily removed by reduction with powdered Zn in HOAc. The reaction of **2a** with **3d** at −40 °C for 12 h yielded **4a** and three diastereomers (drs) in a 68.6:27.4:2.8:1.2 ratio (see the Supporting Information). Treatment of crude **4a** and corresponding drs with Zn/HOAc furnished **1b** in 90% yield with 96:4 diastereoselectivity (entry 10). Lowering the reaction

Table 1. Optimization of Conditions for Mukaiyama Aldol Reactions of 2a with Ketene Silyl Acetals 3[a]



entry	3	Lewis acid	temp (°C)	time (h)	yield[b] (%)	dr[c,d]
1	**3a**	$BF_3{\cdot}OEt_2$	−20	12	60	60:40
2	**3b**	$BF_3{\cdot}OEt_2$	−20	12	80	75:25
3	**3b**	$BF_3{\cdot}OEt_2$	−40	12	90	77:23
4	**3b**	$BF_3{\cdot}OEt_2$	−60	12	95	80:20
5	**3b**	$TiCl_4$	−20	60	60 (50)[e]	16:84
6	**3b**	$SnCl_4$	−25	60	62 (50)[e]	20:80
7	**3b**	$ZnBr_2$	−40	20	74	42:58
8	**3c**	$BF_3{\cdot}OEt_2$	0	22	35	>99:1[f]
9	**3c**	$BF_3{\cdot}OEt_2$	−25	22	40	>99:1[f]
10	**3d**	$BF_3{\cdot}OEt_2$	−40	12	90	96:4[g]
11	**3d**	$BF_3{\cdot}OEt_2$	−60	12	92	97:3[g]
12	**3d**	$BF_3{\cdot}OEt_2$	−78	24	92	97:3[g]

[a]Reactions were performed on a 0.5 mmol scale at a **2a**/**3** ratio of 1:1.5 with 2.2 equiv of Lewis acid in 3 mL of CH_2Cl_2. [b]Yields are for combined isolated diastereomers. [c]Absolute stereochemistry was determined by independent synthesis (see the Supporting Information). [d]Crude product ratios were determined by HPLC (Chiralcel AD-H column). [e]The value in parentheses is the conversion rate. [f]The dr was determined after desilylation. [g]The dr was determined after dechlorination.

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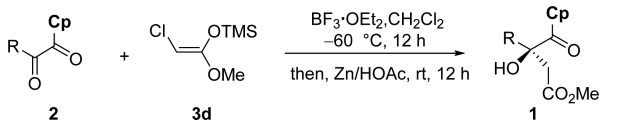
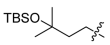
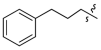
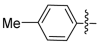
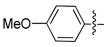
temperature to −60 or −78 °C slightly increased both the yield and diastereoselectivity (entries 11 and 12). In summary, the incorporation of a readily removable chlorine substituent to the α-position of the ketene silyl acetal substantially increased the yield and diastereoselectivity of the reaction, providing an efficient method for stereoselectively installing the chiral oxygen-containing tetrasubstituted tertiary carbon stereocenter of the cephalotaxus ester side chains.

Several α-ketoesters **2** derived from **1a** were allowed to react with **3d** under the optimized reaction conditions, and the results are summarized in Table 2. Variation of the alkyl group of **2** had little effect on the yield. Changing the R group from isopentyl (**2a**) to isobutyl (**2b**) slightly decreased the diastereoselectivity: nordeoxyharringtonine (**1c**) was obtained with 90:10 diastereoselectivity (entry 2). Substrates with a phenyl ring at the terminus of the R group, **2c** and **2h**, provided homoneoharringtonines **1f** and **1l**, respectively, with 95:5 diastereoselectivity (entries 3 and 8). A substrate with an *n*-pentyl group (**2g**) afforded **1k** with a yield (92%) and diastereoselectivity (dr = 92:8) comparable to those obtained with **2a** (compare entries 7 and 1). α-Ketoester **2d**, which has a *tert*-butyldimethylsilyl-protected hydroxyl (TBSO) group and is a precursor to harringtonine (**1e**), also reacted smoothly with **3d** to yield **1h** with good to high diastereoselectivities (entries 4). Olefin-containing α-ketoesters **2e** and **2f**, which are precursors to deoxyharringtonine (**1b**) and homodeoxyharringtonine or homoharringtonine (**1d**), respectively, provided **1i** and **1j** with high diastereoselectivities (entries 5 and 6). β-Aryl-substituted α-ketoesters **2i** and **2j**, which have *p*-methyl and *p*-methoxy groups, respectively, on their phenyl rings, were also good substrates for this transformation. These substrates showed high reactivity, providing corresponding products **1m** and **1n** with dr values of 94:6 and 95:5, respectively (entries 9 and 10). Substrates with a *m*-methoxy group, that is, **2k** and **2l**, afforded products **1o** and **1p**, respectively, with dr values of 95:5 and 97:3; however, these reactions were sluggish and provided slightly lower yields (88% and 90%) and low conversions (66% and 50%) even after reaction for 24 h (entries 11 and 12).

Table 2. Mukaiyama Aldol Reactions of α-Ketoesters 2 with 3d[a]

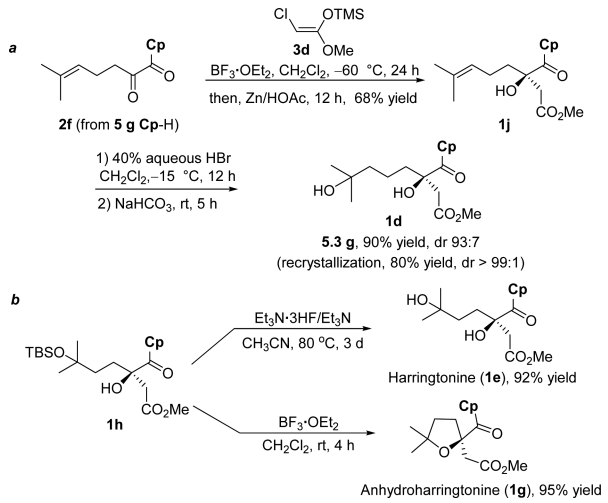


entry	sub	R	product	yield (%)	dr[b]
1	**2a**		**1b**	92	97:3
2	**2b**		**1c**	92	90:10
3	**2c**		**1f**	93	95:5
4	**2d**		**1h**	90	96:4
5	**2e**		**1i**	94	93:7
6	**2f**		**1j**	93	94:6
7	**2g**		**1k**	92	92:8
8	**2h**		**1l**	94	95:5
9	**2i**		**1m**	93	94:6
10	**2j**		**1n**	93	95:5
11	**2k**		**1o**	88(66)[c]	95:5
12	**2l**		**1p**	90(50)[c]	97:3

[a]Reaction conditions were the same as those described in Table 1, entry 11. [b]The dr values of crude products were determined by HPLC. [c]The value in parentheses is the conversion.

To demonstrate the practical application of this efficient new protocol, we selected homoharringtonine (**1d**) as a target molecule and performed a multigram-scale synthesis (Scheme 2, a). The reaction of crude **2f** (synthesized from 5 g of cephalotaxine) with **3d** under the optimized reaction conditions and subsequent dechlorination with Zn/HOAc in a one-pot fashion yielded crude product **1j** in 68% yield. Hydroxylation of **1j** with 40% aqueous HBr at −15 °C for 12 h followed by treatment with $NaHCO_3$ for 5 h at room temperature afforded **1d** in 90% yield with 93:7 diastereoselectivity. Recrystallization from ethyl ether afforded 4.2 g (80%) of **1d** with improved diastereoselectivity (>99:1). Thus, homoharringtonine (**1d**) was enantioselectively synthesized on a multigram scale from cephalotaxine (**1a**) in 60% overall yield via five steps.

Scheme 2. Multigram Scale Synthesis of 1d and Conversions of 1h to Other *Cephalotaxus* Esters



We also converted product **1h** to other cephalotaxus esters (Scheme 2, b). Protodesilylation of **1h** with $Et_3N{\cdot}3HF$ in CH_3CN at 80 °C for 3 d yielded harringtonine (**1e**) in 92% yield. In contrast, treatment of 1 h with $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at room temperature for 4 h resulted in desilylation and subsequent cyclization to afford anhydroharringtonine (**1g**) in 95% yield.

To elucidate the rational for the high diastereoselectivities of the reactions of α-ketoesters **2** with ketene silyl acetal **3d**, we obtained X-ray crystal structures of **2a** and the major aldol product **4a** (Figure 2). Based on these crystal structures and references,[13b,15] we propose the following explanation for the stereochemistry of the reactions. The Lewis acid $BF_3{\cdot}Et_2O$ activates the keto group of **2**, and ketene silyl acetal **3d** approaches **2a** from the *Re* face to yield **4a** preferentially due to

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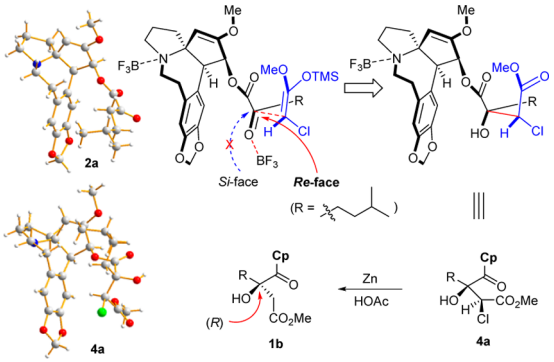

Figure 2. Proposed explanation for the observed stereoselectivity.

the steric bulk of the chlorine atom at the α-position of the ketene. Treatment of **4a** with Zn/HOAc then yields **1b** with the *R*-configuration at the chiral oxygen-containing tetrasubstituted tertiary carbon center.

In conclusion, we have developed an asymmetric Mukaiyama aldol reaction involving alkaloid **1a** as a chiral auxiliary as an efficient method for the enantioselective construction of the chiral oxygen-containing tetrasubstituted tertiary carbon stereocenter of the side chains of cephalotaxus esters. Using this method, we synthesized several cephalotaxus esters and analogues in high yields (up to 94%) with high diastereoselectivities (up to 97:3). This protocol, which could be carried out on a multigram scale, provides highly efficient access to cephalotaxus esters and their analogues.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00743.

Experimental and characterization data, including ^{1}H and ^{13}C NMR spectra for all new compounds, chiral HPLC spectra for the products, and crystallographic data (PDF)
X-ray data for compound **2a** (CIF)
X-ray data for compound **1d** (CIF)
X-ray data for compound **1e** (CIF)
X-ray data for compound **s-2-A** (CIF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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(14) The NMR spectroscopic data and the optical rotation ($[\alpha]_D^{20}$ −122 (*c* 0.6, $CHCl_3$), lit.[6] $[\alpha]_D^{26}$ −119 (*c* 0.6, $CHCl_3$)) of the isolated major isomer were identical to those reported for the natural product (see refs 6 and 9a).
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