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Asymmetric Construction of Three Contiguous Stereogenic Centers by Conjugate Addition−Alkylation of Lithium Ester Enolate

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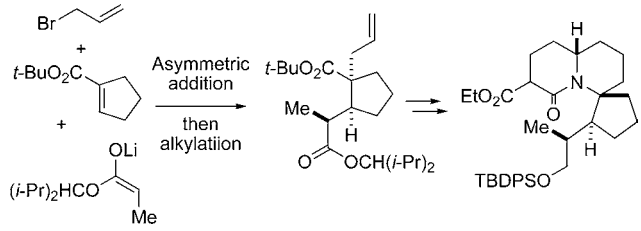
ABSTRACT



A chiral ligand- and lithium amide-assisted asymmetric conjugate addition of lithium enolate of propionate to cyclopentenecarboxylate gave the corresponding lithium enolate, whose allylation gave the key intermediate of the marine alkaloid halichlorine as a single diastereomer with moderate enantioselectivity.

Efficient construction of contiguous stereogenic centers is a challenging pursuit in organic synthesis.[1] An asymmetric conjugate addition−alkylation sequence is a powerful method that installs two new C−C bonds and multiple stereocenters in a single operation.[2,3] Lithium enolates are useful in this context. We recently reported a highly enantioselective conjugate addition of lithium ester enolate to acyclic enoates assisted by a chiral diether ligand and lithium amide, giving synthetically useful functionalized 1,5-diesters.[4] We describe herein the asymmetric construction of three contiguous stereogenic centers by a tandem conjugate addition−alkylation reaction of lithium ester enolate of propionate and its application to the synthesis of azaspirobicyclic core of the marine alkaloid halichlorine (**1**), isolated from the marine sponge *Halichondria okadai* Kadota in 1996 by Uemura and co-workers (Figure 1).[5] The related natural products, pinnaic acid (**2**) and tauropinnaic acid (**3**), were also isolated by the same research group from the Okinawan bivalve *Pinna*

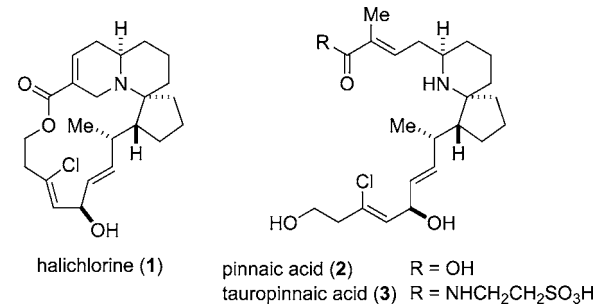


Figure 1. Halichlorine (**1**), pinnaic acid (**2**), and tauropinnaic acid (**3**).

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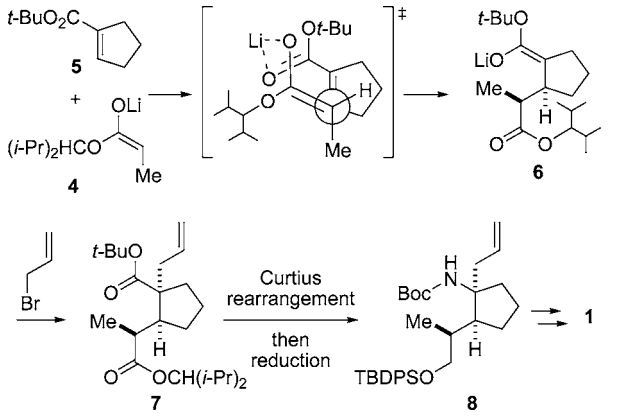
muricata.[6] Their complex spirobicyclic structures and significant biological properties, including selective inhibition of the induction of vascular cell adhesion molecule-1 (halichlorine) and inhibition of a cytosolic phospholipase $cPLA_2$ (pinnaic and tauropinnaic acids), are of interest to synthetic chemists.[7] Asymmetric[8] and racemic[9] total syntheses of **1**−**3** have been reported by some research groups. Efficient construction of the characteristic structural feature, an azaspirobicyclic core, is key for the synthesis of these alkaloids.[10,11]

Our synthetic strategy begins with the addition of the lithium enolate **4** of propionate to cyclopentenecarboxylate **5** that would proceed by keeping the methyl group of **4** away from the cyclopentene moiety of **5** to give enolate **6**, whose allylation was expected to proceed trans to the introduced propionate, giving adduct **7** with three contiguous stereogenic centers of **1**.[12] Subsequent Curtius rearrangement and reduction of the ester groups would give the synthetic precursor **8** of **1**, as reported by Danishefsky's group (Scheme 1).[8a−c,13]

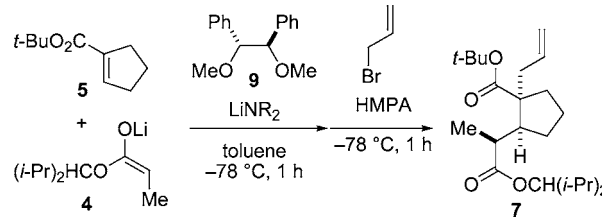
Scheme 1. Synthetic Strategy



The lithium ester enolate **4** was prepared by α-deprotonation of 2,4-dimethylpentan-3-yl propionate with LDA, and (*Z*)-enolate was expected to be predominantly generated.[14] The addition of **4** to **5** in THF proceeded smoothly, and after alkylation, the addition product **7** was obtained in 74% yield as a single diastereomer. The asymmetric reaction in the presence of chiral ligand **9** in toluene was not efficient and gave **7** in only 37% ee. The lithium amide-assisted asymmetric conjugate addition of **4** to **5** in the presence of *i*-Pr(*c*-Hex)NLi (lithium *N*-isopropyl-*N*-cyclohexylamide) and ligand **9** proceeded even at −78 °C and gave addition product **7** with 64% ee in 74% yield (Table 1).[4]

Production of carboxylic acid with TFA and optical resolution by (*S*)-1-phenethylamine gave carboxylic acid **10**

Table 1. Tandem Asymmetric Conjugate Addition−Alkylation[a]



entry	lithium amide	yield/%	ee/%	de/%
1[b]	none	54	37	>98
2	*i*-Pr_2NLi	57	56	>98
3	*i*-Pr(*c*-Hex)NLi	74	64	>98
4	(*c*-Hex)$_2$NLi	50	50	>98

[a] Enolate **4** was prepared from the corresponding ester and lithium amide. All reactions were performed using **4** (1.3 equiv), **9** (1.7 equiv), and $LiNR_2$ (1.3 eqiv). In the alkylation step, allyl bromide (4 equiv) and HMPA (4 equiv) were used. [b] Asymmetric conjugate addition was performed at −50 °C for 1 h and −40 °C for 4 h. The alkylation step was performed at −40 to 0 °C for 5 h.

with greater than 99% ee in 72% yield. Curtius rearrangement of **10** with DPPA (diphenylphosphoryl azide) gave isocyanate,[15] which was inert to a nucleophilic addition of *t*-BuOH under refluxing conditions. The addition of TMSCl[16] was effective to give Boc-amide **11** in 93% yield from **7** in two steps. Reduction of the ester group with $NaBH_4$ in DMSO followed by protection with TBDPSCl gave the established intermediate **8**.[13] The stereochemistry of **8** was confirmed by spectroscopic data and the specific rotation of **12**, which

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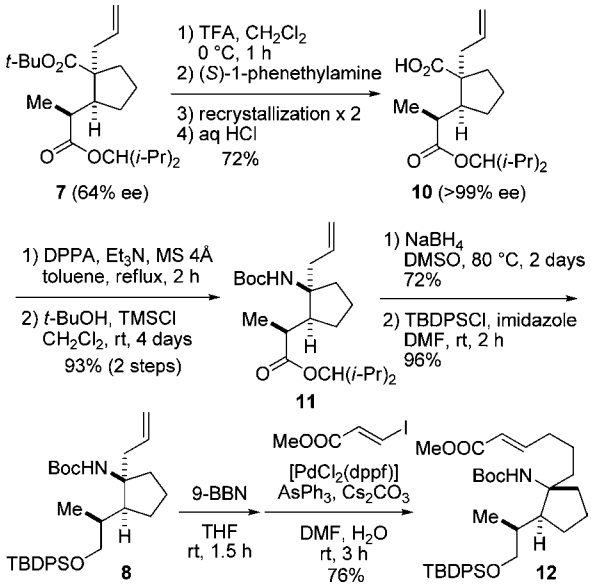
was prepared by hydroboration of **8** followed by the Suzuki coupling reaction, to be opposite that of natural halichlorine (Scheme 2).[13]

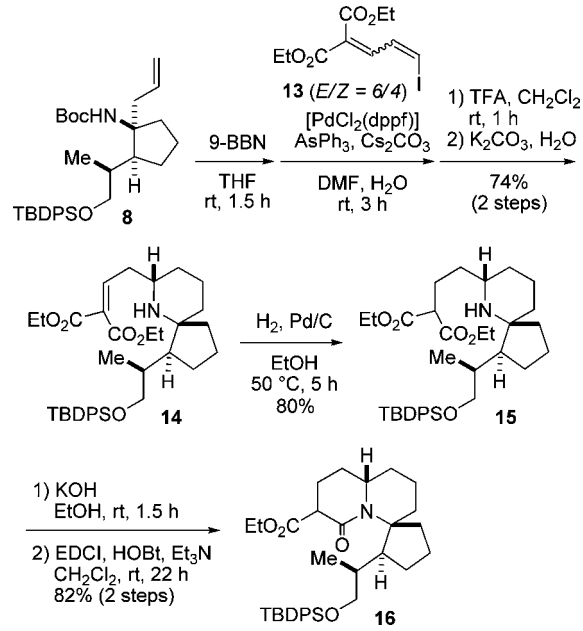
Scheme 2. Formal Synthesis of (−)-Halichlorine



Next, we studied the construction of the tricyclic core structure of halichlorine **1** (Scheme 3). Hydroboration and a Suzuki coupling reaction of **8** with dienyl iodide **13**, followed by removal of the Boc group, gave cyclized product **14** in 74% yield in two steps. The next stage was amide formation between the secondary amine and the ester moiety. Heating of **14** in refluxing toluene did not give the desired amide and resulted in recovery of the starting material. After reduction of the double bond of **14**, we again tried the amide formation. Treatment of **15** with NaOEt in EtOH did not give the desired lactam **16**; instead, monosaponification proceeded. KOH treatment also gave monosaponificated product, and subsequent condensation of the amine with the carboxylic acid gave lactam **16** with a tricyclic core of halichlorine.

In summary, we developed an efficient method of constructing three contiguous chiral stereocenters by tandem

Scheme 3. Construction of the Tricyclic Core of Halichlorine



asymmetric conjugate addition of a lithium enolate to an enoate and subsequent in situ alkylation. Formal synthesis and construction of the tricyclic core of halichlorine successfully exemplified the strategic application of the asymmetric conjugate addition−alkylation protocol.

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Supporting Information Available: Experimental details and characterization data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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