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# Synthetic Studies on Halichlorine and Pinnaic Acid. Stereospecific Preparation of the Azaspiro Core Structure

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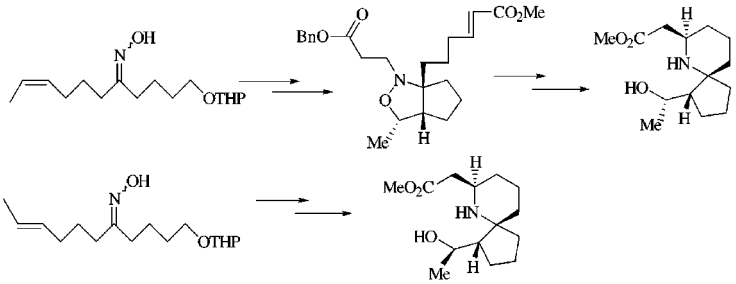
## ABSTRACT




**Halichlorine and pinnaic acid are two novel marine natural products isolated from a Japanese sponge and an Okinawan bivalve, respectively. The unique azaspiro[4.5]decane core structure present in both compounds provides a synthetic challenge. Herein, we describe a synthetic approach to the azaspiro[4.5]decane core structure through an intramolecular [3 + 2] cycloaddition followed by an intramolecular Michael addition and in situ isomerization to afford the azaspirocyclic core structures stereospecifically in 10 steps with 40% overall yield.**

Halichlorine (**1**) and pinnaic acid (**2**) are two novel marine natural products (Figure 1) isolated by Uemura and co-workers from the Japanese sponge *H. okadai* Kadota and the Okinawan bivalve *Pinna muricata* respectively.[1,2] Halichlorine inhibits the induction of VCAM-1 (vascular cell adhesion molecule-1) with an $IC_{50}$ of 7 $\mu$g/mL.[1] Pinnaic acid is an inhibitor of $cPLA_2$ (phospholipase $A_2$) with an $IC_{50}$ of 0.2 mM.[2] Both halichlorine and pinnaic acid contain an azaspiro[4.5]decane core structure. The absolute stereochemistry of halichlorine has recently been determined by chemical correlation of a degradation product with a synthetic fragment.[3] The relative stereochemistry at C17 of pinnaic acid (**2**) has not been reported. Halichlorine (**1**) and pinnaic acid (**2**) were tentatively assigned opposite configurations at C14.[3]

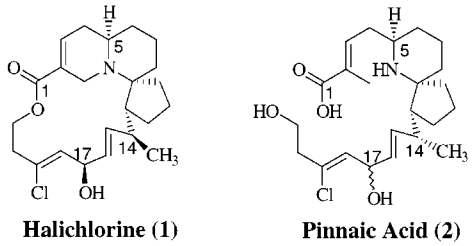



**Figure 1.** Structures of halichlorine and pinnaic acid.

Recently Weinreb and co-workers have reported an approach toward the C15−C21 chlorinated divinyl alcohol chain.[4] Uemura and co-workers have reported an asymmetric construction of the azaspiro core system via an intramolecular iminium salt formation followed by hydrogenation.[5] Herein,

(1) Kuramoto, M.; Tong, C.; Yamada, K.; Chiba, T.; Hayashi, Y.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 3867.
(2) Chou, T.; Kuramoto, M.; Otani, Y.; Shikano, M.; Yazawa, K.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 3871.
(3) Arimoto, H.; Hayakawa, I.; Kuramoto, M.; Uemura, D. *Tetrahedron Lett.* **1998**, *39*, 861.
(4) Keen, S. P.; Weinreb, S. M. *J. Org. Chem.* **1998**, *63*, 6739.

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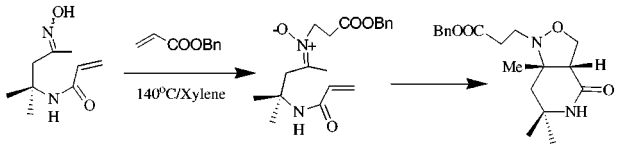
we describe a unique approach which constructs the azaspiro-[4.5]decane core structure efficiently and stereospecifically.

Grigg and co-workers have demonstrated a series of both inter- and intramolecular aza[3 + 2] cycloadditions via in situ generation of a nitrone by the addition of an oxime to an electron-withdrawing alkene and subsequent 1,3-dipolar cycloaddition of the resulting nitrone to an appropriate olefin (Scheme 1).[6] In most cases, the cycloaddition reaction is both

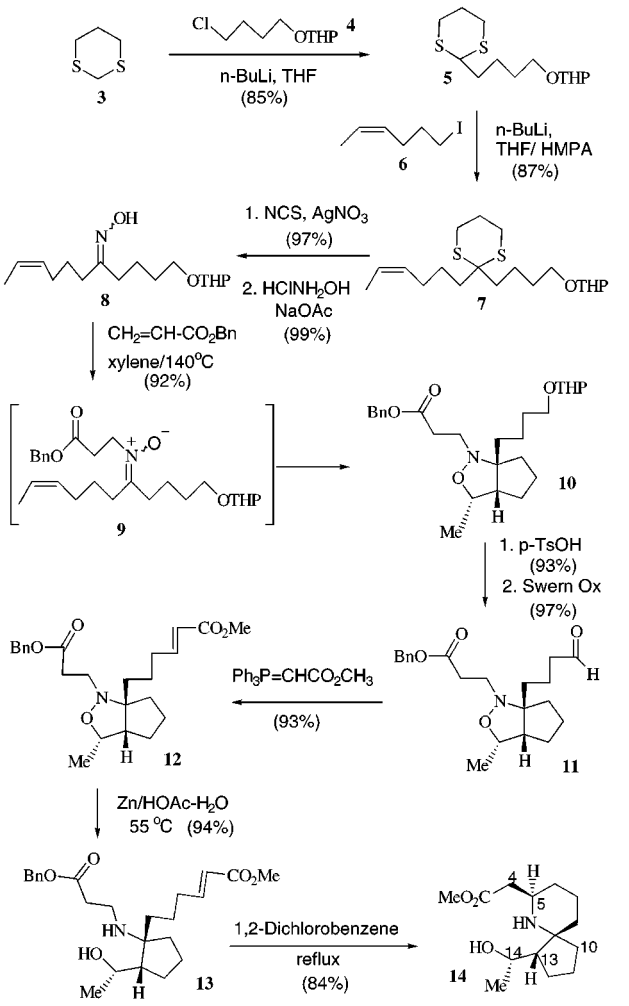
**Scheme 1**




regio- and stereospecific. We envisioned that a similar cycloaddition reaction could be used to set up the tertiary amine function of the azaspiro core structure in halichorine and pinnaic acid.

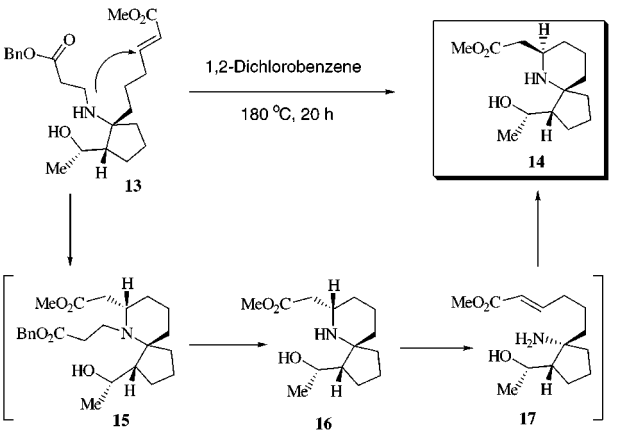
Our synthesis started with the sequential alkylation of 1,3-dithiane (**3**) with alkyl chloride **4** and alkyl iodide **6**[7] to yield dialkylated dithiane **7** (Scheme 2). The dithiane was selectively hydrolyzed with *N*-chlorosuccinimide and silver nitrate and then treated with hydroxylamine hydrochloride to afford oxime **8** as an approximate 1:1 mixture of *E* and *Z* isomers. Heating oxime **8** with benzyl acrylate in xylene at 140 °C in a similar manner as described by Grigg and co-workers afforded cyclized adduct **10** as a sole diastereoisomer. The reaction proceeded through nitrone **9** that was generated by Michael addition of oxime **8** to benzyl acrylate. The THP protecting group in **10** was removed under acidic conditions, and the resulting alcohol was oxidized under Swern oxidation conditions to yield aldehyde **11**. Aldehyde **11** was then homologated via Wittig olefination to afford enonate **12**. The reductive N−O bond cleavage of **12** with zinc in aqueous acetic acid afforded amino alcohol **13**. Refluxing amine **13** in 1,2-dichlorobenzene for 24 h provided azaspiro[4.5]decane **14** as a single diastereoisomer in 84% yield. Each proton of **14** was assigned by COSY and NOESY experiments,[8] and **14** has the desired stereochemistry for the synthesis of halichlorine (**1**).

**Scheme 2**




The formation of **14** from **13** has been observed to proceed through the pathway illustrated in Scheme 3. Under refluxing condition, **13** undergoes an intramolecular Michael addition first to afford intermediates **15**, which eliminated benzyl

**Scheme 3**




(5) Arimoto, H.; Asano, S.; Uemura, D. *Tetrahedron Lett.* **1999**, *40*, 3583.

(6) (a) Grigg, R.; Markandu, J.; Surendrakumar, S.; Thornton-Pett, M.; Warnock, W. J. *Tetrahedron* **1992**, *48*, 10399. (b) Armstrong, P.; Grigg, R.; Warnock, W. J. *J. Chem. Soc., Chem. Commun.* **1987**, 1325. (c) Armstrong, P.; Grigg, R.; Surendrakumar, S.; Warnock, W. J. *J. Chem. Soc., Chem. Commun.* **1987**, 1327. (d) Grigg, R.; Jordan, M.; Tangthongkum, A. *J. Chem. Soc., Perkin Trans. 1* **1984**, 47.

(7) Iodide **6** and **18** were prepared in 88% yield from the corresponding alcohols by mesylation (MsCl, $Et_3N$), followed by the treatment with sodium iodide.

(8) **14**: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.07(d, $J$ = 6.6 Hz, 3H), 1.10 (m, 1H, H6), 1.23 (m, 1H, H8), 1.25 (m, 1H, H7), 1.32 (m, 1H, H13), 1.44 (m, 1H, H10), 1.54 (m, 1H, H6), 1.63 (m, 1H, H12), 1.66 (m, 1H, H10), 1.67 (m, 1H, H12), 1.69 (m, 1H, H11), 1.72 (m, 1H, H7), 1.74 (m, 1H, H11), 2.12 (m, 1H, H8), 2.25 (dd, $J$ = 16.5, 9.0 Hz, 1H, H4), 2.37 (dd, $J$ = 16.5, 3.6 Hz, 1H, H4), 3.05 (m, 1H, H5), 3.62 (s, 3H), 4.21 (qd, $J$ = 6.6, 2.1 Hz, 1H, H14); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 172.7 (C3), 65.2 (C14), 64.5 (C9), 53.7 (C13), 51.5 (Me), 47.8 (C5), 41.3 (C4), 33.9 (C8), 33.8 (C7), 32.0 (C6), 22.0 (C10), 21.6 (Me), 20.3 (C12), 19.7 (C11). Anal. Calcd for $C_{14}H_{25}NO_3$: C, 65.85; H, 9.87; N, 5.48. Found: C, 65.90; H, 9.66; N, 5.37.

acrylate to afford **16**. Intermediate **16** is finally isomerized to diastereomer **14** via retro- Michael intermediate **17**. This hypothesis is supported by the isolation of **15** and **16** from the reaction mixture after 4 h and by the complete and independent conversion of the isolated esters **15** and **16** to **14** under the reaction conditions.[9]

Computer modeling using molecular mechanics revealed that there is 3.8 kcal/mol energy difference between **16** and **14**.[10] The energy difference represents an equilibrium ratio of >100:1 favoring the more stable isomer (**14**). Thus, the isomerization effectively converted the kinetic product **16** to the thermodynamically more stable product **14**.

The stereochemistry of **14** and **16** was established by NOESY and COSY experiments (Figure 2). We observed

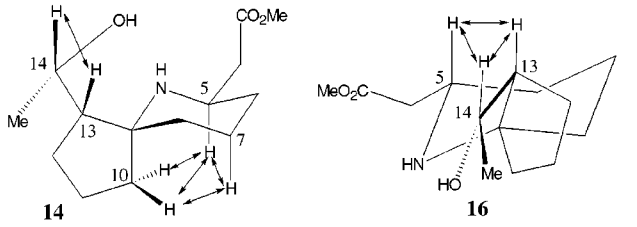
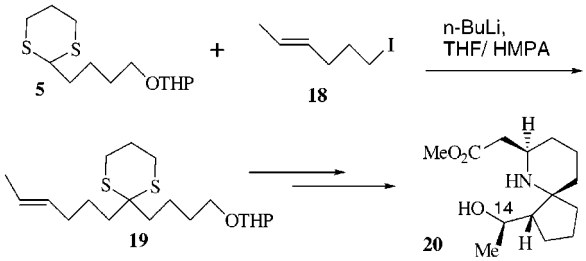



**Figure 2.** NOESY results of **14** and **16**.

cross NOE effects among H5, H13, and H14 in **16**. For compound **14**, we observed cross NOE effects among H5, H7, and H10, but no NOE effect was observed between H5 and H13 or between H5 and H14. These results indicated the opposite stereochemistry between **14** and **16** at C5.

For the synthesis of pinnaic acid (**2**), azaspiro decane **20** that is epimeric to **14** at C14 is required. Compound **20** was prepared from dithiane **5** and *trans*-olefinic iodide **18**[7] in the same manner as that described for **14** in Scheme 2 (Scheme 4). The difference in olefin geometry in **7** and **19** has thus

**Scheme 4**




set up the opposite stereochemistry at C14 in **14** and **20**. The stereochemistry of **20** was established by NOESY and COSY experiments as that described for **14**.

In summary, we have developed an efficient route for the synthesis of the core aza[4.5]spiro ring systems of halichlorine and pinnaic acid in 10 steps and 40% overall yield from 1,3-dithiane. The synthetic route employed an intramolecular [3 + 2] cycloaddition followed by a Michael addition reaction and in situ isomerization to achieve the desired stereochemistry. The different stereochemistries at C14 in halichlorine and pinnaic acid were controlled by the different olefin geometry in the intramolecular aza[3 + 2] cycloaddition reaction step. Our current efforts are focused on the total synthesis of the two natural products.

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

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(9) Compound **15**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.10 (d, $J$ = 6.3 Hz, 3H), 1.23−1.71 (m, 10H), 1.87−1.96 (m, 2H), 2.02 (m, 1H), 2.30 (dd, $J$ = 14.7, 8.1 Hz, 1H), 2.44 (dd, $J$ = 15.0, 6.9 Hz, 1H), 2.53 (q, $J$ = 7.8 Hz, 2H), 2.77−2.96 (m, 2H), 3.37 (m, 1H), 3.68 (s, 3H), 4.31 (m, 1H), 5.11 (s, 2H), 7.35 (m, 5H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 172.2, 172.1, 135.7, 128.4, 128.3, 128.2, 70.3, 66.2, 65.7, 56.6, 51.6, 46.3, 41.2, 39.8, 39.7, 38.5, 29.2, 24.2, 22.9, 21.7, 21.6, 20.3. Compound **16**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.00−1.24 (m, 2H), 1.09 (d, superimposed on m, $J$ = 6.0 Hz, 3H), 1.44−1.78 (m, 10H), 1.88−1.98 (m, 1H), 2.32 (dd, $J$ = 15.9, 8.1 Hz, 1H), 2.43 (dd, $J$ = 15.6, 5.1 Hz, 1H), 3.25 (m, 1H), 3.70 (s, 3H), 4.31 (qd, $J$ = 6.3, 1.8 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 172.2, 66.5, 63.1, 51.6, 50.7, 48.2, 44.3, 41.9, 38.0, 32.1, 24.2, 22.0, 20.5, 20.4. Anal. Calcd for $C_{14}H_{25}NO_3$: C, 65.85; H, 9.87; N, 5.49. Found: C, 65.69; H, 9.66; N, 5.61.

(10) The modeling was performed by using the MacroModel and the AMBER* force field models: (a) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caulfield, C. Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440. (b). Kolossvary, I.; Guida, W. C. J. *Am. Chem. Soc.* **1996**, *118*, 5011.