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An efficient approach to the azaspirocyclic structure of halichlorine and pinnaic acid

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Abstract

Two new classes of alkaloids, halichlorine and pinnaic acid, were isolated from marine organisms. A tandem cycloaddition and isomerization have accomplished a short and general synthesis of the azaspirocyclic core structure of halichlorine and pinnaic acid. © 1999 Elsevier Science Ltd. All rights reserved.

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Halichlorine (**1**), isolated from the marine sponge *Halichondria okadai* Kodota, is an inhibitor of VCAM-1 (vascular cell adhesion molecule-1) induction that renders it a potential compound for the treatment of atherosclerosis, coronary artery disease and angina.[1] Structurally related alkaloids pinnaic acid (**2a**) and tauropinnaic acid (**2b**), which were isolated from the Okinawan bivalve *Pinna muricata*, exhibit cytotoxic activity against phospholiphase A_2.[2] The absolute configuration of halichlorine (**1**) was determined by comparison of a degradation product with a synthetic compound.[3] The stereochemistry of pinnaic acid (**2a**) and tauropinnaic acid (**2b**) at C17 is not established, and their configuration at C14 was tentatively assigned opposite to that of halichlorine (**1**). These alkaloids possess a unique azaspiro[4.5]decane core skeleton. Recently, Arimoto and co-workers have reported an approach towards the azaspirocyclic core structure of pinnaic acid based on Michael-initiated ring closure and imine formation followed by hydrogenation.[4] We have recently reported a synthetic approach towards the core structure of the two natural products via an intramolecular [3+2] cycloaddition and Michael addition reaction.[5] Herein we report a different approach to the azaspiro[4.5]decane core skeleton of halichlorine and pinnaic acid by utilizing a tandem cyclization and thermal isomerization.

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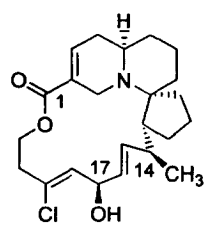

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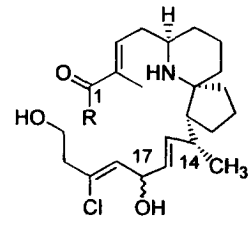
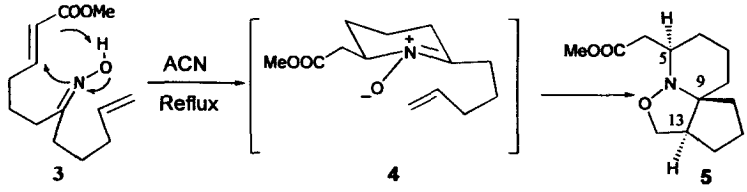


2a R = OH
2b R = $NHCH_2CH_2SO_3H$

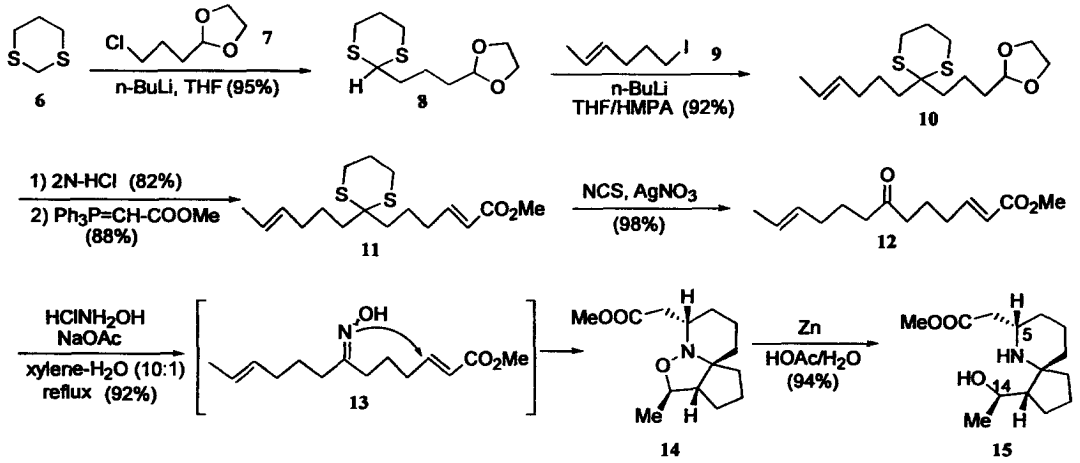
R. Grigg and co-workers have developed a series of tandem intramolecular cycloaddition reactions to yield different azaspiro-ring systems (Scheme 1).[6] The process precedes first through a 1,3-azaprotio cyclotransfer reaction to yield nitrone **4** that undergoes a 1,3-dipolar cycloaddition reaction to yield the azaspiro-ring system **5**. The tandem cyclization set up three chiral centers (C5, C9, and C13) stereospecifically. We envisioned that the synthesis of the azaspiro[4.5]decane fragment in halichlorine (**1**) and pinnaic acid (**2**) can be achieved by first a similar tandem cyclization with proper substitution pattern and then an inversion of the stereochemistry at C5.



3 4 5

Scheme 1.

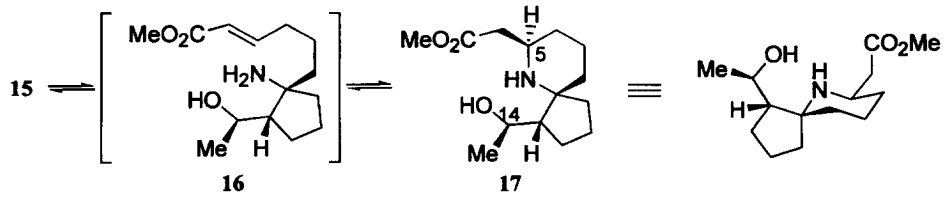
Our synthesis started with the alkylation of 1,3-dithiane with alkyl chloride **7** and subsequent alkylation with alkyl iodide **9**[7] to afford the dialkylated adduct **10** (Scheme 2). Selective hydrolysis of the acetal function in **10** and Wittig olefination of the resulting aldehyde afforded enoate **11**. Oxidative hydrolysis of the dithiane in **11** with *N*-chlorosuccinimide and silver nitrate yielded ketone **12**. Accordingly, heating ketone **12** with hydroxylamine hydrochloride and sodium acetate in a mixture of xylene and H_2O (10:1) at 140°C afforded cycloaddition adduct **14** as a sole diastereomer similar to that observed by Grigg et al.[6a] Compound **14** has all the required stereochemistry for the synthesis of halichlorine except the stereochemistry at C5. The reductive cleavage of the nitrogen–oxygen bond in **14** with zinc and aqueous acetic acid afforded amino alcohol **15**.[8,9]



6 8 10 11 12 13 14 15

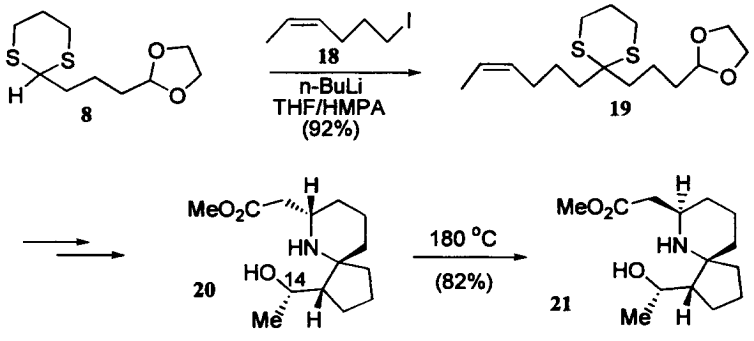
Scheme 2.

At this stage, the configuration of **15** at C5 needs to be inverted for the synthesis of halichlorine. Since the tandem cycloaddition adduct **14** (or subsequent intermediate **15**) is a kinetic controlled product, it was envisioned that **14** (or **15**) can be converted to its thermodynamically favorable isomer under thermodynamic conditions.[10] Thus, refluxing **15** in 1,2-dichlorobenzene for 24 h resulted in epimerization at C5 to yield the thermodynamically more stable isomer **17** in 84% yield via retro-Michael intermediate **16** (Scheme 3). The stereochemistry of **15** and **17** were established by NOESY and COSY experiments.[8,11]



Scheme 3.

To further demonstrate the validity of this reaction as a general strategy for the synthesis of pinnaic acid, **20**[12] was subjected to the same condition to yield the thermodynamically favored isomer **21**[13] in 82% yield (Scheme 4). Compound **20** that is epimeric to **15** at C14 was prepared from **8** and *cis*-olefinic iodide **18**[7] by employing the same condition outlined in Scheme 2.



Scheme 4.

In summary, we have developed a concise approach to the azaspirocyclic core structure of halichlorine and pinnaic acid from 1,3-dithiane in eight steps with 43% overall yield. The synthesis features a tandem cycloaddition followed by isomerization.

Acknowledgements

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References

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

5. Lee, S.; (Spring) Zhao, Z. *Organic Letters* **1999**, *1*, 681.
6. (a) Grigg, R.; Markandu, J.; Surendrakumar, S.; Thornton-Pett, M.; Warnock, W. J. *Tetrahedron* **1992**, *48*, 10399, and references cited therein. (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 **9** and **18** were prepared in high yield from the corresponding alcohols by mesylation (MsCl, Et_3N), followed by the treatment with sodium iodide.
8. The stereochemisry of **15**, **17**, **20** and **21** were confirmed by NOESY experiments.
9. Compound **15**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.02–1.11 (m, 2H), 1.17 (d, *J*=6.3 Hz, 3H), 1.20–1.36 (m, 2H), 1.52–1.83 (m, 9H), 2.41 (d, *J*=4.2 Hz, 1H), 2.43 (d, *J*=4.8 Hz, 1H), 3.29 (m, 1H), 3.67 (s, 3H), 3.75 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 69.7, 64.2, 51.4, 49.7, 48.5, 40.5, 39.3, 36.6, 31.0, 26.9, 22.0, 20.0, 19.8. Anal. calcd for $C_{14}H_{25}NO_3$: C, 66.85; H, 9.87; N, 5.49. Found: C, 65.58; H, 9.85; N, 5.25.
10. Our initial attempts to invert the configuration of **14** at C5, via a retro-Michael addition followed by an intramolecular Michael addition, using a variety of bases (NaH, KOBu-*t*, DBU, LiHMDS, NaHMDS) failed.
11. Compound **17**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.09–1.20 (m, 2H), 1.15 (d, superimposed on m, *J*=6.0 Hz, 3H), 1.37–1.73 (m, 10H), 1.99–2.06 (m, 1H), 2.32 (dd, *J*=16.8, 9.0 Hz, 1H), 2.42 (dd, *J*=16.8, 3.6 Hz, 1H), 3.06 (m, 1H), 3.59–3.69 (m, 1H), 3.67 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 69.6, 63.4, 57.6, 51.3, 48.4, 41.1, 38.1, 37.7, 31.9, 29.7, 24.4, 22.0, 21.8. Anal. calcd for $C_{14}H_{25}NO_3$: C, 65.85; H, 9.87; N, 5.48. Found: C, 65.90; H, 9.90; N, 5.34.
12. Compound **20**: ^1H NMR (300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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.
13. Compound **21**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.06–1.92 (m, 12H), 1.11 (d, superimposed on m, *J*=6.6 Hz, 3H), 2.16 (m, 1H), 2.28 (dd, *J*=16.5, 9.0 Hz, 1H), 2.40 (dd, *J*=16.5, 3.6 Hz, 1H), 3.08 (m, 1H), 3.66 (s, 3H), 4.24 (qd, *J*=6.6, 2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 65.1, 64.4, 53.7, 51.4, 47.7, 41.3, 33.9, 33.8, 32.0, 22.0, 21.5, 20.3, 19.6. 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.