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A Formal Total Synthesis of (±)-Halichlorine and (±)-Pinnaic Acid

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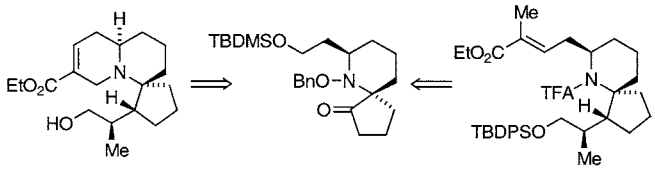
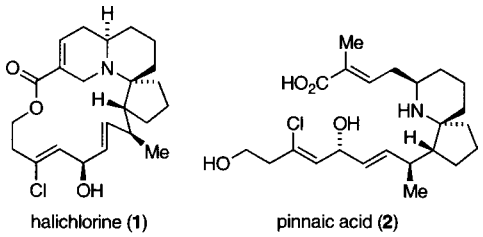
ABSTRACT



A stereocontrolled approach for the preparation of the Danishefsky intermediates has been developed starting with the azaspirobicyclic ketone as a common precursor, representing a formal total synthesis of (±)-halichlorine and (±)-pinnaic acid. This approach involves the construction of the 1,7-disubstituted 6-azaspiro[4.5]decane with the proper stereochemistry established by olefin hydrogenation followed by C-methylation of the spirotricyclic lactam and the subsequent processes involving lactam ring-opening using methyl triflate and RCM to form the azaspirotricyclic quinolizidine skeleton.

Halichlorine (**1**), a structurally unique marine alkaloid was isolated from the Japanese sponge *Halichondria okadai* Kadota by Uemura and co-workers in 1996.[1] It was found to act as a selective inhibitor of the induction of vascular cell adhesion molecule-1 (VCAM-1) at IC_{50} 7 μg/mL.[1a] The structurally related natural product, pinnaic acid (**2**), was isolated around the same time by the same research group from the Okinawan bivalve *Pinna muricata* and shown to inhibit $cPLA_2$ activity in vitro with IC_{50} values of 0.2 mM.[2] The unusual structures of **1** and **2**, coupled with the valuable biological activities, have inspired numerous synthetic investigations, culminating in several routes to the core azaspirodecane system.[3] The total syntheses of halichlorine (**1**) and pinnaic acid (**2**) were recently achieved by Danishefsky's group,[4,5] leading to revision of the structure originally proposed for pinnaic acid and establishment of the relative and absolute stereochemistry of alkaloids **1** and **2**. These syntheses of **1** and **2** reported by Danishefsky are based on the use of key intermediates **3** and **4**, respectively.

Very recently, Arimoto et al. reported[6] the synthesis of the Danishefsky intermediate **4**, which was converted to (±)-pinnaic acid according to the known procedure.[5]



In our efforts directed toward the synthesis of these alkaloids, we have previously disclosed an efficient strategy for the synthesis of the ketone **10** with the azaspirobicyclic core via construction of the 6-azaspiro[4.5]decane skeleton **9** in one step by employing intramolecular ene reaction of an acylni-

(1) (a) Kuramoto, M.; Tong, C.; Yamada, K.; Chiba, T.; Hayashi, Y.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 3867−3870. (b) Arimoto, H.; Hayakawa, I.; Kuramoto, M.; Uemura, D. *Tetrahedron Lett.* **1998**, *39*, 861−862.

(2) Chou, T.; Kuramoto, M.; Otani, Y.; Shikano, M.; Yazawa, K.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 3871−3874.

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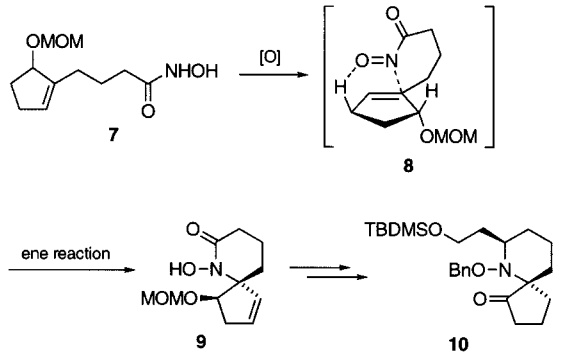
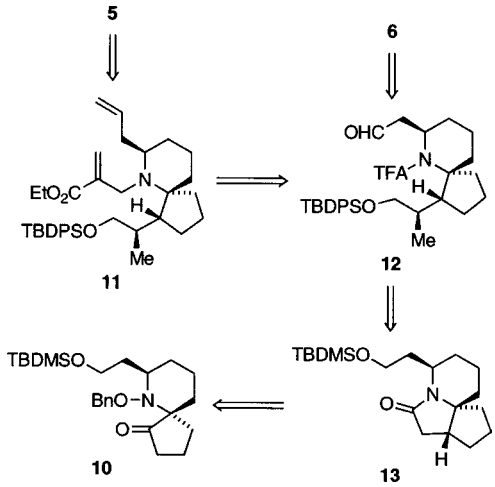
Scheme 1



troso compound **8** as outlined in Scheme 1.[7] In this paper, we describe the utilization of this azaspirobicyclic ketone **10** as a common precursor in the synthesis of the Danishefsky intermediates **5** and **6**, representing a formal total synthesis of (±)-halichlorine and (±)-pinnaic acid.

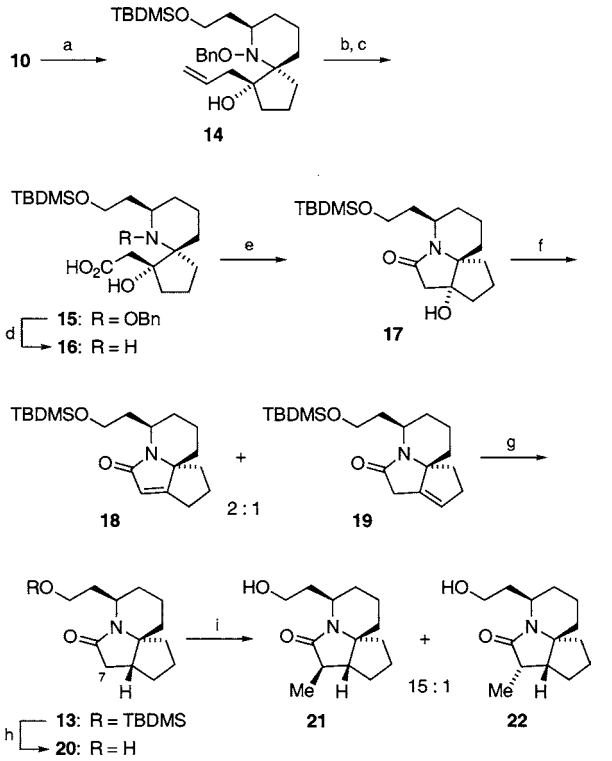
Our approach to the synthesis of **5** and **6** as outlined retrosynthetically in Scheme 2 relies on the stereoselective

Scheme 2



introduction of a methyl group into the spirotricyclic lactam **13** followed by lactam ring-opening to yield the appropriately

Scheme 3[a]



[a] Reagents and conditions: (a) $H_2C{=}CHCH_2MgBr$, THF, 0 °C, 99 %; (b) OsO_4, $NaIO_4$, H_2O, THF, rt, 82%; (c) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, H_2O, *t*-BuOH, rt, 95%; (d) H_2, Pd−C, EtOH, 97%; (e) $ClCO_2CH_2CHMe_2$, Et_3N, toluene, rt, 90%; (f) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C, 92%; (g) H_2, Pd−C, MeOH, 99%; (h) 1 M HCl, THF, rt, 99%; (i) MeI, LDA, THF, −78 °C, 78%.

functionalized spirobicyclic aldehyde **12**. Subsequent transformation of **12** to **5** and **6** could be achieved via ring-closing metathesis reaction (RCM) with Grubbs catalyst and Horner−Wadsworth−Emmons homologation, respectively.

According to the envisioned synthetic plan, the above-described ketone **10** underwent addition of allylmagnesium bromide in THF to give exclusively the *β*-adduct **14** in 99% yield. In this case, the α-face of the cyclopentanone carbonyl group is severely hindered by the *N*-benzyloxy group. Consequently, the nucleophilic allyl attack occurred highly preferentially at the less hindered *β*-face. After conversion of **14** to the aldehyde by oxidative cleavage of the olefinic bond using OsO_4 and $NaIO_4$, oxidation with $NaClO_2$ provided the carboxylic acid **15**. Palladium-catalyzed hydrogenolytic cleavage of the benzyloxy group followed by lactam cyclization under the mixed anhydride conditions afforded the hydroxy tricyclic lactam **17**, which was dehydrated with $SOCl_2$ and Et_3N to yield a 2:1 mixture of the

(3) (a) Lee, S.; (Spring) Zhao, Z. *Org. Lett.* **1999**, *1*, 681−683. (b) Arimoto, H.; Asano, S.; Uemura, D. *Tetrahedron Lett.* **1999**, *40*, 3583−3586. (c) Lee, S.; (Spring) Zhao, Z. *Tetrahedron Lett.* **1999**, *40*, 7921−7924. (d) Clive, D. L. J.; Yeh, V. S. C. *Tetrahedron Lett.* **1999**, *40*, 8503−8507. (e) Koviach, J. L.; Forsyth, C. J. *Tetrahedron Lett.* **1999**, *40*, 8529−8532. (f) Shindo, M.; Fukuda, Y.; Shishido, K. *Tetrahedron Lett.* **2000**, *41*, 929−932. (g) Wright, D. L.; Schulte, J. P., II.; Page, M. A. *Org. Lett.* **2000**, *2*, 1847−1850. (h) White, J. D.; Blakemore, P. R.; Korf, E. A.; Yokochi, A. F. T. *Org. Lett.* **2001**, *3*, 413−415. (i) Fenster, M. D. B.; Patrick, B. O.; Dake, G. R. *Org. Lett.* **2001**, *3*, 2109−2112. (j) Yokota, W.; Shindo, M.; Shishido, K. *Heterocycles* **2001**, *54*, 871−885. (k) Takasu, K.; Ohsato, H.; Ihara, M. *Org. Lett.* **2003**, *5*, 3017−3020.

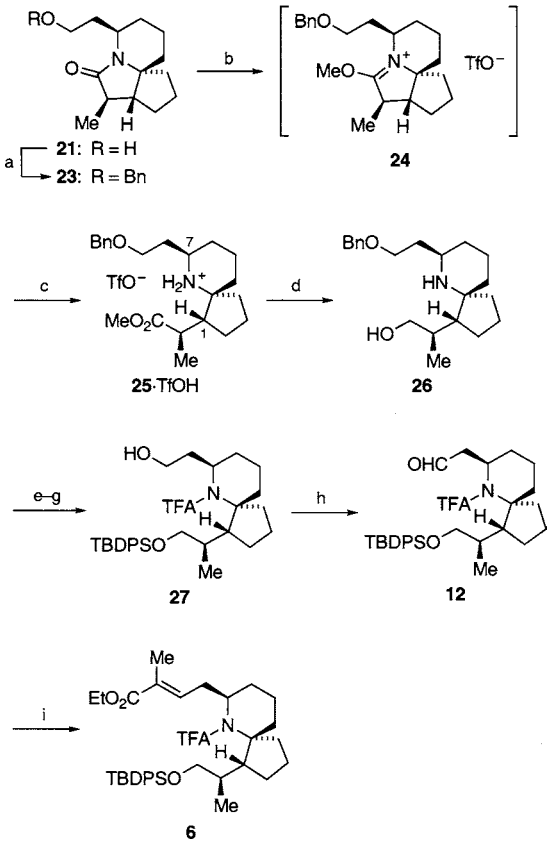
(4) For the synthesis of halichlorine, see: (a) Trauner, D.; Danishefsky, S. J. *Tetrahedron Lett.* **1999**, *40*, 6513−6516. (b) Trauner, D.; Schwarz, J. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 3542−3545. (c) Trauner, D.; Churchill, D. G.; Danishefsky, S. J. *Helv. Chim. Acta* **2000**, *83*, 2344−2351.

(5) For the synthesis of pinnaic acid, see: (a) Carson, M. W.; Kim, G.; Hentemann, M. F.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4450−4452. (b) Carson, M. W.; Kim, G.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4453−4456.

(6) Hayakawa, I.; Arimoto, H.; Uemura, D. *Heterocycles* **2003**, *59*, 441−444.

(7) Matsumura, Y.; Aoyagi, S.; Kibayashi, C. *Org. Lett.* **2003**, *5*, 3249−3252.

Scheme 4[a]



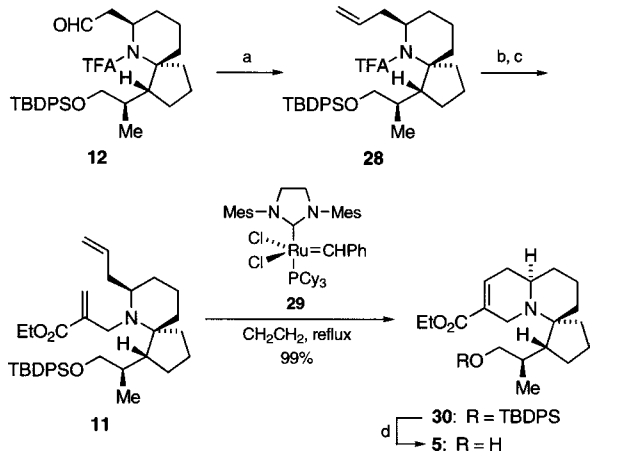
[a] Reagents and conditions: (a) BnBr, NaH, THF, rt, 90%; (b) TfOMe, $ClCH_2CH_2Cl$, 60 °C; (c) H_2O, THF, rt; (d) $LiAlH_4$, THF, 0 °C, 74% from **23**; (e) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, rt, 95%; (f) TFAA, *i*-Pr_2NEt, $ClCH_2CH_2Cl$, 0 °C, 99%; (g) H_2, $Pd(OH)_2$–C, MeOH, 99%; (h) Dess–Martin periodinane, CH_2Cl_2, rt, 95%; (i) $EtO_2CCH(Me)P(O)(OEt)_2$, NaH, THF, −78 °C, 76%.

α,β- and β,γ-unsaturated lactams **18** and **19**. Catalytic hydrogenation of this mixture produced the tricyclic lactam **13** as a single product. Attempted C-methylation of **13** with iodomethane and LHMDS in THF indicated that the reaction was very sluggish and did not yield the expected product.[8] In contrast, when the alcohol **20**, obtained by desilylation of **13**, was used as the substrate, LDA-mediated C7 methylation with iodomethane (THF, −78 °C) occurred at the uncongested convex face (β-face) of the azaspirotricyclic skeleton to give predominantly **21** in 15:1 selectivity.

After protection of the primary alcohol group to form the benzyl ether **23**, reductive lactam ring-opening was tried with $LiNH_2BH_3$;[9] however, no reaction was observed at all.[10] Upon treatment with aqueous KOH in THF, **23** was completely resistant to hydrolytic ring opening and the unreacted lactam was also recovered after 40 h at reflux.[11] We were gratified to find that the cleavage of the lactam **23** to produce the amino ester **25** could be achieved by using methyl triflate[12] via O-methylation of the amide carbonyl group to form an iminium intermediate **24** and subsequent hydrolysis (Scheme 4). The 1,7-disubstituted spirobicyclic compound **25** with the proper stereochemistry thus obtained as the triflate salt underwent ester reduction ($LiAlH_4$, THF) to give the alcohol **26**, which was converted to the trifluoroacetamide **27** by sequential TBDPS protection of the alcohol group, N-trifluoroacetylation, and catalytic O-debenzylation. Dess–Martin oxidation[13] of **27** afforded the corresponding aldehyde **12**, which was subjected to Horner–Wadsworth–Emmons homologation using triethyl 2-phosphonopropionate to provide the TBDPS-protected Danishefsky intermediate **6**. Since **6** has previously been converted to pinnaic acid (**2**),[5] a formal synthesis of racemic **2** was thus achieved.

Our attention was next directed toward the synthesis of the azaspirotricyclic quinolizidine **5**, the ethyl ester analogue of the Danishefsky key intermediate **3** in the total synthesis of halichlorine (**1**).[4b] Following the envisioned synthetic plan depicted in Scheme 2, the azaspirobicyclic aldehyde **12** was converted to the diene **11** by sequential Wittig methylenation, N-deprotection with $NaBH_4$, and introduction of the alkenyl chain into the secondary amine (Scheme 5). Subsequent

Scheme 5[a]



[a] Reagents and conditons: (a) $Ph_3P^+MeBr^-$, BuLi, THF, 0 °C, 80%; (b) $NaBH_4$, EtOH, rt, 83%; (c) $H_2C{=}C(CH_2Br)CO_2Et$, K_2CO_3, MeCN, 60 °C, 88%; (d) TREAT·HF, Et_3N, MeCN, rt, 94%.

RCM using Grubbs ruthenium catalyst **29**[14] proceeded very smoothly to furnish **30** in 99% yield. Removal of the TBDPS protecting group from **30** to give **5** was accomplished by brief exposure to triethylamine trihydrofluoride (TREAT·HF)[15] in acetonitrile at room temperature and thus completed a formal total synthesis of (±)-halichlorine (**1**).

In summary, we have developed a stereocontrolled approach for the preparation of the Danishefsky intermediates starting with the azaspirobicyclic ketone **10** as a common precursor, representing a formal total synthesis of (±)-

(8) Very recently, stereoselective C7-methylation of a TES-protected tricyclic lactam with iodomethane and LDA has been reported (see ref 3k).

(9) (a) Myers, A. G.; Yang, B. H.; Kopecky, D. J. *Tetrahedron Lett.* **1996**, *37*, 3623–3626. (b) For application of $LiNH_2BH_3$ for lactam ring opening, see: Aoyagi, S.; Tanaka, R.; Naruse, M.; Kibayashi, C. *J. Org. Chem.* **1998**, *63*, 8397–8406. Abe, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **2000**, *122*, 4583–4592.

(10) Very recently, reductive cleavage of the C–N bond of a TES-protected tricyclic lactam using $LiNH_2BH_3$ has been reported (see ref 3k).

halichlorine and (±)-pinnaic acid. This approach involves the construction of the 1,7-disubstituted 6-azaspiro[4.5]-decane with the proper stereochemistry established by olefin hydrogenation followed by C-methylation of the tricyclic lactam and the subsequent processes involving lactam ring-opening using methyl triflate and RCM to form the aza-spirotricyclic quinolizidine skeleton. The developed method is applicable to the enantioselective synthesis of natural halichlorine and pinnaic acid by using an optically active ketone **10** as a starting material available by the intramolecular ene reaction with a chiral hydroxamic acid (*R*)-**7**. Efforts in this direction are underway.

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

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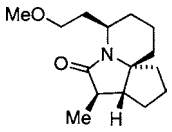
(11) The difficulty of the lactam hydrolysis was also observed when the acidic conditions using concentrated HCl at 110 °C in a sealed tube were applied to the methyl-protected tricyclic lactam **i**. Employing these reaction conditions did not effect the desired ring-opening even after a reaction time of 17 h but rather led to cleavage of the methoxy group.



i

(12) For a review on application of perfluoroalkanesulfonic esters in organic chemistry, see: Stang, P. J.; Hanack, M.; Subramanian, L. R. *Synthesis* **1982**, 85−126.

(13) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287. (c) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

(14) Scholl, M.; Ding, S.; Lee, C. W.; Grubss, R. H. *Org. Lett.* **1999**, *1*, 953−966.

(15) For a review, see: McClinton, M. A. *Aldrichim. Acta* **1995**, *28*, 31−35.