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The efficient entry into the tricyclic core of halichlorine

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Abstract

An efficient and diastereoselective synthesis of the tricyclic core structure **3** found in the marine alkaloid halichlorine **1** has been accomplished starting from Grigg's tricyclic isoxazolidine **5**, which was prepared by the tandem intramolecular Michael addition–[3+2] cycloaddition of the corresponding oxime of **4**.

Keywords: alkaloids; marine metabolites; cycloadditions; Mitsunobu reactions.

Halichlorine **1**[1] and pinnaic acid **2**[2] have been isolated by Uemura and co-workers from the marine sponge *Halichondria okadai* Kadota and the Okinawan *Pinna muricata*, respectively (Fig. 1). These compounds have attracted considerable interest because of their significant biological profiles as potent inhibitors of VCAM-1 induction in cultured human umbilical vein endothelial cells[1] and as specific inhibitors of phospholipase A_2,[2] and because of their unprecedented intriguing chemical structures.[3] Although previous synthetic efforts directed toward halichlorine and pinnaic acid have resulted in constructing the spirocyclic core[4,5] of **2**, the spiroquinolizidine subunit of **1**,[6] and side chain synthons,[7] no total synthesis has thus far been accomplished. We report herein the efficient entry into the tricyclic core **3** of halichlorine, employing Grigg's tricyclic isoxazolidine **5**[8] as the starting material. Recent communications by Lee and Zhao[5] on the synthesis of the azaspiro core structure for the alkaloids have prompted us to report our own efforts in this area.

The keto ester **4**, prepared from 1,3-dithiane in a five-step sequence in 75% overall yield according to the literature procedure,[8] was heated with hydroxylamine hydrochloride and sodium acetate in refluxing ethanol for 4 h to give the spiro-fused isoxazolidine **5** in 90% yield. This compound was generated from a two-step reaction sequence — intramolecular Michael addition of the initially formed oxime, followed by [3+2] dipolar cycloaddition of the resulting six-membered cyclic nitrone. Although the valuable tandem reaction was first developed by Grigg et al., and reported to proceed via the two-step sequence[8] (in 70% overall yield for the methyl ester), we were able to improve it as a concise one-pot procedure. The structure, including stereochemistry, was confirmed by a single crystal X-ray

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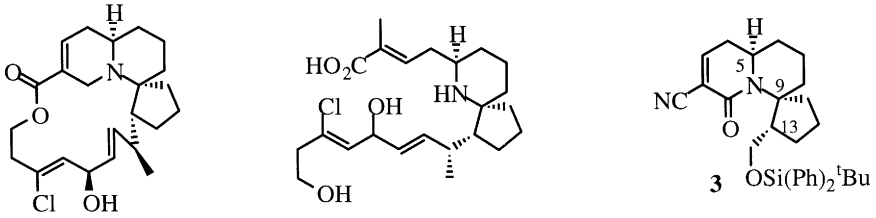


Fig. 1.

analysis[9] of the hydrochloride of amino alcohol **6**, which was derived by a catalytic hydrogenation of **5** (Fig. 2). Since the stereochemistry at C_5 was undesired, we attempted to invert it by using several reaction conditions. However, treatment of a solution of the silyl ether **7**[10] in CH_2Cl_2 with triethylamine at room temperature resulted in only recovered starting material. We next turned our attention to the diastereoselective reduction of the C_4–C_5 double bond for the desired C_5 stereochemistry. Sequential bromination and dehydrobromination of **5** provided the unsaturated ester *E*-**8**,[11] which was reduced by catalytic hydrogenation to afford **5** in 92% yield. This result suggested that the β-face of the double bond should be covered by a sterically bulky group in order to obtain the desired product by hydrogenation diastereoselectively. Accordingly, the carbon–nitrogen bond was cleaved by treatment with zinc and acetic acid. Reduction (H_2, PtO_2) of the resulting amino alcohol *Z*-**9**[11] produced a 2.6:1 mixture of **11** and **6** in 92% yield. Encouraged by this result, we examined the reduction of hydroxyl-protected substrates. In the end, the *t*-butyldiphenylsilyl ether **10** proved to be the best choice. On exposure of a solution of **10** in methanol to an atmosphere of hydrogen (5 atm) in the presence of catalytic PtO_2, the amino ester **12**,[10] with the desired stereochemistry at the C_5, C_9 and C_{13} positions, was obtained quantitatively (Scheme 1).

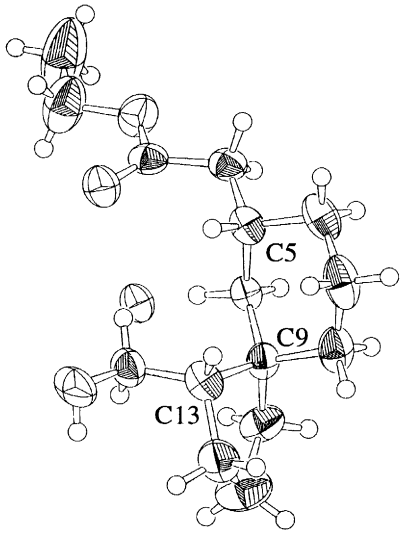
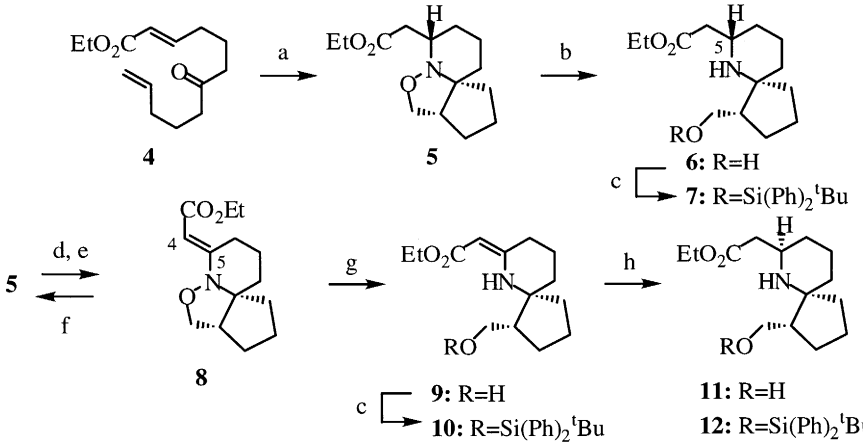


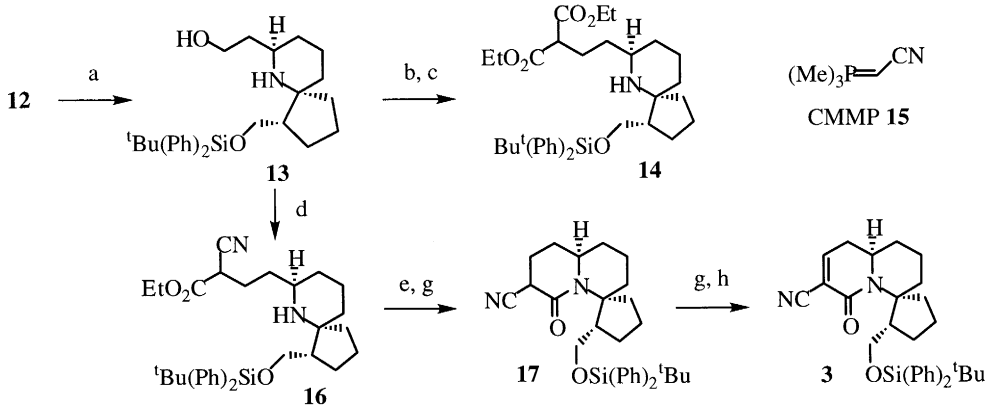
Fig. 2. ORTEP drawing of the X ray structure of **6**·HCl

With the desired aza–spiro compound in hand, we next examined the carbon chain elongation for assembling the quinolizidine. Reduction of the ester moiety in **12** with lithium aluminum hydride provided the alcohol **13**, which was mesylated and alkylated with the anion of diethyl malonate to afford the expected diester **14** in only 23% overall yield from **12**. Ultimately, a successful conversion was



Scheme 1. *Reagents and conditions*: (a) $NH_2OH \cdot HCl$, NaOAc, EtOH, reflux, 4 h, 90%; (b) H_2, 10% Pd–C, EtOH, 5 atm, rt, 25 h, quant.; (c) $^tBu(Ph)_2SiCl$, imidazole, 4 DMAP, CH_2Cl_2, rt, 11 h, quant.; (d) LDA, $Br(CF_2)_2Br$, THF, −78°C, 30 min, 90%; (e) DBU, benzene, reflux, 3 days, 79%; (f) H_2, PtO_2, AcOEt:AcOH=2:1, rt, 30 min, 92%; (g) Zn, AcOH, H_2O, 50°C, 20 min, quant.; (h) H_2, PtO_2, MeOH, 5 atm, rt, 5 h, quant.

realized by using the Tsunoda–Mitsunobu[12] coupling. Thus, treatment of **13** with ethyl cyanomalonate[13] in the presence of cyanomethylenetriphenylphosphorane (CMMP) in benzene at room temperature for 24 h produced **16** in 74% yield. Since the attempted direct cyclization of **16** into the lactam **17** was unsuccessful, the ester moiety in **16** was hydrolyzed. The resulting carboxylic acid was then treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), 1-hydroxybenzotriazole (HOBT) and triethylamine[14] to provide the tricyclic quinolizidinone **17** in 61% yield for the two steps. Introduction of the double bond by sequential phenylselenylation and *syn*-elimination of the resulting selenoxide afforded **3**[15] in 91% yield (Scheme 2).



Scheme 2. *Reagents and conditions*: (a) $LiAlH_4$, THF, rt, 15 min, quant.; (b) MsCl, Et_3N, CH_2Cl_2, 0°C, 10 min, quant.; (c) diethyl malonate, NaH, NaI, benzene, reflux, 6 h, 23%; (d) ethyl cyanomalonate, CMMP **15**, benzene, rt, 24 h, 74%; (e) KOH, EtOH, rt, 11 h; (f) EDC, HOBT, Et_3N, CH_2Cl_2, rt, 10 h, 61% (two steps); (g) LDA, PhSeCl, THF, −78°C, 15 min; (h) *m*CPBA, CH_2Cl_2, rt, 2 h, 91% (two steps)

In summary, a concise and diastereoselective construction of the tricyclic core structure **3** of the biologically significant marine alkaloid halichlorine **1** has been achieved starting from a readily available cycloadduct **5** in the racemic series. Further studies toward the total syntheses of halichlorine and pinnaic acid will be reported in due course.

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9. X Ray diffraction data for **6**·HCl, $C_{14}H_{26}NO_3Cl$: triclinic, space group *P* 1, *a*=9.163(6) Å, *b*=10.686(9) Å, *c*=9.053(6) Å, α=99.24(8)°, β=111.05(5)°, γ=97.25(7)°, *V*=800(1) Å^3, *Z*=2, *Dx*=1.211 g/cm^3, *F*(000)=316, and *m*(Mo*K*α)=2.427 cm^{-1}. The final refinement converged to *R*=0.058 and *Rw*=0.076 for 184 parameters.
10. Data for **7**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.08 (s, 9H), 1.13 (t, *J*=7.6 Hz, 3H), 1.35–1.61 (m, 9H), 1.74 (m, 1H), 1.99 (m, 1H), 2.05–2.18 (m, 4H), 2.48 (m, 1H), 3.54 (dd, *J*=10.0, 10.0 Hz, 1H), 3.83 (dd, *J*=4.0, 10.0 Hz, 1H), 3.91 (dq, *J*=2.0, 7.6 Hz, 2H), 7.33–7.42 (m, 6H), 7.68–7.70 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 19.0, 19.2, 21.0, 26.1, 27.0, 32.1, 35.5, 40.7, 41.5, 42.6, 49.3, 60.1, 63.4, 63.5, 127.5, 129.5, 134.1, 135.9, 172.0; IR (neat): 1732, 2858, 2931, 3340 cm^{-1}; MS (EI): *m/z* 493 (M$^+$); HRMS (EI): *m/z* calcd for $C_{30}H_{43}NO_3Si$: 493.3012; found: 493.2978. Data for **12**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.05 (s, 9H), 1.21 (t, *J*=7.2 Hz, 3H), 1.30–1.89 (m, 14H), 2.28 (d, *J*=6.8 Hz, 2H), 3.04 (m, 1H), 3.69 (dd, *J*=5.6, 10.0 Hz, 1H), 3.84 (dd, *J*=6.0, 10.0 Hz, 1H), 4.08 (q, *J*=7.2 Hz, 2H), 7.36–7.43 (m, 6H), 7.67–7.71 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 19.2, 22.3, 26.9, 27.7, 32.7, 35.3, 36.4, 42.2, 48.7, 52.1, 60.1, 62.8, 64.1, 127.5, 129.5, 133.9, 135.7, 172.4; IR (neat): 1732, 3329 cm^{-1}; MS (EI): *m/z* 493 (M$^+$); HRMS (EI): *m/z* calcd for $C_{30}H_{43}NO_3Si$: 493.3012; found: 493.3018.
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13. When the reaction was conducted using diethyl malonate, the coupled product **14** was obtained in only 13% yield because of competitive *O* alkylation.
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15. Data for **3**: ^{1}H NMR (400 MHz, $CDCl_3$ at 50°C): δ 1.04 (s, 9H), 1.46–1.89 (m, 8H), 2.02–2.07 (m, 1H), 2.13–2.16 (m, 2H), 2.16 (ddd, *J*=4.0, 4.0, 6.8 Hz, 1H), 2.62 (ddd, *J*=4.0, 6.8, 19.6 Hz, 1H), 2.79 (br s, 1H), 3.53 (dd, *J*=6.8, 10.0 Hz, 1H), 3.69 (dd, *J*=4.8, 10.0 Hz, 1H), 3.70 (m, 1H), 7.11 (dd, *J*=3.7, 3.7 Hz, 2H), 7.32–7.39 (m, 6H), 7.64–7.67 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.1 (s), 19.4 (br t), 19.9 (t), 26.5 (br t), 26.8 (q), 30.4 (t), 30.9 (br t), 33.1 (br t), 50.7 (br d), 53.9 (d), 64.2 (t), 70.1 (s), 114.3 (s), 114.7 (s), 127.5 (d), 127.5 (d), 129.4 (d), 129.4 (d), 133.6 (s), 134.0 (s), 135.5 (d), 135.6 (d), 150.6 (d), 161.2 (s); IR ($CHCl_3$): 1630, 1669, 2237 cm^{-1}; MS (EI): *m/z* 498 (M$^+$); HRMS (EI): *m/z* calcd for $C_{31}H_{38}N_2O_2Si$: 498.2703; found: 498.2708.