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Total synthesis of sporochnols, fish deterrents from a marine alga

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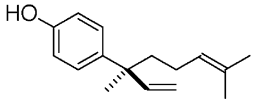
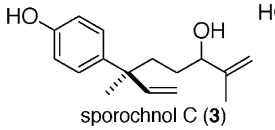
Abstract—Sporochnols, fish deterrents from a marine alga, were synthesized, using intramolecular C–H insertion of alkylidenecarbene as a key step to construct the chiral quaternary center. © 2002 Elsevier Science Ltd. All rights reserved.

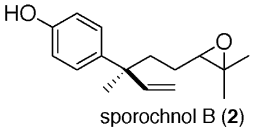
Sporochnols (**1**–**3**) are monoterpene-substituted phenols isolated from the marine alga *Sporochnus bolleanus*.[1] They are known to be chemical defense substances and to exhibit feeding deterrence activity toward reef fishes. Configuration of the asymmetric center of (+)-sporochnol A (**1**) was determined as *S* by the enantioselective synthesis of (–)-ent-**1** by Ogasawara's group in 1997.[2] Each sporochnol B (**2**) and C (**3**) which includes two stereocenters in one molecule is a 1:1 diastereomeric mixture. Syntheses of racemic or optically active sporochnol A (**1**) have recently been reported by several groups.[3] We describe here the synthesis of (±)-**1** and both enantiomers of **1**, using the C–H insertion reaction of alkylidenecarbene as the key step.[4] (+)-**1** was also converted into **2** and **3** enriched with one of the diastereomers to make assignment of NMR spectra of all the diastereomers possible.



sporochnol A (+)-(**1**)



sporochnol C (**3**)



sporochnol B (**2**)

Alkylation of the enolate of the ester **4** with iodomethane in the presence of DMPU in THF gave (±)-**5** in good yield. Reduction of ester (±)-**5** with lithium aluminum hydride gave alcohol (±)-**6**, which was oxidized under Swern's conditions followed by Wittig reaction with 1-triphenylphosphoranylidene-2-propanone to afford α,β-unsaturated ketone (±)-**7**. Hydrogenation of **7** in the presence of palladium on charcoal gave methyl ketone (±)-**8**. Exposure of (±)-**8** with lithiotrimethylsilyldiazomethane[5] produced cyclopentene (±)-**9** cleanly via intramolecular C–H insertion of the alkylidenecarbene. It is known that the reaction proceeds with a retention of configuration.[6] The high yield (92%) of this reaction is attributable to the low dissociation energy of the benzylic C–H bond and/or the electron donating effect of *p*-methoxy group.

Cyclopentene (±)-**9** was subjected to epoxidation with *m*-chloroperbenzoic acid to give epoxide (±)-**10** as a diastereomeric mixture. The reaction of (±)-**10** with diethylaluminum *N*,*N*-tetramethylpiperazide[7] at room temperature gave the rearranged allyl alcohol (±)-**11**. The possible isomer, which contains an *endo* double bond in the five-membered ring, was not produced at all. Dihydroxylation of the double bond of (±)-**11** using OsO_4 under catalytic conditions gave triol (±)-**12** as a diastereomeric mixture. The stereochemistry of (±)-**10** and (±)-**12** was not examined in detail because stereocenters except the benzylic quaternary center would disappear in the next step. Cleavage of two C–C bonds of (±)-**12** occurred by treatment with excess $NaIO_4$ via the intermediate (±)-**13** to give aldehyde (±)-**14**. Direct reaction of (±)-**14** with excess methylenetriphenylphosphorane in DMSO gave the desired product (±)-**15** in good yield. Reduction of acid (±)-**15** with lithium aluminum hydride in THF gave alcohol (±)-**16**. The con-

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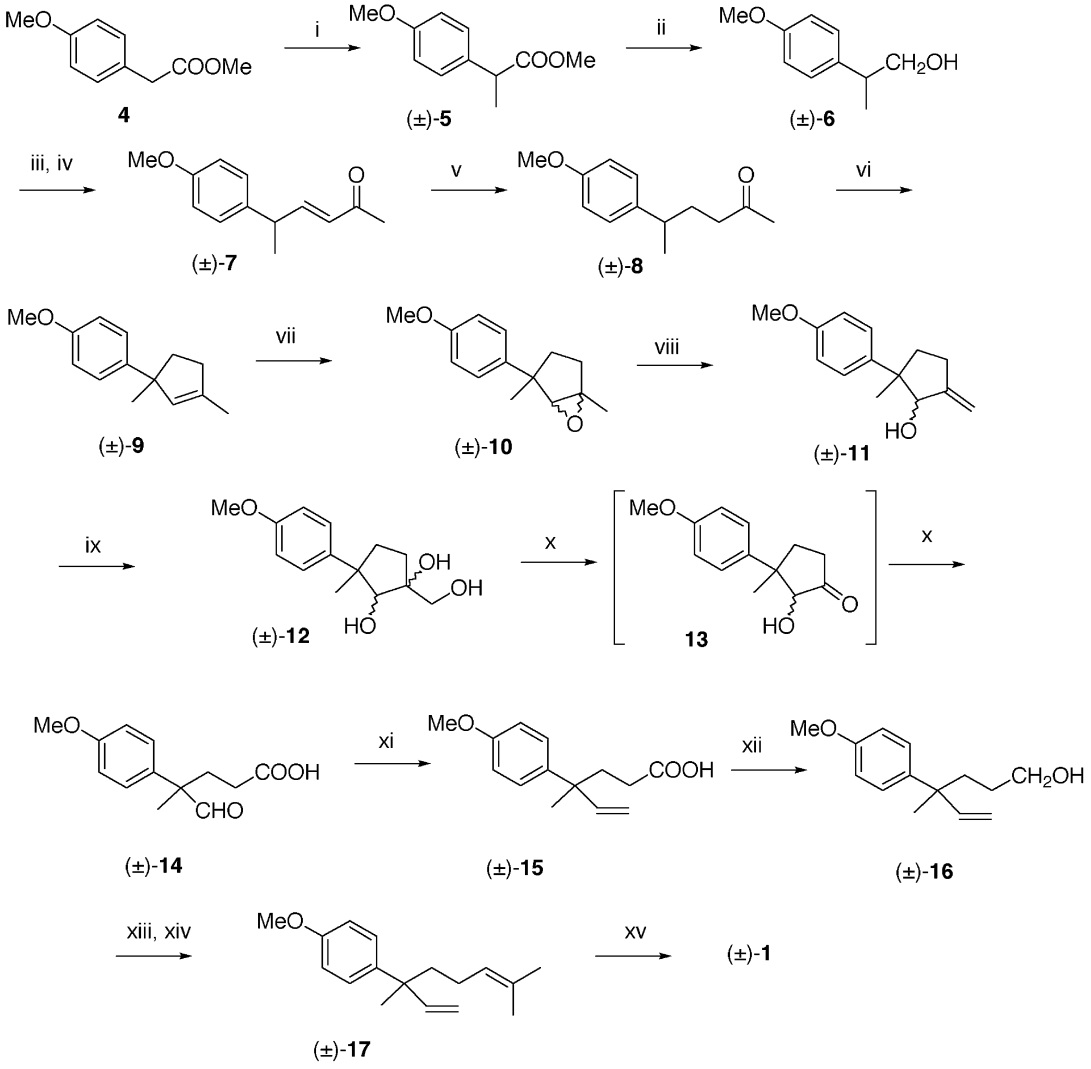
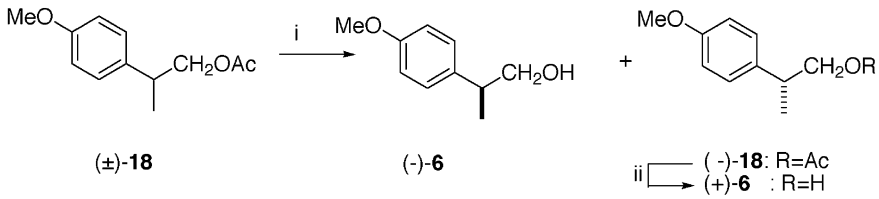
version of (±)-**12** to (±)-**16** was achieved without chromatographic separation of intermediates in 65% overall yield. Swern oxidation of alcohol (±)-**16**, followed by the Wittig reaction using isopropyridenetriphenylphosophorane gave diene (±)-**17**. Although the reaction of (±)-**17** and boron tribromide gave no desired product due to the addition of generated hydrogen bromide to double bonds, treatment of (±)-**17** with Ph_2PLi[8] at 50°C afforded the (±)-**1** in good yield. ^1H NMR, ^{13}C NMR, IR, and MS spectra of the synthetic compound were essentially identical to those of the natural product.[1]

Establishing the pathway from ester **4** to (±)-**1**, our attention then turned to the preparation of optically active sporochnols. Since Matsumoto et al. reported the effective enzymatic resolution of 1-acetoxy-2-(aryl)propanes,[9] we applied their conditions to acetate (±)-**18**, derived from (±)-**6**. (±)-**18** was hydrolyzed with PPL in methanol to give acetate (−)-**18** and alcohol (−)-**6** ($[\alpha]_D^{25}$ −16.8 (*c* 1.25, $CHCl_3$) in 49% and 51% yield, respectively (Scheme 1). Hydrolysis of (+)-**18** with aqueous KOH in methanol gave (+)-**6** ($[\alpha]_D^{25}$ +16.8 (*c* 1.37, $CHCl_3$) (Scheme 2). The absolute configuration of the alcohol (**6**) was known[10] and the enantiomeric excess of (−)-**6** and (+)-**6** was calculated from NMR spectra of MTPA esters of the alcohols as 93% ee and 95% ee, respectively. *E* value of the kinetic resolution was 96.4.

In the same way as the synthesis of (±)-**1**, (+)-**6** was converted to (−)-**7** and then into (+)-**8**. Although the small value of the optical rotations of (−)-**7** (−1.3°) and (+)-**8** (1.5°) implied occurrence of partial racemization of the intermediate, (+)-**8** was converted into the final compound **1**. The synthetic sporochnol A thus obtained showed essentially no optical rotation. Racemization of the aldehyde during the Wittig reaction was significant,



Scheme 1. *Reagent and conditions*: (i) LDA; MeI, DMPU, THF, −78°C (quant.); (ii) $LiAlH_4$, Et_2O, rt (98%); (iii) DMSO $(COCl)_2$, Et_3N, CH_2Cl_2, −78°C; (iv) $Ph_3P{=}CHCOCH_3$, benzene, 60°C (67% from **6**); (v) H_2, EtOAc, Pd/C, rt (89%); (vi) $TMSC(Li)N_2$, THF, 0°C (92%); (vii) *m*CPBA, $NaHCO_3$, CH_2Cl_2, rt (91%); (viii) LTMP, Et_2AlCl, toluene, 0°C (quant.); (ix) OsO_4, NMO, THF-H_2O, rt (96%); (x) $NaIO_4$, THF, H_2O, rt; (xi) $Ph_3P{=}CH_2$, DMSO, 40°C; (xii) $LiAlH_4$, (65% from **12**); (xiii) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78°C; (xiv) $Ph_3P{=}C(CH_3)_2$, DMSO, 40°C (74% from **16**); (xv) Ph_2PLi, THF, 50°C (85%).

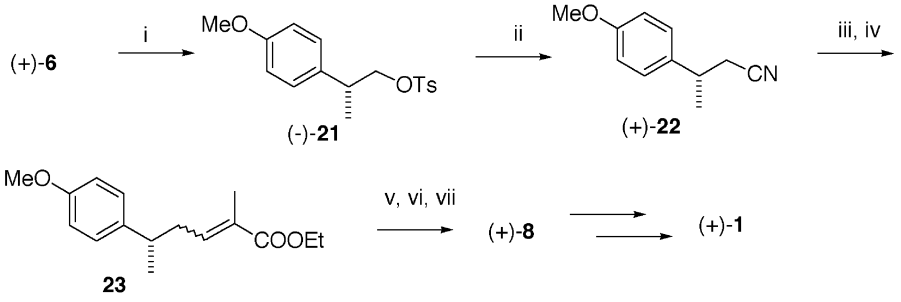


Scheme 2. *Reagent and conditions:* (i) PPL, MeOH, buffer, 35°C (quant.); (ii) KOH, MeOH, H_2O, rt (97%).

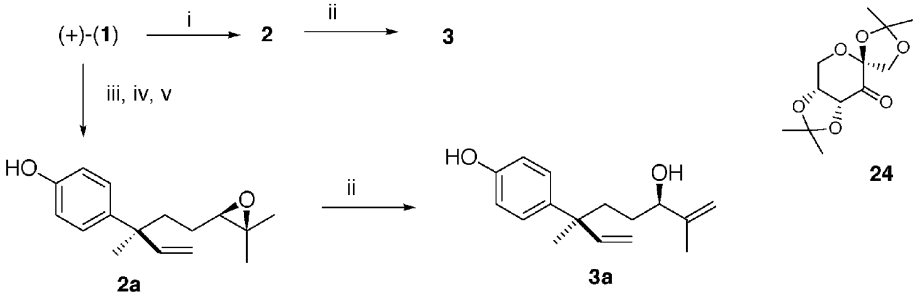
so that modification of the route which excludes the aldehyde as an intermediate is imperative.

After many trials, we found that the tosylate **21** obtained from (+)-**6** reacted with sodium cyanide cleanly to give nitrile (+)-**22** ($[\alpha]_D^{25}$ +8 (*c* 0.19, $CHCl_3$)) (Scheme 3). (+)-**22** was reduced with DIBAL to the aldehyde that was submitted to Wordsworth–Emmons reaction using triethyl phosphonoacetate and butyllithium, giving α,β-unsaturated ester **23** as a *cis–trans* mixture. After hydrolysis of the ester, the carboxylic acid was treated with DPPA and triethylamine under Shioiri's conditions.[11] The Curtius rearrangement product thus obtained was hydrolyzed without isolation to give methyl ketone (+)-**8** ($[\alpha]_D^{25}$ +17 (*c* 0.29, $CHCl_3$). (+)-**8** was transformed to (+)-**1** ($[\alpha]_D^{25}$ +5.8 (*c* 0.95, $CHCl_3$); lit.[3a]: $[\alpha]_D^{30}$ +2.9 (*c* 1, $CHCl_3$); natural[1]: $[\alpha]_D$ +10 (*c* 1, $CHCl_3$)), using the established sequence as shown in Scheme 1. The physical properties of synthetic sporochnol A were identical to those of the natural product. (−)-**1** ($[\alpha]_D^{25}$ −5.4 (*c* 1.48, $CHCl_3$); lit.[3b]: $[\alpha]_D^{20}$ −2.5 (*c* 1, $CHCl_3$)) was also obtained in the same way from (−)-**6**. As the yield of each step was good, we were able to obtain about 0.5 g of both enantiomers of sporochnol A.

Conversions of (+)-**1** into other sporochnols were achieved as follows (Scheme 4). Epoxidation of (+)-**1** with *m*-chloroperbenzoic acid gave **2** as a 1:1 diastereomeric mixture. Treatment of **2** with diethylaluminum *N*,*N*-tetramethylpiperazide afforded **3** in good yield. ^1H NMR and ^{13}C NMR spectra of **2** and **3** were identical with those of natural products. For the complete assignment of the NMR spectra of **2** and **3**, one of the diastereomers of **2** (**2a**, 62% de) was prepared in three steps (protection, Shi asymmetric epoxidation[12] and deprotection). Rearrangement of **2a** afforded **3a**, thus all signals of ^1H NMR and ^{13}C NMR of **2** and **3** were assigned to each diastereomer.[13]



Scheme 3. *Reagent and conditions:* (i) TsCl, Py, CH_2Cl_2, rt (93%); (ii) NaCN, DMSO, 80°C (89%); (iii) DIBAL, toluene, rt; (iv) $(EtO)_2P(O)CH(Me)COOEt$, BuLi, THF, rt (93% from **22**); (v) KOH, H_2O, MeOH, rt; (vi) DPPA, Et_3N, toluene, rt; (vii) HCl, H_2O (62% from **23**).



Scheme 4. *Reagent and conditions:* (i) *m*CPBA, $NaHCO_3$, CH_2Cl_2, rt (quant.); (ii) LTMP, Et_2AlCl, toluene, 0°C (96%); (iii) TBDMSOTf, 2,6-di-*tert*-butyl-4-methylpyridine, CH_2Cl_2, 0°C (95%); (iv) **24**, oxone, *n*-Bu_4NHSO_4, buffer, dimethoxymethane, rt (65%); (v) TBAF, THF, 0°C (98%).

Acknowledgements

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13. **2a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.166 (2H, d, $J=8.7$ Hz), 6.769 (2H, d, $J=8.7$ Hz), 5.987 (1H, dd, $J=10.7$, 17.4 Hz), 5.086 (1H, dd, $J=10.7$, 1.2 Hz), 5.035 (1H, dd, $J=17.4$, 1.2 Hz), 2.691 (1H, t, $J=6.3$ Hz), 1.909 (1H, dt, $J=12.8$, 4.6 Hz), 1.805 (1H, dt, $J=12.8$, 4.9 Hz), 1.24–1.50 (2H, m), 1.347 (3H, s), 1.284 (3H, s), 1.170 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.66, 146.81, 138.98, 127.77, 114.88, 111.73, 64.81, 58.70, 43.39, 37.46, 24.87, 24.83, 24.21, 18.61. **2b** (diastereomer of **2a**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.166 (2H, d, $J=8.7$ Hz), 6.769 (2H, d, $J=8.7$ Hz), 5.980 (1H, dd, $J=10.7$, 17.4 Hz), 5.105 (1H, dd, $J=10.7$, 1.2 Hz), 5.045 (1H, dd, $J=17.4$, 1.2 Hz), 2.694 (1H, t, $J=6.3$ Hz), 1.994 (1H, ddd, $J=13.4$, 9.6, 7.6 Hz), 1.723 (1H, ddd, $J=13.4$, 9.4, 7.4 Hz), 1.24–1.50 (2H, m), 1.342 (3H, s), 1.293 (3H, s), 1.206 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.68, 146.56, 139.15, 127.69, 114.90, 111.96, 64.81, 58.70, 43.37, 37.38, 24.87, 24.98, 24.25, 18.56. **3a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.147 (2H, d, $J=8.3$ Hz), 6.746 (2H, d, $J=8.3$ Hz), 5.984 (1H, dd, $J=10.7$, 6.7 Hz), 5.070 (1H, d, $J=12.2$ Hz), 5.012 (1H, d, $J=17.7$ Hz), 4.915 (1H, bs), 4.834 (1H, bs), 4.012 (1H, t, $J=6.4$ Hz), 1.764 (1H, dt, $J=13.0$, 4.9 Hz), 1.670 (1H, dt, $J=13.0$, 4.9 Hz), 1.34–1.51 (2H, m), 1.621 (3H, s), 1.329 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.70, 147.03, 147.02, 139.13, 127.74, 114.91 111.60, 111.50, 76.58, 43.26, 36.64, 29.60, 25.08, 17.35. **3b** (diastereomer of **3a**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.147 (2H, d, $J=8.3$ Hz), 6.746 (2H, d, $J=8.3$ Hz), 5.977 (1H, dd, $J=10.7$, 6.7 Hz), 5.070 (1H, d, $J=12.2$ Hz), 5.012 (1H, d, $J=17.7$ Hz), 4.915 (1H, bs), 4.834 (1H, bs), 4.012 (1H, t, $J=6.4$ Hz), 1.853 (1H, dt, $J=12.9$, 4.6 Hz), 1.587 (1H, dt, $J=12.9$, 4.6 Hz), 1.34–1.51 (2H, m), 1.648 (3H, s), 1.329 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.71, 147.03, 147.00, 139.18, 127.73, 114.91, 111.64, 111.47, 76.60, 43.26, 36.64, 29.64, 25.01, 17.40.