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Synthesis of (±)-Halipanicine, a Marine Sesquiterpene Isothiocyanate Isolated from an Okinawan Marine Sponge *Halichondria panicea*

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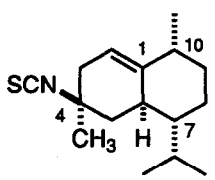
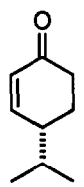
Key words: Halipanicine: Marine sesquiterpene isothiocyanate: Marine sponge; *Halichondria panicea* .

Abstract: *(±)-Halipanicine, 4-isothiocyanato-1-cadinene, isolated from an Okinawan marine sponge* Halichondria panicea *was synthesized from (±)-cryptone in 21 steps in 7.7% total yield. The regio- and stereospecific synthesis esablished the relative stereochemistry of halipanicine.*

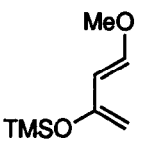
Isocyanates and isothiocyanates are found in marine organisms such as marine sponges and nudibranches as well as in plants and microorganisms[1] and they display various biological activities including antimicrobial, cytotoxic, antifeedant, and anticarciogenic activities.[1,2] In the course of our studies on bioactive marine natural products from Okinawan marine organisms, we have isolated a sesquiterpene isothiocyanate, halipanicine (**1**), from the Okinawan marine sponge *Halichondria panicea*.[3] In this communication, we describe an efficient synthesis of halipanicine as a racemic form started from the Diels-Alder reaction of racemic cryptone (**2**) and Danishefsky diene (**3**) by a sequence of reactions involving stereospecific introduction of methyl groups at C-4 and C-10 and regioselective formation of a double bond at C-1.



halipanicine (**1**)



(±)-cryptone (**2**)



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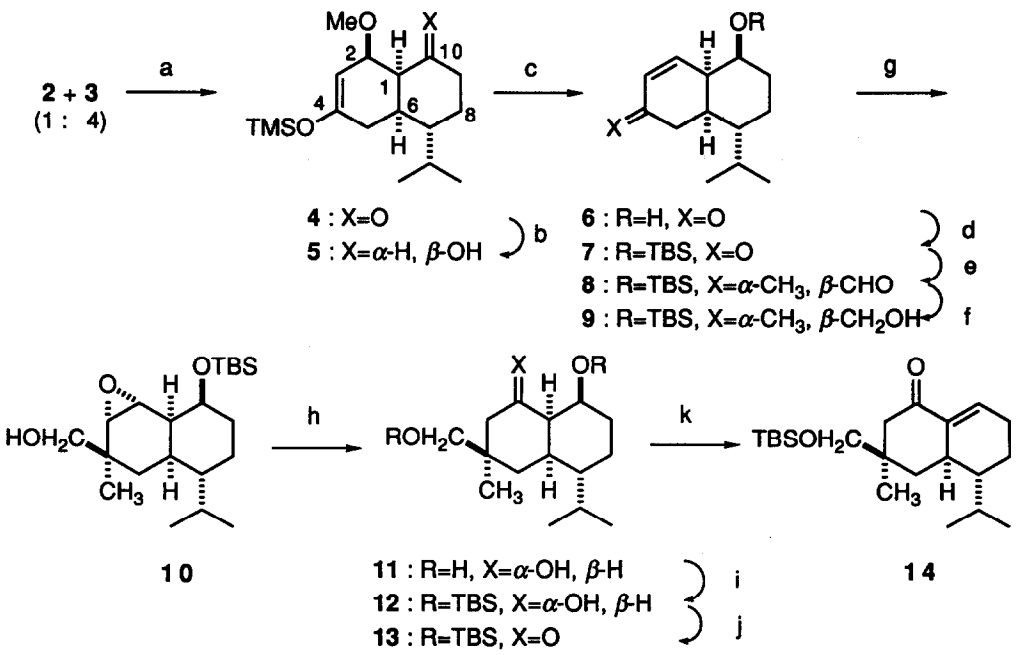
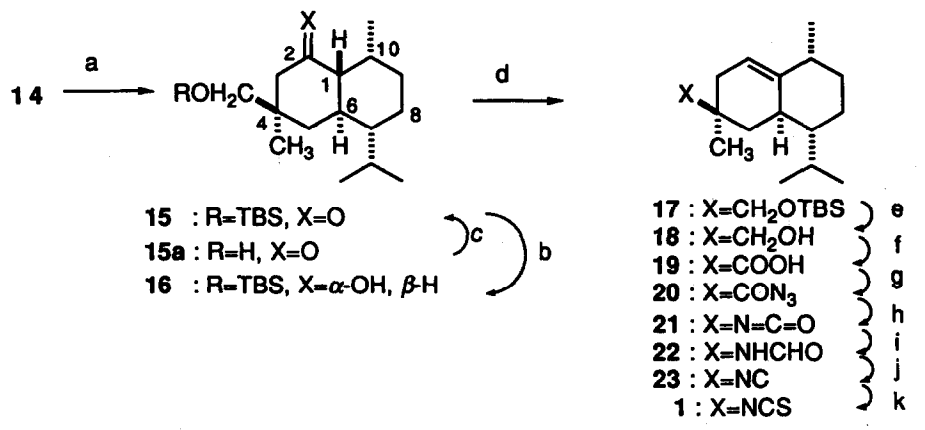
The construction of the properly functionalized *cis*-decalin framework with a correct configuration of an isopropyl group at C-7 commenced with the Diels-Alder reaction of a 1:4 mixture of racemic cryptone[4] and Danishefsky diene in the presence of a small amount



Reagents and conditions: a) 0.5% mol 2,6-di-*t*-butyl-p-cresol, 180-185 °C, 22 h. b) DIbal-H, CH_2Cl_2, -78 °C, 1h. c) 0.5 M HCl-THF (1:10), 20 °C, 12 h, 50 % from **2**. d) TBSCl, imidazole, DMF, 20 °C, 3h, 96%. e) i) Ph-CH=N-C$^-$H-P(=O)$(OEt)_2$-Li^+, THF, -78-25 °C, 2 h; ii) *n*-BuLi, -78 °C, 1h, then MeI, -78 - 20 °C, 2h; iii) 1M HCl, 20 °C, 2 h, 87%. f) $NaBH_4$, MeOH, 0 °C, 30 min, 91%. g) *m*-CPBA, CH_2Cl_2, 20 °C, 5 h, 100%. h) $LiAlH_4$, dioxane, 80-85 °C, 1.5 h, 75%. i) TBSOTf, Et_3N, DMAP, CH_2Cl_2, -20 °C, 30 min, 87%. j) PDC, MS4A, CH_2Cl_2, 20 °C, 5 h, 99%. k) DBU, xylene, reflux, 5h, 95%.

of 2,6-di-*t*-butyl-*p*-cresol at 180-185 °C for 22 h. The enol ether (**4**) was reduced with diisobutylaluminium hydride to afford the corresponding alcohol (**5**), which, upon treatment with hydrochrolic acid, yielded the enone (**6**) in 50% total yield from cryptone. The compound (**6**) was converted to the *t*-butyldimethylsilyloxy enone (**7**)[5] and subjected to the geminal acylation-alkylation reaction developed by Martin.[6] Treatment of **7** with diethyl lithio benzylideneaminomethylphosphonate Ph-CH=N-C(Li)H-P(=O)$(OEt)_2$ gave the corresponding 2-azadiene Ph-CH=N-CH=CRR'. Regiospecific addition of *n*-butyllithium to the 2-azadiene produced the metalloenemine Ph-C(n-Bu)H-NLi-CH=CRR'. Methylation of the metalloenamine with methyl iodide proceeded stereospecifically from the convex side to give the aldehyde (**8**) as a single isomer in 87% total yield after acid hydrolysis. The aldehyde was reduced with $NaBH_4$ to yield the corresponding alcohol (**9**). The configuration of the newly formed quaternary carbon was established on the basis of an NOE increment of H-6 proton signal by irradiation at the tertiary methyl group of **9**.[7]



Reagents and conditions: a) $Me_2CuLi{\cdot}LiI$, $BF_3{\cdot}OEt_2$, THF, -78 °C, 77%. b) $NaBH_4$, MeOH, 20 °C, 86%. c) TBSOTf, Et_3N, DMAP, CH_2Cl_2, -20 °C, 30 min, 98%. d) $SOCl_2$, Py, 0 °C, 1 h, 100%. e) TBAF, THF, 40-45 °C, 12 h, 100%. f) Jones oxidation, 0 °C, 50 min, 94%. g) KH, $(PhO)_2P(=O)N_3$, THF, 0-20 °C, 3 h. h) xylene, reflux, 5 h, 98% from **19**. i) $LiEt_3BH$, THF, -78 °C, 1 h, 96%. j) TsCl, Py, 20 °C, 15 h, 87%. k) S_8, xylene, 120-130 °C, 4 h, 64%.

Epoxidation of **9** with *m*-chloroperbenzoic acid followed by reduction with $LiAlH_4$ in 1,4-dioxane produced the triol (**11**) in 75% total yield.[8] Selective protection of **11** with 2 eq of TBSOTf at -20 °C formed the alcohol (**12**) in 87 % yield. The alcohol (**12**) was converted to the enone **14** in a quantitative yield by oxidation with pyridinium dichromate followed by β-elimination reaction with 1,8-diazabicylo[5.4.0]undec-7-ene.

Stereoselective introduction of a methyl group at C-10 was achieved by a use of a copper reagent. Upon treatment of **14** with Me_2CuLi in the presence of $BF_3{\cdot}Et_2O$,[9] addition of a methyl group proceeded predominantly from an axial side as expected to produce the ketone (**15**) and the alcohol (**15a**) in 77% and 15% yields, respectively. The stereostructure of **15** was determined from the NOE experiment (10-Me→H-6).[10] The ketone (**15**) was reduced with $NaBH_4$, and then dehydrated with $SOCl_2$ in pyridine to yield the olefin (**17**) in 84% total yield.

The olefin (**17**) was transformed to halipanicine (**1**) in 49% total yield by a sequence of the following reactions:[11] 1) deprotection with tetra-*n*-butylammonium fluoride; 2) Jones oxidation; 3) acyl azide formation with KH and $(PhO)_2P(=O)N_3$; 4) Curtius rearrangement; 5) $LiEt_3BH$ reduction; 6) dehydration with TsCl in pyridine; 7) sufurization with S_8. The synthetic compound was identical with natural halipanicine (**1**).

Halipanicine was synthesized for the first time as a racemic form in the 21-step procedure involving regio- and stereospecific reactions from racemic cryptone in 7.7% overall yield, which confirmed the relative stereostructure of halipanicine. Further studies toward the enantiospecific synthesis are in progress.

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4. (±)-Cryptone was prepared from 4-isopropylphenol in the following three-step procedure: 1) methylation with NaOH and dimethyl sufate; 2) Birch reduction; 3) hydrolysis and isomerization with sulfuric acid; Soffer, M. D. and Jevnik, M., *J. Am. Chem. Soc.*, **1955**, *77*, 1003-1006.
5.. **7**: a colorless oil; IR (neat), ν_{max} 2960, 2930, 2900, 2860, 1690, 890 cm^{-1}; ^1H NMR ($CDCl_3$) δ7.16 (1H, dt, J= 10, 2 Hz, H-2), 6.07 (1H, dd, J=10, 3 Hz, H-3), 3.77 (1H, dt, J=11, 5 Hz, H-10), 2.85 (1H, br m, $W_{1/2}$=10 Hz, H-1), 2.73 (1H, dd, J=16, 2 Hz, H-5*b*), 2.38 (1H, dd, J=16, 4 Hz, H-5α), 2.13 (1H, m, $J_{1\text{-}6}$=8 Hz, $J_{6\text{-}7}$=11 Hz, H-6), 1.88 (1H, m, CH_3-C<u>H</u>-CH_3), 1.73 (1H, m, H-9α), 1.63 (1H, dq, J=13, 3 Hz, H-8β), 1.40-1.22 (3H, m, H-7, H-8α, H-9β), 0.90 (9H, s, TBS), 0.86 (3H, d, J=7 Hz), 0.72 (3H, d, J=7 Hz), 0.08 (3H, s, TBS), 0.07 (3H, s, TBS); HR-EIMS *m/z* 323.2390 $(M+H)^+$. Calcd. for $C_{19}H_{35}O_2Si$, 323.2406.
6. Martin, S. F. , Phillips, G. W., Puckett, T. A., and Colapret, J. A., *J. Am. Chem. Soc.*, **1980**, *102*, 5866-5872.
7. **9**: a colorless oil; IR (neat), ν_{max} 3651, 2980, 1647, 912 cm^{-1}; ^1H NMR ($CDCl_3$) δ5.57 (1H, dd, J= 10, 4 Hz, H-2), 5.50 (1H, dd, J=10, 3 Hz, H-3), 3.79 (1H, dt, J=7, 3 Hz, H-10), 3.35 (2H, s), 2.28 (1H, br m, $W_{1/2}$=10 Hz, H-1), 2.12 (1H, dd, J=13, 8 Hz, H-5β), 1.84 (1H, m), 1.80 (1H, m, H-6), 1.68 (1H, m), 1.59 (1H, m, H-9α), 1.40 (1H, m, H-9β), 1.21 (1H, m), 1.12 (1H, dd, J=13, 3 Hz, H-5α), 1.02 (3H, s), 0.91 (3H, d, J=7 Hz), 0.88 (9H, s), 0.79 (3H, d, J=7 Hz), 0.03 (3H, s, TBS), 0.01 (3H, s, TBS); HR-EIMS, Found, *m/z* 352.2772 (M^+). Calcd. for $C_{21}H_{40}O_2Si$, 352.2798.
8. Large amounts of regioisomeric alcohols were formed when the reduction was carried out under the following conditions: $LiAlH_4$ in THF , $LiAlH_4$ in 2-methoxyethyl ether, or Li-ethylenediamine.
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10. **15**: a colorless oil; IR (neat), ν_{max} 2956, 2854, 1732, 1470, 1389, 837 cm^{-1}; ^1H NMR ($CDCl_3$) δ3.29 (1H, d, J= 10 Hz, CH_2OH), 3.22 (1H, d, J=10 Hz, CH_2OH), 2.37 (1H, br m, H-10), 2.32 (1H, d, J=14 Hz, H-3β), 2.01 (1H, m, CH_3-C<u>H</u>-CH_3), 1.97 (1H, dd, J=14, 3 Hz, H-3α), 1.92 (1H, dd, J=11, 3 Hz, H-1), 1.86 (1H, qd, J=11, 3 Hz, H-6), 1.67 (1H, dt, J=14, 2 Hz, H-5α), 1.62 (1H, dq, J=14, 4 Hz, H-9α), 1.43 (1H, m, H-9β), 1.41 (1H, m, H-8β), 1.31 (1H, t J= 12 Hz, H-5β), 1.26 (1H, m, H-8α), 1.14 (1H, tt, J=10, 3 Hz, H-7), 0.95 (3H, d, J=7 Hz, 10-Me), 0.93 (3H, d, J=7 Hz), 0.89 (9H, s, TBS), 0.79 (3H, s, 4-Me), 0.76 (3H, d, J=7 Hz), 0.07 (3H, s, TBS), 0.03 (3H, s, TBS); HR-EIMS, Found, *m/z* 366.2927 (M^+). Calcd. for $C_{22}H_{42}O_2Si$, 366.2954.
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