Keywords: asymmetric catalysis · epoxidations · heterogeneous catalysis · surface chemistry · tantalum

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[15] This already known surface reaction[14] leads to the liberation of neopentane (ca. 1.5 mol per mol of grafted Ta) with the formation of a mixture of two well-defined surface species, **2a** and **2b**.
[16] Step 2: 2.5 mol of neopentane evolved per mol of surface tantalum.
[17] [Ta]#1: 4.92 wt% Ta, C/Ta = 8.9; [Ta]#2: 5.40 wt% Ta, C/Ta = 7.2; [Ta]#3: 5.63 wt% Ta, C/Ta = 7.1. For a mixture of **3a** (50%) and **3b** (50%) a theoretical value of C/Ta = 7 should be observed; this is the case for [Ta]#2 and [Ta]#3. For [Ta]#1 the higher value may be explained by the presence of SiOEt species.
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Total Synthesis of (+)-Halichlorine: An Inhibitor of VCAM-1 Expression[**]

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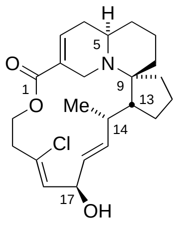
Samuel J. Danishefsky[*]

Vascular cell adhesion molecule-1 (VCAM-1), a member of the immunoglobulin superfamily, monitors and regulates leukocyte recruitment into inflamed tissue.[1] Since leukocyte infiltration is involved in various allergic inflammatory disorders as well as pathogenic processes such as asthma and arteriosclerosis VCAM-1 has emerged as a potential target for drug discovery. In principle, blockade or inhibition of VCAM-1 could have consequences in regulating leukocyte trafficking. Given such considerations an agent that specifically inhibits induced VCAM-1 expression could be of particular interest. While screening for active compounds from marine organisms Uemura and colleagues isolated a substance from the marine sponge *Halichondria okadai* Kadota, which they named halichlorine, and identified its structure as **1**.[2] A related structure, pinnaic acid (**2**), had been isolated from an Okinawan bivalve *Pinna muricata*.[3]



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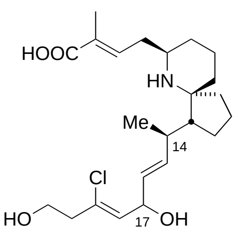

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Aside from several provocative features of halichlorine, which might pose stimulating opportunities to the organic chemist, this compound commands particular attention because it selectively inhibits the induced expression of VCAM-1 with an IC_{50} of 7 $\mu g\,mL^{-1}$. Interestingly, pinnaic acid was obtained from a screen designed to identify specific inhibitors of cytosolic phospholipase A_2 ($cPLA_2$).

Among the challenges posed by halichlorine is that of its total synthesis.[4] Aside from providing the setting for addressing several interesting chemical issues, its total synthesis holds the prospect of providing probe structures to document structure–activity relationships. Elsewhere we

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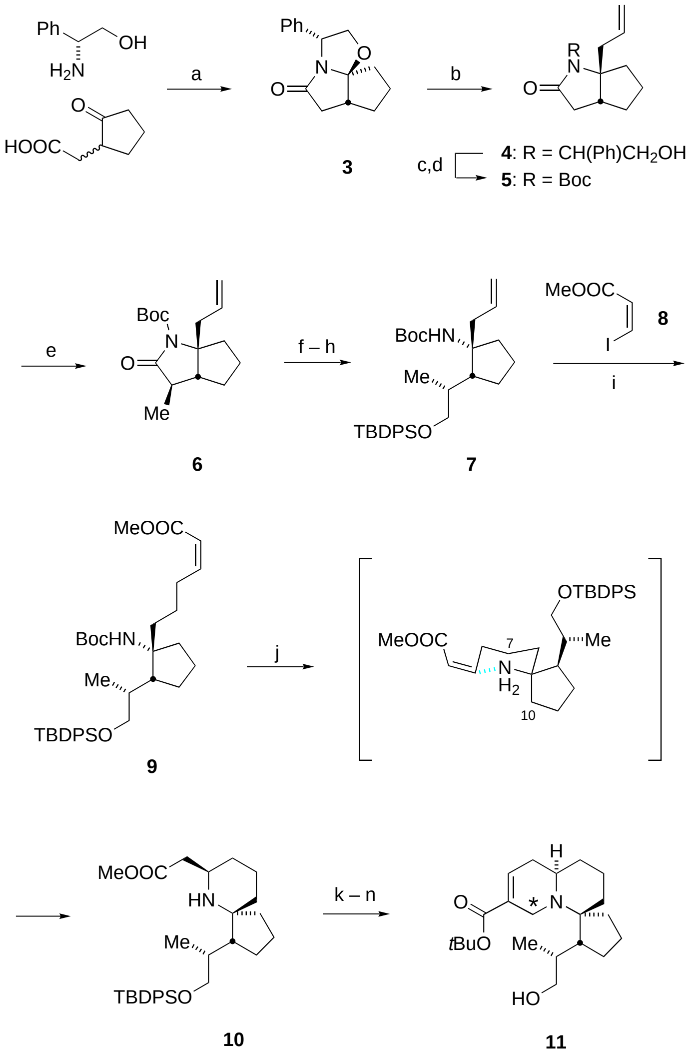
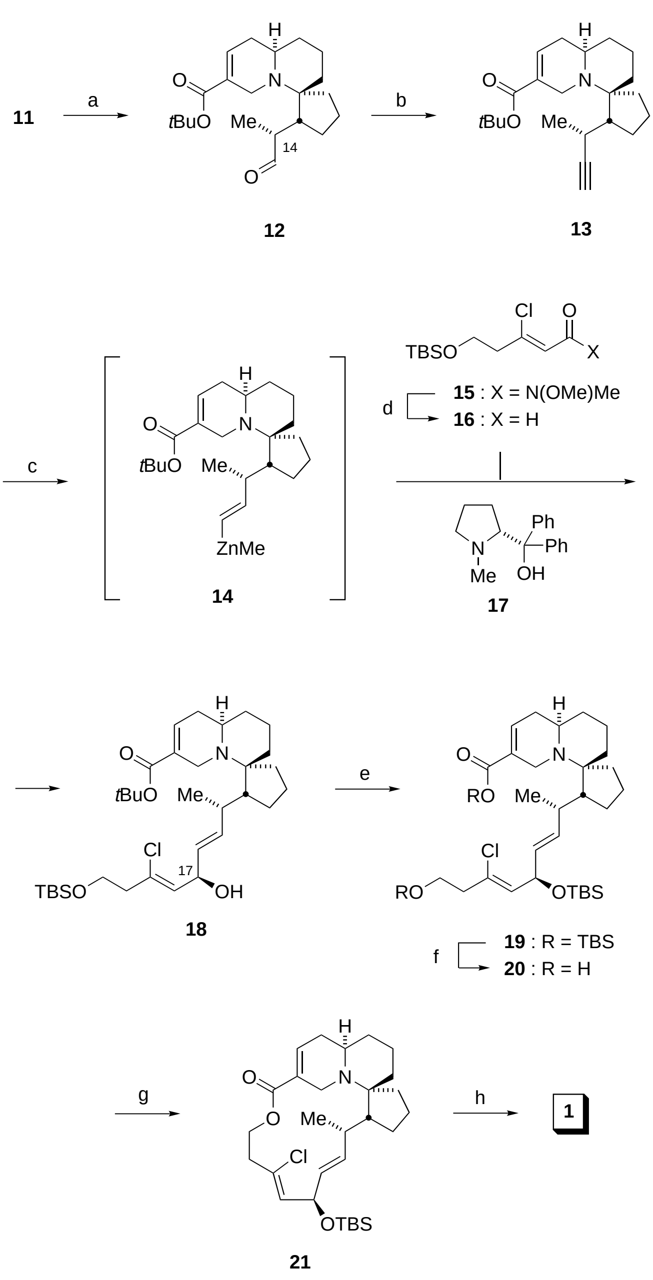
disclosed the basics of our approach to a stereocontrolled synthesis of halichlorine (Scheme 1).[5] The readily prepared Meyers lactam **3**[6] provides a valuable entry to **4**, and thence **5**, by Sakurai methodology. Stereoselective methylation from the convex face of the cuplike structure **5** afforded **6**. This alkylation provided the stereochemical imprint at the future C14 atom following conversion of **6** into **7** as shown. Elongation in a functionally constructive way was much simplified by application of the powerful *B*-alkyl Suzuki method (→**9**) using (*Z*)-iodoacrylate **8** as the coupling partner.[7] The unmasking of the primary amine set the stage for a stereoselective Michael reaction, which resulted in the elaboration of the aza-spirobicyclic core containing the chirality imprints at C5, C9, C13, and C14 appropriate to our target (**9**→**10**). The tetrahydropyridine was constructed from a two carbon atom chain extension of **10** through a crossed Claisen condensation and a Mannich closure using formaldehyde as the linchpin (see asterisk in **11**).



Scheme 1. a) PhMe, Δ (95%); b) allyltrimethylsilane, $TiCl_4$, CH_2Cl_2, −78°C→r.t. (99%); c) Na, NH_3, THF, EtOH, −78°C (92%); d) Boc_2O, DMAP, THF (96%); e) 1. LiHMDS, THF, −40°C; 2. MeI, −78→0°C (90%); f) LiOH, THF, H_2O (89%); g) 1. ClCOOEt, Et_3N, THF; 2. $NaBH_4$, MeOH (82%); h) TBDPSCl, Et_3N, DMAP, CH_2Cl_2 (95%); i) 1. 9-BBN, THF; 2. **8**, [Pd(dppf)Cl_2], $AsPh_3$, Cs_2CO_3, DMF, H_2O; j) 1. TFA, CH_2Cl_2; 2. H_2O, K_2CO_3 (77% overall from **7**); k) *t*BuOAc, LiHMDS, THF, −50°C→r.t. (86%); l) H_2CO, EtOH (73%); m) 1. LiHMDS, THF, 0°C; 2. [$Cp_2Zr(H)Cl$], r.t. (91%); n) HF/pyridine, pyridine, THF (94%). 9-BBN = 9-borabicyclo[3.3.1]nonane; Boc = *tert*-butoxycarbonyl; DMAP = 4-dimethylaminopyridine; dppf = 1,1′-bis(diphenylphosphinyl)ferrocene; HMDS = 1,1,1,3,3,3-hexamethyldisilazane; TBDMSCl = *tert*-butyl dimethyl silyl chloride; TFA = trifluoroacetic acid.

Severe (and unanticipated) difficulties awaited us as we attempted to progress beyond **11** (Scheme 2). The original



Scheme 2. a) TPAP, NMO, MeCN, r.t.; b) $N_2CHP(O)(OMe)_2$, KO*t*Bu, THF, −78°C (57% from **11**); c) 1. [$Cp_2Zr(H)Cl$], CH_2Cl_2; 2. Zn_2Me, heptane, −65°C; 3. **17** (10%), −65→−30°C; 4. **16**, −30°C→r.t. (67% overall, 4:1 mixture in favor of **18**); d) DIBAH, PhMe, CH_2Cl_2, −78°C (82%); e) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78°C→r.t.; f) NH_4F, MeOH, H_2O (66% overall from **18**); g) EDCI, DMAP, DMAP·HCl, $CHCl_3$, THF, Δ (54%); h) HF-pyridine, pyridine, THF (95%). Cp = cyclopentadienyl; DIBAH = diisobutylaluminum hydride; EDCI = 3(3-dimethylaminopropyl)-3-ethylcarbodiimide.

plan called for oxidation of the primary alcohol in **11** to the aldehyde (**12**), which would serve as a platform for mounting carbon atoms 16–21 into place through one of several possible convergent olefinations. Many attempted oxidations to reach **12** from **11** failed, perhaps as a consequence of the proximal tertiary amine. A further complication was the surprising vulnerability of the α-chiral center to partial epimerization. After extensive experimentation, the oxidation could be carried out with tetra-*n*-propyl ammonium perrhuthenate (TPAP) and excess *N*-methylmorpholine *N*-oxide (NMO) in acetonitrile.[8] Compound **12** was used without the benefit of full purification owing to its partial epimerization during silica gel chromatography. Unfortunately, all attempts to conduct variations of the Horner-Wadsworth-Emmons methodologies with **12** were unsuccessful or led to complete racemization at C14.[9] It is once again tempting to attribute this breakdown of seemingly straightforward conventional chemistry to the presence of the proximal tertiary amine. The only reaction conducted on crude **12** that proved to be reasonably efficient and appropriate to progression toward our goal involved the use of the Gilbert reagent[10] to produce alkyne **13** in 57 % overall yield. Less than 5 % epimerization at C14 occurred under the conditions shown.

At this point we were positioned to explore significant extensions of the chemistry laid down by Wipf et al.[11] Hydrozirconation of **13** according to the Schwartz protocol was followed by metal exchange with dimethylzinc. The resultant vinyl zinc species **14** underwent smooth coupling with aldehyde **16**, prepared from the known Weinreb amide **15**,[4a] as shown. This key addition, when conducted in the presence of Soai's chiral amino alcohol **17**,[12] afforded a 4:1 mixture of the desired 17*R* diastereomer **18** and its 17*S* epimer (not shown). In the absence of a chiral additive, the ratio of 17*R*:17*S* was essentially 1:1. Clearly, there is a need and room for optimization of this step. For the present, the 4:1 mixture was advanced without separation of the diastereomers.

Even with the critical coupling accomplished, serious issues remained to be overcome. Deprotection of the *tert*-butyl ester group had to be conducted with circumspection because of the acid sensitivity of the divinylcarbinol moiety. Treatment of **18** with *tert*-butyldimethylsilyl triflate (TBSOTf) generated the corresponding silyl ester of the carboxylic acid while protecting the secondary alcohol (→**19**).[13] Exposure of **19** to ammonium fluoride in aqueous methanol[14] cleaved the silyl groups from the carboxyl and primary alcohol functions while maintaining the valuable protection at the secondary alcohol center (**19**→**20**). Macrolactonization under Keck conditions[15] produced 17-TBS-halichlorine (**21**) in 54 % yield. It was at this stage that the separation of the 17*R* and 17*S* series (8:1 mixture) was carried out. The total synthesis was completed by deprotection at C17 with HF/pyridine to afford synthetic **1**. Comparisons of the ^{1}H NMR, ^{13}C NMR, IR, and mass spectra as well as chromatographic profiles of fully synthetic halichlorine with the corresponding properties of a small specimen sample showed them to be identical.[16] Comparison of the optical rotations of synthetic halichlorine ($[\alpha]^{25}_{D} = +234.9$, $c = 1.04$, MeOH) with that reported for the natural product ($[\alpha]^{25}_{D} = +240.7$, $c = 0.54$, MeOH) further supported the claim of identity. Given the clarity of the assignment of absolute configuration of the synthetic product, the absolute configuration of the material derived from the marine sponge is further documented.

In summary, the total synthesis of (+)-halichlorine has been accomplished. Among the key reactions were the chain extension–Michael sequence (**7**→**10**), the crossed Claisen–intramolecular Mannich sequence (**10**→**11**) and the novel vinyl zirconium→vinyl zinc→allylic alcohol chemistry (**13**→**18**). The application of our strategy to the synthesis of pinnaic acid is being evaluated. However, the main focus of the halichlorine project now shifts to the exploration of important biological issues discussed at the outset using material obtained from this efficient total synthesis.

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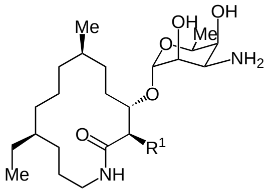
Asymmetric Total Synthesis of Fluvirucinine A_1**

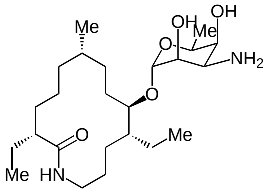
Young-Ger Suh,* Soon-Ai Kim, Jae-Kyung Jung, Dong-Yun Shin, Kyung-Hoon Min, Bon-Am Koo, and Hwa-Soon Kim

Fluvirucins, a class of macrolactam antibiotics produced by actinomycete strains, have attracted considerable attention owing to their interesting structural features and promising biological properties.[1] Fluvirucins A_1 (**1a**) and A_2 (**1b**) are particularly attractive within the fluvirucin A series because of their low toxicity;[2] however, they show less potent antiinfluenza virus activity than fluvirucin B_1 (**2**), a representative of the fluvirucin B series. In addition, none of the members of the fluvirucin A series has been synthesized yet, while two recent syntheses have focused on fluvirucin B_1.[3] We herein report the first, asymmetric total synthesis of fluvirucinine A_1 (**3**; see Scheme 1), an aglycon of fluvirucin A_1, by our unique strategy, which is capable of readily introducing a variety of substituents at all chiral centers.



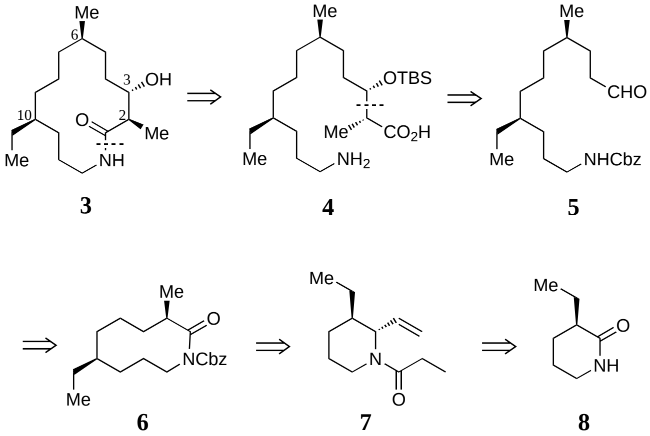
Fluvirucin A_1 $R^1 = CH_3$: **1a**

A_2 $R^1 = CH(OH)CH_3$: **1b**



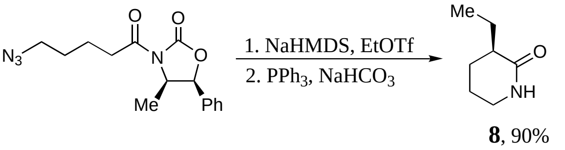
Fluvirucin B_1 **2**

Our approach (Scheme 1) envisions efficient, remote stereocontrol of the C6 stereocenter by a key two-step sequence. The stereoselective vinyl addition to the carbonyl group of lactam **8**, possessing the initially established C10 chiral unit, and the subsequent amide enolate induced aza-Claisen rearrangement[4] of **7** provides the ultimate 1,5-chiral transfer for the C6 chiral unit. Moreover, the chiral centers C2 and C3 are efficiently introduced by the protocol of Evans et al.[5] For the cyclization in the final stage, we employed macrolactamization, which is one of the most attractive processes for the preparation of a 14-membered lactam skeleton, from the viewpoint of synthetic versatility and generality.[6]



Scheme 1. Strategy for the asymmetric total synthesis of fluvirucinine A_1 (**3**). Cbz = benzyloxycarbonyl, TBS = *tert*-butyldimethylsilyl.

Our synthesis was commenced by preparation of the optically active *trans*-2,3-disubstituted piperidine **7**, as a precursor for the aza-Claisen rearrangement, from 3-ethylvalerolactam (**8**), which is readily accessible from 3-azidopentanoyl-4-methyl-5-phenyl-oxazolidinone by a two-step sequence [Eq. (1)].[7] The initial stereogenic center corresponding to C10 of fluvirucinine A_1, which ultimately controls the configuration at C6, is conveniently introduced during the preparation of **8**. For the synthesis of the key lactam intermediate **6**, **8** was protected with benzyl bromide and then efficiently converted into the *trans*-disubstituted piperidine **9** (Scheme 2). After numerous attempts, we developed the direct diastereoselective vinyl addition to the lactam carbonyl group with the assistance of $LiAl(OEt)_3H$,[8] which provides the desired and separable *trans* isomer **9** along with



(1)

8, 90%

$[\alpha]_D^{25} = -64.1$

($c = 2.6$, CH_2Cl_2)

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