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Natural Product Synthesis

A Concise Total Synthesis of (±)-Vigulariol**

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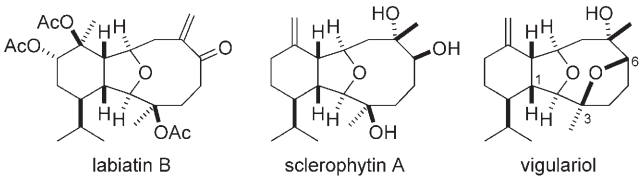
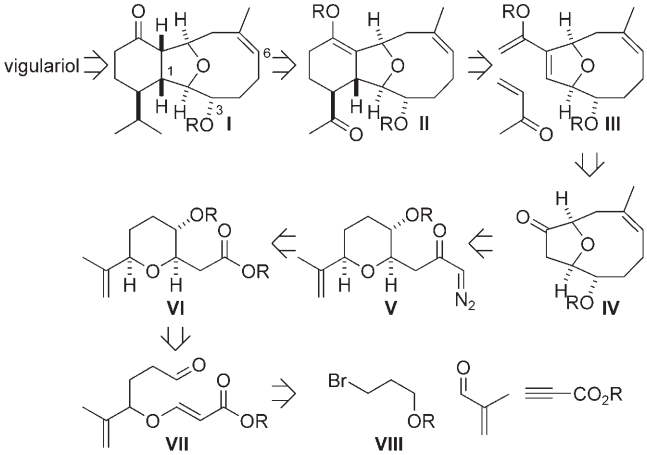
The cladiellins (eunicellins) are the most numerous members of a family of ether-bridged 2,11-cyclized cembranoid marine natural products which also comprises the briarellins, asbestinins, and sarcodictyins.[1] The cladiellins possess substantial and varied biological activities, and some (for example, labiatin B and sclerophytin A; Scheme 1) display cytotoxicity against tumor cells. The structural complexity of these ether-bridged marine natural products as well as their biological activities make them attractive synthetic targets, and in recent years there have been intensive efforts to synthesize these compounds. Several research groups have been engaged in the synthesis of members of this family, which has culminated in the syntheses of deacetoxyalcyonin acetate,[2a–d] cladiell-11-ene-3,6,7-triol,[2c,e] the sclerophytins A and B,[2b,c,e,f] the briarellins E and F,[2g] 11-acetoxy-4-deoxyasbestinin D,[2h] orphirin B, and astrogorgin.[2i,j]



Scheme 1. Representative members of the cladiellin family of marine natural products.

Vigulariol was isolated from the octocoral *Vigularia juncea* (Pallas) by Sheu and co-workers and was found to possess in vitro cytotoxic activity against human-lung adenocarcinoma cells ($IC_{50} = 18$ nM).[3] The natural product possesses an additional ring in comparison to most of the other cladiellins; the tetracyclic ring system contains two ether bridges and is adorned with eight stereocenters. Interestingly, vigulariol was obtained as a side product by Paquette and co-workers during synthetic studies on the sclerophytins A and B, prior to its identification as a natural product, but full characterization was not reported.[2f]

Our retrosynthetic analysis of vigulariol is shown in Scheme 2. Opening of the C3–C6 (cladiellin numbering) ether bridge, replacement of the methylene group with a carbonyl group, deoxygenation, and removal of the C3 methyl group reveals the ketone **I** as a late-stage intermediate in the synthesis. Conversion of the carbonyl group into an enol ether and the isopropyl group into a methyl ketone gives compound **II** as a key intermediate. A Diels–Alder disconnection then reveals the bridged bicyclic diene **III** and methyl vinyl ketone. Conversion of the diene unit into a carbonyl group leads to the ketone **IV**, and this suggests the diazo ketone **V** as a precursor. Removal of the diazo group and ring-opening of the resulting tetrahydropyranyl ester **VI** leads to the aldehyde **VII**. Further disconnection gives the bromide **VIII**, methacrolein, and a simple propiolate ester, which are all commercially available starting materials.



Scheme 2. Retrosynthetic analysis of vigulariol.

The analysis shown in Scheme 2 suggests three important ring-forming reactions that must be performed in a highly stereoselective manner: 1) tetrahydropyran formation by reductive cyclization of an aldehyde onto a β-alkoxy acrylate (**VII**→**VI**), 2) carbenoid generation followed by ylide formation and rearrangement with ring-expansion (**V**→**IV**), and 3) an intermolecular Diels–Alder cycloaddition (**III**→**II**). Construction of the oxabicyclic core system **IV** was the

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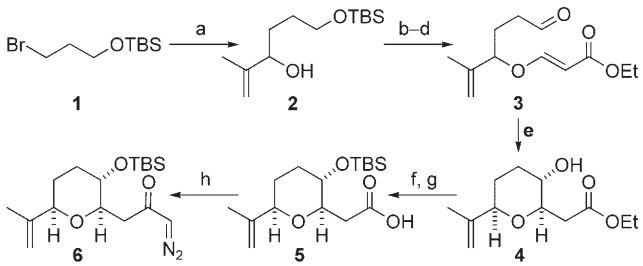
critical transformation and relied on a tandem ylide formation and rearrangement sequence. We have previously used this reaction to prepare the oxabicyclo[5.3.1]undecane systems of neoliacinic acid and labiatin A,[4] but herein we describe the first application of this reaction to the synthesis of the oxabicyclo[6.2.1]undecane system **IV**.

The precursor required for the sequence of carbenoid formation, ylide generation, and sigmatropic rearrangement was prepared by the route shown in Scheme 3. Reaction of

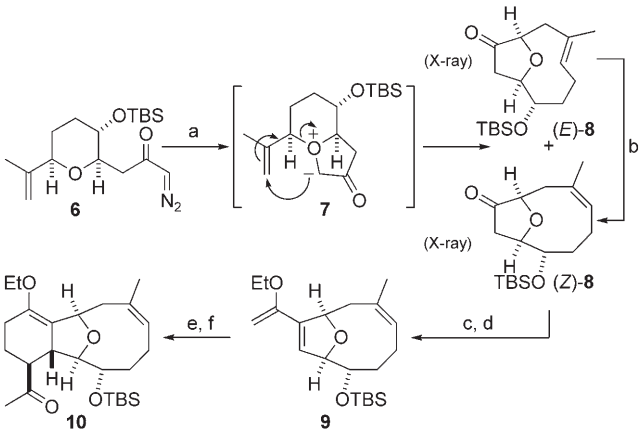


Scheme 3. Synthesis of the diazo ketone **6**. a) Mg, THF, reflux; then methacrolein, RT (90%); b) $HCCCO_2Et$, *N*-methylmorpholine, CH_2Cl_2, RT (91%); c) nBu_4NF, THF, RT (91%); d) $(COCl)_2$, Me_2SO, CH_2Cl_2, −78°C; then Et_3N, RT (83%); e) SmI_2, MeOH, THF, RT (76%); f) TBSCl, imidazole, Me_2NCHO, RT (91%); g) aqueous LiOH, MeOH, RT (82%); h) $iBuO_2CCl$, Et_3N, Et_2O, RT; then CH_2N_2, Et_2O, 0°C→RT (81%). TBS = *tert*-butyldimethylsilyl.

methacrolein with the Grignard reagent prepared from the bromide **1** delivered the allylic alcohol **2**. Alkylation of the hydroxy group with ethyl propiolate[5] to produce a vinylogous carbonate, followed by removal of the TBS group, and Swern oxidation of the resulting alcohol afforded the aldehyde **3**. Reductive cyclization was accomplished by treatment of **3** with freshly prepared SmI_2 in the presence of methanol[6] to furnish the tetrahydropyranol **4** as a single diastereoisomer. The hydroxy group was protected as a TBS ether and cleavage of the ethyl ester furnished the acid **5** in excellent yield. Conversion of the carboxylic acid **5** into an anhydride and subsequent treatment with excess diazomethane delivered the diazo ketone **6** in good yield.

Access to multigram quantities of the diazo ketone **6** by using the route shown in Scheme 3 allowed the key ring-forming reaction in the synthetic sequence to be explored. Treatment of **6** with copper(II) hexafluoroacetylacetonate (5 mol%) produced an electrophilic copper carbenoid that underwent tandem formation and [2,3] sigmatropic rearrangement of the oxonium ylide **7** with a three-carbon ring expansion (Scheme 4).[7] The reaction delivered a 5:1 mixture of the compounds (*Z*)-**8** and (*E*)-**8** in excellent yield. Both alkenes were highly crystalline and X-ray analysis confirmed the relative stereochemical assignment.[8] The relatively strained alkene (*E*)-**8** was converted into the alkene (*Z*)-**8** upon treatment with AIBN and a sub-stoichiometric amount of ethanethiol in benzene at reflux.[4a,b]

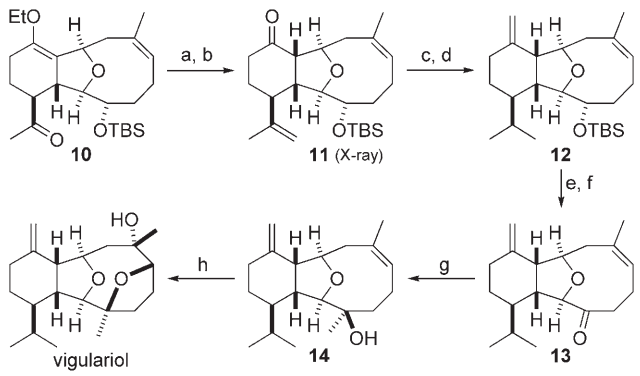
The next stage in the synthetic sequence was construction of the third (cyclohexane) ring by using an intermolecular Diels–Alder reaction (Scheme 4). Diene **9**, required for the cycloaddition reaction, was prepared by using Stille cross-



Scheme 4. Construction of the tricyclic cladiellin skeleton **10**. a) $Cu(CF_3COCHCOCF_3)_2$ (5 mol%), CH_2Cl_2, reflux (96%, 5:1 *Z*/*E*); b) AIBN, EtSH, PhH, reflux (56%); c) $PhN(O_2SCF_3)_2$, $NaN(SiMe_3)_2$, THF, −78°C; d) $CH_2C(OEt)SnBu_3$, LiCl, $[Pd(PPh_3)_4]$, THF, reflux; e) methyl vinyl ketone, PhMe, reflux (67%, 3 steps); f) K_2CO_3, MeOH, RT (87%). AIBN = azobisisobutyronitrile.

coupling[9] of the commercially available tributyl(1-ethoxyvinyl)tin with the enol triflate generated by regioselective deprotonation of the ketone (*Z*)-**8** and immediate trapping of the enolate with *N*-phenyltrifluoromethanesulfonimide. The unstable diene **9** was then subjected to Diels–Alder cycloaddition with methyl vinyl ketone in toluene at reflux. The reaction was both highly regioselective and exhibited high facial diastereoselectivity on the diene, and delivered a 2:1 mixture of *exo* and *endo* diastereoisomers. Treatment of the mixture with potassium carbonate in methanol resulted in epimerization at the stereogenic center adjacent to the carbonyl group to give the required ketone **10** (*exo* adduct) exclusively.

The polycyclic core of vigulariol was essentially complete, but further functionalization was required to conclude the synthesis of the natural product (Scheme 5). Wittig methyl-



Scheme 5. Completion of the synthesis of vigulariol. a) Ph_3PCH_2Br, *t*BuOK, THF, RT (85%); b) 5% aqueous HCl, THF, RT, (86%); c) H_2, PtO_2, RT, 81%; d) Ph_3PCH_2, PhMe, reflux (98%); e) nBu_4NF, THF, RT (84%); f) Dess–Martin periodinane, pyridine, CH_2Cl_2, RT; g) MeMgCl, THF, 0°C (89%, 2 steps); h) *m*-CPBA, CH_2Cl_2, 0°C (69%). *m*-CPBA = *meta*-chloroperoxybenzoic acid.

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enation of the ketone **10** followed by acid hydrolysis of the enol ether delivered the crystalline ketone **11**, whose relative stereochemistry was confirmed by X-ray analysis.[8] Regioselective hydrogenation of the exocyclic alkene of the diene **11** and subsequent ketone methylenation furnished the diene **12**. Removal of the TBS group and oxidation of the resulting alcohol by using the Dess–Martin protocol gave the ketone **13**.[10] Addition of methylmagnesium chloride then produced the tertiary alcohol **14** as a single diastereoisomer, the spectroscopic properties of which corresponded to those reported by Paquette and co-workers.[2f]

To complete the synthesis of vigulariol it was necessary to perform the regioselective and stereoselective alkene epoxidation and subsequent nucleophilic ring-opening of the epoxide with the tertiary hydroxy group. Gratifyingly, this sequence was accomplished in a single operation by treatment of the alkene **14** with freshly purified *m*-CPBA at 0 °C.[11] Thus (±)-vigulariol was obtained in good yield and the spectroscopic properties for the synthetic material corresponded to those reported for the natural product by Sheu and co-workers.[3]

In summary, a concise and highly efficient synthesis of (±)-vigulariol has been completed in a total of 20 steps and with an overall yield of 4.0 % starting from inexpensive and commercially available starting materials. The route is very short for a target of such complexity (4 rings, 8 stereogenic centers) and is very efficient (> 85 % yield for each step). Our synthesis is significantly higher yielding than most, if not all, reported syntheses of the cladiellin natural products, and it is also one of the shortest. The key feature of our synthesis is the use of a copper carbenoid to deliver a bicyclic oxonium ylide which then rearranges to give the oxabicyclo[6.2.1]undecene system **8** in 96 % yield. This is one of the highest yields recorded for a tandem catalytic oxonium ylide generation and rearrangement reaction, and the reaction has not previously been used to prepare this ring system. Other notable transformations in the synthesis include the use of a samarium-mediated cyclization reaction to prepare the key tetrahydropyranyl alcohol (**3**→**4**)[6] and a highly regioselective Diels–Alder cycloaddition (**9**→**10**) to construct the cyclohexane ring.

In the course of the synthesis, seven of the eight stereogenic centers found in vigulariol are introduced in a highly diastereoselective manner relative to the single stereogenic center present in the alcohol **2**. The alcohol (*S*)-**2** has been prepared in a highly enantioselective manner by Williams et al. by using a route in which a Sharpless asymmetric epoxidation reaction was employed to set the configuration of the stereogenic center.[12] Consequently, although we have prepared vigulariol in racemic form, the synthesis would be rendered enantioselective simply by using the enantiomerically enriched alcohol **2** as the starting material.

It should be noted that many other cladiellin natural products could be prepared from the late-stage intermediates **11** and **12**, and therefore our synthesis delineates a novel and entirely general strategy for the construction of this entire class of natural products. The syntheses of other cladiellin natural products from the intermediates **11** and **12** are currently under investigation and the results of these studies will be reported in due course.

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[8] Crystal data for (*E*)-**8**: $C_{17}H_{30}O_3Si$, $M_r = 310.50$, crystal dimensions $0.55 \times 0.36 \times 0.25\ mm^3$, triclinic, space group $P\bar{1}$, $a = 8.1960(9)$, $b = 9.2690(10)$, $c = 12.2514(13)$ Å, $\alpha = 100.492(2)$, $\beta = 100.704(2)$, $\gamma = 95.904(2)°$, $V = 890.19(17)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.158\ Mg\,m^{-3}$, $\mu(Mo_{K\alpha})$ $0.140\ mm^{-1}$, $T = 150(2)$ K; 7654 reflections collected of which 4022 independent, $2\theta_{max} = 55°$. Structure solved by direct methods (SHELXS-97) and refined by full-matrix least squares against F^2 (SHELXTL), $R_1 = 0.046$, $wR_2 = 0.127$, 190 parameters. Crystal data for (*Z*)-**8**: $C_{17}H_{30}O_3Si$, $M_r = 310.50$, crystal dimensions $0.42 \times 0.38 \times 0.36\ mm^3$, monoclinic, space group $P2_1/n$, $a = 10.6859(7)$, $b = 7.8670(6)$, $c = 21.4912(15)$ Å, $\beta = 93.131(1)°$, $V = 1804.0(2)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.143\ Mg\,m^{-3}$, $\mu(Mo_{K\alpha})$ $0.138\ mm^{-1}$, $T = 150(2)$ K; 11219 reflections collected of which 4114 independent, $2\theta_{max} = 55°$. Structure solved by direct methods (SHELXS-97) and refined by full-matrix least squares against F^2 (SHELXTL), $R_1 = 0.046$, $wR_2 = 0.131$, 191 parameters. Crystal data for **11**: $C_{24}H_{40}O_3Si$, $M_r = 404.65$, crystal dimensions $0.55 \times 0.42 \times 0.30\ mm^3$, triclinic, space group $P\bar{1}$, $a = 9.1284(10)$, $b = 9.7964(11)$, $c = 15.784(2)$ Å, $\alpha = 72.185(2)$, $\beta = 77.639(2)$, $\gamma = 63.070(2)°$, $V = 1193.3(2)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.126\ Mg\,m^{-3}$, $\mu(Mo_{K\alpha})$ $0.119\ mm^{-1}$, $T = 150(2)$ K; 8997 reflections collected of which 5153 independent, $2\theta_{max} =$

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55°. Structure solved by direct methods (SHELXS-97) and refined by full-matrix least squares against F^2 (SHELXTL), $R_1 = 0.045$, $wR_2 = 0.131$, 258 parameters. CCDC-621085–621087 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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