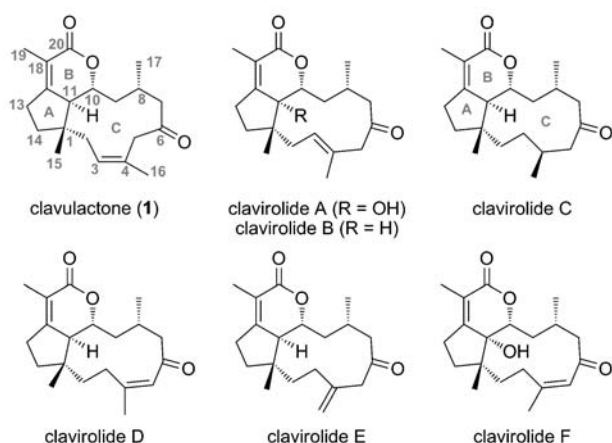


Enantioselective Total Synthesis of Marine Diterpenoid Clavulactone**

Zhen-Yu Yang, Hong-Ze Liao, Kang Sheng, Yong-Fei Chen, and Zhu-Jun Yao*

Dedicated to Dr. Terrence R. Burke Jr. on the occasion of his 60th birthday

Clavulactone (**1**) and clavirolides A–F (Scheme 1) are cytotoxic tricyclic diterpenoids of the dolabellane family, isolated from samples of the Pacific soft coral *Clavularia*

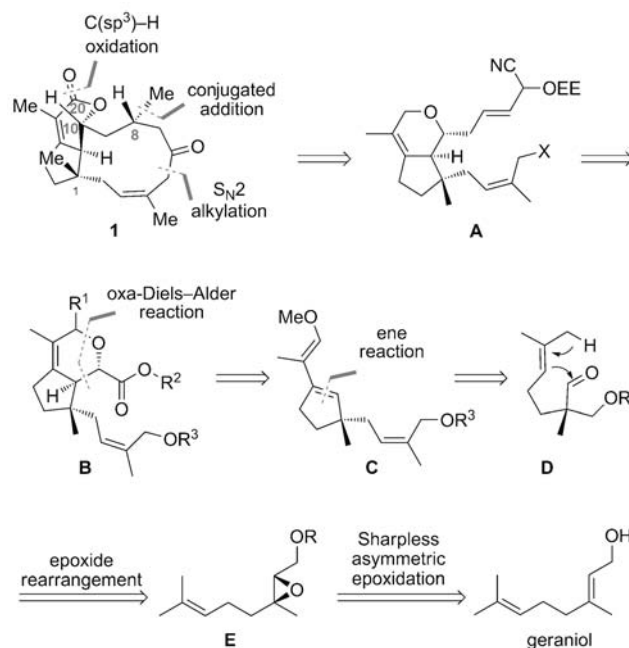


Scheme 1. Clavulactone (**1**) and clavirolides A–F.

viridis, which was collected off the Xisha Islands in the South China Sea.^[1] The unique molecular architecture of these compounds is characterized by a *trans*-bicyclo[9.3.0]-tetradecane core bearing a bridging α,β -unsaturated lactone, four stereogenic centers, including a quaternary carbon center, and a multisubstituted cycloundecanone moiety that has a position-variable C=C bond (except clavirolide C). The limited availability, structural complexity, and biological

activity of these diterpenoids have made them interesting synthetic targets for several research groups.^[2] However, only one total synthesis of clavirolide C has been disclosed to date.^[3] Herein we report the second completed total synthesis for these diterpenoids, the first enantioselective total synthesis of clavulactone.

Compared with the other members of this class of compounds, the existence of an unconjugated *cis*-olefin functionality at the C3/C4 position makes the *trans*-fused cycloundecanone of clavulactone more rigid and less stable. Worried that isomerization of this sensitive olefin functionality might occur under various reaction conditions, we decided to adopt a different strategy for construction of the three rings (A $\rightarrow$ B $\rightarrow$ C, Scheme 1) from that employed in the total synthesis of clavirolide C (A $\rightarrow$ C $\rightarrow$ B).^[3] The early construction of the A/B rings in the synthesis would provide a conformationally favorable intermediate with multiple stereogenic centers established (A, Scheme 2), thus facilitating the crucial closure of the eleven-membered ring. Formation of this medium-sized ring at a later stage in the synthesis could also avoid unwanted side reactions of the *cis*-olefin moiety. Four distinctive protocols were considered in



Scheme 2. Retrosynthetic analysis of clavulactone (**1**). EE = 1-ethoxyethyl.

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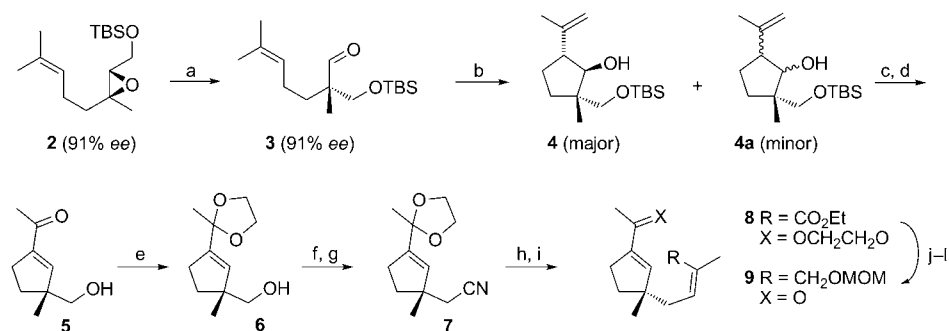
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the construction of the key elements of clavulactone, including 1) synthesis of the fully functionalized cyclopentene fragment, which contains an all-carbon quaternary stereogenic center, by an epoxide rearrangement followed by a carbonyl-ene cyclization; 2) formation of the 3,4-dihydro-2H-pyran fragment by an oxa-Diels-Alder reaction; 3) closure of the eleven-membered ring by an intramolecular S_N2 alkylation, and 4) final generation of the lactone functionality by a chemoselective allylic $C(sp^3)$ -H oxidation. According to the retrosynthetic analysis, the total synthesis of clavulactone could be started from geraniol, an economic and commercially available material.

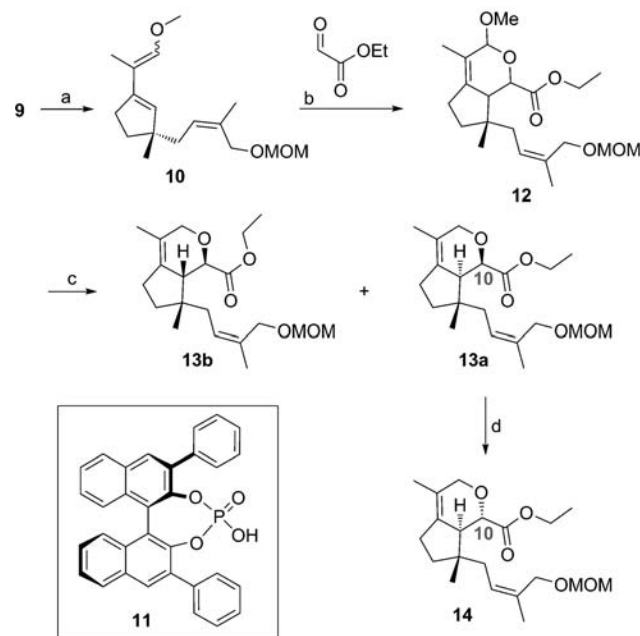
Our synthesis started from the known enantiopure epoxide **2**, which could be easily prepared by the Sharpless asymmetric epoxidation of geraniol (Scheme 3).^[4] Epoxide rearrangement of **2** was smoothly carried out under Yamamoto's conditions,^[5] providing the quaternary carbon center containing aldehyde **3** (96% yield, $[\alpha]_D^{22}=6.26$ ($c=1.0$, $CHCl_3$, 91% ee by HPLC); Ref. [5] $[\alpha]_D^{24}=6.45$ ($c=1.0$, $CHCl_3$)). To achieve a scalable intramolecular carbonyl-ene cyclization, a number of Lewis acids were screened. Unexpectedly, we found that SmI_2 performed as a highly efficient catalyst in the conversion of **3** into the *trans*-cyclopentanol **4** (major product)^[6] and its stereoisomers **4a** (minor products, <10%) on a 17 gram scale. It is noteworthy that few applications of Sm^{III} have been reported, and this is the first example of a Sm^{III} -salt-catalyzed ene reaction. Oxidative cleavage of the *exo*-olefin functionality of **4** and **4a** (mixture) with K_2OsO_4 (catalyst) and $NaIO_4$ ^[7] followed by treatment with aqueous HCl (6M) in THF provided **5** as the single product (70%, 2 steps). Protection of the ketone carbonyl group of **5** afforded the corresponding *O,O'*-acetal **6** (82%), which was further subjected to mesylation and cyanide substitution to give nitrile **7** (78%, 2 steps). Reduction of nitrile **7** with DIBAL-H (1.0 equiv) in dichloromethane at $-78^\circ C$ followed by Horner-Emmons reaction with $(PhO)_2P(O)CH(CH_3)CO_2Et$ in THF using NaH as the base afforded α,β -unsaturated ester **8** (80%, 2 steps) with 100% *Z* selectivity on a 5 gram scale.^[8,9] Ester **8** was again reduced with excess DIBAL-H in dichloromethane to afford the desired allylic alcohol, which was further converted into the enone **9** (75%, 3 steps) by protection with MOMCl and selective *O,O'*-acetal deprotection under mild acidic conditions.

Wittig olefination of enone **9** with methoxymethyltriphenylphosphonium chloride in the presence of *t*BuOK was accomplished at $-20^\circ C$ in THF, and afforded the corresponding dienes **10** (85%, Scheme 4). Formation of the 3,4-dihydro-



Scheme 3. Enantioselective synthesis of functionalized cyclopentene. a) Yamamoto epoxide rearrangement (Ref. [5]), 96%; b) $[SmI_2](THF)_{3.5}$ (5 mol %), CH_2Cl_2 , RT, 91% (17 g scale); c) $NaIO_4$, K_2OsO_4 (cat.), 2,6-lutidine, $tBuOH/H_2O$ (3:1); d) HCl (6M)/THF (1:1), 70% (2 steps); e) $HC(OEt)_3$, $BF_3 \cdot Et_2O$, $(CH_2OH)_2$, CH_2Cl_2 , $-78^\circ C$, 82%; f) $MsCl$, Et_3N , CH_2Cl_2 ; g) $NaCN$, HMPA, $90^\circ C$, 78% (2 steps); h) DIBAL-H, CH_2Cl_2 , $-78^\circ C$; i) NaH , THF, $-78^\circ C$, $(PhO)_2P(O)CH(CH_3)CO_2Et$, 80% (2 steps; 5 g scale, *Z* only); j) DIBAL-H, CH_2Cl_2 , $0^\circ C$; k) MOMCl, DIEA, CH_2Cl_2 , l) PPTS (cat.), acetone/ H_2O (5:1), 80% (3 steps). $MsCl$ = methanesulfonyl, HMPA = hexamethylphosphoramide, DIBAL-H = diisobutylaluminum hydride, THF = tetrahydrofuran, MOM = methoxymethyl, DIEA = *N,N*-diisopropylethylamine, PPTS = pyridinium *p*-toluenesulfonate.

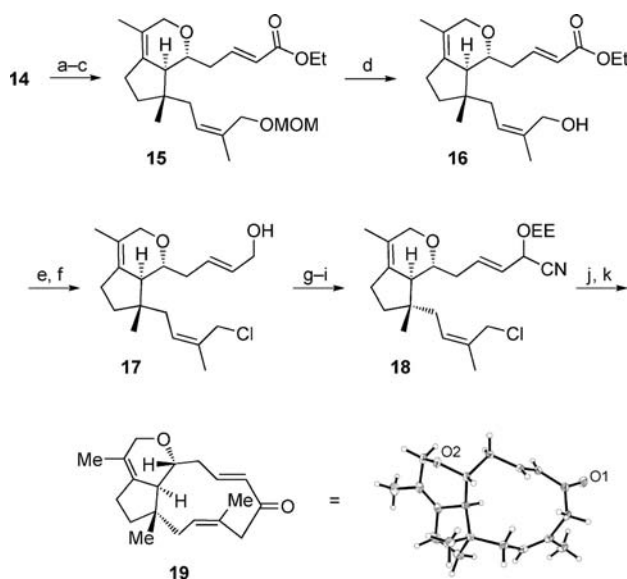
2H-pyran ring was carried out with a chiral phosphoric acid promoted *anti*-diastereoselective hetero-Diels-Alder reaction.^[10,11] Exposure of an *E/Z* mixture of diene **10** and ethyl glyoxylate to chiral phosphoric acid **11** (10 mol %) in toluene in the presence of 4 Å molecular sieves gave the adducts **12** (70%), the anomeric methoxy group of which was immediately reduced with Et_3SiH in the presence of $BF_3 \cdot OEt_2$ to afford a mixture of stable compounds **13a** (major product)



Scheme 4. Construction of the six-membered ring through an organo-catalyzed oxa-Diels-Alder reaction. a) Ph_3PClCH_2OMe , $tBuOK$, THF, $-20^\circ C$, 85%; b) 4 Å M.S., **11** (10 mol %), $PhMe$, 70%, d.r. = 3:1 (**13a**:**13b**); c) $BF_3 \cdot Et_2O$, Et_3SiH , $-78^\circ C$, 84%; d) $NaHMDS$, THF, $-78 \rightarrow 0^\circ C$, 98%.

and **13b** (minor product) in a ratio of 3:1.^[12] Fortunately, reversal of the stereochemistry at C10 of **13a** to obtain desired compound **14** was realized nearly quantitatively (98 %) by treatment with NaHMDS (2 equiv). The bicyclic intermediate **14** is characterized by the highly constrained spatial conformation of its two side chains, which are positioned so that the closure of the eleven-membered ring is favored.

Conversion of ester **14** into the corresponding aldehyde with DIBAL-H followed by treatment with methoxymethyl-triphenylphosphorane and NaHMDS gave the homologated enol ether, which was further hydrolyzed (to afford the aldehyde) and continuously subjected to Horner–Emmons olefination conditions with (EtO)₂P(O)CH₂CO₂Et and NaHMDS in order to give α,β -unsaturated ester **15** (Scheme 5). The stereochemistry of **15** was determined by

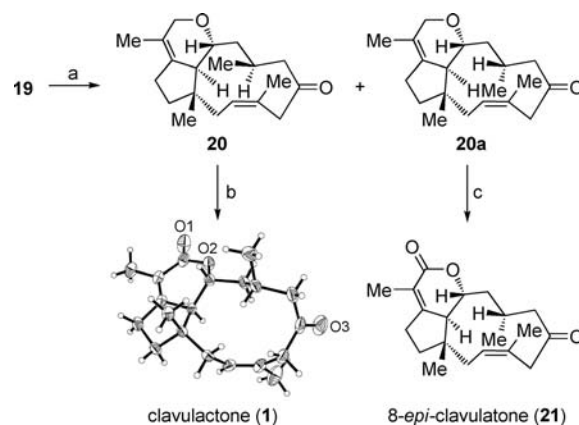


Scheme 5. Closure of the eleven-membered ring with an intramolecular S_N2 reaction. a) DIBAL-H, CH₂Cl₂, –78 °C; b) Ph₃PCH₂OMeCl, NaHMDS, 0 °C, THF, then TsOH·H₂O, acetone/H₂O (10:1); c) NaHMDS, THF, POCH(CH₃)COOEt, 78 °C (3 steps); d) HCl (6 M), THF, 0 °C → RT, 90%; e) MsCl, LiCl, Et₃N, DMF/CH₂Cl₂; f) DIBAL-H, CH₂Cl₂, 0 °C, 95% (2 steps); g) DMP, NaHCO₃; h) TMSCN, [18]crown-6, KF, CH₂Cl₂, then HCl (1 M)/THF; i) PPTS, vinyl ethyl ether, CH₂Cl₂, 85% (3 steps); j) NaHMDS, THF, 40 °C; k) PPTS (cat.), MeOH/H₂O; then NaOH (2%), Et₂O, 71% (2 steps). Thermal ellipsoids in crystal structure at 50% probability. NaHMDS = sodium hexamethyldisiazide, Ts = *p*-toluenesulfonyl, DMF = *N,N'*-dimethylformamide, DMP = Dess–Martin periodinane, TMS = trimethylsilyl.

NOESY experiments. Removal of the MOM protection group of **15** with aqueous HCl (6 M) in THF gave primary alcohol **16**, which was then transformed into the stable allylic chloride by reaction with MsCl in the presence of LiCl, before the ester was reduced with DIBAL-H. Further elaboration of the resulting allylic alcohol **17** (oxidation by Dess–Martin periodinane, cyanohydration, and conversion of OTMS to the more stable OEE protecting group) gave immediate precursor **18** for the crucial cyclization of the eleven-membered ring. As expected, the intramolecular S_N2 alkylation of the conformation-constrained precursor **18** was smoothly accom-

plished in the presence of NaHMDS under highly diluted conditions.^[13] Subsequent release of the ketone functionality led to the tricyclic skeleton **19** (71 %, 2 steps), the structure of which was confirmed by X-ray crystallographic analysis.

Final conversion of tricyclic enone **19** to clavulactone (Scheme 6) included the Michael addition of Me₂CuLi·LiCN to enone **19** at 10–15 °C, and led to ketones **20** and **20a** with



Scheme 6. Completion of the total synthesis of clavulactone (**1**) and 8-*epi*-clavulactone (**21**). a) CuCN, MeLi, THF, 1) 5 → 10 °C, 90%, d.r. ≈ 5:1 (**21:21a**), 2) 10 → 15 °C, 84%, d.r. > 20:1 (**21:21a**); b) PCC, PhH, reflux, 4 Å M.S., 60%; c) PCC, PhH, reflux, 4 Å M.S., 56%. Thermal ellipsoids in crystal structure at 50% probability. PCC = pyridinium chlorochromate.

high diastereoselectivity (> 20:1).^[14] After considerable experimentation, the PCC-mediated chemoselective allylic C(sp³)–H oxidation in dry benzene (in the presence of 4 Å molecular sieves) proved to be the best procedure for the final lactonization of **20** and **20a** to afford clavulactone (**1**, 60%) and 8-*epi*-clavulactone (**21**, 56%), respectively. The structure of **1** was determined by NMR spectroscopic methods and further confirmed by X-ray crystallographic analysis. The physical properties of the synthetically obtained sample of clavulactone matched those reported for the naturally occurring material (synthetic: $[\alpha]_D^{26} = -214.6$ ($c = 0.037$, MeOH); Ref. [1 d] $[\alpha]_D^{26} = -232$ ($c = 0.031$, MeOH)).^[15]

It is noteworthy that the late-stage oxidation of the C(sp³)–H functionality represents a strategic advantage, because it successfully circumvented the need for extraneous protecting groups and additional redox manipulations, and avoided side reactions of the sensitive trisubstituted *cis* olefin at the C3/C4 position (a thermodynamically unstable β,γ -unsaturated ketone moiety) during the synthesis. In addition, 8-*epi*-clavulactone (**21**) showed significant differences in its NMR chemical shifts from those of clavulactone (**1**), although only the methyl group at C8 is epimerized. This difference indicates that the conformation of the medium-sized ring of these diterpenoids is considerably sensitive to small changes in their structures. Such information should be very useful for future research regarding the use of these cytotoxic diterpenoids in medicinal chemistry. The conjugated addition to unsaturated ketone **19** employed in this synthesis could

provide an excellent platform for potential biologically interesting modifications at C8 of clavulactone.

In summary, the enantioselective total synthesis of clavulactone has been accomplished in 29 steps (the longest linear sequence from known epoxide **2**) in 1.9% overall yield. Features of this synthesis include formation of the enantiopure cyclopentane precursor by an epoxide rearrangement and a scalable SmI_2 -catalyzed intramolecular carbonyl-ene reaction, construction of the 3,4-dihydro-2*H*-pyran ring by an organocatalyzed intermolecular hetero-Diels-Alder reaction, closure of the eleven-membered ring by an intramolecular $\text{S}_{\text{N}}2$ alkylation with a conformation-constrained precursor, and finally generation of the lactone functionality by a chemoselective allylic $\text{C}(\text{sp}^3)\text{-H}$ oxidation. We expect that the reported synthetic strategy and methods will be applied to the synthesis of other diterpenoids in this family.

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- [14] When the reaction temperature was set at 0°C or lower, the diastereomeric ratio of products **20** and **20a** became poorer ($\approx 1.5:1$).
- [15] The optical rotation of the synthetic sample of clavulactone measured in chloroform ($[\alpha]_{\text{D}}^{26} = -221.5$ ($c = 0.105$, CHCl_3)) is different from that reported in Ref. [1a] ($[\alpha]_{\text{D}}^{30} = -32.3$ ($c = 1.81$, CH_2Cl_2)), while its optical rotation in MeOH matched that reported in Ref. [1d] (see main text).