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General synthetic approach to bicyclo[9.3.0]tetradecenone: a versatile intermediate to clavulactone and clavirolides

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Abstract—An efficient and stereoselective approach to the bicyclo[9.3.0]tetradecenone core structure of clavulactone starting from readily and abundantly available 2-methyl-1,3-cyclopentandione employing microbial desymmetrization and cyanohydrin alkylation as the key steps is described. The synthetic route described herein is applicable to the syntheses of the core structures of Clavirolides A–F.

Since the first structure elucidation some 30 years ago, dolabellanes have become one of the principal groups among the wide array of diterpenoids.[1] Dolabellanes are obtained mainly from marine sources and characterized as an unusual *trans*-bicyclo[9.3.0]tetradecane nucleus decorated with one angular methyl group. Of considerable interest are the findings that many dolabellanes exhibit pharmacologically important effects.[1f,2c] They are also biogenetic and chemical precursors of fusicoccanes, dolastanes, neodolabellanes, and recently revealed guanacastepens.[1f,2] These features have rendered the dolabellanes irresistible to the synthetic community.[1f,2c,3] Clavulactone and clavirolides A–F are novel tricyclic diterpenoids of the dolabellane family isolated from the Pacific soft coral *Clavularia viridis* collected off the Xisha Islands in South China Sea (Fig. 1).[4]

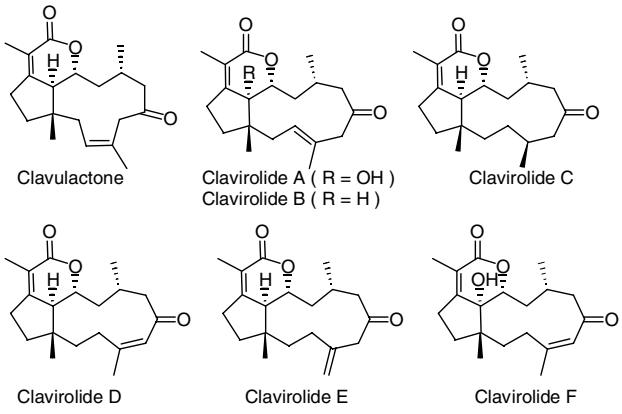

Figure 1. Clavulactone and clavirolides.

Clavulactone and clavirolides A–F possess interesting and diverse biological activities,[4b] including cytotoxicity toward carcinoma cells, blockage of Ca^{+} channels, negative inotropic activity as well as bradycardia effect. The unusual *trans*-bicyclo[9.3.0]tetradecane framework, biological significance, as well as limited availability of these compounds have rendered them interesting targets for synthetic laboratories.[5] We herein disclose a stereoselective approach to the bicyclo[9.3.0]tetradecenone core structure of clavulactone, the most prominent member of this class of compounds.

In view of the lability of the six-membered α,β-unsaturated lactone moiety, clavulactone could be retrosynthetically reduced to the properly functionalized bicyclo[9.3.0] tetradecenone **1** with chemically differentiated olefins. Enone **1** could be visualized from the coupling/macrocyclization sequence of segment **2** and the known aldehyde **3** (Scheme 1).

In our approach to segment **2**, a reliable and efficient method was explored to construct the desired asymmetric quaternary carbon center[6] as well as a proper functionalization on the five-membered ring part. The sequence of reactions was outlined in Scheme 2. Our establishment of the five-membered ring with quaternary carbon center took advantage of the literature

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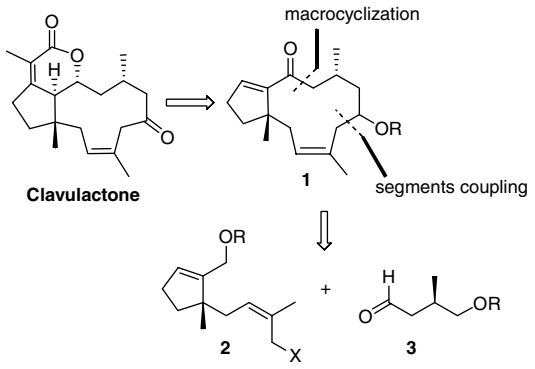
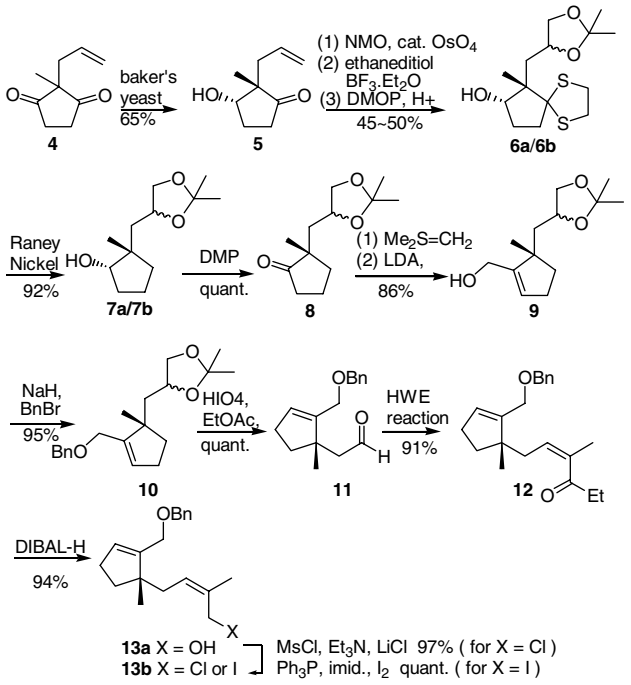


Scheme 1. Retrosynthetic analysis of clavulactone.



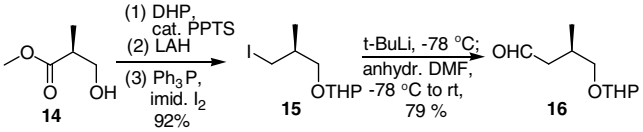
Scheme 2. Synthesis of allylic halide **13b**.

precedence[7] so that the readily available prochiral diketone **4** was desymmetrized through microbial reduction to provide keto alcohol **5** with consistent >99% ee value. To the best of our knowledge, keto alcohol **5** was never employed in syntheses of complex molecules, partly due to the inconvenience of removal of the hydroxy or carbonyl group from the cycle suffering from their bulky neighboring quaternary center. In fact, our initial attempts to reduce the carbonyl group in **5** or its various hydroxy protected versions employing Clemmensen reduction[8] or Wolff–Kishner reduction (Huang–Minlon modification)[9] was abortive. Eventually, **5** was successfully transformed to a separable mixture of **6a/6b** through sequential dihydroxylation of the terminal olefin, protection of the carbonyl group, and protection of the dihydroxy group in good overall yield. Subsequent desulfurization of **6a/6b** with Raney nickel[10] afforded **7a/7b** in excellent yield. Since the stereochemistry of the newly generated tethered stereogenic centers in **7a/7b** was of no significance and would be extinguished later, **7a/7b** was oxidized with Dess–Martin periodinane to give ketone **8** in nearly quantitative yield. A convenient four-step procedure was then carried out to furnish the key aldehyde **11**. Treatment of **8** with $Me_3S^+I^-$/NaH produced the epoxide,[11] which, upon exposure to LDA, rearranged[12] to the allylic alcohol **9** in satisfactory yield. Subsequent protection of the hydroxy group followed by cleavage of the protected dihydroxy group converted **9** to aldehyde **11**, which underwent smooth Horner–Emmons reaction[13] with $(PhO)_2P(O)CH(CH_3)CO_2Et$/NaH to deliver the (*Z*)-favored α,β-unsaturated ester **12** along with trace of its (*E*)-isomer. It is worthy of note that the (*E*)-isomer, which should be utilizable in syntheses of clavirolides, could be obtained as the major product when the corresponding Wittig reagent ($Ph_3P{=}C(CH_3)CO_2Et$) was applied in the olefination.[14] Ester **12** was then reduced with DIBAL-H to afford the desired allylic alcohol **13a**, which was subsequently converted to the halide **13b**. The geometry of the tethered double bond in **13a** remained intact in terms of its spectral data.

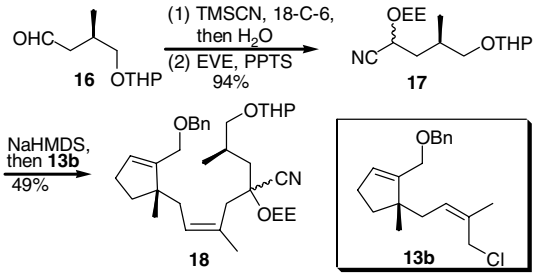
With segment **2** in hand, we turned our attention to the procurement of aldehyde **3**. From the commercially available chiron, methyl (*S*)-3-hydroxy-2-methylpropionate (**14**), segment **C** was efficiently achieved in four steps. By the known sequence,[15] **14** was transformed to iodide **15** in excellent yield. Then, **15** was treated with *t*-BuLi at −78 °C to effect halogen–lithium exchange followed by quenching with anhydrous DMF to furnish the aldehyde **16** as a mixture of the THP acetals in rather good yield (Scheme 3).

Initially, we attempted to accomplish the coupling of **13b** and **16** in the following sequence: conversion of iodide **13b** to the allyl carbanion followed by the addition to aldehyde **16** to deliver a homoallylic alcohol. Hence, we attempted to lithiate **13b** (X = I) with *n*-BuLi or *t*-BuLi at −78 °C followed by an addition of **16**, which to our disappointment resulted in a complex mixture. This could be ascribed to the possible decomposition of the labile allyl benzyl ether moiety. Thus, an alternative pathway was entailed to circumvent these disadvantages and difficulties.

Protected cyanohydrin alkylation proved to be an effective method in connecting two segments and was well applied in total synthesis of natural products.[16] Thus, aldehyde **16** was treated with TMSCN to give the TMS protected cyanohydrin followed by manipulation into its EE protected version **17** as a mixture of eight possible diastereomers. Coupling between substrates **17** and **13b** (X = Cl) was successfully realized in the presence of NaHMDS affording mixture **18** in good yield. The configuration of the tethered trisubstituted alkene



Scheme 3. Synthesis of aldehyde **16**.



Scheme 4. Segments coupling.

in **18** was confirmed by its spectral data. And in this reaction, neither the regioisomer nor the stereoisomer of the tethered double bond was detected (Scheme 4).

After successful assembly of the two segments, the following task was to achieve the annulation of the 11-membered carbocycle. Protected cyanohydrin alkylation also proved to be an excellent tool in cyclizing carbocycles of various sizes, including those constrained rings of medium sizes,[17] so we were to employ it in our synthesis again.

As shown in Scheme 5, concomitant deprotection of the two hydroxy groups in compound **18** gave a mixture of diol **19**, of which the primary hydroxy group was then selectively silylated followed by basic elimination of HCN to afford the unstable β,γ-unsaturated ketone **20** as a single isomer. Treatment of **20** with $NaBH_4$ followed by protection of the alcohol with MOMCl gave mixture **21**, which was further converted into α,β-unsaturated aldehyde **22** as two diastereomers through successive removal of the benzyl group and oxidation of the corresponding deprotected allylic alcohol. Enal **22** was then elaborated into the protected cyanohydrin followed by desilylation to furnish alcohol **23** as a mixture of eight possible diastereomers. Iodation of alcohol **23** afforded the proper substrate for macrocyclic alkylation, which proceeded smoothly in the presence of LiHMDS under high dilution condition. Subsequent release of the ketone function led to the formation of the desired bicyclo[9.3.0]tetradecenone, as a 4:1 mixture of the MOM protected hydroxy group. The major component was determined as **24** through analysis of its data including ^1H, ^{13}C, ESI, HRESI, COSY, NOESY, HMQC, and HMBC.[18]

In summary, we have developed a very efficient approach for the bicyclo[9.3.0]tetradecenone core structure of the novel diterpene Clavulactone starting from the readily and abundantly available 2-methyl-1,3-cyclopentandione by employing microbial desymmetritization and cyanohydrin alkylation as the key steps. The synthetic route devised is efficient and convergent, and should be readily adapted for the syntheses of clavirolides A–F. The focus of future investigations will lie in the incorporation of the six-membered α,β-unsaturated lactone moiety into the framework. Studies are currently well underway in our laboratories and will be reported in due course.

Acknowledgments

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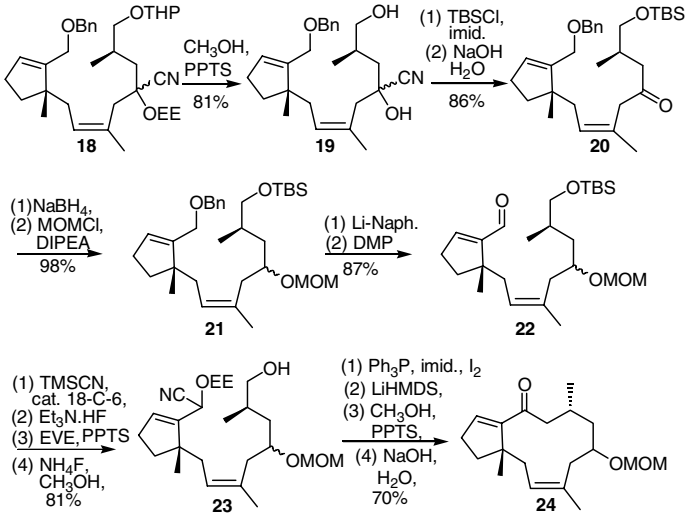

Scheme 5. Synthesis of bicyclo[9.3.0]tetradecenone **24**.

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18. Characteristic data of compound **24**: $[\alpha]_D^{20}$ +82.8 (*c* 0.625, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 6.66 (br, 1H), 5.29 (dd, 1H, $J_1 = 11.4$ Hz, $J_2 = 5.8$ Hz), 4.61 (AB, 2H, $J = 7.4$ Hz, $J = 6.8$ Hz), 3.90 (m, 1H), 3.35 (s, 3H), 2.83 (d, 1H, $J = 11.4$ Hz), 2.80 (d, 1H, $J = 11.5$ Hz), 2.48–2.25 (m, 3H), 2.15 (m, 1H), 2.00 (d, 1H, $J = 11.9$ Hz), 1.85–1.55 (m, 3H), 1.64 (s, 3H), 1.49 (m, 2H), 1.38 (s, 3H), 1.095 (d, 3H, $J = 6.85$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.33, 150.82, 145.89, 134.34, 124.60, 94.64, 73.29, 55.29, 50.94, 47.69, 37.21, 36.72, 34.94, 31.23, 28.58, 27.97, 26.20, 24.34; ESI-MS (*m*/*z*): 345.1 ($[M+K]^+$), 329.2 ($[M+Na]^+$), 307.2 ($[M+H]^+$); HRMS(ESI) *m*/*z* calcd for $[C_{19}H_{30}O_3Na]^+$: 329.2087; found: 329.2079; IR(film): 2952, 2928, 1653, 1608, 1449, 1149, 1098, 1042 cm^{-1}.