Asymmetric Total Synthesis of Pseudoplexaurol and 14-Deoxycrassin, two Antitumor Marine Cembrane Diterpenoids

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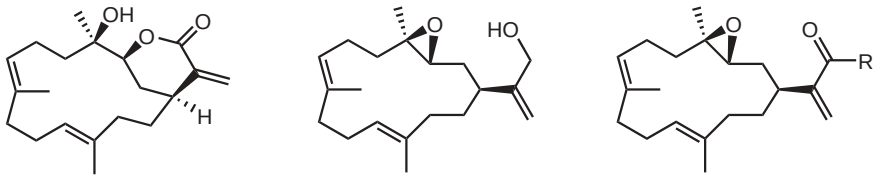
Abstract: The first asymmetric total synthesis of two naturally occurring antitumor pseudoplexaurol and 14-deoxycrassin were achieved via two convergent synthetic sequences featured a chiral pool protocol to implement C-1 stereogenic center and Ti(0)-mediated cyclization leading to cembrane ring.

Key words: 14-deoxycrassin, diterpenoids, cembranoids, total synthesis

Cembrane diterpenoids belong to a family of natural products possessing a characteristic 14-membered carbocyclic ring skeleta.[1] Although cembranes were found in insects, animals and various terrestrial plants (i.e. pine trees and tobaccos), marine invertebrates have proven to be a rich source of this type of diterpenoids,[2] which have emerged as a unique class of structurally diverse and complex marine natural products. A number of highly oxygenated cembrane diterpenoids with variety of functionalities and intriguing biological and physiological activities have been discovered from tropical or subtropical marine invertebrates.[2] Considerable efforts have been devoted to the chemical synthesis of cembranolides in the past decades.[3]

14-Deoxycrassin (**1**) and pseudoplexaurol (**2**), two novel crassin-like cembrenoids, were first isolated from the Caribbean gorgonian *Pseudoplexaura porosa* by Rodríguez and Martínez in 1993. Although the chemical structure of **1** and **2** were characterized on the basis of spectral data and chemical degradation, the relative as well as the absolute configurations of three stereogenic centers (C-1, C-3 and C-4) were postulated biogenetically as shown (Figure 1) and remained to be assigned unambiguously. Both of **2** and **1** have been shown to exhibit significant cytotoxic antitumor activities against several human tumor cell lines.[4] Pseudoplexaural (**3**)[5] and pseudoplexauric acid methyl ester (**4**)[6] have also been found in other Caribbean marine species *Eunicea succinea* (sea wip) and gorgonian *Eunicea mammosa* respectively, and their structures were determined by spectroscopic analysis and chemical correlation[5,6] with natural pseudoplexaurol (**2**). Epoxy alcohol **2** was assumed to be a logical biosynthetic precursor of **1**,[4,6] but attempted synthetic conversion of epoxy alcohol **2** to lactone **1** via pseudoplexauric acid intermediate have failed. A recent successful translactonization of euniolide to crassin reported by Rodríguez and co-workers[7] by aqueous alkaline hydrolysis under the assistance of sonication implies a possible conversion of **2** to **1**. Synthetic studies on the closely related natural cembranolides bearing a 3,4-epoxy and/or lactone functions, such as crassin, euniolide and isolobophytolide, have been conducted over the past decades by several groups.[8] Total syntheses of **1** and **2** have not been reported so far.

In continuation of our ongoing program on the stereoselective synthesis of marine cembranes, we disclose herein the results on the asymmetric synthetic studies of **1** and **2** in view of verifying their structural relationship and confirming the relative and absolute configurations accordingly. The overall strategic plan involves (1) chemical conversion of epoxy alcohol **2** to lactone **1** via an intramolecular lactonization, (2)



14-Deoxycrassin (**1**) Pseudoplexaurol (**2**) Pseudoplexaural (**3**, R = H) Pseudoplexauric acid methyl ester (**4**, R = OMe)

Figure 1 Chemical structures of 14-deoxycrassin (**1**), pseudoplexaurol (**2**) and other structurally related natural cembranolides.

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construction of the 14-membered cembrane ring with geometrically defined double bonds and substituents, (3) implementation of C-1 stereogenic center via a readily available chiral pool [i.e. (*S*)-limonene], and (4) introduction of chiral epoxide function via Sharpless asymmetric epoxidation of corresponding macrocyclic allylic alcohol intermediates. The key reaction we employed for the effective construction of the 14-membered carbocyclic ring includes the low-valent titanium-mediated macrocyclization which is either an intramolecular pinacol-type or olefination coupling (McMurry coupling of dicarbonyl compounds).[9] The synthetic strategy along those lines have been demonstrated in our recent total asymmetric synthesis of several natural epoxy cembrenoids.[10]

Shown in this poster is the mode of McMurry coupling leading to the cembrane ring system and chiral pool protocol to set the C-1 stereogenic center. As shown in Scheme 1, the strategy (Scheme 3) devised a ring closure at C-11, 12 by McMurry coupling leading to a double bond and Sharpless asymmetric epoxidation of allylic alcohol **5** to install the 3,4-epoxy function. Cyclization precursor **6** was constructed by Horner–Emmons coupling of fragments **8**[10a] and **9** prepared readily as shown (Scheme 2). The synthetic sequence was outlined in Scheme 3. Corresponding keto aldehyde ester derivative of intermediate **7** synthesized by selective removal of THP and Swern oxidation was found to be reluctant for the proposed Ti(0)-mediated McMurry coupling and to give low yield of the cyclization product. Reduction of methyl ester and protection of hydroxy group and subsequent Swern oxidation furnished **6** in good overall yield. Cyclization of keto aldehyde **6** was effected by $TiCl_4$–Zn system in DME under reflux condition to give cyclized product **11** in 69% yield, which was desilylated selectively under mild acidic condition and the resulting allylic alcohol was epoxidized by standard Sharpless epoxidation condition with L-(+)-DET as chiral mediator to afford the desired epoxy alcohol **12**. Standard iodination of **12** followed by reductive dehalogenation as described previously gave the 3,4-epoxy alcohol **13** in 87% yield, which was desilylated to produce the pseudoplexaurol (**2**).[11] Finally, the proposed synthetic conversion of epoxy alcohol **2** to lactone **1** was detailed in Scheme 4, which involved (1) MnO_2 oxidation to form aldehyde derivative **3**, (2) Corey oxidative esterification[12] leading to methyl ester **4**, and (3) $ZnCl_2$-catalyzed lactonization with inversion of configuration at C-3 to produce the desired 14-deoxycrassin (**1**).[13] The identity of synthetic **1** was confirmed to be natural **1** by spectroscopic comparison as well as the optical rotation value. We are currently working on the optimization of this synthetic route and determination of the relative and absolute configurations of C-3 and C-4 unambiguously by NOE experiment of **1** bearing a *S*-configurated C-1 carbon.

In summary, first asymmetric total synthesis of two naturally occurring antitumor cembranolides **1** and **2** were achieved via two convergent synthetic sequences featured a chiral pool protocol to implement C-1 stereogenic center and Ti(0)-mediated cyclization leading to cembrane ring. Chemical conversion of pseudoplexaurol (**2**) to 14-deoxycrassin (**1**) was realized by a Lewis acid-catalyzed lactonization process, which will provide a direct means for the determination of the relative and absolute stereochemistry of both of **2** and **1**.

Acknowledgment

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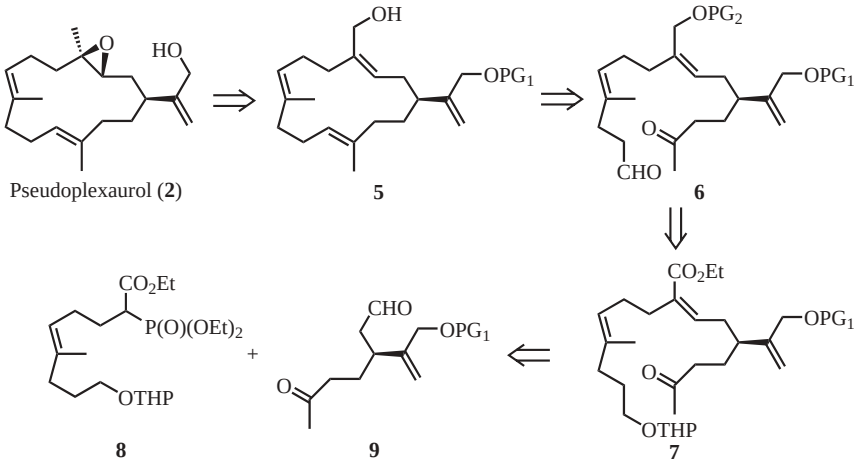
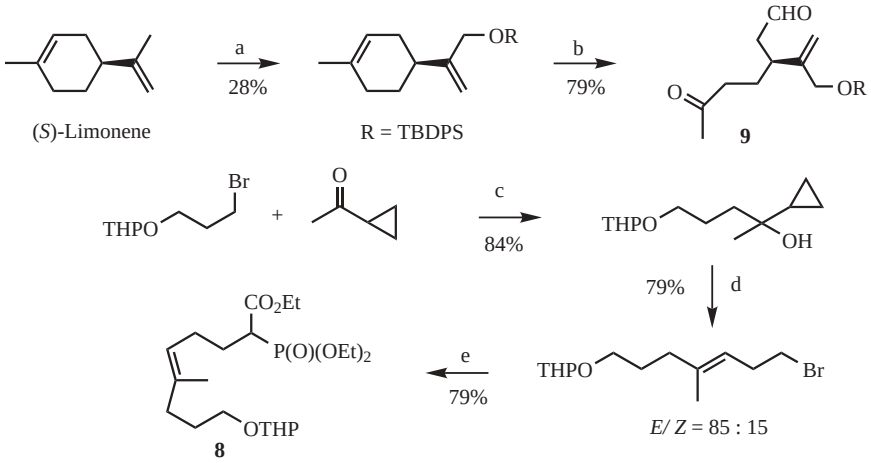
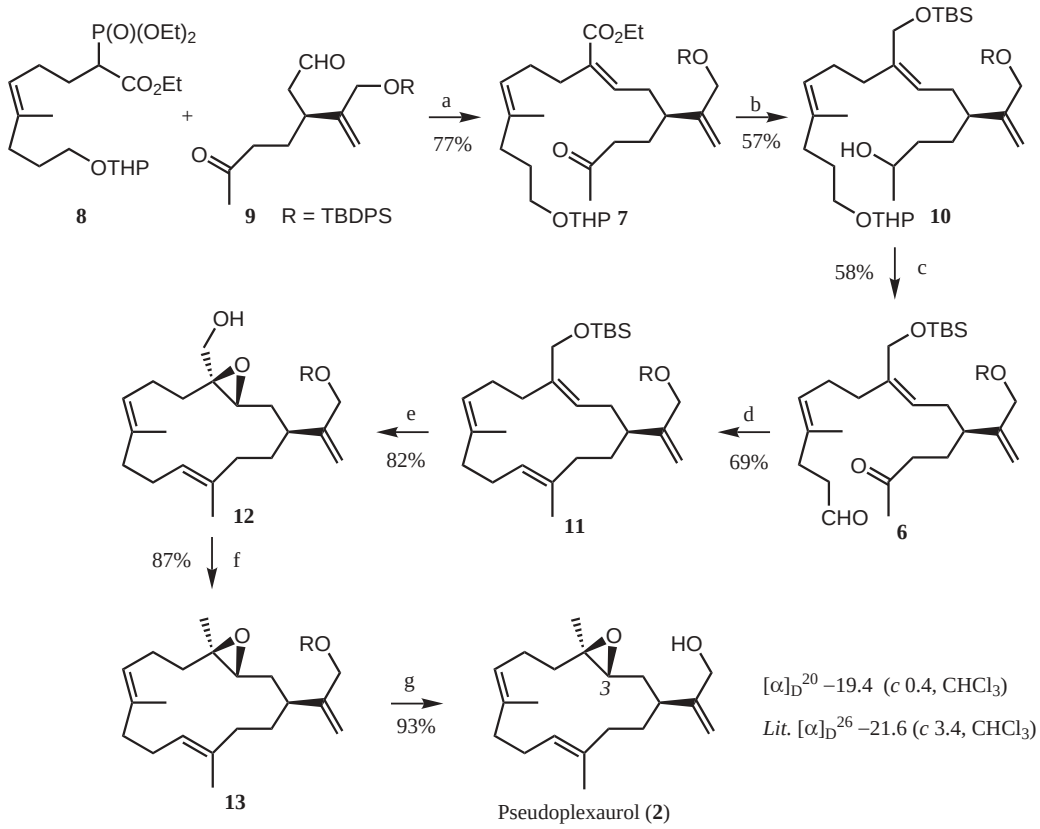


Scheme 1 Retrosynthesis of pseudoplexaurol (**2**) based on McMurry macro-olefination and Sharpless Asymmetric Epoxidation (SAE).



Scheme 2 Synthesis of fragments **8** and **9**. *Reagents and conditions*: (a) 1. *n*-BuLi, TMEDA, THF, 23 °C, 24 h, then O_2; 2. TBDPS-Cl, imidazole, DMF; (b) O_3, CH_2Cl_2, –78 °C, then Me_2S; (c) Li, THF, r.t., then cyclopropyl methyl ketone; (d) LiBr, TMSCl, CH_2Cl_2, r.t.; (e) $(EtO)_2P(O)CH_2CO_2Et$, NaH, DMF, 60 °C.



Scheme 3 *Reagents and conditions*: (a) *n*-BuLi, THF, –78 °C; (b) 1. DIBALH, CH_2Cl_2, –78 °C; 2. TBSCl, imidazole, DMF; (c) 1. $MgBr_2$, Et_2O, r.t.; 2. Swern oxidation; (d) $TiCl_4$, Zn, pyridine, DME, reflux; (e) 1. PPTs, EtOH, r.t.; 2. Ti(*i*-PrO)$_4$, L-(+)-DET, *t*-BuOOH, CH_2Cl_2, –20 °C; (f) 1. I_2, Ph_3P, imidazole, Et_2O–CH_3CN, 0 °C; 2. $NaBH_3(CN)$, THF–HMPA, 60 °C; (g) TBAF, THF.

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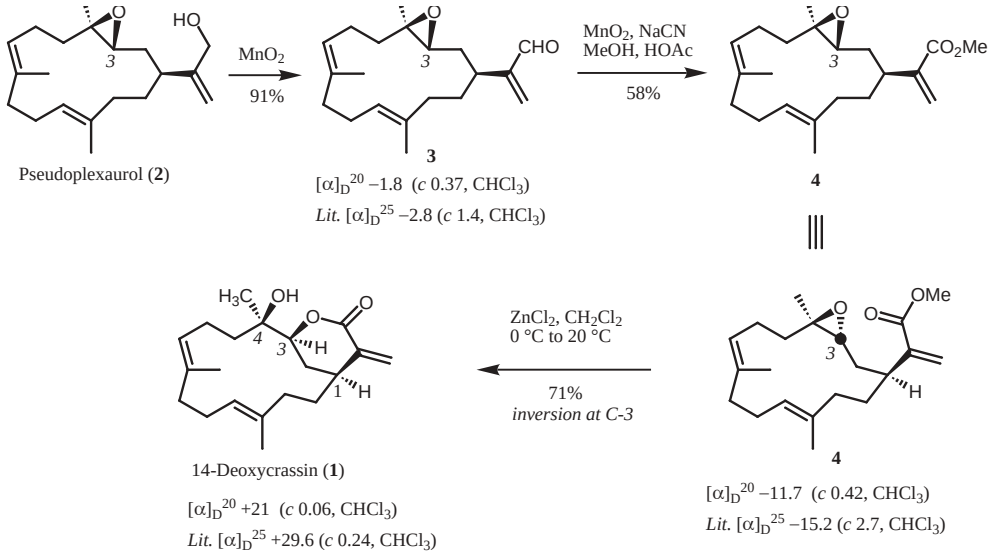

Scheme 4 Chemical conversion of **2** to **1** by Lewis acid-catalyzed lactonization.

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(11) Data of pseudoplexaurol (**2**): $[\alpha]_D^{20}$ –19.5 (*c* 0.40, $CHCl_3$). IR (film): ν_{max} = 3413 (brs), 2924, 2855, 1647, 1449, 1381, 1031, 898 cm^{-1}. LRMS (EI): *m/z* (%) = 304 (M, 0.9), 286 (2.8), 273 (7.2), 255 (4.9), 215 (7.2), 201 (8.3), 189 (12), 173 (15), 161 (27), 147 (39), 133 (78), 119 (70), 107 (77), 93 (90), 81 (100), 79 (77), 67 (87), 55 (67), 43 (55), 41 (59). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.14 (1 H, d, *J* = 1.0 Hz, CH=), 5.06 (1 H, t, *J* = 6.4 Hz, CH=), 5.05 (1 H, dd, *J* = 6.4 Hz, CH=), 4.96 (1 H, d, *J* = 1.4 Hz, CH=), 4.11 (2 H, s, CH_2O), 2.65 (1 H, dd, *J* = 3.7, 7.0 Hz, epoxy H), 2.25–2.00 (11 H, m, 5 CH_2, CH), 1.72–1.52 (4 H, m, 2 CH_2), 1.63 (3 H, s, CH_3), 1.59 (3 H, s, CH_3), 1.22 (3 H, s, CH_3). HRMS (ESI) calcd for $C_{20}H_{32}O_2Na$: 327.2295. Found for $[M + Na]^+$: 327.2295.

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(13) Data of 14-deoxycrassin (**1**): $[\alpha]_D^{20}$ +21 (*c* 0.06, $CHCl_3$). IR (film): ν_{max} = 3393 (brs), 2928, 2851, 1726, 1642, 1437, 1382, 1105, 1065, 906 cm^{-1}. LRMS (EI): *m/z* (%) = 318 (M, 14), 300 (M – 18, 43), 285 (25), 272 (14), 257 (18), 247 (9), 243 (14), 229 (22), 215 (21), 193 (82), 175 (52), 161 (41), 147 (66), 133 (55), 121 (69), 107 (73), 93 (73), 81 (100), 79 (68), 67 (22), 55 (48), 53 (46), 43 (44). ^1H NMR (400 MHz, $CDCl_3$): δ = 6.58 (1 H, s, CH=), 5.76 (1 H, s, 1 H), 5.19 (1 H, t, *J* = 6.5 Hz, CH=), 5.07 (1 H, t, *J* = 6.4 Hz, CH=), 4.48 (1 H, d, *J* = 11.5 Hz, CHO), 2.74–2.67 (1 H, m, CH), 2.55–2.48 (2 H, m, CH_2), 2.16–2.06 (6 H, m, 3 CH_2), 1.95–1.81 (4 H, m, 2 CH_2), 1.76 (3 H, s, CH_3), 1.72 (3 H, s, CH_3), 1.46–1.40 (2 H, m, CH_2), 1.25 (3 H, s, CH_3). HRMS (ESI) calcd for $C_{21}H_{32}O_3Na$: 341.2087. Found for $[M + Na]^+$: 341.2082.