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The Total Synthesis of 14-Deoxycrassin and Pseudoplexaurol: A Convergent Synthesis of Cyclization Precursor

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Abstract: The synthesis of epoxy aldehyde **4**, a cyclization precursor for the total synthesis of 14-deoxycrassin and pseudoplexaurol, starting from geraniol in a convergent and stereoselective manner, is described.

Keywords: Cembranolides, total synthesis, 14-deoxycrassin, pleaxaurol.

Considerable efforts have been devoted to the chemical synthesis of cembranolides in the past decades[1]. Cembranolides have been found in a variety of marine invertebrates[2, 3] and represent a family of diterpene natural products characterized by the presence of a 14-membered carbocyclic ring skeleton and exhibiting intriguing biological properties[2].

14-Deoxycrassin **1** and pseudoplexaurol **2**, two novel cembranoids, were discovered[4] from the Caribbean gorgonian *Pseudoplexaura porosa* by Rodríguez and Martínez in 1993, from which more abundant and complex congeners crassin **3** and its C-14 acetate were identified previously as potent antitumor agents[4]. The chemical structure of **1** and **2** were determined on the basis of spectroscopic data and chemical degradation. Epoxy alcohol **2** was assumed to be a logical biosynthetic precursor of **1**. Both **2** and **1** have been shown to exhibit significant cytotoxic activities against several human tumor cell lines in the primary biological screening in vitro[4]. Synthetic studies on natural cembranolides bearing a 3, 4-epoxy or lactone functions, such as crassin **3**, euniolide and isolobophytolide, have been conducted over the past decades by several groups[5], however, the total synthesis of **1** and **2** have not been reported so far.

In connection with our ongoing studies on the total synthesis of cembrenoids[6], we embarked on the total synthesis of **1** and **2**. Here we report the synthesis of a cyclization precursor **4** based on the synthetic plan as shown in **Scheme 1**. Pseudoplexaurol **2**, a proposed synthetic precursor of 14-deoxycrassin **1**, could be transformed[7] to **1** through oxidation and subsquent lactonization with the inversion of C-3 stereochemistry. Epoxy aldehyde **4**, a devised synthetic precursor for the elaboration of the macrocyclic ring of **2** could be prepared from the Morita-Baylis-Hillman adduct **5** of the corresponding aldehyde derived from epoxy alcohol **6** (**Scheme 1**).

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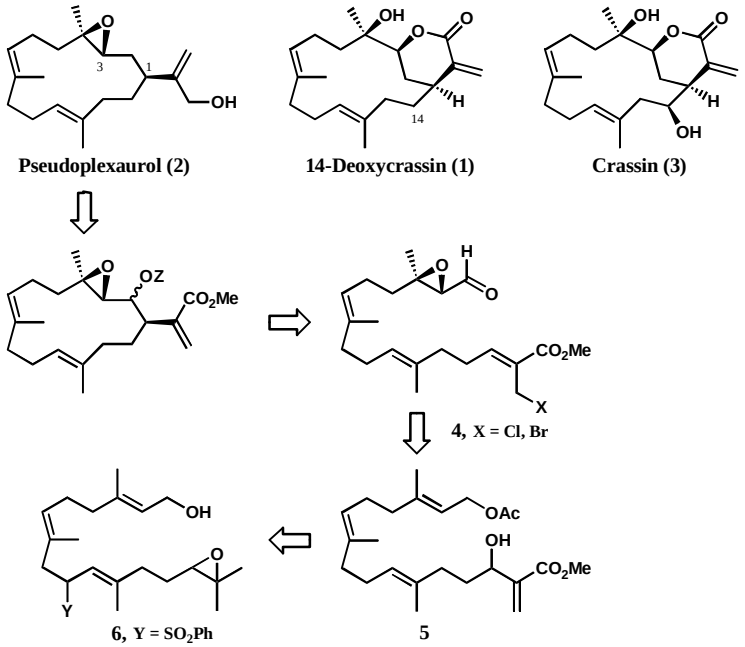
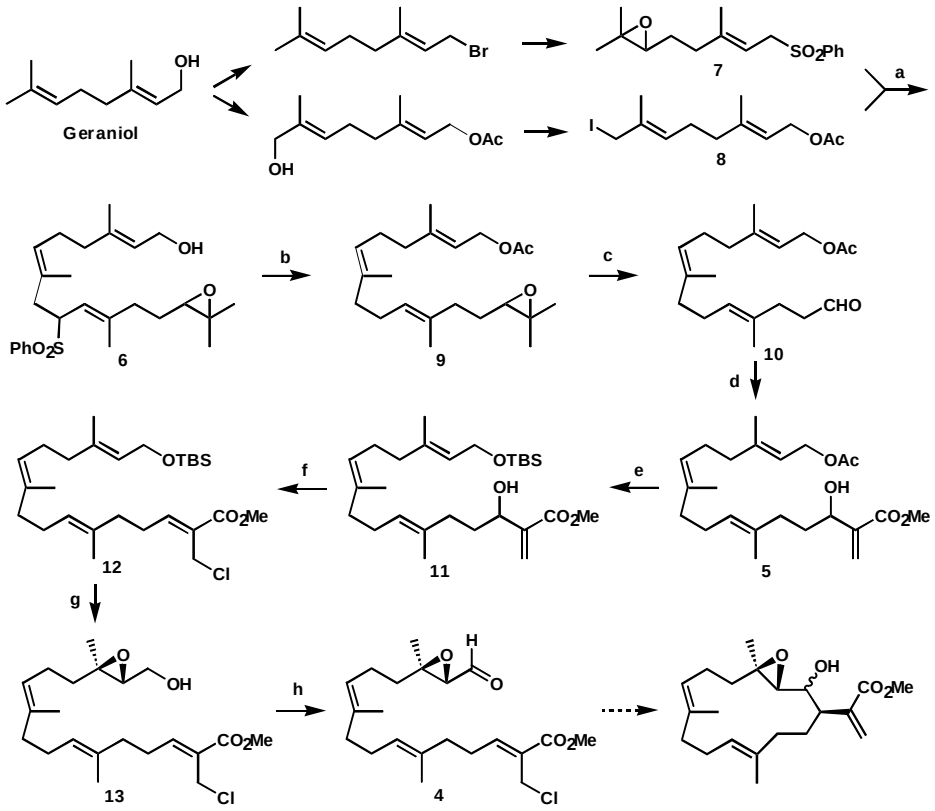
Scheme 1



A convergent and efficient synthesis of precursor **4** was depicted in **Scheme 2**. Sulfone **7** was prepared from geraniol by three standard operations (bromination, sulfonation and epoxidation) in 58% overall yield[8]. Allylic iodide **8** was also prepared from geraniol in three steps (hydroxyl protection, SeO_2 oxidation and iodination) in 68% overall yield[9]. Alkylative coupling of sulfone **7** with iodide **8** (LDA, THF, −78°C; then **8**, −78°C → r.t.) was followed by saponification of the coupling product to afford the sulfonyl alcohol **6** in 68% yield. Reductive desulfonation[8] of **6** with 6% Na(Hg) in anhydrous MeOH in the presence of NaH_2PO_4 followed by acetylation gave the acetate **9** in 70% yield. Oxidative cleavage of the epoxide **9** by $HIO_4{\cdot}2H_2O$ at 0 °C afforded the aldehyde **10** in 88% yield. Morita–Baylis–Hillman addition[10] of methyl acrylate to **10** was conducted in THF at 50°C catalyzed[11] by *n*-Bu_3P in the presence of 1,1'-bi-2-naphthol (BiNOL, racemic) to give the desired adduct **5**[12] in 79% yield[13]. Saponification of acetate **5** was followed by silylation of the resulting primary allylic hydroxyl group to give *tert*-butyldimethylsilyl ether **11** in 85% yield. The changing of protective group is necessary for the successful release of the allylic hydroxy function following the chlorination step. Chlorination of ester **11** was performed effectively in CCl_4 in the presence of *n*-Bu_3P[13] to give (*Z*)-2-chloromethyl-2-alkenoic ester **12** exclusively in 70% yield[14]. Desilylation of **12** with pyridinium *p*-toluenesulfonate (PPTs) in ethanol at 40°C provided the corresponding allylic alcohol intermediate in 91% yield, which was subjected to the Sharpless epoxidation to give the epoxy alcohol **13** in 92% yield. Conversion of **13** to the epoxy aldehyde precursor **4**[12] was achieved by Swern oxidation in 95% yield.

Scheme 2



Reagents and conditions: a) 1. LDA, THF, −78°C – r.t.; 2. K_2CO_3, MeOH, r.t. (68%); b) 1. 6% Na(Hg), NaH_2PO_4, MeOH, r.t. (70%); 2. Ac_2O, Py, r.t. (100%); c) $HIO_4{\cdot}2H_2O$, Et_2O/THF (2/3 *v/v*), 0°C (88%); d) methyl acrylate, *n*-Bu_3P, (±)-BiNOL, THF, 50°C (79%); e) 1. K_2CO_3, MeOH, r.t. (100%); 2. TBSCl, imidazole, THF, r.t. (85%); f) *n*-Bu_3P, CCl_4, r.t. (70%); g) 1. PPTs, absolute EtOH, 40 °C (91%); 2. Ti(O-^{i}Pr)$_4$, D-DET, TBHP, CH_2Cl_2, –40~–20°C (92%); h) Swern oxi. (95%).

The synthetic sequence for epoxy aldehyde **4** described above is convergent, stereoselective, high-yielding and features the application of the phosphine-catalyzed Morita–Baylis–Hillman addition and chlorination reactions. Macrocyclization of epoxy aldehyde **4** mediated by Cr(II)[15] is underway in our laboratory.

Acknowledgments

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References and Notes

1. (a) M. A. Tius, *Chem. Rev.*, **1988**, *88*, 719. (b) N. J. G. Cox, S. D. Mills, G. Pattenden, *J. Chem. Soc., Perkin Trans. I*, **1992**, 1313 and references cited therein.
2. B. Tursch, J. C. Braeckman, D. Dolaze, M. Kaisin, In *Marine Natural Products: Chemical and Biological Perspectives*, ed. P. J. Scheuer, Academic Press, New York, **1978**, Vol. 2, pp. 247–296.
3. A. D. Rodríguez, *Tetrahedron*, **1995**, *51*, 4571.
4. A. D. Rodríguez, N. Martínez, *Experientia*, **1993**, *49*, 179.
5. See, for examples: (a) M. A. Tius, N. K. Reddy, *Tetrahedron Lett.*, **1991**, *32*, 3605. (b) W. G. Dauben, T. Z. Wang, R. W. Stephens, *Tetrahedron Lett.*, **1990**, *31*, 2393. (c) J. E. McMurry, R. G. Dushin, *J. Am. Chem. Soc.*, **1990**, *112*, 6942. (d) idem, *ibid*, **1989**, *111*, 8928. (e) J. A. Marshall, R. C. Andrews, L. Lebioda, *J. Org. Chem.*, **1987**, *52*, 2378. (f) W. G. Dauben, R. K. Saugier, I., Fleischhauer, *ibid*, **1985**, *50*, 3767. (g) J. A. Marshall, R. D. Royce, Jr. *ibid*, **1982**, *47*, 693.
6. For recent synthetic works on epoxy cembranolides from our Laboratory, see: (a) Z. S. Liu, W. D. Z. Li, Y. L. Li, *Tetrahedron: Asymmetry*, **2001**, *12*, 95. (b) Z. S. Liu, W. D. Z. Li, L. Z. Peng, Y. Li, Y. L. Li, *J. Chem. Soc., Perkin Trans. I*, **2000**, 4250.
7. For a recent translactonization example, see: A. D. Rodríguez, I. C. Piña, A. L. Acosta, C. Ramírez, J. J. Soto, *J. Org. Chem.*, **2001**, *66*, 648.
8. J. M. Mao, Y. Li, Z.J. Hou, Y. L. Li,; X.T. Liang, *Science in China* (series B), **1992**, *35*, 257.
9. W. D. Z. Li, Y. Li, Y. L. Li, *Tetrahedron Lett.*, **1999**, *40*, 965.
10. E. Ciganek, *Organic React.*, **1997**, *51*, 201.
11. Y. M. A. Yamada, S. Ikegami, *Tetrahedron Lett.* **2000**, *41*, 2165.
12. Spectral data: **5**, colorless oil. IR (film): ν 3445, 1730(br s), 1624 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 1.59 (s, 3 H, CH_3), 1.61 (s, 3 H, CH_3), 1.70 (s, 3 H, CH_3), 1.56–1.80 (m, 8 H, 4 CH_2), 1.98–2.09 (m, 4 H, 2 CH_2), 2.05 (s, 3 H, $COCH_3$), 3.80 (s, 3 H, CH_3O), 4.38 (t, 1 H, J = 6.2 Hz, CHOH), 4.58 (d, 2 H, J = 7.0 Hz, CH_2O), 5.10–5.42 (m, 3 H, 3 CH=), 5.81 (t, 1 H, J = 1 Hz, CH_2=), 6.23 (t, 1 H, J = 1 Hz, CH_2=); EIMS *m/z*: 300 (5%, M–HOAc–MeOH), 286 (67), 257 (19), 239 (17), 187 (18), 147 (92), 119 (100). **4**, $[\alpha]_D^{20}$ – 42 (*c* 1.8, $CHCl_3$); IR (film): ν 2856, 1721 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, δ ppm): 1.44 (br s, 6 H, 2 CH_3), 1.60 (s, 3 H, CH_3), 1.52–1.74 (m, 4 H, 2 CH_2), 2.04–2.26 (m, 8 H, 4 CH_2), 3.17 (d, 1 H, J = 5.0 Hz, epoxy H), 3.79 (s, 3 H, OCH_3), 4.31 (d, 2 H, J = 4.0 Hz, CH_2Cl), 5.09 (m, 2 H, 2 CH=), 7.00 (t, 1 H, J = 6.6 Hz, H-14), 9.45 (d, 1 H, J = 5.0 Hz, CHO); EIMS *m/z* 347 (5%, M–Cl), 323 (8), 297 (6), 282 (15), 247 (35), 215 (23), 187 (6), 161 (7), 147 (17), 119 (50), 93 (86), 81(100); HRMS (ESI): calcd for $C_{21}H_{31}O_4Cl$ $[M+H]^+$: 383.1984, found for $[M+H]^+$: 383.1978.
13. For an alternative preparation *via* a 3-step sequence, see: K. Nishitani, T. Konomi, Y. Mimaki, T. Tsunoda, K. Yamakawa, *Heterocycles*, **1993**, *36*, 1957.
14. The geometry of allylic chloride **12** was deduced as *Z* by ^1H NMR analysis and compared with literature data[13].
15. For applications in total synthesis, see: A. Fürstner, *Chem. Rev.*, **1999**, *99*, 991.

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