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Central core of uprolides D and E: a survey of some ring closing metathesis approaches

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Abstract—A preliminary study dealing with the feasibility of ring closing metathesis and ene-yne ring closing metathesis to construct the central bicyclic cores of uprolides D and E was investigated.

Cembranolides are a class of diterpenoids consisting of a 14-membered ring. Numerous cembranolides have been isolated from corals and other marine sources as well as from tobacco and other plants.[1] The remarkable wide range of biological activity that has been recorded for these diterpenoids and their key role in the ecological behavior of soft corals[1d] has attracted the attention of synthetic chemists.[2] Uprolide D (**2**) and uprolide E (**3**), isolated from a gorgonian species of the genus *Eunicea mammosa* (Lamoroux),[3,4] possess unique structural features characterized by the presence of the rare 4,7-oxa-bridged functionality (Fig. 1) and promising antitumor activity (IC_{50} levels of μg/mL against leukemia, colon, and breast cancer cells) and have stimulated substantial synthetic work, culminating in several approaches toward their synthesis.[5] Recently, we documented a RCM approach for the central tricyclic core of eunicin-like tricyclic cembranolides where it was indicated that a *syn*-configuration between the reacting tethers substituted at the 2,6-position of the dihydropyran ring was a prerequisite for the successful ring closure.[6] In continuation of our synthetic studies toward structurally novel cembranolides employing RCM, herein, we report metathetic approaches to the central bicyclic core of the

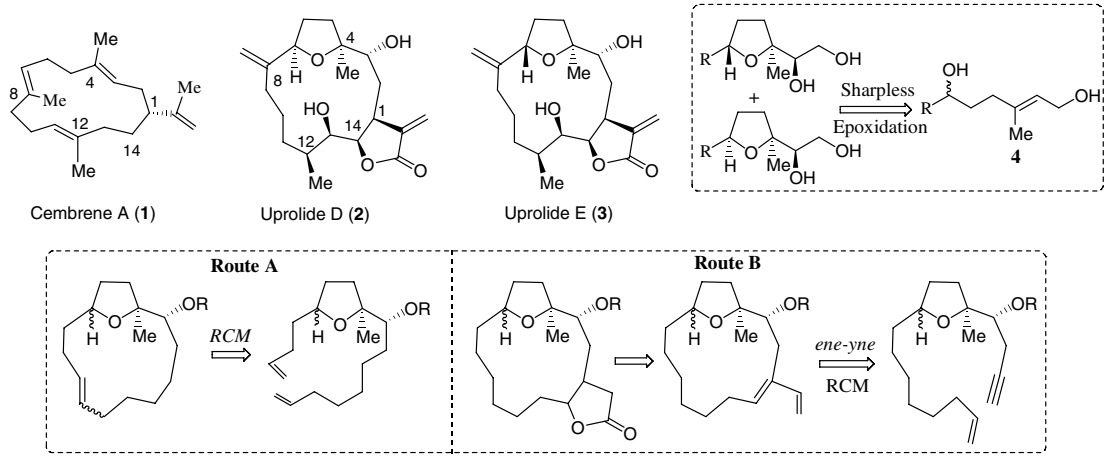

Figure 1. Uprolides D and E and the RCM, ene-yne ring closing metathetic approaches for the central macrocyclic core.

Keywords: Cembranolides; Uprolides D and E; Sharpless asymmetric epoxidation; Ring closing metathesis; Ene-yne metathesis.
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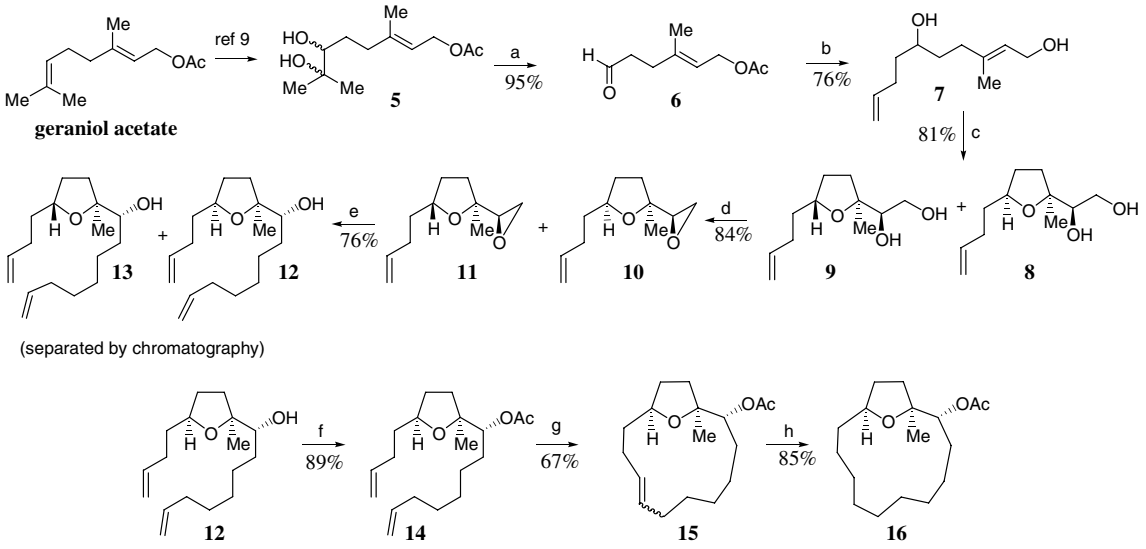
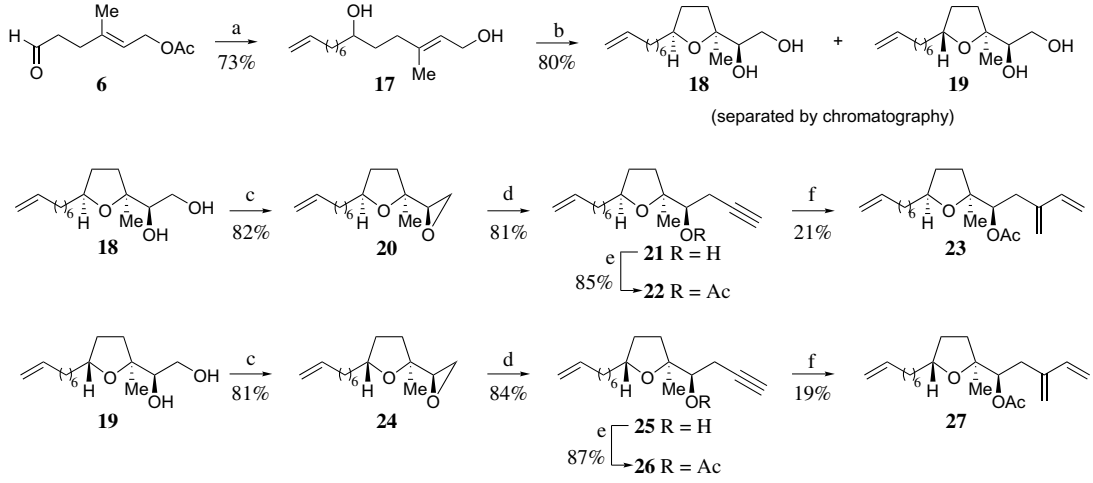


Scheme 1. Reagents and conditions: (a) $NaIO_4$, acetone–water, rt, 2 h; (b) (i) 3-butenylmagnesium bromide, THF, 0 °C, 2 h; (ii) K_2CO_3, MeOH, rt, 4 h; (c) D-(−)-DIPT, Ti(O*i*Pr)$_4$, *t*-BuOOH, CH_2Cl_2, −20 °C, 6 h; (d) (i) TsCl, Bu_2SnO, Et_3N, CH_2Cl_2, rt, 4 h; (ii) K_2CO_3, MeOH, rt, 0.5 h; (e) 5-hexenylmagnesium bromide, CuI, THF, −40 °C, 3 h; (f) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 1 h; (g) Grubbs' 1st Gen. catalyst, CH_2Cl_2, rt, 36 h and (h) Pd/C, H_2, EtOAc, 4 h.

uprolides. The retrosynthetic analysis is represented by two closely related metathetic approaches, route A and route B. The major issue with both the routes would be the feasibility of RCM with the 2,5-*anti*-configured tetrahydrofuran ring systems, and the ease of an intramolecular ene-yne ring closing metathesis forming large ring systems.[7] Kinetic resolution of 6-substituted hex-2-en-1,6-diol (**4**) by means of Sharpless asymmetric epoxidation is envisaged to address the synthesis of the key 2,5-*syn*- and *anti*-configured tetrahydrofurans present in uprolides D and E, respectively.[8]

The synthesis started with selective dihydroxylation of commercially available geraniol acetate and periodate cleavage of the resulting diol **5** to give the aldehyde **6** (Scheme 1).[9] Addition of 3-butenylmagnesium bromide to **6** was facile and gave the key dienol **7** in a 76% yield. Racemic dienol **7** was subjected to Sharpless asymmetric epoxidation using diisopropyl D-tartrate and titanium isopropoxide to afford tetrahydrofurans **8** and **9** as an inseparable mixture (1:1). Regioselective tosylation of diols **8** and **9** followed by the treatment with K_2CO_3 in methanol gave a diastereomeric mixture of epoxides **10** and **11** in a 84% yield. The mixture of epoxides was treated with the cuprate derived from 5-hexenylmagnesium bromide and CuI in THF at −40 °C to afford dienols **12** and **13** in a 76% yield, which were characterized by spectral and analytical data.[10] The stereochemistries of the tetrahydrofuran rings in **12** and **13** were confirmed by NOESY spectra. The absolute configuration and ee



Scheme 2. Reagents and conditions: (a) (i) 7-octenylmagnesium bromide, THF, 0 °C, 2 h; (ii) K_2CO_3, MeOH, rt, 4 h; (b) D-(−)-DIPT, Ti(O*i*Pr)$_4$, *t*-BuOOH, CH_2Cl_2, −20 °C, 8 h; (c) (i) TsCl, Bu_2SnO, Et_3N, CH_2Cl_2, rt, 4 h; (ii) K_2CO_3, MeOH, rt, 0.5 h; (d) lithium acetylide–EDA complex, DMSO, rt, 2 h; (e) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 1 h and (f) Grubbs' 2nd Gen. catalyst, ethylene gas, CH_2Cl_2, reflux, 24 h.

(94.5%, based on ^{19}F NMR spectra)[11] of **13** were determined on the basis of (*S*)- and (*R*)-MTPA derivatization.

The critical RCM reaction of **12** with the 1st generation Grubbs' catalyst was unsatisfactory and only traces of the macrocyclic derivative were isolated. The RCM reaction of the corresponding acetate **14** with the 1st generation Grubbs' catalyst was satisfactory and produced the 13-membered macrocyclic derivative **15** as an inseparable *E*/*Z* (1:1) mixture in a 67% yield. Hydrogenation of compound **15** using Pd/C in ethyl acetate gave bicyclic derivative **16**. The spectral and analytical data of **16** were in agreement with the assigned structure.[12]

After establishing the feasibility of RCM in accessing the central bicyclic core of uprolide D, we next turned our attention to implement the same with furan derivative **13**, which is a model substrate for the synthesis of uprolide E. However, RCM of *anti*-configured furan **13** and its acetate was found to be problematical using either the 1st or 2nd generation Grubbs' catalysts under the various conditions attempted, including stirring at rt or refluxing in solvents such as dichloromethane or toluene.

In order to investigate an ene-yne RCM approach, the synthesis of the requisite tetrahydrofuran derivatives was attempted. The addition of 7-octenylmagnesium bromide to aldehyde **6** followed by acetate hydrolysis gave dienol **17** in a 73% yield (Scheme 2). Sharpless asymmetric epoxidation of **17** using diisopropyl D-tartrate provided the diastereomeric tetrahydrofurans **18** and **19**. The stereochemistries of the tetrahydrofuran rings in **18** and **19** were established by NOESY spectra.[13] Regioselective tosylation of **18** followed by the treatment with K_2CO_3 gave epoxide **20** in an 82% yield. Opening of **20** with lithium acetylide ethylenediamine complex in DMSO afforded the alkynol **21** in an 81% yield. The absolute configuration and ee (91.5%, based on ^{19}F NMR spectra)[11] of **21** were determined on the basis of (*S*)- and (*R*)-MTPA derivatization. The ene-yne RCM reactions of alkynol **21** using Grubbs' 1st or 2nd generation catalyst under argon or ethylene in refluxing DCM were found to be unsuccessful. However, treatment of the corresponding acetate **22** with the 2nd generation Grubbs' catalyst in refluxing DCM under ethylene gave triene **23** in a 21% yield. The structure of **23** was established from spectral and analytical data.[14] In a similar manner, the ene-yne RCM of 2,5-*anti*-configured furan **26** prepared from **19** resulted in the formation of triene **27**.

To conclude, the RCM based synthetic strategy to build the macrocyclic core of uprolide D was successful. However, the RCM approach to the bicyclic core of uprolide E and the ene-yne RCM approach to both uprolides D and E were unsuccessful.

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10. *Spectral data of compound* **12**: Colorless oil. IR ($CHCl_3$): 3568, 3014, 2929, 1640, 1216 cm^{-1}. $[\alpha]_D^{25}$ −3.4 (*c* 1.2, $CHCl_3$). ^1H NMR ($CDCl_3$, 200 MHz); δ 1.12 (s, 3H), 1.35 (m, 7H), 1.56 (m, 5H), 2.05 (m, 6H), 2.27 (br s, 1H), 3.49 (dd, $J = 9.5$, 2.0 Hz, 1H), 3.91 (m, 1H), 4.97 (m, 4H), 5.82 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz); δ 24.6 (q), 26.6 (t), 28.8 (t), 29.1 (t), 30.2 (t), 31.0 (t), 31.5 (t), 31.9 (t), 33.7 (t), 35.9 (t), 76.6 (d), 80.3 (d), 85.6 (s), 114.1 (t), 114.4 (t), 138.3 (d), 139.0 (d). ESI-MS: *m*/*z* 267.13 $[M+1]^+$, 289.10 $[M+Na]^+$. Anal. Calcd for $C_{17}H_{30}O_2$: C, 76.64; H, 11.35. Found C, 76.41; H, 11.72. *Spectral data of compound* **13**: Colorless oil. IR ($CHCl_3$): 3583, 3016, 2930, 1640, 1216 cm^{-1} $[\alpha]_D^{25}$ +10.7 (*c* 2.5, $CHCl_3$). ^1H NMR ($CDCl_3$, 200 MHz); δ 1.12 (s, 3H), 1.36 (m, 8H),1.60 (m, 4H), 2.05 (m, 6H), 2.35 (br s, 1H), 3.46 (dd, $J = 9.7$, 2.0 Hz, 1H), 3.97 (m, 1H), 4.97 (m, 4H), 5.81 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz); δ 23.2 (q), 26.6 (t), 28.8 (t), 29.2 (t), 30.2 (t), 30.3 (t), 31.5 (t), 31.7 (t), 33.7 (t), 35.0 (t), 75.9 (d), 77.2 (d), 85.9 (s), 114.2 (t), 114.7 (t), 138.2 (d), 138.9 (d). ESI-MS: *m*/*z* 267.13 $[M+1]^+$, 289.11 $[M+Na]^+$ Anal. Calcd for $C_{17}H_{30}O_2$: C, 76.64; H, 11.35. Found C, 76.34; H, 11.59.

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12. *Spectral data of compound* **16**: Colorless oil. IR ($CHCl_3$): 2927, 1730, 1248 cm^{-1}. $[\alpha]_D^{25}$ −14.8 (*c* 1.2, $CHCl_3$). ^1H NMR ($CDCl_3$, 200 MHz) δ 1.18 (s, 3H), 1.29 (m, 7H), 1.47 (m, 7H), 1.59 (m, 2H), 1.69 (m, 4H), 1.83 (m, 1H), 1.94 (m, 1H), 2.04 (s, 3H), 3.94 (tq, $J = 10.6$, 2.1 Hz, 1H), 4.90 (t, $J = 6$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz); δ 21.3 (q), 21.9 (q), 23.8 (t), 24.7 (t), 25.7 (t), 25.9 (t), 26.3 (t), 26.6 (t), 27.5 (t), 29.5 (t), 33.1 (t), 34.8 (t), 37.3 (t), 76.4 (d), 78.9 (d), 82.8 (s), 170.8 (s). ESI-MS: *m/z* 283.15 $[M+1]^+$, 305.13 $[M+Na]^+$. Anal. Calcd for $C_{17}H_{30}O_3$: C, 72.30; H, 10.71. Found: C, 72.01; H, 10.50.
13. *Spectral data of compound* **18**: Colorless oil. IR ($CHCl_3$): 3435, 3077, 2973, 2930, 1639, 1475, 1216, 1088 cm^{-1}. $[\alpha]_D^{25}$ −1.7 (*c* 1.4, $CHCl_3$). ^1H NMR ($CDCl_3$, 200 MHz); δ 1.19 (s, 3H), 1.32 (m, 10H), 1.54 (m, 2H), 2.05 (m, 4H), 2.54 (br s, 2H), 3.64 (m, 3H), 3.95 (m, 1H), 4.96 (m, 2H), 5.81 (ddt, $J = 16.8$, 13.3, 6.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz); δ 22.4 (q), 25.9 (t), 28.6 (t), 28.8 (t), 29.3 (t), 31.4 (t), 32.8 (t), 33.6 (t), 35.7 (t), 63.0 (t), 76.3 (d), 78.1 (d), 84.1 (s), 114.0 (t), 138.9 (d). ESI-MS: *m/z* 278.6 $[M+Na]^+$ Anal. Calcd for $C_{15}H_{28}O_3$: C, 70.27; H, 11.01. Found C, 70.70; H, 10.90. *Spectral data of compound* **19**: Colorless oil. IR ($CHCl_3$): 3401, 2971, 2928, 2856, 1640, 1456, 1089 cm^{-1}. $[\alpha]_D^{25}$ −9.61 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 200 MHz); δ 1.16 (s, 3H), 1.31 (m, 10H), 1.62 (m, 2H), 2.02 (m, 4H), 2.49 (br s, 2H), 3.56 (m, 1H), 3.70 (m, 2H), 3.90 (m, 1H), 4.95 (m, 2H), 5.83 (ddt, $J = 16.8$, 13.3, 6.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz); δ 23.7 (q), 25.8 (t), 28.7 (t), 28.9 (t), 29.4 (t), 31.5 (t), 33.0 (t), 33.6 (t), 36.5 (t), 63.1 (t), 76.7 (d), 80.6 (d), 83.8 (s), 114.0 (t), 138.9 (d). ESI-MS: *m/z* 278.6 $[M+Na]^+$ Anal. Calcd for $C_{15}H_{28}O_3$: C, 70.27; H, 11.01. Found C, 70.32; H, 11.08.
14. *Spectral data of compound* **23**: Colorless oil. IR ($CHCl_3$): 3394, 3019, 2930, 2400, 1731, 1216 cm^{-1}. $[\alpha]_D^{25}$ −2.9 (*c* 2.9, $CHCl_3$)). ^1H NMR ($CDCl_3$, 200 MHz); δ 1.22 (s, 3H), 1.31 (m, 10H), 1.58 (m, 3H), 1.91 (m, 1H), 1.99 (s, 3H), 2.04 (m, 2H), 2.26 (dd, $J = 14.2$, 10.7 Hz, 1H), 2.72 (td, $J = 14.2$, 1.2 Hz, 1H), 3.96 (m, 1H), 4.93 (m, 2H), 5.01 (br s, 3H), 5.10 (d, $J = 10.8$ Hz, 1H), 5.29 (d, $J = 17.6$ Hz, 1H), 5.78 (ddt, $J = 16.8$, 13.3, 6.6 Hz, 1H), 6.34 (dd, $J = 17.6$, 10.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ 21.0 (q), 21.9 (q), 26.2 (t), 28.9 (t), 29.1 (t), 29.6 (t), 31.5 (t), 31.9 (t), 33.8 (t), 35.3 (t), 36.3 (t), 75.9 (d), 79.5 (d), 83.3 (s), 113.9 (t), 114.3 (t), 117.9 (t), 138.4 (d), 139.0 (d), 143.1 (s), 170.1 (s). ESI-MS: *m/z* 335.41 $[M+1]^+$, 357.41 $[M+Na]^+$. Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.41; H, 10.25. Found C, 75.23; H, 10.10.