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Synthetic studies toward tricyclic cembranoids: a modular approach for the construction of the tricyclic framework of eunicin

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Dedicated to Dr. A.V. Rama Rao on the occasion of his 70th birthday

Abstract—The synthesis of a sugar derived allene and its intramolecular silver mediated etherification followed by ring closing metathesis has been explored for building the tricyclic framework of eunicin.

Cembranoids belong to a class of diterpenoids possessing a 14-membered ring. Cembrane A (Fig. 1) compounds form the basic skeleton of these macrocyclic diterpenoids. Numerous cembranoids have been isolated from corals and other marine sources as well as from tobacco and other plants.[1] The remarkably wide range of biological activity that has been recorded for these diterpenoids[1] and their key role in the ecological behavior of soft corals[1d] has attracted the attention of synthetic chemists.[2] Eunicin,[3] cuenicin,[4] eunicenolide,[5] and uproeunicin[5] belong to the category of cembranes containing an internal tetrahydropyran ring. Although, eunicin was isolated about 45 years ago, no total synthesis has yet been reported. On several occasions, other cembranes have been transformed into eunicin and related analogues by means of partial epoxidation of the requisite olefin and an intramolecular cyclo-etherification.[6] Herein we report our modular approach to the synthesis of the central tricyclic core of the eunicin type cembranoids using a RCM, as the key reaction. As shown in Figure 1, the immediate precursor for the key RCM is a furo[2,3-*c*]pyran diene. We opted for a silver mediated cyclo-etherification reaction of a suitably functionalized allene in order to control the stereochemistry in the construction of the tetrahydropyran ring.

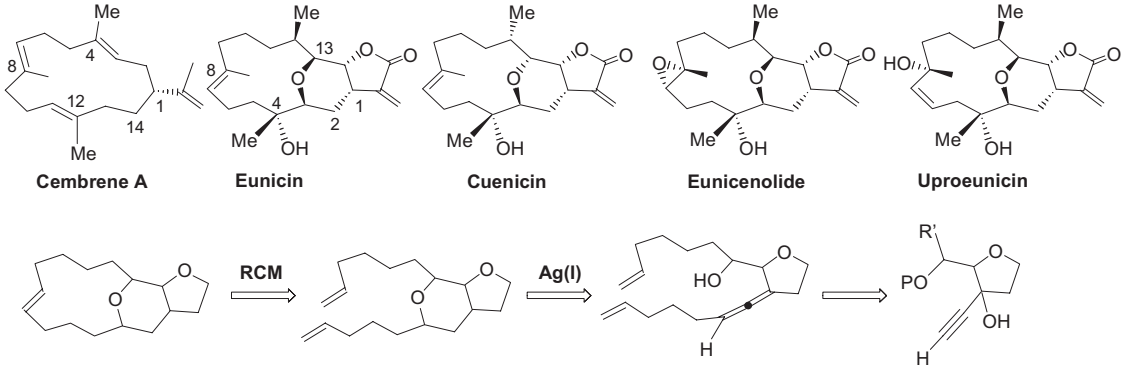

Figure 1. Representative cembranoids and the intended retrosynthetic strategy for the eunicin-like tricyclic cembranoids.

Keywords: Cembranoid; Eunicin; Allene; Carbohydrate; Ring closing metathesis.
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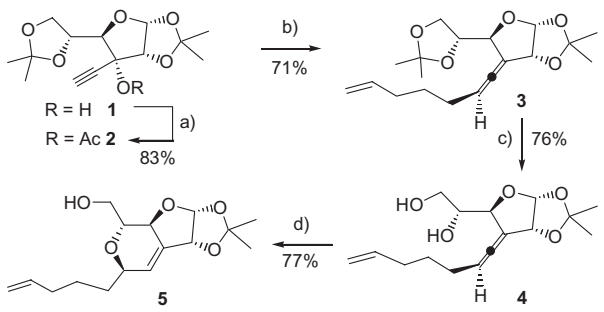
An advantage of this approach is that the relative stereochemistry of ring formation is entirely governed by the stereochemistry of the allene and the carbon atom bearing the reactive nucleophile.[7] In order to test the feasibility of this retrosynthetic strategy initial efforts were focused on model substrates. In this context, a sugar template was selected bearing in mind that allene containing sugars are scarcely reported and their synthetic potential is not explored.[8]

The synthetic endeavor started with the sugar acetylene **1**[9] which can be made in three steps from D-glucose. After exploring several sets of reaction conditions,[10] addition of pentenylmagnesium bromide[10b] to the acetate **2** was found to be facile and diastereoselective giving the allene **3**[11a] in good yield. The formation of an allene was clearly evident from the ^{1}H NMR spectrum in which the allene-H appeared at 5.82 ppm as a multiplet. In the ^{13}C NMR spectrum, the three allene carbons resonated at δ 198.5 (s), 101.9 (s), and 96.2 (d). The stereochemistry of the allene was established at a later stage. The 5,6-isopropylidene group of **3** was selectively deprotected and the resulting diol **4** was subjected to silver nitrate mediated cyclo-etherification[7a] which gave exclusively the bicyclic derivative **5**.[11b] The stereochemistry of the pyran ring of **5** was established as *trans* based on NOESY studies. This clearly indicated that the stereochemistry of the allene precursor was as shown in Scheme 1. The resultant diastereoselectivity can be explained by the preferential β-selective nucleophilic attack at C-3 of the glucose diacetonide derivatives[9,12] and also by the disposition of the leaving group [10] and its expected transannular departure.

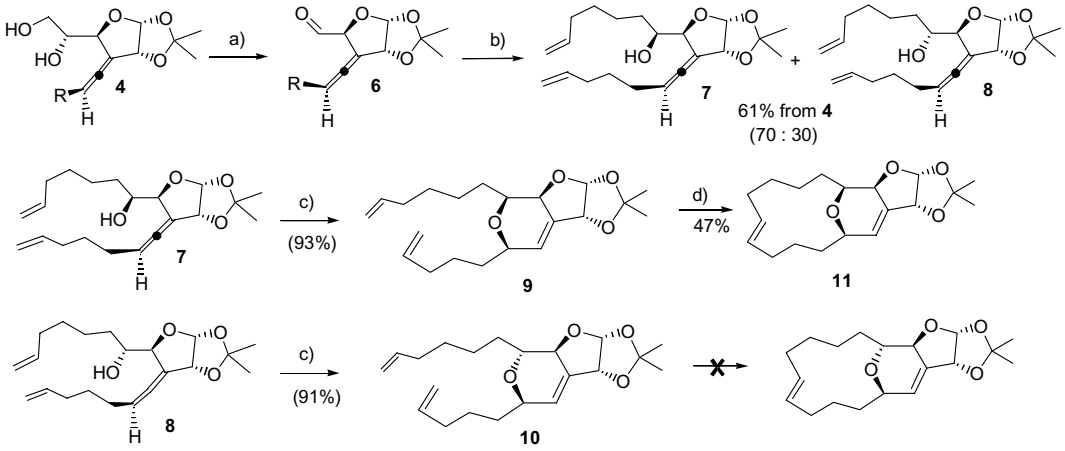


Scheme 1. Reagents and conditions: (a) Ac_2O, py, rt, 1 h; (b) 4-pentenylMgBr, THF, CuBr, −10 °C, 1 h; (c) cat H_2SO_4, MeOH, 0 °C–rt, 9 h; (d) $AgNO_3$, acetone, rt, 7 h.

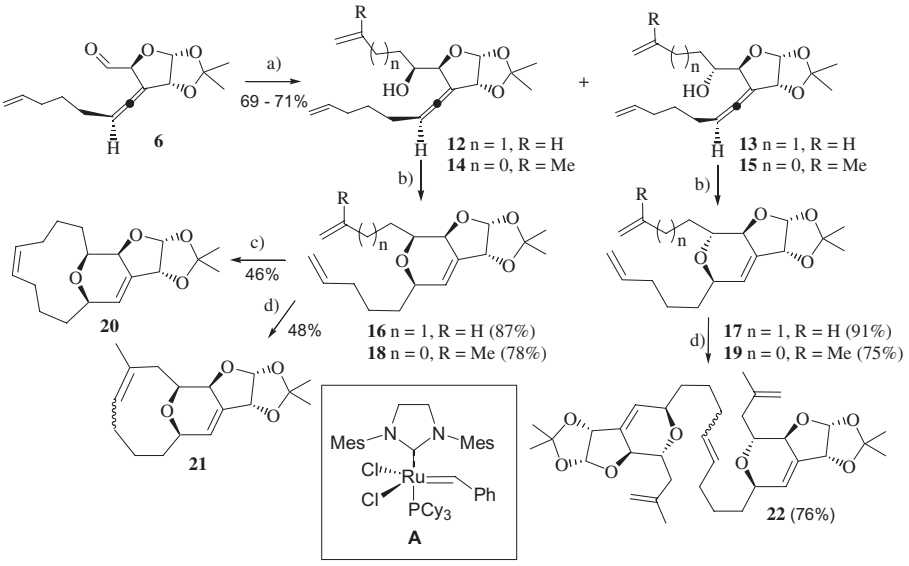
After establishing the stereochemistry of allene **3**, model studies to test the feasibility of RCM were used to construct the requisite 12-membered macrocycle from the key allene intermediate **4** (Scheme 2). Oxidative cleavage of **4** using sodium periodate and addition of 5-hexenylmagnesium bromide gave the dienes **7** and **8**, which were separated by simple column chromatography.[13] The silver nitrate mediated cyclo-etherification[7a] of allenes **7** and **8** gave exclusively the bicyclic derivatives **9** and **10**. The stereochemistry of the newly formed dihydropyran rings in the bicyclic derivatives **9** and **10** were established as *cis* and *trans*, respectively, with the help of NOESY experiments.

The RCM of **9** proceeded efficiently with the 1st generation Grubbs' catalyst and gave the requisite *E* isomer **11**.[14] The *E*-configuration for the olefinic protons was evident from the large coupling constant (J = 15.3 Hz). However, the RCM of **10** was found to be sluggish and resulted in an intractable polymeric mixture.

After establishing a strategy for the construction of the core of the eunicin-like cembranoids, we next focused our attention on the generalization of our strategy for the synthesis of macrocyclic analogues where the size of ring C could be modified. Accordingly, treatment of allene **6** with a suitable alkenyl Grignard, followed by cyclo-etherification and RCM of the resulting 2,6-*cis*-/*trans*-tetrahydropyran derivatives **16**–**19** was carried out. The RCM was successful only for the 2,6-*cis*-dihydropyrans **16** and **18** and the corresponding tricyclic compounds **20**[15] (with the *Z*-configuration, J = 10.8 Hz) and **21**[16] were obtained in good yields. As expected, the RCM of **17** was sluggish and resulted in a mixture of unidentifiable products. Surprisingly, the RCM of 2,6-*trans*-tetrahydropyran derivative **19** gave the



Scheme 2. Reagents and conditions: (a) $NaIO_4$, CH_2Cl_2, rt, 1 h; (b) 5-hexenyl-MgBr, THF, 0 °C, 1 h; (c) $AgNO_3$, acetone, rt, 36 h; (d) $(PCy_3)_2Ru(Cl)_2$=CH–Ph (20 mol%), benzene, reflux, 12 h.



Scheme 3. Reagents and conditions: (a) C_5H_9MgBr, THF, 0 °C, 1 h, 71% and **12**:**13** = 7:3 or C_4H_7 MgBr, THF, 0 °C, 1 h, 69%, **14**:**15** = 75:25; (b) $AgNO_3$, acetone, rt, 36–48 h; (c) $(PCy_3)_2Ru(Cl)_2{=}CH{-}Ph$ (20 mol%), benzene, reflux, 12 h. (d) **A** (5 mol%), CH_2Cl_2, rt, 4 h.

corresponding dimer **22** in 76% yield. Although, we obtained only single isomers of **21** and **22**, the stereochemistry of the newly formed olefin was not determined as the corresponding olefinic protons appeared as complex multiplets in the ^1H NMR spectra (see Scheme 3).

In summary, we have reported a simple and short strategy for the construction of the core skeleton of tetrahydropyran-containing tricyclic cembranoids. Further application of our strategy toward the total synthesis of eunicin and its related natural cembranoids is in progress.

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11. (a) *Spectral data of compound* **3**: $[\alpha]_D^{25}$ +164.8 (*c* 2.7, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 5.84 (d, J = 3.9 Hz, 1H), 5.82–5.72 (m, 1H), 5.57–5.48 (m, 1H), 5.04–4.94 (m, 3H), 4.83 (t, J = 3.9 Hz, 1H), 4.12 (dt, J = 4.3, 6.6 Hz, 1H), 3.95 (br ddd, J = 2.5, 6.8, 8.1 Hz, 1H), 3.84 (br ddd, J = 2.4, 6.4, 8.1, 1H), 2.12–2.06 (m, 4H), 1.56–1.50 (m, 2H), 1.52 (s, 3H), 1.42 (s, 3H), 1.36 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 198.5 (s), 138.1 (s), 115.1 (t), 112.4 (s), 109.62 (2s), 105.2 (d), 101.9 (s), 96.2 (d), 82.1 (d), 78.4 (d), 77.5 (d), 65.4 (t), 33.1 (t), 28.1 (t), 28.0 (t), 27.4 (q), 26.4 (q), 25.4 (q); IR = 3017, 2988, 2936, 1977, 1640, 1064, 1045 cm^{-1}. Anal. Calcd for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39. Found: C, 67.77; H, 8.61; (b) *Spectral data of compound* **5**: $[\alpha]_D^{25}$ +33.8 (*c* 2.4, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ: 5.86 (t, J = 1.8, 1H), 5.79 (d,

J = 3.7 Hz, 1H), 5.78 (ddt, J = 6.8, 10.2, 16.9 Hz, 1H), 5.02 (ddd, J = 1.4, 3.2, 16.9 Hz, 1H), 4.99–4.95 (m, 1H), 4.88 (d, J = 3.7 Hz, 1H), 4.38 (br dt, J = 1.8, 8.4 Hz, 1H), 4.30 (ddd, J = 1.8, 4.3, 8.2 Hz, 1H), 3.87 (dd, J = 2.8, 11.8 Hz, 1H), 3.70 (dd, J = 6.1, 11.8 Hz, 1H), 3.23 (ddd, J = 2.8, 6.1, 8.2 Hz, 1H), 2.11 (br dt, J = 1.8, 8.2 Hz, 2H), 1.67–1.58 (m, 2H), 1.54 (s, 3H), 1.52–1.44 (m, 2H), 1.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 138.1 (d), 136.4 (s), 126.4 (d), 115.1 (t), 113.1 (s), 105.53 (d), 79.9 (d), 73.1 (d), 72.1 (d), 71.3 (d), 63.3 (t), 33.4 (t), 32.6 (t), 27.2 (t), 26.8 (q), 25.7 (q) ppm. Anal. Calcd for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16. Found: C, 65.07; H, 7.90.

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14. *Spectral data of compound* **11**: $[\alpha]_D^{25}$ +22.6 (c 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.86 (t, J = 1.8, 1H), 5.67 (d, J = 3.7, 1H), 5.33 (dt, J = 7.5, 15.3 Hz, 1H), 5.11 (dt, J = 6.9, 15.3 Hz, 1H), 4.79 (d, J = 3.7 Hz, 1H), 4.40 (br dt, J = 1.8, 5.5 Hz, 1H), 3.90 (br ddd, $J \approx$ 2.0, 4.2, 12.1 Hz, 1H), 3.75 (ddd, J = 1.5, 5.4, 11.9 Hz, 1H), 2.03 (dt, J = 6.8, 12.1 Hz, 1H), 1.96–1.90 (m, 1H), 1.87–1.79 (m, 2H), 1.58–1.49 (m, 8H), 1.47 (s, 3H), 1.39–1.32 (m, 2H), 1.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 135.1 (s), 133.7 (d), 129.4 (d), 129.0 (d), 112.3 (s), 104.4 (d), 79.7 (d), 73.0 (d), 72.5 (d), 71.3 (d), 33.6 (t), 31.5 (t), 30.7 (t), 28.9 (t), 26.9 (q), 26.6 (d), 26.2 (t), 25.3 (t), 19.6 (t); Anal. Calcd for $C_{19}H_{28}O_4$: C, 71.25; H, 8.75. Found: C, 71.65; H, 8.80.
15. *Spectral data of compound* **20**: $[\alpha]_D^{25}$ +25.2 (c 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.89 (t, J = 1.9 Hz, 1H), 5.74 (d, J = 3.7 Hz, 1H), 5.28 (br dt, J = 7.2, 10.8 Hz, 1H), 5.23 (br dt, J = 7.2, 10.8 Hz, 1H), 4.85 (d, J = 3.7 Hz, 1H), 4.36–4.31 (m, 1H), 3.89 (br d, J = 10.8 Hz, 1H), 3.73 (t, J = 6.3 Hz, 1H), 2.54–2.44 (m, 1H), 2.34–2.28 (m, 1H), 2.21–2.13 (m, 2H), 1.78–1.67 (m, 4H), 1.63–1.56 (m, 2H), 1.52 (s, 3H), 1.49–1.39 (m, 2H), 1.34 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 135.4 (d), 130.5 (d), 130.4 (d), 112.3 (s), 104.3 (d), 79.8 (d), 75.2 (d), 74.0 (d), 72.3 (d), 33.8 (t), 28.3 (t), 27. 8 (t), 26.9 (q), 26. 6 (q), 26.0 (t), 25.6 (t). Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.24; H, 8.75.
16. *Spectral data of compound* **21**: $[\alpha]_D^{25}$ −8.9 (c 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.94 (t, J = 1.9 Hz, 1H), 5.84 (d, J = 3.7 Hz, 1H), 5.58 (t, J = 7.7 Hz, 1H), 4.97 (t, J = 3.7 Hz, 1H), 4.92–4.89 (m, 1H), 4.49–4.46 (m, 1H), 4.32 (br ddd, $J \approx$ 4.7, 6.4, 12.2 Hz, 1H), 2.22 (t, J = 13.0 Hz, 1H), 2.04 (dt, J = 7.6, 13.8 Hz, 1H), 1.93–1.85 (m, 4H), 1.72 (s, 3H), 1.66–1.61 (m, 2H), 1.54 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 135.7, 133.6, 127.2, 127.0, 112.7, 105.2, 79.9, 76.6, 73.1, 71.9, 34.2, 32.4, 29.7, 27.3, 26.9, 23.6, 23.0. Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.65; H, 8.14.