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## Total Synthesis of Neodolabellenol.

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Abstract: A total synthesis of both naturally occurring epimers of neodolabellenol has been achieved. Macrocyclization reactions, performed on cyclopentenes bearing two appropriately functionalized alkyl chains, provided eleven-membered carbocycles which were further elaborated into dolabellane natural products.

The dolabellanes are cytotoxic, antibacterial diterpenes first isolated from the digestive glands of the softbodied sea hare, *Dolabella californica*.<sup>1</sup> The presence of these metabolites in marine invertebrates is believed to result from dietary accumulation.<sup>2</sup> The naturally occurring neodolabellenol C<sub>5</sub> epimers <u>1a</u> and <u>1b</u> were first isolated in 1978 from a soft coral, genus *Cespitularia*.<sup>3</sup> The neodolabellenols were subsequently found in the soft coral, genus *Efflatounaria* and the octacoralia *Clavularia inflata*<sup>4</sup> and *Clavularia koellikeri*.<sup>5</sup> Numerous highly-oxidized examples, such as the dolabella-2,7-dien-9-one 2,<sup>6a</sup> and 4,5-deoxyneodolabelline <u>3</u><sup>6b</sup> have also been characterized.



Recent efforts directed towards synthesis of these novel carbocycles have been reported,<sup>7</sup> although a total synthesis of a dolabellane natural product has not yet been realized. Herein, we report the total synthesis of  $(\pm)$ - $\beta$ -neodolabellenol (<u>1b</u>), in which ring closure of the eleven-membered macrocycle was achieved by two complementary independent strategies.

One objective of our studies was to direct a macrocyclization with C<sub>5</sub> functionality which could be directly converted to the alcohol <u>1</u>. Thus, our previous effort<sup>7a</sup> for use of an intramolecular Julia condensation of a C<sub>6</sub>-sulfonyl carbanion was envisioned to offer a stereoselective approach to C<sub>5</sub> hydroxylation with C<sub>6</sub>  $\rightarrow$  C<sub>5</sub> bond formation. To this end, the vinyl iodide <u>4</u>, available in several steps from 2-methyl-2-cyclopentenone,<sup>7a</sup> was converted into the corresponding silyl ether <u>5</u> by the standard means (<u>Scheme 1</u>). The addition of 3,4epoxy-3-methyl-1-butene<sup>8</sup> to a solution of a higher order cyanocuprate, generated from the metal-halogen exchange of alkenyl iodide <u>5</u>, afforded a separable mixture (8:1) of the *E*- and *Z*-allylic alcohol adducts <u>6a</u> and <u>6b</u>, as anticipated based upon the reports of Normant and coworkers.<sup>9</sup> The assignment of <u>6a</u> as the major product from this cross-coupling procedure was confirmed by <sup>13</sup>C NMR analyses of the two products.<sup>10</sup> Interestingly, the direct use of the vinyl lithium species from <u>5</u> in this coupling process reversed the stereochemical outcome with preferential formation of the *Z*-allylic alcohol <u>6b</u> (7:1 Z/E ratio in 30-40% yields).





Conversion of <u>6a</u> to the aldehydic sulfone <u>8</u> was achieved by the transformations presented in <u>Scheme 1</u>. Intramolecular Julia condensation<sup>7a</sup> of <u>8</u> under conditions for kinetic deprotonation afforded a separable mixture (6:1) of the diequatorial  $\beta$ -hydroxy sulfone <u>9a</u> and its C<sub>5</sub> epimer <u>9b</u>.<sup>11</sup> Unlike our previous efforts,<sup>7a</sup> the reaction of <u>8</u> proceeded with rapid destruction of starting material, and formation of several byproducts, including bicyclic vinyl sulfone <u>9c</u> arising via intramolecular Michael addition.<sup>12</sup> Indeed, the macrocyclization is recognized as a rather remarkable event considering the ease for  $\gamma$ -deprotonation and C=C isomerization of the nonconjugated dienal.<sup>13</sup> Desulfonylation of pure <u>9a</u> with freshly prepared sodium amalgam in methanol provided ( $\pm$ )- $\beta$ -neodolabellenol (<u>1b</u>). The assignment of <u>1b</u> as  $\beta$ -neodolabellenol from <sup>1</sup>H NMR data was complicated by a dynamic exchange process involving conformers of the eleven-membered dolabellane macrocycle. Our spectrum for <u>1b</u> exhibited broadened resonances at high field strengths (500 MHz). At elevated probe temperatures (70 °C), the coalesence of proton signals correlated well with the low field (100 MHz) proton NMR data reported in the literature for <u>1b</u>.<sup>14</sup>

The assignment of our synthetic material <u>1b</u> was further corroborated by an independent synthesis of  $\beta$ neodolabellenol from the allylic chloride <u>10</u> via an intramolecular alkylation (<u>Scheme 2</u>). Scheme 2



Thus, conversion of benzoate 10 to the cyanohydrin derivative 11<sup>15</sup> afforded macrocyclization to ketone 12 (70% yield) upon inverse addition to a solution of sodium *bis*(trimethylsilyl)amide in THF at 35 °C followed by mild hydrolysis (aqu. HCl/MeOH at pH = 3; then 2% aqu NaOH). Unfortunately, reduction of dolabelladienone 12<sup>16</sup> with several hydride reagents gave mixtures of  $\alpha$ - and  $\beta$ -neodolabellenols 1a and 1b. However, slow fractional crystallization of the mixture from chloroform (-20 °C) permitted isolation of  $\beta$ -neodolabellenol 1b as fine white needles.<sup>17</sup> A more convenient separation of 1a and 1b required benzoylation of the mixture (benzoyl chloride, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>), separation of the individual benzoates and saponification (LiOH, MeOH) to provide pure neodolabellenols 1a and 1b. Data for 1a precisely matched the spectral data (<sup>1</sup>H NMR, IR, MS) for  $\alpha$ -neodolabellenol reported by Coll.<sup>3</sup>

In summary, the first total synthesis of a dolabellane natural product has been realized. The bicyclic framework of these diterpenes has been generated by two complementary intramolecular macrocyclization pathways. The application of these ring closure strategies to other dolabellane natural products is underway. Acknowledgements: We thank the National Institutes of Health (GM-42897) for support of this research. References:

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- 10. The chemical shift of the C<sub>5</sub> methylene carbon in the minor Z-isomer <u>6b</u> is shielded (61.4 ppm) relative to this corresponding resonance in the major E-isomer <u>6a</u> (68.5 ppm).
- 11. The major isomer of the Julia coupling procedure was assigned as  $\underline{9a}$  based upon the vicinal coupling constant for H<sub>5</sub>-H<sub>6</sub> (J = 11.0 Hz) (see reference 7a). The minor isomer  $\underline{9b}$  was assigned as the equatorial C<sub>6</sub> sulfone ( $J_{6,7} = 9.1$  Hz) based upon decoupling studies. Desulfonylation of  $\underline{9b}$  provided the diastereomeric  $\alpha$ -neodolabellenol 1a, indicating the C<sub>5</sub> hydroxyl in  $\underline{9b}$  is axial as shown.
- 12. The production of vinyl sulfone <u>9c</u> (undetermined stereochemistry at C<sub>3</sub>, C<sub>4</sub> and C<sub>13</sub>) was increased to 25% yield by use of sodium *bis*(trimethylsilyl)amide.
- 13. The nonconjugated dienal <u>8</u> undergoes rapid C=C conjugation upon treatment with weak bases, including *tetra*-n-butylammonium fluoride.
- 14. The temperature of coalesence increases with field strength. See: Friebolin, H. <u>Basic One- and Two-Dimensional NMR Spectroscopy</u>, VCH Publishers: New York, **1991**, pp. 269-270. Proton NMR data for  $\beta$ -neodolabellanol (500 MHz, C<sub>6</sub>D<sub>6</sub>, 70 °C)  $\delta$  6.35 (s, 10H), 5.32 (s, 1H), 5.02 (m, 1H), 4.82 (t, J = 7.6 Hz, 1H), 4.01 (t, J = 6.5 Hz, 1H), 2.82-2.53 (AB of ABX,  $\Delta v_{AB} = 109.0$  Hz,  $J_{AB} = 14.0$  Hz,  $J_{AX} = 9.9$  Hz,  $J_{BX} = 4.8$  Hz, 2H), 2.31 (m, 1H), 2.19 (m, 2H), 2.10 (m, 1H), 1.93 (m, 3H), 1.67 (m, 2H), 1.48 (s, 3H), 1.45 (s, 3H), 1.41 (m, 1H), 0.93 (d, J = 6.6 Hz, 3H), 0.90 (s, 3H), 0.88 (d, J = 6.5 Hz, 3H) ppm.
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- 16. The proton NMR (500 MHz, C<sub>6</sub>D<sub>6</sub>, 65 °C) of ketone <u>12</u> exhibited similar coalesence characteristics as shown for <u>1b</u>: (<u>12</u>) δ 5.79 (dd, J = 7.7, 5.8 Hz, 1H), 5.23 (s, 1H), 5.07 (t, J = 7.6 Hz, 1H), 3.20 (br s, 1H), 3.04 (dd, J = 16.3, 5.0 Hz, 1H), 2.75-2.49 (AB of ABX, Δv<sub>AB</sub> = 108.2 Hz, J<sub>AB</sub> = 14.6 Hz, J<sub>AX</sub> = 9.2 Hz, J<sub>BX</sub> = 5.0 Hz, 2H), 2.25 (ddd, J = 15.8, 8.16, 2.1 Hz, 1H), 2.00 (m, 3H), 1.85 (m, 1H), 1.71 (s, 3H), 1.61 (m, 2H), 1.46 (m, 1H), 1.37 (s, 3H), 0.90 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H), 0.82 (s, 3H) ppm.
- 17. The melting point of our *racemic*  $\beta$ -neodolabellenol (<u>1b</u>) is 147-148 °C, whereas that reported for the *optically pure* natural product is mp 161-162 °C.

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