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A New Synthesis of (-)-Furodysin

Tse-Lok Ho,* Kwang-Yuan Lee

Department of Applied Chemistry, National Chiao Tung University, Hsinchu, Taiwan, ROC

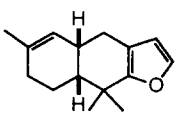
Department of Chemistry, National Taiwan Univeristy, Taipei, Taiwan, ROC

Abstract. A synthesis of furodysin from *trans*-limonene oxide involves transformation into the phenylcarbamate of 2,8-menthadien-1-ol, allylic displacement with lithium di-(β-furylmethyl)cuprate, and cyclization.

A number of furanosesquiterpenes occur in marine invertebrates.[1] Interestingly, furodysin and furodysinin have been elaborated in both enantiomeric forms, e.g., the (+)-isomers by an Australian variety of sponges *Dysidea herbacea*[2] and the (-)-isomers by those collected in Fiji[3] and by the Mediterranean species *D. tupha*.[4] These metabolites show significant antiparasitic activities.

The synthesis of (-)-furodysin **1** and (-)-furodysinin **2** has been accomplished starting from (+)-9-bromocamphor,[5] and also their racemates obtained from a longer route.[6] Here we wish to report a convenient approach to furodysin from *trans*-limonene oxide **3**.

Reaction of **3** with dimethylamine (40% aqueous solution) in a sealed vessel at 150°C gave the amino alcohol **4**[7] which was converted into the *N*-oxide with 30% hydrogen peroxide and then pyrolyzed to afford *trans-p*-2,8-menthadien-1-ol **5**[8] in an overall 44% yield. We planned to effect an S_N 2' displacement of the allylic alcohol with a furylmethyl substituent on the same side as the oxygen functionality which is *cis* to the isopropenyl group at C-4. Previous experience[9] indicated that allylic carbamates undergo *syn*-selective S_N 2' reactions with cuprate reagents therefore the *N*-phenylcarbamate **6** was prepared (77% yield) by a DMAP-catalyzed reaction of **5** with phenyl isocyanate with the intention of using it in such a reaction. Toward this



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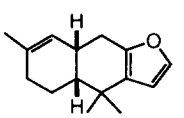

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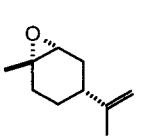

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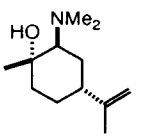

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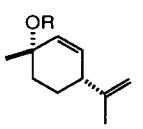
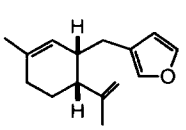


5; R = H
6; R = CONHPh



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end, the reaction of **6** with lithium di-(β-furylmethyl)cuprate[10] furnished compound **7** (91% yield) whose spectral data is in total agreement with those reported.[5] The final cyclization to culminate in a furodysin synthesis was effected following the established protocol[4] of mercuration, trapping, and reduction.

Some Physical data: **5:** $[\alpha]_D$ +63.9° (c=0.325 $CHCl_3$). δ_H (300 MHz, $CDCl_3$) 1.29 (3H, s), 1.4-1.65 (4H, m), 1.73 (3H, s), 1.8-1.85 (1H, m), 2.65 (1H, m), 4.73 (1H, s), 4.77 (1H, s), 5.66 (1H, d, *J* 11 Hz), 5.68 (1H, d, *J* 11 Hz). δ_C (75 MHz, $CDCl_3$) 20.83, 24.85, 29.37, 36.68, 43.41, 67.45, 110.57, 132.13, 133.88, 148.13.

6: mp 57-59°C. $[\alpha]_D$ -55° (c=0.369 $CHCl_3$). M^+ 271.1577. ν 3375, 1685 cm^{-1}. δ_H 1.5-1.8 (3H, m), 1.62 (3H, s), 1.70 (3H, s), 2.18 (1H, m), 2.20 (1H, m), 2.68 (1H, m), 4.74 (2H, s), 5.72 (1H, dd, *J* 9, 2 Hz), 6.16 (1H, d, *J* 9 Hz), 6.43 (1H, br.), 6.98 (1H, m), 7.2-7.35 (4H, m). δ_C 20.56, 24.20, 26.13, 35.22, 43.38, 77.73, 110.74, 118.43, 122.92, 128.83, 130.61, 133.55, 138.22, 147.83, 152.70.

7: $[\alpha]_D$ +300° (c=0.092 $CHCl_3$). δ_H 1.62 (3H, s), 1.76 (3H, s), 4.70 (1H, s), 4.87 (1H, s), 5.38 (1H, m), 6.23 (1H, d, *J* 1.5 Hz), 7.16 (1H,d, *J* 0.9 Hz), 7.33 (1H, dd, *J* 1.5, 0.9 Hz). δ_C 22.46, 22.81, 23.54, 25.93, 30.76, 36.79, 43.79, 110.13, 111.50, 123.83, 124.93, 133.88, 139.41, 142.47, 147.66.

2: $[\alpha]_D$ -40° (c=0.116 $CHCl_3$). δ_H 1.25 (3H, s), 1.27 (3H, s), 1.66 (3H, s), 2.19 (1H, m), 2.56 (2H, m), 5.60 (1H, m), 6.10 (1H, d, *J* 2 Hz), 7.23 (1H, d, *J* 2 Hz). δ_C 19.51, 23.21, 23.77, 27.29, 30.73, 31.58, 31.72, 34.51, 45.59, 109.78, 112.95, 126.39, 133.11, 140.40, 156.77.

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