

## Efficient Preparation of (*R*)-(-)-Cryptone from (+)-Nopinone and Its Transformation into Noroxopenlanfuran

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Starting with (*R*)-(-)-cryptone, prepared in 42% overall yield from (+)-nopinone in five steps, the first synthesis of noroxopenlanfuran was accomplished, confirming its absolute configuration.

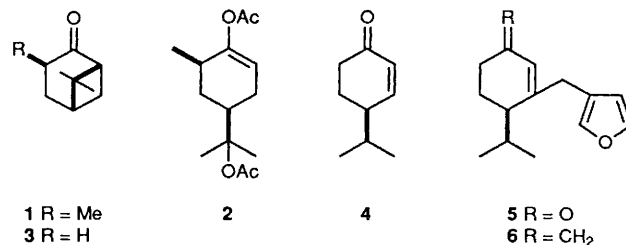
We have recently reported that treatment of (+)-*cis*-3-methylnopinone **1** with boron trifluoride-diethyl ether-zinc acetate in acetic anhydride led to the regioselective cyclobutane cleavage followed by acetylation to give a high yield of the optically pure diacetate **2**.<sup>1</sup> The main features of this reaction are (i) formation of the cyclobutane-opened product with little loss of optical integrity, (ii) regioselective formation of an enol acetate function suitable for further regioselective manipulation and (iii) mild reaction conditions which would allow acid or base-labile nopinone derivatives to be utilized as starting materials.

We have been studying natural product synthesis starting from (+)-nopinone **3**, and report here a practical synthesis of (*R*)-(-)-cryptone **4**<sup>2</sup> and its transformation to noroxopenlanfuran **5**,<sup>3</sup> isolated from the marine sponge *Dysidea fragilis* of the North Brittany Sea, whose absolute configuration is uncertain. From this species, penlanfuran **6** was isolated and chemically correlated with **5**.<sup>3</sup>

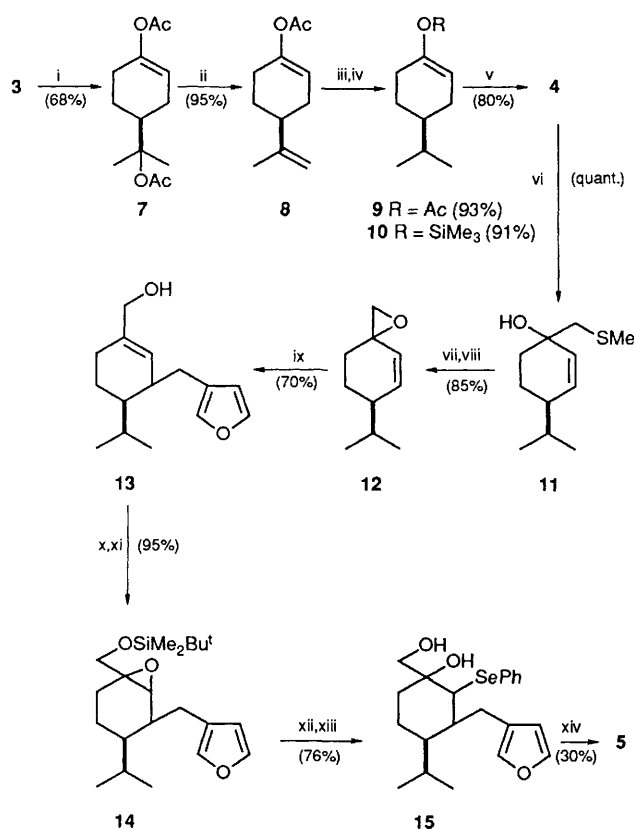
(+)-Nopinone **3**, [ $\alpha$ ]<sub>D</sub><sup>23</sup> +36.9° (*c* 4.2, MeOH); 92% optical purity,<sup>1</sup> boron trifluoride-diethyl ether promoted cyclobutane cleavage gave a good yield of the diacetate **7**, [ $\alpha$ ]<sub>D</sub><sup>14</sup> -49.5° (*c* 2.00, CHCl<sub>3</sub>) (Scheme 1). Pyrolysis of **7** followed by regioselective hydrogenation of the resulting diene **8** provided the enol acetate **9**, [ $\alpha$ ]<sub>D</sub><sup>14</sup> -59.2° (*c* 1.52, CHCl<sub>3</sub>), in 88% overall yield from **7**. Regioselective enone formation involving the enol acetate function in **9** was successfully performed by the following two-step sequence: **9** was regioselectively

converted into the enol silyl ether **10** by treatment with methyllithium followed by chlorotrimethylsilane. Palladium catalysed dehydrosilylation<sup>4</sup> of **10** provided (*R*)-(-)-cryptone **4**, [ $\alpha$ ]<sub>D</sub><sup>29</sup> -98.2° (*c* 0.54, EtOH),<sup>†</sup> in 69% overall yield from **9** (42% overall yield from **3** in five steps).

With the desired (-)-cryptone **4** available, the synthesis of noroxopenlanfuran **5** was next examined. Attempted Michael reaction of **4** with the Grignard reagent prepared from 3-(chloromethyl)furan in the presence of copper(I) iodide resulted in starting material recovery. Hence, according to the method of Tanis,<sup>7</sup> the allylic alcohol **11** was prepared by the addition of methylthiomethylolithium to **4**. Methylation of **11**



<sup>†</sup> (*R*)-(-)-Cryptone **4** was first reported to show [ $\alpha$ ]<sub>D</sub><sup>20</sup> -119.3° (*c* 2.0, EtOH),<sup>5</sup> whereas **4** obtained from optical purification *via* (-)-cryptol showed [ $\alpha$ ]<sub>D</sub><sup>20</sup> -91.7° (*c* 2.2, EtOH).<sup>6</sup>



**Scheme 1** Reagents and conditions: i,  $\text{BF}_3 \cdot \text{OEt}_2$ ,  $\text{Zn}(\text{OAc})_2$ ,  $\text{Ac}_2\text{O}$ , room temp., 30 h; ii, 500 °C, toluene; iii,  $\text{H}_2$ ,  $(\text{Ph}_3\text{P})_3\text{RhCl}$ ,  $\text{PhH}$ ; iv,  $\text{MeLi}$ ,  $\text{Me}_3\text{SiCl}$ , HMPA, diethyl ether, -78 to 0 °C, 4 h; v,  $\text{Pd}(\text{OAc})_2$ , acetonitrile, room temp., 7 h; vi,  $\text{BuLi}$ ,  $\text{Me}_2\text{S}$ , TMEDA, THF; vii,  $\text{MeI}$ , acetone, room temp.; viii,  $\text{Bu}^t\text{OK}$ , THF, room temp., 4 h; ix,  $(\text{C}_4\text{H}_9\text{O})\text{CH}_2\text{MgCl}$ ,  $\text{CuCN}$ , THF, -78 to -5 °C, 5 h; x,  $\text{Bu}^t\text{OOH}$ ,  $\text{VO}(\text{acac})_2$ , toluene, 0 °C, 3 h; xi,  $\text{Bu}^t\text{Me}_2\text{SiCl}$ , imidazole, DMF; xii,  $\text{PhSeSePh}$ ,  $\text{NaBH}_4$ , ethanol, reflux, 7 h; xiii,  $\text{Bu}_4\text{NF}$ , THF, room temp.; xiv,  $\text{NaIO}_4$ , aq. THF, 0 °C to room temp., 3 h; HMPA = hexamethylphosphoric triamide; TMEDA = *N,N,N',N'*-tetramethylethylenediamine; THF = tetrahydrofuran; Hacac = pentane-2,4-dione; DMF = dimethylformamide

followed by treatment of the resulting sulphonium salt with potassium *t*-butoxide gave a *ca.* 1:1 mixture of diastereoisomeric epoxides **12** in 85% overall yield from **11**. Since attempted separation of the mixture of diastereoisomers was unsuccessful, the following sequence of reactions was carried out using a mixture of stereoisomers. Making use of the method by Stevens,<sup>8</sup> **12** was converted to the adduct **13** by treatment with the Grignard reagent derived from 3-(chloromethyl)furan in the presence of copper(i) cyanide. The Sharpless epoxidation of **13** followed by protection of the hydroxy group with *t*-butyldimethylsilyl chloride provided **14** in 95% overall yield from **13**. Regioselective opening of the oxirane in **14** with diphenyl diselenide–sodium borohydride followed by desilylation furnished the diol **15**. Finally, treatment of **15** with excess of sodium periodate caused oxidative cleavage of the 1,2-diol function and concomitant selenoxide fragmentation to provide noroxopenlanfuran **5**,  $[\alpha]_{\text{D}}^{19} -82.6^\circ$  (*c* 0.21,  $\text{CHCl}_3$ ) {lit<sup>3</sup>  $[\alpha]_{\text{D}}^{20} -91.0^\circ$  (*c* 0.79,  $\text{CHCl}_3$ )}, whose physical data are in good accordance with those of the natural product<sup>3</sup> in all respects. It was thus demonstrated that the absolute stereostructures of noroxopenlanfuran **5** and penlanfuran **6** are *R*-(–)-3-(3-furyl)-methyl-4-isopropylcyclohex-2-en-1-one and (*R*)-(–)-(3-furyl)methyl-6-isopropyl-3-methylenecyclohex-1-ene, respectively.

The synthesis of penlanfuran **6** from **13** is being studied.

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