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

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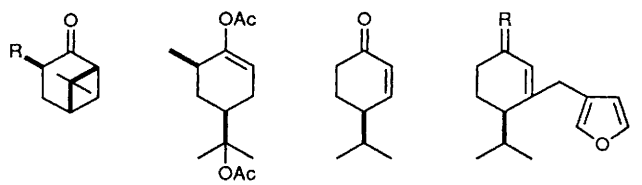
Starting with (*R*)-(−)-cryptone, prepared in 42% overall yield from (+)-nopinone in five steps, the first synthesis of noroxopenlanfuran was accomplished, confirming its absolute configuration.

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**.[1] 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**[2] and its transformation to noroxopenlanfuran **5**,[3] 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**.[3]

(+)-Nopinone **3**, $[\alpha]_D^{23}$ +36.9° (*c* 4.2, MeOH); 92% optical purity,[1] boron trifluoride–diethyl ether promoted cyclobutane cleavage gave a good yield of the diacetate **7**, $[\alpha]_D^{14}$ −49.5° (*c* 2.00, $CHCl_3$) (Scheme 1). Pyrolysis of **7** followed by regioselective hydrogenation of the resulting diene **8** provided the enol acetate **9**, $[\alpha]_D^{14}$ −59.2° (*c* 1.52, $CHCl_3$), 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[4] of **10** provided (*R*)-(−)-cryptone **4**, $[\alpha]_D^{29}$ −98.2° (*c* 0.54, EtOH),† 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,[7] the allylic alcohol **11** was prepared by the addition of methylthiomethyllithium to **4**. Methylation of **11**



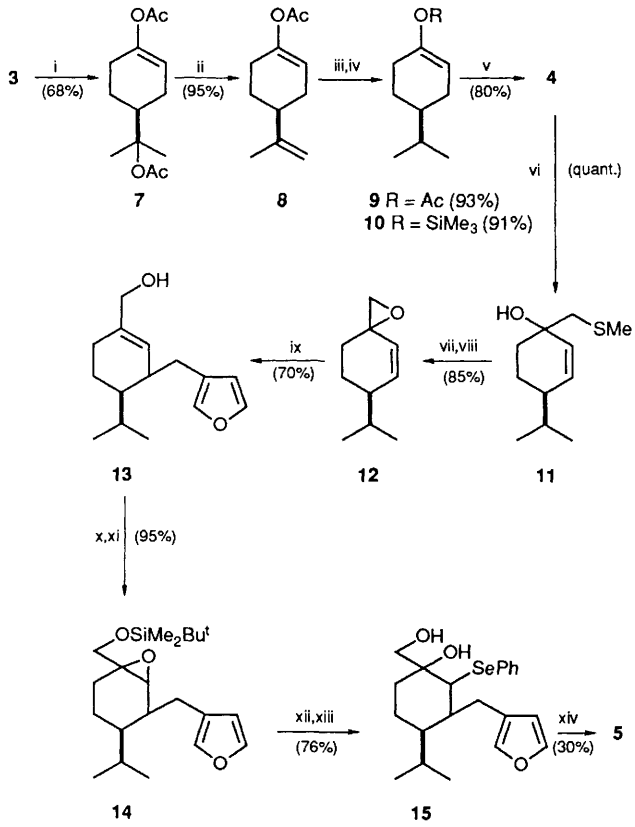
1 R = Me
3 R = H

2

4

5 R = O
6 R = CH_2

† (*R*)-(−)-Cryptone **4** was first reported to show $[\alpha]_D^{20}$ −119.3° (*c* 2.0, EtOH),[5] whereas **4** obtained from optical purification *via* (−)-cryptol showed $[\alpha]_D^{20}$ −91.7° (*c* 2.2, EtOH).[6]



Scheme 1 *Reagents and conditions:* i, BF_3·OEt_2, $Zn(OAc)_2$, Ac_2O, room temp., 30 h; ii, 500 °C, toluene; iii, H_2, $(Ph_3P)_3RhCl$, PhH; iv, MeLi, Me_3SiCl, HMPA, diethyl ether, −78 to 0 °C, 4 h; v, $Pd(OAc)_2$, acetonitrile, room temp., 7 h; vi, BuLi, Me_2S, TMEDA, THF; vii, MeI, acetone, room temp.; viii, Bu^tOK, THF, room temp., 4 h; ix, $(C_4H_3O)CH_2MgCl$, CuCN, THF, −78 to −5 °C, 5 h; x, Bu^tOOH, $VO(acac)_2$, toluene, 0 °C, 3 h; xi, Bu^tMe_2SiCl, imidazole, DMF; xii, PhSeSePh, $NaBH_4$, ethanol, reflux, 7 h; xiii, Bu_4NF, THF, room temp.; xiv, $NaIO_4$, 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,[8] **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**, $[\alpha]_D^{19}$ −82.6° (*c* 0.21, $CHCl_3$) {lit[3] $[\alpha]_D^{20}$ −91.0° (*c* 0.79, $CHCl_3$)}, whose physical data are in good accordance with those of the natural product[3] 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.

Received, 14th August 1990; Com. 0/03734F

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