Efficient Preparation of a Key Intermediate Suitable for the Asymmetric Synthesis of (+)-Vernolepin and (−)-Vernomenin

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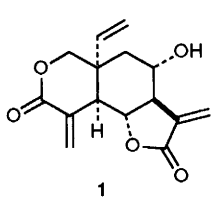
Starting with (1*R*,5*S*)-4,6,6-trimethyl-3-(phenylthio)bicyclo[3.1.1]hept-3-en-2-one, readily obtainable in large quantities from (+)-nopinone, (4a*R*,6*RS*,8a*R*)-6-methoxy-5-methylene-8a-vinyl-7-oxaoctahydronaphthalen-2(1*H*)-one, a promising key intermediate for the asymmetric synthesis of C_{14}-oxygenated elemanolides, (+)-vernolepin and (−)-vernomenin, are prepared in 14 steps and *ca.* 25% overall yield.

(+)-Vernolepin **1** and (−)-vernomenin **2**, isolated from Ethiopian Compositae, *Veronia hymenolepis*, by Kupchan in 1968,[1] are well-known elemanolide sesquiterpene dilactones. A variety of synthetic approaches and total syntheses[2] for **1** and **2** have been carried out, not only from a synthetic standpoint based on both a stereochemically novel and highly oxygenated 2-oxa-*cis*-decalin unit having an angular vinyl group, but also from the remarkable cytotoxic and antitumour activity of vernolepin **1**. However, unexpectededly, no previous synthetic study for **1** and **2** in an optically active form has been reported.

We have been studying the utility of reactive nopinone derivative, (1*R*,5*S*)-4,6,6-trimethyl-3-(phenylthio)bicyclo-[3.1.1]hept-3-en-2-one **3**,[3,4] readily obtainable from (+)-nopinone **4** in four steps and >80% overall yield, toward asymmetric synthesis of natural products, and recently reported the total synthesis of elemanoids, (+)-β-elemenone[3] and (+)-eleman-8β,12-olide,[4] starting from 3 *via* (4*S*)-(−)-4-methyl-4-vinylnopinone **5**. In connection with our programme dealing with asymmetric synthesis of elemanoid natural products, we present here a preparation of a promising key-intermediate, (4a*R*,6*RS*,8a*R*)-6-methoxy-5-methylene-8a-vinyl-7-oxaoctahydronaphthalen-2(1*H*)-one **6**, necessary for the asymmetric synthesis of (+)-vernolepin **1** and its congener (−)-**2**.



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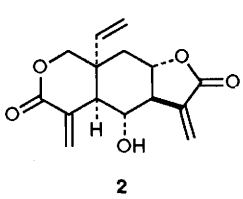

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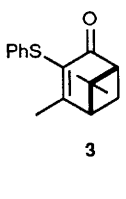

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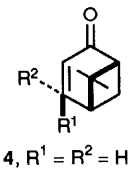
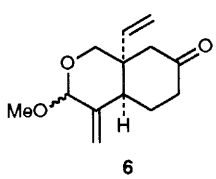


4, $R^1 = R^2 = H$
5, $R^1 = Me$, $R^2 = CH{=}CH_2$



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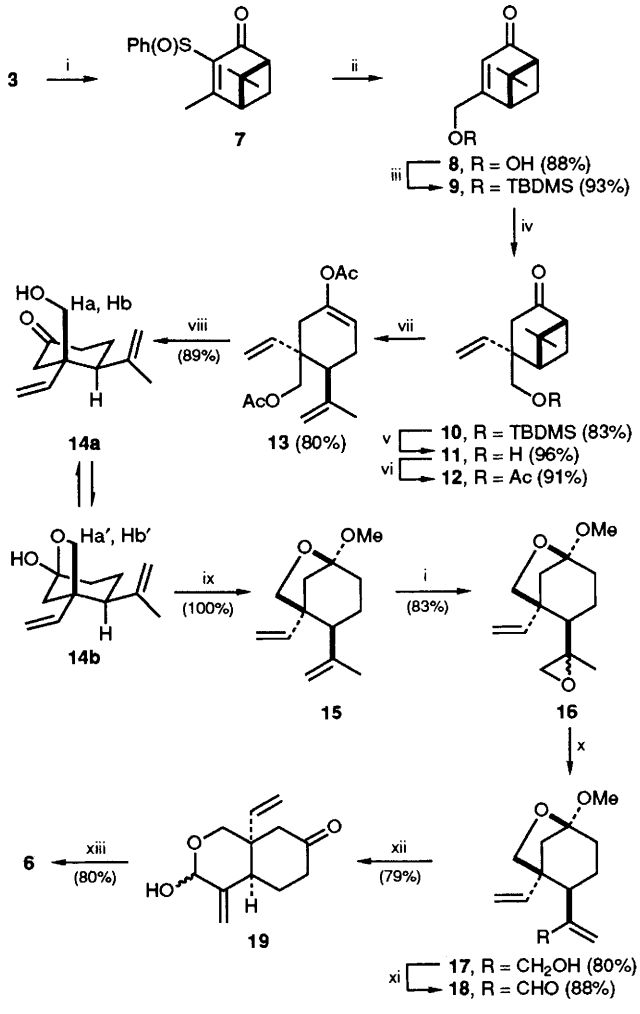
As compared with the synthetic intermediate **5** employed for the aforementioned elemanoid synthesis,[3,4] the present synthesis requires, as the first synthetic intermediate, 4,4-disubstituted nopinone **11** possessing a hydroxymethyl group whose oxygen atom acts as the ether-oxygen of 2-oxa-*cis*-decalin skeleton in a later stage. Thus, the sulfoxide **7**, readily obtainable by oxidation of **3** with *m*-chloroperoxybenzoic acid (mCPBA), was gently warmed in aqueous pyridine, wherein deconjugated enone formation followed by sulfoxide–sulfenate rearrangement[5] occurred to provide alcohol **8** $[\alpha]_D^{17}$ +270 (*c* 1.18, $CHCl_3$) in high yield (Scheme 1). The compound **8** was then protected as the *tert*-butyldimethylsilyl (TBDMS) ether **9**. Conjugate addition of **9** with vinylmagnesium bromide in the presence of a catalytic amount of copper(I) bromide–dimethyl sulfide complex proceeded smoothly in a highly stereoselective fashion[3,4] to give the adduct **10** as the sole product. Subsequent deprotection of **10** afforded the requisite **11** in 61% overall yield from **3**.

We have confirmed the combined reagent, boron trifluoride ether–zinc acetate in acetic anhydride to be suitable for regioselective ring-opening of nopinone derivatives with little loss of optical integrity.[3,4,6] Upon treatment under our reaction conditions was realized the cyclobutane-ring opening of the acetate **12** derived from acetylation of **11**, giving the enol acetate **13**, $[\alpha]_D^{20}$ +10.9 (*c* 1.81, $CHCl_3$), in high yield.

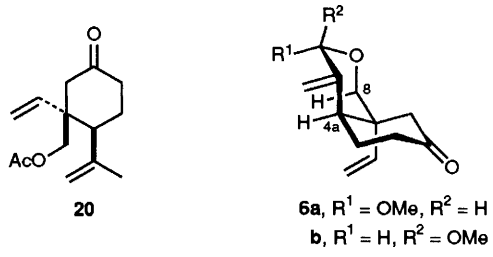
Upon hydrolysis of **13** with K_2CO_3 in methanol, the initially formed hydroxy ketone **14a** resulted in equilibrium with 7-oxabicyclo[3.2.1]octan-1-ol **14b** owing to neighbouring participation of an axially oriented hydroxymethyl group to a ketone function. The ^1H NMR (400 MHz, $CDCl_3$) spectrum



Scheme 1 *Reagents and conditions*: i, *m*CPBA (1.0 equiv.), CH_2Cl_2; ii, py, H_2O, 60 °C; iii, TBDMSCl, imidazole, DMF; iv, CH_2=CHMgBr, CuBr·Me_2S, THF; v; TBAF, THF; vi; Ac_2O, Et_3N, DMAP, CH_2Cl_2; vii; BF_3·OEt_2, $Zn(OAc)_2$, Ac_2O, room temp., 4 days; viii, K_2CO_3, MeOH; ix, $CH(OMe)_3$, *p*-TsOH, PhH; x, diethylaluminium 2,2,6,6-tetramethylpiperidide, toluene; xi, MnO_2, CH_2Cl_2; xii, CSA, THF, H_2O; xiii, $CH(OMe)_3$, PPTS, CH_2Cl_2; py = pyridine; TBDMSCl = *tert*-butyldimethylsilyl chloride; THF = tetrahydrofuran; TBAF = tetrabutylammonium fluoride; DMAP = 4-dimethylaminopyridine; CSA = 10-camphorsulfonic acid; PPTS = pyridinium toluene-*p*-sulfonate

shows two resonances (a 1:1 ratio) due to the methylene protons bonded with the ether oxygen atom at δ 4.00 (br s, exchangeable with D_2O to d, *J* 9.5 Hz) and 3.75 (d, *J* 9.5 Hz), respectively. At −60 °C, two pairs of AB pattern centred at δ 4.02 ($J_{Ha,Hb}$ = 8.5 Hz; Δ_v = 156 Hz) and 3.68 ($J_{Ha',Hb'}$ = *ca.* 10 Hz, Δ_v = 54 Hz) occurred, indicating the presence of an equilibrium mixture of **14b** and **a** in a ratio of 6:1 from integration. The structural assignment of **14a** and **b** was supported by the IR(neat) analyses; the carbonyl stretching band of **14** is obtained at 1707 cm^{-1} with medium intensity at room temperature, whereas at 1705 cm^{-1} with a very weak one at −60 °C. Chemically, acetylation (Ac_2O, py) of **14** provided the acetoxy ketone **20** as the sole product, whereas methylation (NaH, MeI, THF and methyl orthoformate, toluene-*p*-sulfonic acid, CH_2Cl_2) gave the bridged compound **15** in 80 and 100% yield, respectively.

To introduce an oxygen function into the isopropenyl side chain, **15** was oxidised with mCPBA to give epoxide **16**, which on warming with diethylaluminium 2,2,6,6-tetramethylpiperidide[7] afforded allyl alcohol **17** in 80% overall yield.



Finally, the aldehyde **18** obtained by Swern oxidation of **17** was treated with CSA in aqueous THF to yield hemiacetal **19**, which was converted on treatment with trimethyl orthoformate to the desired acetal **6** as an epimeric mixture (a 3:1 ratio) with respect to the methoxy group in 80% overall yield from **17**. In the ^1H NMR (400 MHz, $CDCl_3$) analyses, the resonances owing to the angular proton (C_{4a}) of the major **6a**, $[\alpha]_D^{22}$ −27.0 (*c* 0.76, $CHCl_3$), and the minor **6b**, $[\alpha]_D^{22}$ +109.5 (*c* 0.60, $CHCl_3$), exhibit a broad singlet with half band width (10 Hz) at δ 2.78 and 2.53, respectively, indicating that the two isomers exist predominantly in the steroidal conformation with equatorial configuration of the C_{4a}–H in the *B* ring. In addition, comparison of the chemical shifts of the above protons is indicative of the stereochemical assignment of the methoxy group in the *A* ring; axial orientation of the methoxy group in **6a** causes the C_{4a} proton to shift downfield by 0.25 ppm. The similar trend (*ca.* 0.2 ppm downfield shift) was observed in comparison of the resonances due to the axial proton of C_8 methylene group between the two epimers, **6a** and **b**.

For the asymmetric synthesis of our target elemanolides, the utility of the compound **6** as the key-intermediate can be fully evaluated because the acetal function in the *A* ring is synthetically equivalent to δ-lactone function, and because the ketone function in the *B* ring serves as an important clue necessary for construction of the *exo*-methylene γ-lactone moiety, as can be surmised from the successful total syntheses wherein functionalised 2-oxa-*cis*-decalin derivatives similar to **6** were first synthesised, and elaborated to (±)-**1** and (±)-**2**.[2]

A synthetic study of (+)-**1** and (−)-**2** from **6** is in progress.

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