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A Key Intermediate for the Chiral Synthesis of Elemanoids. Synthesis of (+)-β-Elemenone

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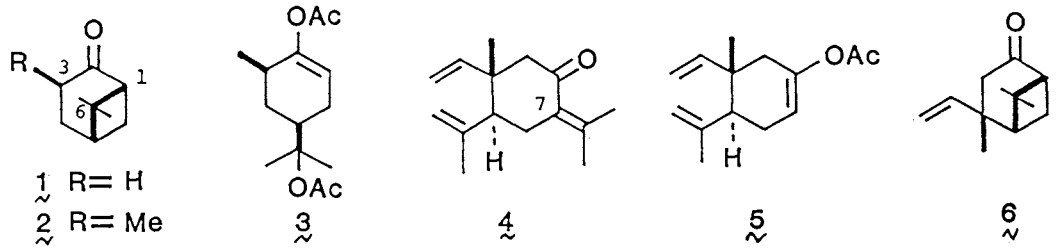
(1R,5S)-3-Phenylsulfenyl-6,6-dimethylbicyclo[3.1.1]heptanone obtained from (+)-nopinone was transformed into (1R,4S,5S)-4-methyl-4-vinylbicyclo[3.1.1]heptan-2-one, whose cyclobutane ring was cleaved with $BF_3 \cdot EtO_2$-$Zn(OAc)_2$ in acetic anhydride to provide (4S,5S)-1-acetoxy-4-isopropenyl-5-methyl-5-vinyl-1-cyclohexene (**5**), the key intermediate, in a highly regio- and stereoselective manner. Regioselective introduction of a three-carbon unit to **5** with acetone followed by dehydration yielded (+)-β-elemenone.

Nopinone (**1**) has frequently been employed as a chiral and versatile starting material for natural product synthesis.[1] One of useful transformation reactions of **1** is the mineral acid-catalyzed cleavage of a cyclobutane bond giving cyclohexanone derivatives having a C(4)-isopropyl unit,[2] and this reaction was also extended to substituted nopinones such as (+)-cis-3-methylnopinone (**2**)[2b,3] A serious problem, however, was arisen from almost complete racemization of the products in this reaction.[2b,3,4] Thus an adequate solution of the problem in connecting substituted nopinones with cyclobutane ring-opened products without loss of optical purity has been awaited.[5] We recently found a combined reagent, $BF_3 \cdot OEt_2$-$Zn(OAc)_2$-Ac_2O, to be highly effective to solve this problem: treatment of **2** with this reagent at ambient temperature gave diacetate **3** in high yield with virtually no loss of optical purity.[6] This reaction is featured by (i) regioselective C(1)-C(6) cyclobutane bond cleavage without loss of optical purity, (ii) regioselective formation of an enol acetate such as **3**, and (iii) mild reaction conditions.

We then focused our attention on the general application of this fascinating cleavage reaction to natural product synthesis. In this study, elemanoid sesquiterpenes were chosen as synthetic targets. Since the sesquiterpenes of this class have a functionalized isopropyl unit commonly at the C(7) position as seen in β-elemenone (**4**), enol acetate **5** was envisioned as the crucial synthetic intermediate that would allow regioselective introduction of an isopropyl unit to the desired position. Compound **5** would be derivable, under the cyclobutane cleavage conditions mentioned above, from the 4,4-disubstituted nopinone **6**,



3 4 5 6

which would be prepared by conjugate addition of a vinyl equivalent to a verbenone derivative such as **11**.

Phenylsulfenylation of the lithium enolate of (+)-nopinone (**1**) with phenyl benzenethiosulfate[7] at -78 °C followed by warming up to room temperature provided **7a** (mp 97-98 °C) and **7b** as the major and minor products, respectively (Scheme 1). The former product is thermodynamically stable while the latter is the kinetically controlled product as evidenced by ready isomerization of the latter to the former with DBU in refluxing benzene.[8]

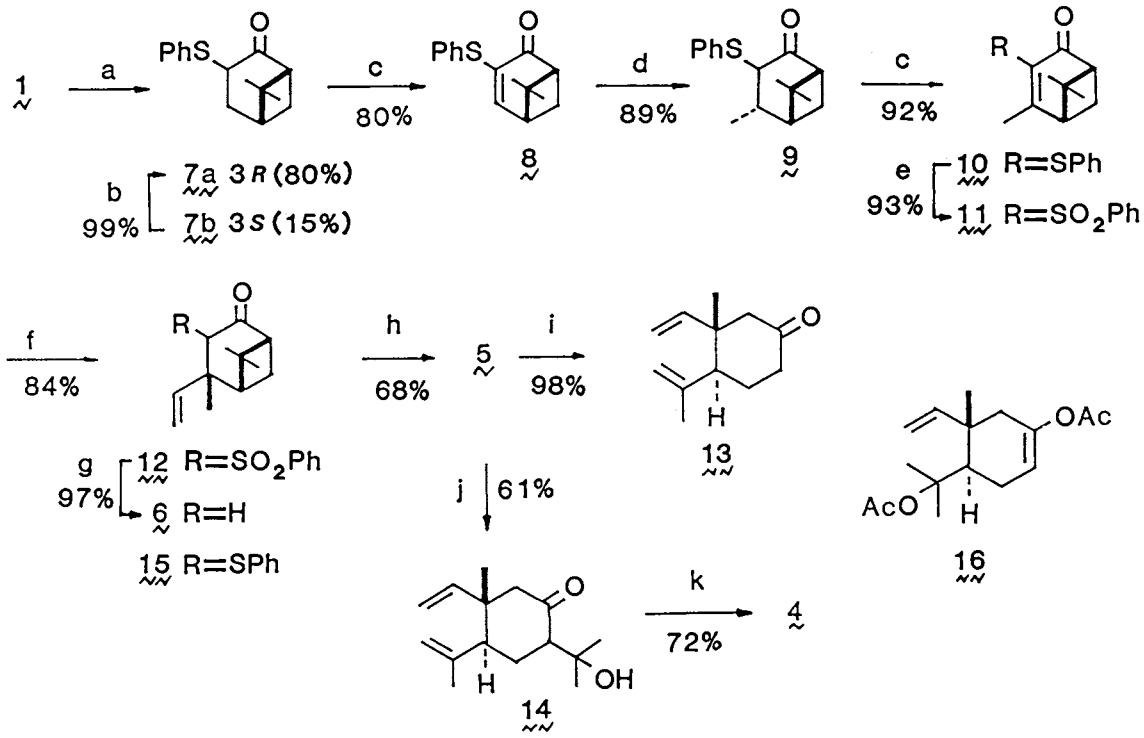
The epimeric mixture **7** was then treated with an equimolar amount of mCPBA and the resulting sulfoxides were submitted to the Pummerer rearrangement with Ac_2O containing a catalytic amount of MsOH to give **8** in good yield. Conjugate addition of lithium dimethylcuprate to **8** in THF proceeded stereoselectively to give (4S)-methylnopinone derivative **9**[9] as the sole product. The configurational assignment of the newly introduced methyl group in **9** was based on the well-documented stereoselectivity in reactions of pinane derivatives.[10] Conversion of **9** to enone **10** was achieved by repetition of the above two-step sequence of reactions, i.e. oxidation of **9** with mCPBA followed by the Pummerer rearrangement of the resulting sulfoxide with Ac_2O containing MsOH. This led **9** to the desired **10**,[11] mp 64-65 °C, in almost quantitative yield.

The enone **10** was treated with an organocopper reagent prepared from vinylmagnesium bromide and $CuBr \cdot Me_2S$ in THF. The conjugate addition, however, afforded the desired adduct **15** in disappointingly low yield (37%). The excellent result was realized by the use of sulfone **11**, obtained from oxidation of **10** with two equiv. of mCPBA, in the reaction with the same organocopper reagent, and adduct **12**[9] was obtained in 84% yield. Desulfurization of **12** with Li in liq. NH_3 provided the desired **6**, $[\alpha]_D^{21}$ +87.9° (c 2.15, $CHCl_3$), in high yield (27% overall yield from **1**). Thus, the phenylsulfenyl group of **8** served not only as an activator in the successive conjugate additions but also to generate the double bond in **10** for the second conjugate addition.[11]

Having the 4,4-disubstituted nopinone **6** in hand, attention was focused on the cyclobutane ring opening of **6** under our standard conditions. Treatment of **6** with $BF_3 \cdot OEt_2$ (0.1 equiv.) and $Zn(OAc)_2$ (1.0 equiv.) in Ac_2O at room temperature for 20 h followed by aqueous workup provided the key intermediate **5**, $[\alpha]_D^{19}$ -7.6° (c 0.48, $CHCl_3$), as the sole ring-opened product. Unlike our previous observations,[6] it is noteworthy that even a trace of diacetate **16** was not detectable.[12] Hydrolysis of **4** with methanolic K_2CO_3 furnished the known cyclohexanone **13**, $[\alpha]_D^{21}$ -29.2° (c 1.44, $CHCl_3$)(lit[13b] $[\alpha]_D^{23}$ -26.2°, $CHCl_3$) which has been recognized as a potential synthetic intermediate for elemanoids.[13]

The utility of the compound **5** toward natural product synthesis was first

demonstrated by the regioselective synthesis of β-elemenone (**4**)[14] in the optically active form. The lithium enolate generated from **5** with MeLi (2 equiv.) in Et_2O was treated with acetone in the presence of $ZnCl_2$ at -78 °C to give hydroxy ketone **14** in good yield along with a small amount of **13**. Dehydration of **14** with $SOCl_2$ in pyridine at 0 °C for 2 h followed by stirring at room temperature for 5 h provided (+)-β-elemenone (**4**), $[\alpha]_D^{18}$ +46.0° (c 0.80, $CHCl_3$)(lit[13b] $[\alpha]_D^{23}$ +39.3°, $CHCl_3$), whose physical data were identical with those of the authentic compound[13b] in all respects.



(a) LDA, $PhSO_2SPh$, THF, -78 °C - rt, 15 h; (b) DBU, PhH, refl., 1 h; (c) (i) mCPBA, CH_2Cl_2, (ii) MsOH, Ac_2O, CH_2Cl_2; (d) Me_2CuLi, THF; (e) mCPBA (2 equiv), CH_2Cl_2; (f) CH_2=CHMgBr, CuBr·Me_2S, THF; (g) Li, NH_3(l); (h) BF_3·OEt_2, $Zn(OAc)_2$, Ac_2O, rt, 20 h; (i) K_2CO_3, MeOH; (j) MeLi, $ZnCl_2$, acetone, Et_2O, -78 °C; (k) $SOCl_2$, Py, rt.

Scheme 1.

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8) Stereospecificity in the α-alkylation of **1** is well-known. For example, methylation of **1** with MeI under basic and kinetically controlled conditions afforded less stable trans-3-methylnopinone, which easily isomerized to the thermodynamically stable cis isomer on treatment with alkoholic KOH (ref. 5b).

9) **9** and **12** are epimeric mixtures with respect to the phenylsulfenyl and phenylsulfonyl groups, respectively.

10) This assignment was correct as evidenced by derivation to the known compound **13** as described later.

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