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# Total Synthesis of (±)-Carpesiolin

Total synthesis of (±)-carpesiolin (1) is described using a new and general synthetic route to helenanolide sesquiterpenes. The scheme includes the stereocontrolled introduction of the C-10 α-methyl group in the perhydroindanone (3) and its conversion to the perhydroazulenone (4) *via* the regiospecific ring expansion reaction.

**Keywords**——carpesiolin; total synthesis; pseudoguaianolide; helenanolide; ring expansion reaction; perhydroindanone; perhydroazulenone

The pseudoguaianolides constitute one of the largest groups of sesquiterpene lactones with wide distribution in plant kingdom. Due mainly to their unique structures and the interesting biological activities associated with some of them, many synthetic studies have recently been undertaken, especially of the helenanolides (those with an α-oriented C-10 methyl group).[1]

Here we would like to present a new and straightforward route to helenanolides using a ring expansion reaction as the key step, and its application to the total synthesis of (±)-carpesiolin (1), an antibiotic substance isolated from *Carpesium abrotanoides* L. by Maruyama and Omura.[2] This compound, named 6α-hydroxy-2,3-dihydroaromaticin, is also isolated from *Telekia speciosa* (Schreber) Baumg.[3]

The synthetic scheme is shown in Chart 1. The features of this route are; i) complete control of the C-10 methyl group in α-orientation in a perhydroindanone, ii) a regiospecific

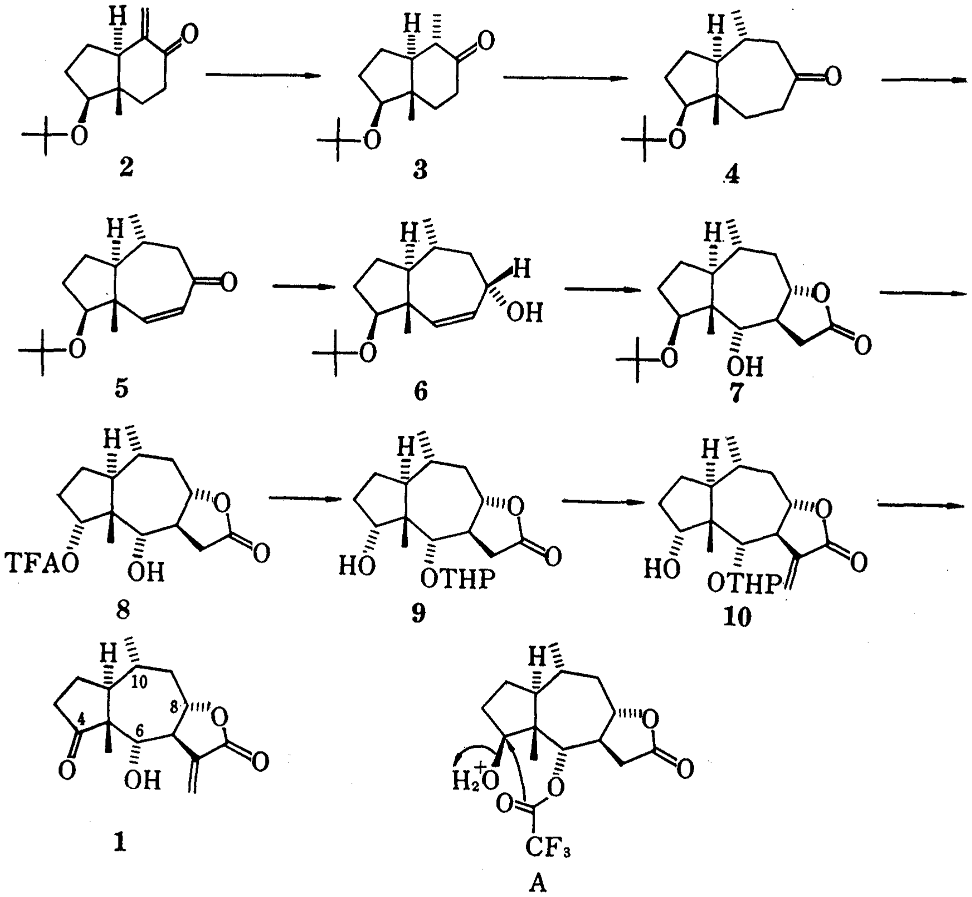

Chart 1

ring expansion to a perhydroazulenone and iii) complete control of other chiralities on the 7-membered ring.

The readily available α-methylene ketone (**2**)[4] was hydrogenated [$H_2$ (3 atm)/$PtO_2$/MeOH] and equilibrated (MeONa/MeOH) to give stereospecifically the desired α-methyl ketone (**3**)[5] in 77% yield. The crucial regiospecific ring expansion was examined using **3** and the derivatives thereof, but the best result was obtained by using Nozaki's procedure;[6] the reaction of **3** with dibromomethyllithium generated *in situ* [lithium diisopropylamide(LDA)–$CH_2Br_2$/THF/−78°C], followed by treatment with butyllithium, gave the perhydroazulenone (**4**) in 40% yield.[7,8]

The regiospecific introduction of the double bond into **4** was accomplished using phenylselenenylation–deselenenylation sequence [i) LDA/THF, PhSeBr, ii) $H_2O_2$/THF] in 68% yield. The stereospecific reduction of the enone (**5**) thus obtained was achieved with $LiAlH_4$ in THF to give the allylic alcohol (**6**) in 90% yield. Its stereochemistry was deduced from the results of reduction in similar cases.[1] Henbest-type epoxidation of **6** (*m*-chloroperbenzoic acid/$CH_2Cl_2$), followed by nucleophilic epoxide ring opening by excess dilithioacetate (DME–HMPA/55°C), gave the desired γ-lactone (**7**) in 44% yield.

Treatment of **7** with trifluoroacetic anhydride in pyridine followed by *p*-TsOH in boiling toluene (to remove the *tert*-butyl group), afforded the unexpected hydroxy-ester (**8**) in 89% yield. Its structure was established as follows: in its PMR spectrum the methine proton at C-6 was found to resonate at $\delta$ 3.47 (t, $J$=8 Hz; d, $J$=8 Hz upon $D_2O$ addition), in contrast to the value of 5.10 (d, $J$=8 Hz) for the trifluoroacetate of **7**.[9] Although the occurrence of **8** was quite surprising, its functionalities were suitable for the subsequent steps.

The conversion of **8** to the lactone (**9**) was achieved in the usual manner [i) dihydropyran–pyridinium *p*-toluenesulfonate/$CH_2Cl_2$, ii) 5% $K_2CO_3$/THF] in 95% yield. Grieco's methylenation sequence [i) LDA/THF, $CH_2O$, ii) MsCl/pyridine, iii) DBU/$C_6H_6$] was successfully applied to **9** to give the α-methylene lactone (**10**) in 56% yield. The final sequence of reactions [i) pyridinium chlorochromate (PCC)-AcONa/$CH_2Cl_2$, ii) *p*-TsOH/$C_6H_6$–$H_2O$] gave (±)-**1** in 50% yield, whose IR and PMR spectra were completely identical with those of the natural product.[10,11] Application of the scheme to the synthesis of other helenanolides is in progress.

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## References and Notes

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2) M. Maruyama and S. Omura, *Phytochemistry*, **16**, 782 (1977). The structure was established by synthesis; see ref. 1*d*).

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5) All new compounds formulated in this report showed satisfactory spectral data and elemental analyses.

6) H. Taguchi, H. Yamamoto, and H. Nozaki, *Bull. Chem. Soc. Jpn.*, **50**, 1588, 1592 (1977).

7) The structure of this compound was ascertained by comparison with the C-9 oxo-regioisomer, prepared in an alternative way.

8) During this work Schlessinger *et al.* synthesized this compound *via* a different route, which was converted into helenalin; see ref. 1*c*).

9) Further supporting evidence for the structure of **8** were: i) cycloheptanone formation (IR: 1700 $cm^{-1}$) upon PCC oxidation, ii) acetonide formation [$Me_2C(OMe)_2$–*p*-TsOH/$Me_2CO$] from its corresponding diol,

indicating the α-orientation of hydroxyl group at C-4. This type of acyl migration with concomitant inversion of the hydroxyl group may best be explained by the acyl group participation as A shown in Chart 1.

10) Our synthetic compound showed the following characteristics. Mp 197—200°C ($CHCl_3$–hexane).[11] IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 3470, 1765, 1730. PMR ($CDCl_3$) $\delta$: 6.22 (1H, d, $J=3.6$ Hz), 5.99 (1H, d, $J=3.2$ Hz), 4.38 (1H, ddd, $J=2.9$, 9.8, 10.7 Hz), 4.01 (1H, dd, $J=8.8$, 3.0 Hz; d, $J=8.8$ Hz on $D_2O$ addition), 2.94 (1H, d, $J=3.0$ Hz, disappeared on $D_2O$ addition), 1.09 (3H, d, $J=6.1$ Hz), 1.03 (3H, s).

11) The mp of (±)-carpesiolin reported in ref. 1*d*) is 145—148°C (sublimes). In a private communication Vandewalle explained that their sample probably includes water of crystalization.

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