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Stereocontrolled Synthesis of the Key Intermediate for the Enantioselective Synthesis of Clerodane Natural Products

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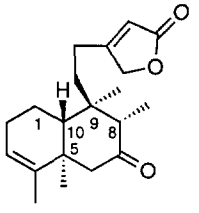
Abstract: Stereocontrolled synthesis of (+)-*trans*-decalone **7** (R = $CH{=}CH_2$) from (-)-verbenone (**5**), readily obtainable from (+)-nopinone (**2**), is described. The compound **7** possesses four correctly arranged chiral centers, C(5)-C(10)-C(9)-C(8), necessary for the enantioselective synthesis of *neo-trans*-clerodanes. © 1997 Elsevier Science Ltd.

Clerodanes constitute a large class of diterpenoids.[1] The majority of them display unique biological activities among which the insect antifeedant represented by clerodin[2] is well known. Since the most important characteristic of stereostructures in this class is the four contiguously arranged chiral centers; C(5)-C(10)-C(9)-C(8) (for example, see *neo-trans*-clerodane **1**), synthetic efforts have been practically focused on realization of this characteristic carbon-carbon arrangement in a stereocontrolled fashion.[1]

We have been studying the utility of (1*R*,5*S*)-(+)-Nopinone (**2**), obtainable in large quantities by ozonolysis of (-)-β-pinene, as the chiral source for the enantioselective synthesis of natural products. Recently, we have demonstrated that enol acetates **3** obtained from $BF_3{\cdot}OEt_2$-catalyzed cyclobutane opening of (1*R*,4*S*)-(+)-4,4-disubstituted nopinone **4**, readily accessible from **2**, act as a versatile building block for the enantioselective synthesis of elemane natural products.[3] In addition, since (+)-β-pinene is scarcely found in nature,[4] we have developed a general and convenient transformation of **2** into (-)-verbenone (**5**).[5] The compound **5** is a synthetic precursor of the enantiomer of **4**, thus indicating that the compound **2** serves as a common chiral source for both sets of compounds with respect to the absolute configuration of the target natural products. We now show, starting with (-)-**5**, the enantioselective synthesis of the compound **7** (R = $CH{=}CH_2$), which we want to use as the chiral key intermediate for the *neo-trans*-clerodanes.



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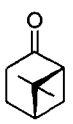

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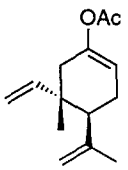

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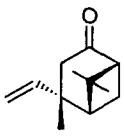

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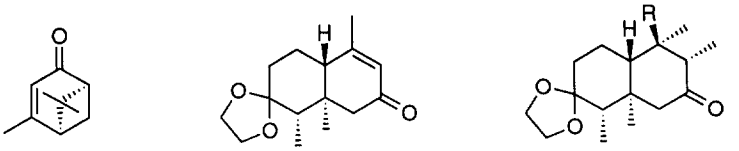
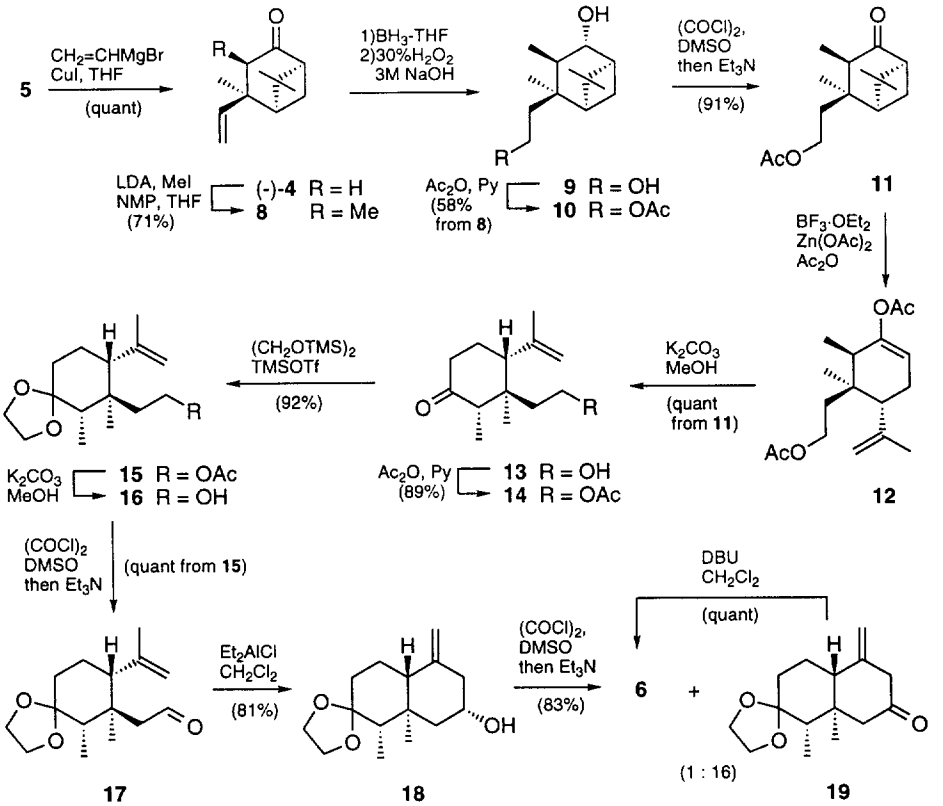


5 6 7

We designed the *trans*-octalone **6** as the promising key compound for this purpose, because stereocontrolled conjugate addition of carbon nucleophiles (Ṙ) to **6** followed by methylation of the resulting enolate anion and epimerization with a base could lead to the thermodynamically more stable intermediates **7**. The compound **7** possesses alkyl substituents with the same stereochemistry on the *trans*-decalone skeleton as those of the target clerodanes.

Conjugate addition of **5** with a vinyl Grignard reagent under standard conditions proceeded in a stereoselective fashion to give (1*S*,4*R*)-(-)-**4** in a quantitative yield[6] (Scheme 1). Subsequent methylation in the presence of 1-methyl-2-pyrrolidinone (NMP) provided trisubstituted nopinone **8** in good yield.[7] Chemical transformation of the vinyl to a 2-acetoxyethyl group was achieved by a sequence of conventional reactions: (1) hydroboration of **8** followed by oxidation with 30% H_2O_2, leading to the alcohol **9**, (2) regioselective acetylation, and (3) Swern oxidation of the resulting hydroxy acetate **10** with formation of the keto-acetate **11**.

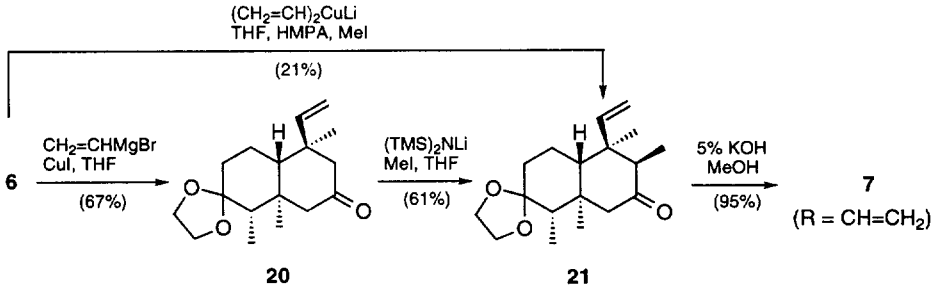


Scheme 1

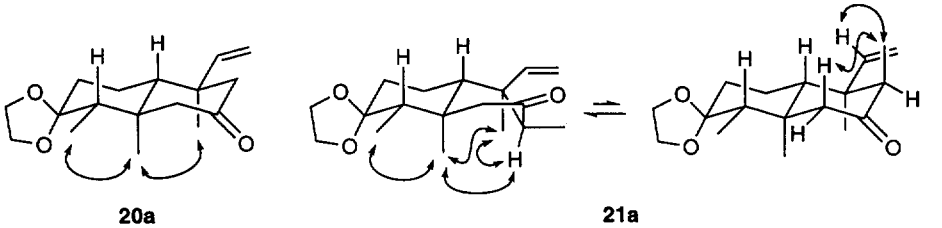
Regio- and stereoselective cyclobutane cleavage of **11** with our combined reagent, $BF_3{\cdot}OEt_2/Zn(OAc)_2/Ac_2O$,[8] proceeded cleanly to give the enol acetate **12**, whose hydrolysis with K_2CO_3 in methanol provided the cyclohexanone **13** with concomitant epimerization of the secondary methyl group in a quantitative overall yield from **11**. Protection of the hydroxyl group followed by acetalization of the resulting acetate **14** gave the acetal **15.** Hydrolysis and subsequent Swern oxidation of the resulting alcohol **16** provided the aldehyde **17** in a quantitative yield.

Stereoselective ene reaction of **17** with Et_2AlCl in CH_2Cl_2 underwent cleanly to give *trans*-decalol **18** with an axial hydroxyl group, as can be assumed by the well-documented reaction mechanism.[6,9] Finally, Swern oxidation of **18** provided a mixture (a 16 : 1 ratio) of the deconjugated enone **19** and the conjugated one **6** in 83% yield. The former was smoothly isomerized to the latter with DBU. Finally, the compound **6** was obtainable in 13 steps and ca. 20% overall yield from (-)-**5**.

With the requisite enone **6** in hand available, attention was focused on the key conjugate addition reaction in the present synthesis. The choice of the nucleophile depends on the C(9)-substituent of the target clerodanes. First, we planned, in this preliminary experiment, installment of a vinyl group which is equivalent to the synthetically versatile ethanol moiety. Conjugate addition of **6** with vinylmagnesium bromide in the presence of CuI proceeded smoothly in stereoselective fashion to give **20**[10] with the desired stereostructure (Scheme 2 and NOE correlations shown in **20a**). Trapping the enolate anion, generated from the conjugate addition of lithium divinylcuprate, with methyl iodide in the presence of HMPA proceeded in stereoelectronic fashion to provide the desired compound **21**.[10] However, the yield was low (21%). In addition, attempted methylation *via* cleavage of the TMS enol ether, prepared from the enolate anion with TMSCl, with MeLi proved fruitless.[11] Fortunately, treatment of **20** with $(TMS)_2NLi$ followed by methylation with methyl iodide provided **21** in 61 % isolated yield. For the stereochemistry of **21**, NOE correlations suggested the existence of equilibrium between boat and chair conformation of the B-ring, as depicted in **21a**.[12] Epimerization of **21** with 5% KOH in ethanol provided in a high yield (+)-**7** (R = $CH{=}CH_2$),[10] the promising intermediate for the synthesis of *neo-trans*-clerodanes.



Scheme 2



The acetal function at the C(3) position of **7** would serve as a clue for construction of not only the C(4)-olefin methyl or exomethylene group which most clerodanes possess as a common functional group from the viewpoint of biogenesis,[1,13] but also the oxygenated A ring.[1] In addition, the present synthesis of **7** (R = $CH{=}CH_2$) from **2** *via* (-)-**4** is a formal synthesis of its enantiomer, the key intermediate for the synthesis of *ent-neo-trans*-clerodanes, since chemical transformation of **2** to (+)-**4** has been accomplished as aforementioned. Further studies on the synthesis of clerodane natural products are in progress.

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6. For the related synthesis, see Kato, M.; Watanabe, M.; Masuda, Y. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2071-2075.
7. All new compounds exhibited satisfactory ^1H NMR, IR, and elementary analytical data.
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10. ^1H NMR(400MHz, $CDCl_3$): **20**; δ 0.81 (d, *J*=6.8 Hz, 3H), 0.95 (s, 3H), 1.03 (s, 3H), 1.38-1.52 (m, 1H), 1.56-1.64 (m, 3H), 1.77 (q, *J*=6.8 Hz, 1H), 1.89 (dd, *J*=9.6, 2.7 Hz, 1H), 2.09 and 2.39 (dd, *J*=14.0, 2.0 Hz, 1H each), 2.13 and 2.43 (d, *J*=14.0 Hz, 1H each), 3.75-4.03 (m, 4H), 4.97 (d, *J*=17.1 Hz, 1H), 5.04 (d, *J*=10.7 Hz, 1H), 5.76 (dd, *J*=17.1, 10.7 Hz, 1H). **21**; δ, 0.83 (d, *J*=6.8 Hz, 3H), 1.02 (d, *J*=7.0 Hz, 3H), 1.10 (s, 3H), 1.13 (s, 3H), 1.36-1.41 (m, 1H), 1.46-1.51 (m, 2H), 1.61 (m, 1H), 1.69 (q, *J*=6.8 Hz, 1H), 1.86 (dd, *J*=10.1, 1.6 Hz, 1H), 2.24 and 2.32 (d, *J*=15.0 Hz, 1H each), 2.42 (q, *J*=7.0 Hz, 1H), 3.77-4.02 (m, 4H), 4.93 (d, *J*=17.4 Hz, 1H), 5.06 (d, *J*=10.9 Hz, 1H), 5.58 (dd, *J*=17.4, 10.9 Hz, 1H). **7** (R = $CH{=}CH_2$); δ 0.80 (d, *J*=6.8 Hz, 3H), 0.80 (s, 3H), 0.85 (d, *J*=6.8 Hz, 3H), 0.90 (s, 3H), 1.41-1.52 (m, 2H), 1.57-1.65 (m, 2H), 1.79 (q, *J*=6.8 Hz, 1H), 1.87 (dd, *J*=10.0, 2.4 Hz, 1H), 2.18 and 2.42 (d, *J*=11.7 Hz, 1H each), 2.41 (q, *J*=6.8 Hz, 1H), 3.78-4.00 (m, 4H), 4.94 (d, *J*=17.3 Hz, 1H), 5.14 (d, *J*=10.8 Hz, 1H), 5.62 (dd, *J*=17.3, 10.8 Hz, 1H).
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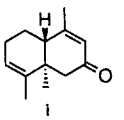
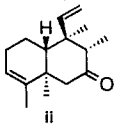
12. In the structures **21a**, the principal NOE correlations are shown. The molecular mechanics calculations (CAChe system/MM2 force field) of **21a** indicated the conformer having a boat form in the B-ring is more stable by 0.56 kcal/mol than that having a chair form. Details will be reported elsewhere.
13. Starting with **14**, preparation of another key intermediate **ii** has been performed in a synthetically satisfactory overall yield *via* the enone **i** according to the present synthetic route with a slight modification.



i



ii

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