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Asymmetric Michael-type Alkylation of Chiral Imines. Enantioselective Syntheses of (–)-Geosmin and Two Other Related Natural Terpenes, as well as *enant*-(+)-Geosmin

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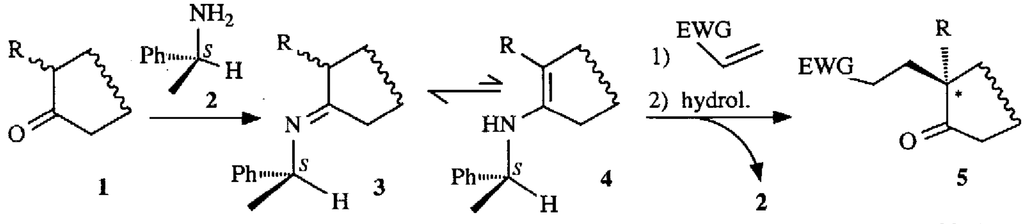
Summary : Natural (–)-geosmin **11**, (+)-octalone **14** (from *Vetiveria zizanioides*), and (+)-octalin **15** (from *Bazzania fauriana* and *B. angustifolia*) have been prepared in high chemical and enantiomeric yields *via* the asymmetric process involving Michael-type alkylation of chiral imines **6** and **12**. *Enant*-(+)-geosmin has been also synthesized by the same procedure.

A very efficient deracemizing alkylation of 2-monosubstituted cyclanone **1** leading to optically active functionalized 2,2-disubstituted cyclanone **5** has been achieved in our Laboratory[1]. The process relies on an asymmetric regioselective Michael-type alkylation of a chiral secondary enamine **4** –which is in equilibrium with imines **3** derived from racemic ketone **1**– by various electrophilic olefins. Thus, a carbonyl compound **5** bearing an α quaternary carbon center is obtained in very high chemical yield and enantiomeric excess[1,2].



racemic

Yield ~ 90 %

EWG : electron withdrawing group

ee ~ 90 %

Theoretical[3] as well as experimental[4] studies have been devoted to the mechanism of the reaction, the scope and limitations of which being also studied at present[5].

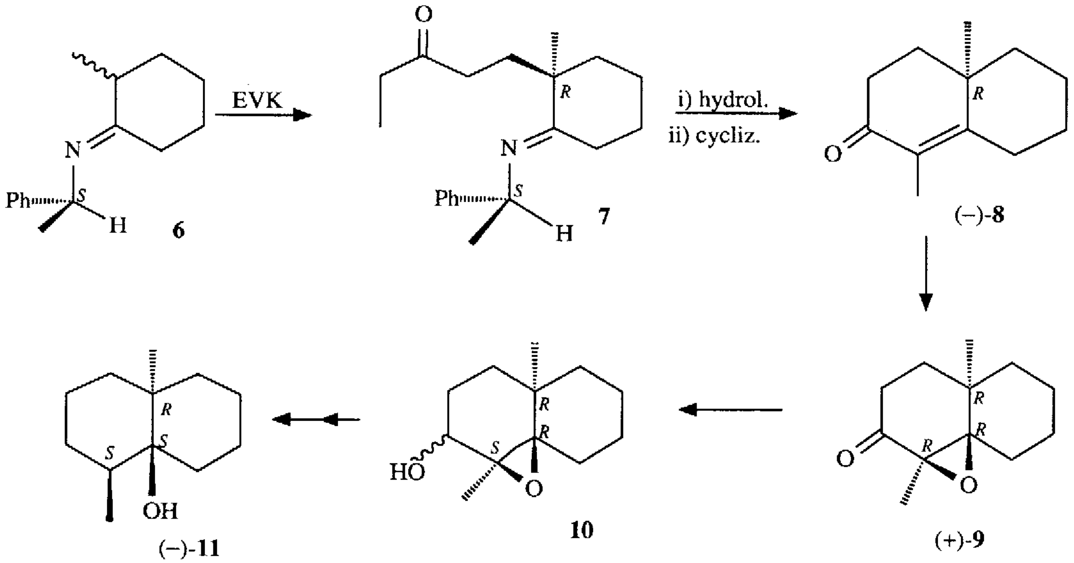
Substances of general formula **5** are useful building blocks for the synthesis of natural compounds and related ones. So far they have been used for total syntheses in the *steroid* field[6,7].

In this paper we report the use of the chiral imine method to the first total asymmetric syntheses of some optically pure *terpene* compounds.

Our first target was natural (−)-geosmin **11**, a metabolite of many actinomycetes, several blue-green algae, and some fungi, first isolated by Gerber and Lechevalier in 1965[8]. It is one of the pollutants responsible for an undesirable earthy-musty odor and taste in lakes and tap water[9]. In aqueous solution the olfactive threshold[10] is *5 parts in 10^{11}.*

Marshall[11,12] and Gerber[13] recognized the structure of geosmin as being *trans*-1,10-dimethyl-*trans*-9-decalol, through its first racemic total synthesis. Ayer, in 1976, determined the absolute configuration of geosmin by an hemi-synthesis from cybullol[14] and reported the same year another racemic total synthesis[15]. However, a very efficient (±)-geosmin synthesis was achieved only recently[16], starting from (±)-1,10-dimethyl-1(9)-octalone-2.

Our own enantioselective geosmin synthesis relies on this last approach, using optically pure octalone **8** obtained by alkylation of imines **6** by ethylvinylketone[17].

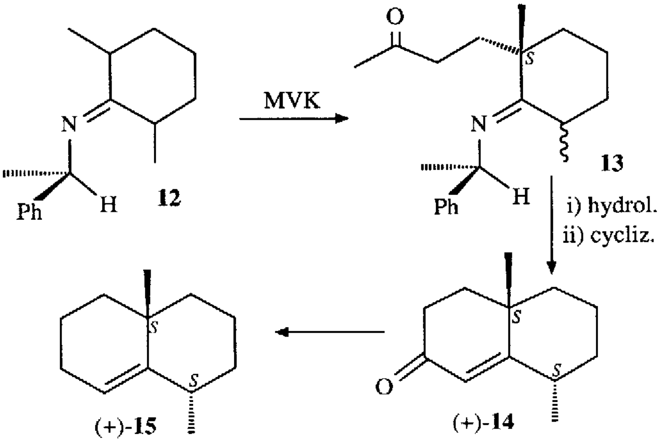


Thus, 2-methylcyclohexanone imines **6** (prepared in almost quantitative yield from 2-methylcyclohexanone and commercially available (*S*)-(−)-α-methylbenzylamine **2** by azeotropic removal of water in refluxing toluene) and one equivalent ethylvinylketone (r.t., 30 h) lead to the corresponding dialkylated imine **7** which, after hydrolysis (AcOH 20 %, r.t. 30 mn), cyclization (catal. NaOH, MeOH reflux, 12 h), and distillation, give chemically pure (−)-1,10-dimethyl-1(9)-octalone-2 **8** (ee ~ 85 %) in 67 % overall yield[18] from 2-methylcyclohexanone. Octalone **8** is efficiently obtained in at least 98.5 % optical purity through three successive recrystallizations from pentane (−20 °C → −78 °C) followed by distillation ; it has been identified (^{1}H NMR, IR, $[\alpha]^{20}_D$) with an authentic sample[19].

The aforementioned method[16] is then used with pure octalone **8** instead of its racemic counterpart[20]. (−)-Geosmin **11** (41 % overall yield from octalone **8**) is recrystallized twice from methanol (0 °C → −50 °C) and distilled, its optical purity thus being raised to at least 99.5 %[21].

Comparison of effects observed with each enantiomer of biologically active compounds is a subject of much interest[22]. In particular, olfactive properties regarding perception thresholds as well as odor and taste qualities are increasingly studied[23]. For this reason, *enant*-(+)-geosmin was a target of choice too. Starting with the enantiomers of imines **6** (prepared from 2-methylcyclohexanone and commercially available (*R*)-(+)-α-methylbenzylamine) it has been therefore synthesized along the same way used for (–)-geosmin **11**[24].

Our other targets were (+)-*trans*-8,10-dimethyl-1(9)-octalone-2 **14** isolated from *Vetiveria zizanioides* (L.) Nash[25] and its derived octalin **15**. This last compound (or its enantiomer) was isolated last year by Wu and Chang from *Bazzania fauriana* (Steph.) Hatt and from *Bazzania angustifolia* Horik[26]. Thus, synthesis of octalin **15** would also allow to determine the absolute configuration of the natural product.



Imines **12** (prepared in 76 % yield from 2,6-dimethylcyclohexanone and 3 equivalents (*R*)-(+)-methylbenzylamine in presence of $TiCl_4$ according to the procedure of Weingarten *et al.*[27]) and 1.2 equivalents methylvinylketone afford the corresponding alkylated imines **13**. Hydrolysis of crude imines **13** (AcOH 20 %, r.t., 30 mn), followed by cyclization (catal. KOH, MeOH reflux, 1 h) and distillation gives chemically pure octalone **14**[28] in 61 % overall yield from 2,6-dimethylcyclohexanone, as a crystalline material (ee = 73 %). In this case also, optically pure octalone **14** is obtained through several recrystallizations from a 3:1 pentane-ether mixture followed by distillation[29].

Marshall's route for the reduction of the racemic counterpart of compound **14**[12] has been followed, yielding (+)-*trans*-8,10-dimethyl-1(9)-octalin **15**[30]. Since compound **15** is dextrorotatory, the absolute configuration of the natural compound[26,31] is as depicted (*S*,*S*).

The optically active octalones **8** and **14** which are reported in this paper have been already used in racemic form as starting materials for the syntheses of racemic natural products[32].

Acknowledgments : *We wish to thank Drs. M. Pfau and D. Joulain for helpful discussions.*

References and Notes

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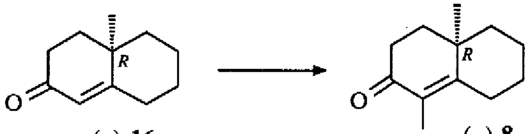

(−)-**16** (−)-**8**

20 Intermediate epoxy-ketone is flash chromatographied and distilled to afford the pure new chiral *trans*-compound **9** : bp 80 °C (0.02 torr), $[\alpha]^{20}_{D}$ −44° (*c* 3, EtOH).
Epoxy-ketone **9** is then reduced to a mixture of epoxy-alcohols **10** which is used directly for the final steps leading to (−)-geosmin **11**. An analytical sample of the major new chiral *equatorial* alcohol **10** is obtained through flash chromatography and distillation : bp 100 °C (0.02 torr), $[\alpha]^{20}_{D}$ +77° (*c* 2, EtOH).

21 **11** : mp 4 °C, bp 120 °C (15 torr), $[\alpha]^{20}_{D}$ −18° (*c* 15.3, EtOH), litt.[8], $[\alpha]^{25}_{D}$ −16.5° (*c* 0.5, $CHCl_3$).

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29 **14** : bp 80°C (0.02 torr), mp 57 °C, $[\alpha]^{20}_{D}$ +203° (c 2, $CHCl_3$), litt.[25], $[\alpha]^{20}_{D}$ +201.7° (*c* 2, $CHCl_3$).

30 **15** : bp 90 °C (15 torr), $[\alpha]^{20}_{D}$ +110° (*c* 2.5, $CHCl_3$).

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