Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 61 (2005) 3873–3879

First enantiospecific synthesis of (+)-β-herbertenol

Subhash P. Chavan,[a,*] Mahesh Thakkar,[a] Rajendra K. Kharul,[a] Ashok B. Pathak,[a] Gaurav V. Bhosekar[b] and Mohan M. Bhadbhade[b]

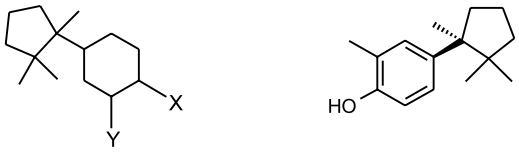
[a]*Division of Organic Chemistry: Technology, National Chemical Laboratory, Pune 411008, India*
[b]*Center for Materials Characterisation, National Chemical Laboratory, Pune 411008, India*

Received 4 August 2004; revised 23 December 2004; accepted 14 January 2005

Abstract—The first enantiospecific synthesis of (+)-β-herbertenol, from naturally occurring *R*-(+)-citronellal, employing Taber's diazo decomposition protocol as the key step, is described.

1. Introduction

Numerous herbertene type sesquiterpenoids, an expanding group of natural products possessing a 3-methyl-1-(1,2,2-trimethylcyclopentyl) cyclohexane skeleton **1**, have been isolated from *Herbertous* species and other *liverworts*.[1,2] Recently, Asakawa and co-workers reported the isolation of seven new herbertanes and two new cuperanes from Japanese liverworts.[3] Many of these compounds, particularly those with an oxygenated aromatic six membered ring, show a wide spectrum of biological properties, which include potent antifungal, neurotrophic and anti-lipid peroxidation activities (Fig. 1).[1a,b,4,5]



X= H, Y= Me; Herbertene skeleton (**1**)

X= Me, Y= H; Cuparene skeleton (**2**)

(-)-β-Herbertenol (**3**)

Figure 1. Herbertene and cuparene skeleton.

Because of the difficulties associated with the construction of the vicinal quaternary carbons in the cyclopentane ring, herbertanes and cuparanes have become popular synthetic targets in recent years.[6] Although, there are synthetic strategies reported towards (±)-β-herbertenol, not a single asymmetric synthesis is reported. Our interest in these skeletons has led to the synthesis of cuparenones[6i,j] and recently in the facile synthesis of (±)-β-herbertenol.[6k] In continuation of our efforts towards the synthesis of homochiral β-herbertenol, we describe herein the first enantiospecific synthesis of (+)-β-herbertenol.

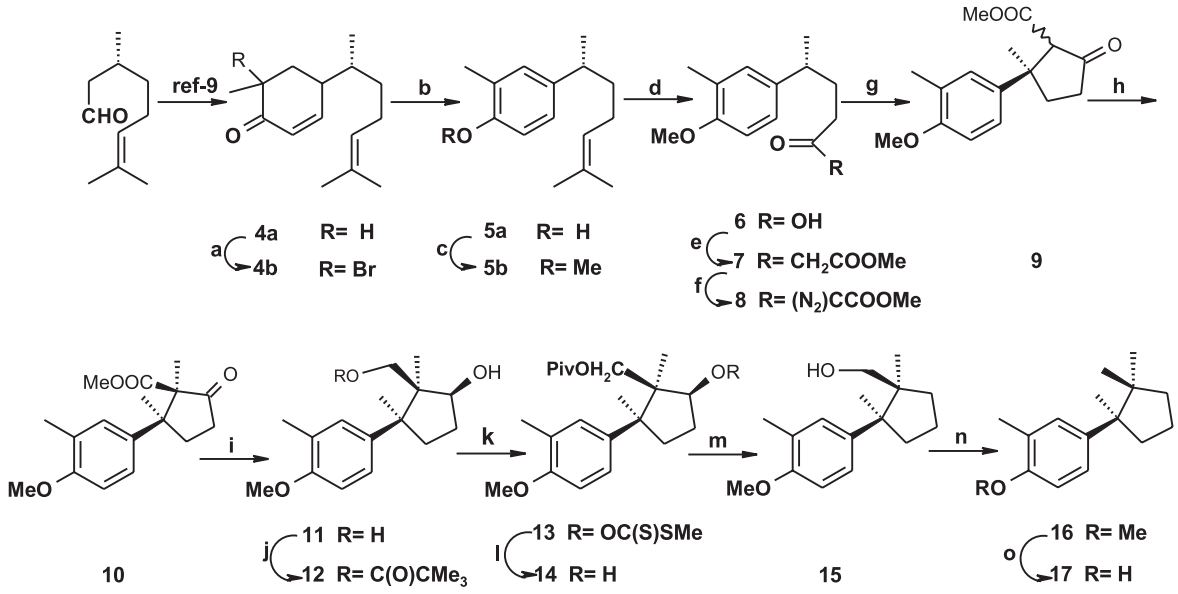
2. Results and discussion

The idea central to our synthetic route is to make use of naturally occurring chiral citronellal for asymmetric synthesis of β-herbertenol using Taber's protocol of diazo decomposition of α-diazo-β-ketoester **8** by $Rh_2(OAc)_4$ to provide the five membered ring with retention of configuration at the chiral center.[7,8]

To investigate the idea, *R*-(+)-citronellal was converted into α-diazo-β-ketoester **8** as depicted in Scheme 1. Enone **4a** was synthesized from *R*-(+)-citronellal.[9] It was then converted into its silyl enol ether using LDA as base,[10] and the resultant silyl enol ether was treated with NBS[11] to give the corresponding haloderivative **4b** as a mixture of diastereomers, and as we were going to destroy the centers during aromatization in the next step, we did not establish the diastereomeric ratio. Thus, the halo derivative **4b** on dehydrohalogenation[12] provided the phenol **5a** in 75% overall yield. The phenol thus obtained was then protected as methyl ether **5b** and converted into acid **6**, by Weinreb's method.[13] Acid **6** was then converted into β-ketoester **7** using Meldrum's acid in 78% yield. Diazotransfer was carried out by Regitz's protocol to give α-diazo-β-ketoester **8**.[14] The crucial insertion reaction was performed on **8** using rhodium catalyzed cyclization to furnish cyclized β-ketoester **9** as a diastereomeric mixture in 40% overall yield starting from **7**. Having secured the key

Keywords: Enantiospecific; Diazo decomposition; Citronellal.
* Corresponding author. Tel.: +91 25893300 2289; fax: +91 2025893614; e-mail: spchavan@dalton.ncl.res.in

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.01.050



Scheme 1. Reagents and conditions: (a) (i) LDA, THF, −78 °C, TMSCl; (ii) NBS, THF, 0 °C, 0.5 h; (b) Li_2CO_3, LiBr, DMF, 135 °C, 4 h, 75% from **4a**; (c) K_2CO_3, Me_2SO_4, acetone, reflux, 12 h, 90%; (d) OsO_4 (cat), Jones' reagent, acetone, rt, 5 h, 80%; e) (i) $SOCl_2$, CH_2Cl_2, reflux, 2 h; (ii) Meldrum's acid, pyridine, CH_2Cl_2, 0 °C–rt, 2 h; (iii) MeOH, reflux, 4 h, 78%; (f) Et_3N, MsN_3, CH_2Cl_2, −10 °C–rt, overnight; (g) $Rh_2(OAc)_4$ (cat.), CH_2Cl_2, rt, 40% for 2 steps; (h) K_2CO_3, MeI, acetone, rt, 85%; (i) LAH, THF, 0 °C–rt, 5 h, 80%; (j) Pivaloyl chloride, Et_3N, CH_2Cl_2, −10 °C–rt, 4 h, 65%; (k) NaH, CS_2, THF, 0 °C, 1.5 h, then MeI, rt, 5 h, 95%; (l) TBTH, AIBN (cat), toluene, reflux, 2 h, 80%; (m) LAH, THF, rt, 2 h, 95%; (n) (i) PDC, CH_2Cl_2, 0 °C, 3 h; (ii) NH_2NH_2–H_2O, diethyleneglycol, 150 °C, 4 h, 190 °C, 3 h, 73% for 2 steps; (o) BBr_3, CH_2Cl_2, −78 °C–rt, overnight, 93%.

cyclopentanone in place, the remaining problem was to convert **9** into the geminal dialkylated cyclopentane skeleton. Accordingly, ester **9** was methylated using K_2CO_3, MeI in dry acetone, which gave single diasteteomer **10** in which methyl group and the aryl group on the adjacent quaternary carbon are anti to each other. The ^{1}H NMR spectrum of the compound **10** support this, in which the ester methyl signal appeared at 3.33 ppm because of the shielding of methoxy carbonyl group by the vicinal *cis* aryl group. The β-ketoester **10** was then reduced using LAH to the corresponding diol **11** as a single diastereomer. The stereochemistry of compound **11** was deduced by X-ray analysis of the racemic alcohol diol **11** (Fig. 2). The X-ray structure not only confirms the relative configuration of newly generated hydroxy group in **11**, but also the relative stereochemistry of methyl group in **10**. The primary alcohol of diol **11** was protected as a pivaloyl ester to give **12**. The secondary alcohol group was then deoxygenated by employing Barton's protocol[15] to give pivaloyl ester **14**, which on reduction using LAH gave the corresponding alcohol **15**. This alcohol was then oxidized to the corresponding aldehyde using PDC, followed by deoxygenation under Huang–Minlon conditions to give the methyl ether of β-herbertenol **16**, which on deprotection using BBr_3 gave the final product, that is, (+)-β-herbertenol **17**.

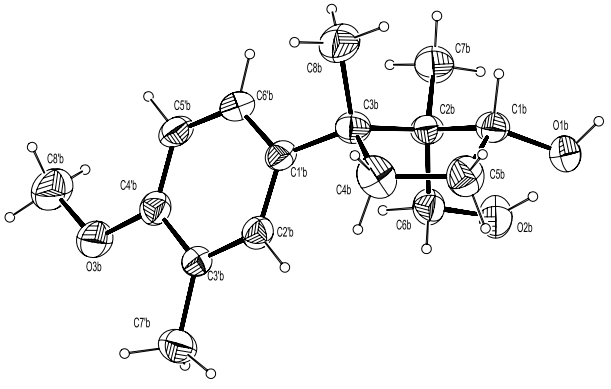


Figure 2. ORTEP view of *rac*-**11**.

3. Conclusion

Thus, (+)-β-herbertenol has been synthesized from naturally occurring *R*-(+)-citronellal employing carbene insertion as the key step. The same idea can be applicable to the synthesis of naturally occurring (−)-β-herbertenol and other herbertanes.

4. Experimental

4.1. General methods

All solvents were freshly distilled before use and dry solvents were distilled under argon from Na/benzophenone. Melting points are uncorrected. Chemical shifts in ^{1}H and ^{13}C NMR are reported relative to residual solvents. Abbreviations for ^{1}H NMR: s=singlet, d=doublet, m=multiplet. Progress of the reactions were monitored by TLC using Merck silica gel 60 F_{254} precoated plates and visualized by flourescence quenching or by charring after treatment with the mixture of *p*-anisaldehyde-H_2SO_4 in ethanol. The products were purified by column chromatography (SiO_2). Analytical data of all known compounds were compared with the literature, and new compounds were fully characterized.