Pergamon

Tetrahedron Letters 41 (2000) 5243–5247

TETRAHEDRON LETTERS

Enantioselective synthesis of (1*S*,3*S*,7*R*)-3-methyl-α-himachalene, the sex pheromone of the sandfly *Lutzomyia longipalpis* from Jacobina, Brazil

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Received 24 April 2000; revised 15 May 2000; accepted 19 May 2000

Abstract

(1*S*,3*S*,7*R*)-3-Methyl-α-himachalene, the sex pheromone of the male sandfly (*Lutzomyia longipalpis*) from Jacobina, Brazil, was synthesized enantioselectively by employing Evans' or Oppolzer's asymmetric methylation as the key step. The absolute configuration at the ring junction of this pheromone is opposite to that of the known (1*R*,7*R*)-α-himachalene of plant origin.

Keywords: asymmetric synthesis; circular dichroism; Diels–Alder reaction; pheromones; terpenes and terpenoids.

The sandfly *Lutzomyia longipalpis* is the vector of the protozoan parasite *Leishmania chagasi*, the causative agent of visceral leishmaniasis in South and Central America.[1] The structure and absolute configuration of the male-produced sex pheromone of *L. longipalpis* from Lapinha, Brazil, was firmly established in 1999 as (*S*)-9-methylgermacrene-B (**A**, Scheme 1)[2] by our synthesis of (±)-**A**[3] as well as (*S*)-**A**[4] and their comparison with the natural pheromone. As to the structure and relative configuration of the pheromone of the male *L. longipalpis* from Jacobina, Brazil, it was shown to be (1*RS*,3*RS*,7*SR*)-3-methyl-α-himachalene (**1**)[5] by our synthesis of (±)-**1**.[6] Its absolute configuration, however, remained unknown, although that of the parent sesquiterpene α-himachalene (**B**) of plant origin had been known as 1*R*,7*R* since 1968.[7] Our recent preparation of the enantiomers of **1** enabled Pickett and his co-workers to assign 1*S*,3*S*,7*R*-configuration to the natural pheromone **1**.[8] It thus has become clear that the biosynthesis of 3-methyl-α-himachalene (**1**) by *L. longipalpis* takes a steric course different from that of (1*R*,7*R*)-α-himachalene (**B**) in plants such as Himalayan deodar *Cedrus deodara*.[9]

We previously resolved (±)-**C** (=**18**) by preparative HPLC on Chiralcel® OD to give its enantiomers (≥99% ee).[8] Their CD spectral analysis coupled with MM3 calculation to deduce their most stable conformation allowed us to assign their absolute configuration on the basis of the octant

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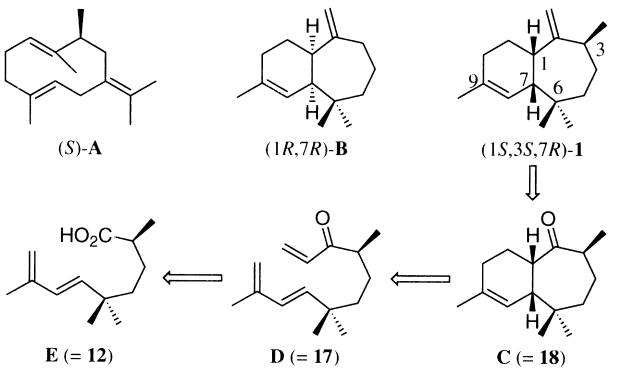
PII: S0040-4039(00)00831-5

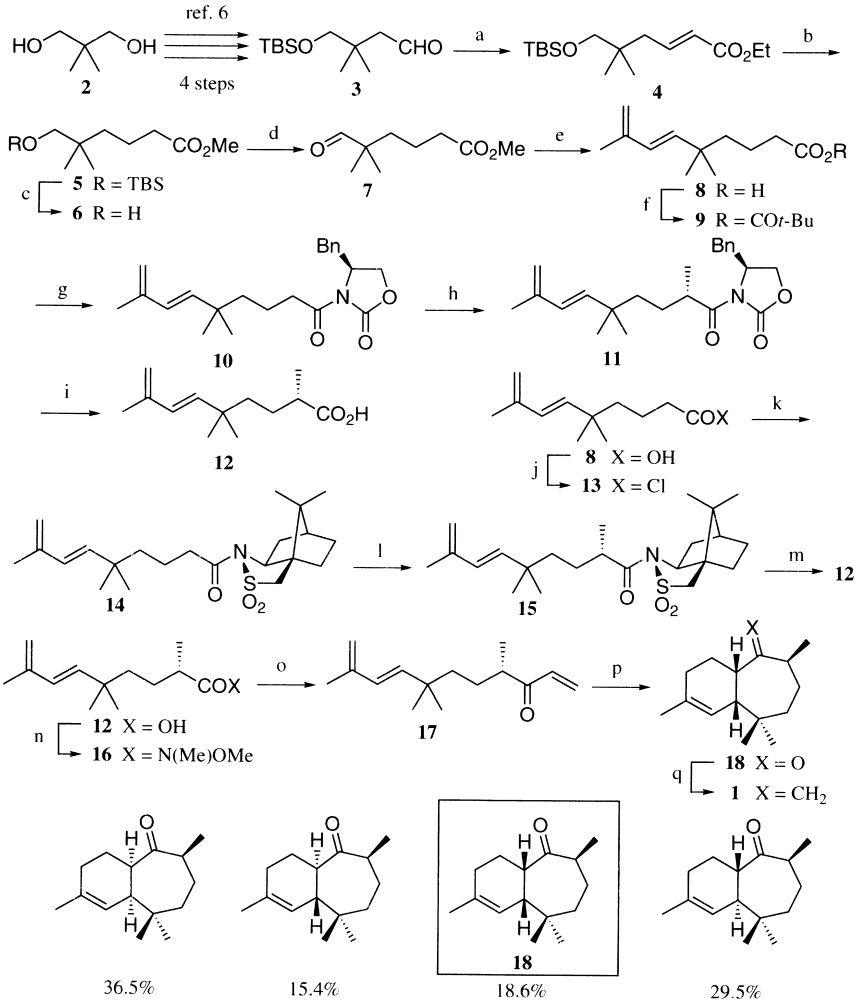


Scheme 1. Structure of 3-methyl-α-himachalene (**1**) and related compounds together with the retrosynthetic analysis of **1**.

rule:[10] the ketone **C** with a positive Cotton effect at 296 nm was thought to be (1*S*,3*S*,7*R*)-**C**. Applicability of the octant rule to such a cycloheptanone system, however, is uncertain. We therefore decided to prepare optically active **C** by the intramolecular Diels–Alder reaction of optically active **D**, which would be derived from (*S*)-acid **E**. The acid **E** would be obtainable by asymmetric methylation of the corresponding 2-demethyl acid derivatives.

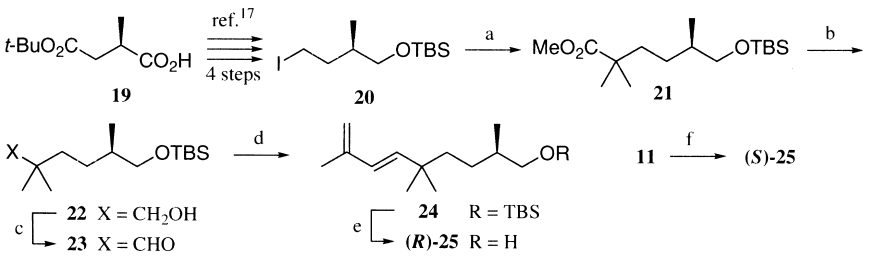
Scheme 2 summarizes our enantioselective synthesis of (1*S*,3*S*,7*R*)-**1**. The commercially available diol **2** was converted to the known aldehyde **3**.[6] Chain-elongation of **3** by Wittig reaction yielded **4**. Although catalytic hydrogenation of the double bond of **4** was unsuccessful, it could be reduced with magnesium and methanol[11] to give **5**. Removal of the TBS protective group of **5** furnished **6**, which was subjected to Swern oxidation to afford aldehyde **7**. Olefin formation by Wittig reaction converted **7** to **8** after hydrolysis with methanolic potassium hydroxide. The *E*/*Z* ratio of **8** was 98:2 as estimated by its GC analysis on TC-WAX®. Activation of acid **8** as mixed anhydride **9** by treatment with pivaloyl chloride was followed by acylation with it of the Evans' chiral auxiliary, (*S*)-4-benzyl-2-oxazolidinone,[12] yielding **10**.

Methylation of **10** with sodium hexamethyldisilazide (NaHMDS) and methyl iodide[13] furnished **11**. Removal of the chiral auxiliary[14] gave carboxylic acid **12** $[\alpha]_D^{22} = +4.70$ ($c = 1.02$, $CHCl_3$), >99% ee by chiral GC on Chirasil-DEX®-CB, whose absolute configuration must be *S* according to the empirical rule generally accepted.[13] To further support the assigned *S* configuration of (+)-**12**, an alternative method was employed for its preparation. Oppolzer's (1*R*,2*S*)-(+)-camphorsultam[15] was acylated with acyl chloride **13** derived from acid **8** to afford *N*-acyl sultam **14**. Methylation of **14** with *n*-butyllithium and methyl iodide[16] gave **15**, whose chiral auxiliary was removed to furnish (+)-acid **12**, $[\alpha]_D^{22} = +4.64$ ($c = 1.08$, $CHCl_3$), >99% ee by chiral GC on Chirasil-DEX®-CB. According to Oppolzer et al.,[16] this acid should possess *S* absolute configuration. This result was in accord with the previous one by employing the Evans' method. The final and definitive proof of the *S* configuration of (+)-**12** is summarized in Scheme 3. The commercially available (*R*)-**19** was converted to **20** by the known method.[17] Alkylation of methyl isobutyrate with **20** gave **21**, which was converted to (*R*)-**25** $[\alpha]_D^{22} = +9.89$ ($c = 1.14$, $CHCl_3$), in a conventional manner via **22**, **23**, and **24**. The alcohol **25** obtained by reduction of **11** with lithium aluminum hydride was levorotatory, $[\alpha]_D^{22} = -9.31$ ($c = 1.15$, $CHCl_3$), and therefore it was (*S*)-**25**. Accordingly, the (+)-acid **12** must possess *S* configuration.



Scheme 2. Synthesis of (+)-3-methyl-α-himachalene (**1**). Reagents: (a) $Ph_3P{=}CHCO_2Et$, C_6H_6, reflux (89%). (b) Mg, MeOH (77%). (c) HF aq., MeCN (93%). (d) $(COCl)_2$, DMSO, CH_2Cl_2, then Et_3N (83%). (e) $CH_2{=}C(Me)CH_2PPh_3^+Cl^-$, *t*-BuOK, THF; KOH, MeOH (83% two steps). (f) PivCl, Et_3N, CH_2Cl_2. (g) (*S*)-4-Benzyl-2-oxazolidinone, *n*-BuLi, THF (78% two steps). (h) NaHMDS, MeI, THF (70%). (i) LiOH, H_2O_2, THF–H_2O (4:1) (92%). (j) $(COCl)_2$, Et_3N, CH_2Cl_2 (75%). (k) (1*R*,2*S*)-(+)-2,10-Camphorsultam, NaH, toluene (88%). (l) *n*-BuLi, MeI, THF–HMPA (81%). (m) LiOH, H_2O_2, THF–H_2O (63%). (n) EDC, MeO(Me)NH·HCl, *i*-Pr_2NEt, DMAP, CH_2Cl_2 (80%). (o) $CH_2{=}CHMgBr$, THF. (p) $LiClO_4$, (+)-CSA, Et_2O–THF (83% two steps). (q) Tebbe reagent [$Cp_2Ti(Cl)CH_2AlMe_2$], toluene–THF (quant.).

Conversion of (*S*)-**12** to the pheromone (1*S*,3*S*,7*R*)-**1** followed the route previously employed for the synthesis of (±)-**1**.[6] The (*S*)-acid **12** yielded the corresponding *N*-methoxy-*N*-methylamide **16** [18% overall yield based on **3** (10 steps)] by treatment with *N*,*O*-dimethylhydroxylamine hydrochloride under the Weinreb conditions.[18] Treatment of **16** with vinylmagnesium bromide furnished **17**. Because our attempts to achieve asymmetric Diels–Alder reaction of **17** by means of chiral Lewis acid catalysis were all fruitless, **17** was cyclized under the Grieco conditions[19] in the presence of lithium perchlorate and (+)-camphor-10-sulfonic acid in diethyl ether and THF to give **18** as a 55.1:44.9 mixture of the rings A/B *cis*- and *trans*-adducts. Precise GC analysis on Chirasil-DEX®-CB of the mixture revealed its composition as shown in the bottom part of Scheme 2.



Scheme 3. Synthesis of (*R*)-**25**. Reagents: (a) MeCH(Me)CO_2Me, LDA, THF (93%). (b) DIBAL-H, CH_2Cl_2 (88%). (c) Dess–Martin Periodinane, CH_2Cl_2 (78%). (d) CH_2=C(Me)$CH_2PPh_3^+Cl^-$, *t*-BuOK, THF (69%). (e) TBAF, THF (81%). (f) $LiAlH_4$, THF (82%)

Disappointingly, the desired **18** was the second minor product. Fortunately, however, the *S* configuration at C-3 was almost perfectly retained (vide infra). Further purification of the stereoisomeric mixture of **18** by MPLC afforded pure (1*S*,3*S*,7*R*)-**18** $[\alpha]_D^{22}=+166$ ($c=0.32$, $CHCl_3$), ca. 99% ee as checked by GC on Chirasil-DEX®-CB. This (1*S*,3*S*,7*R*)-ketone **18** exhibited a strong positive Cotton effect [$\lambda_{max}=297$ nm, $\Delta\varepsilon=+1.55$ ($c=0.032$ M in hexane)] in accordance with our earlier resolution and CD studies on **18**.[8] Finally, methylenation of (1*S*,3*S*,7*R*)-**18** with Tebbe reagent[20,21] afforded (1*S*,3*S*,7*R*)-3-methyl-α-himachalene (**1**) $[\alpha]_D^{21}=+181$ ($c=0.32$, $CHCl_3$), ca. 99% ee as determined by chiral GC on Chirasil-DEX®-CB. The spectral data [IR, MS, ^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz)] of (1*S*,3*S*,7*R*)-**1** were identical with those reported for (±)-**1**. The overall yield of (1*S*,3*S*,7*R*)-**1** was 12% based on **12** (four steps) or 2.7% based on **3** (13 steps). It should be added that the naturally occurring (1*R*,7*R*)-α-himachalene (**B**) was reported to be levorotatory: $[\alpha]_D^{25}=-192.3$ ($CHCl_3$).[9]

In conclusion, the enantioselective synthesis of (1*S*,3*S*,7*R*)-(+)-3-methyl-α-himachalene (**1**)[22] was achieved to give highly enantiomerically pure **1**, although there is still room for improvement in the efficiency of the overall process.

Acknowledgements

We thank Professor J. A. Pickett (IACR-Rothamsted, U.K.) for his cooperation. We acknowledge the financial support of this work by a Grant-in-Aid for Scientific Research (No. 11480165), Japanese Ministry of Education, Science, Sports, and Culture.

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22. In Refs. 2, 3, 5 and 6, (1*S*,3*S*,7*R*)-**1** was erroneously described as (1*S*,3*S*,7*S*)-**1**. We thank a referee for his kind correction.