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A stereoselective total synthesis of (−)-seychellene

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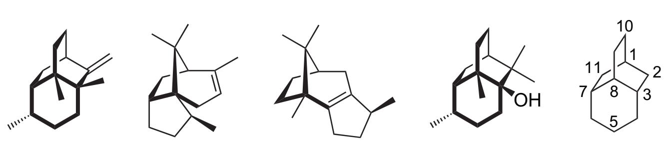
Abstract

A stereoselective total synthesis of the tricyclic sesquiterpene (−)-seychellene, starting from (*R*)-carvone via (*R*)-3-methylcarvone has been accomplished, employing a combination of intermolecular Michael addition–intramolecular Michael addition sequence, a stereoselective hydrogenation, and an intramolecular alkylation reaction.

Keywords: Seychellene; Sesquiterpene synthesis; Intramolecular alkylation; Carvone; Double Michael reaction

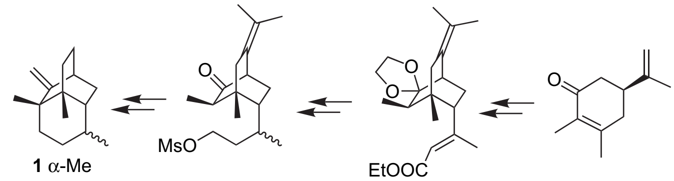
1. Introduction

The structurally novel tricyclic sesquiterpene (−)-seychellene **1** was first isolated from the patchouli oil (from the leaves of *Pogostemon cablin* Benth obtained from the Seychelles Islands) as one of the minor components along with α- and β-patchoulene **2** and **3** and patchouli alcohol **4**.[1] It was subsequently isolated from a variety of species belonging to *Pogostemon* and *Nardostachys jatamansi*. The relative structure as well as the absolute configuration of seychellene **1** was established by Ourisson and Wolff based on the degradation studies.[1] Structurally and biogenetically, seychellene **1** is closely related to the tricyclic alcohol patchouli alcohol **4**.



1 **2** **3** **4** **5**

The tricyclic structure containing a carbon framework tricyclo[5.3.1.0^{3,8}]undecane (homoisotwistane **5**) incorporating two vicinal quaternary carbon atoms attracted the attention of synthetic chemists and a number of reports appeared on the synthesis of seychellene **1** in its racemic form.[2] As a part of our interest in the enantiospecific synthesis of tricyclic sesquiterpenes starting from the readily available monoterpene (*R*)-carvone, such as neopupukeananes, pupukeananes, valerianoids, patchouli alcohol, etc.,[3] we have recently reported[4] the first enantiospecific synthesis of *ent*-seychellene **1** and *epi*-seychellene **6** via intramolecular alkylation of ketomesylate **7** (Scheme 1) followed by the degradation of the isopropylidene group. A one step reduction of the olefin as well as the ester group in the α,β-unsaturated ester **8** using lithium in liquid ammonia conditions was employed for the creation of the secondary methyl group. Since the stereoselectivity in the lithium–liquid ammonia reaction was not good, an alternative strategy via the catalytic hydrogenation of the olefin in **8** was explored and herein, we describe a stereoselective synthesis of (−)-seychellene **1**.



1 α-Me
6 β-Me
7
8
(*S*)-**9**

Scheme 1. Earlier route to (+)-seychellene.

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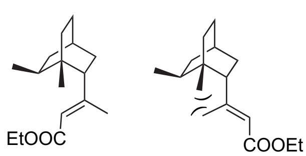
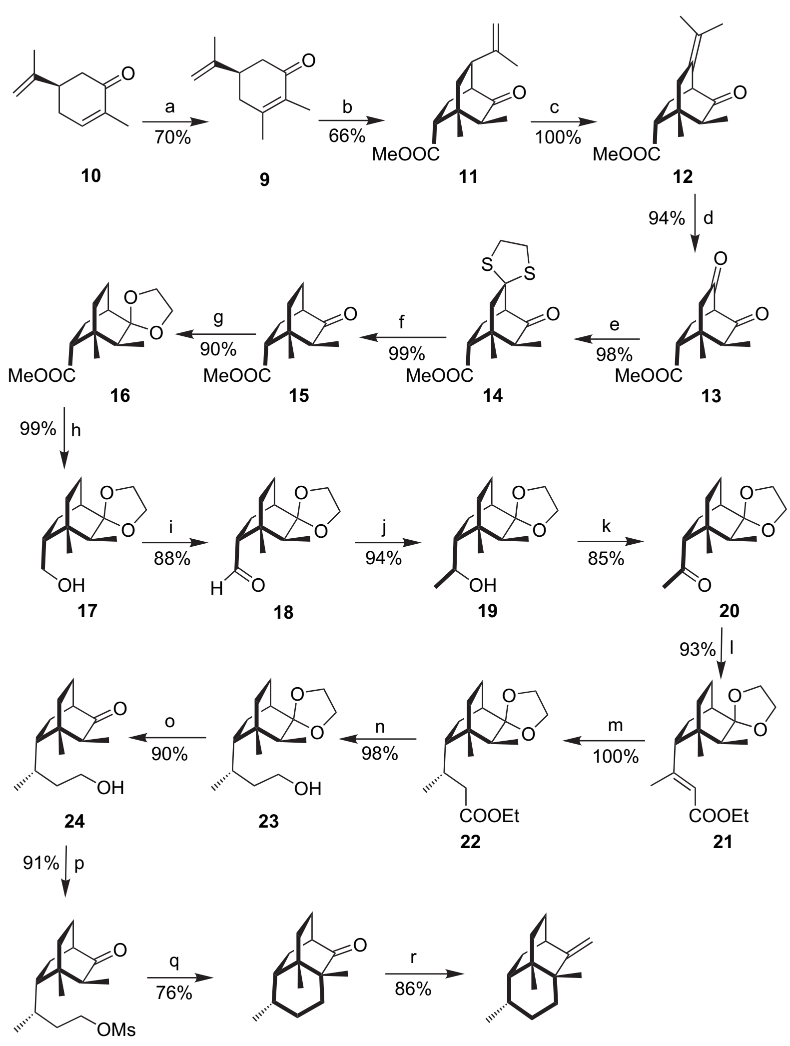
2. Results and discussion

It was contemplated that among the two rotamers **A** and **B** (considering that the methyl group of the crotonyl side chain prefers to occupy outside the bicyclo[2.2.2]octane framework and hydrogen adds from the less hindered face of the molecule), although molecular mechanics calculations indicated that both rotamers are energetically very similar, in rotamer **B** hydrogenation takes place preferably from the α-face of the molecule due to the steric crowding of the bridgehead methyl (located on the β-face of the molecule), whereas in rotamer **A** it takes place from the β-face of the molecule as the α-face is blocked by the bicyclic system, leading to the required isomer in a stereoselective manner.



A **B**

Since the selective hydrogenation of the trisubstituted double bond in the presence of tetrasubstituted double bond in the α,β-unsaturated ester **8** was found to be unsuccessful, it was decided to degrade the isopropylidene group prior to the elaboration of the side chain. As (*S*)-3-methylcarvone (*S*)-**9** resulted in *ent*-seychellene (+)-**1**, for generating (−)-seychellene **1**, the sequence was started with (*R*)-3-methylcarvone (*R*)-**9**, which was prepared using an earlier developed method[5] via a 1,3-dipolar cycloaddition of diazomethane to (*R*)-carvone **10** followed by thermolysis of the resultant pyrazoline derivative, Scheme 2. Generation of the kinetic lithium dienolate of 3-methylcarvone (*R*)-**9** with 1.1 equivalents of lithium hexamethyldisilazide in hexane followed by treatment with 1 equiv of methyl acrylate generated the bicyclic keto ester **11** via tandem intermolecular Michael addition−intramolecular Michael addition sequence.[6]



Scheme 2. Reagents: (a) (i) CH_2N_2, Et_2O; (ii) 190 °C, $(CH_2OH)_2$; (b) LiHMDS, hexane, $CH_2{=}CHCOOMe$; (c) PTSA, C_6H_6; (d) (i) O_3−O_2, MeOH−CH_2Cl_2; (ii) Me_2S; (e) $(CH_2SH)_2$, $BF_3\cdot Et_2O$, CH_2Cl_2; (f) Raney Ni, EtOH; (g) $(CH_2OH)_2$, PTSA, C_6H_6; (h) LAH, Et_2O; (i) PDC, CH_2Cl_2; (j) MeMgI, Et_2O; (k) PCC, NaOAc, CH_2Cl_2; (l) $(EtO)_2P(O)CH_2COOEt$, NaH, THF; (m) 10% Pd−C, H_2 (1 atm), hexane; (n) LAH, Et_2O; (o) H_2O−AcOH (1:1); (p) MsCl, Py, CH_2Cl_2; (q) NaH, THF; (r) Mg, $TiCl_4$, CH_2Cl_2, THF.