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Revision of the absolute configuration of the tricyclic sesquiterpene (+)-kelsoene by chemical correlation and enantiospecific total synthesis of its enantiomer

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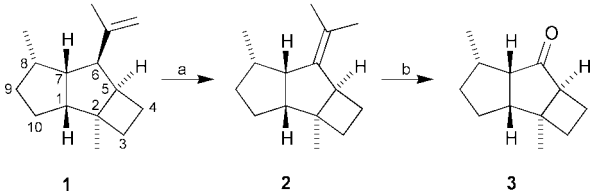
The absolute configuration of the recently identified sesquiterpene (+)-kelsoene was revised by chemical correlation with (*R*)-(+)-pulegone; the correct structure is (1*R*,2*S*,5*R*,6*R*,7*R*,8*S*)-2,8-dimethyl-6-(1-methylethenyl)tricyclo[5.3.0.0^{2,5}]decane.

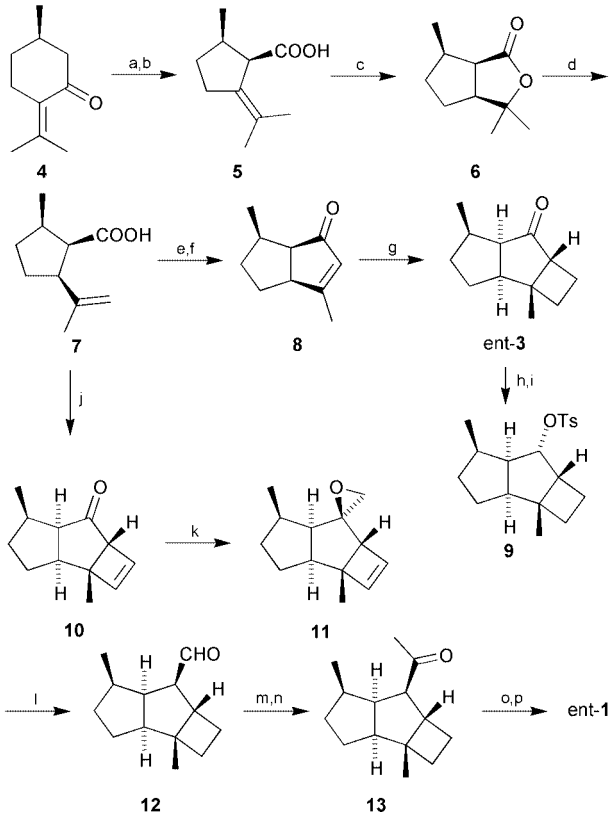
Recently the sesquiterpene hydrocarbon (+)-kelsoene (**1**, also called tritomarene) was isolated from the marine sponge *Cymbastela hooperi*[1] as well as from the liverworts *Ptychanthus straitus*,[2] *Calypogeia muelleriana*,[3] and *Tritomaria quinquedentata*.[4] The relative configuration was elucidated during these studies; **1** contains a rare *cis,anti,cis* 4-5-5 carbotricyclic ring system, previously only found in the tetraterpene poduran[5] and the sesquiterpenoid sulcatine G.[6] The analysis of NMR data obtained from two dihydroisoxazoles formed after addition of (a*S*)-2′-methoxy-1,1′-binaphthalene-2-carbohydroximoyl chloride (MBCC) to the double bond of **1** according to the method of Fukui *et al.*[7] led to the conclusion that (+)-**1** possesses a (1*S*,2*R*,5*S*,6*S*,7*S*,8*R*)-2,8-dimethyl-6-(1-methylethenyl)tricyclo[5.3.0.0^{2,5}]decane structure.[8] In the present study we will show by chemical correlation with the ketone **3** and further with (*R*)-(+)-pulegone (**4**) that this assignment is incorrect. We will also present the first synthesis of enantiomerically pure **1**, which has previously only been synthesized in racemic form.[9]

Natural **1** can be isomerized by a short treatment with toluene-*p*-sulfonic acid into the more stable isomer **2**, which in turn is cleaved by ozonolysis to the tricyclic ketone **3**. Under the reaction conditions no excessive degradation of **3** or **1** or formation of byproducts occurs. The ketone **3** was the target of a short enantiospecific synthesis, because we reasoned that its racemate may be well suited to separation by GC on chiral phases due to its rigidity. It would also be formed by degradation of other terpenes exhibiting the same ring system, such as *e.g.* the tetraterpene poduran recently identified by us,[5] thus allowing its use for the determination of the absolute configuration of several natural products.

The ketone **3** was synthesized starting from (*R*)-(+)-pulegone (**4**), which was transformed by bromination and Favorskii-rearrangement into a mixture of *cis*- and *trans*-pulegonic acids (**5**),[10] separable by column chromatography. Isomerization of the double bond into the terminal position was achieved by lactonization of pure *cis*-**5** to **6**, followed by elimination with a bulky base, as has been described for *anti*-**5**.[10,11] The double bond of the resulting acid **7** was now internally acylated *via* the acid chloride to form the ketone **8**, which was photochemically transformed by a [2 + 2]-cycloaddition with ethylene into the desired ketone (1*S*,2*R*,5*R*,7*R*,8*R*)-2,8-dimethyltricyclo-[5.3.0.0^{2,5}]decan-6-one (*ent*-**3**). The ethylene attack occurs from the less hindered side. In an identical manner, *rac*-**3** was synthesized starting from *rac*-**4**. To exclude the unlikely possibility of inversion of the stereogenic centers in the course of our synthesis, *ent*-**3** was reduced with $LiAlH_4$. Preferential attack of the hydride from the less hindered side and reaction of the alcohol with tosyl chloride resulted in formation of the



Scheme 1 *Reagents and conditions*: (a) p-TSA, 15 min, CH_2Cl_2, Δ; (b) O_3, CH_2Cl_2, −78 °C, then Me_2S.



Scheme 2 *Reagents and conditions*: (a) Br_2, Et_2O, 0 °C; (b) 25% aq. KOH, Δ, column separation; (c) aq. HCl, MeOH, Δ; (d) *t*-BuOK, DMF, 140 °C; (e) $(COCl)_2$, CH_2Cl_2; (f) $AlCl_3$, CH_2Cl_2; (g) $CH_2{=}CH_2$, h*ν*, CH_2Cl_2, 0 °C; (h) $LiAlH_4$, Et_2O; (i) *p*-TsCl, py; (j) see[9,13]; (k) Me_3SOI, DMSO; (l) H_2, Pd/C, Et_2O; (m) MeLi, THF, −78 °C; (n) PDC, CH_2Cl_2; (o) NaOMe, MeOH, Δ; (p) Cp_2TiMe_2, THF, Δ.

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tosylate **9**. An X-ray analysis of **9**† allowed the determination of its absolute configuration.[12] This tosylate could be thus identified as (1*S*,2*R*,5*R*,6*S*,7*R*,8*R*)-2,8-dimethyltricyclo-[5.3.0.0^{2,5}]dec-6-yl tosylate, exhibiting the expected absolute configuration.

Being confident on the absolute configuration of *ent*-**3**, we were now able to perform GC analyses. The absolute configuration of natural (+)-**1** can be deduced by analysis of its degradation product **3**, because its relative configuration has been elucidated during its isolation.[1] Separation of *rac*-**3** was achieved on a chiral Hydrodex-6-TBDMS stationary phase.‡ The (−)-enantiomer of **3** eluted first, as did the degradation product of synthetic (−)-kelsoene. The ketone **3** derived from natural (+)-kelsoene eluted as second peak. In addition, the synthetic (−)-**1** prepared by us showed the expected sign of optical rotation of $[\alpha]_D^{20} = -78.3$. These data unequivocally prove that natural (+)-kelsoene has the opposite configuration as previously reported and possesses a (1*R*,2*S*,5*R*,6*R*,7*R*,8*S*)-2,8-dimethyl-6-(1-methylethenyl)tricyclo[5.3.0.0^{2,5}]decane structure.

We proceeded with the synthesis of enantiomerically pure (−)-**1** to further underline the consistency of our data set. In their synthesis of *rac*-**1**, Mehta and Srinivas showed that ketone **3** is strongly hindered and not readily attacked by nucleophiles. We therefore chose their strategy to reduce steric hindrance: The bicyclic ketone **8** was transformed into the cyclobutene derivative **10** as described.[9,13] The side chain was then elaborated in a new way. Even after reduction of the steric hindrance, only small nucleophiles can be used to attack the carbonyl carbon atom. Nevertheless, epoxidation with trimethylsulfoxonium iodide was feasible with satisfactory yield. The epoxide **11** was then hydrogenated and rearranged in one step to form the aldehyde **12**. Addition of methyllithium followed by oxidation with PDC afforded the ketone **13** in a 80 : 20 dr in favor of the unwanted diastereomer. Obviously the less hindered hydrogen moves more readily in the epoxide–aldehyde rearrangement of **12**. Nevertheless, simple treatment with base epimerized this center to the thermodynamically more favored arrangement, which is also found in the natural product. Kelsoene was then formed by final methenylation with Me_2TiCp_2,[14] because Wittig olefination, despite reported by Mehta and Srinivas,[13] did not proceed with satisfactory yields. Thus enantiomerically pure (−)-**1** has been synthesized, confirming our previous assignments.§,¶

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Note added in proof. Similar results were obtained recently by G. Mehta and K. Srinivas, *Tetrahedron Lett*., 2001, **42**, 2855, using a different synthetic strategy.

Notes and references

† *Crystal data* for **9**: orthorhombic, space group $P2_12_12_1$, a = 9.1578(8), b = 11.7038(10), c = 16.1527(14) Å, U = 1731.3 Å^3, Z = 4, T = −130 °C. *Data collection*: a crystal *ca*. 0.4 × 0.16 × 0.09 mm was used to record 26944 intensities on a Bruker SMART 1000 CCD diffractometer (Mo-Kα radiation, $2\theta_{max}$ 57°). *Structure refinement*: the structure was refined anisotropically on F^2 (program *SHELXL*-97, G. M. Sheldrick, University of Göttingen) to *wR*2 0.083, *R*1 0.032 for 211 parameters and 4388 unique reflections. The hydrogens were refined using a riding model or rigid methyl groups. The Flack parameter refined to −0.07(5). CCDC 171200. See http://www.rsc.org/suppdata/cc/b1/b101579f/ for crystallographic files in .cif or other electronic format.

‡ Separations were performed on a 15 m Hydrodex-6-TBDMS capillary column (Macherey & Nagel), id 0.25 mm, programmed from 60 to 180 with 5 min after a 2 min isothermal period with H_2 as the carrier gas (45 psi).

§ The ^{1}H NMR, ^{13}C NMR, and MS data are identical to those reported in the literature.[1] $[\alpha]_D^{25} = -78.3$ (c = 0.31, $CHCl_3$). Literature data for (+)-**1**: $[\alpha]_D^{25} = +78.1$ (c = 1.98, $CHCl_3$).[1]

¶ We also tried to find out why the NMR study by Nabeta *et al*.[8] furnished the opposite result. In their work Nabeta *et al*. presented a preferred conformation for one of the two formed kelsoene-MBCC adducts. Unfortunately, they did not explain how they obtained this conformation. These adducts contain a single bond between the heterocyclic ring and the cyclic core of **1**, while in the original paper introducing this method[7] all examples contain a dihydroisoxazole ring directly linked to the parent cyclic hydrocarbon, thus reducing the inherent flexibility. Finally, only one of two formed diastereomers was investigated by NMR and no comparison with the respective (a*R*)-MBCC was performed, as should be done in Mosher-like methods. In essence, their determination of the absolute configuration relies on several NOE signals observed, while in the present study a sound chemical correlation is performed. It should be noted that recently a very informative critique of the Mosher method has been published, which also applies to related methods.[15]

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