Process-Scale Total Synthesis of Nature-Identical (−)-(*S*,*S*)-7-Hydroxycalamenal in High Enantiomeric Purity through Catalytic Enantioselective Hydrogenation

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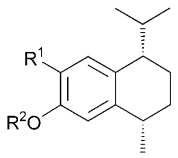
Dedicated to Professor *Rolf Huisgen*, the highest example to us of combined scientific creativity and method

A process-scale stereoselective synthesis of nature-identical (−)-(*S*,*S*)-7-hydroxycalamenal (=(−)-(5*S*,8*S*)-5,6,7,8-tetrahydro-3-hydroxy-5-methyl-8-(1-methylethyl)naphthalene-2-carbaldehyde; (−)-**1a**) in 96% enantiomeric excess (ee) with the aid of chiral Ru complexes has been developed. The key step was the enantioselective hydrogenation of easily accessible 2-(4-methoxyphenyl)-3-methylbut-2-enoic acid (**10**) to (+)-**11** in a 86% ee (*Scheme 5* and *Table 1*). A substantial increase in optical purity (96% ee) was achieved by induced crystallization of the intermediate (+)-3,4-dihydro-4-(1-methylethyl)-7-methoxy-2*H*-naphthalen-1-one ((+)-**3**). Computational conformation analysis carried out on the analog (−)-**9** rationalized the high diastereoselectivity achieved in the catalytic hydrogenation of the C=C bond.

1. Introduction. – 7-Hydroxycalamenal[1]), which corresponds to (−)-(5*S*,8*S*)-5,6,7,8-tetrahydro-3-hydroxy-5-methyl-8-(1-methylethyl)naphthalene-2-carbaldehyde ((−)-**1a**), is a sesquiterpene with a cadinene skeleton, isolated for the first time by extraction from the heartwood of different types of elm (*Ulmus rubra* and *U. glabra*) in 1968 [1]. The production of hydroxycalamenal was found to increase in a narrow zone at the interface between healthy and diseased trees infected with some species of fungi, and to have *in vitro* antifungal activity [2]. Like several other sesquiterpene derivatives, it could be employed in perfumery for the formulation of new types of fragrances, provided that a reliable synthetic access were available.



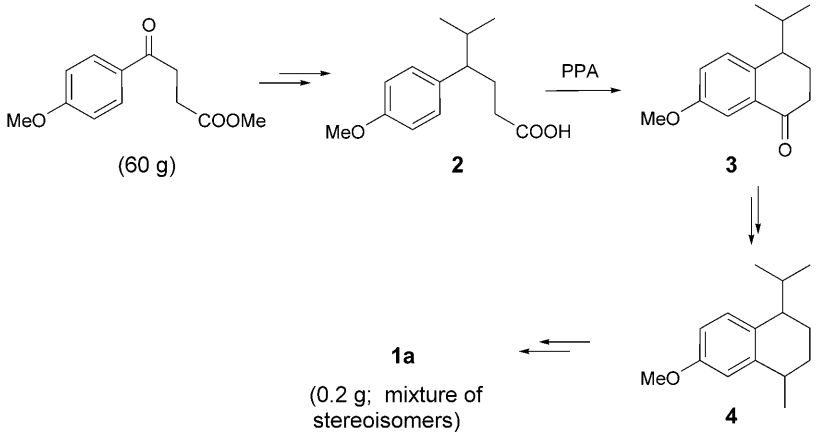
(−)-**1a** R^1 = CHO R^2 = H
(−)-**1b** R^1 = CHO R^2 = Me
(−)-**1c** R^1 = Me R^2 = Me

[1]) Trivial name and atom numbering.

The structure of natural hydroxycalamenal ((−)-**1a**), with its relative *cis*-configuration [3] and absolute configuration [4], was elucidated through chemical correlation and spectroscopic analysis. As for the syntheses of (−)-**1a**, there are a large number of publications claiming successful achievement in terms of efficiency, chemical yield, and optical purity, but the accurate examination of the experimental details of these reports raises several doubts on the reliability and applicability of many of them. Thus, we considered worth summarizing the stereoselective synthetic approaches to (−)-**1a** on account of the fact that the aim of the research reported in this paper was to find access to enantiomerically pure, nature-identical hydroxycalamenal, which would have high preparative value and might even be transferred to pilot-scale level.

Of the many nonstereoselective or partially stereoselective approaches reported in the literature [5], the first synthesis of **1a** deserves mention, since it involves some intermediates, like the ester of acid **2**, α-tetralone **3**, and tetraline **4**, which, at different stereochemical-purity levels, are the key intermediates also in many recent synthetic approaches (*Scheme 1*) [6].

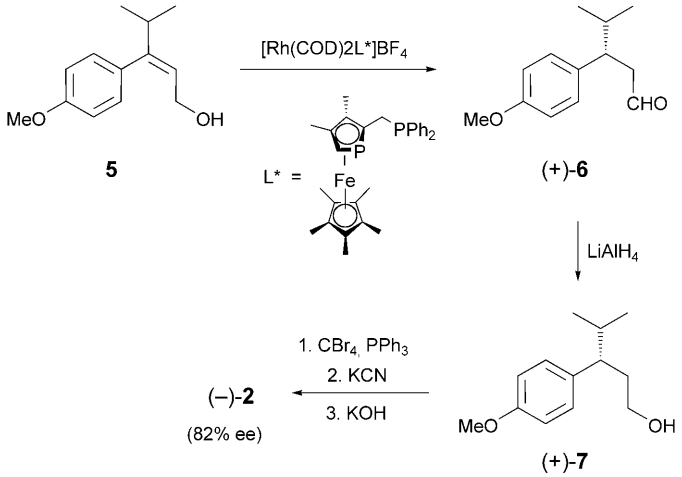
Scheme 1



A formal total synthesis of (−)-**1a** in good enantiomeric purity is based on the isomerization of the nonchiral allyl alcohol **5** to the aldehyde (+)-**6**, promoted by the Rh complexes of a chiral ferrocenyl phosphine [7], followed by reduction to the aldehyde (+)-**7**. The sequence was stopped at the level of acid (−)-**2**, obtained in 82% enantiomeric excess (ee), and the six remaining steps were considered to be 'trivial' (*Scheme 2*).

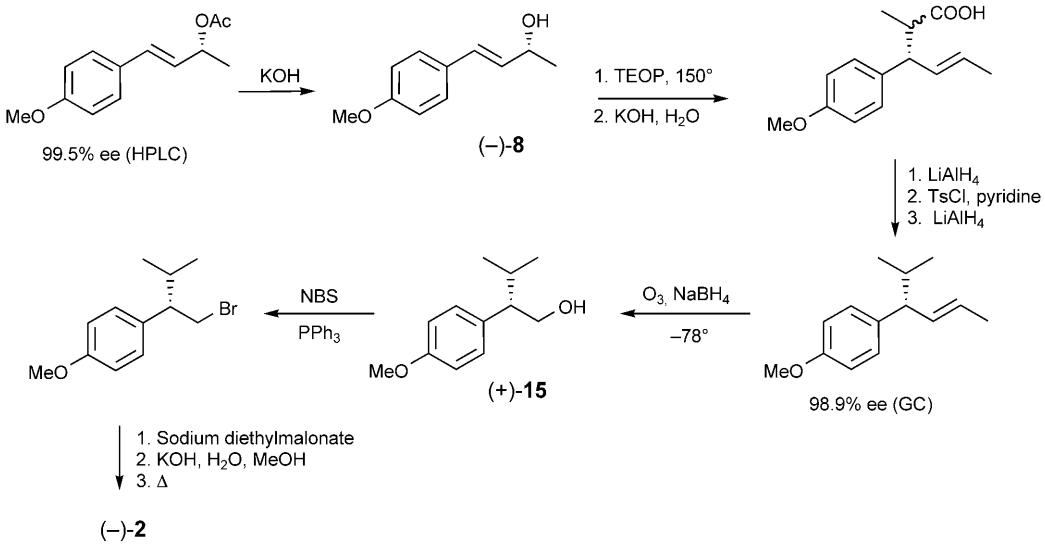
This reaction scheme for preparing enantiomerically enriched (−)-**2** is original, but its preparative value is rather modest for several reasons. The chiral ligand and the starting alcohol **5** are commercially not available. The synthesis of the latter requires $LiAlH_4$ reduction of an ester that is prepared, in turn, through two technologically difficult procedures in modest yield (40%) [8]. Furthermore, a substrate/catalyst ratio of 20:1 (mol-equiv.) employed in the rearrangement of **5** to (+)-**6** is unacceptable for larger-scale preparations.

Scheme 2



The most-recent work in this field refers to an enantioselective synthesis of (−)-7-methoxycalamenenal ((−)-**1b**) as an intermediate in the synthesis of *cis*-7-methoxy-calamenene ((−)-**1c**) [9]. Once more, the approach is based on the synthesis of acid (−)-**2** as the key intermediate, which was obtained in 21% yield from allyl alcohol (−)-(*R*)-**8** through an original, but ten-step-reaction sequence (*Scheme 3*). The synthesis is characterized by a stereocontrolled *Claisen–Johnson* rearrangement of (−)-**8**, effected with triethyl orthopropionate (TEOP) [10]. The latter was obtained in 99.5% ee by kinetic resolution of the racemate (not commercially available, but easy to prepare), by

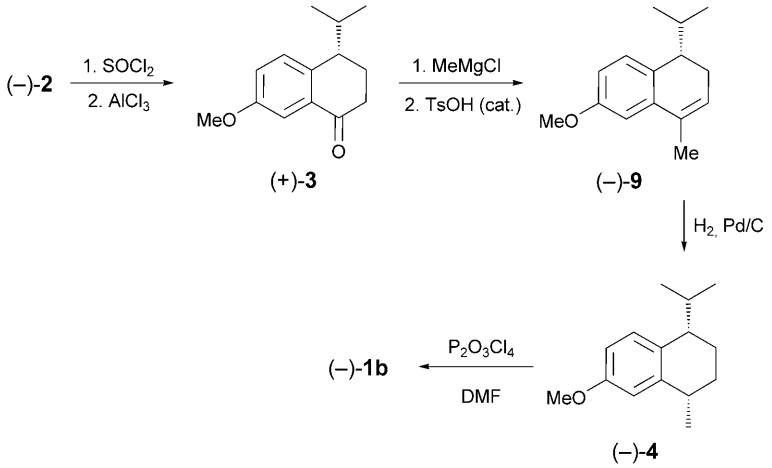
Scheme 3



means of an enzyme-catalyzed asymmetric esterification, followed by alkaline hydrolysis and column chromatography of the enantiomerically pure (*R*)-acetate (*Scheme 3*). Given the high number of steps, the use of critical reagents such as O_3 and $LiAlH_4$ (twice), and the extensive use of chromatographic purification procedures, this approach appears more an academic exercise than a method of true preparative value for the synthesis of (−)-**2**.

The conversion of acid (−)-**2** to (−)-**1b** follows the sequence outlined in the first synthesis of **1a**, as summarized in *Scheme 1*. The *Friedel–Crafts* cyclization of the acid chloride of (−)-**2** to the α-tetralone (+)-**3**, followed by reaction of the latter with MeMgCl afforded an alcohol which was dehydrated to the dihydronaphthalene (−)-**9** (*Scheme 4*). Catalytic hydrogenation of the non-aromatic C=C bond of **9** proceeded highly diastereoselectively, affording (−)-(*S*,*S*)-**4** in high yield. The facial selection was attributed to a preferred conformation in which the i-Pr group of (−)-**9** is in axial position. Finally, *Vilsmeier*-type formylation of (−)-(*S*,*S*)-**4** proceeded regioselectively in position 5 to afford (−)-(*S*,*S*)-7-methoxycalamenal ((−)-**1b**) in modest yield.

Scheme 4



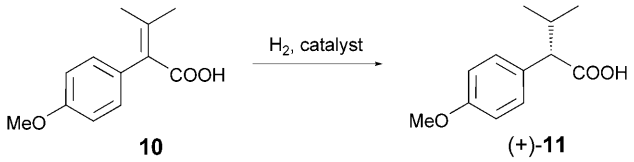
There are some points of the synthesis described above that deserve further investigation, in particular the accurate check of the enantiomeric purity of intermediates and final products, since chiral chromatographic analyses were stopped before ozonization (see *Scheme 3*), and specific rotatory power was used as the only criterion to assess the enantiomeric purity of all the subsequent products.

As mentioned above, our aim was to find a superior synthetic access to (−)-**1a**. Thus, the synthesis had to be as short as possible and involve inexpensive and commercially available starting materials, and safe and environmentally friendly reactions. Furthermore, we wanted to unequivocally establish the enantiomeric purities of both the intermediates and the final product *via* chiral HPLC analysis, which required that we also had to perform a diastereoselective synthesis of (±)-**1a** for the chromatographic comparison of enantiomers. Furthermore, we considered it worthwhile to verify the conformation of **9** through reliable computational data in order to

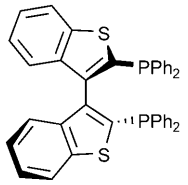
have a scientifically valid, not only intuitive, justification for the remarkable diastereoselection observed in the catalytic hydrogenation of **9** to **4**.

2. Results and Discussion. – 2.1. *Synthesis.* As a key step in the synthesis of (−)-**1a**, we chose an enantioselective hydrogenation to introduce the stereogenic center bearing the i-Pr group, namely the hydrogenation of 2-(4-methoxyphenyl)-3-methyl-but-2-enoic acid (**10**) to (+)-**11** (*Scheme 5*). The double homologation of acid (+)-**11** should then afford (−)-**2**, from which the route to calamenal (−)-**1a** had been already opened (*Schemes 1* and *4*).

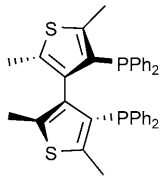
Scheme 5



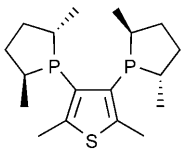
This strategy was based on two considerations. Acid **10** could be easily prepared in good yields (81%) by *Wittig* reaction [11] of commercially available ethyl (4-methoxyphenyl)glyoxylate and isopropylidene(triphenyl)phosphorane, followed by alkaline hydrolysis of the product. As a second advantage, we have designed and synthesized some chiral diphosphine ligands with atropisomeric, biheteroaromatic backbones that form transition-metal (Ru, Rh, Pd) complexes that can be used as very active, stereoselective catalysts in many homogeneous reactions. By introducing electron-rich or electron-poor five-membered aromatic heterocycles as scaffolds for the phosphorus functions, we had prepared a series of electronically tunable diphosphines, exhibiting high performances both in the hydrogenation of pro-stereogenic C=C and C=O bonds [12], where electron-rich ligands are required [13], and in some C−C bond-forming reactions [14], where electronically medium-rich mediators are the ligands of choice. Thus, as candidates for the hydrogenation discussed above, we selected the electron-rich, industrial diphosphines BITIANP and TetraMe-BITIOP, as well as UlluPHOS [15], which is currently under development.



(+)-(*R*)-BITIANP



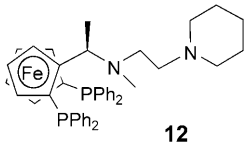
(–)-(*R*)-TetraMe-BITIOP



(+)-(*R*,*R*,*R*,*R*)-UlluPHOS

The enantioselective hydrogenation of **10** has already been described in the literature with the Rh complexes of different chiral diphosphines as promoters. $Rh(NBD)BF_4$ complexes of BINAP and Cy-BINAP afforded acid **11** in 60% and 72% ee, respectively, when the hydrogenation was carried out in MeOH solution at 50 bar H_2 pressure and a substrate/catalyst molar ratio of 160:1 [16].

Excellent stereoselectivities (96.7% ee) have been reported, when a similar Rh complex of the (diaminoalkyl)-ferrocenyl-diphosphine **12** was employed under analogous experimental conditions in the presence of 5 mol-% of Et_3N. A lower substrate/catalyst ratio of 150:1, the commercial unavailability of ligand **12**, and a reaction time of 30 h were the drawbacks of this otherwise appealing synthetic method [17].



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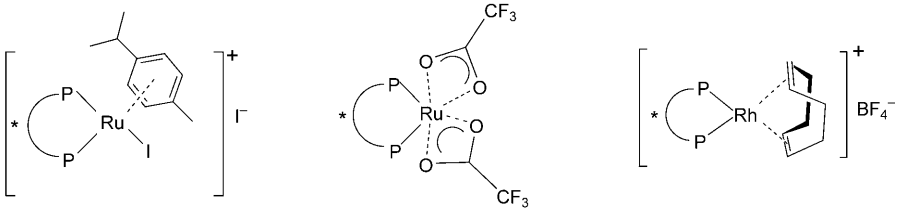
The Ru and Rh complexes of TetraMe-BITIOP, BITIANP, and UlluPHOS were then tested as promoters in the hydrogenation of **10**. Complexes **13a**,**b** and **14a**,**b** were prepared *in situ* by reaction of the free diphosphines with $[Ru(p\text{-cymene})I_2]_2$ and $[Rh(COD)_2]BF_4$ in MeOH or CH_2Cl_2 solution, respectively. Complex **13c**, which is being produced on an industrial scale, was supplied by the company owner of the patent [18].



13a $\hat{PP}$* = TetraMe-BITIOP
13b $\hat{PP}$* = BITIANP
13c $\hat{PP}$* = TetraMe-BITIOP
14a $\hat{PP}$* = TetraMe-BITIOP
14b $\hat{PP}$* = UlluPHOS

Hydrogenation experiments on **10** (*Table 1*), and its ethyl ester, have been performed at temperatures between 0 and 50° under different H_2 pressures (3–100 bar), in line with literature reports for the reduction of α,β-unsaturated carboxylic acids and esters. We found the ethyl ester to be completely unreactive under a great variety of experimental conditions. Promising results, however, were obtained with acid **10** and Ru catalyst **13c**. Here, compound **11** was obtained after 15 h in quantitative chemical yield, with 86% ee (HPLC), when working at 100 bar H_2 pressure at a temperature of 35°, and with a **10**/**13c** ratio of 500:1 (*Table 1*, *Entry 1*). Increasing the substrate/catalyst ratio up to 2000:1 gave rise to longer reaction times, without affecting stereoselectivity (*Entries 2* and *3*).

Negative effects both on kinetics and stereoselectivity were observed at lower pressure (*Entry 4*) and, surprisingly, at lower temperature (*Entry 5*). Also, the Ru complexes **13a**,**b** turned out to be less enantioselective than **13c** (*Entries 6* and *7*). In addition, the BITIANP complex **13b** was kinetically less active than **13a**, as expected on the consideration of the lower electronic availability of the former ligand. Finally, the two Rh complexes **14a**,**b** exhibited unexpectedly poor activities (*Entries 8* and *9*).

Table 1. *Enantioselective Hydrogenation of* **10** *to* **11** (see *Scheme 5*)

Entry	Catalyst	**10**/Catalyst[a])	Temperature [°]	H_2 Pressure [psi]	Time [h]	Conversion [%]	ee[b]) [%]
1	**13c**	500 : 1	35	1470	15	100	86
2		1000 : 1	25	1470	20	100	86
3		2000 : 1	25	1470	48	100	86
4		500 : 1	25	730	24	100	70
5		500 : 1	0	1470	48	100	75
6	**13a**	500 : 1	25	1470	48	100	83
7	**13b**	500 : 1	25	1470	48	70	80
8	**14a**	500 : 1	50	40	24	10	–
9	**14b**	500 : 1	30	40	24	13	–

[a]) Molar ratio. [b]) Enantiomeric excess.

As for the stereochemical outcome of the hydrogenation reaction of **10**, we found that the (−)-(*R*)-TetraMe-BITIOP–Ru complex **13c** produced the (+)-(*S*) antipode of **11**. Even though 86% ee was somewhat below our expectations, we considered this as acceptable, at first instance, given the simplicity, the reliability, and the economical validity of the process. Moreover, as the benzylic H-atom of **11** is quite acidic due to the α-COOH group, manipulations directed at improving the optical purity were risky, and we, thus, decided to continue the synthesis, and to increase the enantiomeric purity of a more-advanced intermediate.

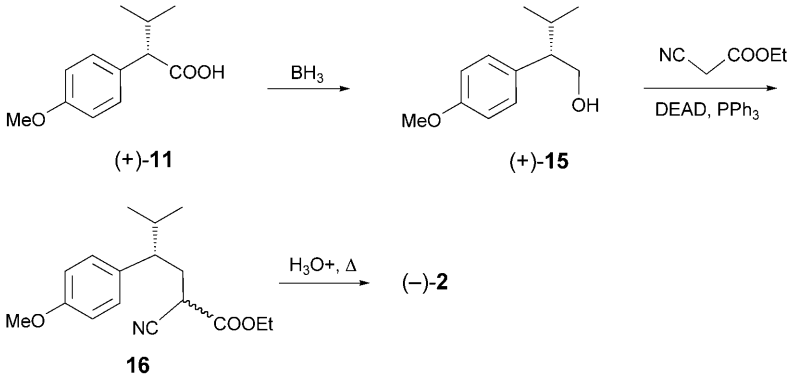
Next, (+)**-11** was quantitatively reduced with BH_3 in THF to the corresponding alcohol (+)-**15** (*Scheme 6*), with no loss in enantiomeric purity (86% ee by HPLC). The specific optical rotatory power of this product, $[\alpha]_D^{25} = +9.2$ ($c = 1.06$, $CHCl_3$), was found to be nearly identical to that reported in the literature for a material claimed as 'nearly enantiomerically pure' ($[\alpha]_D^{25} = +9.4$ ($c = 1.07$, $CHCl_3$)) [9]. This observation further confirmed the validity of our investigation.

Next, we considered alternative approaches to shorten the reaction sequence described in the literature to convert alcohol (+)-**15** into the carboxylic acid (−)-**2a**, involving the conversion into the corresponding halogenated derivative, followed by nucleophilic substitution of the halogen atom with diethyl malonate, alkaline hydrolysis of the product, and decarboxylation, as outlined in *Scheme 3*. We felt it necessary to change this synthetic sequence because, in our hands, halogen displacement was accompanied by elimination as an undesired side reaction.

We directly performed the *Mitsunobu* reaction on alcohol (+)-**15** with ethyl cyanoacetate to give a 2.3 : 1 mixture (^{1}H-NMR) of two diastereoisomers **16**. This mixture was directly submitted to alkaline hydrolysis with KOH in ethylene glycol at 110°. Decarboxylation of the resulting diastereoisomeric acids was effected in refluxing xylene in the presence of copper chromite (5 weight-%), followed by filtration of the crude product on a silica-gel pad to remove tarry materials. By this sequence, (−)-**2** was obtained in 80% overall yield (*Scheme 6*).

The enantiomeric excess of (−)-**2** was still 86% (HPLC), indicating that the whole sequence proceeded without loss in optical purity. As expected, the *Mitsunobu* reaction gave rise to poor yields, when diethyl malonate was used in place of ethyl cyanoacetate [19]. We did not succeed in substantially improving the optical purity of (−)-**2** by

Scheme 6



fractional crystallization of the diastereoisomeric salts with (+)- or (−)-α-phenylethylamine. We found that well-formed crystals were grown with the dextro-rotatory amine from solvents such as AcOEt or $(i\text{-}Pr)_2O$, but the benefit was too modest in terms of both ee and yield to consider this route practicable.

Conversion of (−)-**2** to nature-identical 7-hydroxycalamenal ((−)-**1a**) was then effected *via* the traditional route described in *Scheme 4*. However, we decided to perform the cyclization to (+)-**3** directly with the acid, rather than its chloride, to avoid equimolar amounts of $AlCl_3$, which is difficult to dispose. The yield of the polyphosphoric acid (PPA) promoted internal acylation was acceptable (70%). HPLC analysis showed that the enantiomeric excess (86%) was fully maintained in crude (+)-**3**.

We made the interesting observation that careful crystallization from MeOH produced nice crystals of enantiomerically pure (+)-**3** (99.4% ee by HPLC; $[\alpha]_D^{25} = +74$ ($c = 1.0$, $CHCl_3$)), even though in low yield. However, when a saturated hexane solution of (+)-**3** (86% ee) was seeded with crystals of enantiomerically pure (+)-**3**, crystallization started immediately, and material of 95.5% ee (by HPLC; $[\alpha]_D^{25} = +71$ ($c = 1.0$, $CHCl_3$) was formed in good yield, a residue (56% ee) being obtained from the mother liquors. This fortunate observation was rationalized on the basis of the higher solubility of the racemate than that of the pure antipodes. This situation is typical for conglomerates, and was suggested for tetralone **3** on the basis of different, consistent observations: the trend in melting points of mixtures of different composition of (+)- and (−)-**3** was typical for conglomerates; the IR spectra of mixtures of different composition of (+)- and (−)-**3** were found to be identical; X-ray-diffraction analysis of a crystal of **3** (*Fig. 1*) selected from a slightly unbalanced mixture (the racemate is an oil at room temperature) demonstrated that the crystal was chiral and constituted by homochiral molecules. The latter experiment provided the structure of **3**, even though the absence of atoms with large anomalous scattering did not permit the determination the absolute configuration.

On the basis of this result, the route to (−)-**1a** in high enantiomeric purity was open, since the synthetic procedures from α-tetralone **3** to 7-hydroxycalamenal (**1a**) are described in detail in the literature [5][9]. The reaction of (+)-**3** with MeMgBr,

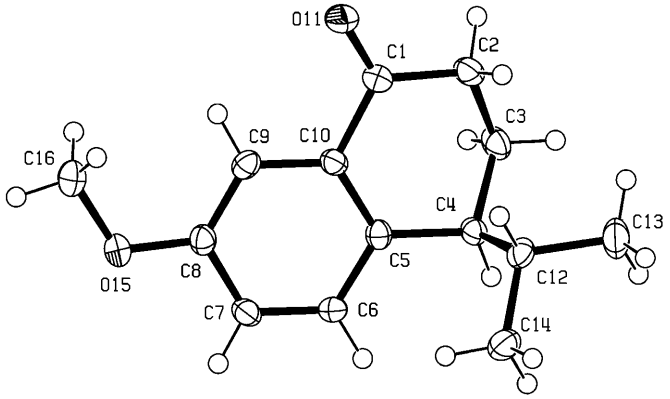


Fig. 1. *ORTEPIII Projection of the X-ray crystal structure of* **3** *at 150 K*. Atomic displacement parameters at the 50% probability level; H-Atoms not to scale.

immediately followed by acid-promoted dehydration of the resulting alcohol in refluxing toluene, gave (−)-**9** in 95% overall yield. The latter was immediately[2]) submitted to catalytic hydrogenation (5% Pd/C) to afford (−)-**4** in 96% ee (HPLC). The minor (1*S*,4*R*)-diastereoisomer, could be removed by chromatography (SiO_2; hexane/AcOEt 95 : 5)[3]). The high diastereoselectivity observed in the hydrogenation of **9** was justified by a computational study (see below). Then, a classic *Vilsmeier* reaction was performed on (−)-**4** with $P_2O_3Cl_4$ and DMF in refluxing 1,2-dichloroethane (*Scheme 4*). The reaction was slow (20 h), and required continuous addition of $P_2O_3Cl_4$ to go to completion. Compound (−)-**1b** was thus obtained in 80% yield (96% ee by HPLC). Its rapid demethylation to (−)-**1a** was effected in high yield with BBr_3. The enantiomeric purity of nature-identical (−)-7-hydroxycalamenal was found to be 96% (HPLC).

2.2. *Conformational Analysis.* Due to the size of compound **9** (118 electrons), calculations were performed at the B3LYP/6-31G(*d*) level on a model system (M**9**), where the Me group in 4-position and the MeO group are replaced by a H-atom and an OH group, respectively. This alleviates the computational burden and has no foreseeable effect on the conformational analysis. Minimum-energy structures were located for the two isomers with the i-Pr group in axial (M_a**9**) or equatorial position (M_e**9**), and characterized by harmonic analysis. The energy of both isomers was also calculated as a function of the relative conformation of the i-Pr group with respect to the 'cyclohexadiene' ring, specifically as a function of the dihedral angle H(20)−C(15)−C(21)−H(22) (*Fig. 2*). For each dihedral angle, all other geometrical parameters were optimized with the Gaussian98 suite [20].

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[2]) Exposure of **9** to O_2 (air) leads to complete aromatization, and the resulting naphthalene by-product is difficult to remove by conventional techniques.

[3]) The progress of the hydrogenation must be carefully followed, since prolonged reaction times give rise to the formation of diastereoisomeric methoxydecalines as side products, which have to be removed by chromatography.

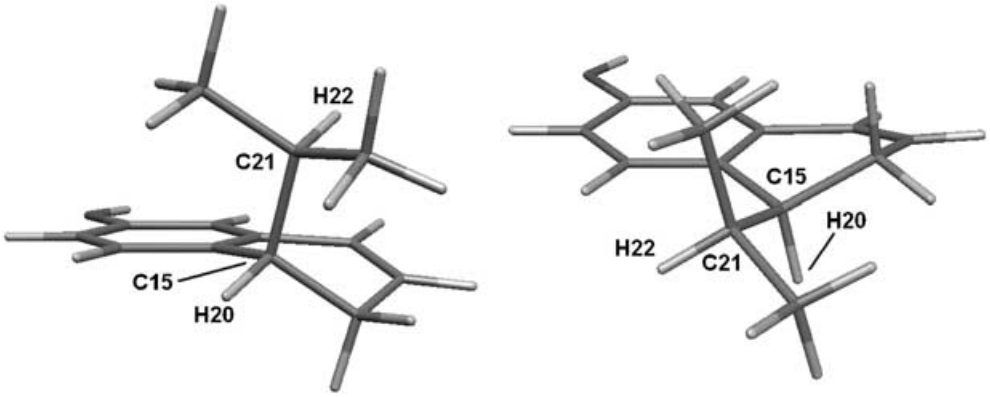

Fig. 2. *B3LYP/6-31G(*d*) Minimum-energy structure of the* M_a**9** (left) *and* M_e**9** (right) *isomers*

In both isomeric models, M_a**9** and M_e**9**, the lowest-energy structure has a strictly planar arene ring and a distorted 'cyclohexadiene' ring. Indeed, the non-aromatic C=C bond is not perfectly coplanar with the arene ring. This distortion amounts to 15.6 and $-14.0°$ for the axial and equatorial conformer, respectively. As for the relative conformation of the i-Pr group with respect to the 'cyclohexadiene' moiety, the former assumes a staggered conformation about the C(15)–C(21) bond in both isomers. In M_a**9**, H(22) of the i-Pr group points toward the ring center (dihedral angle θ[H(20)–C(15)–C(21)–H(22)] = $-178.9°$), whereas in M_e**9** it roughly points towards the aromatic H-atom in position 8 ($\theta = -64.0°$). As expected for a 'cyclohexadiene' system lacking any 1,3 diaxial interactions, M_a**9** is more stable than M_e**9** by 0.79 kcal mol^{-1}. This seemingly tiny difference translates into a 79:21 ratio of M_a**9**/M_e**9** at room temperature. Furthermore, both isomers have two more lowest-energy structures corresponding to the other possible staggered conformations of the i-Pr group. In M_a**9**, these corresponds to conformations where one of the i-Pr Me groups points toward the center of the 'cyclohexadiene' moiety, thus most effectively hindering one side of the C=C bond ($\theta = -66.9$ and $64.2°$). In M_e**9**, the two other stable conformations have dihedral angles of $\theta = -156.8$ and $72.4°$. It is worth noting that the equatorial–equatorial interactions between the i-Pr group and the neighboring H-atoms in positions 2 and 8 give rise to θ values significantly different from the nominal values of $180°$ and $60°$. The relative energies of the six most-stable conformers are summarized in *Table 2*.

Applying the *Boltzmann* distribution, it turns out that 89% of the molecules display the i-Pr group in axial position, with a preference for the conformer with $\theta = -178.9°$. The remaining conformers (11%) exhibit an equatorial i-Pr group, of which only the conformer with $\theta = -64.0°$ is appreciably populated. Finally, the energy of both conformers was calculated for a fixed θ value, and by optimizing all other geometric parameters, thus outlining a potential-energy curve for the rotation about the C(15)–C(21) bond in both isomers (*Fig. 3*).

The rotation of the i-Pr group with respect to the cyclic moiety can be considered free, since the rotation barriers were calculated to be lower than *ca.* 8 kcal mol^{-1}. It is

Table 2. *Relative Energy* (*E*) *and Dihedral Angle* θ (rotation about the C(15)–C(21) bond, see *Fig. 2*) *of the Most-Stable Structures of the Axial and Equatorial Conformers* M_a**9** *and* M_e**9**, *Respectively.* Populations refer to estimated *Boltzmann* distributions.

Conformer	θ [°]	*E* [kcal/mol]	Population [%]		
			two minima[a])	six minima[b])	continuum[c])
M_a**9**	– 178.9	0.00	79	43	63
	– 66.9	0.22		30	22
	64.2	0.58		16	9
M_e**9**	– 64.0	0.79	21	11	6
	– 156.8	2.71		< 1	< 0.1
	72.4	3.24		< 1	< 0.1

[a]) Obtained by considering only the most-stable conformers. [b]) Obtained considering all stable conformers. [c]) Obtained by interpolating the calculated energy by a sixth-order *Fourier* series.

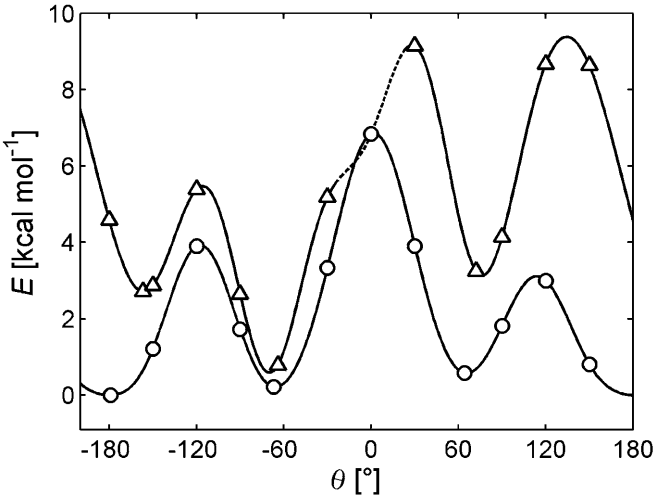

Fig. 3. *B3LYP/6-31G*(d) *Relative Energies* (*E*) *of* M_a**9** (circles) *and* M_e**9** (triangles) *as a function of the H(20)–C(15)–C(21)–H(22) dihedral angle* θ. Near or at $\theta = 0°$, there is no stable structure with the i-Pr group in equatorial position. The curves represent energy interpolations by a sixth-order *Fourier* series.

noteworthy that for conformers with θ values equal or close to 0°, there is no stable M_e**9** structure because of steric repulsion between the i-Pr group and the neighboring H-atoms.

By a *Fourier* series analysis up to sixth order, the energies of M_a**9** and M_e**9** can be interpolated over the whole θ range and the *Boltzmann* distribution. Partitioning such distribution, another estimate of the population of the various isomers is obtained, as reported in *Table 2*. In this case, the M_a**9** isomer population is 94%, even larger than in the 'six-minima case'. In conclusion, the present conformational analysis based on B3LYP/6-31G(*d*) calculations, and on three different population estimates, provides evidence that the axial isomer is largely predominant over the equatorial one, which

supports the view that the large diastereoselectivity in the catalytic reduction of **9** is caused by a conformational effect.

3. Conclusions. – We have developed a reliable synthesis of both enantiomers of 7-hydroxycalamenal (**1a**) in high enantiomeric purities. The 13-step synthesis is the shortest reported to date, starting from commercially available materials, and lacking any risky or environment-polluting reagents. Each step was carefully verified with respect to both reproducibility and enantiomeric purity. Several points left unclear by previous work on these subjects were re-investigated and clarified. Hence, our synthetic scheme represents the currently solely efficient and reliable approach to nature-identical 7-hydroxycalamenal (**1a**).

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Experimental Part

General. Unless otherwise specified, all solvents and reagents were reagent-grade, and used without purification. For the preparations of the complexes and for hydrogenation reactions, solvents were degassed with Ar. Complex **13c** was supplied by *Chemi S.p.A.* (Italy), and complexes **13a,b** were prepared according to literature procedures [11], starting from the appropriate diphosphine ligand and $[Ru(p\text{-cymene})I_2]_2$. Complexes **14a,b** were prepared by reaction between $[Rh(COD)_2BF_4]$ and tetraMe-BITIOP or UlluPHOS [15], respectively, in CH_2Cl_2 solution at room temperature. All reactions were performed using standard *Schlenk* techniques. HPLC Analyses were performed on a *Jasco* instrument (model *980-PU* pump with *975-UV* detector), with a *Chiracel OD* column at a flow rate of 0.8 ml/min, detection at 254 nm, the mobile phase being different hexane/i-PrOH mixtures. ^{1}H-NMR spectra were recorded in $CDCl_3$ soln. on 200- or 300-MHz *Bruker* spectrometers; δ in ppm, J in Hz.

*(*2S*)-2-(4-Methoxyphenyl)-3-methylbutanoic Acid* ((+)-**11**). *General Procedure*. Asymmetric hydrogenation reactions were carried out in a stirred (550 rpm), 100-ml *Parr Hastelloy* autoclave equipped with a sampling pipe extending to the bottom of the vessel. The autoclave was purged with Ar (5×). Then, a soln. of *2-(4-methoxyphenyl)-3-methylbut-2-enoic acid* (**10**) in degassed MeOH (15 ml) and the suitable catalyst were loaded into the autoclave by means of a syringe. The autoclave was pressurized with H_2 at the desired pressure, and the soln. was stirred for the time indicated in *Table 1*. When the reaction was complete, the pressure was released, and the solvent was evaporated under reduced pressure. The residue was dissolved in a hexane/AcOEt 9:1 mixture, and filtered over a pad of SiO_2 to remove the catalyst. The enantiomeric purity of (+)-**11** was determined by chiral HPLC (hexane/i-PrOH/HCO_2H 88:12:0.1).

*(*2S*)-2-(4-Methoxyphenyl)-3-methylbutan-1-ol* ((+)-**15**). A 1M BH_3 soln. in THF (60 ml, 0.06 mol) was dropped slowly under N_2 to a soln. of (+)-**11** (6.5 g, 0.031 mol) in anh. THF (30 ml), keeping the temp. at $-5°$. The mixture was stirred for 1 h at 0°, then allowed to warm to room temperature, and stirring was maintained for a further 8 h. A soln. of AcOH (5 ml) and H_2O (5 ml) was cautiously added, and the mixture was stirred until gas evolution stopped. The THF was evaporated *in vacuo*, and a sat. aq. Na_2CO_3 soln. was added to the residue. After 20 min of stirring, CH_2Cl_2 was added, and the org. layer was separated, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was filtered over a pad of SiO_2 (hexane/AcOEt 1:1) to afford pure (+)-**15** in 99% yield and 86% ee (chiral HPLC; hexane/i-PrOH/HCO_2H 90:10:0.1). $[\alpha]_D^{25} = +9.2$ ($c = 1.07$, $CHCl_3$).

*Ethyl (*2RS,4S*)-2-Cyano-4-(4-methoxyphenyl)-5-methylhexanoate* (**16**). A 40% toluene soln. of diethyl azodicarboxylate (DEAD; 14.7 ml, 0.032 mol) was diluted with THF (25 ml), and the resulting mixture was added to a soln. of Ph_3P (8.6 g, 0.032 mol) in anh. THF (25 ml), and cooled to $-20°$. Then, a soln. of (+)-**15** (5.5 g, 0.028 mol) and ethyl cyanoacetate (3 ml, 0.028 mol) in THF (50 ml) was added. The mixture was stirred for 3 h at $-20°$, and then at r.t. for 20 h. The solvent was removed under reduced pressure, and the residue was subjected to column chromatography (CC) (SiO_2; hexane/AcOEt 8:2). The first fractions eluted gave **16** (92%) as a mixture of diastereoisomers in a 2.3:1 ratio, as calculated on the basis of the NMR integrals of H–C(2) at δ(H) 3.04 (major) and 3.24 (minor). Most of the other signals were superimposed. ^{1}H-NMR (300 MHz,

$CDCl_3$): 0.74, 0.77 (2*d*, *J* = 6.7, 1 *Me*CH of each isomer); 0.99, 1.02 (2*d*, *J* = 6.7, 1 *Me*CH of each isomer); 1.27, 1.29 (2*t*, *J* = 7.2, *Me*CH_2 of each isomer); 1.83 (2*m* (superimposed), H–C(5)); 2.17, 2.35 (2*m* (superimposed), CH_2(3)); 2.53 (2*m* (superimposed), H–C(4)); 3.04 (*dd*, *J* = 12.1, 4.3, H–C(2) of major isomer); 3.24 (*dd*, *J* = 9.6, 3.9, H–C(2) of minor isomer); 3.82 (2*s* (superimposed), MeO of both isomers); 4.14, 4.23 (2*q*, *J* = 7.2, MeCH_2 of each isomer; 6.87, 7.04 (2*d*, *J* = 8.74, 2 arom. H of minor isomer); 6.89, 7.11 (2*d*, *J* = 8.66, 2 arom. H of major isomer).

(S)-4-(4-Methoxyphenyl)-5-methylhexanoic Acid ((−)-**2**). Compound **16** (6.4 g) was added to a soln. of KOH (37 g) in ethylene glycol (110 ml), and the mixture was heated at 110° for 36 h. The solvent was evaporated *in vacuo*, the residue was taken up in CH_2Cl_2 (60 ml), and extracted with H_2O (60 ml). The org. layer was separated, dried (Na_2SO_4), and evaporated under reduced pressure. The resulting residue was dissolved in xylene (100 ml), and this mixture was refluxed for 1 h in the presence of reduced copper (0.15 g) as catalyst. The solvent was evaporated *in vacuo* to give a residue, which was purified by CC (SiO_2; hexane/AcOEt 7:3) to afford (−)-**2** in 85% yield and 86% ee (chiral HPLC; hexane/i-PrOH/HCO_2H 95:5:0.1). $[\alpha]_D = -4$ (*c* = 3.01, CH_2Cl_2).

(4S)-3,4-Dihydro-4-(1-methylethyl)-7-methoxy-2*H*-naphthalen-1-one* ((+)-**3**). Acid (+)-**2** (3 g) was added to polyphosphoric acid (PPA; 30 g) preheated at 80°. The mixture was stirred for 1 h, then poured onto ice (30 g), and extracted with CH_2Cl_2 (20 ml). The org. layer was separated, dried, and concentrated *in vacuo*, and the resulting residue was filtered over a pad of SiO_2 (hexane/AcOEt 7:3) to afford (+)-**3** in 70% yield. An anal. sample (86% ee) was subjected to chiral HPLC (hexane/i-PrOH 98:2) to confirm the enantiomeric purity. Another sample was slowly crystallized from MeOH at 0° to afford crystals of (+)-**3** [m.p. 73° for 99.4% ee; $[\alpha]_D^{25} = +74$ (*c* = 1.0, $CHCl_3$)]. These crystals were used as seeds for the crystallization of the whole batch of **3** from hexane. The product recovered by filtration (1.5 g) had an $[\alpha]_D^{25}$ value of +71 (*c* = 1.0, $CHCl_3$), corresponding to 95.5% ee.

(1S,4S)-1,2,3,4-Tetrahydro-6-methoxy-4-methyl-1-(1-methylethyl)-naphthalene ((−)-**4**). The enantiomeric excess (ee) was determined by chiral HPLC (*Chiracel OD*; hexane/i-PrOH/HCO_2H 95:5:0.1).

(1S,4S)-cis-*7-Methoxycalamenal* (=*(−)-(5S,8S)-5,6,7,8-Tetrahydro-3-methoxy-5-methyl-8-(1-methylethyl)-naphthalene-2-carbaldehyde*; (−)-**1b**). The enantiomeric excess was determined by chiral HPLC (*Chiracel OD*; hexane/i-PrOH/HCO_2H 99:1:0.1).

(1S,4S)-cis-*7-Hydroxycalamenal* (=*(−)-(5S,8S)-5,6,7,8-Tetrahydro-3-hydroxy-5-methyl-8-(1-methylethyl)-naphthalene-2-carbaldehyde*; (−)-**1a**). The enantiomeric excess was determined by chiral HPLC (*Chiracel OD*; hexane/i-PrOH/HCO_2H 99.8:0.2:0.1).

X-Ray Crystallographic Analysis of Compound **3**[4]. Crystallized from hexane. Crystallographic data: formula, $C_{14}H_{18}O_2$; M_r, 218.28; crystal size: 0.37 × 0.14 × 0.05 mm; orthorhombic, space group $P2_12_12_1$; *a* = 7.6924(9), *b* = 8.6127(12), *c* = 17.796 (3) Å; *V* = 1179.0(3) Å^3; *T* = 150 K; *Z* = 4; *Bruker SMART-APEX* CCD area-detector diffractometer, MoK_α radiation (λ = 0.71073 Å); D_x = 1.230 g cm^{-3}; μ = 0.080 mm^{-1}; ω and φ scans, θ_{max} = 30.06°; 18775 reflections collected, 1989 unique, 1890 with $I_0 > 2\sigma(I_0)$, R_{aver} = 0.0305. The structure was solved with SIR2002 [21], and refined by full-matrix least-squares based on F^2 using SHELX97 [22]. Anisotropic C- and O-atoms, H-atoms isotropic; 217 parameters, $R(F) = 0.0426$, $wR(F^2) = 0.1021$, $S = 1.158$; final residues on *Fourier* map in the range −0.22 to 0.312 e Å^{-3}. Without atoms with large anomalous scattering, we could not determine the absolute configuration, which was, thus, assigned arbitrarily; *Fig. 1* was generated with ORTEPIII [23].

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[4]) The full crystallographic data of **3** were deposited with the *Cambridge Crystallographic Data Centre*, 12 Union Road, Cambridge CB2 1EZ, UK. The data can be obtained, free of charge, via the internet at www.ccdc.cam.ac.uk/data_request/cif by referring to CCDC-267608.

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