Enantioselective Syntheses and Fragrance Properties of the Four Stereoisomers of *Magnolione*® (Magnolia Ketone)[1])

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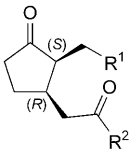
Enantioselective total syntheses of the four stereoisomers of the fragrance *Magnolione*® (**1**) are described. Key step is a Pd-catalyzed asymmetric allylic alkylation displaying enantiomer excess of ≥99% (*Scheme 2*). The resultant methyl α-acetyl-2-pentylcyclopent-2-ene-1-acetate) was subjected to demethoxycarbonylation, carbonyl protection by acetalization, and epoxidation (*Schemes 2* and *3*). Subsequent *Lewis* acid catalyzed epoxide/ketone rearrangement followed by deprotection gave *cis/trans* mixtures of *Magnolione*® in 28% overall yield (*Scheme 3*). The *cis*/*trans* isomers were separated by prep. HPLC, and fragrance properties as well as odor threshold values were determined (*Table 2*).

Introduction. – Derivatives of jasmonic acid (*Fig. 1*), such as methyl jasmonate or methyl dihydrojasmonate (*Hedione*®), are of great importance for the fragrance industry [1][2]. A compound with similar structure and odor characteristics is *Magnolione*®, which is produced by *Givaudan AG* and is used, *e.g.*, in 'Coriandre' (*Couturier* 1973) and 'Eden' (*Cacharel* 1994) [1], causing a pleasant flowery bouquet. Although it induces a more intense scent than methyl dihydrojasmonate, odor characteristics of all four stereoisomers of *Magnolione*® have not been well characterized so far.



R^1 = (*Z*)-C_2H_5–CH=CH, R^2 = OH, jasmonic acid

R^1 = (*Z*)-C_2H_5–CH=CH, R^2 = MeO, methyl jasmonate

R^1 = Pr, R^2 = MeO, methyl dihydrojasmonate

R^1 = Pr, R^2 = Me, Magnolione®

Fig. 1. *Jasmonic Acid and Its Derivates*

Until recently, jasmonoids were produced as racemates, consisting of mixtures of the *trans*- (>90%) and *cis*-isomers. The issue of configuration of the jasmonoids became of interest for the fragrance industry after *Acree* and co-workers prepared

[1]) The results of this article were presented in a lecture (*G. H.*) at the conference 'Flavours & Fragrances', Manchester, UK, May 12–14, 2004, and in a poster (*A. Q. S.*) at the ' 5th International Symposium on Transition Metals in Organic Synthesis', University of Strathclyde, Glasgow, UK, September 15–17, 2004.

the four possible stereoisomers of methyl jasmonate and demonstrated that mainly the (2*S*,3*R*)-*cis*-isomer possesses the characteristic odor [3]. Remarkably, the (2*S*,3*R*)-*cis*-isomers of jasmonoids occurring in plants also display the highest biologic activity [4]. Today, (2*S*,3*R*)-methyl dihydrojasmonate is produced and marketed by *Firmenich SA* [2].

Nothing is known about the fragrance properties of the individual stereoisomers of *Magnolione*® (**1**; *Fig. 2*), and in particular the *cis*-enantiomers, likely to be the more active compounds. We describe here the first enantioselective total syntheses of all four stereoisomers (ee > 99%) of *Magnolione*® and an evaluation of their fragrance properties.

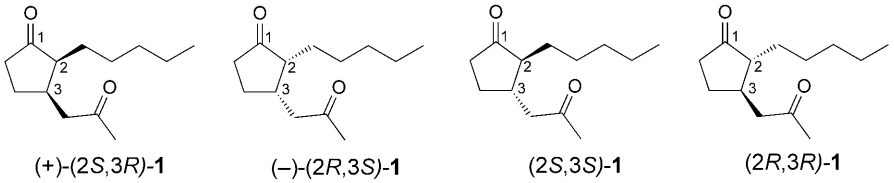


Fig. 2. *Stereoisomers of* Magnolione®

Magnolione® was first described, as racemate, by *Lenfant* and *Wolff* in 1963 [5]. Its use as fragrance component was patented in 1973 by *Celli* [6], who observed that the odor of the compound is reminiscent of magnolia[2]). Since this time, the racemic *cis*/*trans* mixture is used in perfumery. While a large number of enantioselective total syntheses of jasmonates have been published, there was, to the best of our knowledge, only one report on an enantioselective total synthesis of *trans-Magnolione*® with an enantiomer excess (ee) of 76% [7] when this article was submitted. In the meantime, an enantioselective synthesis and description of odor properties of (+)-(2*S*,3*R*)-*cis-Magnolione*® with an ee of 93% has been published [8].

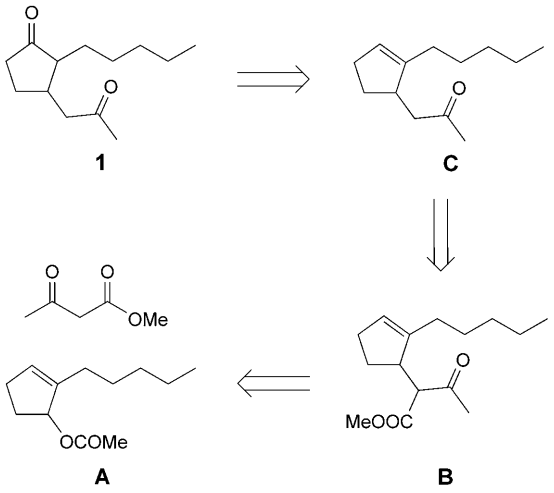
Synthesis. – The strategy of our synthesis of *Magnolione*® is described in *Scheme 1* as a retrosynthesis. Key step was an asymmetric Pd-catalyzed allylic alkylation of the known allylic acetate **A** with methyl acetoacetate (=methyl 3-oxobutanoate) to give β-keto ester **B**. This was subjected to demethoxycarbonylation to give ketone **C**, which was finally transformed into *Magnolione*® *via* a route analogous to one worked out for methyl jasmonate and *Hedione*® by *Fehr* and *Galindo* [9].

We have previously reported that the chiral β-phosphinocarboxylic acids **L*** and *ent*-**L*** (*Fig. 3*) used as ligands in Pd-catalyzed allylic substitutions produce excellent results with cyclic substrates [10]. Using these ligands seemed an obvious choice for the synthesis of *Magnolione*® while **L*** gives the (1*S*)- and *ent*-**L*** the (1*R*)-enantiomer [11].

The requisite allylic acetate **2** was prepared in 85% yield from the commercially available 2-pentylcyclopent-2-enone via *Luche* reduction and acetylation of the resultant alcohol [12]. Palladium-catalyzed allylic alkylation of acetate **2** with methyl aceto-

[2]) We were unable to find a report on the occurrence of *Magnolione*® as a natural product.

Scheme 1. *Retrosynthesis of* Magnolione® (**1**)



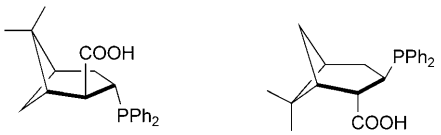


Fig. 3. *Ligands used for palladium-catalyzed allylic alkylations*

acetate in the presence of *ent*-L* gave β-keto ester (1*R*)-**3** with two stereogenic centers as a 1:1 mixture of diastereoisomers (*Scheme 2*). The ee of (1*R*)-**3** could not be determined directly. Fortunately, saponification/decarboxylation of (1*R*)-**3** with 1M NaOH in MeOH gave ketone (+)-(1′*R*)-**4** (95% yield), for which the ee was assessed by GC analysis.

The allylic alkylation was carried out in the presence of 1.5 mol-% of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ as catalyst and 9 mol-% of **L*** or *ent*-**L***(*Scheme 2*). The air-sensitive ligands **L*** and *ent*-**L*** were prepared from their air-stable borane complexes **L***·BH_3 and *ent*-**L***·BH_3. Reactions were performed under various conditions (*Table 1*). Best results were obtained with methyl sodioacetoacetate prepared by reaction of methyl acetoacetate with NaH in THF as solvent. The alkylation product was eventually obtained in excellent yield and an ee of $\geq$99% (*Entries 1* and *2*). Good enantioselectivities could also be achieved with MeCN as solvent, however, the yield was lower because of low solubility of the nucleophile. Li^+ turned out to be a less desirable counterion because reactivity as well as enantioselectivity was decreased.

The second carbonyl group present *in Magnolione*® was introduced *via* epoxidation of (+)-(1′*R*)-**4** followed by *Lewis* acid catalyzed epoxide rearrangement [9]. First, the carbonyl group of (+)-(1′*R*)-**4** was protected by standard acetalization with ethylene glycol affording acetal (+)-(1′*R*)-**5** in 93% yield (*Scheme 3*). Reaction of (+)-(1′*R*)-**5** with 3-chloroperbezoic acid (MCPBA) proceeded in 95% yield with a selectivity of

Scheme 2. *Allylic Alkylation and Demethoxycarbonylation*

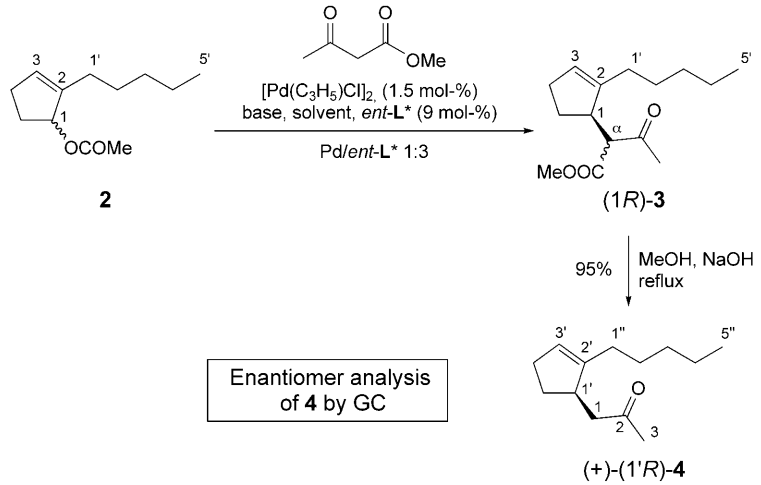


Table 1. *Palladium-Catalyzed Allylic Alkylations*

Entry	Solvent	Nucleophile[a])	Ligand	*T* [°]	Time [d]	Yield of **3** [%]	% ee of **4** (abs. conf.)
1	THF	$NaCHR^1R^2$	**L***	25	3	82	99.3 (*S*)
2	THF	$NaCHR^1R^2$	*ent*-**L***	25	3	91	99.1 (*R*)
3	MeCN	$NaCHR^1R^2$	**L***	25	4	55	98.4 (*S*)
4	dioxane	$NaCHR^1R^2$	**L***	25	3	72	97.4 (*S*)
5	dioxane	$LiCHR^1R^2$	**L***	50	1	25	90.0 (*S*)
6	dioxane	$LiCHR^1R^2$	**L***	25	–	–	–

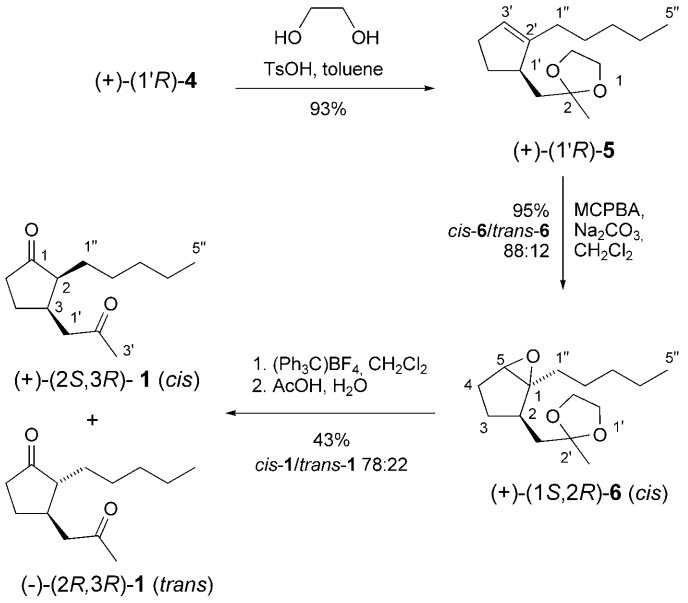
[a]) Prepared from methyl acetoacetate by deprotonation with NaH or LHMDS (=lithium hexamethyldisilazanide); R^1=COMe, R^2=COOMe.

88:12 in favor of the *cis*-isomer (+)-(1*S*,2*R*)-**6**. For the epoxide rearrangement, after extensive experimentation, the *Lewis* acid $(Ph_3C)BF_4$ was found to be well suited. Lithium perchlorate and $BF_3 \cdot OEt_2$ also catalyzed the rearrangement but yields were low[3]).

The acetal was deprotected by treatment with an aqueous soln. of AcOH to give *Magnolione*® in 43% yield over two steps as 78:22 (GC) mixture of the *cis*- and the *trans*-isomer, *i.e.*, of (+)-(2*S*,3*R*)- and (−)-(2*R*,3*R*)-**1**. GC/MS Analysis showed that during the deprotection and purifying procedure, only little isomerization (*ca.* 5–7%) occurs. Separation by prep. HPLC on silica gel (hexane/i-PrOH 95:5) afforded the *trans*-isomer (−)-(2*R*,3*R*)-**1** in high purity (>98%, GC/MS) and the enriched *cis*-isomer (+)-(2*S*,3*R*)-**1** (*cis*/*trans* 91:9, GC/MS). The assignment of the relative configurations

[3]) We have also accomplished epoxidation of the unprotected ketone (+)-(1′*R*)-**4** with MCPBA (CH_2Cl_2, 0°) in 90% yield. However, attempts to affect the rearrangement with $(Ph_3C)BF_4$ or $BF_3 \cdot OEt_2$ did not yield *Magnolione*®. During refereeing of our manuscript, we learned that epoxidation of **4** with CF_3CO_3H proceeds with selectivity >88:12, and the rearrangement of the unprotected epoxide, to give a bridged ketal, is possible (*C. Fehr*, *Firmenich SA*, personal communication).

Scheme 3. Magnolione®: *Final Steps*



relies on comparison of GC/MS data of our substances with those of the equilibrium mixture containing 91% of *trans*- and 9% of *cis*-*Magnolione*® (GC). This sample of the racemic compounds was provided by *Givaudan*.

The rate of c*is*/*trans*-isomerization of *Magnolione*® is smaller than that of methyl *cis*-jasmonate. *Weinges* and *Lernhardt* [13], *e.g.*, reported that upon addition of 0.1N HCl to a 2% solution of pure methyl *cis*-jasmonate in MeOH, equilibrium was reached after 24 h to give a 95 : 5 mixture of methyl *trans*- and methyl *cis*-jasmonate. In contrast, addition of a drop (10 mg) of 0.1N HCl to a solution of a 67 : 33 mixture of *cis*- and *trans*-*Magnolione*® in MeOH gave rise to a 44 : 56 and 20 : 80 ratio of *cis*- and *trans*-isomers after 3 and 12 days, respectively, at room temperature.

Olfactory Evaluation. – The odor threshold values and fragrance characterization of the stereoisomers of *Magnolione*® (**1**) are described in *Table 2*. Odor threshold values were determined by five panelists, who smelled the effluents of pure diastereoisomers from a GC column. Analogously to the jasmonates, the *cis*-isomer (2*S*,3*R*)-**1** displays the lowest odor threshold, while the threshold of the *trans*-isomer (2*R*,3*R*)-**1** is only slightly higher. Two of the panelists could not smell the *trans*-isomer (2*R*,3*R*)-**1** at all; this fact is not included in the threshold determination. In contrast, among the (3*S*)-isomers, the *trans*-isomer (2*S*,3*S*)-**1** possesses a remarkably lower threshold than the *cis*-isomer (2*R*,3*S*)-**1**, which displayed by far the highest threshold of all four stereoisomers.

The evaluation of the odor qualities was carried out by a professional perfumer with 5% solutions of the compounds in EtOH. In addition, opinions of the aforementioned panelists, who smelled the pure *cis*- and *trans*-isomers directly from the GC column,

Table 2. *Odor Thresholds and Fragrance Description of the* Magnolione® *Isomers*

	Odor threshold [ng]	Fragrance description	Intensity
(+)-(2*S*,3*R*)-**1** (*cis*)	0.29	floral, jasmine, fruity, fresh	most intense
(2*R*,3*R*)-**1** (*trans*)	0.74	floral, jasmine, animalic touch, metallic	weak
(−)-(2*R*,3*S*)-**1** (*cis*)	7.10	citrus, fruity, floral, fresh, green, jasmine	very weak
(2*S*,3*S*)-**1** (*trans*)	0.60	mushrooms, food like, metallic, floral, jasmine	weak

were considered. A summary of the evaluation is presented in *Table 2*. The (3*R*)-isomers both hold a pleasant floral and jasmine-like note and, as expected, the *cis*-isomer displays the more intense odor. The scent of (2*R*,3*R*)-**1** (*trans*) is pleasant and more discreet than that of (2*S*,3*R*)-**1** (*cis*), while (2*R*,3*R*)-**1** (*trans*) displays a slightly animalic touch. The (3*S*)-isomers both display a light jasmine note; however, their flavor is not as characteristic as that of the (3*R*)-isomers.

Experimental Part

General. – All reactions requiring exclusion of O_2 and moisture were carried out under dry Ar. TLC: *Macherey & Nagel-Polygram-Sil-G/UV*-precoated sheets; visualization by treatment with phosphomolybdic acid soln. in EtOH or aq. $KMnO_4$ soln. Column chromatography: *Fluka* silica gel *60* (0.04–0.063 mm); FC = flash chromatography. Anal. HPLC: *Hewlett-Packard-HP-1090* chromatograph; column: silica gel (*Eurosphere 80-5*, 5μ; 5×250 mm); t_R in min. Prep. HPLC: *Gilson-305* pump coupled with a *Knauer*-UV/VIS-filter photometer; column: silica gel (*Latek*, 5μ; 21×250 mm). GC: *Hewlett-Packard-HP-5890* chromatograph coupled with a flame-ionization detector (FID); capillary column *HP-1* (cross-linked methyl silicone; 25 m×0.2 mm; 0.33 μm film thickness), or *Chrompack*-permethyl-β-cyclodextrin column (50 m×0.25 mm); He as carrier gas; t_R in min. Optical rotation: *Perkin-Elmer-241* polarimeter. ^{1}H- and ^{13}C-NMR Spectra: *Bruker-ARX-250*, *-DRX-300*, or *-DRX-500* instrument; δ in ppm rel. to $CDCl_3$ (δ(H) 7.26 and δ(C) 77.0). GC/MS: *Hewlett-Packard-HP-5890-Series-II-Plus* system, coupled with a *HP-5972* mass selective detector; capillary column *HP-1* (cross-linked methyl silicone; 25 m×0.2 mm; 0.33 μm film thickness); He as carrier gas; t_R in min. MS: *Jeol-JMS-700* spectrometer; in *m*/*z*. Elemental analyses were carried out by the Microanalytical Laboratory of the Chemisches Institut der Universität Heidelberg.

(±)-2-Pentylcyclopent-2-en-1-yl Acetate (**2**). Cer(III) chloride heptahydrate (36.6 g, 98.2 mmol) and $NaBH_4$ (3.75 g, 98.7 mmol) were added portionwise to a soln. of 2-pentylcyclopent-2-enone (15.0 g, 98.5 mmol) in MeOH (250 ml), and the mixture was stirred at r.t. for 1 h (TLC (petroleum ether/AcOEt 10:1; $KMnO_4$): complete conversion; R_f (2-pentylcyclopent-2-en-1-ol) 0.21). H_2O (150 ml) was added, the mixture saturated with NaCl and extracted with Et_2O (5×100 ml), and the org. layer dried (Na_2SO_4) and evaporated to give 14.7 g of 2-pentylcyclopent-2-en-1-ol.

An aliquot (13.7 g, 88.6 mmol) was added dropwise to a soln. of Et_3N (28.8 g, 0.28 mol) and *N*,*N*-dimethylpyridin-4-amine (DMAP; 100 mg, 0.82 mmol) in Ac_2O (32.9 g, 0.37 mol). After 16 h (TLC (petroleum ether/AcOEt 10:1; $KMnO_4$): complete conversion; R_f (**2**) 0.54), the mixture was cooled to 0°, and sat. NH_4Cl soln. (50 ml) was added. After 1 h stirring, the aq. soln. was extracted with Et_2O (3×100 ml), the combined org. phase washed with sat. aq. $CuSO_4$ soln. (1×80 ml), sat. aq. $NaHCO_3$ soln. (3×100 ml), and brine (1×100 ml), dried (Na_2SO_4), and evaporated, and the crude product purified by FC (silica gel, petroleum ether/AcOEt 10:1): **2** (15.3 g, 80%). Colorless thin oil. ^{1}H-NMR ($CDCl_3$, 250 MHz): 0.86 (*t*, *J* = 6.7, Me(5′)); 1.25–1.48 (*m*, 6 H, CH_2); 1.70–1.78 (*m*, 2 H, CH_2); 2.02–2.36 (*m*, 4 H, CH_2); 2.02 (*s*, MeC=O); 5.64 (*m*, H–C(1), H–C(3)). ^{13}C-NMR ($CDCl_3$, 75 MHz): 14.0 (*q*, Me(5′)); 21.3 (*q*, MeC=O); 22.5, 27.2, 28.1, 30.1, 31.0, 31.7 (6*t*, CH_2); 81.3 (*d*, C(1)); 129.7 (*d*, C(3)); 142.8 (*s*, C(2)); 171.1 (*s*, C=O). HR-EI-MS: 196.1463 (M^+, $C_{12}H_{20}O_2^+$; calc. 196.1467).

(1R)-Methyl α-Acetyl-2-pentylcyclopent-2-ene-1-acetate ((1*R*)-**3**). Under Ar in a *Schlenk* flask, a stirred soln. of ligand *ent*-**L***·BH_3 (154.5 mg, 0.43 mmol) and 1,4-diazobicyclo[2.2.2]octane (DABCO; 54.9 mg, 0.46 mmol) in dry toluene (8 ml) was heated under reflux for 3 h. After cooling to r.t., the solvent was evaporated. The residue was dissolved in dry THF (5 ml), and $[Pd(C_3H_5)Cl]_2$ (26.5 mg, 0.071 mmol) and 20 min later acetate

2 (1.00 g, 5.06 mmol) were added to the yellow soln. In a second *Schlenk* flask, methyl acetoacetate (967.5 mg, 8.28 mmol) was added dropwise to a suspension of NaH (189.6 mg, 7.88 mmol) in dry THF (20 ml). The resultant colorless soln. was dropwise added within 5 min into the other *Schlenk* flask. The mixture was stirred until TLC (petroleum ether/AcOEt 10:1; $KMnO_4$): R_f (0.38) showed complete conversion. Then sat. NH_4Cl soln. (20 ml) was added, the mixture extracted with Et_2O (3×30 ml), the combined org. layer washed with brine (1×20 ml), dried (Na_2SO_4), and evaporated, and the residual yellow oil subjected to FC (silica gel, petroleum ether/AcOEt 10:1): (1*R*)-**3** as a 1:1 diastereoisomer mixture that could not be separated. Colorless oil. Diastereoisomer mixture: $[\alpha]_D^{22} = +25.6$ ($c = 1.08$, MeOH; 99.1% ee[4])). ^{1}H-NMR ($CDCl_3$, 250 MHz): 0.87 (*t*, $J = 6.7$, Me(5′)); 1.29–2.27 (*m*, 6 CH_2); 2.19 (*s*, MeC=O); 2.23 (*s*, MeC=O); 3.29 (*m*, H–C(1)); 3.52 (*d*, $J = 7.6$, H–C(α)); 3.60 (*d*, $J = 6.0$, H–C(α)); 3.67 (*s*, MeO); 3.70 (*s*, MeO); 5.42–5.45 (*m*, H–C(3)). ^{13}C-NMR (H,H-COSY, H,C-COSY, DEPT; $CDCl_3$, 75 MHz): 14.0 (*q*, Me(5′)); 22.5 (*t*, C(4′); 27.2, 27.3, 27.4, 28.2, 29.2, 29.4, 30.4, 30.7, 31.7, 31.8 (10*t*, 5 CH_2); 29.5, 29.8 (2*q*, *Me*C=O); 126.2, 126.4 (2*d*, C(3)); 144.0, 144.7 (2*s*, C(2)); 169.7, 170.2 (2*s*, *C*OOMe); 203.1, 203.3 (2*s*, C=O). GC/MS (injector temp. 250°; temp. program: 50° for 1 min, heating at a rate of 20°/min, 250° for 10 min): t_R 10.64, 10.69. HR-EI-MS: 252.1711 (M^+, $C_{15}H_{26}O_3^+$; calc. 252.1726). Anal. calc. for $C_{15}H_{26}O_3$; (252.45): C 71.39, H 9.59; found: C 71.19, H 9.59.

(1S)-Methyl α-Acetyl-2-pentylcyclopent-2-ene-1-acetate ((1*S*)-**3**). As described for (1*R*)-**3**, with **L***·BH_3 instead of *ent*-**L***·BH_3. $[\alpha]_D^{22} = -29.1$ ($c = 0.97$, MeOH; 91.5% ee[4])).

(+)-1-[(1R)-2-Pentylcyclopent-2-en-1-yl]propanone ((+)-(1′*R*)-**4**). A soln. of (1*R*)-**3** (937.6 mg, 3.715 mmol) in 1N NaOH (5 ml)/MeOH (10 ml) was heated under reflux for 4 h (TLC (petroleum ether/AcOEt 10:1; $KMnO_4$): complete conversion; R_f (**4**) 0.51). After cooling to r.t., the mixture was treated with brine (20 ml) and extracted with Et_2O (3×40 ml). The org. phase was dried (Na_2SO_4), filtered, and evaporated, and the residue purified by FC (silica gel, pentane/Et_2O 20:1): (+)-(1′*R*)-**4** (687.8 mg, 95%). Colorless, thin oil. GC (permethyl-β-cyclodextrin; injector temp. 200°, isothermal 115°): t_R 26.17 ((+)-(1′*R*)-**4**), 28.23 ((−)-(1′*S*)-**4**). $[\alpha]_D^{22} = +33.2$ ($c = 1.08$, MeOH; 98.5% ee). ^{1}HNMR (H,H-COSY; $CDCl_3$, 300 MHz): 0.89 (*t*, $J = 6.8$, Me(5″)); 1.20–1.48 (*m*, 3 CH_2, H_a–C(5′)); 1.84–2.28 (*m*, 2 CH_2, H_b–C(5′), H_a–C(1)); 2.15 (*s*, MeC=O); 2.68 (*dd*, $J = 16.1$, 4.0, H_b–C(1)); 2.94–2.96 (*m*, H–C(1′)); 5.36 (*m*, H–C(3′)). ^{13}C-NMR (H,C-COSY, DEPT; $CDCl_3$, 75 MHz): 14.1 (*q*, Me(5″); 22.5 (*t*, C(4″)); 27.3, 29.0, 30.5, 30.6, 31.8 (5*t*, CH_2); 30.3 (*q*, *Me*C=O); 42.5 (*d*, C(1′)); 48.0 (*t*, C(1)); 124.1 (*d*, C(3′)); 146.4 (*s*, C(2′)); 209.0 (*s*, C=O). HR-EI-MS: 194.1656 (M^+, $C_{13}H_{22}O^+$; calc. 194.1671). Anal. calc. for $C_{13}H_{22}O$ (194.31): C 80.35, H 11.41; found: C 80.38, H 11.29.

(−)-1-[(1S)-2-Pentylcyclopent-2-en-1-yl]propanone ((−)-(1′*S*)-**4**). As described for (+)-(1′*R*)-**4**, from (1*S*)-**3**. GC (permethyl-β-cyclodextrin; injector temp. 200°, isothermal 115°): t_R 26.22 ((+)-(1′*R*)-**4**), 28.00 ((−)-(1′*S*)-**4**). $[\alpha]_D^{28} = -32.2$ ($c = 1.07$, MeOH; 98.1% ee).

(+)-2-Methyl-2-{[(1R)-2-pentylcyclopent-2-en-1-yl]methyl}-1,3-dioxolane ((+)-(1′*R*)-**5**). A mixture of (+)-(1′*R*)-**4** (443.0 mg, 2.280 mmol), ethylene glycol (30 ml), and a cat. amount of TsOH in toluene (40 ml) was refluxed under a *Dean Stark* trap. After 4 h, the mixture was allowed to cool to r.t., and toluene was evaporated. The residue was extracted with AcOEt (3×100 ml), the extract washed with sat. aq. $NaHCO_3$ soln. (3×100 ml) and brine (2×100 ml), dried (Na_2SO_4), and evaporated, and the residue subjected to FC (silica gel, pentane/Et_2O 20:1): (+)-(1′*R*)-**5** (507 mg, 93%). Colorless oil. $[\alpha]_D^{26} = +25.3$ ($c = 1.15$, MeOH; 99.1% ee[4])). ^{1}H-NMR (H,H-COSY, H,C-COSY, DEPT; $CDCl_3$, 300 MHz): 0.89 (*t*, $J = 6.8$, Me(5″); 1.20–1.50 (*m*, 3 CH_2, 1 H of CH_2–C(2)); 1.36 (*s*, Me–C(2)); 1.63–1.76 (*m*, H_a–C(5′)); 1.88–2.30 (*m*, 2 CH_2, H_b–C(5′)); 1.96 (*dd*, $J = 14.1$, 2.1, 1 H of CH_2–C(2)); 2.60–2.62 (*m*, H–C(1′)); 3.89–3.97 (*m*, 2 CH_2O); 5.31–5.32 (*m*, H–C(3′)). ^{13}C-NMR (H,C-COSY, DEPT; $CDCl_3$, 75 MHz): 14.03 (*q*, Me(5″)); 22.54 (*t*, C(4″)); 24.28 (*q*, *Me*–C(2)); 27.29, 28.96, 30.85, 31.59, 31.81 (5*t*, CH_2); 41.84 (*t*, *C*H_2–C(2)); 42.55 (*d*, C(1′)); 64.29; 64.64 (2*t*, CH_2O); 110.43 (*s*, C(2)); 123.28 (*d*, C(3′)); 147.56 (*s*, C(2′)). HR-EI-MS: 238.1917 (M^+, $C_{15}H_{26}O_2^+$; calc. 238.1933). Anal. calc. for $C_{15}H_{26}O_2$ (238.37): C 75.58, H 10.99; found: C 75.53, H 11.12.

(−)-2-Methyl-2-{[(1S)-2-pentylcyclopent-2-en-1-yl]methyl}-1,3-dioxolane ((−)-(1′*S*)-**5**). As described for (+)-(1′*R*)-**5**, from (−)-(1′*S*)-**4**. $[\alpha]_D^{22} = -22.8$ ($c = 1.08$, MeOH, 98.7% ee[4])).

(+)-(1S,2R)-2-[(2-Methyl-1,3-dioxolan-2-yl)methyl]-1-pentyl-6-oxabicyclo[3.1.0]hexane ((+)-(1*S*,2*R*)-**6**). A cold (0°), stirred mixture of (+)-(1′*R*)-**5** (695.4 mg, 2.917 mmol), K_2CO_3 (1.21 g, 8.94 mmol), and CH_2Cl_2 (10 ml) was treated dropwise with a soln. of 60% MCPBA (1.49 g, 5.36 mmol) in CH_2Cl_2 (49 ml). Conversion was complete after 4 h GC/MS monitoring. Sat. aq. Na_2SO_3 soln. (70 ml) was then added, and the mixture was extracted with Et_2O (3×50 ml). The combined org. phase was washed with H_2O (1×100 ml) and sat. aq. $NaHCO_3$ soln. (1×100 ml), dried (Na_2SO_4), and evaporated, and the crude product purified by bulb-to-bulb distillation:

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[4]) This value was determined with (+)-(1′*R*)- or (−)-(1′*S*)-**4**, resp.

(+)-(1*S*,2*R*)-**6** (708.1 mg, 95%) with a *cis*/*trans* (=(1*S*,2*R*)/(1*R*,2*R*)) ratio of 88:12 (^{1}H-NMR). $[\alpha]_D^{23} = +10.7$ ($c = 1.09$, MeOH; 99.1% ee[4]). ^{1}H-NMR (H,H-COSY, H,C-COSY, DEPT; $CDCl_3$, 300 MHz): *cis*-**6**: 0.88 (*t*, $J = 6.3$, Me(5″)); 1.09–2.03 (*m*, 7 CH_2, H–C(2)); 1.33 (*s*, Me–C(2′)); 3.25 (*s*, H–C(5)); 3.88–3.99 (*m*, 2 CH_2O); *trans*-**6**: 0.88 (*t*, $J = 6.3$, Me(5″)); 1.09–2.32 (*m*, 7 CH_2, H–C(2)); 1.33 (*s*, Me–C(2′)); 3.22 (*s*, H–C(5)); 3.88–3.99 (*m*, 2 CH_2O). ^{13}C-NMR (H,C-COSY, DEPT; $CDCl_3$, 75 MHz): *cis*-**6**: 14.0 (*q*, Me(5″)); 22.5 (*t*, C(4″)); 24.2 (*q*, *Me*–C(2′)); 24.7, 27.1, 27.6, 29.2, 31.9, 38.5 (6*t*, CH_2); 36.5 (*d*, C(2)); 61.9 (*d*, C(5)); 64.3, 64.6 (CH_2O); 69.3 (C(1)); 110.0 (C(2′)). *trans*-**6**: 14.0 (*q*, Me(5″)); 22.5 (*t*, C(4″)); 24.3 (*q*, *Me*–C(2′)); 24.6, 24.9, 25.6, 28.9, 32.1, 38.3 (6*t*, CH_2); 35.8 (*d*, C(2)); 62.2 (*d*, C(5)); 64.3, 64.8 (CH_2O); 69.4 (C(1)); 110.17 (C(2′)). GC/MS (injector temp. 250° temp. program: 50° for 1 min, heating at a rate of 20°/min, 250° for 10 min): t_R 10.34 ((1′*R*)-**5**), 11.1 ((+)-(1*S*,2*R*)-**6**[5]). HR-EI-MS: 254.1855 (M^+, $C_{15}H_{26}O_3^+$; calc. 254.1882). Anal. calc. for $C_{15}H_{26}O_3$ (254.37): C 70.83, H 10.30; found: C 70.58, H 10.29.

*(−)-(1*R*,2*S*)-2-[(2-Methyl-1,3-dioxolan-2-yl)methyl]-1-pentyl-6-oxabicyclo[3.1.0]hexane* ((−)-(1*R*,2*S*)-**6**). As described for (+)-(1*S*,2*R*)-**6**, from (−)-(1′*S*)-**5**. $[\alpha]_D^{22} = -12.5$ ($c = 1.08$, MeOH; 98.7% ee[4]).

*(+)-(2*S*,3*R*)-3-(2-Oxopropyl)-2-pentylcyclopentanone* (=(2*S*,3*R*)-*Magnolione*®; (+)-(2*S*,3*R*)-**1**). Under Ar, $(Ph_3C)BF_4$ (28.0 mg, 0.09 mmol) was added to a cold (0°) soln. of (+)-(1*S*,2*R*)-**6** (391.3 mg, 1.538 mmol; containing (1*R*,2*R*)-**6**) in dry CH_2Cl_2 (50 ml). The resulting deep red soln. was stirred at 0° for 4 h (GC/MS: complete conversion). Sat. aq. $NaHCO_3$ soln. (60 ml) was then added. The mixture was stirred for 1 h at r.t., and extracted with Et_2O (3×100 ml). The combined org. layers were washed with brine (1×100 ml) and evaporated. A soln. of the residue in petroleum ether/Et_2O 7:3 was filtered through a pad of silica gel, and the filtrate was evaporated. The resultant pale yellow oil was dissolved in 50% aq. AcOH (10 ml) and the soln. stirred at r.t. for 2 h (TLC (petroleum ether/Et_2O 7:3; phosphomolybdic acid): complete conversion; R_f 0.15). The mixture was treated with sat. aq. K_2CO_3 soln. until pH 8–10 was reached and extracted with Et_2O (3×50 ml). The combined org. phase was dried (Na_2SO_4), and evaporated and the crude product subjected to FC (silica gel, pentane/Et_2O 7:3) and bulb-to-bulb distillation: (+)-(2*S*,3*R*)-**1**/(2*R*,3*R*)-**1** (140.4 mg, 43% over both steps) as a colorless oil with a *cis*/*trans* (=2*S*,3*R*)/(2*R*,3*R*)) ratio 78:22 (GC). The isomers were separated by prep. HPLC silica gel (5 μ; 21×250 mm), hexane/i-PrOH 95:5, flow 20 ml/min, det. at 254 nm; t_R 9 ((+)-(2*S*,3*R*)-**1**), 10 (2*R*,3*R*)-**1**) to afford (2*R*,3*R*)-*Magnolione*® ((2*R*,3*R*)-**1**; *trans*/*cis* 98:2 by GC/MS) and (2*S*,3*R*)-*Magnolione*® ((+)-(2*S*,3*R*)-**1**; *cis*/*trans* 91:9 by GC/MS).

Anal. HPLC (silica gel (*Eurosphere 80-5*, 5 μ, 5×250 mm), hexane/i-PrOH 95:5, flow 0.5 ml/min, det. at 280 nm): t_R 17.68 ((+)-(2*S*,3*R*)-**1**), 19.50 ((2*R*,3*R*)-**1**). GC (injector temp. 200°; temp. program: 160° for 15 min, heating at a rate of 10°/min, 180° for 10 min): t_R 15.5 ((2*R*,3*R*)-**1**), 16.7 ((+)-(2*S*,3*R*)-**1**). $[\alpha]_D^{25} = +43.9$ ($c = 1.14$, MeOH; 99.1% ee[4]); *cis*/*trans* 78:22[6]). ^{1}H-NMR (H,H-COSY, H,C-COSY, DEPT; $CDCl_3$, 500 MHz): *cis*-(2*S*,3*R*): 0.85–0.88 (*m*, Me(5″)); 1.11–1.41 (*m*, 3 CH_2, H_a–C(4)); 1.48–1.60 (*m*, H_b–C(4)); 1.68–1.75 (*m*, H_a–C(1″)); 1.96–2.04 (*m*, H_b–C(1″)); 2.08–2.38 (*m*, 1 CH_2, H_a–C(1′), H–C(2)); 2.16 (*s*, MeC=O); 2.42–2.49 (*m*, H_b–C(1′)); 2.81–2.87 (*m*, H–C(3)); *trans*-(2*R*,3*R*): 0.85–0.88 (*m*, Me(5″)); 1.21–1.41 (*m*, 3 CH_2, H_a–C(4)); 1.48–1.60 (*m*, 1 CH_2); 1.68–1.75 (*m*, H–C(2)); 2.08–2.38 (*m*, 1 CH_2, H_b–C(4), H–C(3)); 2.17 (*s*, MeC=O); 2.42–2.49 (*m*, H_a–C(1′)); 2.74 (*dd*, $J = 16.9, 4.0$, H_b–C(1′)). ^{13}C-NMR (H,C-COSY, DEPT; $CDCl_3$, 75 MHz): *cis*-(2*S*,3*R*): 14.0 (*q*, Me(5″)); 22.4 (*t*, C(4″)); 24.8, 25.7, 27.1 (3*t*, CH_2); 30.4, (*q*, MeC=O); 31.8 (*t*, CH_2); 34.36 (*d*, C(3)); 35.2 (*t*, C(5)); 42.7 (*t*, C(1′)); 52.4 (*d*, C(2)); 207.4 (C(2′)=O); 219.60, (C(1)=O); *trans*-(2*R*,3*R*): 14.00 (*q*, Me(5″)); 22.42 (*t*, C(4″)); 26.38, 27.37, 27.88 (3*t*, CH_2); 30.48 (*q*, MeC=O); 32.06 (*t*, CH_2); 36.91, (*d*, C(3)); 37.72 (*t*, C(5)); 48.40 (*t*, C(1′)); 54.16 (*d*, C(2)); 207.42 (C(2′)=O); 219.84 (C(1)=O). GC/MS (injector temp. 250°; temp. program: 50° for 1 min, heating at a rate of 20°/min, 250° for 10 min): t_R 10.06 ((2*R*,3*R*)-**1**), 10.14 ((+)-(2*S*,3*R*)-**1**). HR-EI-MS: 210.1624 (M^+, $C_{13}H_{22}O_2^+$; calc. 210.1620). Anal. calc. for $C_{13}H_{22}O_2$ (210.31): C 74.245, H 10.54; found: C 74.24, H 10.72.

*(−)-(2*R*,3*S*)-3-(2-Oxopropyl)-2-pentylcyclopentanone* (=(2*R*,3*S*)-*Magnolione*®; (−)-(2*R*,3*S*)-**1**). As described for (+)-(2*S*,3*R*)-**1**, from (−)-(1*R*,2*S*)-**6**. Prep. HPLC gave (2*S*,3*S*)-*Magnolione*® ((2*S*,3*S*)-**1**; *trans*/*cis* 98:2 by GC/MS) and (2*R*,3*S*)-*Magnolione*® ((−)-(2*R*,3*S*)-**1**; *cis*/*trans* by GC/MS). $[\alpha]_D^{23} = -37.0$ ($c = 0.96$, MeOH; 98.7% ee[4]); *cis*/*trans* (=(2*R*,3*S*)/(2*S*,3*S*)) 66:34[7]). $[\alpha]_D^{23} = -43.6$ ($c = 1.33$, $CHCl_3$; 98.7% ee; *cis*/*trans* 53:47[7]) ([7]: $[\alpha]_D^{20} = +22.0$, $CHCl_3$; 76% ee, (2*S*,3*S*)-**6** (*trans*)).

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[5]) The *cis*- and *trans*-isomer were not separated.

[6]) The *cis*/*trans*-isomer (=(2*S*,3*R*)/(2*R*,3*R*)) ratio was determined by GC analysis immediately before measurement of the optical rotation.

[7]) The *cis*/*trans*-isomer (=(2*R*,3*S*)/(2*S*,3*S*)) ratio was determined by GC analysis immediately before measurement of the optical activity.

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