Available online at www.sciencedirect.com
SCIENCE DIRECT®
C. R. Chimie 8 (2005) 867–874
COMPTES RENDUS CHIMIE
http://france.elsevier.com/direct/CRAS2C/

Full paper / Mémoire

Enantioselective synthesis of the fragrance *trans*-magnolione under asymmetric phase transfer catalysis

Stefano Superchi [a], Mariangela Nardiello [a], Maria Irene Donnoli [a], Patrizia Scafato [a], Rita Menicagli [b], Carlo Rosini [a,*]

[a] *Dipartimento di Chimica, Università della Basilicata, via N. Sauro 85, 85100 Potenza, Italy*
[b] *Dipartimento di Chimica e Chimica Industriale, Università di Pisa, via Risorgimento 35, 56126 Pisa, Italy*

Received 2 November 2004; accepted after revision 13 December 2004

Available online 17 March 2005

Abstract

The stereoselective synthesis of the fragrance *trans*-magnolione (**1**) through conjugate Michael addition of alkyl acetoacetates to 2-pentyl-2-cyclopentenone (**2**) under solid/liquid phase transfer catalysis (PTC) is reported. Under optimized conditions, the 1,4-addition of *tert*-butyl acetoacetate to enone **2** catalyzed by *N*-9-anthracenylmethylquininium chloride (**4**) affords, after hydrolysis and decarboxylation, *trans*-(*2S*,*3S*)-**1** with 85/15 d.r. and 74% ee. The use of the *pseudo*-enantiomeric catalyst *N*-9-anthracenymethylquinidinium chloride (**5**) allows obtaining the enantiomer *trans*-(*2R*,*3R*)-**1** with comparable enantio- and diastereoselectivity. ***To cite this article: S. Superchi et al., C. R. Chimie 8 (2005)***.

Résumé

Nous illustrons dans cet article la synthèse stéréosélective de la fragrance *trans*-magnolione (**1**), obtenue par addition conjuguée des alkyl acétoacétates à la 2-pentyl-2-cyclopentenone (**2**) dans des conditions de catalyse à transfert de phase solide/liquide (CTP). Dans les conditions optimales, la 1,4-addition de l'acétoacétate *tert*-butylique à l'énone **2**, catalysée par le chlorure de *N*-9-anthracénylméthylquininium (**4**), donne, après hydrolyse et décarboxylation, le *trans*-(*2S,3S*)-**1** avec 85/15 d.r. et 74 % e.e. L'usage du catalyseur *pseudo*-énantiomérique chlorure de *N*-9-anthracènylméthylquinidininium (**5**) permet d'obtenir l'énantiomère *trans*-(*2R,3R*)-**1** avec des énantiosélectivité et diastéréosélectivité comparables. ***Pour citer cet article : S. Superchi et al., C. R. Chimie 8 (2005)***.

Keywords: Fragrances; Phase transfer catalysis; Asymmetric catalysis; Michael addition; Magnolione

Mots clés : Fragrances ; Catalyse à transfert de phase ; Catalyse asymétrique ; Addition de Michael ; Magnolione

* Corresponding author.
E-mail address: rosini@unibas.it (C. Rosini).

1631-0748/$ - see front matter © 2005 Published by Elsevier SAS on behalf of Académie des sciences.
doi:10.1016/j.crci.2005.02.017

1. Introduction

Many floral, jasmine-like fragrances, very important for the perfume industry, possess a 2,3-disubstituted cyclopentanone backbone [1]. In the last few years several stereoselective syntheses of methyl dihydrojasmonate (Fig. 1), the most popular cyclopentanone fragrance, have been reported [2], allowing to evaluate the olfactory properties of its single stereoisomers. It was then observed that in jasmonates the olfactory active stereoisomers have (*R*) stereochemistry at C(3), with the *cis* stereoisomer being more active than the *trans* one [2c,3]. A structurally related cyclopentanone fragrance is magnolione (**1**), in which the substitution of the methyloxycarbonyl moiety of jasmonates with an acetyl group confers a greater odor strength, a better stability, and a more floral, intense jasminic note [1c]. Despite its industrial importance, until now **1** has been prepared and used in the perfume and cosmetic industry as a racemic mixture of *cis*/*trans* stereoisomers [4]. Therefore the correlation between its olfactory properties and stereostructure is not known. The knowledge of such correlation is very important since in many chiral fragrances, as seen in the jasmonates, the olfactory properties of the several stereoisomers differ significantly. We then faced the diastereo- and enantioselective synthesis of both enantiomers of *trans*-**1** with the scope to establish its structure/odor relationship. The use of phase transfer catalysis (PTC), recently applied to the enantioselective syntheses of related *trans*-dihydrojasmonates [2d], looked very appealing also for our purposes. The PTC approach requires, in fact, simple experimental procedures and very mild conditions, which make this process easy to scale-up and interesting for industrial preparation [5,6]. The synthesis of *trans*-**1** was then approached (Scheme 1) by Michael addition of ethyl acetoacetate to 2-pentyl-2-cyclopentenone (**2**) under PTC conditions in the presence of chiral ammonium salts, leading, after hydrolysis and decarboxylation of the addition product **3**, to *trans*-**1** with moderate to good diastereo- and enantioselectivity [7]. We decided then to extend our previous investigation using other acetoacetic esters, other enantiopure ammonium salts, and employing different experimental conditions. We report herein the results of this full study on the asymmetric PTC synthesis of cyclopentanone fragrance *trans*-**1** with the aim to improve the diastereo- and enantio-selectivity of the reaction.

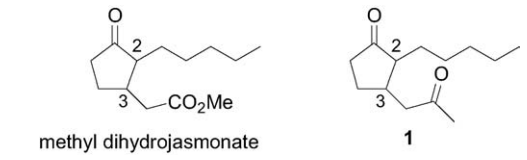
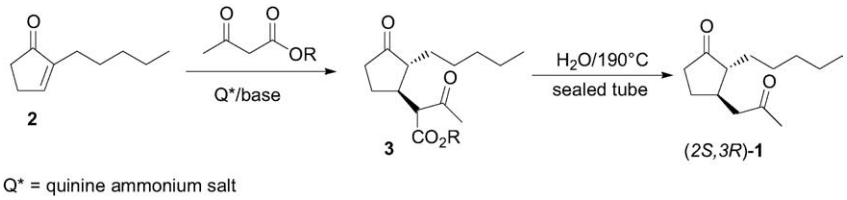


Fig. 1. Fragrances methyl dihydrojasmonate and magnolione (**1**).

2. Results and discussion

The conjugate addition of ethyl or *tert*-butyl acetoacetate to enone **2** under solid/liquid PTC conditions, in the presence of a catalytic amount of enantiopure quaternary ammonium salts, was then carried out. We tested several reaction conditions (solvent, base, acetoacetic ester) and the efficiency of different chiral ammonium salts (Fig. 2). We then decided to test *N*-9-anthracenylmethylquininium chloride (**4**) [8] and *N*-9-anthracenymethylquinidinium chloride (**5**) [8], i.e. the ammonium salts employed in the PTC synthesis of jasmonates [2d] and, for the first time in this reaction, the two 1,1′-binaphthylazepine salts (*S,S*)-**6** e (*S*)-**7**. Our group had in fact a large experience in the synthesis of 1,1′-binaphthylazepine chiral ligands and in their use in asymmetric catalysis [9], therefore the use of 1,1′-binaphthylazepine chiral salts, successfully employed in asymmetric synthesis of aminoacids by PTC alkylation [10], seemed very intriguing.



Scheme 1.

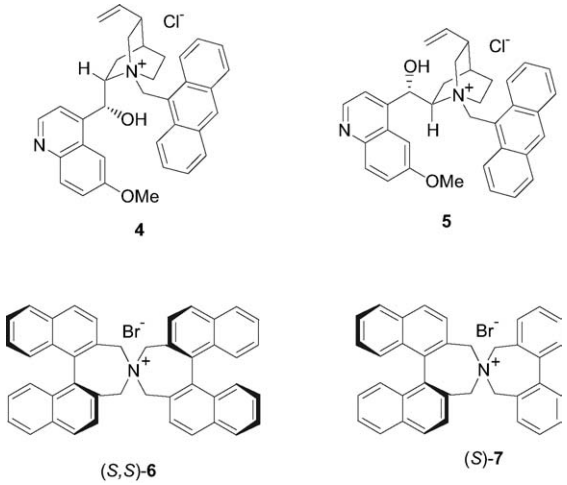


Fig. 2. *Cinchona*-derived ammonium salts **4**, and **5**. 1,1′-Binaphthylazepine ammonium salts (*S*,*S*)-**6** and (*S*)-**7**.

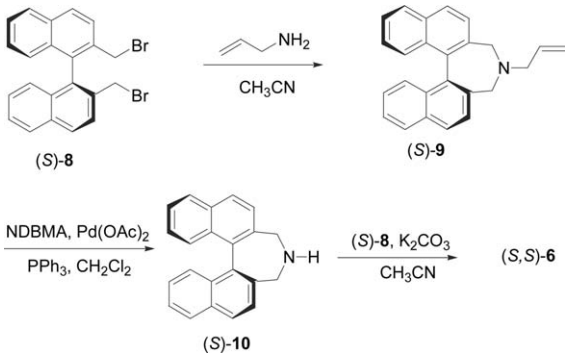
2.1. Synthesis of chiral ammonium salts

The salts **4** and **5** were obtained by simple alkylation of the parent *Cinchona* alkaloids, quinine and quinidine, with 9-chloromethylanthracene [2d]. The 1,1′-binaphthylazepine salt (*S,S*)-**6** was obtained following the procedure described by Maruoka et al. [11] starting from (*S*)-2,2′-bis(bromomethyl)-1,1′-binaphthalene (**8**) (Scheme 2) [12,9a]. The dibromide (*S*)-**8** was reacted with allylamine in acetonitrile at 50 °C for 5 h obtaining the *N*-allyl-1,1′-binaphthylazepine (*S*)-**9** in 92% yield. The amine (*S*)-**9** was deprotected by treatment with $Pd(OAc)_2$ (2 mol%) in the presence of *N*,*N*-dimethylbarbituric acid (NDMBA) (0.3 equiv) and triphenylphosphine (10 mol%), leading to the 1,1′-binaphthylazepine (*S*)-**10** in 54% yield. Finally, (*S*)-**10** was bis-alkylated by the dibromide (*S*)-**8** by refluxing in acetonitrile for 7 h in the presence of K_2CO_3, obtaining the ammonium salt (*S,S*)-**6** in 74% yield. The biphenyl-binaphthylazepine salt (*S*)-**7** was similarly prepared from 2,2′-bis(bromomethyl)-1,1′-biphenyl (**11**) (Scheme 3), in turn easily obtainable from commercially available 1,1′-diphenic acid. The dibromide **11** was converted into the hydroxylamine **12** by reaction with hydroxylamine hydrochloride at reflux in triethylamine for 2 h. The hydroxylamine **12** was then reduced in 96% yield to the corresponding biphenylamine **13** by treatment with zinc metal in the presence of a catalytic amount of indium (0.05 equiv) in a 1:1 mixture of $EtOH/NH_4Cl$ [13]. Finally, the ammonium salt (*S*)-**7** was obtained in 62% yield by reaction of biphenylamine **13** with the dibromide (*S*)-**8**.

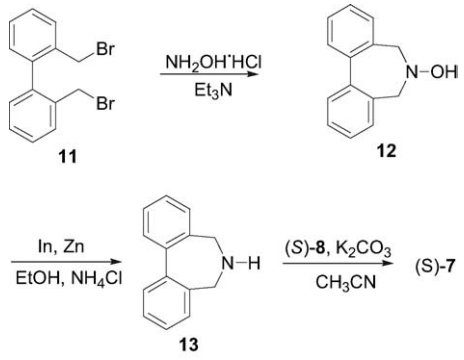
2.2. Asymmetric PTC Michael additions

The Michael addition of alkyl acetoacetates to enone **2** was performed at room temperature under nitrogen, in the presence of a base (K_2CO_3 or KOH) and a catalytic amount (10 mol%) of the chiral ammonium salt, affording the addition product **3**. The latter was then hydrolyzed and decarboxylated by heating in water at 190 °C in a sealed tube, leading to the target compound *trans*-**1**. In Table 1 the results of the addition reaction using the *Cinchona*-derived salts **4** and **5** are reported.

By reacting enone **2** without solvent with an excess of ethyl acetoacetate, in the presence of K_2CO_3 (20 mol%) and salt **4** (10 mol%), product **3** was obtained in 60% yield, leading after decarboxylation to (*2S*,*3S*)-**1**



Scheme 2.



Scheme 3.

Table 1
Conjugate addition of ethyl acetoacetate to enone **2** in the presence of *Cinchona*-ammonium salts [a]

Run	Acetoacetate (equiv)	Solvent	Base (equiv)	Time	Yield (%) [b]	ee (%) [c,d] (a.c.) [e]
1	30	–	K_2CO_3 (0.2)	7 d	60	68[f] (*2S,3S*)
2[g]	30	–	K_2CO_3 (0.2)	7 d	60	64[f] (*2R,3R*)
3[h]	30	–	K_2CO_3 (0.2)	7 d	0	–
4	3.0	Toluene	K_2CO_3 (1.0)	4 d	53	47[f] (*2S,3S*)
5	3.0	Toluene	KOH (3.0)	3 d	48	28 (*2S,3S*)
6[h]	3.0	Toluene	K_2CO_3 (1.0)	4 d	20	–
7	3.0	THF	K_2CO_3 (1.0)	6 d	58	17 (*2S,3S*)
8	3.0	THF	KOH (1.0)	3 d	64	29 (*2S,3S*)
9	3.0	CH_2Cl_2	K_2CO_3 (1.0)	6 d	50	25 (*2S,3S*)
10	3.0	CH_2Cl_2	KOH (1.0)	4 d	50	16 (*2S,3S*)
11	3.0	Et_2O	K_2CO_3 (1.0)	2 d	77	0
12	3.0	Et_2O	KOH (1.0)	2 d	49	27 (*2S,3S*)
13[i]	30	–	K_2CO_3 (0.2)	2 d	50	74[f] (*2S,3S*)
14[i]	3.0	Toluene	K_2CO_3 (1.0)	2 d	52	60[f] (*2S,3S*)

[a] Reactions performed at RT, in the presence of salt **4** (0.1 equiv).
[b] Isolated yield in addition product **3**.
[c] In all the runs a 85:15 *trans*/*cis* ration for **1** was determined by GC.
[d] Ee of *trans*-**1** determined by HPLC on Chiralcel OJ-H column.
[e] For assignment of absolute configuration, see [7].
[f] Ee of *trans*-**1** determined by GC on a Cydex-B column.
[g] Catalyst 5 (0.1 equiv) was employed.
[h] No catalyst added.
[i] *tert*-Butyl acetoacetate was used.

in 85:15 *trans*/*cis* diastereoselectivity and 68% ee [1]. In the same conditions the *pseudo*-enantiomeric [14] catalyst **5** allowed to obtain the opposite enantiomer *trans*-(*2R,3R*)-**1** with the same diastereoselectivity and slightly lower (64%) ee. Both reactions did not afford total conversion of the product and did not proceed further after 7 days. It has in fact to be taken into account that *Cinchona*-derived ammonium salts with a free hydroxyl function, like the present ones, can undergo rearrangements and decomposition when left for prolonged time in basic conditions [15]. Therefore, due to such decomposition, the amount of catalyst decreases progressively, then slowing down the reaction. Run 3 in fact reveals that, in these reaction conditions, the uncatalyzed process does not proceed at all. Chiral GC analysis of the reaction mixtures of **1** (Fig. 3) showed that in all the trials the same ee is obtained for both *trans* and *cis* stereoisomer and a 85:15 *trans*/*cis* ratio is constantly achieved, as obtained in the synthesis of racemic **1** via the acetoacetate addition to **2** in EtOH/EtONa [4,7]. We can then confidently consider the diastereomeric ratio simply due to the relative thermodynamic stability of the *trans* and *cis* isomer. It is in fact reasonable that the chiral salt just affects the facial addition of the acetoacetate anion to the prochiral C(3), but it does not exert any effect on the following enolate protonation which determines the absolute configuration at C(2). It must also be taken into account that in the analogous dihydrojasmonates the *cis*-isomer spontaneously isomerizes to the 90:10 *trans*/*cis* thermodynamic ratio outside the narrow 5–7 pH range [1,2c], therefore also compound **1** could be affected by such an equilibration. The conjugate addition of ethyl acetoacetate was slightly faster when performed in solution. In toluene and in the presence of catalyst **4** (run 4) **3** was recovered in 4 days, but lower (47%) ee of (2*S*,3*S*)-**1** was obtained. The use of KOH in toluene (run 5) did not modify the yield in **3**, but further lowered the ee to 28%. Interestingly, in toluene the reaction proceeds also without the catalyst (run 6) although with a very low conversion. Therefore it is reasonable that for prolonged reaction time, when catalyst decomposition can occur, the non enantioselective uncatalyzed reaction can compete, lowering the overall ee. As enantio-selectivity is

[1] See Ref. [7] for assignment of the relative and absolute stereochemistry of the major stereoisomer of **1** by NMR and CD spectroscopy, respectively.

Table 2
Conjugate addition of ethyl acetoacetate to enone **2** in the presence of 1,1′-binaphthylazepine ammonium salts [a]

Run	Catalyst	Acetoacetate (equiv)	Solvent	Base (equiv)	Time (days)	Yield (%) [b]	ee (%) [c,d] (a.c.) [e]
1	(*S*,*S*)-**6**	30	–	K_2CO_3 (0.2)	6	50	10 (*2R,3R*)
2	(*S*,*S*)-**6**	3.0	Toluene	K_2CO_3 (1.0)	6	47	9 (*2R,3R*)
3	(*S*)-**7**	30	–	K_2CO_3 (0.2)	6	60	12 (*2R,3R*)
4	(*S*)-**7**	3.0	Toluene	K_2CO_3 (1.0)	6	40	8[f] (*2R,3R*)

[a] Reactions performed at RT, in the presence of 10 mol% of catalyst.
[b] Isolated yield in addition product **3**.
[c] In all the runs a 85:15 *trans*/*cis* ration for **1** was determined by GC.
[d] Ee of *trans*-**1** determined by HPLC on Chiralcel OJ-H column.
[e] For assignment of absolute configuration see Ref. [7].
[f] Ee of *trans*-**1** determined by GC on a Cydex-B column.

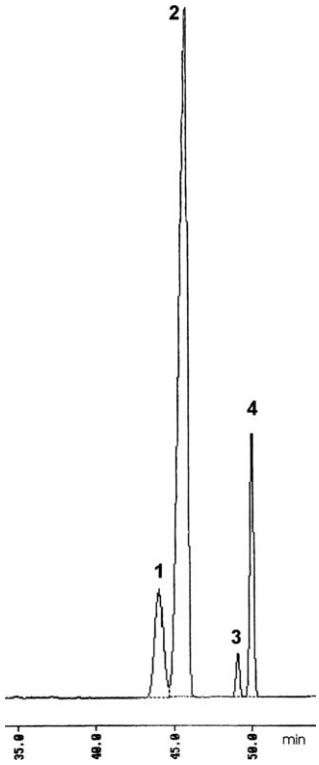


Fig. 3. GC chromatographic trace of mixture of **1** from Table 1, run 13 on Cydex-B chiral column. Peak 1 (*2R,3R*)-**1**, peak 2 (*2S,3S*)-**1**, peak 3 (*2S,3R*)-**1**, peak 4 (*2R,3S*)-**1**.

concerned, an inverse behavior in respect to toluene was observed in THF (runs 7 and 8), were KOH afforded a 29% ee, higher than K_2CO_3, although still modest. Both in CH_2Cl_2 and Et_2O (runs 9–12), with both K_2CO_3 and KOH, ee's lower than 30% were achieved. The reaction carried out in Et_2O and in the presence of K_2CO_3 (run 11) instead afforded higher yields, but a racemic product. In order to verify if an increase of the size of the alcoholic moiety of the acetoacetate could enhance the enantio-selectivity we tested *tert*-butyl acetoacetate in this reaction, using the best reaction conditions (K_2CO_3 either without solvent or in toluene) established. The use of the *tert*-butyl ester allowed a faster reaction in respect to the ethyl one and higher ee's. In fact, a 74% ee of (2*S*,3*S*)-**1** was obtained when the reaction was carried out without solvent (run 13) and a 60% ee was achieved in toluene (run 14) [2]. The higher enantio-selectivity obtained when *tert*-butyl acetoacetate was used can be ascribed either to its larger size, which ensure a better facial discrimination, or to the slightly higher lipophilicity of its anion, which accelerates the reaction. In fact, as showed before, when the reaction is too slow a decrease of ee could occur. The 1,1′-binaphthylazepine salts (*S*,*S*)-**6** and (*S*)-**7** were then tested, still using the optimized reaction conditions (Table 2). With both (*S*,*S*)-**6** and (*S*)-**7** the (*2R,3R*) of *trans*-**1** was obtained. Unfortunately, with both catalysts the addition reaction was rather slow and, most importantly, low enantio-selectivity (ee < 12%) was obtained both in toluene and in absence of solvent. Probably these salts are too lipophilic to act, in our reaction conditions, as efficient carrier of the very polar acetoacetate anion.

3. Conclusions

In this investigation a wide screening of the reaction condition for the stereoselective conjugate addition of

[2] It is noteworthy that in the addition product **3**, coming from reaction of *tert*-butyl acetoacetate, a better chromatographic separation of the *cis* and *trans* isomers is observed. Therefore, collecting different chromatographic fractions, enriched samples of both *trans*-**1** and *cis*-**1** were obtained.

acetoacetates to enone **2** under PTC conditions have been performed, establishing an optimized procedure which allowed to obtain *trans* isomer of the fragrance magnolione (**1**) in 85:15 *trans*/*cis* ratio and ee up to 74%. The use of salts **4** and **5**, derived from *pseudo*-enantiomeric alkaloids, allowed to obtain both enantiomers of *trans*-**1** with comparable enantio- and diastereoselectivity. Lower ee's were instead obtained using the less polar 1,1′-binaphthylazepine salts (*S*,*S*)-**6** and (*S*)-**7**. Even if the enantioselectivities obtained are still moderate this approach, carried out under mild conditions, appears very promising.

This investigation represents in fact an important step in order to undertake the study of the structure/odor relationship of such artificial fragrance, as well as to make available to the perfume industry other valuable ingredients.

4. Experimental section

4.1. General procedures

Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ either on a Varian Inova spectrometer or on a Bruker Aspect 300 spectrometer. Optical rotations were measured by a JASCO DIP-370 digital polarimeter. Enantiomeric excess of compound **1** was determined either or by HPLC on Chiralcel OJ-H c.s.p. (hexane/*i*-PrOH = 99:1 v/v; flow = 0.5 ml/min; λ = 280 nm) or by GC analysis on a Cydex-B c.s.p. 2-Pentyl-2-cyclopenten-1-one (**2**) and ethyl acetoacetate were distilled prior their use. KOH and K_2CO_3 were pulverized and dried under vacuum. THF, Et_2O, and toluene were freshly distilled prior the use on sodium benzophenone ketyl and stored under nitrogen atmosphere. CH_2Cl_2 and CH_3CN were freshly distilled on CaH_2 and stored under nitrogen atmosphere. Triethylamine was distilled over CaH_2 and stored under nitrogen on KOH. Enantiopure *N*-9-anthracenylmethyl quininium chloride (**4**) and *N*-9-anthracenylmethyl quinidinium chloride (**5**) were prepared according to literature procedures [2d,8]. Enantiopure (*S*)-2,2′-bis(bromomethyl)-1,1′-binaphthalene (*S*)-**8** was prepared as previously described [9a]. Chiral ammonium salt (*S*,*S*)-(–)-**6** was prepared as reported by Ooi et al. [11] starting from dibromide (*S*)-**8**. 2,2′-Bis(bromomethyl)-1,1′-biphenyl (**11**) was prepared by PBr_3 bromination of 2,2′-bis(hydroxymethyl)-1,1′-biphenyl, in turn obtained by $LiAlH_4$ reduction of commercially available diphenic acid. Analytical TLC were performed on 0.2 mm silica gel plates Merck 60 F-254 and column chromatographies were carried out with silica gel Merck 60 (70–230 mesh). GC analyses were carried out on GC/MS Hewlett Packard 5080 series II, detector HP 5971, column Supelco 57300-U (polydimethylsiloxane phase, PDMS). Chiral GC analyses were carried out on a Perkin Elmer Autosystem gas chromatograph (detector: FID; injector mode: split; carrier gas: He) equipped with an SGE Cydex-B capillary colum (25 m × 0.22 mm ID, 0.25 μm film).

4.2. 6,7-Dihydro-5H-dibenz[c,e]azepine-N-hydroxy (**12**)

A solution of dibromide (**11**) (6.0 g, 18.0 mmol), triethylamine (53 ml) and hydroxylamine hydrochloride (3.7 g, 54.0 mmol), was heated at reflux and stirred for 2 h under nitrogen atmosphere. The mixture was then filtered under vacuum and the resulting solution was distilled to remove the triethylamine. The crude product was purified by column chromatography on silica gel (from petroleum ether/diethyl ether 4:1 v/v, to petroleum ether/diethyl ether 2:1 v/v) gave product **12** (1.7 g, 50% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.15 (d, J = 12 Hz, 2H), 3.95 (d, J = 12 Hz, 2H), 7.5 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 60.44, 127.81, 129.51, 130.15, 133.92, 14.95.

4.3. 6,7-Dihydro-5H-dibenz[c,e]azepine (**13**)

The hydroxylamine **12** (1.7 g, 8.0 mmol) was dissolved into a 1:1 solution of EtOH and saturated aqueous NH_4Cl (40 ml; pH 6). Indium powder (5 mol%, 0.046 g, 0.4 mmol) and zinc powder (2 equiv, 1.04 g, 16.0 mmol) were added and the mixture was heated at reflux for 7 h. The mixture was cooled, filtered over Celite and concentrated. A solution of saturated aqueous Na_2CO_3 was then added and the mixture was extracted with ethyl acetate. The organic phase was dried over anhydrous Na_2SO_4 and concentrated to afford 1.5 g (95% yield) of **13** as a white solid.

M.p. = 229–231 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 4.04 (s, 5H), 7.48 (m, 2H), 7.57 (m, 4H), 7.64 (d, J = 7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 45.90, 128.61, 129.22, 129.54, 130.50, 131.27, 140.81.

4.4. Chiral ammonium salt (S)-(–)-7

A mixture of **13** (0.186 g, 0.95 mmol), dibromide (*S*)-**8** (0.467 g, 1.1 mmol), and K_2CO_3 (0.204 g, 1.5 mmol) in CH_3CN was heated at reflux, and stirred for 48 h. The resulting mixture was poured into water and extracted with CH_2Cl_2. The organic extracts were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (MeOH/CH_2Cl_2 1:9 v/v) to furnish 0.376 g (62% yield) of (*S*)-**7** as a white solid.

$[\alpha]_D^{21} = -94$ (*c* = 1.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 3.97 (d, *J* = 13 Hz, 2H), 4.06 (d, *J* = 13 Hz, 2H), 4.35 (d, *J* = 13 Hz, 2H), 4.80 (d, *J* = 13 Hz, 2H), 7.40 (t, *J* = 8 Hz, 2H), 7.46 (d, *J* = 9 Hz, 2H), 7.64 (t, *J* = 7 Hz, 4H), 7.76 (m, 4H), 7.89(d, *J* = 6 Hz, 2H), 8.08 (dd, *J* = 8, 9 Hz, 4H), 8.30 (d, *J* = 9 Hz, 2H); ^{13}C NMR (125 MHz) ($CDCl_3$) δ (ppm): 61.0, 62.0, 125.9, 126.7, 127.8, 127.9, 128.0, 128.1, 129.0, 129.8, 130.1, 131.2, 131.8, 132.3, 132.4, 134.8, 137.1, 141.3.

*4.5. 2-Pentyl-3-(1-carbethoxy-2-oxopropyl)-1-cyclopentanone (**3**)*

4.5.1. General procedure without solvent. To a solution of **2** (203 mg, 1.3 mmol) in the alkyl acetoacetate (39.0 mmol, 30 equiv), the catalyst (0.11 equiv), and potassium carbonate (54 mg, 0.392 mmol, 0.028 equiv) were added in sequence. After stirring at room temperature for some days (see Tables 1 and 2), the reaction mixture was diluted with diethyl ether (40 ml). The organic layer was washed in sequence with 10% aqueous HCl (2 × 10 ml), water (10 ml) and brine (2 × 10 ml). The organic layer was then dried over anhydrous Na_2SO_4, filtered and evaporated. The crude pale yellow oil was distilled under reduced pressure to remove the alkyl acetoacetate. Finally, chromatography on silica gel (petroleum ether/diethyl ether 70:30 v/v) of the crude residue yielded product **3** as a colorless oil. Product **3** was obtained, by addition of ethyl acetoacetate to **2**, as a mixture of four diastereoisomers. Here only the ^{1}H and ^{13}C NMR spectra of the two more abundant isomers have been accounted.

^{1}H NMR (600 MHz, $CDCl_3$): δ 0.87 (t, *J* = 7 Hz, 3H); 1.23 (m, 5H); 1.30 (t, *J* = 7 Hz, 3H); 1.40–1.45 (m, 2H); 1.57–1.70 (m, 2H); 1.96 (m, 1H); 2.16 (m, 2H); 2.27 (s, 3H); 2.33 (m, 1H); 2.65–2.73 (m, 1H); 3.47–3.57 (d, *J* = 7 Hz, 1H); 4.22 (q, *J* = 7 Hz, 2H). ^{13}C NMR (150.9 MHz, $CDCl_3$) *Isomer* **1** δ 13.97 (CH_3); 14.09 (CH_3); 22.41 (CH_2); 23.91 (CH_2); 26.04 (CH_2); 26.04 (CH_2); 28.43 (CH_2); 29.60 (CO*CH*$_3$); 31.93 (CH_2); 37.18 (CH_2); 39.80 (CH); 52.24 (CH); 61.50 (CO*CH*$_2$); 62.18 (CH); 168.55 (quat, COO); 201.88 (quat, CO); 219.14 (quat, CO). *Isomer* **2** δ 13.96 (CH_3); 14.03 (CH_3); 22.39 (CH_2); 24.95 (CH_2); 24.95 (CH_2); 25.89 (CH_2); 28.78 (CH_2); 29.56 (CO*CH*$_3$); 32.00 (CH_2); 37.03 (CH_2); 39.72 (CH); 52.51 (CH); 61.66 (CO*CH*$_2$); 63.84 (CH); 168.70 (quat, COO); 201.88 (quat, CO); 219.02 (quat, CO). MS (EI): *m*/*z* 282 (M^+, 1), 239 (1), 212 (1), 169 (62), 153 (79), 139 (67), 131 (100), 123 (19), 97 (25), 83 (43), 55 (27), 43 (72). Anal. Calc. for $C_{16}H_{26}O_4$: C, 68.06; H, 9.28. Found: C, 68.0; H, 9.1.

4.5.2. General procedure with solvent. A solution of enone **2** (1.0 equiv), catalyst (0.11 equiv), base (1.0 equiv) and alkyl acetoacetate (3.0 equiv) in a dry solvent (6.5 ml) was stirred at room temperature for several days (see Tables 1 and 2). The reaction mixture was diluted with diethyl ether and the organic layer was washed in sequence with 10% aqueous HCl (2 × 10 ml), water (10 ml) and brine (2 × 10 ml). The organic phase was dried over anhydrous Na_2SO_4, filtered and evaporated. The crude product, purified by chromatography on silica gel (petroleum ether/diethyl ether 70:30 v/v), afforded **3** as a colorless oil.

*4.6. 2-Pentyl-3-(2-oxopropyl)-1-cyclopentanone (Magnolione) (**1**)*

A mixture of **3** (1.5 mmol) in water (750 µl) was introduced in a 2 ml vial. The vial was sealed by flame and the mixture was heated at 190 °C for 12 h. The cooled mixture was extracted with diethyl ether (10 ml) and the organic phase was dried over anhydrous Na_2SO_4, then filtered and evaporated. The crude residue, purified on silica gel (petroleum ether/diethyl ether 60:40), afforded **1** as a light yellow oil. GC analysis showed an 85/15 *trans*-**1**:*cis*-**1** ratio. The use of catalyst **4** gave (2*S*,3*S*)-**1** as major enantiomer, the opposite was obtained when catalysts **5** (*S*,*S*)-**6** and (*S*)-**7** were used.

For *trans*-**1**: ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.88 (t, *J* = 7 Hz, 3H); 1.25 (m, 2H); 1.29 (m, 3H); 1.38 (m, 2H); 1.53 (m, 2H); 1.74 (m, *J* = 10 Hz, *J* = 6 Hz, *J* = 2 Hz, 1H); 2.13 (m, *J* = 9 Hz, *J* = 11 Hz, *J* = 19 Hz, 1H); 2.19 (s, 3H); 2.25 (m, 1H); 2.32 (m, 1H); 2.35 (m,

1H); 2.46 (dd, $J = 9$ Hz, $J = 17$ Hz, 1H); 2.75 (dd, $J = 4$ Hz, $J = 17$ Hz, 1H); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ 13.85 (CH_3); 22.30 (CH_2); 26.26 (CH_2); 27.24 (CH_2); 27.77 (CH_2); 30.45 (CO*C*H_3); 36.86 (CH); 37.72 (CH_2); 47.82 (CO*C*H_2); 54.12 (CH); 207.65 (quat, CO); 220.09 (quat, CO). MS (EI): *m*/*z* 210 (M^+, 4), 153 (52), 140 (21), 125 (12), 97 (18), 82 (100), 55 (18), 43 (49). Anal. Calc. for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.21; H, 10.23.

Acknowledgements

Financial support from MIUR-COFIN2002 'Synthesis of flavors and fragrances' and Università della Basilicata is gratefully acknowledged.

References

[1] (a) G. Ohloff, Scent and Fragrances, Springer, Berlin, 1994, p. 151; (b) G. Frater, J.A. Bajgrowicz, P. Kraft, Tetrahedron 54 (1998) 7633; (c) P. Kraft, J.A. Bajgrowicz, C. Denis, G. Frater, Angew. Chem. Int. Ed. Engl. 39 (2000) 2980.

[2] (a) C. Fehr, J. Galindo, O. Etter, E. Ohleyer, Chimia 53 (1999) 376; (b) C. Fehr, J. Galindo, O. Etter, E. Ohleyer, Angew. Chem. Int. Ed. Engl. 39 (2000) 569; (c) D.A. Dobbs, K.P.M. Vanhessche, E. Brazi, V. Rautenstrauch, J.-Y. Lenoir, J.-P. Genêt, J. Wiles, S.H. Bergens, Angew. Chem. Int. Ed. Engl. 39 (2000) 1992; (d) T. Perrard, J.-C. Plaquevent, J.-R. Desmurs, D. Hébrault, Org. Lett. 2 (2000) 2959.

[3] V. Rautenstrauch, J.-J. Riedhauser, (Firmenich SA), WO 9600206, 1996 [Chem. Abstr. 1996, 124, 232126c].

[4] C. Celli, (Givaudan Roure), DE2242463, Prior. September 1, 1971 [Chem. Abstr. 1973, 78, 147433; AN 1973: 147433].

[5] For general references about PTC see (a) E.V. Dehmlow, S.S. Dehmlow, Phase Transfer Catalysis, Verlag Chemie, Deerfield Beach, FL, 1983; (b) C.M. Starks, C. Liotta, Phase Transfer Catalysis, Academic Press, New York, 1978. For general reference on asymmetric PTC see: (c) M.J. O'Donnell, Aldrichim. Acta 34 (2001) 3; (d) M.J. O'Donnell, Asymmetric phase-transfer reaction, in: I. Ojima (Ed.), Catalytic Asymmetric Synthesis, 2nd ed., Wiley-VCH, New York, 2000, p. 727.

[6] For papers about asymmetric Michael additions in PTC see (a) A. Loupy, A. Zaparucha, Tetrahedron Lett. 34 (1993) 473; (b) D.Y. Kim, S.C. Huh, Tetrahedron 57 (2001) 8933; (c) D.Y. Kim, S.C. Huh, S.M. Kim, Tetrahedron Lett. 42 (2001) 6299; (d) F.-Y. Zhang, E.J. Corey, Org. Lett. 2 (2000) 1097.

[7] M.I. Donnoli, P. Scafato, M. Nardiello, D. Casarini, E. Giorgio, C. Rosini, Tetrahedron 60 (2004) 4975.

[8] B. Lygo, P.G. Wainwright, Tetrahedron Lett. 38 (1997) 8595.

[9] (a) T. Mecca, S. Superchi, E. Giorgio, C. Rosini, Tetrahedron Asymm. 12 (2001) 1225; (b) S. Superchi, T. Mecca, E. Giorgio, C. Rosini, Tetrahedron Asymm. 12 (2001) 1235; (c) S. Superchi, E. Giorgio, P. Scafato, C. Rosini, Tetrahedron Asymm. 13 (2002) 1385.

[10] K. Maruoka, T. Ooi, Chem. Rev. 103 (2003) 3013.

[11] T. Ooi, M. Kameda, K. Maruoka, J. Am. Chem. Soc. 125 (2003) 5139.

[12] (a) M. Gingras, F. Dubois, Tetrahedron Lett. 40 (1999) 1309; (b) D. Xiao, Z. Zhang, X. Zhang, Org. Lett. 1 (1999) 1679.

[13] S. Cicchi, M. Bonanni, F. Cardona, J. Revuelta, A. Goti, Org. Lett. 5 (2003) 1773.

[14] H. Wynberg, Top. Stereochem. 16 (1982) 86.

[15] D.L. Huges, U.-H. Dolling, K.M. Ryan, E.F. Schoenewaldt, E.J.J. Grabowski, J. Org. Chem. 52 (1987) 4745.