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Deoxycholic acid-based phosphites as chiral ligands in the enantioselective conjugate addition of dialkylzincs to cyclic enones: preparation of (–)-(*R*)-muscone

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Abstract—Four phosphites, obtained by linking enantiomerically pure binaphthylchlorophosphite to the two different hydroxy substituted positions of deoxycholic acid, were used as chiral ligands in the enantioselective copper catalysed 1,4-addition of diethylzinc to 2-cyclohexenone and dimethylzinc to 2-cyclopentadecenone. Various reaction parameters were changed in order to select the experimental conditions that would maximise yield and ee. The four ligands were screened for activity and enantioselectivity under the optimised reaction conditions for comparative purposes, in order to establish the influence of the absolute configuration of the binaphthyl moiety as well as the position on the cholestanic backbone of the phosphite moiety. The ligand possessing a (*R*)-binaphthylphosphite moiety at position 12 of the cholestanic backbone proved to be the most enantioselective affording (−)-(*R*)-muscone in 63% ee.

1. Introduction

The asymmetric copper catalysed 1,4-addition of organozinc reagents to conjugated enones is a useful synthetic transformation that involves a carbon–carbon bond formation together with the introduction of a new stereogenic centre at the β-position.[1] High levels of enantioselectivity have been reached using diphosphines,[2] diphosphites,[3] phosphoramidites,[4] phosphites[5] and aminophosphines[6] as copper ligands. More recently, attention has been paid to the development of tunable ligands,[7] which allow the effects of changes in conformational and stereochemical properties of the chiral catalyst on activity and enantioselectivity to be evaluated. Following this idea, we synthesised the four chiral phosphites **1** and **2** (Fig. 1), by linking

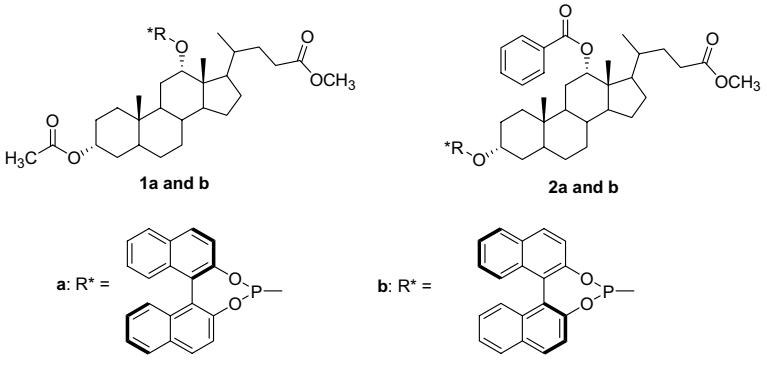

Figure 1. Structure of the phosphites.

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enantiomerically pure binaphthylchlorophosphite to the two different hydroxy groups of deoxycholic acid, which were used as copper ligands in the enantioselective conjugate addition of diethylzinc to acyclic enones.[8] The obtained results demonstrated that the copper complexes of ligands **1** and **2** show high activity in the conjugate addition of diethylzinc to acyclic enones, affording high isolated yields (up to 88%) of the alkylated products at −70 °C in 3 h.[8] The enantioselectivity of the reaction depended on the absolute configuration of the binaphthyl moiety as well as on its position on the cholestanic backbone; the best combination of these two parameters was found in ligand **1a**, which afforded the highest enantioselectivity levels (up to 78%).[8]

It is well known that the catalytic efficiency of phosphorus ligands depends strongly on the nature of the substrate.[1a,9] In fact, at present, only a few ligands afford copper catalysts showing uniformly good enantioselectivity against a wide range of substrates, such as acyclic and cyclic enones or differently sized cyclic enones: among these, there are the phosphoramidites from Feringa[4a] and the BINOL based phosphites from Pfaltz and co-workers.[5b,10] Therefore, we became interested in checking the possibility of extending the use of deoxycholic based phosphites **1** and **2** to the asymmetric conjugate addition of dialkylzincs to cyclic enones. Herein we report on the screening of the four chiral ligands in the conjugate addition of diethylzinc to cyclohexenone, as a model of cyclic enones,[1] as well as in the addition of dimethylzinc to 2-cyclopentadecenone, a model of macrocyclic enone, which affords (−)-muscone, a compound having high commercial value.[11,12]

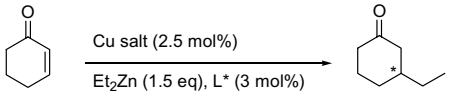
2. Results and discussion

2.1. Using ligands 1 and 2 in the copper catalysed conjugate addition of diethylzinc to cyclohexenone

The results obtained using chiral auxiliaries **1** and **2** in the copper catalysed conjugate addition of diethylzinc to cyclohexenone are listed in Table 1.

The catalytic system was generated in situ by stirring a solution containing the ligand and the copper salt for 1 h at room temperature. All the reactions were stopped when the conversion of the substrate was complete or did not proceed further, as judged by GC–MS analysis. To determine the enantiomeric excess of the alkylation product, 3-ethylcyclohexanone was reacted with (*R*,*R*)-1,2-diphenylethane-1,2-diol and the diastereomeric composition of the dioxolane derivative was obtained by HPLC. The influence of different reaction parameters, such as temperature, solvent and copper salt were evaluated using ligand **1a**. The catalytic species obtained starting from **1a** and $Cu(OTf)_2$ was very active affording complete substrate conversion in 15 min at room temperature (entry 1); the alkylation product was isolated in 96% yield and 25% ee. On lowering the temperature to 0 °C, no improvement in stereoselectivity was observed (entry 2). Better results were obtained by reacting cyclohexenone at −20 °C; the alkylation product was obtained in 89% yield and 50% ee (entry 3). No improvement was observed at lower temperatures. In fact at −40 °C, the same enantioselectivity was obtained, whereas at −70 °C both activity and enantioselectivity dropped with the alkylation product obtained after

Table 1. Catalytic enantioselective conjugate addition of diethylzinc to 2-cyclohexen-1-one



Entry	L*	Solvent	Cu salt	T (°C)	Time (h)	Conv.[a] (%)	Yield[b] (%)	Ee[c,d] (%)
1	**1a**	Toluene	$Cu(OTf)_2$	rt	15 min[e]	100	96	25 (*R*)
2	**1a**	Toluene	$Cu(OTf)_2$	0	30 min	96	62	24 (*R*)
3	**1a**	Toluene	$Cu(OTf)_2$	−20	30 min[e]	100	89	50 (*R*)
4	**1a**	Toluene	$Cu(OTf)_2$	−40	1[e]	100	61	50 (*R*)
5	**1a**	Toluene	$Cu(OTf)_2$	−70	17	83	73	20 (*R*)
6	**1a**	Et_2O	$Cu(OTf)_2$	−20	1	90	89	30 (*R*)
7	**1a**	THF	$Cu(OTf)_2$	−20	3[e]	100	75	6 (*R*)
8	**1a**	CH_2Cl_2	$Cu(OTf)_2$	−20	1[e]	100	88	3 (*R*)
9	**1a**	Toluene	$Cu(OAc)_2 \cdot H_2O$	−20	1[e]	100	75	20 (*R*)
10	**1a**	Toluene	$CuBr \cdot SMe_2$	−20	6	50	82	2 (*S*)
11	**1a**[f]	Toluene	$Cu(OTf)_2$	−20	1.5	88	74	35 (*R*)
12	**1a**	Toluene[g]	$Cu(OTf)_2$	−20	1	85	85	41 (*R*)
13	**1b**	Toluene	$Cu(OTf)_2$	−20	1[e]	100	80	12 (*S*)
14	**2a**	Toluene	$Cu(OTf)_2$	−20	1[e]	100	71	5 (*R*)
15	**2b**	Toluene	$Cu(OTf)_2$	−20	1[e]	100	91	20 (*S*)

[a] Determined by GC/MS.
[b] Isolated product.
[c] Determined by HPLC analyses after derivatisation with (*R*,*R*)-1,2-diphenylethane-1,2-diol: Daicel Chiralcel OD, hexane/2-propanol 99.7:0.3, 0.5 mL/min, $\lambda = 254$ nm.
[d] Absolute configuration assigned by the sign of the specific rotation.
[e] Optimised time.
[f] L* (6.0 mol%) were used.
[g] Double the amount of solvent was used.

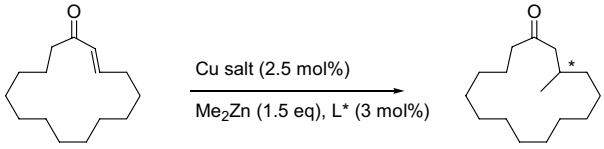
17 h in only 20% ee (entry 5). Toluene proved to be the best reaction solvent. When Et_2O was used, complete substrate conversion was reached in 1 h and 3-ethylcyclohexanone obtained in 30% ee (entry 6). THF and dichloromethane gave even worse results, mainly as far as enantioselectivity was concerned (entries 7 and 8). The copper salt had a remarkable influence on the outcome of the reaction. The alkylation product was obtained in lower ee by replacing $Cu(OTf)_2$ with a different Cu^{II} salt (entry 9), whereas the use of Cu^{I} was detrimental both for activity and enantioselectivity (entry 10). Increasing the ligand to copper salt ratio had a negative influence on the outcome of the reaction, affording the alkylation product in lower yield and lower ee (entry 11). Dilution of the reaction mixture did not improve the yield, but only lowered the enantioselectivity (entry 12), indicating that the concentration used in the previous runs is the most favourable. Once the optimal reaction conditions were found, that is, ligand to copper ratio 1:1.2, toluene as solvent, $Cu(OTf)_2$ as the copper salt and a temperature of −20 °C, the other chiral auxiliaries were tested under these experimental conditions, for comparative purposes. All the ligands showed comparable activity, affording complete conversion of the substrate after 1 h and high yield of the alkylation product. Changing the absolute configuration of the binaphthyl moiety, as well as the substitution position on the cholestanic backbone, strongly affected the enantioselectivity. Ligand **1b**, possessing a (*S*)-binaphthylphosphite moiety linked at position 12 of the cholestanic skeleton afforded the alkylation product in 12% ee (entry 13). Therefore, as previously observed in the alkylation of chalcone,[8] when the binaphthylphosphite moiety is linked at position 12 of the cholestanic backbone, the matched couple is that possessing the (*R*)-binaphthyl system. When the binaphthylphosphite moiety is linked to position 3 of the cholestanic backbone, less enantioselective ligands are obtained. In fact both diastereoisomers **2a** and **2b** afforded lower ees of the alkylation product (entries 14 and 15). These results are similar to those obtained in the alkylation of chalcone[8] and can be explained by considering that the presence of the binaphthylphosphite moiety on the more stereochemically demanding position 12 results in the achievement of a more enantioselective ligand. When the binaphthylphosphite moiety is linked at position 3, the matched stereochemical relationship is obtained with a (*S*)-binaphthyl system. In fact, the use of ligand **2b**, possessing a (*S*)-configured binaphthyl unit, afforded the alkylation product in 20% ee (entry 15), whereas only 5% ee was obtained with diastereoisomer **2a** (entry 14). These results are contrary to those obtained in the alkylation of chalcone, where the matched couple was always the one possessing the (*R*)-configured binaphthyl moiety.[8] As already observed, using chalcone as the substrate,[8] the deoxycholic moiety does not exert its influence on the sense of the asymmetric induction: a (*R*)-configured product was always obtained using ligands possessing a (*R*)-binaphthyl moiety.

2.2. Using ligands 1 and 2 in the copper catalysed conjugate addition of dimethylzinc to cyclopentadecenone

Table 2 reports on the results obtained in the copper catalysed addition of dimethylzinc to cyclopentadecenone using **1** and **2** as ligands.

The reaction performed at room temperature using **1a** as the ligand with $Cu(OTf)_2$, in toluene as the solvent, afforded complete conversion of the substrate in 15 min (entry 1); the alkylation product was obtained in 59% yield and 34% ee. The yield is lower than that observed in the alkylation of cyclohexenone (59 vs 96) because of the formation of a by-product, generated by the attack

Table 2. Catalytic enantioselective conjugate addition of dimethylzinc to *E*-cyclopentadec-2-enone



Entry	L*	Cu salt	T (°C)	Time (h)	Conv.[a] (%)	Yield[b] (%)	Ee[c] (%)
1	**1a**	$Cu(OTf)_2$	25	15 min[d]	100	59	34 (*R*)
2	**1a**	$Cu(OTf)_2$	0	1[d]	100	30	41 (*R*)
3	**1a**	$Cu(OTf)_2$	−10	1[d]	100	66	29 (*R*)
4	**1a**	$Cu(OTf)_2$	−40	7	60	33	32 (*R*)
5	**1a**	$Cu(OAc)_2{\cdot}H_2O$	0	7	65	41	63 (*R*)
6	**1b**	$Cu(OAc)_2{\cdot}H_2O$	0	7	68	16	19 (*S*)
7	**1b**	$Cu(OTf)_2$	0	15 min[d]	100	47	41 (*S*)
8	**2a**	$Cu(OAc)_2{\cdot}H_2O$	0	7	58	34	53 (*R*)
9	**2b**	$Cu(OAc)_2{\cdot}H_2O$	0	7	65	39	52 (*S*)
10	**2a**	$Cu(OTf)_2$	0	1[d]	100	47	41 (*R*)
11	**2b**	$Cu(OTf)_2$	0	1.5[d]	100	50	37 (*S*)

[a] Determined by GC/MS.
[b] Isolated product.
[c] Determined by specific rotation; for (*R*)-(−)-muscone $[\alpha]_D = -12.7$ (*c* 0.9, MeOH).[12]
[d] Optimised time.

of the in situ formed enolate on another molecule of unreacted substrate.[8,13] Lowering the temperature to 0 °C causes an improvement in enantioselectivity (entry 2), flanked by a lower yield of the alkylation product, due to the formation of a greater amount of the dimeric by-product. This most likely happens because when the alkylation reaction is slower the formation of the dimeric product becomes competitive.[8] On lowering the reaction temperature until −10 °C, a lower ee was obtained (entry 3). By contrast, the yield of the alkylated product is higher, suggesting that, at this temperature, the formation of the dimeric product is slower with respect to the alkylation reaction. By lowering the temperature until −40 °C, we obtained worse results. Complete conversion of the substrate was not reached in 7 h and, in addition, no improvement in either yield or enantio- selectivity was observed (entry 3). Better results were obtained by changing the copper salt. The use of $Cu(OAc)_2{\cdot}H_2O$ at 0 °C afforded in 7 h only 65% substrate conversion (entry 5), but a higher yield of the alkylation product and greater enantioselectivity (ee 63%) were obtained. This result suggests that using this copper salt not only gives the (−)-muscone in higher ee but also the formation of the dimeric product is slowed to a greater extent with respect to the alkylation reaction. The best reaction conditions for obtaining both the highest yield and enantioselectivity (i.e., $Cu(OAc)_2{\cdot}H_2O$ as the copper salt at 0 °C in toluene as the solvent) were used to check the activity and enantioselectivity of the catalyst obtained from **1b**. Both yield and ee were remarkably lower (entry 6), suggesting that changing the absolute configuration of the binaphthyl moiety gives rise to a less efficient chiral ligand. However, the use of $Cu(OTf)_2$ as the copper salt, under the reaction conditions that had afforded the best ee using **1a** as ligand (entry 2), provided significantly better results (entry 7), both in terms of yield and ee. In addition, under these reaction conditions, **1b** gave a more active catalyst than that obtained using **1a**. In fact, complete conversion of the substrate was achieved in only 15 min along with a higher yield (47 vs 30) of the alkylation product. The two chiral ligands afford the same enantioselectivity but an opposite sense of asymmetric induction, giving the same ee of products having opposite absolute configurations. Taking into account this result, chiral ligands **2a** and **2b** were checked not only under the best conditions found for the use of ligand **1a**, but also under those that afforded the best results with ligand **1b**. By using $Cu(OAc)_2{\cdot}H_2O$ as copper salt, both **2a** and **2b** afforded in 7 h similar substrate conversions and yields with respect to **1a** (entries 8 and 9). The ee obtained using the two diastereomeric ligands are almost identical (52 vs 53) but lower with respect to that obtained using **1a**. The use of $Cu(OTf)_2$ as the copper salt, afforded analogous results to those observed in the case of **1a**. The activity of the chiral catalysts is better, providing complete conversion of the substrate and higher yields of alkylation product in shorter reaction times. In contrast, the enantioselectivity was inferior, even if very similar values of ee were obtained for the diastereoisomeric ligands. As observed with ligands **1a** and **1b**, the two diastereoisomers **2a** and **2b** also showed an opposite sense of asymmetric induction, affording enantiomeric alkylation products. The results obtained in the asymmetric conjugate addition of $Zn(CH_3)_2$ to cyclopentadecenone show the different behaviour of the deoxycholic based chiral phosphites **1** and **2**, with respect to that observed in the conjugate addition of diethylzinc not only to acyclic enones[8] but also to cyclohexenone. The best copper salt for obtaining the most enantioselective catalysts was $Cu(OAc)_2{\cdot}H_2O$ in three cases, instead of $Cu(OTf)_2$ as usually observed. Activity and enantioselectivity of the chiral catalysts did not proceed in step. The more active catalysts were obtained using $Cu(OTf)_2$ as the copper salt, whereas the use of $Cu(OAc)_2{\cdot}H_2O$ guaranteed the formation of a more enantioselective catalytic species. The entity of the asymmetric induction still seemed affected by the cholestanic backbone, but not by the stereochemistry of the binaphthyl moiety. In fact the introduction of the binaphthylphosphite unit at position 12 of the cholestanic backbone still afforded more efficient ligands. In contrast by changing the absolute configuration of the binaphthyl moiety we obtained ligands affording comparable ee values. However, the binaphthyl moiety still determines the sense of the asymmetric induction: ligands possessing the (*R*)-binaphthyl unit afford the (−)-(*R*)-muscone, whereas the (+)-(*S*)-muscone is obtained using ligands having the (*S*)-binaphthyl fragment.

3. Conclusion

The results obtained using the four deoxycholic acid based phosphites **1a** and **1b** and **2a** and **2b** as copper ligands in the enantioselective conjugate addition of diethylzinc to 2-cyclohexenone and dimethylzinc to 2-cyclopentadecenone allowed us to reach the following conclusions. Although these ligands give more enantioselective catalysts for the conjugate addition of diethylzinc to acyclic enones,[8] the accurate screening of various reaction parameters, aimed at maximising the yields and ees, allowed us to obtain acceptable levels of asymmetric induction also in the 1,4-addition of dialkylzinc to cyclic substrates and to obtain (−)-(*R*)-muscone in 63% ee. The phosphite structure affects differently the activity and enantioselectivity of the catalyst depending on the nature of the substrate. As far as the substitution pattern on the deoxycholic moiety is concerned, catalysts obtained from the ligand possessing the binaphthylphosphite unit on the 12 position of the cholestanic backbone are still the most enantioselective. The sense of the asymmetric induction is still governed by the absolute configuration of the binaphthylphosphite moiety. Conversely, the best enantioselectivities were not always obtained with ligands possessing a (*R*)-binaphthyl moiety, as found previously. When the binaphthylphosphite unit was linked at position 3 of the cholestanic backbone, the highest ee in the conjugate addition of diethylzinc to 2-cyclohexenone was obtained using ligand **2b**, which possesses a (*S*)-configured binaphthyl system. On the contrary, the diastereoisomeric couples show the same enantioselectivity in the conjugate addition of dimethylzinc to 2-cyclopentadecenone, suggesting that the different stereochemical relationship between binaphthylphosphite and cholestanic

backbone does not affect the extent of the asymmetric induction.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker Aspect 300 300 MHz NMR spectrometer, using TMS as the external standard. TLC analysis were performed on silica gel 60 Macherey–Nagel sheets; flash chromatography separations were carried out on adequate dimension columns using silica gel 60 (70–230 or 230–400 mesh). HPLC analyses were performed on a JASCO PU-1580 intelligent HPLC pump equipped with a Varian 2550 UV detector. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. Gas chromatographic analyses were carried out on GC/MS Hewlett–Packard 6890, mass selective detector HP 5973, capillary column HP-5MS (5% phenyl methyl siloxane). Unless otherwise indicated, all experiments were carried out under a dry N_2 atmosphere. Toluene, diethyl ether and THF were dried over sodium/benzophenone and distilled before use. Dichloromethane was dried and distilled over CaH_2 before use. Commercially available 2-cyclohexenone was distilled before use. Cyclopentadec-2-en-1-one was synthesised from commercially available cyclopentadecanone.[14] Ligands **1** and **2** were synthesised according to previously reported methods.[8]

4.2. Enantioselective conjugate addition of diethylzinc to 2-cyclohexen-1-one: general procedure

A solution of $Cu(OTf)_2$ (9.0 mg, 0.025 mmol) and phosphite (0.03 mmol) in toluene (or other solvent) (6 mL) was stirred at room temperature for 1 h. The solution was cooled to a suitable temperature and 2-cyclohexenone (97 μL, 1.0 mmol) added. After a few minutes, diethylzinc (1.0 M in hexane, 1.5 mmol) was slowly added and the reaction monitored by GC–MS analyses. After complete conversion, the reaction mixture was poured into 25 mL of 1 M HCl and extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and filtered. Removal of diethyl ether under reduced pressure (500–350 mbar) at room temperature yielded the crude product in toluene, which was purified by column chromatography (SiO_2, pentane/diethyl ether 5/1) to afford 3-ethylcyclohexanone as a colourless liquid. The ee was determined by HPLC analyses after derivatisation with (*R*,*R*)-1,2-diphenylethan-1,2 diol. 3-Ethylcyclohexanone (63 mg, 0.5 mmol) was then dissolved in 12 mL of dichloromethane and 4 Å molecular sieves added, followed by (*R*,*R*)-1,2-diphenylethan-1,2-diol (126 mg, 0.6 mmol) and traces of *p*-toluenesulfonic acid. The mixture was stirred at room temperature and the reaction monitored by GC–MS analyses. After complete conversion (2 h), molecular sieves were removed by filtration and the crude dioxolane purified by column chromatography (SiO_2, light petroleum/diethyl ether 98/2). ^{1}H NMR (300 MHz, $CDCl_3$, δ) (*R*,*R*,*R*): 0.99 (t, 3H, J = 4.5 Hz), 1.32–1.48 (m, 4H), 1.65–1.89 (m, 5H), 2.09 (d, 1H, J = 14.5 Hz), 2.18 (d, 1H, J = 14.5 Hz), 4.76 (d, 1H, J = 9.0 Hz), 4.84 (d, 1H, J = 9.0 Hz), 7.26 (m, 4H), 7.34 (m, 6H); (*R*,*R*,*S*): 0.96 (t, 3H, J = 4.5 Hz), 1.32–1.48 (m, 4H), 1.65–1.89 (m, 5H), 2.12 (d, 1H, J = 15.5 Hz), 2.15 (d, 1H, J = 15.5 Hz), 4.78 (s, 2H), 7.26 (m, 4H), 7.34 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 11.69, 23.20, 23.60, 29.96, 31.74, 36.35, 37.06, 43.54, 85.64, 110.73, 127.03, 128.47, 128.69, 137.36; MS(EI): *m*/*z* 322 (M^+, 2), 293 (5), 279 (6), 216 (100), 180 (36), 167 (22), 105 (12), 91 (47), 55 (14); HPLC analyses: Chiralcel OD, hexane/2-propanol 99.7/0.3, 0.5 mL/min, 254 nm, t = 8.0 (*R*,*R*,*R*), t = 10.0 (*R*,*R*,*S*).

4.3. Enantioselective conjugate addition of dimethylzinc to 2-cyclopentadecenone: general procedure

A solution of $Cu(OTf)_2$ (4.5 mg, 0.013 mmol) and chiral ligand (0.015 mmol) in solvent (6 mL) was stirred at room temperature for 1 h. The solution was cooled to the suitable temperature and 2-cyclopentadecenone (111 mg, 0.5 mmol) added followed by dimethylzinc (2.0 M in toluene, 1.5 equiv). The reaction was monitored by GC–MS analyses. 10 mL of 1 M HCl and 5 mL of diethyl ether were added to the reaction mixture, which was stirred for a few minutes and then extracted with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, light petroleum/diethyl ether 95/5), affording muscone as colourless oil.

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14. (a) To prepare (*E*)-cyclopentadec-2-en1-one, the procedure of Tanaka, K.; Ushio, H.; Kawabata, Y.; Suzuki, H. *J. Chem. Soc., Perkin Trans.1* **1991**, 1445, was followed, except for the oxidation of the 2-phenylthiocyclopentadecanone intermediate. In this case, using the method of H_2O_2/CF_3COCH_3, as described by: (b) Lupattelli, P.; Ruzziconi, R.; Scafato, P.; Degl'Innocenti, A.; Paolobelli, A. *Synth. Commun.* **1997**, *27*, 441, no sulfone was formed with the desired sulfoxide obtained in higher yield.