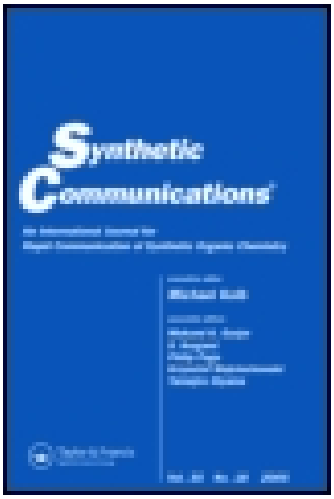


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

New Derivatives of 4,4-Diphenyl-2-cyclohexen-one

Jean-Luc Malleron [a], Eric Bacqué [a], Pascal Desmazeau [a], Claudine M'Houmadi [a], Jean-Marc Paris [a] & Jean-François Peyronel [a]

[a] Centre de Recherche de Vitry-Alfortville RhôTne-Poulenc-Rorer, S.A. 13 Quai Jules Guesde BP 14, 94403, Vitry sur Seine, Cedex, France

Published online: 04 Jan 2007.

To cite this article: Jean-Luc Malleron, Eric Bacqué, Pascal Desmazeau, Claudine M'Houmadi, Jean-Marc Paris & Jean-François Peyronel (1995) New Derivatives of 4,4-Diphenyl-2-cyclohexen-one, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 25:16, 2355-2371, DOI: 10.1080/00397919508015439

To link to this article: http://dx.doi.org/10.1080/00397919508015439

SYNTHETIC COMMUNICATIONS, 25(16), 2355-2371 (1995)

NEW DERIVATIVES OF 4,4-DIPHENYL-2-CYCLOHEXEN-ONE

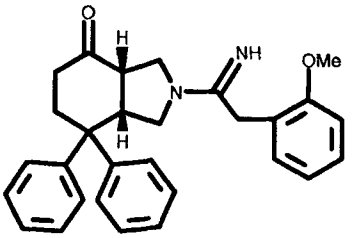
Jean-Luc Malleron*, Eric Bacqué*, Pascal Desmazeau,
Claudine M'Houmadi, Jean-Marc Paris, Jean-François Peyronel

Centre de Recherche de Vitry-Alfortville
Rhône-Poulenc-Rorer S.A.
13 Quai Jules Guesde BP 14
94403 Vitry sur Seine Cedex France

Abstract : The syntheses of some new derivatives of 4,4-diphenyl-2-cyclohexen-one are reported. In particular, we described a palladium-based strategy for the preparation of dienes (1) and (2).

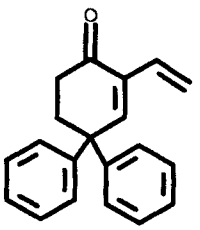
Some years ago, we initiated a program aimed at discovering non-peptidic antagonists of Substance P (SP), an ubiquitous undecapeptide involved in pain transmission[1]. We rapidly identified potential candidates among the diphenyl perhydroisoindolones family and, as a first result of this work, RP 67580 was recognized as a potent antagonist of SP[2].

RP 67580

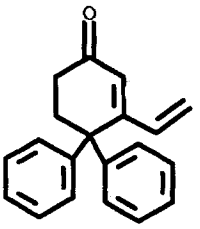


As a continuation of our investigation of the structure-activity relationships in this family, we were interested in substituting the pyrrolidine ring for other rings. In line with this goal, dienes (1) and (2) appeared particularly attractive as possible substrates for Diels-Alder reactions. We report herein the synthesis of these

compounds and some of their derivatives as well as preliminary results concerning their behaviour in cycloadditions.



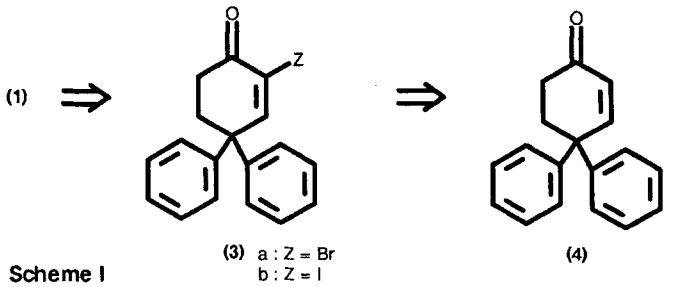
(1)



(2)

Results and discussion

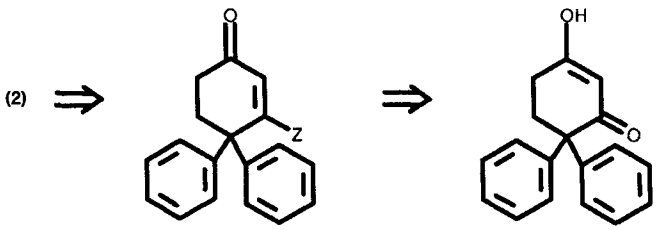
Retrosynthetically, we selected for the synthesis of both dienes an obvious strategy which relied upon palladium-catalysed coupling reactions between a vinyl-stannane and a suitably functionalized diphenyl cyclohexenone such as (3) or (5)[3,4].



(3) a : Z = Br
b : Z = I

(4)

Scheme I



(5) Z = OTf

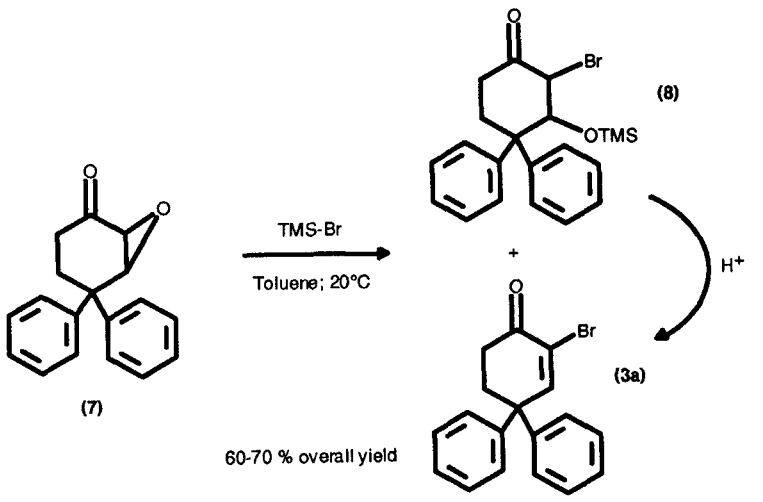
(6)

These precursors in turn, clearly stemmed from respectively 4,4-diphenyl cyclohexenone (4)[5] and 4,4-diphenyl cyclohexane 1,3-dione (6)[6,7] (*see Scheme I*).

Both compounds are especially convenient starting material owing to their chemical versatility and their synthetic availability. An alternative strategy for the synthesis of (2) could have consisted in 1,4-addition of a vinyl equivalent to enone (4) followed by the regeneration of the endocyclic double bond. However, unpublished results from our laboratories had previously demonstrated that enone (4) was particularly reluctant to undergo a wide range of Michael additions. These results had been ascribed to the steric hindrance generated by the gem-diphenyl group. At the onset of this work, we therefore decided to discard this approach and to examine whether palladium chemistry could overcome this steric effect.

With this question in mind, we first examined the preparation of (3a). This known compound had been synthesized in modest yields (*9-38%*), as a mixture with the corresponding 6-bromo enone[8], by a bromination-dehydrobromination sequence starting from (4). We considered this result as unsatisfactory and decided to look for an alternative synthesis, using keto-epoxide (7)[9] as a possible precursor of (3a). Compound (7) was initially shown to be inert to hydrogen bromide in acetic acid at 80°C. However, we were delighted to find that a slight excess of trimethylsilyl bromide (TMS-Br), a known reagent for the opening of alkyl-substituted epoxides[10,11], did react with (7), at room temperature, in toluene, to afford a mixture of two compounds of close polarity, according to TLC analysis. Upon addition of hydrochloric ether, the more polar, minor component of the initial mixture disappeared to leave only the other product. After purification, the later was shown by spectroscopic analysis to be the expected bromo-enone (3a). Overall yields for this sequence consistently ranged between 60 and 70 %. Our observations were easily taken into account by the hypothesis that, following the opening of the epoxide by trimethylsilyl bromide, the resulting bromo-silyloxy derivative (8) was partially converted into (3a) under the initial reaction conditions. Further addition of acid brought about the complete elimination of "TMS-OH".

Moreover, no trace of the regioisomeric 3-bromo 4,4-diphenyl 2-hydroxy cyclohexanone could be found in the final reaction mixture. To the best of our knowledge, this reaction is the first example of a successive, regioselective ring *opening* of a keto-epoxyde by trimethylsilyl bromide. Noteworthy was also the

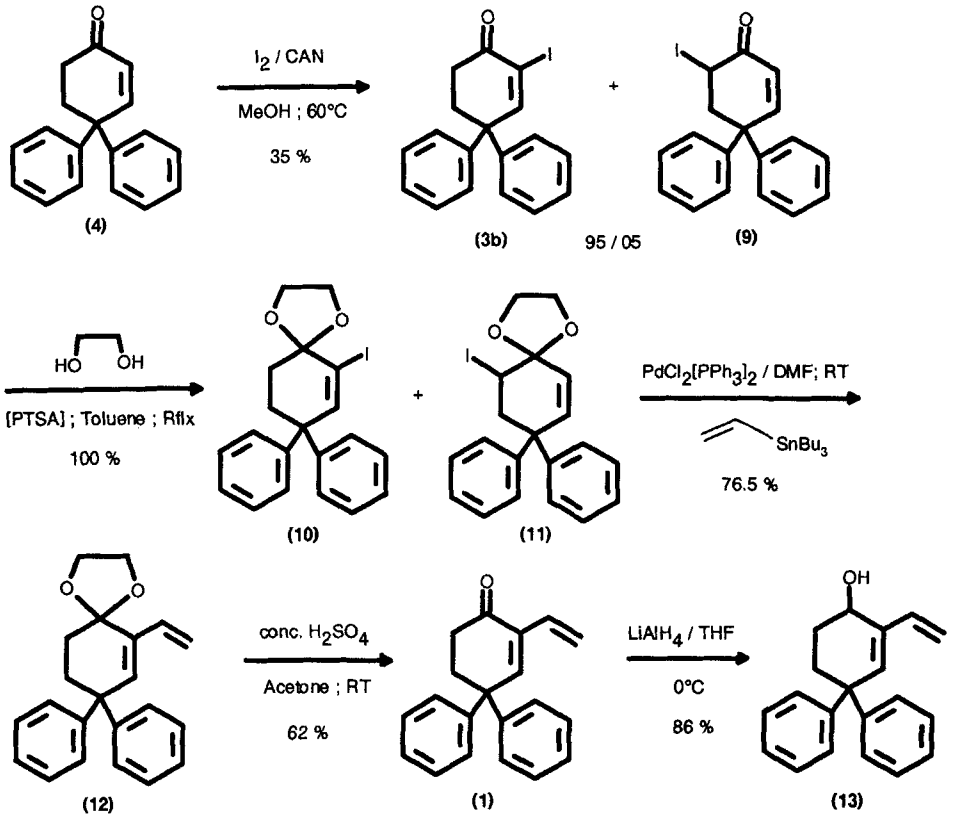


observation that initial addition of triethylamine to the reaction mixture, as previously recommended for alkyl-substituted epoxides[11], inhibited totally the above transformation. This result suggested a possible acidic catalysis for the opening of the epoxide.

Unfortunately, (3a) turned out to be unreactive toward vinyl tributyl tin, under Stille's conditions[3]. Consequently, we shifted to (3b) and encouraged by the above results, we decided to investigate the reaction of trimethylsilyl iodide with (7), as a possible route to compound (3b). Disappointingly, no reaction took place when trimethylsilyl iodide was reacted with (7). Therefore, we were forced to return to known reactions to prepare (3b). Reaction of ceric ammonium nitrate (CAN) and iodine[12] with enone (4) afforded, in 35 % yield after chromatography, (3b) along with a small amount of the regioisomer (9) (*95/5*). This material was subsequently used as such without further purification.

Preliminary attempts of Stille's reaction featuring (3b) and vinyl tributyl stannane were to no avail. No coupling could be detected, which was rather unexpected on the grounds of previous literature reports[3]. As we suspected some electronic effect of being responsible for this failure, we decided to mask the carbonyl group and to examine the coupling reactions of the resulting dioxolane (10) which was prepared

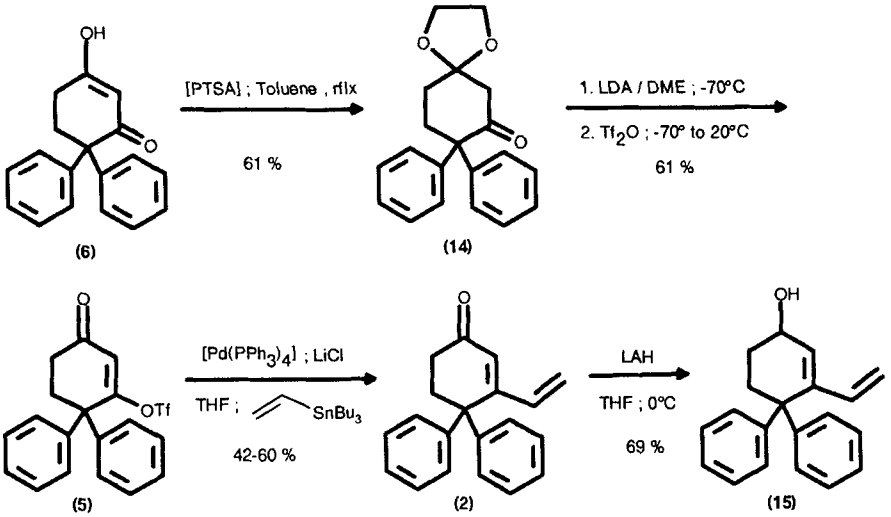
from (3b) in quantitative yield, by standard procedure. As expected[13], compound (10) (*along with dioxolane (11)*) underwent Stille's coupling without event to afford diene (12) in 76.5 % purified yield.



Deprotection under acidic conditions finally gave diene (1) (62 % yield; 17 % overall yield from enone (4)) which, upon reduction by $LiAlH_4$, cleanly led to dienol (13) in 86 % yield.

At that point, we turned our attention toward the synthesis of diene (2), starting from diketone (6)[6,7]. In order to prepare a precursor such as (5), we had to reverse the natural direction of enolisation of (6) shown in scheme I. We envisioned that initial reaction of (6) with ethylene glycol would mask the sterically non-crowded carbonyl

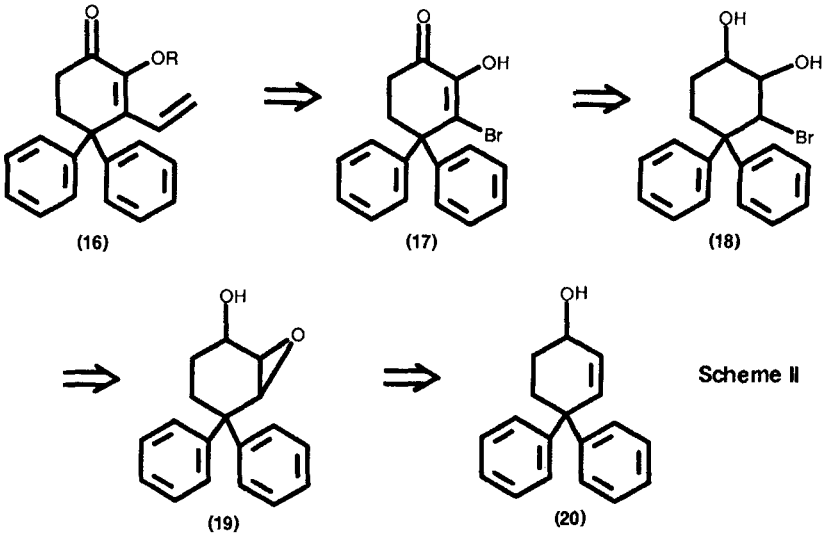
group of (6) and that subsequent triflatation of the corresponding enolate followed by deprotection would afford compound (5) (*Z = OTf*). This was indeed the case : dioxolane (14) was obtained in 61 % yield as the only regioisomer. The enolate of (14) was formed upon reaction of LDA in DME at -70°C and then quenched by triflic anhydride at the same temperature. Final reaction at RT was followed by aqueous work-up and chromatography to afford directly compound (5) in 61 % yield.



We were pleased to discover that triflate (5) was a reasonable substrate for Stille's coupling with vinyl tributyl tin[4,14]. Diene (2) was indeed isolated in this reaction in 42-60 % yield depending on the scale of the reaction. Apparently, steric hindrance was not a major concern in this case for palladium insertion and the subsequent coupling with the vinyl moiety. Overall yield for the synthetic sequence leading to (2) was close to 20 %. Finally, diene (2) was reduced to dienol (15) by LAH in 69 % yield.

In a related endeavour, we were interested in diketone (17) as a possible precursor of diene (16), a more electron-rich modified diene (2). (17) was regarded as a derivative of alcohol (20), via diol (18) and alcohol (19) (*Scheme II*).

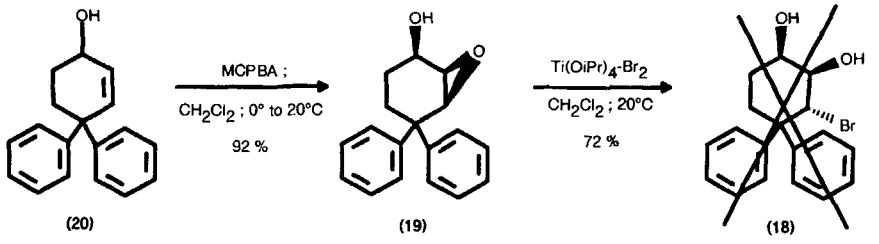
Epoxidation under standard conditions of alcohol (20) (*prepared from enone (4) by $NaBH_4$ reduction*[15]), afforded (19) in 92 % yield as the cis form, according to NMR.

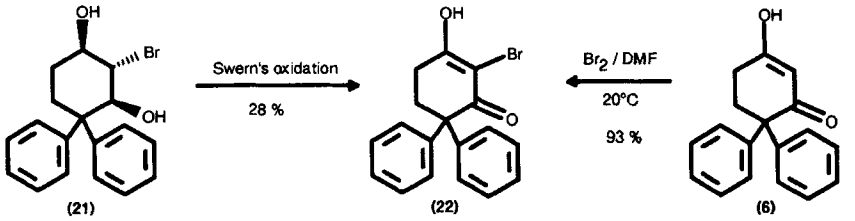


Scheme II

Upon reaction with bromine and titanium tetra-isopropoxide in CH_2Cl_2 at 20°C, (19) was expected to lead to (18) on the basis of a previous report[16]. As a matter of fact, this reaction afforded diol (21) in 72 % isolated yield and no trace of the expected (18). This result was best accounted for by the steric hindrance of the gem-diphenyl group which prevented the approach of the reactive bromide entity from this side of the molecule so that the delivery of the bromine atom alongside the hydroxy group was favoured.

Though the structure of (21) was secured by NMR studies, we confirmed this assignment by a chemical correlation : compound (21) was oxidized by Swern's method[17] to afford, in a modest 28 % yield, diketone (22) which was identical to the product obtained by bromination of diketone (6).





Finally, we briefly examined the reactivity of diene (1) and (2) in inverse electron demand Diels-Alder reactions. Both compounds were poor substrates under these conditions. Likewise, dienol (13) was unreactive in normal Diels-Alder cycloadditions. On the other hand, dienol (15) was slightly more reactive but was also abandoned since in the few successful cases, it generated inseparable mixtures of isomers, with little selectivity.

In conclusion, we have prepared new derivatives of 4,4-diphenyl 2-cyclohexen-one and developed two convenient routes to dienes (1) and (2) based upon palladium chemistry and readily available precursors. During the course of these syntheses, we encountered and used : a new method of cleavage of an epoxy-ketone by trimethylsilyl bromide to afford a 2-bromo-enone, a method for reversing the direction of enolisation of a 1,3-diketone and an anomalous ring opening of an hydroxy epoxide as a new example of the never-ending story of steric versus electronic effects. Further elaboration of the compounds described in this paper into potential antagonists of Substance P are still underway in our laboratories.

EXPERIMENTAL

General : Melting point (Kofler apparatus) are uncorrected. ^{1}H-NMR spectra were recorded on Brucker AC 200, 300, and WM 250 spectrometers. Chemical shifts are given in ppm relative to an internal tetramethylsilane standard. IR spectra were recorded on Nicolet 510 or 60 SXR spectrophotometers. Mass spectra were obtained from a Finnigan 3300 (EI, 70 ev). Purification by flash-chromatography were carried out on silica gel (Merck; 0.04-0.063 mm). Solvents and reagents were used as received from suppliers. TLC analyses were carried out on pre-coated TLC plates (Merck; F254).

2-Bromo 4,4-diphenyl 2-cyclohexen-one (3a) :

TMS-Br (0.78 mL; 5.8 mmoles) was slowly syringed onto a solution of epoxide (7)[9] (1.45 g; 5.5 mmoles) and toluene (55 mL) in a 250-mL three-necked flask equipped with a magnetic bar, a nitrogen inlet, a septum and a bubbler. After addition, the reaction mixture was stirred at RT for 16 hours. Concentration yielded a yellow solid which was dissolved in CH_2Cl_2 (20 mL) and stirred with 2N hydrochloric ether (10 mL) for 3 hours at RT. The resulting solution was concentrated and the residue (1.8 g) was flash-chromatographed (Cyclohexane / Ethyl acetate : 95/5) to afford (3a) as a pale yellow solid (1.14 g; 64 % yield). ^{1}H-NMR (300 MHz; DMSO d_6) δ : 2.52 (m, 2H, CH_2), 2.77 (m, 2H, CH_2), 7.2-7.5 (m, 10H, aromatic CH), 8.19 (s, 1H, CH=C-Br), *NOE effects between the vinylic proton and the ortho aromatic protons*; IR : *see reference 8*; MS (EI) m/z : 247, 205, 191, 169, 165; (DCI; NH_3) : 344 ($MNH_4^{+\cdot}$), 327 ($MH^{+\cdot}$); Rf = 0.42 (Cyclohexane / Ethyl acetate : 90/10). An analytical sample was obtained by recrystallisation from Cyclohexane / Toluene (3 / 1 v / v) as a white solid : mp 165 °C; Calculated for $C_{18}H_{15}BrO$: C 66.07, H 4.62, Br 24.42 ; Found : C 66.4, H 4.7, Br 23.9.

4,4-Diphenyl 2-iodo 2-cyclohexen-one (3b) :

In a 4-liter three-necked flask equipped with a magnetic bar, a nitrogen inlet, a thermometer and a condenser connected to a bubbler was dissolved enone (4)[5] (60 g ; 0.24 mole) in 1.5 L of acetonitrile. Iodine (79.2 g ; 0.312 mole) and CAN (157 g , 0.268 mole) were successively and rapidly added to this solution. The reaction mixture was then stirred at 60°C for 3 days before cooling and partition between water and CH_2Cl_2. After elimination of the excess iodine by addition of a 37% aqueous solution of $NaHSO_3$, the organic layer was separated, washed with brine and water, dried over $MgSO_4$ and concentrated to leave a brown oil (90.1 g). This residue was flash chromatographed. Elution with Cyclohexane / Ethyl acetate (97/3) afforded starting material and (3b) as a yellow solid (31,6 g ; 35 % yield), contaminated with 5% of compound (9). ^{1}H-NMR (300 MHz; DMSO d_6) δ : 2.5 (t, J = 6 Hz, 2H, CH_2), 2.7 (t, J = 6 Hz, 2H, CH_2), 7.2-7.5 (m, 10H, aromatic CH), 8.19 (s, 1H, CH=C-I); IR (KBr) : 3100-3000, 3000-2825, 1685, 1585, 1495, 1450, 755, 700 cm^{-1}; MS (EI) m/z : 375, 247, 189, 165, 141, 115, 91.

4,4-Diphenyl 2-iodo 2-cyclohexen-one ethylene acetal (10) :

In a 4-liter three-necked flask equipped with a magnetic bar, a thermometer, a Dean-Stark trap and a condenser connected to a bubbler were introduced iodo-enone (3b) (37.9 g ; 0.101 mole), toluene (800 mL), ethylene glycol (23 mL ; 0.41 mole) and PTSA (0.45 g). The resulting mixture was refluxed until no starting material was left (1 to 3 days). After cooling, the solution was filtered over K_2CO_3 and then concentrated to give a brown oil (42.5 g) which was shown by spectroscopic analyses to be the expected compound (100 % yield) along with c.a. 5% of compound (11). ^{1}H-NMR (300 MHz; $CDCl_3$) δ : 2.1 (t, J = 6 Hz, 2H, CH_2), 2.7 (t, J = 6 Hz, 2H, CH_2), 4.15 (t, J = 6 Hz, 2H, CH_2), 4.4 (t, J = 6 Hz, 2H, CH_2), 7.2 (s, 1H, CH=C-I), 7.2-7.6 (m, 10H, aromatic CH). IR (CCl_4) : 3100-3000, 3000-2825, 1600, 1495, 1445, 1140, 1105, 1060, 1040, 700 cm^{-1}; MS (EI) m/z : 418 ($M^{+\cdot}$), 291, 247, 219, 190, 165, 140, 115, 99, 91; (DCI; NH_3) : 419 ($MH^{+\cdot}$), 374.

4,4-Diphenyl 2-vinyl 2-cyclohexen-one ethylene acetal (12) :

In a 4-liter three-necked flask equipped with a magnetic bar, a nitrogen inlet, a thermometer and a bubbler were successively introduced (10) (42.5 g ; 0.102 mole), anhydrous DMF (400 mL), vinyl tributyl tin (38.5 mL ; 0.132 mole) and dichloro bis(triphenyl phosphine) palladium (1.4 g ; 0.002 mole). The resulting mixture was stirred at RT for 3 days and then partitioned between water (250 mL) and CH_2Cl_2 (300 mL). The organic layer was separated, washed with water (3x250 mL), dried over $MgSO_4$, treated with activated charcoal, filtered and finally concentrated to afford a yellow oil (70.2 g). Flash-chromatography of this residue (Cyclohexane / Ethyl acetate: 95 / 5) afforded diene (12) as a pale yellow oil (24.7 g ; 76 %).^{1}H-NMR (200 MHz; DMSO d_6) δ : 1.7 (m, 2H, CH_2), 2.2 (m, 2H, CH_2), 4.0 (m, 4H, CH_2), 5.15 (dd, J = 2 Hz and 12 Hz, 1H, vinylic CH), 5.55 (dd, J = 2 Hz and 17 Hz, 1H, vinylic CH), 6.35 (dd, J = 12 Hz and 17 Hz, 1H, vinylic CH), 6.6 (s, 1H, vinylic CH), 7.2-7.5 (m, 10H, aromatic CH).; IR (CCl_4) : 3100-3000, 3000-2825, 1600, 1495, 1445, 1120, 1065, 1035, 990, 912, 700 cm^{-1}; MS (EI) m/z : 318 ($M^{+\cdot}$), 232, 217, 202, 165, 141, 128, 115, 99, 91, 55.

4,4-Diphenyl 2-vinyl 2-cyclohexen-one (1) :

In a 500-mL three-necked flask equipped with a magnetic bar, a nitrogen inlet, a thermometer, a dropping funnel and a condenser connected to a bubbler were successively introduced diene (12) (21.25 g ; 0.067 mole) and acetone (200 mL). To the resulting orange solution was added dropwise concentrated sulfuric acid (3.5 mL). After addition, the reaction mixture was stirred at RT for 30 minutes before neutralisation by a 30 % NaOH aqueous solution (20 mL). Acetone was removed under vacuum and the residue extracted by CH_2Cl_2. The organic layer was washed with brine and water, dried over $MgSO_4$, filtered and concentrated to leave an orange solid (16.9 g). Purification of this solid by flash chromatography (Cyclohexane / Ethyl acetate: 85 / 15) led to diene (1) (11.4 g ; 62 % yield) as an light orange solid (mp : 122°C).^{1}H-NMR (200 MHz; DMSO d_6) δ : 2.3 (t, J = 7 Hz, 2H, CH_2), 2.65 (t, J = 7 Hz, 2H, CH_2), 5.25 (dd, J = 2 Hz and 12 Hz, 1H, vinylic CH), 5.9 (dd, J = 2 Hz and 17 Hz, 1H, vinylic CH), 6.55 (dd, J = 12 Hz and 17 Hz, 1H, vinylic CH), 7.15-7.4 (m, 10H, aromatic CH), 7.6 (s, 1H, vinylic CH); MS (EI) m/z : 274 ($M^{+\cdot}$), 256, 231, 217, 202, 170, 154, 141, 128, 115, 91; (DCI, NH_3) : 292 ($MNH_4^{+\cdot}$), 275 ($MH^{+\cdot}$).

4,4-Diphenyl 2-vinyl 2-cyclohexen-ol (13) :

To a slurry of LAH (1.5 g ; 0.039 mole) and anhydrous THF (60 mL) in a 500-mL three-necked flask equipped with a magnetic bar, a thermometer, a dropping funnel and a bubbler was added dropwise at 0°C, a solution of (1) (9.4 g ; 0.034 mole) in 60 mL of THF. After addition, the reaction mixture was stirred at RT for 30 minutes and then quenched at -10°C by slow addition of AcOEt (3 mL) and KOH (10 % solution; 9 mL). After stirring at RT for 30 minutes, the reaction mixture was filtered and the filtrate concentrated. The residue (9.6 g) was stirred in iPr_2O and then filtered to afford pure (13) as a white solid (7.2 g ; mp : 110°C). A second crop of (13) (0.9 g; overall yield : 86 %) was obtained by flash chromatography (Cyclohexane / Ethyl acetate : 95 / 5) of the filtrate.^{1}H-NMR (250 MHz; DMSO d_6) δ : 1.5-1.8 (m, 2H, CH_2), 2.2 (bd, J = 12 Hz, 1H, CH_2), 2.45 (dd, J = 3 Hz and 12 Hz, 1H, CH_2), 4.25 (m, , 1H, CH), 4.75 (d, J = 5 hz, 1H, OH), 5.1 (dd, J = 2 Hz and 12 Hz, 1H, vinylic CH), 5.5 (dd, J = 2 Hz and 17 Hz, 1H, vinylic CH), 6.25 (s, 1H, vinylic CH), 6.4 (dd, J = 12

Hz and 17 Hz, 1H, vinylic CH), 7.1-7.4 (m, 10H, aromatic CH); IR (CCl_4) : 3225; 3100-3000; 3000-2825, 1635, 1595, 1490, 1445, 1060, 995, 910, 755, 700 cm^{-1}; MS (EI) m/z : 276 ($M^{+\cdot}$), 258, 231, 217, 202,178, 165, 156, 141, 129, 115, 105, 91; DCI (NH_3) : 294 ($MNH_4^{+\cdot}$), 276, 259, 233, 167.

6,6-Diphenyl 3,3-ethylene dioxy cyclohexanone (14) :

In a 2-liter three-necked flask equipped with a magnetic bar, a thermometer, a Dean-Stark trap and a condenser connected to a bubbler were introduced diketone (6)[6,7] (20 g ; 0.076 mole), toluene (900 mL), APTS (0.4 g) and ethylene glycol (16.9 mL ; 0.3 mole). The resulting mixture was refluxed overnight. Following addition of K_2CO_3 (3 g), the final solution was concentrated to yield a yellow solid. Recrystallization from isopropanol afforded (14) as pale yellow crystals (13.05 g). The mother liquor was concentrated and the residual solid reacted as above (toluene, PTSA, ethylene glycol, reflux overnight). Flash chromatography (Cyclohexane / Ethyl acetate : 90 / 10) of the concentrated reaction mixture afforded a further 1.3 g of pure (14) (overall yield : 61 %). Recrystallization from a mixture Cyclohexane / Toluene afforded an analytical sample : mp 139 °C. Calculated for $C_{20}H_{20}O_3$: C 77.9, H 6.54, O 15.56; Found : C 77.9, H 6.7, O 15.2. ^{1}H-NMR (250 MHz; DMSO d_6) δ : 1.9 (t, J = 6 Hz, 2H, CH_2), 2.6 (t, J = 6 Hz, 2H, CH_2), 2.63 (s, 2H, CH_2), 3.9 (s, 4H, CH_2), 7.0 (d, J = 7 Hz, 4H, aromatic CH), 7.2-7.45 (m, 6H, aromatic CH). IR (KBr) : 3100-3000, 3000-2850, 1710, 1600, 1580, 1495, 1445, 1125, 1105, 1060, 1035, 755, 700 cm^{-1}; MS (EI) m/z : 308 ($M^{+\cdot}$), 266, 180, 165, 115, 86.

4,4-Diphenyl 3-vinyl 2-cyclohexen-one (2) :

In a 100-mL three-necked flask equipped with a magnetic bar, a nitrogen inlet, a thermometer, a dropping funnel and a bubbler were introduced diisopropyl amine (0.35 mL; 2.43 mmoles) and anhydrous DME (9 mL). To this solution cooled to -70°C, was added nBuLi (1.6 M in Hexane; 1.52 ml). After 25 minutes at this temperature, a solution of (14) in DME (6 mL) was added dropwise over 10 minutes. The resulting mixture was stirred at -70°C for 20 minutes before addition of triflic anhydride (0.33 mL ; 1.95 mmoles) in DME (3 mL). Stirring at -70°C was continued for 30 minutes and

then the reaction mixture was allowed to warm to RT. After 4 hour at RT, the resulting mixture was concentrated and the oily residue partitioned between ethyl acetate (50 mL) and water (30 mL). The organic layer was separated, washed with water (3x30 mL), dried over $MgSO_4$, filtered and concentrated. The residual oil was purified by flash-chromatography (Cyclohexane / Ethyl acetate : 95 / 5) to afford triflate (5) as a pale yellow oil (0.39 g; 61 % yield).; IR (CCl_4) : 3100-3000, 3000-2850, 1695, 1630, 1600, 1495, 1450, 1435, 1420, 1225, 1145, 700 cm^{-1}; MS (EI) m/z : 396 ($M^{+\cdot}$), 263, 247, 221, 208, 178, 165, 115, 105, 91, 69.

To a mixture of tetrakis (triphenyl phosphine) palladium (0.49 g ; 0.42 mmole), lithium chloride (5.1 g ; 0.12 mole) and THF (100 mL) in a 1-liter three-necked flask equipped with a magnetic bar, a nitrogen inlet, a thermometer, a dropping funnel and a condenser connected to a bubbler was added dropwise over 30 minutes a solution of crude triflate (5) (15.89 g ; 0.04 moles) and vinyl tributyl tin (12.3 mL ; 0.042 mole) in THF (250 mL). After addition, the reaction mixture was refluxed for 3 days. The cooled mixture was then diluted by 500 mL of pentane and the resulting mixture was washed successively with water (2x250 mL), an aqueous saturated solution of $NaHCO_3$ (200 mL), brine (200 mL) and water (200 mL). The final organic layer was separated, dried over $MgSO_4$, filtered and concentrated to leave a greenish oil (33.45 g). This residue was flash-chromatographed (Cyclohexane / Ethyl acetate : 95 / 5) to afford diene (2) (4.63 g ; 42 % (*on a small scale, yields could be as high as 60 %*)) as a pale yellow solid (mp : 107 °C). ^{1}H-NMR (200 MHz; DMSO d_6) δ : 2.05 (t, J = 6 Hz, 2H, CH_2), 2.75 (t, J = 6 Hz, 2H, CH_2), 5.25 (dd, J = 4 Hz and 9 Hz, 1H, vinylic CH), 5.7-5.9 (m, 2H, vinylic CH), 6.5 (s, 1H, vinylic CH), 7.2-7.5 (m, 10H, aromatic CH); IR (CCl_4) : 3100-3000, 3000-2825, 1660, 1600, 1580, 1495, 1450, 995, 900, 760, 700 cm^{-1}; MS (EI) m/z :275, 217, 202, 183, 165, 155, 141, 115, 91; (DCI; NH_3) : 292 ($MNH_4^{+\cdot}$), 275 ($MH^{+\cdot}$).

4,4-Diphenyl 3-vinyl 2-cyclohexen-ol (15) :

To a slurry of LAH (0.54 g ; 14 mmole) in anhydrous THF (60 mL) in a 250-mL three-necked flask equipped with a magnetic bar, a thermometer, a dropping funnel and a bubbler was added dropwise at -5°C, a solution of (2) (3.38 g ; 12.3 mmoles) in 40 mL

of THF. After addition, the reaction mixture was stirred at RT for 20 minutes and then quenched at -15°C by slow addition of AcOEt (2.5 mL) and KOH (10 % solution; 6 mL). After stirring at RT for 30 minutes, the reaction mixture was filtered, the insoluble material washed with THF (2x10 mL) and the filtrate concentrated. The yellow oil left (3.98 g) was filtered on a pad of silica gel (Cyclohexane / Ethyl acetate : 90 / 10) to afford (15) as a yellow tacky solid (2.15 g; 63 % yield). ^{1}H-NMR (300 MHz; DMSO d_6) δ : 1.25 (m, 1H, CH_2), 1.5 (m, 1H, CH_2), 2.3 (m, 1H, CH_2), 2.4 (m, 1H, CH_2), 4.25 (bs, 1H, CH), 4.9 (bs, 1H, OH), 5.15 (d, J = 17 Hz, 1H, vinylic CH), 5.75 (dd, J = 12 Hz and 17 Hz, 1H, vinylic CH), 6.25 (d, J = 2 Hz, 1H, vinylic CH), 7.0-7.5 (m, 10H, aromatic CH); IR (CCl_4) : 3630, 3550-3200, 3090, 3060, 3030, 3020, 2950, 2875, 1600, 1495, 1450, 1050, 990, 910, 700 cm^{-1}; MS (EI) m/z ; 276 ($M^{+\cdot}$), 258, 217, 202, 180, 167, 141, 128, 115, 105, 91, 77; (DCI; NH_3) : 276, 259.

Cis 4,4-diphenyl cyclohexanol 2,3-epoxide (19) :

To a cooled (0°C) solution of alcohol (18) (0.95 g ; 3.8 mmoles) and CH_2Cl_2 (10 mL) in a 100-mL flask, equipped with a magnetic bar and a bubbler , was added portion wise, over 5 minutes, solid MCPBA (70 %; 1.23 g; 5 mmoles). After addition, the reaction mixture was stirred at RT for 21 hours. Addition of water (10 mL) was followed by separation of the organic layer from the aqueous layer. The latter was extracted with CH_2Cl_2 (2x10 mL). The combined organic extracts were successively washed with a 20% aqueous solution of Na_2SO_3 , a 20 % aqueous solution of $NaHCO_3$ and water (20 mL each). Filtration of the resulting layer on a pad of $MgSO_4$ and concentration of the filtrate afforded 0.95 g of (19) as a white solid (0.95 g; 94 %). ^{1}H-NMR (300 MHz; DMSO d_6) δ : 1.38 (m, 2H, CH_2), 1.62 (m, 1H, CH_2), 2.47 (m, 1H, CH_2), 3.53 (t, J = 4.5 Hz, 1H, CH), 3.93 (d, J = 4.5 Hz, 1H, CH), 4.03 (m, 1H, CH), 4.92 (d, J = 7.1 Hz, 1H, OH), 7.1-7.45 (m, 10H, aromatic CH); MS (EI) m/z : 266 ($M^{+\cdot}$), 206, 193, 165, 115, 91; Rf = 0.3 (Cyclohexane / Ethyl acetate : 70/30).

2-Bromo 4,4-diphenyl cyclohexane 1,3-diol (21) (1R*,2R*,3S*):

$Ti(OiPr)_4$ was syringed onto a cold (0°C) solution of CH_2Cl_2 (35 ml) and bromine (0.2 ml; 4.2 mmoles) in a 100-mL three-necked flask equipped with a magnetic bar, a

nitrogen inlet, a thermometer, a dropping funnel and a bubbler. To the resulting solution was added dropwise at 0°C, a solution of epoxide (19) (0.93 g; 3.5 mmoles) and CH_2Cl_2 (10 mL). After addition, the reaction mixture was stirred for 5 hours and then quenched by addition of a 5 % aqueous solution of H_2SO_4 (30 mL) and a 37 % aqueous solution of $NaHSO_3$ (10 mL). After stirring for a few minutes, the organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2x25 mL). The combined organic layers were successively washed with a saturated aqueous solution of $NaHCO_3$ (25 mL) and with water (25 mL), filtered over $MgSO_4$ and concentrated. The resulting orange solid was purified by flash-chromatography (Cyclohexane / Ethyl acetate : 80/20) to afford diol (21) as a white solid (0.875 g; 72 % yield). This solid was recrystallized from a mixture Cyclohexane / Toluene (5 mL/ 2,5 mL per g) to give white crystals (mp : 100-102°C). ^{1}H-NMR (250 MHz; DMSO d_6) δ : 1.18 (m, 1H, CH_2 ax), 1.79 (m, 1H, CH_2 eq), 2.3 (m, 2H, CH_2), 3.79 (dt, J = 10 Hz and 5 Hz, 1H, CH-O ax), 4.0 (dd, J = 10 Hz and 4.5 Hz, 1H, CH-O ax), 4.24 (t, J = 10 Hz, 1H, CH-Br ax), 5.18 (m, 1H, OH), 5.63 (d, J = 4.5 Hz, 1H, OH), 7.0-7.8 (m, 10H, aromatic CH); IR (CCl_4) : 3585, 3460, 1600, 1580, 1495, 1445, 1030, 700 cm^{-1}; MS (EI) m/z : 249, 231, 178, 165, 115, 105, 91; (DCI) : 364 ($MNH_4^{+\cdot}$); Rf = 0.67 (50/50 Cyclohexane / Ethyl acetate).

2-Bromo 4,4-diphenyl cyclohexane 1,3-dione (22) :

by Swern's oxidation of (21) : (21) (0.104 g; 0.3 mmole) was oxidised in CH_2Cl_2 (3.5 mL) according to Swern's procedure[17] (DMSO : 0.1 mL; Oxalyl chloride : 0.06 mL; TEA : 0.42 mL) to afford after the usual work-up and chromatography (Cyclohexane / Ethyl acetate : 50/50) 34 mg (28 % yield) of a white solid which was identical by TLC and its spectroscopic properties to compound (22) prepared from (6) by bromination (see below).

by bromination of (6) : In a 1-liter two-necked flask equipped with a magnetic bar, a a thermometer, a dropping funnel connected to a bubbler was dissolved diketone (6) (10 g; 37.8 mmoles) in DMF (210 mL). To the resulting solution was added dropwise at RT, over 20 minutes, bromine (2.05 mL; 39.7 mmoles) in DMF (40 mL). After addition, the dark orange solution was stirred at RT for 6 hours. Water (400 mL) was then added as well as some solid $Na_2S_2O_5$ to destroy the excess bromine. A white

solid precipitated which was dissolved by addition of CH_2Cl_2 (500 mL). The two layers were separated and the aqueous layer extracted with CH_2Cl_2 (3x200 mL). The combined organic layers were filtered over $MgSO_4$ and concentrated to leave a white solid. Final purification was achieved by stirring this material with cyclohexane overnight and subsequent filtration. (21) (12.2 g; 94 % yield) was obtained as a white solid shown by spectroscopic analyses to be the enolic form shown in the text. An analytical sample was obtained by recrystallization from ethanol (7 mL per g) mp : 210-211°C. ^{1}H-NMR (200 MHz; DMSO d_6) δ : 2.58 (m, 2H, CH_2), 2.78 (m, 2H, CH_2), 6.9-7.5 (m, 10H, aromatic CH); IR (KBr) : 3350, 3100, 2725-2100, 1640, 1610, 1580, 1500, 1450, 760, 700 cm^{-1}; MS (EI) m/z : 342 ($M^{+\cdot}$), 263, 247, 180, 165, 115, 91; Rf = 0.15 (Cyclohexane / Ethyl acetate : 50/50). Calculated for $C_{18}H_{15}BrO_2$: C 62.99, H 4.41, Br 23.28, O 9.32; Found : C 62.7, H 4.4, Br 22.7, O 9.6.

Acknowledgement : We are indebted to M. VUILHORGNE and his collaborators for spectroscopic analyses.

References and notes :

1. LOWE, III J.A.; SNIDER, R.M., *Annual Reports in Medicinal Chemistry*, 1993, 28, 99
2. PEYRONEL, J.F.; TRUCHON, A.; MOUTONNIER, C.; GARRET, C., *Bioorg. Med. Chem. Lett.*, 1992, 2, 37
3. JOHNSON, C.R.; ADAMS, J.P., BRAUN, M.P; SENANAYAKE, C.B.W., *Tetrahedron Lett.*, 1992, 33, 919
4. HETTRICK, C.M.; KLING, J.K.; SCOTT, W.J., *J. Org. Chem.*, 1991, 56, 1489
5. ZIMMERMAN, H.E.; SCHUSTER, D.E., *J. Am. Chem. Soc.*, 1962, 84, 4527
6. ZIMMERMAN, H.E.; PASTERIS, R.J., *J. Org. Chem.*, 1980, 45, 4876
7. BACQUE, E.; PARIS, J.M., *Synthetic Commun.*, 1992, 22, 2259
8. BORDWELL, F.G.; WELLMAN, K.M., *J. Org. Chem.*, 1963, 28, 2544
9. MATOBA, K.; KAWAGOSHI, F; YAMAZAKI, T., *Chem. Pharm. Bull.*, 1984, 32, 4721
10. KRICHELDORF, H.R.; MORCER, G.; REGEL, W., *Synthesis*, 1981, 383
11. DENIS, J.N.; KRIEF, A., *Tetrahedron Lett.*, 1981, 22, 1429

12. KIM, T.H.; ASAKURA, J.; ASAKA, Y., *Chem. Express*, 1990, 5, 221
13. LEE, J.; SNYDER, J.K., *J. Am. Chem. Soc.*, 1989, 111, 1522
14. STILLE, J.K.; SCOTT, W.J., *J. Am. Chem. Soc.*, 1986, 108, 3033
15. a : VITORELLI, P.; PETER-KATALINIC, J.; MUKHERJEE-MUELLER, G.; HANSEN, H.J.; SCHMID, H., *Helv. Chim. Acta*, 1975, 58, 1379; b : PERKINS, M.J.; ATKINSON, D.J.; WARD, P., J. *Chem. Soc. C*, 1971, 3240
16. ALVAREZ, E.; MUNEZ, M.T.; MARTIN, V., *J. Org. Chem.*, 1990, 55, 3429
17. MANCUSO, A.J.; BROWNFAIN, D.S.; SWERN, D., *J. Org. Chem.*, 1979, 44, 4148

(Received in the UK 05 December 1994)