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The asymmetric hydrogenation of 1,1,4,4,7-pentamethyl-2-methylen-1,2,3,4-tetrahydro-naphthalene, a viable catalytic approach to the synthesis of non-racemic Fixolide®

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Abstract

Asymmetric hydrogenation of 1,1,4,4,7-pentamethyl-2-methylen-1,2,3,4-tetrahydro-naphthalene **2** or 1,1,2,4,4,7-hexamethyl-1,4-dihydro-naphthalene **3** leads to 1,1,2,4,4,7-hexamethyl-1,2,3,4-tetrahydro-naphthalene **4** an immediate precursor of the fragrance Fixolide®. Promising results (with 33% *ee*) have been obtained starting from olefin **2** using a cationic Iridium catalyst in combination with a chiral phosphino-oxazoline ligand.

Keywords: Fixolide; Asymmetric hydrogenation; Fragrances; Iridium; Rhodium

1. Introduction

Fixolide® i.e. 1-(3,5,5,6,8,8-hexamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-ethanone (Fig. 1) [1][1] is an important musk odorant.

It has been shown that only the (*S*) enantiomer of Fixolide® is responsible for the strong musk odour, while the opposite enantiomer has only a light and sweet aromatic odour [2,3]. Although a stoichiometric approach to both enantiomers of Fixolide® has been already described by Suzukamo [3], the fragrance is currently manufactured and commercialised as a racemate.

Fixolide®, as well as other aromatic musk odorants, has been found to be hardly biodegradable and has the tendency to be bioaccumulated; for instance, it has been found in the adipose tissues of many aquatic species [4,5]. The synthesis of the only bioactive stereomers would contribute to reduce the amount of these chemicals dispersed in the environment.

These concerns and our interest in the application of asymmetric catalysis in fragrance chemistry [6] prompted us to devise a catalytic approach to non-racemic Fixolide®.

2. Experimental

^{1}H and ^{13}C NMR spectra were registered on a Bruker Avance 300 NMR spectrometer operating at 300.11 and 75.44 MHz, respectively. GLC analyses were performed on a Agilent 6850 gas chromatograph; GC-MS analyses were performed on a HP 5890 series II gas chromatograph interfaced to a HP 5971 quadrupole mass-detector.

The *ee*'s were inferred by comparing the obtained optical rotation values with the literature data [2] for 1,1,2,4,4,7-hexamethyl-1,2,3,4-tetrahydro-naphthalene: $[\alpha]_{25}^{546} = -48.9$ (*c* 1.0, $CHCl_3$). Optical rotation values were measured with a Perkin Elmer Mod. 241 polarimeter. All reactions, unless otherwise stated, were carried out under an inert atmosphere (argon). Commercial solvents (Aldrich or Fluka) were purified before the use following literature procedures [7]. Dimethylsulfoxide (Fluka) was distilled from CaH_2. CH_2Cl_2 was distilled from $LiAlH_4$. $[Ph_3PCH_3]Br$, NaH and *n*-BuLi were purchased from Aldrich.

2.1. 1,1,4,4,6-Pentamethyl-3,4-dihydro-1H-naphtalen-2-one

1,1,4,4,6-Pentamethyl-3,4-dihydro-1*H*-naphtalen-2-one was synthesised as described in the literature [8,9] by

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[1] Fixolide® is a registered trade mark of Givaudan.

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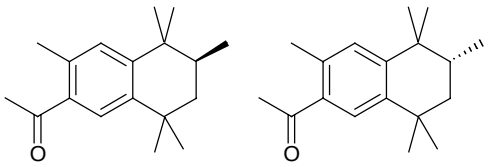


Fig. 1. Chemical structure of Fixolide®.

reacting 2,2,5,5-tetramethyltetrahydro-furan-3-one [8] with toluene in the presence of $AlCl_3$.

$[Rh(COD)I]_2$ (COD = 1,5-cyclooctadiene) was prepared as described in the literature [10].

$[Ir(COD)(P\text{-}N)]^+$ $(BARF)^-$ (**5**) (COD = 1,5-cyclooctadiene; P-N = 4-tert-butyl-2-(2-diphenylphosphanylphenyl)-4,5-dihydrooxazole [11–13]; $(BARF)^-$ = tetrakis-[3,5-bis(trifluoromethyl)-phenyl]borate [14]) was prepared as described in the literature [15].

2.2. 1,1,4,4,7-Pentamethyl-2-methylen-1,2,3,4-tetrahydronaphthalene (2)

To 25 mL of anhydrous dimethylsulfoxide (DMSO) were added 1.10 g of a 55% (wt) dispersion of sodium hydride in mineral oil (46.0 mmol), and the mixture was heated at 75–80 °C until the evolution of hydrogen ceased (about 50 min). The resulting solution of the dimethylsulfinyl carbanion was cooled to 0 °C, then 16.4 g (46.0 mmol) of methyltriphenylphosphonium bromide in 40 mL of warm DMSO were added dropwise. The resulting orange solution was stirred at room temperature for 10 min, then a solution of 1,1,4,4,7-pentamethyl-3,4-dihydro-1*H*-naphtalen-2-one **1** (5.0 g, 23.0 mmol) in DMSO (40 mL) was added dropwise at r.t.. Then, the mixture was stirred for 24 h at 80 °C, then cooled to room temperature and poured in 250 mL of icy water. The aqueous phase was extracted with *n*-pentane (4 × 100 mL), and the combined *n*-pentane extracts were washed with water. The organic layer was dried over anhydrous magnesium sulfate and the solvent distilled off leaving an oil which was purified by flash chromatography (silica gel, eluent = *n*-pentane: ethyl acetate 95:5) to give 1,1,4,4,7-pentamethyl-2-methylen-1,2,3,4-tetrahydro-naphthalene as a colourless oil (4.38 g, 89%).

^{1}H NMR ($CDCl_3$): δ = 1.28 (s, 6H), 1.50 (s, 6H), 2.36 (s, 3H), 2.41 (m, 2H), 4.85 (m, 1H), 5.03 (m, 1H), 6.09–7.02 (m, 1H), 7.20–7.24 (m, 2H).

^{13}C NMR ($CDCl_3$): δ = 21.21, 30.77, 31.57, 35.65, 40.36, 46.75, 107.9, 125.25, 126.66, 127.48, 135.18, 142.32, 144.12, 153.28. MS (70 eV): *m/z* (%) 214 (17) $[M]^+$, 199 (100) $[M–CH_3]^+$.

2.3. 1,1,2,4,4,7-Hexamethyl-1,4-dihydronaphthalene (3)

A solution of 2.5 g (11.60 mmol) of 1,1,4,4,7-pentamethyl-3,4-dihydro-1*H*-naphtalen-2-one **1** in diethyl ether (10 mL) was added dropwise to a cold (0 °C) solution of MeLi (17.0 mmol) in diethylether (32 mL). After the addition was complete, the resulting solution was allowed to warm to 25 °C under stirring during 6 h. The solution was partitioned between *n*-pentane and aqueous NH_4Cl; the organic layer collected and concentrated by distillation. The residual crude tertiary alcohol was treated with 30 mL of aqueous 5% H_2SO_4 and the mixture refluxed for 4 h. The mixture was cooled to r.t. and extracted with *n*-pentane (2 × 30 mL). The combined *n*-pentane extracts were washed with a aqueous saturated solution of $NaHCO_3$, then dried over anhydrous Na_2SO_4 and the solvent eliminated by distillation to give an oil. On standing, pure 1,1,2,4,4,7-hexamethyl-1,4-dihydronaphthalene crystallized as white needles (1.74 g, 70%).

^{1}H NMR ($CDCl_3$): δ = 1.32 (s, 6H), 1.40 (s, 6H), 1.84 (s, 3H), 2.37 (s, 3H), 5.34 (s, 1H), 7.03 (d, 1H), 7.24–7.28 (m, 2H).

^{13}C NMR ($CDCl_3$): δ = 19.44, 21.26, 30.02, 32.81, 34.72, 37.97, 125.81, 126.67, 126.94, 131.25, 134.96, 135.23, 139.57.

MS (70 eV): *m/z* (%) 214 (4) $[M]^+$, 199 (100) $[M–CH_3]^+$.

2.4. Hydrogenation experiments

In a typical experiment (entry 3 of Table 1), a Schlenk flask, containing a small stirring bar, was charged, under an inert atmosphere, with CH_2Cl_2 (10 mL), olefin **2** (0.100 g, 0.47 mmol) and catalyst **5** (0.073 g, 0.047 mmol). The resulting solution was transferred via cannula into a magnetically stirred stainless steel autoclave (volume = 150 mL) which was pressurised with H_2 (100 atm). The reactor was cooled to −20 °C by circulating a thermostatic fluid. After 120 h the reactor was allowed to come to room temperature and the residual gas vented off. The solvent was removed in high vacuum, and the residue purified by flash chromatography (silica gel, eluent: *n*-pentane) affording **4** as a white solid (0.91 g, 90%), $[\alpha]_{25}^{546}$ = +17 (*c* 1.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 1.05 (d, 3H), 1.09 (s, 3H), 1.27 (s, 3H), 1.31 (s, 3H), 1.34 (s, 3H), 1.38 (dd, 1H), 1.65 (t, 1H), 1.89 (m, 1H), 2.33 (s, 3H), 6.97–6.99 (m, 1H), 7.18–7.23 (m, 2H).

^{13}C NMR ($CDCl_3$): δ = 16.87, 21.17, 24.96, 28.56, 32.09, 32.43, 33.98, 34.56, 37.63, 43.73, 126.34, 126.43, 127.44, 134.74, 141.69, 145.81.

Table 1
Asymmetric hydrogenation of olefins **2** and **3**[a]

Entry	Olefin	Cat.	*T* (°C)	Conv. (%)	*ee*[b]	Config.[b]
1	**2**	**5**	20	100	24	R
2	**2**	**5**	0	100	27	*R*
3	**2**	**5**	−20	100	33	*R*
4	**2**	**6**	0	100	12	*R*
5	**3**	**5**	0	48	7	*S*

[a] Reaction conditions: $P(H_2)$ = 100 atm; cat.: 0.047 mmol; olefin/cat. = 10; solvent: CH_2Cl_2 (10 ml); reaction time 120 h.

[b] The *ee* and the configuration of **4** were inferred on the basis of the specific rotation values reported in Ref. [2].

MS (70 eV): *m/z* (%) 216 (24) $[M]^+$, 201 (100) $[M–CH_3]^+$.

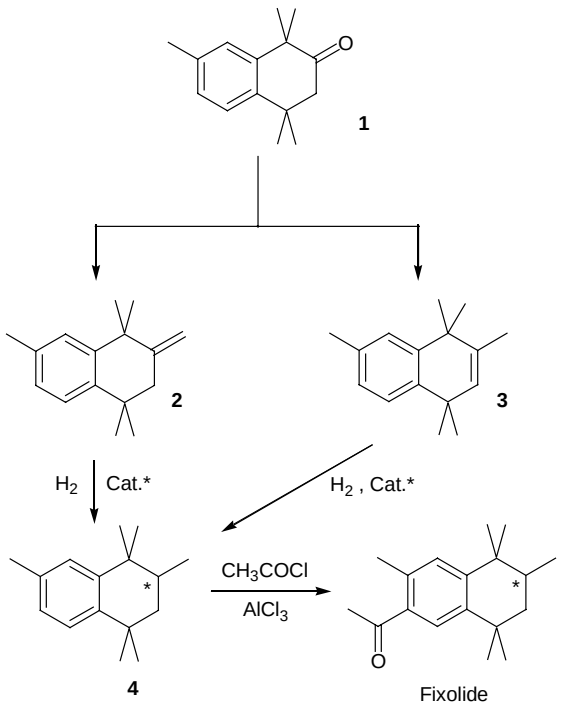
3. Results and discussion

The major steps of the synthetic scheme devised are shown in Scheme 1.

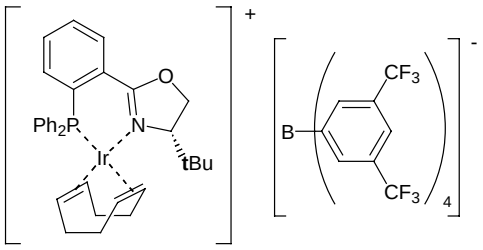
From ketone **1** well-established synthetic methodologies lead to the two prochiral olefins **2** and **3**. The key intermediate is the saturated benzocycloalkane **4** which can be obtained by asymmetric hydrogenation of either olefin **2** or olefin **3**. In particular, the study of the asymmetric hydrogenation of olefin **2** appeared us very fascinating. Upon acetylation **4** leads directly to Fixolide [16].

First, a Wittig reaction was employed to convert ketone **1** into the exocyclic olefin **2**. This step deserves some comments. As a matter of fact, under the classical Wittig conditions (i.e. using *n*-BuLi in combination with $[Ph_3PCH_3]Br$ [17]) **2** was obtained in ca. 18% yield, whereas using the method developed by Corey [18,19] (i.e. using $[Ph_3PCH_3]Br$/NaH in dimethylsulfoxide) yields of up to 89% were obtained. On the other hand, olefin **3** was synthesised from **1** in two steps: (i) reaction of **1** with MeLi followed by hydrolytic treatment, and (ii) dehydration of the intermediate alcohol in acidic conditions [20]. The reaction affords a mixture of olefins **2** and **3**, from which **3** crystallized on standing (70% yield).

It is generally accepted that, in order to obtain good enantioselectivities in asymmetric hydrogenation, it is desiderable the presence of some functional groups able



Scheme 1.



5

Fig. 2. Chemical structure of catalyst **5**.

to strengthen the interaction between the substrate and the metal centre on the olefin molecule [21–23]. Nevertheless, particularly remarkable results have been obtained in the 1990s by different research groups using early or late transition-metal catalysts [15,24,25,26].

We considered particularly well suited to our case the system devised by Pfaltz who obtained very interesting results in the asymmetric hydrogenation of unfunctionalised olefins using iridium-cyclooctadiene cationic complexes with chiral phosphinooxazoline ligands $[Ir(COD)((S)\text{-PHOX})]^+ X^-$ such as **5** [COD = 1,5-cyclooctadiene, PHOX = (*S*)-4-*tert*-butyl-2-(2-diphenylphosphanyl-phenyl)-4,5-dihydro-oxazole, X^- = tetrakis[3,5-bis(trifluoromethyl)-phenyl]borate] (Fig. 2) [15].

Moreover, the good asymmetric inductions obtained by Takaya in the hydrogenation of 1-methylene-2,3-benzocycloalkanes stimulated us to also test his catalytic system prepared *in situ* by combining $[Rh(COD)_2I]$ with BINAP [25].

The data relevant to the most significant results obtained in the hydrogenation experiments are reported in Table 1. Regardless the catalyst employed, both olefins appeared rather resistant to hydrogenation and in order to obtain high substrate conversions it was necessary to use high catalyst loadings (substrate/cat. = 10), high $P(H_2)$ (100 atm) and long reaction times (up to 120 h). Using catalyst **5** at 20 °C, the hydrogenation of olefin **2** proceeds affording the expected hydrogenation product with moderate asymmetric inductions (*ee* of 24%). On lowering the temperature to 0 °C, and then further to −20 °C, the enantioselectivity increased up to 33%. On further lowering the temperature, the reaction rate becomes sluggish. With the same olefin under comparable reaction conditions, the system $[Rh(COD)_2I]$/(*R*)-BINAP **6** (BINAP:Rh = 2:1) displays an alike reactivity, but the asymmetric induction is substantially lower (compare entries 2 and 4 of Table 1).

As it emerges from the results reported in Table 1, using $[Ir(COD)((S)\text{-PHOX})]^+$ the configuration of prevailing enantiomer is not the sought (*S*), but the less useful (*R*); this would not be a problem since among the advantages offered by asymmetric catalysis there is the possibility of get the desired stereomer by a suitable choice of the ligands configuration [21].

The hydrogenation of olefin **3** turned out to be even more challenging: as a matter of fact, whereas at 0 °C complete

hydrogenation of **2** is obtained by ca. 120 h, in the same time the hydrogenation of **3** yields only 48% of saturated product. Most badly, the asymmetric induction is only 7%. It is worth noting that the hydrogenation of olefin **3** leads to (*S*)-**4**. These results are in accordance with the general trend found by Takaya [25], who observed that endo olefins are hydrogenated more slowly than the exo ones, and that the hydrogenation products have opposite absolute configuration.

The low reactivity of olefins **2** and **3** is probably due to the steric hindrance induced by the methyl groups present on the cyclohexane ring. As suggested by Takaya [25], coplanarity between the C=C bond and the aromatic ring might play an important role in enhancing the asymmetric induction, though the reason of this fact is not clear; accordingly, the moderate enantioselectivity obtained could be tentatively ascribed to the lack of coplanarity between C=C bond and benzene ring in both olefins **2** and **3**. On the other hand, olefins **2** and **3** are different from the substrates studied by Takaya or Pfaltz in two aspects: (i) they suffer from steric hindrance which might make the substrate coordination to the metal centre particularly troublesome; (ii) the double bond is not conjugated with the aromatic ring.

4. Conclusions

Following the approach devised, the new olefins **2** and **3** have been synthesised in good yields. The asymmetric hydrogenation of the olefins turned out to be the most challenging task. The catalysts used allowed to obtain the saturated intermediate **4** in moderate *ee* (maximum 33%) which cannot be considered satisfactory. It is to point out that in the literature there are no examples of asymmetric hydrogenation of substrates similar to **2** and **3**, i.e. unfunctionalised, highly hindered cyclic olefins, where the C=C bond is not conjugated with the aromatic ring. However, the results obtained are promising and suggest that the process based on the hydrogenation of the substrate **2** could be of practical interest allowing the synthesis of (*S*)-Fixolide in few simple steps. Accordingly, it is necessary to achieve better asymmetric inductions by developing more efficient or more specialized catalytic systems for the hydrogenation of challenging substrates such as **2**.

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