Pergamon

Tetrahedron: *Asymmetry* 13 (2002) 2193–2195

TETRAHEDRON: *ASYMMETRY*

Asymmetric catalysis in fragrance chemistry: a new synthesis of Galaxolide®

Alessandra Ciappa, Ugo Matteoli and Alberto Scrivanti*

Dipartimento di Chimica, Università di Venezia, Dorsoduro 2137, I-30123 Venezia, Italy

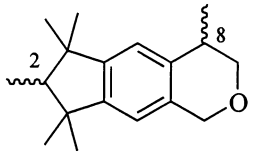
Received 22 August 2002; accepted 3 September 2002

Dedicated to the memory of Carlo Botteghi

Abstract—A new synthesis of the olfactorally active stereoisomers of the musk odorant Galaxolide® is reported. The key step is the ruthenium-catalysed asymmetric hydrogenation of an α-aryl acrylic acid: asymmetric inductions up to 89% have been achieved using a catalytic system prepared in situ by mixing $[Ru(benzene)Cl_2]_2$ with (*S*)-BINAP.

Galaxolide® (1,1,2,3,3,8-hexamethyl-1,2,3,5,7,8-hexahydro-6-oxacyclopenta[*b*]naphthalene, see Fig. 1)[1] is an important powerful musk odorant. In the Galaxolide® molecule, the C-2 and C-8 centres are stereogenic, and recently, Frater and co-workers[2] have established that the strong musk odour is due only to the (8*S*,2*S*)- and (8*S*,2*R*)-diastereomers, while the pair of (8*R*,2*S*)- and (8*R*,2*R*)-isomers is almost odourless.

Even if today almost all synthetic fragrances are marketed as racemates, in the future it will be advisable to develop new syntheses leading only to the olfactorally active stereoisomers. Environmental preservation will be the driving force because most fragrances are almost non-biodegradable and the introduction of stereoisomers with no olfactory activity into the environment should be minimised. For example, as far as Galaxolide® is concerned, it has been found in surface waters



Galaxolide ®: 1,1,2,3,3,8-Hexamethyl-1,2,3,5,7,8-hexahydro-6-oxa-cyclopenta[*b*]naphthalene

Figure 1. Chemical structure of Galaxolide®.

at considerable concentrations (up to the μg/L-level),[3] and it has a significant tendency to be bioaccumulated in aquatic species.[4]

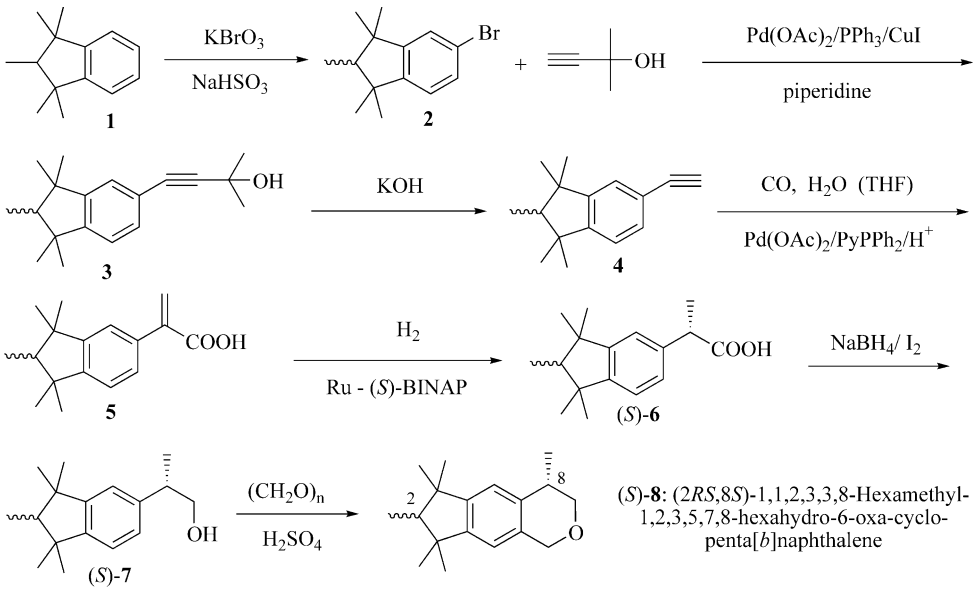
Frater and co-workers[2] have already disclosed a synthetic route allowing the preparation of all four stereoisomers of Galaxolide®. However, their stoichiometric approach involves some steps that are not viable on an industrial scale. Thus, we wish to report herein a practical catalytic process for the synthesis of the epimers of Galaxolide® which have olfactory activity (see Scheme 1).

As in the IFF synthesis of Galaxolide®,[5] the starting material is pentamethylindane **1**,[6] which upon treatment with $KBrO_3/NaHSO_3$[7] afforded 5-bromo-1,1,2,3,3-pentamethylindane **2**.[8] Total selectivity in the preparation of **2** can be achieved by keeping the conversion of **1** under 85%; owing to the large difference in the boiling points of **1** and **2**, unreacted **1** can be easily recovered.

$Pd(OAc)_2/CuI/PPh_3$-catalysed coupling of **2** with 2-methylbut-3-yn-2-ol in piperidine[9] then gave the protected alkyne **3**.[10] This compound does not need to be isolated, but, after removal of piperidine and its hydrobromide, treatment of crude **3** with KOH in isopropanol[11] affords 5-ethynyl-1,1,2,3,3-pentamethylindane **4**[12] in an overall yield of 70% after chromatographic purification (silica gel, hexane). Hydrocarbonylation of **4** in the presence of $Pd(OAc)_2/PyPPh_2/CH_3SO_3H$[13,14] then afforded the α-arylpropenoic acid **5**[15] in near-quantitative yield.

* Corresponding author. Tel.: +39 04 12348903; fax: +39 04 12348572; e-mail: scrivant@unive.it

0957-4166/02/$ - see front matter
PII: S0957-4166(02)00538-4



Scheme 1.

Asymmetric hydrogenation of **5** in the presence of a Ru/BINAP catalyst allows the formation of the 2-arylpropanoic acid **6**[16] in ca. 90% isolated yield. The use of (*S*)-BINAP gave (*S*)-(+)-**6** with enantioselectivity up to 89% (see below). The two last steps of the synthesis involved: i) the reduction of **6** to the alcohol **7**[17] under mild conditions by treatment with $NaBH_4/I_2$[18] (yield: 95%); and ii) final ring closure with paraformaldehyde in the presence of H_2SO_4[2,5] leading to the desired pair of epimers of Galaxolide® in 78% yield.

The key step in the process is the enantioselective hydrogenation of the 2-arylpropenoic acid **5**. The asymmetric hydrogenation of this type of substrate has received much attention owing to its relevance in the asymmetric synthesis of 'profens' (an important class of NSAI drugs). Excellent results have been achieved using ruthenium dicarboxylate complexes with atropisomeric diphosphines such as BINAP.[19–21] For an initial evaluation of the practical feasibility of the proposed synthetic scheme, we thought it convenient to employ a catalytic system prepared by mixing $[Ru(benzene)Cl_2]_2$ with (*S*)-BINAP in situ (Ru/BINAP = 1/1).[22]

The data from a few of the most significant experiments are reported in Table 1 together with the reaction conditions. In methanol at a substrate/catalyst ratio of 300 the hydrogenation requires less than 24 h to reach completion affording the requisite propanoic acid **6** in quantitative yield. Owing to the presence of two stereogenic centres in the molecule, **6** may form as a mixture of four possible stereoisomers, that is as a mixture of two diastereomeric pairs of enantiomers. Inspection of the ^{13}C NMR spectrum reveals that, independently of the actual hydrogenation conditions, the resonance of the methyl group of the propanoic acid moiety is split into two singlets of equal intensity at 18.22 and 18.29 ppm. The equal intensity of the two signals indicates that the two diastereomers are formed in a 1:1 ratio. This ratio is confirmed by the fact that also alcohol **7**, obtained by reducing **6** with $NaBH_4/I_2$, is a 1:1 mixture of diastereomers (also for **7** the diastereomeric composition is deduced from the ^{13}C NMR spectrum[2]).

Since (according to the ^{13}C NMR data) **7** has the same diastereomeric composition of the alcohol synthesised by Frater, we have used the specific rotation value and the optical rotation–configuration correlation reported in Ref. 2 to evaluate the diastereomeric purity of **7** and hence the enantiomeric purity of **6** (see Table 1).

The enantioselectivity achieved is very close to that obtained in the hydrogenation of other α-arylpropenoic acids[19–21] and appears particularly promising owing to

Table 1.

Run	*T* (°C)	*P*(H_2) (atm)	**6** Yield (%)	[a]$[\alpha]_D^{25}$	O.P. (%)[b]	Config.
1	50	100	91	+2.4	–	*S*
2	25	100	93	+25.5	62	*S*
3	0	100	94	+36.4	89	*S*
4	0	50	91	+34.2	83	*S*

Reaction conditions: substrate: 2.33 mmol; NEt_3: 2.33 mmol; solvent: methanol (15 mL); $[Ru(C_6H_6)Cl_2]_2$: 0.0078 mmol; (*S*)-BINAP. 0.0078 mmol; substrate/Ru = 300; *t* = 24 h.

[a] (*c* 1.0, $CHCl_3$)

[b] Determined on the alcohol **7**, by assuming $[\alpha]_{D\ max}^{21} = -5.8$ from Ref. 2.

the minimal optimisation of the catalytic system at present. The data reported in Table 1 adequately illustrate the main features of the asymmetric hydrogenation. As already observed for other substrates of this type,[21] the enantioselectivity is strongly dependent on the reaction temperature: while at 50°C almost no asymmetric induction is attained, on lowering the temperature to 25°C, and further to 0°C, the enantioselectivity increases up to 89%. By comparing the results of runs 3 and 4, it emerges that high $P(H_2)$ are necessary in order to achieve high asymmetric inductions.[21] Finally, it is worth noting that, since the diastereomers form in a 1:1 molar ratio, it appears that the configuration of C-2 in the indanyl moiety does not influence the stereoselectivity of the hydrogenation, probably owing to the distance between the two stereogenic centres.

Upon treatment with paraformaldehyde in the presence of H_2SO_4[2] a sample of (*S*)-(−)-**7** of enantiomeric purity 89% afforded (*S*)-(−)-**8** having $[\alpha]_D^{21} = -16.0$ (enantiomeric purity = 88% calculated according to the rotation data reported in Ref. 2) as a white solid in 78% yield after chromatographic purification.

In conclusion, the results reported here indicate the practical feasibility of our catalytic approach to the synthesis of the olfactorally active couple of epimers of Galaxolide®, as a matter of fact: (i) all of the reactions involved proceed under mild conditions affording the requisite products in high yield and with high selectivities; (ii) the enantioselectivity of the asymmetric hydrogenation already appears to be satisfactory for application in the fragrance field and, in any case, further improvement is possible by an appropriate optimisation study.

Acknowledgements

This work has been performed with the Financial Support of the MIUR (Cofin 2000).

References

1. Galaxolide® is a trademark registered by International Flavour and Fragrances.
2. Frater, G.; Muller, U.; Kraft, P. *Helv. Chim. Acta* **1999**, *82*, 1656.
3. Heberer, T.; Gramer, S.; Stan, H. *J. Acta Hydrochim. Hydrobiol.* **1999**, *27*, 150.
4. Franke, S.; Meyer, C.; Heinzel, N.; Gatermann, R.; Hühnerfuss, H.; Rimkus, G.; König, W. A.; Francke, W. *Chirality* **1999**, *11*, 795.
5. Specker, M. A.; Theimer, E. T. (to International Flavour and Fragrances) US Patent 4,162,256, 1986.
6. Spoelstra, D. B.; Weber, S. H.; Kleipool, R. J. C. *Recl. Trav. Chim. Pays Bas* **1963**, *82*, 1100.
7. Kikuchi, D.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **1998**, *63*, 6023.
8. Compound **2**: pale yellow oil; bp 80°C (0.1 torr); ^{1}H NMR ($CDCl_3$): δ 0.97 (d, 3H, J=7.2 Hz, CH_3), 1.03 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 1.23 (s, 6H, CH_3), 1.84 (q, 1H, CH), 7.00 (d, 1H, J=7.0 Hz, arom), 7.26 (br s, 1H, arom), 7.25 (dd, 1H, J=7.0 and 2.0 Hz, arom); ^{13}C NMR ($CDCl_3$): δ 8.47 (1C), 25.70 (1C), 25.75 (1C), 28.84 (1C), 28.86 (1C), 44.44 (1C), 44.85 (1C), 54.21 (1C), 120.21 (1C, CBr), 124.27 (1C), 125.90 (1C), 129.61 (1C), 150.24 (1C), 153.68 (1C); MS (70 eV): m/z (%) 266 (40) [M+].
9. See for example: Menchi, G.; Scrivanti, A.; Matteoli, U. *J. Mol. Catal. A* **2000**, *152*, 77.
10. Formation of **3** was confirmed by GC–MS: MS (70 eV): m/z (%) 270 (38) [M+].
11. Melissaris, A. P.; Litt, M. H. *J. Org. Chem.* **1994**, *59*, 5818.
12. Compound **4** was obtained as pale yellow oil; ^{1}H NMR ($CDCl_3$): δ 0.96 (d, 3H, J=7.2 Hz, CH_3), 1.03 (s, 6H, CH_3), 1.24 (s, 6H, CH_3), 1.82 (q, 1H, CH), 3.03 (s, 1H, CH), 7.08 (d, 1H, J=7.6 Hz, arom), 7.20 (br s, 1H, arom), 7.25 (dd, 1H, J=7.6 and 2.0 Hz, arom); ^{13}C NMR ($CDCl_3$): δ 8.41 (1C), 25.62 (1C), 25.72 (1C), 28.77 (1C), 28.83 (1C), 44.53 (1C), 44.68 (1C), 54.05 (1C), 75.98 (1C), 84.39 (1C), 120.20 (1C), 122.54 (1C), 126.46 (1C), 130.74 (1C), 151.31 (1C), 152.25 (1C); MS (70 eV): m/z (%) 212 (25) [M+].
13. Drent, E.; Arnoldy, P.; Budzelaar, P. H. M. *J. Organomet. Chem.* **1993**, *455*, 247.
14. Scrivanti, A.; Matteoli, U. *Tetrahedron Lett.* **1995**, *36*, 9015.
15. Compound **5** was obtained as a white solid after chromatographic purification (silica gel, hexane/ethyl acetate: 70/30); ^{1}H NMR ($CDCl_3$): δ 0.97 (d, 3H, J=7.2 Hz, CH_3), 1.05 (s, 6H, CH_3), 1.249 (s, 3H, CH_3), 1.250 (s, 3H, CH_3), 1.81 (q, 1H, CH), 5.96 (d, 1H, J=1.2 Hz, CH), 6.44 (d, 1H, J=1.2 Hz, CH), 7.16 (d, 1H, J=8.0 Hz, arom), 7.22 (br s, 1H, arom), 7.28 (dd, 1H, J=8.0 and 2.0 Hz, arom), 12.50 (br s, 1H, COOH); ^{13}C NMR ($CDCl_3$): δ 8.45 (1C), 25.76 (1C), 25.86 (1C), 28.92 (2C), 44.53 (1C), 44.67 (1C), 54.31 (1C), 122.24 (1C), 122.74 (1C), 127.01 (1C), 128.37 (1C), 134.57 (1C), 141.15 (1C), 151.24 (1C), 151.70 (1C), 172.39 (1C); MS (70 eV): m/z (%) 258 (18) [M+].
16. Compound **6** was obtained as pale yellow solid; ^{1}H NMR ($CDCl_3$): δ 1.00 (d, 3H, J=7.2 Hz, CH_3), 1.07 (s, 6H, CH_3), 1.27 (br s, 6H, CH_3), 1.50 (d, 3H, J=7.2 Hz, CH_3), 1.87 (q, 1H, CH), 3.74 (q, 1H, CH), 7.08–7.20 (m, 3H, arom), 12.45 (br s, 1H, COOH); ^{13}C NMR ($CDCl_3$): δ 8.47 (1C), 18.22 (0.5C), 18.29 (0.5C), 25.84 (1C), 25.87 (1C), 28.93 (1C), 28.96 (1C), 44.40 (1C), 44.69 (1C), 45.36 (1C), 54.34 (1C), 121.85 (0.5C), 121.90 (0.5C), 122.68 (1C), 125.86 (0.5C), 125.90 (0.5C), 137.94 (0.5C), 137.96 (0.5C), 150.53 (1C), 151.77 (1C), 181.15 (1C); MS (70 eV): m/z (%) 260 (14).
17. For the characterisation of **7**, see Ref. 2.
18. Bhaskar Kant, J. V.; Periasamy, M. *J. Org. Chem.* **1991**, *56*, 5964.
19. Nojori, R.; Otha, M.; Hsiao, Y.; Kitamura, M.; Otha, T.; Takaya, H.; Ohkuma, T. *J. Am. Chem. Soc.* **1986**, *108*, 7117.
20. Otha, T.; Takaya, H.; Kitamura, M.; Nagai, K.; Nojori, R. *J. Org. Chem.* **1987**, *52*, 3176.
21. Ohkuma, T.; Kitamura, M.; Nojori, R. In *Catalytic Asymmetric Synthesis*; 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; p. 21.
22. Matteoli, U.; Beghetto, V.; Scrivanti, A. *J. Mol. Catal. A* **1999**, *140*, 131.