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Dissimilar reactivities of diastereomeric 1,1,1-trifluoro-3-(4-methoxyphenyl)-2,3-diphenylpropan-2-ols in an attempted elimination reaction

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Abstract

Attempted dehydration of a diastereomeric mixture of 1,1,1-trifluoro-3-(4-methoxyphenyl)-2,3-diphenyl-propan-2-ols (**6a**) with thionyl chloride in the presence of pyridine afforded the rearranged derivative **8** as the main product and only small amounts of the expected olefins (**4**, **5**). Similar treatment of (2*RS*,3*RS*)-**6a** gave the rearrangement product **8** exclusively, while transformation of (2*RS*,3*SR*)-**6a** resulted in the formation of compounds **4**, **5** and **8**. The different reactivity of the diastereomers is rationalised. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Diastereospecific reaction; Trifluoromethyl group substituent effect; Field effect; Wagner–Meerwein type rearrangement of 1-(trifluoromethyl)-1,2,2-triarylethanols; Destabilised carbocation

1. Introduction

Recently we reported a new practical synthesis of panomifene (**1**, EGIS-5650, GYKI-13504), a mammary-tumour inhibiting antiestrogen [1]. We have also discussed there the acid-catalysed dehydration of diastereomeric 3,3,3-trifluoro-1-(4-methoxyphenyl)-1,2-diphenylpropan-1-ols **2** and **3** demonstrating that either alcohol affords practically the same 7.7:1 ratio of the *E* (**4**) and *Z* (**5**) isomers of the olefinic product (Scheme 1). The stereoselectivity of this dehydration has been explained by different stabilities of the conformers of the common carbenium ion intermediate. The cation stabilising effect of the *p*-methoxyphenyl group is assisted by the electron donating field effect of the nearly parallel adjacent phenyl group in conformer **A** contrary to conformer **B** bearing the electron-withdrawing trifluoromethyl group in the same position.

In continuation of these studies, we report here the results obtained in the course of attempted dehydration of the diastereomeric alcohols **6**, which differ from the pair **2** and **3** in the position of the hydroxy group. The observed unexpected reactivity is rationalised also by the interaction of the neighbouring aryl rings, which helps to stabilise a cationic centre adjacent to a trifluoromethyl group. This interaction obviously has a crucial effect on the outcome of cationic reactions of 1,1,1-trifluoro-2,3,3-triarylpropanols [1,2].

2. Results and discussion

A mixture of the diastereomeric alcohols **6a** was prepared by the reaction of ketone **7a** [2] with phenylmagnesium bromide (Scheme 2). Dehydration of this alcohol mixture proved difficult. The starting material was recovered when using the same conditions as for dehydration of alcohols **2** and **3** (hydrochloric acid in refluxing ethanol). Related α-(trifluoromethyl)triarylethanols were dehydrated with thionyl chloride in pyridine [3]. When using these reagents in refluxing chloroform the unexpected rearrangement product **8** was obtained from **6a** in 32% yield as a practically pure single diastereomer (for the assignment of the stereostructure see below). Olefins **4** and **5** as minor products could be

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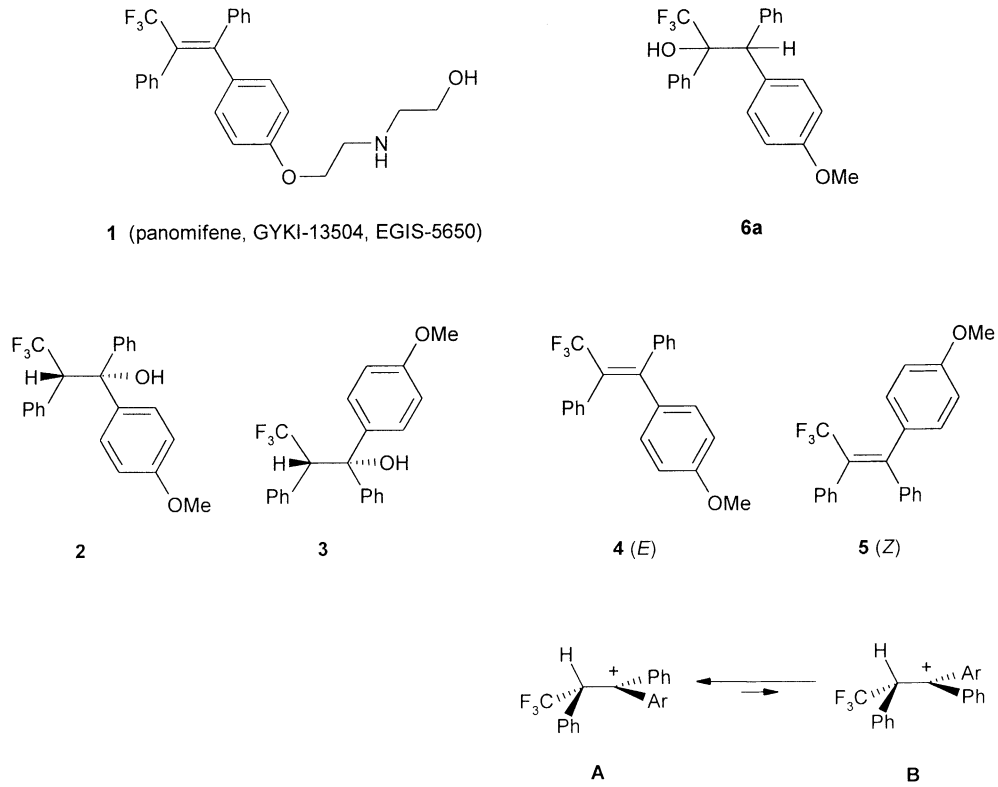
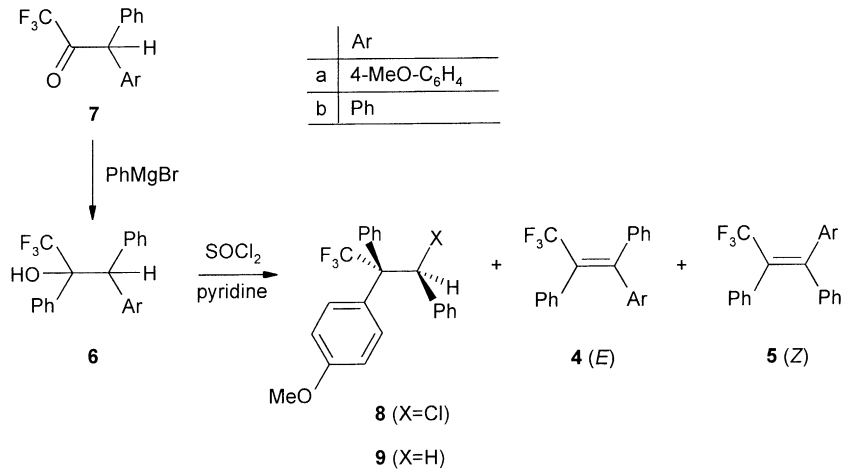


Scheme 1.



Scheme 2.

detected in the mother liquor by TLC together with several unidentified compounds. Triphenylethanol **6b** was also treated with thionyl chloride in refluxing chloroform in the presence of pyridine. No rearrangement was observed in this case, only elimination occurred and olefin **4b** (**5b**) was obtained in 85% yield.

The constitution of chloride **8** is based on spectral data and on its transformation to the benzyl compound **9** by catalytic hydrogenation. The configuration of compound **8** was determined by single crystal X-ray diffraction analysis (Fig. 1).[1] Formation of compound **8** can be explained by Wagner–Meerwein rearrangement of alcohol **6a** (Scheme 3). The *p*-methoxyphenyl group migrates towards the cationic centre destabilised by the trifluoromethyl substituent [4]. The new carbocation stabilises itself by recombination with

[1] Crystallographic data for the structure reported in this paper have been deposited at the Cambridge Crystallographic Data Centre. Copies of the data can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

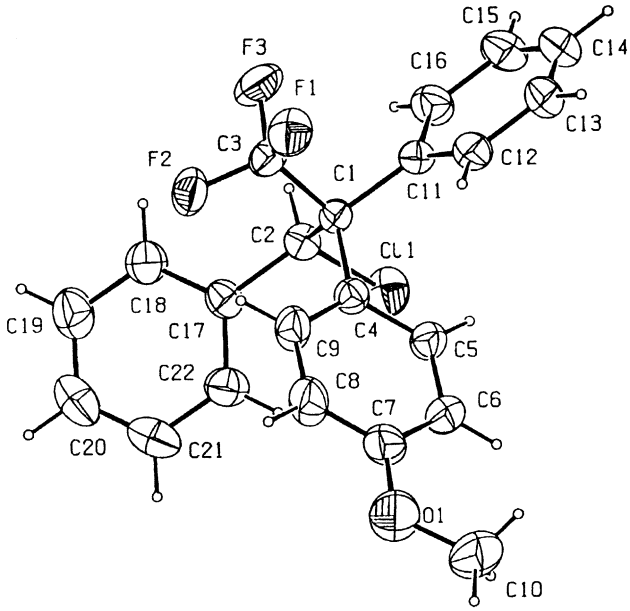


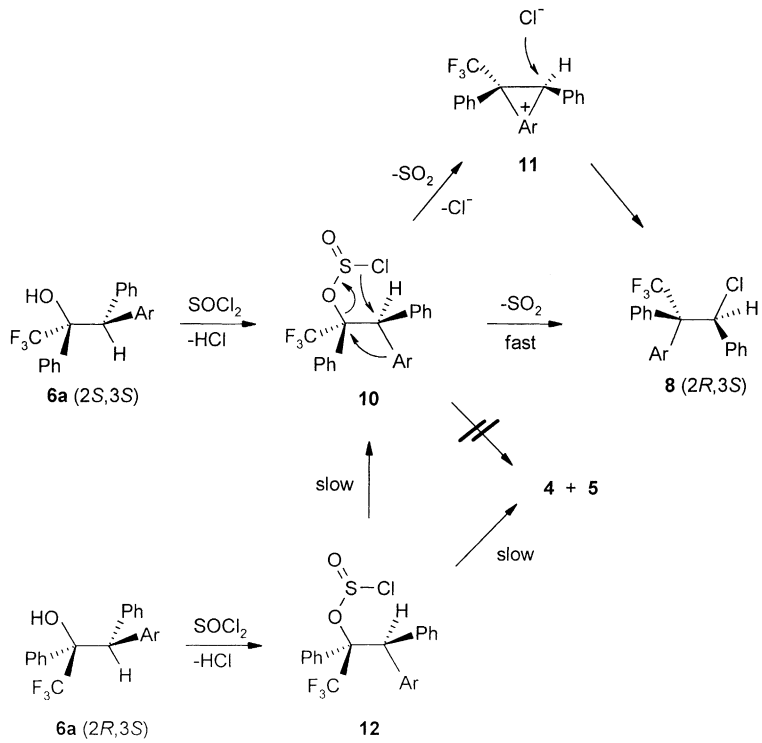
Fig. 1. Perspective view and atom labelling of the crystal structure of (2*RS*,3*SR*)-3-chloro-1,1,1-trifluoro-2-(4-methoxyphenyl)-2,3-diphenylpropane (**8**). Atomic displacement ellipsoids represent 50% probabilities.

the chloride anion. Similar rearrangements resulting in the separation of the positive charge apart from the trifluoromethyl group are known from the literature [5–7].

In order to study the effect of the configuration of **6a** on the outcome of the reaction with thionyl chloride in refluxing chloroform in the presence of pyridine, the diastereoisomers of **6a** were separated. The structures of the individual diastereoisomers were determined by single crystal X-ray diffraction analysis (Fig. 2). As indicated by the ^{1}H NMR spectra, both diastereoisomers exist predominantly in the same conformations in solution as in the crystalline state. Since the bulky benzene rings on the neighbouring carbon atoms are nearly parallel (propeller-like arrangement, Fig. 2), their mutual anisotropic effects result in diamagnetic shifts of the aromatic proton signals. This shift of the protons of the *p*-methoxyphenyl ring is characteristic of the 2*RS*,3*RS* isomer of **6a**. Similar diamagnetic shifts of the protons of the *para*-substituted benzene ring were observed for the diastereoisomeric pairs of 1,1,2-triarylethanes, 1,1,2-triarylethanols [8,9] and trifluoromethyl substituted 1,1,2-triarylethanols (**2**, **3**) [1].

The two diastereomers of **6a** reacted in a significantly different manner when treated with thionyl chloride in refluxing chloroform in the presence of catalytic pyridine. After refluxing for 2 h, the 2*RS*,3*RS* diastereomer gave exclusively compound **8** as a single diastereomer in 76% yield (isolated). Conversion of the 2*RS*,3*SR* diastereomer was much slower and resulted in a product mixture containing olefins **4**, **5** (36%) and the rearranged product **8** (31%).

These experiments suggest that the 2*SR*,3*SR* diastereomer of **6a** possesses the structure required for rearrangement to **8** (Scheme 3). The observation that triphenylethanol **6b** did not afford a rearranged product indicates that the assistance of the *p*-methoxyphenyl group in the departure of the leaving group is essential for the rearrangement to take place. The formation of a single diastereomer **8** can be explained by a



Scheme 3.

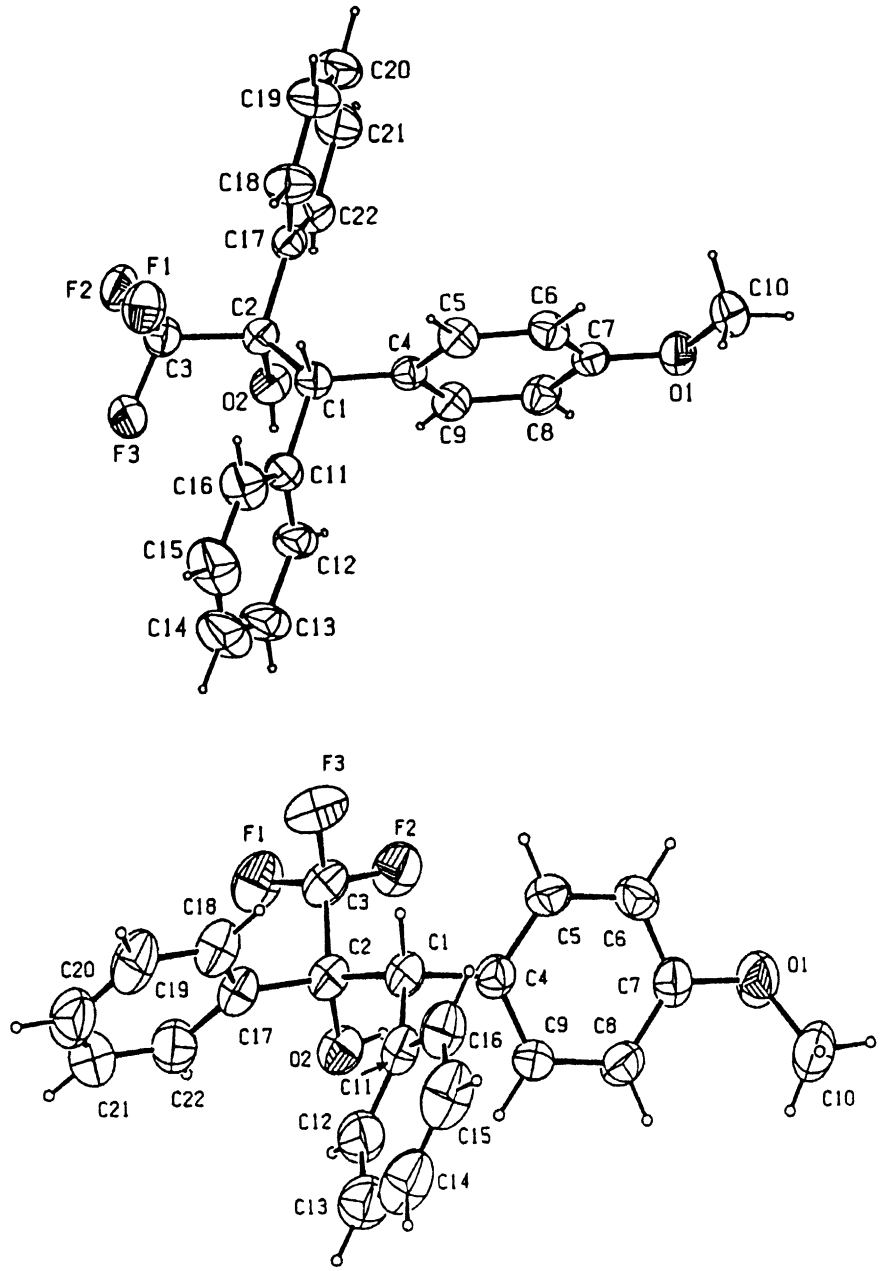


Fig. 2. Perspective view and atom labelling of the crystal structure of the 2*S*,3*S* and 2*R*,3*S* enantiomers (top and bottom, respectively) of 1,1,1-trifluoro-3-(4-methoxyphenyl)-2,3-diphenylpropan-2-ol diastereomeric racemates (**6a**). Atomic displacement ellipsoids represent 40 and 50% probabilities, respectively.

concerted transformation of intermediate **10** to the final product **8** or to the bridged phenonium ion **11**, which can be opened by the chloride anion only from the less shielded side.

The dissimilar reactivities of the diastereomers **6a** can be explained by assuming a transition state, in which C–OSOCl bond breaking somewhat precedes C–Ar bond making, developing thereby some positive charge at the central carbon atom. A very strong demand for stabilisation in the transition state of the formation of α-trifluoromethyl cation is expected. The stabilisation of the carbenium ion by the α-aryl substituent is known to be assisted by the electron donating field effect of the adjacent β-aryl group, provided that the two benzene rings on the neighbouring carbon atoms are in gauche relation, resulting a nearly parallel, propeller-like arrangement [1,10].

Comparison of the antiperiplanar conformations of intermediates **10** and **12** shows (Scheme 3) that only the intermediate **10** derived from 2*S*,3*S*-**6a** exhibits α- and β-phenyl groups in the required arrangement permitting more effective stabilisation of the partial positive charge in the transition state of the rearrangement, which results in a fast transformation. In the case of intermediate **12** derived from the 2*R*,3*S* diastereomer of **6a** the steric requirements for a

similar stabilisation are missing. However, the slow formation of **8** from 2*RS*,3*SR*-**6a** indicates that, prior to the rearrangement, a slow epimerisation is taking place at the 2-position. A similar procedure, racemisation of optically active α-trifluoromethyl triflate, is known from the literature [10]. In addition to the slow epimerisation-rearrangement sequence a competing elimination process leading to **4** and **5** is also occurring in this case.

3. Experimental section

Melting points were determined on a Büchi 535 apparatus. IR spectra were recorded on an aspect 2000 computer controlled Bruker IFS-113v vacuum optic FT spectrometer, using KBr pellets for solids or liquid films. NMR spectra were run on Bruker WM-250 FT, Varian Gemini-200 and Varian Unity Inova 400 spectrometers. Mass spectra were obtained by EI (70 eV, evaporation temperature 120°C) using a KRATOS MS 902 mass spectrometer.

3.1. Structure determinations by X-ray crystallography

Intensity data were collected at room temperature on an Enraf Nonius CAD4 diffractometer. The structures were solved by direct methods [12,13] (see footnote).

8: $C_{22}H_{18}ClF_3O$, $M = 390.81$, colourless, prism, size: 0.50 mm × 0.30 mm × 0.20 mm, monoclinic, space group *Cc*; $a = 13.555(2)$ Å, $b = 21.069(4)$ Å, $c = 7.515(1)$ Å, $\beta = 100.56(1)^\circ$, $V = 1849.0(5)$ Å^3, $Z = 4$, $D_{calc} = 1.404$ Mg/m^3. Refinement [13] on F^2 values for all non-hydrogen atoms yielded $R1 = 0.0397$ and $wR2 = 0.0952$ for 5219 [$I > 2\sigma(I)$] observations, $R1 = 0.0725$ and $wR2 = 0.1029$ for all 8079 data.

6a (2*RS*,3*RS*): $C_{22}H_{19}F_3O_2$, $M = 372.37$, colourless, prism, size: 0.60 mm × 0.50 mm × 0.45 mm, triclinic, space group $P\bar{1}$, $a = 9.605(1)$ Å, $b = 11.804(1)$ Å, $c = 17.356(1)$ Å, $\alpha = 90.27(1)^\circ$, $\beta = 102.62(1)^\circ$, $\gamma = 105.44(1)^\circ$, $V = 1846.8(3)$ Å^3, $Z = 4$, $D_{calc} = 1.339$ Mg/m^3. Refinement [13] on F^2 for all non-hydrogen atoms yielded $R1 = 0.0415$ and $wR2 = 0.1303$ for 5551 [$I > 2\sigma(I)$] observations, $R1 = 0.0454$ and $wR2 = 0.1338$ for all 6236 data.

6a (2*RS*,3*SR*): $C_{22}H_{19}F_3O_2$, $M = 372.37$, colourless, prism, size: 0.60 mm × 0.20 mm × 0.08 mm, monoclinic, space group $P2_1$, $a = 12.015(1)$ Å, $b = 6.206(1)$ Å, $c = 12.129(1)$ Å, $\beta = 92.38(1)^\circ$, $V = 903.62(18)$ Å^3, $D_{calc} = 1.369$ Mg/m^3. Refinement [13] on F^2 for all non-hydrogen atoms yielded $R1 = 0.0333$ and $wR2 = 0.0944$ for 3349 [$I > 2\sigma(I)$] and $R1 = 0.0361$ and $wR2 = 0.0968$ for all 3571 data.

*3.2. 1,1,1-Trifluoro-3-(4-methoxyphenyl)-2,3-diphenylpropan-2-ol (**6a**)*

A solution of 1,1,1-trifluoro-3-(4-methoxyphenyl)-3-phenylpropan-2-one (**7a** [2], 6.0 g, 20.4 mmol) in ether (30 ml) was added to a solution of phenylmagnesium bromide, prepared from magnesium (0.98 g, 40 mmol) and bromobenzene (4.2 ml, 6.28 g, 40 mmol) in ether (40 ml). The mixture was stirred for 30 min at ambient temperature and saturated aqueous ammonium chloride solution (40 ml) was added. The ethereal solution was washed with brine, dried over magnesium sulphate and evaporated to dryness. The residual oil was distilled in vacuo (0.2 Hgmm, vapour temperature 140–145°C) to give a 2:1 diastereomeric mixture of alcohols (2*RS*,3*SR*)-**6a** and (2*RS*,3*RS*)-**6a** (6.5 g, 88%). 3.25 g of this oil was dissolved in hexane at ambient temperature. (2*RS*,3*SR*)-**6a** (1.48 g, diastereomeric purity ~90%) separated on standing, mp 139–140°C (hexane). 1H NMR ($CDCl_3$, 400 MHz) δ 7.60–6.90 (14H, m), 4.93 (1H, s), 3.75 (3H, s), 3.09 (1H, s). The mother liquor of this product was evaporated to dryness and the residue was dissolved in pentane at ambient temperature. (2*RS*,3*RS*)-**6a** (0.96 g, diastereomeric purity >98%) separated on standing, mp 108–109°C (pentane). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.60–7.10 (12H, m), 6.57 (2H, d, $J = 8.8$ Hz), 4.91 (1H, s), 3.62 (3H, s), 3.08 (1H, s).

*3.3. 1,1,1-Trifluoro-2,3,3-triphenylpropan-2-ol (**6b**)*

Compound **6b** was prepared as described above for **6a**, starting from 1,1,1-trifluoro-3,3-diphenylpropan-2-one (**7b** [2], 22.3 g, 84.4 mmol): yield 69.2%, b.p. 138–140°C (0.1 Hgmm), mp 134–135°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.60–6.95 (15 H, m), 4.97 (1H, s), 3.12 (1H, s). High resolution MS (EI) calcd for $C_{21}H_{17}F_3O$ (M^+) *m/z* 342.1231, found 342.1198.

*3.4. Reactions of 1,1,1-trifluoro-2,3,3-triarylpropan-2-ols (**6**) with thionyl chloride*

*3.4.1. 1,1,1-Trifluoro-3-(4-methoxyphenyl)-2,3-diphenylpropan-2-ol (**6a**, mixture of diastereomers)*

A solution of **6a** (mixture of diastereomers, 1.5 g, 4.0 mmol), thionyl chloride (3.0 ml, 1.83 g, 42 mmol) and pyridine (0.2 ml) in chloroform (15 ml) was refluxed for 2 h. The solvent was evaporated to dryness and the residue was triturated with methanol (5 ml) to give (2*RS*,3*SR*)-3-chloro-1,1,1-trifluoro-2-(4-methoxyphenyl)-2,3-diphenyl-propane (**8**, 0.5 g, 32%). Diastereomeric purity ~95%, mp 130–131°C (methanol). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.55–6.65 (14H, m), 6.08 (1H, s), 3.87 (3H, s). High resolution MS (EI) calcd for $C_{22}H_{18}ClF_3O$ (M^+) *m/z* 390.0998, found 390.0988.

*3.4.2. (2RS,3RS)-1,1,1-trifluoro-3-(4-methoxyphenyl)-2,3-diphenylpropan-2-ol [(2RS,3RS)-**6a**]*

A solution of (2*RS*,3*RS*)-**6a** (0.5 g, 1.3 mmol), thionyl chloride (1.0 ml, 0.61 g, 14 mmol) and pyridine (0.07 ml) in chloroform (5 ml) was refluxed for 2 h. The solvent was evaporated to dryness and the residue was triturated with methanol (5 ml) to give compound **8** (0.4 g, 76%,

diastereomeric purity ~95%) identical with the sample obtained above.

*3.4.3. (2RS,3SR)-1,1,1-trifluoro-3-(4-methoxyphenyl)-2,3-diphenylpropan-2-ol [(2RS,3SR)-**6a**]*

A solution of (2*RS*,3*SR*)-**6a** (0.5 g, 1.3 mmol), thionyl chloride (1.0 ml, 0.61 g, 14 mmol) and pyridine (0.07 ml) in chloroform (5 ml) was refluxed for 10 h. After evaporation to dryness the residue was separated by preparative TLC (repeated elutions with a mixture of hexane and ethyl acetate, 10:0.1) to give compound **8** (0.16 g, 31%, diastereomeric purity ~95%) identical with the sample obtained above, and a 92:8 mixture of olefins **4** and **5** (0.17 g, 36%) as indicated by GC measurements, the ^{1}H NMR spectrum and comparison with the spectra and GC of authentic samples [1].

*3.4.4. 1,1,1-Trifluoro-2,3,3-triphenylpropan-2-ol (**6b**)*

A solution of **6b** (1.0 g, 2.9 mmol), thionyl chloride (2.0 ml, 1.22 g, 28 mmol) and pyridine (0.1 ml) in chloroform (10 ml) was refluxed for 2 h. The solvent was evaporated to dryness and the residue recrystallised from methanol to give 3,3,3-trifluoro-1,1,2-triphenylpropene (0.80 g, 85%), mp 85–86°C, lit. [11] mp 83–85°C. High resolution MS (EI) calcd for $C_{21}H_{15}F_3$ (M^+) *m/z* 324.1126, found 324.1128.

*3.5. Catalytic hydrogenation of (2RS,3SR)-3-chloro-1,1,1-trifluoro-2-(4-methoxyphenyl)-2,3-diphenyl-propane (**8**)*

A solution of compound **8** (0.39 g, 1 mmol) in dichloromethane (10 ml) was hydrogenated in the presence of 10% palladium on charcoal (0.2 g) at atmospheric pressure and ambient temperature. The catalyst was filtered off, the filtrate evaporated to dryness and the residue crystallised from methanol to give 1,1,1-trifluoro-2-(4-methoxyphenyl)-2,3-diphenyl-propane (**9**, 0.30 g, 84%), mp 110–111°C. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.42–6.60 (14H, m), 3.80 (3H, s), 3.72 (2H, s). High resolution MS (EI) calcd for $C_{22}H_{19}F_3O$ (M^+) *m/z* 356.1388, found 356.1384.

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