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Enantioselectivity in the reduction of tricyclic hydroaromatic ketones by baker's yeast

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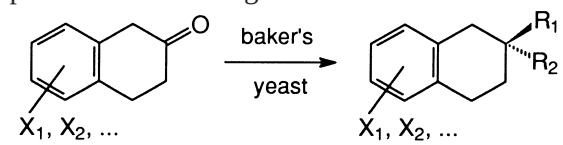
Abstract

Three benzo-2-tetralones were hydrogenated to the corresponding alcohols by non-fermenting baker's yeast. Satisfactory yields but modest enantioselectivities were observed. The prevalent enantioform of the benzo-2-tetralol was found to be in agreement with the predictive abstract model previously proposed for the enzymatic hydrogenation of aromatic ring substituted 2-tetralones.

1. Introduction

The possibility of obtaining optically active 2-tetralols **2** by baker's yeast reduction of the corresponding ketones has recently been explored in the case of 2-tetralones **1**, differing in their hydroxy/methoxy substitution at the aromatic ring.[1] The enantioselectivity of the reaction carried out under 'non-fermenting' conditions was found to be moderate and variable, with the exception of the conversion of 5-methoxy-2-tetralone (e.e. ≥98%, 87% yield). We showed that enantioselectivity resulted from the action of a single enzyme rather than from the competition between two or more dehydrogenases, thus allowing a simple abstract model to be developed relating the prevalent enantioform of the product **2** and its excess to the substitution pattern of the starting 2-tetralone **1**.[1]



1 $X_1, X_2, ... = OH, OMe$ **2** $R_1, R_2 = H, OH$

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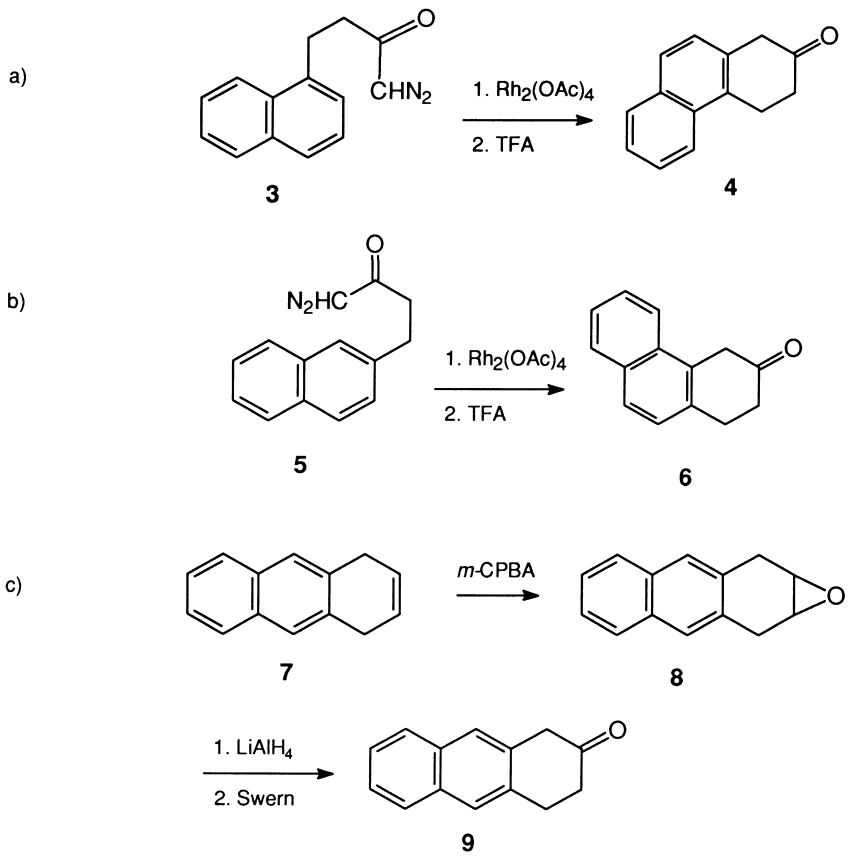
Although the microbial reduction of polycyclic hydroaromatic α-oxo compounds has been examined,[2] to our knowledge no analogous investigations have been performed on β-oxo derivatives. This situation, together with the possibility of extending our predictive model to tricyclic hydroaromatic ketones, prompted us to test the baker's yeast reduction of compounds **4**, **6** and **9**.

2. Results and discussion

3,4-Dihydrophenanthren-2(1*H*)-one **4**[3a] and 1,2-dihydrophenanthren-3(4*H*)-one **6**[3b] were prepared by rhodium(II)-catalyzed decomposition of α-diazoketones **3** and **5**, respectively, and subsequent acidic treatment of the reaction mixture with trifluoroacetic acid (Scheme 1a,b).[3] 3,4-Dihydroanthracen-2(1*H*)-one **9** was conveniently synthesized starting from 1,4-dihydroanthracene **7**, prepared in turn according to Jadot and Roussel[4] via the sequence reported in Scheme 1c.



Scheme 1.

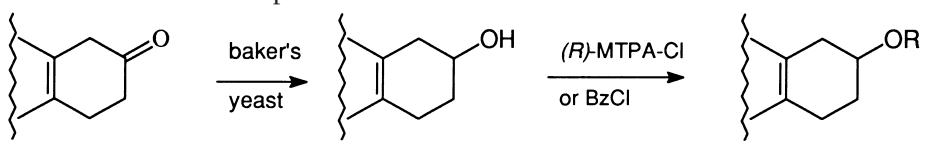
The conversion of ketones **4**, **6** and **9** into the corresponding alcohols **4a**, **6a** and **9a** by *Saccharomyces cerevisiae* was carried out under standard conditions (see Experimental). Benzo-2-tetralols were isolated by flash chromatography of the ether extract of the reaction medium; the purity of each compound was checked by TLC (three eluents) and the structure confirmed by NMR spectroscopy. The most abundant enantioform of each benzo-2-tetralol and its excess were determined through the ^{19}F NMR spectra of the corresponding (*S*)-MTPA esters **4b**, **6b** and **9b**, on the assumption that the CF_3 signal at higher field was due to the (*R*)-form. Although this empirical rule has been widely tested with 2-tetralols,[1]

Table 1
Reduction of ketones **4**, **6** and **9** using baker's yeast

Ketone	Prevalent alcohol ([a])	Isolated yield %	Enantiomeric ratio *R* : *S* ([a])
4	(*S*)-**4a**	75	14 : 86
6	(*R*)-**6a**	62	65 : 35
9	(*S*)-**9a**	58	44 : 56

([a]) See text for the analytical method used.

its application to Mosher's esters of benzo-2-tetralols was confirmed via a non-empirical chiroptical method.[5] Thus, the exciton coupled CD spectra of the benzo-2-tetralols benzoates **4c**, **6c** and **9c** were compared with those reported in the literature for the corresponding enantiopure compounds.[6–8] The results of all biotransformation experiments are summarized in Table 1.



4, 6, 9 **4a, 6a, 9a** R = (*S*)-MTPA : **4b, 6b, 9b**
R = C_6H_5-CO- : **4c, 6c, 9c**

The prevalent (*S*)-configuration of the alcohol **4a** was predictable on the basis of our model.[1] In fact, if one considers the minimal destabilizing interactions visualized when the molecule of the dihydrophenanthrenone **4**, as represented by its van der Waals surface, is lodged in the virtual boundaries of the dehydrogenase active site (Fig. 1a), the (*R*)-orientation appears to be disfavoured due to an overlap of H-10 with the Y-boundary and to counter-clockwise α to α′ rotation.

Analogous considerations led to the forecast of a preference for an (*R*)-configuration in the case of the dehydrogenation of compound **6** (Fig. 1b). Finally, the fact that the enantioselectivity of the bioconversion of the dihydroanthracenone **9** into the alcohol **9a** was practically nil can be interpreted as the result of a very similar extent of destabilization for both (*S*)- and (*R*)-orientations of the substrate in the enzyme active site (Fig. 1c).

3. Experimental

TLC was performed on silica gel F_{254} precoated aluminum sheets (0.2 mm layer, Merck); eluent systems: A, hexane:ethyl acetate (2:1); B, hexane:ethyl acetate (3:2); C, chloroform:ether (5:1). Hexane:ethyl acetate (3:1) and hexane:ether (7:3) were used as additional eluents to check the purity of benzo-2-tetralols. Silica gel (40–63 μm) from Merck was used for flash chromatography. ^{1}H NMR (200.12 or 300.13 MHz), ^{13}C NMR (50.32 or 75.47 MHz) and ^{19}F NMR (282.40 MHz) spectra were recorded in $CDCl_3$ solution. The solvent signal was used as an internal standard for ^{1}H NMR and ^{13}C NMR (7.25 and 77.00 ppm), while $CFCl_3$ was added for measuring ^{19}F NMR chemical shifts. EIMS spectra were run on a VG 7070 EQ mass spectrometer operating at 70 eV. UV spectra were obtained in $CHCl_3$ on an HP 8452A spectrophotometer. Optical rotations were measured in $CHCl_3$ at 25°C on a Perkin–Elmer 241 polarimeter. Circular dichroism curves were recorded in MeOH:dioxane (9:1) at

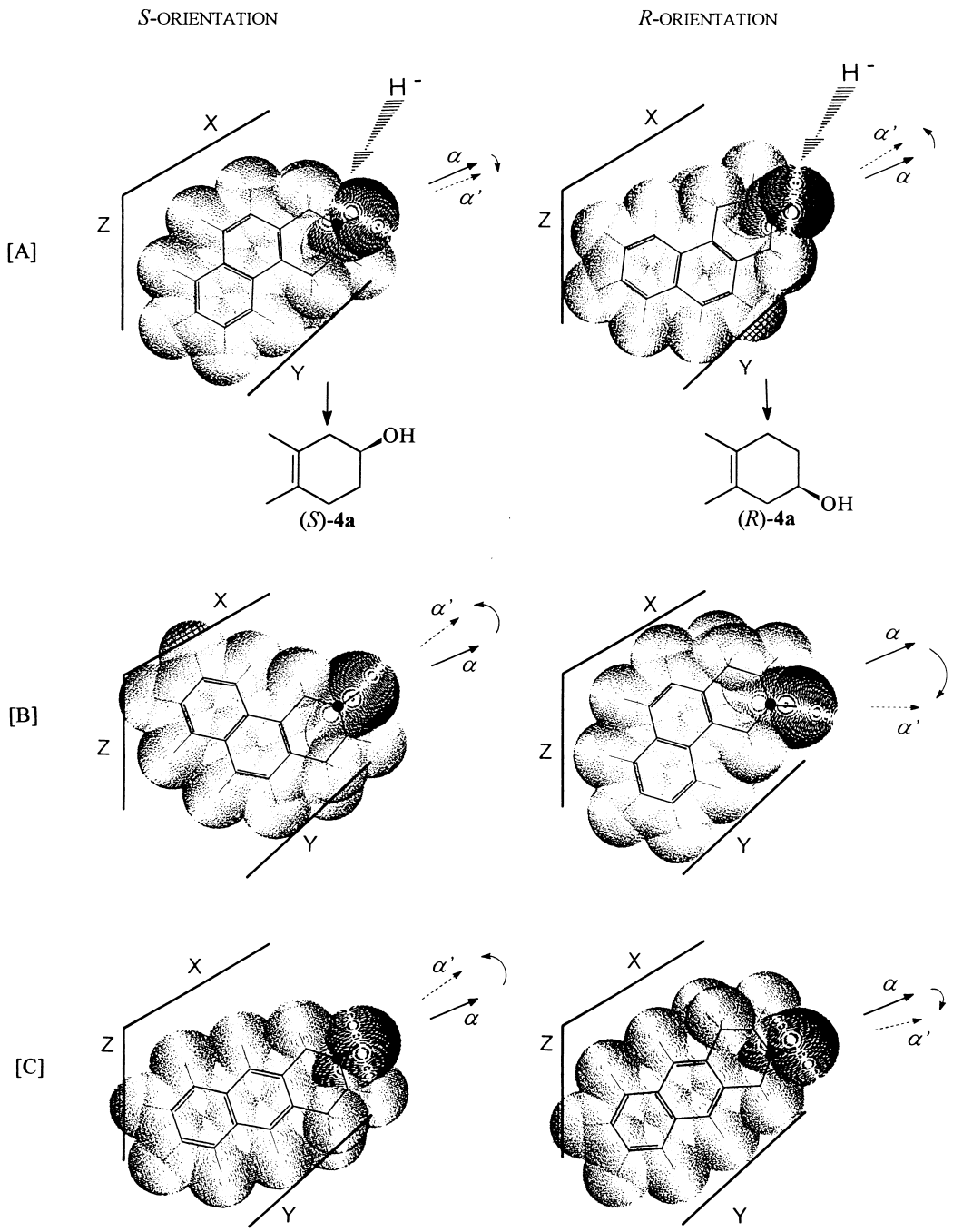


Fig. 1. Schematic representation of tricyclic aromatic ketones **4** [A], **6** [B], **9** [C] (van der Waals surfaces) into the virtual active site of the baker's yeast dehydrogenase. See Manitto et al.[1] for the construction of the enzyme-pocket model and for the order of destabilizing interactions

room temperature on a Jasco J-500C spectropolarimeter. Baker's yeast was from Distillerie Italiane (S. Quirico-Trecasali, Parma, Italy).

3.1. 2,3-Epoxy-1,2,3,4-tetrahydroanthracene **8**

To a solution of **7** (1.09 g, 6.05 mmol)[4] in 10 mL of CH_2Cl_2 at −10°C was added a filtered solution of *m*-CPBA (2 g, 6.35 mmol) in CH_2Cl_2 (16 mL) dropwise, and the reaction mixture stirred for 12 h. Excess oxidant was destroyed by adding a 37% aqueous $NaHSO_3$ solution (10 mL). The organic layer was separated, washed with 5% aqueous $NaHCO_3$, and dried (Na_2SO_4). Removal of solvent under reduced pressure and purification by flash chromatography (eluent A) gave 900 mg of pure **8** (4.6 mmol, 76% yield). TLC R_f 0.1 (eluent A); ^{1}H NMR (200 MHz) δ 3.32–3.58 (m, 6H, H_2-1, H-3 and H_2-4), 7.39 (dd, 2H, *J*=6.2, 3.2 Hz, H-6 and H-7), 7.55 (s, 2H, H-9 and H-10), 7.73 (dd, 2H, *J*=6.2, 3.2 Hz, H-5 and H-8); ^{13}C NMR (50 MHz) δ 30.21 (t), 51.58 (d), 125.22 (d), 126.96 (d), 127.42 (d), 130.47 (s).

3.2. 3,4-Dihydroanthracen-2(1H)-one **9**

Compound **8** (886 mg, 4.52 mmol) was transferred to a suspension of $LiAlH_4$ (0.342 g, 9 mmol) in 200 mL of dry ether by means of continuous extraction with ether using a Soxhlet apparatus. After refluxing for 5 h under N_2, the reaction mixture was quenched by adding in sequence 0.5 mL of water, 1 mL of 5 N NaOH, and 0.5 mL of water. The white slurry was filtered and the residue washed with ether. The combined ether extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give 790 mg of 1,2,3,4-tetrahydroanthracen-2-ol **9a** (3.99 mmol, 88% yield) which was homogeneus by TLC analysis. TLC R_f 0.27 (eluent C); ^{1}H NMR (300 MHz) δ 1.75 (br s, 1H, OH), 1.82–1.98 (m, 1H, H-3*a*), 2.10–2.19 (m, 1H, H-3*b*), 2.91–3.05 (m, 2H, H-1*a* and H-4*a*), 3.12 (app dt, 1H, *J*=16.8, 5.8 Hz, H-4*b*), 3.29 (dd, 1H, *J*=16.1, 4.7 Hz, H-1*b*), 4.20–4.29 (m, 1H, H-2), 7.36–7.42 (m, 2H, H-6 and H-7), 7.57 (s, 2H, H-9 and H-10), 7.69–7.77 (m, 2H, H-5 and H-8); ^{13}C NMR (75 MHz) δ 27.10 (t), 31.83 (t), 38.74 (t), 67.34 (d), 125.13 (d), 125.21 (d), 126.29 (d), 126.98 (d), 127.42 (d), 132.20 (s), 132.27 (s), 133.26 (s), 134.47 (s); UV λ_{max} (log ε): 242 (3.61), 278 (3.48), 288 (3.49).

The above 1,2,3,4-tetrahydroanthracen-2-ol was oxidized by the Swern procedure[9] giving rise to a brown oil, which was flash chromatographed (eluent hexane with increasing portions of ethyl acetate) to obtain **9** as a white solid (30% overall yield). TLC R_f 0.56 (eluent C); ^{1}H NMR (300 MHz) δ 2.58 (app t, *J*=7.0 Hz, 2H, H_2-3), 3.21 (app t, *J*=7.0 Hz, 2H, H_2-4), 3.76 (s, 2H, H_2-1), 7.41–7.48 (m, 2H, H-6 and H-7), 7.58 and 7.69 (2×s, 2×1H, H-9 and H-10), 7.73–7.80 (m, 2H, H-5 and H-8); ^{13}C NMR (75 MHz) δ 28.43 (t), 38.29 (t), 45.92 (t), 125.53 (d), 125.70 (d), 125.82 (d), 126.47 (d), 127.23 (d), 131.36 (s), 132.55 (s), 135.12 (s), 210.22 (s).

3.3. General procedure for biotransformations

A suspension of baker's yeast (100 g) in preboiled distilled water (1 L) was kept at 37°C for 30 min. Then the substrate (1 g), dissolved in the smallest amount of 1,4-dioxane, was gradually added and the mixture vigorously stirred for 3–5 days at 37°C. Progress of the reduction was monitored by TLC analysis. When the reaction was complete, the product was continously extracted with ethyl ether. The ether extract was dried (Na_2SO_4), evaporated under reduced pressure and purified by flash chromatography using the same eluent as for TLC (see Table 1 for yields and enantiomeric ratios). For the preparation and analysis of MTPA esters, see Manitto et al.[1]

3.4. General procedure for the preparation of benzoyl derivatives

To a solution of alcohol (0.2 mmol) in 0.6 mL of dry CH_2Cl_2 and 0.6 mL of dry pyridine, was added 50 μL of freshly distilled benzoyl chloride and the reaction mixture was refluxed until completion. After the usual workup the crude product was purified by flash chromatography using the same eluent as for TLC.

3.5. (S)-1,2,3,4-Tetrahydrophenanthren-2-ol **4a**

TLC R_f 0.29 (eluent A); $[\alpha]_D^{25}$ −51.0 (*c* 0.42, 72% e.e.) (*cf.* Koreeda et al.[7]); ^{1}H NMR (300 MHz) δ 1.91–2.06 (m, 2H, H-3*a* and OH), 2.17–2.34 (m, 1H, H-3*b*), 2.92 (dd, 1H, *J*=15.6 and 7.8 Hz, H-1*a*), 3.12 (app dd, 1H, *J*=17.1, 6.8 Hz, H-4*a*), 3.21 (dd, 1H, *J*=15.6, 4.9 Hz, H-1*b*), 3.35 (app dt, 1H, *J*=17.1, 5.9 Hz, H-4*b*), 4.18–4.26 (m, 1H, H-2), 7.18 (d, 1H, *J*=8.5 Hz, H-10), 7.42–7.53 (m, 2H, H-6 and H-7), 7.64 (d, 1H, *J*=8.5 Hz, H-9), 7.79 (d, 1H, *J*=6.8 Hz, H-8), 7.95 (d, 1H, *J*=8.8 Hz, H-5); ^{13}C NMR (50 MHz) δ 23.68 (t), 31.24 (t), 39.17 (t), 66.89 (d), 122.90 (d), 124.94 (d), 125.98 (d), 126.32 (d), 128.10 (d), 128.35 (d), 130.25 (s), 131.24 (s), 132.00 (s), 132.26 (s); UV λ_{max} (log ε) 288 (3.57), 278 (3.56), 244 (3.65), 324 (2.62); **4a** (*S*)-MTPA ester **4b**, TLC R_f 0.48 (eluent B); ^{19}F NMR δ −71.99 (14%), −71.78 (86%).

3.6. (S)-1,2,3,4-Tetrahydrophenanthren-2-ol benzoate **4c**

TLC R_f 0.52 (eluent A); UV λ_{max} (log ε) 228 (4.94), 280 (3.85); $[\alpha]_D^{25}$ −74.8 (*c* 0.72, 72% e.e.); CD λ_{max} (Δε) 219 (+13.6), 229 (−25.2) (*cf.* Koreeda et al.[7]); ^{1}H NMR (200 MHz) δ 2.24–2.37 (m, 2H, H-3), 3.14–3.49 (m, 4H, H-1 and H-4), 5.54–5.65 (m, 1H, H-2), 7.21 (d, 1H, *J*=8.5 Hz), 7.38–7.56 (m, 6H) 7.67 (d, 1H, *J*=8.5 Hz), 7.83 (d, 1H, *J*=7.5 Hz) and 8.01 (app t, 2H, *J*=8.1 Hz) (aromatic H); ^{13}C NMR (75 MHz) δ 23.16 (t), 27.63 (t), 35.39 (t), 70.01 (d), 122.93 (d), 125.07 (d), 126.10 (d), 126.45 (d), 127.95 (d), 128.29 (d), 128.47 (d), 129.57 (d), 130.23 (s), 130.56 (s), 130.72 (s), 132.10 (s), 132.35 (s), 132.80 (d), 166.20 (s).

3.7. (R)-1,2,3,4-Tetrahydrophenanthren-3-ol **6a**

TLC R_f 0.25 (eluent B); $[\alpha]_D^{25}$ +13.8 (*c* 0.40, 30% e.e.) [lit.[6] −49, for optically pure (*S*)-**6a**]; ^{1}H NMR (300 MHz) δ 1.83–1.97 (m, 2H, H-2*a* and OH), 2.11–2.16 (m, 1H, H-2*b*), 2.93–3.14 (m, 3H, H_2-1 and H-4*a*), 3.51 (dd, 1H, *J*=16.7, 2.0 Hz, H-4*b*), 4.26–4.34 (m, 1H, H-3), 7.21 (d, 1H, *J*=8.4 Hz, H-10), 7.42–7.53 (m, H-6 and H-7), 7.63 (d, 1H, *J*=8.4 Hz, H-9), 7.79 (d, 1H, *J*=9.1 Hz, H-8), 7.93 (d, 1H, *J*=8.3 Hz, H-5); ^{13}C NMR (75 MHz) δ 28.02 (t), 31.32 (t), 35.02 (t), 67.67 (d), 122.73 (d), 125.00 (d), 126.12 (d), 126.29 (d), 127.48 (d), 128.49 (d), 128.5 (s), 132.28 (s), 132.31 (s), 133.03 (s); UV λ_{max} (log ε) 244 (3.63), 282 (3.69), 276 (3.66); **6a** (*S*)-MTPA ester **6b**, TLC R_f 0.70 (eluent B); ^{19}F NMR δ −71.32 (65%), −71.14 (35%).

3.8. (R)-1,2,3,4-Tetrahydrophenanthren-3-ol benzoate **6c**

TLC R_f 0.67 (eluent A); UV λ_{max} (log ε) 228 (5.00), 280 (3.93); $[\alpha]_D^{25}$ −8.54 (*c* 0.57, 30% e.e.); CD λ_{max} (Δε) 222 (+21), 229 (−30) (*cf.* Boyd et al.[6]); ^{1}H NMR (200 MHz) δ 2.17–2.33 (m, 2H, H_2-2), 3.00–3.41 (m, 3H, H_2-1 and H-4*a*), 3.65 (dd, 1H, *J*=17.1, 5.3 Hz, H-4*b*), 5.68 (app quint., 1H, *J*=5.7 Hz, H-3), 7.27 (d, 1H, *J*=8.4 Hz, H-10), 7.40–7.61 (m, 4H, H-6, H-7, H-2′, H-3′, H-5′ and H-6′), 7.69

(d, 1H, *J*=8.4 Hz, H-9), 7.84 (dd, 1H, *J*=8.3, 1.9 Hz, H-8), 7.94 (d, 1H, *J*=7.8 Hz, H-4′), 8.07 (dd, 1H, *J*=7.9, 1.0 Hz, H-5); ^{13}C NMR (50 MHz) δ 27.21 (t), 27.53 (t), 31.35 (t), 70.45 (d), 122.61 (d), 124.99 (d), 126.09 (d), 126.32 (d), 127.42 (d), 128.24 (d), 129.56 (d), 130.59 (s), 132.17 (s), 132.31 (s), 132.82 (s), 166.18 (s).

3.9. (S)-1,2,3,4-Tetrahydroanthracen-2-ol ***9a***

$[\alpha]_D^{25}$ −7.1 (*c* 0.42, 12% e.e.) [lit.[10] −47, for 90% optically pure (*S*)-**9a**]; spectral data matched those reported above for the racemic compound; **9a** (*S*)-MTPA ester **9b**, TLC R_f 0.69 (eluent B); ^{19}F NMR δ −71.40 (44%), −71.23 (56%).

3.10. (S)-1,2,3,4-Tetrahydroanthracen-2-ol benzoate ***9c***

TLC R_f 0.66 (eluent A); UV λ_{max} (log ε) 228 (5.00), 280 (3.82), 276 (3.85); $[\alpha]_D^{25}$ +1.95 (*c* 0.2); CD λ_{max} (Δε) 222 (−4.8), 229 (+5.6) (*cf.* Akhtar et al.[8]); ^{1}H NMR (300 MHz) δ 2.15–2.28 (m, 2H, H_2-3), 3.03–3.13 (app dt, 1H, *J*=16.6, 6.8 Hz, H-4*a*), 3.18–3.27 (m, 2H, H-1*a* and H-4*b*), 3.42 (dd, 1H, *J*=16.6, 4.9 Hz, H-1*b*), 5.52–5.6 (m, 1H, H-2), 7.37–7.74 (m, 8H), 7.99 (dd, 1H, *J*=6.8, 2.0 Hz) and 8.15 (d, 2H, *J*=6.8 Hz) (aromatic H); ^{13}C NMR (50 MHz) δ 26.50, 28.22, 34.93, 70.29, 125.19, 125.29, 126.35, 127.02, 127.37, 128.27, 128.82, 129.52, 130.51, 132.15, 132.5, 132.81, 134.47, 162.5.

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