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Enantioselective synthesis of arylmethoxyacetic acid derivatives

F. Javier Moreno-Dorado,[a] Francisco M. Guerra,[a] María J. Ortega,[b] Eva Zubía[b] and Guillermo M. Massanet[a,*]

[a]*Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Cádiz, Apartado 40, 11510 Puerto Real, Cádiz, Spain*

[b]*Departamento de Química Orgánica, Facultad de Ciencias del Mar y Ambientales, Universidad de Cádiz, Apartado 40, 11510 Puerto Real, Cádiz, Spain*

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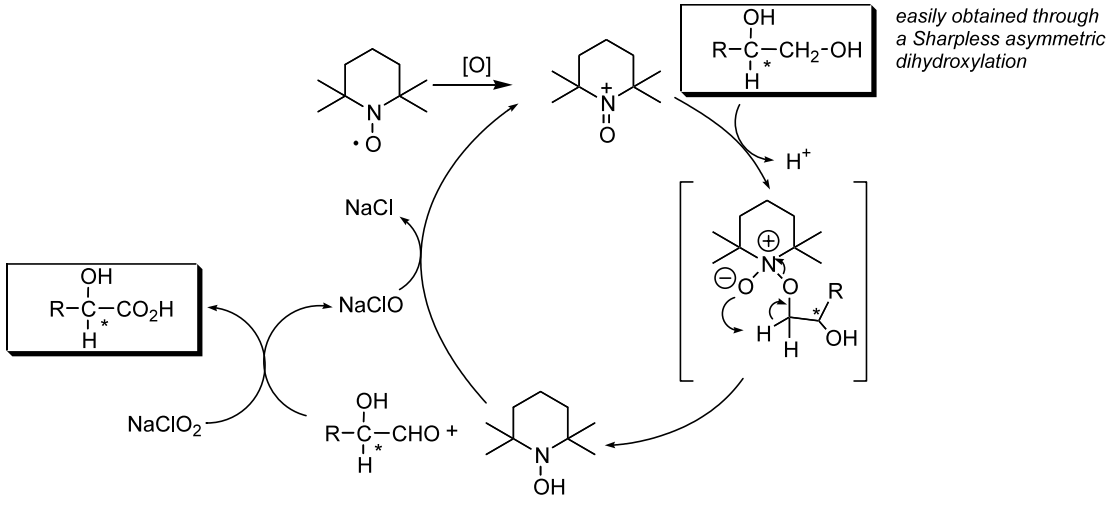
Abstract—The preparation of several arylmethoxyacetic acids by a sequence of asymmetric dihydroxylation and further oxidation of the resulting glycol with TEMPO/NaClO/$NaClO_2$ is described. The scope and limitations of the reaction are discussed.

1. Introduction

In a previous paper, we have reported a convenient method to prepare α-hydroxyacids enantioselectively, which consists of the oxidation of a chiral glycol with the commercially available radical TEMPO, followed by oxidation in situ of the resulting aldehyde with $NaClO_2$.[1] TEMPO was used in a catalytic amount and regenerated with the NaClO formed from the reduction of the $NaClO_2$, according to the catalytic cycle shown in Scheme 1.[2] The reported method oxidised, under mild conditions, several substrates bearing a wide array of functional groups, and neither cleavage of the HO–CH–CH_2–OH bond nor racemization of the stereogenic centre α to the carbonyl group was observed.

α-Hydroxyacids can be considered as the ideal precursors of arylmethoxyacetic acids (AMAAs), useful auxiliary reagents employed for the determination of the



Scheme 1.

* Corresponding author. Tel.: +34 956 016405; fax: +34 956 016193; e-mail: francisco.guerra@uca.es

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absolute configuration of organic compounds by NMR. The general procedure relies on the ^{1}H chemical shift differences observed between the two diastereomers obtained by reaction of the chiral molecule with both antipodes of the chiral derivatizing agent. MPA (methoxyphenylacetic acid) and, in particular MTPA (methoxytrifluoromethylphenylacetic acid) have been the most widely used reagents to determine the absolute configuration of secondary alcohols and amines by ^{1}H NMR.[3]

More recently, Riguera et al. have introduced novel auxiliary reagents such as 1-NMA (1-naphthylmethoxyacetic acid), 2-NMA (2-naphthylmethoxyacetic acid) and 9-AMA (9-anthrylmethoxyacetic acid) which can lead, in some instances, to more confident assignments and have also extended the methodology to a broader range of chiral substrates (e.g. primary alcohols).[4] Although MPA and MTPA are commercially available, this is not the case of the new reagents 1-NMA, 2-NMA and 9-AMA. A conventional sequence to prepare α-aryl-α-hydroxyacetic acids, also employed by Riguera et al., consists of the nucleophilic addition of cyanide anion to the corresponding aldehyde, further acidic hydrolysis of the resulting cyanohydrin and resolution of the racemic mixture through chiral HPLC.[4a] However, this method is not easy to scale up since preparative chiral HPLC is expensive, time-consuming and not available in all laboratories.

Herein we report our attempts to develop a methodology for an effective enantioselective preparation of AMAAs by using a reaction sequence involving a Sharpless asymmetric dihydroxylation and subsequent oxidation of the selectively protected diol with the TEMPO/NaClO/$NaClO_2$ system.

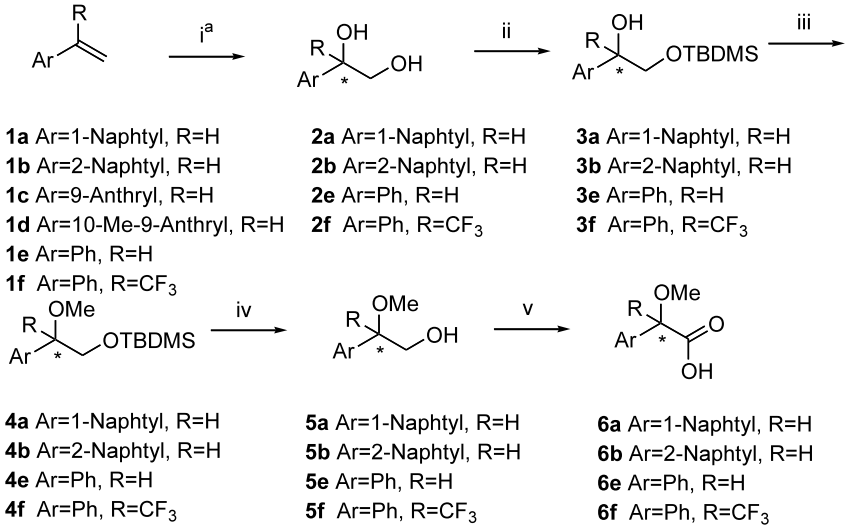
2. Results and discussion

Our general procedure to access α-aryl-α-methoxyacetic acids starting from vinyl arenes **1** is depicted in Scheme 2. The synthetic approach begins with the Sharpless asymmetric dihydroxylation of the double bond using either AD-mix α or β to prepare each enantiomer of the corresponding 1,2-diol **2**, followed by selective protection of the primary hydroxyl group as its *t*-butyldimethylsilyl ether **3**. The methylation of the secondary hydroxyl group was complicated by the fact that under the first assayed reaction conditions (KOMe, MeI or NaH, MeI) the silyl group of **3** switched between both hydroxyl groups, leading to a mixture of silyl derivatives. The nature of the base employed in this step was decisive in avoiding this unwanted exchange of the protecting group, and after trying several reaction conditions, it was finally found that the use of MeI and ^{t}BuOK effectively led to the methyl ether **4**.

The selective deprotection of the primary alcohol group with TBAF in acetonitrile yielded the methoxyalcohol derivative **5** in excellent yield. Finally, the resulting alcohol was oxidised with the TEMPO/NaClO/$NaClO_2$ system to produce the corresponding optically active arylmethoxyacetic acid **6** (Scheme 2).

This procedure was applied to different substrates using both AD-mixes in each case. In particular, the treatment of each vinylarene with AD-mix α led to the (*S*)-diol that was transformed through the described sequence into the corresponding (*S*)-AMAA, while reaction of the vinylarene with AD-mix β yielded the (*R*)-diol and therefore the (*R*)-AMAA.

Thus, starting from 1-vinylnaphthalene **1a**, each enantiomer of the chiral derivatizing agent 1-NMA **6a** was



Scheme 2. *Reagents and conditions*: (i) AD-mix α or β, ^{t}BuOH/H_2O 1:1, rt, 2 h. (ii) TBDMSCl, Et_3N, DMAP, CH_2Cl_2, rt, 2 h. (iii) MeI, ^{t}BuOK, CH_3CN, 12 h, rt. (iv) TBAF, CH_3CN, 4 h, rt. (v) TEMPO (0.25 equiv.), NaClO (2 equiv.), $NaClO_2$ (0.02 equiv.), CH_3CN/KH_2PO_4 buffer pH 6.5 (1:1), 4 h, 55°C. [a]AD mix α leads to the *S* isomer in all cases. From this point onwards all the isomers present *S* configuration along the series. The same occurs when AD mix β is employed, yielding the *R* series.

easily synthesised with good overall yields. Similarly, the (*R*)-and (*S*)-antipodes of 2-NMA **6b** were efficiently prepared from 2-vinylnaphthalene **1b**. The specific rotation values determined for each enantiomeric form of **6a** and **6b** were in good agreement with those reported in the literature (see Section 4).

However, in the case of 9-AMA, the reaction of 9-vinylanthracene **1c** with AD-mix led unavoidably to anthraquinone, and only a minor amount of the desired diol could be isolated.[5] During our research on olefin oxidation with AD-mixes we had observed that these reagents can eventually oxidise other functional groups present in the substrate, such as hydroxyl or amino groups, but the oxidation of the aromatic system of anthracene was not expected. In fact, a survey of literature has shown that only very recently has this behaviour of anthracene been reported by Wang et al.[6] All attempts to block this unwanted cleavage by changing the reaction conditions were unfruitful. Furthermore, a methyl group at C-10 in the anthracene nucleus, opposite to the vinyl group at C-9 (as in **1d**), did not prevent the oxidation of these positions, leading to the dihydroxylation of the central ring instead of the expected one of the vinyl group (Scheme 3).

Finally, the five step synthesis shown in Scheme 2 constitutes an alternative route, easy to perform and to scale up, to obtain the well known chiral auxiliary reagents MTA **6e** and MTPA **6f** from styrene **1e** and 1-(trifluoromethylvinyl)benzene **1f**, respectively. In both cases good overall yields were obtained, and the specific rotations determined for each enantiomer of **6e** and **6f** were in agreement with the literature values (see Section 4).

3. Conclusion

Summing up, this method provides an alternative route to optically active arylmethoxyacetic acids. Disadvantages of the method are due mainly to oxidative processes in the aromatic ring and not to cleavage of the glycol bond. The broad availability of suitable starting materials and the technical simplicity of the involved procedures are among the main advantages of the described methodology.

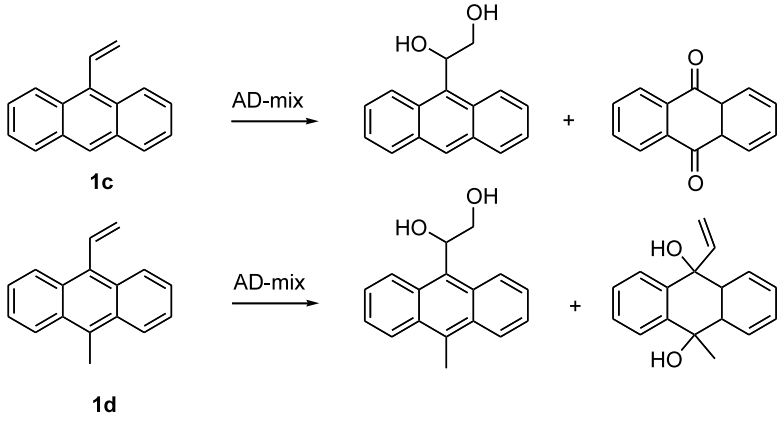
4. Experimental

4.1. General

All non-aqueous reactions were carried out under a nitrogen atmosphere. Air- and moisture-sensitive liquids and solutions were transferred via syringe. Reactions were monitored through TLC on commercial silica gel plates. Visualization of the developed plate was performed by fluorescence quenching and/or aqueous ceric ammonium molybdate/anisaldehyde stains. Melting points are uncorrected and were measured in a Reichert–Jung apparatus. NMR spectra were recorded on a Varian Gemini 300 or on a Varian Inova 400. ^{1}H chemical shifts were referenced to the residual $CHCl_3$ signal at δ 7.26 ppm or at δ 3.31 ppm in the case of CD_3OD. ^{13}C NMR spectra were referenced to the central peak of $CDCl_3$ at δ 77.0 ppm or at δ 49.0 ppm when CD_3OD is used. Data for ^{1}H are reported as follows: chemical shift (δ, ppm), integration, multiplicity and coupling constant (J, Hz). Data for ^{13}C are reported in terms of chemical shift (δ, ppm). IR spectra were recorded in a Mattson Genesis Series FTIR, using NaCl plates; data are reported in cm^{-1}. Mass spectra were obtained in a Voyager GC-MS or in a VG Autospec-Q.

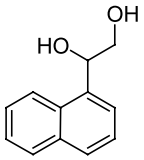
4.2. General procedure to α-methoxyacids starting from alkenes

4.2.1. Sharpless dihydroxylation of alkenes 1. The olefin (1 mmol) is dissolved in ^{t}BuOH:H_2O (1:1, 10 mL) and AD-mix (1.49 g) is added. The mixture is stirred at room temperature for 2 h. The reaction is then quenched with 500 mg of sodium sulfite and stirred for 10 min. ^{t}BuOH was removed under vacuum and the aqueous layer was extracted with EtOAc (3×25 mL). The organic layer was dried over anhydrous sodium sulfate and the solvent was removed under vacuum to afford the corresponding diol.



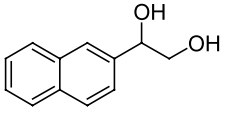
Scheme 3.

4.2.1.1. (*R*)- and (*S*)-1-Naphthalen-1-ylethane-1,2-diol 2a.



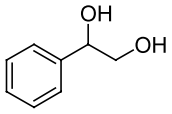
Obtained as white crystals, mp = 39.2–40.1°C. (*S*)-Isomer: obtained from AD-mix α, 92% yield, $[\alpha]_D = +90.2$ (*c* 0.12, $CHCl_3$). (*R*)-Isomer: obtained from AD-mix β, 94% yield, $[\alpha]_D = -84.0$ (*c* 0.11, $CHCl_3$). IR (film): ν = 3295, 2943, 1066, 800, 777 and 738 cm^{-1}. HREIMS calcd for $C_{12}H_{12}O_2$ $[M]^+$ 188.0837, found 188.0834. EIMS, *m*/*z* (rel. int.) 188 $[M]^+$ (29.4), 157 (100), 129 (82.1), 127 (27.9). ^1H NMR δ 7.93 (1H, d, J = 8.4 Hz), 7.80 (1H, d, J = 8.8 Hz), 7.70 (1H, d, J = 8.0 Hz), 7.61 (1H, d, J = 6.8 Hz), 7.44–7.34 (3H, m), 5.57 (1H, d, J = 8.0 Hz), 4.30 (1H, s, OH), 3.94 (1H, s, OH), 3.89 (1H, d, J = 9.2 Hz), 3.71 (1H, dd, J = 9.2, 8.0 Hz). ^{13}C NMR δ 136.0, 133.5, 130.2, 128.8, 128.1, 126.1, 125.5, 125.3, 123.3, 122.6, 71.5, 67.4.

4.2.1.2. (*R*)- and (*S*)-1-Naphthalen-2-ylethane-1,2-diol 2b.



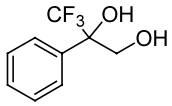
Obtained as white crystals, mp = 120.5–121.5°C. (*S*)-Isomer: obtained from AD-mix α, 89% yield, $[\alpha]_D = +50.8$ (*c* 0.12, $CHCl_3$). (*R*)-Isomer: obtained from AD-mix β, 91% yield, $[\alpha]_D = -47.1$ (*c* 0.07, $CHCl_3$). IR (film): ν = 3249, 2942, 2894, 1078, 825 and 741 cm^{-1}. HREIMS calcd for $C_{12}H_{12}O_2$ $[M]^+$ 188.0837, found 188.0844. EIMS, *m*/*z* (rel. int.) 188 $[M]^+$ (27.7), 157 (100), 129 (85.5), 77 (5.4). ^1H NMR δ 7.85–7.83 (4H, m), 7.49–7.45 (3H, m), 5.00 (1H, dd, J = 8.0, 3.5 Hz), 3.85 (1H, dd, J = 11.4, 3.5 Hz), 3.75 (1H, dd, J = 11.4, 8.0 Hz). ^{13}C NMR δ 138.4, 132.7, 132.6, 128.9, 128.5, 128.2, 126.8, 126.6, 125.5, 124.4, 75.3, 68.5.

4.2.1.3. (*R*)- and (*S*)-1-Phenylethane-1,2-diol 2e.



Obtained as white crystals, mp = 56.2–58.6°C. (*S*)-Isomer: obtained from AD-mix α, 97% yield, $[\alpha]_D = +64.8$ (*c* 0.12, $CHCl_3$). (*R*)-Isomer: obtained from AD-mix β, 98% yield, $[\alpha]_D = -62.7$ (*c* 0.11, $CHCl_3$). IR (film): ν = 3316, 3204, 2966, 2936, 1495, 1449, 1089, 1078, 761, 748 and 700 cm^{-1}. HREIMS calcd for $C_8H_{10}O_2$ $[M]^+$ 138.0681, found 138.0679. EIMS, *m*/*z* (rel. int.) 138 $[M]^+$ (9.5), 107 (100), 91 (5.5), 79 (74.9). ^1H NMR δ 7.36–7.28 (5H, m), 4.82 (1H, dd, J = 8.0, 3.6 Hz), 3.76 (1H, dd, J = 11.2, 3.6 Hz), 3.66 (1H, dd, J = 11.2, 8.0 Hz). ^{13}C NMR δ 140.5, 128.5, 128.5, 128.0, 126.0, 74.7, 68.1.

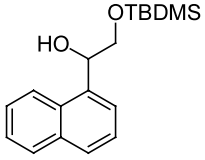
4.2.1.4. (*R*)- and (*S*)-3,3,3-Trifluoro-2-phenylpropane-1,2-diol 2f.



Obtained as white crystals, mp = 34.5–36.7°C. (*S*)-Isomer: obtained from AD-mix α, 98% yield, $[\alpha]_D = +17.2$ (*c* 0.36, MeOH). (*R*)-Isomer: obtained AD-mix β: 98% yield, $[\alpha]_D = -18.0$ (*c* 0.35, MeOH). IR (film): ν = 3434, 2957 and 1165 cm^{-1}. HREIMS calcd for $C_9H_9F_3O_2$ $[M]^+$ 206.0555, found 206.0554. EIMS, *m*/*z* (rel. int.) 206 $[M]^+$ (7.0), 175 (80.0), 156 (13.2), 105 (100), 91 (15.6), 77 (34.9). ^1H NMR δ 7.54–7.49 (2H, m), 7.39–7.35 (3H, m), 4.16 (1H, d, J = 11.6 Hz), 3.84 (1H, d, J = 11.6 Hz). ^{13}C NMR δ 135.7, 129.2, 128.9, 126.5, 125.5 (q, J_{C-F} = 284.6 Hz), 76.8 (q, J_{C-F} = 25.4 Hz), 65.0.

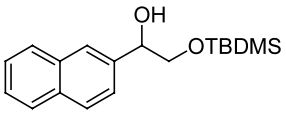
4.2.2. Treatment with TBDMSCl of diols 2. The corresponding diol (1 mmol) and DMAP (0.1 mmol) were dissolved in dry dichloromethane (5 mL) under a N_2 atmosphere. Then, Et_3N (1.5 mmol) and TBDMSCl (1.5 mmol, 1 M in dichloromethane) were added dropwise. The reaction mixture was stirred for 2 h, after which time 5 mL of a saturated aqueous NH_4Cl solution (5 mL) was added. The aqueous layer was extracted with dichloromethane (2×5 mL) and the combined organic layers were dried over anhydrous sodium sulfate. The solvent was removed by rotary evaporation yielding the corresponding silyloxy derivative.

4.2.2.1. (*R*)- and (*S*)-2-(*tert*-Butyldimethylsilyloxy)-1-naphthalen-1-ylethanol 3a.



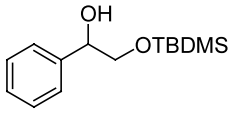
Colourless oil. (*S*)-Isomer: 89% yield, $[\alpha]_D = +38.3$ (*c* 0.12, $CHCl_3$). (*R*)-Isomer: 92% yield, $[\alpha]_D = -40.2$ (*c* 0.09, $CHCl_3$). IR (film): ν = 3448, 3051, 2953, 2929, 2885, 2857, 1512, 1470, 1106, 875, 838 and 777 cm^{-1}. HREIMS calcd for $C_{18}H_{26}O_2Si$ $[M]^+$ 302.1702, found 302.1702. EIMS, *m*/*z* (rel. int.) 302 $[M]^+$ (1.1), 285 (2.2), 271 (5.5), 245 (16.7), 227 (21.6), 153 (100), 129 (34.9), 75 (99.6). ^1H NMR δ 8.06 (1H, d, J = 8.4 Hz), 7.88 (1H, d, J = 8.0 Hz), 7.80 (1H, d, J = 8.4 Hz), 7.74 (1H, d, J = 7.2 Hz), 7.54–7.46 (3H, m), 5.57 (1H, dd, J = 8.8, 3.2 Hz), 4.01 (1H, dd, J = 10.4, 3.2 Hz), 3.68 (1H, dd, J = 10.4, 8.8 Hz), 0.94 (9H, s), 0.09 (3H, s), 0.07 (3H, s). ^{13}C NMR δ 135.7, 133.6, 130.6, 128.9, 128.1, 126.0, 125.5, 125.4, 123.7, 122.7, 71.3, 68.3, 25.9, 18.3, −5.3, −5.4.

4.2.2.2. (*R*)- and (*S*)-2-(*tert*-Butyldimethylsilyloxy)-1-naphthalen-2-ylethanol 3b.



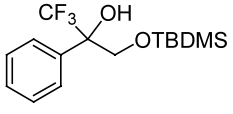
Colourless oil. (*S*)-Isomer: 90% yield, $[\alpha]_D = +27.5$ (*c* 0.40, $CHCl_3$). (*R*)-Isomer: 92% yield, $[\alpha]_D = -31.9$ (*c* 0.48, $CHCl_3$). IR (film): $\nu = 3461$, 2954, 2928, 2857, 1471, 1255, 1105, 838 and 779 cm^{-1}. HREIMS calcd for $C_{18}H_{26}O_2Si$ $[M]^+$ 302.1702, found 302.1699. EIMS, *m*/*z* (rel. int.) 302 $[M]^+$ (16.8), 271 (3.8), 245 (100), 227 (90.6), 157 (53.4), 141 (30.5), 129 (36.0), 75 (99.7). ^1H NMR δ 7.86–7.81 (4H, m), 7.49–7.45 (3H, m), 4.92 (1H, dd, $J = 8.5$, 3.6 Hz), 3.86 (1H, dd, $J = 10.2$, 3.6 Hz), 3.63 (1H, dd, $J = 10.2$, 8.5 Hz), 0.93 (9H, s), 0.08 (3H, s), 0.07 (3H, s). ^{13}C NMR δ 137.9, 133.5, 133.3, 128.2, 127.9, 126.3, 126.1, 125.3, 124.5, 74.7, 69.1, 26.1, 18.6, −5.1, −5.2.

4.2.2.3. (*R*)- and (*S*)-2-(*tert*-Butyldimethylsilyloxy)-1-phenylethanol 3e.



Colourless oil. (*S*)-Isomer: 92% yield, $[\alpha]_D = +30.5$ (*c* 0.09, $CHCl_3$). (*R*)-Isomer: 91% yield, $[\alpha]_D = -28.2$ (*c* 0.11, $CHCl_3$). IR (film): $\nu = 3433$, 3065, 3032, 2958, 2929, 2858, 1471, 1259, 1103, 1027, 803 and 699 cm^{-1}. HREIMS calcd for $[C_{13}H_{21}OSi]^+$ 221.1362, found 221.1370; calcd for $[M-C(CH_3)_3]^+$ 195.0869, found 195.0847. EIMS, *m*/*z* (rel. int.) 221 $[C_{13}H_{21}OSi]^+$ (35.6), 195 $[M-C(CH_3)_3]^+$ (60.0), 177 (43.6), 147 (9.5), 75 (100). ^1H NMR δ 7.38–7.25 (5H, m), 4.75 (1H, dd, $J = 8.6$, 3.6 Hz), 3.76 (1H, dd, $J = 10.0$, 3.6 Hz), 3.54 (1H, dd, $J = 10.0$, 8.6 Hz), 0.91 (9H, s), 0.06 (3H, s), 0.05 (3H, s). ^{13}C NMR δ 140.2, 128.3, 127.7, 126.2, 74.3, 68.9, 25.9, 18.3, −5.4, −5.5.

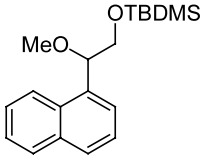
4.2.2.4. (*R*)- and (*S*)-3-(*tert*-Butyldimethylsilyloxy)-1,1,1-trifluoro-2-phenylpropan-2-ol 3f.



Colourless oil. (*S*)-Isomer: 96% yield, $[\alpha]_D = +10.8$ (*c* 0.26, $CHCl_3$). (*R*)-Isomer: 94% yield, $[\alpha]_D = -9.7$ (*c* 0.26, $CHCl_3$). IR (film): $\nu = 3401$, 2955, 2931, 2859, 2888, 1596, 1186, 1163, 1105, 1075 and 835 cm^{-1}. HREIMS calcd for $[C_{13}H_{18}F_3O_2Si]^+$ 291.1028, found 291.1028; calcd for $[M-C(CH_3)_3]^+$ 263.0715, found 263.0759. EIMS, *m*/*z* (rel. int.) 291 $[C_{13}H_{18}F_3O_2Si]^+$ (6.2), 263 $[M-C(CH_3)_3]^+$ (24.1), 208 (8.6), 141 (100), 91 (24.6), 75 (67.6). ^1H NMR δ 7.55–7.52 (2H, m), 7.42–7.35 (3H, m), 4.30 (1H, d, $J = 10.4$ Hz), 3.96 (1H, s, OH), 3.69 (1H, dq, $J = 10.4$ Hz, $J_{H-F} = 2.0$ Hz), 0.86 (9H, s), 0.10 (3H, s), 0.05 (3H, s). ^{13}C NMR δ 135.9, 128.7, 128.3, 125.6, 125.2 (q, $J_{C-F} = 285.7$ Hz), 77.8 (q, $J_{C-F} = 25.8$ Hz), 65.5, 25.6, 18.2, −5.6, −5.7.

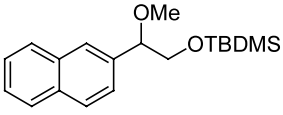
4.2.3. Methylation of the silyloxy alcohols 3. 1 mmol of the hydroxy silyloxy derivative and 3 mmol of MeI were solved in acetonitrile (10 mL) and 1.1 mmol of ^{t}BuOK was added. The reaction mixture was stirred overnight and 10 mL of saturated aqueous solution of NH_4Cl was added. The crude reaction was extracted with EtOAc (3×10 mL) and the combined organic layers dried over anhydrous sodium sulfate. The solvent was removed under vacuum and the resulting oil was purified by column chromatography (EtOAc/hexane, 1:9) to afford the corresponding methylated compounds.

4.2.3.1. (*R*)- and (*S*)-2-(*tert*-Butyldimethylsilyloxy)-1-methoxy-1-naphthalen-1-ylethane 4a.



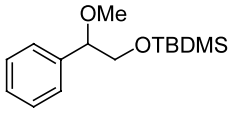
Colourless oil. (*S*)-Isomer: 82% yield, $[\alpha]_D = +88.6$ (*c* 0.10, $CHCl_3$). (*R*)-Isomer: 83% yield, $[\alpha]_D = -85.5$ (*c* 0.11, $CHCl_3$). IR (film): $\nu = 3050$, 2953, 2928, 2884, 2856, 1254, 1129, 1108, 838 and 777 cm^{-1}. HREIMS calcd for $C_{19}H_{28}O_2Si$ $[M]^+$ 316.1859, found 316.1843. EIMS, *m*/*z* (rel. int.) 316 $[M]^+$ (13.2), 301 (26.2), 271 (38.2), 259 (16.5), 171 (92.4), 153 (100), 89 (53.2). ^1H NMR δ 8.18 (1H, dm, $J = 9.0$ Hz), 7.90–7.77 (2H, m), 7.60–7.44 (4H, m), 5.03 (1H, dd, $J = 7.0$, 4.4 Hz), 3.93 (1H, dd, $J = 11.2$, 7.0 Hz), 3.84 (1H, dd, $J = 11.2$, 4.4 Hz), 3.37 (3H, s), 0.84 (9H, s), −0.02 (3H, s), −0.08 (3H, s). ^{13}C NMR δ 135.0, 133.8, 131.5, 128.8, 128.1, 125.9, 125.4, 125.3, 124.6, 123.3, 82.8, 67.9, 57.4, 25.9, 18.4, −5.3, −5.5.

4.2.3.2. (*R*)- and (*S*)-2-(*tert*-Butyldimethylsilyloxy)-1-methoxy-1-naphthalen-2-ylethane 4b.



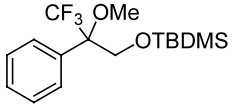
Colourless oil. (*S*)-Isomer: 81% yield, $[\alpha]_D = +42.0$ (*c* 0.91, $CHCl_3$). (*R*)-Isomer: 84% yield, $[\alpha]_D = -46.7$ (*c* 0.91, $CHCl_3$). IR (film): $\nu = 2928$, 2857, 1471, 1253, 1131, 1104, 838 and 777 cm^{-1}. HREIMS calcd for $C_{19}H_{28}O_2Si$ $[M]^+$ 316.1859, found 316.1851. EIMS, *m*/*z* (rel. int.) 316 $[M]^+$ (3.2), 301 (52.2), (11.6), 259 (40.3), 227 (30.6), 171 (100), 89 (88.3). ^1H NMR δ 7.86–7.80 (4H, m), 7.50–7.46 (3H, m), 4.43 (1H, dd, $J = 7.0$, 4.7 Hz), 3.93 (1H, dd, $J = 10.8$, 7.0 Hz), 3.78 (1H, dd, $J = 10.8$, 4.7 Hz), 3.38 (3H, s), 0.89 (9H, s), 0.04 (3H, s), −0.01 (3H, s). ^{13}C NMR δ 137.4, 133.5, 128.3, 128.1, 128.0, 126.5, 126.3, 126.0, 125.1, 85.4, 68.3, 57.5, 26.2, 18.7, −5.0, −5.2.

4.2.3.3. (*R*)- and (*S*)-2-(*tert*-Butyldimethylsilyloxy)-1-methoxy-1-phenylethane 4e.



Colourless oil. (*S*)-Isomer: 87% yield, $[\alpha]_D = +56.3$ (*c* 0.20, $CHCl_3$). (*R*)-Isomer: 85% yield, $[\alpha]_D = -51.2$ (*c* 0.21, $CHCl_3$). IR (film): $\nu = 3065$, 3031, 2961, 2929, 2858, 1464, 1412, 1361, 1260, 1099, 1020, 801 and 700 cm^{-1}. HREIMS calcd for $[M-CH_3O]^+$ 235.1518, found 235.1515, calcd for $[C_{13}H_{21}OSi]^+$ 221.1362, found 221.1360. EIMS, *m*/*z* (rel. int.) 235 $[M-CH_3O]^+$ (2.3), 221 $[C_{13}H_{21}OSi]^+$ (78.8), 209 (13.0), 177 (10.3), 147 (100), 75 (17.5). ^1H NMR δ 7.35–7.25 (5H, m), 4.23 (1H, dd, $J = 7.2$, 4.6 Hz), 3.80 (1H, dd, $J = 10.8$, 7.2 Hz), 3.65 (1H, dd, $J = 10.8$, 4.6 Hz), 3.31 (3H, s), 0.86 (9H, s), 0.00 (3H, s), −0.04 (3H, s). ^{13}C NMR δ 139.6, 128.2, 127.7, 127.1, 85.0, 68.1, 57.2, 25.9, 18.4, −5.3, −5.5.

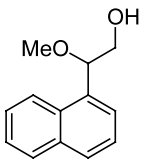
4.2.3.4. (*R*)- and (*S*)-3-(*tert*-Butyldimethylsilyloxy)-1,1,1-trifluoro-2-methoxy-2-phenylpropane 4f.



Colourless oil. (*S*)-Isomer: 96% yield, $[\alpha]_D = -3.2$ (*c* 1.01, $CHCl_3$). (*R*)-Isomer: 94% yield, $[\alpha]_D = +3.0$ (*c* 0.29, $CHCl_3$). IR (film): $\nu = 2961$, 2952, 2887, 2858, 1471, 1259, 1169, 1124, 957, 840, 778 and 701 cm^{-1}. HREIMS calcd for $[M-C(CH_3)_3]^+$ 277.0872, found 277.0864. EIMS, *m*/*z* (rel. int.) 277 $[M-C(CH_3)_3]^+$ (17.3), 189 (3.5), 141 (66.4), 89 (100). ^1H NMR δ 7.51–7.47 (2H, m), 7.42–7.34 (3H, m), 4.21 (1H, dq, $J = 11.4$ Hz, $J_{H-F} = 1.0$ Hz), 4.12 (1H, dq, $J = 11.4$ Hz, $J_{H-F} = 1.2$ Hz), 3.41 (3H, s), 0.82 (9H, s), 0.03 (6H, s). ^{13}C NMR δ 133.9, 128.5, 128.1, 127.9, 125.0 (q, $J_{C-F} = 288.0$ Hz), 82.1 (q, $J_{C-F} = 25.5$ Hz), 64.0, 52.9, 25.6, 18.0, −5.8, −5.9.

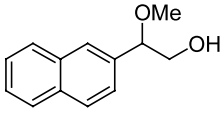
4.2.4. α-Methoxy alcohols 5. The methoxy silyloxy derivative (1 mmol) was solved in acetonitrile (5 mL) and TBAF (2 mmol) was added. The reaction mixture was stirred for 4 h, after which time brine (15 mL) was added. The crude reaction was extracted with EtOAc (3×15 mL), the combined organic layers were dried and the solvent was removed under vacuum to yield the α-methoxy hydroxy derivative.

4.2.4.1. (*R*)- and (*S*)-2-Methoxy-2-naphthalen-1-ylethanol 5a.



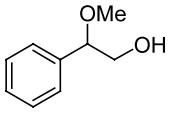
Colourless oil. (*S*)-Isomer: 98% yield, $[\alpha]_D = +126.2$ (*c* 0.10, $CHCl_3$). (*R*)-Isomer: 97% yield, $[\alpha]_D = -122.3$ (*c* 0.11, $CHCl_3$). IR (film): $\nu = 3417$, 2960, 2939, 2874, 1624, 1486, 1466, 1382, 1110, 1055, 882, 804 and 783 cm^{-1}. HREIMS calcd for $C_{13}H_{14}O_2$ $[M]^+$ 202.0994, found 202.0976. EIMS, *m*/*z* (rel. int.) 202 $[M]^+$ (13.1), 171 (100), 128 (26.2). ^1H NMR δ 8.14 (1H, dm, $J = 8.8$ Hz), 7.88 (1H, m), 7.81 (1H, d, $J = 8.0$ Hz), 7.58 (1H, dm, $J = 6.4$ Hz), 7.54–7.45 (3H, m), 5.11 (1H, dd, $J = 7.2$, 4.8 Hz), 3.82–3.80 (3H, m), 3.39 (3H, s). ^{13}C NMR δ 133.8, 133.5, 131.2, 129.0, 128.4, 126.2, 125.7, 125.4, 124.3, 122.8, 82.3, 66.9, 57.1.

4.2.4.2. (*R*)- and (*S*)-2-Methoxy-2-naphthalen-2-ylethanol 5b.



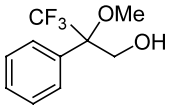
Amorphous solid. (*S*)-Isomer: 96% yield, $[\alpha]_D = +118.0$ (*c* 0.10, $CHCl_3$). (*R*)-Isomer: 94% yield, $[\alpha]_D = -123.2$ (*c* 0.74, $CHCl_3$). IR (film): $\nu = 3406$, 2928, 2875, 1110, 1041, 821, 746 and 479 cm^{-1}. HREIMS calcd for $C_{13}H_{14}O_2$ $[M]^+$ 202.0994, found 202.0982. EIMS, *m*/*z* (rel. int.) 202 $[M]^+$ (9.7), 171 (100), 155 (16.3), 127 (15.5). ^1H NMR δ 7.89–7.81 (3H, m), 7.78 (1H, s), 7.51–7.43 (2H, m), 7.44 (1H, dd, $J = 8.3$, 1.6 Hz), 4.48 (1H, dd, $J = 8.8$, 4.1 Hz), 3.80 (1H, dd, $J = 11.9$, 9.3 Hz), 3.71 (1H, m), 3.36 (3H, s). ^{13}C NMR δ 135.7, 133.3, 133.2, 128.5, 127.9, 127.7, 126.3, 126.2, 126.1, 124.4, 84.7, 67.3, 57.0.

4.2.4.3. (*R*)- and (*S*)-2-Methoxy-2-phenylethanol 5e.



Colourless oil. (*S*)-Isomer: 100% yield, $[\alpha]_D = +108.5$ (*c* 0.11, $CHCl_3$). (*R*)-Isomer: 100% yield, $[\alpha]_D = -99.0$ (*c* 0.10, $CHCl_3$). IR (film): $\nu = 3379$, 2934, 2875, 2825, 1492, 1454, 1110, 1066, 1027, 759 and 702 cm^{-1}. HREIMS calcd for $C_9H_{12}O_2$ $[M]^+$ 152.0837, found 152.0829. EIMS, *m*/*z* (rel. int.) 152 $[M]^+$ (9.7), 121 (100), 107 (10.4), 77 (30.3). ^1H NMR δ 7.33–7.18 (5H, m), 4.23 (1H, dd, $J = 7.7$, 4.3 Hz), 3.66–3.50 (2H, m), 3.22 (3H, s), 2.72 (1H, br s, OH). ^{13}C NMR δ 138.2, 128.5, 128.1, 126.8, 84.7, 67.2, 56.8.

4.2.4.4. (*R*)- and (*S*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropanol 5f.

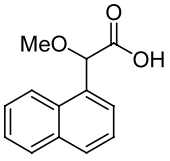


Colourless oil. (*S*)-Isomer: 100% yield, $[\alpha]_D = +17.4$ (*c* 0.22, $CHCl_3$). (*R*)-Isomer: 98% yield, $[\alpha]_D = -17.9$ (*c*

0.35, $CHCl_3$). IR (film): $\nu = 3442$, 2952, 2847, 1451, 1266, 1168, 1077, 947, 762 and 703 cm^{-1}. HREIMS calcd for $C_{10}H_{11}F_3O_2$ $[M]^+$ 220.0711, found 220.0696. EIMS, m/z (rel. int.) 220 $[M]^+$ (2.1), 189 (100), 148 (28.5), 105 (79.3), 91 (29.5), 77 (29.4). ^1H NMR δ 7.47–7.36 (5H, m), 4.19 (1H, d, $J = 12.4$ Hz), 3.95 (1H, dq, $J = 12.4$ Hz, $J_{H-F} = 2.0$ Hz), 3.42 (3H, q, $J_{H-F} = 0.8$ Hz). ^{13}C NMR δ 133.1, 129.0, 128.7, 127.3, 125.1 (q, $J_{C-F} = 286.9$ Hz), 82.2 (q, $J_{C-F} = 25.6$ Hz), 64.4, 52.9.

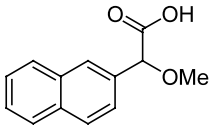
4.2.5. TEMPO oxidation of α-methoxy alcohols 5. The α-methoxy alcohol (1 mmol) was dissolved in a 1:1 mixture of acetonitrile and potassium dihydrogen phosphate buffer solution (8 mL, pH 6.5). Then, TEMPO (0.125 mmol, 19 mg), sodium chlorite (2 mmol) and diluted bleach (0.02 mmol, 4% active chlorine) were added. The reaction mixture was heated to 55°C in a oil bath for 4 h, after which time, the reaction was allowed to cool to room temperature and water (10 mL) was added. The pH was set to 8 with NaOH (1 N) and cool aqueous sodium sulfite (0.2 g in 4 mL of water) was added. The pH was lowered to 2 with HCl (1 N) and the reaction mixture was extracted with EtOAc (3×10 ml). The organic layer was dried over anhydrous sodium sulfate and the solvent removed by rotary evaporation. The resulting crude reaction was mixture that was essentially only the desired α-methoxy acids, although in some cases some TEMPO-derived impurities remained that were removed by column chromatography.

4.2.5.1. (*R*)- and (*S*)-α-Methoxynaphthalen-1-ylacetic acid, 1-NMA, 6a.



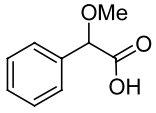
Obtained as white crystals, mp = 113.2–114.4°C. (*S*)-Isomer: 62% yield, $[\alpha]_D = +138.8$ (*c* 0.10, EtOH) (lit.:[4a] $[\alpha]_D = +134.5$ (*c* 0.004, EtOH)). (*R*)-Isomer: 60% yield, $[\alpha]_D = -132.6$ (*c* 0.10, EtOH) (lit.:[4a] $[\alpha]_D = -130.7$ (*c* 0.003, EtOH)). IR (film): $\nu = 3424$, 2955, 2939, 1727, 1197, 1106 and 773 cm^{-1}. HREIMS calcd for $C_{13}H_{12}O_3$ $[M]^+$ 216.0786, found 216.0795. EIMS, m/z (rel. int.) 216 $[M]^+$ (13.2), 171 (100), 155 (11.3), 128 (26.5). ^1H NMR δ 8.22 (1H, dm, $J = 9.2$ Hz), 7.88–7.85 (2H, m), 7.59 (1H, dd, $J = 7.2$, 0.8 Hz), 7.54–7.43 (3H, m), 5.39 (1H, s), 3.42 (3H, s). ^{13}C NMR δ 175.5, 134.0, 131.1, 131.0, 129.8, 128.7, 127.0, 126.7, 126.0, 125.2, 123.8, 80.6, 57.3.

4.2.5.2. (*R*)- and (*S*)-α-Methoxynaphthalen-2-ylacetic acid, 2-NMA, 6b.



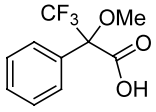
Obtained as white crystals, mp = 96.2–98.3°C. (*S*)-Isomer: 60% yield, $[\alpha]_D = +128.7$ (*c* 0.01, EtOH) (lit.:[4a] $[\alpha]_D = +120.0$ (*c* 0.0015, EtOH)). (*R*)-Isomer: 58% yield, $[\alpha]_D = -133.0$ (*c* 0.01, EtOH) (lit.:[4a] $[\alpha]_D = -120.8$ (*c* 0.005, EtOH)). IR (film): $\nu = 3395$, 2921, 2875, 1636, 1586, 1411 and 1078 cm^{-1}. HREIMS calcd for $[C_{12}H_{11}O]^+$ 171.0810, found 171.0817; calcd for $[C_{11}H_8O]^+$ 156.0575, found 156.0592. EIMS, m/z (rel. int.) 171 $[C_{12}H_{11}O]^+$ (98.2), 155 (11.3), 127 (46.2), 98 (100), 73 (39.1). ^1H NMR (CD_3OD) δ 7.91 (1H, s), 7.86–7.76 (3H, m), 7.57 (1H, m), 7.46 (2H, m), 4.84 (1H, s), 3.37 (3H, s). ^{13}C NMR (CD_3OD) δ 175.1, 133.4, 133.1, 132.9, 128.6, 128.0, 127.5, 126.9, 126.4, 126.3, 124.2, 82.2, 57.6.

4.2.5.3. (*R*)- and (*S*)-α-Methoxyphenylacetic acid, MPA 6e.



Obtained as white crystals, mp = 65–67°C. (*S*)-Isomer: 80% yield, $[\alpha]_D = +146.0$ (*c* 1.04, EtOH) (lit.:[7a] $[\alpha]_D = +143.4$ (*c* 1.0, EtOH)). (*R*)-Isomer: 79% yield, $[\alpha]_D = -144.0$ (*c* 1.03, EtOH) (lit.:[7b] $[\alpha]_D = -149.4$ (*c* 1.0, EtOH)). IR (film): $\nu = 3406$, 2961, 2921, 1624, 1456, 1407, 1260, 1087, 1022 and 799 cm^{-1}. HREIMS calcd for $[C_8H_9O]^+$ 121.0653, found 121.0657. EIMS, m/z (rel. int.) 121 $[C_8H_9O]^+$ (100), 105 (18.8), 87 (14.9), 77 (31.5). ^1H NMR (CD_3OD) δ 7.45 (2H, m), 7.32–7.26 (3H, m), 4.62 (1H, s), 3.28 (3H, s). ^{13}C NMR (CD_3OD) δ 178.3, 139.8, 129.3, 129.1, 128.8, 86.7, 57.0.

4.2.5.4. (*R*)- and (*S*)-α-Methoxy-α-(trifluoromethyl)phenylacetic acid, MTPA 6f.



Obtained as white crystals, mp = 42–44°C. (*S*)-Isomer: 78% yield, $[\alpha]_D = -71.6$ (*c* 0.226, EtOH) (lit.:[8] $[\alpha]_D = -71.8$ (*c* 3.28, MeOH)). (*R*)-Isomer: 82% yield, $[\alpha]_D = +69.8$ (*c* 0.22, EtOH) (lit.:[8] $[\alpha]_D = 68.5$ (*c* 1.49, MeOH)). IR (film): $\nu = 3329$, 1740, 1269, 1161, 1121, 1081, 1013 and 703 cm^{-1}. HREIMS calcd for $C_{10}H_9F_3O_3$ $[M]^+$ 234.0504, found 234.0487. EIMS, m/z (rel. int.) 234 $[M]^+$ (1.2), 189 (100), 175 (31.9), 119 (26.6), 105 (41.9), 91 (8.6), 77 (22.6). ^1H NMR (CD_3OD) δ 7.64–7.60 (2H, m), 7.46–7.42 (3H, m), 3.58 (3H, br s). ^{13}C NMR (CD_3OD) δ 171.3, 131.2, 130.0, 128.6, 127.4, 123.1 (q, $J_{C-F} = 287.2$ Hz), 84.5 (q, $J_{C-F} = 27.6$ Hz), 55.5.

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References

1. Aladro, F. J.; Guerra, F. M.; Moreno-Dorado, F. J.; Bustamante, J. M.; Jorge, Z. D.; Massanet, G. M. *Tetrahedron Lett*. **2000**, *41*, 3209.
2. Zhao, M.; Li, J. L.; Song, Z.; Tschaen, D. M.; Grabowsky, E. J. J.; Rinder, P. J. *J. Org. Chem*. **1999**, *64*, 2564.
3. (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc*. **1973**, *95*, 512; (b) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem*. **1986**, *51*, 2370; (c) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc*. **1991**, *113*, 4092; (d) Kusumi, T.; Fukushima, T.; Ohtani, I.; Kakisawa, H. *Tetrahedron Lett*. **1991**, *32*, 2939; (e) Trost, B. M.; Bunt, R. C.; Pulley, S. R. *J. Org. Chem*. **1994**, *59*, 4202; (f) Latypov, Sh. K.; Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Org. Chem*. **1995**, *60*, 1538; (g) Hoye, T. R.; Renner, M. K. *J. Org. Chem*. **1996**, *61*, 8489.
4. (a) Latypov, Sh. K.; Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Org. Chem*. **1995**, *60*, 504; (b) Seco, J. M.; Latypov, Sh. K.; Quiñoá, E.; Riguera, R. *Tetrahedron* **1997**, *53*, 8541; (c) Latypov, Sh. K.; Ferreiro, M. J.; Quiñoá, E.; Riguera, R. *J. Am. Chem. Soc*. **1998**, *120*, 4741; (d) Seco, J. M.; Quiñoá, E.; Riguera, R. *Tetrahedron: Asymmetry* **2001**, *12*, 2915.
5. Compounds **1c** and **1d** were prepared starting from the corresponding aldehyde by standard Wittig methodology.
6. Gao, S. H.; Wang, W.; Wang, B. H. *Chem. Lett*. **2001**, *1*, 48.
7. (a) The Aldrich Library of NMR Spectra, Pouchert, C. J., Ed.; Aldrich Chemical Company, 1983, Vol. II, p. 141; (b) The Aldrich Library of NMR Spectra, Pouchert, C. J., Ed.; Aldrich Chemical Company, 1983, Vol. II, p. 171.
8. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem*. **1969**, *34*, 2543.