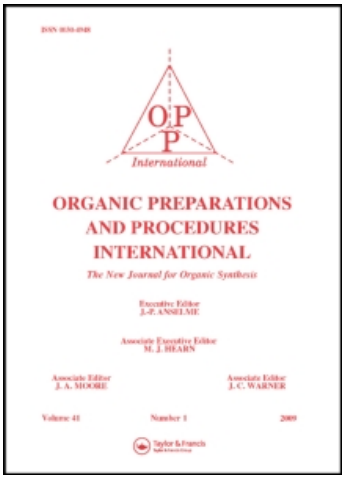

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SYNTHESIS OF α-HYDROXYTAMOXIFEN AND ITS 4-HYDROXY ANALOG

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SYNTHESIS OF α-HYDROXYTAMOXIFEN AND ITS 4-HYDROXY ANALOG

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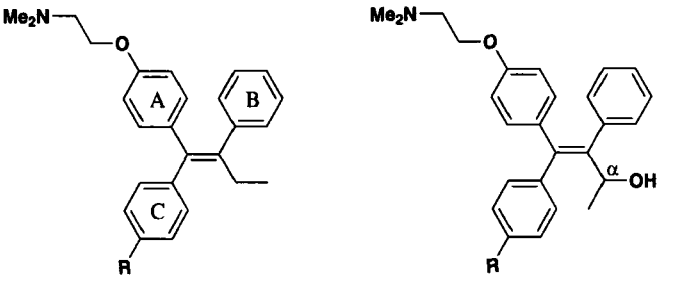
Tamoxifen is an anti-estrogen prescribed for the treatment of estrogen receptor-positive (ER+) breast cancer[1] and approved in the US for use as a chemopreventive agent for women who have an increased risk of developing cancer.[2] Although tamoxifen is a widely used adjuvant drug therapy, it is known to cause human endometrial cancer[3] as well as liver cancer in rats.[4] These observations have prompted many efforts to determine whether tamoxifen-induced endometrial carcinogenesis involves a genotoxic or hormonal mechanism.[5] Recent studies on tamoxifen-

DNA adduct formation have identified that α-hydroxytamoxifen (**7a**, *Fig. 1*), a metabolite of tamoxifen, contributes significantly to the damage induced in rat liver DNA.[6] Furthermore, DNA



tamoxifen (R = H)
4-hydroxytamoxifen (R = OH)

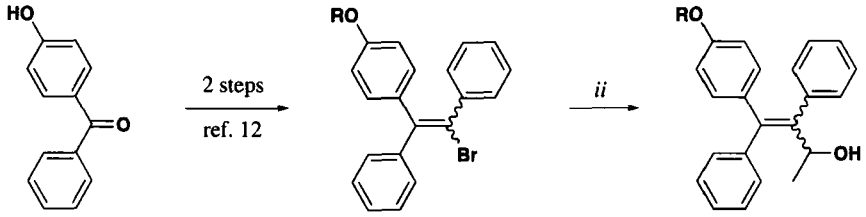
7a, R = H
7b, R = OH

Tamoxifen and its metabolites

Fig. 1

adducts derived from this metabolite also have been detected in human endometrial tissue.[7] Consequently, α-hydroxytamoxifen and its acetate ester are of great interest as tools for studying the mechanism of tamoxifen-DNA adduct formation and also for producing adducted oligonucleotides for use in biological studies aimed at understanding the mutagenic process.[8] Moreover, 4-hydroxytamoxifen (*Fig. 1*), a primary metabolite of tamoxifen, also generates DNA-adducts as a consequence of α-hydroxylation[9] and thus is used in similar fashion to probe the pathway for DNA-adduct formation.[10] We report herein new syntheses of α-hydroxytamoxifen and its analog, α-hydroxy-4-hydroxytamoxifen (**7b**).

The sole reported synthesis of **7a** by Foster *et al.*[11] began with 4-hydroxybenzophenone (**1**, *Scheme 1*), and proceeded in two steps to give vinyl bromide **2** as a mixture of diastereomers.[12] Phenol alkylation gave aminobromide **3** as a 2:1 *E:Z* mixture of products. After



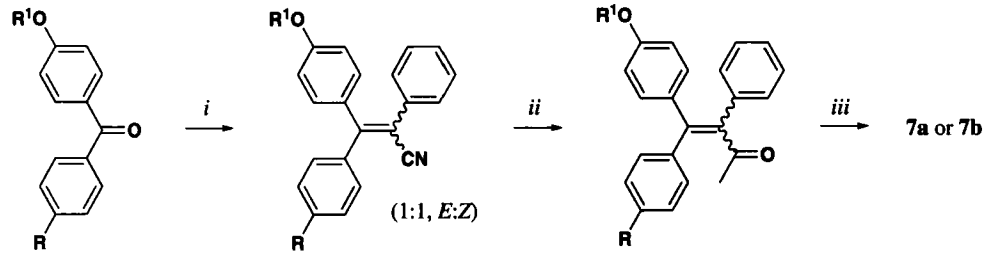
i) NaH, $ClCH_2CH_2NMe_2$, DMF, 60°C, 89%. *ii*) a. *n*-BuLi, THF, -78 to 0°C, b. CH_3CHO, 55%

Scheme 1

recrystallization to separate the isomers, lithium-halogen exchange on (*E*)-**3** followed by reaction with ethanal afforded α-hydroxytamoxifen as a 3:2 E:Z mixture in 55% yield. The facile *E:Z* isomerization of tamoxifen and its analogs is well documented,[13] and *in vivo* studies have shown that both the (*E*)- and (*Z*)-isomers readily isomerize during the process of DNA-adduct forma-

tion.[14] With these considerations in mind, we opted to use a similar approach for installation of the A, C-ring system, but sought to improve introduction of the α-hydroxy moiety by using a reduction strategy.

Our syntheses of the title compounds began by condensation of phenylacetonitrile with ketones **4a**[15] and **4b**[16] (*Scheme 2*). The 1,2-addition reactions of metallated phenylacetonitrile with aldehydes and ketones has been the subject of several recent studies.[17] We found that treatment of either **4a** or **4b** with the sodium salt of phenylacetonitrile under forcing conditions



4a, R = H
4b, R = OMOM

5a, R = H (92%)
5b, R = OMOM (97%)

6a, R = H (87%)
6b, R = OH (86%)

$R^1 = CH_2CH_2NMe_2$; *i*) a. PhCH(CN)Na (5 equiv), THF, reflux, 12 h; b. 2.5:2.5:1.0 THF: MeOH:10% HCl, rt,1.5 h; *ii*) a. MeLi (4 equiv.), THF, -78°C to rt, 12 h; b. 1:2 THF:2N HCl, reflux, 6.5 h (for **10**), 14 h (for **11**); *iii*) $CeCl_3$ (4 equiv), $NaBH_4$ (16 equiv.), MeOH, rt, 3 h

Scheme 2

followed by acid treatment to induce β-elimination of the corresponding tertiary alcohols gave vinyl nitriles **5a** and **5b**, respectively. The vinyl nitriles were obtained as 1:1 *E*:*Z* mixtures in 92% and 97% yields, respectively. Conversion of **5a** and **5b** to the corresponding methyl ketones was accomplished by reaction with excess methyllithium and subsequent hydrolysis of the isolable[18] imine intermediates. The imine derived from the reaction of nitrile **5b** required a longer period of exposure to acid for hydrolysis to be complete, and these conditions also cleaved the methoxymethyl (MOM) protection group. 1,2-Reduction of enone **6a** to the title alcohol was achieved using the Luche conditions.[19] The reduction using excess $CeCl_3 \cdot NaBH_4$ was superior to our attempts using either lithium aluminum hydride or diisobutylaluminum hydride, giving alcohol **7a** as a 1:1 *E*:*Z* mixture in 91% yield. Though clean, similar reduction of enone **6b** was sluggish and afforded lower yields of the corresponding alcohol, which was isolated in 32% yield as an *E*:*Z* mixture with a 48% recovery of unreacted starting material. Column chromatographic separation of the product mixture required the addition of 1% triethylamine to the MeOH-CH_2Cl_2 eluent to separate **7b** (also as a mixture of isomers).

EXPERIMENTAL SECTION

THF and Et_2O were distilled from Na-benzophenone ketyl immediately prior to use. All reagents were purchased from Aldrich Chemical Company (Milwaukee, WI) and used as received. NMR spectra were recorded in $CDCl_3$ with a Varian spectrometer (^1H at 300 MHz, ^{13}C at 75 MHz).

Infrared spectra were recorded on a Mattson FTIR 3000 spectrometer. Melting points are uncorrected. Elemental analyses were performed by Midwest Microlabs (Indianapolis, IN).

(*E*,*Z*)-3-[4-(2-Dimethylaminoethoxy)phenyl]-2,3-diphenylacrylonitrile (5a).- To a suspension of NaH (2.40 g, 11.0 mmol) in Et_2O (100 mL) at rt was added phenylacetonitrile (11.5 mL, 100 mmol). The reaction mixture was heated to reflux for 2.5 h and then cooled to rt whereupon a solution of ketone **4a** (5.39 g, 20 mmol) in THF (60 mL) was added *via* cannula. The resultant maroon solution was heated overnight at reflux. The reaction mixture was cooled to rt and the solvents were removed by rotary evaporation. The residue was dissolved in a 2.5 : 2.5 : 1 solvent mixture of THF : MeOH : 2N HCl (120 mL) and stirred at rt for 1.5 h. The solvents were concentrated by rotary evaporation and the aqueous layer was extracted with Et_2O. The ethereal extract was discarded and the aqueous layer was then extracted several times with $CHCl_3$. The combined $CHCl_3$ extract containing the hydrochloride was washed successively with sat'd aq. $NaHCO_3$, water and brine, and then dried (Na_2SO_4). The solvents were removed *in vacuo* and the residue was chromatographed (SiO_2), eluting first with ethyl acetate followed by a 19:1 solvent mixture of $CHCl_3$:MeOH, to yield nitrile **5a** (6.65 g, 92%) as a 1:1 mixture of *E*:*Z* diastereomers as a light orange oil; R*f* = 0.27 (CH_2Cl_2:MeOH, 9:1); IR: 2942, 2204, 1604, 1508 cm^{-1}; ^1H NMR: δ 7.44-7.38 (m, 6H), 7.29-7.16 (m, 14H), 7.02-6.89 (m, 6H), 6.70 (d, *J* = 8.8 Hz, 2H), 4.10 (t, *J* = 5.8 Hz, 2H), 3.99 (t, *J* = 5.8 Hz, 2H), 2.74 (t, *J* = 5.8 Hz, 2H), 2.68 (t, *J* = 5.8 Hz, 2H), 2.34 (s, 6H), 2.30 (s, 6H); ^{13}C NMR: δ 159.9, 159.1, 157.18, 157.13, 140.3, 138.9, 134.9, 134.8, 132.3, 132.2, 131.3, 130.8, 130.6, 129.7, 129.5, 129.4, 129.3, 128.6, 128.2, 128.12, 128.11, 127.8, 127.7, 120.3, 120.2, 114.0, 13.9, 109.9, 109.6, 66.89, 66.82, 58.0, 45.8, 45.7.

Anal. Calcd for $C_{25}H_{24}N_2O$: C, 81.49; H, 6.57; N, 7.60. Found: C, 81.37, H, 6.53, N, 7.57

(*E*,*Z*)-3-[4-(2-Dimethylaminoethoxy)phenyl]-3-(4-methoxymethoxyphenyl)-2-phenylacrylonitrile (5b).- To a suspension of NaH (2.26 g, 94.3 mmol) in Et_2O (95 mL) was added phenylacetonitrile (10.8 mL, 93.4 mmol) at rt. The reaction mixture was heated to reflux for 2.5h and then cooled to rt before addition of a solution of ketone **4b** (6.15 g, 18.7 mmol) in THF (62 mL) via cannula. The resultant maroon solution was heated to reflux overnight. The reaction solution was then cooled to rt and the solvents were removed by rotary evaporation. The residue was dissolved in a 2.5:2.5:1 solvent mixture of THF: MeOH: 2N HCl (120 mL) and stirred 1.5h at rt. The solvents were then removed by rotary evaporation and the aqueous layer was extracted with Et_2O. The ethereal extract was discarded and the aqueous layer was extracted with $CHCl_3$ (4x). The combined $CHCl_3$ extract was washed successively with sat'd aq. $NaHCO_3$, water and brine, and then dried (Na_2SO_4). The solvents were removed *in vacuo* and the residue was chromatographed (SiO_2), eluting first with ethyl acetate and followed by $CHCl_3$:MeOH (19:1), to give nitrile **5b** (7.76 g, 97%) as a 1:1 mixture of E/Z diastereomers as a light orange oil; R*f* = 0.43 (CH_2Cl_2:MeOH, 9:1); IR: 2945, 2202, 1654, 1598 cm^{-1}; ^1H NMR: δ 7.38 (d, *J* = 8.8 Hz, 2H), 7.38-7.19 (m, 12H), 7.05 (d, *J* = 8.8 Hz, 2H), 6.93 (m, 4H), 6.81 (d, *J* = 8.8 Hz, 2H), 6.70 (d, *J* = 8.8 Hz, 2H), 5.22 (s, 2H), 5.13 (s, 2H), 4.11 (t, *J* = 5.7 Hz, 2H), 4.00 (t, *J* = 5.7 Hz, 2H),

3.50 (s, 3H), 3.45 (s, 3H), 2.75 (t, J = 5.6 Hz, 2H), 2.69 (t, J = 5.7 Hz, 2H), 2.35 (s, 6H), 2.31 (s, 6H); ^{13}C NMR: δ 160.1, 159.3, 158.4, 157.7, 157.0, 156.9, 135.2, 133.8, 132.7, 132.5, 132.3, 131.6, 131.2, 129.54, 129.53, 129.2, 128.6, 128.2, 127.8, 120.8, 120.7, 115.6, 115.5, 114.16, 114.1, 113.9, 108.8, 108.7, 94.1, 94.0, 65.9, 65.8, 58.0, 56.0, 45.8, 45.8; HRMS (DEI): Calcd for $C_{27}H_{28}N_2O_3$: 428.2100. Found: 428.2097 (M^+).[20]

(*E*,*Z*)-4-[4-(2-Dimethylaminoethoxy)phenyl]-3,4-diphenyl-but-3-en-2-one (6a).- To a solution of MeLi (50 mL, 1.4 M solution in Et_2O) in THF (18 mL) at -78° was added dropwise *via* cannula a -78° solution of nitrile **5a** (6.45 g, 17.5 mmol) in THF (68 mL). The resulting purple solution was allowed to warm to rt overnight and then poured over 10% aq. Na_2CO_3 and extracted with CH_2Cl_2 (3x). The combined organic extract was concentrated by rotary evaporation. The imine residue was dissolved in a 2:1 mixture of 2N HCl:THF (120 mL) and heated 6.5 h at 70°. The reaction mixture was then cooled, carefully basified with 10% aq. Na_2CO_3 and extracted with Et_2O (3x). The combined ethereal extract was washed with water and brine, and dried (Na_2SO_4). The solvents were removed *in vacuo* and the residue was chromatographed (SiO_2) using gradient elution ($CHCl_3$ to $CHCl_3$:MeOH, 19:1) to obtain ketone **6a** (5.80 g, 87%) as a light yellow oil; R*f* = 0.41 (CH_2Cl_2:MeOH, 9:1); IR: 2944, 1684, 1605, 1508 cm^{-1}; ^{1}H NMR: δ 7.34 – 6.97 (m, 22H), 6.87 (m, 4H), 6.64 (d, J = 6.7 Hz, 2H), 4.07 (t, J = 5.8 Hz, 2H), 3.97 (t, J = 5.8 Hz, 2H), 2.74 (t, J = 5.8 Hz, 2H), 2.67 (t, J = 5.8 Hz, 2H), 2.34 (s, 6H), 2.30 (s, 6H), 2.08 (s, 3H), 2.04 (s, 3H); ^{13}C NMR: δ 206.1, 205.7, 158.9, 157.9, 144.7, 144.6, 141.8, 141.26, 141.21, 140.5, 138.7, 133.7, 132.6, 132.0, 130.9, 130.6, 129.8, 129.7, 129.5, 128.0, 127.9, 127.8, 127.2, 127.1, 126.8, 126.7, 114.0, 113.3, 65.5, 65.3, 57.7, 57.1, 45.4, 45.4, 31.0, 30.9; HRMS (DEI): Calcd for $C_{26}H_{27}NO_2$: 385.2042. Found: 385.2031 (M^+).[20]

(*E*,*Z*)-4-[4-(2-Dimethylaminoethoxy)phenyl]-4-(4-hydroxyphenyl)-3-phenyl-but-3-en-2-one (6b).- To a solution of MeLi (32 mL, 1.4 M in Et_2O) in THF (16 mL) at -78° was added dropwise *via* a cannula a solution of nitrile **5b** (5.50 g, 12.8 mmol) in THF (48 mL) at –78°. The resulting purple solution was allowed to warm to rt overnight and then poured over 10% aq. Na_2CO_3 and extracted with CH_2Cl_2. The organic extract was concentrated by rotary evaporation and the residue was dissolved in a 2:1 mixture of 2N HCl:THF and heated to 70° for 14 h. The reaction mixture was cooled to rt, carefully basified with 10% aq. Na_2CO_3 and extracted with Et_2O (3x). The combined ether extract was washed with water and brine, dried (Na_2SO_4), and the solvents were removed *in vacuo*. The residue was chromatographed (SiO_2) using gradient elution ($CHCl_3$ to $CHCl_3$:MeOH, 9:1) to obtain ketone **6b** (4.45 g, 86%) as an off-white solid; mp. 194.3-195.7°; R*f* = 0.47 (CH_2Cl_2:MeOH, 4:1); IR 3340, 2950, 1693, 1602, 1507 cm^{-1}; ^{1}H NMR: δ 7.20-7.10 (m, 6H), 7.01 (m, 6H), 6.77 (m, 8H), 6.51 (d, J = 6.6 Hz, 2H), 6.46 (d, J = 8.8 Hz, 2H), 6.24 (d, J = 9.0 Hz, 2H), 4.05 (t, J = 5.3 Hz, 2H), 3.93 (t, J = 5.3 Hz, 2H), 2.84 (t, J = 4.9 Hz, 2H), 2.78 (t, J = 4.9 Hz, 2H), 2.43 (s, 6H), 2.38 (s, 6H), 2.04 (s, 3H), 2.01 (s, 3H); ^{13}C NMR δ 207.7, 207.6, 159.0, 158.4, 158.0, 157.1, 146.4, 146.1, 140.1, 139.8, 133.5, 133.0, 132.6, 132.4, 132.0, 131.5, 131.3, 130.38, 130.30, 129.3, 128.29, 128.23, 126.8, 116.1, 115.4, 113.9,

113.1, 64.0, 63.8, 58.0, 45.6, 44.9, 31.6, 31.4; HRMS (DEI): Calcd for $C_{26}H_{27}NO_3$: 401.1991. Found: 401.1998 (M+).[20]

(*E,Z*)-4-[4-(2-Dimethylaminoethoxy)phenyl]-3,4-diphenyl-but-3-en-2-ol (7a).- To a solution of ketone **6a** (0.24 g, 0.62 mmol) in CH_3OH (6 mL) at rt was added $CeCl_3$ (0.307 g, 1.24 mmol). The reaction mixture was stirred 30 min. before addition of $NaBH_4$ (0.19 g, 5.0 mmol) in eight portions over 20 min. The reaction mixture was stirred 30 minutes at rt before a second addition of $CeCl_3$ (0.307 g, 1.24 mmol) in one portion followed again by the addition of $NaBH_4$ (0.19 g, 5.0 mmol) in eight portions over 20 min. After 30 min., the reaction mixture was poured over sat'd aq. NH_4Cl and extracted with Et_2O. The organic extract was washed with water and brine, and then dried (Na_2SO_4). The solvents were removed *in vacuo* and the residue was chromatographed (SiO_2) using a gradient elution ($CHCl_3$ to $CHCl_3$:MeOH, 95:5). Alcohol **7a** (0.129 g, 91%) was obtained as a 1:1 mixture of *E*:*Z* diastereomers as a light yellow oil, and spectral analysis of this product agreed with reported values;[11] IR: 3216, 2937, 1605, 1508 cm^{-1}; ^1H NMR: δ 7.36-7.13 (m, 16H), 6.99 (m, 4H), 6.90 (m, 4H), 6.80 (d, *J* = 6.8 Hz, 2H), 6.54 (d, *J* = 6.8 Hz, 2H), 4.91 (q, *J* = 6.6 Hz, 1H), 4.83 (q, *J* = 6.6 Hz, 1H), 4.07 (t, *J* = 5.9 Hz, 2H), 3.88 (t, *J* = 5.9 Hz, 2H), 2.73 (t, *J* = 5.9 Hz, 2H), 2.61 (t, *J* = 5.9 Hz, 2H), 2.33 (s, 6H), 2.26 (s, 6H), 2.08 (m, 2H) 1.20 (m, 4H); ^{13}C NMR: δ 157.8, 156.9, 142.3, 142.1, 141.9, 141.5, 140.6, 138.3, 138.2, 134.4, 133.9, 131.3, 131.1, 131.0, 130.6, 130.1, 129.5, 128.1, 127.6, 127.5, 127.2, 126.9, 126.4, 125.9, 114.1, 113.2, 67.9, 67.7, 65.8, 65.5, 58.2, 58.1, 45.8, 45.7, 22.4, 22.3.

4-{1-[4-(2-Dimethylaminoethoxy)phenyl]-3-hydroxy-2-phenyl-but-1-enyl}-phenol (7b).- To a solution of ketone **6b** (0.67 g, 1.8 mmol) in CH_3OH (15 mL) at rt was added $CeCl_3 \cdot 7H_2O$ (1.42 g, 3.81 mmol). The reaction mixture was stirred 30 min. before addition of $NaBH_4$ (0.58 g, 15.0 mmol) in eight portions over 20 min. The reaction mixture was stirred 30 minutes at rt before the second addition of $CeCl_3 \cdot 7H_2O$ (1.42 g, 3.81 mmol) in one portion followed again by addition of $NaBH_4$ (0.58 g, 15.0 mmol) in eight portions over 20 min. After 30 min., the reaction mixture was poured over sat'd aq. $NaHCO_3$ and extracted with Et_2O. The combined organic extract was washed with water and brine, and then dried (Na_2SO_4). The solvents were removed *in vacuo* and the residue was purified by SiO_2 column chromatography ($CHCl_3$:MeOH:Et_3N, 94:5:1) to obtain ketone **6b** (0.32 g, 48% recovery) and alcohol **7b**. To remove accompanying triethylamine, the alcohol fraction was dissolved in CH_2Cl_2 and washed successively with sat'd NH_4Cl and $NaHCO_3$. The solvent was removed to obtain **7b** (0.22g, 32%) as a 1:1 mixture of *E*:*Z* isomers as a light yellow oil. Stereochemical assignment of the isomers was made by comparison to data reported for the (*E*)-isomer.[9] **(*E*)-7b**: R*f* = 0.18 (CH_2Cl_2:MeOH, 4:1); IR: 3325, 2971, 1608, 1505 cm^{-1}; ^1H NMR: δ 7.21-7.12 (m, 5H), 7.02 (d, *J* = 8.7 Hz, 2H), 6.76 (d, *J* = 8.7 Hz, 2H), 6.71 (d, *J* = 8.7 Hz, 2H), 6.25 (d, *J* = 8.7 Hz, 2H), 4.94 (q, *J* = 6.6 Hz, 1H), 3.90 (t, *J* = 5.4 Hz, 2H), 2.76 (m, 2H), 2.37 (s, 6H), 1.18 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR: δ 157.4, 156.5, 156.2, 155.1, 140.6, 140.4, 138.8, 135.0, 134.5, 133.6, 132.7, 131.6, 131.5, 131.1, 130.8, 130.7, 127.6, 126.2, 115.5, 114.6, 113.8, 112.8, 68.7, 64.6, 64.1, 57.9, 45.2, 45.0, 22.3.

(Z)-7b: R*f* = 0.16 (CH_2Cl_2:MeOH, 4:1); IR: 3419, 2965, 1604, 1506 cm^{-1}; ^1H NMR: δ 7.22-7.12 (m, 5H), 7.08 (d, *J* = 9.0 Hz, 2H), 6.75 (d, *J* = 8.4 Hz, 2H), 6.71 (d, *J* = 8.4 Hz, 2H), 6.43 (d, *J* = 8.4 Hz, 2H), 4.90 (q, *J* = 6.6 Hz, 1H), 4.07 (t, *J* = 5.4 Hz, 2H), 2.70 (m, 2H), 2.44 (s, 6H), 1.20 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR: δ 156.8, 156.4, 140.8, 140.7, 139.1, 135.2, 133.0, 131.7, 131.3, 131.0, 127.9, 126.5, 115.7, 113.0, 68.4, 64.1, 58.2, 45.2, 22.6.

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18. The imines derived from **8** and **9** display diastereomeric methyl singlet signals in their ^{1}H NMR spectra (300 MHz, $CDCl_3$) at δ 2.01, 1.97 and δ 1.99, 1.98, respectively.

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20. Michael acceptors **5b**, **6a** and **6b** appear to be somewhat sensitive to storage at room temperature and are known to equilibrate upon exposure to light. Several attempts to obtain elemental analyses always gave combustion data that were slightly off the acceptable tolerance of 0.30.