Notes

Enantiomerically Pure Ketals: Diastereofacial Selectivity in the Halogenation of Enol Ethers

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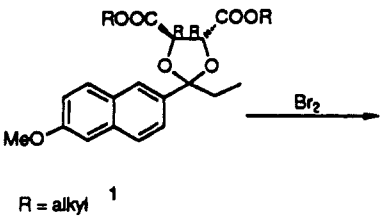
(2*R*,3*R*)- and (2*S*,3*S*)-Tartaric acids are often used as chiral auxiliaries in directing asymmetric functionalization of prochiral olefins.[1-3] For example, the electrophilic bromination of tartrate ketals constitutes the key step (Scheme I) in the industrial asymmetric synthesis of (*S*)-(+)-2-(6-methoxy-2-naphthyl)propanoic acid (Naproxen).[1d,e] The diastereoselectivity of the bromination depends upon the geometry of the enol ether and the diastereofacial selectivity of attack on the enol ether. The lack of information on the stereochemical integrity and composition of the enol ether(s) **4** (Scheme II) forms a major deficiency in providing a mechanistic understanding.

Studying enol ethers of defined geometry provides an opportunity to explore the question of diastereofacial selectivity induced by a chiral auxiliary. The present paper reports that halogenating ketals **5** (n = 1) and **6** (n = 0), where the corresponding enol ethers are constrained to a single geometry, produces *unprecedently* high diastereoselective chlorination and iodination as well as bromination (Scheme III).

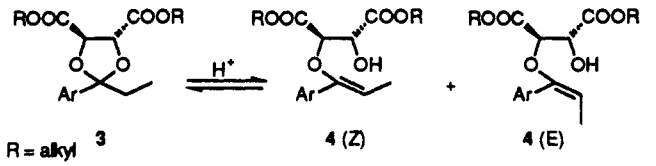
Sulfuryl chloride, iodine chloride, and bromine react in methylene chloride at −10 °C with **5** (n = 1) to provide, in yields higher than 95% (Table I, entries 1–3), epimeric mixtures of α-chloro **8a**, **9a**, α-iodo **8b**, **9b**, and α-bromo **8c**, **9c** ketals,[4] respectively. The epimer having the *S* configuration at the carbon bearing the halogen, i.e. **8a**, **8b**, **8c**, strongly prevails over the other (**9a**, **9b**, **9c**) (see Table I). The ready crystallization of the major epimers allows their isolation, in a ca. 70% yield, in diastereomeric pure form from the crude reaction (see the Experimental Section), thus enhancing the diastereomerically purity of the α-halo ketals to 100%. The epimeric ratio for both α-bromo and α-iodo ketals changes slowly under the reaction conditions, until the equilibrium ratio of ca. 1:1 is reached. α-Chloro ketals require the addition of hydrobromic acid to epimerize to the 1:1 equilibrium ratio.

Due to the easier epimerization of the α-halo ketals **10,11a–c** the halogenation of ketal **6** (n = 0) is carried out at lower temperature. Analysis of the data reported in Table I (entries 4–6) reveals that the halogenation of **6** (n = 0) parallels that of ketal **5** (n = 1) providing, in high

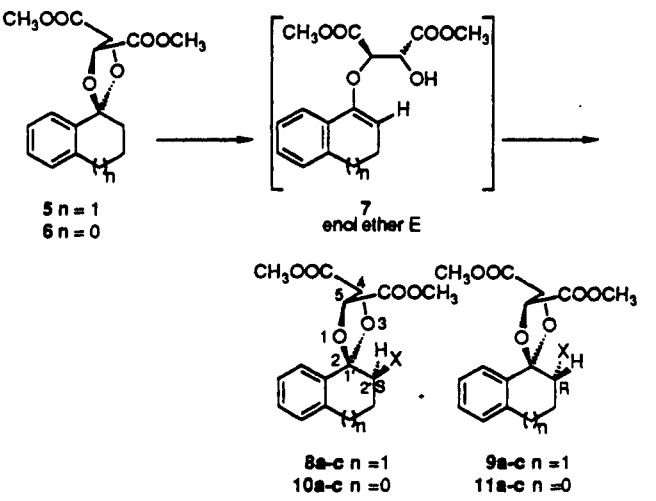
Scheme I



Scheme II



Scheme III



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(4) An independent synthesis of ketals **8,9a–c** consists of submitting to ketalization α-chloro-, α-bromo-, and α-iodotetralone with dimethyl ester of (2*R*,3*R*)-tartaric acid, respectively. In all the cases a ca. 1:1 epimeric mixture is obtained (see the Experimental Section).

(5) All the products are new and are fully characterized by ^1H and ^{13}C NMR, IR, and mass spectra and elemental analyses.

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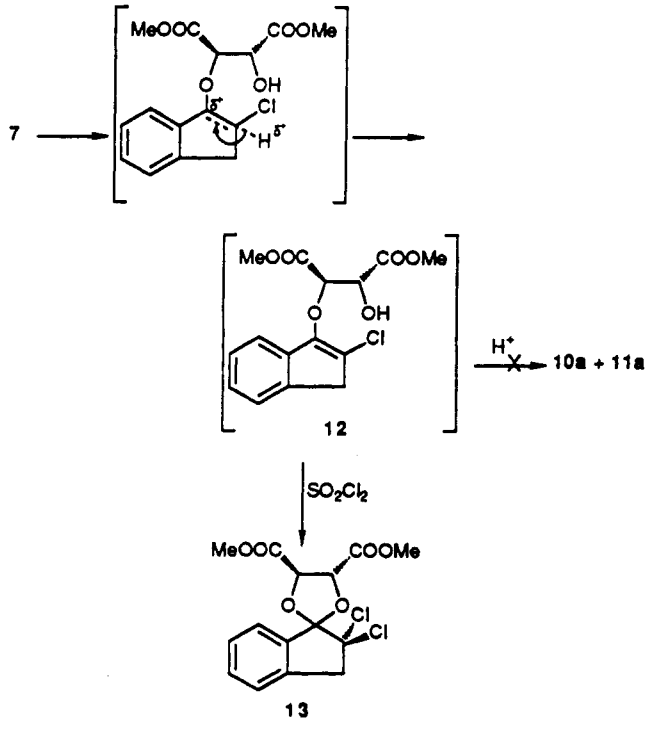
Table I[a] Halogenation of 5 and 6[b]

entry	n	X	products	T, °C	t, min [h]	yield, %	ratio of 8/9 or 10/11
1	1	Cl	**8a + 9a**	-10	[2.5]	98	88:12
2	1	I	**8b + 9b**	-10	2	99	80:20
3	1	Br	**8c + 9c**	-10	1.5	99	86:14
4	0	Cl	**10a + 11a**	-10	5	80	80:20
5	0	I	**10b + 11b**	-40	2	96	81:19
6	0	Br	**10c + 11c**	-40	12	95	89:11

[a] Halogenating agent: (SO_2Cl_2, ICl, Br_2) (5 mmol), substrate (5 mmol), solvent methylene chloride. Yields are based on the starting ketals and are determined by HPLC and ^1H NMR analyses on the crude reaction.

Scheme IV



yields, diastereomeric mixtures of α-halo ketals (**10,11a**,[6] **10,11b**, **10,11c**) enriched in the epimer (**10a**, **10b**, **10c**) having the *S* configuration at the carbon bearing the halogen. For all the α-halo ketals **10,11a–c**, a ca. 1:1 epimeric ratio represents the equilibrium composition in the solvent of the reaction. Thus chlorination, iodination, and bromination of both **5** and **6** occur under kinetically controlled conditions.

The relative configuration of the stereogenic centers of chloro derivative **8a** is determined by X-ray structure analysis. Since the absolute configuration of the tartrate moiety is known to be *R,R*, the absolute configuration at C_2' can be assigned as *S*. The great similarity of the CD as well as the NMR spectra of **8a–c** (see the Experimental Section) suggests the identity of the absolute configuration for the bromo **8c** and the iodo **8b** analogues. The configuration at the C_2' for compounds **10,11a–c** is determined by nuclear Overhauser effect (NOE). The enhancement of 8% observed between the hydrogen on C_2' and the one on C_4 (known to be *R*) in the case of compounds **10a–c**, which is absent for the epimers **11a–c**, establishes the configuration at the C_2' as *S* for the former and *R* for the latter.

The above results appear to be of particular interest for three main reasons: (i) this is the first example of diastereoselective iodination and chlorination of enantiomerically pure ketals, the latter being particularly noteworthy because of the high reactivity of chlorinating agents intuitively lead one to expect low selectivity; (ii) the reaction shows high diastereoselectivity for very different halogenating species: Br_2, SO_2Cl_2, and ICl; (iii) the diastereoselectivity favoring the *S* epimer observed in the halogenation of the *E* enol ethers (Scheme III), generated under the reaction conditions from **5** and **6**, contrasts with the mechanism proposed for the bromination of **3** (Scheme II) as far as it predicts the predominance of the *R* epimer from the *E* enol ether.[1c]

The above considerations suggest that the previous mechanism proposed for the bromination of ketals **3** of acyclic alkyl aryl ketones[1c] needs to be reconsidered.

Experimental Section

^1H NMR spectra were taken at 300 MHz for solutions in deuterated solvents. The chemical shifts are expressed in ppm (δ) and are relative to internal tetramethylsilane. ^{13}C NMR spectra were run at 75.4 MHz for solutions in deuterated solvents, by using coupled and uncoupled techniques. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. CD spectra were taken on a JASCO J500C dichrograph. IR spectra were taken on a Perkin-Elmer 1420 instrument. Analytical TLC analyses were performed by using precoated silica gel 60 F_{254} plates supplied by Merck; visualization was accomplished under ultraviolet light (λ 254, λ 366 nm) and with iodine vapor. Chromatographic separations were accomplished by flash column chromatography by using silica gel (230–400 mesh; Merck). Melting points were measured on a Koefler apparatus and are not corrected. Chemical ionization mass spectra were recorded on a Finnigan MAT 8220 mass system operating at 110 eV, equipped with a Data General Nova 4X data system with 2-methylpropane as ionizing agent. The removal of solvents under reduced pressure refers to the evaporation of the solvent at ca. 20 mmHg on a Büchi rotary evaporator. The distillations in vacuo were carried out by using a Leybold-Hereaus TRIVAC-B diffusive pump. All reactions were run under nitrogen atmosphere. All solvents and reagents were commercially available (reagent grade) and were used without further purification.

Ketals 5 and 6. A mixture of (2*R*,3*R*)-tartaric acid dimethyl ester (17.81 g, 0.1 mol), trimethylorthoformate (10.61 g, 0.1 mol), and sulfuric acid (0.01 mol) was heated at 70 °C (external heating) for 30 min, while methanol distilled off. α-Tetralone (0.1 mol) or α-indanone (0.1 mol) was added under stirring at 20 °C to the residue dissolved in methylene chloride (50 mL), and the mixture was stirred until disappearance of the starting ketone (TLC; *n*-hexane–diethyl ether, 7:3). The solution was poured into a 10% aqueous sodium bicarbonate solution (100 mL) and extracted with methylene chloride (50 mL). Removal of the solvent under reduced pressure from the combined organic extracts gave an oily residue which was purified by distillation in vacuo.

5: yield 94%; bp 185–190 °C (4×10^{-5} mbar); mp 54 °C (from diisopropyl ether); $[\alpha]^{20}_D = -9.4°$ ($c = 1$, $CHCl_3$); IR (1% in KBr) ν 1740, 1760 cm^{-1} (C=O stretching); ^1H NMR ($CDCl_3$) 1.93–2.15 (m, 4 H), 2.77–2.82 (m, 2 H), 3.83 (s, 3 H), 3.84 (s, 3 H), 4.95 (AB q, 2 H, $\Delta\nu = 7$ Hz), 7.07–7.65 (m, 4 H); ^{13}C NMR ($CDCl_3$) 20.16, 28.57, 33.93, 52.51, 76.63, 77.24, 111.87, 126.00, 126.56, 128.23, 128.85, 134.66, 138.50, 169.08, 170.95; MS *m/e* 306 (M^+), 278 (M – CO)$^+$, 247 (M –COOMe)$^+$. Anal. Calcd for $C_{16}H_{18}O_6$: C, 62.74; H, 5.92; O, 31.33. Found: C, 62.90; H, 5.96; O, 30.96.

6: Yield 50%; bp 164 °C (4×10^{-5} mbar); ^1H NMR ($CDCl_3$) 2.36 (part A, $AA'B_2$, 1 H, $J = 13.7$ Hz, $J = 6.8$ Hz, $J = 6.8$ Hz), 2.50 (part A', $AA'B_2$, 1 H, $J = 13.7$ Hz, $J = 6.8$ Hz, $J = 6.8$ Hz), 2.98 (part B_2, $AA'B_2$, 2 H, $J = 6.8$ Hz, $J = 6.8$ Hz), 3.84 (s, 3 H), 3.85 (s, 3 H), 4.98 (AB q, 2 H, $J = 5.4$ Hz, $\Delta\nu = 13.1$ Hz), 7.21–7.47 (m, 4 H); ^{13}C NMR ($CDCl_3$) 28.18, 37.25, 52.44, 77.11, 77.19, 121.63,

(6) Dichloro derivative **13** is the major byproduct (8% yield) in the chlorination of **6**. The fact that neither the ratio between **10a** and **11a** nor the ratio between **13** and the monochloro ketals (**10a + 11a**) change under the reaction conditions at different conversions of **6** suggests **12** to be intermediate in the formation of **13** (Scheme IV).

124.72, 126.65, 129.90, 139.58, 143.69, 169.34, 169.74; MS m/e 292 (M^+).

Halogenation of 5 and 6 (Table I). General Procedure. One milliliter of a freshly prepared 5 M methylene chloride solution of the halogenating reagent (SO_2Cl_2, ICl, or Br_2) was added under stirring at the temperature given in Table I to a solution of **5** (0.005 mol) or **6** (0.005 mol) in methylene chloride (10 mL). The reaction mixture was stirred for the time given in Table I and poured into a 10% aqueous sodium carbonate solution (25 mL) cooled to 0 °C. The aqueous phase was extracted with methylene chloride (2 × 15 mL). The combined organic extracts were washed with water and dried over sodium sulfate. Evaporation of the solvent under reduced pressure gave a residue consisting of the epimeric α-halo ketals. In the case of **5**, crystallization of the residue afforded **8a**, **8b**, and **8c** in diastereomerically pure form.

8a: yield 75%; mp 107–108 °C (from 2-propanol); $[\alpha]^{20}_D$ = +18° (c = 1; chloroform); CD (MeOH) λ_{max}, nm (ϵ, M^{-1} cm^{-1}), 253 sh (−0.15), 257 (−0.26), 264 (−0.38), 270 sh (−0.29), 290 (−0.03); IR (1% in KBr) ν 1760, 1725 cm^{-1} (C=O stretching); ^1H NMR (DMSO) 2.15–2.45 (m, 2 H), 2.80–3.05 (m, 2 H), 3.69 (s, 3 H), 3.77 (s, 3 H), 4.61 (dd, 1 H, J = 7 Hz, J = 3 Hz), 5.18 (AB q, 2 H, J = 5.9 Hz, $\Delta\nu$ = 12.7 Hz), 7.16–7.57 (m, 4 H); ^{13}C NMR (DMSO) 24.41, 28.05, 52.51, 60.81, 77.25, 77.79, 110.02, 126.03, 126.56, 128.31, 129.14, 133.40, 136.52, 168.58, 168.97; MS m/e 341 $(M + 1)^+$. Anal. Calcd for $C_{16}H_{17}ClO_6$: C, 56.39; H, 5.03; Cl, 10.40; O, 28.17. Found: C, 56.28; H, 5.01; Cl, 10.35; O, 28.19.

9a: ^1H NMR (DMSO) 2.2 (m, 1 H), 2.5 (m, 1 H), 2.83 (m, 1 H), 3.03 (m, 1 H), 3.76 (s, 3 H), 3.81 (s, 3 H), 4.60 (dd, 1 H, J = 6.1 Hz, J = 2.5 Hz), 5.06 (AB q, 2 H, J = 6.6 Hz, $\Delta\nu$ = 17.7 Hz), 7.13–7.71 (m, 4 H); ^{13}C NMR (DMSO) 24.03, 27.54, 52.49, 59.56, 76.94, 77.35, 110.11, 126.10, 126.84, 128.10, 129.09, 132.72, 136.51, 168.36, 169.14; MS m/e 341 $(M + 1)^+$.

8b: yield 71%, mp 151–153 °C (from methanol); $[\alpha]^{20}_D$ = +69.2° (c = 1, chloroform); CD (MeOH) λ_{max}, nm (ϵ, M^{-1} cm^{-1}), 253 sh (−0.58), 257 sh (−0.94), 266 (−1.38), 272 (−1.33), 290 sh (−0.25); IR (1% in KBr) ν 1760, 1730 cm^{-1} (C=O stretching); ^1H NMR (DMSO) 2.13–2.35 (m, 2 H), 2.86–2.93 (m, 2 H), 3.67 (s, 3 H), 3.79 (s, 3 H), 4.83 (dd, 1 H, J = 5.5 Hz, J = 3 Hz), 5.18 (AB q, 2 H, J = 6 Hz, $\Delta\nu$ = 8.07 Hz), 7.17–7.51 (m, 4 H); ^{13}C NMR (DMSO) 27.00, 29.86, 34.92, 52.56, 76.95, 77.61, 110.12, 125.96, 126.37, 128.43, 129.17, 133.47, 136.21, 168.42, 169.03; MS m/e 433 $(M + 1)^+$. Anal. Calcd for $C_{16}H_{17}IO_6$: C, 44.46; H, 3.96; I, 29.37; O, 22.21. Found: C, 44.68; H, 3.96; I, 29.22; O, 22.26.

9b: ^1H NMR (DMSO) 2.14 (m, 1 H), 2.35 (m, 1 H), 2.92 (m, 1 H), 3.77 (s, 3 H), 3.81 (s, 3 H), 4.87 (dd, 1 H, J = 4.8 Hz, J = 2.8 Hz), 5.06 (AB q, 2 H, J = 6.5 Hz, $\Delta\nu$ = 24.9 Hz), 7.19–7.71 (m, 4 H); ^{13}C NMR (DMSO) 26.60, 28.98, 34.20, 52.73, 76.33, 77.06, 110.12, 126.17, 126.56, 128.39, 129.29, 132.91, 136.27, 168.56, 169.54; MS m/e 433 $(M + 1)^+$.

8c: yield 70%; mp 135–137 °C (from 2-propanol); $[\alpha]^{20}_D$ = +43.4° (c = 1; chloroform); CD (MeOH) λ_{max}, nm (ϵ, M^{-1} cm^{-1}), 259 sh (−0.48), 264 (−0.62), 271 (−0.48); IR (1% in KBr) ν 1755, 1725 cm^{-1} (C=O stretching); ^1H NMR (DMSO) 2.19–2.30 (m, 1 H), 2.41–2.51 (m, 1 H), 2.81–2.91 (m, 1 H), 2.93–3.04 (m, 1 H), 3.67 (s, 3 H), 3.77 (s, 3 H), 4.74 (dd, 1 H, J = 6 Hz, J = 2.7 Hz), 5.19 (AB q, 2 H, J = 5.9 Hz, $\Delta\nu$ = 11.7 Hz), 7.17–7.55 (m, 4 H); ^{13}C NMR (DMSO) 25.18, 28.55, 52.50, 54.19, 77.09, 77.72, 109.77, 126.00, 126.43, 128.35, 129.14, 133.38, 136.36, 168.48, 168.98; MS m/e 385, 387 $(M + 1)^+$. Anal. Calcd for $C_{16}H_{17}BrO_6$: C, 49.89; H, 4.45; Br, 20.75; O, 24.92. Found: C, 49.99; H, 4.44; Br, 20.86; O, 24.91.

9c: ^1H NMR (DMSO) 3.76 (s, 3 H), 3.81 (s, 3 H), 4.79 (dd, 1 H, J = 5.4 Hz, J = 2.4 Hz), 5.11 (AB q, 2 H, J = 6.6 Hz, $\Delta\nu$ = 20.5 Hz), 7.20–7.70 (m, 4 H); ^{13}C NMR (DMSO) 24.62, 27.76, 52.39, 53.08, 76.60, 77.07, 109.72, 125.87, 126.32, 128.19, 129.02, 132.75, 136.31, 168.39; MS m/e 385, 387 $(M + 1)^+$.

10a: ^1H NMR (DMSO) 3.02 (dd, 1 H, J = 16.4 Hz, J = 4.6 Hz), 3.47 (dd, 1 H, J = 16.4 Hz, J = 6.2 Hz), 3.74 (s, 3 H), 3.77 (s, 3 H), 4.63 (dd, 1 H, J = 6.2 Hz, J = 4.6 Hz), 5.11 (AB q, 2 H, J = 5.9 Hz, $\Delta\nu$ = 6.89 Hz), 7.27–7.47 (m, 4 H); ^{13}C NMR (DMSO) 38.60, 52.53, 63.20, 76.56, 77.65, 118.02, 123.95, 125.24, 127.37, 130.57, 137.56, 139.73, 168.33, 168.64; MS m/e 327 $(M + 1)^+$.

11a: ^1H NMR (DMSO) 3.02 (dd, 1 H, J = 16.4 Hz, J = 7.3 Hz), 3.48 (dd, 1 H, J = 16.4 Hz, J = 7.3 Hz), 3.76 (s, 3 H), 3.78 (s, 3 H), 4.70 (dd, 1 H, J = 7.3 Hz, J = 7.3 Hz), 5.18 (AB q, 2 H, J = 4.8 Hz, $\Delta\nu$ = 27 Hz), 7.27–7.47 (m, 4 H); ^{13}C NMR (DMSO) 38.51, 52.63, 63.03, 76.56, 77.36, 117.86, 124.27, 124.84, 127.55, 130.80, 137.37, 139.64, 168.91, 169.22; MS m/e 327 $(M + 1)^+$.

13: ^1H NMR ($CDCl_3$) 3.82 (s, 3 H), 3.88 (s, 3 H), 5.27 (AB q, 2 H, J = 5 Hz, $\Delta\nu$ = 32.5 Hz), 7.2–7.5 (m, 4 H).

10b: ^1H NMR (CD_3COCD_3) 3.22 (dd, 1 H, J = 15.9 Hz, J = 6.1 Hz), 3.65 (dd, 1 H, J = 15.9 Hz, J = 6.1 Hz), 3.78 (s, 3 H), 3.81 (s, 3 H), 4.81 (dd, 1 H, J = 6.1 Hz, J = 6.1 Hz), 5.05 (AB q, 2 H, J = 6.4 Hz, $\Delta\nu$ = 6.98 Hz), 7.28–7.67 (m, 4 H); ^{13}C NMR (DMSO) 40.89, 52.53, 52.59, 76.99, 77.34, 118.38, 123.58, 125.04, 127.19, 130.24, 137.46, 140.97, 167.86, 168.52; MS m/e 419 $(M + 1)^+$.

11b: ^1H NMR (CD_3COCD_3) 3.28 (dd, 1 H, J = 15.9 Hz, J = 6.8 Hz), 3.65 (dd, 1 H, J = 15.9 Hz, J = 6.8 Hz), 3.79 (s, 3 H), 3.82 (s, 3 H), 4.91 (dd, 1 H, J = 6.8 Hz, J = 6.8 Hz), 5.16 (AB q, 2 H, J = 5.3 Hz, $\Delta\nu$ = 4 Hz), 7.28–7.67 (m, 4 H); ^{13}C NMR (DMSO) 41.22, 52.59, 52.69, 77.09, 77.54, 118.92, 123.95, 124.57, 127.31, 130.44, 137.15, 141.51, 168.67, 169.10; MS m/e 419 $(M + 1)^+$.

10c: ^1H NMR (DMSO + $CDCl_3$) 3.12 (dd, 1 H, J = 16.5 Hz, J = 4.4 Hz), 3.54 (dd, 1 H, J = 16.5 Hz, J = 6.1 Hz), 3.73 (s, 3 H), 3.76 (s, 3 H), 4.67 (dd, 1 H, J = 6.1 Hz, J = 4.4 Hz), 5.06 (AB q, 2 H, J = 5.7 Hz, $\Delta\nu$ = 4.9 Hz), 7.23–7.48 (m, 4 H); ^{13}C NMR (DMSO + $CDCl_3$) 39.10, 52.29, 54.28, 76.58, 77.47, 117.81, 123.64, 124.84, 127.08, 130.23, 137.40, 139.89, 167.83, 168.29; MS m/e 371, 373 $(M + 1)^+$.

11c: ^1H NMR (DMSO + $CDCl_3$) 3.14 (dd, 1 H, J = 16.5 Hz, J = 6.8 Hz), 3.54 (dd, 1 H, J = 16.5 Hz, J = 6.8 Hz), 3.75 (s, 3 H), 3.77 (s, 3 H), 4.74 (dd, 1 H, J = 6.8 Hz, J = 6.8 Hz), 5.12 (AB q, 2 H, J = 5.0 Hz, $\Delta\nu$ = 6.6 Hz), 7.23–7.48 (m, 4 H); ^{13}C NMR (DMSO + $CDCl_3$) 39.24, 52.41, 53.91, 77.23, 77.47, 118.02, 124.03, 124.41, 127.24, 130.47, 137.12, 140.11, 168.50, 168.96; MS m/e 371, 373 $(M + 1)^+$.

Independent Synthesis of Ketals 8,9a–c. A mixture of 2-chlorotetralone,[7] 2-iodotetralone,[7] or 2-bromotetralone[8] (0.0345 mol), 1,2-dichloroethane (13 mL), (2*R*,3*R*)-tartaric acid dimethyl ester (40.08 g, 0.225 mol), and dimethyl sulfite (14.87 g, 0.135 mol) was heated with stirring at 40 °C until a solution was obtained. Trifluoromethanesulfonic acid (6.6 g, 0.044 mol) was added dropwise. After 24 h of stirring, the reaction mixture was poured into a 10% aqueous sodium carbonate solution (200 mL). The aqueous phase was extracted with methylene chloride (2 × 30 mL); the combined organic extracts were washed with water and then dried over sodium sulfate. Removal of the solvent under reduced pressure gave a crude oily residue. Column chromatography on silica gel (*n*-hexane/diethyl ether, 7/3) afforded a mixture of epimeric **8,9a–c**. **8a + 9a**: 8.82 g, 0.026 mol, 74% yield; **8a:9a** = 40:60 (determined by ^1H NMR analysis). **8b + 9b**: 5.3 g, 0.012 mol, 35% yield; **8b:9b** = 40:60 (determined by ^1H NMR analysis). **8c + 9c**: 7.28 g, 0.019 mol, 54% yield; **9b:8b** = 40:60 (determined by ^1H NMR analysis).

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Registry No. **5**, 128412-56-6; **6**, 128412-57-7; **8a**, 128412-58-8; **8b**, 128412-59-9; **8c**, 128412-60-2; **9a**, 128523-92-2; **9b**, 128523-93-3; **9c**, 128523-94-4; **10a**, 128412-61-3; **10b**, 128412-63-5; **10c**, 128412-64-6; **11a**, 128523-95-5; **11b**, 128523-96-6; **11c**, 128523-97-7; **13**, 128412-62-4; α-Tetralone, 529-34-0; α-Indanone, 83-33-0; 2-Iodotetralone, 41099-31-4; 2-Bromotetralone, 13672-07-6; 2-Chlorotetralone, 17215-80-4; (2*R*,3*R*)-Tartaric acid dimethyl ester, 608-68-4.

Supplementary Material Available: X-ray data and ORTEP drawing for compound **8a** (5 pages). Ordering information is given on any current masthead page.

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