Tartaric Acid, an Efficient Chiral Auxiliary: New Asymmetric Synthesis of 2-Alkyl-2-arylacetic Acids

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A highly enantioselective synthesis of 2-alkyl-2-arylacetic acids, an important class of antiinflammatory agents, based on a new diastereoselective α-bromination of homochiral acetals **1** and on the stereospecific silver-promoted rearrangement of the corresponding homochiral α-bromo acetals **2** and **3**, is reported. The new methodology represents a meaningful example of the use of tartaric acid as efficient and economic chiral auxiliary. The asymmetric bromination of **1** is of general character and occurs with very high diastereoselectivity, even at room temperature; a mechanism for the new reaction is proposed. The overall process has been successfully applied to the preparation of enantiomerically pure 2-alkyl-2-arylacetic acids, among them (2*S*)-(+)-2-(6-methoxy-2-naphthyl)propanoic acid (Naproxen).

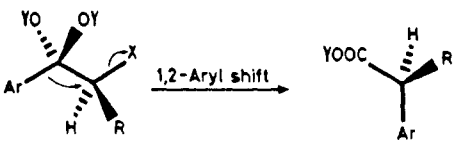
Introduction

2-Alkyl-2-arylacetic acids are well-known on the market as antiinflammatory and analgesic drugs.[1] Most of them have a stereogenic carbon α to the carboxylic group and therefore they exist as a mixture of enantiomers. Very often a higher biological activity is associated with one of the two enantiomers.[1b,2] hence the necessity of being able to produce the physiologically more active compound in an enantiomerically pure form.

Generally, crystallization of diastereomeric salts of 2-alkyl-2-arylacetic acids with optically active amines is undertaken to reach the goal.[3] The main disadvantages, related to the use of this methodology, are the recycle of the undesired isomer, the recovery of the amine, and the difficulty of finding the experimental conditions under which the separation works.

For the above reasons the asymmetric synthesis of 2-alkyl-2-arylacetic acids became a target of synthetic methodology and many sophisticated approaches have been developed.[4]

Recently, several methods for the synthesis of racemic 2-alkyl-2-arylacetic acids have been studied that are based on the 1,2-aryl shift in acetals of α-functionalized alkyl aryl ketones (eq 1).[5] Generally, activation of the carbon-leaving



(1)

group (X) bond, by the use of soft and borderline Lewis acids[5] as well as of protic polar solvents,[6] is required in order to promote the rearrangement.

This approach, because of its simplicity, selectivity, and economy, has been developed for industrial productions of some 2-alkyl-2-arylacetic acids such as Ibuprofen and Naproxen.[7]

The rearrangement of acetals of α-functionalized alkyl aryl ketones into esters of 2-alkyl-2-arylacetic acids could be also effective for the synthesis of enantiomerically pure 2-alkyl-2-arylacetic acids if two main requisites were fullfilled: (i) the carbon atom in the position α to the acetal group were of the *R* or *S* absolute configuration; (ii) the 1,2-aryl shift, leading to esters of 2-alkyl-2-arylacetic acids, were stereospecific.

Recently, we reported, in a preliminary paper,[8] the asymmetric α-bromination of homochiral acetals, obtained from tartaric acid derivatives and alkyl aryl ketones, as the

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(8) Castaldi, G.; Cavicchioli, S.; Giordano, C.; Uggeri, F. *Angew. Chem.* **1986**, *98*, 273; *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 259.

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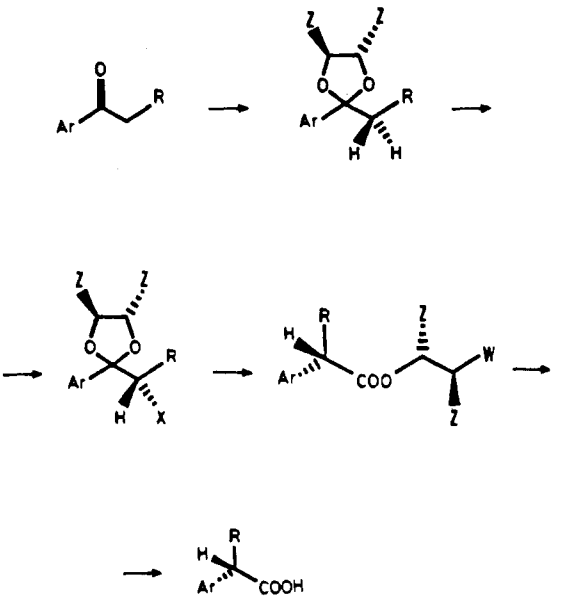
Scheme I



first asymmetric α functionalization of homochiral acetals.[9,10] This asymmetric bromination gives a satisfactory answer to the first requisite stated above.

Now we report that the second requirement is satisfied by the silver ion promoted rearrangement of the optically active α-bromoalkyl aryl acetals into esters of optically active 2-alkyl-2-arylacetic acids. This paper then summarizes the study of the new asymmetric bromination and of the new stereospecific rearrangement of α-bromoalkyl aryl acetals, which together constitute a new asymmetric synthesis of 2-alkyl-2-arylacetic acids.

The synthetic strategy chosen to achieve the overall transformation of alkyl aryl ketones into enantiomerically pure 2-alkyl-2-arylacetic acids (EPC synthesis[10f,11]) is the following: (i) in the first step, the acetalization, a chiral auxiliary is introduced into the molecule as the result of the reaction between a homochiral 1,2-diol with an alkyl aryl ketone; (ii) the α functionalization of the homochiral acetal occurs under reaction conditions that make the diastereomeric transition states as different as possible in free energy; (iii) the rearrangement of α-functionalized acetals into esters of 2-alkyl-2-arylacetic acids occurs in a highly stereoselective way; (iv) in the last step, the chiral auxiliary is removed, under nonracemizing conditions, to furnish the optically active 2-alkyl-2-arylacetic acids (Scheme I).

It is worth noting that the present asymmetric synthesis of 2-alkyl-2-arylacetic acids does not require any additional chemical step when compared to the racemic synthesis.[5,6] The chiral auxiliary is introduced in the acetalization step and removed in the hydrolysis of esters: acetalization and hydrolysis are included also in the synthesis of racemic 2-alkyl-2-arylacetic acids.[5,6]

Table I. Yields and Diastereomeric Ratios for the Bromination of 1a–i to 2a/3a–2i/3i in CCl_4 at 15 °C

acetal 1	aryl	R	R[1]	reactn time, (min)	yield 2 + 3 (%)	ratio 2:3
a	6-methoxy-2-naphthyl[a]	Me	Me	45	98	91:9
b	6-methoxy-2-naphthyl[a]	Me	Et	45	94	91:9
c	6-methoxy-2-naphthyl[a]	Me	*i*-Pr	45	93	91:9
d	6-methoxy-2-naphthyl[a]	Me	*n*-Bu	45	94	91:9
e	4-methoxyphenyl	Me	Me	45	95	91:9
f	4-isobutylphenyl[b]	Me	Me	120	90	82:18
g	phenyl	Me	Me	60	94	93:7
h	4-chlorophenyl	Me	Me	75	93	94:6
i	4-chlorophenyl	*i*-Pr	Me	75	93	92:8

[a] The bromination of **1a–d** requires 2 mol of bromine per mol of **1a** because of the concomitant bromination of the aromatic ring; therefore, aryl is 5-bromo-6-methoxy-2-naphthyl in the case of products **2a–d/3a–d**. The mixture of **2a** and **3a** was easily converted into a mixture of **2j** and **3j** (ratio 91:9) (aryl = 6-methoxy-2-naphthyl) by treatment with phenol under acidic conditions (see Experimental Section). [b] Deoxygenated 1,2-dichloroethane was used as reaction solvent (see Experimental Section).

Results and Discussion

Alkyl esters of optically active tartaric acids[11] have shown to be efficient and practical chiral auxiliaries: they introduce, in the acetalization step, without loss of enantiomeric purity, two stereogenic centers into the acetal moiety and can be recovered, at the end of the synthesis, unchanged.

Thus, acetals **1** (eq 2) having *R,R* or *S,S* configuration were prepared in high yields by reacting, in the presence of an acidic catalyst, alkyl aryl ketones with alkyl esters of (2*R*,3*R*)- or (2*S*,3*S*)-tartaric acid (see Experimental Section).

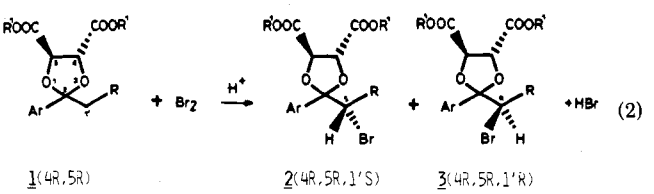
Acetals **1** were fully characterized by IR, ^1H and ^{13}C NMR, mass, and elemental analyses. They were found to be enantiomerically pure as determined by ^1H NMR analysis in the presence of the optically active shift reagent $Eu(hfc)_3$.[12]

Acetals can be α-functionalized with electrophilic reagents thanks to the fact that, in the presence of an acidic catalyst, they provide the corresponding enol ethers.[13]

Among the investigated functionalizations of acetals **1**,[9] the bromination has shown to be the most interesting and useful from a synthetic as well as from a stereochemical point of view.

The forthcoming considerations on the bromination will concern the use of bromine, which showed, among many brominating agents, the highest diastereoselectivity.[9]

The bromination of **1** occurs, under a large variety of conditions, in the presence of an acidic catalyst. In the absence of the catalyst an induction period has been observed until a trace of HBr is formed, which grows as soon as the bromination initiates (eq 2). Acetals **1** were bro-



(2)

1(4R,5R) **2**(4R,5R,1'S) **3**(4R,5R,1'R)

(9) Castaldi, G.; Cavicchioli, S.; Giordano, C.; Uggeri, F. It. Pat. Appl. 7204 A84 (filing date: April 6, 1984) Eur. Pat. Appl. EP 158 913, 1985; *Chem. Abstr.* **1986**, *104*, 148566a; EP 158 255, 1985; *Chem. Abstr.* **1986**, *104*, 168205k.

(10) Recently, other asymmetric functionalizations of homochiral acetals, obtained from α,β-unsaturated carbonyl compounds and tartaric acid derivatives, have been reported: (a) Fujiwara, J.; Fukutani, Y.; Hasegawa, M.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1984**, *106*, 5004. (b) Fukutani, Y.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1984**, *25*, 5911. (c) Arai, I.; Mori, A.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 8254. (d) Suzuki, M.; Kimura, Y.; Terashima, S. *Chem. Lett.* **1985**, 367; *Tetrahedron Lett.* **1985**, *26*, 6481; *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3559. (e) Maruoka, K.; Nakai, S.; Sakurai, M.; Yamamoto, H. *Synthesis* **1986**, 130. (f) Seebach, D.; Imwinkelried, R.; Weber, T. *Modern Synthetic Methods*; Springer Verlag: Berlin, 1986; Vol. 4, pp 128–248.

(11) Seebach, D.; Hungerbühler, H. *Modern Synthetic Methods*; Scheffold, R., Ed.; Salle-Sauerländer: Aarau, 1980; Vol. 2, pp 91–171.

(12) Acetals prepared from alkyl esters of tartaric acid and carbonyl compounds have at the stereogenic carbon centers the same absolute configuration of the corresponding carbons of the starting tartaric acid.

(13) Marquet, A.; Dvolaitzky, M.; Kagan, H. B.; Mamlock, L.; Ouannes, C.; Jaques, J. *Bull. Soc. Chim. Fr.* **1961**, 1822.

Table II. Bromination of Acetal 1a: Solvent Effect on the Diastereoselectivity

solvent	conditions: temp, °C/ time, h	2a + 3a yield (%)	ratio 2a:3a
carbon tetrachloride	−10, 2	98	93:7
	15, 1	98	92:8
dichloromethane	−10, 1	96	90:10
chloroform	−10, 1	97	92:8
1,2-dichloroethane	−10, 1	89	90:10
toluene	−10, 2.5	88	93:7
chlorobenzene	−10, 1	95	91:9
ethyl acetate	−10, 8.5	89	94:6
acetic acid	15, 1	70	88:12

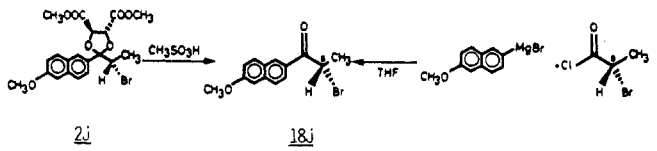
minated at 15 °C in carbon tetrachloride in the presence of a catalytic amount of hydrobromic acid (Table I). An equimolar amount of bromine converts the starting acetal 1 into a mixture of α-bromo acetals 2 and 3 and HBr: thus the stoichiometry of the reaction is established.

The bromination of acetals 1, prepared from esters of (2*R*,3*R*)-tartaric acid, provides in yields higher than 90% a mixture of epimeric α-bromo acetals 2 and 3 in which the isomer having the *S* configuration at the carbon bearing bromine, i.e., 2, strongly prevails over the other;[14,15] generally, 2 can be obtained as pure compound by chromatography on silica gel (see Experimental Section). The ratio between the two diastereomers appears to be independent of the nature of the aryl substituent as well as of the R^1 group (Table I).

It is worth noting that the epimeric ratio 2 to 3 does not change at different conversions nor by leaving the reaction mixture to stand for several reaction times (see Experimental Section).

As far as mode and time of adding bromine is concerned, bromine can be added in 5 min or in 3 h to the solution of the substrate and the substrate can be added to a solution of an excess of bromine, without observing any significant change in yields and in the diastereomeric ratios (see Experimental Section).

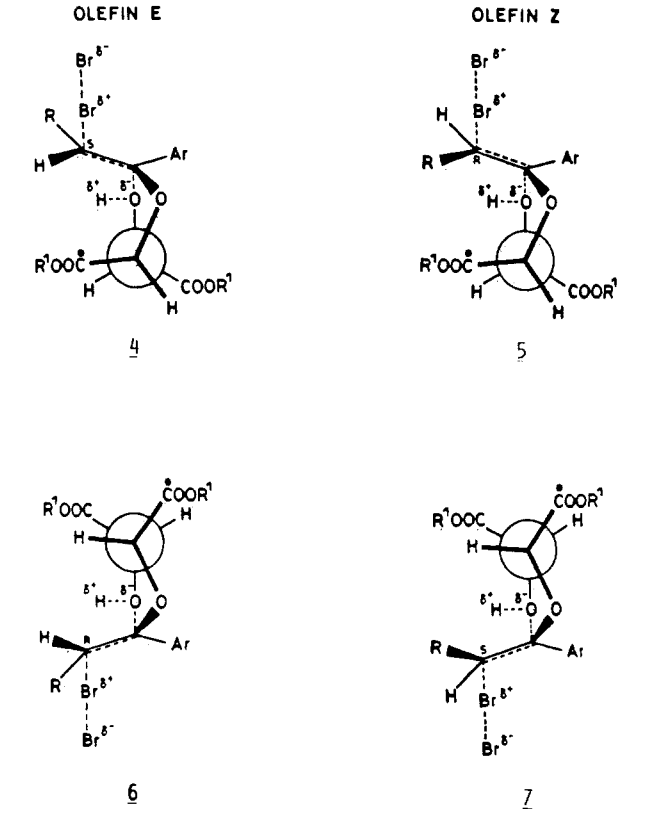
The bromination of the acetal **1a**, carried out in many different solvents, other than carbon tetrachloride, such as dichloromethane, ethyl acetate, acetic acid, etc., provided **2a** and **3a** in high yield and diastereoselectivity vs. **2a** (Table II). A small change (Table II) in the ratio between the two diastereomers is observed from one solvent to another, indicating that the diastereoselectivity of the reaction is only slightly affected by the polarity of the reaction medium.



2j 18j

(14) Acetals 2 and 3 were converted into the corresponding optically active α-bromo ketones. Castaloi, G.; Giordano, C. *Synthesis*, submitted for publication. Thus a mixture of **2j** and **3j** in a ratio of 90:10 was hydrolyzed into (+)-**18j** (ee 80%), without racemization, by treatment with a mixture of methanesulfonic acid–methanol (see Experimental Section). The homochiral (+)-**18j** has been shown to have the same chiroptical properties of the bromo ketone prepared from (6-methoxy-2-naphthyl)magnesium bromide and 2(*S*)-bromopropionyl chloride, according to a known procedure.[4n] On the basis of the above findings the absolute configuration at the carbon-bearing bromine in 2 and 3 was assigned.

(15) Starting from acetal 1, prepared from alkyl esters of (2*S*,3*S*)-tartaric acid, a mixture of two diastereomeric α-bromo acetals were obtained in yields and diastereomeric ratios expected on the basis of the above results: the major diastereomer being that of *R* configuration at the new stereogenic center.



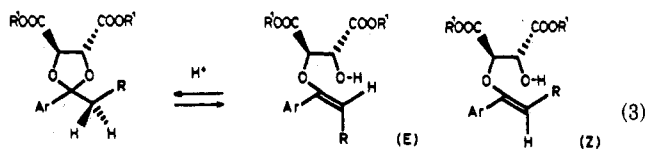
4 5

6 7

Figure 1.

The ratio between the two diastereomers does not change in nonpolar solvents such as carbon tetrachloride while it does change slowly in polar solvents. Thus, the bromination of **1a** in 1,2-dichloroethane at 15 °C gave **2a** and **3a**, in ratios of 86:14 (95% yield) and 79:21 (92% yield) (see Experimental Section) after 1 and 24 h, respectively. These results suggest that the bromination occurs under kinetically controlled conditions.

The high diastereoselectivity of the reaction is consistent with the mechanism proposed below for the reaction of 1 (4*R*,5*R*) with bromine. In the absence of bromine an acid-catalyzed equilibrium between the acetal 1 and the enol ethers E and Z certainly exists (eq 3).[16] At present,



(3)

1

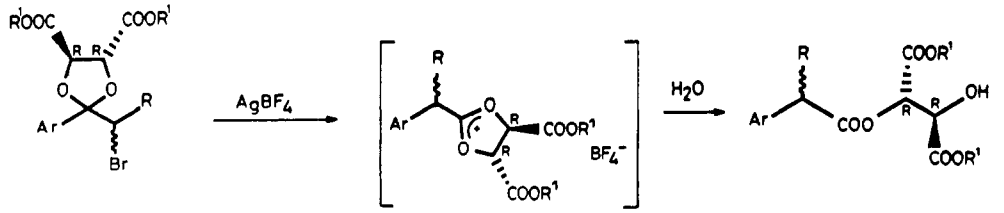
we have no evidence that a single olefin or a mixture of isomeric olefins, E and Z, are formed, this because the amount of olefin(s) at the equilibrium, under acidic conditions, is too small to be detected by any spectroscopic method. The fast reaction of the electrophilic bromine with the highly reactive enol ether(s) makes their concentration still smaller while it shifts the equilibrium of eq 3 to the right.

In our opinion the diastereoselectivity of the bromination is determined in the interaction between the enol ether(s) and electrophilic bromine.

The fact that a high diastereoselectivity has been observed under a large variety of conditions, even at room temperature, implies, whatever mechanism is involved, a strong interaction between the asymmetric moiety and the

(16) Garbisch, E. W. *J. Org. Chem.* **1965**, *30*, 2109.

Scheme II



2,3 8,9 10,11

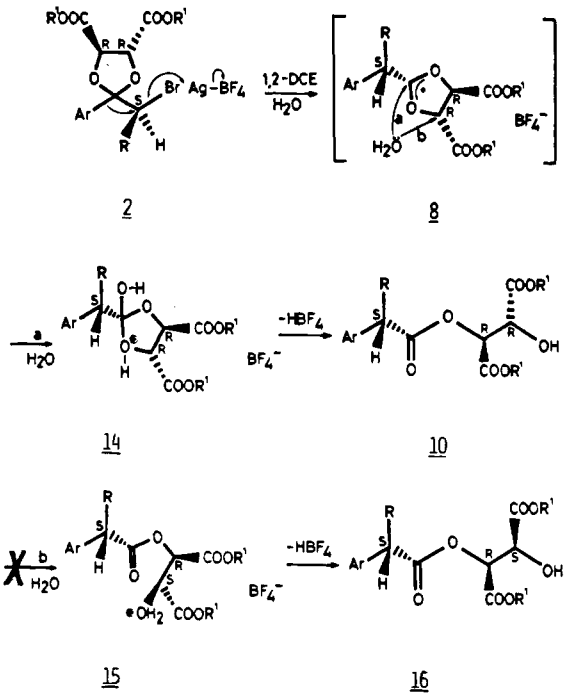
reactive site in the transition state. The anchimeric assistance of the hydroxy group of the tartaric moiety to the positive charge developed at the benzylic position in the transition state can be accounted for the expected interaction between the stereogenic centers and the reactive site. On this basis, the four transition states 4–7 are proposed for the interaction of enol ethers E and Z with bromine (Figure 1). The higher proximity of the carboxyalkyl group (*$COOR^1$) to the double bond in the transition states 4 with respect to that in 6 and 5 with respect to that in 7 determines a greater electron-withdrawing field effect, which makes the double bond of 6 and 7 more reactive than that of 4 and 5, respectively.

The experimental results, i.e., diastereoselectivity vs. the epimer having *S* configuration at the new stereogenic carbon, show that the transition state 7 strongly prevails on 6. This implies that, taking into account the very high reactivity[16] and the low discriminant ability of bromine toward activated olefins, enol ether Z should prevail on E in eq 3.

As far as the rearrangement of α-bromoalkyl aryl acetals is concerned, it is worth noting that all the investigations on the rearrangement of α-haloalkyl aryl acetals are relative to racemic compounds.[5,17-19] Now, the availability of optically active α-bromoalkyl aryl acetals opens a new route to the synthesis of optically active 2-alkyl-2-arylacetic acids and provides the possibility of collecting new mechanistic informations. Thus, we have studied the silver-promoted rearrangement of diastereomeric α-bromoalkyl aryl acetals into esters of 2-alkyl-2-arylacetic acids. A mixture of α-bromo acetals **2a** and **3a** (**2a**:**3a** = 94:6) was reacted with anhydrous silver tetrafluoroborate in dichloromethane-d_2 at 15 °C, and the insoluble silver bromide was filtered. ^{1}H NMR (300 MHz) analysis of the solution suggested the formation of two diastereomeric dioxolonium ion **8a** and **9a** in almost quantitative yield[20] and in the ratio **8a**:**9a** = 91:9. Treatment of **8a**, **9a** with water provided esters **10a** and **11a** in 90–95% yield and in the ratio **10a**:**11a** = 91:9 (Scheme II, see Experimental Section).[21] The epimers ratio **8a**:**9a** and consequently the ratio **10a**:**11a** decreases at longer reaction time.

It is likely that the observed epimerization is the result of an acid-catalyzed equilibrium between the two diastereomeric dioxolonium ion intermediates **8a**, **9a** and **13** as depicted in eq 4.

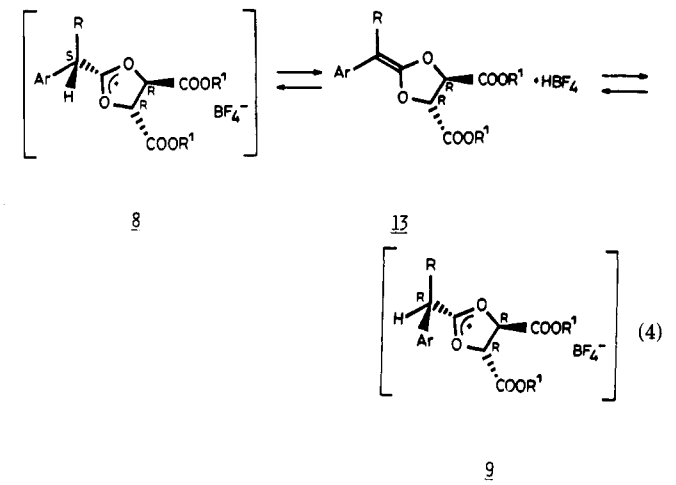
Scheme III



2 8

14 10

15 16



8 13 9 (4)

In principle, water, used as quencher for the reaction, can react with dioxolonium salts **8a**, **9a** following the two different pathways A and B (Scheme III).[22] Pathway B is not consistent with the experimental results, requiring an inversion of configuration at one of the two stereogenic carbons of the tartaric moiety. To avoid the epimerization reactions were carried out in the presence of water. As a

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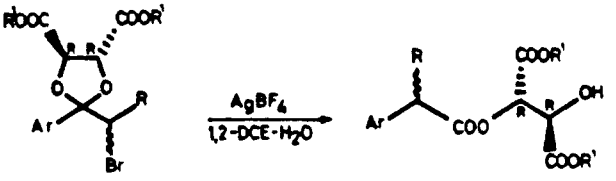
(19) Recently reported is a stereospecific rearrangement of homochiral α-sulfonyloxalkyl aryl acetal: Tsuchihashi, G.; Mitamura, S.; Kitajima, K.; Kobayashi, K. *Tetrahedron Lett.* **1982**, *23*, 5427.

(20) Structures of **8a** and **9a** (Scheme II) were assigned on the basis of ^{1}H NMR data and on the analogy of the present reaction with that of racemic α-bromoalkyl aryl acetals and silver hexafluoroantimonate in dichloromethane, where dioxolonium salts of type **8a** were isolated in high yield[18] and converted quantitatively, by treatment with water, into esters of 2-alkyl-2-arylacetic acids.[18]

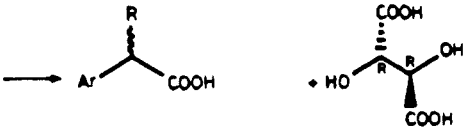
(21) The structure of esters **10a** and **11a** has been established on the basis of ^{1}H NMR, IR, and mass spectral analyses and by their independent synthesis (see Experimental Section).

(22) (a) Mesdagh, H.; Pancrazi, A. *Tetrahedron* **1984**, *38*, 3799. (b) Hünig, S. *Angew. Chem.* **1964**, *3*, 548.

Table III. Synthesis of Optically Active 2-Alkyl-2-arylacetic Acid 17 via Rearrangement of 2 and 3 into Esters 10 and 11



2,3 10,11



17

2, 3	Ar	R	R^1	substrate ratio 2:3	conditions: temp, °C/time, h	10 + 11 yield, (%)	ratio 10:11	17 yield (%)	ratio 17S:17R
a	5-bromo-6-methoxy-2-naphthyl	Me	Me	91:9	15, 22	94	91:9	95	91:9[a]
a	5-bromo-6-methoxy-2-naphthyl	Me	Me	99:1	15, 22	95	99:1	95	99:1
b	5-bromo-6-methoxy-2-naphthyl	Me	Et	91:9	15, 22	92	91:9	96	91:9
c	5-bromo-6-methoxy-2-naphthyl	Me	*i*-Pr	91:9	15, 22	95	91:9	96	91:9
e	4-methoxyphenyl	Me	Me	95:5	15, 4.5	90	95:5	95	95:5
g	phenyl	Me	Me	95:5	35, 28	90	95:5	96	95:5
h	4-chlorophenyl	Me	Me	94:6	50, 8	90	93:7	93	93:7
i	4-chlorophenyl	*i*-Pr	Me	97:3	50, 7	76	97:3	94	97:3
j	6-methoxy-2-naphthyl	Me	Me	91:9	15, 18	94	91:9	96	91:9
j	6-methoxy-2-naphthyl	Me	Me	99:1	15, 18	97	99:1	96	99:1[a]

[a] The compound **17j** is well-known on the market under the commercial name of Naproxen.[1]

matter of fact, reaction of α-bromo acetals **2** and **3** with silver tetrafluoroborate, carried out in 1,2-dichloroethane in the presence of water, afforded esters **10** and **11** in high yields and in ratios that reflect those of the starting α-bromo acetals (Table III, see Experimental Section).

The reaction occurs smoothly at room temperature when electron-donating groups are present on the aromatic ring, while higher temperatures are required with deactivated aromatics. For example, a mixture of α-bromo acetals **2e** and **3e** was converted completely at 15 °C in 4.5 h, whereas α-bromo acetals **2h** and **3h** require 8 h at 50 °C. Generally, esters **10** can be obtained as pure by chromatography or crystallization of the diastereomeric mixture (see Experimental Section). Hydrolysis of esters **10** and **11**, carried out under aqueous acidic conditions (see Experimental Section), afforded in almost quantitative yields the corresponding 2-alkyl-2-arylacetic acids **17** having enantiomeric purity identical with the diastereomeric purity of the starting esters (Table III).

The rearrangement of homochiral α-bromo acetal **2a** provided the homochiral ester **10a** in 95% yield. Ester **10a** was hydrolyzed into enantiomerically pure **17a** and into (2*R*,3*R*)-tartaric acid, which was recovered and recycled.

The above results indicate that the 1,2-aryl shift occurs with complete inversion of configuration at the carbon-bearing bromine. The method has shown to be useful for the synthesis of enantiomerically pure 2-alkyl-2-arylacetic acids of both *S* and *R* configurations. Bromo acetals **2** and esters **10** can be obtained as pure diastereomers by crystallization or chromatography, thus making the method suitable for the preparation of enantiomerically pure 2-alkyl-2-arylacetic acids (see Experimental Section).

Conclusion

The combination of the new highly diastereoselective bromination of homochiral acetals **1** and of the stereospecific rearrangement of the corresponding homochiral α-bromo acetals allows the development of an highly useful method for the synthesis of enantiomerically pure 2-alkyl-2-arylacetic acids.

At the same time, the new asymmetric bromination has shown to have very high synthetic potentiality for the preparation of optically active compounds under very mild conditions and with reagents of very low cost, as it is unusual in asymmetric synthesis.

The basic knowledges drawn from the present study have been very useful for the development of a new industrial process of (2*S*)-(+)-2-(6-methoxy-2-naphthyl)-propanoic acid (Naproxen)[1] in which the rearrangement is carried out in acidic water.[9]

Experimental Section

^{1}H NMR spectra were taken at 200 and 300 MHz for solutions in deuteriochloroform. The chemical shifts are expressed in ppm (δ) and are relative to internal tetramethylsilane. Coupling constants are expressed in hertz. ^{13}C NMR spectra were run at 80 MHz of solutions in deuteriochloroform, by using coupled and uncoupled techniques. Optical rotations were measured at the sodium D line in a 1-dm cell on a Perkin-Elmer 241 polarimeter. IR spectra were taken on a Perkin-Elmer 1420 instrument; positions of interesting absorptions are quoted to ±2.5 cm^{-1}. HPLC analyses were carried out on a Hewlett-Packard 1090 liquid chromatograph equipped with a Merck (50329) Lichrospher (5 μm; 250 mm × 4 mm) column. 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[23] by using silica gel (230–400 mesh) (Merck).

Melting points were measured on a Koefler apparatus and were 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 isobutane as ionizing agent. Satisfactory elemental analyses (C

(23) Still, A. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 293.

±0.2%; H ±0.2%; Br ±0.3%) were obtained for all new compounds. The removal of solvent in vacuo refers to the evaporation of solvent at ca. 20 mmHg on a Büchi rotary evaporator. All reactions were run under nitrogen atmosphere. All solvents and reagents were commercially available (reagent grade) and were used without further purification. 1-(6-Methoxy-2-naphthyl)-propan-1-one was prepared according to the previously reported procedure.[24]

Preparation of Homochiral Acetals 1. Enantiomeric purities of acetals **1** were determined by ^1H NMR analysis in the presence of the optically active shift reagent tris[(3-[(heptafluoropropyl)hydroxymethylene]-*d*-camphorato]europium(III), Eu(hfc)$_3$.

(4*R*,5*R*)-2-Ethyl-2-(4-methoxyphenyl)-1,3-dioxolane-4,5-dicarboxylic Acid Dimethyl Ester (1e). Methanesulfonic acid (1.73 g, 0.018 mol) was added, at 60 °C, in 5 min, to a stirred solution of 1-(4-methoxyphenyl)propan-1-one (41 g, 0.25 mol), (2*R*,3*R*)-tartaric acid dimethyl ester (89.1 g, 0.50 mol), and trimethyl orthoformate (53.1 g, 0.50 mol). The solution was heated at 100 °C and kept at this temperature for 3 h, while volatile compounds were distilled off. The reaction mixture was cooled to room temperature, poured into a vigorously stirred 10% aqueous sodium carbonate solution (200 mL), and extracted with dichloromethane (2 × 200 mL). The combined organic extracts were washed with water (2 × 200 mL) and dried over sodium sulfate. Evaporation of the solvent under reduced pressure gave a residue (96.4 g), which was chromatographed on silica gel (diethyl ether/*n*-hexane = 3:7): fractions containing **1e** were combined together, and the solvent was removed under reduced pressure. The residue was heated at 50 °C (external bath) under stirring at 0.5 mmHg to give **1e** (73 g, 0.225 mol, 90% yield) as an oil: $[\alpha]^{20}_D$ +15.6° (*c* 1, $CHCl_3$); IR (neat) 1755 cm^{-1} (C=O stretching); ^1H NMR (200 MHz) 0.91 (t, 3 H, J = 7.4), 1.98 (q, 2 H, J = 7.4), 3.56 (s, 3 H), 3.78 (s, 3 H), 3.82 (s, 3 H), 4.79 (AB q, 2 H, J = 5.8, $\Delta\nu$ = 18.05), 6.8–7.4 (AA'BB', 4 H); ^{13}C NMR 7.6, 33.7, 52.2, 52.6, 55.1, 76.1, 77.3, 113.1, 115.1, 127.2, 132.7, 159.5, 169.3; MS, *m/e* 325 (M + 1)$^+$, 295 [(M + 1)$^+$ – CH_2O], 217 [(M + 1)$^+$ – CH_3O – C_6H_5], 165 [(M + 1)$^+$ – $C_6H_8O_5$].

(4*R*,5*R*)-2-Ethyl-2-phenyl-1,3-dioxolane-4,5-dicarboxylic Acid Dimethyl Ester (1g). Acetal **1g** was obtained as an oil in 79% yield by following the procedure described for the preparation of acetal **1e** with a 5-h reaction time: $[\alpha]^{20}_D$ +18.5 °C (*c* 1, $CHCl_3$); IR (neat) 1755 cm^{-1} (C=O stretching); ^1H NMR (300 MHz) 0.93 (t, 3 H, J = 7.4), 2.02 (q, 2 H, J = 7.4), 3.54 (s, 3 H), 3.84 (s, 3 H), 4.81 (AB q, 2 H, J = 5.9, $\Delta\nu$ = 14.4), 7.26–7.49 (m, 5 H); ^{13}C NMR 7.6, 33.7, 52.2, 52.6, 76.3, 77.4, 115.2, 125.9, 127.8, 128.2, 140.7, 169.3; MS, *m/e* 295 (M + 1)$^+$, 265 [(M + 1)$^+$ – CH_2O].

(4*R*,5*R*)-2-Ethyl-2-[4-(2-methylpropyl)phenyl]-1,3-dioxolane-4,5-dicarboxylic Acid Dimethyl Ester (1f). A mixture of 1-[4-(2-methylpropyl)phenyl]propan-1-one (110 g, 0.58 mol), (2*R*,3*R*)-tartaric acid dimethyl ester (206 g; 1.16 mol) and trimethyl orthoformate (122.7 g, 1.16 mol) was gradually heated up to complete solution (50 °C); then methanesulfonic acid (3.9 g, 0.04 mol) was added dropwise. The reaction mixture was heated at 85 °C and kept at this temperature for 2 h, cooled to room temperature, and worked up as described for the preparation of compound **1g**. Acetal **1f** was then obtained as an oil in 86% yield: IR (neat) 1755 cm^{-1} (C=O stretching); ^1H NMR (200 MHz) 0.90 (d, 6 H, J = 6.4), 1.00 (t, 3 H, J = 7.5), 1.80 (m, 1 H, J_{H-CH_3} = 6.4, J_{H-CH_2} = 7.1), 1.97 (q, 2 H, J = 7.5), 2.41 (d, 2 H, J = 7.1), 3.48 (s, 3 H), 3.78 (s, 3 H), 4.78 (AB q, 2 H, J = 5.43, $\Delta\nu$ = 15.58), 7.0–7.4 (AA'BB', 4 H, aromatic protons).

(4*R*,5*R*)-2-Ethyl-2-(4-chlorophenyl)-1,3-dioxolane-4,5-dicarboxylic Acid Dimethyl Ester (1h). Methanesulfonic acid (1.03 g, 0.011 mol) was added, at 60 °C, in 5 min, to a stirred solution of 1-(4-chlorophenyl)propan-1-one (25.0 g, 0.149 mol), (2*R*,3*R*)-tartaric acid dimethyl ester (62.7 g, 0.352 mol), and trimethyl orthoformate (34.6 g, 0.326 mol). The solution was heated to 96 °C and kept at this temperature for 3 h, while the volatile compounds were distilled off. The reaction mixture was cooled to room temperature, poured into a vigorously stirred 10% aqueous sodium carbonate solution (100 mL), and extracted with dichloromethane (2 × 100 mL). The organic phases were combined together and washed with water (2 × 250 mL) and dried over sodium sulfate, and the solvent was removed in vacuo to give an oil (55.4 g). A mixture of the oily residue, methanesulfonic acid (1.56 g, 0.016 mol) and (2*R*,3*R*)-tartaric acid dimethyl ester (116.9 g, 0.657 mol) was heated to 95 °C with stirring and kept at this temperature for 1 h.

The reaction mixture was cooled to room temperature and worked up as previously described to provide an oily residue (45.3 g), which was chromatographed on silica gel (diethyl ether/*n*-hexane = 3:7); fractions containing **1h**, were combined together and the solvent was removed under reduced pressure. The residue was kept at 50 °C (external bath) at 0.5 mmHg to give **1h** (42.8 g, 0.130 mol, 87% yield) as an oil: $[\alpha]^{20}_D$ +20.6° (*c* 1, $CHCl_3$); IR (neat) 1755 cm^{-1}; ^1H NMR (300 MHz) 0.91 (t, 3 H, J = 7.4), 1.98 (q, 2 H, J = 7.4), 3.58 (s, 3 H), 3.84 (s, 3 H), 4.78 (s, 2 H), 7.3–7.4 (m, 4 H); ^{13}C NMR 7.6, 33.8, 52.4, 52.8, 76.5, 77.6, 114.8, 127.6, 128.0, 134.4, 139.4, 169.1, 169.3; MS, *m/e* 329/331 (M + 1)$^+$ (chlorine isotopes), 299/301 [(M + 1)$^+$ – CH_2O], 169/171 [(M + 1)$^+$ – $C_6H_8O_5$].

(4*R*,5*R*)-2-(4-Chlorophenyl)-2-(2-methylpropyl)-1,3-dioxolane-4,5-dicarboxylic Acid Dimethyl Ester (1i). A mixture of 1-(4-chlorophenyl)-3-methyl-butan-1-one (40.0 g, 0.204 mol), (2*R*,3*R*)-tartaric acid dimethyl ester (72.4 g, 0.407 mol), and trimethyl orthoformate (43.1 g, 0.406 mol) was heated gradually until complete solution (60 °C). Methanesulfonic acid (1.4 g, 0.015 mol) was added dropwise to the solution, which was then heated to 75 °C and kept at this temperature for 3 h. The reaction mixture was worked up as described for the preparation of acetal **1h**. Acetal **1i** was then obtained in 56% yield: mp 40 °C; $[\alpha]^{20}_D$ +21.6° (*c* 1, $CHCl_3$); IR (Nujol) 1755 cm^{-1} (C=O stretching); ^1H NMR (200 MHz) 0.87 (d, 6 H, J = 6.9), 1.67 (m, 1 H, J_{CH-CH_3} = 6.9, J_{CH-CH_2} = 7.2), 1.86 (d, 2 H, J = 7.2), 3.55 (s, 3 H), 3.82 (s, 3 H), 4.74 (AB q, 2 H, J = 6, $\Delta\nu$ = 5.3), 7.2–7.4 (AA'BB', 4 H, aromatic protons).

(4*R*,5*R*)-2-Ethyl-2-(6-methoxy-2-naphthyl)-1,3-dioxolane-4,5-dicarboxylic Acid Dimethyl Ester (1a) and (4*S*,5*S*)-2-Ethyl-2-(6-methoxy-2-naphthyl)-1,3-dioxolane-4,5-dicarboxylic Acid Dimethyl Ester. Acetal **1a** was obtained as a crystalline compound in 81% yield by following the procedure described for the preparation of acetal **1e** (reaction time 4 h): mp 77–78 °C (methanol); $[\alpha]^{20}_D$ +35° (*c* 1, $CHCl_3$); IR (Nujol) 1755 cm^{-1} (C=O stretching); ^1H NMR (200 MHz) 0.94 (t, 3 H, J = 7.5), 2.08 (q, 2 H, J = 7.5), 3.46 (s, 3 H), 3.84 (s, 3 H), 3.90 (s, 3 H), 4.86 (AB q, 2 H, J = 5.8 $\Delta\nu$ = 10.8), 7.1–7.9 (m, 6 H); ^{13}C NMR 7.75, 33.7, 52.2, 52.7, 55.3, 76.4, 77.5, 105.7, 115.4, 119.0, 124.6, 125.0, 126.6, 128.1, 129.8, 134.4, 135.7, 158.1, 169.5; MS, *m/e* 375 (M + 1)$^+$, 345 [(M + 1)$^+$ – CH_2O], 217 [(M + 1)$^+$ – CH_3O – $C_{10}H_7$].

According to the above procedure (4*S*,5*S*)-2-ethyl-2-(6-methoxy-2-naphthyl)-1,3-dioxolane-4,5-dicarboxylic acid dimethyl ester was prepared starting from (2*S*,3*S*)-tartaric acid dimethyl ester; $[\alpha]^{20}_D$ –35 ° (*c* 1, $CHCl_3$).

(4*R*,5*R*)-2-Ethyl-2-(6-methoxy-2-naphthyl)-1,3-dioxolane-4,5-dicarboxylic Acid Diethyl Ester (1b). Methanesulfonic acid (0.68 g, 7.1 mmol) was added, at 85 °C, in 5 min, to a stirred solution of 1-(6-methoxy-2-naphthyl)propan-1-one (20 g, 0.093 mol), (2*R*,3*R*)-tartaric acid diethyl ester (160 g, 0.777 mol), and triethyl orthoformate (37.0 g, 0.250 mol). The reaction mixture was heated at 100 °C and kept at this temperature for 1 h. The reaction mixture was poured into a vigorously stirred 10% aqueous sodium carbonate solution (250 mL) and extracted with dichloromethane (2 × 250 mL). The combined organic phases were washed with water and dried over sodium sulfate. The solvent was removed under reduced pressure to give an oil (65 g), which was heated up to 200 °C (external bath), under stirring, at 0.1–0.2 mmHg to remove compounds having a lower boiling point with respect to **1b**. The oily residue was chromatographed on silica gel (diethyl ether/*n*-hexane = 3:7) to give acetal **1b** as pure compound (32.7 g, 0.081 mol, 87% yield): $[\alpha]^{20}_D$ +20.6° (*c* 1, $CHCl_3$); IR (neat) 1755 cm^{-1}; ^1H NMR (200 MHz) 0.95 (t, 3 H, J = 6.4), 1.03 (t, 3 H, J = 7.3), 1.31 (t, 3 H, J = 7.3), 2.08 (q, 2 H, J = 6.4), 3.88 (dq, 2 H, J = 11.0, J = 7.3), 3.90 (s, 3 H), 4.30 (q, 2 H, J = 7.3), 4.82 (AB q, 2 H, J = 5.9, $\Delta\nu$ = 10.5), 7.1–8.0 (m, 6 H).

(4*R*,5*R*)-2-Ethyl-2-(6-methoxy-2-naphthyl)-1,3-dioxolane-4,5-dicarboxylic Acid Diisopropyl Ester (1c). Methanesulfonic acid (0.37 g, 3.9 mmol) was added, at 85 °C, in 5 min, to a stirred solution of 1-(6-methoxy-2-naphthyl)propan-

(24) Haworth, R. D.; Sheldrick, G. *J. Chem. Soc.* **1934**, 864.

1-one (10.3 g, 0.048 mol), (2*R*,3*R*)-tartaric acid diisopropyl ester (94 g, 0.402 mol), and trimethyl orthoformate (7.6 g, 0.072 mol). The solution was heated to 90 °C and kept at this temperature for 2.5 h. The reaction mixture was cooled to room temperature, poured into a vigorously stirred 10% aqueous sodium carbonate solution (100 mL), and extracted with dichloromethane (2 × 100 mL). The combined organic phases were washed with water (2 × 100 mL) and dried over sodium sulfate. The solvent was removed under reduced pressure to give an oily residue (94 g). The residue was gradually heated at 200 °C (external bath) at 0.2–0.3 mmHg, while volatile compounds were evaporated off. The residue was chromatographed on silica gel (diethyl ether/*n*-hexane = 2:8) to yield the acetal **1c** (14.2 g, 0.033 mmol, 69% yield) as an oil: $[\alpha]^{20}_D$ +21.6° (*c* 1, $CHCl_3$); IR (neat) 1755 cm^{-1}; ^1H NMR (200 MHz) 0.95 (t, 3 H, *J* = 7.6), 0.96 (d, 3 H, *J* = 6.4), 1.05 (d, 3 H, *J* = 6.4), 1.29 (d, 6 H, *J* = 6.4), 2.08 (q, 2 H, *J* = 7.6), 3.8 (s, 3 H), 4.75 (AB q, 2 H, *J* = 6, $\Delta\nu$ = 10.5), 4.79 (q, 1 H, *J* = 6.4), 5.14 (ept., 1 H, *J* = 6.4), 7.05–8.00 (m, 6 H).

(4*R*,5*R*)-2-Ethyl-2-(6-methoxy-2-naphthyl)-1,3-dioxolane-4,5-dicarboxylic Acid Di-*n*-butyl Ester (1d). Acetal **1d** was obtained, as an oil, in 80% yield by following the procedure described for the preparation of acetal **1b** using (2*R*,3*R*)-tartaric acid di-*n*-butyl ester and tri-*n*-butyl orthoformate: $[\alpha]^{20}_D$ +14° (*c* 1, $CHCl_3$); IR (neat) 1755 cm^{-1} (C=O stretching); ^1H NMR (300 MHz) 0.79 (t, 3 H, *J* = 7.3), 0.94 (t, 3 H, *J* = 7.3), 0.95 (t, 3 H, *J* = 7.3), 1.16 (m, 2 H), 1.37 (m, 4 H), 1.70 (m, 2 H), 2.09 (q, 1 H, *J* = 7.3), 3.92 (s, 3 H), 4.25 (t, 4 H, *J* = 7), 4.80 (AB q, 2 H, *J* = 7.3, $\Delta\nu$ = 12.28), 7.1–7.9 (m, 6 H).

Alternatively, by refluxing a mixture of 1-butanol (160 mL), (2*R*,3*R*)-tartaric acid (31.5 g, 0.21 mol), 1-(6-methoxy-2-naphthyl)propan-1-one (15 g, 0.07 mol), and sulfuric acid (0.1 g, 0.01 mol) and removing water azeotropically, a crude containing acetal **1d** was obtained.

Bromination of Acetals 1 in CCl_4 (Table I). General Procedure. Brominations of **1e,g–i** were carried out in the presence of 2-methoxynaphthalene which, generates HBr in the reaction with bromine. A solution of bromine (2.77 g, 17.3 mmol) in carbon tetrachloride (3 mL) was added at 15 °C with stirring in 5 min to a solution of acetal **1** (15 mmol) and 2-methoxynaphthalene (0.24 g, 1.5 mmol) in carbon tetrachloride (30 mL). The reaction mixture was stirred at 15 °C for 1 h, poured into a 10% aqueous sodium carbonate solution (100 mL), and extracted with dichloromethane (2 × 50 mL). The combined organic extracts were washed with water (100 mL) and dried over sodium sulfate. Evaporation of the solvent under reduced pressure gave a residue that was analyzed by HPLC (eluent $MeOH/H_2O$ = 55–65/45–35; flow 1.6–1.8 mL/min, *T* = 40–45 °C, λ 230 nm) to determine the ratio **2**:**3**. The reaction crude was chromatographed on silica gel, using a mixture of diethyl ether/*n*-hexane as eluent, to give a mixture of **2** and **3**. Yields and diastereomeric ratios (determined by HPLC and ^1H NMR) are given in Table I.

The ratios determined by HPLC were found to be in accordance with ^1H NMR data within the range ±1 and were found identical, within the experimental error, with those determined on the reaction crude. Physical data of compounds **2a–i** and **3a–i**: MS, ^{13}C and ^1H NMR are of mixtures of **2** and **3**.

2a: ^1H NMR (200 MHz) 1.64 (d, 3 H, *J* = 6.8), 3.52 (s, 3 H), 3.88 (s, 3 H), 4.05 (s, 3 H), 4.46 (q, 1 H, *J* = 6.8), 4.94 (AB q, 2 H, *J* = 6, $\Delta\nu$ = 27.35), 7.3–7.8 (m, 6 H); ^{13}C NMR 20.6, 52.5, 52.9, 57.1, 77.3, 78.1, 108.6, 113.4, 114.1, 126.0, 126.3, 127.0, 128.8, 129.6, 133.1, 133.3, 154.6, 168.3, 168.7; MS, *m/e* 531/533/535 $(M + 1)^+$ (triplet due to two bromine atoms), 295/297 $[(M + 1)^+ - CH_3O - C_{10}H_5Br]$.

3a: ^1H NMR (200 MHz) 1.63 (d, 3 H, *J* = 6.8), 3.56 (s, 3 H), 3.87 (s, 3 H), 4.05 (s, 3 H), 4.48 (q, 1 H, *J* = 6.8), 4.91 (AB q, 2 H, *J* = 6, $\Delta\nu$ = 35.5), 7.3–7.8 (m, 6 H).

2b: ^1H NMR (200 MHz) 1.04 (t, 3 H, *J* = 7.0), 1.31 (t, 3 H, *J* = 7.0), 1.65 (d, 3 H, *J* = 6.8), 3.92 (dq, 2 H, *J* = 11.0, *J* = 7.0), 3.98 (s, 3 H), 4.30 (q, 2 H, *J* = 7.0), 4.48 (q, 1 H, *J* = 6.8), 4.88 (AB q, 2 H, *J* = 6, $\Delta\nu$ = 28), 7.2–8.2 (m, 5 H).

3b: ^1H NMR (200 MHz) 1.09 (t, 3 H, *J* = 7.0), 1.29 (t, 3 H, *J* = 7.0), 1.62 (d, 3 H, *J* = 6.8), 3.92 (dq, 2 H), 3.89 (s, 3 H), 4.29 (q, 2 H, *J* = 7.0), 4.85 (AB q, 2 H, *J* = 6, $\Delta\nu$ = 35.7), 7.2–8.2 (m, 5 H).

2c: ^1H NMR (200 MHz) 0.96 (d, 3 H, *J* = 6.4), 1.06 (d, 3 H, *J* = 6.4), 1.30 (d, 6 H, *J* = 6.4), 1.67 (d, 3 H, *J* = 7.2), 3.98 (s, 3 H), 4.47 (q, 1 H, *J* = 7.2), 4.80 (AB q, 2 H, *J* = 6.1, $\Delta\nu$ = 31.58), 4.80 (ept, 1 H, *J* = 6.4), 5.15 (ept, 1 H, *J* = 6.4), 7.2–8.2 (m, 5 H).

3c: ^1H NMR (200 MHz) 0.98 (d, 3 H, *J* = 6.4), 1.08 (d, 3 H, *J* = 6.4), 1.28 (d, 6 H, *J* = 6.4), 1.63 (d, 3 H, *J* = 7.2), 3.98 (s, 3 H), 4.47 (q, 1 H, *J* = 7.2), 4.75 (AB q, 2 H, *J* = 6.5, $\Delta\nu$ = 40.35), 4.80 (ept, 1 H, *J* = 6.4), 5.15 (ept, 1 H, *J* = 6.4), 7.2–8.2 (m, 5 H).

2e: ^1H NMR (300 MHz) 1.64 (d, 3 H, *J* = 7.0), 3.61 (s, 3 H), 3.81 (s, 3 H), 3.81 (s, 3 H), 3.87 (q, 1 H, *J* = 7.0), 4.89 (AB q, 2 H, *J* = 6, $\Delta\nu$ = 69.45), 6.8–7.4 (AA'BB', 4 H); ^{13}C NMR 20.5, 52.4, 52.8, 55.2, 77.0, 77.9, 113.1, 113.3, 128.5, 128.9, 160.2, 168.4, 168.8; MS, *m/e* 403/405 $(M + 1)^+$ (bromine isotopes), 295/297 $[(M + 1)^+ - CH_3O - C_6H_5]$.

3e: ^1H NMR (300 MHz) 1.56 (d, 3 H, *J* = 7.0), 3.64 (s, 3 H), 3.81 (s, 3 H), 3.85 (s, 3 H), 4.34 (q, 1 H, *J* = 7.0), 4.84 (AB q, 2 H, *J* = 5.78, $\Delta\nu$ = 43.71), 6.8–7.4 (AA'BB', 4 H).

2g: ^1H NMR (300 MHz) 1.61 (d, 3 H, *J* = 6.9), 3.54 (s, 3 H), 3.83 (s, 3 H), 4.38 (q, 1 H, *J* = 6.9), 4.88 (AB q, 2 H, *J* = 6, $\Delta\nu$ = 36.22), 7.2–7.6 (m, 5 H); ^{13}C NMR 20.5, 52.3, 52.5 52.8, 77.1, 78.0, 113.3, 127.0, 127.7, 129.0, 137.2, 168.3, 168.7; MS, *m/e* 373/375 $(M + 1)^+$ (bromine isotopes), 295 $[(M + 1)^+ - Br + H]$, 265 $(295 - CH_2O)$.

3g: ^1H NMR (300 MHz) 1.59 (d, 3 H, *J* = 6.9), 3.60 (s, 3 H), 3.82 (s, 3 H), 4.83 (q, 1 H, *J* = 6.9), 4.85 (AB q, 2 H, *J* = 6.3, $\Delta\nu$ = 44.78), 7.2–7.6 (m, 5 H).

2h: ^1H NMR (300 MHz) 1.63 (d, 3 H, *J* = 7.0), 3.60 (s, 3 H), 3.85 (s, 3 H), 4.34 (q, 1 H, *J* = 7.0), 4.86 (AB q, 2 H, *J* = 6, $\Delta\nu$ = 47.62), 7.3–7.5 (AA'BB', 4 H); ^{13}C NMR 20.2, 52.0, 52.4, 52.8, 76.8, 77.9, 112.9, 127.8, 128.5, 135.0, 135.6, 168.0, 168.4; MS, *m/e* 407/409/411 $(M + 1)^+$ (triplet due to one bromine and one chlorine atom), 373/375 $[(M + 1)^+ - Cl + H]$, 329/331 $[(M + 1)^+ - Br + H]$, 327/329 $[(M + 1)^+ - HBr]$, 299/301 $(329/331 - CH_2O)$.

3h: ^1H NMR (300 MHz) 1.60 (d, 3 H, *J* = 7.0), 3.63 (s, 3 H), 3.85 (s, 3 H), 4.34 (q, 1 H, *J* = 7.0), 4.83 (AB q, 2 H, *J* = 6, $\Delta\nu$ = 71.75), 7.3–7.5 (AA'BB', 4 H).

2i: ^1H NMR (300 MHz) 0.93 (d, 3 H, *J* = 6.9), 0.98 (d, 3 H, *J* = 6.6), 1.70 (m, 1 H, J_{CH-CH} = 1.8, J_{CH-CH_3} = 6.6, J_{CH-CH_3} = 6.9), 3.59 (s, 3 H), 3.85 (s, 3 H), 4.28 (d, 1 H, *J* = 1.8), 4.87 (AB q, 2 H, *J* = 6.2, $\Delta\nu$ = 45), 7.3–7.5 (AA'BB', 4 H, aromatic protons).

Bromination of Acetal 1f (Table I). A solution of bromine (3.2 g, 20 mmol) in 1,2-dichloroethane (deoxygenated prior the use) was added at 15 °C with stirring in 5 min to a solution of acetal **1f** (5.25 g, 15 mmol) and HBr (0.16 g, 2 mmol) in 1,2-dichloroethane (30 mL, deoxygenated prior the use). The reaction mixture was kept at 15 °C for 120 min and then worked up as described in the General Procedure of Bromination of Acetals 1. Bromo acetals **2f** and **3f** were obtained in 90% yield.

2f: ^1H NMR (200 MHz) 0.87 (d, 6 H, *J* = 6.4), 1.61 (d, 3 H, *J* = 7.1), 1.84 (m, 1 H, J_{CH-CH_3} = 6.4, J_{CH-CH_2} = 7.1), 2.45 (d, 2 H, *J* = 7.1), 3.53 (s, 3 H), 3.84 (s, 3 H), 4.38 (q, 1 H, *J* = 7.1), 4.9 (AB q, 2 H, *J* = 5.97, $\Delta\nu$ = 30.42), 7.0–7.4 (AA'BB', 4 H, aromatic protons).

3f: ^1H NMR (200 MHz) 0.89 (d, 6 H, *J* = 6.4), 1.58 (d, 3 H, *J* = 7.1), 1.87 (m, 1 H, J_{CH-CH_3} = 6.4, J_{CH-CH_2} = 7.1), 2.53 (d, 2 H, *J* = 7.1), 3.6 (s, 3 H), 3.83 (s, 3 H), 4.41 (q, 1 H, *J* = 7.1), 4.85 (AB q, 2 H, *J* = 6.3, $\Delta\nu$ = 54.82), 7.0–7.4 (AA'BB', 4 H, aromatic protons).

Epimerization of a Mixture of α-Bromo Acetals 2e and 3e in Polar and Nonpolar Solvents. A solution of bromine (0.92 g, 5.8 mmol) in carbon tetrachloride (1 mL) was added at 15 °C, with stirring, in 5 min to a solution of acetal **1e** (1.62 g, 5.0 mmol) and 2-methoxynaphthalene (0.08 g, 0.5 mmol) in carbon tetrachloride (10 mL). The reaction mixture was stirred at 15 °C for 45 min, poured into a 10% aqueous sodium carbonate solution (40 mL), and extracted with dichloromethane (2 × 15 mL). The combined organic extracts were washed with water (30 mL) and dried over sodium sulfate. Evaporation of the solvent under reduced pressure gave a residue which, on the basis of HPLC analysis (eluent $MeOH/H_2O$ = 55/45, flow 1.6 mL/min, *T* = 40 °C, λ 230 nm), was shown to contain a mixture of **2e** and **3e** (1.92 g, 4.8 mmol, 95% yield) in ratio **2e**:**3e** = 91:9. A parallel experiment was worked up after 19.5 h to give a mixture of α-bromo acetals **2e** and **3e** (1.89 g, 4.7 mmol, 94% yield) in ratio **2e**:**3e** = 91:9.

A solution of bromine (0.92 g, 5.8 mmol) in 1,2-dichloroethane (1 mL) was added in 5 min at 15 °C to a stirred solution of acetal **1e** (1.62 g, 5 mmol) and 2-methoxynaphthalene (0.08 g, 0.5 mmol)

in 1,2-dichloroethane (10 mL). The reaction mixture was stirred at 15 °C for 1 h and worked up as above described to give a residue, which was shown by HPLC analysis to consist of a mixture of **2e** and **3e** (1.92 g, 4.8 mmol, 95% yield) (**2e:3e** = 86:14) and 2-bromo-1-(4-methoxyphenyl)propan-1-one (61.0 mg, 0.25 mmol). A parallel experiment was worked up after 24 h to give a mixture of **2e** and **3e** (1.85 g, 4.6 mmol, 92% yield) (ratio **2e:3e** = 79:21) and 2-bromo-1-(4-methoxyphenyl)propan-1-one (97.2 mg, 0.4 mmol).

Synthesis of (2*S*)-(+)-2-Bromo-1-(6-methoxy-2-naphthyl)propan-1-one (18j) (Scheme IV). Bromine (28.5 g, 178.1 mmol) was added at −10 °C in 1 h to a stirred solution of acetal **1a** (29.0 g, 77.5 mmol) and nitrobenzene (3.9 g) in toluene (120 mL). The reaction mixture was kept under stirring for 1 h at −10 °C (HPLC analysis showed that a mixture of **2a** and **3a** was formed in 95% yield and in ratio **2a:3a** = 90:10) and added with phenol (43.68 g, 0.46 mol). The reaction mixture was warmed up to 15 °C and stirred at this temperature for 3 h. The reaction mixture was poured into a 10% aqueous sodium carbonate solution (250 mL); the layers were separated and the aqueous phase was extracted with toluene (100 mL). The combined organic extracts were washed with sodium hydroxide aqueous solution (18.8 g of NaOH, 0.47 mol in 200 mL). The organic phase was dried over sodium sulfate, the solvent removed in vacuo and the residue chromatographed on silica gel (diethyl ether/*n*-hexane = 7:3) to give a mixture of **2j** and **3j** in ratio **2j:3j** = 90:10 (24.6 g, 54.3 mmol, 70% yield), as determined by HPLC and ^{1}H NMR (200 MHz).

2j: ^{1}H NMR (200 MHz) 1.68 (d, 3 H, J = 7.5), 3.54 (s, 3 H), 3.90 (d, 3 H), 4.03 (s, 3 H), 4.48 (q, 1 H, J = 7.5), 4.94 (2 H, AB q, $\Delta\nu$ = 26.8; J = 7.2), 7.1–8.0 (6 H, m).

3j: ^{1}H NMR (200 MHz) 1.64 (d, 3 H, J = 7.5), 3.58 (s, 3 H), 3.89 (d, 3 H), 4.08 (s, 3 H), 4.50 (q, 1 H, J = 7.5), 4.89 (2 H, AB q, $\Delta\nu$ = 36.3, J = 6.3), 7.1–8.0 (6 H, m).

A mixture of **2j** and **3j** in a ratio of 90:10 (12.5 g, 29.3 mmol) was added, at 20 °C, to a solution of methanol (15 mL) in methanesulfonic acid (60 mL). The reaction mixture was kept at 20 °C for 4 h, poured into crushed ice, and extracted with dichloromethane. The organic phase was washed with water and with a 2% aqueous sodium bicarbonate solution of sodium bicarbonate and dried over sodium sulfate. Evaporation of the solvent under reduced pressure gave a residue. Chromatography (eluent dichloromethane/*n*-hexane = 4:6) of the reaction crude afforded pure 2-bromo-(6-methoxy-2-naphthyl)propan-1-one (**18j**) (7.7 g, 26.4 mmol, 90% yield): mp 101–103 °C; $[\alpha]^{20}_D$ +177.6° (*c* 0.5, $CHCl_3$) [The enantiomeric ratio *S*:*R* determined by ^{1}H NMR (300 MHz) analysis with the optically active Eu(hfc)$_3$, was 90:10.]; IR (Nujol mull) cm^{-1} 1680 (C=O stretching); ^{1}H NMR (300 MHz) 1.98 (d, 3 H, J = 6.7), 3.97 (s, 3 H), 5.45 (q, 1 H, J = 6.7), 7.2–8.5 (aromatic protons, 6 H).

Crystallization of **18j** (80% ee) from methanol gave (2*S*)-(+)-**18j**: mp 105–106 °C; $[\alpha]^{20}_D$ +212.6° (*c* 0.5, chloroform) as enantiomerically pure product.

A solution of 2-bromo-6-methoxynaphthalene (20 g, 0.084 mol) in tetrahydrofuran (80 mL) was added in 3 h to a suspension of magnesium turnings (7.2 g, 0296 mol) in tetrahydrofuran, kept at 65–68 °C under stirring. The reaction mixture was kept at 68 °C for an additional hour, then it was diluted with tetrahydrofuran (70 mL), cooled to 40–50 °C, and filtered. The filtrate was cooled to 25 °C and added in 2 h to a stirred cold (−45 °C) solution of 2(*S*)-bromopropionyl chloride[25] (14.7 g, 0.086 mol) in tetrahydrofuran (50 mL). The reaction mixture was stirred at −45 °C for 2 h, poured with stirring into a 5% aqueous hydrochloric acid solution (400 mL), and extracted with dichloromethane. The organic phase was washed with water and dried over sodium sulfate and the solvent removed in vacuo. The reaction crude (22.6 g) was chromatographed on silica gel (diethyl ether/*n*-hexane = 15:85) to give a residue, which after crystallization from methanol gave analytically pure (2*S*)-(+)-2-bromo-1-(6-methoxy-2-naphthyl)propan-1-one (**18j**) (50% ee).

Bromination of Acetal 1a: Solvent Effect on the Diastereoselectivity (Table II). A solution of bromine (1.68 g, 10.5 mmol) in the appropriate solvent (2 mL), kept at the temperature given in Table II, was added, in 5 min, to a stirred solution of acetal **1a** (1.87 g, 5.0 mmol) in the same solvent (20 mL), kept at the same temperature. The reaction mixture was stirred at the temperature and for the time reported in Table II; then it was poured into a 10% aqueous sodium carbonate solution (30 mL) and extracted with dichloromethane (2 × 15 mL). The combined organic layers were washed with water (30 mL) and dried over sodium sulfate. Evaporation of the solvent under reduced pressure gave a mixture of **2a** and **3a** as a residue. Yields and diastereomeric ratios were determined by HPLC (eluent $MeOH/H_2O$ = 63/37, flow 1.8 mL/min, T = 45 °C, λ 230 nm) and ^{1}H NMR (300 MHz) analyses. The diastereomeric ratios determined by HPLC were found to be in accordance with ^{1}H NMR data within the range ±1.

Preparation of 2a. A mixture of diastereomers **2a** and **3a** (**2a:3a** = 91:9) was chromatographed on silica gel (diethyl ether/*n*-hexane = 2:8). The fractions were separately analyzed by HPLC: those containing pure **2a** were collected and the solvent was removed in vacuo. The residue was heated to 50 °C (external bath) at 0.1 mmHg for 1 h to give **2a**: $[\alpha]^{20}_D$ +43.0° (*c* 1, $CHCl_3$)).

Influence of Mode and Timing of Bromine Addition on Yields and Diastereoselectivity. A solution of bromine (0.92 g, 5.8 mmol) in carbon tetrachloride (1 mL) was added in 3 h, at 15 °C, to a stirred solution of acetal **1h** (1.64 g, 5.0 mmol) and 2-methoxynaphthalene (0.08 g, 0.5 mmol) in carbon tetrachloride (10 mL). The reaction mixture was stirred at 15 °C for 1.3 h and worked up as usual to give a residue that was shown by HPLC analysis to contain a mixture of **2h** and **3h** (1.96 g, 4.8 mmol, 96% yield) (**2h:3h** = 93.5:6.5). In a parallel experiment, where the bromine solution was added in 5 min, a mixture of **2h** and **3h** (1.90 g, 4.7 mmol, yield 93%) in a ratio of **2h:3h** = 94:6 was obtained.

A solution of acetal **1h** (1.64 g, 5.0 mmol) in carbon tetrachloride (3 mL) was added in 30 min, at 15 °C, to a stirred solution of bromine (4.1 g, 25.5 mmol) and 2-methoxynaphthalene (0.08 g, 0.5 mmol) in carbon tetrachloride (8 mL). The reaction mixture was stirred at 15 °C for 1.5 h and worked up as usual to give a mixture of **2h** and **3h** (2.01 g, 4.9 mmol, 98% yield) in a ratio of **2h:3h** = 91:9, as determined by HPLC analysis.

Reaction of Bromo Acetals 2a and 3a with $AgBF_4$ in CD_2Cl_2. Anhydrous silver tetrafluoroborate (129 mg, 0.663 mmol) was added under argon at once, at 5 °C, to a stirred solution of acetals **2a** and **3a** (ratio **2a:3a** = 94:6) (248 mg, 0.466 mmol) in CD_2Cl_2 (1 mL). The reaction mixture was kept at 15 °C for 1 h and silver bromide was filtered off under argon. The CD_2Cl_2 solution was collected, under argon, in a NMR tube that was sealed. ^{1}H NMR (300 MHz) analysis indicated the conversion of **2a** and **3a** into **8a** and **9a**[18] in the ratio of **8a:9a** = 91:9). **8a** significant resonances: 1.97 (d, 3 H, J = 7), 4.90 (q, 1 H, J = 7), 6.36 (s, 2 H, CHCH). **9a** significant resonances: 1.99 (d, 3 H, J = 7), 4.90 (q, 1 H, J = 7), 6.33 (s, 2 H, CHCH). Treatment of the solution with water gave rise to the formation of esters **10a** and **11a** in a ratio of **10a:11a** = 91:9.

10a: ^{1}H NMR (300 MHz, CD_2Cl_2) 1.62 (d, 3 H, J = 7), 3.10 (d, 1 H, J = 7), 3.24 (s, 3 H), 3.82 (s, 3 H), 4.05 (s, 3 H), 4.05 (q, 1 H, J = 7), 4.70 (dd, 1 H, J = 7, J = 2), 5.37 (d, 1 H, J = 2), 7.3–8.3 (m, 5 H).

11a: ^{1}H NMR (300 MHz, CD_2Cl_2) 1.60 (d, 3 H, J = 7), 3.12 (d, 1 H, J = 7), 3.67 (s, 3 H), 3.72 (s, 3 H), 4.05 (s, 3 H), 4.05 (q, 1 H, J = 7), 4.76 (dd, 1 H, J = 7, J = 2), 5.46 (d, 1 H, J = 2), 7.3–8.3 (m, 5 H).

The ratio of dioxolonium salts **8a** and **9a** was observed to decrease during the time.

Synthesis of Optically Active 2-Alkyl-2-arylacetic Acids 17 via $AgBF_4$-Promoted Rearrangement of 2 and 3 into Esters 10 and 11 (Table III). General Procedure. A solution (91.3 mL) of silver tetrafluoroborate (13.7 g, 70.3 mmol) in 1,2-dichloroethane was added at 15 °C, in 10 min, to a stirred mixture of **2** and **3** (50.2 mmol) in the ratio given in Table III, water (1.35 g, 75.0 mmol), and 1,2-dichloroethane (84 mL). The reaction mixture was stirred at the temperature and for the time given in Table III. The reaction mixture was poured into water (200 mL) and filtered on Celite and the Celite was washed with methylene chloride (200 mL). The organic layer was collected, dried over Na_2SO_4, and evaporated under vacuum to give a residue; ^{1}H NMR spectra taken on the residue solution in $CDCl_3$

(25) (a) Fu, S. C. J.; Birnbaum, S. M.; Greenstein, J. P. *J. Am. Chem. Soc.* **1954**, *76*, 6054. (b) Ruud-Christensen, M.; Skjetne, T.; Krane, J.; Aasen, A. J. *Acta Chem. Scand., Ser. B* **1984**, *38*, 331.

allowed for determination of the diastereomeric ratio of **10**:**11**. The residue was chromatographed on silica gel, using a mixture of diethyl ether–*n*-hexane as eluent, to provide a mixture of **10** and **11** in yields and ratios given in Table III. Diastereomeric ratios were determined by ^{1}H NMR and were found to be identical, within the experimental error, with those determined on the reaction crude. Physical data of compounds **10a–j** and **11a–j**: MS, ^{13}C and ^{1}H NMR data are of mixtures of **10** and **11**.

10a: ^{1}H NMR (200 MHz) 1.58 (d, 3 H, J = 7.1), 3.10 (d, 1 H, J = 7.2), 3.12 (s, 3 H), 3.79 (s, 3 H), 3.98 (s, 3 H), 3.98 (q, 1 H, J = 7.1), 4.65 (dd, 1 H, J_{CHOH} = 7.2, J_{CH-CH} = 2.5), 5.34 (d, 1 H, J = 2.5), 7.0–8.2 (m, 5 H); ^{13}C NMR 17.8, 44.5, 52.7, 52.8, 57.0, 70.3, 73.1, 108.3, 114.0, 126.4, 126.6, 127.4, 128.8, 129.7, 132.3, 135.6, 153.8, 166.8, 170.5, 173.0; MS, m/e 469/471 $(M + 1)^+$ (bromine isotopes), 263/265 $[(M + 1)^+ - C_7H_{10}O_7]$.

11a: ^{1}H NMR (300 MHz) 1.61 (d, 3 H, J = 7.1), 3.1 (d, 1 H, J = 7.2), 3.56 (s, 3 H), 3.68 (s, 3 H), 3.98 (s, 3 H), 4.03 (q, 1 H, J = 7.1), 4.73 (dd, 1 H, J_{CHOH} = 7.2, J_{CHCH} = 2.5), 5.44 (d, 1 H, J = 2.5), 7.0–8.2 (m, 5 H).

10b: ^{1}H NMR (200 MHz) 0.76 (t, 3 H, J = 7.2), 1.27 (t, 3 H, J = 7.2), 1.58 (d, 3 H, J = 7.0), 3.10 (d, 1 H, J = 7.1), 3.58 (AB q, 2 H, J = 12.0, J = 7.2), 4.00 (q, 1 H, J = 7.0), 4.01 (s, 3 H), 4.27 (q, 2 H, J = 7.2), 4.65 (dd, 1 H, J_{CHOH} = 7.1, J_{CHCH} = 2.4), 5.32 (d, 1 H, J = 2.4), 7.2–8.2 (m, 5 H).

11b: ^{1}H NMR (200 MHz) 1.08 (t, 3 H, J = 7.2), 1.14 (t, 3 H, J = 7.2), 1.62 (d, 3 H, J = 7.0), 3.1 (d, 1 H, J = 7.1), 3.58 (AB q, 2 H, J = 12.0, J = 7.2), 4.00 (q, 1 H, J = 7.0), 4.01 (s, 3 H), 4.07 (q, 2 H, J = 7.2), 4.65 (dd, 1 H, J_{CHOH} = 7.1, J_{CHCH} = 2.4), 5.44 (d, 1 H, J = 2.4), 7.2–8.2 (m, 5 H).

10c: ^{1}H NMR (200 MHz) 0.55 (d, 3 H, J = 6.1), 1.02 (d, 3 H, J = 6.1), 1.24 (d, 3 H, J = 6.1), 1.27 (d, 3 H, J = 6.1), 1.61 (d, 3 H, J = 7.0), 3.17 (d, 1 H, J = 6.8), 4.00 (q, 1 H, J = 7.0), 4.02 (s, 3 H), 4.52 (ept, 1 H, J = 6.1), 4.62 (dd, 1 H, J_{CH-CH} = 2.2, J_{CH-OH} = 6.8), 5.13 (ept, 1 H, J = 6.1), 5.30 (d, 1 H, J = 2.2), 7.2–8.2 (m, 5 H).

11c: ^{1}H NMR (200 MHz) 0.95 (d, 3 H, J = 6.1), 1.12 (d, 3 H, J = 6.1), 1.14 (d, 3 H, J = 6.1), 1.19 (d, 3 H, J = 6.1), 1.62 (d, 3 H, J = 7.0), 3.17 (d, 1 H, J = 6.8), 4.00 (q, 1 H, J = 7.0), 4.02 (s, 3 H), 4.52 (ept, 1 H, J = 6.1), 4.62 (dd, 1 H, J_{CHCH} = 2.2, J_{CHOH} = 6.8), 5.13 (ept, 1 H, J = 6.1), 5.41 (d, 1 H, J = 2.2), 7.2–8.2 (m, 5 H).

10e: ^{1}H NMR (300 MHz) 1.48 (d, 3 H, J = 7.3), 3.09 (d, 1 H, J = 7.2), 3.39 (s, 3 H), 3.77 (s, 3 H), 3.81 (s, 3 H), 3.77 (q, 1 H, J = 7.3), 4.67 (dd, 1 H, J_{CHOH} = 7.2, J_{CHCH} = 2.3), 5.35 (d, 1 H, J = 2.3), 6.8–7.2 (AA′BB′, 4 H); ^{13}C NMR 18.0, 44.0, 52.8, 55.2, 70.4, 72.9, 114.1, 128.5, 131.9, 158.9, 166.9, 170.6, 173.4; MS, m/e 341 $(M + 1)^+$, 340 $[(M + 1)^+ - H]$, 323 $[(M + 1)^+ - H_2O]$, 135 $[(M + 1)^+ - C_7H_{10}O_7]$.

11e: ^{1}H NMR (300 MHz) 1.51 (d, 3 H, J = 7.3), 3.09 (d, 1 H, J = 7.2), 3.67 (s, 3 H), 3.73 (s, 3 H), 3.77 (s, 3 H), 3.77 (q, 1 H, J = 7.3), 6.73 (dd, 1 H, J_{CHOH} = 7.2, J_{CHCH} = 2.3), 5.4 (d, 1 H, J = 2.3), 6.8–7.2 (AA′BB′, 4 H).

10g: ^{1}H NMR (300 MHz) 1.50 (d, 3 H, J = 7.2), 3.08 (d, 1 H, J = 7), 3.32 (s, 3 H), 3.80 (s, 3 H), 3.83 (q, 1 H, J = 7.2), 4.67 (dd, 1 H, J = 7, J = 2.4), 5.35 (d, 1 H, J = 2.4), 7.2–7.3 (m, 5 H); ^{13}C NMR 18.0, 44.9, 52.8, 70.4, 73.0, 127.3, 127.5, 128.7, 139.9, 167.0, 170.6, 173.2; MS, m/e 311 $(M + 1)^+$, 310 $[(M + 1)^+ - H]$, 293 $[(M + 1)^+ - H_2O]$.

11g: ^{1}H NMR (300 MHz) 1.52 (d, 3 H, J = 7.2), 3.11 (d, 1 H, J = 7), 3.64 (s, 3 H), 3.71 (s, 3 H), 3.83 (q, 1 H, J = 7.2), 4.72 (dd, 1 H, J = 7, J = 2.4), 5.43 (d, 1 H, J = 2.4), 7.2–7.3 (m, 5 H).

10h: ^{1}H NMR (200 MHz) 1.49 (d, 3 H, J = 7.1), 2.0–3.0 (br, 1 H), 3.43 (s, 3 H), 3.81 (s, 3 H), 3.81 (q, 1 H, J = 7.1), 4.68 (d, 1 H, J = 2.3), 5.35 (d, 1 H, J = 2.3), 7.1–7.3 (AA′BB′, 4 H); ^{13}C NMR 17.9, 44.0, 52.8, 70.3, 73.1, 128.8, 128.9, 134.0, 138.2, 166.8, 170.6, 172.7; MS, m/e 345/347 $(M + 1)^+$ (chlorine isotopes), 327/329 $[(M + 1)^+ - H_2O]$, 139/141 $[(M + 1)^+ - C_7H_{10}O_7]$.

11h: ^{1}H NMR (200 MHz) 1.50 (d, 3 H, J = 7.1), 2.0–3.0 (br, 1 H), 3.69 (s, 3 H), 3.72 (s, 3 H), 3.83 (q, 1 H, J = 7.1), 4.74 (d, 1 H, J = 2.3), 5.42 (d, 1 H, J = 2.3), 7.1–7.3 (AA′BB′, 4 H).

10i: ^{1}H NMR (300 MHz) 0.68 (d, 3 H, J = 6.9), 1.07 (d, 3 H, J = 6.2), 2.33 (m, 1 H, J_{CH-CH} = 10.6, J_{CH-CH_3} = 6.9, J_{CH-CH_3} = 6.2), 3.22 (d, 1 H, J = 6.9), 3.24 (d, 1 H, J = 10.6), 3.30 (s, 3 H), 3.77 (s, 3 H), 4.63 (dd, 1 H, J_{CH-OH} = 6.9, J_{CH-CH} = 2.6), 5.36 (d, 1 H, J_{CH-CH} = 2.6), 7.2–7.3 (AA′BB′, 4 H, aromatic protons).

10j: ^{1}H NMR (200 MHz) 1.62 (d, 3 H, J = 8.0), 3.11 (s, 3 H), 3.21 (d, 1 H, J = 7.2), 3.83 (s, 3 H), 3.92 (s, 3 H), 3.95 (q, 1 H, J = 8.0), 4.68 (dd, 1 H, J_{CH-OH} = 7.2, J_{CH-CH} = 2.5), 5.37 (d, 1 H, J = 2.5), 7.1–7.8 (m, 6 H).

11j: ^{1}H NMR (200 MHz) 1.66 (d, 3 H, J = 8.0), 3.24 (d, 1 H, J = 7.6), 3.58 (s, 3 H), 3.72 (s, 3 H), 3.92 (s, 3 H), 3.97 (q, 1 H, J = 8.0), 4.78 (dd, 1 H, J_{CH-OH} = 7.6, J_{CH-CH} = 2.5), 5.45 (d, 1 H, J = 2.5), 7.1–7.8 (m, 6 H).

A mixture of diastereomeric esters **10** and **11** (11 mmol), CH_3COOH (9.5 mL), concentrated HCl (11.4 mL), and water (11.4 mL) was stirred at 85 °C up to complete hydrolysis of **10** and **11** (the reaction was monitored by TLC). The reaction mixture was cooled to room temperature and extracted with methylene chloride (2 × 100 mL). The organic phase was washed with water (2 × 50 mL) and dried over Na_2SO_4; the solvent was removed in vacuo to give a residue that was chromatographed on silica gel by using a mixture of diethyl ether and *n*-hexane as eluent to give **17**; enantiomeric purities and yields of **17** are given in Table III. The enantiomeric ratios were determined by optical rotations measurements and by ^{1}H NMR analysis of the corresponding methyl esters carried out in the presence of the optically active shift reagent Eu(hfc)$_3$. The ratios determined by the two techniques were found to be in accordance with one another within a range ±1. **17a,j** are known compounds and were identified by comparison with authentic samples.

From **2,3a,c**, **2,3e**, **2,3f**, **2,3g**, **2,3h**, **2,3i**, and **2,3j**, the following acids were obtained respectively: 2(*S*)-(+)-(5-bromo-6-methoxy-2-naphthyl)propanoic acid (**17a**);[26] 2(*S*)-(+)-(4-methoxyphenyl)propanoic acid (**17e**);[27] 2(*S*)-(+)-phenylpropanoic acid (**17g**);[28] 2(*S*)-(+)-(4-chlorophenyl)propanoic acid (**17h**);[29] 2(*S*)-(+)-(4-chlorophenyl)-3-methylbutanoic acid (**17i**);[30] 2(*S*)-(+)-(6-methoxy-2-naphthyl)propanoic acid (**17j**) (Naproxen).[3c]

Preparation of 2(*S*)-(+)-(6-Methoxy-2-naphthyl)-propanoic Acid (17j) (Naproxen). A diastereomeric mixture of esters **10a** and **11a** in a ratio of **10a**:**11a** = 91:9 was crystallized from methanol to give **10a** as pure isomer: mp 124–126 °C; $[\alpha]^{20}_D$ +61.4° (*c* 1, $CHCl_3$): ^{1}H NMR, ^{13}C NMR, and MS were found to be identical with those reported above for **10a**. The hydrolysis of **10a** (6.1 g, 13.0 mmol), carried out following the General Procedure given before, afforded 2(*S*)-(5-bromo-6-methoxy-2-naphthyl)propanoic acid (3.8 g, 12.3 mmol, 95% yield), which was found enantiomerically pure by ^{1}H NMR (300 MHz) analysis of its methyl ester in the presence of the optically active shift reagent Eu(hfc)$_3$: mp 168–170 °C; $[\alpha]^{20}_D$ +42.5° (*c* 0.5, $CHCl_3$). The aqueous phase was concentrated in vacuo until a solid residue was obtained. The crude material was suspended under stirring for 1 h in refluxing ethyl ether. The mixture was cooled to room temperature and the insoluble was collected by filtration, affording (2*R*,3*R*)-tartaric acid (1.4 g, 9.3 mmol, 72% yield): $[\alpha]^{20}_D$ +12.1° (*c* 20, water) [lit.[31] $[\alpha]^{20}_D$ +12.0° (*c* 20, water)].

Enantiomerically pure 2(*S*)-(+)-(5-bromo-6-methoxy-2-naphthyl)propanoic acid was debrominated according to a known procedure,[26] affording 2(*S*)-(+)-(6-methoxy-2-naphthyl)propanoic acid (Naproxen), which was shown to be enantiomerically pure by ^{1}H NMR (300 MHz) analysis of the corresponding dimethyl ester in the presence of the optically active Eu(hfc)$_3$: mp 154–155 °C; $[\alpha]^{20}_D$ +67.5° (*c* 1, $CHCl_3$) [lit.[3c] $[\alpha]^{20}_D$ +66° (*c* 1, $CHCl_3$)].

Preparation of 10a. A solution of oxalyl chloride (400 g, 3.15 mol) in toluene (300 mL) was added at 25 °C to a stirred mixture of 2(*S*)-(6-methoxy-2-naphthyl)propanoic acid (200 g, 0.87 mol) and toluene (500 mL). The reaction mixture was gradually heated up to 90 °C and kept at this temperature for 4 h. The mixture was concentrated (60 °C, 130 mmHg) to a final volume of about 150 mL to give a residue which, after crystallization from toluene (200 mL) afforded 2(*S*)-(6-methoxy-2-naphthyl)propanoyl chloride (115 g, 0.46 mol, 53% yield).

A solution of 2(*S*)-(6-methoxy-2-naphthyl)propanoyl chloride (10.0 g, 40.2 mmol) in dichloromethane (50 mL) was added under

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stirring in 25 min to a cold solution (-10 °C) of (2R,3R)-tartaric acid dimethyl ester (89.0 g, 0.5 mol) and triethylamine (8.9 g, 87.9 mmol) in dichloromethane (200 mL). The reaction mixture was stirred at -10 °C for 15 min and poured into a 5% HCl solution (200 mL). The aqueous phase was extracted with dichloromethane (200 mL). The combined organic extracts were washed with water (2 × 200 mL), dried over sodium sulfate, and concentrated under reduced pressure. A solid residue (14.3 g) was obtained, which was chromatographed on silica gel (diethyl ether/*n*-hexane = 3:7) to give pure **10j** (13.3 g, 34.0 mmol, 85% yield): mp 79-81 °C, $[\alpha]^{20}_D$ +72.4° (*c* 1, $CHCl_3$). According to the above procedure, **11j** was prepared starting from 2(*R*)-(6-methoxy-2-naphthyl)-propanoyl chloride.

A solution of bromine (0.43 g, 2.7 mmol) in 1,2-dichloroethane (2 mL) was added in 15 min with stirring at 0 °C to a solution of **10j** (1.01 g, 2.6 mmol) in 1,2-dichloroethane (10 mL). The reaction mixture was stirred at 0 °C for 45 min and poured into a 10% aqueous sodium carbonate solution (20 mL). The aqueous phase was extracted with dichloromethane (2 × 10 mL). The combined organic extracts were washed with a 5% aqueous solution of sodium thiosulfate (20 mL) and with water (20 mL). The organic phase was dried over sodium sulfate and the solvent was removed in vacuo to give a residue (1.14 g). Crystallization from methanol of the crude material afforded **10a** (1.04 g, 2.2 mmol, 85% yield): mp 123-125 °C; $[\alpha]^{20}_D$ +61.4° (*c* 1, $CHCl_3$); MS and ^{13}C and ^1H NMR data were found to be identical with those reported above.

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Registry No. **1a** (isomer 1), 101154-44-3; **1a** (isomer 2), 101154-60-3; **1b**, 101154-49-8; **1c**, 101154-55-6; **1d**, 105785-45-3; **1e**, 100791-76-2; **1f**, 101154-61-4; **1g**, 100791-77-3; **1h**, 100791-78-4; **1i**, 101154-75-0; **2a**, 100791-79-5; **2b**, 101154-50-1; **2c**, 101154-56-7; **2d**, 107576-63-6; **2e**, 100791-83-1; **2f**, 101154-63-6; **2g**, 100791-85-3; **2h**, 100791-87-5; **2i**, 101154-76-1; **2j**, 101154-45-4; **3a**, 100791-80-8; **3b**, 101154-51-2; **3c**, 101154-57-8; **3d**, 107576-64-7; **3e**, 100791-84-2; **3f**, 101154-64-7; **3g**, 100791-86-4; **3h**, 100791-88-6; **3i**, 101154-77-2; **3j**, 101154-46-5; **8a**, 105817-50-3; **9a**, 105817-52-5; **10a**, 105926-81-6; **10b**, 105785-50-0; **10c**, 105879-58-1; **10d**, 105785-51-1; **10g**, 105785-52-2; **10h**, 105785-53-3; **10i**, 105857-33-8; **10j**, 101527-01-9; **11a**, 105785-48-6; **11b**, 105879-57-0; **11c**, 105785-49-7; **11d**, 105879-59-2; **11g**, 105879-60-5; **11h**, 105879-61-6; **11i**, 107741-22-0; **11j**, 101628-18-6; (*S*)-**17a**, 84236-26-0; (*R*)-**17a**, 92471-85-7; (*S*)-**17e**, 24470-14-2; (*R*)-**17e**, 4842-49-3; (*S*)-**17g**, 7782-24-3; (*R*)-**17g**, 7782-26-5; (*S*)-**17h**, 105879-63-8; (*R*)-**17h**, 105879-62-7; (*S*)-**17j**, 22204-53-1; (*R*)-**17j**, 23979-41-1; (*S*)-**18j**, 102849-62-7; (*R*)-**18j**, 107656-29-1; 1-(4-methoxyphenyl)propan-1-one, 121-97-1; (2*R*,3*R*)-tartaric acid dimethyl ester, 608-68-4; 1-phenylpropanone, 93-55-0; 1-(4-chlorophenyl)propan-1-one, 6285-05-8; 1-(4-chlorophenyl)-3-methylbutan-1-one, 71573-93-8; 2-acetyl-6-methoxynaphthalene, 3900-45-6; (2*S*,3*S*)-tartaric acid dimethyl ester, 13171-64-7; (2*R*,3*R*)-tartaric acid diisopropyl ester, 2217-15-4; (2*R*,3*R*)-tartaric acid dibutyl ester, 87-92-3; 1-(6-methoxy-2-naphthyl)propan-1-one, 2700-47-2; 2-methoxynaphthalene, 93-04-9; 2-bromo-1-(4-methoxyphenyl)propan-1-one, 21086-33-9; 2(*S*)-bromopropionyl chloride, 22592-73-0; 2(*S*)-(6-methoxy-2-naphthyl)propanoyl chloride, 51091-84-0; (2*R*,3*R*)-tartaric acid diethyl ester, 87-91-2; 1-[4-(2-methylpropyl)phenyl]propan-1-one, 59771-24-3; 1-butanol, 71-36-3; 2-bromo-6-methoxynaphthalene, 5111-65-9; acetic acid, 64-19-7.

Hydroxide-Initiated Gas-Phase Chemistry of Anthraquinone and Related Quinones

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Low-pressure gas-phase reactions of OH^-, $^{18}OH^-$, and OD^- with anthraquinone, naphthoquinone, benzoquinone, and various alkyl-substituted analogues have been characterized via Fourier transform mass spectrometry. The primary reactions are proton abstraction to yield M - H anions. In addition, anthraquinone, naphthoquinone, and benzoquinone produce abundant $(M + 17)^-$ ions. Ejection studies establish that these ions are formed from secondary reactions of $(M - H)^-$ with water and are represented as $[M - H + (H_2O)]^-$. The $(M - H)^-$ anions from anthraquinone and naphthoquinone react with their neutral precursors to produce anionic adducts, $(M - H + M)^-$, with *m/z* 415 and 315, respectively. Collision-activated dissociation confirms the structure of the adducts. Significant H/D exchange and oxygen-16/oxygen-18 exchange occurs when D_2O or $H_2{}^{18}O$ are present. The results are discussed in relation to the mechanisms that have been proposed for OH^-/quinone reactions in solution.

Introduction

Single-electron-transfer reactions, which result from the interaction of electron acceptors with electron donors, often are implicated in the mechanisms of heterolytic chemical reactions. There have been several reports[2,3] of anion radical formation from the interaction of bases and/or nucleophiles with a variety of organic electron acceptors. However, in many cases, the mechanisms by which such ions are generated remain unknown.

The various quinoid species (Q) react with OH^- in aqueous and nonaqueous solution to generate the corresponding semiquinone anion radicals ($Q^{\bullet -}$).[4,5] The redox chemistry of quinones has been well-documented in the condensed[6,7] and gas phase.[8] In view of these data, the reduction of Q by OH^- is intriguing because radical products are produced from nonradical reagents in a reaction that is thermodynamically disfavored (the redox potential for the $OH^-/OH^{\bullet}$ couple is +0.8 V vs. NHE in acetonitrile whereas that for most quinone/semiquinone

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