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Communications

Br_3^- vs Br_2: Opposite Diastereoselectivity in the Bromination of Enantiomerically Pure Ketals

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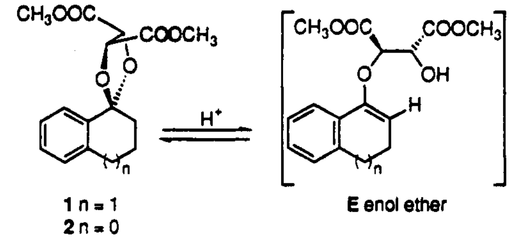
Summary: For the first time different brominating species (Br_3^- vs Br_2) have been shown to react with chiral alkenes generating resolved stereogenic carbon centers of opposite configuration using the same chiral auxiliary.

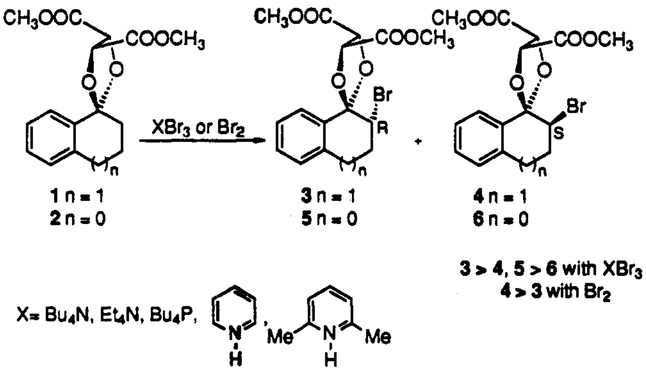
Solid organic tribromide salts have been shown to be a practical source of electrophilic bromine.[1] The different stereo- and regioselectivities between the tribromide ion and free bromine in addition reactions and the role of the tribromide ion in the addition of bromine to alkenes are still under active investigation.[2] It is surprising how many different electrophilic brominating agents but not tribromide salts have been tested in the bromination of chiral auxiliary bound alkenes.[3] In particular, it has been reported that different electrophilic halogenating species react with chiral auxiliary bound enol ethers[3d] (generated in situ from the corresponding ketals) and enolates[3e] with high diastereoselectivity, the sense of asymmetric induction being the same for the same substrate.

The above considerations prompted us to investigate the tribromide salt bromination of (2*R*,3*R*)-dimethyltartrate ketals **1** ($n = 1$) and **2** ($n = 0$), precursors of *E* enol ethers (Scheme I), which have been shown to undergo highly diastereoselective halogenations when treated with Br_2, SO_2Cl_2, ICl.[3d]

Scheme I



Scheme II



Now we wish to report that the bromination of the said ketals with "onium" tribromides provides α-bromo ketals with high diastereoselectivity and that the sense of diastereoselection is opposite to that with Br_2, SO_2Cl_2, and ICl (Scheme II).

Tetra-*n*-butylammonium tribromide reacts at 0 °C with **1** ($n = 1$) in greater than 95% yield (Table I, entries 1, 6, 9) to provide epimeric mixtures of α-bromo ketals **3** and **4**.[4,5] The diastereoselectivity, which always favors the

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[1] For a recent leading reference see: Kajigashi, S.; Mariwashi, M.; Tanabe, T.; Fujisaki, S.; Kakiuami, T.; Okamoto, T. *J. Chem. Soc., Perkin Trans. 1* **1990**, 897.

[2] (a) Bellucci, G.; Bianchini, R.; Ambrosetti, R.; Ingrosso, G. *J. Org. Chem.* **1985**, *50*, 3313. (b) Bellucci, G.; Bianchini, R.; Chiappe, C.; Marioni, F. *J. Org. Chem.* **1990**, *55*, 4094. (c) Ruasse, M. F.; Motallebi, S.; Galland, B. *J. Am. Chem. Soc.* **1991**, *113*, 3440.

[3] (a) Hiroi, K.; Yamada, S. *Chem. Pharm. Bull.* **1973**, *21*, 54. (b) Suzuki, M.; Kimura, Y.; Terashima, S. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3559. (c) Oppolzer, W.; Dudfield, P. *Tetrahedron Lett.* **1985**, *26*, 5037. (d) Giordano, C.; Coppi, L.; Restelli, A. *J. Org. Chem.* **1990**, *55*, 5400. (e) Evans, D. A.; Britton, T. C.; Ellman, J.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011. (f) Angibaud, P. Ph.D. Dissertation, *Halogénation énantiosélective et diastéréosélective d'acétals de cétène*; University of Rouen, 1991: Angibaud reports the bromination with tetra-*n*-butylammonium tribromide (THF, −70 °C) of a 1,2,5,6-di-*O*-isopropylidene-α-D-glucofuranose-bound silyl ketene acetal (de = 17%); the sense of diastereoselectivity is the same as shown by bromine and other brominating reagents.

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Table I. Bromination of 1 and 2 with "Onium" Tribromide at 0 °C[4]

ent	n	X	solvent	reaction time[8] (min)	3/4[a] or 5/6[b] ratio
1	1	tetrabutylammonium	CH_2Cl_2	10	56/44
2	1	tetraethylammonium	CH_2Cl_2	30	62/38
3	1	pyridinium	CH_2Cl_2	30	58/42
4	1	2,6-dimethylpyridinium	CH_2Cl_2	1	53/47
5	1	tetrabutylphosphonium	CH_2Cl_2	100	55/45
6	1	tetrabutylammonium	CH_3CN	5	85/15
7	1	tetraethylammonium	CH_3CN	30	86/14
8	1	tetrabutylphosphonium	CH_3CN	45	86/14
9	1	tetrabutylammonium	THF	60	94/6
10	1	tetraethylammonium	THF	30	95/5
11	1	pyridinium	THF	30	95/5
12	1	2,6-dimethylpyridinium	THF	30	95/5
13	1	tetrabutylphosphonium	THF	120	94/6
14	0	tetrabutylammonium	CH_3CN	1	80/20

[a] 3/4 ratio (3 + 4 = 95% yield) determined by ^{1}H-NMR (300 MHz, $CDCl_3$) at complete conversion of 1. The ratio does not change after several reaction times. [b] 5/6 ratio (5 + 6 = 81% yield) determined by ^{1}H-NMR (300 MHz, $CDCl_3$) at complete conversion of 2. The ratio becomes the equilibrium ratio 70/30.

epimer 3 having *R* configuration at the carbon bearing the bromine, strongly depends on the nature of the solvent, increasing in the following order: methylene chloride (de = 6), acetonitrile (de = 70), tetrahydrofuran (de = 88).

Other "onium" salts such as tetraethylammonium, pyridinium, 2,6-dimethylpyridinium, and tetra-*n*-butylphosphonium tribromides behave similarly in the bromination of 1 (see Table I). Thus, the diastereoselection is independent of the nature of the "onium" counterion.

Ketal 2 (n = 0) reacts at 0 °C in acetonitrile with tetra-*n*-butylammonium tribromide (Table I, entry 14) providing in 81% yield an epimeric mixture of α-bromo ketals 5 and 6. Epimer 5 of *R* configuration prevails over the other with a de (60) which approaches the one observed in acetonitrile for ketal 1 (Table I, entry 6).

Epimer 4 as well as 3, 4 mixtures of *any* epimeric composition kept under the above reaction conditions for several reaction times, were recovered quantitatively unchanged. The 5/6 ratio under the reaction conditions becomes the equilibrium ratio of 70/30.

From the above findings it comes out that the tribromide salt bromination of both 1 and 2 occurs under kinetically controlled conditions.

The sense of the diastereoselection with Br_3^- is opposite to that of the previously reported bromination of ketals 1 and 2 with bromine in methylene chloride (Table II, entry 1).[3d]

Table II. Bromination of 1 with Bromine[4]

ent	n	solvent	T (°C)	reaction time[8]	3/4 ratio
1	1	CH_2Cl_2	−10	10 s	12/88[a]
				1 h	25/75
				20 h	46/54[b]
2	1	CH_3CN	−10	30 min	22/78[a]
3	1	CH_3CN	15	1 min	29/71[a]
				3 min	30/70
				20 h	55/45[b]
4	1	THF	−10	30 min	1/99[c]
				40 min	42/58[b]

[a] 3/4 ratio determined by ^{1}H-NMR (300 MHz, $CDCl_3$) at complete conversion of 1. [b] Thermodynamic ratio. [c] 3/4 ratio determined at 20% conversion of 1.

For a more complete comparison between bromine and tribromide salts, the bromination of 1 with bromine was carried out in acetonitrile and in tetrahydrofuran (Table II, entries 2–4).

From the analysis of data reported in Table II (entries 2–4) it comes out that the bromination occurs under kinetically controlled conditions and that the sense of diastereoselectivity is independent of the nature of the solvent, the highest diastereoselectivity being observed in THF.

On the basis of the above findings it is possible to synthesize in high yield either one epimer or the other from the same ketal. This opens the route to the asymmetric synthesis of structurally related 2-bromo ketones[6] and 2-arylalkanoic acids[7] of both configurations in enantiomerically pure form by using the same chiral auxiliary [(2*R*,3*R*) tartaric acid].

The bromination of 1 and 2 underlines the difference between bromine and tribromide ion in electrophilic attack to activated alkenes.

The opposite diastereoselection observed between Br_2 and Br_3^- can be accounted for by the different electrophilicity of the two species and for the major ability of Br_2 vs Br_3^- to form charge-transfer complexes.

Work is in progress to extend the scope of the reaction and to clarify the reaction mechanisms.

Supplementary Material Available: Experimental procedures (1 page). Ordering information is given on any current masthead page.

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[4] **General Experimental Procedure.** The brominating reagent (5 mmol) was added in one portion with stirring under nitrogen at the temperature given in the tables to a solution of 1 or 2 (5 mmol) in the solvent (10 mL). The reaction mixture was stirred for the time given in the tables. After workup with aqueous sodium carbonate mixtures of 3 and 4 or 5 and 6, in yields and in ratios given in the tables, were obtained.

[5] 2,6-Dimethylpyridinium tribromide, the only unknown compound (mp = 100–101 °C from acetic acid), has been prepared according to: Fieser, L. F.; Fieser M. *Reagents for Organic Synthesis*; John Wiley & Sons: New York, 1967; Vol. 1, p 967.

[6] Castaldi, G.; Giordano, C. *Synthesis* **1987**, 1039.

[7] Castaldi, G.; Cavicchioli, S.; Giordano, C.; Uggeri, F. *J. Org. Chem.* **1987**, *52*, 3018; *J. Org. Chem.* **1987**, *52*, 5642.

[8] It is likely that the rate-determining step of the reaction is the acid-catalyzed formation of the enol ether (Scheme I). In the absence of an acidic catalyst, an induction period is required until a trace of HBr is formed, which grows as soon as the bromination initiates. The nature of the solvent affects the acidity of the reaction medium and consequently the reaction time.

Synthesis of Macrocyclic Propargylic Alcohols by Ene-Type Cyclization of Unsaturated Acetylenic Aldehydes

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Summary: Ene type cyclizations of ynals 6, 21, and 30 can be effected by $EtAlCl_2$ in CH_2Cl_2 at −78 °C to afford 14- and 12-membered homoallylic propargylic alcohols in 66–89% yield.

The continuing discovery of biologically important macrocyclic natural products has stimulated interest in developing cyclization methodology for rings of 12 or more members.[1] Several years ago, we reported that the in-

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