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Differentiation of diastereotopic bromine atoms in S_N2 reactions of *gem*-dibromides†

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A novel directed S_N2 reaction of conformationally biased *gem*-dibromides and an arenesulfinate anion is described. The reaction results in the diastereoselective formation of α-bromosulfones. The selectivity originates from pre-coordination of the nucleophile to a free hydroxyl group in the γ-position.

The differentiation of diastereotopic groups is an important yet underdeveloped strategy for stereoselective synthesis.[1] Diastereotopic halogen atoms have been used so far only for diastereoselective halogen–metal exchange reactions with aliphatic *gem*-dibromides.[2,3] The selective intermolecular substitution of one halogen substituent in a *gem*-dibromide by a nucleophile would be not only a valuable contribution to a basic organic reaction (S_N2) but also of general significance for stereoselective synthesis.

A successful stereoselective S_N2 reaction at an aliphatic *gem*-dihalogenide has to meet three requirements:

- The nucleophilic substitution has to dominate over competing elimination side reactions.
- The second nucleophilic substitution of the remaining halogen has to be much slower.
- A conformational bias of the substrate in combination with an element of stereocontrol (stereocenter) to achieve a diastereoselective attack of the incoming nucleophile.

Scheme 1 summarizes this challenge for the case of an aliphatic *gem*-dibromide **1** bearing diastereotopic bromine atoms. Its reaction with the nucleophile should lead predominantly to a monobromide **3**. Elimination side reactions of the substrate to **5** or the product to **6** have to be avoided as well as the nucleophilic substitution of the remaining bromide in **3** leading to **4**.

Nucleophilic substitution reactions of bromine in α-bromosulfones are hard to accomplish.[4] In contrast to π-substituents (C═O, C═C), the sulfone group does not accelerate S_N2 reactions. Therefore, the synthesis of α-bromosulfones from aliphatic *gem*-dibromides and sulfinates should stop at the monosubstitution stage and represents a promising solution for the present task. Dibromomethane so far was the only aliphatic substrate that was converted into α-bromosulfones.[4]

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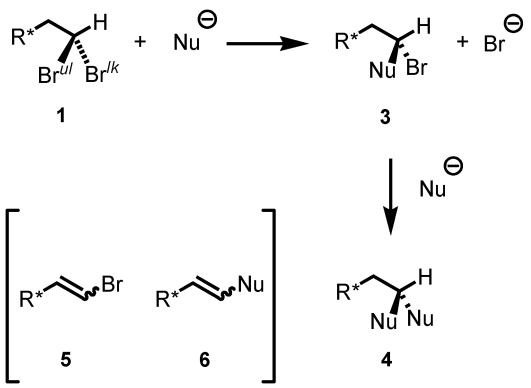
† Electronic supplementary information (ESI) available: Experimental details and spectroscopic characterization information. CCDC 850197 (**10**) and 850198 (**13**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc17599a

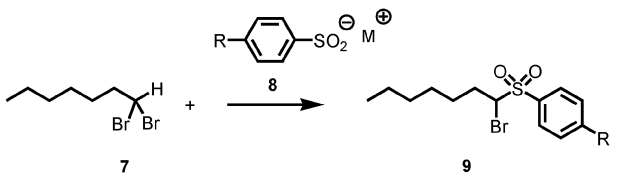


Scheme 1 Stereoselective S_N2 reaction of a *gem*-dibromide.

1,1-Dibromoheptane **7**[5] was chosen as a substrate for optimizing the S_N2 reaction conditions (Table 1). It was found that a noncoordinating counter ion (Et_4N^+)[6] in the arenesulfinate **8** gave the best yield of α-bromosulfone **9**. A reaction temperature with maximum 60 °C and DMSO as solvent gave a minimum of elimination side products.[6,7] No alkyl sulfinate formation (O-alkylation) was observed under these conditions.

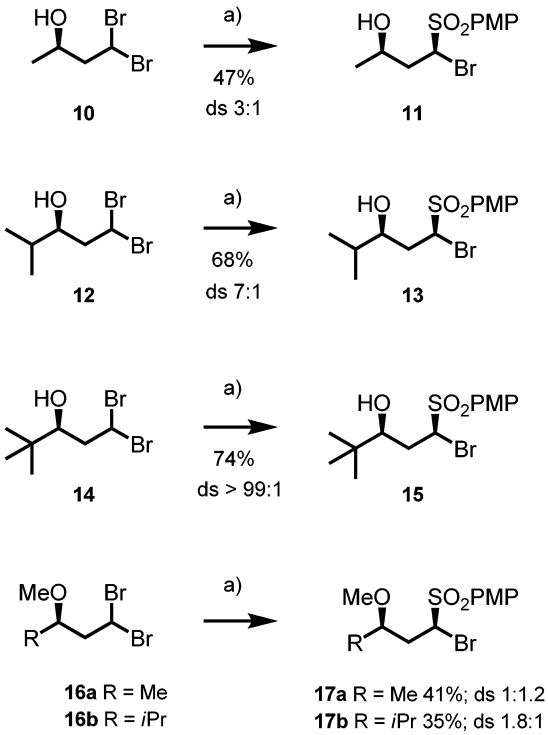
γ-Substituted aliphatic *gem*-dibromides were selected for the diastereoselectivity studies because of their conformational bias due

Table 1 Optimization of the bromosulfone synthesis



Entry	M	R	Solvent	Additive[a]	Temp/t^b [°C/h]	Yield [%]
1	Na	Me	MeCN	15-C-5 (3 equiv.)	80/72	21
2	Na	Me	MeCN	15-C-5 (1 equiv.)	80/192	46
3	Li	Me	MeCN	12-C-4 (1 equiv.)	80/192	6
4	Li	Me	DMSO	Bu_4NBr (0.4 equiv.)	70/22	58
5	Et_4N	Me	DMSO	—	60/48	62
6	Et_4N	Me	DMSO	—	70/48	55
7	Et_4N	OMe	DMSO	—	50/48	57
8	Et_4N	OMe	DMSO	—	60/64	76

[a] 15-C-5 = 15-crown 5-ether, 12-C-4 = 12-crown 4-ether. [b] t = reaction time.



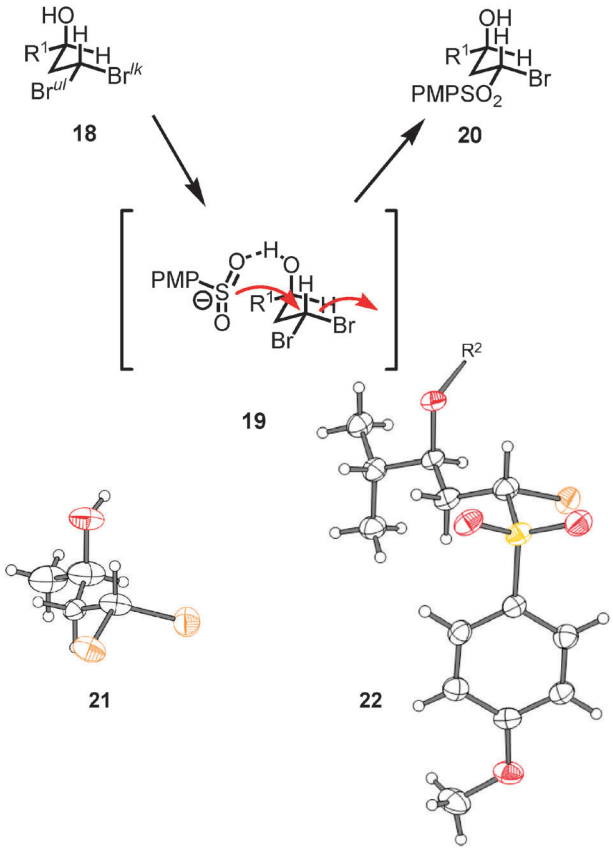
Scheme 2 Diastereoselective synthesis of γ-hydroxy-α-bromo-sulfones. (a) $PMPSO_2(Et_4N)$, DMSO 60 °C. PMP = *para*-methoxy phenyl.

to avoidance of *syn*-pentane interactions.[8] A γ-hydroxy substituent offers the possibility for various derivatization (ether, ester). Details for the synthesis of γ-hydroxy aliphatic *gem*-dibromides **10**, **12** and **14** (racemic series) are given in the ESI.† Treatment of compounds **10**, **12**, and **14** with tetraethylammonium *p*-methoxy-benzenesulfinate gave the α-bromosulfones **11**, **13** and **15** in good yields (Scheme 2). The methyl terminated *gem*-dibromide **10** showed a moderate diastereoselectivity. The isopropyl terminated substrate **11** gave a very good diastereoselectivity and for the *tert*-butyl substituted *gem*-dibromide **14** only one stereoisomer was formed. The stereochemical assignment of the main diastereomer was possible by X-ray structure of the dinitro-benzoates of compounds **13** and **15** (Scheme 3).

The free hydroxyl group in the γ-position is a prerequisite for the good yields and diastereoselectivities. The corresponding methyl ethers **16** gave lower yields and nearly no diastereo-selectivity of the corresponding α-bromosulfones **17**.[9]

A possible rationale for the increased reactivity and stereo-selectivity of γ-hydroxy aliphatic *gem*-dibromides is given in Scheme 3. All *gem*-dibromides examined show a preferred confor-mation **18**, which is supported by the X-ray structure of **21** obtained for dibromide **10** and by earlier observations.[8,10] The incoming sulfinate is precoordinated to the substrate *via* hydrogen bonding (nucleophile fishing) which results in an increased reactivity and a selective nucleophilic substitution of the like-bromine atom. The main diastereomer α-bromosulfone formed is compound **20**. The increasing diastereoselectivity in the series **10**, **12**, and **14** can be explained by their increasing conformational bias.

In summary, a differentiation of diastereotopic bromine atoms in S_N2 reactions of *gem*-dibromides was achieved. A possible explanation for the observed diastereoselective formation of α-bromosulfones is a precoordination of the



Scheme 3 Conformational bias of *gem*-dibromide **18** leads *via* nucleophile fishing in the transition state **19** to a selective substitution of Br^{lk} and the formation of α-bromosulfone **20**; **21**: X-ray structure of compound **10**; **22**: part of the X-ray structure of dinitrobenzoate prepared from compound **13**, $R^2 = COC_6H_3$-3,5-$(NO_2)_2$.

sulfinate nucleophile (nucleophile fishing). The stereochemical control in the preparation of α-bromosulfones shall allow their use for further synthetic applications.[11]

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