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Implication and Improvement of Stereoselective Methylenation of a Chiral Aldehyde Related to Total Synthesis of the Furaquinocins†

Takeshi Saito, Takao Suzuki, Kazuhiro Takeuchi, Takashi Matsumoto, and Keisuke Suzuki*

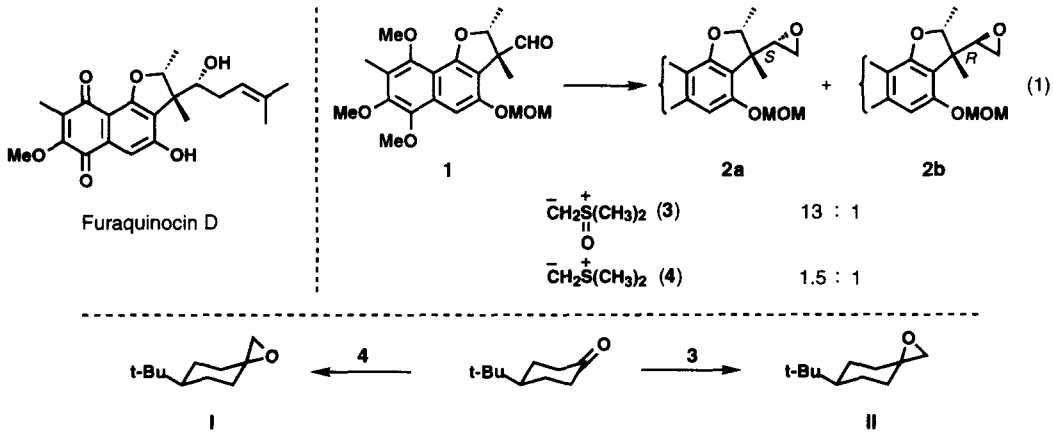
Department of Chemistry, Tokyo Institute of Technology, Meguro, Tokyo 152, Japan
Department of Chemistry, Keio University, Hiyoshi, Kohoku, Yokohama 223, Japan

Abstract: In relation to the total synthesis of the furaquinocins, stereoselective methylenation of chiral aldehyde **5** is described. The diastereoselectivity of epoxides **6a/6b** is high when stabilized sulfur ylides are employed. A double stereo-differentiation phenomenon was observed for the aminosulfoxonium ylide **8**: the selectivity with (*S*)-**8** was 30:1, while 5:1 with (*R*)-**8**.

The furaquinocins are the *Streptomyces* metabolites isolated by Ōmura, which show cytocidal activity against HeLa S_3 cells.[1] In spite of their rather small molecular architecture, these compounds pose several synthetic issues that include the stereocontrol of three contiguous stereogenic centers with a quaternary one.

We found a clue to solve this problem in our recent synthesis of furaquinocin D (eq.1):[2] Dimethyloxosulfonium methylide (**3**) reacts with aldehyde **1** to give the epoxide **2** with the desired stereochemistry in high selectivity (**2a**:**2b** = 13:1). A relevant reaction furnished an important additional detail to this gratifying outcome: the selectivity diminished to a 1.5:1 level when a more reactive ylide, dimethylsulfonium methylide (**4**), was employed. Such a stereochemical contrast as shown by these two ylides is reminiscent of the famous example of their reaction with 4-*t*-butylcyclohexanone, which appears in many textbooks: Oxirane **I** is available by the irreversible axial attack of sulfonium ylide **4** followed by elimination, whereas reversible attack of the oxosulfonium ylide **3** accumulates the equatorially coupled betaine that leads to isomer **II**.[3]

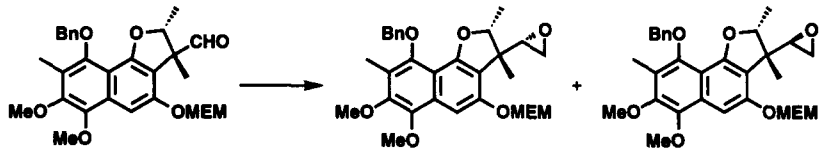
In an effort to gain insight for further improving the stereoselectivity, we studied this methylenation reaction in detail, which is the subject of this communication.



† Dedicated to the memory of the late Professor Masaru Yamaguchi.

Optically active aldehyde **5**,[4] related to **1** (*vide supra*), was chosen as the model substrate for the present study, and the reactions with various methylene transfer agents were examined (Table 1).[5] Even though aldehyde **5** differs from **1** in the protecting groups, the two sulfur ylides show exactly the same stereochemical contrast (runs 1 and 2): Oxosulfonium ylide **3** led to the predominant formation of **6a**, arising formally from the ylide attack on the *re*-face of **5** (run 1). On the other hand, the sulfonium ylide **4** led only to 1.5:1 selectivity (run 2). The selectivity by the sulfonium ylide remained poor even when a more sterically demanding one **7**[6] was employed (run 3).

Table 1. Stereoselectivity of methylene transfer to **5**.

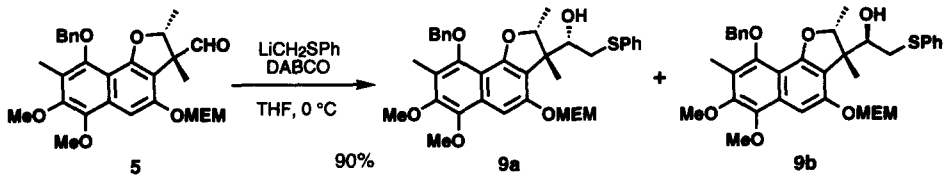


5 **6a** **6b**

run[a]	ylide[b]	reaction period	yield/%	**6a/6b**[c]
1	$\bar{C}H_2-\overset{+}{S}(CH_3)_2$ $\overset{\|\|}{O}$ **3**	2 h	65	13/1
2	$\bar{C}H_2-\overset{+}{S}(CH_3)_2$ **4**	45 min	73	1.5/1
3[d]	$\bar{C}H_2-\overset{+}{S}(C_6H_5)_2$ **7**	3 h	88	2/1
4	$\bar{C}H_2-\overset{O}{\overset{\|\|}{\overset{+}{S}}}-C_6H_5$ $N(CH_3)_2$ (±)-**8**	6 days	75	13/1
5	$\bar{C}H_2-\overset{O}{\overset{\|\|}{\overset{+}{S}}}-C_6H_5$ $N(CH_3)_2$ (*R*)-**8**	7 days	44	5/1
6	$\bar{C}H_2-\overset{O}{\overset{\|\|}{\overset{+}{S}}}\cdots C_6H_5$ $N(CH_3)_2$ (*S*)-**8**	6 days	87	30/1[e]

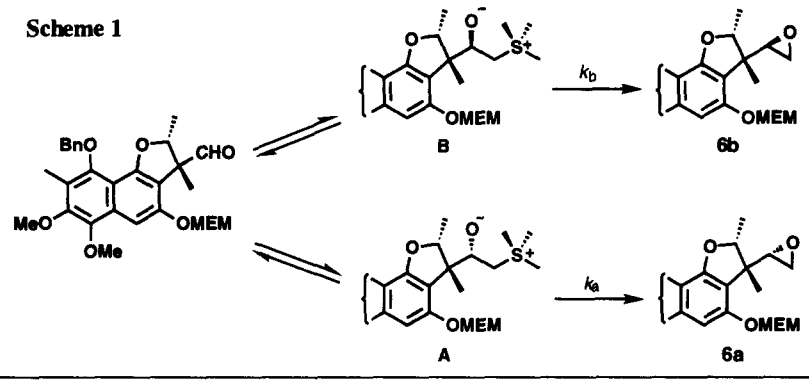
a: Carried out in DMSO at room temperature. b: Generated *in situ* from the corresponding onium salts with NaH. c: Determined by weighing the isolated isomers **6a** and **6b**. d: THF was used as the solvent. e: Determined by HPLC (see ref. 14).

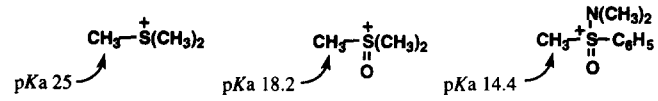
The kinetic facial selectivity of the nucleophilic attack to aldehyde **5** seems intrinsically poor as suggested by the reaction shown in eq. 2, which we assume is irreversible.[3d,7] A mixture of diastereomers **9a** and **9b**[8] resulted in 1:1.5 selectivity, which were correlated to the epoxides **6a** and **6b**, respectively.[9] Thus, the *si*-face of the aldehyde **5** is attacked preferentially, albeit slightly, which is opposite to the outcome of runs 1–3 in Table 1. Apparently, the high selectivity (run 1) is not related to the kinetic facial selectivity.



Scheme 1 illustrates our current view of the process. Given the reversibility of the carbonyl addition of stabilized sulfur ylides,[3] we assume that the equilibration of **A** and **B** is more rapid than the collapse of betaines **A** and **B**. If such a Curtin-Hammett system applies,[10] the large ratio **6a/6b** is given by $k_a[\mathbf{A}]/k_b[\mathbf{B}]$, which could result from either the *somehow* large ratio of the betaine populations ([**A**]/[**B**]) or that of the kinetic parameters (k_a/k_b) or both of these, although the origin cannot be specified.[11]

Scheme 1





Such a dynamic equilibration of **A** and **B** for the case of the *oxo*sulfonium ylide is reasonable if we consider the p*K*a values of the parent salts (see above),[3c] which led us to examine an even more stabilized ylide, *N*,*N*-dimethylaminosulfoxonium ylide by Johnson.[12] It turned out that the ylide **8** reacted with aldehyde **5** slowly but cleanly (run 4), leading to a high selectivity comparable to run 1. Furthermore, we were intrigued to observe a double stereo-differentiation[13] with the antipodal aminosulfoxonium ylides.[12b] While the reaction of (*R*)-**8** was sluggish resulting in poor selectivity (run 5), (*S*)-**8** reacted smoothly, thereby leading to an excellent selectivity (run 6).[14,15] This significant ligand effect on the sulfur atom stands in contrast to the case of the reactive ylides (runs 2 and 3).

In conclusion, a highly stereoselective access is now available to epoxide **6a**, which would serve as a versatile intermediate in the synthesis of the furaquinocins. Further study along these lines is now in progress.

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4) A full account of the total synthesis including the preparation of aldehyde **5** will appear in due course.
5) Stereochemical assignment of **6a** and **6b** relies on the correlation to the natural product, furaquinocin D, according to a similar route described in ref. 2a.
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8) The diastereomers were separated by silica-gel PTLC. **9b** (major): R_f = 0.28 (benzene/acetone = 19/1, double development); ^{1}H NMR ($CDCl_3$) δ 7.10–7.53 (m, 11H), 5.49 (d, J = 6.6 Hz, 1H), 5.43 (d, J = 6.6 Hz, 1H), 4.83 (d, J = 10.6 Hz, 1H), 4.79 (d, J = 10.6 Hz, 1H), 4.55 (q, J = 6.9 Hz, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 3.83–3.87 (m, 2H), 3.78–3.87 (broad, 1H), 3.56–3.59 (m, 2H), 3.38 (s, 3H), 3.16 (dd, J_1 = 1.7, J_2 = 13.9 Hz, 1H), 3.00 (d, J = 7.3 Hz, 1H), 2.60 (dd, J_1 = 10.1, J_2 = 13.9 Hz, 1H), 2.29 (s, 3H), 1.59 (s, 3H), 1.33 (d, J = 6.9 Hz, 3H). **9a** (minor): R_f = 0.32 (benzene/acetone = 19/1, double development); ^{1}H NMR ($CDCl_3$) δ 7.15–7.58 (m, 11H), 5.40 (d, J = 6.3 Hz, 1H), 5.27 (d, J = 6.3 Hz, 1H), 4.92 (d, J = 10.1 Hz, 1H), 4.79 (d, J = 10.1 Hz, 1H), 4.55 (q, J = 6.6 Hz, 1H), 3.95 (s 3H), 3.93 (s, 3H), 3.86–3.90 (broad, 1H), 3.70–3.82 (m, 2H), 3.55 (t, J = 4.6 Hz, 2H), 3.39 (s, 3H), 3.24 (d, J = 13.9 Hz, 1H), 3.04 (dd, J_1 = 11.2, J_2 = 13.9 Hz, 1H), 2.46–2.48 (broad, 1H), 2.29 (s, 3H), 1.64 (d, J = 6.6 Hz, 3H), 1.56 (s, 3H).
9) Both isomers of **9** were stereospecifically converted to the respective isomer of **6** ($Me_3O^+BF_4^-$, then NaOH), and no crossover was observed for either case. See 7b.
10) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83.
11) Some reports have appeared recently that propose an oxathiethane, rather than a betaine, is more plausible as the intermediate of such reactions. See: Kawashima, T.; Ohno, F.; Okazaki, R.; Ikeda, H.; Inagaki, S. *J. Am. Chem. Soc.* **1996**, *118*, 12455.
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14) Reaction was carried out as follows: To NaH (18 mg, 60% oil dispersion, ca. 0.46 mmol), washed with hexane, was added DMSO (0.5 mL) at 20 °C, and the mixture was stirred for 45 min. To the resulting solution was added (*S*)-(dimethylamino)methylphenyloxosulfonium fluoroborate[12b] (161 mg, 0.594 mmol), and the mixture was stirred for 40 min at room temperature. A solution of **5** (122 mg, 0.238 mmol) in DMSO (2 mL) was added, and the mixture was stirred for 6 days. The reaction was quenched with pH 7 phosphate buffer, and the products were extracted with EtOAc (× 5). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by PTLC (benzene/acetone = 9/1 for separating epoxides **6** from *N,N*-dimethylphenylsulfinamide) to afford a mixture of epoxide **6a** and **6b** (110 mg), which was subjected to HPLC analysis (Zorbax sil, 4.6 mm × 25 cm, hexane/THF = 8/2, flow rate 0.5 mL/s, **6a**: 34.3 min, **6b**: 51.4 min). The diastereomers were separated by PTLC (hexane/EtOAc = 3/2) to afford epoxide **6a** (105 mg, 84%) and **6b** (3.8 mg, 3%). **6a**: R_f = 0.35 (hexane/acetone = 3/1). **6b**: R_f = 0.39 (hexane/acetone = 3/1).
15) The reaction of (*R*)-**8** was much slower, thereby giving many unidentified side products. In contrast, (*S*)-**8** gave rise to a clean reaction.

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