ABSOLUTE CONFIGURATION DETERMINATION OF A SILAFURAN USING THE MODIFIED MOSHER'S METHOD

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TÓM TẮT

XÁC ĐỊNH CẤU HÌNH TUYỆT ĐỐI CỦA SILAFURAN
BẰNG PHƯƠNG PHÁP MOSHER CẢI TIẾN

*Silafuran **2** là hợp phần quan trọng trong tổng hợp hợp chất ức chế enzim làm tăng huyết áp của tim người. Tổng hợp lập thể silafuran **2** bằng phản ứng hyđrosilyl hóa có mặt xúc tác ferrotane Ru (I). Do silafuran **2** không bền nên việc xác định cấu hình tuyệt đối được thực hiện trên sản phẩm mở vòng của nó là ancol bậc 1 **2b** tương ứng của silafuran **2** bằng tác nhân Grignard. Sử dụng phương pháp Mosher cải tiến đã xác định được cấu hình tuyệt đối của ancol bậc 1 **2b** là S. Tương ứng silafuran **2** cũng mang cấu hình tuyệt đối S. Những hợp chất mới được xác định cấu trúc bằng các phương pháp phổ IR, NMR và MS.*

1. INTRODUCTION

Silafuran **2** can be used to synthesize the enzyme mimics for human heart chymase **4** [1]. An asymmetric hydrosilylation of the silyl ether **3** followed the Swapnil Singh's protocol, using catalytic ferrotane to give the silafuran **2**. The silafuran **1** was confirmed *S* based on the well known compound [2]. Although the silafuran **2**'s absolute configuration is supposed to be the same as silafuran **1**'s, this stereogenic center has not been determined by any practical methods yet, Figure 1.

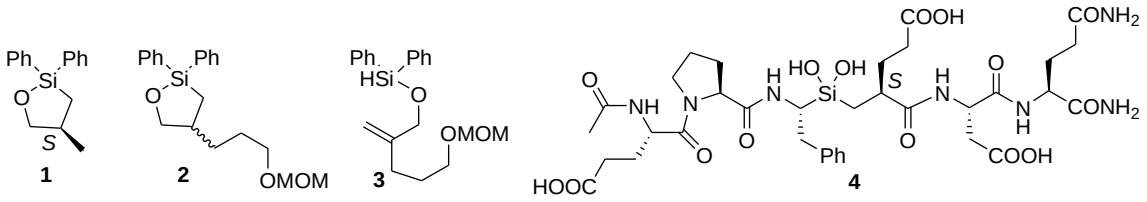


Figure 1. Structure of silafurana and a silanediol inhibitor for human heart chymase

The determination of absolute configurations of the secondary alcohols and primary amines are normally done with the Modified Mosher's method using α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) [3-5]. However assignment of an absolute configuration in primary alcohols is difficult due to $\Delta\delta$s (δ_S-δ_R) of protons at stereogenic centers are not in law. Recently, Kobayashi *et al.* [6] have used the diastereotopic protons of the methylene groups of the alcohol moiety in Mosher esters to determine the stereochemistry of the adjacent position. Diastereomers with (*S,S*) or (*R,R*) configurations have chemical shift difference of about δ 0.2 ppm. In contrast, the (*S,R*) or (*R,S*) diastereomers have very similar chemical shift values. In addition, in 1977, Yamaguchi *et al.* reported the use of ^{1}H NMR spectra to determine the absolute configuration of compound **5** (26% de) with Eu(fod)$_3$ (**6**), Figure 2. The methoxy signals were recorded using 0.25 M and 0.68 M of Eu(fod)$_3$[7].

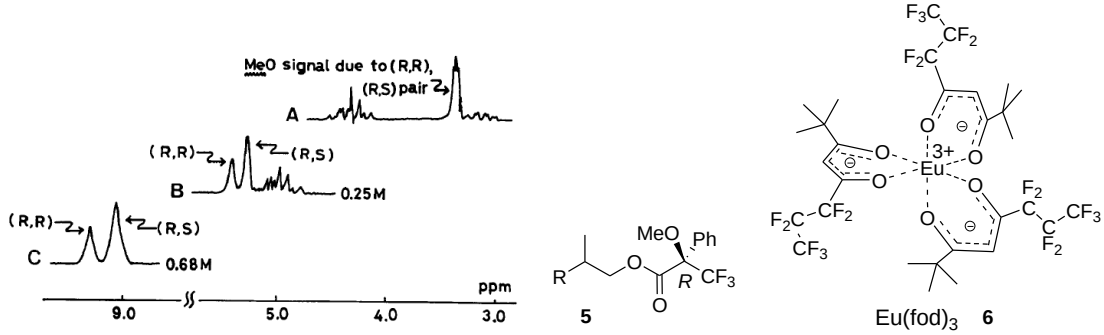
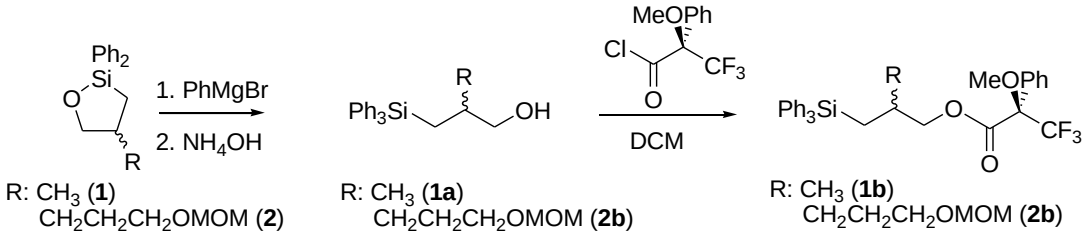


Figure 2. Absolute configuration determination with ^{1}H NMR spectra and Eu(fod)$_3$

In the absence of Eu(fod)$_3$, the chemical shift of the methoxy group was the same for both diastereomers (Figure 2A). Addition of Eu(fod)$_3$ (0.25M), Figure 2B, caused a separation of the methoxy signals of the (*R,R*)-diastereomer moving further than that of the (*R,S*) diastereomer. Increasing the concentration of Eu(fod)$_3$ to 0.68 M, Figure 2C, led to an even larger chemical shift difference. The difference in chemical shift has been attributed to the greater stability of the complex between (*R,R*)-diastereomer compared to that with the (*R,S*)-diastereomer with the Eu^{3+}[8].



Scheme 1. Synthesis of Mosher esters

In this paper, silafuran **1**, and **2** were opened up with Grignard reagent to form 1° alcohols **1a** and **2a**. Then these alcohols were esterificated with (*R*)-(-)-α-methoxy-α-(trifluoromethyl)phenyl acetyl chloride ((*R*)-MTPACl) yielding esters **1b** and **2b,** Scheme 1. The absolute configuration determination of silafuran **2** was well done with both observation of O-methylene proton chemical shifts and methoxy proton chemical shifts in presence of $Eu(fod)_3$.

2. EXPERIMENTAL

Solvents and other chemicals were purchased from Sigma-Aldrich or TCI and were used as received otherwise indicated. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 500 or 400 NMR spectrometer in d_3-$CDCl_3$ at Temple university. Chemical-shift data for each signal were reported in ppm units. MS spectra were recorded on the Agilent 6210 TOF mass spectrometer at Mass Spectrometry Facility of the University of California.

Synthesis of 2b *(dr:4/1)*

To a solution of **2a** (50 mg, 0.12 mmol, 83% ee) in dry dichloromethane (3 mL) was added dry pyridine (30.0 µL, 0.37 mmol) and then (*R*)-(-)-α-methoxy-α-(trifluoromethyl)phenyl acetyl chloride ((*R*)-MTPACl) (33.6 µL, 0.18 mmol). The solution was stirred at room temperature for overnight, and then diluted with DCM (5 mL). The aqueous phase was extracted with DCM (3 x 3 mL). Combined organic layers were washed with 5% HCl (2 x 5 mL), brine (2 x 5 mL), dried over with Na_2SO_4, concentrated *in vacuo* and purified with prep-TLC to give **2b** *(dr: 4/1)* (69 mg, 87%) as a colorless oil. R_f = 0.4 (hexane / ethyl acetate 4:1) $[\alpha]_D^{20}$ = -1.403 (*c* 0.620, $CHCl_3$) IR: 3068, 2929, 2823, 1746, 1731, 1588, 1427, 1258, 1107, 1027, 699 cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$): δ 7.5-7.3 (m, 20H), 4.5 (s, 2H), 4.10-4.08 (dd, *J* = 2.8 Hz, *J* = 5.5 Hz), 3.5 (s, 3H), 3.3 (s, 3H), 3.24-3.21 (t, *J* = 6.5 Hz, 2H), 2.1-2.0 (m, 1H), 1.5-1.3 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 135.9, 135, 132.7, 130, 128.7, 128.3, 128, 127, 125, 96.6, 84.7 (q, *J* = 27.3 Hz), 70, 67.8, 55.7, 55.3, 33.8, 30.8, 30, 26.9, 14.5; Exact mass: $[M\text{-}Na]^+$ calcd. for $[C_{36}H_{39}F_3O_5SiNa]^+$ 659.2411, found 659.2403

Synthesis of 2b *(dr: 1/1)* Following the procedure for synthesis of **2b**, using **2a** *(racemix)* (50 mg, 0.12 mmol) in dry dichloromethane (3 mL), dry pyridine (30.0 µL, 0.37 mmol), and (*R*)-(-)-MTPACl (33.6 µL, 0.18 mmol) gave **2b** *(dr: 1/1)* (69 mg, 87%) as a mixture of diastereomers. R_f = 0.4 (hexane / ethyl acetate 4:1), IR: 3068, 2929,

2823, 1746, 1731, 1588, 1427, 1258, 1107, 1027, 699 cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$): δ 7.5-7.3 (m, 20H), 4.48 (s, 2H), 4.47 (s, 2H), 4.2- 4.1 (dd, *J* = 11.0 Hz, 5.2 Hz, 1H), 4.10-4.08 (dd, *J* = 5.3, 2.7 Hz, 2H), 4.03-3.99 (dd, *J* = 11.0, 5.2 Hz, 1H), 3.5 (s, 3H), 3.49 (s, 3H) 3.2 (s, 3H), 3.25 (s, 6H), 3.24-3.19 (ddd, *J* = 6.5, 4.4, 4H), 2.08-2.01 (m, 2H), 1.5-1.24 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 135.9, 135, 132.7, 130, 128.7, 128.3, 128, 127, 125, 96.6, 89.3 (q, *J* = 27.3 Hz), 70, 67.8, 55.7, 55.3, 33.8, 30.8, 30, 26.9, 14.5

Synthesis of 1b *(dr = 3/1)* Following the procedure for synthesis of **2b**, using **1a** (56 mg, 0.17 mmol, 50.5 ee%) in dry dichloromethane (3 mL), dry pyridine (35.0 µL, 0.42 mmol), and (*R*)-(-)-MTPACl (36.6 µL, 0.18 mmol) gave **1b** (72 mg, 77%) as a mixture of diastereomers (dr: 3/1). R_f = 0.6 (hexane / ethyl acetate 8:1) ^{1}HNMR: (500 MHz, $CDCl_3$): δ 7.56 – 7.37 (m, 20H), 4.2-4.0 (m, 2H), 3.55 (s, 3H), 2.22-2.19 (m, 1H), 1.57 (dd, *J* = 15.2, 5.3 Hz, 1H), 128 (dd, *J* = 15.2, 9.3 Hz, 1H), 0.87 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.5 135.6, 134.8, 132.4, 129.8, 128.4, 128.0, 127.3, 124.5, 122.2, 100.0, 84.7 (q, *J* = 27.3 Hz), 73.1, 55.4, 19.0, 19.9, 17.1.

Preparation of NMR samples: Compounds **1b** (dr: 3/1); **2b** (dr: 4/1); **2b** (dr: 1/1) was dissolved in $CDCl_3$ (0.6 mL) making 0.055 M. The solutions were added slowly with the $Eu(fod)_3$ solution then recorded ^{1}H NMR in different concentration of.

3. RESULTS AND DISCUSSION

To investigate the use of Mosher esters with our silanes, esters **1b** *(dr 3/1)* **2b** *(dr 4/1)* and **2b** *(dr 1/1)* were prepared by reaction of (*R*)-α-methoxy-α-trifluoromethylphenylacetyl chloride with alcohols **1a** (50.5% ee), **2a**(83% ee) and the racemate of **2a**, Scheme 1. Chiral centers of compound **1** were known [2]

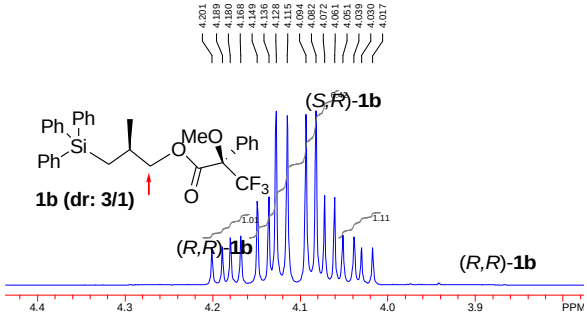


Figure 3. Diastereotopic protons on ^{1}H NMR of compound 1b (dr 3/1) in $CDCl_3$

First of all, it was important to establish that the results of Kobayashi *et al.* are relevant to our silanes **1b** and **2b**. The ^{1}H NMR spectrum of known compound **1b** shows that the diastereotopic protons (identified with a red arrow, Figure 3) of (*S,R*)-**1b** have a 0.055 ppm difference in chemical shift. On the other hand, the diastereotopic protons of diastereomer (*R,R*)-**1b** have a 0.149 ppm difference in chemical shift, Figure 24. The "Kobayashi's rule" can therefore be used to determine absolute configurations of silanes related to compound **1b**.

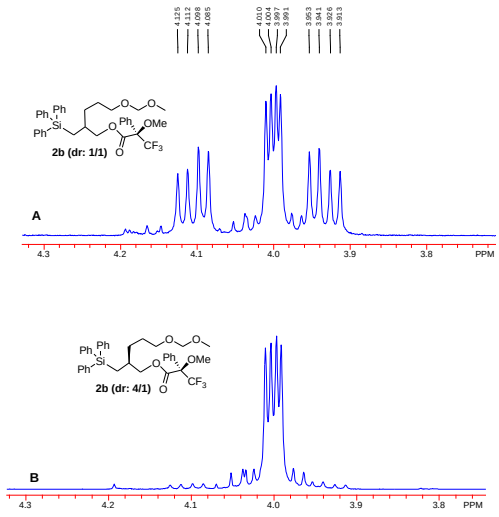


Figure 4. ^{1}H NMR of Mosher esters in $CDCl_3$

Compound **2b** *(dr 4/1)* and **2b** *(dr 1/1)* were then analyzed by ^{1}HNMR. The methylene protons, identified by an arrow, are shown in Figure 4. These protons have nearly the same chemical shift ($\Delta\sigma \sim 0.0$ ppm), Figure 5A. On the other hand, spectrum B shows that one set of diastereotopic protons have very different chemical shift ($\Delta\sigma =$ 0.173 ppm). It was therefore determined that compound **2b** *(dr 4/1)* had the (*S*) configuration which is predominant in the mixture based on similarity to compound **1b**.

To further establish this result, Eu(fod)$_3$ (**5**) was added to both compounds **2b** *(dr 4/1)* and mixture **2b** *(dr 1/1)* until the methoxy signals for both diastereomers (labeled **a**, Figure 5) were distinguishable in $CDCl_3$ at rt. Spectrum A, Figure 5, clearly shows a pair of methoxy signals at 3.42 ppm for the two diastereomers **2b** *(dr 1/1)* without adding Eu(fod)$_3$. Addition of Eu(fod)$_3$ (0.0327 M) to solution of **2b** *(dr 1/1)* (0.030 M), two peaks of the same height with a ratio of 1:1 for mixture of diastereomers **2b** were shifted to down field, Figure 5B. In spectrum C of compound **2b** *(dr 1/1)* (0.030 M), one major peak can be seen with a small right hand shoulder in Eu(fod)$_3$ (0.032 M), Figure 5C. When the two samples were mixed, spectrum D (Figure 5), a definite increase in height can be seen for the peak of each diastereomer.

Presumably, differences in stability of the complexes (*R*)-**2c** and (*S*)-**2c** are the source of these observations, Figure 6. Diastereomeric esters (*R*)-**2c** and (*S*)-**2c** coordinate with Eu(fod)$_3$ with the carbonyl and methoxy (**a**) groups, Figure 6. If the complexation constant K_R (equation 1) for the formation of complex (*R*)-**2c** from (*R*)-**2b** is smaller than the constant K_S (equation 2) for the formation of (*S*)-**2c** from (*S*)-**2b**, then the steady state concentration of (*S*)-**2c** should exceed that of (*S*)-**2c** so that a larger chemical shift should be induced in (*R*)-**2c** than (*S*)-**2c**, as is observed. It is proposed that this happens because of the lower steric interaction of the Eu(fod)$_3$ with the hydrogen atom on the chiral center in (*S*)-**2c** than with methoxymethoxypropanyl group

in (*R*)-**2c**. In other words, the diastereomer (*S*)-**2b** is more than the diastereomer (*R*)-**2b** in the mixture **2b**. This result agrees with the results mentioned above.

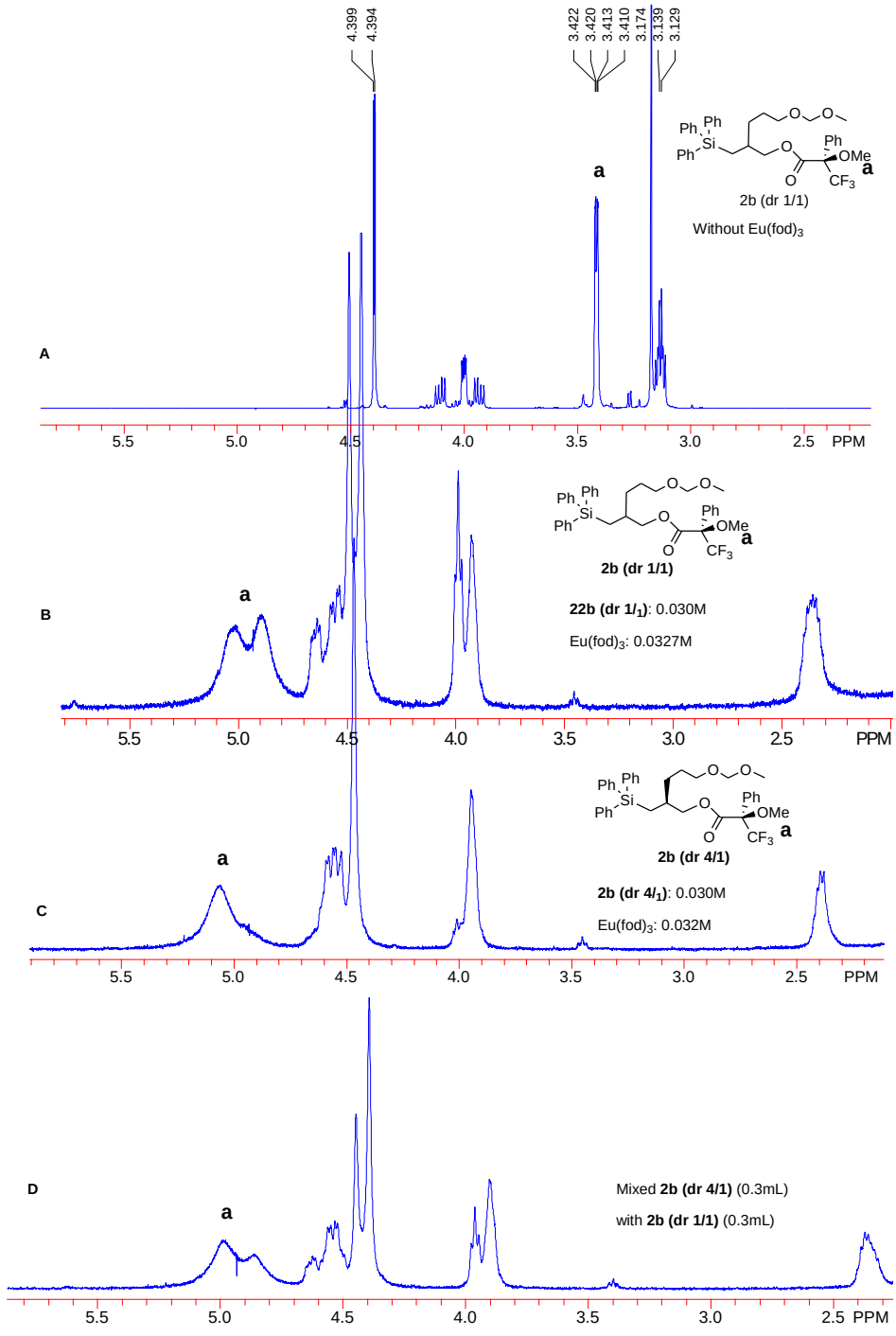
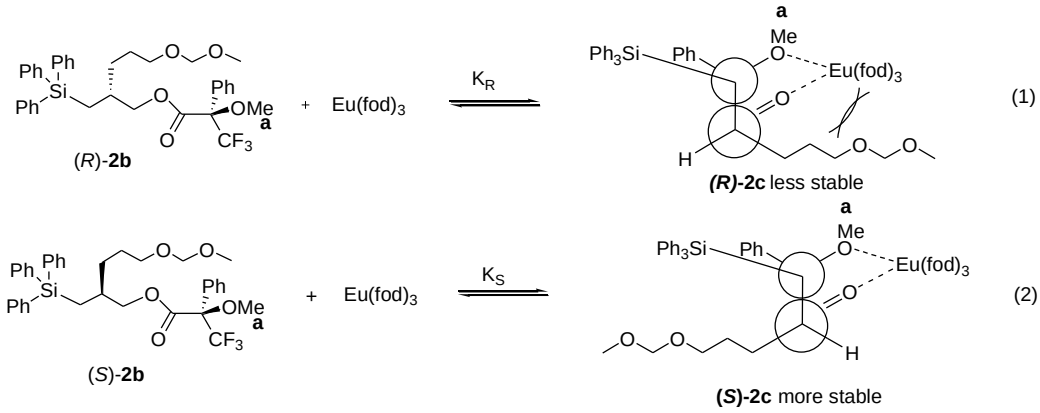


Figure 5. ^{1}H NMR of Mosher esters in Eufod in $CDCl_3$ at rt.



Scheme 2 Complexes of the Mosher esters with Eu(fod)$_3$

4. CONCLUSIONS

In conclusion, the absolute configuration of the silafuran **2** was determined to be (*S)* using ^{1}H NMR analysis of the Mosher's ester **2b** based on the change of chemical shifts of the O-diasteomeric protons and the chemical shifts of the methoxy group in the Mosher's moiety when these compounds formed complexes with Eu(fod)$_3$. These results provide a simple method can be used for absolute configuration determination of silane alcohols.

Acknowledgements

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