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Conformational Analysis of the 16-Membered Epoxyenone and Complete Stereoselection in the Reduction of its C9 Carbonyl Group, the Key Reaction in the Synthesis of Maridonolides[1]

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Abstract: *16-membered epoxyenone (2), the key synthetic intermediate of maridonolides, has two distinct conformational isomers in solution. The conformational analysis of them by virtue of NMR measurement and the profound effect of their conformations on reactivity and stereoselectivity in the reduction of the C9 carbonyl group are discussed.*

Introduction

For the past decade, since Still and Galynker showed the attractive effects of conformational control on the reactivity of macrocyclic compounds,[2] the conformational analysis and stereoselection on the macrocyclic systems have been one of the most stimulative fields for organic chemists.[3] With the functionalized macrocyclic compounds in solution, there is a possibility of having several major conformations, which usually can be detected only by NOE measurement because of their rapid interconversion. Thus, the conformational analysis of them almost relies on the NMR studies and computer calculations, and determination of the correct conformational structures is very important for prediction of the stereochemical outcome of a reaction on the macrocyclic systems.

Recently,[4] we have reported the conformational analysis of the several 16-membered lactones represented by the dienone derivative (**1**) based on their NMR studies and MMP2-CONFLEX2[5] calculations, which allowed to synthesize the typical 16-membered macrolide aglycons[6] using stereoselective reactions on the macrolactone rings. In these studies, we adopted the epoxyenone derivative (**2**) as the key synthetic intermediate of maridonolides,[7] which has also a very interesting property for our conformational studies, that is, **2** exists as a mixture of two interconvertible conformational isomers easily detectable by TLC analysis and ^{1}H NMR measurement. Although several workers have discussed the conformational analysis of such macrolactones, so

far as we know, this is the first case that the conformers of macrolactone can be easily detected by the usual analyses as described.

We report here the conformational analysis of these appreciably stable isomers of **2**, the relation between their conformation and reactivity in the reduction of the C9 carbonyl group, the key reaction in the synthesis of maridonolides.[4b,d]

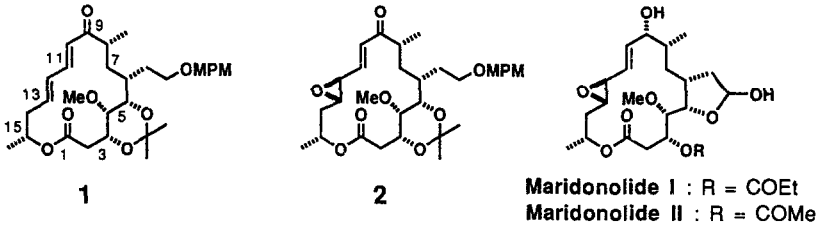


Fig. 1

Results and Discussion

As described, **2** is detected as two separated spots corresponding to the conformer A and B on a silica gel TLC using ethyl acetate - hexane (1:1) as the eluant (Rf = 0.64, 0.58). Furthermore, these two conformers give obviously different patterns on the ^{1}H NMR spectrum (A:B = 2:3), especially the olefin protons at C10 and C11 of each conformer are observed as clearly resolved peaks (Fig. 2).[8]

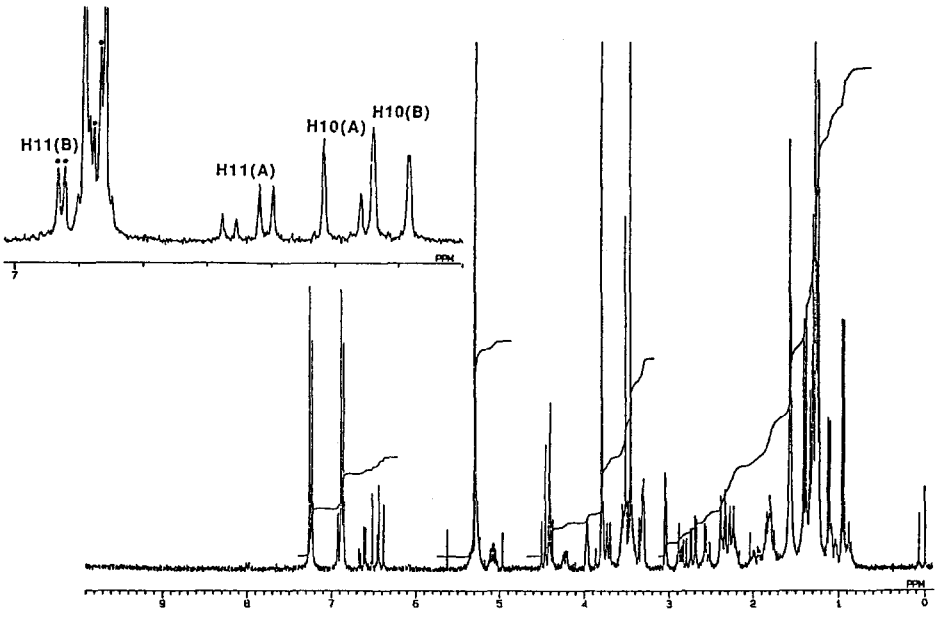


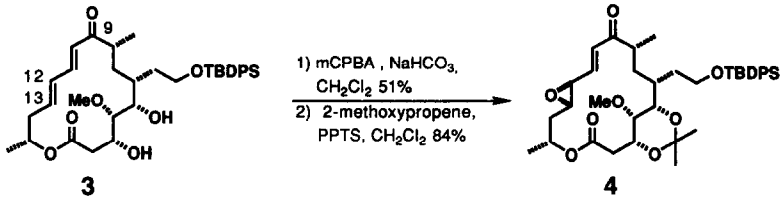
Fig. 2. ^{1}H NMR spectrum of **2** in $CDCl_3$

Unfortunately, efforts to isolate each conformer by chromatographic techniques were unsuccessful because there is an interconversion between these conformers at room temperature, and it was proved by the following simple two dimensional TLC analysis.

At room temperature, these conformers were detected as two separated spots at the first development. However, on standing for 15 minutes at room temperature after the first development, their interconversion occurred on the TLC plate, and each spot corresponding to the conformer appeared as two separated spots again at the second development. Consequently, total four spots were observed diagonally at room temperature. Although each conformer of **2** can not be isolated at room temperature, the conformational interconversion is relatively slow unlike that of **1** reported in the previous papers.[4b,d] So we next examined whether it could be stopped at lower temperature using above two dimensional TLC analysis.

At 4°C (in the refrigerator), on standing for 15 minutes after the first development, each conformer remained unchanged and only initial two spots were detected at the second development. However, prolonging time after the first development (for 30 minutes) caused their interconversion. On the other hand, at -35°C (in the freezer), no interconversion occurred even after standing for 1 week. It is noteworthy that the conformational interconversion of such a macrolactone can be stopped by moderate cooling.

The conformational control is sometimes crucial for the introduction of new chiral centers into macrocyclic systems.[3,4] Since we had to produce the 9*R* alcohol by stereoselective reduction of the C9 carbonyl group of **2**, we next tried to determine both conformations by the NMR studies.[9] Actually, easily available siloxy derivative (**4**) was examined. **4** was obtained by epoxidation of the degradation product of josamycin (**3**) (Scheme 1)[10] and gave more clearly resolved peaks on the ^{1}H NMR spectrum.



Scheme 1

As shown in Table 1, on comparison of J values of both conformers A and B, $J_{2,3}$, $J_{6,7}$, $J_{7,8}$ and $J_{13,14}$ are considerably different. According to the NOESY data (Table 2), in conformer A, saturation of H10 causes remarkable enhancements of H4, H7 and H13 signals, saturation of H11 enhances H12 signal. On the other hand, in conformer B, characteristic enhancements of H8 and H13 signals arise from saturation of H10, and saturation of H11 produces NOE with H12.

J_{H-H}	A	B
2-3	4.0,10.0	3.0,4.5
3-4	1.0	1.5
4-5	0	0
5-6	6.5	6.5
6-7	2.0,8.5	3.0,4.0
7-8	6.5,7.0	2.0,10.0
10-11	15.5	15.0
11-12	6.0	3.0
12-13	2.0	0
13-14	6.0,6.5	0,9.5
14-15	3.0,9.5	2.0,11.5

Table 1. Vicinal coupling constants (J ; Hz) of conformers A and B of **4**

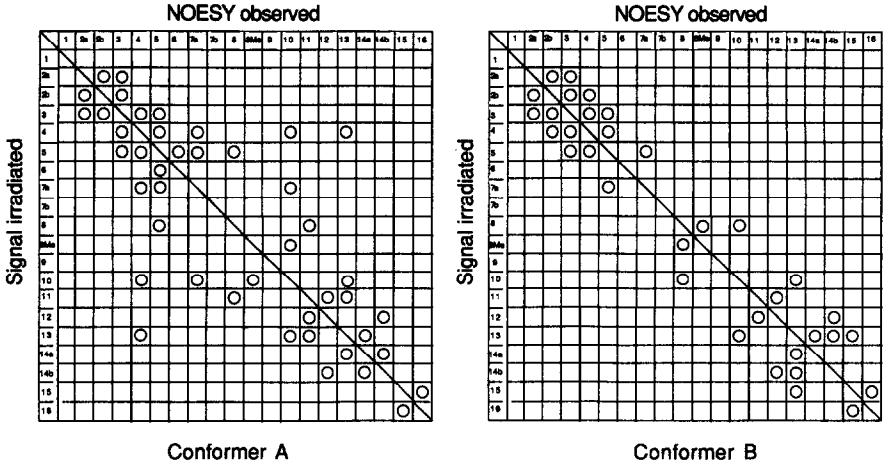


Table 2. The matrix of NOESY spectra obtained for conformers A and B of **4**

On the basis of above results, both conformations of A and B are estimated as shown in Fig. 3.[11] These conformers are the rotamers of the epoxyenone and C3,5 acetonide ring. While conformer A has 9,10-*s-cis*, 11,12-*s-trans* conformation and its epoxyenone lies nearly in the plane of the 16-membered ring, that of conformer B is 9,10-*s-cis*, 11,12-*s-cis* form and approximately perpendicular to the 16-membered ring. It is also found that the direction of the 6-membered acetonide ring is quite different between them. The chair form ring of A is situated in the plane of the macrolactone like the epoxyenone, and that of B has a vertical location.

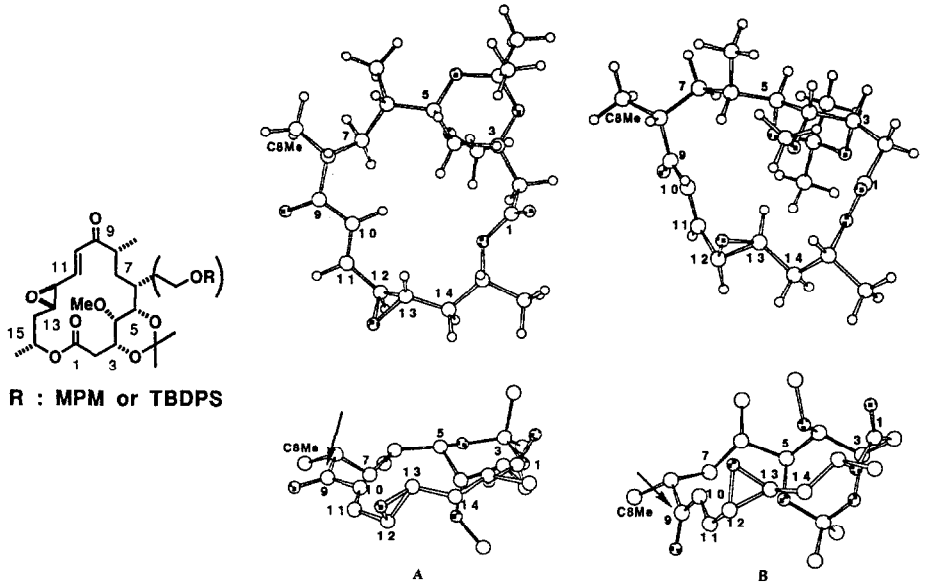


Fig. 3. Estimated conformations of A and B

Fortunately, in this examination, **4** crystallized in methanol and the conformation in the solid state was determined by X-ray diffraction (Fig. 4). As can be seen from Fig. 3 and 4, conformer B estimated by the NMR data is found to be almost identical with the crystal structure. On the macrolactone ring, the oxygen of the epoxide is fixed to the outside of the ring to avoid the transannular stereoelectronic repulsion. So, unlike the conformers of **1** mainly caused by easy rotation of the dienone without unfavorable transannular interaction,[4b,d] conformers A and B of **4** need somewhat forced rotation of the acetonide ring as well as the epoxyenone in their conformational interconversion. As the result, it becomes to be slow and easily detectable.

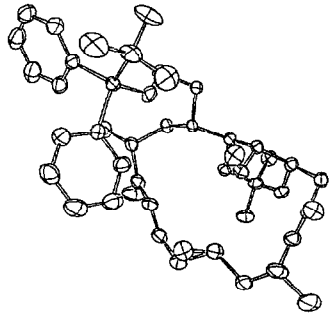
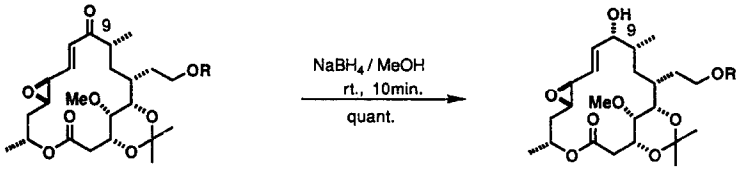


Fig. 4. ORTEP drawing of the crystal structure of **4**

The above conformational analysis also gave a precious information for prediction of the stereoselectivity of the reduction of the C9 carbonyl group. If the reduction proceeded from conformer A, to avoid the steric

hindrance by the C7 methylene group, the hydride would attack from *si* face (arrow) to give the desired 9*R* alcohol. Also conformer B was expected to afford the 9*R* alcohol by hydride's attack from the outside (*si* face) of the 16-membered ring. That is, in the reduction of the C9 carbonyl group, **2** and **4** are effectively controlled their conformations by protection of their C3,5 diol with an acetonide.

Actually, when **2** and **4** were treated with sodium borohydride in methanol at room temperature, the reduction proceeded smoothly to give the expected 9*R* alcohol derivatives (**5**, **6**) as a single product in quantitative yield (Scheme 2).[4b,d]



2 : R=MPM
4 : R=TBDPS

5 : R=MPM
6 : R=TBDPS

Scheme 2. The stereoselective reduction of the C9 carbonyl group

Also focusing on the reactivity of both conformers, conformer A seemed to be reduced more faster than B because the C9 carbonyl group of B is sterically hindered by the C8 methyl group. To prove this assumption, a following reaction was examined. At -40°C, since no interconversion occurs between A and B as described above, careful treatment of **4** with 0.5 equivalent of sodium borohydride in deutero methanol caused the selective reduction of A, which was easily detected by ^{1}H NMR measurement of the reaction mixture (Fig. 5).

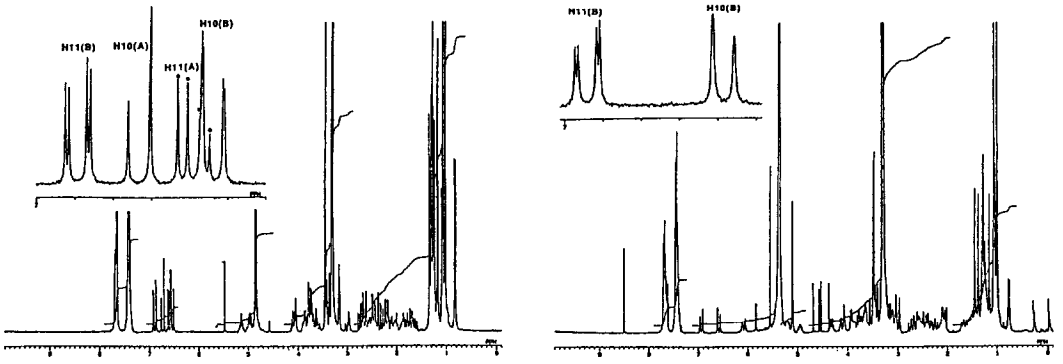


Fig. 5. ^{1}H NMR spectra of **4** and the reaction mixture in CD_3OD measured at -40°C

Although the details of conformer A are not clear yet, the above successful results make our conformational analysis to be reliable. The conversion of **5** into maridonolides has been already reported in the previous papers.[4b,d]

Experimental

Melting point was measured with Yamato melting point apparatus model MP-21. Optical rotations were measured with a JASCO DIP-370 degital polarimeter. IR spectra were recorded on a JASCO IRA-2-spectrometer. ^{1}H NMR spectra were recorded on a JEOL JNM GX-270 or JEOL JNM GX-500 instrument. Low- and high-resolution mass (MS) were taken on a JEOL JMS HX-110 or JEOL JMS DX-303 spectrometer.

6"-Dihydro-12*S*,13*R*-epoxy-3,5-isopropylidene-6"-*O*-(*tert*-butyldiphenylsilyl)niddanolide (4)

mCPBA (159 mg, 0.78 mmol; 85% activity) was added to a stirred solution of **3** (160.9 mg, 0.26 mmol) and $NaHCO_3$ (68 mg, 0.80 mmol) in CH_2Cl_2 (4 ml) at room temperature. After 23hr, the reaction mixture was diluted with ether, washed with saturated aqueous $NaHCO_3$ and brine, and dried over anhydrous $MgSO_4$. After removal of the solvent, the residual oil was chromatographed on a silica gel column with ethyl acetate-hexane (2:1) as the eluant to give 6"-dihydro-12*S*,13*R*-epoxy-6"-*O*-(*tert*-butyldiphenylsilyl)niddanolide as a colorless oil (83.6 mg, 51%). A stirred solution of the above epoxide (83.6 mg, 0.13 mmol) in CH_2Cl_2 (2 ml) was treated with 2-methoxypropene (63 µl, 0.66 mmol) and pyridinium *p*-toluenesulfonate (2 mg) at room temperature under an urgon atomosphere. After 20min, triethylamine (100 µl) was added, and the reaction mixture was evaporated *in vacuo*. The residue was subjected to a silica gel column chromatography with ethyl acetate-hexane (1:1) as the eluant to afford **4** as colorless prisms (74.6 mg, 84%). mp 136-137°C. $[\alpha]_D^{21}$ -1.4° (c=0.60, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500MHz) δ 0.88 (1.8H, d, *J*=6.0Hz, B C8Me), 0.97 (0.6H, ddd, *J*=14.5, 4.0, 2.0Hz, B H7), 1.00-1.48 (2H, m), 1.03 (3.6H, s, A ^{t}Bu), 1.06 (5.4H, s, B ^{t}Bu), 1.12 (1.2H, d, *J*=6.0Hz, A C8Me), 1.23 (1.8H, s, B acetonide Me), 1.27 (1.8H, s, B acetonide Me), 1.29 (1.8H, d, *J*=6.0Hz, B C15Me), 1.32 (1.2H, s, A acetonide Me), 1.33 (1.2H, d, *J*=6.0Hz, A C15Me), 1.36 (0.4H, ddd, *J*=14.5, 7.0, 2.0Hz, A H7), 1.38 (1.2H, s, A acetonide Me), 1.76 (0.6H, ddd, *J*=14.5, 10.0, 3.0Hz, B H7), 1.84 (0.4H, ddd, *J*=14.0, 9.5, 6.0Hz, A H14), 1.89 (0.4H, ddd, *J*=14.5, 8.5, 6.5Hz, A H7), 1.90 (0.6H, ddd, *J*=14.5, 9.5, 2.0Hz, B H14), 1.96 (0.4H, ddd, *J*=14.0, 6.5, 3.0Hz, A H14), 2.16-2.24 (0.4H, m, A H6), 2.28-2.38 (0.6H, m, B H6), 2.31 (0.6H, dd, *J*=14.5, 12.0Hz, B H14), 2.37 (0.6H, dd, *J*=14.5, 3.0Hz, B H2), 2.47 (0.6H, ddq, *J*=10.0, 2.0, 6.0Hz, B H8), 2.55 (0.4H, dd, *J*=14.0, 4.0Hz, A H2), 2.56 (0.4H, ddq, *J*=7.0, 6.5, 6.0Hz, A H8), 2.72 (0.6H, dd, *J*=14.5, 4.5Hz, B H2), 2.84 (0.4H, dd, *J*=14.0, 10.0Hz, A H2), 2.91 (0.4H, dt, *J*=2.0, 6.0Hz, A H13), 3.02 (0.4H, brs, A H4), 3.03 (0.6H, brs, B H4), 3.28-3.84 (2H, m), 3.30 (0.6H, brd, *J*=3.0Hz, B H12), 3.31 (0.4H, dd, *J*=6.0, 2.0Hz, A H12), 3.34 (0.6H, d, *J*=9.5Hz, B H13), 3.43 (1.8H, s, B C4MeO), 3.50 (1.2H, s, A C4MeO), 3.72 (0.4H, brd, *J*=6.5Hz, A H5), 3.72 (0.6H, brd, *J*=6.5Hz, B H5), 3.96 (0.6H, ddd, *J*=4.5, 3.0, 1.5Hz, B H3), 4.20 (0.4H, ddd, *J*=10.0, 4.0, 1.0Hz, A H3), 5.08 (0.6H, ddq, *J*=11.5, 2.0, 6.0Hz, B H15), 5.29 (0.4H, ddq, *J*=9.5, 3.0, 6.0Hz, A H15), 6.46 (0.6H, d, *J*=15.0Hz, B H10), 6.51 (0.4H, d, *J*=15.5Hz, A H10), 6.63 (0.4H, dd, *J*=15.5, 6.0Hz, A H11), 6.91 (0.6H, dd, *J*=15.0, 3.0Hz, B H11), 7.34-7.46 (6H, m), 7.60-7.70 (4H, m). MS *m/z* (relative intensity): 663 (M^+-Me, 1.9%), 621 (39), 563 (11), 531 (9.4), 447 (11), 281 (83), 213 (49), 199 (100), 183 (33), 161 (31), 135 (67), 121 (31), 109 (65), 95 (65), 71 (78), 55 (40), 41 (48). Exact MS Calcd for $C_{35}H_{45}O_8Si$ (M^+-^{t}Bu): 621.2884. Found: 621.2905. IR ν (neat)cm^{-1}: 2900, 1710, 1670, 1610, 1370, 1250, 1100, 730, 690.

Crystal structure of 4. Colorless prism crystal of approximate dimensions 0.5x0.4x0.2 mm was mounted on an automated Rigaku AFC-5 X-ray diffractometer using Cu Kα radiation. The unit cell parameters are *a*=13.052(1), *b*=15.545(2), *c*=9.4904(5) Å, β=91.26(1)° in space group $P2_1$ (*Z*=2). Of the 3330 reflections measured with 2θ≤130° employing a 2θ/ω scan, 3146 were independently observed at level $F \geq 3\sigma(F)$. Three reflections measured every 102 reflections showed no significant variation in intensity. The structure was solved by MULTAN78[12] and successive Fourier syntheses and refined using the block-diagonal least-squares technique with anisotropic temperature factors for non-hydrogen atoms. Hydrogen atoms except one attached to the methyl group located in the difference Fourier map and refined isotropically. The refinement was terminated at *R*=0.038. Calculations were performed with the DIRECT-SEARCH program system.[13] Four tables consisting of atomic fractional coordinates, temperature factors, bond lengths, and bond angles have been deposited as supplementary material.

6"-Dihydro-12*S*,13*R*-epoxy-3,5-isopropylidene-6"-*O*-(*tert*-butyldiphenylsilyl)leuconolide A1 (6)

$NaBH_4$ (2.5 mg, 63 μmol) was added to a stirred solution of **4** (15.6 mg, 23 μmol) in methanol (1.5 ml) at room temperature and the reaction mixture was stirred for 10mim. Powdered NH_4Cl was added to the reaction mixture to quench the reaction and the solvent was evaporated off *in vacuo*. The residue was extracted with CH_2Cl_2, and the extract was washed with saturated aqueous NH_4Cl and dried. After removal of the solvent, the residue was chromatographed on a silica gel column with ethyl acetate-hexane (1:1) as the eluant to give **6** as a colorless oil (15.5 mg, quant.). $[\alpha]_D^{22}$ +13.3° (c=1.00, $CHCl_3$). ^1H NMR (CD_3OD, 270MHz) δ 1.02 (9H, s), 1.05 (3H, d, *J*=6.5Hz), 1.23 (1H, ddd, *J*=14.5, 7.5, 3.0Hz), 1.30 (3H, d, *J*=6.5Hz), 1.36 (3H, s), 1.44 (3H, s), 1.49 (1H, ddd, *J*=14.5, 9.5, 2.0Hz), 1.58 (1H, ddd, *J*=14.5, 10.0, 8.0Hz), 1.20-1.50 (2H, m), 1.97-2.02 (1H, m) 2.06 (1H, ddd, *J*=14.5, 3.5, 2.0Hz), 2.43 (1H, dd, *J*=15.5, 3.0Hz), 2.43 (1H, ddq, *J*=9.5, 3.0, 6.5Hz), 2.77 (1H, dd, *J*=15.5, 10.5Hz), 2.98 (1H, brs), 3.01 (1H, ddd, *J*=8.0, 3.5, 2.0Hz), 3.13 (1H, dd, *J*=6.0, 2.0Hz), 3.47 (3H, s), 3.66 (1H, dd, *J*=10.5, 6.0Hz), 3.73 (1H, dd, *J*=6.0, 1.0Hz), 4.12 (1H, brd, *J*=7.0Hz), 4.29 (1H, ddd, *J*=10.5, 3.0, 1.0Hz), 5.22 (1H, ddq, *J*=10.0, 2.0, 6.5Hz), 5.46 (1H, ddd, *J*=15.5, 7.0, 1.0Hz), 6.04 (1H, dd, *J*=15.5, 6.0Hz), 7.30-7.50 (6H, m) 7.60-7.75 (4H, m). MS *m/z* (relative intensity): 665 (M^+-Me, 1.5%), 605 (1.5), 565 (2.6), 533 (4.4), 515 (5.0), 281 (23), 213 (29), 199 (96), 183 (27), 163 (21), 135 (65), 121 (61), 95 (50), 71 (100), 55 (75), 41 (78). Exact MS Calcd for $C_{38}H_{53}O_8Si$ (M^+-Me): 665.3510. Found: 665.3506. IR ν (neat)cm^{-1}: 3500~3200, 2900, 1720, 1370, 1190, 1100, 1070, 960, 690.

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8. **2** gave broad unresolved peaks at 100°C (in DMSO-d_6). This result shows the interconversion between A and B was accelerated by heating.
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