# Studies on Selectivity of *O*-Methylation of Erythromycin Derivatives Based on Molecular Mechanics and Molecular Orbital Methods[1)]

Yutaka KAWASHIMA,*[,a] Shigeo MORIMOTO,[a] Tohru MATSUNAGA,[a] Masato KASHIMURA,[a] Takashi ADACHI,[a] Yoshiaki WATANABE,[a] Katsuo HATAYAMA,[a] Shuichi HIRONO[b] and Ikuo MORIGUCHI[b]

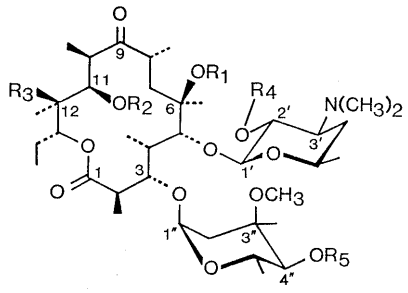
*Research Center, Taisho Pharmaceutical Co., Ltd.,[a] Yoshino-cho, Ohmiya, Saitama 330, Japan and School of Pharmaceutical Sciences, Kitasato University,[b] Shirokane 5-chome, Minato-ku, Tokyo 108, Japan.* *Received November 6, 1989*

**The regioselectivity on *O*-methylation of the C6- and C11-hydroxyl groups of 2′,4″-*O*-bis(trimethylsilyl)erythromycin A (3, TMS-EM-A) and that in the case of 2′,4″-*O*-bis(trimethylsilyl)erythromycin B (4, TMS-EM-B) were examined in relation to the ease of deprotonation and the stability of the anion state. *O*-Methylation of 3 gave 11-methoxy-TMS-EM-A (5) and 6-methoxy-TMS-EM-A (6) in the ratio of *ca.* 3 : 1, whereas that of 4 gave predominantly 6-methoxy-TMS-EM-B (7). To understand how the steric and electronic structures of EM-A (1) and EM-B (2) affect the selectivities, we carried out theoretical calculations using a semi-empirical molecular orbital method, MNDO. From the frontier electronic density of the lowest unoccupied molecular orbital (LUMO), it was suggested that the activities of deprotonation at the C11-hydroxyl groups of 3 and 4 are higher than those of the C6-hydroxyl groups. On the other hand, it was shown from the total energies of the molecules that the C6-$O^-$-derivatives (3a and 4a) of 3 and 4 are more stable than the C11-$O^-$-derivatives (3b and 4b). The difference of total energies between 4a and 4b is greater than that of 3a and 3b by 5.1 kcal/mol, suggesting the possibility of hydrogen bonding between C11-$O^-$ and C12-OH of 3b.**

**Keywords** regioselectivity; *O*-methylation; erythromycin; molecular mechanics; molecular orbital method; MM-2′; MNDO; LUMO; total energy; deprotonation

Erythromycin A (**1**, EM-A), a basic 14-membered macrolide antibiotic, possesses strong antibacterial activity against gram-positive bacteria and *Mycoplasma* spp. Many chemical modifications of EM-A and erythromycin B (**2**, 12-deoxy EM-A, EM-B) have been conducted in order to improve upon its biological properties.[2)] In the previous paper, we reported the synthesis and antibacterial activity of O-methylerythromycin A[3,4)] and *O*-methylerythromycin B.[5)]

In the present study, *O*-methylations of 2′,4″-*O*-bis(trimethylsilyl)erythromycin A (**3**, TMS-EM-A) and 2′,4″-*O*-bis(trimethylsilyl)erythromycin B (**4**, TMS-EM-B) were carried out to examine the regioselectivities of the C6 and C11-hydroxyl groups, and the differences of *O*-methylation between **3** and **4** were evaluated theoretically using the semi-empirical molecular orbital method, MNDO, to understand how the steric and electronic structures of **3** and **4** affect the regioselectivity in the *O*-methylation of both molecules.




| | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ |
|---|---|---|---|---|---|
| **1** | H | H | OH | H | H |
| **2** | H | H | H | H | H |
| **3** | H | H | OH | $Si(CH_3)_3$ | $Si(CH_3)_3$ |
| **4** | H | H | H | $Si(CH_3)_3$ | $Si(CH_3)_3$ |
| **5** | H | $CH_3$ | OH | $Si(CH_3)_3$ | $Si(CH_3)_3$ |
| **6** | $CH_3$ | H | OH | $Si(CH_3)_3$ | $Si(CH_3)_3$ |
| **7** | $CH_3$ | H | H | $Si(CH_3)_3$ | $Si(CH_3)_3$ |
| **8** | $CH_3$ | $CH_3$ | OH | $Si(CH_3)_3$ | $Si(CH_3)_3$ |

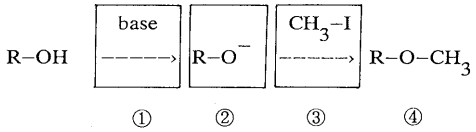
Chart 1

## Results and Discussion

***O*-Methylation Procedure** TMS-EM-A (**3**) and TMS-EM-B (**4**) were obtained by the reaction of the corresponding **1** and **2** with chlorotrimethylsilane and *N*-(trimethylsilyl) imidazole. TMS-EM-A (**3**) was methylated with $CH_3I$ and KOH in dimethyl sulfoxide (DMSO)–tetrahydrofuran (THF) to give 11-methoxy-TMS-EM-A (**5**) and 6-methoxy-TMS-EM-A (**6**) in the ratio of *ca.* 3 : 1. On the other hand, *O*-methylation of TMS-EM-B (**4**) proceeded almost regioselectively to give 6-methoxy-TMS-EM-B (**7**).

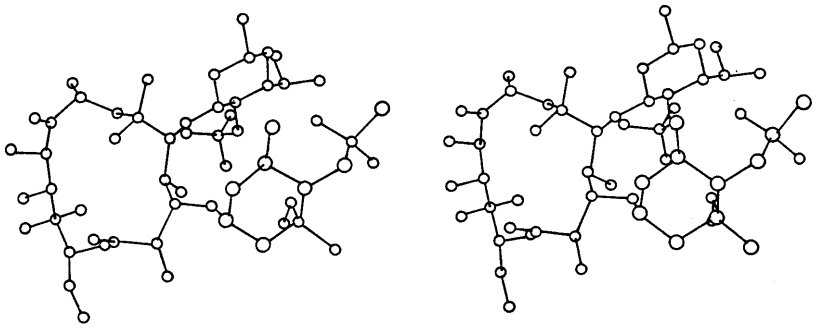
**Construction of Structures** When reactivity is discussed theoretically in terms of the physicochemical properties of organic compounds, molecular mechanics and molecular orbital calculations are useful and powerful methods. We used the molecular mechanics program MM2′ mainly to obtain 3-dimensional coordinates and MNDO to evaluate the physicochemical properties of molecules. In generally, the reactivity of *O*-methylation (under basic conditions without consideration of solvent effect) is controlled mainly by 4 factors which are summarized in Chart 2.

In this study, we examined the regioselectivity from the viewpoints of the activity of deprotonation and the stability of the anion state. The frontier electronic density of the

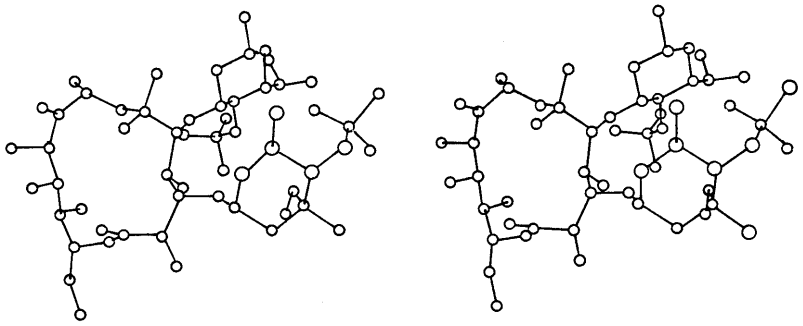



1. activity of deprotonation
2. stability of alkoxide ion
3. interaction of reagent
4. stability of product

Chart 2



TMS-EM-A (3)



TMS-EM-B (4)

Chart 3. Stereoscopic Views of **3** and **4**

lowest unoccupied molecular orbital (LUMO) was used as the index of the activity of deprotonation; and the total energy, as the index of the stability of the anion state.

First, we constructed the structure of **1**. The X-ray structure analysis of **1** has been reported by Harris *et al.* except for its coordinates.[6] We have done an X-ray analysis[7] of 6-methoxy-EM-A (clarithromycin, TE-031) which was found to exhibit excellent antimicrobial activity and superior pharmacokinetic properties.[3] It would be reasonable, therefore, to employ the X-ray data of 6-methoxy-EM-A as the initial structure. The modeling of **1** was done and followed by optimization and conformation analysis of the aglycone-cladinose and aglycone-desosamine moieties using MM-2′.

Secondly, the molecular structure of **3** was constructed on the basis of the structure of **1** in a similar manner. However, a molecule such as **3** consists of too many atoms for molecular mechanics or molecular orbital calculations on the whole molecule to be feasible from the viewpoint of computing time. Furthermore, we can not use O–Si bond parameters in MM-2′ programs. So, the sugar moieties were separated from the molecule of **1**, then the structures of the *O*-TMS-cladinose and *O*-TMS-desosamine moieties were constructed and optimized using MNDO. The conformation analysis of the aglycone-cladinose and aglycone-desosamine moieties of **3** was done using MNDO.

Thirdly, the molecular structures of 6-$O^-$-TMS-EM-A (**3a**) and 11-$O^-$-TMS-EM-A (**3b**) were constructed on the basic of this optimized **3**. Further, the length of the C–$O^-$ bond (C6 position) of **3a** was optimized using MNDO. In the case of **3b**, the length and dihedral angle of the C–O bond moiety (C12 position) and the length of the C–$O^-$-bond (C11 position) were optimized by consideration of the effect of vicinal hydroxyl groups using MNDO.

The X-ray structure analysis of **2** has not been reported, so we similarly constructed the structures of **2** and **4** using MM2′ and MNDO on the basis of the X-ray data of 6-methoxy-EM-A. The structures of 6-$O^-$-TMS-EM-B (**4a**) and 11-$O^-$-TMS-EM-B (**4b**) were constructed similarly using MNDO. The structures of **3** and **4** are shown in Chart 3.

Table I. Frontier Electron Densities of Hydrogen Atoms of 6- and 11-Hydroxyl Groups in **3** and **4**

| Compd. | Frontier electron densities $((LUMO)^2 \times 10^{-4}$ A.U.$) \times 2$ | |
|---|---|---|
| | 6-OH | 11-OH |
| TMS-EM-A (**3**) | 1.84 | 2.74 |
| TMS-EM-B (**4**) | 1.34 | 1.86 |

Table II. Difference of Total Energy of Anion State

| Compd. | | $\Delta E$ (kcal/mol) |
|---|---|---|
| TMS-EM-A (**3**) | $\Delta E_{3a-3b}=E_{3a}-E_{3b}$ | −6.4 |
| TMS-EM-B (**4**) | $\Delta E_{4a-4b}=E_{4a}-E_{4b}$ | −11.5 |

**Analysis of Regioselectivity** Analysis of regioselectivity was conducted by using the optimized structures of **3** and **4**.

**Activity of Deprotonation** The frontier electron densities of LUMO of the C6 and C11-hydroxyl potons of **3** and **4** were calculated using MNDO. These results are summarized in Table I. The electron density at the C11-hydroxyl proton of **3** was higher than that of the C6-hydroxyl proton. The electron densities at the C6 and C11-hydroxyl protons of **4** also showed similar results. Thus, it was suggested that the activities of deprotonation at the C11-hydroxyl groups were higher than those of the C6-hydroxyl groups.

**Stability of the Anion State** The total energy of each of **3a**($E_{3a}$), **3b**($E_{3b}$), **4a**($E_{4a}$), **4b**($E_{4b}$) was calculated using MNDO, and the stabilities were examined using the values

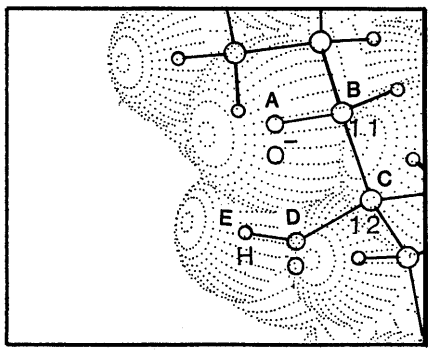



Chart 4. Proposed Structure for C-11 and C-12 Position of 11-O$^-$-TMS-EM-A (**3b**)

| No. | atom | length (Å) | angle | dihedral angle | connection |
|---|---|---|---|---|---|
| A | O$^-$ | | | | |
| B | C | 1.322 | | | A |
| C | C | 1.559 | 109.000 | | B A |
| D | O | 1.420 | 108.650 | 54.520 | C B A |
| E | H | 0.948 | 112.350 | −39.880 | D C B |

of $\Delta E_{3a-3b}$ and $\Delta E_{4a-4b}$. These results are summarized in Table II. The values of total energy of the molecules showed that **3a** is more stable than **3b** and **4a** is much more stable than **4b**. The absolute difference of total energies between **4a** and **4b** is greater than that of **3a** and **3b** by 5.1 kcal/mol.

In conclusion, the activities of deprotonation at the C11-hydroxyl groups of **3** and **4** estimated from the frontier electron density are higher than those of the C6-hydroxyl groups. On the other hand, it was apparent from the total energies of the molecules that the C6-O$^-$-derivatives of **3** and **4** are more stable than the C11-O$^-$-derivatives. In particular, the C6-O$^-$-derivative of **4** is preferred compared to that of **3**. The difference of stabilities between **4a** and **4b** is greater than that of **3a** and **3b** by 5.1 kcal/mol. The distance between the 11-O$^-$ atom and 12-OH of **3b** is 2.298 Å.

It is suggested that the 11-O$^-$ anion of **3b** is stabilized by the hydrogen bonding interaction (Chart 4).

Supposing that both the reactivity of C11-OH of **3** and the stability of **3a** resulted in the observed predominant formation of the 11-methoxy derivative (**5**) over the 6-methoxy derivative (**6**), it may be reasonable to consider that the stability of **4a** led to the preponderance of the 6-methoxy derivative (**7**) in the *O*-methylation of **4**. These results appear to explain the regioselectivities in the *O*-methylation of EM-A derivatives (**3**) and EM-B derivatives (**4**) at least qualitatively.

Further evaluation of erythromycin derivatives, including conformational analysis of the macrolide ring, is in progress.

## Experimental

Melting points were determined with a Yanaco micro melting point apparatus and are uncorrected. Infrared (IR) spectra were taken on a Perkin-Elmer 1760 FT-IR spectrometer. Mass spectra (MS) were measured on a Jeol JMS-SX 102 spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded in $CDCl_3$ on Jeol JNM-GX 400, Varian VXR-300 or Varian XL-200 spectrometers. Optical rotations were determined with a Jasco DIP-360 digital polarimeter. Analytical high performance liquid chromatography (HPLC) was conducted on a octadecylsilanized silica gel column (TSK gel ODS 120A, 4.6 i.d. × 300 mm) using MeOH–water (96 : 4) containing 0.04% ethanolamine.

**2′,4″-*O*-Bis(trimethylsilyl)erythromycin A (3)** A mixture of chlorotrimethylsilane (1.63 g, 15 mmol) and *N*-(trimethylsilyl)imidazole (2.1 g, 15 mmol) in EtOAc (10 ml) was added to a solution of erythromycin A (7.34 g, 10 mmol) in EtOAc (200 ml). The mixture was stirred for 30 min at ambient temperature, and then poured into 5% $NaHCO_3$ solution. The organic layer was separated, washed with water, dried over anhydrous $MgSO_4$, and evaporated *in vacuo*. The residue was crystallized from hexane to give 6.67 g (76%) of **3** as colorless crystals. mp 194—197 °C. FAB-MS *m/z*: 878 (M+H). IR (KBr): 3516 (OH), 1715 (lactone C=O) cm$^{-1}$. $[\alpha]_D^{24}$: −69.1° (*c*=0.525, $CHCl_3$). $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$: 3.30 (3H, s, 3-$OCH_3$), 2.23 (6H, br s, $N(CH_3)_2$), 0.15 (9H, s, 4″-$OSi(CH_3)_3$), 0.11 (9H, s, 2′-$OSi(CH_3)_3$). $^{13}$C-NMR (100 MHz, $CDCl_3$) $\delta$: 221.4 (C-9), 176.5 (C-1), 49.8 (3″-$OCH_3$), 41.1 ($N(CH_3)_2$), 1.02 (2′-$OSi(CH_3)_3$), 0.96 (4″-$OSi(CH_3)_3$). *Anal.* Calcd for $C_{43}H_{83}NO_{13}Si_2$: C, 58.80; H, 9.53; N, 1.60. Found: C, 58.90; H, 9.59; N, 1.50.

**2′,4″-*O*-Bis(trimethylsilyl)erythromycin B (4)** According to the method described for **3**, erythromycin B (14.4 g, 20 mmol) provided 12.6 g (73%) of **4** as a colorless foam. mp 90—95 °C. FAB-MS *m/z*: 862 (M+H). IR (KBr): 3513 (OH), 1732 (lactone C=O), 1702 (ketone C=O) cm$^{-1}$. $[\alpha]_D^{24}$: −75.4° (*c*=0.448, $CHCl_3$). $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$: 3.31 (3H, s, 3″-$OCH_3$), 2.24 (6H, br s, $N(CH_3)_2$), 0.15 (9H, s, 4″-OSi $(CH_3)_3$), 0.11 (9H, s, 2′-OSi $(CH_3)_3$). $^{13}$C-NMR (100 MHz, $CDCl_3$) $\delta$: 218.2 (C-9), 177.1 (C-1), 49.8 (3″-$OCH_3$), 41.0 ($N(CH_3)_2$), 1.02 (2′-$OSi(CH_3)_3$), 0.96 (4″-$OSi(CH_3)_3$).

***O*-Methylation of 3** Iodomethane (205 mg, 1.5 mmol) and 85% freshly powdered KOH (90 mg, 1.4 mmol) were added successively to a solution of **3** (1.0 g, 1.1 mmol) in DMSO–THF (5 ml–5 ml) with stirring at 0—5 °C. The mixture was stirred for 1 h, and then 50% dimethylamine (0.5 ml) was added to quench the reaction. The reaction mixture was poured into water, and extracted with EtOAc. The EtOAc layer was washed with brine, dried (anhydrous $MgSO_4$), and evaporated *in vacuo* to afford 1.05 g of the crude product as a foam. The resulting product (1.0 g) was chromatographed over a silica gel column with $Me_2CO$–hexane–$Et_3N$ (1 : 10 : 0.2) to afford the polar product A and the less polar product B as colorless solids. The product A was recrystallized from hexane to give 631 mg (65%) of 11-*O*-methyl-2′,4″-*O*-bis(trimethylsilyl)erythromycin A (**5**) as colorless crystals. mp 139—141 °C. FAB-MS *m/z*: 892 (M+H). IR (KBr): 3479 (OH), 1732 (lactone C=O), 1709 (ketone C=O) cm$^{-1}$. $[\alpha]_D^{24}$: −46.5° (*c*=0.529, $CHCl_3$). $^1$H-NMR (200 MHz, $CDCl_3$) $\delta$: 3.31 (3H, s, 11-$OCH_3$), 3.28 (3H, s, 3″-$OCH_3$), 2.27 (6H, br s, N $(CH_3)_2$), 1.42 (3H, s, 6-$CH_3$), 0.17 (9H, s, 4″-$OSi(CH_3)_3$), 0.13 (9H, s, 2′-$OSi(CH_3)_3$). $^{13}$C-NMR (50 MHz, $CDCl_3$) $\delta$: 177.5 (C-1), 108.7 (C-9), 94.6 (C-11), 85.2 (C-6), 75.2 (C-12), 56.7 (11-$OCH_3$), 49.6 (3″-$OCH_3$), 41.0 ($N(CH_3)_2$), 0.94 (2′-$OSi(CH_3)_3$), 0.94 (4″-$OSi(CH_3)_3$). *Anal.* Calcd for $C_{44}H_{85}NO_{13}Si_2$: C, 59.23; H, 9.60; N, 1.57. Found: C, 59.03; H, 9.58; N, 1.45.

The product B was crystallized from hexane to give 204 mg (*ca.* 21%) of colorless crystals which could not be further purified. The crystals were identified as a mixture of **6** and **8** in a ratio of 4 : 1 by comparison of the NMR and HPLC data with those of authentic samples of **6** and **8**.

HPLC analysis of the crude product (foam) showed the ratio of **5**:**6**:**8**=66 : 19 : 5.

**6-*O*-Methyl-2′,4″-*O*-bis(trimethylsilyl)erythromycin A (6)** According to the method described for **3**, silylation was carried out with the use of dichloromethane (200 ml) instead of EtOAc as a reaction solvent. 6-*O*-Methylerythromycin A[3] (7.48 g, 10 mmol) provided 7.1 g (80%) of **6**, which was crystallized from hexane. mp 106—108 and 117—180 °C. FAB-MS *m/z*: 892 (M+H). IR (KBr): 3469 (OH), 1737 (lactone C=O), 1693 (ketone C=O) cm$^{-1}$. $[\alpha]_D^{24}$: −156.7° (*c*=0.529, $CHCl_3$). $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 3.31 (3H, s, 3″-$OCH_3$), 3.03 (3H, s, 6-$OCH_3$), 2.22 (6H, br s, $N(CH_3)_2$), 0.15 (9H, s, 4″-$OSi(CH_3)_3$), 0.10 (9H, s, 2′-$OSi(CH_3)_3$). $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$: 221.0 (C-9), 176.3 (C-1), 78.7 (C-6), 50.5 (6-$OCH_3$), 49.7 (3″-$OCH_3$), 41.0 ($N(CH_3)_2$), 1.08 (2′-$OSi(CH_3)_3$), 0.90 (4″-$OSi(CH_3)_3$). *Anal.* Calcd for $C_{44}H_{85}NO_{13}Si_2$: C, 59.23; H, 9.60; N, 1.57. Found: C, 59.13; H, 9.60; N, 1.45.

**6,11-Di-*O*-methyl-2′,4″-*O*-bis(trimethylsilyl)erythromycin A (8)** According to the method described for **6**, 6,11-di-*O*-methylerythromycin A[3] (2.0 g, 2.6 mmol) provided 1.93 g (81%) of **8**, which was crystallized from hexane. mp 195—197 °C. FAB-MS *m/z*: 906 (M+H). IR (KBr): 3516 (OH), 1734 (lactone C=O), 1714 (ketone C=O) cm$^{-1}$. $[\alpha]_D^{24}$: −88.9° (*c*=0.404, $CHCl_3$). $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 3.59 (3H, s, 11-$OCH_3$), 3.31 (3H, s, 3″-$OCH_3$), 3.11 (3H, s, 6-$OCH_3$), 2.22 (6H, br s, $N(CH_3)_2$), 0.15, (9H, s, 4″-$OSi(CH_3)_3$), 0.10 (9H, s, 2′-$OSi(CH_3)_3$). $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$: 217.4 (C-9), 176.0 (C-1), 79.3 (C-6), 60.8 (11-$OCH_3$), 50.5 (6-$OCH_3$), 49.7 (3″-$OCH_3$), 41.0 ($N(CH_3)_2$), 1.10 (2′- $OSi(CH_3)_3$), 0.89

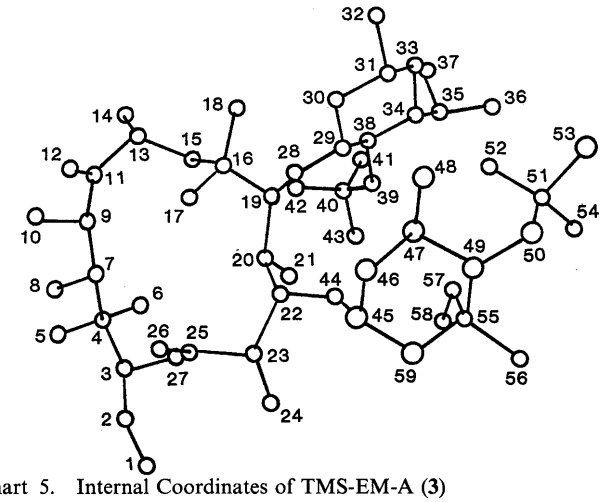


Chart 5. Internal Coordinates of TMS-EM-A (3)

| No. | atom | length (Å) | angle | dihedral angle | connection |
|---|---|---|---|---|---|
| 1 | 6 | | | | |
| 2 | 6 | 1.535 | | | |
| 3 | 6 | 1.541 | 112.268 | | |
| 4 | 6 | 1.559 | 115.623 | −177.482 | 3 2 1 |
| 5 | 8 | 1.419 | 108.815 | 52.075 | 4 3 2 |
| 6 | 6 | 1.545 | 110.377 | −65.604 | 4 3 2 |
| 7 | 6 | 1.559 | 110.042 | 171.012 | 4 3 2 |
| 8 | 8 | 1.418 | 109.000 | −64.517 | 7 4 3 |
| 9 | 6 | 1.548 | 118.430 | 168.789 | 7 4 3 |
| 10 | 6 | 1.536 | 115.260 | 71.141 | 9 7 4 |
| 11 | 6 | 1.528 | 110.482 | −163.133 | 9 7 4 |
| 12 | 8 | 1.220 | 120.957 | −57.170 | 11 9 7 |
| 13 | 6 | 1.526 | 119.449 | 120.193 | 11 9 7 |
| 14 | 6 | 1.539 | 110.992 | 58.034 | 1311 9 |
| 15 | 6 | 1.543 | 112.267 | −67.142 | 1311 9 |
| 16 | 6 | 1.554 | 117.301 | −73.873 | 151311 |
| 17 | 8 | 1.418 | 110.108 | 51.607 | 161513 |
| 18 | 6 | 1.546 | 110.678 | −67.540 | 161513 |
| 19 | 6 | 1.565 | 110.785 | 171.147 | 161513 |
| 20 | 6 | 1.626 | 114.053 | −76.316 | 191615 |
| 21 | 6 | 1.542 | 114.456 | 132.619 | 201916 |
| 22 | 6 | 1.564 | 108.274 | −98.682 | 201916 |
| 23 | 6 | 1.558 | 109.134 | 163.816 | 222019 |
| 24 | 6 | 1.538 | 116.917 | 172.053 | 232220 |
| 25 | 6 | 1.523 | 110.155 | −65.752 | 232220 |
| 26 | 8 | 1.221 | 124.580 | −73.227 | 252322 |
| 27 | 8 | 1.342 | 109.696 | 109.328 | 252322 |
| 28 | 8 | 1.430 | 108.534 | 48.123 | 191615 |
| 29 | 6 | 1.424 | 114.648 | 112.750 | 281916 |
| 30 | 8 | 1.425 | 109.125 | −73.609 | 292819 |
| 31 | 6 | 1.417 | 112.866 | 173.816 | 302928 |
| 32 | 6 | 1.536 | 108.718 | −177.067 | 313029 |
| 33 | 6 | 1.535 | 110.416 | 60.066 | 313029 |
| 34 | 6 | 1.542 | 111.448 | −53.464 | 333130 |
| 35 | 7 | 1.473 | 113.828 | −179.014 | 343331 |
| 36 | 6 | 1.466 | 111.570 | 78.169 | 353433 |
| 37 | 6 | 1.466 | 114.004 | −46.126 | 353433 |
| 38 | 6 | 1.555 | 109.297 | 53.329 | 343331 |
| 39 | 8 | 1.431 | 109.652 | −173.812 | 383433 |
| 40 | 14 | 1.434 | 117.751 | −126.050 | 393834 |
| 41 | 6 | 1.542 | 111.889 | 66.125 | 403938 |
| 42 | 6 | 1.544 | 113.414 | −58.550 | 403938 |
| 43 | 6 | 1.547 | 105.784 | −177.275 | 403938 |
| 44 | 8 | 1.429 | 107.302 | −74.105 | 222019 |
| 45 | 6 | 1.426 | 109.501 | 164.000 | 442220 |
| 46 | 8 | 1.424 | 113.194 | −89.439 | 454422 |
| 47 | 6 | 1.428 | 114.341 | −70.673 | 464544 |
| 48 | 6 | 1.540 | 106.052 | −178.332 | 474645 |
| 49 | 6 | 1.550 | 111.093 | −56.020 | 474645 |
| 50 | 8 | 1.431 | 116.166 | −163.117 | 494746 |
| 51 | 14 | 1.435 | 124.241 | −72.272 | 504947 |
| 52 | 6 | 1.537 | 116.973 | 35.644 | 515049 |
| 53 | 6 | 1.554 | 104.414 | 152.954 | 515049 |
| 54 | 6 | 1.544 | 111.789 | −93.127 | 515049 |
| 55 | 6 | 1.554 | 113.215 | 55.964 | 494746 |
| 56 | 6 | 1.544 | 111.593 | −170.002 | 554947 |
| 57 | 8 | 1.425 | 108.120 | 65.544 | 554947 |
| 58 | 6 | 1.418 | 116.743 | 179.264 | 575549 |
| 59 | 6 | 1.547 | 104.807 | −52.991 | 554947 |

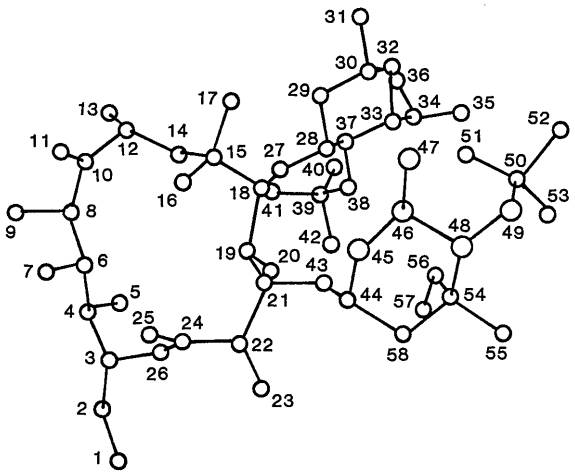


Chart 6. Internal Coordinates of TMS-EM-B (4)

| No. | atom | length (Å) | angle | dihedral angle | connection |
|---|---|---|---|---|---|
| 1 | 6 | | | | |
| 2 | 6 | 1.535 | | | |
| 3 | 6 | 1.540 | 112.144 | | |
| 4 | 6 | 1.551 | 114.084 | −174.442 | 3 2 1 |
| 5 | 6 | 1.541 | 111.037 | −64.596 | 4 3 2 |
| 6 | 6 | 1.552 | 110.482 | 170.276 | 4 3 2 |
| 7 | 8 | 1.419 | 109.456 | −61.074 | 6 4 3 |
| 8 | 6 | 1.546 | 116.624 | 173.981 | 6 4 3 |
| 9 | 6 | 1.536 | 113.936 | 69.875 | 8 6 4 |
| 10 | 6 | 1.527 | 110.711 | −163.592 | 8 6 4 |
| 11 | 8 | 1.220 | 121.126 | −61.928 | 10 8 6 |
| 12 | 6 | 1.526 | 119.213 | 115.816 | 10 8 9 |
| 13 | 6 | 1.539 | 110.837 | 59.210 | 1210 8 |
| 14 | 6 | 1.543 | 112.558 | −66.065 | 1210 8 |
| 15 | 6 | 1.554 | 117.170 | −74.054 | 141210 |
| 16 | 8 | 1.418 | 110.030 | 52.036 | 151412 |
| 17 | 6 | 1.546 | 110.613 | −66.981 | 151412 |
| 18 | 6 | 1.566 | 111.006 | 171.649 | 151412 |
| 19 | 6 | 1.629 | 114.397 | −75.247 | 181514 |
| 20 | 6 | 1.542 | 114.268 | 132.882 | 191815 |
| 21 | 6 | 1.564 | 108.341 | −98.340 | 191815 |
| 22 | 6 | 1.558 | 109.175 | 164.807 | 211918 |
| 23 | 6 | 1.538 | 116.815 | 171.090 | 222119 |
| 24 | 6 | 1.523 | 110.253 | −66.781 | 222119 |
| 25 | 8 | 1.221 | 124.101 | −72.251 | 242221 |
| 26 | 8 | 1.343 | 109.941 | 109.827 | 242221 |
| 27 | 8 | 1.430 | 108.593 | 49.315 | 181514 |
| 28 | 6 | 1.424 | 114.648 | 111.300 | 271815 |
| 29 | 8 | 1.425 | 109.125 | −73.268 | 282718 |
| 30 | 6 | 1.417 | 112.866 | 173.816 | 292827 |
| 31 | 6 | 1.536 | 108.717 | −177.067 | 302928 |
| 32 | 6 | 1.535 | 110.416 | 60.065 | 302928 |
| 33 | 6 | 1.542 | 111.449 | −53.464 | 323029 |
| 34 | 7 | 1.473 | 113.829 | −179.014 | 333230 |
| 35 | 6 | 1.466 | 111.570 | 78.169 | 343332 |
| 36 | 6 | 1.466 | 114.004 | −46.124 | 343332 |
| 37 | 6 | 1.555 | 109.296 | 53.330 | 333230 |
| 38 | 8 | 1.431 | 109.652 | −173.811 | 373332 |
| 39 | 14 | 1.434 | 117.749 | −126.049 | 383733 |
| 40 | 6 | 1.542 | 111.890 | 66.124 | 393837 |
| 41 | 6 | 1.544 | 113.413 | −58.552 | 393837 |
| 42 | 6 | 1.547 | 105.783 | −177.275 | 393837 |
| 43 | 8 | 1.429 | 107.354 | −73.230 | 211918 |
| 44 | 6 | 1.426 | 109.500 | 164.499 | 432119 |
| 45 | 8 | 1.424 | 113.195 | −88.011 | 444321 |
| 46 | 6 | 1.428 | 114.343 | −70.671 | 454443 |
| 47 | 6 | 1.540 | 106.053 | −178.332 | 464544 |
| 48 | 6 | 1.550 | 111.092 | −56.021 | 464544 |
| 49 | 8 | 1.431 | 116.166 | −163.118 | 484645 |
| 50 | 14 | 1.435 | 124.241 | −72.273 | 494846 |
| 51 | 6 | 1.537 | 116.973 | 35.644 | 504948 |
| 52 | 6 | 1.554 | 104.414 | 152.955 | 504948 |
| 53 | 6 | 1.544 | 111.789 | −93.126 | 504948 |
| 54 | 6 | 1.554 | 113.215 | 55.963 | 484645 |
| 55 | 6 | 1.544 | 111.592 | −170.002 | 544846 |
| 56 | 8 | 1.425 | 108.120 | 65.545 | 544846 |
| 57 | 6 | 1.418 | 116.744 | 179.265 | 565448 |
| 58 | 6 | 1.547 | 104.807 | −52.991 | 544846 |

(4″-OSi($CH_3$)$_3$). *Anal.* Calcd for $C_{45}H_{87}NO_{13}Si_2$: C, 59.63; H, 9.68; N, 1.55. Found: C, 59.94; H, 9.68; N, 1.42.

***O*-Methylation of 4** The *O*-methylation of **4** (1.76 g, 2 mmol) with iodomethane (433 mg, 3.1 mmol) and 85% KOH (170 mg, 2.6 mmol) was carried out according to the procedure described in the case of **3**. The resulting crude product was purified by silica gel column chromatography ($Me_2CO$–hexane–$Et_3N$, 1:10:0.1) to give 1.58 g (88%) of 6-*O*-methyl-2′,4″-*O*-bis(trimethylsilyl)erythromycin B (**7**), which was crystallized from $Me_2CO$–water. mp 184—186 °C. FAB-MS *m/z*: 876 (M+H). IR (KBr): 3522 (OH), 1730 (lactone C=O), 1699 (ketone C=O) $cm^{-1}$. $[\alpha]_D^{24}$: −88.0° ($c$=0.35, $CHCl_3$). $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 3.31 (3H, s, 3″-$OCH_3$), 3.09 (3H, s, 6-$OCH_3$), 2.22 (6H, br s, $N(CH_3)_2$), 0.15 (9H, s, 4″-OSi($CH_3$)$_3$), 0.10 (9H, s, 2′-OSi($CH_3$)$_3$). $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$: 219.5 (C-9), 176.4 (C-1), 50.8 (6-$OCH_3$), 49.7 (3″-$OCH_3$), 41.0 ($N(CH_3)_2$), 1.05 (2′-OSi($CH_3$)$_3$), 0.87 (4″-OSi($CH_3$)$_3$). *Anal.* Calcd for $C_{44}H_{85}NO_{12}Si_2$: C, 60.31; H, 9.78; N, 1.60. Found: C, 60.22; H, 9.72; N, 1.49.

**Method** A model builder program MOLDA5,[8] was used to generate the initial coordinates of the erythromycin derivatives, which were constructed on the basis of X-ray results on 6-methoxy-EM-A.

Energy minimizations were performed using the molecular mechanics program MM2′ and the semi-empirical molecular orbital method called modified neglect of diatomic overlap (MNDO). The frontier electron densities of the LUMO and total energy were calculated using MNDO.

**Acknowledgement** We wish to thank Dr. E. Osawa in Hokkaido University for helpful discussions.

**References and Notes**

1) A part of this work was presented at the 109th Annual Meeting of the Pharmaceutical Society of Japan, Nagoya, April 1989.
2) H. Sakakibara and S. Ōmura, "Macrolide Antibiotics," Academic Press, Orlando, 1984, p. 85.
3) S. Morimoto, Y. Takahashi, Y. Watanabe and S. Ōmura, *J. Antibiot.*, **37**, 187 (1984).
4) S. Morimoto, Y. Misawa, T. Adachi, T. Nagate, Y. Watanabe and S. Omura, *J. Antibiot.*, **43**, 286 (1990).
5) S. Morimoto, T. Adachi, Y. Misawa, Y. Watanabe and S. Omura, *J. Antibiot.*, in press.
6) D. R. Harris, S. G. Mcgeachin and H. H. Mills, *Tetrahedron Lett.* **11**, 679 (1965).
7) H. Iwasaki, Y. Sugawara, T. Adachi, S. Morimoto and Y. Watanabe, submitted for publication in *Acta Cryst.*
8) MOLDA & GRIMM ver. 5.1, Science House Co., Tokyo, 1988.