COMMUNICATIONS TO THE EDITOR

Absolute Configuration of Migrastatin, a Novel 14-Membered Ring Macrolide

Sir:

Migrastatin (**1**), a novel 14-membered ring macrolide, was isolated from a culture broth of *Streptomyces* sp. MK929-43F1.[1] It inhibits both anchorage-independent growth and migration of human tumor cells.[2]

Previously, we reported the planar structure and geometry of the three olefins in the 14-membered ring of **1**.[3] In this communication, we describe the absolute structure of **1** determined by X-ray crystallographic analysis as shown in Fig. 1.

Treatment of **1** (28.9mg) with *p*-bromophenacyl bromide (56.0 mg) and K_2CO_3 (9.0 mg) in DMF (1 ml) for 40 hours at room temperature gave crude *N*-phenacylated migrastatin. Pure *N*-*p*-bromophenacylmigrastatin (**2**, 7.2 mg) was obtained, after purification on preparative SiO_2 TLC twice with toluene - acetone (2 : 1, Rf 0.71) and then hexane - ethyl acetate (1 : 1, Rf 0.20). Crystalline plates of **2** were obtained from MeOH - H_2O. Physico-chemical properties: mp 134~137°C; $[\alpha]_D^{20}$ +9.9° (*c* 0.48, MeOH); FAB-MS *m/z* 686 and 688 (MH^+); IR (KBr, cm^{-1}) 1707, 1682; ^1H NMR (500 MHz, $CDCl_3$) δ 0.97 (3H, d, *J*=7.0 Hz, 22-H), 1.13 (3H, d, *J*=7.0 Hz, 24-H), 1.87 (3H, d, *J*=1.5 Hz, 23-H), 2.53 (2H, t, *J*=7.0 Hz, 16-H), 3.31 (3H, s, 27-H), 2.79 (1H, s, 9-OH), 5.10 (1H, d, *J*=10.0 Hz, 13-H), 5.16 (2H, s, 28-H), 7.64 (2H, m, 32-H and 34-H), 7.82 (2H, m, 31-H and 35-H).

The X-ray crystallographic study of **2** was carried out as described below.

A colorless plate crystal of **2** ($C_{35}H_{44}NO_8Br$) having approximate dimensions of 0.20×0.08×0.03 mm was mounted in a loop. All measurements were made on a Rigaku RAXIS-RAPID Imaging Plate diffractometer with graphite monochromated Mo-Kα radiation at −150°C. The crystal data of **2** are shown in Table 1. Of the 11552 reflections which were collected, 4179 were unique (R_{int}=0.112); equivalent reflections were merged. The linear absorption coefficient, μ, for Mo-Kα radiation is 12.3 cm^{-1}. A symmetry-related absorption correction using the program ABSCOR[4] was applied which resulted in transmission factors ranging from 0.75 to 0.96. The data were corrected for Lorentz and polarization effects. The structure was solved by direct methods[5] and expanded using Fourier techiniques.[6] The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement[7] was based on 4161 observed reflections ($I>3.00\sigma(I)$, $2\theta<54.77$) and 407 variable parameters and converged with unweighted and weighted agreement factors of R=0.146, Rw=0.268 and R1=0.086 (for $I>2.0\sigma(I)$ data). The maximum and minimum peaks on the final difference Fourier map corresponded to 0.63 and $-0.77e^-/Å^3$, respectively. The absolute configuration of the molecule was determined based on Flack's parameter, 0.044(32), and confirmed by the method of Bijvoet

Fig. 1. Structure of migrastatin (**1**) and *N*-*p*-bromophenacylmigrastatin (**2**).

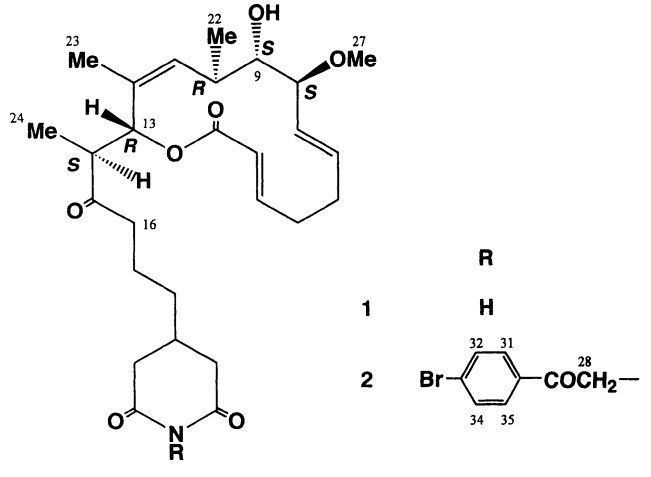


Table 1. Crystal data of **2**.

Formula	$C_{35}H_{44}NO_8Br$
Formula weight	686.64
Crystal system	monoclinic
Cell constants	
a	10.696(3)Å
b	5.773(2) Å
c	28.357(8) Å
β	96.430(4)°
V	1739.9(8) Å^3
Space group	$P2_1$
Z	2
D_{calc}	1.31 g/cm^3
μ (MoKα)	12.3cm^{-1}

Fig. 2. Molecular structure of **2**.

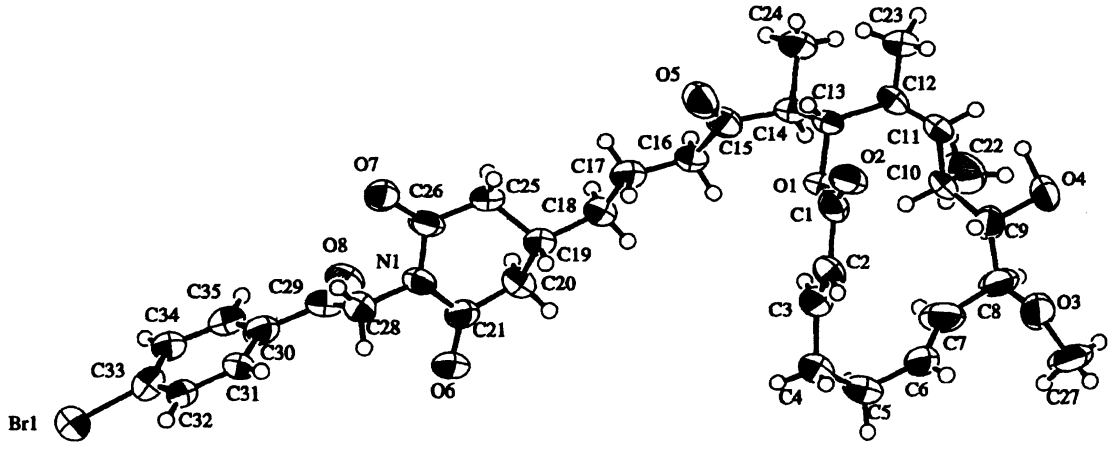
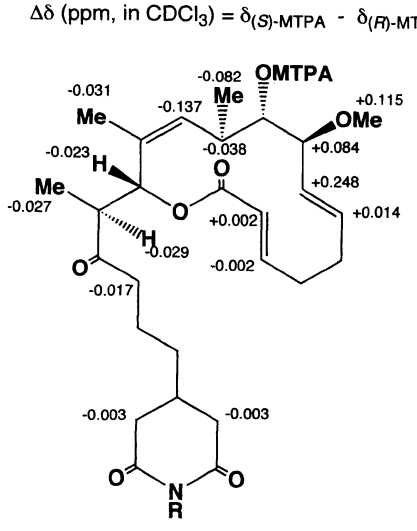


Fig. 3. Result of modified Mosher's method.



inequality relationships. Comparing $|Fo(hkl)|/|Fo(\bar{h}\bar{k}\bar{l})|$ and $|Fc(hkl)|/|Fc(\bar{h}\bar{k}\bar{l})|$ for 172 Friedel pairs for which the differences $||Fc(hkl)|-|Fc(\bar{h}\bar{k}\bar{l})||/\sqrt{\sigma F_0(hkl))^2+\sigma(F_0(\bar{h}\bar{k}\bar{l}))^2}$ are greater than 1.0, 159 pairs showed consistently the absolute configuration in Fig. 2. All calculations were performed using the teXsan[8] crystallographic software package of Molecular Structure Corporation.

Results of modified Mosher's method[9] were also in agreement with the absolute stereochemistry elucidated by the X-ray crystallographic analysis as shown in Fig. 3.

Consequently, four asymmetric centers in the lactone ring and one in the side chain of migrastatin (**1**) were determined to be 8*S*, 9*S*, 10*R*, 13*R* and 14*S*, respectively. Among them, stereochemistries of C8, 10 and 13 are consistent with a configurational model for macrolide antibiotics proposed by CELMER.[10]

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