On the structure, chemistry, and ^{13}C nuclear magnetic resonance of ravidomycin

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Full spectral details in support of the earlier proposed structure **1***a* for the antitumor antibiotic ravidomycin are presented together with an account of chemical degradation products. A complete corroboration of structure is provided by cross correlation of ^{1}H and ^{13}C nmr for ravidomycin and its diacetate **1***b*.

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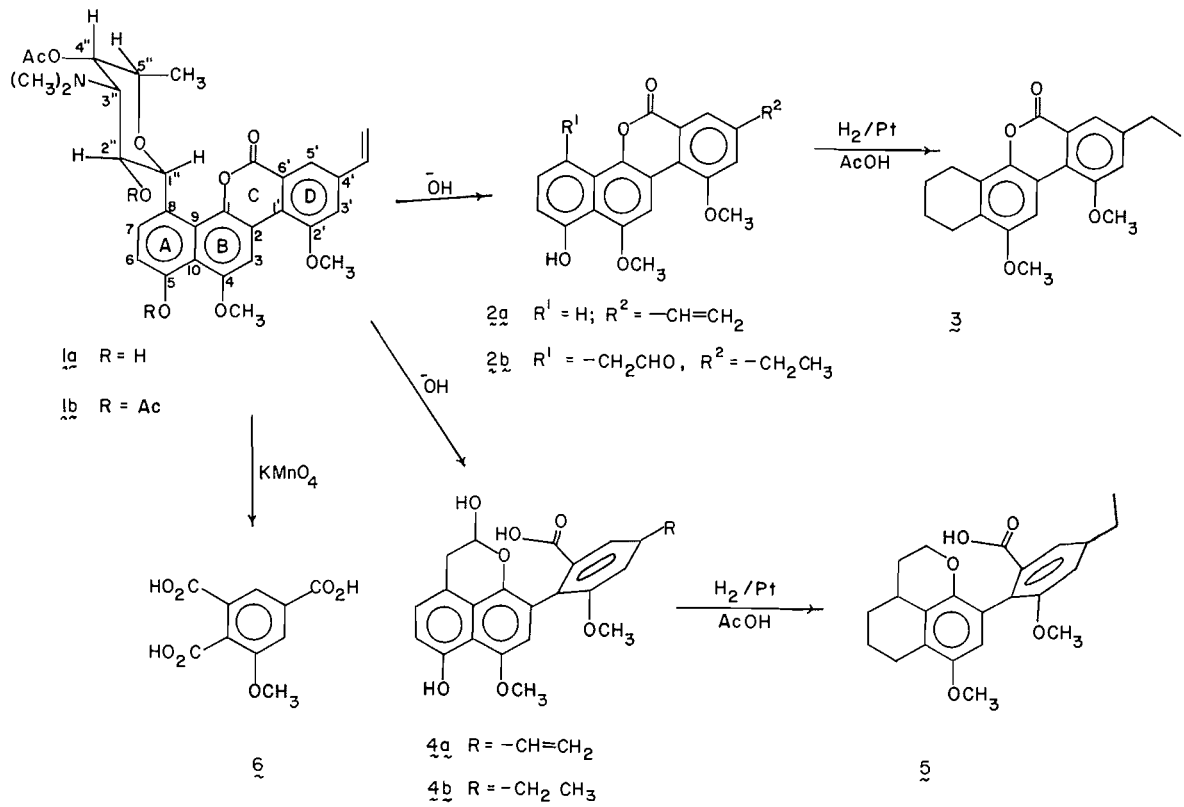
On présente toutes les données spectrales qui confirment la structure **1***a* proposé pour la ravidomycine l'antibiotique antituméreux, ainsi qu'une analyse des produits de dégradation. On obtient une corroboration complète de structure grâce à une corrélation croisée de la rmn du ^{1}H et du ^{13}C de la ravidomycine et de son diacétate **1***b*.

[Traduit par le journal]

In a recent preliminary report (1) we proposed structure **1***a* for ravidomycin, an antitumor antibiotic isolated (2) from the fermentation broth of *Streptomyces ravidus*. This proposal was based on analysis of ^{1}H nmr, infrared, and ultraviolet spectral data on **1***a*, its diacetate **1***b*, the alkali fusion derived aglycone **2***a* and tranformation products **3**, **4***a*, **4***b*, and **5**. We now provide full spectral characteristics for the latter together with appropriate mechanistic rationale for their formation. In addition, a detailed corroboration of structure is forthcoming from cross correlation of the ^{1}H and ^{13}C nmr spectra of ravidomycin **1***a* and ravidomycin diacetate **1***b*.

In our structural elucidation of ravidomycin the key chemical degradative products were the aglycone **2***a* and the optically inactive diastereomeric mixture (1 : 1) of hemiacetal carboxylic acids **4***a* which were obtained in 13% and 45% yield, respectively, from alkaline fusion of **1***a* in 50% KOH at reflux temperature for 6 h. Since our conclusions about the structures of these compounds led directly to the placement of the relative positions of the *C*-glycosidic moiety and the lactone ring ether oxygen on the phenyl naphthalene skeleton it is appropriate to account for their generation. Scheme I portrays a mechanistic proposal to rationalize the formation of aglycone **2***a* via a



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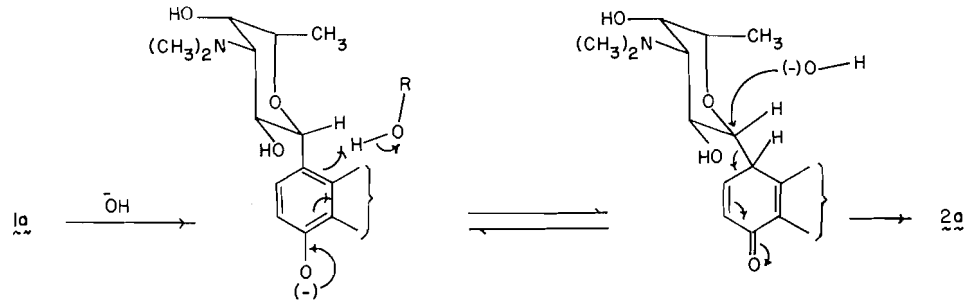
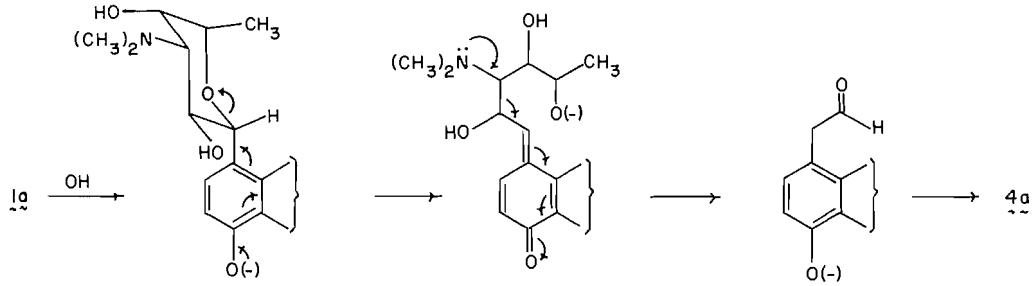


SCHEME 1



SCHEME 2

reverse electrophilic aromatic substitution in which the phenol is dealkylated at the *para* position via a quinonoid sigma complex. A possible mode of generation of the masked aldehyde **4***a* is portrayed in Scheme 2 in which the essential cleavage of the *C*-glycoside ether bond is accomplished by base catalysed generation of quinone methine **7** and followed by the rupture of the vinylogous β-aminoketone to provide the free aldehyde group which interacts with the B ring phenolate to produce the diastereomeric hemiacetals **4***a*.

The dihydro derivatives **4***b* were obtained from **4***a* in quantitative yield by catalytic (PtO) hydrogenation in ethanol and this mixture was transformed in 50% yield to the achiral isomeric lactone aldehyde **2***b* by heating in quinoline at 180°C in the presence of copper powder. The ir spectrum (KBr) of the latter gave no evidence of a carboxyl group but a strong absorption centred at 1710 cm^{-1} due to the conjugated lactone and aldehyde, while the ^1H nmr spectrum ($CDCl_3$) displayed the aldehyde proton as a singlet at δ 10.17 ppm.

It may be noted that the ready oxidative degradation of ravidomycin **1***a* to the known (5) anisole 2,3,5-tricarboxylic acid **6**, which affords corroboration of the juxtaposition of groups in ring D, is paralleled in the behaviour towards alkaline permanganate of the structurally related *C*-glycoside toromycin (3) which possesses the same aglycone as **1***a* but is devoid of nitrogen in its sugar moiety.

Complete corroborative evidence for the formulation of ravidomycin and its diacetate as in **1***a* and **1***b* is now available from our complementary ^{13}C nmr spectral analyses. The results are summarized in Table 1. To obtain these data, the following experiments were carried out. Broad band decoupled and off-resonance decoupled $^{13}C-\{^1H\}$ spectra were recorded to yield carbon chemical shifts and cross-correlations between proton-bearing carbons and their respective hydrogen atoms. The assignment of quaternary carbon signals was deduced from a series of single frequency selective (low power) $^{13}C-\{^1H\}$ double resonance experiments (correlating the quaternary carbon multiplets with individual protons in terms of long-range carbon–proton coupling constants), observed acetylation shifts, and the substantial differences in the $^{13}C-\{^1H\}$ (non-selective) nOe values of signals due to quaternary carbon atoms with and without proton(s) in *ortho* position (high and reduced nOe, respectively). Distinction between two-bond and three-bond coupling interactions (geminal vs. vicinal carbon–proton couplings) was usually based on the magnitude of the observed splittings (typical values: ^2J = 1 to 2 Hz and ^3J = 7 to 10 Hz). For couplings with 3 to 4.5 Hz moduli, the nature of the interaction was inferred either from SPT (selective population transfer) measurements (by selective inversion of one of the components of the pertinent proton satellites) affording the sign of the pertinent long-range coupling, or from the occurrence or absence of a selective $^{13}C-\{^1H\}$ nOe during selective proton decoupling experiments (the former case being characteristic of geminal coupling).

The formulation of the polycyclic backbone rests on the following evidence.

Single frequency selective $^{13}C-\{^1H\}$ decoupling experiments disclosed that the doublet splitting of the carbonyl carbon resonance of **1***b* at 160.3 ppm arises from three-bond coupling to H5′ (+4.2 Hz) and the *only* coupling exhibited by the quaternary carbon atom bearing the lactone oxygen (C1) was due to its three-bond spin–spin interaction (8.6 Hz) with H3. Selective decoupling experiments, furthermore, showed that C1′ was vicinally coupled to H5′, H3′, and H3. These findings, combined with other pertinent carbon-13 data (see Table 1), confirm that the arrangement of rings A, B, C, and D of the aglycone (as well as their respective patterns of substitution) must be as in formula **1***b*.

Low power selective irradiation of C4-OMe protons caused the C4 multiplet to collapse into a doublet due to the two-bond interaction with H3 (−4.5 Hz). This indicated the absence of vicinal interaction with ring A protons. Since the same conclusion has been reached for C1 (*vide supra*), both *peri* positions of ring A (i.e. C5 and C8) must be substituted.

Selective irradiation of the lower field *ortho*-coupled proton resonance (7.98 ppm, H-7 in **1***b*) caused the 8.4 Hz coupling of the signal at 125.16 ppm (C-9) to collapse, which showed the

TABLE 1. ^{13}C nuclear magnetic resonance data of ravidomycin **1***a* and its diacetate **1***b*[a]

Carbon	Chemical shift **1***a*	Chemical shift **1***b*	Multiplicity[b]	^nJ(C,H) Coupling constants[c]
C1	142.60	142.16	S,d	^3J(H3) = 8.6
C2	113.79	114.71	S,d	^2J(H3) = 1.6
C3	101.78	104.86	D,s	^1J(H3) = 164.55
C4	151.68	151.34	S,d,q	^2J(H3) = −4.5; ^3J(OCH$_3$) = 4.4
C5	154.67	146.64	S,d,d	^2J(H6) = −4.6; ^3J(H7) = 10.1
C6	112.24	121.25	D,s	^1J(H6) = 164.4
C7	129.48	127.85	D,d	^1J(H7) = 162.3; ^3J(H1″) = 4.1
C8	125.00	132.53	S,d,d,d	^2J(H7) = 2.1; ^3J(H6) = 4.8; ^3J(H2″) = 6.9
C9	125.14[e]	125.16[e]	S,d,d	^3J(H1″) = 1.7; ^3J(H7) = 8.4
C10	116.00[e]	120.89[e]	S,d,d	^3J(H3) = 6.2; ^3J(H6) = 5.7
C1′	123.10[e]	123.65[e]	S,d,d,d	^3J(H3) = 6.1; ^3J(H5′) = 6.2; ^3J(H3′) = 3.7
C2′	156.95	157.62	S,d,q	^2J(H3′) = −4.5; ^3J(OCH$_3$) = 4.4
C3′	113.72	114.38	D,d,d	^1J(H3′) = 156.8; ^3J(H5′) = 7.2; ^3J(=CH) = 4.9
C4′	138.49	139.14	S,d,d,d,d,d[d]	
C5′	119.46	120.17	D,d,d	^1J(H5′) = 166.14; ^3J(H3′) = 6.4; ^3J(=CH) = 4.9
C6′	122.00	122.79	S,s	
CO (lactone)	160.55	160.31	S,d	^3J(H5′) = +4.2
CH=	135.20	135.32	D,d,d,d	^1J(H) = 155.8; ^2J(H*cis*) = −2.5; ^3J(H3′) = 4.9; ^3J(H5′) = 4.9
=CH$_2$	116.28	116.71	T,s	^1J(H) = 158.01
C5-O*C*OCH$_3$	—	169.62	S,q,d	^2J(CH$_3$) = 7.4; ^4J(H6) = 0.8
C5-OCO*CH*$_3$	—	20.73	Q	
C4-OCH$_3$	55.87[f]	56.35[f]	Q	
C2′-OCH$_3$	55.80[f]	56.26[f]	Q	
C1″	80.48	78.60	D	
C2″	69.55	71.44	D	
C3″	65.35	67.30	D	
C4″	69.37	69.58	D	
C5″	74.97	75.47	D	
C6″	16.76	16.71	Q	
N(CH$_3$)	40.77	41.74	Q	
C2″-O*C*OCH$_3$	—	169.56	S,q,d	^2J(CH$_3$) = 6.8; ^3J(H2″) = 4.2
C2″-OCO*CH*$_3$	—	20.90	Q	
C4″-O*C*OCH$_3$	170.80	170.80	S,q,d	^2J(CH$_3$) = 7.2; ^3J(H4″) = 3.8
C4″-OCO*CH*$_3$	21.58	21.57	Q	

[a]Chemical shifts are in delta ppm relative to internal TMS, $CDCl_3$.
[b]Capital letters refer to multiplicity resulting from directly bonded protons and small letters to long range ^{13}C, ^1H couplings.
[c]Coupling constants (±0.2 Hz) were obtained from first-order treatment of the SFSD and undecoupled spectra run at 50.32 MHz. Four-bond and two-bond couplings with nearly zero moduli are not reported.
[d]Multiplet pattern not analyzed.
[e]Resonance with highly reduced nOe indicating the absence of α-CH proton(s).
[f]Assignments may be interchanged.

existence of a three-bond interaction between these nuclei. The lack of appreciable acetylation shift, on the other hand, indicated a *meta* relationship between this (low nOe) carbon and the C5-OAc (OH) substituent. Further selective decoupling experiments involving ring A and B protons revealed that the multiplet at 116.0 (ravidomycin) or 120.89 (diacetate) was due to the (low nOe) quaternary carbon atom (C10) which was vicinally coupled to H3 *and* the higher field (H6) ring A proton (7.22 ppm in **1***b*). The observed +5 ppm acetylation shift attested to the *ortho* relationship between the C10 carbon atom and the OAc (OH) function.

The ^{13}C chemical shift assignments for the ravidomycin nucleus are in close agreement with those of Takashima *et al.* (4) for the structurally related antitumor antibiotic gilvogarcin which possesses the same aglycone linked to a furanose moiety. In view of this the assignment of ^{13}C signals in the published inventory of chemical shifts for carbon atoms in the toromycin (3) aglycone is facilitated.

Experimental

All melting points were determined on a Kofler hot stage apparatus and are uncorrected.

High resolution mass spectra were recorded on an AE1 MS-50 spectrometer at the Mass Spectrometry Lab., University of Alberta. Low resolution mass spectra were recorded on an Hitachi Perkin–Elmer RMU-6D spectrometer. The infrared spectra were measured on a Perkin–Elmer 727B or 598 infrared spectrophotometer and ultraviolet spectra were obtained with a Beckman 25 instrument.

The ^1H spectra of compounds **2***a* to **6** inclusive were determined on a Nicolet NIC-360 spectrometer at Toronto Biomedical NMR Centre while ^1H and ^{13}C spectra of ravidomycin **1***a* and ravidomycin diacetate **1***b* were recorded on a disk-augmented Varian XL-100/15FT instrument. Proton-coupled and single frequency (low-power) selective ^{13}C–{^1H} double resonance spectra were run at 50.32–{200.13} MHz using a Bruker WP 200/SY spectrometer. The amplitude of the decoupling field in the SFSD experiments varied from 2.5 to 10 Hz and the decoupler power employed in selective population transfer measurements runs for relative sign determination was usually set to 2 Hz.

Purification of ravidomycin **1**a

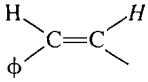
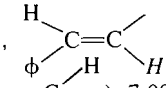
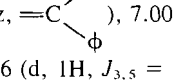
The ravidomycin (1.1 g), supplied by Ayerst Research Laboratories, was dissolved in chloroform (10 mL) and applied to the top of a dry column of silica gel G (polyethylene pellicle column 2.6 × 46 cm), which was developed with choroform/methanol (8:1). As soon as the solvent reached the bottom of the column, the main yellow band was cut out of the column and eluted with chloroform/methanol (5:1) immediately . The eluate was concentrated and the residue was crystallized from ethyl acetate. Fine needles were obtained, mp 248–250°C; $[\alpha]_D$ −105.5° (*c* 0.20, $CHCl_3$); ir (KBr) ν_{max}: 3380 (OH), 1740, 1240 (acetate), 1720 (lactone), 1620, 1600, 1580 (aromatic ring) cm^{-1}; uv (MeOH)λ_{max} nm (log ϵ): 244 (4.68), 263 (4.54, sh), 277 (4.60), 285 (4.65), 308 (4.33), 320 (4.30), 335 (4.20), 350 (4.08), 392 (4.24); uv ($CHCl_3$) λ_{max} nm: 246, 265, 278, 288, 308, 322, 334, 350, 395; ms *m/e*: 563.2148 (52.09%, calcd. for $C_{31}H_{33}NO_9$: 563.2155, M^+); cd (*c* = 0.0081, $CHCl_3$) $[\theta]^{26}$ nm: −2659 (245), −1095 (264), −1877 (275), −2502 (288), −1870 (300), −1877 (310), −1880 (320), −1408 (330), −1410 (340), −1870 (400).

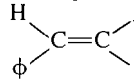
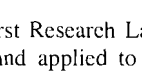
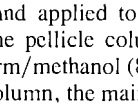
Ravidomycin acetate **1**b

Ravidomycin (20 mg) was acetylated in pyridine (1.5 mL) and acetic anhydride (1.5 mL) at room temperature for 2 days, affording its diacetate **1***b* in quantitative yield, a colloidal solid from dichloromethane/methanol, mp 238–239°C; $[\alpha]_D^{26}$ + 33.3° (*c* 0.072, $CHCl_3$); ir ($CHCl_3$) ν_{max}: 1740 (acetyl), 1725 (lactone), 1610, 1590 (aromatic ring) cm^{-1}, no hydroxyl; uv (MeOH) λ_{max} nm (log ϵ): 245 (4.50), 278 (4.48), 285 (4.51), 306 (4.17, sh), 323 (4.08), 335 (4.06), 346 (4.01, sh), 383 (4.13); ms *m/e*: 647.2361 (3.77%, calcd. for $C_{35}H_{37}NO_{11}$: 647.2367, M^+).

Aglycone **2**a *and hemiacetals* **4**a

Ravidomycin (0.5 g) in 50% potassium hydroxide (8 mL) was refluxed for 6 h under nitrogen. The reaction mixture was acidified with concentrated hydrochloric acid in an ice bath, and provided the yellow products which were chromatographed on a silica gel column eluting with chloroform, then chloroform/methanol (20:1). The early fractions eluted by chloroform gave the aglycone **2***a* (40 mg), yellow needles from chloroform/methanol, mp 265–266°C $[\alpha]_D^{20}$ 0° (*c* 0.50, $CHCl_3$). The middle fraction eluted by chloroform/methanol (20:1) yielded the yellow granular crystals (160 mg) **4***a*, mp 227–230°C after recrystallization with chloroform/methanol; $[\alpha]_D^{20}$ 0° (*c* 1.00, $CHCl_3$). The ^1H nmr spectrum indicates a mixture (1:1) of diastereomers.

Aglycone **2***a*: ir (KBr) ν_{max}: 3350 (br, OH), 1720 (lactone), 1625, 1600, 1580 (aromatic ring) cm^{-1}; uv (MeOH) λ_{max} nm (log ϵ): 243 (4.66), 263 (4.50), 273 (4.55), 283 (4.54), 307 (4.26), 386 (4.21); ^1H nmr ($CDCl_3/CD_3OD$) δ_{TMS}: 3.51 (br, 1H, OH), 4.12 (s, 6H, OCH_3 × 2), 5.47 (d, 1H, J_{cis} = 11.0 Hz, ), 5.96 (d, 1H, J_{trans} = 17.4 Hz, ), 6.81 (dd, 1H, J_{cis} = 11.0 Hz, J_{trans} = 17.4 Hz, ), 7.00 (dd, 1H, $J_{6,7}$ = 8.0 Hz, $J_{6,8}$ = 0.8 Hz, H-6), 7.36 (d, 1H, $J_{3,5}$ = 1.6 Hz, H-3′), 7.50 (dd, $J_{6,7}$ = 8.0 Hz, $J_{7,8}$ = 8.0 Hz, H-7), 8.04 (dd, 1H, $J_{7,8}$ = 8.0 Hz, $J_{6,8}$ = 0.8 Hz, H-8), 8.10 (d, 1H, $J_{3',5'}$ = 1.6 Hz, H-5′), 8.31 (s, 1H, H-3); ms *m/e*: 348.0997 (100.00%, calcd. for $C_{21}H_{16}O_5$: 348.0998, M^+).

Hemiacetals **4***a*: ir (KBr) ν_{max}: 3600–2500, 1700 (OH, COOH), 1620, 1600, 1570 (aromatic ring) cm^{-1}; uv (MeOH) λ_{max} nm (log ϵ): 228 (4.76), 260 (4.38), 308 (4.07), 336 (4.01), 353 (4.11); ^1H nmr ($CDCl_3/CD_3OD$) δ_{TMS}: 2.82 (br, 3H, COOH, OH × 2), 3.00–3.30 (m, 2H, Ar-CH_2), 3.80, 3.79 (s, each 1.5 H, OCH_3-2′), 4.01 (s, 3H, OCH_3-4), 5.38 (dd, 0.5 H, *J* = 3.0/7.2 Hz, axial hemiacetal proton), 5.67 (dd, 0.5 H, *J* = 3.0/3.0 Hz, equatorial hemiacetal proton), 5.37 (d, 1H, J_{cis} = 11.0 Hz, ), 5.86 (d, 1H, J_{trans} = 17.7 Hz, ), 6.77, 6.76 (dd, each 0.5 H, J_{trans} = 17.7 Hz, J_{cis} = 11.0 Hz, ), 6.73, 6.69 (s, each 0.5 H, H-3), 6.82 and 6.83, 7.08 and 7.10 (two pair of AB, each 0.5 H, $J_{6,7}$ = 8.0 Hz, H-7, H-6), 7.18, 7.19 (d, each 0.5 H, $J_{3',5'}$ = 1.5 Hz, H-3′), 7.51, 7.55 (d, each 0.5 H, $J_{3',5'}$ = 1.5 Hz, H-5′); ms *m/e*: 408.1205 (10.0%, calcd. for $C_{23}H_{20}O_7$: 408.1209, M^+).

Compound **3**

The aglyone **2***a* (5 mg) in acetic acid (20 mL) was hydrogenated in the presence of platinum oxide (20 mg) at 70–75°C for 4 h, giving colorless needles (3 mg) which were crystallized from methanol, mp 190–192°C; ir (KBr) ν_{max}: 1710 (lactone), 1610, 1585 (aromatic ring) cm^{-1}, no hydroxyl; uv (MeOH) λ_{max} nm (log ϵ): 212 (4.58, sh), 221 (4.61, sh), 232 (4.69, sh), 238 (4.70), 262 (4.29, infl), 274 (4.29), 350 (4.16); ^1H nmr ($CDCl_3$) δ_{TMS}: 1.30 (t, 3H, *J* = 7.6 Hz, CH_2CH_3), 2.78 (q, 2H, *J* = 7.6 Hz, CH_2CH_3), 1.82 (m, 4H, —CH_2—CH_2—), 2.73, 2.96 (m, each 2H, Ar-CH_2 × 2), 3.90 (s, 3H, OCH_3-4), 4.07 (s, 3H, OCH_3-2′), 7.16 (d, $J_{3',5'}$ = 1.5 Hz, H-3′), 7.95 (d, $J_{3',5'}$ = 1.5 Hz, H-5′), 8.30 (s, 1H, H-3); ms *m/e*: 338.1512 (100.00%, calcd. for $C_{21}H_{22}O_4$: 338.1518, M^+).

Compound **5**

The mixture of hemiacetals **4***a* (5 mg) was hydrogenated by the above-mentioned method and the reaction product was separated on tlc (solvent system: chloroform/methanol 30:1). The main product **5** was crystallized from methanol, plates (2 mg), mp 224–226°C; ir (KBr) ν_{max}: 3600–2500, 1690, 1670 (COOH), 1600 (aromatic ring) cm^{-1}; uv (MeOH) λ_{max} nm (log ϵ): 209 (4.60), 300 (3.78); ^1H nmr ($CDCl_3/CD_3OD$) δ_{TMS}: 1.29 (t, 3H, *J* = 7.5 Hz, CH_2CH_3), 2.70 (q, 2H, *J* = 7.5 Hz, CH_2CH_3), 1.60–2.05 (m, 7H, aliphatic CH_2 × 3 and COOH, covered), 2.50–2.90 (m, 3H, Ar-CH × 3), 3.73 (s, 3H, OCH_3-4), 3.76, 3.77 (s, each 1.5 H, OCH_3-2′), 4.05 (m, 1H, axial α-hydropyran proton), 4.24 (m, 1H, equatorial α-hydropyran proton), 6.55, 6.57 (s, each 0.5 H, H-3), 6.94 (d, 1H, $J_{3',5'}$ = 1.4 Hz, H-3′), 7.27 (d, $J_{3',5'}$ = 1.4, H-5′); ms *m/e*: 382.1780 (100.00%, calcd. for $C_{23}H_{26}O_5$: 382.1780, M^+).

4-Carboxyl-6-methoxyphthalic acid **6**

Ravidomycin (100 mg) in 1% potassium hydroxide (15 mL) was oxidized with an aqueous solution of potassium permanganate under stirring and refluxing until persistence of the pink color for half an hour. After filtration of the manganese dioxide the solution was concentrated in vacuum and then acidified with concentrated hydrochloric acid to pH 1 and extracted by ethyl acetate. The evaporated extract was chromatographed on silica gel with chloroform/methanol/acetic acid (6:1:1). The early fraction yielded 4-carboxyl-6-methoxylphthalic acid (25 mg), plates from dilute hydrochloric acid, mp 240–241°C, which were identical in ir spectra and mixture melting point with the authentic sample of **6** synthesized according to a known procedure (5). The acid was methylated in methanol with diazomethane, giving trimethyl ester, plates from chloroform/methanol, mp 145°C.

4-Carboxyl-6-methoxylphthalic acid: ir (KBr) ν_{max}: 3500–2500, 1700 (COOH), 1600, 1575 (aromatic ring) cm^{-1}; ^2H nmr (unisol) δ_{TMS}: 4.00 (s, 3H, OCH_3), 7.90 (d, 1H, *J* = 1.0 Hz, H-5), 8.25 (d, 1H, *J* = 1.0 Hz, H-3); ms *m/e*: 222 (M − H_2O), 194 (M − H_2O − CO), 164 (M-COOH-OCH_3).

Trimethyl ester: ir (KBr) ν_{max}: 1740, 1730, 1720 (—$COOCH_3$), 1600, 1580 (aromatic ring) cm^{-1}, no carboxyl; ^1H nmr ($CDCl_3$) δ_{TMS}: 3.97, 4.00 (s, each 6H, OCH_3, $COOCH_3$ × 3), 7.83 (d, 1H, *J* = 1.0 Hz, H-5), 8.30 (s, 1H, *J* = 1.0 Hz, H-3); ms *m/e*: 282 (M^+), 251 (M-OCH_3), 223 (M-$COOCH_3$), 192 (M-$COOCH_3$-OCH_3), 165.

Compound **4**b

The diastereomer mixture **4***a* (50 mg) in ethanol (10 mL) was hy-

drogenated in the presence of platinum oxide (20 mg) at room temperature, affording dihydro derivative **4***b* (45 mg), which was crystallized as yellow plates from methanol, mp 220–222°C; ir (KBr) ν_{max}: 3540 (OH), 3500–2400, 1690 (COOH), 1615, 1595 (aromatic ring) cm^{-1}; uv (MeOH) λ_{max} nm (log ϵ): 227 (4.63), 248 (sh, 4.22), 288–300 (plateau, 3.82), 317 (3.86), 336 (3.90), 351 (3.97); ^1H nmr ($CDCl_3/CD_3OD$) δ_{TMS}: 1.32, 1.33 (t, each 1.5 H, J = 7.5 Hz, —CH_2—CH_3), 2.74, 2.75 (q, each 1H, J = 7.5 Hz, —CH_2CH_3), 3.00–3.30 (m, 2H, Ar-CH_2), 3.76, 3.77 (s, each 1.5 H, OCH_3-2′), 4.00, 4.01 (s, each 1.5 H, OCH_3-4), 5.37 (dd, 0.5 H, J = 7.4/3.0 Hz, axial hemiacetal proton), 5.64 (dd, 0.5 H, J = 3.0/3.0 Hz, equatorial hemiacetal proton), 6.69, 6.73 (s, each 0.5 H, H-3), 6.80 and 6.81, 7.07 and 7.09 (two pair of AB, each 0.5 H, J = 7.9 Hz, H-7, H-6), 7.00, 7.01 (d, each 0.5 H, J = 1.4 Hz, H-3′), 7.31, 7.34 (d, each 0.5 H, J = 1.4 Hz, H-5′); ms m/e: 410.1367 (72.22%, calcd. for $C_{23}H_{22}O_7$: 410.1365, M^+).

Aldehyde lactone **2**b

The dihydro derivative **4***b* (100 mg) in quinoline (2 mL, freshly distilled) was heated at 180°C for 10 min in the presence of copper powder (250 mg) with stirring. After removal of copper powder, the reaction solution was mixed with ether (15 mL), then extracted with 1.5 *N* HCL and washed with water. The residue from the ethereal layer was chromatographed on a silica gel column eluting with chloroform and chloroform/methanol (20:1) in turn. The fractions eluted with chloroform/methanol gave the aldehyde lactone **2***b* (50 mg), which crystallized as yellow needles from chloroform/methanol, mp 220–222°C; ir (KBr) ν_{max}: 3300 (OH), 1715 (>C=O), 1620, 1610, 1590 (aromatic ring) cm^{-1}, no carboxyl; ^1H nmr ($CDCl_3$) δ_{TMS}: 10.17 (s, 1H, aldehyde proton), 9.73 (s, 1H, exchangeable with D_2O, OH), 8.47 (s, 1H, H-3), 7.92 (d, 1H, J = 1.5 Hz, H-5′), 7.22, 6.95 (AB, each 1H, J = 8.0 Hz, H-7, H-6), 7.19 (d, 1H, J = 1.5 Hz, H-3′), 4.50 (s, 2H, Ar-CH_2—CO—), 4.13, 4.08 (s, each 3H, OCH_3-2′, OCH_3-4), 2.80 (q, 2H, J = 7.6 Hz, CH_3—CH_2), 1.34 (t, 3H, J = 7.6 Hz, CH_3—CH_2); ms m/e: 392 (M^+), 363 (M − CHO).

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