



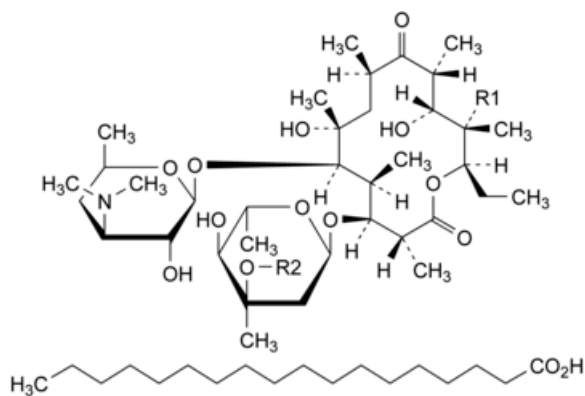
Edition: BP 2025 (Ph. Eur. 11.6 update)

Erythromycin Stearate



General Notices

(Ph. Eur. monograph 0490)



Erythromycin (stearate)	Mol. Formula	<i>M</i> _r	R1	R2
A	C ₅₅ H ₁₀₃ NO ₁₅	1018	OH	CH ₃
B	C ₅₅ H ₁₀₃ NO ₁₄	1002	H	CH ₃
C	C ₅₄ H ₁₀₁ NO ₁₅	1004	OH	H

Action and use

Macrolide antibacterial.

Preparation

[Erythromycin Stearate Tablets](#)

Ph Eur

DEFINITION

Mixture of the stearate salts of erythromycin and stearic acid.

Main component (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-4-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl- α -*L*-ribo-hexopyranosyl)oxy]-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexamethyl-6-[[3,4,6-trideoxy-3-(dimethylamino)- β -*D*-xylo-hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione octadecanoate (erythromycin A stearate).

Salt of a product obtained by fermentation using a strain of *Streptomyces erythreus*.

Content

- *sum of erythromycins A, B and C expressed as stearates*: 79.0 per cent to 102.0 per cent (anhydrous substance);
- *erythromycin B stearate*: maximum 5.0 per cent (anhydrous substance);
- *erythromycin C stearate*: maximum 5.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, soluble in acetone and in methanol.

Solutions may be opalescent.

IDENTIFICATION

Infrared absorption spectrophotometry ([2.2.24](#)).

Comparison [erythromycin stearate CRS](#).

TESTS

Free stearic acid

Maximum 14.0 per cent (anhydrous substance) of $C_{18}H_{36}O_2$.

Dissolve 0.400 g in 50 mL of [methanol R](#). Titrate with [0.1 M sodium hydroxide](#), determining the end-point potentiometrically ([2.2.20](#)). Calculate the volume of [0.1 M sodium hydroxide](#) required per gram of the substance to be examined (n_1 mL).

Dissolve 0.500 g in 30 mL of [methylene chloride R](#). If the solution is opalescent, filter and shake the residue with 3 quantities, each of 25 mL, of [methylene chloride R](#). Filter, if necessary, and rinse the filter with [methylene chloride R](#). Reduce the volume of the combined filtrate and rinsings to 30 mL by evaporation on a water-bath. Add 50 mL of [glacial acetic acid R](#) and titrate with [0.1 M perchloric acid](#), determining the end-point potentiometrically ([2.2.20](#)). Calculate the volume of [0.1 M perchloric acid](#) required per gram of the substance to be examined (n_2 mL).

Calculate the percentage content of $C_{18}H_{36}O_2$ using the following expression:

$$2.845 (n_1 - n_2) \times \frac{100}{100-h}$$

h = percentage water content.

Related substances

Liquid chromatography ([2.2.29](#)). *Prepare the solutions immediately before use.*

Solution A Dissolve 11.5 g of [dipotassium hydrogen phosphate R](#) in 900 mL of [water R](#), adjust to pH 8.0 with [dilute phosphoric acid R](#) and dilute to 1000 mL with [water R](#).

Solvent mixture [methanol R](#), solution A (40:60 V/V).

Test solution Dissolve 55.0 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture. Centrifuge and use the clear solution.

Reference solution (a) Dissolve 40.0 mg of [erythromycin A CRS](#) in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 10.0 mg of [erythromycin B CRS](#) and 10.0 mg of [erythromycin C CRS](#) in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (c) Dilute 1.0 mL of reference solution (a) to 100.0 mL with the solvent mixture.

Reference solution (d) Dissolve 4 mg of [erythromycin for system suitability CRS](#) (containing impurities A, B, C, D, E, F, H and L) in the solvent mixture and dilute to 1 mL with the solvent mixture.

Reference solution (e) Dissolve 4 mg of [erythromycin stearate for impurity S identification CRS](#) in the solvent mixture and dilute to 1 mL with the solvent mixture.

Column:

- **size:** $l = 0.25$ m, $\varnothing = 4.6$ mm;
- **stationary phase:** [end-capped polar-embedded octadecylsilyl amorphous organosilica polymer R](#) (3.5 μ m);
- **temperature:** 65 °C; preheating the mobile phase may be required, for instance by extending the inlet tubing in the oven to 30 cm.

Mobile phase:

- **mobile phase A:** [phosphate buffer solution pH 7.0 R7](#), [acetonitrile R1](#), [water for chromatography R](#) (5:35:60 V/V/V);
- **mobile phase B:** [phosphate buffer solution pH 7.0 R7](#), [water for chromatography R](#), [acetonitrile R1](#) (5:45:50 V/V/V);

Time (min)	Mobile phase A (per cent V/V)	Mobile phase B (per cent V/V)
0 - t_R	100	0
$t_R - (t_R + 2)$	100 \rightarrow 0	0 \rightarrow 100
$(t_R + 2) - (t_R + 15)$	0	100

t_R = retention time of erythromycin B, determined by injecting 10 μ L of reference solution (b) and eluting with mobile phase A

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 210 nm.

Autosampler Set at 4 °C.

Injection 100 μ L.

Identification of impurities Use the chromatogram supplied with [erythromycin for system suitability CRS](#) and the chromatogram obtained with reference solution (d) to identify the peaks due to impurities A, B, C, D, E, F and L; use the chromatogram supplied with [erythromycin stearate for impurity S identification CRS](#) and the chromatogram obtained with reference solution (e) to identify the peak due to impurity S; use the chromatogram obtained with reference solution (b) to identify the peaks due to erythromycins B and C.

Relative retention With reference to erythromycin A (retention time = about 23 min): impurity A = about 0.4; impurity B = about 0.5; erythromycin C = about 0.55; impurity L = about 0.63; impurity C = about 0.9; impurity D = about 1.61; erythromycin B = about 1.75; impurity F = about 1.81; impurity S = about 2.1; impurity E = about 2.3.

System suitability Reference solution (d):

- **resolution:** minimum 1.2 between the peaks due to impurity B and erythromycin C;
- **peak-to-valley ratio:** minimum 1.5, where H_p = height above the baseline of the peak due to impurity F and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to erythromycin B; minimum 2.0, where H_p = height above the baseline of the peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to erythromycin A. If necessary, adjust the concentration of [acetonitrile R1](#) in the mobile phases and/or the gradient to obtain the required separation.

Calculation of percentage contents:

- **correction factors:** multiply the peak areas of the following impurities by the corresponding correction factor: impurity D = 2; impurity E = 0.08; impurity F = 0.08; impurity L = 0.11;

— for each impurity, use the concentration of erythromycin A in reference solution (c).

Limits:

- *impurity C*: maximum 3.0 per cent;
- *impurities A, B*: for each impurity, maximum 2.0 per cent;
- *impurities D, E, F, S*: for each impurity, maximum 1.0 per cent;
- *impurity L*: maximum 0.4 per cent;
- *any other impurity*: for each impurity, maximum 0.4 per cent;
- *total*: maximum 7.0 per cent;
- *reporting threshold*: 0.2 per cent; disregard the peaks due to erythromycins B and C.

Water (2.5.12)

Maximum 4.0 per cent, determined on 0.300 g.

Use a 100 g/L solution of *imidazole R* in *anhydrous methanol R* as the solvent.

Sulfated ash (2.4.14)

Maximum 0.5 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Injection Test solution and reference solutions (a) and (b).

System suitability Reference solution (a):

- *symmetry factor*: maximum 2.5 for the peak due to erythromycin A;
- *repeatability*: maximum relative standard deviation of 1.0 per cent determined on 6 injections.

Calculate the percentage content of erythromycin A ($C_{37}H_{67}NO_{13}$) using the chromatogram obtained with reference solution (a). Calculate the percentage contents of erythromycin B ($C_{37}H_{67}NO_{12}$) and erythromycin C ($C_{36}H_{65}NO_{13}$) using the chromatogram obtained with reference solution (b).

Express the results as erythromycin A stearate, erythromycin B stearate and erythromycin C stearate by multiplying the percentage content of erythromycin A by 1.3869, the percentage content of erythromycin B by 1.3955 and the percentage content of erythromycin C by 1.3944.

For the calculation of content of erythromycin stearate, use the sum of erythromycins A, B and C expressed as stearates as described above.

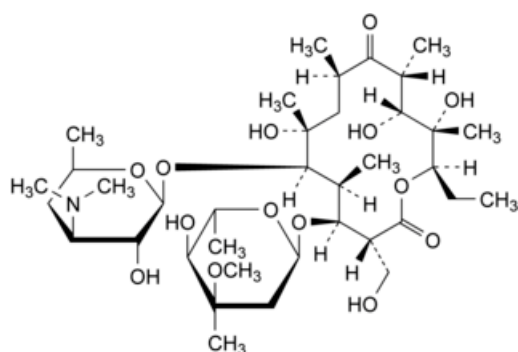
STORAGE

Protected from light.

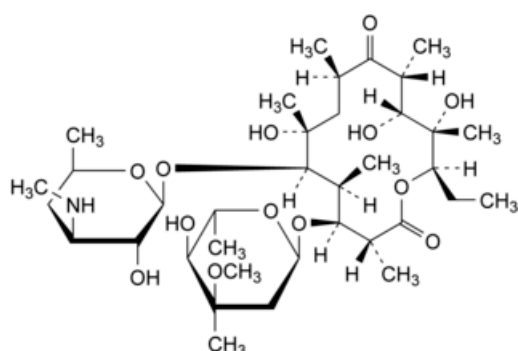
IMPURITIES

Specified impurities A, B, C, D, E, F, L, S.

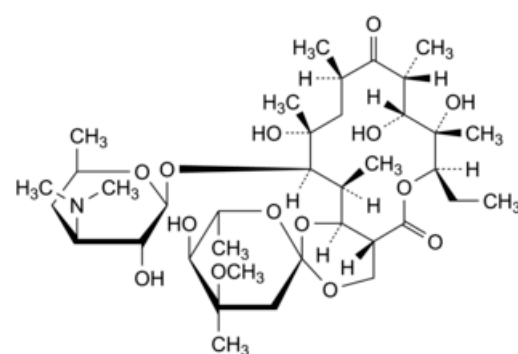
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is



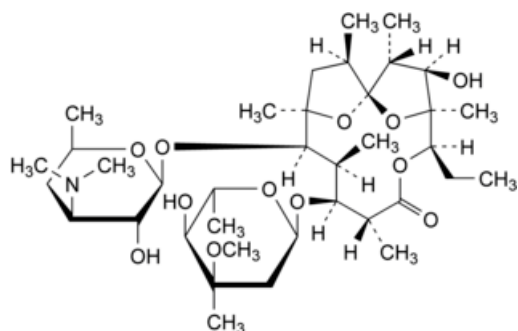
A. (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-4-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl- α -L-ribo-hexopyranosyl)oxy]-14-ethyl-7,12,13-trihydroxy-3-(hydroxymethyl)-5,7,9,11,13-pentamethyl-6-[[3,4,6-trideoxy-3-(dimethylamino)- β -D-xylo-hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione (erythromycin F),



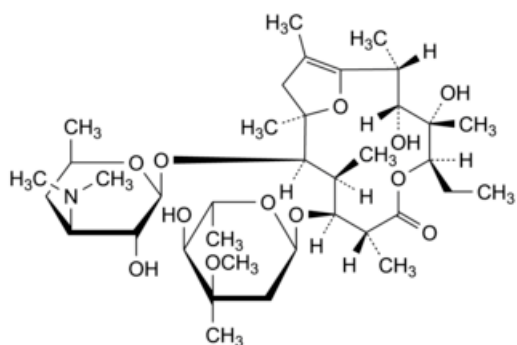
B. (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-4-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl- α -L-ribo-hexopyranosyl)oxy]-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexamethyl-6-[[3,4,6-trideoxy-3-(methylamino)- β -D-xylo-hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione (3''-*N*-demethylerythromycin A),



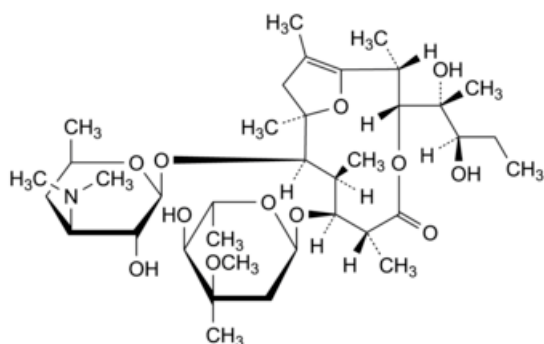
C. (2*S*,4*aR*,4'*R*,5'*S*,6'*S*,7*R*,8*S*,9*R*,10*R*,12*R*,14*R*,15*R*,16*S*,16*aS*)-7-ethyl-5',8,9,14-tetrahydroxy-4'-methoxy-4',6',8,10,12,14,16-heptamethyl-15-[[3,4,6-trideoxy-3-(dimethylamino)- β -D-xylo-hexopyranosyl]oxy]hexadecahydrospiro[5*H*,11*H*-1,3-dioxino[5,4-*c*]oxacyclotetradecin-2,2'-pyrane]-5,11-dione (erythromycin E),



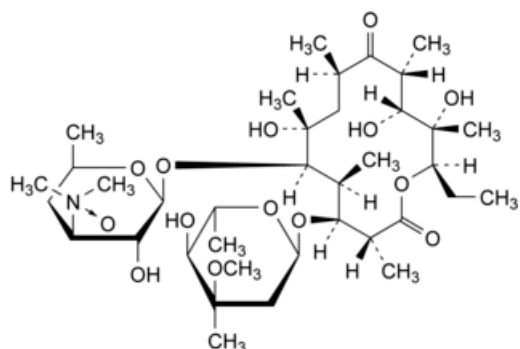
D. (1*S*,2*R*,3*R*,4*S*,5*R*,8*R*,9*S*,10*S*,11*R*,12*R*,14*R*)-9-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl- α -*L*-*ribo*-hexopyranosyl)oxy]-5-ethyl-3-hydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)- β -*D*-*xylo*-hexopyranosyl]oxy]-6,15,16-trioxatricyclo[10.2.1.1⁴]hexadecan-7-one (anhydroerythromycin A),



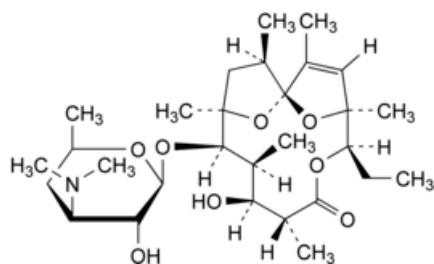
E. (2*R*,3*R*,4*S*,5*R*,8*R*,9*S*,10*S*,11*R*,12*R*)-9-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl- α -*L*-*ribo*-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)- β -*D*-*xylo*-hexopyranosyl]oxy]-6,15-dioxabicyclo[10.2.1]pentadec-1(14)-en-7-one (erythromycin A enol ether),



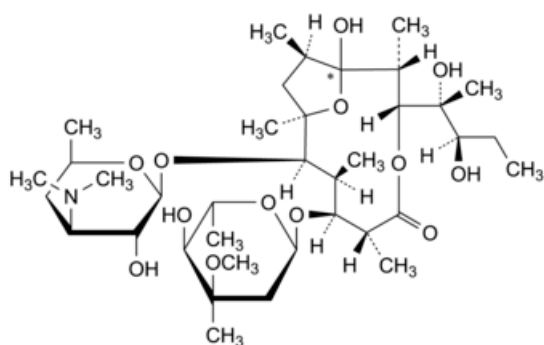
F. (2*R*,3*R*,6*R*,7*S*,8*S*,9*R*,10*R*)-7-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl- α -*L*-*ribo*-hexopyranosyl)oxy]-3-[(1*R*,2*R*)-1,2-dihydroxy-1-methylbutyl]-2,6,8,10,12-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)- β -*D*-*xylo*-hexopyranosyl]oxy]-4,13-dioxabicyclo[8.2.1]tridec-1(12)-en-5-one (pseudoerythromycin A enol ether),



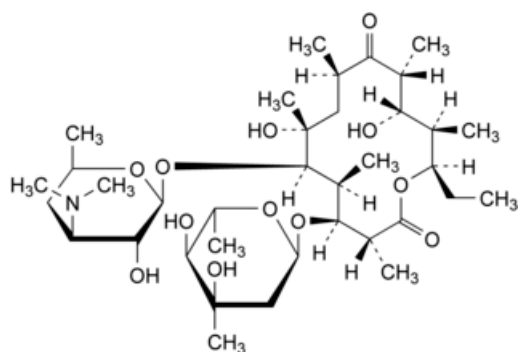
H. (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-4-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl- α -*L*-ribo-hexopyranosyl)oxy]-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexamethyl-6-[[3,4,6-trideoxy-3-(dimethylamino)- β -*D*-xylo-hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione (*N*-oxide) (erythromycin A 3''-*N*-oxide),



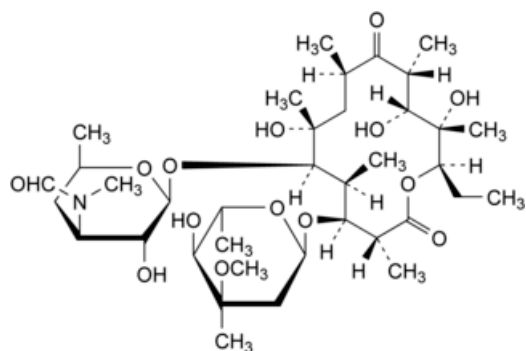
I. (1*S*,4*S*,5*R*,8*R*,9*S*,10*S*,11*R*,12*R*,14*R*)-5-ethyl-9-hydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)- β -*D*-xylo-hexopyranosyl]oxy]-6,15,16-trioxatricyclo[10.2.1.1^{1,4}]hexadec-2-en-7-one (erythralosamine),



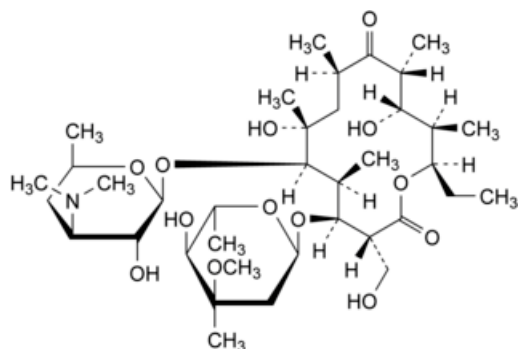
J. (1*RS*,2*R*,3*R*,6*R*,7*S*,8*S*,9*R*,10*R*,12*R*)-7-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl- α -*L*-ribo-hexopyranosyl)oxy]-3-[[1*R*,2*R*]-1,2-dihydroxy-1-methylbutyl]-1-hydroxy-2,6,8,10,12-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)- β -*D*-xylo-hexopyranosyl]oxy]-4,13-dioxabicyclo[8.2.1]tridecan-5-one (pseudoerythromycin A hemiketal),



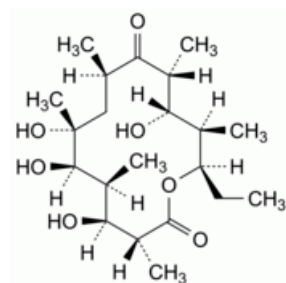
K. (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*S*,13*R*,14*R*)-4-[(2,6-dideoxy-3-*C*-methyl- α -*L*-ribo-hexopyranosyl)oxy]-14-ethyl-7,12-dihydroxy-3,5,7,9,11,13-hexamethyl-6-[[3,4,6-trideoxy-3-(dimethylamino)- β -*D*-xylo-hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione (erythromycin D),



L. (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-4-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl- α -L-*ribo*-hexopyranosyl)oxy]-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexamethyl-6-[[3,4,6-trideoxy-3-(formylmethylamino)- β -D-*xylo*-hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione (3''-*N*-demethyl-3''-*N*-formylerythromycin A),



M. (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*S*,13*R*,14*R*)-4-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl- α -L-*ribo*-hexopyranosyl)oxy]-14-ethyl-7,12-dihydroxy-3-(hydroxymethyl)-5,7,9,11,13-pentamethyl-6-[[3,4,6-trideoxy-3-(dimethylamino)- β -D-*xylo*-hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione (erythromycin G),



N. (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*S*,13*R*,14*R*)-14-ethyl-4,6,7,12-tetrahydroxy-3,5,7,9,11,13-hexamethyloxacyclotetradecane-2,10-dione (erythronolide B),

S. unknown structure.

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