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Biotransformations of Lipoglycopeptides to Obtain Novel Antibiotics

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Abstract The emergence of resistance among Gram-positive pathogens towards glycopeptide antibiotics has stimulated the research of second-generation molecules with improved activity and expanded antimicrobial spectrum. In this paper we investigate biotransformations as a way to generate novel teicoplanin- and A40926-like molecules. A range of commercial enzymes, fungi and actinomycetes were tested on A40926 and on its semi-synthetic derivatives (MDL 63,246 and dalbavancin). Oxidation of dalbavancin to MDL 63,246 was achieved by *Nonomuraea* sp. ATCC 39727 and *Actinomadura parvosata* ATCC 53463, while *Actinoplanes* sp. NRRL 3884, *Actinoplanes missouriensis* ATCC 23342 and *Actinoplanes teichomyceticus* ATCC 31121 deacylated MDL 63,246, dalbavancin and A40926. It is worth noting that the actinomycetes able to catalyze the deacylation of lipoglycopeptides are themselves producers of microbiologically active glycopeptides. Structurally related antibiotics (mideplanin and teicoplanin) were not transformed. Biotransformation conditions were optimised and scaled-up for the use of *Actinoplanes* sp. NRRL 3884 in the production of novel deacylated derivatives.

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Introduction

Lipoglycopeptides are an important class of antibiotics produced by actinomycetes. They act by blocking the peptidoglycan synthesis in bacterial cell walls. Vancomycin and teicoplanin have been in clinical use since 1958 and 1988, respectively [1]. They still represent the drugs of last resort against multi-resistant enterococci and methicillin-resistant staphylococci. The emergence of resistance to lipoglycopeptides among enterococci and more recently the occurrence of the first two highly vancomycin resistant *Staphylococcus aureus* isolates has prompted the search for second generation drugs of this class [2]. Promising results were obtained with the development of semisynthetic derivatives with improved activity, expanded antibacterial spectrum or better pharmacokinetics [3, 4]. The lipoglycopeptide antibiotic A40926 is produced by fermentations of the actinomycete *Nonomuraea* sp. ATCC 39727 (formerly *Actinomadura* sp. ATCC 39727) [5～7]. It belongs to the teicoplanin family, possessing the heptapeptide structure of the D-alanyl-D-alanine binding glycopeptides (Fig. 1). Besides showing an intrinsic antibacterial activity, A40926 and the structurally related teicoplanin have been used as scaffolds for the preparation of semi-synthetic derivatives such as mideplanin, MDL 63,246 and dalbavancin (formerly MDL 62,397), the latter being in clinical development for its improved activity and better pharmacokinetics [2, 8～12]. Mideplanin and dalbavancin were prepared by chemical ammidation with *N*,*N*-dimethylammino propylamine of teicoplanin and A40926 respectively, while MDL63,246 was the

product of reduction of the carboxylic group of the *N*-acylaminoglucuronic moiety of dalbavancin (Fig. 1). Various derivatives of A40926 have been more recently obtained by manipulation of the producing strain or by biotransformation with actinomycetes [13～16]. Biotransformation techniques often represent a preferential route to introduce modifications into structurally complex molecules such as lipoglycopeptides due to the molecule instability and/or the reactivity of other functional groups. In this work, we tested actinomycetes, fungi and commercial enzymes to exploit their potential in the biotransformations of different lipoglycopeptides (A40926, MDL 63,246, dalbavancin and mideplanin). Different screening approaches were employed and their results compared and discussed.

Materials and Methods

Microorganisms

Actinomycetes were from the proprietary collection of Biosearch Italia S.p.A., (Gerenzano-Varese, Italy) and from commercial collections (NRRL, Northern Utilization Research Branch, USDA, Peoria, Illinois, USA and ATCC, American Type Culture Collection, LGC Promochem, Sesto San Giovanni, Milano, Italy) (Table 1). Fungi were from CBS (Centraal Bureau voor Schimmelculteres, Baar, Holland), MAAE (Microbiologia Agraria Alimentare ed Ecologica, Università di Milano) and MIM (Microbiologia Industriale, Università di Milano). Spores of actinomycetes were maintained in Nutrient Glycerol (Nutrient broth Difco 8.0 g/liter, glycerol 150 ml/liter) in 96-well microtitre plates at −20°C, while fungi were maintained on Solid Malt Extract (8.0 g/liter, agar 15.0 g/liter, pH 5.6).

Enzymes

The tested 52 commercial enzymes were acylases, proteases, lipases of fungal, bacterial and mammalian origin purchased from Sigma (St. Louis, MO 63178, USA) or generously donated by Amano Pharmaceuticals, Nagoya, Japan.

Culture Conditions

Actinomycetes were inoculated into a vegetative medium composed with glucose 20 g, yeast extract 2.0 g, soybean meal 8.0 g, NaCl 4.0 g and $CaCO_3$ 1.0 g in 1.0 liter tap water at pH 7. After incubation for 72～96 hours at 28°C, the mycelia suspension (4%) was transferred into the

Table 1 Actinomycetes used for the biotransformation screening described in this paper

	Microroganims	Product
1	*Actinoplanes utahensis* NRRL12052	—
2	*Actinoplanes missouriensis* ATCC23342	Actaplanin
3	*Actinoplanes* sp. NRRL3884	A-477
4	*Actinoplanes teichomyceticus* ATCC31121	Teicoplanin
5	*Nonomuraea* sp. ATCC 39727	A40926
6	*Actinomadura parvosata* ATCC53463	Parvodicin
7	*Actinoplanes missouriensis* NRRL 15646	CUC-014/CSV-558
8	*Kibdelosporangium aridum* ATCC39922	Aridicins
9	*Streptosporangium roseum* NRRL12064	A672
10	*Actinoplanes* sp. ATCC 33076	Teicoplanin
11	*Actinoplanes* sp. ATCC 53533	UK 68597
12	*Actinoplanes* sp.NRRL 15647	Vancomycin-like
13	*Amycolatopsis orientalis* NRRL 2450	Vancomycin
14	*Streptomyces roseosporum* NRRL 11379	A21978C
15	*Streptomyces candidus* NRRL 3218	Vancomycin-like
16	*Streptomyces candidus* NRRL 8156	A 35512B
17	*Streptomyces virginiae* NRRL 12525	A41030
18	*Streptomyces toyocaensis* NRRL 15156	A47934
19	*Streptomyces* sp.NRRL 15009	A47934
20	*Streptomyces hygroscopicus* ATCC 31613	OA-7653

The strains chosen were lipoglycopeptide-producers, except for *Actinoplanes utahensis*, which was previously reported for its deacylation activity on lipoglycopeptides [22, 23].

following fermentation media: M8 (meat extract 2.0 g, yeast extract 2.0 g, casein hydrolysate 4.0 g, glucose 10 g soluble starch 20 g and $CaCO_3$ 3.0 g, in 1.0 liter tap water at pH 7), AUR/M (maltose 20 g, dextrin 10 g, yeast extract 2.0 g, meat extract 4.0 g, peptone 4.0 g, soybean meal 15 g and $CaCO_3$ 2.0 g, in 1.0 liter tap water at pH 7), Medium C (glucose 20 g, yeast extract 5.0 g, asparagine 1.5 g, $CaCO_3$ 5.0 g, NaCl 0.1 g, $MgSO_4 \times 7H_2O$ 0.5 g, $CaCl_2 \times 2H_2O$ 0.1 g, in 1.0 liter distilled water added with 1.0 ml mineral solution containing: boric acid (0.5 g), $CuSO_4 \times 5H_2O$ (0.04 g), KI (0.1), $FeCl_3 \times 6H_2O$ (0.2 g), $MnSO_4 \times H_2O$ (0.4 g), $FeSO_4 \times 7H_2O$ (0.4 g) and ammonium molybdate (0.2 g), Medium T (glucose 5.0 g, meat extract 4.0 g, yeast extract 1.0 g, peptone 4.0 g, soybean meal 10 g, $CaCO_3$ 1.0 g, NaCl 2.5 g in 1.0 liter tap water at pH 7), S/bis (glucose 10 g, peptone 4.0 g, yeast extract 4.0 g, $MgSO_4 \times 7H_2O$ 0.5 g, K_2HPO_4 4.0 g, in 1.0 liter tap water at pH 7) and PM3 (peanut meal 10 g, sucrose 20 g, KH_2PO_4 0.5 g, K_2HPO_4 1.2 g, $MgSO_4 \times 7H_2O$ 0.25 g, in 1.0 liter tap water at pH 7). The cultures were incubated for 96 hours at 28°C on rotary shaker (200 rpm). The fungi were inoculated into AF/soybean medium (glucose 20 g/liter, soy bean meal 8.0 g/liter, yeast extract 2.0 g/liter and NaCl 1.0 g/liter) used as vegetative and fermentative medium. The microorganisms were incubated for 72 hours at 28°C on a reciprocal shaker (100 spm). *Actinoplanes* sp. NNRL 3884 was grown in AUR/M medium in a 20-liter Chemap fermenter (Model CF 3000-DCU, Type SG) for 96 hours at 28°C, stirrer speed at 600 rpm and aeration rate 0.5 vvm.

Biotransformation of Lipoglycopeptides

The screening was carried out by adding substrates (dalbavancin, A40926, MDL 63,246, mideplanin and teicoplanin) at the final concentration of 0.4 mg/ml to the cultures after 72 or 96 hours of growth and incubated at 28°C. Aliquots were collected at different times to monitor the biotransformation by HPLC analysis. Biotransformations were also carried out with re-suspended cells: the 96 hours grown culture (100 ml) was centrifuged and washed twice with physiological solution. Wet mycelium (2.5 ml) was suspended into 20 ml of physiological solution in a 50-ml flask. Enzymes (10 mg/ml) were suspended in phosphate buffer 0.1 M pH 7.5. Experimental design for optimising the biotransformation of dalbavancin with *Actinoplanes* sp. NRRL 3884 was done by employing the Multisimplex® 2.0 software [17] using temperature, pH, biocatalyst concentration and agitation as control variables.

Analytical Methods

Aliquots (10 ml) of the biotransformation media were withdrawn and brought to pH 10 with NaOH 1 M. After centrifugation (300 rpm for 10 minutes), the supernatant was brought to pH 7 with H_2SO_4 (10%). The sample was mixed with an equal volume of acetonitrile and analysed. HPLC analysis was performed on a Waters instrument (Waters Chromathography, Milford, MA, USA) equipped with a Waters Symmetry-column RP18, 5 μ (250× 4.6 mm). The solvent system consisted of an aqueous solution of trifluoracetic acid (0.1%) (solvent A) and acetonitrile (solvent B). A linear gradient from solvent A (100%) to solvent B was applied over a period of 40 minutes followed by isocratic elution with solvent B (100%) for an additional time (10 minutes). The flow-rate was 1.0 ml/minute. Injection volume was 20 μl and UV detector (270 nm). The effluent from the column was split in a ratio 5 : 95 and the majority (*ca.* 950 μl min^{-1}) was diverted to photodiode array detector. The remaining 50 μl min^{-1} were diverted to the ESI interface of a Finnigan LCQ ion trap mass spectrometer (Thermoquest, Finnigan MAT, San Josè CA, USA). The mass spectrometric analysis was performed under the following conditions. Sample inlet conditions: Sheat gas (N_2) 60 psi; Aux gas (N_2) 5 psi; capillary heater 250°C; Sample inlet voltage settings: Polarity both positive and negative; Ion spray voltage ±5 kV; Capillary voltage ±19 V. Scan conditions: maximum ion time 200 msec; ion time 5 msec; ion time 5 msec; Full micro scan 3; Segment: duration 30 minutes, scan events positive (150~2000 *m*/*z*) and negative (150~2000 *m*/*z*).

Results and Discussion

Screening for the Modification of MDL 63,246 and Dalbavancin

A screening for the modification of dalbavancin and MDL 63,246 was carried out using 97 actinomycetes (including rare genera, 60 newly isolated previously selected for their lipase/esterase and acylase activity [18] and 37 from public collections), 27 fungi possessing mycelium-bound lipases and esterases [19] and 52 commercially available enzymes (acylases and lipases). The only modification detected was the conversion of MDL 63,246 into dalbavancin, namely the oxidation of the primary alcohol on the *N*-acyl-glucosammine moiety into the corresponding carboxylic acid (Fig. 1). This oxidation was obtained using *Nonomuraea* sp. ATCC 39727, the A40926 producer [5, 7], and *Actinomadura parvosata* ATCC 53463, the parvodicin producer [20]. The reaction was completed within 36 hours and occurred with complete chemo- and regio-selectivity. Since it did not give any novel chemical structure, it was not further developed. Indeed, the observation that the

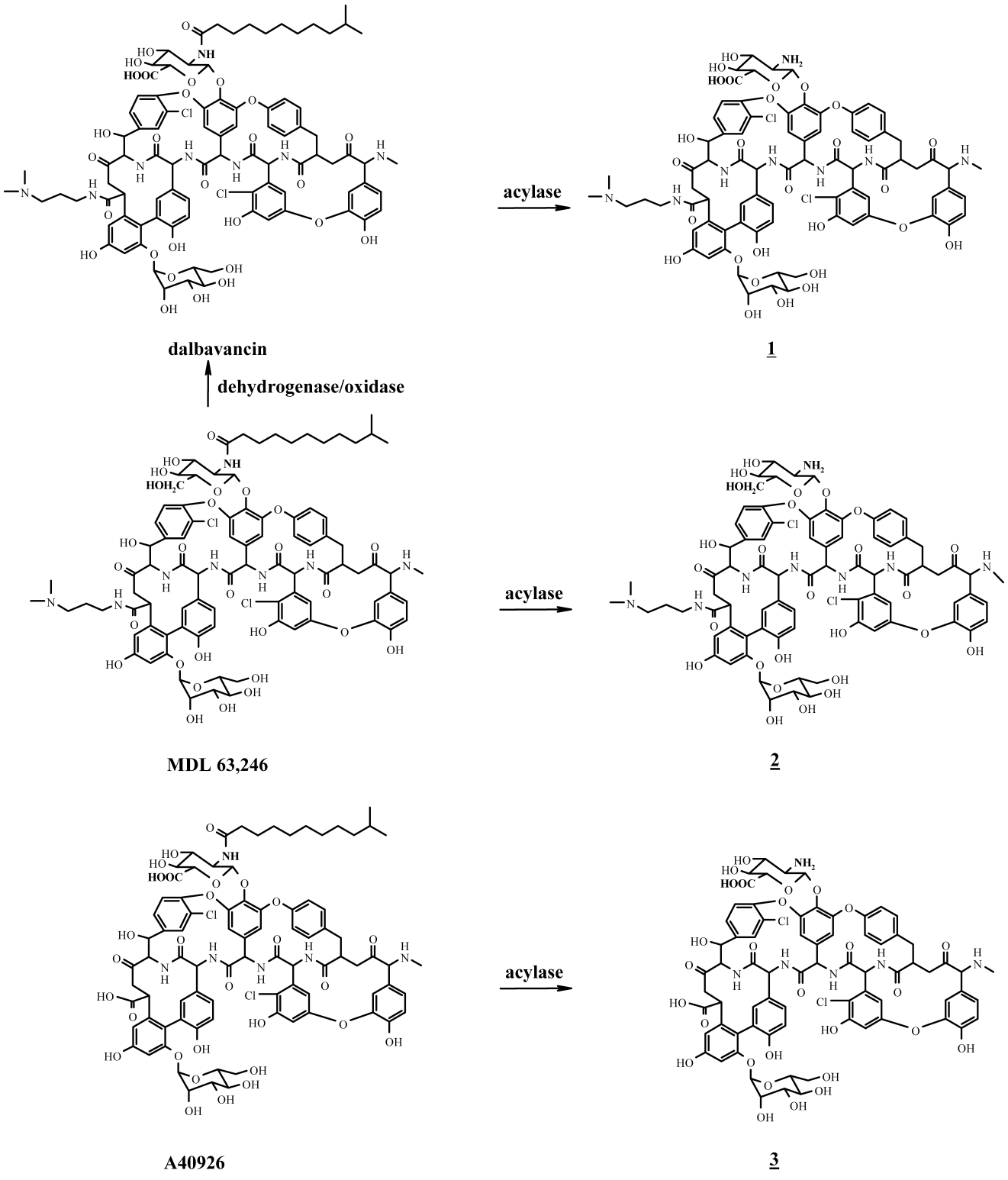

Fig. 1 Enzymatic modifications of dalbavancin, MDL 63,246 and A40926.

only microorganisms able to modify MDL 63,246 and dalbavancin were two actinomycetes known as producers of structurally-related lipoglycopeptides, lead us to focus the screening on a group of lipoglycopeptide-producing actinomycetes, mainly belonging to *Streptomyces*, *Actinoplanes*, *Nonomuraea* and *Actinomadura* genera (Table 1). Twenty lipoglycopeptide-producing actinomycetes were selected by querying the proprietary Antibiotic Literature Database (Biosearch Italia S.p.A., Gerenzano-Varese, Italy), describing bioactive microbial products reported in the literature and patents since 1950 [21]. *Actinoplanes utahensis* NRRL 12052 was also included in this screening since it has been previously reported for its deacylating activity on the lipopeptides echinocandin B and A-21978C [22, 23]. The microorganisms were grown in liquid AUR/M medium for 96 hours and the biotransformation was carried out by adding the substrates directly to whole cultures or to the mycelium suspended in physiological solution. The only strains able to carry out transformation of the substrates were *Actinoplanes* sp. NRRL 3884, *Actinoplanes missouriensis* ATCC 23342 and *Actinoplanes teichomyceticus* ATCC 31121, which were the producers of the glycopeptide A-477 [24], actaplanin [25] and teicoplanin [26, 27], respectively. The only products of the biotransformations from both the substrates were identified as the deacylated compounds **1** and **2** (Fig. 1) on the basis of spectroscopic and chromatographic data. *Actinoplanes* sp. NRRL 3884 was the best biocatalyst for both of the substrates (Table 2) and was further employed for the optimisation of the bioconversion.

Deacylation of Lipoglycopeptides with *Actinoplanes* sp. NRRL 3884

The deacylation of dalbavancin by *Actinoplanes* sp. NRRL 3884 was optimised: conventional parameters influencing both the growth (type of cultural medium, culturing time, pH, temperature) and bioconversion (temperature, pH, biocatalyst concentration and agitation levels) were simultaneously evaluated using the Multisimplex experimental design. The effect of the substrate concentration was independently studied under optimised conditions (mycelium grown for 96 hours in AUR/M medium at pH 7.0; bioconversion performed at pH 6.8 and at 28°C and 200 rpm using 6.9 g/liter dry mycelium) and it is reported in Fig. 2. The highest reaction rate leading to the complete molar conversion within 48 hours was achieved using 0.6 g/liter of dalabavancin. The biotransformation was scaled-up to 20 liters giving similar results. *Actinoplanes* sp. NRRL 3884 was also used for the deacylation of structurally related antibiotics: MDL 63,246, A40926, teicoplanin and mideplanin under the optimised conditions set up for dalbavancin (Fig. 2). Despite the structural similarity, teicoplanin and mideplanin were not converted, while dalbavancin, MDL 63,246 and A40926 were completely deacylated, although at different rates (Fig. 3). These data are in agreement with those previously reported on *Actinoplanes teichomycetics*, which is used to deacylate A40926 and its *tert*-BOC derivative (a *tert*-butossi group is linked to the amine group on the peptidic core), but it is unable to deacylate its own product, teicoplanin [15, 16].

Actinoplanes sp. NRRL 3884 proved a suitable biocatalyst for the selective deacylation of different lipoglycopeptide antibiotics. This selection was made after a large screening of microorganisms and enzymes known for generic acylase/amidase/carboxylesterase activity, but none of these biocatalysts showed hydrolytic activity on dalbavancin and MDL 63,246. A restricted screening among glycopeptide producer actimomycetes showed that few strains of *Actinoplanes* sp. were able to deacylate dalbavancin and MDL 63,246, *Actinoplanes* sp. NRRL 3884 being the best biocatalyst for the deacylation of both the substrates and showing also good activity towards A40926. The selected actinomycetes were not able to modify structurally related molecules, such as teicoplanin and mideplanin. The acylase from *Actinoplanes utahensis* NRRL 12052, which is industrially used to produce anidulafungin from

Table 2 Deacylation of MDL 63,246 and dalbavancin with selected *Actinoplanes* strains

Microorganism	Molar conversion (%)	
	MDL 63,246	Dalbavancin
Actinoplanes sp. NRRL 3884	75	100
Actinoplanes missouriensis ATCC 23342	10	40
Actinoplanes teichomyceticus ATCC 31121	<5	20

Substrates (0.4 g/liter) were added to mycelium grown for 96 suspended in physiological solution. Molar conversion was measured after 72 hours of biotransformation.

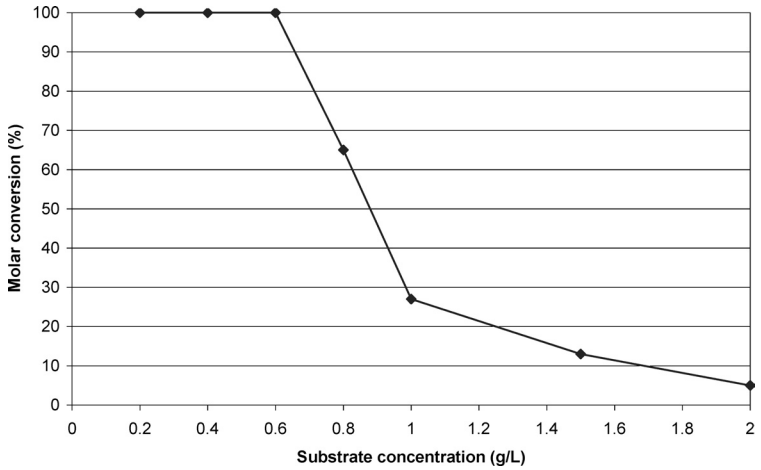

Fig. 2 Effect of substrate concentration on the conversion of dalbavancin into its corresponding deacylated derivative **2**, after 48 hours of biotransformation.

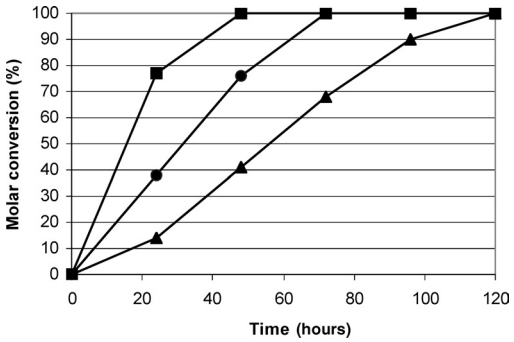

Fig. 3 Time-courses of the deacylation of different lipoglycopeptide antibiotics by *Actinoplanes* sp. NRRL 3884.

● Dalbavancin, ■ A 40926, ▲ MDL 63,246.

echinocandin B and daptomycin from A-21978C [28, 29], was unable to deacylate any of the lipoglycopeptides tested. Two other glycopeptide producers (*Nonomuraea* sp. ATCC 39727 and *Actinomadura parvosata* ATCC 53463) oxidized dalbavancin into MDL 63,246.

In conclusion, the enzymatic activities found after screening for generic activity on standard substrates were not useful for the modification lipoglycopeptides. Once again we learned from this work that it is more rewarding to screen directly for the given activity, especially if you search for the specific modification of complex molecules such as antibiotics.

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