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Synthesis of new semi-synthetic dipodands and tripodands from naturally occurring polyether ionophores

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ABSTRACT

A new method to synthesize novel esters of Lasalocid acid **2**–**5** and of Monensin A, **7**–**9** (semi-synthetic di- and tripodands) is described. These new compounds are characterized by spectroscopic and microbiological methods.

Typical podands have non-cyclic structures, in which several polyether chains are linked to the same binding centre, which can be N, P, Si or S atoms. Because of their specific properties, they are the so-called open-chain analogues of crown ethers and cryptands. Like these compounds, podands are able to form stable complexes with monovalent cations.[1] Due to this property, podands are used as promising anion activators in organic reactions and as suitable ligands for solid–liquid phase transfer catalysis.[1–5] The two parameters that influence the ability of podand complex formation with cations[1] are the number of oxygen atoms and the varying length of the polyoxaalkyl chains. Typical podands show relatively low cation selectivity during complex formation as well as a limited capacity to recognize selectively chiral compounds.[1,3–5]

In the present study, we report the synthesis, spectroscopic and microbiological characterization of several new derivatives of Monensin A and Lasalocid acid, which can be defined as semi-synthetic dipodands and tripodands. In these new compounds the natural polyether ionophore moieties are connected by a hexamethylene linker or bound to a benzene-1,3,5-trimethylene species.

Lasalocid acid **1** and Monensin A **6** (Scheme 1) are carboxylic polyether ionophores isolated from *Streptomyces lasaliensis* and *Streptomyces cinnamonensis,* respectively. They are lipophilic chelating agents of cations and are able to transport cations across lipid membranes of cells.[6] Monensin A exhibits significant preference to form complexes with monovalent cations,[7] such as Li^+, Na^+, K^+, Rb^+, Ag^+ and Tl^+, whereas Lasalocid acid is able to form complexes with mono- and bivalent metal cations,[8] such as Na^+, Ag^+, Ca^{2+} and Ba^{2+}. Both Monensin and Lasalocid derivatives also exhibit excellent enantiomer selectivity for chiral amines.[9]

Both Monensin A and Lasalocid acid are very sensitive to acidic conditions and heating. For this reason we investigated mild reaction conditions for their esterification. We found a reliable strategy for the esterification of **1** and **6** based on direct alkylation of the carboxylate ions using alkyl bromides [1,3,5-tris(bromomethyl)benzene or 1,6-dibromohexane] and 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) as the catalyst.[10,11] The syntheses of compounds **2–5** and **7–9** are shown in Scheme 1. Using this esterification procedure, the thermally unstable carboxylic ionophores yielded stable esters without any indication of decomposition such as decarboxylation or other degradation processes. This esterification reaction shows, however, a remarkable solvent dependence. Among the solvents used (dichloromethane, chloroform, acetonitrile and toluene) the highest yield of the respective ester was obtained in toluene, probably because of the optimal solubility of the reactants and products in this solvent.

All the products were purified easily by column chromatography on silica gel. The structures of the esters were determined

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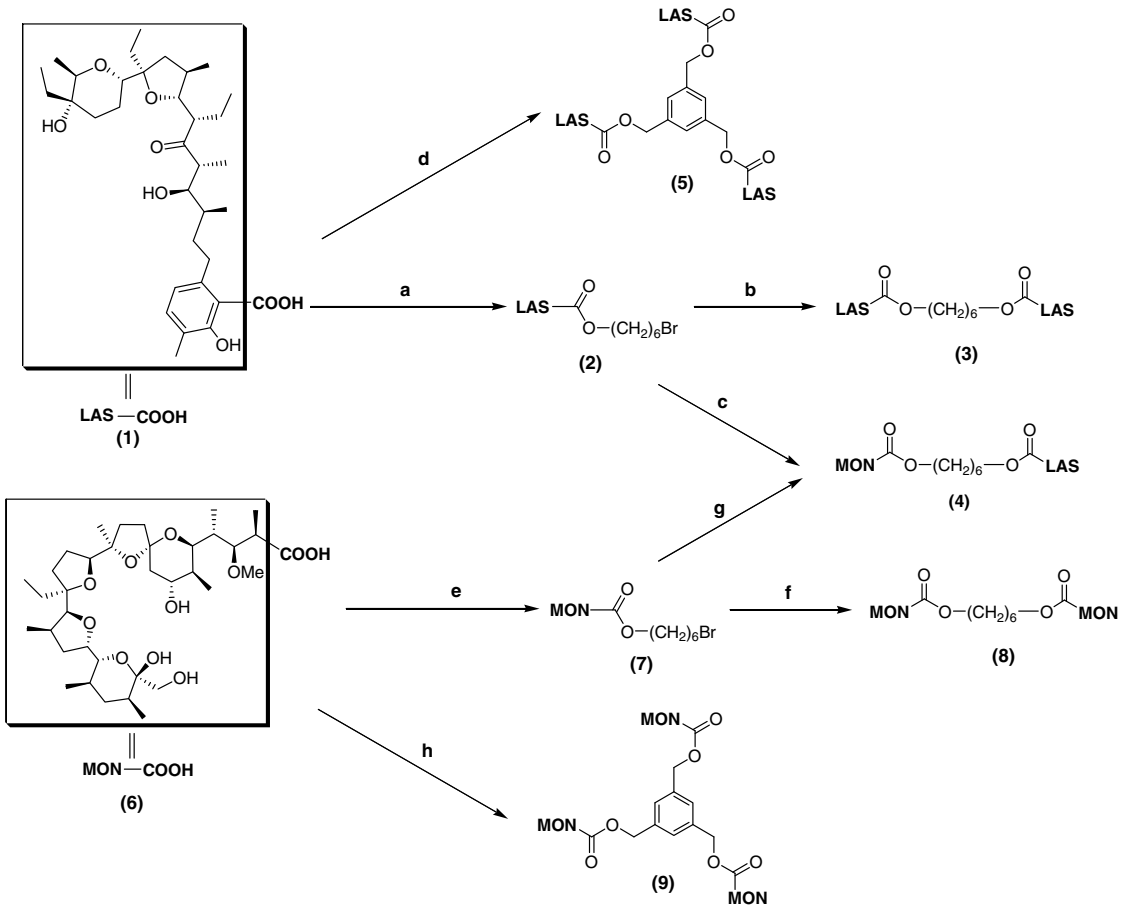

Scheme 1. Synthesis of semi-synthetic dipodands **3**, **4** and **8** and tripodands **5** and **9** from Lasalocid acid (**1**) and Monensin A (**6**). Reagents and conditions: (a) (**1**) (1.0 equiv), DBU (1.2 equiv), 1,6-dibromohexane (6.0 equiv), toluene, 90 °C, 5 h, 66%; (b) (**1**) (3.0 equiv), DBU (3.6 equiv), (**2**) (1.0 equiv), toluene, 90 °C, 5 h, 60%; (c) (**6**) (3.0 equiv), DBU (3.6 equiv), (**2**) (1.0 equiv), toluene, 90 °C, 5 h, 36%; (d) (**1**) (6.0 equiv), DBU (6.6 equiv), 1,3,5-tris(bromomethyl)benzene (1.0 equiv), toluene, 90 °C, 5 h, 68%; (e) (**6**) (1.0 equiv), DBU (1.2 equiv), 1,6-dibromohexane (6.0 equiv), toluene, 90 °C, 5 h, 55%; (f) (**6**) (3.0 equiv), DBU (3.6 equiv), (**7**) (1.0 equiv), toluene, 90 °C, 5 h, 43%; (g) (**1**) (3.0 equiv), DBU (3.6 equiv), (**7**) (1.0 equiv), toluene, 90 °C, 5 h, 40%; (h) (**6**) (6.0 equiv), DBU (6.6 equiv), 1,3,5-tris(bromomethyl)benzene (1.0 equiv), toluene, 90 °C, 5 h, 49%.

Table 1
Antimicrobial activity of Lasalocid acid (**1**) and Monensin A (**6**) and their derivatives: **3**, **5**, **8** and **9**; diameter of the growth inhibition zone (GIZ) (mm) and minimum inhibitory concentration (MIC) (μg/ml)[14–16]

Strain	Growth inhibition zone (GIZ) (mm) and minimum inhibitory concentration (MIC) (μg/ml)											
	1		**6**		**3**		**5**		**8**		**9**	
	GIZ	MIC	GIZ	MIC	GIZ	MIC	GIZ	MIC	GIZ	MIC	GIZ	MIC
S. aureus NCTC 4163	35	12.5	22	2	24	12.5	12	400	22	12.5	25	25
S. aureus ATCC 25923	29	12.5	22	1	25	12.5	–	>400	22	6.25	22	25
S. aureus ATCC 6538	31	12.5	20	2	24	12.5	12	400	22	6.25	23	25
S. aureus ATCC 29213	30	12.5	18	1	25	12.5	12	400	21	6.25	22	25
S. epidermidis ATCC 12228	27	12.5	15	2	23	12.5	15	400	20	6.25	22	25
B. subtilis ATCC 6633	28	6.25	22	1	25	6.25	13	400	25	12.5	28	12.5
B. cereus ATCC 11778	28	6.25	18	2	28	6.25	11	400	22	6.25	22	25
E. hirae ATCC 10541	20	12.5	–	12.5	17	12.5	–	>400	–	100	–	200
M. luteus ATCC 9341	26	12.5	12	4	22	12.5	14	400	16	50	15	100
M. luteus ATCC 10240	32	12.5	12	2	28	12.5	16	200	20	12.5	19	25

–: denotes lack of a growth inhibition zone.

using elemental analysis and FT-IR, ^{1}H and ^{13}C NMR and ESI-MS methods.[12]

In the ^{1}H NMR spectra of tripodands **5** and **9**, the most characteristic signals were observed for the aromatic protons of the 1,3,5-trimethylenebenzene moiety and for the protons assigned to methylene benzyl group (C(1′)H$_2$) (Fig. 1). The signals of the aromatic protons occurred as singlets at 7.61 ppm and 7.33 ppm for **5** and **9**, respectively. In the ^{1}H NMR spectrum of **9**, the signal for the two protons of the CH_2 group occurred as a singlet at 5.17 ppm, whereas in the spectrum of **5**, this signal was observed at 5.51 ppm as a doublet of doublets due to geminal (^{2}J) spin–spin coupling (Fig. 1). This kind of coupling indicates that both protons are located in different electronic environments and a typical AB spin–spin coupling structure is realized.[13] The presence of the ester groups in all the di- and tripodands was evident by FT-IR spectroscopy, since the ν(C=O) vibrations of the ester group are one of the

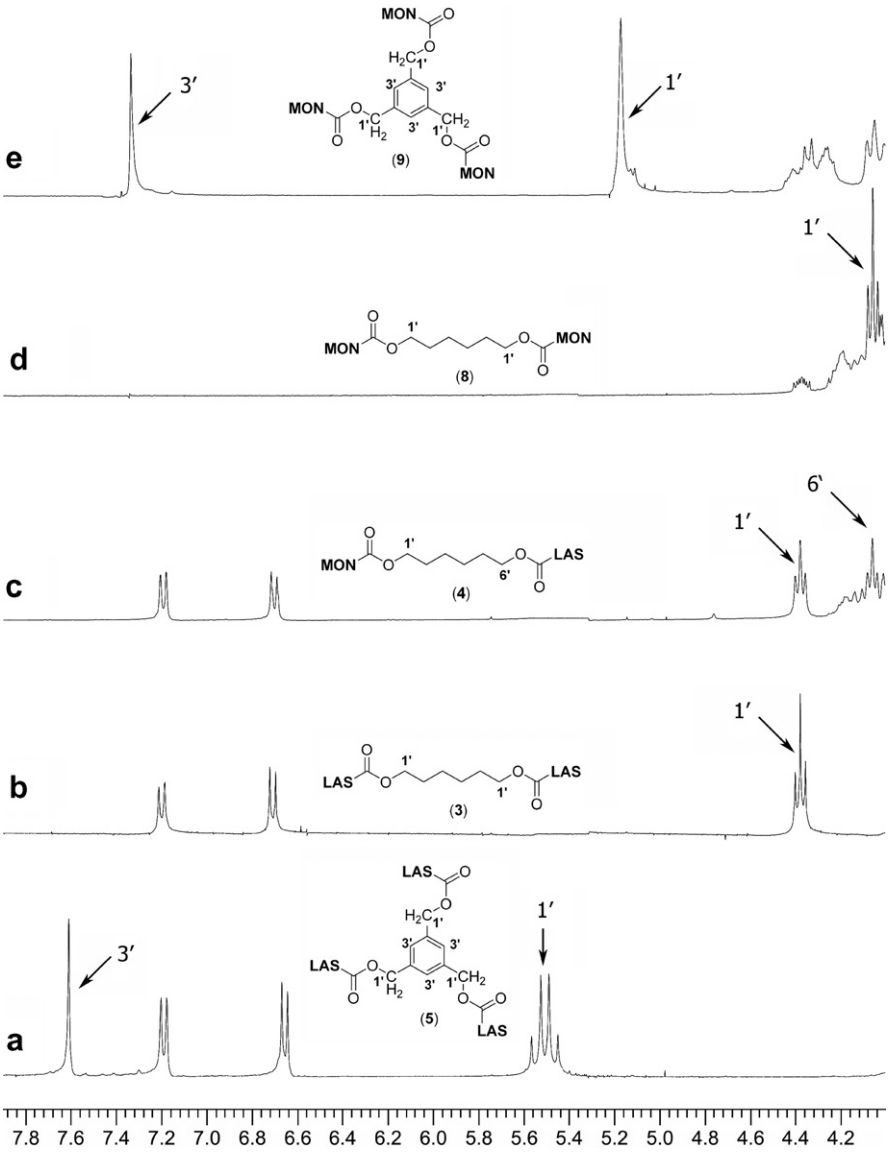

Figure 1. ^{1}H NMR spectra in the region of the most characteristic signals of: (a) **5**, (b) **3**, (c) **4**, (d) **8**, (e) **9**.

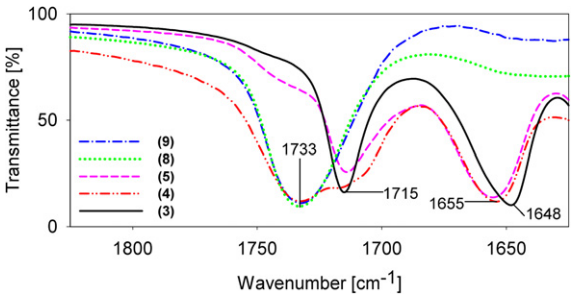

Figure 2. FT-IR spectra in the *ν*(C=O) stretching vibration regions of compounds **3**–**5** and **8**–**9**.

most characteristic bands in the infrared spectra (Fig. 2). In the spectra of the Monensin and Lasalocid esters, these *ν*(C=O) vibrations were evident at about 1733 cm^{-1} and 1655 cm^{-1}, respectively. Additionally, in the FT-IR spectra of Lasalocid derivatives **2–5**, a band assigned to the stretching vibrations of the keto group C(13)=O at 1715 cm^{-1} was also observed.

Lasalocid acid (**1**), Monensin A (**6**) and their di- and tripodand derivatives **2–5** and **7–9** were tested in vitro for their antibacterial and antifungal activities using various micro-organisms such as gram-positive bacteria, gram-negative rods and yeasts (Table 1).[14,15]

The antimicrobial properties of all the active compounds are characterized by the minimum inhibitory concentration (MIC) and the results obtained for the compounds studied are presented in Table 1.[14–16] Lasalocid acid (**1**) as well as Monensin A (**6**) exhibited relatively high activity against gram-positive bacteria. Esters **2, 7** and **4** were inactive against all the micro-organisms tested. Podands **8** and **9**, obtained from Monensin A, show considerably better activity against gram-positive bacteria than the corresponding podands **3** and **5**, obtained from Lasalocid acid. All the compounds **1–9** tested were inactive against strains of *Candida (C. albicans* and *C. parapsilosis)*. Moreover, as expected, the cell walls of gram-negative bacteria do not permit the penetration of hydrophobic molecules with high molecular weights and thus the microorganisms are not susceptible to Monensin A and Lasalocid acid as well as their derivatives.

In this Letter, we have described an efficient method for obtaining new semi-synthetic dipodands and tripodands from naturally occurring carboxylic ionophores. We have provided evidence that the new derivatives of Lasalocid and Monensin A (**3**, **5**, **8** and **9**) show antibacterial activity against human pathogenic bacteria.

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10. *Synthesis of Monensin A* (**6**) (or Lasalocid acid (**1**)): Monensin A sodium salt (Fluka) (or Lasalocid sodium salt from Avatec (Fa. Spezialfutter Neuruppin)) was dissolved in dichloromethane and stirred vigorously in the presence of aqueous sulfuric acid (40 ml) (pH 1.5). The organic layer containing **6** (or **1**) was washed with distilled water, and the dichloromethane was evaporated under reduced pressure.
11. *Representative procedure for* (**5**): A mixture of 1,3,5-tris(bromomethyl)benzene (Aldrich) (45 mg, 0.125 mmol), Lasalocid acid (**1**) (443 mg, 0.75 mmol), DBU (137 mg, 0.9 mmol) and 40 ml of toluene was heated at 90 °C for 5 h. After cooling, the precipitated DBU-hydrobromide (DBU·HBr) was filtered and washed with hexane. The filtrate and the washings were combined and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (Fluka type 60) to give **5** (160 mg, 68% yield) as a colourless oil showing a tendency to form a glass state. Compounds **2–4** and **7–9** were obtained according to Scheme 1.
12. *Selected spectral data for* (**5**): ESI-MS (*m*/*z*) 630 $(M+3H)^{3+}$; ^{1}H NMR (300 MHz, CD_3CN): δ 11.23 (3H, s, O(3)-H), 7.61 (3H, s, 3′-H), 7.19 (3H, d, *J* = 7.3 Hz, 5-H), 6.65 (3H, d, *J* = 7.9 Hz, 6-H), 5.51(6H, dd, *J* = 12.2, 10.4 Hz, 1′-H), 3.96 (3H, s, OH), 3.86 (3H, dd, *J* = 4.3, 6.1 Hz, 19-H), 3.78 (3H, d, *J* = 9.2, 15-H), 3.64 (3H, q, *J* = 6.7 Hz, 23-H), 3.40 (3H, d, *J* = 10.3 Hz, 11-H), 3.29 (6H, s, OH), 2.90–0.67 pattern of 129 protons (6 strongly overlapped); ^{13}C NMR (75 MHz, CD_3CN): δ 213.99 (C-13), 172.17 (C-1), 160.97 (C-3), 144.43 (C-7), 137.45 (C-2′), 135.82 (C-5), 130.03 (C-3′), 124.47 (C-4), 122.53 (C-6), 112.15 (C-2), 86.83 (C-18), 85.12 (C-15), 78.01 (C-23), 74.29 (C-11), 71.95 (C-19), 70.67 (C-22), 67.51 (C-1′), 55.20 (C-14), 48.56 (C-12), 39.34 (C-17), 37.35 (C-9), 35.78 (C-16), 35.19 (C-8), 35.01 (C-10), 31.67 (C-27), 31.32 (C-25), 30.14 (C-21), 21.33 (C-20), 17.61 (C-30), 15.96 (C-29), 15.75 (C-34), 14.71 (C-24), 14.05 (C-32), 12.82 (C-31), 12.57 (C-33), 8.98 (C-28), 6.83 (C-26); FT-IR (KBr, cm^{-1}) 3454 ν(O–H), 1714 ν(C(13)═O), 1655 ν(C(1)═O); Elemental Anal. Calcd for $C_{111}H_{168}O_{24}$: C, 70.67; H, 8.98. Found: C, 70.42; H, 9.13.
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15. The micro-organisms used in the tests were the following: Gram-positive cocci: *Staphylococcus aureus* NCTC 4163, *Staphylococcus aureus* ATCC 25923, *Staphylococcus aureus* ATCC 6538, *Staphylococcus aureus* ATCC 29213, *Staphylococcus epidermidis* ATCC 12228, *Bacillus subtilis* ATCC 6633, *Bacillus cereus* ATCC 11778, *Enterococcus hirae* ATCC 10541, *Micrococcus luteus* ATCC 9341, *Micrococcus luteus* ATCC 10240, gram-negative rods: *Escherichia coli* ATCC 10538, *Escherichia coli* ATCC 25922, *Escherichia coli* NCTC 8196, *Proteus vulgaris* NCTC 4635, *Pseudomonas aeruginosa* ATCC 15442, *Pseudomonas aeruginosa* NCTC 6749, *Pseudomonas aeruginosa* ATCC 27853, *Bordetella bronchiseptica* ATCC 4617 and yeast-like organisms: *Candida albicans* ATCC 10231, *Candida albicans* ATCC 90028 and *Candida parapsilosis* ATCC 22019. The micro-organisms used here were provided by the Department of Pharmaceutical Microbiology, Medical University of Warsaw, Poland. The antimicrobial activities of the studied compounds were performed according to the method given in Ref. 16.
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