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Synthesis of *Z*-Di/tetra/hexa/ydrodinaphtho[2,1-*b*:1',2'-*d*][1,6]dioxacycloalkenes via Microwave–Accelerated Ring Closing Metathesis and Their Antimicrobial Activity[1]

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Abstract—*Z*-Di/tetra/hexa/hydrodinaphtho[2,1-*b*:1',2'-*d*][1,6]dioxacycloalkenes have been synthesized under microwave-accelerated ring closing metathesis (RCM) of 2,2'-bis(alkenyloxy)-1,1'-binaphthalenes. Microwave irradiation improved the efficiency of ring closing metathesis and dramatically reduced reaction time. Structures of newly synthesized compounds have been elucidated by means of elemental analysis, IR, ^{1}H and ^{13}C NMR and mass spectral data. All compounds were tested for their antibacterial activity against Gram-positive bacteria *Staphylococcus aureus, Bacillus subtilis and* Gram-negative bacteria *Pseudomonas aeruginosa, Escherichia coli* and antifungal activity against fungal strains *Aspergillus niger, Penicillium italicum* and *Fusarium oxysporum.*

Keywords*:* ring closing metathesis, microwave irradiation, dinaphtho [2,1-*b*:1',2'-*d*][1,6]-dioxacycloalkenes, antimicrobial activity

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INTRODUCTION

Ring closing metathesis has been established as an important, versatile and most powerful tool for construction of macrocyclic ring systems [1–3]. Important applications of RCM are formation of cycloalkenes from dienes and synthesis of biologically active macrocyclic compounds including natural products [4–8]. Microwave assisted synthesis is the promising alternative to traditional methods as it is a clean, efficient, economically feasible and environmentally benign [9]. As a part of our ongoing study [10–13] of microwave assisted synthesis of biologically active compounds, herein we report the synthetic approach to some new dinaphtho [2,1-*b*:1',2'-*d*][1,6]dioxacycloalkenes (Scheme 1).

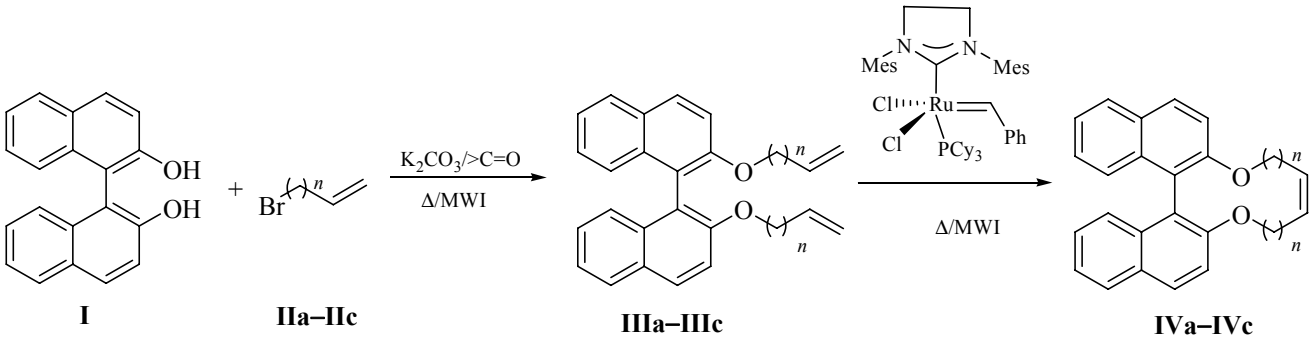
RESULTS AND DISCUSSION

Di/tetra/hexa/hydrodinaphtho[2,1-*b*:1,2-*d*][1,6]dioxacycloalkenes have been synthesized by microwave-accelerated ring closing metathesis of 2,2'-bis(alkenyloxy)-1,1'-binaphthalenes (**IIIa–IIIc**) using the Grubbs second generation (G-II) catalyst (Scheme 1). Synthesis of the title compounds was also carried out by conventional heating. Under microwave irradiation the reaction completed within minutes with high yields compared to the conventional synthesis (Tables 1, 2). Structures of the products were elucidated by elemental and spectral analysis.

Antimicrobial activity. The synthesized compounds were screened for their antimicrobial activity [14] against two strains of Gram-positive bacteria (Table 3) (*Staphylococcus aureus* and *Bacillus subtilis*), two strains of Gram-negative bacteria (*Echerichia coli* and *Pseudomonas aeruginosa*) as well as three strains of fungi (Table 4) (*Aspergillus niger*, *Penicillium italicum* and *Fusarium oxysporum*). Standard antibiotic drugs *Amoxicillin* for bacteria and *Mycostatin* for fungi were used at a concentration of 100μg/mL for comparison. Biological activity of the compounds has been evaluated by filter paper disc method in DMF solution (100 μg/mL). Inhibition zones of microbial growth surrounding the filter paper disc (5 mm) were measured in millimeters upon completion of the incubation period of 3 days at 37°C

[1] The text was submitted by the authors in English.

Scheme 1. Synthesis of *Z*-di/tetra/hexa/ydrodinaphtho[2,1-*b*:1,2-*d*][1,6]dioxacycloalkenes (**IVa–IVc**)



I **IIa–IIc** **IIIa–IIIc** **IVa–IVc**

n = 1 (**a**), 2 (**b**), 3 (**c**).

for *Echerichia coli* and at 28°C for other bacteria and fungi. No inhibition zone was detected for pure DMF. Compounds **IVa** and **IVc** demonstrated moderate antibacterial activity and **IVb** and **IVc** demonstrated high antifungal activity.

EXPERIMENTAL

All reagents and solvents were reagent grade and used without further purification. Melting points were determined in open capillary tubes and uncorrected. Purity of the compounds was tested routinely by silica gel F_{254} (Merck). Microwave assisted reaction was carried out in Milestone multi SYNTH microwave system. IR spectra were recorded on Shimadzu FTIR 8400s spectrophotometer. NMR spectra were measured on Avance 300 spectrometer (300 MHz, $CDCl_3$) and mass spectra were measured on Shimadzu mass spectrometer. Elemental analysis was carried out with a Thermofinnigan CHNS analyzer.

Synthesis of 2,2'-Bis(alkenyloxy)-1,1'-binaphthalenes (IIIa–IIIc). *Conventional heating.* A mixture of 1,1'-bi-2-naphthol (BINOL) solution (1 mmol), appropriate alkenyl bromides **IIa–IIc** (4 mmol) and potassium carbonate (10 mmol) in dry acetone (20 mL) was refluxed for 5–6 h. Upon completion of the reaction (as indicated by TLC) the reaction mixture was concentrated under vacuum to remove the solvent and ice cold water was added to the residual mixture. The solid formed was filtered, dried, and recrystallized from methanol to afford compounds **IIIa–IIIc**.

Table 1. Physical data of 2,2'-bis(alkenyloxy)-1,1'-binaphthalenes (**IIIa–IIIc**)

Comp. no.	Compound	mp, °C	Conventional heating		Microwave irradiation	
			time, h	yield, %	time, h	yield, %
IIIa	2,2'-Bis(allyloxy)-1,1'-binaphthalene	134	6	85	4	95
IIIb	2,2'-Bis(but-3-en-1-yloxy)-1,1'-binaphthalene	126	5	85	5	90
IIIc	2,2'-Bis(pent-4-en-1-yloxy)-1,1'-binaphthalene	120	6	84	4	92

Table 2. Physical data of Z-di/tetra/hexa/ydrodinaphtho[2,1-*b*:1',2'-*d*][1,6]dioxacycloalkanes (**IVa–IVc**)

Comp. no.	Compound	mp, °C	Conventional heating		Microwave irradiation	
			time, h	yield, %	time, h	yield, %
IVa	*Z*-4,7-Dihydrodinaphtho[2,1-*b*:1',2'-*d*][1,6]dioxecine	180	8	85	6	93
IVb	*Z*-2,3,6,7-Tetrahydrodinaphtho[2,1-*b*:1',2'-*d*][1,6]-dioxacyclododecine	186	9	88	5	96
IVc	*Z*-2,3,4,7,8,9-Hexahydrodinaphtho[2,1-*b*:1',2'-*d*][1,6]-dioxacyclotetradecine	172	8	82	7	94

Table 3. Antibacterial activity of *Z*-di/tetra/hexa/ydrodinaphtho[2,1-*b*:1,2-*d*][1,6]dioxacycloalkenes (**IVa–IVc**)

Comp. no.	Zone of inhibition, mm			
	Gram-positive bacteria		Gram-negative bacteria	
	Staphylococcus aureus	*Bacillus subtilis*	*Pseudomonas aeruginosa*	*Escherichia coli*
IVa	22	9	8	23
IVb	23	6	7	10
IVc	24	8	8	18
Amoxicilin	30	12	10	10

Microwave irradiation. A thoroughly blended mixture of BINOL (1 mmol), appropriate alkenyl bromides (4 mmol) and ignited potassium carbonate (10 mmol) was loaded into a quartz tube and inserted into a Teflon vial with a screw cap and subjected to microwave irradiation at 160 W for 4–5 min. Upon completion of the reaction, as indicated by TLC, it was diluted with ice cold water. The solid obtained was filtered off, dried and recrystallized from methanol to afford compounds **IIIa–IIIc**.

Synthesis of *Z*-Di/tetra/hexa/ydrodinaphtho[2,1-*b*:1,2-*d*][1,6]dioxa cycloalkenes (IVa–IVc). *Conventional heating.* A solution of 2,2'-bis(alkenyloxy)-1,1'-binaphthalenes (**IIIa–IIIc**) (1 mmol) in dry DCM (10 mL) was degassed for one hour at RT. The Grubbs second generation catalyst (0.3 mol %) was added to the reaction mixture. The latter was refluxed for 8–9 h. Progress of the process was monitored by TLC. Upon completion of the process the reaction mixture was filtered off, concentrated under vacuum. The crude residue was purified by column chromatography using 10% EtOAc in hexane as an eluent to afford pure products **IVa–IVc**.

Microwave irradiation. A solution of 2,2'-bis-(alkenyloxy)-1,1'-binaphthalenes (**IIIa–IIIc**) (1 mmol) in dry DCM (5 mL) was degassed for one hour at RT.

Table 4. Antifungal activity of *Z*-di/tetra/hexa/ydrodinaphtho-[2,1-*b*:1,2-*d*][1,6]dioxacycloalkenes (**IVa–IVc**)

Comp. no.	Zone of inhibition, mm		
	Aspergillus niger	*Penicillium italicum*	*Fusarium oxysporum*
IVa	08	16	22
IVb	09	15	25
IVc	11	20	22
Mycostatin	12	20	25

The Grubbs second generation catalyst (0.3 mol %) was added to the reaction mixture. The reaction mixture was loaded into a quartz tube and inserted into a Teflon vial with a screw cap and subjected to microwave irradiation at 160 W for 5–7 min. Upon completion of the process, as indicated by TLC, the reaction mixture was filtered off and concentrated under vacuum. The crude residue was purified by column chromatography using 10% EtOAc in hexane as an eluent to afford pure products **IVa–IVc**.

Compound IIIa. IR spectrum (KBr), ν, cm^{-1}: 1619 (C=C). ^{1}H NMR spectrum, δ, ppm: 7.98–8.0 d (2H, *J* 7.45, Ar-H), 7.81–7.83 d (2H, *J* 7.50, Ar-H), 7.32 t (2H, Ar-H), 7.25 t (2H, Ar-H), 7.12–7.14 d (4H, *J* 7.45, Ar-H), 5.0 d.d (4H, $=CH_2$), 4.51 d (4H, $O–CH_2$), 5.70–5.82 m (2H, –CH=). ^{13}C NMR spectrum, δ_C, ppm: 153.95, 134.07, 133.66, 129.24, 129.08, 127.8, 126.1, 125.42, 123.52, 120.29, 116.34, 115.62, and 69.86. LCMS *m/z* = 367 (100%) $[M + H]^+$. Found, %: C 85.23; H 6.08. $C_{26}H_{22}O_2$. Calculated, %: C 85.22; H 6.05.

Compound IIIb. IR spectrum (KBr), ν, cm^{-1}: 1622 (C=C). ^{1}H NMR spectrum, δ, ppm: 7.94–7.96 d (2H, *J* 7.45, Ar-H), 7.84–7.86 d (2H, *J* 7.42, Ar-H), 7.41–7.43 d (2H, *J* 7.54, Ar-H), 7.32 t (2H, Ar-H) , 7.12–7.28 m (4H, Ar-H), 3.95–4.05 m (4H, $O–CH_2$), 2.10–2.20 m (4H, $–CH_2$), 4.70–4.80 m (4H, $=CH_2$), 5.40–5.50 m (2H, –CH=). ^{13}C NMR spectrum, δ_C, ppm: 155.82, 133.97, 133.56, 130.14, 129.18, 128.0, 127.1, 126.22, 124.42, 121.39, 117.42, 114.92, 71.76 and 40.2. LCMS *m/z* = 395 (100%) $[M + H]^+$; Found, %: C 85.30; H 6.69. $C_{28}H_{26}O_2$. Calculated, %: C 85.25; H 6.64.

Compound IIIc. IR, (KBr), ν, cm^{-1}: 1620 (C=C). ^{1}H NMR spectrum, δ, ppm: 7.94–7.96 d (2H, *J* 7.45, Ar-H), 7.82–7.84 d (2H, *J* 7.42, Ar-H), 7.40–7.42 d (2H, *J* 7.50, Ar-H), 7.31 t (2H, Ar-H) , 7.05–7.12 m

(4H, Ar-H), 3.9–4.1 m (4H, O–CH_2), 1.6–1.8 m (4H, –CH_2), 1.4–1.55 m (4H, –CH_2), 5.4–5.6 m (4H, =CH_2), 4.65–4.80 m (2H, –CH_2). ^{13}C NMR spectrum, δ_C, ppm: 157.72, 135.02, 134.21, 131.24, 129.28, 127.1, 126.1, 125.12, 123.72, 121.89, 120.92, 115.72, 70.86, 41.34 and 38.20. LCMS *m/z* = 423 (100%) $[M + H]^+$. Found, %: C 85.30; H 7.21. $C_{30}H_{30}O_2$. Calculated, %: C 85.27; H 7.16.

Compound IVa. IR spectrum (KBr), ν, cm^{-1}: 1620 (C=C). ^{1}H NMR spectrum, δ, ppm: 7.90–7.92 d (2H, *J* 7.42, Ar-H), 7.78–7.91 d (2H, *J* 7.52, Ar-H), 7.35 t (2H, Ar-H), 7.20 t (2H, Ar-H) , 7.12–7.14 d (2H, *J* 7.42, Ar-H), 7.07 d (2H, *J* 7.45, Ar-H), 4.4 d.d (4H, O–CH_2), 5.52 t (2H, olefinic protons). ^{13}C NMR spectrum, δ_C, ppm: 153.68, 134.02, 129.02, 128.35, 127.81, 127.07, 126.14, 125.33, 123.35, 119.65, 114.75, 68.32. LCMS *m/z* = 339 (100%) $[M + H]^+$. Found, %: C 85.25; H 5.42. $C_{24}H_{18}O_2$. Calculated, %: C 85.18; H 5.36.

Compound IVb. IR spectrum (KBr), ν, cm^{-1}: 1621 (C=C). ^{1}H NMR spectrum, δ, ppm: 7.99–8.01 d (2H, *J* 7.40, Ar-H), 7.89–7.91 d (2H, *J* 7.52, Ar-H), 7.45 t (2H, Ar-H), 7.3 t (2H, Ar-H) , 7.04–7.06 d (2H, *J* 7.45, Ar-H), 7.14–7.16 d (2H, *J* 7.42, Ar-H), 4.0 d.d (4H, O–CH_2), 1.9–2.1 m (4H, –CH_2), 4.95 t (2H, olefinic protons). ^{13}C NMR spectrum, δ_C, ppm: 154.1, 133.9, 130.5, 129.1, 128.8, 127.5, 125.7, 124.9, 123.1, 120.4, 115.9, 69.0, 28.7. LCMS *m/z* = 367 (60%) $[M + H]^+$. Found, %: C 85.25; H 6.07. $C_{26}H_{22}O_2$. Calculated, %: C 85.22; H 6.05.

Compound IVc. IR spectrum (KBr), ν. cm^{-1}: 1620 (C=C). ^{1}H NMR spectrum, δ, ppm: 7.9–7.93 d (2H, *J* 7.42, Ar-H), 7.59–7.61 d (2H, *J* 7.50, Ar-H), 7.38 t (2H, Ar-H), 7.2 t (2H, Ar-H) , 7.01–7.03 d (2H, *J* 7.45, Ar-H), 7.11–7.13 d (2H, *J* 7.42, Ar-H), 3.6–3.8 d.d (4H, O–CH_2), 1.25–1.4 m (4H, –CH_2), 1.6–1.7 m (4H, –CH_2), 4.9 t (2H, olefinic protons). ^{13}C NMR spectrum, δ_C, ppm: 155.6, 134.4, 129.8, 128.2, 128.1, 127.2, 126.3, 125.2, 124.3, 123.2, 117.7, 69.2, 29.6, 28.7; LCMS *m/z* = 395 (78%) $[M + H]^+$. Found, %: C 85.29; H 6.69. $C_{28}H_{26}O_2$. Calculated, %: C 85.25; H 6.64.

CONCLUSIONS

An easy to handle, high yield and environmentally friendly synthesis of *Z*-di/tetra/hexa/ydrodinaphtho-[2,1-*b*:1',2'-*d*][1,6]dioxacycloalkanes promoted by microwave irradiation has been developed.

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