NOVEL ENTRY INTO RARE AND BIOACTIVE 5-DECARBOXY DIBENZOFURANS

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Introduction

The depsides and to some extent the depsidones are isolated from lichens as major constituents; however, diphenyl ethers and dibenzofurans are relatively rare (Huneck and Yoshimura, 1996). We report herein the oxidative cyclization with Pd $(OAC)_2$ of the synthetic diphenyl ether **2** and **3** (starting from the naturally occurring lichen compound erythrin **1)** containing a free carboxylic acid group leading to the novel synthesis of 5-decarboxy dibenzofurans **4** and **5**, which are structural analogues of the decarboxylated dibenzofurans hypostrpselic acid and ascomatic acid derivatives **6-9** reported from the lichen *Bundophorum pantagonicum*.

Materials and Methods

Diphenyl ether 3

Diphenyl ether **2** (1.30 g) was refluxed with excess methanolic NaOH. MeOH was evaporated and the residue was acidified and extracted into ethyl acetate. The crude product was subjected to column chromatography on silica gel (CH_2Cl_2 to 50 % CH_2Cl_2: MeOH) to give diphenyl ether **3** (0.69 g, 65 %) as the major product.

Dibenzofuran 4 and 5

Diphenyl ether **2** (0.18 g,) was dissolved in acetic acid (5 mL). To this solution palladium II acetate (0.15 g,) in trifluroacetic acid (5 mL) was added, and stirred at 37 °C for 4 h. The solvents evaporated, and the crude reaction mixture was subjected to column chromatography *via* silica gel (hexane: CH_2Cl_2, 10: 90, to 50 % CH_2Cl_2: MeOH) to yield the dibenzofuran **4** (0.1 g, 65 %). The diphenyl ether **3** (0.1 g,), when subjected to similar procedure as above, yielded the dibenzofuran **5** (0.07 g) in 77 % yield.

Bioassays

Super oxide inhibition (SOI) activities of the test compounds were determined by using the method described by Gaulejac *et al.*, The formation of super oxide was monitored by measuring the absorbance of the blue formazan dye at λ560 nm against the corresponding blank solutions. Propyl gallate (PG) was used as a positive control. DPPH (1, 1-Diphenyl-picrylhydrazyl) free radical scavenging activity were determined by measuring the change in absorbance of DPPH (1, 1,-diphenyl-2-picrylhydrazyl radical) at 517 nm by the spectrophotometric method developed by

Lee *et al.*, Propyl gallate and butyrated hydroxyanisole (BHA) were used as positive controls. β-Glucuronidase inhibitory activity was determined spectrometrically by measuring the absorbance at λ 405 nm of *p*-nitrophenol formed when the substrate *p*-nitrophenyl- β-D-glucuronide was hydrolysed by the enzyme (Atta-ur-Rahman and Choudhary, 2001).

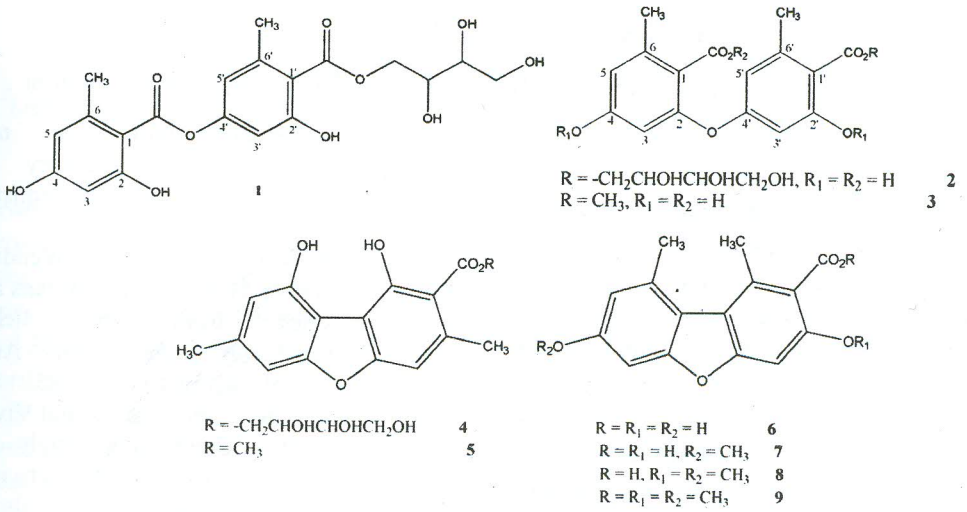

Figure 1. Structures of compounds 1-9

Results and Discussion

Erythrin **1** was successfully converted to its diphenyl ether **2** *via* Smiles rearrangement (Thadhani and Karunaratne, 2005). Compound **2** underwent transesterification upon refluxing in methanol and base to form the diphenyl ether **3**. Palladium(II) acetate mediated oxidative coupling (Shiotani and Itatani, 1976) of diphenyl ethers **2** and **3** containing a free carboxylic acid at C-1 led to the synthesis of members of a rare class of 5-decarboxy dibenzofurans **4** and **5**, where the carboxyl group had been lost during the oxidative cyclisation. Importantly, four structural analogues of compounds **4** and **5**, namely hypostrepsilic acid **6**, 6-*O*-methylnorascomatic acid **7**, ascomatic acid **8** and methyl ascomate **9**, were reported in 1994 by Elix *et al.*, as minor constituents from the lichen *B. patagonicum*, where C-1 and C-8 carried CH_3 groups whereas C-3 and C-6 had OH groups, which are the only examples of naturally occurring 5- decarboxy dibenzofurans isolated from lichens. Studies on bioactivities of lichen metabolites are scarce. Thus, compounds **1-5** were subjected to antioxidant activity in SOI assay (Gaulejac *et al.*, 1999)

Table 1. SOI, DPPH and β-glucuronidase activity of some lichen

Compound	% Inhibition (0.5 μM) *		
	SOI	DPPH	β-Glucuronidase
4	63.7 (276.0 ± 14.6)	82.1 (201.0 ± 0.9)	99.2 (46.9 ± 0.2)
5	13.7	70.2 (81.9 ± 3.8)	45.1
PG	(106.0 ± 1.7)	(30.0 ± 0.27)	-
BHA	(96.0 ± 1.8)	(44.0 ± 2.0)	-

NI = No Inhibition; * IC_{50} values (in μM) of strongly inhibiting compounds are given in

and DPPH (Lee *et al.*, 2004) assay and enzyme inhibitory activity against β-glucuronidase (Atta-ur-Rahman and Choudhary, 2001). There has been a resurgence of interest in free radicals because they play an important role in carcinogenesis. β-Glucuronidase is an exoglycosidase enzyme which is implicated in certain diseases such as cancer, inflammatory joint disease, and AIDS where the activity of β-glucuronidase increases. Bioassay results (Table 1) showed that the novel dibenzofurans **4** and **5,** which are structural analogues of naturally occurring very rare decarboxy dibenzofurans **6-9** (for which bioactivity data are not available), showed relatively high antioxidant activity in the DPPH assay when compared to the two standards propyl gallate and BHA. Moreover, compound **4** showed superior β-glucuronidase activity almost the same potency as the standard D-saccharic acid 1, 4- lactone (D-SAL).

References

Atta-ur-Rahman and Choudhary, M. I. (2001). Bioactive natural products as a potential source of new pharmacophores. A theory of memory. Pure Applied Chemistry, 73:555.

Elix, J. A., Venables, D.A. and Wendins, M. (1994). New dibenzofurans and depsides from the lichen *Bundophoron patagonicum*. Aust. Journal of Chemistry, 47: 1335.

Gaulejac, N. S. C., Provost, C. and Vivas, N.(1999). Compartive study of polyphenol scavenging activities assessed by different methods. Journal of Agriculture Food Chemistry, 47: 425.

Huneck, S. and Yoshimura, I. (1996). Identification of Lichen substances. Springer, 493.

Lee, S., Son, D., Ryu, J., Lee, Y.S., Jung, S.H., Lee, S.Y., Kim, H. S., and Shin, K. H. (2004). Antioxidant activities of *Acanthopanax senticosus* stems and their lignan components. Arch. Pharm. Res., 27: 106.

Shiotani, A. And Itatani, H. (1976). Palladium catalyzed dibenzofuran synthesis by dehydrogenative ring closure. Journal of Chemical Society. Perkin I:1236.

Thadhani,V.M. and Karunaratne V. (2005). Smiles re-arrangement on naturally occurring depsides–Erythrin and Lecanoric acid. Proceedings of PURSE 10, 148.