Synthesis of natural ether lipids and 1-O-hexadecylglycerol-arylboronates via an epoxide-ring opening approach: Potential antifouling additives to marine paint coatings.

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Abstract—In this paper a new and efficient procedure for the synthesis of natural 1-O-alkyl glyceryl ethers such as chimyl (1), batyl (2) and selachyl (3) is described. Alkyl glycidyl ethers (4-6) were synthesized using solvents free reactions. A stereospecific ring-opening reaction of epoxides (4-6) with phenylboronic acid in dry dioxane, giving rise to cyclic arylboronates in high yields (90-98%). Seven new 1-O-hexadecylglycerol-arylboronates (7-f) and chimyl alcohol (1) were evaluated in laboratory antifouling assays.

Keywords—Antifouling paints, Ethers lipids, Marine biofouling, Synthesis.

I. INTRODUCTION

Marine biofouling is a problem capable of generating great damages to the oil exploitation and transport sectors since platforms and vessels require constant repairs, especially on submerged surfaces. To address this issue, several coating paints and antifouling additives have been developed, since the 1950s, in order to decrease the growth of this biological community (marine bacteria, algae, mollusks). The problem is that these additives containing tin, zinc and cooper are expensive and very harmful to the environment[1-5].

In an attempt to reduce the damage caused by marine biofouling in an economically viable manner and according to prevailing environmental standards, our group of research has been using the residues of production of refined soybean oil and biodiesel, such as lecithins and glycerol, as raw material to produce new biocides to be added in antifouling paints and in the treatment of ships ballast water [6-12].

The 1-O-alkyl-sn-glycerols containing palmityl (C16:0), stearyl (C18:0), and oleyl (C18:1) in alkyl chains are dubbed chimyl (1), batyl (2) and selachyl (3) alcohols (Fig. 1). They are isolated from marine animals such as Batoidae (rays), Chimearids (ratfish), and Selachii (sharks) [13]. We have no knowledge of biofouling process being observed on the skin of these animals.

![Fig. 1 - The most prevalent 1-O-alkyl-sn-glycerols found in nature, batyl (1), chimyl (2) and selachyl (3) alcohols.](image-url)

II. EXPERIMENTAL

General Experimental Methods. All the chemicals were purchased commercially and used without further purification and anhydrous solvents were used in two steps. Yields refer to chromatographically pure compounds, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates (60F-254) using UV light as a visualizing agent and an acid solution of cerium sulfate, and heat. Silica gel (particle size: 230–400 mesh) was used for flash column chromatography. Neat compounds were used for recording IR spectra. Infrared spectra were obtained using a Perkin-Elmer 1600 FTIR spectrometer and were recorded using KBr pellets for solid compounds or as liquid films in the case of oily samples. NMR spectra were recorded on either 400 (¹H, 400 MHz; ¹³C, 100 MHz) or 300 (¹H, 300 MHz; ¹³C, 100 MHz) or 200 (¹H, 200 MHz; ¹³C, 100 MHz). Mass spectrometric data were obtained using QToF-6530 ESI-MS instruments. Melting points measurements were made using a hot stage.
The yield of the alkyl glycidyl ethers reported in the present study was obtained under pressure to afford the desired cyclic ethers; therefore, a similar experimental procedure was carried out using epichlorohydrin as starting material and performed with stearyl and oleylic alcohols giving the corresponding 1-O-octadecyl-2,3-epoxypropene (4) and 1-O-oleyl-2,3-epoxypropene (6) in 98% and 92% yield respectively. A similar experimental procedure was described by Yoon and coworkers [14].

The treatment of 1-O-hexadecyl-2,3-epoxypropene (4), 1-O-octadecyl-2,3-epoxypropene (5) and 1-O-oleyl-2,3-epoxypropene (6) with catalytic amounts of boron trifluoride etherate and 1.3 equivalents of phenyl boronic acid dissolved in dry dioxane, provided the 1-O-hexadecylglycerophenylboronate (7), 1-O-octadecylglycerophenylboronate (8) and 1-O-oleylglycerophenylboronate (9) in 100%, 99%, 97% yields. These products were not purified given their lack of stability under flash chromatography conditions; therefore, all yields were determined by 1H NMR techniques. A transesterification reaction using 1,3-propanediol in CHCl₃ promoted the cleavage of five-membered ring boronates (7, 8, 9) furnishing after flash chromatography purification the desired natural products chimyl (1), batyl (2) and selachyl (3) alcohols in 87%, 85%, 77% yields. (Scheme 1)

Compared to other procedures described in the present literature [13, 16, 17, 18, 19, 20, 21, 22] the synthesis of chimyl (1), batyl (2) and selachyl (3) alcohols described herein is an efficient synthetic approach, which presents a straightforward chemical transformation of an epoxide function to cyclic phenylboronate intermediates.

### Scheme 1 - Synthetic route for the preparation of compounds 1-3.

In order to confirm this result solutions of chimyl (1), batyl (2) and selachyl (3) alcohols with phenyl boronic acid in...
dry THF were stirred for 24.0 hours, and after the removal of the solvent only the corresponding 1-O-hexadecylglycero-phenylboronate (7), 1-O-octadecylglycero-phenylboronate (8) and 1-O-oleylglycero-phenylboronate (9) were obtained in quantitative yields. (Scheme 2)

Scheme 2 - Reaction of boronation of 1,2-diols with phenylboronic acid in dry THF, in good overall yields.

On scheme 3 we demonstrate other examples of this same type of chemical transformation to obtain the new 1-O-hexadecylglycero-arylboronates (7a-7f) in good overall yields (Scheme 3). Unfortunately, this type of conversion does not work with the heteroaryl boronic acids such as 2-furyl boronic acid and 3-piridinyl boronic acid to form the corresponding 1-O-hexadecylglycero-heteroarylboronates (7g-7h).

Scheme 3 - Chemical transformation of epoxide 4 to obtain the new 1-O-hexadecylglycero-arylboronates.

The unsuccessful attempt to yield the 1-O-hexadecylglycero-furfurylboronate (7g) is probably related to the opening of the furan ring system by BF₃·monohydrated (H₂O·BF₃) which is an efficient and strong acid catalyst formed during the reactional process [23]. In addition to that, the reaction also did not work well to obtain (7h) due the reactivity of BF₃·O (C₂H₅₃) which interacts preferably with the nitrogen atom of the pyridinyl ring instead of promoting the desired pathway of chemical transformation (Table 1).

Table 1 - The effects of the boronic acid type on the conversion rate of epoxide 4 to the boronic ester.

| Boronic acids        | Product                                      | Yield (%) |
|----------------------|----------------------------------------------|-----------|
| 4-methoxyphenyl      | 1-O-hexadecylglycero-4-methoxyphenylboronate  | 90%       |
| 3,4-methylenedioxy   | 1-O-hexadecylglycero-3,4-methylenedioxyphenylboronate | 93%       |
| dimethoxyphenyl      | 1-O-hexadecylglycero-3,5-dimethoxyphenylboronate | 91%       |
| 3,4-dimethoxyphenyl  | 1-O-hexadecylglycero-3,4-dimethoxyphenylboronate | 93%       |
| 3,5-dimethoxyphenyl  | 1-O-hexadecylglycero-3,5-dimethoxyphenylboronate | 91%       |

* All yields and diastereoselectivity were determined by ¹H NMR (300 MHz).

Regioselective and stereoselective epoxy-ring opening reactions are widely employed as important tools on the synthesis of natural products with biological activities [24, 25, 26].

We observed herein that in all epoxy-ring opening using the O-alkyl-glycidyl esters (4, 5, 6) as starting materials in the presence of aryl boronic acids using dioxane as solvent, and catalyzed by BF₃·O(C₂H₅₃) only products (7-7f, 8, 9) with the configuration syn (I) were formed. We did not observe ant (II) or six-membered ring products (III) which could be formed via epoxionium ions as described by Miyashita and coworkers [27] via a ring-opening mechanism of the epoxy sulfides by a similar reaction through the formation of the episulphonium ions (Figure 2).

Fig. 2 - Chemical structure of the possible aryl boronic esters produced in this step.

R = C₁₆H₃₃ or C₁₈H₃₇ or C₁₈H₃₅

Theoretical studies were carried out for compounds (I) and (II) using Density Functional Theory (DFT), with a GAUSSIAN 09 program with the B3LYP hybrid density functional combined with the 6-31G (d, p) basis set [28]. The calculation of frequencies used to find the minimum geometries does not have imaginary values. Analysis of the geometry optimization showed that compound (I) is 50 Kcal/mol more stable than compound (II), indicating the greater stability compound (I) with respect to compound (II), as observed experimentally in the synthesis of these compounds.
The 1-O-hexadecyglycerol-aryboronates (7-7f) were obtained in a single step from (4). A mechanistic proposal to explain this result is demonstrated on scheme 4. Due to the nucleophilic character of the intermediates (10-10f) to promote an internal attack through the hydroxyl groups of the phenyl boronic species on the carbon attached to the leaving group the corresponding 1-O-hexadecyglycerol-aryboronates (7-7f) will be promptly generated (Scheme 4).

Scheme 4- Mechanistic proposal for the formation of 1-O-hexadecyglycerol-aryboronates (7-7f).

Compounds (1 and 7-f) were selected and evaluated against biofilm-forming bacteria and the best results are demonstrated on Figure 1. The chimyl (1) and 1-O-hexadecyglycerol-aryboronates (7a, e) showed potential activity to be used as additives in antifouling paint coatings on ships and platforms. Specifically, chimyl (1) demonstrated better antibacterial activity compared to CuSO4 [29, 30] (Table 2).

Table 2 - Representative results of antifouling activity tests performed in laboratory. Degree of inhibition of bacteria growth (+++++ = higher; +++ = promising; ++ = acceptable, + = minimum); CuSO40.4miliM (main active component of standard commercial antifouling paints).

IV. BACTERIA PRESENT ON BIOFOULING PROCESS

| Compounds | P. fluorescens | Pseudoaero mo- nas | Vibrio estuarians |
|-----------|---------------|-------------------|------------------|
| (100 mg L⁻¹) |  |  |  |
| (1) | ++++ | +++ | ++++ |
| (7a) | ++ | + | ++ |
| (7e) | + | + | ++ |
| (7) | + | + | + |
| (7b) | + | + | + |
| (7c) | + | + | + |
| (7d) | + | + | + |
| (7f) | ++ | +++ | +++ |
| CuSO₄ | +++ | +++ | +++ |

Chimyl alcohol (1): (0.9g) 87%; pale yellow solid (mp. 62-64°C); IR (KBr, νmax/cm⁻¹) : 3368 (OH), 2954 – 2850 (CH), 1471 (CH), 1.124 (C-O); ¹H NMR (400 MHz, CDCl₃) δ 3.73 (m, 3H), 3.50 (m, 4H), 3.87 (m, 2H), 1.58 (m, 4H), 1.26 (s, 24H), 0.89 (t, J = 6.0, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 72.02, 71.41, 70.02, 63.82, 31.46, 25.62, 13.65.

Batyl alcohol (2) : (0.9g) 85%; white solid (mp. 70-72°C); IR (KBr, νmax/cm⁻¹) : 3363 (OH), 2954 – 2850 (CH), 1471 (CH), 1.123 (C-O); ¹H NMR (400 MHz, CDCl₃) δ 3.87 (m, 2H), 3.73 (m, 3H), 3.65 (m, 4H), 1.58 (d, J = 6Hz, 4H), 1.26 (s, 26H); 0.89 (t, J = 6.6 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 72.04, 71.41, 69.99, 63.83, 31.47, 25.62, 13.65.

Selachyl alcohol (3): (0.8g) 77%; colorless oil; IR (KBr, νmax/cm⁻¹) : 3383 (OH), 3004 – 2854 (CH), 1732 – 1654 (C=C), 1464 (CH), 1120 (C-O); ¹H NMR (400 MHz, CDCl₃) δ 5.36 (m, 5H), 3.86 (m, 2H), 3.67 (m, 3H), 3.48 (m, 4H), 2.03(d, J = 6Hz, 4H), 1.59 (m, 6H), 1.28 (d, J = 6Hz, 18), 0.89 (t, J = 6.6 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 129.52, 72.06, 71.40, 69.97, 63.84, 31.45, 28.86, 26.76, 25.62, 22.23, 13.66.

1-O- hexadecyl-2,3-epoxypropane (4): was obtained with a yield of 95% (1.2 g) as a white solid (mp. 24-26°C); IR (KBr, νmax/cm⁻¹) : 3048- 2851 (CH), 1467 (CH), 1253 (C-O), 1114 (C-O), 906 (C-C), 852 (C-C); ¹H NMR (400 MHz, CDCl₃) δ 3.72 (dd, J = 11.6 e 3.1 Hz, 2H), 3.51 – 3.35 (m, 2H), 3.18 – 3.13 (m, 1H), 2.79 (t, J = 9 Hz, 1H), 2.61 (dd, J = 4.9 e 2.9 Hz, 1H), 1.60 – 1.56 (m, 2H), 1.25 (s, 26H); 0.88 (t, J = 6.6 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 72.1, 71.8, 51.3, 44.7, 32.3, 30.8, 29.9, 29.7, 29.5, 23.1, 14.5.

1-O- Octadecyl-2,3-epoxypropane (5): 1.1 g (98%), white solid (mp. 42-45°C); IR (KBr, νmax/cm⁻¹) : 3052 (CH), 3000- 2850 (CH), 1473-1378 (CH), 1251 (C-O), 1125 (C-O), 906 (CH), 852 (CH), 729 (CH); ¹H NMR (500 MHz, CDCl₃) δ 3.72 (dd, J = 11.6 e 3.1 Hz, 2H), 3.53 – 3.37 (m, 2H), 3.18 – 3.15 (m, 1H), 2.80 (t, J = 5 Hz, 1H), 2.61 (dd, J = 5 and 5 Hz, 1H), 1.64 – 1.57 (m, 2H), 1.26 (s, 30H); 0.88 (t, J = 6.6 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 71.5, 71.2, 50.6, 44.1, 31.6, 30.8, 29.4, 29.1, 25.8, 22.4, 13.8.

1-O- oleyl-2,3- epoxy propane (6): 1.1 g (92%), colorless oil, IR (KBr, νmax/cm⁻¹) : 3052 (CH), 3002-2854 (CH), 1732 – 1655 (C=C), 1465 (CH), 1253 (C-O), 1125 (C-O); ¹H NMR (300 MHz, CDCl₃) δ 5.36 (m, 2H); 3.72 (dd, J = 11.5 and 3.2 Hz, 2H); 3.52 – 3.36 (m, 2H), 3.19 – 3.14 (m, 1H), 2.80 (t, J = 9 Hz, 1H), 2.62 (dd, J = 4.9 and 2.9 Hz, 2H), 2.02 – 1.98 (m, 4H), 1.63 – 1.54 (m, 2H), 1.30 (d, J = 6, 22H), 0.88 (t, J = 6.6 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 129.5, 129.5 , 72.1, 71.9, 51.3, 44.7, 32.3, 30.1, 29.7, 29.6, 26.5, 23.1, 14.5.

1-O-hexadecylglycerol-phenylboronate (7): 1.3g (100%); colorless oil; IR (KBr, νmax/cm⁻¹) : 2852 – 2920 (CH), 1354 (B-O), 1121 – 1219 (C-O), 700 – 756 (CH); ¹H NMR (400 MHz, CDCl₃) δ 7.85 (d, J = 6, 2H), 7.54 – 7.39 (m, 3H), 4.74- 4.71 (m, 2H), 4.44 (t, J=9, 1H), 4.19 (t, J=...
1-O-hexadecyglycido-4-methoxyphenylboronate (7a): 1.3g (90%); dark brown oil; \(\text{IR (KBr, }\nu_{\text{max}}/\text{cm}^{-1}) : 2850 – 2917 \text{ (CH)}, 1379 (B-O), 1123 (C-O); \text{1H NMR (200 MHz, CDCl}_3) \delta 7.76 (d, J = 4, 2H), 6.94 (d, J = 8, 2H), 4.78-4.67 (2H, 4.41 (t, J = 8, 1H), 4.16 (t, J = 6, 2H), 3.61-3.49 (2H), 1.58 (m, 2H), 1.27 (s, 26H), 0.90 (t, J = 6, 3H); \text{13C NMR (100 MHz, CDCl}_3) \delta 162.3, 136.7, 110.8, 76.1, 72.8, 72.1, 68.5, 32.0, 29.7, 29.6, 29.5, 29.4, 26.1, 22.7, 14.1.

1-O-hexadecyglycido-3,4-methylenedioxyphenylboronate (7b): 1.4g (93%); brown oil; \(\text{IR (KBr, }\nu_{\text{max}}/\text{cm}^{-1}) : 2851 – 2920 \text{ (C-H), 1339 (B-O), 1121 (C-O), 1029 (B-C), 679 – 760 (C-H); \text{1H NMR (200 MHz, CDCl}_3) \delta 7.37 (d, J = 8, 1H), 6.87 (d, J = 8, 1H), 5.98 (s, 2H), 4.73 – 4.63 (m, 2H), 4.40 (t, J=8, 1H), 4.16 (t, J = 6, 3H), 3.62-3.48 (2H), 1.58 (m, 2H), 1.27 (s, 26H), 0.90 (t, J = 6, 3H); \text{13C NMR (100 MHz, CDCl}_3) \delta 150.4, 147.3, 136.7, 110.8, 76.2, 72.7, 72.1, 68.6, 32.0, 29.7, 29.5, 29.4, 26.1, 22.7, 14.1.

1-O-hexadecyglycido-3,5-dimethoxyphenylboronate (7c): 1.4g (91%); brown oil; \(\text{IR (KBr, }\nu_{\text{max}}/\text{cm}^{-1}) : 2851 – 2917 \text{ (CH), 1348 (B-O), 1120 (C-O), 674 – 798 (CH); \text{1H NMR (200 MHz, CDCl}_3) \delta 6.99 (s, 1H), 6.98 (s, 2H), 4.76 – 4.689(m, 2H), 4.43 (t, J = 8, 1H), 4.19 (t, J = 6, 2H), 3.82 (s, 6H), 3.64-3.48 (m, 2H), 1.58 (m, 2H), 1.27 (s, 26H), 0.90 (t, J = 6, 3H); \text{13C NMR (100 MHz, CDCl}_3) \delta 160.5, 111.8, 104.7, 76.3, 72.7, 76.3, 68.6, 32.0, 29.7, 29.5, 29.4, 26.1, 22.7, 14.1.

1-O-hexadecyglycido-3,4-dimethoxyphenylboronate (7d): 1.5g (98%); pale yellow oil; \(\text{IR (KBr, }\nu_{\text{max}}/\text{cm}^{-1}) : 2850 – 2918 \text{ (CH), 1380 (B-O), 1122 (C-O), 1038 (B-C), 671 – 734 (CH); \text{1H NMR (200 MHz, CDCl}_3) \delta 7.47 (d, J = 6, 3H, 7.32 (s, 1H), 6.93 (d, J = 8, 1H, 4.78 – 4.68(m, 2H), 4.42 (t, J = 8, 1H), 4.17 (t, J = 6, 2H), 3.93 (s, 6H), 3.64-3.48 (m, 2H), 1.58 (m, 2H), 1.27 (s, 26H), 0.90 (t, J = 6, 3H); \text{13C NMR (100 MHz, CDCl}_3) \delta 151.9, 148.4, 128.8, 116.8, 110.8, 76.2, 72.8, 72.1, 68.5, 55.9, 55.7, 32.0, 29.7, 29.5, 29.4, 26.1, 22.7, 14.1.

1-O-hexadecyglycido-2,3-dimethoxyphenylboronate (7e): 1.3g (93%); dark brown oil; \(\text{IR (KBr, }\nu_{\text{max}}/\text{cm}^{-1}) : 2852 – 2921 \text{ (CH), 1347 (B-O), 1263 – 1059 (C-O), 721 – 792 (CH); \text{1H NMR (200 MHz, CDCl}_3) \delta 7.09 (d, J = 8, 2H), 6.93 (m, 1H), 4.78 – 4.68(m, 2H), 4.43 (t, J=8, 1H), 4.20 (t, J = 6, 2H), 3.82 (s, 6H), 3.61-3.48 (m, 2H), 1.58 (m, 2H), 1.27 (s, 26H), 0.90 (t, J = 6, 3H); \text{13C NMR (100 MHz, CDCl}_3) \delta 154.7, 152.6, 128.1, 124.1, 120.9, 111.8, 75.9, 72.7, 72.0, 68.5, 56.0, 55.9, 32.0, 29.7, 29.5, 29.4, 26.1, 22.7, 14.1.

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