

## Modifications of total synthesis of mycophenolic acid

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### ABSTRACT

The total synthesis of mycophenolic acid (MPA), a potent immunosuppressant, was modified.

The obtained mycophenolic acid was suitable for further preparation of new prospective immunosuppressants with improved therapeutic properties.

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## 1. Introduction

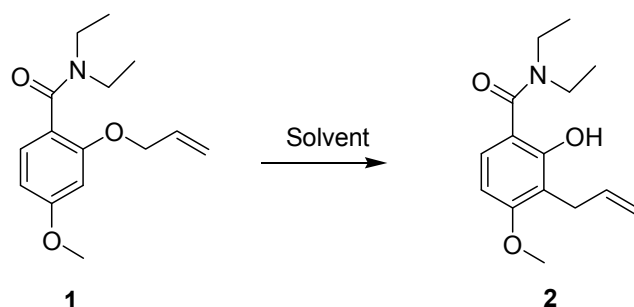
Mycophenolic acid (MPA) is an immunosuppressive drug widely applied in prophylaxis of organ transplant rejection.<sup>1-6</sup> However, the risks of rejection and side effects in the course of clinical treatment were not eliminated. As a result, numerous MPA modifications together with their biological evaluations were reported.<sup>7-18</sup> Although MPA is produced in industrial scale via fermentation processes,<sup>19</sup> its price for laboratory scale is still high. In the chemical literature are described attempts of total synthetic MPA from commercially available substrates. Some of them enable to prepare MPA analogs which are difficult to obtain by a modification of starting MPA molecule, since the structure of target derivative can be altered at the relevant synthetic stages.

In our research we decided to prepare some new MPA derivatives for examination of their immunosuppressive activity. For this purpose we choose Patterson's synthetic strategy as the most convenient one for obtaining of MPA in several grams scale.<sup>20-22</sup> In this article we report implemented in our work practical modifications of MPA synthesis.

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## 2. Results and discussion

One of the key intermediate in Patterson's synthetic route to mycophenolic acid is *N,N*-diethyl-2-hydroxy-4-methoxy-3-(prop-2-enyl)benzamide **2** (**Scheme 1**) obtained through the Claisen rearrangement of *N,N*-diethyl-4-methoxy-2-(prop-2-enyloxy)benzamide **1** (prepared from methyl 2-hydroxy-4-methoxybenzoate in two stages according to literature<sup>20</sup>) in tetramethylbenzene at reaction temperature of 210 °C the yield of the product was 86 % after 6 h of stirring.<sup>20</sup> Noteworthy, there are three isomeric tetramethylbenzenes available commercially: 1,2,3,4-tetramethylbenzene (bp 205 °C),<sup>23</sup> 1,2,3,5-tetramethylbenzene (bp 198 °C),<sup>24</sup> 1,2,4,5-tetramethylbenzene (bp 197 °C).<sup>25</sup> Both 1,2,3,4- and 1,2,3,5- isomers are rare and expensive chemicals. In contrast to that, 1,2,4,5-tetramethylbenzene is an easy available compound which we have used as a solvent in synthesis of *N,N*-diethyl-2-hydroxy-4-methoxy-3-(prop-2-enyl)benzamide (**2**). However, the reaction carried out in boiling 1,2,4,5-tetramethylbenzene gave product with only 15 % yield (**Table 1**).



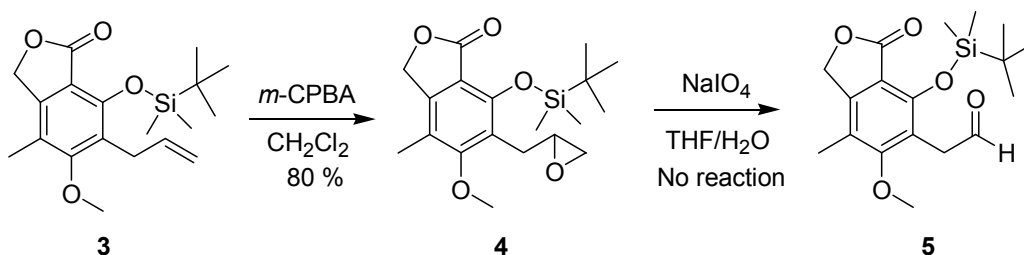
**Scheme 1.** Claisen rearrangement of *N,N*-diethyl-4-methoxy-2-(prop-2-enyloxy)benzamide **1**

**Table 1.** Conditions for conversion of *N,N*-diethyl-4-methoxy-2-(prop-2-enyloxy)benzamide **1** to *N,N*-diethyl-2-hydroxy-4-methoxy-3-(prop-2-enyl)benzamide **2**.

Entry	Solvent	Temp. (°C)	Time (h)	Yield (%)
1	1,2,4,5-tetramethylbenzene	197	12	15
2	tetralin	206-208	2	73
3	nitrobenzene	210 – 211	2	72
4	3,4-dimethylchlorobenzene	221 – 223	2	56

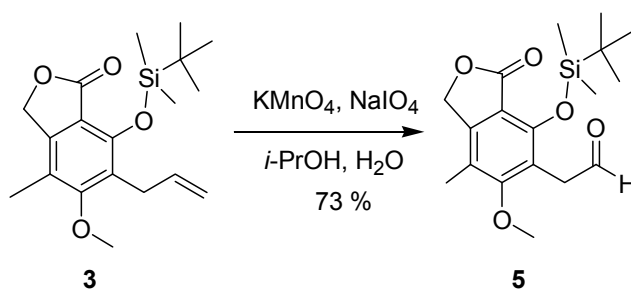
The Claisen rearrangement proceeds according to pericyclic, one step mechanism, which is very important in the case of stereocontrolled synthesis.<sup>22</sup> This reaction was extensively studied and solvent is one of the most important parameters to be optimised.<sup>26</sup> We concluded, that the solvents with a higher boiling points should be more appropriate. Thus, we examined tetralin, nitrobenzene, 3,4-dimethylchlorobenzene. Data, collected in the **Table 1** show, that tetralin and nitrobenzene with similar boiling points about 210 °C gave the good 72-73% yields after relative short (2 h) reaction time, while the reaction run in 3,4-dimethylchlorobenzene at 221 °C furnish product **2** in slightly lower 56% yield, which could be due to decomposition and undesired side reactions at elevated temperature. Subsequent reaction steps towards mycophenolic acid required 1,3-dihydro-4-[(*tert*-butyldimethylsilyloxy)-6-methoxy-7-methyl-3-oxo-5-(propan-3-allyl)isobenzofuran **5** (**Scheme 2**). Similarly to procedure described by Plé,<sup>27</sup> we oxidized 1,3-dihydro-4-[(*tert*-butyldimethylsilyloxy)-6-methoxy-7-methyl-3-oxo-5-(prop-2-enyl)isobenzofuran **3** (prepared from **2** in six stages according to literature<sup>20</sup>) to 1,3-dihydro-4-[(*tert*-butyldimethylsilyloxy)-6-methoxy-7-methyl-3-oxo-5-(2,3-epoxypropanyl)isobenzofuran **4** which is an obvious precursor of aldehyde **5**. Reaction of alkene **3** with *m*-CPBA occurred with 80 % yield, but epoxide **4** turned out to be a stable one and its conversion with sodium periodate to aldehyde **5** was not successful. As a results, transformation of alkene **3** to **5** needed

ozonolysis,<sup>20</sup> however we decided to rational explain the lack of reactivity of intermediate **4** and use alternative protocol for synthesis of aldehyde **5**.



**Scheme 2** Synthetic approach to aldehyde **5** via epoxide **4**.

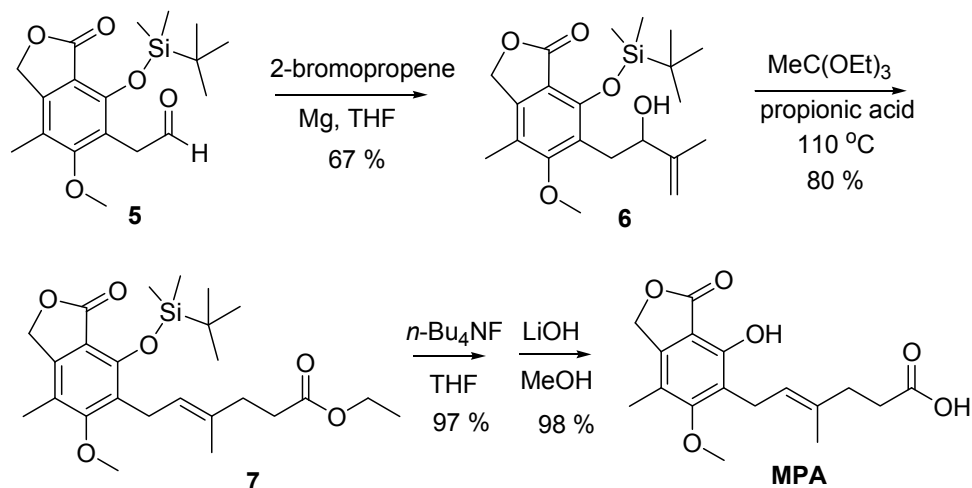
Epoxides constitute a class of the significant intermediates,<sup>28</sup> and their oxidation with sodium periodate to respective carbonyls was also examined.<sup>29</sup> Binder and co-workers concluded, that some epoxides give this reaction with lower yield due to incomplete hydrolysis.<sup>29</sup> The oxidation of **4** with sodium periodate we observed no aldehyde **5** formation what could be explain by steric hindrance preventing the epoxide ring in **4** from opening. The detailed characteristics of epoxide **4** were reported by our research group previously and its X-ray structure was also determined.<sup>30</sup> The cleavage of 1,2-diols to aldehydes or ketones with periodic acid is a widely used reaction,<sup>29,31</sup> however it was demonstrated, that oxidation of epoxides does not have to proceed through respective diols.<sup>32</sup> In case of epoxide **4**, a possible periodate complex might not be formed since the steric hindrance from near methoxyl and TBDMS ( $t\text{-BuMe}_2\text{Si-}$ ) substituents. Moreover, compound **4** is stable under storing for several months. In contrast to that, ozonolysis of alkene **3** proceeds smoothly and gives aldehyde **5** in good yield.<sup>20</sup> We concluded, that neighbouring methoxyl and TBDMS groups do not interrupt in formation of respective ozonide – an intermediate upon dipolar [3+2] cycloaddition of ozone to alkene<sup>33</sup> because of lower steric requirements if compared with a periodate moiety. Subsequently, we treated alkene **3** successfully with mixture of potassium permanganate and sodium periodate to desired aldehyde **5** (**Scheme 3**) in 73 % yield, which could be explained by another reaction mechanism and higher oxidative potency of  $\text{KMnO}_4/\text{NaIO}_4$  system.



**Scheme 3.** Oxidation of alkene **3** to aldehyde **5**.

Possessing intermediate **5** we were able to continue our approach to mycophenolic acid (MPA) according to synthetic pathway described by Patterson (**Scheme 4**).<sup>20-22</sup>





**Scheme 4.** Synthesis of mycophenolic acid (MPA) from aldehyde **5** according to methods described by Patterson.<sup>20-22</sup>

In this method aldehyde **5** underwent nucleophilic addition with isopropenylmagnesium bromide to 6-(2-hydroxy-3-methylbut-3-enyl)-5-methoxy-7-(2-(*tert*-butyldimethylsilyl)oxy)-4-methyl-3*H*-isobenzofuran-2-one **6**. Subsequently, allylic alcohol **6** was treated with ethyl orthoacetate to form upon the orthoester Claisen rearrangement ethyl ester of (*E*)-6-[1,3-dihydro-4-(*tert*-butyldimethylsilyl)oxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl]-4-methylhex-4-enoic acid **7**. Finally, removing of *tert*-butyldimethylsilyl group with tetrabutylammonium fluoride followed by hydrolysis of ethyl ester gave (*E*)-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methylhex-4-enoic acid (MPA).<sup>20-22</sup>

### 3. Conclusion

Application of easy available tetralin as a solvent in the Claisen rearrangement of allyl ether **1** gave phenol derivative **2** with similar yield as obtained under conditions described by Patterson.<sup>20</sup> In the next part of synthetic pathway towards mycophenolic acid (MPA), oxidation of alkene **3** with *m*-CPBA provided unexpectedly stable epoxide **4**, and synthesis of aldehyde **5** required direct oxidation of alkene **3**. The final mycophenolic acid was identical with purchased one (Tocris Bioscience), and we were able to use it in synthesis of the novel analogues of MPA.<sup>34-37</sup>

1.

### 4. Experimental section

NMR spectra were recorded with Varian Unity Plus 500 MHz in CDCl<sub>3</sub> according to TMS. Coupling constants are given in Hz. Column chromatography was carried out on silica gel Merck 60 (0.063-0.2 mm), eluent: petroleum ether - ethyl acetate 10:1 v/v. The reactions were followed with TLC technique on plates Merck 60 F<sub>254</sub>, eluent: petroleum ether - ethyl acetate 10:1 v/v. Solvents used in the Claisen rearrangement of *N,N*-diethyl-4-methoxy-2-(prop-2-enyloxy)benzamide **1**, and THF, isopropanol were distilled before use.

#### 4.1. Synthetic procedures

4.1.1. The Claisen rearrangement of *N,N*-diethyl-4-methoxy-2-(prop-2-enyloxy)benzamide **1** to *N,N*-diethyl-2-hydroxy-4-methoxy-3-(prop-2-enyl)benzamide **2** (Table 1)



*N,N*-Diethyl-4-methoxy-2-(prop-2-enyloxy)benzamide **1**<sup>20</sup> (2 mmol) was refluxed in boiling solvent (2 mL), and the reaction progress was followed by TLC (petroleum ether - ethyl acetate 10:1 v/v). When the starting material disappeared, the solvent was evaporated under vacuum, and *N,N*-diethyl-2-hydroxy-4-methoxy-3-(prop-2-enyl)benzamide **2** purified with column chromatography (petroleum ether - ethyl acetate 10:1 v/v). *N,N*-Diethyl-2-hydroxy-4-methoxy-3-(prop-2-enyl)benzamide **2**, characteristics in agreement with literature data<sup>20</sup>, additionally appeared resonance signal from phenol group:

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>), δ [ppm]: 1.30 (t, 6H, *J*=7.1Hz, CH<sub>2</sub>CH<sub>3</sub>), 3.46 (d, 2H, *J*=5.9Hz, CH<sub>2</sub>-CH), 3.53 (q, 4H, *J*=7.1Hz, CH<sub>2</sub>CH<sub>3</sub>), 3.87 (s, 3H, OCH<sub>3</sub>), 5.0 (m, 2H, CH=CH<sub>2</sub>), 6.0 (m, 1H, CH=CH<sub>2</sub>), 6.42 (d, 1H, *J*=8.3Hz, C<sub>6</sub>H<sub>5</sub>), 7.18 (d, 1H, *J*=8.8Hz, C<sub>6</sub>H<sub>5</sub>), 10.55 (s, 1H, OH).

#### 4.1.2. [4-(*tert*-Butyldimethylsilyloxy)-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl]-acetaldehyde **5**

Synthesis and structural characteristic of 1,3-dihydro-4-[(*tert*-butyldimethylsilyloxy)-6-methoxy-7-methyl-3-oxo-5-(2,3-epoxypropyl)isobenzofuran **4** were reported previously.<sup>30</sup> Attempts to oxidize of 1,3-dihydro-4-[(*tert*-butyldimethylsilyloxy)-6-methoxy-7-methyl-3-oxo-5-(2,3-epoxypropyl)isobenzofuran **4** to 1,3-dihydro-4-[(*tert*-butyldimethylsilyloxy)-6-methoxy-7-methyl-3-oxo-5-(propan-3-yl)isobenzofuran aldehyde **5** with sodium periodide, analogically to procedures described in literature, where other epoxides were converted to respective aldehydes.<sup>27,38</sup> To a stirred and cooled (-70 °C) solution of **4** (0.5 mmol) in THF (5 mL) was added dropwise sodium periodate (0.5 mmol) in water (25 mL) and stirred at room temperature for 24 h. The reaction mixture was monitored with TLC technique and only starting materials were indicated. Addition of sodium periodate at 0°C did not cause any reaction. Use of two molar excess of sodium periodate did not result in reaction progress, and decomposition of the substrate **4** was observed. The <sup>1</sup>H NMR spectrum of the crude reaction mixture did not contain characteristic peak from aldehyde **5**.

#### 4.1.3. Synthesis of [4-(*tert*-butyldimethylsilyloxy)-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl]-acetaldehyde **5** from alkene **3**<sup>20</sup> with KMnO<sub>4</sub>/NaIO<sub>4</sub>.

Alkene **3** (5.7 mmol) was dissolved in *i*-PrOH (30 mL) and potassium permanganate (16 mmol) was added portionwise. Then reaction was monitored with TLC technique (petroleum ether - ethyl acetate 10:1 v/v) and when starting material was consumed, sodium periodate (16 mmol) in water (5 mL) was added. The reaction mixture was stirred until the whole substrate reacted. Then, the reaction mixture was poured into water and extracted with ethyl acetate. The combined organic layers were washed with NaHCO<sub>3</sub> until pH 7 was achieved, dried over MgSO<sub>4</sub>, filtered, evaporated under vacuum. The crude material was purified with column chromatography (petroleum ether - ethyl acetate 10:1 v/v) to give aldehyde **5** with 73 % yield.

[4-(*tert*-Butyldimethylsilyloxy)-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl]-acetaldehyde **5**, was reported in literature<sup>20</sup> as intermediate in MPA synthesis without NMR data.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>), δ [ppm]: 0.24 (s, 6H, SiCH<sub>3</sub>), 1.03 (s, 9H, Si-*t*-Bu), 2.19 (s, 3H, C<sub>6</sub>H<sub>5</sub>-CH<sub>3</sub>), 3.73 (m, 5H, OCH<sub>3</sub>, C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>), 5.12 (s, 2H, OCH<sub>2</sub>), 9.63 (s, 1H, CHO).

## 5. Conflict of interest

There is no conflict of interest.

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