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CHEMICAL SCIENCES

Straightforward synthesis of cytosporone analogs AMS35AA and AMS35BB

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Abstract: Cytosporones, a class of octaketide resorcinolic lipids, have drawn the attention of researchers for exhibiting a number of notable biological properties. Herein, we describe routes to synthesize the bioactive synthetic resorcinolic lipids AMS35AA and AMS35BB with excellent overall yields using 3,5-dimethoxybenzoic acid as the starting material. The methods proved remarkably efficient to achieve the target compounds and comprise the synthesis of AMS35AA catalyzed by ascorbic acid (vitamin C).

Key words: cytosporones, Friedel–Crafts acylation, organocatalysis, methanolysis, vitamin C.

INTRODUCTION

Octaketide resorcinolic lipids named cytosporones have attracted a great deal of interest from many researchers. They exhibit notable biological potential, comprising fungicidal, allelopathic, bactericidal, and cytotoxic activities (Meza et al. 2015). Recently, novel, structurally similar octaketides have been isolated and a few approaches for the synthesis of these molecules were reported (Meza et al. 2015, Cochrane et al. 2016, Zamberlam et al. 2012, Dos Santos et al. 2009, Zhenga et al. 2019, Dos Santos et al. 2020). These findings also revealed that cytosporones are potentially pharmaceutical and agrochemical agents (Meza et al. 2015, von Delius et al. 2017). The most representative compounds in this class of resorcinolic lipids are cytosporones A-E (**1-5**, Figure 1), isolated from the endophytic fungi *Cytospora* sp. and *Diaporthe* sp. (Brady et al. 2000, Voblikova et al. 1985).

In recent investigations, our group has demonstrated that three synthetic cytosporone analogs, termed AMS35AA (**6**), AMS35BB (**7**), and AMS049 (**8**), have the ability to enhance the mutagenic effect of cyclophosphamide and to induce apoptosis in mice (Figure 1). Additionally, the analogs are neither genotoxic nor mutagenic and do not affect biochemical parameters (Navarro et al. 2014, 2012, Oliveira et al. 2015, Rabacow et al. 2018). Furthermore, strong evidence has recently shown (Oliveira et al. 2020) that AMS35AA itself or associated with cyclophosphamide (CY), has no toxic effects on spermatogenesis, suggesting that it might be used in association with CY in chemotherapy without adverse effects on testicular function. However, the method available for preparing **6** and **7** provides low yields (Navarro et al. 2014), which is a critical drawback for *in vitro* and *in vivo* bioassays.

Herein we report improved experimental approaches to obtain the cytosporone analogs **6** and **7** with excellent yields. We also highlight the preparation of **6** using ascorbic acid (vitamin C) as organocatalyst.

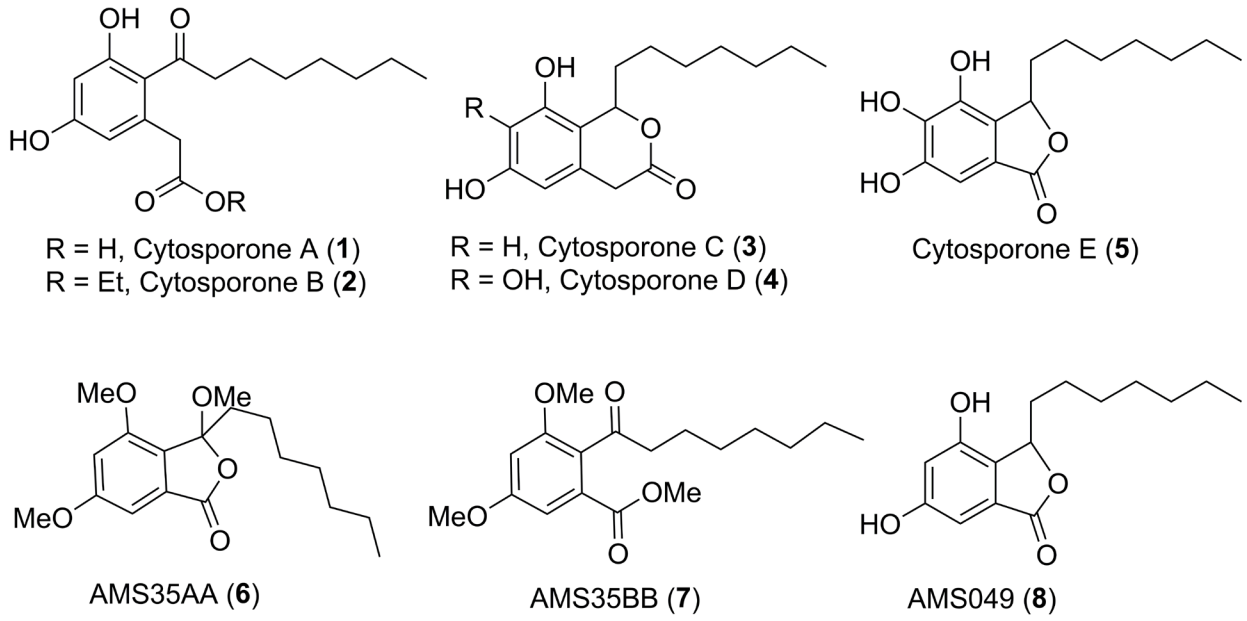


Figure 1. Molecular structures of cytosporones A-E (1-5) and synthetic analogs AMS35AA (6), AMS35BB (7), and AMS049 (8).

MATERIALS AND METHODS

All reagents and solvents were commercially obtained (Merck, São Paulo, Brazil and/or Labsynth, São Paulo, Brazil) and used as purchased. TLC was performed on glass plates coated with silica gel 60 F254 (Merck, São Paulo, Brazil). The plates were visualized using UV radiation (254 nm), iodine, or both. Column chromatography was performed on Merck silica gel (60 × 120 mesh) in a glass column. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX-300 apparatus. Chemical shifts were reported in δ (ppm) relative to tetramethylsilane (TMS) or residual solvent signals as the internal standard ($CHCl_3$, δ = 7.26), and coupling constants (*J*) given in hertz. Multiplicity: br = broad, s = singlet, d = doublet, t = triplet, m = multiplet.

Phthalide **9** was prepared as per Navarro et al. (2014) with a 98% yield. NMR spectra (^{1}H and ^{13}C) for compound **9** can be found in the Supplementary Material (Figures S1 and S2, respectively).

Experimental procedure

Synthesis of methyl 3,5-dimethoxybenzoate (12)

Concentrated sulfuric acid (2.5 mL) was slowly added to a solution of 3,5-dimethoxybenzoic acid (5 g, 27.46 mmol) in methanol. The reaction mixture was then heated to reflux. After 6 h, the reaction mixture was cooled to room temperature. The solvent was evaporated under reduced pressure. The residue was solubilized in ethyl acetate (50 mL), and the organic phase neutralized with 8% sodium bicarbonate solution (2 × 20 mL) and washed with distilled water (2 × 20 mL) and brine (2 × 5 mL). The organic phase was dried over $MgSO_4$, filtered, and the solvent evaporated by reduced pressure, resulting in ester **12** and used with no further purification steps. ^{1}H NMR (300 MHz, acetone-d6) δ: 3.67 (6H, s), 3.71 (3H, s), 6.54 (t, 1H, *J* 2.1), 6.95 (d, 1H, *J* 2.1 Hz). ^{13}C NMR (75 MHz, acetone-d6) δ: 52.5, 55.9, 105.8, 107.8, 133.1, 161.9, 167.0. (See figures S9 and S10 in the Supplementary Material)

Synthesis of 3-heptyl-3-hydroxy-4,6-dimethoxyisobenzofuran-1(3H)-one (13)

A mixture of phthalide **9** (0.2 mmol, 0.058 g) and 1M Na_2CO_3 aqueous solution (20 mL) was refluxed for 3 h. The product was extracted with dichloromethane (3 × 10 mL) and washed with 1 M HCl solution (5 mL) and distilled water (5 mL). The organic phase was dried over $MgSO_4$, filtered, and the solvent evaporated by reduced pressure. The product was purified by silica gel column chromatography, using hexane : ethyl acetate (7:3) as the eluent, resulting in a white solid with a 98% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.84 (3H, t, *J* 6.8 Hz), 1.15-1.30 (10H, m), 2.17-2.30 (2H, m), 3.84 (3H, s), 3.87 (3H, s), 6.57 (1H, br), 6,85 (1H, br). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.1, 22.7, 23.5, 29.1, 29.3, 31.8, 37.5, 56.0, 56.1, 99.2, 105.3, 105.3, 128.9, 129.8, 155.6, 163.4, 168.8. (See figures S3 and S4 in the Supplementary Material)

Synthesis of 3-heptyl-3,4,6-trimethoxyisobenzofuran-1(3H)-one (6)

From methyl 3,5-dimethoxy-2-octanoylbenzoate (**7**): $NaBH_4$ (35 mg, 0.92 mmol) was added to a solution of **7** (2 g, 6.21 mmol) in methanol (20 mL). The mixture was stirred at room temperature for 72 h. The solvent was then evaporated under reduced pressure, resulting in a yellowish liquid subsequently purified by chromatographic column using a mixture of hexane : ethyl acetate (7:3) as the eluent, yield: 60%, yellowish oil.

From 3-heptyl-3-hydroxy-4,6-dimethoxyisobenzofuran-1(3*H*)-one (**13**): Ascorbic acid (17 mg, 0.10 mmol) was added to a solution of **13** (33 mg, 100 mmol) in methanol (20 mL) and the mixture was stirred at room temperature for 48 h. The resulting product was extracted with ethyl acetate (3 × 20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The product was purified by chromatographic column using hexane:ethyl acetate (7:3) as the eluent, yield: 80%, yellowish oil. AMS35AA (**6**): ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.75 (3H, t, *J* 6.7 Hz), 0.9-1.3 (10H, m), 1.96-2.05 (1H, m), 2.13-2.23 (1H, m), 2.97 (3H, s), 3.80 (s, 3H), 3.82 (s, 3H), 6.63 (1H, d, *J* 1.8 Hz), 6.83 (1H, d, *J* 1.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.9 (CH_3), 22.5 (CH_2), 23.1 (CH_2), 28.9 (CH_2), 29.2 (CH_2), 31.6 (CH_2), 36.8 (CH_2), 51.0 (CH_3), 55.9 (CH_3), 98.9 (CH), 104.8 (CH), 111.13 (C), 126.0 (C), 130.9 (C), 155.5 (C), 163.6 (C), 168.2 (C). (See figures S5 and S6 in the Supplementary Material)

Synthesis of methyl 3,5-dimethoxy-2-octanoylbenzoate (7)

From methyl 3,5-dimethoxybenzoate (**12**): Under N_2 atmosphere, $AlCl_3$ (0.4 g, 3 mmol) was added to a solution of ester **12** (0.4 g, 2 mmol) in dichloromethane (15 mL), followed by dropwise addition of octanoyl chloride (0.5 mL, 477 mg, 2.9 mmol). The resulting mixture was stirred at room temperature for 72 h, after which a previously prepared 1 M KOH solution (50 mL) was added. The reaction mixture was vacuum-filtered with additions of dichloromethane and subsequently extracted using the same solvent and dried over $MgSO_4$. The reaction mixture was concentrated by reduced pressure and the product was purified by chromatographic column using hexane:ethyl acetate (10:1) as the eluent, yield: 75%, yellowish oil.

From 3-heptyl-3-hydroxy-4,6-dimethoxyisobenzofuran-1(3*H*)-one (**13**): K_2CO_3 (0.3 g, 2.17 mmol) and methyl iodide (1.6 mmol) were added to a solution of **13** (0.4 g, 1.3 mmol) in acetone (20 mL) and cooled in an ice-and-water bath. After 30 min, the bath was removed and the reaction mixture was stirred at room temperature for a further 24 h, then, distilled water (50 mL) was added and the product extracted with

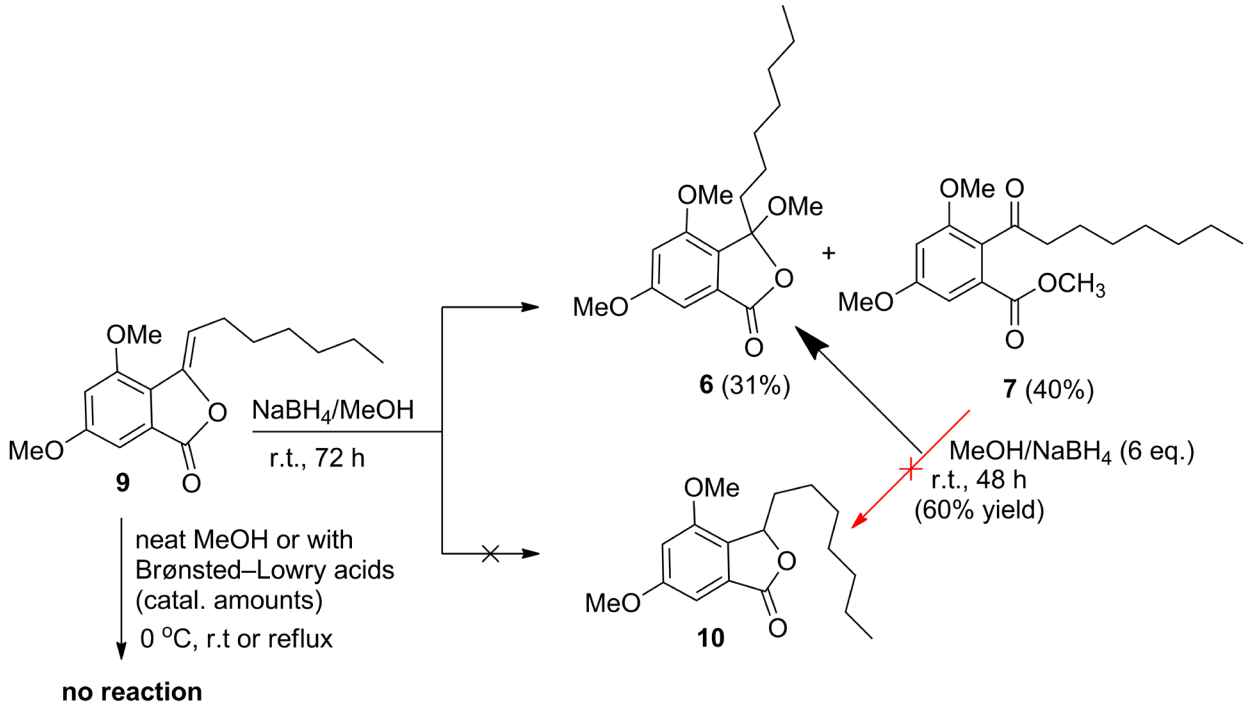
ethyl acetate (3 × 20 mL). The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated by reduced pressure. The product was purified by chromatographic column using hexane:ethyl acetate (7:3) as the eluent, yield: 98%, yellowish oil.

AMS35BB (**7**): ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.8 (3H, t, *J* 6.6 Hz), 1.17-1.31 (m, 8H), 1.60-1.70 (2H, m), 2.69 (2H, t, *J* 7.4 Hz), 3.71 (3H, s), 3.76 (6H, s), 6.54 (1H, d, *J* 2.0 Hz), 6.94 (1H, d, *J* 2.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.1 (CH_3), 22.7 (CH_2), 23.5 (CH_2), 29.2 (CH_2), 29.2 (CH_2), 31.8 (CH_2), 44.3 (CH_2), 52.5 (CH_3), 55.7 (CH_3), 56.0 (CH_3), 102.9 (CH), 105.4 (CH), 127.0 (C); 129.3 (C), 157.1 (C), 160.6 (C), 166.4 (C), 205.8 (C). (See figures S7 and S8 in the Supplementary Material).

RESULTS AND DISCUSSION

In a previous study (Navarro et al. 2014), we reported that treatment of phthalide **9** with $NaBH_4$ in methanol (Scheme 1) failed to provide **10**, the precursor of AMS049. Instead, the products **6** (31% yield) and **7** (40% yield) were generated. This result prompted us to inspect the general behavior of this reaction system under different conditions in methanol. Initially, **9** was treated with pure methanol under reflux, and the starting material was recovered. The same result was obtained using methanol acidified with catalytic amounts of H_2SO_4, HNO_3, and *p*-TsOH, at different temperatures (0 °C, room temperature, and reflux) (Scheme 1).

Treating the keto-ester **7** with pure methanol under reflux caused no reaction, and the starting material was recovered. However,

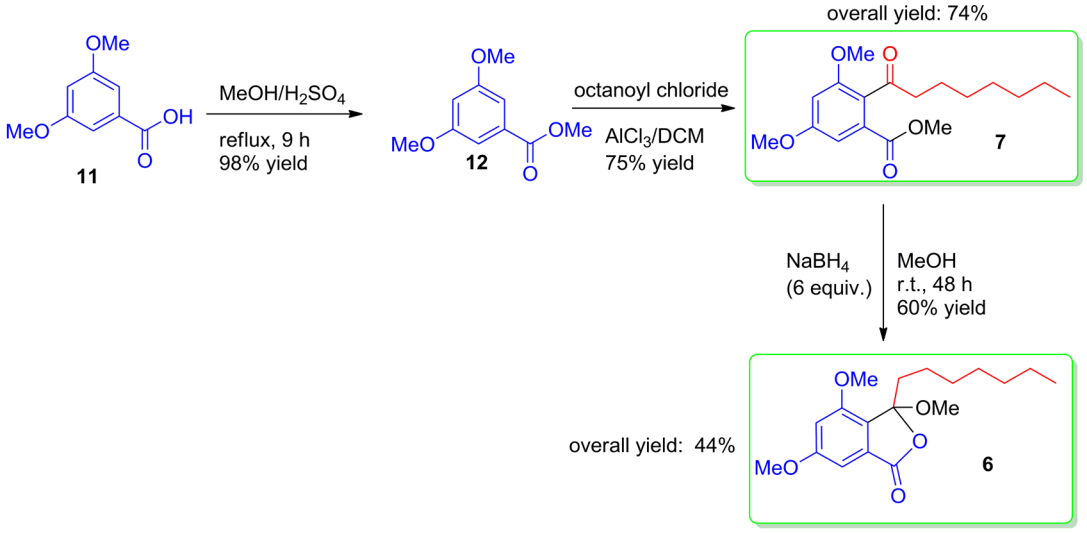


Scheme 1. Methanolysis reactions of phthalide 9.

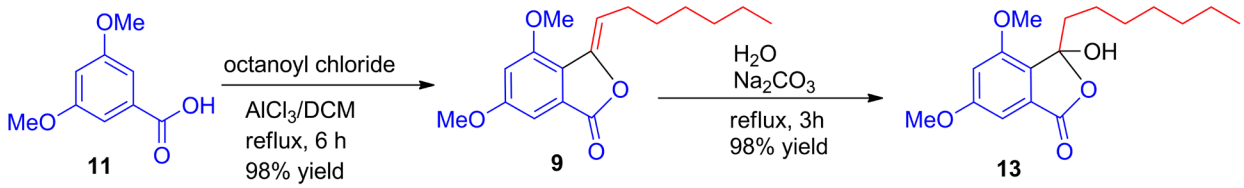
when compound **7** was treated with excess $NaBH_4$ in methanol at room temperature, isomer **6** was generated with a 60% yield (Scheme 1). $NaBH_4$ suffers methanolysis to form the borate $NaB(OCH_3)_4$ and H_2. The former seems to catalyze methanol addition to the ketone carbonyl, which is followed by cyclization, via ester transesterification, to generate the corresponding lactone **6.** Boron derivatives are reported to exert catalytic activities under neutral conditions (Davis & Gottbrath 1962). In addition, Campaña et al. (2007) have described successful Michael addition reactions using carbon nucleophiles. No product from reduction was obtained, probably due to high steric hindrance factors (Rios et al. 1998) and electronic effects of the methoxy groups attached to the aromatic ring.

In a first attempt to achieve better yields of **6** and **7**, a new route was designed (Route I, Scheme 2). Starting from commercial 3,5-dimethoxybenzoic acid (**11**), the corresponding methyl ester (**12**) was prepared via reaction with methanol in the presence of H_2SO_4. Next, **12** was subjected to Friedel–Crafts acylation, catalyzed by Lewis acid ($AlCl_3$) with octanoyl chloride to generate **7** (Scheme 2)**.** The adduct **6** was then prepared from **7** using methanol in the presence of excess $NaBH_4$. This route allowed the preparation of **6** with a slightly improved yield (44% overall).

To further improve the overall yields of **6** and **7**, the alkaline methanolysis of phthalide **9** was investigated, employing methanol and a catalytic amount of KOH at room temperature, drawing on alkylidene-phthalide reactivity studies (Rios et al. 1998, Banerjee et al. 1982). Under this condition, the potential monodemethylated intermediate **13** (Scheme 3) was obtained as a sole product (5% yield). However, when 1.5 KOH



Scheme 2. Route I to obtain AMS35AA (6) and AMS35BB (7).



Scheme 3. Synthesis of compound 13.

eq. was tested, the yield was increased to 90% at room temperature, and 91% under reflux. Fortuitously, when an aqueous Na_2CO_3 solution (1 M) was tested under reflux, the reaction provided an additional increase in the yield, to nearly quantitative (98%). Synthesis of **13** had been previously reported by our group as part of a program for discovery of novel herbicides (Dos Santos et al. 2009), but the overall yield proved low (2%). The new two-step synthesis (Scheme 3) rendered an isolated overall yield of 96%.

Carrying out methylation of the hydroxyl on **13** would lead to compound **6**, and these compounds can be interconverted using the protocols shown in Scheme 1 and 2. Considering that **13** can be prepared from **9** by simple basic hydration, the reversible dehydration in acidic medium is possible. However, it is conceivable that **13** is reactive in methanol, provided a catalyst is used to activate the lactone carbonyl for nucleophilic attack, without dehydration, allowing the formation of the keto ester **7**, or even its isomer **6**.

Then, our attention was drawn to L-ascorbic acid (vitamin C, **14**; Figure 2a), a green, robust, efficient organocatalyst employed for direct synthesis of several organic compounds. Vitamin C has been successfully used as a highly efficient hydrogen bond donor for the multi-component synthesis of a number of compounds, with reasonably good yields in both water (Shaabani et al. 2019) and ethanol (Napoleon et al. 2014). The mechanistic principle of this activation is based on reduction of the electronic density of electrophiles due to an interaction between the organocatalyst and these species through hydrogen bonds, thus activating the electrophiles to suffer nucleophilic attack, as exemplified in Figure 2b.

To test our hypothesis, the reaction was initially investigated in the absence of a catalyst, using only **13** dissolved in methanol at room temperature. After 12 h, only the starting material was recovered. Performing the reaction in the presence of vitamin C (20 mol%) for 48 h at room temperature generated product **6** with an 80% yield (Scheme 4). Therefore, **6** could be synthesized from the 3,5-dimethoxybenzoic acid (**11**), with an overall yield of 94% Route II (Scheme 4).

The reaction probably involves the mechanism proposed in Scheme 5, whereby it is shown that compound **7** is the precursor of **6**, formed via hydrogen bonding activation by the catalyst (Figure 2).

It seems reasonable to conclude that in methanol the keto-ester **7** is formed initially, being subsequently isomerized to **6** in the presence of a catalyst. To further exploit the functional features of **13,** and considering the ease of its preparation, we chose to convert this compound into **7** through treatment with a basic solution of iodomethane in the absence of methanol. The treatment of **13** with iodomethane and K_2CO_3 in acetone at room temperature for 48 h (Scheme 4) led to formation of ester **7** at a nearly quantitative yield (98%).

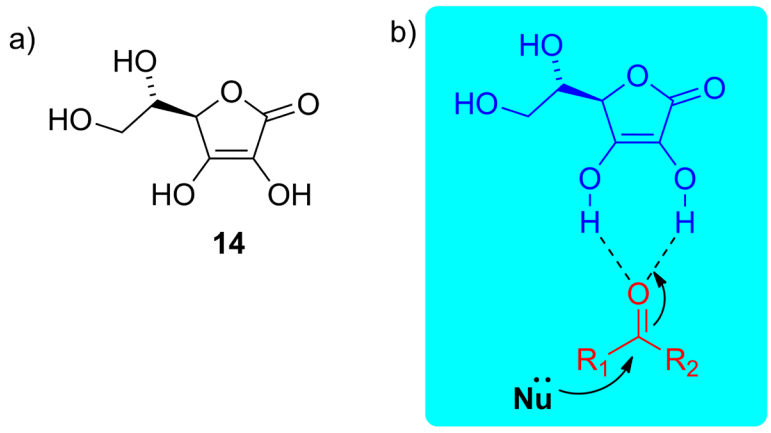
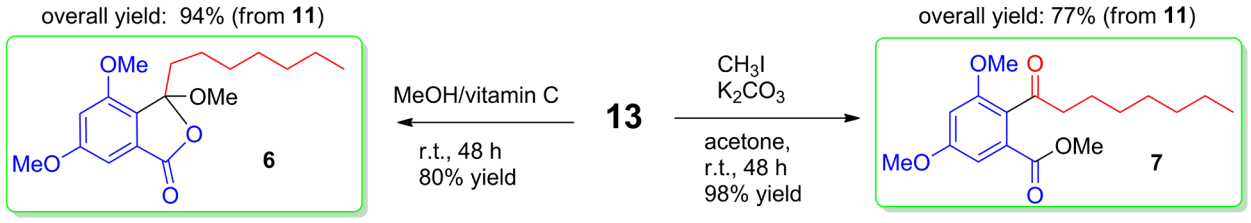
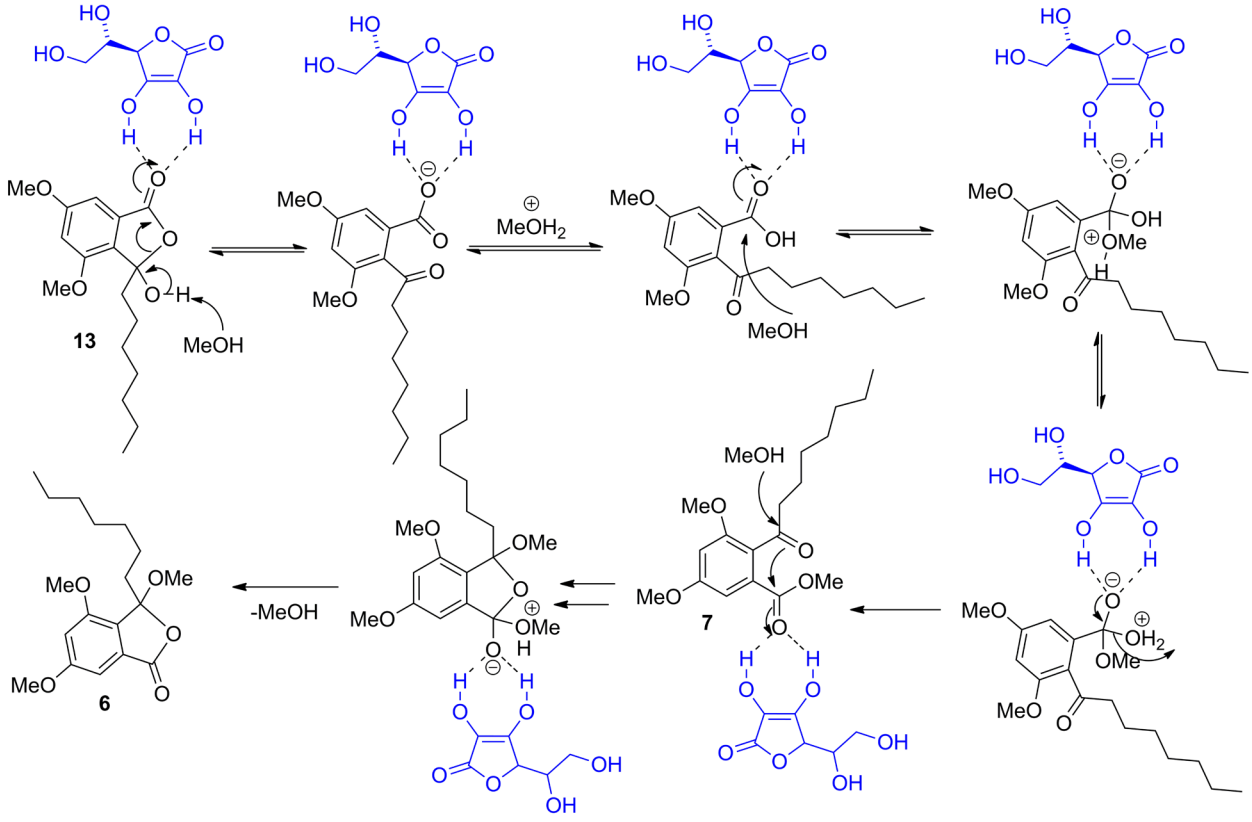


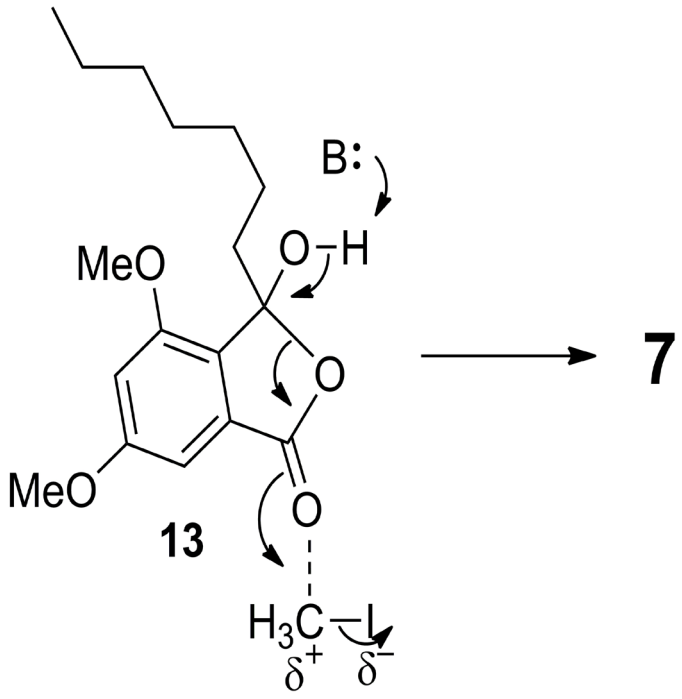
Figure 2. (A) L-ascorbic acid (vitamin C, **14**). (B) Carbonyl activation by **14**.



Scheme 4. Route II for synthesizing AMS35AA (**6**) and AMS35BB (**7**).



Scheme 5. Proposed mechanism for the vitamin C of methanol addition to compound **13**.



Scheme 6. Mechanistic proposal for the formation of 7 from 13.

Thus, **7** was obtained in three steps, with an overall yield of 77%, calculated from compound **11** (Route II). Scheme 6 depicts a proposed approach to rationalize the transformation of **13** into **7**.

CONCLUSIONS

The present work describes flexible and straightforward synthetic routes to achieve the cytosporone analogs AMS35AA (**6**) and AMS35BB (**7**) with excellent overall yields, using easily accessible starting materials. The syntheses shared the same intermediate 3-heptyl-3-hydroxy-4,6-dimethoxyisobenzofuran-1(3*H*)-one (**13**), which was prepared with a high yield (98%) via simple treatment of phthalide **9** with aqueous Na_2CO_3 solution. Moreover, a methanolic solution of ascorbic acid (vitamin C) proved to be highly efficient for catalyzing the reaction to attain compound **6**.

Acknowledgments

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SUPPLEMENTARY MATERIAL

Figure S1. ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of 9.
Figure S2. ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of 9.
Figure S3. ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of 13.
Figure S4. ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of 13.
Figure S5. ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of 6.
Figure S6. ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of 6.
Figure S7. ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of 7.
Figure S8. ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of 7.
Figure S9. ^{1}H NMR spectrum (300 MHz, $(CD_3)_2CO$) of 12.
Figure S10. ^{13}C NMR spectrum (75 MHz, $(CD_3)_2CO$) of 12.

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Neimar Vitor and Alisson Meza: were responsible for the data curation, investigation, and for the writing of original draft. Roberto da Silva Gomes: responsible for the formal analysis, funding acquisition, conceptualization and writing review and editing. Jamal Rafique: responsible for the formal analysis, funding acquisition, conceptualization and writing review and editing. Dênis P. de Lima: was responsible for the formal analysis, funding acquisition, conceptualization and writing review and editing. Adilson Beatriz: was responsible for the formal analysis, funding acquisition, conceptualization and writing review and editing. Was also responsible for the project administration, resources, validation, and visualizations.