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Synthetic studies of lignanes: Attempted synthesis of arctigenin and enterolactone

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Abstract: A synthetic approach to bioactive lignans was devised, which relies on photocatalyzed [2+2] cycloaddition of cinnamyl cinnamates, followed by catalytic hydrogenolysis of C–C bond between two benzylic positions in the strained cycloadduct. However, while feasible in the model study, this approach could not be applied to the synthesis of bioactive derivatives arctigenin and enterolactone. Calculations were performed in order to rationalize the surprising lack of reactivity of substituted cinnamates and cyclobutane-fused γ-butyrolactone.

Keywords: photocycloaddition; photocatalysis; butanolide; hydrogenolysis; natural products.

INTRODUCTION

Lignans are an important class of plant natural products, composed of phenylpropanoid fragments.[1,2] They have important physiological roles in planta, notably as defense chemicals – hence their antioxidant, allelopathic, antifungal, antimicrobial, insecticidal, nematocidal, antifeedant and (occasionally) poisonous properties. In addition, oligomerization and deposition of lignans has a structural role. Apart from plants, these compounds have an important role in human nutrition, health protection and disease treatment.[3] The spectrum of their activities encompasses protection against onset of breast and prostate cancer, antitumor properties, hepatotoxic preventive effect, antiviral properties, anti-inflammatory, antiasthmatic and antidepressant effects, *inter alia*. In this context, three compounds originating from *Arctium lappa* L. – a well-known medicinal plant in the traditional Chinese, as well as in Kampo medicine – are particularly noteworthy: arctigenin

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1, its glycoside arctiin **2** and its metabolite enterolactone **3** (Fig. 1). In addition to the abovementioned biological properties of lignanes, some specific features of these three lactones are noteworthy. Thus, arctigenin exhibits antiinflammatory, antioxidant, immunomodulatory, multiple sclerosis fighting, antitumor and anti--leukemia properties.[4,5] Remarkably, arctigenin possesses preferential cytotoxicity, targeting selectively nutrient-deprived cells, thus allowing for the antiausterity treatment – a possible therapeutic approach against, *e.g.*, pancreatic cancer, which is resistant to chemotherapy.[6–8] Comprehensive reviews of molecular mechanisms of anticancer activity of arctigenin[9] and the corresponding glycoside – arctiin – are available.[10] Enterolactone, which is the first lignane to be found in the mammalian gut, inhibits tumour growth and metastasis in ovarian cancer allograft mouse model. This effect is especially efficient in combination of enterolactone with 3TSR, which act synergistically, mostly by inhibiting tumour angiogenesis.[11] It was also found to act as phytoestrogen, and is reported to protect against breast cancer and cardiovascular disease.[12]

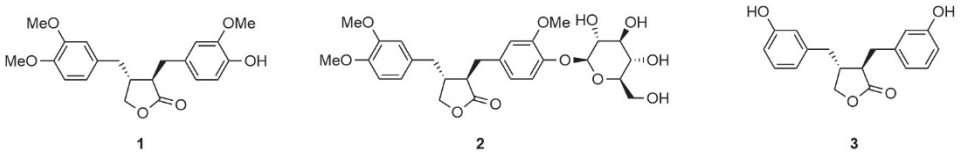
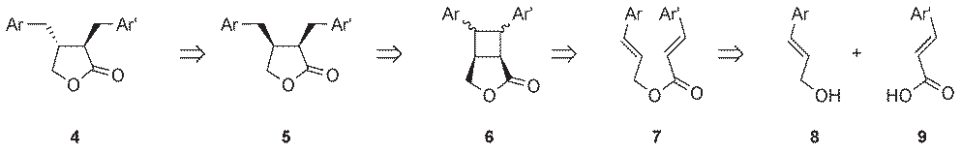


Fig. 1. Structures of arctigenin **1**, arctiin **2** and enterolactone **3**.

Due to a wide range of important biological activities, arctigenin and enterolactone have attracted considerable attention from the synthetic community. Pharmacology and total synthesis of arctigenin have been recently reviewed,[13] as well as biological properties and total synthesis of enterolactone.[14] Several total syntheses of arctigenin have been reported, based on radical carboxyarylation,[15] intermolecular radical addition,[16] α-alkylation of dihydrocinnamic acid chiral oxazolidinone[17] and intramolecular carbene insertion.[18] An interesting isomerization of 3,5- into 4,5-dibenzylated butanolides was successfully applied in synthesis of arctigenin;[19] this approach also provided the nonnatural *cis*-isomer.[20] Enterolactone was also an inspiring challenge for synthetic chemists, whose efforts encompassed alkylation of succinic acid-derived Evans oxazolidinones,[21] enantioselective radical addition to fumarate-derived oxazolidinone,[16] alkylation of dihydrocinnamic oxazolidinones,[22] chiron-based synthesis starting from malic acid,[23] catalytic asymmetric intramolecular carbene insertion (for the formation of the optically enriched butanolide structural unit),[24] alkylation of π-allylpalladium complex,[25] allylic nucleophilic substitution with organocuprates,[26] organocatalyzed aldolization,[27] enzymatic resolution,[28] Michael addition of a benzylic dithiane to an optically pure butanolide,[29] as well as semisynthesis from the readily available natural lignan 7-hydroxymatairesinol.[30]

RESULTS AND DISCUSSION

Naturally occurring lignanes are of *trans*-stereochemistry, and virtually all syntheses reported so far target *trans*-lignanes. However, structure–bioactivity relationship studies have shown that *cis*-configured products also possess bioactivity;[20] thus, *cis*-arctigenin was shown to be a more potent inhibitor of cyclic AMP phosphodiesterase than the *trans*-isomer.[31] Therefore, we set out to develop a method that would allow for synthesis of both *cis*- and *trans*-stereoisomers, and which would allow for a modular synthesis of a small library of lignanes suitable for structure–activity relationship (SAR) study. Our approach, blueprinted in Scheme 1, relies on [2+2] cycloaddition of cinnamyl cinnamates (**7** → **6**) as a pivotal step for the construction of the bicyclic framework **6**, from which the non-natural, *i.e.*, *cis*-configured butanolides of type **5** should be obtained by hydrogenolysis. Base-catalyzed isomerization of *cis*-derivatives (**5**) into thermodynamically more stable *trans*-ones should then provide lignans **4** from the natural series. The cyclization substrates **7** are readily available cinnamyl cinnamates, which makes the whole sequence suitable for the creation of a library of arctigenine analogues for SAR studies.

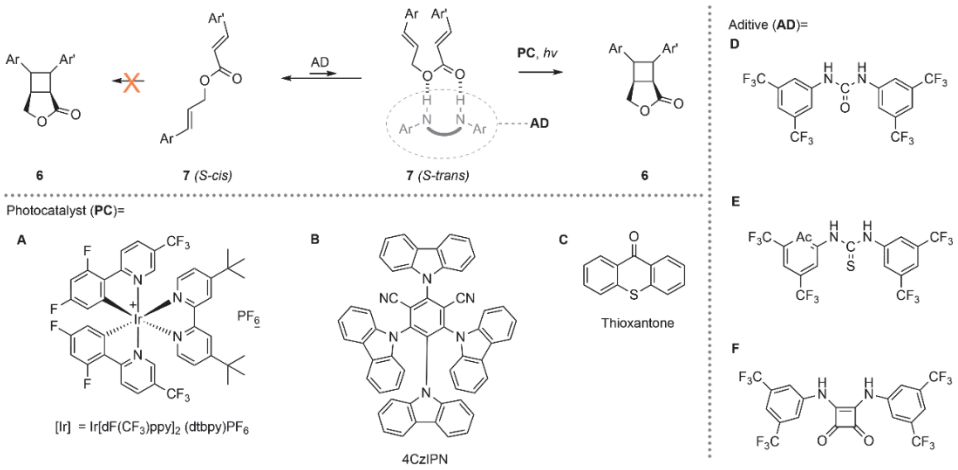


Scheme 1. Synthetic approach to *cis*- and *trans*-configured arctigenine and analogues thereof.

The feasibility of this approach was tested on the parent cinnamyl cinnamate **7a** (Ar, Ar' = Ph) as a model substrate. Exposure of this compound to UV-light (254 nm) gave no formation of product **6a**, as only decomposition of the starting material was observed. We then recurred to photoredox conditions:[32] exposure of **7a** to blue LED light (440 nm) in the presence of Ir-catalyst (**A**) provided cycloadduct **6a** in 55 % yield. Performing the reaction at 55 °C compared favorably with the literature (29 % at 80 °C). The moderate yield may be attributed to the known propensity of esters to adopt in solution the *S-cis*-conformation, which is unfavorable for the cyclization. Therefore, to surmount *S-cis*/*S-trans* energy barrier and facilitate conformational interconversion, we postulated that additives which may engage into hydrogen bonding with both ester oxygen atoms may invert the conformational equilibrium and promote cyclization (Scheme 2).

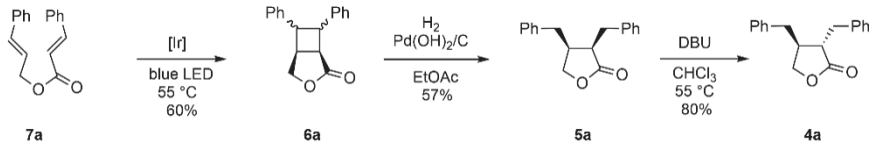
To this end, several urea- and squaramide-based catalysts were tried (**D**, **E** and **F**, Scheme 2), unfortunately to no avail: urea **D** and thiourea **E** actually slowed the reaction and lowered the yield, whereas squaramide **F** catalyst induced only modest yield improvement (from 55 to 60 %). We also tested few organic dyes as

photocatalysts 4-CzIPN **B** and thioxantone **C** (Scheme 2), with medium to poor outcome (38 and 14 %, respectively).



Scheme 2. Postulated organocatalyst-induced inversion of *S-cis*/*S-trans* conformational equilibrium of esters.

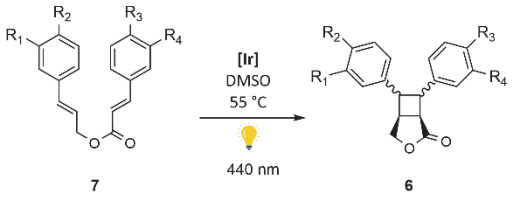
The cycloadduct **6a** was obtained as a mixture of isomers with the ratio 3.6:1 (regarding the relative positions of Ph groups with respect to each other), which was inconsequential for the synthesis, as the stereogenic centers at Ph-bearing carbon atoms are to be destroyed in the next step. Our plan called for the cyclobutane ring scission, where the bond between two benzylic positions was expected to cleave selectively. Surprisingly, to the best of our knowledge, only two such precedents exist in the literature: 1) palladium hydroxide-catalyzed hydrogenolysis[33] and 2) reductive cleavage under the conditions of Birch reduction.[34] To our pleasure, upon exposure to hydrogen atmosphere in the presence of palladium hydroxide on charcoal (10–20 %), bicyclic lactone **6a** was converted into *cis*-configured butanolide **5a** in 57 % yield. Finally, treatment of **5a** with a stochiometric amount of DBU in chloroform, at 55 °C afforded the *trans*-isomer **4a** in 80 % yield (Scheme 3).



Scheme 3. Synthesis of *cis*- and *trans*-1,2-dibenzylbutanolides **5a** and **4a**.

The successful accomplishment of the model-study encouraged us to apply this protocol in the synthesis of substituted, natural targets. However, and much to

our surprise, out of eleven structurally different cinnamic esters, only three underwent cyclization, in modest yields (Scheme 4, Table I, entries **6b**, **6c** and **6e**). The reasons for this lack of reactivity are not clear, as the catalyzed reaction was expected to proceed *via* energy transfer, where the presence of electron-donating substituents at the aromatic rings should not be a handicap; in fact, two such cyclizations occurred, albeit in modest yields (Table I, entries **6b** and **6e**).



Scheme 4. General scheme for the photocycloaddition reaction.

TABLE I. Attempts to cyclize cinnamyl cinnamates

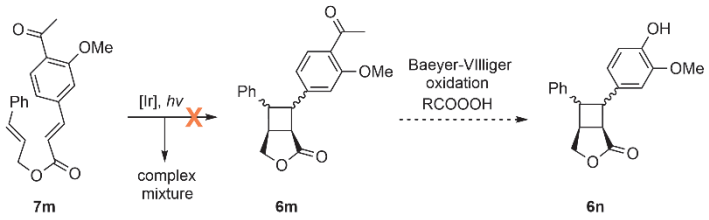
Entry	R_1	R_2	R_3	R_4	Yield, %
6a	–H	–H	–H	–H	55
6b	–OBn	–H	–H	–OBn	38
6c	–Br	–H	–H	–Br	25
6d	–OMe	–H	–H	–OMe	0[a]
6e	–OMe	–OMe	–H	–H	25
6f	–OMe	–OMe	–OBn	–OMe	0[b]
6g	–OMe	–OMe	–Ac	–OMe	0[b]
6h	–H	–H	–Ac	–OMe	0[b]
6i	–H	–H	–H	$–NO_2$	0[a]
6j	–OBn	–H	–H	$–NO_2$	0[a]
6k	$–NO_2$	–H	–H	–H	0[a]
6l	$–NO_2$	–H	–H	–OBn	0[a]

[a]Mixture of starting material isomers; [b]complex mixture

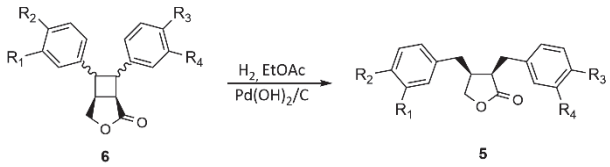
Suspecting that electron-donating substituents at the aromatic ring may be responsible for the diminished reactivity, we prepared 4-acetyl cinnamic derivative **7m**, which should be electron deficient enough to cyclize to product **6m**, from which the desired compound **6n** should be obtained by Baeyer–Villiger reaction (Scheme 5). However, upon exposure to photocatalytic conditions **7m** gave a complex mixture of products.

Photocatalytic [2+2] cycloaddition was not the only obstacle hampering the extension of the model study to natural products and structural analogues, as cycloadducts (Table I, entries **6b**, **6c** and **6e**) proved resilient to hydrogenolytic cyclobutane ring opening with $Pd(OH)_2$ (Scheme 6). Attempts to force the bond cleavage using other catalysts, such as Pd/C or PtO_2/C as catalysts, or by increasing pressure and/or temperature resulted in partial or total reduction of benzene rings

(Table II, entries **5a** and **5e,** in addition to the expected debenzylation in the case of **5b**), as well as debromination (in the case of **5c,** Table II).



Scheme 5. An attempt towards indirect preparation of 4-hydroxy-substituted cycloadduct **6n**.



Scheme 6. General reaction scheme for hydrogenolytic cyclobutane ring opening.

TABLE II. Attempts of hydrogenolytic cyclobutane ring opening

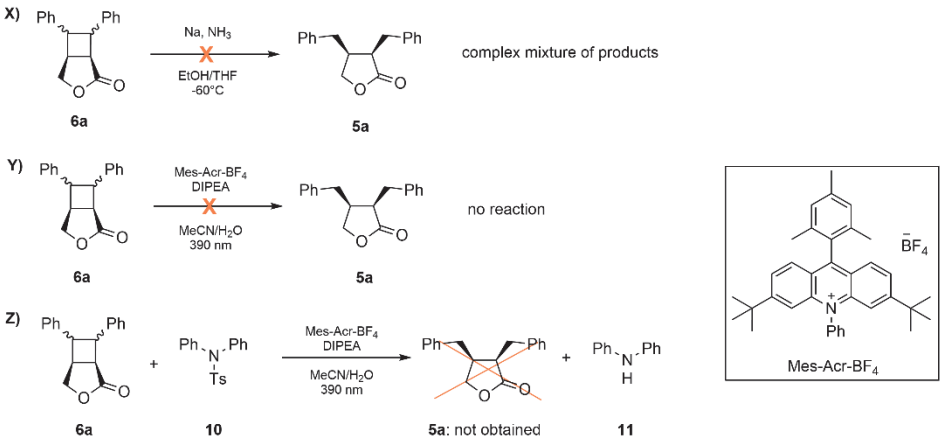
Entry	R_1	R_2	R_3	R_4	Yield, %
5a	-H	-H	-H	-H	57[a]
5b	-OBn	-H	-H	-OBn	0
5c	-Br	-H	-H	-Br	0
5e	-OMe	-OMe	-H	-H	0
5o	-OAc	H	H	-OAc	0

[a]Determined by ^{1}H-NMR spectroscopy using TMB as an internal standard

Other reductive attempts to effect hydrogenolytic scission included Birch reduction (Scheme 7, **X**)[33] and photoredox-catalysis (Scheme 7, **Y**),[35] both to no avail as, in the case of Birch reduction only decomposition of the starting material was observed, whereas **6a** didn't react under photoredox conditions, with the recovery of the starting material. As for the latter reaction – we performed a control experiment (Scheme 7, **Z**), with competitive reduction of compound **10** (described in the literature)[35] and our substrate **6a** in the same reaction vessel. Whereas tosylamine **10** underwent reductive detosylation, as described, and provided diphenylamine **11**, substrate **6a** remained unchanged, thus proving that selective reduction of **6a** into **5a** under these photoredox conditions is not possible.

To explain the lack of reactivity of substituted analogues, we performed density functional theory (DFT) calculations. The [2+2] cycloaddition reaction is presumed to occur *via* the energy-transfer mechanism, where the energy of the excited photocatalyst in the triplet state should equal or exceed the corresponding triplet energy gap of cinnamyl cinnamate. We hypothesized that if substituents on the

aromatic ring significantly increased this energy gap (*i.e.*, $S_0 \rightarrow T_1$), it could result in the inability of the catalyst to excite the substrate, and subsequent lack of reactivity. To test this, vertical triplet excitation energies were calculated *via* time-dependent DFT (TD-DFT) at the wB97x-D4rev/def2-TZVP level of theory for derivatives bearing –H (**7a**), –OBn (**7b**) and –OMe (**7d**) substituents at the meta-positions. The calculations yielded vertical excitation values of 2.75, 2.71 and 2.73 eV for the **7a**, **7b** and **7d** derivatives, respectively. Although range-separated hybrids typically exhibit a systematic blueshift, leading to slightly higher absolute vertical excitation energies (on the order of 0.2–0.4 eV), the relative differences within the series remain negligible ($\Delta\Delta E \leq 0.04$ eV). Thus, substituents do not perturb the triplet energy in a way that could account for the observed reactivity differences. Instead, other factors, such as alternative quenching pathways, steric hindrance, or further nuances of the reaction mechanism, may be at play.



Scheme 7. Other attempts of reductive cyclobutane ring opening.

We also performed calculations to clarify the lack of reactivity of substituted cyclobutane-fused γ-butyrolactones towards hydrogenolytic cleavage, which contrasted with the smooth reaction of the parent compound **6a**. Although counter-intuitive, our initial hypothesis was that substituents may increase the strength of the C–C bond between the two benzylic positions. To evaluate this, we calculated the corresponding C–C bond dissociation energy comparing the parent system **6a** to the substituted analogue **6e**. The Gibbs energy difference between the closed cyclobutane form and the homolytically cleaved open-shell singlet form was calculated at the wB97x-D4rev/def2-TZVP level. We obtained values of 169.03 kJ/mol for the H-substituted system and 166.52 kJ/mol for the OMe-substituted system. This marginal difference suggests that the aromatic substituents do not inherently strengthen the C–C bond. Consequently, the lack of reactivity in these

cases might be attributed to kinetic barriers or catalyst-surface interactions that a simple thermodynamic bond-strength model does not capture. Additional studies are required to elucidate this mechanistic divergence fully.

EXPERIMENTAL

General experimental

All chromatographic separations were performed on Silica gel 60 (0.063–0.2 mm), Merck. Standard techniques were used for the purification of reagents and solvents.[36] NMR spectra were recorded on Varian/Agilent 400 (^{1}H-NMR at 400 MHz, ^{13}C-NMR at 100 MHz) and on Bruker Avance III 500 (^{1}H-NMR at 500 MHz, ^{13}C-NMR at 125 MHz), in deuterated chloroform, if not otherwise stated. Chemical shifts are expressed in ppm (δ) using tetramethylsilane as internal standard, coupling constants (J) are in Hz. IR spectra were recorded on Thermo Scientific Nicolet Summit FT-IR instrument and are expressed in cm^{-1}. Mass spectra were obtained on Orbitrap Exploris 240 spectrometer. Blue light irradiation was performed using blue LED KessilPR160L 440 nm lamp. Additional synthetic procedures are listed in the Supplementary material to this paper.

Experimental procedures

*Synthesis of 6,7-diphenyl-3-oxabicyclo[3.2.0]heptan-2-one (**6a**)*.[32] The solution of compound **7a** (43.8 mg, 0.166 mmol, 1 eq.) and [Ir(dtbbpy)(dF(CF$_3$)ppy)$_2$]PF$_6$ (4.0 mg, 0.0035 mmol, 0.02 eq.) in DMSO (4.0 mL) was sparged with Ar for 10 min and stirred at 55 °C for 2 h with a blue LED setup (see Supplementary material for details). After completion, the reaction mixture extracted with diethyl ether, organic phase was washed with brine and dried over anhydrous MgSO$_4$ and concentrated on rotovap. The residue was purified by dry-flash chromatography (petroleum ether/ethyl acetate = 9:1), to afford 26.5 mg (55 %) of compound **6a** as a mixture of isomers in a relative ratio 3:1, as a colorless oil. Spectral data (Supplementary material) are in accordance with the literature.

Synthesis of cis-*(3*R*,4*R*)-dihydro-3,4-bis(phenylmethyl)-2(3*H*)-furanone (**5a**)*.[37] A suspension of compound **2** (18 mg; 0.068 mmol, 1 eq.) and Pd(OH)$_2$/C (10–20 %, 64 mg, 0.068 mmol, 1eq.) in ethyl acetate (1.2 mL) was stirred under hydrogen atmosphere (2 bar) for 48 h at room temperature. The reaction mixture was then filtered through the Celite. The product yield (57 %) was determined *via* ^{1}H-NMR spectroscopy with iodoform as internal standard. Spectroscopic data are in accordance with the literature.

Synthesis of trans-*(3*R*,4*R*)-dihydro-3,4-bis(phenylmethyl)-2(3*H*)-furanone (**4a**)*.[37] To a solution of compound **5a** (12 mg, 0.045 mmol, 1 eq.) in 0.5 mL (CDCl$_3$) in NMR tube was added DBU (6.8 μL, 0.045 mmol, 1 eq.) and stirred at 55 °C for 96 h. Upon completion, monitored by ^{1}H-NMR spectroscopy, the reaction mixture was purified by dry-flash chromatography (petroleum ether/ethyl acetate = 9:1), to afford 8 mg (80 %) of the product **4a**, as a colorless oil. Spectroscopic data in accordance with the literature.

*Synthesis of 6,7-bis(3-(benzyloxy)phenyl)-3-oxabicyclo[3.2.0]heptan-2-one (**6b**)*. The solution of compound **7b** (380.0 mg, 0.79 mmol, 1 eq.) and [Ir(dtbbpy)(dF(CF$_3$)ppy)$_2$]PF$_6$ (18.0 mg, 0.016 mmol, 0.02 eq.) in DMSO (16 mL) was spared with Ar for 10 min and stirred at 55 °C for 6.5 h with a blue LED setup. After completion, the reaction mixture extracted with diethyl ether, organic phase was washed with brine and dried over anhydrous MgSO$_4$ and concentrated on rotovap. The residue was purified by dry-flash chromatography (benzene/ethyl acetate = 99:1), to afford 145.3 mg (38 %) of compound **6b** as a mixture of isomers in a relative ratio 3:1, as a colorless oil.

Synthesis of 6,7-bis(3-bromophenyl)-3-oxabicyclo[3.2.0]heptan-2-one (**6c**). The solution of compound **7c** (100.0 mg, 0.24 mmol, 1 eq.) and $[Ir(dtbbpy)(dF(CF_3)ppy)_2]PF_6$ (5.3 mg, 0.005 mmol, 0.02 eq.) in DMSO (4.7 mL) was sparged with Ar for 10 min and stirred at 55 °C for 4 h with a blue LED setup. After completion, the reaction mixture was extracted with diethyl ether, organic phase washed with brine and dried over anhydrous $MgSO_4$ and concentrated on rotovap. The residue was purified by dry-flash chromatography (benzene/ethyl acetate = 925:75), to afford 25 mg (25 %) as a mixture of isomers of compound **6c** in a relative ratio 5.8:1, as a colorless oil.

*Synthesis of 6-(3,4-dimethoxyphenyl)-7-phenyl-3-oxabicyclo[3.2.0]heptan-2-one (**6e**)*. The solution of compound **7e** (27.2 mg, 0.08 mmol, 1 eq.) and $[Ir(dtbbpy)(dF(CF_3)ppy)_2]PF_6$ (2.0 mg, 0.0017 mmol, 0.02 eq.) in DMSO (1.6 mL) was sparged with Ar for 10 min and stirred at 55 °C for 4 h with a blue LED setup. After completion, the reaction mixture was extracted with diethyl ether, organic phase washed with brine and dried over anhydrous $MgSO_4$ and concentrated on rotovap. The residue was purified by dry-flash chromatography (benzene/ethyl acetate = 9:1), to afford 9.3 mg (25 %) of compound **6e**, as a mixture of isomers of compound **6e** in a relative ratio 1:1, as a colorless oil.

*Synthesis of (2-oxo-3-oxabicyclo[3.2.0]heptane-6,7-diyl)bis(3,1-phenylene) diacetate (**6o**)*. To compound **13** (see Supplementary material) (12.0 mg, 0.04 mmol, 1 eq.) were added acetic anhydride (31 μL) and pyridine (2 μL) and reaction mixture was stirred at 120 °C for 15 min. After completion, the reaction mixture was purified by column chromatography (petroleum ether/ethyl acetate = 1:1), to afford 13.9 mg (91 %) of compound **6o** as a mixture of isomers in a relative ratio 2.8:1, as a colorless oil.

Spectral data of comporids **6b**, **6c**, **6e** and **6o** are given in the Supplementary material.

Computational details

All electronic structure calculations were conducted using the ORCA 6.1.1 software package.[38] Initial conformational ensembles for **6a**, **7a** and their substituted derivatives were generated using the global geometry optimization and ensemble generator (GOAT) module[39] at the GFN2-xTB level.[39] These ensembles were refined using the B97-3c composite method,[40] followed by final geometry optimizations and frequency analysis with wB97x-D4rev[41] range-separated hybrid functional and def2-TZVP basis set. The nature of the final stationary points was confirmed as true minima by the absence of imaginary frequencies. Vertical singlet–triplet ($S_0 \rightarrow T_1$) energy gaps were evaluated *via* TD-DFT vertical excitations at the wB97x-D4rev/ /def2-TZVP level of theory. Bond dissociation energies were determined as the Gibbs energy difference between the closed-shell bicyclic lactone and the open-shell singlet biradical resulting from homolytic cleavage of the C–C bond between the two benzylic positions.

CONCLUSIONS

To summarize, a synthetic approach to both *cis*- and *trans*-configured lignane--type butanolides was devised, which works well on the parent compound, but fails with substituted substrates and structurally more complex targets. Further studies are required to clarify the reasons behind this lack of reactivity and to expand the method scope to the naturally occurring lignanes and the analogues thereof.

SUPPLEMENTARY MATERIAL

Additional data and information are available electronically at the pages of journal website: https://www.shd-pub.org.rs/index.php/JSCS/article/view/14007, or from the corresponding author on request.

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The authors acknowledge the contribution of Djordje Stefanovic, an undergraduate student, who performed the synthesis and characterization of compounds **7b**, **7c** and **7e**.

ИЗВОД

СИНТЕТИЧКЕ СТУДИЈЕ ЛИГНАНА: ПОКУШАЈ СИНТЕЗЕ АРКТИГЕНИНА И ЕНТЕРОЛАКТОНА

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Осмишљен је синтетички приступ биолошки активним лигнанима, који се заснива на фотокатализованој [2+2] циклоадицији цинамил-цинамата, праћеној хидрогенолизом везе угљеник–угљеник између два бензилна положаја у угаоно-напетом циклоадукту. Међутим, иако је ова реакциона секвенца успешно реализована на модел-једињењу, није могла бити примењена у синтези биоактивних деривата арктигенина и ентеролактона, јер присуство супституената на ароматичном језгру инхибира жељене реакције. Изненађујући изостанак реактивности супституисаних цинамата (према [2+2] циклоадицији) и циклобутанобутиролактона (према хидрогенолизи) анализиран је рачунарским методама.

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