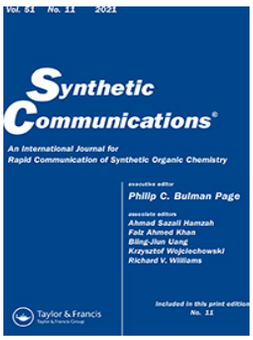

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Activation of phenolic oxygen atom using polyphosphoric acid: Synthesis of carbonyl-containing dihydrobenzofurans/dihydrobenzopyrans

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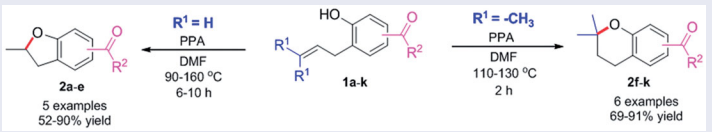
ABSTRACT

Carbonyl-containing dihydrobenzofurans/dihydrobenzopyrans were prepared from carbonyl-containing *ortho*-allyl/prenylphenols by activation of phenolic oxygen atom using polyphosphoric acid (PPA). Various substrates were investigated, and the corresponding dihydrobenzofurans/dihydrobenzopyrans were obtained in good to excellent yields.

GRAPHICAL ABSTRACT



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KEYWORDS
Cyclization; dihydrobenzofurans; dihydrobenzopyrans; ortho-allyl/prenylphenols; polyphosphoric acid

Introduction

Dihydrobenzofuran/dihydrobenzopyran system is found in a variety of biologically active compounds[1] and exhibit significant biological activity, such as antigenotoxic,[2] antiproliferative,[3] anticancer,[4] and antiinflammatory.[5] The most common synthetic method reported for the preparation of dihydrobenzofurans/dihydrobenzopyrans is the cyclization of *ortho*-allyl/prenylphenols.[6]

Recently, we disclosed a procedure promoted by PPA for the preparation of coumarins from salicylaldehydes and acetic anhydride,[7] wherein the intramolecular cyclization of 3-allyl-2-hydroxybenzalde was occurred to generate the dihydrobenzofuran (Scheme 1(a)). This cyclization of *ortho*-allylphenol had attracted our interests, and found that carbonyl-containing substrates could undergo the cyclization yielding desirable products in good yields (Scheme 1(b)). Carbonyl group on the nucleophilic component of the

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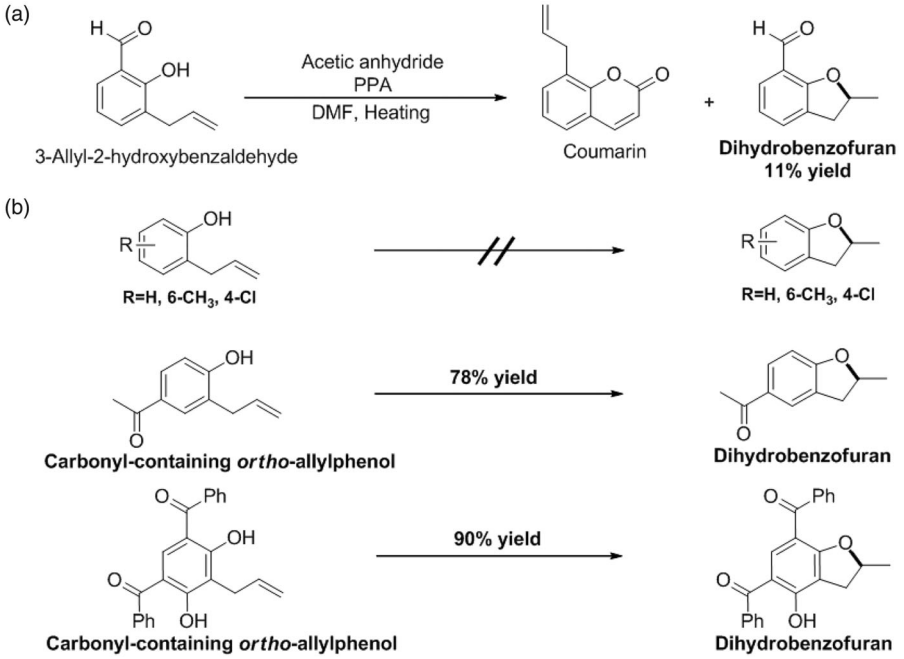


Scheme 1. (a) Intramolecular cyclization of 3-allyl-2-hydroxybenzalde was occurred during the Perkin condensation promoted by PPA; (b) cyclization of carbonyl-containing *ortho*-allylphenols gave dihydrobenzofurans in good yields.

reaction would, theoretically, appear detrimental to the reaction sequence, but in this case, the phenolic oxygen nucleophilicity was reversed. We envisioned that it would be possible to generate phosphorylated adduct and then formed phenoxy anion due to the carbonyl-aromatic π-stacked interaction.

Carbonyl-containing dihydrobenzofurans/dihydrobenzopyrans also have varied bioactivities including anticancer activity,[8] antiproliferative activity,[9] and inhibitory activity on D-amino acid oxidase[10] (Fig. 1). To the best of our knowledge, methods to accomplish the cyclization of carbonyl-containing *ortho*-allyl/prenylphenols include the use of I_2,[11] H_2SO_4,[12] HCl,[13] *p*-TsOH,[14] TFA[8b], $AlCl_3$[8b], and $ZrCl_4$[6d]. However, these reported methods suffer some disadvantages, such as unsatisfactory products yields,[11–14] relatively long reaction time[13,6d], and narrow substrate scope[11–13,14b,8b,6e] maybe because of the decrease of phenolic oxygen nucleophilicity.

Herein, we report an efficient procedure for the preparation of carbonyl-containing dihydrobenzofurans/dihydrobenzopyrans from *ortho*-allyl/prenylphenols by activation of phenolic oxygen atom using PPA.

Results and discussion

Our initial studies were carried out with the commercially available 3-allyl-2-hydroxybenzaldehyde **1a** as test substrate. A mixture of **1a** (1 equiv.) and PPA (3 equiv.) in *N,N*-dimethylformamide (DMF) was stirred at 130 °C for 10 h under an air atmosphere to give the desired product **2a** in 52% yield (Table 1, entry 1). To further improve the

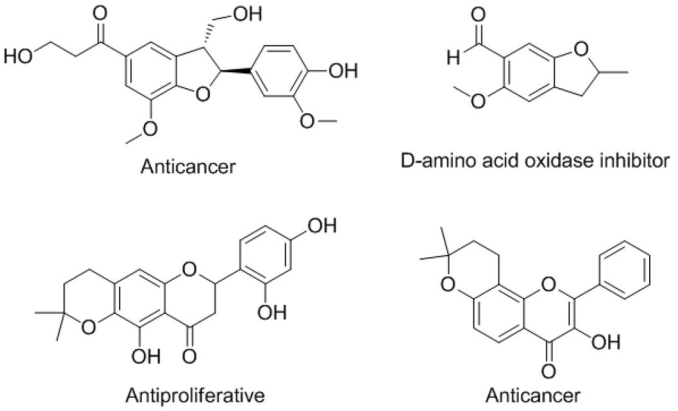
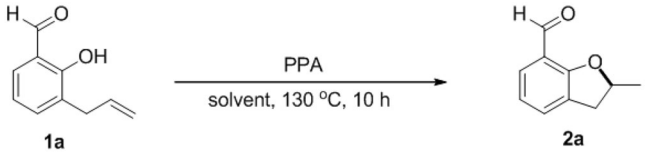


Figure 1. Selected bioactive carbonyl-containing dihydrobenzofurans and dihydrobenzopyrans.

Table 1. Optimization of reaction conditions[a].



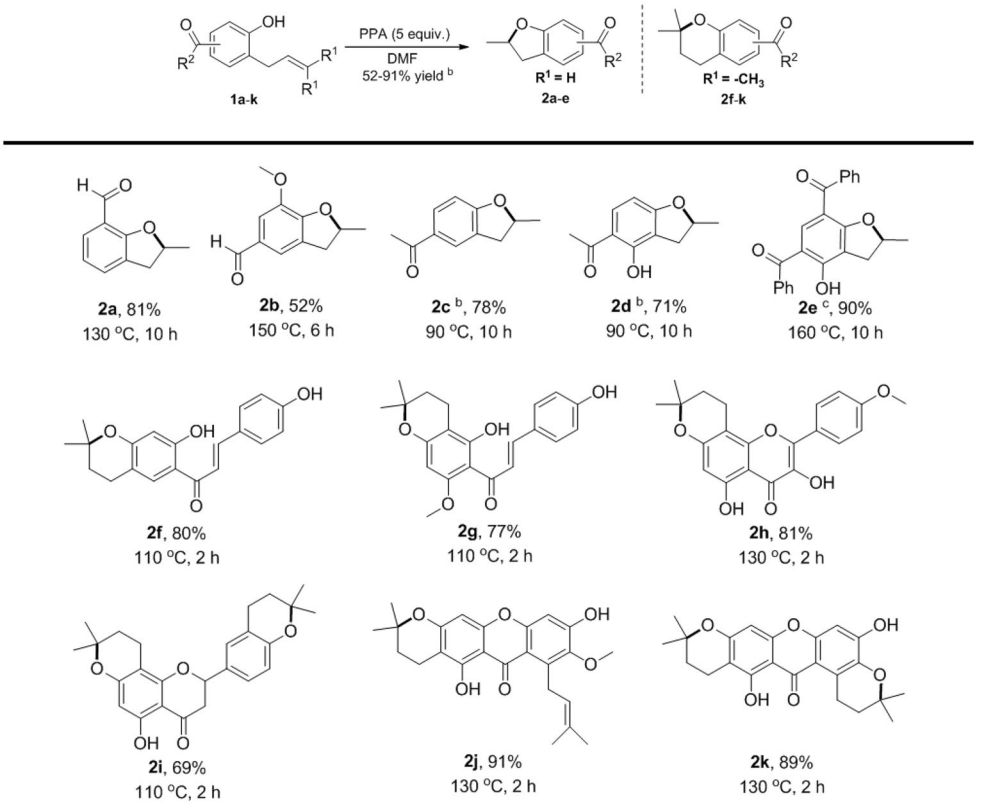
Entry	PPA (equiv.)	Solvent	**2a** (%)[b]
1	3	DMF	52
2	1	DMF	27
3	5	DMF	81
4	7	DMF	79
5[c]	5	THF	/
6[d]	5	1,4-Dioxane	18
7	5	DMSO	/
8	5	DMA	23
9[e]	5	Toluene	8

[a]Reaction conditions: **1a** (0.2 mmol), solvent (0.3 mL).
[b]Isolated yield.
[c]Reaction temperature: 66 °C.
[d]Reaction temperature: 106 °C.
[e]Reaction temperature: 110 °C.

reaction yield, control experiment was performed. Decreasing the amount of PPA resulted in a lower yield (Table 1, entry 2). To our delight, we found that increasing the amount of PPA to 5 equiv. further increased the yield (Table 1, entry 3). However, further increased the amount of PPA had no obvious effect on the reaction (Table 1, entry 4). Subsequently, we investigated the effect of solvents on the efficiency of the cyclization. Unfortunately, the reaction performed in THF, 1,4-dioxane, DMSO, DMA, or toluene exerted detrimental effect on the yield (Table 1, entries 5–9). Therefore, the optimized reaction conditions were determined as **1a** (1 equiv.) and PPA (5 equiv.) in DMF at 130 °C for 10 h under a normal atmosphere (Table 1, entry 3).

With the optimized reaction conditions in hand, the substrate scope of this cyclization was examined by varying carbonyl-containing *ortho*-allyl/prenylphenols **1a–k** (Table 2). Notably, *ortho*-allylphenol containing two carbonyl substituents was obtained in excellent yield (**2a**, **2b**, **2c,** and **2d** *vs.* **2e**). When an electron-donating group

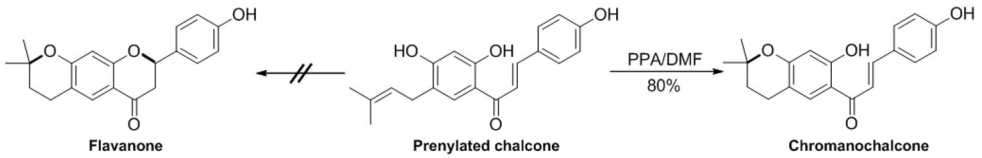
Table 2. Evaluation of substrate scope[a].



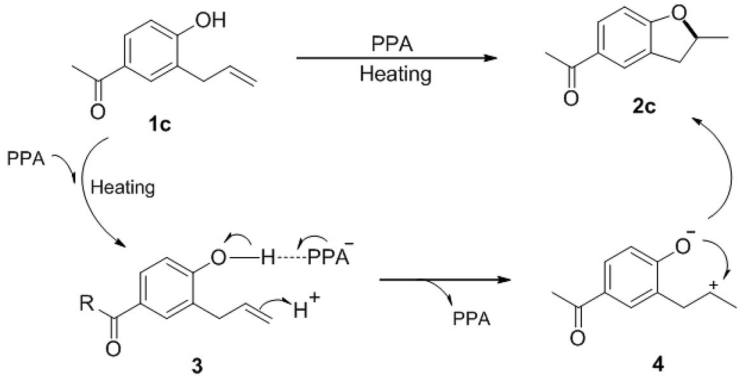
[a]Reaction conditions: **1a** (0.2 mmol), PPA (1.0 mmol), and DMF (0.3 mL).
[b]PPA (20 equiv., 4.0 mmol).
[c]PPA (30 equiv., 6.0 mmol).

(OMe or OH) was bonded to the benzene ring, the cyclization proceeded to give the corresponding dihydrobenzofurans in lower yields (**2b** and **2d**). Next, we selected some available prenylated flavonoids and anthraquinones as substrates, which led to the formation of dihydrobenzopyrans in good to excellent yields, and no five-membered cyclic ether was observed (**2f**–**k**). This indicated that the conditions we developed tolerate flavonoids and anthraquinones and the cyclization reaction proceeded at the double bond carbon atom with more substituents that follows Markovnikov selectivity. Obviously, anthraquinones reacted better and gave excellent yields (**2j**–**k** *vs.* **2f**–**i**). Besides, it was observed that dihydroflavone had lower reactivity than chalcone or flavone (**2i** *vs.* **2f**–**h**). Gratifyingly, we only observed the regioselective cyclization of allyl/prenyl group with the *p*-hydroxy of the carbonyl group (**2d**, **2g**, **2j,** or **2k**) based on NMR spectra and in accordance with literature reports[14a,15] In addition, regioselective cyclization of the prenyl group occurred to give exclusively chromanochalcone from prenylated chalcone, but we did not observe formation of the corresponding flavanone (Scheme 2; **2f** and **2g**).

A plausible mechanism for the synthesis of carbonyl-containing dihydrobenzofurans/dihydrobenzopyrans is depicted in Scheme 3. Firstly, phosphorylated adduct **3** is formed



Scheme 2. Regioselective cyclization of prenylated chalcone using PPA.



Scheme 3. Plausible mechanism for the synthesis of carbonyl-containing dihydrobenzofurans/dihydrobenzopyrans.

from **1c** and PPA under elevated reaction temperature. Electron delocalization within π–π conjugated **3** due to more polarized the O–H bond and better stabilization of the negative charge on the oxygen atom[16] forming intermediate **4**. Finally, the nucleophilic attack leads to the desired product **2c**.

Conclusion

In summary, we have developed an efficient method for the synthesis of dihydrobenzofurans/dihydrobenzopyrans from ortho-allyl/prenylphenols by activation of phenolic oxygen atom using PPA.

Experimental section

General procedure for the preparation of carbonyl-containing dihydrobenzofurans/dihydrobenzopyrans 2 (2a–2k)

To a stirred solution of *N*,*N*-DMF (0.3 mL) were added PPA (1 mmol) and carbonyl-containing *ortho*-allyl/prenylphenols **1** (0.2 mmol) in 5 mL pressure-resistant reaction bottle. The reaction mixture was stirred at 90–160 °C until all starting materials were consumed (2–10 h). The reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate solution, dried over Na_2SO_4, and evaporated. The resulting crude compound was purified by

silica gel column chromatography, affording the pure dihydrobenzofurans/dihydrobenzopyrans **2**.

Detailed procedures and spectral characterization data for all compounds reported herein can be accessed on the publisher's website.

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References

[1] (a) Sih, C. J.; Ravikumar, P. R.; Huang, F. C.; Buckner, C.; Whitlock, H. Letter: Isolation and Synthesis of Pinoresinol Diglucoside, a Major Antihypertensive Principle of Tu-Chung (Eucommia Ulmoides, Oliver). *J. Am. Chem. Soc.* **1976**, *98*, 5412–5413. DOI: 10.1021/ja00433a070. (b) Nagai, M.; Noguchi, M.; Iizuka, T.; Otani, K.; Kamata, K. Vasodilator Effects of Des(Alpha-Carboxy-3,4-Dihydroxyphenethyl)Lithospermic Acid (8-Epiblechnic Acid), a Derivative of Lithospermic Acids in Salviae Miltiorrhizae Radix. *Biol. Pharm. Bull.* **1996**, *19*, 228–232. DOI: 10.1248/bpb.19.228.(c) Nikaido, T.; Ohmoto, T.; Kinoshita, T.; Sankawa, U.; Nishibe, S.; Hisada, S. Inhibition of Cyclic AMP Phosphodiesterase by Lignans. *Chem Pharm Bull (Tokyo).* **1981**, *29*, 3586–3592. DOI: 10.1248/cpb.29.3586.(d) Harada, T.; Hayashiya, T.; Wada, I.; Iwaake, N.; Oku, A. Enantioselective Functionalization of Prochiral Diols *via* Chiral Spiroketals: Preparation of Optically Pure 2-Substituted 1,3-Propanediol Derivatives and Asymmetric Synthesis of Chroman Ring and Side Chain of.alpha.-Tocopherol. *J. Am. Chem. Soc.* **1987**, *109*, 527–532. DOI: 10.1021/ja00236a034.(e) Inoue, S.; Ikeda, H.; Sato, S.; Horie, K.; Ota, T.; Miyamoto, O.; Sato, K. Improved General Method of Ortho Alkylation of Phenols Using Alkyl Isopropyl Sulfide, Sulfuryl Chloride, and Triethylamine. An Expedient Synthesis of Representative Oxygen Heterocycles and (2R,4'R,8'R)-.Alpha.-Tocopherol. *J. Org. Chem.* **1987**, *52*, 5495–5497. DOI: 10.1021/jo00233a047.(f) Seeram, N. P.; Jacobs, H.; McLean, S.; Reynolds, W. F. A Prenylated Benzopyran Derivative from Peperomia Clusiifolia. *Phytochemistry* **1998**, *49*, 1389–1391. DOI: 10.1016/S0031-9422(97)00932-1.(g) Tanaka, T.; Asai, F.; Iinuma, M. Phenolic Compounds from Peperomia Obtusifolia. *Phytochemistry* **1998**, *49*, 229–232. DOI: 10.1016/S0031-9422(97)01050-9.

[2] Castillo, W. O.; Aristizabal-Pachon, A. F.; de Lima Montaldi, A. P.; Sakamoto-Hojo, E. T.; Takahashi, C. S. Galanthamine Decreases Genotoxicity and Cell Death Induced by *β*-Amyloid Peptide in SH-SY5Y Cell Line. *Neurotoxicology* **2016**, *57*, 291–297. DOI: 10.1016/j.neuro.2016.10.013.

[3] Nunzio, C.; Luana, P.; Carmela, S.; Nicolò, M.; Vincenza, B.; Daniele, F. C.; Corrado, T. Dihydrobenzofuran Neolignanamides: Laccase-Mediated Biomimetic Synthesis and Antiproliferative Activity. *J. Nat. Prod.* **2016**, *79*, 2122–2134. DOI: 10.1021/acs.jnatprod.6b00577.

[4] Hirota, M.; Matsuno, T.; Fujiwara, T.; Sugiyama, H.; Mineshita, S. Enhanced Cytotoxicity in a Z-Photoisomer of a Benzopyran Derivative of Propolis. *J. Nat. Prod.* **2000**, *63*, 366–370. DOI: 10.1021/np990463m.

[5] Bermejo, A.; Collado, A.; Barrachina, I.; Marqués, P.; El Aouad, N.; Franck, X.; Garibotto, F.; Dacquet, C.; Caignard, D. H.; Suvire, F. D.; Enriz, R.D.; Piqueras, L.; Figadère, B.; Sanz, M.; Cabedo, N.; Cortes, D. Polycerasoidol, a Natural Prenylated Benzopyran with a Dual PPARα/PPARγ Agonist Activity and Anti-Inflammatory Effect. *J. Nat. Prod.* **2019**, *82*, 1802–1812. DOI: 10.1021/acs.jnatprod.9b00003.

[6] (a) Maier, L. Organic Phosphorus Compounds 68. The Direct Synthesis of Tri(Alkyl- and Arylseleno)Phosphites and of Tris(p-Anisyltelluro)Phosphite [1]. *Helv. Chim. Acta.* **1976**, *59*, 252–256. DOI: 10.1002/hlca.19760590129. (b) Cho, J. Y.; Baik, K. U.; Yoo, E. S.; Yoshikawa, K.; Park, M. H. In Vitro Antiinflammatory Effects of Neolignan Woorenosides from the Rhizomes of Coptis Japonica. *J. Nat. Prod.* **2000**, *63*, 1205–1209. DOI: 10.1021/np9902791.(c) Bergman, J.; Engman, L. Oxidative Cyclization of Some. gamma.- and. delta.-Hydroxy Olefins Induced by Tellurium Dioxide. *J. Am. Chem. Soc.* **1981**, *103*, 5196–5200. DOI: 10.1021/ja00407a041.(d) Meshram, H. M.; Premalatha, K.; Rameshbabu, K.; Eeshwaraiah, B.; Yadav, J. S. Zirconium(IV) Chloride Catalyzed Cyclization of Ortho -Allylphenols: Synthesis of 2-Methyl-2,3-Dihydrobenzofurans. *Synth. Commun.* **2004**, *34*, 3091–3097. DOI: 10.1081/SCC-200028551.(e) Narender, T.; Reddy, K. P. BF3–Et2O Mediated Biogenetic Type Synthesis of Chromanochalcones from Prenylated Chalcones *via* a Regioselective Cyclization Reaction. *Tetrahedron Lett.* **2007**, *48*, 7628–7632. DOI: 10.1016/j.tetlet.2007.08.124.(f) Hu, Y.; Zhang, Y.; Yang, Z.; Fathi, R. Palladium-Catalyzed Carbonylative Annulation of o-Alkynylphenols: Syntheses of 2-Substituted-3-Aroyl-Benzo[b]Furans. *J. Org. Chem.* **2002**, *67*, 2365–2368. DOI: 10.1021/jo010839c.

[7] Yang, L.-S.; Wang, Y.; Wang, E.-H.; Yang, J.; Pan, X.; Liao, X.; Yang, X.-S. Polyphosphoric Acid-Promoted Synthesis of Coumarins Lacking Substituents at Positions 3 and 4. *Synth. Commun.* **2020**, *50*, 3080–3085. DOI: 10.1080/00397911.2020.1792498.

[8] (a) Jiang, Z.-H.; Liu, Y.-P.; Huang, Z.-H.; Wang, T.-T.; Feng, X.-Y.; Yue, H.; Guo, W.; Fu, Y.-H. Cytotoxic Dihydrobenzofuran Neolignans from Mappianthus Iodoies. *Bioorg. Chem.* **2017**, *75*, 260–264. DOI: 10.1016/j.bioorg.2017.10.003. (b) Jarosław, P.; Eliza, T.; Sandra, S.; Tomasz, T.; Agnieszka, B.; Ewa, H. Synthesis and Antiproliferative Activity of Minor Hops Prenylflavonoids and New Insights on Prenyl Group Cyclization. *Molecules* **2018**, *23*, 776.DOI: 10.3390/molecules23040776.

[9] Wabo, H. K.; Kikuchi, H.; Katou, Y.; Tane, P.; Oshima, Y. Xanthones and a Benzophenone from the Roots of Pentadesma Butyracea and Their Antiproliferative Activity. *Phytochem. Lett.* **2010**, *3*, 104–104. DOI: 10.1016/j.phytol.2010.02.006.

[10] Nichols, D. E.; Hoffman, A. J.; Oberlender, R. A.; Riggs, R. M. Synthesis and Evaluation of 2,3-Dihydrobenzofuran Analogues of the Hallucinogen 1-(2,5-Dimethoxy-4-methyl-phenyl)-2-aminopropane: Drug Discrimination Studies in Rats. *J. Med. Chem.* **1986**, *29*, 302–304. DOI: 10.1002/chin.198623205.

[11] Kim, K. M.; Ryu, E. K. Unexpected Iodine Catalyzed Cyclization for Synthesis of 2,2-Dialkyl-2,3-dihydrobenzofurans. *Heterocycles* **1995**, *41*, 219–223. DOI: 10.3987/COM-94-6937.

[12] (a) Huang, Z.; Zhao, Q.; Huang, R.; Wang, Q. Design and Synthesis of Novel N-Tert-butyl-N-substitutedbenzoyl-N- [Dihydrobenzofuran(Chroman)]Carbohydrazide Derivatives as Potential Insect Growth Regulators. *Lett. Organ. Chem.* **2009**, *6*, 29–36. DOI: 10.2174/157017809787003070. (b) Kantevari, S.; Addla, D.; Sridhar, B. Cerium(III)-Catalyzed Facile Synthesis of Dihydrobenzofuran-Tethered Pyridines and Dihydroquinolin-5(6H)-Ones from *β*-Enaminones. *Synthesis* **2010**, *2010*, 3745–3754. DOI: 10.1055/s-0030-1258236. (c) Nguyen, V. S.; Dong, L.- P.; Wang, S.- C.; Wang, Q. The First Total

Synthesis of Sophoflavescenol, Flavenochromane C, and Citrusinol. *Eur. J. Org. Chem.* **2015**, *10*, 2297–2302. DOI: 1002/ejoc.201403689.

[13] Shirataki, Y.; Komatsu, M.; Yokoe, I.; Manaka, A. Studies on the Constituents of Sophora Species. XVI. Constituents of the Root of Euchresta Japonica Hook. f. ex Regel (1). *Chem. Pharm. Bull.* **1981**, *29*, 3033–3036. DOI: 10.1248/cpb.29.3033.

[14] (a) Yates, P.; Bhat, H. B. Acid-Catalyzed Cyclization of Mangostin. *Can. J. Chem.* **1970**, *48*, 680–684. DOI: 10.1139/v70-109. (b) Chi, X.-Q.; Zi, C.-T.; Li, H.-M.; Yang, L.; Lv, Y.-F. ; Li, J.-Y.; Hou, B.; Ren, F.-C.; Hu, J.-M.; Zhou, J. Design, Synthesis and Structure–Activity Relationships of Mangostin Analogs as Cytotoxic Agents. *RSC Adv.* **2018**, *8*, 41377–41388. DOI: 10.1039/C8RA08409B.

[15] (a) Devakumar, C.; Mukerjee, S. K. Synthesis of New Analogues of Furapiole, a Potent Insecticide Synergist. *Indian J. Chem. Sect. B.* **1986**, *11*, 1150–1154. DOI: 10.1002/chin.198718159. (b) Krishnamoorthi, B.; Krishnamoorthi, R. Novel Xanthones from Garcinia Mangostana, Structures of BR-xanthone-A and BR-xanthone-B. *Phyro. Mntrp.* **1988**, *27*, 1552–1554. DOI: 10.1016/0031-9422(88)80242-5. (c) Michael, D.; Andreas, D.; Thomas, H. Sensomics Analysis of Key Bitter Compounds in the Hard Resin of Hops (Humulus lupulus L.) and Their Contribution to the Bitter Profile of Pilsner-Type Beer. *J. Agric. Food. Chem.* **2015**, *63*, 3402–3418.DOI: 10.1021/acs.jafc.5b00239.

[16] Cuadri, A. A.; Navarro, F. J.; Partal, P. Synergistic Ethylcellulose/Polyphosphoric Acid Modification of Bitumen for Paving Applications. *Mater. Struct.* **2020**, *53*, 6. DOI: 10.1617/s11527-019-1437-7.