A Short, Efficient, and Stereoselective Synthesis of Piperine and its Analogues

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Abstract A quantitative synthesis of piperine from commercially available starting material is presented. The synthesis relies on a stereoselective nucleophilic attack of an in situ generated cuprate onto a cyclobutene lactone. The so-formed aryl-substituted cyclobutene spontaneously undergoes a conrotatory 4π-electrocyclic ring opening to form the 4-aryl pentadienoic acid as a single diastereoisomer. The high-yielding synthesis can be easily modulated on the aryl and on the amide moiety for the synthesis of a wide range of piperine analogues.

Key words total synthesis, piperine, alkaloid, cyclobutene, pericyclic reaction, stereoselective, organometallic chemistry

In 1820, the Danish physicist and chemist Hans Christian Ørstedt, pursuing an interest in the isolation of ‘new alkalis’, reported a new alkaloid from pepper (piper nigrum), which he called piperine. Piperine would ultimately gain the attention of the chemistry and physiology communities mostly due to its wide range of biological activities. This was foreshadowed by the original communication itself, where Ørstedt noted that an ethanolic solution of piperine has an ‘exceptionally pungent taste’. The pungency of piperine can be attributed to its agonistic nature towards the heat- and acidity-sensing TRPV ion channels, which are associated with temperature and pain regulation in the human body. A range of human disorders are linked to the overexpression of TRPV1, including inflammatory bowel disease (ulcerative colitis and Crohn’s disease) and chronic breast pain. Studies have shown that piperine is a potent desensitizer of human TRPV1, rendering its structure a potent scaffold for the design of improved TRPV1 agonists.

Moreover, piperine has been recently identified as an allosteric modulator of the γ-aminobutyric acid type A (GABAA) receptor. The mode of action of piperine is thus analogous to commonly used drugs such as benzodiazepines, widely used as sleep-inducing agents. In addition, it has been shown that piperine derivatives are efficient inhibitors of vascular smooth muscle cell proliferation. Anti-depressant and antitumor activities along with insecticidal properties are also attributed to this intriguing molecule which can be technically found in almost every modern kitchen in the world.

Despite the numerous demonstrated beneficial therapeutic properties of piperine, biological applications are limited by its poor solubility in aqueous media. This implies that new synthetic routes towards piperine analogues are highly desirable.

Piperine can be easily extracted and its basic hydrolysis, yielding piperic acid, opens up the preparation of many amide analogues for biological evaluation. This approach is unfortunately limited by nonexchangeability of the aryl moiety. Most approaches for the synthesis of 1-carbonyl-4-aryl-substituted dienes typically make use of a (2 + 2), (3 + 1), or a (1 + 2 + 1) carbon disconnection. In this regard Wittig olefination, olefin metathesis, palladium-catalyzed cross-coupling, or ruthenium-catalyzed vinyl–alkyne coupling have been employed as dominant strategies.
A rather unconventional approach is the direct coupling of the aryl moiety with the diene or a diene precursor. Mihovilovic and coworkers reported an efficient Heck reaction approach in which an aryl bromide is coupled to a pentadienoic amide (Scheme 1, a).4,12 Another intriguing, earlier approach, relies on the addition of a Grignard reagent to a furfural hydrazone, which rearranges to the corresponding pentadienal under the reaction conditions (Scheme 1, b).13 Herein we would like to present a different strategy towards the synthesis of piperine analogues. The bicyclo[2.2.0] lactone 2 and its derivatives have been deployed in previous work by our group and others as a versatile electrophile.14 In particular, we have shown that copper-mediated nucleophilic addition is a very robust method for a trans-selective allylic substitution of 2.14f

The installation of an electron-rich moiety (such as –OR or –N3) in this position has been earlier shown to facilitate a spontaneous 4π-electrocyclic opening. This is likely due to a push–pull relationship between the carboxylic acid and the electron-donating substituent.15 We hypothesized that an aryl moiety might be sufficiently electron donating in order to induce a similar push–pull effect and enable facile electrocyclic ring opening, either spontaneously at room temperature or upon mild heating. Importantly, the transient trans-configured cyclobutene should undergo opening according to a thermally allowed, conrotatory movement torque-selective for the E,E-diene product.

Lactone 2 was prepared in quantitative yield photochemically, as previously reported.14f In the event, we found that addition of the in situ formed cuprate (from its corresponding Grignard reagent 3a) directly led to piperic acid (4a) as the sole product in a single, quantitative step.16 As expected, 4a was formed exclusively as the E,E-diene isomer in a clean reaction.17 Straightforward amide formation via acyl chloride substitution with piperidine afforded piperine in more than 95% isolated yield.18 Through the route presented herein, this alkaloid was thus available in only three quantitative steps from pyrone 1 and with full stereoselectivity (Scheme 2).

Encouraged by these results, we investigated the synthesis of three different piperic acid analogues by using different Grignard reagents for the ring opening of bicyclolactone 2. The 5-phenylpentadienoic acid (4b) was prepared in quantitative yield, while the para-methoxyphenyl- and the 2-thiophenyl- analogues were formed in slightly lower yields. Nevertheless, geometric selectivity was excellent in all cases (Scheme 3).19 Finally, the corresponding amides were formed as before via standard acyl chloride substitution (Scheme 4).18 It should be noted that amides 5bb and 5cb have been previously reported to enhance GABA A-induced chloride currents more strongly than natural piperine (789% ± 72% and 883% ± 70%, respectively).12
Stereoselectivity. This enabled a preparation of the natic acids and their amides in excellent yield and geometrical approach to the synthesis of 4-aryl-substituted pentadieno-support of our research programs.

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S Supporting Information

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**References and Notes**

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In conclusion, we herein presented a conceptually new approach to the synthesis of 4-aryl-substituted pentadienionic acids and their amides in excellent yield and geometrical stereoselectivity. This enabled a preparation of the natural product pipeline in quantitative yield over three steps from commercially available 2-pyrone 1. Analogues can be readily synthesized through this modular and operationally simple procedure.

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In a flame-dried Schlenk tube the carboxylic acid which was previously flushed with argon. A solution of an arylbromide in dry THF (1.60 mmol, 1.0 equiv. in 2 mL) was added dropwise under stirring. The mixture was stirred at room temperature until the magnesium was fully solubilized. LiCl (3.20 mmol, 6 equiv.) was flame-dried in another Schlenk tube under vacuum. After flushing with argon and cooling to room temperature CuCN (1.60 mmol, 3 equiv.) was added to the solid, suspended in anhydrous THF (5 mL), and stirred for 20 min at room temperature. The green solution was cooled down to –40 °C, followed by an addition of the Grignard (1.60 mmol, 3 equiv.) which was previously flushed with argon. A solution of an aryl-bromide in dry THF (1.60 mmol, 3 equiv.) was dissolved in anhydrous DCM (1 mL), followed by the addition of thionyl chloride (0.40 mmol, 2.0 equiv.). The resulting residue anhydrous DCM was added (1 mL), and the amine was added dropwise (0.40 mmol, 2.0 equiv.). Afterwards, the solution was stirred for 1 h at room temperature. Finally, the reaction mixture was quenched with saturated aqueous NaHCO3 solution, and the aqueous layer was extracted 3 times with DCM. The combined organic layer was dried over Na2SO4, filtered, and the solvent was removed under reduced pressure. Purification of the crude acid was achieved by column chromatography (EtOAc/heptane 10:90 to EtOAc/heptane 60:40).

The crude NMR of 4b, 4c, and 4d suggested that traces (<5% NMR yield) of another geometrical isomer was present which was easily separated by column chromatography. We were not able to find this side product after purification.

Characterization of 5da

1H NMR (400 MHz, CDCl3): δ = 7.37 (ddd, J = 14.6, 11.1, 0.6 Hz, 1 H), 7.23 (d, J = 5.0 Hz, 1 H), 7.07 (d, J = 3.5 Hz, 1 H), 7.01–6.93 (m, 2 H), 6.70 (dd, J = 15.3, 11.2 Hz, 1 H), 6.45 (d, J = 14.7 Hz, 1 H), 3.60 (d, J = 24.6 Hz, 2 H), 3.52 (s, 2 H), 1.71–1.55 (m, 7 H). 13C NMR (151 MHz, CDCl3): δ = 165.40, 142.03, 131.18, 127.97, 127.90, 126.80, 125.99, 120.62, 47.04, 43.38, 26.86, 25.74, 24.78. HRMS (ESI): m/z calcld for [M + Na]+: 270.0923; found: 270.0926. ATR-FTIR: 3001, 2935, 2854, 2237, 1631, 1588, 1513, 1435, 1358, 1295, 1254, 1222, 1190, 1133, 1118, 1043, 1018, 990, 953, 907, 872, 853, 833, 805, 726, 644, 575, 543, 532 cm–1.