

Synthesis of sinapine and its unprecedented ruthenium-catalyzed [2+2] photodimerization

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Abstract: Sinapine (**1**) was easily synthesized from commercially available starting materials in an overall yield of 32% while 0.47% were obtained by its extraction from white mustard. Irradiation of **1** in the presence of $\text{Ru}(\text{dndp})_3\text{Cl}_2$ furnished in a [2+2] cycloaddition cyclobutanoid dimer **12**, a δ -truxinic acid. The putative mechanism of this reaction was supported by DFT calculations.

Keywords: sinapic acid, sinapine, dimerization, photoinduced, truxinic acid, ruthenium catalyst

1. Introduction

Secondary natural products have been of great importance to humankind for thousands of years¹. Whereas in ancient times extracts from different plants were used to treat or alleviate diseases based on empirical observations, today these compounds have become indispensable as leads for the development of selective and most important drugs²⁻³. Refined analytical methods allow the discovery of highly active compounds that occur only in small amounts in plants, and advances in synthesis ensure the accessibility of these substances.

Thus, cyclobutanes have been isolated from many natural products starting with the isolation of α - and β -pinenes and caryophyllene by O. Wallach in the 1890er years⁴. Although these strained mono-cyclic rings were regarded in the beginning to be somewhat exotic; they could be found and isolated in many plants but only in a very tiny amount, but curiosity in these molecules together with the better isolation techniques and the development of synthetic strategies enable access to many of them. This development was driven in particular by the fact that some cyclobutanoid dimers⁵⁻¹⁰, such as innovanoside A, showed high biological activity. Furthermore, numerous cyclobutanoids of superior biological activity were isolated from the *Piper* genus, such as dipiperamides A-E¹¹⁻¹⁸ and piperarborenines A-E¹⁹⁻²⁸ (Scheme 1) and several total syntheses have been developed. However, there are only a limited number of synthetic approaches to these strained semi-dimers and homo-dimers, such as cross-

coupling, re-arrangement, C-H-functionalization and cycloaddition reactions.

A couple of years ago, piperlongumine (isolated from *Piper longum*)²⁹⁻³¹ has been found to exhibit superior cytotoxic properties. Recently, we were able to access several dimers of piperlongumine³²⁻³³, and to show them of even higher cytotoxicity than the parent compound.

These dimers were obtained by solid-state photodimerization. Photochemical transformations are of increasing importance for the synthesis of natural products as unique structures can be accessed otherwise being challenging to synthesize, and products can be obtained through high energy intermediates that remain unreachable by thermal-driven reactions³⁴. As a consequence, in the last decades, the importance of light-induced reactions increased, and the introduction of LEDs presented a new state-of-the-art in science and technology³⁵.

Recently, we became interested in sinapine (**1** as its thiocyanate, Scheme 1)³⁶⁻³⁷, an alkaloid which can be found in white mustard (*Sinapis alba*)³⁸⁻³⁹ and canola (*Brassica sp.*)⁴⁰⁻⁴¹ because some interesting biological activities have been reported for this hybrid composed from (*E*) 4-hydroxy-3,5-dimethoxycinnamic acid and choline. Among other activities, this molecule holds anti-inflammatory⁴²⁻⁴³, anti-oxidative⁴⁴ and anti-angiogenic²⁹⁻³⁰ properties, as well as some potential as an inhibitor for the enzyme acetylcholinesterase⁴⁵. Shown as early in 1852⁴⁶, it can be extracted from plant material, and there is also one lengthy synthesis reported by E. Späth in 1920⁴⁷.

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DOI:

Received August 22, 2019
Accepted October 5, 2019
Published November 5, 2019

2. Results and Discussion

To investigate the cytotoxicity as well as other biological activities of sinapine dimers, it was necessary to obtain larger amounts by synthesis. For comparison, authentic sinapine was obtained by extraction from white mustard (obtained from a local supermarket) using *n*-hexane and methanol followed by precipitation with an aqueous solution of KSCN gave sinapine as its thiocyanate (**1**) as a colorless solid in an overall yield of 0.47%.

For a synthesis of sinapine thiocyanate, 4-hydroxy-3,5-dimethoxy-benzaldehyde (**2**) was silylated to yield 94% of **3**, whose Wittig olefination with carbomethoxymethyl triphenylphosphonium bromide/sodium hydroxide furnished **4** in 88% isolated yield. Compound **4** was hydrolysed with sodium hydroxide in ethanol (yielding **5**) and finally allowed to react with *N, N, N*-trimethyl-*N*-(2-chloroethyl)-ammonium chloride (**7** that has been prepared from choline chloride (**6**) with thionyl chloride in 76.9% yield) followed by precipitation with KSCN in 46% yield. Thus, the overall yield of 32% was achieved. The material from the synthesis was identical to the material obtained by the extraction of the white mustard seeds (m.p., m.m.p, NMR, IR, MS).

Previously, the irradiation of piperlongumine, on a silica gel TLC plate with UV light $\lambda = 254$ nm was reported to afforded dimerization products ³². Interestingly, under the same conditions, the irradiation of **4** for 2 h led to the exclusive formation of **8**. Compound **8** is the corresponding (*Z*) stereoisomer of the starting material. In the ¹H NMR spectrum for **8** a vicinal coupling constant for the protons of the olefinic bond $^3J = 12.9$ Hz was determined while for parent **4** $^3J = 15.9$ Hz was found, the latter being typical for a *trans*-configured double bond. Hydrolysis of **8** gave acid **9**.

Several drawbacks are found with large-scale photo-dimerization reactions using standard UV lamps, such as the development of heat and the high-energy consumption of the lamps. However, a couple of years ago, a [2+2] cycloaddition of acyclic enones using visible light and a ruthenium catalyst has been published by Du and Yoon ⁴⁸. Irradiation of methyl cinnamate under the conditions as described by these authors, however, failed to give any dimer even after prolonged periods of irradiation (1 week).

Investigation of the reaction mixture by ESI-MS showed (besides products of deterioration) only the presence of unchanged starting material but no dimer. It can be assumed that the substitution pattern of the aromatic system has a high impact on this reaction, since ethyl sinapate (**10**) afforded in the presence of Ru(bpy)₃Cl₂ hexahydrate dimer **11**, a δ truxinic acid

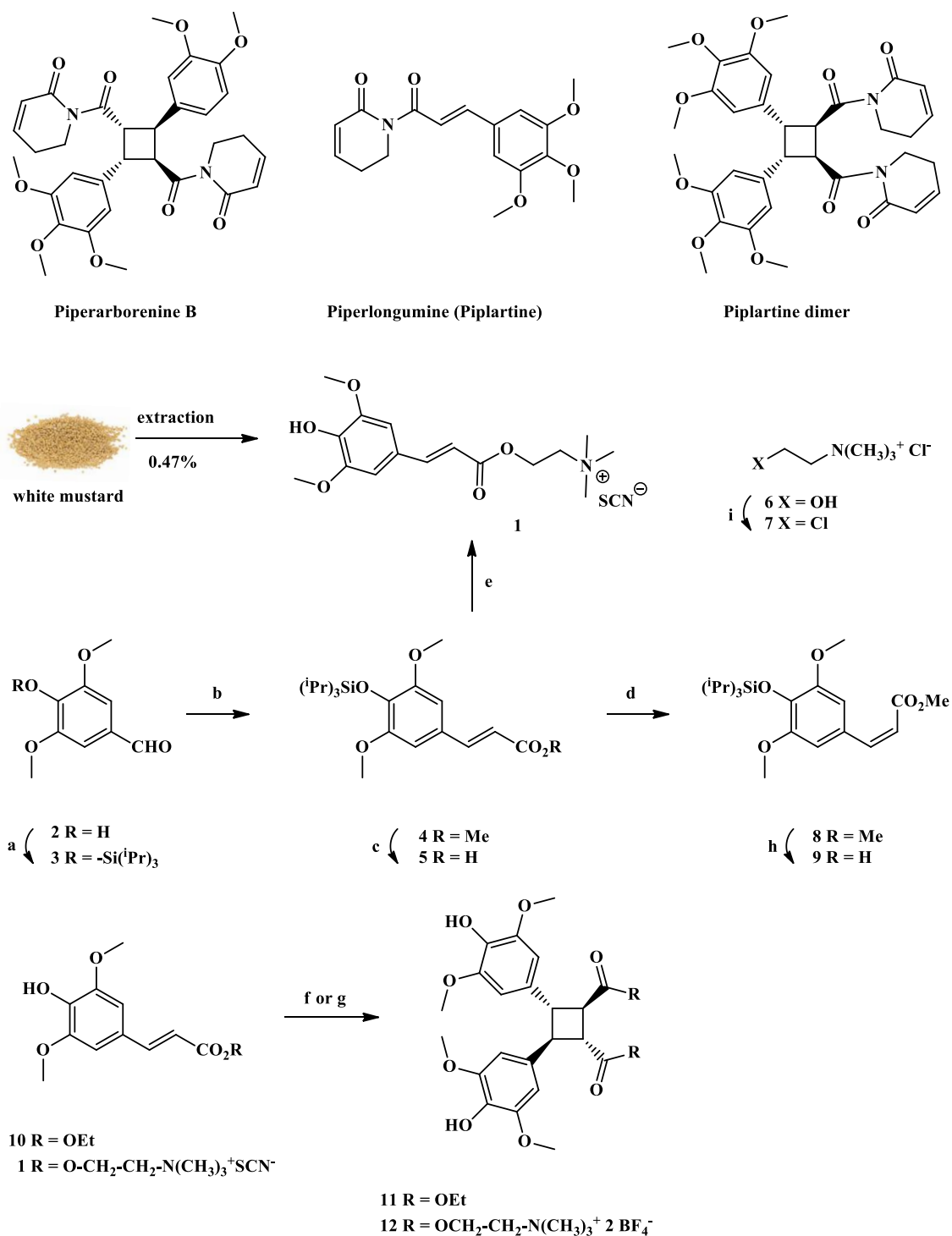
derivative whose relative configuration was determined by comparison of its ¹H NMR spectra with those of compounds of known configuration. Thus, in the ¹H NMR spectrum of **11** an AA'BB' spin system was observed for the cyclobutane protons (being typical for δ -truxinic acid derivatives).

The coupling constants were determined by simulation (see exp. part). Furthermore, for this product of a head-to-head dimerization, in the ESI-MS spectra fragments of the quasi-molecular ion [M+H]⁺ at *m/z* = 253 (C₁₃H₁₇O₅⁺) and *m/z* = 173 (C₈H₁₃O₄⁺) were observed. Irradiation ($\lambda = 470$ nm) of sinapin thiocyanate (**1**) using Ru(dndp)₃Cl₂ (dndp = 4,4'-dinonyl-2,2'-dipyridine) ⁴⁹ as a catalyst for 5 days gave dimer **12**. The latter catalyst proved superior to Ru(bpy)₃Cl₂ due to its high solubility in organic solvents. Furthermore, after completion of the reaction, the catalyst can be easily removed by extraction with organic solvents.

The fact that methyl cinnamate does not react under these reaction conditions while the starting materials **1** and **10** lead to the formation of dimeric products **11** and **12** is astonishing at first sight. According to the mechanism, however, postulated by Ischay et al. ⁵⁰ the triplet state of [Ru(bpy)₃]²⁺ is decisive for the reaction. If the triplet energy of the molecule is significantly higher than the energy of the catalyst, the reaction will not take place. To get a deeper insight, triplet energies (E_T(n) in kJ/mol) were calculated (GAUSSIAN) and compared to the triplet energy reported for the ruthenium catalyst. For cinnamic acid as well as for methyl cinnamate triplet energies of 253 kJ/mol were found, and for ethyl sinapate (**10**) and for sinapine (**1**) energies of ca. 230 kJ/mol were calculated.

Furthermore, even lower triplet energy (166 kJ/mol) was obtained for the corresponding phenolate of **10** which may be formed in equilibrium due to the presence of a base (DIPEA) in the reaction medium. For [Ru(bpy)₃]²⁺ triplet energy of 208 kJ/mol has been reported. From these results, it seems to be plausible why the Ru-catalyst enables dimerization of the sinapic acid derivatives while this is not the case for cinnamic acid and methyl cinnamate.

Biological testing of the dimers [SRB assay for cytotoxicity employing cell lines FaDu (hypopharyngeal carcinoma), A2780 (ovarian carcinoma), HT29 (colorectal carcinoma), MCF-7 (breast adenocarcinoma), SW1736 (thyroid carcinoma), A375 (melanoma), A549 (epithelial carcinoma) and non-malignant fibroblasts (NIH 3T3); Ellman's assay for cholinesterase inhibition using acetylcholinesterase (from electric eel) or butyrylcholinesterase (from equine serum)] did not reveal any biological activity associated with these dimers.



Scheme 1. Structure of some naturally occurring cyclobutanes, viz. piperarborenine B, cytotoxic piperlongumine (= piplartine) and an even more cytotoxic synthetic piplartine dimer. Reactions and conditions: a) TEA, DMAP, DMF, DCM, TRIS-Cl, 25°C, 30 min, 94%; b) BrCH₂CO₂Me, Ph₃P, NaOH, DCM, 25°C, 3 h, 88%; c) EtOH, NaOH, 60°C, 15 min, 84%; d) silica-TLC-plate, hv, λ = 254 nm, 2 h, 25%; e) K₂CO₃, dioxane/water, 25°C, 3h, then **7**, DMSO, 70°C, 1 day, 46%; f) from **10**: Ru(bpy)₃Cl₂ hexahydrate, LiBF₄, MeCN, DIPEA, hv, λ = 470 nm, 25°C, 8 days, 65%; g) from **1**, Ru(dndp)₃Cl₂, DIPEA, LiBF₄, hv, λ = 470 nm, 25°C, 31%; h) MeOH, NaOH, 60°C, 15 min, 84%; i) 120°C 2 h, then SOCl₂, reflux, 1 h, 77%.

3. Conclusion

A straightforward synthesis for sinapine (**1**) has been developed starting from commercially available starting materials in an overall yield of 32% while the

extraction of **1** from white mustard gave **1** in 0.47%. Irradiation of **1** in the presence of Ru(dndp)₃Cl₂ furnished in a [2+2] cycloaddition cyclobutanoid dimer **12**, a δ-truxinic acid. Thereby, this catalyst proved superior to Ru(bpy)₃Cl₂ due to its high solubility

in organic solvents. The putative mechanism of this reaction was supported by DFT calculations. In contrast to pipartine dimers, the dimer derived from sinapine did not show any cytotoxic activity for a variety of human tumor cell lines.

4. Acknowledgments

Many thanks are due to Dr. D. Ströhl and his team for the NMR spectra. IR- and UV-vis spectra were recorded by Ms V. Simon. Biological assays were performed by A. Loesche and S. Hoenke; experimental help in the lab was provided by A.M. Deckelmann, J. Wiese and T.L.T. Luong.

5. Experimental

5.1. General

The reagents were bought from commercial suppliers and used without further purification. Mustard seeds (Waldenheimer Gewürze) were purchased from a local supermarket. The solvents were dried according to usual procedures. For the photolysis, the diode LIU470A (470 nm, 1 W) from Thorlabs was used. Melting points were determined on Büchi Melting Point M-565 or LEICA hot stage microscope and are uncorrected, NMR spectra were recorded on Agilent 400 MHz VNMRS and 500 MHz DD2 spectrometers (δ given in ppm, J in Hz), ESI mass spectra were obtained on a Finnigan MAT LCQ (spray voltage 4.1 kV, sheath gas nitrogen) instrument. Macherey-Nagel ALUGRAM® Xtra SIL G/UV₂₅₄ pre-coated silica gel 60 F254 plates were used for thin-layer chromatography (detection with cerium molybdate spray reagent and UV absorption). IR spectra were recorded on a Perkin-Elmer FT-IR spectrometer Spectrum 1000 and wavenumbers are expressed in cm^{-1} . The absorption spectra were measured on Perkin Elmer Lambda14 spectrometer. Microanalyses were performed with an Elementar Vario EL (CHNS) instrument.

5.2. Quantum chemical calculations

The triplet energies were calculated as vertical excitation energies by time-dependent DFT with the Gaussian 09 package using the B3LYP functional 6-311++G(2d,2p) basis set, and as solvation model IEFPCM with the solvent acetonitrile after optimization of the ground state geometry.

Sinapine thiocyanate: (*E*) 2-[(3-(4-hydroxy-3,5-dimethoxyphenyl)acryloyl)oxy]-*N,N,N*-trimethylethan-1-aminium thiocyanate (**1**)

From **5**: Compound **5** (0.19 g, 0.49 mmol) was dissolved in a dioxane-water-mixture (3:2, 5 mL), and a solution of K_2CO_3 (0.03 g, 0.24 mmol) in water (1 mL) was added, and stirring at room temperature was continued for another 3 h. The volatiles were removed under reduced pressure. Chlorocholine chloride (**7**, 0.07 g, 0.56 mmol) was added, and the solids were dried at 70°C under reduced pressure for 1 h. Dry DMSO (5 mL) was added, and the mixture

was stirred at 60°C for 2 days. The solvent was removed under reduced pressure, and the residue was washed with chloroform (3 x 4 mL), dissolved in water (4 mL) and extracted with chloroform (4 mL). To the aqueous phase, an aqueous solution of KSCN (20%, 25 mL) was added, and the mixture was allowed to stand at 0°C for 48 h. The precipitate was filtrated off and recrystallized from ethanol. Compound **1** (0.08 g, 46%) was obtained as a colorless solid; m.p. 178–180°C; m.m.p. 178–180°C.

By extraction: Mustard seeds (330 g) were crushed with a kitchen mill and extracted in a Soxhlet apparatus with *n*-hexane (900 mL) for 8 h. The dried grist was extracted with 70% methanol for 1 h at 60°C (ultrasound-assisted) and filtered. The methanol was removed under reduced pressure, and the aqueous phase was washed with chloroform (4 x 100 mL). To the resulting aqueous phase an aqueous solution of KSCN (20%, 200 mL) was added, and the mixture was allowed to rest at 0°C for 2 days. The precipitate was filtrated off and recrystallized from ethanol to yield **1** (1.56 g, 0.47%) as a colorless solid; $R_F = 0.35$ (silica gel, *n*-butanol/*n*-propanol/water 1:1:1); m.p. 178–180°C (lit.: 178°C⁵¹);

IR (KBr) : = 3448_w, 2060_s, 1710_m, 1637_s, 1516_m, 1457_m, 1336_w, 1168_s, 1110_m cm^{-1} ;

UV-vis (H_2O): λ (log ϵ) = 243 (3.82), 355 (3.88) nm;

¹H NMR (400 MHz, DMSO-*d*₆): δ = 9.03 (s, 1H, OH), 7.60 (d, J = 15.9 Hz, 1H, 3-H), 7.03 (s, 2H, arom.), 6.55 (d, J = 15.9 Hz, 1H, 2-H), 4.57 (m, 2H, OCH₂), 3.80 (s, 6H, 2 x OCH₃), 3.74–3.69 (m, 2H, NCH₂), 3.17 (s, 9H, NMe₃⁺) ppm;

¹³C NMR (100 MHz, DMSO-*d*₆): δ = 165.9 (C=O), 148.1 (C, 2 x arom. C-OCH₃), 146.2 (C-3), 138.7 (C, arom. C-OH), 129.5 (SCN⁻), 124.2 (C, arom.), 114.1 (C-2), 106.5 (2 x CH, arom.), 64.0 (OCH₂), 57.7 (NCH₂), 56.2 (2 x OCH₃), 53.0 (NMe₃⁺) ppm;

MS (ESI, MeOH): m/z (%) = 251.1 ([M-SCN, -NMe₃]⁺, 24), 310.1 ([M-SCN]⁺, 100);

analysis calcd for C₁₇H₂₄N₂O₅S (368.45): C 55.42, H 6.57, N 7.60, S 8.70; found: C 55.18, H 6.79, N 7.36, S 8.56.

3,5-Dimethoxy-4-[(triisopropylsilyloxy)-benzaldehyde (**3**)

To a solution of 3,5-dimethoxy-4-hydroxybenzaldehyde (**2**, 0.60 g, 3.3 mmol), triethylamine (0.6 mL, 4.0 mmol) and DMAP (catalytic) in dry DMF (5 mL), a solution of triisopropylsilylchloride (0.9 mL, 4.0 mmol) in dry DCM (2 mL) was added, and the mixture was stirred at 25°C for 30 min at room temperature. Usual aqueous workup followed by chromatography (flash, silica gel, *n*-hexane/ethyl acetate 9:1) gave **3** (1.05 g, 94%) as a slightly yellowish liquid; $R_F = 0.54$ (silica gel, *n*-hexane/ethyl acetate 9:1);

IR (KBR) ν = 3449_w, 2944_m, 2867_m, 2361_w, 1693_m, 1584_m, 1507_s, 1464_m, 1424_w, 1389_w, 1337_s, 1268_w, 1231_w, 1131_s cm^{-1} ;

UV-vis (CHCl₃): λ (log ϵ) = 232 (4.09),

311 (4.09) nm;

^1H NMR (500 MHz, CDCl_3): δ = 9.81 (s, 1H, 1-H, CHO), 7.08 (s, 2H, arom.), 3.85 (s, 6H, 2 x OCH_3), 1.25 (m, 3H, 3 x CH-Si), 1.07 (d, J = 7.4 Hz, 18H, 6 x CH_3) ppm;

^{13}C NMR (125 MHz, CDCl_3): δ = 191.5 (CH, C=O), 151.8 (C, 2 x arom. C-OCH₃), 141.3 (C, arom. C-OSi), 128.8 (C, arom.), 106.6 (2 x CH, arom.), 55.6 (2 x OCH₃), 17.8 (6 x CH₃), 13.9 (CH, 3 x CH-Si) ppm;

MS (ESI, MeOH): m/z (%) = 339.1 ([M+H]⁺, 100); analysis calcd for $\text{C}_{18}\text{H}_{30}\text{O}_4\text{Si}$ (338.52): C 63.87, H 8.93; found: C 63.55, H 9.15.

Methyl (E) 3-(3,5-dimethoxy-4-((triisopropylsilyloxy)phenyl)acrylate (4)

To a solution of **3** (0.2 g, 0.6 mmol) in dry DCM (4 mL), methyl bromoacetate (0.08 mL) and PPh_3 (0.2 g, 0.9 mmol) were added. An aqueous solution of NaOH (7 mL, 0.5 M) was slowly added, and the reaction mixture was stirred for 3 h at room temperature. Usual aqueous work-up followed by column chromatography (silica gel, *n*-hexane/ethyl acetate, 9:1) gave **4** (0.18 g, 88%) as a colorless solid; R_F = 0.43 (silica gel, *n*-hexane/ethyl acetate, 9:1); m.p. 84–87°C;

IR (KBr): ν = 3447w, 2943m, 2865m, 1699s, 1631w, 1579m, 1508s, 1464m, 1424w, 1344m, 1266m, 1248w, 1161w, 1130s cm^{-1} ;

UV-vis (CHCl_3): λ (log ϵ) = 236 (4.27), 324 (4.32) nm;

^1H NMR (500 MHz, CDCl_3): δ = 7.60 (d, J = 15.9 Hz, 1H, 3-H), 6.71 (s, 2H, arom.), 6.29 (d, J = 15.9 Hz, 1H, 2-H), 3.81 (s, 6H, 2 x OCH_3), 3.79 (s, 3H, OCH_3), 1.24 (m, 3H, 3 x CH-Si), 1.10 (d, J = 7.4 Hz, 18H, 3 x CH_3) ppm; ^{13}C NMR (125 MHz, CDCl_3): δ = 167.7 (C-1, C=O), 151.8 (C, 2 x arom. C-OCH₃), 145.3 (CH, C-3), 137.9 (C, arom. C-OSi), 127.1 (C, arom.), 115.7 (CH, C-2), 105.5 (CH, arom.), 55.6 (2 x OCH₃), 51.6 (OCH₃), 17.8 (3 x CH₃), 13.3 (3 x CH-Si) ppm;

MS (ESI, MeOH): m/z (%) = 395.1 ([M+H]⁺, 100); analysis calcd for $\text{C}_{21}\text{H}_{34}\text{O}_5\text{Si}$ (394.58): C 63.92, H 8.69; found: C 63.77, H 8.92.

(E) 3-(3,5-Dimethoxy-4-((triisopropylsilyloxy)phenyl)acrylic acid (5)

To a solution of **4** (1.5 g, 4.3 mmol) in ethanol (20 mL) and NaOH (2 M, 8.5 mL) was stirred for 15 min at 60°C. The precipitate was dissolved in water (3 mL), and diluted HCl (2 M, 6 mL) was added. The precipitate was filtered off and dried; compound **5** (1.36 g, 84%) was obtained as a white solid; R_F = 0.55 (silica gel, *n*-hexane/ethyl acetate, 9:1); m.p. 149–152°C;

IR (KBr): ν = 3447ss, 2944w, 2361w, 1685w, 1631m, 1582w, 1509s, 1458w, 1288m, 1160w, 1133m cm^{-1} ;

UV-vis (CHCl_3): λ (log ϵ) = 237 (4.27), 321 (4.16) nm;

^1H NMR (500 MHz, CD_3OD): δ = 7.61 (d, J = 15.9 Hz, 1H, 3-H), 6.88 (s, 2H, arom.), 6.38 (d, J = 15.9 Hz, 1H, 2-H), 3.83 (s, 6H, 2 x OCH_3), 1.26 (m, 3H, 3 x CH-Si), 1.09 (d, J = 7.4 Hz, 18H, 3 x CH_3) ppm;

^{13}C NMR (125 MHz, CD_3OD): δ = 170.8 (C-1, C=O), 153.1 (C, 2 x arom. C-OCH₃), 147.1 (CH, C-3), 138.5 (C, arom. C-OSi), 128.6 (C, arom.), 117.1 (CH, C-2), 106.5 (CH, arom.), 56.2 (2 x OCH₃), 18.7 (6 x CH₃), 15.0 (3 x CH-Si) ppm;

MS (ESI, MeOH): m/z (%) = 381.1 ([M+H]⁺, 100); analysis calcd for $\text{C}_{20}\text{H}_{32}\text{O}_5\text{Si}$ (380.55): C 63.12, H 8.48; found: 62.95, H 8.69.

2-Chloro-N,N,N-trimethyl-ethanaminium chloride (7)

Commercial cholin chloride (**6**, 2.89 g, 20.7 mmol) was dried *in vacuo* at 120°C for 2 h. Freshly distilled thionyl chloride (20 mL) was added, and the mixture was heated under reflux for 1 h. The volatiles were removed under diminished pressure, methanol (20 mL; 3 x) was added, and removed under diminished pressure. The remaining solid was dried at 80°C under reduced pressure to afford **7** (2.45 g, 77%) as a colorless solid; R_F = 0.44 (RP18-silica gel, MeCN/water, 10:1); m.p. 240°C (decomp.; lit.: 240°C⁵²);

IR (KBr): ν = 3449s, 3006m, 2362w, 1636w, 1482s cm^{-1} ;

^1H NMR (500 MHz, CD_3OD): δ = 3.24 (s, 9H, 3 x CH_3), 3.81 (t, J = 7.2 Hz, 2H, N-CH₂), 4.06 (t, J = 7.2 Hz, 2H, Cl-CH₂) ppm;

^{13}C NMR (125 MHz, CD_3OD): δ = 67.7 (N-CH₂), 54.3 (N-CH₃), 36.7 (Cl-CH₂) ppm;

MS (ESI, MeOH): m/z (%) = 122.1 ([M-Cl]⁺, 100).

Methyl (Z) 3-(3,5-dimethoxy-4-[(triisopropylsilyloxy)phenyl]acrylate (8)

A solution of **4** (0.2 g, 0.5 mmol) in chloroform (2 mL) was applied onto a silica gel TLC plate and irradiated for 2 h (λ = 2154 nm). The silica gel was removed from the plate, extracted with methanol, filtered, and the filtrate was evaporated. The residue was subjected to chromatography (silica gel, *n*-hexane/ethyl acetate, 9:1) to yield **8** (0.05 g, 25%) as a viscous oil; R_F = 0.68 (silica gel, *n*-hexane/ethyl acetate, 9:1);

IR (film): ν = 3442br, 2946m, 2866m, 1720m, 1624m, 1578m, 1512s, 1464m, 1420w, 1344m, 1246m, 1132s, 886m, 684w cm^{-1} ;

UV-vis (CHCl_3): λ_{max} (log ϵ) = 232 (4.27), 321 (3.95) nm;

^1H NMR (500 MHz, CDCl_3): δ = 7.13 (s, 2H, arom.), 6.78 (d, J = 12.9 Hz, 1H, CH=), 5.82 (d, J = 12.9 Hz, CH=), 3.82 (s, 6H, 2 x OCH_3), 3.73 (s, 3H, CO_2CH_3), 1.26 (sept., J = 7.3 Hz, 3H, 3 x CH-Si), 1.09 (d, J = 7.3 Hz, 18H, 6 x CH_3) ppm;

^{13}C NMR (125 MHz, CDCl_3): δ = 166.8 (C-1, C=O), 150.6 (C, 2 x arom. C-OCH₃), 143.8 (CH, C-3), 136.7 (C, arom. C-OSi), 116.3 (CH, C-2), 108.1 (CH, arom.), 55.6 (2 x OCH₃), 51.3 (CO_2CH_3), 17.9 (6 x CH₃), 13.3 (3 x CH-Si) ppm;

MS (ESI, MeOH): m/z (%) = 395.1 ([M+H]⁺, 100); analysis calcd. for $\text{C}_{21}\text{H}_{34}\text{O}_5\text{Si}$ (394.58): C 63.92, H 8.69; found: C 63.65, H 8.96.

(Z) 3-(3,5-Dimethoxy-4-[(triisopropylsilyloxy)phenyl]-acrylic acid (9)

To a solution of **8** (0.18 g, 0.47 mmol) in methanol (5 mL), an aqueous solution of NaOH (2 M, 1.0 mL) was added, and stirring at 60°C was continued for 15 min. The precipitate was suspended in water (3 mL) and aq. hydrochloric acid (2 M, 4 mL) was added. The precipitate was filtered off and re-crystallized from 2-propanol to yield **9** (0.15 g, 84%) as a colorless solid; m.p. 86-89°C; $R_F = 0.61$ (silica gel, $\text{CHCl}_3/\text{MeOH}$, 9:1);

IR (KBr): $\nu = 3452s, 2941m, 2886m, 1684w, 1613m, 1575m, 1512s, 1464s, 1422m, 1348m, 1236m, 1130s \text{ cm}^{-1}$; UV-vis (MeOH): $\lambda_{\text{max}} (\log \epsilon) = 204 (4.31), 313 (3.92) \text{ nm}$;

$^1\text{H NMR}$ (500 MHz, CD_3OD): $\delta = 7.16 (s, 2\text{H, arom.}), 6.83 (d, J = 12.9 \text{ Hz}, 1 \text{ H, CH=}), 5.85 (d, J = 12.9 \text{ Hz}, 1\text{H, CH=}), 3.80 (s, 6\text{H}, 2 \times \text{OCH}_3), 1.27 (\text{sept.}, J = 7.2 \text{ Hz}, 3\text{H}, 3 \times \text{CH-Si}), 1.10 (d, J = 7.2 \text{ Hz}, 6 \times \text{CH}_3) \text{ ppm}$;

$^{13}\text{C NMR}$ (125 MHz, CD_3OD): $\delta = 169.5 (\text{C-1, C=O}), 151.6 (\text{C}, 2 \times \text{arom. C-OCH}_3), 143.7 (\text{CH, C-3}), 136.9 (\text{C, arom. C-OSi}), 128.1 (\text{arom.}), 118.2 (\text{CH, C-2}), 108.5 (\text{CH, arom.}), 55.5 (2 \times \text{OCH}_3), 17.7 (6 \times \text{CH}_3), 13.8 (2 \times \text{CH-Si}) \text{ ppm}$;

MS (ESI, MeOH): $m/z (\%) = 381.1 ([\text{M}+\text{H}]^+, 100)$; analysis calcd for $\text{C}_{20}\text{H}_{32}\text{O}_5\text{Si}$ (380.56): C 63.12, H 8.48; found: 62.90, H 8.72.

Ethyl (E) 3-(4-hydroxy-3,5-dimethoxyphenyl)-acrylate^[17] (10)

Sinapic acid (2.0 g, 8.92 mmol) was dissolved in EtOH (10 mL) and sulfuric acid (0.09 mL, 8.92 mmol) was added. The reaction mixture was stirred under reflux for 6 h. The solvent was removed *in vacuo*, and the residue was suspended in cold water. The aqueous phase was washed with ethyl acetate (3 x 50 mL), NaHCO_3 -solution (2 x 20 mL) and brine (1 x 50 mL). The organic phase was dried over MgSO_4 , and the solvent was removed under reduced pressure. Compound **10** was obtained as an off-white solid (2.0 g, 89%); $R_F = 0.27$ (silica gel, chloroform); m.p. 80–82°C (lit.: ¹⁸ 83°C);

IR (KBr): $\nu = 3506m, 2940w, 2834w, 1692s, 1633m, 1609m, 1517s, 1468m, 1429s, 1368w, 1336s, 1289s, 1201s, 1157s, 1106s, 1045m, 978m, 819m \text{ cm}^{-1}$;

UV-vis (CHCl_3): $\lambda (\log \epsilon) = 259 (3.81), 354 (4.28) \text{ nm}$;

$^1\text{H NMR}$ (500 MHz, CDCl_3): $\delta = 7.59 (d, J = 15.9 \text{ Hz}, 1\text{H, CH=}), 6.77 (s, 2\text{H, arom.}), 6.30 (d, J = 15.9 \text{ Hz}, 1\text{H, CH=}), 4.26 (q, J = 7.1 \text{ Hz}, 2\text{H, O-CH}_2), 3.92 (s, 6\text{H}, 2 \times \text{OCH}_3), 1.34 (t, J = 7.1 \text{ Hz}, 3\text{H, CH}_3) \text{ ppm}$;

$^{13}\text{C NMR}$ (125 MHz; CDCl_3): $\delta = 167.3 (\text{C-1, C=O}), 147.4 (\text{C}, 2 \times \text{arom. C-OCH}_3), 145.0 (\text{CH, C-3}), 137.2 (\text{C, arom. C-OH}), 126.1 (\text{C, arom.}), 116.2 (\text{CH, C-2}), 105.2 (\text{CH, arom.}), 60.5 (\text{OCH}_2), 56.5 (2 \times \text{OCH}_3), 14.5 (\text{CH}_3) \text{ ppm}$;

MS (ESI, MeOH): $m/z (\%) = 207.1 ([\text{M}+\text{H-EtOH}]^+, 100), 253.0 ([\text{M}+\text{H}]^+, 91), 275.1 ([\text{M}+\text{Na}]^+, 32)$.

Diethyl (1RS,2RS,3SR,4SR)-3,4-Bis(4-hydroxy-3,5-dimethoxyphenyl)cyclobutan-1,2-dicarboxylate (11)

To a solution of **10** (0.41 g, 1.62 mmol), $\text{Ru}(\text{bpy})_3\text{Cl}_2 \cdot 6 \text{ H}_2\text{O}$ (0.017 g, 0.023 mmol) and LiBF_4 (0.172 g, 1.82 mmol) in dry acetonitrile (5 mL), DIPEA (0.157 mL, 0.119 g, 0.907 mmol) was added. The reaction mixture was irradiated ($\lambda = 470 \text{ nm}$) for 8 days at room temperature. The solvent was removed under reduced pressure, and the residue was dissolved in chloroform (80 mL). The organic phase was washed with water (3 x 40 mL), brine (1 x 40 mL) and was dried over MgSO_4 . The raw product was purified by column chromatography (silica gel, toluene/chloroform/acetone, 5:3:2), and compound **11** was obtained as an off-white solid (0.266 g, 65%); $R_F = 0.39$ (silica gel, toluene/chloroform/acetone, 5:3:2); m.p. 129°C;

IR (KBr): $\nu = 3425w, 2939w, 1723m, 1611m, 1518m, 1455m, 1369w, 1339m, 1322m, 1247m, 1208s, 1105s, 1018m, 833m, 820m, 734m, 635m, 586m, 534m \text{ cm}^{-1}$;

UV-vis (CHCl_3): $\lambda (\log \epsilon) = 260 (4.81), 358 (3.70) \text{ nm}$;

$^1\text{H NMR}$ (400 MHz, CDCl_3): $\delta = 6.53 (s, 4\text{H, arom. CH}), 5.44 (s, 2\text{H}, 2 \times \text{OH}), 4.21 (q, J = 7.1 \text{ Hz}, 4\text{H}, 2 \times \text{OCH}_2), 3.86 (s, 12\text{H}, 4 \times \text{OCH}_3), 3.57, 3.39 (\text{AA'BB' }, ^3J_{\text{AA'}} = 9.7 \text{ Hz}, ^3J_{\text{BB'}} = 9.6 \text{ Hz}, ^3J_{\text{AB}} = ^3J_{\text{A'B'}} = 9.3 \text{ Hz}, ^4J_{\text{AB}} = ^4J_{\text{A'B}} = -0.2 \text{ Hz}, 4\text{H, cyclobutane H's}), 1.28 (t, J = 7.1 \text{ Hz}, 6\text{H}, 2 \times \text{CH}_3) \text{ ppm}$;

$^{13}\text{C NMR}$ (100 MHz; CDCl_3): $\delta = 172.8 (2 \times \text{C=O}), 147.2 (\text{C}, 4 \times \text{arom. C-OCH}_3), 134.0 (\text{C}, 2 \times \text{arom. C-OH}), 132.6 (2 \times \text{C, arom.}), 103.6 (4 \times \text{CH, arom.}), 61.2 (2 \times \text{OCH}_2), 56.5 (4 \times \text{OCH}_3), 48.0 (2 \times \text{CH, C-3, C-4}), 44.8 (2 \times \text{CH, C-1, C-2}), 14.4 (2 \times \text{CH}_3) \text{ ppm}$;

MS (ESI, MeOH): $m/z (\%) = 459.1 ([\text{M}+\text{H-EtOH}]^+, 38), 504.9 ([\text{M}+\text{H}]^+, 100), 521.9 ([\text{M}+\text{NH}_4]^+, 23), 527.1 ([\text{M}+\text{Na}]^+, 39)$;

analysis calcd for $\text{C}_{26}\text{H}_{32}\text{O}_{10}$ (504.53): C 61.90, H 6.39; found C 61.65, H 6.61.

2,2'-(((1RS,2RS,3SR,4SR)-3,4-Bis(4-hydroxy-3,5-dimethoxyphenyl)-cyclobutan-1,2-dicarbonyl)-bis(oxy))-bis(N,N,N-trimethylethan-1-aminium) bis(tetrafluoroborate) (12)

To a solution of **1** (0.5 g, 1.36 mmol), $\text{Ru}(\text{dndp})_3\text{Cl}_2$ (0.032 g, 0.023 mmol) and LiBF_4 (0.172 g, 1.82 mmol) in dry acetonitrile (7 mL), DIPEA (0.157 mL, 0.119 g, 0.907 mmol) was added, and the reaction mixture was irradiated ($\lambda = 470 \text{ nm}$) for 5 days at room temperature. The solvent was removed under reduced pressure; the residue was dissolved in water (20 mL) and was washed with chloroform (3 x 40 mL). The aqueous phase was concentrated to 10 mL and purified by column chromatography (Sephadex G10, water). Lyophilisation gave **12** (0.17 g, 31%) as a white amorphous solid; $R_F = 0.63$ (silica gel, *n*-butanol/*n*-propanol/water, 1:1:1);

$^1\text{H NMR}$ (400 MHz, D_2O): $\delta = 6.75 (s, 2\text{H}, 2 \times \text{OH}), 6.37 (s, 4\text{H, arom.}), 4.67 (m, 4\text{H}, 2 \times \text{OCH}_2), 4.29, 4.18 (\text{AA'BB' }, 4\text{H, cyclobutane H's}), 3.76 (m, 4\text{H}, 2 \times \text{CH}_2\text{NMe}_3^+), 3.70 (s, 12\text{H}, 4 \times \text{OCH}_3), 3.12 (s, 18\text{H}, 2 \times \text{NMe}_3^+) \text{ ppm}$;

$^{13}\text{C NMR}$ (125 MHz, CD_3CN): $\delta = 173.3 (2 \times \text{C=O}), 148.1 (\text{C}, 4 \times \text{arom. C-OCH}_3), 132.3 (\text{C}, 2 \times \text{arom.})$

C-OH), 131.3 (2 x C, arom.), 106.8 (4 x CH, arom.), 65.6 (2 x OCH₂), 59.2 (2 x NCH₂), 57.0 (4 x OCH₃), 54.8 (2 x NMe₃⁺), 46.6 (2 x CH, C-3, C-4), 42.9 (2 x CH, C-1, C-2) ppm;
 MS (ESI, MeOH): m/z (%) = 310.2 ([M-2BF₄]²⁺, 100), 707.3 ([M-BF₄]⁺, 31);
 analysis calcd for C₃₂H₄₈B₂F₈N₂O₁₀ (794.35): C 48.39, H 6.09, N 3.53; found: C 48.00, H 6.28, N 3.21.

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