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RESEARCH ARTICLE

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Total Synthesis of Salviachinensine A Using a Matteson Homologation Approach

Merlin Kempf,[a] Oliver Andler,[a] and Uli Kazmaier*[a]

[a] Organic Chemistry, Saarland University, Campus C4.2, DE-66123 Saarbrücken, Germany,
e-mail: u.kazmaier@mx.uni-saarland.de

Dedicated to Prof. Dr. *Alois Fürstner*, President of the 56th Bürgenstock-Conference 2023

Salviachinensine A, a natural product obtained from the Chinese medicinal plant *Salvia chinensis*, was synthesized for the first time by employing Donald Matteson's boronic ester homologation. The use of (*R*,*R*)-dicyclohexylethane-1,2-diol (DICHED) enabled the generation of the required stereogenic centers in a highly stereoselective fashion. Salviachinensine A was formed in a one-pot protecting group cleavage/lactonization/intramolecular Friedel–Crafts alkylation, followed by Lewis acid-catalysed cleavage of the acetal protecting groups.

Keywords: boron, boronic esters, Chinese medicine, Matteson homologation, natural products, Friedel–Crafts alkylation.

Introduction

In 2018, Wang et al. reported the isolation of six new phenolic acid derivatives, called salviachinensines, from the Chinese medicinal plant *Salvia chinensis*.[1] The structures were elucidated through NMR spectroscopy, electronic circular dichroism (ECD), and quantum chemical calculations. A biosynthetic pathway describing the synthesis of all six derivatives from caffeic acid was proposed. This rather simple unsaturated phenolic acid is widespread, found in plants of the *Salvia* species, and many of its derivatives show interesting biological activities. Salviachinensine A (*Figure 1*) was found to be the most active compound, displaying antiproliferative properties and inducing apoptosis and the arrest of cell cycle progression in acute myeloid leukemia cell lines MOLM-13 and MOLM-14 (IC_{50}: 2.3 and 7.1 μM, respectively).

Results and Discussion

Due to our interest in the synthesis of natural products with anti-cancer activity[2–4] we became interested in the synthesis of salviachinensine A by employing Matteson homologations to generate the stereogenic centers.[5–8] We recently used this approach in the synthesis of several polyketide-peptide conjugates.[9–12] In general, alkylboronic esters **A** were used as the starting material and after reaction with deprotonated dichloromethane, the stereoselectively formed α-chloroboronic ester **B** can be reacted with a

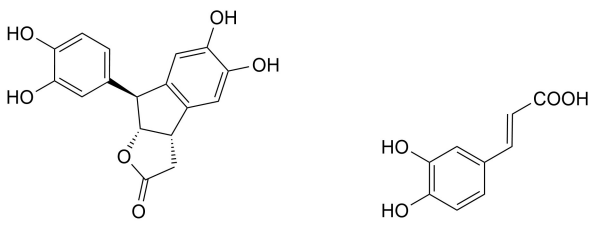

Figure 1. Phenolic acid derivatives from *Salvia chinensis*.

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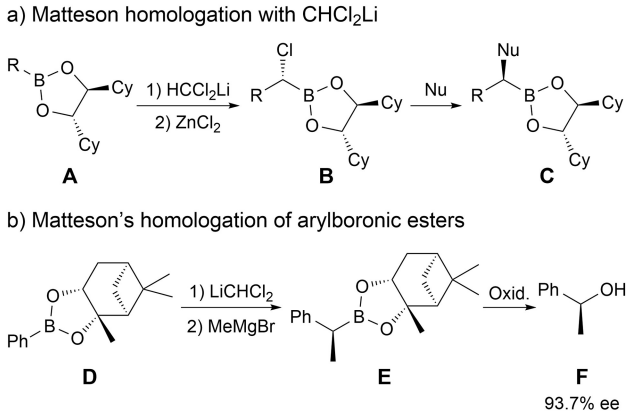
variety of nucleophiles, such as Grignard reagents or alkoxides, to afford a modified boronic ester **C** (*Scheme 1,a*).[5–8] In principle, aryl boronic esters can also be employed in this reaction;[13] surprisingly, however, only a very few examples have been reported until recently. It is astonishing that aryl boronic esters are not used more often in the stereoselective synthesis of aryl-substituted natural products, given that hundreds of substituted aryl boronic acids are commercially available.

In 1980, Matteson first investigated the homologation of pinanediol-based chiral phenylboronic ester **D** using MeMgBr as a nucleophile (*Scheme 1,b*).[14] Acceptable conversion was observed, although subsequent oxidation of the homologation product **E** to the corresponding alcohol **F** resulted in an enantiomeric excess (*ee*) of 'only' 93.7%. While this selectivity may be sufficient for synthetic purposes, it is considerably lower than that of the corresponding alkyl boronic esters. Kabalka[15] and Brown[13] reported similar results. Detailed mechanistic investigations by Matteson *et al.* indicated that the epimerization is caused by the LiCl liberated in the first step of α-chloroboronic ester formation. For arylboronic esters, epimerization proceeds around 20 times faster than that of the alkyl derivatives.[16]

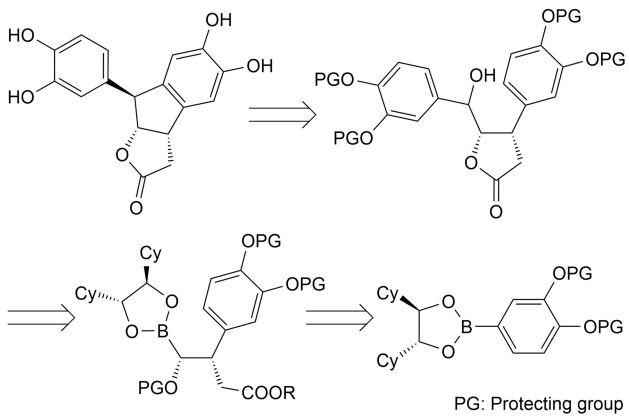
This might explain the modest interest in Matteson homologations of these aryl boronic esters, and to the best of our knowledge only pinanediol has been used as a chiral auxiliary to date.[17–20] This led us to investigate arylboronic ester homologations using the C_2-symmetric dicyclohexyl-1,2-ethanediol (DICHED)-ligand as an auxiliary and to optimize the reaction conditions.[21] By far the best yields and selectivities with Grignard reagents were obtained when $LiCHCl_2$ was added slowly at −100 °C and if the α-chloroboronic ester was reacted directly without prior isolation. Good results were obtained with electron-rich arylboronic esters, while electron-withdrawing groups on the aromatic ring increased the epimerization tendency. It was also possible to introduce alkoxy nucleophiles. Surprisingly, however, the α-alkoxyboronic esters obtained were unstable and could not be further homologated.[21]

Therefore, we were interested to determine if aryl-substituted α-chloroboronic esters could be reacted with ester enolates.[22] In a second homologation step, the introduction of an alkoxy functionality should not pose any difficulties. Moreover, if a substituted aryl-Grignard reagent can be employed to introduce a second aryl substituent in a third step, a linear precursor should be available to afford salviachinesine A through a Friedel–Crafts type cyclisation. The stereochemical outcome of this step should be controlled by the stereogenic centers generated through the first two homologation steps. Our retrosynthetic plan is summarized in *Scheme 2*.

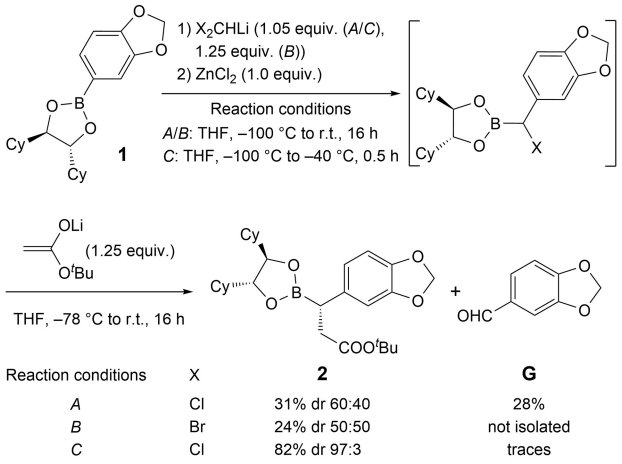
Based on our previous results,[9–12] we began our investigations with chiral boronic ester **1**, which is easily obtained from the corresponding commercially available boronic acid and (*R*,*R*)-DICHED.[23,24] Under the previously optimized reaction conditions, $LiCHCl_2$ was generated from dichloromethane and *n*-BuLi at −100 °C, and **1** was added in the presence of one equivalent $ZnCl_2$ (*Scheme 3*). The mixture was allowed to warm to room temperature overnight before it was cooled again to −78 °C, and the lithium enolate of *tert*-butyl acetate was added. After rewarming to room temperature overnight, the reaction mixture was hydrolyzed. For analytical purposes, the homologated boronic ester **2** was oxidized to the corresponding alcohol **2′**, with an *ee* determined by HPLC. Unfortu-



Scheme 1. Matteson homologations.



Scheme 2. Retrosynthesis of salviachinensine A.

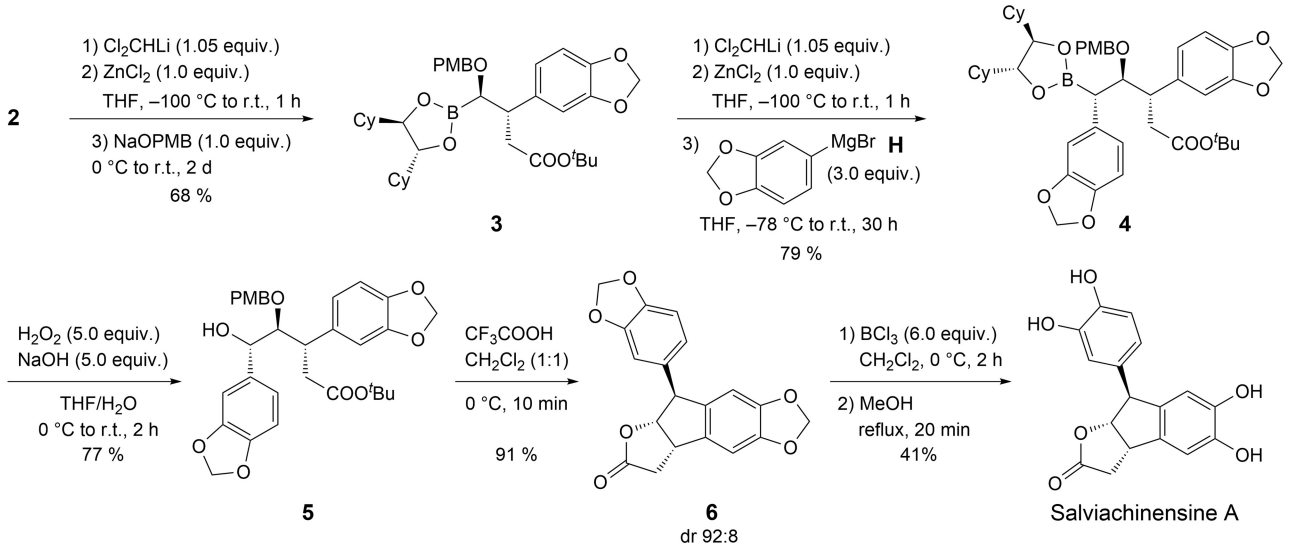


Scheme 3. Attempts to homologate aryl boronic ester **1** with ester enolates.

nately, under these conditions, the desired product **2** was obtained in only 31% yield and as a 6:4 diastereomeric mixture. Interestingly, aldehyde **G** was also formed, a side product typically observed when the α-chloroboronic ester does not react properly and decomposes under the reaction conditions.[21] The low conversion rate compelled us to also investigate the corresponding α-bromoboronic ester obtained from dibromomethane. In this case, however, the yield was even worse, and the product was completely epimerized. Moreover, **G** was the major side product formed (not isolated).

We assumed that the epimerization most likely occurred on the level of the α-haloboronic ester, either through an epimerization protocol as reported by Matteson *et al.*[16] or through an S_N1-type mechanism, as the corresponding benzylic carbocation should be sufficiently stabilized by the alkoxy substituents on the aryl ring. We therefore decided to use only the dichloro-carbenoid, which seems to be a little less sensitive to epimerization, in our further attempts. In addition, the next time we warmed the reaction mixture only to −40 °C for 0.5 h in the first step, before the precooled ester enolate (−78 °C) was cannulated to the mixture at −40 °C. Indeed, under these conditions the yield could be increased to 82% and afforded the desired product **2** with a high degree of stereoselectivity. No significant aldehyde formation was observed, which clearly indicates that at −40 °C the α-chloroboronic ester intermediate is stable and undergoes neither epimerization nor decomposition.

For the next homologation step, we used deprotonated *p*-methoxybenzyl alcohol as a nucleophile to give rise to the PMB-protected boronic ester **3** (*Scheme 4*). Our strategy was to use only acid-labile protecting groups that could be cleaved in the last step, in combination with an intramolecular Friedel–Crafts-type reaction. Although the reaction with the alkoxide was relatively slow and required two days for the complete conversion of the α-chloroboronic ester, the desired product was obtained as single stereoisomer. To introduce the second aromatic ring system, we reacted **3** with Grignard reagent **H**, the concentration of which was determined by a protocol



Scheme 4. Total synthesis of salviachinensine A.

described by Knochel *et al.*[25] Even with an excess of Grignard reagent, however, a yield of only 79% was obtained. We observed that **4** was not stable at room temperature and in the presence of oxygen and should therefore be either stored in the refrigerator (4 °C) under Ar or used directly in the next reaction step. Oxidation to the corresponding alcohol **5** proceeded cleanly. The liberated (*R*,*R*)-DICHED in the hydrolysis step was converted to the corresponding boronic ester with methylboronic acid, which was separable from the desired alcohol **5**.[9]

For the final step, the intramolecular Friedel–Crafts alkylation, compound **5** was dissolved in dichloromethane at 0 °C, after which trifluoracetic acid was added. The solution turned dark pink immediately and after 10 min a complete conversion of **5** to the protected salviachinesine A **6** was observed. The product was formed in a highly diastereoselective fashion, indicating that lactonization likely occurs prior to the Friedel–Crafts reaction and that the two stereogenic centers from the first two Matteson reactions control the stereochemical outcome of the cyclization step. Unfortunately, the two acetals were not directly cleaved under the reaction conditions employed, as we had hoped, so they had to be cleaved separately.

In general, formaldehyde acetals are relatively stable and can be cleaved with strong Lewis acids such as BCl_3 or $AlCl_3$.[26] Addition of BCl_3 to a solution of **6** in dichloromethane immediately generated a dark pink solution. After two hours, the complete consumption of **6** was observed and the desired natural product was obtained in 41% yield after chromatography. It is imperative to use anhydrous and degassed solvents in this step as the product is likely easily oxidized on the catechol moieties,[27] an effect that is demonstrated by the wide range of colors the reaction exhibits at various stages.

Conclusions

In conclusion, we have shown that salviachinesine A can be synthesized in only six steps from chiral aromatic boronic ester **1**. Three consecutive Matteson homologations generate two stereogenic centers of the natural product, the last one is formed in a highly stereoselective fashion during the deprotection/lactonization/intramolecular Friedel–Crafts alkylation.

Experimental Section

General Information

Ethyl acetate and pentane were distilled prior to use. Dry solvents were also distilled and dried as follows: THF over sodium and benzophenone, diisopropylamine over calcium hydride. Anhydrous dichloromethane and DMSO were obtained from *Acros Organics*. If dry solvents were used in the synthetic protocol, reactions were carried out under nitrogen atmosphere and the reaction vessels were heated under vacuum prior to use. Zinc chloride was always heated *in vacuo* prior to use. Therefore, it was heated with a heat gun to around 250 °C *in vacuo* (0.1 mbar) while shaking continuously. The flask was recharged with nitrogen. The cycle was repeated twice or until a fine, colorless powder was obtained. Thin-layer chromatography was performed on TLC-plates *POLYGRAM® SIL G* by *Macherey-Nagel* (Fluorescence indicator 254 nm, layer thickness 0.2 mm, dimensions 4×8 cm). Spots were detected through UV-Extinction at 254 nm or $KMnO_4$ or cerium(IV) ammonium molybdate stains. LC-MS analysis was performed on a *LC-2030* by *Shimadzu*. An *Onyx Monolithic C-18* column (50×4.6 mm) by *Phenomenex* was used as stationary phase. A diode array (190–300 nm) and mass detector *Shimadzu LCMS-2020* was used for detection. Ionization was carried out by electrospray (LR-MS, ESI). Normal-phase flash chromatography was carried out on a *Pure C-815 Chromatography System* by *Büchi*. Prepacked columns of the type *RediSep® Rf* by *Teledyne Isco* were used as stationary phase. For Reversed-phase flash chromatography and preparative HPLC a *Reveleris® Prep Chromatography System* by *Büchi* was used. Prepacked columns of the type *FlashPure Select C-18* by *Büchi* (Reversed-phase flash chromatography) and a *Luna C18(2)* column (250×21.1 mm, grain size 5 μm) by *Phenomenex* (preparative HPLC) were used. ^{1}H-NMR spectroscopy was performed on a *Avance II 400*, *Avance I 500* or *Avance Neo 500* by *Bruker*. Chemical shifts are reported in ppm (δ) with respect to TMS, and $CHCl_3$ (δ = 7.26 ppm) or DMSO-d_6 (δ = 2.50 ppm) was used as the internal standard. The spectra were analyzed with the software ACD/NMR Processor Academic Edition (Version 12.01). The multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad signal. ^{13}C-NMR spectroscopy was performed on the aforementioned devices and analyzed with the same software. The spectra were referenced to the solvent signals ($CDCl_3$: δ = 77.0 ppm, DMSO-d_6: δ = 39.5 ppm). The samples were measured with broad-band decoupling. The multiplicities in the

analysis indicate: s = singlet (quaternary carbon atom), d = doublet (CH moiety), t = triplet (CH_2 moiety), q = quartet (CH_3 moiety), br. s = broad signal. Chiral HPLC was performed on a model *D-7000* by *Merck Hitachi*. A column of the type *Reprosil-100-Chiral-NR* (250×4.6 mm, grain size 8 μm) by *Maisch GmbH* was used. Melting points were determined on a *MEL-TEMP II* by *Laboratory Devices* in glass capillaries open on one side. Specific optical rotation was measured on a polarimeter *P8000-T80* by *Krüss*. The measurement was performed at 20 °C with a sodium lamp (589 nm). $[\alpha]_D^{20}$ values are given in $10^{-1}\,cm^2\,g^{-1}$. High-resolution masses were measured on a *MAT 95* sector field spectrometer (CI) by *Finnigan*.

General Procedures

GP1: Matteson Homologation and Substitution with Nucleophiles

Matteson Homologation. 1.05 equiv. of *n*-butyllithium were added dropwise (through the rim of the flask) to a solution of 1.7 equiv. of anhydrous dichloromethane in anhydrous THF (2 mL/mmol) at −100 °C. After stirring for 0.5 h a solution of 1.0 equiv. of a boronic ester in anhydrous THF (1.5 mL/mmol) was added dropwise. After stirring for another 0.5 h a solution of 2.0–3.0 equiv. of zinc chloride (heated in high vacuum) in anhydrous THF (0.8 mL/mmol of zinc chloride) was added dropwise. The reaction was stirred for 1 h at room temperature.

Substitution with Nucleophile

The reaction mixture was cooled to 0 °C or −78 °C and the solution of the nucleophile was added dropwise. The reaction was slowly warmed to room temperature and stirred for 2 d. The reaction was then stopped by addition of sat. ammonium chloride solution and was diluted with pentane. The layers were separated, and the aqueous layer was extracted twice with pentane. The combined organic layers were dried over magnesium sulfate. The solvents were removed *in vacuo*. The crude product was purified by column chromatography.

GP2: Oxidation of Boronic Esters to Alcohols

5.0 equiv. of hydrogen peroxide (33 % in water) and a solution of 5.0 equiv. of sodium hydroxide in water (3 mL/mmol) were added to a solution of 1.0 equiv. of a boronic ester in THF (3 mL/mmol) at 0 °C. The reaction was warmed to room temperature and stirred for 1–2 h. It was stopped by addition of sat. sodium chloride solution and diluted with diethyl ether. The layers were separated, and the aqueous layer was extracted twice with diethyl ether. The combined organic layers were dried over magnesium sulfate and the solvent was removed *in vacuo*. The crude product was purified by column chromatography. If separation of (*R*,*R*)-DICHED was not possible by column chromatography, the crude product was dissolved in diethyl ether (10 mL/mmol) and 1.2 equiv. of methylboronic acid as well as an excess of magnesium sulfate were added. The reaction was stirred for 12 h before it was filtered. The solvent was removed *in vacuo* and the product was purified by column chromatography.

Synthesis of the Compounds

5-[(4*R*,5*R*)-4,5-Dicyclohexyl-1,3,2-dioxaborolan-2-yl]-2*H*-1,3-benzodioxole (**1**). 2*H*-1,3-Benzodioxol-5-ylboronic acid (880 mg, 5.30 mmol, 1.2 equiv.) and (*R*,*R*)-DICHED (1.00 g, 4.42 mmol, 1.0 equiv.) were dissolved in diethyl ether (60 mL) and stirred with magnesium sulfate (1.06 g, 8.84 mmol, 2.0 equiv.) over night. The mixture was filtered, and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (pentane/AcOEt 8:2) to yield compound **1** (1.55 g, 4.35 mmol, 98 %) as a colorless solid. M.p. 83 °C. $[\alpha]_D^{20} = +8.1$ ($c = 1.0$, $CHCl_3$). R_f 0.63 (pentane/AcOEt 8:2). ^{1}H-NMR (400 MHz, $CDCl_3$): 7.38 (dd, $^3J_{1,2} = 7.8$, $^4J_{1,6} = 1.0$, 1 H, 1-H), 7.26 (d, $^3J_{6,1} = 0.7$, 1 H, 6-H), 6.84 (d, $^3J_{2,1} = 7.7$, 1 H, 2-H), 5.96 (d, $^2J_{4a,4b} = 2.3$, 1 H, 4-Ha), 5.95 (d, $^2J_{4b,4a} = 2.2$, 1 H, 4-Hb), 4.00 (m, 2 H, 8-H), 1.85 (m, 2 H, 10-H), 1.73–1.81 (m, 4 H, 11-H, 12-H), 1.68 (m, 2 H, 12-H′), 1.64 (m, 2 H, 10-H′), 1.42 (m, 2 H, 9-H), 0.94–1.30 (m, 10 H, 10-H″, 11-H′). ^{13}C-NMR (100 MHz, $CDCl_3$): 150.1 (s, C-3), 147.2 (s, C-5), 129.8 (d, C-1), 114.0 (d, C-6), 108.4 (d, C-2), 100.7 (t, C-4), 83.8 (d, C-8), 43.1 (d, C-9), 28.4 (t, C-10), 27.4 (t, C-10′), 26.5 (t, C-12), 26.0 (t, C-11), 25.9 (t, C-11′). HR-CI-MS: 356.2160 ($C_{21}H_{29}BO_4^+$, M^+; calc. 356.2153).

***tert*-Butyl (3*S*)-3-(2*H*-1,3-Benzodioxol-5-yl)-3-[(4*R*,5*R*)-4,5-dicyclohexyl-1,3,2-dioxaborolan-2-yl]propanoate** (**2**). *Homologation*: Anhydrous dichloromethane (675 μL, ρ = 1.33 g/mL, 10.6 mmol, 1.7 equiv.) was dissolved in anhydrous THF (12.6 mL) and cooled to −100 °C. *n*-Butyllithium (4.08 mL, 1.6 M in hexane, 6.53 mmol, 1.05 equiv.) was added dropwise (through the rim of the flask). After stirring for 0.5 h a solution of boronic ester **1** (2.22 g, 6.22 mmol, 1.0 equiv.) in anhydrous THF (9.5 mL) was added dropwise. After stirring for

another 0.5 h a solution of zinc chloride (heated in high vacuum, 894 mg, 6.22 mmol, 1.0 equiv.) in anhydrous THF (5.0 mL) was added dropwise. The reaction was warmed to −40 °C over 0.5 h.

Substitution with Enolate: Anhydrous diisopropylamine (1.20 mL, ρ = 0.71 g/mL, 8.40 mmol, 1.35 equiv.) was dissolved in anhydrous THF (15.8 mL) and cooled to −40 °C. *n*-Butyllithium (4.86 mL, 1.6 M in hexane, 7.78 mmol, 1.25 equiv.) was added dropwise. The mixture was warmed to room temperature and stirred for 20 min. After cooling to −78 °C *tert*-butyl acetate (1.05 mL, ρ = 0.87 g/mL, 7.78 mmol, 1.25 equiv.) was added dropwise to the LDA solution and the reaction mixture was stirred for 0.5 h at −78 °C, before it was cannulated to the solution of the freshly prepared α-chloroboronic ester at −40 °C. The mixture was slowly warmed to room temperature and stirred overnight. The reaction was stopped by addition of sat. ammonium chloride solution and diluted with pentane. The layers were separated, and the aqueous layer was extracted twice with pentane. The combined organic layers were dried over sodium sulfate and the solvent was removed *in vacuo*. Boronic ester **2** (2.47 g, 5.11 mmol, 82 %) was obtained as colorless oil after purification by column chromatography (cyclohexane/AcOEt 0–10 %). $[\alpha]_D^{20} = +20.0$ ($c = 1.0$, $CHCl_3$). R_f 0.27 (pentane/AcOEt 9 : 1). ^{1}H-NMR (400 MHz, $CDCl_3$): 6.73 (d, $^4J_{6,1} = 1.5$, 1 H, 6-H), 6.69 (d, $^3J_{2,1} = 8.0$, 1 H, 2-H), 6.65 (dd, $^3J_{1,2} = 8.1$, $^4J_{1,6} = 1.6$, 1 H, 1-H), 5.89 (s, 2 H, 4-H), 3.82 (m, 2 H, 13-H), 2.67–2.75 (m, 2 H, 8-H, 9-Ha), 2.57 (dd, $^2J_{9b,9a} = 18.5$, $^3J_{9b,8} = 10.5$, 1 H, 9-Hb), 1.69–1.81 (m, 6 H, 15-H, 16-H, 17-H), 1.66 (m, 2 H, 17-H′), 1.54 (m, 2 H, 15-H′), 1.38 (s, 9 H, 12-H), 1.30 (m, 2 H, 14-H), 1.06–1.25 (m, 6 H, 15-H″, 16-H′), 0.83–1.06 (m, 4 H, 15-H‴, 16-H″). ^{13}C-NMR (100 MHz, $CDCl_3$): 172.5 (s, C-10), 147.5 (s, C-5), 145.4 (s, C-3), 135.7 (s, C-7), 121.1 (d, C-1), 109.0 (d, C-6), 108.1 (d, C-2), 100.6 (t, C-4), 83,7 (d, C-13), 80.2 (s, C-11), 42.9 (d, C-14), 38.5 (t, C-9), 28.3 (t, C-15), 28.0 (q, C-12), 27.5 (t, C-16), 27.3 (br. s, C-8), 26.4 (t, C-17), 26.0 (t, C-15′), 25.9 (t, C-16′). HR-CI-MS: 427.2285 ($C_{24}H_{32}O_6B^+$, $[M-C_4H_9]^+$; calc. 427.2286).

***tert*-Butyl (3*S*)-3-(2*H*-1,3-Benzodioxol-5-yl)-3-hydroxypropanoate** (**2′**). According to *GP2*, boronic ester **2** (61.1 mg, 120 μmol, 1.0 equiv.) was reacted with hydrogen peroxide (56.0 μL, 33 % in water, ρ = 1.11 g/mL, 0.600 mmol, 5.0 equiv.) and sodium hydroxide (24.0 mg, 0.600 mmol, 5.0 equiv.) for 1 h. After purification by column chromatography (cyclohexane /AcOEt 0–25 %), a mixture of (*R*,*R*)-DICHED (9.9 mg) and the desired product (28.6 mg, 107 μmol, 89 %, 94 % *ee* according to HPLC) was obtained. To isolate the pure alcohol **2′** for analytical purposes, (*R*,*R*)-DICHED was removed by esterification with methylboronic acid and subsequent column chromatography. R_f 0.24 (pentane/AcOEt 8 : 2). ^{1}H-NMR (400 MHz, $CDCl_3$): 6.88 (d, $^4J_{6,1} = 1.5$, 1 H, 6-H), 6.81 (dd, $^3J_{1,2} = 8.0$, $^4J_{1,6} = 1.3$, 1 H, 1-H), 6.76 (d, $^3J_{2,1} = 8.0$, 1 H, 2-H), 5.94 (s, 2 H, 4-H), 4.98 (dd, $^3J_{8,9a} = 8.8$, $^3J_{8,9b} = 4.0$, 1 H, 8-H), 2.99 (br. s, 1 H, 8-OH), 2.64 (dd, $^2J_{9a,9b} = 16.3$, $^3J_{9a,8} = 8.8$, 1 H, 9-Ha), 2.57 (dd, $^2J_{9b,9a} = 16.3$, $^3J_{9b,8} = 4.0$, 1 H, 9-Hb), 1.45 (s, 9 H, 12-H). ^{13}C-NMR (100 MHz, $CDCl_3$): 171.8 (s, C-10), 147.7 (s, C-5), 147.0 (s, C-3), 136.7 (s, C-7), 119.1 (d, C-1), 108.1 (d, C-6), 106.4 (d, C-2), 101.0 (t, C-4), 81.5 (s, C-11), 70.2 (d, C-8), 44.3 (t, C-9), 28.1 (q, C-12). HPLC: hexane/isopropanol 9 : 1, flow 1.0 mL/min, 20 °C, $t_R(S) = 14.21$ min, $t_R(R) = 17.72$ min. HR-CI-MS: 266.1166 ($C_{14}H_{18}O_5^+$, M^+; calc. 266.1149).

***tert*-Butyl (3*S*,4*R*)-3-(2*H*-1,3-Benzodioxol-5-yl)-4-[(4*R*,5*R*)-4,5-dicyclohexyl-1,3,2-dioxaborolan-2-yl]-4-[(4-methoxyphenyl)methoxy]butanoate** (**3**). According to *GP1*, boronic ester **2** (2.00 g, 4,10 mmol, 1.0 equiv.) was reacted with anhydrous dichloromethane (450 μL, ρ = 1.33 g/mL, 7.00 mmol, 1.7 equiv.), *n*-butyllithium (2.70 mL, 1.6 M in hexane, 4.30 mmol, 1.05 equiv.) and zinc chloride (1.12 g, 8.20 mmol, 2.0 equiv.). Sodium hydride (328 mg, 60 % in mineral oil, 8.20 mmol, 2.0 equiv.) was suspended in anhydrous THF (2.5 mL) and anhydrous DMSO (7.4 mL). 4-Methoxybenzyl alcohol (1.07 mL, ρ = 1.11 g/mL, 8.61 mmol, 2.1 equiv.) was added and the mixture was stirred for 5 h. The alkoxide solution was employed as the nucleophile solution according to *GP1* and was added dropwise to the solution of the freshly prepared α-chloroboronic ester at 0 °C. The reaction was warmed to room temperature and stirred for 2 d. Boronic ester **3** (1.75 g, 2.76 mmol, 68 %) was obtained as colorless oil after purification by column chromatography (cyclohexane/AcOEt 0–10 %). $[\alpha]_D^{20} = +37.2$ (c = 1.0, $CHCl_3$). R_f 0.37 (pentane/AcOEt 9 : 1). ^{1}H-NMR (500 MHz, $CDCl_3$): 7.23 (m, 2 H, 16-H), 6.90 (d, $^4J_{6,1} = 1.6$, 1 H, 6-H), 6.85 (m, 2 H, 17-H), 6.76 (dd, $^3J_{1,2} = 7.9$, $^4J_{1,6} = 1.6$, 1 H, 1-H), 6.66 (d, $^3J_{2,1} = 7.9$, 1 H, 2-H), 5.90 (d, $^2J_{4a,4b} = 1.3$, 1 H, 4-Ha), 5.88 (d, $^2J_{4b,4a} = 1.6$, 1 H, 4-Hb), 4.56 (d, $^2J_{14a,14b} = 11.7$, 1 H, 14-Ha), 4.30 (d, $^2J_{14b,14a} = 11.7$, 1 H, 14-Hb), 3.80 (s, 3 H, 19-H), 3.77 (m, 2 H, 20-H), 3.51 (d, $^3J_{13,8} = 5.4$, 1 H, 13-H), 3.33 (ddd, $^3J_{8,9b} = 9.1$, $^3J_{8,9a} = 6.3$, $^3J_{8,13} = 5.4$, 1 H, 8-H), 2.70 (dd, $^2J_{9a,9b} = 15.1$, $^3J_{9a,8} = 6.3$, 1 H, 9-Ha), 2.63 (dd, $^2J_{9b,9a} = 15.5$, $^3J_{9b,8} = 9.1$, 1 H, 9-Hb), 1.67–1.75 (m, 4 H, 22-H, 24-H), 1.65 (m, 2 H, 24-H′), 1.60 (m, 2 H, 22-H′), 1.42 (m, 2 H, 21-H) 1.30 (s, 9 H, 12-H), 1.06–1.20 (m, 8 H, 22-H″,

23-H), 0.92 (m, 2 H, 22-H‴), 0.77 (m, 2 H, 23-H′). ^{13}C-NMR (125 MHz, $CDCl_3$): 171.8 (s, C-10), 158.9 (s, C-18), 147.0 (s, C-5), 145.9 (s, C-3), 136.0 (s, C-7), 131.1 (s, C-15), 129.3 (d, C-16), 122.1 (d, C-1), 113.5 (d, C-17), 109.4 (d, C-6), 107.6 (d, C-2), 100.6 (t, C-4), 83.7 (d, C-20), 80.0 (s, C-11), 72.5 (t, C-14), 55.2 (q, C-19), 44.2 (d, C-8), 42.7 (d, C-21), 39.4 (t, C-9), 28.1 (t, C-22), 28.0 (q, C-12), 27.3 (t, C-23), 26.4 (t, C-24), 25.9 (t, C-22′), 25.8 (t, C-23′). The signal of C-13 could not be detected. HR-CI-MS: 604.3567 ($C_{35}H_{47}O_6B^+$, $[M-CH_2O]^+$; calc. 604.3566).

(2*H*-1,3-Benzodioxol-5-yl)magnesium Bromide (**H**). 2 mL of a solution containing 5-bromo-2*H*-1,3-benzodioxole (1.81 mL, ρ = 1.67 g/mL, 15.0 mmol, 1.0 equiv.) in anhydrous THF (15 mL) were added to magnesium turnings (547 g, 22.5 mmol, 1.5 equiv.) that were heated in high vacuum. A grain of iodine was added. When the reaction started the remaining solution of 5-bromo-2*H*-1,3-benzodioxole was added dropwise. The mixture was stirred for 5 h at room temperature. The concentration of the Grignard stock solution was determined by titration against iodine (1.87 mmol/mL).[25]

***tert*-Butyl (3*S*,4*R*,5*S*)-3,5-Bis(2*H*-1,3-benzodioxol-5-yl)-5-[(4*R*,5*R*)-4,5-dicyclohexyl-1,3,2-dioxaborolan-2-yl]-4-[(4-methoxyphenyl)methoxy]pentanoate** (**4**). According to *GP1*, boronic ester **3** (1.12 g, 1.77 mmol, 1.0 equiv.) was reacted with anhydrous dichloromethane (192 µL, δ = 1.33 g/mL, 3.01 mmol, 1.7 equiv.), *n*-butyllithium (1.16 mL, 1.6 M in hexane, 1.86 mmol, 1.05 equiv.) and zinc chloride (723 mg, 5.31 mmol, 3.0 equiv.). The stock solution of (2H-1,3-benzodioxol-5-yl)magnesium bromide (2.84 mL, 5.31 mmol, 3.0 equiv.) was used as nucleophile solution according to *GP1* and was added dropwise to the solution of the freshly prepared α-chloroboronic ester at −78 °C. The mixture was warmed to room temperature and stirred for 30 h. Boronic ester **4** (1.08 g, 1.40 mmol, 79%) was obtained as colorless oil after purification by column chromatography (cyclohexane/AcOEt 0–10%). $[\alpha]_D^{20} = +11.2$ (c = 0.5, $CHCl_3$). R_f 0.24 (pentane/AcOEt 9:1). ^{1}H-NMR (400 MHz, $CDCl_3$): 7.26 (m, 2 H, 16-H), 6.89 (m, 2 H, 17-H), 6.78 (d, $^4J_{6,1} = 1.5$, 1 H, 6-H), 6.67 (d, $^3J_{26,27} = 8.2$, 1 H, 26-H), 6.66 (d, $^4J_{22,27} = 2.1$, 1 H, 22-H), 6.63 (d, $^3J_{2,1} = 8.0$, 1 H, 2-H), 6.54 (dd, $^3J_{27,26} = 8.0$, $^4J_{27,22} = 1.6$, 1 H, 27-H), 6.50 (dd, $^3J_{1,2} = 8.1$, $^4J_{1,6} = 1.6$, 1 H, 1-H), 5.92 (d, $^2J_{24a,24b} = 1.5$, 1 H, 24-Ha), 5.90 (d, $^2J_{24b,24a} = 1.5$, 1 H, 24-Hb), 5.89 (s, 2 H, 4-H), 4.79 (d, $^2J_{14a,14b} = 11.3$, 1 H, 14-Ha), 4.59 (d, $^2J_{14b,14a} = 11.3$, 1 H, 14-Hb), 4.08 (dd, $^3J_{13,20} = 10.0$, $^3J_{13,8} = 3.3$, 1 H, 13-H), 3.82 (s, 3 H, 19-H), 3.72 (m, 2 H, 28-H), 3.13 (m, 1 H, 8-H), 2.67 (dd, $^2J_{9a,9b} = 14.9$, $^3J_{9a,8} = 7.0$, 1 H, 9-Ha), 2.54 (dd, $^2J_{9b,9a} = 14.9$, $^3J_{9b,8} = 8.8$, 1 H, 9-Hb), 2.46 (d, $^3J_{20,13} = 10.2$, 1 H, 20-H), 1.52–1.68 (m, 8 H, 30-H, 31-H, 32-H), 1.38 (m, 2 H, 30-H′), 1.31 (s, 9 H, 12-H), 1,10 (m, 2 H, 29-H), 0.95–1.04 (m, 6 H, 30-H″, 31-H′), 0.86 (m, 2 H, 30-H‴), 0.74 (m, 2 H, 31-H″). ^{13}C-NMR (100 MHz, $CDCl_3$): 171.7 (s, C-10), 158.7 (s, C-18), 147.3 (s, C-23), 147.0 (s, C-5), 145.9 (s, C-3), 145.4 (s, C-25), 133.9 (s, C-7), 133.5 (s, C-21), 131.3 (s, C-15), 128.1 (d, C-16), 123.2 (d, C-1), 122.5 (d, C-27), 113.6 (d, C-17), 110.0 (d, C-6), 109.7 (d, C-22), 108.0 (d, C-26), 107.4 (d, C-2), 101.1 (t, C-4), 100.6 (t, C-24), 84.2 (d, C-13), 83.6 (d, C-28), 80.2 (s, C-11), 73.5 (t, C-14), 55.3 (q, C-19), 44.7 (d, C-8), 42.9 (d, C-29), 39.7 (t, C-9), 28.3 (t, C-30), 28.0 (q, C-12), 27.6 (t, C-31), 26.3 (t, C-32), 25.9 (t, C-30′), 25.7 (t, C-31′). The signal of C-20 could not be detected. HR-MS of boronic ester **4** could not be measured due to the instability.

***tert*-Butyl (5*S*)-3-(2*H*-1,3-Benzodioxol-5-yl)-5-*C*-(2*H*-1,3-benzodioxol-5-yl)-2,3-dideoxy-4-*O*-[(4-methoxyphenyl)methyl]-D-*threo*-pentonate** (**5**). According to *GP2*, boronic ester **4** (607 mg, 0.790 mmol, 1.0 equiv.) was reacted with hydrogen peroxide (370 µL, 33% in water, ρ = 1.11 g/mL, 4.00 mmol, 5.0 equiv.) and sodium hydroxide (164 mg, 4.00 mmol, 5.0 equiv.) in water (2.4 ml) for 2 h. (*R*,*R*)-DICHED was separated by esterification with methylboronic acid (58.0 mg, 0.960 mmol, 1.2 equiv.). Alcohol **5** (336 mg, 0.610 mmol, 77%) was obtained as colorless solid after purification by column chromatography (cyclohexane/AcOEt 0–30%). M.p. 42–45 °C. $[\alpha]_D^{20} = +28.0$ (c = 1.0, $CHCl_3$). R_f 0.23 (pentane/ AcOEt 8:2). ^{1}H-NMR (400 MHz, $CDCl_3$): 7.16 (m, 2 H, 16-H), 6.86 (m, 2 H, 17-H), 6.83 (d, $^4J_{6,1} = 1.9$, 1 H, 6-H), 6.77 (d, $^3J_{23,22} = 7.9$, 1 H, 23-H), 6.76 (d, $^4J_{27,22} = 1.6$, 1 H, 27-H), 6.71 (d, $^3J_{2,1} = 7.9$, 1 H, 2-H), 6.68 (dd, $^3J_{22,23} = 8.2$, $^4J_{20,27} = 1.6$, 1 H, 22-H), 6.63 (dd, $^3J_{1,2} = 7.9$, $^4J_{1,6} = 1.9$, 1 H, 1-H), 5.96 (s, 2 H, 25-H), 5.93 (d, $^2J_{4a,4b} = 1.6$, 1 H, 4-Ha), 5.92 (d, $^2J_{4b,4a} = 1.6$, 1 H, 4-Hb), 4.45 (d, $^2J_{14a,14b} = 10.7$, 1 H, 14-Ha), 4.41 (d, $^2J_{14b,14a} = 10.7$, 1 H, 14-Hb), 4.38 (dd, $^3J_{20,13} = 5.7$, $^3J_{20,20\text{-OH}} = 4.7$, 1 H, 20-H), 3.81 (s, 3 H, 19-H), 3.73 (dd, $^3J_{13,20} = 5.7$, $^3J_{13,8} = 4.4$, 1 H, 13-H), 3.11 (ddd, $^3J_{8,9b} = 8.5$, $^3J_{8,9a} = 6.9$, $^3J_{8,13} = 4.4$, 1 H, 8-H), 2.73 (dd, $^2J_{9a,9b} = 15.1$, $^3J_{9a,8} = 6.9$, 1 H, 9-Ha), 2.67 (d, $^3J_{20\text{-OH},20} = 4.4$, 1 H, 20-OH), 2.60 (dd, $^2J_{9b,9a} = 15.1$, $^3J_{9b,8} = 8.5$, 1 H, 9-Hb), 1.32 (s, 9 H, 12-H). ^{13}C-NMR (100 MHz, $CDCl_3$): 171.4 (s, C-10), 159.3 (s, C-18), 147.7 (s, C-24), 147.3 (s, C-5), 147.1 (s, C-26), 146.2 (s, C-3), 135.3 (s, C-21), 134.0 (s, C-7), 130.0 (s, C-15), 129.8 (d, C-16), 122.5 (d, C-1), 120.4 (d, C-22), 113.8 (d, C-17), 109.4 (d, C-6), 108.0 (d, C-23), 107.8 (d, C-2), 107.2 (d, C-27), 101.0 (t, C-25), 100.8 (t,

C-4), 86.0 (d, C-13), 80.6 (s, C-11), 75.3 (t, C-14), 74.2 (d, C-20), 55.2 (q, C-19), 43.5 (d, C-8), 39.3 (t, C-9), 27.9 (q, C-12). HR-CI-MS: 551.2273 ($C_{31}H_{34}O_9^+$, $[M+H]^+$; calc. 551.2276).

(5*S*,5a*S*,8a*S*)-5-(2*H*-1,3-Benzodioxol-5-yl)-5,5a,8,8a-tetrahydro-2*H*,7*H*-furo[2′,3′:2,3]indeno[5,6-*d*][1,3]dioxol-7-one (**6**). Alcohol **5** (65.0 mg, 0.120 mmol, 1.0 equiv.) was dissolved in dichloromethane (0.6 mL). Trifluoroacetic acid (0.600 mL, 7.80 mmol, 65 equiv.) was added at 0 °C. The mixture was stirred for 10 min. The solvent was evaporated in a stream of nitrogen. Compound **6** (36.8 mg, 0.110 mmol, 91 %, dr = 92:8 according to NMR) was obtained as colorless oil after reversed-phase column chromatography (water/MeCN 9:1→MeCN). $[\alpha]_D^{20} = -21.6$ ($c = 0.5$, $CHCl_3$). Major diastereomer: ^{1}H-NMR (400 MHz, $CDCl_3$): 6.73 (d, $^3J_{16,17} = 8.0$, 1 H, 16-H), 6.69 (s, 1 H, 5-H), 6.56 (s, 1 H, 2-H), 6.51 (dd, $^3J_{17,16} = 8.0$, $^4J_{17,13} = 1.6$, 1 H, 17-H), 6.44 (d, $^4J_{13,17} = 1.6$, 1 H, 13-H), 5.97 (s, 2 H, 19-H), 5.92 (m, 2 H, 18-H), 4.99 (d, $^3J_{10,7} = 5.6$, 1 H, 10-H), 4.49 (s, 1 H, 11-H), 4.02 (dd, $^3J_{7,8a} = 8.7$, $^3J_{7,10} = 5.9$, 1 H, 7-H), 2.95 (dd, $^2J_{8a,8b} = 17.9$, $^3J_{8a,7} = 9.2$, 1 H, 8-Ha), 2.67 (dd, $^2J_{8b,8a} = 17.7$, $^3J_{8b,7} = 0.9$, 1 H, 8-Hb). ^{13}C-NMR (100 MHz, $CDCl_3$): 175.7 (s, C-9), 148.6 (c, C-3), 148.5 (s, C-4), 148.1 (s, C-14), 146.7 (s, C-15), 135.8 (s, C-1), 135.0 (s, C-12), 135.0 (s, C-6), 120.9 (d, C-17), 108.5 (d, C-16), 108.0 (d, C-13), 105.9 (d, C-2), 104.3 (d, C-5), 101.6 (t, C-19), 101.1 (t, C-18), 91.6 (d, C-10), 56.6 (d, C-11), 43.9 (d, C-7), 35.1 (t, C-8). Minor diastereomer (selected signals): ^{1}H-NMR (400 MHz, $CDCl_3$): 5.96 (s, 2 H, 19-H), 5.94 (m, 2 H, 18-H), 5.20 (dd, $^3J_{10,7} = 5.3$, $^3J_{10,11} = 5.3$, 1 H, 10-H), 3.92 (m, 1 H, 7-H), 2.76 (dd, $^2J_{8b,8a} = 17.7$, $^3J_{8b,7} = 1.0$, 1 H, 8-Hb). HR-CI-MS: 338.0800 ($C_{19}H_{14}O_6^+$, M^+; calc. 338.0785).

Salviachinensine A. Compound **6** (22.0 mg, 65.0 μmol, 1.0 equiv.) was dissolved in anhydrous and degassed (bubbled through with argon for 10 min) dichloromethane (0.8 mL) and cooled to 0 °C. Boron trichloride (390 μL, 1 M in hexane 390 μmol, 6.0 equiv.) was added dropwise. After stirring for 2 h at 0 °C, anhydrous and degassed methanol (2 mL) was added, and the mixture was heated to reflux for 20 min. The volatiles were removed in high vacuum. Salviachinensine A (8.4 mg, 27.0 μmol, 41 %, dr = 92:8 according to NMR) was obtained as off-white solid after purification by preparative HPLC (water/MeCN 9:1→MeCN). M.p. 122–126 °C. $[\alpha]_D^{20} = -22.0$ ($c = 0.1$, MeOH). $R_f = 0.39$ (AcOEt). ^{1}H-NMR (500 MHz, DMSO-d_6): 8.51–9.24 (m, 4 H, OH), 6.70 (s, 1 H, 5-H), 6.63 (d, $^3J_{16,17} = 8.5$, 1 H, 16-H), 6.45 (s, 1 H, 2-H), 6.33 (d, $^4J_{13,17} = 2.0$, 1 H, 13-H), 6.32 (dd, $^3J_{17,16} = 8.4$, $^4J_{17,13} = 2.0$, 1 H, 17-H), 4.90 (d, $^3J_{10,7} = 5.3$, 1 H, 10-H), 4.22 (s, 1 H, 11-H), 3.92 (dd, $^3J_{7,8a} = 8.7$, $^3J_{7,10} = 5.5$, 1 H, 7-H), 3.00 (dd, $^2J_{8a,8b} = 17.6$, $^3J_{8a,7} = 8.7$, 1 H, 8-Ha), 2.52 (d, $^2J_{8b,8a} = 17.9$, 1 H, H-8b). ^{13}C-NMR (125 MHz, DMSO-d_6): 176.2 (s, C-9), 145.8 (s, C-4), 145.7 (s, C-3), 145.3 (s, C-14), 144.1 (s, C-15), 133.9 (s, C-6), 132.9 (s, C-12), 132.8 (s, C-1), 118.2 (d, C-17), 115.6 (d, C-16), 114.7 (d, C-13), 111.8 (d, C-2), 111.2 (d, C-5), 91.5 (d, C-10), 55.1 (d, C-11), 43.7 (d, C-7), 35.0 (t, C-8). The NMR spectra of Salviachinensine A are in accordance with those reported in the literature (see *Supporting Information*).[1] HR-CI-MS: 313.0705 ($C_{17}H_{13}O_6^+$, $[M-H]^+$; calc. 313.0707).

Supporting Information

Supporting information for this article (containing copies of the NMR spectra of all compounds and HPLC chromatogram of alcohol **2′**) are available on the WWW under https://doi.org/hlca.202300136.

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Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Author Contribution Statement

All authors contributed to writing this manuscript. *O. A.* and *U. K.* designed and *M. K.* synthesized the compounds.

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