Synthesis of Leprapinic Acid, Calycine and Analogues by Sequential "[3+2] Cyclization/Suzuki/Lactonization" Reactions

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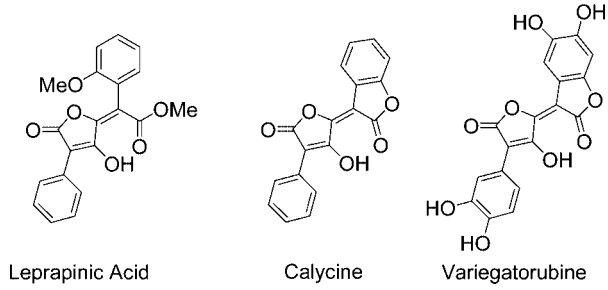
Calycine and analogues were prepared on the basis of Suzuki cross-coupling reactions of γ-alkylidene-α-hydroxybutenolides – readily available by cyclization of 1,3-dicarbonyl dianions or 1,3-bis(silyl enol ether)s with oxalyl derivatives – and subsequent boron tribromide-mediated lactonization. Leprapinic acid was prepared by chemoselective boron tribromide-mediated deprotection of permethylated leprapinic acid.

The natural products calycine and variegatorubine represent pigment dyes containing a γ-alkylidenebutenolide and a benzofuran-2-one moiety and are related to pulvinic acids which exhibit antibiotic activity.[1] Calycine has been isolated from the lichen *Lepraria candelaris* Shaer and represents a red pigment (Scheme 1).[2] The related variegatorubine has been found[3] in *Suillus piperatus* and other *Boletaceae* and can be obtained by oxidation of variegatic acid.[4] Leprapinic acid has been isolated from *Lepraria citrina* Schaer.[5] Calycin was previously prepared by Åkermark on the basis of the pulvinic dilactone methodology:[6] The reaction of *o*-methoxybenzyl cyanide with diethyl oxalate afforded ethyl 3-cyano-3-(*o*-methoxyphenyl)pyruvate which was condensed with benzyl cyanide to give 2-(*o*-methoxyphenyl)-3,4-dioxo-5-phenyladiponitrile. The latter was transformed into *o*-methoxypulvinic dilactone, which was subsequently converted into calycine by acid-mediated lactone cleavage. A synthesis of Leprapinic acid has been previously reported as well.[7]

We and others have reported the functionalization of γ-alkylidene-α-hydroxybutenolides, readily available by cyclization of 1,3-bis(silyl enol ether)s[8,9] with oxalyl chloride,[10] by Stille and Suzuki cross-coupling reactions.[11–13] The application of the Suzuki reaction allowed a convenient synthesis of pulvinic acids[11] and of an analogue of the natural product norbadione A.[12] Herein, we wish to report the application of our methodology to the synthesis of calycine and analogues. In addition, a new and convenient synthesis of leprapinic acid by chemoselective deprotection of permethylated leprapinic acid is reported. The methodology outlined herein competes well with classic syntheses based on the pulvinic dilactone method in terms of yield, regioselectivity and flexibility. Notably, a convenient synthesis of analogues can be realized by functionalization of common synthetic intermediates.



Scheme 1. Leprapinic acid, calycine and variegatorubine.

Results and Discussion

The reaction of methyl methoxyacetate (**1**) with methyl (*o*-methoxyphenyl)acetate (**2**) afforded the β-keto ester **3** which was transformed into the silyl enol ether **4** (Scheme 2). The latter was converted into the 1,3-bis(silyl enol ether) **5**. The Me_3SiOTf-mediated cyclization of **5** with oxalyl chloride afforded the γ-alkylidenebutenolide **6** as a 2:1 mixture of *E*/*Z*-isomers (vide infra). The Suzuki reaction of phenylboronic acid with triflate **7**, prepared from **6**, afforded the butenolide **8a** again as a 2:1 mixture of *E*/*Z*-isomers. Treatment of the latter with BBr_3 (4 equiv.) resulted in cleavage of the arylmethyl ether groups and lactonization. The desired product, calycine (***E*-9a**), was isolated in form of the pure (*E*)-diastereomer (33% yield). Besides, a small amount of *Z*-configured isocalycine (***Z*-9a**) was isolated (14%). To the best of our knowledge, NMR

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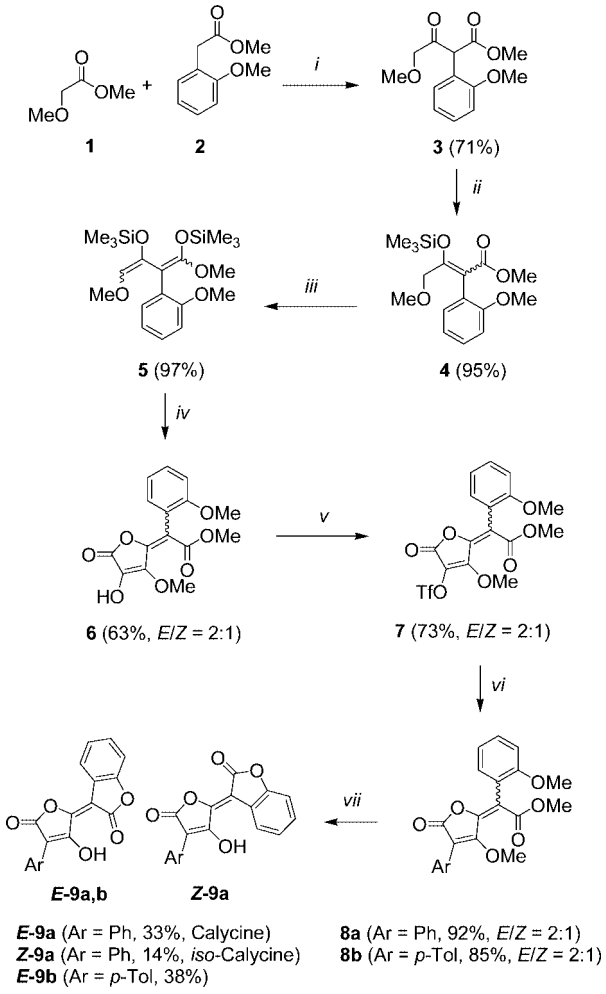
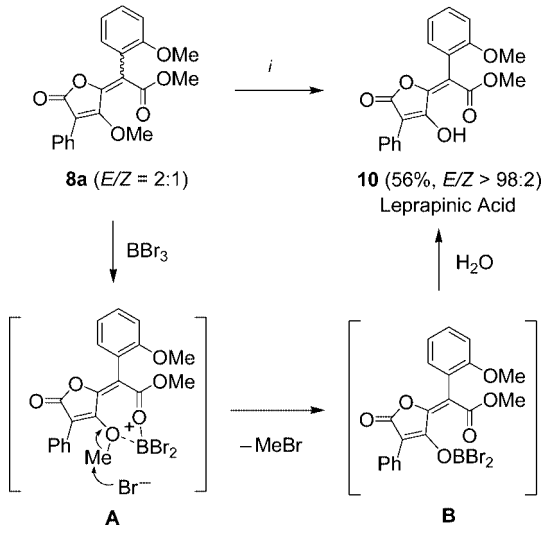
and MS data of calycine have not yet been reported. The UV and IR data and the melting point of calycine (***E*-9a**) are identical with those reported in the literature.[6] Our methodology allows the convenient synthesis of calycine analogues via the common synthetic intermediate **7**. The reaction of **7** with *p*-tolylboronic acid gave **8b** as a 2:1 mixture of *E*/*Z*-isomers. Treatment of **8b** with BBr_3 afforded the calycine analogue ***E*-9b** (38%). The configuration of the butenolide was established in analogy to related reactions[10–12] and based on the known structure of calycine.



Scheme 2. Synthesis of calycine (***E*-9a**) and analogues: *i*, 1) LDA, THF, 2) 2 (0.5 equiv.), –78 → 20 °C; *ii*, Me_3SiCl, NEt_3, toluene, 20 °C; *iii*, 1) LDA, THF, –78 °C, 2) Me_3SiCl, –78 → 20 °C; *iv*, oxalyl chloride, Me_3SiOTf (0.6 equiv.), CH_2Cl_2, –78 → 20 °C; *v*, Tf_2O, pyridine, –78 → –10 °C; *vi*, $ArB(OH)_2$ (Ar = Ph, *p*-Tol), $[Pd(PPh_3)_4]$ (3 mol-%), K_3PO_4 (1.5 equiv.), dioxane, reflux; *vii*, BBr_3 (4 equiv.), CH_2Cl_2, 0 °C.

As mentioned above, treatment of the butenolide **8a** with four equivalents of BBr_3 resulted in cleavage of both methyl ether groups to give calycine. During the synthesis of pinastric acid,[11c] we have observed that butenolide methyl ethers are more rapidly cleaved by BBr_3 than aryl methyl ethers. Treatment of **8a** (*E*:*Z* = 2:1) with only one (rather than four) equivalent of BBr_3 (0 °C, 6 h) resulted in selective cleavage of the butenolide methyl ether to give the pure *E*-configured leprapinic acid (**10**) in 56%. The spectroscopic data of leprapinic acid (**10**) are identical with those reported in the literature.[7] The high regioselectivity of the reaction of **8a** with BBr_3 can be explained by the better leaving group ability of the tetronate compared to the phenolate moiety. In addition, chelation of BBr_3 to the ester carbonyl group to exert a regiodirective bias can be discussed in this context (intermediate **A**, Scheme 3). However, this chelation is possible for both the butenolide and the arylmethyl ether and should, therefore, not be responsible for the regioselectivity.

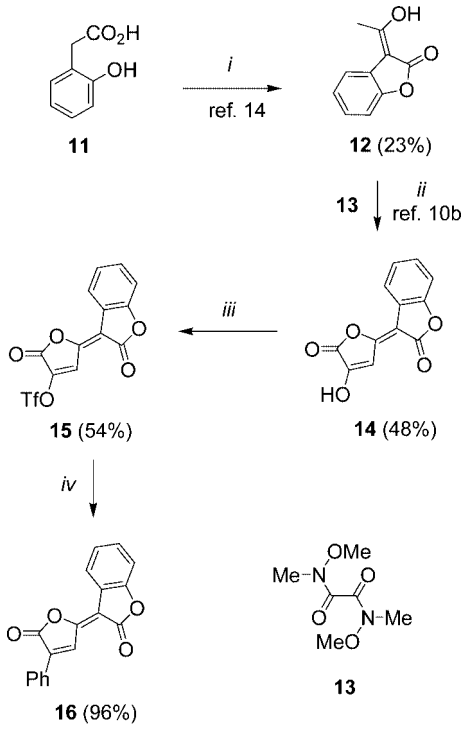


Scheme 3. Synthesis of leprapinic acid by regioselective deprotection of **8**: *i*, BBr_3 (1 equiv.), CH_2Cl_2, 0 °C, 6 h.

It has been noted above that the butenolide **6** was obtained as 2:1 mixture of *E*/*Z*-isomers. This observation initially caused us some trouble, since we previously observed a high degree of *E*-selectivity during the synthesis of pulvinic acids by related cyclization reactions.[11b,11c] However, the dramatic decrease of the selectivity can be explained by facile *E*/*Z*-isomerization during the cyclization. Some years ago, Ramage and Griffiths reported the synthesis of leprapinic acid based on a biomimetic approach which relies on a base-mediated lactonization to give an analogue of **10** containing a *tert*-butyl rather than a methyl ester.[7b] They observed the formation of 1:3- and 1:2-mixtures of *E*/*Z*-isomers. Due to the steric effect of the bulky *tert*-butyl ester, the *Z*-isomer was predominantly formed. As a consequence, we believe that the loss of *E*/*Z*-selectivity is a result of the presence of the *ortho*-methoxy group.

The reaction of (*o*-hydroxyphenyl)acetic acid with acetic anhydride afforded, following a known procedure,[14] 3-acetylbenzofuran-2-one (**12**), which resides exclusively in its enolic form (Scheme 4). The reaction of the dianion of **12** with *N*,*N*′-dimethoxy-*N*,*N*′-(dimethyl)ethanediamide (**13**)[15] afforded, as we have reported earlier,[10b] the γ-alkylidenebutenolide **14** with very good *E*-selectivity. The butenolide **14** was transformed into the triflate **15**. The Suzuki reaction of the latter with phenylboronic acid afforded the caly-

cine analogue **16**. Notably, the synthetic approach outlined in Scheme 4 could not be applied to the synthesis of calycine.

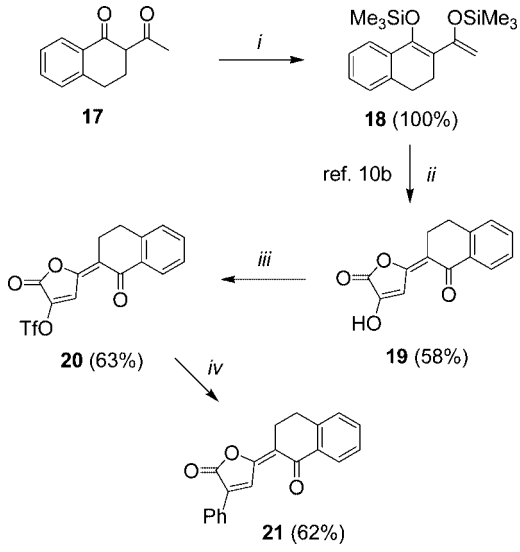


Scheme 4. Synthesis of calycine analogue **16**: *i*, 1) Pyridine, Ac_2O, reflux, 2) HCl, H_2O; *ii*, 1) LDA (2.3 equiv.), THF, 0 °C, 1 h, 2) 13, –78 → 20 °C, 12 h; *iii*, Tf_2O, pyridine, –78 → –10 °C; *iv*, $PhB(OH)_2$, $[Pd(PPh_3)_4]$ (3 mol-%), K_3PO_4 (1.5 equiv.), dioxane, reflux.

The reaction of the dianion of 2-acetyltetralone (**17**) with Me_3SiCl afforded the 1,3-bis(silyl enol ether) **18** (Scheme 5). Recently, we have reported the synthesis of γ-alkylidenebutenolide **19** by *E*-selective cyclization of **18** with oxalyl chloride.[10b] The butenolide **19** was transformed into the triflate **20**. The Suzuki reaction of **20** with phenylboronic acid afforded the desired calycine analogue **21**.

A brief comparison of our methodology to known syntheses seems to be appropriate. Calycine was prepared by Åkermark in 4 steps; the yields had not been reported for all steps.[6] We have reported a synthesis of calycine in 7 steps (9.1% overall yield). In contrast to the work of Åkermark, our approach allows a convenient synthesis of analogues via the common synthetic intermediate **7**. Ramage and co-workers reported a synthesis of leprapinic acid in 4 steps in 8% overall yield (calculated from a non-commercially available phosphorane which had to be prepared in two steps).[7] Our synthesis has been carried out in 7 steps in 16% overall yield (calculated from the commercially available ester **2**). Therefore, our approach seems to be more efficient in terms of yield. In addition, it again allows a convenient and flexible synthesis of analogues via the common synthetic intermediate **7**.

In summary, we have reported the synthesis of calycine and analogues on the basis of Suzuki cross-coupling reactions of γ-alkylidene-α-hydroxybutenolides, readily available by cyclization of 1,3-dicarbonyl dianions or 1,3-bis(silyl enol ether)s with oxalyl derivatives and subsequent boron tribromide-mediated lactonization. Leprapinic acid was prepared by chemoselective boron tribromide-mediated deprotection of permethylated leprapinic acid. Our approach competes well with the classic approach which is based on the pulvinic dilactone method in terms of yield, regioselectivity and flexibility.



Scheme 5. Synthesis of calycine analogue **21**: *i*, 1) 2.5 equiv. LDA, THF, 0 °C, 1 h, 2) 3 equiv. Me_3SiCl, –78 → 20 °C; *ii*, oxalyl chloride, Me_3SiOTf (0.4 equiv.), CH_2Cl_2, –78 → 20 °C; *iii*, Tf_2O, pyridine, –78 → –10 °C; *iv*, $PhB(OH)_2$, $[Pd(PPh_3)_4]$ (3 mol-%), K_3PO_4 (1.5 equiv.), dioxane, reflux.

Experimental Section

General Comments: All solvents were dried by standard methods and all reactions were carried out under an inert atmosphere. For the ^1H and ^{13}C NMR spectra the deuterated solvents indicated were used. Mass spectroscopic data (MS) were obtained by electron ionization (70 eV), chemical ionization (CI, H_2O) or the electrospray ionization (ESI). For preparative scale chromatography silica gel (60–200 mesh) was used. Melting points are uncorrected.

Synthesis of β-Keto Ester 3: The reaction was carried out analogous to a known procedure.[11b,12] To a stirred solution of LDA (76.64 mmol) in THF (150 mL) was added methyl 2-(*o*-methoxyphenyl)acetate (13.83 g, 76.65 mmol) at –78 °C. After stirring for one hour methyl methoxyacetate (4.00 g, 38.32 mmol) was added. The temperature of the solution was rised to 20 °C during 12 h. A saturated aqueous solution of NH_4Cl was added, the layers were separated and the aqueous layer was extracted with dichloromethane (3 × 150 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent of the filtrate was removed in vacuo. The residue was purified by chromatography (silica gel, hexane/EtOAc) to give **3a** as a yellow solid (6.90 g, 71%), m.p. 52–53 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.36 (s, 3 H, OCH_3), 3.74 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 4.11 (d, J = 7.2 Hz, 2 H, OCH_2), 5.32 (s, 1 H, CH), 6.88–6.94 (m, 2 H, ArH), 7.23–7.33 (m, 2 H, ArH) ppm. IR (KBr): $\tilde{\nu}$ = 2999 cm^{-1} (w), 2949 (m), 2837 (w), 1747 (s), 1730 (s), 1495 (m), 1462 (m), 1440 (m), 1326 (m), 1295 (m), 1248 (s), 1203 (m), 1155 (m), 1106 (m), 1042 (m), 757 (m). MS

(EI, 70 eV): *m*/*z* (%) = 251.8 (18) [M$^+$], 219.7 (12), 178.8 (21), 147.3 (78), 120.9 (23), 90.8 (33). $C_{13}H_{16}O_5$ (252.26): calcd. C 61.89, H 6.39; found: C 61.93, H 6.50.

Synthesis of Silyl Enol Ether 4: The reaction was carried out analogous to a known procedure.[11b,12] To a stirred benzene solution (10 mL) of **3** (6.90 g, 27.35 mmol) was added triethylamine (6.10 mL, 43.76 mmol). After stirring for 2 h, chlorotrimethylsilane (6.21 mL, 49.23 mmol) was added. After stirring for 72 h, the solvent was removed in vacuo and to the residue was added hexane (100 mL) to give a suspension. The latter was filtered under Argon. The filtrate was distilled in vacuo to give **4** as a yellow oil (8.44 g, 95%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = –0.14, 0.21 (s, 9 H, CH_3, *E*/*Z* isomers), 3.11, 3.32, (s, 3 H, OCH_3, *E*/*Z* isomers), 3.53, 3.56 (s, 3 H, OCH_3, *E*/*Z* isomers), 3.67, 3.69 (s, 3 H, OCH_3, *E*/*Z* isomers), 3.63, 4.45 (s, 2 H, OCH_2, *E*/*Z* isomers), 6.76–6.86 (m, 2 H, ArH, *E*/*Z* isomers), 7.05–7.20 (m, 2 H, ArH, *E*/*Z* isomers) ppm.

Synthesis of 1,3-Bis(silyl enol ether) 5: The reaction was carried out analogous to a known procedure.[11b,12] To a stirred THF solution (100 mL) of LDA (39.01 mmol, 1.5 equiv.) was added **4** (8.44 g, 26.01 mmol) at –78 °C. After stirring for 1 h, chlorotrimethylsilane (6.00 mL, 46.82 mmol) was added. The solution was warmed to room temperature during 12 h with stirring. The solvent was removed in vacuo and to the residue was added hexane (100 mL) to give a suspension. The latter was filtered under Argon. The filtrate was distilled in vacuo to give **5** as a yellow oil (10.00 g, 97%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.02, 0.03 (s, 9 H, CH_3, *E*/*Z* isomers), 0.29, 0.31 (s, 9 H, CH_3, *E*/*Z* isomers), 3.38, 3.41 (s, 3 H, OCH_3, *E*/*Z* isomers), 3.45, 3.51 (s, 3 H, OCH_3, *E*/*Z* isomers), 3.78, 3.79 (s, 3 H, OCH_3, *E*/*Z* isomers), 5.67, 5.81 (s, 1 H, OCH, *E*/*Z* isomers), 6.84–6.89 (m, 2 H, ArH, *E*/*Z* isomers), 7.13–7.19 (m, 2 H, ArH, *E*/*Z* isomers) ppm.

Synthesis of the Butenolide 6: The reaction was carried out analogous to a known procedure.[11b,12] To a CH_2Cl_2 solution (120 mL) of oxalyl chloride (1.06 mL, 12.01 mmol) and of **5** (3.66 g, 9.24 mmol) was added a CH_2Cl_2 solution (5 mL) of Me_3SiOTf (1.01 mL, 5.54 mmol) at –78 °C. The temperature of the reaction mixture was rised to 20 °C during 12 h. After stirring for 2 h at 20 °C, a saturated aqueous solution of NaCl was added. The aqueous layer was separated and extracted with CH_2Cl_2. The combined organic layers were washed with an aqueous solution of HCl (10%), dried (Na_2SO_4) and filtered. The solvent of the filtrate was removed in vacuo and the residue was purified by column chromatography (silica gel, hexane/EtOAc) to give **6** as a yellow solid (1.78 g, 63%, *E*:*Z* = 2:1), m.p. 136–137 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.70, 3.73 (s, 3 H, OCH_3, *E*/*Z* isomers), 3.72, 3.74 (s, 3 H, OCH_3, *E*/*Z* isomers), 3.76, 4.11 (s, 3 H, OCH_3, *E*/*Z* isomers), 6.79–6.93 (m, 2 H, ArH), 7.09–7.33 (m, 2 H, ArH) ppm. ^{13}C NMR (150 MHz, $(CD_3)_2DO$): δ = 52.32, 52.41, 56.07, 56.25, 59.48, 60.14 (CH_3), 111.47, 112.51 (CH), 112.55, 113.52 (C), 120.50, 121.27 (CH), 122.83, 122.87, 126.68, 127.65 (C), 130.85, 131.28, 133.16, 133.39 (CH), 143.67, 144.16, 144.30, 146.30, 158.39, 158.95, 164.58, 164.82, 166.10, 167.50 (C) ppm. IR (KBr): $\tilde{\nu}$ = 3321 cm^{-1} (m), 1789 (s), 1764 (s), 1718 (s), 1676 (s), 1369 (m), 1322 (m), 1278 (m), 1248 (m), 1148 (m), 1106 (m) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 306.0 (7) [M$^+$], 203.9 (15), 180.0 (29), 147.4 (39), 91.0 (44). $C_{15}H_{14}O_7$ (306.27): calcd. C 58.82, H 4.60; found: C 58.79, H 4.27.

Preparation of Triflate 7: The reaction was carried out analogous to a known procedure.[11b,12] To a dichloromethane solution (16 mL) of **6** (500 mg, 1.63 mmol) and triflic anhydride (0.30 mL, 1.79 mmol) was added pyridine (0.26 mL, 3.26 mmol) at –78 °C. The solution was warmed to –10 °C within 4 hours. The product was isolated by rapid chromatography (silica gel, dichloromethane) of the reaction mixture as a yellow solid (522 mg, 73%, *E*:*Z* = 2:1), m.p.112–114 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.80, 3.82 (s, 3 H, OCH_3, *E*/*Z* isomers), 3.81, 3.83 (s, 3 H, OCH_3, *E*/*Z* isomers), 3.94, 4.29 (s, 3 H, OCH_3, *E*/*Z* isomers), 6.89–7.03 (m, 2 H, ArH), 7.19–7.45 (m, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.70, 52.84, 55.65, 55.85, 60.21, 60.91 (CH_3), 110.60, 111.45 (CH), 114.89, 115.62, 118.19, 119.03 (C), 118.31 (q, 2 CF_3, *J* = 319.5 Hz), 119.87, 119.96 (C), 120.13, 120.87, 131.05, 131.67 (2 C), 131.93 (CH), 139.44, 141.47, 155.45, 156.45, 157.22, 157.44, 159.51, 159.93, 164.75, 165.75 (C) ppm. IR (KBr): $\tilde{\nu}$ = 1799 cm^{-1} (s), 1720 (s), 1659 (s), 1425 (s), 1325 (m), 1280 (m), 1226 (s), 1129 (s), 1086 (s), 810 (m), 759 (m) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 438.7 (23) [M$^+$], 249.0 (53), 221.0 (100), 91.0 (51). $C_{16}H_{13}O_9SF_3$ (437.74): calcd. C 43.90, H 2.99; found: C 44.06, H 3.12.

Synthesis of Butenolides 8a: A dioxane solution (5 mL per 1 mmol of triflate) of triflate **7** (438 mg, 1.00 mmol), phenylboronic acid (158 mg, 1.30 mmol), K_3PO_4 (340 mg, 1.60 mmol) and [Pd(PPh_3)$_4$] (35 mg, 0.03 mmol) was refluxed for four hours. A saturated aqueous solution of ammonium chloride was added. The organic and the aqueous layer were separated and the latter was extracted (3 ×) with ether. The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, EtOAc/hexane) to give **8a** as a yellow solid (335 mg, 92%, *E*:*Z* = 2:1), m.p. 168–169 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.32, 3.78 (s, 3 H, OCH_3, *E*/*Z* isomers), 3.81, 3.82 (s, 3 H, OCH_3, *E*/*Z* isomers), 3.83, 3.85 (s, 3 H, OCH_3, *E*/*Z* isomers), 6.90–7.03 (m, 2 H, ArH, *E*/*Z* isomers), 7.25–7.51 (m, 7 H, ArH, *E*/*Z* isomers) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.52, 52.63, 55.67, 55.88, 60.49, 61.19 (CH_3), 109.05, 111.23 (C), 110.49, 111.38 (CH), 113.50, 114.34 (C), 120.02, 120.87 (CH), 121.07, 121.49 (C), 128.32 (4 C), 128.36 (2 C, CH), 128.51, 130.91 (C), 128.88, 128.99, 129.66, 129.94 (2 C), 130.41, 132.10, 132.21 (CH), 143.83, 145.90, 157.24, 157.66, 162.48, 163.45, 165.81, 167.00, 167.05, 167.61 (C) ppm. IR (KBr): $\tilde{\nu}$ = 3511 cm^{-1} (w), 3465 (w), 2975 (m), 2949 (m), 1771 (s), 1722 (s), 1628 (s), 1598 (s), 1492 (m), 1438 (m), 1245 (m), 1224 (m), 755 (m), 724 (m) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 366.7 (100) [M$^+$], 251.5 (25), 219.3 (31), 144.9 (10), 89.1 (39). $C_{21}H_{18}O_6$ (366.37): calcd. C 68.84, H 4.95; found: C 68.34, H 5.15.

Synthesis of 8b: The synthesis was carried out according to the procedure given for **8a**. Starting with triflate **7** (300 mg, 0.68 mmol), *p*-tolylboronic acid (121 mg, 0.89 mmol), K_3PO_4 (232 mg, 1.09 mmol), [Pd(PPh_3)$_4$] (24 mg, 0.02 mmol) and dioxane (3.5 mL), **8b** was isolated as a yellow solid (222 mg, 85%, *E*:*Z* = 2:1), m.p. 140 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.35, 2.38 (s, 3 H, CH_3, *E*/*Z* isomer), 3.31, 3.78 (s, 3 H, OCH_3, *E*/*Z* isomers), 3.81, 3.82 (s, 3 H, OCH_3, *E*/*Z* isomers), 3.83, 3.84 (s, 3 H, OCH_3, *E*/*Z* isomers), 6.89, 7.55 (m, 8 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.31 (2 C, CH_3), 52.50, 52.59, 55.63, 55.84, 60.33, 61.02 (CH_3), 109.19, 111.47 (C), 110.43, 111.32 (CH), 113.18, 114.04 (C), 119.97, 120.82 (CH), 121.07, 121.48, 125.35, 125.43, 126.72, 129.36 (C), 129.04 (2 C), 129.07 (2 C), 129.44 (2 C), 129.74 (2 C), 130.36, 130.83, 132.12, 132.22 (CH), 138.97, 139.14, 143.93, 146.02, 157.19, 157.62, 162.14, 163.00, 167.10, 167.75 (C) ppm. IR (KBr): $\tilde{\nu}$ = 2948 cm^{-1} (w), 1768 (s), 1721 (s), 1621 (s), 1490 (m), 1458 (m), 1275 (s), 1249 (s), 1039 (m), 933 (m) cm^{-1}. MS (EI, 70 eV) = *m*/*z* (%): 380.1 (2) [M$^+$], 309.1 (2), 182.0 (15), 32.0 (26), 28.0 (100). $C_{22}H_{20}O_6$ (380.40): calcd. C 69.46, H 5.29; found: C 69.31, H 5.67.

Synthesis of Calycine (*E*-9a) and Isocalycine (*Z*-9a): To a CH_2Cl_2 (5 mL) solution of **8a** (90 mg, 0.24 mmol) was added BBr_3

(0.09 mL, 0.98 mmol) at 0 °C, and the mixture was stirred for 6 h at 0 °C. An aqueous solution of HCl (5%) was added. The aqueous layer was separated and extracted with CH_2Cl_2 (3 ×). The combined organic layers were dried (Na_2SO_4), filtered and the solvent of the filtrate was removed in vacuo. The residue was purified by chromatography (silica gel, EtOAc, *n*-hexane) to give calycine ***E*-9a** (24 mg, 33%) and isocalycine ***Z*-9a** (10 mg, 14%) as red solids. **Data of *E*-9a:** M.p. 249 °C (ref.:[6] m.p. 249–249.5 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.21–7.50 (m, 6 H, ArH), 7.97 (d, J = 7.8 Hz, 1 H, ArH), 8.18 (d, J = 7.5 Hz, 2 H, ArH), 12.58 (s, 1 H, OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 106.22, 106.52 (C), 111.35 (CH), 122.02 (C), 126.00, 126.03, 128.32 (2 C, CH), 128.67 (C); 128.87 (2 C), 129.32, 131.62 (CH), 153.52, 153.97, 160.31, 165.57, 173.34 (C)ppm. IR (KBr): $\tilde{\nu}$ = 2964 cm^{-1} (m), 1801 (s), 1712 (m), 1642 (s), 1474 (m), 1262 (s), 1157 (m), 1095 (s), 1035 (s), 804 (s), 690 (m) cm^{-1}. UV/Vis (cyclohexane) = λ_{max} (log ε) = 237 (3.94), 241 (3.94), 252 (3.87), 430 (4.14) nm. MS (EI, 70 eV): *m*/*z* (%) = 305.9 (80) [M$^+$], 250.0 (6), 160.9 (100), 117.9 (46), 89.0 (40). HRMS (FT-ICR): calcd. for $C_{18}H_{11}O_5$ ([M + 1]$^+$): 307.0606; found: 307.0603. **Data of *Z*-9a:** ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 6.98–7.44 (m, 6 H, ArH), 8.49 (d, J = 6.9 Hz, 2 H, ArH), 9.39 (dd, J = 7.8, J = 1.2 Hz, 1 H, ArH). MS (EI, 70 eV): *m*/*z* (%) = 305.6 (39) [M$^+$], 160.7 (18), 28.0 (100).

Synthesis of Calycine Analogue *E*-9b: Starting with the butenolide **8b** (240 mg, 0.50 mmol), BBr_3 (0.18 mL, 2.00 mmol) and CH_2Cl_2 (10 mL), ***E*-9b** (60 mg, 38%) was isolated as a red solid, m.p. 258–260 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.40 (s, 3 H, CH_3), 7.20–7.34 (m, 4 H, ArH), 7.44 (dt, J = 1.5 Hz, 8.1 Hz, 1 H, ArH), 7.96 (dd, J = 1.2 Hz, 7.8 Hz, 1 H, ArH), 8.91 (d, J = 8.4 Hz, 2 H, ArH), 12.49 (s, 1 H, OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.52 (CH_3), 106.00 (C), 111.09 (CH), 121.75, 125.56 (C), 125.70 (2 C), 127.94 (2 C, CH), 129.15 (C), 129.39 (2 C), 131.26 (CH), 139.42, 153.33, 153.57, 159.33, 165.52, 173.10 (C) ppm. IR (KBr): $\tilde{\nu}$ = 1792 cm^{-1} (s), 1719 (s), 1637 (s), 1608 (m), 1460 (m), 1157 (m), 1033 (s), (s), 893 (m) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 319.8 (29) [M$^+$], 235.9 (1), 160.8 (11), 131.9 (8), 77.3 (4). UV/Vis (cyclohexane): λ_{max} (log ε) = 241 (4.14), 341 (3.78), 441 (4.25) nm. $C_{19}H_{12}O_5$ (320.30): calcd. C 71.24, H 3.77; found: C 70.90, H 3.60.

Synthesis of Leprapinic Acid (10):[7b] Starting with **8a** (300 mg, 0.81 mmol, *E*:*Z* = 2:1), BBr_3 (0.08 mL, 0.81 mmol) and CH_2Cl_2 (17 mL), **10** was isolated as a yellow solid (160 mg, 56%, *E*/*Z* > 98:2), m.p.162–163 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.78 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 6.91, 7.44 (m, 7 H, ArH), 8.12 (d, J = 7.5 Hz, 2 H, ArH), 13.70 (s, 1 H, OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 54.12, 55.56 (CH_3), 104.86 (C), 110.78 (CH), 112.95 (C), 120.42 (CH), 121.14 (C), 127.72 (2 C), 128.12, 128.31 (2 C, CH), 129.01 (C), 130.32, 131.13 (CH), 154.11, 156.86, 160.26, 166.10, 171.75 (C) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2625 cm^{-1} (w), 1774 (s), 1681 (m), 1617 (s), 1492 (m), 1439 (s), 1318 (s), 1284 (s), 1071 (s) cm^{-1}. UV/Vis (CH_3CN): λ_{max} (log ε) = 274 (4.20), 372 (4.07) nm. MS (EI, 70 eV): *m*/*z* (%) = 352.2 (66) [M$^+$], 320.1 (100), 292.1 (11), 175.1 (55), 91.1 (32), 28.1 (82). HRMS (FT-ICR): calcd. for $C_{20}H_{17}O_6$ ([M + 1]$^+$): 353.10251; found: 353.10189.

Synthesis of 3-(1-Hydroxyethylidene)-3*H*-benzofuran-2-one (12):[14] 2-Hydroxyphenylacetic acid (3.0 g, 19.7 mmol) was dissolved in pyridine (30 mL). Acetic anhydride (8 mL) was added and the mixture was heated for 30 min under reflux. After cooling to 20 °C, diluted HCl was added until a precipitate was formed. After filtration of the latter, the residue was dissolved in an aqueous solution of $NaHCO_3$. To the solution was added charcoal followed by addition of an aqueous solution of HCl. The resulting suspension was filtered, the residue was recrystallized from benzene/hexane to give **12** as grey crystals (0.80 g, 4.5 mmol, 23%), m.p. 133 °C (ref.:[14] m.p. 133–134 °C). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.48 (s, 3 H, CH_3), 7.16–7.28 (m, 3 H, CH), 7.32–7.37 (m, 1 H, CH), 11.72 (br., 1 H, OH) ppm. MS (EI, 70 eV): *m*/*z* (%) = 176 (100) [M$^+$], 158 (12), 134 (57), 106 (42), 78 (30). IR (KBr): $\tilde{\nu}$ = 3419 cm^{-1} (m), 3067 (w), 2928 (w), 1724 (s), 1705 (s), 1635 (s), 1517 (w), 1457 (s), 1433 (w) cm^{-1}. $C_{10}H_8O_3$ (176.17): calcd. C 68.18, H 4.58; found: C 68.16, H 4.48.

Synthesis of *N*,*N*′-Dimethoxy-*N*,*N*′-dimethyloxalamide (13):[15] To a CH_2Cl_2 solution (15 mL) of *N*-methoxy-*N*-methylamine hydrochloride (2.15 g, 22.0 mmol) was added oxalyl chloride (1.26 g, 10.0 mmol) and pyridine (1.74 g, 22.0 mmol) at 0 °C and the solution was stirred for 24 h at 20 °C. Water (15 mL) was added, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried with Na_2SO_4, filtered and the solvent removed in vacuo to give **13** as a colourless solid (1.413 g, 80%), m.p. 93 °C (ref.:[15] m.p. 93 °C). The spectroscopic data were identical to those reported in the literature.[15]

Synthesis of 3-(4-Hydroxy-5-oxo-5*H*-furan-2-ylidene)-3*H*-benzofuran-2-one (14):[10b] To a THF solution (10 mL) of HN*i*Pr$_2$ (0.465 g, 4.6 mmol) was added *n*-butyllithium (2.9 mL, 4.6 mmol, 1.6 M) at 0 °C. After stirring for 30 min, a THF solution (5 mL) of **12** (0.352 g, 2.0 mmol) was added at –78 °C. After stirring for 1 h, a THF solution (5 mL) of **13** (0.294 g, 1.7 mmol) was added. The solution was warmed to 0 °C within 6 h and an aqueous solution of HCl (10%, 10 mL) was added. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were extracted with brine (20 mL), dried with Na_2SO_4, filtered and the solvent of the filtrate was removed in vacuo. The residue was purified by chromatography (silica gel, hexane/EtOAc = 1:2) to give butenolide **14** as a yellow solid (0.184 g, 48%). The spectroscopic data were identical to those reported in the literature.[10b]

Synthesis of Triflate 15: The synthesis was carried out according to the procedure given for **7**. Starting with butenolide **14** (0.184 g, 0.8 mmol), pyridine (0.127 g, 1.6 mmol) and triflic anhydride (0.27 g, 1.0 mmol) in 8 mL of CH_2Cl_2, **15** was obtained as a yellow solid (0.151 g, 0.43 mmol, 54%), m.p. 156 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.16 (d, ^3J = 8 Hz, 1 H, CH), 7.27 (dt, ^3J = 8, ^4J = 1 Hz, 1 H, CH), 7.45 (dt, ^3J = 8, ^4J = 1 Hz, 1 H, CH), 7.86 (d, ^3J = 8 Hz, 1 H, CH), 8.34 (s, 1 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 108.82 (C), 110.24 (CH), 114.32, 119.92, 120.72 (C), 123.94, 124.26, 125.25, 132.20 (CH), 138.90, 148.49, 153.27, 157.92, 164.80 (C) ppm. MS (EI, 70 eV): *m*/*z* (%) = 362 (12), 201 (10), 173 (36), 160 (6), 101 (12), 28 (100). IR (KBr): $\tilde{\nu}$ = 3136 cm^{-1} (w), 2962 (w), 2920 (w), 1857 (w), 1805 (s), 1781 (s), 1664 (s), 1614 (s), 1564 (w), 1442 (s) cm^{-1}. UV/Vis (lg ε) = 368.38 (4.10) nm. $C_{13}H_5F_3O_7S$ (362.25): calcd. C 43.10, H 1.39; found: C 42.93, H 1.31.

Synthesis of Calycine Analogue 16: The synthesis was carried out according to the procedure given for **8a**. Starting with **15** (0.084 g, 0.24 mmol), phenylboronic acid (0.046 g, 0.31 mmol), K_3PO_4 (0.082 g, 0.38 mmol) and [Pd(PPh$_3$)$_4$] (0.008 g, 0.007 mmol) in 0.5 mL of dioxane, **16** was obtained as a yellow solid (0.060 g, 96%), m.p. 262 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.14 (d, ^3J = 8 Hz, 1 H, CH), 7.24 (dt, ^3J = 8, ^4J = 1 Hz, 2 H, CH), 7.40 (dt, ^3J = 8, ^4J = 1 Hz, 1 H, CH), 7.51 (t, ^3J = 3 Hz, 2 H, CH), 7.92 (dd, ^3J = 8, ^4J = 1 Hz, 1 H, CH), 8.05–8.08 (m, 2 H, CH), 8.61 (s, 1 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 105.27 (C), 110.83 (CH), 121.84 (C), 124.79, 125.52, 128.00 (CH), 128.43 (C), 129.17, 130.96, 131.39, 131.55 (CH), 134.52, 153.64, 154.52, 166.42, 167.00 (C) ppm. IR (KBr): $\tilde{\nu}$ = 3423 cm^{-1} (m), 1773 (s), 1648 (s), 1612 (w),

1594 (w), 1455 (m) cm^{-1}. UV/Vis: λ_{max} (lg ε) = 414.07 (4.28) nm. MS (EI, 70 eV): *m/z* = 290 (75) [M^+], 261 (3), 233 (5), 204 (4), 160 (100). The exact molecular mass for $C_{18}H_{10}O_4$ *m/z* = 290.0579 ± 2 ppm [M^+] was confirmed by HRMS (EI, 70 eV).

3-Hydroxy-5-(1-oxo-2,4-dihydro-1*H*-naphthalen-2-ylidene)-5*H*-furan-2-one (19):[10b] To a THF solution (40 mL) of HN*i*Pr$_2$ (2.53 g, 25.0 mmol) was added *n*-butyllithium (15.6 mL, 25.0 mmol, 1.6 M) at 0 °C. After stirring for 30 min, a THF solution (10 mL) of 2-acetyltetralone (**17**) (1.88 g, 10.0 mmol) was added. After stirring for 1 h, chlorotrimethylsilane (3.52 g, 30.0 mmol) was added at –78 °C. After warming to 20 °C within 6 h, the solvent was removed in vacuo and the residue was filtered and washed with hexane (4 × 25 mL). The solvent of the filtrate was removed in vacuo to give 1,3-bis(silyl enol ether) **18** which was used without further purification. 1,3-Bis-silyl enol ether **18** was dissolved in CH_2Cl_2 (40 mL). Oxalyl chloride (1.27 g, 10.0 mmol) and TMSOTf (0.89 g, 4.0 mmol) were added at –78 °C. After warming to 20 °C within 16 h, an aqueous solution of HCl (30 mL, 1 M) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), the combined organic layers were extracted with brine (20 mL), dried with Na_2SO_4, filtered and the solvent of the filtrate was removed in vacuo. The residue was purified by chromatography (silica gel, *n*-hexane/EtOAc, 2/1) to give the butenolide **19** as a yellow solid (1.404 g, 5.8 mmol, 58%), m.p. 198 °C. The spectroscopic data were identical to those reported in the literature.[10b]

Synthesis of Triflate 20: The synthesis was carried out according to the procedure given for **7**. Starting with butenolide **19** (0.484 g, 2.0 mmol), pyridine (0.318 g, 4.0 mmol) and triflic anhydride (0.648 g, 2.4 mmol) in 20 mL of CH_2Cl_2, **20** was obtained as a yellow solid (0.471 g, 1.26 mmol, 63%), m.p. 84 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.08 (t, ^3J = 6 Hz, 2 H, CH_2), 3.18 (dt, ^4J = 2, ^3J = 6 Hz, 2 H, CH_2), 7.31 (d, ^3J = 7 Hz, 1 H, CH), 7.40 (t, ^3J = 7 Hz, 1 H, CH), 7.56 (dt, ^4J = 2, ^3J = 7 Hz, 1 H, CH), 8.08 (dd, ^4J = 2, ^3J = 7 Hz, 1 H, CH), 8.38 (s, 1 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 26.26, 28.30 (CH_2), 117.61, 119.75, 124.40 (C) 127.63, 128.11, 128.21, 128.79, (C), 134.54 (CH), 140.22, 143.57, 148.42, 160.08, 186.54 (C) ppm. MS (70 eV): *m/e* (%) = 374 [M^+, 34], 241 (7), 213 (19), 197 (5), 185 (100). IR (KBr): $\tilde{\nu}$ = 1790 cm^{-1} (s), 1677 (m), 1616 (s), 1434 (s) cm^{-1}. $C_{15}H_9F_3O_6S$ (374.31): calcd. C 48.13, H 2.42; found: C 47.91, H 2.72.

Synthesis of Calycine Analogue 21: The synthesis was carried out according to the procedure given for **8a**. Starting with **20** (0.748 g, 2.0 mmol), phenylboronic acid (0.317 g, 2.6 mmol), K_3PO_4 (0.679 g, 3.2 mmol) and [Pd(PPh$_3$)$_4$] (0.069 g, 0.06 mmol) in dioxane (1.5 mL), **21** was obtained as a yellow solid (0.374 g, 1.24 mmol, 62%), m.p. 146 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.07 (t, ^3J = 7 Hz, 2 H, CH_2), 3.19 (t, ^3J = 7 Hz, 2 H, CH_2), 7.30 (d, ^3J = 7 Hz, 1 H, CH), 7.39–7.52 (m, 5 H, CH), 8.00 (dd, ^3J = 7, ^4J = 1 Hz, 2 H, CH), 8.10 (dd, ^3J = 7, ^4J = 1 Hz, 1 H, CH), 8.67 (s, 1 H, CH) ppm. ^{13}C NMR (150 MHz, [D$_6$]acetone): δ = 26.87, 28.94 (CH_2), 120.13 (C), 128.00, 128.30, 128.51, 129.65, 129.85 (CH), 130.31 (C), 131.28 (CH), 134.43 (C), 134.67 (CH), 134.84 (C), 135.17 (CH), 144.72, 153.94 (C), 167.85, 187.58 (CO). MS (EI, 70 eV): *m/z* (%) = 302 (40) [M^+], 273 (16), 248 (6), 144 (23), 115 (60), 102 (100) ppm. IR (KBr): $\tilde{\nu}$ = 3437 cm^{-1} (s), 1774 (s), 1664 (s), 1606 (s), 1490 (w), 1452 (s) cm^{-1}. UV/Vis: λ_{max} (lg ε) = 357.1 (4.51) nm. $C_{20}H_{14}O_3$ (302.33): calcd. C 79.46, H 4.67; found: C 79.23, H 4.34.

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