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SYNTHETIC STUDIES ON NATURAL ISOCOUMARINS AND ISOCARBOSTYRIL DERIVATIVES HAVING AN ALKYL SUBSTITUENT AT THE 3-POSITION: TOTAL SYNTHESIS OF SCOPARINES A AND B, AND RUPRECHSTYRIL

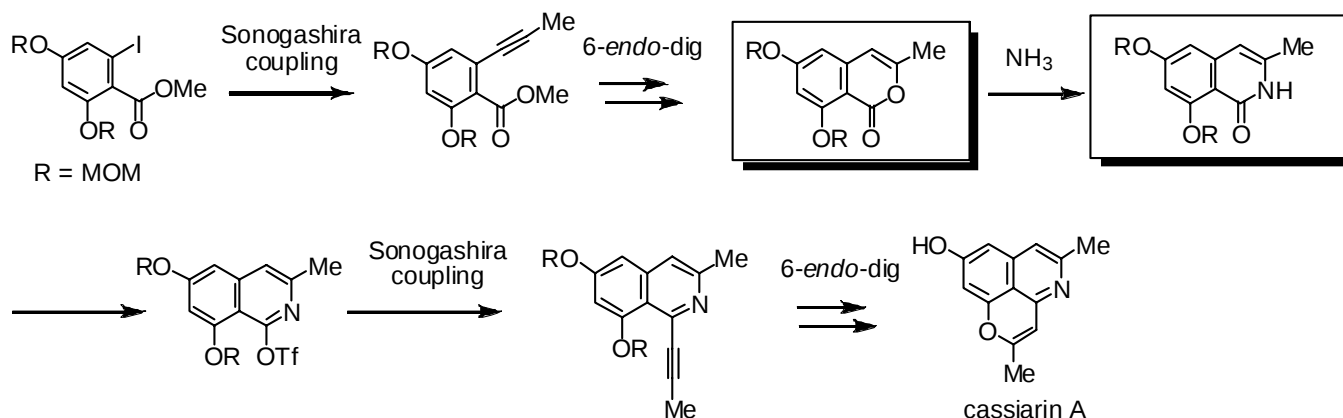
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Abstract – Two isocoumarins, scoparines A and B, having *n*-propyl group at the 3-position, and a new isocarbostyril, ruprechstyril, bearing *n*-pentyl substituent at the 3-position were synthesized via Sonogashira coupling of the corresponding aromatic halides and alkynes, followed by regioselective 6-*endo*-dig cyclization.

INTRODUCTION

The isocoumarins are becoming an increasingly interesting class of naturally occurring lactones with a wide range of biological activities.^{1,2} The isocarbostyril derivatives, the nitrogen analogue of isocoumarins are recognized not only as bioactive natural products³ but also as potential medicinal compounds.⁴ Those natural products usually possess a various types of substituents such as alkyl, alkenyl, and aryl group, at their 3-positions.



Scheme 1. Previous synthesis of cassiarin A

Very recently, we have established⁵ the synthesis of an antimalarial natural alkaloid, cassiarin A, by employing sequential Sonogashira coupling⁶ of aromatic halides and alkynes, followed by regioselective 6-*endo*-dig cyclization⁷ of oxygen functions to carbon-carbon triple bonds, as key steps, as shown in Scheme 1. In this synthesis, both 3-substituted isocoumarin and isocarbostyryl derivatives were involved as key intermediates.

As an extension of this work, we are interested in synthesizing and studying the biological activity of compounds related to the natural isocoumarin and isocarbostyryl having an alkyl group at the 3-position, and report here the first syntheses of scoparines A and B having *n*-propyl group, and ruprechstyryl bearing *n*-pentyl substituent at the 3-position, respectively, although a number of synthetic approaches to those classes of natural products have been appeared to date.⁷

RESULTS AND DISCUSSION

First, we investigated the synthesis of 3-substituted isocoumarins, scoparines A and B (Figure 1), since these isocoumarins have not been synthesized yet.

Scoparines A **1** and B **2** were isolated from the ethyl acetate extract of the root of *Pituranthos scoparius*, and their structures were determined by spectroscopic analyses to be 3-*n*-propyl-5-methoxy-6-hydroxyisocoumarin and 3-*n*-propyl-5,7-dimethoxy-6-hydroxyisocoumarin, respectively.⁸ *Pituranthos scoparius* is a toxic plant and used as a decoction in the treatment of asthma and a local application of the leaves alleviates pains linked to rheumatism in traditional medicine.⁹

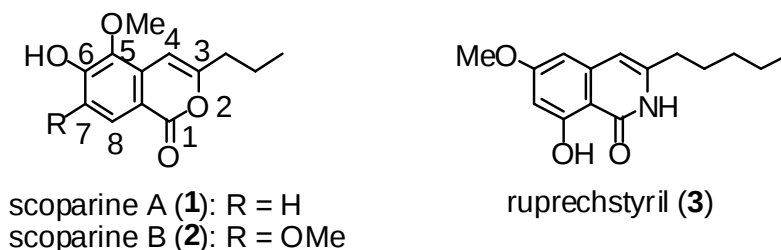
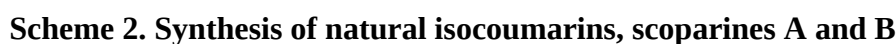


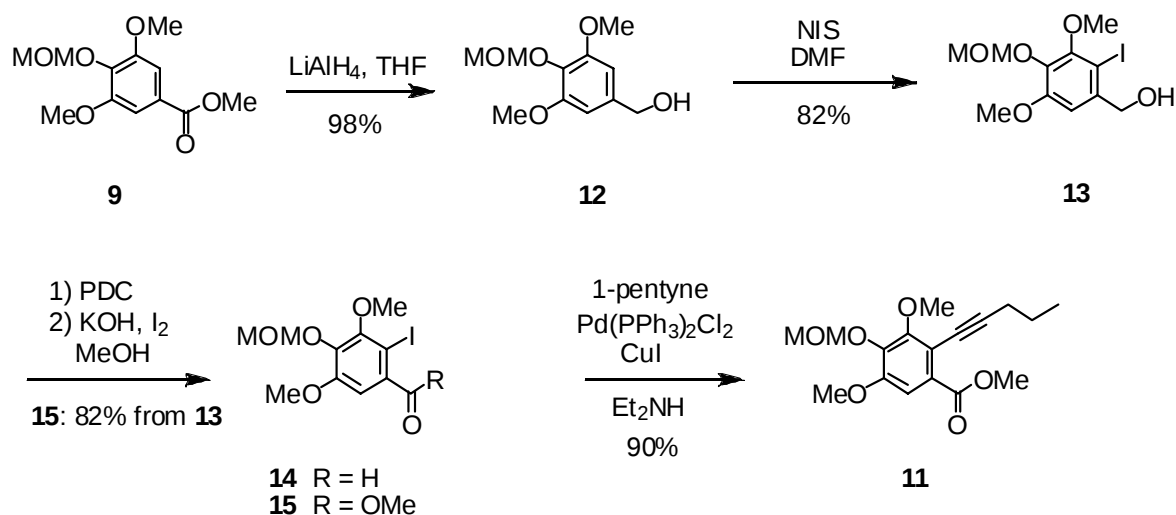
Figure 1. Structures of scoparines A and B, and ruprechstyryl

To apply the same synthetic strategy used in the preparation of cassiarin A to the synthesis of scoparine A, the known acid **4**¹⁰ was reacted with diethylamine in the presence of 2-chloro-*N*-methylpyridinium iodide (CMPI) to give the amide **5**. A site-selective iodination of the amide **5** according to Hegedus's procedure¹¹ gave the iodide **6**. Sonogashira coupling⁶ of **6** with 1-pentyne in diethylamine in the presence of bis(triphenylphosphine)palladium dichloride and copper(I) iodide provided the desired alkyne **7** in quantitative yield. Treatment of **7** with trimethyloxonium tetrafluoroborate in acetonitrile, followed by further treatment with methanol afforded the ester **8**, in 79% yield, accompanied with deprotection of the

Synthesis of scoparine B was also achieved by application of the above strategy starting from methyl 3,5-dimethoxy-4-methoxymethoxy benzoate **9**.¹² First, we investigated a direct iodination for **9** under the various reaction conditions, however, the desired iodide could not be isolated in reasonable yields, unfortunately. Therefore, the ester **9** was converted to the bromide **10** by treatment with NBS. Attempted Sonogashira coupling of **10** with 1-pentyne under the same reaction conditions as described for the preparation of **7** at 60 °C for 8 days, provided the desired alkyne **11** in 78% yield. Since the alkyne **11** was obtained in reasonably good yield, its further conversion to the natural product was achieved by its acid hydrolysis providing scoparine B **2**, whose physicochemical properties were identical with those reported in the literature.⁸



Although **11** could be derived from the bromide **10**, the coupling with the alkyne required a relatively long reaction time. To improve the reaction conditions for Sonogashira coupling, a preparation of the corresponding iodide **15** was carried out as follows. Iodination of the alcohol **12**, derived from **9** by LiAlH_4 reduction, with NIS gave the iodide **13**, in 82% yield, which on oxidation with pyridinium dichromate (PDC), followed by treatment of the resulting aldehyde **14** with iodine and potassium hydroxide in MeOH afforded the ester **15**, in 82% yield from **13**. Sonogashira coupling of **15** with 1-pentyne in diethylamine in the presence of bis(triphenylphosphine)palladium dichloride and copper(I) iodide was achieved at 60 °C for 15 h to give **11** in 90% yield.

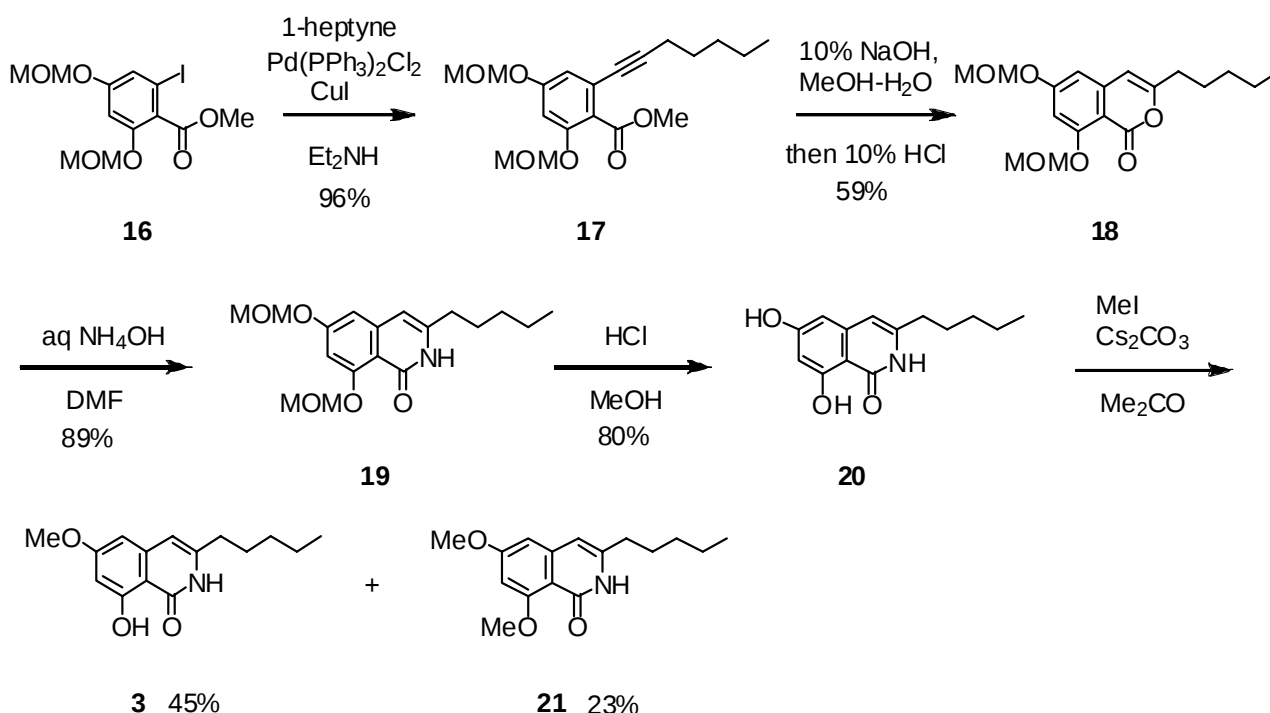


Scheme 3. Alternative synthesis of the key intermediate 11

Next, our attention was focused on the first total synthesis of a natural isocarbostryl, ruprechstyryl **3**, bearing *n*-pentyl group at the 3-position. Ruprechstyryl **3** was isolated from *Ruprechtia tangarana* as a new isocarbostryl derivative, and its structure was determined by X-ray crystal analysis.¹³ As the extract of this plant exhibited anticancer activity against the KB cell line and P388 lymphocytic leukemia,¹³ this plant was expected to be the sources of new anticancer agents. However, further investigation of the bioactive principles for this plant revealed that ruprechstyryl did not show any significant activity against the murine P388 lymphocytic leukemia cell line.¹³

Our synthesis of ruprechstyryl **3** commenced with the use of the iodide **16**^{5a} employed in the synthesis of cassiarin A. Treatment of **16** with 1-heptyne in the presence of $\text{Pd(PPh}_3)_2\text{Cl}_2$ and copper(I) iodide in diethylamine gave the alkyne **17** in 96% yield. Hydrolysis of **17** with 10% NaOH solution, followed by acidic treatment afforded the coumarin derivative **18**. Conversion of **18** to the isocarbostryl **19** was achieved by treatment with 25-28% ammonium hydroxide in DMF. Deprotection of the methoxymethyl groups of **19** afforded the diol **20**, which on treatment with iodomethane and cesium carbonate gave

ruprechstyryl **3** and *O*-methyleruprechstyryl **21**, in 45 and 23% yields, respectively. The physicochemical properties of the synthetic ruprechstyryl were identical with those reported.¹³



Scheme 4. Synthesis of ruprechstyryl 3

In summary, we disclose a general synthesis of natural isocoumarin and isocarbostryl compounds by employing Sonogashira coupling and a regioselective 6-*endo*-dig cyclization. The strategy described here would be applicable to a preparation of medicinally important bioactive compounds structurally related to the natural products.

EXPERIMENTAL

Melting points were measured with a Yanagimoto MP apparatus and are uncorrected. IR spectra were obtained using a JASCO FT/IR-200 spectrophotometer. ¹H- and ¹³C-NMR spectra were obtained on JEOL Bruker AV-400 (¹H-NMR: 270 MHz, ¹³C-NMR: 67.8 MHz) instrument for solutions in CDCl₃ unless otherwise noted, and chemical shifts are reported on the δ scale from internal TMS. MS spectra were measured with a JEOL JMS-D 300 spectrometer. Elemental analyses were performed on a Yanaco-MT5.

***N,N*-Diethyl-3-methoxy-4-(methoxymethoxy)benzamide (5).** To 2-chloro-*N*-methylpyridinium iodide (CMPI) (14.3 g, 67.2 mmol) were successively added a solution of diethylamine (11.4 mL, 107.5 mmol) and 3-methoxy-4-methoxymethoxybenzoic acid (**1**) (25.8 g, 100.8 mmol) in CH₂Cl₂ (670 mL), and

triethylamine (22.7 mL, 107.5 mmol). The mixture was stirred at rt for 1 h and at 45 °C for 5 h. After treatment with saturated aqueous NaHCO₃, the mixture was extracted with Et₂O. The ethereal layer was washed with brine and dried over Na₂SO₄. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane:AcOEt (4:1 to 1:1, v/v) gave the amide (**5**) (17.7 g, 99%) as a pale yellow oil. IR (neat) cm⁻¹: 1627 , 1583. ¹H NMR δ: 1.20 (6H, br s), 3.45 (4H, br s), 3.52 (3H, s), 3.89 (3H, s), 5.25 (2H, s), 6.91 (1H, dd, *J* = 1.9, 8.2 Hz), 6.97 (1H, d, *J* = 1.9 Hz), 7.14 (1H, d, *J* = 8.2 Hz); ¹³C NMR δ: 55.8, 56.1, 95.2, 110.5, 115.5, 118.9, 131.1, 147.1, 149.5, 170.9. MS (EI) *m/z* 267 (M⁺). HRMS (EI): Calcd for C₁₄H₂₁NO₄ (M⁺) 267.1470, Found 267.1462 .

***N,N*-Diethyl-2-iodo-3-methoxy-4-(methoxymethoxy)benzamide (**6**)**. To a stirred solution of **5** (0.2 g, 0.75 mmol) in THF (3.8 mL) was added *N,N,N',N'*-tetramethylethylenediamine (0.27 ml, 1.73 mmol) at -60 °C, and the mixture was stirred at the same temperature for further 10 min. *sec*-BuLi (1.74 mL, 2.5 mmol) was added to the solution and the whole was stirred at the same temperature for 5 h. To this solution was added a solution of iodine (0.48 g, 2.5 mmol) in THF (3.0 mL) dropwise, and the resulting mixture was stirred for further 2 h. After treatment with saturated aqueous NH₄Cl and 10% aqueous sodium thiosulfate solution, the mixture was extracted with Et₂O. The ethereal layer was washed with brine and dried over Na₂SO₄. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane:AcOEt (2:1, v/v) gave the iodide (**6**) (0.19 g, 63%) as a pale yellow oil. IR (neat) cm⁻¹: 1632 , 1586. ¹H NMR δ: 1.07 (3H, t, *J* = 7.1 Hz), 1.24-1.30 (4H, m), 3.11-3.17 (2H, m), 3.25-3.30 (1H, m), 3.52 (3H, s), 3.86 (3H, s), 5.23 (2H, s), 6.91 (1H, d, *J* = 8.4 Hz), 7.15 (1H, d, *J* = 8.4 Hz); ¹³C NMR δ: 12.2, 13.8, 38.9, 42.8, 56.3, 60.5, 91.9, 95.1, 99.7, 117.0, 122.5, 137.4, 149.7, 170.0. MS (EI) *m/z* 393 (M⁺). HRMS (EI): Calcd for C₁₄H₂₀NO₄I (M⁺) 393.0437, Found 393.0456.

***N,N*-Diethyl-3-methoxy-4-(methoxymethoxy)-2-(pent-1-yn-1-yl)benzamide (**7**)**. To a solution of **6** (0.52 g, 1.32 mmol) in diethylamine (6.6 mL) were added 1-pentyne (0.20 mL, 1.98 mmol), Pd(PPh₃)₂Cl₂ (47.2 mg, 0.07 mmol) and CuI (52.9 mg, 0.26 mmol) under argon, and the resulting mixture was heated in a sealed tube at 60 °C for 35 h. The mixture was concentrated by evaporation and the residue was subjected to column chromatography on silica gel. Elution with hexane:AcOEt (4:1, v/v) afforded the alkyne (**7**) (0.44 g, 100%) as a pale yellow oil. IR (neat) cm⁻¹: 2230, 1634, 1593. ¹H NMR δ: 1.02-1.07 (6H, m), 1.24 (3H, t, *J* = 7.1 Hz), 1.57-1.66 (2H, m), 1.66-1.67 (2H, m), 2.40 (2H, t, *J* = 7.0 Hz), 3.17-3.19 (2H, m), 3.51 (3H, s), 3.93 (3H, s), 5.21 (2H, s), 6.90 (1H, d, *J* = 8.4 Hz), 7.09 (1H, d, *J* = 8.4 Hz); ¹³C NMR δ: 12.7, 13.5, 14.0, 21.6, 21.9, 38.7, 42.8, 56.2, 60.9, 73.7, 95.1, 98.2, 116.3, 116.4, 121.5, 134.9, 150.1, 150.9, 169.2. MS (EI) *m/z* 333 (M⁺). HRMS (EI) Calcd for C₁₉H₂₇NO₄ (M⁺) 333.1940,

Found 333.1944.

Methyl 4-hydroxy-3-methoxy-2-(pent-1-yn-1-yl)benzoate (8). To a stirred solution of **7** (0.10 g, 0.30 mmol) in MeCN (1.5 mL) were added Na₂HPO₄ (63.9 mg 0.45 mmol) and trimethyloxonium tetrafluoroborate (0.22 g, 1.5 mmol) at rt, and the whole was stirred for further 38 h at the same temperature. After treatment of the solution with MeOH and saturated aqueous NaHCO₃, the resulting mixture was stirred for 28 h and then concentrated to leave a residue, which was extracted with Et₂O. The extract was washed with brine and dried over Na₂SO₄. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane:AcOEt (7:1, v/v) gave the ester (**8**) (58.9 mg, 79%) as a pale yellow oil. IR (neat) cm⁻¹: 1711, 3381. ¹H NMR δ: 1.02 (3H, t, *J* = 7.4 Hz), 1.58-1.67 (2H, m), 2.46 (2H, t, *J* = 7.0 Hz), 3.80 (3H, s), 3.92 (3H, s), 6.26 (1H, br s), 6.82 (1H, d, *J* = 8.6 Hz), 7.58 (1H, d, *J* = 8.6 Hz); ¹³C NMR δ: 13.6, 22.0, 29.6, 51.9, 61.0, 74.3, 101.8, 114.1, 118.4, 124.7, 127.7, 148.7, 152.2, 166.4. MS (EI) *m/z* 249 (M⁺). HRMS (EI) Calcd for C₁₄H₁₇O₄ (M⁺) 249.1127, Found 249.1123.

Scoparine A (1). A solution of **8** (23.8 mg, 0.096 mmol) in TFA (0.12 mL) was stirred at rt for 13 h. The solution was concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane:AcOEt (9:2, v/v) gave scoparine A (**1**) (11.5 mg, 51%) as a colorless solid. Mp 155-156 °C [lit.,⁸ mp 159-160 °C]. Spectral data (IR, NMR, MS) of the synthesized scoparine A were identical to those of the published data.⁸

Methyl 2-bromo-3,5-dimethoxy-4-(methoxymethoxy)benzoate (10). To a stirred solution of **9** (3.82 g, 14.9 mmol) in CHCl₃:AcOH = 1:1 (30 mL) was added *N*-bromosuccinimide (4.06 g, 22.4 mmol) at rt and the resulting mixture was stirred for further 43 h at the same temperature. The mixture was treated with saturated aqueous NaHCO₃ and extracted with CHCl₃. The extract was washed with brine and dried over Na₂SO₄. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane:AcOEt (9:1, v/v) afforded the bromide (**10**) (3.67 g, 74%) as a yellow oil. IR (neat) cm⁻¹: 2949, 2848, 1733, 1581, 1567. ¹H NMR δ: 3.59 (3H, s), 3.88 (6H, s), 3.93 (3H, s), 5.19 (2H, s), 7.17 (1H, s); ¹³C NMR δ: 52.5, 56.2, 57.3, 60.9, 98.6, 109.6, 110.1, 127.9, 142.8, 151.8, 152.4, 166.4. MS (CI) *m/z* 335 (M⁺+1). HRMS (CI): Calcd for C₁₂H₁₆O₆ (M⁺+1) 335.0130, Found 335.0158.

Methyl 3,5-dimethoxy-4-(methoxymethoxy)-2-(pent-1-yn-1-yl)benzoate (11). To a stirred solution of **10** (2.96 g, 8.8 mmol) in diethylamine (44.2 mL) were added 1-pentyne (1.04 mL, 10.6 mmol), (*tert*-Bu)₃P (0.2 mL, 0.88 mmol), Pd(PPh₃)₂Cl₂ (0.32 g, 0.44 mmol) and CuI (0.35 g, 1.77 mmol) at rt under argon, and the resulting mixture was heated in a sealed tube at 60 °C for 8 days. The mixture was concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane:AcOEt (9:1, v/v) afforded the alkyne (**11**) (2.22 g, 78%) as a yellow oil. IR (neat) cm⁻¹: 2962,

1733, 1713, 1591. ^1H NMR δ : 1.09 (3H, t, $J = 7.3$ Hz), 1.64-1.73 (2H, m), 2.51 (2H, t, $J = 7.0$ Hz), 3.59 (3H, s), 3.89-3.94 (9H, m), 5.18 (2H, s), 7.25 (1H, s); ^{13}C NMR δ : 13.5, 21.9, 22.1, 52.0, 56.0, 57.2, 60.9, 74.1, 98.5, 98.8, 109.3, 112.9, 128.3, 142.4, 152.3, 155.5, 166.5. MS (EI) m/z 322 (M^+). HRMS (EI): Calcd for $\text{C}_{17}\text{H}_{22}\text{O}_6$ (M^+) 322.1416, Found 322.1403.

Scoparine B (2). A solution of **11** (0.1 g, 0.31 mmol) in TFA (0.5 mL) was stirred at rt for 7 h. After evaporation of the solvent, the residue was purified by column chromatography on silica gel. Elution with hexane:AcOEt (5:2, v/v) afforded scoparine B (**2**) (64 mg, 78%) as a colorless solid. Mp 148-150 °C [lit.,⁸ mp 151-152 °C]. Spectral data (IR, NMR, MS) of the synthesized scoparine B were identical to those of the published data.⁸

3,5-Dimethoxy-4-(methoxymethoxy)benzyl alcohol (12). To a stirred suspension of lithium aluminum hydride (0.16 g, 4.29 mmol) in THF (13 mL) was added a solution of ester (**9**) (1.0 g, 3.9 mmol) in THF (13 mL) at 0 °C, and the resulting mixture was stirred for further 15 min at rt. After treatment with 4N NaOH and H_2O , the mixture was filtered through Celite to remove the insoluble materials. The filtrate was concentrated to leave a residue, which was purified by column chromatography on silica gel. Elution with hexane:AcOEt (1:1, v/v) gave the alcohol (**12**) (0.87 g, 98 %) as a colorless oil. IR (neat) cm^{-1} : 3415, 2941, 2841, 1594, 1505. ^1H NMR δ : 2.51 (1H, br s), 3.59 (3H, s), 3.84 (6H, s), 4.58 (2H, s), 5.09 (2H, s), 6.57 (2H, s); ^{13}C NMR δ : 55.9, 57.0, 65.1, 98.0, 103.6, 133.4, 137.1, 153.2. MS (EI) m/z 228 (M^+). HRMS (EI) Calcd for $\text{C}_{11}\text{H}_{16}\text{O}_5$ (M^+) 228.0998, Found 228.0986.

2-Iodo-3,5-dimethoxy-4-(methoxymethoxy)benzyl alcohol (13). To a stirred solution of **12** (4.5 g, 19.7 mmol) in DMF (65.7 mL) was added *N*-iodosuccinimide (13.3 g, 59.2 mmol) at rt, and the resulting mixture was stirred for further 5 days at the same temperature. The solution was treated with saturated aqueous NH_4Cl and 10% aqueous sodium thiosulfate, and extracted with Et_2O . The organic layer was washed with brine and dried over Na_2SO_4 . Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel. Elution with hexane:AcOEt (3:1, v/v) gave the iodide (**13**) (5.7 g, 82%) as a pale yellow oil. IR (neat) cm^{-1} : 3424, 2936, 1582, 1566, 1465. ^1H NMR δ : 2.35 (1H, br s), 3.60 (3H, s), 3.87 (6H, s), 4.64 (2H, s), 5.12 (2H, s), 6.94 (1H, s); ^{13}C NMR δ : 56.1, 57.3, 60.7, 69.3, 84.6, 98.5, 108.0, 137.9, 138.9, 153.1, 154.0. MS (EI) m/z 353 (M^+). HRMS (EI) Calcd for $\text{C}_{11}\text{H}_{15}\text{O}_5\text{I}$ (M^+) 353.9964, Found 353.9951.

Methyl 3,5-dimethoxy-4-(methoxymethoxy)benzoate (15). To a stirred solution of **13** (5.7 g, 16.1 mmol) in DMF (80.5 mL) was added pyridinium dichromate (12.1 g, 32.2 mmol) portionwise at rt, and the mixture was stirred for further 1 h at the same temperature. The mixture was treated with Celite (30g) and Et_2O (80.5 mL) and stirred for 3 h. After filtration, the filtrate was concentrated by evaporation of the solvent, and the residue was treated with H_2O . The aqueous layer was extracted with CHCl_3 , and the

extract was washed with brine and dried over Na_2SO_4 . Evaporation of the solvent gave a crude aldehyde (**14**), which without purification, was used in the next reaction. To a stirred solution of the aldehyde in MeOH (161 mL) were successively added a solution of KOH (2.4 g, 41.9 mmol) in MeOH (52.3 mL), iodine (5.31 g, 20.9 mmol) and MeOH (41.8 mL) at 0 °C, and the whole was stirred for further 23 h at 0 °C. The solution was treated with saturated aqueous NH_4Cl and 10% aqueous sodium thiosulfate, and extracted with Et_2O . The organic layer was washed with brine and dried over Na_2SO_4 . Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel. Elution with hexane:AcOEt (5:1, v/v) gave the ester (**15**) (5.1 g, 82%) as a pale yellow oil. IR (neat) cm^{-1} : 2948, 1733, 1577, 1561. ^1H NMR δ : 3.59 (3H, s), 3.88 (6H, s), 3.93 (3H, s), 5.19 (2H, s), 7.17 (1H, s); ^{13}C NMR δ : 52.5, 56.2, 57.3, 60.9, 98.6, 109.6, 110.1, 127.9, 142.8, 151.8, 152.4, 166.4. MS (EI) m/z 381 (M^+). HRMS (EI): Calcd for $\text{C}_{12}\text{H}_{15}\text{O}_6\text{I}$ (M^+) 381.9913, Found 381.9902.

Alternative synthesis of the alkyne 11 from 15. To a stirred solution of **15** (0.1 g, 0.26 mmol) in diethylamine (1.3 mL) were added 1-pentyne (0.031 mL, 0.31 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (9.4 mg, 0.013 mmol) and CuI (10.6 mg, 0.052 mmol) under argon, and the resulting mixture was heated in a sealed tube at 60 °C for 15 h. Work-up was carried out by the same procedure as for the preparation of **11** from **10** to give the alkyne (**11**) (76.8 mg, 90%).

Methyl 6-(hept-1-yn-1-yl)-2,4-bis(methoxymethoxy)benzoate (17). To a solution of iodine compound **16** (2.05 g, 5.37 mmol) in diethylamine (35 mL) was added 1-heptyne (0.81 mL, 6.18 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (0.19 g, 0.27 mmol) and CuI (0.10 g, 0.54 mmol). The resulting mixture was stirred at 60 °C for 19 h. The solvent was evaporated under reduced pressure. The residue was partitioned between saturated aqueous NH_4Cl solution and Et_2O . After separation, the aqueous layer was extracted three times with Et_2O . The combined organic layers were dried over Na_2SO_4 and concentrated. Purification of the crude product by column chromatography with hexane:EtOAc (4:1, v/v) as an eluent provided the alkyne **17** (1.81 g, 96%) as a colorless liquid. IR (neat) cm^{-1} : 1732, 1597, 1216, 1149. ^1H NMR δ : 0.92 (3H, t, $J=7.2$ Hz), 1.31-1.45 (4H, m), 1.61-1.63 (2H, m), 2.37 (2H, t, $J=7.1$ Hz), 3.46 (3H, s), 3.89 (3H, s), 5.14 (2H, s), 6.76 (1H, d, $J=2.2$ Hz), 6.78 (1H, d, $J=2.2$ Hz). ^{13}C NMR δ : 13.9, 19.3, 22.1, 28.2, 30.9, 52.2, 56.1, 56.2, 77.5, 94.3, 94.4, 94.7, 103.8, 112.4, 121.1, 123.7, 155.0, 158.5, 167.3. MS (CI) m/z 351 (M^++1). HRMS Calcd for $\text{C}_{19}\text{H}_{27}\text{O}_6$ (M^++1): 351.1807, Found: 351.1801.

6,8-Bis(methoxymethoxy)-3-pentylisochromen-1-one (18). To a solution of compound **17** (716.4 mg, 2.04 mmol) in MeOH (25 mL) was added 20% aqueous NaOH (25 mL). The mixture was stirred at 60 °C for 23 h. After cooling to 0 °C, to the mixture was added dropwise 10% HCl solution until pH $\approx$ 3. The mixture was extracted three times with EtOAc. The extract was concentrated by evaporation of the solvent. The concentrated extract was kept overnight at rt to complete the cyclization. Column

chromatography with CHCl_3 :MeOH (200:1, v/v) as an eluent gave the isocoumarin **18** (403.1 mg, 59%) as colorless oil. IR (neat) cm^{-1} : 1732, 1602, 1152. ^1H NMR δ : 0.88-0.92 (3H, m), 1.32-1.36 (4H, m), 1.64-1.71 (2H, m), 3.45 (2H, t, $J=7.6$ Hz), 3.49 (3H, s), 3.55 (3H, s), 5.23 (2H, s), 5.34 (2H, s), 6.09 (1H, s), 6.58 (1H, d, $J=2.3$ Hz), 6.79 (1H, d, $J=2.3$ Hz). ^{13}C NMR δ : 13.9, 22.4, 26.4, 31.1, 33.2, 56.4, 56.5, 94.1, 95.1, 102.9, 103.48, 103.50, 104.6, 142.0, 159.0, 159.3, 160.7, 162.6. MS (CI) m/z 337 (M^++1): HRMS Calcd for $\text{C}_{18}\text{H}_{25}\text{O}_6$ (M^++1): 337.1651, Found: 337.1629.

6,8-Bis(methoxymethoxy)-3-pentyl-2H-isoquinolin-1-one (19). Isocoumarin **18** (302.2 mg, 0.90 mmol) was dissolved in DMF (7 mL) in a round bottom flask. To the solution was added NH_4OH (25-28% solution in water, 7 mL), and then the flask was sealed with rubber septum. The mixture was stirred at rt for 60 h. After removing the septum, the mixture was stirred at 90-100 °C for 2 h. The solvent was removed by distillation under reduced pressure to give crude product. Column chromatography of the crude product with CHCl_3 :MeOH (30:1, v/v) as an eluent gave the isocarbostyryl **19** (266.8 mg, 89%) as white prisms (recrystallized from methanol), mp 93-95 °C. IR (neat) cm^{-1} : 3171, 1646, 1605, 1152. ^1H NMR δ : 0.87-0.91 (3H, m), 1.32-1.38 (4H, m), 1.67-1.75 (2H, m), 2.55 (2H, t, $J=7.6$ Hz), 3.50 (3H, s), 3.58 (3H, s), 5.24 (2H, s), 5.33 (2H, s), 6.14 (1H, s), 6.72 (1H, d, $J=2.3$ Hz), 6.75 (1H, d, $J=2.3$ Hz), 10.52 (1H, s). ^{13}C NMR δ : 13.9, 22.4, 27.6, 31.2, 32.9, 56.3, 56.4, 94.1, 95.9, 103.6, 103.7, 103.9, 110.4, 142.8, 143.1, 159.7, 166.6, 162.7. MS (CI) m/z 336 (M^++1). HRMS Calcd for $\text{C}_{18}\text{H}_{26}\text{NO}_5$ (M^++1): 336.1811, Found: 336.1807. Anal Calcd for $\text{C}_{18}\text{H}_{25}\text{NO}_5$: C 64.46, H 7.51, N 4.18; Found: C 64.29, H 7.44, N 4.09.

6,8-Dihydroxy-3-pentyl-2H-isoquinolin-1-one (20). Compound **19** (232.6 mg, 0.69 mmol) was dissolved in a MeOH (5 mL). To the solution was added 6 drops of concentrated HCl, and the resulting mixture was stirred at 50 °C for 24 h. The solvent was evaporated in reduced pressure. The residue was purified by column chromatography with CHCl_3 :MeOH (30:1, v/v) as an eluent to give the diol **20** (165.0 mg, 80%) as white needles (recrystallized from MeOH), mp 170-172 °C. IR (neat) cm^{-1} : 3297, 3168, 3067, 1653. ^1H NMR δ : 0.92 (3H, t, $J=6.8$ Hz), 1.35-1.38 (4H, m), 1.64-1.71 (2H, m), 2.50 (2H, t, $J=7.6$ Hz), 6.21 (1H, s), 6.28 (1H, d, $J=2.1$ Hz), 6.33 (1H, d, $J=2.1$ Hz). ^{13}C NMR δ : 13.0, 21.8, 27.5, 30.6, 32.3, 99.6, 100.4, 103.8, 104.5, 140.9, 131.1, 162.1, 162.5, 166.1. MS (CI) m/z 228 (M^++1). HRMS Calcd for $\text{C}_{14}\text{H}_{18}\text{NO}_3$ (M^++1): 248.1286, Found: 248.1293.

Ruprechstyryl (3) and O-methylruprechstyryl (21). Compound **20** (102.8 mg, 0.42 mmol) was dissolved in acetone (8 mL). To the solution were added iodomethane (25.9 μL , 0.42 mmol) and cesium carbonate (135.5 mg, 0.42 mmol). The resulting mixture was stirred at rt for 23 h. The solvent was evaporated in reduced pressure. To the residue were added saturated aqueous NH_4Cl solution and a mixture of CHCl_3 :MeOH (10:1, v/v). After separation, the aqueous layer was extracted three times with CHCl_3 :MeOH (10:1, v/v). The organic layers were combined, washed with brine, dried over Na_2SO_4 , and

concentrated. Purification by column chromatography with CHCl_3 :MeOH (50:1, v/v) as an eluent provided ruprechstyryl (**3**) (49.0 mg, 45%) (white solids), mp 138-140 °C [lit.,¹³ mp 139-141 °C], along with *O*-methylyruprechstyryl (**21**) (25.9 mg, 23%) and recovered **20** (22.4 mg, 22%) (white solid). Spectral data (IR, NMR, MS) of the synthesized ruprechstyryl (**3**) are identical to those of the published data.¹³

Spectral data of *O*-methylyruprechstyryl (**21**): IR (neat) cm^{-1} : 3073, 1652, 1600, 1162. ^1H NMR δ : 0.91-0.95 (3H, m), 1.34-1.43 (4H, m), 1.62-1.69 (2H, m), 2.60 (2H, t, $J=7.8$ Hz), 3.52 (3H, s), 3.84 (3H, s), 6.27 (1H, s), 6.31 (1H, d, $J=2.3$ Hz), 6.41 (1H, d, $J=2.3$ Hz), 13.07 (1H, s). ^{13}C NMR δ : 13.9, 22.4, 27.9, 29.7, 31.4, 33.3, 55.3, 98.2, 99.5, 105.4, 106.4, 139.0, 143.3, 162.8, 164.4, 166.1. MS (EI) m/z 275 (M^+). HRMS Calcd for $\text{C}_{16}\text{H}_{21}\text{NO}_3$ (M^+): 275.1521, Found: 275.1545.

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