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Total Synthesis

Total Synthesis of Two 8-Oxoprotoberberine Alkaloids: Alangiumkaloids A and B

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Abstract: A new and versatile synthetic route for 8-oxoprotoberberine **17** through synthesis of isoquinolinone **16** and construction of a B-ring is described. The key step is the synthesis of isoquinolinone **14** through thermal cyclization of 2-alkynylbenzaldehyde oxime **12** to afford isoquinoline *N*-oxide **13**, followed by a Reissert–Henze-type reaction. The first total synthesis of 8-oxoprotoberberine alkaloid alangiumkaloids A and B was achieved by using this strategy.

Introduction

Two 8-oxoprotoberberine alkaloids, alangiumkaloids A (**1**) and B (**2**), were isolated from *Alangium salviiforlium* by Kittakoop and co-workers in 2011 (Figure 1).[1] The cytotoxic activity of **1** and **2** along with that of other alangiumkaloids was evaluated against four cancer cell lines: MOLT-3, HepG2, A549, and HuCCA-1. Alangiumkaloid A (**1**) was reported to exhibit weak cytotoxic activity toward the MOLT-3 cancer cell line (IC_{50} 13.0 μM). The structures of protoberberines and 8-oxoprotoberberines, which include isoquinoline moieties, are interesting, and these compounds exhibit a wide range of pharmacological properties, which include antitumor activity. Many approaches for synthesis of the biologically active protoberberine alkaloids have been reported; these routes involve the construction of either B- or C-rings in the final or semifinal stage.[2]

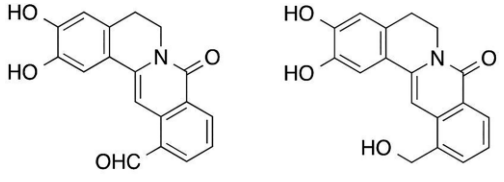

Figure 1. Alangiumkaloid A (**1**) and B (**2**).

We have been interested in the unique structure and pharmacological action of condensed heteroaromatic compounds, which includes those that are natural products, and have achieved the total synthesis of several heteroaromatic compounds (e.g., scorpinone,[3] calothrixins,[4] benzo[*c*]phenanthridines,[5] cassiarin C,[6] dichotomines,[7] marinacarbolines,[8] and isocryptolepine[9]) by using an electrocyclic reaction of the 6π-electron system as our original method.[10] Moreover, we have been searching for highly active compounds based on these naturally occurring compounds and their derivatives.[11] We have also published the total syntheses of (*R*)-(–)-pyridindolols,[12] which are β-carboline alkaloids, my means of a route that includes the construction of key intermediate β-carboline *N*-oxides by thermal cyclization of 3-alkynylindole-2-aldoxime in accordance with a modified Sakamoto's method.[13]

Herein, we describe the details of the first total synthesis of alangiumkaloids A (**1**) and B (**2**) through construction of an isoquinolinone framework formed by thermal cyclization of 2-alkynylbenzaldehyde oxime to produce isoquinoline *N*-oxide, followed by a Reissert–Henze-type reaction.

Results and Discussion

Scheme 1 illustrates the strategy used in this paper to synthesize alangiumkaloids. Alangiumkaloids are prepared from isoquinolinones **3**, which are derived by the disconnection of the C6–N7 bond of an 8-oxoprotoberberine framework, by the construction of the B-ring. We hypothesized that isoquinolinones **3** could be obtained from isoquinoline *N*-oxides **4** by thermal cyclization of 2-alkynylbenzaldehyde oximes **5** followed by heating with acetic anhydride. We further hypothesized that 2-alkynylbenzaldehyde oximes **5** could be prepared from 2-iodophenylacetate (**6**) and 2-ethynylbenzaldehyde **7** by a Sonogashira reaction.

To synthesize alangiumkaloids A and B, we prepared 2-ethynylbenzaldehydes **7** as starting materials. On the basis of the sequence in Scheme 2, treatment of 2-bromo-3-hydroxymethylbenzaldehyde (**8**) with chloromethyl methyl ether (MOMCl) afforded desired *O*-MOM ether **9** by Ojima's

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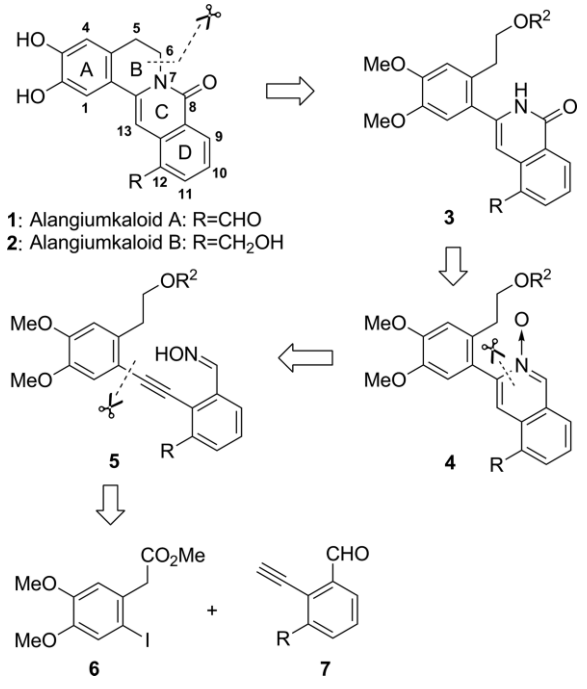
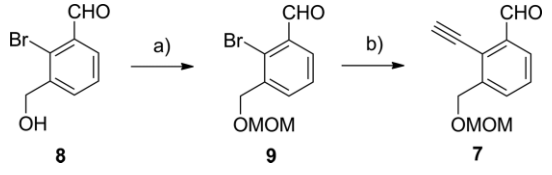


Scheme 1. Retrosynthetic analysis of alangiumkaloid A and B.

method.[14] Subsequently, the Sonogashira reaction of **9** with trimethylsilyl (TMS)-acetylene afforded 2-ethynylbenzaldehyde **7** in 68 % yield.

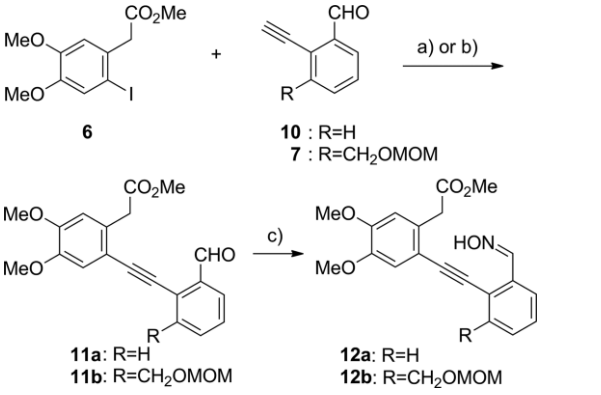


Scheme 2. Reagents and conditions: a) MOMCl, iPr_2NH, CH_2Cl_2, room temp., 30 min, 96 %; b) (i) TMS-C≡CH, $PdCl_2(PPh_3)_2$, CuI, iPr_2NH, 100 °C, 3 h; (ii) H_2O, 68 %.

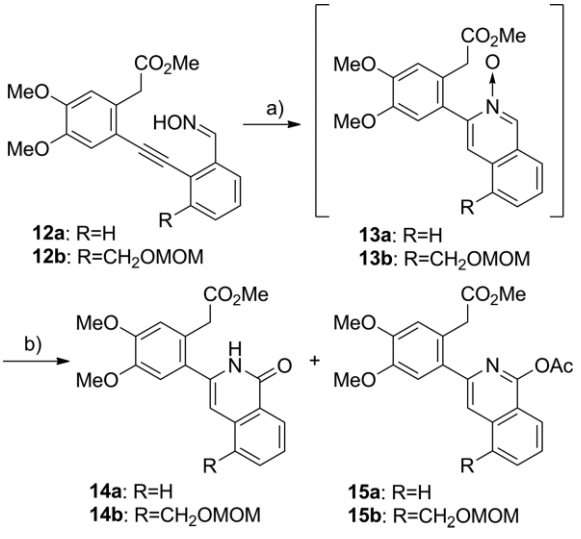
We then prepared important substrates **12** to synthesize isoquinolinones **14** (Scheme 3). The Sonogashira reaction of 2-iodophenylacetate **6** with 2-ethynylbenzaldehydes **10** and **7** in the presence of $PdCl_2(PPh_3)_2$ and CuI provided 3-alkynylbenzaldehydes **11a** and **11b** in 81 and 77 % yields, respectively.[15] Treatment of **11a** and **11b** with hydroxylamine gave oximes **12a** and **12b** in 98 and 92 % yields, respectively.

As shown in Scheme 4, we next examined the construction of isoquinoline *N*-oxide **13a** from oxime **12a** by heating at 180 °C in 1,2-dichlorobenzene. However, desired isoquinoline *N*-oxide **13a** could not be isolated because of its high polarity. Therefore, after 1,2-dichlorobenzene was removed, crude *N*-oxide **13a** (without purification) was heated at 110 °C in acetic anhydride to give isoquinolinone **14a**. As a result, desired isoquinolinone **14a** and 2-acetoxyisoquinoline **15a** were obtained in 44 and 31 % yields, respectively.

Similarly, thermal cyclization of oxime **12b** by using the same procedure afforded isoquinolinone **14b** and 2-acetoxyisoquinoline **15b** in 33 and 25 % yields, respectively.



Scheme 3. Reagents and conditions: a) CuI, $PdCl_2(PPh_3)_2$, iPr_2NH, THF, reflux, 2.5 h, **11a** (81 %); b) CuI, $PdCl_2(PPh_3)_2$, iPr_2NH, 100 °C, 2 h, **11b** (77 %); c) NH_2OH·HCl, AcONa, EtOH, 80 °C, 2 h, **12a** (98 %), **12b** (92 %).



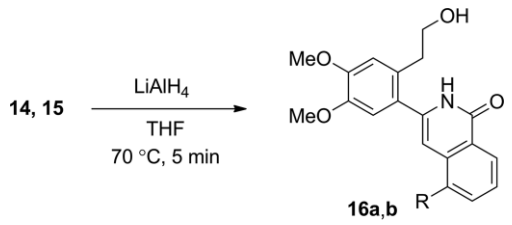
Scheme 4. Reagents and conditions: a) 1,2-dichlorobenzene, 180 °C, 1 h, **13a**; 2 h, **13b**; b) Ac_2O, 110 °C, 5 h, **14a** (44 %) and **15a** (31 %); 3 h, **14b** (33 %) and **15b** (25 %).

Next, selective reduction of the ester part of **14**, **15** was carried out in accordance with Bois-Choussy's procedure.[16] Treatment of **14a** and/or **15a** with $LiAlH_4$ at 70 °C provided alcohol **16a** in 57 and 49 % yields, respectively (Table 1). Subsequent treatment of a mixture of **14a** and **15a** under the same conditions led to **16a** in 62 % yield (three steps from **12a**). Similarly, a mixture of **14b** and **15b** afforded desired alcohol **16b** in 68 % yield (three steps from **12b**).

Next, to construct the B-ring of 8-oxoprotoberberines **17**,[16] treatment of **16a** and **16b** with 4-toluenesulfonyl chloride (TsCl) in the presence of K_2CO_3 afforded 8-oxoprotoberberines **17a** and **17b** in 60 and 56 % yields, respectively (Scheme 5). Deprotection of the Me group and/or MOM group of **17a** and **17b** with BBr_3 afforded 8-oxoprotoberberine **18** and alangiumkaloid B (**2**) in 52 and 62 % yields, respectively. Finally, oxidation of **2** with MnO_2 afforded alangiumkaloid A (**1**) in 42 % yield.

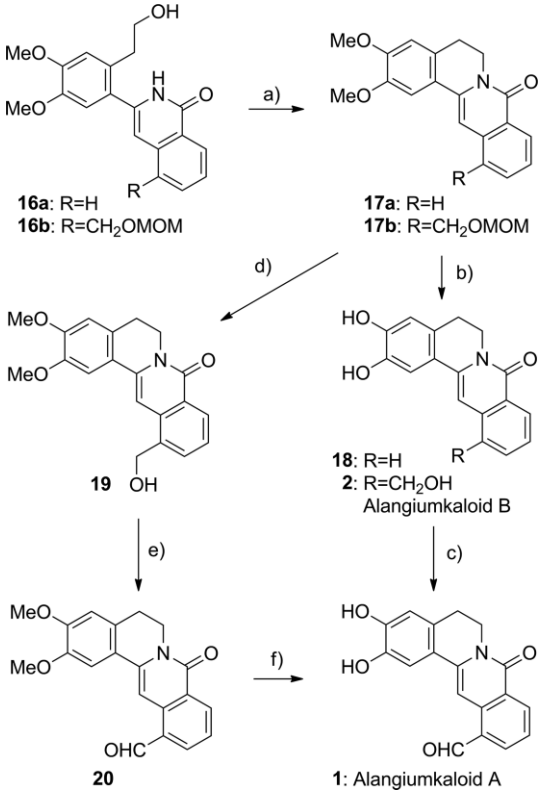
In addition, we investigated another route to synthesize alangiumkaloid A (**1**) from **17b**. Deprotection of the MOM group of **17b** with HCl (6 M) in MeOH, followed by oxidation of

Table 1. Synthesis of isoquinolinone **16** by reduction.



SM	R	Compd. No.	Yield [%]
14a	H	**16a**	57
15a	H	**16a**	49
14a + **15a**	H	**16a**	62[a]
14b	CH_2OMOM	**16b**	71
14b + **15b**	CH_2OMOM	**16b**	68[b]

[a] Three-step yield from **12a**. [b] Three-step yield from **12b**.



Scheme 5. Reagents and conditions: a) TsCl, K_2CO_3, DMF, 100 °C, 24 h, **17a** (60 %), **17b** (56 %); b) BBr_3, CH_2Cl_2, room temp., 2 h, **18** (52 %), **2** (62 %); c) MnO_2, CH_2Cl_2, room temp., 48 h, 42 %; d) 6 M HCl, MeOH, room temp., 20 h, 81 %; e) MnO_2, CH_2Cl_2, room temp., 70 h, 56 %; f) BBr_3, CH_2Cl_2, room temp., 2 h, 65 %.

alcohol **19** with MnO_2, afforded aldehyde **20**. Finally, treatment of **20** with BBr_3 afforded alangiumkaloid A (**1**) in 65 % yield. The synthetic yield of **1** from **17b** was better in the latter route (26.0 versus 29.5 %). We synthesized the 8-oxoprotoberberine framework in six steps from phenylacetate **6** and achieved the first total syntheses of alangiumkaloids A (**1**) and B (**2**). The structures of all synthetic compounds were supported by ^1H and ^{13}C NMR spectra, and by mass spectra. The physical and spectroscopic data for our synthetic alangiumkaloid A (**1**) and B (**2**) are consistent with those for natural alangiumkaloids A (**1**) and B (**2**) in all respects.[1]

Conclusions

In conclusion, a versatile synthesis of 8-oxoprotoberberines from appropriate 2-iodophenylacetate and 2-ethynylbenzaldehydes was achieved through a six-step sequence. The key step is the synthesis of an isoquinolinone through thermal cyclization of a 2-alkynylbenzaldehyde oxime, followed by a Reissert–Henze-type reaction to an isoquinoline *N*-oxide. The first total synthesis of 8-oxoprotoberberine alkaloid alangiumkaloids A and B was achieved by using this strategy. This will be a useful procedure for the synthesis of other 8-oxoprotoberberine alkaloids. In addition, the biologic activity of alangiumkaloids A (**1**) and B (**2**) and their derivatives is under evaluation.

Experimental Section

General: All non-aqueous reactions were carried out under an atmosphere of nitrogen in dried glassware. Solvents were dried and distilled in accordance with standard protocols. Analytical thin-layer chromatography was performed with Silica gel $60PF_{254}$ (Merck). Silica-gel column chromatography was performed with Silica gel 60 (70–230 mesh, Kanto Chemical Co. Lit.). All melting points were determined with a Yanagimoto micro melting point apparatus. ^1H NMR spectra were recorded with a JEOL AL-300 at 300 MHz. Chemical shifts are reported relative to Me_4Si (δ = 0.00 ppm). Signal multiplicity is indicated by one or more of the following: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet); br. (broad). ^{13}C NMR spectra were recorded with a JEOL AL-300 at 75 MHz. Chemical shifts are reported relative to $CDCl_3$ (δ = 77.0 ppm) and [D_6]dimethyl sulfoxide ([D_6]DMSO; δ = 39.7 ppm). Infrared spectra were recorded by using the ATR method with a Shimadzu FTIR-8000 spectrophotometer and Technologies DuraScop. Low- and High-resolution mass spectra were recorded with a JEOL JMS-700 spectrometer equipped with a direct inlet system.

2-Bromo-3-[(methoxymethoxy)methyl]benzaldehyde (9): To a solution of 2-bromo-3-hydroxymethylbenzaldehyde (**8**; 1.5 g, 6.98 mmol) and diisopropylamine (*i*Pr_2NH; 6.1 mL, 34.9 mmol) in CH_2Cl_2 (30 mL) was added MOMCl (1.59 mL, 20.9 mmol). The reaction mixture was stirred at room temp. for 30 min. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with water and brine, dried with Na_2SO_4, and evaporated in vacuo. The residue was purified by column chromatography (EtOAc/hexane 3:7 v/v) to give *O*-MOM ether **9** (1.74 g, 96 %) as a yellow oil. IR (ATR): $\tilde{\nu}$ = 1732 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.45 (s, 3 H), 4.75 (s, 2 H), 4.81 (s, 2 H), 7.45 (t, *J* = 7.7 Hz, 1 H), 7.76 (tdd, *J* = 0.8, 1.8, 7.5 Hz, 1 H), 7.85 (dd, *J* = 1.8, 7.7 Hz, 1 H), 10.46 (d, *J* = 0.8 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.6, 68.3, 96.3, 127.2, 127.6, 128.9, 133.8, 134.4, 139.1, 192.0 ppm. MS (EI): *m/z* = 257 [M^+], 259 [M^+ + 2]. HRMS (EI): calcd. for $C_{10}H_{11}BrO_3$ 257.9892; found 257.9888.

2-Ethynyl-3-[(methoxymethoxy)methyl]benzaldehyde (7): To a solution of *O*-MOM ether **9** (300 mg, 1.12 mmol), CuI (22 mg, 0.11 mmol) and $PdCl_2(PPh_3)_2$ (77 mg, 0.11 mmol) in *i*Pr_2NH (5 mL) was added TMS-acetylene (0.19 mL, 1.34 mmol). The reaction mixture was stirred for 3 h at 100 °C. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with water and brine, dried with Na_2SO_4, and evapo-

rated in vacuo. The residue was purified by column chromatography (EtOAc/hexane 1:9 v/v) to give 2-ethynylbenzaldehyde **7** (155 mg, 68 %) as a yellow oil. IR (ATR): $\tilde{\nu}$ = 1693 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.44 (s, 3 H), 3.73 (s, 1 H), 4.79 (s, 2 H), 4.84 (s, 2 H), 7.50 (t, *J* = 7.5 Hz, 1 H), 7.78 (d, *J* = 7.5 Hz, 1 H), 7.88 (d, *J* = 7.5 Hz, 1 H), 10.58 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.5, 66.8, 76.4, 89.3, 96.3, 123.7, 126.2, 128.9, 132.8, 136.7, 142.0, 191.5 ppm. MS (EI): *m/z* = 204 [M^+]. HRMS (EI): calcd. for $C_{12}H_{12}O_3$ 204.0786; found 204.0793.

Methyl 2-[2-(2-Formylphenyl)ethynyl]-4,5-dimethoxyphenylacetate (11a): To a solution of 2-iodophenylacetate **6** (749 mg, 2.23 mmol), CuI (35 mg, 0.186 mmol), $PdCl_2(PPh_3)_2$ (130 mg, 0.186 mmol) and *i*Pr_2NH (3 mL, 16.7 mmol) in tetrahydrofuran (THF; 6 mL) was added the solution of 2-ethynylbenzaldehyde (**10**; 242 mg, 1.86 mmol) in THF (4 mL). The reaction mixture was stirred for 2.5 h at 100 °C. After removal of solvent, the residue was purified by column chromatography (EtOAc/hexane 3:7 v/v) to give 3-alkynylbenzaldehyde **11a** (509 mg, 81 %). M.p. 90–91 °C (EtOAc/hexane). IR (ATR): $\tilde{\nu}$ = 1731, 1693 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.71 (s, 3 H), 3.87 (s, 2 H), 3.92 (s, 3 H), 3.93 (s, 3 H), 6.85 (s, 1 H), 7.05 (s, 1 H), 7.45 (t, *J* = 7.7 Hz, 1 H), 7.59 (t, *J* = 7.7 Hz, 1 H), 7.64 (d, *J* = 7.7 Hz, 1 H), 7.92 (d, *J* = 7.7 Hz, 1 H), 10.63 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 39.6, 52.2, 56.0 (×2), 56.1, 88.0, 94.7 (×2), 112.9, 114.5, 126.9, 128.5, 129.9, 133.2, 133.8, 135.6, 148.0, 150.1, 171.6, 191.7 ppm. MS (EI): *m/z* = 338 [M^+]. HRMS (EI): calcd. for $C_{20}H_{18}O_5$ 338.1154; found 338.1162.

Methyl 2-{2-[2-Formyl-6-(methoxymethoxymethyl)phenyl]ethynyl}-4,5-dimethoxyphenylacetate (11b): To a solution of 2-iodophenylacetate **6** (670 mg, 1.63 mmol), CuI (26 mg, 0.136 mmol) and $PdCl_2(PPh_3)_2$ (95 mg, 0.136 mmol) in *i*Pr_2NH (6 mL) was added a solution of 2-ethynylbenzaldehyde **7** (340 mg, 1.36 mmol) in *i*Pr_2NH (4 mL). The reaction mixture was stirred for 2 h at 100 °C. After removal of solvent, the residue was purified by column chromatography (EtOAc/hexane 3:7 v/v) to give 3-alkynylbenzaldehyde **11b** (431 mg, 77 %). M.p. 93–94 °C (EtOAc/hexane). IR (ATR): $\tilde{\nu}$ = 1731, 1693 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.42 (s, 3 H), 3.71 (s, 3 H), 3.89 (s, 2 H), 3.92 (s, 3 H), 3.93 (s, 3 H), 4.80 (s, 2 H), 4.91 (s, 2 H), 6.87 (s, 1 H), 7.06 (s, 1 H), 7.47 (t, *J* = 7.7 Hz, 1 H), 7.79 (d, *J* = 7.7 Hz, 1 H), 7.90 (d, *J* = 7.7 Hz, 1 H), 10.67 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 39.4, 52.2, 55.5, 56.0, 56.1, 67.0, 85.1, 96.2, 99.8, 112.8, 114.5, 114.6, 125.3, 126.5, 128.3, 129.7, 133.0, 136.0, 141.1, 148.1, 150.3, 171.5, 191.9 ppm. MS (EI): *m/z* = 412 [M^+]. HRMS (EI): calcd. for $C_{23}H_{24}O_7$ 412.1522; found 412.1534.

Methyl 2-[2-(2-Hydroxyiminophenyl)ethynyl]-4,5-dimethoxyphenylacetate (12a): A mixture of aldehyde **11a** (146 mg, 0.43 mmol), NH_2OHHCl (60 mg, 0.86 mmol), and AcONa (71 mg, 0.86 mmol) in EtOH (5 mL) was stirred at 80 °C for 2 h. After removal of solvent, the mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried with Na_2SO_4, and evaporated in vacuo. The residue was purified by column chromatography (EtOAc/hexane 3:7 v/v) to give oxime ether **12a** (149 mg, 98 %) as white solid. M.p. 136–138 °C (EtOAc/hexane). IR (ATR): $\tilde{\nu}$ = 1728, 1604 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.72 (s, 3 H), 3.90 (s, 2 H), 3.92 (s, 3 H), 3.92 (s, 3 H), 6.85 (s, 1 H), 7.04 (s, 1 H), 7.31–7.38 (m, 1 H), 7.55–7.58 (m, 1 H), 7.77–7.82 (m, 2 H), 8.38 (br. s, 1 H), 8.68 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 39.5, 52.2, 55.9 (×2), 56.1, 89.5, 93.1 (×2), 112.8, 114.5, 115.0, 122.9, 125.7, 128.4, 129.5, 132.8, 147.9, 149.0, 149.7, 172.0 ppm. MS (EI): *m/z* = 353 [M^+]. HRMS (EI): calcd. for $C_{20}H_{19}NO_5$ 353.1263; found 353.1245.

Methyl 2-{2-[2-Hydroxyimino-6-(methoxymethoxymethyl)phenyl]ethynyl}-4,5-dimethoxyphenylacetate (12b): The same procedure as above was carried out with aldehyde **11b** (300 mg, 0.73 mmol) to give oxime ether **12b** (286 mg, 92 %) as white solid. M.p. 111–112 °C (EtOAc/hexane). IR (ATR): $\tilde{\nu}$ = 1731, 3460 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.42 (s, 3 H), 3.72 (s, 3 H), 3.91 (s, 2 H), 3.92 (s, 3 H), 4.79 (s, 2 H), 4.87 (s, 2 H), 6.86 (s, 1 H), 7.06 (s, 1 H), 7.35 (t, *J* = 7.7 Hz, 1 H), 7.55 (d, *J* = 7.7 Hz, 1 H), 7.68 (s, 1 H), 7.77 (d, *J* = 7.7 Hz, 1 H), 7.83 (br. s, 1 H), 8.71 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 39.4, 52.3, 55.5, 56.0, 56.1, 67.5, 86.6, 96.2, 98.3, 112.8, 114.6, 115.1, 121.4, 125.0, 128.3, 128.9, 129.3, 133.3, 140.5, 148.0, 129.3, 149.9, 171.9 ppm. MS (EI): *m/z* = 427 [M^+]. HRMS (EI): calcd. for $C_{23}H_{25}NO_7$ 427.1631; found 427.1618.

3-[2-(Methoxycarbonylmethyl)-4,5-dimethoxyphenyl]isoquinolin-1-one (14a) and 1-Acetoxy-3-[2-(methoxycarbonylmethyl)-4,5-dimethoxyphenyl]isoquinoline (15a): A solution of oxime ether **12a** (100 mg, 0.28 mmol) in 1,2-dichlorobenzene (6 mL) was stirred at 180 °C for 1 h. After removal of solvent, acetic anhydride (6 mL) was added to the residue, and the mixture was stirred at 110 °C for 5 h. After removal of the solvent, the residue was purified by column chromatography (EtOAc/hexane 1:1 v/v) to give corresponding isoquinolone **14a** (42 mg, 44 %) as an orange oil and 1-acetoxyisoquinoline **15a** (34 mg, 31 %). **14a**. IR (ATR): $\tilde{\nu}$ = 1732, 1631 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.64 (s, 2 H), 3.77 (s, 3 H), 3.92 (s, 3 H), 3.94 (s, 3 H), 6.49 (s, 1 H), 6.82 (s, 1 H), 6.95 (s, 1 H), 7.49 (t, *J* = 7.7 Hz, 1 H), 7.55 (d, *J* = 7.7 Hz, 1 H), 7.68 (t, *J* = 7.7 Hz, 1 H), 8.42 (d, *J* = 7.7 Hz, 1 H), 9.59 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 38.5, 52.7, 56.1, 56.1, 106.5, 112.6, 113.2, 124.8, 125.1, 126.3, 126.7, 127.6, 127.9, 132.8, 138.0, 139.1, 148.4, 149.9, 162.9, 173.0 ppm. MS (EI): *m/z* = 353 [M^+]. HRMS (EI): calcd. for $C_{20}H_{19}NO_5$ 353.1263; found 353.1247. **15a**. IR (ATR): $\tilde{\nu}$ = 1636 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.17 (s, 3 H), 3.53 (s, 2 H), 3.61 (s, 3 H), 3.86 (s, 3 H), 3.96 (s, 3 H), 6.92 (s, 1 H), 6.94 (s, 1 H), 7.67 (dt, *J* = 1.2, 7.7 Hz, 1 H), 7.55 (dt, *J* = 1.2, 7.7 Hz, 1 H), 7.82 (d, *J* = 7.7 Hz, 1 H), 8.07 (d, *J* = 7.7 Hz, 1 H), 9.23 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.5, 38.1, 51.8, 55.9, 112.7, 113.6, 120.7, 125.6, 127.7, 127.7, 128.4, 129.1, 129.1, 130.6, 131.1, 140.1, 144.7, 147.6, 148.9, 149.8, 168.8, 172.2 ppm. MS (EI): *m/z* = 395 [M^+]. HRMS (EI): calcd. for $C_{22}H_{21}NO_6$ 395.1369; found 395.1372.

3-[2-(Methoxycarbonylmethyl)-4,5-dimethoxyphenyl]-5-(methoxymethoxymethyl)isoquinolin-1-one (14b) and 1-Acetoxy-3-[2-(methoxycarbonylmethyl)-4,5-dimethoxyphenyl]-5-(methoxymethoxymethyl)isoquinoline (15b): The same procedure as above was carried out with aldehyde **12b** (70 mg, 0.16 mmol) to give isoquinolone **14b** (23 mg, 33 %) as a yellow solid and 1-acetoxyisoquinoline **15b** (19 mg, 25 %). M.p. 144–145 °C (EtOAc/hexane). **14b**. IR (ATR): $\tilde{\nu}$ = 1731, 1650 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.40 (s, 3 H), 3.65 (s, 2 H), 3.78 (s, 3 H), 3.91 (s, 3 H), 3.94 (s, 3 H), 4.73 (s, 2 H), 4.86 (s, 2 H), 6.71 (s, 1 H), 6.83 (s, 1 H), 6.96 (s, 1 H), 7.47 (t, *J* = 7.4 Hz, 1 H), 7.72 (d, *J* = 7.4 Hz, 1 H), 8.41 (d, *J* = 7.4 Hz, 1 H), 9.59 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 38.5, 52.7, 55.6, 56.1, 56.1, 66.8, 95.7, 102.8, 112.6, 113.2, 124.8, 125.6, 126.2, 127.7, 128.0, 132.7, 133.2, 136.6, 139.3, 148.4, 150.0, 162.9, 172.9 ppm. MS (EI): *m/z* = 427 [M^+]. HRMS (EI): calcd. for $C_{23}H_{25}NO_7$ 427.1631; found 427.1620. **15b**. IR (ATR): $\tilde{\nu}$ = 1650 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.00 (s, 3 H), 3.36 (s, 3 H), 3.47 (s, 2 H), 3.65 (s, 3 H), 3.88 (s, 3 H), 3.95 (s, 3 H), 4.62 (s, 2 H), 5.09 (br. s, 2 H), 6.94 (s, 1 H), 6.95 (s, 1 H), 7.62 (t, *J* = 7.7 Hz, 1 H), 7.84 (d, *J* = 7.7 Hz, 1 H), 8.01 (d, *J* = 7.7 Hz, 1 H), 9.22 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.1, 38.0, 51.8, 55.4, 56.0, 56.0, 56.1, 67.7, 94.7, 113.1, 113.5, 125.5, 127.2, 128.3, 129.5, 130.4, 131.7, 132.7, 140.3, 146.8, 147.6, 148.9, 150.5, 168.7, 172.3 ppm. MS (EI): *m/z* = 469 [M^+]. HRMS (EI): calcd. for $C_{25}H_{27}NO_8$ 469.1737; found 469.1758.

3-(2-Hydroxyethyl-4,5-dimethoxyphenyl)isoquinolin-1-one (16a): A solution of 1-acetoxyisoquinoline **14a** (80 mg, 0.23 mmol)

in THF (5 mL) was added dropwise to an ice/water-cooled suspension of $LiAlH_4$ (43 mg, 1.15 mmol) in THF (5 mL). After stirring at 70 °C for 10 min, the reaction mixture was quenched with water, and filtered through a Celite pad. The filtrate was extracted with EtOAc. The organic layer was washed with brine, dried with Na_2SO_4, and evaporated in vacuo. The residue was purified by column chromatography (EtOAc/hexane 1:1, v/v) to give alcohol **16a** (43 mg, 57 %) as a yellow oil. IR (ATR): $\tilde{\nu}$ = 1635 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.83 (t, J = 5.3 Hz, 2 H), 3.88 (s, 3 H), 3.93 (s, 3 H), 4.10 (t, J = 5.3 Hz, 2 H), 4.92 (br. s, 1 H), 6.54 (s, 1 H), 6.81 (s, 1 H), 6.89 (s, 1 H), 7.46 (t, J = 7.9 Hz, 1 H), 7.56 (d, J = 7.9 Hz, 1 H), 7.66 (t, J = 7.9 Hz, 1 H), 8.35 (d, J = 7.9 Hz, 1 H), 11.61 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 34.7, 56.0, 56.1, 63.1, 106.4, 112.4, 112.8, 124.5, 126.1, 126.3, 127.4, 128.0, 130.3, 132.5, 138.4, 140.6, 147.4, 150.1, 163.4 ppm. MS (EI): m/z = 325 [M^+]. HRMS (EI): calcd. for $C_{19}H_{19}NO_4$ 325.1314; found 325.1304.

3-(2-Hydroxyethyl-4,5-dimethoxyphenyl)-5-(methoxymethoxymethyl)isoquinolin-1-one (16b): The same procedure as above was carried out with isoquinolone **14b** (70 mg, 0.16 mmol) to give alcohol **16b** (46 mg, 71 %) as a yellow solid. M.p. 177–178 °C (EtOAc/hexane). IR (ATR): $\tilde{\nu}$ = 3733, 1735 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.85 (t, J = 5.1 Hz, 2 H), 3.41 (s, 3 H), 3.88 (s, 3 H), 3.94 (s, 3 H), 4.09 (t, J = 5.1 Hz, 2 H), 4.74 (s, 2 H), 4.89 (s, 2 H), 6.75 (s, 1 H), 6.82 (s, 1 H), 6.92 (s, 1 H), 7.44 (t, J = 7.7 Hz, 1 H), 7.71 (d, J = 7.7 Hz, 1 H), 8.40 (d, J = 7.7 Hz, 1 H), 11.34 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 34.7, 55.6, 56.0, 56.1, 63.2, 67.0, 95.8, 102.7, 112.5, 112.9, 125.0, 125.8, 127.6, 128.2, 130.5, 132.4, 133.1, 137.1, 140.9, 147.5, 150.2, 163.4 ppm. MS (EI): m/z = 399 [M^+]. HRMS (EI): calcd. for $C_{22}H_{25}NO_6$ 399.1682; found 399.1666.

16a from 12a: A solution of oxime ether **12a** (100 mg, 0.28 mmol) in 1,2-dichlorobenzene (5 mL) was stirred at 180 °C for 1 h. After removal of solvent, acetic anhydride (5 mL) was added to the residue, and then stirred at 110 °C for 5 h. After removal of solvent, the residue was purified by column chromatography (EtOAc/hexane 1:1 v/v) to give a mixture of isoquinolone **14a** and 1-acetoxyisoquinoline **15a**. The mixture in THF (5 mL) was added dropwise to an ice/water-cooled solution of $LiAlH_4$ (16 mg, 0.42 mmol) in THF (5 mL). After stirring at 70 °C for 10 min, the reaction mixture was quenched with water, and filtered through a Celite pad. The filtrate was extracted with EtOAc. The organic layer was washed with brine, dried with Na_2SO_4, and evaporated in vacuo. The residue was purified by column chromatography (EtOAc/hexane 1:1, v/v) to give alcohol **16a** (56 mg, 62 %).

16b from 12b: The same procedure as above was carried out with oxime ether **12b** (200 mg, 0.47 mmol) to give alcohol **16b** (127 mg, 68 %).

2,3-Dimethoxy-8-oxoprotoberberine (17a): A mixture of alcohol **16a** (68 mg, 0.21 mmol), K_2CO_3 (116 mg, 0.84 mmol), and *p*-toluenesulfonyl chloride (104 mg, 0.55 mmol) in dimethylformamide (DMF; 5 mL) was stirred at 100 °C for 18 h. The reaction mixture was quenched with water, and extracted with EtOAc. The organic layer was washed with water, HCl (1 M), $NaHCO_3$ (aq. 20 %) and brine, dried with Na_2SO_4, and evaporated in vacuo. The residue was purified by column chromatography (EtOAc/hexane 1:1, v/v) to give 8-oxoprotoberberine **17a** (39 mg, 60 %) as a yellow solid. M.p. 132–134 °C (EtOAc/hexane). IR (ATR): $\tilde{\nu}$ = 1643 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.96 (t, J = 5.9 Hz, 2 H), 3.95 (s, 3 H), 4.01 (s, 3 H), 4.38 (t, J = 5.9 Hz, 2 H), 6.75 (s, 1 H), 6.90 (s, 1 H), 7.28 (s, 1 H), 7.44 (dt, J = 1.3, 7.6 Hz, 1 H), 7.57 (d, J = 7.6 Hz, 1 H), 7.63 (dt, J = 1.3, 7.6 Hz, 1 H), 8.44 (d, J = 7.6 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.1, 39.7, 56.1, 56.3, 101.5, 107.9, 110.5, 122.3, 124.6, 125.9, 126.2, 128.0, 128.8, 132.3, 136.7, 137.4, 148.5, 150.4, 162.3 ppm. MS (EI): m/z = 307 [M^+]. HRMS (EI): calcd. for $C_{19}H_{17}NO_3$ 307.1208; found 307.1222.

2,3-Dimethoxy-12-(methoxymethoxymethyl)-8-oxoprotoberberine (17b): The same procedure as above was carried out with alcohol **16b** (60 mg, 0.14 mmol) to give 8-oxoprotoberberine **17b** (26 mg, 56 %) as a yellow solid. M.p. 147–148 °C (EtOAc/hexane). IR (ATR): $\tilde{\nu}$ = 1735 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.95 (t, J = 6.2 Hz, 2 H), 3.45 (s, 3 H), 3.95 (s, 3 H), 4.00 (s, 3 H), 4.37 (t, J = 6.2 Hz, 2 H), 4.77 (s, 2 H), 4.94 (s, 2 H), 6.76 (s, 1 H), 7.15 (s, 1 H), 7.33 (s, 1 H), 7.42 (t, J = 7.8 Hz, 1 H), 7.67 (d, J = 7.8 Hz, 1 H), 8.44 (d, J = 7.8 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.1, 39.8, 55.7, 56.1, 56.3, 67.0, 95.7, 97.8, 108.4, 110.5, 122.6, 125.1, 125.7, 128.4, 129.0, 132.1, 133.1, 135.5, 137.7, 148.5, 150.5, 162.3 ppm. MS (EI): m/z = 381 [M^+]. HRMS (EI): calcd. for $C_{22}H_{23}NO_5$ 381.1576; found 381.1585.

2,3-Dihydroxy-8-oxoprotoberberine (18): BBr_3 (0.01 mL, 0.121 mmol) was added dropwise to a solution of 8-oxoprotoberberine **17a** (33 mg, 0.11 mmol) in CH_2Cl_2 (10 mL) at –78 °C. After stirring at room temp. for 1 h, the reaction mixture was quenched with ice-water, and extracted with CH_2Cl_2. The organic layer was washed with brine, dried with Na_2SO_4, and evaporated in vacuo. The residue was purified by column chromatography (EtOAc/hexane 1:1, v/v) to give 8-oxoprotoberberine **18** (16 mg, 52 %). M.p. 152–153 °C (EtOAc/hexane). IR (ATR): $\tilde{\nu}$ = 1639 cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 2.81 (t, J = 6.5 Hz, 2 H), 4.17 (t, J = 6.5 Hz, 2 H), 6.70 (s, 1 H), 7.00 (s, 1 H), 7.30 (s, 1 H), 7.43 (t, J = 7.3 Hz, 1 H), 7.64–7.71 (m, 2 H), 8.19 (d, J = 7.3 Hz, 1 H), 9.07 (br. s, 1 H), 9.57 (br. s, 1 H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 26.9, 40.7, 99.8, 112.1, 114.5, 120.4, 123.5, 125.7, 126.3, 127.0, 127.2, 132.3, 136.7, 137.8, 144.8, 147.4, 161.0 ppm. MS (EI): m/z = 279 [M^+]. HRMS (EI): calcd. for $C_{17}H_{13}NO_3$ 279.0895; found 279.0884.

Alangiumkaloid B (2): The same procedure as above was carried out with 8-oxoprotoberberine **17b** (27 mg, 0.071 mmol) to give alangiumkaloid B (**2**; 13 mg, 62 %) as a yellow solid. M.p. 123–126 °C (EtOAc/hexane). IR (ATR): $\tilde{\nu}$ = 1636 cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 2.88 (t, J = 6.5 Hz, 2 H), 4.23 (t, J = 6.5 Hz, 2 H), 5.21 (s, 2 H), 6.77 (s, 1 H), 7.16 (s, 1 H), 7.43 (t, J = 7.6 Hz, 1 H), 7.51 (s, 1 H), 7.85 (d, J = 7.6 Hz, 1 H), 8.26 (d, J = 7.6 Hz, 1 H), 9.20 (br. s, 1 H), 9.74 (br. s, 1 H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 27.0, 60.9, 96.4, 112.3, 114.6, 120.5, 123.8, 125.2, 126.3, 127.4, 130.7, 134.6, 137.0, 137.7, 144.9, 147.7, 161.2 ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 28.5, 41.5, 63.0, 99.2, 113.1, 115.3, 122.5, 125.3, 126.7, 128.1, 129.2, 132.9, 136.8, 137.4, 139.2, 146.2, 148.9, 164.1 ppm. MS (EI): m/z = 309 [M^+]. HRMS (EI): calcd. for $C_{18}H_{15}NO_4$ 309.1001; found 309.1017.

12-Hydroxymethyl-2,3-dimethoxy-8-oxopotoberberine (19): HCl (aq. 6 M, 2 mL) was added dropwise to a solution of 8-oxoprotoberberine **17b** (28 mg, 0.073 mmol) in MeOH (2 mL). After stirring at room temp. for 48 h, the reaction mixture was quenched with water, and extracted with EtOAc. The organic layer was washed with brine, dried with Na_2SO_4, and evaporated in vacuo. The residue was purified by column chromatography (EtOAc/hexane 1:1, v/v) to give alcohol **19** (20 mg, 81 %) as white solid. M.p. 211–212 °C (EtOAc/hexane). IR (ATR): $\tilde{\nu}$ = 1735 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.09 (br. s, 1 H), 2.93 (t, J = 6.0 Hz, 2 H), 3.96 (s, 3 H), 4.00 (s, 3 H), 4.35 (t, J = 6.0 Hz, 2 H), 5.03 (d, J = 6.0 Hz, 2 H), 6.74 (s, 1 H), 7.15 (s, 1 H), 7.30 (s, 1 H), 7.34 (t, J = 7.7 Hz, 1 H), 7.61 (d, J = 7.7 Hz, 1 H), 8.34 (d, J = 8.1 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.1, 39.8, 56.1, 56.4, 63.4, 97.9, 108.4, 110.5, 122.4, 125.0, 125.7, 128.2, 129.0, 131.8, 135.1, 135.1, 137.7, 148.5, 150.6, 162.3 ppm. MS (EI): m/z = 337 [M^+]. HRMS (EI): calcd. for $C_{20}H_{19}NO_4$ 337.1314; found 337.1314.

2,3-Dimethoxy-8-oxoprotoberberine-12-carbaldehyde (20): A suspension of alcohol **19** (18 mg, 0.053 mmol) and active MnO_2 (22 mg, 0.25 mmol) in CH_2Cl_2 (3 mL) was stirred at room temp. for 70 h. The reaction mixture was filtered through a Celite pad. The filtrate was evaporated in vacuo. The residue was purified by column chromatography (EtOAc/hexane 1:1, v/v) to give aldehyde **20** (10 mg, 56 %) as white solid. M.p. 233–235 °C (EtOAc/hexane). IR (ATR): $\tilde{\nu}$ = 1646, 1735 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.97 (t, J = 6.2 Hz, 2 H), 3.96 (s, 3 H), 4.04 (s, 3 H), 4.38 (t, J = 6.2 Hz, 2 H), 6.75 (s, 1 H), 7.41 (s, 1 H), 7.57 (t, J = 7.7 Hz, 1 H), 8.08 (d, J = 7.7 Hz, 1 H), 8.41 (s, 1 H), 8.71 (d, J = 7.7 Hz, 1 H), 10.30 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.9, 39.8, 56.1, 56.3, 98.1, 108.6, 110.4, 122.0, 125.1, 125.6, 129.1, 129.8, 134.4, 136.0, 140.8, 140.9, 148.7, 151.0, 161.6, 193.0 ppm. MS (EI): m/z = 335 [M^+]. HRMS (EI): calcd. for $C_{20}H_{17}NO_4$ 335.1158; found 335.1144.

Alangiumkaloid A (1) from 2: A suspension of alangiumkaloid B (**2**; 10 mg, 0.032 mmol) and active MnO_2 (28 mg, 0.32 mmol) in CH_2Cl_2 (5 mL) was stirred at room temp. for 48 h. The reaction mixture was filtered through a Celite pad. The filtrate was evaporated in vacuo. The residue was purified by column chromatography (EtOAc/hexane 1:1, v/v) to give aldehyde **20** (4 mg, 42 %) as a yellow solid. M.p. 152–154 °C (EtOAc/hexane). IR (ATR): $\tilde{\nu}$ = 1636, 1756 cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 2.83 (t, J = 6.7 Hz, 2 H), 4.18 (t, J = 6.7 Hz, 2 H), 6.71 (s, 1 H), 7.34 (s, 1 H), 7.62 (t, J = 7.6 Hz, 1 H), 8.15 (s, 1 H), 8.27 (d, J = 7.6 Hz, 1 H), 8.50 (d, J = 7.6 Hz, 1 H), 9.34 (br. s, 1 H), 9.64 (br. s, 1 H), 10.32 (s, 1 H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 26.6, 95.8, 112.2, 114.7, 120.0, 124.5, 125.1, 128.0, 129.4, 133.6, 135.5, 140.7, 141.0, 145.0, 148.2, 160.6, 194.0 ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 28.2, 41.4, 98.9, 113.3, 115.4, 122.0, 125.9, 126.3, 128.8, 129.7, 131.4, 134.8, 137.3, 142.5, 146.3, 149.5, 163.3, 164.8 ppm. MS (EI): m/z = 307 [M^+]. HRMS (EI): calcd. for $C_{18}H_{13}NO_4$ 307.0845; found 307.0855.

Alangiumkaloid A (1) from 20: BBr_3 (0.01 mL, 0.1 mmol) was added dropwise to a solution of aldehyde **20** (30 mg, 0.1 mmol) in CH_2Cl_2 (5 mL) at –78 °C. After stirring at room temp. for 1 h, the reaction mixture was quenched with water, and extracted with CH_2Cl_2. The organic layer was washed with brine, dried with Na_2SO_4, and evaporated in vacuo. The residue was purified by column chromatography (EtOAc/hexane 1:1, v/v) to give alangiumkaloid A (**1**; 20 mg, 65 %).

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