Total Synthesis of Surinamensinols A and B

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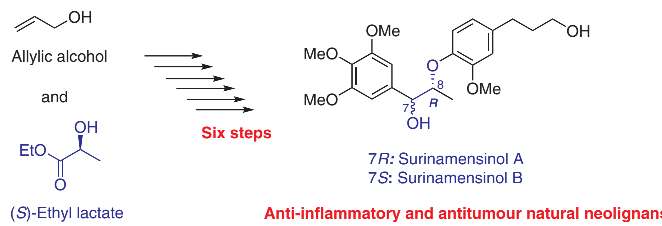


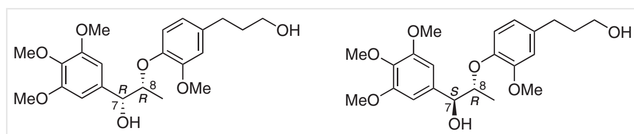
Received: 08.09.2020
Accepted after revision: 24.09.2020
Published online: 15.10.2020
DOI: 10.1055/s-0040-1707325; Art ID: so-2020-d0031-op
Crowd-Reviewed

Abstract An efficient total synthesis of the naturally occurring anti-inflammatory and antitumour 8-*O*-4′-neolignans, surinamensinols A and B, has been accomplished from commercially available allyl alcohol and (*S*)-ethyl lactate. The synthetic sequence involves a palladium-catalysed Suzuki–Miyaura cross-coupling reaction followed by a chiral Mitsunobu reaction as the key steps. This is the first report of the simultaneous stereoselective total synthesis of surinamensinols A and B through a single approach involving only six steps.

Keywords Surinamensinol A B, anti-inflammatory and antitumour neolignans, stereoselective total synthesis, Suzuki–Miyaura cross coupling, Mitsunobu reaction

Lignans and neolignans are common, naturally occurring secondary plant metabolites that are generated via the shikimic acid pathway.[1,2] Large numbers of natural products of these categories have been found in plants.[3,4] These plant metabolites exhibit a wide range of biological properties, such as antileishmanial, platelet activity factor (PAF) antagonism, antiparasitic, trypanocidal, antimalarial and anticancer activities.[5–8] The surinamensinols are recently disclosed examples of these classes of compounds. Two new diastereomeric 8-*O*-4′-neolignans, surinamensinols A (**1**) and B (**2**) (Figure 1), along with thirteen other phenolic derivatives, have recently been isolated from the rhizome extracts of an aquatic perennial herbaceous plant, *Acorus gramineus* Soland (*Araceae*), which is widely distributed in China, Korea and Japan.[9]

Surinamensinol A (**1**) possesses the (7*R*,8*R*)-configuration, whereas surinamensinol B (**2**) possesses the (7*S*,8*R*)-configuration (Figure 1). Compounds **1** and **2** exhibit impressive anti-inflammatory and antitumour activities and significant inhibition of nitric oxide (NO) levels in LPS-stimulated BV-2 cells.[9] They also showed potentially useful cytotoxicity towards the A549 cell line and displayed significant antiproliferative activity against SK-OV-3, SK-MEL-2, and HCT-15 cell lines.[9]

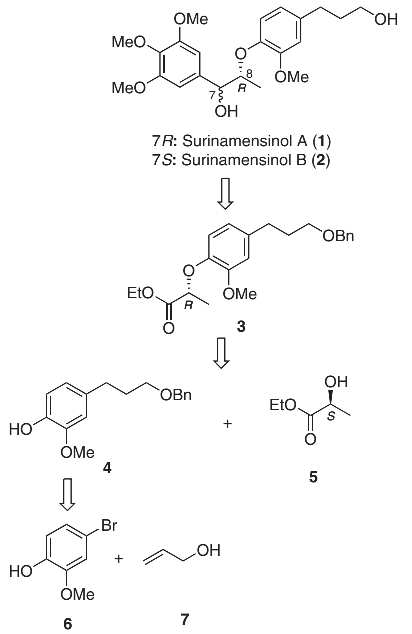


Surinamensinol A (**1**) Surinamensinol B (**2**)

Figure 1 Chemical structures of surinamensinols A (**1**) and B (**2**)

In a continuation of our work[10,11] on the synthesis of natural products, we herein disclose the stereoselective total synthesis of surinamensinols A (**1**) and B (**2**). Our present work involves the preparation of both diastereomeric 8-*O*-4′-oxyneolignans, surinamensinols A (**1**) and B (**2**) simultaneously from easily available allyl alcohol and (*S*)-ethyl lactate. Previously, surinamensinol A (**1**) was synthesized by Das et al. in 16 steps in an overall yield of 10%.[12] On the other hand, surinamensinol B (**2**) was synthesized by Lalwani and Sudalai by following a synthetic sequence that involved 18 steps, with the target molecule **2** being formed in an overall yield of 17%.[13]

The retrosynthetic analysis of compounds **1** and **2** indicated that both molecules could be synthesized from the chiral ester **3**, derived from the phenol benzyl ether **4** and (*S*)-ethyl lactate **5**. Compound **4** can, in turn, be obtained from 4-bromo-2-methoxyphenol **6** and allyl alcohol **7** (Scheme 1).

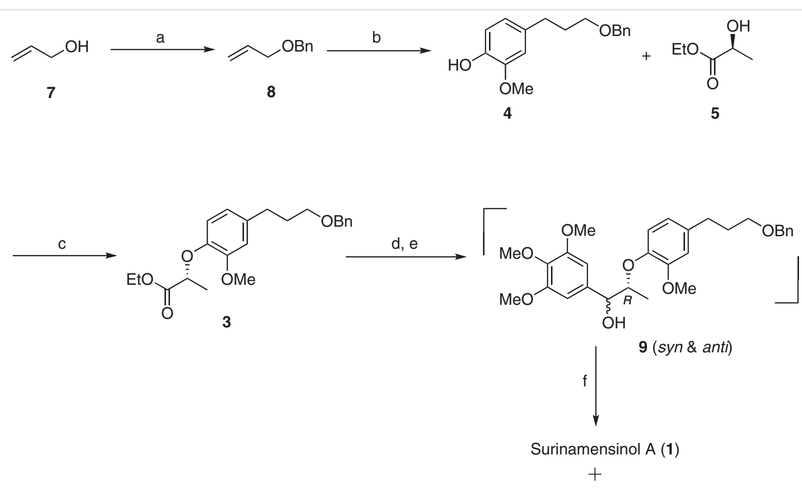


Scheme 1 Retrosynthetic analysis of surinamensinols A (**1**) and B (**2**)

Our synthesis was initiated with allyl alcohol **7** (Scheme 2), which was reacted with benzyl bromide in the presence of NaH in anhydrous THF when the primary hydroxyl group of the former was protected to furnish the product **8** in high yield (98%). We also attempted the reaction with the TBS protecting group but due to the low volatility of the product it was difficult to isolate. Compound **8** underwent hydroboration[14] with 9-BBN (9-borabicyclo[3.3.1]nonane solution 0.5 M in THF) to form a protected allyl diorganoborane adduct that was not isolated, but was treated in situ with 4-bromo-2-methoxyphenol (**6**) in the presence of $Pd(PPh_3)_4$ in anhydrous THF at reflux for 12 h (Suzuki–Miyaura coupling reaction conditions) to yield the phenol benzyl ether **4** (86%), which was further purified and separated.[15] Compound **4** was coupled with (*S*)-ethyl lactate (**5**) under Mitsunobu reaction conditions using diisopropyl azodicarboxylate (DIAD) and PPh_3 in anhydrous THF to afford the desired chiral ester **3** in high yield (88%).[16,17] The Mitsunobu reaction with similar substrates is well known and previous workers also obtained products with clean inversion.[18] We followed the experimental procedure of these earlier studies to generate compound **3**.

Reduction of compound **3** with DIBAL-H at –78 °C to 0 °C gave the corresponding aldehyde in good yield, which was then treated with 3,4,5-trimethoxyphenyl magnesium bromide in anhydrous THF.[18] A mixture of products was formed. We presumed this mixture might contain the *syn*- and *anti*-diastereomers of compound **9** (as evident from the next step and also from the HRMS, which showed *m*/*z* 519.2347 $[M+Na^{+\cdot}]$) along with a similar amount of starting materials. TLC and HPLC examination did not result in clean resolution of the constitutes of the mixture. We were also unable to obtain a meaningful ^1H NMR spectrum of the mixture due to solubility problems with the product mixture.

Finally, we attempted the removal of the benzyl ether from the mixture **9** by hydrogenation in the presence of 10% Pd-C.[19] We were pleased to observe that this conversion yielded a separable mixture of surinamensinol A (**1**) and surinamensinol B (**2**), which could be separated and



Scheme 2 *Reagents and conditions*: (a) NaH, BnBr, anhydrous THF, 0 °C to room temperature, 4 h, 98%; (b) (i) 9-BBN, anhydrous THF, 0 °C to room temperature, 2 h (ii) 4-bromo-2-methoxyphenol **6**, $Pd(PPh_3)$, anhydrous THF, reflux, 12 h, 86% (2 steps); (c) PPh_3, DIAD, anhydrous THF, reflux, 24 h, 88%; (d) DIBAL-H, anhydrous DCM, –78 °C, 30 min (e) (3,4,5-trimethoxyphenyl) magnesium bromide, anhydrous THF, 0 °C to room temperature, 19 h; (f) 10% Pd/C, H_2, EtOAc, room temperature, 2 h, 49% (combined **1** and **2** from compound **3**).

purified by column chromatography. The physical and spectroscopic properties of these compounds were found to be identical to those reported for the natural products.[9]

In conclusion, an efficient approach to the total synthesis of anti-inflammatory and antitumour 8-*O*-4′-neolignans, surinamensinols A (**1**) and B (**2**), has been described. The key steps in the synthetic sequence include a Pd-catalysed Suzuki–Miyaura cross-coupling reaction and a chiral Mitsunobu protocol as key steps. This approach resulted in the preparation of **1** and **2**, which were subsequently separated by column chromatography. The overall yields of **1** and **2** starting from **7** were 14 and 22%, respectively, from only six synthetic steps. This is the first report of the total synthesis of surinamensinols **A** and **B** by a common approach.

All experiments were carried out in dry reaction vessels under dry nitrogen atmosphere. All reagents were purchased from Sigma–Aldrich, Germany. Solvents were purified and dried according to standard procedures. Analytical data were recorded with the following instruments: Specific rotations were measured using the sodium D line with a Kruss Optronic polarimeter. IR spectra were recorded with a Perkin Elmer RX FT-IR spectrophotometer, wave numbers (ν) being reported in cm^{-1}. High-resolution electrospray ionization mass spectra (HR-ESI-MS) were recorded with an Agilent 6530 LC Q-TOF. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker NMR spectrometer operating at 600 MHz (150 MHz for ^{13}C) and 200 MHz (50 MHz for ^{13}C) using the solvent peak as the internal reference ($CDCl_3$, δ_H = 7.26 ppm; δ_C = 77.0 ppm). Data are reported in the following order: chemical shift (δ, ppm), multiplicities and coupling constants (*J*, Hz). Column chromatography was carried out by using 100–200 mesh particle size silica gel. All reactions were monitored by thin-layer chromatography (TLC) using silica gel F_{254} pre-coated plates. Visualization was accomplished with UV-light and I_2 staining. Solvents for column chromatography (EtOAc, *n*-hexane) were technical grade and distilled prior to use. Organic extracts were dried over anhydrous $MgSO_4$.

Allyl Benzyl Ether 8

To a suspension of NaH (0.155 g, 6.48 mmol) in anhydrous THF (25 mL) a solution of **7** (0.250 g, 4.31 mmol) in anhydrous THF (10 mL) was added dropwise at 0 °C under nitrogen. After stirring for 30 min, benzyl bromide (0.62 mL, 5.17 mmol) was added slowly dropwise and the reaction mixture was stirred at r.t. for 4 h. After completion of the reaction, the reaction was quenched with saturated aq. NH_4Cl at 0 °C and the mixture was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with water (2 × 20 mL) and brine solution (10 mL), and dried over anhydrous $MgSO_4$. After filtration, the solvent was removed under reduced pressure. The crude product was purified by column chromatography to afford compound **8**.

Yield: 0.624 g (98%); pale-yellow liquid; R_f = 0.78 (hexane/EtOAc, 9:1).

IR (KBr): 2854, 1495, 1453, 1227, 1067, 1027, 919, 735, 694 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.35–7.32 (m, 4 H), 7.29–7.25 (m, 1 H), 5.94 (ddt, *J* = 17.2, 10.4, 5.6 Hz, 1 H), 5.29 (dq, *J* = 17.2, 1.7 Hz, 1 H), 5.19 (dq, *J* = 10.4, 1.4 Hz, 1 H), 4.51 (s, 2 H), 4.02 (dt, *J* = 5.6, 1.5 Hz, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 138.3, 134.7, 128.4, 127.7, 127.6, 117.1, 72.1, 71.1.

HRMS (ESI$^+$): *m*/*z* [$M^{+\cdot}$] calcd for $C_{10}H_{12}O$: 148.1139; found: 148.1137; *m*/*z* [M + H^+] calcd for $C_{10}H_{13}O$: 149.1156; found: 149.1158.

4-(3-Benzyloxypropyl)-2-methoxyphenol (4)

To compound **8** (0.300 g, 2.02 mmol) in anhydrous THF (10 mL) at 0 °C under nitrogen was added 9-BBN (0.5 M in THF, 4.85 mL, 2.42 mmol) dropwise. The reaction mixture was warmed to r.t. and stirred for 2 h. The flask was covered with foil and aq. NaOH (3 M, 2.02 mL) was slowly added at 0 °C (**CARE**: H_2 evolution) and then flushed for 10–15 min with nitrogen. A solution of Pd $(PPh_3)_4$ (0.040 g, 0.034 mmol) in anhydrous THF (15 mL) was added, and then a solution of 4-bromo-2-methoxyphenol (**6**; 0.451 g, 2.22 mmol) in anhydrous THF was added dropwise to the reaction mixture at 0 °C under nitrogen. The reaction mixture was heated to reflux for 12 h. After completion of the reaction, as monitored by TLC, the reaction was quenched with sat. aq. NH_4Cl at 0 °C. The crude reaction product was dissolved in THF (3 mL, 0.2 mmol of alkene) and aqueous NaOH (1 M, 1 mL, 0.2 mmol of alkene) was added, followed by aqueous H_2O_2 (60 % w/v, 0.2 mmol: 0.2 mmol of alkene) and the mixture was stirred vigorously for 10–15 minutes at 0 °C. The residue was filtered and extracted with ether (3 × 10 mL). The combined organic extracts were washed with water (2 × 20 mL) and brine (10 mL), filtered, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude product, was purified by column chromatography to afford compound **4**.

Yield: 0.473 g (86%); pale-brown liquid; R_f = 0.56 (hexane/EtOAc, 9:1).

IR (KBr): 3332, 2940, 2830, 1495, 1446, 1397, 1250, 1220, 1181, 1132, 840, 769 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.33 (d, *J* = 4.4 Hz, 4 H), 7.27 (ddd, *J* = 8.8, 4.9, 3.9 Hz, 1 H), 6.80 (d, *J* = 8.0 Hz, 1 H), 6.68–6.64 (m, 2 H), 5.43 (brs, 1 H), 4.49 (s, 2 H), 3.83 (s, 3 H), 3.47 (t, *J* = 6.3 Hz, 2 H), 2.63 (dd, *J* = 8.6, 6.8 Hz, 2 H), 1.91–1.87 (m, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 146.3, 143.6, 138.6, 133.9, 128.4, 127.7, 127.5, 121.0, 114.1, 111.0, 73.0, 69.5, 55.8, 32.1, 31.7.

HRMS (ESI$^+$): *m*/*z* [M + H^+] calcd for $C_{17}H_{21}O_3$: 273.1506; found: 273.1508.

(*R*)-Ethyl 2-(4-(3-(Benzyloxy)propyl)-2-methoxyphenoxy)propanoate (3)

A mixture of **5** (0.150 g, 1.27 mmol), **4** (0.415 g, 1.52 mmol), triphenylphosphine (0.432 g, 1.65 mmol), and DIAD (0.33 mL, 1.65 mmol) in anhydrous THF (15 mL) was heated to reflux for 24 h under nitrogen. After completion of the reaction, as monitored by TLC, the mixture was cooled to 0 °C, the reaction was quenched with sat. aq. NH_4Cl and the mixture was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with water (2 × 20 mL), brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by column chromatography to afford compound **3**.

Yield: 0.415 g (88%); pale-brown liquid; R_f = 0.60 (hexane/EtOAc, 9:1); $[\alpha]_D^{22}$ = +0.94 (*c* = 0.016, $CHCl_3$).

IR (KBr): 2984, 1734, 1589, 1493, 1444, 1396, 1250, 1195, 1179, 1046, 849, 783 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.33 (d, *J* = 4.4 Hz, 4 H), 7.29–7.25 (m, 1 H), 6.75 (d, *J* = 8.1 Hz, 1 H), 6.70 (d, *J* = 2.0 Hz, 1 H), 6.63 (dd, *J* = 8.1, 2.0 Hz, 1 H), 4.68 (q, *J* = 6.8 Hz, 1 H), 4.49 (d, *J* = 3.4 Hz, 2 H), 4.19 (qd, *J* = 7.1, 4.4 Hz, 2 H), 3.81 (s, 3 H), 3.46 (t, *J* = 6.4 Hz, 2 H), 2.65–2.62 (m, 2 H), 1.91–1.87 (m, 2 H), 1.60 (d, *J* = 6.8 Hz, 3 H), 1.23 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.4, 149.9, 145.1, 138.6, 136.6, 128.4, 127.6, 127.5, 120.3, 116.4, 112.7, 74.4, 73.0, 69.5, 61.0, 55.9, 32.0, 31.5, 18.6, 14.1.

HRMS (ESI$^+$): *m*/*z* [M + H$^+$] calcd for $C_{22}H_{29}O_5$: 373.1314; found: 373.1312.

(2*R*)-2-(4-(3-(Benzyloxy)propyl)-2-methoxyphenoxy)-1-(3,4,5-trimethoxyphenyl)propan-1-ol (9)

To a stirred solution of ester **3** (0.160 g, 0.43 mmol) in anhydrous CH_2Cl_2 (10 mL), DIBAL-H (1 M in THF, 0.64 mL, 0.64 mmol) was added dropwise at –78 °C under nitrogen and the reaction mixture was stirred for 30 min. The reaction was quenched with 2 M HCl (8 mL) and the mixture was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were washed with water (2 × 20 mL), and brine (10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The aldehyde (0.128 g, 0.38 mmol) thus obtained as a colourless oil was immediately used after flash column chromatography for the subsequent reaction.

To a stirred solution of the aldehyde (0.128 g, 0.38 mmol) from the preceding step in anhydrous THF (10 mL), 3,4,5-trimethoxyphenyl magnesium bromide (0.5 M in THF, 1.80 mL, 0.90 mmol) was added dropwise at 0 °C under nitrogen and the reaction mixture was stirred at r.t. for 19 h. After completion of the reaction, as monitored by TLC, the mixture was cooled to 0 °C, the reaction was quenched with sat. aq. NH_4Cl, and the mixture was extracted with Et_2O (2 × 25 mL). The combined organic extracts were washed with water (2 × 20 mL), brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to obtain a brown gum (0.164 g) that was presumed to be a mixture of *syn*- and *anti*-diastereomers of **9** (as evident from the next reaction) along with starting materials. We proceeded with the next step with this crude material.

Surinamensinols A (1) and B (2)

To a stirred solution of crude compound **9** (0.082 g) in anhydrous EtOAc (5 mL) was added a catalytic amount of Pd/C (10%) and the reaction mixture was stirred at r.t. under hydrogen for 2 h. After completion of the reaction, as monitored by TLC, the mixture was filtered, washed with EtOAc (3 × 10 mL) and the filtrate was concentrated under reduced pressure to furnish a gum. This was purified by silica gel column chromatography, using hexane and EtOAc as eluent, to afford **1** (0.018 g) and **2** (0.027 g). The combined yields of **1** and **2** were 49% from compound **3** and the overall yield from the whole sequence of **1** was 14% and that of **2** was 22%.

Surinamensinol A (1)

R_f = 0.30 (hexane/EtOAc, 3:2); $[\alpha]_D^{22}$ = –60.5 (*c* = 1.0, $CHCl_3$; 95% *ee*).

IR (KBr): 3432, 2927, 2845, 1459, 1233, 1125 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.92 (d, *J* = 8.0 Hz, 1 H), 6.78 (d, *J* = 2.0 Hz, 1 H), 6.73 (dd, *J* = 8.0, 2.0 Hz, 1 H), 6.60 (s, 2 H), 4.62 (d, *J* = 7.0 Hz, 1 H), 4.06 (m, 1 H), 3.88 (s, 9 H), 3.85 (s, 3 H), 3.69 (t, *J* = 7.0 Hz, 2 H), 2.63 (t, *J* = 7.0 Hz, 2 H), 1.91–1.82 (m, 2 H), 1.21 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 153.3, 150.7, 146.2, 145.3, 138.2, 137.3, 135.2, 121.1, 119.3, 112.2, 104.7, 83.3, 77.5, 62.2, 56.2, 34.3, 32.1, 17.0.

HRMS (ESI$^+$): *m*/*z* [M + Na$^+$] calcd for $C_{22}H_{30}O_7Na$: 429.1994; found: 429.1992.

Surinamensinol B (2)

R_f = 0.24 (hexane/EtOAc, 3:2); $[\alpha]_D^{25}$ = –11.4 (*c* = 0.2, CH_3OH; 96% *ee*).

IR (KBr): 3389, 2952, 1601, 1510, 1278, 1036 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.95 (d, *J* = 8.0 Hz, 1 H), 6.78 (d, *J* = 2.0 Hz, 1 H), 6.76 (dd, *J* = 8.0, 2.0 Hz, 1 H), 6.57 (s, 2 H), 4.80 (d, *J* = 3.5 Hz, 1 H), 4.35 (dq, *J* = 6.5, 3.5 Hz, 1 H), 3.88 (s, 3 H), 3.85 (s, 6 H), 3.83 (s, 3 H), 3.68 (t, *J* = 6.5 Hz, 2 H), 2.70 (t, *J* = 7.5 Hz, 2 H), 1.89 (m, 2 H), 1.17 (d, *J* = 6.5 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 153.1, 151.0, 144.5, 137.3, 135.9, 121.0, 119.3, 112.5, 103.4, 82.1, 73.8, 62.0, 60.8, 56.1, 55.8, 34.4, 31.6, 13.2.

HRMS: *m*/*z* [M + Na$^+$] calcd for $C_{22}H_{30}O_7Na$: 429.1990; found: 429.1992.

Funding Information

The authors would like to thank the University of Nizwa for the generous support of this project.

Acknowledgment

We thank the technical and analytical staff of the University of Nizwa for assistance.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707325.

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