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Concise enantioselective synthesis of diospongins A and B

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Abstract

Ether transfer methodology is capable of stereoselectively generating 1,3-diol mono- and diethers in good yield. Surprisingly, allylic and benzylic substrates provide none of the desired products when exposed to previously optimized conditions of iodine monochloride. Herein, second-generation activation conditions for ether transfer have been developed that circumvents undesired side reactions for these substrates. The application of this chemistry to the enantioselective synthesis of diospongins A and B has now been accomplished.

Keywords

Ether transfer; Diospongin; Antiosteoporotic activity; Radical cyclization

1. Introduction

Polyketide natural products have attracted the attention of numerous academic laboratories for their potential use as chemotherapeutic agents. Often limited by natural supplies, the community has harnessed powerful synthetic methods for practical syntheses of complex molecules to enable exploration of their therapeutic potential. The repeating pattern of 1,3-oxygenation is very common to polyketides. We have recently developed an ether transfer methodology that enables the formation of *syn*-1,3-diol mono- or diethers through electrophilic activation of a homoallylic alkoxyether.¹ As highlighted in Scheme 1, activation of **1a** with iodine monochloride in toluene at low temperature led to the formation of ether transfer product **4a** in excellent yield and diastereoselectivity. The use of iodine monochloride proved critical by generating the chloromethyl ether intermediate **3** in situ, as observed by NMR analysis.

However, during the course of these studies we observed that certain substrates failed to provide the expected reactivity. A comparison of substrates **1a** and **1b** demonstrated a remarkable effect of the proximity of phenyl substitution on the ether transfer. In fact, subjecting **1b** to the identical conditions led predominantly to the isolation of a complex mixture of ICl addition products, **5b** (Scheme 1). Similarly, in planned application of this methodology to the syntheses of synthetic fragments related to zampanolide and pelurosides A, undesired ICl addition products were also observed with diene substrates **6** and **7**. Thus, the proximity of sp²-hybridized substituents adjacent to the reacting alkoxyethyl ether had a significant effect on the rate of cyclization. Application of ether transfer to the syntheses of

the diastereomeric pyran natural products, diospongins A and B, would require a solution to this issue.

Diospongins A and B were isolated in 2004 from rhizomes of *Dioscorea spongiosa*,² a Chinese plant used for the treatment of rheumatism as well as urethra and renal infections in traditional medicine.³ Diospongin B has shown significant antiosteoporotic activity and potent inhibitory activities on bone resorption by inhibiting calcium release. Due to their relatively simple structure and their potential application to the treatment of osteoporosis, diospongins A and B have attracted the attention of the synthetic community leading to several syntheses.⁴ We envisioned a divergent synthetic strategy that would allow access to both diospongins from a common intermediate, such as 1,3-*syn*-diol monoether **4b**. As proposed in Scheme 2, complementary methods for pyran generation would provide stereoselective access to each of the diastereomeric natural products.

2. Results and discussion

2.1. Access to *syn*-1,3-diol monoether

Iodine monochloride has shown unique ability to affect stereo-selective ether transfer in good yield. However, it has also shown limitations with some substrates, vide supra. For example, significant amount of ICl addition was observed with **1b** leading to lower yield of the desired ether transfer product **4b**. The inductively electron-withdrawing aryl or vinyl group is likely to slow the rate of cyclization and formation of the intermediate oxonium ion **2**. However, an alternative rationale includes the potentially stabilizing cationic- π interaction, such as intermediate **8**, which would populate an unproductive conformation and allow intermolecular chloride addition to compete with the ether transfer (Scheme 3). Sterics were eliminated as a factor by substituting the aromatic ring in **1b** with a cyclohexyl group. Here, only trace amounts of dihalogenation products were detected and the *syn*-1,3-diol monoether **10** was isolated in good yield and excellent diastereoselectivity.⁵

We envisioned that modulating the nucleophilicity and availability of counterions in solution, such as chloride, could eliminate undesired olefin addition products. We thus focused our efforts on finding alternative electrophilic activating conditions, to induce ether transfer in substrate **1b** and the results are listed in Table 1. Substitution of ICl by other sources of I^+ , such as Ipy_2BF_4 , $I(collidine)_2PF_6$, bromodiethylsulfonium bromopentachloroantimonate (BDSB), and the iodine analogue (IDS1) led to either poor reactivity or decomposition (Entries 3–7). However, much to our delight, we found that conditional adjustments to *N*-iodosuccinimide enabled the formation of *syn*-1,3-diol monoether **4b** in higher yield and satisfactory diastereoselectivity (Entry 8). Unfortunately, an appreciable amount of the water addition product **11** was also observed. However, changing the solvent to nitromethane not only diminished the formation of this undesired product but also increased the yield and diastereoselectivity of the transformation (Entry 12).

2.2. Access to *syn*-1,3-diol diether

The results of this study make clear that the presence of water was crucial in the transfer as it likely both activates *N*-iodosuccinimide and also serves as a nucleophilic trap for the intermediate oxonium ion (Scheme 4). Intrigued by this transformation, we thought to access *syn*-1,3-diol diethers by replacing water with other weak Brønsted acids.

Successful demonstration of this concept is highlighted in Table 2. In the presence of *N*-iodosuccinimide, a variety of activating agents, such as acetic acid, 1-phenyl-1*H*-tetrazole-5-thiol, benzyl imidate, or propionaldehyde oxime were able to initiate the ether transfer providing access to *syn*-1,3-diol diethers in good yield and diastereomeric ratio. In some

cases a significant amount of byproduct **13** was observed, although sensitivity of the reaction to the counterion remains unclear. Unfortunately attempts to use sulfur or phosphorus as nucleophiles were unsuccessful.

2.3. Synthesis of diospongins A and B

With the reliable methodology in hand, we focused our efforts on the synthesis of diospongins A and B. Starting from the MOM protected homoallylic alcohol **1b**, obtained in two steps from benzaldehyde, we realized the challenge of a late stage cleavage of the methyl group in the total synthesis. Unable to execute the deprotection, even at various points along the synthesis, we chose to investigate alternative transferring ethers, which would readily be deprotected when desired. Previous efforts from our group reported that the use of benzyloxy methyl ether (BOM) and, more recently, 2-naphthylmethoxymethyl ether (Naph)^{1b} as a substrates for ether transfer proved to be particularly useful since these groups can be removed under hydrogenolysis or mild aqueous oxidation conditions, respectively. Surprisingly, we found that the newly developed NIS conditions with BOM and Naph-protected versions of **1b**, provided products with relatively poor diastereomeric ratio and low yields.

We found that the 2-bromoethoxymethyl ether **14** transferred efficiently to provide **15** in good yield and satisfactory diastereoselectivity when activated with NIS/1-phenyl-1*H*-tetrazole-5-thiol (Scheme 5).⁶ Oxidative cleavage with *m*-CPBA enabled quick access to the *syn*-1,3-diol monoether **15**.⁷ Tributylphosphine catalyzed conjugate addition of **15** to phenyl ketone **16** provided access to the vinylogous ester **17**.⁸ Selective radical generation and cyclization⁹ provided exclusively the 4-alkoxy-2,6-*cis*-trisubstituted pyran. A final reductive deprotection of the 2-bromoethyl ether yielded diospongin A.

We have recently demonstrated that quenching the ether transfer process with nucleophiles, such as sulfide can provide access to 2-sulfonyl pyrans as intermediates to 2,6-*cis* or 2,6-*trans* pyran systems via an anionic cyclization.^{1e} While sulfur nucleophiles were not compatible with these NIS activation conditions, the identical intermediate **19** was available from ether transfer product **15** through alkylation with ((diazomethyl)sulfonyl)toluene **18** (Scheme 6).¹¹ The sulfonyl pyran was then generated as an inconsequential mixture of diastereomers by treatment of **19** with lithium bis(trimethylsilyl)amide. In analogy to our previously published procedures, exposure to aluminum chloride, in the presence of the TBS-enol ether derived from acetophenone, provided the 2,6-*trans*-pyran through axial attack on an intermediate oxonium ion. A final zinc-mediated deprotection of the 2-bromoethyl group yielded diospongin B.

In conclusion we have achieved a divergent synthesis of diospongins A and B from common intermediate **15**. Stereoselective access to **15** required further development of our ether transfer methodology since iodine monochloride cannot be employed with sp²-hybridized substituents adjacent to the reacting alkoxymethyl ether. We identified *N*-iodosuccinimide in wet nitromethane as useful in obtaining the desired ether transfer products in good yields and diastereoselectivities for the benzylic substrates presented above. Moreover, preliminary studies suggest that the new conditions also promote ether transfer in allylic substrates. These additional efforts as well as the results of our continued investigation of the scope and mechanism of the ether transfer will be reported in due course.

3. Experimental section

3.1. General

Unless otherwise noted, all materials were used as received from a commercial supplier without further purification. All anhydrous reactions were performed using oven-dried or

flame-dried glassware under nitrogen atmosphere. Tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), toluene, and diethyl ether (Et_2O) were filtered through activated alumina under nitrogen. Nitromethane was distilled over CaH_2 , and kept over 4 Å molecular sieves. All reactions were monitored by Whatman analytical thin layer chromatography (TLC) plates (AL SIL G/UV, aluminum back) and analyzed with 254 nm UV light and/or anisaldehyde/sulfuric acid treatment. Silica gel for column chromatography was purchased from E. Merck (Silica Gel 60, 230–400 mesh). Unless otherwise noted, all ^1H and ^{13}C NMR spectra were obtained in CDCl_3 on Varian Unity Plus 300, 500 or 600 spectrometers (operating at 299.701, 499.864 MHz, 599.876 MHz for ^1H and 75.368 MHz, 125.706 MHz and 150.84 MHz for ^{13}C , respectively). Chemical shifts (δ) were reported in parts per million relative to residual CDCl_3 as an internal reference (^1H : 7.27 ppm, ^{13}C : 77.23 ppm) and coupling constants (J) were reported in hertz (Hz). Peak multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), m (multiplet), q (quartet), b (broad). Mass spectra (FAB) were obtained at the Department of Chemistry and Biochemistry, University of Notre Dame. Substrates **1a**, **4a**, **5a**, **6**, **7**, and **9** have been prepared according to previously reported procedures.^{1,5}

3.2. (±)-1-Cyclohexyl-4-iodo-3-methoxybutan-1-ol (**10**)

Iodine monochloride (0.832 ml, 1.0 M in DCM) was added dropwise to a solution of **9** (0.110 g, 0.555 mmol) in toluene (10 ml) at -78°C under inert atmosphere. The reaction was quenched after 20 min by addition of 1:10 mixture of H_2O /diisopropylamine (11 ml), warmed to room temperature, and stirred for 1 h. The mixture was diluted with water (10 ml), extracted with AcOEt (3×10 ml), and washed with brine (20 ml). The combined organic layers were dried over MgSO_4 and concentrated. Purification by column chromatography on silica gel (Hexane/ AcOEt 6:1) provided **10** (95 mg, 55% yield, >20:1 dr) as an oil. ^1H NMR (600 MHz, CDCl_3): (ppm)=3.55 (1H, ddd, $J=1.8, 5.4, 10.2$ Hz), 3.40 (3H, s), 3.32 (1H, dd, $J=1.2, 4.8$ Hz), 3.31 (1H, dd, $J=2.4, 4.8$ Hz), 3.27 (1H, m), 1.83 (1H, dd, $J=1.8, 3.6$ Hz), 1.80 (1H, dd, $J=1.8, 3.6$ Hz), 1.73–1.79 (2H, m), 1.70 (1H, m), 1.63–1.67 (2H, m), 1.33 (1H, m), 1.15–1.25 (3H, m), 1.15 (1H, m), 1.03 (1H, m). ^{13}C NMR (150 MHz, CDCl_3): (ppm)=80.4, 75.1, 56.8, 44.1, 38.5, 28.9, 28.1, 26.7, 26.4, 26.3, 9.2. HRMS calculated for $\text{C}_{11}\text{H}_{22}\text{IO}_2$ $[\text{M}+\text{H}]^+$ 313.0665, found 313.0659.

3.3. (±)-1-(1-(Methoxymethoxy)but-3-en-1-yl)benzene (**1b**)

To a solution of benzaldehyde (20 g, 196 mmol) in diethyl ether (300 ml) was added allylmagnesium chloride (117 ml, 2.0 M) dropwise at 0°C over 30 min and stirred for 1 h under inert atmosphere. Saturated NH_4Cl (300 ml) was added and the aqueous layer extracted with diethyl ether (3×50 ml). The combined organic layers were dried over MgSO_4 and concentrated to provide 29 g (99% yield) of the corresponding allylic alcohol as an oil.

The allylic alcohol (29 g, 195 mmol) was diluted in dry DCM (200 ml), followed by addition of DIPEA (68 ml, 392 mmol) and *n*- Bu_4NI (0.72 g, 0.19 mmol). A solution of MOMCl^{10} (115 ml, 2.21 M in toluene) was added dropwise at 0°C over 30 min and stirred overnight at reflux. Saturated NH_4Cl (300 ml) was added and extracted with diethyl ether (3×100 ml). The combined organic layers were dried over MgSO_4 and concentrated. Purification by column chromatography on silica gel (hexane/ AcOEt 10:1) provided **1b** (32 g, 85% yield) as an oil. ^1H NMR (600 MHz, CDCl_3): (ppm)=7.26–7.34 (5H, m), 5.80 (1H, dddd, $J=7.2, 7.2, 10.2, 13.8$ Hz), 5.08 (1H, m), 5.04 (1H, m), 4.63 (1H, dd, $J=5.4, 7.8$ Hz), 4.55 (1H, d, $J=6.6$ Hz), 4.53 (1H, d, $J=6.6$ Hz), 3.36 (3H, s), 2.44–2.63 (2H, m). ^{13}C NMR (150 MHz, CDCl_3): (ppm)=141.5, 134.8, 128.4, 127.7, 126.9, 117.1, 94.1, 77.6, 55.5, 42.4. HRMS calculated for $\text{C}_{12}\text{H}_{16}\text{NaO}_2$ $[\text{M}+\text{Na}]^+$ 215.1043, found 215.1067.

3.4. (±)-4-Iodo-3-methoxy-1-phenylbutan-1-ol (**4b**)

Iodine monochloride (2.10 ml, 1.0 M in DCM) was added drop-wise to a solution of **1b** (0.309 g, 1.607 mmol) in toluene (50 ml) at -78°C under inert atmosphere. The reaction was quenched after 10 min by addition of 1:5 mixture of H_2O /diisopropylamine (25 ml) and warmed to room temperature. The mixture was diluted with water (20 ml) and extracted with AcOEt (3×15 ml). The combined organic layers were dried over MgSO_4 and concentrated. Purification by column chromatography on silica gel (hexane/AcOEt 10:1–4:1) provided **4b** (108 mg, 22% yield, >20:1 dr) as an oil. ^1H NMR (600 MHz, CDCl_3): (ppm)=7.26–7.37 (5H, m), 4.87 (1H, dd, $J=4.2, 9.0$ Hz), 3.39 (3H, s), 3.36 (1H, br), 3.28–3.33 (2H, m), 3.22 (1H, dddd, $J=3.6, 5.4, 7.2, 12.6$ Hz), 1.94–2.07 (2H, m). ^{13}C NMR (150 MHz, CDCl_3): (ppm)=144.1, 128.5, 127.6, 125.8, 78.9, 72.8, 56.6, 43.9, 8.9. HRMS calculated for $\text{C}_{11}\text{H}_{15}\text{I}\text{NaO}_2$ $[\text{M}+\text{Na}]^+$ 329.0014, found 329.0023.

(±)-(4-Chloro-3-iodo-1-(methoxymethoxy)butyl)benzene—**5b** (438 mg, 77% yield, 1:1 mixture of regioisomers) was isolated. ^1H NMR (600 MHz, CDCl_3): (ppm)=7.28–7.38 (5H, m), 4.85 (1H, dd, $J=2.4, 10.2$ Hz), 4.60 (1H, dddd, $J=3.0, 4.8, 7.2, 12.0$ Hz), 4.56 (1H, d, $J=6.6$ Hz), 4.55 (1H, d, $J=6.6$ Hz), 4.09 (1H, dd, $J=4.8, 11.4$ Hz), 3.82 (1H, dd, $J=9.6, 11.4$ Hz), 3.43 (3H, s), 2.42 (1H, ddd, $J=2.4, 10.2, 15.0$ Hz), 1.95 (1H, ddd, $J=2.4, 11.4, 15.0$ Hz). ^{13}C NMR (150 MHz, CDCl_3): (ppm)=141.0, 128.6, 128.1, 126.9, 94.3, 77.5, 56.3, 50.6, 45.9, 29.9. HRMS calculated for $\text{C}_{12}\text{H}_{16}\text{ClI}\text{NaO}_2$ $[\text{M}+\text{Na}]^+$ 376.9776, found 376.9801.

3.4.1. NIS/ H_2O activation—Water (4.7 μl , 261 μmol) was added to a mixture of **1b** (50 mg, 260 μmol) and *N*-iodosuccinimide (71 mg, 312 μmol) in dry nitromethane (3 ml) and stirred overnight in the dark. The reaction was quenched by addition of half saturated $\text{Na}_2\text{S}_2\text{O}_3$ (5 ml) and diluted with AcOEt (5 ml). The mixture was extracted with AcOEt (5×3 ml), dried over MgSO_4 , and concentrated. Purification by column chromatography on silica gel (hexane/AcOEt 6:1–2:1) provided **4b** (63 mg, 65% yield, 6:1 dr) as an oil.

3.4.2. NIS/oxime activation—*E/Z* Propionaldehyde oxime (0.171 g, 2.34 mmol) was added to a mixture of **1b** (45 mg, 234 μmol) and *N*-iodosuccinimide (0.536 g, 2.34 mmol) in dry nitromethane (3 ml) and stirred 48 h in the dark under inert atmosphere. The reaction was quenched by addition of half saturated $\text{Na}_2\text{S}_2\text{O}_3$ (5 ml) and diluted with AcOEt (5 ml). The mixture was extracted with AcOEt (5×3 ml), dried over MgSO_4 , and concentrated. Purification by column chromatography on silica gel (hexane/AcOEt 6:1–2:1) provided **4b** (46 mg, 64% yield, 99% br sm, 5:1 dr) as an oil.

3.5. (±)-(4-Iodo-3-methoxy-1-phenylbutoxy)methyl acetate (**12a**)

Acetic acid (30 μl , 531 μmol) was added to a solution of **1b** (51 mg, 265 μmol) and NIS (120 mg, 531 μmol) in dry nitromethane (3 ml). The mixture was stirred in the dark for 2 h under inert atmosphere, quenched by addition of half saturated $\text{Na}_2\text{S}_2\text{O}_3$ (5 ml), and diluted with AcOEt (5 ml). The mixture was extracted with AcOEt (5×3 ml), dried over MgSO_4 , and concentrated. Purification by column chromatography on silica gel (hexane/AcOEt 8:1) provided **12a** (74 mg, 74% yield, 6:1 dr) as an oil. ^1H NMR (600 MHz, CDCl_3): (ppm)=7.29–7.37 (5H, m), 5.31 (1H, d, $J=6.6$ Hz), 4.99 (1H, d, $J=6.6$ Hz), 4.72 (1H, dd, $J=7.2, 7.2$ Hz), 3.34 (1H, dd, $J=5.5, 10.8$ Hz), 3.27 (3H, s), 3.24 (1H, dd, $J=3.6, 10.8$ Hz), 2.81 (1H, dddd, $J=3.6, 4.8, 4.8, 7.2$ Hz), 2.20 (1H, ddd, $J=7.2, 13.8, 14.4$ Hz), 1.94 (3H, s), 1.89 (1H, ddd, $J=5.4, 7.2, 14.4$ Hz). ^{13}C NMR (150 MHz, CDCl_3): (ppm)=170.5, 140.6, 128.6, 128.2, 126.9, 86.9, 78.1, 75.9, 56.6, 42.4, 20.9, 9.6. HRMS calculated for $\text{C}_{14}\text{H}_{19}\text{I}\text{NaO}_4$ $[\text{M}+\text{Na}]^+$ 401.0220, found 401.0227.

3.6. (±)-1-((4-iodo-3-methoxy-1-phenylbutoxy)methyl)-4-phenyl-1*H*-tetrazole-5(4*H*)-thione (12b)

1-phenyl-1*H*-tetrazole-5-thiol (104 mg, 583 μmol) was added to a solution of **1b** (56 mg, 291 μmol) and NIS (131 mg, 583 μmol) in dry nitromethane (3 ml). The mixture was stirred in the dark for 12 h under inert atmosphere, quenched by addition of half saturated Na₂S₂O₃ (5 ml), and diluted with AcOEt (5 ml). The mixture was extracted with AcOEt (5×3 ml), dried over MgSO₄, and concentrated. Purification by column chromatography on silica gel (hexane/AcOEt 8:1) provided **12b** (91 mg, 63% yield, 6:1 dr) as an oil. ¹H NMR (600 MHz, CDCl₃): (ppm)=7.83–7.85 (2H, m), 7.26–7.55 (8H, m), 5.70 (1H, d, *J*=11.4 Hz), 5.56 (1H, d, *J*=11.4 Hz), 4.90 (1H, dd, *J*=7.8, 7.8 Hz), 3.32 (1H, dd, *J*=5.4, 10.8 Hz), 3.26 (3H, s), 3.20 (4.2, 10.8 Hz), 2.82 (1H, dddd, *J*=4.2, 5.4, 5.4, 7.8 Hz), 2.26 (1H, ddd, *J*=7.2, 7.2, 14.4 Hz), 1.94 (1H, ddd, *J*=5.4, 7.2, 14.4 Hz). ¹³C NMR (150 MHz, CDCl₃): (ppm)=164.3, 139.8, 134.5, 129.7, 129.3, 129.2, 128.6, 128.6, 128.4, 127.0, 126.8, 123.9, 123.6, 79.1, 76.0, 74.6, 56.6, 42.5, 9.5. IR (cm⁻¹): $\tilde{\nu}$ =2984, 2940, 2907, 1740, 1498, 1446, 1373, 1298, 1241, 1096, 1047, 938, 847, 634, 607. HRMS calculated for C₁₉H₂₂IN₄O₂S [M+H]⁺ 497.0503, found 497.0524.

3.7. (±)-2,2,2-Trichloro-*N*-((4-iodo-3-methoxy-1-phenylbutoxy)methyl)acetamide (12c)

Benzyl imidate (168 μg, 905 μmol) was added to a solution of **1b** (58 mg, 302 μmol) and NIS (204 mg, 905 μmol) in dry nitromethane (3 ml). The mixture was stirred in the dark for 12 h under inert atmosphere, quenched by addition of half saturated Na₂S₂O₃ (5 ml), and diluted with AcOEt (5 ml). The mixture was extracted with AcOEt (5 × 3 ml), dried over MgSO₄, and concentrated. Purification by column chromatography on silica gel (hexane/AcOEt:8:1) provided **12c** (65 mg, 45% yield, 8:1 dr) as an oil. ¹H NMR (600 MHz, CDCl₃): (ppm)=7.23–7.37 (5H, m), 7.12 (1H, br s), 4.79 (1H, dd, *J*=7.2, 10.8 Hz), 4.71 (1H, dd, *J*=6.6, 10.8 Hz), 4.60 (1H, dd, *J*=5.4, 7.2 Hz), 3.31 (1H, dd, *J*=5.4, 10.8 Hz), 3.26 (3H, s), 3.22 (1H, dd, *J*=4.2, 10.8 Hz), 2.83 (1H, dddd, *J*=4.2, 5.4, 5.4, 7.8 Hz), 2.19 (1H, ddd, *J*=7.2, 7.2, 13.8 Hz), 1.89 (1H, ddd, *J*=5.4, 6.6, 13.8 Hz). ¹³C NMR (150 MHz, CDCl₃): (ppm)=162.1, 140.6, 128.7, 128.2, 127.0, 78.1, 76.0, 70.7, 56.6, 42.5, 9.4. HRMS calculated for C₁₄H₁₇Cl₃INNaO₃ [M+Na]⁺ 501.9216, found 501.9214.

3.8. 1-Bromo-2-(chloromethoxy)ethane

A suspension of paraformaldehyde (3.51 g, 111.10 mmol), 2-bromoethanol (7.50 ml, 105.81 mmol) in 10:1 mixture of pentane/DCM (65 ml) was cooled to 0 °C. HCl gas was bubbled under vigorous stirring until the mixture became homogeneous (approximately 30 min). In a separatory funnel, the aqueous solution was removed and distillation over CaCl₂ (82–87 °C/10 mmHg) provided 1-bromo-2-(chloromethoxy)ethane (18 g, 99% yield) as an oil, which can be kept over CaCl₂ for months in a freezer. ¹H NMR (600 MHz, CDCl₃): (ppm)=5.52 (2H, s), 4.00 (2H, t, *J*=5.4 Hz), 3.51 (2H, t, *J*=5.4 Hz). ¹³C NMR (150 MHz, CDCl₃): (ppm)=82.3, 70.1, 29.0.

3.9. (S)-1-((2-Bromoethoxy)methoxy)but-3-en-1-yl)benzene (14)

1-Bromo-2-(chloromethoxy)ethane (2.82 g, 16.31 mmol) was added slowly to a solution of (S)-1-phenylbut-3-en-1-ol (1.86 g, 12.55 mmol) and DIPEA (3.93 ml, 22.59 ml) in dry DCM (25 ml). The mixture is stirred for 24 h under argon at room temperature. Saturated NH₄Cl (50 ml) was added and the aqueous layer was extracted with AcOEt (3×10 ml). The organic layers were combined, dried over MgSO₄, and concentrated. After purification by column chromatography on silica gel hexane/AcOEt (12:1), **14** was obtained as an oil (2.68 g, 77% yield). ¹H NMR (600 MHz, CDCl₃): (ppm)= 7.26–7.35 (5H, m), 5.78 (1H, dddd, *J*=7.2, 7.2, 10.2, 17.4 Hz), 5.03–5.10 (2H, m), 4.68 (1H, m), 4.68 (1H, d, *J*=7.2 Hz), 4.61 (1H, d, *J*=7.2 Hz), 3.96 (1H, ddd, *J*=6.0, 6.0, 10.8 Hz), 3.74 (1H, ddd, *J*=6.0, 6.0, 10.8 Hz),

3.41 (2H, ddd, $J=1.2, 6.0, 6.0$ Hz), 2.43–2.63 (2H, m). ^{13}C NMR (150 MHz, CDCl_3): (ppm)=141.3, 134.6, 128.4, 127.8, 127.0, 117.4, 93.0, 78.2, 67.9, 42.3, 30.7. HRMS calculated for $\text{C}_{13}\text{H}_{17}\text{BrNaO}_2$ $[\text{M}+\text{Na}]^+$ 307.0304, found 307.0313. $[\alpha]_D^{20} -116.8$ (c 0.75, CHCl_3).

3.10. (1*S*,3*R*)-3-(2-Bromoethoxy)-4-iodo-1-phenylbutan-1-ol (15)

To a solution of **14** (1.00 g, 3.51 mmol) in dry nitromethane (70 ml) was successively added NIS (6×0.78 g, 24.54 mmol) and 1-phenyl-1*H*-tetrazole-5-thiol (6×0.62 g, 24.54 mmol) every 6 h in the dark at room temperature under inert atmosphere. AcOEt (100 ml) was added, and the solvent evaporated. The crude material was portioned in half saturated $\text{Na}_2\text{S}_2\text{O}_3/\text{Et}_2\text{O}$ (200 ml:200 ml) and stirred for 30 min. After extraction with AcOEt (5×20 ml), the organic layers were combined, dried over MgSO_4 , and concentrated. Purification by column chromatography on silica gel (hexane/AcOEt 10:1–6:1) provided the ether transfer product (1.19 g, 64% yield) as an oil. ^1H NMR (500 MHz, CDCl_3): (ppm)=7.84–7.86 (2H, m), 7.30–7.58 (8H, m), 5.71 (1H, d, $J=10.8$ Hz), 5.55 (1H, d, $J=10.8$ Hz), 4.96 (1H, dd, $J=6.6, 6.6$ Hz), 3.80 (1H, ddd, $J=5.4, 5.4, 10.2$ Hz), 3.60 (1H, ddd, $J=5.4, 5.4, 10.2$ Hz), 3.42 (2H, m), 3.26 (1H, dd, $J=4.8, 11.4$ Hz), 3.22 (1H, dd, $J=4.8, 11.4$ Hz), 3.09 (1H, dddd, $J=4.8, 4.8, 4.8, 7.2$ Hz), 2.28 (1H, ddd, $J=7.2, 7.2, 14.4$ Hz), 2.00 (5.4, 7.2, 14.4 Hz). ^{13}C NMR (150 MHz, CDCl_3): (ppm)=164.3, 139.6, 134.5, 129.7, 129.3, 129.2, 128.7, 128.6, 127.1, 126.9, 123.9, 123.6, 78.8, 75.5, 74.5, 69.2, 42.7, 30.5, 9.2. HRMS calculated for $\text{C}_{20}\text{H}_{23}\text{BrIN}_4\text{O}_2\text{S}$ $[\text{M}+\text{H}]^+$ 588.9764, found 588.9745. $[\alpha]_D^{20} -43.0$ (c 1.5, CHCl_3).

m-CPBA (0.475 g, 2.121 mmol) was added to a mixture of the ether transfer product (0.625 g, 1.061 mmol) and NaHCO_3 (0.445 g, 5.311 mmol) in AcOEt (30 ml) and vigorously stirred at room temperature open to air. After 1 h, a 1:1 mixture of saturated $\text{NaHCO}_3/\text{Na}_2\text{S}_2\text{O}_3$ (30 ml) was added and stirred for 10 min. The aqueous layer was extracted with DCM (5×5 ml), dried over MgSO_4 , and concentrated (without heating the water bath). Purification by column chromatography on silica gel (hexane/AcOEt 4:1) provided **15** (275 mg, 65% yield) as an oil. ^1H NMR (600 MHz, CDCl_3): (ppm)=7.27–7.40 (5H, m), 4.95 (1H, dd, $J=3.6, 8.4$ Hz), 3.99 (1H, ddd, $J=5.4, 5.4, 10.8$ Hz), 3.68 (1H, ddd, $J=5.4, 5.4, 10.8$ Hz), 3.51 (2H, m), 3.44 (1H, dddd, 4.2, 4.2, 6.0, 7.8 Hz), 3.31 (2H, m), 3.00 (1H, br s), 2.00–2.15 (2H, m). ^{13}C NMR (150 MHz, CDCl_3): (ppm)=143.9, 128.5, 127.7, 125.8, 78.1, 72.7, 69.0, 44.1, 30.5, 8.7. HRMS calculated for $\text{C}_{12}\text{H}_{17}\text{BrIO}_2$ $[\text{M}+\text{H}]^+$ 398.9451, found 398.9459. $[\alpha]_D^{20} -41.5$ (c 1.2, CHCl_3). Remark: compound **15** proved to be fairly unstable and cannot be kept as an oil. It can be stored in benzene solution in a freezer for a long period of time.

3.11. (E)-3-(3-(2-Bromoethoxy)-4-iodo-1-phenylbutoxy)-1-phenylprop-2-en-1-one (17)

To a mixture of **15** (260 mg, 650 μmol) and 1-phenylprop-2-yn-1-one (0.17 g, 1.30 mmol) in dry DCM (65 ml) was added PBU_3 (0.32 ml, 1.30 mmol) dropwise at 0 °C over 15 min under inert atmosphere. After 1 h, the mixture was concentrated and purified by column chromatography on silica gel (hexane/AcOEt 7:1) provided **17** (292 mg, 85% yield) as an oil. ^1H NMR (MHz, CDCl_3): (ppm)=7.80–7.82 (2H, m), 7.67 (1H, d, $J=12.0$ Hz), 7.48–7.52 (1H, m), 7.32–7.43 (7H, m), 6.45 (1H, d, $J=12.0$ Hz), 5.27 (1H, dd, $J=6.0, 7.8$ Hz), 3.91 (1H, ddd, $J=4.8, 4.8, 10.2$ Hz), 3.54 (1H, ddd, $J=4.8, 4.8, 10.2$ Hz), 4.49 (2H, m), 3.29 (1H, dd, $J=6.0, 10.8$ Hz), 3.25 (1H, dd, $J=3.6, 10.8$ Hz), 3.08 (1H, dddd, $J=4.2, 4.2, 5.4, 7.8$ Hz), 2.44 (1H, ddd, $J=6.0, 8.4, 14.4$ Hz), 2.19 (1H, ddd, $J=3.6, 8.4, 14.4$ Hz). ^{13}C NMR (150 MHz, CDCl_3): (ppm)=190.4, 162.6, 140.0, 138.6, 132.3, 129.0, 128.4, 128.00, 126.8, 126.0, 104.0, 81.9, 75.1, 69.1, 42.0, 30.7, 8.0. HRMS calculated for $\text{C}_{21}\text{H}_{23}\text{BrIO}_3$ $[\text{M}+\text{H}]^+$ 528.9870, found 529.9881. $[\alpha]_D^{20} -43.5$ (c 0.75, CHCl_3).

3.12. Diospongin A

AIBN (0.5 mg, 2.8 μ mol) was added to **17** (15.0 mg, 28.3 μ mol) and *n*-Bu₃SnH (16 μ l, 57 μ mol) in dry benzene (3 ml). The mixture was rapidly brought to reflux and stirred for 5 min under argon. After cooling down, the reacting mixture was concentrated and purified by column chromatography on silica gel (hexane/AcOEt 10:1–6:1), to provide 2-((2*R*,4*S*,6*S*)-4-(2-bromoethoxy)-6-phenyltetrahydro-2*H*-pyran-2-yl)-1-phenylethanone as an oil (9.7 mg, 87% yield). ¹H NMR (600 MHz, CDCl₃): (ppm)=7.99 (2H, dd, *J*=1.2, 7.2 Hz), 7.55 (1H, m), 7.45 (2H, dd, *J*=7.2, 7.8 Hz), 7.26–7.30 (5H, m), 4.86 (1H, dd, *J*=1.8, 12.0 Hz), 4.57 (1H, dddd, *J*=1.8, 6.6, 6.6, 13.2 Hz), 3.86 (1H, p, 3.0 Hz), 3.50–3.64 (4H, m), 3.38 (1H, dd, *J*=6.0, 15.6 Hz), 3.04 (1H, dd, *J*=6.6, 15.6 Hz), 2.12 (1H, q, *J*=3.0 Hz), 2.05 (1H, q, 3.0 Hz), 1.66 (1H, ddd, *J*=3.0, 12.0, 14.4 Hz), 1.51 (1H, ddd, *J*=3.0, 11.4, 14.4 Hz). ¹³C NMR (150 MHz, CDCl₃): (ppm)=198.3, 142.7, 137.3, 133.1, 128.5, 128.3, 128.2, 127.2, 125.8, 74.1, 72.4, 69.4, 68.5, 45.1, 37.7, 35.1, 31.1. HRMS calculated for C₂₁H₂₄BrO₃ [M+H]⁺ 403.0903, found 403.0928. [α]_D²⁰ –21.5 (*c* 0.5, CHCl₃).

2-((2*R*,4*S*,6*S*)-4-(2-Bromoethoxy)-6-phenyltetrahydro-2*H*-pyran-2-yl)-1-phenylethanone (11.0 mg, 27.3 μ mol) was diluted in a 14:1 mixture of *i*-PrOH/H₂O (4 ml). Solid NH₄Cl (7.3 mg, 136.5 μ mol) was added followed by purified zinc dust (0.178 g, 2.72 mmol) and the mixture was refluxed for 8 h. After concentration, the crude material was purified by column chromatography on silica gel (hexane/AcOEt 2:1) to provide diospongin A (6.0 mg, 75% yield). ¹H NMR (600 MHz, CDCl₃): (ppm)=7.98 (2H, dd, *J*=1.2, 7.8 Hz), 7.56 (1H, m), 7.46 (dd, 2H, *J*=7.2, 8.4 Hz), 7.30 (5H, m), 4.93 (1H, dd, *J*=1.8, 12.0 Hz), 4.65 (1H, m), 4.38 (1H, q, *J*=3 Hz), 3.42 (1H, dd, *J*=6.0, 15.6 Hz), 3.07 (1H, dd, *J*=6.6, 15.6 Hz), 1.94–1.98 (2H, m), 1.67–1.79 (2H, m), 1.64 (1H, br s). ¹³C NMR (150 MHz, CDCl₃): (ppm)=198.3, 142.6, 137.3, 133.1, 128.5, 128.3, 128.3, 127.2, 125.8, 73.8, 69.1, 64.7, 45.1, 40.0, 38.5.

HRMS calculated for C₁₉H₂₁O₃ [M+H]⁺ 297.1485, found 297.1496. [α]_D²⁰ –18.6 (*c* 0.12, CHCl₃); lit.: –21.2 (*c* 0.8, CHCl₃). The spectral data and optical rotation are in full agreement with that reported for both natural as well as synthetic sources of diospongin A.

3.13. 1-((((1*S*,3*R*)-3-(2-Bromoethoxy)-4-iodo-1-phenylbutoxy) methyl)sulfonyl)-4-methylbenzene (**19**)

HBf₄·OEt₂ (32 μ l, 238 mmol) was added dropwise at 0 °C to a mixture of **15** (380 mg, 952 mmol) and 1-((diazomethyl)sulfonyl)-4-methylbenzene (0.280 mg, 1.428 mmol) in dry DCM (10 ml) under argon atmosphere. After 2 h, saturated NH₄Cl (10 ml) was added and the aqueous layer was extracted with DCM (3×5 ml), dried over MgSO₄, and concentrated. Purification by column chromatography on silica gel (hexane/AcOEt 6:1) provided **19** (355 mg, 66% yield) as an oil. ¹H NMR (600 MHz, CDCl₃): (ppm)=7.80 (2H, d, *J*=6.6 Hz), 7.22–7.40 (7H, m), 4.95 (1H, t, *J*=6.6 Hz), 4.40 (1H, d, *J*=12.0 Hz), 4.28 (1H, d, *J*=12.0 Hz), 3.41–3.77 (4H, m), 3.36 (1H, dd, *J*=4.8, 10.8 Hz), 3.27 (1H, dd, *J*=4.8, 10.8 Hz), 3.10 (1H, p, 5.4 Hz), 2.47 (3H, s), 2.17 (1H, ddd, *J*=6.6, 7.8, 14.4 Hz), 1.93 (1H, ddd, *J*=6.0, 6.0, 14.4 Hz). ¹³C NMR (150 MHz, CDCl₃): (ppm)=145.2, 138.7, 134.4, 130.0, 128.9, 128.8, 127.2, 125.5, 82.9, 80.5, 75.3, 69.1, 42.5, 30.3, 21.8, 9.5. HRMS calculated for C₂₀H₂₄BrINaO₄S [M+Na]⁺ 588.9516, found 588.9497. [α]_D²⁰ –47.6 (*c* 1.5, CHCl₃).

3.14. Diospongin B

LiHMDS (0.5 ml, 0.45 M in THF) was added slowly at –78 °C to a solution of **19** (86 mg, 152 mmol) and HMPA (80 μ l, 455 mmol) in dry THF (6 ml) under argon. After 45 min, the reaction was quenched by addition of saturated NH₄Cl (10 ml) and extracted with Et₂O (3×5 ml). The organic layers were dried over MgSO₄, concentrated, and purified by column chromatography on silica gel (hexane/AcOEt 5:1) to provide the corresponding sulfonyl

pyran (55 mg, 82% yield) as an oil. ^1H NMR (500 MHz, CDCl_3): (ppm)= 7.83 (2H, d, $J=8.0$ Hz), 7.23–7.34 (7H, m), 7.96 (1H, dd, $J=2.0$, 12.0 Hz), 4.86 (1H, d, $J=10.5$ Hz), 4.03 (1H, m), 3.51–3.91 (4H, m), 2.42–2.48 (5H, m), 1.87 (1H, ddd, 2.5, 14.0, 14.0 Hz), 1.63 (1H, ddd, $J=2.0$, 14.5, 14.5 Hz). ^{13}C NMR (125 MHz, CDCl_3): (ppm)=145.3, 141.4, 133.4, 130.0, 129.8, 128.5, 127.8, 125.7, 88.1, 75.3, 71.7, 69.0, 37.6, 31.3, 28.1, 22.0. HRMS calculated for $\text{C}_{20}\text{H}_{23}\text{BrNaO}_4\text{S}$ $[\text{M}+\text{Na}]^+$ 461.0393, found 461.0395. $[\alpha]_D^{20}$ –1.2 (c 0.2, CHCl_3).

The sulfonyl pyran (51 mg, 116 μmol) in DCM (1 ml), dried over molecular sieves, was added to a suspension of AlCl_3 (46 mg, 348 μmol) in dry DCM (6 ml) and stirred for 5 min. *tert*-Butyldimethyl((1-phenylvinyl)oxy)silane (41 mg, 174 μmol) in dry DCM (1 ml) was added at -78°C and slowly warmed to -40°C , which showed complete consumption of the starting material. The reaction was quenched by addition of saturated Rochelles' salt (10 ml) and stirred overnight. The aqueous layer was extracted with DCM (3×5 ml), and the combined organic layers dried over MgSO_4 , and concentrated. Purification by column chromatography on silica gel (hexane/AcOEt 5:1) provided the corresponding 2,6-*trans* pyran (38 mg, 82% yield) as a single diastereomer. ^1H NMR (600 MHz, CDCl_3): (ppm)=8.00 (2H, dd, $J=1.2$, 8.4 Hz), 7.57 (1H, m), 7.47 (2H, m), 7.32–7.37 (5H, m), 5.17 (1H, t, $J=4.8$ Hz), 4.33 (1H, m), 3.77–3.81 (2H, m), 3.74 (1H, m), 3.47 (1H, dd, $J=6.6$, 16.2 Hz), 3.45–3.47 (2H, m), 3.51 (1H, dd, $J=6.0$, 16.2 Hz), 2.41 (1H, dddd, $J=1.2$, 4.8, 4.8, 4.8 Hz), 2.10 (1H, dddd, $J=1.2$, 3.6, 3.6, 7.8 Hz), 1.99 (1H, ddd, $J=4.8$, 8.5, 13.2 Hz), 1.61 (1H, m). ^{13}C NMR (150 MHz, CDCl_3): (ppm)= 198.4, 140.6, 137.2, 133.1, 128.6, 128.5, 128.2, 127.2, 126.2, 72.1, 71.6, 68.1, 67.3, 44.2, 36.2, 34.3, 31.1. HRMS calculated for $\text{C}_{21}\text{H}_{24}\text{BrO}_3$ $[\text{M}+\text{H}]^+$ 403.0903, found 403.0928. $[\alpha]_D^{20}$ –45.5 (c 2.5, CHCl_3).

The 2,6-*trans* pyran (8.0 mg, 19.3 μmol) was diluted in a 14:1 mixture *i*-PrOH/ H_2O (3 ml). Solid NH_4Cl (5.5 mg, 99.2 μmol) was added followed by purified zinc dust (0.130 g, 1.98 mmol) and the mixture was refluxed for 10 h. After concentration, the crude material was purified by column chromatography on silica gel (hexane/AcOEt 2:1) to provide diospongin B (4.5 mg, 76% yield). ^1H NMR (600 MHz, CDCl_3): (ppm)=7.98 (2H, d, $J=7.8$ Hz), 7.57 (1H, t, $J=7.2$ Hz), 7.47 (2H, t, $J=7.8$ Hz), 7.34 (5H, m), 5.20 (1H, t, $J=4.2$ Hz), 4.23 (1H, m), 4.03 (1H, m), 3.45 (1H, dd, $J=7.2$, 15.6 Hz), 3.18 (1H, dd, $J=6.0$, 15.6 Hz), 2.51 (1H, m), 2.05 (1H, m), 1.92 (1H, ddd, $J=5.4$, 10.2, 15.0 Hz), 1.62 (1H, br s), 1.50 (1H, dd, $J=9.0$, 12.0 Hz). ^{13}C NMR (150 MHz, CDCl_3): (ppm)=198.3, 140.2, 137.2, 133.2, 128.6, 128.5, 128.3, 127.1, 126.3, 72.3, 66.9, 64.344.6, 40.2, 36.7. HRMS calculated for $\text{C}_{19}\text{H}_{21}\text{O}_3$ $[\text{M}+\text{H}]^+$ 297.1485, found 297.1496. $[\alpha]_D^{20}$ –22.5 (c 0.08, CHCl_3); lit. –23.4 (c 0.6, CHCl_3). The spectral data and optical rotation are in full agreement with that reported for both natural as well as synthetic sources of diospongin B.

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Scheme 1.
Electrophile-induced ether transfer.

Scheme 2.
Divergent strategy for the syntheses of diospongins.

Scheme 3.
Through-space stabilization of the iodonium ion.

Scheme 4.
Activation of *N*-iodosuccinimide with water.

Scheme 5.
Synthesis of diospongins A.

Scheme 6.
Synthesis of diospongin B.

Table 1

Ether transfer activated with *N*-iodosuccinimide

Entry	Conditions	4b Yield ^a (dr) ^b	4b:11 ^c
1	ICl, PhCH ₃ , -78 °C, 10 min	22% (20:1)	–
2	IBr, PhCH ₃ , -78 °C, 10 min	20% (20:1)	–
3	I ₂ , PhCH ₃ , -78 °C	NR	–
4	Ipy ₂ BF ₄ , DCM, rt	NR	–
5	I(collidine) ₂ PF ₆ , DCM, rt	NR	–
6	IDSi, CH ₃ NO ₂ , rt	Decomp.	–
7	BDSB, CH ₃ NO ₂ , rt	Decomp.	–
8	NIS, 10% H ₂ O in CH ₃ CN, rt, 1 h	40%	3:2
9	NIS, 10% H ₂ O in PhCH ₃ , rt, 1 h	0%	0:1
10	NIS, 10% H ₂ O in DCM, rt, 1 h	75% (11:1)	1:1
11	NIS, 10% H ₂ O in CH ₃ NO ₂ , rt, 1 h	72% (6:1)	3.5:1
12	NIS, H ₂ O (2 equiv), CH ₃ NO ₂ , rt, 6 h	64% (6:1)	5:1
13	NIS, H ₂ O (5 equiv), CH ₃ NO ₂ , rt, 5 h	64% (6:1)	5:1
14	NIS, CH ₃ NO ₂ , 4 ÅMS	NR	–

^aIsolated yield.^bDiastereomeric ratio determined by NMR analysis.^cRegioisomeric ratio of **11** was 1:1 by ¹³C NMR analysis.

Table 2

Activation of NIS with a variety of electrophiles

Entry	Nuc-H	12	Yield ^a (dr) ^b	12 : 13
1	AcOH		12a 74% (5:1)	5:1
2			12b 64% (6:1)	5:1
3			12c 45% (8:1)	10:1
4			4b 64% (3:1)	10:1

Regioisomeric ratio of **13** was 1:1 by ¹³C NMR analysis.^a Isolated yield.^b Diastereomeric ratio determined by NMR analysis.