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A short synthesis of (*S*)-(+)-siphonodiol

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Abstract—A short synthesis of the enantiomer of the polyacetylenic natural product siphonodiol is described. The synthesis is based on the strategy of taking advantage of the hidden symmetry of the target molecule and minimizing the use of protecting groups, thereby reducing the total number of steps and increasing the overall efficiency.

1. Introduction

Siphonodiol (Fig. 1) was isolated from the marine sponge *Siphonochalina truncata* in the gulf of Suruga.[1,2] Similar to other polyacetylenic natural products, a variety of biological activities have been reported for siphonodiol. The first total synthesis of the natural siphonodiol was reported in 2005.[3] Herein we report a short synthesis of its enantiomer, (*S*)-(+)-siphonodiol.

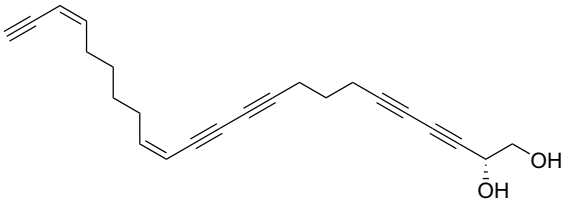

Figure 1. The structure of (−)-siphonodiol **1** from *Siphonochalina truncata*.

2. Results and discussion

Recently, we completed the total syntheses of several polyacetylenic natural products including adociacetylene, minquartynoic acids, and bidensyneosides.[4–10] As previously reported,[11,12] polyacetylenic compounds are sensitive to light and air and in general are very reactive in Nature. In order to obtain these natural products efficiently, we have developed some general strategies for our synthetic effort. The first consideration was to take advantage of the symmetry of the structure, which can be applied to any total synthesis.[13] This is especially important for polyacetylenic compounds because each extra step means a large difference in overall yield. Fewer steps can be achieved if molecular symmetry is used advantageously. The second consideration was to limit the use of functional protecting groups. For each protecting group employed, two additional synthetic steps are generally required. Therefore, to minimize the synthetic operations, use of protecting groups needs to be minimized. With these considerations, our retro-synthesis lead to three fragments as shown in Figure 2. Both fragments **2** and **3** are symmetrical and the coupling reaction applied to these compounds needs not be at one specific terminal. Therefore, one needs only to control the equivalency of the coupling partner and the operational details of addition, but it is not necessary to use a protecting group.

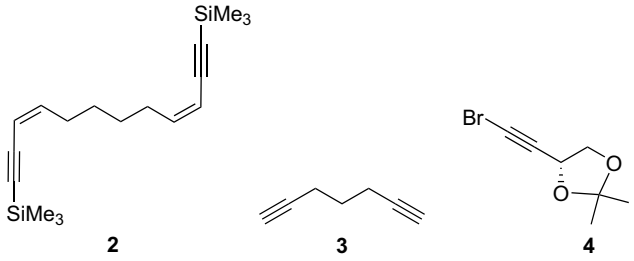

Figure 2. Retrosynthetic analysis: components needed for the synthesis of siphonodiol.

Compound **2** was recently reported by Lopez et al. in their work related to the synthesis of callyberynes.[14] Compound **3** is commercially available. Compound **4** is one of the

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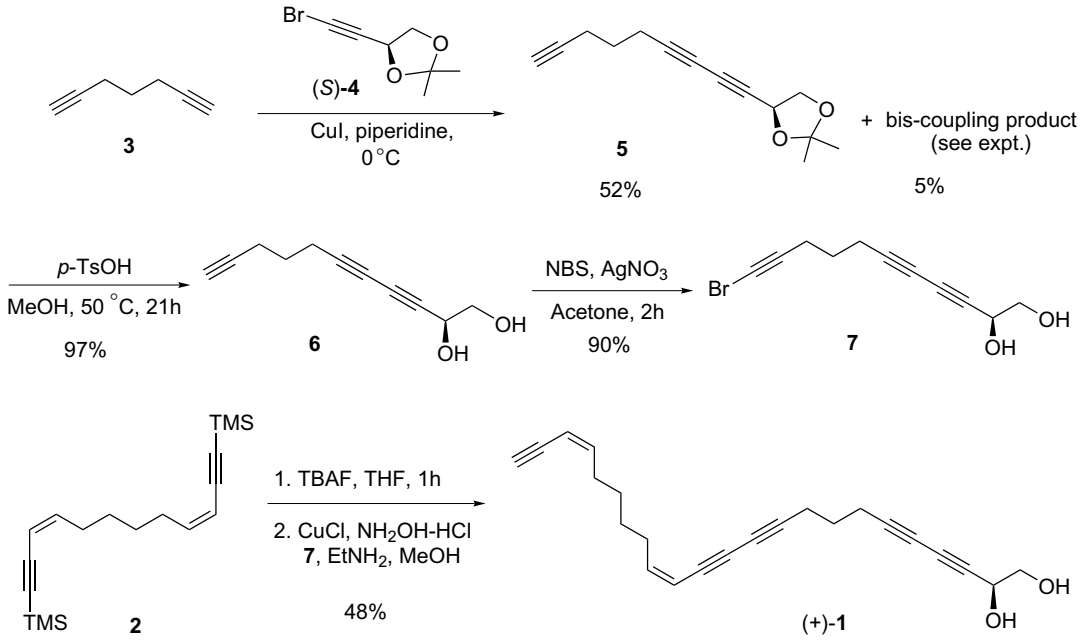

Scheme 1.

frequently observed functional group motifs in polyacetylenic natural products.[15] We have developed a synthesis of this useful building block starting from 2,3-isopropylidene–glyceraldehyde, which involved the formation of a dibromoolefin intermediate followed by the elimination of 1 M amount of HBr.[15] Since D-mannitol is less expensive than L-mannitol, as a study for proof of the concept, we employed the readily available enantiomer of **4** in this short synthesis of (*S*)-(+)-siphonodiol.

Starting from the commercially available diyne **3**, a copper(I) catalyzed coupling with bromoalkyne (*S*)-**4**[15] afforded the desired diyne **5** along with 5% of the bis-coupling by-product (Scheme 1).[16] Although the concurrent production of the bis-coupling product reduced the yield of the desired product, the separation was straightforward. In practice it was more efficient than conducting the coupling with a one-end protected diyne followed by deprotection.

The terminal alkyne was converted to bromoalkyne after removal of the acetonide protecting group for the diol.[17] The final step involved a one-pot deprotection-cross coupling operation. The symmetrical alkyne **2** was treated with 2.2 equiv of tetrabutylammonium fluoride in THF for 1 h, followed by the addition of bromoalkyne **7**. The slow addition of 1 equiv of **7** over 1 h led to a coupling reaction at only one-end of alkyne **2** despite the TMS groups at both terminals being removed. The cross coupling was under the classical Cadiot–Chodkiewicz conditions yielding the enantiomer of the natural siphonodiol in 48% (unoptimized). A small amount of the additional, more polar material was shown on TLC, which presumably was the bis coupling product, but was not characterized. We believe a better yield is possible for this final coupling reaction through optimization. The spectroscopic data of the major product obtained through this synthesis are consistent with the enantiomer of the natural siphonodiol. It was reported that natural siphonodiol was highly unstable.[2] In our hands, (*S*)-**1** survived silica gel column chromatographic separation and a postal trip to a mass spectrometry facility. Overnight ^{13}C NMR data collection did not show any change in peak appearance. This is consistent with our previous experience related to polyacetylenic natural products, that is, they are fairly stable once the structure is completely assembled and purified. On the other hand, polyacetylenic intermediates with terminal diyne or triynes are extremely unstable.

3. Conclusion

In conclusion, by adopting a strategy to minimize the use of protecting groups and by taking advantage of the hidden symmetry of the target molecule we have completed a short synthesis of the enantiomer of the natural product siphonodiol. This synthesis took only four linear steps and afforded the (+)-siphonodiol in 22% overall yield. Currently we are planning to use this general strategy to the total synthesis of more challenging natural products.

4. Experimental

4.1. General

All reactions were carried out under an atmosphere of nitrogen in oven-dried glassware with magnetic stirring. Reagents were purchased from commercial sources and used directly without further purification. Methylene chloride was dried over P_2O_5 and freshly distilled before use. Purification of the reaction products was carried out by flash chromatography using silica gel 40–63 μm (230–

400 mesh) unless otherwise stated. Reactions were monitored by ^{1}H NMR and/or thin-layer chromatography. Visualization was accomplished with UV light, staining with 5% $KMnO_4$ solution followed by heating or with *p*-anisaldehyde in EtOH solution. Chemical shifts were recorded in ppm (δ) using tetramethylsilane (H, C) as the internal reference. Data are reported as (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; integration; coupling constant(s) in Hz). Optical rotations were measured using Autopol III. Melting points were measured with a Gallenkamp melting point apparatus. Infrared spectra were recorded on a Perkin–Elmer 1600 series FTIR for liquids and on a Perkin–Elmer Spectrum 2000 FTIR for solids. High-resolution mass spectra were recorded at the Ohio State University.

4.2. (*S*)-(+)-3,4-*O*-Isopropylidene-1-bromobut-1-yn-3,4-diol 4

In a 200 ml round bottomed flask under an atmosphere of nitrogen, (3*S*)-3,4-*O*-isopropylidene-1,1-dibromobut-1-en-3,4-diol **8**[18] (3.5 g, 12.3 mmol) was added in 120 ml of dry THF. The solution was cooled to −100 °C and NaHMDS (1 M, 14.7 ml, 14.7 mmol) was added dropwise via a syringe. After 1 h, TLC indicated that the starting material had all disappeared. The reaction was diluted with 100 ml of ether and washed twice with saturated NH_4Cl solution. The aqueous layer was extracted with ether and the combined organic layers were washed with brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified over silica gel (2–5% EtOAc/Hex) to provide 2.17 g (86%) of a colorless oil. $[\alpha]_D = +36.1$ (*c* 0.10, $CHCl_3$), $[\alpha]_D = +29.9$ (*c* 0.10, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.4 (3H, s), 1.5 (3H, s), 3.9 (1H, dd, $J = 6.1$, 4.3 Hz), 4.1 (1H, dd, $J = 6.4$, 1.7 Hz), 4.7 (1H, dd, $J = 4.5$, 1.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 110.4, 79.0, 69.9, 66.4, 46.1, 26.1, 25.6. IR (film) 2900, 2253, 1253, 1096.

4.3. (2*S*)-1,2-Isopropylidene-3,5,10-undecatriyne 5

In a 50 ml round bottomed flask under an atmosphere of N_2 with magnetic stirring was added piperidine (15 ml), 1,6-heptadiyne (570 mg, 6.20 mmol), and CuI (71 mg, 0.37 mmol). The mixture was cooled to 0 °C using an ice bath and (2*S*)-4-bromo-1,2-isopropylidene-3-butyne (310 mg, 1.55 mmol) was then added via a syringe over a period of 1 h. The reaction was allowed to stir for 2 h at 0 °C and TLC indicated that the reaction was complete. A saturated solution of NH_4Cl (10 ml) was then added under vigorous stirring. The mixture was extracted with CH_2Cl_2 (3 × 15 ml). The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue purified over silica gel (5–10% EtOAc/Hex) to afford 174 mg (52%) of a colorless oil **5**, and 26 mg (5%) of a colorless oil **5a**. (2*S*)-1,2-Isopropylidene-3,5,10-undecatriyne **5**: $[\alpha]_D = +58.3$ (*c* 0.04, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.40 (3H, s), 1.52 (3H, s), 1.80 (2H, m), 2.01 (1H, t, $J = 2.6$ Hz), 2.31 (2H, dt, $J = 2.6$, 6.8 Hz), 2.39 (2H, t, $J = 6.8$ Hz), 3.93 (1H, dd, $J = 8.1$, 6.1 Hz), 4.13 (1H, dd, $J = 8.1$, 6.3 Hz), 4.79 (1H, t, $J = 6.2$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.8, 18.5, 26.1, 26.3, 27.3, 65.3, 66.0, 69.7, 69.9, 70.7, 73.7, 80.9, 83.1, 110.8. HRMS calcd for $C_{23}H_{24}O_2$ + Na, 355.1674; found, 355.1676. (2*S*,14*S*)-1,2,14,15-Diisopropylidene-3,5,10,12-Pentadecatetrayne **5a**: $[\alpha]_D = +59.8$ (*c* 0.016, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33 (6H, s), 1.46 (6H, s), 1.65–1.77 (2H, m), 2.36–2.41 (4H, t, $J = 6.9$), 3.92 (2H, m), 4.10 (2H, m), 4.72 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.7, 26.1, 26.9, 65.6, 66.1, 70.0, 73.8, 77.9, 80.6, 110.9. HRMS calcd for $C_{21}H_{24}O_4$ + Na, 363.1572; found, 363.1572.

4.4. (2*S*)-Undeca-3,5,10-triyne-1,2-diol 6

In a 100 ml round bottomed flask under an atmosphere of nitrogen with magnetic stirring were added 24 ml of MeOH, (2*S*)-1,2-isopropylidene-3,5,10-undecatriyne (261 mg, 1.2 mmol), and *p*-toluenesulfonic acid (23 mg, 0.12 mmol). The flask was equipped with a condenser and heated to 50 °C. The reaction mixture was allowed to stir at this temperature for 21 h after which TLC indicated that the reaction was complete. $NaHCO_3$ (200 mg, 2.4 mmol) was then added and the mixture stirred for 15 min. The solids were removed by filtration and the solvent was removed under reduced pressure. The residue was purified over silica gel (40–50% EtOAc/Hex) to afford 206 mg (97%) of a white solid. $[\alpha]_D = +41.4$ (*c* 0.06, $CHCl_3$). Mp = 59–61 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.75 (2H, m), 1.97 (1H, t, $J = 2.6$ Hz), 2.28 (2H, m) 2.40 (2H, t, $J = 7.0$ Hz), 3.64 (2H, m), 4.4–4.5 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.4, 18.2, 26.9, 63.3, 64.7, 66.2, 69.3, 70.8, 73.6, 80.7, 82.9.

4.5. (2*S*)-11-Bromo-undeca-3,5,10-triyne-1,2-diol

To a solution of (2*S*)-undeca-3,5,10-triyne-1,2-diol (139 mg, 0.79 mmol) in 6.6 ml of acetone was added $AgNO_3$ (27 mg, 0.16 mmol) followed by NBS (170 mg, 0.95 mmol). After stirring at rt for 2 h, TLC indicated that the starting material had been consumed. The reaction mixture was diluted with ether (15 ml) and water (15 ml). The aqueous layer was extracted with ether (3 × 15 ml) and the combined organic layers were washed with brine. The solution was dried over $MgSO_4$ and the solvent removed under reduced pressure. The residue was purified over silica gel (40% EtOAc/Hex) to yield 178 mg (90%) of a white solid. $[\alpha]_D = +24.0$ (*c* 0.009, $CHCl_3$). Mp = 61–62 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.76 (2H, m), 2.29–2.46 (4H, m), 3.67–3.81 (2H, m), 4.49–4.54 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.7, 19.1, 27.1, 64.0, 65.3, 66.6, 71.4, 73.8, 77.6, 79.1, 81.1. HRMS calcd for $C_{11}H_{11}BrO_2$ + Na, 276.9840; found, 276.9836.

4.6. (*S*)-(+)-Siphonodiol

In a 25 ml round bottomed flask under an atmosphere of N_2 were added 1 ml of THF and (3*Z*,9*Z*)-1,12-bis(trimethylsilyl)dodeca-3,9-diene-1,11-diyne (200 mg, 0.66 mmol). TBAF (1.45 ml, 1.45 mmol, 1 M in THF) was then added dropwise at rt via syringe. The solution was stirred for 1 h after which TLC indicated that the starting material had been consumed. The reaction mixture was then cooled

to 0 °C and 2.2 ml of MeOH and 2.2 ml of a 70% aqueous solution of $EtNH_2$ were added. Next, CuCl (3 mg, 0.03 mmol) and NH_2OH–HCl (2 mg, 0.03 mmol) were added and the reaction was stirred for 10 min. (2*S*)-11-Bromo-undeca-3,5,10-triyne-1,2-diol (167 mg, 0.66 mmol) in THF (1.5 ml) was then added via syringe over a period of 1 h. The reaction mixture was stirred for 3 h and then diluted with ether (10 ml) and quenched with a saturated solution of NH_4Cl (15 ml). The aqueous layer was extracted with ether (3×15 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, and the solvent removed under reduced pressure. The residue was purified over silica gel (60% EtOAc/Hex) to afford 105 mg (48%) of a yellow oil. $[\alpha]_D = +6.5$ (*c* 0.004, MeOH). ^1H NMR (300 MHz, $CDCl_3$): δ 1.4–1.59 (4H, m), 1.74–1.81 (2H, m), 2.31–2.47 (8H, m), 2.92 (1H, br s), 3.09 (1H, d, $J = 2.0$ Hz), 3.39 (1H, br s), 3.67–3.78 (2H, m), 4.48 (1H, m), 5.44–5.49 (2H, m), 6.0–6.09 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.7, 19.1, 27.1, 28.5, 28.6, 30.3, 30.8, 63.9, 65.5, 66.5, 66.6, 71.2, 72.9, 74.1, 78.3, 80.7, 80.8, 81.7, 83.3, 108.6, 108.7, 146.1, 148.1. HRMS calcd for $C_{23}H_{24}O_2 + Na$, 355.1674; found, 355.1676.

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