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Total synthesis of Neocosmosin A

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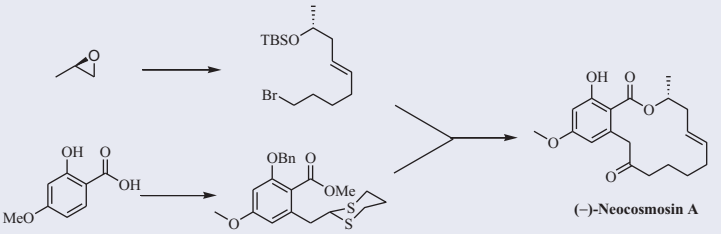
ABSTRACT

An alternative synthetic route to (−)-Neocosmosin A has been synthesized from commercially available (*R*)-propylene oxide and 4-Methoxysalicylic acid as starting materials. The key steps involved in the synthesis are alkylation of 1,3-dithiane and Yamaguchi macrolactonization.

GRAPHICAL ABSTRACT



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KEYWORDS
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Introduction

Resorcylic acid lactones (RALs) have been known for decades, with the first isolation of radicicol (monorden) in 1953,[1] followed by zearalenone,[2] LL-Z1640-2,[3] and hypothemycin.[4] Todate, more than 130 RALs have been described, which were mainly obtained from fungal species of genera Caryospora, Hamigera, Hypomyces, Paecilomyces etc.[5] Many of them exhibit a diverse array of biological activities, such as inhibition of heat shock protein 90 and kinases,[6,7] cytotoxic,[8] antiviral,[9] anti-inflammatory,[10,11] estrogenic,[12] and nematocidal activities.[13] Several RAL compounds are, in fact, currently under development for clinical applications.

Neocosmosin A is a 14 membered Resorcylic acid lactone, isolated with neocosmosins B and C from the fungus *Neocosmospora sp.* (UM-031509) in 2012.[14,15] It exhibits a strong binding affinity for human opioid and cannabinoid receptors.[16] The Structure of neocosmosin A (**1**) was elucidated on the basis of extensive 1D and 2D NMR spectroscopic analysis, mass spectrometric (ESI-MS) data, and X-ray crystallography (Figure 1).

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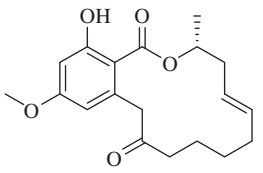
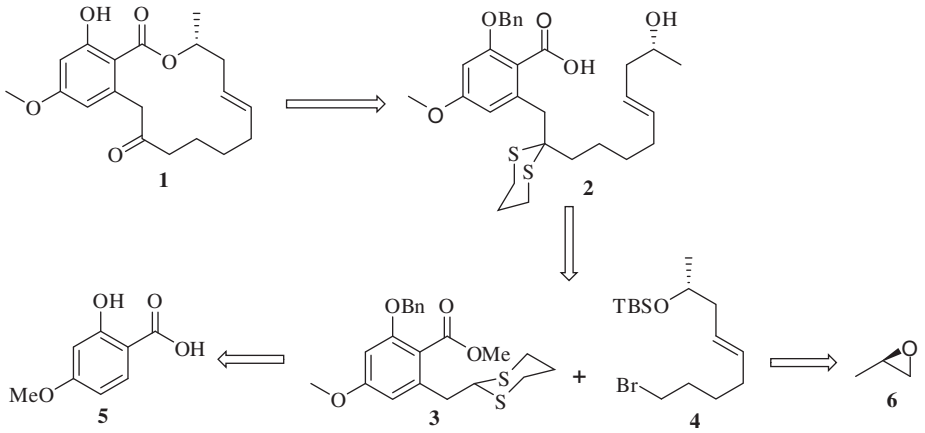


Neocosmosin A (**1**)

Figure 1. Structure of Neocosmosin A.



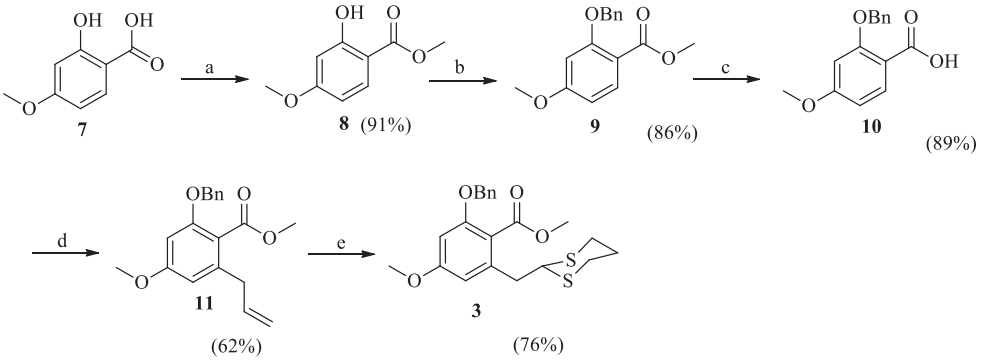
Scheme 1. Retro synthesis.

The first total synthesis of neocosmosin A was reported by Saibal Das and Coworkers in 2014[17a]. Due to the promising biological activity and the impressive structural features, neocosmosin A (**1**) appeared to be an attractive target for total synthesis[17b,c]. In this communication, we herein, report an alternative synthetic strategy to achieve the total synthesis of neocosmosin A (**1**) utilizing the alkylation of 1,3-dithiane and Yamaguchi macrolactonization as the key steps.

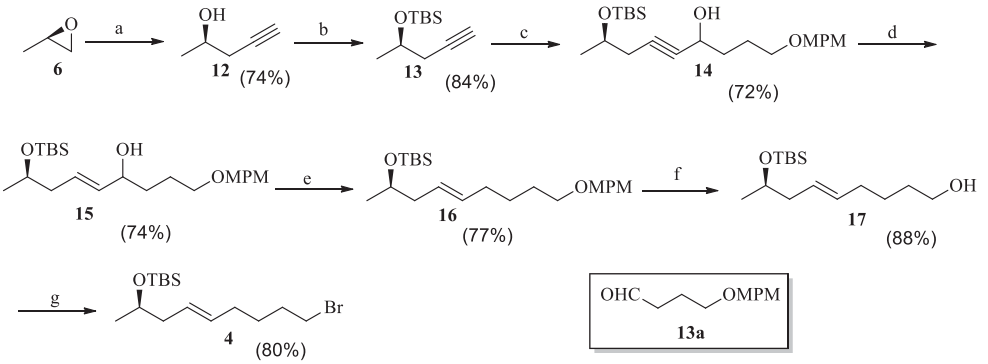
Results and discussion

According to the retrosynthetic analysis of neocosmosin A (**1**) as shown in Scheme 1, the target molecule **1** could be synthesized from seco-acid **2** via Yamaguchi macrolactonization followed by removal of protecting groups. Hydroxy acid **2** could be accessible by the coupling reaction of dithiane **3** and bromide **4**. wherein, **3** could be envisaged from the 4-Methoxysalicylic acid **5**, while, bromide **4** could be achieved from the commercially available chiral epoxide **6**.

As discussed in retrosynthetic analysis, the synthesis of the dithiane **3** commenced from known 4-Methoxysalicylic acid **7** (Scheme 2), which was subjected to esterification using diazomethane to generate 4-Methoxy methyl salicylate **8** in quantitative yield (Scheme 2). The hydroxyl group in compound **8** was protected with benzyl ether by treating with benzyl bromide and K_2CO_3 to give **9** in 86% yield. Later, the ester group



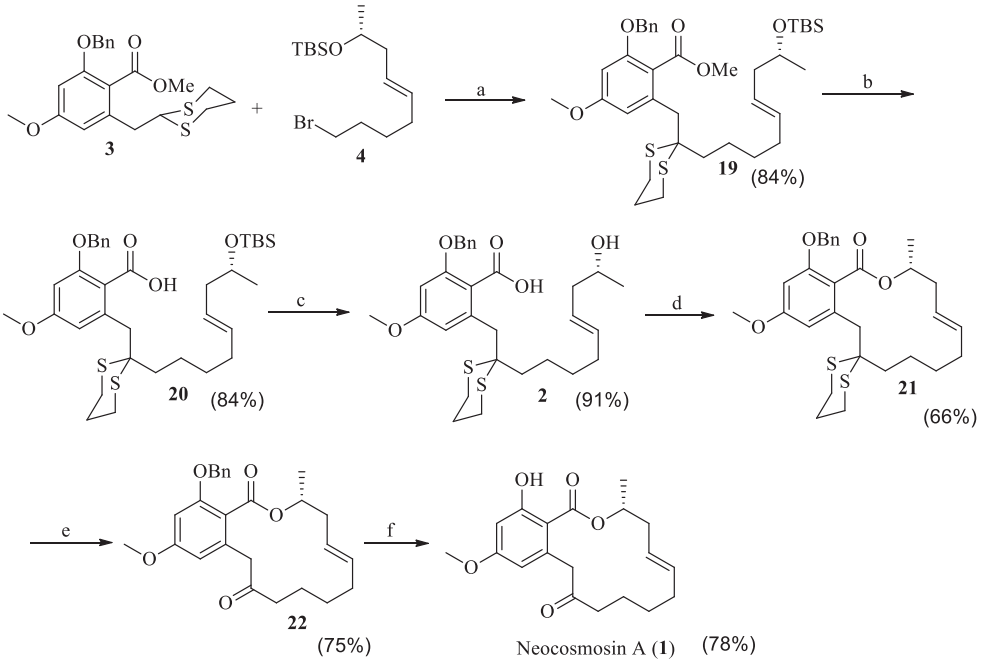
Scheme 2. Synthesis of fragment **3**.
Synthesis of fragment **3**; *Reagents and conditions*: (a) CH_2N_2, ether, 0 °C, 15 min; (b) BnBr, K_2CO_3, DMF, 0 °C to rt, 6h; (C) LiOH, THF:MeOH:H_2O (3:1:1), rt, 4 h; (d) (i) sBuLi, TMEDA, allyl bromide, THF, –90 °C, 4h; (ii) MeI, DBU, THF, 0 °C to rt, 24h; (e) (i) O_3, CH_2Cl_2, –78 °C, 30 min; (ii) 1,3-propanedithiol, CAN, $CHCl_3$, 0 °C to rt, 4 h.



Scheme 3. Synthesis of fragment **4**.
Synthesis of fragment **4**; *Reagents and conditions*: (a) lithium acetylide-ethylene diamine complex, DMSO, rt, 24 h; (b) TBSCl, Imidazole, CH_2Cl_2, rt, 4 h; (c) *n*-BuLi, dry THF, –78 °C, **13a**, 3 h; (d) Red-Al, dry ether, rt, 4 h; (e) i) *p*-TsCl, Et_3N, CH_2Cl_2, rt, 4 h; ii) LAH, THF, rt to 25 °C, 3h; (f) DDQ, aq. CH_2Cl_2, 0 °C to rt, 1 h; (g) CBr_4, Ph_3P, CH_2Cl_2, 0 °C to rt, 3 h.

in compound **9** was subjected to base (LiOH) hydrolysis in THF:MeOH:H_2O (3:1:1) to afford the corresponding acid **10**, which was allylated[13] via the dianion followed by esterification to afford compound **11** in 62% yield. Ozonolysis of **11** in CH_2Cl_2 at −78 °C for 30 min gave the corresponding aldehyde, which was transformed into 1,3-dithiane **3** in 76% with 1,3-propanedithiol and ceric ammonium nitrate as a catalyst in chloroform.

After successful synthesis of one key intermediate **3**, we next turned our attention to the synthesis of another key fragment **4** (Scheme 3). Accordingly, the synthesis was initiated with (*R*)-propylene oxide **6** as a chiral synthon, which was readily prepared from racemic-propylene oxide through Jacobsen hydrolytic kinetic resolution.[18] Thus treatment of (R)-propylene oxide **6** with lithium acetylideethylenediamine complex



Scheme 4. Synthesis of target compound **1**.
Synthesis of target compound **1** *Reagents and conditions*: (a) *n*-BuLi, dry THF, −20 °C, 3 h; (b) LiOH, THF:MeOH:H_2O (3:1:1), rt, 4 h; (c) TBAF, THF, 0 °C to rt, 3 h; (d) i) 2,4,6-trichlorobenzoyl chloride, Et_3N, dry THF, rt, 2 h; ii) DMAP, toluene, 90 °C, 10 h; (e) $CaCO_3$, MeI, CH_3CN:H_2O (9:1), 45 °C, 3 h; (f) $TiCl_4$, CH_2Cl_2, 0 °C to rt, 2 h.

proceeded cleanly to afford the corresponding homopropargylic alcohol, in which the secondary hydroxyl group was protected as its TBS ether **13** using TBSCl, imidazole in CH_2Cl_2 in 84% yield.

Next, alkyne **13** was treated with *n*-BuLi in THF at −78 °C and the resulting acetylenic anion was treated with known aldehyde **13a** furnished alcohol **14** as a 1:1 mixture of diastereomers in 72% yield. Reduction of **14** with Red-Al in dry ether at room temperature for 4 h afforded **15** as a 1:1 mixture of diastereomers in 74% yield. The hydroxyl group in **15** was transformed as tosylate **15a** by treatment with *p*-TsCl in CH_2Cl_2 at room temperature for 4 h, which on subsequent treatment with LAH in dry THF to furnish compound **16** in 77% yield. The PMB protecting group in compound **16** was oxidatively removed upon treatment with DDQ in aq. CH_2Cl_2 afforded alcohol **17** in 84% yield. Finally, treatment of alcohol **17** with CBr_4 in the presence of Ph_3P in CH_2Cl_2 gave the required bromo intermediate **4** in 80% yield.

Having synthesized both the desired fragments in a simple and efficient manner, we turned our attention to couple the dithiane **3** and the bromide **4** toward the synthesis of neocosmosin A. Accordingly, dithiane **3** was lithiated by n-BuLi at −20 °C and then coupled with bromide **4** to provide the desired product **19** in 84% yield (Scheme 4).

The ester functionality of **19** was hydrolyzed under basic conditions with LiOH in THF:MeOH:H_2O (3:1:1) to afford the corresponding acid **20**, which on desilylation with TBAF in THF at 0 °C to room temperature for 3 h afforded hydroxy acid **2** in 91%

yield. After successful synthesis of hydroxy acid fragment **2**, which was subjected to macrolactonisation under Yamaguchi high dilution conditions[19] to provide the lactone **21** in 66% yield. Next, the 1,3 dithaine group in compound **21** was successfully removed with $CaCO_3$ and MeI, in CH_3CN:H_2O for 3 h to afford the lactone **22** in 75% yield. In the final step, deprotection of benzyl ether in lactone **22** was removed successfully using $TiCl_4$ at 0 °C to rt to afford neocosmosin A (**1**) in 78% yield. The spectral data of **1** (^{1}H NMR, ^{13}C NMR and HRMS) and optical rotation are in good agreement with the reported values of natural neocosmosin A (**1**).

Experimental section

General

Solvents were dried over standard drying agents on freshly distilled prior to use. Chemicals were purchased and used without further purification. All column chromatographic separations were performed using silica gel (60–120 mesh). Organic solutions were dried over anhydrous Na_2SO_4 and concentrated below 40 °C in *vacuo*. ^{1}H NMR spectra were acquired at 300 MHz, 500 MHz and 600 MHz, while, ^{13}C NMR at 75 MHz and 125 MHz with TMS as internal standard for solutions in $CDCl_3$. *J* values were given in Hz. IR-spectra were recorded on FT IR spectrophotometer with NaCl optics. Optical rotations were measured on digital polarimeter at 25 °C. Mass spectra were recorded on direct inlet system or LC by MSD trap SL, the HRMS data were obtained using Q-TOF mass spectrometry.

Neocosmosin A (1)

To a stirred solution of **22** (0.10 g, 0.23 mmol) in dichloromethane (3 mL), $TiCl_4$ (90 mg, 0.47 mmol) in dichloromethane was added at 0 °C and stirred for 2 h. After completion of reaction sat. aq. $NaHCO_3$ solution (10 mL) was added and extracted with dichloromethane (3 × 10 mL). The combined organic layers were washed with water (15 mL), brine (10 mL), dried (Na_2SO_4) and concentrated. The crude residue purified by column chromatography (60–120 Silica gel, 20% EtOAc in pet. ether) to afford **1** (61 mg, 78%) as a Pale yellow liquid. $[\alpha]_D^{25}$ −43.1 (*c* 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.1 (s. 1H), 6.42 (d, 1H, $J = 2.6$ Hz), 6.22 (d, 1H, $J = 2.6$ Hz), 5.49–5.40 (m, 2H), 5.37–5.29 (m, 1H), 4.37 (d, $J = 16.4$ Hz, 1H), 3.81 (s, 3H) 3.49 (d, $J = 16.4$ Hz, 1H), 2.63–2.50 (m, 2H), 2.41–2.34 (m, 1H), 2.29–2.21 (m, 1H), 2.17–2.07 (m, 2H), 1.67–1.51 (m, 3H), 1.44–1.39 (m, 1H), 1.36 (d, $J = 6.3$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.2, 170.5, 166.1, 163.8, 139.1, 135.3, 124.6, 112.1, 105.7, 99.9, 73.0, 55.5, 50.3, 40.9, 37.7, 32.7, 25.3, 22.2, 18.8; HRMS (ESI): *m/z* calculated for $C_{19}H_{25}O_5$ $[M+H]^+$ 333.1702, found 333.1708.

Conclusions

Thus, In summary, we have demonstrated an efficient synthetic route for the total synthesis of neocosmosin A in a stereoselective manner. The overall yield of longest linear sequence in this synthesis i.e., From compound **6** to compound **1** (total number of steps

are **13**) is 4.45%. The key steps involved in this synthesis are alkylation of 1,3-dithiane and Yamaguchi macrolactonization.

Acknowledgments

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