Tetrahedron Letters 55 (2014) 5629–5631

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

# First stereoselective total synthesis of Neocosmosin A: a facile approach

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ARTICLE INFO

*Article history:*
Received 24 May 2014
Revised 11 August 2014
Accepted 16 August 2014
Available online 23 August 2014

*Keywords:*
Neocosmosin A
Resorcylic acid lactones
Total synthesis

ABSTRACT

First stereoselective concise synthesis of Neocosmosin A, with in vitro binding affinity for human opioid and cannabinoid receptors, has been reported using readily available starting materials such as methylacetoacetate, cyclohexanone, and homoallyl alcohol involved in the key transformations. There are three fragments involved in the synthesis of target molecule, bearing acid functionality, (*R*)-pent-4-en-2-ol, and Weinreb amide which are synthesized in four, eight, and three steps, respectively. Then the fragments were coupled in four steps to yield the target molecule in an overall yield of 28.6%.



In 2012, Cutler's bioassay-guided fractionation of a fungus Neocosmospora sp. (UM-031509) resulted in the isolation of three new resorcylic acid lactones,[1] Neocosmosin A (**1**), Neocosmosin B (**2**), and Neocosmosin C (**4**) (Fig. 1). Structures of these compounds were established on the basis of extensive 1D and 2D NMR spectroscopic analysis, mass spectrometric (ESI-MS) data, and X-ray crystallography. Neocosmosin A (**1**) has in vitro binding affinity for human opioid receptors and is reported to inhibit selectively $\delta$-44.7%, $\kappa$-11.4%, and $\mu$-22.4% with reference to naloxone and for cannabinoid receptor CB2-44.5% with reference to CP 55,940.[2]

According to Cutler compound **1** is a white amorphous solid, and it is structurally similar to monocillin IV (**3**), as shown by its NMR data, optical rotation, and X-ray diffraction. The asymmetric carbon atom C-2 in monocillin IV was determined as *R*-configuration from single-crystal X-ray diffraction. Therefore, the absolute configuration of the asymmetric carbon atom C-2 in compound **1** was proposed to be analogous to that of monocillin IV (**3**).

Furthermore, the geometry of the double bond in compound **1** ($C_4$–$C_5$) was difficult to determine by coupling constants because of the overlap of H-4 and H-5. The geometry of the double bond ($C_4$–$C_5$) in monocillin IV was found to be *E* configuration from single-crystal X-ray diffraction.[3] Therefore, they propose the geometry of the double bond ($C_4$–$C_5$) in compound **1** to be the *E* configuration. Due to its strong affinities for human opioid receptors, we became interested in developing a general synthesis of Neocosmosin A by employing simple reaction sequence.

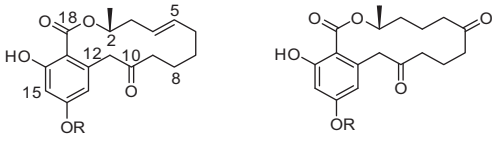


**Figure 1.** Structures of Neocosmosin A–C and monocillin IV.

In the retrosynthetic analysis of compound **1** (Scheme 1), we envisioned the construction of the target compound **1** by using Grubb's RCM on **5**, which could be easily achieved by lithiation of compound **8** with compound **6** and Mitsunobu esterification of compound **7**, respectively. On the other hand compounds **6**, **7**, and **8** could easily be obtained from commercially available starting material cyclohexanone **9**, homoallyl alcohol **10**, and methylacetoacetate **11**, respectively.

Our synthesis commenced with the construction of fragment **8** by using methyl acetoacetate **11** (Scheme 2) which was treated with NaH, *n*-BuLi mediated intramolecular condensation[4] in THF under reflux to produce the corresponding aromatic dihydroxy methyl ester **12** in 72% yield. This was allowed to react with TPP, DIAD, and MeOH in THF at room temperature to obtain exclusively mono methylated compound **13** in 84% yield. In compound **13**, the phenolic proton signal at $\delta$ 11.78 in $^1$H NMR is attributed for the selective methylation at para to methyl ester of **12**. Then it was treated with MOM chloride, DIPEA, in $CH_2Cl_2$ at 0 °C to room temperature to furnish compound **14** in 98% yield. Compound **14** on

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http://dx.doi.org/10.1016/j.tetlet.2014.08.065
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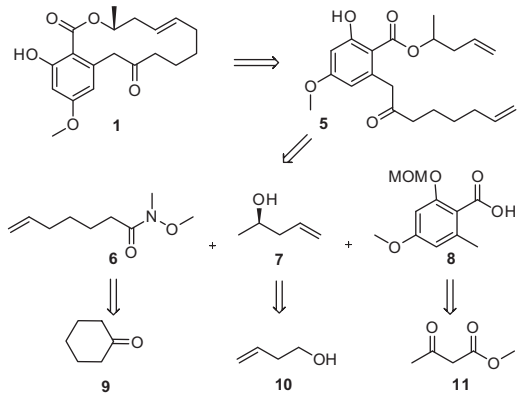


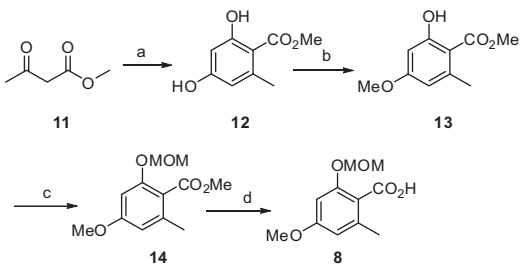
**Scheme 1.** Retrosynthetic analysis of compound **1**.

further saponification[5] with KOH in MeOH/$H_2O$ (1:1) gave the desired aromatic intermediate **8** in 91% yield, which was then used later for Mitsunobu lactonization with compound **7** as per plan.

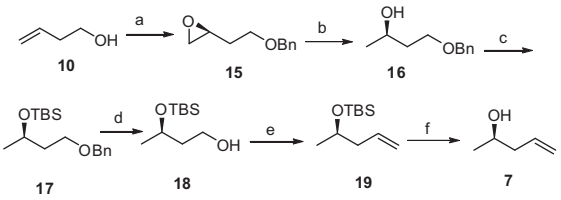
The synthesis of fragment **7** began using commercially available homoallyl alcohol **10** (Scheme 3), which was protected as benzyl ether using BnBr, NaH, and a catalytic amount of TBAI in THF to afford benzyl protected alcohol in 96% yield. Then it was subjected to *m*-CPBA epoxidation to give racemic epoxide in 97% yield, which was then subjected to hydrolytic kinetic resolution[6] using the (*S*,*S*)-Jacobsen catalyst to obtain optically pure (*S*)-2-allyloxirane **15** in 47% yield. The regioselective ring opening of epoxide **15** with $LiAlH_4$ in THF afforded compound **16** in 96% yield. Compound **16** was subsequently protected with TBSCl in imidazole and $CH_2Cl_2$ to obtain **17** in 97% yield. Deprotection of the benzyl group with Li/naphthalene in THF afforded **18** in 86% yield followed by oxidation with DMSO, oxalyl chloride, $Et_3N$ in $CH_2Cl_2$ to give the corresponding aldehyde. It was then used directly for the one carbon Wittig reaction to furnish compound **19** in 67% yield (for 2 steps). Removal of the TBS group from **19** with TBAF furnished the required alcohol (*R*)-pent-4-en-2-ol **7** in 85% yield.

Fragment **6** was synthesized from readily available cyclohexanone **9** (Scheme 4). Compound **9** on treatment with $K_2S_2O_8$, $H_2SO_4$ in EtOH produced[7] **20** in 80% yield which was oxidized with DMSO, oxalyl chloride, $Et_3N$ in $CH_2Cl_2$ to furnish the desired aldehyde, which was converted to compound **21** using the Wittig reaction[8] in 78% yield (for 2 steps). Then treatment of the Weinreb salt with LiHMDS followed by ester **21** in THF at −78 °C gave the corresponding compound **6** in 90% yield.[9]

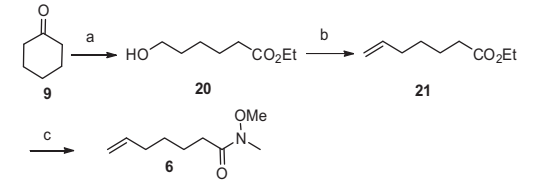
The coupling between **7** and **8** was performed using the Mitsunobu protocol (Scheme 5) to furnish the key intermediate **22** in 92% yield. With both the ester **22** and the Weinreb amide **6** in hand, lithiation[10] of **22** at the 1′-position using in situ formation of LDA at −78 °C followed by reaction with the Weinreb amide **6** provided the desired ketone **23** in 82% yield.



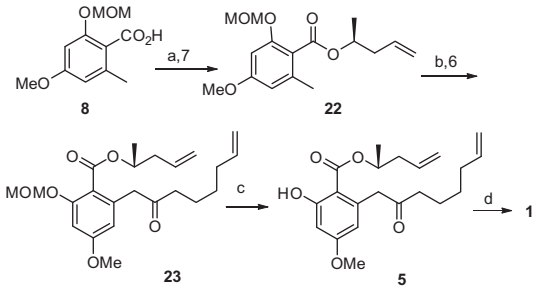
**Scheme 2.** Reagents and conditions: (a) NaH, BuLi, THF, −78 °C to 0 °C to rt, reflux, 26 h, 72%; (b) TPP, DIAD, MeOH, THF, rt, 1.5 h, 84%; (c) MOMCl, DIPEA, $CH_2Cl_2$, 10 h, 98%; (d) KOH, MeOH/$H_2O$ (1:1), reflux 12 h then AcOH, pH 6, 91%.



**Scheme 3.** Reagents and conditions: (a) (i) BnBr, NaH, TBAI THF, 0 °C to rt, 12 h, 96%; (ii) *m*-CPBA, $CH_2Cl_2$, 0 °C to rt, 12 h, 97%; (iii) (*S*,*S*)-(salen)-$Co^{III}$·OAc (0.5 mol %), $H_2O$ (0.55 equiv), 0 °C to rt, 18 h, 47%; (b) $LiAlH_4$, THF, 0 °C to rt, 0.5 h, 96%; (c) TBSCl, imidazole, $CH_2Cl_2$, 0 °C to rt, 3 h, 97%; (d) Li–naphthalene, THF, rt to −20 °C, 1.5 h, 86%; (e) (i) DMSO, oxalyl chloride, $Et_3N$, $CH_2Cl_2$, −78 °C, 2 h; (ii) *t*-KOBu,$CH_3PPh_3I$, THF, 0 °C to rt, 1 h, 67%; (f) TBAF, THF, 0 °C to rt, 4 h, 85%.



**Scheme 4.** Reagents and conditions: (a) (i) $K_2S_2O_8$, $H_2SO_4$, EtOH rt, 15 h, 80%; (b) (i) DMSO, oxalyl chloride, $Et_3N$, $CH_2Cl_2$, −78 °C; (ii) *t*-KOBu,$CH_3PPh_3I$, THF, 0 °C to rt, 1 h. (78% over 2 steps) (c) LiHMDS, Weinreb salt, **21**, THF, −78 °C, 0.5 h, 90%.



**Scheme 5.** Reagents and conditions: (a) DIAD, $Ph_3P$, **7**, THF, rt, 0.5 h, 92%; (b) LDA, −78 °C to 0 °C, THF then **6**, 0 °C, 0.5 h, 82%; (c) 4 N HCl, 48 h, rt, 80%; (d) $CH_2Cl_2$, reflux, Grubbs 2nd catalyst (10 mol %), 3 h, 89%.

After the successful synthesis of **23**, we employed RCM protocol followed by MOM deprotection using 10 mol % of Grubbs 2nd generation catalyst and 4 N HCl, respectively to achieve **1**. But unexpectedly even at high dilution conditions formation of compound **1** with desired *E* configuration was unsuccessful. Nearly (1:1) mixture of inseparable *E* and *Z* isomers was observed (confirmed by $^1$H NMR). In order to overcome this challenge, deprotection of the MOM group was employed in 4 N HCl, at room temperature for 48 h to furnish the desired compound **5** in 80% yield. RCM on **5** using 10 mol % of Grubbs 2nd generation catalyst in high dilution conditions[11] gave *E* olefin **1** as a white amorphous solid in 89% yield as the major isomer (confirmed by $^1$H NMR and HPLC). Selectivity may be due to the chelation of Ru-complex with the free phenolic group. The specific rotation is $[\alpha]_D^{26}$ −43.6 (*c* 0.6, $CHCl_3$) [lit. $[\alpha]_D^{32}$ −43 (*c* 0.6, $CHCl_3$)].[1] Spectral and physical data[12] were found to be in agreement with reported values.[1]

In conclusion, we believe that this reaction sequence is a short route to the stereoselective total synthesis of the natural product, Neocosmosin A. The synthesis involves direct and straightforward reaction conditions such as Mitsunobu lactonization, lithiation using LDA, and Grubbs ring closing metathesis.

## Acknowledgments

D.S.S. and K.B.K. thank the Council of Scientific and Industrial Research (CSIR), New Delhi for fellowship. S.D. is grateful to the Council of Scientific and Industrial Research (CSIR)-New Delhi for research funding under the ORIGIN (CSC-0108) programme of the 12th five year plan.

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.08.065.

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12. Neocosmosin A: IR (KBr): 3413, 2922, 1713, 1612, 1256, 1044 $cm^{-1}$; $[\alpha]_D^{32}$ −43.5 (*c* 0.7, $CHCl_3$ [lit. $[\alpha]_D^{20}$ −43 (*c* 0.6, $CHCl_3$)];$^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 12.0 (s, 1H), 6.42 (d, *J* = 2.5 Hz, 1H), 6.22 (d, *J* = 2.5 Hz, 1H), 5.42–5.50 (m, 2H), 5.28–5.38 (m, 1H), 4.40 (d, *J* = 16.8 Hz, 1H), 3.80 (s, 3H), 3.49 (d, *J* = 16.8 Hz, 1H), 2.45–2.65 (m, 2H), 2.20–2.43 (m, 2H), 1.87–2.17 (m, 4H), 1.38 (d, *J* = 6.5 Hz, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 208.1, 170.7, 166.0, 163.8, 139.0, 135.0, 124.5, 105.6, 100.1, 72.8, 55.3, 50.2, 40.7, 37.6, 32.6, 25.2, 22.1, 18.9; MS (ESI) (*m*/*z*): 333 $[M+H]^+$, 355 $[M+Na]^+$; HRMS-ESI: calcd for $C_{19}H_{25}O_5$: 333.16977, found 333.16965 $[M+H]^+$.