Tetrahedron Letters 56 (2015) 5930–5932

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Stereoselective synthesis of the C21–C29 fragment of (+)-Sorangicin A employing iodocyclization reactions

Debendra K. Mohapatra *, Shivalal Banoth, Jhillu S. Yadav

Natural Products Chemistry Division, CSIR-Indian Institute of Chemical Technology, Hyderabad 500007, India
Academy of Scientific and Innovative Research, New Delhi 110001, India

ARTICLE INFO

Article history:
Received 26 August 2015
Revised 11 September 2015
Accepted 13 September 2015
Available online 14 September 2015

Keywords:
Natural products
Iodocyclization
trans-2,6-Disubstituted dihydropyran
Isomerization
Asymmetric α-aminoxylation of aldehyde

ABSTRACT

A stereoselective synthesis of the C21–C29 fragment of (+)-Sorangicin A has been described following our recently developed iodine-catalyzed tandem isomerization followed by C–O and C–C bond formation for the construction of *trans*-2,6-disubstituted dihydropyran as the key step. In this Letter, the problem of installing the C25 asymmetric center has been sorted out by utilizing an iodolactonization strategy.

Introduction

Antibiotics have been used to fight against infectious disease caused by bacteria and other microbes. Antibacterial chemotherapy has been a leading cause for the dramatic rise of average life expectancy. However, in a world of ever-increasing antibiotic resistance, the discovery and development of new, potent antibiotics are of utmost importance. The secondary metabolite (+)-Sorangicin A (**1**) was isolated by Höfle and co-worker[1] in 1985 from the gliding myxobacteria *Sporangium cellulosum*. This shows extraordinary antibiotic activity against a broad panel of both Gram-positive (MIC value of average 10 ng/mL) and Gram-negative bacteria (MIC value of average 10 μg/mL).[2] The mechanism of action was subsequently determined to entail inhibition of RNA polymerase in both *Escherichia coli* and *Staphylococcus aureus* without affecting the eukaryotic cells.[2] In addition, Sorangicin A is active in vitro against several cancer cell lines.[3] The structure of Sorangicin A contains 31-membered macrocyclic lactone with C1–C8 carboxylic acid side Chain and 15 stereogenic centers, and was secured by X-ray crystallographic techniques. Owing to its potent antibiotic activity and architectural complexity, the stereoselective total synthesis of Sorangicin A (**1**) has attracted considerable interest from a number of groups including pioneering studies from Morken,[4] Scinzer,[5] Lee,[6] Yadav,[7] and Hong[8] research groups, with only total synthesis from Smith and co-workers[9] and a formal synthesis from Crimmins and co-workers.[10] As part of our ongoing research on total synthesis of complex natural products[11] following our own developed protocol of tandem isomerization followed by C–O and C–C bond formation reaction leading to *trans*-2,6-disubstituted dihydropyran, we have recently reported the synthesis of C28–C37 fragment of Sorangicin A.[12]

In continuation of our effort toward the total synthesis of Sorangicin A, herein, we describe our successful attempt on the synthesis of the C21–C29 fragment and installation of the C25 hydroxyl by employing iodocyclization and base-induced isomerization strategy.

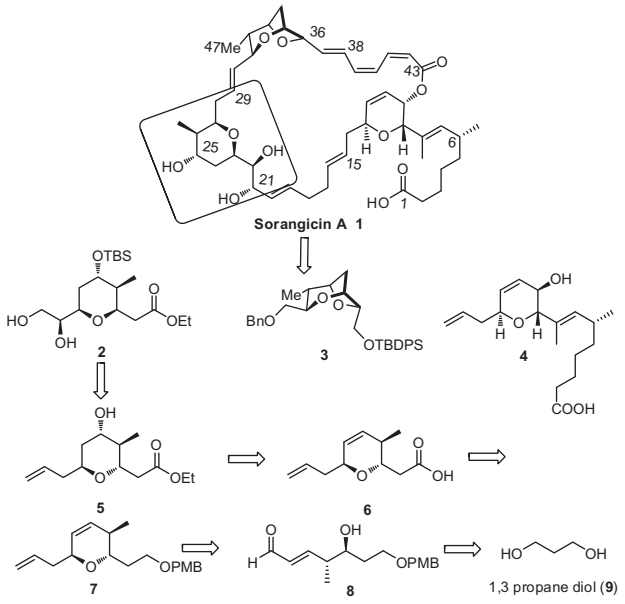
Results and discussion

The retrosynthetic route to C21–C29 fragment **2** of (+)-Sorangicin A is presented in Scheme 1. For the stereoselective introduction of the C22 hydroxyl group, we planned to perform an organocatalytic α-carbonyl oxidation using MacMillan's protocol[13] to the aldehyde which would be obtained from compound **5** by following Jin's oxidative strategy.[14] The functionalized pyran **5** could be formed by 6-*exo* trig iodolactonization reaction of the corresponding acid **6**. The required precursor **7** in turn would be synthesized from δ-hydroxy α,β-unsaturated aldehyde **8**, which in turn could be accessed from commercially available 1,3-propanediol (**9**).

Synthesis of *trans*-2,6-disubstituted-3,4-dihydropyran **7** began with 1,3-propane diol **9** as detailed in (Scheme 2). Accordingly by

* Corresponding author. Tel.: +91 40 2719 3128; fax: +91 40 2716 0512.
E-mail address: mohapatra@iict.res.in (D.K. Mohapatra).

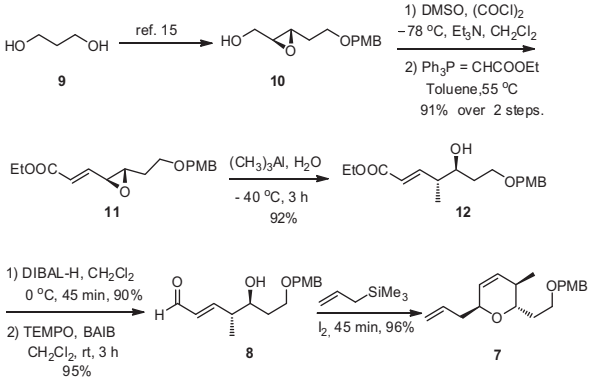
http://dx.doi.org/10.1016/j.tetlet.2015.09.037
0040-4039/



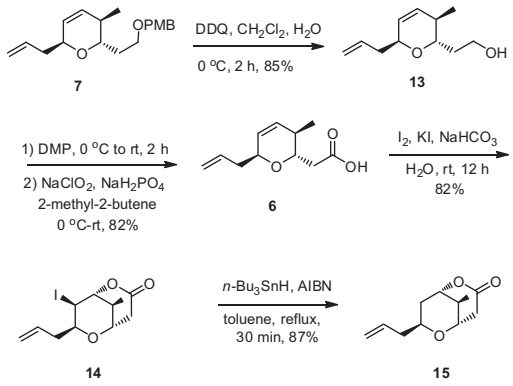
Scheme 1. Retrosynthetic analysis of Sorangicin A.

following an earlier reported sequence,[15] epoxy alcohol **10** was synthesized in 92% ee $[\alpha]_D^{25}$ −24.7 (*c* 1.7, $CHCl_3$). The resulting epoxy alcohol **10** was oxidized to the corresponding aldehyde by Swern oxidation[16] followed by a two carbon Wittig homologation with PPh_3 = $CHCO_2Et$ giving an γ,δ-epoxy acrylate **11** as a single isomer in 91% yield (over 2 steps). Following Miyashita's protocol of stereospecific methylation reaction, the epoxy ester **11** was converted to homoallylic alcohol **12** in the presence of trimethyl aluminum (TMA).[17] The α,β-unsaturated ester **12** was converted to the δ-hydroxy α,β-unsaturated aldehyde **8** in 95% yield by DIBAL-H reduction of the ester functionality followed by a subsequent selective oxidation of the primary hydroxyl group with TEMPO/BAIB.[18] A novel allylation strategy was performed with **8** by using our previous reaction condition (1.5 equiv of allyltrimethylsilane and 0.25 equiv of iodine).[12] Wherein the allylation occurred stereoselectively, giving rise to the *trans*-3-methyl-3,6-dihydropyran **7** as the sole product in 96% yield.

The oxidative removal of *p*-methoxybenzyl group of **7** with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) afforded primary alcohol **13** in 85% yield.[19] Oxidation of primary alcohol **13** with Dess–Martin periodinane[20] gave the corresponding aldehyde, which on further successive oxidation under Pinnick conditions[21] furnished acid **6** in 82% yield over two steps (Scheme 3).



Scheme 2. Synthesis of *trans*-3-methyl-3,6-dihydropyran **7**.

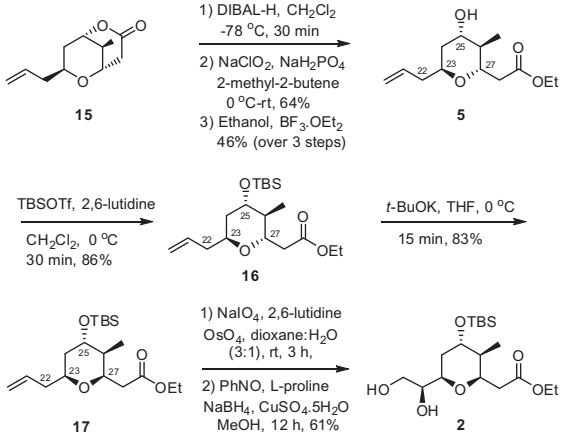


Scheme 3. Synthesis of compound **15**.

With good quantities of acid **6** in hand, we performed the key iodolactonization reaction using our previous reported reaction conditions[11e] for the installation of the hydroxyl functionality at C25 of **1**. Iodolactonization of **6** with molecular iodine in the presence of KI in aqueous $NaHCO_3$ solution proceeded via a 6-*exo* trig manner to furnish the desired iodo-lactone **14** as a single diastereomeric product in 82% yield. Deiodination was achieved smoothly by treatment of **14** with tri-*n*-butyltinhydride and in the presence of catalytic amount of AIBN in toluene under reflux condition to obtain **15** in 87% yield.[22]

The direct transformation of the lactone **15** under basic condition (sodium ethoxide in ethanol) yielded a complex mixture containing a traceable amount of the hydroxy ester **5**. Similarly, the basic hydrolysis condition (LiOH in THF) was unfruitful to produce the corresponding hydroxy acid. Therefore, the lactone **15** was first converted into hydroxy aldehyde. The controlled reduction of **15** with DIBAL-H at −78 °C afforded the required aldehyde, which on oxidation (Pinnick condition) and esterification (EtOH in $BF_3{\cdot}OEt_2$) smoothly afforded the hydroxy ethyl ester **5** (46% over 3 steps). The stereochemistry of the ester **5** was assumed to be the *trans* geometry at C23 and C27 positions by 2D-NMR analysis, wherein the NOESY experiment for **5** displayed NOE interactions for the C25 proton and C27 proton and did not show any interactions for the C23 and C27 protons (δ 3.99 and 3.76 ppm).[23] The resulting secondary alcohol **5** was protected as its TBS–ether using TBSOTf and 2,6-lutidine in anhydrous CH_2Cl_2 to obtain **16** in 86% yield (Scheme 4).

With the required skeleton present in **16**, we sought to perform epimerization of the stereochemistry at C27 via a retro-oxy-Michael/oxy-Michael process. Thus, the base induced



Scheme 4. Synthesis of C21–C29 fragment of Sorangicin A.

epimerization using *t*-BuOK was carried out at 0 °C. Gratifyingly, the first attempt for the epimerization proceeded smoothly in a stereoselective manner, favoring the desired C27 β-epimer **17** in 83% yield.[24] The stereochemical configuration of **17** was confirmed by NOESY measurement, which revealed strong NOE cross-peaks between C23 and C27 protons (δ 4.36 and 3.86–3.77).[23] Suggesting that the H-23 and H-27 are diaxially oriented with respect to each other. One-step conversion of terminal olefin to aldehyde was achieved by following Jin's modified oxidative protocol in 83% yield.[14] For the installation of C22 β-hydroxyl functionality, we adopted the direct catalytic asymmetric α-aminoxylation of the resulting aldehyde by using enantiopure proline as the catalyst and nitrosobenzene as the oxygen source and in situ reduction gave the 1,2-diol **2** via one pot three steps procedure in 61% yield (dr = 95:5, separated by column chromatography).[13] The integrity of the product was confirmed by its spectral and analytical data.

Conclusions

In conclusion, synthesis of the C21–C29 fragment of (+)-Sorangicin A was achieved following our recently developed protocol for the highly stereoselective synthesis of *trans*-2,6-disubstituted dihydropyran through tandem isomerization followed by C–O and C–C bond formation as the key steps. The other important reactions include iodolactonization, base-induced isomerization, and a proline-catalyzed asymmetric α-aminoxylation of aldehyde. In addition, the problem of fixing the C25 asymmetric center by following iodolactonization strategy has been sorted out.

Acknowledgments

The authors thank the Council of Scientific and Industrial Research (CSIR), New Delhi, India, for financial support as Part of XII Five Year Plan Programme under title ORIGIN (CSC-0108). D. K.M. thanks the Council of Scientific and Industrial Research (CSIR), New Delhi, India, for a research grant (INSA Young Scientist Award Scheme). S.B. thanks the Council of Scientific and Industrial Research (CSIR), New Delhi, India, for financial assistance in the form of research fellowship.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.09.037.

References and notes

1. Jansen, R.; Wray, V.; Irschik, H.; Reichenbach, H.; Höfle, G. *Tetrahedron Lett.* **1985**, *26*, 6031.
2. Irschik, H.; Jansen, R.; Gerth, K.; Höfle, G.; Reichenbach, H. *J. Antibiot.* **1987**, *40*, 7.
3. Stavbers, S.; Jereb, M.; Zupan, M. *Synthesis* **2008**, 1487.
4. Danek, S. C. The total synthesis of natural products and evaluating new assay techniques for identification of novel catalysts using combinatorial chemistry (Ph.D. Thesis); Morken Group, University of North Carolina at Chapel Hill, 2003.
5. Schinzer, D.; Schulz, C.; Krug, O. *Synlett* **2004**, 2689.
6. Park, S. H.; Lee, H. W. *Korean Bull. Chem. Soc.* **2008**, *29*, 1661.
7. Srihari, P.; Kumaraswamy, B.; Yadav, J. S. *Tetrahedron* **2009**, *65*, 6304.
8. Lee, K.; Kim, H.; Hong, J. *Eur. J. Org. Chem.* **2012**, *1025*.
9. (a) Smith, A. B., III; Fox, R. J. *Org. Lett.* **2004**, *6*, 1477; (b) Smith, A. B., III; Fox, R. J.; Vanecko, J. A. *Org. Lett.* **2005**, *7*, 3099; (c) Smith, A. B., III; Dong, S. *Org. Lett.* **2009**, *1099*, 11; (d) Smith, A. B., III; Dong, S.; Brenneman, J. B.; Fox, R. J. *J. Am. Chem. Soc.* **2009**, *131*, 12109.
10. (a) Crimmins, M. T.; Haley, M. W. *Org. Lett.* **2006**, *8*, 4223; (b) Crimmins, M. T.; Haley, M. W.; O'Bryan, E. A. *Org. Lett.* **2011**, *13*, 4712.
11. (a) Reddy, D. S.; Padhi, B. K.; Mohapatra, D. K. *J. Org. Chem.* **2015**, *80*, 1365–1374; (b) Mohapatra, D. K.; Krishnarao, P. S.; Bhimireddy, E.; Yadav, J. S. *Synthesis* **2014**, *46*, 1639; (c) Pradhan, T. R.; Das, P. P.; Mohapatra, D. K. *Synthesis* **2014**, *46*, 1177; (d) Mohapatra, D. K.; Maity, S.; Rao, T. S.; Yadav, J. S.; Sridhar, B. *Eur. J. Org. Chem.* **2013**, 2859; (e) Mohapatra, D. K.; Bhimireddy, E.; Krishnarao, P. S.; Das, P. P.; Yadav, J. S. *Org. Lett.* **2011**, *13*, 744; (f) Yadav, J. S.; Pattanayak, M. R.; Das, P. P.; Mohapatra, D. K. *Org. Lett.* **2011**, *13*, 1710.
12. Mohapatra, D. K.; Das, P. P.; Pattanayak, M. R.; Yadav, J. S. *Chem. Eur. J.* **2010**, *16*, 2072.
13. (a) Northrup, Alan B.; MacMillan, David W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798–6799; (b) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Tetrahedron Lett.* **2003**, *44*, 8293; (c) Zhong, G. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4247.
14. Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett.* **2004**, *6*, 3217.
15. Oka, T.; Murai, A. *Tetrahedron* **1998**, *54*, 1; (b) Gao, Y.; Hanson, R. M.; Ktunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, B. *J. Am. Chem. Soc.* **1987**, *109*, 5765; (c) Zhou, B.; Li, Y. *Tetrahedron Lett.* **2012**, *53*, 502.
16. (a) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651; (b) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
17. Pfaltz, A.; Mattenberger, A. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 71.
18. Mico, A. D.; Maragrita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974.
19. Horita, K.; Yoshioka, T.; Tanaka, T.; Yoikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021.
20. (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277; (b) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
21. (a) Ballakrishna, S. B.; Childers, W. E.; Pinnick, H. W., Jr. *Tetrahedron* **1981**, *37*, 2091; (b) Dalcanale, E.; Montanari, F. *J. Org. Chem.* **1986**, *51*, 567.
22. Schultz, A. G.; Kirincich, S. J. *J. Org. Chem.* **1996**, *61*, 5626.
23. See ESI† for NOESY analysis.
24. Yakambram, P.; Puranik, V. G.; Gurjar, M. K. *Tetrahedron Lett.* **2006**, *47*, 3781.