

RESEARCH ARTICLE

View Article Online

View Journal | View Issue



Cite this: *Org. Chem. Front.*, 2015, **2**, 913

Received 5th April 2015,

Accepted 13th May 2015

DOI: 10.1039/c5qo00109a

rsc.li/frontiers-organic

Formal synthesis of (–)-platensimycin†

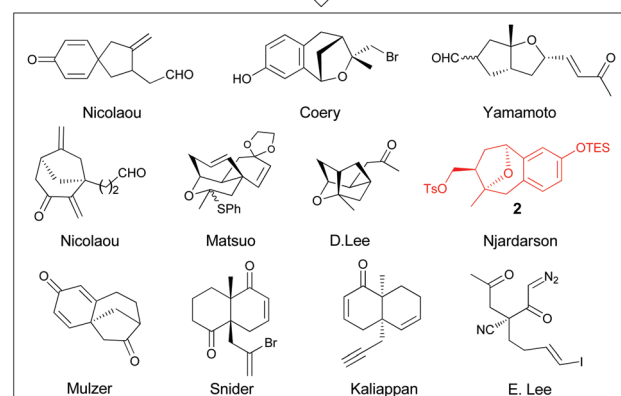
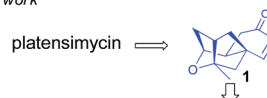
Zhi-Wei Jiao,^a Yong-Qiang Tu,^{a,c} Qing Zhang,^a Wen-Xing Liu,^a Shao-Hua Wang^a and Min Wang^{*b}

A formal synthesis of (–)-platensimycin has been successfully carried out using a tandem C–H oxidation/C–C coupling (cyclization)/rearrangement as the key step.

Exploring new antibiotics is an evergreen topic in the field of drug discovery because of the continuous emergence of multi-resistant bacteria.¹ Among the antibiotics developed/discovered in the past several years, (–)-platensimycin (Fig. 1), as a potential antibiotic drug candidate, was firstly isolated from a strain of *Streptomyces platensis* by Merck scientists in 2006.² Subsequent biological activity test of such a polycyclic natural product showed that it could selectively inhibit FabF, a key enzyme in the fatty acid synthetic pathway in bacteria, in the 48–160 nM range.

Due to its special bioactivity and structural molecular skeleton, this molecule has been an ideal target for total synthesis. Right after its isolation, Nicolaou's group reported the first total synthesis of platensimycin in its racemic form.^{3a} Since then, a number of research groups have also attempted the synthesis of the molecule. Most of them take compound **1** as the key intermediate to develop the corresponding synthetic strategies (Scheme 1).^{3,4} Among them, the strategy reported by Njardarson and co-workers, who used compound **2** with a benzoxa[3.2.1]octane skeleton to afford precursor **1**,^{3o} has drawn our attention as such type of an intermediate might be readily obtained through a tandem C–H oxidation/C–C coupling

a) previous work



b) This work



Scheme 1 Key intermediates used for the synthesis of core structure **1**.

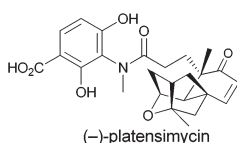


Fig. 1 The structure of (–)-platensimycin.

^aSchool of Pharmacy & State Key Laboratory of Applied Organic Chemistry Lanzhou University, Lanzhou, 730000, P. R. China

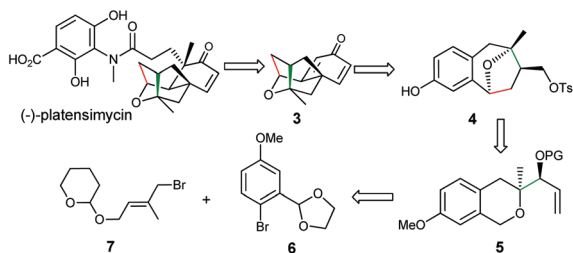
^bCollege of Material, Chemistry and Chemical Engineering, Hangzhou Normal University, Hangzhou 310036, P. R. China. E-mail: mwang@hznu.edu.cn

^cCollaborative Innovation Center of Chemical Science and Engineering, Tianjin, P. R. China

†Electronic supplementary information (ESI) available. See DOI: 10.1039/c5qo00109a

ring (cyclization)/rearrangement of isochroman-derived allylic silylether, which has been recently developed by our group and has been applied to the asymmetric total syntheses of (–)-brussonol and (–)-przewalskine *E*.^{5,6} Based on the above information and combined with our long interest in α -C–H bond functionalization of oxygen atoms⁷ and synthesis of bioactive natural products,⁸ we proposed a strategy toward the synthesis of (–)-platensimycin (Scheme 1). In this study, we present our results of the formal synthesis of (–)-platensimycin using the above-mentioned tandem reaction as the key step.

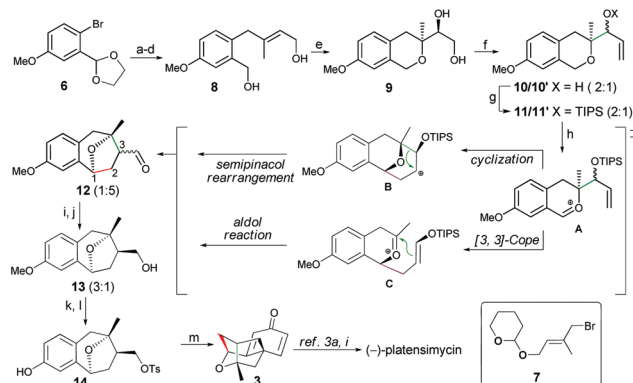
Our retrosynthetic analysis is illustrated in Scheme 2 and mainly focused on the synthesis of the key intermediate **3**, which could be obtained through the corresponding dearomatization/cyclization reaction of compound **4**.⁹ Compound **4**



Scheme 2 Retrosynthetic analysis of (–)-platensimycin.

with a benzoxa[3.2.1]octane skeleton could be prepared through our newly developed methodology from precursor 5, which could be assembled *via* a simple construction of the isochroman moiety from readily available bromide 6¹⁰ and 7.¹¹

As shown in Scheme 3, our synthesis started with the bromide 6, which was coupled with segment 7 followed by sequential transformations including acetal-deprotection/reduction/THP-deprotection to provide smoothly the allylic alcohol 8. Next, we investigated the tandem Sharpless asymmetric epoxidation/epoxy opening reaction of 8, and careful condition screening showed that the use of the classical Sharpless catalyst (1.5 equiv.) at –50 °C could give the best result (90% yield, 91% ee) of the expected diol 9. However, when the catalyst loading was less than 1.0 equiv., the reaction gave product 9 with both low yield and poor enantioselectivity. For example, only 33% ee was achieved while a 0.3 equiv. Sharpless catalyst was employed. Cleavage of the diol 9 with NaIO₄ followed by the Grignard reaction with excess vinyl magnesium bromide afforded the allylic alcohol 10 as two diastereoisomers (2:1), which were protected as TIPS ethers 11



Scheme 3 Formal synthesis of (–)-platensimycin. Reagents and conditions: (a) *t*-BuLi, Et₂O, –78 °C to –30 °C, then 7; (b) PTS·H₂O, acetone/H₂O, RT; (c) NaBH₄, MeOH, 0 °C; (d) PTS·H₂O, MeOH, RT, 32% yield (4 steps); (e) (+)-DET, Ti(*i*-PrO)₄, *t*-BuO₂H, –25 °C to –50 °C, CH₂Cl₂, 90% yield, 91% ee; (f) (i) NaIO₄, NaHCO₃ (aq.), CH₂Cl₂; (ii) vinylMgBr, THF, (10', 29%; 10, 59% yield (2 steps)); (g) TIPSOTf, pyridine, CH₂Cl₂, (11', 88% yield; 11, 86% yield); (h) 4 Å MS, 2, 6-dibromopyridine, InCl₃, DDQ, CH₂Cl₂, RT; (i) Na₂CO₃, MeOH, 30 °C; (j) NaBH₄, MeOH, 0 °C, 43% (three steps); (k) TsCl, Et₃N, CH₂Cl₂, 98% yield; (l) AlCl₃, EtSH, CH₂Cl₂, RT, 80%; (m) TBAF, xylene, 130 °C, 85%.

(2 isomers, dr = 2 : 1). To our delight, when 11 (2 isomers) was subjected to the standard conditions of 0.1 eq. InCl₃ and 2.0 eq. DDQ, the expected aldehyde 12 with a benzoxa[3.2.1]octane skeleton was obtained as two diastereoisomers (dr = 1 : 5) in moderate 52% yield. As mentioned in our previous report, there are two possible ways to go through after the formation of intermediate A with a benzylic oxacarbenium cation under the oxidative conditions. One is a tandem cyclization/semipinacol rearrangement to give B and the other is a tandem [3,3]-cope rearrangement/aldol reaction.¹²

Although the major isomer of 12 did not possess the desired C-3 configuration, fortunately, a final basification of the reaction system with Na₂CO₃/MeOH could reverse the stereochemistry of aldehyde 12, which was directly reduced with NaBH₄ without purification to give alcohol 13 in 43% yield (dr = 3 : 1).¹³ Tosylation of the major isomer of 13 followed by demethylation with AlCl₃/EtSH¹⁴ gave precursor 14. Finally, treatment of 14 with anhydrous TBAF in xylene could initiate the dearomatization/intramolecular cyclization to afford the tetracyclic core 3 in 85% yield. Intermediate 3 showed the identical spectroscopic data (¹H and ¹³C NMR, IR, HRMS, and optical rotation) with the previously reported compound,^{3o} and could be easily converted to (–)-platensimycin by using the methods described by Corey³ⁱ and Nicolaou.^{3a}

Conclusions

In conclusion, the formal synthesis of (–)-platensimycin has been finished through the use of a new strategy, in which a newly developed tandem C–H oxidation/C–C coupling (cyclization)/rearrangement has been used as the key step. These results not only further demonstrate the utility of such a tandem reaction, but also provide additional choice for the construction of molecules with a benzoxa[3.2.1]octane skeleton.

Acknowledgements

This work was supported by the NSFC (no.: 21202073, 21290180, 21272097, 21372056, 21372104 and 21472077), the “111” Program of MOE, the Project of MOST (2012ZX09201101-003) and the fundamental research funds for the central universities (lzujbky-2013-236, lzujbky-2014-k20 and lzujbky-2015-k12).

Notes and references

- (a) S. B. Singh and J. F. Barrett, *Biochem. Pharmacol.*, 2006, **71**, 10062; (b) M. S. Butler and A. D. Buss, *Biochem. Pharmacol.*, 2006, **71**, 919.
- (a) J. Wang, S. M. Soisson, K. Young, W. Shoop, S. Kodali, A. Galgoci, R. Painter, G. Parthasarathy, Y. Tang, R. Cummings, S. Ha, K. Dorso, M. Motyl, H. Jayasuriya, J. Ondeyka, K. Herath, C. Zhang, L. Hernandez, J. Alloco,

- J. R. A'BasilioTormo, O. Genilloud, F. Vicente, F. Pelaez, L. Colwell, S. H. Lee, B. Michael, T. Felcetto, C. Gill, L. L. Silver, J. Hermes, K. Bartizal, J. Barrett, D. J. Schmatz, W. Becker, D. Cully and S. B. Singh, *Nature*, 2006, **441**, 358; (b) S. B. Singh, H. Jayasuriya, J. G. Ondeyka, K. B. Herath, C. Zhang, D. L. Zink, N. N. Tsou, R. G. Ball, A. Basilio, O. Genilloud, M. T. Diez, F. Vicente, F. Pelaez, K. Young and J. Wang, *J. Am. Chem. Soc.*, 2006, **128**, 11916.
- 3 For the total synthesis of platensimycin and related strategies, see: (a) K. C. Nicolaou, A. Li and D. J. Edmonds, *Angew. Chem., Int. Ed.*, 2006, **45**, 7086; (b) K. C. Nicolaou, D. J. Edmonds, A. Li and G. S. Tria, *Angew. Chem., Int. Ed.*, 2007, **46**, 3942; (c) Y. Zou, C.-H. Chen, C. D. Taylor, B. M. Foxman and B. B. Snider, *Org. Lett.*, 2007, **9**, 1825; (d) K. P. Kaliappan and V. Ravikumar, *Org. Lett.*, 2007, **9**, 2417; (e) P. Li, J. N. Payette and H. Yamamoto, *J. Am. Chem. Soc.*, 2007, **129**, 9534; (f) A. K. Ghosh and X. Kai, *Org. Lett.*, 2007, **9**, 4013; (g) A. K. Ghosh and K. Xi, *J. Org. Chem.*, 2009, **74**, 1163; (h) K. Tiefenbacher and J. Mulzer, *Angew. Chem., Int. Ed.*, 2007, **46**, 8074; (i) G. Lalic and E. J. Corey, *Org. Lett.*, 2007, **9**, 4921; (j) K. C. Nicolaou, D. Pappo, K. Y. Tsang, R. Gibe and D. Y.-K. Chen, *Angew. Chem., Int. Ed.*, 2008, **47**, 944; (k) C. H. Kim, K. Jang, P. S. Choi, Y. Y. K. Chung and E. Lee, *Angew. Chem., Int. Ed.*, 2008, **47**, 4009; (l) J. Matsuo, K. Takeuchi and H. Ishibashi, *Org. Lett.*, 2008, **10**, 4049; (m) S. Y. Yun, J.-C. Zheng and D. Lee, *J. Am. Chem. Soc.*, 2009, **131**, 8413; (n) K. C. Nicolaou, A. Li, S. P. Ellery and D. J. Edmonds, *Angew. Chem., Int. Ed.*, 2009, **48**, 6293; (o) N. A. McGrath, E. S. Bartlett, S. Sittihan and J. T. Njardarson, *Angew. Chem., Int. Ed.*, 2009, **48**, 8543; (p) S. T.-C. Eey and M. J. Lear, *Org. Lett.*, 2010, **12**, 5510; (q) P. Magnus, H. Rivera and V. Lynch, *Org. Lett.*, 2010, **12**, 5677; (r) E. Z. Oblak and D. L. Wright, *Org. Lett.*, 2011, **13**, 2263; (s) J. Wang and H. O. Sintim, *Chem. – Eur. J.*, 2011, **17**, 3352; (t) L. Zhu, Y. Han, G. Du and C.-S. Lee, *Org. Lett.*, 2013, **15**, 524; (u) S. Hirai and M. Nakada, *Tetrahedron*, 2011, **67**, 518; (v) E. Z. Oblak and D. L. Wright, *Org. Lett.*, 2011, **13**, 2263; (w) Y. Ueda, K. Iwahashi, K. Iguchi and H. Ito, *Synthesis*, 2011, 1532; (x) M.-A. Beaulieu, K. C. Guérard, G. Maertens, C. Sabot and S. Canesi, *J. Org. Chem.*, 2011, **76**, 9460; (y) S. Horii, M. Torihata, T. Nagasawa and S. Kuwahara, *J. Org. Chem.*, 2013, **78**, 2798; (z) L. Zhu, C. Zhou, W. Yang, S. He, G. Cheng, X. Zhang and C. Lee, *J. Org. Chem.*, 2013, **78**, 7912; (aa) S. Xing, W. Pan, C. Liu, J. Ren and Z. Wang, *Angew. Chem., Int. Ed.*, 2010, **49**, 3215.
- 4 recent reviews of synthesis of platensimycin, see: (a) K. Tiefenbacher and J. Mulzer, *Angew. Chem., Int. Ed.*, 2008, **47**, 2548; (b) D. T. Manallack, I. T. Crosby, Y. Khakham and B. Capuano, *Curr. Med. Chem.*, 2008, **15**, 705; (c) Y.-S. Yao and Z.-J. Yao, *Chin. J. Org. Chem.*, 2008, **28**, 1553; (d) P. Harsh and G. A. O'Doherty, *Chemtracts*, 2009, **22**, 31; (e) K. C. Nicolaou, J. S. D. Chen, J. Edmonds and A. A. Estrada, *Angew. Chem., Int. Ed.*, 2009, **48**, 660; (f) K. C. Nicolaou, J. S. Chen and S. M. Dalby, *Bioorg. Med. Chem.*, 2009, **17**, 2290; (g) X. Lu and Q. You, *Curr. Med. Chem.*, 2010, **17**, 1139; (h) K. Palanichamy and K. P. Kaliappan, *Chem. – Asian J.*, 2010, **5**, 668; (i) M. Saleem, H. Hussain, I. Ahmed, T. van Ree and K. Krohn, *Nat. Prod. Rep.*, 2011, **28**, 1534.
- 5 Z.-W. Jiao, Y.-Q. Tu, Q. Zhang, W.-X. Liu, S.-Y. Zhang, S.-H. Wang and F.-M. Zhang and S. Jiang, *Nat. Commun.*, 2015, DOI: 10.1038/ncomms8332.
- 6 For references on other DDQ mediated C–H oxidative coupling reactions, see reviews: (a) C.-J. Li, *Acc. Chem. Res.*, 2009, **42**, 335; (b) C. J. Scheuermann, *Chem. – Asian J.*, 2010, **5**, 436; (c) S. A. Girard, T. Knauber and C.-J. Li, *Angew. Chem., Int. Ed.*, 2014, **53**, 74 For selected recent examples: (d) Y. Zhang and C.-J. Li, *Angew. Chem., Int. Ed.*, 2006, **45**, 1949; (e) Z. Li and C.-J. Li, *J. Am. Chem. Soc.*, 2006, **128**, 56; (f) Y. Zhang and C.-J. Li, *J. Am. Chem. Soc.*, 2006, **128**, 4242; (g) L. Zhao and C.-J. Li, *Angew. Chem., Int. Ed.*, 2008, **47**, 7075; (h) W. Tu, L. Liu and P. E. Floreancig, *Angew. Chem., Int. Ed.*, 2008, **47**, 4184; (i) W. Tu and P. E. Floreancig, *Angew. Chem., Int. Ed.*, 2009, **48**, 4567; (j) L. Liu and P. E. Floreancig, *Org. Lett.*, 2009, **11**, 3132; (k) L. Liu and P. E. Floreancig, *Angew. Chem., Int. Ed.*, 2010, **49**, 3069; (l) L. Liu and P. E. Floreancig, *Angew. Chem., Int. Ed.*, 2010, **49**, 5894; (m) Y.-Z. Li, B.-J. Li, X.-Y. Lu, S. Lin and Z.-J. Shi, *Angew. Chem., Int. Ed.*, 2009, **48**, 3817; (n) B. Yu, T. Jiang, J. Li, Y. Sun, X. Pan and X. She, *Org. Lett.*, 2009, **11**, 3442; (o) A. K. Ghosh and X. Cheng, *Tetrahedron Lett.*, 2012, **53**, 2568; (p) Z. Meng, S. Sun, H. Yuan, H. Lou and L. Liu, *Angew. Chem., Int. Ed.*, 2014, **53**, 543; (q) Z. Lu, M. Yang, P. Chen, X. Xiong and A. Li, *Angew. Chem., Int. Ed.*, 2014, **53**, 13840.
- 7 For reviews, see: (a) S.-Y. Zhang, F.-M. Zhang and Y.-Q. Tu, *Chem. Soc. Rev.*, 2011, **40**, 1937; For recent examples, see: (b) L. Shi, Y.-Q. Tu, M. Wang, F.-M. Zhang, C.-A. Fan, Y.-M. Zhao and W.-J. Xia, *J. Am. Chem. Soc.*, 2005, **127**, 10836; (c) K. Cao, Y.-J. Jiang, S.-Y. Zhang, C.-A. Fan, Y.-Q. Tu and Y.-J. Pan, *Tetrahedron Lett.*, 2008, **49**, 4652; (d) S.-Y. Zhang, Y.-Q. Tu, C.-A. Fan, F.-M. Zhang and L. Shi, *Angew. Chem., Int. Ed.*, 2009, **48**, 8761; (e) Z.-W. Jiao, S.-Y. Zhang, C. He, Y.-Q. Tu, S.-H. Wang, F.-M. Zhang, Y.-Q. Zhang and H. Li, *Angew. Chem., Int. Ed.*, 2012, **51**, 8811.
- 8 For reviews, see: (a) Z.-L. Song, C.-A. Fan and Y.-Q. Tu, *Chem. Rev.*, 2011, **111**, 7523; (b) B. Wang and Y.-Q. Tu, *Acc. Chem. Res.*, 2011, **44**, 1207; (c) S. H. Wang, B. S. Li and Y.-Q. Tu, *Chem. Commun.*, 2014, **50**, 2393; For recent examples, see: (d) X.-M. Zhang, Y.-Q. Tu, F.-M. Zhang, H. Shao and X. Meng, *Angew. Chem., Int. Ed.*, 2011, **50**, 3916; (e) J. Peng, X. Hou, S. Zhang and Y. Tu, *Acta Chim. Sin.*, 2012, **70**, 2232; (f) J.-M. Tian, X. Zhao, Y.-Q. Tu, W. Gong, F.-M. Zhang, S.-Y. Zhang and S.-H. Wang, *Chem. – Asian J.*, 2014, **9**, 724.
- 9 (a) W. Winstein and R. Baird, *J. Am. Chem. Soc.*, 1957, **79**, 756; (b) S. Masamune, *J. Am. Chem. Soc.*, 1961, **83**, 1009.

- 10 M.-Y. Lin, A. Das and R.-L. Liu, *J. Am. Chem. Soc.*, 2006, **128**, 9340.
- 11 J. Kuk, B. S. Kim, H. Jung, S. Choi, J.-Y. Park and S. Koo, *J. Org. Chem.*, 2008, **73**, 1991.
- 12 M. H. Hopkins, L. E. Overman and G. M. Rishton, *J. Am. Chem. Soc.*, 1991, **113**, 5354.
- 13 The relative configuration of **13** was determined by comparing it with a known compound reported by Njardarson and co-workers: ref. 3*o*.
- 14 M. Node, K. Nishide, K. Fuji and E. Fujita, *J. Org. Chem.*, 1980, **45**, 4275.