Tetrahedron Letters 52 (2011) 3266–3270

Contents lists available at ScienceDirect

Tetrahedron Letters

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

An improved synthesis of 2-oxa-7-azaspiro[3,5]nonane and analogs as novel reagents in medicinal chemistry

Ruo Xu [a], Michael Czarniecki [a], Jos de Man [b], Jianping Pan [a], Li Qiang [a], Yuriko Root [a], Shihong Ying [a], Jing Su [a,*], Xijun Sun [c], Yuping Zhang [c], Tao Yu [c], Yang Zhang [c], Tao Hu [c], Shu-Hui Chen [c]

[a] Department of Chemical Research, Merck Research Laboratory, 2015 Galloping Hill Road, Kenilworth, NJ 07033, United States
[b] Department of Medicinal Chemistry, Merck Research Laboratory, PO Box 20, 5349 BH, Oss, The Netherlands
[c] Wuxi AppTec Co., 288 Fute Zhong Road, Waigaoqiao Free Trade Zone, Shanghai 200131, China

ARTICLE INFO

Article history:
Received 24 February 2011
Revised 11 April 2011
Accepted 12 April 2011
Available online 27 April 2011

Keywords:
Spirocyclic oxetane
2-Oxa-7-azaspiro[3,5]nonane
2-Oxa-6-azaspiro[3,5]nonane
2-Oxa-6-azaspiro[3,4]octane

ABSTRACT

A detailed synthesis of novel spirocyclic oxetane analogs is described for the first time.

1. Introduction

The four-membered heterocyclic ring oxetane has been known in literature for almost a century.[1] It has been found in pharmaceutically important natural products such as paclitaxol,[2] oxetin[3] and oxetanocin[4] although the contribution of the oxetanes to their pharmacological properties is not clear. In 2006, Carreira and co-workers[5] reported that introduction of an oxetane ring into a molecule as an isostere of a *gem*-dimethyl group could have several advantages from the medicinal chemistry point of view. Although these two moieties have roughly the same van der Waals volume, the oxetane ring could significantly improve the physical properties of a scaffold by lowering the lipophilicity and enhancing aqueous solubility. Stability testing in pH 1–10 aqueous buffers indicates that oxetanes are quite stable in general. Metabolically, they can potentially improve microsomal stability in humans and mice. In a further study by the same group, a series of spirocyclic oxetanes such as 2-oxa-7-azaspiro[3,5]nonane **1b** (Fig. 1) were synthesized and experimental data supported the above conclusion.[6] They suggested the oxetane ring as a surrogate of a carbonyl group and compound **1a** (Fig. 1) as a surrogate of morpholine, a widely used fragment in medicinal chemistry, making them as promising modules in medicinal chemistry.

The six-step synthesis of 2-oxa-7-azaspiro[3,5]nonane **1b** starting from the unstable and expensive oxetan-3-one **4** was described in the above Letter (Fig. 2).[6] Similarly, compound **3b** was synthesized from Michael acceptor **5** in 3 steps while compound **2b**[6] was made via 2,6-dioxaspiro[3,3]heptane **7**[7] in 4 steps. All starting materials are either quite expensive or not commercially available. Furthermore, the synthesis of parent compounds **1a**, **2a** and **3a** (Fig. 1) was not described in the paper. We realized the importance of such novel small molecules in medicinal chemistry and believed that a more economic route could be developed to synthesize such spirocyclic oxetanes in large quantity. Herein, we describe our own efforts for the synthesis of compounds **1a** via a literature route[8] with modification and the synthesis of closely related analogs **2a** and **3a**.

We decided to adopt a published route to synthesize **1a** from the readily available starting material ethyl isonipecotate **10** (Scheme 1). The reported procedure included a five-step synthesis, three chromatographic purifications and an overall yield of 4%,

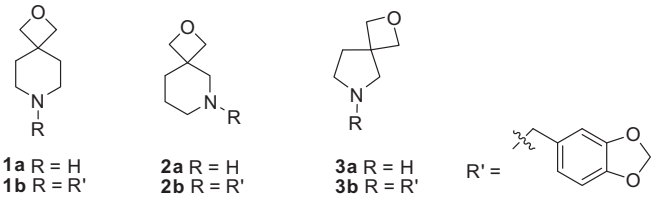


Figure 1. Examples of spirocyclic oxetanes.

* Corresponding author. Tel.: +1 908 740 7489; fax: +1 908 740 7164.
E-mail address: jing.su2@Merck.com (J. Su).

0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.04.054

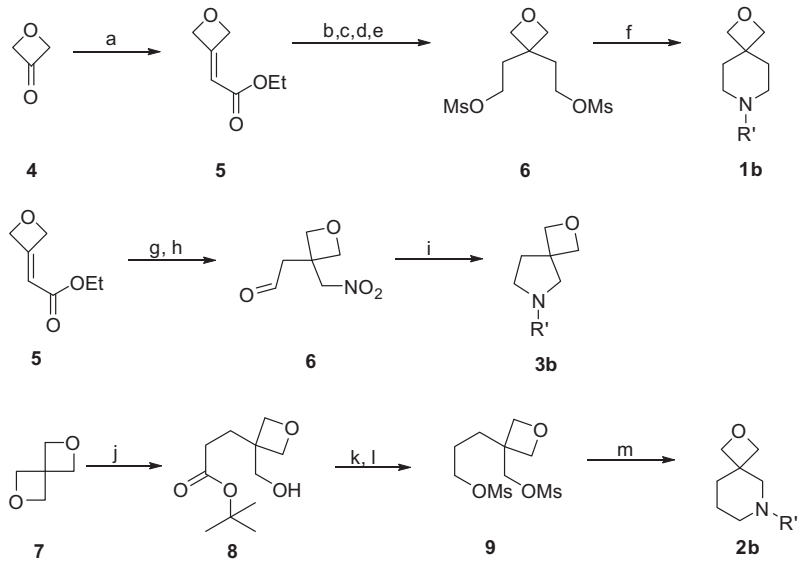
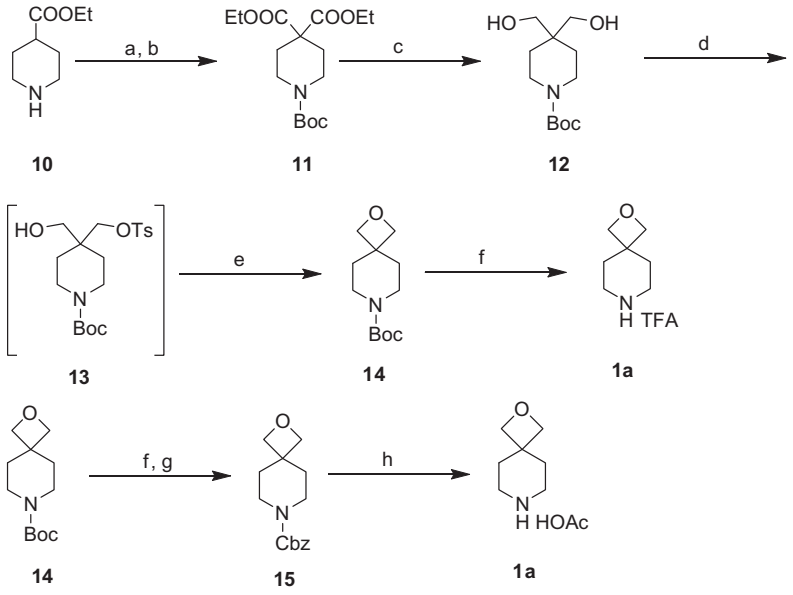


Figure 2. Literature synthesis of spirocyclic oxetanes. Reagents and conditions: (a) Ph_3PCHCO_2Et, DCM, rt, 89%; (b) $H_2C(CO_2Me)_2$, NaH; (c) NaCl, DMSO, 160 °C, 1.5 h, 82% (2 steps); (d) $LiAlH_4$; (e) MsCl, Et_3N, 100%; (f) $R'NH_2$, 38% (3 steps); (g) $MeNO_z$, cat. DBU, 92%; (h) DIBAL-H, 73%; (i) H_2, Pd/C, then piperonal, $NaBH(OAc)_3$, 53%;(j) $LiO(tBuO)C{=}CH_2$, BF_3Et_2O; (k). $LiAlH_4$, 0 °C; (I) MsCl, Et_3N; (m) $R'NH_2$, 80 °C, 49% (3 steps).



Scheme 1. Synthesis of 2-oxa-7-azaspiro[3,5]nonane **1a**. Reagents and conditions: (a) BOC_2O, DCM, rt, 100%; (b) LDA, $ClCO_2Et$; (c) $LiBH_4$, Toluene/THF, 60 °C, 39–52% (2 steps); (d) nBuLi, TsCl; (e) nBuLi, 65%; (f) TFA, DCM; (g) CbzCl, K_2CO_3, 84% (2 steps); (h) H_2, Pd/C, then HOAc, 83%.

mainly due to a poor deprotection reaction as the last step (17% yield, 8 mg final product as TFA salt). In our hands, the Boc protection, C-4 carbon–carbon bond formation and reduction of diester **11** were carried out sequentially and a simple recrystallization provided the diol **12** in 39–52% yield in three steps without chromatographic purification.[9] Several conditions were subsequently explored for the formation of the oxetane **14**. The use of triethylamine and *p*-toluenesulfonyl chloride to form monotosylate **13** in situ followed by the addition of NaH was difficult since the reaction would proceed further to afford the bistosylate product. The desired product **14** was not observed under this condition. This result led us to use a stronger base such as NaH to better control the deprotonation/monotosylate formation step. The application of NaH (1 equiv)/TsCl (1 equiv) followed by another equivalent of NaH turned out to afford a complex product mixture and the desired product **14** was isolated in less than 10% yield. Eventually, nBuLi and toluenesulfonyl chloride were used to selectively generate the monotosylate intermediate **13**, which, without isolation and purification, was treated with another equivalent of nBuLi to form the oxetane **14** in 65% after chromatography.[10]

The deprotection of the N-Boc group on compound 14 was indeed troublesome. The reaction required an excess of TFA (6–8 equiv) at 0 °C–room temperature for several hours. The removal of the excess TFA led to the partial decomposition of the product, presumably via oxetane ring opening. If the TFA was not removed and the pH was adjusted to 7–8 with sodium bicarbonate, extraction could afford the desired TFA salt of **1a**. However, the excess sodium salt of TFA always remained even after rigorous aqueous wash. We also attempted to make the HCl salt of **1a** by directly treating compound **14** with 2 M HCl in ethyl acetate at 0 °C and

this led to complete opening of the oxetane ring. These results prompted us to slightly modify the deprotection procedure. After TFA treatment of compound **14**, the in situ generated compound **1a** was immediately protected with a Cbz group to afford **15** in 84% yield by recrystallization. After the deprotection of the Cbz group, the product was treated with one equivalent of acetic acid to give **1a** as the HOAc salt in 83% yield. Overall, this modified procedure required one purification step by chromatography and the overall yield was improved from 4% to 18%, allowing us access to multi-gram quantities of the material.

Based on the above results, we used the same route to synthesize compound **2a** starting from ethyl nipecotate **16** (Scheme 2). This time, the piperidine N was protected with a Cbz group and the final product **2a** as the HOAc salt was obtained in 13% yield in five steps. Since the diol intermediate **18** was not a solid, one extra purification step by chromatography was required.

The synthesis of 2-oxa-6-azaspiro[3,4]octane **3a** was accomplished in a similar manner (Scheme 3). The starting material **21** was made via the 1,3-dipolar cycloaddition in 75% yield. Treatment with LDA and methyl chlorolformate provided the diester **22** in 75% yield. Reduction with $LiAlH_4$ provided the diol **23** in 74% yield. The monotosylation of **22** was successful with nBuLi/TsCl. However, the cyclization with nBuLi failed to proceed at room temperature. Further heating led to the decomposition of the monotosylate intermediate. This observation prompted us to try weaker bases for the cyclization and eventually, the use of NaOMe afforded the cyclization product **24** in 59% yield from **22**. The final debenzylation reaction smoothly afforded the desired product 2-oxa-6-azaspiro[3,4]octane **3a** as the HOAc salt in 88% yield (5 steps, 21% overall yield).

In summary, we have provided for the first time the detailed synthesis of novel reagents 2-oxa-7-azaspiro[3,5]nonane **1a** and its analogs **2a** and **3a**. The improved synthetic procedure allowed us quick access to these reagents in multi-gram quantities and making them more accessible as morpholine surrogates or novel building blocks in medicinal chemistry.

2. Representative experimental procedure

2.1. Preparation of compound 12

To a solution of LDA (940 mL, 2 M, 1.87 mol) in dry THF (1.5 L) at −78 °C was added N-Boc ethyl isonepicotate (160.0 g, 0.622 mol) in dry THF (1 L) at −78 °C dropwise. The mixture was stirred at −78 °C for 2 h and at −40 °C for 3 h. The solution was cooled to −78 °C and ethyl chloroformate (202.4 g, 1.87 mol) in dry THF (1 L) was added slowly. The reaction was stirred at −78 °C for 0.5 h and at rt overnight. The reaction was quenched with saturated NH_4Cl (800 mL) at 0 °C. The aqueous layer was extracted with EtOAc (500 mL × 2). The combined organic phase was washed with HCl (1 M, 1 L), brine (1 L × 1), dried over Na_2SO_4 and concentrated to get compound **11** (crude, 350.0 g, 0.622 mol) as an oil. MS: 229.9 $[M-Boc+H]^+$.

To a solution of the above compound **11** (350.0 g, 0.622 mol, crude) in dry toluene/THF (1:1, 4.0 L) was added $LiBH_4$ (108.4 g, 4.98 mol) in portions at 5–10 °C. The reaction was stirred at 60 °C overnight. The reaction was quenched by saturated NH_4Cl at 0 °C until the organic phase was clear. 500 mL of EtOAc was added and the organic layer was separated. The aqueous layer was extracted with EtOAc (1 L × 3). The combined organic phase was washed with brine (1 L × 1), dried over Na_2SO_4 and concentrated to get crude product (230.0 g). The residue was purified by recrystallization (PE: EtOAc = 3:1) to give compound **12** (60.0 g, 0.245 mol, 39% yield in two steps) as a white solid.

^1H NMR ($CDCl_3$): δ 1.40 (s, 9H), 1.42 (m, 4H), 2.49 (br s, 2H), 3.32 (m, 4H), 3.60 (s, 4H).

MS: 146.3 $[M-Boc+H]^+$.

2.2. Preparation of compound 14

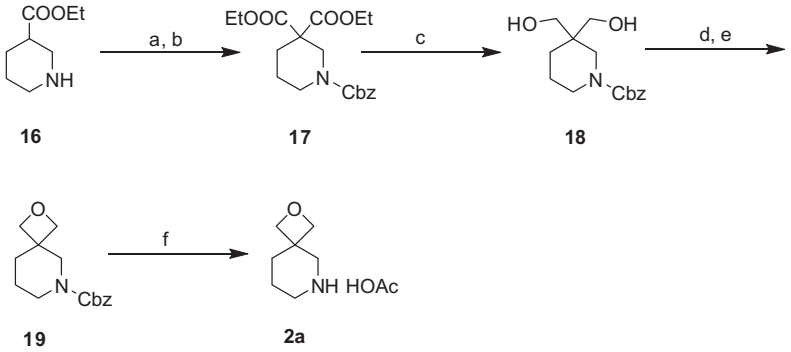
To a solution of compound **12** (60.0 g, 244.58 mmol) in dry THF (1.2 L) at 0 °C was added nBuLi (97.8 mL, 0.245 mol, 2.5 M) and the mixture was stirred at 0 °C for 0.5 h. TsCl (46.6 g, 0.245 mmol) in dry THF (600 mL) was added dropwise and stirred at 0 °C for 1.5 h when TLC showed that compound **12** was consumed completely. To the reaction mixture was added *n*-BuLi (97.8 mL, 0.245 mmol, 2.5 M) at 0 °C and stirred at 0 °C for 0.5 h. The reaction mixture was then stirred at 60 °C for 1 h. The reaction was quenched by saturated NH_4Cl (400 mL) at 0 °C. After separation, the aqueous layer was extracted with EtOAc (300 mL × 3). The combined organic phase was washed with brine (800 mL × 2), dried over Na_2SO_4 and concentrated to get crude product (65 g). The residue was purified by flash chromatography (PE: EtOAc = 30:1–10:1) to give compound **14** (37.0 g, 66% yield) as a white solid.

^1H NMR ($CDCl_3$): δ 1.47 (s, 9H), 1.83 (t, 4H, J = 5.6 Hz), 3.35 (t, 4H, J = 5.6 Hz), 4.46 (s, 4H).

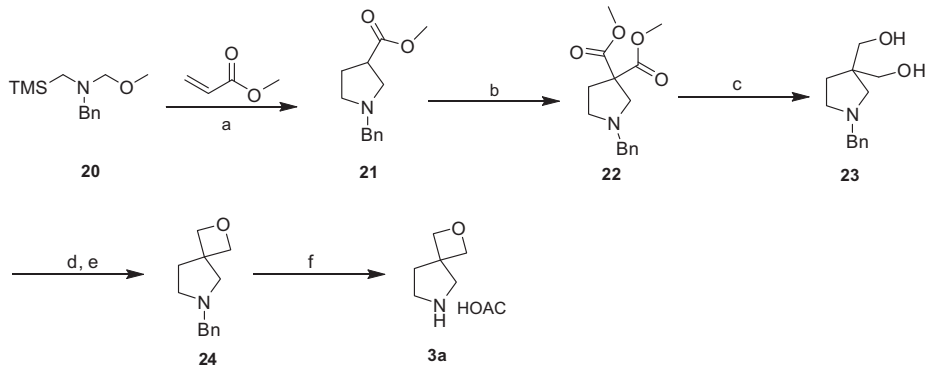
MS: 127.9 $[M-Boc+H]^+$.

2.3. Preparation of compound 15

To a solution of compound **14** (29.0 g, 127.6 mmol) in DCM (230 mL) at 0 °C was added TFA (58 mL) in DCM (60 mL) and the mixture was stirred at rt for 3 h. The reaction mixture was cooled to 0 °C and water (100 mL) was added. After separation, the organic phase was washed with water (50 mL × 2). The combined aqueous layer was extracted with DCM (100 mL × 2). The aqueous layer was adjusted to pH to 7–8 by adding solid K_2CO_3. Dioxane



Scheme 2. Synthesis of 2-oxa-6-azaspiro[3,5]nonane **2a**. Reagents and conditions: (a) CbzCl, K_2CO_3, 99%; (b) LDA, $ClCO_2Et$; (c) $LiBH_4$, Toluene/THF, 34% (2 steps); (d) nBuLi, TsCl; (e) nBuLi, 46% (2 steps); (f) H_2, Pd/C, then HOAc, 83%.



Scheme 3. Synthesis of 2-oxa-6-azaspiro[3,4]octane **3a**. Reagents and conditions: (a) cat. TFA, DCM, 75%; (b) LDA, $ClCO_2Me$, 75%; (c). 2 equiv $LiAlH_4$, 74%; (d). 1.1 equiv. nBuLi, 0.9 equiv TsCl; (e) 2 equiv NaOMe, 59% (2 steps); (f) H_2, $Pd(OH)_2/C$, then HOAc, 88%.

(200 mL), K_2CO_3 (35.3 g, 255.17 mmol) was added followed by dropwise addition of CbzCl (23.9 g, 140.3 mmol). The reaction was stirred at rt for 2 h. The mixture was added to EtOAc (200 mL) and the organic layer separated. The aqueous layer was extracted with EtOAc (500 mL × 1). The combined organic phase was washed with brine (500 mL × 1), dried over Na_2SO_4 and concentrated to get crude product (32.0 g). The residue was purified by recrystallization (PE: EtOAc = 10:1) to get compound **15** (28.0 g, 107.4 mmol, 84% yield) as a white solid.

^{1}H NMR (DMSO-d_6): δ 1.65 (m, 4H) 3.30 (m, 4H) 4.30 (s, 4H) 5.02 (s, 2H) 7.28–7.42 (m, 5H).

MS: 261.8 $[M+H]^+$.

2.4. Preparation of compound 1a (HOAc salt)

To a solution of compound **15** (15.0 g, 57.4 mmol) in MeOH (150 mL) was added wet Pd/C (10%/w, 1.5 g). The reaction was stirred under H_2 balloon at rt overnight. The reaction mixture was filtered through a pad of celite and the filtrate was concentrated to give the crude product (7.0 g), which was dissolved in DCM (200 mL). HOAc (3.5 g, 57.9 mmol) was added and the mixture was stirred at 0 °C for 15 min and concentrated at 0 °C to get a solid. The solid was further washed with PE: EtOAc = 20:1 (50 mL) to afford **1a** (8.9 g, 83%) as HOAc salt (a white solid).

^{1}H NMR (DMSO-d_6): δ 1.70 (t, 4H, J = 5.6 Hz) 1.75 (s, 3H) 2.64 (t, 4H, J = 5.6 Hz) 4.20 (s, 4H).

^{13}C NMR (DMSO-d_6): δ 23.3 34.7 38.9 42.6 81.5 173.9.

HRMS for $C_7H_{13}NO^+$ $[M+H]^+$ Calcd 128.1070; Found 128.1068.

2.4.1. Compound 17

^{1}H NMR ($CDCl_3$): δ 1.10–1.25 (m, 6H) 1.60–1.70 (m, 2H) 2.08–2.11 (m, 2H) 3.44–3.50 (m, 2H) 3.97 (s, 2H) 4.11–4.18 (m, 4H) 5.12 (s, 2H) 7.30–7.35 (m, 5H).

MS: 364.0 $[M+H]^+$.

2.4.2. Compound 18

^{1}H NMR (DMSO): δ 1.32–1.40 (m, 2H) 1.41–1.50 (m, 2H) 3.18–3.34 (m, 8H) 5.03 (s, 2H) 7.30–7.38 (m, 5H).

MS: 279.9 $[M+H]^+$.

2.4.3. Compound 19

To a solution of compound **18** (99.0 g, 0.35 mol) in dry THF (2 L) at 0 °C was added *n*-BuLi (2.5 M, 141.8 mL, 0.35 mol) at 0 °C over 0.5 h. Then TsCl (67.6 g, 0.35 mol) in dry THF (1 L) was added dropwise at 0 °C and stirred for 2 h. Once the TLC showed that compound **18** was consumed completely, *n*-BuLi (2.5 M, 141.8 mL, 0.35 mol) at 0 °C was added to the mixture and stirred at 0 °C for 30 min and warmed to 25–30 °C overnight. The reaction was quenched by saturated NH_4Cl (1 L) at 0 °C and separated. The aqueous layer was extracted with EtOAc (400 mL × 2). The combined organic phase was washed with brine (800 mL × 2), dried over Na_2SO_4 and concentrated to get crude product (100.0 g). The residue was purified by flash chromatography (PE: EtOAc = 10:1–5:1) to give compound **19** (43.0 g, 0.16 mol, 46 % yield) as an oil.

^{1}H NMR ($CDCl_3$): δ 1.42–1.51 (m, 2H) 1.83–1.87 (m, 2H) 3.30–3.40 (m, 2H) 3.68 (s, 2H) 4.30–4.50 (m, 4H) 5.14 (s, 2H) 7.26–7.38 (m, 5H).

MS: 261.9 $[M+H]^+$.

2.5. Compound 2a (HOAc salt)

^{1}H NMR (DMSO-d_6): δ 1.34 (m, 2H) 1.68 (m, 2H) 1.70 (s, 3H) 2.48–2.56 (m, 2H) 2.82 (br s, 2H) 4.18 (d, 2H, J = 6.0 Hz) 4.22 (d, 2H, J = 6.0 Hz).

^{13}C NMR (DMSO-d_6): δ 22.6 23.3 34.0 39.6 45.7 54.0 80.5 173.4.

HRMS for $C_7H_{13}NO^+$ $[M+H]^+$ Calcd 128.1070; Found 128.1068.

2.5.1. Compound 22

^{1}H NMR (CD_3OD): δ 2.43–2.47 (m, 2H) 2.68–2.70 (m, 2H) 3.09 (s, 2H) 3.66 (s, 2H) 3.71 (s, 6H) 7.29–7.35 (m, 5H).

MS: 278.1 $[M+H]^+$.

2.5.2. Compound 23

^{1}H NMR (CD_3OD): δ 1.75–1.78 (m, 2H) 2.75 (s, 2H) 2.93–2.95 (m, 2H) 3.50–3.53 (m, 4H) 3.90 (s, 2H) 7.33–7.44 (m, 5H).

MS: 222.1 $[M+H]^+$.

2.5.3. Compound 24

To a stirred solution of compound **23** (130.8 g, 0.59 mol) in THF (1.5 L) was added *n*-BuLi dropwise (256 mL, 0.64 mol, 2.5 M in hexane) at −78 °C. After addition, the mixture was stirred for 0.5 h at the same temperature followed by the addition of TosCl (100.9 g, 0.53 mol) in THF (150 mL) at −78 °C. The reaction mixture was allowed to warm up to rt and stirred for 1 h before freshly prepared NaOMe (27.5 g Na in 300 mL MeOH, 1.19 mol, 2 equiv) was added. After addition the resulting mixture was heated to reflux overnight. After TLC showed the starting material was consumed completely, the reaction mixture was quenched with saturated NH_4Cl (100 mL). The solvent was concentrated in *vacuum*, and the residue was separated using EtOAc (1200 mL) and water (500 mL). The aqueous layer was extracted with EtOAc (500 mL × 3), and the combined organic layer was dried over Na_2SO_4, then the filtrate

was concentrated. The crude was purified by flash chromatography (PE: EtOAc = 25:1–5:1) to afford compound **24** (71.2 g, 0.35 mol, 59% yield) as a yellowish oil.

^{1}H NMR ($CDCl_3$): δ 2.12–2.15 (m, 2H) 2.57–2.60 (m, 2H) 2.85 (s, 2H) 3.62 (s, 2H) 4.57–4.61 (m, 4H) 7.23–7.30 (m, 5H).

MS: 204.1 $[M+H]^+$.

2.6. Compound 3a (HOAc salt)

^{1}H NMR (CD_3OD): δ 1.75 (s, 3H) 2.15–2.19 (m, 2H) 3.08–3.12 (m, 2H) 3.33 (s, 2H) 4.45 (d, 2H, J = 6.4 Hz) 4.54 (d, 2H, J = 6.4 Hz).

MS: 114.0 $[M+H]^+$.

HRMS for $C_6H_{11}NO^+$ $[M+H]^+$ Calcd 114.0914; Found 114.0912.

Acknowledgments

We thank Drs. Tin-Yau Chan, William Greenlee, Malcolm MacCoss and Wuxi AppTec supporting teams for their strong support. We also thank Drs. Robert Aslanian and Andrew Stamford for their valuable suggestion to the manuscript.

References and notes

1. Deric, C. G.; Bissel, D. W. *J. Am. Chem. Soc.* **1916**, *38*, 2748.
2. Kingston, D. G. I. *J. Nat. Prod.* **2000**, *63*, 726.
3. Omura, S.; Murata, M.; Imamura, N.; Iwai, Y.; Tanaka, H.; Furusaki, A. *J. Antibiot.* **1984**, *37*, 1324.
4. Shimada, N.; Hasegawa, S.; Harada, T.; Tomisawa, T.; Fujii, A.; Takita, T. *J. Antibiot.* **1986**, *39*, 1623.
5. (a) Wuitschik, G.; Rogers-Evans, M.; Muller, K.; Fischer, H.; Wagner, B.; Schuler, F.; Polonchuk, L.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 7736; (b) Wuitschik, G.; Carreira, E. M.; Wagner, B.; Fischer, H.; Parrilla, I.; Schuler, F.; Rogers-Evans, M.; Muller, K. *J. Med. Chem.* **2010**, *53*, 3227.
6. Wuitschik, G.; Rogers-Evans, M.; Buckl, A.; Bernasconi, M.; Marki, M.; Godel, T.; Fischer, H.; Wagner, B.; Parrilla, I.; Schuler, F.; Scheider, J.; Alker, A.; Schweizer, W. B.; Muller, K.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4512.
7. Churcher, I.; Harrison, T.; Kerrad, S.; Oakley, P.; Shaw, D.; Teall, M.; Williams, S. PCT Int. Appl. WO2004031137 A1.
8. Castropineiro, J. L.; Dinnell, K.; Elliott, J. M.; Hollingworth, G. J.; Shaw, D. E.; Swain, C. J. PCT Int. Appl. WO200187838 A1.
9. The mother liquor still contained the desired product but was not further purified.
10. The use of MsCl, Et_3N followed by the treatment with NaH led to the desired product **14** in 38% yield according to Ref. [8].