Tetrahedron: *Asymmetry* xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

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

Formal asymmetric synthesis of (+)-tofacitinib

Hao-Chun Liao, Biing-Jiun Uang *

Department of Chemistry, National Tsing Hua University, No. 101, Sec 2, Kuang-Fu Rd., Hsinchu City 30013, Taiwan

ARTICLE INFO

Article history:
Received 23 September 2016
Revised 11 November 2016
Accepted 25 November 2016
Available online xxxx

ABSTRACT

Tofacitinib is an efficient and selective Janus kinase 3 (JAK3) inhibitor, and is used as an immunosuppressant drug for the treatment of rheumatoid arthritis and transplant patients. Herein we report a concise formal asymmetric synthesis of tofacitinib from homochiral 1,3-dioxolanone **10b**, which was elaborated through a highly stereoselective Michael addition followed by solvent-free removal of the chiral auxiliary and ring cyclization to furnish chiral imide **8**. The preparation of tofacitinib's precursor **16** could be obtained after reduction of **8** followed by sequential oxidation, reductive amination and S_NAr reactions.

1. Introduction

The development of safe immunosuppressants for organ transplantation and autoimmune related diseases is an important issue. (+)-Tofacitinib **1**, also known as CP-690,550 and 3-((3*R*,4*R*)-4-methyl-3-(methyl(7*H*-pyrrolo-[2,3-*d*]pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopro-panenitrile, was first reported by Pfizer in 2003.[1] The structure of tofacitinib features a (3*R*,4*R*)-disubstituted piperidine that is linked to a deazapurine fragment. Tofacitinib has been demonstrated to be an efficient and selective Janus kinase 3 (JAK3) inhibitor, and is an immunosuppressant drug for the treatment of rheumatoid arthritis and transplant patients. Due to its highly potent biological activities, many groups have tried to develop an efficient and stereoselective strategy for the synthesis of tofacitinib.[2,3]

Although strategies for the synthesis of tofacitinib are known in the literature, asymmetric synthesis is rare.[3] Most of reported syntheses require resolution of racemic 3,4-disubstituted piperidines **2**[2j,k,o] or **3**[3], the key intermediates for the synthesis of (+)-tofacitinib, through di-*p*-toluoyltartrate salts. Chiral 3,4-disubstituted piperidine **2** is then reacted with 6-chloro-7-deazapurine **4** through an S_NAr mechanism or a Mitsunobu reaction[5] of **3** with 6-amino-7-deazapurine **5** to give the advanced intermediate for the synthesis of (+)-tofacitinib (Fig. 1). Herein we report an efficient formal asymmetric strategy for the synthesis of (+)-tofacitinib.

2. Results and discussion

Our retrosynthetic analysis for (+)-tofacitinib **1** is outlined in Scheme 1. In principle, (+)-tofacitinib could be furnished from **6** through functional group transformation of a benzyl group to an α-cyanoacetyl group. Compound **6** could be prepared via stereoselective reductive amination[4] of 6-amino-7-deazapurine **5** with piperidinone **7**. Key intermediate **7** could be prepared from imide **8** by the reduction of the imide followed by oxidation of the hydroxyl group. Imide **8** could be obtained from a double amidation of Michael adduct **9** derived from a stereoselective Michael reaction of chiral 1,3-dioxolanone to a crotonate.[6]

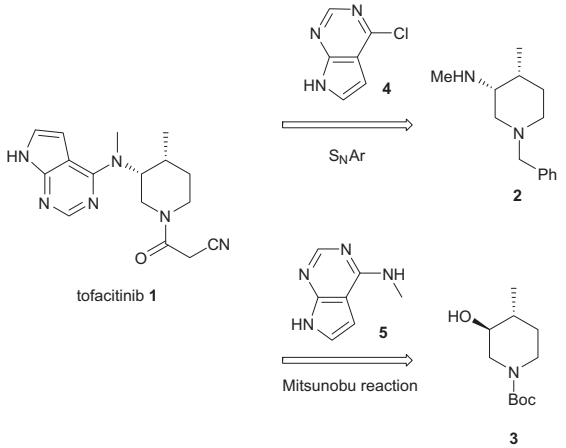
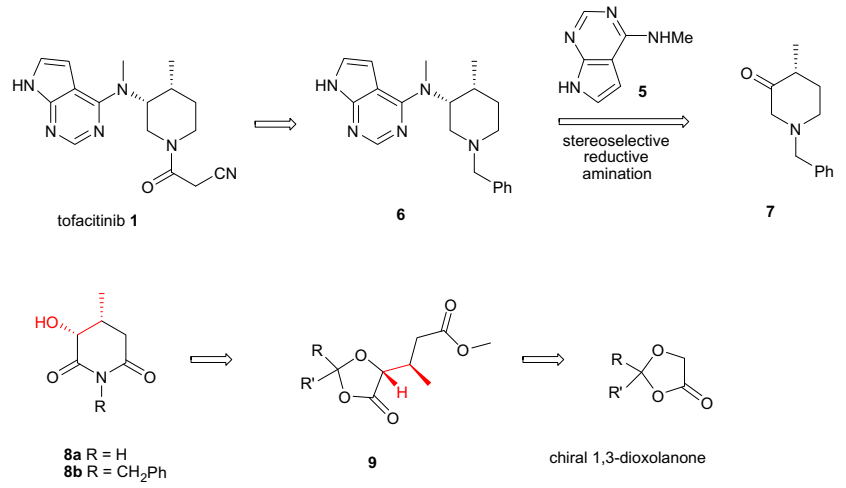


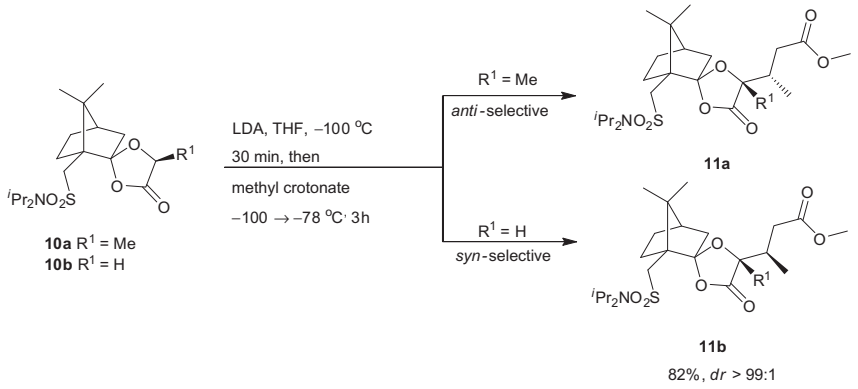
Figure 1. Known synthetic strategies for the synthesis of tofacitinib.

* Corresponding author. Tel.: +886 3 5715131 33410; fax: +886 3 5711082.
E-mail address: bjuang@mx.nthu.edu.tw (B.-J. Uang).

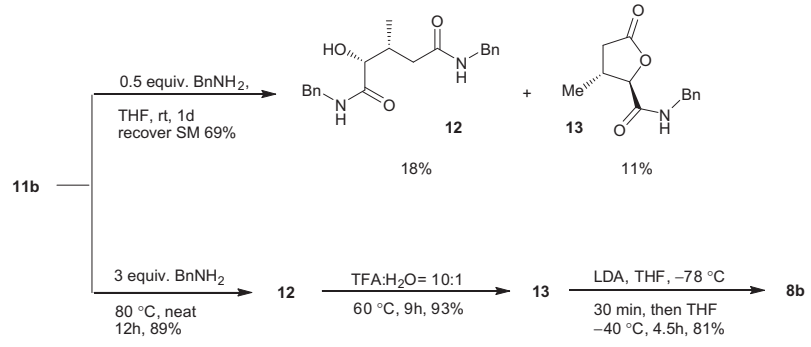
http://dx.doi.org/10.1016/j.tetasy.2016.11.013
0957-4166/



Scheme 1. Retrosynthetic analysis of (+)-tofacitinib **1**.



Scheme 2. Michael addition of enolate from protected α–hydroxy acid **10** to α,β-unsaturated esters.

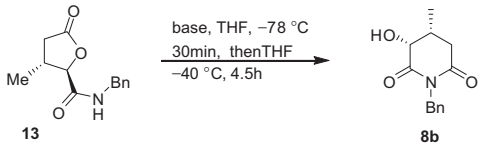


Scheme 3. Synthesis of imide **8b** from **10b**.

The preparation of chiral 1,3-dioxolanones from glycolic acid and their α-alkylation has been reported by Pearson et al.,[6a] Ley et al.,[6b] and our group.[6c] The diastereoselective Michael reactions of chiral 4-unsubtituted-1,3-dioxolanones have been reported by Ley et al.,[6d] and our group.[6e] We demonstrated that the Michael reaction of **10** and α,β-unsaturated esters could give the Michael adducts with excellent diastereo- and enantioselectivity (Scheme 2). In our previous studies,[6e] the Michael addition of the enolate of chiral 1,3-dioxolanone **10b** to methyl crotonate was achieved to give **11b** in 82% yield and with high diastereoselectivity (dr >99:1). With this advantage in hand, we set out our formal asymmetric synthesis of (+)-tofacitinib.

An attempt to prepare imide **8a** by treating Michael adduct **11b** with ammonia gave an intractable mixture. Heating Michael adduct **11b** with benzylamine in THF gave poor yield of a mixture of **12** and **13** (Scheme 3). For example, it gave diamide **12** and **13** in 18% and 11% yields respectively when the reaction was conducted in THF. However, heating **11b** in benzylamine alone furnished diamide **12** in 89% yield. This solvent free procedure provided an efficient way of removing the chiral auxiliary and gave the product in

Table 1
Optimization of the ring expansion from lactone **13**



Entry	Base	Reaction concentration (M)	Molecular sieves 4 Å (wt %)	Yield (%)
1	^{t}BuOK	0.5	10%	10
2	LDA	0.5	10%	60
3	LDA	0.2	10%	66
4	LDA	0.1	10%	70
5	LDA	0.05	10%	64
6	LDA	0.1	16%	81
7	LDA	0.1	20%	50

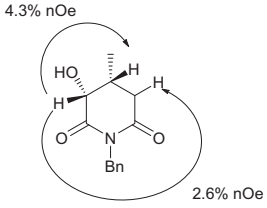


Figure 2. NOE experiment of **8b**.

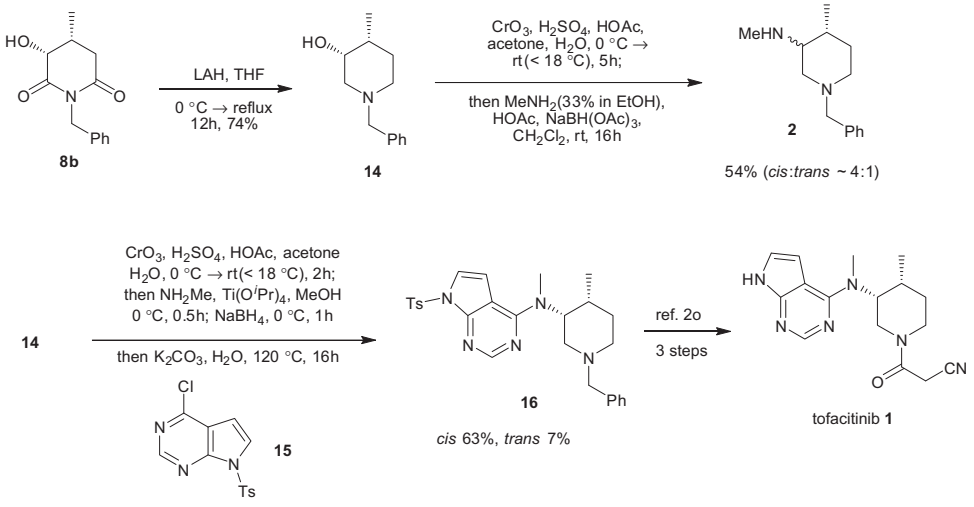
a higher yield. Treatment of diamide **12** in TFA–H_2O (10:1) gave γ-lactone **13** in 93% yield. When we attempted to convert γ-lactone **13** into imide **8b** by treatment with potassium *tert*-butoxide[7] (Table 1, entry 1), it gave a small amount of the desired product with decomposition of starting material. Ring expansion was then achieved to give imide **8b** with freshly prepared LDA, and the yield could be increased to 81% after dilution and the treatment of γ-lactone **13** with molecular sieves to absorb water (Table 1, entries 2–7). In order to prevent unexpected intermolecular reactions, dilution was required after deprotonation. However, too much dilution with THF or increasing the amount of molecular sieves did not improve the yield further. Ring expansion was slower at lower concentrations (entry 5), and the reaction might be disturbed by excessive amount of molecular sieves (entry 7). Entry 6 was the optimum conditions for the ring expansion of lactone **13**.

The resulting product **8b** showed no epimerization as confirmed by NOE experiment (Fig. 2).

With imide **8b** in hand, we next focused on the synthesis of piperidinone **7**. The conversion of **8b** into disubstituted piperidine **14** could be achieved in 74% yield after reduction with LAH (Scheme 4). Jones oxidation of 3-hydroxypiperidine **14** gave piperidinone **7**. Piperidinone **7** was unstable and so was used without purification. Reductive amination of piperidinone **7** with 6-amino-7-deazapurine **5** gave an intractable material. However, reductive amination of piperidinone **7** with methylamine in the presence of acetic acid and $NaBH(OAc)_3$ furnished **2**, a precursor for the synthesis of tofacitinib. The *cis*/*trans* ratio in **2** was approximately 4:1. Since amine **2** was also unstable, piperidine **14** was oxidized followed by reductive amination using $NaBH_4$ as the reducing agent and an S_NAr reaction with **15** to give coupling products *cis*-**16** and *trans*-**16** in 63% and 7% yield respectively without the isolation of **2**. After optimization, imine formation with $Ti(O^{i}Pr)_4$ followed by reduction with $NaBH_4$ afforded a cleaner product with higher diastereoselectivity. Therefore, it is more suitable for a sequential three-step reaction. The desired *cis*-**16** could be transformed into tofacitinib by a reported procedure[2o] in three steps.

3. Conclusions

We have developed a concise and highly enantioselective route for the formal asymmetric synthesis of (+)-tofacitinib in 8 steps in



Scheme 4. The synthesis of tofacitinib precursor **16** from imide **8b**.

26% overall yield from homochiral 1,3-dioxolanone **10b** to *cis*-**16** without using chemical resolution. Compared to known literature procedures,[2n,3] the synthetic steps for tofacitinib are reduced substantially. This synthetic strategy provides reliable new entries for the synthesis of tofacitinib, as well as the synthesis of piperidine based natural products and therapeutics with high enantiopurity.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded with a Varian Mercury-400 (400 MHz) spectrometer. Data are reported as follows: chemical shift values referenced to $CDCl_3$ (δ = 7.24 ppm), multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quadruplet, sept = septuplet, m = multiplet) and integration. ^{13}C NMR spectra were recorded with a Varian Mercury-400 (100 MHz) spectrometer. Chemical shift values are referenced to $CDCl_3$ (δ = 77.00 ppm) or DMSO-d_6 (δ = 39.40 ppm). HRMS data were recorded with mass spectrometers at the NSC Instrumentation Center at NTHU. IR spectra were obtained with a Bomen MB 100FT spectrometer. Thin-layer chromatography was performed with silica gel G60 F254 (Merck) with short-wavelength UV light for visualization. Silica Gel 60 (particle size 63–200 μm, purchased from Merck) was used for column chromatography.

4.2. Experimental procedures and characterization data

4.2.1. (2*R*,3*R*)-*N*^{1},*N*^{5}-Dibenzyl-2-hydroxy-3-methyl-pentanediamide 12

The known Michael adduct **11b**[6e] (1.2 g, 2.54 mmol) was dissolved in benzylamine (0.83 mL, 7.6 mmol) and stirred at 80 °C for 12 h. When the reaction mixture became solid, n–hexane containing 20% EtOAc was added and sonicated to crush the dissolution of solid. The insoluble product was collected by filtration and washed with *n*-hexane containing 20% EtOAc to give diamide **12** (0.64 g, 75%) as a white solid. The remaining filtrate was concentrated in vacuo and purified by silica gel column chromatography (MeOH/CH_2Cl_2, 1:20) to give additional diamide **12** (0.12 g, 14%, the total yield of diamide **12** was 89%). R_f = 0.25 (MeOH/CH_2Cl_2, 1:20). Mp 186–186.6 °C $[\alpha]_D^{28}$ = +22.6 (*c* 1.0 CH_3OH). IR (KBr, film): 3271, 2926, 1648, 1633, 1561, 1542, 696 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.50 (br s, 1H), 7.35–7.20 (m, 10H), 6.19 (br s, 1H), 4.45 (d, *J* = 6.4 Hz, 2H), 4.43–4.34 (m, 2H), 4.08 (d, *J* = 3.6 Hz, 1H), 2.65–2.60 (m, 1H), 2.46–2.41 (m, 1H), 2.31–2.25 (m, 1H), 1.12 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 173.0, 171.7, 139.7, 139.7, 128.2 (2C), 128.2 (2C), 127.2 (2C), 127.1 (2C), 126.7 (2C), 74.8, 42.0, 41.7, 37.4, 34.1, 15.8. HRMS (ESI) calcd for $C_{20}H_{25}N_2O_3$ $[M+H]^+$: 341.1865, found: 341.1868.

4.2.2. (2*R*,3*R*)-*N*-Benzyl-3-methyl-5-oxotetrahydrofuran-2-carboxamide 13

A stirred solution of **12** (0.5 g, 1.47 mmol) in TFA/H_2O (10:1, 2.9 mL) was heated to 90 °C. After stirring for 12 h at 90 °C, the reaction mixture was cooled to rt, basified to pH 7–8 with satd aq $NaHCO_3$, and the mixture was extracted with EtOAc (4 × 25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/hexanes, 1:1) to give **13** (0.32 g, 93%) as a colorless oil. R_f = 0.5 (EtOAc/hexanes, 1:1). $[\alpha]_D^{28}$ = +7.4 (*c* 1.0 $CHCl_3$). IR (KBr, film): 3300, 2968, 2931, 1787, 1661, 1535, 1150, 699 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38–7.20 (m, 5H), 6.67 (br s, 1H), 4.45–4.37 (m, 3H), 2.72–2.65 (m, 2H), 2.22 (dd, J_1 = 20.4 Hz, J_2 = 8.8 Hz, 1H), 1.36 (d, *J* = 3.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.9, 168.8, 137.3, 128.7, 127.8 (2C), 127.7 (2C), 83.3, 43.1, 36.0, 35.1, 18.8. HRMS (ESI) calcd for $C_{13}H_{16}NO_3$ $[M+H]^+$: 234.1130, found: 234.1131.

4.2.3. (3*R*,4*R*)-1-Benzyl-3-hydroxy-4-methylpiperidine-2,6-dione 8b

To a stirred solution of dry THF (1.5 mL) containing dry diisopropylamine (0.38 mL, 2.87 mmol) was added butyllithium (1.1 mL, 2.33 M in hexane, 2.65 mmol) at 0 °C under argon and stirred for 30 min. Lactone **13** in dry tetrahydrofuran (4.7 mL) was transferred to a flask contained 4 Å molecular sieves (80 mg), and this solution was added to a lithium diisopropylamide mixture dropwise at −78 °C for 10 min under argon. After stirring for 30 min at −78 °C, additional dry THF (19.5 mL) was added. The reaction was warmed to −40 °C and stirred at the same temperature for 4.5 h. The reaction was quenched by the addition of 1% aq oxalic acid (1 mL) and neutralized to pH 7 with 1% aq oxalic acid. The resulting mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/hexanes/toluene, 1:1:1) to give **8b** (0.42 g, 81%) as a colorless oil. R_f = 0.6 (EtOAc/hexanes, 1:1). $[\alpha]_D^{28}$ = +49.3 (*c* 1.0 $CHCl_3$). IR (KBr, film): 2963, 1730, 1671, 1338, 700, 628 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36–7.20 (m, 5H), 4.93 (s, 2H), 4.34 (d, *J* = 4 Hz, 1H), 3.47 (d, *J* = 1.2 Hz, 1H), 3.51–3.45 (m, 2H), 2.78–2.75 (m, 1H), 0.91 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.6, 170.6, 136.5, 128.7 (2C), 128.5 (2C), 127.7, 71.3, 43.5, 38.3, 29.7, 12.4. HRMS (ESI) calcd for $C_{13}H_{16}NO_3$ $[M+H]^+$: 234.1130, found: 234.1134.

4.2.4. (3*R*,4*R*)-1-Benzyl-4-methylpiperidin-3-ol 14

To a suspension of $LiAlH_4$ (366 mg, 9.65 mmol) in dry THF (18.8 mL) was added **8b** (450 mg, 1.93 mmol) in THF (9.8 ml) at 0 °C under argon and the mixture was refluxed for 12 h. After cooling to 0 °C, the reaction was quenched with EtOAc (5 mL) and then added to satd aq potassium sodium tartrate. The resulting mixture was stirred vigorously for 12 h at room temperature and extracted with EtOAc (3 × 25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/hexanes, 1:1) to give **14** (293 mg, 74%) as a colorless oil. R_f = 0.25 (EtOAc/hexanes, 1:1). $[\alpha]_D^{28}$ = +50.5 (*c* 1.0 $CHCl_3$). IR (KBr, film): 2928, 2800, 1453, 1013, 739, 678 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.31–7.24 (m, 5H), 3.58 (s, 1H), 3.56 (s, 2H), 3.00 (d, *J* = 11.2 Hz, 1H), 2.87–2.83 (m, 1H), 2.60 (br s, 1H), 2.20 (d, *J* = 11.2, 1H), 2.03–2.00 (m, 1H), 1.60–1.55 (m, 1H), 1.55–1.40 (m, 2H), 0.97 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.7, 129.1 (2C), 128.3 (2C), 127.2, 69.2, 62.5, 59.9, 53.2, 34.7, 28.1, 17.7. HRMS (ESI) calcd for $C_{13}H_{20}NO$ $[M+H]^+$: 206.1545, found: 206.1544.

4.2.5. *N*-((3*R*,4*R*)-1-Benzyl-4-methylpiperidin-3-yl)-*N*-methyl-7-tosyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine 16

A mixture of chromium trioxide (49 mg, 0.49 mmol) in sulfuric acid (0.16 mL), acetic acid (0.16 mL) and water (0.11 mL) was added to a stirred solution of **14** (50 mg, 0.24 mmol) in acetone (0.5 mL) at 0 °C. After 2 h at <20 °C the reaction was basified to pH 12 with 33% aq NH_3 at 0 °C and extracted with ether (4 × 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was dissolved in MeOH (0.17 mL) followed by addition of NH_2Me (40% in MeOH, 0.05 mL, 0.49 mmol) and Ti(O^iPr)$_4$ (0.08 mL, 0.27 mmol) at 0 °C. After stirring 30 min at room temperature, the reaction mixture was added sodium borohydride (46.5 g, 1.23 mol) in a small portion in 30 min at 0 °C and stirred for an additional hour at the same temperature. The reaction mixture was filtered off to obtain crude amine. The

crude amine in water (0.65 mL) was added K_2CO_3 (65 mg, 0.47 mmol) and **15** (120 mg, 0.39 mmol), and the mixture was refluxed (120 °C) for 16 h under argon. After cooling to rt, the resulting mixture was added CH_2Cl_2 (5 ml) and sonicated crush the solid. The mixture was extracted with CH_2Cl_2 (4 × 5 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/hexanes, 1:1) to give *trans*-**16** (8 mg, 7%) as a white solid and *cis*-**16** (75 mg, 63%) as a white solid. R_f = 0.4 (*trans*-**16**), 0.48 (*cis*-**16**) (EtOAc/hexanes, 1:1). *trans*-**16**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.35 (s, 1H), 8.03 (d, J = 8.8 Hz, 2H), 7.37 (d, J = 4 Hz, 1H), 7.32–7.18 (m, 7H), 6.53 (br s, 1H), 3.56, 3.45 (ABq, J_{AB} = 12.8 Hz, 2H), 3.08 (s, 3H), 2.90–2.84 (m, 2H), 2.36 (s, 3H), 2.10–1.95 (m, 2H), 1.80–1.65 (m, 3H), 1.50–1.39 (m, 1H), 0.81 (d, J = 6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.0, 152.8, 151.7, 145.2, 138.1, 135.1, 129.6, 129.0, 128.2, 127.1, 120.9, 105.6, 104.7, 62.8, 55.4, 53.4, 33.6, 33.4, 21.6, 18.3. *cis*-**16**: $[\alpha]_D^{28}$ = +19.3 (*c* 1.0 $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.31 (s, 1H), 8.03 (d, J = 8 Hz, 2H), 7.40 (d, J = 3 Hz, 1H), 7.27–7.17 (m, 7H), 6.63 (d, J = 3.2 Hz, 1H), 5.16 (br s, 1H), 3.56 (s, 3H), 3.47, 3.42 (ABq, J_{AB} = 13.2 Hz, 2H), 2.79–2.76 (m, 1H), 2.75 (br s, 1H), 2.52 (d, J = 10.8, 1H), 2.36 (s, 2H), 2.35–2.22 (m, 1H), 2.10–2.03 (m, 1H), 1.70–1.610 (m, 2H), 0.87 (d, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 189.3, 157.9, 152.5, 151.8, 145.2, 135.1, 129.6, 128.9, 128.2, 128.1, 127.1, 120.6, 106.2, 104.6, 63.5, 55.2 (br), 53.1 (br), 51.6 (br), 35.8 (br), 32.5, 31.2, 21.6, 15.7 (br). HRMS (ESI) calcd for $C_{27}H_{31}N_5O_2S$ $[M+H]^+$: 490.2277, found: 490.2273.

Acknowledgements

We thank the Ministry of Science and Technology, Taiwan (ROC) for financial support (NSC 102-2113-M-007-009-MY3).

A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetasy.2016.11.013.

References

1. Changelian, P. S.; Flanagan, M. E.; Ball, D. J.; Kent, C. R.; Magnuson, K. S.; Martin, W. H.; Rizzuti, B. J.; Sawyer, P. S.; Perry, B. D.; Brissette, W. H.; McCurdy, S. P.; Kudlacz, E. M.; Conklyn, M. J.; Elliot, E. A.; Koslov, E. R.; Fisher, M. B.; Strelevitz, T. J.; Yoon, K.; Whipple, D. A.; Sun, J.; Munchhof, M. J.; Doty, J. L.; Casavant, J. M.; Blumenkopf, T. A.; Hines, M.; Brown, M. F.; Lillie, B. M.; Subramanyam, C.; Shang-Poa, C.; Milici, A. J.; Beckius, G. E.; Moyer, J. D.; Su, C.; Woodworth, T. G.; Gaweco, A. S.; Beals, C. R.; Littman, B. H.; Fisher, D. A.; Smith, J. F.; Zagouras, P.; Magna, H. A.; Saltarelli, M. J.; Johnson, K. S.; Nelms, L. F.; Des Etages, S. G.; Hayes, L. S.; Kawabata, T. T.; Finco-Kent, D.; Baker, D. L.; Larson, M.; Si, M.-S.; Paniagua, R.; Higgins, J.; Holm, B.; Reitz, B.; Zhoa, Y.-J.; Morris, R. E.; O'Shea, J. J.; Borie, D. C. *Science* **2003**, *302*, 875.
2. (a) Kulagowski, J. J.; Blair, W.; Bull, R. J.; Chang, C.; Deshmukh, G.; Dyke, H. J.; Eigenbrot, C.; Ghilardi, N.; Gibbons, P.; Harrison, T. K.; Hewitt, P. R.; Liimatta, M.; Hurley, C. A.; Johnson, A.; Johnson, T.; Kenny, J. R.; Bir Kohli, P.; Maxey, R. J.; Mendonca, R.; Mortara, K.; Murray, J.; Narukulla, R.; Shia, S.; Steffek, M.; Ubhayakar, S.; Ultsch, M.; Van Abbema, A.; Ward, S. I.; Waszkowycz, B.; Zak, M. *J. Med. Chem.* **2012**, *55*, 5901–5921; (b) Blumenkopf, T. A.; Flanagan, M. E.; Munchhof, M. J. U.S. Patent USRE41783E, 2010; (c) Flanagan, M. E.; Munchhof, M. J. U.S. Patent US7301023B2, 2007; (d) Ernest, W. G.; Christian, K.; Ton, V.; Edward, F. M.; Munchhof, M. J. PCT WO 02096909, 2002; (e) Stavber, G.; Cluzean, J. PCT WO 2014016338A1, 2014.; (f) Kristin, E. P.; Claude, L.-A.; Brett, M. L.; Robert, W. M.; Jason, M.; Kevin, W. H.; Jeol, M. H.; Rajappa, V. *Org. Lett.* **2009**, *11*, 2003–2006; (g) Ruggeri, S. G.; Hawkins, J. M.; Makowski, T. M.; Rutherford, J. L.; Urban, F. J. PCT WO 2007012953, 2007; (h) Rao, T. S.; Zhang, C. PCT WO 2010123919, 2010.; (i) Iorio, M. A.; Ciuffa, P.; Damia, G. *Tetrahedron* **1970**, *26*, 5519–5527; (j) Brown Ripin, D. H.; Abele, S.; Cai, W.; Blumenkopf, T.; Casavant, J. M.; Doty, J. L.; Flanagan, M.; Koecher, C.; Laue, K. W.; McCarthy, K.; Meltz, C.; Munchhoff, M.; Pouwer, K.; Shah, B.; Sun, J.; Teixeira, J.; Vries, T.; Whipple, D. A.; Wilcox, G. *Org. Process Res. Dev.* **2003**, *7*, 115–120; (k) Cai, W.; Colony, J. L.; Frost, H.; Hudspeth, J. P.; Kendall, P. M.; Krishnan, A. M.; Makowski, T.; Mazur, D. J.; Phillips, J.; Brown Ripin, D. H.; Ruggeri, S. G.; Stearns, J. F.; White, T. D. *Org. Process Res. Dev.* **2005**, *9*, 51–56; (l) Brown Ripin, D. H. PCT WO 2004/046112, 2004.; (m) Hu, X. E.; Kim, N. K.; Ledoussal, B. *Org. Lett.* **2002**, *4*, 4499–4502; (n) Jiang, J.-K.; Ghoreschi, K.; Deflorian, F.; Chen, Z.; Perreira, M.; Pesu, M.; Smith, J.; Nguyen, D.-T.; Liu, E. H.; Leister, W.; Costanzi, S.; O'Shea, J. J.; Thomas, C. J. *J. Med. Chem.* **2008**, *51*, 8012–8018; (o) Patil, Y. S.; Bonde, N. L.; Kekan, A. S.; Sathe, D. G.; Das, A. *Org. Process Res. Dev.* **2014**, *18*, 1714–1720.
3. Adolfo, M.; Mario, J. S.; Leonardo, S. S. *Tetrahedron Lett.* **2013**, *54*, 5096.
4. Abdel-Magid, A. F.; Mehrman, S. J. *Org. Process Res. Dev.* **2006**, *10*, 971.
5. (a) Kumara Swamy, K. C.; Bhuvan Kumar, N. N.; Balaraman, E.; Pavan Kumar, K. V. P. *Chem. Rev.* **2009**, *109*, 2551; (b) Fletcher, S. *Org. Chem. Front.* **2015**, *2*, 739.
6. (a) Pearson, W. H.; Cheng, M.-C. *J. Org. Chem.* **1986**, *51*, 3746; (b) Ley, S. V.; Boons, G.-J.; Downham, R.; Kim, K.-S.; Woods, M. *Tetrahedron* **1994**, *50*, 7157; (c) Chang, J.-W.; Jang, D.-P.; Liao, F.-L.; Wang, S.-L.; Uang, B.-J. *Org. Lett.* **1999**, *1*, 2061; (d) Dixon, D. J.; Ley, S. V.; Rodriguez, F. *Org. Lett.* **2001**, *3*, 3753; (e) Jang, D.-P.; Chang, J.-W.; Uang, B.-J. *Org. Lett.* **2001**, *3*, 983.
7. Liu, L.-X.; Wei, B.-G.; Ruan, Y.-P.; Huang, P.-Q. *Org. Lett.* **2003**, *5*, 1927–1929.