HETEROCYCLES, Vol. 94, No. 10, 2017, pp. 1923 - 1930. © 2017 The Japan Institute of Heterocyclic Chemistry
Received, 26th June, 2017, Accepted, 15th August, 2017, Published online, 25th August, 2017
DOI: 10.3987/COM-17-13772

SYNTHESIS OF (5,6-DIHYDRO-4*H*-PYRROLO[1,2-*b*]PYRAZOL-3-YL)METHANAMINE

Zhong-Gang Bai,[1] Hui Qi,[1] Qun-Zheng Zhang,[2] Yu Ma,[2] Qing Pan,[3] and Xun-Li Zhang[2]*

[1] Wuqi Oil Production Factory, Yanchang Oilfield Co. Ltd, Yan'an 717600, China

[2] College of Chemistry and Chemical Engineering, Xi'an Shiyou University, Xi'an 710065, China

[3] Department of Pharmacy, School of Medicine, Xi'an Jiaotong University, Xi'an 710061, China

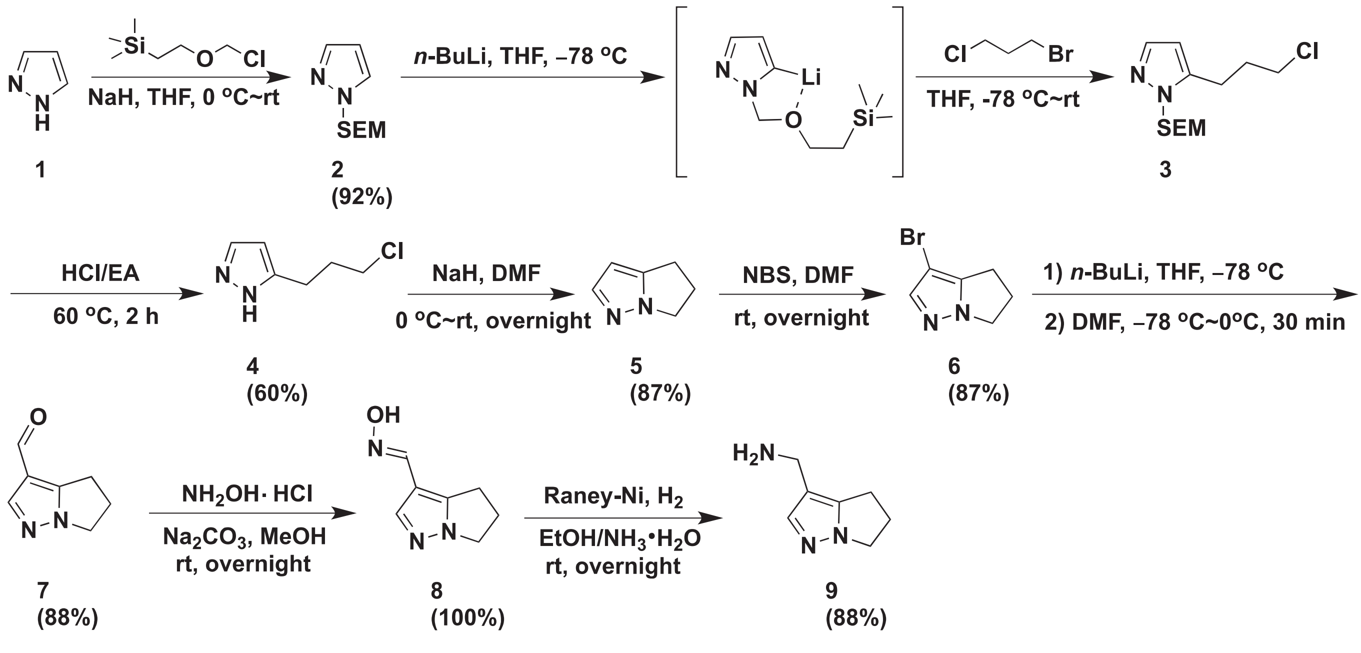
* Corresponding author. Tel/Fax: +86 29 8838 2693; Email: xlzhang@xsyu.edu.cn

Abstract – This short paper reports the development of a new method for the synthesis of (5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazol-3-yl)methanamine. Pyrazole was initially protected with an *N*-SEM protective group, followed by alkylation at C-5 position with 1-bromo-3-chloropropane. Following SEM deprotection, the intramolecular ring was closed and then a bromine atom (Br) was introduced with *N*-bromosuccinimide (NBS) by electrophilic aromatic substitution (S_EAr), forming 3-bromo-5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazole. The Br group was subsequently converted into aldehyde group, then into oxime. The final step of hydrogenation resulted in the desired product. The overall yield through the 8-step reaction process was found to be 29.4%. The intermediates and final product were identified by HPLC-MS and ^{1}H NMR. This development provides a novel synthetic route to the formation of 5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazole skeleton.

Heterocyclic compounds, in the form of either aromatic or non-aromatic rings, are important in modern drug design and drug discovery. Among heterocyclic aromatic compounds, pyrazole and its derivatives have continued to be an active research topic, although they have been studied for over a century following Knorr's pioneer work in 1883.[1] This is largely due to the broad range of their biological activities, including anticancer, anti-inflammatory, antiviral, antibacterial and antifungal activities.[2-5] It also provides great opportunities in searching for potential drugs carrying such moieties with pharmacological activities.[6]

Danusertib (formerly PHA-739358), which is a small-molecule 3-aminopyrazole derivative based on a bicyclic tetrahydropyrrolo[3,4-*c*]pyrazole scaffold, is regarded as one of the first Aurora kinase inhibitors to enter the clinic and has been studied in Phase I and II trials.[7,8] Studies have shown its great therapeutic potential in anticancer therapy for a wide range of cancers including both advanced solid tumors and leukemias.[9,10] For developing new and/or improved antibiotics, 6-methylidene penem derivatives bearing heterobicyclic substituents have been demonstrated to be broad-spectrum β-lactamase inhibitors, e.g., (5*R*,6*Z*)-6-(5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazol-2-yl-methylene)-7-oxo-4-thiazabicyclo[3.2.0]hept-2-ene-2-carboxylic acid sodium salt.[11]

Using 5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazole derivatives as key intermediates, a range of pharmaceutically potential substrates have been investigated, e.g., for treating PI3K-delta-mediated diseases,[12] as anaplastic lymphoma kinase inhibitors to treat abnormal cell proliferative disorders,[13] as tyrosine kinase antagonists,[14,15] and for the treatment of PDE4-mediated disease.[16] Our previous work on the synthesis and evaluation of a range of 5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazole derivatives have also shown potential pharmaceutical activity of (5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazol-3-yl)methanamine.[17]



Scheme 1. Overall synthetic route used for the synthesis of (5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazol-3-yl)methanamine with yields given

However, there has been limited research which is dedicated to the synthesis of 5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazole derivatives, while their syntheses generally involve complicated synthetic routes requiring a large number of steps and giving poor overall yields.[18-21] The aim of the present study was to develop a novel synthetic route for the synthesis of 5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazole derivatives, in particular, for synthesizing (5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazol-3-yl)methanamine.

Scheme 1 outlines the overall synthetic route used in this study for the synthesis of the target compound, (5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazol-3-yl)methanamine.

Using pyrazole as the starting material, a suitable protective group was firstly introduced in order to protect the nitrogen atom of pyrazole that enabled the next step reaction involving *n*-butyllithium (*n*-BuLi), and also directed lithiations.[22] In this study, a 2-(trimethylsilyl)ethoxymethyl (SEM) group was employed, based on that fact that it has been a widely used heterocyclic NH protecting group and also an effective group for directing lithiation at the neighboring position.[23,24]

Following lithiation of pyrazole, the alkylation reaction took place with haloalkanes to enable ring-closing after SEM deprotection. 1,3-Dihaloalkanes are typically-used haloalkanes, containing two different types of halogen atoms with different activities,[22] and 1-bromo-3-chloropropane was employed in this study. It was found that the residues of the haloalkane were difficult but inessential to remove, therefore the unpurified alkylation intermediate **3** was used for the next step reaction.

It is worthwhile to note that, if an alternative haloalkane, e.g., 1-bromo-4-chlorobutane was used instead of 1-bromo-3-chloropropane, it would result in the formation of 5-(4-chlorobutyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole, followed by SEM deprotection and ring closure, to finally form 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine, as demonstrated in our previous studies.[17] With intermediate **5**, different electrophilic reagents can react in order to introduce other substituent groups such as nitro group.[18]

For the preparation of intermediate **6**, DMF and *N*-bromosuccinimide (NBS) were employed, resulting in a yield of 87% which was markedly higher than that reported (77%),[25] where either Br_2 in acetic acid and sodium acetate or NBS in chloroform were used. Intermediate **6** can be further introduced with various groups through coupling reactions such as Suzuki coupling.[26] Intermediate **7** can also be converted to a range of derivatives through different reactions such as redox, Grignard addition and Wittig reactions.[27-29]

The target product was finally obtained by the reduction of oxime through hydrogenation catalyzed by Raney-Ni, where ammonia was added in order to suppress the formation of by-products such as dimer amines. The purity of **9** was confirmed to be 96.93%.

To summarize, in the present study a new route for the synthesis of **9** was developed. The process started with pyrazole as a starting material, which was protected with an *N*-SEM protective group, followed by alkylation at C-5 position with 1-bromo-3-chloropropane. Following SEM deprotection, intramolecular ring closure was performed and then a Br group was introduced with NBS by electrophilic aromatic substitution (S_EAr) to form **6**. The Br group was subsequently converted to aldehyde group, then to oxime. The final step of hydrogenation was carried out to afford the desired final product. The overall yield through the 8-step process was found to be 29.4%. The intermediates and final product were identified by HPLC-MS and ^{1}H NMR. This development has provided a novel synthetic route for the synthesis of pyrrolo[1,2-*b*]pyrazole skeleton. In terms of pharmaceutical potential of **9**, further investigations are underway in our laboratories on its biological activities and capacity.

EXPERIMENTAL

Chemicals and Instrument. All starting materials and reagents were purchased from Alfa Aesar Chemical Reagent (Tianjin, China) and used without further purification unless otherwise indicated. THF was purified by distillation from sodium/benzophenone immediately before use. DMF was distilled from CaH_2 under Argon. Air-sensitive and/or moisture-sensitive reagents were transferred via syringe or cannula, and introduced into reaction vessels through rubber septa. Solvent removal was performed with a rotary evaporator at ~10-50 Torr.

Analytical thin-layer chromatography (TLC) was performed on aluminum plates which were pre-coated with silica gel 60 F-254 (Merck). Analytical instrument Agilent 1100 Series high performance liquid chromatography mass spectrometry (HPLC-MS) and Varian INOVA-300 MHz NMR (TMS as internal standard) were employed for analysis.

Synthesis procedure. The eight-step procedure for the synthesis of (5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazol-3-yl)methaneine is detailed, as follows.

Preparation of 1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (2): To a stirred solution of NaH (1.05 equiv, 8.4 g, 60% dispersion in mineral oil, 0.21 mol) in THF (300 mL) cooled at 0 ºC was added dropwise a solution of pyrazole (1.0 equiv, 13.6 g, 0.2 mol) in THF (200 mL). After addition, the mixture was stirred for 30 min at 0 ºC under N_2. Then, a solution of SEM-Cl (1.05 equiv, 35.0 g, 0.21 mol) in THF (100 mL) was added dropwise over 30 min. The resulting solution was allowed to warm to room temperature and stirred overnight under N_2. The reaction was quenched by adding H_2O (200 mL). The organic layer was separated and the aqueous phase was extracted with EtOAc (2 × 200 mL). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by silica gel chromatography eluted with PE/EtOAc (10/1) to produce **2** (36.5 g). Yield: 92% of colorless oil; ESI(+)-MS: m/z: 199.0 (M+1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.60-7.55 (m, 2 H), 6.37-6.36 (m, 1 H), 5.42 (s, 2 H), 3.58 (t, J = 5.4 Hz, 2 H), 0.93 (t, J = 5.4 Hz, 2 H), 0.01 (s, 9 H).

Preparation of 5-(3-chloropropyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (3): To a stirred solution of **2** (1.0 equiv, 19.8 g, 0.1 mol) in THF (400 mL) cooled at −78 °C was added a solution of *n*-BuLi (1.1 equiv, 44.0 mL, 2.5 M in hexane, 0.11 mol) dropwise over 30 min under N_2. The resulting solution was stirred for 1 h at this temperature. Then, a solution of 1-bromo-3-chloropropane (2.0 equiv, 31.5 g, 0.2 mol) in THF (100 mL) was dropwise added. After addition, the solution was allowed to warm to room temperature slowly and stirred overnight under N_2. The reaction was cooled to 0 °C and quenched with H_2O (100 mL). The organic layer was separated and the aqueous phase was extracted with EtOAc (2 × 200 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to form the crude product (45.6 g, crude) as a yellow oil, which was then used in the next step without further treatment.

Preparation of 5-(3-chloropropyl)-1*H*-pyrazole (4): To a stirred solution of **3** (1.0 equiv, 45.6 g, crude, 0.1 mol) in EtOAc (200 mL) was added dropwise 300 mL of EtOAc saturated with HCl (gas). The solution was heated at 60 °C for 2 h and then concentrated under reduced pressure. The residue was poured into ice-water (100 mL) and neutralized with Na_2CO_3 (solid) until no gas was released. The resulting mixture was then extracted with EtOAc (2 × 200 mL). The combined organic layer was washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and then concentrated under a reduced pressure. The crude product was purified by silica gel chromatography eluted with PE/EtOAc (1/1) to give **4** (8.7 g). Yield (over 2 steps): 60% of colorless thick oil; ESI(+)-MS: *m/z*: 144.1 (*M*+1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.51 (d, J = 1.8 Hz, 1 H), 6.14 (d, J = 1.8 Hz, 1 H), 3.61-3.56 (m, 2 H), 2.87 (t, J = 7.2 Hz, 2 H), 2.19-2.09 (m, 2 H).

Preparation of 5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazole (5): To a stirred solution of **4** (1.0 equiv, 8.0 g, 55.3 mmol) in anhydrous DMF (100 mL) cooled at 0 °C was added NaH (1.1 equiv, 2.4 g, 60% dispersion in mineral oil, 60.8 mmol) in portions. The resulting mixture was left to warm up to room temperature, and stirred overnight under N_2. The reaction was quenched by adding H_2O (2 mL), and then concentrated under vacuum. The residue was diluted with EtOAc (100 mL), washed with brine (2 × 30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography eluted with PE/EtOAc (2/1) to form **5** (5.2 g). Yield: 87% of brown oil; ESI(+)-MS: *m/z*: 108.1 (*M*+1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.48 (d, J = 1.2 Hz, 1 H), 5.93 (d, J = 1.2 Hz, 1 H), 4.11 (t, J = 7.2 Hz, 2 H), 2.86 (t, J = 7.2 Hz, 2 H), 2.60-2.54 (m, 2 H).

Preparation of 3-bromo-5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazole (6): To a stirred solution of **5** (1.0 equiv, 4.3 g, 40.0 mmol) in DMF (50 mL) was added NBS (1.1 equiv, 7.8 g, 44.0 mmol) in portions at room temperature, and the resulting solution was stirred overnight. After concentration under vacuum, the residue was diluted with EtOAc (100 mL), washed with brine (2 × 30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by silica gel chromatography eluted with

PE/EtOAc (2/1) to afford **6** (6.5 g). Yield: 87% of yellow solid; ESI(+)-MS: *m*/*z*: 187.0 (*M*+1); ^{1}H NMR ($CDCl_3$, 300 MHz) *δ*: 7.43 (s, 1 H), 4.16 (t, *J* = 7.2 Hz, 2 H), 2.85 (t, *J* = 7.2 Hz, 2 H), 2.64-2.57 (m, 2 H).

Preparation of 5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazole-3-carbaldehyde (7): To a stirred solution of **6** (1.0 equiv, 5.6 g, 30.0 mmol) in THF (100 mL) cooled at −78 °C was added dropwise a solution of *n*-BuLi (1.1 equiv, 13.2 mL, 2.5 M in hexane, 33.0 mmol) under N_2. The resulting solution was stirred for 1 h at this temperature. Then, a solution of DMF (2.0 equiv, 4.4 g, 60.0 mmol) in THF (10 mL) was added dropwise at −78 °C. After addition, the solution was allowed to warm to 0 °C slowly and stirred for 30 min. The reaction was quenched by the addition of H_2O (30 mL) dropwise. The organic layer was separated and the aqueous phase was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by silica gel chromatography eluted with PE/EtOAc (3/1) to produce **7** (3.6 g). Yield: 88% of yellow solid; ESI(+)-MS: *m*/*z*: 137.1 (*M*+1); ^{1}H NMR ($CDCl_3$, 300 MHz) *δ*: 9.80 (s, 1 H), 7.52 (s, 1 H), 4.19 (t, *J* = 7.2 Hz, 2 H), 2.95 (t, *J* = 7.2 Hz, 2 H), 2.70-2.63 (m, 2 H).

Preparation of 5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazole-3-carbaldehyde oxime (8): To a solution of **7** (1.0 equiv, 3.4 g, 25.0 mmol) in MeOH (50 mL) was added hydroxylamine hydrochloride (1.2 equiv, 2.1 g, 30.0 mmol), followed by Na_2CO_3 (1.2 equiv, 3.2 g, 30.0 mmol) in portions at room temperature. The resulting mixture was stirred overnight and then concentrated. The residue was suspended in DCM (50 mL) and MeOH (10 mL). The solid was filtered off and the filtrate was concentrated under vacuum to form the crude **8** (4.1 g). Yield: 100% of yellow solid.

Preparation of (5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazol-3-yl)methanamine (9): To a solution of **8** (1.0 equiv, 4.1 g, crude, 25.0 mmol) in EtOH (100 mL) and ammonia (10 mL) was added Raney-Ni (2.0 g) under N_2. The mixture was then degassed and purged with H_2 for several times. The resulting mixture was then stirred at room temperature overnight under H_2 (20 psi). The mixture was filtered through a pad of celite and the filter cake was washed with MeOH (50 mL). The filtrate was concentrated under reduced pressure and the crude product was purified by silica gel chromatography eluted with DCM/MeOH (15/1) to produce **9** (3.0 g). Yield: 88% of light yellow solid; ESI(+)-MS: *m*/*z*: 121.2 $(M{-}NH_2)^+$, 139.2 $(M{-}NH_2{+}H_2O)^+$; ^{1}H NMR ($CDCl_3$, 300 MHz) *δ*: 7.43 (s, 1 H), 4.10 (t, *J* = 7.2 Hz, 2 H), 3.71 (s, 2 H), 2.87 (t, *J* = 7.2 Hz, 2 H), 2.65-2.55 (m, 2 H).

ACKNOWLEDGEMENTS

This research was financially supported by the grants of Development and Application of Supercritical Fluid Chromatography (2013YQ170525), Application Research of Supercritical Fluid Chromatography in Chinese Traditional Medicine and Its Metabolites (2013YQ17052509), and Xi'an Shiyou University Graduate Innovation & Practical Skill Training projects (YCS16212074).

REFERENCES

1. J. J. Li, 'Name Reactions: A Collection of Detailed Mechanisms and Synthetic Applications Fifth Edition', Springer International Publishing, 2014.
2. P. C. Lv, H. Q. Li, J. Sun, Y. Zhou, and H. L. Zhu, *Bioorg. Med. Chem.*, 2010, **18**, 4606.
3. V. Kumar, K. Kaur, G. K. Gupta, and A. K. Sharma, *Eur. J. Med. Chem*., 2013, **69**, 735.
4. A. K. Tewari, V. P. Singh, P. Yadav, G. Gupta, A. Singh, R. K. Goel, P. Shinde, and C. G. Mohan, *Bioorg. Chem.*, 2014, **56**, 8.
5. H. Ichikawa, R. Watanabe, Y. Fujino, and Y. Usami, *Tetrahedron Lett*., 2011, **52**, 4448.
6. Shamsuzzaman, T. Siddiqui, M. G. Alam, and A. M. Dar, *J. Saudi Chem. Soc.*, 2015, **19**, 387.
7. H. J. Meulenbeld, R. H. Mathijssen, J. Verweij, R. de Wit, and M. J. de Jonge, *Expert Opin. Investig. Drugs*, 2012, **21**, 383.
8. G. Borthakur, H. Dombret, P. Schafhausen, T. H. Brummendorf, N. Boissel, E. Jabbour, M. Mariani, L. Capolongo, P. Carpinelli, C. Davite, H. Kantarjian, and J. E. Cortes, *Haematologica*, 2015, **100**, 898.
9. P. Carpinelli, R. Ceruti, M. L. Giorgini, P. Cappella, L. Gianellini, V. Croci, A. Degrassi, G. Texido, M. Rocchetti, P. Vianello, L. Rusconi, P. Storici, P. Zugnoni, C. Arrigoni, C. Soncini, C. Alli, V. Patton, A. Marsiglio, D. Ballinari, E. Pesenti, D. Fancelli, and J. Moll, *Mol. Cancer Ther.*, 2007, **6**, 3158.
10. L. Xie and F. L. Meyskens, *Melanoma Res.*, 2013, **23**, 102.
11. A. A. Nikitenko, M. W. Winkley, J. Zeldis, K. Kremer, A. W. Y. Chan, H. Strong, M. Jennings, I. Jirkovsky, D. Blum, G. Khafizova, G. T. Grosu, and A. M. Venkatesan, *Org. Process Res. Dev.*, 2006, **10**, 712.
12. A. A. Achab, M. D. Altman, Y. Deng, T. Guzi, S. Kattar, J. D. Katz, J. L. Methot, H. Zhou, M. McGowan, and M. P. Christopher, International Patent, 2014, WO/2014/075392.
13. S. Bailey, B. J. Burke, M. R. Collins, J. J. Cui, J. G. Deal, R. L. Hoffman, Q. Huang, T. W. Johnson, R. S. Kania, and J. C. Kath, US Patent, 2015, US9133215 B2.
14. J. J. Crawford, D. F. Ortwine, B. Q. Wei, and W. B. Young, US Patent, 2014, US8754077.
15. M. D. Andrews, S. K. Bagal, K. R. Gibson, K. Omoto, T. Ryckmans, S. E. Skerratt, and P. A. Stupple, US Patent, 2014, US20140364415 A1.
16. G. Andrews, R. J. Cox, S. C. De, P. Meghani, H. J. Sanganee, and D. J. Warner, International Patent, 2009, WO/2009/144494.
17. Q.-Z. Zhang, *unpublished data*, 2016.
18. O. Kulinkovich, N. Masalov, V. Tyvorskii, N. DeKimpe, and M. Keppens, *Tetrahedron Lett.*, 1996, **37**, 1095.

19. D. Fancelli, J. Moll, M. Varasi, R. Bravo, R. Artico, D. Berta, S. Bindi, A. Cameron, I. Candiani, P. Cappella, P. Carpinelli, W. Croci, B. Forte, M. L. Giorgini, J. Klapwijk, A. Marsiglio, E. Pesenti, M. Rocchetti, F. Roletto, D. Severino, C. Soncini, P. Storici, R. Tonani, P. Zugnoni, and P. Vianello, *J. Med. Chem.*, 2006, **49**, 7247.
20. J. Galeta, L. Tenora, S. Man, and M. Potacek, *Tetrahedron*, 2013, **69**, 7139.
21. M. D. Altman, C. E. Bienstock, J. W. Butcher, K. K. Childers, F. M. E. Di, A. Donofrio, J. M. Ellis, C. Fischer, A. M. Haidle, and J. P. Jewell, US Patent, 2013, US9216173.
22. P. G. M. Wuts, 'Greene's Protective Groups in Organic Synthesis', 2014.
23. G. Luo, L. Chen, and G. Dubowchik, *J. Org. Chem.*, 2006, **71**, 5392.
24. G. Tran, D. G. Pardo, T. Tsuchiya, S. Hillebrand, J. P. Vors, and J. Cossy, *Org. Lett.*, 2013, **15**, 5550.
25. M. R. Machacek, M. D. Altman, E. T. Romeo, D. Vitharana, B. Cash, T. Siu, M. Christopher, S. D. Kattar, A. M. Haidle, and K. K. Childers, US Patent, 2013, US9242984.
26. H. Y. Li, Y. Wang, C. R. Heap, C. H. R. King, S. R. Mundla, M. Voss, D. K. Clawson, L. Yan, R. M. Campbell, B. D. Anderson, J. R. Wagner, K. Britt, K. X. Lu, W. T. McMillen, and J. M. Yingling, *J. Med. Chem.*, 2006, **49**, 2138.
27. R. R. Frey, M. L. Curtin, D. H. Albert, K. B. Glaser, L. J. Pease, N. B. Soni, J. J. Bouska, D. Reuter, K. D. Stewart, P. Marcotte, G. Bukofzer, J. Li, S. K. Davidsen, and M. R. Michaelides, *J. Med. Chem*., 2008, **51**, 3777.
28. B. Cottineau, J. Chenault, and G. Guillaumet, *Tetrahedron Lett.*, 2006, **47**, 817.
29. R. W. Burli, C. A. Luckhurst, O. Aziz, K. L. Matthews, D. Yates, K. A. Lyons, M. Beconi, G. McAllister, P. Breccia, A. J. Stott, S. D. Penrose, M. Wall, M. Lamers, P. Leonard, I. Muller, C. M. Richardson, R. Jarvis, L. Stones, S. Hughes, G. Wishart, A. F. Haughan, C. O'Connell, T. Mead, H. McNeil, J. Vann, J. Mangette, M. Maillard, V. Beaumont, I. Munoz-Sanjuan, and C. Dominguez, *J. Med. Chem.*, 2013, **56**, 9934.