


 CrossMark
 click for updates
Cite this: *RSC Adv.*, 2017, 7, 1814Received 5th December 2016
Accepted 21st December 2016

DOI: 10.1039/c6ra27790j

www.rsc.org/advances

Stereoselective synthesis of 2'-modified nucleosides by using *ortho*-alkynyl benzoate as a gold(i)-catalyzed removable neighboring participation group†

 Haixin Ding,^{‡ab} Chuang Li,^{‡b} Yirong Zhou,^b Sanguo Hong,^a Ning Zhang^{*a}
 and Qiang Xiao^{*b}

In the present paper, we report a novel strategy for highly efficient stereoselective synthesis of 2'-modified nucleosides by using *ortho*-alkynyl benzoate as neighboring participation group. Subsequently, *ortho*-alkynyl benzoate can be removed smoothly in the presence of 5 mol% Ph₃PAuCl–AgOTf in dichloromethane with H₂O (1 eq.) and ethanol (6 eq.) to afford 2'-OH nucleosides in high yields and selectivity.

Introduction

In the past decades, tremendous efforts have been devoted to the synthesis of novel nucleosides and the evaluation of their biological activities. Accordingly, a large number of nucleosides have been successfully developed as antiviral and antitumor drugs.¹ Among these chemical entities, C-2' substituted nucleosides have showed special importance.^{2–5} For instance, clofarabine, gemcitabine, nelarabine, clofarabine and most recently FDA approved sofosbuvir for chronic HCV treatment all contain the C-2' substituted nucleoside core structure (Fig. 1).^{6–8} On the other hand, 2'-modified nucleosides have also been used as biochemical probes to investigate the structure and function of nucleic acid.^{9–11}

Currently, there are generally two synthetic methodologies to access 2'-modified ribonucleosides, namely the convergent approach and the linear approach (Fig. 2). In the convergent approach, the nucleoside was produced by glycosylation of nucleobase with the corresponding sugar moiety. In the linear approach, the nucleoside was prepared by chemical modification of commercially available natural nucleosides or related compounds. From the synthetic point of view, the linear approach offers a relatively convenient way because of it could avoid the glycosylation step, which is often cumbersome.

However, compared with the linear approach, the convergent approach is potentially more flexible. It could provide abundant structural diversity by using Vorbrüggen glycosylation of a variety of nucleobase with modified carbohydrate. But in absence of neighboring group participation (NGP), Vorbrüggen glycosylation always generated a mixture of α and β isomer in low selectivity and yield. Moreover, the separation is often time-consuming and labor intensive. Therefore, a general and efficient synthetic approach for C-2' substituted nucleosides is highly desired.

In the literature, some examples were reported using acyl group as neighboring participation group, which could be removed selectively by using NH₂NH₂, CH₃NH₂ or NH₂CH₂CH₂NH₂ *etc.*¹² Nevertheless, these approaches' reproducibilities were far from satisfied by our evaluation. At the meantime, acetyl transfer from 3'-OH to 2'-OH was inevitable, which will make the purification troublesome and sometimes impossible. So a general strategy is highly desired to solve this potential problem.

Gold(i) complexes are mild electrophiles and have wide usage in homogeneous catalysis. In recent years, the application of gold(i)-catalyzed electrophilic activation of alkynes has been

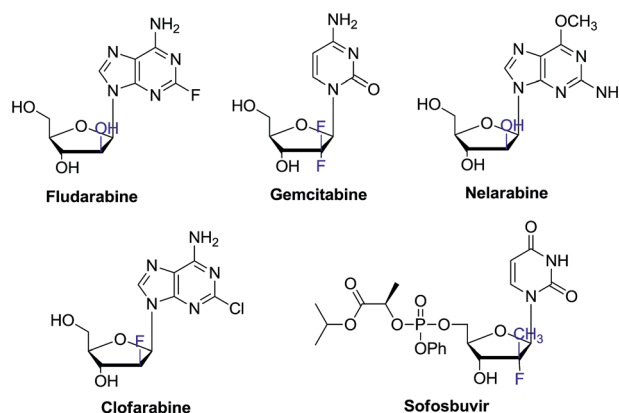


Fig. 1 Examples of 2'-modified nucleoside drugs.

^aDepartment of Chemistry, Nanchang University, Nanchang, Jiangxi 330031, China

^bJiangxi Key Laboratory of Organic Chemistry, Jiangxi Science & Technology Normal University, Nanchang, Jiangxi 330013, China. E-mail: xiaoqiang@tsinghua.org.cn

† Electronic supplementary information (ESI) available: Experimental procedure, characterization data, ¹H and ¹³C NMR spectra of compounds. See DOI: 10.1039/c6ra27790j

‡ These authors contributed equally.



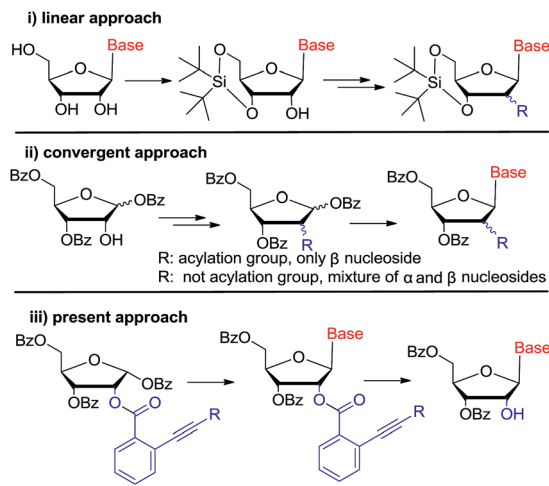
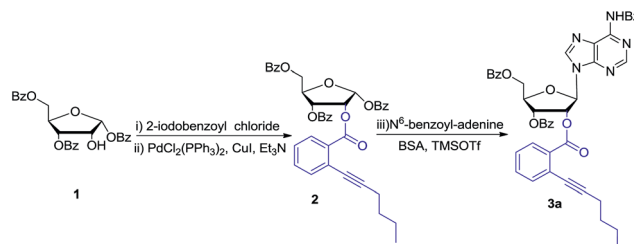


Fig. 2 Synthetic methods of 2'-modified ribonucleosides.

extensively used for the construction of carbon–carbon or carbon–heteroatom bonds,¹³ especially in glycosylation for oligosaccharide synthesis by Yu's group.¹⁴ In 2008, Asao reported the first gold(i)-catalyzed transesterification of *ortho*-alkynylbenzoic acid esters with ethanol and its potential application as protecting group for alcohols and phenols.¹⁵ Afterwards, this approach was not further investigated. According to this preliminary report, we reasoned that *ortho*-alkynylbenzoic acid ester may act as neighboring participation group to prepare nucleosides stereoselectively by using Vorbrüggen glycosylation. Then, *ortho*-alkynylbenzoic acid ester could be removed regioselectively by gold(i) complexes to liberate 2'-OH (Fig. 2(iii)). If our assumption works, it could provide a practical alternative protocol for the synthesis of C-2' substituted nucleosides.

Bearing the above considerations in mind, *ortho*-alkynyl benzoate **2** was firstly prepared starting from commercially available 1,3,5-tri-*O*-benzoyl- α -D-ribofuranose **1** in two steps with high overall yield. Then adenosine **3a** was synthesized by using Vorbrüggen glycosylation. To our delight, in the presence of trimethylsilyl triflate (TMSOTf), *ortho*-alkynyl benzoate group of compound **2** acted as an excellent neighbouring participation group to form dioxolanylium with anomeric cation, which led to nucleophilic attack from β -face by silylated N^6 -benzoyl adenine to afford adenosine **3a** stereoselectively in 82% yield (Scheme 1). Under the similar condition, a series of nucleosides **3(a–i)** were successfully obtained in high yields and stereoselectivity.

Then as a proof of concept, adenosine **3a** was subjected to react with EtOH (6.0 eq.) in the presence of 5 mol% of AuCl in dichloromethane (DCM). After 5 hours, we were pleased to find that the desired 2'-OH nucleoside **4a** can be obtained in 70% yield (entry 1). The *ortho*-alkynyl benzoate was released as isocoumarin **5**. In Asao's preliminary report, gold-catalysed transesterification should give *ortho*-alkynylbenzoic acid ethyl ester as the main product together with a small amount isocoumarin. Because the reagent grade ethanol and DCM were directly used in our experiment, we reasoned that residue H₂O in EtOH could have participated the reaction.

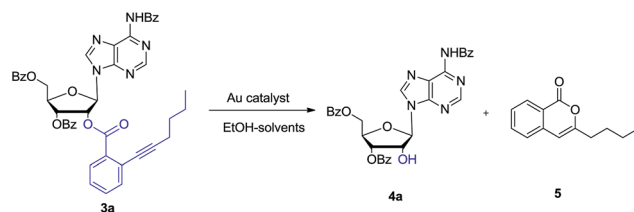


Scheme 1 Synthesis of model substrate **3a**: (i) 2-iodobenzoyl chloride, pyridine, r.t., 94%; (ii) PdCl₂(PPh₃)₂, CuI, Et₃N, THF, 50 °C, 72%; (iii) N^6 -benzyladenine, *N,O*-bis(trimethylsilyl) acetamide (BSA), trimethylsilyl-triflate (TMSOTf), acetonitrile, 82%.

In order to further investigate the reaction, the freshly dried ethanol and 4 Å MS in DCM were used. It showed that the reaction became very sluggish. After 24 hours, the reaction still did not finish. In consistent with Asao's work, *ortho*-alkynylbenzoic acid ethyl ester was identified in the reaction mixture. Then H₂O (1 eq.) was added to the reaction. After another 5 hours, the reaction proceeded smoothly. Both nucleoside **4a** and isocoumarin **5** were obtained in high yields. So it was concluded that H₂O (1 eq.) was essential for the reaction. In the absence of EtOH, the reaction was also sluggish. The reason might be that EtOH could improve the solubility of H₂O in DCM.

Based on this promising result, a series of gold(i) catalysts were evaluated under H₂O (1 eq.) and ethanol (6 eq.) (Table 1). Ph₃PAuCl gave only trace amount of product (entry 2). Nearly quantitative yield of **4a** was isolated by reaction with 5 mol%

Table 1 Optimization of gold(i)-catalysed deprotection of *ortho*-alkynyl benzoate



Entry ^a	Catalyst (mol%)	Solvent	Time (h)	Yield ^b (%)
1	AuCl (5%)	DCM	5	70%
2	Ph ₃ PAuCl (5%)	DCM	5	Trace
3	AgOTf (10%)	DCM	5	NR
4	Ph ₃ PAuCl–AgOTf (1.0%)	DCM	5	49%
5	Ph ₃ PAuCl–AgOTf (2.5%)	DCM	5	81%
6	Ph₃PAuCl–AgOTf (5.0%)	DCM	5	96%
7	Ph ₃ PAuCl–AgNTf (5.0%)	DCM	5	31%
8	Ph ₃ PAuCl–AgOTf (5.0%)	Toluene	5	Trace
9	Ph ₃ PAuCl–AgOTf (5.0%)	DMF	5	Trace
10	Ph ₃ PAuCl–AgOTf (5.0%)	CH ₃ CN	5	32
11	Ph ₃ PAuCl–AgOTf (5.0%)	THF	5	26
12	Ph ₃ PAuCl–AgOTf (5.0%)	EtOH	5	49

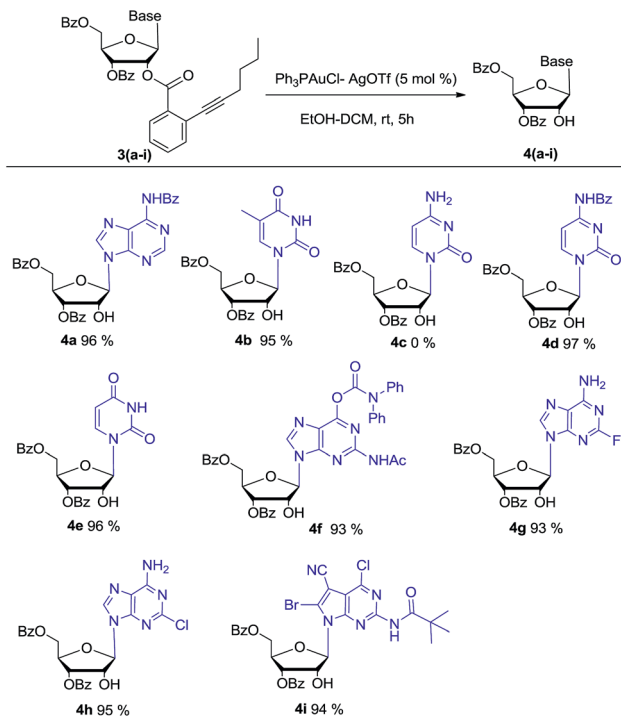
^a Each reaction was carried out with β -nucleoside **3a** (0.20 mmol) with H₂O (1 eq.) and ethanol (6 eq.) in the presence of catalyst at room temperature under N₂ atmosphere for 5 hours. ^b Isolated yield.



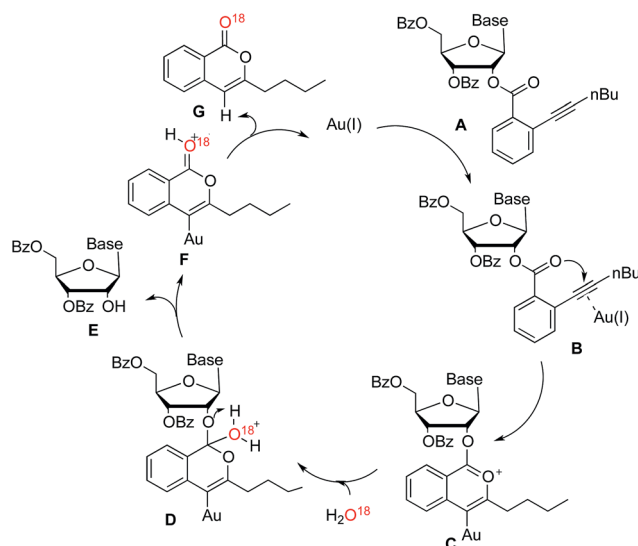
$\text{Ph}_3\text{PAuCl-AgOTf}$ (entry 6). But $\text{Ph}_3\text{PAuCl-AgNTf}$ afforded **4a** in low yield (31%) (entry 7). When the catalysis loading of $\text{Ph}_3\text{PAuCl-AgOTf}$ was decreased to 2.5 mol% and 1 mol%, the corresponding yields were reduced to 81% and 49% respectively (entries 4–5).

After 5 mol% $\text{Ph}_3\text{PAuCl-AgOTf}$ was identified as the best catalyst loading, the solvents effect was also investigated by performing the reaction in a series of organic solvents under room temperature conditions (entries 8–12). It was observed that toluene and dimethylformamide (DMF) only gave a trace amount of product **4a** (<5%). The reaction also proceeded less efficiently in THF, acetonitrile or ethanol. DCM was found to be the optimum solvent.

With the optimized condition in hand, the synthesized β -nucleoside substrates **3a–i** were subjected to 5 mol% $\text{Ph}_3\text{PAuCl-AgOTf}$, ethanol (6 eq.) and H_2O (1 eq.) in DCM. The results are summarized in Scheme 2. Except for cytidine derivative **4c**, the reaction of pyrimidine nucleosides (**3b**, **3d–e**), purine nucleosides (**3a**, **3f–h**), and 7-deazaguanine nucleoside (**3i**) all proceeded smoothly and the desired products (**4a–b**, **4d–i**) were obtained in nearly quantitative yield. For cytidine derivative **4c**, it was speculated that the unprotected *N*-4 primary amine group may chelate with gold(i) ion to deactivate its catalytic activity. The speculation was further proved that the reaction can afford corresponding nucleoside **4d** in high yield after its *N*-4 amine was protected by benzoate. For nucleosides **3g** and **3h**, the electron-withdrawing substituents (F and Cl) in purine base might reduce the nucleophilicity of *N*-6 amine, but they did not interfere the gold(i) catalyst's activity. Therefore, nucleosides **4g** and **4h** could be obtained successfully. HPLC analysis of **4a–**



Scheme 2 Gold(i)-catalyzed selective deprotection of β -nucleosides (**4a–i**).

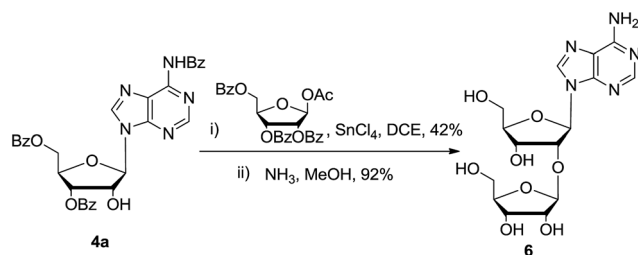


Scheme 3 Proposed catalytic cycle for the gold(i)-catalyzed removing *ortho*-alkynyl benzoate.

b and **4d–i** showed that the no transesterification of 3'-benzoate to 2'-OH was noticed, which was crucial for following synthesis of 2'-modified ribonucleosides.

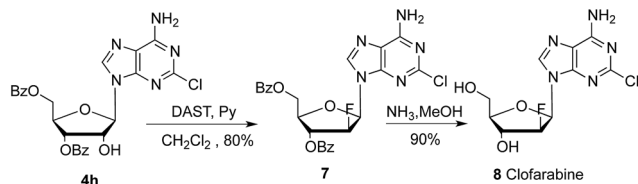
In order to further investigate the reaction mechanism, H_2O^{18} was used in the control reaction. After reaction accomplished, O^{18} -labeled isocoumarin **G** was obtained, which was confirmed by HRMS. According to the above evidences, a plausible catalytic cycle is proposed in Scheme 3. The coordination of the carbon–carbon triple bond of nucleoside **A** to the gold(i) catalyst improved the electrophilicity of alkyne (**B**). Subsequently, the carbonyl oxygen could attack the electron-deficient alkyne to form the intermediate **C**. While H_2O addition to the formed onium ion would generate the intermediate **D**. After hydrogen atom transferred, nucleoside **E** would be released along with the generation of the intermediate **F**. Finally, isocoumarin **G** was yielded and the corresponding active gold(i) species were liberated to participate in the next catalytic cycle.

In order to testify this strategy to prepare 2'-modified nucleosides, disaccharide nucleoside **6** (9-(2-*O*- β -D-ribofuranosyl- β -ribofuranosyl)-adenine) was synthesized. Disaccharide nucleoside is an important family of natural compounds, which is widely found in t-RNA, antibiotics, and other physiologically



Scheme 4 Synthesis of 2'-*O*- β -D-ribofuranosyladenosine: (i) 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl- β -D-ribofuranose, SnCl_4 , 1,2-dichloroethane, -10°C , 8 hours, 42%; (ii) NH_3 , MeOH, 60°C , 5 hours, 92%.





Scheme 5 Synthesis of clofarabine 9: (i) Tf₂O, pyridine, −20 °C, 5 hours, 95%; (ii) Et₃N·3HF, ethyl acetate, 70 °C, 24 hours, 66%; (iii) NH₃, MeOH, 60 °C, 5 hours, 90%.

active compounds.^{16,17} Several synthetic approaches were reported. As shown in Scheme 4, glycosylation of nucleoside 4a with a little excess of 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose gave the corresponding disaccharide nucleoside in 42% yield. After deprotection of all ester groups, nucleoside 6 (10 grams) was obtained in high purity. All the characterization spectra were identified with the reported data.

To further extend the application of this methodology, we also attempted to develop a new approach for synthesis of antitumor drug clofarabine 9.^{18,19} As presented in Scheme 5, the reaction of nucleoside 4h with trifluoromethanesulfonic anhydride (Tf₂O) in pyridine gave corresponding trifluoromethanesulfonic ester of 2'-OH in almost quantitative yield. After fluorination with Et₃N·HF, deacylation with ammonia in methanol gave clofarabine (16 grams) in 56% overall yield. HPLC analysis showed the purity is above 99% and coincidence with reference standard from Sigma Aldrich.

In summary, *ortho*-alkynyl benzoate was proved to be an efficient neighboring participation group in stereoselective synthesis of nucleosides by using Vorbrüggen glycosylation. It could be removed as isocoumarin 5 using gold(I)-catalysis to afford 2'-OH nucleosides in high yield and selectivity. The powerfulness of present strategy was further demonstrated by the synthesis of 9-(2-O-β-D-ribofuranosyl-β-ribofuranosyl)-adenine 6 and antitumor drug clofarabine 9 in high overall yields. This novel protocol could be used as a general alternative approach for the synthesis of 2'-modified nucleosides. Its application in carbohydrate synthesis is under way.

Acknowledgements

We thank National Science Foundation of China (No. 21462019 and No. 21676131), Bureau of Science & Technology of Jiangxi Province (20143ACB20012) for financial support.

Notes and references

- (a) E. De Clercq, *Med. Res. Rev.*, 2010, **31**, 118–160; (b) E. De Clercq, *Curr. Opin. Pharmacol.*, 2010, **10**, 507–515.
- (a) A. H. Cory, V. Samano, M. J. Robins and J. G. Cory, *Biochem. Pharmacol.*, 1994, **47**, 365–371; (b) H. Awano, S. Shuto, M. Baba, T. Kira, S. Shigeta and A. Matsuda, *Bioorg. Med. Chem. Lett.*, 1994, **4**, 367–370.

- S. Ganguly, V. V. Vithlani and K. A. Kesharwani, *Acta Pharm.*, 2011, **61**, 187–201.
- J. Kim, J. Yu and V. Alexander, *Eur. J. Med. Chem.*, 2014, **83**, 208–225.
- V. Alexander, J. Song and J. Yu, *Arch. Pharmacol. Res.*, 2015, **38**, 966–972.
- N. Goris, A. De Palma, J. F. Toussaint, I. Musch, J. Neyts and K. De Clercq, *Antiviral Res.*, 2007, **73**, 161–168.
- J. L. Clark, J. C. Mason, L. Hollecker, L. J. Stuyver, P. M. Tharnish, T. R. McBrayer, M. J. Otto, P. A. Furman, R. F. Schinazi and K. A. Watanabe, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 1712–1715.
- (a) E. Lawitz, A. Mangia, D. Wyles, M. Rodriguez, *et al.*, *N. Engl. J. Med.*, 2013, **368**, 1878–1887; (b) M. Lagging, R. Wejstal, G. Norkrans, O. Karlstorm, F. Josephson, *et al.*, *Infect. Dis.*, 2016, **48**, 251–261; (c) P. Wang, B. K. Chun, S. Rachakonda, J. Du, N. Khan, J. Shi, W. Stec, D. Cleary, B. S. Ross and M. J. Sofia, *J. Org. Chem.*, 2009, **74**, 6819–6824.
- J. Ye, N. Li, Q. Dai and J. A. Piccirilli, *Angew. Chem., Int. Ed.*, 2007, **46**, 3714–3717.
- S. N. Mikhailov, M. Oivanen, P. Oksman and H. Lonnberg, *J. Org. Chem.*, 1992, **57**, 4122–4126.
- M. Tanaka, R. Kozakai, Y. Saito and I. Saito, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 7021–7024.
- (a) Y. Ishido, N. Sakairi, K. Okazaki and N. Nakazaki, *J. Chem. Soc., Perkin Trans. 1*, 1980, 563–573; (b) S. Nishino, A. M. Rahman, H. Takamura and Y. Iahido, *Tetrahedron*, 1985, **41**, 5503–5506; (c) I. Nowak, C. T. Jones and M. J. Robins, *J. Org. Chem.*, 2006, **71**, 3077–3081.
- (a) R. Dore and A. M. Echavarren, *Chem. Rev.*, 2015, **115**, 9028–9072; (b) A. Corma, A. L. Perez and M. J. Sabater, *Chem. Rev.*, 2011, **111**, 1657–1712.
- (a) M. Jia and M. Bandini, *ACS Catal.*, 2015, **5**, 1638–1652; (b) Q. Zhang, J. Sun, Y. Zhu, F. Zhang and B. Yu, *Angew. Chem., Int. Ed.*, 2011, **50**, 4933–4936; (c) Y. Zhu and B. Yu, *Angew. Chem., Int. Ed.*, 2011, **50**, 8329–8332; (d) Y. Tang, J. Li, Y. Zhu, Y. Li and B. Yu, *J. Am. Chem. Soc.*, 2013, **135**, 18396–18405; (e) B. Yu, J. Sun and X. Yang, *Acc. Chem. Res.*, 2012, **45**, 1227–1236.
- (a) N. Asao, H. Aikawa, S. Tago and K. Umetsu, *Org. Lett.*, 2007, **9**, 4299–4302; (b) K. Umetsu and N. Asao, *Tetrahedron Lett.*, 2008, **49**, 7046–7049.
- S. N. Mikhailov, E. V. Efimtseva, A. A. Rodionov, G. V. Bobkov, I. V. Kulikova and P. Herdewijn, *Curr. Protoc. Nucleic Acid Chem.*, 2007, **27**, 1.14.1–1.14.19.
- E. V. Efimtseva and S. N. Mikhailov, *Russ. Chem. Rev.*, 2004, **73**, 401–414.
- P. L. Bonate, L. Arthaud, W. R. Cantrell, K. Stephenson, J. A. Secrist and S. Weitman, *Nat. Rev. Drug Discovery*, 2006, **5**, 855–863.
- R. Xia, Z. Guo, B. Qin, Z. Ji, M. Xie, G. Qu and H. Guo, *Chin. J. Org. Chem.*, 2014, **34**, 1154–1160.

