



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Total synthesis of remdesivir [☆]

Kishore Kumar Palli ^{a,b}, Palash Ghosh ^{a,b}, Shiva Krishna Avula ^{a,b},
B. Sridhara Shanmukha Rao ^{a,b}, Amol D. Patil ^{a,b}, Subhash Ghosh ^{a,b}, Gangarajula Sudhakar ^{a,b},
Chada Raji Reddy ^{a,b}, Prathama S. Mainkar ^{a,b}, Srivari Chandrasekhar ^{a,b,*}

^a Department of Organic Synthesis & Process Chemistry, CSIR-Indian Institute of Chemical Technology (CSIR-IICT), Hyderabad 500007, India

^b Academy of Scientific and Innovative Research (AcSIR), Ghaziabad 201002, India



ARTICLE INFO

Article history:

Received 19 October 2021

Revised 1 December 2021

Accepted 6 December 2021

Available online 9 December 2021

Keywords:

Remdesivir

Nucleotide

Nucleoside

COVID-19

RdRp

ABSTRACT

Remdesivir, the first drug approved by the FDA to treat COVID-19, is in high demand for patients infected with the SARS-CoV-2 virus. Herein, we report a facile approach minimizing the protecting group manipulations to afford remdesivir in good overall yield.

© 2021 Elsevier Ltd. All rights reserved.

Introduction

The COVID-19 pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has created a devastating health crisis around the globe [1–6]. To combat this pandemic, effective and affordable treatments are still being urgently sought. In 2020, the FDA approved remdesivir (**1**, GS-5734) as the first drug for the treatment of COVID-19 [7,8], and subsequently, related molecules such as galidesivir (**2**), sofosbuvir (**3**), and molnupiravir (**4**) were also found to be effective (Fig. 1) [9].

Remdesivir (**1**), was initially developed by Gilead Sciences for the treatment of hepatitis C and Ebola virus infections [10,11]. However, the clinical trials against Ebola were not successful [12]. Remdesivir is a prodrug with good cell permeability and hydrolyzes inside the cell to release a nucleotide triphosphate that targets the key RNA dependent RNA polymerase (RdRp) enzyme responsible for viral replication.

The synthetic route developed by Gilead Sciences for the commercial production of remdesivir [10,11], involves protecting group manipulations of the sugar part during the synthesis,

providing an opportunity for further improvements. Conversion of D-ribose (**5**) to 2,3,5-tri-O-benzyl-D-ribonolactone (**6**) followed by addition of modified nucleobase 4-amino-7-iodopyrrolo[2,1-f][1–2,4]triazine (**7**) onto the lactone gave C-glycosylated product **8** in low yield (40%). After cyanation, all three benzyl groups were deprotected using BCl₃ and the two secondary alcohols of the resulting triol were subsequently protected as isopropylidene ketal **10**. Finally, introduction of phosphonate ester **11** to ketal **10** followed by hydrolysis of the ketal leads to the target compound remdesivir (**1**) (Scheme 1) [10]. Later, to improve the yield of the C-glycosylation reaction, expensive NdCl₃ was used as an additive in stoichiometric amounts, which improved the yield to 69% [13,14].

In view of the importance of this being the only FDA-approved drug for COVID-19 mitigation, we reasoned any improvement on the synthetic route would have a large impact on supplies. The opportunities we realized include (a) protecting group manipulations, viz, replacing the benzyl groups with those which could be introduced and removed by catalytic processes avoiding stoichiometric reagents, (b) avoiding the use of NdCl₃, and (c) achieving anomeric selectivity with better yields.

We planned our synthesis from D-ribonolactone (**12**), which is in the correct oxidation form to introduce the heterocyclic fragment at the anomeric carbon. It was also assumed that a bulky protecting group at the C-5 hydroxyl would enable better selectivity at the anomeric position. Thus, the primary hydroxyl group of

[☆] This work is dedicated to the memory of Dr. Surendar Reddy Bathula (Principal Scientist, CSIR-IICT), who lost the battle with COVID-19 infection after a fierce fight.

* Corresponding author at: Department of Organic Synthesis & Process Chemistry, CSIR-Indian Institute of Chemical Technology (CSIR-IICT), Hyderabad 500007, India.

E-mail address: srivari@iict.res.in (S. Chandrasekhar).

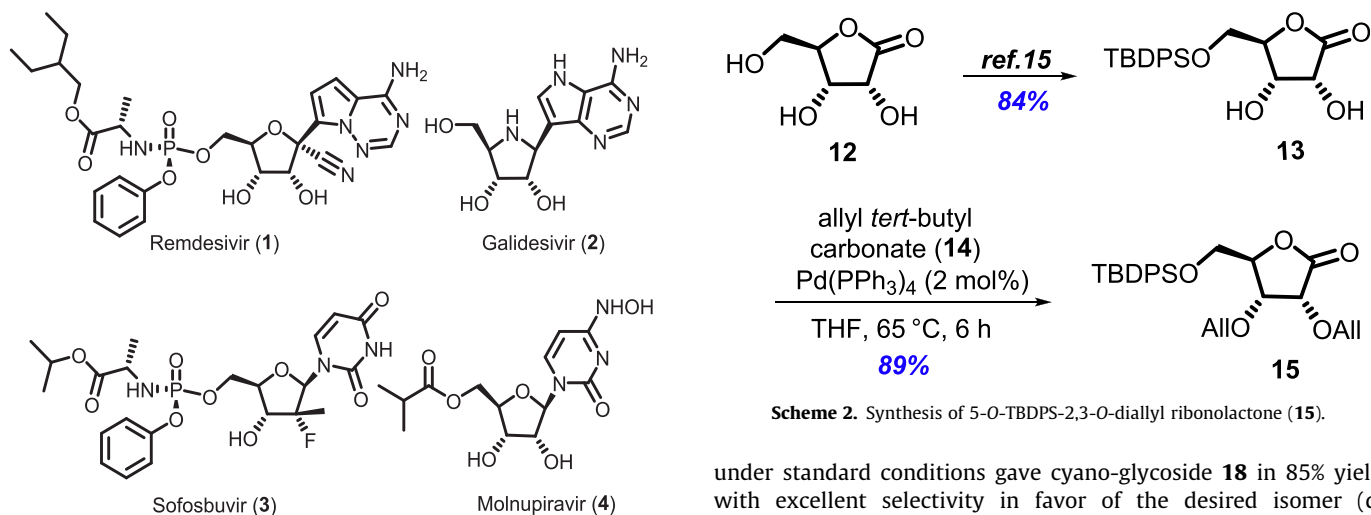


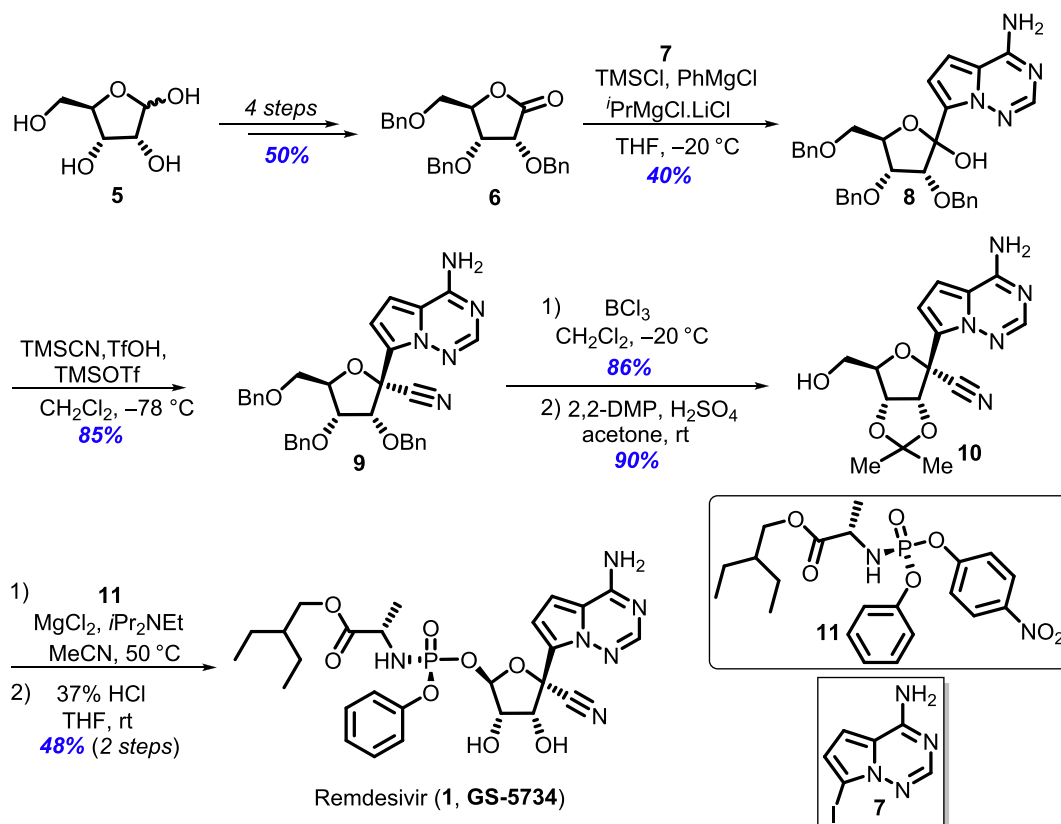
Fig. 1. Structures of remdesivir and other related antiviral drugs.

commercially available *D*-ribonolactone (12, can also be synthesized from *D*-ribose in one step) was silylated with *tert*-butyldiphenyl silyl (TBDPS) group to afford the corresponding silyl ether (13) in 84% yield [15]. Further protection of the remaining two secondary alcohols using allyl *tert*-butyl carbonate (14) in the presence of 2 mol% Pd(PPh₃)₄ furnished diallylated ribonolactone (15) in 89% yield (Scheme 2) [16].

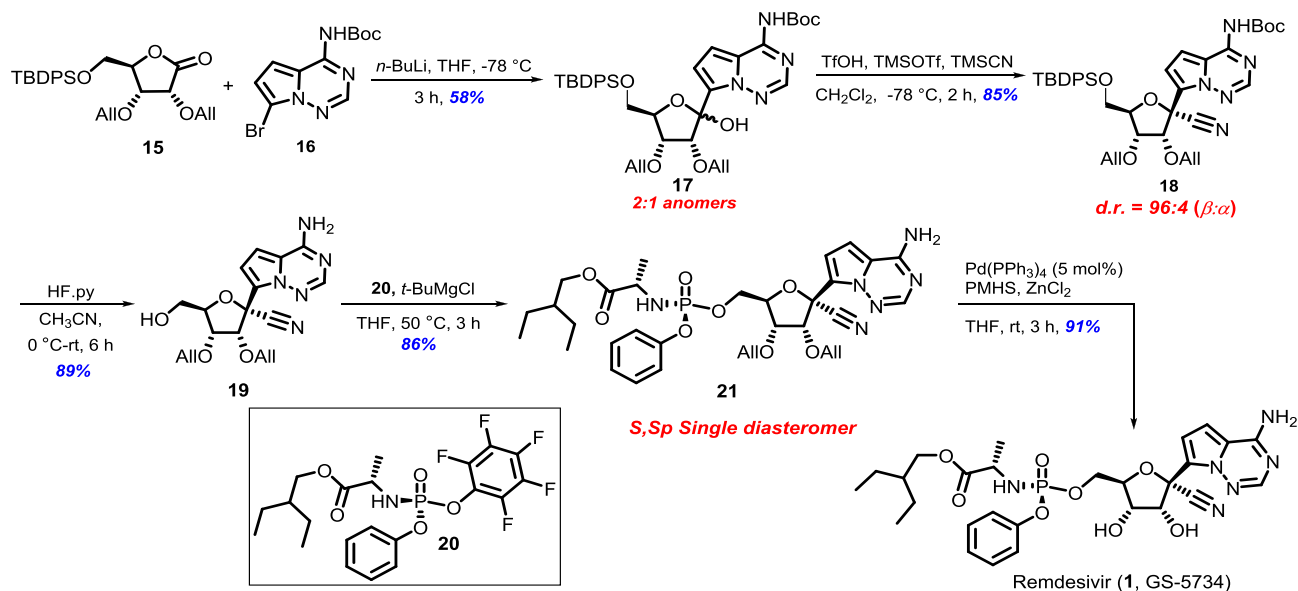
Next, lactone (15) was subjected to C-glycosylation [10,11,13,14,17] with the protected nucleobase *tert*-butyl(7-bromopyrrolo[2,1-*f*] [1-2,4] triazin-4-yl) carbamate (16) which in presence of *n*-BuLi provided an anomeric mixture (2:1) of C-glycosylated product (17) in 58% yield. The cyanation [10–11,13,18] of 17

under standard conditions gave cyano-glycoside (18) in 85% yield with excellent selectivity in favor of the desired isomer (d. r. = 96:4; β:α). To introduce the desired phosphonate on the primary hydroxyl group, deprotection of the silyl group and Boc group was achieved under HF, pyridine conditions in one-pot to afford amino-alcohol (19) in 89% yield [19]. The next task was to carry out the P-chiral phosphorylation, a key step in the synthesis of remdesivir [20]. Coupling of (19) with the known chiral pentafluoro-phosphoramidate (20) [21] in the presence of *t*-BuMgCl gave phosphoramidate ester (21) in 86% yield as a single diastereoisomer. Finally, removal of the diallyl groups from (21) was accomplished by Pd-catalyzed reductive deallylation, using a method developed by our group [22], to obtain the target molecule remdesivir (1) in 91% yield, whose spectral data were in good agreement with the reported data (Scheme 3).

In conclusion, a short synthetic approach to access remdesivir has been developed in seven longest linear steps (LLS) with 25%



Scheme 1. Gilעד route for the synthesis of remdesivir (1, GS-5734).



Scheme 3. Total synthesis of remdesivir (1, GS-5734).

overall yield starting from D -ribose derivative (**12**). The present strategy using a silyl/allyl protected sugar **15** has advantages including (i) avoiding the use of hazardous BCl_3 for benzyl deprotection, (ii) improvement in the coupling yield without any additive, (iii) use of catalytic methods for protection and deprotection of the allyl groups. We believe that the present approach is scalable and can be used for the synthesis of novel analogues in addition to remdesivir as anti-viral agents.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Srivari Chandrasekhar reports financial support was provided by Science and Engineering Research Board.

Acknowledgments

We thank the Council of Scientific and Industrial Research (CSIR), Ministry of Science and Technology, Government of India, for research funding (COVID-19 Mission Mode Project, HCP 0029). K.K.P thanks the University Grants Commission (UGC), New Delhi, for a research fellowship. P.G. thanks the CSIR, New Delhi, for a research fellowship. S.C. thanks the Science and Engineering Research Board (SERB), Government of India for the J C Bose fellowship (SB/S2/JCB-002/2015). We also thank Dr. B. Jagadeesh, Head, Centre for NMR, CSIR-IICT, for NMR analytical support.

CSIR-IICT Manuscript Communication Number: IICT/Pubs./2021/279.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.tetlet.2021.153590>.

References

- [1] A.E. Gorbalenya, S.C. Baker, R.S. Baric, R.J. de Groot, C. Drosten, A.A. Gulyaeva, B. L. Haagmans, C. Lauber, A.M. Leontovich, B.W. Neuman, D. Penzar, S. Perlman, L.L.M. Poon, D.V. Samborskiy, I.A. Sidorov, I. Sola, J. Ziebuhr, *Nat. Microbiol.* **5** (2020) 536–544.
- [2] P. Zhou, X.-L. Yang, X.-G. Wang, B. Hu, L. Zhang, W. Zhang, H.-R. Si, Y. Zhu, B. Li, C.-L. Huang, H.-D. Chen, J. Chen, Y. Luo, H. Guo, R.-D. Jiang, M.-Q. Liu, Y. Chen, X.-R. Shen, X. Wang, X.-S. Zheng, K. Zhao, Q.-J. Chen, F. de, L.-L. Liu, B. Yan, F.-X. Zhan, Y.-Y. Wang, G.-F. Xiao, Z.-L. Shi, *Nature* **579** (2020) 270–273.
- [3] E.D. Wit, F. Feldmann, J. Cronin, R. Jordan, A. Okumura, T. Thomas, D. Scott, T. Cihlar, H. Feldmann, *Proc. Natl. Acad. Sci. USA* **117** (2020) 6771–6776.
- [4] K. Kupferschmidt, J. Cohen, *Science* **367** (2020) 610–611.
- [5] P. Habibzadeh, E.K. Stoneman, *Int. J. Occup. Environ. Med.* **11** (2020) 65–71.
- [6] J.F.-W. Chan, S. Yuan, K.-H. Kok, K.K.-W. To, H. Chu, J. Yang, F. Xing, J. Liu, C.C.-Y. Yip, R.W.-S. Poon, H.-W. Tsoi, S.K.-F. Lo, K.-H. Chan, V.C.-C. Cheng, H. Chen, C.K.-M. Hui, K.-Y. Yuen, *Lancet* **395** (2020) 514–523.
- [7] J.H. Beigel, K.M. Tomashek, L.E. Dodd, A.K. Mehta, B.S. Zingman, A.C. Kalil, E. Hohmann, H.Y. Chu, A. Luetkemeyer, S. Kline, D.L. de Castilla, R.W. Finberg, N. Engl. *J. Med.* **383** (2020) 1813–1826.
- [8] (a) J. Grein, N. Ohmagari, D. Shin, G. Diaz, E. Asperges, A. Castagna, T. Feldt, G. Green, M.L. Green, F.X. Lescure, E. Nicastri, R. Oda, N. Engl. *J. Med.* **382** (2020) 2327–2336; (b) R.T. Eastman, J.S. Roth, K.R. Brimacombe, A. Simeonov, M. Shen, S. Patnaik, M.D. Hall, *ACS Cent. Sci.* **6** (2020) 672–683.
- [9] M.N. Namchuk, *ACS Infect. Dis.* **7** (2021) 1298–1302.
- [10] T.K. Warren, R. Jordan, M.K. Lo, A.S. Ray, R.L. Mackman, V. Soloveva, D. Siegel, M. Perron, R. Bannister, H.C. Hui, N. Larson, R. Strickley, J. Wells, K.S. Stuthman, S.A.V. Tongeren, N.L. Garza, G. Donnelly, A.C. Shurtleff, C.J. Retterer, D. Gharaibeh, R. Zamani, T. Kenny, B.P. Eaton, E. Grimes, L.S. Welch, L. Gomba, C.L. Wilhelmsen, D.K. Nichols, J.E. Nuss, E.R. Nagle, J.R. Kugelman, G. Palacios, E. Doerffler, S. Neville, E. Carra, M.O. Clarke, L. Zhang, W. Lew, B. Ross, Q. Wang, K. Chun, L. Wolfe, D. Babusis, Y. Park, K.M. Stray, I. Trancheva, J.Y. Feng, O. Barauskas, Y. Xu, P. Wong, M.R. Braun, M. Flint, L.K. McMullan, S.-S. Chen, R. Fearnis, S. Swaminathan, D.L. Mayers, C.F. Spiropoulou, W.A. Lee, S.T. Nichol, T. Cihlar, S. Bavari, *Nature* **531** (2016) 381–385.
- [11] D. Siegel, H.C. Hui, E. Doerffler, M.O. Clarke, K. Chun, L. Zhang, S. Neville, E. Carra, W. Lew, B. Ross, Q. Wang, L. Wolfe, R. Jordan, V. Soloveva, J. Knox, J. Perry, M. Perron, K.M. Stray, O. Barauskas, J.Y. Feng, Y. Xu, G. Lee, A.L. Rheingold, A.S. Ray, R. Bannister, R. Strickley, S. Swaminathan, W.A. Lee, S. Bavari, T. Cihlar, M.K. Lo, T.K. Warren, R.L. Mackman, *J. Med. Chem.* **60** (2017) 1648–1661.
- [12] S. Mulangu, L.E. Dodd, R.T. Davey, O.T. Mbaya, M. Proschan, D. Mukadi, M.L. Manzo, D. Nzolo, A.T. Oloma, A. Ibanda, R. Ali, S. Coulibaly, A.C. Levine, R. Grais, J. Diaz, H.C. Lane, J.-J. Muyembe-Tamfum, N. Engl. *J. Med.* **381** (2019) 2293–2303.
- [13] T. Vieira, A.C. Stevens, A. Chtchemeliline, D. Gao, P. Badalov, L. Heumann, *Org. Process Res. Dev.* **24** (2020) 2113–2121.
- [14] F. Xue, X. Zhou, R. Zhou, X. Zhou, D. Xiao, E. Gu, X. Guo, J. Xiang, K. Wang, L. Yang, W. Zhong, Y. Qin, *Org. Process Res. Dev.* **24** (2020) 1772–1777.
- [15] (a) M.G.B. Drew, J. Mann, A. Thomas, *J. Chem. Soc. Perkin Trans. 1* (1986) 2279–2285; (b) J.D. Williams, V.P. Kamath, P.E. Morris, L.B. Townsend, *Org. Synth.* **82** (2005) 75–79.
- [16] A.R. Haight, E.J. Stoner, M.J. Peterson, V.K. Grover, *J. Org. Chem.* **68** (2003) 8092–8096.
- [17] (a) T. Butler, A. Cho, C.U. Kim, O.L. Saunders, L. Zhang, U.S. Patent 2009041447 Apr. 22 (2009); (b) T.V. Keutz, J.D. Williams, C.O. Kappe, *Org. Process Res. Dev.* **24** (2020) 2362–2368; (c) T. Butler, A. Cho, B.R. Graetz, C.U. Kim, S.E. Metobo, O.L. Saunders, A.W. Waltman, J. Xu, L. Zhang, U.S. Patent

- 20100459508 Sep. 20 (2010); (d) S.E. Metobo, J. Xu, O.L. Saunders, T. Butler, E. Aktoudianakis, A. Cho, C.U. Kim, *Tetrahedron Lett.* 53(2012) 484–486; (e) Y. Xie, T. Hu, Y. Zhang, D. Wei, W. Zheng, F. Zhu, G. Tian, H.A. Aisa, J. Shen, *J. Org. Chem.* 86(2021) 5065–5072.
- [18] (a) Y. Xie, T. Hu, Y. Zhang, D. Wei, W. Zheng, F. Zhu, G. Tian, H.A. Aisa, J. Shen, *J. Org. Chem.* 86 (2021) 5065–5072;
(b) C.D. Savi, D.L. Hughes, L. Kvaerno, *Org. Process. Res. Dev.* 24 (2020) 940–976;
(c) D.F. Vargas, E.L. Larghi, T.S. Kaufman, *ACS Omega* 6 (2021) 19356–19363.
- [19] (a) B. Mishra, S. Manmode, G. Walke, S. Chakraborty, M. Neralkar, S. Hotha, *Org. Biomol. Chem.* 19 (2021) 1315–1328;
(b) A. Sugawara, H. Takada, T. Hirose, A. Kimishima, T. Yamada, M. Toda, T. Kojima, T. Matsumaru, T. Sunazuka, *Org. Lett.* 23 (2021) 1758–1763;
(c) S. Nagamalla, D.K. Johnson, S. Sathyamoorthi, *Med. Chem. Res.* 30 (2021) 1348–1357;
- (d) G. Liu, Z. Zhang, S. Fu, B. Liu, *Org. Lett.* 23 (2021) 290–295;
(e) S. Matsuura, C.-H. Niu, J.S. Cohen, *JCS Chem. Comm.* (1976) 451–452.
- [20] (a) B.S. Ross, P.G. Reddy, H.-R. Zhang, S. Rachakonda, M.J. Sofia, *J. Org. Chem.* 76 (2011) 8311–8319;
(b) M. Wang, L. Zhang, X. Huo, Z. Zhang, Q. Yuan, P. Li, J. Chen, Y. Zou, Z. Wu, W. Zhang, *Angew. Chem., Int. Ed.* 59 (2020) 20814–20819;
(c) V. Gannedi, B.K. Villuri, S.N. Reddy, C.-C. Ku, C.-H. Wong, S.-C. Hung, *J. Org. Chem.* 86 (2021) 4977–4985;
(d) M. Wang, L. Zhang, X. Huo, Z. Zhang, W. Zhang, *Curr. Protocols* (2021), <https://doi.org/10.1002/cpz1.303>.
- [21] (a) B.K. Chun, M.O. Clarke, E. Doerffler, H.C. Hui, R. Jordan, R.L. Mackman, A.S. Ray, D. Siegel, Patent WO2016/69826 (2016); (b) M.O. Clarke, R. Jordan, R.L. Mackman, A.S. Ray, D. Siegel, Patent WO2017/184668 (2017); (c) O. Moukha-Chafiq, M.J. Suto, J. Liu, R. Boohaker, Patent WO2020/247633, (2020).
- [22] S. Chandrasekhar, C.R. Reddy, R.J. Rao, *Tetrahedron* 57 (2001) 3435–3438.