ACS Medicinal Chemistry Letters

pubs.acs.org/acsmedchemlett Letter

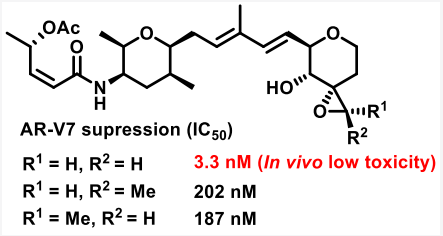
Design and Synthesis of 1,2-Deoxy-pyranose Derivatives of Spliceostatin A toward Prostate Cancer Treatment

Yusuke Yoshikawa,[‖] Airi Ishibashi,[‖] Tsunayoshi Takehara, Takeyuki Suzuki, Kenichi Murai, Yasufumi Kaneda, Keisuke Nimura,* and Mitsuhiro Arisawa*

Cite This: *ACS Med. Chem. Lett.* 2020, 11, 1310−1315 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: We designed and synthesized a novel 1,2-deoxy-pyranose and terminal epoxide methyl substituted derivatives of spliceostatin A using Julia−Kocienski olefination as a key step. With respect to the biological activity, the 1,2-deoxy-pyranose analogue of spliceostatin A suppressed AR-V7 expression at the nano level (IC_{50} = 3.3 nM). In addition, the *in vivo* toxicity test showed that the 1,2-deoxy-pyranose analogue was able to avoid severe toxicity compared to spliceostatin A.



KEYWORDS: *Prostate cancer, splicing, splicing variant, spliceostatin A, toxicity*

In men, one of most common cancers is prostate cancer, which is treated with androgen deprivation therapy (ADT). However, after ADT, most of them develop castration-resistant prostate cancer (CRPC). These CRPC patients are then treated with hormonal therapies using androgen receptor (AR) signaling pathway inhibitors such as enzalutamide or abiraterone, but many CRPC patients become resistant to these medicines after a few years.[1−3] One of the reasons for the resistance is the expression of the splicing variant of AR, specifically AR-V7, which gets activated constitutively without hormone ligands and promotes prostate cancer growth.[4,5] Therefore, the development of inhibitors targeting AR-V7 expression is important for drug resistant CRPC therapy, and, to this end, some inhibitors have been developed (SF3b complex inhibitor and ROR-γ antagonist).[6−10]

Previously, it was discovered that the target protein of the splicing modulators spliceostatin A (**1**) (Figure 1), pladienolide B, and *GEX1A* (herboxidiene) (Scheme S1), which showed strong antitumor activity toward solid tumors in mice and several cancer cells, was an SF3b complex in U2SnRNP (main factor of pre-mRNA splicing).[11−19] Until now, several synthetic studies (including analog synthesis) and mRNA splicing inhibition activity studies of **1**, pladienolide B, and *GEX1A* have been conducted by several research groups,[20−37] but there are only a few reports of splicing modulators which can inhibit the expression of AR-V7.

Recently, our group and the Hsieh group discovered that **1** and its relative pladienolide B and thailanstatins (Scheme S1) can inhibit the expression of AR-V7.[6−8] Specifically pladienolide B significantly reduced the tumor volume of CRPC model mice overexpressing AR-V7.[7] However, pladienolide B analogue E7107 entered phase I clinical trials, and as a result some patients suffered from vision loss.[38,39] Consequently, we

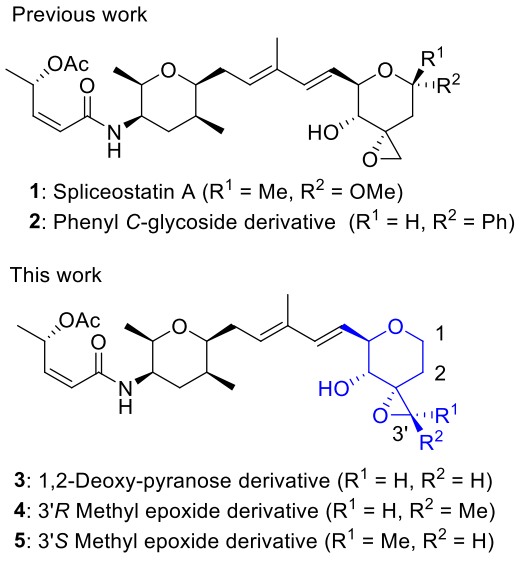
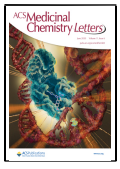


Figure 1. Structure of spliceostatin A and its derivatives (**1**−**5**).

focused our research on **1** and its derivatives.[40] Very recently, we designed and synthesized **2** which was more easily synthesized and acid stable than **1** but had weak AR-V7 suppression inhibitory activity (IC_{50} = 132 nM).[8] To discover

Received: March 24, 2020
Accepted: May 1, 2020
Published: May 1, 2020



https://dx.doi.org/10.1021/acsmedchemlett.0c00153
ACS Med. Chem. Lett. 2020, 11, 1310−1315

easily synthesizable derivatives of **1** with potent AR-V7 suppression inhibitory activity, we designed and synthesized new derivatives **3**−**5** based on much more detailed theoretical considerations.[41]

Our considerations in designing derivatives **3**−**5** are shown in Figure 2.

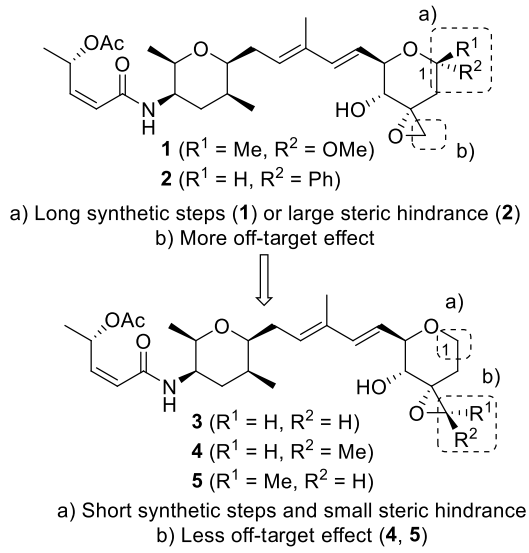


Figure 2. Design strategy for derivatives **3**−**5**.

For **3**, the AR-V7 expression inhibitory activity of phenyl-*C*-glycoside derivative **2** was weaker than that of **1**. We hypothesized that the weaker biological activity could be due to the presence of the bulky phenyl group, and therefore, we designed 1,2-deoxy-pyranose derivative **3** which had no functional group at the anomeric site and could have higher acid stability than **1**. In addition, it was considered that the C1 unsubstituted pyran fragment of **3** could be synthesized more easily than the C1 methyl ketal pyran fragment of **1**. (Figure 1a).

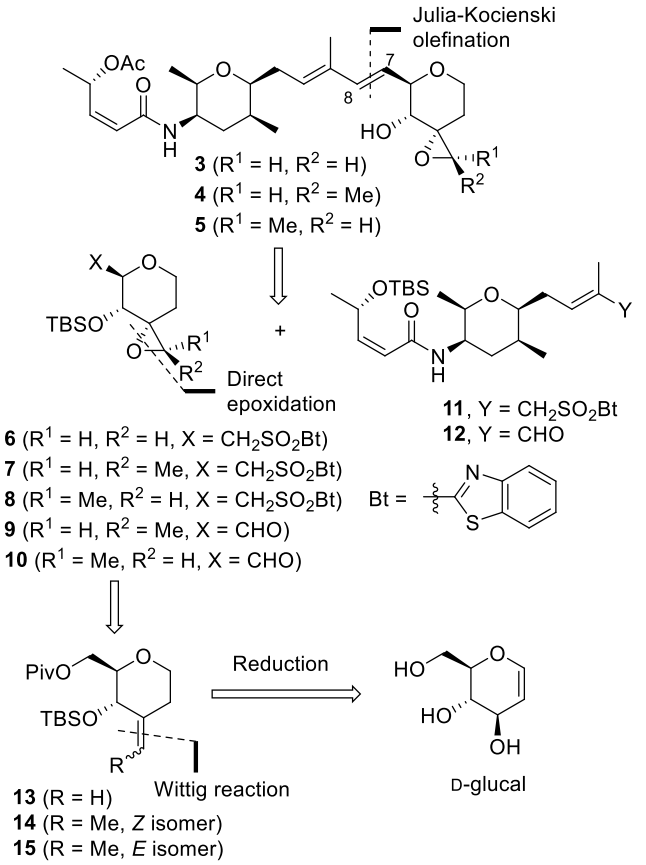
For **4** and **5**, we hypothesized that the presence of the terminal epoxide of **1** and/or **2** was required for biological activity expression. However, the epoxide is typically associated with instability or toxicity derived from off-target effects (forming covalent bonding with amino acid residues of other proteins).[42] Thus, we designed derivatives **4** (3′*R*) and **5** (3′*S*) to a methyl group on the epoxide of derivative **3** (Figure 2b), which could improve the stability of the epoxide.

Scheme 1 illustrates our retrosynthetic analysis for **3**−**5**. An internal double bond on C7 and C8, was constructed by Julia−Kocienski olefination between an appropriate aldehyde **9**, **10**, or **12**[8]) and a sulfone (**11**[21] or **6**−**8**). The structures **6**−**10** were prepared from the corresponding olefins **13**−**15** by diastereoselective direct epoxidation, and the olefins **13**−**15** could be prepared by a Wittig reaction of the corresponding ketone, which was derived from D-glucal.

The synthesis of olefin key intermediates **13**−**15** is summarized in Scheme 2.

For **13** in Scheme 2a, the hydroxy group of the protected 1,2-deoxy pyranose **16**, which was prepared from commercially available D-glucal,[43] was oxidized to the corresponding ketone with Dess−Martin periodinane (DMP) and the subsequent Wittig reaction produced the olefin **17** in 55% yield over two steps. The *p*-methoxy benzyl acetal **17** was reduced to the

Scheme 1. Retrosynthetic Analysis for 3−**5**



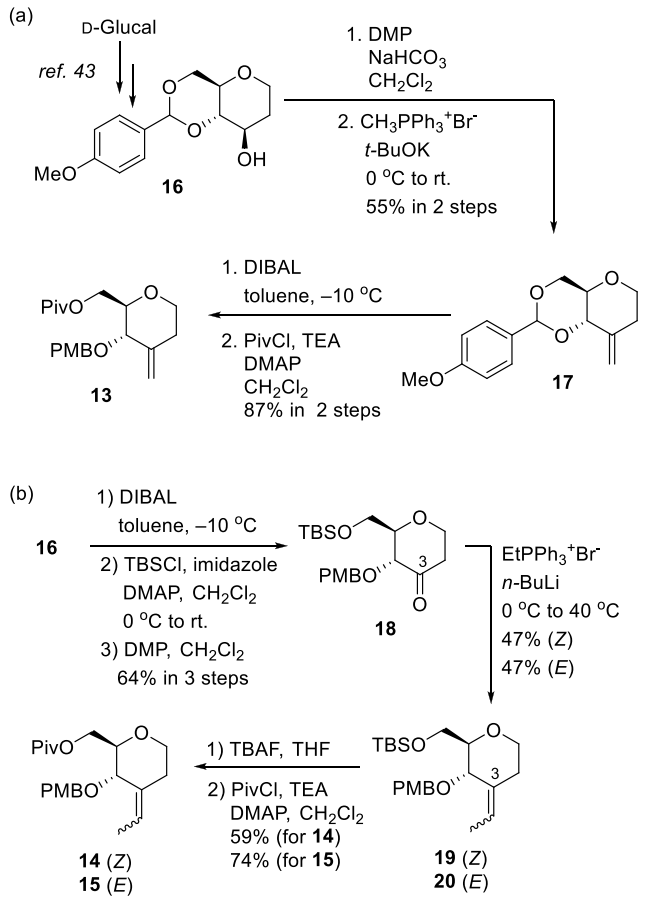
corresponding primary alcohol by *i*-Bu_2AlH (DIBAL) at −10 °C, and the generated primary alcohol was protected with *t*-BuCOCl (PivCl) to generate **13** in 87% yield (two steps).

For **14** and **15** in Scheme 2b, the acetal **16** was reduced by DIBAL in the same manner as described above, the primary hydroxyl group was protected with a Si-*t*-$BuMe_2$ (TBS) group and the generated secondary alcohol was oxidized with DMP to produce ketone **18**. Subsequent Wittig reaction proceeded to furnish internal olefins **19** and **20**. The reaction proceeded smoothly ($EtPPh_3^+Br^-$, *n*-BuLi, THF, 0−40 °C) to create the geometric isomer **19** (*Z*) and **20** (*E*) in 47% yield, respectively. To construct trisubstituted olefins on the C3 position, other reaction conditions are actually applied (changing reaction temperature, base, substrate). The details of the reaction conditions are shown in Scheme S2. Finally, the TBS groups of **19** (*Z*) and **20** (*E*) were removed with Bu_4NF (TBAF) to synthesize the corresponding primary alcohol. The alcohol was further protected with PivCl to produce ester **14** (*Z*) and **15** (*E*) in 59% and 74% yield over two steps, respectively.

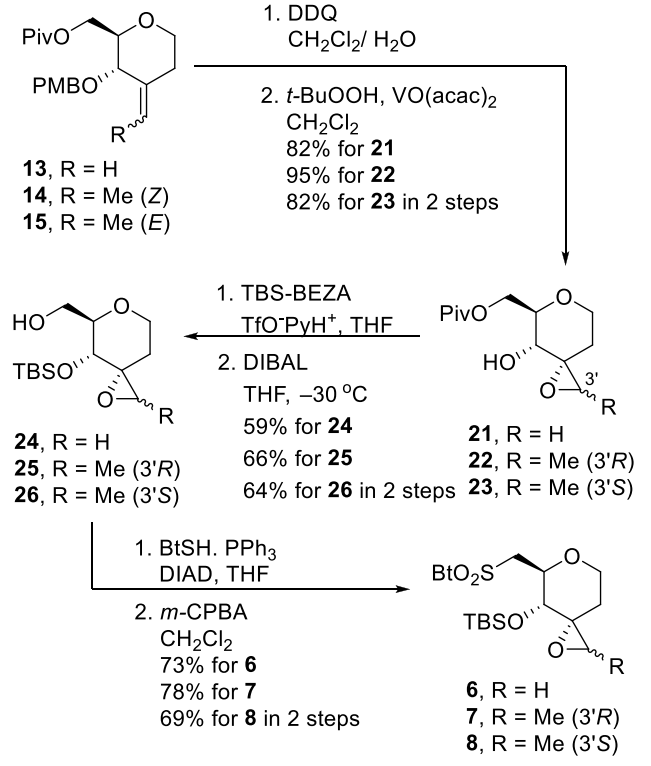
The synthesis of benzothiazoles **6**−**8** is summarized in Scheme 3. The *p*-methoxy benzyl groups of **13**−**15** were removed by 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) to produce the corresponding alcohol. Subsequent diastereoselective epoxidation of the double bond with catalytic vanadyl acetylacetonate ($VO(acac)_2$) (10 mol %) and *t*-BuOOH afforded the corresponding epoxide **21**−**23** as a single diastereomer in 82%, 95%, and 82% yield over two steps, respectively. The relative configuration of **22** was determined by X-ray crystal structure analysis (See SI CIF file). Next, the secondary hydroxyl groups of **21**−**23** were protected as TBS-

https://dx.doi.org/10.1021/acsmedchemlett.0c00153
ACS Med. Chem. Lett. 2020, 11, 1310−1315

Scheme 2. (a) Synthesis of Intermediate 13 and (b) Synthesis of Intermediates 14 and 15



Scheme 3. Intermediates 6–8



ether with *O*-(*t*-butyldimethylsilyl)benzanilide (TBS-BEZA) and TfO$^-$PyH$^+$. The pivalic ester was removed by DIBAL in THF at −30 °C to give the alcohols **24**–**26** in 59%, 66%, and 64% yield over two steps, respectively. Finally, the alcohols **24**–**26** were treated with 2-mercaptobenzothiazole (BtSH), PPh_3, and diisopropyl azodicarboxylate (DIAD) to afford the benzothiazolyl sulfide, which was oxidized with *m*-chloroperoxybenzoic acid (*m*-CPBA) to generate the sulfones **6**–**8** in 73%, 78%, and 69% yield over two steps, respectively.

The sulfone **6** and aldehyde **12** were treated with LiN(SiMe$_3$)$_2$ (LHMDS) at −78 °C in THF (Julia–Kocienski olefination) to give the diene compound, which was treated with HCl/MeOH (0.05%) to give alcohol **27** in 63% yield over two steps (Scheme 4a).[44] Next, to synthesize the coupling compounds **28** and **29**, we initially tried the Julia–Kocienski olefination with sulfones **7**, **8** and aldehyde **12**, but the reaction was unsuccessful. The details of the reaction conditions are shown in Scheme S3. As shown in Scheme 4b, we tried another coupling combination. The oxidation of the primary alcohols **24** and **25** with DMP afforded the corresponding aldehydes **9** and **10**, and treatment of the sulfone **11**[21] and aldehydes **9** and **10** with LHMDS produced the corresponding coupling product in acceptable yield, which was treated with HCl/MeOH (0.05–0.1%) to give alcohols **28** and **29** in 39% and 59% yields over three steps, respectively.[45] Acetylation of the alcohols **27**–**29** with Ac_2O, triethyl amine (TEA), and *N*,*N*-dimethyl-4-amino pyridine (DMAP) gave the corresponding acetate, and after removal of the TBS group with TBAF it generated **3**–**5** in 72%, 82%, and 86% yields over two steps, respectively (Scheme 4c).

The biological activity study is presented in Table 1. Derivatives **3**–**5** suppressed AR-V7 splicing (IC_{50} = 3.3, 202, and 187 nM, respectively). The biological activity of **4** and **5** was almost identical to that of **2** (IC_{50} = 132 nM), but the activity of **3** was significantly improved over that of **2**. The result of **3** suggested that the phenyl group at the C1 position could produce a steric hindrance within the SF3b complex and removing the phenyl group considerably improved the biological activity. The results of **4** and **5** suggested that the introduced methyl group on the epoxide might block the hydrogen bonding network around the epoxide and weaken the interaction with the SF3b complex. Since there were various amino acid residues that could interact with the epoxide of **4** or **5**, the difference of stereochemistry (*R* and *S*) of the epoxy methyl did not affect the biological activity. With respect to the *in vivo* toxicity test, wild type mice administered **1** (280 nM/body, n = 6) showed severe toxicity (mice died within 24 h).

However, none of the mice treated with **3** (280 nM/body, n = 7) died, and they did not show any significant weight loss compared to mice that were treated with DMSO alone (n = 8) (Figure 3).[46–49]

In conclusion, we designed, synthesized, and biologically evaluated the derivatives of spliceostatin A, 1,2-deoxy-pyranose derivative **3**, and terminal epoxide methyl substituted derivatives (**4**, **5**). The 1,2-deoxy-pyranose fragment and its terminal epoxide methyl substituted fragment were synthesized from commercially available D-glucal, and the synthetic steps for **24** were rather short.[21] We also investigated Julia–Kocienski olefination for appropriate combinations. Furthermore, the IC_{50} values on suppression of AR-V7 for compounds **3**–**5** were weaker than that of **1**; however, compound **3** exhibited potency (IC_{50}) in the low nanomolar range. The *in*

https://dx.doi.org/10.1021/acsmedchemlett.0c00153
ACS Med. Chem. Lett. 2020, 11, 1310–1315

Scheme 4. (a) Synthesis for 27, (b) Synthesis for 28 and 29, and (c) 1,2-Deoxy-pyranose Derivative 3 and Its Epoxide Substituent Derivative 4 and 5.

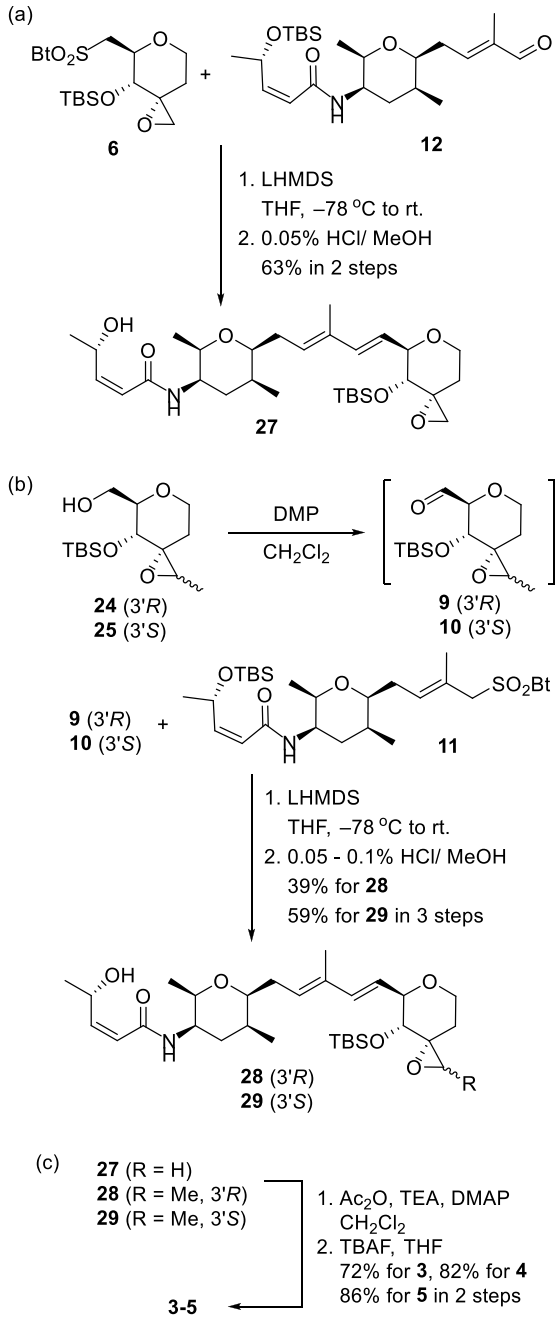


Table 1. AR-V7 Expression Inhibitory Activity Evaluation for 1 and 3–5

	IC_{50} (nM)			
	3	4	5	spliceostatin A (1)
AR-V7-GFP negative population	3.3	202	187	0.6

vivo toxicity test showed that wild type mice treated with **1** died within 24 h, but those mice treated with **3** did not die for 14 days and did not show weight loss. Therefore, we successfully created **3** with high AR-V7 expression inhibitory activity and low *in vivo* toxicity.

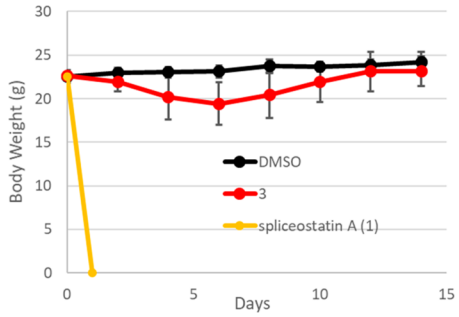


Figure 3. *In vivo* toxicity evaluation of DMSO, **3** and spliceostatin A (**1**) for wild type mice (injected on day 0, 2, 4, 280 nmol/body, n = 6–8). Spliceostatin A killed all the treated mice (n = 6).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsmedchemlett.0c00153.

Experimental procedures, characterization data, and NMR spectra (PDF)

Crystallographic data of compound **22** (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

Mitsuhiro Arisawa – *Graduate School of Pharmaceutical Sciences, Osaka University, Suita, Osaka 565-0871, Japan*; orcid.org/0000-0002-7937-670X; Email: arisaw@phs.osaka-u.ac.jp

Keisuke Nimura – *Graduate School of Medicine, Osaka University, Suita, Osaka 565-0871, Japan*; Email: nimura@gts.med.osaka-u.ac.jp

Authors

Yusuke Yoshikawa – *Graduate School of Pharmaceutical Sciences, Osaka University, Suita, Osaka 565-0871, Japan*

Airi Ishibashi – *Graduate School of Medicine, Osaka University, Suita, Osaka 565-0871, Japan*

Tsunayoshi Takehara – *Comprehensive Analysis Center, The Institute of Scientific and Industrial Research, Osaka University, Ibaraki, Osaka 567-0047, Japan*; orcid.org/0000-0002-4113-7578

Takeyuki Suzuki – *Comprehensive Analysis Center, The Institute of Scientific and Industrial Research, Osaka University, Ibaraki, Osaka 567-0047, Japan*

Kenichi Murai – *Graduate School of Pharmaceutical Sciences, Osaka University, Suita, Osaka 565-0871, Japan*; orcid.org/0000-0002-1689-6492

Yasufumi Kaneda – *Graduate School of Medicine, Osaka University, Suita, Osaka 565-0871, Japan*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsmedchemlett.0c00153

Author Contributions

‖Y.Y. and A.I. contributed equally to this work.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was partially supported by a Grant-in-Aid from the JSPS KAKENHI for Precisely Designed Catalysts with Customized Scaffolding (Grant No. JP A16H010260 and

18H04260, and A262880510, T15K149760, and T15KT00630), by the Platform Project for Supporting Drug Discovery and Life Science Research (Basis for Supporting Innovative Drug Discovery and Life Science Research (BINDS)) from the AMED under Grant Number JP19am0101084, by the Shorai Foundation for Science and Technology.

■ ABBREVIATIONS

ADT, androgen deprivation therapy; CRPC, castration-resistant prostate cancer; AR, androgen receptor; AR-V7, AR splicing variant 7; DMP, Dess−Martin periodinane; DIBAL, *i*-Bu_2AlH; PivCl, *t*-BuCOCl; TBS, Si-*t*-$BuMe_2$; TBAF, Bu_4NF; $VO(acac)_2$, vanadyl acetylacetonate; TBS-BEZA, *O*-(*t*-butyldimethylsilyl)benzanilide; BtSH, 2-mercaptobenzothiazole; DIAD, diisopropyl azodicarboxylate; *m*-CPBA, *m*-chloroperoxybenzoic acid; LHMDS, $LiN(SiMe_3)_2$; TEA, triethyl amine; DMAP, *N*,*N*-dimethyl-4-amino pyridine

■ REFERENCES

(1) Beer, T. M.; Armstrong, A. J.; Rathkopf, D. E.; Loriot, Y.; Sternberg, C. N.; Higano, C. S.; Iversen, P.; Bhattacharya, S.; Carles, J.; Chowdhury, S.; Davis, I. D.; de Bono, J. S.; Evans, C. P.; Fizazi, K.; Joshua, A. M.; Kim, C. S.; Kimura, G.; Mainwaring, P.; Mansbach, H.; Miller, K.; Noonberg, S. B.; Perabo, F.; Phung, D.; Saad, F.; Scher, H. I.; Taplin, M. E.; Venner, P. M.; Tombal, B. Enzalutamide in metastatic prostate cancer before chemotherapy. *N. Engl. J. Med.* **2014**, *371*, 424−433.

(2) Ryan, C. J.; Smith, M. R.; de Bono, J. S.; Molina, A.; Logothetis, C. J.; de Souza, P.; Fizazi, K.; Mainwaring, P.; Piulats, J. M.; Ng, S.; Carles, J.; Mulders, P. F.; Basch, E.; Small, E. J.; Saad, F.; Schrijvers, D.; Van Poppel, H.; Mukherjee, S. D.; Suttmann, H.; Gerritsen, W. R.; Flaig, T. W.; George, D. J.; Yu, E. Y.; Efstathiou, E.; Pantuck, A.; Winquist, E.; Higano, C. S.; Taplin, M. E.; Park, Y.; Kheoh, T.; Griffin, T.; Scher, H. I.; Rathkopf, D. E. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N. Engl. J. Med.* **2013**, *368*, 138−148.

(3) Scher, H. I.; Fizazi, K.; Saad, F.; Taplin, M. E.; Sternberg, C. N.; Miller, K.; de Wit, R.; Mulders, P.; Chi, K. N.; Shore, N. D.; Armstrong, A. J.; Flaig, T. W.; Flechon, A.; Mainwaring, P.; Fleming, M.; Hainsworth, J. D.; Hirmand, M.; Selby, B.; Seely, L.; de Bono, J. S. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N. Engl. J. Med.* **2012**, *367*, 1187−1197.

(4) Antonarakis, E. S.; Armstrong, A. J.; Dehm, S. M.; Luo, J. Androgen receptor variant-driven prostate cancer. *Prostate Cancer Prostatic Dis.* **2016**, *19*, 231−241.

(5) Changxue, L.; Jun, L. Decoding the androgen receptor splice variants. *Androl. Urol.* **2013**, *2*, 178−186.

(6) Wang, B.; Lo, U. G.; Wu, K.; Kapur, P.; Liu, X.; Huang, J.; Chen, W.; Hernandez, E.; Santoyo, J.; Ma, S. H.; Pong, R. C.; He, D.; Cheng, Y. Q.; Hsieh, J. T. Developing new targeting strategy for androgen receptor variants in castration resistant prostate cancer. *Int. J. Cancer* **2017**, *141*, 2121−2130.

(7) Kawamura, N.; Nimura, K.; Saga, K.; Ishibashi, A.; Kitamura, K.; Nagano, H.; Yoshikawa, Y.; Ishida, K.; Nonomura, N.; Arisawa, M.; Luo, J.; Kaneda, Y. SF3B2-mediated RNA splicing drives human prostate cancer progression. *Cancer Res.* **2019**, *79*, 5204−5217.

(8) Yoshikawa, Y.; Ishibashi, A.; Murai, K.; Kaneda, Y.; Nimura, K.; Arisawa, M. Design and synthesis of a phenyl C-glycoside derivative of spliceostatin A and its biological evaluation toward prostate cancer treatment. *Tetrahedron Lett.* **2019**, *60*, 151313.

(9) Wang, J.; Zou, J. X.; Xue, X.; Cai, D.; Zhang, Y.; Duan, Z.; Xiang, Q.; Yang, J. C.; Louie, M. C.; Borowsky, A. D.; Gao, A. C.; Evans, C. P.; Lam, K. S.; Xu, J.; Kung, H. J.; Evans, R. M.; Xu, Y.; Chen, H. W. ROR-γ drives androgen receptor expression and represents a therapeutic target in castration-resistant prostate cancer. *Nat. Med.* **2016**, *22*, 488−496.

(10) Zhang, Y.; Wu, X.; Xue, X.; Li, C.; Wang, J.; Wang, R.; Zhang, C.; Wang, C.; Shi, Y.; Zou, L.; Li, Q.; Huang, Z.; Hao, X.; Loomes, K.; Wu, D.; Chen, H.-W.; Xu, J.; Xu, Y. Potent and orally bioavailable inverse agonists of RORγt resulting from structure-based design. *J. Med. Chem.* **2019**, *62*, 4716−4730.

(11) Nakajima, H.; Sato, B.; Fujita, T.; Takase, S.; Terano, H.; Okuhara, M. New antitumor substances, FR901463, FR901464 and FR901465. I. Taxonomy, fermentation, isolation, physico-chemical properties and biological activities. *J. Antibiot.* **1996**, *49*, 1196−1203.

(12) Kaida, D.; Motoyoshi, H.; Tashiro, E.; Nojima, T.; Hagiwara, M.; Ishigami, K.; Watanabe, H.; Kitahara, T.; Yoshida, T.; Nakajima, H.; Tani, T.; Horinouchi, S.; Yoshida, M. Spliceostatin A targets SF3b and inhibits both splicing and nuclear retention of pre-mRNA. *Nat. Chem. Biol.* **2007**, *3*, 576−583.

(13) Sakai, T.; Sameshima, T.; Matsufuji, M.; Kawamura, N.; Dobashi, K.; Mizui, Y. Pladienolides, new substances from culture of streptomyces platensis Mer-11107. *J. Antibiot.* **2004**, *57*, 173−179.

(14) Sakai, T.; Asai, N.; Okuda, A.; Kawamura, N.; Mizui, Y. Pladienolides, new substances from culture of streptomyces platensis Mer-11107. *J. Antibiot.* **2004**, *57*, 180−187.

(15) Mizui, Y.; Sakai, T.; Iwata, M.; Uenaka, T.; Okamoto, K.; Shimizu, H.; Yamori, T.; Yoshimatsu, K.; Asada, M. Pladienolides, new substances from culture of streptomyces platensis Mer-11107. *J. Antibiot.* **2004**, *57*, 188−196.

(16) Kotake, Y.; Sagane, K.; Owa, T.; Mimori-Kiyosue, Y.; Shimizu, H.; Uesugi, M.; Ishihama, Y.; Iwata, M.; Mizui, Y. Splicing factor SF3b as a target of the antitumor natural product pladienolide. *Nat. Chem. Biol.* **2007**, *3*, 570−575.

(17) Sakai, Y.; Yoshida, T.; Ochiai, K.; Uosaki, Y.; Saitoh, Y.; Tanaka, F.; Akiyama, T.; Akinaga, S.; Mizukami, T. Identification of SAP155 as the Target of GEX1A (Herboxidiene), an Antitumor Natural Product. *J. Antibiot.* **2002**, *55*, 855−862.

(18) Hasegawa, M.; Miura, T.; Kuzuya, K.; Inoue, A.; Ki, S. W.; Horinouchi, S.; Yoshida, T.; Kunoh, T.; Koseki, K.; Mino, K.; Sasaki, R.; Yoshida, M.; Mizukami, T. GEX1 compounds, novel antitumor antibiotics related to herboxidiene, produced by Streptomyces sp. I. Taxonomy, production, isolation, physicochemical properties and biological activities. *ACS Chem. Biol.* **2011**, *6*, 229−233.

(19) Spliceostatin A, pladienolide B, and GEX1A have a common pharmacore (epoxide, acetyl, and diene groups, respectively), and some analogue synthesis of **1** using its pharmacore has been reported. Bonnal, S.; Vigevani, L.; Valcárcel, J. The Spliceosome as a Target of Novel Antitumour Drugs. *Nat. Rev. Drug Discovery* **2012**, *11*, 847−859.

(20) Thompson, C. F.; Jamison, T. F.; Jacobsen, E. N. FR901464: Total Synthesis, Proof of Structure, and Evaluation of Synthetic Analogues. *J. Am. Chem. Soc.* **2001**, *123*, 9974−9983.

(21) Motoyoshi, H.; Horigome, M.; Watanabe, H.; Kitahara, T. Total synthesis of FR901464: second generation. *Tetrahedron* **2006**, *62*, 1378−1389.

(22) Ghosh, A. K.; Chen, Z.-H. Enantioselective syntheses of FR901464 and spliceostatin A: potent inhibitors of spliceosome. *Org. Lett.* **2013**, *15*, 5088−5091.

(23) Ghosh, A. K.; Chen, Z.-H.; Effenberger, K. A.; Jurica, M. S. Enantioselective total syntheses of FR901464 and spliceostatin A and evaluation of splicing activity of key derivatives. *J. Org. Chem.* **2014**, *79*, 5697−5709.

(24) Osman, S.; Albert, B. J.; Wang, Y.; Li, M.; Czaicki, N. L.; Koide, K. Structural requirements for the antiproliferative activity of pre-mRNA splicing inhibitor FR901464. *Chem. - Eur. J.* **2011**, *17*, 895−904.

(25) Nicolaou, K. C.; Rhoades, D.; Kumar, S. M. Total syntheses of thailanstatins A−C, spliceostatin D, and analogues thereof. Stereodivergent synthesis of tetrasubstituted dihydro- and tetrahydropyrans and design, synthesis, biological evaluation, and discovery of potent antitumor agents. *J. Am. Chem. Soc.* **2018**, *140*, 8303−8320.

(26) Ghosh, A. K.; Reddy, G. C.; Kovela, S.; Relitti, N.; Urabe, V. K.; Prichard, B. E.; Jurica, M. S. Enantioselective synthesis of a

https://dx.doi.org/10.1021/acsmedchemlett.0c00153
ACS Med. Chem. Lett. 2020, 11, 1310−1315

cyclopropane derivative of spliceostatin A and evaluation of bioactivity. *Org. Lett.* **2018**, *20*, 7293−7297.
(27) Kanada, R. M.; Itoh, D.; Nagai, M.; Niijima, J.; Asai, N.; Mizui, Y.; Abe, S.; Kotake, Y. Total Synthesis of the Potent Antitumor Macrolides Pladienolide B and D. *Angew. Chem., Int. Ed.* **2007**, *46*, 4350−4355.
(28) Ghosh, A. K.; Anderson, D. D. Enantioselective Total Synthesis of Pladienolide B: A Potent Spliceosome Inhibitor. *Org. Lett.* **2012**, *14*, 4730−4733.
(29) Mandel, A. L.; Jones, B. D.; La Clair, J. J.; Burkart, M. D. A synthetic entry to pladienolide B and FD-895. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5159−5164.
(30) Müller, S.; Mayer, T.; Sasse, F.; Maier, M. E. Synthesis of a Pladienolide B Analogue with the Fully Functionalized Core Structure. *Org. Lett.* **2011**, *13*, 3940−3943.
(31) Gundluru, M. K.; Pourpak, A.; Cui, X.; Morris, S. W.; Webb, T. R. Design, Synthesis and Initial Biological Evaluation of a Novel Pladienolide Analog Scaffold. *MedChemComm* **2011**, *2*, 904−908.
(32) Kumar, V. P.; Chandrasekhar, S. Enantioselective Synthesis of Pladienolide B and Truncated Analogues as New Anticancer Agents. *Org. Lett.* **2013**, *15*, 3610−3613.
(33) Blakemore, P. R.; Kocienski, P. J.; Morley, A.; Muir, K. A synthesis of herboxidiene. *J. Chem. Soc., Perkin Trans. 1* **1999**, 955−968.
(34) Murray, T. J.; Forsyth, C. J. Total Synthesis of GEX1A. *Org. Lett.* **2008**, *10*, 3429−3431.
(35) Ghosh, A. K.; Li, J. A Stereoselective Synthesis of (+)-Herboxidiene/GEX1A. *Org. Lett.* **2011**, *13*, 66−69.
(36) Thirupathi, B.; Mohapatra, D. K. Gold-Catalyzed Hosomi-Sakurai Type Reaction for the Total Synthesis of Herboxidiene. *Org. Biomol. Chem.* **2016**, *14*, 6212−6224.
(37) Edmunds, A. J. F.; Arnold, G.; Hagmann, L.; Schaffner, R.; Furlenmeier, H. Synthesis of SimpliÆed Herboxidiene Aromatic Hybrids. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1365−1368.
(38) Eskens, F. A. L. M.; Ramos, F. J.; Burger, H.; O'Brien, J. P.; Piera, A.; de Jonge, M. J. A.; Mizui, Y.; Wiemer, E. A. C.; Carreras, M. J.; Baselga, J.; Tabernero, J. Phase I pharmacokinetic and pharmacodynamic study of the first-in-class spliceosome inhibitor E7107 in patients with advanced solid tumors. *Clin. Cancer Res.* **2013**, *19*, 6296−6304.
(39) Hong, D. S.; Kurzrock, R.; Naing, A.; Wheler, J. J.; Falchook, G. S.; Schiffman, J. S.; Faulkner, N.; Pilat, M. J.; O'Brien, J.; LoRusso, P. A phase I, open-label, single-arm, dose-escalation study of E7107, a precursor messenger ribonucleic acid (pre-mRNA) splicesome inhibitor administered intravenously on days 1 and 8 every 21 days to patients with solid tumors. *Invest. New Drugs* **2014**, *32*, 436−444.
(40) Because AR-V7 expression inhibitory activity of GEX1A has not been reported, we did not focus on it.
(41) In this research, we did not know the target protein which related to AR-V7 expression inhibitory activity.
(42) By the introduction of an alkyl group on the epoxide, the chemical reactivity is reduced. Thus, the reactivity of **3** and **4** with biological substances related to the onset of toxicity (DNA, etc.) could decrease. Gonzalez-Perez, M.; Gomez-Bombarelli, R.; Arenas-Valganon, J.; Perez-Prior, M. T.; Garcia-Santos, M. P.; Calle, E.; Casado, J. Connecting the chemical and biological reactivity of epoxides. *Chem. Res. Toxicol.* **2012**, *25*, 2755−2762.
(43) Catino, A. J.; Sherlock, A.; Shieh, P.; Wzorek, J. S.; Evans, D. A. Approach to the tricyclic core of the tigliane−daphnane diterpenes. Concerning the utility of transannular aldol additions. *Org. Lett.* **2013**, *15*, 3330−3333.
(44) Methods for selective removal of the TBS group on allyl alcohol have been reported (ref 21).
(45) Differences of chemical yields (39% for **28** and 59% for **29**) stem from Julia−Kocienski olefination.
(46) One reason for the toxicity of **1** could be due to an unsaturated ketone or a furan ring formed by cleavage of a ketal at the C1 position of **1**.
(47) Albert, B. J.; Sivaramakrishnan, A.; Naka, T.; Czaicki, N. L.; Koide, K. Total Syntheses, Fragmentation Studies, and Antitumor/Antiproliferative Activities of FR901464 and Its Low Picomolar Analogue. *J. Am. Chem. Soc.* **2007**, *129*, 2648−2659.
(48) Koleva, Y. K.; Madden, J. C.; Cronin, M. T. D. Formation of Categories from Structure-Activity Relationships to Allow ReadAcross for Risk Assessment: Toxicity of α,β-Unsaturated Carbonyl Compounds. *Chem. Res. Toxicol.* **2008**, *21*, 2300−2312.
(49) As a result of dissection of the dead mouse, intestinal bleeding was observed in all mice.

https://dx.doi.org/10.1021/acsmedchemlett.0c00153
ACS Med. Chem. Lett. 2020, 11, 1310−1315