Serendipitous One-Step Synthesis of Cyclopentene Derivatives from 5′-Deoxy-5′-Heteroarylsulfonylnucleosides as Nucleoside-Derived Julia–Kocienski Reagents

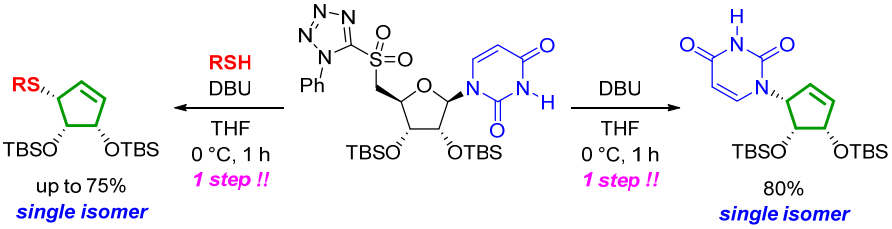
Natsuhisa Oka,[1,2,3,*] Mayuka Kanda,[1] Minami Furuzawa,[1] Wakaba Arai,[1] and Kaori Ando[1,*]

[1] *Department of Chemistry and Biomolecular Science, Faculty of Engineering, Gifu University*

[2] *Center for Highly Advanced Integration of Nano and Life Sciences, Gifu University (G-CHAIN)*

[3] *Institute for Glyco-core Research (iGCORE), Gifu University, 1-1 Yanagido, Gifu 501-1193, Japan*

oka@gifu-u.ac.jp, ando@gifu-u.ac.jp



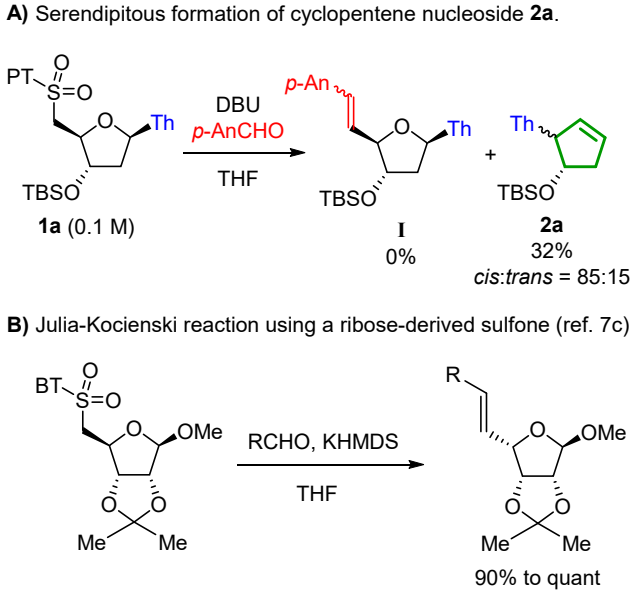
ABSTRACT: A serendipitous one-step transformation of 5′-deoxy-5′-heteroarylsulfonylnucleosides into cyclopentene derivatives is reported. This unique transformation likely proceeds via a domino reaction initiated by α-deprotonation of the heteroaryl sulfone and subsequent elimination reaction to generate a nucleobase and an α,β-unsaturated sulfone that contains a formyl group. The Michael addition of the nucleobase to the α,β-unsaturated sulfone and subsequent intramolecular Julia–Kocienski reaction eventually generate the cyclopentene ring. Heteroarylthio and acylthio groups can be incorporated into the cyclopentene core in place of the nucleobase by conducting this reaction in the presence of a heteroarylthiol and a thiocarboxylic acid, respectively. *Cis*,*cis*-trisubstituted cyclopentene derivatives are obtained as a single stereoisomer from ribonucleoside-derived Julia–Kocienski sulfones.

INTRODUCTION

The Julia–Kocienski reaction is a powerful tool for the synthesis of alkenes,[1] and is widely used for the synthesis of complex natural products and bioactive compounds.[2] Because its application to the synthesis of nucleoside and nucleic acid derivatives has been rather limited,[3] we aimed to study the Julia–Kocienski reaction using 5′-deoxy-5′-heteroarylsulfonylnucleosides, which had not been reported in the literature, for the synthesis of 5′-alkylidene-5′-deoxynucleosides.[4] 5′-Deoxy-5′-heteroarylsulfonylthymidine derivative **1a** was synthesized from 3′-*O*-TBS-thymidine via 5′-*O*-mesylation, substitution with 5-mercapto-1-phenyl-1*H*-tetrazole, and oxidation.[5] The resulting sulfone (**1a**) was then allowed to react with *p*-anisaldehyde in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). However, it did not afford the expected 5′-alkylidene-5′-deoxythymidine derivative **I** but cyclopentene nucleoside derivative **2a** in 32% yield with a *cis*:*trans* ratio of 85:15 (Scheme 1A).[6] Practically the same result was obtained in the absence of *p*-anisaldehyde (35% yield, *cis*:*trans* = 84:16). These results stand in stark contrast with the olefination reactions using sugar-derived sulfones reported in the literature.[7] For example, the Julia–Kocienski reaction using a ribose-derived sulfone and aldehydes gives the corresponding 5-alkylidene-5-

deoxyribofuranosides, albeit with concomitant epimerization at the C4-position (Scheme 1B).[7c]

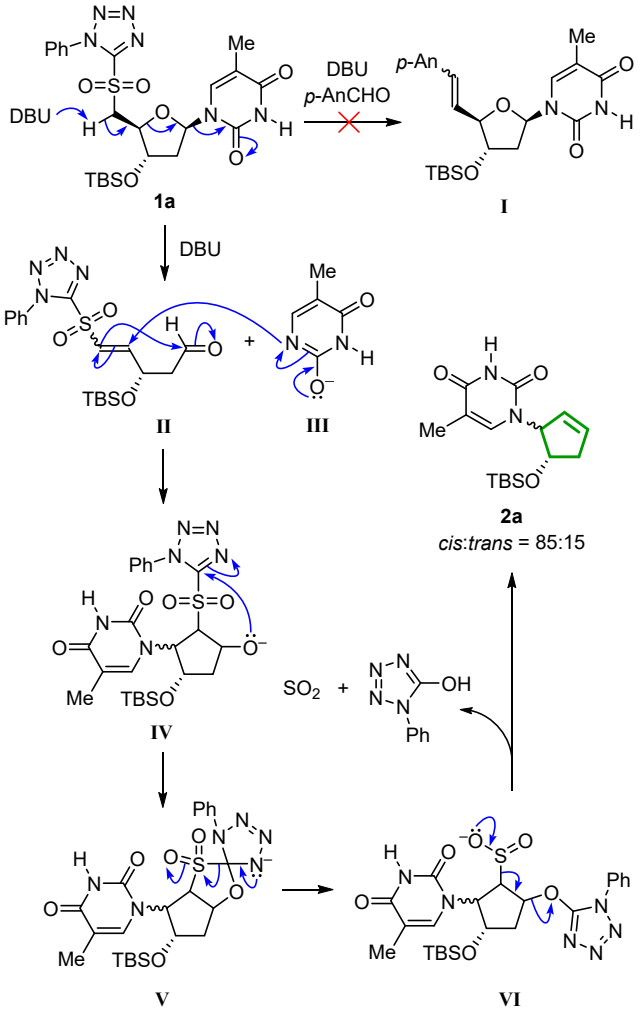
Scheme 1. (A) Serendipitous Transformation of Thymidine-Derived Julia–Kocienski Sulfone 1a into Cyclopentene Nucleoside Derivative 2a,[a,b] and (B) Julia–Kocienski Reaction Using a Ribose-Derived Sulfone.[c]



[a] Th: thymin-1-yl; PT: 1-phenyl-1*H*-tetrazol-5-yl. [b] Reaction conditions: DBU (2.8 equiv), *p*-AnCHO (1.5 equiv), 0 °C, 1.5 h. [c] BT: 2-benzothiazolyl.

A plausible reaction mechanism for this unprecedented transformation is proposed in Scheme 2. α-Deprotonation of heteroaryl sulfone **1a** with DBU triggers an elimination reaction, generating an α,β-unsaturated sulfone that contains a formyl group (**II**)[8] and a thymine anion (**III**). The Michael addition of **III** to **II** generates a carbanion at the α-position of the sulfone, which then intramolecularly attacks the formyl group. This is followed by an intramolecular Julia–Kocienski olefination via **IV**, **V**, and **VI** to afford cyclopentene nucleoside **2a**. The Michael addition of **III** preferentially occurs from the opposite side of the bulky 3′-TBS group of **II**. The thymine residue and the TBS group come to the same side of the cyclopentene ring when the intramolecular nucleophilic attack occurs to afford *cis*-**2a** as the major isomer. α,β-Unsaturated sulfones are commonly used Michael acceptors[9] and can react with both deprotonated nucleobases[3b,10] and alcohols.[10b,c,11] Therefore, the contrasting results in Schemes 1A and B can be attributed to the difference in the leaving groups at the anomeric positions. The thyminyl group of **1a** is a better leaving group compared to the methoxy group and thus is cleaved by the DBU-mediated elimination and acts as a Michael donor.

Scheme 2. Plausible Reaction Mechanism.

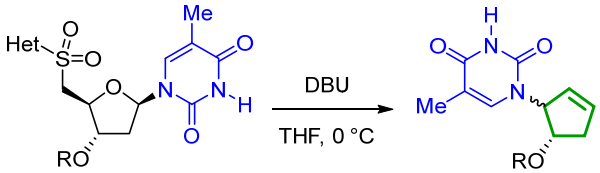


Domino reactions, which are sets of sequential reactions in which each reaction generates new functional group(s) for the next without changes in the reaction conditions or the addition of reagents or catalysts, simplify the synthesis of complex molecules.[12] They have also attracted great attention from a green chemistry viewpoint, as work-up and purification procedures for the intermediates can be avoided and the time, energy, and materials required for the overall process are reduced.[13] There have been many reports of domino reactions consisting of the ring-opening of sugars and subsequent carbocyclization.[14–21] However, to the best of our knowledge, there are no reports on domino reactions that consist of the tetrahydrofuran ring-opening of a nucleoside and carbocyclization to produce a carbocyclic nucleoside. We envisioned that such a domino reaction could be a novel efficient route to carbocyclic nucleosides. Carbocyclic nucleosides have been widely studied for therapeutic applications, and some are used clinically as anti-HIV and anti-HBV drugs.[22] Great attention has also been paid to the antiviral activity of these compounds against SARS-CoV-2 due to the current COVID-19 pandemic.[23] The chemical synthesis of carbocyclic nucleosides is generally accomplished by coupling the corresponding nucleobases with chiral carbocyclic units, but the synthesis of the latter is often laborious.[24]

RESULTS AND DISCUSSION

Thymidine-derived heteroaryl sulfones with different heteroaryl groups and 3′-protecting groups (**1a**–**d**, Table 1) were synthesized and applied to the DBU-promoted domino reaction. As mentioned above, 1-phenyl-1*H*-tetrazol-5-yl (PT)[1] sulfone **1a** afforded cyclopentene nucleoside **2a** in 35% yield with a *cis*:*trans* ratio of 84:16 (entry 1). 1-Methyl-1*H*-tetrazol-5-yl (MT)[25] sulfone **1a′** and 2-benzothiazolyl (BT)[26] sulfone **1a″** also afforded cyclopentene nucleoside **2a** (entries 2, 3). Among these, PT sulfone **1a** was the best in terms of the reaction rate and diastereoselectivity; accordingly, **1a** was subsequently used for further investigations. The yield of **2a** was improved from 35% to 55% by increasing the concentration of **1a** from 0.1 M to 0.6 M (entry 4). Lowering the reaction temperature from 0 °C to −20 °C slowed the reaction without improving the diastereoselectivity (entry 5); the yield of **2a** was not improved by changing the number of molar equivalents of DBU (entries 6, 7). 3′-*tert*-Butyldiphenylsilyl-protected sulfone **1b** afforded **2b** with a *cis*:*trans* ratio similar to that of **1a** (entry 8). Triisopropylsilyl- and benzoyl-protected sulfones **1c** and **1d** gave lower *cis*:*trans* ratios (entries 9, 10). As a result, the conditions in entry 4 were chosen as optimal and used for further investigations.

Table 1. **Synthesis of Cyclopentene Nucleosides 2 Using Thymidine-Derived Sulfones 1.**



1a : Het = PT, R = TBS
1a' : MT, TBS
1a": BT, TBS
1b : PT, TBDPS
1c : PT, TIPS
1d : PT, Bz

2a: R = TBS
2b: TBDPS
2c: TIPS
2d: Bz

entry	sulfone (conc.)	DBU (equiv)	time (h)	yield (%)	*cis*:*trans*[a]
1	**1a** (0.1 M)	2.8	1	35	84:16
2	**1a′** (0.1 M)	2.8	21	37	61:39
3	**1a″** (0.1 M)	2.8	5	30	82:18
4	**1a** (0.6 M)	2.8	1	55	84:16
5[b]	**1a** (0.6 M)	2.8	3	43	84:16
6	**1a** (0.6 M)	1.4	1	34	84:16
7	**1a** (0.6 M)	5	1	39	82:18
8	**1b** (0.6 M)	2.8	1	49	83:17
9	**1c** (0.6 M)	2.8	1	51	76:24
10	**1d** (0.6 M)	2.8	1	19	59:41

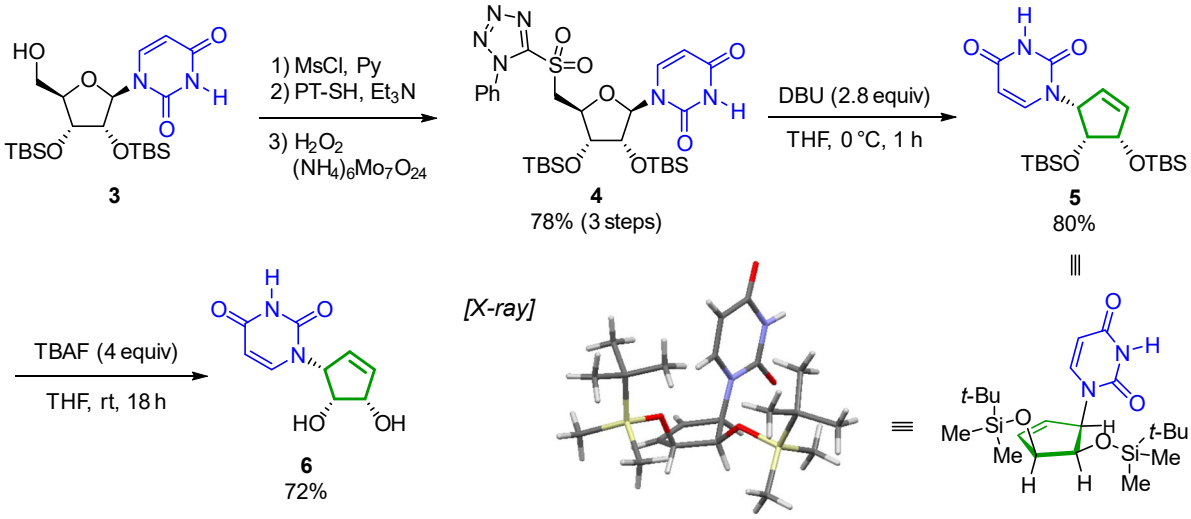
[a] Determined by ^{1}H NMR spectroscopy.

[b] −20 °C.

Next, we synthesized PT sulfone **4** from 2′,3′-bis-*O*-TBS-uridine **3** and subjected it to the domino

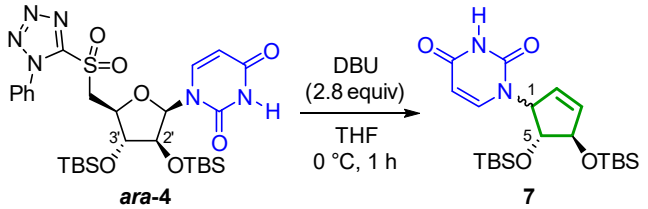
reaction (Scheme 3). To our delight, the corresponding cyclopentene nucleoside (**5**) was produced in 80% yield with complete *cis*-selectivity. The structure of *cis*,*cis*-**5** was confirmed by a single-crystal X-ray diffraction analysis. The TBS groups were removed using TBAF to afford the fully deprotected cyclopentene nucleoside derivative **6** in 72% yield.

Scheme 3. Synthesis of Uridine-Derived Cyclopentene Nucleoside 6.



To study the effect of the sugar configuration, an *arabino*-configured PT sulfone (***ara*-4**) was synthesized from commercially available arabinofuranosyluracil in a similar manner.[5] The reaction of ***ara*-4** with DBU also afforded the corresponding cyclopentene nucleoside **7** (Scheme 4). The 1,5-*cis* to 1,5-*trans* ratio was 84:16, which is identical to that obtained with *2′-deoxyribose*-derived PT sulfone **1a** (Table 1, entry 4). The results shown in Scheme 4 and Table 1 indicate that the bulky TBS group at the 3′-position induces a *cis*-selectivity of up to >80%, which is further enhanced by the presence of another 2′-TBS group on the same side of the sugar ring in the case of *ribo*-configured PT sulfone **4**.

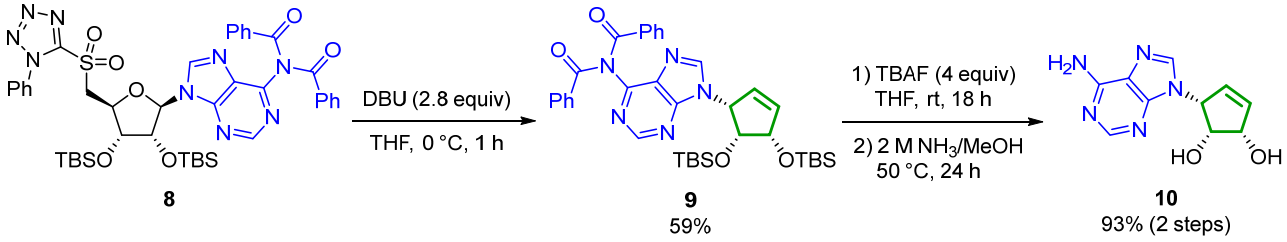
Scheme 4. Synthesis of Cyclopentene Nucleoside 7 from *ara*-4.



The reaction was also attempted with adenosine-derived PT sulfone **8** in order to investigate the applicability of this reaction to purine nucleosides (Scheme 5). Bulky dibenzoyl protection at the N6-position was employed to cover the N1- and N7-positions of adenine so that undesired addition of the liberated adenine would not occur at these positions. The desired cyclopentene adenosine derivative **9** was obtained in 59% yield as a single *cis*,*cis*-isomer. It was then fully deprotected by treatment with

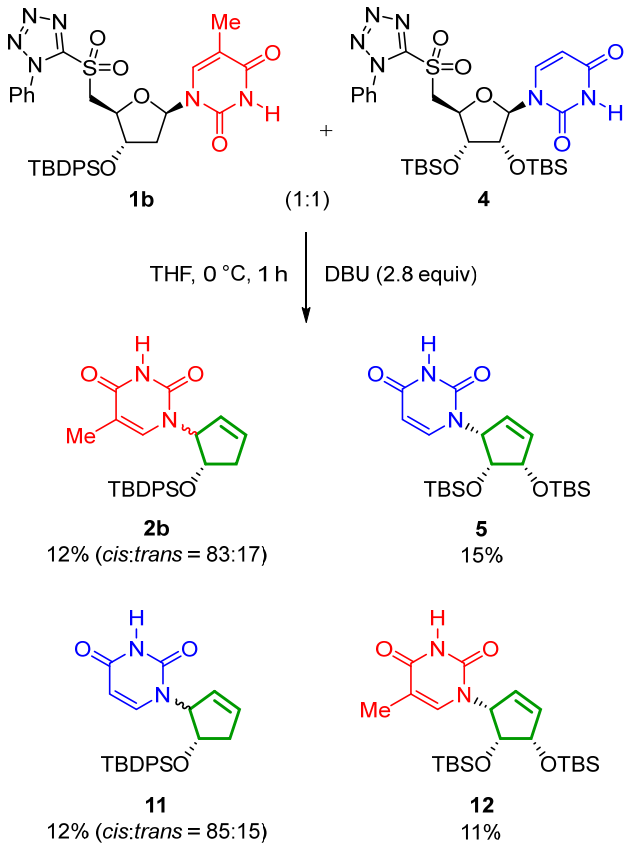
TBAF and methanolic ammonia to afford **10** in 93% yield. Thus, the nucleoside-derived Julia–Kocienski reagents **1**, **4**, ***ara*-4**, and **8** afforded cyclopentene nucleoside derivatives **2**, **5**, **7**, and **9** in one step. Such 'truncated' carbocyclic nucleosides lacking the 4′-hydroxymethyl group have been intensively studied as potential antiviral agents.[27] The resulting cyclopentene nucleosides should also be useful as intermediates for the synthesis of carbocyclic nucleosides. In particular, the *cis*,*cis*-trisubstituted cyclopentene nucleosides derived from ribonucleosides should be applicable to the synthesis of *lyxo*-configured bioactive carbocyclic nucleosides.[28]

Scheme 5. Synthesis of Adenosine-Derived Cyclopentene Nucleoside 10.



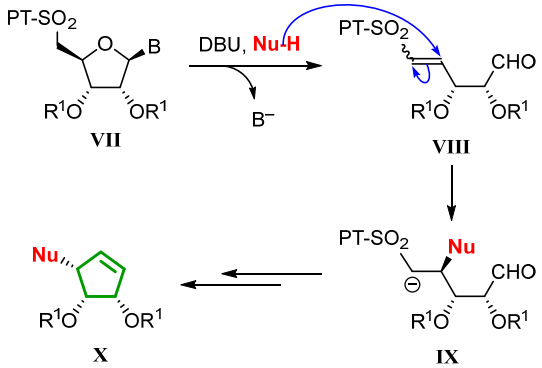
To obtain insight into the reaction mechanism, we conducted the domino reaction using a 1:1 mixture of thymidine-derived and uridine-derived PT sulfones **1b** and **4** (Scheme 6). In addition to cyclopentene nucleosides **2b** and **5**, nucleobase-exchange products **11** and **12** were isolated. This result clearly demonstrates that the nucleobases are cleaved from the sulfones and then reincorporated during the reaction.

Scheme 6. Nucleobase Exchange During the Domino Reaction.



The nucleobase exchange shown in Scheme 6 suggests that the nucleobase of the substrate can be replaced by another nucleophile during the domino reaction. As shown in Scheme 7, we hypothesized that if the external nucleophile attacks the α,β-unsaturated sulfone **VIII**, cyclopentene **X** would be obtained. If various nucleophiles are applicable, this domino reaction could be a useful route to a variety of optically active trisubstituted cyclopentenes.

Scheme 7. Working Hypothesis.[a]

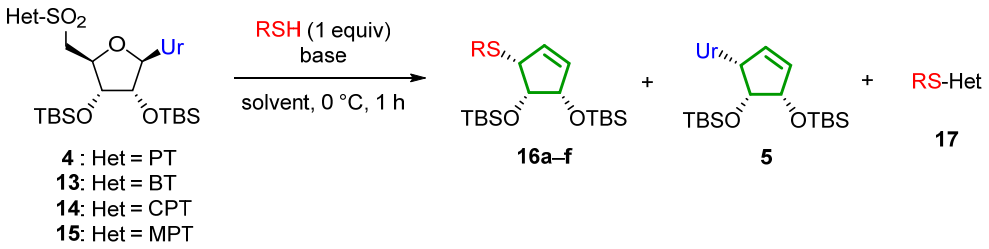


[a] B = nucleobase. Nu–H = nucleophile.

As the first step toward this goal, we studied the applicability of thiols and thiocarboxylic acids[29] (RSH **a**–**f**, Table 2). 2-Mercaptopyridine (**a**) was chosen as a model nucleophile to optimize the reaction conditions given that it has been reported to act as a good Michael donor toward α,β-

unsaturated sulfones.[11d] PT sulfone **4** was treated with 2.8 equiv of DBU under the same conditions as above in the presence of 1 equiv of 2-mercaptopyridine **a** (Table 2, entry 1). As expected, a 2-pyridylthio group was incorporated into the cyclopentene in the place of uracil, and trisubstituted cyclopentene **16a** was isolated in 40% yield. It was obtained as a single *cis*,*cis*-isomer, and its configuration was confirmed using NOESY experiments.[5] The modest yield of **16a** was partly ascribed to the generation of two kinds of byproducts, i.e., cyclopentene nucleoside **5** and **17a**[30] were isolated in 4% and 20%, respectively. **17a** was generated by the nucleophilic attack of thiol **a** at the *ipso*-carbon of the phenyltetrazolyl group. The formation of **5** was completely suppressed by reducing the quantity of DBU (entries 2–4). The yield of **16a** was also improved up to 59%, but the formation of **17a** was still observed at similar levels. Increasing the quantity of **a** from 1.0 to 1.5 equiv did not improve the **16a**/**17a** ratio (entry 5). BT, 1-(3,4-dichlorophenyl)-1*H*-tetrazol-5-yl (CPT),[25b] and 1-(2,6-dimethylphenyl)-1*H*-tetrazol-5-yl (MPT)[25b] sulfones **13**–**15** were also prepared from uridine via similar procedures[5] and applied to the reaction to investigate the effect of the heteroaryl group. However, the *ipso*-attack was not prevented, and the **16a**/**17a** ratios decreased (entries 6–8). Screening of the base (entries 9–13) and solvent (entries 14–19) resulted in comparable or lower yields of **16a** relative to that obtained using DBU and THF (entry 3). Only 1,5-diazabicyclo[4.3.0]-5-nonene (DBN) slightly improved the yield of **16a** (entry 9). The stronger base potassium bis(trimethylsilyl)amide (KHMDS) greatly increased the *ipso*-attack (entry 13). Finally, we studied the applicability of other thiols and thiocarboxylic acids (entries 20–24). 5-Nitro-2-mercaptopyridine (**b**) and 2-mercaptobenzothiazole (**c**) afforded the desired cyclopentenes **16b** and **16c**, albeit that the yields were lower than those obtained from **a** (entries 20, 21). *p*-Toluenethiol **d** afforded only the byproduct **17d** because of its high nucleophilicity. Gratifyingly, we found that the use of thioacetic acid (**e**) completely suppressed the generation of byproducts **5** and **17**, and the desired **16e** was obtained in 75% yield (entry 23). Thiobenzoic acid (**f**) also did not generate **17**, although the yield of **16f** was lower. This is attributed to the low nucleophilicity of **f**, which allows the competitive Michael addition of uracil (entry 24).

Table 2. Synthesis of Cyclopentenes 16a–f Using Uridine-Derived Sulfones 4, 13–15 and Thiols/Thiocarboxylic Acids a–f.[a]

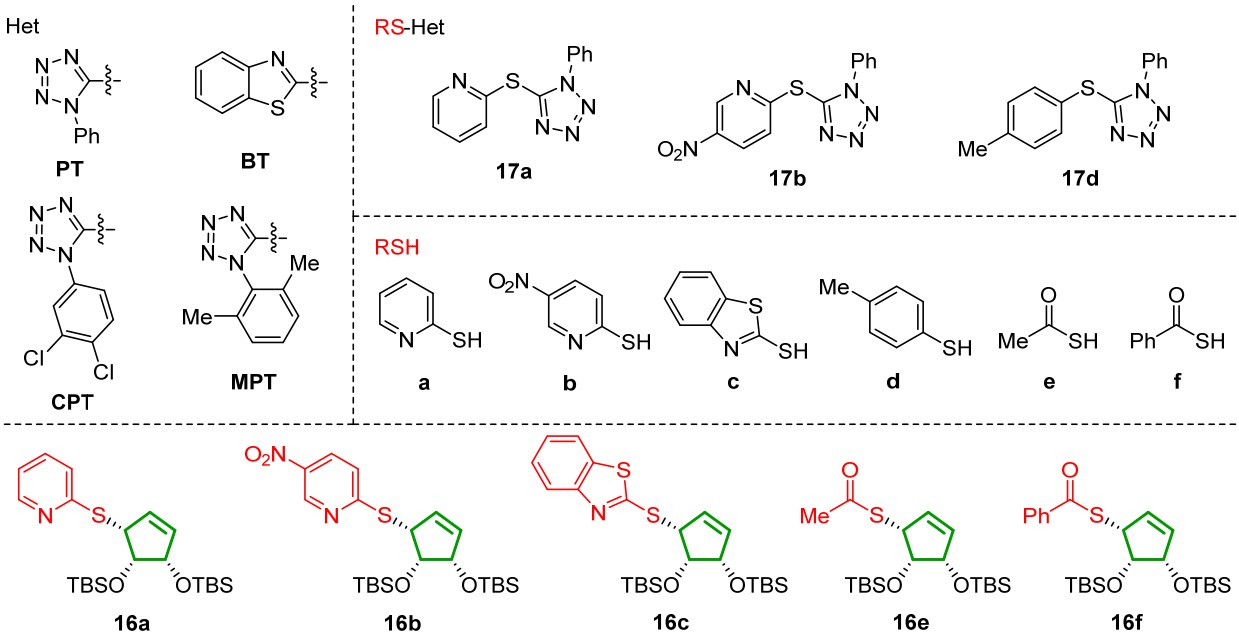


4 : Het = PT
13: Het = BT
14: Het = CPT
15: Het = MPT

16a–f **5**

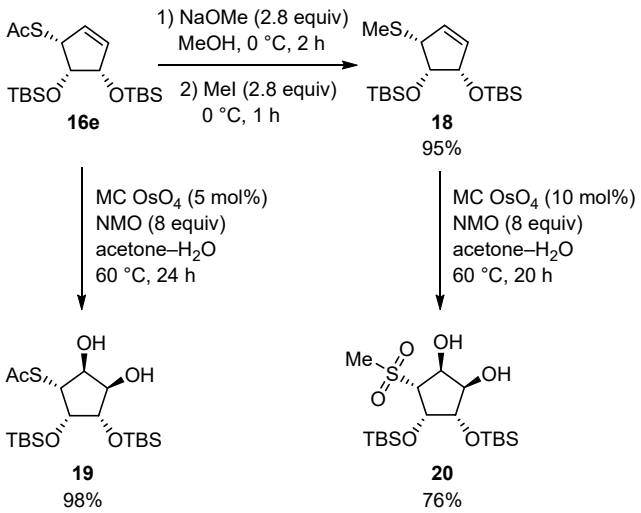
entry	Het	RSH	base (equiv)	solvent	**16** (%)	**5** (%)	**17** (%)
1	**PT**	**a**	DBU (2.8)	THF	40	4	20
2	**PT**	**a**	DBU (2.0)	THF	59	2	19
3	**PT**	**a**	DBU (1.5)	THF	59	3	24
4	**PT**	**a**	DBU (1.0)	THF	54	0	20
5	**PT**	**a**[b]	DBU (1.5)	THF	57	0	28
6	**BT**	**a**	DBU (1.5)	THF	16	0	20
7	**CPT**	**a**	DBU (1.5)	THF	46	0	32
8	**MPT**	**a**	DBU (1.5)	THF	41	13	35
9	**PT**	**a**	DBN (1.5)	THF	61	0	17
10	**PT**	**a**	MTBD (1.5)	THF	58	0	19
11	**PT**	**a**	TMG (1.5)	THF	57	2	18
12	**PT**	**a**	TBD (1.5)	THF	48	0	24
13	**PT**	**a**	KHMDS (1.5)	THF	9	0	69
14	**PT**	**a**	DBU (1.5)	CH_2Cl_2	52	0	25
15	**PT**	**a**	DBU (1.5)	1,4-dioxane	41	4	35
16	**PT**	**a**	DBU (1.5)	MeCN	58	0	20
17	**PT**	**a**	DBU (1.5)	DMF	59	0	16
18	**PT**	**a**	DBU (1.5)	NMP	42	0	16
19	**PT**	**a**	DBU (1.5)	DMSO	43	4	14
20	**PT**	**b**	DBU (1.5)	THF	53	6	10
21	**PT**	**c**	DBU (1.5)	THF	19	37	0
22	**PT**	**d**	DBU (1.5)	THF	0	0	78
23	**PT**	**e**	DBU (1.5)	THF	75	0	0
24	**PT**	**f**	DBU (1.5)	THF	45	14	0

[a] Ur = uracil-1-yl; MTBD = 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene; TMG = 1,1,3,3-tetramethylguanidine; TBD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene. [b] 1.5 equiv.



Thus, our study has demonstrated that the ribonucleoside-derived Julia–Kocienski sulfones afford thio-substituted cyclopentenes in one step. Methods for the synthesis of optically pure 1-thio-4,5-dioxycyclopentenes are very limited,[31] and, to the best of our knowledge, there is no reported method for the stereocontrolled synthesis of *cis*,*cis*-isomers such as **16**. Cyclopentenes **16** can be useful synthetic intermediates for the synthesis of polysubstituted cyclopentane derivatives via reactions at their C=C bond. For example, the dihydroxylation of **16e** catalyzed by microencapsulated OsO_4[32] afforded pentasubstituted cyclopentane **19** (Scheme 8). The dihydroxylation occurred exclusively from the opposite side of the three substituents and **19** was obtained as a single diastereomer. The acetylthio group of **16e** can be deprotected and *S*-alkylated to give **18**. The methylthio group was oxidized under the dihydroxylation conditions and sulfonyl-substituted cyclopentane **20** was obtained as a single isomer.

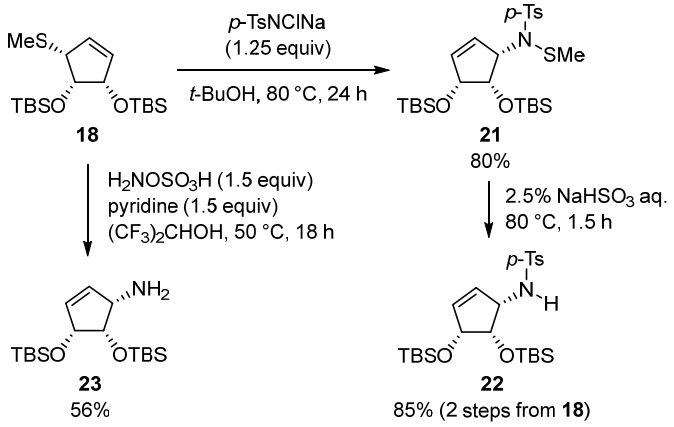
Scheme 8. Dihydroxylation of 16e and 18.



Methylthio-substituted cyclopentene **18** could also be used for the synthesis of animo-substituted cyclopentenes as shown in Scheme 9. The treatment of **18** with chloramine T afforded *N*-methylthio-*p*-toluenesulfonamide **21** in 80% yield via the [2,3] sigmatropic rearrangement of the intermediate *S*-allylsulfilimine.[33] *p*-Toluenesulfonamide **22** was isolated in 85% yield after aqueous workup with aqueous $NaHSO_3$. Cyclopentylamine **23** was directly obtained in 56% yield when **18** was treated with hydroxylamine *O*-sulfonic acid.[34]

Polyhydroxylated thiocyclopentanes are the core structures of some bioactive natural products, such as mannostatins[35] and tagetitoxin.[36] A wide range of natural products and bioactive synthetic compounds have polyhydroxylated aminocyclopentane cores.[37] The trisubstituted *cis*,*cis*-cyclopentenes shown in this study should be useful as synthetic intermediates of such complex natural products and bioactive compounds.

Scheme 9. Reaction of 18 with Chloramine T and Hydroxylamine-*O*-Sulfonic Acid.



In conclusion, we have serendipitously discovered that 5′-deoxy-5′-heteroarylsulfonylnucleosides afford cyclopentene nucleoside derivatives in one step by treatment with a base. This transformation most likely proceeds via a domino reaction initiated by a base-promoted elimination reaction of the heteroaryl sulfone, followed by the Michael addition of the resulting nucleobase and α,β-unsaturated sulfone, and an intramolecular Julia–Kocienski reaction. The proposed reaction mechanism is supported by the experimentally observed nucleobase exchange during the reaction. This novel domino reaction can be expected to be useful for the synthesis of bioactive carbocyclic nucleosides, especially those that contain truncated or *lyxo*-carbasugars. It has also been demonstrated that the nucleobases of the substrates can be replaced by more reactive Michael donors, such as heteroarylthiols and thiocarboxylic acids, to afford 1-thio-4,5-dioxycyclopentenes in one step with complete *cis*-selectivity. The acetylthio-substituted cyclopentene was stereospecifically transformed into amino-substituted cyclopentenes. α,β-Unsaturated sulfones are well-known Michael acceptors that react with many types of Michael donors in addition to thiols and thiocarbocylic acids. We envision that the scope of products can be expanded by further studying the applicability of other Michael donors to this reaction.

Acknowledgments

We thank Toshifumi Maruyama (Gifu University) for his assistance in X-ray crystallographic analysis. This work was partially supported by JSPS KAKENHI Grant Number JP21K05411 and iGCORE collaboration grant.

Supporting information

Experimental procedures, characterization data, and NMR spectra for new compounds. X-ray crystal data for **5**.

Accession Codes

CCDC 2076609 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

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