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Highly Stereoselective Synthesis of Aristeromycin through Dihydroxylation of 4-Aryl-1-azido-2-cyclopentenes

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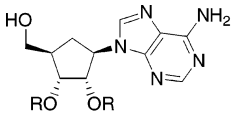
Dihydroxylation of 4-aryl-1-azido-2-cyclopentenes **6**, in which an aryl group is used as a synthetic equivalent of CH_2OH, was studied to improve the low to moderate stereoselectivity previously reported for cyclopentenes **3** possessing CH_2X and nitrogen atom-containing groups. 2-Furyl, Ph, and *p*-$MeOC_6H_4$ groups were chosen as the aryl groups. Compounds **6a**−**c** possessing such aryl groups were prepared by CuCN-catalyzed reaction between 2-cyclopentene-1,4-diol monoacetate **9** and the corresponding Grignard reagents followed by substitution of the hydroxyl group with $(PhO)_2P(=O)N_3$. The desired diols **7a**−**c** were obtained with higher selectivities of >7:1 when dihydroxylation of **6a**−**c** was carried out at 0 °C with OsO_4 (catalyst) and NMO in a mixed solvent of MeCN, THF, *t*-BuOH, and H_2O. Among them, the furyl compound recorded the highest selectivity of 14:1. The furyl and azido groups on diol **7a** were converted into hydroymethyl and adeninyl groups, respectively, to produce acetonide **2**, which upon hydrolysis affords aristeromycin **1**.

Introduction

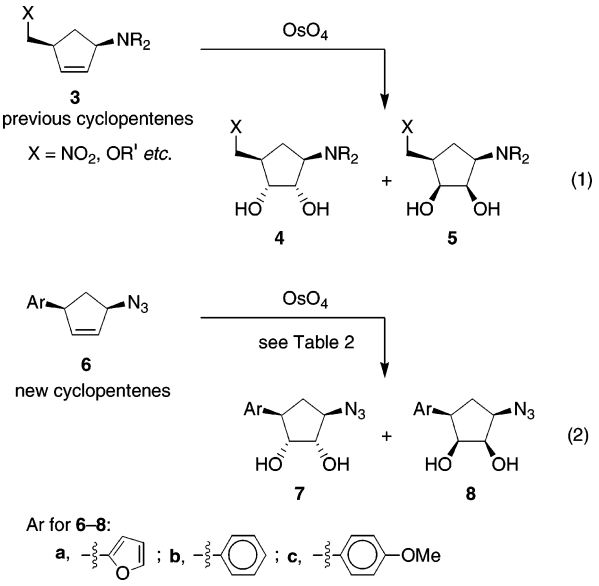
Aristeromycin (**1**) is a naturally occurring analogue of adenosine,[1] and the adenosine-like biological properties as well as the chemical stability have attracted considerable interest in this molecule as a lead compound in the development of new drugs and, recently, as a mimic of adenosine in complex molecules such as vitamin B_{12} and cyclic ADP-ribose.[2]



Aristeromycin (**1**): R = H
Acetonide of aristeromycin (**2**): R = C(Me)$_2$

The syntheses of aristeromycin and its derivatives published so far have been summarized in reviews.[3] Among the syntheses, the osmium-catalyzed dihydroxylation of cyclopentenes **3** has been frequently employed as the key step to furnish the diol functionality on the ring because of its convenience.[4] This strategy was originally reported by Vince[4a] to afford a mixture of the key diols **4** and stereoisomer **5** in a ratio of 1:2 (eq 1 of Scheme 1).

SCHEME 1. Previous and New Cyclopentenes for Dihydroxylation



Although efficient preparation of **3** has later been investigated,[4,5] the ratio of **4** to **5** was improved only to some extent. Presently, the ratios are usually between 1:1 and 2.4:1 and at best 5.7:1.[6] Thus, realization of highly stereoselective dihydroxylation is a challenging task, though the corresponding lactam attained exclusive stereoselection due to conformational bias.[7]

The stereoselectivity is rationalized by Katagiri by using conformers A and B for **3**.[8,9] Conformer A affords the desired diol **4** exclusively for the steric reason attributable to the two substituents (CH_2X and NR_2) (Scheme 2), while conformer B prefers production of

(1) Kusaka, T.; Yamamoto, H.; Shibata, M.; Muroi, M.; Kishi, T.; Mizuno, K. *J. Antibiot.* **1968**, *21*, 255−263.

(2) (a) Lott, W. B.; Chagovetz, A. M.; Grissom, C. B. *J. Am. Chem. Soc.* **1995**, *117*, 12194−12201. (b) Shuto, S.; Shirato, M.; Sumita, Y.; Ueno, Y.; Matsuda, A. *J. Org. Chem.* **1998**, *63*, 1986−1994. (c) Fukuoka, M.; Shuto, S.; Minakawa, N.; Ueno, Y.; Matsuda, A. *Tetrahedron Lett.* **1999**, *40*, 5361−5364.

(3) (a) Crimmins, M. T. *Tetrahedron* **1998**, *54*, 9229−9272. (b) Agrofoglio, L.; Suhas, E.; Farese, A.; Condom, R.; Challand, S. R.; Earl, R. A.; Guedj, R. *Tetrahedron* **1994**, *50*, 10611−10670. (c) Borthwick, A. D.; Biggadike, K. *Tetrahedron* **1992**, *48*, 571−623. (d) Huryn, D. M.; Okabe, M. *Chem. Rev.* **1992**, *92*, 1745−1768.

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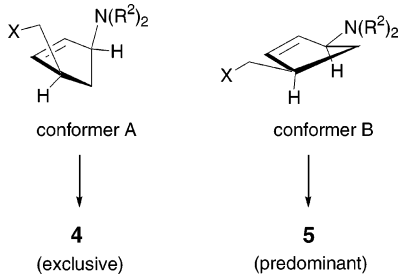
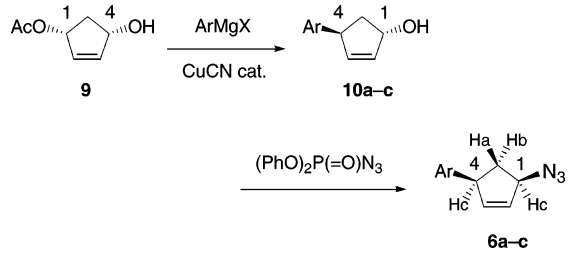
SCHEME 2. Conformers A and B Proposed by Katagiri for 3



stereoisomer **5** for the electronic reason. In other words, the substituents in the latter conformer hardly contribute to the selective production of **4**, though projecting slightly toward the β face (the upper side of the cyclopentene ring). Thus, the proportion of the conformers A and B is definitely responsible for the overall stereoselectivity.

Although the above rationale seems to rule out any possibility, we supposed simply that a big CH_2X equivalent would obstruct the β face in conformer B effectively, thus providing a bias for high stereoselection in favor of **4**. The 2-furyl, Ph, and *p*-$MeOC_6H_4$ groups were chosen as the CH_2X equivalent. Herein, we present successful dihydroxylation of azides **6a**−**c** (eq 2 of Scheme 1) and synthesis of the acetonide of aristeromycin (**2**).[10]

SCHEME 3. Preparation of Azides 6



Results and Discussion

Azides **6a**−**c** were synthesized from cyclopentenyl monoacetate **9**[11] by a sequence of reactions shown in Scheme 3.[12] Among the two types of reagent systems (the corresponding lithium borates/Ni(0) catalyst; ArMgCl/CuCN catalyst) developed for the first step,[13,14] the latter type of reagents[14] was used for preparation of **10b** and **10c** (PhMgCl (3 equiv)/CuCN (30 mol %) and *p*-$MeOC_6H_4$-MgCl (3 equiv)/CuCN (30 mol %), respectively), since higher regioselectivity and yield are recorded with ArMgCl/CuCN catalyst. On the other hand, a reagent based on (2-furyl)MgBr and CuCN catalyst was studied for synthesis of **10a**, because 2-furyl chloride required for the high regioselectivity is hardly accessible.[15] As expected, a somewhat low ratio of 85:15 was obtained for **10a** and the regioisomer (structure not shown) (Table 1, entry 2). The ratio was improved considerably when $MgCl_2$ (1−3 equiv based on (2-furyl)MgBr) was added as an additive (entry 3). This result implies that the regioselective reagent system (2-furyl)MgCl/CuCN catalyst was indeed generated. However, the reaction was slow at 0 °C, and thus the reaction was repeated at room temperature to provide **10a** in 86% yield with 94% selectivity (entry 4).

The second reaction of racemic **10a**−**c** with $(PhO)_2P(=O)N_3$ according to Thompson's procedure[16] proceeded in a stereo- and regiospecific[17] fashion to yield racemic azides **6a**−**c** in 75−84% yields. In the same way, (1*S*,4*S*)-**10a** derived from (1*R*,4*S*)-**9**[11a,b] of >95% ee (determined by the MTPA method) was converted into enantiomerically enriched **6a**, i.e., (1*R*,4*S*)-**6a**. The cis stereochemistry between Ar and N_3 in products **6a**−**c** was confirmed by ^{1}H NMR spectroscopy: $\Delta\delta$ values between Ha and Hc in **6a**−**c** were 0.83−1.17 ppm, which are within the standard difference for the cis 1,4-disubstituted 2-cyclo-

(4) (a) Vince, R.; Daluge, S. *J. Org. Chem.* **1980**, *45*, 531−533. (b) Trost, B. M.; Kuo, G.-H.; Benneche, T. *J. Am. Chem. Soc.* **1988**, *110*, 621−622. (c) Deardorff, D. R.; Shulman, M. J.; Sheppeck, J. E., II. *Tetrahedron Lett.* **1989**, *30*, 6625−6628. (d) Roberts, S. M.; Shoberu, K. A. *J. Chem. Soc., Chem. Commun.* **1991**, 2605−2607. (e) Trost, B. M.; Li, L.; Guile, S. D. *J. Am. Chem. Soc.* **1992**, *114*, 8745−8747. (f) Saville-Stones, E. A.; Turner, R. M.; Lindell, S. D.; Jennings, N. S.; Head, J. C.; Carver, D. S. *Tetrahedron* **1994**, *50*, 6695−6704. (g) Csuk, R.; Dörr, P. *Tetrahedron* **1995**, *51*, 5789−5798. (h) Aggarwal, V. K.; Monteiro, N.; Tarver, G. J.; Lindell, S. D. *J. Org. Chem.* **1996**, *61*, 1192−1193. (i) Deardorff, D. R.; Savin, K. A.; Justman, C. J.; Karanjawala, Z. E.; Sheppeck, J. E., II.; Hager, D. C.; Aydin, N. *J. Org. Chem.* **1996**, *61*, 3616−3622. (j) Burlina, F.; Favre, A.; Fourrey, J.-L.; Thomas, M. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 247−250. (k) Zhang, D.; Miller, M. J. *J. Org. Chem.* **1998**, *63*, 755−759. (l) Brown, B.; Hegedus, L. S. *J. Org. Chem.* **2000**, *65*, 1865−1872.

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(6) Highest ratio (5.7:1) was obtained by running the reaction at a low temperature (from −5 to −15 °C) by Deardorff.[4i] Cf. also ref 4c.

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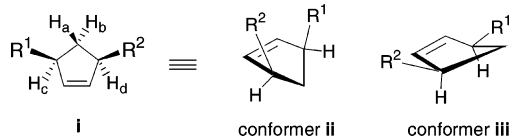
(9) According to Katagiri, conformers **ii** and **iii** for cyclopentenes **i** generally take smaller (<5 Hz) and larger (>5.5 Hz) coupling constants between Ha and Hc/Hd (J_{Ha-Hc} and J_{Ha-Hd}), respectively. However, it is suitable to use <4.5 Hz for **ii** possessing NR_2 and CH_2X as R^1 and R^2, respectively, on the basis of our observation (see the text).



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(12) Monoacetate **9** and the corresponding diacetate have been employed in the previous syntheses of aristeromycin without improvement in the dihydroxylation.[4b,c,e,i]

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(15) According to our recent observation,[14] the high regioselectivity is attained only with ArMgCl in the presence of CuCN catalyst.

(16) Thompson, A. S.; Humphrey, G. R.; DeMarco, A. M.; Mathre, D. J.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 5886−5888.

TABLE 1. Reaction of 9 with the 2-Furyl Reagents[a]

entry	reagent[b]	catalyst[c]	temp	regio-**10a**: isomer	yield (%)
1[d]	lithium borate	$NiCl_2(PPh_3)_2$	rt	89:11	56
2	(2-furyl)MgBr	CuCN	0 °C	85:15	71[e]
3	(2-furyl)MgBr $MgCl_2$[f]	CuCN	0 °C	95:5	70[e]
4	(2-furyl)MgBr $MgCl_2$[f]	CuCN	rt	94:6	86

[a] Reactions were carried out for several hours. [b] Performed with 3−4 equiv. [c] Ni catalyst (10 mol %); Cu catalyst (30 mol %). [d] Data from ref 13. [e] Substrate **9** was recovered in 8−21% yields. [f] Performed with 3 equiv of (furyl)MgBr.

TABLE 2. Dihydroxylation of Azides 6a−c

entry	substrate[a]	Ar for **6**−**8**	reagent	solvent	temp (°C)	time (h)	product	ratio[b] **7**: **8**	yield (%)[c]
1	**6a**	2-furyl	OsO_4,[d] NMO	MeCN/*t*-BuOH/H_2O (4:1:1)	rt	16	**7a**,**8a**	4:1	71
2	**6a**	2-furyl	OsO_4,[d] NMO	MeCN/*t*-BuOH/H_2O (4:1:1)	0	24	**7a**,**8a**	15:1	57[e]
3	**6a**	2-furyl	OsO_4,[d] NMO	MeCN/THF/*t*-BuOH/H_2O (4:2:1:1)	0	7	**7a**,**8a**	14:1	72
4	**6a**	2-furyl	OsO_4,[d] NMO	acetone/THF/H_2O (8:4:1)	0	7	**7a**,**8a**	11:1	65
5	**6a**	2-furyl	AD-mix-α	*t*-BuOH/H_2O (1:1)	0	24	**7a**,**8a**	3:1	f
6	**6a**	2-furyl	AD-mix-*β*	*t*-BuOH/H_2O (1:1)	0	24	**7a**,**8a**	6:1	34
7	**6a**	2-furyl	OsO_4,[g] $K_3Fe(CN)_6$, K_2CO_3	*t*-BuOH/H_2O (1:1)	0 to rt	24	**7a**,**8a**	4:1	f
8	**6b**	Ph	OsO_4,[d] NMO	MeCN/THF/*t*-BuOH/H_2O (4:2:2:1)	0	22	**7b**,**8b**	8:1	77
9	**6c**	*p*-$MeOC_6H_4$	OsO_4,[d] NMO	MeCN/THF/*t*-BuOH/H_2O (4:2:2:1)	0	22	**7c**,**8c**	7:1	91

[a] Racemic substrates **6a**−**c** were used in entries 1 and 7−9, while (1*R*,4*S*)-**6a** was used in entries 2−6. [b] Determined by ^1H NMR spectroscopy. [c] Isolated yields. [d] Performed with 3 mol %. [e] Data were not reproducible. [f] Not determined. [g] Performed with 1.25 mol %.

pentenes.[18] On the other hand, the coupling constant between Ha and Hc indicates the existence of the two conformers for **6a** (J_{Ha-Hc} = 5.4 Hz) and of single conformer B for **6b** and **6c** (both J_{Ha-Hc} = 6.2 Hz).

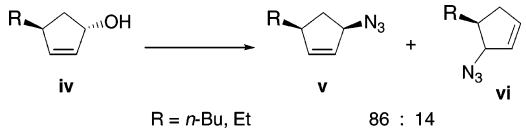
Dihydroxylation of **6a**−**c** is summarized in Table 2. Racemic **6a**−**c** were used for entries 1 and 7−9 for convenience and enantiomerically enriched **6a** for entries 2−6. A 4:1 ratio of the desired product **7a** and isomer **8a**, which is higher than that previously reported, was obtained with OsO_4 (3 mol %) and NMO even at room temperature, and the result clearly indicates that our idea proposed above is reasonable.

Since the above selectivity is certainly low from a synthetic point of view, the reaction was run again at 0 °C to afford higher selectivity (entry 2). The result was, however, marginally reproducible, perhaps due to the low solubility of the substrate at 0 °C in this mixed solvent system. Fortunately, similar selectivity was attained reproducibly with a mixture of solvents containing THF (entry 3). Use of acetone as a solvent slightly decreased the selectivity (entry 4). Examined next was double diastereoselection between the optically enriched (1*R*,4*S*)-**6a** and the Sharpless reagent (AD-mix-α or -*β*).[19] Efficient enhancement was, however, not observed (entries 5 and 6).[20] A reagent[21] lacking the chiral ligand for the AD-mix showed intermediate selectivity (entry 7) compared to entries 5 and 6.

Next, the best conditions explored for furan **6a** (entry 3) were applied to **6b** (Ar = Ph) and **6c** (Ar = *p*-$MeOC_6H_4$). Higher selectivity than that reported previously for cyclopentenes **3** was recorded (entries 8 and 9) but was lower than that obtained for **6a** (entry 3).[22]

Since hydrolysis of acetonide **2** furnishes aristeromycin (**1**),[4b,23] **2** was chosen as the target compound in the present investigation. As presented in Scheme 4, a 14:1 mixture of optically active **7a** and **8a**, prepared by the dihydroxylation of (1*S*,4*S*)-**10a**, was submitted to acetonide formation to give **11** in 92% yield after chromatography on silica gel. The furyl group of **11** was transformed into a methoxycarbonyl group by oxidation using $RuCl_3$ catalyst/$NaIO_4$[24] followed by esterification with CH_2N_2 to afford **12** in 80% yield. The ester and the azido groups in **12** were reduced with $LiAlH_4$ to give amino alcohol **13**, which was converted into **2** by the standard procedure.[23c,25,26] The ^1H NMR (300 MHz)

(17) Size of the substituents (2-furyl, phenyl, and *p*-$MeOC_6H_4$) substantially contributes to the regioselectivity since **iv** (R = *n*-Bu, Et) produced a 86:14 mixture of cyclopentene **v** and isomer, probably 1,2-regioisomer **vi**, in 70 and 59% yields, respectively. This result led us to halt further investigation with **v**.



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(20) Probably due to the fact that cis olefins are generally poor substrates for AD reaction.

(21) Minato, M.; Yamamoto, K.; Tsuji, J. *J. Org. Chem.* **1990**, *55*, 766−768.

(22) Higher selectivity obtained with **6a** among **6a**−**c** is best understood by the higher proportion of conformer **A** over **B** for **6a** than that for **6b** and **6c**.

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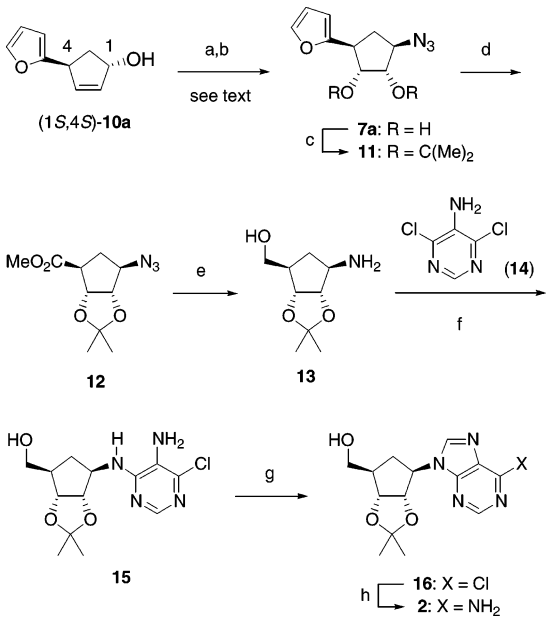
SCHEME 4[a]



[a] Reaction conditions: (a) $(PhO)_2P(=O)N_3$, DBU, 75%; (b) OsO_4, NMO, 0 °C, **7a**/**8a** = 14:1, 72%; (c) $Me_2C(OMe)_2$, PPTS, 92%; (d) $RuCl_3 \cdot 3H_2O$ (catalyst), $NaIO_4$, then CH_2N_2, 80%; (e) $LiAlH_4$; (f) **14**, Et_3N, BuOH, 130 °C, 61% from **12**; (g) $(EtO)_2CHOAc$, reflux, then *p*-TsOH·H_2O, toluene, 52%; (h) NH_3, EtOH, 90 °C, 75%.

spectrum of the synthetic acetonide **2** in $CDCl_3$ was fully consistent with the reported data.[27]

Conclusion

Cyclopentenes with a large CH_2OR equivalent such as 2-furyl, phenyl, and *p*-$MeOC_6H_4$ groups afforded high stereoselectivity in the OsO_4-catalyzed dihydroxylation to furnish the corresponding key diols for the synthesis of aristeromycin. Since the principle presented herein will be applicable to substituted furyl groups and other functionalized aryl groups, aristeromycin analogues with such a group or a polyoxygenated group as the side chain at the 4 position of the ring would be synthesized by taking advantage of the reactions specific to the given group and the method summarized in Scheme 4. The side chain modifications in aristeromycin are important in developing carbocyclic sugars of the next generation.[28]

Experimental Section

(1*S,4*S**)-4-(2′-Furyl)-2-cyclopenten-1-ol (10a).** To a mixture of Mg (37 mg, 1.52 m-atom) and THF (1 mL) was added $CH_2{=}CHCH_2Cl$ (0.29 mL, 3.56 mmol) slowly. After the addition, the mixture was refluxed for 10 min. Most volatile compounds were removed under reduced pressure, and remaining $MgCl_2$ was diluted with THF (2 mL) for the reaction.

An ice-cold solution of (2-furyl)MgBr in THF (1.20 mL, 1.07 M, 1.28 mmol) was diluted with THF (1 mL), and the above slurry of $MgCl_2$ in THF was added to the solution. After 10 min at 0 °C, CuCN (10 mg, 0.11 mmol) was added, and the mixture was stirred for 20 min. To this was added a solution of monoacetate **9** (49 mg, 0.34 mmol) dissolved in THF (0.5 mL) at 0 °C. The resulting mixture was stirred at room temperature for 3.5 h, and poured into saturated NH_4Cl and EtOAc with vigorous stirring. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined extracts were dried and concentrated to leave an oil, which was purified by chromatography to afford **10a** (47 mg, 86%), which showed ^1H and ^{13}C NMR spectra identical to those previously reported.[13]

(1*R*,4*S*)-1-Azido-4-(2′-furyl)-2-cyclopentene (6a). To an ice-cold solution of (1*S*,4*S*)-**10a** (250 mg, 1.67 mmol) ($[\alpha]^{29}_D$ +190 (*c* 0.46, $CHCl_3$)), prepared from (1*R*,3*S*)-**9** (>95% ee), and $(PhO)_2P(O)N_3$ (0.43 mL, 2.0 mmol) in toluene (2.7 mL) was added DBU (0.35 mL, 2.34 mmol). The resulting mixture was stirred at room temperature for 20 h and poured into brine and EtOAc with vigorous stirring. The layers were separated, and the aqueous layer was extracted with EtOAc repeatedly. The combined organic layers were dried and concentrated to give an oil, which was subjected to chromatography to afford **6a** (220 mg, 75%): $[\alpha]^{25}_D$ +56 (*c* 0.45, $CHCl_3$); IR (neat) 2096, 1251 cm^{-1}; ^1H NMR δ 1.93 (dt, J = 14, 5.4 Hz, 1 H), 2.76 (dt, J = 14, 8 Hz, 1 H), 3.92−4.00 (m, 1 H), 4.41−4.49 (m, 1 H), 5.91 (dt, J = 5.5, 2.5 Hz, 1 H), 6.04−6.10 (m, 2 H), 6.30 (dd, J = 3, 2 Hz, 1 H), 7.34 (d, J = 2 Hz, 1 H); ^{13}C NMR δ 156.9, 141.7, 136.5, 130.5, 110.4, 104.7, 66.5, 43.4, 36.5. HRMS (EI) *m/e* calcd for $C_9H_9N_3O$ (M^+) 175.0746, found 175.0755.

(1*R,4*S**)-1-Azido-4-phenyl-2-cyclopentene (6b).** The above procedure was applied to reaction of **10b** (160 mg, 0.999 mmol) with $(PhO)_2P(O)N_3$ (0.246 mL, 1.16 mmol) and DBU (0.142 mL, 0.95 mmol) in toluene (1.7 mL) at room temperature overnight to afford the title compound **6b** (147 mg, 79%): IR (neat) 2093, 1251 cm^{-1}; ^1H NMR δ 1.72 (dt, J = 14, 6.2 Hz, 1 H), 2.87 (dt, J = 14, 8 Hz, 1 H), 3.84−3.92 (m, 1 H), 4.48−4.56 (m, 1 H), 5.94 (dt, J = 5, 2 Hz, 1 H), 6.04 (dt, J = 5, 2 Hz, 1 H), 7.19−7.43 (m, 5 H).

(1*R,4*S**)-1-Azido-4-[(4-methoxy)phenyl]-2-cyclopentene (6c).** The above procedure was applied to reaction of **10c** (103 mg, 0.541 mmol) with $(PhO)_2P(O)N_3$ (0.14 mL, 0.65 mmol) and DBU (0.113 mL, 0.757 mmol) in toluene (1 mL) at room temperature overnight to afford the title compound **6c** (98 mg, 84%): IR (neat) 2092, 1512, 1248 cm^{-1}; ^1H NMR δ 1.68 (dt, J = 14, 6.2 Hz, 1 H), 2.84 (dt, J = 14, 8 Hz, 1 H), 3.80 (s, 3 H), 3.79−3.87 (m, 1 H), 4.45−4.53 (m, 1 H), 5.91 (dt, J = 5, 2 Hz, 1 H), 6.01 (dt, J = 5, 2 Hz, 1 H), 6.86 (d, J = 9 Hz, 2 H), 7.13 (d, J = 9 Hz, 2 H).

(1*R*,2*S*,3*R*,5*S*)-3-Azido-5-(2′-furyl)cyclopentane-1,2-diol (7a). To an ice-cold mixture of **6a** (55 mg, 0.31 mmol), NMO (45 mg, 0.38 mmol), MeCN (0.6 mL), THF (0.3 mL), and H_2O (0.15 mL) was added OsO_4 (0.19 mL, 0.05 M in *t*-BuOH, 0.0095 mmol) dropwise. The resulting mixture was stirred at 0 °C for 7 h and diluted with brine. The resulting mixture was extracted with EtOAc repeatedly. The combined extracts were dried and concentrated to give a mixture of **7a** and **8a** (47 mg, 72%) in a ratio of 14:1 by ^1H NMR spectroscopy. The mixture was used for the next reaction without further purification. The spectra of **7a**: IR (neat) 3396, 2104 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.77 (ddd, J = 14, 9, 8 Hz, 1 H), 2.53 (dt, J = 14, 8 Hz, 1 H), 2.64 (br s, 1 H), 2.78 (br s, 1 H), 3.25 (dt, J = 6, 9 Hz, 1 H), 3.92 (dt, J = 5, 8 Hz, 1 H), 3.99−4.06 (m, 1 H), 4.13−4.20 (m, 1 H), 6.11 (d, J = 3 Hz, 1 H), 6.30−6.32 (m, 1 H), 7.35 (dd, J = 2, 1 Hz, 1 H). HRMS (EI) *m/e* calcd for $C_9H_{11}N_3O_3$ (M^+) 209.0800, found 209.0800.

(1*R,2*S**,3*R**,5*R**)-3-Azido-5-phenylcyclopentane-1,2-diol (7b).** Dihydroxylation of **6b** (61 mg, 0.33 mmol) was

(26) Use of EtOH in the last step is a better choice than the standard solvent of MeOH since NH_3 in MeOH gave the corresponding methoxide as a byproduct.

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carried out according to the procedure for the dihydroxylation of **6a** with OsO_4 (0.30 mL, 0.05 M in *t*-BuOH, 0.015 mmol), NMO (69 mg, 0.59 mmol), MeCN (0.6 mL), THF (0.3 mL), and H_2O (0.15 mL) at 0 °C for 13 h to afford, after chromatography, a mixture of **7b** and **8b** (55 mg, 77%) in a ratio of 8:1 by ^{1}H NMR spectroscopy. The spectra of **7b**: IR (neat) 3398, 2101, 1258 cm^{-1}; ^{1}H NMR δ 1.68 (ddd, J = 14, 10, 8 Hz, 1 H), 2.55 (dt, J = 14, 8 Hz, 1 H), 2.68 (br s, 1 H), 2.99 (br s, 1 H), 3.11 (ddd, J = 10, 8, 7 Hz, 1 H), 3.91 (dt, J = 5, 8 Hz, 1 H), 3.98−4.10 (m, 2 H), 7.22−7.39 (m, 5 H).

(1*R,2*S**,3*R**,5*R**)-3-Azido-5-[(4-methoxy)phenyl]cyclopentane-1,2-diol (7c).** Dihydroxylation of **6c** (50 mg, 0.232 mmol) was carried out according to the procedure for the dihydroxylation of **6a** with OsO_4 (0.21 mL, 0.05 M in *t*-BuOH, 0.0105 mmol), NMO (48 mg, 0.41 mmol), MeCN (0.44 mL), THF (0.22 mL), and H_2O (0.11 mL) at 0 °C for 13 h to afford, after chromatography, a mixture of **7c** and **8c** (55 mg, 91%) in a ratio of 7:1 by ^{1}H NMR spectroscopy. The spectra of **7c**: IR (neat) 3401, 2101, 1515 cm^{-1}; ^{1}H NMR ($CDCl_3$ + D_2O) δ 1.64 (ddd, J = 14, 10, 8 Hz, 1 H), 2.53 (dt, J = 14, 8 Hz, 1 H), 3.01−3.14 (m, 1 H), 3.80 (s, 3 H), 3.87−4.07 (m, 3 H), 6.85−6.91 (m, 2 H), 7.14−7.20 (m, 2 H).

(1*R*,2*S*,3*R*,4*S*)-1-Azido-4-(2′-furyl)-2,3-(dimethylmethylenedioxy)-1-cyclopentane (11). To the 14:1 mixture of **7a** and **8a** (36 mg, 0.17 mmol), obtained above from **6a**, were added sequentially CH_2Cl_2 (1.4 mL), $Me_2C(OMe)_2$ (0.11 mL, 0.85 mmol), and PPTS (15 mg, 0.06 mmol). After the solution was stirred at room temperature for 12 h, a few drops of pyridine were added. Volatile compounds were evaporated, and the resulting residue was purified by chromatography to afford **11** (39 mg, 92%): $[\alpha]^{25}_D$ −59 (*c* 0.71, $CHCl_3$); IR (neat) 2105, 1211 cm^{-1}; ^{1}H NMR δ 1.32 (s, 3 H), 1.52 (s, 3 H), 2.11 (dt, J = 14, 7 Hz, 1 H), 2.51 (dt, J = 14, 7 Hz, 1 H), 3.37 (dt, J = 4, 7.5 Hz, 1 H), 4.02 (dt, J = 3, 7 Hz, 1 H), 4.50 (dd, J = 7, 3 Hz, 1 H), 4.80 (dd, J = 6, 4 Hz, 1 H), 6.12 (dt, J = 3, 1 Hz, 1 H), 6.31 (dd, J = 3, 2 Hz, 1 H), 7.35 (d, J = 2 Hz, 1 H); ^{13}C NMR δ 154.6, 141.9, 112.7, 110.4, 105.3, 84.9, 83.8, 66.3, 43.5, 34.1, 26.9, 24.6. HRMS (CI) *m*/*e* calcd for $C_{12}H_{16}N_3O_3$ (M + H)$^+$ 250.1192, found 250.1195.

Methyl (1*S*,2*R*,3*S*,4*R*)-4-Azido-2,3-(dimethylmethylenedioxy)cyclopentanecarboxylate (12). To an ice-cold mixture of **11** (379 mg, 1.52 mmol), $NaIO_4$ (3.25 g, 15.2 mmol), CCl_4 (4 mL), MeCN (4 mL), and H_2O (6 mL) was added a catalytic amount of $RuCl_3$·$3H_2O$ at 0 °C. The mixture was stirred at room temperature for 1 h, and the product was extracted with CH_2Cl_2 repeatedly. The combined extracts were dried and concentrated to give the corresponding acid.

The above crude acid in Et_2O was treated with an ethereal solution of CH_2N_2 at 0 °C for 15 min. The solution was concentrated, and the residue was purified by chromatography to furnish **12** (293 mg, 80% yield from **11**): $[\alpha]^{25}_D$ −68 (*c* 0.43, $CHCl_3$); IR (neat) 2108, 1736, 1209 cm^{-1}; ^{1}H NMR δ 1.30 (s, 3 H), 1.44 (s, 3 H), 2.22−2.39 (m, 2 H), 2.93−2.99 (m, 1 H), 3.73 (s, 3 H), 4.00 (ddd, J = 5, 4, 2 Hz, 1 H), 4.42 (d, J = 6 Hz, 1 H), 5.11 (d, J = 6 Hz, 1 H); ^{13}C NMR δ 172.9, 111.3, 84.0, 81.7, 66.1, 52.3, 49.1, 31.4, 26.4, 24.1. HRMS (CI) *m*/*e* calcd for $C_{10}H_{16}N_3O_4$ (M + H)$^+$ 242.1141, found 242.1139.

(1*R*,2*R*,3*S*,4*R*)-4-(5-Amino-6-chloro-4-pyrimidinylamino)-2,3-(dimethylmethylenedioxy)-1-cyclopentanemethanol (15). To an ice-cold solution of **12** (87 mg, 0.36 mmol) in THF (2 mL) was added $LiAlH_4$ (35 mg, 0.92 mmol). The reaction was carried out at 0 °C for 1.5 h and quenched by addition of H_2O (0.05 mL, 2.7 mmol) and NaF (114 mg, 2.71 mmol). The resulting mixture was stirred vigorously at 0 °C for 1 h and filtered through a pad of Celite with MeOH. The filtrate was concentrated to give amine **13**, which was used for the next reaction without further purification.

A solution of amine **13**, 5-amino-4,6-dichloropyrimidine (**14**) (148 mg, 0.902 mmol), and Et_3N (0.45 mL, 3.25 mmol) in *n*-BuOH (10 mL) was heated to 130 °C for 40 h and poured into saturated $NaHCO_3$. The mixture was extracted with CH_2Cl_2 repeatedly. The combined organic layers were dried and concentrated to afford a residue, which was purified by chromatography to afford **15** (70 mg, 61% yield from **12**): $[\alpha]^{25}_D$ +7 (*c* 0.42, $CHCl_3$); IR ($CHCl_3$) 3348, 1577 cm^{-1}; ^{1}H NMR δ 1.28 (s, 3 H), 1.49 (s, 3 H), 1.53−1.78 (m, 2 H), 2.38−2.47 (m, 1 H), 2.70 (ddd, J = 14, 10, 8 Hz, 1 H), 3.41 (br s, 2 H), 3.77 (dd, J = 10, 3 Hz, 1 H), 3.96 (dd, J = 10, 3 Hz, 1 H), 4.43 (d, J = 6 Hz, 1 H), 4.61−4.69 (m, 2 H), 6.63 (br s, 1 H), 8.06 (s, 1 H); ^{13}C NMR δ 153.6, 149.0, 140.5, 122.6, 110.7, 87.0, 84.3, 64.2, 56.5, 47.4, 33.2, 26.9, 24.4. HRMS (FAB) *m*/*e* calcd for $C_{13}H_{20}ClN_4O_3$ (M + H)$^+$ 315.1224, found 315.1223.

2′,3′-(Dimethylmethylenedioxy)-(−)-aristeromycin (2). A solution of **15** (57 mg, 0.18 mmol) in diethoxymethyl acetate (1.8 mL) was refluxed for 12 h and concentrated under reduced pressure. The residue was diluted with toluene (4 mL), and *p*-TsOH·H_2O (2 mg) was added to it. After 1 h at room temperature, the solution was concentrated to leave an oil, which was purified by chromatography to furnish **16** (31 mg, 52%): ^{1}H NMR δ 1.32 (s, 3 H), 1.58 (s, 3 H), 1.69 (br s, 1 H), 2.44−2.60 (m, 3 H), 3.79−3.91 (m, 2 H), 4.73 (dd, J = 7, 4 Hz, 1 H), 4.82−4.91 (m, 1 H), 5.03 (t, J = 6 Hz, 1 H), 8.22 (s, 1 H), 8.74 (s, 1 H). HRMS (FAB) *m*/*e* calcd for $C_{14}H_{18}ClN_4O_3$ (M + H)$^+$ 325.1067, found 325.1068.

A solution of **16** (30 mg, 0.093 mmol) in EtOH (2 mL, saturated with NH_3 by gently bubbling NH_3 gas at 0 °C for 20 min) was heated in a sealed tube at 90 °C for 42 h. The resulting solution was concentrated, and the residue was purified by chromatography to give **2** (22 mg, 75%): $[\alpha]^{25}_D$ −44 (*c* 0.41, MeOH); IR ($CHCl_3$) 3269, 1685, 1608 cm^{-1}. The ^{1}H NMR spectrum of synthetic **2** was consistent with the data reported[27] and was updated as follows: δ 1.33 (s, 3 H), 1.59 (s, 3 H), 1.71 (br s, 1 H), 2.41−2.67 (m, 3 H), 3.79−3.91 (m, 2 H), 4.73−4.81 (m, 2 H), 5.02 (t, J = 6 Hz, 1 H), 5.67 (br s, 2 H), 7.83 (s, 1 H), 8.33 (s, 1 H).

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Supporting Information Available: Copies of ^{1}H NMR spectra of compounds **6a**−**c**, **7a**−**c**, **11**, **12**, **15**, **16**, and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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