A Novel, One-Pot Ring Expansion of Cyclobutanones. Syntheses of Carbovir and Aristeromycin

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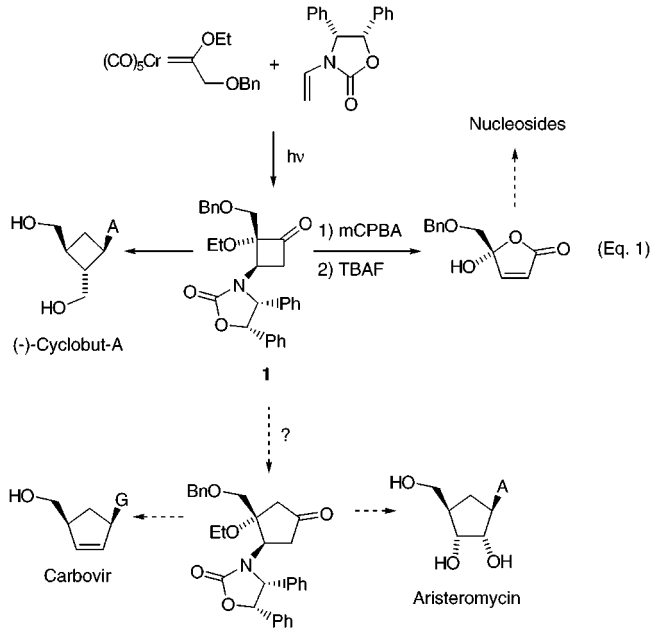
A novel, one-pot ring-expansion procedure was developed using $Me_3S(O)I$, NaH, and $Sc(OTf)_3$. The scope and limitations were briefly examined, and a tentative mechanism was proposed. Application of the methodology to known cyclobutanone **1** provided the corresponding cyclopentanone, which was successfully advanced to (+)-carbovir and (+)-aristeromycin.

Introduction

An efficient synthesis of optically active α-alkyl-α-alkoxycyclobutanones via the photolytic reaction of chromium carbene complexes with optically active ene-carbamates has been developed in these laboratories.[1] These underwent clean Baeyer−Villiger oxidation to butyrolactones with retention of configuration of the migrating quaternary center. This chemistry was used to synthesize (+)-tetrahydrocerulenin,[2] (+)-cerulenin,[3] optically active spiroketals,[4] as well as a template for the synthesis of nucleoside analogues.[5] Cyclobutanone **1** was converted to (−)-cyclobut-A,[6] a carbocyclic analogue of oxetanocin A having potent antiviral activity and good metabolic stability[7] (eq 1). Five-membered carbocyclic nucleoside analogues are also of current interest for similar reasons of high antiviral activity and metabolic stability and have recently been the focus of substantial synthetic efforts.[8] Since cyclobutanones are known to undergo carbocyclic ring expansion to cyclopentanones under a variety of conditions,[9] the chemistry in eq 1 offers a potential synthetic approach to carbocyclic nucleoside analogues such as carbovir and aristeromycin, provided the expansion occurs with the desired regioselectivity. Below are presented studies addressing the development of novel carbocyclic ring expansion methodology and its application to the synthesis of carbovir and aristeromycin.



Results and Discussion

Diazomethane methodology offers a simple, one-step procedure for the ring expansion of cyclobutanones to cyclopentanones.[10] With unsymmetrical cyclobutanones, migration of the less-substituted α-carbon is generally favored, but regioselectivity is dependent on many other factors, and predictions are difficult. Treatment of trisubstituted cyclobutanone **1** with diazomethane resulted in efficient ring expansion to cyclopentanones **2** and **3** in a 3:1 ratio, with the undesired regioisomer **2** (migration of the less substituted carbon) predominating. α-Deoxygenation with SmI_2, to produce disubstituted cyclobutanone **4**, followed by treatment with diazomethane produced cyclopentanones **5** and **6**, again in good yield, but with little regioselectivity (eq 2). Use of $TMSCHN_2$, with and without use of Lewis acid additives, also failed to provide the desired compounds. Thus, attention was turned from diazoalkanes in search of more effective reagents for the desired ring expansion.

A variety of sulfur-stabilized anions have been used to mediate carbocyclic ring expansions.[10] Specifically,

(1) (a) Hegedus, L. S.; Bates, R. W.; Söderberg, B. C. *J. Am. Chem. Soc.* **1991**, *113*, 923. (b) Riches, A. G.; Wernersbach, L. A.; Hegedus, L. S. *J. Org. Chem.* **1998**, *63*, 4691. (c) For a review of photochemical reactions of chromium carbene complexes, see: Hegedus, L. S. *Tetrahedron* **1997**, *53*, 4105.

(2) Miller, M. W.; Hegedus, L. S. *J. Org. Chem.* **1993**, *58*, 6779.

(3) Kedar, T. E.; Miller, M. W.; Hegedus, L. S. *J. Org. Chem.* **1996**, *61*, 6121.

(4) Bueno, A. B.; Hegedus, L. S. *J. Org. Chem.* **1998**, *63*, 684.

(5) (a) Reed, A. D.; Hegedus, L. S. *Organometallics* **1997**, *16*, 2313. (b) Reed, A. D.; Hegedus, L. S. *J. Org. Chem.* **1995**, *60*, 3787. (c) Umbricht, G.; Hellman, M. D.; Hegedus, L. S. *J. Org. Chem.* **1998**, *63*, 5173.

(6) Brown, B.; Hegedus, L. S. *J. Org. Chem.* **1998**, *63*, 8012.

(7) Norbeck, D. W.; Kern, E.; Hayashi, S.; Rosenbrook, W.; Sham, H.; Herrin, T.; Plattner, J. J.; Erikson, J.; Clement, J.; Swanson, R.; Shipkowitz, N.; Hardy, D.; Marsh, K.; Arnett, G.; Shannon, W.; Broder, S.; Matsuya, H. *J. Med. Chem.* **1990**, *33*, 1281.

(8) For a review see: Crimmins, M. T. *Tetrahedron* **1998**, *54*, 9229.

(9) For a review see: (a) Bellus, D.; Ernst, B. *Angew. Chem., Int. Ed. Engl.* **1987**, *27*, 797. (b) Lee-Ruff, E. New Synthetic Pathways from Cyclobutanones. In *Advances in Strain in Organic Chemistry*; Halton, B., Ed.; JAI Press: Greenwich, CT, 1991; Vol. 1.

(10) Wong, H. C. N. In *Houben-Weyl Methods of Organic Chemistry*; de Meijere, A., Ed.; Georg Thieme Verlag: Stuttgart, Germany, 1997; Vol. E17e, pp 495−521.

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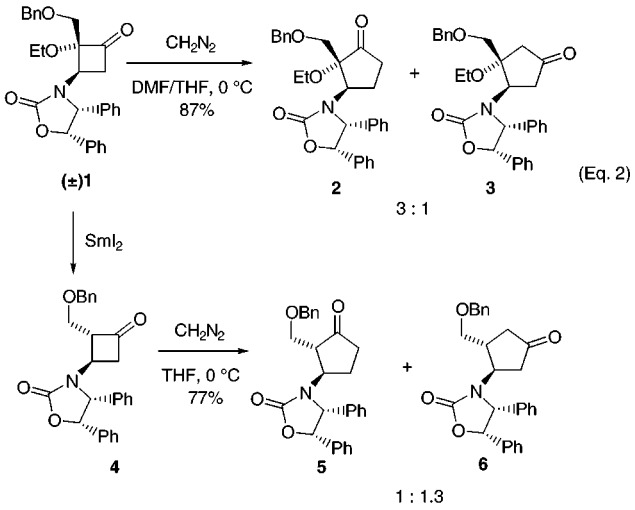
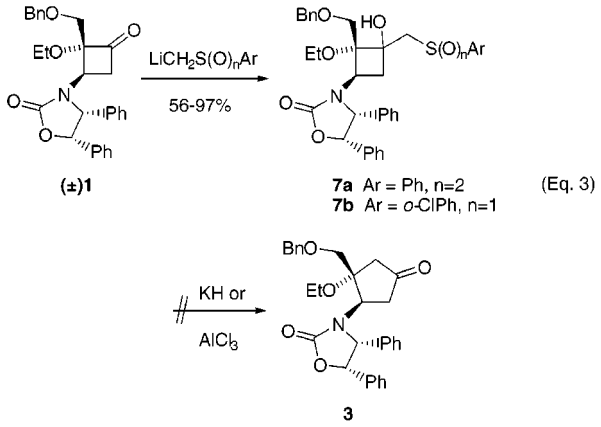
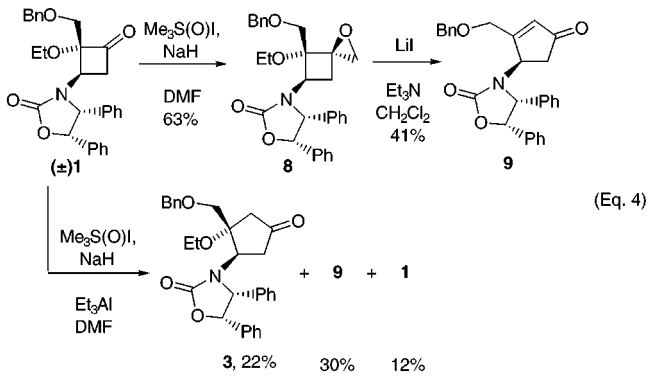
Trost has added substituted α-lithiomethyl phenyl sulfones to cyclic ketones to form intermediate alkoxides,



which were rearranged under Lewis acidic conditions to ring-expanded products.[12a] Additionally, Gadwood has employed a similar method using methyl *o*-chlorophenylsulfoxide anions, where the intermediate alcohol was isolated and rearranged using KH.[12b] Subjecting cyclobutanone **1** to similar conditions resulted in the formation of the intermediate cyclobutanols **7**. However, attempted ring expansions under basic or acidic conditions failed to provide the desired cyclopentanone products, either returning starting materials or leading to decomposition depending on the reaction conditions (eq 3).



Cyclobutanones have also been converted to cyclopentanones in a two-step process involving conversion to the spiro epoxides by reaction with a sulfur ylide followed by treatment with lithium iodide.[13] Treatment of cyclobutanone **1** with dimethylsulfonium methylide resulted in extensive decomposition, presumably by initial enolization, with no formation of the desired epoxide. In contrast, the less basic dimethylsulfoxonium methylide produced the desired spiro epoxide **8** as a single diastereomer in fair yield, with the stereochemistry being determined by X-ray analysis. Treatment of **8** with lithium iodide and triethylamine resulted in ring expansion along with elimination of ethanol to produce cyclopentenone **9** as the sole regioisomer, but in poor yield (eq 4).



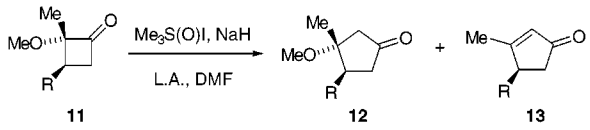
In an attempt to shorten this route, and patterned after Trost's Lewis acid-induced rearrangements mentioned above, Et_3Al was added to the reaction of cyclobutanone **1** with dimethylsulfoxonium methylide to promote ring expansion over epoxidation. This novel, one-pot procedure did form the ring-expanded products, solely of the desired regiochemistry, although in modest yield and selectivity. In experiments to gain insight into this reaction, the isolated epoxide **8** was treated with Et_3Al in DMF, which provided only recovered starting material. This indicated that the reaction was not simply a Lewis acid-catalyzed rearrangement of an epoxide intermediate. When NaI (concomitantly generated with the ylide in the reaction of $Me_3S(O)I$ with NaH) was included in the experiment above, the ring expansion products were again observed. Iodohydrin **10** was also found when the corresponding 2-methoxy-2-methylcyclobutanone was treated under the same conditions. Therefore, the reaction is believed to occur via epoxidation, followed by Lewis acid-catalyzed iodohydrin formation, and rearrangement to the cyclopentyl compounds. Other experiments demonstrated the requirement for DMSO (generated in the epoxide formation) in effecting smooth rearrangement. Its exact function, however, is still not understood, and further mechanistic studies will be required.

The scope of this one-pot ring expansion of trisubstituted cyclobutanones was briefly examined (Table 1). In all cases, the yields were modest, and alkoxide elimination was noted. With some substrates rearrangement was incomplete, and varying amounts of epoxide were obtained.

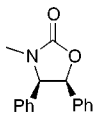
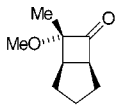
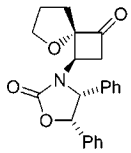
Because both the starting cyclobutanones and the product cyclopentanones were somewhat unstable to acidic conditions, and due to the incompatibility of Et_3Al with DMF, a milder Lewis acid was sought. In recent years, lanthanide triflates have come to the fore as highly reactive yet selective Lewis acids with a high tolerance for a range of functional groups.[14] Replacing Et_3Al with scandium triflate greatly improved the reaction, providing higher yields, no recovered epoxide, and little if any alkoxide elimination (Table 1). Furthermore, the reaction proceeds with complete selectivity favoring only the desired regioisomer. The procedure proved fairly general within the limited range of substrates examined. However, one important exception should be noted. With

(11) Molander, G. A. *Org. React.* **1994**, *46*, 211.
(12) (a) Trost, B. M.; Mikhail, G. K. *J. Am. Chem. Soc.* **1987**, *109*, 4124. (b) Gadwood, R. C.; Mallick, I. M.; DeWinter, A. J. *J. Org. Chem.* **1987**, *52*, 2, 774.
(13) Trost, B. M.; Latimer, H. *J. Org. Chem.* **1978**, *43*, 1031.
(14) For an overview, see: *Lanthanides: Chemistry and Uses in Organic Synthesis*; Kobayashi, S., Ed.; Springer: New York, 1999.

Table 1

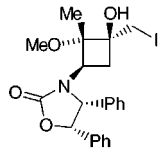


11 **12** **13**

	R	Conditions[a]	**12** / **13** (%)[b]
11a	OBn	A	18/29
		B	65/0
11b	Ph	A	10/44
		B	71/9
11c	*p*-(OMe)Ph	A	18/32
		B	66/0
11d		A	0/35[c]
		B	79/0
11e		A	[d]
		B	68/0
11f		A	0/55
		B	54/25[e]

[a] Conditions: (A) 3 equiv of Et_3Al, 25 °C, 9 h; (B) 0.25 equiv of $Sc(OTf)_3$, 50 °C, 5 h. [b] Isolated yields of **12**/**13**. [c] Material accompanied by 10% epoxide. [d] Only epoxide (46%) was obtained. [e] Elimination occurred during purification. The crude material was 96:4 **12**:**13**.

α-deoxygenated substrates, none of the desired products were obtained. In the case of **4** and **14**, only oxazolidinone and benzyl alcohol, respectively, were recovered. Reaction of **15** under these conditions returned only a low yield of starting material. Presumably, the starting materials enolize and decompose through either the cyclobutene or cyclobutenone, as with similar 3-heterosubstituted cyclobutanones bearing α-protons.[15]



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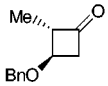

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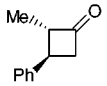


15

With this new ring-expansion methodology in hand, attention was turned to its use in the synthesis of carbocyclic nucleoside analogues. Some carbocyclic nucleosides, including aristeromycin[16] and carbovir[17] (eq 1), display impressive antiviral activity. A wide range of enantioselective synthetic approaches to these cyclopentyl nucleosides have been developed,[8] among which the palladium-catalyzed desymmetrization of *meso*-cyclopent-2-en-1,4-biscarbonates[18] has proven broadly useful. The syntheses of carbovir and aristeromycin utilizing both palladium methodology and the previously mentioned ring-expansion procedure are shown in Scheme 1. The syntheses were optimized using racemic material and repeated with the corresponding optically active compounds.

Cyclobutanone **1** was prepared in excellent yield as a single diastereoisomer by the previously reported[5c] photolysis of the chromium carbene complex with the ene carbamate[19] shown in Scheme 1. Ring expansion, followed by elimination of ethanol, led to cyclopentenone **9** in good yield. Reduction of the enone was best achieved by hydrogenation. Using palladium on carbon as a catalyst offered little (3:2) facial selectivity. Since these diastereomers, which were difficult to separate, become enantiomeric in the following oxazolidinone elimination step, attention was turned to other catalysts to increase selectivity. It was anticipated that the oxazolidinone could be used to direct hydrogenation from the α-face with a cationic Rh or Ir catalyst.[20] However, only poor selectivity was observed under these conditions, with Crabtree's catalyst[21] and [Rh(COD)dppb]BF_4 each providing an approximately 2:1 ratio of trans/cis products in CH_2Cl_2. Interestingly, use of a coordinating solvent led to much greater selectivity, but now favored attack from the *β*-face. Thus, the use of [Rh(COD)dppb]BF_4 in DMF gave a 12:1 ratio of trans/cis products, affording **16** in 77% isolated yield.

Elimination of the oxazolidinone (which could be recovered in 96% yield) with LDA followed by reduction of the cyclopentenone with DIBAL occurred primarily (7:1 dr) from the face opposite the benzyloxymethyl group to give *cis*-cyclopentenol **17**.[22] Sodium borohydride/cerium(III) chloride was less selective (4:1 dr). Treatment of **17** with ethyl chloroformate gave allylic carbonate **18**, the key intermediate for the synthesis of both carbovir and aristeromycin, in high yield and 98% ee (Chiralcel OD HPLC analysis). Palladium-catalyzed amination of carbonate **18** with 2-amino-6-chloropurine proceeded in good yield, giving 63% of **19** (96% ee by Chiralcel OD HPLC analysis), along with 20% of the N7 isomer,[23] which was easily separated. Debenzylation (BCl_3) of **19**, followed by conversion of the chloropurine to guanine, completed the synthesis of (+)-carbovir.

Palladium-catalyzed coupling of carbonate **18** with adenine gave a 3.5:1 mixture of N9:N7 regioisomers, providing **21** in 65% isolated yield. Cis-dihydroxylation of compounds of this type proceed with limited facial bias.[24] In some systems, the use of RuO_4 has overcome this problem,[25] while in others varying the solvent used for osmylations has provided high stereoselectivity.[26] Initial attempts to dihydroxylate **21** by catalytic osmylation proceeded with almost no selectivity and generally

(15) Seebach, D. In *Houben-Weyl Methoden der Organischen Chemie*; Muller, E., Ed.; Georg Thieme Verlag: Stuttgart, Germany, 1971; Vol. IV, pp 192−196.
(16) Kusaka, T.; Yamamoto, H.; Shibata, M.; Muroi, M.; Kishi, T.; Mizuno, K. *J. Antibiot.* **1968**, *34*, 359.
(17) Vince, R.; Hua, M. *J. Med. Chem.* **1990**, *33*, 17.
(18) Trost, B. M.; Madsen, R.; Guile, S. G.; Elia, A. E. H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1569.
(19) Akiba, T.; Tamura, O.; Terashima, S. *Org. Synth.* **1998**, *75*, 45.
(20) For a review of substrate directed hydrogenations, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem Rev.* **1993**, *93*, 1307 and references therein.
(21) Crabtree, R. H.; Davis, M. W. *Organometallics* **1983**, *2*, 681.
(22) For an efficient synthesis of unprotected **17**, see: Hodgson, D. M.; Witherington, J.; Moloney, B. A. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3373.
(23) The same yield and N9/N7 ratio had been observed in the closely related coupling of the dicarbonate of **18**. See: Nokami, J.; Matsumura, H.; Nakashima, K.; Shibata, S. *Chem. Lett.* **1994**, 1071.
(24) For some rationalizations of OsO_4 selectivity, see: (a) Katagiri, N.; Ito, Y,; Kitano, K.; Toyota, A.; Kaneko, C. *Chem. Pharm. Bull.* **1994**, *42*, 2653. (b) Poli, G. *Tetrahedron Lett.* **1989**, *30*, 7385.
(25) Mulvihill, M. J.; Miller, M. J. *Tetrahedron* **1998**, *54*, 6605.
(26) Tokoro, Y.; Kobayashi, Y. *Chem. Commun.* **1999**, 807.

Scheme 1

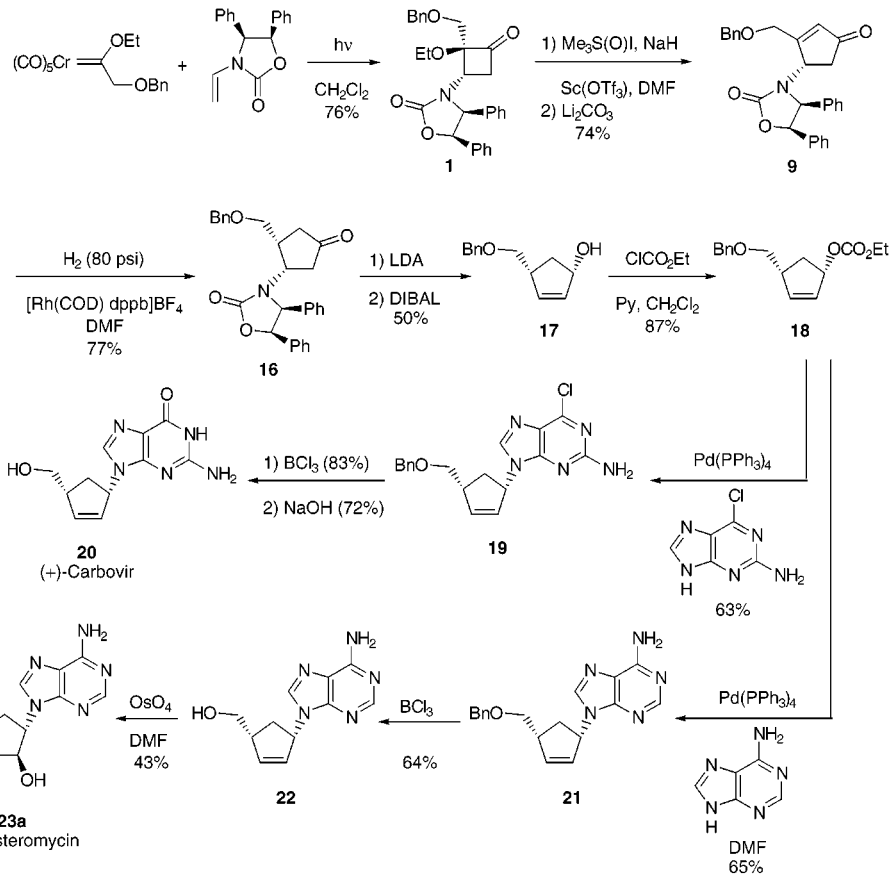
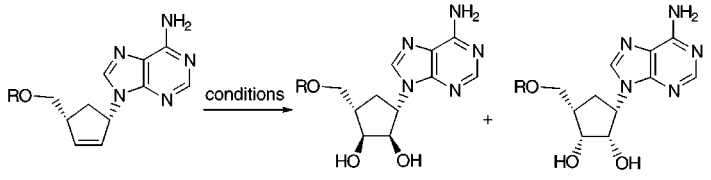


Table 2



compd	conditions	**24a**:**b**	compd	conditions	**23a**:**b**
21	K_2OsO_4, NMO acetone/MeOH/H_2O	1.1:1.0	**22**	K_2OsO_4, NMO THF/H_2O (30:1), 10 °C	1.0:1.6
	K_2OsO_4, NMO, MeCN/THF/*t*-BuOH/H_2O	1.1:1.0		OsO_4, NMO, THF/H_2O (30:1), 10 °C	1.2:1.0
	AD Mix-α *t*-BuOH/H_2O	1.0:4.0		AD Mix-α *t*-BuOH/H_2O	1.0:2.4
	AD Mix-*β* *t*-BuOH/H_2O	1.0:3.3		AD Mix-*β* *t*-BuOH/H_2O	1.0:1.4
	OsO_4 (1.1 equiv), CH_2Cl_2, 25 °C	1.0:1.8		OsO_4 (1.1 equiv), DMF, −15 °C	2.3:1.0 (81%)

favored the undesired all-cis compound (Table 2). Trost reported a 2.4:1 ratio of trans/cis diols by catalytic osmylation of **22** in THF/H_2O.[27] Therefore, **21** was deprotected with BCl_3 to afford alcohol **22**. Unfortunately, in our hands dihydroxylation of **22** under these conditions provided only a 1.2:1 ratio favoring aristeromycin over its 2′,3′-bis-epimer. Further examination of reaction conditions, however, did provide aristeromycin as the major isomer in an improved 2.3:1 ratio through the use of 1.2 equiv of OsO_4 in DMF, delivering the racemic target compound in 55% isolated yield (the nonracemic run yielded 43% of (+)-aristeromycin).

The nonracemic syntheses followed similarly to the racemic series, except that (+)-aristeromycin (94% ee by Chiralpak AD analysis of its 3′,5′-(1,1,3,3-tetraisopropyldisiloxane) derivative of **23a**) remained contaminated with 10% of an unidentified impurity.

Although this study provided the inactive enantiomers of these analogues, it detailed a method for the formation of "unnatural" L-nucleosides. Analogues of this configuration are becoming increasingly important, since a number of these derivatives are more potent and less toxic than their D-counterparts,[28] and relatively few approaches toward these compounds have been described.[29]

(27) Trost, B. M.; Li, L.; Guile, S. D. *J. Am. Chem. Soc.* **1992**, *114*, 8745.

(28) Schinazi, R. F.; Chu, C. K.; Peck, A.; McMillan, A.; Mathis, R.; Cannon, D.; Jeong, L. S.; Beach, J. W.; Choi, W. B.; Yeola, S.; Liotta, D. C. *Antimicrob. Agents Chemother.* **1992**, *36*, 672.

Experimental Section

General Methods. Compounds **4**,[6] **11a**,[30] **11b**,[31] **11c**,[30] and **11e**[30] were prepared by the published methods. THF was distilled from sodium−benzophenone ketyl; CH_2Cl_2, DMF, and Et_3N were distilled from CaH_2. ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) were recorded in $CDCl_3$ except where noted, and chemical shifts are given in ppm relative to Me_4Si (0 ppm, ^1H), $CDCl_3$ (77.0 ppm, ^{13}C). Column chromatography was performed with ICN 32−63 nm, 60 Å silica gel using flash column techniques. Elemental analyses were performed by M−H−W Laboratories, Phoenix, AZ. All reactions were performed under an atmosphere of Ar unless otherwise noted.

Cyclobutanone 1. A solution of (benzyloxymethyl)(ethoxy)-pentacarbonylchromium (9.29 g, 24.7 mmol) and (4*S*,5*R*)-oxazolidinone **1** (10.0 g, 37.7 mmol) in CH_2Cl_2 (82 mL, degassed) in a Pyrex pressure tube was placed under CO (∼80 psi), cooled to −35 °C, and irradiated with a 450 W Hg-vapor lamp for 6 days. Concentration of the crude reaction mixture followed by removal of $Cr(CO)_6$ by sublimation gave 15.9 g of a light green solid. Purification by flash chromatography (80% Hex/CH_2Cl_2 to 25% EtOAc/Hex gradient elution) provided 2.82 g of recovered oxazolidinone **1** (10.6 mmol) as a white solid and cyclobutanone **1** (8.13 g, 17.2 mmol, 70%) as a white foam: ^1H NMR δ 7.38−7.50 (m, 5H), 6.97−7.10 (m, 6H), 6.74−6.80 (m, 2H), 6.54 (br s, 2H), 5.59 (d, J = 7.5 Hz, 1H), 5.03 (d, J = 7.5 Hz, 1H), 4.81 (t, J = 10.2 Hz, 1H), 4.70 (d, J = 11.1 Hz, 1H), 4.55 (d, J = 11.1 Hz, 1H), 4.06 (d, J = 9.0 Hz, 1H), 3.7 (d, J = 9.0 Hz, 1H), 3.75 (m, 2H), 2.71 (dd, J = 18, 9.6 Hz, 1H), 2.45 (dd, J = 10.6, 18 Hz, 1H), 1.23 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.4, 158.5, 137.2, 135.5, 133.6, 128.7, 128.3, 128.1, 128.0, 127.9, 127.7, 126.7, 125.9, 97.7, 80.3, 74.4, 69.0, 64.8, 61.6, 48.0, 46.1, 15.6; IR (film) 1791, 1752 cm^{-1}; $[\alpha]_D$ +42.4 (*c* 1.0, $CHCl_3$).

Cyclopentanones 2/3. Freshly prepared CH_2N_2 was bubbled through a 0 °C solution of cyclobutanone **1** (39.0 mg, 0.0827 mmol) in 1:1 THF/DMF (1.4 mL), and the yellow solution was allowed to stand for 2.5 h. Evaporation and flash chromatographic purification (20−33% EtOAc/Hex gradient elution) provided cyclopentanones **2** (23.7 mg, 0.0488 mmol, 59%) and **3** (8.2 mg, 0.017 mmol, 20%) as clear films. **2**: ^1H NMR δ 7.43−7.34 (m, 5H), 7.15−6.95 (m, 7H), 6.85−6.77 (m, 3H), 5.57 (d, 7.2 Hz, 1H), 4.99 (d, J = 7.2 Hz, 1H), 4.95 (dd, J = 7.8, 11.1 Hz, 1H), 4.64 (d, J = 11.7 Hz, 1H), 4.47 (d, J = 11.7 Hz, 1H), 3.98 (d, J = 9.0 Hz, 1H), 3.81 (quin, J = 6.9 Hz, 1H), 3.73 (d, J = 9.3 Hz, 1H), 3.32 (quin, J = 6.9 Hz, 1H), 2.32 (ddd, J = 2.4, 9.0, 19.5 Hz, 1H), 2.08 (dt, J = 9.9, 19.5 Hz, 1H), 1.78 (m, 1H), 1.62 (m, 1H), 1.20 (t, J = 6.9 Hz, 3H); ^{13}C NMR δ 215.0, 158.6, 136.9, 136.4, 133.6, 128.7, 128.3, 128.1, 127.9, 127.7, 126.1, 84.1, 80.6, 74.6, 71.7, 64.1, 59.9, 54.7, 36.7, 22.3, 15.5; IR (film) 1751 cm^{-1}; mp 181−183 °C. Anal. Calcd for $C_{30}H_{31}NO_5$: C, 74.21; H, 6.43; N, 2.88. Found: C, 74.17; H, 6.49; N, 2.86. **3**: ^1H NMR δ 7.45−7.33 (m, 6H), 7.15−6.97 (m, 7H), 6.75−6.70 (m, 2H), 5.51 (d, J = 7.3 Hz, 1H), 4.98 (dd, J = 7.6, 8.5 Hz, 1H), 4.71 (d, J = 7.3 Hz, 1H), 4.66 (d, J = 11.4 Hz, 1H), 4.56 (d, J = 11.4 Hz, 1H), 4.05 (d, J = 9.5 Hz, 1H), 3.70−3.67 (m, 2H), 3.55 (quin, J = 7.0 Hz, 1H), 2.70 (dd, J = 1.0, 18.6 Hz, 1H), 2.57 (d, J = 18.6 Hz, 1H), 2.23 (dd, J = 8.5, 18.2 Hz, 1H), 2.08 (ddd, J = 1.0, 7.6, 18.2 Hz, 1H), 1.18 (t, J = 6.9, 3H); ^{13}C NMR δ 211.5, 158.6, 137.0, 135.9, 133.5, 128.8, 128.3, 128.2, 127.9, 126.0, 83.7, 80.4, 74.4, 71.8, 63.8, 58.6, 55.3, 44.9, 40.8, 15.8; IR (film) 1748 cm^{-1}; mp 145−147 °C; HRMS *m*/*z* (M + H) calcd 486.2280, obsd 486.2281.

Alternatively, **3** was prepared in 73% from cyclobutanone **1** using the ring-expansion procedure described below.

Cyclopentanones 5/6. Freshly prepared CH_2N_2 was bubbled through a 0 °C solution of cyclobutanone **4** (98.9 mg, 0.231 mmol) in THF (1 mL), and the yellow solution was allowed to stand overnight with gradual warming. Evaporation and flash chromatographic purification (20% EtOAc/Hex) provided cyclopentanone **5** (31.6 mg, 0.072 mmol, 31%) as a clear gum and **6** (47.2 mg, 0.107 mmol, 46%) as a white solid. **5**: ^1H NMR δ 7.37−7.25 (m, 5H), 7.12−7.03 (m, 6H), 6.95−6.85 (m, 4H), 5.59 (d, J = 8.0 Hz, 1H), 5.03 (d, J = 8.0 Hz, 1H), 4.44−4.34 (m, 3H), 3.77−3.72 (m, 2H), 2.92 (m, 1H), 2.32 (m, 1H), 2.16−2.02 (m, 2H), 1.67−1.55 (m, 1H); ^{13}C NMR δ 213.2, 158.0, 137.8, 135.7, 134.3, 128.5, 128.4, 128.3, 128.2, 127.9, 127.8, 127.7, 126.0, 80.0, 73.6, 67.8, 63.7, 55.9, 51.4, 37.4, 25.4; IR (film) 1746 cm^{-1}; mp 129−130 °C. Anal. Calcd for $C_{28}H_{27}NO_4$: C, 76.16; H, 6.18; N, 3.17. Found: C, 76.40; H, 6.36; N, 3.17. **6**: ^1H NMR δ 7.40−7.26 (m, 5H), 7.09−7.03 (m, 6H), 6.91−6.83 (m, 4H), 5.58 (d, J = 8.0 Hz, 1H), 5.00 (d, J = 8.0 Hz, 1H), 4.50 (d, J = 11.7 Hz, 1H), 4.45 (d, J = 11.7 Hz, 1H), 4.43−4.33 (m, 1H), 3.63−3.59 (m, 2H), 2.87 (m, 1H), 2.53 (dd, J = 8.4, 18.3 Hz, 1H), 2.38 (dd, J = 7.7, 18.3 Hz, 1H), 2.10 (dd, J = 9.9, 18.7 Hz, 1H), 1.98 (ddd, J = 1.9, 11.0, 18.7 Hz, 1H); ^{13}C NMR δ 212.6, 158.1, 137.7, 135.3, 134.1, 128.6, 128.4, 128.3, 127.9, 127.8, 127.6, 126.1, 126.0, 80.1, 73.6, 71.1, 63.4, 54.9, 42.7, 41.0, 39.9; IR (film) 1748 cm^{-1}; mp 125−126 °C. Anal. Calcd for $C_{28}H_{27}NO_4$: C, 76.16; H, 6.18; N, 3.17. Found: C, 76.08; H, 6.26; N, 3.17.

Cyclobutanol 7a. Following the method of Trost,[12b] BuLi (1.6 M/Hex, 0.153 mL, 0.242 mmol) was added dropwise to a −78 °C solution of $PhSO_2Me$ (38 mg, 0.242 mmol) in THF (1.2 mL) and stirred for 20 min. A solution of **1** (103 mg, 0.218 mmol) in THF (1.0 mL) was added dropwise and stirred for 5.5 h. The reaction was quenched with saturated NH_4Cl (10 mL) and extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4) and concentrated to give 137 mg of white foam. Flash chromatography provided **7a** as a white solid (75.0 mg, 0.122 mmol, 56%): ^1H NMR δ 7.87 (d, J = 7.1 Hz, 2H), 7.65−7.35 (m, 8H), 7.11−6.91 (m, 6H), 6.83−6.71 (m, 2H), 6.52 (br s, 2H), 5.52 (d, J = 7.4 Hz, 1H), 4.99 (d, J = 7.4 Hz, 1H), 4.69 (d, J = 11.3 Hz, 1H), 4.63 (d, J = 11.3 Hz, 1H), 4.22 (t, J = 10.1 Hz, 1H), 4.04 (d, J = 10.4 Hz, 1H), 3.95 (d, J = 10.4 Hz, 1H), 3.91 (br s, 1H), 3.85 (dd, J = 7.0, 8.8 Hz, 1H) 3.60−3.46 (m, 2H), 3.39 (d, J = 13.1 Hz, 1H), 2.42 (dd, J = 9.9, 13.1 Hz, 1H), 1.73 (br t, J = 11 Hz, 1H), 1.15 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ 158.1, 141.2, 136.9, 135.6, 133.6, 133.5, 129.1, 128.9, 128.5, 128.2, 128.0, 127.8, 126.0, 87.5, 80.4, 74.5, 73.5, 68.2, 64.6, 60.6, 59.8, 50.2, 34.8, 15.8; IR (film) 3484, 1746 cm^{-1}.

Cyclobutanol 7b. Following Gadwood's general procedure,[12c] LDA (0.72 M/THF, Hex, 0.19 mL, 0.14 mmol) was added dropwise to a −78 °C solution of *o*-chlorophenyl methylsulfoxide (25 mg, 0.14 mmol) in THF (0.75 mL) and stirred for 15 min. A solution of **1** (57 mg, 0.12 mmol) in THF (0.40 mL) was added dropwise, stirred at −78 °C for 10 min, and allowed to warm to room temperature. The mixture was diluted with saturated NH_4Cl (10 mL) and extracted with CH_2Cl_2. The organic extract was washed with brine, dried ($MgSO_4$), and concentrated to give 61 mg of a milky gum. Gadwood reports using the crude product directly. However, the following reaction failed and **7b** was isolated after flash chromatography (30−50% EtOAc/Hex) of the reaction mixture as a yellow gum (12.3 mg): ^1H NMR δ 7.95−7.84 (m, 1H), 7.61−7.33 (m, 8H), 7.17−7.00 (m, 6H), 6.83−6.71 (m, 2H), 6.63 (br s, 2H), 5.53 (d, J = 7.5 Hz, 1H), 5.03 (d, J = 7.5 Hz, 1H), 4.50 (s, 2H), 4.47 (br s, 1H), 4.29 (t, J = 10.2 Hz, 1H), 4.10 (d, J = 10.8 Hz, 1H), 4.04 (d, J = 10.8 Hz, 1H), 3.85 (dq, J = 7.0, 9.0 Hz, 1H), 3.62 (dq, J = 7.1, 9.0 Hz, 1H), 3.38 (d, J = 13.8 Hz, 1H), 2.97 (dd, J = 2.0, 13.8 Hz, 1H), 2.31 (dd, J = 9.7, 12.6 Hz, 1H), 1.88 (ddd, J = 2.0, 10.5, 12.6 Hz, 1H), 1.12 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ 158.1, 141.6, 137.4, 136.1, 133.7, 132.3, 129.9, 129.6, 128.8, 128.3, 127.9, 126.1, 125.9, 87.5, 80.3, 74.9, 74.5, 68.6, 64.5, 60.9, 59.3, 50.6, 35.1, 15.9; IR (film) 3319, 1748 cm^{-1}.

Epoxide 8. A suspension of $Me_3S(O)I$ (101 mg, 0.457 mmol) and NaH (60 wt % in mineral oil, 18.4 mg, 0.460 mmol) in DMF (2.5 mL) was stirred for 10 min and cooled to 0 °C. A solution of **1** (202 mg, 0.43 mmol) in DMF (2.0 mL) was added dropwise, and the mixture was stirred for 2.5 h and allowed to warm slightly, at which time the bath was removed. After another 20 h, the mixture was diluted with H_2O (10 mL) and extracted with CH_2Cl_2. The organic phase was washed with brine (10 mL), dried (Na_2SO_4), and concentrated to give 0.35

(29) For a synthesis of L-carbocyclic nucleosides starting from D-glucose, see: Wang, P.; Agrofoglio, L. A.; Chu, C. K. *Tetrahedron Lett.* **1997**, *38*, 4207.

(30) Reeder, L. M.; Hegedus, L. S. *J. Org. Chem.* **1999**, *64*, 3306.

(31) Soderburg, B. C.; Hegedus, L. S.; Sierra, M. A. *J. Am. Chem. Soc.* **1990**, *112*, 4364.

g of brown oil. Flash chromatography (CH_2Cl_2 to 1% MeOH/CH_2Cl_2) provided 0.131 g of **8** as a white solid (0.270 mmol, 63%): ^{1}H NMR δ 7.55−7.35 (m, 5H), 7.10−6.93 (m, 6H), 6.79−6.71 (m, 2H), 6.51 (br s, 2H), 5.55 (d, J = 7.5 Hz, 1H), 5.10 (d, J = 7.5 Hz, 1H), 4.78 (d, H=11.0 Hz, 1H), 4.65 (d, J = 11.0 Hz, 1H), 4.63 (t, J = 10.2 Hz, 1H), 4.00 (d, J = 10.0 Hz, 1H), 3.86 (dq, J = 7.1, 8.7 Hz, 1H), 3.76 (d, J = 10.0 Hz, 1H), 3.75 (dq, J = 7.0, 8.7 Hz, 1H), 2.95 (d, J = 5.4 Hz, 1H), 2.63 (d, J = 5.4 Hz, 1H), 2.12 (dd, J = 10.2, 12.9 Hz, 1H), 1.82 (dd, J = 10.0, 12.9 Hz, 1H), 1.20 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ 158.2, 138.0, 136.3, 133.9, 128.7, 128.1, 127.8, 126.8, 126.0, 86.8, 80.3, 74.5, 69.2, 64.5, 60.5, 49.7, 49.0, 29.9, 15.9; IR (film) 1750 cm^{-1}; mp 134−136 °C.

Cyclobutanone 11d. According to the published general procedure,[30] a solution of pentacarbonyl[(methyl)(methoxy)-carbene]chromium(0) (0.500 g, 2.00 mmol) and *cis*-4,5-diphenyl-3-vinyl-2-oxazolidinone (0.796 g, 3.00 mmol) in CH_2Cl_2 (20 mL, degassed) was placed under CO (80 psi) and irradiated (450 W Hg vapor lamp) for 6.5 h at 35 °C. The mixture was concentrated, triturated with MeOH, and filtered to remove $Cr(CO)_6$. Purification of the crude tan solid by flash chromatography (2% EtOAc/CH_2Cl_2) afforded **11d** as a white solid (0.329 g, 0.937 mmol, 47%): ^{1}H NMR δ 7.17−7.04 (m, 6H), 7.03−6.95 (m, 2H), 6.89−6.80 (m, 2H), 5.93 (d, J = 7.4 Hz, 1H), 5.10 (d, J = 7.4 Hz, 1H), 4.54 (t, J = 9.8 Hz, 1H), 3.40 (s, 3H), 2.92 (dd, J = 9.3, 18.1 Hz, 1H), 2.58 (dd, J = 10.2, 18.1 Hz, 1H), 1.53 (s, 3H); ^{13}C NMR δ 205.9, 158.2, 134.5, 133.5, 128.6, 128.2, 127.9, 127.1, 126.0, 96.1, 80.2, 65.8, 52.8, 48.5, 43.5, 14.5; IR (film) 1789, 1738 cm^{-1}; mp 186−187 °C. Anal. Calcd for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.46; H, 6.15; N, 3.85.

Cyclobutanone 11f. A solution of pentacarbonyl[(tetrahydrofuran-2-yl)carbene]chromium (0)[32] (1.09 g, 4.15 mmol) and *cis*-4,5-diphenyl-3-vinyl-2-oxazolidinone (1.65 g, 6.23 mmol) in CH_2Cl_2 (20 mL, degassed) was treated as above for 2 days. Workup and flash chromatographic purification (30 to 40% EtOAc/Hex gradient elution) provided **11f** as a white solid (0.732 g, 2.01 mmol, 49%): ^{1}H NMR δ 7.15−7.09 (m, 6H), 7.03−6.97 (m, 2H), 6.90−6.85 (m, 2H), 5.96 (d, J = 7.6 Hz, 1H), 5.06 (d, J = 7.6 Hz, 1H), 4.31 (t, J = 9.9 Hz, 1H), 3.99 (dd, J = 7.0, 13.5 Hz, 1H), 3.86 (dd, J = 7.7, 13.5 Hz, 1H), 3.06 (dd, J = 9.5, 17.6 Hz, 1H), 2.61 (dd, J = 9.9, 17.6 Hz, 1H), 2.30−2.11 (m, 2H), 2.07−1.94 (m, 2H); ^{13}C NMR δ 207.8, 157.8, 134.4, 133.7, 128.7, 128.5, 128.1, 128.0, 127.4, 125.9, 99.4, 80.1, 70.1, 66.4, 51.5, 43.4, 28.4, 25.9; IR (film) 1792, 1745 cm^{-1}; mp 194−195 °C. Anal. Calcd for $C_{22}H_{21}NO_4$: C, 72.71; H, 5.82; N, 3.85. Found: C, 72.83; H, 5.80; N, 3.87.

General Procedure for the Ring Expansion of Cyclobutanones. A suspension of NaH (60 wt %, 1.2 mmol) and $Me_3S(O)I$ (1.3 mmol) in DMF (5 mL) was stirred for 30 min at room temperature and cooled to 0 °C. A solution of cyclobutanone in DMF (5 mL) was added slowly (5−30 min). The ice bath was removed, and the mixture was stirred for 15 min. Solid $Sc(OTf)_3$ (0.25 mmol) was added to the reaction and allowed to react for 10 min, at which point the mixture was heated to 50 °C for 4−5 h. The mixture was diluted with H_2O (40 mL) and extracted with Et_2O. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a yellow solid. Purification by flash chromatography gave the desired products.

Cyclopentanone 12a. From cyclobutanone **11a** (42.1 mg, 0.191 mmol), flash chromatography (15% EtOAc/Hex) afforded **12a** (29.0 mg, 0.124 mmol, 65%) as a clear oil: ^{1}H NMR δ 7.39−7.30 (m, 5H), 4.61 (d, J = 11.9 Hz, 1H), 4.50 (d, J = 11.9 Hz, 1H), 3.98 (m, 1H), 3.21 (s, 3H), 2.61 (dd, J = 5.5, 18.3 Hz, 1H), 2.47−2.31 (m, 3H), 1.43 (s, 3H); ^{13}C NMR δ 215.0, 137.9, 128.4, 127.7, 127.6, 82.9, 80.9, 71.5, 50.0, 47.1, 42.8, 16.8; IR (film) 1748 cm^{-1}; HRMS m/z (M + H) calcd 234.1256, obsd 234.1254.

Cyclopentenone 13a: ^{1}H NMR δ 7.39−7.30 (m, 5H), 5.99 (s, 1H), 4.67 (d, J = 11.7 Hz, 1H), 4.54 (m, 2H), 2.67 (dd, J = 5.9, 18.0 Hz, 1H), 2.39 (dd, J = 2.2, 18.0 Hz, 1H), 2.16 (s, 3H); ^{13}C NMR δ 205.2, 175.7, 137.5, 132.0, 128.5, 128.0, 127.8, 78.7, 72.1, 42.3, 16.2; IR (film) 1712 cm^{-1}.

Cyclopentanone 12b/Cyclopentenone 13b. From cyclobutanone **11b** (42.1 mg, 0.221 mmol), flash chromatography (8−12% EtOAc/Hex gradient elution) afforded **12b** (32.1 mg, 0.157 mmol, 71%) as a clear oil and **13b** as a clear film (3.5 mg, 0.020 mmol, 9%). **12b**: ^{1}H NMR δ 7.36−7.22 (m, 3H), 7.21−7.15 (m, 2H), 3.62 (dd, J = 6.6, 8.4 Hz, 1H), 3.28 (s, 3H), 2.87 (ddd, J = 1.1, 8.6, 18.3 Hz, 1H), 2.59 (dd, J = 6.2, 18.3 Hz, 1H), 2.55 (d, J = 18.0 Hz, 1H), 2.42 (dd, J = 1.1, 18.0 Hz, 1H), 1.01 (s, 3H); ^{13}C NMR δ 216.2, 139.9, 128.4, 128.1, 127.3, 127.0, 83.1, 50.4, 50.0, 48.8, 43.1, 19.1; IR (film) 1744 cm^{-1}; HRMS m/z (M + H) calcd 204.1150, obsd 204.1150. **13b**: ^{1}H NMR δ 7.37−7.22 (m, 3H), 7.14−7.09 (m, 2H), 6.09 (m, 1H), 3.90 (d, J = 7.0 Hz, 1H), 2.93 (dd, J = 7.3, 18.7 Hz, 1H), 2.40 (dd, J = 2.2, 18.7 Hz, 1H), 1.91 (s, 3H); ^{13}C NMR δ 208.9, 180.1, 141.2, 131.2, 129.0, 127.2, 50.6, 45.7, 17.6; IR (film) 1710 cm^{-1}; HRMS m/z (M + H) calcd 173.0966, obsd 173.0964.

Cyclopentanone 12c. From cyclobutanone **11c** (45.3 mg, 0.206 mmol), flash chromatography (15 to 33% EtOAc/Hex gradient elution) afforded **12c** (31.6 mg, 0.135 mmol, 66%) as a clear oil: ^{1}H NMR δ 7.10 (d, J = 8.8 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 3.80 (s, 3H), 3.57 (t, J = 7.7 Hz, 1H), 3.28 (s, 3H), 2.85 (dd, J = 8.8, 18.7 Hz, 1H), 2.54 (dd, J = 7.7, 18.7 Hz, 1H), 2.53 (d, J = 19.1 Hz, 1H), 2.41 (dd, J = 1.1, 19.1 Hz, 1H), 1.01 (s, 3H); ^{13}C NMR δ 216.3, 158.5, 131.9, 129.0, 113.7, 83.1, 55.2, 50.5, 49.2, 48.8, 43.3, 19.0; IR (film) 1743 cm^{-1}.

Cyclopentenone 13c: ^{1}H NMR δ 7.04 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.5 Hz, 2H), 6.03 (m, 1H), 3.86 (d, J = 6.9 Hz, 1H), 3.80 (s, 3H), 2.91 (dd, J = 7.0, 18.7 Hz, 1H), 2.37 (dd, J = 2.2, 18.7 Hz, 1H), 1.90 (s, 3H); ^{13}C NMR δ 209.1, 180.4, 158.7, 133.1, 131.0, 128.2, 114.3, 55.2, 49.9, 45.8, 17.6; IR (film) 1706 cm^{-1}; mp 98−99 °C.

Cyclopentanone 12d. From cyclobutanone **11d** (44.4 mg, 0.126 mmol), flash chromatography (35% EtOAc/Hex) afforded **12d** (36.6 mg, 0.100 mmol, 79%) as a white solid: ^{1}H NMR δ 7.15−7.06 (m, 6H), 6.99−6.92 (m, 2H), 6.86−6.79 (m, 2H), 5.84 (d, J = 7.4 Hz, 1H), 4.86 (d, J = 7.4 Hz, 1H), 4.55 (dd, J = 5.3, 9.0 Hz, 1H), 3.22 (s, 3H), 2.55 (m, 2H), 2.48 (dd, J = 9.0, 19.0 Hz, 1H), 2.09 (dd, J = 5.3, 19.0 Hz, 1H), 1.48 (s, 3H); ^{13}C NMR δ 212.6, 158.4, 135.0, 133.6, 128.8, 128.5, 128.1, 128.0, 127.9, 127.4, 126.2, 126.1, 126.0, 83.4, 80.3, 65.4, 57.1, 50.3, 48.8, 40.7, 18.5; IR (film) 1743 cm^{-1}; mp 186−188 °C. Anal. Calcd for $C_{22}H_{23}NO_4$: C, 72.31; H, 6.34; N, 3.83. Found: C, 72.10; H, 6.21; N, 3.83.

Cyclopentenone 13d: ^{1}H NMR δ 7.15−7.05 (m, 6H), 7.00−6.94 (m, 2H), 6.92−6.83 (m, 2H), 6.11 (m, 1H), 5.86 (d, J = 8.0 Hz, 1H), 4.88 (m, 1H), 4.81 (d, J = 8.0 Hz, 1H), 2.50 (dd, J = 7.4, 18.3 hz, 1H), 2.23 (s, 3H), 2.12 (dd, J = 2.9, 18.3 Hz, 1H); ^{13}C NMR δ 203.9, 173.1, 157.7, 134.7, 133.9, 133.4, 128.6, 128.3, 128.0, 127.7, 125.9, 80.3, 63.5, 56.7, 39.4, 16.6; IR (film) 1752, 1710 cm^{-1}; mp 163−166 °C. Anal. Calcd for $C_{21}H_{19}NO_3$: C, 75.66; H, 5.74; N, 4.20. Found: C, 75.74; H, 5.87; N, 4.09.

Cyclopentanone 12e. From cyclobutanone **11e** (42.9 mg, 0.278 mmol), flash chromatography (7% EtOAc/Hex gradient elution) afforded **12e** (31.6 mg, 0.188 mmol, 68%) as a clear oil: ^{1}H NMR δ 3.20 (s, 3H), 2.82 (td, J = 3.3, 9.8 Hz, 1H), 2.70 (m, 1H), 2.44 (dt, J = 1.8, 18.3 Hz, 1H), 2.22 (d, J = 18.3 Hz, 1H), 2.10−1.94 (m, 1H), 1.94−1.81 (m, 1H), 1.78−1.62 (m, 2H), 1.62−1.45 (m, 1H), 1.34 (s, 3H), 1.29−1.10 (m, 1H); ^{13}C NMR δ 221.3, 80.7, 52.3, 51.4, 49.4, 46.6, 29.7, 29.2, 26.9, 18.8; IR (film) 1741 cm^{-1}; HRMS m/z (M + H) calcd 168.1150, obsd 168.1151.

Cyclopentanone 12f/Cyclopentenone 13f. From cyclobutanone **11f** (44.7 mg, 0.123 mmol), flash chromatography (30% EtOAc/Hex to 5% MeOH/CH_2Cl_2 gradient elution) afforded **12f** (25.0 mg, 0.0662 mmol, 54%) and **13f** (12.5 mg, 0.0312 mmol, 25%) as white solids. **12f**: ^{1}H NMR δ 7.15−7.05 (m, 6H), 6.99−6.92 (m, 2H), 6.87−6.77 (m, 2H), 5.83 (d, J = 7.7 Hz, 1H), 4.81 (d, J = 7.7 Hz, 1H), 4.45 (dd, J = 2.2, 8.6 Hz, 1H), 3.83 (m, 2H), 2.70 (d, J = 19.0 Hz, 1H), 2.68 (dd, J = 8.5, 19.0 Hz, 1H), 2.45 (d, J = 19.0 Hz, 1H), 2.35−2.25 (m, 1H), 2.20−1.92 (m, 4H); ^{13}C NMR δ 213.3, 158.4, 134.8, 133.6, 128.8, 128.5, 128.1, 128.0, 127.4, 125.9, 89.6, 80.3, 67.8, 65.2, 58.5, 49.2, 41.7, 31.1, 25.9; IR (film) 1735 cm^{-1}; mp 184−186 °C.

(32) Betschart, C.; Hegedus, L. S. *J. Am. Chem. Soc.* **1992**, *114*, 5010.

Anal. Calcd for $C_{23}H_{23}NO_4$: C, 73.19; H, 6.14; N, 3.71. Found: C, 72.91; H, 6.02; N, 3.76. **13f**: ^{1}H NMR δ 7.15−7.05 (m, 6H), 7.01−6.93 (m, 2H), 6.90−6.83 (m, 2H), 6.13 (m, 1H), 5.90 (d, J = 8.0 Hz, 1H), 5.01 (m, 1H), 4.81 (d, J = 8.0 Hz, 1H), 3.78 (t, J = 5.8 Hz, 2H), 2.76 (m, 1H), 2.54−2.41 (m, 2H), 2.11 (dd, J = 3.3, 18.7 Hz, 1H), 2.02−1.87 (m, 4H); ^{13}C NMR δ 203.9, 177.2, 158.0, 134.8, 133.7, 132.0, 128.8, 128.6, 128.0, 127.7, 125.9, 80.5, 63.2, 61.3, 55.7, 39.2, 29.7, 26.4; IR (film) 3448, 1749, 1716, 1687 cm^{-1}; mp 127−129 °C.

Cyclopentenone 9. Following the general procedure, cyclobutanone **1** (0.500 g, 1.06 mmol) was ring-expanded to provide the cyclopentanone **3** as a white solid (0.375 g, 0.772 mmol, 73%) and cyclopentenone **9** as a clear film (15.6 mg, 0.0355 mmol, 3.3%). To a solution of **3** in THF (2.2 mL) and MeOH (4.5 mL) was added Li_2CO_3 (71 mg, 0.96 mmol). The resulting suspension was stirred for 2.5 h. It was then diluted with saturated NH_4Cl (15 mL) and extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and concentrated to give a yellow gum. Flash chromatographic purification (33% EtOAc/Hex) provided cyclopentenone **9** as a white foam (0.327 g, 0.744 mmol, 96%; 0.343 g, 0.780 mmol, 74% over two steps): ^{1}H NMR δ 7.45−7.30 (m, 5H), 7.15−7.00 (m, 6H), 6.90−6.75 (m, 4H), 6.37 (m, 1H), 5.56 (d, J = 8.2 Hz, 1H), 5.09 (m, 1H), 4.73 (d, J = 8.2 Hz, 1H), 4.68 (AB, J = 11.9 Hz, 2H), 4.43 (AB, J = 16.5 Hz, 2H), 2.49 (dd, J = 7.2, 18.7 Hz, 1H), 2.10 (dd, J = 3.0, 18.7 Hz, 1H); ^{13}C NMR δ 203.4, 172.0, 157.8, 137.0, 134.8, 133.8, 133.0, 128.8, 128.6, 128.2, 127.9, 127.6, 125.9, 80.2, 73.6, 67.2, 63.2, 54.2, 39.3; IR (film) 1754, 1718, 1632 cm^{-1}; mp 123−125 °C; $[\alpha]^{24}_D$ 38.0 (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{28}H_{25}NO_4$: C, 76.52; H, 5.73; N, 3.19. Found: C, 76.47; H, 5.46; N, 3.13.

Cyclopentanone 16. A solution of cyclopentenone **9** (0.206 mg, 0.468 mmol) and [Rh(COD)dppb]BF_4 (31 mg, 0.043 mmol) in DMF (3.0 mL) was stirred under H_2 (80 psi) for 5.5 h, at which point more catalyst was added (30 mg). The black solution was stirred for an additional 13 h and then evaporated to give a black gum. Flash chromatographic (25% EtOAc/Hex) purification provided impure **16** as a white foam (0.190 g). Recrystallization (EtOAc/Hex/MeOH) afforded pure **16** (0.139 g) as a white solid. Preparative HPLC purification (97:3 10% CH_2Cl_2/Hex/*i*-PrOH, 10 mL/min) of the mother liquor gave an additional 19.2 mg of **16** as a white solid (0.158 mg total, 0.359 mmol, 77%): ^{1}H NMR δ 7.50−7.35 (m, 4H), 7.10−7.00 (m, 6H), 6.90−6.81 (m, 3H), 6.80−6.55 (br s, 2H), 5.49 (d, J = 7.7 Hz, 1H), 4.77 (d, J = 7.7 Hz, 1H), 4.69 (d, J = 12.0 Hz, 1H), 4.61 (m, 1H), 4.47 (d, J = 12.0 Hz, 1H), 4.00 (dd, J = 2.6, 9.5 Hz, 1H), 3.59 (dd, J = 3.2, 9.5 Hz, 1H), 3.05 (m, 1H), 2.53−2.25 (m, 3H), 1.83 (dd, J = 9.2, 17.0 Hz, 1H); ^{13}C NMR δ 213.7, 158.2, 137.7, 135.5, 133.7, 128.7, 128.4, 128.2, 128.0, 126.0, 80.5, 74.1, 70.1, 64.6, 53.4, 41.5, 41.3, 38.5; IR (film) 1745 cm^{-1}; mp 138−139 °C; $[\alpha]^{24}_D$ 1.3 (*c* 1.0, CH_2Cl_2). Anal. Calcd for $C_{28}H_{27}NO_4$: C, 76.17; H, 6.16; N, 3.17. Found: C, 75.91; H, 5.93; N, 3.16.

Cyclopentenol 17. To a 0 °C solution of cyclopentanone **16** (0.241 g, 0.547 mmol) in THF (5.0 mL) was added dropwise a solution LDA (0.87 M in THF/Hex, 0.31 mL, 0.27 mmol). The reaction mixture was stirred 15 min, diluted with saturated NH_4Cl (7 mL), and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a white solid, which was dissolved in THF (4.0 mL) and cooled to −78 °C. To this solution was added dropwise a solution of DIBAL (1 M in THF, 1.30 mL, 1.30 mmol), and the resultant solution was stirred for 2 h, allowing it to slowly warm to 0 °C. The reaction mixture was quenched with 1 N HCl (15 mL) and stirred for 5 min, after which it was extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a white solid. Purification by flash chromatography (20% EtOAc/Hex) gave **17** as a clear oil (55.4 mg, 0.271 mmol, 50%): ^{1}H NMR δ 7.37−7.25 (m, 5H), 5.95 (dt, J = 2.0, 5.5 Hz, 1H), 5.82 (dd, J = 2.6, 5.5 Hz, 1H), 4.62 (d, J = 6.5 Hz, 1H), 4.55 (d, J = 11.9 Hz, 1H), 4.52 (d, J = 11.9 Hz, 1H), 3.47 (m, 2H), 2.85 (m, 1H), 2.69 (br s, 1H), 2.32 (ddd, J = 7.0, 8.6, 13.9 Hz, 1H), 1.57 (dt, J = 1.9, 13.9 Hz, 1H); ^{13}C NMR δ 137.6, 135.1, 135.0, 128.4, 127.8, 75.8, 73.4, 71.4, 44.6, 37.3; IR (film) 3414, 1712 cm^{-1}; HRMS *m*/*z* (M + H) calcd 205.1236, obsd 205.1229; $[\alpha]^{24}_D$ −34.2 (*c* 1.0, CH_2Cl_2).

Carbonate 18. Ethyl chloroformate (0.10 mL, 1.0 mmol) was added to a solution of cyclopentanol **17** (55.4 mg, 0.271 mmol) and pyridine (0.11 mL, 1.4 mmol) in CH_2Cl_2 (2.5 mL). The mixture was stirred for 20 min, quenched with saturated $NaHCO_3$ (7 mL), and extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and concentrated to give a yellow oil. Purification by flash chromatography (5% EtOAc/Hex) afforded **18** as a clear oil (65.5 mg, 0.237 mmol, 87%): ^{1}H NMR δ 7.37−7.24 (m, 5H), 6.10 (m, 1H), 5.90 (dt, J = 1.8, 5.5 Hz, 1H), 5.58 (m, 1H), 4.51 (s, 2H), 4.18 (q, J = 6.9 Hz, 2H), 3.42 (dq, J = 7.4, 9.2 Hz, 2H), 2.94 (m, 1H), 2.51 (dt, J = 8.0, 14.3 Hz, 1H), 1.64 (dt, J = 4.4, 14.3 Hz, 1H), 1.30 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ 154.8, 138.8, 138.3, 130.0, 128.4, 127.5, 82.9, 74.2, 73.1, 63.7, 44.9, 33.4, 14.2; IR (film) 1739 cm^{-1}; $[\alpha]^{24}_D$ −1.3 (*c* 1.0, $CHCl_3$).

Purine 19. A −40 °C suspension of carbonate **18** (29.0 mg, 0.105 mmol), 2-amino-6-chloropurine (19.5 mg, 0.115 mmol), and $Pd(PPh_3)_4$ (12.0 mg, 0.0104 mmol) in DMF (1.0 mL) was stirred for 3.5 h, allowing it to warm slowly to 10 °C. Concentration and flash chromatographic purification (1.5−3% MeOH/CH_2Cl_2 gradient elution) gave **19** containing a ∼10% impurity as a clear film (23.6 mg, 0.663 mmol, 63%), which was taken on without further purification: ^{1}H NMR δ 7.89 (s, 1H), 7.37−7.24 (m, 5H), 6.19 (dt, J = 1.9, 5.6 Hz, 1H), 5.85 (dt, J = 2.2, 5.6 Hz, 1H), 5.58 (m, 1H), 5.16 (br s, 2H), 4.52 (s, 2H), 3.48 (m, 2H), 3.10 (m, 1H), 2.80 (dt, J = 8.8, 14.2 Hz, 1H), 1.70 (dt, J = 5.5, 14.2 Hz, 1H); ^{13}C NMR δ 158.8, 153.4, 151.0, 141.0, 139.1, 137.8, 132.1, 129.0, 128.5, 127.7, 125.5, 73.2, 72.3, 59.2, 45.6, 34.9; IR (film) 3319, 1608, 1561 cm^{-1}.

Carbovir (20). A solution of BCl_3 (1 M in CH_2Cl_2, 1.0 mL, 1.0 mmol) was added dropwise to a −78 °C solution of purine **19** (mg, mmol) in CH_2Cl_2 (0.50 mL). The resultant mixture was stirred at −78 °C for 2 min and then allowed to warm with stirring over 40 min. Methanol (3 mL) was added, and the mixture was concentrated. This was repeated twice, followed by the addition of a saturated 0 °C solution of NH_3 in MeOH (2 mL). Concentration of the solution gave a tan solid, which was purified by flash chromatography (3% MeOH/CH_2Cl_2) to provide the corresponding free alchohol as a clear gum (22.0 mg, 0.0853 mmol, 83%): ^{1}H NMR (DMSO) δ 7.88 (s, 1H), 6.17 (dt, J = 2.2, 5.5 Hz, 1H), 5.82 (dt, J = 2.2, 5.5 Hz, 1H), 5.53 (m, 1H), 5.09 (br s, 2H), 3.89 (dd, J = 4.0, 10.7 Hz, 1H), 3.76 (dd, J = 3.7, 10.7 Hz, 1H), 3.36 (br s, 1H), 3.13 (m, 1H), 2.83 (dt, J = 9.6, 14.0 Hz, 1H), 2.03 (dt, J = 5.5, 14.0 Hz, 1H); ^{13}C NMR (DMSO) δ 158.5, 152.9, 151.4, 141.8, 138.9, 129.7, 125.7, 64.7, 60.9, 47.6, 32.9; IR (film) 3319, 1612, 1562 cm^{-1}; HRMS *m*/*z* (M + H) calcd 266.0809, obsd 266.0802; $[\alpha]^{24}_D$ 74.8 (*c* 0.84, MeOH).

Combined portions of the alcohol (57.2 mg, 0.215 mmol) were heated to 100 °C in 0.5 N NaOH (2 mL) for 3.5 h. Adsorption of the crude mixture onto Florisil, followed by purification by flash chromatography (15% MeOH/CH_2Cl_2), afforded carbovir (**20**) as a white solid (38.2 mg, 0.185 mmol, 72%): ^{1}H NMR (DMSO) δ 10.53 (br s, 1H), 7.57 (s, 1H), 6.43 (br s, 2H), 6.10 (dt, J = 2.0, 5.8 Hz, 1H), 5.85 (dt, J = 2.0, 5.8 Hz, 1H), 5.32 (m, 1H), 4.71 (t, J = 5.4 Hz, 1H), 3.42 (t, J = 5.4 Hz, 1H), 2.84 (m, 1H), 2.57 (dt, J = 8.6, 13.9 Hz, 1H), 1.55 (dt, J = 5.4, 13.9 Hz, 1H); ^{13}C NMR (DMSO) δ 156.9, 153.6, 150.7, 138.2, 134.9, 129.7, 116.6, 64.0, 58.4, 47.7, 34.3; IR (film) 3326, 1691 cm^{-1}; mp 235−239 °C dec; HRMS *m*/*z* (M + H) calcd 248.1147, obsd 248.1147; $[\alpha]^{24}_D$ 60.3 (*c* 0.4, MeOH) [lit.[33] mp 210−220 °C, dec; $[\alpha]^{24}_D$ 59.5 (*c* 0.4, MeOH)].

Purine 21. A suspension of carbonate **18** (53.2 mg, 0.193 mmol), adenine (38.7 mg, 0.286 mmol), and $Pd(PPh_3)_4$ (30.1 mg, 0.0260 mmol) in DMF (2 mL) was stirred at room temperature for 90 min. The mixture was concentrated and purified by flash chromatography (3% MeOH/CH_2Cl_2) to afford **21** as a white foam (40.1 mg, 0.125 mmol, 65%): ^{1}H NMR δ 8.37 (s, 1H), 7.90 (s, 1H), 7.37−7.25 (m, 5H), 6.20 (dt, J = 1.9,

(33) Evans, C. T.; Roberts, S. M.; Shoberu, K. A.; Sutherland, A. G. *J. Chem. Soc., Perkin Trans I* **1992**, 589.

5.6 Hz, 1H), 6.00 (br s, 2H), 5.89 (dt, J = 2.0, 5.6 Hz, 1H), 5.75 (m, 1H), 4.52 (s, 2H), 3.50 (m, 2H), 3.12 (m, 1H), 2.86 (dt, J = 8.8, 14.0 Hz, 1H), 1.73 (dt, J = 5.5, 14.0 Hz, 1H); ^{13}C NMR δ 155.5, 152.7, 149.7, 139.0, 138.8, 137.9, 129.4, 128.4, 128.1, 127.6, 119.7, 73.2, 72.5, 59.2, 45.6, 35.3; IR (film) 3318, 1648, 1598 cm^{-1}; mp 147−149 °C; $[\alpha]^{24}_D$ 39 (*c* 0.81, $CHCl_3$). Anal. Calcd for $C_{18}H_{19}N_5O$: C, 67.27; H, 5.96; N, 21.79. Found: C, 67.41; H, 5.84; N, 22.00.

Alcohol 22. A solution of BCl_3 (1 M in CH_2Cl_2, 0.80 mL, 0.80 mmol) was added dropwise to a solution of purine **21** (36.5 mg, 0.101 mmol) in CH_2Cl_2 (0.90 mL) at −78 °C. The resulting mixture was stirred at −78 °C for 15 min and then allowed to warm with stirring over 20 min. Methanol (2 mL) was added, and the mixture was concentrated. This was repeated twice, followed by the addition of a solution of NH_3 in MeOH (saturated at 0 °C, 2 mL). Concentration of the solution gave a tan solid, which was purified by flash chromatography (7% MeOH/CH_2Cl_2) to provide alchohol **22** containing a ∼15% impurity as a clear gum, which was used without further purification (15.0 mg, 0.0649 mmol, 64%). A portion of (±)-**22** was recrystallized (MeOH/EtOAc) to provide analytically pure material: ^{1}H NMR (DMSO) δ 8.13 (s, 1H), 8.04 (s, 1H), 7.20 (br s, 2H), 6.13 (dt, J = 1.8, 5.5 Hz, 1H), 5.91 (m, 1H), 5.58 (m, 1H), 4.74 (t, J = 5.1 Hz, 1H), 3.46 (t, J = 5.1 Hz, 2H), 2.90 (m, 1H), 2.67 (dt, J = 8.7, 13.7 Hz, 1H), 1.65 (dt, J = 5.5, 13.7 Hz, 1H); ^{13}C NMR (DMSO) δ 155.9, 152.3, 149.2, 138.7, 138.3, 129.7, 118.9, 63.9, 59.0, 47.7, 34.2; IR (film) 3172, 1672, 1648, 1604, 1575 cm^{-1}; mp (±) 183−186 °C. Anal. Calcd for $C_{11}H_{13}N_5O$: C, 57.13; H, 5.67; N, 30.28. Found: C, 57.27; H, 5.81; N, 30.43.

Aristeromycin (23a). To a −10 °C solution of (±)-**22** (21.8 mg, 0.0943 mmol) in DMF (1.5 mL) was added OsO_4 (26.7 mg, 0.103 mmol), and the resultant solution was allowed to stand for 36 h at −15 °C. The mixture was then diluted with MeOH (0.5 mL), quenched with saturated aqueous $NaHSO_3$ (0.5 mL), and stirred for 20 min. The suspension was filtered through Celite, diluted with MeOH, and filtered again to give 30 mg of a clear gum, determined to be a 2.3:1 mixture of diastereomers (NMR). Purification by preparative HPLC (95:5 to 80:20 H_2O/MeOH gradient elution over 55 min) provided (±)-aristeromycin (**23a**) as a clear film, which was crytallized (MeOH/EtOAc) to give a white solid (13.7 mg, 0.0516 mmol, 55%), and (±)-2′,3′-bis-*epi*-aristeromycin (**23b**) as a clear film (6.6 mg, 0.025 mmol, 26%). **23a**: ^{1}H NMR (DMSO) δ 8.20 (s, 1H), 8.12 (s, 1H), 7.18 (br s, 2H), 4.98 (d, J = 5.9 Hz, 1H), 4.82−4.64 (m, 3H), 4.34 (m, 1H), 3.84 (m, 1H), 3.47 (m, 1H), 3.17 (d, J = 4.3 Hz, 1H), 2.23 (dt, J = 8.7, 12.5 Hz, 1H), 2.04 (m, 1H), 1.72 (m, 1H); ^{13}C NMR (DMSO) δ 155.9, 152.1, 149.7, 140.1, 74.6, 71.7, 63.0, 59.3, 45.3, 29.3; IR (film) 3329, 3207, 1648, 1603 cm^{-1}; mp (±) 228−231 °C dec [lit.[34] mp 238−242 °C]; HRMS *m*/*z* (M + H) calcd 266.1253, obsd 266.1249.

(+)-Aristeromycin (**23a**) was prepared as above using (+)-**22** (9.5 mg, 0.041 mmol) and OsO_4 (12.8 mg, 0.050 mmol) to afford (+)-**23a**, contaminated with a 10% unidentified impurity (4.7 mg, 0.018 mmol, 43%): $[\alpha]^{24}_D$ 31 (*c* 0.2, DMF) [lit.[35] $[\alpha]^{23}_D$ 51 (*c* 0.3, DMF)].

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **7a**,**b**, **8**, **12c**, **13a**,**c**,**f**, and **18** and an ORTEP diagram from the X-ray crystal structure of **8**. This information is available free of charge via the Internet at http://pubs.acs.org.

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(34) Shealy, Y. F.; Clayton, J. D. *J. Am. Chem. Soc.* **1966**, *88*, 3885.
(35) Secrist, J. A. III; Montgomery, J. A.; Shealy, Y. F.; O'Dell, C. A.; Clayton, S. J. *J. Med. Chem.* **1987**, *30*, 746.