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Synthesis of Racemic 6′β-Hydroxyaristeromycin. A Hydroxycarbocyclic Analogue of Adenosine[1]

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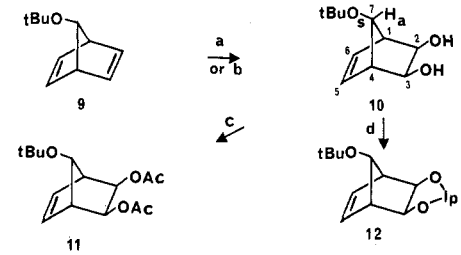
The synthesis of racemic 6′β-hydroxyaristeromycin (**8**) is described. 7-*tert*-Butoxynorbornadiene (**9**) was oxidized to the corresponding cis-exo diol **10**. Compound **10** was acetylated to give diacetate **11**. Isopropylidenation gave ketal **12**. Oxidation of diacetate **11** afforded dicarboxylic acid **13** which was converted into monoamide **14**. Esterification with CH_2N_2 led to amide ester **15**. Similarly, ketal **12** was oxidized to diacid **16** which was transformed to monoamide **18** via anhydride **17**. Esterification afforded amide ester **19**. Alternatively, diacid **16** was converted to monoester **20** which was then transformed to amide **19** by a mixed anhydride method. Hofmann rearrangement of **19** in *tert*-butyl alcohol resulted in N-protected amino ester **21a**, whereas in benzyl alcohol cyclic imide **22** was obtained. Reduction of ester **21a** gave alcohol **23**. Total deprotection of **23** afforded amino tetrol **24**. The latter was converted to compound **8** by a stepwise construction of an adenine ring via intermediates **25**, **26**, and **27**. 6′β-Hydroxyaristeromycin (**8**) is not a substrate for calf intestine adenosine deaminase. It inhibited the growth of murine leukemia L 1210 cells in vitro (ID_{50} 1.1×10^{-4} M).

Nucleoside analogues in which the carbohydrate (ribose) moiety is replaced by a carbocyclic ring are of current interest in chemistry, biochemistry, and biology of nucleosides.[4,5] Thus, replacement of the furanose oxygen in adenosine with a methylene group has led to the corresponding cyclopentane derivative—aristeromycin (**1**) (Chart I).[2,6] Compound **1**, as well as several analogues thereof, exhibits interesting biological activity including antitumor and antiviral properties.[5] More recently, another group of antibiotics, neplanocins A–C and F (formulas **2–5**) were isolated.[7] These compounds extended the area of carbocyclic analogues to structures where the C_4'–O bond of adenosine was replaced with a C=C function (neplanocin A, **2**) and to derivatives of aristeromycin (**1**) which carry an oxygen atom at C_6' (neplanocins B, C, and F). Antibiotics **2–5**, and particularly neplanocin A (**2**), possess significant antileukemic and antiviral activity.[8] Isolation of neplanocins B, C, and F (formulas **3–5**) from natural sources as well as their biological activity indicated that aristeromycin derivatives functionalized at C_6' might

Scheme I



[a] (a) $KMnO_4$, Me_2CO, −70 °C (see Table I and Experimental Section for alternate reaction conditions); (b) OsO_4 (catalytic), $Me_3N{\rightarrow}O$, aqueous Me_2CO; (c) Ac_2O, pyridine; (d) Me_2CO, $CuSO_4$.

(1) Presented in part at the 7th International Round Table on "Nucleosides, Nucleotides and Their Biological Applications", September 29–October 3, 1986, Konstanz, Germany, Abstracts, p 29. See also: Ben Cheikh, A.; Zemlicka, J. *Nucleosides Nucleotides* **1987**, *6*, 265. Abbreviations: Ac, acetyl, Ade, adenine, BOC, *tert*-butoxycarbonyl, CBZO, benzyloxycarbonyl, Me, methyl, DCC, dicyclohexylcarbodiimide, DMF, dimethylformamide, Et, ethyl, *i*-Bu, isobutyl, Ip, isopropylidene (dimethylmethylene), *t*-Bu, *tert*-butyl, THF, tetrahydrofuran. Nomenclature: Nomenclature and numbering of norbornane and cyclopentane derivatives conforms with the literature.[2,3] For examples of numbering, see structures **10** (Scheme I) and **14** (Scheme II). Subscripts a and s denote an anti and syn arrangement of substituents at C_7 of a norbornane system as defined in ref 2. The numbering of aristeromycin (**1**) also follows the literature.[3]

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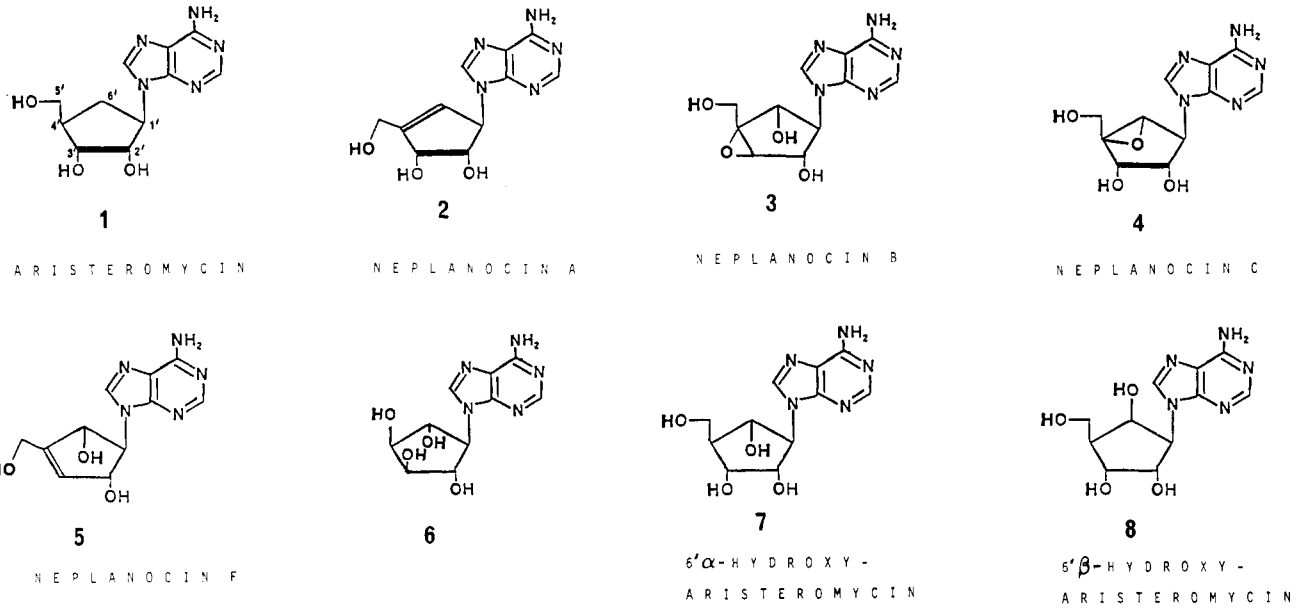
0022-3263/88/1953-0929$01.50/0

Chart I



be of considerable interest.[9] Although three ingenious synthetic avenues to neplanocin A (2) have recently been reported,[13-16] little attention has been paid to analogues more closely related to neplanocins carrying an oxygen function at the C_6'. In earlier studies, several cyclopentyl derivatives structurally related to neplanocins **3–5**, but lacking the hydroxymethyl group, e.g. compound **6**, were obtained.[17-19] According to a recent patent[20] 6′α-hydroxyaristeromycin (**7**) was obtained by a novel approach[3] but it was characterized only by a melting point and its specific biological activity was not disclosed. We have become interested in epimer of **7**, 6′β-hydroxyaristeromycin (**8**). The synthesis of analogue **8** and some preliminary biological investigations are the subject of this paper.

Results and Discussion

Synthesis. In view of the fact that nonstereospecific methods[21,22] for synthesis of carbocyclic nucleoside analogues gave erratic results,[23] a "norbornane" strategy[2,13,14,25-29] was adopted for the synthesis of 6′β-hydroxyaristeromycin (**8**) (Chart I).

We have used 5-*tert*-butoxynorbornadiene (**9**), which is readily accessible[30] and therefore a convenient starting material. Cis hydroxylation of olefin **9**, effected under a variety of conditions (Table I), gave the anticipated[2] exo diol **10** at the least sterically hindered double bond (Scheme I). The most effective from all variants, including oxidation in the presence of crown ether (expts 2 and 3), with cetyltrimethylammonium permanganate[31] (expts 4 and 5) or phase-transfer procedures[32] (expts 6–10), is ox-

Table I. Cis Hydroxylation of 7-*tert*-Butoxynorbornadiene (9)

expt no.	batch size (mmol of 9)	reagent, solvent, temp[a] (°C)	yield of 10 (%)
1	25	$KMnO_4$, acetone, −60	36[b]
2[c]	25	$KMnO_4$, acetone, 18-crown-6, −70	55
3	75	$KMnO_4$, acetone, dibenzo-18-crown-6, −70	46
4	25	cetyl$Me_3N^+MnO_4^-$, CH_2Cl_2, 25	0
5	12.5	cetyl$Me_3N^+MnO_4^-$, CH_2Cl_2, −70 to −60	20
6	25	$KMnO_4$, benzyl$Me_3N^+Cl^-$, CH_2Cl_2/H_2O, −10	10
7	10	$KMnO_4$, $NBu_4^+OH^-$, $CHCl_3$/aq NaOH, 0	19
8	10–25	$KMnO_4$, benzyl$Me_3N^+Cl^-$, CH_2Cl_2/aq NaOH, 0	32–34
9	25	$KMnO_4$, benzyl$Me_3N^+Cl^-$, CH_2Cl_2/acetone, 0	25
10	25	$KMnO_4$, THF/H_2O, $NBu_4^+OH^-$, 0	40
11[d]	60	OsO_4, $Me_3N{\rightarrow}O$, acetone/H_2O, 25	50–60

[a] For workup and further details, see Experimental Section, methods A–C. [b] Based on $KMnO_4$ because diene **9** was used in excess (method A). [c] Method B. [d] Method C.

(9) It has to be noted that unlike the published reports[7,10] the original patent literature[11] gives structures of neplanocin B, C, and F with configuration at the C_6' opposite to that in formula **3**, **4**, and **5**. Only the configuration of neplanocin C (structure **4**) has been rigorously established to date.[12]

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Table II. ^{1}H NMR Constants of Norbornane Derivatives [chemical shifts, δ (mult, no. of protons)[a]]

compd	H_1, H_4	H_2, H_3	H_5, H_6	H_7	CH_3	OH
10	2.75 (q, 2)	3.62 (d, 2)	6.01 (q, 2)[b]	4.40 (br s, 1)	1.21 (s, 9)	3.50 (br s, 2)
10 (*t*-BuO = H)[c]	2.69 (m)	3.69 (m)	6.03 (t)	1.62[d] (m), 1.88[e] (m)		ca. 3.41 (m)
11	2.81 (q, 2)	4.63 (s, 2)	6.12 (q, 2)	4.49 (bs, 1)	1.20 (s, 9, *t*-Bu), 2.07 (s, 6, Ac)	
11 (*t*-BuO = H)[c]	2.82 (m)	4.73 (d)	6.16 (t)	1.72[d] (m), 2.03[e] (m)	2.05 (s, Ac)	
12	2.80 (q, 2)	4.12 (s, 2)	6.05 (q, 2)	4.51 (s, 1)	1.18 (s, 9, *t*-Bu), 1.33, 1.53 (2 s, 6, Ip)	

[a] $CDCl_3$. [b] A clear sextet was observed in a 100-MHz spectrum. [c] Data was taken from ref 2. [d] H_s. [e] H_a.

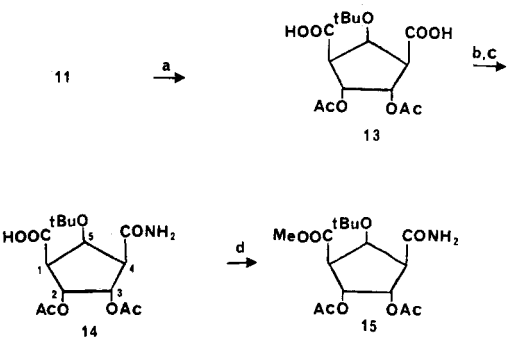
idation with a catalytic (ca. 1%) amount of OsO_4 in aqueous acetone in the presence of trimethylamine *N*-oxide[33] at room temperature (expt 11). Diol **10** was readily transformed to the corresponding diacetate **11** by conventional acetylation.

Protection of diol **10**, in the form of a 2,3-*O*-dimethylmethylene (isopropylidene) derivative, was equally successful. Thus, reaction with acetone in the presence of $CuSO_4$ at room temperature gave tricyclic derivative **12**. This procedure, which was previously employed in the norbornene series,[34] is of a particular advantage in case of diol **10** because it permits introduction of an acetal grouping under nonacidic condition in the presence of another acid-labile group (*tert*-butoxy function). The best results were obtained when ordinary reagent grade acetone, not dried with molecular sieves,[35] was used. Product **12** was then isolated simply by distillation in vacuo in 98% yield.

The structures of compounds **10–12** were confirmed by ^{1}H NMR spectra. Thus, the $H_{2,3}$ signal of **10** appeared, after deuterium exchange, as a sharp singlet, indicating a lack of coupling with $H_{1,4}$ and, consequently, an exo diol structure[2] (Table II). The olefinic protons $H_{5,6}$ form a sextet[37] which is in accord with H_7 being anti to the double bond.[38,39] This was further confirmed by double-resonance experiments. Thus, irradiating the H_7 signal transformed the $H_{5,6}$ signal into a triplet. The original quartet of $H_{1,4}$ also collapsed to a triplet. When the olefinic protons were irradiated, the broad singlet of H_7 changed into a sharp triplet and $H_{1,4}$ afforded a doublet. Conversely, a decoupling at the $H_{1,4}$ led to a collapse of both H_7 and olefinic $H_{5,6}$ to singlets whereas, as expected, the $H_{2,3}$ remained unchanged. In addition, the chemical shifts of the $H_{5,6}$, $H_{2,3}$, and $H_{1,4}$ of diol **10** resemble very closely those of 5-norbornene-*exo*-2,3-diol[2] (Table II). Comparison of diacetate **11** with the respective 7-unsubstituted counterpart[2] showed essentially the same pattern. It is also noteworthy that the chemical shifts of the tricyclic system in **12**, with the exception of $H_{2,3}$, also compare well with those of diol **10** and diacetate **11** (Table II). It is then possible to conclude that **10** has the H_7 in a syn position to the vicinal exo diol moiety.

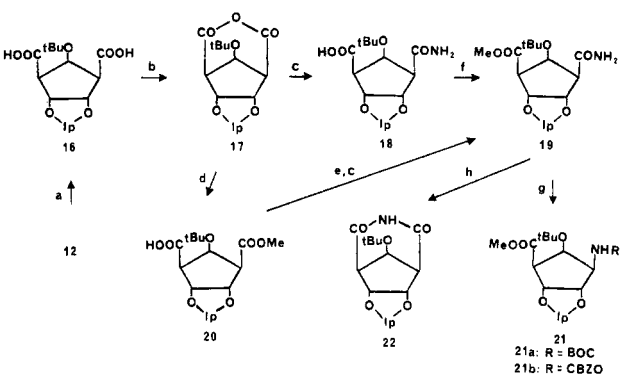
The next step in our strategy dictated oxidation of the olefinic linkage of suitably protected diol **10** to the corresponding dicarboxylic acid. Initially, diacetate **11** was used for such a purpose (Scheme II). The latter compound was readily oxidized with aqueous $KMnO_4$ buffered[2] with CO_2 to give dicarboxylic acid **13** isolated after extraction and

Scheme II



[a] (a) Aqueous $KMnO_4$, pH <8; (b) DCC, pyridine; (c) NH_3, THF; (d) CH_2N_2, ether.

Scheme III



[a] (a) Aqueous $KMnO_4$; (b) DCC, pyridine; (c) NH_3, THF; (d) MeOH, NEt_3, THF; (e) *i*-BuOCOCl, NEt_3, THF; (f) CH_2N_2, ether; (g) $Pb(OAc)_4$, *t*-BuOH, Δ; (h) $Pb(OAc)_4$, $C_6H_5CH_2OH$, Δ.

acidification with 1 M HCl in 65% yield. Compound **1** was transformed to the corresponding monoamide **14**, via a cyclic anhydride, by reaction with DCC and subsequent ammonolysis in 68% yield. Esterification of **14** with diazomethane then afforded methyl ester **15** (96%). It would probably be possible to use intermediate **15** for subsequent steps of the synthesis of 6′β-hydroxyaristeromycin (**8**). However, it was recognized that the presence of a group stable in alkaline media and toward hydride reagents could add to the versatility of the synthetic scheme. Therefore, dioxolane derivative **12** was exclusively used in further experiments.

Intermediate **12** was readily oxidized with aqueous $KMnO_4$ to afford the corresponding dicarboxylic acid **16** in 80% yield (Scheme III). Because of the presence of the acid-labile (dimethylmethylene)dioxy group, compound **16** was isolated from a medium buffered with a citric acid to pH 3.3. Under these conditions, the conversion to free dicarboxylic acid **16** was incomplete and the product contained, according to elemental analysis, ca. 0.5 mol of alkali metal (sodium). This material was readily converted to the pyridinium salt by treatment with Dowex 50 cation exchange resin in pyridinium form. Both forms of diacid **16** were successfully used in subsequent synthetic steps.

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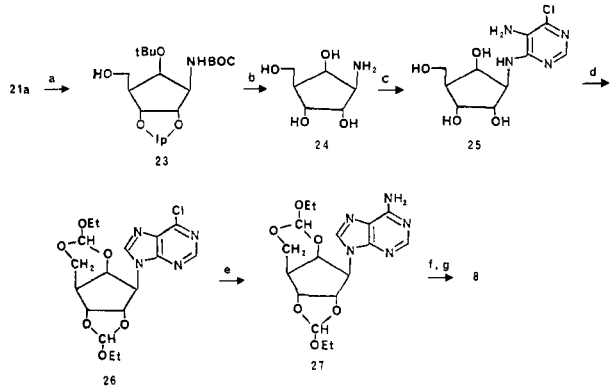
Scheme IV



[a] (a) $Ca(BH_4)_2$, THF, Δ; (b) 2 M HCl, MeOH; (c) 5-amino-4,6-dichloropyrimidine, NEt_3, BuOH, Δ; (d) $CH(OEt)_3$, TsOH; (e) NH_3, MeOH, Δ; (f) 1 M HCl, MeOH; (g) concentrated NH_4OH.

Diacid **16** was converted to the corresponding anhydride **17** by using DCC in pyridine. The subsequent ammonolysis of **17** with NH_3 in THF was performed in situ to give monoamide 18 in 80% yield (Scheme III). An attempted Hofmann rearrangement of **18** was unsuccessful with either aqueous NaOBr or Br_2 and CH_3ONa in methanol[40] which contrasts with the success experienced with a similar cyclopentane derivative lacking the *tert*-butoxy group.[2] Therefore, compound **18** was esterified with diazomethane to give the corresponding amide ester **19** in 70% yield. The use of diazomethane was avoided in an alternate procedure. Cyclic anhydride **17** prepared in situ was methanolyzed in the presence of triethylamine to give monoester **20** in almost 80% yield. Compound **20** was then transformed to desired amide ester **19** by a mixed anhydride procedure (isobutyl chloroformate and triethylamine followed by NH_3) in 90% yield.

A Hofmann rearrangement of **19** was then effected with lead tetraacetate in *tert*-butyl alcohol.[13,41] The oxidant/substrate ratio was of crucial importance. Thus, with a ratio of 2:1 the yield of the protected amine **21a** was ca. 30% whereas with 5 equiv of lead tetraacetate the reaction was virtually quantitative. Attempts to prepare an *N*-benzyloxycarbonyl derivative **21b** were not successful. Thus, reaction of amide ester **19** with lead tetraacetate in benzyl alcohol gave cyclic imide **22** as the only product in 40% yield. By contrast, a similar reaction in the camphor series gave the expected *N*-benzyloxycarbonyl derivatives albeit in lower yields.[41] Unlike tertiary alcohols (*tert*-butyl alcohol) primary and secondary alcohols can consume the oxidizing agent during oxidation with lead tetraacetate.[41] Thus, it is possible that oxidation of benzyl alcohol is faster than that of the sterically hindered carboxamide group of **19**. Another process, such as cyclization to imide **22**, can then become predominant. Reduction of the ester group of **21a** was readily effected[42] with $Ca(BH_4)_2$ in THF to give alcohol **23** in 80% yield (Scheme IV). Other reagents such as $LiAlH_4$ and $LiBH_4$ were less successful, giving, according to TLC and NMR spectra, in addition to **23** products of elimination of the 2,3-(dimethylmethylene)oxy group. Total deprotection of **23** with 2 M HCl in methanol gave the desired amino tetrol **24** as a hydrochloride in 80% yield.

Compound **24** was then employed as a key building block for the synthesis of 6′β-hydroxyaristeromycin (**8**) following the conventional strategy.[2] Nevertheless, some important modifications had to be made. Condensation of **24** with 5-amino-4,6-dichloropyrimidine gave the expected intermediate **25** (81%), which, in turn, was cyclized to the corresponding 6-chloropurine derivative **26** in 70% yield by using *p*-toluenesulfonic acid and triethyl orthoformate reagent.[14] By contrast, concentrated HCl in conjunction[2] with triethyl orthoformate did not afford any defined product whereas cyclization with dimethylformamide dimethyl acetal gave, according to a UV spectrum, an N^6,N^6-dimethyladenine derivative. The latter result indicated that the purine ring was formed but the chloro atom was replaced with a *N*,*N*-dimethylamino function.[43] Formation of cyclic bis(ortho ester) **26** independently confirmed the relative stereochemistry of relevant oxygen atoms. The crude **26** was ammonolyzed to give the corresponding adenine derivative **27** (70%), which, in turn was deprotected with 6 M HCl in methanol followed by treatment with NH_4OH. 6′β-Hydroxyaristeromycin (**8**) was obtained in almost quantitative yield after chromatography on Dowex 50 cation exchange resin. Thus, the overall yield of the last four steps, which were performed without extensive purification of the intermediates, was 39%. Complex ^1H NMR spectra of **26** and **27** reflect the fact that introduction of two cyclic orthoester functions has created two new asymmetric centers and hence eight stereoisomers of each product are possible (precursor **25** is a racemic mixture of two enantiomeric forms). Nevertheless, the signals of endo and exo protons of the dioxolane orthoester moiety were clearly discernable in both **26** and **27** as two singlets which indicated an exo/endo ratio of 3:2. This is in excellent agreement with findings in the ribonucleoside series.[44] It is then apparent that the presence of cyclopentane moiety with an extra 1,3-dioxane ring has a little influence on the exo/endo isomer ratio of **26** and **27**.

Biology. In a stark contrast to aristeromycin (**1**)[45] 6′β-hydroxyaristeromycin (**8**) is completely resistant to calf intestine adenosine deaminase as determined by both spectrophotometric[46] and electrophoretic[47] assay. Likewise, the arabino analogue of aristeromycin (cyclaradine), which also has a hydroxy group in the β-cis position relative to the heterocyclic base, is not deaminated.[49] 6′β-Hydroxyaristeromycin (**8**) inhibited the growth of murine leukemia L 1210 in culture but the activity (ID_{50} 1.1×10^{-4} M) was lower than that of aristeromycin[50] (**1**) or cyclaradine in a P 388 system.[49]

Experimental Section

General Procedures. All solvents and starting materials used were of the highest available purity or they were purified as specified. Solvents were generally stored over 3A or 4A Linde molecular sieves unless stated otherwise. THF was distilled from $LiAlH_4$ and it was kept over a sodium ribbon in the dark. Pyridine was distilled from KOH. Diazomethane was generated by using a Mini Diazald apparatus or Macro Diazald set (Aldrich Chemical Co., Milwaukee, WI). Whereas the former was perfectly suitable for the purpose, excessive losses of diazomethane were observed

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Table III. ^{1}H NMR Constants of Cyclopentane Derivatives [chemical shifts, δ (mult, no. of protons)]

cmpd	H_1	H_4	H_2	H_3	H_5	CH_3 and other signals
13[a]	3.12 (t, 2)		5.49 (d, 2)		4.72 (t, 1)	1.05 (s, 9, *t*-Bu), 1.96 (s, 6, Ac)
14[a]	2.97 (m, 2)		5.53 (d, 2)		4.70 (t, 1)	1.09 (s, 9, *t*-Bu), 2.00 (s, 6, Ac), 7.47, 6.87 (2 s, 2, NH_2)
15[b]	3.18[c] (t, 1)	3.10[c] (t, 1)	5.73[c,d] (m, 2)		4.83 (t, 1)	1.12 (s, 9, *t*-Bu), 1.98, 1.95 (2 s, 6, Ac), 3.66 (s, 3, MeO), 6.86, 6.46 (2 s, 2, NH_2)
16[b]	3.02 (m, 2)		5.05 (dd, 2)		4.86 (t, 1)	1.15 (s, 9, *t*-Bu), 1.28, 1.39 (2 s, 6, Ip)
18[a]	2.70 (dd, 2)		4.93[c] (q, 1)	4.87[c] (q, 1)	4.71 (t, 1)	1.01 (s, 9, *t*-Bu), 1.22, 1.35 (2 s 6, Ip), 7.31, 6.99 (2 s, 2 NH_2), 12.45 (br s, 1, COOH)
19[e]	3.04[c] (d, 1)	3.01[c] (d, 1)	5.29 (d, 1)	4.79 (d, 1)	4.69 (t, 1)	1.27 (s, 9, *t*-Bu), 1.30, 1.46 (2 s, 6, Ip), 3.65 (s, 3, MeO), 7.26, 5.77 (2 s, 2, NH_2)
20[e]	3.01[c] (dd, 1)	3.11[c] (dd, 1)	5.29 (dd, 1)	4.80 (dd, 1)	4.77 (t, 1)	1.31, 1.46 (2 s, 15, *t*-Bu + Ip), 3.68 (s, 3, MeO)
21[a]	3.05[e] (q, 1)	4.85 (q, 1)	4.82 (m, 2)		4.12 (m, 1)	1.13, 1.44, (2 s, 18, *t*-Bu), 1.28, 1.46 (2 s, 6, Ip), 3.70 (s, 3, MeO), 5.36 (d, NH)
22[e]	3.16 (m, 2)			4.65 (m, 3)		1.22 (s, 9, *t*-Bu), 1.34, 1.56 (2 s, 6, Ip), 5.18 (s, 1, NH)
23[e]	2.40 (m, 1)	3.88 (t, 1)		4.50 (m, 3)		1.26 and 1.44 (2 s, 18, *t*-Bu), 1.28 and 1.46 (2 s, 6, Ip), 2.78 (br s, 1, OH), 3.80 (m, 2, CH_2), 5.18 (d, 1, NH)
24[f]	2.20 (m, 1)	3.50 (m, 1)	4.18[c] (t, 1)	3.95[c] (t, 1)	4.38 (t, 1)	3.80 (m, 2, CH_2)

[a] CD_3SOCD_3. [b] CD_3COCD_3. [c] Tentative assignments. [d] Overlapping signals. [e] $CDCl_3$. [f] D_2O.

Table IV. ^{13}C NMR Chemical Shifts of Cyclopentane Derivatives[a]

cmpd	C_1, C_4	C_2, C_3	C_5	C=O	CH_3	C (Ip)	C–O (*t*-BuO)
13	54.79	72.34	71.47	169.87 170.85	20.0 (Ac), 28.56 (*t*-Bu)		75.14
14	55.34, 54.59	72.50, 72.16	71.47	170.13, 170.99, 171.41	20.86 (Ac), 28.15 (*t*-Bu)		74.90
15	55.31, 55.25	73.96, 73.20	71.82	169.70, 169.82, 170.37, 170.47	20.33, 20.28 (Ac), 28.12 (*t*-Bu), 51.59 (MeO)		75.72
16	57.04	81.17	77.53	171.50	24.80, 27.39 (Ip), 28.31 (*t*-Bu)	111.87	76.20
18	57.52, 57.16	79.78, 79.73	78.42	170.98, 171.39	24.69, 27.17 (Ip), 28.12 (*t*-Bu)	112.04	73.86
19	55.12, 53.13	80.36, 78.63	72.40	170.95, 172.27	23.95, 26.66 (Ip), 27.73 (*t*-Bu), 51.41 (MeO)	110.01	76.38
20	55.51, 52.72	80.58, 78.88	78.09	169.99, 170.96	26.49, 27.57 (Ip), 23.78 (*t*-Bu), 51.57 (MeO)	110.59	72.88
21a	55.67, 59.35	79.43, 84.54	79.21	172.88, 155.73	24.50, 26.96 (Ip), 28.03, 28.44 (*t*-Bu), 51.82 (MeO)	111.57	74.84, 76.65
23	51.82, 60.00	79.43, 84.54	79.21	157.00	24.50, 26.96 (Ip), 28.03, 28.44 (*t*-Bu)[b]	111.87	74.87, 76.65

[a] For solvents, see Table III. [b] 62.00 (CH_2).

while working with a Macro Diazald set. Therefore, the apparatus[51] was modified as follows. The outlet E connected with a dry ice trap (see Figure 1 in ref 51) was relocated just above the (male) ground-glass joint D and the glass tube carrying the diazomethane solution was extended through the joint D ca. 1 cm inside the receiving flask. This arrangement is similar to that used in a Mini Diazald apparatus.

TLC was performed on 6 × 2 cm precoated TLC sheets of silica gel 60 F_{254} (Merck). Detection was performed by charring with aqueous 10% $HClO_4$ or 10% H_2SO_4 in 30% aqueous methanol. Where appropriate, 1% aqueous $KMnO_4$ or UV light were also used. Plates which were sprayed with $KMnO_4$ were immediately rinsed with tap water and air-dired for storage. The following solvent systems were employed: S_1, CH_2Cl_2–MeOH (95:5); S_2, CH_2Cl_2–THF (9:1); S_3, C_6H_6–AcOEt (9:1); S_4, C_6H_6–AcOEt (95:5); S_5, CH_2Cl_2–Me_2CO (1:1); S_6, CH_2Cl_2–MeOH (9:1); S_7, CH_2Cl_2–THF (95:5); S_8, CH_2Cl_2–MeOH (4:1); S_9, 2-propanol–NH_4OH–H_2O (7:1:2); S_{10}, CH_2Cl_2–MeOH (97:3); S_{11}, 1-butanol–AcOH–H_2O (5:2:3). Column chromatography was performed with Kieselgel 60 (230–400-mesh ASTM Merck) without indicator.

Melting points were determined with a Thomas-Hoover apparatus or microscopic hot-stage (Reichert, Austria) and they were not corrected. UV spectra were obtained on a Perkin-Elmer Lambda 5 spectrophotometer. The wavelengths of maxima are given in nm. IR spectra (KBr pellets) were determined with a Perkin-Elmer Model 1330 infrared spectrophotometer and the relevant maxima are expressed in cm^{-1}. ^{1}H NMR spectra were obtained with a QE-300 instrument (General Electric) at 300 MHz with Me_4Si as an internal reference. Most of the data are summarized in Tables II and III. Assignments were verified by spin-decoupling and deuterium exchange where appropriate. Spectra in CD_3SOCD_3 were determined in "100 Atom % D" solvent (Aldrich, Milwaukee, WI). The proton-decoupled ^{13}C NMR spectra were obtained at 75.48 MHz in the same solvents as ^{1}H NMR. Most of the results are given in Table IV. Electron-impact mass spectra (EI-MS) were run with a Kratos MS80 RFA high resolution instrument. Occassionally, chemical ionization spectra (CI-MS) were determined to enhance intensity of molecular ions (M + H) by using 2-methylpropane as an ionization gas. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ.

***syn*-7-*tert*-Butoxy-5-norbornene-*exo*-2,3-diol (10). A. Oxidation of 7-*tert*-Butoxynorbornadiene (9) with $KMnO_4$.** A solution of 7-*tert*-butoxynorbornadiene (**9**, 4.1 g, 25 mmol) in acetone (60 mL) was cooled to −60 °C. Finely powdered $KMnO_4$ (1.58 g, 10 mmol) was added in small portions with vigorous stirring which continued for 1 h at −60 °C. A cooled solution of Na_2SO_3 (13 g, 103 mmol) and NaOH (4 g, 100 mmol) in water (70 mL) was then added dropwise with stirring at −50 to −60 °C. The temperature was then allowed to rise and stirring was continued for 1.5 h at room temperature. The MnO_2 was filtered off, it was washed with acetone (3 × 20 mL), and the filtrate was concentrated in vacuo. The aqueous solution was saturated with NaCl and it was extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were dried ($MgSO_4$) and evaporated to give a black oil. The latter was chromatographed on a silica gel column (30 g, 13.5 × 2.5 cm) which was eluted with benzene (300 mL) to remove starting diene **9**. The elution was then continued with CH_2Cl_2 (360 mL) and CH_2Cl_2–CH_3OH (99:1, 750 mL). The fractions containing diol **10** were evaporated to give tan needles, 0.72 g (36%). The product was dissolved in benzene (5 mL), cyclohexane (25 mL) was added, and a white crystalline product was filtered off, 0.2 g (10%), mp 93 °C. Mother liquors afforded two more crops (0.27 g, 14%). Compound **10** is homogeneous on TLC (S_1 or S_2): ^{13}C NMR 132.43 (C_5 + C_6), 84.88 (C_7), 74.07 (>Co, *t*-Bu), 66.64 (C_2 + C_3), 53.47 (C_1 + C_4), 28.24 (CH_3); EI-MS, *m/z* (relative intensity) 199 (M + H 3.0), 124 (21.1), 107 (9.8), 95 (51.7), 78 (100.0), 67 (31.0), 57 (100.0). Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.83; H, 9.31.

B. Oxidation of Diene 9 with $KMnO_4$ in the Presence of 18-Crown-6. The reaction was performed as in method A using an *equivalent* amount of $KMnO_4$ (3.95 g, 26 mmol) in acetone (100 mL) at −70 °C. $KMnO_4$ and 18-crown-6 (6.61 g, 25 mmol) were added as a solution in benzene–acetone (1:3, 200 mL). After the oxidation, the solution of Na_2SO_3 (11.7 g, 93 mmol) and NaOH

(51) Hudlicky, M. *J. Org. Chem.* **1980**, *45*, 5377.

(3.6 g, 90 mmol) in water (90 mL) was added to quench the oxidant. Further workup included saturation of the aqueous reaction mixture with KCl, extraction with CH_2Cl_2, and chromatography on a silica gel column. The latter gave diol **10** homogeneous on TLC (S_1), 2.71 g (55%). Crystallization from cyclohexane (8 mL) afforded 2.51 g (51%) of **10**, mp 89–90 °C, identical (TLC, mp) with the compound obtained by method A.

C. Oxidation of Diene 9 with OsO_4 and Trimethylamine *N*-Oxide. Osmium tetraoxide (1.44 g, 5.7 mmol) in ether (10 mL) was added to a solution of diene **9** (100 g, 0.61 mol) and trimethylamine *N*-oxide dihydrate (80 g, 0.72 mol) in acetone (1.125 L) and water (225 mL) at room temperature with stirring. The resultant mixture was treated with *tert*-butyl alcohol (225 mL) and a dark green solution was stirred for 91 h at room temperature. Water (200 mL) and Na_2SO_3 (25 g, 0.2 mol) were added, the mixture was stirred for an additional hour, and then it was extracted with CH_2Cl_2 (5 × 0.6 L). The organic phase was dried (Na_2SO_4) and it was evaporated to give a red-brown oil (152.07 g) which was chromatographed on a silica gel column (950 g, i.d. 7.5 cm). The column was washed with CH_2Cl_2 (3 L), CH_2Cl_2–acetone (9:1, 2 L), CH_2Cl_2–acetone (4:1, 2.5 L, CH_2Cl_2–methanol (9:1, 0.5 L), and CH_2Cl_2–methanol (4:1, 1.5 L). The major fraction gave diol **10**, 69.95 g (58%). Crystallization from cyclohexane (300 mL) yielded pure **9**, 54.57 g (45%), mp 96–98 °C, which was identical (TLC S_3, IR) with compound prepared by methods A and B.

***exo*-2,3-Diacetoxy-*syn*-7-*tert*-butoxy-5-norbornene (11).** A mixture of diol **10** (0.4 g, 2 mmol), acetic anhydride (1 mL, 10 mmol), and pyridine (10 mL) was kept at room temperature for 67 h; TLC in S_1 and S_6 showed a complete absence of the starting material. Methanol (5 mL) was added, the solution was evaporated, and the residue was partitioned between water (10 mL) and CH_2Cl_2 (25 mL). The dried ($MgSO_4$) organic phase was evaporated to give a syrup which crystallized during drying in vacuo at room temperature, 0.59 g (104%), mp 50–53 °C. This product was dissolved in petroleum ether (17 mL), the solution was filtered through a cotton plug, and the filtrate was evaporated to give diacetate **11**, 0.56 g (99%), homogeneous on TLC (S_3), mp 56–58 °C, after crystallization from cyclohexane 57–59 °C: ^{13}C NMR 169.98 (CO), 132.58 ($C_5 + C_6$), 85.37 (C_7), 74.07 (>CO, *t*-Bu), 68.80 ($C_2 + C_3$), 51.16 ($C_1 + C_4$), 28.17 (Me of *t*-Bu), 20.70 (Me of Ac); EI-MS, *m/z* (relative intensity) 283 (M + H, 0.2), 223 (19.8), 166 (34.7), 124 (20.8), 106 (38.9), 95 (27.4), 78 (89.9), 57 (100.0). Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.86. Found: C, 63.75; H, 7.69.

***exo-cis*-2,3-[(Dimethylmethylene)dioxy]-*anti*-7-*tert*-butoxy-5-norbornene (12).** A mixture of diol **10** (6.51 g, 33 mmol), anhydrous $CuSO_4$ (51.72 g, 324 mmol), and acetone (dried with Linde molecular sieves 4A, 150 mL) was vigorously stirred for 20 h at room temperature. TLC (S_4) showed the presence of **12** as the only permanganate-positive, UV-nonabsorbing, and -nonvolatile component.[35] The solids were filtered off, they were washed with acetone (50 mL), and the filtrate was evaporated. The resultant brown oil was distilled, major fraction bp 64–66 °C/0.025 Torr, 7.96 g, still containing UV-absorbing permanganate-positive and volatile contaminants.[35] This material was chromatographed on a short column of silica gel (50 g, 7.5 cm) in cyclohexane–benzene (99:1, 10 L). The fractions containing **12** were combined, they were evaporated, and the resultant yellow oil (6.09 g, 78%), homogeneous on TLC (S_4), was subjected to a short-path distillation, bp 68–70 °C/0.025 Torr, 5.88 g (75%), n^{22} 1.4578: ^{13}C NMR 113.82 (>(O)CO, Ip), 133.00 ($C_5 + C_6$), 85.72 (C_7), 78.59 ($C_2 + C_3$), 74.24 (>CO, *t*-Bu), 50.50 ($C_1 + C_4$), 28.31 (Me of *t*-Bu), 26.17 and 24.12 (Me of Ip); EI-MS, 239 *m/z* (relative intensity) (M + H, 15.2), 183 (27.7), 124 (51.9), 107 (27.2), 95 (29.5), 78 (69.1), 57 (100.0). Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31. Found: C, 70.46; H, 9.06.

No UV-absorbing and permanganate-positive contaminants were observed in an experiment run on a 0.2-mol scale with reagent grade acetone which was not dried with molecular sieves. Column chromatography was not necessary and compound **12** was isolated in 98% yield by a vacuum distillation.

2α,3α-Diacetoxy-5β-*tert*-butoxy-1β,4β-cyclopentanedicarboxylic Acid (13). Carbon dioxide was introduced into a vigorously stirred mixture of diacetate **11** (1.3 g, 4.6 mmol), petroleum ether (20 mL), and water (50 mL) cooled in an ice bath. A solution of $KMnO_4$ (2.3 g, 14.5 mmol) in water (50 mL) was then added dropwise, the mixture containing MnO_2 was allowed to warm to room temperature, and it was stirred for 1.5 h with a continuous introduction of CO_2. It was cooled again in an ice bath and SO_2 was introduced until all MnO_2 dissolved. The clear solution was concentrated in vacuo to about one-third of the original volume whereupon it was extracted with ether (3 × 50 mL). The dried ($MgSO_4$) extract was evaporated to give a white solid (1.3 g) consisting of diacid and the corresponding potassium salt, mp 198 °C (softening between 125 and 130 °C). This product was washed with 1 M HCl and dried to give analytically pure diacid **13** (1 g, 65%), mp 165–166 °C, homogeneous on TLC (S_5). Anal. Calcd for $C_{15}H_{22}O_9$: C, 52.01; H, 6.42. Found: C, 52.21; H, 6.44.

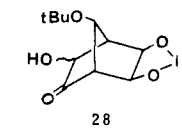
(±)-4β-Carbamoyl-2α,3α-diacetoxy-5β-*tert*-butoxy-1β-cyclopentanecarboxylic Acid (14). Diacid **13** (0.5 g, 1.45 mmol) was dissolved in THF (15 mL), DCC (0.33 g, 1.6 mmol) was added, and the mixture was stirred for 30 min at room temperature. Anhydrous ammonia NH_3 was then introduced into the mixture for 3 h. The mixture was then stirred for additional 1 h, THF was evaporated, water (50 mL) was added to the residue, and the pH was adjusted to 8.5 with NH_4OH. After stirring for 15 min, the solids were filtered off and the filtrate was acidified with 1 M HCl to pH 3. The resultant solution was concentrated in vacuo until a crystalline product separated. The latter was collected by filtration; it was washed with 1 M HCl and dried to give amide **14** (0.34 g, 68%), mp 193–194 °C; homogeneous on TLC (S_5): IR 3400–3200 (OH + NH_2), 1745 (CO, ester), 1700 (COOH), 1660 ($CONH_2$). Anal. Calcd for $C_{15}H_{23}NO_8$: C, 52.16; H, 6.73; N, 4.06. Found: C, 51.93; H, 6.62; N, 3.95.

(±)-Methyl 4β-Carbamoyl-2α,3α-diacetoxy-5β-*tert*-butoxy-1β-cyclopentanecarboxylate (15). Diazomethane (4.7 mmol) was introduced into a stirred mixture of amide **14** (1 g, 2.8 mmol) and ether (20 mL). The solution containing an excess of diazomethane was stirred for 1 h at room temperature and then it was evaporated to give a syrup that crystallized during drying in vacuo at room temperature to give compound **15** (1 g, 96%). Crystallization from benzene afforded an analytical sample, homogeneous on TLC (S_5), mp 118–119 °C: IR 3470–3180 (NH_2), 1745 (CO, ester), 1670 ($CONH_2$); CI-MS, *m/z* (relative intensity) 360 (M + H, 46.4), 304 (M + H – 2-methylpropene, 85.6). Anal. Calcd for $C_{16}H_{25}NO_8$: C, 53.46; H, 7.03; N, 3.90. Found: C, 53.28; H, 6.98; N, 3.92.

2α,3α-[(Dimethylmethylene)dioxy]-5β-*tert*-butoxy-1β,4β-cyclopentanedicarboxylic Acid (16). A mixture of compound **12** (2.61 g, 10.8 mmol), petroleum ether (30 mL), and water (180 mL) was cooled in an ice bath. Solid $KMnO_4$ (5.6 g, 35.3 mmol) was then added in small portions with efficient stirring and cooling within 30 min. After addition of ca. one-third of $KMnO_4$, the mixture was diluted with water (50 mL). The mixture was then stirred at room temperature for 5 h with excess $KMnO_4$ present. Solid Na_2SO_3 (3.2 g, 2 mmol) was added, MnO_2 was filtered off, and it was washed several times with 5% aqueous $NaHCO_3$ (total of 150 mL). The pH of the clear filtrate was adjusted to 7 with concentrated HCl (pH meter) and an insoluble solid[52] was filtered off (130 mg, mp 167–169 °C). The ice-cold solution was then acidified with citric acid (8.3 g, 43.2 mmol) to pH 3.3 and extracted immediately with ether (5 × 100 mL). The dried ($MgSO_4$) organic phase was evaporated to give a white solid, mp 178–180 °C dec, 2.35 g (81%) of diacid **16**, homogeneous on TLC (S_1 or S_6): IR 3530, 3480 (OH), 1720 (CO). Anal. Calcd for $C_{14}H_{21.5}Na_{0.5}O_7 \cdot {}^1/_5H_2O$: C, 53.06; H, 6.97. Found (two preparations): C, 53.05, 53.27; H, 7.34, 7.01.

This material as well as the corresponding pyridinium salt obtained by its passage through a column of Dowex 50 (WX 4, 200-400 mesh, pyridinium form) and evaporation of the eluate

(52) This product was resolved into two components having the structures of α-hydroxy ketone **28** and cis diol **29**. A more rigorous structure assignment will be reported at a later date.



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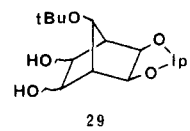

29

was used directly in the subsequent steps.

(±)-4β-Carbamoyl-2α,3α-[(dimethylmethylene)dioxy]-5β-*tert*-butoxy-1β-cyclopentanecarboxylic Acid (18). A solution of diacid **16** (314 mg, 1 mmol) in pyridine (20 mL) was cooled to 0 °C. DCC (336 mg, 1.5 mmol) was then added and the mixture was stirred for 2 h at room temperature. The precipitated dicyclohexylurea was filtered off and the filtrate was evaporated to give a gummy solid which was dissolved in CH_2Cl_2 (40 mL). The solution was again filtered and evaporated leaving crude anhydride **17** (IR 1760 and 1820, CO). The latter was dissolved in THF (50 mL), the solution was cooled to 0 °C, and a stream of NH_3 was introduced with stirring and external ice-cooling for 1.5 h. The mixture was evaporated and the residue was stirred with NH_4OH (pH 8.0, 50 mL). A small insoluble portion (dicyclohexylurea) was filtered off; the pH of the filtrate was adjusted (after cooling) with concentrated HCl to 7 and finally with citric acid to 3.3 (pH meter). The solution was immediately extracted with CH_2Cl_2 (3 × 50 mL), the extract was dried ($MgSO_4$), and it was evaporated to give solid **18** (250 mg, 80%), mp 196–198 °C, homogeneous on TLC (S_6): IR 3500–3200 (OH and NH_2), 1720 (COOH), 1660 ($CONH_2$); EI-MS, *m/z* (relative intensity) 302 (M + H, 6.9), 246 (41.3), 228 (9.1), 187 (11.3), 170 (13.1), 142 (12.4), 126 (13.3), 109 (25.7), 88 (47.4), 57 (100.0). Anal. Calcd for $C_{14}H_{23}NO_6$: C, 55.80; H, 7.69; N, 4.65. Found: C, 55.66; H, 7.64; N, 4.52.

(±)-4β-(Methoxycarbonyl)-2α,3α-[(dimethylene)dioxy]-5β-*tert*-butoxy-1β-cyclopentanecarboxylic Acid (20). DCC (3.57 g, 17.3 mmol) was added to a well-stirred and chilled (ice-salt bath) solution of diacid **16** (5 g, 16.5 mmol) in CH_2Cl_2 (300 mL). The mixture was stirred for 20 min, whereupon the cooling bath was removed and the reaction which was monitored by IR (see compound **18**) was continued at room temperature for 2 h. Dicyclohexylurea was filtered off and the filtrate was cooled again (ice-salt bath). Methanol (50 mL) followed by triethylamine (10 mL) were added with stirring which continued for 30 min and then 23 h at room temperature. The solution was evaporated and the residue was partitioned between water (150 mL) and ether (3 × 150 mL). The aqueous portion was chilled (ice-bath), and it was acidified with citric acid (4.97 g, 26 mmol) to pH 3.3 (pH meter). A white precipitate of monoester **20** was collected by filtration and dried, 4 g (76%), mp 142–145 °C, homogeneous on TLC (S_1): IR 3600–2500 (OH), 1730 (CO, ester), 1705 (CO, acid). An analytical sample was crystallized from cyclohexane, mp 147–149 °C: EI-MS, *m/z* (relative intensity) 317 (M + H, 0.3), 301 (M + H − Me, 28.7), 261 (13.9), 245 (18.7), 185 (25.4), 109 (16.3), 57 (100.0); CI-MS, *m/z* (relative intensity) 317 (M + H, 5.0), 301 (M + H − Me, 38.8), 261 (100.0), 245 (25.8), 185 (33.8). Anal. Calcd for $C_{15}H_{24}O_7$: C, 56.95; H, 7.65. Found: C, 56.70; H, 7.62. Extraction of the filtrate with ether (3 × 200 mL) gave another crop of **20** (0.55 g, 11%) as a white foam containing a trace of diacid **16** according to TLC (S_1).

(±)-Methyl 4β-Carbamoyl-2α,3α-[(dimethylmethylene)dioxy]-5β-*tert*-butoxy-1β-cyclopentanecarboxylate (19). A. From Monoamide 18. Diazomethane (33 mmol) was introduced into a stirred suspension of amide **18** (3.59 g, 12 mmol) in ether (15 mL) cooled in an ice-bath. An excess of diazomethane was quenched with 10% acetic acid and the solution was evaporated to give a partly crystalline residue. The latter was extracted with hot benzene (15 mL). After cooling, the solution was poured on the top of a silica gel column (50 g, 7 × 5 cm) which was eluted with benzene (400 mL), toluene (700 mL), and toluene–ethyl acetate (9:1, 600 mL). The appropriate fractions were pooled and they were evaporated to give a white solid **19** (2.54 g, 71%), homogeneous on TLC (S_1). An analytical sample was obtained by crystallization from cyclohexane, mp 84–86 °C: IR 3390 (NH_2), 1730 (CO, ester), 1660 ($CONH_2$); EI-MS, *m/z* (relative intensity) 316 (M + H, 1.1), 300 (M − Me, 2.6), 260 (12.1), 201 (25.4), 184 (21.3), 142 (37.4), 88 (68.8), 57 (79.2). Anal. Calcd for $C_{15}H_{25}NO_6$: C, 57.13; H, 7.98; N, 4.44. Found: C, 56.98; H, 7.87; N, 4.30.

B. From Monoester 20. A solution of monoester **20** (3.8 g, 12 mmol) in THF (100 mL) was cooled to 0 °C under nitrogen. Triethylamine (1.96 mL, 14 mmol) followed by isobutyl chloroformate (1.82 mL, 14 mmol) were added with stirring. The mixture was stirred at 0 °C for 30 min, whereupon THF saturated with NH_3 at 0 °C (75 mL) was added during 10 min. The stirring was continued for an additional 30 min. at 0° and then 1 h at room temperature. Triethylamine hydrochloride was filtered off, the filtrate was evaporated and the residue was dissolved in ether. The solution was again filtered and the solvent was removed to give a syrup that was crystallized from cyclohexane–acetone (4:1, 50 mL) at 0 °C. Crystalline amide ester **19** was obtained in three crops, 3.41 g (90%), mp 113–115 °C (first crop), homogeneous on TLC (S_1). Compound **19** was identical (TLC S_1, IR, ^1H NMR) with a sample prepared by method A.

(±)-Methyl 2α,3α-[(Dimethylmethylene)dioxy]-5β-*tert*-butoxy-4β-[(*tert*-butylcarbonyl)amino]-1β-cyclopentanecarboxylate (21a). Compound **19** (664 mg, 2.1 mmol) was dissolved in a mixture of *tert*-butyl alcohol (10 mL) and DMF (5 mL) at 40 °C with stirring. Lead tetraacetate (4.47 g, 10 mmol) was added and the solution that immediately turned brown was refluxed for 15 min. The cooled solution was evaporated and the residue was chromatographed on a silica gel column (15 g, 7 × 2 cm) using solvent system S_7. The fractions containing carbamate **21a** were evaporated to give a white solid, 650 mg (98%), homogeneous on TLC (S_7). Crystallization from methanol gave **21a** (630 mg, 95%), mp 104–106 °C: IR 3380 (NH), 1745 (CO, ester), 1720 (CO, urethane), 1510 (NH, amide II); EI-MS, *m/z* (relative intensity) 388 (M + H, 0.1), 276 (5.5), 260 (5.2), 230 (16.1), 217 (11.8), 172 (7.6), 154 (6.0), 140 (6.3), 128 (8.6), 116 (9.3), 103 (16.7), 100 (12.0), 72 (7.1), 57 (100.0); CI-MS, *m/z* (relative intensity) 388 (M + H, 2.9), 332 (6.7), 288 (80.4), 276 (84.2), 258 (27.9), 232 (100.0), 218 (31.3). Anal. Calcd for $C_{19}H_{33}NO_7 \cdot {}^1/_5H_2O$: C, 58.35; H, 8.61; N, 3.58. Found: C, 58.36; H, 8.67; N, 3.57.

2α,3α-[(Dimethylmethylene)dioxy]-5β-*tert*-butoxy-1β,4β-cyclopentanedicarboxylic Acid Imide (22). A solution of amide ester **19** (50 mg, 0.6 mmol) in DMF (4 mL) and benzyl alcohol (4 mL) was heated to 40 °C. Lead tetraacetate (1.35 g, 4 mmol) was added and the heating was continued for 1 h at 40 °C. After cooling the solids were filtered off and the filtrate was evaporated. The residue was partitioned between petroleum ether (10 mL) and water (10 mL). The organic phase was dried ($MgSO_4$) and evaporated to give syrup **22** which crystallized during drying at 0.1 Torr at room temperature, 20 mg (40%), homogeneous on TLC (S_1), mp 166–167 °C: IR 3400 (br), 3220 (NH), 1710 (CO); EI-MS, *m/z* (relative intensity) 284 (M + H, 88.0), 268 (M − Me, 86.3), 228 (43.6), 141 (28.0), 109 (54.1), 81 (46.8), 57 (100.0). Anal. Calcd for $C_{14}H_{21}NO_5$: C, 59.35; H, 7.47; N, 4.94. Found: C, 59.03; H, 7.53; N, 4.50.

(±)-2α,3α-[(Dimethylmethylene)dioxy]-4β-[(*tert*-butoxycarbonyl)amino]-5β-*tert*-butoxy-1β-cyclopentanemethanol (23). A mixture of finely powdered anhydrous $CaCl_2$ (342 mg, 3.1 mmol) and $NaBH_4$ (233 mg, 6.2 mmol) was stirred in THF (20 mL) for 1 h at room temperature. A solution of ester carbamate **21a** (400 mg, 1 mmol) in THF (5 mL) was then added and the resultant mixture was refluxed with continuous stirring for 3.5 h. The solids were filtered off, the filtrate was cooled, water (20 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 40 mL). The dried ($MgSO_4$) organic phase was evaporated to give colorless syrup **23** (324 mg, 81%). The latter was chromatographed on a silica gel column (15 g, 7 × 2 cm) in benzene–ethyl acetate (9:1) and (4:1, total volume 400 mL). The appropriate fractions were combined and evaporated to a syrup (280 mg, 70%) which soon crystallized to give white solid **23**, homogeneous on TLC (S_1), mp 94–96 °C: IR 3360, 3420 (OH, NH), 1720, 1680 (CO); CI-MS, *m/z* (relative intensity) 360 (M + H, 1.0), 260 (100.0), 248 (24.4), 230 (7.3), 204 (58.3), 146 (14.1). Anal. Calcd for $C_{18}H_{33}NO_6$: C, 60.14; H, 9.24; N, 3.89. Found: C, 60.29; H, 9.43; N, 4.00.

(±)-4β-Amino-2α,3α,5β-trihydroxy-1β-cyclopentanemethanol Hydrochloride (24). A solution of the protected alcohol **23** (400 mg, 1.1 mmol) in 2 M HCl in methanol (10 mL) was stirred for 5 h at room temperature. The solution was evaporated and the resultant syrup was crystallized from ethanol–ether (1:2, 4 mL) to give hydrochloride **24**, 330 mg (83%), mp 134–136 °C, homogeneous on TLC (S_8): IR 3330 (OH + NH), 1600 (NH_3^+); EI-MS, *m/z* (relative intensity) 164 (M + H, free base, 1.7), 114 (6.5), 102 (10.5), 97 (20.5), 86 (16.2), 72 (98.1), 59 (100.0). Anal. Calcd for $C_6H_{13}NO_4 \cdot HCl$: C, 36.10; H, 7.06; N, 7.01; Cl, 17.76. Found: C, 36.14; H, 6.92; N, 6.84; Cl, 17.72.

(±)-6′β-Hydroxyaristeromycin (8). A mixture of amine hydrochloride **24** (390 mg, 1.2 mmol), 5-amino-4,6-dichloropyrimidine (500 mg, 3 mmol), 1-butanol (15 mL), and triethyl-

amine (1.5 mL, 9.5 mmol) was refluxed for 18 h. After cooling, the solution was evaporated and the residue was partitioned between water (20 mL) and CH_2Cl_2 (3 × 50 mL). The aqueous portion was evaporated to a brown syrup (390 mg) which was chromatographed on a silica gel column (20 g, 8 × 3 cm) in solvent S_9 to give intermediate **25** as a light yellow powder, homogeneous on TLC (S_9), 360 mg (81%). This product, containing according to the ^1H NMR and UV spectra 0.5 mol of triethylamine hydrochloride, was used in the subsequent step without further purification: IR 3600–3100 (OH + NH), 1570 and 1390 (aromatic C=C and C=N); UV max (ethanol) 297 (ε 9100), 267 (ε 10 100), 207 (ε 18 200); ^1H NMR (CD_3SOCD_3) 7.72 (s, 1, pyrimidine ring H), 6.87 (br s, 1, NH), 5.26 (br s, 2, NH_2), 4.79, 4.56 and 4.38 (3 br s, 4, OH), 4.11 and 4.01 (2 br s, 3, $H_1 + H_2 + H_5$), 3.65 (2 s, 3, $CH_2 + H_3$); NEt_3·HCl, 3.08 (q, 3, CH_2), 1.23 (t, 4.5, Me); ^{13}C NMR 152.28, 145.40; 136.73; 123.78 (pyrimidine ring C), 72.81 (C_2), 69.46 (C_3), 66.95 (C_5), 61.96 (C_1), 59.19 (CH_2), 52.33 (C_4); NEt_3·HCl, 45.41 (CH_2), 8.46 (Me); EI-MS, m/z (relative intensity) 290 (M, 4.1), 213 (13.0), 199 (8.8), 187 (5.8), 169 (25.1), 144 (pyrimidine base, 36.0).

A mixture of intermediate **25** (280 mg, 0.78 mmol), *p*-toluenesulfonic acid hydrate (300 mg, 1.53 mmol), triethyl orthoformate (20 mL), and DMF (10 mL) was stirred for 6 h at room temperature. Triethylamine (0.3 mL, 1.5 mmol) was then added and the solution was evaporated to give a brown syrup which was chromatographed on a 3-mm thick loose layer of silica[53] gel GF_{254} (35 × 15 cm) in solvent S_1. The band of compound **26** was eluted with methanol and the eluate was evaporated to give a colorless hygroscopic syrup, 280 mg (70%), homogeneous on TLC (S_{10}): UV max (ethanol) 264 (ε 8000); IR 1640–1600, 1250 (aromatic C=C and C=N); ^1H NMR (CD_3SOCD_3) 8.88, 8.87, 8.86, 8.85; 8.811, 8.807 (4 + 2s, 2, H_2- and H_8-purine), 6.14 and 6.01 (2 s, 1, CH, dioxolane $CH(O-)_3$, 38% endo, 62% exo), 2.50 (m, 1, H_4'), 1.19, 1.09 and 1.01 (cluster of m, 8, Me of Et, ortho ester + NEt_3·HCl); EI-MS, m/z (relative intensity) 412 (M, 5.3), 366 (30.5), 291 (19.1), 246 (17.8), 234 (32.0), 155 (6-chloropurine + H, 100.0), 103 (68.2). Compound **26** was 80% pure as estimated by UV spectrophotometry using ε 9300 as a reference.[54] According to ^1H NMR it contained 2 mol of H_2O and 0.2 mol of NEt_3·HCl.

A stream of NH_3 was introduced at −70 °C into a solution of crude intermediate **26** (60 mg, 0.12 mmol) in methanol (30 mL) which was placed in a stainless steel bomb for 1 h. The bomb was then closed and heated at 100 °C (bath temperature) for 24 h. After cooling to −70 °C, the bomb was carefully opened and the contents were evaporated. Compound **27** was homogeneous on TLC (S_6), 50 mg (70%), mp 238–240 °C: UV (ethanol) 258 nm (ε 9500), 66% purity; ^1H NMR (CD_3SOCD_3) 8.37, 8.33, 8.12 (2 + 1 s, 2, H_2- and H_8-purine), 6.15 and 6.08 (2 s, 1, CH, dioxolane $CH(O-)_3$, 38% endo, 62% exo), 2.43 (m, 1, H_4'), 1.23 and 1.07 (cluster of m, 6, Me); EI-MS, m/z (relative intensity) 394 (M + H, 5.2), 393 (M, 4.3), 348 (56.7), 290 (28.4), 216 (49.5), 135 (Ade, 100.0).

A solution of crude ortho ester **27** (280 mg, 0.5 mmol) in 1 M HCl in methanol (30 mL) was stirred overnight at room temperature. The mixture was evaporated and the residue was absorbed on a column of Dowex 50 (WX 4, 200–400 mesh, H^+, 10 g wet wt, 6 × 1.5 cm). The column was washed with water (300 mL) and then with 0.14 M NH_4OH (300 mL). The elution was monitored by UV at 254 nm (Uvicord II, LKB, Bromma, Sweden) and, visually, by disappearance of the white product 8 which crystallized in the column. The appropriate fractions were pooled and evaporated to give crude 6′β-hydroxyaristeromycin (**8**) as a solid. EI-MS showed the presence of *O*-formyl derivative(s) (m/e 309, 310) of 8. Therefore, the crude product was kept in concentrated NH_4OH (50 mL) for 24 h at room temperature. The solution was evaporated and the residue was crystallized from water to give 130 mg (98%) of **8**, homogeneous on TLC (S_{11}), mp 280–282 °C: UV (ethanol) 261 (ε 14 500); IR 3400 (NH + OH), 1660–1600, 1570, 1370–1220 (aromatic C=N and C=C); ^1H NMR (CD_3SOCD_3) 8.53, 8.52 (2 s, 2, $H_2 + H_8$), 7.51 (s, 2, NH_2), 5.42 (d, 1, 2′-OH), 5.26 (d, 1, 6′-OH), 5.06 (d, 1, 3′-OH), 5.04 (d, 1, H_1'), 4.90 (qt, 1, H_6'), 4.74 (t, 1, 5′-OH), 4.50 (q, 1, H_2'), 4.17 (q, 1, H_3'), 4.01 (m, 2, H_5'), 2.50 (sextet, 1, H_4'); ^{13}C NMR 155.76 (C_6), 151.97 (C_2), 150.14 (C_4), 140.14 (C_8), 118.54 (C_5), 71.80 (C_2'), 69.43 (C_3'), 67.60 (C_6'), 62.90 (C_1'), 59.17 (C_5'), 52.50 (C_4'); EI-MS, m/z (relative intensity) 282 (M + H, 1.9), 281 (M, 3.8), 264 (M − OH, 6.5), 206 (8.6), 178 (Ade-CH=CHOH + H, 49.1), 163 (8.5), 148 (18.1), 136 (Ade + H, 100.0), 135 (Ade, 92.6), 108 (20.2); exact mass calcd 281.11237, found 281.1130. Anal. Calcd for $C_{11}H_{15}N_5O_4$: C, 46.97; H, 5.37; N, 24.89. Found: C, 46.98; H, 5.47; N, 24.71.

Attempted Deamination of (±)-6′β-Hydroxyaristeromycin (8) with Adenosine Deaminase. A. UV Spectrophotometric Assay. Adenosine deaminase from calf intestine (Type II, Sigma Chemical Co., St. Louis, Mo, 0.02 unit) was added to a 0.135 mM solution of **8** in 0.05 M Na_2HPO_4 (pH 7.5, 3 mL) at room temperature. No change in absorbance at 265 nm or shift of UV max was noted during 10 min. Conversion of adenosine to inosine was quantitative as shown by a control experiment.

B. Electrophoretic Assay. Adenosine deaminase (0.4 unit) was added to a 6 mM solution of **8** in 0.05 M Na_2HPO_4 (pH 7.5, final volume 0.4 mL), and the mixture was kept at room temperature for 23 h. An aliquot examined by paper electrophoresis (flat plate, Savant Instruments, Hicksville, NY) in 1 M acetic acid showed only the presence of starting material **8**. The same result was obtained after incubation at 38 °C.

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