Regiospecific synthesis of cyclopentane analogs of (2′- and 3′-deoxy-*threo*-pentofuranosyl)-uracil and -2-thiouracil nucleosides

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Aminohydroxycyclopentanemethanols are important precursors for the synthesis of cyclopentane analogs of purine and pyrimidine nucleosides. The regiospecific synthesis of two new aminohydroxycyclopentanemethanols, **17** and **22**, is described. In these syntheses the desired configuration in the cyclopentane ring is obtained by opening the *cis*-acetoxy-1,3-cyclopentanedicarboxylic acid anhydride **3** with either ammonia or methanol. The attack by each nucleophile occurs at the carbonyl carbon farthest away from the acetoxy group to give a carbamoyl or an ester function at this position. Since the ester function is destined to become the hydroxymethyl substituent and the carbamoyl function the amino substituent, the type of nucleophile used to open the anhydride determines whether the 2-deoxy or the 3-deoxy isomer is obtained. Coupling of the aminohydroxycyclopentanemethanols with 3-ethoxypropenoyl isocyanate followed by cyclization of the acyl ureas in 2 *N* H_2SO_4 gave two new cyclopentane analogs of uracil nucleosides. Coupling of the aminohydroxycyclopentanemethanols with 3-ethoxypropenoyl isothiocyanate followed by cyclization of the acyl thioureas in 15 *N* aqueous ammonia gave two new cyclopentane analogs of 2-thiouracil nucleosides.

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Les aminohydroxycyclopentaneméthanols sont des précurseurs importants dans la synthèse des analogues cyclopentaniques des nucléosides de la pyrimidine ainsi que de la purine. On décrit des synthèses régiospécifiques des deux nouveaux aminohydroxycyclopentaneméthanols **17** et **22**. Dans ces synthèses, on obtient la configuration désirée du cyclopentane en procédant à l'ouverture de l'anhydride de l'acide acétoxy cyclopentanedicarboxylique-1,3-*cis*, **3**, à l'aide d'ammoniac ou de méthanol. Chaque nucléophile attaque le carbone du carbonyle le plus éloigné du groupe acétoxy; cette réaction donne naissance à une fonction carbamoyle ou à une fonction ester dans cette position. Puisque la fonction ester est destinée à devenir le substituant hydroxyméthyle alors que la fonction carbamoyle est destinée à devenir le substituant amino, le type de nucléophile utilisé pour ouvrir l'anhydride détermine la nature de l'isomère déoxy-2 ou déoxy-3 qui sera obtenu. Le couplage des aminohydroxycyclopentaneméthanols avec de l'isocyanate d'éthoxy-3 propénoyle, suivi d'une cyclisation des acylurées en présence de H_2SO_4 2 *N*, conduit à deux nouveaux analogues cyclopentaniques des nucléosides de l'uracile. Le couplage des aminohydroxycyclopentaneméthanols avec de l'isothioocyanate d'éthoxy-3 propénoyle, suivi d'une cyclisation des acyl-thiourées en présence d'ammoniaque 15 *N*, conduit à deux nouveaux analogues cyclopentaniques des nucléosides du thio-2 uracile.

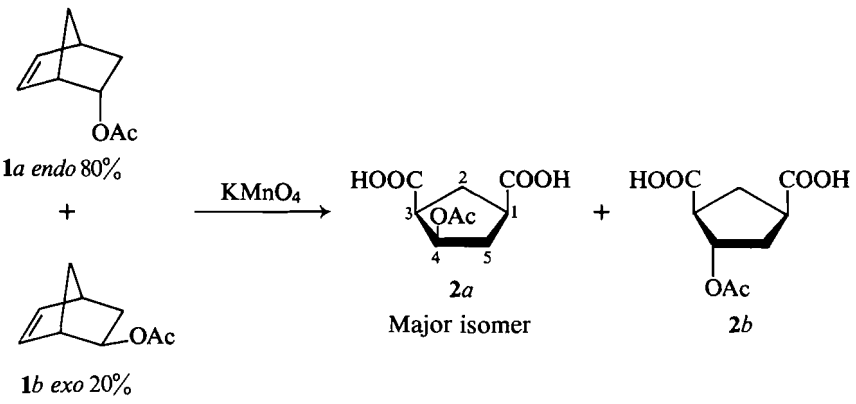
[Traduit par le journal]

Introduction

The replacement of the furanose-ring oxygen by a methylene group can have a profound effect on a nucleoside's biochemical and biological activity. Guranowski *et al.* (1) showed that the cyclopentane analog of adenosine was several orders of magnitude less effective as a substrate for the beef liver enzyme *S*-adenosylhomocysteine hydrolase than adenosine and also that it is the most potent inhibitor of this enzyme with a K_i of 5×10^{-9} *M*, results which indicated the necessity of the oxygen of the ribofuranose ring for the enzymatic reaction but not for binding to the active site. A large number of cyclopentane analogs of both purine and pyrimidine nucleosides have been synthesized and many have shown antiviral and (or) anticancer activity (see, for example, refs. 2–7).

Virtually all of the syntheses of cyclopentane analogs of nucleosides described to date involve the prior preparation of an appropriately functionalized cyclopentylamine followed by the coupling of this amine with an appropriate base precursor. The central problem, therefore, in the synthesis of the cyclopentane analogs is the synthesis of a cyclopentane ring with the different substituents having the required configurations. Shealy *et al.* (8) have synthesized cyclopentane analogs of nucleosides having the "deoxy*ribo*" (8*a*) and *ribo* (8*b*) configurations by the oxidation of *exo*-5-norbornen-2-yl acetate and *exo-cis*-norbornen-2,3-diyl diacetate, respectively, with sodium permanganate. More recently, cyclopentylamines having the *ribo* (9, 10), *lyxo* (10), and *arabino* (11) configurations have been prepared from the readily available 2-azabicyclo-[2.2.1]hept-5-en-3-one (12), which is structurally analogous to norbornene. Holý (13) reported the preparation of the cyclopentane analog having the *ribo* configuration by catalytic hydrogenation of diethyl cyclopentane-2,3-dione-1,4-dicarboxylate. In the preparation of cyclopentane analogs of *C*-nucleosides, bin Sadikun *et al.* (4) achieved the *lyxo* configuration using norborn-5-ene-2-*endo*,3-*endo*-dicarboxylic acid anhydride. Just *et al.* achieved the *arabino* configuration using 5-carbomethoxy-2-*exo*,3-*endo*-dipivaloyoxybicyclo-[2.2.1]hept-5-ene (14) and the "2-deoxy*ribo*" configuration using 2-carbomethoxy-*exo*-5-*p*-nitrobenzoyloxybicyclo-[2.2.1]hept-2-ene (15). Paulsen and Maass (16) prepared cyclopentane rings having substituents in various orientations by allylhydroxylation of epoxides of cyclopentanemethanols using phenyl selenide. Shealy and O'Dell (7) obtained the cyclopentane analog of Ara-C from the cyclopentane analog of cytidine by way of the 2,2′-anhydro derivative.

In most of the above-mentioned syntheses (2–6, 8–11, 14, 15) the configurations of the cyclopentane rings are determined by the intermediacy of a bicyclo[2.2.1] derivative. The methods of Paulsen and Maass (16) and Holý (13), which do not utilize such a bicyclo[2.2.1] intermediate, give mixtures of isomers which must be resolved. Some of the methods (8*a*, 11) which utilize a bicyclo[2.2.1] intermediate also produce mixtures of isomers. The present article describes the synthesis of new aminohydroxycyclopentanemethanols, **17** and **22**,



SCHEME 1

by regiospecific routes from the common precursor (±)-(1β,3β,4β)-4-acetoxy-1,3-cyclopentanedicarboxylic acid anhydride (**3**), and the conversion of each of them into uracil and 2-thiouracil nucleosides.

Results and discussion

The starting material for the synthesis of (±)-(1β,3β,-4β)-4-amino-3-hydroxycyclopentanemethanol (**17**) and (±)-(1β,2β,4β)-4-amino-2-hydroxycyclopentanemethanol (**22**) was a commercial sample (see experimental section) of 5-norbornen-2-yl acetate, which was shown to contain 80% of the *endo* (**1***a*) and 20% of the *exo* (**1***b*) isomers. An efficient method has been described by Birch *et al.* (17) for the oxidation of norbornene using $NaMnO_4$ to give cyclopentane-*cis*-1,3-dicarboxylic acid in 95% yield, and the method has been adapted for the preparation of *cis*-diacids from *exo*-5-norbornen-2-yl acetate and the *exo-cis*- and *endo-cis*-5-norbornen-2,3-diyl diacetates by Shealy *et al.* (8). In the present work the methods of the above workers (8, 17) have been utilized; however, instead of using $NaMnO_4$ as the oxidant, the more readily available $KMnO_4$ has been used to give the described diacid **2***a*[1] (Scheme 1) in 77% yield after recrystallization and a crude sample of **2** in 93%. This high yield has been consistently obtained in experiments in which the reaction temperature was maintained below 12°C; however, when the reaction temperature was allowed to rise above 40°C the yield of the desired diacid was greatly reduced.

The *cis* (**2***a*) and the *trans* (**2***b*) isomers were observed to have significantly different ^{1}Hmr spectra using a 200-MHz spectrometer; however, two spectral features which allow one to easily distinguish these isomers even on a 60-MHz instrument are the significantly different chemical shifts of the acetoxy methyls, which resonate at δ 1.90 in the case of the *cis* isomer (**2***a*) and at δ 2.00 in the case of the *trans* isomer (**2***b*). In addition, although the chemical shifts of the H-4 protons in the two isomers are identical at δ 5.20, the coupling patterns are quite distinct. In the *cis* isomer this proton couples with two *cis* vicinal protons and one *trans* vicinal proton to give a triplet-of-doublets coupling pattern, whereas in the *trans* isomer this proton couples with two *trans* vicinal protons and one *cis* vicinal proton to give a coupling pattern approximating an overlapping doublet of triplets.

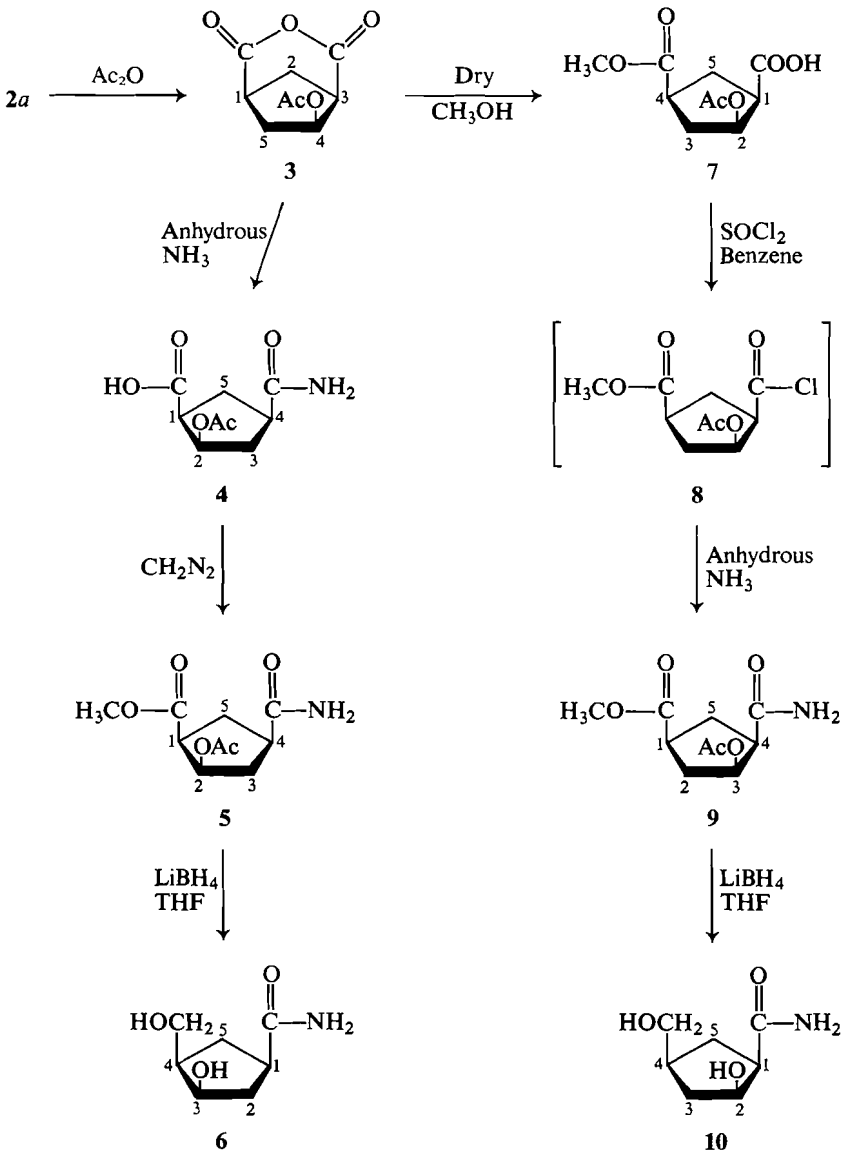
Regiospecific opening of anhydride 3

The opening of the anhydride **3** (see Scheme 2) with anhydrous methanol followed by conversion of the carboxylic acid group into the carbamoyl function produced a single regioisomer **9**. Analysis of the ^{1}Hmr spectra of both the crude oily product (see experimental section) and the components separated by column chromatography on silica gel failed to reveal signals attributable to **5**. Similarily, the ^{1}Hmr spectrum of **4**, a compound which was produced by opening of the anhydride **3** with anhydrous ammonia, did not reveal any traces of a second regioisomer. In this second case, however, only the crystalline solid that represented a 91.3% yield was analyzed, and thus the possibility of the presence of a small amount of the other regioisomer, which may have been present in the crude mother liquor, was not eliminated. In both cases, however, the nucleophile attacks the carbonyl carbon farthest away from the acetoxy group. Compound **4** was esterified using diazomethane to give compound **5**. Therefore, since the carbamoyl function is destined to become N-1 in the pyrimidine nucleoside and the ester function the hydroxymethyl group at C-4′ in the nucleoside, it is possible to obtain the "2-deoxy*lyxo*" or the "3-deoxy*lyxo*" configuration selectively (as shown in Scheme 2). In contrast, in the case of (±)-(1β,3β,4α)-4-acetoxy-1,3-cyclopentanedicarboxylic acid anhydride, in which the acetoxy group has the *trans* configuration, Shealy and O'Dell (8*a*) obtained the two regioisomers having the 2-deoxy*ribo* and "3-deoxy*ribo*" configurations in approximately equal amounts, thus requiring the separation of the two regioisomers by column chromatography. From these observations and a consideration of a model of anhydride **3** it seems likely that the large *cis*-acetoxy group prevents facile attack by nucleophiles on the nearby carbonyl carbon by steric interactions.

The ester functions of compounds **5** and **9** were reduced using $LiBH_4$. In the case of **5** it was observed that the percentage yield of the product **6** was greatly dependent on the time of reflux during the reduction, ranging from 29% after 2 h to 81% when the time of reflux was only 20 min.

The configurations of compounds **4**–**10** (Scheme 2) have been assigned with the aid of ^{1}Hmr decoupling experiments. The chemical shifts of the methylene protons of the hydroxymethyl substituent in compounds **6** and **10** are of particular interest. In compound **10** these two protons are equivalent and give rise to a single multiplet (doublet of doublet due to coupling with O*H* and H-4) at δ 3.33; however, in the case of

[1] Structures **1**–**10** and **17**–**30** depict only one enantiomer of racemic mixtures. The relative configurations of substituent groups on the cyclopentane ring are specified by the α,β system used for steroids (31). Substituents which are written below the plane of the cyclopentane ring are designated α and those above the plane of the ring as β.



SCHEME 2

compound **6** two separate multiplets are observed for these two methylene protons, at δ 3.35 and 3.59. This non-equivalence of the hydroxymethyl methylene protons indicates that rotation of the hydroxymethyl substituent in compound **6** is restricted.

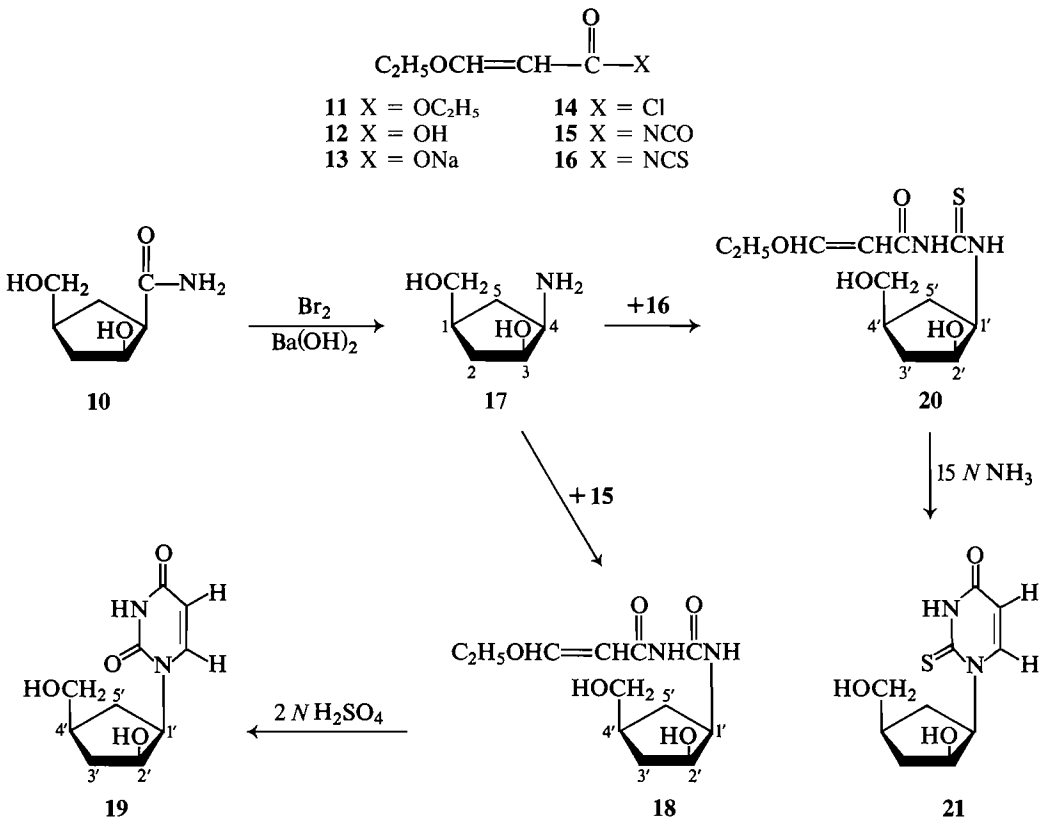
*Synthesis of the carbocyclic analogs (**19** and **21**) of 3-deoxy-*threo*-pentofuranosyl nucleosides*

The carbamoyl substituent in **10** was converted into the amino substituent in **17** (see Scheme 3) by the Hofmann reaction (18) using the procedure described by O'Dell and Shealy (19) for the preparation of aminohydroxycyclopentanemethanols having the "deoxy*ribo*" configurations. The amine **17** was coupled then with 3-ethoxypropenoyl isocyanate (**15**), which was prepared by previously described methods (20–23), to give compound **18**. Nucleoside analog **19** was prepared by heating **18** in 2 *N* H_2SO_4 at reflux temperature for 30 min. The ^{1}Hmr spectrum of compound **19** is very complex; however, it is different from that of the nucleoside analog having the "3-deoxy*ribo*" configuration, a sample of which had been prepared by previously described methods (22). The ^{1}Hmr signals in the spectra of these nucleosides have been assigned with the aid of spin–spin decoupling experiments.

Compound **20** was prepared by coupling **17** with 3-ethoxypropenoyl isothiocyanate (**16**) (see Scheme 3), which was prepared as described by Shaw and Warrener (21). Nucleoside analog **21** was obtained by heating **20** in 15 *N* aqueous ammonia at 100°C for 20 min. The multiplet patterns of the ^{1}Hmr spectra of nucleoside analogs **19** and **21** were observed to be very similar using a 200-MHz spectrometer; however, in general, the signals of protons in nucleoside analog **21** are found farther downfield than the signals of corresponding protons in nucleoside analog **19**. For example, the signal of H-1′ resonates at δ 4.49 in the case of **19** and at δ 5.41 in the case of **21**. The coupling constants found in the H-1′ multiplet are virtually identical for both nucleoside analogs. The largest difference in chemical shifts occurs for the H-3 proton, which in the case of **19** resonates at δ 11.20 while in the case of **21** it resonates at δ 12.59. In both of these analogs H-5 has a long-range coupling constant of 1.7–1.9 Hz to H-3 in addition to the vicinal coupling constant of 7.8–8.1 Hz to H-6.

*Synthesis of the carbocyclic analogs (**24** and **26**) of 2-deoxy-*threo*-pentofuranosyl nucleosides*

Two approaches have been utilized for the conversion of the



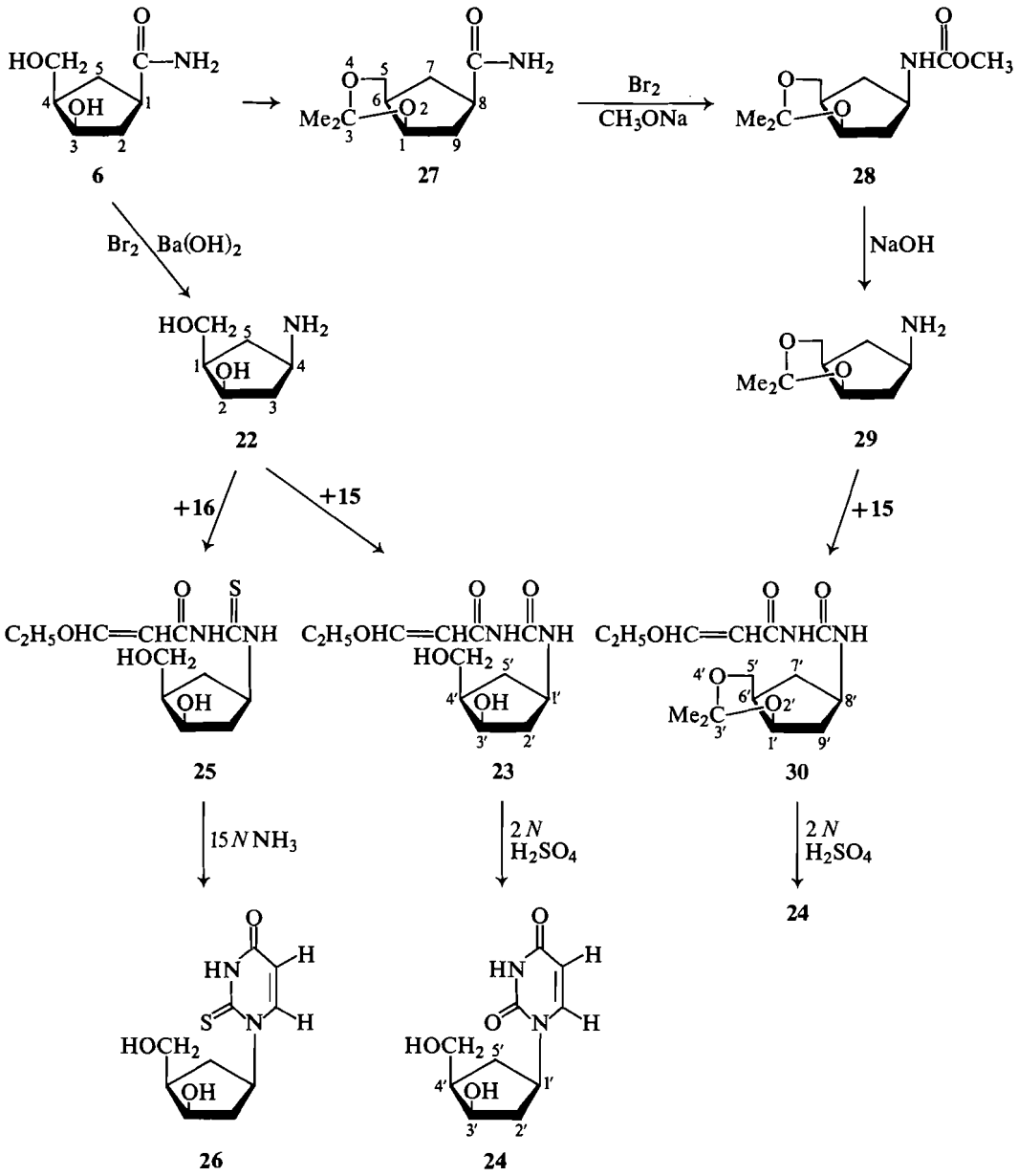
SCHEME 3

carbamoyl substituent in compound **6** to the amino substituent (see Scheme 4). In the first approach the Hofmann reaction was performed directly on **6**, which gave the amine **22** after purification on a cation-exchange resin in 27% yield. In the second approach the hydroxyls in compound **6** were protected by an isopropylidene group and the Hofmann reaction (18) was performed on **27** in methanol using sodium methoxide as the base to give the carbamate **28**. Hydrolysis of the carbamate with sodium hydroxide gave the amine **29** in 54% yield from **6**. The advantages of this latter route, despite the fact that it involves three steps instead of one, are not only the much greater overall yield but also the fact that the work-up in this latter approach is greatly simplified. In addition, the protected compound **29** gives significantly better yields in the subsequent steps leading to nucleoside analog **24** (see Scheme 4). Thus, **24** has been prepared in 26.4% yield from **6** by the latter route compared to 7.5% yield by the first route, a 3.5-fold improvement. Nucleoside analog **26** has been obtained by coupling the unprotected compound **22** with **16** to give **25**, followed by heating at 100°C in 15 *N* aqueous ammonia.

An attempt was made also to synthesize the amine **22** by first converting the carbamoyl substituent of compound **4** to an amino group by a Hofmann hypobromite reaction; however, the conditions lead to the elimination of acetic acid as shown in Scheme 5.

As was observed in the cases of the nucleoside analogs **19** and **21**, the multiplet patterns of the ^{1}Hmr spectra of analogs **24** and **26** are very similar also, with the multiplets of the 2-thiouracil-containing analog **26** occurring farther downfield than the multiplets of corresponding protons in the uracil-containing analog **24**. This difference in chemical shifts between corresponding protons in the uracil- and 2-thiouracil-containing nucleosides decreases with distance from the thio group such that the protons in the hydroxymethyl substituent resonate at virtually the same chemical shifts in the cases of both nucleoside analogs (**24** and **26**). Also, as previously observed for compound **6**, the ^{1}Hmr spectra of compounds **22**–**26** (Scheme 4) each show two well-separated multiplets for the methylene protons of the hydroxymethyl substituent. In contrast, only a single multiplet was observed for these protons in the spectra of compounds **10** and **17**–**21** (Scheme 3). The chemical shifts and the coupling constants of one of the methylene multiplets are very similar in the cases of compounds **6** and **22**–**26**; in the cases of all of these compounds this multiplet occurs in the δ 3.58–3.60 region. In the spectrum of compound **22** coupling to the hydroxyl proton is not observed. The chemical shift of the other multiplet varies over a greater range between the different compounds (**6**, **22**–**26**); in compound **6** it occurs at δ 3.35, in **22** at δ 3.37, in **23** and **25** at δ 3.40, and in the nucleoside analogs **24** and **26** at δ 3.43 and 3.44, respectively. The non-equivalence of the two methylene hydrogens in the hydroxymethyl substituent may be in part due to intramolecular hydrogen bonding between the hydroxyls. That hydrogen bonding alone may not account for these observations is indicated by the fact that, when the two hydroxyls in each of compounds **6**, **19**, and **24** are acetylated, non-equivalence is still observed to the extent of approximately 0.10 ppm for the corresponding methylene protons in the acetates of **6** and **24**, and also in the acetate of **19**; however, in this last acetate the difference in chemical shifts between these methylene protons is much smaller than in the first two.

In the ^{1}Hmr spectra of compounds **27**–**30**, in which these methylene protons are part of a heterocyclic six-membered ring, the multiplets arising from these protons are also well separated but appear farther downfield. The chemical shifts of one of the multiplets are in the δ 3.50–3.54 region and those



SCHEME 4

of the other in the δ 3.96–4.03 region.

Ultraviolet spectra of the nucleoside analogs

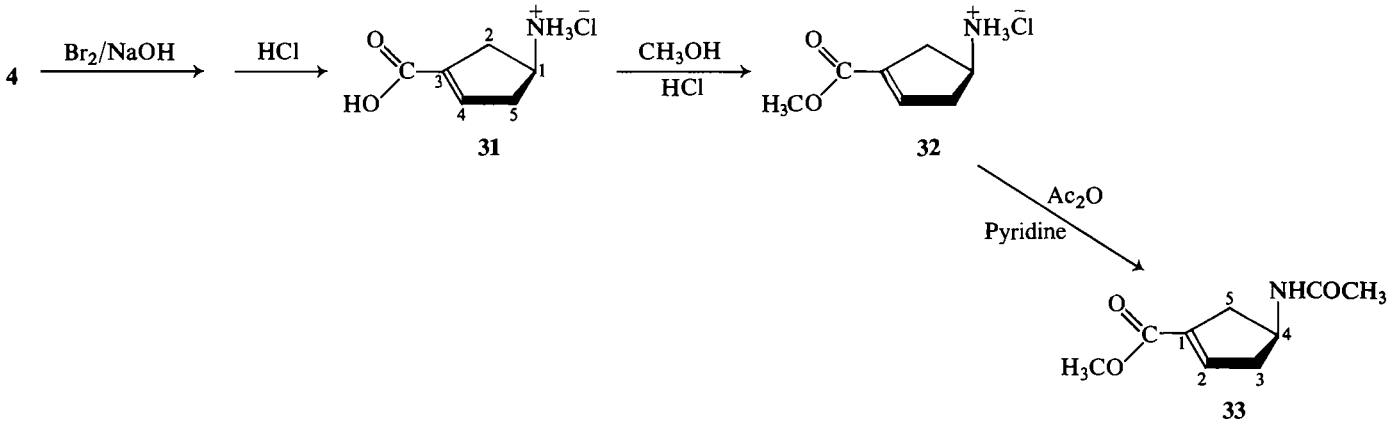
The ultraviolet spectra of the uracil-nucleoside analogs **19** and **24** exhibit virtually identical absorption maxima in both acidic and alkaline ethanol and they closely resemble the spectra of 1-methyluracil (24) at the corresponding pH's. The spectra of the 2-thiouracil-nucleoside analogs **21** and **26** are also similar in both acidic and alkaline ethanol, although quite different from those of **19** and **24**. The absorption maxima in the spectra of **21** and **26** occur at longer wavelengths and the spectra have a shoulder at approximately 290 nm in acidic and neutral ethanol. The molar absorptivities at the absorption maxima are also much greater in the cases of the 2-thiouracil-nucleoside analogs, especially in alkaline ethanol in which they are more than 2-fold greater. The ultraviolet spectra of the 2-thiouracil-nucleoside analogs **21** and **26** closely resemble those of 1-methyl-2-thiouracil (24) at the corresponding pH's.

Conclusions

Two new cyclopentane analogs of uracil nucleosides having the "2-deoxy*lyxo*" and "3-deoxy*lyxo*" configurations have been synthesized regiospecifically. In addition, the corresponding analogs of 2-thiouracil nucleosides have been synthesized; this work represents the first reported synthesis of cyclopentane analogs of nucleosides having the 2-thiouracil base. The synthetic routes also provide the possibility of regiospecific synthesis of cyclopentane analogs of nucleosides having the "deoxy*ribo*" configurations, by an inversion of configuration at C-2′ or C-3′ in the corresponding "deoxy*lyxo*" analogs. Analogs having the "2-deoxy*ribo*" configuration have been found to be biologically active in a variety of systems (2, 25).

Experimental

Melting points were determined on a Fisher–Johns apparatus and are uncorrected. The ^{1}Hmr spectra were recorded on a Bruker CXP-



SCHEME 5

200 spectrometer at 200 MHz. Chemical shifts (δ) are given downfield from the signal of Me_4Si. Assignments of chemical shifts and coupling constants were made with the aid of spin-decoupling experiments. The following abbreviations are used in describing ^{1}Hmr signals: singlet (s), doublet (d), triplet (t), quartet (q), quintuplet (qu), sextuplet (se), multiplet (m), and broadened (br). Ultraviolet spectra were recorded on a Perkin–Elmer 552 spectrophotometer. Thin-layer chromatography (tlc) was performed using silica gel 60 F-254. The developed plates were dried and sprayed with a solution of ceric sulfate (1%) and molybdic acid (1.5%) in 10% aqueous sulfuric acid, and heated at ~150°C.

*(±)-(1β,3β,4β)-4-Acetoxy-1,3-cyclopentanedicarboxylic acid (**2**a) and (±)-(1β,3β,4α)-4-acetoxy-1,3-cyclopentanedicarboxylic acid (**2**b)*

5-Norbornen-2-yl acetate[2] (98 g, 0.64 mol) in 2,2,4-trimethylpentane (500 mL) was added to water (4 L) and the mixture was cooled to 10°C. To the stirred mixture $KMnO_4$ (325 g, 2.06 mol) in water (6 L) was added over a period of 3.5 h. During the addition of $KMnO_4$ a steady stream of CO_2 was passed through the reaction mixture and the temperature was maintained between 10 and 12°C using an ice bath. After the $KMnO_4$ had been added, SO_2 was passed through the reaction mixture until it became clear, with the temperature being maintained below 20°C. The volume of the reaction mixture was reduced to 1.6 L, and the mixture was cooled to 5°C and acidified with concentrated HCl (100 mL). It was extracted then with diethyl ether (5 × 400 mL); evaporation of the ether afforded a white solid (115.3 g). The reaction solution was reduced further to 900 mL, the solution was cooled to 5°C, and additional concentrated HCl (20 mL) was added; extraction again with ether (4 × 225 mL) gave an additional 14.3 g of solid, for a total yield of crude product of 129.6 g. The crude solid was recrystallized from ethyl acetate – hexanes and gave, in several crops, 81.3 g of a crystalline solid having mp 131–132°C and 4.0 g having mp 128–131°C, for a total yield of 85.3 g (77%) of **2***a*; ^{1}Hmr (200 MHz, Me_2SO-d_6) δ: 1.90 (3H, s, OAc), 1.95 (1H, m, J_{gem} = 14.7, $^3J_{5,1}$ = 6.1, $^3J_{5,4}$ = 2.7 Hz, H-5), 2.0–2.2 (2H, m, H-2 and H-2′), 2.20 (1H, m, J_{gem} = 14.7, $^3J_{5',1}$ = 10.1, $^3J_{5',4}$ = 5.2 Hz, H-5′), 2.83 (1H, m, H-1), 2.99 (1H, m, $^3J_{3,2}$ = 10.8, $^3J_{3,2'}$ = 8.4, $^3J_{3,4}$ = 5.4 Hz, H-3), 5.20 (1H, t of d, ^3J = 5.3, $^3J_{4,5}$ = 2.7 Hz, H-4), 12.31 (2H, br s, CO_2H at positions 1 and 3); spin–spin decoupled at H-4.

[2] 5-Norbornen-2-yl acetate (bp 73–76°C/14 Torr; 1 Torr = 133.3 Pa) was purchased from the Aldrich Chemical Company and was shown to contain 80% of the *endo* (**1***a*) and 20% of the *exo* (**1***b*) isomers by integration of the well-resolved C-2 proton signals in the ^{1}Hmr spectrum (26). This determination is in good agreement with previous estimates of isomer composition in 5-norbornen-2-yl acetate samples prepared by the Diels–Alder reaction between vinyl acetate and cyclopentadiene (27, 28) which showed the *exo* isomer to comprise about 19% (28).

Two additional crops from the mother liquor of **2***a* gave 22.4 g of a white solid, mp 85–111°C, which was shown by ^{1}Hmr to consist primarily of **2***b*. Compound **2***b* was prepared also from *exo*-5-norbornen-2-yl acetate (**1***b*) (8*a*, 29) by the above oxidation method; mp 114–115°C (lit. (8*a*) mp 116–117°C); ^{1}Hmr (200 MHz, Me_2SO-d_6) δ: 1.79–1.95 (2H, m, H-2 and H-5), 2.00 (3H, s, OAc), 2.09 (1H, m, J_{gem} = 14.1, $^3J_{5',1}$ = 9.0, $^3J_{5',4}$ = 6.6 Hz, H-5′), 2.30 (1H, m, J_{gem} = 13.3, $^3J_{2',1}$ = 9.2, $^3J_{2',3}$ = 8.6 Hz, H-2′), 2.82 (1H, t of d, ^3J = 8.6, $^3J_{3,4}$ = 4.6 Hz, H-3), 2.92 (1H, qu, ^3J = 8.6 Hz, H-1), 5.20 (1H, d of t, $^3J_{4,5'}$ = 6.6, ^3J = 3.9 Hz, H-4), 12.46 (2H, br s, CO_2H at positions 1 and 3); spin–spin decoupled at H-4.

*(±)-(1β,3β,4β)-4-Acetoxy-1,3-cyclopentanedicarboxylic acid anhydride (**3**)*

A stirred mixture of **2***a* (85.1 g, 0.394 mol) in acetic anhydride (1 L) was heated at reflux temperature gently for 45 min. The reaction solution was cooled to room temperature and the solvent was removed under reduced pressure. The residual oil was shaken in the presence of diethyl ether (500 mL) and several seed crystals. The resulting white crystalline solid was collected by filtration and washed with diethyl ether to give **3** (54.6 g) having an initial mp 77–78°C which dropped to a sharp mp of 70°C overnight. The volume of the mother liquor was reduced to 200 mL and cooled in an ice bath to give an additional 4.75 g of a white crystalline solid having mp 70°C. The mother liquor was then evaporated to an oil which was heated at reflux temperature in acetic anhydride (200 mL) for 15 min to give a crystalline grey-brown solid (11.91 g), mp 69°C, for a total yield of 71.2 g (91.3%); ^{1}Hmr (200 MHz, $CDCl_3$) δ: 1.94 (1H, d of t, J_{gem} = 13.1, ^3J = 4.0 Hz, H-2), 2.00 (1H, m, J_{gem} = 15.3, $^3J_{5,4}$ = 3.7, $^4J_{5,2'}$ = 2.7 Hz, H-5), 2.07 (3H, s, OAc), 2.36 (1H, m, J_{gem} = 13.1, $^4J_{2',5}$ = 2.7 Hz, H-2′), 2.65 (1H, d of d of d, J_{gem} = 15.3, $^3J_{5',4}$ = 9.8, $^3J_{5',1}$ = 7.0 Hz, H-5′), 3.26 (1H, m, $^3J_{1,5'}$ = 7.0, $^3J_{1,2}$ = 4.0, $^4J_{1,3}$ = 1.5 Hz, H-1), 3.66 (1H, m, $^3J_{3,4}$ = 6.4, $^3J_{3,2}$ = 4.0, $^4J_{3,1}$ = 1.5 Hz, H-3), 5.44 (1H, d of d of d, $^3J_{4,5'}$ = 9.8, $^3J_{4,3}$ = 6.4, $^3J_{4,5}$ = 3.7 Hz, H-4). Spin–spin decoupling was performed at each of the protons. *Anal.* calcd. for $C_9H_{10}O_5$: C 54.55, H 5.09; found: C 54.22, H 5.22.

*(±)-(1β,2β,4β)-2-Acetoxy-4-carbamoylcyclopentanecarboxylic acid (**4**)*

Dry ammonia was bubbled through a stirred solution of **3** (71.2 g, 0.359 mol) in tetrahydrofuran (450 mL) which had been cooled to 5°C. The bubbling of ammonia was continued for 30 min at a rate which allowed the reaction temperature to be maintained between 10 and 12°C with an ice bath. The reaction mixture was flushed then with N_2 for 30 min. The solid was collected by filtration and dissolved in water (500 mL). The solution was then cooled to ice-bath temperature, acidified with concentrated HCl (35 mL), and left in the ice bath to crystallize. The crystalline product was collected by filtration and washed with a small amount of cold water to give a solid (57.7 g), mp 161–163°C. The volume of the mother liquor was reduced to 100 mL to give an additional 12.9 g of a light grey-brown solid, mp

161–163°C, for a combined yield of 70.6 g (91.3%). An analytical sample was prepared by recrystallization twice from water; mp 164–165°C; ^{1}Hmr (200 MHz, Me_2SO-d_6) δ: 1.82 (1H, d of d of d, J_{gem} = 14.4, $^3J_{3,4}$ = 7.7, $^3J_{3,2}$ = 3.1 Hz, H-3), 1.91 (3H, s, OAc), 1.93–2.14 (2H, m, H-5 and H-5′), 2.19 (1H, m, J_{gem} = 14.4, $^3J_{3',4}$ = 9.7, $^3J_{3',2}$ = 6.0 Hz, H-3′), 2.63 (1H, qu, ^3J = 8.9 Hz, H-4), 2.95 (1H, d of d of d, $^3J_{1,5}$ = 10.8, $^3J_{1,5'}$ = 8.1, $^3J_{1,2}$ = 6.0 Hz, H-1), 5.21 (1H, t of d, $^3J_{2,1}$ = 6.0, $^3J_{2,3'}$ = 6.0, $^3J_{2,3}$ = 3.1 Hz, H-2), 6.84 (1H, br s, $CONH_2$), 7.29 (1H, br s, $CONH_2$), 12.29 (1H, br s, CO_2H); spin–spin decoupled at H-1, H-2, and H-4. D_2O exchange caused the disappearance of signals at δ 6.84, 7.29, and 12.29. *Anal.* calcd. for $C_9H_{13}O_5N$: C 50.23, H 6.09, N 6.51; found: C 49.98, H 6.14, N 6.53.

(±)-Methyl (1β,2β,4β)-2-acetoxy-4-carbamoylcyclopentane-carboxylate (5)

Diazomethane was prepared as described in Vogel (30) and was distilled into the flask containing **4** (30.8 g, 0.143 mol) in methanol (400 mL) until the reaction solution acquired a persistent bright yellow color. After several hours the yellow color faded and the product was crystallized in several crops by reducing the reaction solution's volume, diluting with ethyl acetate, and cooling to give **5** (25.94 g, 79.1%) as a crystalline solid, mp 122–124°C, and an orange oil (6.5 g) that was not examined further. An analytical sample of the solid was obtained by recrystallization from ethyl acetate; mp 123–124°C; ^{1}Hmr (200 MHz, Me_2SO-d_6) δ: 1.81 (1H, d of d of d, J_{gem} = 14.3, $^3J_{3,4}$ = 8.0, $^3J_{3,2}$ = 3.5 Hz, H-3), 1.90 (3H, s, OAc), 1.96–2.11 (2H, m, H-5 and H-5′), 2.21 (1H, m, J_{gem} = 14.3, $^3J_{3',4}$ = 9.6, $^3J_{3',2}$ = 6.2 Hz, H-3′), 2.64 (1H, qu, ^3J = 8.9 Hz, H-4), 3.06 (1H, m, $^3J_{1,5}$ = 11.0, $^3J_{1,5'}$ = 8.0, $^3J_{1,2}$ = 6.2 Hz, H-1), 3.58 (3H, s, OMe), 5.22 (1H, t of d, $^3J_{2,1}$ = 6.2, $^3J_{2,3'}$ = 6.2, $^3J_{2,3}$ = 3.5 Hz, H-2), 6.84 (1H, br s, $CONH_2$), 7.30 (1H, br s, $CONH_2$); spin–spin decoupled at H-1, H-2, and H-4. *Anal.* calcd. for $C_{10}H_{15}O_5N$: C 52.40, H 6.60, N 6.11; found: C 51.97, H 7.01, N 6.06.

(±)-(1β,3β,4β)-3-Hydroxy-4-(hydroxymethyl)cyclopentane-carboxamide (6)

A solution containing $LiBH_4$ (12.6 g, 0.578 mol) in tetrahydrofuran (500 mL, the Aldrich Chemical Company, 99+%) was heated at reflux temperature for 20 min and cooled to about 40°C. To this solution compound **5** (25.0 g, 0.109 mol) was added as a solid and the stirred reaction mixture was heated at reflux temperature for 20 min. The reaction mixture was cooled to ice-bath temperature, water (350 mL) was slowly added, and then Amberlite IR-120 resin (H^+ form) (350 mL). The mixture was stirred for 1.5 h, and the resin was removed by filtration and washed with water. The combined filtrate and washings were stored in the cold room overnight, the solvent was evaporated, and the residue was evaporated with methanol (4 × 100 mL) to remove boric acid. This procedure gave a viscous oil which was stirred overnight in the cold room in the presence of tetrahydrofuran (70 mL). The white solid (12.45 g) was collected by filtration; R_f 0.37 (tlc) (9:1 (v/v) acetonitrile–water). The volume of the mother liquor was reduced to about 10 mL; treatment with tetrahydrofuran (20 mL) as above gave a solid (1.56 g), R_f 0.37, and a trace of impurity having R_f 0.51, for a total yield of 14.01 g (81%). An analytical sample was prepared by recrystallization from methanol – ethyl acetate – hexanes; mp 135–136°C; ^{1}Hmr (200 MHz, Me_2SO-d_6) δ: 1.31–1.51 (1H, m, H-5), 1.65 (1H, d of d of d, J_{gem} = 13.6, $^3J_{2,1}$ = 5.0, $^3J_{2,3}$ = 2.7 Hz, H-2), 1.82 (1H, m, $^3J_{3,4}$ = 4.6 Hz, H-4), 1.8–2.0 (1H, m, H-5′), 1.93 (1H, m, J_{gem} = 13.6, $^3J_{2',1}$ = 9.6, $^3J_{2',3}$ = 4.9 Hz, H-2′), 2.65 (1H, m, $^3J_{1,2}$ = 5.0 Hz, H-1), 3.35 (1H, m, J_{gem} = 10.7, $^3J_{to\ H\text{-}4}$ = 5.9, $^3J_{to\ OH}$ = 5.3 Hz, CH_2OH), 3.59 (1H, m, J_{gem} = 10.7, $^3J_{to\ H\text{-}4}$ = 6.9, $^3J_{to\ OH}$ = 5.3 Hz, CH_2OH), 4.01 (1H, m, $^3J_{to\ OH}$ = 6.7, $^3J_{3,4}$ = 4.6, $^3J_{3,2'}$ = 4.9, $^3J_{3,2}$ = 2.7 Hz, H-3), 4.24 (1H, t, $^3J_{to\ CH_2OH}$ = 5.3 Hz, CH_2OH), 4.71 (1H, d, $^3J_{to\ H\text{-}3}$ = 6.7 Hz, OH at position 3), 6.92 (1H, br s, $CONH_2$), 7.45 (1H, br s, $CONH_2$); spin–spin decoupled at H-1, H-3, H-5, and CH_2OH. D_2O exchange caused the disappearance of signals at δ 4.24, 4.71, 6.92, and 7.45. *Anal.* calcd. for $C_7H_{13}O_3N$: C 52.82, H 8.23, N 8.80; found: C 53.00, H 8.03, N 8.91.

(±)-Methyl (1β,3β,4β)-3-acetoxy-4-carbamoylcyclopentane-carboxylate (9)

A solution of **3** (50.5 g, 0.255 mol) in anhydrous methanol (800 mL) was stirred at room temperature for 22 h. The methanol was evaporated to give **7** as an oil; ^{1}Hmr (200 MHz, Me_2SO-d_6) δ: 1.91 (3H, s, OAc), 1.91–2.33 (4H, m, H-3, H-3′, H-5, and H-5′), 2.87–3.08 (2H, m, H-1 and H-4), 3.62 (3H, s, OMe), 5.23 (1H, t of d, H-2), 12.33 (1H, br s, CO_2H). The oil was dissolved in benzene (950 mL) and 150 mL were distilled to remove traces of moisture. Heating was discontinued and $SOCl_2$ (85 mL) was added. The mixture was stirred for 5 min, pyridine (2 drops) was added, and stirring was continued until the vigorous evolution of gases had subsided. *N,N*-Dimethylformamide (2 drops) was then added, and the solution was heated at reflux temperature for 2 h. The solution was kept at room temperature overnight. The volatile components were evaporated to give **8** as an orange oil that was used immediately for the preparation of **9**. The oil (**8**) was dissolved in dry benzene (450 mL), and anhydrous ammonia was bubbled through the reaction solution for 30 min; there then was a 10-min purge with nitrogen. An additional 250 mL of benzene were added and the reaction mixture was heated to boiling, treated with charcoal, and filtered through a pad of Celite. The filtrate was evaporated to give an orange-brown oil (62.3 g) that was revealed by tlc (1:1 (v/v) acetone–toluene) to consist of a single major component having R_f 0.40 and several minor components. The oil was diluted with acetone (10 mL) to reduce its viscosity and resolved by liquid chromatography (Waters Associates PrepLC/System 500) to give the major component (42.2 g), mp 78–88°C, which was recrystallized from ethyl acetate – hexanes to give a white solid (35.7 g, 61.1%), mp 92–93°C. An analytical sample of **9** was prepared by a second recrystallization from ethyl acetate – hexanes, mp 93–94°C; ^{1}Hmr (200 MHz, Me_2SO-d_6) δ: 1.90 (3H, s, OAc), 1.90–2.27 (4H, m, H-2, H-2′, H-5, and H-5′), 2.78 (1H, d of d of d, $^3J_{4,5}$ = 11.1, $^3J_{4,5'}$ = 7.7, $^3J_{4,3}$ = 5.4 Hz, H-4), 2.91 (1H, q of d, ^3J = 9.4, ^3J = 6.5 Hz, H-1), 3.61 (3H, s, OMe), 5.24 (1H, t of d, ^3J = 5.4, $^3J_{3,2}$ = 2.9 Hz, H-3), 6.84 (1H, br s, $CONH_2$), 7.22 (1H, br s, $CONH_2$); spin–spin decoupled at H-3. *Anal.* calcd. for $C_{10}H_{15}O_5N$: C 52.40, H 6.60, N 6.11; found: C 52.15, H 6.91, N 6.05.

(±)-(1β,2β,4β)-2-Hydroxy-4-(hydroxymethyl)cyclopentane-carboxamide (10)

A solution of $LiBH_4$ (5.0 g, 228 mmol) in tetrahydrofuran (250 mL) was heated at reflux temperature for 1 h, cooled to about 40°C, **9** (13.1 g, 57 mmol) in tetrahydrofuran (60 mL) was added, and the heating was continued for 2 h. The reaction solution was then cooled to ice-bath temperature, water (200 mL) was added slowly, and then Amberlite IR-120 resin (H^+ form) (150 mL). The reaction mixture was stirred overnight, and the resin was removed by filtration and washed with water (300 mL). The pH of the combined filtrate and washings was adjusted to neutrality by treatment with Dowex 1-X8 resin (OH^- form) (~200 mL). The resin was removed by filtration and washed with water (~250 mL). The volume of the combined filtrate and washings was reduced by evaporation and the resulting oil was evaporated with methanol (3 × 50 mL). The oil was then stirred in the presence of tetrahydrofuran (45 mL). The white solid that formed (5.5 g, 60.6%) was collected by filtration; mp 113–116°C; R_f 0.44 (tlc) (3:1 (v/v) chloroform–methanol). An analytical sample was prepared by recrystallization from methanol – diethyl ether, mp 117–118°C; ^{1}Hmr (200 MHz, Me_2SO-d_6) δ: 1.34 (1H, d of d of d, J_{gem} = 13.4, $^3J_{3,4}$ = 5.0, $^3J_{3,2}$ = 2.6 Hz, H-3), 1.60 (1H, m, J_{gem} = 12.2, $^3J_{5,1}$ = 11.6, $^3J_{5,4}$ = 8.9 Hz, H-5), 1.75–1.89 (2H, m, H-3′ and H-5′), 2.04 (1H, m, H-4), 2.44 (1H, m, $^3J_{1,5}$ = 11.6, $^3J_{1,5'}$ = 7.0, $^3J_{1,2}$ = 4.6 Hz, H-1), 3.33 (2H, d of d, $^3J_{to\ CH_2OH}$ = 5.1, $^3J_{to\ H\text{-}4}$ = 6.6 Hz, CH_2OH), 4.18 (1H, m, $^3J_{2,3'}$ = 7.3, $^3J_{2,1}$ = 4.6, $^3J_{2,3}$ = 2.6, $^3J_{to\ CHOH}$ = 3.4 Hz, H-2), 4.58 (1H, t, $^3J_{to\ CH_2OH}$ = 5.1 Hz, CH_2OH), 4.84 (1H, d, $^3J_{to\ H\text{-}2}$ = 3.4 Hz, CHO*H*), 6.91 (1H, br s, $CONH_2$), 7.28 (1H, br s, $CONH_2$); spin–spin decoupled at H-1, H-2, H-3, H-4, and CH_2OH. *Anal.* calcd. for $C_7H_{13}O_3N$: C 52.82, H 8.23, N 8.80; found: C 52.90, H 8.02, N 8.85.

(±)-(1β,3β,4β)-4-Amino-3-hydroxycyclopentanemethanol (17)

A freshly prepared solution of $Ba(OH)_2 \cdot 8H_2O$ (90.9 g, 288 mmol) in water (1.85 L) was filtered to remove any $BaCO_3$ present and cooled to 5°C. To this solution was added Br_2 (3.6 mL, 70.3 mmol) and, immediately after the Br_2 had dissolved, compound **10** (10.2 g, 64 mmol) in water (50 mL) was added and the reaction solution was left to warm to room temperature during the next 2 h. The reaction solution was heated at 65–70°C for 1 h, cooled to about 10°C, acidified with 3 *M* H_2SO_4 (76 mL), and stirred for 1 h. The reaction mixture was kept in the cold room overnight and the $BaSO_4$ was removed by centrifugation. The solution was passed through Amberlite CG-120 resin (H^+ form) (150 g). The resin was then washed with water (1.1 L) and eluted with 2 *N* aqueous ammonia. Most of the product (**17**) was obtained after 1.5 L of 2 *N* ammonia solution had been used, and only traces were obtained with the next 0.5 L. The solvent was evaporated and the resulting oil was dissolved in ethanol; the solution was filtered to remove particulate matter and the filtrate was evaporated to give a pale orange oil (2.90 g, 34.5%). The ^{1}Hmr spectrum did not show any signals attributable to impurities; ^{1}Hmr (200 MHz, Me_2SO-d_6) δ: 1.08 (1H, d of t, J_{gem} = 12.5, ^3J = 7.5 Hz, H-5), 1.31 (1H, m, J_{gem} = 12.9, $^3J_{2,1}$ = 6.2, $^3J_{2,3}$ = 5.1 Hz, H-2), 1.71–1.89 (2H, m, H-2′ and H-5′), 1.85–2.08 (1H, m, H-1), 2.95 (1H, m, ^3J = 7, $^3J_{4,3}$ = 5.1 Hz, H-4), 3.29 (2H, d, $^3J_{\text{to H-1}}$ = 5.8 Hz, CH_2OH), 3.73 (1H, q, ^3J = 5.1 Hz, H-3); spin–spin decoupled at H-3, H-4, and H-5.

3-Ethoxypropenoyl chloride (14)

Ethyl 3-ethoxypropenoate (**11**) was prepared from ethyl bromoacetate and ethyl orthoformate by the Reformatsky reaction as described previously (20–22). The rate of elimination of ethanol from the crude acetal precursor was accelerated by the addition of *p*-toluenesulfonic acid or $KHSO_4$ to the refluxing solution; ^{1}Hmr (200 MHz, Me_2SO-d_6) δ: 1.20 (3H, t, ^3J = 7.1 Hz, CH_3), 1.25 (3H, t, ^3J = 7.1 Hz, CH_3), 3.97 (2H, q, ^3J = 7.1 Hz, —CH_2O—), 4.08 (2H, q, ^3J = 7.1 Hz, —CH_2O—), 5.24 (1H, d, ^3J = 12.5 Hz, H-2), 7.59 (1H, d, ^3J = 12.5 Hz, H-3); ^{1}Hmr (200 MHz, $CDCl_3$) δ: 1.28 (3H, t, ^3J = 7.2 Hz, CH_3), 1.35 (3H, t, ^3J = 7.1 Hz, CH_3), 3.91 (2H, q, ^3J = 7.1 Hz, —CH_2O—), 4.17 (2H, q, ^3J = 7.2 Hz, —CH_2O—), 5.19 (1H, d, ^3J = 12.9 Hz, H-2), 7.59 (1H, d, ^3J = 12.9 Hz, H-3).

The following compounds were prepared as described previously (21–22): 3-ethoxypropenoic acid (**12**) by alkaline hydrolysis of **11**; ^{1}Hmr (200 MHz, Me_2SO-d_6) δ: 1.24 (3H, t, ^3J = 7.1 Hz, CH_3), 3.94 (2H, q, ^3J = 7.1 Hz, —CH_2O—), 5.14 (1H, d, ^3J = 12.5 Hz, H-2), 7.52 (1H, d, ^3J = 12.5 Hz, H-3), 11.78 (1H, br s, CO_2H); ^{1}Hmr (200 MHz, $CDCl_3$) δ: 1.34 (3H, t, ^3J = 7.1 Hz, CH_3), 3.95 (2H, q, ^3J = 7.1 Hz, —CH_2O—), 5.19 (1H, d, ^3J = 12.6 Hz, H-2), 7.69 (1H, d, ^3J = 12.6 Hz, H-3), 12.15 (1H, br s, CO_2H); sodium 3-ethoxypropenoate (**13**) by neutralization of **12** with NaOH; ^{1}Hmr (200 MHz, Me_2SO-d_6 + D_2O) δ: 1.25 (3H, t, ^3J = 7.1 Hz, CH_3), 3.87 (2H, q, ^3J = 7.1 Hz, —CH_2O—), 5.16 (1H, d, ^3J = 12.7 Hz, H-2), 7.23 (1H, d, ^3J = 12.7 Hz, H-3); and 3-ethoxypropenoyl chloride (**14**) from **13**, using $SOCl_2$ in diethyl ether; ^{1}Hmr (200 MHz, $CDCl_3$) δ: 1.40 (3H, t, ^3J = 7.1 Hz, CH_3), 4.07 (2H, q, ^3J = 7.1 Hz, —CH_2O—), 5.51 (1H, d, ^3J = 12.1 Hz, H-2), 7.80 (1H, d, ^3J = 12.1 Hz, H-3).

3-Ethoxypropenoyl isocyanate (15) (refs. 22, 23)

A stirred mixture of silver cyanate (21.3 g, 142 mmol) in dry benzene (125 mL) was heated at reflux temperature for 0.5 h and 3-ethoxypropenoyl chloride (**14**) (9.57 g, 71 mmol) in benzene (25 mL) was added over a period of 10 min. The mixture was heated for an additional 0.5 h and stirred at room temperature for 2.5 h. The solid was allowed to settle and the solution of **15** was used immediately for the preparation of **18** and **23** as described below.

(±)-3-Ethoxy-N-{N′-*[(1β,2β,4β)-2-hydroxy-4-(hydroxymethyl)-cyclopentyl]carbamoyl}propenamide (18)*

To a dried (4 Å molecular sieves), cooled (−15°C) solution of compound **17** (2.06 g, 15.7 mmol) in *N*,*N*-dimethylformamide (50 mL) were added, under a nitrogen atmosphere, 40 mL of the solution of the isocyanate **15** obtained above; the reaction temperature was maintained below −10°C. After the addition of **15** was complete, the reaction solution was stirred at room temperature overnight. The solution was filtered and the solvents were removed under vacuum. The residue was evaporated with ethanol (2 × 20 mL) and fractionated by column chromatography on silica gel using toluene – ethyl acetate – 2-propanol (3:3:2, v/v/v) to give **18** (1.80 g, 42%, based on the amount of the amine) as a pale yellow solid, R_f 0.39 (tlc); ^{1}Hmr (200 MHz, Me_2SO-d_6) δ: 1.15–1.36 and 1.86–2.05 (5H, m, H-3′, H-3″, H-4′, H-5′, and H-5″), 1.25 (3H, t, ^3J = 7.1 Hz, CH_3), 3.28–3.40 (2H, m, CH_2OH), 3.76–4.08 (2H, m, H-1′ and H-2′), 3.94 (2H, q, ^3J = 7.1 Hz, CH_3CH_2O), 4.59 (1H, t, ^3J = 5.0 Hz, CH_2OH), 4.91 (1H, d, $^3J_{\text{to H-2′}}$ = 4.6 Hz, OH at position 2′), 5.51 (1H, d, $^3J_{2,3}$ = 12.3 Hz, H-2), 7.55 (1H, d, $^3J_{3,2}$ = 12.3 Hz, H-3), 8.74 (1H, br d, $^3J_{\text{to H-1′}}$ = 7.8 Hz, CONHCONH), 9.95 (1H, br s, CONHCO); spin–spin decoupled at δ 3.28–3.40, H-2 and δ 1.25.

(±)-1-[(1β,2β,4β)-2-Hydroxy-4-(hydroxymethyl)cyclopentyl]-2,4(1H,3H)-pyrimidinedione (19)

A solution of **18** (1.78 g, 6.54 mmol) in 2 *N* sulfuric acid (50 mL) was heated at reflux temperature under a nitrogen atmosphere for 30 min. The solution was cooled to room temperature, treated with charcoal, filtered, and the charcoal was washed with 10 mL of water. The combined filtrate and washings were cooled to ice-bath temperature and neutralized with 2 *N* sodium hydroxide. The solvent was evaporated and the residue was extracted with ethanol (4 × 20 mL). Evaporation of the ethanol gave an oil which was fractionated by column chromatography on silica gel to give **19** (1.00 g, 68%) as a white solid, R_f 0.34 (tlc) (1:1:1 (v/v/v) toluene – ethyl acetate – 2-propanol). An analytical sample was prepared by recrystallization from ethanol – diethyl ether, mp 158–160°C; uv λ_{max} (C_2H_5OH): 210 nm (ε 9480), 268 (11 100); λ_{max} (0.01 *N* HCl in C_2H_5OH): 210 nm (ε 9570), 268 (11 100); λ_{max} (0.01 *N* NaOH in C_2H_5OH): 220 nm (ε 9330), 265 (8310); ^{1}Hmr (200 MHz, Me_2SO-d_6) δ: 1.30 (1H, m, $^3J_{3′,2′}$ = 2.0 Hz, H-3′), 1.62–1.90 (2H, m, H-4′ and H-5′), 1.96–2.16 (2H, m, H-3″ and H-5″), 3.33–3.42 (2H, m, CH_2OH), 4.02 (1H, m, H-2′), 4.49 (1H, m, $^3J_{\text{to H at 5′}}$ = 12.2, $^3J_{\text{to H at 5′}}$ = 7.1, $^3J_{1′,2′}$ = 4.9 Hz, H-1′), 4.65 (1H, t, $^3J_{\text{to } CH_2OH}$ = 5.2 Hz, CH_2OH), 4.94 (1H, d, $^3J_{\text{to H-2′}}$ = 4.5 Hz, CHOH), 5.48 (1H, d of d, $^3J_{5,6}$ = 7.8, $^4J_{5,3}$ = 1.7 Hz, H-5), 7.60 (1H, d, $^3J_{6,5}$ = 7.8 Hz, H-6), 11.20 (1H, br s, H-3); spin–spin decoupled at H-3′, H-2′, and H-3. *Anal.* calcd. for $C_{10}H_{14}O_4N_2$: C 53.09, H 6.24, N 12.38; found: C 53.16, H 6.24, N 12.35.

3-Ethoxypropenoyl isothiocyanate (16)

Compound **16** was prepared from 3-ethoxypropenoyl chloride (**14**) and potassium thiocyanate as described by Shaw and Warrener (21) and was used immediately after distillation under vacuum to prepare compounds **20** and **25**.

(±)-3-Ethoxy-N-{N′-*[(1β,2β,4β)-2-hydroxy-4-(hydroxymethyl)-cyclopentyl]thiocarbamoyl}propenamide (20)*

To a solution of **17** (0.379 g, 2.89 mmol) in methanol (5 mL) and diethyl ether (10 mL) was added the isothiocyanate **16** (0.454 g, 2.89 mmol) at room temperature. The reaction solution was kept at room temperature overnight, filtered, and the filtrate was evaporated to give an orange oil (1.0 g) that was fractionated by column chromatography on silica gel to give **20** (0.57 g, 68%) as a pale yellow solid, R_f 0.48 (tlc) (4:4:1 (v/v/v) toluene – ethyl acetate – 2-propanol); ^{1}Hmr (200 MHz, Me_2SO-d_6) δ: 1.17–1.43 (2H, m, H-3′ and H-5′), 1.26 (3H, t, ^3J = 7.0 Hz, CH_3), 1.91–2.09 (2H, m, H-3″ and H-4′), 2.18 (1H, d of t, J_{gem} = 11.5, ^3J = 7.1 Hz, H-5″), 3.31–3.36 (2H, m, CH_2OH), 3.98 (2H, q, ^3J = 7.0 Hz, CH_3CH_2O), 3.99–4.03 (1H, m, H-2′), 4.31 (1H, m, H-1′), 4.64 (1H, t, $^3J_{\text{to } CH_2OH}$ = 5.1 Hz, CH_2OH), 5.15 (1H, d, $^3J_{\text{to H-2′}}$ = 4.9 Hz, OH at position 2′), 5.71 (1H, d, $^3J_{2,3}$ = 12.6 Hz, H-2), 7.59 (1H, d, $^3J_{3,2}$ = 12.6 Hz, H-3), 10.79 (1H, br s, CONHCS), 11.10 (1H, br d, $^3J_{\text{to H-1′}}$ = 7.7 Hz, CONHCSNH); spin–spin decoupled at H-1′, and δ 1.26 and 4.0.

(±)-2,3-Dihydro-1-[(1β,2β,4β)-2-hydroxy-4-(hydroxymethyl)-cyclopentyl]-2-thioxo-4(1H)-pyrimidinone (21)

A stirred solution of **20** (0.53 g, 1.84 mmol) in 15 *N* aqueous ammonia (20 mL) was heated in an oil bath at 100°C for 20 min. The reaction solution was cooled to room temperature and the solvent evaporated to give an oil, which was then evaporated with ethanol (3 × 10 mL). The residual oil was fractionated by column chromatography on silica gel to give **21** (0.135 g, 30%) as a white solid, R_f 0.40 (tlc) (2:2:1 (v/v/v) toluene – ethyl acetate – 2-propanol); mp 180–187°C. An analytical sample was prepared by recrystallization from methanol – diethyl ether, mp 184–186°C; uv λ_{max} (C_2H_5OH): 221 nm (ε 17 300), 274 (12 700); λ_{max} (0.01 *N* HCl in C_2H_5OH): 221 nm (ε 17 300), 274 (12 700); λ_{max} (0.01 *N* NaOH in C_2H_5OH): 241 nm (ε 21 300), 274 (15 400); ^{1}Hmr (200 MHz, Me_2SO-d_6) δ: 1.34 (1H, m, H-3′), 1.69–2.13 (4H, m, H-3″, H-4′, H-5′, and H-5″), 3.40 (2H, m, CH_2OH), 4.20 (1H, m, H-2′), 4.68 (1H, t, $^3J_{to\ CH_2OH}$ = 5.1 Hz, CH_2OH), 5.04 (1H, d, $^3J_{to\ H\text{-}2'}$ = 4.3 Hz, OH at position 2′), 5.41 (1H, m, $^3J_{1',5'}$ = 12.2, $^3J_{1',5''}$ = 6.8, $^3J_{1',2'}$ = 5.1 Hz, H-1′), 5.88 (1H, d of d, $^3J_{5,6}$ = 8.1, $^4J_{5,3}$ = 1.9 Hz, H-5), 7.75 (1H, d, $^3J_{6,5}$ = 8.1 Hz, H-6), 12.59 (1H, br s, H-3); spin–spin decoupled at δ 1.34, 4.20, 4.68, 5.04, 5.41, 5.88, and 7.75. *Anal.* calcd. for $C_{10}H_{14}O_3N_2S$: C 49.57, H 5.82, N 11.56, S 13.23; found: C 50.04, H 6.08, N 11.73, S 13.27.

(±)-(1β,2β,4β)-4-Amino-2-hydroxycyclopentanemethanol (22)

Compound **22** was prepared from **6** (9.74 g, 61.2 mmol), according to the procedure described for the preparation of **17**, to give an orange-brown oil (2.19 g, 27%). The ^{1}Hmr spectrum did not show any signals attributable to impurities; ^{1}Hmr (200 MHz, Me_2SO-d_6) δ: 1.12 (1H, m, H-5), 1.39 (1H, d of d of d, J_{gem} = 13.5, $^3J_{3,4}$ = 4.4, $^3J_{3,2}$ = 2.8 Hz, H-3), 1.71–1.97 (3H, m, H-1, H-3′, and H-5′), 3.23 (1H, m, H-4), 3.37 (1H, d of d, J_{gem} = 10.6, $^3J_{to\ H\text{-}1}$ = 6.2 Hz, CH_2OH), 3.59 (1H, d of d, J_{gem} = 10.6, $^3J_{to\ H\text{-}1}$ = 7.2 Hz, CH_2OH), 4.00 (1H, m, H-2); spin–spin decoupled at δ 1.12, 1.39, 3.59, and 4.00.

*(±)-3-Ethoxy-*N*-{N′-[(1β,3β,4β)-3-hydroxy-4-(hydroxymethyl)-cyclopentyl]carbamoyl}propenamide (23)*

Compound **23** was prepared from **22** (1.57 g, 12 mmol) and the solution of the isocyanate **15** (32 mL) according to the procedure described for the preparation of **18**. Fractionation by column chromatography on silica gel afforded a crude sample of **23** (1.5 g, 49%, based on the amount of the amine) as a pale yellow, oily solid, R_f 0.34 (tlc) (3:3:2 (v/v/v) toluene – ethyl acetate – 2-propanol). The ^{1}Hmr spectrum showed several minor signals attributable to impurities; ^{1}Hmr (200 MHz, Me_2SO-d_6) δ: 1.17–1.34 (1H, m, H-5′), 1.25 (3H, t, ^3J = 7.0 Hz, CH_3), 1.45 (1H, m, H-2′), 1.83 (1H, m, H-4′), 1.98–2.14 (2H, m, H-2″ and H-5″), 3.40 (1H, m, J_{gem} = 10.9, $^3J_{to\ CH_2OH\ and\ H\text{-}4'}$ = 5.5 Hz, CH_2OH), 3.57 (1H, d of d of d, J_{gem} = 10.9, $^3J_{to\ H\text{-}4'}$ = 7.2, $^3J_{to\ CH_2OH}$ = 5.5 Hz, CH_2OH), 3.93 (2H, q, ^3J = 7.0 Hz, CH_3CH_2O), 4.03–4.22 (2H, m, H-1′ and H-3′), 4.28 (1H, t, $^3J_{to\ CH_2OH}$ = 5.5 Hz, CH_2OH), 4.57 (1H, d, $^3J_{to\ H\text{-}3'}$ = 3.8 Hz, OH at position 3′), 5.50 (1H, d, $^3J_{2,3}$ = 12.4 Hz, H-2), 7.53 (1H, d, $^3J_{3,2}$ = 12.4 Hz, H-3), 8.72 (1H, br d, $^3J_{to\ H\text{-}1'}$ = 8.3 Hz, CONHCON*H*), 9.92 (1H, br s, CON*H*CONH); spin–spin decoupled at δ 1.26 and 8.72.

(±)-1-[(1β,3β,4β)-3-Hydroxy-4-(hydroxymethyl)cyclopentyl]-2,4(1H,3H)-pyrimidinedione (24)

Compound **24** was prepared from **23** (1.53 g, 5.6 mmol) according to the procedure described for the preparation of **19**. Fractionation by column chromatography on silica gel afforded **24** (0.726 g, 57%) as a white solid, R_f 0.31 (tlc) (1:1:1 (v/v/v) toluene – ethyl acetate – 2-propanol). An analytical sample was prepared by recrystallization from ethanol–hexanes; mp 154–155°C; uv λ_{max} (C_2H_5OH): 209 nm (ε 9120), 268 (10 300); λ_{max} (0.01 *N* HCl in C_2H_5OH): 210 nm (ε 9140), 268 (10 300); λ_{max} (0.01 *N* NaOH in C_2H_5OH): 221 nm (ε 8310), 265 (7610); ^{1}Hmr (200 MHz, Me_2SO-d_6) δ: 1.37 (1H, t of d, J_{gem} = $^3J_{5',4'}$ = 11.8, $^3J_{5',1'}$ = 9.0 Hz, H-5′), 1.51 (1H, d of d, J_{gem} = 15.1, $^3J_{2',1'}$ = 3.9 Hz, H-2′), 1.89 (1H, m, H-4′), 2.05 (1H, m, J_{gem} = 11.8, ^3J = 7.3 Hz, H-5″), 2.30 (1H, m, J_{gem} = 15.1, $^3J_{2'',1'}$ = 11.1, $^3J_{2'',3'}$ = 4.6 Hz, H-2″), 3.43 (1H, m, J_{gem} = 10.9, $^3J_{to\ H\text{-}4'}$ = 6.1, $^3J_{to\ CH_2OH}$ = 5.3 Hz, CH_2OH), 3.60 (1H, d of d of d, J_{gem} = 10.9, $^3J_{to\ H\text{-}4'}$ = 7.3, $^3J_{to\ CH_2OH}$ = 5.3 Hz, CH_2OH), 4.11 (1H, m, H-3′), 4.39 (1H, t, $^3J_{to\ CH_2OH}$ = 5.3 Hz, CH_2OH), 5.03 (1H, d, $^3J_{to\ H\text{-}3'}$ = 3.6 Hz, OH at position 3′), 5.04 (1H, m, H-1′), 5.67 (1H, d of d, $^3J_{5,6}$ = 8.2, $^4J_{5,3}$ = 2.0 Hz, H-5), 7.90 (1H, d, $^3J_{6,5}$ = 8.2 Hz, H-6), 11.20 (1H, br s, H-3); spin–spin decoupled at δ 4.11 and 4.39. *Anal.* calcd. for $C_{10}H_{14}O_4N_2$: C 53.09, H 6.24, N 12.38; found: C 53.13, H 6.41, N 12.34.

*(±)-3-Ethoxy-*N*-{N′-[(1β,3β,4β)-3-hydroxy-4-(hydroxymethyl)-cyclopentyl]thiocarbamoyl}propenamide (25)*

Compound **25** was prepared from **22** (0.234 g, 1.78 mmol) and **16** (0.285 g, 1.81 mmol) according to the procedure described for the preparation of **20**. Fractionation by column chromatography on silica gel afforded **25** (0.275 g, 54%) as a colorless oil, R_f 0.56 (tlc) (2:2:1 (v/v/v) toluene – ethyl acetate – 2-propanol); ^{1}Hmr (200 MHz, Me_2SO-d_6) δ: 1.20–1.35 (1H, m, H-5′), 1.25 (3H, t, ^3J = 7.0 Hz, CH_3), 1.56 (1H, m, J_{gem} = 14.1, $^3J_{2',1'}$ = 2.3 Hz, H-2′), 1.87 (1H, m, H-4′), 2.06 (1H, m, J_{gem} = 14.1, $^3J_{2'',1'}$ = 8.5, $^3J_{2'',3'}$ = 4.7 Hz, H-2″), 2.21 (1H, d of t, J_{gem} = 13.0, ^3J = 8.2 Hz, H-5″), 3.40 (1H, m, J_{gem} = 10.7, $^3J_{to\ CH_2OH}$ = 5.3, $^3J_{to\ H\text{-}4'}$ = 5.3 Hz, CH_2OH), 3.58 (1H, d of d of d, J_{gem} = 10.7, $^3J_{to\ H\text{-}4'}$ = 7.2, $^3J_{to\ CH_2OH}$ = 5.3 Hz, CH_2OH), 3.96 (2H, q, ^3J = 7.0 Hz, CH_3CH_2O), 4.10 (1H, m, H-3′), 4.31 (1H, t, $^3J_{to\ CH_2OH}$ = 5.3 Hz, CH_2OH), 4.58–4.73 (1H, m, H-1′), 4.64 (1H, d, $^3J_{to\ H\text{-}3'}$ = 3.3 Hz, OH at position 3′), 5.70 (1H, d, $^3J_{2,3}$ = 12.2 Hz, H-2), 7.57 (1H, d, $^3J_{3,2}$ = 12.2 Hz, H-3), 10.73 (1H, br s, CON*H*CSNH), 11.10 (1H, br d, $^3J_{to\ H\text{-}1'}$ = 8.0 Hz, CONHCSN*H*); spin–spin decoupled at δ 4.10 and 4.65.

(±)-2,3-Dihydro-1-[(1β,3β,4β)-3-hydroxy-4-(hydroxymethyl)-cyclopentyl]-2-thioxo-4(1H)-pyrimidinone (26)

Compound **26** was prepared from **25** (0.27 g, 0.94 mmol) according to the procedure described for the preparation of **21**. Fractionation by column chromatography on silica gel afforded **26** (0.153 g, 67%) as a white solid, R_f 0.44 (tlc) (2:2:1 (v/v/v) toluene – ethyl acetate – 2-propanol). An analytical sample was prepared by recrystallization from ethanol–hexanes, mp 156–157°C; uv λ_{max} (C_2H_5OH): 219 nm (ε 16 600), 273 (13 700); λ_{max} (0.01 *N* HCl in C_2H_5OH): 219 nm (ε 16 600), 273 (13 800); λ_{max} (0.01 *N* NaOH in C_2H_5OH): 240 nm (ε 19 400), 272 (16 200); ^{1}Hmr (200 MHz, Me_2SO-d_6) δ: 1.35 (1H, t of d, J_{gem} = 12.3, $^3J_{5',1'}$ = 9.3 Hz, H-5′), 1.56 (1H, d of d, J_{gem} = 15.4, $^3J_{2',1'}$ = 3.7 Hz, H-2′), 1.91 (1H, m, H-4′), 2.17 (1H, m, J_{gem} = 12.3, ^3J = 7.5 Hz, H-5″), 2.36 (1H, m, J_{gem} = 15.4, $^3J_{2'',1'}$ = 11.2, $^3J_{2'',3'}$ = 4.4 Hz, H-2″), 3.44 (1H, m, J_{gem} = 10.6, $^3J_{to\ H\text{-}4'}$ = 6.2, $^3J_{to\ CH_2OH}$ = 5.2 Hz, CH_2OH), 3.60 (1H, m, J_{gem} = 10.6, $^3J_{to\ H\text{-}4'}$ = 7.6, $^3J_{to\ CH_2OH}$ = 5.2 Hz, CH_2OH), 4.14 (1H, m, H-3′), 4.40 (1H, t, $^3J_{to\ CH_2OH}$ = 5.2 Hz, CH_2OH), 5.15 (1H, d, $^3J_{to\ H\text{-}3'}$ = 3.4 Hz, OH at position 3′), 5.99 (1H, m, H-1′), 6.09 (1H, d, $^3J_{5,6}$ = 8.2 Hz, H-5), 8.11 (1H, d, $^3J_{6,5}$ = 8.2 Hz, H-6), 12.55 (1H, br s, H-3); spin–spin decoupled at δ 4.14 and 5.99. *Anal.* calcd. for $C_{10}H_{14}O_3N_2S$: C 49.57, H 5.82, N 11.56, S 13.23; found: C 49.61, H 5.97, N 11.80, S 13.25.

(±)-(1β,6β,8β)-3,3-Dimethyl-2,4-dioxabicyclo[4.3.0]nonane-8-carboxamide (27)

To a stirred mixture of **6** (14.0 g, 88 mmol) in acetone (200 mL) and 2,2-dimethoxypropane (50 mL) was added *p*-toluenesulfonic acid monohydrate (~20 mg) and the mixture was heated gently at reflux temperature for 30 min. The reaction mixture was cooled to room temperature, and the white solid was collected by filtration and washed with acetone to give **27** (10.88 g), R_f 0.31 (tlc) (2:2:1 (v/v/v) toluene – ethyl acetate – 2-propanol). The volume of the mother liquor was reduced and a second crop of **27** (2.47 g) was obtained for a total yield of 13.35 g. The volatile components were evaporated from the filtrate and the resulting oil was dissolved in acetone (30 mL) and 2,2-dimethoxypropane (10 mL). About 10 mg of the acid catalyst was added and the reaction mixture was stirred at room temperature for 30 min to give an additional 2.08 g of **27** as a white solid for a total yield of 15.43 g (88%). Thin-layer chromatography showed that this material contained trace amounts of a second component having R_f 0.08.

An analytical sample was prepared by fractionation on a column of alumina gel followed by recrystallization of the material from acetone; mp 169°C; ^{1}Hmr (200 MHz, Me_2SO-d_6) δ: 1.22 (3H, s, CH_3), 1.35 (3H, s, CH_3), 1.65–1.95 (4H, m, H-6, H-7, H-7′, and H-9), 2.07 (1H, m, J_{gem} = 14.3, $^3J_{9',8}$ = 10.1, $^3J_{9',1}$ = 5.5 Hz, H-9′), 2.56 (1H, m, H-8), 3.54 (1H, d of d, J_{gem} = 11.7, $^3J_{5,6}$ = 2.3 Hz, H-5), 3.99 (1H, d of d, J_{gem} = 11.7, $^3J_{5',6}$ = 3.7 Hz, H-5′), 4.23 (1H, m, H-1), 6.75 (1H, br s, $CONH_2$), 7.13 (1H, br s, $CONH_2$); spin–spin decoupled at δ 3.99 and 4.23. *Anal.* calcd. for $C_{10}H_{17}O_3N$: C 60.28, H 8.60, N 7.03; found: C 60.01, H 8.74, N 7.19.

(±)-Methyl [(1β,6β,8β)-3,3-dimethyl-2,4-dioxabicyclo[4.3.0]non-8-yl]carbamate (28)

A solution of sodium (1.65 g, 0.0718 g atom) in methanol (50 mL) was added to a solution of **27** (7.16 g, 35.9 mmol) in methanol (65 mL). To this solution Br_2 (1.84 mL, 35.9 mmol) was added with thorough mixing and the reaction solution was heated on a steam bath for 10 min. The solution was made just acidic with acetic acid and the solvent was evaporated. The residue was washed with water (10 mL) and the solid was collected by filtration to give **28** (6.34 g, 77%), R_f 0.72 (tlc) (2:2:1 (v/v/v) toluene – ethyl acetate – 2-propanol); tlc showed that this material contained traces of more-polar components. A small, oily sample of **28** was obtained by column chromatography on silica gel; ^{1}Hmr (200 MHz, Me_2SO-d_6) δ: 1.25 (3H, s, CH_3C), 1.34 (3H, s, CH_3C), 1.39 (1H, d of d of d, J_{gem} = 14.4, $^3J_{9,8}$ = 6.5, $^3J_{9,1}$ = 1.9 Hz, H-9), 1.65–1.93 (3H, m, H-6, H-7, and H-7′), 2.18 (1H, m, J_{gem} = 14.4, $^3J_{9',8}$ = 8.8, $^3J_{9',1}$ = 5.7 Hz, H-9′), 3.51 (3H, s, CH_3O), 3.51 (1H, d of d, J_{gem} = 11.9, $^3J_{5,6}$ = 2.1 Hz, H-5), 3.84 (1H, m, H-8), 3.98 (1H, d of d, J_{gem} = 11.9, $^3J_{5',6}$ = 3.7 Hz, H-5′), 4.20 (1H, m, H-1), 7.02 (1H, br d, $^3J_{to\ H\text{-}8}$ = 7.7 Hz, NH); spin–spin decoupled at δ 2.18 and 4.20.

(±)-(1β,6β,8β)-8-Amino-3,3-dimethyl-2,4-dioxabicyclo[4.3.0]-nonane (29)

A solution of **28** (6.02 g, 26.2 mmol) in 5 *N* aqueous sodium hydroxide (60 mL) and methanol (30 mL) was heated at reflux temperature for 4 h. The reaction solution was cooled to room temperature and extracted with dichloromethane (40 mL). The dichloromethane extract was evaporated under vacuum to give **29** (3.55 g, 79%) as a light yellow-green oil, R_f 0.45 (tlc) (5:1 (v/v) acetonitrile – 15 *N* aqueous ammonia). The ^{1}Hmr spectrum did not show any signals attributable to impurities; ^{1}Hmr (200 MHz, Me_2SO-d_6) δ: 1.24 (3H, s, CH_3), 1.30 (1H, m, H-9), 1.34 (3H, s, CH_3), 1.47 (1H, m, J_{gem} = 10.8, ^3J = 7.6 Hz, H-7), 1.69–1.82 (1H, m, H-6), 1.87 (1H, d of t, J_{gem} = 10.8, ^3J = 7.2 Hz, H-7′), 2.04 (1H, d of d of d, J_{gem} = 13.5, $^3J_{9',8}$ = 8.4, $^3J_{9',1}$ = 5.5 Hz, H-9′), 3.15 (1H, m, H-8), 3.50 (1H, d of d, J_{gem} = 11.6, $^3J_{5,6}$ = 3.2 Hz, H-5), 3.96 (1H, d of d, J_{gem} = 11.6, $^3J_{5',6}$ = 4.2 Hz, H-5′), 4.17 (1H, m, $^3J_{1,9'}$ = 5.5, $^3J_{1,9}$ = 2.2 Hz, H-1); spin–spin decoupled at δ 1.47, 3.15, 3.96, and 4.17.

(±)-Ethoxy-N-{N′-*[(1β,6β,8β)-3,3-dimethyl-2,4-dioxabicyclo-[4.3.0]non-8-yl]carbamoyl}propenamide (30)*

Compound **29** (1.60 g, 9.3 mmol) was dissolved in benzene (16 mL) and ~2 mL were removed by distillation. The solution was cooled to ice-bath temperature and a benzene solution (45 mL) containing **15** (13.4 mmol) was added dropwise over a period of 12 min; the reaction solution was then stirred at room temperature overnight. The solvent was evaporated and the residual oil was evaporated with ethanol (2 × 10 mL). Fractionation by column chromatography on silica gel gave **30** (2.2 g, 76%, based on the amount of the amine), R_f 0.42 (tlc) (8:8:1 (v/v/v) toluene – ethyl acetate – 2-propanol); ^{1}Hmr (200 MHz, Me_2SO-d_6) δ: 1.24 (3H, t, ^3J = 7.1 Hz, CH_3CH_2), 1.31 (3H, s, CH_3C), 1.37 (3H, s, CH_3C), 1.49 (1H, m, J_{gem} = 14.4 Hz, H-9′), 1.62 (1H, m, J_{gem} = 12.5, ^3J = 9.7, ^3J = 5.4 Hz, H-7′), 1.83 (1H, m, H-6′), 2.03 (1H, m, J_{gem} = 14.4, ^3J = 8.8, ^3J = 4.7 Hz, H-9″), 2.15 (1H, d of t, J_{gem} = 12.5, ^3J = 8.3 Hz, H-7″), 3.53 (1H, d of d, J_{gem} = 11.7, $^3J_{5',6'}$ = 2.2 Hz, H-5′), 3.94 (2H, q, ^3J = 7.1 Hz, CH_3CH_2O), 4.03 (1H, d of d, J_{gem} = 11.7, $^3J_{5'',6'}$ = 3.9 Hz, H-5″), 4.18–4.35 (2H, m, H-1′ and H-8′), 5.49 (1H, d, $^3J_{2,3}$ = 12.3 Hz, H-2), 7.52 (1H, d, $^3J_{3,2}$ = 12.3 Hz, H-3), 8.77 (1H, br d, $^3J_{to\ H\text{-}8'}$ = 8.6 Hz, CONHCON*H*), 9.95 (1H, br s, CON*H*CONH); spin–spin decoupled at δ 1.83 and 3.53.

Preparation of 24 from 30

A stirred mixture of **30** (2.2 g, 70 mmol) in 2 *N* H_2SO_4 (70 mL) was heated at reflux temperature for 20 min. The solution was cooled to ice-bath temperature and neutralized with 2 *N* NaOH. The solvent was evaporated and the residue was extracted with warm ethanol. The ethanol extract was evaporated and the residual oil was fractionated by column chromatography on silica gel to give **24** (1.034 g, 65%) as a white solid having an R_f (tlc) and ^{1}Hmr spectrum identical to those of the sample of **24** prepared from **23**.

(±)-(3-Carboxycyclopent-3-enyl)amine hydrochloride (31)

To a 1 *N* NaOH solution (1 L) at 5°C was added bromine (7.3 mL, 142 mmol); as soon as the bromine had dissolved, **4** (25.77 g, 120 mmol) in 0.7 *N* NaOH solution (175 mL) was added. The reaction solution was left at room temperature for 1 h and then heated in a water bath at 70°C for 1 h. The solution was cooled to 0°C and acidified with concentrated HCl (93 mL). The reaction solution was then passed through Amberlite CG-120 cation-exchange resin (H^+ form) (500 g), and the resin was washed with water (3.5 L) and eluted with 2 *N* HCl; the elution was monitored by tlc using *n*-butanol – water – acetic acid (5:3:2, v/v/v) as the developing solvent. The first 2.2 L contained mostly NaCl and some **31**; the solvent was evaporated and the residue was extracted with methanol (6 × 50 mL) to yield a solid (4.8 g). The next 1.3 L contained mostly **31** and gave a white solid (12.4 g) after evaporation of solvent, for a total yield of 17.2 g (88% yield) of a solid containing predominantly **31**; the sample was used directly in the next reaction; ^{1}Hmr (200 MHz, Me_2SO-d_6) δ: 2.45–2.95 (4H, m, H-2, H-2′, H-5, and H-5′), 3.87 (1H, m, H-1), 6.60 (1H, m, H-4), 8.30 (3H, br s, $\overset{+}{N}H_3$), 12.50 (1H, br s, CO_2H).

(±)-[3-(Methoxycarbonyl)cyclopent-3-enyl]amine hydrochloride (32)

Anhydrous HCl was bubbled for 1 h through a solution of compound **31** (17.0 g) in dry methanol (800 mL). The solution was stirred for an additional 1 h with cooling and then at room temperature overnight. The clear liquid was decanted from a small amount of solid and evaporated to give an orange oil of crude **32**; ^{1}Hmr (200 MHz, Me_2SO-d_6) δ: 2.56–2.94 (4H, m, H-2, H-2′, H-5, and H-5′), 3.67 (3H, s, OMe), 3.78–3.96 (1H, m, H-1), 6.67 (1H, m, H-4), 8.42 (3H, br s, $\overset{+}{N}H_3$).

(±)-Methyl 4-acetamido-1-cyclopentenecarboxylate (33)

A solution of crude **32** in pyridine (500 mL) was cooled to Dry Ice – acetone bath temperature and acetic anhydride (175 mL) was added. The reaction solution was stirred at room temperature for 18 h and then the solvent was evaporated to give a red-brown oil (48 g). This oil was mixed with crushed ice (300 g) and the mixture was extracted with methylene chloride (4 × 200 mL). The organic layer was washed sequentially with ice-cold 3 *N* HCl (2 × 30 mL), a saturated solution (30 mL) of sodium hydrogen carbonate, and a saturated solution (30 mL) of sodium chloride. The organic layer was dried over Na_2SO_4 and the solvent evaporated to give an orange-brown oil (18.7 g). This material was kept for 2 days in the cold room; a crystalline solid separated, which was collected by filtration and which, after recrystallization from diethyl ether – hexanes, gave **33** (11.63 g, 53% from **4**), mp 74–76°C. An analytical sample was obtained by recrystallization from diethyl ether; mp 75–76°C; ^{1}Hmr (200 MHz, Me_2SO-d_6) δ: 1.77 (3H, s, OAc), 2.20–2.40 and 2.68–2.87 (4H, m, H-3, H-3′, H-5, and H-5′), 3.67 (3H, s, OMe), 4.33 (1H, m, H-4), 6.68 (1H, m, H-2), 8.10 (1H, br d, $^3J_{to\ H\text{-}4}$ = 6.4, N*H*COMe). Spin–spin decoupling was performed at δ 4.33; ^{1}Hmr (200 MHz, $CDCl_3$) δ: 2.28–2.51 and 2.88–3.08 (4H, m, H-3, H-3′, H-5, and H-5′), 3.75 (3H, s, OMe), 4.63 (1H, m, H-4), 5.69 (1H, br m, N*H*COMe), 6.74 (1H, m, H-2). *Anal.* calcd. for $C_9H_{13}O_3N$: C 59.00, H 7.15, N 7.65; found: C 58.87, H 7.04, N 8.06.

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