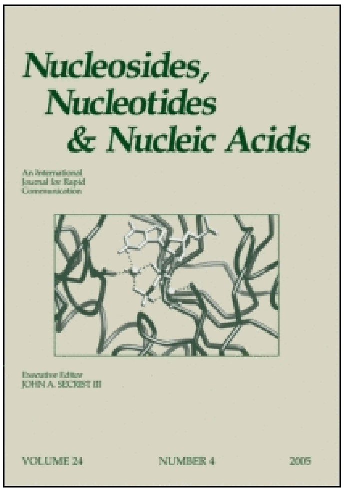

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# Studies on the Synthesis of *N*-Acetyl AZA-Analogues of *Ganciclovir*—Unexpected Liability of *N*-(2-Hydroxyethyl)-Azanucleosides Under Basic Conditions

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# STUDIES ON THE SYNTHESIS OF *N′*-ACETYL AZA-ANALOGUES OF *GANCICLOVIR*—UNEXPECTED LIABILITY OF *N′*-(2-HYDROXYETHYL)-AZANUCLEOSIDES UNDER BASIC CONDITIONS

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□ *The* O′*-pivaloyl diesters of* N′*-acetyl-azanucleosides were obtained from* N*-[1,3-di(pivaloyloxy)prop-2-yl]-*N*-(pivaloyloxymethyl)acetamide and a silylated nucleobase under Vorbrüggen's conditions. Unexpectedly, de-pivaloylation of the diesters under basic conditions afforded the corresponding nucleobase and* N*-acetylserinol. Mechanistic investigations showed that these products result from the following cascade of spontaneous transformations initiated by the mono de-pivaloylation of the starting diesters.* N′*-Deacetylation of the resultant mono-esters via the intramolecular* N-O *acetyl migration is the key step of the cascade; the corresponding* NH*-azanucleosides in the form of* O*-acetyl-*O′*-pivaloyl diesters are formed. Fragmentation of these diester intermediates gives the nucleobase and* O*-acetyl-*O′*-pivaloylserinol. Conversion of the latter to* N*-acetylserinol involves the selective* O-N *acetyl migration followed by de-pivaloylation of the resulting* N*-acetyl-*O*-pivaloylserinol.*

**Keywords** Nucleoside analogues; aza-nucleosides; N-(2-hydroxyethyl)amides; N-O acyl migration; O-N acyl migration

## INTRODUCTION

Acyclovir and ganciclovir (Figure 1) are drugs used for treatment of virus infections.[1] In search of their novel analogues, azanucleosides shown in Figure1 have recently been developed at this laboratory. The compounds were derived from *N*-(2-hydroxyethyl)arenosulfonamides (derivatives **1**[2]), *N*-(1,3-dihydroxyprop-2-yl)metanosulfonamide (derivatives **2**[3]), or 5,5-bis(hydroxymethyl)pyrrolidin-2-one (derivatives **3**[4]). Among them the thymine, guanine, or cytosine derivatives **3** showed a modest antiviral activity.

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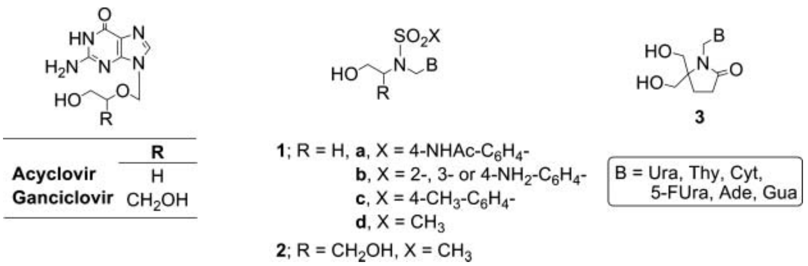
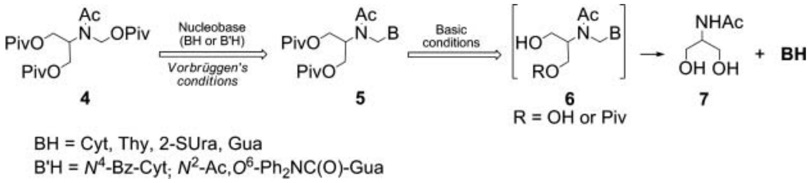


**FIGURE 1** Selected antiviral drugs and their aza analogues **1–3**.

Herein, the studies on the synthesis of azanucleosides **6** derived from *N*-(1,3-dihydroxyprop-2-yl)acetamide are reported (Scheme 1). Structurally, compounds **6** are a combination of derivatives **2** and **3**. In relation to **3**, a greater conformational freedom of **6** resulting from the replacement of the pyrrolidin-2-one ring with the flexible acyclic backbone, such as that of **2**, would be expected to have an effect on their biochemical properties. According to the methodology developed for the aforementioned azanucleosides **1–3**, the synthetic approach to **6** involved coupling of *N*-[1,3-di(pivaloyloxy)prop-2-yl]-*N*-(pivaloyloxymethyl)acetamide **4** with a nucleobase under Vorbrüggen's conditions followed by ammonolysis of the resulting *O*′-pivaloylated azanucleosides **5** (Scheme 1). Azanucleosides **6** were labile under basic conditions. The nature of the final products obtained in a majority of the examined reactions, that is, those of the corresponding nucleobase (BH) and *N*-acetylserinol **7**, suggested that the liability of **6** was associated with the presence of the $\beta$-hydroxyamide system in their structure; the *N*—*O* acyl migration process seemed to be involved in releasing of the nucleobase from the examined compounds. In the course of investigating these observations, it has been found that the *N-O* acyl migration in *N*-acyl-($\beta$-hydroxyalkyl)amines under basic[5] conditions has been postulated as an initial step of a base-induced hydrolysis of pseudoephedrine amides. Nevertheless, this hypothesis was not supported by experimental evidences. On the other hand, the interconversion of *N*-acyl-($\beta$-hydroxyalkyl)amines into *O*-acyl-($\beta$-hydroxyalkyl)ammonium salts under acidic conditions via *N-O* acyl migration is well documented in the literature.[6] The mechanistic



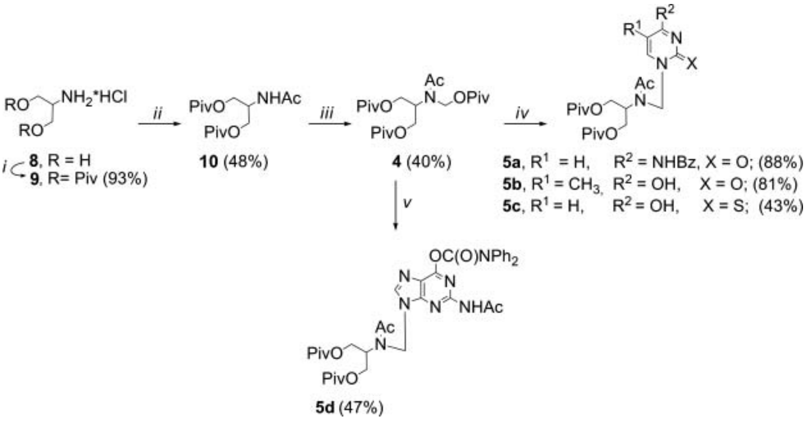
**SCHEME 1** Synthetic strategy for *O*′-pivaloylated azanucleosides **5** and their further transformations.

considerations[6] and experimental evidences[7,8] reveal that the interconversion is reversible and, under basic conditions, the resulting *O*-acyl-($\beta$-hydroxyalkyl)ammonium salt smoothly isomerises to the parent *N*-acyl-($\beta$-hydroxyalkyl)amine via *O-N* acyl migration. The latter direction of this pH-dependent equilibrium was successfully employed for creation of prodrugs of HIV protease inhibitors,[9] or anticancer agents.[10] To the best of author's knowledge, the chemical behavior of *N*-acyl-($\beta$-hydroxyalkyl)amines has not been considered with reference to the stability and potential applications of nucleoside analogues. Therefore, the reported studies on the liability of **6** were focused on two aspects: (a) the nature of the $\beta$-hydroxy group participation in the liberation of the nucleobase, and (b) the difference in the behavior of **6** and the 5-(hydroxymethyl)-containing lactams **3** under the examined conditions.

It is worth noting that nucleobase derivatives capable of releasing a free nucleobase have been studied as potential carriers for nucleobases, mainly for fluorouracil. The derivatives with the following functionality were examined in this respect: a carbamoyl [RNHC(O)—], carbamoylmethyl [RNHC(O)$CH_2$—], aminomethylcarbamate [ROC(O)NH$CH_2$—], or 1-amido-1-carboxyalkyl [RC(O)NHC($CO_2H$)(alkyl)].[11,12]

## RESULTS AND DISCUSSION

The synthesis of the *O*′-pivaloylated azanucleosides **5a-d** is shown in Scheme 2. The starting *N*-[1,3-bis(pivaloyloxy)prop-2-yl]acetamide **4**

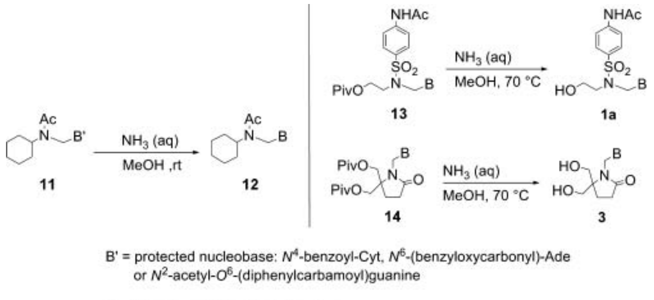


**SCHEME 2** Reagents and conditions: (i) PivCl, 90°C, 4 hours; (ii) $Ac_2O$, pyridine, room temerpature, 1 day; (iii) $ClCH_2OPiv$, NaH, DMF, 4 days; (iv) 1). nucleobase ($N^4$-benzoylcytosine, thymine, or 2-thiouracil), BSA, acetonitrile, room temperature 1 hour; 2). **4**, TMSOTf, acetonitrile, room temperature, 2 days; (v) 1). $N^2$-acetyl-$O^6$-(diphenylcarbamoyl)guanine, BSA, $CH_2Cl_2$, 80°C, 15 minutes; 2). **4**, TMSOTf, toluene, 80°C, 1 hour.

was prepared by: (i) *O*-pivaloylation of serinol hydrochloride **8** with pivaloyl chloride (PivCl); (ii) *N*-acetylation of **9** with acetic anhydride ($Ac_2O$); and (iii) *N*-pivaloyloxymethylation of **10** with chloromethyl pivalate ($ClCH_2OPiv$). The reaction (iii) was performed under the conditions optimized during *N*-pivaloyloxymethylation of *N*-cyclohexylacetamide (50% yield[13]), *N*-cyclohexylmethanesulfonamide (75% yield[13]), and *N*-(1,3-dipivaloyloxyprop-2-yl)methanesulfonamide (72% yield[3]). The *N*-pivaloyloxymethylation of **10** occurred with 48% yield, that is, a lower yield than *N*-(1,3-dipivaloyloxyprop-2-yl)methanesulfonamide, but comparable to that of *N*-cyclohexylacetamide. Presumably, the observed tendency in the *N*-pivaloyloxymethylation results from a lower N-H acidity of amides than the N-H acidity of sulfonamides.[14]

Coupling of **4** with a silylated nucleobase in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) afforded **5a-d** in good to satisfactory yield (88–43%). Derivatives **5a**, **5b**, or **5c** were obtained from $N^4$-benzoylcytosine, thymine or 2-thiouracil, respectively, (conditions iv). Compound **5d** was prepared from $N^2$-acetyl-$O^6$-(diphenylcarbamoyl)guanine (conditions v). Effectiveness of the couplings with $N^4$-benzoylcytosine (88%), thymine (81%), or $N^2$-acetyl-$O^6$-(diphenylcarbamoyl)guanine (47%) was higher than (or at least comparable to) those previously performed.[3,4,13] The coupling with 2-thiouracil gave **5c** in 43% yield. In the previous studies on the synthesis of 2′-azanucleosides, 2-thiouracil was not examined. However, the literature data reveal that coupling of 2-thiouracil is often less effective than the coupling of uracil or thymine with the same sugar mimic under Vorbrüggen's conditions.[15]

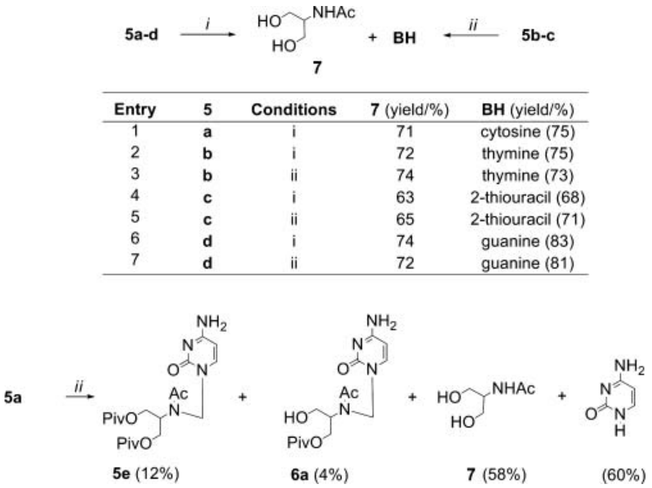
According to the literature data, ammonolysis is the most common procedure used for the removal of the *O*-acyl protecting groups or the *N*-acyl protecting groups from nucleoside analogues.[15] In the previous studies, the ammonolysis of the protected azanucleosides was routinely accomplished by the use of aqueous ammonia in methanol (Scheme 3). The deprotection of the nucleobase moiety of the cyclohexyl derivatives **11** was effective at room



B' = protected nucleobase: $N^4$-benzoyl-Cyt, $N^6$-(benzyloxycarbonyl)-Ade or $N^2$-acetyl-$O^6$-(diphenylcarbamoyl)guanine

B = Ura, Thy, Cyt, 5-FUra, Ade, Gua

**SCHEME 3** The routine ammonolysis conditions used for the preparation of azanucleosides **1a**, **3**, and **12**.



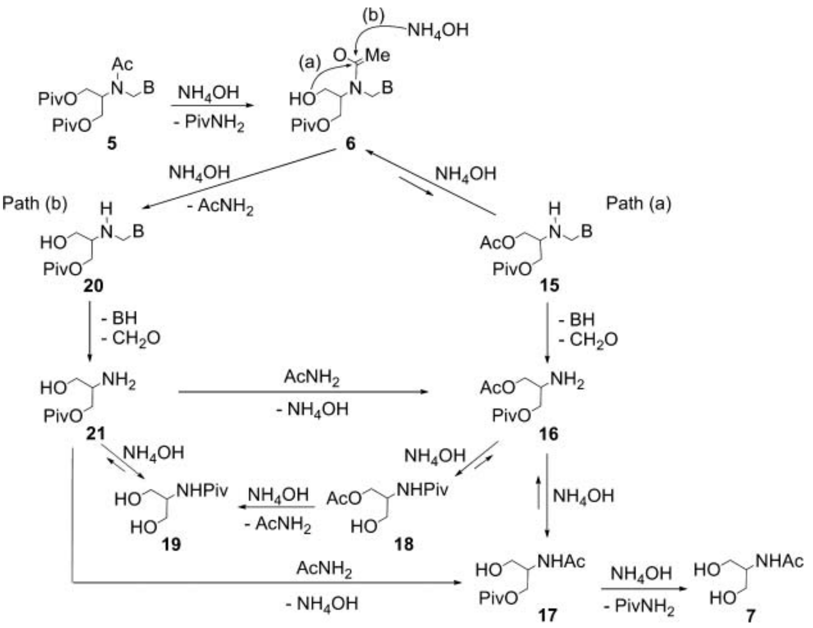
| Entry | 5 | Conditions | 7 (yield/%) | BH (yield/%) |
|---|---|---|---|---|
| 1 | **a** | i | 71 | cytosine (75) |
| 2 | **b** | i | 72 | thymine (75) |
| 3 | **b** | ii | 74 | thymine (73) |
| 4 | **c** | i | 63 | 2-thiouracil (68) |
| 5 | **c** | ii | 65 | 2-thiouracil (71) |
| 6 | **d** | i | 74 | guanine (83) |
| 7 | **d** | ii | 72 | guanine (81) |

**SCHEME 4** Reagents and conditions: **5**, $NH_4OH_{conc}$/MeOH, sealed tube, 1 hour: (i) 70°C; (ii) room temperature.

temperature.[13] In contrast to **11**, the removal of the *O*′-pivaloyl function required heating of the reaction mixture at 70°C at least for 1 day. Under those conditions, the ammonolysis of derivatives with both the *O*′-pivaloyl function and the *N*′-acyl one in the azasugar moiety (such as **13**[2a] or **14**[4]) occurred chemoselectively. The desired products **1a** or **3**, resulting from the selective removal of the *O*′-pivaloyl function, were obtained in high yields.

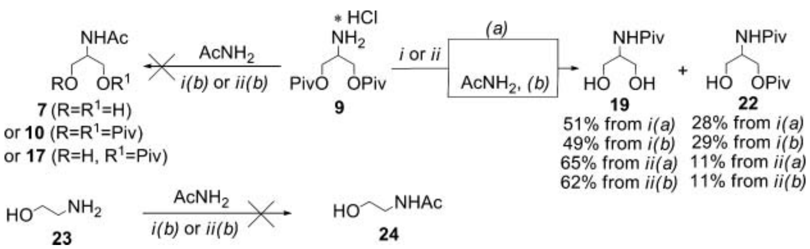
Preliminary trials on the ammonolysis of **5a-d** with aqueous ammonia in methanol at 70°C (Scheme 4, conditions i) afforded *N*-acetylserinol **7** and the corresponding nucleobase (BH = cytosine, thymine, 2-thiouracil, or guanine) as the only products. The reactions performed at room temperature gave the same results for **5b**, **5c**, or **5d** (conditions ii), whereas the reaction of the $N^4$-benzoylcytosine derivative **5a** yielded diester **5e** (12%) resulting from deprotection of the cytosine moiety, monoester **6a** (4%), **7** (58%), and cytosine (60%). The corresponding nucleobase was also liberated when **5a** or **5b** was treated, in a methanolic solution, with tetrabutylammonium hydroxide or a solid potassium carbonate at room temperature.

The results from the ammonolysis of **5a-d**, particularly the formation of the monoester **6a** from the $N^4$-benzoylcytosine derivative **5a**, suggested that the liberation of the nucleobase from **6** was initiated by the deprotection of the hydroxy group. The cleavage of azanucleosides leading to the formation of an azasugar and a free nucleobase was reported when the removal of the *N*′-protecting group was attempted.[16] Therefore, it is assumed that the liberation of the free nucleobase from **6** has resulted from their initial *N*′-deacetylation. Scheme 5 illustrates two possibilities of the *N*′-deacetylation of **6**, as well as further transformations leading to *N*-acetylserinol **7**.



**SCHEME 5** Plausible pathways for liberation of the nucleobase from **6**.

Path (a) involves the intramolecular *N-O* acetyl migration leading to the *O*-acetyl-*O′*-pivaloyl amine **15**, followed by the liberation of the free nucleobase (BH) and formation of *O*-acetyl-*O′*-pivaloylserinol **16**. The intramolecular *O-N* acetyl migration in **16** gives *N*-acetyl-*O*-pivaloylserinol **17** which, after ammonolysis of the *O*-pivaloyl protection, transforms into *N*-acetylserinol **7**. *O*-Acetyl-*O′*-pivaloylserinol **16** may also isomerise to *N*-pivaloyl-*O*-acetylserinol **18** via the intramolecular *O-N* pivaloyl migration. This interconversion leads to *N*-pivaloylserinol **19** as an accompanying product. The fact that **19** was not detected among the products of the ammonolysis may suggest that, if path (a) is operative, **16** does not undergo the *O-N* pivaloyl migration or the migration occurs much slower than the *O-N* acetyl migration leading to **17**. Path (b) involves ammonolysis of the acetamide linkage in **6** leading to the *O*-pivaloyl amine **20** and acetamide (AcNH$_2$), followed by releasing of the free nucleobase (BH) and formation of *O*-pivaloylserinol **21**. The intramolecular *O-N* pivaloyl migration in **21** gives *N*-pivaloylserinol **19**, whereas its competing reaction with the previously formed acetamide leads to *O*-acetyl-*O′*-pivaloylamine **16** and/or *N*-acetyl-*O*-pivaloylserinol **17**. Consequently, formation of **21** in the tested ammonolysis reactions may give the free nucleobase accompanied by: (i) *N*-pivaloylserinol **19**, as the only product formed from **21**; (ii) *N*-acetylserinol **7** resulted from reaction(s) of **21** with acetamide, when **21** does not undergo the *O-N* pivaloyl migration; or (iii) a mixture of **7** and **19**. The fact that the ammonolysis of **5** has afforded the free nucleobase and **7** as the only products may suggest that, when



**SCHEME 6** Reagents and conditions: $NH_4OH_{conc}$/MeOH, sealed tube, 1 day: (ia) or (ib) room temperature; (iia) or (iib) 70°C.

path (b) is operative, the reaction of **21** with acetamide (i.e., transamidation to **17**, or alcoholysis to **16**) predominates over the *O-N* pivaloyl migration. However, the literature data on transamidation reveal that such exchange reaction occurs between the salt of amine and amide (usually a substituted urea[17]) at an elevated temperature, or between neutral amine and a specific derivative of *N,N*-diacetylaniline.[18] Analogously, the alcoholysis of amides proceeds under catalysis by a mineral acid,[19] alkoxide,[20] or a transition-metal salt,[21] for instance. To gain an information on a behavior of the potential intermediate **21** under the ammonolysis conditions, the reactions shown in Scheme 6 were performed.

Treatment of *O,O′*-dipivaloylserinol hydrochloride **9** with a methanolic solution of ammonium hydroxide at room temperature for 1 day gave **19** and *O,N*-dipivaloylserinol **22** in 51% and 28% yield, respectively. The same products were obtained from the reaction performed at 70°C; the yield of **19** and **22** were 65% and 11%, respectively. As expected, **19** and **22** were also the only products obtained, when an equimolar mixture of **9** and acetamide ($AcNH_2$) was treated with a methanolic solution of ammonium hydroxide under the previously used conditions; the yield of the products were comparable to those obtained from the reactions curried out in the absence of acetamide; acetamide was recovered in the yields exciding 90%. Compounds corresponding to potential acetylation products of *O,O′*-dipivaloylserinol (i.e., the *N*-acetyl derivatives **7**, **10** or **17**) were not obtained (for preparation of the authentic reference **17** see, Experimental section). Furthermore, treatment of an equimolar mixture of ethanolamine **23**, an unbranched counterpart of **21**, and acetamide with a methanolic solution of ammonium hydroxide under the previously used conditions did not afford *N*-acetylethanolamine **24**, as the potential product resulting from *O*-acylation of **23** by acetamide and the subsequent *O-N* acyl migration. Instead, the starting material (by NMR) was recovered. These results indicate that the *N′*-deacetylation of **6** by the ammonolysis of the acetamide function leading to intermediate **21**, that is, in accordance with path (b), should give **19** as the only product. In view of these results, it is suggested that the liberation of the nucleobase from **6** under the tested conditions is a consequence of their initial *N′*-deacetylation via the intramolecular *N-O* acetyl migration, that is, in accordance with path (a). Although an equilibrium of the *N*-acyl-(*β*-hydroxyalkyl)amine-*O*-acyl-(*β*-hydroxyalkyl)amine interconversion is shifted toward the amide under basic[6] or hydrolytic[22] conditions, the liberation of the free nucleobase from **15**, typical for *N′*-unprotected azanucleosides,[16] seems to be the driving force of the process. Taking into account the ability of **9** to undergo rearrangement to *O*,*N*-dipivaloylserinol **22** under the ammonolysis conditions (Scheme 6), it is suggested that the transformation of the postulated **16** into **17** via the *O-N* acetyl migration proceeded faster than its transformation into **18** via the *O-N* pivaloyl migration under the examined conditions; probably due to a less steric effect of the acetyl group in relation to that of the pivaloyl one.[9a] Therefore, *N*-acetylserinol **7** is the only product resulting from the serinol moiety of **6**.

As mentioned earlier, the behavior of **6** under the ammonolysis conditions was in contrast to that previously observed for the 5,5-bis(hydroxymethyl)pyrrolidin-2-on-1-yl nucleosides **3**[4] as well as to those reported in the literature for *N*-acetyl-5-(hydroxymethyl)pyrrolidin-2-yl nucleosides **25** (Figure 2).[23] To rationalize this difference in behavior of the compounds, energetic requirements for the *N*-acyl-(*β*-hydroxyalkyl)amine-*O*-acyl-(*β*-hydroxyalkyl)amine interconversion were considered. The literature-based pathway for the interconversion (shown in Figure 2) involves: (i) transformation of *N*-(*β*-hydroxyalkyl)amide **A** into alkoxide **B** by the

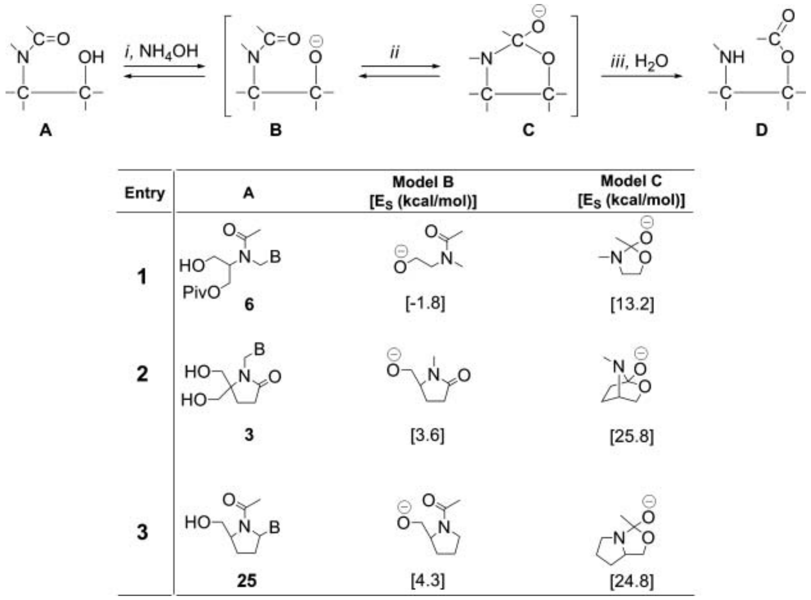


**FIGURE 2** Total strain energy ($E_S$) evaluated for intermediates involved into the *N*-(2-hydroxyalkyl)amide-*O*-(2-aminoalkyl)ester interconversion.

action of ammonium hydroxide;[24] (ii) the intramolecular attack of the alkoxide anion on the carbonyl carbon to form 1,3-oxazolidin-2-olate **C**;[6] and (iii) conversion of **C** to the final *O*-($\beta$-aminoalkyl)ester **D**. The second step of the sequence, that is, the formation of 1,3-oxazolidin-2-olate **C**, is the rate-determining step of the overall process.[25] Therefore, in line with the Hammond postulate,[26] the reaction is believed to take place via the transition state, which should closely resemble 1,3-oxazolidin-2-olate **C**. Consequently, the ease of the conversion of *N*-($\beta$-hydroxyalkyl)amides **A** to *O*-($\beta$-aminoalkyl)esters **D** might be discussed in relation to the stability of 1,3-oxazolidin-2-olates **C**. Since the Ruzicka hypothesis,[27] the stability of the ring being formed is considered as a major factor affecting the ease of ring closure and it is expressed as strain energy of the ring. Therefore, the total strain energy ($E_S$) in both 1,3-oxazolidin-2-olates **C** and the corresponding starting alkoxides **B** related to compounds **3**, **6**, or **25** was evaluated by the MM2 molecular mechanics method.[28] Taking into account the fact that complex structures of the considered systems might result in many local minima of the evaluated strain energy, calculations were performed on the simplified systems corresponding to alkoxides **B** (i.e., Model B; Figure 2) and 1,3-oxazolidin-2-olates **C** (i.e., Model C; Figure 2) where a nucleobase ring (Figure 2, entries 1–3) as well as the pivaloyloxymethyl function (entry 1) (or the hydroxymethyl one, entry 2) were replaced with hydrogen atoms.

The calculations showed that the monocyclic intermediates **C** formed from **6** were much less strained than both the fused bicyclic intermediates **C** formed from **25** and the bridged ones formed from **3** (Figure 2).[29] The lowest strain energy in 1,3-oxazolidin-2-olates **C** formed from **6** is believed to reflect in the lowest energy in their transition states. For that reason, in contrast to **3** or **25**, derivatives **6** proved to be capable of rearranging to the corresponding esters **15** (shown in Scheme 5) under relatively mild conditions.

## CONCLUSION

In summary, the pivaloyl esters of *N*′-acetyl-azanucleosides **5a-d** were obtained from *N*-[1,3-bis(pivaloyloxy)prop-2-yl)-*N*-(pivaloyloxymethyl)] acetamide **4** and the corresponding silylated nucleobase under Vorbrüggen's conditions. The ammonolysis of **5a-d** gave the corresponding nucleobase (BH) and *N*-acetylserinol **7** as the only products in a majority of the reactions performed (Scheme 4); only **5a** afforded the monoester **6a** at room temperature. It was proved that the free nucleobase and **7** result from the following cascade of spontaneous transformations initiated by the depivaloylation of **5** (Scheme 5, path a): (i) the intramolecular *N-O* acetyl migration in monoesters **6**; (ii) fragmentation of the *O*-acetyl-*O′*-pivaloyl *NH*-intermediates **15** to the free nucleobase (BH) and *O*-acetyl-*O′*-pivaloylserinol **16**; (iii) the *O-N* acetyl migration in **16**; and (iv) de-pivaloylation of *N*-acetyl-*O*-pivaloylserinol **17** leading to *N*-acetylserinol **7**. The selective transformation of **16** into **17** (the precursor of **7**) represents an example of a structural competition[7b,30] in the *N*-acyl-($\beta$-hydroxyalkyl)amine-*O*-acyl-($\beta$-hydroxyalkyl)amine interconversion. The transformation results from predomination of the *O-N* acetyl migration in **16** over the alternative *O-N* pivaloyl one under the examined conditions. Occurrence of the *O-N* pivaloyl migration under the ammonolysis conditions has been confirmed by the formation of *N*-pivaloylserinol **19** from *O,O′*-dipivaloylserinol hydrochloride **9** (Scheme 6). The observation that the *O-N* acyl migration can occur selectively when *O*-acyl groups of a starting amino-diester, for instance of a derivative relative to **16**, are significantly different in steric bulk can be a clue to effective design a synthesis. The literature data on the selective *O-N* acyl migration in unsymmetrical diesters of serinol is rather limited. Among the known compounds of this type,[31] only 1-acetoxy-2-amino-3-benzoyloxy-1-phenylpropane hydrochloride and 1-benzoyloxy-2-amino-3-acetoxy-1-phenylpropane hydrochloride were examined in this respect.[31a] The compounds underwent the *O-N* acetyl migration to give the corresponding benzyloxyacetamides under alkaline conditions.

The molecular modeling supports the postulate that the proclivity of **6** to undergo *N′*-deacetylation via the intramolecular *N-O* acyl migration under basic conditions may be attributed to the formation of the monocyclic 1,3-oxazolidin-2-olate intermediate (Figure 2, entry 1). It is clear that this intermediate is much less strained, that is, it is much easier to be formed, than the fused or bridged bicyclic one required for the *N′*-deacylation of **3** or **25**, respectively, by the same mode.

In light of the reports on *N-N* acyl migrations in nucleoside analogues with an *N*-acyl-($\beta$-aminoalkyl)amine backbone,[32] the findings on the liability of **6** are expected to be of interest for investigators involved in the synthesis of nucleoside analogues with an *N*-acyl-($\beta$-hydroxyalkyl)amine backbone, for example, as potential antimicrobials,[32a] intermediates for preparing of novel anticancer agents,[33] or precursors of peptide nucleic acid monomers.[34] The results show that possible proclivity of compounds from this class to undergo *N-O* acyl migration should be considered before their treatment with ammonium hydroxide or potassium carbonate, that is, with agents typically used for removal of protecting groups from nucleoside derivatives.

On the other hand, the transformations leading to liberation of the nucleobase from **6** may be of interest for whose who are involved in creation of novel prodrug strategies. From a structural point of view, *N*-acyl-($\beta$-hydroxyalkyl)aminomethyl functionality, when linked to the NH acidic group of a drug, can be considered as a useful promoiety. The intramolecular *N-O* acyl migration would be expected to initiate the interconversion cascade leading to release of the parent drug from the resultant *N*-($\beta$-acyloxyalkyl)aminomethyl-containing intermediate. This prodrug concept is expected to be worthy of consideration as a supplement to the current prodrug strategies for drugs containing the NH acidic group.[11,35]

## EXPERIMENTAL

### General

High resolution mass spectra (Electrospray Ionisation, ESI) were performed on a Mariner spectrometer in a positive ionization mode. The infrared (IR) spectra were recorded on a Specord M80 (Carl-Zeiss Jena) spectrometer; absorption maxima ($\nu_{max}$) are given in cm$^{-1}$. $^1$H- and $^{13}$C-NMR spectra were recorded on a Varian Gemini 200 spectrometer ($^1$H at 200 MHz, $^{13}$C at 50 MHz). $^1$H and $^{13}$C chemical shifts are reported in ppm relative to the solvent signals: $CDCl_3$, $\delta_H$(residual $CHCl_3$) 7.26 ppm, $\delta_C$ 77.16 ppm) or DMSO-$d_6$, $\delta_H$(residual DMSO) 2.50 ppm, $\delta_C$ 39.52 ppm; signals are quoted as s (singlet), d (doublet), dd (doublet of doublets), dtt (doublet of triplets of triplets), m (multiplet), br s (broad singlet), and q (quartet). Coupling constants *J* are reported in Hz. Precoated Merck silica gel 60 $F_{254}$ (0.2 mm) plates were used for thin-layer chromatography (TLC), and the spots were detected under UV light (254 nm). Column chromatography was performed using silica gel (200–400 mesh, Merck). Anhydrous $MgSO_4$ was employed as a drying agent. Solvents were distilled off under reduced pressure on a rotary evaporator.

### *1. N-[1,3-bis(pivaloyloxy)prop-2-yl]acetamide (10)*

A mixture of serinol hydrochloride **8** (8.72 g, 68 mmol) and pivaloyl chloride (16.44 g, 136 mmol, 16.8 cm$^3$) was heated on an oil bath at 90°C for 4 hours. When the evolution of hydrogen chloride ceased, the mixture became solid. The crude **9** was kept at a vacuum desiccator over KOH for 1 day. Yield 18.83 g (93%, crude). Analytical sample was crystallized from dry acetone. $\delta_H$ (DMSO-$d_6$) 1.15 (18H, s) 3.55–3.78 (1H, m), 4.06–4.37 (4H, m), 8.77 (3H, br s). $\delta_C$ (DMSO-$d_6$) 26.88, 48.06, 58.66, 61.05, 177.26. $\nu_{max}$ (KBr) 3648, 2928, 2856, 1728, 1460, 1156. HRMS m/z 260.1856 calcd for $C_{13}H_{26}NO_4$ $(M+H)^+$, found 260.1861.

A mixture of the crude **9** (17.93 g, 61 mmol), dry pyridine (120 cm$^3$) and acetic anhydride (12.25 g, 120 mmol, 11.3 cm$^3$) was kept at room temperature for 1 day. The mixture was poured into cold water (30 cm$^3$). The organic phase was separated and the aqueous phase was extracted with chloroform (3 × 30 cm$^3$). The extracts and the organic phase were combined, washed with water and dried. The solvent was distilled off. Product **10** was isolated from the residue by column chromatography (chloroform). Yield 48% (8.83 g, m.p. 56–58°C). $\delta_H$ ($CDCl_3$) 1.18 (18H, s), 1.97 (3H, s), 4.04 (2H, dd, $^2J$ 11.4, $^3J$ 5.5), 4.21 (2H, dd, $^2J$ 11.4, $^3J$ 5.9), 4.51 (1H, dtt, $^2J$ 8.6, $^3J$ 5.9, $^3J$ 5.5), 5.81 (1H, d, $^2J$ 8.6). $\delta_C$ ($CDCl_3$) 23.42, 27.26, 39.04, 47.94, 62.72, 169.89, 178.53. $\nu_{max}$ (KBr) 2928, 1732, 1644, 1460, 1376, 1152. HRMS m/z 324.1781 calcd for $C_{15}H_{27}NO_5Na$ $(M+Na)^+$, found 324.1790.

### 2. N-(1,3-dipivaloyloxyprop-2-yl)-N-(pivaloyloxymethyl)acetamide (4)

A mixture of **10** (3.0 g, 10 mmol), sodium hydride (60% suspension in mineral oil, 1.0 g, 25.0 mmol) and dry dimethylformamide (DMF) (40 $cm^3$) was stirred at room temperature for 1 hour and then cooled on an ice bath. Chloromethyl pivalate (6.89 g, 46 mmol, 4.9 $cm^3$) was added to the resulting suspension in one portion. After 4 days of stirring at room temperature the mixture was poured into ice water (120 $cm^3$) and the phases were separated. The aqueous phase was extracted with ethyl acetate (4 × 30 $cm^3$). Extracts and the organic phase were combined, washed with brine and dried. The low boiling solvents were distilled off and the residual DMF was removed under vacuum (80°C, 0.05 mmHg). Product **4** was isolated from the residue by column chromatography (dichloromethane). Yield 40% (1.69 g, m.p. 43–45°C). $\delta_H$ ($CDCl_3$) 1.18 (18H, s), 1.21 (9H, s), 2.19 (3H, s), 4.16–4.31 (4H, m), 4.88–5.09 (1H, m), 5.44 (2H, s). $\delta_C$ ($CDCl_3$) 21.63, 27.10, 27.23, 38.91, 51.28, 62.13, 71.66, 172.12, 177.98. $\nu_{max}$ (nujol) 2925, 1732, 1672, 1460, 1376, 1280, 1156. HRMS m/z 438.2462 calcd for $C_{21}H_{37}NO_7Na$ $(M+Na)^+$, found 438.2483.

### 3. General Procedure for the Preparation of Pyrimidine Azanucleosides 5a-c

A mixture of the pyrimidine nucleobase (thymine, $N^4$-benzoylcytosine, or 2-thiouracil) (2.0 mmol), *N,O*-bis(trimethtlsilyl)acetamide (BSA, 815 mg, 4.0 mmol, 1.0 $cm^3$) and dry acetonitrile (10 $cm^3$) was stirred at room temperature under an argon atmosphere for 1 hour, and then a solution of **4** (416 mg, 1.0 mmol) in dry acetonitrile (1 $cm^3$) and neat trimethylsilyl trifluoromethanesulfonate (TMSOTf, 370 mg, 1.7 mmol, 0.3 $cm^3$) were added. The mixture was left for 2 days at room temperature, and then ethyl acetate (50 $cm^3$) and a saturated solution of sodium bicarbonate (1 $cm^3$) were added. The mixture was stirred for 1 hour, and then filtered through a Celite pad. The organic phase was separated, washed with brine and dried. The solvent was distilled off. Product **5a** (**5b** or **5c**) was isolated from the residue by column chromatography; the eluting solvents are given bellow.

*3.1. 4-(Benzoylamino)-1-[N-(1,3-dipivaloyloxyprop-2-yl)acetylaminomethyl]-1H-pyrimidin-2-one (5a).* According to the general procedure, **5a** was obtained from **4** and $N^4$-benzoylcytosine. Eluting solvent: $CHCl_3$/acetone, 97/3, v/v. Yield 88% (466 mg, oil). $\delta_H$ ($CDCl_3$) 1.12 (18H, s), 2.21 (3H, s), 4.21–4.48 (5H, m), 5.60 (2H, s), 7.44–7.62 (4H, m), 7.87–7.92 (2H, m), 8.31 (1H, d, $^3J$ 7.6), 9.33 (1H, br s). $\delta_C$ ($CDCl_3$) 22.45, 27.17, 38.89, 52.37, 55.52, 61.07, 97.62, 127.80, 129.11, 133.29, 133.36, 150.07, 155.93, 162.70, 174.42, 177.97. $\nu_{max}$ (nujol) 2906, 1724, 1660, 1624, 1460, 1376, 1292, 1164. HRMS m/z 551.2476 calcd for $C_{27}H_{36}N_4O_7Na$ $(M+Na)^+$, found 551.2501.

*3.2. 1-[N-(1,3-dipivaloyloxyprop-2-yl)acetylaminomethyl]-5-methyl-1H,3H-pyrimidin-2,4-dione (**5b**).* According to the general procedure, **5b** was obtained from **4** and thymine. Eluting solvent: $CHCl_3$/acetone, 95/5, v/v. Yield 81% (356 mg, m.p. 137–140°C). $\delta_H$ ($CDCl_3$) 1.14 (18H, s), 1.88 (3H, d, $^4J$ 1.2), 2.21 (3H, s), 4.16–4.58 (5H, m), 5.40 (2H, s), 7.71 (1H, q, $^4J$ 1.2), 8.66 (1H, br s). $\delta_C$ ($CDCl_3$) 12.44, 22.48, 27.10, 38.86, 50.53, 55.28, 60.89, 111.702, 140.65, 151.65, 164.04, 174.31, 177.90. $\nu_{max}$ (nujol) 3648, 2924, 1736, 1688, 1632, 1460, 1376, 1178. HRMS m/z 462.2211 calcd for $C_{21}H_{33}N_3O_7Na$ $(M+Na)^+$, found 462.2229.

*3.3. 1-[N-(1,3-dipivaloyloxyprop-2-yl)acetylaminomethyl]-5-methyl-1H,3H-pyrimidin-4-on-2-thione (**5c**).* According to the general procedure, **5c** was obtained from **4** and 2-thiouracil. Eluting solvent: $CHCl_3$/acetone, 95/5, v/v. Yield 43% (188 mg, oil). $\delta_H$ ($CDCl_3$) 1.12 (18H, s), 2.21 (3H, s), 4.17–4.91 (5H, m), 5.96 (1H, d, $^3J$ 8.0), 6.03 (2H, s), 7.88 (1H, d, $^3J$ 8.0) 10.93 (1H, br s). $\delta_C$ ($CDCl_3$) 22.49, 27.19, 38.88, 55.97, 60.85, 62.69, 108.02, 144.55, 159.82, 174.45, 176.63, 177.91. $\nu_{max}$ (nujol) 2908, 1732, 1680, 1460, 1376, 1284, 1148. HRMS m/z 464.1826 calcd for $C_{20}H_{31}N_3O_6NaS$ $(M+Na)^+$, found 464.1845.

## *4. 2-(Acetylamino)-6-(diphenylcarbamoyl)-9-[N-(1,3-dipivaloyloxyprop-2-yl)acetylaminomethyl]-9H-purine (5d)*

A mixture of $N^2$-acetyl-$O^6$-(diphenylcarbamoyl)guanine (780 mg, 2 mmol), *N,O*-bis(trimethtlsilyl)acetamide (BSA, 814 mg, 4 mmol, 1 $cm^3$) and dry ethylene chloride (10 $cm^3$) was heated at 80°C in a sealed tube under an argon atmosphere for 15 min. The solvent was removed under vacuum at 40°C (0.05 mmHg), and the residue was dissolved in dry toluene (20 $cm^3$). A solution of **4** (416 mg, 1.0 mmol) in dry toluene (1 $cm^3$) and neat trimethylsilyl trifluoromethanesulfonate (TMSOTf, 370 mg, 1.7 mmol, 0.3 $cm^3$) were added. The mixture was heated at 80°C for 1 hour, and then cooled to room temperature. Ethyl acetate (50 $cm^3$) and saturated solution of sodium bicarbonate (1 $cm^3$) were added. The resulting mixture was stirred for 1 hour at room temperature and filtered through a Celite pad. The organic phase was separated from the filtrate and washed with water, brine and dried. The solvent was distilled off. Product **5d** was isolated from the residue by column chromatography (chloroform/acetone, 95/5, v/v). Yield 47% (331 mg, foam). $\delta_H$ ($CDCl_3$) 1.04 (18H, s), 2.18 (3H, s), 2.41 (3H, s), 4.22–4.31 (2H, m), 4.39–4.50 (3H, m), 5.64 (2H, s), 7.23–7.44 (10H, m), 8.28 (1H, br s), 8.47 (1H, s). $\delta_C$ ($CDCl_3$) 22.13, 25.12, 27.06, 38.78, 48. 18, 55.42, 61.04, 127.01, 129.24, 141.85, 146.40, 150.30, 151.94, 156.28, 169.49, 173.60, 177.95. $\nu_{max}$ (nujol) 2900, 1723, 1656, 1632, 1448, 1370. HRMS m/z 724.3065 calcd for $C_{36}H_{43}N_7O_8Na$ $(M+Na)^+$, found 724.3073.

### 5. Reaction of 5a-d with Ammonium Hydroxide at 70°C (Scheme 4, Path i)

A mixture of **5a-d** (1 mmol), concentrated ammonium hydroxide (20 cm$^3$) and methanol (20 cm$^3$) was kept at 70°C (in a sealed tube) for 1 day. Then the reaction mixture was evaporated to dryness and the residue was treated with methanol (15 cm$^3$). The resulting suspension was filtered; the solid was washed with cold methanol (3 × 10 cm$^3$) and dried in the air to give the corresponding nucleobase in the yields given in Scheme 4. The filtrate and the washings were combined and evaporated to dryness. *N*-Acetylserinol **7** was isolated from the residue by column chromatography (chloroform-methanol, 95/5, v/v); the yields are given in Scheme 4; $^1$H MNR spectrum was consistent with that reported in the literature.[36] $\delta_C$ (DMSO-$d_6$) 22.79, 52.89, 60.20, 169.15.

### 6. Reaction of 5a-d with Ammonium Hydroxide at Room Temperature (Scheme 4, Path ii)

A mixture of **5a-d** (1 mmol), concentrated ammonium hydroxide (20 cm$^3$) and methanol (20 cm$^3$) was kept at room temperature for 1 day. Then the reaction mixture was evaporated to dryness and the residue was treated with methanol (15 cm$^3$). The resulting suspension was filtered; the solid was washed with cold methanol (3 × 10 cm$^3$) and dried in the air to give the corresponding nucleobase in the yields given in Scheme 4. The filtrate and the washings were combined and evaporated to dryness. The residue was passed through a chromatographic column.

6.1. Chromatography of the residue from the reaction of **5a** (chloroform-Methanol, 99/1, v/v) afforded **5e** (12%, 51 mg, oil), **6a** (4%, 14 mg, oil), and N-acetylserinol **7** (58%)

*6.1.1. 4-(Amino)-1-[N-(1,3-dipivaloyloxyprop-2-yl)acetylaminomethyl]-1H-pyrimidin-2-one (5e).* $\delta_H$ (CDCl$_3$) 1.12 (18H, s), 2.17 (3H, s), 4.19–4.39 (5H, m), 5.44 (2H, s), 5.73 (1H, d, $^3J$ 7.2), 6.56 (1H, br s), 6.60 (1H, br s), 7.90 (1H, d, $^3J$ 7.2). $\delta_C$ (CDCl$_3$) 22.47, 27.18, 38.88, 55.41, 61.29, 61.97, 95.43, 146.56, 156.76, 165.93, 174.27. $\nu_{max}$ (nujol) 2908, 1721, 1627, 1426, 1355, 1141. HRMS m/z 447.2233 calcd for $C_{20}H_{32}N_4O_6Na$ $(M+Na)^+$, found 447.2214.

6.2.2. 4-Amino-1-{*N*-[1-hydroxy-3-(pivaloyloxymethyl)prop-2-yl]acetylaminomethyl}-1*H*-pyrimidin-2-one (**6a**). $\delta_H$ (CDCl$_3$) 1.15 (9H, s), 2.20 (3H, s), 3.64–4.31 (6H, m), 5.21 (1H, d, $^2J$ 13.6), 5.36 (1H, d, $^2J$ 13.6), 5.74 (1H, d, $^3J$ 7.2), 6.52 (1H, br s), 6.56 (1H, br s), 7.86 (1H, d, $^3J$ 7.2). $\delta_C$ (CDCl$_3$) 22.77, 27.19, 38.85, 53.53, 59.14, 59.76, 61.93, 95.54, 146.59, 157.30, 166.15, 175.17. $\nu_{max}$ (nujol) 2915, 1721, 1618, 1434, 1366, 1158. HRMS m/z 363.1639 calcd for $C_{15}H_{24}N_4O_5Na$ $(M+Na)^+$, found 363.1639.

6.2. Chromatography of the residue from the reaction of **5b-d** (chloroform-Methanol, 95/5, v/v) gave N-acetylserinol **7** in the yields given in Scheme 4.

### *7. Reaction of 9 with Ammonium Hydroxide (Scheme 6, Reaction i(a) or ii(a))*

A mixture of **9** (2 mmol), concentrated ammonium hydroxide (40 $cm^3$) and methanol (40 $cm^3$) was kept for 1 day at room temperature (Scheme 6, reaction ia) or at 70°C (Scheme 6, reaction iia). The reaction mixture was evaporated to dryness. Column chromatography of the residue (chloroform-methanol, 99/1 → 8/2, v/v) afforded **19** (184 mg, 51%, reaction ia; 233 mg, 65% reaction iia) and **22** (151 mg, 28%, reaction ia; 58 mg, 11% reaction iia).

*7.1. N-(1,3-Dihydroxypropan-2-yl)pivalamide (**19**). A white solid, m.p. 59–61°C.* $\delta_H$ ($CDCl_3$) 1.17 (9H, s), 3.63 (2H, ABX, X = H(2), $^2J_{AB}$ 11.0, $^3J_{AX}$ 5.3), 3.75 (2H, ABX, X = H(2), $^2J_{AB}$ 11.0, $^3J_{BX}$ 4.1), 3.82–3.96 (1H, m), 4.35 (2H, br s, OH), 6.51 (1H, 6.30 (d, $^3J_{HH}$ 7.6, NH). $\delta_C$ ($CDCl_3$) 27.57, 38.94, 52.46, 61.85, 180.05. $\nu_{max}$ (KBr) 3342, 3237, 1632, 1530, 1397, 1364. HRMS m/z 198.1102 calcd for $C_8H_{17}NO_3Na$ $(M+Na)^+$, found 198.1097.

*7.2. 3-Hydroxy-2-pivalamidopropyl pivalate (**22**).* A colorless oil. $\delta_H$ ($CDCl_3$) 1.10 (9H, s), 1.11 (9H, s), 3.50 (1H, ABX, X = H(2), $^2J_{AB}$ 11.4, $^3J_{AX}$ 4.5), 3.61 (1H, ABX, X = H(2), $^2J_{AB}$ 11.4, $^3J_{BX}$ 3.5), 4.41–4.22 (3H, m), 6.30 (1H, d, $^3J_{HH}$ 7.0, NH). $\delta_C$ ($CDCl_3$) 27.11, 27.43, 38.73, 38.83, 50.55, 61.54, 62.86, 179.05, 179.24. $\nu_{max}$ (KBr) 3363, 1728, 1640, 1524, 1397, 1367, 1155. HRMS m/z 282.1645 calcd for $C_{13}H_{25}NO_4Na$ $(M+Na)^+$, found 282.1653.

### *8. Reaction of 9 with Ammonium Hydroxide in the Presence of $AcNH_2$ (Scheme 6, Reaction i(b) or ii(b))*

A mixture of **9** (2 mmol) and acetamide (2 mmol), concentrated ammonium hydroxide (40 $cm^3$) and methanol (40 $cm^3$) was kept for 1 day at room temperature (Scheme 6, reaction ib) or at 70°C (Scheme 6, reaction iib). The reaction mixture was evaporated to dryness. The solid residue was shaken with chloroform (25 $cm^3$) and filtered. The white solid ($AcNH_2$) was washed with chloroform (10 $cm^3$) and dried. The filtrate was evaporated to dryness. Column chromatography of the residue (chloroform-methanol, 99/1 → 8/2, v/v) gave **19** (176 mg, 49%, reaction ib; 223 mg, 62% reaction iib) and **22** (156 mg, 29%, reaction ib; 59 mg, 11% reaction iib). The NMR spectra of the products **19** and **22** were consistent with those described previously. The NMR spectra (DMSO-$d_6$) of the recovered $AcNH_2$ showed: $\delta_H$ 1.76 (3H, s), 6.74 (1H, br s, NH) and 7.32 (1H, br s, NH); $\delta_C$ 22.55 and 172.06.

### *9. 2-Acetamido-3-hydroxypropyl pivalate (17)*

A mixture of **10** (550 mg, 1.8 mmol), concentrated ammonium hydroxide (40 $cm^3$) and methanol (40 $cm^3$) was kept for 1 day at room temperature. The reaction mixture was evaporated to dryness and the oil residue was passed through a short chromatographic column. The column was eluted with a chloroform-methanol mixture (95/5, v/v, 500 $cm^3$) to yield **17** (85 mg, 23%, oil) and then with methanol (200 cm$^3$) to give **7** (111 mg, 46%). $\delta_H$ ($CDCl_3$) 1.16 (9H, s), 1.96 (3H, s), 3.47–3.85 (3H, m), 4.12–4.24 (3H, m), 6.46 (d, $^3J_{HH}$ 6.2, 1H, NH). $\delta_C$ ($CDCl_3$) 23.23, 27.19, 38.96, 50.44, 61.49, 62.51, 170.98, 179.22. $\nu_{max}$ (KBr) 3287, 1715, 1650, 1543, 1399, 1370, 1161. HRMS m/z 240.1207 calcd for $C_{10}H_{19}NO_4Na$ $(M+Na)^+$, found 240.1204.

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