Stereospecific vicinal oxyamination of *N*-substituted 1,2,3,6-tetrahydropyridines and 1,2-dihydropyridines by *N*-chloro-*N*-metallocarbamates

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The vicinal oxyamination of 1-substituted 1,2,3,6-tetrahydropyridines (**2**) affords a mixture of the regioisomeric *cis*-hydroxycarbamates **3** and **4**. The *tert*-butoxycarbonylamino and hydroxyl substituents for **3** and **4** assume the equatorial and axial orientations respectively, irrespective of the substituent position. Acid hydrolysis of **3***a* and **4***a* affords the *cis*-aminoalcohols **5** and **6**. The regiospecific oxyamination of 1-methyoxycarbonyl-1,2-dihydropyridine occurs at the 5,6-olefenic bond to yield the hydroxycarbamates **15** and **16**. Reduction of **15** or **16** with palladium on charcoal affords the same vicinal hydroxy and methoxycarbamates **17** to **20** which may arise via the aziridine intermediate **21**.

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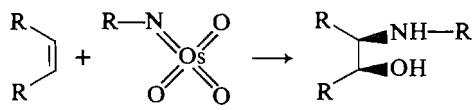
L'oxyamination vicinale des tétrahydro-1,2,3,6 pyridines (**2**) substituées en position 1 donne un mélange d'hydroxycarbamates *cis* régioisomères **3** et **4**. Les substituants *tert*-butoxycarbonylamino et hydroxyle des composés **3** et **4** sont respectivement en positions équatorial et axiale indépendamment de la position du substituant. L'hydrolyse acide des composés **3***a* et **4***a* conduit aux aminoalcools *cis* **5** et **6**. L'oxyamination régiospécifique de la méthoxycarbonyl-1 dihydro-1,2 pyridine a lieu au niveau de la liaison oléfinique en positions 5,6 en donnant les hydroxycarbamates **15** et **16**. La réduction des composés **15** et **16** par le palladium sur du charbon fournit les mêmes hydroxy et méthoxycarbamates vicinaux **17** à **20** qui peuvent être obtenus via un intermédiaire aziridine **21**.

[Traduit par le journal]

The stereospecific vicinal oxyamination reaction of olefins developed by Sharpless and co-workers is a useful procedure for the synthesis of *cis*-β-aminoalcohol derivatives. One of these procedures employs a stoichiometric quantity of a (*tert*-alkylimido)-osmium reagent (**1***a*) (1). The other procedures, which require a catalytic quantity of osmium tetroxide, use Chloramine-T for the *in situ* generation of **1***b* (2) and *N*-chloro-*N*-metallocarbamates for the *in situ* generation of **1***c* (3).



1*a* R = *tert*-Alkyl
b R = Ts
c R = Alkyl(arylalkyl)OCO

In earlier studies, we reported that reduced pyridyl nitrogen heterocycles offer potential for the development of new agents (4) with significant analgesic, hyperglycemic, antiinflammatory, and antimicrobial activities (5). It was therefore of interest to investigate the reaction of reduced pyridines with **1***c* as a method to effect the *cis* addition of hydroxyl (OH) and carbamate (*t*-BuOCONH) moieties across an olefenic bond. Heterocyclic *cis*-β-aminoalcohols are attractive medicinal intermediates for use (6) in the design of pharmacologically active nitrogen heterocycles. We now describe the vicinal oxyamination of *N*-substituted 1,2,3,6-tetrahydropyridines (**2**) and 1,2-dihydropyridines (**14**) using the powerful *N*-chloro-*N*-argento(mercury)carbamate-based oxyamination reagent **1***c*.

The oxyamination of 1-benzoyl-1,2,3,6-tetrahydropyridine (**2***a*) afforded a 1:1 mixture of the regioisomers *cis*-1-benzoyl-3-hydroxy-4-*tert*-butoxycarbonylaminopiperidine (**3***a*) and *cis*-1-benzoyl-3-*tert*-butoxycarbonylamino-4-hydroxypiperidine (**4***a*) in 18 and 63% yield, using Procedures A and B respectively (Scheme 1). Similar reactions employing 1-benzenesulfonyl- (**2***b*), 1-*tert*-butoxycarbonyl- (**2***c*), 1-methoxycarbonyl- (**2***d*), and 1-acetyl- (**2***e*) 1,2,3,6-tetrahydropyridines also yielded a mixture of regioisomers **3** and **4** (Table 1). We found that the *t*-BuOCONClNa + $AgNO_3$ (1:2) carbamate-based oxyamination system (Procedure B) was superior to the *t*-BuOCONClNa + $Hg(NO_3)_2$ + Et_4NOAc (1.5:0.75:1) system (Procedure A) since it provided higher yields of **3** and **4**, required shorter reaction times, and gave rise to a cleaner reaction mixture from which the products could be isolated more easily. The lower yield of **3** and **4** and the failure of **2***b* to react, using Procedure A, may be due to the competitive formation of an organomercury complex (**3***b*). *N*-Benzyl-1,2,3,6-tetrahydropyridine (**2***f*) did not react using either procedure. This is most likely due to some type of complexation with the free electron pair on nitrogen at the 1-position of **2***f*. On the other hand, oxyamination of 1-cyano-1,2,3,6-tetrahydropyridine (**11**) gave 1-aminocarbonyl-1,2,3,6-tetrahydropyridine (**13**) in 16.2 and 20% yield, using Procedures A and B respectively. The most likely intermediate in the oxidation of **11** to **13** is **12** since **11** does not react with osmium tetroxide. Furthermore, **11** did not react with *t*-BuOCOClNa and $AgNO_3$ (Procedure B) when OsO_4 was not present in the reaction mixture. The lone electron pair on the tetrahydropyridine nitrogen of **11** appears to play a significant role in the oxidation of **11** to **13** since the cyano group of acetonitrile[2] and 3-cyanopyridine (Procedure B) does not react under similar conditions.

The *tert*-butoxycarbonyl moiety of **3** and **4** was easily removed, affording the desired *cis*-β-aminoalcohols **5** and **6**. Treatment of **3***a* and **4***a* with 30% hydrogen bromide in acetic acid yielded **5** (76%) and **6** (81%) respectively. Reaction of **5** with thiophosgene and phosgene gave the respective bicyclic

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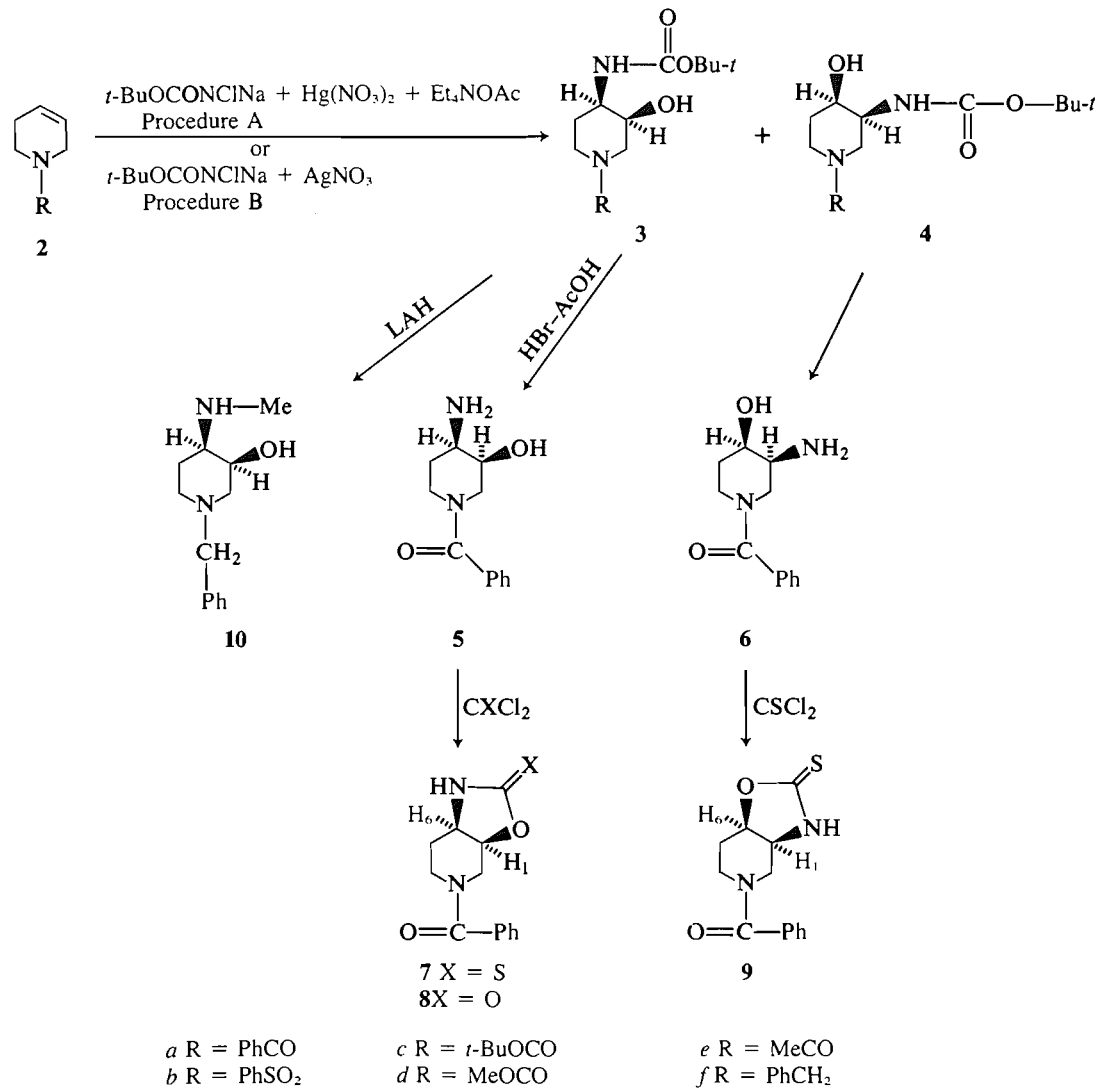
[2]Acetonitrile is employed as solvent in the oxyamination reactions using Procedures A and B.



2 3 4 10 5 6 9

SCHEME 1

products 3-benzoyl-9-oxa-3,7-diazabicyclo[4.3.0]nonan-8-thione (**7**, 12.7%) and the 8-one analogue **8** (34.7%). A similar thiophosgene cyclization of **6** gave rise to **9** (13.3%). The *tert*-butoxycarbonylamino group was readily converted to a methylamino group since reduction of **3***a* using lithium aluminum hydride afforded the *cis*-β-methylaminoalcohol (**10**) in quantitative yield.

The assignment of the regiochemistry and stereochemistry for the two regioisomers **3** and **4** formed in the vicinal oxyamination of **2** was based largely on ^{1}H nmr and mass spectral studies. Proton resonance assignments rest largely on decoupling experiments. The question whether the vicinal oxyamination reaction affords products **3** and **4** in which the hydroxyl and carbamate substituents are *cis* to each other was solved by measurement of the coupling constants or width at half-height (W_H) of the protons at C-3 and C-4 in their ^{1}H nmr spectra. The ^{1}H nmr spectra of **3** and **4***a*,*c*–*e* were poorly resolved at room temperature. The poor resolution observed, even at 200 MHz, may be due to strong hydrogen-bonding (4*i*) and/or to the presence of rotational conformers which differ in configuration at the carbonyl-to-nitrogen (amide) bond of the piperidine ring nitrogen (4*g*, 7). The spectra of **3***a* and **4***a* are well resolved at 120°C which should be sufficient to disrupt hydrogen bonding and/or induce coalescence of the rotamers. In contrast, the spectra of **3***b* and **4***b*, in which hindered internal rotation abut NSO_2Ph is not possible, exhibited well-resolved spectra at room temperature.

Extensive decoupling experiments were performed for **3***a*, **4***a*, **3***b*, and **4***b* to establish the stereochemistry of the substituents at C-3 and C-4, whereas selected double resonance studies were carried out for the remaining products **3** and **4**, as required, to assign the position of the hydroxyl and *tert*-butoxycarbonylamino substituents. The N*H*CO_2-*t*-Bu and OH groups exhibit absorptions in the 4.5 to 6.5 δ range. The hydroxyl group appears at higher field and displays a coupling constant of 4 to 5 Hz while the carbamoyl proton absorbs at lower field and generally appears as a broad multiplet or doublet (J = 7 to 8 Hz) (Table 1).

Irradiation at the resonance frequency for the NH proton at C-4 of **3***a* led to the identification of the signal due to the C-4H appearing at 3.6 δ. Specifically, irradiation at the frequency of the C-4H identified the signals due to the protons at C-3 and C-5. Irradiation of the signal at 3.72 δ due to the C-3 proton identified the methylene protons at C-2 which were assigned the axial and equatorial positions based on the magnitude of their coupling to the H-3 proton. The axial proton at C-2 appears as a doublet (J = 13 Hz) of doublets (J = 2 Hz) with the large coupling due to geminal coupling of the C-2 protons.

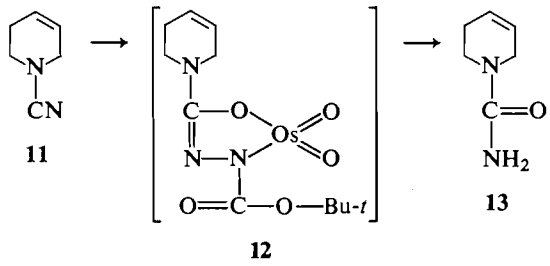
TABLE 1. Physical and spectral data of *cis*-1-substituted-3-hydroxy-4-*tert*-butoxycarbonylaminopiperidines (**3**) and *cis*-1-substituted-3-*tert*-butoxycarbonylamino-4-hydroxypiperidines (**4**)

Compound	R	% Yield, procedure A:B	Melting point, °C	Reaction time (h), procedure A:B	Ratio **3**/**4**	Nuclear magnetic resonance (Me_2SO-d_6), δ	Formula[a]
3*a*[b]	PhCO		169			7.4 (m, 5H, Ph), 5.84 (distorted d, J = 7 Hz, 1H, NH[d]), 4.57 (d, J = 4 Hz, 1H, OH), 3.9–4.07 (m, 1H, H_{6eq}), 3.76–3.9 (m, 1H, H_{2eq}), 3.68–3.76 (m, 1H, H_{3eq}), 3.52–3.68 (m, 1H, H_{4ax}), 3.17 (d, $J_{2ax-2eq}$ = 13 Hz of d, $J_{2ax-3eq}$ = 2 Hz, 1H, H_{2ax}), 2.98 (d, $J_{6ax-6eq}$ = 14 Hz of d, $J_{5ax-6eq}$ = 11 Hz of d, $J_{5eq-6ax}$ = 3.5 Hz, 1H, H_{6ax}), 1.48–1.86 (m, 2H, H_5), 1.42 (s, 9H, *t*-Bu)	$C_{17}H_{24}N_2O_4$
		18:63		72:24	1:1[c]		
4*a*[b]	PhCO		155			7.39 (m, 5H, Ph), 5.72–5.84 (d, J = 7 Hz, NH[d]), 4.58–4.66 (d, J = 4 Hz, 1H, OH), 3.84–3.96 (m, 1H, H_{4eq}), 3.62–3.77 (m, 1H, H_{2eq}), 3.28–3.62 (m, 3H, H_6, H_{3ax}), 3.22 (d, $J_{2ax-2eq}$ = 12 Hz of d, $J_{2ax-3ax}$ = 9 Hz, 1H, H_{2ax}), 1.61–1.72 (m, 2H, H_5), 1.36 (s, 9H, *t*-Bu)	$C_{17}H_{24}N_2O_4$
3*b*[c]	$PhSO_2$		194			7.59–7.8 (m, 5H, Ph), 6.4 (J = 7.2 Hz, 1H, NH[d]), 5.2 (d, J = 4.5 Hz, 1H, OH), 3.68–3.78 (m, 1H, H_{3eq}), 3.24–3.48 (m, 3H, H_{4ax}, H_{2eq}, H_{6eq}), 2.63 (d, $J_{2ax-2eq}$ = 12 Hz of d, $J_{2ax-3eq}$ = 2 Hz, 1H, H_{2ax}), 2.48 (d, $J_{6ax-6eq}$ = 12 Hz of d, $J_{5eq-6ax}$ = 3.5 Hz, 1H, H_{6ax}), 1.64–1.86 (m, 1H, H_{5ax}), 1.46–1.64 (m, 1H, H_{5eq}), 1.38 (s, 9H, *t*-Bu)	$C_{16}H_{24}N_2O_5S$
		0:50		72:96	1:2.5[c]		
4*b*[c]	$PhSO_2$		Viscous oil			7.5–7.9 (m, 5H, Ph), 6.35 (d, J = 8 Hz, 1H, NH[d]), 4.8 (d, J = 3.5 Hz, 1H, OH), 3.64–3.8 (m, 1H, H_{4eq}), 3.42–3.64 (m, 1H, H_{3ax}), 3.12–3.42 (m, 2H, H_{2eq}, H_{6eq}), 2.3–2.64 (m, 2H, H_{2ax}, H_{6ax}), 1.6–1.8 (m, 2H, H_5), 1.41 (s, 9H, *t*-Bu)	$C_{16}H_{24}N_2O_5S$
3*c*[f]	*t*-BuOCO		145			6.05 (m, 1H, NH[d]), 4.6 (d, J = 4.5 Hz, 1H, OH), 3.68–3.84 (m, 2H, H_{2eq}, H_{6eq}), 3.6–3.66 (m, 1H, H_{3eq}), 3.4–3.54 (m, 1H, H_{4ax}), 2.96 (d, $J_{2ax-3eq}$ = 12 Hz of d, $J_{2ax-3eq}$ = 1.5 Hz, 1H, H_{2ax}), 2.76–2.9 (m, 1H, H_{6ax}), 1.58–1.7 (m, 2H, H_5), 1.4 (s, 18H, *t*-Bu)	$C_{15}H_{28}N_2O_5$
		22:29		72:30	1:1[e]		
4*c*[f]	*t*-BuOCO		116			5.84–6.1 (m, 1H, NH[d]), 4.71 (d, J = 4.5 Hz, 1H, OH), 3.64–3.88 (m, 1H, H_{4eq}), 3.3–3.6 (m, 3H, H_{2eq}, H_{3ax}, H_{6eq}), 3.0–3.24 (m, 2H, H_{2ax}, H_{6ax}), 1.48–1.68 (m, 2H, H_5), 1.42 (s, 18H, *t*-Bu)	$C_{15}H_{28}N_2O_5$
3*d*[f]	MeOCO		139			5.98–6.26 (m, 1H, NH[d]), 4.69 (d, J = 4.5 Hz, 1H, OH), 3.72–3.9 (m, 2H, H_{2eq}, H_{6eq}), 3.6–3.72 (m, 1H, H_{3eq}), 3.58 (s, 3H, OMe), 3.4–3.56 (m, 1H, H_{4ax}), 3.0 (d, $J_{2ax-2eq}$ = 14 Hz, of d, $J_{2ax-3eq}$ = 2Hz, 1H, H_{2ax}), 2.79–2.94 (m, 1H, H_{6ax}), 1.42–1.76 (m, 2H, H_5), 1.4 (s, 9H, *t*-Bu)	$C_{12}H_{22}N_2O_5$
		18:54		72:30	1:1[g]		
4*d*[f]	MeOCO		Viscous oil			5.9–6.2 (m, 1H, NH[d]), 4.76 (d, J = 4 Hz, 1H, OH), 3.7–3.88 (m, 1H, H_{4eq}), 3.26–3.69 (m, 6H, H_{2eq}, H_{3ax}, H_{6eq}, OMe), 3.05–3.26 (m, 2H, H_{2ax}, H_{6ax}), 1.32–1.74 (m, 11H, H_5, *t*-Bu)	$C_{12}H_{22}N_2O_5$
3*e*[h]	MeCO		131			5.7–5.92 (m, 1H, NH[d]), 4.4–4.7 (m, 1H, OH), 2.54–4.32 (m, 6H, H_{2ax}, H_{2eq}, H_{3eq}, H_{4ax}, H_{6ax}, H_{6eq}), 1.98 (s, 3H, COMe), 1.3–1.76 (m, 11H, H_5, *t*-Bu)	$C_{12}H_{22}N_2O_4$
		10:46		72:30	1:1[i]		
4*e*[h]	MeCO		188			5.73–5.9 (m, 1H, NH[d]), 4.5–4.68 (m, 1H, OH), 3.76–3.9 (m, 1H, H_{4eq}), 2.84–3.6 (m, 5H, H_2, H_{3ax}, H_6), 1.96 (s, 3H, COMe), 1.49–1.74 (m, 2H, H_5), 1.4 (s, 9H, *t*-Bu)	$C_{12}H_{22}N_2O_4$

[a]All compounds gave analyses for C, H, and N within ± 0.4% of theoretical values.
[b]The nmr spectrum was determined at 120°C.
[c]Products **3** and **4** were separated by silica gel column chromatography.
[d]Exchange with deuterium oxide.
[e]The nmr spectrum was determined at 25°C.
[f]The nmr spectrum was determined at 60°C.
[g]On standing **3***d* cyrstallizes from the reaction mixture. Washing with hexane–ether removes the soluble **4***d*.
[h]The nmr spectrum was determined at 110°C.
[i]Separated by fractional recrystallization from benzene–hexane.

Irradiation at the resonance frequency of the C-3 proton resulted in the collapse of the small coupling (J = 2 Hz) for the C-2_{ax} proton. This small coupling constant of 2 Hz for J_{2ax-3} can only be explained if the proton at C-3 is equatorial and the C-3 hydroxyl substituent is axial. The width at half-height (W_H) for the resonance of the C-4H is large compared to that for the C-3H indicating that the C-4H must be axial (8). These assignments are consistent with the observation that irradiation of the frequency due to the C-4NH results in simplification of the C-4H to a multiplet exhibiting coupling constants of 10.5, 4, and 3 Hz. The large coupling constant of 10.5 Hz is possible if the C-4H is axial, which would be consistent with the large $J_{4ax-5ax}$ and smaller $J_{4ax-5eq}$ and $J_{4ax-3eq}$ coupling constants observed. Thus, the C-4 *tert*-butoxycarbonylamino group must be equatorial with the C-3 and C-4 substituents in a *cis*-configuration.

The ^{1}H nmr spectrum of **4***a* exhibited a doublet (J = 12 Hz) of doublets (J = 9 Hz) for the C-2_{ax} proton with the large 12 Hz coupling due to geminal coupling of the C-2 methylene protons. The 9 Hz coupling is characteristic of a $J_{2ax-3ax}$ interaction indicating that the C-3H must be axial and the carbamate substituent is equatorial. The width at half-height (W_H = 10.5



SCHEME 2

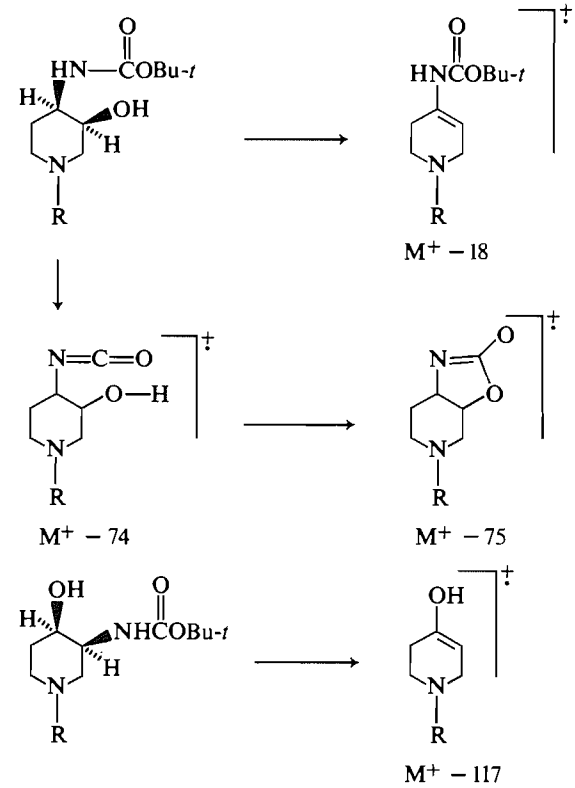
Hz) for the resonance due to the C-4H suggests it is equatorial (8). Irradiation of the resonance due to the C-4 hydroxyl proton resulted in the simplification of the absorption for the C-4H to a multiplet showing three nearly equivalent coupling constants of about 4 Hz at 3.84 to 3.96 δ. These observed couplings also indicate the C-4H is equatorial, in which case one would expect $J_{4eq-5ax}$, $J_{4eq-5eq}$, and $J_{3ax-4eq}$ coupling constants of about 4 Hz, thereby establishing the configuration of the C-4 hydroxyl substituent as axial.

The results of these ^{1}H nmr studies indicate that the vicinal oxyamination reaction of *N*-substituted -1,2,3,6-tetrahydropyridines (**2**) affords *cis*-aminoalcohol derivatives **3** and **4** in which the *tert*-butoxycarbonylamino and hydroxyl substituents assume the equatorial and axial orientations respectively, irrespective of the substituent position.

The regioisomers **3** and **4** are readily distinguished using mass spectrometry. For example, the 3-hydroxy isomers **3** exhibit a low abundance $M^+ - 18$ peak due to the loss of water, a very prominent $M^+ - 75$ ion which corresponds to the bicyclic structure illustrated in Scheme 3, and usually a less abundant $M^+ - 117$ ion due to loss of a *t*-BuOCONH$_2$ fragment. On the other hand, the 4-hydroxy isomers **4** do not exhibit a $M^+ - 18$ ion but they do display a very prominent $M^+ - 117$ ion relative to $M^+ - 74$ and $M^+ - 75$ peaks. The difference in the fragmentation pathways for **3** and **4** suggests 1,3-interactions are important. The regiochemistry of the isomers **3** and **4** can therefore be readily assigned using mass spectrometry (see Table 2).

The oxyamination reaction of 1-substituted 1,2-dihydropyridines was also examined. Thus, reaction of 1-methoxycarbonyl-1,2-dihydropyridine (**14**) with *N*-chloro-*N*-sodio-*tert*-butylcarbamate and silver nitrate afforded a mixture of the two regioisomers **15** and **16** (50%) in a ratio of 1:1. A similar reaction employing mercuric nitrate and tetraethylammonium acetate (Procedure A) in place of silver nitrate (Procedure B) gave a very complex reaction mixture from which **15** and **16** could not be readily isolated. The oxyamination reaction of 1-methyl-1,2-dihydropyridine using Procedures A and B also afforded a complex mixture of products, whereas no reaction occurred with 1-methanesulfonyl-1,2-dihydropyridine and 1-ethoxycarbonyl-1,4-dihydropyridine.

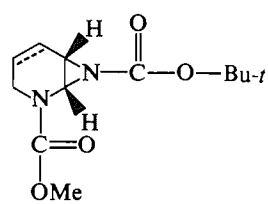
The identification of the two regioisomers **15** and **16** was based primarily on ^{1}H nmr and ir spectral data. The ^{1}H nmr spectra of **15** and **16** clearly indicated that addition occurred at the 5,6- rather than the 3,4-olefenic bond of **14**. The small $J_{2,3}$ coupling constant of 3 Hz suggests the C-2 hydroxyl and C-3 *tert*-butoxycarbonylamino substituents of **15** are in the *cis*-configuration which is consistent with the known mechanism of this reaction (1–3). The dihedral angle between a C-3 pseudoequatorial or pseudoaxial hydrogen and the C-4H is very similar, thereby precluding assignment of the stereochemistry



SCHEME 3

of the C-3H based on the magnitude of the coupling constant for $J_{3,4}$. The ^{1}H nmr spectrum of **16** was very complex, even at 100°C, due to strong hydrogen-bonding effects and/or the presence of two rotational conformers which differ in configuration at the carbonyl-to-nitrogen (carbamate) bond of the tetrahydropyridine ring nitrogen (4*g*, 7).

The 4,5-olefenic bond of the 1,2,3,6-tetrahydropyridines **15** and **16** was hydrogenated using palladium on charcoal and hydrogen gas. It was expected the stereochemistry of the C-3 substituents could then be assigned from the magnitude of the $J_{3,4}$ values. Reduction of **15** in this way afforded **17** (19.5%), **18** (9.7%), **19** (24.5%), and **20** (29.9%). The mechanism for the formation of **17**–**20** is not known. One plausible explanation is attack by methoxyl (**17** and **18**) and hydroxyl (**19** and **20**) species upon an aziridine intermediate such as **21** (6). It is not known why the hydroxy species is incorporated solely into



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the C-3 position and the methoxyl species only into the C-2 position. The hydroxycarbamates **15** and **16** are stable in the presence of 10% palladium on charcoal in methanol at 25°C. A similar reduction of **16** gave **17** (14.1%), **18** (14.1%), **19** (40.6%), and **20** (4%).

The stereochemistry of the C-2 and C-3 substituents in which the C-3H is axial can be assigned the *cis*-configuration based on the small $J_{2,3}$ values for **17** and **19**, which are 2.8 and 5 Hz

TABLE 2. Some mass spectral data for **3** and **4**

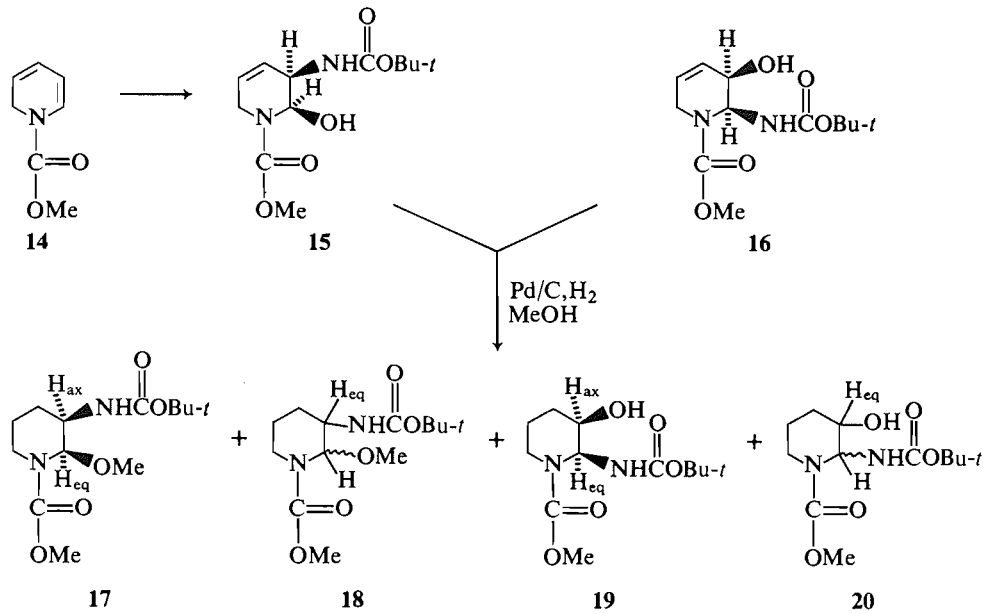
Compound	m/e Measured[a]	m/e Calcd.	Relative intensity	Fragment
3*a*	320.1730	320.1763	0.27	$C_{17}H_{24}N_2O_4$ (M^+)
	302.1625	302.1630	5.9	$C_{17}H_{22}N_2O_3$ ($M^+ - H_2O$)
	247.1068	247.1083	12.5	$C_{13}H_{15}N_2O_3$ ($M^+ - t\text{-}C_4H_9O$)
	246.0999	246.1005	28.2	$C_{13}H_{14}N_2O_3$ ($M^+ - t\text{-}C_4H_9OH$)
	245.0926	245.0927	27.1	$C_{13}H_{13}N_2O_3$ ($M^+ - C_4H_{11}O$)
	203.944	203.9446	6.9	$C_{12}H_{13}NO_2$ ($M^+ - t\text{-}C_4H_9OCONH_2$)
4*a*	321[b]	321	41.0	$C_{17}H_{25}N_2O_4$ ($M + 1$)$^+$
	247.1080	247.1083	7.19	$C_{13}H_{15}N_2O_3$ ($M^+ - t\text{-}C_4H_9O$)
	246.0987	246.1005	1.8	$C_{13}H_{14}N_2O_3$ ($M^+ - t\text{-}C_4H_9OH$)
	245.0923	245.0927	4.1	$C_{13}H_{13}N_2O_3$ ($M^+ - C_4H_{11}O$)
	203.0941	203.0946	100.0	$C_{12}H_{13}NO_2$ ($M^+ - t\text{-}C_4H_9OCONH_2$)
3*b*	357[b]	357	26.4	$C_{16}H_{25}N_2O_5S$ ($M + 1$)$^+$
	283.0726	283.0753	12.5	$C_{12}H_{15}N_2O_4S$ ($M^+ - t\text{-}C_4H_9O$)
	282.0649	282.0674	9.4	$C_{12}H_{14}N_2O_4S$ ($M^+ - t\text{-}C_4H_9OH$)
	281.0596	281.0596	33.1	$C_{12}H_{13}N_2O_4S$ ($M^+ - C_4H_{11}O$)
4*b*	357[b]	357	30.4	$C_{16}H_{24}N_2O_5S$ ($M + 1$)$^+$
	283.0738	283.0753	4.8	$C_{12}H_{15}N_2O_4S$ ($M^+ - t\text{-}C_4H_9O$)
	281.0590	281.0596	8.3	$C_{12}H_{13}N_2O_4S$ ($M^+ - C_4H_{11}O$)
	239.0630	239.0616	32.7	$C_{11}H_{13}NO_3S$ ($M^+ - t\text{-}C_4H_9OCONH_2$)
3*c*	317*b*	317	18.3	$C_{15}H_{29}N_2O_5$ ($M + 1$)$^+$
	219.1894	219.1893	0.3	$C_{15}H_{26}N_2O_4$ ($M^+ - H_2O$)
	242.1243	242.1267	3.0	$C_{11}H_{18}N_2O_4$ ($M^+ - C_4H_9OH$)
	241.1190	241.1192	11.9	$C_{11}H_{17}N_2O_4$ ($M^+ - C_4H_{11}O$)
4*c*	316.1990	316.1999	0.5	$C_{15}H_{28}N_2O_5$ (M^+)
	243.1342	243.1345	0.7	$C_{11}H_{19}N_2O_4$ ($M^+ - C_4H_9O$)
	199.1209	199.1209	17.7	$C_{10}H_{17}NO_3$ ($M^+ - C_4H_9OCONH_2$)
3*d*	275[b]	275	100.0	$C_{12}H_{23}N_2O_5$ ($M + 1$)$^+$
	256.1408	256.1423	0.4	$C_{12}H_{20}N_2O_4$ ($M^+ - 18$)
	200.0791	200.0797	58.2	$C_8H_{12}N_2O_4$ ($M^+ - C_4H_9O$)
	199.0718	199.0718	66.6	$C_8H_{11}N_2O_4$ ($M^+ - C_4H_9OH$)
	157.0735	157.0739	12.6	$C_7H_{11}NO_3$ ($M^+ - C_4H_9OCONH_2$)
4*d*	274.1525	274.1529	0.8	$C_{12}H_{22}N_2O_5$ (M^+)
	201.0861	201.0875	10.7	$C_8H_{13}N_2O_4$ ($M^+ - C_4H_9O$)
	200.0788	200.0797	20.6	$C_8H_{12}N_2O_4$ ($M^+ - C_4H_9OH$)
	199.0717	199.0718	32.7	$C_8H_{11}N_2O_4$ ($M^+ - C_4H_{11}O$)
	157.0743	157.0739	99.8	$C_7H_{11}NO_3$ ($M^+ - C_4H_9OCONH_2$)
3*e*	259.[b]	259	83.5	$C_{12}H_{23}N_2O_4$ ($M + 1$)$^+$
	240.1469	240.1474	2.1	$C_{12}H_{20}N_2O_3$ ($M^+ - H_2O$)
	185.0916	185.0926	26.8	$C_8H_{13}N_2O_3$ ($M^+ - C_4H_9O$)
	184.0845	184.0847	64.2	$C_8H_{12}N_2O_3$ ($M^+ - C_4H_9OH$)
	183.0769	183.0769	37.1	$C_8H_{11}N_2O_3$ ($M^+ - C_4H_{11}O$)
	141.0763	141.0790	67.0	$C_7H_{11}NO_2$ ($M^+ - C_4H_9OCONH_2$)
4*e*	258.1577	258.1580	0.4	$C_{12}H_{22}N_2O_4$ (M^+)
	185.0924	185.0926	6.8	$C_8H_{13}N_2O_3$ ($M^+ - C_4H_9O$)
	184.0839	184.0847	2.2	$C_8H_{12}N_2O_3$ ($M^+ - C_4H_9OH$)
	183.0768	183.0769	3.4	$C_8H_{11}N_2O_3$ ($M^+ - C_4H_{11}O$)
	141.0765	141.0790	100	$C_7H_{11}NO_2$ ($M^+ - C_4H_9OCONH_2$)

[a]High resolution electron impact (70 ev) spectra unless otherwise indicated.
[b]Chemical ionization (NH_3) mass spectra.

respectively. This indicates that the C-2H of **17** and **19** must be equatorial and the respective methoxy and *tert*-butoxycarbonylamino substituents would therefore be axial. On the other hand, when the C-3H is equatorial, as for **18** and **20**, it is not possible to assign the stereochemistry of the C-2 substituents since $J_{2,3ae}$ is similar to $J_{2,3ee}$. The chemical shift values (δ) observed for the H_2 protons of **17** (5.24), **18** (5.14), **19** (5.7), and **20** (5.61) would suggest that the C-2H of **18** and **20** are also equatorial. This assignment would be consistent with the fact that a 2-methyl or 2-(3-pyridyl) substituent on a 1-benzoylpiperidine ring system exists in the axial orientation (10,11).

Experimental

Melting points were determined with a Büchi capillary apparatus and are uncorrected. Infrared spectra (potassium bromide unless otherwise noted) were taken on a Unicam SP 1000 spectrometer. Nuclear magnetic resonance spectra were determined for solutions in deuterochloroform or deuterodimethylsulfoxide with a Bruker WH-200, WH-400, or Varian EM 360A spectrometer. Double resonance studies were used to confirm assignments. Mass spectra were measured on a AEI MS-50 mass spectrometer. Preparative high pressure liquid chromatography was performed using a Water's Prep LC/System 500A using Prep Pak-500 Silica cartridges. The *N*-substituted -1,2,3,6-tetrahydropyridines **2** were prepared using standard procedures for acylation or alkylation of 1,2,3,6-tetrahydropyridine. 1-Methoxy-



SCHEME 4

carbonyl-1,2-dihydropyridine was prepared according to the procedure of Fowler (9).

cis-*1-Substituted-3-hydroxy-4*-tert-*butoxycarbonylaminopiperidines (3) and* cis-*1-substituted-3*-tert-*butoxycarbonylamino-4-hydroxypiperidines (4)*

Procedure A

In a one-necked flask (250 mL), a mixture of *N*-chloro-*N*-sodio-*tert*-butylcarbamate (3*b*) (7.5 mmol) and mercuric nitrate (3.75 mmol) in acetonitrile (100 mL) was stirred for 15 min. To this suspension water (22 mmol), *N*-substituted-1,2,3,6-tetrahydropyridine (**2**, 5 mmol), and a solution of osmium tetroxide (0.05 mmol) in *tert*-butyl alcohol (2*b*) was added. The mixture was stirred at 25°C for 5–10 min after which tetraethylammonium acetate (5 mmol) was added. The reaction was allowed to proceed until the 1,2,3,6-tetrahydropyridine **2** was consumed (see Table 1 for times). When the reaction was completed, a saturated solution of sodium chloride was added to precipitate the remaining metallic ion.[3] The solution was filtered and extracted with chloroform (3 × 50 mL). The combined organic extracts were washed with a saturated solution of sodium chloride, dried (Na_2SO_4), and the solvent removed *in vacuo* to yield the crude hydroxycarbamates **3** and **4**. Regioisomers **3** and **4** were separated by silica gel column chromatography or fractional crystallization as indicated in Table 1.

Procedure B

A mixture of *N*-chloro-*N*-sodio-*tert*-butylcarbamate (3*b*) (7.5 mmol) and silver nitrate (15 mmol) in acetonitrile (100 mL) was allowed to stir for 15 min at 25°C. Water (22 mmol), *N*-substituted 1,2,3,6-tetrahydropyridine (**2**, 5 mmol), and a solution of osmium tetroxide (0.05 mmol) in *tert*-butyl alcohol (2*b*) were added to this suspension. The reaction was allowed to proceed with stirring at 25°C until all the olefin was consumed as indicated by tlc. The isolation procedure was identical to that of Procedure A.

cis-*1-Benzoyl-3-hydroxy-4-aminopiperidine (5)*

A solution of 30% HBr in acetic acid (5 mL) was added to a solution of **3***a* (1.6 g, 5 mmol) in methanol (10 mL) at 0°C with stirring. The reaction was allowed to proceed at 25°C for an additional 20 min. The solvent was removed *in vacuo* and the residue basified to pH 10, using aqueous sodium hydroxide prior to extraction with ether (20 mL) and then chloroform (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent removed *in vacuo* to yield **5** as an oil which solidified on standing at room temperature after several days, yield 0.84 g (76%); mp 130–131°C; ir: 3380, 3300, 3100–3180 (OH and NH_2), 1620–1635 (CO); nmr ($CDCl_3$) δ: 7.48 (m, 5H, Ph), 2.8–5.0 (m, 6H, H_2, H_6, H_3, H_4), 2.28 (br s, 3H, NH_2, OH, exchange with deuterium oxide), 1.4–2.0 (m, 2H, H_5). *Exact Mass* calcd. for $C_{12}H_{16}N_2O_2$: 220.1212; found (high-resolution ms): 220.1210.

cis-*1-Benzoyl-3-amino-4-hydroxypiperidine (6)*

Hydrolysis of **4***a*, using the procedure outlined for the preparation of **5**, afforded **6**: yield (81%); mp 120–122°C; ir: 3360, 3300, 3140–3220 (OH, NH_2), 1635 (CO); nmr ($CDCl_3$) δ: 7.42 (m, 5H, Ph), 2.76–4.24 (m, 6H, H_2, H_6, H_3, H_4), 2.15 (br s, 3H, NH_2, OH, exchanges with deuterium oxide), 1.6–2.0 (m, 2H, H_5). *Exact Mass* calcd. for $C_{12}H_{16}N_2O_2$: 220.1212; found (high resolution ms): 220.1210.

3-Benzoyl-9-oxa-3,7-diazabicyclo[4.3.0]nonan-8-thione (7)

A solution of thiophosgene (0.228 mL, 3 mmol) in dry tetrahydrofuran (5 mL) was added dropwise to a solution of **5** (0.66 g, 3 mmol) and triethylamine (0.9 mL, 6 mmol) in dry tetrahydrofuran (30 mL) at −65°C with stirring over a 20 min period. The reaction was allowed to proceed for 30 min prior to warming to 25°C. Triethylamine hydrochloride was removed by filtration, the filtrate was concentrated *in vacuo*, and the residue was washed with water. Chromatography on a 0.5 cm × 9.0 cm silica gel column with chloroform as eluant afforded **7**, yield (0.1 g, 12.7%); mp 203°C; ir: 3360 (NH), 1630 (CO); nmr ($CDCl_3$ + DMSO-d_6) δ: 7.46 (m, 5H, Ph), 4.82–5.38 (m, 1H, H_1), 4.2–4.62 (m, 1H, H_6), 3.32–4.08 (m, 4H, H_2, H_4), 3.1 (br s, 1H, NH, exchanges with deuterium oxide), 1.76–2.32 (m, 2H, H_5). *Exact Mass* calcd. for $C_{13}H_{14}N_2O_2{}^{32}S$: 262.0776; found (high resolution ms): 262.0773.

3-Benzoyl-9-oxa-3,7-diazabicyclo[4.3.0]nonan-8-one (8)

Reaction of **5** with phosgene using the procedure outlined for the preparation of **7**, afforded **8**, yield (34.7%); mp 145–146°C; ir: 3280 (NH), 1750–1760 (OCO), 1625 (COPh); nmr ($CDCl_3$) δ: 7.4 (m, 5H, Ph), 6.85 (s, 1H, NH, exchanges with deuterium oxide), 4.55–5.05 (m, 1H, H_1), 3.24–4.38 (m, 5H, H_6, H_2, H_4), 1.62–2.18 (m, 2H, H_5). *Exact Mass* calcd. for $C_{13}H_{14}N_2O_3$: 246.1005; found (high resolution ms): 246.1004.

3-Benzoyl-7-oxa-3,9-diazabicyclo[4.3.0]nonan-8-thione (9)

Reaction of **6** with thiophosgene, using the procedure outlined for

[3]The sodium bisulfite treatment to reduce and remove the small amount of osmium that may be bound to the organic products was omitted since this resulted in a more complex reaction mixture.

the preparation of **7**, gave **9**, yield (13.3%); mp 210–211°C; ir: 3360 (NH), 1630 (COPh); nmr ($CDCl_3$ + DMSO-d_6) δ: 7.45 (m, 5H, Ph), 4.97–5.38 (m, 1H, H_6), 4.0–4.54 (m, 1H, H_1), 3.2–3.9 (m, 4H, H_2, H_4), 2.84 (br s, 1H, NH, exchanges with deuterium oxide), 1.9–2.4 (m, 2H, H_5). *Exact Mass* calcd. for $C_{13}H_{14}N_2O_2{}^{32}S$: 262.0776; found (high resolution ms): 262.0775.

cis-*1-Benzoyl-3-hydroxy-4-methylaminopiperidine (10)*

Lithium aluminum hydride (0.3 g, 8 mmol) was added slowly to a solution of **3***a* (0.64 g, 2 mmol) in dry tetrahydrofuran (25 mL) with stirring at 0°C. The reaction mixture was allowed to reflux for 24 h. After cooling, a solution of 10% aqueous sodium hydroxide was added to destroy the lithium aluminum hydride, the mixture was filtered, and the solvent was removed *in vacuo* to give a viscous oil. Purification of the reaction mixture by elution from a 1 cm × 20 cm silica gel column using chloroform–methanol (9:1 v/v) as eluant gave **10** as a viscous oil, yield (0.32 g, 72.7%); nmr ($CDCl_3$) δ: 7.37 (m, 5H, Ph), 3.78–4.1 (m, 1H, H_3), 3.56 (s, 2H, CH_2Ph), 2.0–3.24 (m, 7H, H_2, H_4, H_6, OH, NH), 1.52–2.0 (m, 2H, H_5). *Exact Mass* calcd. for $C_{13}H_{20}N_2O$: 220.1576; found (high resolution ms): 220.1574.

1-Aminocarbonyl-1,2,3,6-tetrahydropyridine (13)

The oxyamination of **11** (5 mmol) as outlined in Procedure A afforded a solid which was purified by elution from a silica gel column using a gradient of hexane–chloroform to afford **13**, yield (16.2%); mp 121–122°C; ir: 3400, 3220 (NH_2), 1660 (CO); nmr ($CDCl_3$) δ: 5.83 (m, 2H, H_4, H_5), 4.7 (br s, 2H, NH_2, exchanges with deuterium oxide), 3.95 (m, 2H, H_6), 3.56 (t, $J_{2,3}$ = 6 Hz, 2H, H_2), 2.25 (m, 2H, H_5). *Exact Mass* calcd. for $C_6H_{10}N_2O$: 126.0794; found (high resolution ms): 126.0795. This product was identical (ir, nmr) to an authentic sample prepared from the reaction of 1-chlorocarbonyl-1,2,3,6-tetrahydropyridine with ammonia.

Oxyamination of **11** using Procedure B afforded **13** (20%).

cis-*1-Methoxycarbonyl-2-hydroxy-3*-tert-*butoxycarbonylamino-1,2,3,6-tetrahydropyridine (15) and* cis-*1-methoxycarbonyl-2*-tert-*butoxycarbonylamino-3-hydroxy-1,2,3,6-tetrahydropyridine (16)*

A mixture of *N*-chloro-*N*-sodio-*tert*-butylcarbamate (7.8 g, 45 mmol) and silver nitrate (15 g, 90 mmol) in acetonitrile (200 mL) was allowed to stir for 15 min at 25°C. Water (132 mmol), 1-methoxycarbonyl-1,2-dihydropyridine (9) (4.17 g, 30 mmol), and a solution of osmium tetroxide (0.3 mmol) in *tert*-butylalcohol was added to this suspension. The reaction was allowed to proceed with stirring at 25°C for 24 h. The mixture of **15** and **16** obtained, following the isolation procedure described in Procedure A, was separated by preparative hplc using hexane–ether (1:4 v/v) at a flow rate of 250 mL/min. Removal of the solvent from the 1000–1500 mL fractions gave **15** (1.85 g, 22.7%), mp 119–120°C; ir: 3340–3360 (OH, NH), 1720 (NHCO), 1680 (NCO_2Me); nmr (Me_2SO-d_6, 50°C) δ: 6.26–6.44 (m, 1H, NH), 5.84 (d, J = 5 Hz, 1H, OH), 5.68–5.8 (d, $J_{4,5}$ = 10 Hz of d, $J_{3,4}$ = 3 Hz of d, $J_{4,6ax}$ = 3 Hz of d, $J_{4,6eq}$ = 3 Hz, 1H, H_4), 5.6–5.68 (m, $J_{2,3}$ = 3 Hz, 1H, H_2), 5.36–5.48 (d, $J_{4,5}$ = 10 Hz of d, $J_{5,6ax}$ = 1.5 Hz of d, $J_{5,6eq}$ = 1.5 Hz, 1H, H_5), 4.03–4.16 (m, 1H, H_3), 3.86–4.03 (d, J_{gem} = 18 Hz of d, $J_{4,6eq}$ = 3 Hz of d, $J_{3,6eq}$ = 3 Hz, 1H, H_{6eq}), 3.66 (s, 3H, CO_2Me), 3.44–3.68 (m, 1H, H_{6ax}), 1.4 (s, 9H, *t*-Bu). *Exact Mass* calcd. for $C_8H_{11}N_2O_5$ (M^+ − 57): 215.0668; found (high resolution ms): 215.0655; CI (NH_3) for $C_{12}H_{20}N_2O_5$: M + 1, 273 and 2 M + 1, 545. Collection of the 1500–1750 mL fraction yielded a mixture of **15** and **16** (0.4 g, 4.9%), whereas the 1750–2750 mL eluate afforded **16** (1.82 g, 22.4%) as a viscous oil; ir: 3420–3460 (OH), 3350–3380 (NH); nmr (Me_2SO-d_6, 100°C) δ: 5.4–6.3 (m, 4H, NH, H_2, H_4, H_5), 5.04 (d, J = 6 Hz, 0.5H, H-bonded OH), 4.24 (m, 0.5H, OH), 3.34–4.08 (6H, H_3, H_6, OMe), 1.4 (s, 9H, *t*-Bu). *Exact Mass* calcd. for $C_{12}H_{20}N_2O_5$: 272.1372; found (high resolution ms): 272.1363.

cis-*1-Methoxycarbonyl-2-methoxy-3*-tert-*butoxycarbonylaminopiperidine (17)*, *1-methoxycarbonyl-2-methoxy-3*-tert-*butoxycarbonylaminopiperidine (18)*, cis-*1-methoxycarbonyl-2*-tert-*butoxycarbonylamino-3-hydroxypiperidine (19)*, *and 1-methoxycarbonyl-2*-tert-*butoxycarbonylamino-3-hydroxypiperidine (20)*

Hydrogenation of **15** (0.6 g, 2.2 mmol) in 200 mL methanol using 100 mg 10% palladium on charcoal and hydrogen gas at 25 psi for 7 h at 25°C, followed by filtration and removal of the solvent *in vacuo*, afforded a mixture of **17–20**. Purification on a 1 cm × 30 cm silica gel column using chloroform as eluant gave initially a mixture of **17** and **18** (0.185 g, 29.2%) in a ratio of 2:1, calculated from the integrals for the C-2H of **17** and **18** at 5.24 and 5.14 δ respectively. Fractional crystallization of this mixture from hexane–ether (1:9 v/v) gave pure samples of **17** and **18** which showed the following spectral data.

Compound **17**, ir: 3360 (NH), 1720 (NHCO), 1695–1705 (NCO_2Me); nmr (Me_2SO-d_6, 70°C) δ: 6.18–6.38 (m, 1H, NH), 5.24 (d, $J_{2eq-3ax}$ = 2.8 Hz, 1H, H_{2eq}), 3.66–3.82 (d, $J_{6eq-6ax}$ = 12.5 Hz of d, $J_{2,3}$ = 3 Hz, 1H, H_{6eq}), 3.66 (s, 3H, CO_2Me), 3.26–3.48 (m, 1H, H_{3ax}), 3.2 (s, 3H, OMe), 2.66–2.90 (m, 1H, H_{6ax}), 1.34–1.86 (m, 13H, H_4, H_5, *t*-Bu); *Exact Mass* calcd. for $C_{13}H_{24}N_2O_5$: 288.1685; found (high resolution ms): 288.1679.

Compound **18**, mp 110–111°C; ir: 3340 (NH), 1720 (NHCO), 1680–1690 (NCO_2Me); nmr δ: 6.70–6.96 (br s, 1H, NH), 5.14 (d, $J_{2,3}$ = 1.5 Hz, 1H, H_2), 3.70–3.82 (d, $J_{6eq-6ax}$ = 12.5 Hz of d, $J_{5,6}$ = 3 Hz, 1H, H_{6eq}), 3.50–3.67 (m, 1H, H_{3eq}), 3.63 (s, 3H, CO_2Me), 3.18 (s, 3H, OMe), 2.8 (ddd, 1H, H_{6ax}), 1.64–1.88 (m, 2H, H_4), 1.2–1.5 (m, 11H, H_5, *t*-Bu). *Exact Mass* calcd. for $C_{13}H_{24}N_2O_5$: 288.1685; found (high resolution ms): 288.1685.

Further elution with chloroform gave **20** (0.18 g, 29.9%), mp 160°C; ir: 3360, 3460 (OH, NH), 1715 (NHCO), 1685–1700 (NCO_2Me); nmr (Me_2SO-d_6, 50°C) δ: 7.24 (d, J = 7.5 Hz, 1H, NH), 6.8–6.9 (br s, 1H, OH), 5.52–5.7 (m, 1H, H_2), 3.78 (m, 4H, H_{6eq}, CO_2Me), 3.38–3.48 (m, 1H, H_{3eq}), 2.91 (sextet, 1H, H_{6ax}), 1.16–2.08 (m, 13H, H_4, H_5, *t*-Bu). *Exact Mass* calcd. for $C_{12}H_{20}N_2O_4$ (M^+ − 18): 256.1423; found (high resolution ms): 256.1427; CI (NH_3): M + 1, 275.

Continued elution with chloroform gave **19** (0.148 g, 24.5%), mp 161–163°C; ir: 3460 (OH), 3340 (NH), 1720 (NHCO), 1685–1700 (NCO_2Me); nmr (Me_2SO-d_6, 50°C) δ: 6.74 (d, J = 8 Hz, 1H, NH), 5.7 (d, $J_{2,NH}$ = 8 Hz of d, $J_{2eq,3ax}$ = 5 Hz, 1H, H_{2eq}), 4.86 (d, J = 5 Hz, 1H, OH), 3.64–3.7 (m, 1H, H_{6eq}), 3.6 (s, 3H, CO_2Me), 3.48 (sextet, $J_{3,4ax}$ = 10 Hz, $J_{3,4eq}$ = 5 Hz, $J_{2,3}$ = 5 Hz, $J_{3,OH}$ = 5 Hz, 1H, H_{3ax}), 2.81 (ddd, 1H, H_{6ax}), 1.2–1.8 (m, 13H, H_4, H_5, *t*-Bu). *Exact Mass* calcd. for $C_{12}H_{22}N_2O_5$: 274.1529; found (high resolution ms): 274.1526.

Hydrogenation of **16** (0.5 g, 1.84 mmol), as outlined for **15** above, afforded a mixture of **17** and **18** (0.15 g, 28.3%) in a ratio of 1:1, **20** (0.021 g, 4%), and **19** (0.215 g, 40.6%).

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