Pergamon

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Tetrahedron: *Asymmetry* 14 (2003) 469–479

TETRAHEDRON: *ASYMMETRY*

Nucleophilic addition to chiral pyridinium salts: stereoselective synthesis of (−)-N_a-methylervitsine

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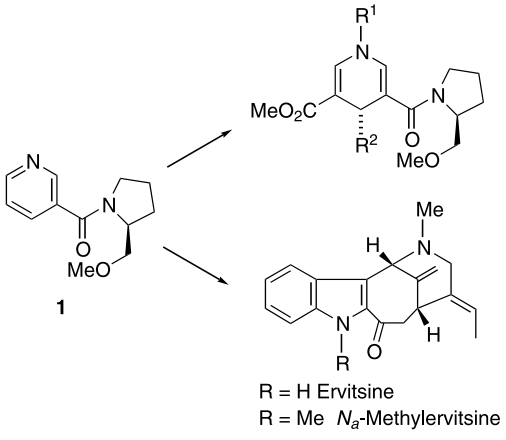
Received 14 November 2002; accepted 16 December 2002

Abstract—Chiral non-racemic 4-substituted 3,5-diacyl-1,4-dihydropyridines **8** are prepared by the regio- and diastereoselective addition of organocopper reagents to chiral pyridinium salt **2**, followed by acylation with trichloroacetic anhydride and subsequent haloform reaction. Additionally, (−)-N_a-methylervitsine is synthesized by reaction of the enolate derived from 2-acetylindole **9** with pyridinium salt **2**, followed by electrophile ($Me_2N^+{=}CH_2I^-$)-induced cyclization and subsequent elaboration of the 16-methylene and (20*E*)-ethylidene substituents.

1. Introduction

Dihydropyridines have attracted considerable attention in medicinal and bioorganic chemistry as potential calcium channel blockers[1] and NADH models,[2] respectively. Due to their high reactivity, dihydropyridines also constitute versatile intermediates in the synthesis of natural products.[3] These dihydropyridines are generally prepared by addition of a broad variety of nucleophiles to pyridinium salts.[4] Over the past years, we have studied the reaction of indole-containing enolates with 3-acyl-*N*-alkylpyridinium salts, followed by suitable manipulation of the resultant highly functionalized 1,4-dihydropyridine adducts, as a general method for the synthesis of indole alkaloids belonging to different structural types.[5,6]

We envisaged the use of chiral non-racemic nucleophiles or chiral non-racemic pyridinium salts as a logical extension of the above methodology for the synthesis of enantiomerically pure alkaloids. In this context, we have recently reported the synthesis of the indole alkaloid (−)-vinoxine[7] and, by a closely related strategy, the pyrroloquinoline alkaloid (+)-camptothecin[8] starting from a chiral nucleophile.[9] Concerning the use of chiral pyridinium substrates, there are several examples in the literature of stereoselective syntheses of chiral 1,4-dihydropyridines[10] by regio- and diastereoselective addition of *C*-nucleophiles (mainly organometallic reagents) to pyridinium salts bearing chiral auxiliaries at the 3-position of the pyridine ring.[11] However, the application of these auxiliary-induced stereoselective processes in the alkaloid field is far less common.[11e,12] The work reported herein deals with our work on the nucleophilic addition to *N*-alkyl derivatives of (*S*)-*O*-methylprolinol nicotinamide (**1**, Scheme 1), the most significant results being the synthesis of chiral 4-substituted 3,5-diacyl-1,4-dihydropyridines and a stereoselective synthetic entry to the ervitsine skeleton.[13]



Scheme 1.

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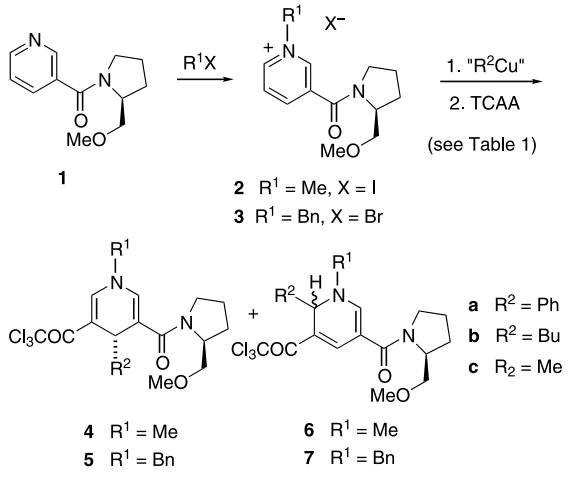
PII: S0957-4166(02)00866-2

2. Results and discussion

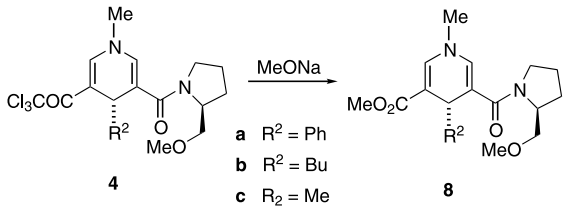
2.1. Synthesis of chiral 4-substituted 3,5-diacyl-1,4-dihydropyridines

Organocopper reagents are known to undergo smooth regioselective addition to the 4-position of pyridinium salts. Although the main work in this area makes use of *N*-acyl derivatives,[14] we have recently shown that these organometallic reagents also react readily with the less electrophilic 3-acyl-*N*-alkylpyridinium salts. Moreover, trapping the intermediate *N*-alkyl-1,4-dihydropyridine with an electrophilic acylating agent (trichloroacetic anhydride, TCAA) allows functionalization at the β-position of the unsubstituted enamine moiety, giving access to valuable 4-substituted 3,5-diacyl-1,4-dihydropyridines.[15]

With the final aim of preparing chiral 1,4-dihydropyridine derivatives, we undertook a brief study of the above addition–TCAA acylation sequence starting from chiral *N*-alkylpyridinium salts **2** or **3** (Scheme 2) and some of the organocopper reagents that had provided better C-4 regioselectivity in the racemic series.[15a,b] Thus, pyridinium salts **2** and **3** were prepared by alkylation of nicotinamide **1** with methyl iodide and benzyl bromide, respectively, and were allowed to react



Scheme 2.



Scheme 3.

with $Ph_2Cu(CN)Li_2$, Bu_2CuLi and Me_2CuLi. After acylation of the crude mixtures, the expected adducts **4**,**5** or **6**,**7** were obtained in the ratios and yields listed in Table 1.

In full agreement with our previous observations, when the organocopper reagents were tested with *N*-methylpyridinium salt **2** the corresponding C-4 adducts **4a**–**c** were formed as the major (or only) products in overall yields of 40–60% (entries 1–3). Dihydropyridines **4** were obtained as diastereomeric mixtures, in which the diastereomer 4-Hβ (*R*) clearly predominated (see below for the assignment of the configuration). The diastereomeric ratio of **4a** (5:1) was determined from the ^{1}H NMR chemical shifts of 4-H, which appear at δ 5.14 (major) and δ 5.05 (minor). For **4b** (dr 9:1) and **4c** (dr 4:1) 2-H was the diagnostic signal, appearing at δ 6.46 or 6.32 (major) or δ 6.34 or 6.22 (minor), respectively. As expected, taking the position of the chiral auxiliary at the pyridinium ring into account, no diastereoselectivity was observed in the formation of C-6 adducts **6**.

However, rather surprisingly, the *N*-benzylpyridinium salt **3** was clearly a less efficient chiral electrophilic substrate as it led to the respective C-4 adducts **5** in lower yields and diastereoselectivities (entries 4 and 5). In the 4-phenyl series (entry 4), the C-4 regioselectivity was also lower. We do not have a convincing explanation for this different behaviour.

As could be expected from our previous work,[15] (trichloroacetyl)-1,4-dihydropyridines **4a** (dr 5:1) and **4c** (dr 4:1) underwent a haloform-type reaction with sodium methoxide in methanol to give the corresponding methyl esters **8a** and **8c** in high yields (90 and 84%,

Table 1. Addition of organocopper reagents to pyridinium salts **2** and **3** followed by TCAA acylation

Entry	Pyridinium salt	R^2Cu	Products (ratio)[a]	dr[a] C-4[b]	Yield (%)
1	**2**	$Ph_2Cu(CN)Li_2$[c]	**4a**+**6a** (4.5:1)	5:1	50
2	**2**	Bu_2CuLi[d]	**4b**	9:1	62
3	**2**	Me_2CuLi[d]	**4c**+**6c** (2:1)	4:1	43
4	**3**	$Ph_2Cu(CN)Li_2$[c]	**5a**+**7a** (1.6:1)	2.5:1	37
5	**3**	Bu_2CuLi[d]	**5b**	4:1	34

[a] Determined by ^{1}H NMR analysis of the crude reaction mixtures.
[b] The diastereomeric ratio of the corresponding C-6 isomer **6** or **7** was 1:1.
[c] Interaction with the pyridinium salt at −78°C.
[d] Interaction at 0°C.

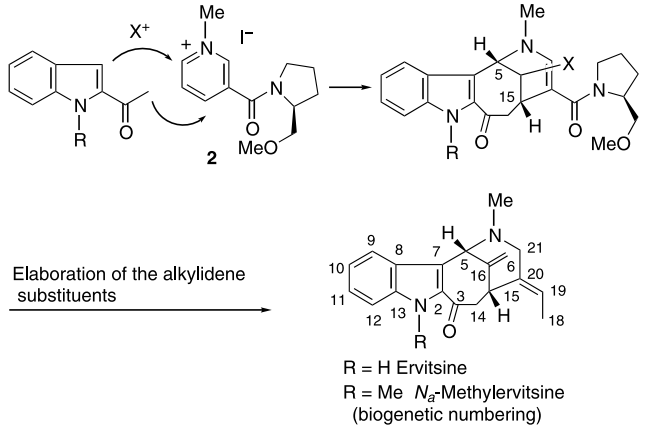
Scheme 3). In both cases, the major diastereomers (*S*)-**8a** and (*S*)-**8c** could be easily isolated from the crude diastereomeric reaction mixtures by column chromatography. Similarly, starting from the diastereomerically pure 4-butyldihydropyridine (*R*)-**4b** the methyl ester (*S*)-**8b** was obtained in 95% yield.

2.2. Synthesis of (−)-N_a-methylervitsine

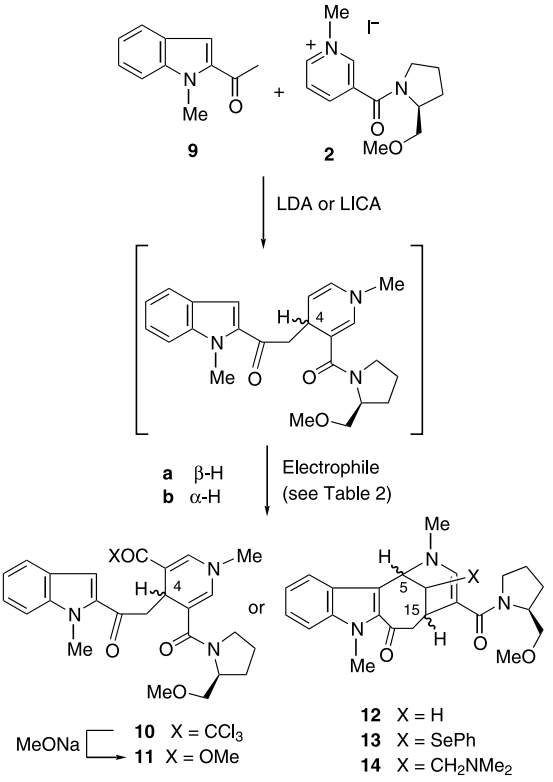
The above synthesis of chiral 1,4-dihydropyridines by diastereoselective addition of organocopper reagents to the *N*-methylpyridinium salt **2** prompted us to study the use of this chiral substrate in a stereoselective synthesis of the N_a-methyl derivative of the 2-acylindole alkaloid ervitsine.

Ervitsine,[16] isolated from *Pandaca boiteaui*,[17] has a particular bridged tetracyclic skeleton incorporating a seven-membered C ring and a piperidine moiety substituted by two different (16-methylene and (20*E*)-ethylidene) exocyclic double bonds. We reasoned that the assembly of its tetracyclic system could be accomplished in a stereoselective manner by nucleophilic addition of a suitable 2-acetylindole enolate to pyridinium salt **2**, followed by electrophile-induced cyclization of the resultant 1,4-dihydropyridine at the indole 3-position (Scheme 4). The chiral auxiliary would allow the stereoselective generation of the stereogenic center at the 4-position of the pyridine ring (corresponding to C-15 of ervitsine) and subsequent cyclization would result in the generation of the C-5 stereogenic center, whose configuration is determined by that of C-15 because of the bridgehead character of both carbons. The remainder of the synthesis, i.e. the elaboration of the alkylidene substituents, would closely parallel our previously reported racemic synthesis.[6b]

We set out to explore the feasibility of this proposal, studying the addition of the enolate derived from 2-acetylindole **9** to pyridinium salt **2**, followed by suitable electrophilic treatment (Scheme 5, Table 2). In comparison with the above organometallic additions, only products arising from nucleophilic attack at C-4 of the pyridinium ring were detected, although both the yields and diastereoselectivities were generally lower. Thus,



Scheme 4.



Scheme 5.

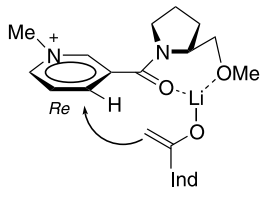
Table 2. Reactions of the enolate derived from acetylindole **9** with pyridinium salt **2**

Entry	Electrophile	Product (yield, %)	dr (a:b)[a]
1	TCAA	**10** (30)	2.1:1
2	HCl–C_6H_6	**12** (25)	2.8:1
3	ClSePh	**13** (40)	2:1
4	$CH_2{=}N^+Me_2I^-$	**14** (40)	2.1:1

[a] Determined by ^{1}H NMR analysis of the crude reaction mixtures.

the 3,5-diacyl-1,4-dihydropyridine **10** was obtained in a modest 30% yield as a 2.1:1 diastereomeric mixture when TCAA was used as the electrophilic acylating agent (entry 1). This dihydropyridine was converted into the methyl ester **11** (80%), a potential intermediate for the stereoselective synthesis of ervatamine alkaloids,[6b] by reaction with sodium methoxide. Treatment of the initially formed dihydropyridine with acid, PhSeCl or $Me_2N^+{=}CH_2I^-$ (Eschenmoser salt) gave the ervitsine-related tetracycles **12**–**14** in similar (25–40%) yields and diastereomeric ratios (entries 2–4).

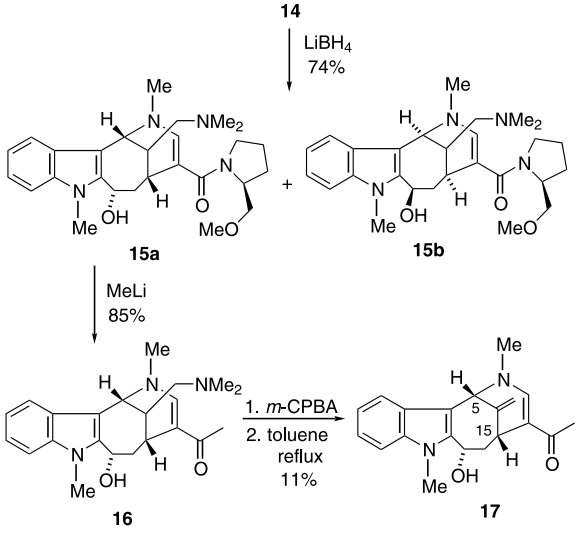
The configuration of the major diastereomers (series a, see below for the assignment of the stereochemistry) implies that the lithium enolate of **9** preferentially approaches the *Re* face of the pyridinium ring of **2**, probably after initial complexation of the lithium cation to both the carbonyl oxygen and the methoxy group of the auxiliary. This model would also be feasible for the addition of organocopper reagents described in Section 2.1.



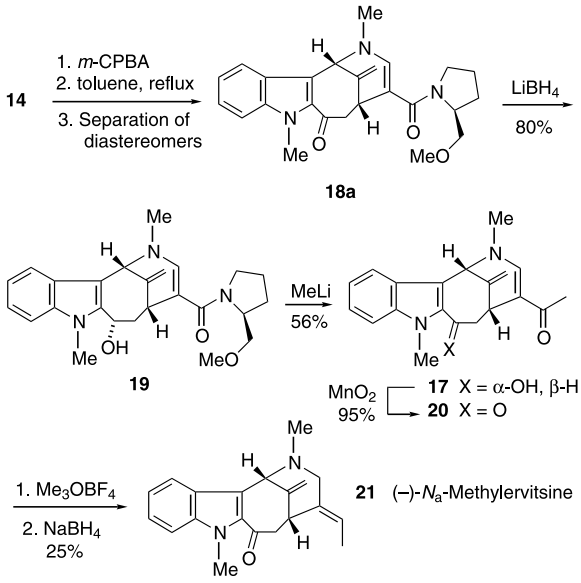
For the synthesis of N_a-methylervitsine from 16-functionalized tetracycles **14**, we devised the following steps: (i) the removal of the auxiliary by reaction with methyllithium,[18] which would allow the concomitant introduction of an additional carbon atom (C-18) for the subsequent ethylidene elaboration, and (ii) the transformation of the 16-(dimethylamino)methyl group into the 16-methylene appendage by Cope elimination through the corresponding *N*-oxide.

Removal of the chiral auxiliary from **14** required the previous reduction of the 2-acylindole carbonyl group. Thus, treatment of the diastereomeric mixture of ketones **14** with $LiBH_4$ stereoselectively gave two alcohols, **15a** and **15b** (74% yield), which were separated by column chromatography (Scheme 6). The configuration of the new C-3 stereogenic center was tentatively assigned as *S* in **15a** and *R* in **15b** taking into account steric factors in the hydride attack. As expected, the major alcohol **15a** was easily converted into the acetyl derivative **16** by reaction with methyllithium (85%). Disappointingly, Cope elimination of **16** via the respective *N*-oxide proved problematic and the desired methylene derivative **17** was obtained in poor yield (11%).

The formation of the 16-methylene substituent was more satisfactory from tetracycles **14**. Thus, when the above Cope elimination protocol was applied to **14**, the corresponding 16-methylene derivatives were obtained in 47% overall yield. (Scheme 7). At this point both diastereomers were efficiently separated by crystallization. The absolute configuration of the major



Scheme 6.



Scheme 7.

diastereomer **18a**, coincident with that of natural (–)-ervitsine, was unambiguously determined by X-ray crystallography.[13] As above, the 2-acylindole carbonyl group of **18a** was reduced with $LiBH_4$ to give alcohol **19** (80%), which was converted into **17** by reaction with methyllithium (56%). Finally, after regeneration of the 2-acylindole carbonyl group with MnO_2 (95%), the stereoselective elaboration of the (20*E*)-ethylidene substituent was effected by treatment of **20** with trimethyloxonium tetrafluoroborate followed by controlled sodium borohydride reduction (25%).[19] The ee (>99%) of the resulting (–)-N_a-methylervitsine **21**, $[\alpha]_D$ −60 (*c* 0.1, $CHCl_3$), was determined by chiral HPLC using racemic N_a-methylervitsine as a reference. Additionally, the NMR spectra of **21** matched those of the racemic material.[6b]

3. Conclusions

In conclusion, the chiral pyridinic substrate **2** undergoes the diastereoselective addition of several nucleophiles to give, after suitable manipulation of the initially formed 1,4-dihydropyridine adducts, valuable chiral 4-substituted 3,5-diacyl-1,4-dihydropyridines or ervitsine-related tetracycles, from which the synthesis of (–)-N_a-methylervitsine has been accomplished. These results evidence the potential of 1,4-dihydropyridines as effective building blocks in organic synthesis.

4. Experimental

4.1. General

All nonaqueous reactions were performed under an argon atmosphere. All solvents were dried by standard methods. Reaction courses and product mixtures were routinely monitored by TLC on silica gel (pre-coated

F_{254} Merck plates). Drying of organic extracts during the workup of reactions was performed over anhydrous Na_2SO_4. Evaporation of the solvents was accomplished under reduced pressure with a rotatory evaporator. Flash chromatography was carried out on SiO_2 (silica gel 60, SDS, 0.04–0.06 mm). Only noteworthy IR absorptions (cm^{-1}) are listed. Unless otherwise indicated, NMR spectra were recorded in $CDCl_3$ solution at 300 MHz (^1H) or 75.4 MHz (^{13}C), using TMS as an internal reference. Microanalyses and HRMS were performed by Centro de Investigación y Desarrollo (CSIC), Barcelona.

4.2. 3-[(2*S*)-(Methoxymethyl)pyrrolidinylcarbonyl]-pyridine, 1

A solution of (*S*)-prolinol nicotinamide[20] (0.22 g, 1 mmol) in THF (10 mL) was added to a suspension of NaH (63 mg, 1.6 mmol) in anhydrous THF (5 mL) cooled at 0°C, and the mixture was stirred at this temperature for 30 min. Then, MeI (0.26 mL, 4.2 mmol) was added and the resulting mixture was stirred at rt for 2 h. The reaction mixture was poured into 10% aqueous Na_2CO_3 solution and extracted with AcOEt. Concentration of the organic extracts followed by flash chromatography (95:5 Et_2O–MeOH) gave pyridine **1**: 0.19 g (81%); $[\alpha]_D^{22}$ −187 (*c* 1, $CHCl_3$); ν_{max} (film) 1628; ^1H NMR δ 1.80 (m, 1H, 4′-H), 2.03 (m, 3H, 3′-H, 4′-H), 3.15 (m, 1H, CH_2O), 3.40 (s, 3H, OMe), 3.55 (m, 1H, CH_2O), 3.66 (m, 2H, 5′-H), 4.45 (br s, 1H, 2′-H), 7.36 (dd, $J=7.5$, 3 Hz, 1H, 5-H), 7.90 (d, $J=7.5$ Hz, 1H, 4-H), 8.66 (d, $J=2$ Hz, 1H, 6-H), 8.78 (br s, 1H, 2-H); ^{13}C NMR δ 25.0 (C-4′), 27.5 (C-3′), 50.4 (C-5′), 56.8 (C-2′), 59.0 (OMe), 72.2 (CH_2O), 123.0 (C-5), 132.8 (C-3), 134.8 (C-4), 148.1 (C-6), 150.6 (C-2), 167.2 (CO). Anal. calcd for $C_{12}H_{16}N_2O_2 \cdot 1/4H_2O$: C, 64.12; H, 7.40; N, 12.46. Found: 64.16; H, 7.35; N, 12.51%.

4.3. 3-[(2*S*)-(Methoxymethyl)pyrrolidinylcarbonyl]-1-methylpyridinium iodide, 2

A solution of MeI (7.3 mL, 0.08 mol) in anhydrous benzene (107 mL) was added to a solution of pyridine **1** (4.4 g, 0.02 mol) in anhydrous acetone (67 mL), and the mixture was stirred at rt for 7 days. The solvents were removed and the resultant residue was digested with Et_2O (3×50 mL) to give pyridinium iodide **2**: 6.6 g (2:1 mixture of rotamers, 92%); $[\alpha]_D^{22}$ −98 (*c* 1, $CHCl_3$); ν_{max} (KBr) 1639; ^1H NMR (500 MHz, assignments aided by HSQC) δ 2.01 (m, 4H, 3′-H, 4′-H), 3.20 (br s, OMe, CH_2O minor rotamer), 3.36 (s, OMe, major rotamer), 3.65 (m, 5′-H, CH_2O major rotamer), 3.85 (m, 5′-H minor rotamer), 4.40 (br s, 1H, 2′-H), 4.71 (s, 3H, NMe), 8.10 (m, 5-H minor rotamer), 8.20 (t, $J=7.5$ Hz, 5-H major rotamer), 8.50 (d, $J=7.5$ Hz, 4-H major rotamer), 8.60 (m, 4-H minor rotamer), 9.10 (s, 2-H major rotamer), 9.29 (m, 2-H minor rotamer), 9.42 (m, 1H, 6-H); ^{13}C NMR 24.3 (21.3) (C-4′), 27.0 (27.9) (C-3′), 49.3 (NMe), 50.1 (45.2) (C-5′), 57.0 (58.2) (C-2′), 58.6 (58.3) (OMe), 71.5 (73.3) (CH_2O), 127.7 (127.4) (C-5), 136.2 (137.1) (C-3), 142.6 (C-4), 143.7 (143.5) (C-6), 145.6 (145.0) (C-2), 161.6 (162.1) (CO). Anal. calcd for $C_{13}H_{19}N_2O_2I \cdot 3/4CH_4O$: C, 42.76; H, 5.74; N, 7.25; I, 32.86. Found: C, 42.92; H, 5.57; N, 7.13; I, 32.48%.

4.4. 1-Benzyl-3-[(2*S*)-(methoxymethyl)pyrrolidinyl-carbonyl]pyridinium bromide, 3

A mixture of pyridine **1** (3.52 g, 16 mmol) and benzyl bromide (2.1 mL, 17 mmol) was heated at 80–100°C for 2 h. The reaction mixture was diluted with Et_2O and filtered to give pyridinium bromide **3**: 5.5 g (3:2 mixture of rotamers, 88%); $[\alpha]_D^{22}$ −106 (*c* 1.7, $CHCl_3$); ν_{max} (KBr) 1638, 1620; ^1H NMR δ 2.10 (m, 4H, 3′-H, 4′-H), 3.10 (2 m, OMe, CH_2O minor rotamer), 3.35 (br s, OMe major rotamer), 3.58 (m, CH_2O, 5′-H major rotamer), 3.95 (m, 5′-H minor rotamer), 4.40 (br s, 1H, 2′-H), 6.36 (m, 2H, Bn), 7.38, 7.68 (2m, 5H, Bn), 8.05 (m, 5-H minor rotamer), 8.15 (m, 5-H major rotamer), 8.53 (d, $J=7.5$ Hz, 1H, 4-H), 9.45 (s, 2-H, major rotamer), 9.65 (s, 2-H minor rotamer), 9.70 (br s, 1H, 6-H); ^{13}C NMR δ 24.7 (21.4) (C-4′), 27.4 (28.0) (C-3′), 50.4 (45.9) (C-5′), 57.3 (58.5) (C-2′), 58.8 (58.5) (OMe), 71.7 (73.5) (CH_2O), 64.0 (Bn), 128.0 (C-5), 128.2, 129.3, 129.7, 135.2 (5C, Ph), 136.8 (C-3); 143.2, 143.4 (C-6, C-4), 145.5 (C-2), 161.9 (CO). Anal. calcd for $C_{19}H_{23}BrN_2O_2 \cdot 2/3CH_2Cl_2$: C, 52.71; H, 5.47; N, 6.25. Found: C, 53.11; H, 5.70; N, 6.22%.

4.5. 3-[(2*S*)-(Methoxymethyl)pyrrolidinylcarbonyl]-1-methyl-4-phenyl-5-(trichloroacetyl)-1,4-dihydropyiridine, 4a

A solution of PhLi (1.8 M in cyclohexane, 0.9 mL, 1.6 mmol) was slowly added to a solution of CuCN (75 mg, 0.8 mmol) in dry THF (6 mL) cooled at −78°C, and the resulting mixture was allowed to rise to 0°C. After the mixture was cooled again to −78°C, pyridinium iodide **2** (0.1 g, 0.27 mmol) was added in portions, and the mixture was stirred at −78°C for 14 h. The reaction mixture was quenched with 10% aqueous NH_4Cl solution and extracted with AcOEt. The organic extracts were concentrated and the resulting residue was dissolved in THF (5 mL), then treated with TCAA (0.15 mL, 0.8 mmol) at 0°C for 2 h. The reaction mixture was poured into a saturated aqueous Na_2CO_3 solution and extracted with Et_2O. The ethereal extracts were dried and concentrated, and the resultant residue was chromatographed (3:7 hexanes–AcOEt) to give a 4.5:1 mixture of 1,4-dihydropyridine **4a** (dr 5:1) and 1,2-dihydropyridine **6a** (dr 1:1): (60 mg, 50%). An additional chromatography allowed the isolation of an analytical sample of **4a** (dr 10:1): ν_{max} (film) 1638, 1569; ^1H NMR δ 1.30 (m, 1H, 4′-H), 1.80 (m, 3H, 3′-H, 4′-H), 3.28, 3.29 (2s, 6H, NMe, OMe), 3.10–3.45 (m, 4H, CH_2O, 5′-H), 4.20 (br s, 1H, 2′-H), 5.14 (s, 1H, 4-H), 6.20 (d, $J=1.2$ Hz, 1H, 2-H), 7.15 (m, 1H, Ph), 7.25 (m, 4H, Ph), 7.92 (d, $J=1.2$ Hz, 1H, 6-H); ^{13}C NMR δ 25.0 (C-4′), 27.4 (C-3′), 38.9 (C-4), 42.3 (NMe), 49.5 (C-5′), 56.3 (C-2′), 59.0 (OMe), 72.6 (CH_2O), 96.0 (CCl_3), 103.0 (C-3), 119.0 (C-5), 126.7, 127.1 (Ph), 127.6 (C-2), 128.4 (Ph), 144.4 (Ph), 144.7 (C-6), 168.5, 178.4 (CO); HRMS calcd for $C_{21}H_{23}Cl_3N_2O_3$ 456.0774, found 456.0791.

4.6. 4-Butyl-3-[(2*S*)-(methoxymethyl)pyrrolidinylcarbonyl]-1-methyl-5-(trichloroacetyl)-1,4-dihydropyridine, 4b

n-BuLi (1.6 M in hexanes, 0.67 mL, 1 mmol) was added to a solution of CuI (0.1 g, 0.5 mmol) in anhydrous THF (5 mL) cooled at −78°C, and the mixture was allowed to rise to 0°C. After the mixture was cooled at −40°C, pyridinium iodide **2** (0.1 g, 0.27 mmol) was added in portions and the mixture was allowed to rise to 0°C (1 h). Workup as above gave a residue, which was dissolved in dry THF (5 mL) and treated with TCAA (0.15 mL, 0.8 mmol) at 0°C for 2 h. Extractive workup (AcOEt) and flash chromatography (4:6 hexanes–AcOEt) afforded 1,4-dihydropyridine **4b** (dr 9:1): 75 mg (62%). A diastereomerically pure sample of (*R*)-**4b** was obtained by an additional chromatography: $[\alpha]_D^{22}$ +102 (*c* 0.6, $CHCl_3$); ν_{max} (film) 1635, 1567; ^{1}H NMR δ 0.84 (t, $J=7$ Hz, 3H, CH_3), 1.23–1.45 (2m, 6H, CH_2), 1.70 (m, 1H, 3′-H), 1.90 (m, 2H, 3′-H, 4′-H), 2.10 (m, 1H, 4′-H), 3.27 (s, 3H, NMe), 3.34 (s, 3H, OMe), 3.52 (m, 4H, CH_2O, 5′-H), 3.90 (m, 1H, 4-H), 4.35 (m, 1H, 2′-H), 6.46 (d, $J=1.2$ Hz, 1H, 2-H), 7.75 (s, 1H, 6-H); ^{13}C NMR 14.0 (CH_3), 22.7 (CH_2), 25.0 (C-4′), 27.3, 27.6 (CH_2, C-3′), 32.3 (C-4), 36.5 (CH_2), 42.3 (NMe), 49.5 (C-5′), 56.5 (C-2′), 59.0 (OMe), 72.7 (CH_2O), 96.2 (CCl_3), 103.1 (C-3), 118.9 (C-5), 131.1 (C-2), 145.2 (C-6), 169.6, 178.8 (CO).

4.7. 1-Benzyl-4-butyl-3-[(2*S*)-(methoxymethyl)pyrrolidinylcarbonyl]-5-(trichloroacetyl)-1,4-dihydropyridine, 5b

Operating as above, from pyridinium bromide **3** (0.1 g, 0.25 mmol) 1,4-dihydropyridine **5b** (dr 4:1) was obtained after flash chromatography (7:3 hexanes/AcOEt): 45 mg (34%); ν_{max} (film) 1646, 1636, 1569; ^{1}H NMR (major diastereomer) δ 0.84 (t, $J=7.5$ Hz, 3H, CH_3), 1.25–1.45 (m, 6H, CH_2), 1.70 (m, 1H, 3′-H), 1.90 (m, 2H, 3′-H, 4′-H), 2.05 (m, 1H, 4′-H), 3.31 (s, 3H, OMe), 3.45 (m, 4H, CH_2O, 5′-H), 3.95 (m, 1H, 4-H), 4.35 (m, 1H, 2′-H), 4.58 (s, 2H, Bn), 6.55 (d, $J=1.2$ Hz, 1H, 2-H), 7.23 (m, 2H, Ph), 7.36 (m, 3H, Ph), 7.88 (s, 1H, 6-H); ^{13}C NMR (major diastereomer) 14.1 (CH_3), 22.6 (CH_2), 25.0 (C-4′), 27.5, 27.7 (CH_2, C-3′), 32.5 (C-4), 36.2 (CH_2), 49.5 (C-5′), 56.7 (C-2′), 58.7 (Bn), 58.9 (OMe), 72.6 (CH_2O), 96.0 (CCl_3), 103.4 (C-3), 118.4 (C-5), 127.4, 128.5, 129.1 (Ph), 130.8 (C-2), 135.2 (Ph), 144.8 (C-6), 169.6, 178.9 (CO).

4.8. 3-[(2*S*)-(Methoxymethyl)pyrrolidinylcarbonyl]-1,4-dimethyl-5-(trichloroacetyl)-1,4-dihydropyridine, 4c

MeLi (1.6 M in Et_2O, 0.67 mL, 1 mmol) was added to a solution of CuI (0.1 g, 0.5 mmol) in anhydrous THF (5 mL) cooled at 0°C, and the mixture was stirred at 0°C for 15 min. After the mixture was cooled to −40°C, pyridinium iodide **2** (0.1 g, 0.27 mmol) was added, the mixture was allowed to rise to 0°C, and stirred at 0°C for 1 h. After TCAA treatment and extractive workup (AcOEt), the residue obtained was chromatographed (3:7 hexanes–AcOEt) to give a 2:1 mixture of 1,4-dihydropyridine **4c** (dr 4:1) and 1,2-dihydropyridine **6c** (dr 1:1): 38 mg (43%). An additional chromatography allowed the isolation of pure **4c** (dr 4:1): ν_{max} (film) 1646, 1570; ^{1}H NMR (major diastereomer) δ 1.03 (d, $J=6.3$ Hz, 3H, CH_3), 1.70 (m, 1H, 4′-H), 1.90 (m, 3H, 4′-H, 3′-H), 3.25 (s, 3H, NMe), 3.35 (s, 3H, OMe), 3.52 (m, 4H, CH_2O, 5′-H), 3.95 (q, $J=6.3$ Hz, 1H, 4-H), 4.30 (m, 1H, 2′-H), 6.32 (d, $J=1.2$ Hz, 1H, 2-H), 7.69 (s, 1H, 6-H); ^{13}C NMR (major diastereomer) δ 22.1 (CH_3), 25.1 (C-4′), 27.7 (C-3′), 27.8 (C-4), 42.2 (NMe), 49.5 (C-5′), 56.5 (C-2′), 59.1 (OMe), 72.7 (CH_2O), 96.0 (CCl_3), 104.5 (C-3), 120.2 (C-5), 129.8 (C-2), 144.9 (C-6), 168.9, 178.7 (CO).

4.9. 3-(Methoxycarbonyl)-5-[(2*S*)-(methoxymethyl)-pyrrolidinylcarbonyl]-1-methyl-4-phenyl-1,4-dihydropyridine, 8a

A solution of 1,4-dihydropyridine **4a** (dr 5:1, 30 mg, 0.06 mmol) in MeOH–THF (1:1, 4 mL) was added dropwise to a solution of MeONa (0.24 mmol) in MeOH (4 mL), and the resulting mixture was stirred at rt for 1 min. The solvent was removed and the residue was partitioned between H_2O and Et_2O, and extracted with Et_2O. Concentration of the dried ethereal extracts afforded 1,4-dihydropyridine **8a**: 20 mg (90%). Flash chromatography (4:6 hexanes–AcOEt) allowed the isolation of the major diastereomer (*S*)-**8a**: $[\alpha]_D^{22}$ +25 (*c* 1, $CHCl_3$); ν_{max} (film) 1730, 1681, 1635; ^{1}H NMR δ 1.80 (m, 4H, 4′-H, 3′-H), 3.17 (s, 3H, NMe), 3.25 (m, 4H, CH_2O, 5′-H), 3.26 (s, 3H, OMe), 3.59 (s, 3H, OMe), 4.20 (m, 1H, 2′-H), 5.01 (s, 1H, 4-H), 6.21 (s, 1H, 6-H), 7.10–7.40 (m, 6H, Ph, 2-H); ^{13}C NMR δ 24.9 (C-4′), 27.5 (C-3′), 38.5 (C-4), 41.4 (NMe), 49.7 (C-5′), 51.1 (OMe), 56.2 (C-2′), 58.9 (OMe), 72.7 (CH_2O), 103.9 (C-5), 115.4 (C-3), 126.3, 127.4, 128.2 (Ph), 130.0 (C-6), 139.6 (C-2), 145.8 (Ph), 167.7, 169.6 (CO); HRMS calcd for $C_{21}H_{26}N_2O_4$ 370.1892, found 370.1898.

4.10. 4-Butyl-3-(methoxycarbonyl)-5-[(2*S*)-(methoxymethyl)pyrrolidinylcarbonyl]-1-methyl-1,4-dihydropyridine, 8b

Operating as above, from 1,4-dihydropyridine (*R*)-**4b** (70 mg, 0.16 mmol) 1,4-dihydropyridine (*S*)-**8b** was obtained after flash chromatography (4:6 hexanes–AcOEt): 53 mg (95%); $[\alpha]_D^{22}$ −64 (*c* 1.3, $CHCl_3$); ν_{max} (film) 1693, 1634, 1589; ^{1}H NMR δ 0.84 (t, $J=7.5$ Hz, 3H, CH_3), 1.30 (m, 6H, CH_2), 1.70 (m, 1H, 3′-H), 1.90 (m, 2H, 3′-H, 4′-H), 2.12 (m, 1H, 4′-H), 3.12 (s, 3H, NMe), 3.35 (s, 3H, OMe), 3.50 (m, 4H, CH_2O, 5′-H), 3.71 (s, 3H, OMe), 3.80 (m, 1H, 4-H), 4.38 (m, 1H, 2′-H), 6.41 (d, $J=1.5$ Hz, 1H, 6-H), 7.11 (d, $J=0.9$ Hz, 1H, 2-H); ^{13}C NMR δ 14.1 (CH_3), 22.8 (CH_2), 25.4 (C-4′), 27.2, 27.7 (CH_2, C-3′), 32.0 (C-4), 37.3 (CH_2), 41.3 (NMe), 49.7 (C-5′), 51.0 (OMe), 56.3 (C-2′), 59.0 (OMe), 72.9 (OCH_2), 104.0 (C-5), 115.1 (C-3), 132.9 (C-6), 140.1 (C-2), 167.9, 170.7 (CO); HRMS calcd for $C_{19}H_{30}N_2O_4$ 350.2205, found 350.2216.

4.11. 3-(Methoxycarbonyl)-5-[(2*S*)-(methoxymethyl)-pyrrolidinylcarbonyl]-1,4-dimethyl-1,4-dihydropyridine, 8c

Operating as above, from 1,4-dihydropyridine **4c** (dr 4:1, 0.1 g, 0.3 mmol) 1,4-dihydropyridine **8c** (80 mg, 84%) was obtained. Flash chromatography (3:7 hexanes–AcOEt) allowed the isolation of major diastereomer (*S*)-**8c**: $[\alpha]_D^{22}$ −110 (*c* 1.5, $CHCl_3$); ν_{max} (film) 1687, 1633, 1591; ^{1}H NMR δ 1.03 (d, $J=6.3$ Hz, 3H, CH_3), 1.75 (m, 1H, 4′-H), 1.95 (m, 2H, 3′-H, 4′-H), 2.10 (m, 1H, 3′-H), 3.09 (s, 3H, NCH_3), 3.35 (s, 3H, OMe), 3.53 (m, 3H, CH_2O, 5′-H), 3.65 (m, 1H, 5′-H), 3.71 (s, 3H, OMe), 3.85 (q, $J=6.3$ Hz, 1H, 4-H), 4.19 (m, 1H, 2′-H), 6.28 (d, $J=1.5$ Hz, 1H, 6-H), 7.04 (d, $J=1.5$ Hz, 1H, 2-H); ^{13}C NMR δ 23.4 (CH_3), 25.2 (C-4′), 27.4 (C-4), 27.7 (C-3′), 41.2 (NMe), 49.6 (C-5′), 51.0 (OMe), 56.3 (C-2′), 59.0 (OMe), 72.9 (CH_2O), 105.5 (C-5), 116.5 (C-3), 131.8 (C-6), 139.6 (C-2), 167.9, 170.1 (CO); HRMS calcd for $C_{16}H_{24}N_2O_4$ 308.1736, found 308.1756.

4.12. 3-[(2*S*)-(Methoxymethyl)pyrrolidinylcarbonyl]-1-methyl-4-[(1-methyl-2-indolyl)carbonylmethyl]-5-(trichloroacetyl)-1,4-dihydropyridine, 10

LDA (1.5 M in cyclohexane, 1.27 mL, 1.9 mmol) was added to a solution of 2-acetylindole **9**[6b] (0.3 g, 1.7 mmol) in anhydrous THF (30 mL) cooled at −78°C, and the mixture was stirred at −78°C for 30 min. Pyridinium iodide **2** (0.62 g, 1.7 mmol) was added, and the resulting mixture was allowed to rise to −30°C and stirred at −30°C for 1 h. Then, TCAA (0.96 mL, 5.2 mmol) was added, and the mixture was stirred at 0°C for 2 h. The reaction mixture was poured into a 10% aqueous Na_2CO_3 solution and extracted with Et_2O. After the organic extracts were dried and concentrated, the resulting residue was chromatographed (2:8 hexanes–AcOEt) to give dihydropyridine **10** (dr 2.1:1): 0.24 g (30%); mp 89–90°C (Et_2O–acetone); ν_{max} (KBr) 1650, 1615, 1563; ^{1}H NMR δ 1.70–1.95 (m, 3H, 3′-H, 4′-H), 2.05 (m, 1H, 3′-H), 2.85 (dd, $J=14$, 7 Hz, CH_2CO 10b), 2.95 (m, CH_2CO 10a), 3.26, 3.27 (2s, 3H, NMe), 3.32, 3.33 (2s, 3H, OMe), 3.45, 3.90 (m, 4H, CH_2O, 5′-H), 3.98 (s, 3H, NMe), 4.30 (m, 1H, 2′-H), 4.44 (t, $J=7$ Hz, 4-H 10b), 4.64 (t, $J=7$ Hz, 4-H 10a), 6.42 (s, 1H, 2-H), 7.10–7.30 (2m, 3H), 7.47 (s, 1H, 3-H indole), 7.70 (d, $J=7.5$ Hz, 1H, 4-H indole), 7.80 (s, 1H, 6-H); ^{13}C NMR δ 25.1 (C-4′), 27.7 (C-3′), 31.9 (C-4), 32.1 (NMe), 42.3 (42.2) (NMe), 47.1 (CH_2CO), 49.8 (C-5′), 56.6 (57.3) (C-2′), 58.9 (59.0) (OMe), 72.6 (72.5) (CH_2O), 95.0 (CCl_3), 101.8 (C-3), 110.0 (C-7 indole), 112.3 (C-3 indole), 117.2 (C-5), 120.2 (C-5 indole), 123.0 (C-4 indole), 125.6 (C-6 indole), 125.9 (C-3a indole), 131.3 (C-2), 134.7 (C-2 indole), 140.0 (C-7a indole), 145.7 (C-6), 168.2, 178.6, 191.7 (CO). Anal. calcd for $C_{26}H_{28}Cl_3N_3O_4{\cdot}2/3H_2O$: C, 55.28; H, 5.23; N, 7.44. Found: C, 54.90; H, 5.17; N, 7.33%.

4.13. 3-(Methoxycarbonyl)-5-[(2*S*)-(methoxymethyl)-pyrrolidinylcarbonyl]-1-methyl-4-[(1-methyl-2-indolyl)carbonylmethyl]-1,4-dihydropyridine, 11

A solution of (trichloroacetyl)dihydropyridine **10** (dr 2.1:1, 0.15 g, 0.27 mmol) in MeOH–THF (14 mL, 1:1) was added dropwise to a solution of MeONa (1.2 mmol) in anhydrous MeOH (14 mL) and the resulting mixture was stirred at rt for 4 min. The solvent was removed and the residue was partitioned between H_2O and Et_2O and extracted with Et_2O. The organic extracts were dried and concentrated to give 0.10 g (80%) of dihydropyridine **11** (dr 2.1:1). An additional chromatography (2:8 hexanes–AcOEt) allowed the isolation of an enriched sample of the major diastereomer **11a**: ν_{max} (KBr) 1684, 1651, 1612, 1590; ^{1}H NMR δ 1.70–1.90 (m, 3H, 3′-H, 4′-H), 2.05 (m, 1H, 3′-H), 2.90 (dd, $J=11$, 7.5 Hz, 1H, CH_2CO), 3.05 (dd, $J=11$, 3.5 Hz, 1H, CH_2CO), 3.13 (s, 3H, NMe), 3.30 (s, 3H, OMe), 3.33 (m, 1H, 5′-H), 3.39 (m, 2H, CH_2O), 3.50 (m, 1H, 5′-H), 3.68 (s, 3H, OMe), 4.00 (s, 3H, NMe), 4.35 (m, 1H, 2′-H), 4.55 (m, 1H, 4-H), 6.40 (s, 1H, 6-H), 7.12 (m, 2H), 7.33 (m, 2H), 7.42 (s, 1H, 2-H), 7.70 (d, $J=7.5$ Hz, 1H, 4-H indole); ^{13}C NMR δ 25.2 (C-4′), 27.8 (C-3′), 31.8 (C-4), 32.0 (NMe), 41.3 (NMe), 48.8 (CH_2CO), 50.0 (C-5′), 51.1 (OMe), 56.5 (C-2′), 58.9 (OMe), 72.9 (CH_2O), 102.9 (C-5), 110.1 (C-7 indole), 111.9 (C-3 indole), 113.6 (C-3), 120.2 (C-5 indole), 122.9 (C-4 indole), 125.4 (C-6 indole), 125.9 (C-3a indole), 133.4 (C-6), 135.0 (C-2 indole), 139.9 (C-7a indole), 140.5 (C-2), 167.3, 169.4, 192.3 (CO); HRMS calcd for $C_{26}H_{31}N_3O_5$ 465.2263, found 465.2255.

4.14. 4-[(2*S*)-(Methoxymethyl)pyrrolidinylcarbonyl]-2,8-dimethyl-7-oxo-2,5,6,7-tetrahydro-1*H*-1,5-methano-azonino[4,3-*b*]indole, 12

The enolate of 2-acetylindole **9**, prepared from **9** (0.2 g, 1.15 mmol) and LDA (1.5 M in cyclohexane, 1.93 mL, 2.9 mmol) in anhydrous THF (10 mL) as described in Section 4.11, was allowed to react with pyridinium iodide **2** (0.42 g, 1.16 mmol) at −30°C for 1.5 h. Then, the reaction mixture was cooled to −78°C and enough of a saturated benzenic solution of dry HCl was added to bring the pH to 3–4, and the mixture was stirred at rt for 2 h. The reaction mixture was poured into a 10% aqueous Na_2CO_3 solution and extracted with AcOEt. After the organic extracts were concentrated, the resulting residue was chromatographed (95:5 AcOEt–MeOH) to give tetracycle **12** (dr 2.8:1): 117 mg (25%). An additional flash chromatography (95:5 AcOEt–MeOH) allowed the isolation of a pure sample of the major diastereomer (1*R*,5*S*)-**12a**: $[\alpha]_D^{22}$ −264 (*c* 0.5, $CHCl_3$); ν_{max} (film) 1652, 1627; ^{1}H NMR (biogenetic numbering) δ 1.80 (m, 3H, 4′-H, 3′-H), 2.10 (m, 1H, 3′-H), 2.55 (m, 2H, 16-H), 2.82 (s, 3H, NMe), 2.90 (dd, $J=15$, 3 Hz, 1H, 14-H), 3.05 (dd, $J=15$, 7.5 Hz, 1H, 14-H), 3.20 (m, 1H, 5′-H), 3.36 (s, 3H, OMe), 3.45 (m, 3H, CH_2O, 5′-H, 15-H), 3.60 (m, 1H, CH_2O), 3.86 (s, 3H, NMe), 4.45 (m, 1H, 2′-H), 4.90 (br s, 1H, 5-H), 6.39 (s, 1H, 21-H), 7.20 (m, 1H), 7.40 (m, 2H), 7.80 (d, $J=7.5$ Hz, 1H, 9-H); ^{13}C NMR δ 25.5 (C-4′), 26.7 (C-15), 27.8 (C-3′), 31.6 (C-16), 32.2 (NMe), 41.6 (NMe), 50.0 (C-14); 50.3 (C-5), 51.7 (C-5′), 56.2 (C-2′), 59.0 (OMe), 73.6 (CH_2O), 103.0 (C-20), 110.4 (C-12), 118.3 (C-7), 120.2 (C-9), 120.6 (C-10), 125.3 (C-11), 126.0 (C-8), 132.0 (C-2), 138.1 (C-13), 140.0 (C-21), 171.2 (CO), 198.5 (C-3).

Anal. calcd for $C_{24}H_{29}N_3O_3 \cdot 2/3CHCl_3$: C, 60.53; H, 6.52; N, 8.58. Found: 60.41; H, 6.40; N, 8.31%.

4.15. 4-[(2*S*)-(Methoxymethyl)pyrrolidinylcarbonyl]-2,8-dimethyl-7-oxo-13-(phenylselenenyl)-2,5,6,7-tetrahydro-1*H*-1,5-methanoazonino[4,3-*b*]indole, 13

2-Acetylindole **9** (0.3 g, 1.7 mmol) in anhydrous THF (5 mL) was allowed to react as above with pyridinium iodide **2** (0.63 g, 1.7 mmol). After the mixture was cooled to −78°C, PhSeCl (0.99 g, 5.2 mmol) was added, and the mixture was stirred at rt for 2 h. Workup as above followed by flash chromatography (2:8 hexanes–AcOEt) gave tetracycle **13** (dr 2:1): 0.35 g (40%); mp 209°C (Et_2O–acetone–hexanes); ν_{max} (KBr) 1652, 1626; ^{1}H NMR (most significant signals) δ 1.80 (m, 4H, 3′-H, 4′-H), 2.78, 2.87 (2s, 3H, NMe), 3.34, 3.37 (2s, 3H, NMe), 3.60 (m, 4H, CH_2O, 5′-H), 3.68 (br s, 1H, 15-H), 3.84, 3.86 (2s, 3H, NMe), 4.21 (s, 1H, 16-H), 4.30, 4.45 (2m, 1H, 2′-H), 4.95 (s, 1H, 5-H), 6.42, 6.60 (2s, 1H, 21-H), 7.20 (m, 1H), 7.40 (m, 5H), 7.60 (d, J=7.5 Hz, 1H, 9-H), 7.70 (m, 2H); ^{13}C NMR (major diastereomer **13a**, from the mixture) δ 25.5 (C-4′), 27.8 (C-3′), 32.0 (NMe), 33.7 (C-15), 42.0 (NMe), 45.2 (C-16), 50.0 (C-14), 51.5 (C-5′), 54.8 (C-5), 56.3 (C-2′), 58.9 (OMe), 73.5 (CH_2O), 101.3 (C-20), 110.4 (C-12), 117.2 (C-7), 119.9 (C-9), 120.8 (C-10), 125.5 (C-8), 125.6 (C-11), 127.8, 129.1 (Ph), 133.4 (C-2), 134.7 (Ph), 138.0 (C-13), 138.9 (C-21), 170.5 (CO), 196.8 (C-3). Anal. calcd for $C_{30}H_{33}N_3O_3Se$: C, 64.05; H, 5.91; N, 7.47. Found: C, 64.04; H, 5.90; N, 7.42%.

4.16. 13-[(Dimethylamino)methyl]-4-[(2*S*)-(methoxymethyl)pyrrolidinylcarbonyl]-2,8-dimethyl-7-oxo-2,5,6,7-tetrahydro-1,5-methano-1*H*-azonino[4,3-*b*]indole, 14

n-BuLi (1.6 M in cyclohexane, 1.62 mL, 2.6 mmol) was added to a solution of isopropylcyclohexylamine (0.44 mL, 2.6 mmol) in anhydrous THF (5 mL) cooled at −78°C, and the solution was stirred at −78°C for 30 min. 2-Acetylindole **9** (0.3 g, 1.7 mmol) in THF (10 mL) was added and the mixture was stirred at −78°C for 30 min. Pyridinium iodide **2** (0.63 g, 1.73 mmol) was added in portions, and the mixture was allowed to rise to −30°C, and stirred at −30°C for 1.5 h. Eschenmoser's salt (1.3 g, 6.9 mmol) was added and the resulting suspension was stirred at rt for 2 h. Workup as above followed by flash chromatography (8:2 AcOEt–MeOH) gave tetracycle **14** (dr 2:1): 0.32 g (40%). An additional chromatography allowed the isolation of an analytical sample of the major diastereomer (1*R*,5*R*,13*R*)-**14a**: $[\alpha]_D^{22}$ −83 (*c* 1.3, $CHCl_3$); ν_{max} (film) 1652, 1629, 1590; ^{1}H NMR δ 1.75 (m, 3H, 4′-H, 3′-H), 2.05 (m, 1H, 3′-H), 2.20 (dd, J=15, 7.5 Hz, 1H, 14-H), 2.30 (s, 6H, NMe), 2.40 (m, 2H, 6-H), 2.60 (m, 1H, 14-H), 2.89 (s, 3H, NMe), 3.04 (s, 1H, 16-H), 3.20–3.60 (m, 5H), 3.36 (s, 3H, OMe), 3.87 (s, 1H, NMe), 4.45 (m, 1H, 2′-H), 5.10 (s, 1H, 5-H), 6.33 (s, 1H, 21-H), 7.20–7.40 (m, 3H), 7.90 (d, J=7.5 Hz, 1H, 9-H); ^{13}C NMR δ 25.5 (C-4′), 27.9 (C-3′), 30.9 (C-15), 32.2 (NMe), 38.7 (C-16), 42.0 (NMe), 45.9 (NMe), 50.0 (C-14), 50.7 (C-5), 51.7 (C-5′), 56.2 (C-2′), 58.9 (CH_2O), 73.6 (OMe), 63.1 (C-6), 101.5 (C-20), 110.3 (C-12), 118.9 (C-7), 120.5 (C-9), 120.7 (C-10), 125.5 (C-11), 126.2 (C-8), 133.7 (C-2), 138.2 (C-13), 138.8 (C-21), 171.5 (CO), 197.8 (C-3). Anal. calcd for $C_{27}H_{36}N_4O_3 \cdot 1/4CH_2Cl_2$: C, 53.75; H, 5.94; N, 8.82. Found: C, 53.29; H, 6.43; N, 9.02%.

4.17. 4-[(2*S*)-(Methoxymethyl)pyrrolidinylcarbonyl]-13-[(dimethylamino)methyl]-7-hydroxy-2,8-dimethyl-2,5,6,7-tetrahydro-1,5-methano-1*H*-azonino[4,3-*b*]indole, 15

$LiBH_4$ (2 M in THF, 2.15 mL, 4.3 mmol) was added to a solution of tetracycles **14** (dr 2.1:1, 0.5 g, 1 mmol) in anhydrous THF (30 mL) and the mixture was stirred at rt for 6 h. After the reaction was quenched with MeOH (drops), the resulting mixture was poured into a 10% aqueous Na_2CO_3 solution and extracted with AcOEt. Concentration of the organic extracts followed by flash chromatography (AcOEt/MeOH, increasing polarity) gave alcohols 15 (dr 2:1). An additional chromatography allowed the separation of both diastereomers. Elution with 99:1 AcOEt–MeOH gave alcohol (1*S*,5*S*,7*R*,13*R*)-**15b**: 0.12 g (24%); $[\alpha]_D^{22}$ +303 (*c* 1, CH_3OH); ν_{max} (film) 3290, 1631; ^{1}H NMR (assignments aided by hetcor) δ 1.80–2.00 (m, 4H, 3′-H, 4′-H), 2.10 (d, J=15 Hz, 1H, 14-H), 2.63, 2.64 (2s, 6H, NMe), 2.64 (masked, 2H, 6-H, 16-H), 2.82 (s, 3H, NMe), 2.84 (masked, 1H, 15-H), 2.90 (m, 1H, 6-H), 3.20 (dm, J=15 Hz, 1H, 14-H), 3.31 (s, 3H, OMe), 3.40 (m, 2H, 5′-H), 3.50 (dd, J=7.5, 3 Hz, 1H, CH_2O), 3.70 (m, 1H, CH_2O), 3.79 (s, 3H, NMe), 4.35 (m, 1H, 2′-H), 4.70 (s, 1H, 5-H), 5.10 (s, 1H, 3-H), 5.30 (s, 1H, OH), 6.40 (s, 1H, 21-H), 7.10–7.30 (m, 3H), 7.70 (d, J=7.5 Hz, 1H, 9-H); ^{13}C NMR δ 24.6 (C-4′), 27.6 (C-3′), 29.5 (NMe), 35.9 (C-15), 38.7 (C-14), 39.2 (C-16), 42.0 (NMe), 50.2 (C-5′), 51.3, 52.5 (NMe), 54.8 (C-5), 56.7 (C-2′), 58.9 (OMe), 63.6 (C-3), 71.2, 72.9 (C-6, CH_2O), 99.1 (C-20), 108.5 (C-7), 109.1 (C-12), 118.2 (C-9), 119.2 (C-10), 121.7 (C-11), 127.6 (C-8), 135.7 (C-2), 138.3 (C-13), 140.1 (C-21), 172.1 (CO). Elution with 98:2 AcOEt–MeOH gave alcohol (1*R*,5*R*,7*S*,13*S*)-**15a**: 0.25 g (50%); $[\alpha]_D^{22}$ −172 (*c* 0.5, $CHCl_3$); mp 183°C (Et_2O–acetone–hexanes); ν_{max} (film) 3354, 1630; ^{1}H NMR (assignment aided by hetcor) δ 1.65–1.90 (m, 4H, 3′-H, 4′-H), 2.05 (m, 1H, 14-H), 2.60 (m, 1H, 6-H), 2.63, 2.66 (2s, 6H, NMe), 2.64 (masked, 2H, 16-H, 14-H), 2.80 (dd, J=11, 3 Hz, 1H, 6-H), 2.94 (s, 3H, NMe), 3.30 (br s, 1H, 15-H), 3.35 (masked, 1H, 5′-H), 3.37 (s, 3H, OMe), 3.42 (m, 2H, CH_2O, 5′-H), 3.60 (dd, J=7.5, 3.5 Hz, 1H, CH_2O), 3.76 (s, 3H, NMe), 4.45 (m, 1H, 2′-H), 4.90 (s, 1H, 5-H). 5.05 (br s, 2H, OH, 3-H), 6.65 (s, 1H, 21-H), 7.10–7.30 (m, 3H), 7.70 (d, J=7.5 Hz, 1H, 9-H); ^{13}C NMR δ 25.5 (C-4′), 27.5 (C-3′), 29.5 (NMe), 34.8 (C-15), 37.4 (C-16), 38.2 (C-14), 42.4 (NMe), 50.5 (C-5′), 51.2, 53.4 (NMe), 55.2 (C-5), 56.8 (C-2′), 59.0 (OMe), 64.4 (C-3), 71.2 (C-6), 73.3 (CH_2O), 100.0 (C-20), 109.4 (C-12), 109.5 (C-7), 118.4 (C-9), 119.5 (C-10), 122.2 (C-11), 127.5 (C-8), 135.9 (C-2), 137.6 (C-13), 140.9 (C-21), 170.6 (CO). Anal. calcd for

$C_{27}H_{38}N_4O_3 \cdot 3/4H_2O$: C, 65.10; H, 8.40; N, 11.25. Found: C, 64.89; H, 8.80; N, 10.95%.

4.18. (1*R*,5*R*,7*S*,13*S*)-4-Acetyl-13-[(dimethylamino)-methyl]-7-hydroxy-2,8-dimethyl-2,5,6,7-tetrahydro-1,5-methano-1*H*-azonino[4,3-*b*]indole, 16

MeLi (1.6 M in Et_2O, 0.9 mL, 1.5 mmol) was added to a solution of alcohol **15a** (0.1 g, 0.2 mmol) in anhydrous THF (5 mL) cooled at 0°C, and the mixture was stirred at 0°C for 4 h. After the reaction was quenched with MeOH (drops), it was poured into H_2O and extracted with AcOEt. Concentration of the organic extracts followed by flash chromatography (99:1 AcOEt–MeOH) gave **16**: 67 mg (85%); $[\alpha]_D^{22}$ −563 (*c* 1, $CHCl_3$); ν_{max} (film) 3348, 1623, 1575; ^{1}H NMR (assignment aided by hetcor) δ 2.00 (dm, J=15 Hz, 1H, 14-H), 2.18 (s, 3H, CH_3CO), 2.35 (m, 1H, 6-H), 2.58, 2.63 (2s, 6H, NMe), 2.60 (masked, 1H, 16-H), 2.75 (m, 1H, 6-H), 3.05 (m, 1H, 14-H), 3.10 (s, 3H, NMe), 3.20 (br s, 1H, 15-H), 3.75 (s, 3H, NMe), 5.10 (br s, 1H, 3-H), 5.20 (s, 1H, 5-H), 7.05–7.35 (m, 4H), 7.70 (d, J=7.5 Hz, 1H, 9-H); ^{13}C NMR δ 23.9 (CH_3CO), 29.5 (NMe), 33.8 (C-15), 36.8 (C-16), 37.1 (C-14), 43.1 (NMe), 50.2, 54.3 (NMe), 55.5 (C-5), 64.5 (C-3), 71.0 (C-6), 107.7 (C-7), 109.3 (C-12), 109.6 (C-20), 118.1 (C-9), 119.8 (C-10), 122.2 (C-11), 127.3 (C-8), 135.8 (C-2), 138.8 (C-13), 146.6 (C-21), 192.8 (CO); HRMS calcd for $C_{22}H_{28}N_3O_2$ 367.2181, found 367.2176.

4.19. Cope elimination from 16

m-CPBA (70%, 0.2 g, 0.5 mmol) was added to a solution of alcohol **16** (70 mg, 0.19 mmol) in dry CH_2Cl_2 (5 mL) at −10°C, and the mixture was stirred at −10°C for 2 h. Solid K_2CO_3 (excess) was then added, and the reaction mixture was stirred at rt for 15 min, filtered under vacuum, and concentrated. The resulting residue was chromatographed (7:3 CH_2Cl_2–MeOH). A solution of this *N*-oxide in dry toluene (20 mL) was heated (reflux) for 1 h. The solvent was removed and the residue was partitioned between H_2O and AcOEt, and extracted with AcOEt. Concentration of the organic extracts followed by flash chromatography (7:3 AcOEt–MeOH) gave alcohol **17**: 7 mg (11%).

4.20. 4-[(2*S*)-(Methoxymethyl)pyrrolidinylcarbonyl]-2,8-dimethyl-13-methylene-7-oxo-2,5,6,7-tetrahydro-1,5-methano-1*H*-azonino[4,3-*b*]indole, 18

Operating as above, from acylindoles **14** (dr 2.1:1, 0.3 g, 0.6 mmol) the methylene derivatives **18** (dr 2:1) were obtained after flash chromatography (AcOEt): 0.12 g (47%). The major diastereomer (1*R*,5*R*)-**18a** was separated by crystallization (Et_2O–acetone–hexanes): $[\alpha]_D^{22}$ −142 (*c* 1, $CHCl_3$); mp 200°C (Et_2O–acetone–hexanes); ν_{max} (KBr) 1653, 1620, 1577; ^{1}H NMR (assignment aided by hetcor) 1.75 (m, 3H, 3′-H, 4′-H), 2.10 (m, 1H, 4′-H), 2.85 (s, 3H, NMe), 2.90 (dd, J=15, 3.5 Hz, 1H, 14-H), 3.10 (dd, J=15, 7.5 Hz, 1H, 14-H), 3.20 (m, 1H, 5′-H), 3.35 (s, 3H, OMe), 3.50 (m, 3H, CH_2O, 5′-H), 3.87 (s, 3H, NMe), 3.95 (br s, 1H, 15-H), 4.45 (m, 1H, 2′-H), 5.19 (s, 1H, 5-H), 5.21, 5.30 (2s, 2H, 6-H), 6.38 (s, 1H, 21-H), 7.20–7.40 (m, 3H), 7.80 (d, J=7.5 Hz, 1H, 9-H); ^{13}C NMR δ 25.6 (C-4′), 27.8 (C-3′), 32.4 (NMe), 36.0 (C-15), 41.2 (NMe), 50.8 (C-14), 51.7 (C-5′), 56.4 (C-2′), 58.2 (C-5), 59.0 (OMe), 73.5 (CH_2O), 102.8 (C-20), 110.5 (C-12), 110.9 (C-6), 117.7 (C-7), 120.2 (C-9), 120.8 (C-10), 125.5 (C-8), 125.6 (C-11), 133.5 (C-2), 138.4 (C-13), 140.1 (C-16), 143.4 (C-21), 170.1 (CO), 197.4 (C-3). Anal. calcd for $C_{25}H_{29}N_3O_3$: C, 71.57; H, 6.96; N, 10.01. Found: C, 71.42; H, 6.96; N, 9.98%.

4.21. (1*R*,5*R*,7*S*)-7-Hydroxy-2,8-dimethyl-13-methylene-4-[(2*S*)-(methoxymethyl)pyrrolidinylcarbonyl]-2,5,6,7-tetrahydro-1,5-methano-1*H*-azonino[4,3-*b*]indole, 19

A solution of ketone **18a** (0.25 g, 0.6 mmol) in anhydrous THF (18 mL) was allowed to react with $LiBH_4$ (2 M in THF, 1.2 mL, 2.4 mmol) as described in Section 4.17. Extractive workup (AcOEt) followed by flash chromatography (99:1 AcOEt–MeOH) gave alcohol **19**: 0.2 g (80%); $[\alpha]_D^{22}$ −218 (*c* 0.5, $CHCl_3$); mp 115°C (Et_2O–acetone–hexane); ν_{max} (film) 3373, 1631, 1572; ^{1}H NMR δ 1.70, 1.90, 2.04 (3m, 5H, 3′-H, 4′-H, 14-H), 2.80 (m, 1H, 14-H), 2.89 (s, 3H, NMe), 3.37 (s, 3H, OMe), 3.55 (m, 4H, CH_2O, 5′-H), 3.77 (s, 3H, NMe), 3.85 (br s, 1H, 15-H), 4.40 (m, 1H, 2′-H), 5.05 (br s, 4H, 5-H, 3-H, 6-H), 6.59 (s, 1H, 21-H), 7.10–7.40 (m, 3H), 7.70 (d, J=7.5 Hz, 1H, 9-H); ^{13}C NMR δ 25.4 (C-4′), 27.6 (C-3′), 29.6 (NMe), 37.5 (C-15), 39.9 (C-14), 41.4 (C-22), 50.3 (C-5′), 56.8 (C-5), 58.0 (C-2′), 59.0 (OMe), 64.6 (C-3), 73.2 (CH_2O), 101.7 (C-20), 109.3 (C-7), 109.4 (C-12), 109.7 (C-6), 118.3 (C-9), 119.5 (C-10), 122.1 (C-11), 126.8 (C-8), 136.2 (C-2), 137.5 (C-13), 140.8 (C-21), 144.8 (C-16), 170.3 (CO). Anal. calcd for $C_{25}H_{31}N_3O_3 \cdot 1/2CH_2Cl_2$: C, 66.01; H, 6.95; N, 9.06. Found: C, 65.92; H, 7.07; N, 9.06%.

4.22. (1*R*,5*R*,7*S*)-4-Acetyl-7-hydroxy-2,8-dimethyl-13-methylene-2,5,6,7-tetrahydro-1,5-methano-1*H*-azonino[4,3-*b*]indole, 17

Operating as described in Section 4.18, from alcohol **19** (93 mg, 0.2 mmol) and MeLi (1.6 M in Et_2O, 1 mL, 0.63 mmol) the acetyl derivative **17** was obtained after flash chromatography (AcOEt): 40 mg (56%); $[\alpha]_D^{22}$ −633 (*c* 0.4, $CHCl_3$); mp 242°C (Et_2O–acetone–hexanes); ν_{max} (film) 3332, 1624, 1574; ^{1}H NMR δ 2.05 (dt, J=15, 2.7, 2.5 Hz, 1H, 14-H), 2.19 (s, 3H, CH_3CO), 2.50 (d, J=9 Hz, 1H, OH), 3.06 (s, 3H, NMe), 3.10 (m, 1H, 14-H), 3.77 (s, 3H, NMe), 3.92 (m, 1H, 15-H), 5.04 (s, 2H, 6-H), 5.10 (br s, 2H, 5-H, 3-H), 7.16 (s, 1H, 21-H), 7.17–7.39 (m, 3H), 7.70 (d, J=7.5 Hz, 1H, 9-H); ^{13}C NMR δ 24.2 (CH_3CO), 29.8 (NMe), 36.3 (C-15), 38.4 (C-14), 42.3 (NMe), 58.6 (C-5), 65.2 (C-3), 108.2 (C-7), 108.4 (C-20), 109.6 (C-12), 110.3 (C-6), 117.9 (C-9), 119.8 (C-10), 122.4 (C-11), 126.5 (C-8), 136.2 (C-2), 137.7 (C-13), 143.7 (C-16), 146.3 (C-21), 192.6 (CO). Anal. calcd for $C_{20}H_{22}N_2O_2 \cdot C_3H_6O$: C, 72.60; H, 7.41; N, 7.36. Found: C, 72.65; H, 7.26; N, 7.70%.

4.23. (1*R*,5*R*)-4-Acetyl-2,8-dimethyl-13-methylene-7-oxo-2,5,6,7-tetrahydro-1,5-methano-1*H*-azonino[4,3-*b*]indole, 20

MnO_2 (0.3 g, 3.4 mmol) was added to a solution of alcohol **17** (62 mg, 0.19 mmol) in anhydrous CH_2Cl_2 (18 mL) and the resulting suspension was stirred at rt for 2 days. The reaction mixture was filtered through Celite® and washed with hot CH_2Cl_2. After concentration of the filtrate, the resulting residue was chromatographed (4:6 hexanes–AcOEt) to give ketone **20**: 59 mg (95%); $[\alpha]_D^{22}$ −885 (*c* 0.5, $CHCl_3$); ν_{max} (KBr) 1665, 1587; ^{1}H NMR δ 2.13 (s, 3H, CH_3CO), 2.95 (s, 3H, NMe), 3.05 (dd, $J=15$, 2 Hz, 1H, 14-H), 3.50 (dd, $J=15$, 5 Hz, 1H, 14-H), 3.86 (s, 3H, NMe), 3.86 (masked, 1H, 15-H), 5.20 (s, 1H, 5-H), 5.22, 5.23 (2s, 2H, 6-H), 7.05 (s, 1H, 21-H), 7.20, 7.40 (2m, 3H), 7.80 (d, $J=7.5$ Hz, 1H, 9-H); ^{13}C NMR 23.9 (CH_3CO), 32.2 (NMe), 35.3 (C-15), 41.7 (NMe), 49.8 (C-14), 58.2 (C-5), 109.4 (C-20), 110.6 (C-12), 111.4 (C-6), 117.4 (C-7), 119.7 (C-9), 121.0 (C-10), 125.3 (C-8), 125.7 (C-11), 133.6 (C-2), 138.2 (C-13), 142.7 (C-16), 146.2 (C-21), 192.0 (CO), 196.9 (C-3). Anal. calcd for $C_{20}H_{20}N_2O_2\cdot 1/4H_2O$: C, 73.94; H, 6.36; N, 8.62. Found: C, 74.20; H, 6.32; N, 8.42%.

4.24. (−)-N_a-Methylervitsine 21

Me_3OBF_4 (60 mg, 0.28 mmol) was added to a solution of tetracycle **20** (62 mg, 0.19 mmol) in dry CH_2Cl_2 (2 mL) and the mixture was stirred at rt for 2 h. The solvent was removed and the resulting residue was dissolved in anhydrous MeOH (4 mL), and then treated with $NaBH_4$ at 0°C (32 mg, 0.75 mmol) for 1 h. The solvent was removed and the resulting residue was partitioned between H_2O and CH_2Cl_2 and extracted with CH_2Cl_2. Concentration of the organic extracts followed by flash chromatography (6:4 hexanes–AcOEt) gave (−)-N_a-methylervitsine **20**: 15 mg (25%); $[\alpha]_D^{22}$ −60 (*c* 0.1, $CHCl_3$); ee >99% (Chiralcel OD, 1:3 hexane–isopropanol).

Acknowledgements

Financial support from the 'Ministerio de Ciencia y Tecnología' (Spain, project BQU2000-0785) is gratefully acknowledged. We also thank the DURSI (Generalitat de Catalunya) for Grant 2001SGR00084. One of us (Y.A.) also thanks the 'Ministerio de Educación, Cultura y Deporte' for a Grant.

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