Synthesis of 20-Deethylsilicine from a Second-Generation 2-Cyano-Δ^3-piperidine Synthon

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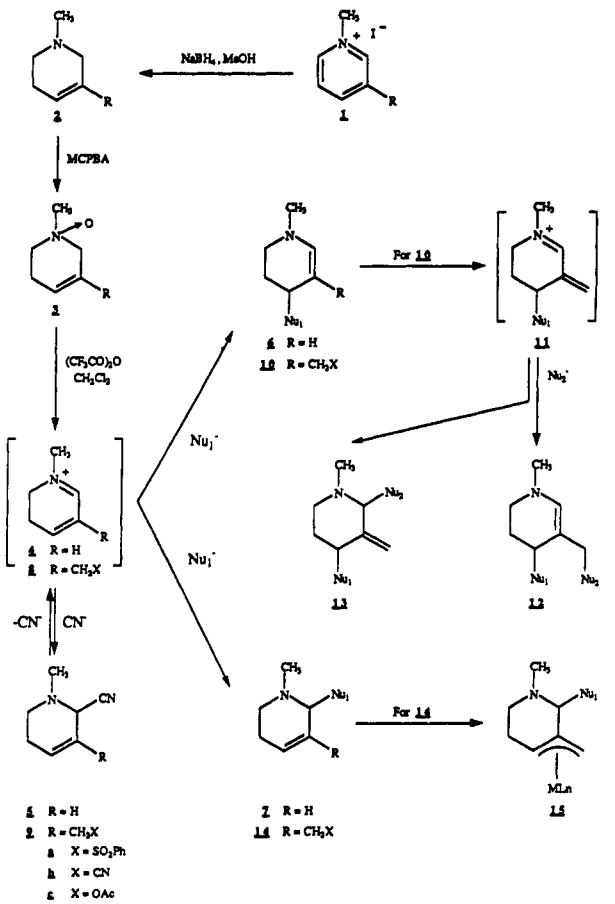
The Zn^{2+} ion mediated reaction of the 2-cyano-Δ^3-piperidine **9a** (X = $SO_2C_6H_5$) with the silyl enol ether of *Na*-methyl-2-acetylindole (**24**) led to formation of compounds **29a,b** (70%) resulting from introduction of the acetylindole moiety at the exocyclic (C-7) carbon center and migration of the phenylsulfonyl group from C-7 to C-4. In contrast, reaction of 2-cyano-Δ^3-piperidine **9b** (X = CN) with **24** gave the desired C-4 acetylindole-substituted products **36a,b** (1:1.3 mixture; 72% overall yield). Attempts to cyclize intermediates **36** to the tetracyclic enamine **27** were unsuccessful. Alternatively, the Zn^{2+}-catalyzed reaction of synthons **9a** and **9b** with indole gave the C-7 indole-substituted aminonitriles **37a,b** and **38**, respectively. These intermediates were converted to Δ^2-piperidine **40** on reaction with sodium dimethyl malonate and $AgBF_4$. Stereoselective hydrogenation of the enamine double bond in **40** furnished the required cis 3,4-disubstituted piperidine **41**, which was cyclized under acidic conditions to the target molecule, 20-deethylsilicine (**20**).

Carbon–carbon bond-forming reactions involving imines (iminium ions) and enamines play an important role in both the in vivo and laboratory synthesis of indole alkaloids.[1,2] Wenkert and co-workers, in particular, were the pioneers in the latter area showing the di- and tetrahydropyridines, generated by partial reduction or addition of carbon nucleophiles to pyridinium salts, are valuable intermediates in the synthesis of a broad range of indole compounds.[3] Similarly interested in the synthetic applications of dihydropyridines, we have introduced the notion that the reactivity of sensitive 5,6-dihydropyridinium salts **4**, generated from 1,2,5,6-tetrahydropyridine *N*-oxides **3** under modified-Polonovski reaction conditions,[4] could be harnessed in the form of their cyanide addition adducts **5** (Scheme I).[5] These stable, versatile 2-cyano-Δ^3-piperidines react regioselectively with a wide range of nucleophiles, via an elimination–addition mechanism involving **4** as an intermediate, to give either the C-4 or C-2 addition products **6** and **7**. In a continuation of our work in this area, in the present paper we describe a new generation of 2-cyano-Δ^3-piperidine synthons **9** bearing a CH_2X group at C-3 whose reactivity was adapted to the synthesis of the tetracyclic 2-acylindole compound **20**, the 20-deethyl derivative of the ervatamine alkaloid, silicine **21**.[6,7,8]

Scheme I



As illustrated in Scheme I, the essential difference expected between synthons **5** and **9** is that the 1,4-addition of a nucleophile (Nu_1) to the 5,6-dihydropyridinium salt **8** generated in situ from **9** will give an intermediate enamine **10** which is set up to undergo spontaneous elimination of X^- ion to produce the exocyclic conjugated im-

(1) See: *Enamines: Synthesis, Structure, and Reactions*; Cook, A. G., Ed.; M. Dekker: New York, 1988.

(2) For an excellent illustrative presentation of indole alkaloid biosynthesis, see: Dalton, D. A. The Alkaloids, Fundamental Chemistry; A Biogenetic Approach. In *Studies in Organic Chemistry*; Gassman, P. G., Ed.; M. Dekker: New York, 1979; Vol. 7, pp 508–628.

(3) (a) Wenkert, E. *Pure Appl. Chem.* **1981**, *53*, 1271–1276. (b) Wenkert, E.; Guo, M.; Pestchanker, M. J.; Shi, Y.-J.; Vankar, Y. D. *J. Org. Chem.* **1989**, *54*, 1166–1174 and references cited therein.

(4) (a) Grierson, D. S. *Org. React.* **1990**, *39*, 85–295. (b) Grierson, D. S.; Husson, H.-P. Polonovski and Pummerer-Type Reactions and the Nef Reaction. In *Comprehensive Organic Synthesis*; Trost, B., Fleming, I.; Pergamon: New York, 1991; Vol. 6, pp 909–947.

(5) (a) Grierson, D. S.; Harris, M.; Husson, H.-P. *J. Am. Chem. Soc.* **1980**, *102*, 1064–1082. (b) For a review on 2-cyanopiperidines, see: Rubiralta, M.; Giralt, E.; Diez, A. *Piperidine, Structure, Preparation, Reactivity and Synthetic Applications of Piperidine and its Derivatives*; Elsevier: Amsterdam, 1991; pp 225–312.

(6) (a) Bui, A.-M.; Debray, M.-M.; Boiteau, P.; Potier, P. *Phytochemistry* **1977**, *16*, 703–706. (b) Vecchietti, V.; Ferrari, G.; Orsini, F.; Pelizzoni, F.; Zajotti, A. *Phytochemistry* **1978**, *17*, 835–836. (c) Langlois, Y.; Potier, P. *Tetrahedron* **1975**, *31*, 423–428. (d) Reis, F.; Bannai, K.; Husson, H.-P. *Tetrahedron Lett.* **1976**, 1085–1088. (e) Husson, H.-P.; Bannai, K. B.; Frieire, R.; Mompon, B.; Reis, F. A. M. *Tetrahedron* **1978**, *34*, 1363–1368.

(7) Preliminary communications, see: Bettiol, J.-L.; Buck, I.; Husson, H.-P.; Grierson, D. S.; Diez, A.; Rubiralta, M. *Tetrahedron Lett.* **1991**, *32*, 5413–5416.

(8) The biogenetic numbering system is used for tetracyclic structures: LeMen, J.; Taylor, W. I. *Experientia* **1965**, *21*, 508–510.

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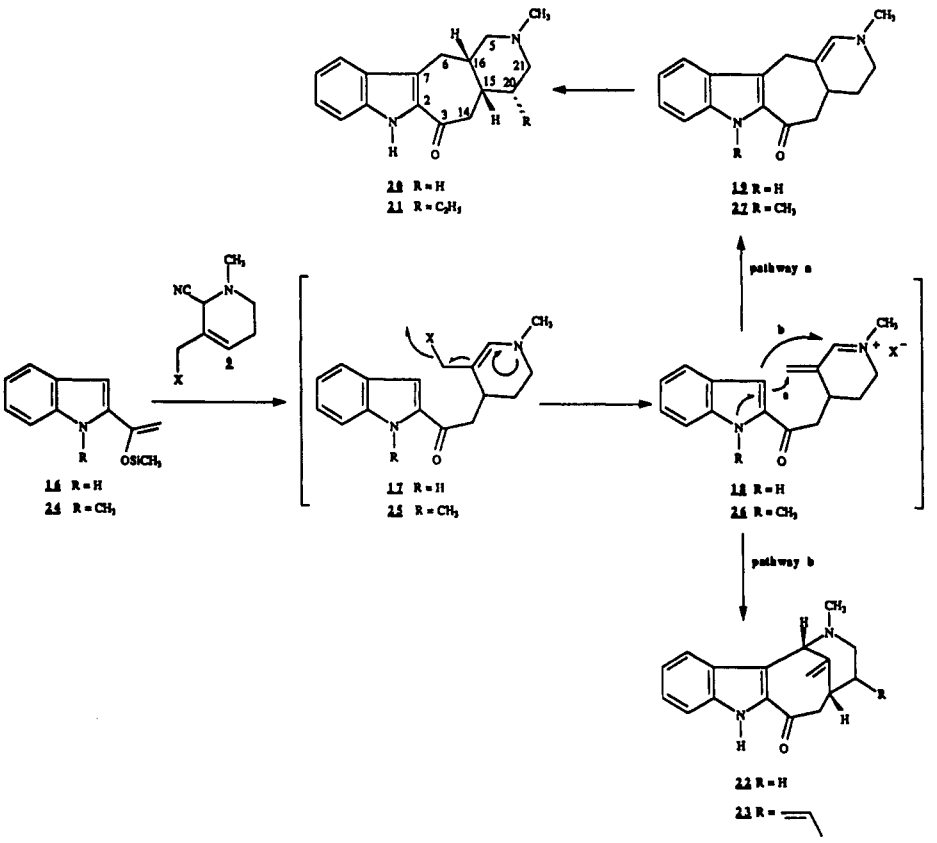
Scheme II



inium ion **11**. This species will in turn be reactive toward a second nucleophile (Nu_2) present in the medium to give either compound **12** or **13**. This consecutive or "tandem" process thus has the advantage that two substituents are added to the piperidine system in a single operation. Another attractive feature of these new synthons is that in cases where addition of Nu_1 occurs at C-2 giving **14**, further substitution at either the C-4 or the external C-7 position by Nu_2 remains possible via formation of a π-allyl palladium or molybdenum complex **15**.[9,10]

In light of this potential for synthon **9** to undergo tandem reaction with nucleophiles one can envisage a synthesis of 20-deethylsilicine **20** in two pivotal steps. This would entail the condensation of the enol silyl ether **16** of 2-acetylindole with **9** leading, via the enamine intermediate **17**, to the conjugated iminium ion **18** which cyclizes through reaction with the indole ring (Scheme II, pathway a). Subsequent stereoselective reduction of the $\Delta^{16,5}$ double bond in **19** would then give the target molecule **20**. It is interesting to note that the cyclization of **18** to **19** mimics the key step in the proposed biosynthesis of this alkaloid family and that the alternate 1,2-cyclization of **18** (Scheme II, pathway b) would provide access to the tetracyclic skeleton **22** of the biogenetically related alkaloid ervitsine **23**.[11,12] It should also be mentioned that, in principle, intermediate **17** could equally be prepared by treatment of the enamine obtained by condensing **16** with the unsubstituted cyano piperidine **5** with formaldehyde. However, reactions of this type are very problematic and hence difficult to optimize due to the inherent fragility of the Δ^2-piperidine system.[13,14] This point further underscores the interest in employing the stable aminonitrile synthon **9**, in which the CH_2X group is already present, for the synthesis of indole **20**.

Results and Discussion

In order to test whether our synthetic strategy was feasible, it was first necessary to prepare compounds **9a–c**. Aminonitrile **9b** was prepared from 3-(cyanomethyl)-pyridine (Aldrich) in four steps according to established procedure (Scheme I).[4,5] This involved quaternization of the pyridine nitrogen through reaction with CH_3I, borohydride reduction of the pyridinium salt **1b** obtained, N-oxidation of the resultant 1,2,5,6-tetrahydropyridine **2b**, and reaction of the derived N-oxide **3b** under modified-Polonovski conditions [$(CF_3CO)_2O$, CH_2Cl_2, 0 °C] with in situ trapping of the intermediate dihydropyridinium salt **8b** that is generated with cyanide ion. Compound **9a** was synthesized in an analogous fashion from 3-[(phenylsulfonyl)methyl]pyridine. This starting material was itself prepared by reaction of 3-(chloromethyl)pyridine with sodium benzenesulfinate in refluxing *n*-butanol (60%).[15] The more fragile 3-acetoxymethyl-substituted synthon **9c** was prepared by O-acetylation of the Δ^3-piperidine derived from borohydride reduction of *N*-methyl-3-(hydroxy-

(9) (a) Trost, B. M. *Tetrahedron* **1977**, *33*, 2615–2649. (b) Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385–393. (c) Tsuji, J. Allylpalladium Complexes. In *The Chemistry of the Metal–Carbon Bond*; Hartley, F. R., Patai, S., Eds.; John Wiley: Chichester, 1985; Vol. 3, pp 163–199.

(10) (a) Trost, B. M.; Braslau, R. *Tetrahedron Lett.* **1988**, 1231–1234. (b) Hansson, S.; Miller, J. F.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1990**, *112*, 9660–9661.

(11) (a) Husson, A.; Langlois, Y.; Riche, C.; Husson, H.-P.; Potier, P. *Tetrahedron* **1973**, *29*, 3095–3098. (b) Thal, C.; Dufour, M.; Potier, P.; Jaouen, M.; Mansuy, D. *J. Am. Chem. Soc.* **1981**, *103*, 4956–4957.

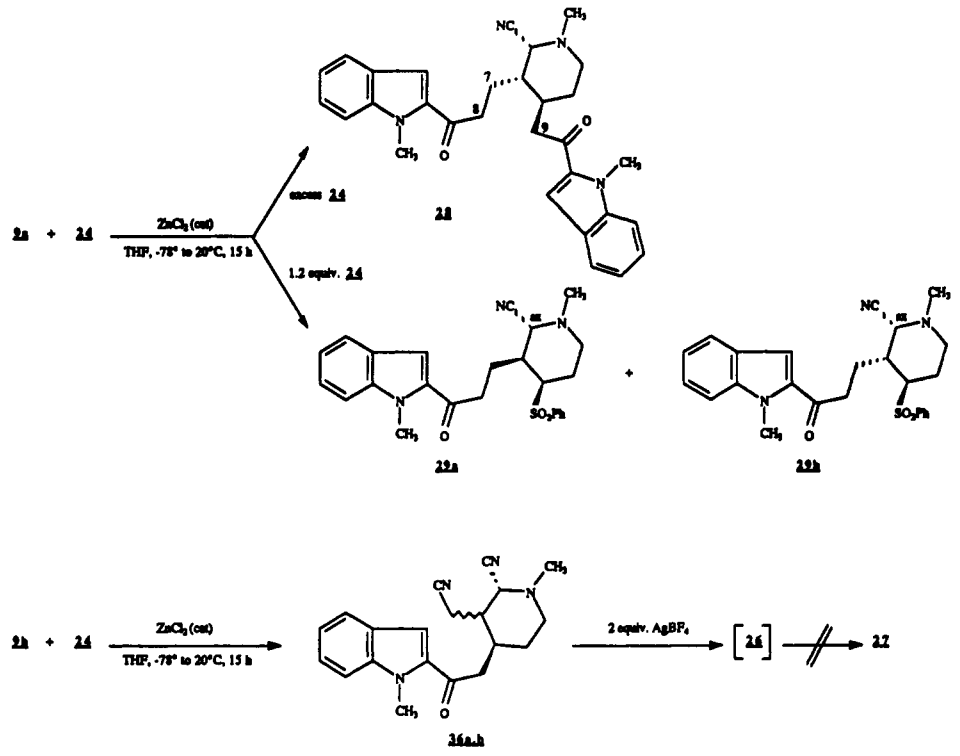
(12) Andriantsiferana, M.; Besselievre, R.; Riche, C.; Husson, H.-P. *Tetrahedron Lett.* **1977**, 2587–2590.

(13) (a) Harris, M.; Grierson, D. S.; Riche, C.; Husson, H.-P. *Tetrahedron Lett.*, **1980**, *21*, 1957–1960. (b) Grierson, D. S.; Harris, M.; Husson, H.-P. *Tetrahedron* **1983**, *39*, 3683–3694. (c) Rubiralta, M.; Marco, M. P. Bolós, J.; Trapé, J. *Tetrahedron* **1991**, *47*, 5585–5602.

(14) (a) Martinez, S. J.; Joule, J. A. *Tetrahedron* **1978**, *34*, 3027–3036. (b) Beeken, P.; Fowler, F. W. *J. Org. Chem.* **1980**, *45*, 1336–1338.

(15) Golding, S.; Katritsky, A. R.; Kucharska, H. Z. *J. Chem. Soc.* **1965**, 3090.

Scheme III



methyl)pyridinium iodide,[16] followed by N-oxidation and the modified-Polonovski–KCN trapping reactions.

With synthon **9a** in hand, we examined its reaction with the readily available *Na*-methyl indole silyl enol ether derivative **24** (Scheme III). Carrying out the reaction in THF in the presence of $ZnCl_2$ (10 mol %)[17,18] (–78 °C to room temperature) using an excess of **24** led to formation of the bis-substitution product **28** in 43% yield. This result appeared encouraging as it suggested that substitution at both the C-4 and exocyclic C-7 positions was possible and that by simply diminishing the quantity of **24** employed its reaction with the iminium ion **26** would be averted, leaving the opportunity for the desired intramolecular ring closure to occur. However, when **9a** was reacted with an approximately equimolar amount of **24** under the same conditions two new products were formed, neither one of which corresponded to tetracyclic enamine **27**. It was apparent from the parent ion at m/z 450 in the IC mass spectra of these products that they were isomers and that the cyano and phenylsulfonyl groups were present in both molecules. In the ^1H NMR spectra singlet absorptions were observed at δ 7.35–7.40 for the indole H-3, indicating that they were not cyclized. It was further deduced from 2D (^1H–^1H) experiments that the 2-acetylindole moiety was attached to C-7. In the ^{13}C spectrum of the chromatographically (Al_2O_3) less polar product **29a** (30%) the peak at δ 58.3 was assigned to the C-4 methine carbon bearing the phenylsulfonyl group and the peak at slightly lower field (δ 61.1) to the C-2 cyano-substituted center.[19] The relative stereochemistry of the three ring substituents was readily determined from the coupling constants for H-4 (δ 3.25; J_{4-5} = 12 Hz, J_{3-4} = 3 Hz) and H-2 (δ 4.10; J_{2-3} = 2 Hz), as well as from the observation of a γ-effect shift in the chemical shift for C-5. The 3,4-diequatorial structure of aminonitrile **29b** (40%) was similarly deduced from the coupling constants for the piperidine ring hydrogens in the ^1H NMR spectrum. It was thus clear from this data that, contrary to expectation, in both isomers the acetyl indole substituent was incorporated at C-7 and not at C-4. Equally unexpected was the observation that the phenylsulfonyl group had migrated from C-7 to the C-4 position in the product molecules.

At first sight, the regiochemical outcome of the reaction of **9a** with **24** appeared inconsistent with the sequence of reactions proposed in Scheme I. However, in its conception, this mechanism was founded upon our experience with the reactions of 2-cyano-Δ^3-piperidines under conditions where cyanide ion is completely removed (precipitated) from the reaction medium through complexation with metal ions ($AgBF_4$).[5] From the results of the experiments using $ZnCl_2$ it would appear that this is not the case, even though the medium was heterogeneous. Indeed, it has been shown that the reaction of cyanopiperidine **5** with Lewis acids such as Et_2AlCN leads to isomerization of the cyano group from the C-2 to the C-4 position.[20] It is probable, therefore, that in the reactions of synthon **9a** Zn^{2+} ion effects initial isomerization to **30**, via the dihydropyridinium salt **8a** (Scheme IV), and that intermediate **30** undergoes vinylogous elimination of phenylsulfinate ion producing the conjugated iminium salt **31** which reacts with the added nucleophile **24** giving **32**. Through a series of equilibria, involving **33** as an intermediate, the phenylsulfonyl and cyano groups are subsequently reintroduced at C-4 and C-2 respectively, producing the observed products **29**. Reintroduction of these groups in the opposite sense is not expected, as, to our

(16) Careful temperature control is required during the $NaBH_4$ reduction of this 3-(hydroxymethyl)pyridinium salt in order to avoid formation of significant (i.e. up to 50%) amounts of the isomeric 1,2,3,6-tetrahydropyridine.

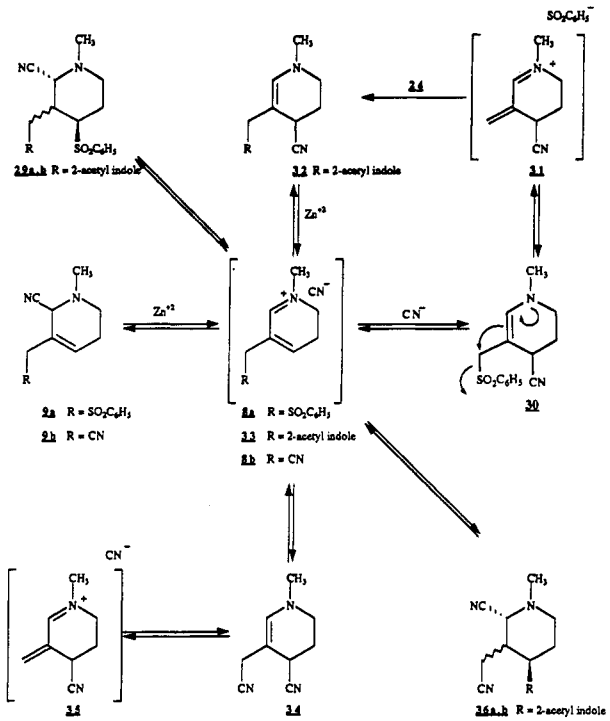
(17) Guibe, F.; Grierson, D. S.; Husson, H.-P. *Tetrahedron Lett.* **1982**, *23*, 5055–5058.

(18) Koskinen, A.; Lounasmaa, M. *J. Chem. Soc., Chem. Commun.*, **1983**, 821–823.

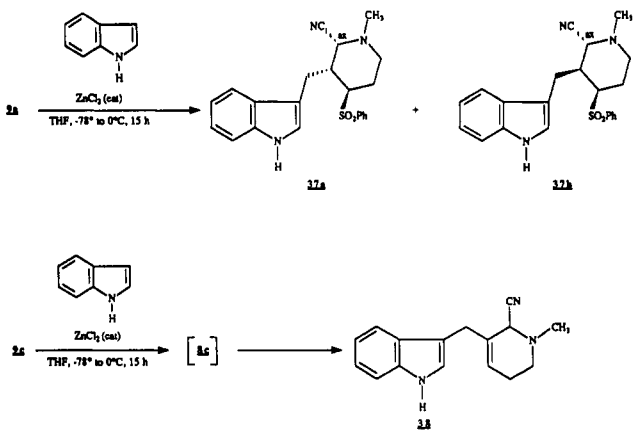
(19) Chemical proof for the presence of an α-amino nitrile function in compounds **29** and **37** was obtained through their conversion to the corresponding 2,3-disubstituted piperidines by reaction with $NaBH_4$ in methanol.

(20) Grierson, D. S.; Harris, M.; Husson, H.-P. *Tetrahedron* **1983**, *39*, 3683–3694.

Scheme IV



Scheme V



knowledge, the addition of phenylsulfinate ion to simple iminium ion does not occur. Furthermore, there are very few examples of the preparation of α-(phenylsulfonyl)-methylamines in the literature.[21-23] This would suggest that, for condensation of phenylsulfinate ion with the conjugated iminium ion **33** to be possible the cyanide addition adduct, compound **29**, must be stable with respect to equilibration under the reaction conditions employed.

From a consideration of the mechanism in Scheme IV, the C-7 cyano-substituted synthon **9b** should react with the silyl enol ether **24** preferentially at the C-4 position. This change in regiochemistry arises from the possibility for either "endo" or "exo" elimination of CN^- from the initially formed enamine intermediate **34**. As an endocyclic double bond is favored in six-membered ring systems, **34** will equilibrate back to **8b**, rather than go onto **35**, giving compounds **36** as the product of nucleophile addition. In the event that this does occur then subsequent conversion of **36** to the tetracyclic indole product **27** may also be observed. In the experiment, the reaction of **9b** with **24** catalyzed by $ZnCl_2$ stopped at the formation of the aminonitrile intermediates **36a** (C-3α) and **36b** (C-3β), isolated in a combined yield of 73% after flash column chromatography (Scheme III). The overall structure and relative stereochemistries of compounds **36** were readily determined from the coupling constants for the piperidine ring protons in the ^1H NMR spectra and from selective irradiation experiments. This result suggests that the exocyclic iminium ion **26**, if generated, reacts more effectively with the liberated cyanide ion than with the C-3 carbon of the indole ring, even though the latter reaction is an intramolecular process. The markedly diminished nucleophilicity of the C-3 carbon in 2-acyl indoles may be responsible for this phenomenon. To circumvent this problem, compound **36** was treated with 2 equiv of $AgBF_4$ in THF so as to form the iminium ion **26** irreversibly. However, attempts to subsequently cyclize this in situ generated intermediate under a variety of conditions, including the use of TsOH in refluxing $CHCl_3$, which is known to effect ring closures of this type, failed.[24] Apparently ring closure to **27** is slow with respect to decomposition of the fragile exocyclic iminium ion by other pathways.

These results required that we reconsider the synthesis of deethylsilicine **20** from the alternate viewpoint of creating the C-6–C-7 bond in the first step through reaction of synthon **9a** with indole itself (Scheme V). As hoped, the formation of the two isomeric products **37a,b** (70% combined yield) was observed in which indole was attached at C-7 and the phenylsulfonyl group was present at C-4. Key features in the ^{13}C NMR of these compounds were signals at δ 56–57 and δ 60–62 for carbons 4 and 2,[19] as well as the upfield position for C-7. The stereochemistry of **37a** was unequivocally assigned on the basis of the coupling constants for protons H-2 (J_{2-3} = 5 Hz) and H-4 (J_{3-4} = 4 Hz, J_{4-5} = 12 Hz). The axial disposition of the C-3 indolylmethyl side chain in **37b** was once again inferred from the observed γ-effect shift for the C-5 and -7 absorptions ($\Delta\delta$ 5 ppm) and from a downfield shift in the position of the C-3 methylene protons ($\Delta\delta$ 0.7 ppm) due to their 1,3-syn diaxial relationship to the lone pair of electrons on nitrogen.[25]

Extension of our study to the reaction of the 7-acetoxy-substituted amino nitrile **9c** with indole was subsequently made. Interestingly, and in spite of the fact that addition of acetate ion to iminium ions can occur,[4] the only nonpolar product formed in the reaction was the 2-cyano-Δ^3-piperidine **38**, isolated in 40% yield after column chromatography on alumina (CH_2Cl_2–heptane (1:1)). The absence of an acetate methyl proton signal, the upfield shift of the C-7 absorption relative to the starting synthon **9c**, and the presence of a broad singlet absorption at δ 5.70 in the ^1H NMR spectrum of **38** were consistent with its assigned structure.

The advantage of the latter reaction is that the allylic aminonitrile system in **38** is ideally set up to undergo condensation, in the presence of silver ion ($AgBF_4$), with

(21) (a) Reutrakul, V.; Prapansiri, V.; Panyachotipun, C. *Tetrahedron Lett.* **1984**, *25*, 1949–1952. (b) Makosa, M.; Golinski, J.; Ostrakowski, S.; Rykowski, A.; Sahasrabudhe, A. B. *Chem. Ber.* **1991**, *124*, 577–585.

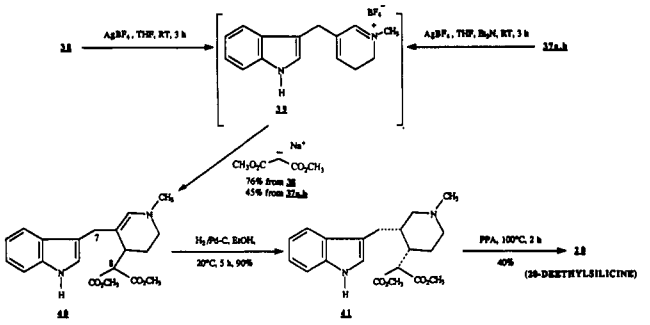
(22) In contrast, it has been shown that *N*-acyl-α-(phenylsulfonyl)-methylamines are both readily prepared and versatile intermediates in synthesis; see: Brown, D. S.; Ley, S. V.; Vile, S.; Thompson, M. *Tetrahedron* **1991**, *47*, 1329–1342.

(23) In contrast to simple enamines, the γ-phenylsulfone-substituted enaminonitrile obtained from propanal is rendered stable by the presence of the cyano group at the α-position; see: De Lombaert, S.; Ghosez, L. *Tetrahedron Lett.* **1984**, *25*, 3475–3478.

(24) Harris, M.; Grierson, D. S.; Riche, C.; Husson, H.-P. *Tetrahedron Lett.* **1980**, *21*, 1957–1960.

(25) Casy, A. F.; Dewar, G. H.; Al-Deed, O. A. A. *Magn. Reson. Chem.* **1989**, *27*, 964–972.

Scheme VI



a two-carbon "acetic acid equivalent" such as sodium dimethyl malonate.[5a] Under these conditions the relatively sensitive enamine **40** was obtained in 76% yield after flash-type chromatography on alumina (CH_2Cl_2). Pertinent NMR data for this compound include singlets at δ 3.68, 3.71, and 5.83 for the two OCH_3 group protons and H-2, as well as peaks at δ 33.2 and 135.6 for C-4 and -2, respectively.[5] Compound **40** was also prepared in 45% yield from the mixture of epimers **37a,b** by treatment with a mixture of $AgBF_4$-triethylamine and sodium dimethyl malonate. Triethylamine was added to promote tautomerization of the iminium ion liberated upon departure of the cyano group in **37** to the corresponding Δ^2-piperidine which would spontaneously lose phenylsulfinate ion to give the reactive 5,6-dihydropyridinium salt **39**. Although we were not able to determine from the NMR spectra the orientation of the dimethylmalonyl substituent in **40**, it is highly probable that this substituent is pseudoaxial so as to limit $A^{1,2}$ type interactions[26] with the adjacent bulky substituent at C-3. In any event, catalytic hydrogenation of the 2,3-double bond in **40** occured stereoselectively, giving the 3,4-cis product **41**, in which hydrogen was delivered from the face opposite the malonyl group, in 90% isolated yield. Subsequent treatment of compound **41** in polyphosphoric acid effected both ring closure and decarboxylation, completing the synthesis of 20-deethylsilicine **20**.[27] Total proton assignment of 20-deethylsilicine was carried out by ^1H–^1H homonuclear correlation (COSY).

Experimental Section

General Methods. Melting points were determined in a capillary tube on a CTP-MP 300 hot plate apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Brüker WP-200, a Varian Gemini-200, or, when indicated, on a Brüker WP-400 instrument. Unless otherwise noted, NMR spectra were registered in $CDCl_3$, and chemical shifts are expressed in parts per million (δ) relative to internal Me_4Si. IR spectra were recorded on a Perkin-Elmer 1430 spectrophotometer. Mass spectra were determined on a Hewlett-Packard 5988A or an AE1 spectrometer. Flash column chromatography was carried out on SiO_2 (silica gel 60, 40–63 mm, Macherey-Nagel) or, when indicated, Al_2O_3 (aluminum oxide 90, activity II–III, 63–200 mm, Merck). TLC was performed on SiO_2 (silica gel 60 F254, Merck) or Al_2O_3 (aluminum oxide 60, F254, neutral Typ E, Merck) and developed with the solvent described in each case for flash chromatography. The spots were located by UV light and Draggendorff reagent. Purification of reagents and solvents was effected according to standard methods. Prior to concentration under reduced pressure, all extracts were dried over anhydrous Na_2SO_4 powder. Microanalyses were performed on a Carlo Erba 1106 analyzer by the Department de Química Orgànica i Biològica, CSIC, Barcelona.

***N*-Methyl-3-[(phenylsulfonyl)methyl]-1,2,5,6-tetrahydropyridine (2a).** To a solution of 3-(chloromethyl)pyridine hydrochloride (16.5 g, 0.1 mol) in *n*-butanol (1 L) were added $NaSO_2C_6H_5$ (16.4 g, 0.1 mol) and potassium acetate (19.72 g, 0.2 mol). The reaction mixture was refluxed for 5 h, poured on ice–water, and extracted with Et_2O. The organic extracts, dried and evaporated, were flash chromatographed (CH_2Cl_2–AcOEt (6:4)) to furnish **3-[(phenylsulfonyl)methyl]pyridine** (13.98 g, 60%) as a solid: mp 128–129 °C (acetone); IR ($CHCl_3$) 1145, 1310 cm^{-1} (SO_2); ^1H NMR 4.31 (s, 2 H, CH_2), 7.27 (dd, J = 8 and 5 Hz, 1 H), 7.49 (t, J = 7 Hz, 1 H, Ar-*p*), 7.51 (d, J = 7 Hz, 2 H, Ar-*o*), 7.57 (d, J = 8 Hz, 1 H), 7.62 (t, J = 7 Hz, 2 H, Ar-*m*), 8.17 (d, J = 2 Hz, 1 H), 8.55 (dd, J = 5, 2 Hz, 1 H); MS *m/z* (relative intensity) 233 (M^+, 50), 168 (12), 93 (21), 92 (100), 77 (51), 65 (68), 51 (39).

To a solution of the above 3-[(phenylsulfonyl)methyl]pyridine (11.65 g, 50 mmol) in dry methanol (200 mL), at 0 °C, under argon atmosphere was slowly added CH_3I (4.66 mL, 0.75 mol). The reaction mixture was refluxed for 5 h and cooled to room temperature. The dispersion was filtered and the solid salt washed with dry pentane, yielding *N*-methyl-3-[(phenylsulfonyl)-methyl]pyridinium iodide (**1a**) as a white solid (16.87 g, 90%): mp 172–173 °C (acetone-CH_3OH); IR ($CHCl_3$) 1140, 1300 cm^{-1} (SO_2); ^1H NMR 2.65 (s, 3 H, NCH_3), 3.35 (s, 2 H, CH_2), 5.90 (t, J = 8 Hz, 1 H, Ar-*p*), 6.01–6.15 (m, 4 H, ArH), 6.40 (dd, J = 7 and 6 Hz, 1 H), 6.60 (d, J = 7 Hz, 1 H), 7.22 (s, 1 H, Pyr-2 H), 7.30 (d, J = 6 Hz, 1 H); ^{13}C NMR 48.2 (NCH_3), 56.5 (C-7), 127.2 (Ph-*o*), 128.1 (C-4), 128.1 (C-5), 129.3 (Ph-*m*), 129.5 (C-6), 134.4 (Ph-*p*), 137.0 (C-2); MS *m/z* (relative intensity) 233 ($M^+ - CH_3$, 23), 168 (5), 142 (42), 127 (27), 92 (100), 77 (32), 65 (33), 51 (24). Anal. Calcd for $C_{13}H_{14}INO_2S$: C, 41.70; H, 3.76; N, 3.74. Found: C, 41.58; H, 3.73; N, 3.70.

To a solution of pyridinium salt **1a** (15g, 40 mmol) in dry CH_3OH (100 mL), cooled at 0 °C, was added $NaBH_4$ (4.43 g, 0.12 mol). After being stirred for 2 h, the reaction was quenched with 10% aqueous NaCl (100 mL). The solvent was evaporated and the residue extracted with CH_2Cl_2. The organic extracts, dried and evaporated, were flash chromatographed (CH_2Cl_2–CH_3OH (95:5) to furnish tetrahydropyridine **2a** as a pale oil (6.02 g, 60%): IR ($CHCl_3$) 1600 (C=C), 1175, 1300 cm^{-1} (SO_2); ^1H NMR 2.05 (br s, 2 H, 5-H), 2.29 (s, 3 H, NCH_3), 2.39 (t, J = 3 Hz, 6-H), 2.95 (br s, 2 H, 2-H), 3.80 (s, 2 H, SCH_2), 5.45 (br s, 1 H, =CH), 7.50–7.70 (m, 3 H, ArH), 7.80 (d, J = 7 Hz, 2 H, Ar-*o*); ^{13}C NMR 25.9 (C-5), 45.1 (NCH_3), 50.4 (C-6), 56.5 (C-2), 62.1 (C-7), 124.3 (C-3), 128.1 (Ph-*o*), 128.6 (C-4), 130.0 (Ph-*m*), 133.3 (Ph-*p*), 137.6 (Ph-ipso); CIMS *m/z* 252 (M^+ + 1), 141, 111, 110, 109, 108, 94, 81, 77, 67, 51. The hydrochloride melted at 204–205 °C (acetone). Anal. Calcd for $C_{13}H_{18}ClNO_2S$: C, 54.24; H, 6.30; N, 4.86. Found: C, 53.97; H, 6.19; N, 4.51.

1-Methyl-3-(cyanomethyl)-1,2,5,6-tetrahydropyrine (2b). To a solution of pyridyl-3-acetonitrile (11.8 g, 0.1 mol) in dry toluene (100 mL) was slowly added methyl iodide (9.33 mL, 0.15 mol) at 0 °C, under argon atmosphere, and the mixture was refluxed for 45 min. The dispersion was filtered, and the white solid was washed with dry pentane and dried to give the pyridinium salt **1b** (24.71 g, 95%) which was used without further purification: IR (KBr) 2250 cm^{-1} (CN); ^1H NMR (CD_3OD) 2.60 (s, 3 H, NCH_3), 3.95 (s, 2 H, $CNCH_2$), 7.5–8.5 (m, 4 H, ArH); ^{13}C NMR (CD_3OD) 20.0 (C-7), 48.5 (NCH_3), 116.7 (CN), 122.9 (C-6), 125.7 (C-3), 134.7 (C-2), 148.2 and 148.3 (C-4 and C-5).

Operating as for the preparation of **2a**, from **1b** (20.81 g, 80 mmol) in dry CH_3OH (500 mL) and $NaBH_4$ (8.86 g, 0.24 mol), **2b** (7.61 g, 70%) was obtained as a yellow oil, after flash chromatography (CH_2Cl_2–CH_3OH (95:5)): IR ($CHCl_3$) 2385 cm^{-1} (CN); ^1H NMR 2.00–2.20 (br s, 2 H, 5-H), 2.15 (s, 3 H, NCH_3), 2.35 (t, J = 5 Hz, 2 H, 6-H), 2.65 (br s, 2 H, 2-H), 2.85 (br s, 2 H, 7-H), 5.60 (br s, 1 H, 4-H); ^{13}C NMR 22.5 (C-5), 25.3 (C-7), 44.9 (NCH_3), 50.5 (C-6), 55.7 (C-2), 116.4 (CN), 123.1 (C-4), 125.2 (C-3). Anal. Calcd for $C_8H_{12}N_2$: C, 70.55; H, 8.88; N, 20.57. Found: C, 70.47; H, 8.91; N, 20.52.

(1-Methyl-1,2,5,6-tetrahydro-3-pyridyl)methyl Acetate (2c): Method A. To a solution of 3-(hydroxymethyl)-1,2,5,6-tetrahydropyridine[7] (12.7 g, 0.1 mol) in pyridine (75 mL) were added acetic anhydride (50 mL) and 4-(dimethylamino)pyridine (1 g, 8 mmol). The reaction mixture was stirred at room temperature

(26) Johnson, F. *Chem. Rev.* **1968**, *68*, 375–412.

(27) For some examples of 2-acylindoles by intramolecular PPA cyclization see: (a) Feliz, M.; Bosch, J.; Mauleón, D.; Amat, M.; Domingo, A. *J. Org. Chem.* **1982**, *47*, 2435–2440. (b) Bosch, J.; Rubiralta, M.; Bolós, J. *Tetrahedron* **1987**, *43*, 391–396.

for 3 h, and the organic solvent was evaporated. The residue was dissolved in CH_2Cl_2 (100 mL), and the solution was washed with 5% aqueous sodium bicarbonate. The organic phase, dried and evaporated, was flash chromatographed (CH_2Cl_2–MeOH (95:5)) to give *N*-methyltetrahydropyridine **2c**[7] (11.83 g, 70%): IR ($CHCl_3$) 1735 cm^{-1} (CO); ^1H NMR 2.09 (s, 3 H, CH_3CO), 2.25 (br s, 2 H, 5-H), 2.41 (s, 3 H, NCH_3), 2.53 (2d, J_{AB} = 5 Hz, 1 H each, 2-H), 2.95 (br s, 2 H, 6-H), 4.53 (s, 2 H, OCH_2), 5.88 (br s, $W_{1/2}$ = 10 Hz, 1 H, =CH); MS *m/z* (relative intensity) 169 (M^+, 13), 168 (18), 125 (13), 110 (100), 96 (30), 57 (43); calcd mass for $C_9H_{15}NO_2$ 169.1099, found 169.1091. The hydrochloride melted at 166–167 °C (Et_2O–acetone): ^1H NMR 2.09 (s, 3 H, $COCH_3$), 2.63 (br s, 2 H, 5-H), 2.90 (s, 3 H, NCH_3), 3.24 (apparent t, *J* = 6 Hz, 2 H, 2-H), 3.64 (br s, 2 H, 6-H), 4.55 (s, 2 H, OCH_2), 6.04 (br s, 1 H, =CH); ^{13}C NMR 20.5 (CH_3CO), 21.6 (C-5), 42.4 (NCH_3), 49.6 (C-6), 52.0 (C-2), 65.3 (C-7), 124.9 (C-4), 127.0 (C-3), 171.0 (C=O). Anal. Calcd for $C_9H_{16}ClNO_2$: C, 52.55; H, 7.84; N, 6.81. Found: C, 52.62; H, 7.81; N, 6.74.

Method B. A solution of 3-(hydroxymethyl)-1,2,5,6-tetrahydropyridine[7] (13 g, 0.1 mol), Et_3N (42 mL, 0.3 mol), and Ac_2O (29 mL, 0.3 mol) in CH_2Cl_2 (150 mL) was stirred at room temperature for 15 h. The reaction mixture was then poured into ice–water, the layers were separated, and the aqueous phase was washed and extracted with CH_2Cl_2. The combined organic phases, dried and evaporated, furnished, after flash chromatography, tetrahydropyridine **2c** (13.5 g, 80%).

2-Cyano-1-methyl-3-[(phenylsulfonyl)methyl]-1,2,5,6-tetrahydropyridine (9a). To a solution of **2a** (5.34 g, 20 mmol) in dry CH_2Cl_2 (200 mL) cooled at 0 °C was slowly added 85% *m*-CPBA (4.33 g, 25 mmol). After the solution was stirred at 0 °C for 1.5 h, K_2CO_3 (5 g) was added and the suspension was stirred for an additional 1.5 h. The reaction mixture was filtered over Celite, and the organic solution was dried, evaporated, and flash filtered through Al_2O_3 (CH_2Cl_2–MeOH (95:5)) to give *N*-oxide **3a** (5.73 g, 95%): IR ($CHCl_3$) 1175, 1310 cm^{-1} (SO_2); ^1H NMR 3.30 (s, 2 H, 5-H), 3.38 (s, 3 H, NCH_3), 3.75 and 3.87 (2d, J_{AB} = 12 Hz, 1 H each, 7-H), 3.97 and 4.27 (2d, J_{AB} = 17 Hz, 1 H each, 6-H), 5.20 (d, J_{AB} = 10 Hz, 1 H, 2-H_A), 5.40 (br s, $W_{1/2}$ = 20 Hz, 1 H, 2-H_B), 7.55–7.75 (m, 2 H, Ar-*m* and Ar-*p*), 7.90 (d, *J* = 7 Hz, 1 H, Ar-*o*); ^{13}C NMR 23.4 (C-5), 57.9 (NCH_3), 61.6 (C-6), 62.2 (C-7), 68.6 (C-2), 120.3 (C-3), 128.1 (Ar-*o*), 129.2 (Ar-*m*), 129.4 (C-4), 134.0 (Ar-*p*), 138.1 (Ar-ipso).

To a solution of **3a** (4 g, 15 mmol) in dry CH_2Cl_2 (100 mL) stirred at 0 °C under argon atmosphere was slowly added trifluoroacetic anhydride (2.38 mL, 30 mmol). After 15 min of stirring an aqueous solution (50 mL) of KCN (1.95 g, 30 mmol) was added and the solution was buffered to pH = 4 by addition of citric acid. After 15 min of stirring, the reaction mixture was basified with K_2CO_3 and extracted with CH_2Cl_2. The organic layer was washed with water, dried, evaporated, and flash filtered (Al_2O_3, CH_2Cl_2) to give **9a** (2.27 g, 55%) as a solid: mp 111–112 °C (acetone); IR ($CHCl_3$) 2210 (CN), 1680 cm^{-1} (C=C); ^1H NMR 2.08 (m, 2 H, 5-H), 2.25–2.80 (m, 2 H, 6-H), 2.47 (s, 3 H, NCH_3), 3.80 (br s, 2 H, SCH_2), 4.50 (s, 1 H, 2-H), 5.60 (br s, 1 H, =CH), 7.45–7.72 (m, 3 H, Ar-H), 7.85 (d, *J* = 7 Hz, 2 H, Ar-*o*); ^{13}C NMR 25.5 (C-5), 42.9 (NCH_3), 46.0 (C-6), 55.1 (C-2), 59.8 (C-7), 115.1 (CN), 120.6 (C-3), 128.4 (C-4), 128.4 (Ph-*o*), 129.0 (Ph-*m*), 133.9 (Ph-*p*), 134.9 (Ph-ipso). Anal. Calcd for $C_{14}H_{16}N_2O_2S$: C, 60.84; H, 5.83; N, 10.13. Found: C, 60.57; H, 5.78; N, 9.97.

2-Cyano-3-(cyanomethyl)-1,2,5,6-tetrahydropyridine (9b). Operating as for the preparation of **9a**, from **2b** (6.8 g, 50 mmol), 85% *m*-CPBA (13 g, 75 mmol) in dry CH_2Cl_2 (300 mL), and K_2CO_3 (7 g) was obtained *N*-oxide **3b** (7.22 g, 95%) as a reddish oil, which was immediately used in the next step.

Operating as for the preparation of **9a**, from *N*-oxide **3b** (6.08 g, 40 mmol), trifluoroacetic anhydride (6.16 mL, 44 mmol), and an aqueous solution (50 mL) of KCN (5.2 g, 80 mmol), in dry CH_2Cl_2 (200 mL), was obtained **9b** (3.99 g, 62%) after flash filtration (Al_2O_3, CH_2Cl_2) as an orange oil: IR ($CHCl_3$) 2300 and 2350 cm^{-1} (CN); ^1H NMR 2.35–2.50 (m, 2 H, 5-H), 2.51 (s, 3 H, NCH_3), 2.70–2.85 (m, 2 H, 6-H), 3.18 and 3.32 (2d, *J* = 16 Hz, 1 H each, CH_2CN), 4.05 (s, 1 H, 2-H), 6.12 (br s, 1 H, 4-H); ^{13}C NMR 21.9 (C-5), 24.8 (C-7), 42.5 (NCH_3), 46.2 (C-6), 55.0 (C-2), 114.5 (CN), 115.7 (CN), 121.4 (C-3), 128.4 (C-4). Anal. Calcd for $C_9H_{11}N_3$: C, 67.05; H, 6.88; N, 26.06. Found: C, 66.99; H, 6.90; N, 26.01.

(2-Cyano-1-methyl-1,2,5,6-tetrahydro-3-pyridyl)methyl Acetate (9c). Operating as for the preparation of **3a**, from tetrahydropyridine **2c** (5.24 g, 31 mmol) in dry CH_2Cl_2 (200 mL), 85% *m*-CPBA (13 g, 75 mmol), and K_2CO_3 (5 g) was obtained *N*-oxide **3c** (5.55 g, 96%) as an oil after flash filtration (Al_2O_3, CH_2Cl_2–CH_3OH (95:5)): IR ($CHCl_3$) 1741 cm^{-1} (CO); ^1H NMR 2.08 (s, 3 H, $COCH_3$), 2.39 and 2.85 (2 br d, *J* = 14 Hz, 1 H each, 2-H), 3.26 (s, 3 H, NCH_3) 3.39 (m, 2 H, 5-H), 3.90 (m, 2 H, 6-H); ^{13}C NMR 20.0 ($COCH_3$), 22.3 (C-5), 57.2 (NCH_3), 62.5 (C-6), 64.9 (C-2), 67.1 (C-7), 123.1 (C-4), 127.2 (C-3), 170.0 (CO). Anal. Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.55. Found: C, 58.01; H, 8.42; N, 7.43.

Operating as the for the preparation of **9a**, from *N*-oxide **3c** (3.98 g, 21.5 mmol) in dry CH_2Cl_2 (100 mL), trifluoroacetic anhydride (4.2 mL, 30 mmol), and an aqueous solution (50 mL) of KCN (2.6 g, 40 mmol) was obtained **9c** (2.13 g, 51%) after flash filtration (Al_2O_3, CH_2Cl_2): IR (NaCl) 3400 (NH), 2200 (CN), 1730 cm^{-1} (CO); ^1H NMR 2.05 (s, 3 H, NCH_3), 2.10–2.25 (m, 2 H, 5-H), 2.45 (s, 3 H, OCH_3), 2.60–2.80 (m, 2 H, 6-H), 4.60 and 4.70 (2d, J_{AB} = 14 Hz, 1 H each, OCH_2), 4.15 (s, 1 H, CHCN), 6.05 (br s, 1 H, =CH); ^{13}C NMR 20.4 ($COCH_3$), 24.9 (C-5), 42.7 (NCH_3), 46.4 (C-6), 53.6 (C-2), 64.7 ($InCH_2$), 115.4 (CN), 127.4 (C-3), 130.0 (C-4), 170.8 (CO); MS *m/z* (relative intensity) 194 (M^+, 1), 168 (5), 151 (6), 134 (100), 119 (32), 93 (42), 42 (88). Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.83; H, 7.26; N, 14.41. Found: C, 61.82; H, 7.25; N, 14.43.

2-Acetyl-1-methylindole Trimethylsilyl Enol Ether (24). To a solution of 2-acetyl-1-methylindole (346 mg, 2 mmol) and Et_3N (0.6 mL, 4.3 mmol) in dry C_6H_6 (15 mL) was added trimethylsilyl trifluorosulfonate (425 μL, 2.2 mmol) dropwise, under argon atmosphere and at 0 °C, and the mixture was refluxed for 2.5 h. The organic phase was decanted and the solvent evaporated to yield the unstable silyl enol ether **24** (441 mg, 90%) which was used without further purification: ^1H NMR (60 MHz, CCl_4) 0.20 (s, 9 H, $SiCH_3$), 2.60 (s, 3 H, NCH_3), 4.50 (d, *J* = 8 Hz, 2 H, $=CH_2$), 6.40 (s, 1 H, In-3H), 6.90–7.50 (m, 4 H, In-H).

2-Cyano-1-methyl-3-[2-[(1-methyl-2-indolyl)carbonyl]-ethyl]-4-[[(1-methyl-2-indolyl)carbonyl]methyl]piperidine (28). To a solution of **9a** (330 mg, 1 mmol) in dry THF (10 mL) were slowly added a solution of silyl enol ether **24** (552 mg, 2 mmol) in dry THF (5 mL) and $ZnCl_2$·Et_2O (2 M, 0.1 mL, 0.2 mmol) at −78 °C and under argon atmosphere. The mixture was stirred overnight, thus allowing the temperature to reach 20 °C. The reaction mixture was poured into water and extracted with Et_2O and CH_2Cl_2. The combined organic layers, dried and evaporated, were flash chromatographed (Al_2O_3, CH_2Cl_2–heptane–ethyl acetate (5:3:2)) to furnish **28** as a foam (206 mg, 43%): IR ($CHCl_3$) 2230 cm^{-1} (CN); ^1H NMR 1.35 (qd, *J* = 12 and 4 Hz, 1 H, 5-Ha), 1.72 (dd, *J* = 12 and 3 Hz, 1 H, 5-He), 1.81 (br d, *J* = 13 Hz, 1 H, 3-Ha), 2.05–2.11 (m, 1 H, 9-H), 2.20–2.30 (m, 2 H, 4-H and 6-Ha), 2.35 (s, 3 H, NCH_3), 2.70 (br, d, *J* = 13 Hz, 1 H, 6-He), 2.75 (dd, *J* = 16 and 12 Hz, 1 H, 7-H_A), 2.95 (m, 1 H, 8-H_A), 3.15 (ddd, *J* = 16, 8, and 5 Hz, 1 H, 8-H_B), 3.25 (dd, *J* = 16 and 4 Hz, 1 H, 7-H_B), 3.95 (d, *J* = 4 Hz, 1 H, 2-He), 4.00 and 4.05 (2s, 3 H each, In-CH_3), 7.05–7.15 (m, 4 H, In-H), 7.23 and 7.24 (2s, 1 H each, In-3H), 7.30–7.40 (m, 2 H, In-H), 7.60–7.65 (m, 2 H, In-4H); ^{13}C NMR 25.1 (C-5), 31.7 (C-7), 32.2 ($COCH_2CH_2$ and In-CH_3), 34.4 (C-4), 36.7 ($COCH_2$), 42.5 (NCH_3), 43.2 ($C4CH_2CO$), 44.1 (C-3), 50.5 (C-6), 59.7 (C-2), 110.4 (In-C3), 111.5 (In-C7), 114.8 (CN), 120.9 (In-C5), 123.0 (In-C4), 125.9 (In-C3a), 126.1 (In-C6), 134.5 (In-C7a), 192.7 (CO), 192.8 (CO); CIMS *m/z* 481 (M^+ + 1), 450, 369, 307, 281, 277, 215, 201, 185, 149, 110. Anal. Calcd for $C_{30}H_{32}N_4O_2$: C, 74.97; H, 6.71; N, 11.65. Found: C, 74.89; H, 6.82, N, 11.56.

2-Cyano-1-methyl-3-[2-[(1-methyl-2-indolyl)carbonyl]-ethyl]-4-(phenylsulfonyl)piperidines (29a and b). Operating as above, from aminonitrile **9a** (1.35 g, 5 mmol), silyl enol ether **24** (1.15 g, 5 mmol), and $ZnCl_2$·Et_2O (2 M, 0.25 mL, 0.5 mmol), in dry THF (15 mL), was obtained a (1:1.3) epimeric mixture of compounds **29a** and **29b**, which was separated by flash chromatography (Al_2O_3, CH_2Cl_2–heptane–ethyl acetate (5:2:3)). **29a** (higher R_f, 675 mg, 30%): IR ($CHCl_3$) 2225 (CN), 1630 cm^{-1} (CO); ^1H NMR (400 MHz) 1.65 (br d, *J* = 12 Hz, 1 H, 5-He), 2.18 (qd, *J* = 12 and 4 Hz, 1 H, 5-Ha), 2.25 (m, 1 H, 7-H_A), 2.30 (br t, *J* = 12 Hz, 1 H, 6-Ha), 2.38 (s, 3 H, NCH_3), 2.50 (m, 1 H, 7-H_B), 2.60 (m, 1 H, 3-He), 2.80 (br d, *J* = 12 Hz, 1 H, 6-He), 3.20 (m, 2 H, $COCH_2$), 3.25 (td, *J* = 12 and 3 Hz, 1 H, 4-Ha), 4.05 (s, 3

H, In-CH_3), 4.10 (d, J = 2 Hz, 1 H, 2-He), 7.10–7.19 (m, 2 H, Ph-*m* and Ph-*p*), 7.35 (s, 1 H, In-3H), 7.40 (d, J = 3 Hz, 1 H, Ph-*o*), 7.60 (t, J = 7 Hz, 1 H, In-5H), 7.69 (t, J = 7 Hz, 1 H, In-6H), 7.72 (d, J = 7 Hz, 1 H, In-7H), 8.80 (d, J = 7 Hz, 1 H, In-4H); ^{13}C NMR 21.0 (C-5), 21.5 (C-7), 32.2 ($InCH_3$), 37.6 (C-3), 38.4 ($COCH_2$), 43.7 (NCH_3), 49.2 (C-6), 58.3 (C-4), 61.1 (C-2), 110.3 (In-C3), 111.7 (In-C7), 115.3 (CN), 120.8 (In-C5), 123.0 (In-C4), 126.0 (In-C6), 127.9 (In-C3a), 128.5 (Ph-*o*), 129.4 (Ph-*m*), 133.9 (Ph-*p*), 134.4 (In-C7a), 138.2 (Ph-ipso), 140.2 (In-C2), 193.3 (CO).

29b (lower R_f, 900 mg, 40%): ^{1}H NMR (400 MHz) 1.65 (qd, J = 13 and 3 Hz, 1 H, 5-Ha), 1.99 (m, 1 H, 7-H_A), 2.21–2.30 (m, 3 H, 3-Ha, 5-He and 6-Ha), 2.32 (s, 3 H, NCH_3), 2.69 (br d, J = 10 Hz, 1 H, 6-He), 2.80 (m, 1 H, 7-H_B), 3.03 (dt, J = 14 and 6 Hz, 1 H, CH_ACO), 3.08 (td, J = 13 and 3 Hz, 1 H, 4-Ha), 3.32 (dt, J = 14 and 6 Hz, 1 H CH_BCO), 4.03 (s, 3 H, $InCH_3$), 4.14 (d, J = 3 Hz, 1 H, 2-He), 7.14–7.20 (m, 2 H, Ph-*m* and Ph-*p*), 7.40 (s, 1 H, In-3H), 7.41 (d, J = 2Hz, 1 H, Ph-*o*), 7.51 (t, J = 7 Hz, 1 H, In-5H), 7.65 (t, J = 7 Hz, 1 H, In-6H), 7.75 (d, J = 7 Hz, 1 H, In-7H), 7.88 (d, J = 7 Hz, 1 H, In-4H); ^{13}C NMR 25.6 (C-5), 26.9 (C-7), 32.1 ($InCH_3$), 37.0 ($COCH_2$), 38.6 (C-3), 43.5 (NCH_3), 48.9 (C-6), 59.4 (C-4), 62.7 (C-2), 110.3 (In-C3), 111.6 (In-C7), 114.3 (CN), 120.7 (In-C5), 123.0 (In-C4), 125.8 (In-C6), 127.8 (In-C3a), 128.7 (Ph-*o*), 129.2 (Ph-*m*), 133.9 (Ph-*p*), 134.3 (In-C7a), 137.6 (Ph-ipso), 140.2 (In-C2), 192.7 (CO); CIMS m/z 450 (M^+ + 1), 423, 331, 308, 283, 281, 143. Anal. Calcd for $C_{25}H_{27}N_3O_3S$: C, 66.80; H, 6.05; N, 9.34. Found: C, 66.79; H, 6.09; N, 9.31.

2-Cyano-3-(cyanomethyl)-1-methyl-4-[[(1-methyl-2-indolyl)carbonyl]methyl]piperidines (36a and b). Operating as above, from cyanopiperidine **9b** (322 mg, 2 mmol), silyl enol ether **24** (552 mg, 2 mmol), and $ZnCl_2$·Et_2O (2 M, 0.1 mL, 0.2 mmol) in dry THF (10 mL) was obtained an (1:1.3) epimeric mixture of compounds **36a** and **36b** which were separated by flash chromatography (Al_2O_3, CH_2Cl_2–CH_3OH (95:5). **36a** (higher R_f, 207 mg, 31%): IR ($CHCl_3$) 2240 and 2225 cm^{-1} (CN); ^{1}H NMR (400 MHz) 1.41 (qd, J = 8 and 2 Hz, 1 H, 5-Ha), 1.75 (br d, J = 8 Hz, 1 H, 5-He), 2.11–2.35 (m, 2 H, 3-He and 4-Ha), 2.40–2.50 (m, 2 H, 6-Ha and 7-H_A), 2.89 (s, 3 H, NCH_3), 2.65 (br d, J = 8 Hz, 1 H, 6-He), 2.60 (dd, J = 10 and 2 Hz, 1 H, 7-H_B), 2.79 (dd, J = 10 and 4 Hz, 1 H, CH_ACO), 3.15 (dd, J = 10 and 2 Hz, 1 H, CH_BCO), 4.10 (s, 3 H, In-CH_3), 4.11 (d, J = 2 Hz, 1 H, 2-He), 7.25 (t, J = 7 Hz, 1 H, In-5H), 7.40 (s, 1 H, In-3H), 7.40 (t, J = 7 Hz, 1 H, In-6H), 7.40 (d, J = 7 Hz, 1 H, In-4H), 7.70 (d, J = 7 Hz, 1 H, In-7H); ^{13}C NMR 15.0 (C-7), 25.9 (C-5), 30.5 (C-4), 32.0 ($InCH_3$), 37.7 (C-3), 42.0 (CH_2CO), 43.6 (NCH_3), 50.1 (C-6), 57.8 (C-2), 110.3 (In-C3), 111.4 (In-C7), 114.8 (CN), 118.4 (CN), 120.7 (In-C5), 122.7 (In-C4), 125.5 (In-C6), 126.0 (In-3a), 134.2 (In-7a), 140.1 (In-C2), 190.7 (CO).

36b (lower R_f, 273 mg, 42%): ^{1}H NMR (400 MHz) 1.45 (qd, J = 8 and 2 Hz, 1 H, 5-Ha), 1.75 (br d, J = 8 Hz, 1 H, 5-He), 2.05–2.20 (m, 2 H, 7-H_A and 4-Ha), 2.35 (s, 3 H, NCH_3), 2.45 (m, 1 H, 3-Ha), 2.59–2.69 (m, 2 H, 6-He and 7-H_B), 2.75 (dd, J = 15 and 4 Hz, 1 H, CH_ACO), 3.00 (dd, J = 15 and 4 Hz, 1 H, CH_BCO), 3.95 (s, 3 H, $InCH_3$), 4.01 (d, J = 3 Hz, 1 H, 2-He), 7.01–7.15 (m, 1 H, In-5H), 7.20 (d, J = 7 Hz, 1 H, In-7H), 7.29–7.35 (m, 2 H, In-6H and In-3H), 7.60 (d, J = 7 Hz, 1 H, In-4H); ^{13}C NMR 18.8 (C-7), 31.0 (C-5), 32.1 ($InCH_3$), 33.1 (C-4), 40.0 (C-3), 42.1 (CH_2CO), 43.6 (NCH_3), 50.0 (C-6), 59.3 (C-2), 110.3 (In-C3), 111.7 (In-C7), 113.6 (C5-*C*N), 117.2 (C2-*C*N), 120.8 (In-C5), 122.9 (In-C4), 125.5 (In-C3a), 126.2 (In-C6), 134.6 (In-C7a), 140.2 (In-C2), 191.4 (CO); calcd mass for $C_{20}H_{22}N_4O$ 334.1789, found 334.1785.

2-Cyano-3-(3-indolylmethyl)-1-methyl-4-(phenylsulfonyl)piperidine (37a,b). To a solution of indole (468 mg, 4 mmol) in dry THF (10 mL), cooled at −78 °C under argon atmosphere, was added dropwise a solution of α-aminonitrile **9a** (1.1 g, 4 mmol) in dry THF (8 mL) followed by $ZnCl_2$·Et_2O (2 M, 0.1 mL, 0.2 mmol). The solution was stirred overnight, quenched with saturated aqueous NH_4Cl (10 mL), and extracted with Et_2O. The organic extracts, dried and evaporated, furnished a (1.5:1) mixture (1.1 g, 70%) of **37a** and **37b**, respectively, which was separated by flash chromatography (Al_2O_3, heptane–AcOEt (1:1)). **37a** (lower R_f, 660 mg, 42%): ^{1}H NMR 1.50–1.60 (m, 1 H, 5-He), 1.72 (qd, J = 12 and 5 Hz, 1 H, 5-Ha), 2.10 (s, 3 H, NCH_3), 2.23 (td, J = 12 and 3 Hz, 1 H, 6-Ha), 2.61 (dt, J = 11 and 4 Hz, 1 H, 6-He), 2.73 (m, 1 H, 3-Ha), 2.79 (d, J_{AB} = 14 Hz, 1 H, 7-H_A), 3.14 (td, J = 12 and 4 Hz, 1 H, 4-Ha), 3.49 (d, J = 5 Hz, 1 H, 2-H), 3.95 (d, J_{AB} = 14 Hz, 1 H, 7-H_B), 7.00 (d, J = 1 Hz, 1 H, In-2H), 7.02–7.20 (m, 2 H, ArH), 7.30 (d, J = 7 Hz, 1 H, ArH), 7.45–7.65 (m, 4 H, ArH), 7.90 (d, J = 7 Hz, 2 H, ArH), 8.00 (br s, 1 H, In-NH); ^{13}C NMR 26.3 (C-7), 26.8 (C-5), 39.1 (C-3), 43.2 (NCH_3), 49.2 (C-6), 58.5 (C-4), 62.6 (C-2), 111.2 (In-C3), 111.2 (In-C-7), 114.6 (CN), 119.8 (In-C5), 122.5 (In-C-4), 123.3 (In-C3a), 128.8 (Ph-*o*), 129.5 (Ph-*m*), 134.1 (Ph-*p*), 134.3 (Ph-ipso), 136.2 (In-C7a).

37b (higher R_f, 450 mg, 28%): IR ($CHCl_3$) 3500 (NH), 2250 cm^{-1} (CN); ^{1}H NMR 1.55–1.75 (m, 1 H, 5-He), 2.20 (s, 3 H, NCH_3), 2.20–2.30 (m, 1 H, 6-Ha), 2.70–2.85 (m, 2 H, 3-He and 5-Ha), 3.25–3.50 (m, 3 H, 4Ha, 6-He and 7-H_A), 3.65 (d, J = 2 Hz, 1 H, 2-He), 4.60 (d, J = 10 Hz, 1 H, 7-H_B), 6.98 (d, J = 1 Hz, 1 H, In-2H), 7.00–7.20 (m, 3 H, ArH), 7.40–7.70 (m, 4 H, ArH), 7.90 (d, J = 7 Hz, 2 H, ArH), 8.10 (br s, 1 H, In-NH); ^{13}C NMR 20.8 (C-7), 21.1 (C-5), 39.0 (C-3), 43.4 (NCH_3), 49.2 (C-6), 56.2 (C-4), 60.8 (C-2), 111.2 (In-C7), 113.5 (In-C3), 116.0 (CN), 119.2 (In-C5), 119.8 (In-C-6), 122.4 (In-C4), 128.2 (Ph-*o*), 129.3 (Ph-*m*), 129.3 (In-C3a), 134.2 (Ph-*p*), 134.6 (Ph-ipso), 136.6 (In-C7a); MS m/z (relative intensity) 393 (M^+, 6), 392 (13), 274 (9), 253 (20), 251 (18), 226 (92), 223 (86), 132 (97), 131 (100); calcd mass for $C_{22}H_{23}N_3O_2S$ 393.1506, found 393.1480.

2-Cyano-1-methyl-3-(3-indolylmethyl)-1,2,5,6-tetrahydropyridine (38). To a solution of indole (643 mg, 5.5 mmol) in anhydrous THF (10 mL) stirred at −78 °C under argon atmosphere was added 2-cyanotetrahydropyridine **9c** (1.067 g, 5.5 mmol) in anhydrous THF (8 mL). After addition of $ZnCl_2$·Et_2O (2 M, 0.3 mL, 0.6 mmol), the reaction mixture was slowly warmed to room temperature and stirred overnight. An aqueous solution (10 mL) of KCN (650 mg, 10 mmol) and citric acid (pH ~4) was added, and after stirred for 15 min, the reaction mixture was basified with K_2CO_3 and extracted with Et_2O. The organic layer, dried and evaporated, was flash chromatographed (Al_2O_3, CH_2Cl_2–heptane (1:1)) to give **38** (551 mg, 40%): IR ($CHCl_3$) 3480 (NH), 2210 (CN), 1720 cm^{-1} (CO); ^{1}H NMR 2.40 (s, 3 H, NCH_3), 3.60 (br s, 2 H, $InCH_2$), 3.90 (s, 1 H, 2-H), 5.75 (br s, 1 H, =CH), 6.97 (s, 1 H, In-2H), 7.05 (d, J = 7 Hz, 1 H, In-6H), 7.15 (t, J = 7 Hz, 1 H, In-5H), 7.30 (d, J = 7 Hz, 1 H, In-4H), 7.52 (d, J = 7 Hz, 1 H, In-7H), 8.30 (br s, 1 H, NH); ^{13}C NMR 25.2 (C-5), 30.0 (C-7), 43.1 (NCH_3), 47.3 (C-6), 55.5 (C-2), 111.1 (In-C7), 111.5 (In-C3), 116.0 (CN), 118.8 (In-C5), 119.2 (In-C4), 121.8 (In-C6), 122.9 (C-4), 124.1 (In-C2), 127.2 (In-C3a), 131.0 (C-3), 136.3 (In-C7a); MS m/z (relative intensity) 251 (M^+, 30), 223 (40), 208 (14), 197 (16), 130 (100), 107 (42), 94 (22), 77 (19), 42 (25). Anal. Calcd for $C_{16}H_{17}N_3 \cdot {}^1/_2H_2O$: C, 73.81; H, 6.91; N, 16.14. Found: C, 73.50; H, 7.29; N, 16.47.

4-[Bis(methoxycarbonyl)methyl]-3-(3-indolylmethyl)-1-methyl-1,4,5,6-tetrahydropyridine (40). Method A. To a solution of **38** (251 mg, 1 mmol) in dry THF was rapidly added $AgBF_4$ (194.7 mg, 1 mmol) at room temperature and under argon atmosphere. Then, sodium dimethyl malonate, prepared from dimethyl malonate (228 μL, 2 mmol) and NaH (48 mg, 2 mmol) in dry THF (2 mL), was added and the reaction mixture was stirred for 3 h. After addition of a 30% NH_4OH solution (50 mL) the reaction mixture was extracted with CH_2Cl_2. The organic layer was washed with 30% NH_4OH solution and with water, dried, evaporated, and flash chromatographed (Al_2O_3, CH_2Cl_2) to give enamine **40** (260 mg, 76%), as an unstable oil: IR ($CHCl_3$) 3650 (NH), 1750 (CO), 1654 cm^{-1} (C=C); ^{1}H NMR 1.75–1.95 (m, 2 H, 5-H), 2.55 (s, 3 H, NCH_3), 2.93 (dd, J = 11, 5 Hz, 1 H, 4-H), 3.32 (br, 2 H, $InCH_2$), 3.68 and 3.71 (2 s, 3 H each, OCH_3), 5.83 (s, 1 H, =CH), 6.98 (s, 1 H, In-2H), 7.10 (t, J = 7 Hz, 1 H, In-6H), 7.16 (t, J = 7 Hz, 1 H, In-5H), 7.35 (d, J = 7 Hz, 1 H, In-4H), 7.60 (d, J = 7 Hz, 1 H, In-7H), 8.15 (br, 1 H, NH); ^{13}C NMR 25.7 (C-5), 29.2 (C-7), 33.2 (C-4), 42.6 (NCH_3), 46.1 (C-6), 51.9 (OCH_3), 55.2 (COCH), 106.6 (C-3), 110.9 (In-C7), 114.1 (In-C3), 118.6 (In-C5), 119.9 (In-C-4), 121.2 (In-C6), 124.3 (In-C2), 127.5 (In-C3a), 135.6 (C-2), 137.1 (In-C7a), 168.7 (CO), 169.4 (CO); MS m/z (relative intensity) 356 (M^+, 12), 354 (5), 293 (5), 279 (6), 277 (7), 243 (12), 225 (51), 149 (32), 130 (100), 96 (25), 77 (38), 42 (25); calcd mass for $C_{20}H_{24}N_2O_4$ 356.1730, found 356.1775.

Method B. To a solution of an epimeric mixture of 2-cyanopiperidines **37a** and **37b** (393 mg, 1 mmol) in dry THF (20 mL), at room temperature under argon atmosphere, was quickly added $AgBF_4$ (194.7 mg, 1 mmol) and the black solution stirred for 5 min. Et_3N (1 mL) followed by a solution of sodium dimethyl malonate in dry THF (1 M, 2 mL) prepared as above was added, and the reaction mixture was stirred overnight. The reaction was

quenched with 30% aqueous NH_4OH (50 mL) and extracted with CH_2Cl_2. The organic phases were washed with 30% NH_4OH and water, dried, evaporated, and flash chromatographed (Al_2O_3, CH_2Cl_2) to yield **40** (135 mg, 38%), which was identified by comparison of its spectral data to the ones previously obtained.

***cis*-4-[Bis(methoxycarbonyl)methyl]-3-(3-indolylmethyl)-1-methylpiperidine (41).** A solution of enamine **40** (250 mg, 0.70 mmol) in absolute EtOH (25 mL) was hydrogenated at room temperature in the presence of 10% Pd–C (56 mg). When the absorption ceased, the catalyst was filtered off, and the solution was evaporated and flash chromatographed (CH_2Cl_2–MeOH (93:7)) to give **41** (231 mg, 92%): IR ($CHCl_3$) 3475 (NH), 1732 cm^{-1} (CO); ^1H NMR (400 MHz) 1.79 (m, 1 H, 4-H), 1.90 (td, J = 12, 3 Hz, 1 H, 5-Ha), 2.01–2.20 (m, 1 H, 5-He), 2.15 (s, 3 H, NCH_3), 2.53 (dd, J = 14, 3 Hz, 1 H, 2-Ha), 2.70 (br d, J = 11 Hz, 1 H, 6-He), 2.85 (br t, J = 11 Hz, 1 H, 6-H), 3.05 (dd, J = 14, 8 Hz, 1 H, 2-He), 3.73 and 3.75 (2 s, 3 H each, OCH_3), 3.98 (d, J = 4 Hz, 2 H, $InCH_2$), 6.90 (s, 1 H, In-2H), 7.03 (d, J = 7 Hz, 1 H, In-6H), 7.09 (t, J = 7 Hz, 1 H, In-5H), 7.30 (t, J = 7 Hz, 1 H, In-4H), 7.50 (d, J = 7 Hz, 1 H, In-7H), 8.90 (br, 1 H, NH); ^{13}C NMR 27.2 (C-5), 27.3 (C-7), 38.6 (C-4), 40.3 (C-3), 46.0 (NCH_3), 52.7 (OCH_3), 55.1 (COCH), 55.1 (C-6), 60.3 (C-2), 111.2 (In-C7), 113.4 (In-C3), 118.1 (In-C5), 119.1 (In-C4), 121.2 (In-C6), 122.4 (In-C2), 127.8 (In-C3a), 136.4 (In-C7a), 168.8 (CO), 169.6 (CO); MS m/z (relative intensity) 358 (M^+, 6), 356 (7), 327 (4), 322 (8), 297 (4), 240 (15), 227 (45), 130 (31), 96 (100). Anal. Calcd for $C_{20}H_{26}N_2O_4$: C, 67.02; H, 7.31; N, 7.81. Found: C, 66.98; H, 7.41; N, 7.80.

20-Deethylsilicine (20). A mixture of **41** (100 mg, 0.28 mmol) and PPA (2 mL) was stirred under argon atmosphere at 100 °C for 2 h. The cooled mixture was poured into ice–water, basified with potassium carbonate, and extracted with CH_2Cl_2. Evaporation of the dried (Na_2SO_4) organic extracts, followed by a flash chromatography (CH_2Cl_2–MeOH (9:1)) furnished **20** as an oil (30 mg, 40%): IR (NaCl) 1650 cm^{-1} (CO); ^1H NMR (1.54 (qd, J = 12, 4 Hz, 1 H, 20-Ha), 1.70–1.78 (m, 1 H, 15-H), 1.79 (br d, J = 12 Hz, 1 H, 20-He), 1.81 (t, J = 12 Hz, 1 H, 5-Ha), 1.91 (td, J = 12, 4 Hz, 1 H, 21-Ha), 2.12–2.21 (m, 1 H, 16-H), 2.36 (s, 3 H, NCH_3), 2.70 (dd, J = 18, 9 Hz, 1 H, 14-H), 2.72 (dd, J = 17, 9 Hz, 1 H, 6-H), 2.79 (dd, J = 18, 2 Hz, 1 H, 14-H), 2.87 (br d, J = 12 Hz, 1 H, 21-He), 3.03 (ddd, J = 12, 4, 2 Hz, 1 H, 5-He), 3.19 (dd, J = 17, 5 Hz, 1 H, 6-H), 7.11 (ddd, J = 8, 7, 2 Hz, 1 H, 10-H), 7.32 (td, J = 8, 1 Hz, 1 H, 11-H), 7.34 (dd, J = 7, 1 Hz, 1 H, 12-H), 7.60 (dd, J = 8, 1 Hz, 1 H, 9-H), 9.00 (br s, 1 H, NH); ^{13}C NMR 30.4 (C-6), 34.2 (C-16), 37.5 (C-14), 40.7 (C-15), 46.3 (NCH_3), 55.7 (C-21), 63.5 (C-5), 112.0 (C-12), 120.0 (C-10), 121.1 (C-9), 122.1 (C-7), 126.6 (C-11), 128.6 (C-8), 130.9 (C-2), 136.5 (C-13), 193.1 (CO); MS m/z (relative intensity) 268 (M^+, 85), 197 (18), 168 (44), 130 (36), 110 (53), 96 (100), 42 (99); calcd mass for $C_{17}H_{20}N_2O$ 268.1571, found 268.1583. Anal. Calcd for $C_{17}H_{20}N_2O$: C, 76.09; H, 7.51; N, 10.44. Found: C, 76.08; H, 7.53; N, 10.46.

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Registry No. **1a**, 1620-40-2; **1b**, 5562-24-3; **2a**, 143924-08-7; **2b**, 143924-17-8; **2c**, 5083-55-6; **2c** alcohol, 4684-84-8; (±)-**3a**, 143924-09-8; (±)-**3b**, 143924-18-9; (±)-**3c**, 143924-20-3; (±)-**9a**, 143924-10-1; (±)-**9b**, 143924-19-0; (±)-**9c**, 137710-66-8; (±)-**20**, 137710-70-4; **24**, 143924-11-2; **24** ketone, 16498-68-3; (±)-**28**, 143924-12-3; (±)-**29a**, 143924-13-4; (±)-**29b**, 143924-21-4; (±)-**36a**, 143924-14-5; (±)-**36b**, 143924-22-5; (±)-**37a**, 143924-15-6; (±)-**37b**, 143924-23-6; (±)-**38**, 137710-67-9; (±)-**40**, 137710-68-0; (±)-**41**, 143924-16-7; 3-(chloromethyl)pyridine hydrochloride, 6959-48-4; 3-[(phenylsulfonyl)methyl]pyridine, 1620-51-5; 3-pyridylacetonitrile, 6443-85-2; indole, 120-72-9.

Supplementary Material Available: A 2D-NMR spectrum of 20-deethylsilicine (**20**) (1 page). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Orthogonally Protected N^3-(Carboxymethyl)-L-2,3-diaminopropanoic Acids and O-(Carboxymethyl)-L-serines for Solid-Phase Peptide Synthesis

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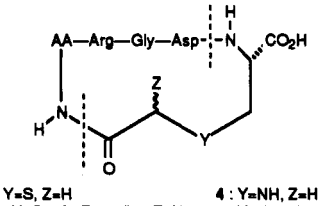
The syntheses of the orthogonally protected N^3-(carboxymethyl)-2,3-L-diaminopropanoic acids **18**, **19**, and **20** and O-(carboxymethyl)-L-serines **35** and **38** are described. All of the diaminopropanoic acids were prepared via reductive amination of the known oxazolidine aldehyde **9**. The carboxymethyl serines were prepared via O-alkylation of N-CBZ-L-serine. To enable incorporation of these amino acids into cyclic peptides, protecting group schemes were designed for compatibility with either Boc or Fmoc solid-phase peptide synthesis.

Introduction

As part of our program focused on the discovery and development of antithrombotic agents, we recently reported that cyclic thioether peptides **1** that incorporate the Arg-Gly-Asp (RGD) tripeptide sequence are potent inhibitors of fibrinogen binding to the platelet glycoprotein II_bIII_a (GP II_bIII_a) receptor.[1] In such peptides, potency in the platelet aggregation assay was sensitive to certain structural changes in the *S*-(carboxymethyl)cysteine bridge. For instance, sulfide oxidation followed by chromatographic separation gave sulfoxide **2b** (AA = D-Tyr)



1 : Y=S, Z=H
2a : Y=S—O (R config), Z=H
2b : Y=S—O (S config), Z=H
3a : Y=S, Z=alkyl
3b : Y=S, Z=phenyl
3c : Y=S, Z=naphthyl
4 : Y=NH, Z=H
5 : Y=N-acyl or N-alkyl, Z=H
6 : Y=NH, Z=alkyl
7 : Y=N-acyl or N-alkyl, Z=alkyl
8 : Y=O, Z=H

which was 5-fold more potent than **1**. Incorporation of acetyl bridge substituents (Z) such as phenyl or naphthyl gave peptides **3b** and **3c** (AA = Gly) that were six and 50 times more potent, respectively, than the unsubstituted parent peptide **1**. Based upon these results, we sought to

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