(DMSO-d_6, 60 °C) δ 1.86 (br s, 2 H), 2.77 (br t, J = 6.7 Hz, 2 H), 2.92 (br t, J = 6.7 Hz, 2 H), 3.08 (s, 6 H), 3.32–3.40 (br m, 2 H), 3.63–3.72 (br m, 2 H), 3.85 (s, 3 H), 3.90 (s, 3 H), 7.10 (s, 2 H), 7.59–7.63 (m, 3 H), 7.73–7.77 (m, 2 H); ^{13}C NMR δ 19.80, 20.51, 24.94, 51.74, 55.66, 55.74, 56.97, 61.60, 112.72, 113.16, 113.26, 118.09, 127.65, 128.91, 129.23, 129.32, 129.63, 147.72, 150.50, 161.45, 167.17. Anal. Calcd for $C_{24}H_{29}IN_2O_3$: C, 55.39; H, 5.62; N, 5.38; I, 24.39. Found: C, 55.32; H, 5.86; N, 5.32; I, 24.39.

Acknowledgment. We gratefully acknowledge the contributions of E. Boll, S. Gangell, A. Hlavac, T. McGuire, and L. McNaughton in generating spectral data and S. Clemans for his aid in analyzing these data.

Registry No. **3**, 123420-50-8; **4**, 104751-08-8; **5**(R = C_6H_5), 698-16-8; **5** (R = 4-ClC_6H_5), 28123-63-9; **5**(R = 4-$CH_3OC_6H_4$), 38435-51-7; (±)-**9a**, 133964-05-3; (±)-**9b**, 133964-02-0; (±)-**9c**, 133964-07-5; (±)-**9f**, 133910-69-7; (±)-**10a**, 133964-06-4; (±)-**10b**, 133964-03-1; (±)-*N-epi*-**10b**, 133964-08-6; (±)-**10c**, 133964-04-2; **11a**, 123420-59-7; **11b**, 123420-57-5; **11c**, 123420-58-6; **11d**, 133910-73-3; **11d**·HBr, 133910-75-5; **11e**, 123420-60-0; **11e**·HCl, 133910-76-6; **11f**, 133910-74-4; **12**, 133910-70-0; **14**, 133910-71-1; **15**, 133910-72-2; **19**, 133930-03-7.

Supplementary Material Available: Details of the X-ray crystallographic analysis of **10a** (10 pages). Ordering information is given on any current masthead page.

Synthesis of a Tetramethyl Analogue of Teleocidin

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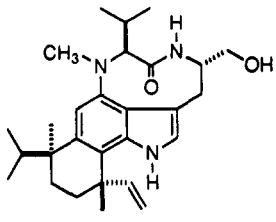
A simplified tetramethyl analogue **3** of Teleocidin B-4 (**1**) has been synthesized from dinitrotoluene **6** via indole **4**. The valine moiety of analogue **3** was provided by the coupling of (*N*-methylamino)indole **16** derived from **4** with the triflate of (*R*)-2-hydroxyvaleric acid benzyl ester, and the tryptophanyl portion was constructed by alkylation of the resulting (*S*)-*N*-valylindole **17** with ethyl (3-bromo-2-oximido)propionate to give the oxime **18**. After reduction to the diastereomeric amines **20** and **21**, closure to the 9-membered lactam–esters **24** and **23** (respectively) was accomplished using BOP. Separation and reduction of the esters led to teleocidin analogue **3** and its epimeric alcohol **25**, respectively.

The teleocidins are a family of indolactam-based alkaloids known for their tumor promoting activity.[1-3] As represented by Teleocidin B-4 (**1**), they possess the core nine-membered ring lactam present in (−)-indolactam-V (IL-V, **2**), as well as a monoterpenoid ring attached to the indole. In addition to potent tumor promotion, they are also known to activate protein kinase C (PKC),[4,5] with activities similar to that displayed by the phorbol esters.[6] Since PKC plays a major role in mediating signal transduction and cell differentiation in many cell types,[4,5] the ability to modulate PKC activity might allow the development of strategies for therapeutic intervention in many disease pathologies.



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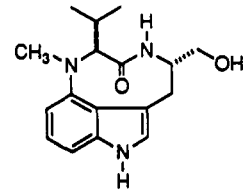

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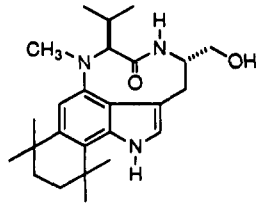

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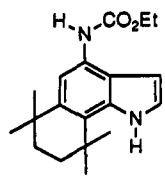

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† Department of Protein Engineering.

Toward this end, we sought to obtain a more potent and synthetically accessible IL-V analogue for biochemical studies. Analogue **3** seemed a reasonable target of this effort, wherein methyl groups would replace the isopropyl and vinyl groups of the monoterpenoid ring of teleocidin B-4 (**1**), yet the saturated six-membered ring would be retained. This would obviate the need for the synthesis of a chiral monoterpene ring appendage but would hopefully retain the level of activity exhibited by the teleocidins. Although much synthetic effort has been directed at IL-V and various 7-substituted derivatives,[7a-g] little activity regarding the synthesis of analogues of teleocidin B-4 (**1**) has been recorded.[8] We report herein the first synthesis of a teleocidin analogue retaining the saturated six-mem-

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(3) Fujiki, H.; Mori, M.; Nakayasu, M.; Terada, M.; Sugimura, T. *Biochem. Biophys. Res. Commun.* **1979**, *90*, 976.
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(7) For recent syntheses of IL-V, note: (a) Kogan, T. P.; Somers, T. C.; Venuti, M. C. *Tetrahedron* **1990**, 6623. (b) Endo, Y.; Shudo, K.; Itai, A.; Hasegawa, M.; Sakai, S. *Tetrahedron* **1986**, *42*(21), 5905. (c) deLaszlo, S. E.; Ley, S. V.; Porter, R. A. *J. Chem. Soc., Chem. Commun.* **1986**, 344. (d) Mascal, M.; Moody, C. J. *J. Chem. Soc., Chem. Commun.* **1988**, 589. (e) Kozikowski, A. P.; Sato, K.; Basu, A.; Lazo, J. S. *J. Am. Chem. Soc.* **1989**, *111*, 6228. (f) Masuda, T.; Nakatsuka, S.; Goto, T. *Agric. Biol. Chem.* **1989**, *53*, 2257. (g) Total synthesis of pendolmycin: Okabe, K.; Muratake, H.; Natsume, M. *Tetrahedron* **1990**, *46*, 5113.
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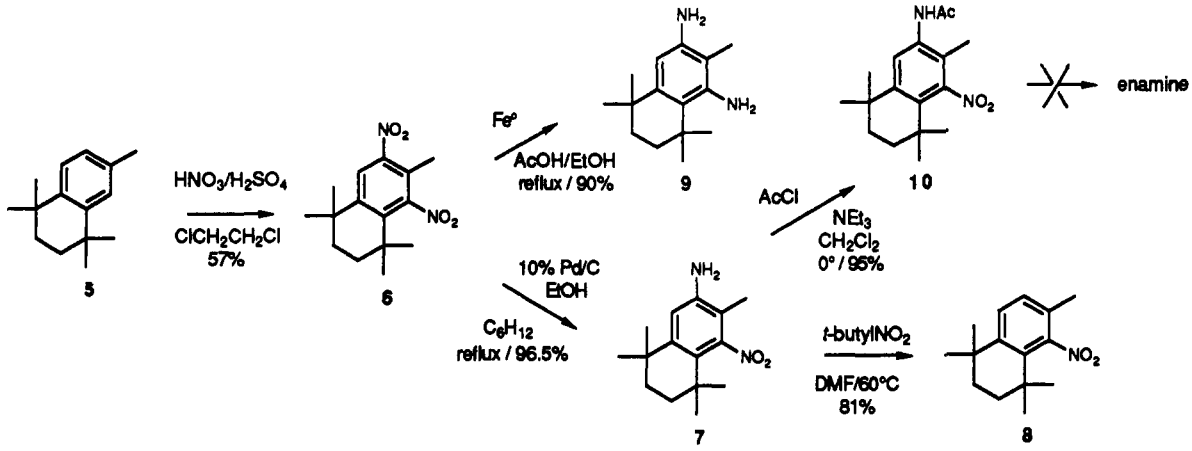
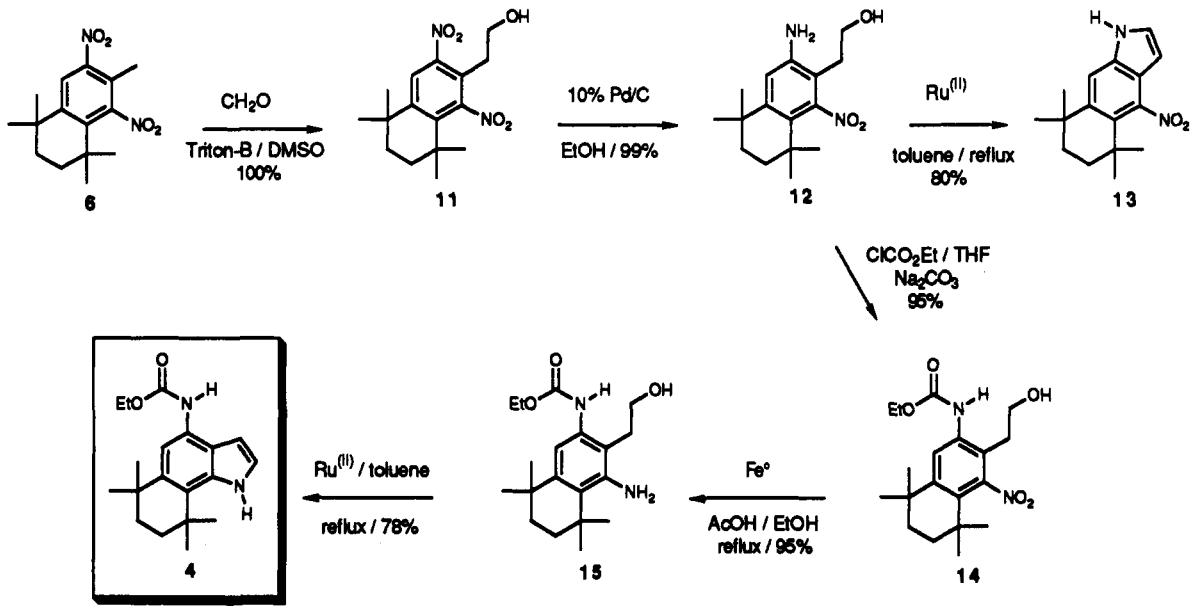
Scheme I



Scheme II. Synthesis of Indole 4



bered ring attached to the indole.

Results

Retrosynthetic analysis of analogue **3** suggested indole **4** as a key intermediate, based on literature precedent for assembly of the nine-membered ring nucleus of IL-V (**2**).[7a-g] Anticipating use of the Leimgruber–Batcho indole synthesis,[9] dinitrotetrahydronaphthalene derivative **6** was chosen as starting material. The strategy was to reduce **6** selectively at the least hindered nitro group, protect the resultant amine, and then proceed with enamine formation using the remaining nitro group for activation. Selective reduction was accomplished by the treatment of **6** with 10% Pd/C in ethanol and 1.2 equiv of cyclohexene[10] to very cleanly yield amine **7** (Scheme I).

Monoreduction was confirmed by treatment of amine **7** with *tert*-butyl nitrite in DMF[11] to yield the mononitrotetrahydronaphthalene **8**, and the absence of overreduction was confirmed by iron reduction (Fe/AcOH/EtOH/reflux)[12] of **6** to give authentic diamine **9**. The monoamine **7** was protected as its corresponding acetamide ($AcCl/NEt_3/CH_2Cl_2$), giving *N*-acetylnitroaniline **10**. Treatment of **10** with DMF–dimethyl acetal and pyrrolidine at 120 °C in DMF[9,13] (Scheme I) failed to produce the required enamine. Higher temperatures and longer reaction times led to dark, intractable mixtures. The use of carbamoyl and trifluoroacetamido nitrogen protecting groups produced no reaction, even with extended reaction times. We suspected that the nitro group in **10** is sufficiently hindered by the flanking toluene methyl and *gem*-dimethyl groups to inhibit its reaching coplanarity with the aromatic ring. This was confirmed by single-crystal X-ray analysis of **6**, which clearly shows that the nitro group oxygens are orthogonal to the plane of the aromatic ring.[14,15]

Next investigated was the selective oxidation of the least hindered amino group in diamine **9** to the corresponding nitro group, with the intent of employing the Bergman–

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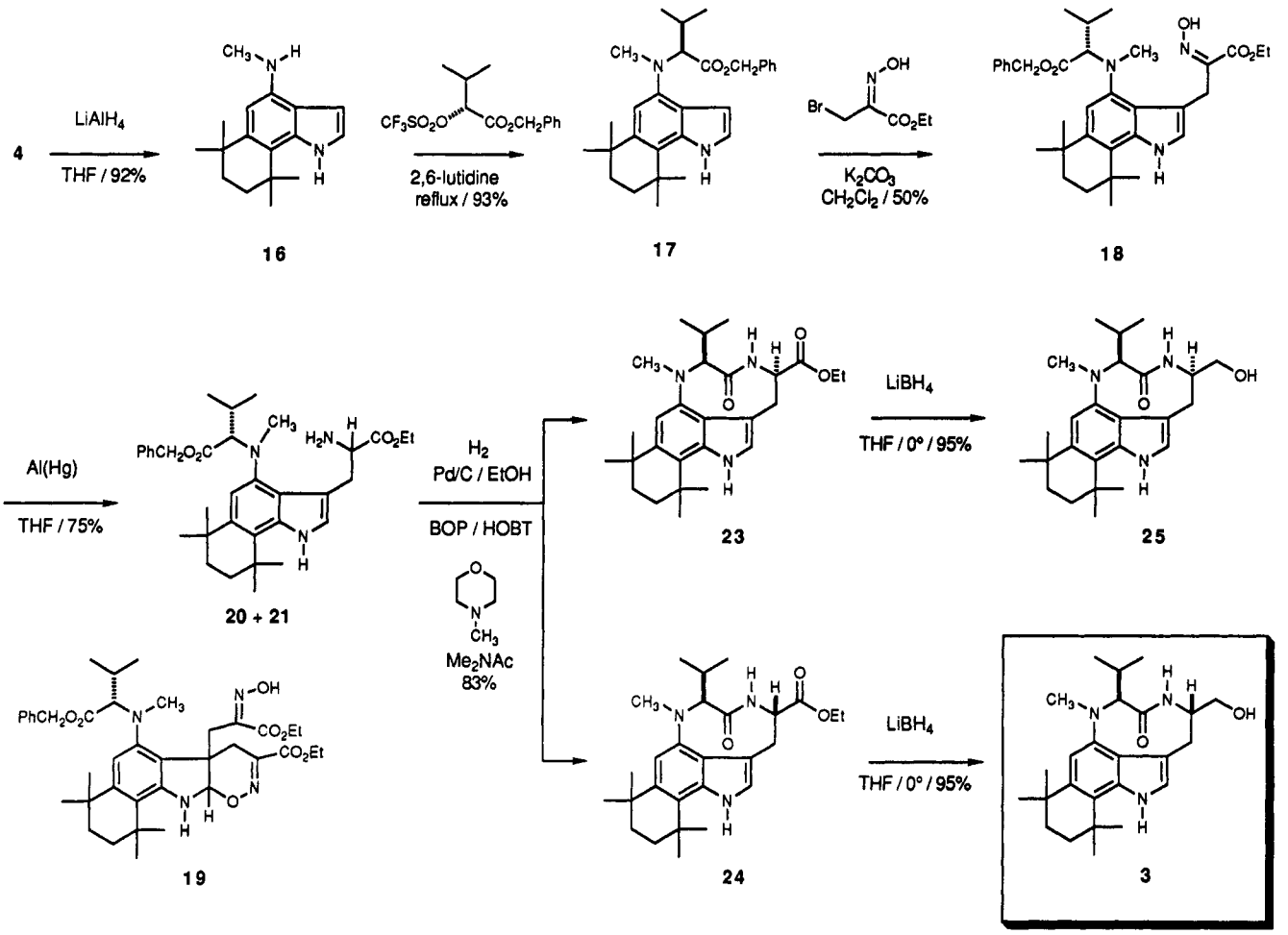
(13) Of note is the fact that compound **6**, when subjected to the Leimgruber–Batcho reaction conditions, failed to provide any of the expected enamine product.
(14) Torsional angles (in degrees): O_1–N_1–C_1–C_2, 97.58, O_1–N_1–C_1–C_6, −80.89 (see supplementary material).
(15) Johnson, C. K. *ORTEP-II*, Oak Ridge National Laboratory Report, ORNL-5138, 1976.

Scheme III. Synthesis of Teleocidins 3 and 25



Sand procedure[16,17] to prepare the desired indole. Diamine **9** was exposed to a variety of conditions known to oxidize amines to nitro compounds, including $NaBO_3$,[18] and *tert*-butyl hydroperoxide (alone, and also assisted by VO(acac)$_2$ and Ti(Oipr$_4$) catalysis).[19] In all cases, decomposition of the starting material was the only result.

An alternative route was provided by a recent report by Watanabe[20] on the preparation of indole from nitrotoluene. Pursuant to this, **6** was treated with paraformaldehyde and triton-B in DMSO.[20] The reaction was rapid, giving a quantitative yield of the 2-arylethanol **11** (Scheme II). Selective reduction of the least hindered nitro group of alcohol **11** was easily accomplished by transfer hydrogenation[10] (Pd/C, cyclohexene–ethanol) to furnish the amine **12**. None of the regioisomeric amine was detected, nor was any of the product of reduction of both nitro groups present. This was confirmed by refluxing amine **12** with tris(triphenylphosphine)ruthenium dichloride in dry toluene for 5 h[20] to yield the regioisomeric nitroindole **13**, and its subsequent comparison with indole **4** (vide supra). To complete the synthesis of indole **4**, the monoamine **12** was protected as the ethyl carbamate **14**. The carbamoyl group serves both as protective group and also as latent methyl group (through $LiAlH_4$ reduction) required in the final product. Reduction of the other nitro group was then accomplished with iron in acetic acid–ethanol to give the derivative amine **15**.[12,21] Oxidation of this amine with ruthenium(II) as above[20] in refluxing toluene gave the desired indole **4**.

With a synthesis of the required indole secured, attachment of the valine moiety and closure of the nine-membered ring remained. Reduction of **4** with lithium aluminum hydride proceeded rapidly in refluxing tetrahydrofuran to give the 4-(*N*-methylamino)indole **16**. According to precedent from a synthesis of IL-V recently reported from these laboratories,[7a] the amine was treated with the triflate of (*R*)-2-hydroxyvaleric acid[7a,22] in refluxing dichloroethane containing 2,6-lutidine to furnish the (*S*)-*N*-valylindole **17** (Scheme III). Coupling of this compound with methyl (3-bromo-2-oximido)pyruvate (Gilchrist's reagent[23]) gave, after chromatography, the oxime **18**. A small amount (ca. 5%) of a more polar compound was also isolated which was tentatively assigned structure **19** based on its proton NMR spectrum, and also based on similar behavior for this reagent that has been observed by others.[7g,23] Reduction of oxime **18** with aluminum amalgam furnished the diastereomeric amines **20** and **21**. Although these amines could be separated, the mixture was hydrogenolyzed to expose the carboxyl group

(16) Bergman, J.; Sand, P. *Org. Synth.* **1987**, *65*, 146.
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(21) In all cases, the iron–acetic acid–ethanol system proved to be the only method effective in reducing the more hindered nitro group.
(22) (a) Kock, P.; Nakatani, Y.; Luu, B.; Ourisson, G. *Bull. Soc. Chim. Fr.* **1983**, *11*, 189. (b) Feenstra, R. L.; Stokkingreef, E. H. M.; Nivard, R. J. F.; Ottenheijm, H. C. J. *Tetrahedron Lett.* **1987**, *28*, 1215.
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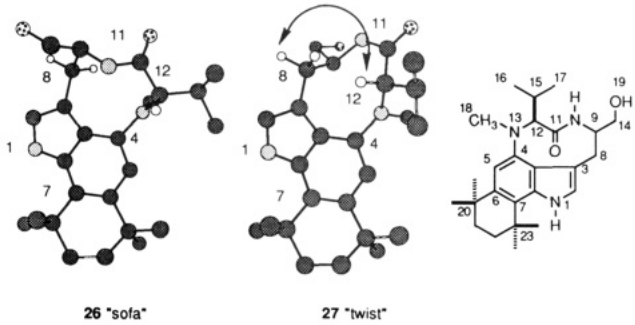

Figure 1. Numbering convention and three-dimensional representations of trans amide "sofa" structure **26** and cis amide "twist" structure **27**. Arrow indicates significant NOE interactions.

(Pd–C/H_2/ethanol), giving the very polar and air-sensitive amino acid **22** as a foam. This amino acid was not characterized but was immediately treated with BOP, HOBT, and *N*-methylmorpholine in dimethylacetamide[7a,24] to give (in a 1:1 ratio) the diastereomeric nine-membered lactams **24** ($[\alpha]^{25}_D = -120°$ (*c* 0.5, $CHCl_3$)) and **23** ($[\alpha]^{25}_D = -222°$ (*c* 0.5, $CHCl_3$)), which could be easily separated by flash column chromatography.

The less polar lactam **24** was an oil that demonstrated the presence of two conformers in the ^1H NMR (vide supra). The more polar lactam **23**, however, displayed a distinct and well-resolved ^1H NMR spectrum. Lactam **23** was highly crystalline, allowing its structure and stereochemistry to be verified by single-crystal X-ray analysis as (−)-(*S*,*R*)-**23** (Scheme III). It follows that the stereochemistry for lactam **24** must therefore be (−)-(*S*,*S*)-**24** as shown (Scheme III).

The ring-closure reaction deserves further comment. Based on precedent in the IL-V literature,[7a-f] epimerization of both the amino esters **20** and **21** and also the cyclic lactams **23** and **24** should be possible. Moreover, this epimerization could occur during the coupling reaction. To determine whether epimerization during ring closure was occurring, the amino esters **20** and **21** were separated, and each was subjected to the conditions for lactamization. Lactams **23** and **24** (respectively) were each isolated without any detectable amounts (HPLC, NMR) of the corresponding epimers. Finally, it was possible to epimerize the more polar lactam **23** to give a 2:1 mixture of **24**/**23**, as determined by HPLC. In this way, the more desirable lactam **24** could be obtained by recycling **23** through the epimerization reaction.

Finishing the synthesis required simple reduction of each of the esters to give the corresponding alcohols. This was accomplished by treatment of lactams **23** and **24** with $LiBH_4$ in tetrahydrofuran[25] (Scheme III), reactions that proceeded quite smoothly and without any apparent epimerization (HPLC/NMR), to give the alcohols **25** ($[\alpha]^{25}_D = -168°$ (*c* 0.5, $CHCl_3$)) and **3** ($[\alpha]^{25}_D = -212°$ (*c* 0.5, $CHCl_3$)), respectively.

Discussion

The more polar diastereomeric alcohol **25** demonstrated the presence of a single conformer, giving a well-resolved proton NMR allowing identification and assignment of all resonances and couplings. The less polar diastereomeric alcohol **3**, on the other hand, demonstrated the presence of two conformers in the ratio 3:1 (^1H NMR). This behavior is referred to as "sofa/twist," and has previously been observed in the teleocidin–olivoretin systems.[8-26] To determine which conformer predominates in this mixture, and to confirm its structure, 2D COSY and ROESY analyses were performed. Examination of models (Figure 1)[27] reveals two possible configurations for the amide bond, i.e. cis vs trans. The cis configuration, otherwise previously referred to as the "twist" conformer, should clearly give cross-peaks for the resonances assigned to the methine proton of the valine residue (position 12, Figure 1) and the methylene protons at position 8. These resonances were located based on their couplings demonstrated in the COSY spectrum. The major conformer in the proton spectrum of **3** gives a doublet at ca. 4.3 ppm (valine methine), which exhibited a cross peak with the A part of an AB quartet (methylene at position 8) at ca. 3.1 ppm in the ROESY[28] spectrum. This observation confirms the close proximity of these two protons predicted by modeling, which can occur only in the cis-amide "twist" structure[26] (**27**, Figure 1). Similar observations have previously been made in the case of IL-V.[26] Cross-peaks were also observed between the aromatic proton at position 5 and the methyl groups on the monoterpene ring, as well as the valine isopropyl methyl groups at positions 16 and 17. In addition, a significant interaction exists between the proton at position 1 (indole NH) and the methyl groups in proximity on the saturated six-membered ring attached to the indole. The minor conformer in the spectrum of alcohol **3** demonstrates no cross-peaks for any of the 9-membered ring protons, thus indicating it to be the trans-amide "sofa" structure **26**.[26]

Table I. [^{3}H]PDBU Binding Data for PMA, Indolactam-V, 7-Octylindolactam-V, Teleocidin 3, and Teleocidin 25

	IC_{50} (nM)	% inhibition at 10 μM
indolactam-V (**2**)	119	99
PMA (**29**)	1.3	100
teleocidin (**3**)	3.4	100
teleocidin (**25**)	4500	67
7-octyl-ILV (**30**)	0.9	100

[^{3}H]PDBU Binding Data. Teleocidins **3** and **25** were evaluated in a standard [^{3}H]PDBU (tritiated phorbol-12,13-dibutyrate, **28**) competitive binding assay.[29] The results, shown in Table I, indicate that compared with PMA (phorbol-12-myristoyl-13-acetate, **29**), indolactam-V, **2**, and 7-octylindolactam-V, **30**, all known tumor promoters, teleocidin **3** showed potent in vitro binding capability, while teleocidin **25** (as expected) showed a significantly lower level of binding.

In summary, simplified teleocidin analogue **3** has been prepared and has been shown to possess activity comparable to other known tumor promoters. The synthetic route discussed above should provide ready access to this and other analogues for biochemical studies.

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(27) Structures **26** and **27** were drawn using Chem 3D. Both **26** and **27** were obtained from MM2 calculation of the minimum energy conformations of teleocidin B-4 (**1**), replacement of the 20-β-isopropyl and 23-α-vinyl groups in **1** with methyl groups, and recalculation of minimum energy conformation using the QCPE Program No. 395; see: Allinger, N. L.; Sprague, J. T. *J. Am. Chem. Soc.* **1973**, *95*, 3893. Kao, J.; Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 975.

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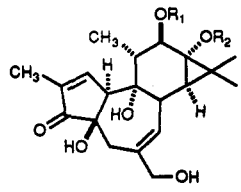
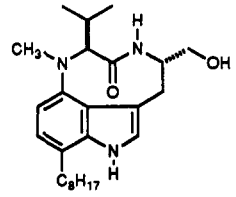


28: $R_1 = R_2 = CO(CH_2)_2CH_3$



30

29: $R_1 = CO(CH_2)_{12}CH_3$, $R_2 = Ac$

Experimental Section[30]

1,2,3,4-Tetrahydro-1,1,4,4,6-pentamethylnaphthalene (5).[31] A stirred solution of 2,5-dichloro-2,5-dimethylhexane[32] (188.0 g, 0.84 mol) in dry $PhCH_3$ (3 L) under a drying tube ($CaCl_2$) was treated, in portions, with $AlCl_3$ (13.0 g, 10 mol %) (**Caution!** *Extreme care should be exercised in the addition; the evolution of HCl gas from this mixture is rapid, vigorous, and often unpredictable*), and the solution was refluxed for 12 h. The solution was then cooled to room temperature and poured over ice. The layers were separated, and the organic phase was washed twice with 10% aqueous HCl, water, and brine. The aqueous phase was back-extracted with 3 × 50 mL of $PhCH_3$ and 3 × 50 mL of Et_2O, and the combined organic layers were dried (Na_2SO_4) and concentrated to an oil. Bulb-to-bulb distillation of the oil yielded 168 g (99%) of **5** as a colorless solid: mp 28–30 °C; bp 90 °C (1.5 mmHg) (lit.[31] 75 °C (0.5 mmHg)); ^1H NMR δ 7.20 (d, J = 9 Hz, 1 H, Ar*H*), 7.10 (s, 1 H, Ar*H*), 6.94 (d, J = 9 Hz, 1 H, Ar*H*), 2.29 (s, 3 H, ArCH_3), 1.66 (s, 4 H, CH_2CH_2), 1.26 (s, 12 H, CH_3); ^{13}C NMR δ 144.60, 141.77, 134.69, 127.96, 127.50, and 127.38 (Ar), 35.20 and 35.14 (CH_2CH_2), 34.09 and 33.87 ($C(CH_3)_2$), 31.91 and 31.84 ($C(CH_3)_2$), 21.11 (ArCH_3); IR (neat) 2950, 1490, 1420, 1370, 821 cm^{-1}; MS (EI) m/e (relative intensity) 202 (17, M^+), 187 (55, $M^+ - CH_3$). Anal. Calcd for $C_{15}H_{22}$: C, 89.03; H, 10.97. Found: C, 88.67; H, 10.73.

1,2,3,4-Tetrahydro-1,1,4,4,6-pentamethyl-5,7-dinitronaphthalene (6).[31] A solution of **5** (60 g, 0.296 mol) in $ClCH_2CH_2Cl$ (100 mL) was added dropwise over 1 h to a mechanically stirred mixture of concentrated sulfuric acid (400 mL), fuming nitric acid (75 mL), and $ClCH_2CH_2Cl$ (200 mL) at 0 °C (ice bath). After the addition was complete, the resulting dark mixture was stirred for 2 h at 0 °C and then carefully poured over ice (**Caution**: *considerable fuming due to the evolution of NO_2 occurs. This procedure should be performed in an efficient fume hood, and proper gloves and eye protection should be worn*). The phases were separated, and the upper phase (organic) was washed with water, saturated aqueous $NaHCO_3$, and brine. The acid phase was neutralized with solid Na_2CO_3 to pH 8 (**Caution**: *spattering and fuming may occur*) and was extracted exhaustively with CH_2Cl_2 and Et_2O. The combined organic layers were dried ($MgSO_4$) and concentrated to a dark oil. The oil was dissolved in boiling EtOH and allowed to cool to room temperature, and the crystals that had formed were collected, washed with cold ethanol, and dried under reduced pressure to yield 49 g (57%) of **6**: mp 110–111 °C (large plates/EtOH[33]); ^1H NMR δ 7.94 (s, 1 H, Ar*H*), 2.29 (s, 3 H, ArCH_3), 1.74 (AB q, J = 6 Hz, 4 H, CH_2CH_2), 1.32 (s, 12 H, $C(CH_3)_2$); ^{13}C NMR δ 152.59 and 148.04 ($ArNO_2$), 147.41, 140.35, 124.34 and 122.50 (Ar), 37.67 (CH_2CH_2), 35.29 and 35.07 ($C(CH_3)_2$), 32.29 and 28.52 ($C(CH_3)_2$), 13.61 (ArCH_3); IR (Nujol) 2800, 1480, 750 cm^{-1}; MS (EI) m/e (relative intensity) 292 (45, M^+), 277 (100, $M^+ - CH_3$), 235 (28, $M^+ - C_4H_9$). Anal. Calcd for $C_{15}H_{20}N_2O_4$: C, 61.61; H, 6.93; N, 9.59. Found: C, 61.64; H, 6.93; N, 9.53.

7-Amino-1,2,3,4-tetrahydro-1,1,4,4,6-pentamethyl-5-nitronaphthalene (7). A solution of **6** (74.0 g, 0.253 mol) and 10% Pd/C (27 g) in absolute ethanol (1 L) was heated to gentle reflux under argon. Cyclohexene (28.0 mL, 0.298 mol) was then added slowly dropwise over 1 h, and the resulting mixture was refluxed for 12 h. The suspension was then filtered hot through a Celite pad, and the pad was washed with several portions of EtOAc. The filtrate was allowed to cool to room temperature, and the crystals that formed were collected and washed with cold EtOH. The filtrate was concentrated, and additional crystals were collected. This procedure was repeated three times to give a combined yield from four crops of 64.0 g (96.5%) of amine **7** as bright yellow plates: mp 209–210 °C; ^1H NMR δ 6.74 (s, 1 H, Ar*H*), 3.64 (br s, 2 H, exch, NH_2), 1.92 (s, 3 H, ArCH_3), 1.65 (m, complex, 4 H, $C(CH_3)CH_2CH_2$), 1.27 (s, 6 H, $C(CH_3)_2$), 1.25 (s, 6 H, $C(CH_3)_2$); ^{13}C NMR δ 152.34 (Ar), 145.74 (Ar), 143.00 (Ar), 124.66 (Ar), 115.06 (Ar), 112.18 (Ar), 38.33 and 34.32 ($C(CH_3)_2CH_2$), 34.61 and 33.84 ($C(CH_3)_2$), 32.58 and 29.10 ($C(CH_3)_2$), 11.85 (ArCH_3); MS (EI) m/e (relative intensity) 262 (40, M^+), 247 (100, $M^+ - CH_3$). Anal. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.66; H, 8.46; N, 10.68. Found: C, 68.61; H, 8.56; N, 10.66.

1,2,3,4-Tetrahydro-1,1,4,4,6-pentamethyl-5-nitronaphthalene (8). A solution of **7** (150 mg, 0.57 mmol) in DMF (2 mL) was added slowly, dropwise, to a mixture of *tert*-butylnitrite (0.2 mL, 1.67 mmol) in DMF (10 mL) at 60 °C. After 1 h, TLC revealed the absence of amine **7** (R_f 0.2 in C) and the presence of naphthalene **8** (R_f 0.8 in C). The solution was cooled and concentrated to give 100 mg (81%) of **8** as a waxy solid: mp 57–59 °C; ^1H NMR δ 7.34 (dd, J = 1, 6 Hz, 1 H, Ar*H*), 7.06 (d, J = 6 Hz, 1 H, Ar*H*), 2.16 (s, 3 H, ArCH_3), 1.68 (m, complex, 4 H, $C(CH_3)_2CH_2$), 1.31 (s, 6 H, $C(CH_3)_2$), 1.26 (s, 6 H, $C(CH_3)_2$); ^{13}C NMR δ 151.85 (Ar), 145.22 (Ar), 134.71 (Ar), 128.93 (Ar), 128.60 (Ar), 127.98 (Ar), 38.17 and 34.23 ($C(CH_3)_2CH_2$), 34.72 and 34.64 ($C(CH_3)_2$), 32.60 and 28.97 ($C(CH_3)_2$), 17.13 (ArCH_3); MS (EI) m/e (relative intensity) 247 (40, M^+), 232 (100, $M^+ - CH_3$). Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.83; H, 8.56; N, 5.67. Found: C, 73.17; H, 8.85; N, 5.65.

5,7-Diamino-1,2,3,4-tetrahydro-1,1,4,4,6-pentamethylnaphthalene (9). A solution of **6** (20.0 g, 0.068 mol), iron powder (20.0 g, 0.357 mol, −395 mesh), EtOH (100 mL), and glacial AcOH (100 mL) was refluxed for 18 h with vigorous stirring. TLC revealed the absence of the starting dinitro compound (R_f 0.95 in A), the absence of intermediate **7** (R_f 0.75 in A), and the presence of diamine **9** (R_f 0.35 in A), which stained reddish-orange. The solution was filtered hot through a Celite pad, and the pad was washed with several portions of EtOAc. The filtrate was concentrated to a syrup, which was partitioned between EtOAc and saturated aqueous Na_2CO_3. The two layers were filtered through a Celite pad to remove iron residue,[34] and the phases were separated. The organic phase was washed with water and brine, dried (K_2CO_3), filtered, and concentrated to an oil, which crystallized on standing: mp 57–59 °C (14.0 g (90%) of colorless crystals/CH_2Cl_2–hexanes); ^1H NMR δ 6.25 (s, 1 H, Ar*H*), 3.61 (br s, 4 H, exch, ArNH_2), 1.95 (s, 3 H, ArCH_3), 1.63 (m, complex, 4 H, $C(CH_3)_2CH_2$), 1.41 (s, 6 H, $C(CH_3)_2$), 1.24 (s, 6 H, $C(CH_3)_2$); ^{13}C NMR δ 144.62 (Ar), 143.65 (Ar), 142.29 (Ar), 120.10 (Ar), 106.19 (Ar), 105.39 (Ar), 39.61 and 34.96 ($C(CH_3)_2CH_2$), 34.46 and 33.11 ($C(CH_3)_2$), 32.18 and 28.31 ($C(CH_3)_2$); MS (EI) m/e (relative intensity) 232 (28, M^+), 217 (100, $M^+ - CH_3$). Anal. Calcd for $C_{15}H_{24}N_2$: C, 77.52; H, 10.42; N, 12.06. Found: C, 77.58; H, 10.55; N, 12.08.

7-(*N*-Acetylamino)-1,2,3,4-tetrahydro-1,1,4,4,6-pentamethyl-5-nitronaphthalene (10). A solution of amine **7** (15.0 g, 0.057 mol) in CH_2Cl_2 (250 mL), Et_2O (250 mL), and NEt_3 (8.0 mL, 0.057 mol) was cooled to 0 °C under argon and treated with acetyl chloride (4.0 mL, 0.057 mol). The resulting suspension was

(30) Thin-layer chromatography was performed using Analtech Silica gel GF plates. Developing solvent systems used were as follows: system A, 1:1 EtOAc–hexanes; system B, 1:3 EtOAc–hexanes; system C, 1:9 EtOAc–hexanes. Staining was accomplished with a stock solution mixture of 28 g of ammonium molybdate and 6 g of ceric sulfate in 500 mL of 10% aqueous H_2SO_4. Mass spectra were provided by the Protein Chemistry Department, Genentech, Inc., and elemental analyses were performed by Oneida Research Services, Inc., Whitesboro, NY.

(31) Wood, T. F.; Easter, W. M.; Carpenter, M. S.; Angiolini, J. *J. Org. Chem.* **1963**, *28*, 2248.

(32) Bruson, H. A.; Kroeger, J. W. *J. Am. Chem. Soc.* **1940**, *62*, 36. This material was recrystallized from ethanol and dried in vacuo prior to use.

(33) Reference 31 records the preparation of tetrahydronaphthalene **5** and refers to a general procedure for the nitration of **5** and similar compounds, but does not report the characterization of dinitrotoluene **6**.

(34) In duplicate runs, the organic and aqueous phases formed an emulsion, which was efficiently separated by spinning down the suspension on a Sorvall centrifuge at 5000 rpm for 10 min and decanting the organic and aqueous phases from the solid residue.

stirred for 1 h at 0 °C, then washed with water and brine, dried ($MgSO_4$), and concentrated. The resulting solid was recrystallized from CH_2Cl_2/hexanes to yield 16.5 g (95%) of **10** as colorless needles: mp 228–230 °C; ^1H NMR δ 7.78 (s, 1 H, Ar*H*), 7.01 (br s, 1 H, N*H*Ac), 2.20 (s, 3 H, CH_3CO), 2.02 (s, 3 H, CH_3), 1.73 (m, complex, 2 H, CH_2), 1.64 (m, complex, 2 H, CH_2), 1.29 (s, 6 H, $C(CH_3)_2$), 1.28 (s, 6 H, $C(CH_3)_2$). Anal. Calcd for $C_{17}H_{24}N_2O_3$: C, 67.07; H, 7.95; N, 9.21. Found: C, 67.26; H, 8.09; N, 9.21.

1,2,3,4-Tetrahydro-6-(2-hydroxyethyl)-1,1,4,4-tetramethyl-5,7-dinitronaphthalene (11).[20] A mixture of **6** (180.0 g, 0.615 mol) and paraformaldehyde (24.0 g, 0.800 mol) in dry DMSO (800 mL) was treated at room temperature with Triton-B (1 mL), and the resulting dark purple mixture was stirred for 12 h. TLC revealed the absence of **6** (R_f 0.70 in B) and the presence of alcohol **11** (R_f 0.45 in B). The mixture was diluted with 800 mL of EtOAc and divided into two portions. Each portion was washed exhaustively with brine and water. The aqueous layers were back-extracted with 4 × 50 mL of EtOAc, and the combined organic layers were dried (K_2CO_3–Darco), filtered through a Celite pad, and concentrated to yield 204 g (100%) of **11** as a light pink solid: mp 133–135 °C (colorless needles/CH_2Cl_2–hexanes); ^1H NMR δ 7.94 (s, 1 H, Ar*H*), 3.81 (q, J = 6 Hz, 2 H, CH_2OH), 2.97 (t, J = 6 Hz, 2 H, $ArCH_2$), 1.74 (AB q, J = 6 Hz, 4 H, $C(CH_3)_2CH_2CH_2$) overlapping 1.67 (m, 1 H, O*H*, exch), 1.34 (s, 6 H, $C(CH_3)_2$), 1.32 (s, 6 H, $C(CH_3)_2$); ^1H NMR ($CDCl_3$–D_2O) δ 3.80 (t, J = 6 Hz, 2 H, CH_2OH), 2.97 (t, J = 6 Hz, 2 H, $ArCH_2$); ^{13}C NMR δ 152.48 and 148.60 ($ArNO_2$), 148.38, 140.66, 124.95 and 123.09 (Ar), 62.24 (CH_2OH), 37.81 and 33.49 ($C(CH_3)_2CH_2CH_2$), 35.49 and 35.22 ($C(CH_3)_2$), 32.28 ($C(CH_3)_2$), 28.47 ($ArCH_2$), 28.61 ($C(CH_3)_2$); IR (Nujol) 3400–3100 (broad) cm^{-1}; MS (EI) m/e (relative intensity) 322 (20, M^+), 287 (35, $M^+ - CH_3$), 292 (75, $M^+ - NO$), 175 (35, $M^+ - HNO_2$), 259 (100, $M^+ - HNO_3$). Anal. Calcd for $C_{16}H_{22}N_2O_5$: C, 59.60; H, 6.88; N, 8.69. Found: C, 59.45; H, 6.91; N, 8.65.

5-Amino-1,2,3,4-tetrahydro-6-(2-hydroxyethyl)-1,1,4,4-tetramethyl-7-nitronaphthalene (12). A solution of alcohol **11** (100.0 g, 0.280 mol) and 10% Pd/C (20 g) in EtOH (1 L) was heated to gentle reflux under argon, and cyclohexene (40 mL, 0.388 mol) was added dropwise over 1 h. After addition was complete, the black suspension was refluxed for 1 h under argon, at which time TLC revealed the absence of alcohol **11** (R_f 0.85 in A) and the presence of amine **12** (R_f 0.6 in A). The solution was filtered hot through a Celite pad, and the pad was washed with several portions of EtOAc. The filtrate was concentrated to yield 87 g (99%) of **12**: mp 185–187 °C (yellow crystals/EtOAc–hexanes); ^1H NMR δ 6.75 (s, 1 H, Ar*H*), 4.14 (br s, 2 H, NH_2, exch), 3.85 (t, J = 6 Hz, 2 H, CH_2OH), 2.56 (t, J = 6 Hz, 2 H, $ArCH_2$), 2.00 (br s, 1 H, O*H*, exch), 1.63 (AB q, J = 6 Hz, 4 H, $C(CH_3)_2CH_2CH_2$), 1.26 (s, 6 H, $C(CH_3)_2$), 1.25 (s, 6 H, $C(CH_3)_2$); ^{13}C NMR δ 152.72 ($ArNO_2$), 146.71, 144.45, 124.99, 116.37 and 114.77 (Ar), 63.49 (CH_2OH), 38.39 an 34.28 ($C(CH_3)_2CH_2CH_2$), 34.71 and 33.89 ($C(CH_3)_2$), 32.60 and 29.10 ($C(CH_3)_2$), 29.80 ($ArCH_2$); IR (Nujol) 3355–3200 (broad), 1500 cm^{-1}; MS (EI) m/e (relative intensity) 292 (40, M^+), 277 (100, $M^+ - CH_3$). Anal. Calcd for $C_{16}H_{24}N_2O_3$: C, 65.71; H, 8.28; N, 9.59. Found: C, 65.57; H, 8.39; N, 9.46.

4-Nitro-5,6-(1,2,3,4-tetrahydro-1,1,4,4-tetramethylbenzo)indole (13). A solution of amine **12** (15.5 g, 0.051 mol) and tris(triphenylphosphine)ruthenium dichloride (1.0 g, 2 mol %) in dry $PhCH_3$ (200 mL) was refluxed for 5 h. TLC revealed the absence of **12** (R_f 0.15 in B) and the presence of indole **13** (R_f 0.4 in B). The $PhCH_3$ was evaporated, and the residue was purified by chromatography using 3:1 hexane/EtOAc as eluant to yield 11 g (80%) of indole **13** as a dark-colored solid: mp 175–177 °C (large light-yellow crystals/CH_2Cl_2–hexanes); ^1H NMR δ 8.15 (br s, 1 H, N*H*), 7.50 (s, 1 H, Ar*H*), 7.18 (t, J = 3 Hz, 1 H, $NCH{=}CH$), 6.31 (t, J = 3 Hz, 1 H, $ArCH{=}CHN$), 1.79 (B part, AB q, complex, 2 H), 1.69 (A part, AB q, complex, 2 H), 1.43 (s, 6 H, $C(CH_3)_2$), 1.36 (s, 6 H, $C(CH_3)_2$); ^{13}C NMR δ 143.48 ($ArNO_2$), 141.37, 135.36, 127.61, 127.31 and 120.83 (Ar), 112.23 ($NCH{=}CH$), 99.38 ($ArCH{=}CH$), 38.43 and 34.50 ($C(CH_3)_2CH_2CH_2$), 35.25 and 34.70 ($C(CH_3)_2$), 33.65 and 29.23 ($C(CH_3)_2$); IR (Nujol) 3400, 2950 cm^{-1}; MS (EI) m/e (relative intensity) 272 (70, M^+), 257 (100, $M^+ - CH_3$). Anal. Calcd for $C_{16}H_{20}N_2O_2$: C, 70.55; H, 7.41; N, 10.29. Found: C, 69.76; H, 7.09; N, 9.97.

7-(Ethoxycarbamoyl)-6-(2-hydroxyethyl)-1,2,3,4-tetrahydro-1,1,4,4-tetramethyl-5-nitronaphthalene (14). A solution of amine **12** (43.25 g, 0.148 mol) in THF (360 mL) and saturated aqueous $NaHCO_3$ (40 mL) was cooled to 0 °C (ice bath) and treated with $ClCO_2Et$ (23.0 mL, 0.222 mol). The resulting light yellow mixture was stirred for 12 h while warming to room temperature and then partitioned between EtOAc and brine. The combined organic layers were dried (K_2CO_3), filtered, and concentrated to yield 45.5 g (95%) of carbamate **14**: mp 166–167 °C (colorless needles/CH_2Cl_2–EtOAc–hexanes); ^1H NMR δ 8.42 (br s, 1 H, Ar*H*), 7.87 (br s, 1 H, N*H*), 4.20 (q, J = 6 Hz, 2 H, OCH_2CH_3), 3.90 (t, J = 6 Hz, 2 H, CH_2OH), 2.60 (t, J = 6 Hz, 2 H, $ArCH_2$), 2.21 (br s, 1 H, O*H*), 1.68 (AB q, complex, 4 H, $C(CH_3)_2CH_2CH_2$), 1.28 (s, 6 H, $C(CH_3)_2$), 1.28 (s, 6 H, $C(CH_3)_2$) overlapping 1.28 (t, J = 6 Hz, 3 H, OCH_2CH_3); ^{13}C NMR δ 154.48 (*C*=O), 151.96, 146.56, 136.01, 128.46, 123.63 and 120.82 (Ar), 63.82 (CH_2OH), 61.25 (CO_2CH_2), 38.21 and 34.24 ($C(CH_3)_2CH_2CH_2$), 35.00 and 34.05 ($C(CH_3)_2$), 32.40 and 28.83 ($C(CH_3)_2$), 29.48 ($ArCH_2$), 14.50 (OCH_2CH_3); IR (Nujol) 3400 (br, s), 3290, 2980, 1701 (s, C=O), 1605 cm^{-1}; MS (EI) m/e (relative intensity) 364 (75, M^+), 349 (80, $M^+ - CH_3$), 319 (100, $M^+ - OEt$). Anal. Calcd for $C_{19}H_{28}N_2O_5$: C, 62.60; H, 7.75; N, 7.69. Found: C, 62.59; H, 7.82; N, 7.66.

5-Amino-7-(ethoxycarbamoyl)-6-(2-hydroxyethyl)-1,2,3,4-tetrahydro-1,1,4,4-tetramethylnaphthalene Hydrochloride (15). A mechanically stirred suspension of carbamate **14** (87 g, 0.238 mol) and iron powder (−395 mesh, 75 g, 1.34 mol) in EtOH (750 mL) and glacial AcOH (750 mL) was heated to gentle reflux protected by a $CaCl_2$ drying tube. After 3 h, TLC revealed the absence of **14** (R_f 0.45 in B) and the presence of amine **15** (R_f 0.1 in B), which stained a characteristic orange-red upon exposure to ammonium molybdate–ceric sulfate stain. The mixture was filtered hot through a Celite pad, and the pad was washed with several portions of EtOAc. The filtrate was concentrated, and the residue was partitioned between cold saturated aqueous Na_2CO_3 and EtOAc. The combined organic layers were dried (K_2CO_3), filtered, and concentrated to yield 76 g (95%) of amine **15** as a light purple syrup that could not be crystallized. An analytical sample was obtained by chromatography over silica gel eluting with 1:1 EtOAc/hexanes to give an oil that was chromatographically homogeneous. A crystalline hydrochloride was obtained by dissolution of the free amine in Et_2O, cooling in an ice bath, and addition of HCl in Et_2O (1 M). The solid that had formed was collected by filtration and recrystallized twice from methanol/ether/hexane to yield the hydrochloride of amine **15** as a mat of fine needles: mp 185 °C (sublimes); ^1H NMR δ 7.60 (s, 1 H, Ar*H*), 4.94 (br s, 4 H, exch, NH_2, O*H*, *H*Cl), 4.22 (q, J = 6 Hz, 2 H, OCH_2CH_3), 3.94 (t, J = 6 Hz, 2 H, CH_2OH), 3.02 (t, J = 6 Hz, 2 H, $ArCH_2$), 1.80 (AB q, J = 9 Hz, 4 H, $C(CH_3)_2CH_2CH_2$), 1.49 (s, 6 H, $C(CH_3)_2$), 1.34 (s, 6 H, $C(CH_3)_2$) overlapping 1.34 (t, J = 6 Hz, 3 H, OCH_2CH_3); ^{13}C NMR δ 157.07 (*C*=O), 147.79, 136.64, 136.31, 129.84, 129.67 and 127.26 (Ar), 63.25 (OCH_2CH_3), 62.05 (CH_2OH), 39.59 and 34.73 ($C(CH_3)_2$), 35.55 and 34.11 ($C(CH_3)_2CH_2CH_2$), 32.10 and 29.05 ($C(CH_3)_2$), 28.65 ($ArCH_2$), 14.58 (OCH_2CH_3); IR (Nujol) 3400–3250 (br), 2400–2650 (br), 1700 (s) cm^{-1}; MS (EI) m/e (relative intensity) 334 (100, $M^+ - HCl$), 319 (95, $M^+ - CH_3$). Anal. Calcd for $C_{19}H_{31}N_2O_3Cl$: C, 61.59; H, 8.44; N, 7.57; Cl, 9.45. Found: C, 61.31; H, 8.52; N, 7.46; Cl, 9.31.

4-(Ethoxycarbamoyl)-6,7-(1,2,3,4-tetrahydro-1,1,4,4-tetramethylbenzo)indole (4). A solution of amine **15** (76.0 g, 0.227 mol) and tris(triphenylphosphine)ruthenium dichloride (10.0 g, 0.01 mol) in dry $PhCH_3$ (600 mL) was refluxed for 3 h at which time TLC revealed the absence of **15** (R_f 0.15 in B) and the presence of indole **4** (R_f 0.4 in B). The $PhCH_3$ was evaporated, and the residue was purified by chromatography using 3:1 hexane/EtOAc as eluant. The appropriate fractions were combined and concentrated to yield 55 g (78%) of indole **4**: mp 176–178 °C (large light-purple crystals/CH_2Cl_2-hexanes); ^1H NMR δ 8.32 (br s, 1 H, N*H*), 7.63 (br s, 1 H, $NHCO_2$), 7.13 (dd, J = 2, 3.5 Hz, 1 H, $NCH{=}CH$), 6.69 (br s, 1 H, Ar*H*), 6.40 (dd, J = 2, 3.5 Hz, 1 H, $ArCH{=}CH$), 4.26 (q, J = 6 Hz, 2 H, OCH_2CH_3), 1.80 (B part, ABq, complex, 2 H, $C(CH_3)_2CH_2CH_2$), 1.71 (A part, ABq, complex, 2 H, $C(CH_3)_2CH_2CH_2$), 1.46 (s, 6 H, $C(CH_3)_2$), 1.28 (s, 6 H, $C(CH_3)_2$) overlapping 1.28 (t, J = 6 Hz, 3 H, OCH_2CH_3); ^{13}C NMR δ154.02 (*C*=O), 139.83, 134.36, 127.84, 123.28 and 122.74 (Ar), 118.61 ($NCH{=}CH$), 109.35 ($ArCH{=}CH$), 97.81 (Ar), 61.08 (OCH_2CH_3), 37.36 and 34.57 ($C(CH_3)_2CH_2CH_2$), 35.26 and 33.43 (*C*-

$(CH_3)_2$), 32.01 and 29.33 ($C(CH_3)_2$), 14.57 ($OHCH_2CH_3$); IR (Nujol) 3355, 1650, 1428 (s) cm^{-1}; MS (EI) *m/e* (relative intensity) 314 (87, M^+), 299 (100, $M^+ - CH_3$). Anal. Calcd for $C_{19}H_{26}N_2O_2$: C, 72.58; H, 8.34; N, 8.91. Found: C, 72.56; H, 8.33; N 8.93.

4-(*N*-Methylamino)-6,7-(1,2,3,4-tetrahydro-1,1,4,4-tetramethylbenzo)indole (16). A solution of indole 4 (20.0 g, 0.063 mol) in dry THF (280 mL) under argon was treated over $^1/_2$ h at room temperature via syringe with $LiAlH_4$ (127 mL, 1.0 M in THF, gas evolution was noted upon addition), and the resulting light yellow suspension refluxed for $^1/_2$ h. TLC revealed the absence of indole 4 (R_f 0.4 in B) and the presence of amine 16, which had an identical R_f (0.4 in B), but which had staining characteristics different from the starting carbamate. The solution was cooled to 0 °C, and the remaining $LiAlH_4$ was destroyed with a mixture of $Na_2SO_4 \cdot 10H_2O$–Celite (1:1). The thick slurry was filtered through a Celite pad, the pad was washed with several portions of 5:1 THF–NEt_3 and EtOAc, and the filtrate was concentrated. The solid remaining was purified by chromatography using 3:1 hexane/EtOAc as eluant to yield 15.0 g (92%) of amine 16: mp 197–199 °C (dec, purple crystals/CH_2Cl_2–hexane); ^{1}H NMR δ 8.19 (s, 1 H, N*H*), 7.03 (t, J = 2.4 Hz, 1 H, NC*H*=), 6.36 (dd, J = 2.4 Hz, 1 H, ArC*H*=), 6.27 (s, 1 H, Ar*H*), 2.96 (s, 3 H, NCH_3), 1.72 (m, complex, 4 H, $CH_2CH_2C(CH_3)_2$), 1.44 (s, 6 H, $C(CH_3)_2$), 1.28 (s, 6 H, $C(CH_3)_2$); ^{13}C NMR δ 140.28 (Ar), 140.15 (Ar), 134.31 (Ar), 121.37 (Ar), 117.66 (ArNCH=C), 116.27 (ArCH=C), 98.25 (Ar), 98.11 (Ar), 37.62 and 35.68 ($C(CH_3)_2CH_2CH_2$), 34.66 and 33.24 ($(CH_3)_2C$), 32.19 ($(CH_3)_2C$), 28.19 (NCH_3), 29.69 ($(CH_3)_2C$); MS (EI) *m/e* (relative intensity) 256 (55, M^+), 241 (100, $M^+ - CH_3$). Anal. Calcd for $C_{17}H_{24}N_2$: C, 79.63; H, 9.44; N, 10.93. Found: C, 79.31; H, 9.43; N, 10.84.

(*S*)-4-(Methyl(1-(((Phenylmethyl)oxy)carbonyl)-2-methylpropyl)amino)-6,7-(1,2,3,4-tetrahydro-1,1,4,4-tetramethylbenzo)indole (17). A mixture of indole 16 (1.20 g, 4.68 mmol) and (*R*)-2-(((trifluoromethyl)sulfonyl)oxy)-3-methylbutanoic acid benzyl ester[7a] (1.55 g, 5.61 mmol) in $ClCH_2CH_2Cl$ (20 mL) and 2,6-lutidine (0.7 mL, 6.08 mmol) was refluxed for 12 h. TLC revealed the absence of 16 (R_f 0.4 in B) and the presence of indole 17 (R_f 0.6 in B). The solvent was evaporated, and the residue was partitioned between EtOAc and saturated aqueous $NaHCO_3$. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by chromatography using 3:1 hexane/EtOAc as eluant to yield 1.95 g (93%) of 17: mp 138–140 °C (purple crystals/CH_2Cl_2–hexanes); ^{1}H NMR δ 8.21 (br s, 1 H, N*H*), 7.25 (m, 3 H, Ar*H*), 7.11 (d, J = 3 Hz, 1 H, ArC*H*=), 7.08 (m, 2 H, Ar*H*), 6.64 (s, 1 H, Ar*H*), 6.61 (dd, J = 2 Hz, 1 H, NC*H*=), 5.07 (q, J = 12 Hz, 2 H, ArCH_2), 4.02 (d, J = 11 Hz, 1 H, CH_3NCH*i*Pr), 3.00 (s, 3 H, NCH_3), 2.39 (m, complex (9 lines), 1 H, $CH(CH_3)_2$), 1.75 (m, 2 H, $(CH_3)_2CCH_2$), 1.66 (m, 2 H, $(CH_3)_2CH_2$), 1.48 (s, 3 H, $C(CH_3)_2$), 1.46 (s, 3 H, $C(CH_3)_2$), 1.25 (s, 3 H, $C(CH_3)_2$), 1.23 (s, 3 H, $C(CH_3)_2$), 1.12 (d, J = 6 Hz, 3 H, $CH(CH_3)_2$), 0.93 (d, J = 6 Hz, 3 H, $CH(CH_3)_2$); ^{13}C NMR δ 171.97 (CO_2Bn), 143.47 (Ar), 139.41 (Ar), 135.87 (Ar), 135.19 (Ar), 128.33 (Ar), 127.95 (Ar), 127.88 (Ar), 121.42 (Ar), 120.98 (ArNCH=), 119.79 (ArC=), 107.56 (Ar), 101.21 (Ar), 70.66 (CO_2CH_2Ar), 65.74 (CH_3NC(iPr)CO_2Bn), 37.67 and 35.47 ($(CH_3)_2CCH_2$), 34.51 and 34.14 ($(CH_3)_2C$), 33.31 ($CH(CH_3)_2$), 32.12, 29.58, 29.50 and 27.92 ($(CH_3)_2C$), 19.87 and 19.38 ($CH(CH_3)_2$); MS (EI) *m/e* (relative intensity) 446 (73, M^+), 431 (10, $M^+ - CH_3$), 403 (50, $M^+ - C_3H_7$), 311 (100, $M^+ - PhCH_2OC$=O). Anal. Calcd for $C_{29}H_{38}N_2O_2$: C, 77.98; H, 8.58; N, 6.28. Found: C, 78.13; H, 8.62; N, 6.24.

Ethyl (*S*)-3-(4-(Methyl(1-(((phenylmethyl)oxy)-carbonyl)-2-methylpropyl)amino)-6,7-(1,2,3,4-tetrahydro-1,1,4,4-tetramethylbenzo)-1*H*-indol-3-yl)-2-oximidopropionate (18). A suspension of 17 (10.0 g, 0.022 mol) in CH_2Cl_2 (28 mL), ethyl 3-bromo-2-oximidopropionate[23] (4.72 g, 0.022 mol), and Na_2CO_3 (1.0 g) was stirred for 12 h. TLC revealed the absence of 17 (R_f 0.45 in B) and the presence of oxime 18 (R_f 0.1 in B). The dark suspension was diluted with EtOAc, filtered, and concentrated. The oil remaining was purified by chromatography using 3:1 hexane/EtOAc and then 1:1 hexane/EtOAc as eluant to yield 6.43 g (50%) of 18 as a white solid: mp 128–131 °C (CH_2Cl_2/hexanes); ^{1}H NMR δ 9.38 (br s, 1 H, exch, NO*H*), 8.02 (br s, 1 H, no exch, ArN*H*CH=C), 7.26 (m, 3 H, CH_2Ar*H*), 7.17 (m, 2 H, CH_2Ar*H*), 6.93 (s, 1 H, Ar*H*), 6.72 (s, 1 H, ArNHC*H*=C), 5.09 (B part, AB q, J = 12 Hz, 1 H, CH_2Ar), 4.95 (A part, AB q, J = 12 Hz, 1 H, CH_2Ar), 4.45 (B part, AB q, J = 15 Hz, 1 H, CH_2C=NOH), 4.37 (A part, AB q, J = 15 Hz, 1 H, CH_2C=NOH), 4.24 (B part AB q, J = 6 Hz, 1 H, OCH_2CH_3), 4.22 (A part, AB q, J = 6 Hz, 1 H, OCH_2CH_3), 3.72 (d, J = 8.5 Hz, 1 H, NC*H*-(iPr)CO_2Bn), 2.94 (s, 3 H, NCH_3), 2.31 (m, complex, 1 H, C*H*-$(CH_3)_2$), 1.71 (m, complex, 2 H, $C(CH_3)_2CH_2$), 1.65 (m, complex, 2 H, $C(CH_3)_2CH_2$), 1.429 (s, 3 H, $C(CH_3)_2$), 1.423 (s, 3 H, $C(CH_3)_2$), 1.24 (t, J = 6 Hz, 3 H, OCH_2CH_3) overlapping 1.24 (s, 3 H, $C(CH_3)_2$), 1.23 (s, 3 H, $C(CH_3)_2$), 1.13 (d, J = 6.5 Hz, 3 H, CH-$(CH_3)_2$), 0.93 (d, J = 6.5 Hz, 3 H, $CH(CH_3)_2$); ^{13}C NMR δ 173.10 (CO_2Et), 163.72 (CO_2Bn), 152.75 (C=NOH), 144.70 (Ar), 139.28 (Ar), 135.99 (Ar), 135.74 (Ar), 128.34 (Ar), 128.29 (Ar), 128.00 (Ar), 123.74 (Ar), 120.98 (ArNHCH=), 120.09 (Ar), 112.51 (Ar), 108.73 (ArC=CHN), 72.48 (OCH_2CH_3), 65.98 (OCH_2Bn), 61.70 (CH_2-C=NOH), 37.66, 35.31, 34.47, 33.38, 32.08, 29.43, 29.12, 28.80, 22.47, 20.24, 28.98, 14.03 (OCH_2CH_3); MS (EI) *m/e* (relative intensity) 575.2 (100, M^+), 532.2 (20, $M^+ - C_3H_7$), 440.2 (62, $M^+ - CO_2$Bn). Anal. Calcd for $C_{34}H_{45}N_3O_5$: C, 70.92; H, 7.88; N, 7.28. Found: C, 70.93; H, 7.77; N, 7.27.

(*S,R* and *S,S*)-Ethyl 3-(4-Methyl(1-(((phenylmethyl)-oxy)carbonyl)-2-methylpropyl)amino)-6,7-(1,2,3,4-tetrahydro-1,1,4,4-tetramethylbenzo)-1*H*-indol-3-yl)-2-aminopropionates (20 and 21). A solution of oxime 18 (11.0 g, 0.019 mol) in dry THF (250 mL) was treated with aluminum foil (5 g, 0.19 mol) that had been cut into small pieces and immersed successively in 2% aqueous $HgCl_2$, distilled H_2O, and THF. The dark gray suspension was stirred for 12 h at room temperature, at which time TLC revealed the absence of 18 (R_f 0.5 in A) and the presence of amino esters 20 and 21 (R_f 0.20 and 0.15 in A, respectively). The suspension was filtered and concentrated to yield 7.8 g (75%) of a mixture of the amines as a light yellow oil. Analytical samples of each of the amino esters was provided by chromatography over silica gel using 1:1 hexane/EtOAc to give the *S,R* diastereomer 20 as an oil: ^{1}H NMR δ 8.14 (s, 1 H, N*H*), 7.23 (q, J = 3 Hz, 3 H, CH_2Ar*H*), 7.05 (m, 2 H, CH_2Ar*H*), 6.96 (d, J = 3 Hz, 1 H, ArNHC*H*=), 6.90 (s, 1 H, Ar*H*), 5.00 (B part, AB q, J = 12 Hz, 1 H, ArCH_2), 4.82 (A part, AB q, J = 12 Hz, 1 H, ArCH_2), 4.11 (q, J = 6 Hz, 2 H, CH_3CH_2O), 3.81 (q, J = 3 Hz, 1 H, NC*H*(iPr)CO_2Bn), 3.68 (br s, 1 H, H_2NCHCO_2Et), 3.33 (AB q, J = 6, 9 Hz, 2 H, $CH_2CH(NH_2)CO_2$Et), 2.87 (br s, 3 H, NCH_3), 2.34 (sextet, J = 9 Hz, 1 H, (iPr)C*H*), 1.73 (m, complex, 2 H, $C(CH_3)_2CH_2$), 1.65 (m, complex, 2 H, $C(CH_3)_2CH_2$), 1.62 (br s, 2 H, exch, NH_2), 1.46 (s, 3 H, $C(CH_3)_2$), 1.45 (s, 3 H, $C(CH_3)_2$), 1.26 (s, 3 H, $C(CH_3)_2$), 1.22 (s, 3 H, $C(CH_3)_2$), 1.16 (t, J = 6 Hz, 3 H, CH_3CH_2O), 1.12 (d, J = 6 Hz, 3 H, $(CH)_3CH$), 0.96 (m, complex, 3 H, $(CH_3)CH$); ^{13}C NMR δ 175.77, 172.47, 144.74, 139.03, 135.86, 135.72, 128.28, 128.02, 127.82, 123.85, 121.45, 121.27, 112.13, 111.49, 72.44 ($CHCO_2$Bn), 65.83 (CH_3CH_2O), 60.53 ($ArCH_2$), 56.38 ($CH_2CH(NH_2)CO_2$Et), 37.74, 35.32, 34.48, 33.38, 32.52, 32.20, 32.09, 32.05, 29.55, 28.90, 28.75, 20.35, 14.11; MS (FAB) *m/e* (relative intensity) 562.2 (100, MH^+); high-resolution MS calcd for $C_{34}H_{48}N_3O_4$ 562.3644, found 562.3690. Further elution gave the *S,S* diastereomer 21 as an oil: ^{1}H NMR δ 8.15 (s, 1 H, N*H*), 7.21 (m, 3 H, CH_2Ar*H*), 6.98 (m, 2 H, CH_2Ar*H*), overlapping 6.94 (m, 1 H, ArNHC*H*=), 6.91 (s, 1 H, Ar*H*), 5.02 (B part, AB q, J = 12 Hz, 1 H, ArCH_2), 4.74 (A part, AB q, J = 12 Hz, 1 H, ArCH_2), 4.17 (q, J = 6 Hz, 2 H, CH_3CH_2O), 3.96 (br s, 1 H), 3.66 (br s, 1 H), 3.62 (dd, J = 3 Hz, 1 H), 2.92 (m, 1 H) overlapping 2.88 (br s, 3 H, NCH_3), 2.33 (sextet, J = 6 Hz, (iPr)C*H*), 1.74 (m, complex, 2 H, $C(CH_3)_2CH_2$), 1.67 (m, complex, 2 H, $C(CH_3)_2CH_2$), 1.48 (s, 3 H, $CCH_3)_2$) overlapping 1.48 (br s, 2 H, exch, NH_2), 1.47 (s, 3 H, $C(CH_3)_2$), 1.29 (s, 3 H, $C(CH_3)_2$), 1.25 (t, J = 6 Hz, 3 H, CH_3CH_2O), 1.24 (s, 3 H, $C(CH_3)_2$), 1.15 (d, J = 9 Hz, 3 H, CH-$(CH_3)_2$), 0.90 (m, complex, 3 H, $CH(CH_3)_2$); ^{13}C NMR δ 175.44, 139.21, 136.14, 135.64, 128.22, 127.94, 127.87, 123.80, 122.05, 120.97, 110.98, 72.53 ($CHCO_2$Bn), 65.83 (CH_3CH_2O), 60.54 ($BnCH_2O$), 54.75 ($CH_2C(NH_2)CO_2$Et), 37.61, 35.29, 34.49, 33.39, 32.10, 31.96, 29.70, 28.92, 28.62, 20.41, 14.18; MS (FAB) *m/e* (relative intensity) 562.2 (100, MH^+); high-resolution MS calcd for $C_{34}H_{48}N_3O_4$ 562.3644, found 562.3674.

(*S,S*)- and (*S,R*)-1,3,4,5,7,8,10,11,12,13-Decahydro-4-(ethoxycarbonyl)-8,10,10,13,13-pentamethyl-7-(1-methylethyl)-6*H*-benzo[*g*][1,4]diazonino[7,6,5-*cd*]indol-6-one (23 and 24). A solution of a mixture of amines 20 and 21 (4.50 g, 8.17 mmol), 10% Pd/C (0.5 g), and camphorsulfonic acid (0.1 g) in EtOH (50 mL) was hydrogenated at 40 psi on a Parr shaker apparatus. After

$^1/_2$ h, TLC revealed the absence of amines **20** and **21** (R_f 0.2 and 0.15 in A) and the presence of the very polar amino acid **22** (R_f 0.4 in 3:1 CH_2Cl_2/MeOH). The suspension was filtered and concentrated, and the residue was immediately dissolved in *N,N*-dimethylacetamide (150 mL) and treated with BOP [(benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate, 5.76 g, 6.50 mmol], HOBT (1-hydroxybenzotriazole hydrate, 1.28 g, 7.80 mmol), and *N*-methylmorpholine (3.0 mL, 0.026 mol), and the resulting mixture was stirred at room temperature for 48 h. TLC revealed the presence of esters **23** and **24** (R_f 0.5 and 0.45 in A, respectively). The mixture was concentrated, and the residue was purified by chromatography using 3:1 hexane/EtOAc as eluant to yield 1.5 g (41.5%) of the *S,S* ester **24** as an oil: $[\alpha]^{25}_D$ −120 (*c* 0.5, $CHCl_3$); ^{1}H NMR shows the presence of two conformers in the ratio 3:1; δ 8.27 (br s, 1 H, ArN*H*), 7.02 (s, 1 H, Ar*H*), 6.85 (d, *J* = 3 Hz, 1 H, ArNHC*H*=), 5.25 (B part, AB q, *J* = 12 Hz, 1 H, ArCH_2), 5.09 (A part, AB q, *J* = 12 Hz, 1 H, ArCH_2) overlapping 5.06 (m, 1 H), 4.19 (m, complex, 5 H), 3.14 (m, 1 H), 2.98 (d, *J* = 12 Hz, 1 H), 2.75 (s, 3 H, NCH_3), 2.37 (m, complex, 1 H, C*H*(iPr)), 2.31 (m, 2 H), 1.75 (m, complex, 4 H, CH_2CH_2C(CH_3)$_2$), 1.46 and 1.44 (s, 3 H each, major conformer, C(CH_3)$_2$) overlapping 1.48 (s, 3 H, minor conformer, C(CH_3)$_2$), 1.32 and 1.28 (s, 3 H each, major conformer, C(CH_3)$_2$), 1.23 (t, *J* = 6 Hz, 3 H, major conformer, CH_3CH$_2$O) overlapping 1.20 (m, 3 H, major conformer, CH(CH_3)$_2$) and 1.19 (m, 3 H, minor conformer, CH(CH_3)$_2$), 1.20 (t, *J* = 6 Hz, 3 H, minor conformer CH_3CH$_2$O), 0.92 (d, *J* = 6 Hz, 3 H, major conformer, CH(CH_3)$_2$), 0.65 (d, *J* = 6 Hz, 3 H, minor conformer, CH(CH_3)$_2$); MS (EI) *m/e* (relative intensity) 453.2 (100, M$^+$), 462.2 (20, M$^+$ − 27), 410.2 (15, M$^+$ − C_3H_7), 380.2 (5, M$^+$ − CO_2Et); MS (FAB) *m/e* (relative intensity) 453.2 (100, M$^+$); high-resolution MS calcd for $C_{27}H_{39}N_3O_3$ 453.2991, found 453.2998. Further elution gave 1.5 g (41.5%) of ester **23** as a white solid. Recrystallization from CH_2Cl_2–ether–hexanes yielded the *S,R* ester **23** as large colorless plates: mp 257–258 °C; $[\alpha]^{25}_D$ −222 (*c* 0.5, $CHCl_3$); ^{1}H NMR δ 8.09 (s, 1 H, ArN*H*), 6.94 (s, 1 H, ArNHC*H*=), 6.80 (s, 1 H, Ar*H*), 6.64 (d, *J* = 7.5 Hz, 1 H, CON*H*), 4.46 (m, complex, 1 H, NC*H*CONH), 4.35 (m, complex, 2 H, OCH_2CH$_3$), 3.71 (d, *J* = 12 Hz, 1 H, C*H*CO$_2$Et), 3.48 (B part, AB qd, *J* = 3, 15 Hz, 1 H, CH_2CH(NH$_2$)CO$_2$Et), 3.24 (A part, AB qd, *J* = 4.5, 15 Hz, 1 H, CH_2(NH$_2$)CO$_2$Et), 3.10 (s, 3 H, NCH_3), 2.68 (m, complex, 1 H, C*H*(iPr)), 1.80 (m, complex, 4 H, C(CH$_3$)$_2$CH_2CH_2), 1.48 (s, 3 H, C(CH_3)$_2$), 1.42 (s, 3 H, C(CH_3)$_2$), 1.39 (t, *J* = 6 Hz, 3 H, OCH$_2$CH_3), 1.28 (s, 6 H, C(CH_3)$_2$), 0.74 (t, *J* = 6 Hz, 6 H, CH(CH_3)$_2$); ^{13}C NMR δ 172.36 (CONH), 172.01 (*C*O$_2$Et), 145.26 (Ar), 139.29 (Ar), 136.12 (Ar), 123.20 (Ar*C*=CH), 121.59 (Ar), 119.22 (Ar), 112.90 (ArN-HCH=), 109.90 (Ar), 69.36 (N*C*H(CH(iPr))CO), 61.92 (CH$_3$*C*-H$_2$O), 57.25 (*C*H$_2$CH(NH$_2$)CO$_2$Et), 37.62, 35.41, 34.96, 34.40, 33.19, 32.42, 31.79, 28.21, 28.31, 28.04, 20.57, 19.79, 14.18; IR ($CHCl_3$) 3694.5, 3508.6, 3369.1, 3156.3, 2970.7 (s), 2928.8 (s), 1735.5 (s, CO_2Et), 1662.5 (vs, CONH), 1602.7, 1463.3, 1370.3, 1204.3 cm^{-1}; MS (EI) *m/e* (relative intensity) 453.2 (100, M$^+$), 462.2 (20, M$^+$ − 27), 410.2 (15, M$^+$ − C_3H_7), 380.2 (5, M$^+$ − CO_2Et); high-resolution MS calcd for $C_{27}H_{39}N_3O_3$ 453.2991, found 453.2997. Anal. Calcd for $C_{27}H_{39}N_3O_3$: C, 71.48; H, 8.67; N, 9.27. Found: C, 71.32; H, 8.65; N, 9.22.

(*S,S*)-1,3,4,5,7,8,10,11,12,13-Decahydro-4-(hydroxymethyl)-8,10,10,13,13-pentamethyl-7-(1-methylethyl)-6*H*-benzo[*g*][1,4]diazonino[7,6,5-*cd*]indol-6-one (3). A solution of ester **24** (250 mg, 0.550 mmol) in dry THF at 0 °C under argon was treated with $LiBH_4$ (28.0 mg, 1.37 mmol). After 3 h, TLC revealed the absence of ester **24** (R_f 0.75 in A) and the presence of alcohol **3** (R_f 0.20 in A). The solution was partitioned between EtOAc and brine, and the organic layer was dried ($MgSO_4$), filtered, and concentrated to a white solid, which was purified by chromatography using 1:1 hexane/EtOAc as eluant to yield 0.220 g (95%) of alcohol **3** as a white solid. An analytical sample was obtained by recrystallization from $CHCl_3$/hexanes to yield a mat of fine crystals: mp 275–276 °C; $[\alpha]^{25}_D$ −212 (*c* 0.5, $CHCl_3$); ^{1}H NMR twist conformer[35] (ratio twist/sofa = 3:1) δ 8.10 (br s, 1 H, 1), 7.37 (br s, 1 H, 10), 6.86 (s, 1 H, 2), 6.49 (s, 1 H, 5), 4.36 (br m, 1 H, 9), 4.29 (d, *J* = 12 Hz, 1 H, 12), 3.72 (m, 1 H, 14), 3.55 (m, 1 H, 14), 3.28 (t, *J* = 6 Hz, 1 H, 19), 3.13 (B part, AB q, *J* = 15 Hz, 1 H, 8), 3.04 (A part, AB qd, *J* = 4, 15 Hz, 1 H, 8), 2.90 (s, 3 H, 18), 2.57 (m, 1 H, 15), 1.72 (m, 4 H, 21 and 22), 1.47 (s, 3 H, 23-CH$_3$), 1.43 (s, 3 H, 23-CH$_3$), 1.31 (s, 3 H, 20-CH$_3$), 1.29 (s, 3 H, 20-CH$_3$), 0.90 (m, 3 H, 16 and 17), 0.63 (d, *J* = 6 Hz, 3 H, 16 and 17); sofa conformer δ 8.36 (br s, 1 H, 1), 7.03 (s, 1 H, 5), 6.97 (d, *J* = 2 Hz, 1 H, 2), 4.78 (d, *J* = 9 Hz, 1 H, 12), 4.42 (m, 1 H, 9), 3.49 (m, 1 H, 14), 3.43 (m, complex, 1 H, 14), 2.96 (B part, AB q, *J* = 9 Hz, 1 H, 8), 2.78 (A part, AB q, *J* = 9 Hz, 1 H, 8), 2.72 (s, 3 H, 18), 2.38 (m, 1 H, 15), 1.75 (m, 4 H, overlapping twist conformer, 21 and 22), 1.48 (s, 6 H, 23-CH$_3$), 1.33 (s, 6 H, 23-CH$_3$), 1.26 (m, 3 H, 16 and 17), 0.935 (m, 3 H, 16 and 17); IR ($CHCl_3$), 3681.2, 3621.5, 3508.6, 3389.1, 2964.1 (vs), 2877.7, 1728.9, 1655.9 (vs, NHC=O), 1602.7, 1549.6, 1503.1, 1469.9, 1376.9, 1250.8, 1051.6; high-resolution MS calcd for $C_{25}H_{37}N_3O_3$ 411.2885, found 411.2899. Anal. Calcd for $C_{25}H_{37}N_3O_3$: C, 72.96; H, 9.07; N, 10.21. Found: C, 73.14; H, 9.44; N, 9.81.

(*S,R*)-1,3,4,5,7,8,10,11,12,13-Decahydro-4-(hydroxymethyl)-8,10,10,13,13-pentamethyl-7-(1-methylethyl)-6*H*-benzo[*g*][1,4]diazonino[7,6,5-*cd*]indol-6-one (25). A solution of ester **23** (700 mg, 1.50 mmol) in dry THF at 0 °C under argon was treated with $LiBH_4$ (700 mg, 2.87 mmol). After 3 h, TLC revealed the absence of ester **23** (R_f 0.70 in A) and the presence of alcohol **25** (R_f 0.15 in A). The solution was partitioned between EtOAc and brine, and the organic layer was dried ($MgSO_4$), filtered, and concentrated to a white solid, which was purified by chromatography using 1:1 hexane/EtOAc as eluant to yield 0.60 g (95%) of alcohol **25** as a white solid: mp 191–192 °C; $[\alpha]^{25}_D$ −168 (*c* 0.5, $CHCl_3$); ^{1}H NMR[35] δ 8.04 (s, 1 H, 1), 7.92 (br s, 1 H, 10), 6.83 (t, *J* = 1.5 Hz, 1 H, 2), 6.76 (s, 1 H, 5), 3.85 (m, 5 H, 12, 14, and 19), 3.25 (B part, AB q, *J* = 15 Hz, 1 H, 8), 3.07 (s, 3 H, 18), 2.97 (A part, AB q, *J* = 15 Hz, 1 H, 8), 2.61 (m, 8 lines, 1 H, 15), 1.74 (m, complex, 4 H, 21 and 22), 1.49 (s, 3 H, 23-CH$_3$), 1.47 (s, 3 H, 23-CH$_3$), 1.29 (s, 6 H, 22-CH$_3$), 0.71 (t, *J* = 6 Hz, 6 H, 16 and 17); ^{13}C NMR δ 175.49 (11-*C*O), 145.35, 139.08, 136.28, 121.38, 121.23 (Ar), 119.40 (2-CH=), 113.68 (Ar), 109.49 (3-C=), 68.57 (12-*C*HCONH), 65.24 (14-CH$_2$OH), 57.91 (8-CH$_2$), 37.68 and 35.37 (20- and 23-*C*(CH$_3$)$_2$), 34.41 (18-NCH$_3$), 33.20 and 32.08 (21- and 22-C(CH$_3$)$_2$*C*H$_2$), 32.56 (9-*C*HCH$_2$OH), 28.21 and 28.28 (20- and 23-(CH$_3$)$_2$), 27.90 (15-*C*H(CH$_3$)$_2$), 20.49 and 19.70 (16- and 17-CH(CH$_3$)$_2$); IR ($CHCl_3$) 3501.9, 2957.4 (vs), 2871.1, 1728.9 (s), 1655.9 (vs, 11-NHC=O), 1602.7, 1549.6, 1463.3 (d), 1370.3 (d), 1250.8, 1224.2 (vs), 1064.8, 1038.3; MS (EI) *m/e* (relative intensity) 411.2 (100, M$^+$); high-resolution MS calcd for $C_{25}H_{37}N_3O_2$ 411.2885, found 411.2921. Anal. Calcd for $C_{25}H_{37}N_3O_2$: C, 72.94; H, 9.07; N, 10.21. Found: C, 72.96; H, 8.99; N, 9.94.

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Supplementary Material Available: Complete experimental details for X-ray structures **6** and **23**, including ORTEP[15] representations, positional parameters, and estimated standard deviations (14 pages). Ordering information is given on any current masthead page.

(35) The numbering convention used is that shown in Figure 1.