with ether, and the organic phase was washed with brine and dried. Evaporation of the solvent followed by column chromatography (eluting with 3:7 AcOEt/*n*-hexane) yielded 9.0 mg (87%) of the unsaturated ester **40** as a colorless oil: IR ($CHCl_3$) [cm^{-1}] 3400, 1720, 1100; ^1H NMR (90 MHz) δ 1.28 (3 H, s), 1.32 (3 H, d, J = 8.0 Hz), 1.68 (3 H, m), 3.26 (1 H, br s), 3.37 (3 H, s), 3.42 (3 H, s), 3.45 (3 H, s), 3.62 (1 H, d, J = 8.0 Hz), 3.74 (3 H, s), 3.94 (1 H, br s), 4.14 (1 H, d, J = 8.0 Hz), 4.38 (1 H, dd, J = 14.0 and 7.0 Hz), 4.98 (1 H, t, J = 8.0 Hz), 5.94 (1 H, d, J = 16.0 Hz), 6.94 (1 H, dd, J = 16.0 and 7.0 Hz); mass spectrum, m/z 381 ($M^+ - H_2O - OCH_3$); $[\alpha]^{26}_D$ -47.6° (c 1.57); exact mass calcd for $C_{20}H_{29}O_7$ 381.1912, found 381.1906.

Methyl Ketone 41. DMSO (0.027 mL, 0.379 mmol) was added to a solution of oxalyl chloride (0.016 mL, 0.189 mmol) in dry CH_2Cl_2 (1 mL), and a solution of the alcohol **40** (37 mg, 0.0861 mmol) in dry CH_2Cl_2 (1 mL) was added to the mixture at -78 °C. After the mixture was stirred for 15 min, NEt_3 (0.120 mL, 0.861 mmol) was added, and stirring was continued for 30 min at room temperature. Water (1 mL) was added, the aqueous phase was extracted wtih CH_2Cl_2, and the organic phase was washed with brine and dried. Evaporation of the solvent followed by column chromatography (eluting with 1:1 AcOEt/*n*-hexane) yielded 32 mg (87%) of the ketone **41** as a colorless oil: IR ($CHCl_3$) [cm^{-1}] 3350, 1720, 1100; ^1H NMR (500 MHz) δ 1.22 (3 H, s), 1.57 (3 H, s), 1.65 (1 H, dd, J = 14.0 and 6.0 Hz), 2.40 (1 H, br s), 2.76 (1 H, m), 3.14 (1 H, br s), 3.39 (6 H, s), 3.41 (3 H, s), 3.49 (1 H, d, J = 9.0 Hz), 3.73 (3 H, s), 3.79 (1 H, br s), 4.08 (1 H, dd, J = 10.0 and 5.0 Hz), 4.89 (1 H, d, J = 9.0 Hz), 5.01 (1 H, t, J = 7.0 Hz), 5.96 (1 H, d, J = 16.0 Hz), 6.65 (1 H, br s, D_2O exchangeable), 6.88 (1 H, dt, J = 16.0 and 7.0 Hz); mass spectrum, m/z 397 ($M^+ - OCH_3$); $[\alpha]^{27}_D$ -108.9 (c 0.30); exact mass calcd for $C_{21}H_{29}O_8$ 397.1862, found 397.1867.

Acknowledgment. We thank Dr. N. Shoji of Tokushima Bunri University for recording the 400-MHz ^1H NMR spectra and Dr. Y. Oshima of our Institute for helpful discussions concerning ^1H NMR analysis. We also thank Miss K. Mushiake, Miss K. Koike, Mrs. E. Niwa, and Mr. K. Kawamura, Pharmaceutical Institute, Tohoku University, for microanalyses and spectral measurement.

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2′-Nitrobenzhydryl Polystyrene Resin: A New Photosensitive Polymeric Support for Peptide Synthesis

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2′-Nitrobenzhydryl polystyrene resin (NBH-resin) was prepared from the commercially available styrene–divinylbenzene cross-linked polymer by a two-step polymer analogous reaction. This resin was employed as a photolytically cleavable polymeric protective support for carboxyl function in amino acids under neutral conditions. The 2′-nitrobenzhydryl resin possesses good stability in 4 N HCl–dioxane required for the deprotection of the temporary N^{α}-*tert*-butyloxycarbonyl protecting group. The advantage of the new resin over the already reported benzhydryl resin is its increased acid stability during the N^{α} deblocking, which permits the peptide synthesis with the commonly available Boc-amino acids. The applicability of this resin is illustrated with the solid-phase synthesis of some model peptides.

Benzhydryl resins have been widely used for the polymer-supported solid-phase synthesis of peptides.[1-4] The cleavage of the finished peptides and peptide amides from these resins after synthesis is usually achieved by treatment with trifluoroacetic acid, trifluoromethanesulfonic acid, or anhydrous HF. The benzhydryl ester linkages are reported to be less stable in acidolytic conditions of N^{α}-*tert*-butyloxycarbonyl (Boc) group removal. In order to overcome this difficulty Southard et al. have employed an enamine-type amino protecting group, cleavable under very mild acid conditions.[2,5] But the use of ordinary benzhydryl resin in solid-phase peptide synthesis is limited because it cannot be used with the commonly available Boc-amino acids. This prompted us to investigate on the use of photoremovable 2′-nitrobenzhydryl polystyrene resin for the solid-phase peptide synthesis. In this paper we report the preparation and use of a new polymeric support, 2′-nitrobenzhydryl polystyrene resin (NBH-resin) which permits peptide synthesis with Boc-amino acids and the final cleavage of the attached peptide under neutral conditions on irradiation at 350 nm in alcoholic solutions. The principle of the photolytic deprotection of the carboxyl group by making use of the internal photoredox reaction of *o*-nitro aromatic compounds is exploited here.[6-8]

Results and Discussion

Preparation of NBH-resin from Cross-Linked Polystyrene. The NBH-resin (**4**) was prepared from the

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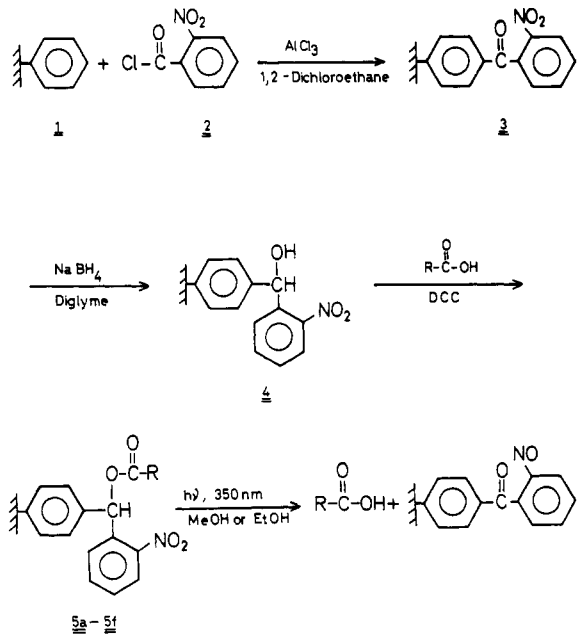
Scheme I



commercially available 2% divinylbenzene cross-linked polystyrene resin 1 by a two-stage polymer analogous reaction as depicted in Scheme I. The first step involves a Friedel–Crafts reaction of resin 1 with *o*-nitrobenzoyl chloride (2) in the presence of anhydrous aluminum chloride. The reaction was followed by the appearance of IR bands at 1665, 1530, and 1340 cm^{-1} characteristic of the >C=O and NO_2 groups in the product resin. The capacity of the resin was determined by the elemental analysis (1.1 mmol of N/g). Reduction of the resin 3 with sodium borohydride in diglyme afforded the NBH–resin (4). The reduction was followed by the disappearance of the carbonyl peak at 1665 cm^{-1} in the product resin and appearance of a new peak at 3500 cm^{-1} characteristic of the OH group. The peaks at 1530 and 1340 cm^{-1} indicated that the nitro group remained intact under the reduction conditions.

Coupling of N^{α}-*tert*-Butyloxycarbonyl Amino Acids with NBH-resin 4. Resins 5a–f. N^{α}-Boc-amino acids underwent esterification with the hydroxyl group of resin 4 by dicyclohexylcarbodiimide (DCC)-mediated coupling to give the 2′-nitrobenzhydryl ester resins **5a–f**. We found that the Boc-amino acids attached to the NBH-resin 4 could be obtained in the free state on irradiation in alcoholic suspensions. As a model reaction the carboxyl group of benzoic acid was esterified with the resin 4 by the DCC-mediated coupling to give resin **5a**. Irradiation of this resin in absolute ethanol at 350 nm resulted in the release of the free benzoic acid in 94% yield. A number of Boc-amino acids were coupled with the resin 4, resulting in resins **5b–f**. The incorporation of amino acids in these resins was determined by the amino acid analysis. Irradiation of these resins in ethanolic solutions at 350 nm for 12–14 h resulted in the release of the carboxyl free N-protected amino acids in 78–82% yield (Table I). The photolytic release of the Boc-amino acid from the resin was followed by withdrawing definite portions of Boc-Gly-NBH-resin **5f** from the photolysate at specific intervals and estimating the amount of amino acid (Figure 1).

Stability of the 2′-Nitrobenzhydryl Ester Resins in Acidolytic Conditions. In order to test the acid stability of the 2′-nitrobenzhydryl ester resin under the usual conditions of the removal of the Boc group, Boc-Gly-NBH-resin was taken as the test sample. The resin was treated with 4 N HCl–dioxane, 30% TFA–CH_2Cl_2, and 50% TFA–CH_2Cl_2 at definite intervals and the amount of amino acid remaining in the resin was estimated. The results are illustrated in Figure 2. No considerable loss of the amino acid was noted in 4 N HCl–dioxane for the usual 30-min treatment required for the complete removal of the Boc group. This points to the increased acid stability of the benzhydryl ester linkage through the introduction of a nitro group at the ortho position of one of the phenyl rings. This is consistent with the observation that a nitro group at the ortho position increases the acid stability of the ordinary benzyl ester linkage in solid-phase peptide synthesis.[9] The present observations indicate that the 2′-nitrobenzhydryl ester linkage is more prone to cleavage

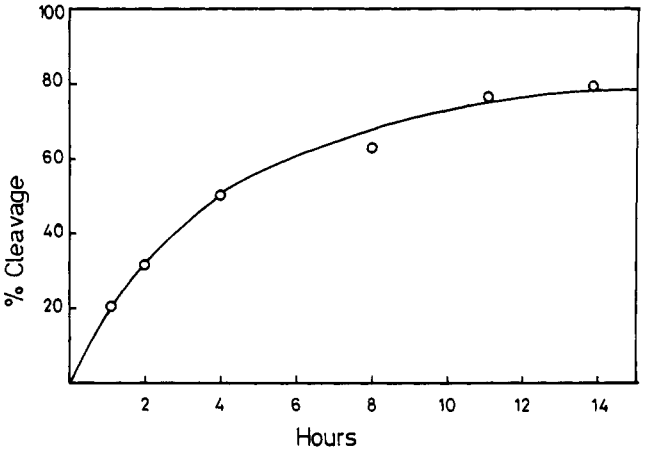


Figure 1. Photolytic cleavage yield of Boc-Gly from Boc-Gly-NBH-resin (**5f**) as a function of time.

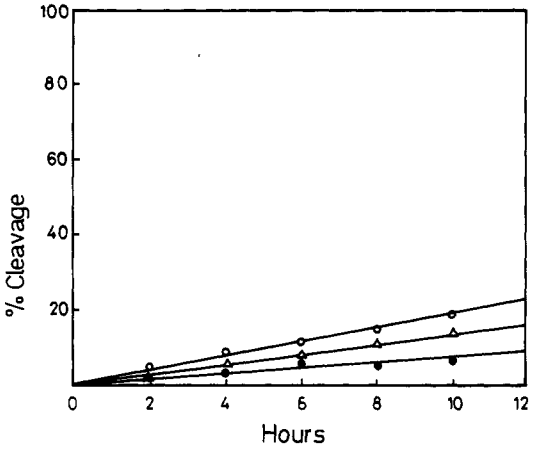


Figure 2. Stability of Boc-Gly-NBH-resin (**5f**) in acidic conditions. The symbols (●), (△), and (○) denote the rate of cleavage by 4 N HCl–dioxane, 30% TFA–CH_2Cl_2, and 50% TFA–CH_2Cl_2, respectively.

Table I. Photolytic Deprotection of Amino Acids from Resins 5a–f

5	R	duration of photolysis (h)	yield (%)	mp (°C)
a	C_6H_5CO	10	94	120–121
b	Boc-Ala	12	82	86–87
c	Boc-Leu	12	80	80–82
d	Boc-Val	14	78	78–80
e	Boc-Asp(Bzl)	14	78	101–103
f	Boc-Gly	14	80	88–90

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Table II. Photolytic Release of Protected Peptides from the NBH-resin

peptide resin	amount of first amino acid (mmol/g)	duration of photolysis (h)	cleavage yield (%)[a]	amino acid analysis
Boc-Pro-Gly-NBH-resin	Gly, 0.72	20	56	Pro, 0.92; Gly, 1.02
Boc-Ala-Gly-Val-NBH-resin	Val, 0.68	24	60	Ala, 0.98; Gly, 1.02; Val, 1.0
Boc-Leu-Ala-Gly-Val-NBH-resin	Val, 0.68	24	58	Leu, 1.0; Ala, 0.95; Gly, 1.03; Val, 1.0

[a] Based on amino acid analysis of the peptide remaining on the polymer after removal of the cleaved peptide.

in 50% TFA–CH_2Cl_2 than 4 N HCl–dioxane. Hence throughout the peptide synthesis using NBH–resin we have used 4 N HCl–dioxane as the Boc-deprotecting reagent.

The Boc group was found to be unaffected under the conditions of the photolytic release of the amino acids or peptides from the 2′-nitrobenzhydryl ester resins. The photosensitive 2-nitrobenzyl and related groups have been established to be stable under a variety of conditions encounted in the synthetic methodology of peptides.[10] The light-induced internal oxidation–reduction reactions of aromatic nitro compounds containing a carbon–hydrogen bond ortho to the nitro group have been made use of in the design of photolytically detachable 2-nitrobenzyl anchoring and protecting groups in the polymer-supported peptide synthesis.[11-14] The mechanism of the photolytic cleavage of the new 2′-nitrobenzhydryl resin is analogous to that of the *o*-nitrobenzyl systems.[15]

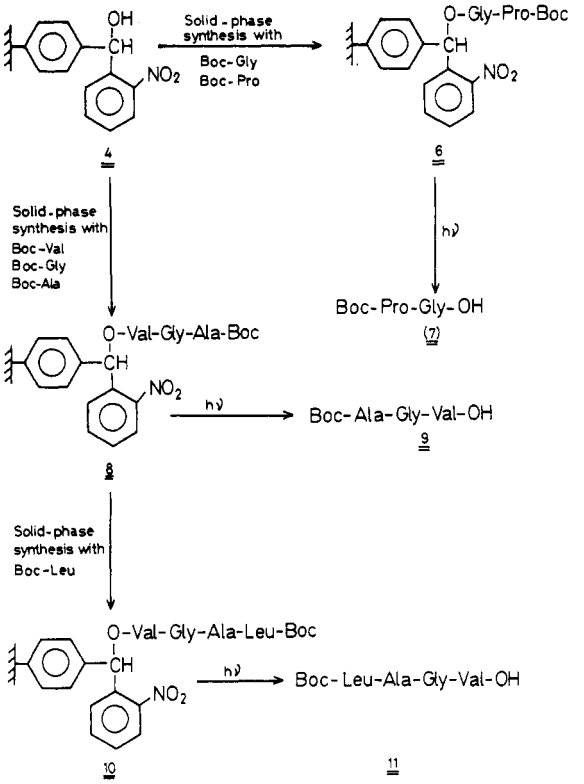
Peptide Synthesis Using NBH-resin (4). All the Boc amino acids were coupled to the resin 4 by the symmetric anhydride method using a three-fold molar excess of the Boc-amino acid and 1.5-fold molar excess of DCC, except in the case of Boc-Pro-OH where a 6-fold molar excess was used. The capacity of the first amino acid was determined by the amino acid analysis. Each step of the coupling was monitored by the semiquantitative Ninhydrin test.[16] Three model peptides, Boc-Pro-Gly-OH, Boc-Ala-Gly-Val-OH, and Boc-Leu-Ala-Gly-Val-OH, were synthesized on resin 4 (Scheme II). The finished peptides were cleaved from the support by photolysis at a wavelength of 350 nm in anhydrous ethanol in the absence of oxygen. Irradiation for 20–24 h resulted in the release of N^{α}-Boc-protected peptides in 56–60% yield (Table II).

These results establish that the protected peptide acids suitable for fragment coupling in solution or on a solid support[17] can be synthesized in good yield by using the photoremovable 2′-nitrobenzhydryl polystyrene resin 4. The new resin is more stable than the already reported benzhydryl resin under the various conditions encountered in the solid-phase peptide synthesis using the commonly available Boc-amino acids.

Experimental Section

Melting points are uncorrected. All the solvents were distilled and purified according to the literature procedure. Copolystyrene–2% divinylbenzene beads (200–400 mesh) were purchased from Fluka. Infrared spectra were recorded on a Pye Unicam Sp3-300 spectrophotometer using KBr pellets. Microanalyses were

Scheme II



done at the Regional Sophisticated Instrumentation Centre, Lucknow. The photochemical irradiations were carried out with a Philips HPK, 125-W mercury lamp housed in a water-cooled immersion-type vessel.

Friedel–Crafts Reaction of Polystyrene Resin 1 with *o*-Nitrobenzoyl Chloride. Preparation of 2′-Nitrobenzoyl Polystyrene Resin (3). Copolystyrene–2% divinylbenzene cross-linked resin (10 g, Fluka, 200–400 mesh) was swelled in 1,2-dichloroethane (100 mL) for 1 h. *o*-Nitrobenzoyl chloride (4.6 g, 30 mmol) was added followed by slow addition of anhydrous $AlCl_3$ (6 g, 45 mmol). The mixture was stirred under reflux for 16 h. Dioxane–4 N HCl (3:1, 100 mL) was added in to the reaction mixture with cooling in an ice bath. The resin was filtered, washed successively with dioxane–4 N HCl (3:1), dioxane–water (3:1), dioxane, MeOH, and CH_2Cl_2, and dried in vacuo to yield the resin 3 (11.6 g): IR (KBr) 1665 cm^{-1} (>C=O), 1530 and 1340 cm^{-1} (NO_2). Anal. N, 1.6% (1.1 mmol/g).

Reduction of Resin 3 with $NaBH_4$. Preparation of NBH-resin (4). Resin 3 (10 g) in diglyme (100 mL) was stirred with a solution of $NaBH_4$ (1.5 g, 39.6 mmol) in diglyme (30 mL) at 0 °C for 30 min and then at 50–55 °C for 24 h. The reaction mixture was cooled to 0 °C and concentrated HCl (20 mL) was added slowly. The resin was collected by filtration and washed thoroughly with hot water, ethanol, methanol, and CH_2Cl_2. The product resin was dried in vacuo. IR (KBr): 3500 cm^{-1} (OH), 1530 and 1340 cm^{-1} (NO_2).

Coupling of Boc-Amino Acids with NBH-resin. Preparation of Resins 5a–f. General Procedure. All the Boc-amino acids were coupled to the NBH-resin by the symmetric anhydride method. In a typical procedure a 3-fold molar excess of the Boc-amino acid in CH_2Cl_2 and a 1.5-fold molar excess of DCC were stirred together for 1 h at 0 °C. This solution containing

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the symmetric anhydride of the Boc-amino acid was filtered directly into the NBH-resin (1 g) swelled in CH_2Cl_2 (10 mL). Pyridine (0.4 mL) was added and the mixture was stirred at room temperature for 24 h. The resin was filtered, washed with CH_2Cl_2 (10 × 3 × 2 min) and methanol (10 mL × 3 × 2 min), and dried in vacuo. The capacity of the resin was determined by amino acid analysis. The acid stability of the NBH-resin ester linkage was studied by using Boc-Gly-NBH-resin (**5f**) as the test sample. Boc-Gly-NBH-resin (200 mg) in 5 mL of 4 N HCl–dioxane, 30 TFA–CH_2Cl_2, or 50% TFA–CH_2Cl_2 was stirred separately for definite intervals and the amount of amino acid remaining in the resin was determined (Figure 2).

Peptide Synthesis Using NBH-resin. General Procedure. All the Boc-amino acids were coupled to the NBH-resin by the symmetric anhydride method using a 1.5-fold molar excess of DCC and a 3-fold molar excess of Boc-amino acids except for Boc-Pro-OH where a 6-fold molar excess was used. The coupling time for the first amino acid was 6 h. A second coupling was performed for 1 h to ensure maximum incorporation of the first amino acid. The subsequent amino acids were coupled for 3 h. The Boc group was removed with 4 N HCl–dioxane (10 mL/g) for 30 min; 10% Et_3N in CH_2Cl_2 was used for neutralization. Each step of the coupling was followed by the semiquantitative ninhydrin test. Using these procedures Boc-Pro-Gly-NBH-resin (**6**), Boc-Ala-Gly-Val-NBH-resin (**8**), and Boc-Leu-Ala-Gly-Val-NBH-resin (**9**) were synthesized (Scheme II).

General Procedure for the Photolytic Cleavage of the Resin-Bound Peptides. The peptide resin (1 g) was suspended in anhydrous ethanol (150 mL) in a water-cooled immersion-type photochemical irradiator. The suspension was deaerated with dry N_2 gas for 1 h and irradiated with a philips HPK, 125-W mercury lamp at 350 nm, under gentle magnetic stirring. A 40% solution of $CuSO_4$ was used to filter out light waves below 320 nm. After irradiation for 20–24 h, the resin was filtered and washed with ethanol, methanol and CH_2Cl_2. The solvent was evaporated from the combined filtrate and washings in a vacuum rotary evaporator. The crude products were purified by chromatography and characterized by amino acid analysis. The analytical details are shown in the Table II.

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Registry No. BOC-Ala-OH, 15761-38-3; BOC-Leu-OH, 13139-15-6; BOC-Val-OH, 13734-41-3; BOC-Asp(OBzl)-OH, 7536-58-5; BOC-Gly-OH, 4530-20-5; BOC-Pro-Gly-OH, 51785-82-1; BOC-Ala-Gly-Val-OH, 56133-97-2; BOC-Leu-Ala-Gly-Val-OH, 61165-83-1; $O_2NC_6H_4$-*o*-COCl, 610-14-0; styrene–divinylbenzene copolymer, 9003-70-7.

Synthesis of (4*S*)- and (4*R*)-Methyl 2-Amino-1-pyrroline-5-carboxylates and Their Application to the Preparation of (4*S*)-(+)- and (4*R*)-(-)-Dihydrokikumycin B

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The syntheses of the two enantiomeric forms of dihydrokikumycin B [(4*S*)-(+)-**7a** and (4*R*)-(-)-**7b**] with enantiomeric excess of 80 ± 4% are described. For this purpose, the 2-amino-1-pyrroline system and the pyrrole unit were prepared separately, and then subsequent coupling of these two groups afforded the carbon framework of **7a** and **7b**. Both antipodal forms of the 2-amino-1-pyrroline synthon, (4*S*)-**11a** and (4*R*)-**11b**, were prepared from the corresponding (*S*)- and (*R*)-pyroglutamic acids. Both enantiomers of the 2-pyrrolidone analogues [(4*S*)-(+)-**20a** and (4*R*)-(-)-**20b**] of dihydrokikumycin B were also synthesized. These optically active compounds bind to duplex native DNA with the following constants: (+)-**7a**, 1.24 ± 0.1; (-)-**7b**, 1.74 ± 0.1; (+)-**20a**, 0.35 ± 0.1; (-)-**20b**, 0.14 ± 0.1 × 10^6 M^{-1}.

The modest family of naturally occurring oligopeptide antibiotics includes kikumycin B (**1**),[1] anthelvencin A (**2**),[2] distamycin (**3**),[3] netropsin (**4**),[4] amidomycin (**5**),[5] and noformycin (**6**)[6] (Figure 1). These agents have generated considerable interest on the part of synthetic chemists and pharmacists, owing to their broad spectrum of biological properties, such as antiviral, antibacterial, and anticancer activities.[3b,7] The biological activities of netropsin and distamycin appear to arise, in part, from their unique ATTT and ATTTT sequence specificity and minor groove-selective binding to DNA.[8] Physical studies, including X-ray analysis of a complex of netropsin with the symmetrical dodecamer $d(CGCGAATTCGCG)_2$,[8b] ^1H NMR investigation,[9] and CD studies,[7,9c] have provided structural details on the nature of the interactions between drug and receptor that contribute to the marked specif-

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