to be D_2O exchangeable, and the ^1H NMR assignments were confirmed using the COSY experiment; ^{13}C NMR (DMSO-d_6) δ 25.05 (C(2')CH_3), 34.29 (C(4)), 66.97 (C(3)), 71.25 (C(3')), 73.42 (C(2')), 76.42 (C(1')), 80.57 (C(6) or C(1)), 80.91 (C(1) or C(6)), 114.38 (C(5a)), 145.03 (C(5)), 165.63 (C(7) or C(9)), 165.83 (C(9) or C(7)); the ^{13}C NMR assignments were confirmed using the APT experiment; MS (+FAB) 303 $[M + 1]^+$; M_r (+FAB) 303.119 22 $[M + 1]^+$ (calcd for $C_{12}H_{18}N_2O_7$ 303.119 27).

(1*R*,2*S*,3*S*,9*R*)-2,3,9-Trihydroxy-1-methoxy-3-methyl-8-methylene-5-oxa-10,12-diazabicyclo[7.2.2]tridecane-11,13-dione (10).[18] A solution of **2** (25 mg, 0.07 mmol) in MeOH (1.0 mL) was stirred at rt (48 h). The solvent was removed in vacuo and the residue was taken up in a minimum amount of MeOH. Preparative TLC (1:3 MeOH–CH_2Cl_2) afforded compound **10** as a colorless solid: yield 8.1 mg (36%); mp 215–218 °C dec; R_f 0.65 (1:3 MeOH–CH_2Cl_2); IR (KBr) 1675 (br) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.05 (s, 3 H, C(2')CH_3), 2.38–2.45 (m, 2 H, C(4)H_2), 2.99 (d, 1 H, C(3')*H*H', J = 9.0 Hz), 3.17 (d, 1 H, C(3')H*H'*, J = 9.0 Hz), 3.22 (s, 3 H, OCH_3), 3.30–3.50 (m, 2 H, C(3)H_2), 3.77 (s, 1 H, C(1')H), 5.06 (s, 1 H, C(5a)*H*H'), 5.42 (s, 1 H, C(5a)H*H'*), 7.39 (s, 1 H), 8.76 (s, 1 H); the remaining exchangeable protons were not detected; ^{13}C NMR (DMSO-d_6) δ 25.07 (C(2')CH_3), 34.26 (C(4)), 49.64 (OCH_3), 66.86 (C(3)), 70.81 (C(3')), 72.62 (C(2')), 76.51 (C(1')), 80.70 (C(6)), 85.48 (C(1)), 115.11 (C(5a)), 145.81 (C(5)), 163.19 (C(7) or C(9)), 166.53 (C(9) or C(7)); the ^{13}C NMR assignments were confirmed using the APT experiment; MS (-FAB) 315 $[M - H]^-$.

Hydrolysis of 10. CH_3SO_3H (0.2 μL, 3 μmol) was added to an aqueous solution (0.4 mL) of **10** (1 mg, 3 μmol) and stirred at rt (6 h). The solution (pH ~2) was neutralized with dilute aqueous KOH and the solvent removed in vacuo. TLC analysis of the reaction prior to workup showed only the presence of **3**. The residue was triturated with MeOH and filtered and the solvent removed: yield 0.8 mg (84%); R_f 0.40 (1:4 MeOH–$CHCl_3$); ^1H NMR (DMSO-d_6) δ 1.05 (s, 3 H, C(2')CH_3), 2.38–2.43 (m, 2 H, C(4)H_2), 3.02 (d, 1 H, C(3')*H*H', J = 9.1 Hz), 3.10 (d, 1 H, C(3')H*H'*, J = 9.1 Hz), 3.20–3.30 (m, 2 H, C(3)H_2), 3.80 (s, 1 H, C(1')H), 4.99 (s, 1 H, C(5a)*H*H'), 5.40 (s, 1 H, C(5a)H*H'*), 7.50 (s, 1 H), 8.40 (s, 1 H); the remaining exchangeable protons were not detected.

Methanolysis of 3. CH_3SO_3H (1 μL, 15 μmol) was added to a MeOH solution (1 mL) of **3** (5 mg, 17 μmol) and stirred at rt (45 min). TLC analysis of the reaction prior to workup showed the presence of **10** and two additional, unidentified minor compounds. The solvent was removed in vacuo, and the residue was immediately subjected to preparative TLC (1:4 MeOH–$CHCl_3$): yield 1.8 mg (33%); R_f 0.65 (1:3 MeOH–CH_2Cl_2); ^1H NMR (DMSO-d_6) δ 1.05 (s, 3 H, C(2')CH_3), 2.37–2.46 (m, 2 H, C(4)H_2), 2.95 (d, 1 H, C(3')*H*H', J = 9.0 Hz), 3.14 (d, 1 H, C(3')H*H'*, J = 9.0 Hz), 3.21 (s, 3 H, OCH_3), 3.30–3.50 (m, 2 H, C(3)H_2), 3.78 (s, 1 H, C(1')H), 5.04 (s, 1 H, C(5a)*H*H'), 5.43 (s, 1 H, C(5a)H*H'*), 7.32 (s, 1 H), 8.65 (s, 1 H); the remaining exchangeable protons were not detected; ^{13}C NMR (DMSO-d_6) δ 25.02 (C(2')CH_3), 34.21 (C(4)), 49.58 (OCH_3), 66.83 (C(3)), 70.78 (C(3')), 72.57 (C(2')), 76.49 (C(1')), 80.68 (C(6)), 85.46 (C(1)), 115.06 (C(5a)), 145.79 (C(5)), 163.12 (C(7) or C(9)), 166.47 (C(9) or C(7)).

Reaction of Compound 3 with Ethanethiol. A solution of **3** (3.0 mg, 0.01 mmol) and EtSH (12 μL, 0.16 mmol) in a THF–H_2O (3:1; 0.3 mL, "pH" 6.8) mixture was degassed with Ar (3 min) and then capped. After the "pH" of the solution was maintained (24 h) at 6.8, then at 10.2 (24 h), and finally at 12.5 (24 h), no reaction was observed (TLC analysis).

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Registry No. **1**, 38129-37-2; **2**, 71993-96-9; **3**, 134757-71-4; **3**·H_2O, 134875-89-1; **10**, 134757-72-5.

Supplementary Material Available: Tables 1–6 giving a complete listing of data collection and processing parameters, atomic coordinates and equivalent isotropic displacement parameters, bond lengths, bond angles, hydrogen-bonding parameters (7 pages). Ordering information is given on any current masthead page.

Use of Tetrabutylammonium Fluoride as a Facile Deprotecting Reagent for 4-Nitrobenzyl, 2,2,2-Trichloroethyl, and Phenacyl Esters of Amino Acids

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A 4-nitrobenzyl (Nbn) ester has better stability than a Bn ester against the acidic conditions used for removal of amino acid and peptide protecting groups and has been recommended for the protection of Glu and Asp side chains in solid-phase peptide synthesis.[1] Several methods to cleave the Nbn ester, such as Na_2S,[2] zinc,[3] or $Na_2S_2O_4$[4] reduction, have been reported besides catalytic hydrogenolysis and Birch reduction.

It is sometimes difficult to remove the yellow byproducts resulting from polymerization of the aromatic amine generated by reductive cleavages. Alkaline hydrolysis avoids this problem but lacks selectivity relative to other esters, except *t*-Bu esters, and is apt to cause racemization. In the course of our study on a total synthesis of nodularin[5] and microcystins,[6] we have found that Bu_4NF selectively cleaves Nbn esters of amino acids and is a useful reagent for this transformation.

Bu_4NF has been widely used for deprotecting silyl ethers and esters since it was introduced for this purpose.[7] This reagent is also used in peptide syntheses as a reagent for the removal of protecting groups labile to hard bases, such as Tmse,[8] Teoc,[9] Fmoc,[10-12] and Ppt[12,13] groups and as a

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Table I. Removal of Amino Acid Protecting Groups with Bu_4NF

entry	starting material	solvent	reagent (equiv)	product[a]	yield, %	$[\alpha]^{25}_D$ (c, 1.0, MeOH), deg: reaction	standard[b]
1	Boc-Glu(ONbn)-OBn (**1a**)	THF	2	Boc-Glu-OBn (**1b**)[c]	72	+18.9	+19.0
2	**1a**	DMF	6	**1b**[c]	82	+19.1	+19.0
3	**1a**	DMSO	6	**1b**[c]	84	+19.0	+19.0
4	Boc-Glu(OBn)-ONbn (**2a**)	THF	6	Boc-Glu(OBn)-OH (**2b**)[c]	92	+13.6	+13.9[d]
5	Boc-Glu(OAll)-ONbn (**3a**)	DMF	5	Boc-Glu(OAll)-OH (**3b**)	96	-3.2	-3.1[e]
6	Cbz-Asp(O-*t*-Bu)-ONbn (**4a**)	THF	5	Cbz-Asp(O-*t*-Bu)-OH (**4b**)[c]	93	+8.5	+8.9[d]
7	Boc-Asp(OChx)-ONbn (**5a**)	THF	3	Boc-Asp(OChx)-OH (**5b**)	94	+0.6	+0.6
8	Cbz-Ala-ONbn (**6a**)	THF	3	Cbz-Ala-OH (**6b**)	93	-19.8	-20.1[d]
9	Boc-Leu-ONbn (**7a**)	THF	3	Boc-Leu-OH (**7b**)	94	-18.6	-18.8
10	Boc-Thr-ONbn (**8a**)	DMF	9	Boc-Thr-OH (**8b**)	90	-2.0	-2.0
11	Cbz-Ala-OTce (**9a**)	THF	2	**6b**	95	-19.7	-20.1[d]
12	Boc-Leu-Pro-OTce (**10a**)	THF	2	Boc-Leu-Pro-OH (**10b**)	95	+5.7	+5.5[e]
13	**10a**	DMF	9	**10b**	96	+5.7	+5.5[e]
14	Cbz-Ala-OPac (**11a**)	DMF	4	**6b**	98	-19.7	-20.1[d]

[a] Abbreviations, see Text. 1 = D isomer, 2–11 = L isomer. [b] Measured before esterification unless otherwise noted. [c] Dicyclohexylamine salt. [d] Analyzed by chiral GC. [e] Value obtained after deprotection with Zn/AcOH.

reagent for cleavage of a peptide chain from a resin support in solid-phase synthesis.[11-14] Recently, Nakata et al. have successfully used this reagent also for the ring opening of an α,β-unsaturated δ-lactone.[15] In the course of our nodularin studies we have independently discovered that Bu_4NF is useful for the deprotection of Nbn, Tce, and Pac esters of amino acids and report our results here.

Nbn esters were hydrolyzed in good yield by Bu_4NF treatment in THF, DMF, or DMSO (Table I, entries 1–10) while Cbz and Boc groups were preserved under these conditions. No remarkable difference was observed among the three solvents employed, and the reaction solvent can be chosen according to the solubility of the substrate. For diesters of Glu and Asp the Nbn esters were hydrolyzed selectively in the presence of Bn, All, *t*-Bu, and Chx esters (entries 1–7). The product from the Nbn group was characterized as NbnOH from the mass and ^1H NMR spectra of the isolated compound. NbnOH was easily removed by extraction, and no yellow byproduct was detected. Although a deep blue color developed when the reagent was introduced to a solution of the Nbn ester, as Ueki et al. observed,[11] the color disappeared on the addition of H_2O for workup. When the reaction was worked up as in the Experimental Section the products were purified easily by recrystallization or column chromatography.

Bn esters as well as Nbn asters have been reported to be cleaved by Bu_4NF in earlier reports,[8,11] although the reported reaction of the Bn ester (benzyl benzoate) was rather slow (77% after 6 h)[11] while the Nbn ester reacted very rapidly. In the present study, however, much greater selectivity was observed (entries 1–4), although some simultaneous cleavage of the α-Bn ester was observed for **1a** in each solvent (and especially in THF) as a small amount of BnOH was detected in the reaction, which gave relatively lower yields (72–84%) for entries 1–3. Thus, the selectivity is not perfect for Nbn vs Bn esters, but, nevertheless, excellent under the present conditions (10–30 min, rt).

The reaction was also applied to Pac and Tce esters, which showed reactivity similar to that of the Nbn ester toward deprotection. The Pac ester was cleaved rapidly (entry 14), as reported,[11,12] and the Tce esters were also deprotected in good yields (entries 11–13). The blue color developed in the reaction of Nbn esters was not observed for these reactions with Pac and Tce esters.

No racemization was reported previously in removing a Tmse ester[8] or in cleaving a peptide chain from a resin support with Bu_4NF.[11] In the present study the products from entries 4 (**2b**), 6 (**4b**), 9 (**6b**), 11 (**6b**), and 14 (**6b**) were deprotected in the usual manner before recrystallization then derivatized for GC analysis on a chiral capillary column. The antipode of each compound was observed in only a trace amount when the sample was injected at very high concentration. Thus, racemization is not a problem with this deprotection.

Bu_4NF can be used for the removal of the Nbn group as an alternative method to reductive cleavages. The simple and mild reaction, high yield, and freedom from the yellow byproduct are considered to be advantageous. We, therefore, feel that cleavage with Bu_4NF can be applied widely for the removal of Nbn, Tce, and Pac groups and will stimulate wider use of the Nbn protecting group.

More recently, we found that KHMDS cleaves Nbn ester at -78 °C in THF (data not shown). Application of the Bu_4NF method to peptide syntheses will be described elsewhere.

Experimental Section

General. NMR spectra were recorded on an XL-200 spectrometer and mass spectra on either a ZAB-SE or a 70-SE-4F spectrometer operating in the FAB mode, using Xe and a matrix of dithiothreitol/dithioerythritol.[16] Specific rotations were measured on a DIP-370 digital polarimeter. Compounds prepared showed satisfactory HRFABMS and ^1H NMR spectra.

Compound **1b** was made by the method of Schröder and Klieger.[17] Compounds **2b** and **4b–8b** were commercial products.

The Nbn esters (**1a**, **2a**, and **4a–8a**) and Pac ester (**11a**) were prepared by reaction of the amino acid with the corresponding bromide and $KHCO_3$[18] or of the amino acid DCHA salt with the bromide[19] in DMF. Compound **3a** was made from Boc-Glu-ONbn DCHA salt[10] and allyl bromide as above. The Tce ester (**9a**) was obtained using the DCC/DMAP method with TceOH.[20] Compound **10a** was synthesized from Boc-Leu-OH and H-Pro-OTce.

A solution of Bu_4NF (1.0 M) in THF and Bu_4NF hydrate, from which a 2 M solution in DMF or DMSO was prepared, were commercial products.

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General Procedure for Reaction with Bu_4NF. To a solution of each protected amino acid (0.2 mmol) was added the designated equivalent of Bu_4NF in the same solvent (total 2 mL), and the solution was stirred for 10–30 min (checked by TLC; $CHCl_3$:MeOH = 9:1) at rt. The reaction mixture was diluted with H_2O (2 mL) and benzene–EtOAc (1:1, 20 mL) and extracted with 5% $NaHCO_3$ (3 × 10 mL). The aqueous extract was acidified to pH 3–4 with saturated $KHSO_4$ and extracted with EtOAc (3 × 10 mL). In the case of Boc-Thr-OH (**8b**), the aqueous solution was saturated with NaCl prior to the EtOAc extraction. For Boc-Leu-Pro-OH (**10b**), alkaline extraction was omitted, but the organic layer was washed with 5% $KHSO_4$. The organic extract was washed with H_2O and saturated brine, dried (Na_2SO_4), and evaporated, and the residue was purified by LH-20 (entries 4–6, 12–14) or silica gel (entries 1–3) column chromatography and/or recrystallization (**1b**, **2b**, **4b–8b**). Compounds **1b**, **2b**, and **4b** were converted to their DCHA salts before recrystallization.

GC Analysis. The products (ca. 0.2 mg) obtained from entries 6 (**4b**), 8 (**6b**), 11 (**6b**), and 14 (**6b**) were deprotected by HBr–AcOH before recrystallization, as was **2b** (entry 4), by H_2–Pd/C followed by HCl–dioxane. Each deprotected amino acid was derivatized as its *N*-trifluoroacetyl isopropyl ester and analyzed on Chirasil Val III.[21]

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Abbreviations: All = allyl; Chx = cyclohexyl; DCHA = dicyclohexylamine; Fmoc = [(9-fluorenylmethyl)oxy]carbonyl; KHMDS = potassium hexamethyldisilazide; Nbn = 4-nitrobenzyl; Pac = phenacyl; Ppt = (diphenylphosphino)thioyl; Tce = 2,2,2-trichloroethyl; Teoc = 2-[(trimethylsilyl)ethoxy]carbonyl; Tmse = 2-(trimethylsilyl)ethyl.

Registry No. **1a**, 134757-73-6; **1b**·DCHA, 34404-29-0; **2a**, 42726-92-1; **2b**·DCHA, 13574-84-0; **3a**, 134757-74-7; **3b**, 132286-79-4; **4a**, 27486-72-2; **4b**·DCHA, 23632-70-4; **5a**, 134757-75-8; **5b**, 73821-95-1; **6a**, 10144-64-6; **6b**, 1142-20-7; **7a**, 77163-64-5; **7b**, 13139-15-6; **8a**, 77313-56-5; **8b**, 2592-18-9; **9a**, 67850-37-7; **10a**, 113317-89-8; **10b**, 64205-66-9; **11a**, 6530-41-2; TceOH, 115-20-8; Bu_4NF, 429-41-4; 4-$BrCH_2C_6H_4NO_2$, 100-11-8; $PhCOCH_2Br$, 70-11-1; BOC-Glu-ONbn·DNHC, 30924-92-6; H-Pro-OTce, 126134-58-5.

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C-Heteroarylation of Sugars by Indolylbromomagnesium Salts. Synthesis of 3-(Alditol-1-yl)indoles and Their Cyclization to Indole *C*-Nucleoside Analogues

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Carbon nucleosides as well as glycosides bearing carbon-linked nitrogen heterocycles have elicited numerous synthetic and biological studies[2] due to their potential antiviral and antitumor activities.[3] Recently, we introduced bromomagnesium salts of hydroxylated aromatic

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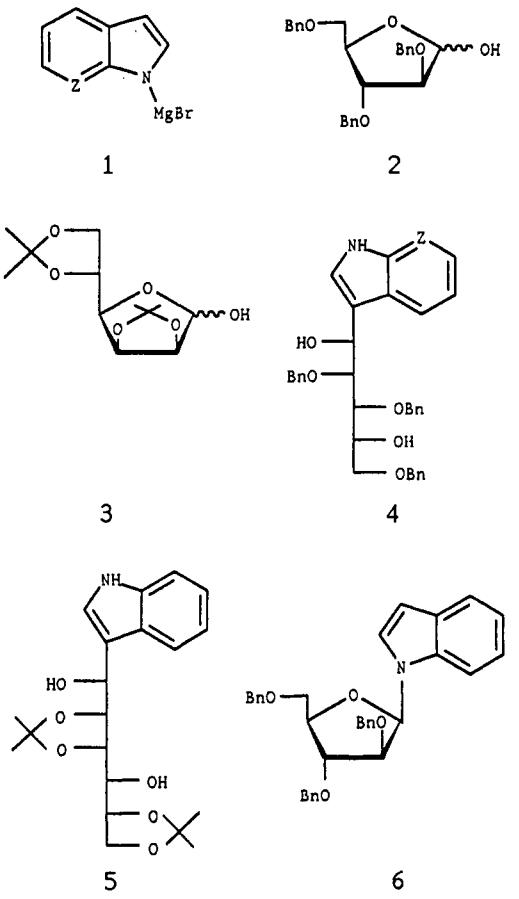
Table I. Synthesis of D-*manno*- and D-*glycero*-D-*talo*-Indolylalditols 4 and 5

run	indole	sugar	product	yield,[a] %
1	**1a**	**2**	**4a**	65
2	**1b**	**2**	**4b**	80
3	**1a**	**3**	**5**	70

[a] Based on pure isolated compound.

Chart I



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