2.5–0.7 (m, 12 H, including a characteristic approximate Me quartet centered at δ 0.94. Calcd for $C_{12}H_{18}O_4$, *m/e* 226.1205; found, *m/e* 226.1202.

Attempted Synthesis of 2d from Dimethyl Glutarate. Via the procedure given above, the dianion of dimethylglutarate was prepared, and either 1,4-dichlorobutane, 1,4-dibromobutane, or 1-bromo-4-chlorobutane added to it. After reaction and workup, GC (OV-101), GC–MS, and ^1H NMR indicated only **11** (i.e., not **2d**) had formed. Further attempts to cyclize **11** with either LDA or KH failed to produce anything but possibly very minor amounts of **2d** (GC analysis, OV-101).

Acknowledgment. We thank Mr. Diem Le for assistance in obtaining some of the ^{13}C NMR spectra.

Registry No. 1b, 42145-38-0; **1b** 2-ethyl, 79028-22-1; **1c**, 75328-54-0; **1d**, 79028-23-2; *cis*-**2b**, 39590-04-0; **2c**, 62638-06-6; **2d** (isomer 1), 54905-30-5; **2d** (isomer 2), 79028-24-3; **3b**, 79028-25-4; **3c** (isomer 1), 79028-26-5; **3c** (isomer 2), 79028-27-6; **3d**, 79028-28-7; **4**, 72566-84-8; **5**, 79028-29-8; (*Z*)-**6**, 79028-30-1; **7**, 79028-31-2; **11a**, 79028-32-3; **11b**, 79028-33-4; bicyclo[3.1.1]heptane-1,5-dicarboxylic acid, 75328-55-1; dimethyl glutarate, 26717-67-9; *cis*-1,4-dichloro-2-butene, 1476-11-5.

Preparation of Protected Amino Aldehydes

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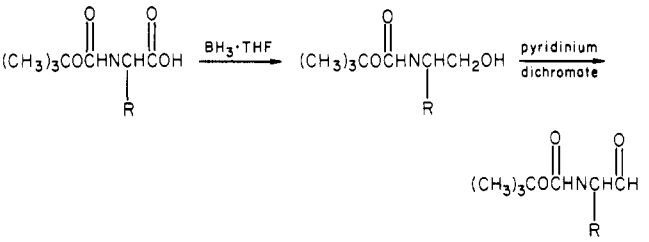
Received May 7, 1981

The recently identified class of peptide aldehydes, which includes leupeptin and antipain, is of increasing interest due to the inhibitory properties of these molecules toward certain classes of proteolytic enzymes.[2] Due to the proposed possible therapeutic use of these molecules as inhibitors of metabolic diseases and muscular dystrophy in particular,[3,4] efficient methods for their preparation are urgently needed. The synthesis of peptide aldehydes is challenging due to the possible modifications of the amino acid side chains, as well as probable racemization and cyclization of the product. Amino acid and peptide aldehydes have been reported either by oxidation of the corresponidng alcohols[5,6] or by reduction of the acids and esters.[7,8] In most cases, the procedures were limited to those peptides and amino acids which did not contain other functional groups sensitive to the oxidizing or reducing conditions. The reported yields were low, and excessive racemization occurred when prolonged silica gel column chromatography was used for purification.[7]

A study was undertaken to evaluate previously utilized procedures for the synthesis of peptide aldehydes, and, if necessary, to establish new ways of preparing such molecules. In our hands, the previously reported procedures[7,8] failed to provide sufficient quantities of optically pure aldehydes. However, high yields of the desired products were obtained by oxidation of the corresponding alcohols with pyridinium dichromate,[9] as shown in the eq 1. This



reagent was introduced by Corey and Schmidt and has not been previously applied to the synthesis of peptide aldehydes. For a reagent to be useful with amino acids and peptides, it must not affect the commonly used protecting groups for the amino acids or lead to product racemization. Due to the variety of side chains of the amino acids, as well as the presence of the amino terminus, different types of protecting groups are required simultaneously even in a short peptide. Compatibility of the reducing and/or oxidizing agent with each of these types of protection has been the most difficult problem to overcome.

Limited information is available on the effect of reducing agents on protecting groups commonly used in peptide synthesis. Previous studies, on the other hand, indicated several ways of producing optically pure amino alcohols from nonprotected amino acids.[10–12] A study was, therefore, performed to determine the optimal reagents and conditions for the preparation of the intermediate alcohols from the corresponding protected amino acids.[13] Two reagents, lithium aluminum hydride ($LiAlH_4$) and lithium diisobutylaluminum hydride (DIBAL), were found to be detrimental to the N-terminal protection. Borane–THF was the only reagent that provided the protected, optically pure amino alcohols.

Experimental Procedures

Tetrahydrofuran (THF) was distilled from $LiAlH_4$ prior to its use. Methylene chloride, HPLC grade, was purchased from Burdick Jackson and was used without any further purification. Borane–THF (1 M solution), $LiAlH_4$, and DIBAL were purchased from Aldrich Chemical Co. Nuclear magnetic resonance spectra (^1H NMR) were obtained on a Varian EM-390 instrument. Chemical shifts are given in δ values (parts per milltion) downfield from tetramethylsilane, and multiplicites are given as follows: s, singlet; d, doublet; t, triplet, q, quartet; m, multiplet (with relative areas as 1 H, 2 H, 3 H, etc.). Infrared spectra were obtained as $CHCl_3$ solutions on a Beckman Acculab instrument. Optical rotations were recorded on a Bausch and Lomb polarimeter in 1-dm cells at 23 °C by using the Na D line. Thin-layer chromatography was performed on silica gel 60 F precoated TLC sheets from E. Merck; the solvent systems for plate development were chloroform–methanol (9:1) and ethyl acetate. The protected amino acids were purchased from Chemical Dynamics Corp., and their purity was established prior to utilization by TLC and melting point.

Reduction of Protected Amino Acids to Alcohols. The amino acid (10.0 mmol) was dissolved in 10 mL of THF and added dropwise over a period of 30 min to a 0 °C solution of BH_3·THF (20 mL, 20.0 mmol), under N_2. After the mixture was stirred for an additional 1–2 h at 0 °C, depending on the amino acid being reduced, the reaction was quenched with a 10-mL solution of 10% HOAc in MeOH, and the solvent was evaporated. The residue was dissolved in EtOAc and extracted with 1 M HCl, H_2O, and 1 M NH_4HCO_3. After being dried over $MgSO_4$, the product was

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0022-3263/81/1946-4797$01.25/0

Table I. Preparation of Protected Amino Aldehydes by Pyridinium Dichromate

amino aldehyde	^{1}H NMR[a] ($CDCl_3$) δ	IR,[b] μM	[α][c] (concn)	% yield	mp of 2,4-DNP deriv, °C
BocAla-al	9.7 (s, 1 H), 1.4 (s, 9 H), 1.3 (d, 3 H)	5.8	1.0 (1.0)	75	143–145
BocVal-al	9.8 (s, 1 H), 1.4 (s, 9 H), 0.9 (d, 6 H)	5.8, 5.9	1.2 (1.0)	95	145–148
BocPhe-al	9.5 (s, 1 H), 7.2 (s, 5 H), 1.4 (s, 9 H)	5.8, 5.9, 14.2	2.9 (3.0)	80	163–164
BocAsp(Bzl)-al	9.7 (s, 1 H), 7.3 (s, 5 H), 5.1 (s, 2 H), 1.4 (s, 9 H)	5.8, 5.9, 15.0	7.7 (1.0)	90	153–155
BocGlu(Bzl)-al	9.5 (s, 1 H), 7.3 (s, 5 H), 5.1 (s, 2 H), 1.4 (s, 9 H)	5.8, 5.9, 15.5	6.2 (1.0)	75	230
BocSer(Bzl)-al	9.5 (s, 1 H), 7.3 (s, 5 H), 5.7 (s, 2 H), 1.4 (s, 9 H)	5.8, 5.9, 15.5	10.3 (1.0)	80	oil
BocThr(Bzl)-al	9.6 (s, 1 H), 1.4 (s, 9 H), 1.2 (d, 3 H)	5.8, 5.9, 15.5	1.4 (1.0)	80	87–88

[a] The side-chain ^{1}H NMR pattern; not shown for all amino acids. [b] Only the carbonyl and aromatic groups are shown. [c] Observed optical rotation; concentration in units of g/100 mL of CH_2Cl_2. [d] Based on isolated yield.

recovered by evaporation of the solvent.

Preparation of Pyridinium Dichromate.[9] The reagent was prepared by dissolving 25.0 g (0.25 mol) of CrO_3 in 50 mL of distilled H_2O and adding 20 mL (0.25 mol) of pyridine dropwise at 0 °C. The color of the solution changed from deep purple to bright orange, and the product precipitated as a bright orange solid. The solution was further diluted with 100 mL of acetone, cooled to −30 °C and allowed to stand for 30 min. The precipitate was filtered, washed with acetone, and dried under vacuum to obtain 40.0 (88% yield) of pyridinium dichromate (mp 144–146 °C).

Preparation of Amino Aldehydes. The protected amino alcohol (2.0 mmol) was dissolved in 10 mL of CH_2Cl_2. The pyridinium dichromate (3.0 mmol) was added as a solid, in one portion, and the mixture was stirred overnight at room temperature. Following filtration, the filtrate was evaporated, and the residue was recovered. To the residue was added 10 mL of EtOAc, the insoluble portion was refiltered, and the filtrate was evaporated. The residue from the filtrate was then dissolved in 1 mL of EtOAc and eluted rapidly through a short (2 cm × 12 cm) silica gel column with EtOAc. This brief chromatography (5–10 min on silica gel) removed any traces of chromium salts present. The product obtained represented highly pure, optically active, protected amino aldehyde. The prepared protected amino aldehydes and their properties appear in Table I.

Results and Discussion

The preparation of peptide aldehydes from the corresponding protected amino acids and esters was originally attempted by using the DIBAL[7] and Vitride[8] reagents. The reaction yields, however, were poor regardless of the starting amino acid. Product purification involved prolonged column chromatography on silica gel, which in agreement with earlier reportes,[7] led to extensive racemization. A change in strategy was decided upon and involved the preparation of an intermediate alcohol which was subsequently to be converted to the aldehyde. Nonprotected amino alcohols had been previously prepared by other investigators using $LiAlH_4$,[10] $NaBH_4$,[11] and borane–dimethyl sulfide.[12] No detectable racemization was observed in any case.[14]

For the protection of protected amino alcohols, the $LiAlH_4$ and DIBAL reagents were initially used by following standard procedures. Both reagents led to low yields, removal of the N-terminal protection (*tert*-butyloxycarbonyl), and product isolation difficulties. Since $LiAlH_4$ reductions usually require a short reflux at 65 °C, it was initially assumed that this refluxing had led to loss of the N-terminal protection. Similar results, however, were obtained at room temperature and at 0 °C. Boc-L-valinol and Boc-L-leucinol were the only amino alcohols recovered in significant yields by the $LiAlH_4$ reduction, even after several modifications of the original procedures. It was concluded that the hydride, in the $LiAlH_4$ as well as in the DIBAL reductions, was consumed primarily by the *tert*-butyloxycarbonyl group prior to its utilization for the reduction of the acid function. However, when the borane–THF reagent was used on a series of amino acids with different side-chain protection, along with the *tert*-butyloxycarbonyl group for N-terminal protection, consistently optically pure, protected amino alcohols were obtained in high yields.[13] The identity and purity of the products were established by ^{1}H NMR, IR, and TLC.

The pyridinium dichromate (PDC) reagent was introduced by Corey and Schmidt[9] as a highly selective and effective, but mild, reagent for the preparation of highly pure aldehydes from alcohols in aprotic media. This reagent had not been previously used with amino acids or protecting groups commonly used in peptide synthesis. The *tert*-butyloxycarbonyl group was used for N-terminal protection and the nitro, benzyl ester, and benzyl ether groups for side-chain protection. These protecting groups were, as expected, unaffected by the PDC oxidation conditions. The high yields of the recovered aldehydes eliminated the need for prolonged column chromatography on silica gel, thus avoiding the possible racemization of the products. The aldehydes were characterized by ^{1}H NMR, IR, optical rotation, TLC, and conversion to the 2,4-dinitrophenylhydrazine derivatives (Table I). The prescence of the N-terminal and side-chain protection was verified by ^{1}H NMR and IR. The aldehydes were found to be unstable when stored for long periods in organic solvents at 4 °C.

In summary, two comparative studies were performed to evaluate known reagents for the preparation of protected, optically pure amino alcohols and aldehydes. Because of the eventual utilization of these methods in peptide synthesis, the reagents must be compatible with commonly used protecting groups. The reagents previously used with nonprotected amino acids proved to be inefficient, leading to excessive loss of the N-terminal protection in the case of alcohols and product racemization in the aldehydes. The newly applied borane–THF and pyridinium dichromate reagents, however, gave highly pure, protected amino alcohols and aldehydes and the possible subsequent preferential removal of such protection at different stages in peptide synthesis.

Acknowledgment. This work was supported by a grant from the Muscular Dystrophy Association of America.

Registry No. BocAla-al, 79069-50-4; BocVal-al, 79069-51-5; BocPhe-al, 72155-45-4; BocAsp(Bzl)-al, 79069-52-6; BocGlu(Bzl)-al, 79069-53-7; BocSer(Bzl)-al, 79069-54-8; BocThr(Bzl)-al, 79069-55-9; BocAla-al 2,4-DNP, 79069-56-0; BocVal-al 2,4-DNP, 79069-57-1; BocPhe-al 2,4-DNP, 79069-58-2; BocAsp(Bzl)-al 2,4-DNP, 79069-59-3; BocGlu(Bzl)-al 2,4-DNP, 79069-60-6; BocThr(Bzl)-al 2,4-DNP, 79069-61-7; BocAla, 15761-38-3; BocVal, 13734-41-3; BocPhe, 13734-34-4; BocAsp(Bzl), 7536-58-5; BocGlu(Bzl), 13574-13-5; BocSer(Bzl), 23680-31-1; BocThr(Bzl), 15260-10-3; BocAla-ol, 79069-13-9; BocVal-ol, 79069-14-0; BocPhe-ol, 66605-57-0; BocAsp(Bzl)-ol, 79069-16-2; BocGlu(Bzl)-ol, 79069-62-8; BocSer(Bzl)-ol, 79069-15-1; BocThr(Bzl)-ol, 79069-63-9; PDC, 20039-37-6.

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