9, 78987-12-9; 10, 78987-13-0; o-nitrobenzaldehyde, 552-89-6; 5,15-bis(o-nitrophenyl)-2,3,7,8,12,13,17,18-octamethylporphyrin, 78987-14-1; 5-[o-(acetylamino)phenyl]-2,3,7,8,12,13,17,18-octamethylporphyrin, 78987-15-2; 3-mercaptopropionic acid, 107-96-0; 2,6-bis(bromomethyl)pyridine, 7703-74-4.

A General Approach to the Synthesis of Bridgehead-Bridgehead Disubstituted Bicyclo[n.1.1]alkanes[1]

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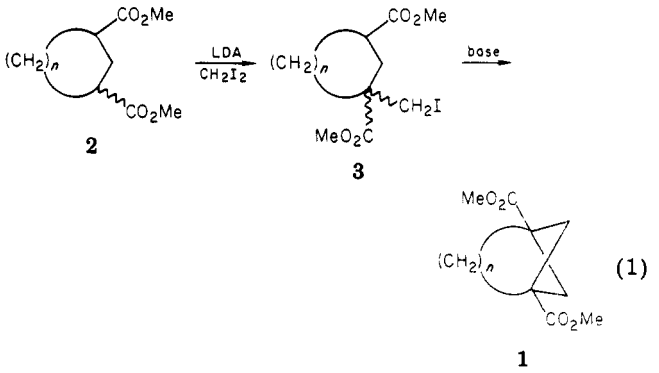
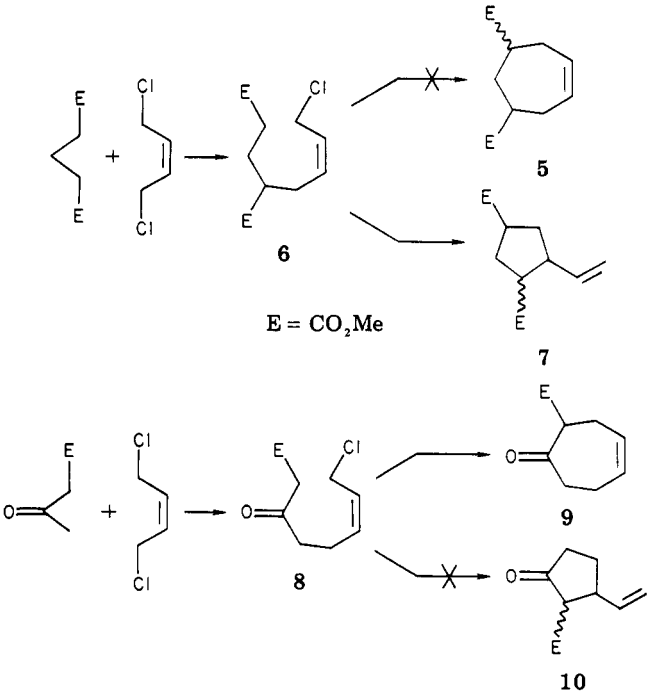
Our interest in bridgehead olefins[3] and paddlanes[4] has necessitated the synthesis of some bicyclo[n.1.1]alkanes in which both bridgeheads are substituted with functionalized groups. In particular, we have been pursuing the group of diesters 1, of which **1a**[5] and **1b**[6] are known. This report relates a simple, general approach (eq 1), so far successful for **1b–1d**.[16]



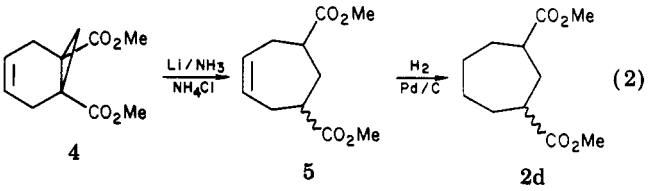
a, $n = 1$; b, $n = 2$; c, $n = 3$; d, $n = 4$

Thus the requisite starting material is the diester **2**, readily obtainable in the cases of **2b**[7] and **2c**,[8] but rather difficultly available for **2a** and **2d**. Diester **2** is alkylated with LDA/CH_2I_2, whereby **3** is produced. Further internal alkylation (i.e., cyclization) is effected with KH or LDA as the base. Our attempts to carry out the conversion of **2** to **1** in one pot (i.e., with excess LDA) have met with failure or very poor yields. (The fact that LDA can be used for the cyclization step suggests that the dianion from **2** does not react smoothly.)

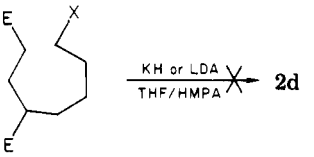
Scheme I



The synthesis of **2d** was ultimately achieved via the reduction of **4**[9] (eq 2). This method was utilized after the



approach involving dimethyl glutarate, patterned after the successful synthesis of **9**,[10] produced **7** rather than **5** (Scheme I), and all attempts to cyclize **11** failed to produce **2d** in useful amounts. The fact that **6** afforded **7**, whereas **8** did not yield the analogous five-membered ring compound, **10**, may be attributed to the prohibition of the 5-endo-trigonal transition state for cyclization,[11] which would be required for **8** to yield **10**. On the other hand, **6** gives **7** via a 5-exo-trigonal transition state.



11a, X = Cl
b, X = Br

Experimental Section

1-(Iodomethyl)-1,3-bis(carbomethoxy)cyclopentane (3b). To a solution of 4.6 g of diisopropylamine and ca. 1 mg triphenylmethane (indicator) in 200 mL of THF was added 18.2 mL of 2.5 M *n*-BuLi (45 mmol) at 0 °C under N_2. The resulting mixture was stirred for 15 min at 0 °C, whereby a red solution was obtained. To this solution at −78 °C was added dropwise a solution of 6.51 g (35 mmol) of *cis*-bis(carbomethoxy)cyclopentane[7] (**2b**) in 15 mL of THF, and the resulting mixture, was stirred for

(1) We thank the donors or the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.
(2) Alfred P. Sloan Foundation Fellow, 1976–1980.
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10 min (longer stirring afforded less satisfactory results). A solution of 9.84 g (37 mmol) of CH_2I_2 in 15 mL of HMPA and 15 mL of THF was then added slowly at −78 °C, and stirring was continued for 2 h at −78 °C. Workup involved the addition of 40 mL of saturated NH_4Cl solution, evaporative concentration, addition of 50 mL of H_2O, and ether extraction (3 × 50 mL). After back-extraction and drying, removal of solvent afforded 12.7 g of crude **3b** [NMR ($CDCl_3$) δ 1.6–2.6 (m, 6 H), 2.6–3.2 (m, 1 H), 3.45 (apparent d, 2 H), 3.7 (center of 2 apparent s, 6 H)], which was utilized in the next step without purification.

1,4-Bis(carbomethoxy)bicyclo[2.1.1]hexane (1b). A solution of 1.4 equiv of LDA (prepared by mixing 12.0 g of diisopropylamine, 44.8 mL of 2.5 M *n*-BuLi, and ca. 1 mg triphenylmethane in 280 mL of THF) was cooled to −78 °C, whereupon a solution of 28.2 g of crude **3b** (prepared from a total of 14.8 g of **2b**) in 30 mL of THF and 65 mL of HMPA was added, and the resulting mixture was stirred for 2.5 h at −78 °C. Workup as for **3b**, followed by a quick pass through a silica gel column (1:2 ether–Skelly B), gave 12.8 g of crude **1b** as a brown liquid. Distillation [69–79 °C (0.2–0.25 torr)] afforded 4.4 g (27.7% from **2b**) of **1b**:[6] ^1H NMR ($CDCl_3$) δ 3.71 (s, 6 H), 1.63–2.3 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 172.9, 51.6, 49.1, 44.6, 29.8. Calcd for $C_{10}H_{14}O_4$, *m/e* 198.0892; found, *m/e* 198. 0898.

1-(Iodomethyl)-1,3-bis(carbomethoxy)cyclohexane (3c). To a solution of 15 mmol of *n*-BuLi in 10 mL of THF held at −30 °C was added 2.1 mL (15 mmol) of diisopropylamine in 10 mL of THF. After the mixture was stirred for 20 min, the resulting solution was cooled to −78 °C, and a solution of 2 g (10 mmol) of **2c**[8,12] in 5 mL of THF was added dropwise. After addition was complete, the reaction mixture was stirred for 30 min at −78 °C, after which a solution of 3.2 g (12 mmol) of CH_2I_2 in 5 mL of THF and 2 mL of HMPA was added dropwise. Stirring was continued for 3 h at −78 °C, 2 h while warming the flask from −78 to 0 °C, and 2 h while warming from 0 °C to room temperature. After quenching with 10 mL of saturated NH_4Cl solution and workup as described for **3b**, 3.24 g of crude **3c** was obtained. This crude material, which was primarily one isomer (GC, OV-101 column, 150 °C), was used without further purification: ^1H NMR ($CDCl_3$) δ 3.80 (s, 3 H), 3.75 (s, 3 H), 3.3 (apparent d, 2 H), 3.0–0.7 (m, 9 H); GC–MS resolved **3c** into two isomers—a major one showing no P^+ but a large $(P - OCH_3)^+$, and a minor one showing the expected P^+ at *m/e* 340.

1,5-Bis(carbomethoxy)bicyclo[3.1.1]heptane (1c). This time LDA cyclization was not productive, wherefore KH was utilized, as follows. To 5.22 g (114 mmol) of KH (oil free) suspended in 50 mL of THF and 50 mL of HMPA was added a solution of 9 g of crude **3c** in 50 mL of THF at room temperature. The reaction mixture was stirred for 5 h, after which it was cooled to 0 °C and 15 mL of HOAc in 50 mL of THF was slowly added. Excess water was then added, and the solution was concentrated and extracted with ether (3 × 150 mL). Back-extraction of the combined extracts, drying, and solvent evaporation gave 5.4 g of crude **1c**. This material was distilled [bp 86–93 °C (0.9 torr)] to give 2.0 g (50% overall from **2c**) of **1c**. In some runs, the **1c** thus obtained had to be purified further by silica gel column chromatography (ether–hexane): ^1H NMR ($CDCl_3$) δ 3.72 (s, 6 H), 2.7–2.3 (m, 6 H), 1.87 (center of apparent dd with splittings of 2.5 and 8 Hz, 4 H); ^{13}C NMR ($CDCl_3$) δ 175.6, 51.7, 42.3, 38.0, 29.5, 16.0. Calcd for $C_{11}H_{16}O_4$, *m/e* 212.1049; found, *m/e* 212.1047.

Compound **1c** was also obtained quantitatively by treating the corresponding diacid (see below) with CH_2N_2.

Bicyclo[3.1.1]heptane-1,5-dicarboxylic Acid. The hydrolysis of **1c** with KOH in $MeOH/H_2O$ (2:1 v/v) for 16 h at room temperature led to a 90% yield of crude dicarboxylic acid. Recrystallization gave the pure diacid, mp 219–221 °C dec.

Anal. Calcd. for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.76; H, 6.57.

1,3-Bis(carbomethoxy)cyclohept-5-ene (5). To 800 mL of freshly distilled NH_3 was added 1.3 g (0.2 mol) of Li (cut up wire) at −78 °C. To the resulting deep blue solution was added 7 g (33 mmol) of **4**[9] in 10 mL of Et_2O. The reaction mixture was allowed to stir for another 90 s, after which 150 g of NH_4Cl was added (over a 30-s period) to quench the reaction.[14] After evaporation of the NH_3, water was added and the mixture extracted with ether (2 × 400 mL). The combined extracts were washed, dried, and concentrated to give 5.2 g of oil, which GC showed was primarily the desired **5**, together with an unknown impurity. Silica gel column chromatography (ether–hexane) afforded 2.2 g of essentially pure (GC, OV-101 column, 140 °C) **5**: ^1H NMR ($CDCl_3$) δ 5.9–5.5 (m, 2 H), 3.68 (s, 6 H), 3.1–2.1 (m, 8 H).

1,3-Bis(carbomethoxy)cycloheptane (2d). A mixture of 220 mg of **5**, 20 mg of 10% Pd/C, and 15 mL of absolute EtOH was stirred for 15 h at room temperature under H_2. Filtration and solvent evaporation afforded 210 mg (90%) of **2d** as a mixture of isomers. The ^1H NMR and GC–MS spectra were very similar to those of the previously reported[15] cis isomer of **2d**.

1-(Iodomethyl)-1,3-bis(carbomethoxy)cycloheptane (3d). To a solution of 2.2 mmol of LDA (prepared from 0.88 mL of 2.2 M *n*-BuLi and 0.3 mL of diisopropylamine) in 5 mL of THF at −78 °C was added 230 mg (1.1 mmol) of **2d** in 2 mL of THF under N_2. After the reaction mixture was stirred for 20 min, 420 mg (1.5 mmol) of CH_2I_2 in 3 mL of THF was added slowly. After being stirred for another 10 h, the reaction mixture was quenched with saturated NH_4Cl solution at −20 °C. After concentration, extraction, drying, and solvent evaporation, 320 mg of crude **3d** was obtained. GC (OV-101, 150 °C) showed some remaining **2d** as well as some cyclized **1d**.

1,6-Bis(carbomethoxy)bicyclo[4.1.1]octane (1d). The above-obtained 230 mg of crude **3d** was dissolved in 5 mL of THF and 2.5 mL of HMPA and the solution was added to a stirring suspension of 210 mg of KH in 5 mL of THF and 2.5 mL of HMPA at 0 °C. After the resulting mixture was stirred for 12 h at room temperature, it was cooled to 0 °C and quenched by adding excess HOAc and water. Concentration was followed by extraction (Et_2O, 3 × 50 mL), washing of the combined extracts, drying, and solvent evaporation. The material thus obtained was chromatographed on a silica gel column (ether–hexane), whereby 100 mg (40%) of pure **1d** was obtained: ^1H NMR ($CDCl_3$) δ 3.65 (s, 6 H), 2.9–2.6 (m, 2 H), 2.3–1.95 (m, 2 H), 1.8 (br s, 8 H); ^{13}C NMR ($CDCl_3$/benzene-d_6) δ 51.8, 42.1, 35.5, 32.9, 24.4 (carbonyl C not observed). Calcd for $C_{12}H_{18}O_4$, *m/e* 226.1205; found, *m/e* 226.1207.

Attempted Synthesis of 5 from Dimethyl Glutarate. In a flame-dried 2-L three-necked flask fitted with a mechanical stirrer and an inlet for a static N_2 atmosphere was placed 187 mL (0.43 mol) of 2.2 M *n*-BuLi in 200 mL of THF. To this was added a solution of 60 mL (0.43 mol) of diisopropylamine in 50 mL of THF, and the resulting solution was stirred for 20 min. After the solution cooled to −78 °C, 300 mL of THF was added, followed by a solution of 29.75 g (0.19 mol) of dimethyl glutarate in 50 mL of THF; stirring was continued for 30 min. At this point, a solution of 21 mL (0.2 mol) of *cis*-1,4-dichloro-2-butene in 60 mL of HMPA and 50 mL of THF was added dropwise, and the resulting reaction mixture was stirred for 7 h at −78 °C.

The reaction was quenched with saturated NH_4Cl solution and worked up via concentration, ether extraction, washing, and drying. The residue after solvent evaporation was flash distilled [~123 °C (1 torr)] and redistilled on a spinning band column to afford 4 g [10%, bp 80–89 °C (0.8 torr)] of material which showed one major peak in the GC (OV-101, 140 °C). Further silica gel chromatography (ether–hexane) of 1.1 g led to the recovery of another 990 mg of material which showed only one peak in the GC. The GC–MS spectrum showed the correct P^+ at *m/e* 212, but the ^1H NMR [($CDCl_3$) δ 6.1–5.45 (m, 1 H), 5.2–4.8 (m, 2 H), 3.7 (s, 3 H), 3.65 (s, 3 H), 3.25–1.8 (m, 7 H)] clearly indicated structure **7** rather than **5**. Calcd for $C_{11}H_{16}O_4$, *m/e* 212.1048; found, *m/e* 212.1045.

Although the chemistry of **7** was not fully investigated, it was converted, via hydrogenation, iodomethylation, and cyclization, to the 2-ethyl derivative of **1b**: ^1H NMR ($CDCl_3$) δ 3.7 (s, 6 H),

(12) Made from isophthalic acid via Rh-catalyzed hydrogenation[13] in 85% overall yield.

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(16) After this paper was submitted, a communication appeared in which the synthesis of **1c** from **2c**, via the same route as ours, was described (Gassman, P. G.; Proehl, G. S. *J. Am. Chem. Soc.* **1980**, *102*, 6862).

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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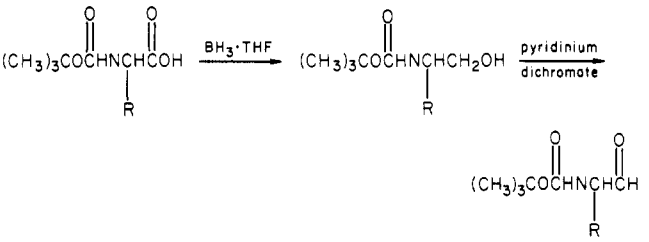
The recently identified class of peptide aldehydes, which includes leupeptin and antipain, is of increasing interest due to the inhibitory properties of these molecules toward certain classes of proteolytic enzymes.[2] Due to the proposed possible therapeutic use of these molecules as inhibitors of metabolic 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

(1) This work done in partial fulfillment for a Master's Degree in Chemistry.
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