HBr Cleavage of Cubane-1,4-dicarboxylic Acid. Easy Entry into the Northwistbrendane(ene) System

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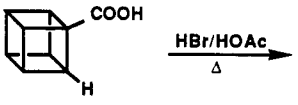
Addition of hydrogen bromide occurs twice over on heating cubane-1,4-dicarboxylic acid with HBr in HOAc giving in good yield a nortwistbrendane (tricyclo[4.2.0.0^{3,8}]octane, C_2-bissecocubane) derivative. Further transformations easily give simply substituted nortwistbrendenes.

Cole observed that treatment of cubanecarboxylic acid (**1**) with hydrogen bromide (32%) in acetic acid at 90 °C results in rapid addition of HBr, producing the secocubane **2** in quantitative yield. The stereochemistry of the addition was assigned based on the ready conversion of **2** (δ CHBr = 4.6 ppm, s) to the lactone **3** (δ CHO = 5.2 ppm, t, J = 6 Hz) on mild treatment with aqueous sodium carbonate and comparison of the relevant coupling constants with those expected from the Karplus relation.[1,2]



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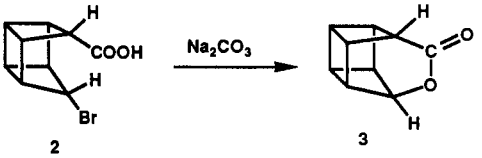
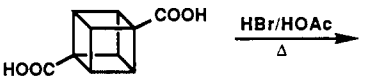


2 **3**

As we are interested in developing the potential of cubanes as starting materials for other valuable systems, we have investigated the course of HBr addition to cubane-1,4-dicarboxylic acid (**4**).[3] As anticipated, reaction of **4** with 32% HBr in HOAc at 70 °C gives quickly the monoaddition product **5a**, characterized as its dimethyl ester **5b**. Treatment of **5a** or **5b** with aqueous base gives, after acidification, the corresponding lactone **6a**, characterized as its methyl ester **6b**.

Further exposure of **5a** to HBr in HOAc leads to cleavage of another carbon–carbon bond by the addition of a second equivalent of HBr. (No further cleavage occurs on prolonged treatment.) If the second cleavage is similar in kind to the first, there are two reasonable pathways for reaction (Scheme I). Path 1 would give **7**, of the rare diasterane ring system (tricyclo[3.1.1.1^{2,4}]octane).[4] Path 2, statistically favored, would lead to **8** in the intrinsically chiral nortwistbrendane, a.k.a. C_2-bissecocubane system



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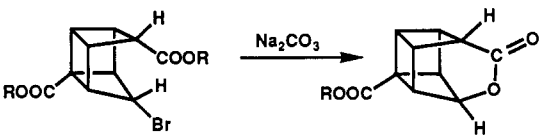

5a, R = H
5b, R = CH_3

6a, R = H
6b, R = CH_3

(tricyclo[4.2.0.0^{3,8}]octane).[5] In the event, little if any of the second HBr addition occurred along path 1. None of the individual spectra which could be dissected mentally out of the ^{1}H NMR spectrum of the crude product mixture is in accord with the mirror plane symmetry of any diasterane like **7**, no matter what its stereochemistry nor the constitution of the four substituents. The main product of the reaction is the nortwistbrendane **8a**, isolated as its methyl ester **8b** in 78% yield. The ^{1}H and ^{13}C NMR spectra are in complete accord with the C_2 symmetry of the structure. However, as there are other substituent arrangements on such a nortwistbrendane that give the same symmetry, confirmation of the details of configuration, assigned first on mechanistic considerations, was obtained by single-crystal X-ray analysis (see the supplementary material).

Lactonization of **8a** occurs rapidly on its treatment with aqueous base. The bromo lactone **9**, characterized as its methyl ester, is formed in high yield. (We were unable to induce formation of the double lactone.) The detailed structure of **9** was established by X-ray crystallography (see the supplementary material). On reaction with zinc dust in acetic acid at 100 °C both the dibromide **8b** and the bromo lactone **9** are converted *cleanly in high yield* to the nortwistbrendene **10**. The structure of this intrinsically chiral olefin follows unambiguously from the origin of the compound and the symmetry apparent in its NMR spectra.

As cubane-1,4-dicarboxylic acid is reasonably available (25% overall yield from cyclopentanone),[3] these conversions of it to **8** and **10** provide *at the very least* new routes to usefully substituted nortwistbrendanes and nortwistbrendenes quite competitive with those already known.[5]

(1) Cole, T. W., Jr. Ph.D. Thesis, The University of Chicago, 1966.
(2) Such "conjugate" additions to strained σ bonds are not typical reactions outside the chemistry of cyclopropanes. Cyclobutanecarboxylic acid is completely stable to HBr in HOAc. Cubyl methyl ketone[1] and most cyclobutane-containing small propellanones undergo carbon–carbon bond reorganizations on treatment with HBr (Eaton, P. E.; Jobe, P. G.; Nyi, K. *J. Am. Chem. Soc.* **1980**, *102*, 6636 and references 1c–h therein). [3.2.2]Propellan-2-one does, however, undergo HBr addition readily across the central strained bond without rearrangement (Nyi, K., Ph.D. Thesis, The University of Chicago, 1971).
(3) (a) Eaton, P. E.; Cole, T. W., Jr. *J. Am. Chem. Soc.* **1964**, *86*, 962, 3157. (b) Chapman, N. B.; Key, J. M.; Toyne, K. J. *J. Org. Chem.* **1970**, *35*, 3860. (c) Luh, T.-Y.; Stock, L. M. *Ibid.* **1972**, *37*, 338.
(4) Oterbach, A.; Musso, H. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 554.
(5) (a) Scherer, K. V.; Lunt, R. S.; Ungefug, G. D. *Tetrahedron Lett.* **1965**, 1199. Askani, R.; Schwertfeger, W. *Chem. Ber.* **1977**, *110*, 3046. (c) Nakazaki, M.; Naemura, K.; Sugano, Y.; Kataoka, Y. *J. Org. Chem.* **1980**, *45*, 3232.

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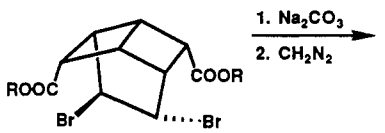
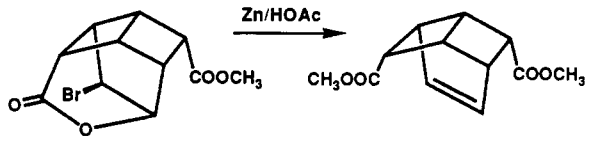


8a, R = H
8b, R = CH_3

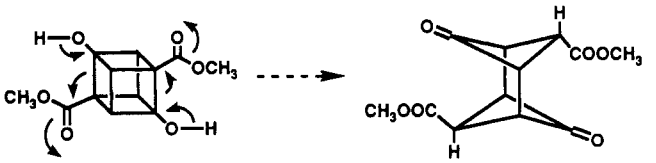


9 10

Ready access to this intrinsically chiral system is now assured.

HBr cleavage to 4 occurs along path 2 regioselectively. This was not altogether surprising; the late Professor Musso and his co-workers had previously observed that catalytic hydrogenations of cubanes proceed via nortwistbrendanes rather than diasteranes.[6] As has been pointed out, the asterane of this size suffers severe H···H transannular interactions and, by molecular mechanics calculations, is some 33 kcal/mol more strained than the isomeric nortwistbrendane.[6b] What is perhaps counterintuitive is that such kinetically diverse cleavage reactions as hydrogenolysis and acid-catalyzed addition would be so fully responsive to this thermodynamic difference.

It seems likely that cubanes could be opened to diasteranes if the requisite bond cleavages could be made favorable by invoking substituent participation. Thus, calling on Zwanenburg's work on homocubanes for precedent,[7] we suggest that cubanes like 11 might well be opened into the diasterane system 12. Such substituted cubanes are just now coming available.[8] We shall report on their chemistry as we obtain further information.



11 12

Experimental Section

Melting points are uncorrected. All NMR spectra were run in chloroform-*d* unless otherwise noted: ^1H NMR on The University of Chicago DS-1000 spectrometer at 500 MHz and referenced to internal tetramethylsilane (0.00 ppm); ^{13}C NMR on a Varian XL-400 at 100 MHz and referenced to the central line of the deuteriochloroform triplet (77.0 ppm). Proton chemical shifts are reported to a precision of ±0.02 ppm and coupling constants to ±1 Hz; carbon chemical shifts are reported to ±0.1 ppm. Mass spectra were recorded at low resolution on a VG Analytical 7070E system operated in chemical ionization mode. Infrared spectra were recorded from chloroform solutions using a Nicolet SX-20 FT-IR at 1-cm^{-1} resolution.

***endo*-1,4-Dicarbomethoxy-*exo*-7-bromotetracyclo-[4.2.0.$0^{2,5}$.$0^{3,8}$]octane (5b).** Powdered 1,4-dicarboxycubane (400 mg) was added to 32% HBr in acetic acid (Fisher; 16 mL). The stirred mixture was heated in an oil bath at 70 °C for 15 min (the diacid dissolved within 5 min). The entire reaction mixture was evaporated in vacuo (ca. 2 Torr, 40 °C H_2O bath). The slightly brown solid residue was taken up in methanol (15 mL) containing a drop of methanesulfonic acid, and the solution was stirred overnight at 70 °C. The methanol was removed in vacuo. The residue was taken up in a minimum amount of methylene chloride and applied to a short column of silica gel (70–270 mesh, 4 g). Elution with chloroform (50 mL) gave the title bromo diester, which was crystallized from ethyl acetate/hexanes (1:2) to give white prisms of **5b** (480 mg, 76%): mp 130–133 °C; ^1H NMR ($CDCl_3$) δ 4.65 (s, 1 H), 3.75 (m, 2 H), 3.75 (s, 3 H), 3.74 (s, 3 H), 3.64 (m, 2 H), 3.44 (br t, *J* = 5 Hz, 1 H), 2.52 ppm (t, *J* = 5 Hz, 1 H); ^1H NMR (benzene-d_6) δ 4.86 (s, 1 H), 3.69 (dt, *J* = 8, 1 Hz, 2 H), 3.39 (s, 3 H), 3.16 (s, 3 H), 3.11 (qd, *J* = 5, 1 Hz, 2 H), 2.86 (tt, *J* = 5, 1 Hz, 1 H), 2.52 ppm (t, *J* = 5 Hz, 1 H); ^{13}C NMR (benzene-d_6) δ 172.3, 169.8, 55.8, 52.4, 51.3, 51.2, 48.5, 42.1, 41.7, 39.6 ppm; IR ($CHCl_3$) ν 1725 cm^{-1}; MS (CI, isobutane) *m/z* 301, 303 (1:1), correct (P + H^+) for $C_{12}H_{13}BrO_4$.

2-Carbomethoxy-9-oxapentacyclo[4.4.0.$0^{2,5}$.$0^{3,10}$.$0^{4,7}$]decan-8-one (6b). Powdered 1,4-dicarboxycubane (110 mg) was treated with 32% HBr in acetic acid (6 mL) at 70 °C for 12 min as described for the preparation of bromide **5b**. The volatiles were removed in vacuo. The residue was taken up in H_2O (10 mL). The solution was titrated to a phenolphthalein endpoint with 1 M NaOH and then heated on the steam bath for 30 min. The pH was maintained by dropwise addition of base as required to maintain the indicator color. The mixture was then cooled in an ice bath to less than 10 °C and carefully acidified to pH 1 by the dropwise addition of concentrated HCl. The acidified mixture was warmed to room temperature, saturated with ammonium sulfate, and extracted with ethyl acetate. The solvent was removed in vacuo; methanol was added, and the solution was treated with excess ethereal diazomethane. Removal of solvents left a yellow solid (120 mg). Filtration through silica gel (70–270 mesh; 1 g) with chloroform (30 mL) gave a pale yellow solid (90 mg) on removal of the solvent. This was crystallized from ethyl acetate/hexanes (1:2) to give colorless needles of ester–lactone **6b** (52 mg, 48%): mp 208.5–210 °C; ^1H NMR ($CDCl_3$) δ 5.46 (t, *J* = 6 Hz, 1 H), 3.84 (m, 1 H), 3.72 (m, 2 H), 3.70 (s, 3 H), 3.64 (t, *J* = 6 Hz, 1 H), 3.43 ppm (br q, *J* = 6 Hz, 2 H); ^1H NMR (benzene-d_6) δ 4.93 (t, *J* = 6 Hz, 1 H), 3.24 (s, 3 H), 3.14 (br t, *J* = 6 Hz, 1 H), 3.07 (t, *J* = 6 Hz, 1 H), 2.96 (br t, *J* = 6 Hz, 2 H), 2.44 ppm (br q, *J* = 6 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 169.94, 169.90, 70.5, 51.9, 45.5, 44.5, 43.5, 38.4, 36.9 ppm; IR ($CHCl_3$) ν 1755 (s), 1740, 1725 (s), 1338 (m) cm^{-1}; MS (CI, isobutane) *m/z* 207, correct (P + H^+) for $C_{11}H_{10}O_4$.

(±)-*trans*-4,5-Dibromo-*endo*,*endo*-2,7-dicarbomethoxytricyclo[4.2.0.$0^{3,8}$]octane (8b). Powdered 1,4-dicarboxycubane (200 mg) was combined with commercial 32% HBr in acetic acid (Fisher; 8 mL) and heated with stirring at 70 °C. The diacid dissolved within 5 min; a white solid precipitated within 30 min. Heating was continued overnight. If the mixture was cooled at this point and an equal volume of water added, the dibromo diacid **8a** was obtained as a white precipitate, mp 250 °C dec. Usually, instead, the mixture was evaporated to dryness (ca. 2 Torr, 40 °C), the brown, solid residue was taken up in methanol (10 mL), and this solution was treated with ethereal diazomethane to make the title diester. The solvents were stripped in vacuo. The residue was applied in a minimum amount of chloroform to a short column of silica gel (70–270 mesh; 5 g). Elution with chloroform (50 mL) gave crude dibromide–diester **8b** as a pale yellow solid. The material from $CHCl_3$ elution was crystallized from ethyl acetate/hexanes (1:2) to give colorless prisms of **8b** (310 mg, 78%): mp 194–195.5 °C; ^1H NMR ($CDCl_3$) δ 5.30 (t, *J* = 1 Hz, 1 H), 3.71 (s, 6 H), 3.44 (m, 2 H), 3.29 (dd, *J* = 8, 4 Hz, 2 H), 2.97 ppm (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 172.0, 53.2, 51.9, 46.5, 42.1, 39.9 ppm; IR ($CHCl_3$) ν 1725 (s), 1441 (m), 1381 (m), 1300 (m) cm^{-1}; MS (CI, isobutane) *m/z* 382, 383, 384 (1:2:1), correct (P + H^+) for $C_{12}H_{14}Br_2O_4$ 301, 303 (1:1), 222. Anal. Calcd for $C_{12}H_{14}Br_2O_4$: C, 37.73; H, 3.69. Found: C, 37.78; H, 3.54.

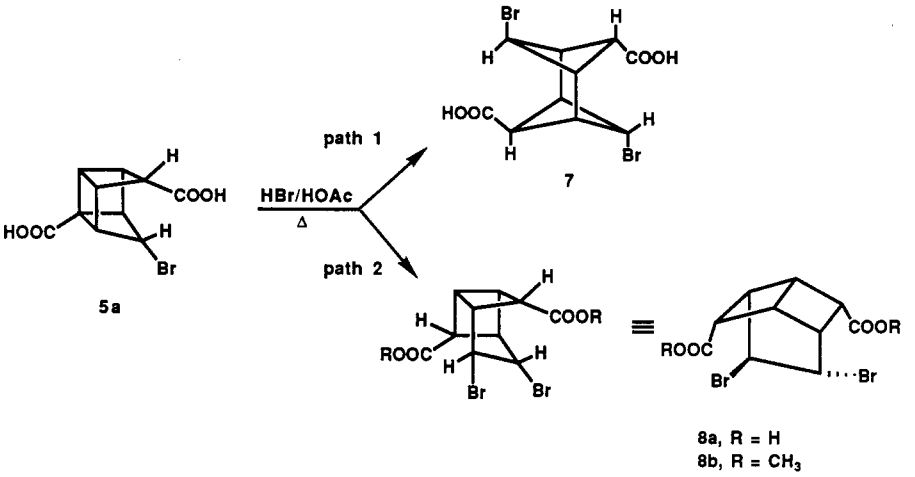
(±)-10-Bromo-*endo*-7-carbomethoxy-2-oxatetracyclo-[4.4.0.$0^{4,9}$.$0^{5,8}$]decan-3-one (9). Dibromo diacid **8a** (1.0 g, taken crude as the precipitate from the reaction of 1,4-dicarboxycubane with 32% HBr in HOAC) was taken up in water (10 mL) and

(6) (a) Stober, R.; Musso, H. *Angew. Chem., Int. Ed. Engl.* **1977**, *89*, 430. (b) Stober, R.; Musso, H.; Osawa, E. *Tetrahedron* **1986**, *42*, 1757.

(7) Klunder, A. J. H.; Zwanenburg, B. *Chem. Rev.* **1989**, *89*, 1035 and references therein.

(8) (a) Eaton, P. E.; Castaldi, G. *J. Am. Chem. Soc.* **1985**, *107*, 724. (b) Eaton, P. E.; Higuchi, H.; Millikan, R. *Tetrahedron Lett.* **1987**, *28*, 1055. (c) Eaton, P. E.; Cunkle, G. T.; Marchioro, G.; Martin, R. M. *J. Am. Chem. Soc.* **1987**, *109*, 948. (d) Eaton, P. E.; Cunkle, G. T. *Tetrahedron Lett.* **1986**, *27*, 6055.

Scheme I



titrated to a phenolphthalein endpoint with 5% NaOH. The solution was heated on a steam bath; the indicator color was maintained by the dropwise addition of base as necessary. After 45 min the mixture was cooled in an ice bath and acidified to pH 1–2 by the dropwise addition of concentrated HCl, keeping the internal temperature below 10 °C. A precipitate formed. The slurry was transferred to a separatory funnel and extracted with ethyl acetate (3 × 15 mL). The extract was concentrated in vacuo. The residual yellow solid was taken up in methanol, and the solution was treated with ethereal diazomethane. On removal of solvents, crude bromo lactone **9** was obtained as a yellow-brown solid. This was taken up in a minimum amount of methylene chloride and put on Florisil (4 g). The column was eluted with 5% ethyl acetate in methylene chloride (50 mL). The nearly colorless eluent was stripped to an off-white solid, which was crystallized from methylene chloride/ether (1:3) to give white needles of fine quality (see the spectra reproduced in the supplementary material) bromo lactone **9** (700 mg, 86%): mp 130–131 °C; ^{1}H NMR ($CDCl_3$) δ 5.18 (m, 1 H), 4.76 (dt, J = 4 Hz, 1 H), 3.77 (s, 3 H), 3.41 (ddd, J = 7, 5, 1 Hz, 1 H), 3.36 (m, 2 H), 3.29 (m, 1 H), 3.21 (m, 1 H), 3.07 ppm (m, 1 H); ^{1}H NMR (benzene-d_6) δ 4.88 (m, 1 H), 4.63 (dt, J = 3, 1 Hz, 1 H), 3.18 (s, 3 H), 2.82 (dd, J = 8 Hz, 1 H), 2.52 (m, 1 H), 2.48 (p, J = 6 Hz, 1 H), 1.98 ppm (p, J = 5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 171.7, 169.1, 76.3 (5), 52.1, 46.9, 41.8, 41.6 (2), 41.5 (9), 39.8, 38.9, 34.3 ppm; IR ($CHCl_3$) ν 1755 (s), 1735 (s), 1366 (m), 1037 (s) cm^{-1}; MS (CI, methane) m/z 287, 289 (1:1) appropriate (P + H$^+$) for $C_{11}H_{11}BrO_4$.

(±)-*endo*,*endo*-2,7-Dicarbomethoxytricyclo[4.2.0.0^{3,8}]oct-4-ene (10). Dibromide **8b** (500 mg) was dissolved in a mixture of dimethylformamide (15 mL) and acetic acid (2 mL). Zinc dust (2 g) was added, and the reaction mixture was stirred under nitrogen in a 100 °C oil bath for 7 h. The mixture was cooled and then filtered through Celite, and the pad was washed thoroughly with methylene chloride. The filtrate and washings were stripped in vacuo. The oily residue, which contained considerable inorganics, was partitioned between chloroform and 5% HCl. The organic phase was washed with brine, dried over Na_2SO_4, and stripped to leave a colorless mobile oil which solidified on standing. This was crystallized from hexanes (10 mL) containing a few drops of benzene to give off-white needles of the nortwistbrendene **10** (240 mg, 87%): mp 68–70 °C; ^{1}H NMR ($CDCl_3$) δ 6.15 (m, 2 H), 3.57 (s, 6 H), 3.33 (m, 4 H), 2.87 (m, 2 H) ppm; ^{1}H NMR (benzene-d_6) δ 6.18 (dd, J = 6, 5 Hz, 2 H), 3.27 (s, 6 H), 3.18 (m, 2 H), 2.97 (dd, J = 7, 3 Hz, 2 H), 2.52 ppm (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7 (s, $C_{9,10}$), 129.0 (d, J = 169 Hz, $C_{4,5}$), 51.1 (q, J = 158 Hz, $C_{10,12}$), 44.3 ppm (d, J = 156 Hz, $C_{1,8}$ or $C_{3,6}$); IR ($CHCl_3$) ν 1730 (br) cm^{-1}; MS (CI, isobutane) m/z 223 correct (P + H$^+$) for $C_{12}H_{14}O_4$. Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 65.08; H, 6.27.

X-ray Determinations. General: The determination of the lattice parameters and intensity measurements were made using the NONIUS CAD4-diffractometer with graphite monochromatized Mo Kα radiation (λ = 0.71069). All independent reflections in the range 1° ≤ 2θ ≤ 60° were measured at T = 20 (2) °C by the ω – 2θ scan technique. The structures were solved by Patterson methods, which gave the bromide atom positions. The light atoms were found by successive Fourier calculations using bromide-phased structure factors. The structure was refined with block-diagonal least-squares calculations. Atomic scattering factors and anomalous dispersion factors for Br ($\Delta f'$ = –0.374, $\Delta f'$ = 2.456) were taken from the literature.[9] H atoms were not detected in a difference Fourier synthesis, and their positions were calculated. Anisotropic temperature factors for the Br, O, and C atoms were applied in the last step of refinement. Because of the heavy Br atom, the position of the light atoms could not be determined very accurately. All calculations and drawing were done using the program system KRIPROG.[10]

Structure of Bromide 8b. A small colorless crystal of **8b**, 0.10 × 0.25 × 0.47 mm in size and platy along the (100) plane, was used. (Formula $C_{12}H_{14}Br_2O_4$, mol wt 382.08, calculated density 1.89 g cm^{-1}). Preliminary Weissenberg photographs with Cu Kα radiation indicated that the crystal belonged to the monoclinic system. Systematic extinctions are hkl: $h + k = 2n$, $h0l$: $l = 2n$, thus defining the space group $C2/c$. Twenty-three reflections determined with the NONIUS peak hunting procedure in the range 8° < 2θ < 32° were carefully centered. Cell parameters were calculated by a least-squares procedure: a = 17.86 (2), b = 7.295 (6), and c = 12.773 (2) Å; β = 126.4 (2)°. Every 200 reflections the orientation of the crystal was controlled, and every 3.8 h the intensity of the 350 reflection was checked. After 32 h a loss of intensity of 18% was observed. At that time a new crystal, 0.13 × 0.28 × 0.45 mm in size, was substituted. Interlayer scale factors were calculated and multiple measurements were averaged. The intensities were scaled for recompensation of intensity loss; 1960 independent reflections remained, of which 538 were unobserved with $I < 2.58\sigma(I)$. The intensities were corrected for Lorentz and polarization effects, and the absorption correction was applied (μ(Mo Kα) = 59.3 cm^{-1}). The final agreement index was R = 0.051 for observed reflections. The molecule has C_2 symmetry and lies on a crystallographic 2-fold axis.

Structure of Bromo Lactone 9. A small colorless crystal of **9**, 0.20 × 0.40 × 0.42 mm, platy along the (100) plane, was used. (Formula $C_{11}H_{11}BrO_4$, mol wt 287.0, calculated density 1.80 g cm^{-1}). Preliminary Weissenberg photographs with Cu Kα radiation indicated the crystal belongs to the monoclinic system. Systematic extinctions are $h0l$: $l = 2n$, $0k0$: $k = 2n$, thus defining the space group $P2_1/c$. Nineteen reflections determined with the NONIUS peak hunting procedure in the range 14° < 2θ < 24° were carefully centered. Cell parameters were calculated by a least-squares procedure: a = 6.228 (4), b = 19.08 (2), and c = 10.481 (5) Å; β = 121.86 (5)°. Every 200 reflections the orientation of the crystal was controlled, and every 2.8 h the intensity of the 23$\bar{2}$ reflection was checked. During the measurement no significant deviation (less than 3σ) was observed. Multiple measurements were averaged; 1785 independent reflections remained,

(9) Ibers, I. A.; Hamilton, W. C. *International Tables for X-ray Crystallography*; Kynoch Press: Birmingham, 1974; Vol. IV, pp 71 and 148.

(10) Engel, P. *Acta Crystallogr.* **1974**, *A34*, S 348.

of which 300 were unobserved with $I < 2.58\sigma(I)$. The intensities were corrected for Lorentz and polarization effects and absorption correction was applied (μ(Mo Kα) = 38.4 cm^{-1}). The final agreement index was $R = 0.032$ for observed reflections.

Acknowledgment. This work was supported by the Office of Naval Research and the National Science Foundation. The NSF and the NIH, the latter through the University of Chicago Cancer Center, provided partial support for the departmental instrumental facility. This paper was prepared while the senior author was Alexander von Humboldt U.S. Senior Scientist at the Institut für Organische Chemie, Universität Köln.

Registry No. 4, 32846-66-5; **5b**, 125848-32-0; **6b**, 125848-33-1; (±)-**8a**, 125848-35-3; (±)-**8b**, 125848-34-2; (±)-**9**, 125848-31-9; (±)-**10**, 125848-30-8.

Supplementary Material Available: ORTEP figures and tables of atomic coordinates, bond lengths, angles, and thermal parameters from the X-ray analysis of compounds **8b** and **9**; NMR spectra for compounds **5b**, **6b**, and **9** (19 pages). Ordering information is given on any current masthead page.

Solid-Phase Synthesis of *N*-Methyl- and *N*-Ethylamides of Peptides Using Photolytically Detachable ((3-Nitro-4-((alkylamino)methyl)benzamido)methyl)polystyrene Resin

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A convenient method for the solid-phase synthesis of C-terminal peptide *N*-alkylamides using a photolytically detachable ((3-nitro-4-((alkylamino)methyl)benzamido)methyl)polystyrene support is described. The method involves prior incorporation of an alkylamine moiety into the ((3-nitro-4-(bromomethyl)benzamido)methyl)-polystyrene resin, on which the peptides were assembled and subsequently cleaved in the form of the peptide *N*-alkylamides by photolysis. The *N*-alkylamino group acts as an anchoring function for the peptide as well as a latent reagent function for the C-terminal modification of the attached peptide. The method is particularly useful if the peptide contains Asp or Glu with a benzyl ester side chain protecting group. The synthetic applicability of the method is illustrated with the solid-phase synthesis of *N*-alkylamides of a few model peptides in 70–77% yields and analogues of the luteinizing hormone-releasing hormone in 48–56% yield.

C-Terminal peptide *N*-alkylamides are among the most important classes of biologically active peptides. C-Terminal modification of peptides has been observed to have significant influence on its biological properties as illustrated in the case of the naturally occurring luteinizing hormone-releasing hormone[1,2] (LH-RH). Several *N*-ethyl- and *N*-methylamides of LH-RH and its analogues are reported to be 200–300 times more active and have wide pharmaceutical applications. Peptide *N*-alkylamides are also used for structure-activity relationship studies and conformational studies.[3,4]

The different methods currently in use for the solid-phase synthesis of peptide *N*-alkylamides have several limitations. In the classical solid-phase method, a peptide–resin ester linkage can be cleaved with an alkylamine to get the corresponding *N*-alkylamides.[5,6] This method is not applicable to peptides containing Asp and/or Glu residues in which the additional carboxyl group is protected as the benzyl ester, which will also undergo aminolysis by the amine, resulting in the formation of Asn(*N*-alkylamide) and Glu(*N*-alkylamide). A solid-phase method for the synthesis of peptide *N*-alkylamides has been reported by Kornreich et al. using *N*-(alkylamino)-methyl resins.[7] Recently, a trifluoroacetic acid (TFA) labile anchoring group[8] and an oxime resin[9] have been reported for the solid-phase synthesis of peptide *N*-alkylamides.

The introduction of a photolytically cleavable anchoring linkage between the polymer and the growing peptide chain is one of the promising alternative methods to avoid the rigorous conditions used to obtain the peptides from the supports.[10,11] The photolabile *o*-nitrobenzyl anchoring group has been successfully used for the solid-phase synthesis of peptides.[12-18] In this paper we report a further

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