oxide (11). Above −10 °C treatment of 8 or mixtures 8, 8′ with desilylating agents gave mixtures of products of transannular cyclization (and protodesilylation) which, being all known compounds, could be identified and determined by quantitative ^{13}C NMR without separation. At lower temperatures (Table II, runs 6–9) a new product was formed, **11**, which was isolated from run 7 by chromatography (silica gel, ether) as the first eluted material; cryst hexane–benzene (80 mg, 33%), mp 110–111 °C. ^{13}C NMR: δ 67.7 (C_7); 58.0 (C_3); 36.0 (C_6); 34.9 (C_1); 29.2, (C_8); 22.8 (C_4); 20.2 (C_5); 11.9 (C_9); −1.8 (CH_3). ^1H NMR: δ 4.12 (ddd, 1 H, J = 10.5, 10.5, 4.7 Hz, HCO); 3.08 m, 2 H, SCH_2); 2.30 (br s 1 H, OH); 1.98 (m, 2 H); 1.72 (m, 2 H); 1.58 (m, 2 H, it comprises 1 H of the cyclopropyl CH_2, the other appearing as a m at 1.09); 1.4 to 1.2 (m, 2 H; it comprises the bridgehead H). Anal. Calcd for $C_{11}H_{22}O_3SiS$: C, 50.34; H, 8.45; S, 12.22. Found: C, 50.86; H, 8.23; S, 12.31.

The second eluted material consisted of the protodesilylation product, **1**, admixed with **2c**.

7-Thiabicyclo[4.3.0]non-1-ene 7,7-Dioxide (13). Proof of Structure of *cis*- (10c) and *trans*-7-Thiabicyclo[4.3.0]nonan-2β-ol 7,7-Dioxide (10t). For the stereochemical correlation of alcohol **10c** via Mitsonobu inversion[9] of the previously prepared α epimer **12**[1] (Scheme II), a solution of the latter (0.43 g, 2.3 mmol) in THF (30 mL) was added with Ph_3P (1.19 g, 4.6 mmol) followed by benzoic acid (0.55 g, 4.6 mmol) and, after cooling to −10 °C, dropwise by DEAD (0.79 g, 4.6 mmol, in 5 mL of THF). After being stirred for 15 h at rt and concentration under reduced pressure, the residue was chromatographed (silica gel, petroleum ether/ethyl acetate 60/40). The reaction product, isolated as the second eluted material (dicarbethoxyhydrazine being eluted first) was not the expected β alcohol but the title alkene sulfone **13** (320 mg, 81%) bp 150 °C (0.3 mm (kugelrhor)). ^{13}C NMR: δ 129.2 (C_1); 126.2 (C_2); 59.3 (C_6); 50.5 (C_8); 27.7 (C_3); 23.7 (C_4); 19.7 (2 signals, C_5, C_9). ^1H NMR (60 MHz): δ 5.85 (br s, 1 H, HC=); 3.15 (m, 5 H); 1.75 (m, 6 H). Anal. Calcd for $C_8H_{12}O_3S$: C, 55.78; H, 7.02; S, 18.61. Found: C, 55.27; H, 7.22; S, 18.40.

A THF solution of **13** (410 mg, 2.4 mmol, in 2 mL of THF) was added dropwise at rt to a stirred solution of 305 μL of 7.8 M borane in 1,4-oxathiane[10] in 2 mL of THF. After 1 h the solution was brought to 0 °C and added dropwise with aqueous NaOH (800 μL, 3 M) followed by 30% H_2O_2 (450 μL) added at such rate that the temperature would not exceed 35 °C. After being stirred for 1 h, the mixture was extracted with THF. The residue from evaporation of the organic layer was dissolved in CH_2Cl_2, dried, and chromatographed (silica gel, ethyl acetate/ethyl ether 5/2) to give as the first eluted material a waxy solid (190 mg, 42%) whose NMR spectral properties are consistent with **7-thiabicyclo[4.3.0]nonan-1-ol (14).** Especially significant is the singlet at 75.6 ppm in the ^{13}C spectrum indicating the hydroxy group is attached to a bridgehead (C_1). The other resonances are: δ 66.7 (C_6); 50.7 (C_8); 36.7 (C_2); 32.0 (C_9); 24.8 (C_4); 23.0, 22.3 (C_3, C_5). ^1H NMR (60 MHZ): δ 3.25 (m, 4 H); 2.00 (m, 10 H). Anal. Calcd for $C_8H_{14}O_3S$: C, 50.50; H, 7.42; S, 16.85. Found: C, 50.31; H, 7.38; S, 17.01. If, as it appears most likely, hydroboration has occurred from the least hindered side, the hydroxy group in **14** should β and the ring fusion cis, as indicated by the structure in Scheme II.

The second eluted material (210 mg, 46%) cryst hexane–benzene, mp 59–60 °C, was *cis*-7-thiabicyclo[4.3.0]nonan-2β-ol 7,7-dioxide whose ^{13}C NMR spectrum was identical to that of **10c** from desilylation–cyclization of **7**. ^{13}C NMR: δ 67.2 (C_2); 58.9 (C_6); 49.5 (C_8); 42.6 (C_1); 30.2 (C_3); 22.2, 22.1 (C_5, C_9); 18.7 (C_4). ^1H NMR: δ 3.40 (m, 1 H, HCO); 3.08 (m, 3 H); 2.45 (m, 2 H, inclusive of OH); 2.08 (m, 3 H); 2.0–1.2 (m, 5 H). Anal. Calcd for $C_8H_{14}O_3S$: C, 50.50; H, 7.42; S, 16.85. Found: C, 50.37; H, 7.48; S, 18.79.

A THF solution of **10c** (95 mg, 0.5 mmol in 10 mL) heated for 4 h at 70 °C in the presence of t-BuOK (0.08 g, 0.75 mmol) gave rise to a 15:85 **10c**:**10t** epimer mixture which by crystallization from acetone gave ***trans*-7-thiabicyclo[4.3.0]nonan-2β-ol 7,7-dioxide (10t)** (50 mg, 62%), mp 133–134 °C. ^{13}C NMR: δ 73.5 (C_2); 63.0 (C_6); 51.2 (C_8); 47.0 (C_1); 34.5 (C_3); 25.2 (C_5); 23.0, 22.0 (C_4, C_9). ^1H NMR: δ 3.29 (m, 1 H, HCO); 3.23, 3.01, 2.59, 2.46 (m's, 1 H each); 2.08 (m, 3 H); 1.9–1.2 (m, 6 H, inclusive of OH). Anal. Calcd for $C_8H_{14}O_3S$: C, 50.50; H. 7.42; S. 16.85. Found: C, 50.23; H, 7.50; S, 16.80.

Registry No. 1, 134333-89-4; **2c**, 134333-93-0; **3c**, 134451-81-3; **3c**–TMS, 134451-87-9; **3t**, 138331-46-1; **3t**–TMS, 138331-47-2; **4**, 79760-37-5; **5**, 138234-75-0; **5′**, 138331-48-3; **6**, 138234-76-1; **6′**, 138331-49-4; **7**, 138234-77-2; **7′**, 138331-50-7; **8**, 138234-78-3; **8′**, 138331-51-8; **9**, 138258-95-4; **10c**, 138331-52-9; **10t**, 138331-53-0; **10t**–TMS, 138380-78-6; **11**, 138234-79-4; **12**, 134333-94-1; **13**, 138234-80-7; **14**, 138234-81-8; (*E*)-thiacyclonon-4-ene, 68013-79-6; 2-vinylthiane, 66120-24-9.

Supplementary Material Available: Geometries and relative energies of diastereomers **7**, **7′** and **8**, **8′** (9 pages). Ordering information is given on any current masthead page.

Optically Active Quaternary Carbon Centers from the Photoaddition of Chromium–Alkoxycarbene Complexes and Optically Active Thiazolines

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Received July 29, 1991

The photolytic reaction of chromium–alkoxycarbene complexes with valine-derived, optically active thiazolines produced optically active β-lactam penam derivatives in fair to good yield and with high diastereoselectivity. In most cases alcoholosis of the β-lactam followed by solvolysis of the thiazolidine ring produced optically active quaternary centers having carbon substituents in four different oxidation states—alkane, alkoxy, aldehyde, and ester. The absolute configuration of the stereogenic center could be inverted by a sequence of redox manipulations of the ester and aldehyde group, making either enantiomer available from the same precursor.

Introduction

For the past several years, research in these laboratories has centered on the development of photolytic reactions of chromium–carbene complexes for use in organic synthesis. Mechanistic studies[1] indicated that photolysis of chromium–carbene complexes with visible light (metal-to-ligand charge-transfer band) promoted a reversible insertion of CO into the metal–carbon carbene double bond, producing species which had ketene-like reactivity.[2] Thus,

(1) Hegedus, L. S.; deWeck, G.; D'Andrea, S. *J. Am. Chem. Soc.* **1988**, *110*, 2122.

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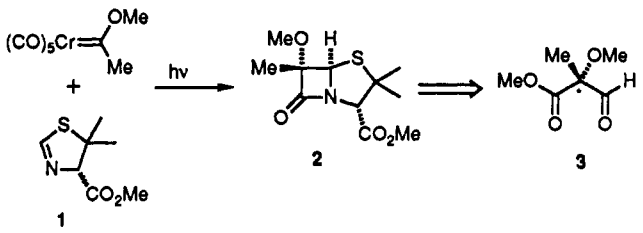
0022-3263/92/1957-1461$03.00/0

photolysis of chromium aminocarbenes[3] in the presence of alcohols produced α-amino acid esters[4] and in the presence of imines produced β-lactams.[5]

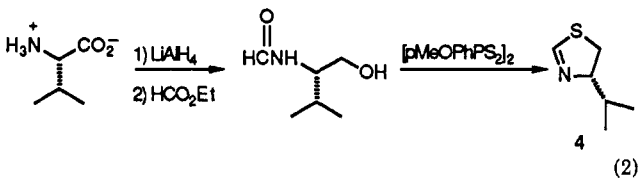
One of the earliest photochemical reactions of carbenes studied in these laboratories was the reaction between alkoxycarbene complexes and imines to produce β-lactams.[6] When the optically active, penicillin-derived thiazoline 1 was used as substrate (eq 1) complete stereospecificity was observed, with the diastereoisomer of 2 shown being the sole product (absolute stereochemistry was proven by X-ray crystallography). Although β-lactams of this type lack the appropriate functionality α- to the carbonyl group for biological activity, the high stereoselectivity observed suggested this process might be useful to generate optically active quaternary carbon centers suitably functionalized for incorporation into diverse compounds having biological activity. To be of practical use, it was necessary to find a more easily synthesized and more configurationally stable thiazoline than 1, to develop efficient β-lactam formation, and to devise mild cleavage reactions to permit the production of compounds such as 3 in reasonable yields. Studies directed toward solving these problems are described below.



(1)

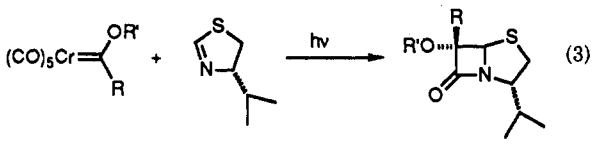
Results and Discussion

Simple optically active thiazolines proved to be readily available from α-amino acids by reduction[7]/N-formylation[8]/cyclization[9] with Lawesson's reagent (eq 2). (Cyclization with P_4S_{10} often gave comparable yields, but irreproducibility was a problem.) Since the valine-derived thiazoline 4 proved efficient in the following reactions, other thiazolines were not considered. The yield of 4 was variable and depended on the scale of the last step. Purification requires a distillation, which carries over a large amount of anisole, followed by precipitation of the hydrochloride salt of the thiazoline to separate it from anisole. Thus, the larger the scale of the reaction, the better the yield of 4. A number of other approaches to 4 were attempted but none proved as simple and efficient as that in eq 2, so it was used, despite its variability.



(2)

Photolysis of a variety of benzyloxycarbene–chromium complexes with 4 produced the corresponding β-lactams in reasonable yield, and, in most cases, with very high stereoselectivity (eq 3). Indeed in cases **6a–6e** only a single diastereoisomer of the product could be detected in the NMR spectra of the crude materials. Selectivity was lower in the cyclic carbene complex case **5f–6f**.



(3)

	R	R		
5a	Me	$PhCH_2$	6a	76%
5b	Bu	$PhCH_2$	6b	78%
5c		$PhCH_2$	6c	39%
5d	Ph	$PhCH_2$	6d	42%
5e	pMeOPh	$PhCH_2$	6e	42%
5f	$-(CH_2)_3-$		6f	87% (5:1)
5g		$PhCH_2$	6g	29%

Cleavage of the penam system was next studied. β-Lactams are readily cleaved under both acidic and basic conditions. Treatment of **6a–6e** with methanol saturated with gaseous hydrogen chloride resulted in clean cleavage of the β-lactam to the methyl ester. Cleavage of the thiazolidine proved to be more difficult, as anticipated. After screening a variety of established methods,[10] the most efficient procedure proved to be heating with excess iodine in aqueous acetone.[11] The resulting aldehyde was obtained in good yield (as assessed by the ^1H NMR spectrum of the crude material) after removal of solvent. Because these aldehydes are relatively unstable, conversion to the acetal under acid catalysis was attempted but failed because of facile decarbonylation. Acetalization under anhydrous conditions[12] also failed. Conversion to the acetal was accomplished by heating the aldehyde, methanol, trimethylorthoformate, and iodine at 80 °C. The overall conversion from penam to acetal is shown in eq 4. Because **6a–6e** were single diastereoisomers and because epimerization of the quaternary optically active center is not possible, **7a–7e** should have high optical purity. (Penams **6f** and **6g** underwent decomposition during the cleavage process.)

The absolute configuration of the newly formed stereogenic center was *assumed* to be as shown, based on the precedent presented in eq 1, for which an X-ray structure

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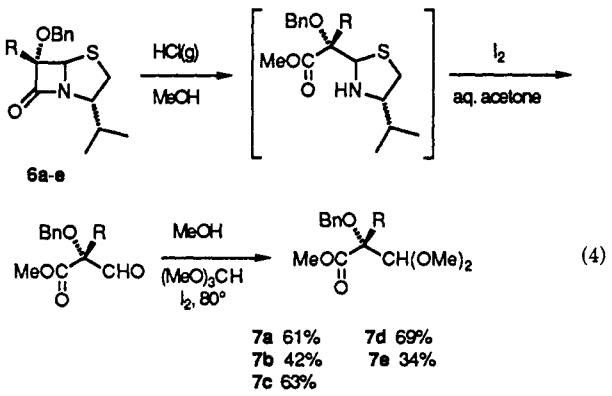

(4)

had been determined.[6] To confirm this chemically, and to concurrently demonstrate the potential synthetic utility of these compounds, the reactions shown in Scheme I were carried out.

Hydrolysis of penam **6a** in ethanol, followed by reduction of the aldehyde, produced hydroxy ester **12** in excellent overall yield. This compound, having the absolute configuration shown, had previously been synthesized from the methyl half ester of (benzyloxy)malonic acid and its absolute configuration demonstrated by conversion to natural vitamin E.[14] Compound **12** produced from penam **6a** was identical in all respects, including sign and magnitude of optical rotation, to that reported, indicating the absolute configuration of **6a** was indeed as shown. Further confirmation was obtained by debenzylation to the known[14] diol ester **13**, ketalization to **14**, and reduction to alcohol **15**. *This* compound had previously been synthesized by Sharpless epoxidation of methallyl alcohol and its absolute configuration proven by a X-ray crystal structure of the camphanyl ester derivative.[15] Again, compound **15** derived from **6a** was identical in all respects, including sign and magnitude of optical rotation, to that reported, confirming the assignment of absolute configuration of **6**. For an additional comparison, conversion of **6a** to aldehyde **10** was carried out. This compound had been previously synthesized from D-glucose,[13] had a reported rotation of +6.0°, and was assigned the absolute configuration shown based on its genesis from glucose. However, reduction of **7a** with lithium aluminum hydride produced **8**, which was shown to be optically pure by conversion to its Mosher's ester. Benzoylation to produce **9** followed by hydrolysis of the ketal produced **10**, which had spectroscopic data identical to that reported. However, this material had a rotation of −1.8° instead of the reported +6.0°. Since both **6a** and **8** appeared to be optically pure, and since none of the reactions involved in the conversion of **6a** to **10** involved the optically active center, this difference in both the sign and magnitude of rotation in combination with the *correct* correlation of compounds **12**, **13**, **15**, **16**, and **16′** with literature values suggests the literature[13] value for **10** is erroneous.

An attractive feature of optically active penams **6** is that *both* enantiomers of the optically active center are available from the *same* diastereomer of the starting material by a simple redox interchange of the ester and aldehyde groups. This is illustrated by the synthesis of the enantiomeric acetals **16** and **16′**, protected aldehydes employed in the synthesis of bicyclomycin,[16] and vitamin E.[14] By operating on the aldehyde first (**6a** → **11** → **12** → **13** → **14**) the (*R*)-(+) enantiomer **16** was obtained, while starting with the ester (**6a** → **7a** → **8** → **17**), the (S)-(−) enantiomer was produced. The fact that these compounds have identical ^1H and ^{13}C NMR spectra but opposite rotations provides additional confirmation that the absolute configuration assignment is correct. Compounds **16**, **16′** are quite volatile, and the low yields reflect losses during purification, rather than poor conversion.

Experimental Section

Materials. (*S*)-(+)-2-Amino-3-methyl-1-butanol (valinol),[7a] pentacarbonyl[(methyl)(benzyloxy)carbene]chromium(0) (**5a**),[17] pentacarbonyl(tetrahydrofuranyl-1-carbene)chromium(0) (**5f**),[18] and *N*-formylvalinol[8] were synthesized using published procedures. All NMR spectra were run in $CDCl_3$ as solvent at 300 MHz for ^1H and 75 MHz for ^{13}C. All rotations were measured at 25 °C.

(*S*)-(−)-4-Isopropyl-2-thiazoline (4). The optically active thiazoline was synthesized from *N*-formylvalinol and Lawesson's reagent by the method of Handrick.[19] A mixture of 1.82 g (13.9 mmol) of *N*-formylvalinol and 3.08 g (7.6 mmol, 0.55 equiv) of Lawesson's reagent in 20 mL of mineral oil was heated at 110–120 °C for 45 min. The mixture was treated with 20 mL of 20% aqueous NaOH and distilled. The distillate was extracted with ether, and the ether was dried (Na_2SO_4) and evaporated giving 0.643 g of crude thiazoline. After further distillation 0.55 g (4.3 mmol, 30%) of **4** was obtained as a pale yellow oil. The thiazoline is adequate for use in the photoreaction with chromium–carbene complexes, but frequently is contaminated by anisole. Anisole can be removed by treating an ether solution of the reaction product with gaseous HCl. The thiazoline hydrochloride salt forms a white solid which can be isolated by filtration, washed with ether, dissolved in CH_2Cl_2, and neutralized with triethylamine. Evaporation of CH_2Cl_2 followed by addition of diethyl ether and filtration removes triethylamine hydrochloride. Evaporation of the ether provides the pure thiazoline: bp 150–155 °C; $[\alpha]_D$ −106° (c 1.0, CH_2Cl_2); ^1H NMR δ 0.96 (d, J = 6.8 Hz, 3 H, CH_3), 1.03 (d, J = 6.8 Hz, 3 H, CH_3), 1.98 (octet, J = 6.7 Hz, 1 H, $CHMe_2$), 2.91 (dd, J = 10.8 and 9.8 Hz, 1 H, CH_2), 3.22 (dd, J = 9.2 and 10.9 Hz, 1 H, CH_2), 4.22 (m, 1 H, $NCHCH_2$), 7.86 (d, J = 2.5 Hz, 1 H, NCHS); ^{13}C NMR δ 18.9 and 19.4 (CH_3), 32.8 and 33.2 (CHMe and SCH_2), 83.1 ($NCHCH_2$), 155.0 (NCHS); IR ν (CN) 1685, 1577 cm^{-1}.

Synthesis of Pentacarbonylchromium Carbene Complexes 5. Tetramethylammonium [pentacarbonylchromium acylate] complexes were synthesized from chromium hexacarbonyl and the appropriate organolithium reagent, in ether, using a literature procedure[20,21] and were converted to carbene complexes **5a–5g** by O-acylation with acetyl bromide followed by addition of benzyl alcohol.[2b,17]

Pentacarbonyl[(*n*-butyl)(benzyloxy)carbene]chromium-(0) (5b). The reaction of 1.69 g (4.8 mmol) of the *n*-butyl-acylate complex and 0.60 g (0.36 mL, 4.9 mmol) of acetyl bromide in 50 mL of CH_2Cl_2 for 1 h at −40 °C, followed by the addition of 0.52 g (0.50 mL, 4.8 mmol) of benzyl alcohol, stirring at room temp for 7 h, and chromatography (hexane/ethyl acetate (9:1)), gave 0.41 g (1.1 mmol, 23%) of **5b** as a yellow solid: mp 34–36 °C; ^1H NMR δ 0.90 (t, J = 7 Hz, 3 H, CH_3), 1.37 (m, 2 H, CH_2), 1.48 (m, 2 H, CH_2), 3.38 (m, $CH_2C{=}Cr$), 6.04 (s, 2 H, OCH_2Ph), 7.44 (s, 5 H, Ph); ^{13}C NMR (75 MHz) δ 13.8 (CH_3), 22.4, 28.5 and 63.0 (CH_2), 83.4 (OCH_2), 128.3, 128.9, and 129.2 (Ph), 134.1 (*i*-Ph), 216.4 (*cis*-CO), 223.1 (*trans*-CO), 361.7 (carbene carbon); IR ν (CO) 2055, 1985, 1945 cm^{-1}. Anal. Calcd for $C_{17}H_{16}CrO_6$: C, 55.44; H, 4.38. Found: C, 55.34; H, 4.46. The reaction times, temperatures, chromatography solvents, and yields are given in abbreviated form for the remainder of the complexes.

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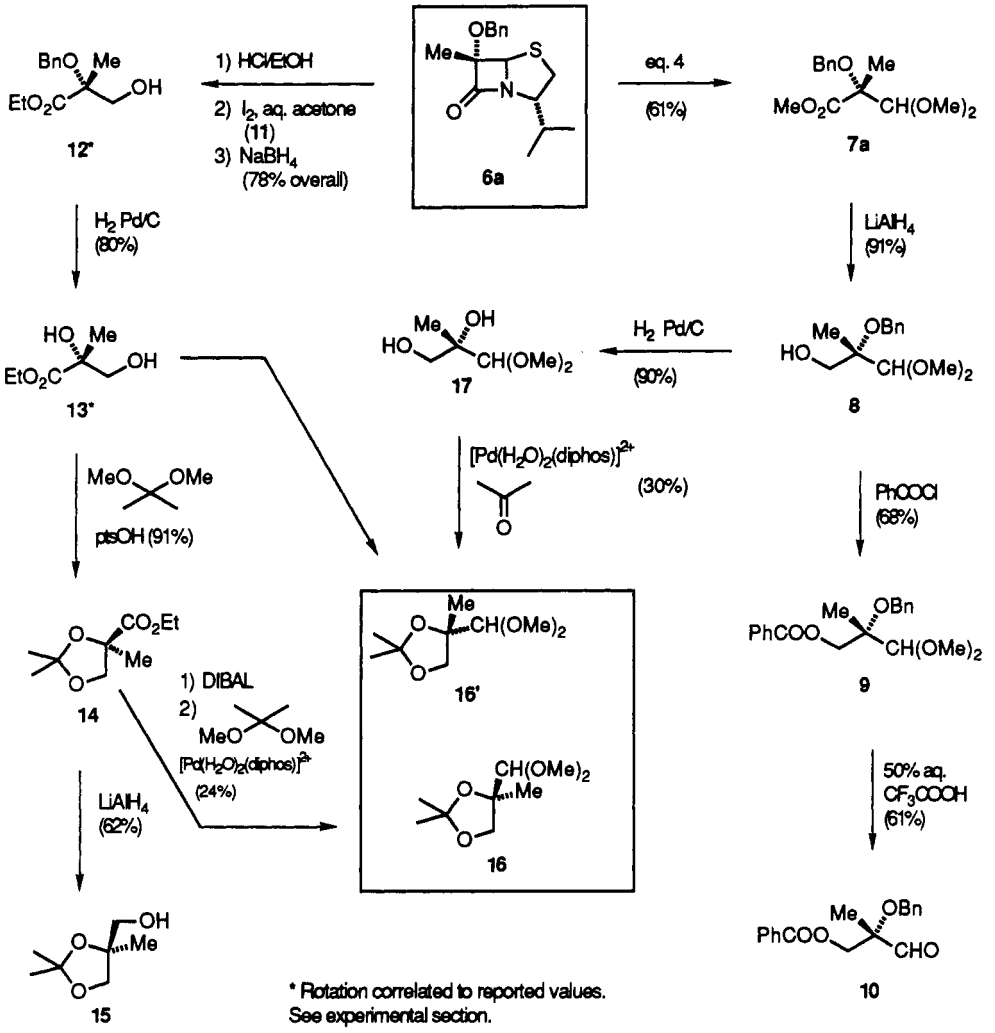
Scheme I



Pentacarbonyl[(cyclopropyl)(benzyloxy)carbene]chromium(0) (5c): cyclopropyl acylate complex, 0.80 g (2.4 mmol); acetyl bromide, 0.30 g (0.18 mL, 2.4 mmol); 50 mL of CH_2Cl_2, −45 °C for 80 min; benzyl alcohol, 0.26 g (0.25 mL, 2.4 mmol), rt for 18 h; chromatography (hexane), yield 0.64 g (1.8 mmol), 76%) of **5c** as a yellow solid; mp 60–62 °C; ^{1}H NMR δ 1.19 (m, 2 H, CH_2), 1.37 (m, 2 H, CH_2), 3.51 (m, 1 H, CH), 5.92 (s, 2 H, OCH_2Ph), 7.4 (m, 5 H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.1 (CH_2), 41.6 (CH), 82.3 (OCH_2), 128.2, 128.9 and 129.1 (Ph), 134.2 (*i*-Ph), 216.7 (*cis*-CO), 223.5 (*trans*-CO), 351.9 (carbene carbon); IR ν (CO) 2058, 1906 cm^{-1}. Anal. Calcd for $C_{16}H_{12}CrO_6$: C, 54.55; H, 3.43. Found: C, 54.44; H, 3.48.

Pentacarbonyl[(phenyl)(benzyloxy)carbene]chromium(0) (5d): phenyl–acylate complex, 0.76 g (2.0 mmol), acetyl bromide, 0.25 g (0.15 mL, 2.0 mmol), 50 mL of CH_2Cl_2, −40 °C for 45 min; benzyl alcohol 0.22 g (0.21 mL, 2.0 mmol), rt for 18 h, chromatography (hexane); yield 0.43 g (1.1 mmol, 54%) of **5d** as an orange solid; mp 68 °C; ^{1}H NMR δ 5.83 (s, 2 H, CH_2), 7.2–7.5 (m, 10 H, Ph); ^{13}C NMR δ 82.3 (OCH_2), 122.8, 128.2, 128.9, and 129.1 (Ph), 130.1 and 153.4 (*i*-Ph), 216.1 (*cis*-CO), 224.2 (*trans*-CO), 349.6 (carbene carbon); IR ν (CO) 2061, 1925 cm^{-1}. Anal. Calcd for $C_{19}H_{12}CrO_6$: C, 58.77; H, 3.12. Found: C, 59.04; H, 3.30.

Pentacarbonyl[(*p*-methoxyphenyl)(benzyloxy)carbene]chromium(0) (5e). The reaction of 0.45 g (1.1 mmol) of the *p*-methoxyphenyl–acylate complex and 0.19 g (0.13 mL, 1.1 mmol) of benzyl bromide in 4 mL of methylene chloride, with stirring at room temperature under an Ar atmosphere for 24 h, after evaporation of the solvent and radial thin-layer chromatography (hexane), gave 0.055 g (0.13 mmol, 12%) of **5e** as a red oil. Due to the small amount of material, elemental analysis was not obtained but the carbene was successfully applied to the synthesis of acetal **7e**: ^{1}H NMR δ 3.87 (s, 3 H, CH_3), 6.10 (s, 2 H, OCH_2Ph), 6.89 (d, J = 9.0 Hz, 2 H, $MeOC_6H_4$), 7.48 (m, 5 H, Ph), 7.73 (d, J = 9.0 Hz, 2 H, $MeOC_6H_4$); ^{13}C NMR δ 55.5 (OCH_3), 82.6 (CH_2), 113.2, 128.4, 129.0, 129.1, 129.7, 134.6, 145.8 and 163.2 (Ph), 216.9 (*cis*-CO), 223.7 (*trans*-CO), 339.0 (carbene carbon); IR ν (CO) 2057, 1915 cm^{-1}.

Pentacarbonyl[(2-furanyl)(benzyloxy)carbene]chromium(0) (5g): 2-furanyl–acylate complex, 1.50 g (4.15 mmol), and acetyl bromide, 0.52 g (0.31 mL, 4.15 mmol), 40 mL of CH_2Cl_2, −30 °C for 1 h; benzyl alcohol 0.45 g (0.43 mL, 4.15 mmol), rt 7 h; chromatography (hexane), yield 0.70 g (1.9 mmol, 45%) of **5g** as a red solid; mp 97–98 °C; ^{1}H NMR δ 6.09 (s, 2 H, $-OCH_2Ph$), 6.55 (dd, J = 1.8 and 3.6 Hz, 1 H, furyl C(4)H), 6.92 (d, J = 3.6 Hz, 1 H, furyl C(3)H), 7.42–7.48 (m, 5 H, Ph), 7.84 (d, J = 1.8 Hz, 1 H, furyl C(5)H); ^{13}C NMR δ 81.5 (OCH_2), 112.5 and 113.0 (furyl C(3), C(4)), 128.2 and 128.9 (Ph), 135.2 (*i*-Ph), 150.2 and 164.5 (furyl, C(2), C(5)), 216.9 (*cis*-CO), 223.8 (*trans*-CO), 311.7 (carbene carbon); IR (w), 2058, 1986, and 1934 cm^{-1}. Elemental analysis was not obtained.

Synthesis of Penams 6. The photoaddition of carbenes **5** with thiazoline **4** was conducted using published procedures.[8] The appropriate carbene complex and thiazoline **4** were dissolved in the indicated solvent in a Pyrex tube under Ar and irradiated with a 450-W Conrad-Hanovia 7825 medium-pressure mercury lamp. The progress of the reaction was monitored by TLC, noting the disappearance of the carbene complex. When the reaction was complete, the solvent was evaporated and the residue was dissolved in a 1:1 mixture of ethyl acetate and hexane. The mixture was placed in bright sunlight, exposed to the air, in a Pyrex Erlenmeyer flask. The oxidized chromium byproducts formed a brown-green solid which was removed by filtration through Celite. When the oxidation of chromium species was complete (by IR spectroscopy, noting the disappearance of metal-bound carbonyl absorption at 1800–2100 cm^{-1}) the solvent was evaporated and the residue was purified by radial layer

chromatography (9:1 hexane/ethyl acetate unless specified otherwise).

(3*S*,5*R*,6*S*)-6-(Benzyloxy)-3-isopropyl-6-methylpenam (6a). The reaction of 0.33 g (1.0 mmol) of carbene **5a** and 0.14 g (1.1 mmol) of thiazoline **4** in ether, under an argon atmosphere, after 3.5 days irradiation, followed by air oxidation of the chromium byproducts and radial thin-layer chromatography (9:1 hexane/ethyl acetate), gave 0.22 g (0.76 mmol, 76%) of the penam **6a** as a white solid: mp 34–36 °C; $[\alpha]_D$ +140° (*c* 0.7, CH_2Cl_2); ^1H NMR δ 0.96 (d, *J* = 7.0 Hz, 3 H, $CHCH_3$), 1.00 (d, *J* = 7.0 Hz, 3 H, $CHCH_3$), 1.50 (s, 3 H, CH_3), 1.68 (octet, *J* = 7.0 Hz, 1 H, $CHMe_2$), 3.04 (m, 2 H, SCH_2), 3.91 (m, 1 H, NCH), 4.68 (d, *J* = 11.0 Hz, 1 H, OCH_2Ph), 4.76 (d, *J* = 11.0 Hz, 1 H, OCH_2Ph), 5.01 (s, 1 H, NCHS), 7.2–7.4 (m, 5 H, Ph); ^{13}C NMR δ 16.9, 19.4 and 19.6 (CH_3), 29.7 ($CHMe_2$), 38.2 (SCH_2), 63.7 ($NCHCH_2$), 68.1 (OCH_2), 70.9 (NCHS), 90.2 (quat. C), 127.4, 127.7, and 128.2 (Ph), 137.2 (*i*-Ph), 173.7 (CO); IR ν (CO) 1770 cm^{-1}. Anal. Calcd for $C_{16}H_{21}NO_2S$: C, 65.95; H, 7.26; N, 4.81; S, 11.00. Found: C, 66.09; H, 7.47; N, 4.81; S, 10.87.

(3*S*,5*R*,6*S*)-6-(Benzyloxy)-6-butyl-3-isopropylpenam (6b): carbene **5b**, 0.41 g (1.1 mmol), thiazoline **4**, 0.16 g (1.2 mmol), acetonitrile, Ar, 36 h, chromatography, yield 0.28 g (0.85 mmol, 78%) of the penam **6b** as a clear oil; $[\alpha]_D$ +150° (*c* 0.25, CH_2Cl_2); ^1H NMR δ 0.8–1.0 (m, 9 H, CH_3), 1.2–1.9 (m, 7 H, $(CH_2)_3$ and $CHMe_2$), 3.04 (m, 2 H, SCH_2), 3.89 (m, 1 H, $NCHCH_2$), 4.69 (d, *J* = 11.0 Hz, OCH_2Ph), 4.76 (d, *J* = 11.0 Hz, OCH_2Ph), 4.95 (s, 1 H, NCHS), 7.1–7.4 (m, 5 H, Ph); ^{13}C NMR δ 13.87, 19.58, 19.74, 22.81, 24.40, 29.94, 30.06 (*n*-Bu and *i*-Pr), 38.55 (SCH_2), 63.73 ($NCHCH_2$), 68.15 (OCH_2Ph), 70.76 (NCHS), 92.62 (quat. C), 127.41, 127.70, and 128.33 (Ph), 137.61 (*i*-Ph), 173.59 (CO); IR ν (CO) 1765 cm^{-1}. Anal. Calcd for $C_{19}H_{27}NO_2S$: C, 68.43; H, 8.16; N, 4.20; S, 9.61. Found: C, 68.18; H, 8.24; N, 4.27; S, 9.76.

(3*S*,5*R*,6*S*)-6-(Benzyloxy)-6-cyclopropyl-3-isopropylpenam (6c): carbene **5c**, 0.64 g (1.8 mmol), thiazoline **4**, 0.26 g (2.0 mmol), acetonitrile, Ar, 38 h, chromatography, yield 0.22 g (0.71 mmol, 39%) of the penam **6c** as a white solid; mp 63–65 °C; $[\alpha]_D$ +151° (*c* 0.9, CH_2Cl_2); ^1H NMR δ 0.5–0.75 (m, 3 H, $CH(CH_2)_2$), 0.74 (m, 1 H, $CH(CH_2)_2$), 0.96 (d, *J* = 7.0 Hz, 3 H, $CH(CH_3)_2$), 0.98 (d, *J* = 7.0 Hz, 3 H, $CH(CH_3)_2$), 1.25 (m, 1 H, $CH(CH_2)_2$), 1.68 (octet, *J* = 7.0 Hz, 1 H, $CHMe_2$), 3.06 (m, 2 H, SCH_2), 3.93 (m, 1 H, NCH), 4.74 (d, *J* = 11.0 Hz, 1 H, OCH_2Ph), 4.76 (d, *J* = 11.0 Hz, 1 H, OCH_2Ph), 5.00 (s, 1 H, NCHS), 7.2–7.4 (m, 5 H, Ph); ^{13}C NMR δ 0.2, 2.5, and 12.2 (c-Pr), 19.7, 19.8, and 30.0 (*i*-Pr), 38.6 (SCH_2), 64.0 ($NCHCH_2$), 68.4 (OCH_2Ph), 71.7 (NCHS), 92.8 (quat. C), 127.5, 127.8, and 128.4 (Ph), 137.7 (*i*-Ph), 172.3 (CO); IR ν (CO) 1766 cm^{-1}. Anal. Calcd for $C_{18}H_{23}NO_2S$: C, 68.11; H, 7.30; N, 4.41; S, 10.10. Found: C, 68.21; H, 7.34; N, 4.32; S, 10.03.

(3*S*,5*R*,6*S*)-6-(Benzyloxy)-3-isopropyl-6-phenylpenam (6d): carbene **5d**, 0.2 g (0.51 mmol), thiazoline **4**, 0.07 g (0.51 mmol), diethyl ether, Ar, 18 h, chromatography; yield 0.074 g (0.21 mmol, 42%) of the penam **6d** as a white solid. An analytical sample was obtained by recrystallization from benzene/hexane; mp 102–103 °C; $[\alpha]_D$ +323.5° (*c* 0.6, CH_2Cl_2); ^1H NMR δ 0.98 (d, *J* = 6.7 Hz, 3 H, CH_3), 1.06 (d, *J* = 6.7 Hz, 3 H, CH_3), 1.71 (sextet, *J* = 6.7 Hz, 1 H, $CH(CH_3)_2$), 2.97 (dd, *J* = 11.4 and 4.8 Hz, 1 H, SCH_2), 3.05 (dd, *J* = 11.4 and 4.8 Hz, 1 H, SCH_2), 4.02 (m, 1 H, $NCHCH_2$), 4.48 (d, *J* = 11 Hz, 1 H, OCH_2Ph), 4.78 (d, *J* = 11 Hz, 1 H, OCH_2Ph), 5.22 (s, 1 H, NCHS), 7.25–7.55 (m, 10 H, Ph); ^{13}C NMR δ 19.7, 19.8 and 30.7 (*i*-Pr), 39.7 (SCH_2), 65.5 ($NCHCH_2$), 69.3 (OCH_2Ph), 73.6 (NCHS), 93.6 (quat. C), 127.8, 128.4, 128.6, and 129.1 (Ph), 134.9 and 137.4 (*i*-Ph), 172.9 (CO); IR ν (CO) 1755 cm^{-1}. Anal. Calcd for $C_{21}H_{23}NO_2S$: C, 71.35; H, 6.56; N, 3.96; S, 9.07. Found: C, 70.88; H, 6.46.

(3*S*,5*R*,6*S*)-6-(Benzyloxy)-3-isopropyl-6-(*p*-methoxyphenyl)penam (6e): carbene **5e**, 0.055 g (0.13 mmol), thiazoline **4**, 0.017 g (0.13 mmol), ether, Ar, 48 h, chromatography; yield 0.021 g (0.05 mmol, 42%) of the penam **6e** as a colorless oil. The material was directly converted to acetal **7e**, so optical rotation and elemental analysis were not obtained on this penam: ^1H NMR δ 0.96 (d, *J* = 7.0 Hz, 3 H, CH_3), 1.04 (d, *J* = 7.0 Hz, 3 H, CH_3), 1.69 (octet, *J* = 7.0 Hz, 1 H, $CHMe_2$), 2.96 (m, 2 H, SCH_2), 3.82 (s, 3 H, OCH_3), 3.98 (m, 1 H, $NCHCH_2$), 4.44 (d, *J* = 11.0 Hz, 1 H, OCH_2Ph), 4.73 (d, *J* = 11.0 Hz, 1 H, OCH_2Ph), 5.19 (s, 1 H, NCHS), 6.93 (m, 2 H, C_6H_4OMe), 7.29 (m, 5 H, Ph), 7.41 (m, 2 H, C_6H_4OMe); ^{13}C NMR δ 19.75, 19.83, and 30.7 (*i*-Pr), 39.7 (SCH_2), 55.2 (OMe), 65.6 ($NCHCH_2$), 69.1 (OCH_2Ph), 73.8 (NCHS), 93.3 (quat. C), 114.0, 126.9, 127.8, 128.4, and 129.3 (Ph), 137.6 and 160.1 (*i*-Ph), 173.1 (CO); IR ν (CO) 1763 cm^{-1}.

Penam 6f: carbene **5f**, 0.54 g (2.1 mmol), thiazoline **4**, 0.268 g (2.1 mmol), acetonitrile, Ar, 48 h chromatography; yield 0.41 g (1.8 mmol, 87%) of the penam **6f** as a 5:1 mixture of diastereomers (based on ^1H NMR integration). The diastereomers were separated by preparative thin-layer chromatography on silica gel (95:5 hexane/diethyl ether). Major diastereomer: $[\alpha]_D$ +159° (*c* 0.7, CH_2Cl_2); ^1H NMR δ 0.93 (d, *J* = 7.0 Hz, 3 H, $CH(CH_3)_2$), 0.97 (d, *J* = 7.0 Hz, 3 H, $CH(CH_3)_2$), 1.66 (septet, *J* = 6.0 Hz, 1 H, $CHMe_2$), 1.90 (m, 1 H, CH_2CH_2O), 2.01 (m, 1 H, CH_2CH_2O), 2.06 (m, 1 H, $CH_2(CH_2)_2O$), 2.28 (m, 1 H, $CH_2(CH_2)_2O$), 3.03 (m, 2 H, SCH_2), 3.89 (m, 3 H, $NCHCH_2$ and OCH_2), 4.87 (s, 1 H, NCHS); ^{13}C NMR δ 19.5, 19.8, and 25.5 (*i*-Pr), 29.6 and 30.1 (*i*-Pr and $CH_2CH_2CH_2O$), 38.6 (SCH_2), 64.3 ($NCHCH_2$), 70.6 and 73.2 (OCH_2 and NCHS), 94.2 (quat. C), 175.6 (CO); IR ν (CO) 1770 cm^{-1}. Minor diastereomer: ^1H NMR δ 0.96 (d, *J* = 6.7 Hz, 3 H, $CH(CH_3)_2$), 1.28 (d, *J* = 6.7 Hz, 3 H, $CH(CH_3)_2$), 1.88 (m, 1 H, OCH_2CH_2), 2.00 (m, 2 H, $OCH_2CH_2CH_2$), 2.35 (m, 2 H, $OCH_2CH_2H_2$ and $CH(CH_3)_2$), 2.58 (t, *J* = 10.0 Hz, 1 H, SCH_2), 2.81 (dt, *J* = 5.0 and 11.0 Hz, $NCHCH_2$), 3.07 (dd, *J* = 5.0 and 10.0 Hz, 1 H, SCH_2), 3.96 (m, 2 H, OCH_2), 4.87 (s, 1 H, NCHS); ^{13}C NMR δ 20.8, 22.7, 25.5, 29.1, and 29.6 (*i*-Pr and $CH_2CH_2CH_2O$), 39.7 (SCH_2), 70.7, 71.1, and 72.6 (OCH_2, NCHS, and $NCHCH_2$), 94.6 (quat. C), 174.1 (CO); IR ν (CO) 1770 cm^{-1}. Anal. Calcd for $C_{11}H_{17}NO_2S$: C, 58.12; H, 7.54; N, 6.16; S, 14.10. Found: C, 57.94; H, 7.69; N, 6.17; S, 14.21.

Penam 6g: carbene **5g**, 0.068 g (0.18 mmol), thiazoline **4**, 0.023 g (0.18 mmol), diethyl ether, under CO pressure (100 psi), 8 days, chromatography; yield 0.018 g (0.05 mmol, 29%) of the penam **6g**. Optical rotation and elemental analysis were not obtained: ^1H NMR δ 0.95 (d, *J* = 6.7 Hz, 3 H, CH_3), 1.01 (d, *J* = 6.7 Hz, 3 H, CH_3), 1.69 (octet, *J* = 6.7 Hz, 1 H, $CH(CH_3)_2$), 3.01 (ddd, *J* = 12.5, 4.4, and 7.1 Hz, 2 H, SCH_2), 4.00 (ddd, *J* = 4.4, 7.1, and 10.3 Hz, 1 H, NCH), 4.52 and 4.76 (ABq, *J* = 11.1 Hz, 2 H, OCH_2Ph), 5.20 (s, 1 H, NCHS), 6.39 (dd, *J* = 3.3 and 1.9 Hz, 1 H, furyl C(4)H), 6.64 (dd, *J* = 3.3 and 0.8 Hz, 1 H, furyl C(3)H), 7.19–7.43 (m, 5 H, Ph), 7.53 (dd, *J* = 1.9 and 0.8 Hz, 1 H, furyl C(5)H); ^{13}C NMR δ 19.6, 19.7, and 30.2 (*i*-Pr), 39.4 (SCH_2), 65.5 (NCH), 69.7 (OCH_2Ph), 72.4 (NCHS), 89.6 (quat. C), 110.1 (furyl C(3)), 113.0 (furyl C(4)), 127.9, 128.4 and 128.6 (Ph), 137.2 (*i*-Ph), 144.5 (furyl C(5)), 146.6 (furyl C(2)), 170.7 (CO).

Conversion of Penams 6 to Acetals 7. The penam was stirred in 10 mL of methanol saturated with gaseous HCl at rt for 18 h. The mixture was neutralized with aqueous $NaHCO_3$ and extracted with ethyl acetate. The solvent was removed under vacuum, and the residue was dissolved in 10 mL of 10% aqueous acetone and treated with 3 equiv of I_2. The mixture was heated at reflux for 3 h, after which I_2 was decomposed with aqueous $Na_2S_2O_3$ and the mixture was extracted with ethyl acetate. Evaporation of the ethyl acetate gave the aldehyde which was used without further purification. The aldehyde was dissolved in 10 mL of anhydrous methanol, 1 mL of trimethylorthoformate, and 3 equiv of I_2 in a sealed tube and heated at 80 °C for 3 h. The mixture was cooled, poured into aqueous $Na_2S_2O_3$, and extracted with ethyl acetate. Evaporation of the ethyl acetate followed by preparative TLC on plates which had been pretreated with triethylamine (9:1 hexane/ethyl acetate) gave the dimethyl acetal **7**.

(*R*)-Methyl 2-(Benzyloxy)-3,3-dimethoxy-2-methylpropanoate (7a). Penam **6a**, 0.077 g (0.26 mmol), gave 0.042 g (0.16 mmol, 60.3%) of acetal **7a** as a colorless oil: $[\alpha]_D$ +1.22° (*c* 3.6, CH_2Cl_2); ^1H NMR δ 1.48 (s, 3 H, CH_3), 3.46 (s, 3 H, OCH_3), 3.58 (s, 3 H, OCH_3), 3.74 (s, 3 H, $CO(O)CH_3$), 4.35 (d, *J* = 11.0 Hz, 1 H, CH_2), 4.52 (s, 1 H, CH), 4.57 (d, *J* = 11.0 Hz, 1 H, CH_2), 7.2–7.4 (m, 5 H, Ph); ^{13}C NMR δ 14.5 (CH_3), 51.6, 56.8, and 58.2 (OCH_3), 66.8 and 83.6 (CH_2 and CH), 108.1 (quat. C), 127.3, 128.1, and 138.6 (Ph), 171.9 (CO); IR ν 1740 (CO) cm^{-1}. Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.67; H, 7.5. Found: C, 62.83; H, 7.49.

(*R*)-Methyl 2-(Benzyloxy)-2-(dimethoxymethyl)hexanoate (7b). Penam **6b**, 0.122 g (0.37 mmol), gave 0.048 g (0.15 mmol, 42%) of acetal **7b** as a colorless oil: $[\alpha]_D$ −5.9° (*c* 0.99, CH_2Cl_2). ^1H NMR δ 0.89 (t, *J* = 7.0 Hz, 3 H, CH_3), 1.32 (m, 3 H, CH_2 and $CH_3CH_2CH_2$), 1.53 (m, 1 H, CH_2), 1.81 (m, 1 H, CH_2), 1.97 (m, 1 H, CH_2), 3.52 (s, 3 H, OCH_3), 3.55 (s, 3 H, OCH_3), 3.76 (s, 3 H, $CO(O)CH_3$), 4.56 (s, 1 H, CH), 4.65 (d, *J* = 12.0 Hz, 1 H, CH_2),

4.75 (d, J = 12.0 Hz, 1 H, CH_2), 7.2–7.5 (m, 5 H, Ph); ^{13}C NMR δ 13.9, 23.0, 25.5, and 33.4 (Bu), 51.8, 57.9, and 58.4 (OCH_3), 67.8 and 85.2 (OCH_2 and quat. C), 109.1 (CH), 127.0, 127.3, 128.0, and 139.3 (Ph), 172.1 (CO); IR ν 1748 (CO) cm^{-1}. Anal. Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44. Found: C, 65.69; H, 8.60.

(*R*)-Methyl 2-(Benzyloxy)-2-cyclopropyl-3,3-dimethoxypropanoate (7c). Penam **6c**, 0.10 g (0.32 mmol), gave 0.058 g (0.20 mmol, 62.5%) of acetal **7c** as a colorless oil: $[\alpha]_D$ −14.39° (c 2.6, CH_2Cl_2); ^1H NMR δ 0.44 (m, 1 H, $CH(CH_2)_2$), 0.56 (m, 1 H, $CH(CH_2)_2$), 0.71 (m, 2 H, $CH(CH_2)_2$), 1.26 (m, 1 H, $CH(CH_2)_2$), 3.52 (s, 3 H, $CH(OCH_3)_2$), 3.58 (s, 3 H, $CH(OCH_3)_2$), 3.75 (s, 3 H, $C(O)OCH_3$), 4.68 (s, 1 H, CH), 4.78 (d, J = 12.0 Hz, 1 H, CH_2), 4.86 (d, J = 12.0 Hz, 1 H, CH_2), 7.2–7.45 (m, 5 H, Ph); ^{13}C NMR δ 0.5, 2.3 and 14.7 (c-Pr), 51.7, 57.5 and 58.0 (OCH_3), 67.9 (OCH_2), 83.6 (quat. C), 108.9 (CH), 126.9, 127.2, 128.0, and 139.6 (Ph), 171.7 (CO); IR ν (CO) 1752, 1730 cm^{-1}. Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.54. Found: C, 65.13; H, 7.39.

(*R*)-Methyl 2-(Benzyloxy)-3,3-dimethoxy-2-phenylpropanoate (7d). Penam **6d**, 0.106 g (0.30 mmol), gave 0.068 g (0.21 mmol, 69%) of acetal **7d** as a pale yellow oil: $[\alpha]_D$ +13.44° (c 3.4, CH_2Cl_2); ^1H NMR δ 3.42 (s, 3 H, $CH(OCH_3)_2$), 3.54 (s, 3 H, $CH(OCH_3)_2$), 3.80 (s, 3 H, $C(O)OCH_3$), 4.58 (d, J = 11.7 Hz, 1 H, CH_2O), 4.70 (d, J = 11.7 Hz, 1 H, CH_2), 4.95 (s, 1 H, CH), 7.2–7.6 (m, 10 H, Ph); ^{13}C NMR δ 52.1, 57.6, and 58.4 (OCH_3), 68.4 (OCH_2), 86.9 (quat. C), 108.7 (CH), 127.2, 127.7, 128.0, 128.1, 135.5, and 138.7 (Ph), 170.7 (CO); IR ν (CO) 1732 cm^{-1}. Anal. Calcd for $C_{19}H_{22}O_5$: C, 69.07; H, 6.71. Found: C, 68.85; H, 6.57.

(*R*)-Methyl 2-(Benzyloxy)-3,3-dimethoxy-2-(*p*-methoxyphenyl)propanoate (7e). Penam **6e**, 0.022 g (0.057 mmol), gave 0.007 g (0.02 mmol, 34%) of acetal **7e** as a colorless oil: $[\alpha]_D$ +22.6° (c 0.35, CH_2Cl_2); ^1H NMR δ 3.42 (s, 3 H, $CH(OCH_3)_2$), 3.53 (s, 3 H, $CH(OCH_3)_2$), 3.78 (s, 6 H, p-CH_3OPh and $COOCH_3$), 4.53 (d, J = 11.7 Hz, 1 H, OCH_2), 4.63 (d, J = 11.7 Hz, 1 H, OCH_2), 4.89 (s, 1 H, CH), 6.86 (d, J = 8.8 Hz, 2 H, o-C_6H_4OMe), 7.33 (m, 5 H, Ph), 7.47 (d, J = 8.8 Hz, 2 H, m-C_6H_4OMe); ^{13}C NMR δ 52.2, 55.2, 57.6, and 58.4 (OCH_3), 68.2 (OCH_2), 86.8 (quat. C), 108.7 (CH), 113.2, 127.2, 127.3, 127.4, 128.2, 129.2, 138.81 and 159.3 (Ar), 171.0 (CO); IR ν (CO) 1747 cm^{-1}. Anal. Calcd for $C_{20}H_{24}O_6$: C, 66.65; H, 6.71. Found: C, 66.42; H, 6.60.

(*S*)-2-(Benzyloxy)-3-hydroxy-2-methylpropanal Dimethyl Acetal (8). To a stirred solution of LAH (40 mg, 1.06 mmol) in THF (20 mL) was added acetal **7a** (95 mg, 0.35 mmol) in THF (10 mL) at rt under Ar. The reaction mixture was heated at reflux for 3 h under Ar. After cooling to 0 °C, the reaction mixture was quenched with 0.04 mL of H_2O, 0.04 mL of 15% NaOH(aq), and 0.12 mL of H_2O followed by heating at reflux for 30 min. The mixture was filtered, and the filtrate was dried over $MgSO_4$ and evaporated. The residue was purified by TLC (silica gel pretreated with Et_3N) (3:1 hexane/ethyl acetate) to give 77 mg (90.5%) of **8**: $[\alpha]_D$ +2.0° (c 1.15, CH_2Cl_2); ^1H NMR δ 1.22 (s, 3 H, CH_3), 2.53 (dd, J = 6.6, 5.9 Hz, 1 H, OH), 3.54 (s, 3 H, $CH(OCH_3)_2$), 3.55 (s, 3 H, $CH(OCH_3)_2$), 3.60–3.71 (m, 2 H, $HOCH_2$), 4.29 (s, 1 H, $CH(OMe)_2$), 4.61 (s, 2 H, OCH_2Ph), 7.26–7.35 (m, 5 H, Ph); IR ν 3850, 3460, 2935, 1497, 1453, 1383, 1187, 1074 cm^{-1}. This material was converted to known compound **10** via **9**.

(*S*)-2-(Benzyloxy)-3,3-dimethoxy-2-methylpropyl Benzoate (9). To a stirred solution of hydroxy dimethyl acetal **8** (65 mg, 0.27 mmol) in $CHCl_3$ (15 mL) and pyridine (1 mL) was added benzoyl chloride (42 mg, 0.3 mmol) at room temperature under Ar. The reaction mixture was stirred at room temperature for 24 h and then 15 mL of H_2O was added. The organic phase was extracted, washed with brine, and dried over $MgSO_4$. The solvent was evaporated, and the residue was purified by TLC (silica gel, pretreated with Et_3N) (9:1 hexane/ethyl acetate) to give 63 mg (67.6%) of **9**: $[\alpha]_D$ −9.36° (c 0.58, CH_2Cl_2); ^1H NMR δ 1.34 (s, 3 H, CH_3), 3.50 (s, 3 H, $CH(OCH_3)_2$), 3.57 (s, 3 H, $CH(OCH_3)_2$), 4.38 (s, 1 H, $CH(OMe)_2$), 4.38 ($^1/_2$ABq, J = 11.9 Hz, 1 H, $-OCH_2-$), 4.58 ($^1/_2$ABq, J = 11.9 Hz, 1 H, $-OCH_2-$), 4.66 (s, 2 H, $-OCH_2Ph$), 7.23–7.56 and 8.04 (m, 10 H, 2Ph); IR ν (CO) 1722 cm^{-1}. This compound was converted to known compound **10**.

(*S*)-2-(Benzyloxy)-2-methyl-3-oxopropyl Benzoate (10). A solution of dimethyl acetal **9** (79 mg, 0.23 mmol) in CH_2Cl_2 (20 mL) and 50% aqueous CF_3COOH (2 mL) was heated at reflux for 5 h. After the solution was cooled to 0 °C, saturated $NaHCO_3$(aq) was added to the mixture slowly until the aqueous phase was neutralized. The organic phase was extracted, washed with brine, and dried over $MgSO_4$. The solvent was evaporated. The residue was purified by TLC silica gel (9:1 hexane/ethyl acetate) to give 42 mg (61.4%) of **10**: $[\alpha]_D$ −1.8° (c 0.55, $CHCl_3$); ^1H NMR δ 1.45 (s, 3 H, CH_3), 4.48 ($^1/_2$ABq, J = 11.9 Hz, 1 H, $-COOCH_2-$), 4.59 ($^1/_2$ABq, J = 13.5 Hz, 1 H, $-OCH_2Ph$), 4.65 ($^1/_2$ABq, J = 13.5 Hz, 1 H, $-OCH_2Ph$), 4.66 ($^1/_2$ABq, J = 11.9 Hz, 1 H, $-COOCH_2-$), 7.27–7.56 and 8.00 (m, 10 H, 2Ph), 9.77 (s, 1 H, $-CHO$). IR ν (CO) 1724, 1740 (shoulder) cm^{-1}. This is identical to the data reported for this compound *except for the rotation* (lit.[13] $[\alpha]_D$ +6.0° (c 0.5, $CHCl_3$)).

(*S*)-2,3-Dihydroxy-2-methylpropanal Dimethyl Acetal (17). A solution of benzyloxy acetal **8** (86 mg, 0.36 mmol) in MeOH (5 mL) with 5% Pd on charcoal (75 mg) was stirred at room temperature with a H_2 balloon until the reaction was complete. The reaction mixture was filtered and evaporated. The volatiles were evaporated (0.3 mmHg, room temperature) to give the pure diol (48 mg, 90%) as a colorless oil: $[\alpha]_D$ + 3.8° (c 0.8, CH_2Cl_2); ^1H NMR δ 1.10 (s, 3 H, CH_3), 2.48 (bs, 1 H, CH_2OH), 2.74 (s, 1 H, C(2)OH), 3.37 and 3.69 (AB quartet δ_A = 3.37, δ_B = 3.69, J_{AB} = 11 Hz, 2 H, CH_2OH), 3.54 (s, 3 H, $CH(OCH_3)_2$), 3.55 (s, 3 H, $CH(OCH_3)_2$), 4.19 (s, 1 H, $-CH(OMe)_2$); IR ν 3444 (OH) cm^{-1}.

(*S*)-2,2,4-Trimethyl-4-(dimethoxymethyl)-1,3-dioxolane (16'). A solution of dihydroxy acetal **17** (45 mg, 0.30 mmol) and $[Pd(H_2O)_2(diphos)](CF_3SO_3)_2$[22] (10 mg) in CH_2Cl_2 (3 mL) and acetone (1 mL) was stirred at room temperature under Ar for 2 days. After careful evaporation of solvent (20 mmHg, 0 °C) the residue was dissolved in Et_2O (4 mL) to precipitate the Pd catalyst. The mixture was filtered. After careful evaporation of solvent, the product was purified by bulb-to-bulb distillation (0.3 mmHg, room temp) to give 17 mg (30%) as a colorless oil; $[\alpha]_D$ −3.42° (c 0.8, CH_2Cl_2). The spectra were identical with those of its enantiomer **16**.

(*R*)-Ethyl 2-(Benzyloxy)-2-methyl-3-hydroxypropionate (12).[14] A solution of penam **6a** (63 mg, 0.22 mmol) in HCl-saturated EtOH (10 mL) was stirred at room temperature overnight. The solvent was evaporated, and the residue was neutralized with saturated aqueous $NaHCO_3$. Ethyl acetate was added. The organic phase was extracted, washed with brine, and dried over $MgSO_4$. The solvent was evaporated, and the residue was purified by TLC silica gel (3:1 hexane/ethyl acetate) to give 64 mg of the intermediate.

A solution of this compound and I_2 (0.144 g, 3 equiv) in 10% aqueous acetone (10 mL) was heated at reflux for 3 h under Ar. After the mixture was cooled to room temperature, excess I_2 was decomposed with aqueous $Na_2S_2O_3$. The volatiles were evaporated, and ethyl acetate (20 mL) was added. The organic phase was extracted, washed with brine, and dried over $MgSO_4$, and the solvent was evaporated to give crude aldehyde **11**.

A solution of crude aldehyde **11** in EtOH (10 mL) was cooled to 0 °C. $NaBH_4$ (4 mg, 0.11 mmol) was added to the reaction mixture, which then was stirred at room temperature under Ar overnight. Saturated $NaHCO_3$(aq) (3 mL) was added and mixture was stirred at rt for 15 min and evaporated. Ethyl acetate (10 mL) and H_2O (4 mL) were added. The organic phase was extracted, washed with brine, and dried over $MgSO_4$. The volatiles were evaporated, and the residue was purified by TLC silica gel (3:1 hexane/ethyl acetate) to give 40 mg of **12** (total, 77.6%): $[\alpha]_D$ +1.7° (c 1.9, EtOH) (lit.[14] $[\alpha]_D$ +1.9° (c 1.9, EtOH); ^1H NMR δ 1.30 (t, J = 7.1 Hz, 3 H, $-OCH_2CH_3$), 1.49 (s, 3 H, $-CH_3$), 2.28 (bs, 1 H, $-OH$), 3.72 and 3.80 (ABq, J = 11.4 Hz, 2 H, $-CH_2OH$), 4.24 (q, J = 7.1 Hz, 2 H, $-OCH_2CH_3$), 4.52 and 4.64 (ABq, J = 10.8 Hz, 2 H, $-OCH_2Ph$), 7.24–7.41 (m, 5 H, Ph); IR (NaCl, neat) ν 3477, 1732 (CO) cm^{-1}.

Aldehyde **11** was also purified by TLC silica gel (4:1 hexane/ethyl acetate); $[\alpha]_D$ +12.7° (c 1.18, CH_2Cl_2). ^1H NMR δ 1.29 (t, J = 7.0 Hz, 3 H, $-OCH_2CH_3$), 1.60 (s, 3 H, $-CH_3$), 4.24 (q, J = 7.0 Hz, 2 H, $-OCH_2CH_3$), 4.58 and 4.62 (ABq, J = 10.7 Hz, 2 H, $-OCH_2Ph$), 7.23–7.42 (m, 5 H, Ph), 9.68 (s, 1 H, $-CHO$); IR ν (CO) 1732, 1751 cm^{-1} (shoulder).

(*R*)-Ethyl 2,3-Dihydroxy-2-methylpropionate (13).[14] To a solution of the benzyloxy compound **12** (233 mg, 0.98 mmol) in ethyl acetate (2 mL) was added 5% Pd/C (120 mg). The

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reaction mixture was stirred at room temperature with a H_2 balloon until the reaction was complete. After filtration, the filtrate was evaporated to give diol **13** (116 mg, 80%). The product was purified by bulb-to-bulb distillation (56–57 °C (0.1 Torr)): $[\alpha]_D$ +10.5° (*c* 1.1, $CHCl_3$) (lit.[14] $[\alpha]_D$ +11.6° (*c* 2.12, $CHCl_3$); ^1H NMR δ 1.31 (t, *J* = 7.2 Hz, 2 H, $-OCH_2CH_3$), 1.35 (s, 3 H, $-CH_3$), 3.58 and 3.81 (ABq, *J* = 11.2 Hz, 2 H, $-CH_2OH$), 4.28 (q, *J* = 7.2 Hz, 2 H, $-OCH_2CH_3$); IR (NaCl, neat) ν 3444, 1732 (CO) cm^{-1}.

(*R*)-2,2,4-Trimethyl-1,3-dioxolane-4-carboxylic Acid Ethyl Ester (14).[14] To a solution of the diol **13** (40 mg, 0.27 mmol) in freshly distilled 2,2-dimethoxypropane (5 mL) was added *p*-toluenesulfonic acid (4 mg). The reaction mixture was stirred at room temperature under Ar overnight. Excess 2,2-dimethoxypropane was removed by distillation at ~40 °C (12 Torr), and the residue was treated with 2 mL of $NaHCO_3$(aq), CH_2Cl_2 (15 mL), and H_2O (10 mL). The organic phase was extracted, washed with H_2O, and dried over $MgSO_4$. Careful evaporation of the solvent resulted in the almost pure 1,3-dioxolane **14** (46 mg 90.5%) which was purified by bulb-to-bulb distillation (81 °C (15 Torr)): ^1H NMR (270 MHz, $CDCl_3$) δ 1.27 (t, *J* = 7.3 Hz, 3 H, OCH_2CH_3), 1.40 (s, 3 H, C(2)CH_3), 1.42 (s, 3 H, C(2)CH_3), 1.49 (s, 3 H, C(4)CH_3), 3.75 ($^1/_2$ABq, *J* = 8.8 Hz, 1 H, OCH_2–), 4.20 (q, *J* = 7.3 Hz, 2 H, $-OCH_2CH_3$), 4.36 ($^1/_2$ABq, *J* = 8.8 Hz, 1 H, OCH_2); IR ν (CO) 1732 cm^{-1}.

(*S*)-2,2,4-Trimethyl-4-(hydroxymethyl)-1,3-dioxolane (15).[16] To a solution of LAH (40 mg) in 7 mL of THF was added a solution of ester **14** (46 mg, 0.24 mmol) in THF (3 mL) slowly at room temperature, and the reaction mixture was heated at reflux for 3 h under Ar. After being cooled to 0 °C it was quenched with 0.04 mL of H_2O, followed by 0.04 mL of 15% NaOH(aq) followed by 0.12 mL of H_2O followed by heating at reflux for 30 min. The mixture was filtered, and the filtrate was dried over $MgSO_4$. The solvent was evaporated carefully, and the residue was purified by careful bulb-to-bulb distillation to give 22 mg (62%) of **15**: $[\alpha]_D$ –5.4° (*c* 1.1, CH_2Cl_2) (lit.[16] $[\alpha]_D$ –5.33° (*c* 0.3, CH_2Cl_2); ^1H NMR (270 MHz, $CDCl_3$) δ 1.27 (s, 3 H, C(4)CH_3), 1.39 (s, 3 H, C(2)CH_3), 1.41 (s, 3 H, C(2)CH_3), 2.50 (bs, 1 H, $-OCH_2OH$), 3.47 (ABq, *J* = 11.7 Hz, 2 H, $-OCH_2OH$), 3.70 ($^1/_2$ABq, *J* = 8.5 Hz, 1 H, $-OCH_2$), 3.96 ($^1/_2$ABq, *J* = 8.5 Hz, 1 H, $-OCH_2$–); IR ν 3391, 2986, 2936, 1875 cm^{-1}.

(*R*)-2,2,4-Trimethyl-4-(dimethoxymethyl)-1,3-dioxolane (16). To a solution of 1,3-dioxolane ester **14** (68 mg, 0.36 mmol) in Et_2O (3 mL) was added DIBAH (0.72 mL, 0.72 mmol) at –78 °C under Ar. The reaction mixture was stirred at –78 °C under Ar for 5 h. A solution of MeOH (0.5 mL) and H_2O (0.5 mL) was added, the cooling bath was removed, and the temperature was raised to rt and recooled to 0 °C. Saturated $NaHCO_3$(aq) (1 mL) was added, and the mixture was stirred at 0 °C for 30 min. The organic phase was extracted, washed with brine, and dried over $MgSO_4$.

$[Pd(H_2O)_2(diphos)](CF_3SO_3)_2$[22] (34 mg) and freshly distilled 2,2-dimethoxypropane (2 mL) in CH_2Cl_2 (8 mL) were added to the mixture which then was stirred at room temperature for 5 days under Ar. After careful evaporation of solvent (20 mmHg, 0 °C), the residue was dissolved in Et_2O (5 mL) and filtered to remove the Pd catalyst. After careful evaporation of solvent, the product was purified by bulb-to-bulb distillation (0.3 mmHg, room temperature). The yield was 16 mg (23%) as colorless oil with mesityl oxide as an impurity. Found $[\alpha]_D$ +1.6°; estimated $[\alpha]_D$ by ^1H NMR integration +3.4° (*c* 0.10, CH_2Cl_2). The amount of **16** in the sample was estimated by the careful comparison of integration of multiple peaks of **16** via the contaminant mesityl oxide, and the rotation was estimated on that amount of material: ^1H NMR δ 1.25 (s, 3 H, C(4)CH_3), 1.38 (s, 3 H, C(2)CH_3), 1.39 (s, 3 H, C(2)CH_3), 3.47 (s, 3 H, $-CH(OCH_3)_2$), 3.53 (s, 3 H, $-CH(OCH_3)_2$), 3.66 and 4.01 (ABq, *J* = 8.8 Hz, 2 H, $-OCH_2$–), 4.08 (s, 1 H, $-CH(OMe)_2$); IR (NaCl, neat) ν 2963, 2360, 1644, 1457, 1261, 1091 cm^{-1}.

Acknowledgment. Support for this research by National Science Foundation Grant CHE 8921992 is gratefully acknowledged. N.S. thanks Mitsubishi Petrochemical Co. Ltd. for support.

Rapid, High-Yield Synthesis of the Marine Sesquiterpenes Debromoaplysin and Aplysin via the Acid-Catalyzed Rearrangement of a Cyclobutachromanol†

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Received May 31, 1991

A short, stereocontrolled, high-yield synthesis of debromoaplysin (**1**) and aplysin (**2**) from the chromone **13** is described. The cycloaddition of ethylene to **13**, followed by the addition of methylmagnesium iodide to the cycloadduct, furnished the cyclobutachromanol **15**. Treatment of **15** in benzene with BF_3·Et_2O furnished a mixture of the alkenes **16** and **17**, which can be visualized as arising by way of the initial 1,2-migration of the external and internal bonds, respectively, of the cyclobutane ring of **15**. Similar rearrangement of **18**, an ethyl analogue of **15**, yielded **19** and **20**. Rearrangement of **15** on treatment with sulfuric acid in petroleum ether at –78 °C furnished, almost exclusively, **17**. In contrast, when performed in nitroethane at –78 °C, the same reaction afforded **16** exclusively. Thus, the solvent exerted a remarkable effect on the outcome of the rearrangement. Since alkene **16** had previously been converted to **1** and **2**, this work represents an improved synthesis of the two sesquiterpenes.

Introduction

The novel structures of the marine sesquiterpenes debromoaplysin (**1**) and aplysin (**2**)[1] have attracted the attention of synthetic organic chemists.[2] Recently, we described[3] a short, stereocontrolled synthesis of **1** and **2** and the related compounds debromoaplysinol (**3**), aplysinol (**4**), and isoaplysin (**5**). Therein an intramolecular ketene-to-alkene cycloaddition was the key step. Here we describe an alternate route to **1** and **2**, one that represents a rapid and improved synthesis of these compounds.

The method described here relies on the acid-catalyzed rearrangement of fused-ring cyclobutyl carbinols to gen-

† This paper is respectfully dedicated to Prof. U. R. Ghatak on his 60th birthday.

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