The products obtained were known products in all cases. Identification was effected through alternate preparation by known procedures. Since the reactions studied here are all similar in many respects, typical reactions will be described as specific examples.

Preparation of 1-(Benzoyloxy)benzotriazole. To a stirred solution of 1-hydroxybenzotriazole (675 mg, 5 mmol) and triethylamine (770 μL, 5.5 mmol) in methylene chloride (4 mL) at room temperature was slowly added benzoyl chloride (580 μL, 5 mmol). The reaction mixture was stirred at room temperature for 20 min, diluted with methylene chloride (40 mL), washed with saturated $NaHCO_3$ solution (20 mL) and brine (20 mL), dried over anhydrous $MgSO_4$, and evaporated to dryness. The crude product was recrystallized from methylene chloride and petroleum ether to afford 1-(benzoyloxy)benzotriazole (1.02 g) in 85% yield: mp 77-79 °C [lit.[5a] mp 77-79 °C, lit.[5b] 80-81 °C]; IR (KBr) 1775 cm^{-1} [lit.[5b] 1770 cm^{-1}].

Selective Benzoylation of 1-Phenyl-1,2-ethanediol. To a stirred solution of 1-phenyl-1,2-ethanediol (280 mg, 2.0 mmol) and 1-(benzoyloxy)benzotriazole (503 mg, 2.1 mmol) in methylene chloride (8 mL) at room temperature was added triethylamine (305 μL, 2.2 mmol). The reaction mixture was stirred at room temperature for 24 h, diluted with methylene chloride (30 mL), washed with saturated $NaHCO_3$ solution (20 mL) and brine (20 mL), dried over anhydrous $MgSO_4$, and evaporated to dryness. The crude product was subjected to silica gel column chromatography using hexane and ethyl acetate (6:1) as an eluant to afford the dibenzoate (34 mg, 5%), the primary monobenzoate (390 mg, 83%), and the secondary monobenzoate (42 mg, 9%). The dibenzoate: mp 91-93 °C; NMR ($CDCl_3$) δ 4.55-4.80 (m, 2 H), 6.35 (t, J = 6 Hz, 1 H), 7.15-8.15 (m, 15 H). The primary monobenzoate: mp 65-66 °C; NMR ($CDCl_3$) δ 3.20 (br s, 1 H), 4.35-4.65 (m, 2 H), 5.15 (dd, J = 4, 6 Hz, 1 H), 7.20-7.60 (m, 8 H), 7.90-8.30 (m, 2 H). The secondary monobenzoate: NMR ($CDCl_3$) δ 2.20 (br s, 1 H), 3.90-4.15 (m, 2 H), 6.05 (q, J = 5 Hz, 1 H), 7.20-7.65 (m, 8 H), 7.95-8.30 (m, 2 H).

Selective Benzoylation of Methyl 4,6-*O*-Benzylidene-α-D-glucopyranoside. To a stirred solution of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (565 mg, 2.0 mmol) and 1-(benzoyloxy)benzotriazole (485 mg, 2.0 mmol) in methylene chloride (8 mL) at room temperature was added triethylamine (300 μL, 2.2 mmol). The reaction mixture was stirred at room temperature for 5 h, diluted with methylene chloride (40 mL), washed with saturated $NaHCO_3$ solution (20 mL) and brine (20 mL), dried over anhydrous $MgSO_4$, and evaporated to dryness. The crude product was subjected to silica gel column chromatography. Elution with hexane and ethyl acetate (6:1) gave the 2,3-di-*O*-benzoate (19 mg, 2%). After the 2,3-di-*O*-benzoate was isolated, elution with hexane and ethyl acetate (3:1) gave the 2-*O*-benzoate (693 mg, 90%), and elution with hexane and ethyl acetate (1:1) gave the 3-*O*-benzoate (29 mg, 4%). Methyl 4,6-*O*-benzylidene-2,3-di-*O*-benzoyl-α-D-glucopyranoside: mp 154 °C [lit.[7a] 154 °C]; $[\alpha]^{25}_D$ +92.2° (0.7, $CHCl_3$) [lit.[7a] $[\alpha]^{26}_D$ +94 ± 2° (1.51, $CHCl_3$)]. Methyl 4,6-*O*-benzylidene-2-*O*-benzoyl-α-D-glucopyranoside: mp 169-170 °C [lit. mp 169-170 °C,[7a] 168-170 °C[7d]]; $[\alpha]^{25}_D$ +107.0° (1.3, $CHCl_3$) [lit. $[\alpha]^{26}_D$ +111 ± 2° (1.64, $CHCl_3$)[7a], $[\alpha]_D$ +108° (1, $CHCl_3$)[7d]]. Methyl 4,6-*O*-benzylidene-3-*O*-benzoyl-α-D-glucopyranoside: mp 217-220 °C [lit. mp 219-220 °C,[7a] 218-220 °C[7e]]; $[\alpha]^{25}_D$ +33.8° (0.7, $CHCl_3$) [lit. $[\alpha]^{26}_D$ +34.1° (1.10, $CHCl_3$),[7a] $[\alpha]^{20}_D$ +33° (2, $CHCl_3$)[7e]].

Selective benzoylation of methyl 4,6-*O*-benzylidene-β-D-glucopyranoside and methyl 4,6-*O*-benzylidene-α-D-altropyranoside was carried out in a similar manner as described above. Methyl 4,6-*O*-benzylidene-2-*O*-benzoyl-β-D-glucopyranoside: mp 198-199 °C [lit. mp 195-196 °C,[7d] 195-197 °C[7e]]; $[\alpha]^{25}_D$ -32.8° (0.6, $CHCl_3$) [lit. $[\alpha]^{20}_D$ -34° (0.5, $CHCl_3$),[7d] $[\alpha]^{20}_D$ -34° (1.5, $CHCl_3$)[7e]]. Methyl 4,6-*O*-benzylidene-3-*O*-benzoyl-β-D-glucopyranoside: mp 180-182 °C [lit. mp 177-178 °C,[7d] 182-183 °C[7f]]; $[\alpha]^{25}_D$ -106.5° (0.2, $CHCl_3$) [lit. $[\alpha]^{20}_D$ -107° (0.5, $CHCl_3$)[7d]]. Methyl 4,6-*O*-benzylidene-2-*O*-benzoyl-α-D-altropyranoside: mp 138-139 °C [lit.[7b] mp 138-139 °C]; $[\alpha]^{25}_D$ -3.9° (1.4, $CHCl_3$) [lit.[7b] $[\alpha]^{19}_D$ -5 ± 1° (1.25, $CHCl_3$)].

Registry No. $CH_3CH(OH)CH_2OH$, 57-55-6; $C_6H_5CH(OH)CH_2OH$, 93-56-1; $CH_3CH(OH)CH_2CH_2OH$, 107-88-0; 1-$C_3H_7CH(OH)CH(C_2H_5)CH_2OH$, 94-96-2; $CH_3CH(OH)CH_2OCOC_6H_5$, 37086-84-3; $CH_3CH(OCOC_6H_5)CH_2OH$, 51591-52-7; $CH_3CH(OCOC_6H_5)CH_2OCOC_6H_5$, 19224-26-1; $C_6H_5CH(OH)CH_2OCOC_6H_5$, 10335-95-2; $C_6H_5CH(OCOC_6H_5)CH_2OH$, 53574-78-0; $C_6H_5CH(OCOC_6H_5)CH_2OCOC_6H_5$, 7717-61-5; $CH_3CH(OH)CH_2CH_2OCOC_6H_5$, 59694-08-5; $CH_3CH(OCOC_6H_5)CH_2CH_2OCOC_6H_5$, 2867-65-4; n-$C_3H_7CH(OH)CH(C_2H_5)CH_2OCOC_6H_5$, 95647-73-7; methyl 4,6-*O*-benzylidene-α-D-glucopyranoside, 3162-96-7; methyl 4,6-*O*-benzylidene-α-D-altropyranoside, 5328-47-2; methyl 4,6-*O*-benzylidene-β-D-glucopyranoside, 14155-23-8; methyl 4,6-*O*-benzylidene-2-*O*-benzoyl-α-D-glucopyranoside, 28642-64-0; methyl 4,6-*O*-benzylidene-3-*O*-benzoyl-α-D-glucopyranoside, 33535-04-5; methyl 4,6-*O*-benzylidene-2,3-*O*-dibenzoyl-α-D-glucopyranoside, 6748-91-0; methyl 4,6-*O*-benzylidene-2-*O*-benzoyl-α-D-altropyranoside, 35823-97-3; methyl 4,6-*O*-benzylidene-2-*O*-benzoyl-β-D-glucopyranoside, 38992-99-3; methyl 4,6-*O*-benzylidene-3-*O*-benzoyl-β-D-glucopyranoside, 38993-00-9; 1-(benzoyloxy)benzotriazole, 54769-36-7; 1-hydroxybenzotriazole, 2592-95-2; benzoyl chloride, 98-88-4.

Synthesis and Absolute Configuration of (*R*)- and (*S*)-Ethyl 3-(4-Oxocyclohex-2-enyl)propionate

Mark L. Elliott and Frank J. Urban*

Pfizer Central Research, Groton, Connecticut 06340

Jon Bordner

North Carolina State University, Department of Chemistry, Raleigh, North Carolina 27695-8204

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The importance of 4-substituted cyclohex-2-en-1-ones as synthetic starting materials continues to attract attention;[1] however, the preparation of relatively few optically active members of this group have been described.[2] In pursuing a synthesis of the cannabinoid derived analgetic CP-55,940,[3] we sought an efficient preparation of resolved alkyl 3-(4-oxocyclohex-2-enyl)propionate ((*S*)-1).[4] The synthesis of each enantiomer of this compound along with assignment of their absolute configuration is the subject of this note.

Due to the potential for racemization through enolization at the asymmetric center in 1, we sought a route which would allow for initial resolution of that center while in protected form and also which would lend itself to eventual asymmetric synthesis. A strategy related to that of Birch[5] for the preparation of 4,4-disubstituted cyclohex-2-en-1-ones through fragmentation of bicyclo[2.2.2]octenes which were derived in turn from a Diels-Alder reaction fulfilled both our requirements.

Hydrolysis of the commercially available Diels-Alder adduct *endo*/*exo*-methyl 1-methoxybicyclo[2.2.2]oct-5-ene-2-carboxylate provided *rac*-2 as a mixture of isomers.[6]

(1) Kinney, W. A.; Crouse, G. D.; Paquette, L. A. *J. Org. Chem.* **1983**, *48*, 4986. Becker, D.; Kalo, J.; Brodsky, N. C. *J. Org. Chem.* **1978**, *43*, 2562.

(2) Silvestri, M. *J. Org. Chem.* **1983**, *48*, 2419. Soffer, M. D.; Gunay, G. E. *Tetrahedron Lett.* **1965**, 1355. Birch, A. J.; Raverty, W. D.; Stephenson, G. R. *J. Chem. Soc., Chem. Commun.* **1980**, 857.

(3) Melvin, L. S.; Johnson, M. R.; Milne, G. M. 186th National Meeting of the American Chemical Society, Washington, D.C., August 28-Sept 2, 1983; Abst. MEDI 2.

(4) Throughout this paper, racemic compounds will be designated by the preface *rac* and drawn with a C-4*S* configuration for both cyclohexenones and bicyclooctenes. The resolved compounds are prefaced as *S* and *R*, which again refers to the absolute configuration C-4. Only the C-4*S* absolute configuration is shown in the text.

(5) Birch, A. J.; Hill, J. S. *J. Chem. Soc. C* **1967**, 125.

(6) Alfaro, I.; Ashton, W.; McManus, L. D.; Newstead, R. C.; Rabone, K. L.; Rogers, N. A. J.; Kernick, W. *Tetrahedron* **1970**, *26*, 201.

0022-3263/85/1950-1752$01.50/0

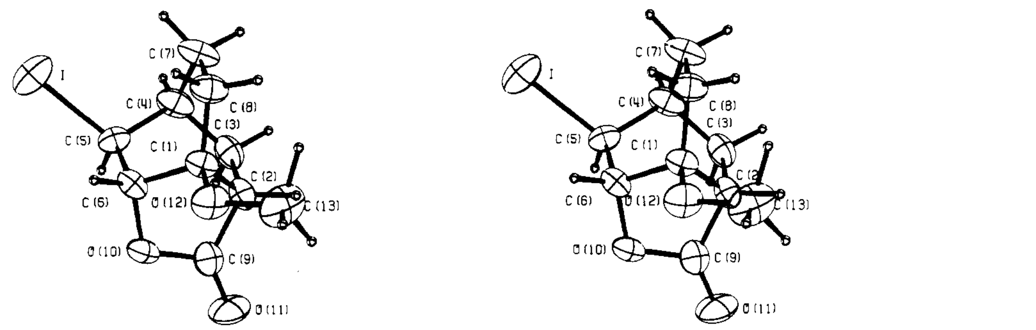
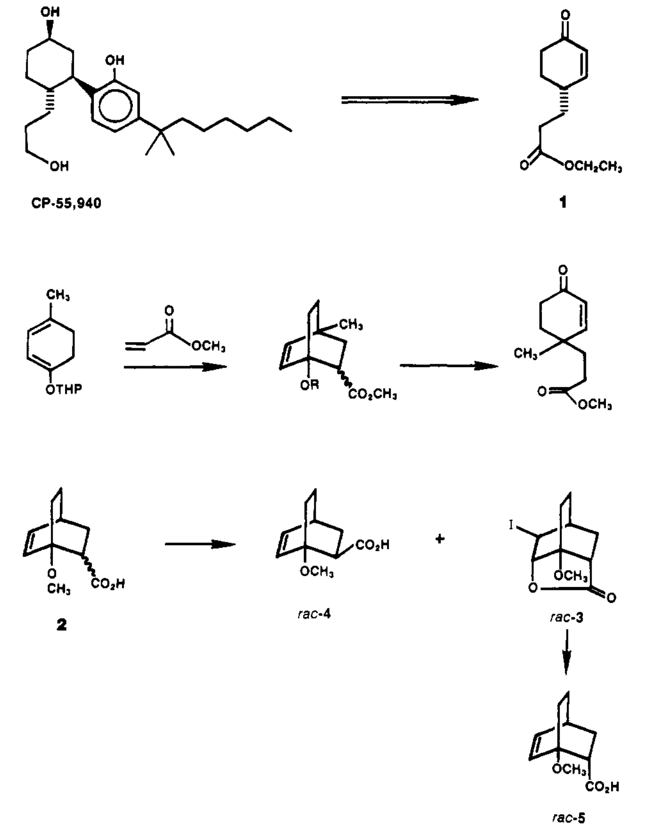
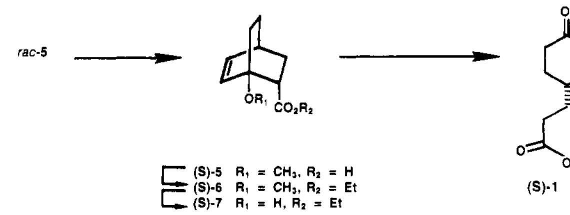


Figure 1. Stereoscopic view of the molecule.

Scheme I



Scheme II



Separation of the endo/exo isomers prior to resolution of each pair was crucial. The isomers were subjected to classical iodo lactonization,[7] giving lactone *rac*-**3** and the pure minor exo acid isomer *rac*-**4**. Reduction of *rac*-**3** with zinc dust in ethanol[7] gave pure endo acid *rac*-**5** in excellent yield (Scheme I).

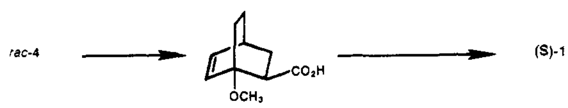
Conversion of *rac*-**5** to (*S*)-**1** is shown in Scheme II. Resolution of the endo acid *rac*-**5** was achieved by crystallization of its salt with *d*-ephedrine from ethyl acetate. Two recrystallizations gave constant rotating diastereomeric salt (−)-(*S*)-**5**·*d*-ephedrine in 33% yield. When *l*-ephedrine was used, (+)-(*R*)-**5**·*l*-ephedrine was isolated in 31% yield. The optical purity of the resolved endo acids was confirmed by their reduction to 1-methoxybicyclo[2.2.2]oct-5-ene-2-*endo*-methanol and derivatization with (−)-Mosher's acid.[8] Both diastereomeric endo esters were distinguished clearly by their 250-MHz NMR spectra without use of shift reagents. Both (*S*)-**5** and (*R*)-**5** acids were found to be ≥98% optically pure. To determine the absolute configuration of the resolved acids, (*S*)-**5** was converted to the chiral iodo lactone (*S*)-**3**. This was submitted to an X-ray crystallographic study, providing the absolute stereochemistry shown in Figure 1.

The enantiomeric acids (*S*)-**5** and (*R*)-**5** were esterified in refluxing ethanol with catalytic *p*-toluenesulfonic acid, giving (*S*)-**6** and (*R*)-**6**, respectively. The ethyl esters were chosen because of their greater stability to the conditions required for the deprotection of the methyl ether. Cleavage of the methyl ether was best achieved with 1 equiv of BBr_3 in CH_2Cl_2 at approximately −20 °C for 1 h. Other conditions examined for this deprotection included various silyl iodide reagents,[9] which gave some desired product as part of a complex mixture. Fragmentation of the bicyclic ring followed conditions used by Schlessinger.[10] Treatment of the bicyclic alcohols with catalytic potassium *tert*-butoxide (5 mol %) in *tert*-butyl alcohol at room temperature effected smooth conversion of (*S*)-**7** and (*R*)-**7** to cyclohexenones (*S*)-**1** and (*R*)-**1**, respectively, within 1 h. Due to the potential for racemization of the asymmetric center in **1**, we sought mild workup conditions. Dilution of the reaction mixture with ethyl acetate followed by washing with neutral aqueous buffer gave **1** with a consistent rotation. Partial racemization of **1** could be caused by treatment of the *tert*-butyl alcohol reaction with 2.4 M HCl prior to extraction of **1** and was accompanied by formation of a small amount of the deconjugated ethyl 3-(4-oxocyclohex-1-enyl)propionate. While we have not proven conclusively the optical purities of **1**, the reproducible optical rotations obtained and lack of detectable 3-cyclohexenone (TLC) suggested that little racemization has occurred. Furthermore, (*S*)-**1** has been converted to a resolved intermediate in the synthesis of CP-55,940 with high optical purity. On the basis of the X-ray structure of (*S*)-**3**, the proposed absolute stereochemistry for CP-55,940[3] has been confirmed.

Returning to the minor exo acid isomer *rac*-**4**, we have found *l*- and *d*-ephedrine resolved this acid, giving (−)-(*S*)-**4**·*l*-ephedrine and (+)-(*R*)-**4**·*d*-ephedrine, respectively. The resolution of (*S*)-**4** with *l*-ephedrine was taken to optical purity by Mosher's ester analysis. A small sample of the (*S*)-**4** acid was converted through the sequence de-

(7) Baldwin, J. E.; Foglesong, W. D. *J. Am. Chem. Soc.* **1968**, *90*, 4303.
(8) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
(9) Schmidt, A. H. *Aldrichimica Acta* **1981**, *14*, 31.
(10) Roberts, M. R.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1981**, *103*, 724.

Scheme III



(S)-4

scribed above to give (*S*)-1, confirming the absolute stereochemistry for the exo acids. The fact that *l*-ephedrine gave the 2*R* isomer from both endo or exo bicyclic acids but these have the opposite absolute configuration at C-4 proved the importance of complete separation of *rac*-4 from *rac*-5.

In summary, 1-methoxybicyclo[2.2.2]oct-5-ene-2-carboxylic acid (*rac*-5) has been converted to optically active (*S*)-1 and (*R*)-1 in good overall yields, 23% and 20.5%, respectively. This route provides a number of highly functionalized bicyclooctenes of assigned absolute configuration which should prove useful in the syntheses of other chiral molecules.

Experimental Section

Methyl 1-methoxybicyclo[2.2.2]oct-5-ene-2-carboxylate and (−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid were purchased from Aldrich Chemical Company. *d*- and *l*-Ephedrine were purchased from Knoll A. G. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and were uncorrected. NMR spectra were obtained on either a Varian T-60 (60 MHz) or Bruker WM 250 (250 MHz) spectrometer in $CDCl_3$, with Me_4Si as internal standard. Infrared spectra were recorded on a Perkin-Elmer 283B spectrophotometer. Mass spectra were determined with a Finnigan 4510 mass spectrometer. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Elemental analyses were performed by the Analytical Department, Pfizer Central Research.

1-Methoxybicyclo[2.2.2]oct-5-ene-2-*exo*-carboxylic Acid (*rac*-4), 1-Methoxy-5-iodo-9-keto-10-oxatricyclo[2.2.2.2^{2,6}]-decane (*rac*-3), and 1-Methoxybicyclo[2.2.2]oct-5-ene-2-*endo*-carboxylic Acid (*rac*-5). The endo/exo mixture of bicyclooctene acids 2 (240 g, 1.32 mol) from base hydrolysis of the commerical methyl ester was dissolved in 0.6 M $NaHCO_3$ (5 L) and 1 N NaOH (263 mL). The solution was treated in the dark with iodine (368 g, 1.45 mol) and potassium iodide (480 g, 2.9 mol) in water (1.5 L) over 20 min. After 22 h, the reaction mixture was extracted twice with CH_2Cl_2 (1.5 L). The combined organic layers were washed with 20% sodium bisulfite (2 × 2 L), 20% $NaHCO_3$ (2 L), and water (2 L). This was stirred with Darco G60 and $MgSO_4$. Filtration and evaporation in vacuo gave the crude iodo lactone *rac*-3 as an orange solid: 265 g, 65% yield; mp 125–126 °C; IR (KBr) 1781 (s) cm^{-1}; mass spectrum, *m/e* 308 (M^+), 181 (M^+ − I, base). The aqueous reaction mixture was acidified to pH 1.6 with concentrated HCl and extracted with CH_2Cl_2 (2 × 1.5 L). The extract was washed with 20% sodium bisulfite (2 × 2 L) and water (2 × 2 L), dried over $MgSO_4$, and evaporated to give *rac*-4 as an off-white solid: 52 g, 21.7% yield; mp 99–103 °C; IR (KBr) 1705 (s) cm^{-1}; NMR (60 MHz) δ 6.38 (s, 1), 6.3 (d, 1 $J_{4,5}$ = 3 Hz), 3.45 (s, 3), 2.9–2.35 (m, 2), 2.1–1.2 (m, 6).

The iodo lactone *rac*-3 (266 g, 0.86 mol) suspended in ethanol (2.5 L) with zinc dust (84.7 g, 1.29 mol) was refluxed for 3 h, cooled, and filtered. The ethanol was evaporated and the product was extracted into 25% NaOH. The basic solution was extracted with CH_2Cl_2 (1 L) and acidified to pH 1.5 with concentrated HCl. The product was extracted into methylene chloride, washed with brine, and dried over $MgSO_4$. Evaporation gave *rac*-5 as a white solid: 148 g, 94% yield; mp 80–82 °C; IR (KBr) 1710 cm^{-1}; NMR (60 MHz) δ 6.2 (d, 1, $J_{4,5}$ = 3 Hz), 6.15 (s, 1), 3.4 (s, 3), 2.8 (t, 1, $J_{2,3}$ = 7 Hz), 2.55 (m, 1), 2.0–1.5 (m, 6).

(2*S*,4*S*)-(−)-1-Methoxybicyclo[2.2.2]oct-5-ene-2-*endo*-carboxylic Acid ((*S*)-5). A refluxing solution of racemic endo acid *rac*-5 (177.9 g, 0.976 mol) and *d*-ephedrine (161.3 g, 0.976 mol) in ethyl acetate (1.5 L) was slowly cooled, giving a crystalline salt. This was repeated twice more with 10 mL of EtOAc/g of salt to yield the *d*-ephedrine·(−)-(*S*)-5 acid salt: 110 g, 32.7% yield; mp 131–135.5 °C; $[\alpha]_D$ +13.15° (*c* 1.11, MeOH). Anal. Calcd for $C_{20}H_{29}NO_4$: C, 69.14;, H, 8.41; N, 4.03. Found: C, 69.25; H, 8.48; N, 4.09.

The above salt (40.5 g, 0.116 mol) was partitioned between CH_2Cl_2 (400 mL) and 2 N HCl (300 mL), and the pure (−) endo carboxylic acid (*S*)-5 was isolated by evaporation of the CH_2Cl_2 as a white solid: 20.4 g, 96% yield; mp 67–69 °C; $[\alpha]_D$ −26.3° (*c* 1.11, CH_2Cl_2); NMR identical with racemic. Anal. Calcd for $C_{10}H_{14}O_3$: C, 66.00; H, 7.75. Found: C, 65.71; H, 7.77.

(2*R*,4*R*)-(+)-1-Methoxybicyclo[2.2.2]oct-5-ene-2-*endo*-carboxylic Acid ((*R*)-5). The filtrates from the above resolution were concentrated and treated with 2 N HCl to give (±)-endo carboxylic acid; 108 g, 0.59 mol, 60.5% recovery. This was crystallized with *l*-ephedrine (97.6 g, 0.59 mol) from hot ethyl acetate (1.5 L), as above. One recrystallization gave the desired salt: 95.7 g, 31% yield; mp 131–133 °C; $[\alpha]_D$ −12.06° (*c* 1.095, MeOH). Anal. Calcd for $C_{20}H_{29}NO_4$: C, 69.14; H, 8.41; N, 4.03. Found: C, 68.88; H, 8.19; N, 4.07.

The (+) endo carboxylic acid (*R*)-5 (7.5 g) was recovered as above from salt (15 g): 96% yield; mp 66–68.5 °C; $[\alpha]_D$ +26.13° (*c* 1.037, CH_2Cl_2). Anal. Calcd for $C_{10}H_{14}O_3$: C, 66.00; H, 7.75. Found: C, 66.38; H, 7.81.

(−)-α-Methoxy-α-(trifluoromethyl)phenylacetates of *endo*- and *exo*-1-Methoxybicyclo[2.2.2]oct-5-ene-2-methanol. The bicyclic acids were reduced with LAH in THF and acylated with (−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride in CCl_4 with 4-(dimethylamino)pyridine. These were analyzed by 250-MHz NMR. The diagnostic absorptions are reported.

From *rac*-5, endo acid: oil; NMR (250 MHz) δ 6.25 (dd) and 6.20 (dd) [1 H], 6.1 (d, 1), 4.60 (dd), and 4.55 (dd) [1 H], 3.75 (t) and 3.77 (t) [1 H], 3.53 (s, 3), 3.32 (s, 3), 2.47 (m, 1), 2.39 (m, 1).

From (*S*)-5, endo acid: oil; NMR (250 MHz) δ 6.25 (dd, 1), 6.1 (d, 1), 4.56 (dd, 1), 3.75 (t, 1), 3.53 (s, 3), 3.32 (s, 3), 2.47 (m, 1), 2.39 (m, 1).

From (*R*)-5, endo acid: oil; NMR (250 MHz) δ 6.2 (dd, 1), 6.1 (d, 1), 4.6 (dd, 1), 3.77 (t, 1), 3.53 (s, 3), 3.3 (s, 3), 2.45 (m, 1), 2.38 (m, 1).

From (*S*)-4, exo acid: oil; NMR (250 MHz) δ 6.4 (d, 1), 6.22 (dd, 1), 4.39 (dd, 1), 4.22 (t, 1), 3.55 (s, 3), 3.35 (s, 3), 2.45 (m, 1), 2.13 (m, 1).

(1*S*,2*S*,4*S*,5*S*,6*S*)-1-Methoxy-5-iodo-9-keto-10-oxatricyclo[2.2.2.2^{2,6}]decane ((*S*)-3). (*S*)-5 (−) endo acid (3 g, 0.0165 mol) was converted to iodo lactone (*S*)-3 as described above. (*S*)-3 was isolated as a colorless crystalline solid from isopropyl ether in 70% yield: mp 112–113 °C; $[\alpha]_D$ +85.06° (*c* 0.997, $CHCl_3$). Anal. Calcd for $C_{10}H_{13}IO_3$: C, 38.96; H, 4.22. Found: C, 38.59; H, 4.19.

Single-Crystal X-ray Analysis of (*S*)-3. A representative crystal was surveyed, and a 1-Å data set (maximum sin θ/λ = 0.5) was collected on a Syntex P1 diffractometer. The diffractometer was equipped with a graphite monochromator and molybdenum radiation (λ = 0.71069 Å). Atomic scattering factors were taken from the International Tables for X-ray Crystallography[11], except for hydrogen, which was taken from Stewart, Davidson, and Simpson,[12] and for iodine, which was taken from Cromer and Mann.[13] All crystallographic calculations were vacilitated by the CRYM system.[14] All diffractometer data were collected at room temperature. Pertinent crystal, data collection, and refinement parameters are summarized in Table I.

A trial structure was obtained by conventional Patterson and Fourier techniques. This trial structure refined routinely. Hydrogen positions were calculated wherever possible. The methyl hydrogens were located by difference Fourier Techniques. The hydrogen parameters were added to the structure–factor calculations but were not refined. The final cycles of full-matrix least-squares refinement contained the scale factor, secondary extinction coefficient, coordinates, and anisotropic temperature factors in a single matrix. The shifts calculated in the final cycle

(11) "International Tables for X-ray Crystallography"; Birmingham: Kynoch Press, 1962; Volume III, p 204, 214.

(12) Stewart, R. F.; Davidson, E. R.; Simpson, W. T. *J. Chem. Phys.* **1965**, *42*, 3175.

(13) Cromer, D.; Mann, J. B. Report LA-3816, Los Alamos Scientific Laboratory, Los Alamos, NM, 1967.

(14) Duchamp, D. J. American Crystallographic Association Meeting, 1964, Bozeman, MT, Paper B-14, p 29.

Table I. Single-Crystal X-ray Crystallographic Analysis

A. Crystal Parameters	
formula	$C_{10}H_{13}IO_3$ (308.11)
crystallization medium	isopropyl ether
crystal size, mm	0.27×0.28×0.38
cell dimensions	
a, Å	6.748 (1)
b, Å	11.258 (2)
c, Å	14.333 (2)
α, deg	90.0
β, deg	90.0
γ, deg	90.0
V, Å^3	1088.8 (3)
space group	$P2_12_12_1$
molecules/unit cell	4
density obsd, g/cm^3	1.87
density calcd, g/cm^3	1.879
linear absorption coefficient, cm^{-1}	29.6
B. Refinement Parameters	
number of reflections	711
non-zero reflections ($I > 1.0\sigma$)	705
R index=$\Sigma\|\|F_o\| - \|F_c\|\|/\Sigma\|F_o\|$	0.040
GOF = $[\Sigma w(F_o^2 - F_c^2)^2/(m - S)]^{1/2}$	3.77
scale factor	0.814 (7)
secondary extinction coefficient	16.1 (6) × 10^{-6}

were all zero. The final R index was 0.040. A final difference Fourier revealed no missing or misplaced electron density. The absolute configuration of the molecule was determined by the method of Ibers and Hamilton.[15] The refined structure was plotted by using the ORTEP computer program of Johnson[16] (Figure 1). This configuration was established as correct at the 0.5% level of significance (i.e., with 99.5% confidence).[17]

Tables of coordinates, anisotropic temperature factors, distances, and angles are available as supplementary material from J. B.

(2*S*,4*S*)-Ethyl 1-Methoxybicyclo[2.2.2]oct-5-ene-2-*endo*-carboxylate ((*S*)-6) and (2*R*,4*R*)-Ethyl 1-Methoxybicyclo-[2.2.2]oct-5-ene-2-*endo*-carboxylate ((*R*)-6). The resolved acids (*S*)-**5** and (*R*)-**5** were esterified in refluxing ethanol with catalytic *p*-toluenesulfonic acid. (*S*)-**5**, (–) endo acid (15 g), gave ethyl ester (*S*)-**6** (14.5 g) as an oil in 86% yield: bp 100–103 °C (0.4 mm); $[\alpha]_D$ –5.08° (*c* 1.103, $CHCl_3$); NMR (250 MHz) δ 6.25 (m, 2), 4.12 (m, 2), 3.38 (s, 3), 2.89 (q, 1), 2.55 (bs, 1), 1.88 (m, 1), 1.24 (t, 3). Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.57; H, 8.57. Found: C, 68.66; H, 8.53.

(*R*)-**5**, (+) endo acid (22.8 g), gave ethyl ester (*R*)-**6** (22.9 g) as an oil in 87% yield: bp 98–102 °C (0.3 mm); $[\alpha_D]$ +6.18° (*c* 1.1, $CHCl_3$); IR (CH_2Cl_2) 1730 cm^{-1}; mass spectrum, *m/e* 196 (M^+).

(2*S*,4*S*)-Ethyl 1-Hydroxybicyclo[2.2.2]oct-5-ene-2-*endo*-carboxylate ((*S*)-7) and (2*R*,4*R*)-Ethyl 1-Hydroxybicyclo-[2.2.2]oct-5-ene-2-*endo*-carboxylate ((*R*)-7). The ester (*R*)-**6** (21 g, 0.1 mol) in CH_2Cl_2 (250 mL) at –25 °C was treated dropwise with 1 M BBr_3 (110 mL). After 1 hour of stirring, the reaction was quenched into cold saturated aqueous $NaHCO_3$. The desired alcohol (*R*)-**7** was isolated from CH_2Cl_2 and distilled in vacuo: 17.7 g, 90%: bp 88–90 °C (0.25 mm); $[\alpha]_D$ –37.5° (*c* 1.12, $CHCl_3$); IR (CH_2Cl_2) 3547 (OH), 1710 cm^{-1}; NMR (250 MHz) δ 6.18 (d, 2), 4.12 (q over bs, 3), 2.69 (q, 1), 2.55 (bs, 1), 1.96 (m, 1), 1.24 (t, 3); mass spectrum, *m/e* 196 (M^+). Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.30; H, 8.16. Found: C, 67.04; H, 8.09.

The (*S*)-**6** ester (4 g, 0.019 mol) was treated with 1 M BBr_3 (20 mL), giving the tertiary alcohol (*S*)-**7**, 3.5 g, 95% yield: bp 85–87 °C (0.2 mm); $[\alpha]_D$ +38.24° (*c* 1.13, $CHCl_3$); IR (CH_2Cl_2) 3546 (OH), 1729/1709 cm^{-1}; mass spectrum, *m/e* 196 (M^+).

(*R*)-Ethyl 3-(4-Oxocyclohex-2-enyl)propionate ((*R*)-1) and (*S*)-Ethyl 3-(4-Oxocyclohex-2-enyl)propionate ((*S*)-1). (–)-Ethyl-1-hydroxybicyclo[2.2.2]oct-5-ene-2-*endo*-carboxylate ((*R*)-**7**) (16.5 g, 0.079 mol) in *tert*-butyl alcohol (165 mL) was treated with *t*-BuOK (0.44g, 0.0039 mol) at room temperature for 45 min. The reaction was diluted with EtOAc and washed with pH 6.0 phosphate buffer (2 × 100 mL), water, and brine. The desired product (*R*)-**1** was recovered from the organic layer and distilled in vacuo, giving a clear liquid; 14.5 g, 88% yield: bp 100–105 °C (0.25 mm); $[\alpha]_D$ –81.9° (*c* 1.15, $CHCl_3$); IR (CH_2Cl_2) 1731 (s), 1678 (s) cm^{-1}; mass spectrum, *m/e* 197 (M^+ + 1), 196 (M^+).

(*S*)-**7** (3 g, 0.015 mol) gave the cyclohexenone (*S*)-**1** (2.6 g, 90%) with *t*-BuOK (85 mg, 0.0008 mol) in *tert*-butyl alcohol (25 mL): bp 103–108 °C (0.4 mm); $[\alpha]_D$ +85.5° (*c* 1.115, $CHCl_3$); IR (CH_2Cl_2) 1730, 1680 cm^{-1}; NMR (250 MHz) δ 6.83 (dq, 1), 6.0 (dd, 1), 4.15 (q, 2), 1.26 (t, 3); mass spectrum, *m/e* 197 (M^+ + 1), 196 (M^+). Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.30; H, 8.16. Found: C, 67.36; H, 8.06.

(2*R*,4*S*)-(–)-1-Methoxybicyclo[2.2.2]oct-5-ene-2-*exo*-carboxylic Acid ((*S*)-4). Racemic exo acid *rac*-**4** (55 g, 0.3 mol) and *l*-ephedrine (49.9 g, 0.3 mol) gave a crystalline salt from refluxing ethyl acetate (350 mL) upon cooling to room temperature. This was recrystallized once from ethyl acetate, giving the (*S*)-**4** salt: 29.3 g, 28%; mp 135–136 °C; $[\alpha]_D$ –40.7° (*c* 1.156, MeOH). Anal. Calcd for $C_{20}H_{29}NO_4$: C, 69.14; H, 8.41; N, 4.03. Found: C, 69.15; H, 8.39; N, 4.32

This salt (5 g, 0.014 mol) was converted to the free acid (*S*)-**4** (2.2 g, 88%) as described: mp 78–81 °C; $[\alpha]_D$ –109.1° (*c* 1.245, CH_2Cl_2); NMR identical with racemate. Anal. Calcd for $C_{10}H_{14}O_3$: C, 66.00; H, 7.75. Found: C, 65.66; H, 7.66.

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Registry No. (*S*)-1, 94050-15-4; (*R*)-1, 95782-19-7; (±)-3, 95782-20-0; (*S*)-3, 95783-35-0; (±)-4, 95782-21-1; (*S*)-4 ((–)-α-methoxy-α-(trifluoromethyl)phenylacetate), 95694-09-0; (*S*)-4·*l*-ephedrine, 94246-61-4; (*S*)-4, 94198-69-3; (±)-5, 95782-22-2; (*S*)-5, 94198-70-6; (*R*)-5, 95782-23-3; (*S*)-5·*d*-ephedrine, 94246-60-3; (*R*)-5·*l*-ephedrine, 95839-07-9; (*S*)-5 ((–)-α-methoxy-α-(trifluoromethyl)phenylacetate), 95782-24-4; (*R*)-5 ((–)-α-methoxy-α-(trifluoromethyl)phenylacetate, 95782-25-5; (*S*)-6, 94132-10-2; (*R*)-6, 95782-26-6; (*S*)-7, 94132-11-3; (*R*)-7, 95782-27-7; (–)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride, 39637-99-5.

Anhydrotetracycline is a Major Product of Tetracycline Photolysis

Tayyaba Hasan,[†] Mark Allen, and Barry S. Cooperman*

Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104

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Tetracycline (TC) is a low molecular weight, broad-spectrum antibiotic that inhibits protein synthesis by preventing the binding of aminoacyl-tRNA to the A site of ribosomes.[1] Its photochemistry is of direct importance to prior photoaffinity labeling studies of this group aimed at identifying the site of TC binding to the Escherichia coli ribosome.[2] We found that even in the presence of β-mercaptoethanol, the addition of which affords the most site-specific photoincorporation of TC, a TC photoproduct was formed that labels the ribosome in a nonspecific manner. This report describes the isolation and identification of 5a,6-anhydrotetracycline (AHTC) as the major product formed on photolysis of TC under the conditions of our photoaffinity labeling experiment. The formation of AHTC accounts not only for our prior results but also

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[†] Current address: Photomedicine Research Unit, Department of Dermatology, Massachusetts General Hospital, Boston, MA 02114.

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