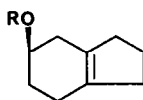


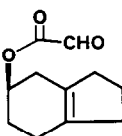
The bicyclic alcohol 6¹⁰ was acylated with excess bromoacetyl bromide in acetone containing sodium carbonate/sodium bicarbonate, affording bromoacetate 7, bp 110-114 °C (0.4 mm), in 87% yield. Following the procedure of Kornblum and Frazier,¹¹ reaction of 7 with silver nitrate in dry acetonitrile gave nitrate ester 8 (99% crude yield), which on exposure to sodium acetate trihydrate in DMSO was converted to glyoxylate ester 9, bp (Kugelrohr) 85 °C (0.3 mm) [¹H NMR (CDCl₃, 80 MHz) δ 9.40 (1H, s), 5.25 (1H, m), IR (neat) 1745 (C=O, ester), 1725 cm⁻¹ (C=O, aldehyde), Calcd for C₁₁H₁₄O₃ 194.09429, Found 194.09402, semicarbazone mp 216-217 °C (dec)], in 74% overall yield from 7.¹²



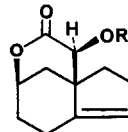
6 R = H

7 R = COCH₂Br

8 R = COCH₂ONO₂



9



10 R = H

11 R = COCH₂Br

Treatment of 9 with stannic chloride (1.06 eq) in freshly distilled, dry nitromethane at 25 °C afforded a single compound,¹³ mp 112.5-113.5 °C (benzene-hexane), in 85% yield after chromatography on silica gel.¹⁴ The spectral characteristics of this compound were consistent with those expected for tricyclic hydroxylactone 10 [MS m/e = 194 (M⁺), IR (KBr) 3410 (OH), 3025 (C=C-H), 1720 cm⁻¹ (C=O), ¹H NMR (CDCl₃, 270 MHz) δ 5.58 (C 4-H,¹⁵ br dd, J_{vic} = 4.3, 2.3), 4.82 (C 8-H, m), 4.05 (C 11-H, s), 2.31 (C 12-H_{eq}, ddd, J_{gem} = 13.5, J_{vic} = 4.3, J_w = 2.0), 1.78 (C 12-H_{ax}, dd, J_{gem} = 13.5, J_{vic} = 1.6), ¹³C NMR (CDCl₃) δ 175.2 (s), 139.2 (C=C-H, s), 125.7 (C=C-H, d), 76.6 (d), 73.7 (d), 50.2 (s), 38.8, 33.7, 31.4, 29.7, and 20.8 (t), Calcd for C₁₁H₁₄O₃ C 68.02 H 7.27, Found C 68.18 H 7.29], but did not unequivocally rule out other possible structures.¹⁶

The structure of the ene-adduct was unambiguously established as 10 by x-ray crystallographic analysis of the bromoacetate derivative (11), which was prepared in 99% yield by acylation of 10 with bromoacetyl bromide and pyridine in dry methylene chloride (-45 to -20 °C). A single crystal of 11, mp 118-119 °C (benzene-hexane), was used for crystallographic data collection.¹⁷ The bromine atom was located from the Patterson function, and the rest of the structure was determined by successive cycles of difference electron density maps and block diagonal least-squares refinements.¹⁸ In the final stages of the refinement, all positional parameters were refined using anisotropic thermal parameters for non-hydrogen atoms and isotropic thermal parameters for hydrogen atoms. The refinement of the structure converged to values of 0.064 and 0.050 for R and R_w, respectively.¹⁹ Stereo drawings of the structure (Figure II)¹⁵ and the unit cell packing

(Figure III) of 11 are shown below

Several points concerning the transformation of glyoxylate ester 9 into hydroxylactone 10 are worth mentioning. As before, only the desired hydroxyl stereochemistry was produced. In this case, however, the bridgehead quaternary carbon center of the tricyclic ring system of anisatin was also generated.²⁰ Furthermore, the reaction was completely regioselective, with the carbon-carbon double bond being transposed exclusively to the appropriate position for introduction of the vicinal diol.

Finally, *cis*-hydroxylation of 10 with osmium tetroxide in ether followed by sodium bisulfite in aqueous pyridine afforded trihydroxylactone 2, mp 145-146 °C (acetone-heptane) [¹H NMR (CDCl₃/D₂O, 270 MHz) δ 4.71 (C 8-H, ¹⁵m), 4.57 (C 4-H, dd, J_{VIC} = 9.6, 5.6), 3.99 (C 11-H, s), 2.41 (C 12-H_{ax}, dd, J_{gem} = 13.6, J_{VIC} = 2.1), 2.16 (C 7-H_{ax}, dddd, J_{gem} = 14.4, J_{VIC} = 12.6, 5.0, 2.4), ¹³C NMR (CDCl₃) δ 175.9 (s), 79.1 (s), 77.0, 76.3, and 75.8 (d), 48.2 (s), 32.8, 32.7, 30.6, 27.9, and 25.5 (t), IR (KBr) 3380 and 3230 (OH), 1720 cm⁻¹ (C=O), Calcd for C₁₁H₁₆O₅ C 57.88 H 7.07 (228.09976), Found C 57.68 H 7.12 (228.09959)], in 78% yield after PTLC on silica gel.

In summary, this work demonstrates that the Lewis acid catalyzed intramolecular ene reaction of glyoxylate esters can be both a highly stereo- and regioselective route to unsaturated α-hydroxy δ-lactones. Studies on the application of this methodology to the total synthesis of anisatin will be reported in due course.

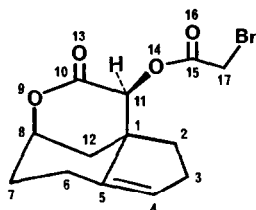


Figure I Numbering scheme for 11

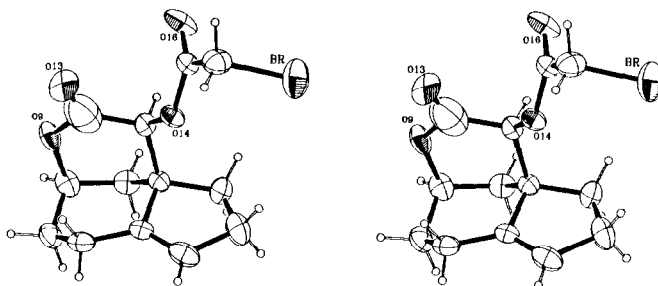


Figure II Stereoscopic view of 11

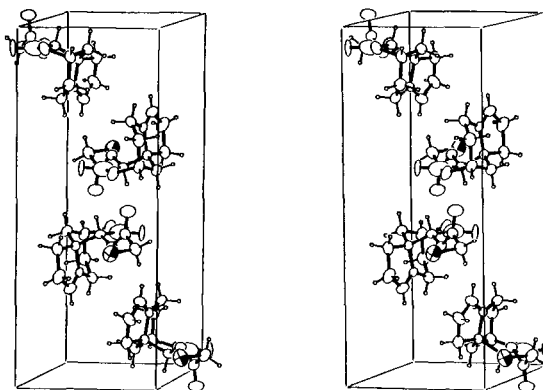


Figure III Stereoscopic view of the unit cell packing of 11

References and Notes

- 1 Taken in part from the Ph D Dissertation(s), Harvard University, of (a) JBD, 1975, and (b) DLL, 1982
- 2 Address correspondence to this author at Pfizer Central Research, Pfizer, Inc, Groton, Connecticut 06340
- 3 Present address Merck Sharp and Dohme Research Laboratories, Merck and Co, Inc, Rahway, New Jersey 07065
- 4 K Yamada, S Takada, S Nakamura, and Y Hirata, *Tetrahedron*, **24**, 199 (1968)
- 5 B B Snider and J W van Straten, *J Org Chem*, **44**, 3567 (1979), and references cited therein
- 6 Since the outset of this study, one example of a non-stereoselective preparation of an α -hydroxy γ -lactone *via* a thermal intramolecular glyoxylate ene reaction has been reported ⁵
- 7 For reviews of the inter- and intramolecular ene reaction, see H M R Hoffmann, *Angew Chem Int Ed Engl*, **8**, 556 (1969), W Oppolzer and V Snieckus, *ibid*, **17**, 476 (1978), and B B Snider, *Acc Chem Res*, **13**, 426 (1980)
- 8 See reference 5 for a study on the stereochemistry of the intermolecular ene reaction of methyl glyoxylate
- 9 For a full account of this initial study, see reference 1a
- 10 J Fried, N A Abraham, and T S Santhanakrishnan, *J Amer Chem Soc*, **89**, 1044 (1967)
- 11 N Kornblum and H W Frazier, *J Amer Chem Soc*, **88**, 865 (1966)
- 12 Alternatively, it was found that treatment of nitrate esters with ethyldiisopropylamine (Hunig's base) in methylene chloride at 0 °C affords high yields of the glyoxylate ester
- 13 No other ene-adducts were detected in the crude product by ¹H NMR, ¹³C NMR, and TLC
- 14 In methylene chloride, other Lewis acids (*eg* boron trifluoride etherate and ferric chloride) were successful in converting 9 into 10 at 25 °C However, stannic chloride was the most effective, working even at -78 °C Thermally, 9 was stable to elevated temperatures up to 265 °C (d⁶-benzene, sealed tube), at which point decomposition occurred
- 15 The numbering system is based on the 9-oxatricyclo[6 3 1 0^{1,5}]dodecane ring system (*ie*, as depicted in Figure I for bromoacetate 11)
- 16 The stereochemistry of the hydroxyl group in 4 and 5 was assigned on the basis of the CH-CH-OH coupling constant (J = 6.5 and 7 Hz, respectively)
- 17 Crystals of 11 were monoclinic, space group P2₁/a, a = 7.499(2) Å, b = 19.215(7) Å, c = 9.212(2) Å, β = 102.86(2)°, V = 1294.1(7) Å³, ρ_c = 1.62 g/cm³, ρ_m = 1.62 ± 0.02 g/cm³, Z = 4, $\mu(\text{MoK}\alpha)$ = 30.89 cm⁻¹ The integrated intensities of 2290 independent reflections (3° ≤ 2 θ ≤ 50°) were measured on a NICOLET R3 automated four circle diffractometer with graphite mono-chromated MoK α radiation (λ = 0.71069 Å) Corrections were made for background, radiation damage, Lorentz and polarization effects, and absorption Only those 1585 reflections (69%) with F_o ≥ 3.0 σ (F_o) were included in further calculations
- 18 G Sheldrick, *Programs for Crystal Structure Determination*, Cambridge, England, 1975
- 19 Complete tables of the fractional coordinates, thermal parameters, bond lengths, and bond angles, all with standard deviations (5 pages), have been deposited with the Cambridge Crystallographic Data Centre A table of the observed and calculated structure factors (10 pages) has been deposited with the British Library, Lending Division
- 20 For a review of methodology for the construction of quaternary carbon centers, see S F Martin, *Tetrahedron*, **36**, 419 (1980)
- 21 Satisfactory spectral data was obtained for all new compounds described

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