Tetrahedron Vol. 37, pp. 383 to 387
Pergamon Press Ltd. 1981 Printed in Great Britain

0040-4020/81/0115-0383 $02.00/0

THE ABSOLUTE CONFIGURATION OF THE DICIPIENE DITERPENES

K. D. CROFT, E. L. GHISALBERTI,* P. R. JEFFERIES and A. D. STUART

Department of Organic Chemistry, University of W.A., Nedlands, Western Australia, 6009

(*Received in U.K. 6 November* 1979)

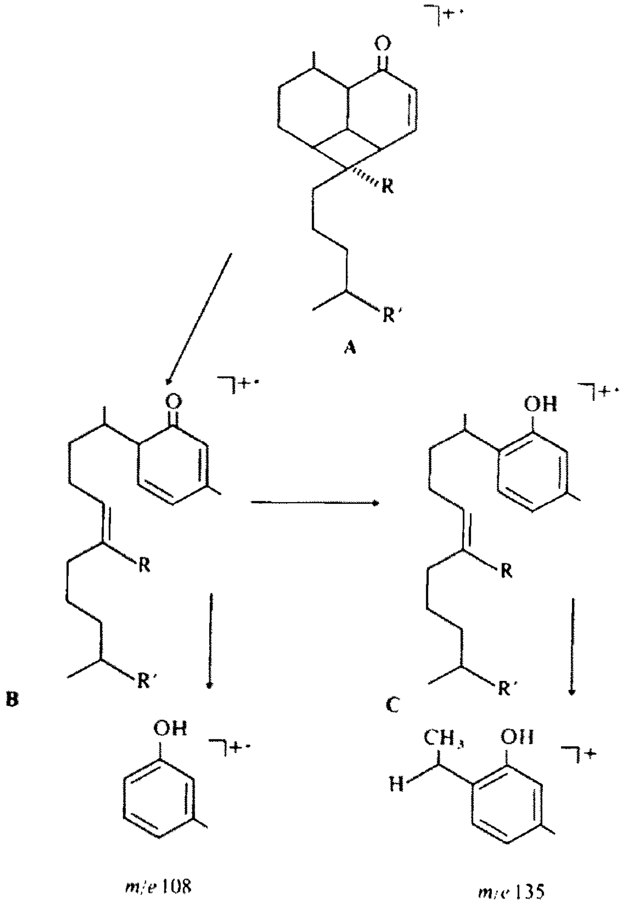
Abstract The absolute configuration of the decipiene diterpenes has been determined by degradation to 4*R*-4-(2-methoxy-4-methylphenyl)-pentanoic acid. Photolysis of 1,18-diacetoxy-13-oxodecipi-14-ene proceeds through a novel photochemical reaction, formally a [2 + 2] cycloreversion, to generate a key intermediate for the degradation.

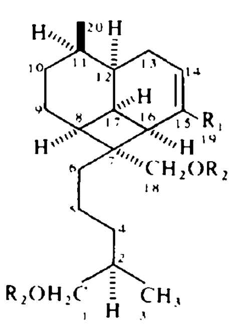
In previous reports we have presented evidence for the structure and relative configuration of some new diterpenes from *Eremophila decipiens*[1,2] and a related species.[3] During this work we observed that the mass spectra of a number of decipiene derivatives containing the cyclohexenone system (**A**) showed base peaks which could be rationalized as arising from the following fragmentations.

It seemed reasonable to expect that a process analogous to **A** → **C** might be induced photochemically resulting in the formation of a phenol (**C**) which constitutes an isoprenologue of the oxygenated α-curcumenes.[4] Apart from the intrinsic interest in achieving this transformation, the compound generated would allow simple degradation of the decipiene skeleton and provide a means of establishing the absolute stereochemistry of this new group of diterpenes.

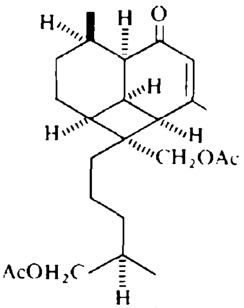
Achievement of both of these objectives is described in this report.

For the photochemical study we chose the enone (**3**) as the substrate. The enone (ν_{max}: 1725 and 1650 cm^{-1}; λ_{max}: 257 nm, ε: 9500) was prepared by CrO_3/pyr_2 oxidation of the diacetate (**2**) which in turn can be

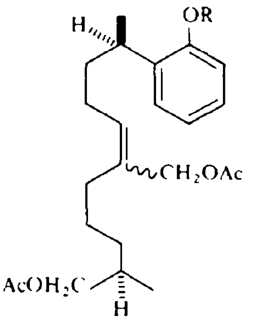




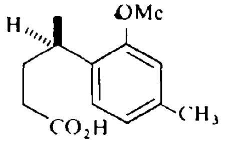
	R_1	R_2
1	CO_2H	H
2	CH_3	Ac



3



4 R = H
5 R = Ac
6 R = Me



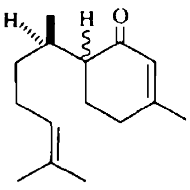
7

obtained[3] from the dihydroxy acid (**1**), the major diterpene constituent of *Eremophila decipiens* var.[3] Irradiation of an ethanolic solution of the enone (**3**) at 254 nm for 20 min gave a product which was shown to contain mainly starting material and the photoisomers (**4**) in a 2:3 ratio. To facilitate separation the reaction mixture was treated with Ac_2O/pyridine and the photoisomers (**4**) were isolated as the acetoxy derivative (**5**). The NMR spectrum of **5** showed resonance signals for an aryl methyl at δ 2.20 and for three aromatic protons (δ 6.67–7.11), whose multiplicity was characteristic of a 1,2,5-trisubstituted benzene, as well as a benzylic proton at δ 2.76. That the photolysis product was a mixture of *E* and *Z* isomers was evident from the signals for the allylic acetoxymethylene protons which showed two resonances at δ 4.37 and δ 4.42 (Integral ratio 3:1) and from the broadness of the vinyl proton signal (δ 5.33) which appeared as two superimposed triplets (J 7 Hz). This strongly suggests that photolysis of the vinylogous cyclobutyl carbonyl system proceeds through a diradical intermediate arising from fission of the C-7 to C-16 bond and is analogous to the first step involved in the photochemical rearrangement of verbenone.[5]

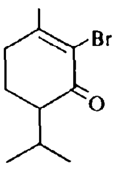
The photoisomers contains only two of the seven chiral centres originally present in the enone (**3**) and oxidative cleavage of the C-7 to C-8 double bond should produce an optically active 4-substituted pentanoic acid, a relatively simple synthetic target. For this purpose, in a repeat photolysis, the photoisomers were isolated as the methyl ethers (**6**). Treatment of **6** with OsO_4 gave a mixture of diastereomeric diols which was oxidized with $NaIO_4$. The resulting product on oxidation with Jones reagent afforded the pentanoic acid (**7**) ($[\alpha]_D = +3.6$) identical with that synthesised from R-(+)-citronellal as described below.

For the synthesis of optically active **7** we used the mixture of diastereomeric enones (**8**) prepared from *R*-citronellal as described[6] previously. We envisaged that aromatization of this mixture followed by methylation and cleavage of the side chain double bond should provide **7**. In practice, attempts to aromatise the enones **8** with DDQ, chloranil, Pd/C or SeO_2 were unsuccessful although piperitone was shown to form thymol on treatment with chloranil over 8 days.

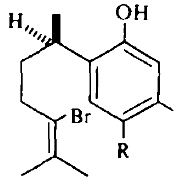
The vinyl bromide (**9**) prepared by dehydrobromination of the dibromide available from the bromination of piperitone has been reported[7] to give a thymol on treatment with base. Investigation of this reaction showed that with longer reaction times both the dibromide and the vinyl bromide disappeared from the reaction mixture from which a phenolic fraction (45%) could be isolated. This was shown to contain



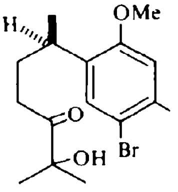
8



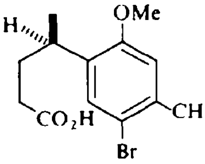
9



10 R = H
11 R = Br



12



13

thymol and 4-bromothymol, the latter probably arising from thymol during the reaction.

The corresponding mixture of phenol and bromophenol (**10** and **11**) could be obtained either by bromination of the enones **8** with two equivalents of Br_2 followed by base treatment or by treatment of **8** with three equivalents of pyridinium bromide perbromide[8] followed by base treatment. The latter method gave increased yield of phenolic material (75% compared to 40%) and a higher ratio of bromophenol (**11**) to phenol **10** (3:2 compared to 2:3). This is an important consideration since it was found that the methyl ether of **10** does not survive treatment with $OsO_4/NaIO_4$. In both cases dehydrobromination of the tertiary Br in the side chain occurred probably as a result of partitioning the phenolic material with Claisen's alkali. The mixture of phenols (**10** and **11**) was methylated and the product treated with $OsO_4/NaIO_4$. The only product that could be isolated from this reaction was the α-ketol (**12**). Neither unchanged phenol (**10**) nor any ether-soluble product derived from **10** could be detected. Treatment of the α-ketol (**12**) with Jones reagent gave the bromo-acid (**13**) which on hydrogenolysis with Pd/C/NaOAc yielded the required 4*R*-4-(2-methoxy-4-methylphenyl) pentanoic acid (**7**) which after purification had $[\alpha]_D$ + 3.0°. The *p*-bromophenacyl ester derivative of **7** could not be crystallized but **7** gave a crystalline *S*-benzyl-iso-thiouronium salt. The spectral and chemical properties of **7** and its derivative were identical with those for the corresponding compounds derived by degradation of the photoisomers (**4**). The specific rotations of the two sets of samples were of the same sign and magnitude.

These results show that the acid (**7**) obtained by degradation of 1,18-dihydroxydecipi-14-en-19-oic acid (**1**) has the *R*-configuration at C-11. Since the relative configuration of **1** is known from X-ray crystallographic analysis,[3] the absolute configuration of **1** is as shown. Furthermore since **1** has been interrelated[2,3] to the decipiene diterpenes from *E. decipiens*, it follows that they have the same absolute configuration.

EXPERIMENTAL

General experimental details have been described[6]

1,18-*Diacetoxy-13-oxodecipi-14-ene* (**3**) A soln of **2** (1.7 g) in anhydrous CH_2Cl_2 (160 ml) under N_2 was treated with a soln of CrO_3/pyr_2 complex, prepared by mixing CrO_3 (1.8 g) with pyridine (2.8 g), in CH_2Cl_2 (30 ml). The mixture was stirred in the dark for 300 hr with further addition of the complex every 24 hr. The organic layer was decanted and the tarry residue washed with ether (2 × 100 ml). The combined organic solutions were washed with 10% NaOH, 10% HCl and brine. Removal of the solvent gave **3** (1.2 g) as a colourless oil $[\alpha]_D - 29$ (*c*, 0.7) (Found: C, 71.40; H, 9.23, M^+ 404.2564. $C_{24}H_{36}O_5$ requires: C, 71.25; H, 9.87%, M^+ 404.2562). NMR ($CDCl_3$, 60 MHz): δ 5.90 (br s, $W_{\frac{1}{2}}$ 5 Hz, 14-H), 4.22 (br s, 18-H_2), 3.90 (AB part of an ABX, 1-H_2), 2.15 and 2.05 (acetoxymethyls), 1.86 (br s, 19-H_3), 1.36 (d, J 6 Hz, 20-H_3), 0.92 (d, J 7 Hz, 3-H_3); $\nu_{max}^{CCl_4}$: 1725, 1650 cm^{-1}; λ_{max}^{EtOH}: 210 (ε, 10000) and 257 nm (ε, 9500). MS: *m/e* 404 (M^+, 5%), 344 (12), 161 (20), 159 (15), 135 (100), 108 (30)

Photolysis of 1,18-diacetoxy-13-oxodecipi-14-ene (**3**)

(a) A soln of **3** (350 mg) in EtOH (50 ml) was flushed with N_2 for 20 min and then irradiated with UV light (254 nm) in an Oliphant photochemical reactor for 20 min. Evaporation of the solvent gave a residue which from TLC was shown to be a mixture of two major components (2:3). To facilitate separation the mixture was treated with Ac_2O/C_5H_5N and the product was separated by preparative tlc to give **3** (90 mg) and **5** (100 mg) as an oil b.p. 180° (bath)/0.2 mm, $[\alpha]_D - 5$° (*c*, 2.0) (Found C, 69.9; H, 8.8 $C_{26}H_{38}O_6$ requires: C, 69.9; H, 8.6%). NMR (90 MHz, CCl_4): δ 0.83 (d, J 7 Hz, 3-H_3), 1.12 (d, J 6.5 Hz, 20-H_3), 1.94 (6 H, acetoxymethyls), 2.20 (s, 19-H_3), 2.28 (acetoxymethyl), 2.76 (m, 11-H), 3.80 (m, 1-H_2), 4.36 (br s, 18-H_2), 5.33 (t, J 7 Hz, 8-H), 6.71 (br s, 14-H), 6.91 (br d, J 8 Hz, 16-H), 7.07 (d, J 8 Hz, 17-H). Extra signals were observed at 0.87 (d, J 7 Hz, 3-H_3), δ 4.42 (s, 18-H_2) and 5.28 (t, J 7 Hz, 8-H). MS: *m/e* 386 (M^+ − 60, 10%), 344 (8), 177 (80), 135 (100); $\nu_{max}^{CCl_4}$: 1750, 1740 cm^{-1}; λ_{max}^{EtOH} 208 (ε, 10500), 268 nm (ε, 800).

(b) A soln of **3** (1.0 g) in EtOH (120 ml) was purged with N_2 and then irradiated with UV light (254 nm) as described in (a) for 2 hr. The solvent was removed under reduced pressure and the residue in acetone (40 ml) was treated with dimethyl sulphate (2.2 g) and anhyd K_2CO_3 (2.0 g) and the mixture refluxed for 18 hr. The product (1.1 g) obtained was adsorbed on a column of silica gel (40 g). Elution with 5–10% ether-light petroleum gave **6** (400 mg) as an oil, $[\alpha]_D - 3$° (*c*, 0.7)

(Found: M^+, 418.2755. $C_{25}H_{38}O_5$ requires: M^+, 418.2719). NMR ($CDCl_3$): δ 0.89 (d, J 6 Hz, 3-H_3), 1.25 (d, J 7 Hz, 20-H_3), 2.01 (6 H, acetoxymethyls), 2.28 (br s, 19-H_3), 3.1 (m, 11-H), 3.72 (s, OMe), 3.85 (d, J 6 Hz, 1-H_2), 4.38 (br s, 18-H_2), 5.2–5.6 (br t, J 7 Hz, 8-H), 6.5–7.1 (ABC system, 14-, 16-, 17-H). Extra signals associated with the 8- and 18-H_2 resonances were observed. ν_{max} 1740 cm^{-1}; MS: *m/e* 418 (M^+, 4%), 376 (1), 359 (1), 358 (2), 149 (100), 135 (15), 119 (12). Continued elution with 50% ether-light petroleum gave **3** (250 mg).

Oxidation of **6**. A soln of **6** (280 mg) in dry pyridine (8 ml) was treated with OsO_4 (172 mg). The soln was stirred for 3 hr, then a soln of sodium metabisulphite (294 mg) in pyridine (1.8 ml) and H_2O (2.8 ml) was added and the mixture was stirred for 3 hr. Recovery of the product gave the mixture of diastereomeric diols (286 mg) as an oil: ν_{max}: 3300, 1740 cm^{-1}; NMR ($CDCl_3$): δ 0.89 (d, J 7 Hz, 3-H_3), 1.27 (d, J 7 Hz, 20-H_3), 2.01 (6 H, acetoxymethyls), 2.28 (br s, 19-H_3), 2.7 (br s, OH), 3.1 (m, 11-H), 3.73 (s, OCH_3), 3.85 (d, J 6 Hz, 1-H_2), 4.0 (m, 18-H_2), 6.6 (br s, 14-H), 6.65 (br d, J 8 Hz, 16-H), 6.96 (d, J 8 Hz, 17-H). A soln of the diols (210 mg) in dioxan (4 ml) and H_2O (5 ml) was treated with $NaIO_4$ (105 mg) and the mixture was stirred for 40 min. The product recovered was dissolved in acetone (10 ml) and treated with Jones reagent at 0 for 1 hr. The product was partitioned into a neutral and $NaHCO_3$ soluble fraction. Recovery of the organic material from the latter gave an oil (60 mg) which was purified by preparative tlc to give **7** as an oil, $[\alpha]^{22}_{589}$ + 3.6; $[\alpha]^{22}_{578}$ + 3.7, $[\alpha]^{22}_{546}$ − 4.1, $[\alpha]^{22}_{436}$ + 11.0 (c 1.9, $CHCl_3$), identical in all respects with a sample of 4*R*-4-(3-methoxy-4-methylphenyl)-pentanoic acid (**7**) prepared as described below. The *p*-bromophenacyl ester of **7**, oil, $[\alpha]^{22}_{589}$ + 2.1, $[\alpha]^{22}_{578}$ + 2.6, $[\alpha]^{22}_{546}$ + 3.1, $[\alpha]^{22}_{436}$ − 7.7, (c 2.5, $CHCl_3$) and the *S*-benzyl-iso-thiouronium salt of **7**, m.p. 110–111, mixed m.p. 110–111, $[\alpha]^{22}_{589}$ + 3.2, $[\alpha]^{22}_{578}$ + 5.9, $[\alpha]^{22}_{546}$ + 7.4, $[\alpha]^{22}_{436}$ + 10.7, (c, 0.5, EtOH) had chemical and spectroscopic properties identical with those prepared from a sample of **7** as described below.

Preparation of thymol and 4-bromothymol from piperitone. A stirred ice-cold soln of piperitone (3.04 g) in CCl_4 (50 ml) was treated with a soln of Br_2 (3.2 g) in CCl_4 (30 ml). Removal of the solvent gave the dibromide (6.2 g) as an oil which slowly eliminated HBr on standing. NMR (CCl_4): δ 0.89 and 0.95 (d, J 7 Hz, secondary Me's), 2.03 (s, bromomethyl), 4.47 and 4.50 (s, bromomethine). A soln of the dibromide (6.0 g) dioxan (250 ml) and 2% aq KOH (150 ml) was stirred for 48 hr. The product recovered was fractionated into neutral and 10% NaOH soluble fractions. Preparative tlc of the neutral fraction gave (a) piperitone (0.73 g) and (b) 6-hydroxy-6-isopropyl-3-methylcyclohex-2-enone (0.63 g) (Found: M^+, 168.1170. $C_{10}H_{16}O_2$ requires: M^+, 168.1150). ν_{max} 3500–3300, 1680 cm^{-1}. NMR (CCl_4; 90 MHz): δ 0.65 and 0.95 (d, J 6.5 Hz, secondary methyls), 1.94 (br s, vinyl Me), 3.3 (OH), 5.78 (br s, vinyl proton). MS: *m/e* 168 (M^+, 4%), 140 (10), 126 (18), 125 (20), 98 (23), 82 (100), 71 (25). The alkaline washing were acidified with 10% HCl and extracted with ether. Preparative GLC of the oil recovered gave (a) thymol (0.90 g) and 4-bromothymol (0.88 g), m.p. and mixed m.p. 55.

Aromatization of the enones (**8**)

(a) A soln of Br_2 (6.4 g) in CCl_4 (60 ml) was added dropwise with stirring to an ice-cold soln of **8** (4.4 g) in CCl_4 (50 ml). Removal of the solvent at room temp gave the tetrabromide (10.7 g) as an oil which eliminated HBr on standing. NMR (CCl_4): δ 0.94 and 1.03 (d, secondary Me's), 1.80 and 2.02 (s, bromomethyls), 4.2 and 4.52 (br s, bromomethines). A mixture of the tetrabromide (4.1 g), dioxan (170 ml) and 2% aq KOH (100 ml) was heated on a steam bath for 18 hr. The product recovered with ether was dissolved in light petroleum and washed with Claisen's alkali (3 × 50 ml). The alkaline washings were diluted with H_2O (300 ml) and extracted with light petroleum. Removal of the solvent gave **10** and **11** (1.0 g, 3:2 respectively).

(b) A mixture of the enones **8** (210 mg) and pyridinium bromide perbromide (916 mg) in AcOH (5 ml) was stirred at room temp for 5 hr. The product recovered with ether was taken up in light petroleum (20 ml) and extracted with Claisen's alkali (4 × 15 ml). The extracts were acidified (10% HCl) and re-extracted with light petroleum. Removal of the solvent gave **10** and **11** (220 mg, 2:3 respectively). NMR (CCl_4): δ 1.19 (d, J 7 Hz, secondary Me's), 1.56 and 1.79 (s, vinyl Me's), 2.21 (s, aryl Me's), 2.99 (m, benzylic methines), 6.41 and 7.05 (s, *p* protons of **11**), 6.5 to 7.1 (ABC system for aromatic protons of **10**). MS: *m/e* 374, 376, 378 (M^+ of **11**, 3%, 6%, 3%), 296, 298 (M^+ of **10**, 10, 10), 295, 297 (5, 5), 217 (35), 213, 215 (25, 25), 148 (40), 135 (100). The mixture of phenols (**10** and **11**) (1.0 g) was methylated with dimethylsulphate and anhyd K_2CO_3 in acetone to give the methyl ethers (1.0 g).

Oxidation of the methyl ethers derivatives of **10** *and* **11** *with* OsO_4–$NaIO_4$. A soln of the methyl ethers of **10** and **11** (0.7 g) in dioxan (80 ml) was treated with OsO_4 (20 mg) and a soln of $NaIO_4$ (2.1 g) in H_2O (25 ml) was added. The soln was stirred for 20 hr and then extracted with ether. The product recovered was filtered through a plug of Act II Alumina to give **12** (0.3 g) as an oil, $[\alpha]_D$ − 9 (c, 0.5) (Found: M^+, 344.0802. $C_{16}H_{23}O_3{}^{81}Br$ requires: M^+, 344.0810). ν_{max}: 3600–3300, 1720 cm^{-1}; NMR (CCl_4): δ 1.1–1.2 (9 H, secondary and hydroxymethyls), 2.3 (s, aryl Me), 3.0 (m, benzylic methine), 3.7 (s, OCH_3), 6.53 and 7.04 (s, *p* protons). MS: *m/e* 342, 344 (M^+, 8%), 300, 302 (10), 284, 286 (20), 240, 242 (60), 227, 229 (100), 205 (45).

4*R*-4-(2-*Methoxy-4-methylphenyl)pentanoic acid* (**7**). A soln of **12** (100 mg) in acetone (2 ml) at 0 was treated with Jones reagent (0.15 ml). The mixture was stirred for 3 hr and the acidic product was extracted with sat $NaHCO_3$ aq. Recovery of the product gave **13** (75 mg) as an oil, $[\alpha]_D$ − 11 (c, 1.0) (Found: M^+, 302.0338. $C_{13}H_{17}O_3{}^{81}Br$ requires: M^+, 302.0341). ν_{max} 3500–3400, 1760, 1720 cm^{-1}; NMR (CCl_4; 90 MHz): δ 1.21 (d, J 7 Hz, benzylic methyl), 1.88 (m, 3-H_2), 2.15 (m, 2-H_2), 2.33 (br s, aryl methyl), 3.15 (m, 4-H), 3.76 (s, OCH_3), 6.62 (s, 3′-H), 7.19 (s, 6′-H), 10.7–11.0 (br, CO_2H). MS: *m/e* 300, 302 (M^+, 30%), 240, 242 (15), 227, 229 (100), 160 (20), 148 (20), 146 (15), 118 (35), 117 (20), 115 (25), 78 (20). Pd/C (10%, 20 mg) and anhyd NaOAc (25 mg) were added to a soln of **13** (60 mg) in EtOH (6 ml). The mixture was stirred under an atmosphere of H_2 until H_2 uptake had ceased. The soln was filtered through a pad of Celite and the residue was washed with ether. The filtrates were combined and the solvent removed to give **7** (40 mg) as an oil, b.p. 120 (bath) 0.01 mm, $[\alpha]^{22}_{589}$ + 3.0 (c, 4, $CHCl_3$). Specific rotations (values corrected for optically pure material), $[\alpha]^{22}_{589}$ + 4.0, $[\alpha]^{22}_{578}$ − 4.2, $[\alpha]^{22}_{546}$ + 4.9, $[\alpha]^{22}_{436}$ + 12.1. (Found, M^+ 222.1259. $C_{13}H_{18}O_3$ requires: M^+, 222.1256). ν_{max}: 3300–3000, 1765, 1715 cm^{-1}. NMR (CCl_4, 90 MHz): δ 1.20 (d, J 7 Hz, benzylic Me), 1.87 (m, 3-H_2), 2.12 (m, 2-H_2), 2.28 (br s, aryl Me), 3.16 (m, 4-H), 3.75 (s, OCH_3), 6.55 (br s, 3′-H), 6.61 (br d, J 7.5 Hz, 5′-H), 7.06 (d, J 7.5 Hz, 6′-H). The *p*-bromophenacyl ester, prepared from *p*-bromophenacyl bromide and the sodium salt of the acid, was purified by preparative tlc and was a colourless oil, $[\alpha]_D$ + 2.4 (c, 1.3, $CHCl_3$). Specific rotations (values corrected for optically pure material), $[\alpha]^{22}_{589}$ + 3.2, $[\alpha]^{22}_{578}$ − 3.7, $[\alpha]^{22}_{546}$ + 4.3, $[\alpha]^{22}_{436}$ − 10.5. (Found: M^+, 420.0723. $C_{21}H_{23}O_4{}^{81}Br$ requires: M^+, 420.0759). ν_{max} 1755, 1715 cm^{-1}; NMR (CCl_4): δ 1.18 (d, J 6 Hz, benzylic methyl), 1.7–2.2 (m, 4 H, 2′, 3′-H$_2$), 2.25 (s, aryl Me), 3.0 (m, 4′-H), 3.72 (s, Me), 4.97 (s, $-\overset{\overset{\displaystyle O}{\|}}{C}-CH_2-O-$), 6.45–7.00 (m, 3′-, 5′-, 6′-H), 7.3–7.8 (AA′BB′, aromatic protons). MS: *m/e* 418, 420 (M^+, 8%), 221 (60), 205 (45), 203 (30), 183, 185 (45), 175 (50), 149 (100). The *S*-benzyl-iso-thiouronium salt, prepared from *S*-benzyl-iso-thiouronium chloride and the sodium salt of the acid, was recrystallised from acetone-n-pentane as needles, m.p. 110–111, $[\alpha]_D$ + 2.7 (c, 0.4, EtOH). Specific rotations (values corrected for optically pure material), $[\alpha]^{22}_{589}$ − 3.3, $[\alpha]^{22}_{578}$ + 6.0, $[\alpha]^{22}_{546}$ + 7.3, $[\alpha]^{22}_{436}$ + 10.9.

Acknowledgements The authors are grateful to CSIRO for a postgraduate studentship (to ADS) and to the Australian Research Grants Committee for financial support.

REFERENCES

[1] E. L. Ghisalberti, P. R. Jefferies and P. N. Sheppard, *Tetrahedron Letters* 1775 (1975)

[2] E. L. Ghisalberti, P. R. Jefferies and P. N. Sheppard, *Tetrahedron Letters* **36**, (1980) **Ms. No. 3092-9038.**

[3] K. D. Croft, E. L. Ghisalberti, P. R. Jefferies, D. G. Marshall, C. L. Raston and A. H. White, *Aust. J. Chem.*, **33**, 1529 (1980).

[4] F. H. Bohlmann and M. Lonitz, *Chem. Ber.* **111**, 843 (1978).

[5] G. W. Shaffer and M. Pesaro, *J. Org. Chem.* **39**, 2489 (1974).

[6] E. L. Ghisalberti, P. R. Jefferies and A. D. Stuart, *Aust. J. Chem.* **32**, 1627 (1979).

[7] O. Wallach and A. Hallstein, *Liebig's Ann* **414**, 287 (1917).

[8] W. L. Meyer, G. B. Clemans and R. A. Manning, *J. Org. Chem* **40**, 3686 (1975).