Factors influencing the Regioselectivity of Reactions involving Organocuprate Reagents and Allyl Acylates: Synthesis of Some Phenylthioprostanoids

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The lactone (4) reacted with the cuprate reagents (5) and (6) under standard conditions to give mainly the products (8) and (12) respectively derived from an S_N' *anti*-process Under the same conditions the lactone (15) reacted with the cuprate reagents (5) and (6) through the S_N2 mode primarily to give as the major products the acids (23) and (19) respectively. The compounds (15), (19), and (23) were converted into the corresponding prostaglandin A_2 analogues (18), (22), and (26).

It has been established that cycloalkenes possessing a good leaving group (X) in the allylic position react readily with homo- and hetero-cuprate reagents to give mainly the products A and B derived from S_N2 and S_N' (*anti*) reactions respectively (Figure 1).[1] For a cyclopentene epoxide (1),[2] halide (2),[3] and acylate (3)[4] we established that the S_N' reaction always predominated over the S_N2 displacement. Herein we report studies involving reactions of cuprate reagents on cyclopent-3-enylacylates in which the approach of a nucleophile to C-1 from the *syn*- or the *anti*-face is sterically hampered by a bulky substituent.

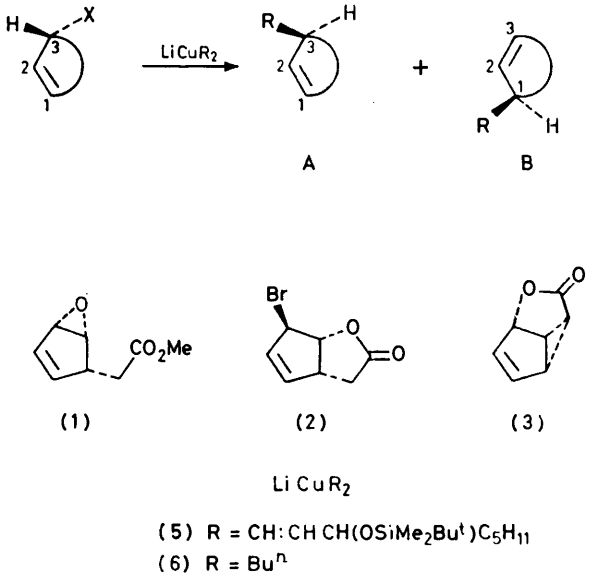


FIGURE 1

RESULTS AND DISCUSSION

The silyloxy-lactone (4) was reported to react with the homocuprate reagent (5) in ether in the S_N2 mode specifically to give, after acid treatment and resilylation, only the prostaglandin A_2 precursor (9).[5] We have repeated this work and found that under the reported conditions the acid (8) resulting from an initial S_N' reaction was the major product. A change in the source of the lithium ion for the cuprate reagent caused only a modest change in the regioselectivity of the reaction (Table). Correspondence with Corey and Mann established that the original reaction was run in ether saturated with lithium iodide. Using these modified conditions, we found that the product of the S_N2 displacement reaction (7) was formed preferentially. A small quantity of the acid (8) was isolated also (Table): the yield of this reaction was not optimized. The isomer ratios reported in the Table were established by separating the acids (7) and (8) by chromatography over silica and converting them independently into the known lactones (9) and (10).[2]

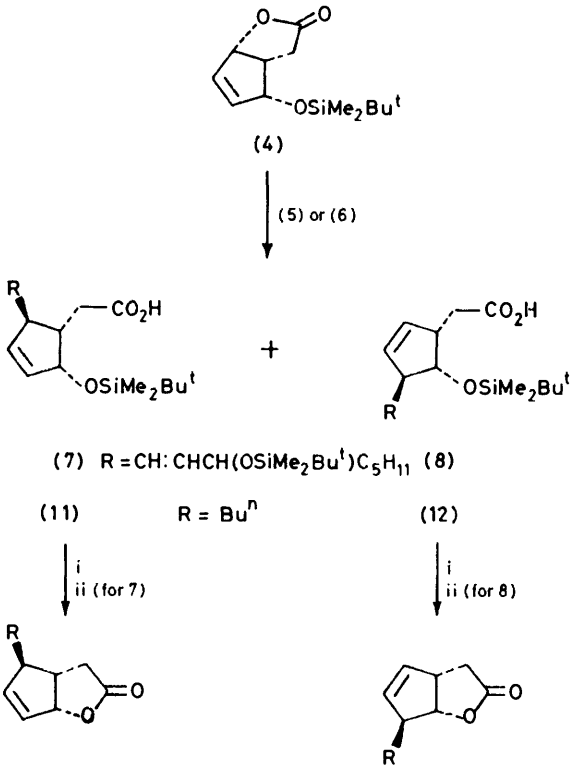
Reaction of the silyloxylactone (4) with the cuprate reagent (5)

Source of Li^+	Solvent	Products formed Yield%	Ratio (7) : (8)
Bu^nLi	Et_2O–pentane (2 : 1)	60	1 : 3
Bu^tLi	Et_2O–pentane (2 : 1)	58	1 : 6
Bu^tLi	Et_2O–LiI–pentane	44	3 : 2

Treatment of the silyloxy-lactone (4) with lithium dibutylcuprate in ether in the range −78 to −20 °C gave a mixture of the acids (11) and (12) (90%). These acids were not separated but were treated directly with aqueous HF in acetonitrile to give the lactones (13) and (14) (100%: ratio 2 : 3). These lactones were identical (n.m.r., t.l.c., and g.l.c.) with samples prepared earlier by two independent routes.[4,6]

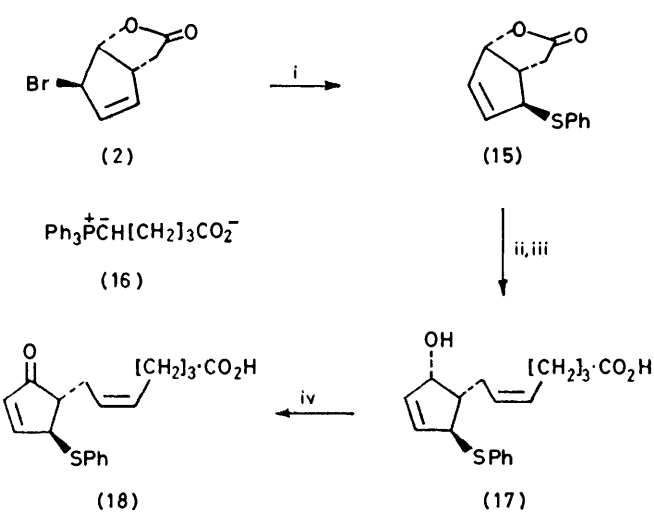
In summary, the *endo*-6-substituted lactone (4) reacted with the cuprate reagents (5) or (6) in ether to give mainly the product resulting from an initial S_N' reaction. Addition of lithium iodide to the reaction involving the former reagent led to a predominance of the product of S_N2 substitution. This salt effect is being investigated further.[7]

The bromo-lactone (2) was converted into the phenylthio-lactone (15) in 83% yield.[2,4] Treatment of this lactone with di-isobutylaluminium hydride followed by the ylide (16) furnished the cyclopentenol (17) which



SCHEME 1 *Reagents:* i, HF, H_2O, MeCN; ii, $ClSiMe_2Bu^t$, imidazole, Me_2NCHO

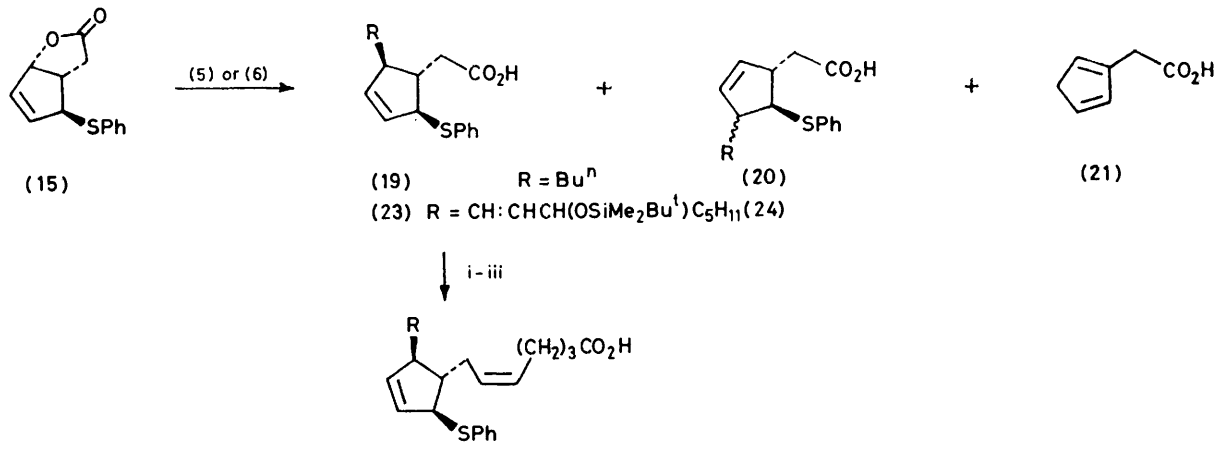
gave the prostaglandin A_2 analogue (18) on oxidation with a pyridine–SO_3 complex in dimethyl sulphoxide [8] (Scheme 2).



SCHEME 2 *Reagents:* i, PhS^-; ii, $AlH(Bu^t)_2$; iii, (16); iv, SO_3, C_5H_5N, Me_2SO

Reaction of the lactone (15) with the cuprate reagent (6) gave three products which were separated by chromatography. The major product (44%) was the carboxylic acid (19) [δ($CDCl_3$) *inter alia* 4.05 (1 H, m, H-5′)] derived from an S_N2 reaction: the acid (20) [δ($CDCl_3$) *inter alia* 3.52br (1 H, t, H-5′), stereochemistry of the butyl group undefined] was produced in 18% yield. The third product was the cyclopentadienylacetic acid (21) [9] (26%) which was formed, presumably, by direct attack of the cuprate reagent on the sulphur atom (Figure 2). The acid (19) was converted into the prostanoid (22) using the standard conditions (Scheme 3).

The cuprate reagent (5) was allowed to react with the phenylthio-lactone (15) to give a mixture which was



SCHEME 3 *Reagents:* i, $LiAlH_4$; ii, CrO_3, C_5H_5N; iii, (16)

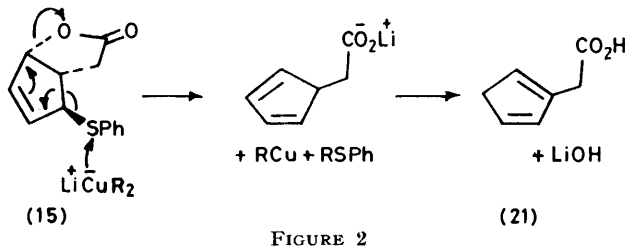


FIGURE 2

separated by chromatography to afford the acids (23) (53%) [δ($CDCl_3$) *inter alia* 4.10 (2 H, m, H-5′ and H-3″), 3.10 (1 H, m, H-2′)], (24) (9%) [δ($CDCl_3$) *inter alia* 4.10 (1 H, m, H-3″), 3.55 (1 H, m, H-5′), 3.10 (2 H, m, H-1′ and H-4′)], and (21) (11%). The acid (23) was converted into the prostanoid (25) which was desilylated to give (±)-9β-phenylthio-9-deoxaprostaglandin A_2 (26) (Scheme 3).

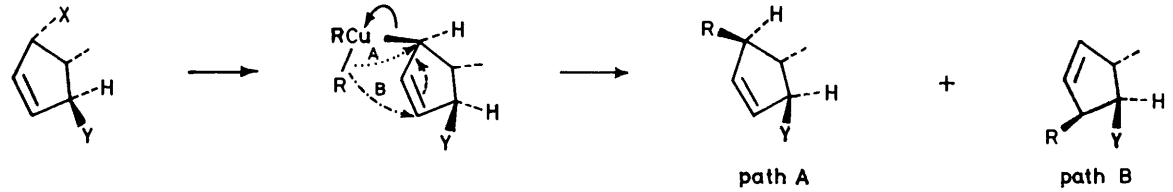


FIGURE 3 For Y = SPh, path A preferred; Y = H, path B preferred

Thus, in the cyclopentenyl ring system under study, a bulky substituent homoallylic and *anti* (*trans*) to the acylate leaving group guides the cuprate reaction along an S_N2 pathway preferentially, probably by sterically inhibiting the approach of the incoming alk(en)yl group to the vicinal carbon atom. These results are in accord with the proposed mechanism [2,10] for S_N2' (*anti*) reactions of this type (Figure 3).

EXPERIMENTAL

I.r. spectra were recorded on a Perkin-Elmer 297 spectrophotometer for neat films. N.m.r. spectra were recorded on a Varian EM-360 or Perkin-Elmer R-32 spectrometer ($CDCl_3$ solvent). G.l.c. was performed on a Hewlett-Packard 5880 instrument using a 4-m OV-225 column at 120 °C rising to 240 °C at 4 °C min^{-1}. T.l.c. was performed using Camlab silica plates. Thick-layer chromatography was conducted using Merck Kieselgel 60H. Anhydrous magnesium sulphate was used for drying solutions in organic solvents. Light petroleum refers to the fraction boiling in the range 60—80 °C. n-Butyl-lithium was used as a 1.6M-solution in hexane.

Reaction of Lithium Dibutylcuprate (6) *with* endo-6-*t-Butyldimethylsilyloxy*-2-*oxabicyclo*[3.3.0]*oct*-7-*en*-3-*one* (4).—A solution of n-butyl-lithium (2.4 equiv. of a 1.6M-solution in hexane) was stirred in ether (10 ml) under an atmosphere of argon at −78 °C and then cuprous bromide–dimethyl sulphide complex (1.2 equiv.) dissolved in ether–dimethyl sulphide (ratio 2 : 1, 3 ml) was added to it. After 15 min the lactone (4) (0.22 g) dissolved in ether (4 ml) was added dropwise with stirring. After 3.5 h at −78 °C the reaction was allowed to warm to −20 °C during 2.5 h and a saturated aqueous solution of ammonium chloride (10 ml) was added to it. The organic layer was separated and the aqueous layer was washed with ether (50 ml). The organic extracts were washed with 1M-sulphuric acid (50 ml) and water (50 ml) and the aqueous washes were combined and extracted with ether (4 × 50 ml). The combined organic fractions were dried and evaporated to give a yellow oil (243 mg), $\nu_{max.}$ 1 710 cm^{-1}. This oil was dissolved in 40% aqueous hydrofluoric acid (0.5 ml) and acetonitrile (4.5 ml). After 30 min at room temperature chloroform (50 ml) was added. After washing with water (3 × 20 ml) and drying, the solvent was removed under reduced pressure to give a yellow oil (140 mg). From n.m.r. and g.l.c. results it was established that this oil contained the lactones (13) and (14) (94%) in the ratio 2 : 3.[4,6]

Reaction of Lithium Dibutylcuprate (6) *with* exo-6-*Phenylthio*-2-*oxabicyclo*[3.3.0]*oct*-7-*en*-3-*one* (15).—To a solution of n-butyl-lithium (2.4 equiv. of a 1.6M-solution in hexane) in ether (30 ml) under an atmosphere of argon at −78 °C was added cuprous bromide–dimethyl sulphide complex (1.2 equiv.) in ether–dimethyl sulphide [10 ml (2 : 1)]. After 15 min the lactone (15) (1.0 g) dissolved in ether (12 ml) was added dropwise with stirring. After 1 h at −78 °C the reaction mixture was warmed to −40 °C during 3.5 h. Work-up as described above furnished a yellow oil (1.16 g) which was chromatographed using ethyl acetate in light petroleum (1 : 10) as eluant. Two fractions were collected: the first contained the acids (19) and (20) (770 mg, ratio 8 : 3 by n.m.r. and g.l.c.) and the second fraction contained the acid (21), $\nu_{max.}$ 1 700 cm^{-1}; δ 9.46br (1 H, s, CO_2H), 6.6—6.2 (3 H, m, H-2′, H-4′ and H-5′), and 3.45—3.05 (4 H, m, 2 × H-2 and 2 × H-3′). The mixture of acids (19) and (20) was separated by thick-layer chromatography using ethyl acetate in light petroleum (2 : 3) as eluant to give exo-2-*butyl*-exo-5-*phenylthiocyclopent*-3-*enylacetic acid* (19), $\nu_{max.}$ 1 700 cm^{-1}; δ 11.2br (1 H, s, CO_2H), 7.8—7.1 (5 H, m, C_6H_5), 5.8br (2 H, s, H-3′ and H-4′), 4.0 (1 H, s, H-5′), 3.2—2.0 (4 H, m, 2 × H-2, H-1′, and H-2′), 1.25 (6 H, m, 3 × CH_2), and 0.85br (3 H, t, Me) (Found: M^+, 290.1328. $C_{17}H_{22}O_2S$ requires M, 290.1340), and 4-*butyl*-exo-5-*phenylthiocyclopent*-2-*enylacetic acid* (20) $\nu_{max.}$ 1 700 cm^{-1}, δ 8.4br (1 H, s, CO_2H), 7.5—7.1 (5 H, m, C_6H_5), 6.0—5.6 (2 H, m, H-2′ and H-3′), 3.5br (1 H, t, J 7 Hz, H-5′), 3.3—2.0 (4 H, m, 2 × H-2, H-1′ and H-4′), 1.25 (6 H, m, 3 × CH_2), and 0.87br (3 H, t, Me) (Found: M^+, 290.1352. $C_{17}H_{22}O_2S$ requires M, 290.1340).

Reaction of the Cuprate Reagent (5) *with* endo-6-*t-Butyldimethylsilyloxy*-2-*oxabicyclo*[3.3.0]*oct*-7-*en*-3-*one* (4).—To a solution of 1-iodo-3-t-butyldimethylsilyloxyoct-1-ene (3 equiv.) in ether (10 ml) at −78 °C was added n-butyl-lithium (3 equiv.). After 30 min cuprous iodide in diisopropyl sulphide (1.5 equiv. of a 1 : 4 w/w solution) was added followed after 15 min by the lactone (4) (0.71 g) in ether (10 ml). After the addition was complete the temperature of the reaction mixture was allowed to rise to −20 °C during 4 h. Work-up in the manner described above gave a yellow oil which was chromatographed over silica using ethyl acetate in light petroleum (1 : 30) as eluant to

give the *acid* (7) (190 mg), $\nu_{max.}$ 1 705 cm^{-1}; δ 9.3br (1 H, s, CO_2H), 5.85 (2 H, m, H-3′ and H-4′), 5.6—5.4 (2 H, m, H-1″, H-2″), 4.85 (1 H, dm, *J* 9 Hz, H-5′), 4.00 (1 H, m, H-3″), 3.0 (1 H, m, H-2′), 2.8—1.8 (3 H, m, 2 × H-2, H-1′), 1.25 (8 H, m, 4 × CH_2), 0.85 (21 H, m), and 0.00 (12 H, s, 2 × $SiMe_2$) [Found: $(M - 57)^+$, 439.2698. $C_{27}H_{52}O_4Si_2$ requires $(M - 57)$, 439.2698], and the *acid* (8) (642 mg), $\nu_{max.}$ 1 705 cm^{-1}; δ 7.0br (1 H, s, CO_2H), 5.9—5.3 (4 H, m, H-2′, H-3′, H-1″, and H-2″), 4.3—3.85 (2 H, m, H-5′ and H-3″), 3.3—2.9 (2 H, m, H-1′ and H-4′), 2.72 (1 H, dd, *J* 18, 6 Hz, H-2), 2.35 (1 H, dd, *J* 18, 8 Hz, H-2), 1.25 (8 H, m, 4 × CH_2), 0.85 (21 H, m), and 0.00 (12 H, s, 2 × $SiMe_2$) [Found: $(M - 57)^+$, 439.2699. $C_{27}H_{52}O_4Si_2$ requires $(M - 57)$, 439.2698].

The acid (7) was converted into the lactone (9) [2] (100%) by treatment with HF as described above and silylation using the standard procedure.[11] The acid (8) was converted into the lactone (10) (86%) in a similar manner.

Reaction of the Cuprate Reagent (5) *with* exo-6-*Phenylthio*-2-*oxabicyclo*[3.3.0]*oct*-7-*en*-3-*one* (15).—To a solution of 1-iodo-3-t-butyldimethylsilyloxyoct-1-ene (3 equiv.) in ether (16 ml) and pentane (16 ml) at −78 °C under an atmosphere of argon was added n-butyl-lithium (3 equiv.) with stirring. After 0.5 h cuprous iodide in di-isopropyl sulphide (1.5 equiv. of a 1 : 4 w/w solution) was added. After 15 min the lactone (15) (980 mg) in ether (16 ml) was added dropwise. When the addition was complete the reaction mixture was stirred for 4 h at −78 °C and then warmed to −30 °C during 2 h. Work-up in the usual manner afforded a yellow oil which was chromatographed over silica using ethyl acetate in light petroleum (1 : 20) as eluant. Starting material (115 mg) was recovered together with the *acid* (23) [(933 mg), $\nu_{max.}$ 1 700 cm^{-1}, δ 11.0br (1 H, s, CO_2H), 7.6—7.0 (5 H, m, C_6H_5), 6.0—5.25 (4 H, m, H-3′, H-4′, H-1″, and H-2″), 4.2—3.8 (2 H, m, H-5′ and H-3″), 3.05 (1 H, m, H-2′), 2.9—2.0 (3 H, m, H-2 and H-1′), 1.25 (8 H, m, 4 × CH_2), 0.9br (12 H, s), and 0.00 (6 H, s, $SiMe_2$) (Found: C, 68.4; H, 9.2. $C_{27}H_{42}O_3SiS$ requires C, 68.3; H, 8.9%)], the *acid* (24) [(151 mg), $\nu_{max.}$ 1 705 cm^{-1}; δ 9.6br (1 H, s, CO_2H), 7.7—7.1 (5 H, m, C_6H_5), 6.2—5.1 (4 H, m, H-2′, H-3′, H-1″, and H-2″), 4.05 (1 H, m, H-3″), 3.55 (1 H, m, H-5′), 3.0 (2 H, m, H-1′ and H-4′), 2.9—1.8 (2 H, m, 2 × H-2), 1.25 (8 H, m, 4 × CH_2), 0.9 (12 H, m), and 0.00 (6 H, s, $SiMe_2$)] and the acid (21) (50 mg) were isolated [Found: $(M - 57)^+$, 417.1900. $C_{27}H_{42}O_3SiS$ requires $(M - 57)$, 417.1920].

12β-*Phenylthio*-12-*octanorprostaglandin* A_2 (18).—To a stirred solution of the lactone (15) (600 mg) in dichloromethane (30 ml) at −78 °C under an atmosphere of nitrogen was added di-isobutylaluminium hydride (1.5 equiv.) in hexane (3.9 ml). After 1 h methanol (30 ml) was added and the mixture was warmed to room temperature. After filtration through Hyflo, dichloromethane (50 ml) was added. The organic phase was dried, filtered, and evaporated to give a colourless oil (581 mg) $\nu_{max.}$ 3 400 cm^{-1}. This oil was allowed to react with the ylide (16) in the usual manner [12] to give a viscous pale oil. This material was chromatographed over silica using ethyl acetate as eluant to give the *hydroxy-acid* (17) (77%), $\nu_{max.}$ 3 300 and 1 710 cm^{-1}; δ 7.5—7.1 (5 H, m, C_6H_5), 6.4—5.7 (4 H, m, H-3′, H-4′, 2 × OH), 5.7—5.2 (2 H, m, H-5 and H-6), 4.70 (1 H, dm, *J* 6 Hz, H-5′), 3.90 (1 H, dm, *J* 6 Hz, H-2′), 2.5—1.9 (7 H, m, 2 × H-2, 2 × H-4, 2 × H-7, and H-1′), and 1.9—1.55 (2 H, m, 2 × H-3) (Found: M^+, 318.1288. $C_{18}H_{22}O_3S$ requires *M*, 318.1288). To a solution of the acid (17) (395 mg) and triethylamine (933 mg) in dimethyl sulphoxide (5.4 ml) at room temperature under an atmosphere of nitrogen was added pyridine–SO_3 complex (603 mg) [8] in dimethyl sulphoxide (7 ml). The mixture was stirred for 1 h before hydrochloric acid (2N; 7 ml) and water (100 ml) were added. The aqueous layer was separated and washed with ether (4 × 100 ml) and the combined organic fractions were washed with water (2 × 100 ml), dried, and evaporated to give a yellow oil. This oil was chromatographed over silica using ethyl acetate in light petroleum as eluant to give the *oxo-acid* (18) (272 mg) as an oil, $\nu_{max.}$ 3 500 and 1 705 cm^{-1}; δ 8.6br (1 H, s, CO_2H), 7.65—7.2 (6 H, m, H-3′ and C_6H_5), 6.15 (1 H, dd, *J* 5.5, 1.5 Hz, H-4′), 5.55—5.25 (2 H, m, H-5 and H-6), 3.97 (1 H, m, H-2′), 2.8—1.9 (7 H, m, 2 × H-2, 2 × H-4, 2 × H-7, and H-1′), and 1.9—1.5 (2 H, m, 2 × H-3) (Found: M^+, 316.1130. $C_{18}H_{20}O_3S$ requires *M*, 316.1131).

9β-*Phenylthio*-9-*deoxaprostaglandin* A_2 (26).—To a stirred solution of lithium aluminium hydride (4 equiv.) in dry ether (15 ml) at 0 °C was added the acid (23) (493 mg) in dry ether (10 ml). The reaction mixture was stirred for 2 h before water (10 ml), and hydrochloric acid (2N; 20 ml) were added. The aqueous layer was separated and washed with ether (3 × 50 ml) and the combined ether fractions were washed with water (2 × 50 ml), dried, and evaporated to give a yellow oil (424 mg), $\nu_{max.}$ 3 380 cm^{-1}. This oil dissolved in dry dichloromethane was added dropwise with stirring to a solution of chromium trioxide–pyridine complex (Collins' reagent, 200 mg) in dry dichloromethane. Further quantities of Collins' reagent (350 mg) were added after 2 and 4 h. The solvent was evaporated and diethyl ether (70 ml) was added. The solution was filtered through Hyflo, washed with hydrochloric acid (2M; 50 ml) and water (2 × 30 ml) dried, and evaporated. The residue was chromatographed over silica using ethyl acetate–light petroleum (1 : 20) as eluant to give a yellow oil (105 mg), $\nu_{max.}$ 1 720 cm^{-1}. This material was treated with the ylide (16) under 'salt-free' conditions [12] to give a brown oil. This oil was chromatographed over silica using ethyl acetate–light petroleum (1 : 20) to give a colourless oil (49 mg), which was dissolved in acetonitrile (4.5 ml) containing 40% aqueous hydrofluoric acid (0.5 ml). After 0.5 h chloroform (50 ml) was added and the organic layer was washed with water (3 × 20 ml), dried, and evaporated to give 9β-*phenylthio*-9-*deoxaprostaglandin* A_2 (26) (40 mg), $\nu_{max.}$ 1 705 cm^{-1}, δ 7.5—7.2 (5 H, m, C_6H_5), 6.3—5.1 (8 H, m, H-5, H-6, H-10, H-11, H-13, H-14, and 2 × OH), 4.1—3.7 (2 H, m, H-9 and H-15), 3.0 (1 H, m, H-12), 2.5—1.3 (17 H, m), and 0.9br (3 H, t, Me) (Found: M^+, 428.2395. $C_{26}H_{36}O_3S$ requires *M*, 428.2385).

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REFERENCES

[1] J. Staroscik and B. Rickborn, *J. Am. Chem. Soc.*, 1971, **93**, 3046; D. M. Wieland, and C. R. Johnson, *ibid.* p. 3047; J. P. Marino and J. S. Farina, *J. Org. Chem.*, 1976, **41**, 3213; H. L. Goering and V. D. Singleton, *J. Am. Chem. Soc.*, 1976, **98**, 7854; A. Kreft, *Tetrahedron Lett.*, 1977, 1035; A. Claesson and L. I. Olsson, *J. Chem. Soc., Chem. Commun.*, 1978, 621; for an exceptional case see C. Gallina and P. G. Ciatrini, *J. Am. Chem. Soc.*, 1979, **101**, 1035.

[2] M. A. W. Finch, T. V. Lee, S. M. Roberts, and R. F. Newton, *J. Chem. Soc., Chem. Commun.*, 1979, 677.

[3] C. B. Chapleo, M. A. W. Finch, T. V. Lee, S. M. Roberts, and R. F. Newton, *J. Chem. Soc., Chem. Commun.*, 1979, 676.
[4] C. B. Chapleo, M. A. W. Finch, S. M. Roberts, G. T. Woolley, R. F. Newton, and D. W. Selby, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1847.
[5] E. J. Corey and J. Mann, *J. Am. Chem. Soc.*, 1973, **95**, 6832.
[6] By oxidation of the corresponding lactol, C. B. Chapleo, S. M. Roberts, and R. F. Newton, *J. Chem. Soc., Chem. Commun.*, 1979, 680.
[7] *Cf.* H. O. House and W. F. Fischer, *J. Org. Chem.*, 1968, **33**, 949.
[8] J. R. Parikh and W. von E. Doering, *J. Am. Chem. Soc.*, 1967, **89**, 5505.
[9] E. L. Mitch, and A. S. Dreiding, *Chimia*, 1960, **14**, 424.
[10] G. Teutsch and A. Belanger, *Tetrahedron Lett.*, 1979, 2051.
[11] E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, 1972, **94**, 6190.
[12] T. V. Lee, S. M. Roberts, M. J. Dimsdale, R. F. Newton, D. K. Rainey, and C. F. Webb, *J. Chem. Soc., Perkin Trans. 1*, 1979, 1176.