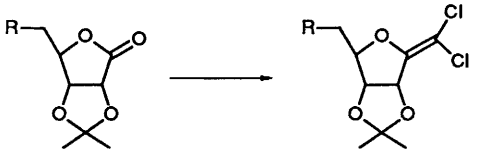
Unusual Behaviour of Some γ- and δ-Lactones Towards Dichloromethylenation using Tris(dimethylamino)phosphine–Tetrachloromethane

Alphonse Bandzouzi, Mohammed Lakhrissi and Yves Chapleur*
Laboratoire de Chimie Organique 3, Unité Associée au CNRS 486 Université de Nancy I, B.P. 239, F-54506 Vandoeuvre-les-Nancy Cedex, France

Lactones derived from D-glucose, D-mannose and L-ascorbic acid reacted unexpectedly with tris(dimethylamino)phosphine–tetrachloromethane to give, respectively, dichloroalkene, anomeric vinyl chloride or acyl chloride; this behaviour supports an ionic mechanism for the alkenation.

We described some time ago a new reaction of some γ-lactones **A** derived from carbohydrates with the tris(dimethylamino)-

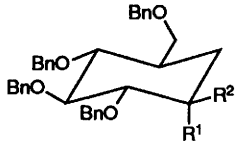


A **B**

Scheme 1 *Reagents and conditions:* $P(NMe_2)_3$–CCl_4, THF, −30 °C

phosphine–tetrachloromethane system [1] (TDAP–CCl_4)† which allows the formation of dichloroalkenes **B** at the anomeric centre. Further useful reactions of this new substituted dichloromethylene entity have been reported in the synthesis of *C*-glycosides [2] and muscarines.[3] More recently, a variant of this methodology was successfully applied for the synthesis of difluoromethylene compounds either from γ or δ-lactones.[4] Owing to the good results obtained with lactones of type **A** having a bicyclo[3.3.0] structure, we have explored the reaction of the TDAP–CCl_4 system with several lactones, and found that those derived from D-glucose, D-mannose and L-ascorbic acid behave rather differently.

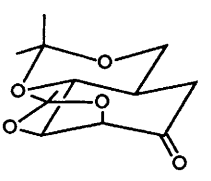
When tetra-*O*-benzyl-D-gluconic acid δ-lactone **1** was treated



1 $R^1, R^2 = O$
2 $R^1, R^2 = CCl_2$
3 $R^1 = H, R^2 = Me$

with TDAP–CCl_4 (3 eq., −30 °C, 2 h), the expected dichloroalkene **2** was formed in rather low yield (25%) together with a number of unidentified compounds.[5] The structure of the main compound was supported by spectroscopic data and subsequent formation of the *C*-glycoside **3** by reduction of the dichloromethylene moiety using Raney nickel. As expected from the probable conformation of **2** in which the α-face is the more accessible, only the 1,2-*trans*-β-anomer was formed.[6]

Under the same conditions, the behaviour of di-*O*-isopropylidene-D-mannonic acid δ-lactone **4** (readily available by



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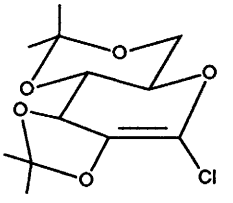

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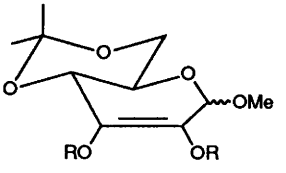
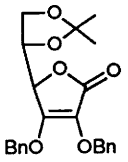


6 R = H
7 R = Ac

oxidation of the corresponding hemiketal) [7] was examined. In sharp contrast with the above experiment, the rather unstable vinyl chloride **5** was formed as the sole product (3 equiv., −30 °C, 2 h, 90%). The structure of **5** was established by ^1H NMR spectroscopy which showed no 2-H signal and δ_H 4.92 (d, *J* 7.5, 3-H). Further evidence was obtained from the comparison of ^{13}C NMR spectra of **4** and **5** obtained using the DEPT technique. It was clearly evident that compound **5** had one 'even' carbon more than **4**. This difference was attributed to the signal of C-2 which changed from sp^3 to sp^2 hybridation. A strong deshielding of the signal of C-2 and to a less extent that of C-3 was observed. In addition, δ_C 162.3 (C-1) was in good agreement with the proposed structure for **5**.[8] In order to obtain indirect proof of its structure, the chloride **5** was treated with sodium methoxide–methanol. The methyl glycoside **6** was formed as a mixture of anomers and the corresponding α-diacetate **7** was fully characterised. The formation of the enediol moiety was explained by a *trans*-acetalation of the 2,3-*O*-isopropylidene in methanol. Finally, attempted reduction of the chloride **5** using Raney nickel W2 in ethyl acetate at room temperature gave only the starting lactone **4** in 80% yield *via* hydrolysis of the unstable glycosyl chloride.

The third case examined, was the protected derivative of ascorbic acid **8**. Although it is a γ-lactone, no dichloromethylenation took place, but only the formation of the acid chloride **9** as a *Z*/*E* (8:1) mixture was observed (3 equiv., −30 °C, 2 h, 73%). Although it was difficult to determine the configuration of the double bond on the basis of the spectroscopic data, one may assume that the major product retained the *Z*-configuration of the starting lactone. The structure of **9** was established on the basis of ^{13}C NMR results which clearly showed that C-4 was sp^2 hybridized, and mass spectrometry which indicated the presence of only one chlorine atom. Further chemical proof was

† We have used the term tris(dimethylamino)phosphine (TDAP) instead of hexamethylphosphorous triamide (HMPT), in order to avoid confusion with the acronym of hexamethylphosphoric triamide (HMPA).



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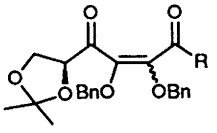
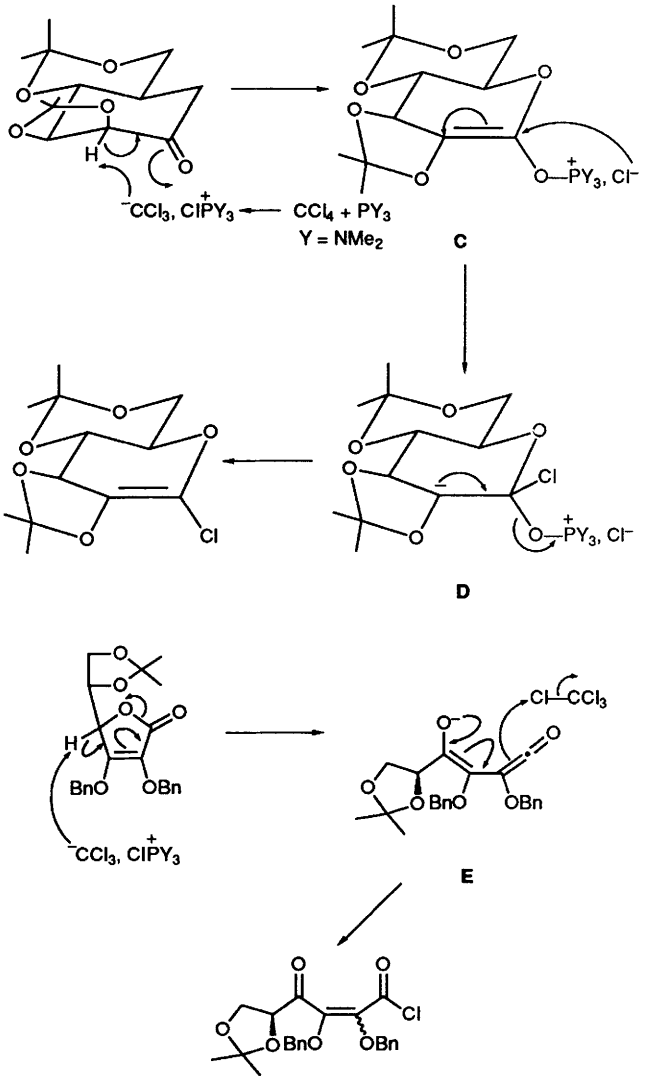


9 R = Cl
10 R = OMe
11 R = OH
12 R = NHBn

obtained from the following standard reactions. Esterification of **9** with methanol and triethylamine or sodium methoxide in methanol gave the methyl ester **10** as a Z/E (5:1) mixture. The treatment of **9** with sodium hydroxide in acetone gave the acid **11** (*Z*/*E* 2:1), whereas benzylamine gave the expected amide **12** (*Z*/*E* 4:1).

The observed reactions could be rationalised as follows. With the lactone **1**, the condensation of trichloromethylide anion on the carbonyl group was followed by deoxygenation *via* an intermediate oxyphosphonium salt.[1] The modest yield may be explained by enolization of the lactone **1** and subsequent elimination of the benzyl group at C-3, followed by further reactions of the unsaturated lactonic system. Such β-elimination during nucleophilic addition onto this lactone had been already reported.[9] The other cases are well explained by two different mechanisms, depicted in Scheme 2. In the case of lactone **4**, it seems that enolisation of the lactone was the main reaction, giving rise to the formation of an anomeric vinylic oxyphosphonium salt **C** which may undergo direct substitution by chlorine, or more probably adds chloride ion to form a 1-chloro-1-oxyphosphonium salt **D**; subsequent elimination of hexamethylphosphoramide gave **5**.[10] The same kind of explanation accounts for the formation of the acyl chloride **9**. Abstraction of the homoenolic 4-H by trichloromethylide anion would lead to the ketene type intermediate **E**. Subsequent reaction with CCl_4 would regenerate the trichloromethylide ion and form the acyl chloride **9**.[11] The proposed intermediate **E** is supported by the observed formation of *Z*/*E* mixtures of **9** due to the rotation around the C(2)–C(3)bond.

In summary, the reaction of TDAP–CCl_4 with lactones gave mainly the corresponding dichloroalkenes, but followed a different course if the lactone was prone to enolisation; these observations strongly support the fact that the trichloromethylide anion is an intermediate in the dichloromethylenation. This is in striking contrast with a Wittig-type mechanism most likely involved in the dichloromethylenation using Ph_3P–CCl_4.[12] Moreover, the formation of the anomeric vinylic chloride **5** is of current synthetic interest because it could be a precursor of a α-alkoxy anomeric vinylic carbanion, the chemistry of which is being studied.



Scheme 2

Experimental

General Procedure for Dichloroalkenation.—To a solution of the lactone (1 mmol) and CCl_4 (6 mmol) in dry tetrahydrofuran (THF) (15 cm^3) was slowly added under nitrogen a solution of $(Me_2N)_3P$ (3 mmol) in THF (8 cm^3) at the temperature indicated in the text. The resulting mixture was poured into water and extracted with diethyl ether (3 × 50 cm^3). The organic phase was washed with hydrochloric acid (3 mol dm^{-3}) and water until neutral, dried ($MgSO_4$) and evaporated to dryness. Flash chromatography on silica gel gave pure compounds.

The eluent for chromatography was hexane (H)–ethyl acetate (A). Unless otherwise stated, optical rotations were measured at 20 °C.

2,6-*Anhydro*-3,4,5,7-*tetra*-O-*benzyl*-1-*deoxy*-1,1-*dichloro*-D-gluco-*hept*-1-*enitol* **2**.—(151 mg, 25%); R_f 0.47 (H/A 6:1); $[\alpha]_D$ 17.2 (*c*, 0.5, $CHCl_3$) (Found: C, 69.2, H, 5.6; Cl, 11.65. $C_{35}H_{34}Cl_2O_5$ requires C, 69.42, H, 5.66; Cl, 11.71%); ν/cm^{-1} 1635 (C=C); δ_H(400 MHz) 3.7 (1 H, dd, $J_{4,5}$ 4.5, $J_{5,6}$ 10, 5-H), 3.74 (1 H, t, $J_{6,7}$ 4, $J_{7,7'}$ 11, 7-H), 3.78 (1 H, dd, $J_{6,7}$ 2, 7′-H), 3.92 (1 H, dd, $J_{3,4}$ 1.5, 4-H), 4.51 (1 H, m, 6-H), 4.7 (1 H, d, 3-H), 4.35–4.7 (8 H, m, CH_2Ph) and 7.15–7.40 (20 H, m, Ph); δ_C(100.5 MHz) 68.63 (C-7), 70.45, 71.60, 72.85, 73.49 (CH_2Ph), 72.17 (C-4), 75.8 (C-3), 77.74 (C-5), 81.47 (C-6), 106.11 (C-1) 127.48, 127.62, 127.75, 127.89, 128.05, 128.13, 128.32, 128.52, 137.31, 137.48 (Ar) and 145.52 (C-2).

2,6-*Anhydro*-3,4,5,7-*tetra*-O-*benzyl*-1-*deoxy*-D-gluco-*heptitol* **3**.—The dichloroalkene **2** (120 mg, 0.2 mmol) in ethyl acetate (10 cm^3) and Raney nickel (1 g) was vigorously shaken under a hydrogen atmosphere until no starting material remained (TLC) (H/A 4:1). Filtration through a pad of Celite and concentration gave the crude product **3** which was purified by column chromatography (H/A 7:1) (85 mg, 80%); R_f 0.54 (H/A 4:1); $[\alpha]_D$ 10 (*c*, 0.6, $CHCl_3$) (Found: C, 78.4, H, 7.0. $C_{35}H_{38}O_5$ requires C, 78.02; H, 7.11%); δ_H(400 MHz) 1.3 (3 H, d, $J_{1,2}$ 6.5, 1-H), 3.2 (1 H, t, $J_{2,3} = J_{3,4}$ 9, 3-H), 3.4 (2 H, m, $J_{5,6}$ 9, $J_{6,7}$ 2, $J_{6,7'}$ 4.5, 2-H, 6-H), 3.6 (1 H, t, $J_{4,5}$ 9, 5-H), 3.62–3.75 (3 H, m, $J_{7,7'}$ 11, 4-H, 7-H, 7′-H), 4.25–4.7 (4 H, m, CH_2Ph) 4.75–4.95 (4 H, m, CH_2Ph) and 7.15–7.4 (20 H, m, Ar).

2,3:4,6-*Di*-O-*isopropylidene*-D-*mannono*-1,5-*lactone* **4**.—The lactone **4** was prepared from the corresponding acetal [7] (1.9 g, 7.3 mmol) by standard Swern oxidation [13] (1.68 g, 93%); m.p. 202; R_f 0.67 (H/A 1:1); $[\alpha]_D$ 43.5 (*c*, 0.5, $CHCl_3$) (Found: C, 55.9, H, 7.2. $C_{12}H_{18}O_6$ requires C, 55.78; H, 7.03%); ν/cm^{-1} 1780 (C=O); δ_H(400 MHz) 1.42 (3 H, s, Me), 1.44 (3 H, s, Me), 1.55 (3 H, s, Me), 1.58 (3 H, s, Me), 3.85 (1 H, m, $J_{5,6}$ 5, $J_{6,6'}$ 12, 6-H), 3.88 (1 H, m, $J_{3,4}$ 6.5, $J_{4,5}$ 3, 4-H), 4.07 (1 H, m, $J_{5,6}$ 5.5, 5-H), 4.11 (1 H, m, 6-H), 4.61 (1 H, dd, $J_{2,3}$ 8.5, 3-H) and 4.78 (1 H, d, 2-H).

1-*Chloro*-1-*deoxy*-2,3:4,6-*di*-O-*isopropylidene*-D-ribo-*hex*-1-*enopyranose* **5**.—The pyranose **5** decomposed rapidly with time, but could be stored for a short time in ether solution (248 mg, 90%); R_f 0.45 (H/A 4:1); ν/cm^{-1} 1785 (C=C); δ_H(400 MHz) 1.48 (3 H, s, Me), 1.60 (3 H, s, Me), 1.65 (3 H, s, Me), 1.72 (3 H, s, Me), 3.82 (1 H, dd, $J_{4,5}$ 10, $J_{3,4}$ 7.5, 4-H), 3.98 (1 H, dd, $J_{5,6'}$ 10, $J_{6,6'}$ 11.5, 6'-H), 4.15 (1 H, dd, $J_{5,6}$ 6, 6-H), 4.43 (1 H, dt, 5-H) and 4.92 (1 H, d, 3-H); δ_C(100.5 MHz) 18.69, 23.59, 26.47, 28.30 (Me), 60.71 (C-6), 67.04 (C-4), 71.69 (C-5), 86.87 (C-3), 92.37 (C-2), 100.06, 116.10 (CMe_2) and 162.34 (C-1).

Methyl 2,3-*Di*-O-*acetyl*-2,3-*dideoxy*-2,3:4,6-*di*-O-*isopropylidene*-D-erythro-*hex*-2-*enopyranoside* **7**.—The vinylic chloride **5** (123 mg, 0.44 mmol) was dissolved in dry MeOH at room temperature and sodium (5 mg) was added. After being stirred for 1 h, the mixture was neutralised with Dowex 50W H^+ resin, filtered and concentrated to give crude **6** as a 2.5:1 mixture of anomers (55 mg, 52%). Conventional acetylation of **6** gave a mixture of anomers **7** which were separated by column chromatography (H/A 3:1). Pure **7α** was obtained: 26 mg; R_f 0.31 (H/A 2:1); $[\alpha]_D$ 1.57 (*c*, 0.5, $CHCl_3$) (Found C, 52.8, H, 6.3; $C_{14}H_{20}O_8$ requires C, 53.16; H, 6.37%); ν/cm^{-1} 1740 (C=O); δ_H(400 MHz) 1.42 (3 H, s, Me), 1.65 (3 H, s, Me), 2.10 (3 H, s, Ac), 2.11 (3 H, s, Ac), 3.86 (3 H, s, OMe), 4.32 (1 H, dd, $J_{5,6}$ 6, $J_{6,6'}$ 12, 6-H), 4.36 (1 H, dd, $J_{5,6'}$ 6, 6'-H), 4.47 (1 H, dt, $J_{4,6}$ 2.5, 5-H), 4.95 (1 H, s, 1-H) and 5.15 (1 H, d, 4-H).

(5R)-2,3-*Dibenzyloxy*-5,6-*dihydroxy*-5,6-*isopropylidene*-4-*oxohex*-2-*enoyl Chloride* **9**.—The lactone **8** [14] (396 mg, 1 mmol) treated according to the above general procedure gave the title acid halide **9** as a gum (314 mg, 73%); R_f 0.56 (H/A 4:1) (Found: C, 64.45, H, 5.3, Cl, 8.15; $C_{23}H_{23}ClO_6$ requires C, 64.09; H, 5.38, Cl, 8.23%); ν/cm^{-1} 1790, 1685 (C=O); δ_H(400 MHz) *Z*-isomer, 1.34 (3 H, s, Me), 1.39 (3 H, s, Me), 4.2 (1 H, dd, $J_{5,6'}$ 7, $J_{6,6'}$ 9, 6'-H), 4.3 (1 H, dd, $J_{5,6}$ 5.5, 6-H) and 4.43 (1 H, dd, 5-H); *E*-isomer, 1.28 (3 H, s, Me), 3.90 (1 H, dd, $J_{5,6'}$ 7, $J_{6,6'}$ 9, 6'-H), 4.1 (1 H, dd, $J_{5,6}$ 5.5, 6-H) and 4.5 (1 H, dd, 5-H); *both isomers*, 5.03–5.27 (4 H, m, CH_2Ph) and 7.2–7.4 (10 H, m, Ar); δ_C(100.5 MHz) *Z*-isomer 25.30 (Me), 25.75 (Me), 65.13 (C-6), 74.07 (CH_2Ph), 74.38 (CH_2Ph), 74.75 (C-5), 94.33 (C-4), 112.0 (CMe_2), 121.77 (C-3), 127.86, 128.71, 128.82, 129.28, 135.35, 135.74 (Ar), 156.33 (C-2) and 165.61 (C-1), *m/z* 430 (M^+), 415, 338, 324, 309, 247, 233, 218, 181, 149, 125 and 91.

Methyl 2,3-*Dibenzyloxy*-(5R)-5,6-*dihydroxy*-5,6-O-*isopropylidene*-4-*oxohex*-2-*enoate* **10**.—Compound **9** (50 mg, 0.12 mmol) in MeOH (5 cm^3) was treated as described above for the formation of **7** to give **10** as a gum (45 mg, 95%); R_f 0.66 (H/A 3:1) (Found: C, 67.8, H, 6.3. $C_{24}H_{26}O_7$ requires C, 67.57; H, 6.14%); ν/cm^{-1} 1770 and 1685 (C=O); δ_H(400 MHz) *Z*-isomer, 1.35 (3 H, s, Me), 1.40 (3 H, s, Me), 3.06 (3 H, s, OMe), 3.88 (1 H, dd, $J_{5,6'}$ 7.5, $J_{6,6'}$ 9, 6'-H), 4.08 (1 H, dd, $J_{5,6}$ 5, 6-H) and 4.28 (1 H, dd, 5-H); *E*-isomer, 1.32 (3 H, s, Me), 1.37 (3 H, s, CH_3), 3.10 (3 H, s, OMe), 4.06 (1 H, dd, $J_{5,6'}$ 7.5, $J_{6,6'}$ 9, 6'-H), 4.14 (1 H, dd, $J_{5,6}$ 5, 6-H) and 4.22 (1 H, dd, 5-H); *both isomers*, 5.14–5.32 (4 H, m, CH_2Ph) and 7.2–7.4 (10 H, m, Ar).

(5R)-2,3-*Dibenzyloxy*-5,6-*dihydroxy*-5,6-O-*isopropylidene*-4-*oxohex*-2-*enoic Acid* **11**.—Compound **9** (100 mg, 23 mmol) was dissolved in acetone (8 cm^3) and aqueous sodium hydroxide (2 mol dm^{-3}; 0.5 cm^3) was added. After being stirred for 4 h at room temperature, the mixture was acidified with hydrochloric acid (3 mol dm^{-3}) and extracted with CH_2Cl_2 (3 × 40 cm^3). The organic layer was washed with water until neutral, dried ($MgSO_4$) and evaporated to afford crude acid **11**, which was purified by column chromatography (H/A 3:1) to give pure **11** as a gum (48 mg, 51%); R_f 0.47 (H/A 2:1) (Found: C, 67.3, H, 5.9. $C_{23}H_{24}O_7$ requires C, 66.96; H, 5.86%); ν/cm^{-1} 3400 (OH), 1775 and 1690 (C=O); δ_H(400 MHz) *Z*-isomer, 1.36, (3 H, s, Me), 1.43, (3 H, s, Me), 4.03 (1 H, dd, $J_{5,6'}$ 7, $J_{6,6'}$ 9, 6'-H), 4.13 (1 H, dd, $J_{6,5}$ 6, 6-H) and 4.22 (1 H, dd, 5-H); *E*-isomer, 1.32, (3 H, s, Me), 1.45, (3 H, s, Me), 3.73 (1 H, dd, $J_{5,6'}$ 7, $J_{6,6'}$ 9, 6'-H), 3.81 (1 H, dd, $J_{6,5}$ 6, 6-H) and 4.32 (1 H, dd, 5-H); *both isomers*, 5.07–5.23 (4 H, m, CH_2Ph) and 7.2–7.4 (10 H, m, Ar).

N-*Benzyl*-2,3-*dibenzyloxy*-(5R)-5,6-*dihydroxy*-5,6-O-*isopropylidene*-4-*oxohex*-2-*enamide* **12**.—To a solution of compound **9** (80 mg, 0.19 mmol) in CH_2Cl_2 (6 cm^3) was added, at 0 °C, benzylamine (107 mg, 1 mmol) and the mixture was allowed to warm to room temperature when it was stirred for 24 h. The mixture was then diluted with CH_2Cl_2, washed with water, dried ($MgSO_4$) and evaporated. Purification of the residue by column chromatography (H/A 3:1) gave pure amide **12** as a gum (54 mg, 84%); R_f 0.25 (H/A 3:1) (Found: C, 71.85, H, 6.2, N, 2.9. $C_{30}H_{31}NO_6$ requires C, 71.84; H, 6.23, N, 2.79%); ν/cm^{-1} 1715 and 1670 (C=O); δ_H(400 MHz) *Z*-isomer, 1.20 (3 H, s, Me), 1.30 (3 H, s, Me), 3.01 (1 H, m, NH), 3.74 (1 H, dd, $J_{5,6'}$ 7, $J_{6,6'}$ 9, 6'-H), 3.91 (1 H, dd, $J_{6,5}$ 6, 6-H) and 4.31 (1 H, dd, 5-H); *E*-isomer, 1.18, (3 H, s, Me), 1.28 (3 H, s, Me), 3.61 (1 H, dd, $J_{5,6'}$ 7, $J_{6,6'}$ 9, 6'-H), 3.78 (1 H, dd, $J_{6,5}$ 6, 6-H) and 4.31 (1 H, dd, 5-H); *both isomers*, 4.55 (1 H, d, *J* 16, NCH_2Ph), 4.73 (1 H, d, NCH_2Ph), 5.10–5.28 (4 H, m, CH_2Ph) and 7.0–7.6 (15 H, m, Ar).

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Paper 2/00925K
Received 21*st February* 1992
Accepted 9*th March* 1992