Carbohydrate Research, 216 (1991) 197 209
Elsevier Science Publishers B.V., Amsterdam

The allylation of dibutylstannylene derivatives of *myo*-inositol*,†

Trupti Desai, Jill Gigg, Roy Gigg‡, Sheila Payne, Soledad Penades**, and Henry J. Rogers

Laboratory of Lipid and General Chemistry, National Institute for Medical Research, Mill Hill, London NW7 1AA (Great Britain)

(Received December 4th, 1990; accepted for publication January 26th, 1991)

ABSTRACT

Reaction of *myo*-inositol or a mixture of racemic 1,4-, 1,6-, and 4,5-di-*O*-allyl-*myo*-inositol in acetonitrile with dibutyltin oxide and allyl bromide in the presence of tetrabutylammonium bromide gave, as the major products, a readily separable mixture of 1,3,4,6- and 1,3,4,5-tetra-*O*-allyl-*myo*-inositol together with small proportions of penta-*O*-allyl-*myo*-inositols and 1,3,5-tri-*O*-allyl-*myo*-inositol (from *myo*-inositol). Parallel results were obtained when crotyl bromide was used. When 3 equiv. of dibutyltin oxide were used with *myo*-inositol or 1 equiv. with the mixture of di-*O*-allyl derivatives, 1,3,4-tri-*O*-allyl-*myo*-inositol was the major product. When 2 equiv. of dibutyltin oxide were used, *myo*-inositol gave a complex mixture of mono-, di-, and tri-*O*-allyl derivatives which was fractionated after conversion into the *O*-isopropylidene derivatives. Racemic 1,3,4,5-tetra-*O*-allyl-*myo*-inositol was resolved *via* the (−)-ω-camphanates.

INTRODUCTION

The inositol phosphates and phosphatidylinositol phosphates of the phosphatidylinositol cycle are the subject of intensive study[4] and this has encouraged a considerable effort in organochemical synthesis[5]. We now describe new methods for the preparation of intermediates required for the synthesis of many of these inositol phosphates and phosphatidylinositol phosphates.

RESULTS AND DISCUSSION

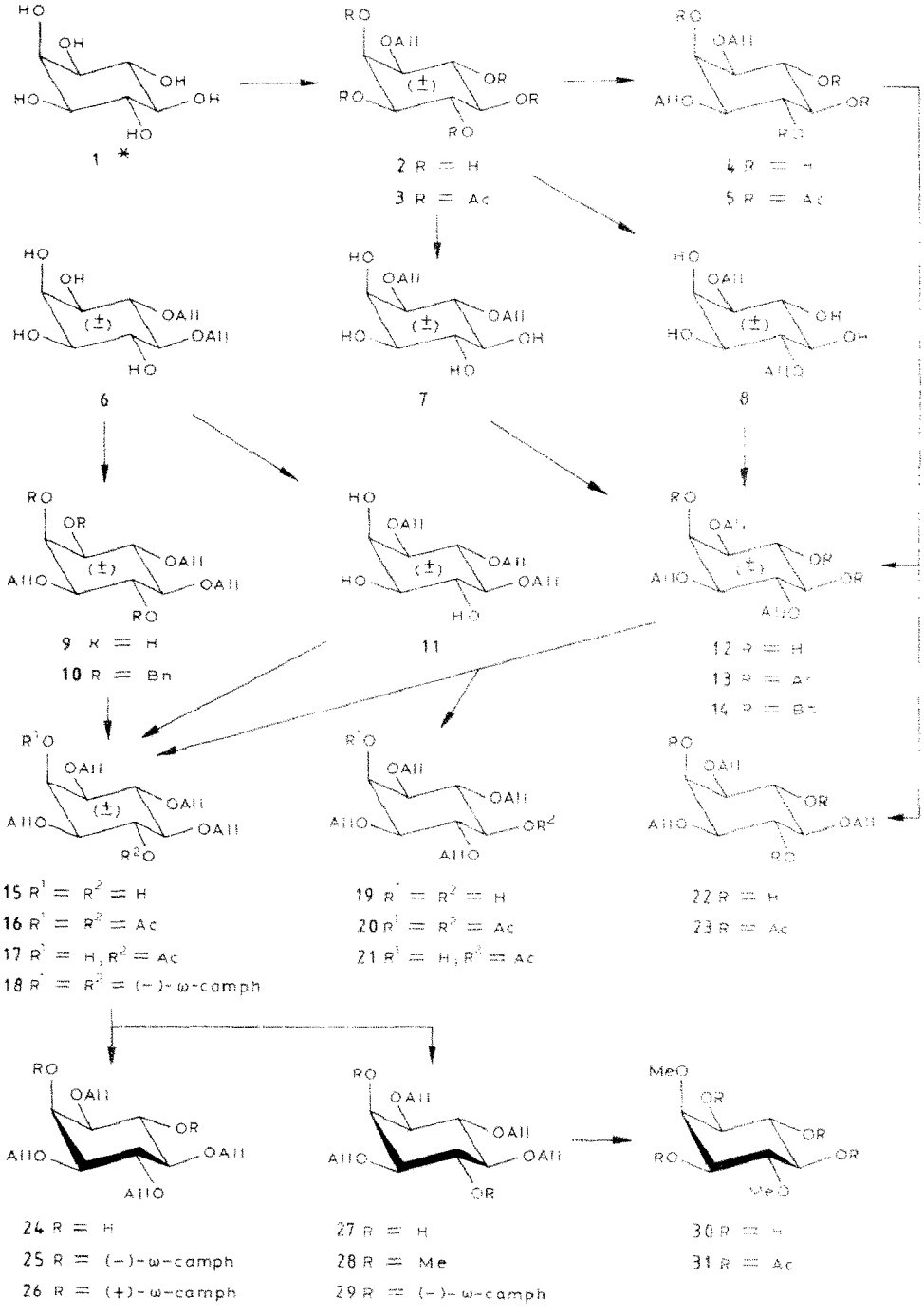
Alkylation of the dibutylstannylene derivative of a vicinal *cis*-diol in 6-membered cyclic derivatives usually results in preferential reaction of the equatorial hydroxyl group[6]. Therefore, it was anticipated that tin-mediated allylation of *myo*-inositol (**1**)

* Dedicated to Professor Grant Buchanan on the occasion of his 65th birthday.

† The Allyl Group for Protection in Carbohydrate Chemistry, Part 23. Presented in part at the XVth International Carbohydrate Symposium, Yokohama, Japan, August 12–17, 1990, and at the 200th National Meeting of the American Chemical Society, Washington DC, U.S.A., August 26–31, 1990. For Part 22, see ref. 1. This work forms part of a thesis[2] and a patent application[3].

‡ To whom correspondence should be addressed.

** Visiting scientist from the Instituto de Quimica Organica General, C.S.I.C., Madrid, Spain.



* In the formulae, racemic inositol derivatives are indicated with (±) in the ring; chiral inositol derivatives, represented in their correct absolute configurations, are shown with thickened lines in the ring, and *meso*-compounds are shown with neither of these modifications.

would proceed through the 1-*O*-allyl derivative **2** to the 1,3-di-*O*-allyl derivative **4** and thence to 1,3,4- (**12**) and 1,3,5-tri-*O*-allyl (**22**) derivatives. Further reaction should convert **12** into the 1,3,4,6- (**19**) and the 1,3,4,5-tetra-*O*-allyl (**15**) derivatives, whereas **22**, which contains no vicinal diol system, should not further react.

myo-Inositol is not readily soluble in organic solvents and the initial stages of this reaction were difficult to follow, so that a crystalline mixture of 4,5- (**6**), 1,6- (**7**), and 1,4-di-*O*-allyl (**8**) derivatives was used. This mixture was obtained readily *via* allylation of the mixture of 1,2:3,4-, 1,2:5,6-, and 1,2:4,5-di-*O*-isopropylidene-*myo*-inositol formed on treatment of *myo*-inositol with 2,2-dimethoxypropane and an acid catalyst in *N,N*-dimethylformamide[7], followed by hydrolysis in aqueous acetic acid. Compounds **6**–**8** have been characterised individually[8]. The 1,4-di-*O*-allyl derivative **8** was much less polar than the other two isomers and was readily isolated by chromatography.

The tin-mediated allylation of the mixture **6**–**8** was expected to be simple and could not yield the symmetrical 1,3,5-tri-*O*-allyl-*myo*-inositol (**22**). Thus, **7** and **8** should yield **12**, whereas **6** should give initially **9** and **11**, and then the 1,3,4,5-tetra-*O*-allyl derivative **15**, whereas **12** should give **15** and the 1,3,4,6-tetra-*O*-allyl derivative **19**.

The tin-mediated allylation of **6**–**8** was carried out as a one-pot reaction using excess of dibutyltin oxide in the presence of tetrabutylammonium bromide[6] in refluxing acetonitrile (see Experimental). The two major products were isolated by chromatography and characterised as the crystalline acetates. ^{1}H-N.m.r. spectroscopy of the acetates indicated that the less polar major product was **19** and that the more polar major product was **15**, which was confirmed by the conversion of **15** into the known[1] chiral 2,4-dimethyl ether **30**.

Under similar reaction conditions for 24 h, *myo*-inositol gave **15** and **19** together with small proportions of penta-*O*-allyl derivatives and the 1,3,5-tri-*O*-allyl derivative **22**. When crotyl bromide was used in place of allyl bromide in the reaction with *myo*-inositol, related products (containing crotyl groups) were obtained.

Reaction with the mixture **6**–**8**, in the presence of 1 equiv. of dibutyltin oxide, gave the 1,3,4-tri-*O*-allyl derivative **12** as the major product which gave a crystalline acetate (**13**). The structure of **12** was confirmed by conversion, *via* the benzyl ether **14**, into known[9] 2,4,5-tri-*O*-benzyl-*myo*-inositol. The ratios of the di-*O*-isopropylidene derivatives in the mixture from which **6**–**8** were prepared was[8] ~1:2:2 and the ratios for **6**–**8** should be similar. Since both **7** and **8** are expected to give **12** in this reaction, theoretically, **12** should represent ~80% of the tri-*O*-allyl derivatives present. Also, since **9** and **11**, both derived from **6**, each contain a vicinal *cis*-diol, they should be more rapidly converted into the tetra-*O*-allyl derivative **15** than **12** (containing a vicinal *trans*-diol) is converted into the mixture of **15** and **19**.

When *myo*-inositol was allylated in the presence of 3 equiv. of dibutyltin oxide, the 1,3,4-tri-*O*-allyl derivative **12** was the major product together with a small proportion of the 1,3,5-tri-*O*-allyl derivative **22**. Small proportions of the tetra-*O*-allyl derivatives **15** and **19** were also formed and a further minor product was identified as 1,2,3,4-tetra-*O*-allyl-*myo*-inositol. The last compound was the source of two of the penta-*O*-allyl derivatives when the allylation was performed in the presence of an excess

of dibutyltin oxide. Treatment of **12** with potassium *tert*-butoxide in methyl sulphoxide and acetylation of the product gave crystalline 2,5,6-tri-*O*-acetyl-1,3,4-tri-*O*-(prop-1-enyl)-*myo*-inositol.

When a crude preparation of **6** was allylated in the presence of 1 equiv. of dibutyltin oxide, a mixture of tri-*O*-allyl derivatives was obtained from which **9** was isolated by chromatography and characterised by conversion into known[8] 1,4,5-tri-*O*-allyl-2,3,6-tri-*O*-benzyl-*myo*-inositol (**10**). In the presence of 2 equiv. of dibutyltin oxide, allylation of **6** gave mainly the 1,2,3,5-tetra-*O*-allyl derivative **15**, as expected.

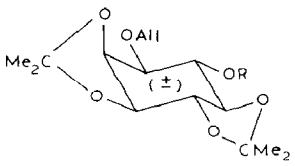
When *myo*-inositol was allylated in the presence of 2 equiv. of dibutyltin oxide, a complex mixture of water-soluble mono-, di-, and tri-*O*-allyl derivatives was obtained, which was fractionated by chromatography after conversion into the *O*-isopropylidene derivatives. Thus, the 1-*O*-allyl-2,3:4,5-di-*O*-isopropylidene (**32**), 1-*O*-allyl-2,3:5,6-di-*O*-isopropylidene[9] (**34**), 3,4-di-*O*-allyl-1,2:5,6-di-*O*-isopropylidene[9] (**33**), and 1,3,4-tri-*O*-allyl-5,6-*O*-isopropylidene (**36**) derivatives were isolated each in ~15% yield. The major product (~25%) was the 1,3-di-*O*-allyl-5,6-*O*-isopropylidene derivative **37**, which is a useful intermediate. Minor products were identified as the 1,4-di-*O*-allyl-2,3:5,6-di-*O*-isopropylidene[9] (**35**, ~8%), 1,3,5-tri-*O*-allyl (**22**, ~5%), and 1,5-di-*O*-allyl-2,3-*O*-isopropylidene (**38**, ~2%) derivatives. The isolation of the di-*O*-allyl derivatives **33** and **35** indicates that the allylation of *myo*-inositol under these conditions is not as simple as might be expected and that 1-*O*-allyl-*myo*-inositol (**2**) can be converted *via* **4**, **7**, and **8** into further products.

The 1,3,4,5-tetra-allyl ether **15** was resolved as the (−)-*o*-camphanates **18**, to give the pure chiral (−)-*o*-camphanate **29** by crystallisation, and this was hydrolysed to the chiral diol **27** which was converted *via* the methyl ether **28** into D-2,4-di-*O*-methyl-*myo*-inositol (**30**) and its known[1] acetate **31**, thus establishing the absolute configuration of **29**. The pure (−)-*o*-camphanate **25** was obtained by chromatography after removal of **29**. As (+)-*o*-camphanic acid is now available commercially, the pure (+)-*o*-camphanate (**26**) (the enantiomer of **29**) should also become available by crystallisation.

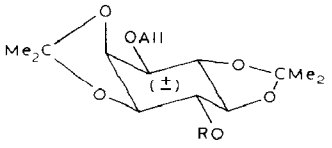
EXPERIMENTAL

General. — The general methods were as described[1].

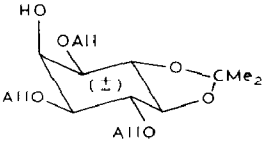
*Preparation of the mixture of the di-O-allyl-*myo*-inositols* **6**–**8**. — A mixture of the *O*-isopropylidene derivatives of *myo*-inositol was prepared by treatment[7] of *myo*-inositol with 2,2-dimethoxypropane and toluene-*p*-sulphonic acid in *N*,*N*-dimethylformamide. An excess of triethylamine was added to neutralise the acid. Toluene was then added and the solvents (methanol, 2,2-dimethoxypropane, and toluene) were evaporated under reduced pressure at 50°. A solution of the mixture[7] of 1,2-*O*-isopropylidene and the three di-*O*-isopropylidene derivatives in *N*,*N*-dimethylformamide was treated with an excess of allyl bromide and sodium hydride, and the mixture was processed in the usual way[1]. Water was then added, and the products were extracted with ether and heated in acetic acid–water (4:1) at 100° for 1 h to remove the *O*-isopropylidene groups. The solvents were evaporated to give a partially crystalline residue that contained **6**–**8**



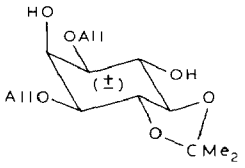
32 R = H
33 R = All



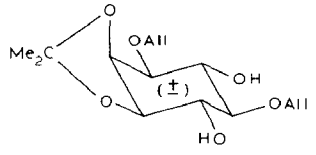
34 R = H
35 R = All



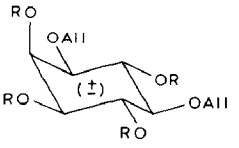
36



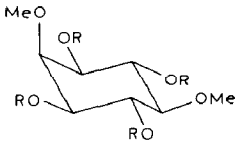
37



38

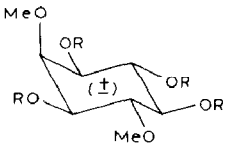


39 R = H
40 R = Ac



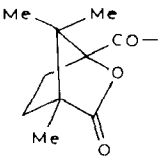
41 R = All
42 R = H
43 R = Ac

All = $-CH_2-CH=CH_2$

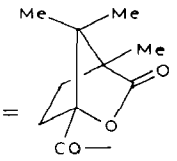


44 R = All
45 R = H
46 R = Ac

(−)-ω-camph =



(+)-ω-camph =



together with some of the 1,4,5,6-tetra-*O*-allyl derivative derived from 1,2-*O*-isopropylidene-*myo*-inositol.

The tetra-*O*-allyl derivative was extracted by trituration with light petroleum. T.l.c. (ethyl acetate–methanol, 8:1) of the crystalline residue revealed two spots (R_F 0.4 and 0.6). An authentic sample[8] of the 1,4-di-*O*-allyl derivative **8** had R_F 0.6, whereas **6** and **7**[8] each had R_F 0.4. Chromatography of the mixture **6**–**8** on silica gel, using the above solvent system, gave **8** identical with the material described[8].

1,5-Di-O-*acetyl-1,3,4,6-tetra*-O-*allyl*- (**20**), (±)-*2,6-di*-O-*acetyl-1,3,4,5-tetra*-O-*allyl*- (**16**), *and 1,3,5-tri*-O-*allyl*-myo-*inositol* (**22**). (*a*) A mixture of **6**–**8** (11.2 g, 43

mmol), dibutyltin oxide (21.4 g, 86 mmol), tetrabutylammonium bromide (27.7 g, 86 mmol), allyl bromide (84 mL, 970 mmol), and acetonitrile (500 mL) was heated under reflux with a Soxhlet apparatus that contained molecular sieve 3Å (20 g) for 20 h. The solvents were evaporated and the residue was partitioned between ether and water (200 mL of each). The ether layer was stirred with saturated aqueous sodium hydrogen carbonate (200 mL) for 1 h, filtered through Celite, dried (K_2CO_3), and concentrated. T.l.c. (ether–light petroleum, 4:1) of the residue (14 g) revealed a minor (R_f 0.9) and two major products (R_f 0.75 and 0.55). Column chromatography on silica gel in the same solvent system gave the minor (R_f 0.9, 1.5 g) and the major (R_f 0.75, 3.2 g) products, a mixed fraction (1.6 g) of the major products, and the other major product (R_f 0.55, 4.5 g). The pure major products were each acetylated with pyridine–acetic anhydride at 50° for 6 h and the products were crystallised from light petroleum. The diacetate from the product with R_f 0.75 had m.p. 73–74°. ^{1}H-N.m.r. data: δ 2.09, 2.13 (2 s, 2 Ac), 3.34 (dd, *J* 2.44 and 9.77 Hz, H-1,3), 3.60 (t, *J* 9.77 Hz, H-4,6), 4.96 (t, *J* 9.16 Hz, H-5), indicating from the symmetry that it was **20** (Found: C, 62.60; H, 7.67. $C_{20}H_{32}O_8$ calc.: C, 62.25; H, 7.60%).

The diacetate from the product with R_f 0.5 had m.p. 88–89°. ^{1}H-N.m.r. data: δ 2.07, 2.12 (2 s, 2 Ac), 3.15–3.36 (m, H-1,3,5), 3.68 (t, *J* 9.8 Hz, H-4), 5.63 (t, *J* 3.1 Hz, H-2) (Found: C, 62.44; H, 7.62%), indicating that it was **16** as established by the experiments described below.

The ^{1}H-n.m.r. spectrum of the acetate derived from the fraction with R_f 0.9 indicated that it was a mixture of penta-*O*-allyl-*myo*-inositols, which was not further investigated.

The symmetrical 1,3,4,6-tetra-*O*-allyl derivative **19** (obtained by saponification of **20**) was acetylated with pyridine–acetic anhydride at 20° for 12 h. T.l.c. (ether–light petroleum, 2:1) revealed conversion into a small proportion of **20** (R_f 0.8) and a major product (R_f 0.5). The latter product was isolated by chromatography on silica gel to give 5-*O*-acetyl-1,3,4,6-tetra-*O*-allyl-*myo*-inositol (**21**), m.p. 103–105° (from light petroleum). ^{1}H-N.m.r. data: δ 2.08 (s, Ac), 2.43 (s, OH), 3.29 (dd, *J* 2.5 and 9.7 Hz, H-1,3), 3.72 (t, *J* 9.5 Hz, H-4,6), 4.92 (t, *J* 9.77 Hz, H-5) (Found: C, 61.37; H, 8.08. $C_{20}H_{30}O_7 \cdot 0.5H_2O$ calc.: C, 61.36; H, 7.98%).

In the same way, the diol **15** (obtained by saponification of **16**) was converted into 6-*O*-acetyl-1,3,4,5-tetra-*O*-allyl-*myo*-inositol (**17**), m.p. 70–72°. ^{1}H-N.m.r. data: δ 2.08 (s, Ac), 2.43 (s, OH), 3.11–3.33 (m, 3 H, H-1,3,5), 3.81 (t, *J* 9.4 Hz, H-4) (Found: C, 62.4; H, 8.1. $C_{20}H_{30}O_7$ calc.: C, 62.8; H, 7.9%).

(*b*) A mixture of *myo*-inositol (7.2 g, 40 mmol), dibutyltin oxide (50 g, 200 mmol), tetrabutylammonium bromide (65 g, 200 mmol), allyl bromide (56 mL, 647 mmol), and acetonitrile (500 mL) was heated under reflux with a Soxhlet apparatus that contained molecular sieve 3Å (30 g) for 24 h. T.l.c., as in (*a*), showed the same three products (R_f 0.9, 0.75, and 0.55) together with a further minor product (R_f 0.35). The solvents were evaporated and the crude product was treated with ether–water as in (*a*). The ether layer was treated as in (*a*) to give a penta-*O*-allyl fraction (R_f 0.9, 747 mg), the 1,3,4,6-tetra-*O*-allyl derivative **19** (R_f 0.75, 3.4 g), and the 1,3,5,6-tetra-*O*-allyl derivative **15** (R_f 0.55, 3.6

g). Compounds **19** and **15** were converted into the crystalline diacetates **20** and **16**, respectively, identical with those described in (*a*).

The aqueous layer from this reaction was concentrated and a mixture of ethanol and toluene was evaporated from the residue to remove the last traces of water. The residue was then stirred with ether (200 mL) for 6 h, the crystalline material was collected, and the filtrate was concentrated. Column chromatography (ethyl acetate) of the residue on silica gel gave the minor product 1,3,5-tri-*O*-allyl-*myo*-inositol (**22**, R_F 0.35, 500 mg), m.p. 68–69.5° (from ethyl acetate–light petroleum, 2:5) (Found: C, 60.17; H, 8.09. $C_{15}H_{24}O_6$ calc.: C, 59.98; H, 8.06%), which gave the 2,4,6-triacetate **23**, m.p. 124–125° (from ethyl acetate–light petroleum, 1:5). The ^{1}H-n.m.r. data [δ 2.07 (6 H) and 2.15 (3 H) (2 s, 3 Ac), 3.36 (dd, *J* 2.45 and 10.37 Hz, H-1,3), 3.53 (t, *J* 9.16 Hz, H-5), 5.69 (t, *J* 2.44 Hz, H-2)] confirmed the symmetrical structure (Found: C, 59.57; H, 7.15. $C_{21}H_{30}O_9$ calc.: C, 59.14; H, 7.09%).

Reaction of myo-*inositol with crotyl bromide.* — A tin-mediated alkylation of *myo*-inositol as in (*b*) above, but using crotyl bromide, gave the following products.

1,3,4,6-Tetra-*O*-(but-2-enyl)-*myo*-inositol, m.p. 50–52° (Found: C, 66.65; H, 9.14. $C_{22}H_{36}O_6$ calc.: C, 66.64; H, 9.15%), which gave a syrupy 2,5-diacetate. ^{1}H-N.m.r. data: δ 1.66, 1.71 (2 s, 4 CH=CH*Me*), 2.10, 2.13 (2 s, 2 Ac), 3.29 (dd, *J* 2.5 and 9.8 Hz, H-1,3), 3.55 (t, *J* 9.5 Hz, H-4,6), 4.90 (t, *J* 9.15 Hz, H-5).

(±)-2,6-Di-*O*-acetyl-1,3,4,5-tetra-*O*-(but-2-enyl)-*myo*-inositol, m.p. 76–78°. ^{1}H-N.m.r. data: δ 1.67, 1.72 (2 s, 4 CH=CH*Me*), 2.08, 2.10 (2 s, 2 Ac), 3.12–3.33 (m, 3 H, H-1,3,5), 3.63 (t, *J* 9.15 Hz, H-4), 5.21 (t, *J* 10 Hz, H-6) (Found: C, 65.06; H, 8.38. $C_{26}H_{40}O_8$ calc.: C, 64.98; H, 8.39%).

6-*O*-Acetyl-1,3,4,5-tetra-*O*-(but-2-enyl)-*myo*-inositol, m.p. 91–93°. ^{1}H-N.m.r. data: δ 1.67, 1.72 (2 s, 4 CH=CH*Me*), 2.08 (s, Ac), 2.41 (s, OH), 3.07–3.28 (m, 3 H, H-1,3,5), 3.75 (t, *J* 9.4 Hz, H-4), 5.29 (t, *J* 9.7 Hz, H-6) (Found: C, 65.40; H, 8.86. $C_{24}H_{38}O_7$ calc.: C, 65.73; H, 8.73%).

2,4,6-Tri-*O*-acetyl-1,3,5-tri-*O*-(but-2-enyl)-*myo*-inositol, m.p. 72–75°. ^{1}H-N.m.r. data: δ 1.62 (6 H) and 1.67 (3 H) (2 s, 3 CH=CH*Me*), 2.08 (6 H), 2.14 (3 H) (2 s, 3 Ac), 3.27–3.52 (m, H-1,3,5), 5.30 (t, *J* 9.77 Hz, H-4,6) (Found: C, 61.45; H, 7.50. $C_{24}H_{36}O_9$ calc.: C, 61.52; H, 7.75%).

*2,5-Di-*O*-methyl-*myo*-inositol* (**42**). — The diacetate **20** was hydrolysed with sodium hydroxide in methanol, and the resulting diol **19** was treated[1] with sodium hydride and methyl iodide in *N,N*-dimethylformamide to give the di-*O*-methyl derivative **41**. A mixture of **41** (500 mg), Pd/C (10%, Fluka, 600 mg), and toluene-*p*-sulphonic acid (50 mg) was heated under reflux in ethanol–water (19:1, 10 mL) for 24 h. T.l.c. (chloroform–methanol, 3:1) then revealed a product with R_F 0.5. After filtration, the solvents were evaporated to give **42**, m.p. 270–272° (from ethanol) (Found: C, 46.29; H, 7.87. $C_8H_{16}O_6$ calc.: C, 46.15; H, 7.75%), which gave the 1,3,4,6-tetra-acetate **43**, m.p. 148–150° (from methanol–water, 1:1). ^{1}H-N.m.r. data: δ 2.06 (s, 4 Ac), 3.39, 3.51 (2 s, 2 OMe), 3.80 (t, *J* 2.44 Hz, H-2), 4.88 (dd, *J* 2.44 and 10.38 Hz, H-1,3), 5.51 (t, *J* 10.1 Hz, H-4,6) (Found: C, 51.36; H, 6.48. $C_{16}H_{24}O_{10}$ calc.: C, 51.06; H, 6.43%).

(±)-*2,4-Di-*O*-methyl-*myo*-inositol* (**45**). — The tetra-*O*-allyl derivative **15** was

converted into **45** (*via* **44** as described above for **42**), m.p. 193–194° (from ethanol) (Found: C, 46.09; H, 7.73. $C_8H_{16}O_6$ calc.: C, 46.15; H, 7.75%), which gave the 1,3,5,6-tetra-acetate **46**, m.p. 176–178° (from ethyl acetate–light petroleum, 1:2) (Found: C, 50.79; H, 6.52. $C_{16}H_{24}O_{10}$ calc.: C, 51.06; H, 6.43%). The ^{1}H-n.m.r. spectrum of **46** was identical with that[1] for D-1,3,5,6-tetra-*O*-acetyl-2,4-di-*O*-methyl-*myo*-inositol (**31**).

(±)-*1,3,4-Tri*-O-*allyl*-myo-*inositol* (**12**). — (*a*) A mixture of 1,4-di-*O*-allyl-*myo*-inositol[8] (**8**; 5 g, 19.2 mmol), dibutyltin oxide (5 g, 20.1 mmol), tetrabutylammonium bromide (6.5 g, 20.2 mmol), and toluene (120 mL) was heated under reflux with removal of water in a Dean and Stark apparatus for 2 h. Allyl bromide (7 mL, 81 mmol) was added and the solution was heated under reflux conventionally for 2 h. Ether (120 mL) was added to the clear cooled solution, and the mixture was stirred for 30 min, filtered, and extracted with water (2 × 100 mL). The combined aqueous extract was concentrated to dryness and ethanol–toluene was evaporated from the residue to remove the last traces of water. Column chromatography (ethyl acetate) of the residue on silica gel gave the major product (3.3 g, R_t 0.5 in ethyl acetate), which was acetylated with acetic anhydride–pyridine to give the racemic 2,5,6-triacetate **13**, m.p. 135–137° (from light petroleum). ^{1}H-N.m.r. data: δ 2.03, 2.05, 2.15 (3 s, 3 Ac), 3.31–3.48 (m, 2 H, H-1,3), 3.70 (t, J 9.15 Hz, H-4), 5.67 (t, J 3.0 Hz, H-2) (Found: C, 59.11; H, 7.32. $C_{21}H_{30}O_9$ calc.: C, 59.14; H, 7.09%).

Compound **13** was saponified with sodium hydroxide in methanol at reflux for 30 min. Solid carbon dioxide was added, the solution was concentrated to dryness, and the residue was extracted with dichloromethane to give syrupy **12** (Found: C, 60.22; H, 7.83. $C_{15}H_{24}O_6$ calc.: C, 59.98; H, 8.06%).

Treatment[1] of **12** with benzyl bromide and sodium hydride in *N,N*-dimethylformamide and deallylation[9] of the product with Pd/C gave 2,4,5-tri-*O*-benzyl-*myo*-inositol identical with the material described[9], thus establishing the structure of the triol **12**.

(*b*) A mixture of **6**–**8** (20 g, 76.8 mmol), dibutyltin oxide (20 g, 80.3 mmol), tetrabutylammonium bromide (26 g, 80.6 mmol), and allyl bromide (50 mL, 578 mmol) in acetonitrile (500 mL) was heated under reflux for 12 h with removal of water by molecular sieve 3Å (30 g) in a Soxhlet apparatus. T.l.c. (ethyl acetate) then revealed tri- (R_t 0.5, major product), tetra- (R_t 0.85), and di-*O*-allyl (R_t 0.1) derivatives. The solvents were evaporated, the residue was partitioned between ether and water (200 mL each), the ether layer which contained the tetra-*O*-allyl derivatives and small proportions of tri- and penta-*O*-allyl derivatives was discarded, and the aqueous layer was concentrated. Toluene and ethanol were evaporated from the residue, ether (200 mL) was added, the crystals which separated after stirring for 3 h were discarded, and the ether solution was concentrated. Column chromatography (ethyl acetate) of the residue on silica gel gave the tri-*O*-allyl fraction (7 g), which was acetylated, and the product was recrystallised to give **13** (6.5 g) identical with the material in (*a*).

(*c*) *myo*-Inositol (16.2 g, 90 mmol), dibutyltin oxide (68.4 g, 274 mmol), tetrabutylammonium bromide (28.8 g, 89.3 mmol), allyl bromide (60 mL, 690 mmol), and acetonitrile (300 mL) were heated under reflux with molecular sieve 3Å (40 g) in a

Soxhlet apparatus for 17 h. T.l.c. (ether) then revealed small proportions of penta- (R_F 1.0) and tetra-*O*-allyl (R_F 0.9 and 0.8) derivatives, a major product (R_F 0.25 that co-migrated with **12**), together with two other minor products (R_F 0.35 which co-migrated with **22**, and R_F 0.5). The solvents were evaporated and the residue was partitioned between water (400 mL) and ether (200 mL). T.l.c. (ether) of the ether layer (after removing tin derivatives with sodium hydrogen carbonate as described above) revealed the penta- (**15**) and tetra-*O*-allyl (**19**) derivatives together with a minor product (R_F 0.5). The minor product (650 mg), isolated by column chromatography (ether) on silica gel, had m.p. 115–117° (from light petroleum) and was 1,2,3,4-tetra-*O*-allyl-*myo*-inositol (Found: C, 63.55; H, 8.47. $C_{18}H_{28}O_6$ calc.: C, 63.51; H, 8.29%). The diacetate had m.p. 100–101° (from light petroleum). ^{1}H-N.m.r. data: δ 2.01, 2.03 (2 s, 2 Ac), 3.24 (dd, *J* 2.44 and 9.7 Hz, H-1 or 3), 3.29 (dd, *J* 2.44 and 9.8 Hz, H-1 or 3), 3.83 (t, *J* 9.1 Hz, H-4), 4.93 (t, *J* 9.4 Hz, H-5) (Found: C, 62.08; H, 7.76. $C_{22}H_{32}O_8$ calc.: C, 62.25; H, 7.60%), which indicated the compound to be 5,6-di-*O*-acetyl-1,2,3,4-tetra-*O*-allyl-*myo*-inositol. This inference was confirmed by allylation of **36**, with subsequent deacetonation and acetylation to give a product having the same m.p. and ^{1}H-n.m.r. spectrum as the above diacetate.

The aqueous layer was concentrated and toluene and ethanol were evaporated from the residue. T.l.c. (ethyl acetate) revealed a major tri-*O*-allyl derivative (R_F 0.5) and a small proportion of the 1,3,5-tri-*O*-allyl derivative (R_F 0.6). This fraction was treated with 2,2-dimethoxypropane (50 mL), acetone (50 mL), and toluene-*p*-sulphonic acid (500 mg) at 20° for 5 h. Triethylamine (1 mL) was added, the solvents were evaporated, the residue was partitioned between ether and water (100 mL of each), and the ether layer was separated and dried (K_2CO_3). T.l.c. (ether–light petroleum, 3:1) revealed minor products [R_F 0.9 and 0.85, which co-migrated with 1,6-di-*O*-allyl-2,3:4,5-di-*O*-isopropylidene-*myo*-inositol[8] (**33**) and 1,4-di-*O*-allyl-2,3:5,6-di-*O*-isopropylidene-*myo*-inositol[8] (**35**), respectively] and minor products (R_F 0.3 and 0.4, which co-migrated with the 1-*O*-allyl-di-*O*-isopropylidene-*myo*-inositols; see below). The major product (R_F 0.75) was 1,3,4-tri-*O*-allyl-5,6-*O*-isopropylidene-*myo*-inositol (**36**, see below).

The ether layer was concentrated, the residue was treated with acetic acid–water (4:1) at 100° for 1 h, and the solvents were evaporated. T.l.c. (ethyl acetate–methanol, 8:1) of the residue revealed a major product (R_F 0.8) with small proportions of di- (R_F 0.4) and mono-*O*-allyl (R_F 0.1) derivatives. Column chromatography on silica gel, in the same solvent, gave the tri-*O*-allyl fraction (12 g) which was acetylated to give **13** (10 g) identical with the material described in (*a*).

1,3,4-Tri-O-*allyl-5,6*-O-*isopropylidene*-myo-*inositol* (**36**). — Compound **12** was treated with 2,2-dimethoxypropane in acetone that contained toluene-*p*-sulphonic acid. T.l.c. (ether–light petroleum, 3:1) revealed almost complete conversion of **12** (R_F 0) into a product with R_F 0.75. Column chromatography on silica gel in this solvent system gave **36** as a syrup (Found: C, 63.45; H, 8.18. $C_{18}H_{28}O_6$ calc.: C, 63.51; H, 8.29%).

2,5,6-Tri-O-*acetyl-1,3,4-tri*-O-*(prop-1-enyl)*-myo-*inositol*. — A solution of **12** (370 mg) and potassium *tert*-butoxide (3 g) in dry methyl sulphoxide (20 mL) was kept at 50° for 6 h with exclusion of moisture and carbon dioxide. Saturated aqueous potassium

chloride (20 mL) was added to the cooled solution which was extracted with ether (3 × 100 mL). The extract was dried (K_2CO_3) and concentrated, and the residue was acetylated with acetic anhydride–pyridine at 50° for 4 h. The cooled solution was diluted with ice–water to give the title compound (360 mg), m.p. 113–115° (from light petroleum containing a little pyridine) (Found: C, 59.42; H, 7.15. $C_{21}H_{30}O_{11}$ calc.: C, 59.14; H, 7.09%).

(±)-*1,4,5-Tri*-O-*allyl*-myo-*inositol* (**9**). — A crude preparation[8] of 5,6-di-*O*-allyl-1,2:3,4-di-*O*-isopropylidene-*myo*-inositol that contained (t.l.c.[5]) ~ 10% of 3,4-di-*O*-allyl-1,2:5,6-di-*O*-isopropylidene-*myo*-inositol was hydrolysed with acetic acid–water (4:1) at 100° for 1 h to give crude diallyl ether **6**. This product was treated with 1 equiv. of dibutyltin oxide and an excess of allyl bromide as described above in the preparation of **12** [method (*b*)]. A portion of the solution was processed as described for the preparation of **12**. T.l.c. (ethyl acetate–methanol, 8:1) revealed two major products (R_f 0.6 and 0.75) in the aqueous phase that were isolated by column chromatography on silica gel in the same solvent mixture. The product with R_f 0.75 was **9**, m.p. 131–132° (from ethyl acetate–light petroleum) (Found: C, 60.34; H, 8.15. $C_{15}H_{24}O_6$ calc.: C, 59.98; H, 8.06%). The 2,3,6-triacetate had m.p. 90–92° (from light petroleum). ^{1}H-N.m.r. data: δ 2.04, 2.09, 2.13 (3 s, 3 Ac), 3.31 (t, *J* 9.2 Hz, H-5), 3.40 (dd, *J* 3.1 and 9.1 Hz, H-1), 3.77 (t, *J* 9.1 Hz, H-4), 4.80 (dd, *J* 3.1 and 9.0 Hz, H-3), 5.58 (t, *J* 2.7 Hz, H-2) (Found: C, 59.31; H, 7.22. $C_{21}H_{30}O_9$ calc.: C, 59.14; H, 7.09%).

Treatment of the product with R_f 0.75 with benzyl bromide and sodium hydride in *N,N*-dimethylformamide in the usual way gave a product with a ^{1}H-n.m.r. spectrum identical with that of 1,4,5-tri-*O*-allyl-2,3,6-tri-*O*-benzyl-*myo*-inositol[9], thus establishing the structure of **9**.

The product with R_f 0.6 was not further investigated but was assumed to be 1,5,6-tri-*O*-allyl-*myo*-inositol (**11**).

The remainder of the reaction mixture was treated with an excess of dibutyltin oxide until reaction was complete. T.l.c. then revealed the major ether-soluble product to be **15** with only a small proportion of **19**, presumably formed from the small amount of **7** in the starting material.

Allylation of myo-*inositol in the presence of 2 equiv. of dibutyltin oxide.* — A mixture of *myo*-inositol (5.4 g, 30 mmol), dibutyltin oxide (15 g, 60 mmol), tetrabutylammonium bromide (19.3 g, 60 mmol), allyl bromide (30 mL, 346 mmol), and acetonitrile (300 mL) was heated under reflux with molecular sieve 3Å (20 g) in a Soxhlet apparatus for 12 h. The solution was concentrated, toluene was evaporated from the residue which was then partitioned between ether (200 mL) and water (100 mL), and the ether layer was washed with ether (100 mL). The product (600 mg) in the ether layer was isolated as described above and shown by t.l.c. to comprise mainly **15** and **19**.

The combined aqueous layers were washed with ether (30 mL) and concentrated, and toluene and ethanol were evaporated from the residue. The residue was stirred with acetone (40 mL), 2,2-dimethoxypropane (100 mL), and toluene-*p*-sulphonic acid (1 g) for 12 h. Triethylamine (2 mL) and sodium hydrogen carbonate (2 g) were added, the solvents were evaporated, and toluene was evaporated from the residue which was

stirred with ether (300 mL) for 12 h. The crystalline precipitate was discarded and the filtrate was concentrated to give an oil (8.2 g). T.l.c. (ether–light petroleum, 3:1) revealed seven major products (R_F 0.9, 0.85, 0.8, 0.5, 0.4, 0.25, 0.1) which were isolated by column chromatography on silica gel in the same solvent followed by ethyl acetate to remove the product R_F 0.1.

The syrupy product with R_F 0.9 (1.1 g) was identical with 1,6-di-*O*-allyl-2,3:4,5-di-*O*-isopropylidene-*myo*-inositol[8] (**33**). The product with R_F 0.85 (500 mg), m.p. 85–87°, was identical with 1,4-di-*O*-allyl-2,3:5,6-di-*O*-isopropylidene-*myo*-inositol[9] (**35**), and the syrupy product with R_F 0.8 (1 g) was identical with 1,3,4-tri-*O*-allyl-5,6-*O*-isopropylidene-*myo*-inositol (**36**, see above). The product with R_F 0.5 (1.3 g) had m.p. 118–119° (from light petroleum that contained triethylamine) (Found: C, 60.33; H, 8.50. $C_{15}H_{24}O_6$ calc.: C, 59.98; H, 8.06%) and gave a crystalline acetate m.p. 95–97° (from light petroleum) (Found: C, 59.80; H, 7.79. $C_{17}H_{26}O_7$ calc.: C, 59.63; H, 7.66%), which indicated that the parent compound (R_F 0.5) was a mono-*O*-allyl-di-*O*-isopropylidene-*myo*-inositol. Hydrolysis of this compound with acetic acid–water (4:1) at 100° for 1 h and acetylation of the product gave 1,2,4,5,6-penta-*O*-acetyl-3-*O*-allyl-*myo*-inositol, m.p. 133–135° (from ethanol), identical with the material prepared by hydrolysis and acetylation of 1-*O*-allyl-2,3:5,6-di-*O*-isopropylidene-*myo*-inositol[9] (**34**). ^{1}H-N.m.r. data: δ 2.00 (9 H), 2.04 (3 H), and 2.19 (3 H) (3 s, 5 Ac), 3.58 (dd, J 3.05 and 9.7 Hz, H-1), 4.95 (dd, J 2.7 and 10.5 Hz, H-3), 5.30 (t, J 2.5 Hz, H-2) (Found: C, 53.24; H, 6.22. $C_{19}H_{26}O_{11}$ calc.: C, 53.02; H, 6.09). Thus, the product with R_F 0.5 was 1-*O*-allyl-2,3:4,5-di-*O*-isopropylidene-*myo*-inositol (**32**).

The product with R_F 0.4 (800 mg) had m.p. 129–131° (from light petroleum with a little triethylamine) and gave an acetate with m.p. 154–156° (from light petroleum). These were identical with 1-*O*-allyl-2,3:5,6-di-*O*-isopropylidene-*myo*-inositol (**34**) and its 4-acetate[9].

The major product with R_F 0.25 (1.6 g) was a syrup, which was hydrolysed with acetic acid–water (4:1) at 100° for 1 h, and the solvents were evaporated. T.l.c. (ethyl acetate–methanol, 8:1) of the residue revealed major (R_F 0.5) and minor (R_F 0.6) products. Recrystallisation from ethyl acetate gave 1,3-di-*O*-allyl-*myo*-inositol (**4**; R_F 0.5; 1.3 g), m.p. 119–121° (Found: C, 55.44; H, 7.72. $C_{12}H_{20}O_6$ calc.: C, 55.37; H, 7.75%), which gave a 2,4,5,6-tetra-acetate (**5**), m.p. 141–143°. ^{1}H-N.m.r. data: δ 2.00 (3 H), 2.03 (6 H), and 2.17 (3 H) (3 s, 4 Ac), 3.46 (dd, 2 H, J 2.7 and 9.16 Hz, H-1,3) (Found: C, 56.21; H, 6.55. $C_{20}H_{28}O_{10}$ calc.: C, 56.07; H, 6.59%).

The minor product (R_F 0.6) was isolated (100 mg) by column chromatography of the contents of the mother liquors and gave a crystalline tetra-acetate, m.p. 142–144°. ^{1}H-N.m.r. data: δ 2.00, 2.05, 2.09, 2.17 (4 s, 4 Ac), 3.46 (t, J 9.5 Hz, H-5), 3.46 (dd, J 3.05 and 10.4 Hz, H-1), 4.88 (dd, J 3.0 and 10.5 Hz, H-3), which COSY experiments (200 MHz) showed to be 2,3,4,6-tetra-*O*-acetyl-1,5-di-*O*-allyl-*myo*-inositol (**40**) (Found: C, 56.15; H, 6.62. $C_{20}H_{28}O_{10}$ calc.: C, 56.07; H, 6.59%).

The 1,5-di-*O*-allyl-*myo*-inositol gave a crystalline isopropylidene derivative (**38**), m.p. 90–92° (from light petroleum) (Found: C, 59.72; H, 7.98. $C_{15}H_{24}O_6$ calc.: C, 59.98; H, 8.06%).

The product (R_f 0.1, 250 mg) from the original column was identical to 1,3,5-tri-*O*-allyl-*myo*-inositol (**22**) described above.

Bis-(−)-α-camphanates (**25** *and* **29**) *of 1,3,4,5-tetra-O-allyl*-myo-*inositol* (**15**). — A mixture of **15** (6 g, 17.6 mmol) and (−)-α-camphanic acid chloride (Fluka, 11.9 g, 55 mmol) in dry pyridine (50 mL) was kept at 20° for 20 h. T.l.c. (ether–light petroleum, 4:1) then revealed the conversion of **15** (R_f 0.55) into two products (R_f 0.65 and 0.70). Water (2 mL) was added to the mixture and, after 15 min, it was diluted with water (100 mL), and the products were extracted with ether. The extract was washed successively with saturated aqueous potassium chloride and saturated aqueous sodium hydrogen carbonate, and dried ($MgSO_4$). The crude product (12 g) [^{1}H-n.m.r. data: δ 0.97 (9 H), 1.01 (3 H), 1.04 (3 H), 1.08 (3 H), 1.11 (15 H), 1.19 (3 H) (6 s, 12 CMe of the camphanate portions)] was crystallised from ether–light petroleum (1:1) to give **29** (R_f 0.65, 4.6 g), m.p. 167–169°, $[\alpha]_D^{25}$ −1.3° (*c* 1, chloroform). ^{1}H-N.m.r. data: δ 0.97 (6 H), 1.08 (3 H), 1.12 (6 H), 1.17 (3 H) (4 s, 6 CMe) (Found: C, 65.39; H, 7.49. $C_{38}H_{52}O_{12}$ calc.: C, 65.12; H, 7.48%). The diastereoisomer **25** (4 g, R_f 0.7), obtained by column chromatography on silica gel (ether–light petroleum, 4:1) of the material in the mother liquors, had m.p. 116.5–119° (from ethyl acetate–light petroleum, 1:3). ^{1}H-N.m.r. data: δ 0.96 (3 H), 1.01 (3 H), 1.04 (3 H), 1.11 (9 H) (4 s, 6 CMe) (Found: C, 65.32; H, 7.63%).

The camphanate **29** was saponified with sodium hydroxide in methanol, and the resulting diol **27** was treated[1] with methyl iodide and sodium hydride in *N,N*-dimethylformamide to give the di-*O*-methyl derivative **28** as a syrup. Deallylation, as described above in the preparation of **42**, gave D-2,4-di-*O*-methyl-*myo*-inositol (**30**), m.p. 146–148°, $[\alpha]_D^{26}$ +3.2° (*c* 1, methanol), which gave a 1,3,5,6-tetra-acetate (**31**), m.p. 164–166°, $[\alpha]_D^{26}$ −6.5° (*c* 1, chloroform). Compounds **30** and **31** and the ^{1}H-n.m.r. spectrum of **31** were identical with those described[1] and established the absolute configurations of the camphanates **25** and **29**.

ACKNOWLEDGMENTS

We thank the Royal Society for a European Exchange Fellowship (to S. Penades), and Miss Sheila Lathwell for determination of the optical rotations.

REFERENCES

1 T. Desai, A. Fernandez-Mayoralas, J. Gigg, R. Gigg, and S. Payne, *Carbohydr. Res.*, 205 (1990) 105–123.
2 T. Desai, *The Chemistry of Inositol Compounds of Biological Interest*, M.Phil. Thesis, C.N.A.A., 1989.
3 R. H. Gigg, Int. Pat. Appl. No. WO 89/00156 (1989); *Chem. Abstr.*, 111 (1989) 174590t.
4 M. Whitman and L. Cantley, *Biochim. Biophys. Acta*, 948 (1988) 327–344; M. J. Berridge and R. F. Irvine, *Nature (London)*, 341 (1989) 197–205; S. R. Nahorski and B. V. L. Potter, *Trends Pharm. Sci.*, 10 (1989) 139–144; J. W. Putney, H. Takemura, A. R. Hughes, D. A. Hortsman, and U. Thastrup, *FASEB J.*, 3 (1989) 1897–1905; S. B. Shears, *Biochem. J.*, 260 (1989) 313–324; C. P. Downes, *Biochem. Soc. Trans.*, 17 (1989) 259–268; K. J. Catt and T. Balla, *Annu. Rev. Med.*, 40 (1989) 487–509; D.-M. Chuang, *Annu. Rev. Pharmacol. Toxicol.*, 29 (1989) 71–110; R. S. Rana and L. E. Hokin, *Physiol. Rev.*, 70 (1990) 115–164; A. P. Dawson, *Essays Biochem.*, 25 (1990) 1–37; C. P. Downes and C. H. Macphee, *Eur. J. Biochem.*, 193 (1990) 1–18; P. W. Majerus, T. S. Ross, T. W. Cunningham, K. K. Caldwell, A. B. Jefferson, and V. S. Bansal, *Cell*, 63 (1990) 459–465; R. H. Michell, H. Drummond, and C. P. Downes, *Inositol Lipids in Cell Signalling*, Academic Press, London, 1989.

5 D. C. Billington, *Chem. Soc. Rev.*, 18 (1989) 83–122; B. V. L. Potter, *Nat. Prod. Reports*, (1990) 1–24; S. Ozaki and Y. Watanabe, *J. Synth. Org. Chem. (Jpn.)*, 47 (1989) 363–373.
6 M. A. Nashed and L. Anderson, *Tetrahedron Lett.*, (1976) 3503–3506; S. David, A. Thieffrey, and A. Veyrières, *J. Chem. Soc., Perkin Trans 1*, (1981) 1796–1801; J. Alais, A. Maranduba, and A. Veyrières, *Tetrahedron Lett.*, 24 (1983) 2383–2386; S. David and S. Hanessian, *Tetrahedron*, 41 (1985) 643–663.
7 J. Gigg, R. Gigg, S. Payne, and R. Conant, *Carbohydr. Res.*, 142 (1985) 132–134.
8 J. Gigg, R. Gigg, S. Payne, and R. Conant, *J. Chem. Soc., Perkin Trans. 1*, (1987) 2411–2414; (1988) 981.
9 J. Gigg, R. Gigg, S. Payne, and R. Conant, *J. Chem. Soc., Perkin Trans. 1*, (1987) 423–429.
10 R. Boss and R. Scheffold, *Angew. Chem. Int. Ed. Engl.*, 15 (1976) 558–559.