Synthesis of Asymmetrically-substituted Cyclopentane Derivatives from Acyclic Sugars

By DEREK HORTON* and TOMOYA MACHINAMI
(*Department of Chemistry, The Ohio State University, Columbus, Ohio* 43210)

Summary Diels–Alder addition of cyclopentadiene and *trans*-α,β-unsaturated sugar derivatives proceeds with high steric control to afford crystalline, optically pure norbornene derivatives that may be transformed into tetra-*C*-substituted cyclopentane derivatives of defined stereochemistry at all four centres; the products are of interest in synthesis of prostaglandin analogues.

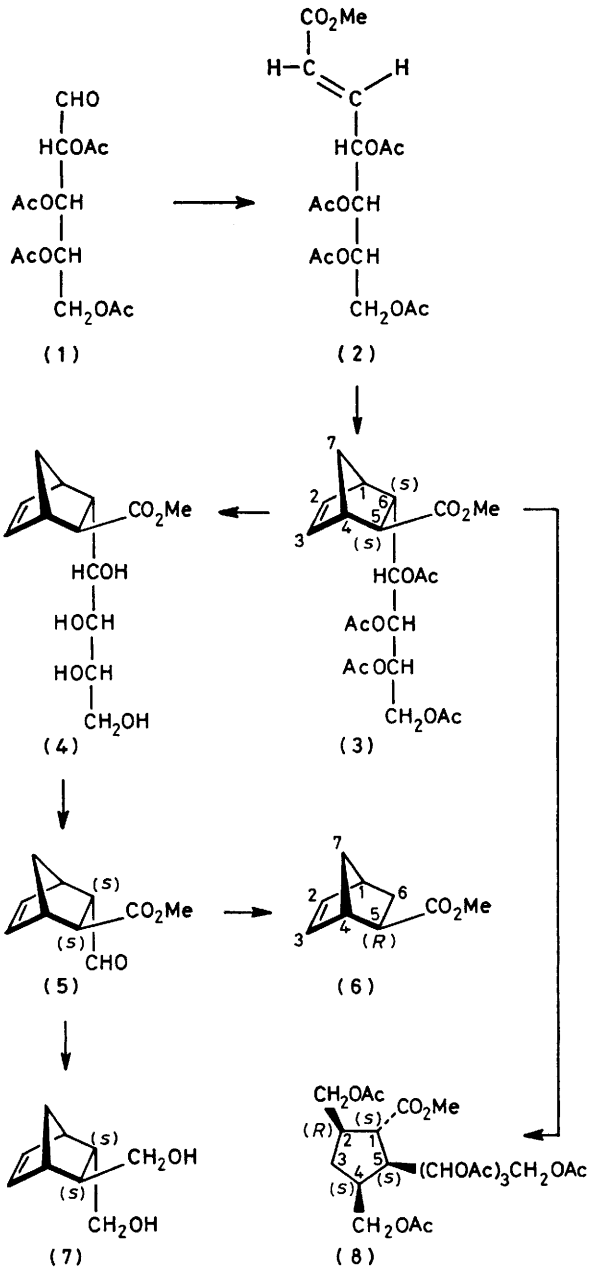
NUMEROUS synthetic routes exist[1] for the substituted cyclopentane nucleus of prostaglandins, although many of them require resolution of racemic products as well as separation of diastereomers, including those at the C-15 hydroxy-group position. Racemic 9,11-bis(hydroxymethyl) analogues of $PGF_{1\alpha}$ have been synthesized[2] and appear to exhibit biological activity.

We show here that addition of cyclopentadiene to a suitable, *trans*-unsaturated sugar derivative may be used to afford good yields of crystalline norbornene adducts under stereochemical control; as few as only one of four possible stereoisomeric products may result, indicating strong directive influence of the disymmetric dienophile. Oxidative cleavage of the double bond in the norbornene adducts leads to optically pure cyclopentane derivatives constituting the chiral core of 9,11-bishomoprostaglandins and their 9,11-epimers.

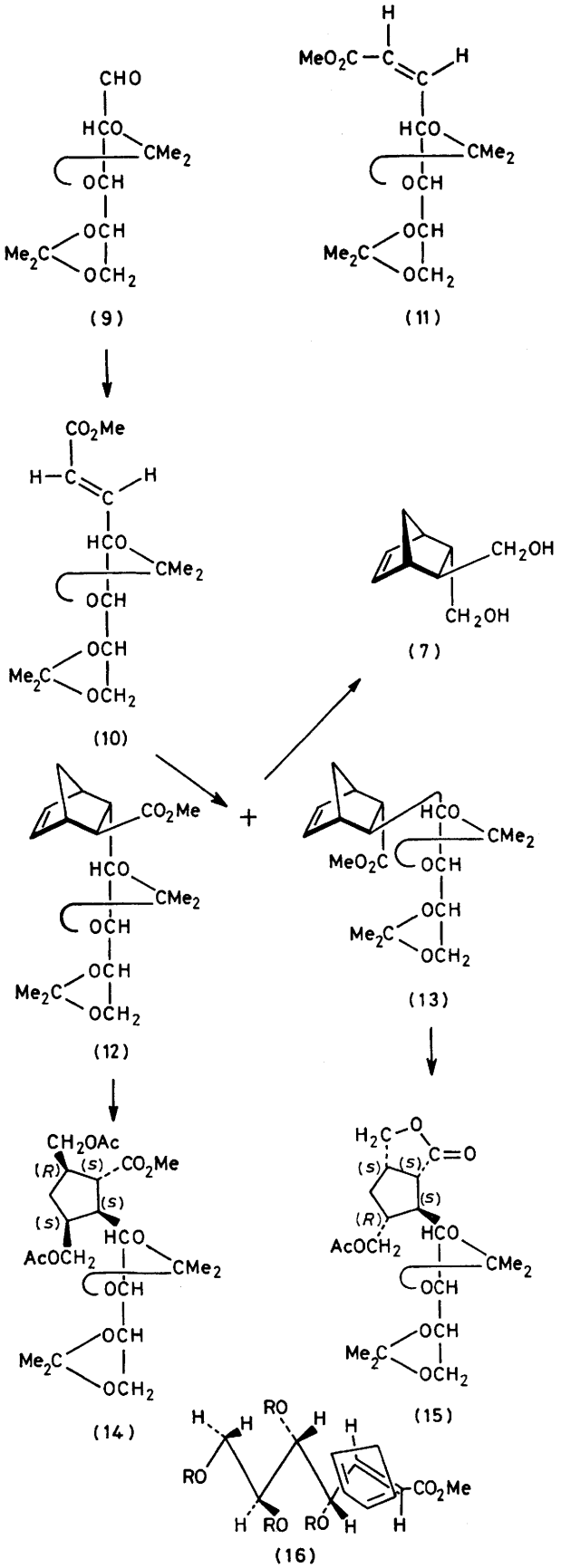
Wittig condensation of 2,3,4,5-tetra-*O*-acetyl-*aldehydo*-L-arabinose[3] (**1**) with Ph_3PCHCO_2Me in hot benzene gave methyl (*E*)-4,5,6,7-tetra-*O*-acetyl-L-*arabino*-hept-2-enonate (**2**) m.p. 117—118 °C, in 83% yield. The dienophile (**2**) and 3 equiv. of cyclopentadiene in toluene were boiled under reflux for 18 h to give 65% of a crystalline adduct (**3**), m.p. 95—97 °C, $[\alpha]_D$ +65° ($CHCl_3$) that was an optically pure, single product, one of the four stereoisomers possible, in principle, from the cycloaddition. Deacetylation of (**3**) with NaOMe–MeOH gave the crystalline tetrol (**4**), m.p. 157—159 °C, whose ^1H n.m.r. spectrum indicated the ester group to be *exo* and the C_4 side-chain to be *endo*. The absolute stereochemistry of (**3**) [and (**4**)] was determined by periodate oxidation of (**4**) to the *exo*-ester *endo*-aldehyde (**5**), which was decarbonylated with[4] $(Ph_3P)_3RhCl$ in PhCN to give the *exo*-norbornene ester (**6**) whose specific rotation (−10° in $CHCl_3$) was essentially identical with that reported[5] for methyl (*R*)-*exo*-2-norbornene-5-carboxylate ($[\alpha]_D$ −10·2°). This result establishes that (**3**) and (**4**) are the 5*S*, 6*S* stereoisomers. Reduction of aldehyde (**5**) with $LiAlH_4$ gave the optically pure, 5*S*, 6*S*-diol (**7**), $[\alpha]_D$ −21° ($CHCl_3$).

Oxidative[6] double-bond cleavage of (**3**) with OsO_4–$NaIO_4$ followed by reduction with $NaBH_4$ and subsequent acetylation gave 32% of the chiral, tetra-*C*-substituted cyclopentane derivative (**8**) having the 1*S*,2*R*,4*S*,5*S*-configuration of the ring substituents.

2,3:4,5-Di-*O*-isopropylidene-*aldehydo*-L-arabinose[7] (**9**) underwent Wittig reaction with Ph_3PCHCO_2Me in boiling benzene to give 60% of methyl (*E*)-4,5:6,7-di-*O*-isopropylidene-L-*arabino*-hept-2-enonate (**10**). At room temperature, a 2:1 mixture of (**10**) and its (*Z*)-isomer (**11**) was formed, and the (*E*):(*Z*) ratio became 2:3 when methanol was used as solvent. The alkene (**10**) reacted with cyclopentadiene under the conditions used for (**2**) and the crude product afforded 62% of a crystalline material, m.p. 81—85 °C, that was shown (n.m.r.) to be a 3:1 mixture of two stereo-



isomers (**12**) and (**13**) difficult to separate by chromatography. Acid-catalysed deacetonation of this mixture, followed by periodate oxidation and subsequent reduction with $LiAlH_4$, afforded (5*S*,6*S*)-5,6-di(hydroxymethyl)-2-norbornene {(**7**), $[\alpha]_D$ −23° in $CHCl_3$}, indistinguishable from a sample of (**7**) prepared from the adduct (**3**). Hydroxylation–oxidative glycol cleavage of the mixture of (**12**) and (**13**) as for (**3**) gave in 45% net yield a readily separable, 3:1 mixture of the syrupy ester derivative (**14**) ($[\alpha]_D$ +25° in $CHCl_3$), arising from (**12**) and the bicyclic lactone (**15**) (m.p. 78 °C, $[\alpha]_D$ −1·6° in $CHCl_3$) derived from (**13**). The correlation of (**12**) + (**13**) *via* the chiral diol (**7**) with (**3**) indicates that the crystalline cycloaddition products arise with essentially complete asymmetric induction from the precursor alkenes, attachment of the cyclopentane ring taking place, in each instance, from the side of the dieno-



phile [(**2**) or (**10**)] opposite the vicinal chiral centre (O-4 of the unsaturated sugar derivative). The crystalline product (**3**) is formed through attack from this face by the cyclopentadiene molecule in only one of its two possible orientations [see formula (**16**)]. Although the same orientation is favoured in the reaction with (**10**) and leads to (**12**), the opposite orientation of the carbocycle, still attacking the same face, leads to the minor component (**13**) of the crystalline product.

The results show how a carbohydrate precursor can serve as a useful template for the production of optically pure carbocycles having four stereochemically defined centres bearing carbon-chain substituents functionalized in a way that allows differential elaboration of these groups. The lactone (**15**) may be considered as the chiral nucleus, of the correct absolute and relative stereochemistry, of 9,11-bis-(hydroxymethyl)prostaglandin $PGF_{1\alpha}$; furthermore, the acetoxy-group at C-3 of the side-chain (corresponding to O-4 of the L-arabinose precursor) has the correct location and stereochemistry for O-15 of $PGF_{1\alpha}$.

(*Received*, 1*st October* 1980; *Com.* 1080.)

[1] A. Mitra, 'The Synthesis of Prostaglandins,' Wiley, New York, 1977.
[2] I. T. Harrison, R. Grayshan, T. Williams, A. Semenovski, and J. H. Fried, *Tetrahedron Lett.*, 1972, 5151.
[3] M. L. Wolfrom, D. I. Weisblat, W. H. Zophy, and S. W. Waisbrot, *J. Am. Chem. Soc.*, 1941, **63**, 201; H. Zinner, *Chem. Ber.*, 1951, **84**, 780.
[4] J. Tsuji and K. Ohno, *Synthesis*, 1969, **1**, 157.
[5] J. A. Berson and D. A. Ben-Efraim, *J. Am. Chem. Soc.*, 1959, **81**, 4083; O. Cervinka and O. Kříž, *Coll. Czech. Chem. Commun.*, 1968, **33**, 2342.
[6] R. Pappo, D. S. Allen, Jr., R. U. Lemieux, and W. S. Johnson, *J. Org. Chem.*, 1956, **21**, 478.
[7] J. English, Jr., and P. H. Griswold, *J. Am. Chem. Soc.*, 1945, **67**, 2039; H. Zinner, E. Wittenburg, and G. Rembarz, *Chem. Ber.*, 1959, **92**, 1614.