6-Diazopenicillanates. Part 1. Reactions with Furans

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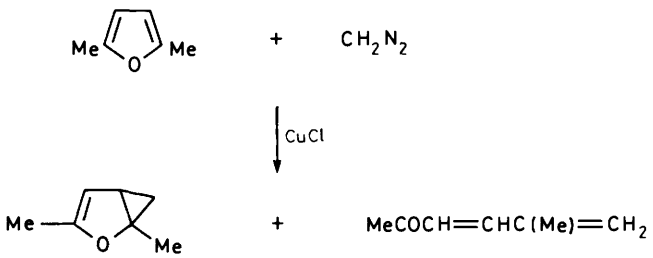
Benzhydryl, *p*-nitrobenzyl, and pivaloyloxymethyl esters of 6-diazopencillanic acid undergo rhodium-catalysed reactions with furan giving 6-(4'-oxobut-2-enylidene)penicillanates in high yields. Substitution on the furan ring results in a strong steric effect at the 2-position and reveals the detrimental effects of electron-withdrawing groups at positions 2 and 3. The absence of a marked steric effect in 3-methylfuran indicates that the reaction does not involve initial, direct cyclopropanation, contrary to earlier claims. Addition of the 6-diazopenicillanate to benzofuran provides the first reported example of a carbenoid ring expansion of the latter.

Diazomethane reacts with furan in the presence of CuBr to give 2-oxabicyclo[3.1.0]hex-3-ene.[1] A similar cyclopropanation of 2-methylfuran gave a 20% yield of the bicyclic product resulting from attack on the 2,3-bond and 30% from attack on the unsubstituted 4,5-bond.[2] In the case of 2,5-dimethylfuran, a mixture of the cyclopropane (**1**) and the dienone (**2**) was produced.[3] 2-t-Butylfuran afforded only the ring-opened product (**3**).



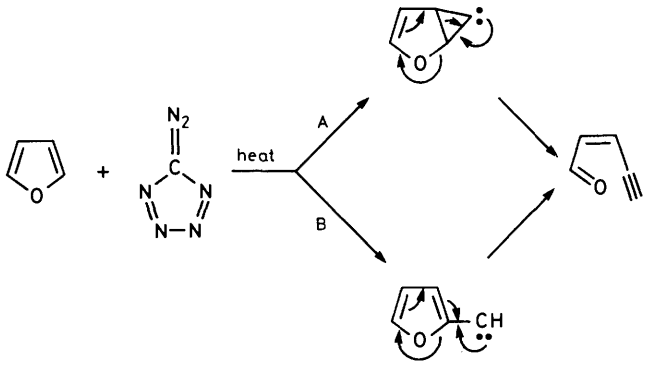
(**1**) (**2**)

$Bu^tCOCH=CHCH=CH_2$

(**3**)

Similar results have been noted in the metal-catalysed reactions of substituted diazo compounds with furan and its derivatives. Cyclopropanation and/or ring opening to diene-carbonyl derivatives is observed, and it has been shown that the cyclopropanes, when isolated, rearrange thermally at high temperatures to give diene-carbonyl derivatives. It has been assumed on this basis that cyclopropanes are always the initial products of the metal-catalysed reactions of diazo compounds with furans and that any ring opened products obtained are the result of further rearrangement.[4] In agreement with this general mechanism, a ^{13}C labelling study[5] of the reaction of 5-diazo-1,2,3,4-tetrazole with furan supported mechanism A (cyclopropanation) rather than mechanism B (C–H insertion) (Scheme 1), although furylcarbenes do undergo this type of rearrangement.[6]

We have reported[7] that the rhodium-catalysed reaction of benzhydryl 6-diazopenicillanate (**4a**) with furan leads to a very efficient ring-opening condensation furnishing isomeric dienals. These were transformed into new penicillin analogues by oxidation, hydrogenation, reduction with $NaBH_4$, and carbonyl group condensations with 2,4-dinitrophenylhydrazine and dimethyl malonate.[7,8] We now report further details of these reactions and a study of the scope of the reactions with substituted furans, leading to the proposal of a new mechanism for the ring opening process.



Scheme 1.

Results and Discussion

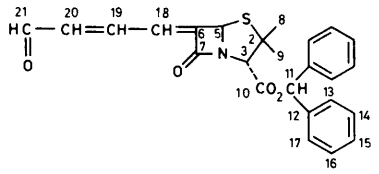
The dienals (**5a**) and (**5b**) were formed rapidly following addition of benzhydryl 6-diazopenicillanate (**4a**) to neat furan containing rhodium acetate. The two products were readily separated by h.p.l.c. or by t.l.c. on silica gel. On prolonged contact with silica, there was some tendency to rearrange to two further isomers (**5c**) and (**5d**) (Scheme 2). The rearrangement occurred very rapidly on contact with acids (*e.g.* trace of HCl) and also took place thermally and on treatment with aqueous sodium hydroxide.

The structures of the four isomers were assigned on the basis of their n.m.r. spectra (Table 1). The two initial products (**5a**) and (**5b**) having a *Z* double bond α,β to the aldehyde group show the aldehyde protons 21-H as low-field doublets which move upfield in the corresponding *E*-isomers (**5c**) and (**5d**). The stereochemistry of the α,β-bond follows from the observed coupling constants of *ca.* 11 Hz for the *Z*-isomers and *ca.* 15 Hz for the *E*-isomers. There is no coupling observable across the γ,δ-bond and the stereochemistry of the latter was deduced by application of the Tobey–Simon rules,[9] which predict the γ-proton to be *ca.* 0.3 p.p.m. to lower field when the γ,δ-bond is *Z* than when it is *E*. A similar downfield shift of the γ-carbon is also seen in the ^{13}C n.m.r. spectra of the dienals (Table 2).

The benzhydryl protecting group could be removed quantitatively from the esters (**5**) by the known method[10] of stirring the ester in trifluoroacetic acid and anisole at 0 °C for a few minutes, followed by quenching with aqueous sodium bicarbonate. However, extensive isomerisation about the side-chain double bonds occurs during this process. The mixture of acids obtained showed no significant antibacterial activity.

Since the trifluoroacetic acid–anisole method of deprotection resulted in loss of stereochemical integrity, and since the al-

Table 1. ^{1}H N.m.r. spectra of dienals (**5a**—**d**)

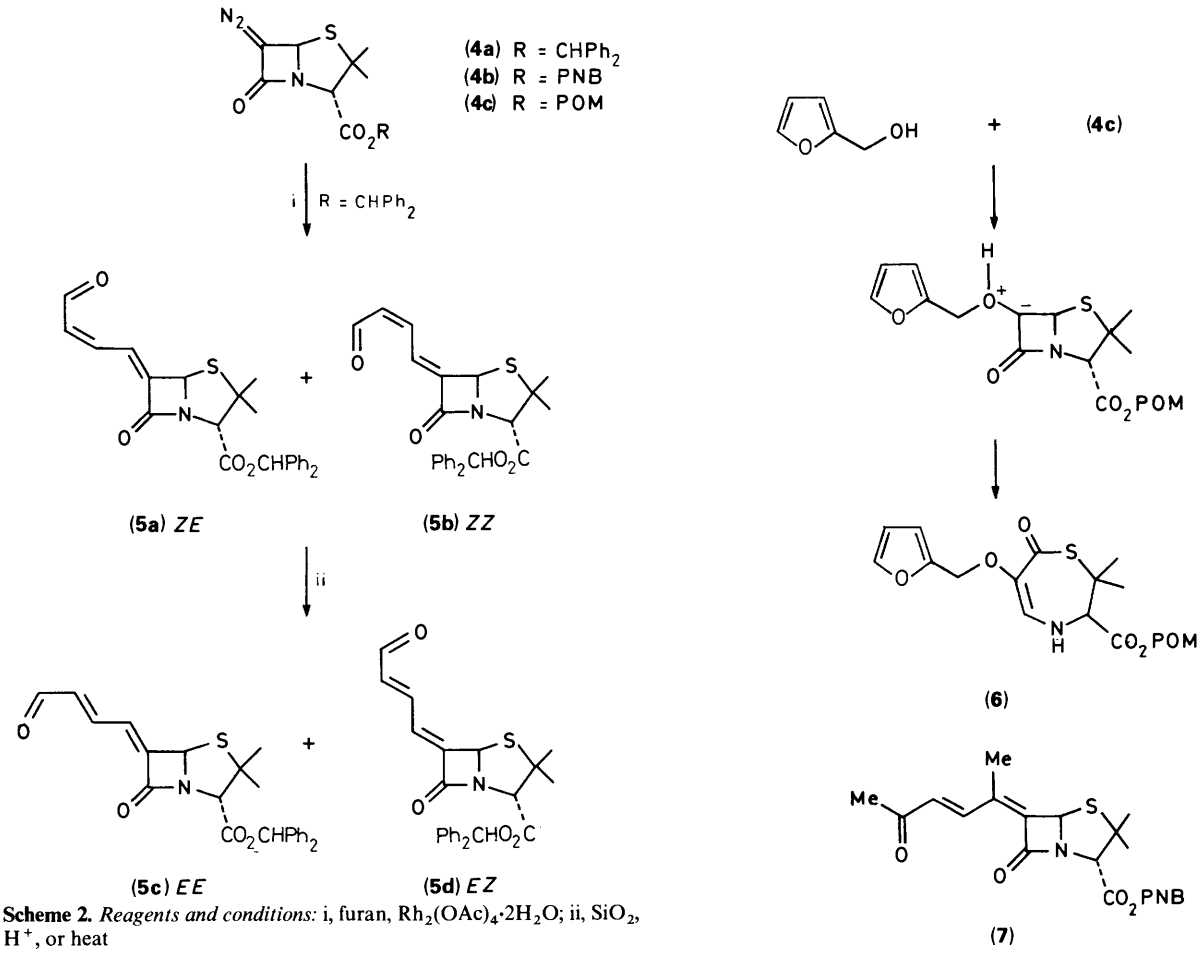


	Chemical shift δ [a]							
	3-H (s, 1 H)	5-H (s, 1 H)	18-H (d, 1 H)	19-H (dd, 1 H)	20-H (d, 1 H)	21-H (d, 1 H)	8-H (s, 3 H)	9-H (s, 3 H)
ZE-(**5a**)	4.70	5.83	7.28 (J 12.7 Hz)	7.62 ($J_{19,20}$ 11.2 Hz)	6.14 ($J_{20,21}$ 6.8 Hz)	10.16	1.59	1.30
ZZ-(**5b**)	4.70	5.96	7.58 (J 12.7 Hz)	6.84 ($J_{19,20}$ 10.7 Hz)	6.26 ($J_{20,21}$ 6.8 Hz)	10.24	1.60	1.34
EE-(**5c**)	4.70	5.84	6.51 (J 11.9 Hz)	7.80 ($J_{19,20}$ 15.9 Hz)	6.38 ($J_{20,21}$ 7.9 Hz)	9.68	1.60	1.34
EZ-(**5d**)	4.70	5.96	6.85 (J 10.4 Hz)	7.14 ($J_{19,20}$ 14.3 Hz)	6.42 ($J_{20,21}$ 7.9 Hz)	9.70	1.40	1.32

[a] Benzhydryl esters (**5**) also show signals at δ 7.0 (s, 1 H) and 7.4 (m, 10 H).

Table 2. ^{13}C N.m.r. spectra of dienals (**5a**—**d**)

Compound	C-2	C-3	C-5	C-6	C-7	C-8	C-9	C-10	C-11	C-12	C-13—C-17	C-18	C-19	C-20	C-21
ZE-(**5a**)	65.8	70.6	78.7	149.8	167.4	33.7	25.6	167.1	68.2	139.5	127—128	131.5	138.5	124.3	190.0
ZZ-(**5b**)	66.0	70.5	78.6	150.5	167.8	33.7	25.5	167.1	67.4	139.5	127—128	133.7	138.0	119.8	189.7
EE-(**5c**)	65.7	70.6	78.6	149.5	167.3	33.7	25.5	167.1	68.2	139.4	127—128	136.8	144.0	127—128	193.6
EZ-(**5d**)	66.0	70.5	78.6	150.5	167.3	33.7	25.5	167.1	67.6	139.4	127—128	138.2	142.6	123.8	192.8



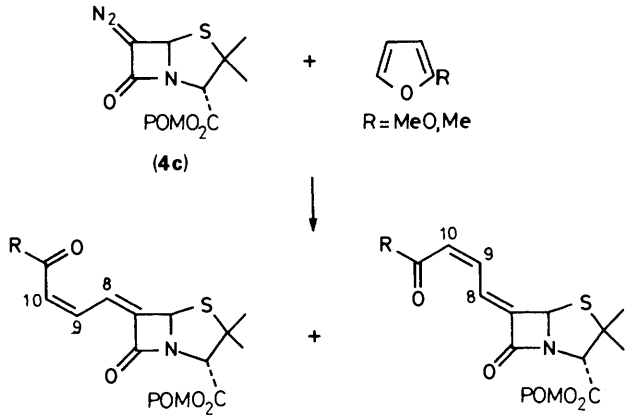
Scheme 2. *Reagents and conditions:* i, furan, $Rh_2(OAc)_4 \cdot 2H_2O$; ii, SiO_2, H^+, or heat

ternative deprotection procedure of hydrogenolysis resulted in side chain hydrogenation,[7] additional acid protecting functions were also adopted to provide flexibility in the subsequent studies. The *p*-nitrobenzyl (PNB) group is convenient,[11] being readily removed by treatment with sodium sulphide; the synthesis is cumbersome however, requiring protection of the 6-amino group by a trityl function before esterification and then detritylation prior to diazotization. We modified the literature method for diazotization,[12] replacing perchloric acid by tosic acid and thus achieving a 90% yield of the diazo ester (**4b**) in 8 min rather than 2 h. An attempt was also made to simplify the synthesis of the *p*-nitrobenzyl ester by using an analogous method to that which is successful for the benzylhydryl ester.[7] 6-Aminopenicillanic acid was treated directly with *p*-nitrophenyldiazomethane and the required *p*-nitrobenzyl 6-aminopenicillanate was thus obtained in one step, rather than three, but in a yield of only 8%.

The pivaloyloxymethyl (POM) group was also adopted, since it is introduced without the need for prior protection of the amino group and also offers the advantage of not requiring removal prior to bioassay of the penicillin derivative.[13] Both the PNB ester (**4b**) and the POM ester (**4c**) gave similar results to the benzhydryl ester (**4a**) in all the reactions studied. For example, the POM ester (**4c**) afforded high yields of the corresponding dienals on reaction with furan in the presence of rhodium acetate.

The scope of the condensation reaction of 6-diazopenicillanic esters with furan was further examined using substituted furans. Simple alcohols react with 6-diazopenicillanates to give a mixture of 6α-alkoxypenicillanate and alkoxythiazepine products, the latter arising by rearrangement of an intermediate oxonium ylide.[14] The product distribution was found to depend on alcohol structure, with methanol giving mainly 6α-methoxypenicillanate and benzyl alcohol giving virtually complete rearrangement to benzyloxy thiazepine. It was therefore of interest to examine the behaviour of furfuryl alcohol, in which competing attack on the ring and on the side chain hydroxy group might be expected. In practice, only a single product was isolated and proved to be the furfuryloxythiazepine (**6**). No products having an intact β-lactam ring could be detected. Thus, the side chain hydroxy group in furfuryl alcohol is evidently considerably more reactive than the ring in the rhodium-catalysed reaction with the diazo group, and the intermediate oxonium ylide follows the same pathway as that from benzyl alcohol in rearranging preferentially to the thiazepine.

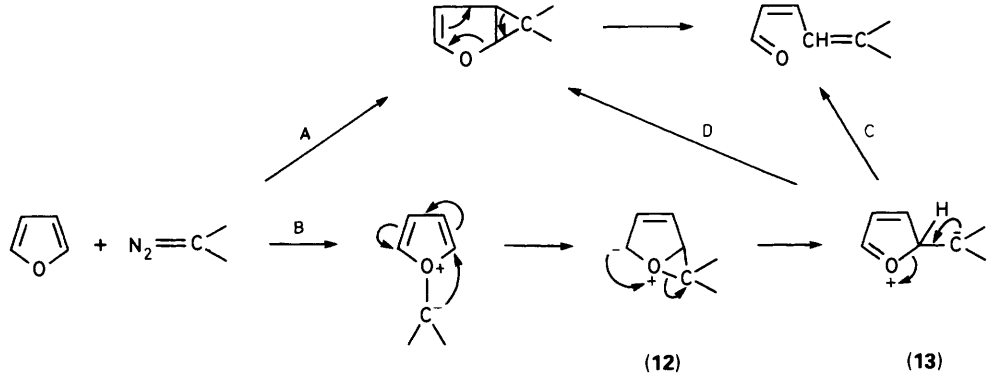
Diethyl furan-3,4-dicarboxylate failed to give any identifiable products on rhodium-catalysed reaction with the PNB ester (**4b**). Since ethyl 2-furoate similarly failed to give any product on reaction with the POM ester (**4c**), the negative result must be due to the deactivating influence of the ester group on the ring, as well as any steric effect. That a steric effect operates is revealed by the poor result with 2,5-dimethylfuran, which gave product (**7**) with the PNB ester (**4b**), isolated pure in a very low yield following preparative h.p.l.c. 2-Methylfuran and 2-methoxyfuran gave exclusively products (**8**) and (**9**), respectively, arising from attack on the unsubstituted side of the ring (Scheme 3).



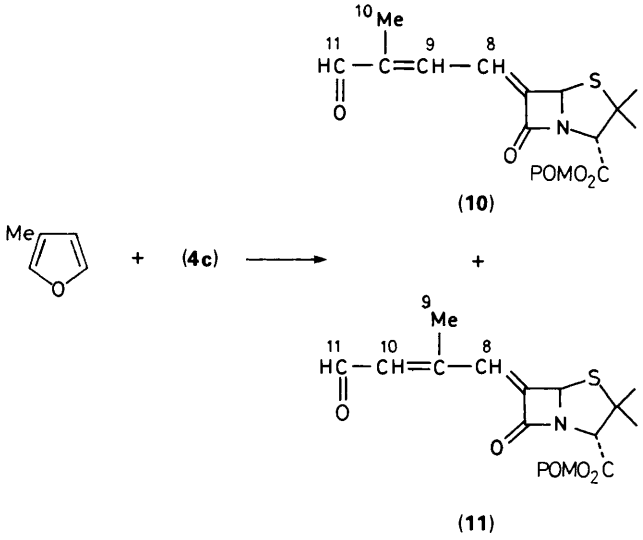
Scheme 3.

Following rhodium-catalysed reaction of the POM ester (**4c**) with 3-methylfuran, the mixture of products was partially separated by preparative t.l.c. into two fractions. In one of these, a single proton was visible in the aldehyde region of the ^{1}H n.m.r. spectrum as a singlet. This is consistent with the product (**10**) bearing the methyl α to the aldehyde group. The second chromatographic fraction showed two sets of aldehyde doublets, indicating a mixture of isomers (**11**) bearing methyls β to the aldehyde groups. Integration of the signals for the aldehyde proton singlet and two aldehyde doublets in the n.m.r. spectrum of the total, crude reaction product prior to chromatography showed that the α-methyl aldehyde and β-methyl aldehyde products were present in the ratio 60:40.

This result is striking in that it indicates only a very small steric effect of the 3-methyl group on the site of attack in 3-methylfuran, in contrast to the large effect of a 2-substituent, and forces a reconsideration of the accepted[4] mechanism. If the reaction involves first a direct cyclopropanation of a double bond in the furan ring, followed by ring opening (Scheme 4; route A) it is difficult to rationalize the difference in steric effects

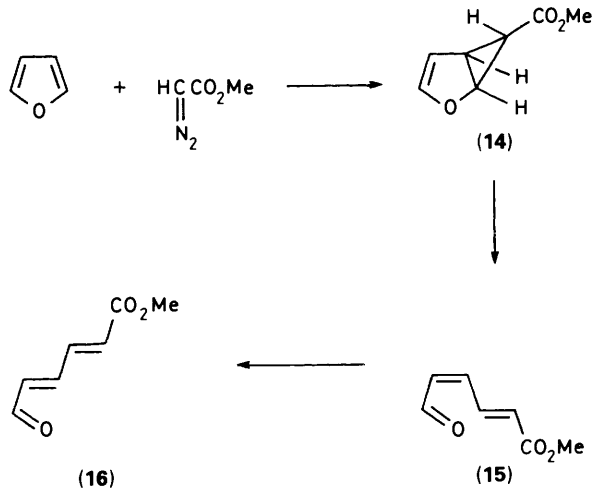


Scheme 4.

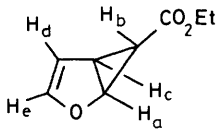


between a methyl group located at C-2 and at C-3. We therefore considered an alternative mechanism (Scheme 4; route B). Formation of an oxonium ylide[14] (analogous to that formed in the case of thiophene[15]) is followed by migration to the 2-position and the betaine (**13**) then collapses directly to the dienal by ring opening (route C) or indirectly *via* closure to a cyclopropane and rearrangement. Whilst, in principle, a direct electrophilic attack at the 2-position of the furan ring could occur, the absence of a major steric effect of the 3-methyl group appears to rule out this possibility.

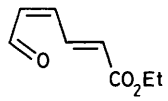
In the light of these results, it was decided to re-examine the reaction of diazoacetic esters with furan. This has been reported [4a] to give the cyclopropane (**14**), which on heating at 150 °C rearranged to the *cis-trans* dienal (**15**); the latter rearranged further to the *trans-trans* isomer (**16**).



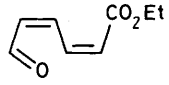
The rhodium acetate induced decomposition of ethyl diazoacetate in neat furan proceeded to completion in 1 h and yielded a mixture of products (**17**)—(**19**), in a 6:1:1 ratio, which were separated by chromatography on silica. The use of copper acetylacetonate in place of the rhodium catalyst gave the same result but required 24 h for completion of the reaction. The *exo* stereochemistry of the cyclopropane (**17**) follows from the observed J_{bc} = 3 Hz and J_{ab} = 1 Hz. By comparison with assignments made previously for dienals,[7,8] it was possible to assign the geometry of the double bond adjacent to the aldehyde group in each of the dienals (**18**) and (**19**) as *cis*. This geometry is the one expected for the initial products of ring opening. The *trans* geometry of the second double bond in (**18**) was readily apparent from the observed J = 15.5 Hz. The spectrum of product (**19**) was more complex, but the *cis* geometry of the second double bond could be assigned with the aid of decouplings and comparison with the related data for dienals such as (**5**).



(17)



(18)



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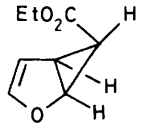
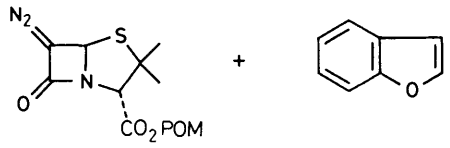


(20)

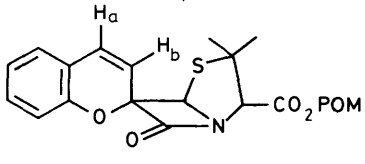
If cyclopropanes were intermediates in dienal formation, then the *cis-trans* isomer (**18**) would arise from concerted rearrangement of the *exo*-2-oxabicyclohexene (**17**) and the *cis-cis* isomer (**19**) from the *endo*-isomer (**20**). However, treatment of the exo compound (**17**) with rhodium acetate gave no ring opening, and this is therefore not the source of the *cis-trans* isomer (**18**) under the reaction conditions used here. Furthermore, the *cis-cis* isomer (**19**) was also submitted to the reaction conditions, but no isomerisation occurred in the presence of rhodium acetate. This rules out the possibility that the mechanism involves the generation of an unstable *endo*-2-oxabicyclohexene isomer (**20**), rearrangement in a concerted fashion to the *cis-cis* olefin (**19**), and further isomerisation to the *cis-trans* isomer (**18**). The remaining possibilities are either (i) that the reaction involves direct collapse of a zwitterion of structure (**13**) to give the 1:1 mixture of isomers (**18**) and (**19**), or (ii) that the reaction produces a mixture of the stable *exo*-2-oxabicyclohexene (**17**) and the unstable *endo*-2-oxabicyclohexene (**20**); the latter rearranges by a non-concerted process leading simultaneously to the *cis-cis* olefin (**19**) and the *cis-trans* isomer (**18**). In view of the considerable stability of the *exo*-isomer (**17**) to both metal-catalysed and thermal rearrangement, the second possibility seems less likely to be correct. We propose that ring opening of the betaine (**13**), formed either by direct attack of a carbenoid on the 2-position or *via* migration in an initially formed oxonium ylide, leads directly to the observed dienals without the intermediacy of a cyclopropane.

The reactions of diazo compounds with benzofuran were also studied. When pivaloyloxymethyl 6-diazopenicillanate (**4c**) was treated with benzofuran (2 equiv.) in dichloromethane containing 1% $Rh_2(OAc)_4 \cdot 2H_2O$, rapid evolution of nitrogen occurred and t.l.c. work-up after 1 h yielded 15% of a single β-lactam-containing product as a yellow oil. Structure (**21**) was assigned to this product on the basis of the spectroscopic data. The stereochemistry follows from n.O.e. difference spectroscopy,[15,16] which revealed an n.O.e. between the 2β-methyl group and the vinylic doublet H_b. This is the first example to be reported of a carbenoid ring expansion of benzofuran to a benzopyran. Internal bond cleavage in an intermediate betaine (**12**) (Scheme 4) can explain the formation of the benzopyran, as can ring opening of the betaine (**13**) to the conjugated *o*-quinonemethide derivative (**22**) and recyclisation. Alternatively, a cyclopropane

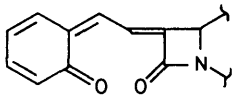
intermediate (**23**) could undergo ring opening to the *o*-quinonemethide (**22**).



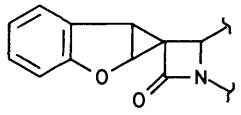
(**4c**)



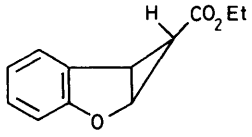
(**21**)



(**22**)



(**23**)



(**24**)

To explore this reaction further, ethyl diazoacetate was treated with benzofuran. This furnished the *exo* adduct (**24**)[17] as the sole product of rhodium-catalysed addition. The cyclopropyl ester (**24**) was stable to prolonged contact with rhodium acetate and was stable thermally up to 150 °C, decomposing at higher temperatures to afford a complex mixture of products in which no evidence was found for the presence of *o*-quinonemethides or for ring expansion to benzopyrans. We again propose that these products do not arise *via* ring opening of cyclopropane intermediates, but rather *via* intermediates of type (**12**).

Experimental

I.r. spectra were recorded on Perkin-Elmer 175G, 475 and 599 instruments and u.v. spectra on a Perkin-Elmer 402. ^{1}H N.m.r. spectra were recorded on a JEOL 100 MHz CW instrument as dilute solutions in $CDCl_3$ with TMS as internal standard, and ^{13}C n.m.r. spectra on a JEOL FX 60 as dilute solutions in $CDCl_3$ with TMS as internal standard and D_2O external lock, unless otherwise indicated. Mass spectra were obtained on a Kratos MS30 machine. M.p.s were determined on a Kofler hot-stage apparatus and are uncorrected. Analytical h.p.l.c. was performed using a Waters 6000M pump, Rheodyne 7125 injector, Cecil 2125 UV monitor and 25 cm × 4.5 mm i.d. columns high-pressure slurry-packed with Hypersil 5 um SiO_2 or ODS-Hypersil 5 um. For preparative h.p.l.c., the pump was changed to an El Minipump (Metering Pumps, Ltd.) the u.v. flowcell was changed from 10 mm to 1 mm pathlength and 30 cm × 1 in. o.d. columns high-pressure slurry-packed (Haskell DST 100 pneumatic pump) with LichroPrep SI60 15—25 um SiO_2 were fitted.[18]

Benzhydryl 6-Diazopenicillanate (**4a**).[12]—A mixture of 6-aminopenicillanic acid (30.7 g, 0.14 mol) and diphenyl diazomethane (27.4 g, 0.14 mol) in dichloromethane (236 ml) and methanol (94 ml) was stirred in an ice bath for 3—4 h, then at room temperature for 15 h, until all the purple colour of the diphenyl diazomethane had disappeared. The reaction mixture was diluted with sodium-dried diethyl ether (700 ml), then the unreacted 6-aminopenicillanic acid (13 g, 42%) was filtered off. The filtrate was kept in an ice-bath and stirred as a saturated solution of HCl in dry ether was added dropwise to give a white precipitate which was filtered off and washed with ether. Yield 29.1 g (85%, based on converted amino acid), m.p. 150—155°; $\nu_{max.}$(Nujol) 3 500, 1 770, and 1 725 cm^{-1}; δ 7.40 (10 H, m, Ar-H), 7.00 (1 H, s, 11-H), 5.57 (1 H, d, *J* 4 Hz, 5-H), 4.56 (1 H, d, 6-H), 4.54 (1 H, s, 3-H), 1.85 (2 H, s, NH), 1.60 (3 H, s, 8-H), and 1.28 (3 H, s, 9-H).

The hydrochloride salt was shaken with a mixture of dichloromethane and 5% aqueous sodium hydrogen carbonate. The organic layer was washed with brine and water and used immediately for diazotisation. To an ice-cold mixture of benzhydryl 6-aminopenicillanate (2.18 g, 5.6 mmol) in dichloromethane (400 ml) and water (400 ml) containing sodium nitrite (0.93 g, 13 mmol) was added 1N perchloric acid (12 ml) with rapid mechanical stirring. The mixture was stirred in an ice-bath for 2 h, the organic layer separated, washed with cold, saturated brine, then water, and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave benzhydryl 6-diazopenicillanate (2.15 g, 98%). The ^{1}H n.m.r. spectrum indicated > 95% purity. The compound was recrystallised from diethyl ether–light petroleum (40—60 °C), m.p. 85—87°; $\nu_{max.}$(Nujol) 2 080 and 1 760 cm^{-1}; $\lambda_{max.}$(MeOH) 256 nm (log ε 3.72); δ 7.40 (10 H, m, Ar-H), 7.00 (1 H, s, 11-H), 6.23 (1 H, s, 5-H), 4.50 (1 H, s, 3-H), 1.62 (3 H, s, 8-H), and 1.22 (3 H, s, 9-H).

p-*Nitrobenzyl 6-Diazopenicillanate* (**4b**).—By a modification of the method of Sheehan and Commons,[12] *p*-nitrobenzyl-6-aminopenicillanate toluene-*p*-sulphonate (2 g, 5.5 mmol) was dissolved in ice-cold water (150 ml) and partitioned with ice-cold dichloromethane (100 ml). The mixture was stirred rapidly in an ice bath while $NaNO_2$ (4.4 g) and toluene-*p*-sulphonic acid (1 g) were added. Stirring was continued for 8 min, then the organic layer was separated and washed with ice-cold brine (100 ml). After drying, the dichloromethane was removed under reduced pressure to afford a yellow oil which crystallised on standing, and which was recrystallised from dichloromethane–light petroleum (40—60 °C) at −50 °C, giving pure diazo ester (**4b**) in 90% yield, m.p. 39—42 °C; $\nu_{max.}$($CHCl_3$) 2 080, 1 780, and 1 747 cm^{-1}; δ 1.40 (3 H, s, Me), 1.64 (3 H, s, Me), 4.43 (1 H, s, 3-H), 5.25 (2 H, s, CH_2), 6.14 (1 H, s, 5-H), 7.56 (2 H, d, *J* 7.5 Hz, Ar-H), and 8.19 (2 H, d, *J* 7.5 Hz, Ar-H).

Pivaloyloxymethyl 6-Diazopenicillanate (**4c**).[13]—6-Aminopenicillanic acid (10 g, 0.046 mol) was dissolved in DMF (80 ml) and triethylamine (10 ml) by stirring at 45 °C for 20 min. To this solution was added pivaloyloxymethyl chloride (14 ml) and the mixture was stirred for a further 4 h at 45 °C. Ethyl acetate (100 ml) was added to dilute the solution and to bring about the precipitation of the triethylamine hydrochloride, which was filtered off. The solution was washed with water (3 × 100 ml) to remove any further triethylamine hydrochloride, dried ($MgSO_4$) and evaporated to half of its volume under reduced pressure. A solution of ethyl acetate (100 ml) containing toluene-*p*-sulphonic acid (8.8 g) was added with stirring, causing precipitation of the product in the form of its tosic acid salt. This was filtered and washed with ethyl acetate followed by ether, affording a pure white solid (81% yield), m.p. 150—151 °C (lit.,[13] m.p. 150—151 °C); $\nu_{max.}$($CHCl_3$) 2 700—2 600, 1 750, and 1 680 cm^{-1}; δ 1.21 (9 H, s, Bu^t), 1.21 (3 H, s, Me), 1.28 (3 H, s, Me), 2.36 (3 H, s, Me), 4.48 (1 H, s, 3-H), 5.00 (1 H, d, *J* 3 Hz, 5-H), 5.40 (1 H, d, *J* 3 Hz, 6-H), 5.79 (2 H, dd, CH_2), 7.15 (2 H, d, *J* 7.5 Hz, Ar-H), and 7.78 (2 H, d, *J* 7.5 Hz, ArH).

Pivaloyloxymethyl 6-aminopenicillanate tosic acid salt (1 g) was stirred in water (75 ml) and partitioned with dichloromethane (50 ml). The mixture was stirred vigorously in an ice bath, and $NaNO_2$ (2.2 g) and toluene-*p*-sulphonic acid (0.5 g) were added. After 8 min, the organic phase was separated, washed with ice-cold brine, dried ($MgSO_4$), and evaporated to give a yellow foam (yield 94%), $\nu_{max.}$($CHCl_3$) 2 960—2 880, 2080 and 1 780—1 670 cm^{-1}; δ 1.24 (9 H, s, Bu^t), 1.48 (3 H, s, Me), 1.65 (3 H, s, Me), 4.40 (1 H, s, 3-H), 5.81 (2 H, dd, CH_2), and 6.19 (1 H, s, 5-H).

ZE- *and* ZZ-*Benzhydryl*-6-(4′-*Oxobut*-2′-*enzylidene*)*penicillanates* (**5a**) *and* (**5b**).—A solution of benzhydryl 6-diazopenicillanate (**4a**) (4 g, 0.01 mmol) in furan was added dropwise with stirring to ice-cooled furan (10 ml) containing rhodium acetate hydrate (20 mg, 0.04 mmol) over 1 h. After the catalyst was filtered off, removal of excess furan under reduced pressure gave a 2:1 mixture of the *ZE* and *ZZ* dienals (**5a**) and (**5b**) as a yellow solid (100%). Separation of the two isomers could be achieved by prep. t.l.c. (CH_2Cl_2–Et_2O, 99:1); (**5a**), yellow solid, m.p. 54—56 °C, (**5b**) oil.

EE- *and* EZ-*Benzhydryl*-6-(4′*Oxobut*-2′-*enylidene*)*penicillanates* (**5c**) *and* (**5d**).—To a solution of the 2:1 mixture of *ZE* and *ZZ* dienals (**5a**) and (**5b**) in MeCH was added aqueous NaOH (0.4—05 equiv.). After work-up, a 1.2:1 mixture of *EE* and *EZ* dienals (**5c**) (m.p. 185—186 °C) and (**5d**) (m.p. 70—71 °C) was recovered. The two isomers could be separated by prep. t.l.c. (CH_2Cl_2–Et_2O, 99:1) or more efficiently by prep. h.p.l.c. (LichroPrep SI60 15—25 um, CH_2Cl_2–MeCN, 99:1). The polarities of the four isomers were in the order *ZE*(**5a**) > *EE*(**5c**) > *EZ*(**5d**) > *ZZ*(**5b**). The spectroscopic and micro-analytical data of the four isomers are shown in Tables 1, 2, and 3.

6-*Furfuryloxy*-2,2-*dimethyl*-3-[(*pivaloyloxy*)*methoxycarbonyl*]-2,3-*dihydro*-1,4-*thiazepin*-7(4H)-*one* (**6**).—Pivaloyloxymethyl 6-diazopenicillanate (121 mg, 0.355 mmol) and furfuryl alcohol (103 mg, 1.06 mmol) were stirred in the presence of rhodium acetate (3 mg) in dichloromethane (3 ml) for 45 min at room temperature. The solvent was removed under reduced pressure, and the mixture was separated by preparative t.l.c., eluting with CH_2Cl_2–EtOAc (95:5). No substituted penicillins were identified, and the major product, the thiazepine (**6**), was isolated in 30% yield; $\lambda_{max.}$(MeOH) 291 (log ε 3.74), 213 (3.56), and 329 nm (3.65); $\nu_{max.}$($CHCl_3$) 1 750 and 1 630 cm^{-1}; δ 1.24 (9 H, s, Bu^t), 1.44 (3 H, s, Me) 1.47 (3 H, s, Me), 4.22 (1 H, d, *J* 4.5 Hz, 3-H), 4.76 (2 H, s, CH_2O), 5.36 (1 H, m, N-H), 5.80 (2 H, dd, *J* 4, 4 Hz, furyl-H), 6.31 (2 H, s, $CO_2CH_2CO_2$), 6.70 (1 H, d, *J* 7.5 Hz, 5-H), and 7.38 (1 H, s, furyl-H); *m/z* 411 (M^+, 0.14%), 274 (13.7), 149 (25.7), 98 (4.8), and 81 (10) (Found: C, 56.1; H, 6.6; N, 3.42. $C_{19}H_{25}NO_7S$ requires C, 55.47; H, 6.08; N, 3.41%).

p-*Nitrobenzyl* 6-(1′-*Methyl*-4′-*oxopent*-2′-*enylidene*)*penicillanate* (**7**).—*p*-Nitrobenzyl 6-diazopenicillanate (0.365 g, 0.96 mmol) was stirred at 0 °C for 2 h with 2,5-dimethylfuran (0.092 g, 0.96 mmol) and rhodium acetate (2 mg) in dichloromethane (5 ml). T.l.c. analysis showed complete decomposition of the diazopenicillanate, and the solvent was removed under reduced pressure. The products were separated by preparative t.l.c., eluting with CH_2Cl_2–EtOAc (98:2). Chromatography was repeated several times in order to obtain a reasonably pure sample of the required dienone (**7**). The final purification was effected by preparative h.p.l.c. on a LichroPrep silica column, eluting with CH_2Cl_2–MeCN (97:3). No further substituted penicillins were isolated from the complex reaction mixture. The final yield of (**7**) was 2.5%; $\lambda_{max.}$(CH_2Cl_2) 273 nm (log ε 4.29); $\nu_{max.}$($CHCl_3$) 1 760—1 740 and 1 690 cm^{-1}; δ 1.44 (3 H, s, Me), 1.59 (3 H, s, Me), 1.95 (3 H, s, Me, 2.31 (3 H, s, MeCO), 4.60 (1 H, s, 3-H), 5.34 (2 H, s, CH_2), 5.79 (1 H, s, 5-H), 6.31 (1 H, d, *J* 12 Hz, C*H*CMe), 6.84 (1 H, d, *J* 12 Hz, MeCOC*H*), 7.62 (2 H, d, *J* 7.5 Hz, Ar-H), and 8.32 (2-H, d, *J* 7.5 Hz, Ar-H); *m/z* 430.1179 (M^+, 5.6%; $C_{21}H_{22}NO_6S$ requires *M*, 430.1198), 387 (40.4, *M* – CH_3CO), 374 (0.2, *M* – CH_3COCH), 361 (9.4, *M* – CH_3COCH=CH), 294 (4.3, *M* – PNB), 250 (2.2, *M* – CO_2PNB), 152 (100), 96 (11.7, CH_3COCH=$CHCCH_3$), and 46 (1.3, NO_2).

Pivaloyloxymethyl 6-(3′-*Methoxycarbonylprop*-2′-*enylidene*)*penicillanate* (**8**).—2-Methoxyfuran (82.5 mg, 0.838 mmol) and pivaloyloxymethyl 6-diazopenicillanate (143 mg, 0.419 mmol) were stirred at 0 °C in dichloromethane (2 ml) with rhodium acetate catalyst (2 mg). After 1 h, the reaction had reached completion. The solvent was evaporated under reduced pressure, and the products were separated by preparative t.l.c. with dichloromethane as eluant, to afford the dienone isomers (**8**), in 26% combined yield.

Z,E-*Isomer:* 4% yield, $\lambda_{max.}$(MeOH) 274 nm (log ε 4.03); $\nu_{max.}$($CHCl_3$) 1 780—1 750, and 1 720 cm^{-1}; δ 1.30 (9 H, s, Bu^t), 1.56 (3 H, s, Me), 1.64 (3 H, s, Me), 3.84 (3 H, s, OMe), 4.60 (1 H, s, 3-H), 5.86 (3 H, m, CH_2 and 5-H overlapping), 6.00 (1 H, d, *J* 10.5 Hz, 10-H), 7.34 (1 H, dd, *J* 10.5 Hz, 10.5 Hz, 9-H), and 7.72 (1 H, d, *J* 10.5 Hz, 8-H); *m/z* 411.1395 (M^+, 7.6%; $C_{19}H_{25}NO_7S$ requires *M*, 411.1351), 252 (1.8), 169 (7.4), 168 (100), 149 (10.4), 99 (18.4), 95 (1.6), and 57 (20.5).

Z,Z-*Isomer:* 22% yield, $\lambda_{max.}$(CH_2Cl_2) 276 nm (log ε 4.51); $\nu_{max.}$($CHCl_3$) 1 780—1 750, and 1 720 cm^{-1}; δ 1.24 (9 H, s, Bu^t), 1.52 (3 H, s, Me), 1.60 (3 H, s, Me), 3.80 (3 H, s, OMe), 4.60 (1 H, s, 3-H), 5.86 (3 H, m, CH_2 and 5-H overlapping), 6.08 (1 H, d, *J* 12 Hz, 10-H), 6.52 (1 H, dd, perturbed, *J* 10.5 Hz, 12 Hz, 9-H), and 7.88 (1 H, d, *J* 10.5 Hz, 8-H); *m/z* 411.1333 (M^+, 1.7%; $C_{19}H_{25}NO_7S$ requires *M*, 411.1351), 380 (0.3, *M* – OMe), 252 (1.8), 167 (4.7), 119 (3.0), 82 (100), 57 (8.4) (Found: C, 55.59; H, 6.31; N, 3.22. $C_{19}H_{25}NO_7S$ requires C, 55.47; H, 6.08; N, 3.41%).

Pivaloyloxymethyl 6-(4′-*Oxopent*-2′-*enylidene*)*penicillanate* (**9**). —Pivaloyloxymethyl 6-diazopenicillanate (141 mg, 0.415 mmol) and 2-methylfuran (2.25 mmol, 0.125 ml) were stirred in dichloromethane (2 ml). To this was added rhodium acetate 12 mg) and stirring was continued at room temperature for 3 h, during which nitrogen evolution occurred. The reaction was shown to have reached completion by the loss of the diazo stretch in the i.r. spectrum. The products were separated by preparative t.l.c., eluting with CH_2Cl_2–EtOAc (90:10), to afford two isomers of the dienone (**9**). Further chromatography was necessary to obtain pure samples, and the final yield was 27%. The isomers were assigned as the *ZE* and *ZZ* isomers by comparison with the unsubstituted dienals (**5**).

Z,E-*Isomer:* $\lambda_{max.}$ 278 nm (log ε 4.56); $\nu_{max.}$($CHCl_3$) 1 760 and 1 690 cm^{-1}; δ 1.25 (9 H, s, Bu^t), 1.52 (3 H, s, Me), 1.60 (3 H, s, Me), 2.30 (3 H, s, COMe), 4.59 (1 H, s, 3-H), 5.80 (1 H, s, 5-H), 5.89 (2 H, dd, *J* 4.5 Hz, 4.5 Hz, CH_2), 6.34 (1 H, d, *J* 11 Hz, 10-H), 7.20 (1 H, dd, perturbed, *J* 11 Hz, 12 Hz, 9-H), and 7.68 (1 H, d, *J* 12 Hz, 8-H); *m/z* 395.1384 (M^+, 0.1%; $C_{19}H_{25}NO_6S$ requires *M*, 395.1402), 168 (8.1), 117 (1), 99 (2.7), 82 (100), and 57 (3.7).

Z,Z-*Isomer:* $\lambda_{max.}$(MeOH) 281 nm (log ε 4.54); $\nu_{max.}$($CHCl_3$) 1 770 and 1 690 cm^{-1}; δ 1.25 (9 H, s, Bu^t), 1.53 (3 H, s, Me), 1.60 (3 H, s, Me), 2.32 (3 H, s, COMe), 4.63 (1 H, s, 3-H), 5.90 (3 H, m, CH_2 and 5-H overlapping), 6.30 (1 H, d, *J* 12 Hz, 10-H), 6.89 (1 H, dd, *J* 10.5 Hz, 12 Hz, 9-H), and 7.88 (1 H, d, *J* 10 Hz, 8-H); *m/z* 395.1389 (M^+, 0.8%; $C_{19}H_{25}NO_6S$ requires *M*, 395.1402), 352 (0.7), 236 (0.8), 198 (0.7), 183 (1.1), 181 (1.4), 168 (2.1), 117 (2.5), 82 (100), and 57 (4).

Pivaloyloxymethyl 6-(3′-*Methyl*-4′-*oxobut*-2′-*enylidene*)*penicillanate* (**10**) *and Pivaloyloxymethyl* 6-(2′-*Methyl*-4′-*oxobut*-2′-*enylidene*)*penicillanate* (**11**).—3-Methylfuran (0.30 g, 3.76

Table 3. Spectroscopic and microanalytical data for dienals (**5a-d**)

Dienal	U.v.[a] $\lambda_{max.}$/nm (log ε)	I.r.[b] $\nu_{max.}$/cm^{-1} β-lactam	ester	aldehyde	Mass spectra[c] Relative intensities of ions 433(M^+)	266	167	108	99	79	59	Microanalysis (%) (Calc. values) C (69.26)	H (5.35)	N (3.23)
ZE-(**5a**)	277 (4.28)	1765	1740	1675	1.2	2.9	100	1.3	2.3	0.9	2.2	68.95	5.4	3.0
ZZ-(**5b**)	277 (4.33)	1770	1740	1675	0.3	0.5	100	1.2	0.6	2.5	1.9	68.95	5.4	2.95
EE-(**5c**)	279 (4.47)	1762	1740	1680, 1670	0.1	0.6	100	2.6	4.7	3.8	6.4	—	—	—
EZ-(**5d**)	279 (4.30)	1765	1740	1685	0.6	1.8	100	1.2	0.6	0.6	0.9	—	—	—

[a] Dienals (**5a**—**d**) in MeCN. [b] Dienals (**5a**—**c**) Nujol, (**5d**) in $CHCl_3$. [c] All compounds gave accurate mass values for M^+ in good agreement with theory.

mmol) and pivaloyloxymethyl 6-diazopenicillanate (0.641 g, 1.88 mmol) were stirred in dichloromethane (2 ml) together with rhodium acetate catalyst (3 mg). Nitrogen evolution commenced immediately. The reaction reached completion within 10 min, as shown by the loss of diazo stretch and the formation of a new carbonyl stretch in the i.r. spectrum. The solvent was removed under reduced pressure and the mixture separated by preparative t.l.c., eluting with CH_2Cl_2–MeCN (98.5:1.5). Two fractions were isolated, one containing the single isomer (**10**) and the other containing a mixture of the two isomers (**11**). Further chromatography afforded separation of the isomers.

Isomer (**10**): $\lambda_{max.}(CH_2Cl_2)$ 291 nm (log ε 4.27); $\nu_{max.}(CHCl_3)$ 1 780—1 750 and 1 680 cm^{-1}; δ 1.25 (9 H, s, Bu^t), 1.55 (3 H, s, Me), 1.62 (3 H, s, Me), 1.98 (3 H, s, 10-H), 4.60 (1 H, s, 3-H), 5.80 (1 H, s, COCMe), 5.86 (2 H, dd, *J* 4.5 Hz, CH_2), 7.28 (1 H, d, *J* 12 Hz, vinylic), 7.68 (1 H, d, *J* 12 Hz, vinylic), and 10.34 (1 H, s, CHO); *m/z* 395.1364 (M^+, 1.8%; $C_{19}H_{25}NO_6S$ requires *M*, 395.1402), 366 (0.5), 236 (2.4), 207 (1.7), 181 (2.5), 139 (4), 122 (2.7), 82 (100), and 57 (19.6).

ZE-*Isomer* (**11a**): $\lambda_{max.}(CH_2Cl_2)$ 286 nm (log ε 4.43); $\nu_{max.}(CHCl_3)$ 1 780—1 750, and 1 670 cm^{-1}; δ 1.25 (9 H, s, Bu^t), 1.53 (3 H, s, Me), 1.64 (3 H, s, Me), 2.13 (3 H, s, 9-H), 4.66 (1 H, s, 3-H), 5.88 (2 H, dd, *J* 4.5 Hz, 4.5 Hz, CH_2), 5.96 (1 H, s, 5-H), 6.12 (1 H, d, *J* 8 Hz, 10-H), 7.19 (1 H, s, 8-H), and 10.06 (1 H, d, *J* 8 Hz, 11-H); *m/z* 395.1496 (M^+, 0.4%; $C_{19}H_{25}NO_6S$ requires *M*, 395.1402), 366 (0.2), 252 (0.2), 117 (1.3), 116 (0.9), 82 (100), and 57 (5.7).

Although the *ZZ*-isomer (**11b**) was separated, a small amount of isomer (**11a**) prevented a complete characterization. However, i.r. and n.m.r. spectra were obtained: $\nu_{max.}$ 1 780—1 750, and 1 670 cm^{-1}; δ 1.25 (9 H, s, Bu^t), 1.53 (3 H, s, Me), 1.64 (3 H, s, Me), 2.13 (3 H, s, 9-H), 4.66 (1 H, s, 3-H), 5.88 (2 H, dd, *J* 4.5 Hz, 4.5 Hz, CH_2), 5.96 (1 H, s, 5-H), 6.16 (1 H, d, *J* 8 Hz, 10-H), 7.64 (1 H, s, 8-H), and 10.21 (1 H, d, *J* 8 Hz, 11-H).

Rhodium-catalysed Reaction of Ethyl Diazoacetate and Furan.—To ethyl diazoacetate (0.3 g, 2.6 mmol) and furan (3 ml) at 0 °C was added rhodium acetate hydrate (6 mg). Rapid evolution of nitrogen occurred. After 1 h, evaporation and preparative t.l.c. afforded three products:

6-exo-(*Ethoxycarbonyl*)-2-*oxabicyclo*[3.1.0]*hex*-3-*ene* (**17**).—δ 0.99 (1 H, d, *J* 3 Hz, H_b), 1.30 (3 H, t, *J* 7.5 Hz, Me), 2.80 (1 H, m, H_c), 4.15 (2 H, q, *J* 7.5 Hz, CH_2), 4.85 (1 H, d, *J* 6 Hz, H_a), 5.48 (1 H, dd, *J* 2, 3 Hz, H_d), and 6.41 (1 H, d, *J* 2 Hz, H_e). Scale expansion revealed a further splitting of *ca.* 1 Hz between H_a and H_b; *m/z* 154 (M^+).

Ethyl 6-*oxohexa*-2E,4Z-*dienoate* (**18**). $\lambda_{max.}(CH_2Cl_2)$ 272 nm; $\nu_{max.}(CHCl_3)$ 1 720 and 1 680 cm^{-1}; δ 1.32 (3 H, t, *J* 7.5 Hz, Me), 4.26 (2 H, q, *J* 7.5 Hz, CH_2), 6.12 (1 H, dd, *J* 8, 11 Hz, 5-H), 6.20 (1 H, d, *J* 15 Hz, 2-H), 7.00 (1 H, dd, *J* 11, 13 Hz, 4-H), 8.08 1(H, dd, *J* 13, 15 Hz, 3-H), and 10.27 (1 H, d, *J* 8 Hz, 6-H); *m/z* 154 (M^+).

Ethyl 6-*oxohexa*-2Z,4Z-*dienoate* (**19**). $\lambda_{max.}(CH_2Cl_2)$ 272 nm. $\nu_{max.}(CHCl_3)$ 1 720 and 1 680 cm^{-1}; δ 1.33 (3H, t, *J* 7.5 Hz, Me), 4.25 (2 H, q, *J* 7.5 Hz, CH_2), 6.06 (1 H, d, *J* 8 Hz, 2-H), 6.21 (1 H, m, 5-H), 7.52 (1 H, dd, *J* 11, 11 Hz, 4-H), 8.16 (1 H, dd, *J* 8, 11 Hz, 3-H), and 10.26 (1 H, d, *J* 8 Hz, 6-H); *m/z* 154 (M^+).

Rhodium-catalysed Reaction of Pivaloyloxymethyl 6-*Diazopenicillanate and Benzofuran.*—Benzofuran (0.24 g, 2.1 mmol) and pivaloyloxymethyl 6-diazopenicillanate (0.35 g, 1.03 mmol) were stirred in dichloromethane (4 ml) together with rhodium acetate catalyst (3 mg) at room temperature. After 1 h, the mixture was separated by column chromatography on silica, eluting initially with CCl_4–CH_2Cl_2, (40:60) to remove unchanged benzofuran, followed by a gradual increase in CH_2Cl_2 concentration to elute the product (**21**) as a bright yellow oil (15%), $\lambda_{max.}$(MeOH) 226 (log ε 3.54) and 272 nm (3.40); $\nu_{max.}(CHCl_3)$ 1 780 and 1 750 cm^{-1}; δ 1.24 (9 H, s, Bu^t), 1.52 (3 H, s, Me), 1.62 (3 H, s, Me), 4.55 (1 H, s, 3-H), 5.56 (1 H, s, 5-H), 5.90 (2 H, dd, *J* 2 Hz, CH_2), 5.95 (1 H, d, *J* 10 Hz, H_b), 6.76 (1 H, d, *J* 10 Hz, H_a), 6.87—7.24 (4 H, m, ArH). On a JEOL 200 MHz instrument, n.O.e. difference spectra were recorded and showed an n.O.e. from the 2β-Me (δ 1.62) to the vinylic doublet for H_b (δ 5.95); *m/z* 431 (M^+, 14.5%), 244 (4.1), 176 (11), 175 (10), 130 (8.3), 82 (100), and 57 (20.9) (Found: C, 61.0; H, 6.2%; N, 3.1. $C_{22}H_{25}NO_6S$ requires C, 61.25; H, 5.80; N, 3.25%).

6-exo-(*Ethoxycarbonyl*)-3,4-*benzo*-2-*oxabicyclo*[3.1.0]*hex*-3-*ene* (**24**).[17]—Benzofuran (0.30 g, 2.54 mmol) and ethyl diazoacetate (0.58 g, 5.1 mmol) were stirred in dichloromethane (1 ml) together with rhodium acetate catalyst (6 mg) at room temperature. After 1 h, the mixture was separated by preparative t.l.c. on silica, affording the adduct (**24**) as an oil, repurified by further preparative t.l.c. (40% yield), $\nu_{max.}(CHCl_3)$ 2 990—2 900 and 1 710 cm^{-1}; δ 1.19 (1 H, d, *J* 3 Hz, 5-H), 1.25 (3 H, t, *J* 7 Hz, Me), 3.22 (1 H, m, 6-H), 4.12 (2 H, q, *J* 7 Hz, CH_2), 5.02 (1 H, d, *J* 6 Hz, 1-H), and 6.76—7.36 (4 H, m, ArH); *m/z* 204 (M^+, 11.2%), 131 (100), 77 (23.6), 51 (10.7).

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