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COPPER (I) CATALYSED REACTIONS OF 6-BROMOPENICILLANOYL MAGNESIUM BROMIDE

A SYNTHESIS OF 6-SPIROCYCLOPROPYL PENICILLANATES

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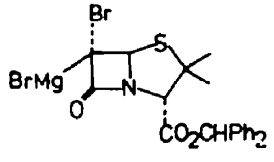
Abstract—2'-Carboethoxyspiro(benzhydryl penicillanate-6-1'-cyclopropane) was prepared from the Cu (I) catalysed reaction of benzhydryl 6-bromopenicillanoyl magnesium bromide with ethyl acrylate. The structure of the product was proved by a difference n.O.e. experiment. Further examples are given with other α-β unsaturated esters, and the mechanism of the reaction is discussed.

Recently a number of "non-classical" β-lactam antibiotics have been isolated from natural sources. These compounds are non-classical in the sense that they lack the usual C-6 amido side chain (penicillin numbering) and have, instead, a carbon based C-6 substituent. The literature reveals several methods of introducing C-6 carbon substituents on to the intact penicillin nucleus. Thus, Sheehan has shown that benzyl 6-oxopenicillanate undergoes Wittig reactions with stabilised phosphoranes to give C-6 olefinic penicillanates;[1] 6-Diazopenicillanic esters have been used as 1,3 dipoles in cycloaddition reactions or as a source of carbene, both of these methods leading to a variety of 6-spiropenicillanates.[2,3] 6-Diazopenicillanic esters can also be decomposed in the presence of allylic sulphides, selenides and halides to give, via a [2,3]-sigmatropic rearrangement, 6-allylpenicillanates.[4] Perhaps the most common method of introducing C-6 carbon substituents is through the reaction of a C-6 carbanion with a carbon electrophile. The C-6 carbanion, generated by metal halogen exchange between 6,6-dibromopenicillanates and Grignard reagents or alkyllithiums, or by proton extraction,[5] has been condensed with acetaldehyde to give the aldol product.[6-8] It should be noted that the stereochemistry of the aldol product is highly dependent on the solvent and metal used in the reaction.[6,7] A versatile carbanion, reported by Bentley *et al.*,[9] is derived from benzyl 6-isocyanopenicillanate and potassium carbonate in DMF and will react with alkyl halides, ketones and acrylates (1,4 Michael addition). It was subsequently shown that the bromide and isocyanide at C-6 in these C-6 carbon substituted penicillanates can be stereoselectively removed using nBu_3SnH.[8,10]

We surmised that the reactivity of 6-bromopenicillanoyl magnesium bromide **1** could be altered by adding Cu (I) salts to generate a nucleophile capable of undergoing Michael additions.[11] Thus addition of an equivalent of CuI to a solution of **1** in THF followed by ethyl acrylate at $-78°$ gave a 73% yield of a single regio- and stereochemically pure product (m.p. 71–73°), for which micro-analysis and mass spectrometry gave a formula $C_{26}H_{27}NO_5S$. This same product was obtained in 44% and 7% yields[12] using 3% molar equivalents of CuI and no CuI respectively. The analytical data showed that this product was not the benzhydryl 6-alkyl-6-



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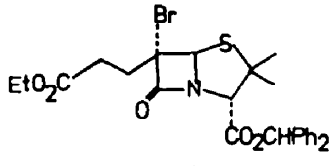

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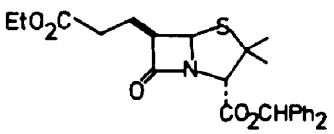

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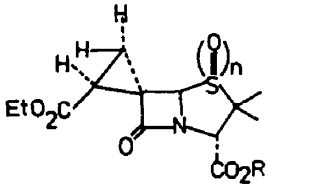
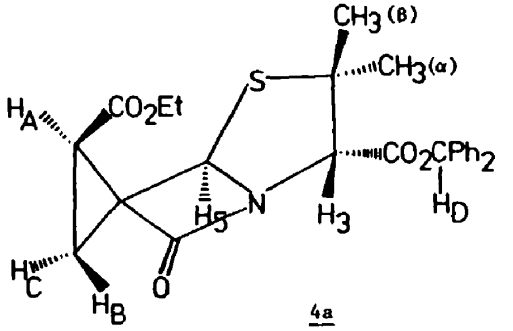


4a R=CHPh$_2$ n=0
4b R=CHPh$_2$ n=2
4c R=H n=0
4d R=H n=2



4a

Chemical Shifts (ppm)

7.25-7.45	(10H,m)	- phenyl protons
6.93	(1H,s)	- H_D
5.35	(1H,s)	- H_5
4.64	(1H,s)	- H_3
4.08-4.32	(2H,AB q of q)	- ester CH_2
2.36	(1H,dd)	- H_A
2.20	(1H,dd)	- H_B
1.65	(1H,dd)	- H_C
1.58	singlet	- water
1.56	(3H,s)	- Me(β)
1.27	(3H,s)	- Me(α)
1.25	(3H,t)	- ester CH_3

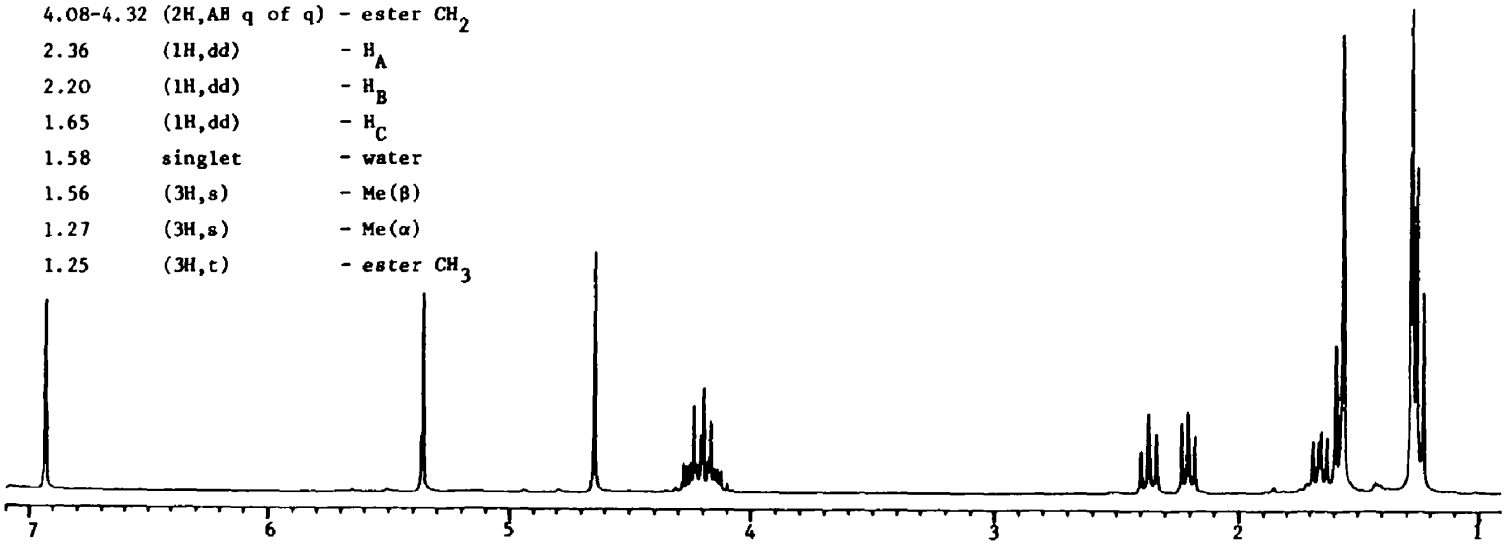


Fig. 1.

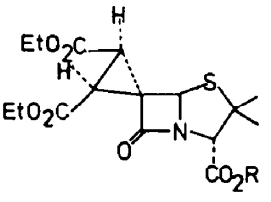
bromopenicillanate **2**, nor was it the 6-olefinic product **3**, since there was no vinylic proton and H-5 appeared as a singlet with no allylic couplings.[1] The ^{1}H-NMR was consistent with the product having the spirocyclopropane structure **4a**. A difference n.O.e. experiment showed the carboethoxy group to be on the β face, "*syn*" to the β-lactam CO as drawn.

n.O.e. Studies on 2'-carboethoxyspiro(benzhydryl penicillanate-6-cyclopropane) **4a**. The 250 m.Hz ^{1}H-NMR spectrum and assignment is shown in Fig. 1. Thus irradiation of the low field Me singlet resulted in enhancement of the highest field methine singlet (20%), which allows assignment of the signals to Me (β) and H-3; assignment of Me (α) and H-5 follow automatically (an enhancement of H-5 (3%) was seen upon irradiation of Me (α)). Pre-irradiation of H_A, H_B and H_C produced H-5 enhancements of 1.8%, no observed enhancement and 4.3% respectively showing that H-C is close to H-5, H-A is somewhat distant whilest H-B is remote. These observations are consistent with the structural assignments shown for H-A and H-C, leading to the conclusion that the carboethoxy group is "*syn*" to the β-lactam CO. The remaining ambiguity is resolved by the observations that pre-irradiation of H-A or H-B produces only one strong enhancement of the cyclopropane proton H-C (14% and 24% respectively), whereas pre-irradiation of H-C strongly enhances both H-A (14%) and H-B (24%). H-C must, therefore, have both vicinal and geminal close neighbours, leading to the final structure shown. The relative sizes of the enhancements of H-C on pre-irradiation of H-A and H-B show, as expected, that the geminal H-B/H-C interaction is the stronger. Further evidence for the structure is provided by the observed enhancement of H-A (2%) on pre-irradiation of Me (β).

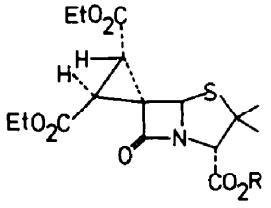
Reaction of benzhydryl 6-bromopenicillanoyl magnesium bromide with other α-β unsaturated esters. Under the same conditions (i.e. one equiv of Cu (I) iodide), **1** and diethyl maleate gave a 12%[12] yield of a 6-spirocyclopropane penicillanate which was shown to have the *cis* structure **5**. Changing the α-β-unsaturated ester to diethyl fumarate gave a 12% yield of the two *trans* substituted cyclopropanes **6** and **7** in an approximately 1:1 ratio. A third product (5%)[12] from this reaction was a *cis* substituted cyclopropane which was shown, by ^{1}H-NMR and mixed m.p., to be **5**, previously isolated from the diethyl maleate experiment. A further experiment using diethyl methylenemalonate gave a 6%[12] yield of the two regioisomers **8** and **9** in a 3:1 ratio. The structures of **5**, **6**, **7**, **8** and **9** were determined by difference n.O.e. experiments similar to those previously described for **4a**.

Selected ^{1}H-NMR data for these spirocyclopropane penicillanates is given in Table 1.

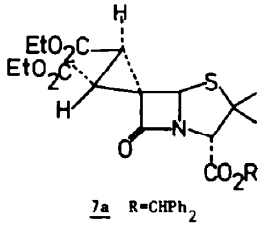
Mechanism for the formation of 6-spirocyclopropane penicillanates. Treatment of a THF solution of benzhydryl 6,6-dibromopenicillanate with MeMgBr results in transmetallation predominalty to the more hindered β face to afford benzhydryl 6-α-bromopenicillanoyl magnesium bromide **10**[7]. Addition of Cu (I) iodide to **10** followed by ethyl acrylate results in a 1,4 addition to give enolate **11**,[13] where Cu can chelate to O atoms of the ethyl ester and the O atom of the β-lactam CO. This chelation holds the central C of the acrylate in close proximity to the C-6 carbon of the penicillin nucleus. Attack of the enolate



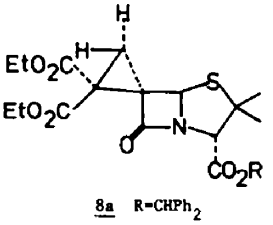
5a R=$CHPh_2$
5b R=H



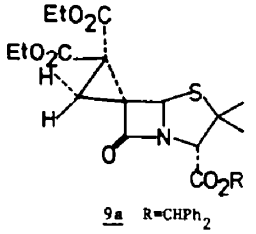
6a R=$CHPh_2$
6b R=H



7a R=$CHPh_2$
7b R=H



8a R=$CHPh_2$
8b R=H



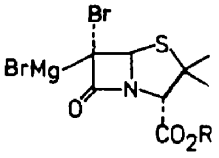
9a R=$CHPh_2$
9b R=H

Table 1. Physical data[a]

Compound	H-A	H-B	H-C	H-D	H-3	H-5	$CH_3(\beta)$	$CH_3(\alpha)$	β-lactam carbonyl (cm^{-1})
4a (m.pt. 71-73°C)	2.36(dd) J_{AB}=7.5H	2.20(dd) J_{BC}=7.0	1.65(dd) J_{AC}=7.5	-	4.64(s)	5.35(s)	1.56(s)	1.28(s)	1783
4b	2.70(dd)	2.05(dd)	1.60(m)	-	4.54(s)	4.59(s)	1.52(s)	1.10(s)	1803
4c	2.1-2.5(m)	2.1-2.5(m)	1.6 (m)	-	4.54(s)	5.3(s)	1.60(s)	1.55(s)	1775
4d	2.70(dd)	1.90-2.20(m)	1.90-2.20(m)	-	4.60(s)	4.40(s)	1.61(s)	1.48(s)	1800
5a (m.pt. 139-140°C)	2.66(ABq) J_{AC}=9	-	2.66(ABq) J_{AC}=9	-	4.71(s)	5.35(s)	1.63(s)	1.28(s)	1785
5b	2.62(ABq) J_{AC}=9	-	2.62(ABq) J_{AC}=9	-	4.68(s)	5.35(s)	1.63(s)	1.57(s)	1780
6a	3.03(d) J_{AB}=5.9	3.03(d) J_{AB}=5.9	-	-	4.50(s)	5.56(s)	1.60(s)	1.27(s)	1785
6b	3.07(d)	3.01(d)	-	-	4.50(s)	5.45(s)	1.62(s)	1.55(s)	1780
7a	-	-	2.89(d)	2.89(d)	4.49(s)	5.66(s)	1.60(s)	1.27(s)	1785
7b	-	-	2.92(d)	2.92(d)	4.50(s)	5.45(s)	1.62(s)	1.55(s)	1780
8a	2.92(ABq) J_{AD}=15	-	-	2.92(ABq)	4.56(s)	5.74(s)	1.60(s)	1.25(s)	1787

8b	2.83(ABq) J_{AD}=15	-	-	2.83(ABq)	4.50(s)	5.67(s)	1.67(s)	1.58(s)	1785
9a	-	3.07(s)	3.07(s)	-	4.57(s)	5.49(s)	1.64(s)	1.28(s)	1787
9b	-	2.83(d) J_{AD}=8	2.83(d) J_{AD}=8	-	4.51(s)	5.39(s)	1.68(s)	1.56(s)	1785
13a (m.pt. 42-44°C)	2.42(dd) J_{AB}=7.5	2.23(dd) J_{BC}=7.0	1.58(dd) J_{AC}=7.5	-	4.58(s)	5.30(s)	1.55(s)	1.27(s)	1780
13b (m.pt. 58-60°C)	2.75(dd)	2.10(dd)	1.60(dd)	-	4.53(s)	4.56(s)	1.50(s)	1.10(s)	1805
13c (m.pt. 158-162°C)	2.36(dd) J_{AC}=7.5	1.9(dd) J_{BC}=7.0	1.6 (m)	-	4.43(s)	5.37(s)	1.58(s)	1.52(s)	1765
13d (m.pt. 58-61°C)	2.70(dd)	1.80-2.15(m)	1.80-2.15(m)	-	4.45(s)	4.43(s)	1.60(s)	1.48(s)	1795
14a	2.72(ABq) J_{AC}=9	-	2.72(ABq) J_{AC}=9	-	4.70(s)	5.35(s)	1.49(s)	1.25(s)	1780
14b	2.79(ABq) J_{AC}=9	-	2.79(ABq) J_{AC}=9	-	4.51(s)	5.39(s)	1.63(s)	1.53(s)	1770

[a] ^{1}H-n.m.r. spectra were recorded in $CDCl_3$ solution and are reported in parts per million downfield from Me_4Si. Coupling constants (J) are reported in Hertz.



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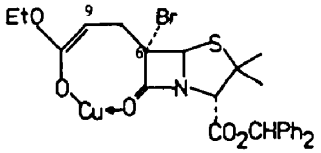

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at C-6 results in an S_N2 displacement of the α-Br, with inversion of stereochemistry, to give the observed product **4**. S_N2 displacement has been observed at C-6 of a penicillin,[14] but not with a carbon nucleophile. This example is also unique in that it involves an intramolecular displacement.

The idea that the Cu is involved in an intermediate chelate is further supported by the observed products from the diethyl fumarate reaction, where, in addition to the two *trans* products **6** and **7**, the sterically more demanding *cis* product **5** was isolated. This product distribution would indicate a stepwise mechanism, where the most rapid step is the 1,4 addition to give either intermediate **12a**, which undergoes ring closure to **6a**, or intermediate **12b** which rotates to intermediate **12c** and ring closes to the *cis* product **5**. The driving force for the rotation of **12b** to **12c**, the latter being sterically more demanding, is the increased chelation with the metal atom in **12c**. This "cup" shaped chelation site, involving three O atoms, is quite apparent when a model of **5** is examined.

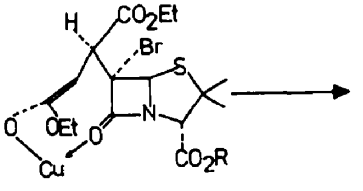
The minor product **7** probably arises from the initial 1,4 attack from the α face, since in THF solution as equilibrium exists between the α-bromo and the β-bromo penicillanoyl magnesium bromides.[7] The product **9a** also arises from α face attack of the diethyl methylenemalonate. As β face attack becomes more difficult (adjudged from the lower yields) then α face attack becomes significant.[15]

The benzhydryl esters **4a, 5–9** were deprotected to their free acids in good yield (>80%) using an $AlCl_3$/anisole/CH_3NO_2 mixture.[16] The products **13a** and **14a** were obtained from benzhydryl acrylate and dibenzyl maleate, respectively. **4a** and **13a** were oxidised to their corresponding sulphones, **4b** and **13b**, using m.c.p.b.a. The acids **13c**, **13d** and **14b** were obtained from their corresponding esters by reductive methods.

The penicillanic acids described in this text showed no significant antibacterial activity.

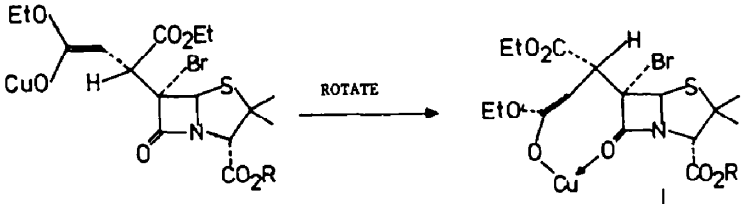
EXPERIMENTAL

Materials and instrumentation. THF was distilled under N_2 from Na. MeMgBr (Ventron) was a 3M sol in ether. Copper (I) iodide was reprecipitated from sat KI aq[12] and dried in the dark under vacuum at 120°. The α-β-unsaturated esters were re-distilled prior to use. Benzhydryl 6,6-dibromopenicillanic acid was recrystallised from EtOAc/hexane, affording colourless needles (m.p. 150–153°), which were dried over P_2O_5. M.p. were determined on an electrothermal apparatus. IR spectra were recorded on a Perkin–Elmer 197 spectrophotometer. NMR spectra and difference n.O.e. spectra were recorded on a



12a

6a

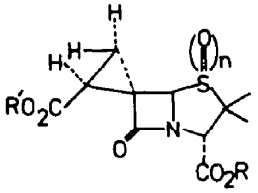


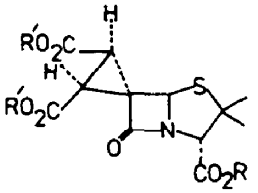
12b

ROTATE

12c

5a





13a R=CHPh$_2$, R'=CH$_2$Ph, n=0
13b R=CHPh$_2$, R'=CH$_2$Ph, n=2
13c R=R'=H n=0
13d R=R'=H n=2

14a R=CH$_2$Ph$_2$, R'=CH$_2$Ph
14b R=R'=H

Bruker WM-250 instrument. Column chromatography was performed on Merck Kieselgel 60H, using hexane mixtures.

Preparation of 2'-carboethoxyspiro(benzhydryl penicillanate-6-1'-cyclopropane) (**4a**). To a stirred soln of 2.9g (5.5 mmol) benzhydryl 6,6-dibromopenicillanate in 70 mL dry THF at −78° under N_2 was added dropwise 2 mL (6 mmol) ethereal MeMgBr and the mixture was stirred for 20 min. To the stirred, pale yellow soln was added 1.05 g (5.5 mmol) solid copper (I) iodide. The suspension was warmed to −25° until dissolution of the CuI occurred and then cooled to −78° before 0.66 g (5.5 mmol) ethyl acrylate was added and the slurry was stirred for 30 min. The reaction was quenched at −78° with 30 mL sat NH_4Cl aq. The THF was removed under reduced pressure and replaced with EtOAc, a dark green soln resulted which was filtered through "Hyflo". The filtrate was separated and the aqueous phase was extracted with EtOAc. The organic phases were combined, dried with $MgSO_4$, filtered and evaporated. The dark green concentrate was purified by chromatography to give 1.9 g (73%) of **4a**. Recrystallisation from EtOAc/hexane gave colourless needles, m.p. 71–73° (Found: C, 67.1; H, 5.8; N, 3.0 $C_{26}H_{27}NO_5S$ requires:C, 67.0; H, 5.9; N, 3.0%). Consult Table 1 for spectral data. Compounds **4–9, 13** and **14** were prepared analogously.

Preparation of 2'-carboethoxyspiro(benzhydryl penicillanate-1,1-dioxide-6-1'-cyclopropane (**4b**). To a stirred soln of 0.5 g (1.1 mmol) of **4a** in 15 mL CH_2Cl_2 cooled to 0° was added, in four portions over 30 min, 0.5 g (2.4 mmol) *m*-chloroperbenzoic acid. After standing at room temp for 24 hr the mixture was diluted with 50 mL CH_2Cl_2 and then washed with $NaHCO_3$ aq (× 2), brine, dried with $MgSO_4$, filtered and evaporated. The concentrate was purified by chromatography to give 0.2 g (38%) of **4b**; m.p. 61–64° (dec). Consult Table 1 for spectral data.

General procedure for the deprotection of benzhydryl esters **4-9**[16]. To a soln of benzhydryl ester (0.22 mmol) and anisole (0.83 mmol) in 3 mL dry CH_2Cl_2, cooled to 0°, was added to a soln of $AlCl_3$ (0.37 mmol) in 1.5 mL CH_3NO_2 in three portions over 20 min. The mixture was diluted with 25 mL EtOAc and washed with 0.5 M HCl. The separated organic phase was extracted with $NaHCO_3$ aq (× 3) and the combined aqueous phases were acidified to pH 2 with 2M HCl and extracted with EtOAc. The EtOAc extract was dried over $MgSO_4$, filtered and evaporated. The residue was re-evaporated from CH_2Cl_2 to afford pure acids, as pale yellow solids, in yields of 80–90%. Consult Table 1 for Spectral Data.

General procedure for the deprotection of benzhydryl esters. **13a, b** *and* **14a**. To a stirred suspension of 100 mg prereduced 30% Pd/C in 2 mL MeOH and 0.5 mL H_2O was added to the benzhydryl ester (0.19 mmol) in 1.5 mL EtOAc and the mixture hydrogenated at atmospheric pressure. A second portion of catalyst was added after 30 min, and a third after 1 hr. Hydrogenation was continued for a further 2 hr before the catalyst was removed by filtration through Solka-Floc and washed with MeOH. The filtrate was evaporated under reduced pressure. The residue was re-evaporated from CH_2Cl_2 to afford pure acids **13c**, **13d** and **14b** as colourless solids. Consult Table 1 for spectral data.

Acknowledgement—We would like to thank Mr. D. Neuhaus (Imperial College, London) for stereochemical assignment of compound **4a**, Dr. M. Kinns (Pfizer) for subsequent n.O.e. experiments and Dr. S. V. Ley (Imperial College, London) for stimulating discussion.

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