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THE SYNTHESIS OF A KEY INTERMEDIATE OF TRICYCLIC BETA-LACTAM ANTIBIOTICS

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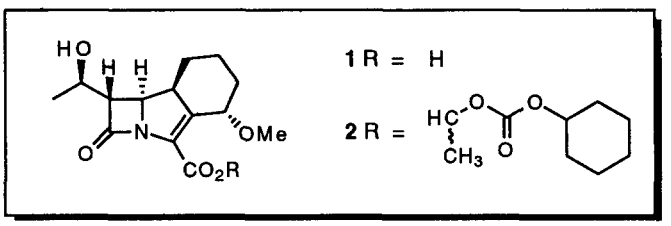
Abstract: By employing an intramolecular Sakurai-type olefination it was possible to obtain the olefin **5**, a key intermediate in the synthesis of the broad spectrum tricyclic β–lactam antibiotic GG-326 **1**.

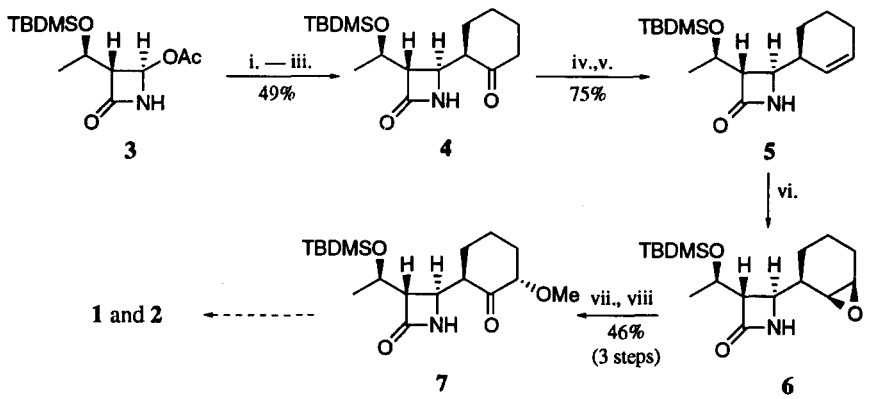
Recently, the tricyclic β–lactam antibiotic GG-326 **1** (formerly referred to as GV104326[1]) and its orally active ester pro-drug **2** (**Fig. 1**) have been the subject of considerable study due to their broad spectrum antibacterial activity, resistance to β–lactamases and stability to renal dehydropeptidases, a potential problem for the penem and carbapenem classes of antibiotics.[1]



(Fig. 1)

The above compounds, and other members of this class, also represent a considerable synthetic challenge.[2] One of the earliest routes to compounds **1** and **2**, used to make multi-kilogram quantities, is outlined in **Scheme 1**. As part of a program aimed at finding shorter, higher yielding routes, we decided to investigate the possibility of synthesising, in a single stereoselective step, the olefin **5**. Our attention was drawn to the elegant exploitation, by Uyeo and co-workers, of an intramolecular Sakurai-type reaction in a highly stereoselective formation of a key intermediate in the synthesis of 1β-methylcarbapenems,[3,4] and we wished to employ a similar strategy for the synthesis of olefin **5**.

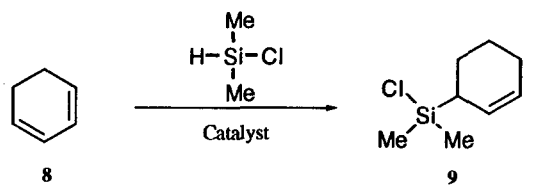
However, in the formation of olefin **5** by this method, there is an added degree of complexity with respect to the (Z)-2-butenylchlorodimethylsilane used by Uyeo.[3] In our case we needed to use cyclohex-2-enyldimethylsilyl chloride **9** bearing an asymmetric centre.



i. TMS-Cl, Et_3N, MeCN,. ii. 1-trimethylsilyloxycyclohexene, TMSOTf, MeCN. iii. KF, MeOH. iv. $TsNHNH_2$. v. LDA, THF. vi. Mg-monoperoxyphthalate, CH_2Cl_2. vii. MeOH, PTSA. viii. Py/ SO_3.

Scheme 1

We also wished to study the influence of this chiral centre on the stereochemistry of product formation. The synthesis of compound **9** was carried out by hydrosilylation of 1,3-cyclohexadiene with chlorodimethylsilane under a variety of conditions (**Scheme 2**).[5,6] The results are outlined in the **Table.**



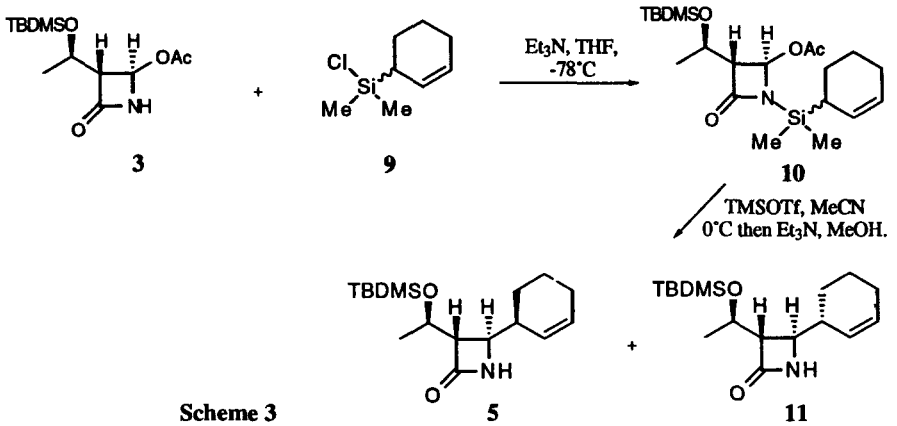
Scheme 2

Entry	Catalyst	Temperature	Time	Yield of 9 ¤
1[6]	$Ni(Acac)_2$/ $AlEt_3$	-78°C - 0°C	1h	72%
2	$Cl_2Pd[PhCN]_2/PPh_3$	100°C*	6h	66%
3	$Pd(PPh_3)_4$	100°C*	6h	82%
4	$ClRh(PPh_3)_3$	100°C*	6h	83%

* Sealed tube. ¤ yield after distillation (66°C, 16 mbar).

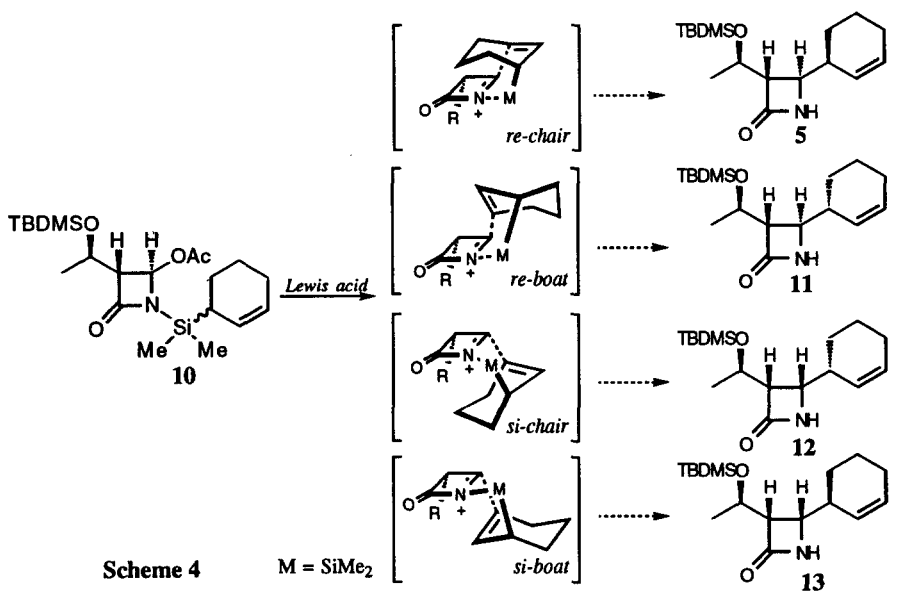
Using a nickel acetylacetonate/triethyl aluminium catalyst system it was possible to obtain the desired product in satisfactory yield at low temperature (**Table**, Entry 1). The other catalysts required higher temperatures to effect the reaction, requiring the use of a sealed reaction tube due to the volatility of dimethylchlorosilane and 1,3-cyclohexadiene.

The chlorosilane **9** was reacted with the 4-acetoxy compound **3** to give the N-silyl derivative **10** which underwent TMSOTf catalysed rearrangement to give the olefins **5** and **11** in a 4:1 ratio respectively and 50% overall yield (**Scheme 3**).[7]



Scheme 3

The stereoselectivity of the process can be explained in terms of the effect of the asymmetric centre generated in the hydrosilylation reaction. The rearrangement of the epimeric mixture **10** presumably proceeds *via* a cyclic transition state which can be represented as in **Scheme 4.**



Scheme 4 M = $SiMe_2$

The epimer of **10** which gives the desired olefin **5** would pass through a *pseudo*-chair transition state on the *re*- face of the reactive azetinone whereas olefin **11** would derive from a less favourable *pseudo*-boat transition state. The formation of isomers **12** or **13** would require the positioning of the cyclohexene ring in the *si*- face of the azetinone, bringing it in close proximity of the sterically demanding 4-silyloxyethyl substituent. No evidence for the presence of isomers **12** or **13** was found in the reaction products. In

summary, the procedure described above allowed us access to a key intermediate in the synthesis of tricyclic β-lactam antibiotics in a single stereoselective step.

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References and Notes

1 Di Modugno, E; Erbetti, I.; Ferrari, L; Galassi, G; Hammond, S.H.; Xerri, L. *Antimicrob. Agents Chemother.* **1994**, *38*, 2362.

2 For a review of the chemistry and biological activity of a series of tricyclic β-lactams see: Perboni, A., Tamburini, B., Rossi, T., Donati, D., Tarzia, G. and Gaviraghi, G. in "Recent Advances in the Chemistry of Anti-infective Agents" - ed. Bentley, P.H.; Ponsford, R., RSC Cambridge, pp 21-35, **1992**. Padova, A., Roberts, S. M., Donati, D., Perboni, A. and Rossi, T., *J. Chem. Soc. Chem. Commun.*, **1994**, 441.

3 a. Uyeo, S. and Itani, H., *Tetrahedron Lett.* **1991**, *32*, 2143. b. Uyeo, S., US Pat. 4960880. c. Imuta, M., Itani, H., Nishi, K., Ona, H. , Uyeo, S. and Kimura, Y., *Bio. Med. Chem. Lett.*, **1993**, *3*, 2199.

4 For a recent review of the use of allylic metals see: Yamamoto, Y. and Asao, N., *Chem. Rev.*, **1993**, *93*, 2207.

5 For a review of the hydrosilylation of olefins see: Ojima, O. in "*The Chemistry of Organic Silicon Compounds*" Eds S. Patai & Z. Rappoport, **1989**, vol 2, 1479.

6 Experimental procedure for **Table** Entry 1: Dry $Ni(Acac)_2$ (0.5g, 1.8mmol) was added to a -78°C solution of 1,3-cyclohexadiene (5.2ml, 54.6mmol) and $Me_2(Cl)SiH$ (4.0ml, 36mmol) under N_2, and the mixture stirred for 15 min. Et_3Al (7.2ml of a 1M solution in hexanes) was then added over 15 min (caution, exotherm!). The reaction was allowed to warm to 0°C and stirred for a further 30 min. The reaction was then filtered under N_2 into a distillation apparatus and volatile residues removed by the careful application of a low vacuum. Distillation (66°C, 16 mbar), gave chlorosilane **9** (4.51g, 72%). ^1H NMR (400MHz, $CDCl_3$): 5.8 (m, 1H); 5.6 (m, 1H); 2.2-1.4 (m, 7H); 0.4 (s, 6H).

7 Triethylamine (0.35ml, 2.5mmol) was added to a -78°C solution of **3** (0.5g, 1.7 mmol) and chlorosilane **9** (1.0g, 5.6 mmol) in dry THF (10ml). The reaction was stirred for 4 h at -78°C before filtering under N_2 and removal of volatile material *in vacuo*. The resulting viscous oil **10** was dissolved in dry MeCN (5ml) and cooled to 0°C. TMSOTf (0.33ml, 1.9mmol) was added over 2 min and the reaction mixture stirred for 30 minutes before adding a mixture of Et_3N (0.7ml) and MeOH (2.8ml) and stirring at room temperature for 4 hours. After partitioning between ethyl acetate and water, the organic phase was dried, filtered and concentrated *in vacuo*. Flash chromatography (1:4 EtOAc:cyclohexane) gave the olefins **5** and **11** (277mg, **50%** from **3**) as an 8:2 inseparable mixture.

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