A Short and Efficient Synthesis of a Key Intermediate for Maytansinoid Construction

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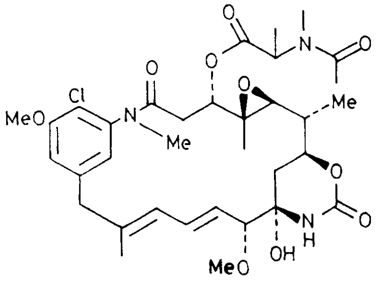
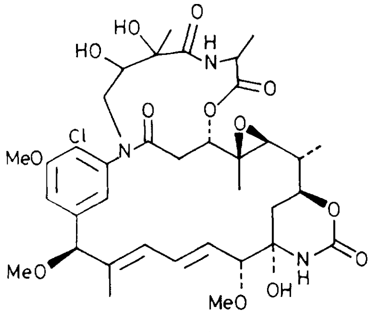
The cyclic carbamate (**3**), a key intermediate for our projected synthesis of trenudine (**2**), has been synthesised from 3,4-epoxycyclohexene (**4**) with ozonolytic cleavage of the cyclopentene (**7**) as a key step.

The maytansinoids are a class of biologically active macrocyclic amides first isolated from the fruit and leaves of *Maytenus ovatus*.[1] Since the isolation of maytansine (**1**) in 1972 several groups have succeeded in its synthesis; these are described in a recent review by Paterson and Mansuri.[2] The maytansinoid trenudine (**2**) was isolated from *Trewia nudiflora* (*Euphorbiaceae*) which possesses exceedingly potent insect antifeedant activity.[3]



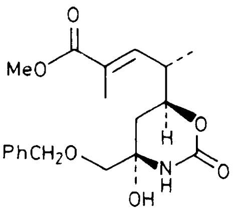
(**1**)



(**2**)

As part of a project aimed at the construction of trenudine (**2**), we have developed an efficient route to the cyclic carbamate (**3**), which constitutes the C-3—C-10 fragment of the macrocycle.

The route to the carbinolamide (**3**) is shown in Scheme 1,† starting with readily available 3,4-epoxycyclohexene (**4**).[4] Compound (**4**) was treated with dimethylmagnesium resulting exclusively in a *trans*-alcohol (83%)[5] which on silylation gave the ether (**5**) (90%). The silyl ether (**5**) was ozonolysed, and reductive workup (H_2, Pd/C, MeOH) gave a dialdehyde which was immediately cyclised using dibenzylammonium trifluoroacetate[6] in dichloromethane solution to yield the cyclopentene aldehyde (**6**) (57% overall yield). Reduction of the



(**3**)

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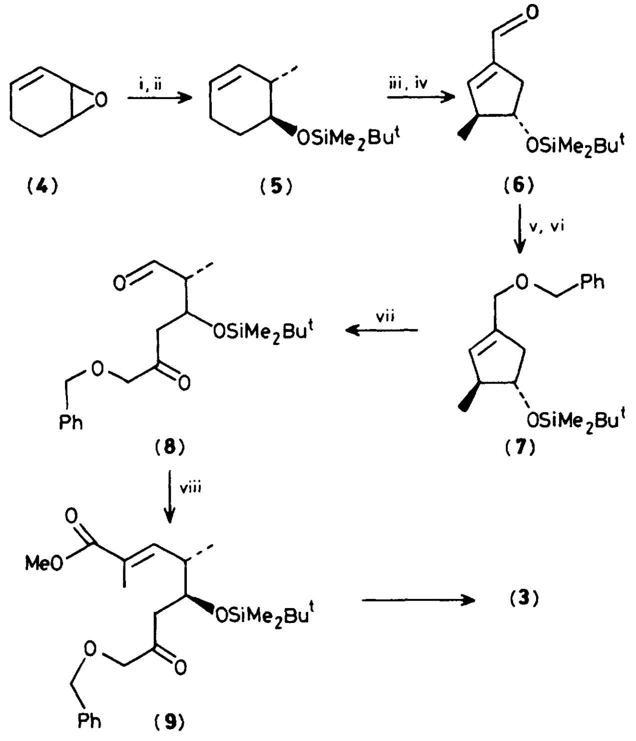
† All compounds are racemic; only one enantiomer is depicted for clarity. All compounds were fully characterised by ^1H and ^{13}C n.m.r., i.r., mass spectrometry and/or microanalysis. All yields refer to isolated compounds of analytical purity.



Scheme 1. *Reagents:* i, Me_2Mg/Et_2O; ii, Bu^tMe_2SiCl, 4-*N*,*N*-dimethylaminopyridine/dimethylformamide; iii, O_3 then $H_2/Pd/C$; iv, $(PhCH_2)_2NH_2CF_3CO_2/CH_2Cl_2$; v, Li $(OBu^t)_3H$; vi, $PhCH_2Br/NaH/NaI$/dimethoxyethane; vii, O_3 then Ph_3P; viii, $Ph_3P{=}C(Me)CO_2Me$.

aldehyde (**6**) with $Li(OBu^t)_3H$ gave an alcohol (95%) which was converted into the benzyl ether (**7**) (90%). Ozonolysis of (**7**), followed by reductive workup with triphenylphosphine, gave the keto-aldehyde (**8**) (43%) which on treatment with (α-methoxycarbonylethylidene)triphenylphosphorane provided the regio- and stereo-chemically pure unsaturated ester (**9**) as the sole product (55%). In order to improve this procedure the ozonide derived from (**7**) was treated with triphenylphosphine and (α-methoxycarbonylethylidene)triphenylphosphorane *in situ*, giving (**9**) directly in 85% overall yield. Removal of the silyl protecting group (84%) with aqueous hydrofluoric acid and reaction of the product with nitrophenyl chloroformate, followed by workup with ammonia,[7] gave the cyclic carbamate (**3**) as a white crystalline solid.

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References

1 S. M. Kupchan, Y. Komoda, W. A. Court, G. J. Thomas, R. M. Smith, A. Karim, C. J. Gilmore, R. C. Haltiwanger, and R. F. Bryan, *J. Am. Chem. Soc.*, 1972, **94**, 1354.
2 I. Paterson and M. M. Mansuri, *Tetrahedron*, 1985, **41**, 3569.
3 R. G. Powell, D. Weisleder, C. R. Smith, Jr., J. Kozlowski, and W. K. Rohwedder, *J. Am. Chem. Soc.*, 1982, **104**, 4929.
4 J. K. Crandall, D. B. Banks, R. A. Colyer, R. J. Watkins, and J. P. Arrington, *J. Org. Chem.*, 1968, **33**, 423.
5 J. Staroscik and B. Rickborn, *J. Am. Chem. Soc.*, 1971, **93**, 3046.
6 E. J. Corey, R. L. Danheiser, S. Chandrasekaran, P. Siret, G. E. Keck, and J.-L. Gras, *J. Am. Chem. Soc.*, 1978, **100**, 8031; J.-L. Gras, *Tetrahedron Lett.*, 1978, 2111.
7 M. Kitamura, M. Isobe, Y. Ichikawa, and T. Goto, *J. Org. Chem.*, 1984, **49**, 3517.