Photochemical transformations of pyridinium salts: mechanistic studies and applications in synthesis

Teresa Damiano,* Daniel Morton* and Adam Nelson

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The discovery, understanding and synthetic exploitation of the photochemical transformation of pyridinium salts are described. The investigations surrounding the remarkable transformation of pyridinium salts into a host of structurally complex motifs have helped extend the comprehension of aromatic and heteroaromatic photochemistry. The synthetic community has, in recent years, recognised the potential inherent in these compounds and has since exploited the irradiation of variously substituted pyridinium salts as key steps in the preparation of advanced intermediates in numerous synthetic programmes.

1. Introduction

Photochemical reactions can transform structurally simple molecules into compounds with complex skeletons, often with high stereo- and regiocontrol.[1] Recently, during a detailed study of a range of photochemical transformations,[2] methods have been developed that enable photochemical reactions to be routinely performed on a large scale, making these processes more accessible to the synthetic organic chemistry community. The irradiation of pyridinium salts provides the facile, stereocontrolled synthesis of a range of molecular architectures such as bicyclic aziridines, fused heterocycles and various functionalised aminocyclopentenes.[1]

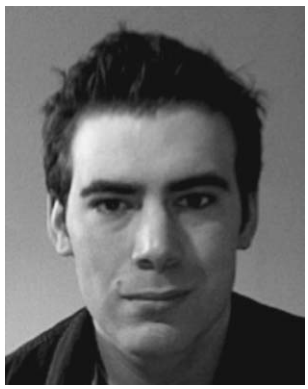
School of Chemistry, University of Leeds, Leeds, UK LS2 9JT

Teresa obtained her PhD from the University of Geneva (Switzerland), where she worked on the application of the phototransformation of pyridinium salts to synthesis of aminocyclopentitols. She then moved as a Marie Curie Fellow to the HTMC department of Sanofi-Aventis (France). In 2005 she joined the group of Prof. Nelson as a post-doctoral fellow. Her work focussed on the synthesis of GSK-3beta inhibitor libraries and in the elucidation of the role of protein kinases in the self-renewal of murine stem cells (in collaboration with Prof. Melanie Welham, University of Bath).

Daniel Morton was born in Louth, UK (1979). He received his MChem in 2001 from the University of East Anglia (UK), where he remained and under the joint supervision of Dr Robert Stockman and Professor Robert Field obtained his PhD in 2005 for work on the reaction of sulfur ylides with tert*-butylsulfinimines for the synthesis of chiral aziridines. He is currently employed at Leeds University under the supervison of Adam Nelson as a postdoctoral fellow involved in studies toward the Diversity-Oriented Synthesis of natural product-like molecules.*

Adam Nelson is Professor of Chemical Biology at the University of Leeds, with research interests in synthetic organic chemistry and chemical biology. He obtained a BA in Natural Sciences from Churchill College, University of Cambridge in 1993, and his PhD (under the supervisor of Dr Stuart Warren) in Synthetic Organic Chemistry, also from Cambridge, in 1996. He undertook postdoctoral research with Prof. E. J. Thomas at the University of Manchester before joining the academic staff at the University of Leeds in 1998.

Teresa Damiano



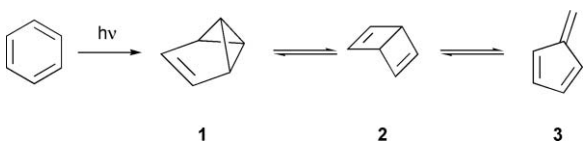
Daniel Morton

Adam Nelson

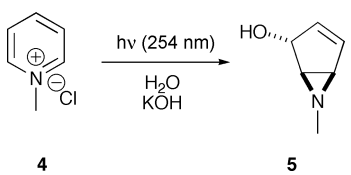
This review covers several aspects of the photochemical reactions of pyridinium salts: their mechanism, their scope and limitations in synthetic chemistry and their exploitation in the synthesis of a variety of biologically active molecules.

1.1. Phototransformations of aromatic compounds

Aromatic compounds have been found to undergo a remarkable range of photochemical reactions. The diversity of scaffolds and transformations accessible through irradiation of aromatic substrates has inspired chemists for over forty years. Key landmarks in the study of the photochemistry of benzene (Scheme 1) include the characterisation of Dewar benzene **2** (in 1962),[3] benzvalene (or tricyclo[2.1.1.$0^{8\,6}$]hex-2-ene) **1** (in 1964)[4] and fulvene **3** (in 1967).[5] These and many other investigations[6] have contributed to build a detailed mechanistic and theoretical understanding of equilibria under photochemical conditions.[7,8] It was from this intense period of investigation that the initial exploration of pyridine and pyridinium salt photochemistry emerged, a logical extension of the fundamental studies into the photochemistry of benzene. In 1970, Wilzbach and Rausch reported their findings on the photoirradiation of pyridine, in which Dewar pyridine was identified and described for the first time.[9] In 1972, Wilzbach, Kaplan and Pavlik expanded upon these studies, describing the photoirradiation of a range of *N*-methyl pyridinium chlorides.[10] Photosolvolysis of pyridinium salts (such as **4**) in basic aqueous solution gave the *exo*-6-methylazabicyclo[3.1.0]hex-3-en-2-ols (such as **5**) with high stereoselectivity (Scheme 2). In more recent years the bicyclic aziridine product **5** has become recognised as a key synthetic intermediate in the preparation of molecules with more complex skeletons.[11]



Scheme 1 Photoisomerisation of benzene.

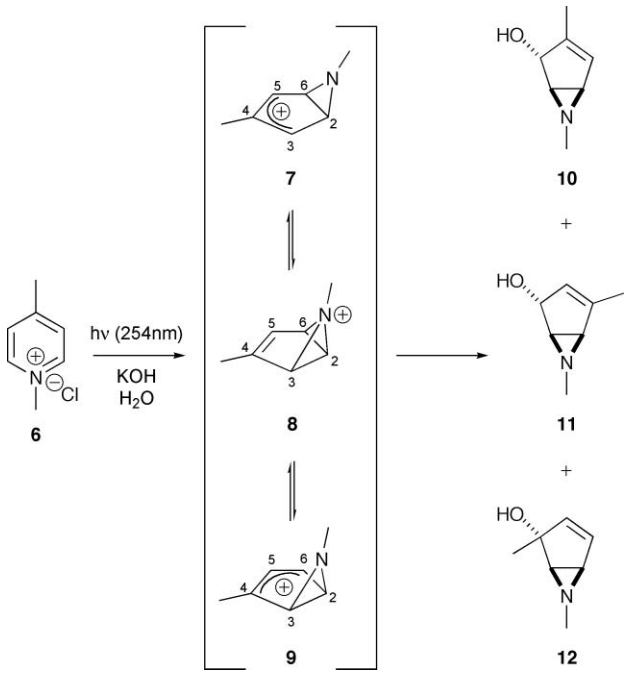


Scheme 2 Photochemical transformation of *N*-methylpyridinium chloride under basic conditions.

2. Mechanistic and theoretical studies on the photochemistry of pyridinium salts

2.1 Initial contributions of Kaplan, Pavlik and Wilzbach

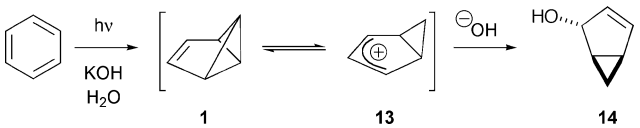
In 1972, Kaplan, Pavlik and Wilzbach described the irradiation of several substituted *N*-methylpyridinium chlorides **6** (Scheme 3).[10] Irradiation of the pyridinium salts **6** at 254 nm in aqueous base furnished the bicyclic aziridines **10–12**. The methylether analogues of the aziridines were obtained when the reaction was performed



Scheme 3 Photosolvation of 1,4-dimethylpyridinium chloride.

in methanol. Moreover, it was found that irradiation of the more substituted pyridinium derivatives, *i.e.* the 3,5-lutidinium salts, furnished analogous products in comparable yields. A key observation was the transposition of the substituents around the ring (as in **10**, **11** and **12**), which was thought to originate from the involvement of a key intermediate: the azabenzvalene cation **8** (see Scheme 3). The relative configuration of the bicyclic aziridine products **10–12** stems from *exo* addition of the incoming nucleophile, *anti* to the aziridine ring of the bicyclic cations **7** and **9**.

The proposed involvement of the azabenzvalene cationic intermediate highlights a key difference between the photochemistry of pyridine derivatives and pyridinium salts: the formation of the azabenzvalene is a consequence of a $\pi \rightarrow \pi^*$ excitation, whereas the irradiation of pyridine, resulting in a $n \rightarrow \pi^*$ excitation, leads to the bicyclic valence isomer, Dewar pyridine.[10,12] Thus, the phototransformation of pyridinium salts is more reminiscent of the photochemistry of benzene, where hydration of benzvalene **1** leads to bicyclo[3.1.0]hex-3-en-2-*exo*-ol **14** (Scheme 4). The mechanism of the photochemical transformation of benzene (→ **1** → **13** → **14**) was proposed by Wilzbach, Kaplan and Rischter,[13] and later ratified by others.[14,15]



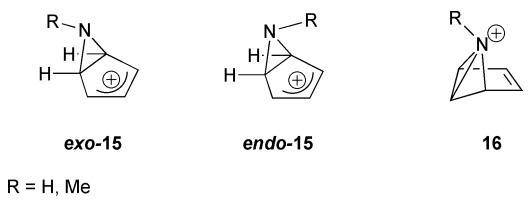
Scheme 4 Photohydration of benzene.

2.2. Theoretical and mechanistic studies of Burger and co-workers

Extensive theoretical studies of the mechanisms of the photochemical reactions of benzene[16] and pyridine[9,17] have been carried out,

however the photochemical reactions of pyridinium salts have only recently received significant attention. In 2001, prompted by the renaissance of the synthetic photochemistry of pyridinium salts, Burger and Lüthi *et al.* reported their insights into the events originating from $\pi \rightarrow p^*$ excitation.[18]

Completely optimised geometries for the equilibrium, intermediate and transition state structures of species arising from pyridinium and methyl pyridinium ions were determined using a combination of restricted Hartree–Fock (RHF) and density functional theory DFT (B3LYP) calculations (Fig. 1). Both the *endo*- and *exo*-methyl bicyclic ions (*endo*- and *exo*-**15**) were minima on the potential energy surface: the RHF calculations predicted that both *endo*- and *exo*-**15** would have C_S symmetry, while B3LYP predicted some distortion of the *exo*- form towards the azabenzvalene structure. The azabenzvalene structure **16** was predicted to be C_S-symmetric. These three structures (*exo*-**15**, *endo*-**15** and **16**) were found to be the only optimisable structures following the initial photoexcitation event. The presence of the nitrogen atom, unsurprisingly, caused the electronic structures of the species **15** and **16** to differ significantly from the analogous species derived from benzene (see Scheme 3 and 4). The *exo*-bicyclic cation **15** was stabilised through overlap of the nitrogen lone-pair with the π-system. The C_S-symmetric nature of the azabenzvalene structure **16** demanded that it would equilibrate with the bicyclic cation *exo*-**15** through statistical cleavage of its enantiotopic allylic C–N bonds, of course, in the case of a substituted azabenzvalene, unselective ring-opening would lead to transposition of the nitrogen atom around the cyclopentene ring (for an example of this transposition see Scheme 3).



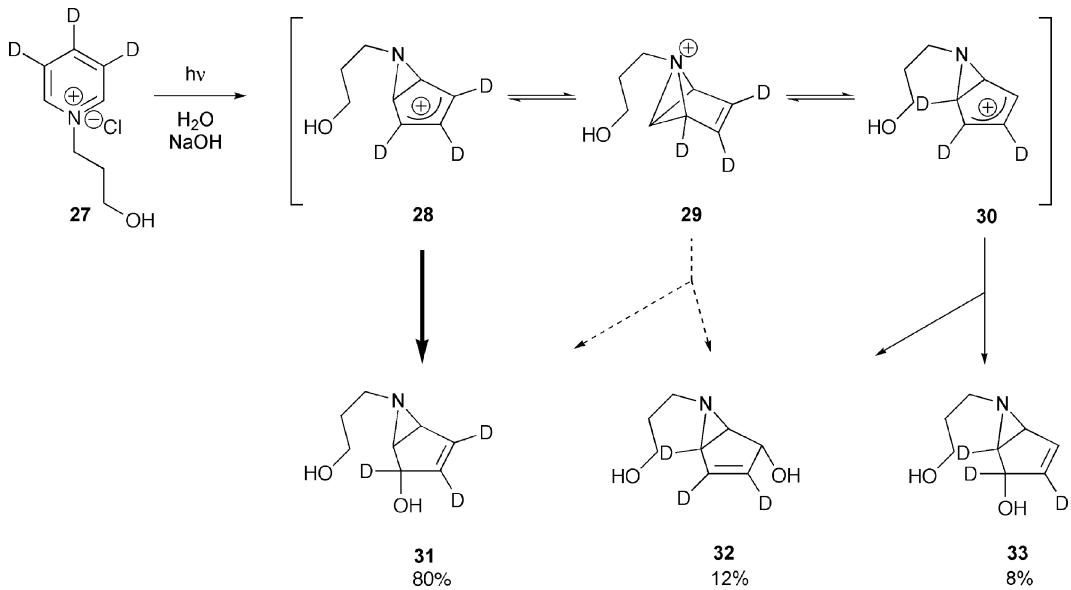
***exo*-15** ***endo*-15** **16**

Fig. 1 Geometric structure of the initial photoproducts.

Having established a detailed picture of the species involved, Burger and Lüthi then turned their focus to the investigation of the reaction mechanism. The study supported a mechanism which was broadly analogous to that of benzene (see Scheme 4); the initial $\pi \rightarrow p^*$ excitation resulted in rearrangement to the *exo*-bicyclic ion **15** *via* a 2,6-bridging mechanism (Fig. 2). For both the pyridinium and methylpyridinium-derived species, there was a strong preference for the *exo*-invertomers *exo*-**18** and *exo*-**23**. In both cases, the transition state for pyramidalisation of the aziridine nitrogen (**19** and **24**) was around 17 kcal mol^{-1} above the *exo* invertomer, a result which was in excellent agreement with the barriers found for other *N*-alkyl aziridines.[19]

The conversion of the *exo*-bicyclic cations **18** and **23** into the corresponding azabenzvalene species was found to proceed *via* a low-lying transition state (*exo*-**18** → **20** → **21** and *exo*-**23** → **25** → **26**). These low-lying transition states are reached through twisting of the cyclopentyl ring to allow attack of the aziridine nitrogen lone pair onto one of the ends of the allylic cation. The facile equilibration between *exo*-**18** and the corresponding azabenzvalene species **21** (Fig. 2) was also observed in more substituted systems.

A series of deuterium labelling experiments have provided further insight into the rearrangement process (Scheme 5).[18] 3,4,5-Trideuterio-*N*-(3-hydroxypropyl)pyridinium chloride was used as the substrate for these studies, as the resulting photoproduct was not prone to Grob fragmentation. The major product **31**, obtained in 80% yield, was clearly the result of rapid trapping of the initially formed allylic cation **28**. The remaining material was presumed to be formed by rearrangement of **28** to the azabenzvalene ion **29** and, hence, **30**, with subsequent trapping with water. Presuming no secondary isotope effects, it was suggested the observed unequal mixture of **32** and **33** was due to some of **32** being formed through direct trapping of the azabenzvalene ion intemediate.



Scheme 5 Deuterium labelling studies of pyridinium salt phototransformations.

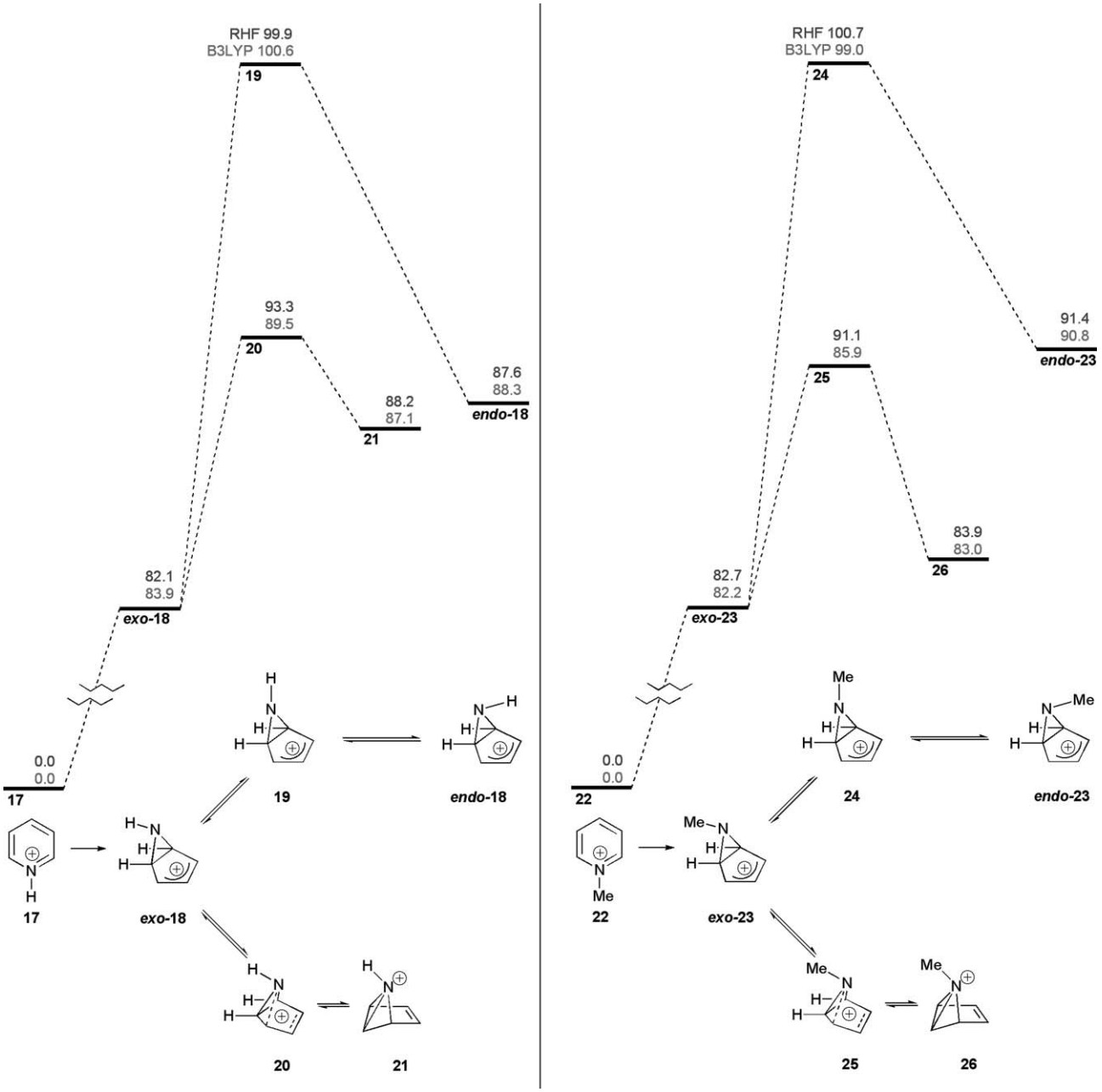
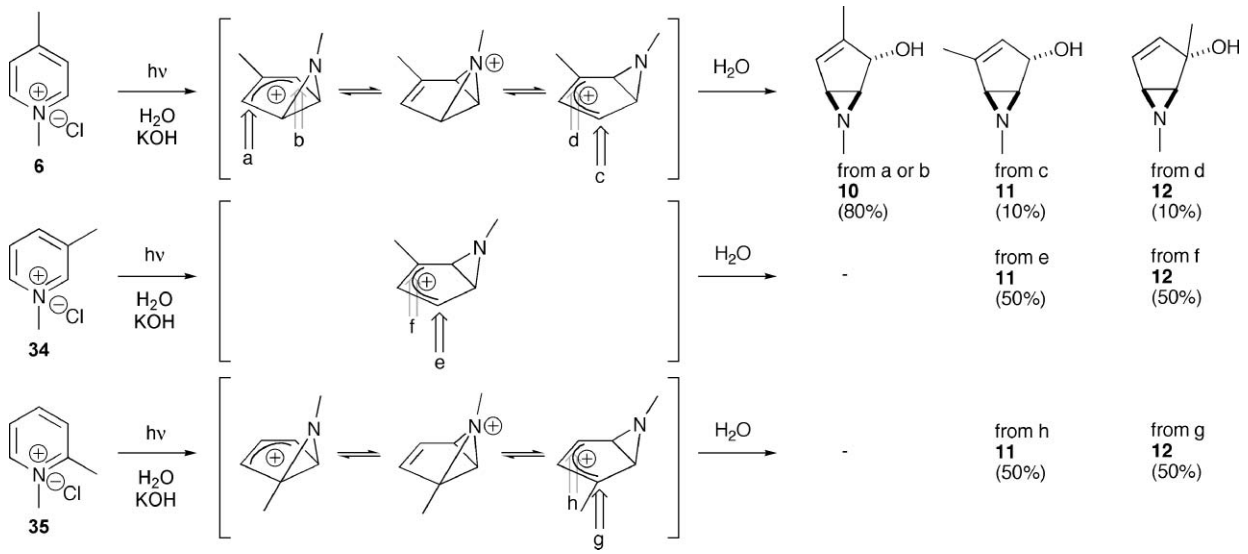


Fig. 2 Adaptation of Burger and Lüthi's representation of the relative energies for the phototransformation of pyridinium and *N*-methylpyridinium salts (kcal mol^{-1}).

The effect of substitution on the rearrangement process was also probed (Scheme 6).[18] A 4-methyl substituent—as in 1,4-dimethylpyridinium chloride **6**—did not have a significant effect on the product distribution of the photosolvolysis reaction. The major product **10** (80%) was formed through direct trapping of the initially formed allylic cation, and the mass balance (→ **11** and **12**) stemmed from rearrangement, followed by trapping. However, with a 3-methyl substituent (**34**), there was no evidence for rearrangement: the equimolar mixture of the products, **11** and **12**, arose from unselective trapping of the initially formed allylic cation. Conversely, with a 2-methyl substituent (**35**), an equimolar mixture of products, **11** and **12**, was formed, this time the products stemmed solely from rearrangement, followed by trapping.

To try and gain an understanding of the effect of methyl substituents on the regioselectivity of the hydration reaction, Burger and Lüthi conducted further theoretical studies (see Fig. 3). With a 4-methyl substituent on the pyridinium ring, the energy profile was rather similar to that for an unsubstituted pyridinium salt (starting at **40**). However, the additional methyl group meant that the allylic C–N bonds in the azabenzvalene **38** were no longer enantiotopic: ring-opening to give **36** was favoured over ring-opening to give **40** due to stabilisation of the developing allylic cation **37** by the methyl group. In contrast, with a 3-methyl group, the initially formed bicyclic cation *exo*-**36** was highly stabilised by the additional methyl group, and was trapped to give both **11** and **12**. With a 2-methyl group in the starting



Scheme 6 Product distribution and yields for the photohydration of the picoline derivatives **6**, **34** and **35**.

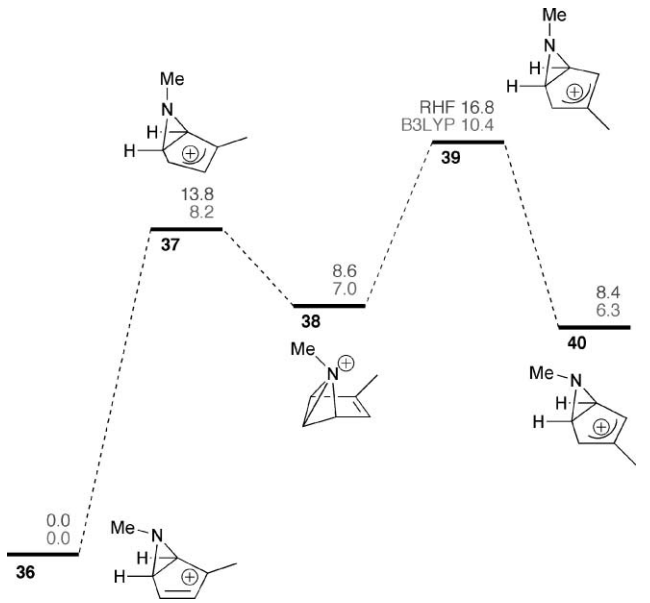


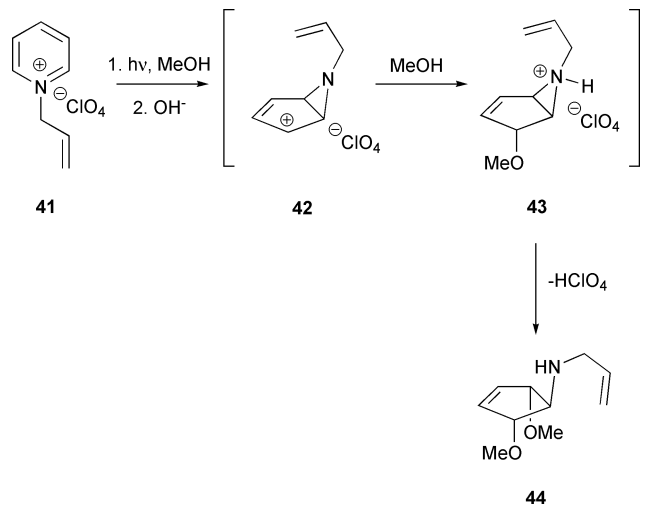
Fig. 3 Adaptation of Burger and Lüthi's representation of the schematic relative energies for reaction of dimethylpyridinium salts (kcal mol^{-1}).

material, the presence of an additional methyl group on the aziridine bridgehead destabilised the initially formed bicyclic cation. Rapid rearrangement to the stabilised bicyclic cation **36**—*via* the azabenzvalene cation **38**—was therefore expected. Indeed with 1,2-dialkylated pyridinium salts, rearrangement of the initially formed allylic cation, prior to nucleophilic addition, is generally observed. These general principles may also be used to rationalise the reactivity of 1,3,5-substituted lutidinium salts.[18]

3. Phototransformation of substituted pyridinium salts

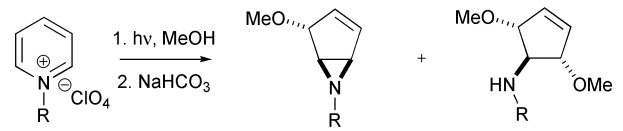
3.1. Photosolvation under acidic conditions

The synthetic potential of this remarkable transformation had remained largely unexplored for over ten years. In 1982 however, Mariano and co-workers almost succeeded in reviving the interest in the photochemistry of pyridinium salts.[20] Irradiation of a methanolic solution of the *N*-allylpyridinium perchlorate **41**, followed by neutralisation and distillation, yielded the *trans*,*trans*-aminocyclopentene **44** in 86% yield (Scheme 7). The authors proposed that attack of methanol on the bicyclic allylic cation **42** was followed by methanolysis of the resulting protonated aziridine **43** to give the trisubstituted cyclopentene **44**.



Scheme 7 Photosolvation of *N*-allylpyridinium perchlorates in methanol.

In 1996, Mariano extended his approach to the synthesis of more highly substituted aminocyclopentene derivatives and dramatically revitalised interest in the synthetic photochemistry of pyridinium salts.[21] Photoreaction of the pyridinium salts **45a–c** gave mixtures of the bicyclic aziridine **46** and 4-aminocyclopentene **47** products (Scheme 8). Remarkably, with the pyridinium perchlorates **45b** and **45c**, participation of the tethered nucleophile was not observed. Indeed, even with less nucleophilic solvents, cyclisation was not observed, presumably because the resulting products would be highly strained. A pertinent observation from these studies was that the efficiency of the phototransformation



45a R = Pr
45b R = CH_2CONH_2
45c R = CH_2CH_2OH

46a 33%
46b 22%
46c 47%

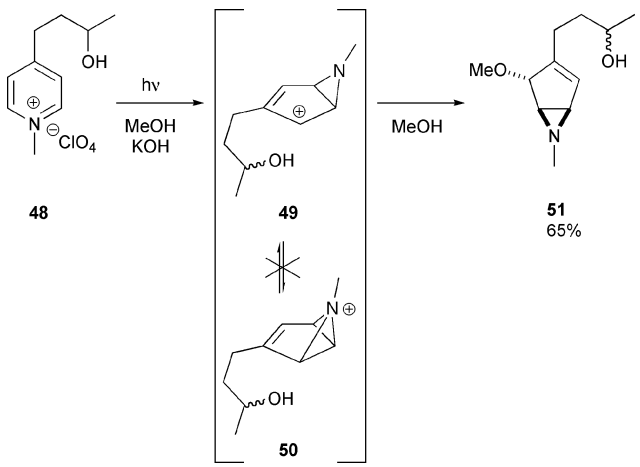
47a 22%
47b 58%
47c 22%

Scheme 8 Photosolvation of *N*-substituted pyridinium salts in methanolic solution.

was strongly dependent upon the polarity of the solvent employed, with more polar solvents affording higher yields. The ratio of the products depended on the work-up procedure: neutralisation prior to concentration allowed the partial survival of the bicyclic aziridine **46**, with the deprotonated bicyclic aziridine **46** not being so susceptible to methanolysis. On the other hand concentration prior to treatment with base gave the resultant methanolysis products, the aminocyclopentenes **47**, exclusively.

3.2. Photosolvation under basic conditions

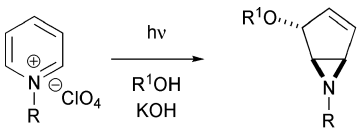
The photochemical reaction of the 4-(3-hydroxybutyl)pyridinium perchlorate **48** provided new mechanistic insights. Participation of the tethered alcohol did not occur and the tricyclic product was not obtained (Scheme 9). Further, the bicyclic aziridine **51** was formed in high yield and regioselectivity, and the transposition of substituents around the ring was not observed. The authors suggested that the high levels of regioselectivity observed for this transformation were due to the rapid capture of the bicyclic cation **49**, preventing the involvement of the azabenzvalene cation **50**.



48 **49** **51** 65% **50**

Scheme 9 Regioselective photoreaction of 4-hydroxybutylpyridinium perchlorate.

To extend their exploration of the scope of photohydration of pyridinium salts, Mariano and co-workers examined the reaction in both methanolic and aqueous potassium hydroxide solution (Scheme 10). The respective hydroxyl- (**52**) and methoxy-substituted (**46**) bicyclic aziridines were formed in good yield.



45a R = Pr
45b R = CH_2CONH_2
45c R = CH_2CH_2OH

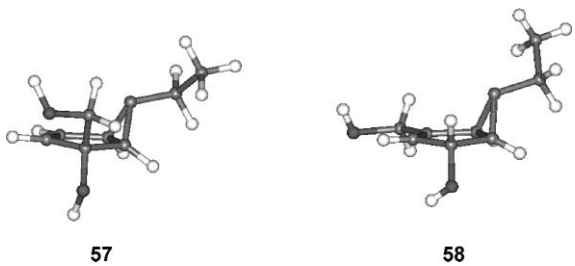
With R^1OH = MeOH
46a R^1 = Me 53%
46b R^1 = Me 90%
46c R^1 = Me 98%

With R^1OH = H_2O
52a R^1 = H 57%
52b R^1 = H 41%
52c R^1 = H 90%

Scheme 10 Photoirradiation of pyridinium salts in methanolic and aqueous potassium hydroxide solutions.

3.3. Photosolvation of *C*-substituted hydroxyalkylpyridinium salts

Burger and co-workers[22] explored the photohydration of the 2-, 3- and 4-hydroxymethylpyridinium halides (**53–55**) in basic media. The photoreactions were typically done on a 0.07 to 0.1 mmol scale, over a period of 45 to 65 h. Photocontraction of the *meta*-substituted derivatives **53** afforded equimolar mixtures of two bridged aziridines, **57** and **58** (Scheme 11), in poor to reasonable (10–49%) yield. The relative configuration of the products **57** and **58** (R = Et) was confirmed by X-ray crystallography (Fig. 4). In accord with the observations of Mariano,[21] participation of hydroxyl-substituted *N*-substituents (R = $(CH_2)_3OH$ and $CH_2CH(OH)CH_2OH$) was not observed. Irradiation of the *ortho*-substituted pyridinium salt **54** under the same conditions, provided, in comparable yield (43%), the same equimolar mixture of the 1,2-diol **57** and 1,4-diol **58**. The outcome of these reactions is consistent with attack of the nucleophile onto the *exo* face of the allylic cation **56**.



57 **58**

Fig. 4 X-Ray structure of the bridged aziridines **57** and **58** (R = Et).

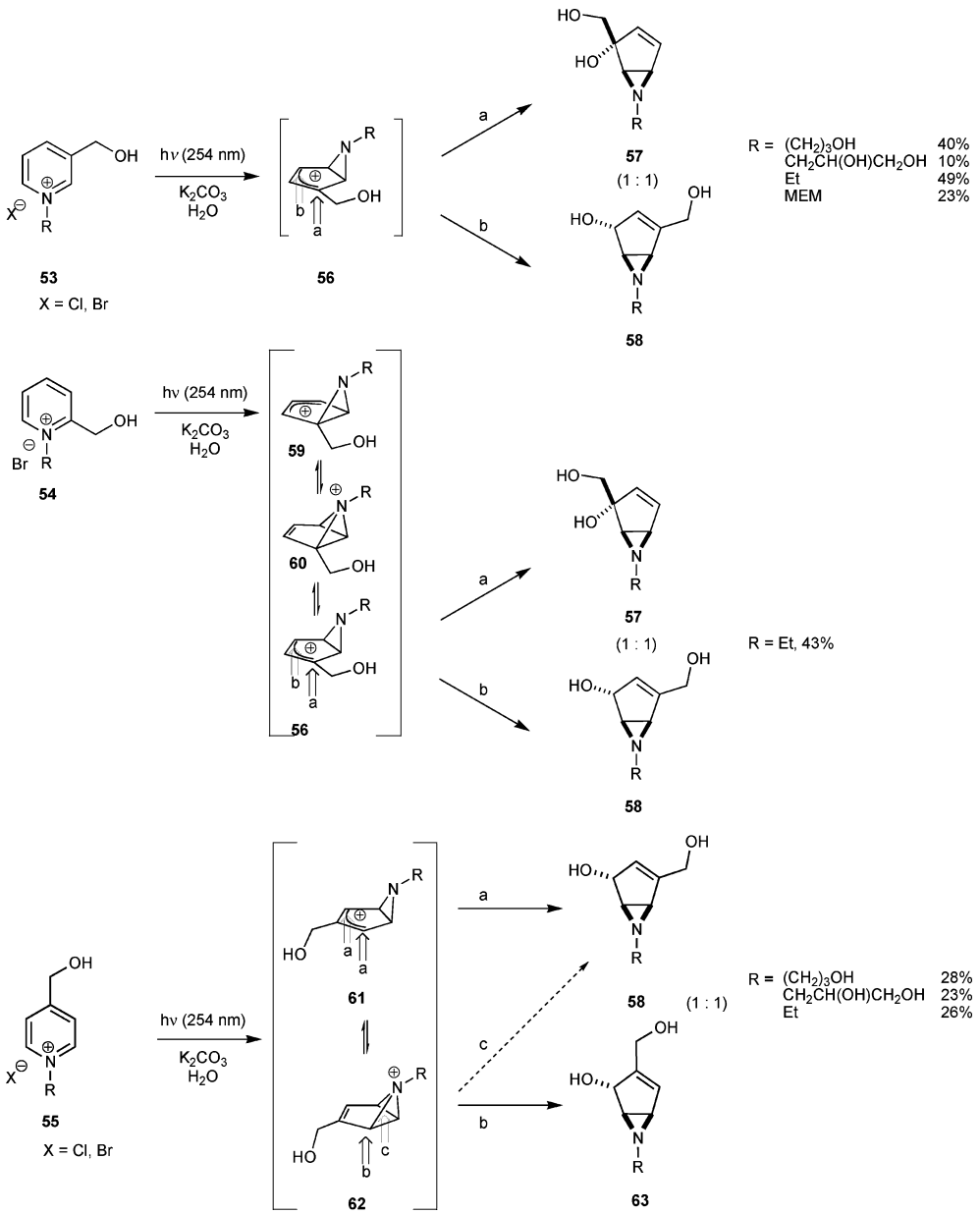
Irradiation of the *para*-substituted derivatives **55** afforded, in modest yield, an equimolar mixture of two bridged aziridines (Scheme 11): **58**, identical to that obtained from irradiation of the *ortho*- and *meta*-substituted pyridinium salts (Scheme 11), and **63**.

3.4. Photosolvation of 3-alkoxypyridinium salts

Penkett and Simpson studied the effect of an electron donating substituent at the 3-position of the pyridinium ring.[23] Irradiation of 5-methoxy-1,2-dimethylpyridinium tetrafluoroborate **64** in methanolic sodium hydroxide gave the intermediate **65** (Scheme 12).†

The presence of the electron donating methoxy substituent directed the regioselective formation of the ketal product, **66**

† For safety reasons, and ease of preparation, the reactions of the pyridinium tetrafluoroborate salts were studied.



Scheme 11 Photohydration of 2-, 3- and 4-hydroxymethylated pyridinium halides.

(Scheme 12). The ketal **66** was formed under basic conditions, and hence was not susceptible to equilibration. To demonstrate that the regiochemistry was kinetically controlled, a series of mixed ketals were prepared (Scheme 13). It was possible to prepare both diastereomers through judicious choice of substrates and conditions (compare entries 11 and 13, Table 1). Initially, the configuration of the product, assigned through NOE studies, was believed to be consistent with attack of the alcohol nucleophile on the *endo* face of the cationic intermediate.[23] However, later work, in which the X-ray crystal structure of an adduct was obtained, suggested that the configuration of the product may have been misassigned, and that *exo* attack was favoured.[24]

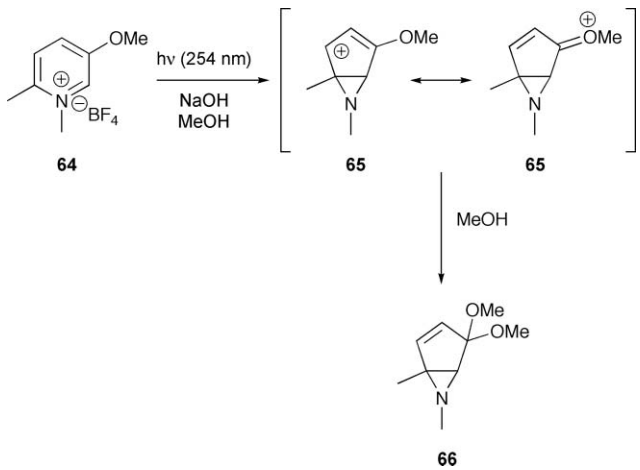
The scope and limitations of the photochemistry of 3-alkoxypyridinium salts in aqueous solution were explored in more detail.[23] Under these conditions, β-hydroxycyclopentenone derivatives **69** were obtained (Scheme 14). Hydrolysis of the cation would yield a hemi-ketal **67** and, hence, an enone **68**; conjugate addition of a second molecule of hydroxide would yield the observed product **69**. The configuration of the products **69** has been tentatively assigned using NOE experiments, and was consistent with addition of nucleophile to the *endo* face of the bicyclic enone **68**. The size of the group at the 2-position of the pyridinium ring had a direct influence on the yield of the reaction: with $R^2 = H$, very poor yields were observed (6%, Table 1, entry 1 and <5%, Table 2, entry 1), which improved with larger R^2 groups [Table 1, $R^2 = Me$, 41% (entry 3); $R^2 = Et$, 77% (entry 4); $R^2 = Pr$, 70% (entry 5); Table 2, $R^2 = Me$, 38% (entry 2), $R^2 = Et$, 40% (entry 3), $R^2 = Pr$, 44% (entry 4)].

Thus through careful choice of solvent and conditions, Penkett developed methods for the synthesis of two different scaffolds.

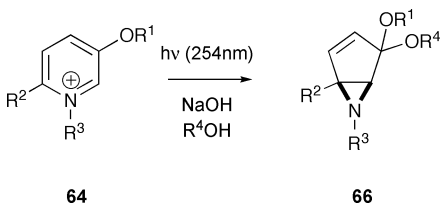
Table 1 Scope and limitations of the photosolvation of 3-alkoxypyridinium salts in alcoholic sodium hydroxide solution

Entry	Substrate	R^4OH	R^1	R^2	R^3	Product[a]	Yield (%)
1	**64a**	MeOH	Me	H	Me	**66a**	6
2	**64b**	MeOH	Me	H	Et	**66b**	17
3	**64c**	MeOH	Me	Me	Me	**66c**	41
4	**64d**	MeOH	Me	Et	Me	**66d**	77
5	**64e**	MeOH	Me	Pr	Me	**66e**	70
6	**64f**	MeOH	Me	Me	Et	**66f**	65
7	**64g**	MeOH	Me	Et	Et	**66g**	92
8	**64h**	MeOH	Me	Me	allyl-	**66h**	46
9	**64i**	MeOH	Me	Me	Bn-	**66i**	22
10	**64j**	MeOH	Pr	H	Et	**66j**	50
11	**64k**	MeOH	Pr	Me	Et	**66k**	81
12	**64b**	PrOH	Me	H	Et	**66b**	0
13	**64f**	PrOH	Me	Me	Et	**66f**	42

[a] See text for a discussion of the configuration of the products.



Scheme 12 Photoirradiation of 3-alkoxypyridinium tetrafluoroborates in basic methanol.



Scheme 13 Photosolvation of 3-alkoxypyridinium salts in alcohol.

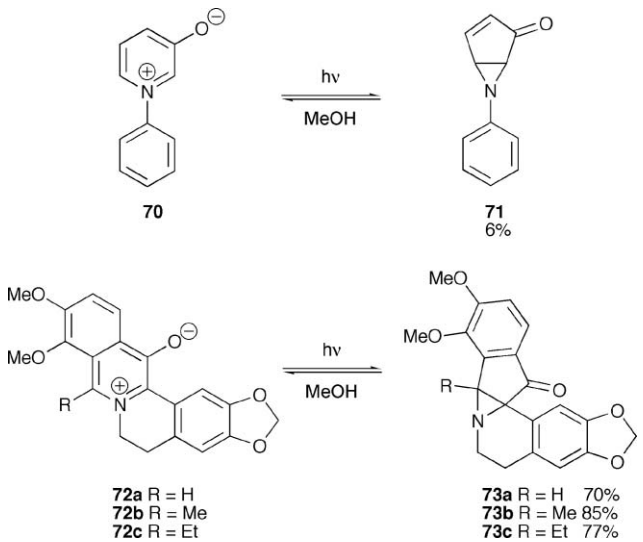
Reaction in basic alcoholic media afforded cyclopentenone ketals (such as **66**), whilst in water, β-hydroxycyclopentanones (such as **69**) were obtained.

Table 2 Scope and limitations of the photosolvation of 3-alkoxypyridinium salts in aqueous sodium hydroxide solution

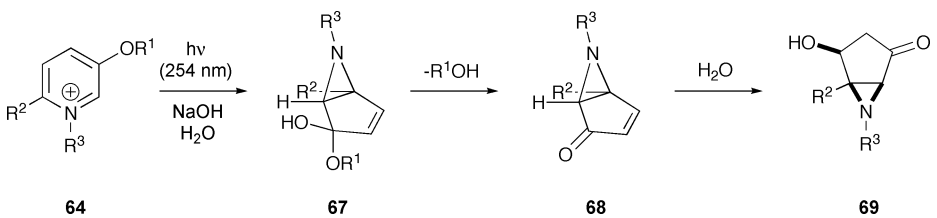
Entry	Substrate	R^1	R^2	R^3	Product	Yield (%)
1	**64a**	Me	H	Me	**69a**	<5
2	**64c**	Me	Me	Me	**69c**	38
3	**64d**	Me	Et	Me	**69d**	40
4	**64e**	Me	Pr	Me	**69e**	44
5	**64f**	Me	Me	Et	**69f**	34
6	**64g**	Me	Et	Et	**69g**	35
7	**64k**	Pr	Me	Et	**69k**	42

3.5. Phototransformation of polycyclic fused pyridinium salts

Irradiation of the berberinephenolbetaine analogues **72a-c** in methanol afforded the corresponding aziridines **73** in high yield (70–85%) (Scheme 15).[25] These results were remarkable as previous studies had shown that irradiation of the 3-oxido-1-phenylpyridinium betaine **70** gave the corresponding aziridine **71** in only 6% yield.[26] Interestingly this phototransformation was shown to be reversible. Irradiation of a methanolic solution of betaine **72** with a 100 W mercury lamp fitted with a Pyrex filter afforded the aziridine **73**, while on the other hand irradiation of a methanolic solution of aziridine **73** with a 400 W mercury lamp furnished the aziridine **72** in 55% yield. Though there is a clear change in the conjugation of this system upon phototransformation, the authors reported no observations regarding possible photochromic properties of the system.



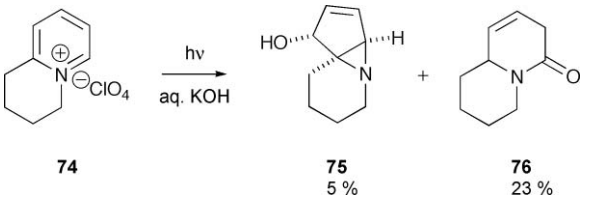
Scheme 15 Irradiation of a series of berberinephenolbetaines.



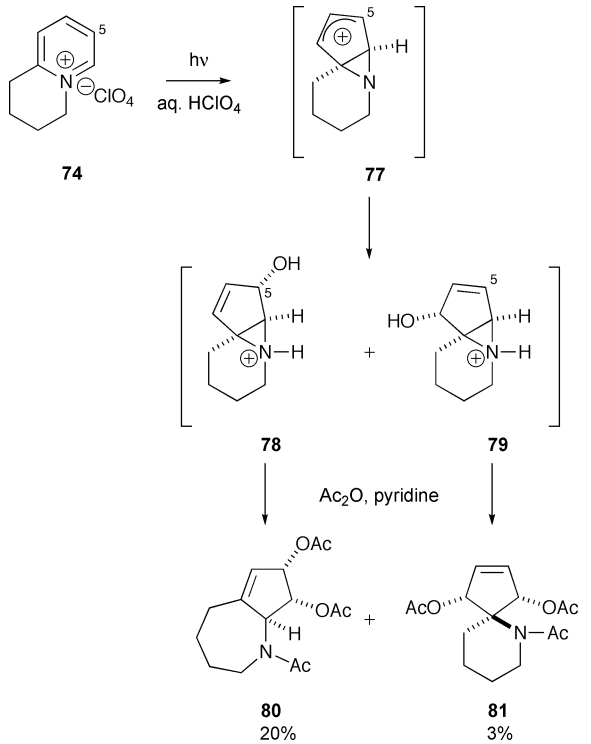
Scheme 14 Photohydration of 3-alkoxypyridinium salts in water.

3.6. Phototransformation of bicyclic fused pyridinium salts

Mariano *et al.* studied the photochemical reactions of fused pyridinium salts **74**.[27] Initial investigations examined the irradiation of the fused pyridinium perchlorate **74** under basic aqueous conditions. Irradiation of **74** furnished a complex mixture of photolysis products, from which the tricyclic allylic alcohol **75** and the dihydropyridone **76**, presumably originating from elimination of **75**, could be isolated (Scheme 16). In contrast, irradiation of **74** under aqueous acidic conditions, followed by treatment with acetic anhydride in pyridine, led to the formation of the spirocyclic diester **81** and the fused hydroazepine **80** (Scheme 17). Presumably, addition of water to the *exo* face of the cation **77** occurred preferentially at the less hindered *C*-5 position, giving a 7 : 1 mixture of the tricycles **78** and **79**; S_N2' (**78** → **80**) or S_N2 (**79** → **81**) ring opening, and peracetylation, would then give the observed products. Irradiation of the cyclopenta-fused pyridinium salt **82** in methanolic potassium hydroxide gave the tricyclic allylic alcohol **84** as the major product (Scheme 18).[27] S_N2 ring-opening of **84**, followed by peracetylation, furnished the *meso* diester **85** in high yield. To understand the selectivity of the process, a series of DFT calculations were undertaken. The authors proposed that the unusual regioselectivity in the nucleophilic attack on the cation **83** stemmed from the strained conformation of the tricyclic aziridine **83** which is peculiar to the cyclopenta-fused ring system.



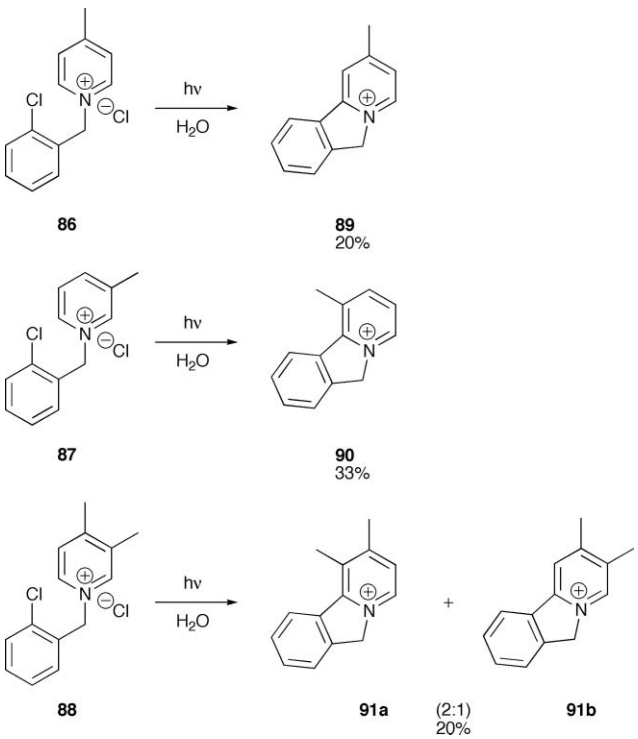
Scheme 16 Photoirradiation of the cyclohexa-fused pyridinium salt under basic conditions.



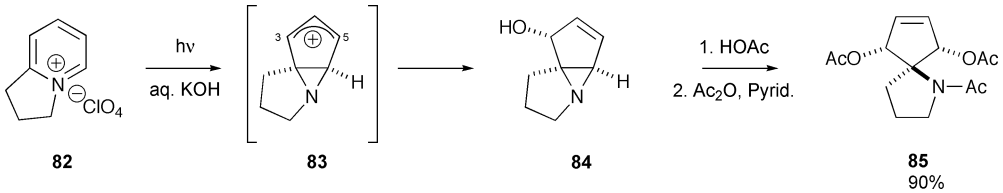
Scheme 17 Photoirradiation of the cyclohexa-fused pyridinium salt under acidic conditions.

3.7. Photocyclisation of aryl-substituted pyridinium salts

Lyle *et al.* examined the reaction of a series of 1-(2-chlorobenzyl)pyridinium chlorides **86–88** (Scheme 19).[28] Irradiation of the pyridinium chlorides **86–88** afforded the cyclisation products **89–91**, in low to modest yield (20–47%). It was found that, even with greater substitution, alkaloid-like skeletons could be prepared with good regiocontrol. Furthermore photocyclisation was shown to be favoured *ortho*- to the methyl substituent on the pyridinium ring. Cyclisation of **87** afforded exclusively **90** and



Scheme 19 Photocyclisation of 1-(2-chlorobenzyl)pyridinium chlorides.

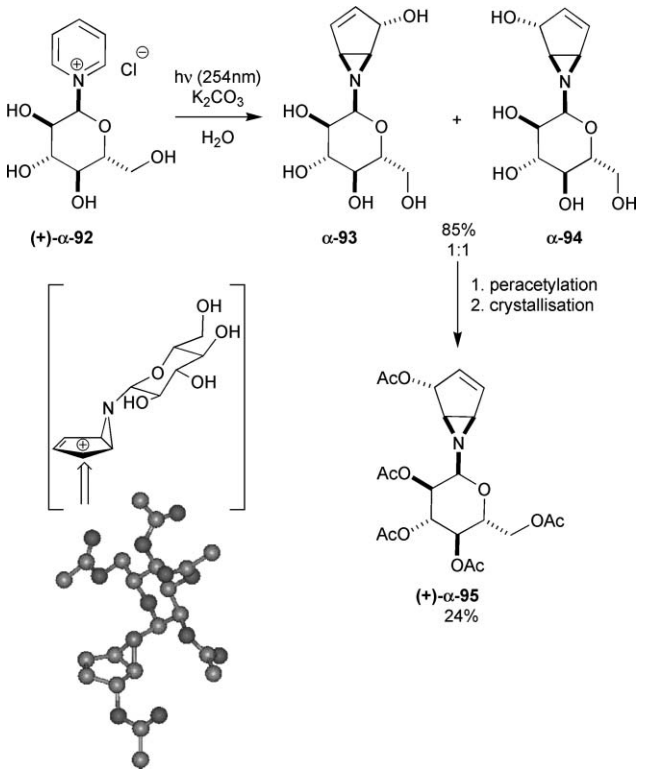


Scheme 18 Photoirradiation of penta-fused pyridinium salts under basic conditions.

transformation of **88** furnished a mixture of **91a** and **91b** in a 2 : 1 ratio.

3.8. Asymmetric photosolvation of pyridinium salts

Burger and co-workers[29] employed a chiral auxiliary approach to control the absolute configuration of the products of photochemical reactions (Scheme 20). Photoirradiation of the (+)-α-glucopyranosyl-*N*-pyridinium chloride **92**[30] under basic conditions gave the diastereomeric bridged aziridines **93** and **94** in a 1 : 1 ratio. Peracetylation, and separation by re-crystallisation, gave the enantiomerically pure bicyclic aziridine (+)-α-**95** whose relative and absolute configuration was determined by X-ray crystallography. The product **95** was subsequently used in a formal total synthesis of (+)-mannostatin A (see Section 6.2).

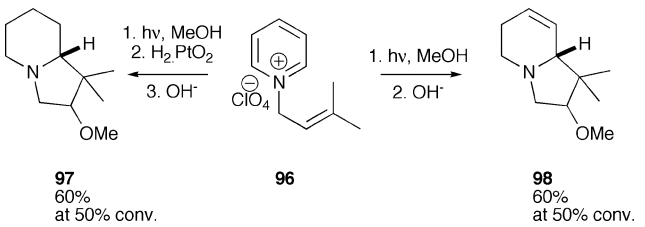


Scheme 20 Photohydration of the enantiomerically pure pyridinium salt **92**.

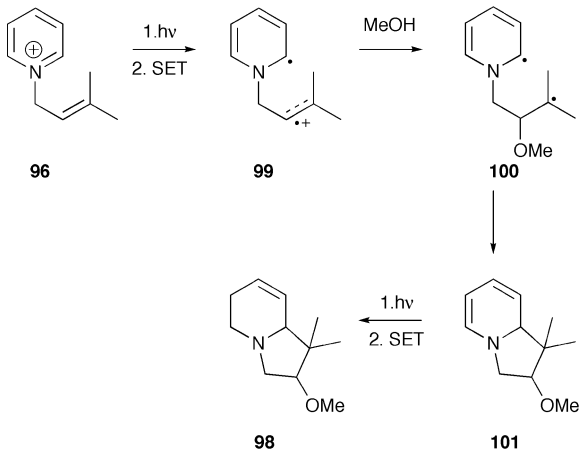
4. Single electron transfer (SET) photochemistry of pyridinium salts

Mariano has investigated the single electron transfer (SET) photochemistry of pyridinium salts bearing an appropriately positioned electron-rich alkene donor.[31] Irradiation of *N*-prenylpyridinium perchlorate **96** in methanol, followed by hydrogenation, neutralisation and distillation, gave the perhydroindolizidine **97** in good yield (Scheme 21).

The hexahydroindolizidine **98** was produced exclusively when the hydrogenation step was omitted. The proposed mechanism of the photoreaction of the pyridinium salt **96** is summarised in Scheme 22. Excited-state electron transfer would yield a diradical cationic intermediate **99**; subsequent nucleophilic addition to **99**,



Scheme 21 Irradiation of *N*-prenylpyridinium perchlorate **96**.



Scheme 22 Proposed intramolecular SET reaction of electron rich olefins and *N*-substituted heteroaromatic salts.

and cyclisation of the resulting 1,5-diradical **100**, would yield the 1,2-dihydropyridine **101**.

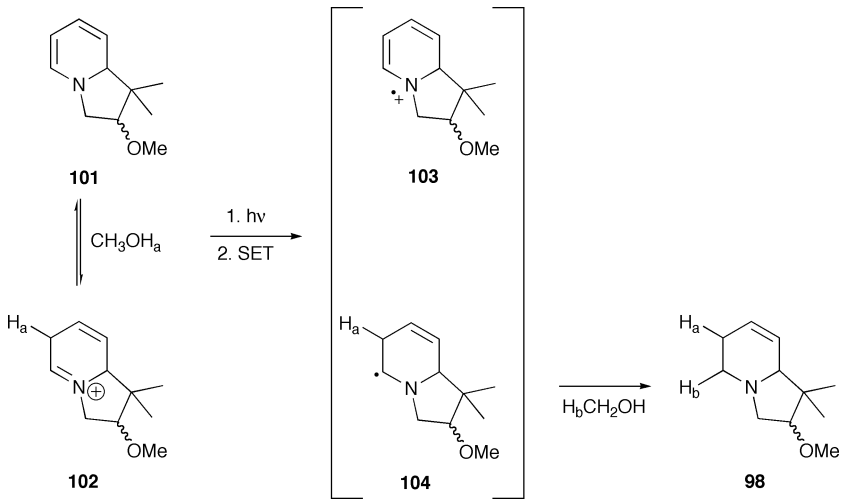
The remarkable photochemical reduction of the dihydropyridine **101** (→ **98**) merits further comment. Mariano proposed that the dihydropyridine **101** may be in dynamic equilibrium with the iminium ion **102** (Scheme 23).[31] Single electron transfer from **101** to **102** would yield the α-amino radical **104** and the radical cation **103**. Abstraction of a hydrogen atom from methanol by **104** would give the observed indolizidine **98**. This mechanism was supported by deuterium labelling studies.

Mariano then focused on the effect of substitution on the electron-transfer process.[31] While it was found that 3-alkoxy substituents could be tolerated, and yielded the expected perhydroindolizidines, incorporation of alkenyl side chain at other positions led to unexpected reactions and complex mixtures of products.

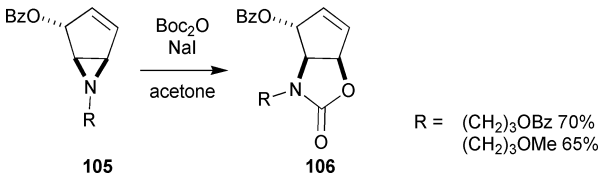
5. Studies on the reactivity of the photoisomerisation products

5.1. Nucleophilic aziridine opening with overall retention at the allylic carbon

The bridged aziridines **105** could be opened with overall retention of configuration at the allylic carbon α to the nitrogen. For instance, application of the Sepúlveda-Arques conditions[32] to the aziridine **105** led to the formation of the oxazolidinone **106**[33] (Scheme 24). The opening of the aziridine ring by iodide was followed by *in situ* protection, and participation of the resulting carbamate: the oxazolidinone **106** was obtained in good yield. With an unprotected aziridine, however, substitution did not occur,



Scheme 23 Proposed photoreduction mechanism for the formation of indolizidine **98**.



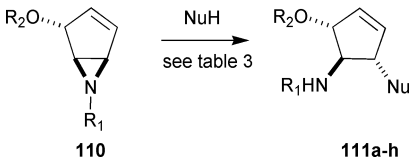
Scheme 24 Synthesis of the oxazolidinone derivatives by the Sepúlveda-Arques reaction.

instead, only a product derived from a Grob fragmentation was observed.[34,35]

Treatment of the aziridines **107** with iron nonacarbonyl afforded air-sensitive complexes **108**.[36] Oxidation of the complexes **108** with cerium ammonium nitrate (CAN) led to the formation of the β-lactams **109** in poor to good yield (Scheme 25).

5.2. Nucleophilic aziridine opening with inversion at the allylic carbon

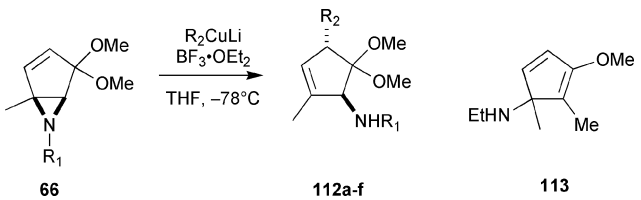
Treatment of the bridged aziridines **110** with oxygen- or sulfur-based nucleophiles resulted in regioselective opening of the aziridine ring with clean inversion of configuration. The cyclopentenes **111**, obtained by substitution at the allylic carbon α to the nitrogen, were obtained in variable yield (Scheme 26 and Table 3). The ring-opened products **111** have been exploited as advanced intermediates in the synthesis of glycosidase inhibitors (Section 6.5).



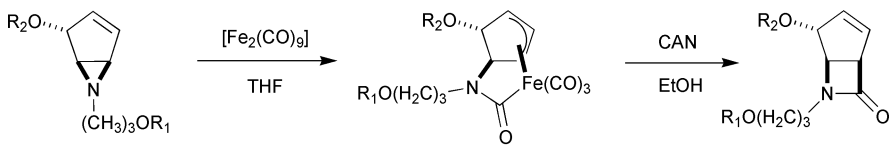
Scheme 26 Stereocontrolled opening of the bicyclic aziridine **110** with various nucleophiles.

5.3. S_N2' Opening with organocuprate reagents

Penkett and Simpson[24] have studied the reaction of bicyclic aziridines **66** with organocuprates. The aminocyclopentenes **112**, stemming from S_N2' attack of the nucleophile *anti* to the aziridine, were obtained in modest to good yield (Scheme 27, Table 4).



Scheme 27 Formation of aminocyclopenteneketals by organocuprate addition.



107	108	109
$R_1 = R_2 = H$	49%	78%
R_1 = Me, R_2 = H	83%	83%
R_1 = H, R_2 = TBS	51%	10%
R_1 = Me, R_2 = TBS	81%	38%

Scheme 25 Synthesis of the β-lactam derivatives **109**.

Table 3 Stereocontrolled opening of the bicyclic aziridine **110** with various nucleophiles

Entry	Substrate	R^1	R^2	NuH; conditions	Product	Yield (%)	Ref.
1	**110a**	$(CH_2)_3OH$	H	$PhCO_2H$; $CHCl_3$, r.t.	**111a**	92	33
2	**110b**	$(CH_2)_3OH$	H	$PhCH(OAc)CO_2H$; $CHCl_3$, r.t.	**111b**	87	33
3	**110c**	$(CH_2)_3OCbz$	PhCO	MeSH; $BF_3{\cdot}OEt_2$, CH_2Cl_2, −48 °C	**111c**	82	21
4	**110d**	Pr	Me	MeOH; $HClO_4$, r.t.	**111d**	42	21
5	**110d**	Pr	Me	H_2O; $HClO_4$, r.t.	**111e**	81	21
6	**110d**	Pr	Me	AcOH; r.t.	**111f**	36	21
7	**110d**	Pr	Me	AcSH; r.t.	**111g**	74[a]	21
8	**110d**	Pr	Me	EtO_2CCl; $CHCl_3$, r.t	**111h**	90[b]	21
9	**110e**	Pr	H	MeOH; $HClO_4$, r.t.	**111i**	67	21
10	**110e**	Pr	H	AcSH; r.t.	**111k**	34	21
11	**110f**	CH_2CONH_2	Me	MeOH; $HClO_4$, r.t.	**111j**	93	21
12	**110f**	CH_2CONH_2	Me	EtOH; $HClO_4$, r.t.	**111l**	79	21
13	**110f**	CH_2CONH_2	Me	AcOH; MeCN, reflux	**111m**	54	21
14	**110f**	CH_2CONH_2	Me	EtO_2CCl; $CHCl_3$, r.t.	**111n**	18[b,c]	21
15	**110g**	$(CH_2)_2OH$	Me	MeOH	**111o**	99	21
16	**110h**	$(CH_2)_2OH$	H	MeOH; $HClO_4$, r.t.	**111p**	99	21

[a] Of the *N*-acylated derivative. [b] Of the *N*-ethoxycarbonyl derivative, Nu = Cl. [c] 40% of a six-membered azalactone also isolated

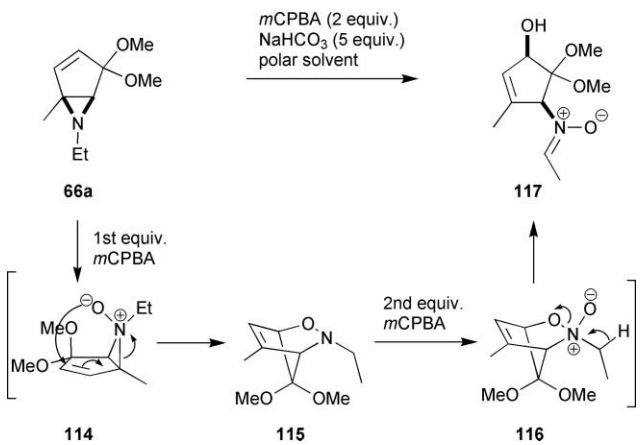
Table 4 Formation of aminocyclopenteneketals by organocuprate addition

Entry	Substrate	R^1	R^2	Product	Yield (%)
1	**66a**	Et	Me	**112a**	40[a]
2	**66a**	Et	Bu	**112b**	39
3	**66a**	Et	Vinyl	**112c**	45
4	**66b**	Allyl	Me	**112d**	51
5	**66b**	Allyl	Bu	**112e**	62
6	**66b**	Allyl	Vinyl	**112f**	35

[a] Also isolated 13% of **113**.

5.4. Oxidation of the phototransformation products

Penkett and Simpson have reported the oxidative rearrangement of the bicyclic aziridine **66a**.[24] Treatment of **66a** with *m*CPBA in a basic medium gave the *endo N*-oxide **114**, which underwent Meisenheimer rearrangement to the oxa-azabicycloheptene **115**; further oxidation (→ **116**) and elimination afforded the nitrone **117** (Scheme 28).



Scheme 28 Oxidation of the ketalaziridine **66a**.

Burger and co-workers have investigated the stereocontrolled epoxidation of *N*-protected cyclopentenols (**118**, **120** and **122**), using *m*CPBA, trifluoroperacetic acid (derived from urea-hydroperoxide, UHP, and trifluoroacetic anhydride), and DDO (Scheme 29).[22,33,37]‡ A high level of stereoselectivity was observed, with epoxidation occurring exclusively *syn* to the allylic alcohol.

6. Applications in the total synthesis of natural products

A rigorous test of a new synthetic methodology is its application in total synthesis. This section provides a chronological summary of the application of the photochemistry of pyridinium salts in the total synthesis of natural products.

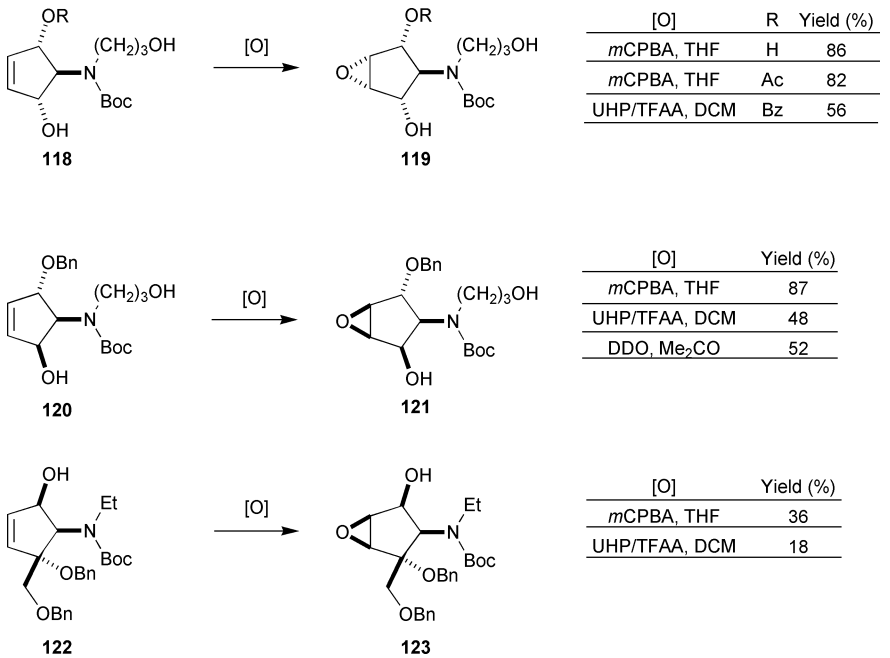
6.1. (±)-Dihydrofumariline-1

In 1985, Hanaoka *et al.* reported the stereoselective total synthesis of (±)-dihydrofumariline-1 **126**, with the irradiation of a berberine betaine as the key stereoselective step (Scheme 30).[38] Irradiation of the betaine **124** in methanol afforded the aziridine **125**, which was converted into the spirobenzylisoquinoline alkaloid, dihydrofumariline-1, **126**, in four further steps. Unlike earlier studies in this area, the reversibility of this reaction was not examined,[25] furthermore no observations on the potential photochromism of the system were reported.

6.2. (+)-Mannostatin A

In 1998, Mariano and Ling reported the total synthesis of mannostatin A **132**,[39] a mannosidase inhibitor (Scheme 31).[40] The aminocyclopentene **128** was obtained by photosolvolysis of pyridinium perchlorate (**127**) under acidic conditions, followed by peracetylation. Enzymatic desymmetrisation of **128** using electric eel acetylcholinesterase (EEACE) afforded the key intermediate **129** in 80% ee. Palladium-catalysed substitution of **130**,[41] with overall retention of configuration, gave the thioether **131**. Inversion of the configuration of the allylic alcohol **131** following Wipf's procedure,[42] and directed dihydroxylation,[43] afforded, after

‡ The relative configuration of the epoxide **119** was initially mis-assigned and later corrected by the authors (ref. 38). Here we report the corrected one.

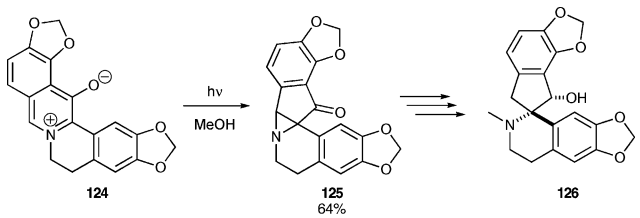


[O]	R	Yield (%)
*m*CPBA, THF	H	86
*m*CPBA, THF	Ac	82
UHP/TFAA, DCM	Bz	56

[O]	Yield (%)
*m*CPBA, THF	87
UHP/TFAA, DCM	48
DDO, Me_2CO	52

[O]	Yield (%)
*m*CPBA, THF	36
UHP/TFAA, DCM	18

Scheme 29 Stereoselective epoxidation of the aminocyclopentenols.

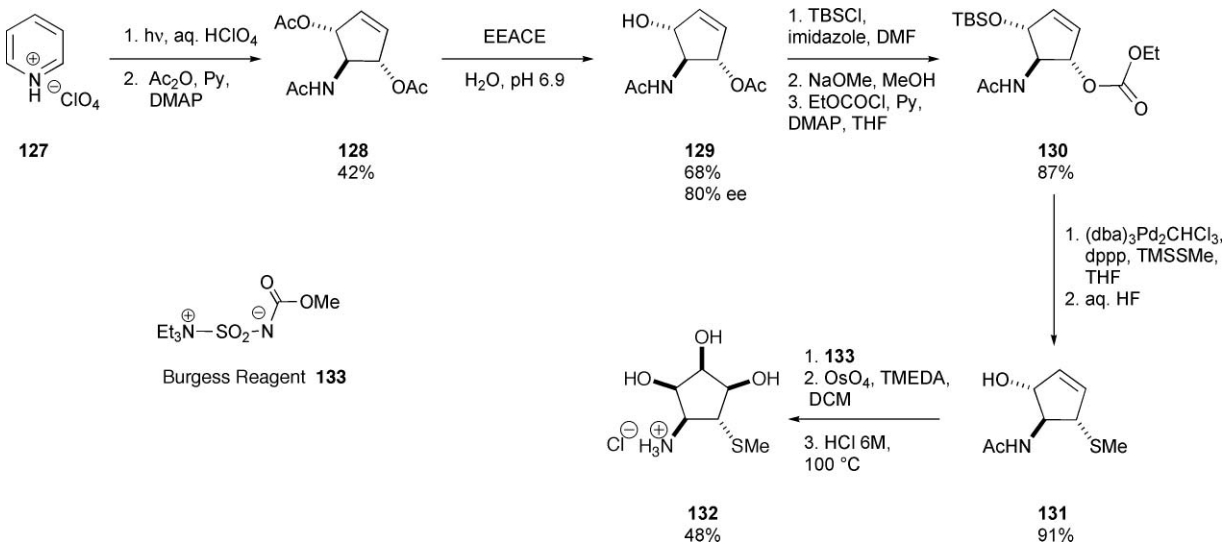


Scheme 30 Photochemical transformation of berberine betaine in the stereoselective synthesis of dihydrofumariline-1 **126**.

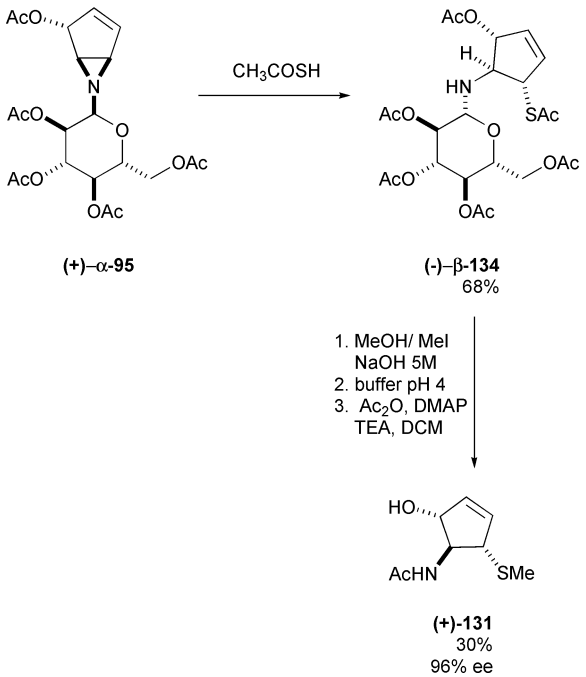
deprotection, the hydrochloride salt of (+)-mannostatin A (**132**). The hydrochloride salt of the natural product was obtained in 11% overall yield in eleven synthetic steps.

The versatility of Mariano's synthetic strategy for the construction of (+)-mannostatin A was later exemplified by the preparation of a series of stereo- and regioisomeric analogues.[44]

In Burger's approach to mannostatin A, a chiral auxiliary was used to induce asymmetry in the photochemical step (see Section 3.8 and Scheme 20). The enantiomerically pure aziridine **95** was opened with thioacetic acid to afford **134** (Scheme 32). It is worth noting that the regio- and stereocontrolled attack of the nucleophile was accompanied by inversion of the anomeric centre.[29] Finally, ester hydrolysis, methylation, removal of the chiral auxiliary, and acetylation, gave the advanced intermediate **131**, in Mariano's synthesis of mannostatin A, obtained in 20% overall yield and 96% ee.[37]



Scheme 31 Total synthesis of (+)-mannostatin A by Mariano and co-workers.



Scheme 32 Formal total synthesis of (+)-mannostatin A by Burger and co-workers.

6.3. The aminocyclopentanol core of allosamidine

In 2001 Mariano *et al.*[45] completed the synthesis of the aminocyclopentanol core of (−)-allosamizoline,[46] the aglycone of the chitinase inhibitor allosamidine **140** (Scheme 33).[47] Inversion of the configuration of the allylic alcohol **129**, an intermediate in their total synthesis of mannostatin A, was accomplished using Burgess' reagent **133**; silylation and ester hydrolysis gave the cyclopentenol **135**. A [2,3]-Wittig rearrangement[48] was used to prepare the alcohol **136**. Stereoselective epoxidation of the *N,O*-acetal **137** gave the epoxide **138** in 84% yield. Regioselective opening of the epoxide **138** under basic conditions and deprotection afforded the aminocyclopentanol core of allosamidine, **139**, in 17% overall yield.

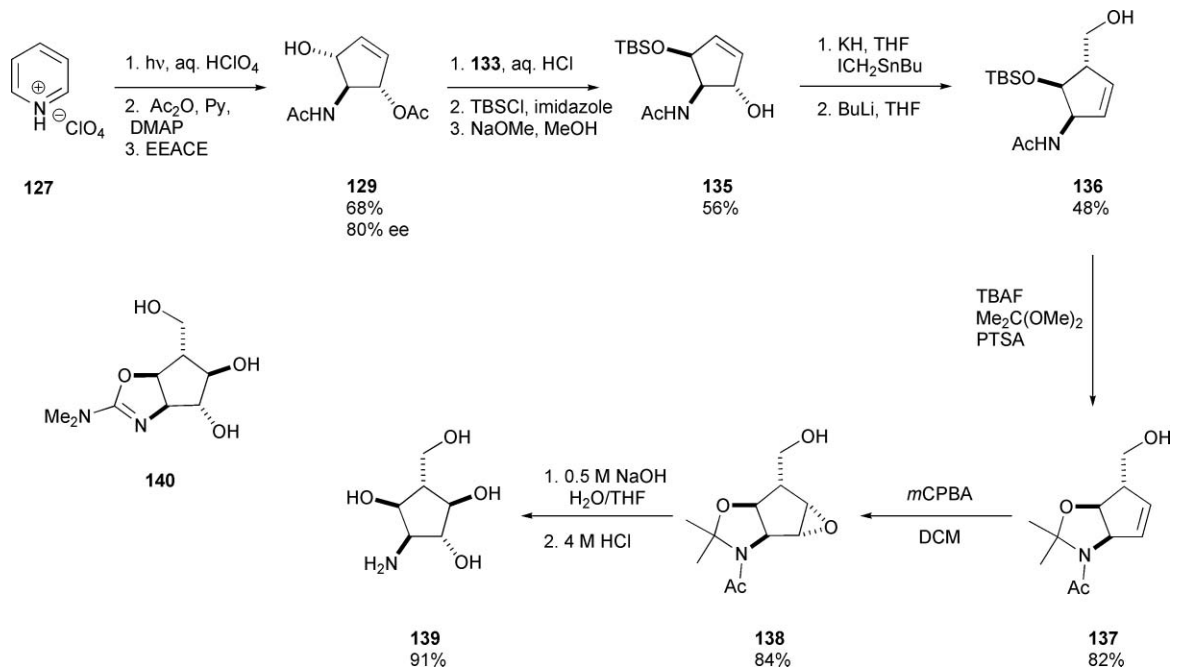
6.4. Trehazoline

Burger and co-workers have worked on a synthetic approach to trehazolamine analogues (Scheme 34).[22] Trehazolamine **146** is the cyclopentenol component of the trehalase inhibitor trehazolamine.[49] Irradiation of *meta*-hydroxymethylpyridinium bromide **53** afforded the separable bridged aziridines **57** and **58** (Section 3.3). The aziridine **141** was converted into the oxazolidinone **143** with overall retention of configuration of the allylic carbon α to nitrogen, hence, inversion of this stereocenter of **142** was followed by Boc-protection of the resulting amine, and cyclisation (→ **143**).§ Basic cleavage of the oxazolidinone afforded the allylic alcohol **144** which directed an epoxidation reaction to yield the *syn* diastereomeric epoxide **145**.

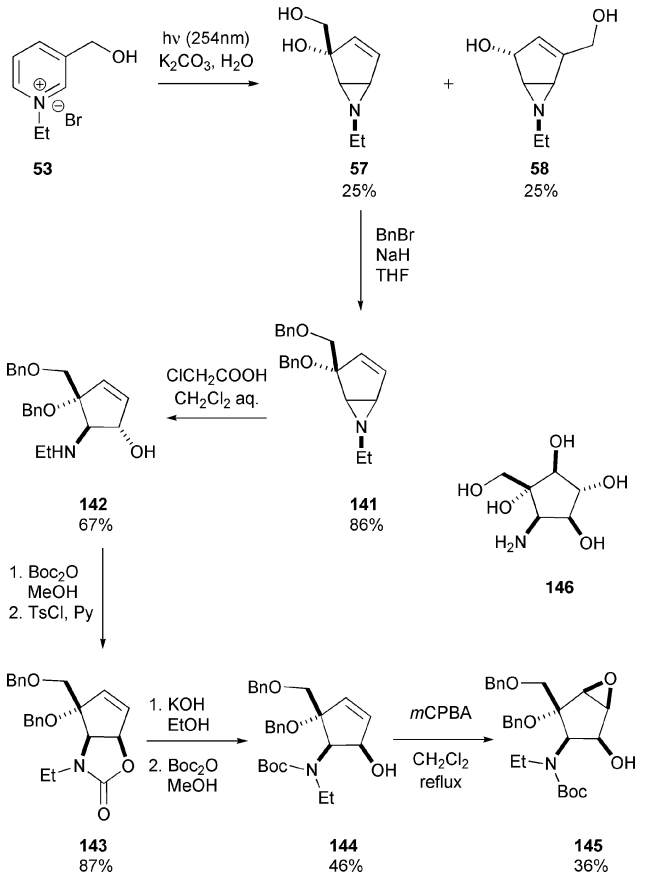
Recently, Mariano and co-workers[50] have reported the total synthesis of the peracetylated trehazolamine using a similar approach (Scheme 35).

Photohydration of the *meta*-substituted pyridinium salt **147** afforded a mixture of the aziridines **148** and **149**. After suitable protecting group manipulations, inversion of the configuration of the allylic alcohol **152** was accomplished using Burgess' reagent **133** and opening of the resulting oxazolidine with sodium dihydrogen phosphate. Opening of the epoxide **154** with aqueous sodium

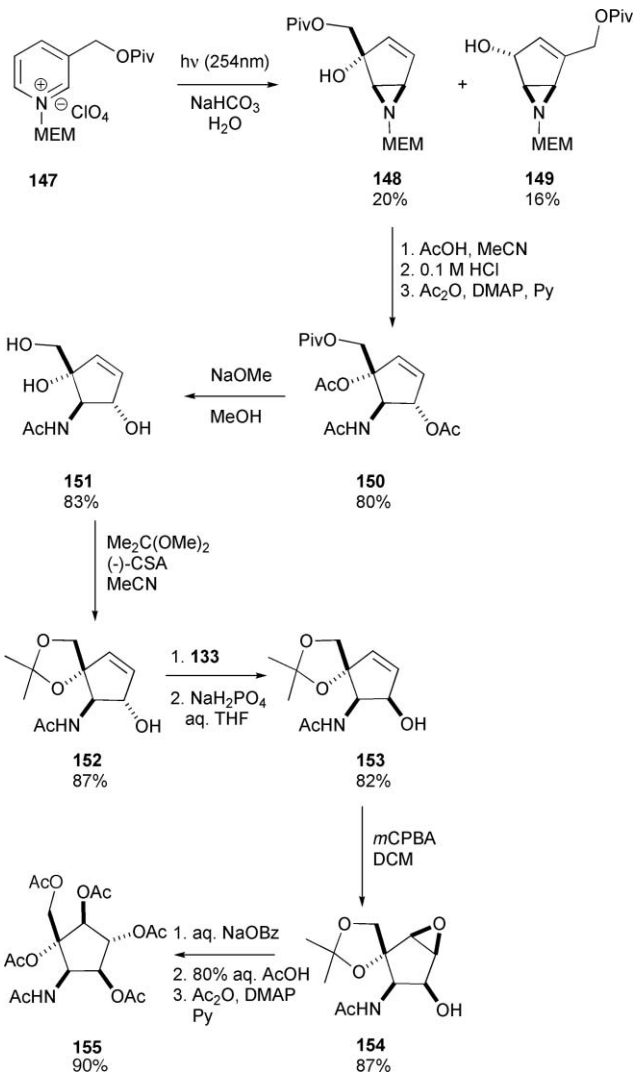
§ The one-pot Sepúlveda-Arques methodology was not successful with this substrate (see Section 5.1).



Scheme 33 Synthetic approach to allosamidine by Mariano and co-workers.



Scheme 34 Synthetic approach to the trehazolamine analogue by Burger and co-workers.



Scheme 35 Synthesis of the peracetylated trehazolamine by Mariano and co-workers.

benzoate, hydrolysis and peracetylation, afforded the known[51] peracetylated trehazolamine derivative **155** in 9.3% overall yield over 12 steps. In the same paper, the use of Burger's chiral auxiliary (see Section 3.8) in an asymmetric synthesis of **150** was also reported.

6.5. Aminosugars

In 2002, Mariano *et al.* reported stereodivergent syntheses of both enantiomers of the aldehyde **158** from the enantiomerically enriched cyclopentenol **129** (Scheme 36).[52] Ozonolysis and reduction of the orthogonally-protected aminocyclopentenol **156** afforded the tetrol **157**; desilylation, acetonide formation and Swern oxidation afforded the D-aminosaccharide **158**. By changing the order of the protection steps, the enantiomeric aminocyclopentenol *ent*-**156** was prepared which could, in principle, be converted into the enantiomeric product *ent*-**158**.

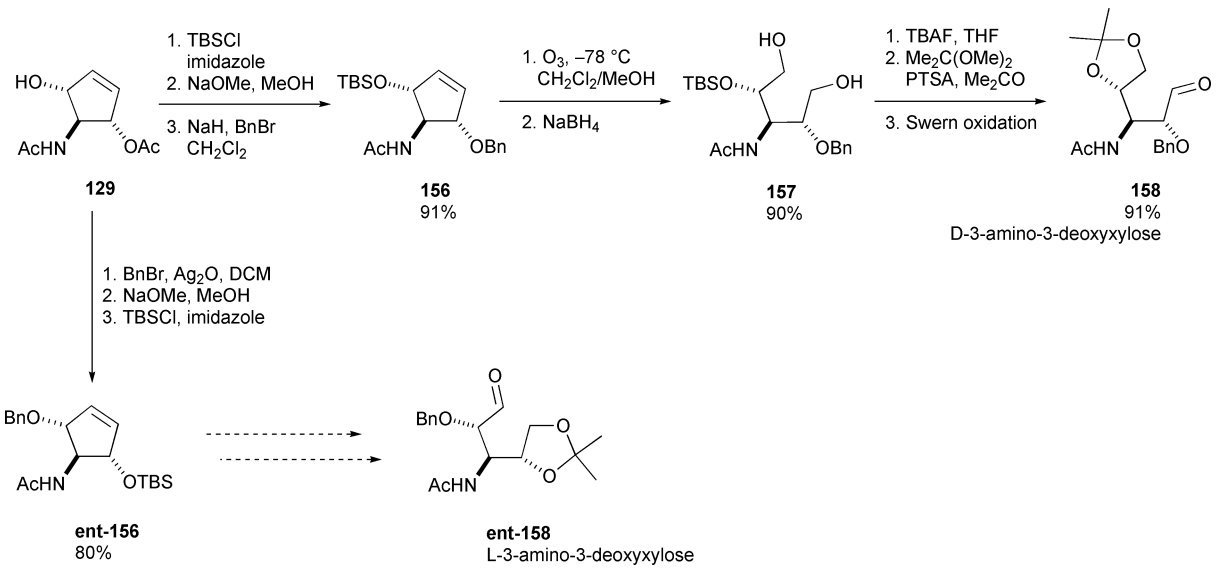
Starting from the key intermediate **129**, the authors also prepared an advanced intermediate, **163**, in a synthesis of *N*-acetylneuraminic acid **164** (Scheme 37).[52] In this instance, the synthetic strategy began by inverting the configuration of the allylic alcohol **129** (→ **159**). Aldehyde **161** was homologated using a stabilised ylide reagent (→ **162**). The *Z*-isomer of **162** underwent Hg(II)-mediated cyclisation to give the intermediate **163** in 30% overall yield over 12 steps.

6.6. (−)-Swainsonine

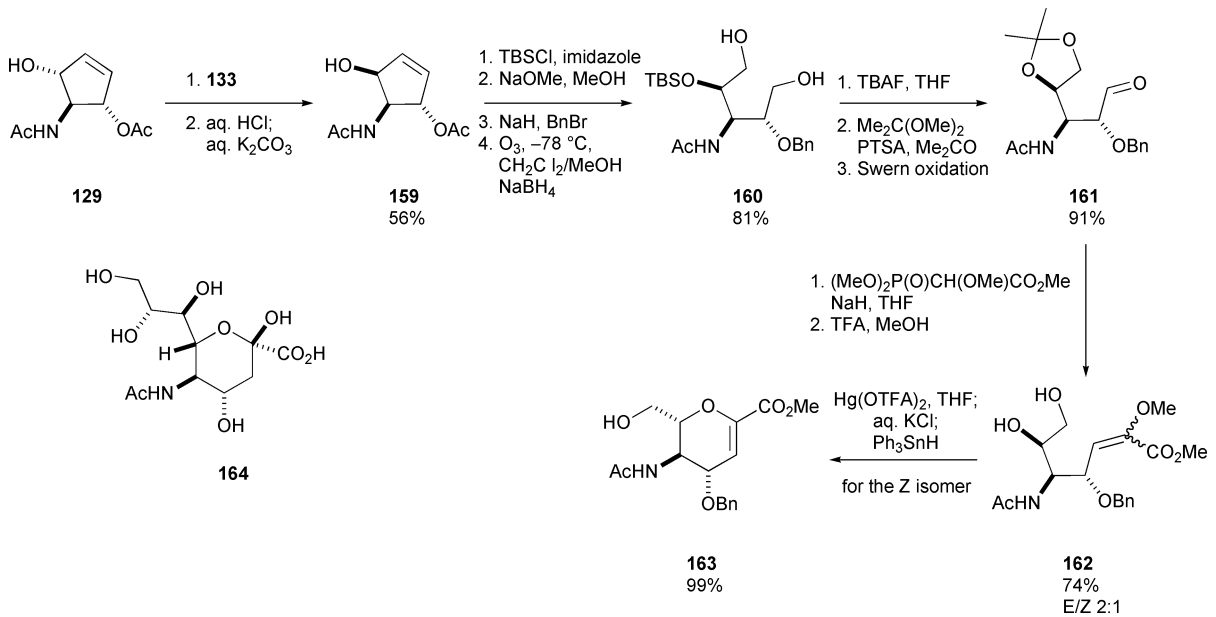
In 2004 Mariano *et al.* prepared (−)-swainsonine, a potent glycosidase inhibitor (Scheme 38).[53] Photoirradiation of pyridinium chloride in acidic aqueous medium, was followed by conversion into the functionalised cyclopentene **165**. Ru-catalysed ring rearrangement metathesis (RRM), and protecting group manipulation, gave the key intermediate **166**. Dihydroxylation of **166** using catalytic OsO_4, with NMO as co-oxidant, provided a diastereomeric 81 : 19 mixture of diols **167**. The major diol was converted into (−)-swainsonine with 80% ee.

6.7. (+)-Castanospermine

In 2005, as a further demonstration of the flexibility of their methodology, Mariano and co-workers applied their RRM strategy to the total synthesis of (+)-castanospermine, a glycosidase inhibitor (Scheme 39).[54] The key intermediate **165**, obtained as previously reported from photohydroxylation of the pyridinium



Scheme 36 Stereodivergent synthesis of aminodeoxyxyloses.



Scheme 37 Formal synthesis of *N*-acetylneuraminic acid.

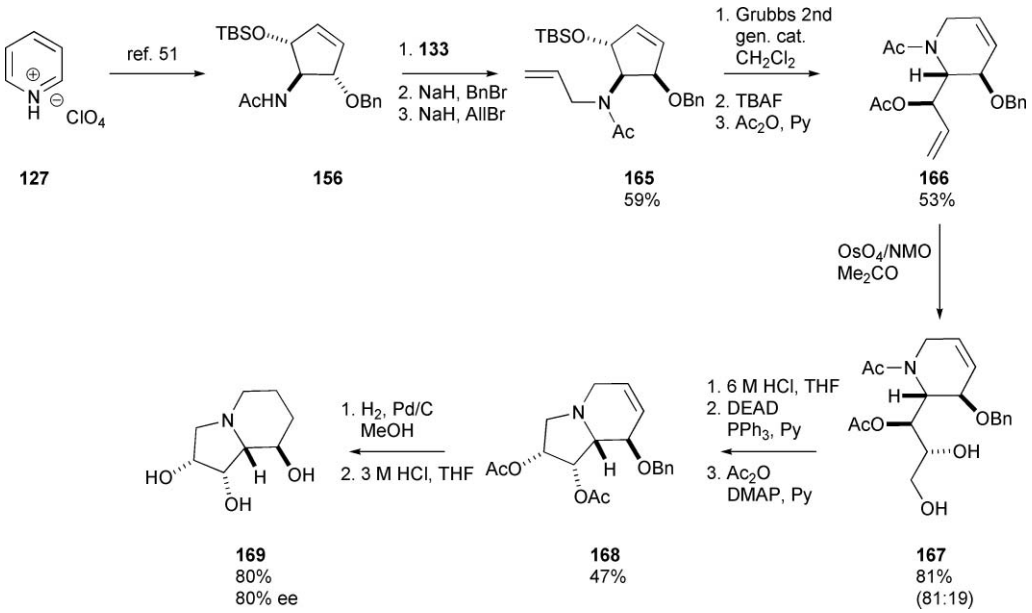
perchlorate and suitable functional group manipulation, underwent smooth RRM to afford tetrahydropyridine **170**.

Regio- and stereoselective epoxidation of the endocyclic double bond was achieved with vanadyl acetylacetonate to afford, after benzylation, the tetraol **171**. Oxidative hydroboration of the terminal alkene afforded the desired primary alcohol with concomitant deacetylation of the nitrogen. Mitsunobu cyclisation followed by hydrogenolytic debenzylation afforded (+)-castanospermine **173** in 6.2% yield over 8 steps (starting from **165**).

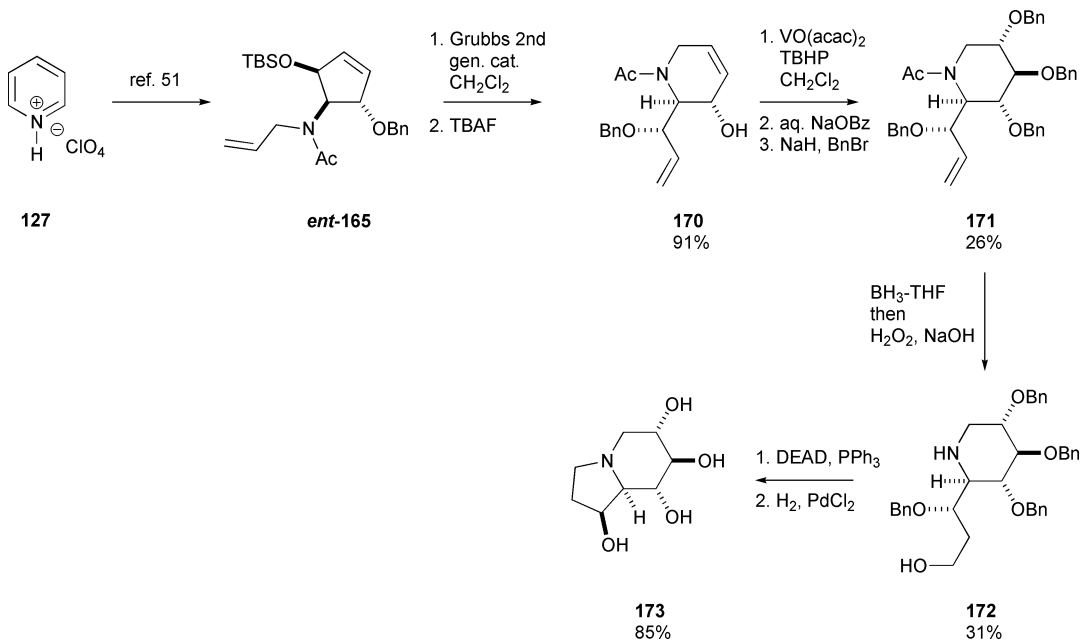
6.8. (−)-Cephalotaxine

In 2006, Mariano and Zhao described the preparation of two late-stage intermediates in the synthesis of (−)-cephalotaxine **177** (Scheme 40).[55] Irradiation of the cyclopenta-fused pyridinium salt **82** (see Section 3.6) gave the *spiro*-fused diester **85** which was desymmetrised in an enzymatic reaction.[55] The rapid assembly of the complex aza-spiro-skeleton **174** was used to great effect to prepare advanced intermediates in two formal syntheses of (−)-cephalotaxine (Scheme 40).

Mariano synthesised the spirocyclic amido-allylic alcohol **174** from the pyridinium salt **82** in eleven steps and 11% yield, the alcohol **176** had previously been prepared by Mori and Isono in the first nonracemic total synthesis of the natural product.[56] Yoshida *et al.*[57] and Tietze and Schirok[58] have independently reported approaches towards (−)-cephalotaxine which exploit a Heck reaction of **176** as a key synthetic step.



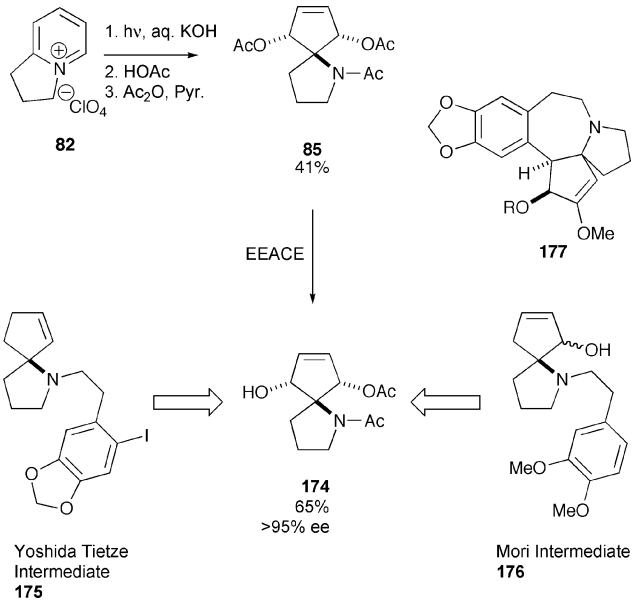
Scheme 38 The total synthesis of (−)-swainsonine.



Scheme 39 Total synthesis of (+)-castanospermine **173** by Mariano and co-workers.

7. Summary and perspectives

Despite the only sporadic attention paid to the phototransformation of pyridinium salts during the first twenty years since its discovery, the concerted effort now apparent from a number of groups demonstrates that the potential of this powerful transformation has begun to be realised. Strategies have emerged that exploit this remarkable rearrangement, the rapid construction of dense functionality and stereochemistry from simple, planar aromatic substrates has inspired the chemical community. The synthetic utility of variously substituted pyridinium salts has been examined and annealed into techniques that provide facile access to advanced intermediates toward biologically active species and synthetically powerful stereochemically enriched synthons. The interest in this transformation is expanding, and with improving photochemical reaction technologies, doubtless there will be further advancements and applications in the photochemistry of pyridinium salts.



Scheme 40 Application of fused 1,2-pyridinium salts to the formal synthesis of (−)-cephalotaxine **177**.

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