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Synthesis and reactions of cyclopentadiene monoaziridine: a concise approach to the core of agelastatin A

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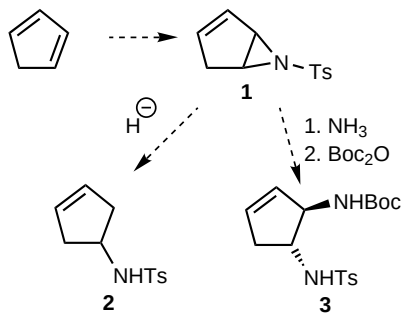
Abstract—An improved protocol for the preparation of cyclopentadiene monoaziridine is described (88% yield). The utility of cyclopentadiene monoaziridine is demonstrated by its use in (i) the shortest synthetic entry into 4-amino substituted cyclopentenes and (ii) the preparation of two key intermediates in a concise synthetic approach to the cyclopentane core of agelastatin A. The agelastatin A model studies make use of a lithium amide-mediated epoxide to allylic alcohol rearrangement reaction.

Acyclic and cyclic 2-vinyl aziridines are useful intermediates in synthesis.[1] For example, Hudlicky and co-workers have demonstrated the synthetic potential of a *N*-*p*-toluenesulfonyl aziridine derived from a chiral cyclohexadiene culminating in the total synthesis of pancratistatin.[2] Such cyclic vinyl aziridines have been successfully ring opened at the activated allylic position by a range of nucleophiles including carbon-based nucleophiles,[3] alcohols[4] and, very recently, amines.[5,6] We have also previously developed a chiral base route to a six-ring vinyl aziridine.[7] In addition, a powerful and direct entry into cyclopentene-based vinyl aziridines, utilising irradiation of pyridinium salts, has been developed by Mariano et al.[8] The photochemical step is followed by aziridine ring opening with water, alcohols and thiols and has recently been applied to the total synthesis of mannostatin A[9] and (–)-allosamizoline.[10]

From a synthetic viewpoint, we became interested in the preparation and subsequent reactivity of the cyclic 2-vinyl aziridine **1** derived from cyclopentadiene. Knight and Muldowney have already described a route to aziridine **1** via the Evans-type direct monoaziridination of cyclopentadiene using [*N*-(*p*-toluenesulfonyl)imino]iodinane (PhI=NTs) and $Cu(acac)_2$.[11] Atkinson and Meades[12] have recently reported a related mono-aziridination using 3-acetoxyaminoquinazolin-4(3*H*)-ones and a three-step route for the synthesis of the benzamide-protected version of **1** has also been described by Olivo and co-workers.[13]



In order to prepare two useful synthetic intermediates (cyclopentenes **2** and **3**), we wished to study the ring opening of aziridine **1** with hydride- and amine-based nucleophiles. Reaction of aziridine **1** with a suitable source of hydride should furnish sulfonamido cyclopentene **2**, considerably improving the usual synthetic entry into 4-amino substituted cyclopentenes.[14] Alternatively, reaction of aziridine **1** with ammonia followed by Boc protection should generate diamine **3** which contains the *trans*-diamine stereochemistry and appropriate functionality for conversion into the cyclopentane core of agelastatin A.[15] Herein we describe our results.

Following Knight and Muldowney's procedure for monoaziridination of dienes,[11] cyclopentadiene was reacted with PhI=NTs and 10 mol% of $Cu(acac)_2$ to give aziridine **1** in variable yields of 30–45% (lit.,[11] 60%). Our optimised procedure for the preparation of **1** involved starting the reaction at 0°C (as the reaction is initially quite exothermic), use of an excess of diene (2

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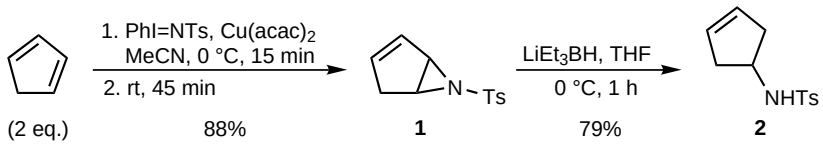
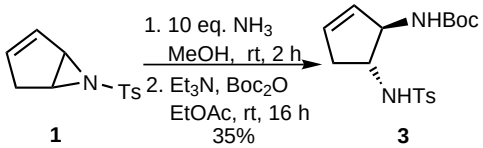


equiv.) and leaving the reaction for no longer than 1 h in total. In this way, a consistently high yield (88%) of aziridine **1** of high purity (after removal of all of the iodobenzene by-product by high vacuum drying for at least 2 h) was obtained.[16]

For the reaction of aziridine **1** with hydride, we utilised a procedure recently reported by White and Wood for ring opening of a terminal aziridine in a route to the kalihinane diterpenoids.[17] Thus, aziridine **1** was treated with lithium triethylborohydride (Superhydride®) at 0°C in THF to give cyclopentene **2** in 79% yield. This two step synthesis of **2** is the shortest synthetic entry into 4-amino substituted cyclopentenes reported to date.[14]

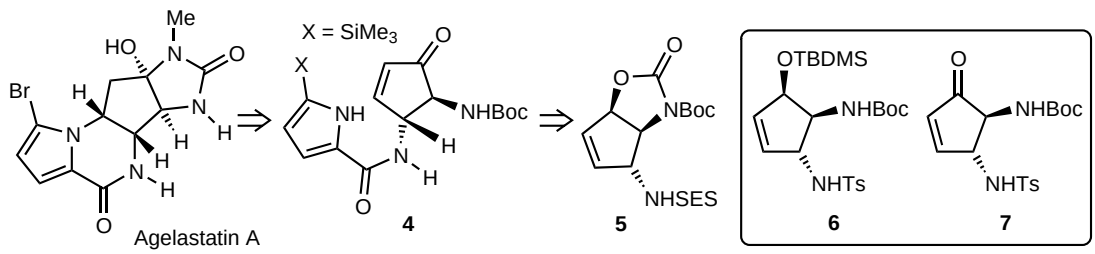
Aziridine **1** has also been utilised in a concise approach to the cyclopentane core of agelastatin A. Isolated in 1993 from the deep water marine sponge *Agelas dendromorpha* collected in Coral Sea near New Caledonia,[15] agelastatin A has an intriguing and unusual alkaloid structure and exhibits anti-tumour and insecticidal activity. In 1999, Weinreb et al. reported the first total synthesis of racemic agelastatin A and two of their late stage synthetic intermediates were enone **4** and allylic sulfonamide **5**.[18] Using aziridine **1** as the key building block, we have now completed the preparation of allylic sulfonamide **6** and enone **7** which contain comparable functionality to Weinreb's intermediates.

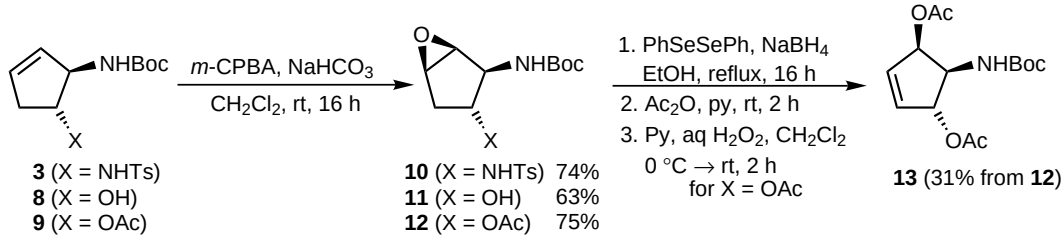
Direct ring opening of aziridine **1** with ammonia followed by Boc protection was the most reliable way of preparing diamino cyclopentene **3**. Thus, reaction of aziridine **1** with an excess of ammonia in methanol at room temperature followed (without isolation) by protection of the resulting amino sulfonamide intermediate (Boc_2O, EtOAc) gave diamino cyclopentene **3** in an acceptable 35% yield. The regio- and stereochemistry of diamino cyclopentene **3** was assigned by analogy with the known[19] ring opening of the corresponding vinyl epoxide under essentially the same conditions.

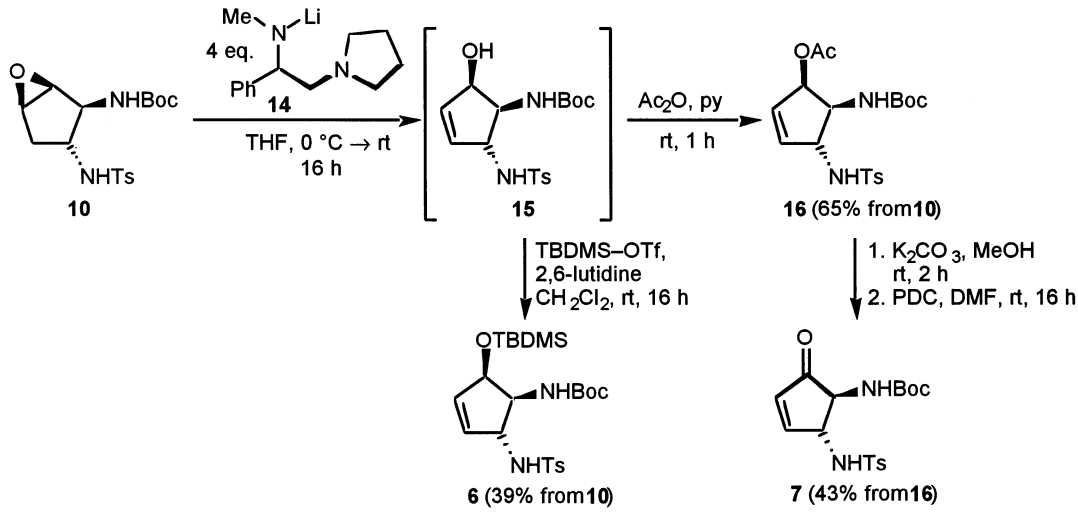


Next, we proposed to epoxidise the alkene in **3**. Reaction of cyclopentene **3** with *m*-CPBA under standard conditions gave a 74% isolated yield of epoxide **10** as a single diastereoisomer. Although the epoxide stereochemistry will ultimately be of no consequence in our route to agelastatin A (vide infra), we have good evidence that epoxidation proceeds *cis* to the NHBoc group and *trans* to the NHTs group. Thus, two related systems, amino alcohol **8** and amino acetate **9**,[19] were also epoxidised and they gave the same sense of diastereoselectivity as each other (shown by conversion of epoxide **11** into **12** by simple acetylation).

The stereochemistry of acetoxy epoxide **12** was established unequivocally by conversion into chiral (but racemic) diacetate **13**. First of all, epoxide **12** was reacted with sodium phenylselenide: the $PhSe^-$ attacked **12** at the least hindered end of the epoxide (as shown by COSY analysis of the hydroxy selenide intermediate) and also deprotected the acetate group. Then, after acetylation of both hydroxyls, selenium oxidation and subsequent elimination afforded diacetate **13** (31% overall from **12**) which was clearly the chiral diastereoisomer as judged by ^1H and ^{13}C NMR







spectroscopy[20] (a *meso* diacetate would have been generated from the other diastereomeric epoxide). Based on this, it seems reasonable to suggest that cyclopentenes **3**, **8** and **9** (X = NHTs, OH and OAc, respectively) are all epoxidised *cis* to the NHBoc group irrespective of the nature of X. It is not clear whether this is due to a simple hydrogen bond NHBoc-directed epoxidation or due to an inherent facial bias in such *trans*-disubstituted cyclopentenes.

In order to set up the required distribution of hydroxyl (or keto) and diamino functionality present in Weinreb's intermediates **4** and **5** for agelastatin A synthesis, we first needed to rearrange the epoxide in **10** into the corresponding allylic alcohol. We elected to use a lithium amide method for this rearrangement because of our interest in chiral base chemistry.[21,22] Thus, epoxide **10** was treated with *four* equivalents of the racemic diamine-derived base **14** (due to the presence of two acidic NH protons in **10** and our preference for two equivalents of base per epoxide) in THF at room temperature. The reaction was generally clean and typically afforded an 80% crude yield of an 85:15 mixture of allylic alcohol **15** and starting epoxide **10** (by ^{1}H NMR spectroscopy). Our attempts at isolating pure allylic alcohol **15** were thwarted as it was inseparable from the epoxide.[23] Instead, this crude epoxide and allylic alcohol mixture was either acetylated or silylated to give **16** or **6**, respectively, and in this way it was possible to generate allylic acetate **16** in 65% yield and silyl protected allylic sulfonamide **6** in 39% yield (yields are over the two steps of rearrangement and protection). Finally, the allylic acetate was deprotected using potassium carbonate in methanol and the crude allylic alcohol was oxidised using PDC in DMF (conditions used by Weinreb et al. in their agelastatin A total synthesis[18]) to give enone **7** in 43% yield over the two steps.

In summary, the readily prepared cyclopentadiene monoaziridine **1** has been used in a new approach to 4-amino substituted cyclopentenes and some intermediates for agelastatin A synthesis. Our model studies on the new route to the core of agelastatin A have led to concise syntheses of allylic sulfonamide **6** and of enone **7** in four and five steps respectively from cyclopentadiene. Furthermore, by running the lithium amide-mediated rearrangement of epoxide **10** to allylic alcohol **15** under kinetic resolution conditions,[24] it should be possible to generate enantiomerically enriched intermediates for use in the first asymmetric synthesis of agelastatin A.

Acknowledgements

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16. Preparation of **1**: PhI=NTs (3.4 g, 9.0 mmol) was added portionwise to a stirred solution of freshly distilled cyclopentadiene (1.2 g, 18.2 mmol) and $Cu(acac)_2$ (240 mg, 0.9 mmol) in MeCN (10 mL) at 0°C under N_2. After stirring for 15 min, the reaction was allowed to warm to rt and stirred for a further 45 min. Then, the reaction mixture was poured into $NaOH_{(aq.)}$ (1 M, 200 mL). Et_2O (50 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (2×50 mL) and the combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The crude product was placed under high vacuum for 2 h to give aziridine **1** (1.88 g, 88%) as a brown solid, mp 93–95°C; R_f (Et_2O) 0.8; IR ($CHCl_3$) 1321, 1159, 719 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz): δ 7.83 (d, 2H, $J=8.5$), 7.34 (d, 2H, $J=8.5$), 5.95 (br s, 2H), 3.86–3.83 (m, 1H), 3.72–3.71 (m, 1H), 2.59 (br s, 2H), 2.45 (s, 3H); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 144.3, 138.1, 135.3, 129.6, 127.9, 127.3, 50.7, 44.5, 35.6, 21.6; MS (CI, NH_3) m/z 236 $M+NH_4^+$, 82; HRMS (CI, NH_3) m/z calcd for $C_{12}H_{14}NO_2S$ $M+H^+$ 236.0745, found 236.0744.
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20. Spectroscopic data for **13**: ^1H NMR ($CDCl_3$, 270 MHz): δ 6.14 (br d, 1H, $J=6.0$), 6.06 (dd, 1H, $J=2.0$, 6.0), 5.74 (br d, 1H, $J=5.0$), 5.57 (br d, 1H, $J=5.0$), 5.01 (d, 1H, $J=5.0$), 4.33–4.29 (m, 1H), 2.09 (s, 3H), 2.07 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 171.5, 170.4, 155.8, 137.2, 132.7, 81.2, 80.4, 75.9, 57.5, 28.7, 21.42, 21.36.
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