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Synthesis of (+)-piclavines A1 and A2

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Abstract

Piclavines A1 and A2 have been synthesised for the first time. The route is short with the key step being the reaction of a bicyclic *N*-acyl iminium ion with 3-trimethysilyl-1-decene. This convergent strategy gave exclusively compounds in which the pendant decenyl group was *axial*, as a 6:1 mixture of *E*:*Z*-alkene diastereoisomers. Reduction of the lactam carbonyl group gave a 6:1 mixture of piclavines A1 and A2. © 2000 Published by Elsevier Science Ltd.

Keywords: *N*-acyliminium ion; indolizidine; piclavines; 1,3-allylic strain.

The organic extract from the Bermudan tunicate *Clavelina picta* has been shown to have cytotoxic and anti-microbial activity. On further purification the cytotoxic agent was found to be clavepictine[1] and the anti-microbial agents were found to be piclavines A–C, of which members A1–A4 are shown in Fig. 1.[2]

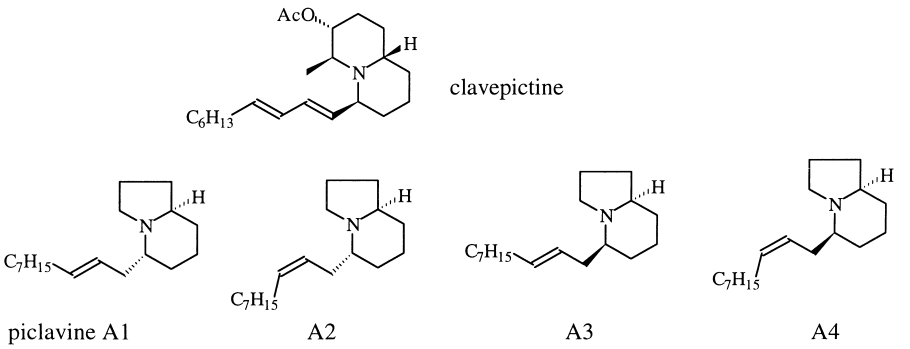

Figure 1. Alkaloids from Bermudan tunicate *Clavelina picta*

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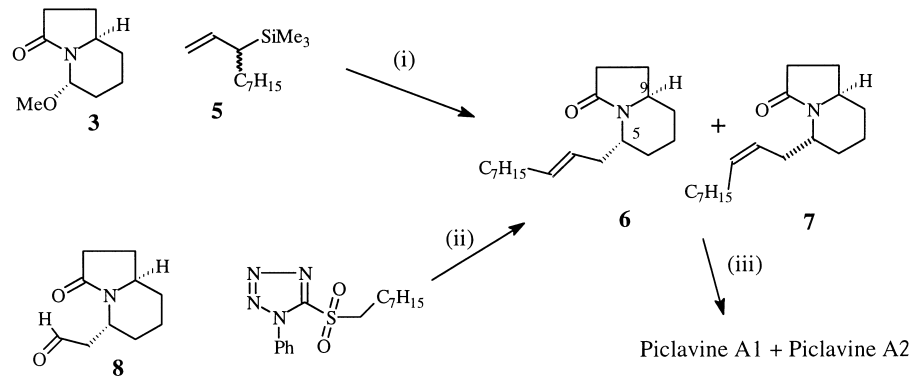
Although indolizidine alkaloids are common in terrestrial environments,[3] the piclavines are unique in that they remain the only known indolizidines of marine origin. Although clavepictine has been the subject of much synthetic endeavour,[4] there has been very little synthetic effort directed towards the piclavines, with only one reported synthesis of piclavine A4.[5] To date, no syntheses of the 5-axially substituted piclavines A1 and A2 have been accomplished.

Recently, we reported that acrylate **1** cyclises to indolizidinone **2** when treated with a catalytic quantity of potassium *t*-butoxide to give solely the 5-*axial* diastereoisomer,[6] and that the bicyclic *N*-acyl iminium ion derived from substrate **3** reacts with allyltrimethyl silane to give exclusively the *axial* 5-allylhexahydroindolizidin-3-one **4**, Scheme 1.[7] The preference for the 5-substituent in indolizidin-3-ones to be *axial* is well-documented, with a pseudo 1,3-allylic strain from the lactam carbonyl group forcing the pendant alkyl group to be *axial*.[8]

Scheme 1.

We now report an extension of this chemistry which gives rapid and convergent access to piclavines A1 and A2. Scheme 2 outlines two syntheses of piclavines A1 and A2.



Scheme 2. Synthesis of piclavines A1 and A2. Reagents: (i) $TiCl_4$ CH_2Cl_2; (ii) $KN(SiMe_3)_2$, DME; (iii) $LiAlH_4$ $AlCl_3$

3-Trimethylsilyl-1-decene **5** was prepared in a one-pot operation from 3-chloro-1-trimethylsilyl-1-propyne and 1-heptene by the method described by Arase.[9] Reaction of 5-methoxyhexahydroindolizidin-3-one **3** with a two-fold excess of 3-trimethylsilyl-1-decene gave a 6:1 mixture of indolizidines **6** and **7** in 60% yield. 5-Methoxyhexahydroindolizidin-3-one **3** was optically pure and the silane **5** was racemic so in principle there are two different diastereoisomeric transition states leading to the product. Given this additional complication, it was pleasing that only the *axial* isomer formed, but somewhat disappointing that the ratio of *E*:*Z*-isomers was only 6:1. Other reports on the use of 3-trimethylsilyl-1-alkenes in *N*-acyl iminium chemistry suggest that the *E*-alkene is

exclusively formed.[10] The double bond stereochemistry of the major adduct was determined to be *E*-based on the coupling constant of 14.7 Hz between the vinyl protons. The pendant alkyl group was determined to be *axial* based on the absence of an NOE on either H5 or H9 on saturation of the other, and the large chemical shift difference, 1 ppm deshielded, of H5 relative to H9. This is due to *equatorial* H5 being in the deshielding zone of the lactam carbonyl group. When H5 is *axial* it has a similar chemical shift to H9.[11] The minor isomer could not be separated from the major one, making it difficult to assign the stereochemistry of this material. Reduction of the 6:1 mixture with hydrogen and palladium gave a single diastereoisomeric product, as determined by ^{13}C NMR spectroscopy, which strongly suggested that the double bond was responsible for the isomeric mixture.

The identity of the minor isomer was further confirmed by conversion of ester **2** to indolizidinones **6** and **7** (ratio 3:1, 62% yield) via the corresponding aldehyde **8**. This was accomplished by a modified Julia reaction.[12] The diastereoisomers produced by this route were identical (^{13}C NMR) to those produced by the allylsilane chemistry, confirming the *Z*-stereochemistry previously postulated for the minor isomer. Reduction of the amide in indolizidinones **6** and **7** gave piclavines A1 and A2 as a 6:1 mixture in a combined yield of 73%, $[\alpha]_D = +24.8$ (*c* 2.3, $CHCl_3$).

Piclavines A1–A4 were originally isolated and characterised as a mixture of four isomers. However, there has been some confusion over the relative amounts of these isomers in the mixture with the original assignment shown in Table 1 (entry 1). On the synthesis of piclavine A4 it was realised that this was not a major component in the mixture and the assignment was changed to reflect this[5] (Table 1, entry 2). However, on comparing the reported ^{13}C data of synthetic piclavine A4 with the actual ^{13}C spectrum of the natural product mixture it was clear to us that piclavine A4 was the minor component in the mixture and this is amended in Table 1 (entry 3). The ^{1}H and ^{13}C NMR spectra of synthetic piclavines A1 and A2 are in good agreement, with a major and intermediate component, respectively, in the piclavine mixture and this is again reported in Table 1 (entry 3).

Table 1

	Piclavine ratios			
Entry	A1	A2	A3	A4
1	1	3	6	6
2	6	6	1	3
3	6	3	6	1

This is the first synthesis of piclavines A1 and A2 and confirms the proposed structures for these unusual marine natural products.[13]

Acknowledgements

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