

Tetrahedron Letters 40 (1999) 6909-6912

TETRAHEDRON LETTERS

Synthesis of the ABCD-rings of the insecticidal indole alkaloid nodulisporic acid

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Received 15 June 1999; revised 28 June 1999; accepted 29 June 1999

Abstract

Lewis acid mediated cyclization of the aldehyde 7 leads to 8, 9 and 10, of which 10 contains the structural and stereochemical elements of the ABC-rings of nodulisporic acid 1. © 1999 Elsevier Science Ltd. All rights reserved.

In 1997 the Merck group reported the isolation and structure of the potent insecticide nodulisporic acid 1 from the fungus *Nodulisporium* sp. (Scheme 1).¹ It is structurally related to the tremorgenic indole alkaloid janthitrem E 2,² and to a similar group of antiinsectan indole alkaloids known as the shearinines.³ While there have been reports of the synthesis of simpler members of this type of terpene alkaloid,⁴ there are no reports of the synthesis of structures related to either 1 or 2.



Scheme 1.



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Our initial efforts have focused on the construction of the ABCD-rings of 1 using the Type II⁵ ene reaction depicted in Eq. 1, which, for the conversion of 2-isopropenyl benzaldehyde 3 into 3a, has no formal literature analogy.⁶ Whether concerted (unlikely), or cationic via 3b, the cyclization of 3 is predisposed to lead to the formation of 3c and benzofulvene 3d as competitive pathways. It is also relevant to know that treatment of 1 with trimethyloxonium tetrafluoroborate resulted in dehydration of the C-24 secondary alcohol resulting in the benzofulvene analog of 1.¹

The A-ring of 1 in the form of the precursor 5 (Scheme 2), is the hydration product of phorone $4.^7$ Bromine–lithium exchange of 5a and addition of the resulting aryl lithium to 5 generated the alkoxide 5b, which on work-up gave 11. The adduct 11 proved to be rather sensitive to acid catalyzed rearrangement to 12, and as a consequence the alkoxide 5b was treated in situ with carbon disulfide (presumably forming 5c) and heated to reflux to give 6 (74% from 5). Acid catalyzed hydrolysis of the ketal 6 provided the aldehyde 7 (81%).



Scheme 2.

Table 1 lists a number of reaction conditions that 7 was exposed to, and the resulting products. The entries 3, 6, 7, 9, and 10 document conditions that provide access to the tricyclic diene 9 as the only isolated product.⁸ The use of either Sc(OTf)₃ (1.1 equiv.) or Me₃SiOTf (0.1 equiv.), entries 4 and 8, respectively, are conditions which allowed the isolation of all three expected products 8, 9 and 10. The relative stereochemistry of 10 was verified by X-ray crystallography.⁹ The overall reaction (entry 8) proceeds with an excellent mass balance (>95%), but little useful selectivity. Since the diene 9 is available, we examined the possibility of reintroducing the benzylic secondary hydroxyl functionality.

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Entry	Lewis acid	Reaction conditions	Product(s)
1.	1.1 eq Et ₂ AlCl	Toluene, reflux	7 (86%)
2.	1.1 eq SnCl4	Toluene, -78 °C to RT	7 (20%), 8 (40%)
3.	1.1 eq SnCl ₄	MeCN, -78 °C to RT	9 (55%)
4.	1.1 eq Sc(OTf) ₃	CH ₂ Cl ₂ , -78 °C to RT	7 (15%), 8 (31%), 9 (17%), 10 (16%)
5.	1.1 eq Yb(OTf) ₃	CH ₂ Cl ₂ , 0 °C to RT	7 (>95%)
6.	1.1 eq Me ₃ SiOTf	CH ₂ Cl ₂ , -78 °C	9 (24%)
7.	1.1 eq Me ₃ SiOTf	CH ₂ Cl ₂ , 0 °C	9 (52%)
8.	0.1 eq Me ₃ SiOTf	CH ₂ Cl ₂ , -78 to -20 °C	8 (51%), 9 (34%), 10 (15%)
9.	0.05 eq Me ₃ SiOTf	CH ₂ Cl ₂ , 0 °C	9 (55%)
10.	1.1 eq TfOH	CH ₂ Cl ₂ , -78 °C to RT	9 (43%)
11.	1.1 eq ZnCl ₂	CH ₂ Cl ₂ , 0 °C to RT	7 (>95%)
12.	None	1,2-Dichlorobenzene, reflux	7 (>95%)

It was found that treatment of 9 with dimethyldioxirane¹⁰ gave the epoxide 13a as the major product. Exposure of 13a to $BF_3 \cdot OEt_2$ resulted in rearrangement to the ketone 13b. Reduction of 13b with NaBH₄/MeOH gave 10 and 14 (82%, 1:3.6), and K-Selectride gave 14 as the only product (83%).

In order to install the indole ring onto 9 it was decided to use the vinyl azide–nitrene insertion methodology (Hemetsberger synthesis)¹¹ which requires that 9 should undergo regioselective formylation, (Scheme 3). Treatment of 9 with Cl₂CHOMe/SnCl₄/CH₂Cl₂ at -40°C gave the aldehyde 15 as the major regioisomer.¹² The crude product contains only small amounts (ca. 5%) of other isomeric aldehydes as indicated by ¹H NMR. Exposure of 15 to α -azido methyl acetate¹³ NaOMe/MeOH/THF at -30°C gave the vinyl azide 16 in modest yield. Addition of 16 to xylene, heated at reflux, gave the separable isomeric indoles 17 and 18 (98%, 1:1).



Scheme 3.

It is clear from the above results that the acid sensitive nature of the homoallylic secondary alcohol 10 will cause difficulties in the synthesis of nodulisporic acid 1, and this array may have to be installed late

in the synthesis of 1. Nevertheless, we have demonstrated that the ABC-tricycles 8, 9 and 10 are available from phorone and 5a, and that the diene 9 can be converted into 17.

Acknowledgements

The National Institutes of Health (GM 32718), Robert A. Welch Foundation, Merck Research Laboratories and Novartis are thanked for their support of this research.

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