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

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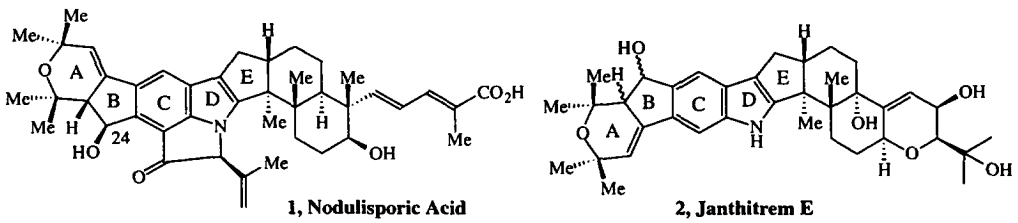
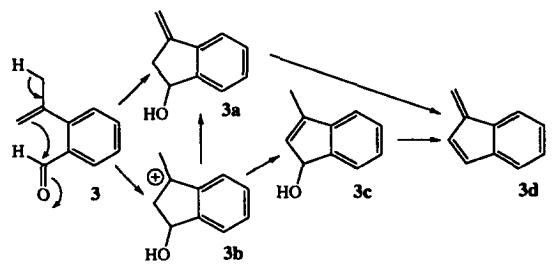
Abstract

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**.

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.



(1)

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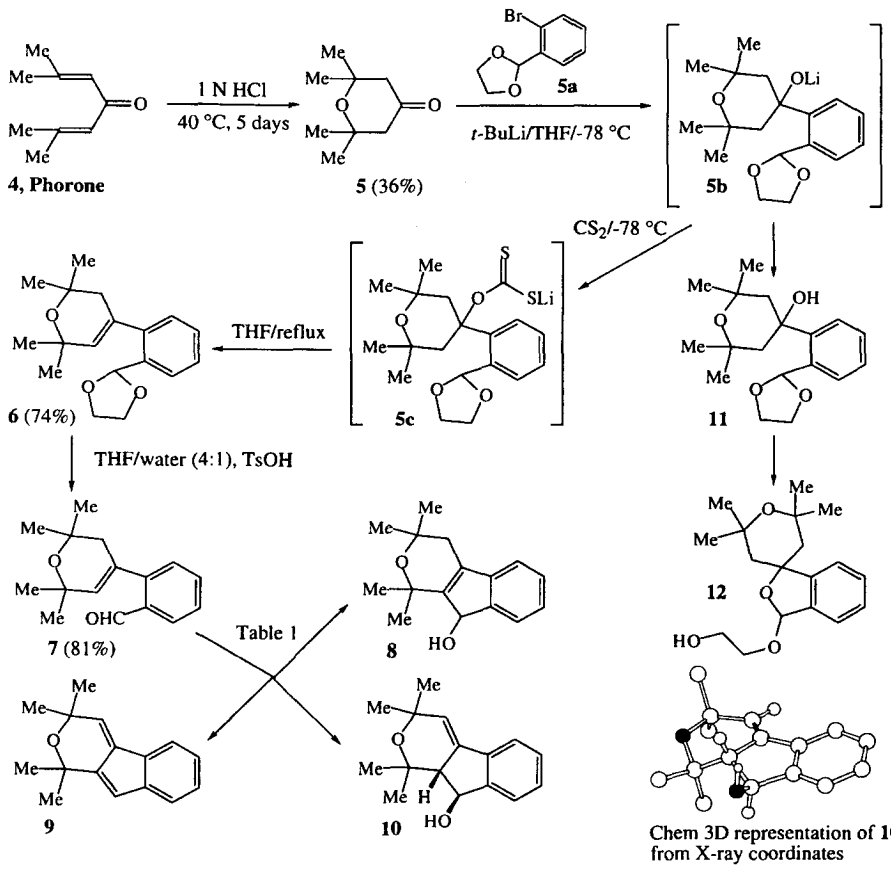
Our initial efforts have focused on the construction of the ABCD-rings of **1** using the Type II[5] ene reaction depicted in Eq. 1, which, for the conversion of 2-isopropenyl benzaldehyde **3** into **3a**, has no formal literature analogy.[6] Whether concerted (unlikely), or cationic via **3b**, the 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.

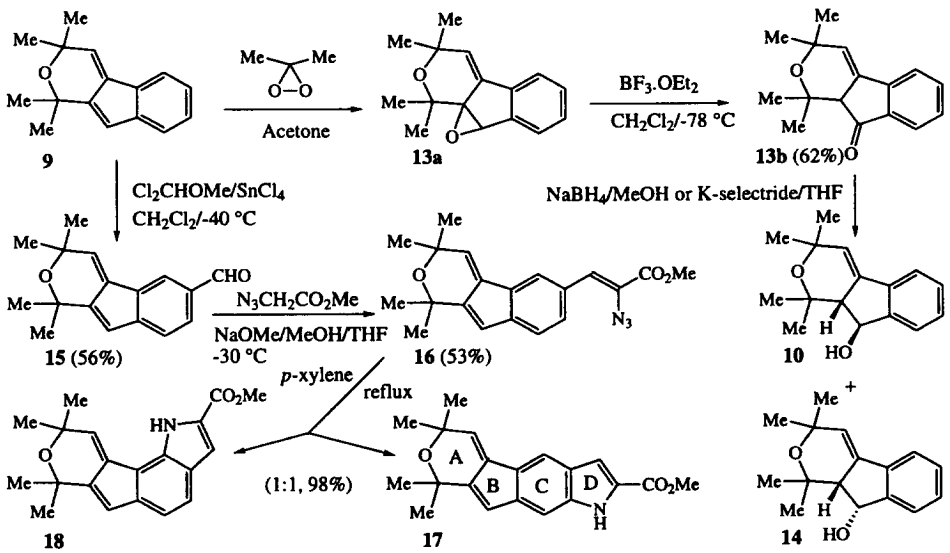
Table 1 lists a number of reaction conditions that **7** was exposed to, and the resulting products. The entries *3, 6, 7, 9,* and *10* document conditions that provide access to the tricyclic diene **9** as the only isolated product.[8] The use of either $Sc(OTf)_3$ (1.1 equiv.) or Me_3SiOTf (0.1 equiv.), 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.

Table 1

Entry	Lewis acid	Reaction conditions	Product(s)
1.	1.1 eq Et_2AlCl	Toluene, reflux	**7** (86%)
2.	1.1 eq $SnCl_4$	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_2Cl_2, -78 °C to RT	**7** (15%), **8** (31%), **9** (17%), **10** (16%)
5.	1.1 eq $Yb(OTf)_3$	CH_2Cl_2, 0 °C to RT	**7** (>95%)
6.	1.1 eq Me_3SiOTf	CH_2Cl_2, -78 °C	**9** (24%)
7.	1.1 eq Me_3SiOTf	CH_2Cl_2, 0 °C	**9** (52%)
8.	0.1 eq Me_3SiOTf	CH_2Cl_2, -78 to -20 °C	**8** (51%), **9** (34%), **10** (15%)
9.	0.05 eq Me_3SiOTf	CH_2Cl_2, 0 °C	**9** (55%)
10.	1.1 eq TfOH	CH_2Cl_2, -78 °C to RT	**9** (43%)
11.	1.1 eq $ZnCl_2$	CH_2Cl_2, 0 °C to RT	**7** (>95%)
12.	None	1,2-Dichlorobenzene, reflux	**7** (>95%)

It was found that treatment of **9** with dimethyldioxirane[10] 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 $NaBH_4$/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 $Cl_2CHOMe/SnCl_4/CH_2Cl_2$ 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 acetate[13] 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

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13. Professor C. J. Moody is thanked for the procedure to make this compound.