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Marine natural products—synthetic exercises and biological activity*

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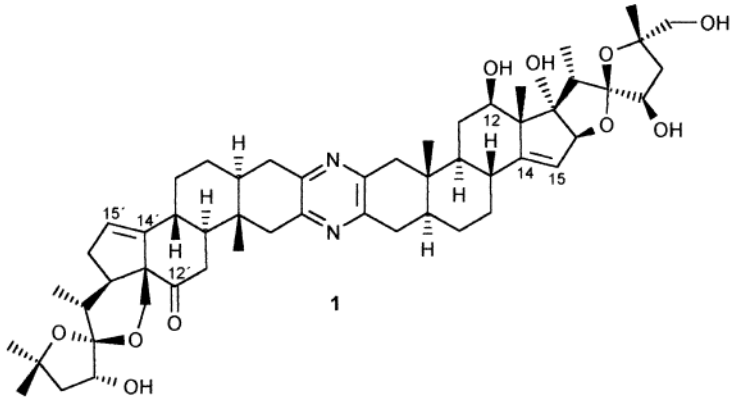
The comparison of the biological activity in the cephalostatin and ritterazin series of marine natural products proved cephalostatin 1 to be the most active compound [1,2]. The very complex and quite unusual bis-steroidal pyrazine structure induced quite some synthetic activity in various laboratories [3–5] that culminated in a total synthesis in the group of P. Fuchs in the United States (Scheme 1) [6].



Scheme 1

In our Hannover group we were well aware of the fact that the total synthesis of compounds of this type would certainly be a many step affair that could barely lead to the proper amount of material for a complete biological evaluation.

So we decided to first of all collect some information on the important structural details, that are indispensable for the tumor inhibiting activity of these compounds and by defining the essential substructures to arrive at easy to make analogues that would hopefully still show biological activity.

Some specialities of these natural products become visible on the first glance.

All of them have the characteristic central pyrazine ring, they show the Δ14,15-double bond, which is not a very common structural feature in naturally occuring steroids, they all carry spiroketal groups on ring D and turn out to be nonsymmetric substances.

These last two properties can be checked most easily by preparing amino-ketone **2** from hecogenine which dimerises spontaneously to yield the symmetric diketone **3**, which is highly insoluble and provided very discouraging data on biological evaluation (Scheme 2).

The decisive role of the 14,15-double bond becomes visible from the corresponding unsaturated diketone **4** which can easily be prepared from Δ14,15 hecogenine derivates. These precursors are easily accessible by the *Bladon–Weltzel* photoisomerisation [7,8].

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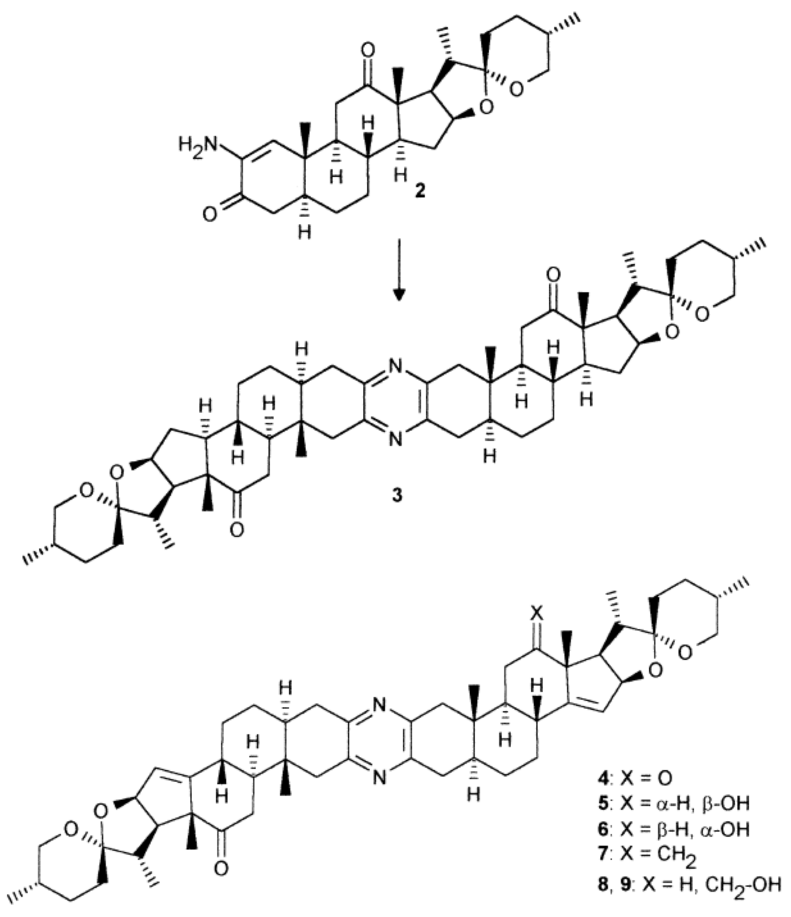


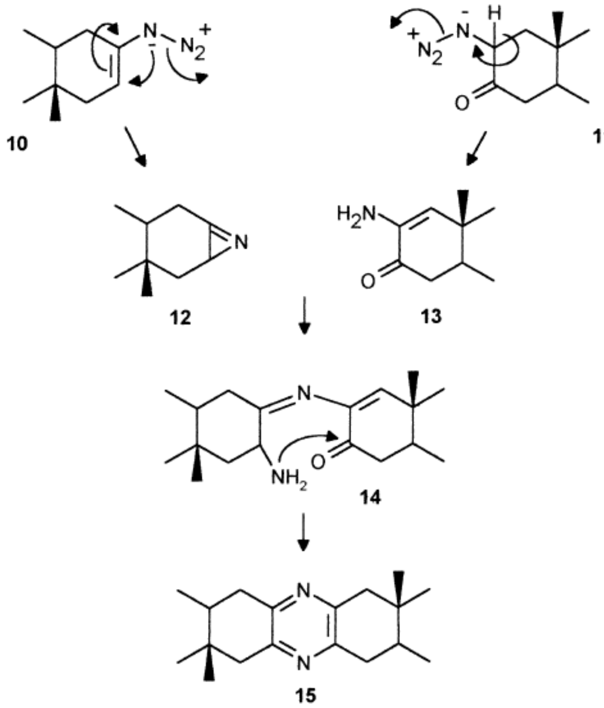
Scheme 2

In contrast to **3** diketone **4** shows comparatively high solubility but still only very modest biological activity. This is improved in a quite remarkable way in the nonsymmetric β- or α-hydroxyketones **5** and **6** which can be prepared in a selective reduction with borohydride or L-selectride, respectively. This indicates very clearly that for good biological activity one is aiming for nonsymmetric Δ14,15-cephalostatin analogues.

The remarkable difference in solubility between the saturated compound **3** and all the unsaturated analogues **4** through **8** called for an explanation on the structural basis. A close investigation of molecular models of the Δ14,15-derivatives indicated very clearly that the β-configuration at carbon-13 together with the planar arrangement at the neighbouring sp^2-centres induce a chiral curvature in the molecule with the five-membered ring carrying the spiroketal hanging down like the wing-tips of some aeroplanes. Since it is well known that pure enantiomers of molecules with a distinct chiral curvature are forming a quite loosely packed crystal lattice one is not surprised to observe the higher solubility with compounds of this structure [9].

Having the symmetric diketone **4** available we looked for further options for desymmetrisation making use of well known ketone transformations and had a remarkable success with the *Wittig* olefination. Although one is dealing with a cyclic ketone next to a quarternary carbon-atom the selective olefination took place under comparatively mild conditions and yielded next to the bisolefinated material 48% of the exomethylene compound **7**. On subsequent hydroboration followed by oxidative work-up an epimeric mixture of the primary carbinols **8** was obtained which again showed impressive biological activity. To explore the structure activity relationship in this case, the two epimers were separated by column chromatography and are on their way for biological evaluation [10].

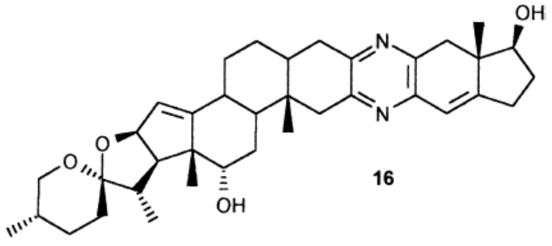
Since all these results underline the importance of nonsymetric Δ14,15-compounds we looked for a reliable version of a dissymmetric pyrazine synthesis. In the essence one needs two different and comparatively stable α-aminoketone equivalents that would not dimerize, which means that the one should operate as electrophile exclusively while the other one should play the part of the nucleophile. Our investigations led to the choice of an azirin (**12**) and enaminoketones of type **13** (Scheme 3).



Scheme 3

The azirine **12** was obtained on thermolysis of vinylazides of type **10** which have been described in the literature [11] and the enamine **13** forms spontaneously from ketoazide **11** on loss of nitrogen via the corresponding imin which rearranges immediately to form **13**.

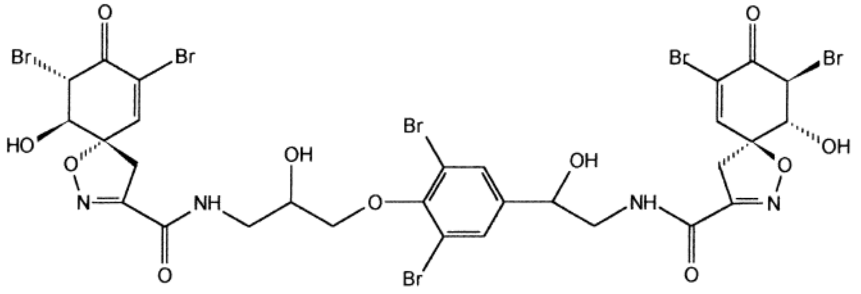
On proton catalyzed condensation nonsymmetric pyrazines were formed in acceptable yields **11** and a number of nonsymmetric pyrazines including compounds like **16** with one ‘shortened’ alicyclic ring system have been prepared this way (Scheme 4).



Scheme 4

In the second part of the lecture a general route was presented for an enantioselective preparation of the spiro-isoxazol moiety that plays an important role in the structure of some marine natural products as for instance Agelorin A **17** (Scheme 5) [12].

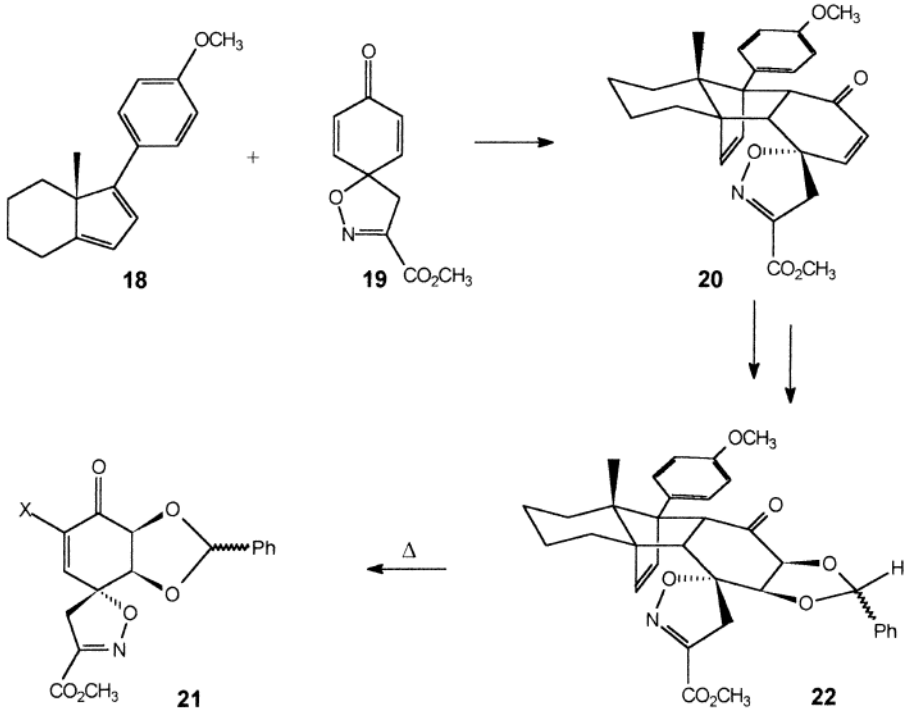
The decisive step in this approach was the differentiation of enantiotopic groups in the spirocyclohexadienone **19**. This was achieved in a face selective and endo-selective *Diels–Alder*



Agelorin A (**17**)

Scheme 5

cycloaddition to the enantiopure cyclopentadiene **18** that had been prepared in our laboratory in both absolute configurations from the corresponding ‘R’ and ‘S’ *Hajos–Wiechert* ketone (Scheme 6) [13].



Scheme 6

As had been shown with similar compounds before the spiro system will always accommodate the less space demanding hetero atom in the α-configuration, as one would expect with endo-adducts [14]. This one arrived at cyclohexenone **20** as the single reaction product. At this very rigid and well defined endo-framework all subsequent reactions will of course show very high diastereoselectivity and one was not surprised therefore to notice the clear cut formation of the β-diol in a flash hydroxylation process, which could easily be protected by benzaldehyde to form acetal **22**.

This cycloadduct generated the enantiopure (> 98% enantiomer excess) cyclohexenone **21** on thermolysis in high yield which was brominated very efficiently and could also be transformed into the corresponding β-epoxide. As all the natural products in this field are amides of these spiroisoxazolin acids, amide formation was studied too. The most easy version of amide formation is of course the α-pyridone catalyzed transamination process with the corresponding ester. This did work nicely with cyclic amines like pyrrolidine and piperidine but turned out to be a very unreliable reaction with no preparative value in the case of primary amines and a closer investigation of this transformation proved the amide formation in this case to be accompanied by conjugate additions to the unsaturated ketone and ring opening processes at the spiro system. This asks for amide formation with the activated acid and investigations into the preparation of the free acid have been successful by employing the corresponding tert.butylester.

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