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Selective transformations of cephalostatin analogues*,**

Mansour M. Nawasreh‡

Applied Sciences Department, Faculty of Engineering Technology, Al-Balqa Applied University, P.B. 15008, Marka, 11134 Amman, Jordan

Abstract: The highly tumor inhibitory cephalostatins (e.g., cephalostatin 1), a marine natural product isolated from *Cephalodiscus gilcristi*, have attracted us to synthesize biologically active analogues. The goal of this study is to shed more light on selective desymmetrization of a symmetrical starting analogue through the F-ring opening route applied to certain analogues using different borane complexes. Previously, we have reported a selective opening of the spiroketal in the northern part of an analogue using catechol-borane and D-(*N*-tosyl) valine-borane complexes. We demonstrate here the possibility of opening the southern part of the same analogue using salicylic acid-borane complex by which extra flexibility is harvested. In contrast, a different reaction type took place when another analogue was treated with 3,4-diaminobenzonitrile-borane complex, which give after H_2O_2 oxidation, products arising from Δ^{14} bond hydration. This led us to conclude that the geometry of both borane complex and substrate govern the regioselectivity of the products. However, the electronic nature of both substrate and borane-complex govern the chemoselectivity.

Keywords: borane complexes; cephalostatin 1; chemoselectivity; desymmetrization; regioselectivity; selective F-ring opening.

INTRODUCTION

The therapeutic potential and cellular target cephalostatin 1 (**1**) is one of the most active *anti*-tumor inhibitor marine natural products with average GI_{50} of 1.8 *n*M against 60 human cancer cell lines (NCI-60) [1]. Its unique differential cytotoxicity profile obtained from the 60-cell-line in vitro screen of the NCI strongly suggested that **1** may utilize a new molecular mechanism to trigger cell death [1]. It belongs to the cephalostatin family, which consists of 19 bis-steroidal pyrazines isolated by Pettit's group from the marine worm *Cephalodiscus gilchristi* [2].

Because of the lack of this compound in nature, a lot of effort has been made to synthesize this natural product or its analogues to understand its biological function. Very early on, Winterfeldt's group at Hannover University was involved in the cephalostatin task through the coupling of two steroidal units together to generate the first symmetrical analogue [3]. Thereafter, Heathcock and co-workers modified the bis-steroidal coupling method [4].

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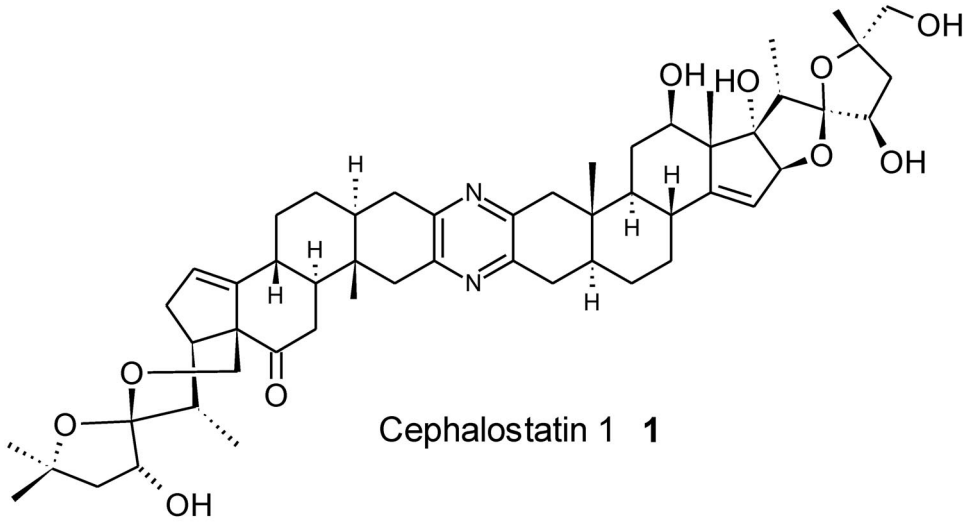
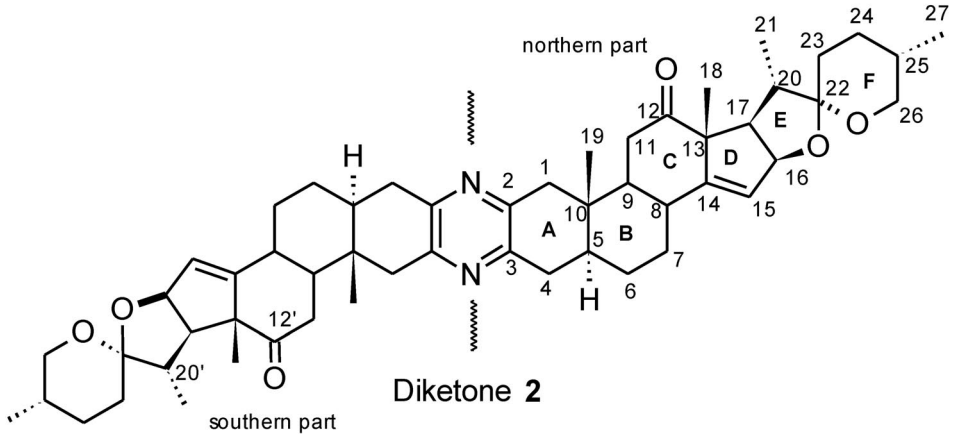
**Dedicated to Prof. Helmut Duddeck on the occasion of his 65th birthday.

‡E-mail: mansreh@yahoo.com, Mansour.Nawasreh@ fet.edu.jo

During the 1990s, Winterfeldt's group was busy in the synthesis of symmetrical and asymmetrical analogues [5]. Meanwhile, Fuchs and co-workers reported the first total synthesis of **1** and other cephalostatin members [6–8]. Very recently, Shair et al. have reported the second total synthesis of **1** using an elegant allylic oxidation method of C-18 [9]. The work of these groups depends on asymmetrical coupling of the proper steroidal parts to generate a rigid desired synthetic target. Despite the number of synthetic procedures in the literature, the interest in alternative and more convenient procedure for the synthesis of **1** is high. Thus, our philosophy is completely different. Based on desymmetrizing of the gram-scaled symmetrical diketone (**2**) followed by remote interconversion methods, we build up our strategy aiming at either the synthesis of flexible analogues or perhaps the natural product itself. This strategy enables us to gather a lot of information about the behavior of the active centers in such complicated structures along with building a helpful spectral database.



Cephalostatin 1 **1**



Diketone **2**

southern part

RESULTS AND DISCUSSION

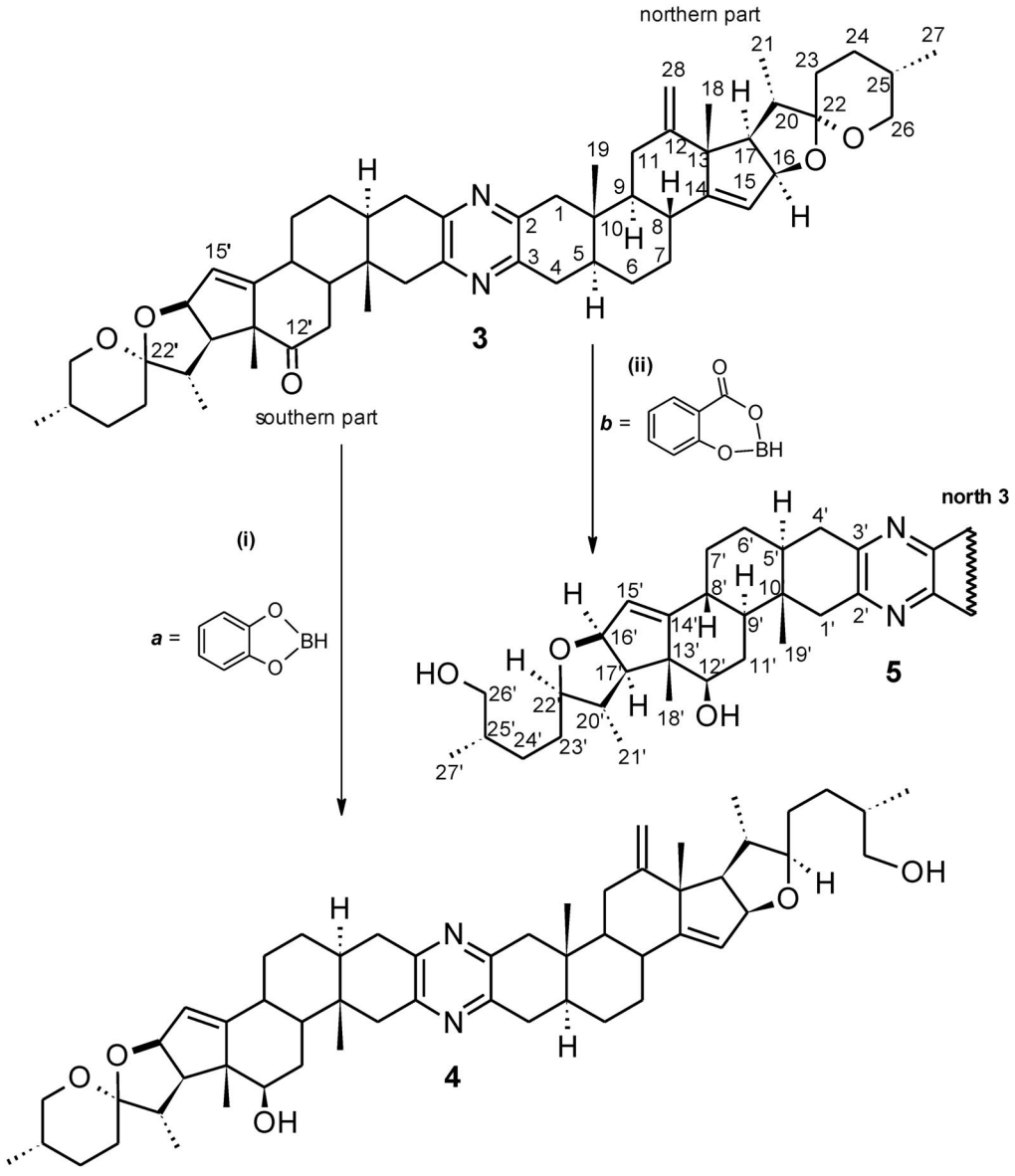
By making use of the well-established gram-scaled synthetic method of the symmetrical diketone starting material (**2**) and based on the fact that asymmetrical analogues showed higher biological activity than the symmetrical ones [2a,b,5a], we build up our strategy on selective desymmetrization of this compound. Thus, we aim at bioactive analogues or, if possible, the natural product itself. The retrosynthetic analysis of **1** required the presence of keto group at C-22 and a stepwise introduction of –OH groups at C-17 and C-18. Consequently, the most crucial routes in our approach are selective opening of the spiroketal and selective introduction of the hydroxyl groups especially at C-17 and C-18 positions.

In contrast to recent work of other groups working on the monomer [10,11], opening the spiroketal in one side of the dimer is more complicated and is the critical stage in this work. A few years ago, we reported selective opening of the F-ring of the dimer (**3**) using catechol-borane complex in which the opening side was from the methylene side [12,13]. However, in this work, and after many attempts, we succeeded in opening the same ring of the same dimer from the other side (keto side) using salicylic acid-borane complex. This encouraged us to pursue the endeavors to invent high controlled process via intensive studying of its chemo- and regioselectivity. The selection of compound **3** as a starting material was because of the biological activity enhancement noticed for the products resulting from hydration of the exocyclic double bond [13,14].

As this process depends on both the nature of the borane complex and the substrate, several combinations have been tested. The selection of the borane complex was on the basis of the space demanded by the geometry and the electronic nature of the ligand. Whereas the substrate was selected due to its suitability to control the following conversions, its biological importance and its property for emphasis declines hypothetical thinking about the process.

Treating the substrate **3** with the catechol-borane complex ***a***, which was obtained from the Wittig reaction of the diketone **2**, led to compound **4** as a major product, wherein the opening was from the methylene side (northern part). However, in this work we provide evidence that by using salicylic acid-borane complex ***b***, the opening of the same substrate was from the keto side (southern part), yielding compound **5** as major product as illustrated in Scheme 1.

The proposed rationalization of this selectivity based on the fact that the complex ***a***, in which the boron atom is a part of a five-membered ring, reacted firstly with the keto group by which the region over the spiroketal moiety is partially blocked from further attack. Whereas the spiroketal in the other half was completely free for attack from the complex according to donor–acceptor rules. Consequently, the whole process led to **4** as a major product in fair yield (regioselectivity). In the case of using complex ***b***, in which the boron atom is a part of a six-membered ring, the attached complex *may* have turned away from the ketal region and there may have been a directed activation of the neighboring spiroketal by the reduced keto group that triggered the selective reduction.



Scheme 1 Different-side spiroketal opening of **3**. (i) 16 equiv ***a***, abs THF, 0–7 °C, two weeks; (ii) 10 equiv ***b***, abs THF, 0–2 °C, four weeks.

As a conclusion, the opening side in **4** and **5** is governed by both the complex geometry and the donor–acceptor behavior between the spiroketal and the complex which is affected by the C-12 functionality. Both structures **4** and **5** were approved using different spectroscopic methods as indicated in Figs. 1a,b. Approving the structure of **5** was more difficult because direct correlations between the key protons were difficult to be found. Nevertheless, we were able to find indirect combinations between these protons and the corresponding carbons.

Determination of the opening side in **5** was with the help of both nuclear Overhauser enhancement spectroscopy (NOESY) and heteronuclear multiple-bond correlation (HMBC) spectra. The key peaks between 12'-H and 17'-H (NOESY) and 17'-H and C-22' (HMBC) were found. Also, from the

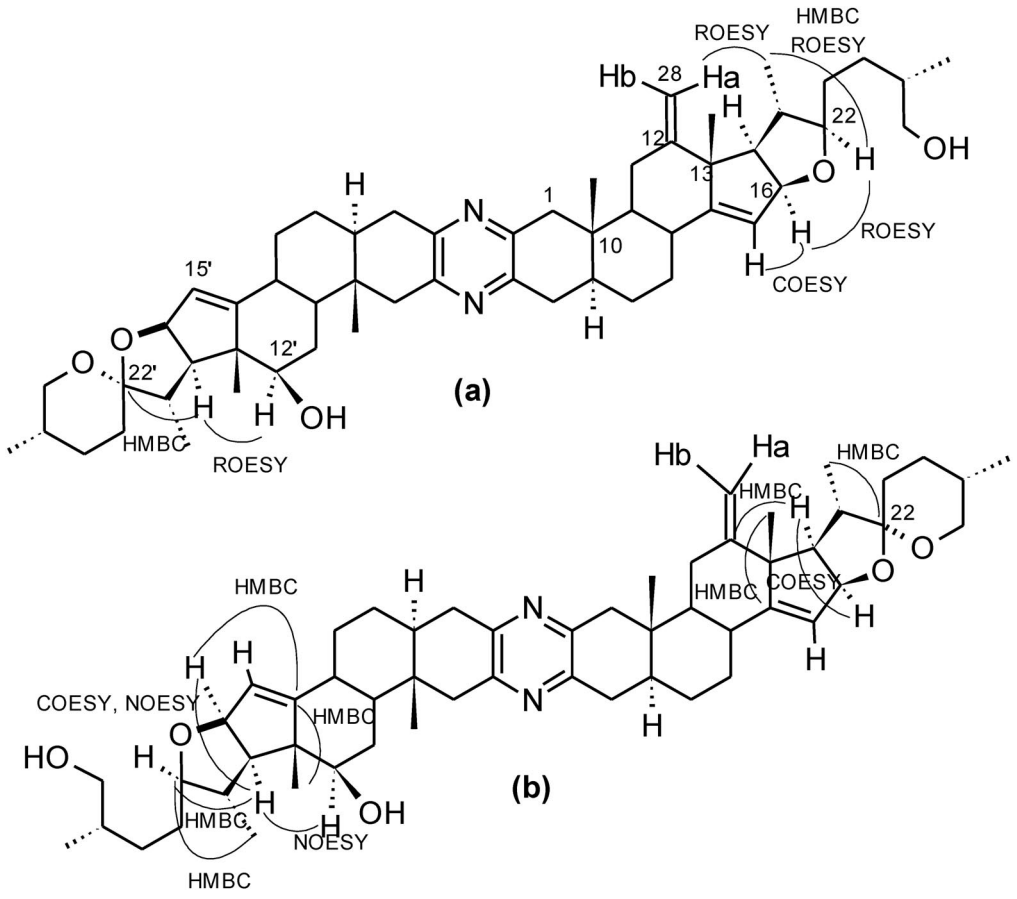
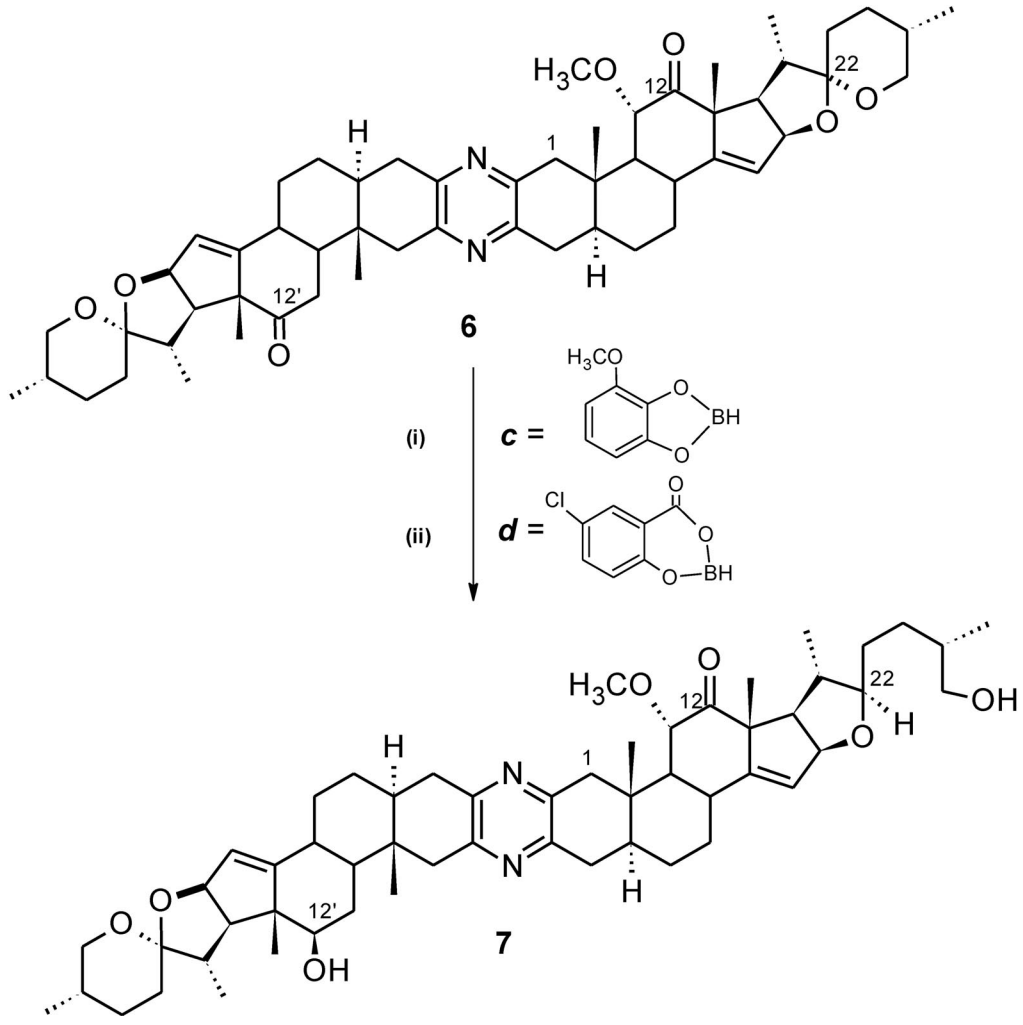


Fig. 1 2D NMR correlations of compounds **4** and **5**. (a) 2D correlations for **4**; (b) 2D correlations for **5**.

correlation spectroscopy (COSY) experiment, it was easy to differentiate between the signals of 17-H and 17'-H through the corresponding correlations with their neighboring 16-H and 16'-H, respectively. These correlations were ensured from the NOESY spectrum. Interestingly, the ^{1}H NMR spectra showed clear differences between compounds **4** and **5** in the chemical shift values especially of 15-H and 16-H. Also, the coupling constant between 28a/28b protons in **5** is 8-fold greater than in **4**. This can help in determining the opening side of the dimer directly without the need for 2D experiments.

Moreover, these differences in NMR may reflect a great electronic effect between the spiroketal and the excocyclic double bond and hence the reactivity toward the ring-opening process in such a remarkable polycyclic system.

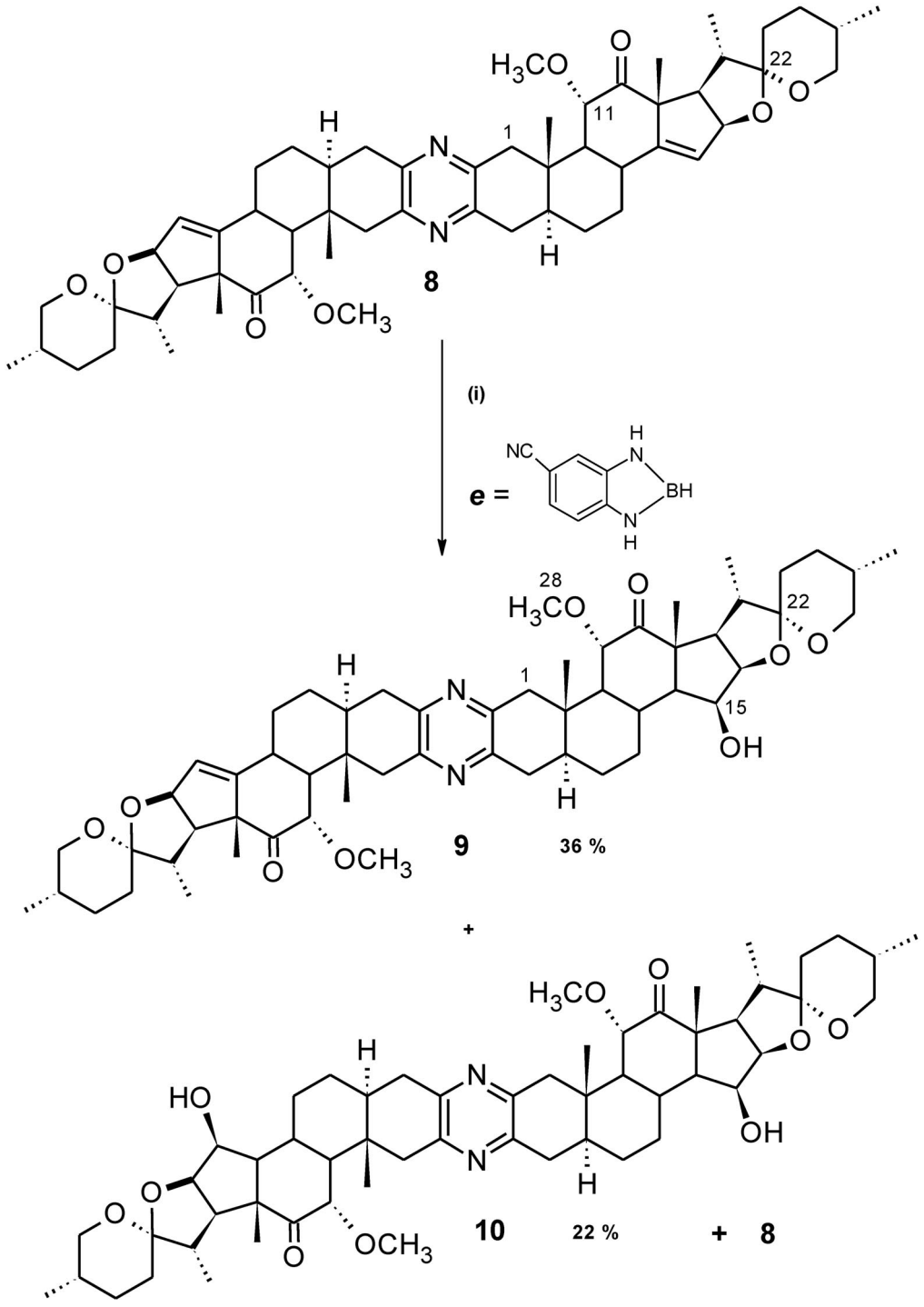
Based on positive results obtained before in regioseletive reduction of the methoxy-free carbonyl of **6** and the biological activity of the reduced product [13], it was selected as a substrate model. Developing the process was extended by employing other borane complexes. Compound **6** was treated first with 3-methoxycatechol-borane complex ***c*** and then with excess of 5-chlorosalicylic acid-borane complex ***d***. This led to **7** in which the opening was only from the methoxy side in a good yield (Scheme 2). This further showed that the selected bulky complex ***c***, which reacts first with the methoxy-free carbonyl, has blocked the region over the spiroketal in this part, leaving the ketal in the other part free for attack from the complex ***d***. Previously, we have reported that the carbonyl beside the methoxy group does not undergo reduction or nucleophilic reaction because its back side is blocked by the α-configurated methoxy group [13].



Scheme 2 Regioselective spiroketal opening of **6**. (i) 1.5 equiv ***c***, 24 h/0–5 °C; (ii) 10 equiv ***d***/3 days/78 %.

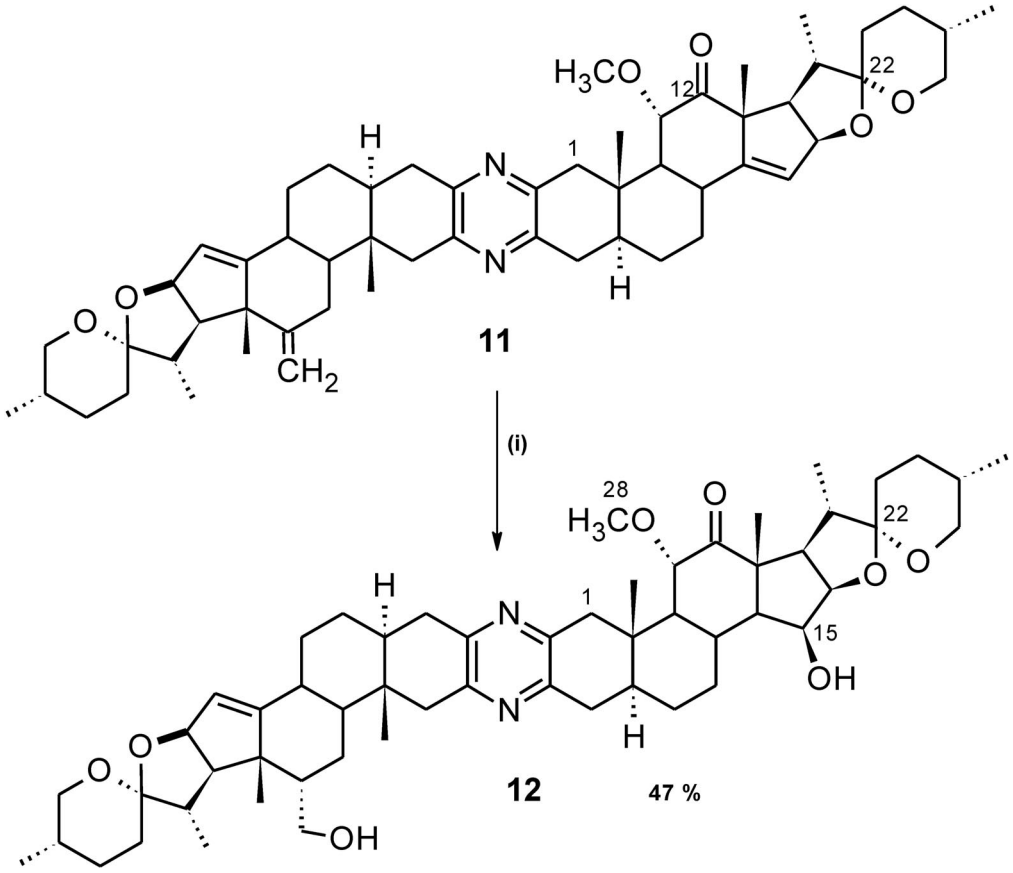
The selection of substrate with multipurpose directing group in addition to the complex variability provides numerous opportunities in the reaction engineering. Inspection of different 2D spectroscopic techniques enabled us to prove the structure of **7**. The rotating frame Overhauser effect spectroscopy (ROESY) experiment showed a cross-peak between 22-H and both 16 and 17-H. In addition, indirect combinations between H-22 and the carbonyl carbon were concluded from the HMBC experiment.

To improve the reaction time, a more electron-rich 3,4-diaminobenzonitrile-borane complex ***e*** was tested with the substrate (**8**). Instead of F-ring opening reaction, a hydroboration of the Δ^{14} bond took place, to give after H_2O_2 oxidation 15β-hydroxylated products (Scheme 3). This limits the complex selection since both spiroketal and Δ^{14} bond are in the *playground*. Compound **9** was obtained as a major product in addition to the symmetrical product (**10**) and the starting material (**8**) along with traces of other minor products. The β-configuration of the hydroxyl group at C-15 was confirmed from the ROESY experiment which showed a very clear cross-peak between 15-H and 16-H.



Scheme 3 Hydroboration–oxidation of **8** using the complex ***e***. (i) 16 equiv ***e***, abs THF/H_2O_2, 0–8 °C.

It is to stress the fact that the Δ^{14} bond in the methoxy half of **11** undergoes hydroboration faster than its counterpart in other half, yielding compound **12** as major product (Scheme 4) [14]. This emphasizes that the methoxy group enhances the electron density on the E-ring double bond, making it more prepared for electrophilic attacks.



Scheme 4 Regioselective hydration of **11**. (i) 5 equiv BH_3·THF, 0–7 °C.

CONCLUSION

In this study, we disclose more applications of the selective opening process of the spiroketal, and thus we conclude that this process is governed by both geometric and electronic properties of the complex as well as of the substrate. Moreover, the functional group at C-12 affects directly the spiroketal behavior. However, the group at position-11 plays an important role in the Δ^{14} bond behavior.

SUPPLEMENTARY INFORMATION

Experimental data is available online (doi:10.1351/PAC-CON-10-08-15).

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