Cortistatin A

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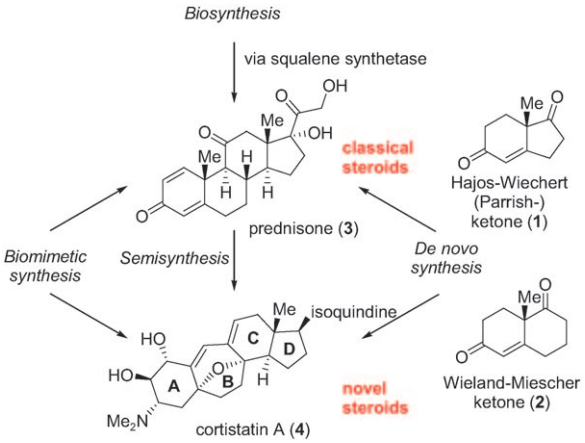
Highlights in Steroid Chemistry: Total Synthesis versus Semisynthesis**

Carl F. Nising and Stefan Bräse**

cortistatin A · natural products · semisynthesis · steroids · total synthesis

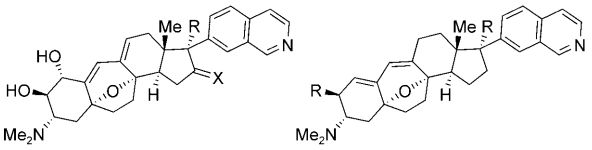
Owing to their unique plethlora of structures and biological activities, natural products with a steroid framework traditionally play an important role in medicinal chemistry.[1] In conjunction with the discovery of the steroids as active hormonal compounds in the middle of the last century, steroid chemistry blossomed. Even today most of the steroids used pharmaceutically are still prepared by modification of natural products (semisynthesis); [2] a number of the most important strategies for the total synthesis of steroids are summarized briefly in Scheme 1.



Scheme 1. Important strategies in steroid syntheses.

The first de novo syntheses based on ring-anellation strategies starting from universal building blocks such as the Hajos–Wiechert (Parrish) ketone (**1**) and the Wieland–Miescher ketone (**2**) proved to be very successful and opened up access (also industrially utilizable!) to important classical steroid hormones such as cortisone, cholesterol, and prednisone (**3**).[3] Yet more impressive, however, were the subsequently developed biomimetic steroid syntheses, driven forward primarily by the work on the stereochemical course of polyolefin ring-closure cascades (Stork, Eschenmoser et al.).[4] Based on this pioneering work Johnson et al. succeeded in the groundbreaking biomimetic total synthesis of progesterone.[5] Although the importance of steroids in medicine remains unchallenged, efforts in steroid total synthesis have declined significantly in recent years.[6a] Apart from a few important exceptions,[6b,c] the steroid framework has served primarily for the development of new synthetic strategies such as domino reactions,[6d] whereby the conventional gonane structures are usually developed on a preparative scale. With this background several current total and semisyntheses of the steroid cortistatin A (**4**) are even more remarkable.[7]

The cortistatins represent a group of steroids of marine origin of the 9-(10,19)-*abeo*-androstane type; of these cortistatin A has the greatest biological activity (Scheme 2).[7] The



R = H, X = H_2: cortistatin A (**4**)
R = OH, X = α-H, β-OH: cortistatin B (**5**)
R = H, X = O: cortistatin C (**6**)
R = OH, X = O: cortistatin D (**7**)

R = H: cortistatin K (**8**)
R = OH: cortistatin L (**9**)

Scheme 2. Cortistatins A–D, K, L (**4**–**9**).

fundamental biological activity is the high antiangiogenetic action, that is, the inhibition of the formation of capillary blood vessels and in this way the blood supply to the surrounding tissue. Since this process is closely associated with different disease patterns, especially oncogenesis, the cortistatins are important as potential active compounds. Noteworthy in this context is the high antiproliferative and highly selective action ($IC_{50} = 1.8$ nM) against human endothelial cells (HUVEC cells), a model system for antiangiogenetic action.

From a preparative point of view, the challenge lies in the bridged seven-membered B ring, which deviates from the

[*] Dr. C. F. Nising
Bayer Cropscience AG
Alfred-Nobel-Strasse 50, 40789 Monheim am Rhein (Germany)
Fax: (+49) 2173-38-3926
E-mail: carlfriedrich.nising@bayercropscience.com
Prof. Dr. S. Bräse
Institut für Organische Chemie, Universität Karlsruhe (TH)
Fritz-Haber-Weg 6, 76131 Karlsruhe (Germany)
Fax: (+49) 721-608-8581
E-mail: braese@ioc.uka.de

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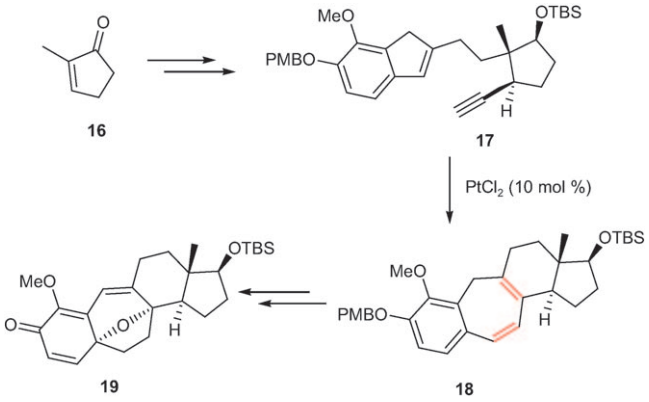
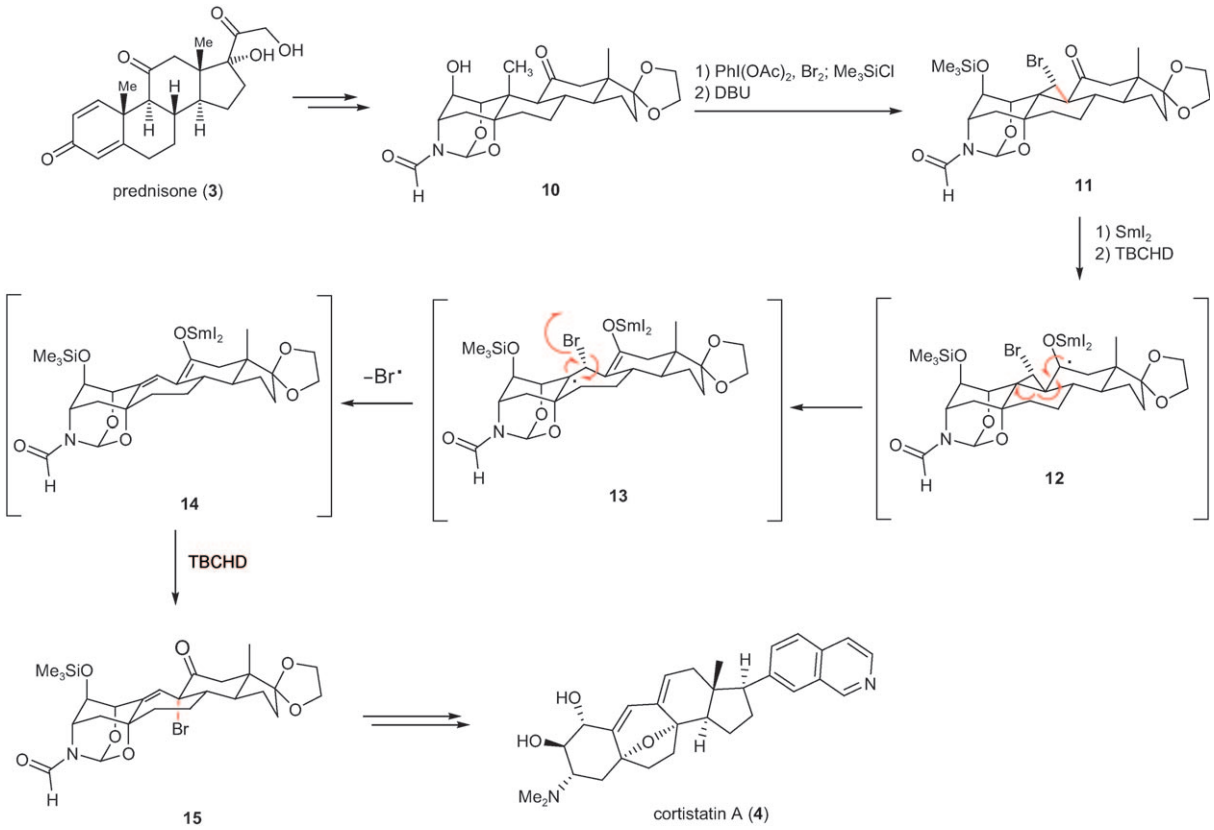
familiar gonane framework. In their retrosynthesis the Baran group decided on a semisynthetic approach: the synthesis of cortistatin A begins with a multistep modification of prednisone, which leads to the intermediate **10** (Scheme 3).[8a] The advantages of this strategy are the readily availability of starting material **3** and its correct configuration at the C- and D-ring junction in the basic framework. The critical subsequent ring expansion exploits the regiospecific functionalization of the angular methyl groups previously used by Barton in his classic work (Barton reaction).[8b] Interestingly, by using in situ generated acetoxyhypobromide as the oxidizing agent an astonishingly selective dibromination of the methyl group was accomplished, which is controlled presumably by the neighboring free alcohol function. Dehydrobromination with α alkylation of the neighboring carbonyl group[8c] generated a three-membered ring (→**11**), which was opened with Kagan's reagent, samarium diiodide, via the radicals **12** and **13** with ring expansion of the B ring to give the seven-membered ring. This reaction sequence was terminated by trapping the resulting enolate **14** with 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TBCHD) as the bromine source. This key reaction was followed by additional steps for the completion of the synthesis of cortistatin A. The Baran group was thus able to complete the total synthesis of cortistatin A in only 21 steps starting from prednisone, which demonstrates impressively the efficiency of semisynthesis exploiting available frameworks.

Recently another group in California, Sarpong and coworkers, succeeded in a direct de novo approach to the pentacyclic ring system of the cortistatin framework (Scheme 4).[9a] The key reaction is a platinum-catalyzed[9b] intramolecular cycloisomerization of indene **17**, which has an ethynyl group, with ring expansion and construction of the C ring (**17**→**18**, Scheme 4). The group was able to construct the bridging oxa function of cortistatin in four additional steps, and it remains to be seen whether the total synthesis based on this strategy will be completed in the near future. Incidently, building block **17** was prepared in a sequence starting from ketone **16** and not as is usual from ketone **1.**

A third group, based in California and Singapore and led by Nicolaou and Chen, was also successful in a total synthesis

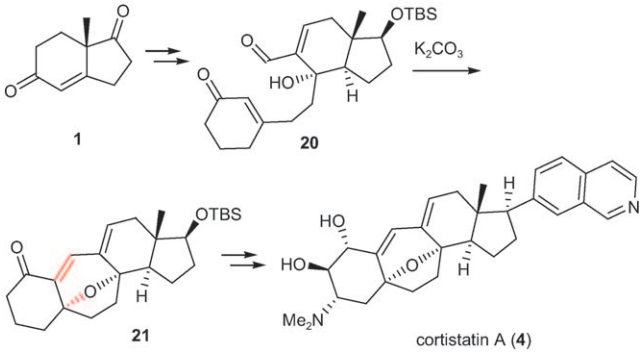


Scheme 4. Synthesis of the basic cortistatin framework **19** according to Sarpong and co-workers.[9a] PMB = *p*-methoxybenzyl, TBS = *tert*-butyldimethylsilyl.



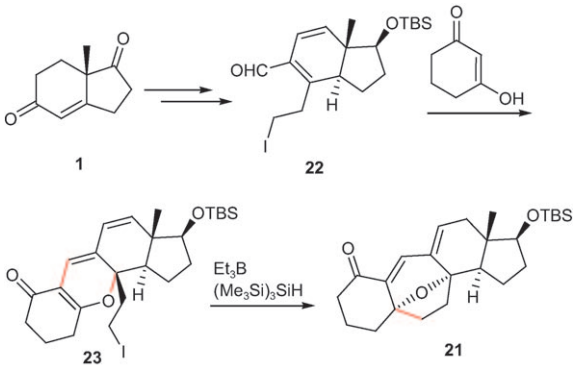
Scheme 3. Semisyntheses of cortistatin A (**4**) according to Baran and co-workers. DBU = diazabicycloundecene, TBCHD = 2,4,4,6-tetrabromo-2,5-cyclohexadienone.[8a]

of cortistatin A by a totally different route (17 steps from **1** to **21**, Scheme 5).[10] Unlike the other approaches, the expanded B ring was in this case constructed in a domino oxa-Michael–aldol reaction[11] (**20**→**21**, Scheme 5). By introduction of the isoquinoline side chain and functionalization of the A ring, the intermediate **21** was finally transformed into cortistatin A (**4**) in 12 additional steps.



Scheme 5. Synthesis of cortistatin A according to Nicolaou, Chen, and co-workers.[10]

The fourth synthesis, by Yamashita et al., is based on a totally different route, namely the bridging of a cyclopenta[*c*]xanthene **23** (Scheme 6).[12a] Here, too, the C/D rings were built up from ketone **1** (10 steps from **1** to **22**). By Knoevenagel condensation of **22** with cyclohexane-1,3-dione the precursor of an electrocyclization is generated, which affords directly the pyran **23**. Unlike the other syntheses the central seven-membered B ring is introduced later by cyclization of the ethyliodido group in **23**. Since **21** corresponds to the intermediate **21** used by Nicolaou, Chen et al. (Scheme 5),[12b] this represents a formal synthesis of cortistatin A.



Scheme 6. Synthesis of the basic cortistatin framework according to Yamashita et al.[12a]

The syntheses discussed herein open up efficient access to the cortistatins, which should facilitate the investigation of structure–activity relationships. Initial studies on this are already in progress.[13] "Steroid chemistry—Quo vadis?" After a few decades of little activity in this field of research this question needs to be asked again. Recent results indicate that there are still a few nuggets buried in this apparently established field.

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