Natural Product Synthesis

Asymmetric Synthesis of the 1-*epi* Aglycon of the Cripowellins A and B**

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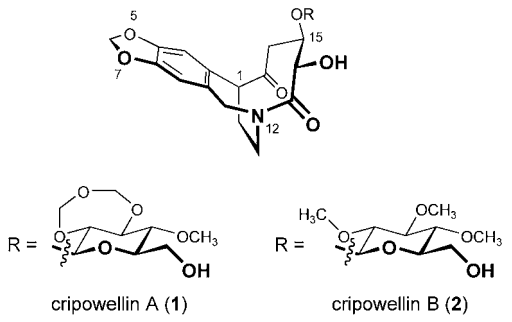
In 1997 researchers at Bayer AG reported on two new *Amaryllidaceae* alkaloids,[1] cripowellins A (**1**) and B (**2**), which had been isolated from the bulbs and roots of *Crinum powellii*, a popular ornamental plant in Europe.[2,3] The two compounds differ only in their glycosidic parts. The assumption that both of these sugar moieties are derived biogenically from β-D-glucose accounts for the depicted absolute stereochemistry. Their common aglycon comprises a [5.3.2]bicyclic core, a structural motif unique among the *Amaryllidaceae* alkaloids. One of both bridgehead atoms is a trisubstituted amide N atom and therefore not a stereogenic center.



In addition to their unusual structure, which contains five-, six-, seven-, nine-, and ten-membered rings, both alkaloids exhibit extraordinary biological properties. Their insecticidal activity compares well to that of natural pyrethroids—not only with regard to their strength but also their broad activity. It is important to note that mainly the aglycon seems to be responsible for their biological activity because it alone shows the same activity as the two glycosides.[2] However, practically nothing is known about the mode of action.[4] In order to clarify that and to determine structure–activity relationships, the synthesis of stereoisomers and derivatives of the cripowellins will be necessary.

Because of their unique structures and their high biological activity, Bayer AG has patented both cripowellins and some of their derivatives.[2] Their exceptional position was also recognized by experts at the Irseer conference on natural products in 1997, where cripowellin A (**1**) was voted the second most interesting new natural product.[5] Despite all this attention, a synthesis of the cripowellins, their aglycon, or one of their stereoisomers has not been described so far. This seems to be highly desirable in the light of the small quantities obtainable from natural sources.[3]

We now report on the first asymmetric synthesis of the skeleton of the cripowellins A and B in the form of their 1-*epi* aglycon **15**. Our remarkably short synthesis started with the asymmetric dihydroxylation[6] of the benzoylated allyl alcohol **3**[7,8] to give the diol **4** (Scheme 1); the 72% yield of this reaction is quite efficient when one considers the obvious problem of regioselectivity. In addition, the asymmetric induction was virtually complete (≥98% *ee*).[9] Acetonide formation and saponification of the ester functionality yielded the primary alcohol **5** in nearly quantitative yield. This alcohol was oxidized to the corresponding acid **6** in two steps, and **6** was subsequently coupled with the amine **10** (available from the reductive amination of bromopiperonal (**9**) with 3-butene-1-amine) to give the amide **7**.

According to our synthetic route a ring-closing metathesis (RCM)[10] of this amide to give the azacyclononene lactam derivative **8** was proposed to follow. The structure of the RCM precursor **7** had to be designed carefully taking into account the "problem of medium sized rings". It had to be restricted conformationally in a way which would favour the metathesis. Both the dioxolane ring[11] and the tertiary amide[12] were assumed to operate synergistically thus favoring the formation of the nine-membered ring.[13] Our assumptions were confirmed by the successful RCM. By employing Grubbs' second-generation catalyst and by performing the reaction under high dilution (1 mM), we were able to obtain **8** in a very good yield of 77%.

After that the [5.3.2]bicyclic core was supposed to be built up by means of a Heck reaction of the piperonyl moiety to the double bond.[14] After extensive studies, we finally succeeded in the selective synthesis of the two Heck products **11** and **12** (Scheme 2). Under neutral reaction conditions, we observed exclusively the formation of product **11**, which has a disubstituted *Z*-configurated double bond. Under cationic conditions, on the other hand, the reaction yielded selectively the trisubstituted olefin **12**.[15] The formation of this anti-Bredt alkene is worth mentioning because the additional ring strain in this bicyclic compound cannot be compensated by stability from the conjugation with the aromatic moiety (both are nearly perpendicular to each other). The double bond of this anti-Bredt alkene is not configurationally stable under the

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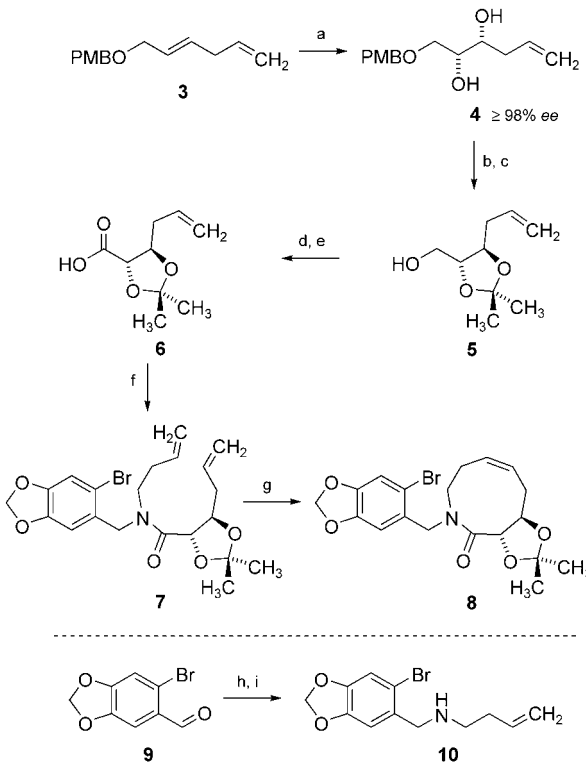
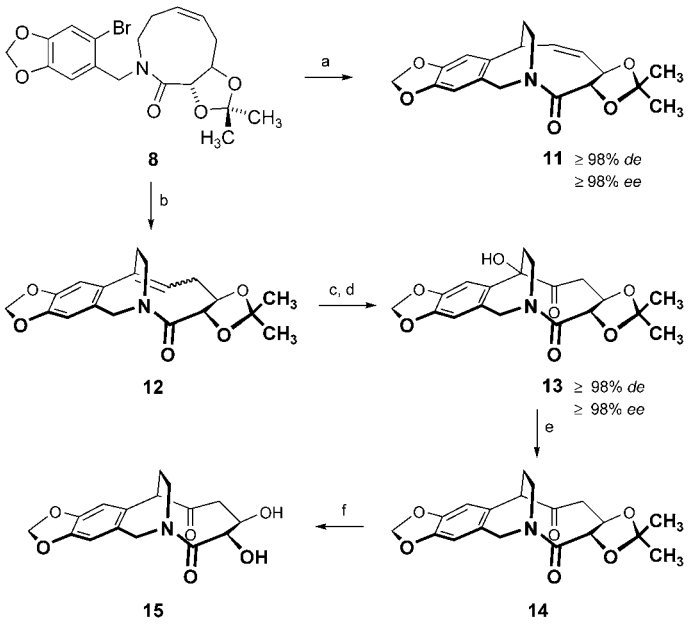


Scheme 1. Synthesis of the nine-membered-ring lactam intermediate **8**. a) AD-mix β, $K_2OsO_4 \cdot 2H_2O$ (0.006 equiv), $MeSO_2NH_2$ (1.0 equiv), *t*BuOH/H_2O (1:1), 0 °C, 2.25 h, 72%; b) 2,2-DMP, PTSA (0.05 equiv), 25 °C, 1 h; c) K_2CO_3 (1.5 equiv), MeOH, 25 °C, 2 h, 97% (two steps); d) CO_2Cl_2 (1.1 equiv), DMSO (2.3 equiv), Et_3N (5.0 equiv), CH_2Cl_2, −78→25 °C; e) $NaClO_2$ (80%, 2.5 equiv), $NaH_2PO_4 \cdot 2H_2O$ (2.0 equiv), 2-methyl-2-butene (18 equiv), acetone/H_2O (1:1), 0→25 °C, 0.5 h; f) FEP (1.2 equiv), amine **10** (1.1 equiv), Et*i*Pr_2N (3.2 equiv), CH_2Cl_2, 0→25 °C, 12 h, 66% (three steps); g) Grubbs' 2nd generation catalyst (0.1 equiv, addition in portions), CH_2Cl_2, reflux, 2.5 h, then DMSO (5.0 equiv), 25 °C, 12 h, 77%; h) 3-butene-1-amine (1.2 equiv), MS 4 Å, CH_2Cl_2, 25 °C, 12 h; i) $NaBH_4$ (1.0 equiv), MeOH, 25 °C, 2 h, 94% (two steps). 2,2-DMP = 2,2-dimethoxypropane, DMSO = dimethyl sulfoxide, FEP = 2-fluoro-1-ethyl pyridinium tetrafluoroborate, MS = molecular sieves, PMB = *p*-methoxybenzoyl, PTSA = *p*-toluenesulfonic acid.



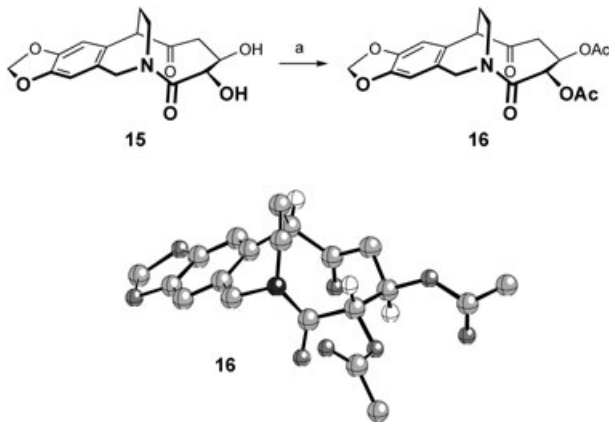
Scheme 2. Completion of the synthesis of the 1-*epi* aglycon **15** of the cripowellins A (**1**) and B (**2**). a) $Pd(OAc)_2$ (0.2 equiv), PPh_3 (0.6 equiv), Et_3N (3.5 equiv), DMF, 110 °C, 6 h, 59%; b) $Pd(OAc)_2$ (0.15 equiv), dppp (0.2 equiv), Ag_2CO_3 (3.0 equiv), toluene, 124 °C, 4 h, 59%; c) $K_2OsO_4 \cdot 2H_2O$ (0.05 equiv), NMO (97%, 3.1 equiv), acetone/H_2O (10:7), 25 °C, 3 h, then Na_2SO_3 (2.3 equiv); d) CO_2Cl_2 (2.5 equiv), DMSO (5.3 equiv), Et_3N (10.0 equiv), CH_2Cl_2, −78→25 °C, 55% (two steps); e) SmI_2 (excess, ca. 7.2 equiv), *t*BuOH (3.0 equiv), THF, 25 °C, 12 h, 99%; f) Dowex-50, H_2O, 25 °C, 4.25 h, 56%. DMF = dimethyl formamide, dppp = 1,3-bis(diphenylphosphanyl)propane, NMO = *N*-methylmorpholine *N*-oxide, THF = tetrahydrofuran.

reaction conditions employed since the *E*/*Z* ratio was observed to be time dependent.[16] To our surprise, both Heck reactions were completely diastereoselective with regard to the orientation of the ethylene bridge; we were able to isolate only compounds **11** and **12**, in which this bridge is on the upper face of the molecule.[17] To the best of our knowledge, this is the first example of a (highly diastereoselective) intramolecular Heck reaction of a highly functionalized (aza)cyclonene derivative.[18]

Olefin **11** proved to be extremely difficult to functionalize. We therefore decided to continue with the *E*/*Z* mixture of olefins **12**, which seemed to be more reasonable to us anyway because a differentiation between the olefinic C atoms was assumed to be easier (singly vs. doubly substituted). Both olefins **12** were first transformed into the α-hydroxy ketone **13** in a two-step sequence consisting of dihydroxylation and Swern oxidation. Deoxygenation of **13** with SmI_2 in the presence of *t*BuOH proceeded smoothly to give **14**.[19] The high yield of 99% in this reaction was astonishing because α-hydroxy ketones are normally not very good substrates for SmI_2-induced defunctionalizations.[20] Likewise, the stability of the acetonide-protected 1,2-diol unit is worth mentioning. In the case of carboxylates, the reductive cleavage of the α-C–O bond is commonly observed.[21] The cleavage of the acetonide protecting group in the presence of Dowex-50 finally yielded the 1-*epi* aglycon **15** of the cripowellins A (**1**) and B (**2**).

At this point we were very much interested in the spatial structure of this compound—especially with regard to the known structure of the bisacetate of cripowellin A and the biological activity of the cripowellins.[2,3] In the search for derivatives of the 1-*epi* aglycon **15** suitable for an X-ray structure analysis, we were finally rewarded by its bisacetate, **16** (Scheme 3).[22] A comparison of its crystal structure with the one obtained from the bisacetate of cripowellin A clearly shows the same spatial orientation of the keto and the lactam carbonyl groups: both are *syn* to each other and in spatial proximity. This substructure had been identified as the probable pharmacophor by researchers at Bayer AG after extensive investigations on structure–activity relationships.[4] Therefore it seems reasonable to expect the 1-*epi* aglycon **15** to be biologically active, too. Yet, this still needs to be proven by biological tests.

In summary, we report the first access to this unique [5.3.2]bicyclic skeleton of the cripowellins A (**1**) and B (**2**). Key steps in our synthesis are a highly enantioselective



Scheme 3. Synthesis and crystal structure of the bisacetylated 1-*epi* aglycon **16**. a) $Sc(OTf)_3$ (0.3 equiv), Ac_2O/CH_3CN (1:1), 25 °C, 2 h, 65 %. Tf = trifluoromethanesulfonyl.[22]

Sharpless dihydroxylation, a properly designed ring-closing metathesis, and a highly diastereoselective intramolecular Heck reaction. Considering the complexity of the target molecule, this synthesis is very short (13 steps in the longest linear sequence, 15 steps altogether; 5.6 % overall yield). In addition, the diastereo- and enantioselectivity are virtually complete ($\geq$ 98 % *de*, $\geq$ 98 % *ee*). The crystal structure of the bisacetate of the 1-*epi* aglycon **16** reveals the same spatial orientation of the ketone and the lactam carbonyl groups as in the cripowellins. Therefore one may be curious whether the 1-*epi* derivatives exhibit the same biological activity as the cripowellins and their aglycon. The 1-*epi* aglycon **15** might at least help to further clarify their hitherto unknown mode of action.[23]

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the crude product the ratio **12**/**11** was determined to be 8.2:1 by means of gas chromatography). However, **11** could be easily separated from **12** by column chromatography on silica gel because of its higher polarity.
[16] After 4 h (complete conversion): $E/Z = 1{:}1.7$; after 24 h: $E/Z = 1{:}1$ (determined by gas chromatography).
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