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

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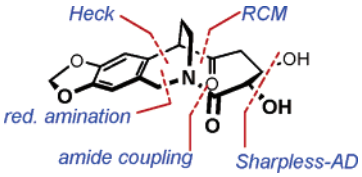

The unusual [5.3.2]-bicyclic structure of the insecticidal Amaryllidaceae alkaloids cripowellin A (**1**) and B (**2**) has been synthesized for the first time via a sequence of Sharpless dihydroxylation, ring-closing metathesis, and intramolecular Heck reaction. The asymmetric synthesis of the 1-*epi*-aglycon **82** proceeds with virtually complete diastereo- and enantioselectivity (de, ee ≥ 98%) in 13 steps and an overall yield of 5.6%. In addition, three alternative approaches toward the aglycon **3** are also described focusing on (1) the alkylation of the 2-benzazepinedithianes **35** and **36** with the electrophile **11**, (2) a radical cyclization of the precursor (*R*/*S*,*S*,*S*)-**39**, and (3) an intramolecular arylation reaction of the aryl ketone **47**.

Introduction

The alkaloids isolated from different species in the Amaryllidaceae plant family certainly represent a unique class among the alkaloids because they have been found to occur only in this family.[1] Conversely, alkaloids of other plant families have not been found in the Amaryllidaceae (with hordenin being the only exception).[2] So far, about 200 alkaloids have been identified, and their often interesting pharmacological properties along with their fascinating molecular structures have rendered them very popular targets for total synthesis.

In 1997, researchers of Bayer AG reported two new Amaryllidaceae alkaloids, cripowellin A (**1**) and B (**2**) (Figure 1), which were isolated from bulbs and roots of *Crinum powellii*, a popular ornamental plant in Europe.[3,4] Their structures were determined by extensive spectroscopic studies, including a combination of MS and 1-D and 2-D NMR techniques. The relative configuration was assigned unambiguously by an X-ray crystallographic analysis of cripowellin A diacetate. Both cripowellins are glycosides whose common aglycon features a [5.3.2]-bicyclic core, an unprecedented structural motif among the Amaryllidaceae alkaloids. Although both sugar entities differ from each other significantly, with an unusual 1,3,5-trioxepane ring in the case of cripowellin A (**1**), it is reasonable to assume that they are derived biogenetically from β-D-glucose, which accounts for the depicted absolute configuration.

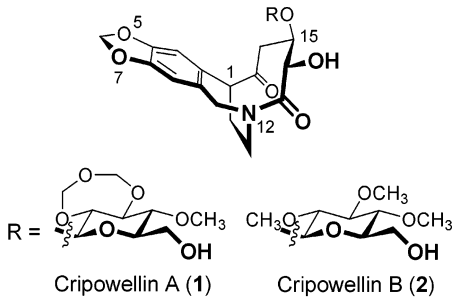

FIGURE 1. Structures of the cripowellins A (**1**) and B (**2**).

In addition to their unusual structure, both alkaloids exhibit extraordinary insecticidal activity comparable to

(1) For representative reviews about the Amaryllidaceae alkaloids, see: (a) Hoshino, O. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1998; Vol. 51, pp 324−424. (b) Martin, S. F. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1987; Vol. 30, pp 251−376. (c) Fuganti, C. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: London, 1975; Vol. 15, pp 83−164.

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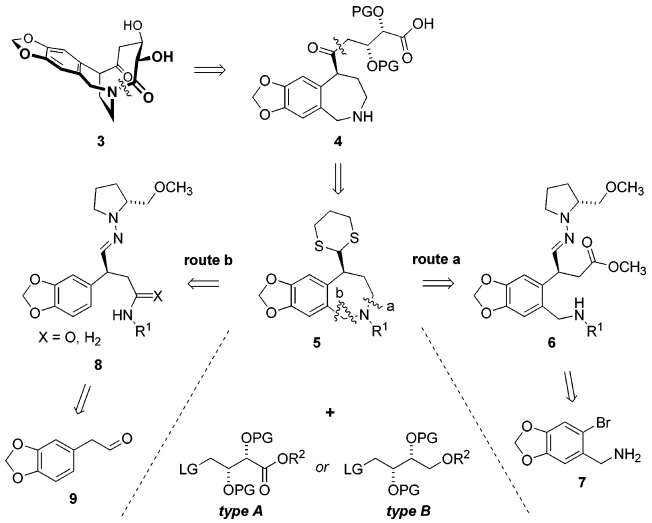
SCHEME 1. Retrosynthesis I with the Alkylation of the 2-Benzazepine Dithiane 5 as the Key Step



that of natural pyrethroids—not only with regard to its potency but also its broad activity. In this respect, it is noteworthy that the aglycon seems to be mainly responsible for their biological activity because it shows the same degree of activity as the two glycosides themselves.[4] However, practically nothing is known about the mode of action.[5] To clarify that aspect and to perform investigations on structure−activity relationships, the synthesis of stereoisomers and derivatives of the cripowellins will be necessary.

Due to their unique structures and their high biological activity, Bayer AG has patented them and some of their derivatives.[3] Their exceptional position was also recognized by experts at the Irseer conference about natural products in 1997 where cripowellin A (**1**) was chosen to be the "second most interesting new natural product".[6]

Despite this attention, a synthetic approach toward the cripowellins or derivatives had not been reported until very recently when we described the asymmetric synthesis of the 1-*epi*-aglycon.[7] Similarly, Moon et al. recently demonstrated an alternative approach leading to the racemic bisdeoxy-aglycon of the cripowellins.[8]

During the course of our work, originally directed toward the synthesis of the "natural" aglycon, a number of conceptually different approaches were investigated, one of which delivered the 1-*epi*-aglycon. In the present paper, we report full details of these efforts.[9]

Results and Discussion

1. Dithiane-Alkylation Approach. Our initial retrosynthetic analysis of the aglycon **3** of the cripowellins A (**1**) and B (**2**) is outlined in Scheme 1.

In the first step, a retro-lactamization of aglycon **3** was considered, giving the partially protected amino acid **4**. We presumed that its synthesis should be possible in a rather straightforward manner by alkylation of the dithiane **5**[10] with either one of the electrophiles of type A or B. For the synthesis of the desired dithiane **5**, two different routes, a and b, were envisaged utilizing a lactamization−reduction sequence and a Pictet−Spengler reaction, respectively. Synthon **8** may be obtained by simple alkylation or aminoethylation[11] of the (*R*)-1-amino-2-methoxymethyl pyrrolidine (RAMP) hydrazone[12] of homopiperonal (**9**). The benzylic stereocenter of **6** could be developed using the RAMP hydrazone methodology. However, its synthesis starting from 6-bromopiperonylic amine **7** was expected to be more laborious.

1.1. Synthesis of Electrophilic A- and B-Type Components. The synthesis of electrophiles of type A and B is summarized in Scheme 2. The iodides **11** and **13** were prepared from their corresponding alcohols **10**[13] and **12**[14] by simple iodination reactions (PPh_3, imidazole, I_2). The synthesis of **17** began from D-tartaric acid (**14**), which furnished the cyclic anhydride **15** after treatment with pivaloyl chloride. A two-step sequence of reduction and acid-catalyzed lactonization converted **15** to the γ-lactone **16**, which was reacted with TMSBr in methanol to afford the bromide **17**.

Monobenzylation of the diol **18**[15] gave the alcohol **19**, which was further transformed into the iodide **20** using conditions similar to those described for **10** and **12** (vide supra).

1.2. Synthesis of 2-Benzazepine Dithianes: Route a. Investigations describing route a are summarized in Scheme 3. With respect to the nitrogen-protecting groups, two different pathways are shown, both commencing with 6-bromopiperonylic amine **7**.[16]

Two different protecting groups for the nitrogen atom, a *p*-methoxybenzyl and a benzyl group, were introduced successively to give **21**. After bromine−lithium exchange, the lithium species was trapped with DMF to obtain the aromatic aldehyde **22**. A sequence consisting of a Wittig reaction with $Ph_3PCHOCH_3$ and hydrolysis of the intermediate enol ether furnished the corresponding homologated aldehyde, which was reacted with RAMP to give the hydrazone **23**. Disappointingly, the alkylation of **23** with methyl 2-bromoacetate under standard conditions proceeded only in moderate yield and with an unsatisfactory degree of diastereoselectivity.

(5) Researchers at Bayer AG have found out that cripowellin A and B are neither acetylcholin esterase inhibitors nor PP1 inhibitors.
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(7) Enders, D.; Lenzen, A.; Raabe, G. *Angew. Chem.* **2005**, *117*, 3832−3835; *Angew. Chem., Int. Ed.* **2005**, *44*, 3766−3769.
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(10) A conceptually different route to the racemic dithianes **5** with R^1 = Cbz, H has already been described: Sánchez, I. H.; Soria, J. J.; López, F. J.; Larraza, M. I.; Flores, H. J. *J. Org. Chem.* **1984**, *49*, 157−163.
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(15) Haag, D.; Scharf, H.-D. *J. Org. Chem.* **1996**, *61*, 6127−6135.
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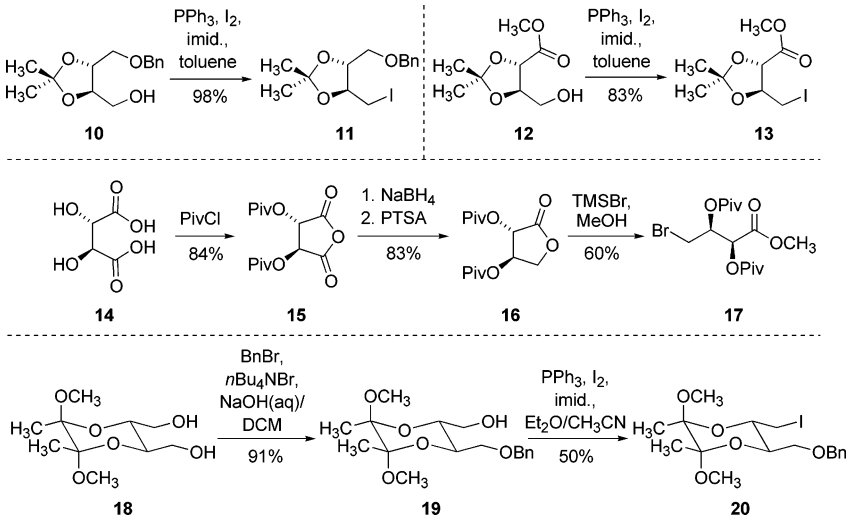
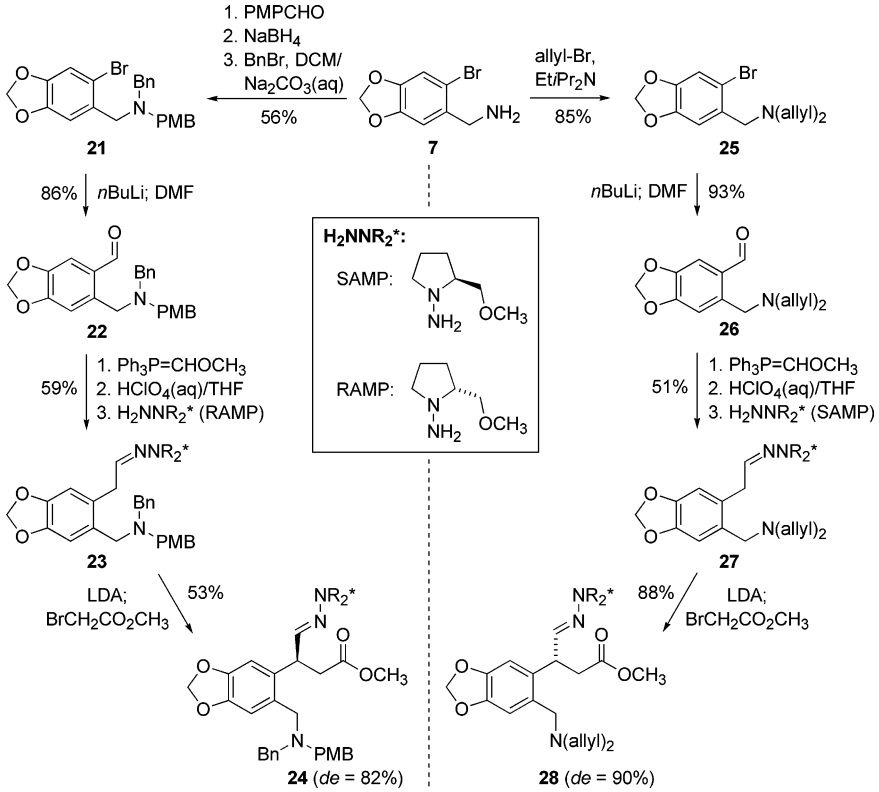
SCHEME 2. Synthesis of A- and B-Type Electrophiles



SCHEME 3. Investigations of Route a of the Retrosynthetic Plan I



We theorized that the combination of two benzyl protecting groups was probably too bulky, diminishing the energy difference between the two possible diastereomeric transition states leading to a lower asymmetric induction in the alkylation. This argument was supported by the alkylation results from the homopiperonal-RAMP-hydrazone **30** bearing no ortho substituent (cf. Scheme 4) and from the corresponding (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP)-hydrazone **27** bearing two allyl protecting groups on the nitrogen atom (it is needless to say that we would have replaced SAMP by RAMP as the chiral auxiliary if we had persued with this approach since only the latter induces the right asymmetric induction at the benzylic stereocenter). The synthesis of **27** was carried out according to the preparation of **23**—except the benzylic protecting groups were both replaced by two allyl groups (cf. **7** → **25**). Alkylation of this hydrazone under identical conditions furnished **28**, which now gave superior results in terms of both yield (88 vs 53%) and stereoselectivity (de = 90 vs 82%).

Unfortunately, the removal of the allyl protecting groups proved problematic. Although various standard reaction conditions for their deprotection had been tested ($Rh(PPh_3)_3Cl$, CH_3CN/H_2O (9:1);[17] $Pd(PPh_3)_4$, DCM, toluenesulfinic acid;[18] $Pd(dba)_2$/dppb (1:1), THF, 2-mercap-

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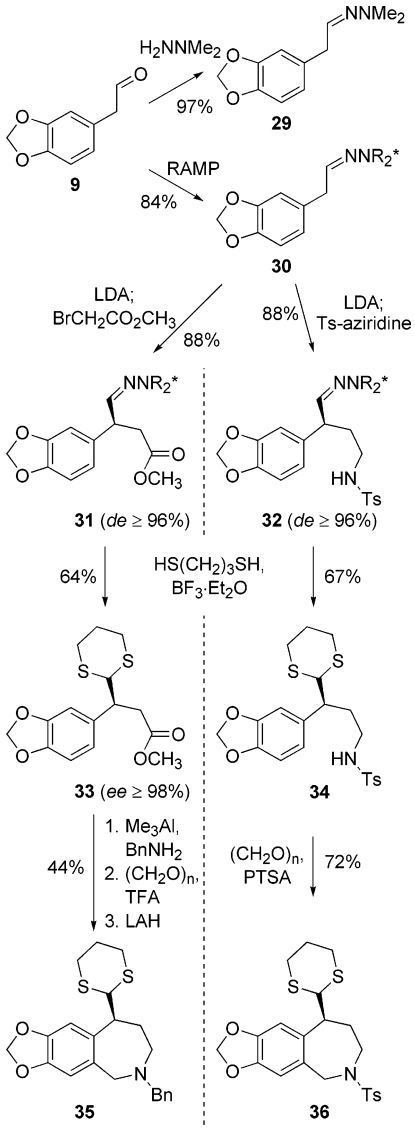
SCHEME 4. Investigations on Route b of Retrosynthesis I

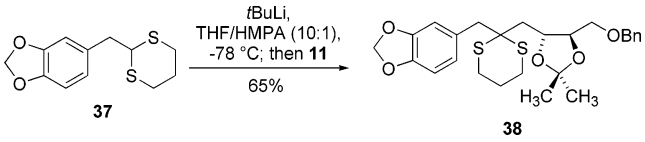


tobenzoic acid[19]), these blocking groups were not removed in the case of **28**.

1.3. Synthesis of 2-Benzazepine Dithianes: Route b. The desired 2-benzazepinedithianes were synthesized in a highly stereoselective fashion by utilizing the Pictet−Spengler reaction as the key step. Scheme 4 outlines the approaches to the 2-benzazepines with a tosyl or a benzyl *N*-protecting group by employing tosylaziridine and methyl 2-bromoacetate, respectively, as the electrophiles.

The condensation of homopiperonal (**9**)[20] with RAMP yielded the hydrazone **30**, whose alkylation with the aforementioned electrophiles gave the hydrazones **31** and **32**, which were obtained with high diastereoselectivity (by ^{13}C NMR spectroscopy). Both of these hydrazones were transformed to the dithianes **33** and **34** according to Lassaletta's procedure.[21] In the case of **33**, the enantiomeric excess was determined to be ≥98% by HPLC analysis on a chiral stationary phase (the racemate of **33** was prepared accordingly, starting from the dimethylhydrazone **29** of homopiperonal). This evidence implied the absence of racemisation in the transformation of hydrazone to dithiane. Although we were not able to prove this for the dithiane **34**, it seems reasonable to make the same assumption.

SCHEME 5. Dithiane 37 Was Used To Optimize the Reaction Conditions for Coupling with 11



Dithiane **34** smoothly underwent the Pictet−Spengler cyclization[22] to the 2-benzazepine **36**. In this respect, it is important to note that the hydrazone **32** could not be cyclized successfully under various conditions, including formaldehyde, NaOH(aq);[11] $(CH_2O)_3$ or $(CH_2O)_n$, CH_3SO_3H;[23] $BF_3{\cdot}OEt_2$, $CH_2(OCH_3)_2$;[24] and $(CH_2O)_n$, TFA.[25] In the case of **33**, the corresponding benzyl amide was initially formed according to the Weinreb protocol.[26] Cyclization was then readily conducted as well.[24] The reduction of the resulting lactam with lithium aluminum hydride yielded the benzyl-protected 2-benzazepine **35**.

1.4. Coupling Reactions. With the 2-benzazepine-dithianes **35** and **36** and various electrophiles **11**, **13**, **17**, and **20** in hand, model studies with the dithiane **37** were conducted in order to optimize reaction conditions for the coupling process (Scheme 5).[27]

We found out, that only the electrophile **11** could be reacted successfully with a metalated species of **37**. After screening of different reaction conditions and further optimization we were finally able to isolate the coupling product **38** in a moderate yield of 65%.

However, similar alkylations of dithianes **35** and **36** with the electrophile **11** under these conditions were not feasible. The screening of other electrophiles showed that only very small electrophiles were amenable to this reaction with CH_3I and D_2O resulting in yields of 30% and 56%, respectively.

2. Intramolecular Radical Cyclization Approach. The preceding section has shown that a polar, umpolung disconnection adjacent to the dithiane **5** using the A-/B-type electrophiles (cf. Scheme 1) did not prove successful. A radical disconnection adjacent to the carbonyl group was also envisaged (Scheme 6). The key step in this approach was the intramolecular radical cyclization from (*S*,*S*,*S*)-**39** to explore addition of the primary carbon radical to the nitrile group.[28] Breaking of the amide bond

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(23) Orazi, O. O.; Corral, R. A.; Giaccio, H. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1977−1982.
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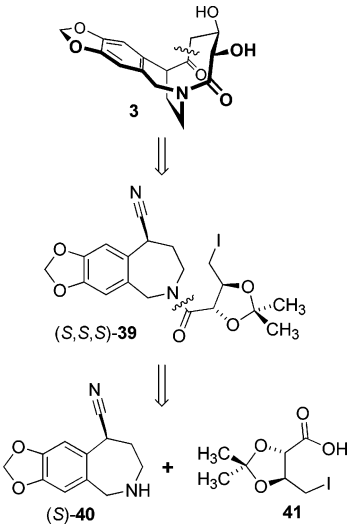
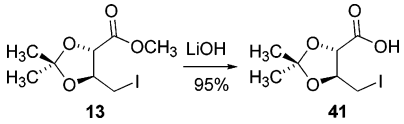
(26) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, *18*, 4171−4173.
(27) For work on 1,3-dithianes, see: (a) Seebach, D. *Synthesis* **1969**, 17−36. (b) Smith, A. B., III; Adams, C. M. *Acc. Chem. Res.* **2004**, *37*, 365−377.
(28) For similar work, see: (a) Ziegler, F. E.; Harran, P. G. *Synlett* **1995**, 493−494. (b) Ziegler, F. E.; Harran, P. G. *J. Org. Chem.* **1993**, *58*, 2768−2773.

SCHEME 6. Retrosynthesis Plan II Featuring an Intramolecular Radical Cyclization



SCHEME 7. Synthesis of the Acid 41



in (*S*,*S*,*S*)-**39** leads to the secondary amine (*S*)-**40** and the acid **41**.

As shown in Scheme 7, saponification of the ester **13** using LiOH gave the desired acid **41** in high yield.

The synthesis of the cyclization precursor is depicted in Scheme 8. Starting from the hydrazone **32** (cf. Scheme 4), magnesium monoperoxyphthalate (MMPP) mediated nitrile formation furnished **42**, which readily underwent a Pictet−Spengler cyclization in quantitative yield to **43**. Although the toluenesulfonyl protecting group was easily removed at this stage using sodium naphthalide, the benzylic nitrile underwent epimerization. Hence, only racemic (*R*/*S*)-**40** could be isolated. Despite this fact, we decided to continue with the synthesis, hoping for a possibility to separate diastereomers after a successful cyclization. Among the different conditions tested for amide bond formation with the acid **41** (2-chloro-1-methylpyridinium iodide, *n*-Bu_3N, DCM (48% yield);[29] $Ph_2P(=O)OC_6F_5$, Et-*i*-Pr_2N, DMF (85% yield)[30]), a combination of HOBT/EDC[31] worked best to give (*R*/*S*,*S*,*S*)-**39** in 89% yield.

The radical cyclization of (*R*/*S*,*S*,*S*)-**39** using Bu_3SnH/AIBN in different solvents did not furnish the desired acetonide aglycon **44**, but instead the unreacted starting material was recovered (when using refluxing benzene or toluene) or product **45** (when using refluxing xylene) resulting from a radical dehalogenation was obtained. Iodine−metal exchange using using *t*-BuLi, *n*-BuLi, and *i*-PrMgCl with (*R*/*S*,*S*,*S*)-**39** was attempted hoping for intramolecular nucleophilic addition to the nitrile group. As one might have anticipated, the presence of the β-oxygen substituent gave rise to olefinic products of β-elimination.

The strategies discussed so far had one thing in common: the characteristic bicycle was planned to be constructed starting from a 2-benzazepine, i.e., a 7-membered ring. Alternatively, because a [5.3.2]-bicycle represents a combination of a 7-, a 9- and a 10-membered ring, one could also think about closing the 10- or the 9-membered ring first. These two concepts have also been followed and will be treated in the following two sections.

3. Intramolecular Ketone-Arylation Approach. If one wants to start with the largest ring, i.e., the 10-membered ring, the ethylene bridge has to be broken first retrosynthetically, which is done most easily by a retro-intramolecular alkylation reaction (Scheme 9). This leads to the ketone **46**, whose synthesis was envisaged to be realized by means of an intramolecular Buchwald−Hartwig arylation (**47** → **46**).[32] Origins of compound **47** can be easily traced to the secondary amine **48** and the acid **49**, and the latter can be obtained by reaction of **50** or **11** with **51**[33] or **52**.

Extensive investigations were carried out for the synthesis of **49** (Scheme 10). Starting with the electrophiles **50** and **11**, utilization of lithiated 1,3-dithiane (**52**) as the synthetic equivalent of a formyl anion delivered **53** and **54**, respectively. The moderate yields obtained in these reactions parallel the observations using the dithianes **35** and **36** (vide supra). The methylation of **53** and **54**, on the other hand, proceeded more smoothly to give **55** and **56**, respectively. After cleavage of the dithiane moiety, the ketones **57** and **58** were obtained in similar yields.

This reaction sequence was significantly shortened by using the lithiated aminonitrile **51** as an equivalent of an acyl anion. Reaction of **50** and **11** with **51** followed by $AgNO_3$-mediated cleavage of the aminonitrile furnished **57** and **58** in only two steps and with improved yields.

So far, both protecting groups did not behave much differently, giving similar yields in each pair of reactions. However, deprotection to the corresponding alcohol **59** proved to be much more efficient with the benzyl derivative **58** (97% vs 27% yield in the case of the TBS protected compound **57**). The basicity of TBAF might be responsible for the low yield observed in the reaction with **57**: formation of the internal enol followed by elimination of the β-oxygen are a possible side reaction. The synthesis of the desired acid **49** was then completed by oxidation with $RuCl_3/NaIO_4$.

The completion of the synthesis of the precursor for the Buchwald−Hartwig arylation is shown in Scheme 11. Reductive amination of bromopiperonal (**60**)[34] with 2-benzyloxyethanamine[35] gave the secondary amine **48**. Amide formation with the carboxylic acid **49** worked best using 2-fluoro-1-ethylpyridinium tetrafluoroborate (FEP)[36] as

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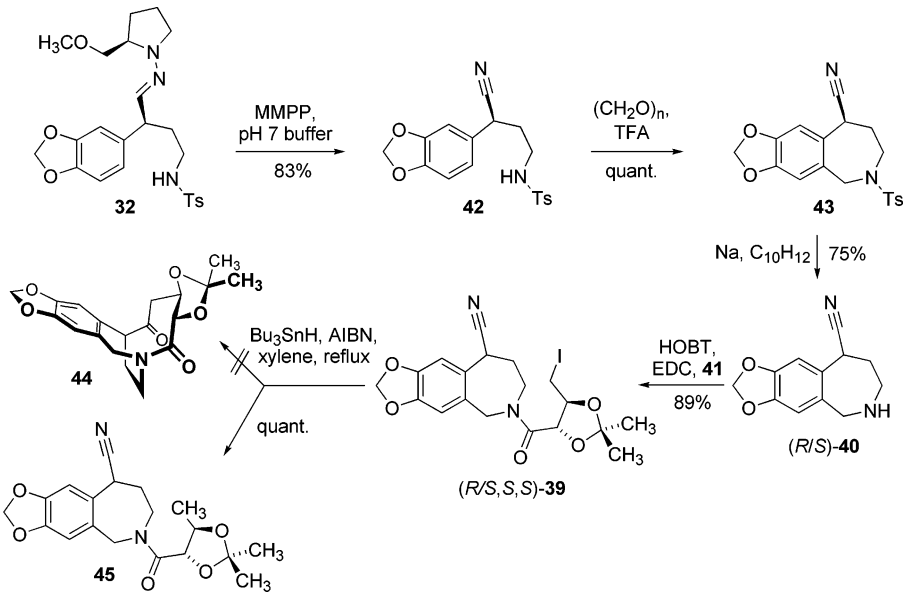
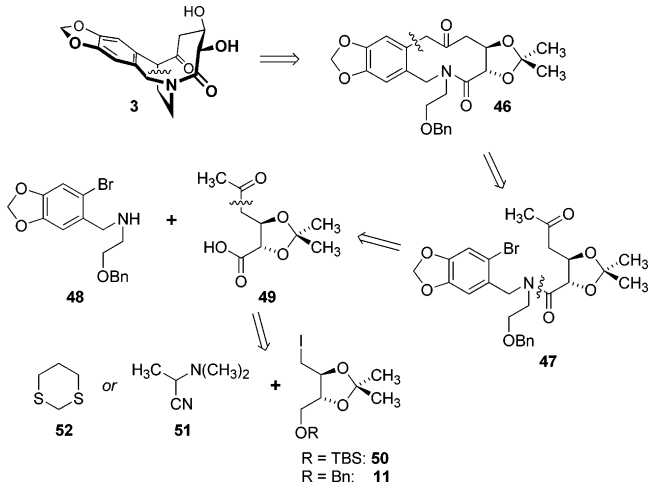
SCHEME 8. Radical Cyclization Approach



SCHEME 9. Retrosynthesis III Based on an Intramolecular Ketone Arylation Reaction



the coupling reagent to give the desired precursor **47** in 84% yield.

Unfortunately, bringing about the desired cyclization to **46** using Buchwald's conditions turned out to be an extremely difficult task.[37] With xantphos as the ligand and Pd_2dba_3 as the Pd^0 source, no conversion of starting material or decomposition were observed under the reaction conditions screened (THF or toluene as solvent, *t*-BuONa or K_3PO_4 as base, ϑ = rt − 80 °C).

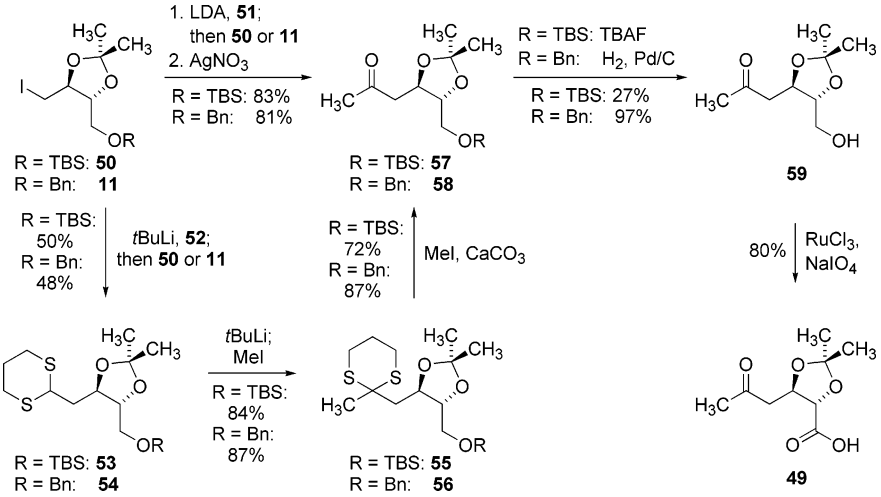
The Buchwald−Hartwig arylation was not the only possibility that could be envisaged for the cyclization of **47** to **46**. The successful synthesis of the corresponding terminal TMS enol ether **61** suggested the possibility for cyclization following the protocol developed by Kuwajima and Urabe,[38] i.e., employing aryl bromides in an arylation of TMS enol ethers using Bu_3SnF and $PdCl_2(P(o\text{-tol})_3)_2$. A Heck arylation of the corresponding TBS enol ether **62** was also investigated under typical conditions ($Pd(OAc)_2$, PPh_3, Et_3N, DMF, 80 °C; Pd_2dba_3, Ag_2CO_3, dppe, toluene, 100 °C). It should be noted that Heck reactions employing alkyl enol ethers have been carried out successfully,[39] although versions using the analogous silyl enol ethers have not been described. Unfortunately, both of these reactions failed to yield **46** (Scheme 12).

The main problem seemed to be the cyclization of the 10-membered cycle and not, e.g., the insertion of Pd^0 into the aryl bromine bond. The occurrence of the latter could be proven by successfully carrying out an intermolecular version of the Kuwajima−Urabe reaction (Scheme 13): the Boc-protected amine **63** and the TMS enol ether **64**, obtained by treatment of **57** with TMSOTf and Et_3N, readily underwent the coupling to give **65** in an unoptimized yield of 52%.

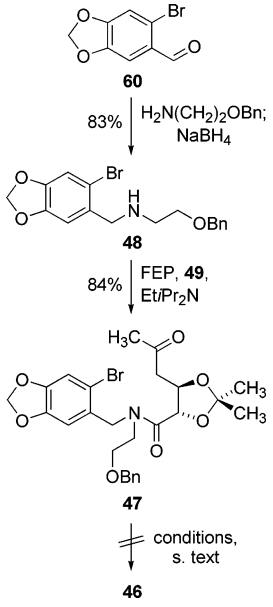
4. Synthesis of the 1-*epi*-Aglycon via a Sharpless AD-RCM-Heck Sequence. From a topological point of view, the last possibility that remained was to focus on the formation of the 9-membered ring. Taking this into account, our new retrosynthesis is depicted in Scheme 14. After the functional group interconversion ketone → *Z*-double bond and protection of the free vicinal hydroxy groups as their acetonide, the bicycle **66** was considered. Retrosynthetically, the Heck reaction,[40] starting from **68**, was assumed to proceed via intermediate **67** which should furnish **66** upon elimination of L_2PdHX. Considering Bredt's rule, an elimination toward the aromatic moiety was judged as rather improbable at the beginning of this project (vide infra). Such an intramolecular Heck

(36) Li, P.; Xu, J. C. *J. Peptide Res.* **2001**, *58*, 129−139.
(37) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360−1370.
(38) Kuwajima, I.; Urabe, H. *J. Am. Chem. Soc.* **1982**, *104*, 6831−6833.
(39) See for example: Andersson, C.-M.; Hallberg, A.; Daves, G. D., Jr. *J. Org. Chem.* **1987**, *52*, 3529−3536.
(40) Representative reviews about the Heck reaction: (a) Bräse, S.; de Meijere, A. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004; pp 217−315. (b) Link, J. T.; Overman, L. E. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; pp 231−269. (c) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945−2963. (d) Link, J. T. *Organic Reactions* **2002**, *60*, 157−534. (e) de Meijere, A.; Meyer, F. E. *Angew. Chem.* **1994**, *106*, 2473−2506; *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379−2411.

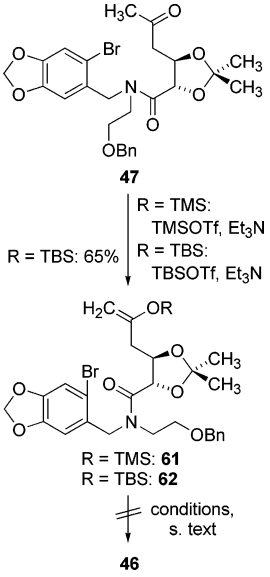
SCHEME 10. Studies Leading to the Keto Acid 49



SCHEME 11. Intramolecular Ketone−Arylation Approach



SCHEME 12. Cyclization Attempts via a Heck or a Kuwajima Reaction



reaction involving a 9-membered ring had not been reported at the time of this project.

Medium-sized rings, as described for the conversion of **68** to **69**, are sometimes very difficult to access by ring-closing metathesis.[41] We tried to advance our strategy by choosing the acetonide as protecting group because it represents a conformational constraint that should favor the RCM process.[42,43] Similarly, the tertiary amide functionality should have the same effect.[44]

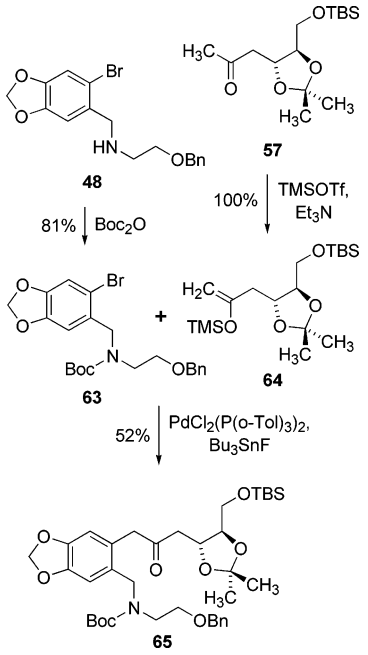
The synthesis of the acid **71** was straightforward and is summarized in Scheme 15. It commenced with the esterification of the known alcohol **72**[45] to give **73**,[46] which was subjected to a slightly modified Sharpless AD.[47] This reaction furnished the diol **74** in good yield (72%) with

(41) Representative reviews about the RCM: (a) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199−2238. (b) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem.* **2003**, *115*, 4740−4782; *Angew. Chem., Int. Ed.* **2003**, *42*, 4592−4633. (c) Fürstner, A. *Angew. Chem.* **2000**, *112*, 3140−3172; *Angew. Chem., Int. Ed.* **2000**, *39*, 3012−3043. (d) Maier, M. E. *Angew. Chem.* **2000**, *112*, 2153-2157; *Angew. Chem., Int. Ed.* **2000**, *39*, 2073−2077. (e) Blechert, S. *Pure Appl. Chem.* **1999**, *71*, 1393−1399. (f) Fürstner, A. *Top. Organomet. Chem*. **1998**, *1*, 37−72. (g) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450. (h) Schuster, M.; Blechert, S. *Angew. Chem.* **1997**, *109*, 2124−2145; *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036−2055. (i) Schmalz, H.-G. *Angew. Chem.* **1995**, *107*, 1981−1984; *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1833−1836. (j) Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693−3712.

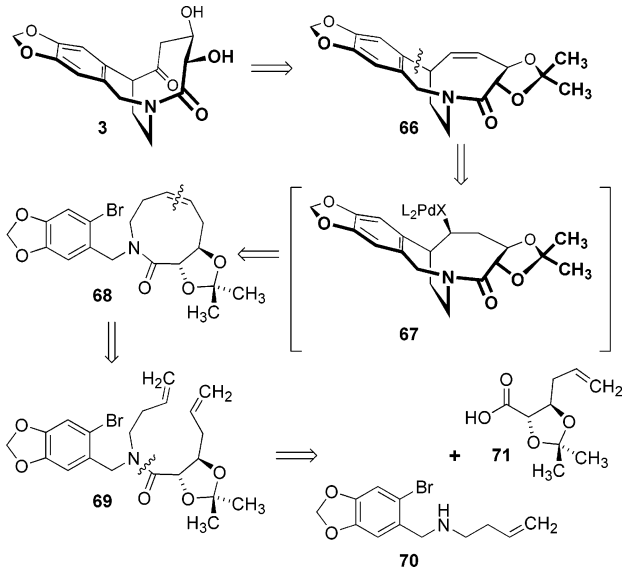
(42) For the metathetic synthesis of 9-membered rings using similar conformational constraints to the dioxolane ring, see: (a) Harris, P. W. R.; Brimble, M. A.; Gluckman, P. D. *Org. Lett.* **2003**, *5*, 1847−1850. (b) Clark, J. S.; Marlin, F.; Nay, B.; Wilson, C. *Org. Lett.* **2003**, *5*, 89−92. (c) Kaliappan, K. P.; Kumar, N. *Tetrahedron Lett.* **2003**, *44*, 379−381. (d) Hirama, M.; Oishi, T.; Uehara, H.; Inoue, M.; Maruyama, M.; Oguri, H.; Satake, M. *Science* **2001**, *294*, 1904−1907. (e) Clark, J. S.; Hamelin, O. *Angew. Chem.* **2000**, *112*, 380−382; *Angew. Chem., Int. Ed.* **2000**, *39*, 372−374. (f) Bamford, S. J.; Goubitz, K.; van Lingen, H. L.; Luker, T.; Schenk, H.; Hiemstra, H. *J. Chem. Soc., Perkin Trans. 1* **2000**, 345−351. (g) Oishi, T.; Nagumo, Y.; Hirama, M. *Chem. Commun.* **1998**, 1041−1042. (h) Delgado, M.; Martín, J. D. *Tetrahedron* Lett. **1997**, *38*, 6299−6300.

(43) There are only very few examples for the metathetic synthesis of 9-membered rings without conformational constraints. They are limited almost exclusively to those 9-membered cyclic ethers for whose synthesis the gauche effect can be exploited: (a) Crimmins, M. T.; Powell, M. T. *J. Am. Chem. Soc.* **2003**, *125*, 7592−7595. (b) Crimmins, M. T.; Emmitte, K. A.; Choy, A. L. *Tetrahedron* **2002**, *58*, 1817−1834. (c) Baba, Y.; Saha, G.; Nakao, S.; Iwata, C.; Tanaka, T.; Ibuka, T.; Ohishi, H.; Takemoto, Y. *J. Org. Chem.* **2001**, *66*, 81−88. (d) Crimmins, M. T.; Choy, A. L. *J. Org. Chem.* **1997**, *62*, 7548−7549.

SCHEME 13. Intermolecular Coupling of 63 and 64 According to Kuwajima and Urabe



SCHEME 14. Retrosynthesis IV with a RCM and an Intramolecular Heck Reaction as Key Steps



regard to the existing problem of regioselectivity, and asymmetric induction was virtually complete (ee ≥ 98%). Acetonide formation and saponification of the ester functionality afforded the primary alcohol **75** in nearly quantitative yield.

This alcohol was oxidized to the corresponding acid **71** over two steps, which was then used in the amide coupling reaction without further purification. The other coupling partner, amine **70**, was synthesized by reductive amination of bromopiperonal (**60**) with 3-buten-1-amine (Scheme 16).

The amide **69** was obtained upon coupling with FEP in a high yield of 66% over three steps. The RCM reaction was first carried out with Grubbs's first-generation catalyst, yielding a mixture of the desired lactam **68** and oligomers. In this reaction, Grubbs's second-generation catalyst led to a significant improvement as no oligomers were detected by TLC analysis, and the lactam **68** was isolated in 77% yield.

4.1. Heck Reactions. With the precursor for the intramolecular Heck reaction in hand, we explored conditions which had been described mainly by Overman et al. in the general synthesis of bicyclic structures.[48] Under these conditions, only starting material could be isolated. As the insertion of Pd^0 into the aryl−bromine bond was to be expected under these conditions (cf. to Scheme 13), the reason for the failure may have been a high activation energy necessary for the Heck reaction. In fact, by changing the reaction solvent to DMF to allow higher reaction temperatures, the formation of the bicyclic compound **76** was observed (Scheme 17).

Surprisingly, the bicyclic compound that is epimeric at C1 in comparison to the natural products (see the observed NOE) was exclusively obtained. Other phosphine ligands were also tested under these reaction conditions (dppe, dppp, P(*o*-tol)$_3$, P(2-furyl)$_3$, $PMePh_2$), but all of them gave the same stereochemical outcome.

The following investigations revealed that it was very hard to selectively functionalize the bicyclic compound **76**. Neither hydroborations (BH_3·THF, THF; 9-BBN, THF, reflux;[49] CB, *N*,*N*-dimethylacetamide, DCM;[50] CB, SmI_3, THF[51]), oxymercurations ($Hg(OAc)_2$, THF/H_2O;[52] $Hg(OAc)_2$, THF/H_2O,)));[53] $Hg(OAc)_2$, THF/H_2O, PTSA), bromohydrin formation (NBS, DMSO/H_2O),[54] oxidation with molecular oxygen ($Co(tfa)_2$, O_2, *i*-PrOH, MS 4 Å, reflux),[55] Wacker oxidations ($PdCl_2$, CuCl, O_2, DMF/H_2O, 60−70 °C;[56] $PdCl_2$, EtOH, reflux[57]), oxidation with chromyl chloride (CrO_2Cl_2, acetone, −78 °C → rt),[58] nor oxidations using Ag^I salts (Ag_2CrO_4, I_2, pyr, DCM, 0 °C → rt;[59] $AgNO_2$, I_2, Et_2O[60]) proved successful in any way.

(44) For secondary and tertiary amides in ring closing metatheses, see: (a) Brouwer, A. J.; Liskamp, R. M. J. *J. Org. Chem.* **2004**, *69*, 3662−3668. (b) Banfi, L.; Basso, A.; Guanti, G.; Riva, R. *Tetrahedron Lett.* **2003**, *44*, 7655−7658.

(45) Rao, J. A.; Cava, M. P. *J. Org. Chem.* **1989**, *54*, 2751−2753.

(46) The asymmetric dihydroxylation of allylic alcohols normally proceeds with only moderate enantioselectivity—in contrast to their corresponding *p*-methoxybenzoic acid esters: Corey, E. J.; Guzman-Perez, A.; Noe, M. C. *J. Am. Chem. Soc.* **1995**, *117*, 10805−10816.

(47) Review: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483−2547.

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(50) Garrett, C. E.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 3224−3225.

(51) Evans, D. A.; Muci, A. R.; Stürmer, R. *J. Org. Chem.* **1993**, *58*, 5307−5309.

(52) Brown, H. C.; Geoghegan, P. J., Jr. *J. Org. Chem.* **1970**, *35*, 1844−1850.

(53) Einhorn, J.; Einhorn, C.; Luche, J. L. *J. Org. Chem.* **1989**, *54*, 4479−4481.

(54) Guss, C. O.; Rosenthal, R. *J. Am. Chem. Soc.* **1955**, *77*, 2549−2549.

(55) Kato, K.; Yamada, T.; Takai, T.; Inoki, S.; Isayama, S. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 179−186.

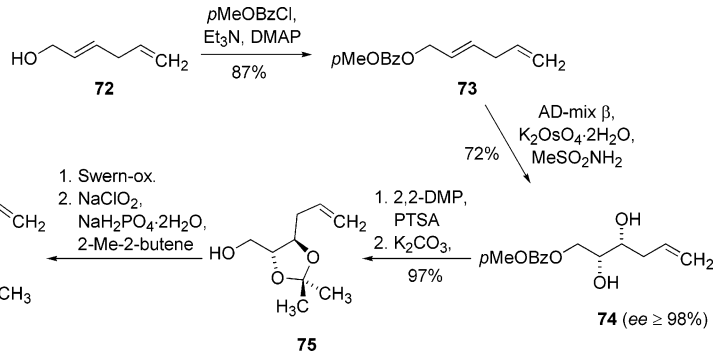
(56) (a) Tsuji, J.; Nagashima, H.; Hori, K. *Tetrahedron Lett.* **1982**, *23*, 2679−2682. (b) Kang, S.-K.; Jung, K.-Y.; Chung, J.-U.; Namkoong, E.-Y.; Kim, T.-H. *J. Org. Chem.* **1995**, *60*, 4678−4679.

(57) Lloyd, W. G.; Luberoff, B. J. *J. Org. Chem.* **1969**, *34*, 3949−3952.

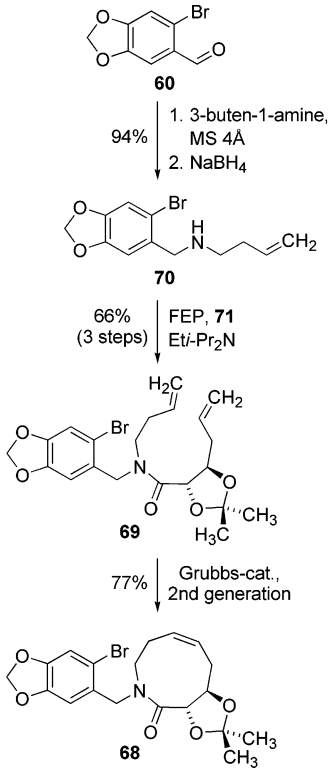
(58) (a) Freeman, F.; Cameron, P. J.; DuBois, R. H. *J. Org. Chem.* **1968**, *33*, 3970−3972. (b) Sharpless, K. B.; Teranishi, A. Y. *J. Org. Chem.* **1973**, *38*, 8, 185−186.

(59) Hassner, A.; Kropp, J. E.; Kent, G. J. *J. Org. Chem.* **1969**, *34*, 2628−2632.

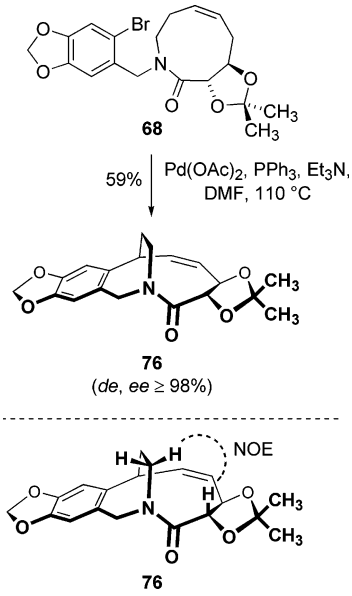
SCHEME 15. Synthesis of the Acid 71



SCHEME 16. Synthesis of the 9-Membered Ring Lactam 68



SCHEME 17. Successful Heck Reaction under Neutral Conditions



Epoxidation of the olefin **76** was feasible. Nevertheless, the reaction had to be carefully optimized. Dimethyldioxirane (DMDO) gave the best results because it permitted the use of an excess of the reagent at lower temperature (Scheme 18), avoiding decomposition which predominated at higher temperatures. The epoxide **77** could be obtained in a moderate yield of 55% after 9 days. The low yield along with the long reaction time did not make this approach very attractive.

Fortunately, screening other reaction conditions for the Heck reaction was continued. Under conditions that are generally regarded as cationic, the outcome of the Heck reaction was completely changed (Scheme 19).

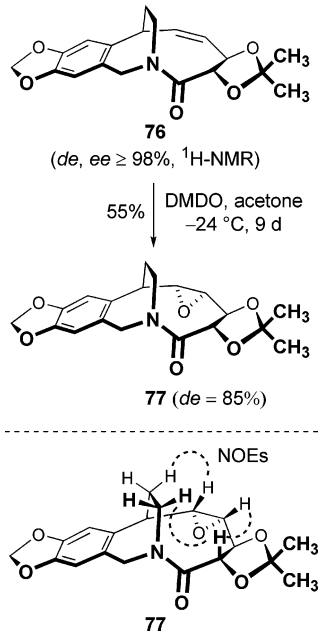
The trisubstituted olefin **78** was isolated in 59% yield as a mixture of *E*- and *Z*-isomers. Along with **78**, minor amounts of **76** were also formed (**78**/**76** = 8.2:1, according to GC), which could be separated easily due to the higher polarity of **76**. The formation of this bridgehead alkene **78**, which can also be considered to be an anti-Bredt alkene, was really astonishing because the additional ring strain in this bicyclic compound could not be compensated by stability from the conjugation with the aromatic moiety. The double bond of this bridgehead alkene was not configurationally stable under the reaction conditions employed since the *E*/*Z*-ratio was observed to be time dependent (after 4 h (complete conversion): *E*/*Z* = 1:1.7, after 24 h *E*/*Z* = 1:1, according to GC). Both isomers could be separated by preparative HPLC, and the major isomer was shown to possess the *Z*-configuration (see the observed NOEs). Once again, the Heck reaction was completely diastereoselective, and only the isomer with the opposite orientation of the ethylene bridge, when compared to the natural products, was formed. To the best of our knowledge, this represents the first successful example of a (highly diastereoselective) intramolecular Heck reaction at a highly functionalized (aza)cyclononene derivative.

With **78** in hand, the synthesis of the 1-*epi*-aglycon was within reach because a regiochemical differentiation between olefinic carbons was assumed to be easier than in the case of **76**.

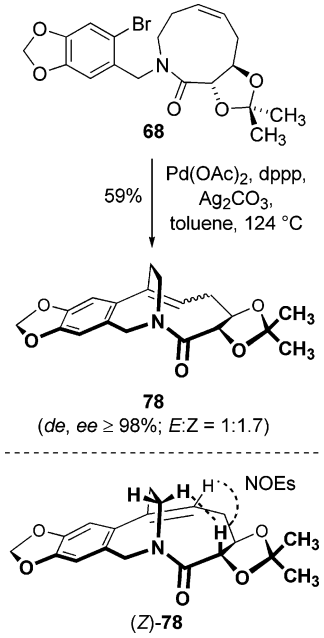
Our first attempt toward this goal is illustrated in Scheme 20. After hydroboration with an excess of borane (5 equiv) and quenching with water, the mixture of

(60) Cardillo, G.; Shimizu, M. *J. Org. Chem.* **1977**, *42*, 4268−4270.

SCHEME 18. Synthesis of the Epoxide 77



SCHEME 19. Successful Heck Reaction under Cationic Conditions

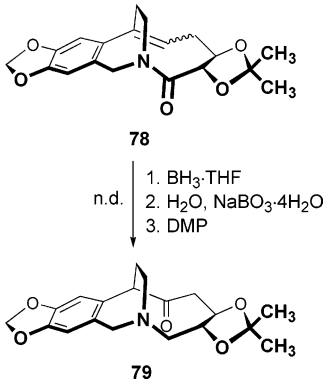


isomeric boronic acids was first oxidized to the corresponding secondary alcohols and then further to the ketone with the Dess−Martin periodinane (DMP).

The spectroscopic data of the isolated compound **79** clearly revealed that the amide group in **78** had undergone an undesired reduction to the corresponding amine. The chemoselectivity problem could not be overcome by performing the same reaction sequence with an equimolar amount of borane.

4.2. Completion of the Synthesis of the 1-*epi*-Aglycon. An alternative sequence proved to be more successful (Scheme 21). The mixture of olefins **78** was initially transformed into the α-hydroxy ketone **80** via a two-step sequence of dihydroxylation and Swern oxidation. With an excess of SmI_2 in the presence of *t*-BuOH, the deoxygenation of **80** proceeded smoothly to give **81**.[61]

SCHEME 20. "Unexpected" Formation of the Amine 79



The high yield of 99% in this reaction was astonishing because α-hydroxy ketones are normally not regarded as good reduction substrates for SmI_2.[62] Likewise, the stability of the acetonide is noteworthy since the reductive cleavage of the α-C−O bond is commonly observed (in the case of carboxylic acid esters).[63]

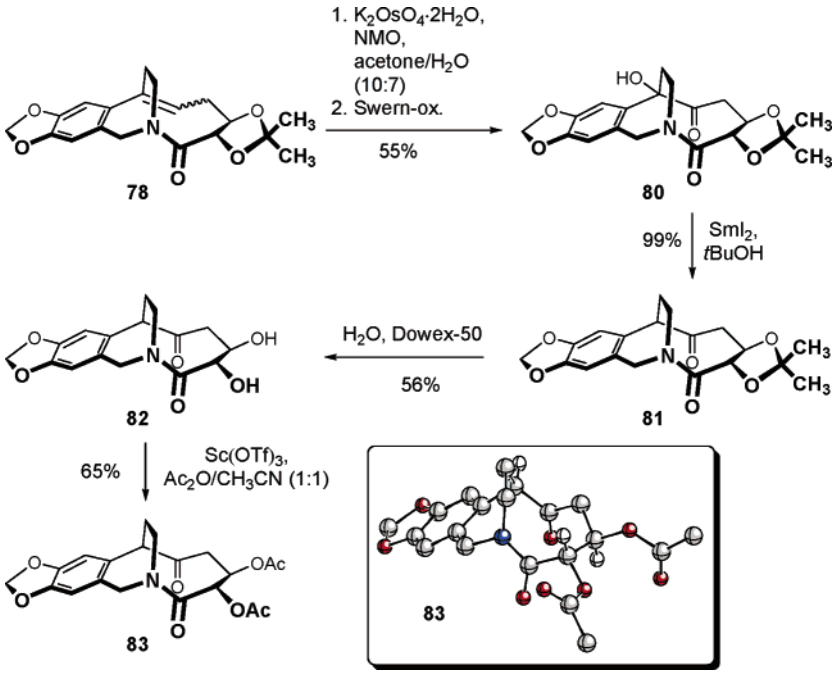
The final cleavage of the acetonide protecting group to give the 1-*epi*-aglycon **82** of the cripowellins A and B was most easily conducted in the presence of the acidic ion-exchange resin Dowex-50[64] because it made further purification of the 1-*epi*-aglycon **82** unnecessary—in contrast to the cleavage using $PdCl_2(CH_3CN)_2$ in refluxing CH_3CN/H_2O (1:1).[65]

With regard to the known structure of the bisacetate of cripowellin A and the biological activity of the cripowellins, we were interested in the conformation of **82**. In the search for derivatives of the 1-*epi*-aglycon **82**, our efforts were rewarded by bisacetate **83**, which provided crystals suitable for an X-ray structure analysis.[66] 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 the same spatial proximity. This substructure had been identified as the probable pharmacophor by researchers of Bayer AG after extensive investigations on structure−activity relationships.[5] Therefore, it seems reasonable to expect the 1-*epi*-aglycon **82** to be biologically active, too. Yet, this still needs to be proven by biological tests.

Apart from confirming the relative stereochemistry of **83** and its predecessors, the X-ray structure also clarified the fact that both the 1-*epi*-aglycon **82** and its bisacetate **83** seemed to have undetected carbonyl carbon signals according to ^{13}C NMR spectroscopy. The matter became

(61) White, J. D.; Somers, T. C. *J. Am. Chem. Soc.* **1994**, *116*, 9912−9920.
(62) Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 1135−1138.
(63) Molander, G. A. *Org. React.* **1994**, *46*, 211−367.
(64) Ho, P.-T. *Tetrahedron Lett.* **1978**, *19*, 1623−1626.
(65) (a) Lipshutz, B. H.; Pollart, D.; Monforte, J.; Kotsuki, H. *Tetrahedron Lett.* **1985**, *26*, 705−708. (b) Schmeck, C.; Hegedus, L. S. *J. Am. Chem. Soc.* **1994**, *116*, 9927−9934.
(66) CCDC 263133 (**83**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

SCHEME 21. Completion of the Synthesis of the 1-*epi*-Aglycon 82 of the Cripowellins A and B



clear after performing a high-temperature NMR experiment on the bisacetate **83** which revealed its carbonyl carbon signal again. One has to conclude that the bicyclic system of both **82** and **83** adopts at least two conformational minima. On the NMR time scale, the exchange between these minima is rather slow at room temperature, which causes significant line broadening (also visible in their ^{1}H NMR spectra, see the Supporting Information). By heating the sample, this interconversion is faster, the line broadening is reduced, and the signal of the carbonyl carbon is easier to observe.

Conclusions. In this paper, we have described attempts to achieve the asymmetric total synthesis of the aglycon **3** of the cripowellins A (**1**) and B (**2**). Our efforts were finally rewarded by featuring a sequence of a highly enantioselective Sharpless dihydroxylation, a ring-closing metathesis and a highly diastereoselective intramolecular Heck reaction. This strategy allowed the construction of the unusual [5.3.2]-bicyclic structure of the aglycon for the first time—in the form of its 1-*epi*-analogue. The synthesis is efficient (13 steps in the longest linear sequence, 15 steps altogether; 5.6% overall yield), and diastereo- and enantioselectivity are virtually complete (de, ee ≥ 98%). The crystal structure of the bisacetate of the 1-*epi*-aglycon, **83**, reveals the same spatial orientation of the ketone and the lactam carbonyl groups as in the case of the cripowellins. Therefore, it is reasonable to assume that the 1-*epi* derivatives may exhibit the same biological activity as the cripowellins and their aglycon themselves. The 1-*epi*-aglycon **82** might clarify the hitherto unknown mode of action of the cripowellins.

Experimental Section

This section comprises all compounds belonging to the AD-RCM-Heck approach (Chapter 4). A general procedure for an aqueous workup, which is summarized in the form (quenching agent; solvent used for extraction; drying agent), can be found in the Supporting Information.

5-(6-Bromobenzo[1,3]dioxol-5-ylmethyl)-2,2-dimethyl-3a,5,6,7,10,10a-hexahydro-1,3-dioxa-5-azacyclopentacyclononen-4-one (68). A flask containing a solution of the bisolefin **69** (0.868 g, 1.9 mmol) in DCM (1.9 L) was evacuated and filled with argon (4×). It was heated to reflux, and a solution of Grubbs' second-generation catalyst (0.163 g, 0.2 mmol) in DCM (10 mL) was added portionwise (2.5 mL each 30 min). After the last addition, reflux was continued for 1 h. The solution was allowed to reach rt, and DMSO (0.68 mL, 9.6 mmol) was added. After stirring overnight and removal of the solvent under reduced pressure, the residue was purified by column chromatography (pentane/ether 1:1) to give 0.629 g (1.5 mmol, 77%) of the olefin **68** as a colorless foam. HPLC: t_R 12.3 min (LiChrosorb Si 60 (pentane/ether 4:6, 0.5 mL/min)); R_f 0.24 (pentane/ether 1:1); $[\alpha]^{25}_D$ +48.3 (c 0.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48 (s, 3H), 1.58 (s, 3H), 2.32−2.44 (m, 1H), 2.50−2.66 (m, 3H), 3.33 (m, 1H), 3.70 (m, 1H), 4.03 (m, 1H), 4.08 (d, J = 14.8, 1H), 4.50 (d, J = 8.4, 1H), 5.05 (d, J = 14.8, 1H), 5.56 (m, 1H), 5.79 (m, 1H), 5.95 (s, 2H), 6.92 (s, 1H), 6.96 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.2, 26.3, 27.2, 28.5, 44.5, 50.4, 76.8, 79.9, 101.9, 110.1, 110.2, 112.3, 114.2, 128.1, 128.3, 129.2, 147.9, 170.4; MS (CI, 100 eV) m/z 345 (17), 344 (100), 215 (15), 213 (17); IR ($CHCl_3$) 2990, 2938, 1657, 1480, 1377, 1238, 1167, 1091, 1039, 931, 886, 849, 802, 755, 665, 515. Anal. Calcd for $C_{19}H_{22}BrNO_5$: C, 53.79; H, 5.23; N, 3.30. Found: C, 53.53; H, 5.14; N, 2.99.

(4*S*,5*R*)-5-Allyl-2,2-dimethyl[1,3]dioxolane-4-carboxylic Acid (6-Bromobenzo[1,3]dioxol-5-ylmethyl)but-3-enylamide (69). A solution of DMSO (3.51 mL, 49.4 mmol) in DCM (15 mL) was slowly added to a solution of oxalyl chloride (2.03 mL, 23.7 mmol) in DCM (100 mL) at −78 °C. After 15 min, a solution of the alcohol **75** (3.701 g, 21.5 mmol) in DCM (15 mL) was added dropwise. Stirring was continued for 30 min, after which Et_3N (15.1 mL, 107 mmol) was added slowly. Ten minutes later, the cold bath was removed, and stirring was continued at room temperature for 10 min. An aqueous workup (H_2O; DCM; $MgSO_4$) yielded the corresponding aldehyde, which was purified by column chromatography (pentane/ether 2:1). It was directly used for the next step: it was dissolved in a mixture of water (60 mL) and acetone (60 mL), and the solution was cooled to 0 °C. 2-Methyl-2-butene (42.0 mL, 395 mmol), $NaH_2PO_4 \cdot 2H_2O$ (6.705 g, 43.0 mmol), and $NaClO_2$ (80%, 6.074 g, 53.7 mmol) were added successively

(vigorous stirring!). The ice bath was removed, and the reaction was stirred at room temperature for 30 min. It was extracted with EtOAc several times. The organic extracts were combined, dried over $MgSO_4$, and concentrated. All volatiles were removed under high vacuum to yield the crude acid **71** (3.027 g, 16.3 mmol), which was dissolved in DCM (60 mL). The solution was cooled to 0 °C, and the amine **70** (5.108 g, 18.0 mmol) and FEP (4.233 g, 19.9 mmol) were added. Et*i*-Pr_2N (8.6 mL, 52.0 mmol) was added dropwise, and the reaction was allowed to warm to room temperature overnight. The reaction mixture was concentrated to a small volume, which was subjected to column chromatography (pentane/ether 4:1) to yield 6.398 g (14.1 mmol, 66% over three steps) of the amide **69** as a colorless oil. R_f 0.30 (pentane/ether 4:1); $[\alpha]^{25}_D$ +18.0 (c 0.7, $CHCl_3$). The NMR spectra clearly show the presence of two rotamers (ratio about 1:1). For the interpretation of their ^{1}H NMR spectra they are treated as two different compounds: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 6H), 1.43 (s, 3H), 1.46 (s, 3H), 2.28−2.51 (m, 8H), 3.22 (m, 1H), 3.33 (m, 1H), 3.40−3.61 (m, 2H), 4.13 (d, J = 7.4, 1H), 4.27 (d, J = 7.4, 1H), 4.51 (d, J = 4.1, 1H), 4.55 (d, J = 2.2, 1H), 4.68−4.80 (m, 4H), 5.00−5.19 (m, 8H), 5.70−5.93 (m, 4H), 5.95 (m, 2H), 5.98 (m, 2H), 6.66 (s, 1H), 6.70 (s, 1H), 6.98 (s, 1H), 7.02 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.1, 27.0, 31.6, 33.2, 37.1, 45.4, 46.3, 48.0, 50.6, 76.8, 76.9, 77.0, 101.6, 101.8, 107.9, 108.5, 110.0, 112.4, 112.7, 113.0, 113.6, 116.8, 117.5, 117.6, 129.0, 129.3, 133.35, 133.44, 134.1, 134.8, 147.4, 147.6, 168.9, 169.0; MS (EI, 70 eV) *m/z* 453 ($M^{+\bullet}$, 1), 451 (1), 373 (21), 372 (100), 215 (33), 213 (33), 141 (14), 83 (32), 55 (13); IR ($CHCl_3$) 3077, 2985, 2934, 1652, 1480, 1374, 1239, 1163, 1111, 1040, 996, 925, 855, 803, 756, 672, 516. Anal. Calcd for $C_{21}H_{26}BrNO_5$: C, 55.76; H, 5.79; N, 3.10. Found: C, 55.79; H, 5.80; N, 3.35.

(6-Bromobenzo[1,3]dioxol-5-ylmethyl)but-3-enylamine (70). Molecular sieves 4 Å (17 g) and 3-buten-1-amine (3.690 g, 51.9 mmol) were added to a solution of bromopiperonal (**60**) (9.836 g, 43.0 mmol) in DCM (80 mL). After being stirred overnight, the molecular sieves were removed by filtration, and the solvent was evaporated under reduced pressure. The crude imine was dissolved in methanol (130 mL) and $NaBH_4$ (1.626 g, 43.0 mmol) was added portionwise. After the evolution of hydrogen had ceased, stirring was continued for 1 h. All volatiles were evaporated under reduced pressure, and the residue was subjected to an aqueous workup (H_2O; DCM; Na_2SO_4). Purification by column chromatography (pentane/ether 3:1 → 2:1 → 1:1 → ether) gave 11.432 g (40.2 mmol, 94%) of the amine **70** as a colorless oil: R_f 0.24 (pentane/ether 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50 (s, 1H), 2.28 (m, 2H), 2.68 (t, J = 6.8, 2H), 3.76 (s, 2H), 5.01−5.13 (m, 2H), 5.79 (m, 1H), 5.95 (s, 2H), 6.89 (s, 1H), 6.99 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 34.3, 48.0, 53.5, 101.6, 110.1, 112.7, 114.0, 116.4, 132.7, 136.4, 147.3, 147.4; MS (EI, 70 eV) *m/z* 285 ($M^{+\bullet}$, 2), 283 (2), 244 (35), 242 (36), 215 (100), 213 (94); IR ($CHCl_3$) 3075, 2976, 2899, 2829, 1640, 1501, 1477, 1411, 1356, 1238, 1115, 1040, 995, 932, 866, 833, 780, 722, 657, 559. Anal. Calcd for $C_{12}H_{14}BrNO_2$: C, 50.72; H, 4.97; N, 4.93. Found: C, 50.29; H, 5.06; N, 5.25.

(2*E*)-4-Methoxybenzoic Acid hexa-2,5-dienyl Ester (73). Et_3N (20 mL, 142 mmol) and a catalytic amount of DMAP were added to a solution of (*E*)-2,5-hexadien-1-ol (4.549 g, 46.4 mmol) in DCM (120 mL) at 0 °C. A solution of *p*-methoxybenzoyl chloride (9.500 g, 55.7 mmol) in DCM (20 mL) was added, and the reaction was allowed to warm to room temperature overnight. An aqueous workup (1 M HCl; DCM; $MgSO_4$) and column chromatography (pentane/ether 10:1) gave 9.389 g (40.4 mmol, 87%) of the ester **73** as a clear oil: R_f 0.58 (pentane/ether 4:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.84 (m, 2H), 3.85 (s, 3H), 4.76 (m, 2H), 5.01−5.11 (m, 2H), 5.66−5.92 (m, 3H), 6.91 (m, 2H), 8.00 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.3, 55.4, 65.1, 113.6, 115.9, 122.8, 125.3, 131.6, 133.3, 135.9, 163.3, 166.1; MS (EI, 70 eV) *m/z* 232 ($M^{+\bullet}$, 7), 135 (100), 80 (28), 79 (16); IR (film) 3077, 3006, 2938, 2840, 1713, 1607, 1511, 1460, 1422, 1378, 1316, 1260, 1169, 1104, 1031, 976, 944, 919, 849, 771, 697, 614, 512. Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.13; H, 6.87.

(2*R*,3*R*)-4-Methoxybenzoic Acid 2,3-Dihydroxyhex-5-enyl Ester (74). The olefin **73** (6.965 g, 30.0 mmol), $MeSO_2NH_2$ (2.854 g, 30.0 mmol), $K_2OsO_4{\cdot}2H_2O$ (66.3 mg, 0.18 mmol, 0.6 mol %), and AD-mix β (42 g, 1.4 g/mmol olefin) were added successively to a mixture of water (150 mL) and *t*-BuOH (150 mL) at 0 °C. This suspension was stirred vigorously for 2.25 h, after which it was quenched by the addition of Na_2SO_3 (45 g, 1.5 g/mmol olefin). After the mixture was stirred for 5 min, an aqueous workup (H_2O; EtOAc; $MgSO_4$) and column chromatography (pentane/EtOAc 1:2) gave 5.737 g (21.5 mmol, 72%) of the diol **74** as an amorphous solid. Note: The column chromatography has to be conducted carefully in order to separate the byproduct bearing the benzoyl group at one of the secondary hydroxy groups (resulting from a migration of the benzoyl protecting group under the basic conditions of the Sharpless-AD). It is more polar than **74**: R_f 0.80 (EtOAc); ee ≥ 98% (Chiralpak AD (*n*-heptane/*i*-PrOH 8:2, t_R 14.5 min, 0.7 mL/min)); $[\alpha]^{23}_D$ +8.9 (c 1.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.31−2.48 (m, 3H), 2.75 (s, 1H), 3.73 (m, 1H), 3.86 (m, 1H), 3.87 (s, 3H), 4.38 (dd, J = 11.6, 6.4, 1H), 4.47 (dd, J = 11.6, 4.7, 1H), 5.13−5.22 (m, 2H), 5.87 (m, 1H), 6.93 (m, 2H), 8.00 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.1, 55.5, 66.2, 70.4, 71.8, 113.7, 118.5, 122.0, 131.8, 134.1, 163.7, 166.8; MS (EI, 70 eV) *m/z* 266 ($M^{+\bullet}$, 2), 195 (11), 153 (28), 152 (25), 136 (10), 135 (100); IR (KBr) 3297, 2976, 2937, 2844, 1716, 1608, 1513, 1472, 1423, 1385, 1318, 1261, 1170, 1127, 1065, 1031, 995, 918, 848, 769, 696, 615, 542, 509. Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.15; H, 6.81. Found: C, 62.93; H, 7.10.

(2*S*,3*S*)-4-Methoxybenzoic Acid 2,3-Dihydroxyhex-5-enyl Ester (*ent*-74). Analogous to the synthesis of **74**, the olefin **73** (0.232 g, 1.0 mmol) was reacted with AD-mix α to give 0.176 g (0.66 mmol, 66%) of the diol *ent*-**74** as an amorphous solid (no additional $K_2OsO_4{\cdot}2H_2O$ was added in this case, which accounts for the slightly lower yield): ee ≥ 98% (Chiralpak AD (*n*-heptane/*i*-PrOH 8:2, R_t 16.3 min, 0.7 mL/min)); $[\alpha]^{23}_D$ −8.2 (c 0.8, $CHCl_3$). The other analytical data correspond to those of its enantiomer **74**.

(4*R*,5*R*)-(5-Allyl-2,2-dimethyl[1,3]dioxolan-4-yl)methanol (75). PTSA (0.205 g, 1.1 mmol) was added to a solution of the diol **74** (5.737 g, 21.5 mmol) in 2,2-DMP (150 mL). After 1 h, the reaction was worked up (satd $NaHCO_3$ solution/H_2O 1:1; Et_2O; $MgSO_4$). The crude product was dissolved in methanol (150 mL), and K_2CO_3 (4.466 g, 32.3 mmol) was added. Two hours later, the reaction mixture was concentrated to a small volume and subjected to an aqueous workup (H_2O; DCM; $MgSO_4$). Purification by column chromatography (pentane/ether 4:1 → 1:1) yielded 3.594 g of the alcohol **75** (20.9 mmol, 97% over two steps) as a colorless liquid: R_f 0.50 (pentane/ether 1:1); $[\alpha]^{23}_D$ +25.2 (c 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (s, 3H), 1,43 (s, 3H), 2.05 (t, J = 5.9, 1H), 2.40 (m, 2H), 3.60 (m, 1H), 3.77−3.85 (m, 2H), 3.98 (dt, J = 8.2, 6.0, 1H), 5.10−5.20 (m, 2H), 5.85 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.0, 27.3, 37.3, 61.9, 75.8, 81.0, 108.8, 117.9, 133.5; MS (EI, 70 eV) *m/z* 157 (72), 141 (15), 131 (49), 83 (28), 79 (23), 69 (15), 67 (13), 59 (100), 55 (23), 54 (11); IR (film) 3432, 3079, 2986, 2932, 2878, 1643, 1455, 1435, 1376, 1246, 1168, 1062, 998, 917, 842, 694, 615, 515; HRMS calcd for $C_9H_{16}O_3 - CH_3$ 157.0865, found 157.0865.

(1*S*,14*S*,16*Z*,18*R*)-16,16-Dimethyl-5,7,15,17-tetraoxa-12-azapentacyclo[10.8.2.0^{2,10}.0^{4,8}.0^{14,18}]docosa-2,4(8),9,19-tetraen-13-one (76). A Schlenk tube with a screw cap and Teflon seal was charged with $Pd(OAc)_2$ (0.064 g, 0.29 mmol) and PPh_3 (0.223 g, 0.85 mmol). Et_3N (0.70 mL, 5.0 mmol) and a solution of the olefin **68** (0.600 g, 1.4 mmol) in DMF (17 mL) were added in a counterflow of Ar. After the tube had been sealed, it was evacuated and filled with Ar (3×). It was placed in an oil bath at 110 °C. Shortly afterward, a deep red color appeared, and stirring was continued for 6 h. The mixture was allowed to cool to room temperature. It was worked up (H_2O; Et_2O; $MgSO_4$) yielding a crude product that is dried under high

vacuum (to remove residual DMF). Column chromatography (pentane/EtOAc 1:1 → 1/2) gave 0.286 g (0.83 mmol, 59%) of the bicyclic olefin **76** as a beige-brown foam (performing the reaction on a smaller scale yields an almost colorless product): R_f 0.29 (pentane/EtOAc 1:2); de ≥ 98% (GC, ^{1}H NMR); $[\alpha]^{25}_D$ −55.3 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (s, 3H), 1.44 (s, 3H), 1.88 (dt, J = 15.4, 4.5, 1H), 2.66 (m, 1H), 3.46 (dd, J = 13.7, 5.5, 1H), 3.75 (dd, J = 8.4, 4.0, 1H), 3.95 (dt, J = 4.8, 13.1, 1H), 4.02 (m, 1H), 4.14 (d, J = 15.1, 1H), 4.80 (d, J = 8.5, 1H), 4.99 (d, J = 15.1, 1H), 5.90 (m, 4H), 6.60 (s, 1H), 6.70 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.6, 27.1, 29.6, 43.6, 44.0, 47.7, 76.5, 77.0, 101.0, 110.4, 111.2, 111.6, 130.5, 131.5, 132.5, 133.1, 145.3, 146.6, 169.8; MS (EI, 70 eV) *m/z* 344 ($M^{+\bullet}$, 24), 343 (100), 286 (16), 285 (22), 257 (11), 256 (29), 229 (18), 228 (39), 215 (24), 199 (12), 187 (15), 185 (18), 174 (31), 173 (24), 172 (14), 161 (14), 135 (50), 115 (15); IR ($CHCl_3$) 3009, 2938, 2884, 1659, 1486, 1427, 1377, 1347, 1240, 1214, 1163, 1101, 1041, 998, 936, 870, 825, 756, 669, 476; HRMS calcd for $C_{19}H_{21}NO_5$ 343.1420, found 343.1420.

(1*R*,14*S*,18*R*,19*S*,21*S*)-16,16-Dimethyl-5,7,15,17,20-pentaoxa-12-azahexacyclo[10.9.2.0^{2,10}.0^{4,8}.0^{14,18}.0^{19,21}]tricosa-2,4(8),9-trien-13-one (77). The Heck product **76** (0.173 g, 0.50 mmol) was dissolved in a precooled (−24 °C) solution of DMDO in acetone (13 mL of a 0.086 M solution, 1.1 mmol) and stored in a freezer for 9 days at −24 °C. It was warmed to room temperature and concentrated under reduced pressure. Purification by column chromatography (pentane/EtOAc 1:4) gave 0.100 g (0.28 mmol, 55%) of the epoxide **77** as a colorless foam: R_f 0.23 (pentane/EtOAc 1:3); de 85% (GC, ^{13}C NMR). The following NMR data refer to the excess diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (s, 3H), 1.47 (s, 3H), 2.14 (dt, J = 15.6, 4.4, 1H), 2.78 (m, 1H), 2.94 (dd, J = 8.5, 7.6, 1H), 3.17 (dd, J = 7.6, 4.3, 1H), 3.23 (t, J = 4.7, 1H), 3.59 (dd, J = 14.0, 6.1, 1H), 3.98 (m, 2H), 4.11 (d, J = 15.3, 1H), 4.98 (d, J = 15.6, 1H), 5.02 (d, J = 8.6, 1H), 5.91 (m, 2H), 6.67 (s, 1H), 6.74 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.7, 26.1, 27.3, 40.0, 44.6, 47.8, 57.9, 58.3, 73.6, 79.0, 101.2, 110.4, 113.3, 113.9, 127.5, 132.2, 145.8, 146.2, 169.6; MS (EI, 70 eV) *m/z* 360 ($M^{+\bullet}$, 16), 359 (77), 344 (15), 302 (36), 301 (100), 244 (16), 227 (11), 215 (14), 199 (17), 176 (10), 175 (55), 174 (18), 173 (35), 172 (11), 161 (15), 131 (15), 115 (10), 103 (14); IR ($CHCl_3$) 2992, 2937, 2889, 1661, 1486, 1427, 1378, 1336, 1290, 1249, 1214, 1156, 1104, 1060, 1037, 932, 888, 854, 832, 794, 755, 696, 667, 634, 603, 508, 480; HRMS calcd for $C_{19}H_{21}NO_6$ 359.1369, found 359.1369.

(14*S*,18*R*,20*E*/*Z*)-16,16-Dimethyl-5,7,15,17-tetraoxa-12-azapentacyclo[10.8.2.0^{2,10}.0^{4,8}.0^{14,18}]docosa-1(20),2,4(8),9-tetraen-13-one (78). A two-necked flask was charged with the olefin **68** (0.560 g, 1.3 mmol), $Pd(OAc)_2$ (0.045 g, 0.020 mmol), Ag_2CO_3 (1.092 g, 4.0 mmol), and dppp (0.109 g, 0.26 mmol). One neck was sealed with a septum, and the other one was connected to a reflux condenser. A three-way stopcock equipped with a ballon was used to seal the condenser. The apparatus was evacuated and filled with Ar (3×). The ballon was used to maintain a slight overpressure of Ar. Toluene (18 mL) was added through the septum, and the flask was placed in an oil bath at 124 °C. After 4 h, the reaction was cooled to room temperature and filtered through a short plug of silica gel (eluting with EtOAc). The solvent was evaporated and the residue purified by column chromatography (pentane/EtOAc = 2:1 → 1:1 → 1:2) yielding 0.268 g (0.78 mmol, 59%) of the bicyclic olefin **78** as a colorless foam: HPLC t_R 19.9 min (LiChrosorb Si 60 (Et_2O/pentane 8:2), 0.6 mL/min; t_R 15.7 min for the minor diastereomer); R_f 0.50 (pentane/EtOAc 1:2); de = 25% (referring to the double bond isomers); $[\alpha]^{24}_D$ −51.0 (*c* 0.3, $CHCl_3$; *Z*-isomer).

Major diastereomer (*Z*-**78**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (s, 3H), 1.45 (s, 3H), 2.22 (ddd, J = 14.4, 7.8, 4.5, 1H), 2.43 (ddd, J = 12.8, 11.2, 6.8, 1H), 2.71 (dd, J = 12.9, 7.1, 1H), 3.04 (dt, J = 14.3, 10.0, 1H), 3.54 (dd, J = 13.3, 6.7, 1H), 3.81 (m, 1H), 3.92 (d, J = 15.9, 1H), 4.20 (ddd, J = 9.5, 8.5, 4.5, 1H), 4.78 (d, J = 8.2, 1H), 5.25 (d, J = 15.7, 1H), 5.87 (dd, J = 10.4, 8.0, 1H), 5.94 (m, 2H), 6.61 (s, 1H), 6.76 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.1, 27.1, 27.4, 34.5, 51.8, 52.1, 73.2, 84.5, 101.1, 109.3, 110.8, 126.1, 130.6, 131.0, 141.4, 146.1, 146.7, 173.1; MS (EI, 70 eV) *m/z* 344 ($M^{+\bullet}$, 24), 343 (100), 285 (11), 257 (38), 256 (11), 229 (15), 228 (25), 214 (13), 201 (12), 200 (29), 199 (12), 187 (27), 174 (12), 173 (18), 172 (11), 128 (11); IR ($CHCl_3$) 2990, 2941, 1725, 1649, 1503, 1483, 1453, 1416, 1377, 1316, 1240, 1184, 1158, 1103, 1078, 1035, 936, 862, 822, 757, 670, 573, 522; HRMS calcd for $C_{19}H_{21}NO_5$ 343.1420, found 343.1419.

Minor diastereomer (*E*-**78**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (s, 3H), 1.56 (s, 3H), 2.53−2.70 (m, 3H), 3.11 (ddd, J = 12.8, 10.6, 7.6, 1H), 3.47 (m, 1H), 3.94 (d, J = 16.5, 1H), 3.94−4.04 (m, 2H), 4.35 (d, J = 8.2, 1H), 5.46 (dd, J = 9.9, 6.3, 1H), 5.79 (d, J = 16.8, 1H), 5.92 (m, 2H), 6.45 (s, 1H), 6.52 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.2, 27.3, 29.1, 32.6, 43.7, 52.6, 76.4, 80.1, 100.9, 106.4, 107.6, 110.2, 125.6, 134.3, 139.5, 145.9, 146.9, 171.1.

(1*R*,14*R*,18*R*)-16,16-Dimethyl-5,7,15,17-tetraoxa-12-azapentacyclo[10.8.2.0^{2,10}.0^{4,8}.0^{14,18}]docosa-2,4(8),9-trien-20-one (79). BH_3·THF (1.5 mL of a 1 M solution in THF, 1.5 mmol) was added to a solution of the Heck product **78** (0.100 g, 0.29 mmol) in THF (2.5 mL). After 3 h, the reaction was quenched by the addition of water (1 mL). $NaBO_3$·$4H_2O$ (0.090 g, 0.59 mmol) was added, and the resulting slurry was stirred vigorously for 2 h. Workup (Et_2O; $MgSO_4$) and column chromatography (pentane/EtOAc 2:1) yielded a mixture of two diastereomeric alcohols (0.054 g) which was dissolved in DCM (2 mL). DMP (0.095 g, 0.22 mmol) was added, and after stirring for 2.25 h, the reaction was quenched by the addition of $Na_2S_2O_3$ (1 g) and a saturated solution of $NaHCO_3$ (10 mL). The resulting mixture was stirred vigorously for 15 min and worked up (DCM; $MgSO_4$). Purification by column chromatography (pentane/ether 1:2) gave the amine **79** as a colorless foam: R_f 0.66 (pentane/EtOAc 1:2); de ≥ 98% (^{1}H NMR, GC); $[\alpha]^{24}_D$ −99.7 (c 0.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (s, 3H), 1.45 (s, 3H), 1.95−2.02 (m, 1H), 2.38 (t, J = 11.5, 1H), 2.65 (dd, J = 11.6, 3.0, 1H), 2.70−2.77 (m, 3H), 3.06 (t, J = 11.3, 1H), 3.14 (s, 1H), 3.17 (dd, J = 12.1, 4.0, 1H), 3.66 (d, J = 14.5, 1H), 3.75 (m, 1H), 3.79 (d, J = 14.5, 1H), 4.04 (ddd, J = 10.8, 8.7, 3.0, 1H), 5.89 (d, J = 1.5, 1H), 5.93 (d, J = 1.5, 1H), 6.50 (s, 1H), 6.55 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.0, 27.1, 33.6, 39.8, 46.3, 55.8, 56.3, 62.0, 79.0, 80.7, 101.0, 107.9, 108.4, 110.8, 128.2, 130.8, 146.3, 146.5, 197.0; MS (EI, 70 eV) *m/z* 345 ($M^{+\bullet}$, 18), 330 (12), 300 (19), 287 (10), 242 (10), 203 (25), 202 (19), 196 (18), 175 (29), 174 (100), 161 (17), 131 (16), 103 (11); IR ($CHCl_3$) 3012, 2946, 2871, 1668, 1504, 1487, 1460, 1364, 1326, 1277, 1233, 1164, 1132, 1073, 1041, 935, 899, 865, 842, 756, 668, 585, 563, 511, 460; HRMS calcd for $C_{19}H_{23}NO_5$ 345.1576, found 345.1576.

(1*S*,14*S*,18*R*)-1-Hydroxy-16,16-dimethyl-5,7,15,17-tetraoxa-12-azapentacyclo[10.8.2.0^{2,10}.0^{4,8}.0^{14,18}]docosa-2,4(8),9-triene-13,20-dione (80). K_2OsO_4·$2H_2O$ (0.013 g, 0.04 mmol) and NMO (97%, 0.260 g, 2.2 mmol) were added to a solution of the Heck product **78** (0.239 g, 0.70 mmol) in a mixture of acetone (5 mL) and water (3.5 mL). After 3 h, the reaction was quenched by the addition of Na_2SO_3 (0.200 g). After stirring for 5 min, the reaction mixture was worked up (DCM; $MgSO_4$). The crude product could be used for the next step without further purification.

DMSO (0.26 mL, 3.7 mmol) was added in one portion to a solution of oxalyl chloride (0.15 mL, 1.8 mmol) in DCM (5 mL) at −78 °C. After 15 min, a solution of the crude product (vide supra) in DCM (4 mL) was added dropwise. Stirring was continued for 30 min, after which Et_3N (0.98 mL, 7.0 mmol) was added slowly. Ten minutes later, the cold bath was removed and stirring was continued until the reaction had warmed to room temperature. Aqueous workup (H_2O; DCM; $MgSO_4$) and column chromatography (ether) yielded 0.144 g (0.38 mmol, 55% over two steps) of the α-hydroxy ketone **80** as a colorless solid: HPLC t_R 10.1 min (LiChrosorb Si 60 (EtOAc/pentane 7:3), 7 mL/min); R_f 0.52 (EtOAc); de ≥ 98%

(^{1}H NMR, HPLC); $[\alpha]^{22}_D$ −8.9 (*c* 0.4, CH_3OH); melting point: >190 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 1.45 (s, 3H), 1.46 (s, 3H), 2.17 (dd, J = 14.1, 7.8, 1H), 2.69 (dd, J = 12.0, 4.8, 1H), 2.94 (s, 1H), 3.16−3.35 (m, 2H), 3.54 (t, J = 11.7, 1H), 3.99−4.11 (m, 3H), 4.72−4.77 (m, 2H), 5.98 (d, J = 1.1, 1H), 6.01 (d, J = 1.1, 1H), 6.75 (s, 1H), 7.24 (s, 1H); ^{13}C NMR (100 MHz, acetone-d_6) δ 26.7, 27.5, 37.7, 41.3, 41.4, 53.7, 77.6, 80.3, 82.1, 102.0, 107.0, 108.5, 111.4, 128.0, 133.4, 147.3, 147.5, 169.8, 199.7; MS (EI, 70 eV) *m/z* 376 ($M^{+\bullet}$, 11), 375 (55), 347 (27), 289 (40), 288 (28), 272 (49), 263 (71), 260 (11), 243 (17), 242 (12), 233 (29), 232 (100), 204 (48), 190 (19), 189 (48), 188 (40), 177 (18), 176 (21), 175 (29), 163 (69), 136 (21), 135 (23), 85 (34), 59 (16); IR (KBr) 3286, 3061, 2987, 2929, 1711, 1654, 1487, 1452, 1376, 1327, 1231, 1178, 1101, 1039, 930, 884, 837, 785, 728, 650, 629, 568, 533; HRMS calcd for $C_{19}H_{21}NO_7$ 375.1318, found 375.1318.

(1*R*,14*S*,18*R*)-16,16-Dimethyl-5,7,15,17-tetraoxa-12-azapentacyclo[10.8.2.0^{2,10}.0^{4,8}.0^{14,18}]docosa-2,4(8),9-triene-13,20-dione (81). Preparation of a Solution of SmI_2 in THF. A solution of 1,2-diiodoethane (2.508 g, 8.9 mmol) in THF (9 mL) was added to a suspension of Sm powder (1.405 g, 9.3 mmol) in THF (9 mL). Shortly afterward, a vigorous evolution of gas was observed. The mixture was stirred vigorously for 1 h, after which it was ready for use (the resulting deep blue solution was assumed to be ca. 0.5 M).

t-BuOH (0.11 mL, 1.2 mmol) was added to a solution of the α-hydroxy ketone **80** (0.144 g, 0.38 mmol) in THF (4 mL). The freshly prepared SmI_2 solution (ca. 5.5 mL, ca. 2.8 mmol, ca. 7.2 equiv) was then added dropwise until a green color of the solution persisted for at least one minute. (Note: At the beginning of the addition, the color changed from blue to yellow almost instantaneously. The time needed for this color change increased with the amount of SmI_2 that was added to the solution. Finally, a green color persisted for a couple of minutes. Although this green color faded after some time as well, the addition of SmI_2 was stopped at this point.) The reaction was stirred overnight, diluted with ether, and quenched by the addition of water. The phases were separated, and the aqueous phase was extracted several times with DCM (if both phases did not separate, the precipitate could be dissolved by adding a minimum amount of 1 N hydrochloric acid). The organic extracts were combined, dried over K_2CO_3/$MgSO_4$, filtered, and concentrated. Purification by column chromatography (ether) yielded 0.137 g (0.38 mmol, 99%) of the ketone **81** as a colorless solid: HPLC t_R 10.7 min (LiChrosorb Si 60 (EtOAc/pentane 7:3), 0.7 mL/min); R_f 0.52 (EtOAc); de ≥ 98% (^{1}H NMR, HPLC); $[\alpha]^{22}_D$ +11.9 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51 (s, 3H), 1.57 (s, 3H), 2.40 (m, 1H), 2.80 (dd, J = 11.4, 4.8, 1H), 2.97 (m, 1H), 3.26 (t, J = 11.4, 1H), 3.28 (m, 1H), 3.41 (dd, J = 5.5, 1.9, 1H), 3.85 (dd, J = 15.5, 9.2, 1H), 4.02 (d, J = 16.5, 1H), 4.21 (ddd, J = 11.4, 8.7, 4.9, 1H), 4.45 (d, J = 8.8, 1H), 5.01 (d, J = 16.8, 1H), 5.91 (d, J = 1.4, 1H), 5.96 (d, J = 1.4, 1H), 6.48 (s, 1H), 6.65 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.3, 27.2, 32.7, 39.2, 42.4, 52.9, 57.2, 76.7, 80.7, 101.2, 108.4, 111.2, 111.4, 127.0, 127.5, 146.5, 147.1, 169.3, 203.7; MS (EI, 70 eV) *m/z* 359 ($M^{+\bullet}$, 3), 88 (11), 86 (66), 84 (100), 58 (62), 49 (12), 47 (16); IR ($CHCl_3$) 2992, 2938, 2904, 1698, 1670, 1505, 1488, 1446, 1378, 1359, 1275, 1231, 1179, 1119, 1088, 1042, 991, 934, 904, 865, 821, 757, 667, 582, 543, 521; HRMS calcd for $C_{19}H_{21}NO_6$ 359.1369, found 359.1370.

(1*R*,14*S*,15*R*)-14,15-Dihydroxy-5,7-dioxa-12-azatetracyclo[10.5.2.0^{2,10}.0^{4,8}]nonadeca-2,4(8),9-triene-13,17-dione (82). Dowex-50 (0.183 g) and water (14 mL) were added to the ketone **81** (0.104 g, 0.29 mmol). This suspension was stirred vigorously for 4.25 h. The solvent was removed by lyophilization. The residue was taken up in $CHCl_3$, and the solution was filtered through a pad of glass wool (to remove the ion-exchange resin). The solvent was removed under reduced pressure to give 0.052 g (0.16 mmol, 56%) of the 1-*epi*-aglycon of the cripowellins, **82**, as a colorless solid: HPLC t_R 3.7 min (Kromasil 100 Sil (THF), 0.7 mL/min); R_f 0.40 (acetone); de ≥ 98% (^{1}H NMR); $[\alpha]^{23}_D$ +25.4 (c 0.4, $CHCl_3$); mp >190 °C (decomposition); ^{1}H NMR (500 MHz, $CHCl_3$) δ 2.44 (m 1H), 2.66 (dd, J = 13.4, 4.9, 1H), 2.95 (m, 1H), 3.02 (m, 1H), 3.25 (s, 1H), 3.41 (m, 2H), 3.46 (t, J = 3.8, 1H), 3.92 (m, 1H), 3.97 (d, J = 16.8, 1H), 4.07 (m, 1H), 4.36 (t, J = 9.0, 1H), 5.36 (dd, J = 16.6, 1.4, 1H), 5.93 (d, J = 1.5, 1H), 5.97 (d, J = 1.5, 1H), 6.48 (s, 1H), 6.67 (s, 1H); ^{13}C NMR (125 MHz, $CHCl_3$) δ 32.0, 40.7, 43.7, 51.5, 56.2, 72.3, 76.1, 101.4, 108.4, 111.7, 126.8, 128.9, 146.8, 147.4, 172.0; MS (EI, 70 eV) *m/z* 319 ($M^{+\bullet}$, 41), 274 (14), 246 (12), 190 (16), 175 (23), 174 (100), 173 (17), 162 (13), 161 (25), 149 (11), 131 (30), 103 (24), 77 (10); IR ($CHCl_3$) 3392, 3017, 2899, 1696, 1644, 1504, 1488, 1447, 1357, 1218, 1042, 991, 937, 870, 759, 668, 524; HRMS calcd for $C_{16}H_{17}NO_6$ 319.1056, found 319.1056.

(1*R*,14*S*,15*R*)-14-(Acetyloxy)-13,17-dioxo-5,7-dioxa-12-azatetracyclo[10.5.2.0^{2,10}.0^{4,8}]nonadeca-2,4(8),9-triene-15-yl-acetate (83). $Sc(OTf)_3$ (0.011 g, 0.02 mmol) was added to a solution of the diol **82** (0.023 g, 0.07 mmol) in a mixture of Ac_2O (1 mL) and acetonitrile (1 mL). After being stirred for 2.5 h, the reaction was worked up (saturated solution of $NaHCO_3$; DCM; $MgSO_4$). The crude product was dried under high vacuum (to remove residual Ac_2O). Purification by column chromatography (ether/DCM 1:1) gave 0.019 g (0.05 mmol, 65%) of **83** as a colorless solid: HPLC t_R 10.3 min (LiChrosorb Si 60 (EtOAc/pentane 7:3), 0.7 mL/min); R_f 0.52 (ether/DCM 1:1); de ≥ 98% (^{1}H NMR); $[\alpha]^{23}_D$ −0.7 (*c* 0.2, $CHCl_3$); mp >190 °C; ^{1}H NMR (500 MHz, C_5D_5N) δ 2.02 (s, 3H), 2.11 (s, 3H), 2.35 (m, 1H), 2.93 (dd, J = 13.1, 5.5, 1H), 3.14 (s, 1H), 3.41 (m, 2H), 3.69 (t, J = 3.7, 1H), 3.98 (d, J = 16.5, 1H), 4.51 (m, 1H), 5.57 (d, J = 16.2, 1H), 5.81 (d, J = 10.1, 1H), 5.93 (d, J = 1.1, 1H), 6.01 (d, J = 1.1, 1H), 6.10 (s, 1H), 6.66 (s, 1H), 6.67 (s, 1H); ^{13}C NMR (75 MHz, C_5D_5N) δ 20.0, 20.6, 32.8, 39.3, 43.1, 51.4, 56.6, 71.8, 71.9, 101.5, 108.5, 111.6, 128.1, 129.4, 146.7, 147.2, 167.4, 169.4, 170.5; ^{1}H NMR (500 MHz, C_5D_5N, 70 °C) δ 1.99 (s, 3H), 2.07 (s, 3H), 2.32 (m, 1H), 2.84 (dd, J = 13.3, 5.3, 1H), 3.05 (m, 1H), 3.26 (dd, J = 13.1, 9.8, 1H), 3.36 (ddd, J = 15.3, 8.9, 6.4, 1H), 3.61 (t, J = 3.8, 1H), 3.93 (d, J = 16.5, 1H), 4.40 (m, 1H), 5.50 (d, J = 15.9, 1H), 5.73 (d, J = 10.1, 1H), 5.87 (d, J = 1.2, 1H), 5.92 (m, 1H), 5.93 (d, J = 1.2, 1H), 6.59 (s, 1H), 6.64 (s, 1H); ^{13}C NMR (125 MHz, C_5D_5N, 70 °C) δ 19.9, 20.4, 32.8, 39.3, 43.3, 51.2, 56.7, 71.6, 72.3, 101.4, 108.5, 111.6, 128.3, 129.5, 146.8, 147.3, 167.1, 169.2, 170.3, 204.1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.12 (2s, 6H), 2.44 (m, 1H), 2.66−2.78 (m, 2H), 2.96 (m, 1H), 3.43 (ddd, J = 14.7, 8.4, 4.7, 1H), 3.53 (s, 1H), 3.96 (d, J = 16.2, 1H), 4.16 (ddd, J = 15.0, 7.5, 7.5, 1H), 5.24 (d, J = 16.2, 1H), 5.33 (s, 2H), 5.95 (d, J = 1.4, 1H), 5.98 (d, J = 1.4, 1H), 6.47 (s, 1H), 6.72 (s, 1H); MS (EI, 70 eV) *m/z* 403 ($M^{+\bullet}$, 21), 175 (14), 174 (100), 161 (14), 131 (11); IR ($CHCl_3$) 3019, 2976, 2896, 2400, 1741, 1705, 1662, 1507, 1488, 1376, 1218, 1125, 1043, 935, 879, 780, 736, 670; HRMS calcd for $C_{20}H_{21}NO_8$ 403.1267, found 403.1267.

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Supporting Information Available: Experimental procedures and characterization data for compounds **11**, **13**, **15**−**17**, **19**−**43**, **45**, **47**−**50**, **53**−**59**, and **62**−**65** and NMR spectra of compounds **80**−**83**. This material is available free of charge via the Internet at http://pubs.acs.org.

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