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Macrocyclic Lactam Synthesis via a Ring Expansion Reaction: Construction of the Cripowellin Skeleton

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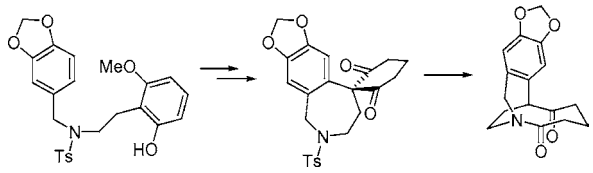
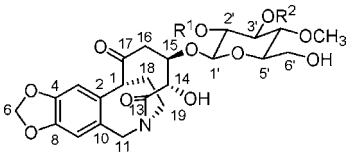
ABSTRACT



The cripowellin ring skeleton, a macrocyclic [2.3.5]-bicyclic ketolactam, was smoothly generated via construction of a spiro(benzazepin-cyclohexane-1,3-dione) employing oxidative cyclization as a key step and a subsequent ring expansion reaction.

Cripowellins A (**1**) and B (**2**) (Figure 1) are members of the *Amaryllidaceae* alkaloids and were isolated from the bulbs of *Crinum powellii* by Velten and colleagues in 1997.[1,2] Their structures were determined unambiguously by extensive spectroscopic methods including X-ray crystallographic analysis of cripowellin A diacetate (C14 and C6′ acetates).



R^1, R^2 = -CH_2OCH_2- : Cripowellin A (**1**)
R^1 = CH_3, R^2 = CH_3 : Cripowellin B (**2**)

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

The absolute stereochemistry was postulated on the assumption that the carbohydrate moiety is biogenetically derived from β-D-glucose.[1] In addition to their interesting insecticidal activity, the 10-membered fused lactam skeleton of the cripowellins appears to be unique to the *Amaryllidaceae* alkaloid series.

Careful structural examination shows that the main skeleton of cripowellin is closely related to other *Amaryllidaceae* alkaloids such as mesembrine (**3**), crinane (**4**, unnatural product), and crinine (**5**) (Figure 2). Oxidative cleavage of the C2−C3 bond of the tetrahydroisoquinoline moiety in the crinane skeleton reveals a structure that is equivalent to the cripowellin skeleton. From this point of view, it would also be interesting to determine if cripowellin is biosynthetically derived from other *Amaryllidaceae* alkaloids such as those of the crinane family.

Our interest in a total synthesis of cripowellin led us to envision that the skeleton could be constructed via a ring expansion reaction of spiro(benzazepine-cyclohexane-1,3-dione) intermediate **6**, as shown in Figure 3. Intramolecular attack of the benzazepinylamine to the more electron-deficient ketone (the α-hydroxy ketone) in **6** should promote

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(1) Velten, R.; Erdelen, C.; Gehling, M.; Göhrt, A.; Gondol, D.; Lenz, J.; Lockhoff, O.; Wachendorff, U.; Wendisch, D. *Tetrahedron Lett.* **1998**, *39*, 1737.

(2) Gehling, M.; Goehrt, A.; Gondol, D.; Lenz, J.; Lockhoff, O.; Moeschler, H.; Velten, R.; Wendisch, D.; Andersch, W.; Erdelen, C.; Harder, A.; Mencke, N.; Turberg, A.; Wachendorff-Neumann, U. German Patent 19610279, 1997.

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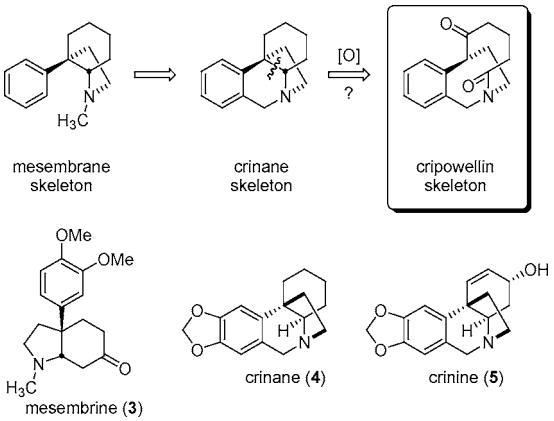


Figure 2. Comparison of the cripowellin skeleton with other *Amaryllidaceae* alkaloids.

a concomitant ring expansion to the keto-macrolactam ring **7**. We hoped that the formation of the thermodynamically more stable amide functionality would provide a driving force for the formation of the fairly strained macrolactam skeleton of **7**.

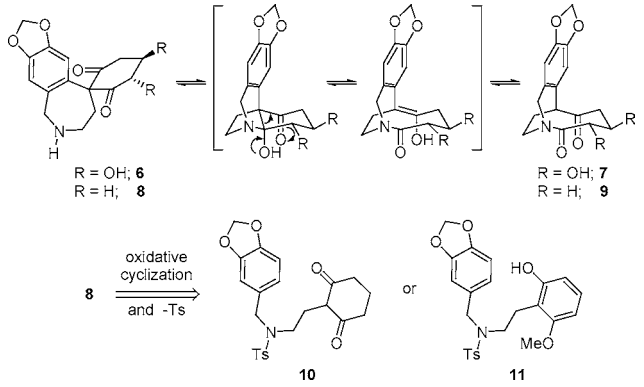


Figure 3. Synthetic plan for the cripowellin skeleton.

In this paper, we describe synthetic efforts toward spiro(benzazepine-cyclohexane-1,3-dione) intermediate **8** from *N*-piperonyl-*N*-[2-(2,6-dioxocyclohexyl)ethyl]-toluenesulfonyl amide (**10**) or *N*-piperonyl-*N*-[2-(6-hydroxy-2-methoxyphenyl)-ethyl]toluenesulfonyl amide (**11**) and a model study of the ring expansion reaction with an *N*-toluenesulfonyl-protected version of dideoxy derivative **8** (compound **19**).

A literature search led to our discovery of various ring expansion reactions of 2-aminoethyl-substituted cyclopentane-1,3-diones that were studied by Ban and colleagues.[3] As shown in Figure 4, medium-sized ketolactams **12**−**14** could be obtained through *controlled crisscross annulation*, involving an acyclic amino alkyl group in the substrates.[4]

(3) Ohnuma, T.; Nagasaki, M.; Tabe, M.; Ban, Y. *Tetrahedron Lett.* **1983**, *24*, 4253.

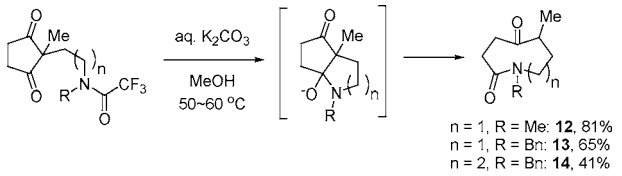


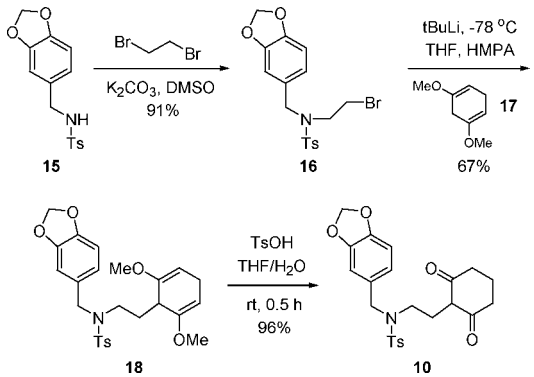
Figure 4. Ban's macrolactam syntheses via ring expansion.[3]

Because, to our knowledge, no similar reaction employing a *cyclic* amino group and a *cyclohexane-1,3-dione* system has been explored so far, we thought it would be interesting to see whether the key reaction shown in Figure 3 could be achieved.

To prepare key substrate **8**, we planned to use an intramolecular oxidative coupling reaction between an aryl moiety and a cyclohexane-1,3-dione, a reaction that has been extensively studied by the Kita group.[5] Kita reported that five- and six-membered spirobenzannulated compounds could be obtained in reasonable yields using phenyl iodide bis(trifluoroacetate) (PIFA) as an oxidant. Although seven-membered ring formation was not reported in their study, we hoped that such a cyclization would occur under similar conditions.

Synthesis of the desired substrate **10** is illustrated in Scheme 1. Alkylation of *N*-piperonyl-*N*-tosyl amide (**15**) with excess 1,2-dibromoethane in the presence of K_2CO_3 in DMSO yielded *N*-bromoethyl-*N*-piperonyl-*N*-tosylamide (**16**) in 91% yield. Because it is known that direct C2-alkylation of cyclohexane-1,3-dione with an alkyl halide is sluggish due to strong competition with O-alkylation, we chose Piers' protocol,[6] which employs alkylation of 1,5-dimethoxy-1,4-cyclohexadiene (**17**) and acid-catalyzed hydrolysis of the resulting product **18** to afford the desired substrate **10**.

Scheme 1. Synthesis of **10**



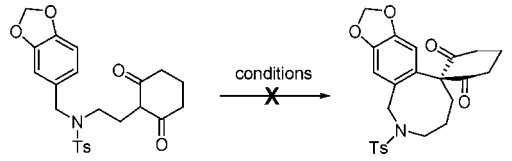
With compound **10** in hand, oxidative cyclization using various oxidants was attempted (Scheme 2). Unfortunately,

(4) Ohnuma, T.; Tabe, M.; Shiiya, K.; Ban, Y. *Tetrahedron Lett.* **1983**, *24*, 4249.

(5) Arisawa, M.; Ramesh, N. G.; Nakajima, M.; Tohma, H.; Kita, Y. *J. Org. Chem.* **2001**, *66*, 59.

(6) Piers, E.; Grierson, J. R. *J. Org. Chem.* **1977**, *42*, 3755.

Scheme 2. Various Cyclization Attempts of **10**

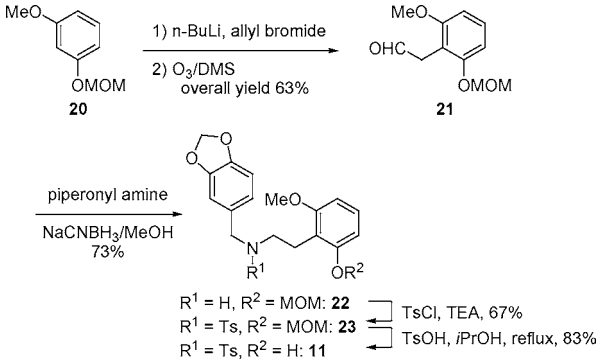


conditions	results
$PhI(CF_3CO_2)_2/CF_3CH_2OH$	unidentifiable products
$PhI(CH_3CO_2)_2/CH_2Cl_2$	unidentifiable products
$Mn(OAc)_3$/AcOH/NaOAc	complex mixture + piperonal

no desired cyclized product **19** was observed under the typical reaction conditions (PIFA in CF_3CH_2OH) developed by Kita and colleagues,[5] and only unidentifiable, complex mixtures were obtained. Trials at highly dilute conditions (~0.001 M) did not result in any improvement. Changing the N-protecting group from *p*-toluenesulfonyl to trifluoroacetate also did not provide any cyclization product under the same conditions. Changing the oxidant to PIDA (phenyl iodide diacetate) in methylene chloride showed no improvement. When the substrate was subjected to a one-electron oxidant, $Mn(OAc)_3$, the reaction also yielded a complex mixture where piperonal was identified as the major component. In this case, it seems that the generated cyclohexane-1,3-dione radical abstracted the benzylic hydrogen via 1,5-hydrogen abstraction followed by further oxidation of the resulting benzylic radical by $Mn(OAc)_3$ to the corresponding tosyl iminium ion, which was transformed to piperonal upon hydrolytic workup. A similar 1,5-hydrogen abstraction under $Mn(OAc)_3$ conditions has been described in the literature.[7]

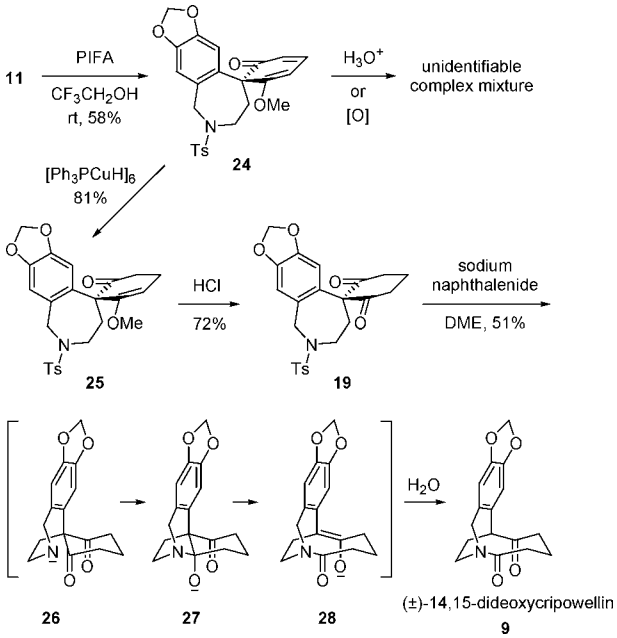
Because the oxidative cyclization approach using the cyclohexane-1,3-dione substrate was problematic, we shifted our strategy toward using 2-alkyl-3-methoxy phenol **11**. Kita and colleagues have reported an intramolecular phenolic coupling reaction using a hypervalent iodine(III) reagent and showed that the reaction is a powerful tool in the syntheses of many *Amaryllidaceae* alkaloids.[8] Compound **11** was prepared in a straightforward manner as shown in Scheme 3. Methoxymethyl (MOM)-directed lithiation of **20** followed by alkylation with allyl bromide and subsequent ozonolysis provided aldehyde **21** in 63% yield over two steps.[9] Reductive amination of aldehyde **21** with piperonylamine provided the corresponding secondary amine **22** in 73% yield. After protecting the amine with a *p*-toluenesulfonyl group (TsCl, TEA, 67%), the MOM group of the resulting tosyl amide **23** was removed by treatment with a catalytic amount of *p*-toluenesulfonic acid in refluxing 2-propanol[10] to give the desired phenol substrate **11**.

Scheme 3. Synthesis of **11**



In contrast to the use of cyclohexane-1,3-dione **10**, when phenol substrate **11** was treated with PIFA in CF_3CH_2OH at room temperature, the oxidatively cyclized spirobenzazepin product **24** was obtained in a moderate yield (58%) (Scheme 4). Having key intermediate **24** in our hands, we next

Scheme 4. Cyclization of **24**



investigated the functionalization of the 5-methoxycyclohexadienone moiety to install the C-14 and C-15 oxidation state of cripowellin at this early stage. Unfortunately, various conditions, including hydrolysis (HCl/H_2O), epoxidation (*t*BuOOH/Triton B[11] or dimethyldioxirane[12]), and reduction (H_2, PtO_2), failed to give any identifiable products. In most cases, the dienone decomposed under these conditions. After

(7) Citterio, A.; Fancelli, D.; Finzi, C.; Pesce, L. *J. Org. Chem.* **1989**, *54*, 2713.

(8) (a) Kita, Y.; Takada, T.; Gyoten, M.; Tohma, H.; Zenk, M. H.; Eichhorn, J. *J. Org. Chem.* **1996**, *61*, 5857. (b) Kita, Y.; Arisawa, M.; Gyoten, M.; Nakajima, M.; Hamada, R.; Tohma, H.; Takada, T. *J. Org. Chem.* **1998**, *63*, 6625.

(9) (a) Simas, A. B. C.; Coelho, A.; Costa, P. R. R. *Synthesis* **1999**, 1017. (b) Pocci, M.; Bertini, V.; Lucchesini, F.; De Munno, A.; Picci, N.; Iemma, F.; Alfei, S. *Tetrahedron Lett.* **2001**, *42*, 1351.

(10) Miyashita, N.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772.

(11) (a) Yang, N. C.; Finnegan, R. A. *J. Am. Chem. Soc.* **1958**, *80*, 5845. (b) Payne, G. C. *J. Org. Chem.* **1960**, *25*, 275.

(12) (a) Adam, W.; Bialas, J.; Hadjiarapoglou, L. *Chem. Ber.* **1991**, *124*, 2377. (b) Murray, R. W.; Singh, M. *Org. Synth.* **1997**, *74*, 91.

extensive screening of various reagents, only Stryker's reagent $[(Ph_3PCuH)_6]$[13] was found to successfully mediate a clean reaction to provide the reduced product **25** in good yield (81%). Fortunately, 1,4-conjugate reduction was favored over 1,6-conjugate reduction in this case. In contrast to cyclohexadienone **24**, hydrolysis of methyl enol ether **25** proceeded cleanly to give cyclohexanedione **19** in 72% yield.

Finally, we treated spiro(benzazepin-cyclohexanedione) *N*-tosyl amide **19** with sodium naphthalenide solution[14] to remove the toluenesulfonyl group, expecting either the amine form of **26** or hemiaminal form of **27** as the product. The starting material disappeared in 10 min and formed a single new product, as judged by TLC analysis. In contrast to the plane-symmetric dione **19**, the resulting product lost significant symmetry, according to ^{1}H NMR spectroscopic analysis. Surprisingly, additional spectroscopic analyses, including IR, ^{13}C NMR, COSY, HMBC, and HR-MS (ESI), of the product revealed that the product was not the predicted intermediate hemiaminal **27** but the desired ketoamide **9**. The IR spectrum of the product showed the characteristic bands for the C17 ketone stretch at 1696 cm^{-1} and the C13 amide C═O stretch at 1635 cm^{-1}, which closely correlate with the values observed for cripowellin A (1692 and 1653 cm^{-1}, respectively[1]). The presence of the ketone and amide functionality was also confirmed by ^{13}C NMR and HMBC (δ 213.8 and 173.5, respectively).

In summary, we have demonstrated that the cripowellin skeleton can be efficiently constructed by ring expansion of spiro(benzazepine-cyclohexane-1,3-dione) **19**, which was obtained by intramolecular oxidative cyclization of phenolic compound **11** followed by a reduction/hydrolysis sequence. We are currently pursuing functionalization of compound **9** to achieve the total synthesis of cripowellin and development of an asymmetric version of this synthetic strategy.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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