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Synthetic studies directed towards asmarines; construction of the tetrahydrodiazepinopurine moiety by ring closing metathesis

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Abstract—Asmarines are tetrahydro[1,4]diazepino[1,2,3-*g*,*h*]purine derivatives isolated from marine sponges (*Raspailia* sp). They possess profound cytotoxic activity towards cancer cell lines, and are thus attractive synthetic targets. The tetrahydrodiazepinopurine ring skeleton has been prepared employing the RCM reaction on Boc-protected 6-allylamino-7-(propen-1-yl)purine as the key step for the construction of the seven-membered ring. 7-(Propen-1-yl)purines were formed by a novel rearrangement of 7-allylpurines under basic conditions. Boc-protected N^6,7-diallylpurine also participated in RCM to give the eight-membered ring analog of the diazepinopurine.

Asmarines have been isolated from marine sponges (*Raspailia* sp). Currently 11 asmarines (asmarine A–K, Fig. 1) are known,[1] and asmarines A and B are reported to possess significant cytotoxic activity against various human cancer cell lines.[1a]

To date, no total synthesis of an asmarine has been published and a major challenge in any synthesis of these natural products will be the construction of the tetrahydrodiazepine ring. Strategies employed previously for the formation of the seven-membered ring in synthesis of model substances are summarized in Scheme 1. Generation of bond 'a' has been achieved by intramolecular attack from the MOM-protected amine **1** at the purine 6-position (Scheme 1).[2] Synthesis of 7-alkylpurine **1** requires several steps and this strategy has never been employed in the synthesis of asmarine analogs carrying substituents on the seven-membered ring. Alternatively, the tetrahydrodiazepine ring can be constructed by formation of bond 'b' when a 6-alkoxyamino group attacks an electrophilic site in the N-7 side chain in purines **2**,[3] but only racemic compounds have been prepared so far. Construction of bond 'e' has not been successful. When compound **3** was treated with thionyl chloride, the chloride formed in situ reacted with N-1 to give compound **4** rather than the seven-membered ring.[4] No attempts have been made so far to form bond 'c' or bond 'd' in synthetic work directed towards asmarines. A successful asmarine synthesis based on bond 'c' formation, must be enantioselective in the ring-closing step. Stereochemistry will not be an issue in the ring-closing reaction in a strategy where bond 'd' is formed. In connection with our synthetic studies of purine-containing antibiotics (agelasines) from marine sponges,[5] we wished to explore the possibility of employing the powerful ring-closing metathesis (RCM) reaction[6,7] in synthesis directed towards asmarine natural products as depicted in Scheme 1.

There were two major challenges in the synthesis of an N^6-allyl-7-alkenylpurine required for the RCM reaction. First of all, N-alkylation of purines preferably takes place at N-9[8] and there are few methods for the synthesis of N-7 alkylated purines in good yields. Furthermore, an alkenyl, not an alkyl group, had to be introduced at N-7 and no feasible methods could be found in the literature. N-Vinylation of purine, guanine or adenine with vinyl acetate in the presence of acid has given mixtures of 7- and 9-vinylpurines, and the 7-vinyl isomers were isolated in low yields.[9] Also 7-cyclopropylidenemethylpurines have been isolated in low yields in N-alkylations with 1-bromo-1-(bromomethyl)cyclopropanes.[10] Copper-mediated N-alkenylation of purines with boronic acids occurs with complete N-9 selectivity.[11]

It is known that 7-allylpurine **5** (Scheme 2) is readily available by regioselective N-allylation of 6-chloropurine in the presence of a Co-complex,[12] and we chose

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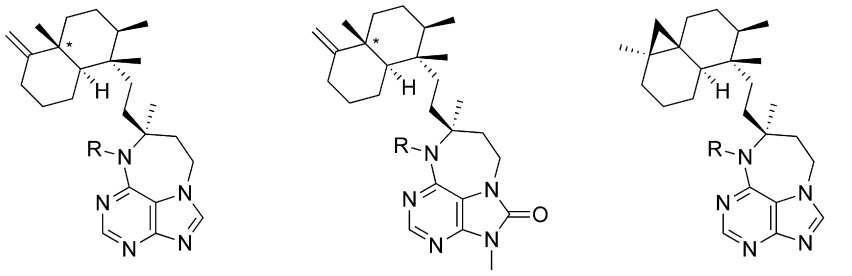
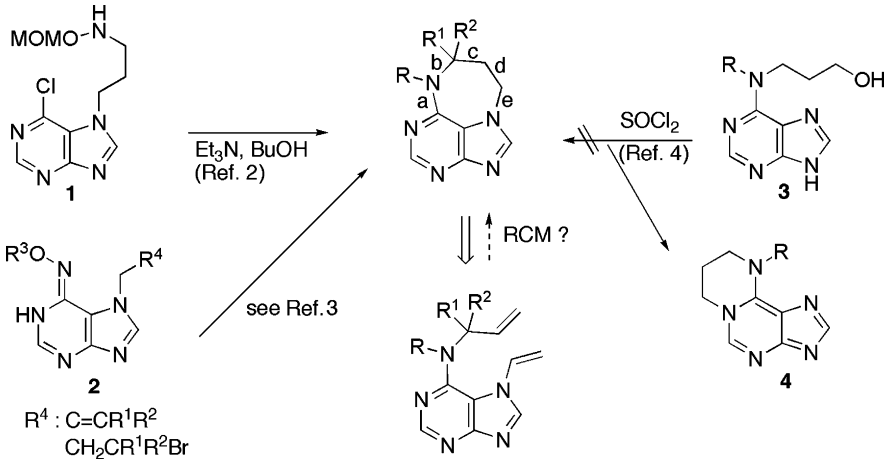
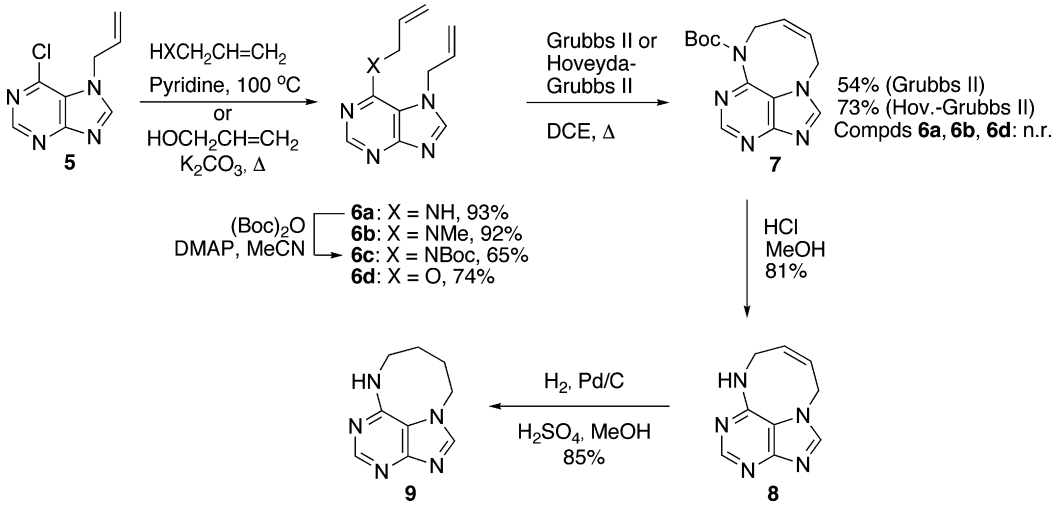


Figure 1. Structures of known asmarines.

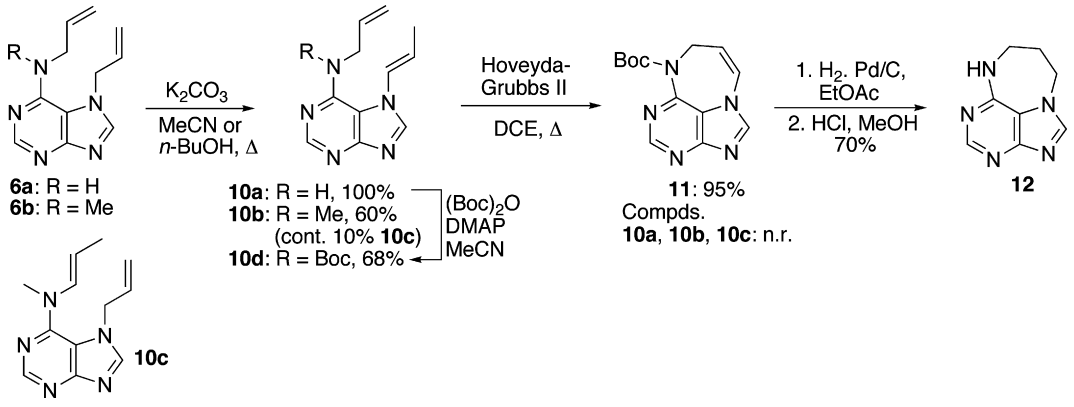


Scheme 1.



Scheme 2.

compound **5** as our starting point. 6-Chloropurine **5** was reacted with allyl amines and allyl alcohol to give compounds **6**. Initially, we attempted the RCM reaction on compounds **6** in order to form an eight-membered ring. The synthesis of eight-membered rings by RCM reactions has often been a challenge,[7a,13] even though there are examples of such rings formed in excellent yields by RCM.[13d,14] Furthermore, in the construction of azacyclooctenes by RCM, the yield is often highly dependent on the nature of the N-substituent.[7a,15] Only **6c** containing the rather bulky *N*-Boc-group reacted under RCM conditions even at elevated temperatures. The



Scheme 3.

Hoveyda-modification of the Grubbs II catalyst gave somewhat better yield than the Grubbs II catalyst, and dihydrodiazocinopurine **7** could be isolated in 73% yield employing the Hoveyda–Grubbs II complex, the Boc group was readily removed and the double bond could be hydrogenated at atmospheric pressure to afford **9**.

In order to be able to construct a seven-membered ring by RCM, we needed a 7-alkenylpurine, and when 7-allyl-6-allylaminopurine **6a** was treated with base in refluxing acetonitrile, we were able to selectively migrate the double bond in the N-7 substituent to give 7-propenylpurine **10a** in quantitative yield (Scheme 3). This represents, to the best of our knowledge, the first efficient synthesis of a 7-alkenylpurine, and the very first synthesis of a 7-(propen-1-yl)purine. Also 6-allylmethylaminopurine **6b** could be rearranged, but the reaction was slower and required refluxing *n*-butanol instead of acetonitrile. Under these conditions, the reaction was not completely selective. 7-Propenylpurine **10b** isolated contained 10% of isomer **10c**. Attempts to rearrange the 7-allyl substituent in 6-chloropurine **5** or 6-allyloxypurine **6d** were less successful.

RCM reactions on secondary amines often fail,[7a,15,16] and N^6-allylpurine **10a** did not react at all in the presence of the Hoveyda–Grubbs II catalyst in refluxing DCE. Also the mixture of *N*-methylaminopurines **10b** and **10c** remained essentially unchanged under these reaction conditions. However, the Boc-protected 7-propenylpurine **10d**, was more reactive than the isomeric 7-allylpurine **6c** in the RCM reaction and dihydrodiazepinopurine **11**, was formed in a high 95% yield after reflux in DCE for 1.5 h. The reaction did not take place at ambient temperature and in refluxing dichloromethane, the conversion was only ca. 40% after 20 h.

Attempts to remove the Boc-group in compound **11** before reduction of the double bond failed, indicating that the double bond in the seven-membered ring **11** is far more labile than in the corresponding eight-membered rings **7** and **8**. However, tetrahydro[1,4]diazepino[1,2,3-*g*,*h*]purine **12**,[3a] identical with the heterocyclic part of asmarines, was available after hydrogenation prior to removal of the N-protecting group.

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Supplementary data

Spectroscopic data and procedures for all new compounds are discussed. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.01.090.

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