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Microwave-Enhanced Synthesis of New (–)-Steganacin and (–)-Steganone Aza Analogues

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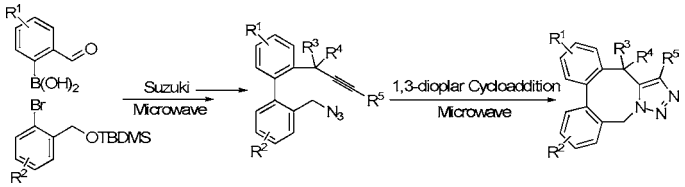
ABSTRACT



A novel, microwave-enhanced, highly efficient protocol for the synthesis of *hitherto* unknown (–)-steganacin and (–)-steganone 7-aza analogues containing a 1,2,3-triazole ring has been presented. Microwave irradiation was found to be highly beneficial in promoting the Suzuki reaction and the 1,3-dipolar cycloaddition reaction to generate the highly strained medium-sized ring system of the title molecules.

Antileukemic bisbenzocyclooctadiene lignan lactones and their aza analogues have attracted considerable synthetic interest in recent years due to their high biological potential. Naturally occurring lactones (−)-steganacin and (−)-steganone (Figure 1), isolated from *Steganotaenia araliacea* by

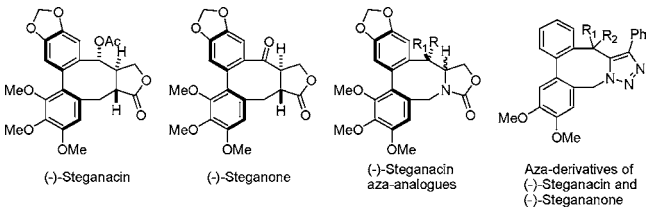


Figure 1. (−)-Steganacin, (−)-steganone, and (−)-steganacin aza analogues.

the late Prof. S. M. Kupchan,[1] have been demonstrated to possess significant in vivo activity against P-388 leukemia in mice and in vitro activity against cells derived from human carcinoma of the nasopharynx (KB).[2] In view of increasing the biological potential and solving the problems associated with stereoselection, Koga et al.[3] proposed the synthesis of unnatural (−)-steganacin 7-aza analogues. Some of them have been shown to exhibit antitumor activity even higher than the corresponding natural lignan lactones.

However, the chemistry of these potent 7-aza analogues has scarcely been developed, as can be surmised from the absence of related literature. Nonphenolic oxidative intramolecular coupling[4] has been demonstrated to be suitable for selective generation of the key biaryl skeleton of the title molecules. However, this synthetic methodology is quite sensitive to the nature of the substituents on both aromatic rings, as for example, the nonphenolic oxidative coupling

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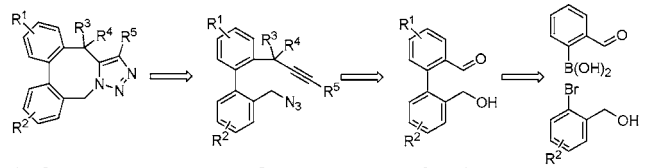
cannot be performed in the absence of electron-rich groups on the participating aromatic rings. Attempts to generate diversely functionalized analogues of the title molecules for the purpose of biological screening are scarcely described in the literature.[5] Furthermore, to the best of our knowledge, there has been no literature precedent related to the synthesis and manipulations of the potent 7-aza analogues after the pioneering work of Koga et al.[3]

As part of our ongoing research focused on the microwave-enhanced synthesis of medium-sized-ring natural product analogues,[6] we have developed a new strategy for the synthesis of novel steganacin and steganone 7-aza analogues. Herein, we wish to delineate the first total synthesis of such analogues containing a 1,2,3-triazole ring. Our new approach for the formation of a [1,5-*a*]azocine skeleton was based on a microwave enhanced Suzuki−Miyaura cross-coupling reaction[7] in combination with microwave-enhanced "click chemistry".[8] Furthermore, partially due to the increased current interest in click chemistry, 1,2,3-triazole moieties are emerging as powerful pharmacophores in their own right.[9]

As can be viewed from the retrosynthetic scheme (Scheme 1), the success of our protocol mainly depends on the

Scheme 1. Retrosynthetic Analysis



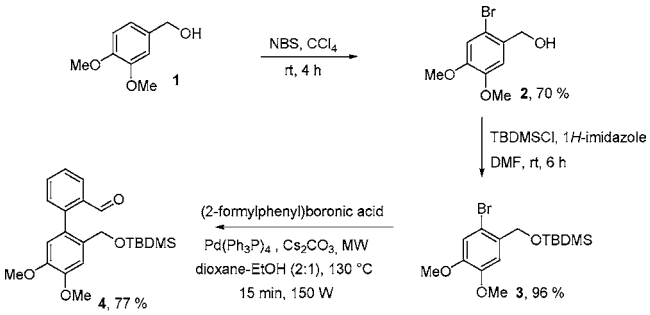
R^1, R^2 = H, Alk, OAlk, OH, etc.; R^5 = H, Alk, Ph, etc.; R^3 = R^4 = O, H, OH, OAlk, etc.

Suzuki−Miyaura cross-coupling reaction and the consecutive heterocyclization resulting in the formation of an eight-member ring fused with a 1,2,3-triazole ring.

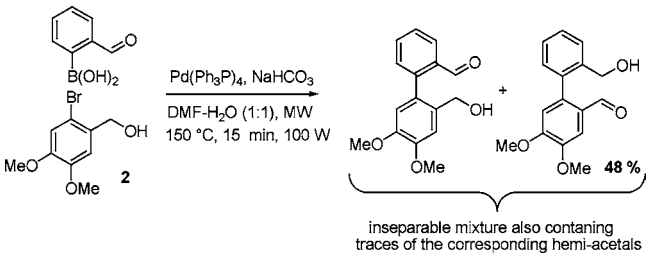
The Huisgen 1,3-dipolar cycloaddition[10] of azides and alkynes is a fast and efficient approach for the synthesis of 1,2,3-triazoles. However, the generation of medium-sized rings in the target molecules will be hampered due to the presumably high activation barrier of the reaction. As we have demonstrated in previous work related to the synthesis of natural product analogues containing difficultly obtainable medium-sized ring systems,[6b] microwave irradiation could greatly contribute to solve this problem.

We started our synthesis from the commercially available 3,4-dimethoxybenzyl alcohol (**1**) (Scheme 2). The regioselective bromination of alcohol **1** was carried out with NBS in CCl_4 and afforded alcohol **2** in 70% yield. To minimize problems associated with the cross-coupling reactions of highly electron-rich halides with boronic acids bearing an electron-withdrawing group, we decided to carry out the Suzuki−Miyaura reaction under our previously optimized microwave-irradiation conditions.[6a] However, attempts to carry out the Suzuki−Miyaura cross-coupling between alcohol **2** and (2-formylphenyl)boronic acid to generate the required biaryl skeleton met with failure, due to the formation of an inseparable mixture of biaryls together with traces of hemi-acetals in a combined yield of 48% (Scheme 3). An intramolecular disproportionation reaction between the alcohol and aldehyde centers of the molecule occurred.

Scheme 2. Suzuki−Miyaura Reaction in the Synthesis of the Key Biaryl Aldehyde **4**



Scheme 3. Suzuki−Miyaura Reaction between Alcohol **2** and (2-Formylphenyl)boronic Acid



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Therefore, the alcohol **2** was protected as the corresponding TBDMS derivative by treatment with *tert*-butyldimethylsilyl chloride (TBDMSCl) in DMF in the presence of 1*H*-imidazole, and the resulting silyl ether **3** was isolated in an excellent yield of 96% (Scheme 2). The Suzuki−Miyaura reaction of **3** with (2-formylphenyl)boronic acid was then carried out under microwave-enhanced conditions, though several attempts furnished the biaryl compound **4** in unsatisfactory yields (Table 1, entries 1−10). Contrary to our previous results,[6] reactions using $NaHCO_3$ as base (Table 1, entries 1,7), as well as using $Ni(dppp)Cl_2$ (Table 1, entry 9) as catalyst gave unexpectedly low yields or met with failure. Increasing the reaction temperature to 150 °C (Table 1, entry 6) or the reaction time to 30 min (Table 1, entry 8) diminished the yield considerably. Decreasing the reaction temperature to 100 °C (Table 1, entry 5) led to a moderate yield. The best result (77% yield) was obtained using Cs_2CO_3 as the base and $Pd(Ph_3P)_4$ as the catalyst in a 2:1 mixture of dioxane and ethanol upon irradiation at a temperature of 130 °C for 15 min (Table 1, entry 14). Reaction performed under conventioal heating, in view of proving the superiority of the microwave-enhanced experiments, resulted in a lower 42% yield at 102 °C in 3 h, where the proto-deboronation product, benzaldehyde, was the major product.

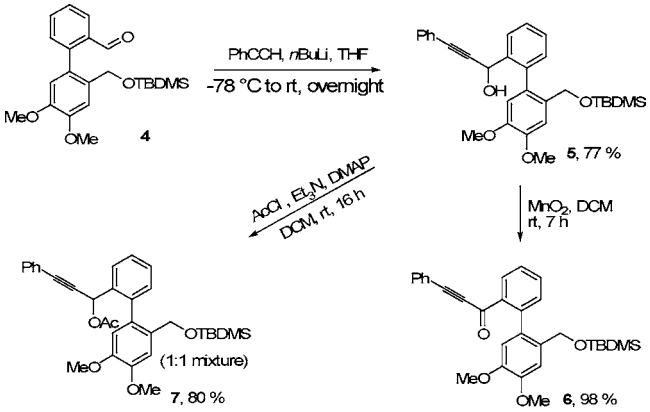
Table 1. Optimization Experiments for the Cross-Coupling of TDDMS Ether **3** with (2-Formylphenyl)boronic Acid[a]

entry	base	catalyst	solvent	time (min)	*T* (°C)	yield (%)
1	$NaHCO_3$	$Pd(Ph_3P)_4$	DMF−H_2O (1:1)	10	150	35
2	K_3PO_4	$Pd(Ph_3P)_4$	*n*-BuOH	15	125	42
3	Cs_2CO_3	$Pd(Ph_3P)_4$	*n*-BuOH	15	125	36
4	K_3PO_4	$(Ph_3P)PdCl_2$	*n*-BuOH	15	125	44
5	K_3PO_4	$Pd(Ph_3P)_4$	*n*-BuOH	15	100	46
6	K_3PO_4	$Pd(Ph_3P)_4$	*n*-BuOH	15	150	20
7	$NaHCO_3$	$Pd(Ph_3P)_4$	*n*-BuOH	15	125	31
8	K_3PO_4	$Pd(Ph_3P)_4$	*n*-BuOH	30	125	21
9	K_3PO_4	$Ni(dppp)Cl_2$	*n*-BuOH	15	125	0
10	K_3PO_4	$(Ph_3P)PdCl_2$	$PhCH_3$−H_2O (1:1)	15	120	0
11	K_3PO_4	$Pd(Ph_3P)_4$	dioxane−EtOH (1:1)	15	130	63
12	K_3PO_4	$Pd(Ph_3P)_4$	dioxane−EtOH (2:1)	15	130	68
13	$NaHCO_3$	$Pd(Ph_3P)_4$	dioxane−EtOH (2:1)	15	130	68
14	Cs_2CO_3	$Pd(Ph_3P)_4$	dioxane−EtOH (2:1)	15	130	77
15	Cs_2CO_3	$Pd(Ph_3P)_4$	dioxane−EtOH (2:1)	180[a]	102	42

[a] All reactions were carried out on 0.5 mmol of bromide with 1.3 equiv of boronic acid, 3.0 equiv of base, and 5 mol % of catalyst under microwave irradiation conditions in 4 mL of solvent at a maximum power level of 150 W. All reactions were carried out using a ramp time of 2 min and a hold time as indicated in the table. [a] Reaction was performed under conventional heating.

The thus obtained biaryl aldehyde **4** was then transformed into the corresponding propargylic alcohol **5** via nucleophillic addition of phenylacetylene in the presence of *n*-BuLi (Scheme 4). The desired product **5** was isolated in 77% yield as a mixture of two diastereoisomers (3:2, based on ^1H NMR analysis), which were found to be inseparable. One part of the mixture of diastereomeric alcohols **5** was converted into the corresponding ketone **6** by oxidation with MnO_2 in CH_2Cl_2 in an excellent yield of 98%, to minimize the stereochemical problems, and in view of generating the hitherto unknown 7-aza-analogues of (−)-steganone.

Scheme 4. Formation of Propargylic Alcohol **5** and Further Conversion into the Intermediates **6** and **7**



The other part of the mixture was converted into the corresponding diastereomeric mixture of acetyl derivative **7**, to keep maximum semblance with (−)-Steganacin. Treatment of **5** with AcCl in the presence of Et_3N and a catalytic amount of DMAP in CH_2Cl_2 resulted in the formation of **7** in 80% yield (1:1 mixture of diastereoisomers, based on ^1H NMR analysis). The difference in the diastereomeric ratio of the C4 center, in comparison with the intermediate **5**, arises presumably from the increased steric crowding around the biaryl axis.

The deprotection of the TBDMS group in **6** and **7**, resulting in the formation of the corresponding primary alcohols **8** (Scheme 5) and **12**, was performed at rt under mild acidic conditions using a mixture of AcOH, THF, and H_2O (3:1:1). Alcohol **12** was isolated as a mixture of diastereoisomers (55:45, based on ^1H NMR analysis).

The formation of the target triazolo[1,5-*a*]azocin-4(13*H*)-one **11** was accomplished starting from alcohol **8** using a pseudo one-pot three-step reaction sequence: (1) Appel bromination[11] of alcohol **8** at rt, in the presence of CBr_4 and Ph_3P afforded the corresponding bromo derivative **9**; (2)

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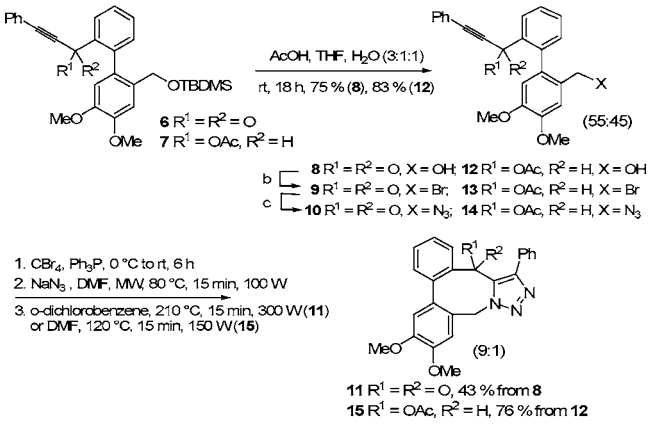
Scheme 5. Intramolecular Heterocyclization of Intermediates **6** and **7** to the Targets **11** and **15**



nucleophilic displacement of the bromo group with an azide functionality using NaN_3 in DMF at 80 °C under microwave-enhanced conditions resulted in the formation of **10**; and (3) microwave-assisted Huisgen 1,3-dipolar cycloaddition of the azide group to the acetylene fragment at 210 °C in *o*-dichlorobenzene as solvent (Scheme 5) yielded the desired target **11** in 43% overall yield. The three steps were performed in a consecutive manner, without the isolation of any of the intermediates. It is noteworthy that this cyclization, when carried out under conventional heating in refluxing *o*-dichlorobenzene for 48 h, failed to furnish the product **11** and the starting azide **10** was found untouched.

Dibenzotriazolo[1,5-*a*]azocine **15** was obtained from alcohol **12** applying a similar procedure in an excellent overall yield of 76%. It is noteworthy that the cyclization of the azide **14** into the target triazolo[1,5-*a*]azocine **15** was possible at a much lower temperature of 120 °C than for compound **11**. This fact can be explained by the lower rigidity of the eight-member ring of compound **15** compared to compound **11**, resulting in a lower activation energy for the reaction. The cyclization of **14** was found to be highly diastereoselective, generating the isomers **15** in a ratio of 9:1. However, the isomers were found to be inseparable applying different chromatographic separations including HPLC. The major isomer was assigned to be diastereomer **15**-(*S*) based on NOE experiments and computational calculations (with SYBYL 7.0 software for molecular modeling) using energy minimization experiments. The high diastereomeric excess of this cyclization could be explained in terms of the high ring strain of the fused heterocyclic skeleton of the target molecule. This was further confirmed by the high torsional energy of the minor diastereomer **15**-(*R*) (18.25 kcal/mol), in comparison with the **15**-(*S*) (11.22 kcal/mol) (Figure 2).

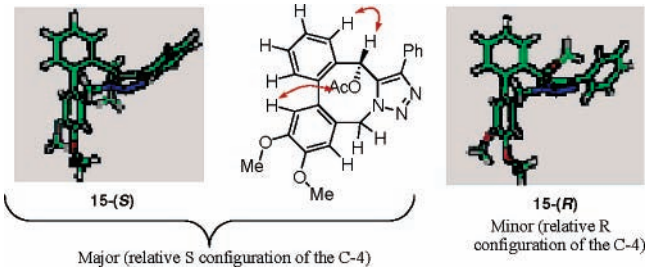


Figure 2. Conformation of the diastereomers according to torsional energy calculations and some indicative NOE-correlations.

In conclusion, we have developed a novel microwave-enhanced synthetic protocol for the formation of new 7-aza analogues of (−)-steganacin and (−)-steganone. The key steps of this methodology, the Suzuki−Miyaura cross-coupling and the Huisgen 1,3-dipolar cycloaddition reactions, were performed under MW irradiation, which was found to be highly beneficial in promoting these reactions. The generated compounds are under current investigation to test their anti-carcinogenic activity.

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Supporting Information Available: Detailed experimental procedures and characterization data for compounds **1**−**15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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