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Diversity Oriented Microwave-Assisted Synthesis of (−)-Steganacin Aza-Analogues

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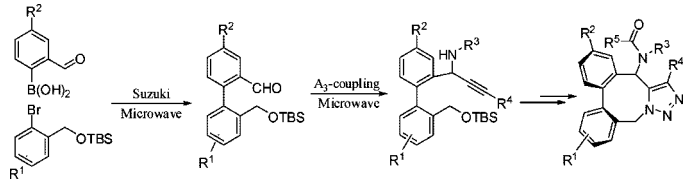

A novel microwave-assisted, highly efficient protocol for the synthesis of *hitherto* unknown aza-analogues of (−)-Steganacin, a naturally occurring bisbenzocyclooctadiene lignan lactone with potent antileukemic and tubulin polymerization inhibitory activity, has been developed. Focused microwave irradiation is demonstrated to be highly beneficial in promoting the three crucial steps of the sequence to effect the final ring closure: the Suzuki−Miyaura reaction, Cu-mediated A_3-coupling, as well as the intramolecular Huisgen 1,3-dipolar cycloaddition.

Introduction

(−)-Steganone and (−)-Steganacin, two bisbenzocyclooctadiene lignan lactones isolated in 1973 by the late S. M. Kupchan *et al*.,[1] have attracted substantial synthetic interest owing to their high biological potential (Figure 1). These naturally occurring lignan lactones possess significant *in vivo* activity against P-388 leukemia in mice and *in vitro* activity against cells derived from a human nasopharynx (KB) carcinoma cell line.[1] (−)-Steganacin inhibits in vitro polymerization of microtubules by 50% at about 2 μM and also binds to the mammalian tubulin with an affinity comparable to that of colchicine.[2] In the light of the increased demand for diversely functionalized structural analogues of the title molecules for biological screening as well as to solve the

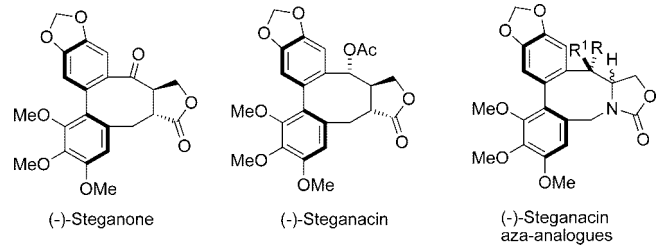

FIGURE 1. (−)-Steganone and (−)-Steganacin aza-analogues.

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problems associated with stereoselectivity, Koga[3] *et al*. proposed the synthesis of unnatural (−)-Steganacin 7-aza-analogues. Moreover, it was found that some of them exhibit *in vitro* and *in vivo* antitumor activity even higher than the corresponding natural lignan lactones.

There have been a plethora of reported protocols on the synthesis of these lignan lactones after the first total synthesis of (±)-Steganacin published in 1976 by Kende[4] and of (±)-Steganone by Raphael.[5] Since the generation of the biaryl backbone of the title molecules was deemed to be the key step, several coupling procedures have been investigated for this purpose, such as nonphenolic oxidative intramolecular coupling using either VOF_3,[4,6c,i,m,n,9] thallium,[6l] ruthenium,[7a,c,d] rhenium,[7b] manganese,[7b] or cerium[7b] reagents. However, this synthetic approach is highly sensitive to the nature of the substituents on both aromatic rings, as biaryl formation does not occur in the absence of electron-rich groups. Other strategies like photocyclization,[5,6a,b,n,p] SNAr reaction,[6a] or Ullmann coupling[2c,6c,e−h,j] generally suffer from lower yields as well as sensitive conditions and longer reaction times, and are often associated with the problem of homodimerization.[8] Even though the Suzuki−Miyaura reaction has been demonstrated to be a viable method for the selective generation of the biaryl skeleton of these compounds,[6r,t,u,9b] this mild and efficient cross-coupling protocol has never been investigated for the generation of more potent aza-analogues whose, synthesis has hardly been explored.[3a,b,10a,b]

We have recently reported an efficient, microwave-assisted protocol for the synthesis of *hitherto* unknown triazole analogues of (−)-Steganacin and (−)-Steganone, based on a combination of Suzuki−Miyaura cross-coupling and Huisgen 1,3-dipolar cycloaddition reaction.[10c] Although the 1,2,3-triazole moiety does not occur in natural products, this might be an interesting structural unit as it is stable to metabolic transformations, such as oxidation, reduction, and both basic and acidic hydrolysis. Additionally, somewhat as a result of the increased current interest in click chemistry, 1,2,3-triazole moieties are rising as potent pharmacophores themselves.[11] We now wish to report a strategy for the synthesis of aza-analogues allowing the introduction of five points of diversity in the system.

Results and Discussion

The synthesis of the proposed aza-analogues is based on a Suzuki−Miyaura cross-coupling reaction to generate the biaryl axis,[9b,12] followed by an A_3-coupling reaction[13] and subsequent ring closure applying "click chemistry".[14] These three key reactions are performed upon microwave irradiation (Scheme 1).

According to our previous investigations,[10c] our sequence started from the commercially available methoxy-substituted benzyl alcohols **1a** (R^1 = H) and **1b** (R^1 = OMe) which were regioselectively brominated with NBS in CCl_4 affording the corresponding 2-bromoalcohols **2a**,**b** in 70% and 74% yield, respectively (Scheme 2).[15] Subsequently, the alcohols **2a**,**b** were

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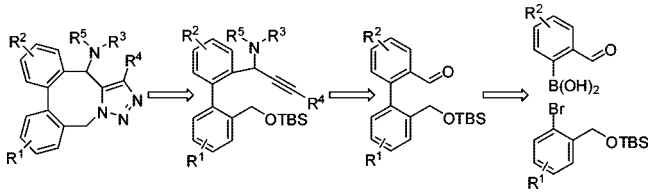
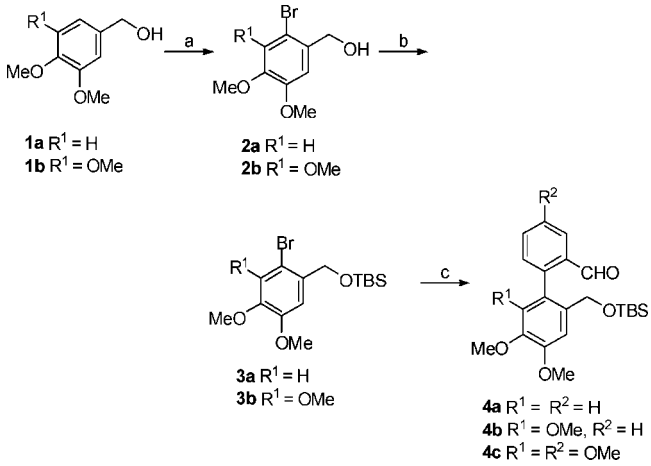
SCHEME 1. Retrosynthetic Analysis



SCHEME 2. Synthesis of the Biaryl Compounds 4a−c[a]

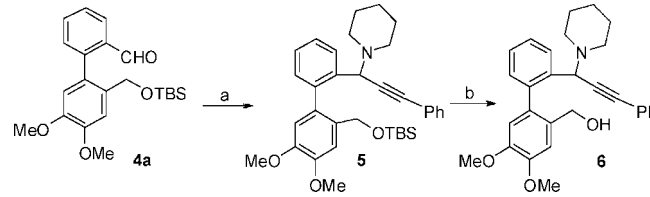


[a] Reagents and conditions: (a) NBS (1.0 equiv), CCl_4, rt, 4 h, 70% (**2a**), 74% (**2b**); (b) TBS-Cl (1.3 equiv), 1*H*-imidazole (3.0 equiv), DMF, rt, 6 h, 96% (**3a**), 94% (**3b**); (c) 2-(formyl) phenyl boronic acid (1.3 equiv), $Pd(Ph_3P)_4$ (5 mol %), Cs_2CO_3 (3.0 equiv), dioxane/2-PrOH (2:1), MW, 130 °C, 15 min, 150 W, 77% (**4a**), 80% (**4b**), 82% (**4c**).

protected as the corresponding TBS derivatives by treatment with *tert*-butyldimethylsilyl chloride (TBS-Cl) in DMF in the presence of 1*H*-imidazole,[6g,15a,c] and the resulting silyl ethers **3a**,**b** were isolated in excellent yields of 96% and 94%, respectively (Scheme 2). The Suzuki−Miyaura cross-coupling reaction of the silyl ethers **3a**,**b** with 2-formylphenylboronic acid and 2-formyl-4-methoxyphenylboronic acid were carried out under microwave irradiation conditions with dioxane/isopropanol (2:1) affording the corresponding biaryl intermediates **4a−c** in yields of 77%, 80%, and 82%, respectively. Only trace amounts of protodeboronation and homocoupling were detected.

Our next goal was the introduction of an additional point of diversity applying an A_3-coupling reaction. This is a multicomponent reaction involving a suitable aldehyde, an amine, and an alkyne, resulting in the formation of a propargylic amine. Reppe[16] performed the first example of A_3-coupling in 1955 using a copper salt as catalyst. In recent years, several catalysts have been used for this reaction, such as salts of Cu,[13f,k,l,p,17] Ni,[13a] Ir,[13c,n] Au,[13i] Ag,[13o,q] Hg,[13u] as well as Cu in combination with chiral ligands[13g,s,w,x] or ionic liquids.[13h,m,t] It has been demonstrated that the reaction highly benefits from microwave irradiation.[13h,k,l] As a proof of concept we investigated the A_3-coupling of aldehyde **4a** with piperidine and phenylacetylene. We chose to investigate simple Cu(I)-based catalytic systems (Scheme 3).

SCHEME 3. A_3-Coupling of Biaryl Aldehyde 4a[a]



[a] Reagents and conditions: (a) phenylacetylene (2.0 equiv), piperidine (1.5 equiv), CuCl (10 mol %), [bmim]PF_6 (1 drop), dioxane, MW, 140 °C, 20 min, 60 W, 70%; (b) AcOH/THF/H_2O (3:1:1), rt, 18 h, 82%.

Initially, CuI was used in water as the sole solvent (Table 1, entry 1) under microwave irradiation at 80 °C, following the procedure described by Shi et al.[13k] However, the reaction met with failure, since the corresponding imine was isolated as the only product. Therefore, we attempted to perform the reaction as a two-step process (Table 1, entry 2), following the procedure described by Li et al.[13y] The imination was carried out previously by reacting the aldehyde and the amine in DMF for 2 h at 60 °C. Then phenylacetylene and the catalyst, a mixture of CuBr (30 mol %) and $RuCl_3 \cdot 3H_2O$ (3 mol%), were added at rt. Disappointingly, as in the previous case, only the imine was isolated after a reaction time of 20 h. However, when the reaction was performed in a one-pot fashion upon microwave irradiation with CuBr as catalyst in THF at a ceiling temperature of 120 °C for 20 min (Table 1, entry 3), the desired propargyl amine was isolated in a moderate yield of 56%, after chromatographic purification. In view of improving the yield, we investigated the use of 1,4-dioxane containing 0.1 mL of the ionic liquid [bmim]PF_6[13j] using CuCl as catalyst (Table 1, entry 4). After 20 min of reaction time at a ceiling temperature of 150 °C, using a maximum irradiation power of 60 W, the desired propargylamine was isolated in 67% yield. Increasing the irradiation power to 150 W (Table 1, entry 5) resulted in a lower yield of 60%. However, carrying out the reaction at 140 °C with a maximum irradiation power of 60 W provided the amine **5** in 70% yield (Table 1, entry 6).

The deprotection of the benzylic alcohol of **5** (Scheme 3) was attempted by applying a solution of 2 equiv of tetrabutylammonium fluoride in THF at rt for 3 h. However, only starting material was isolated. On the contrary, when **5** was treated with a mixture of AcOH/THF/H_2O (3:1:1) at rt for 18 h, a diastereomeric mixture (55:45) of alcohol **6** was isolated in 82% yield.

Next, the formation of the target compound **9** was attempted by using our previously developed one-pot three-step reaction sequence[10c] (Scheme 4): Appel bromination[18] of alcohol **6** at rt was carried out for the generation of the corresponding benzyl bromide **7** followed by nucleophilic displacement of the bromide with azide to generate the corresponding benzyl azide **8**. However, final microwave-assisted intramolecular Huisgen 1,3-dipolar cycloaddition did not work and resulted in the formation of a complex mixture presumably caused by an intramolecular ring closure of the amine on the *in situ* generated bromide in **7**, followed by degradation. Alternative brominating procedures using HBr (48% in water), HBr (33% in AcOH), PBr_3, NBS + PBr_3, and TMSBr or strategies using $SOCl_2$ or CH_3SO_2Cl met with failure.

To evaluate whether the amine is causing the problem, we decided to decrease the nucleophilicity by converting it into

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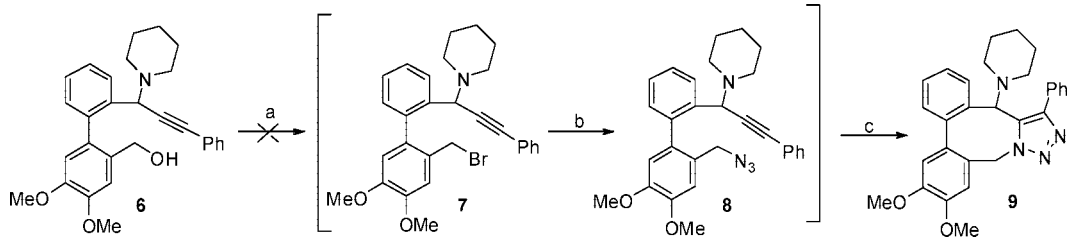
TABLE 1. Optimization of the A_3-Coupling of 4a, Using Microwave Irradiation[a]

entry	**4a**:piperidine: PhC≡CH	temp (°C)	time (min)	power (W)	solvent	catalyst (mol %)	yield[b,c] (%)
1	1:1.3:1.6	80	30	150	H_2O	CuI (15)	0[d]
2[e]	1:1.2:1.2	rt	1200		DMF	CuBr (30) $RuCl_3.3H_2O$ (3)	0[d]
3	1:1.2:1.2	120	20	150	THF	CuBr (8)	56 (51:49)
4	1:1.5:2	150	20	60	dioxane + [bmim]PF_6[f]	CuCl (10)	67 (50:50)
5	1:1.5:2	150	20	150	dioxane + [bmim]PF_6[f]	CuCl (10)	60 (50:50)
6	1:1.5:2	140	20	60	dioxane + [bmim]PF_6[f]	CuCl (10)	70 (48:52)

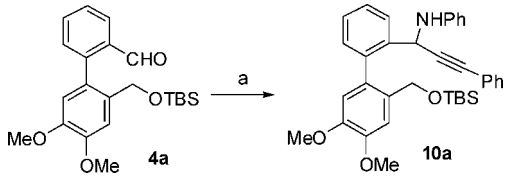
[a] All reactions were carried out on a 1.0 mmol scale in 4 mL of solvent. [b] Yields are isolated yields of the diastereomeric mixtures. [c] Values in parentheses indicate the diastereomeric ratios as determined by NMR spectroscopy. [d] Only imine was formed. [e] The reaction was performed in two steps; the imination was performed previously in DMF at 60 °C for 2 h. [f] 0.1 mL of ionic liquid was used.

SCHEME 4. Attempt for the Synthesis of the Final Product 9[a]



[a] Reagents and conditions: (a) CBr_4 (3.0 equiv), Ph_3P (3.0 equiv), 0 °C to rt, 6 h; (b) NaN_3 (3.0 equiv), DMF, MW, 80 °C, 20 min, 25 W; (c) DMF, MW, 120 °C, 15 min, 50 W.

SCHEME 5. Reinvestigation of the A_3-Coupling of 4a with Aniline As the Primary Amine[a]



[a] Reagents and conditions: (a) Phenylacetylene (3.0 equiv), aniline (1.5 equiv), CuBr (5 mol %), neat, MW, 90 °C, 15 min, 100 W.

TABLE 2. Reinvestigation of the A_3-Coupling of 4a with Aniline As Primary Amine[a]

entry	**4a**:aniline: PhC'CH	temp (°C)	time (min)	power (W)	solvent	catalyst (mol %)	yield (%)[b]
1	1:1.5:2	140	20	60	dioxane + [bmim]PF_6[c]	CuCl (10)	0[d]
2[e]	1:1.2:1.2	rt	1200		DMF	CuBr (30) $RuCl_3 \cdot 3H_2O$ (3)	0[d]
3	1:1.5:3	120	15	100	THF	CuBr (5)	55
4	1:1.5:3	120	15	100	neat	CuBr (5)	65
5	1:1.5:3	90	15	100	neat	CuBr (5)	89
6	1:1.5:3	60	15	100	neat	CuBr (5)	35[f]

[a] All reactions were carried out on a 1.0 mmol scale in 4 mL of solvent. [b] Yields are isolated yields of the diastereomeric mixtures. [c] 0.1 mL of ionic liquid was used. [d] Only imine was formed. [e] The reaction was performed in two steps; the imination was previously performed in DMF at 60 °C for 2 h. [f] Incomplete reaction.

the corresponding acetamide. However, to validate this concept, a primary amine should be introduced during the A_3-coupling reaction. A careful literature survey revealed that in the case where the A_3-coupling is run with primary amines, mostly (substituted) anilines are used.[13f,j,m,w] Therefore, as a proof of concept, we chose aniline to reinvestigate the A_3-coupling reaction of aldehyde **4a** with phenylacetylene (Scheme 5).

Initially, we applied the previously optimized reaction conditions for the A_3-coupling when piperidine was used as amine (Table 2, entry 1). To our surprise, the reaction met with failure as only the imine was recovered. An attempt to carry out the coupling in two steps (Table 2, entry 2) by first forming the imine followed by microwave-assisted reaction of phenylacetylene in the presence of CuBr (30 mol %) and $RuCl_3.3H_2O$ (3 mol %) as the catalyst system (same conditions as in Table 1, entry 2) also met with failure as the imine was isolated as the sole product. However, microwave-assisted reaction of the aldehyde **4a** with 1.5 equiv of aniline and 3 equiv of phenylacetylene in the presence of CuBr as the catalyst in THF at a ceiling temperature of 120 °C for 15 min furnished the propargylamine **10a** in a moderate yield of 55% (Table 2, entry 3). When this reaction was carried out under solvent-free conditions, the desired propargylamine was isolated in a good yield of 65% (Table 2, entry 4). The yield could be further improved up to 89% by lowering the temperature to 90 °C and applying these solvent-free conditions (Table 2, entry 5). Further lowering the temperature to 60 °C resulted in an incomplete reaction as mainly imine was isolated (Table 2, entry 6).

In view of generating a small library of the target aza-analogues, the A_3-coupling reaction was performed by applying a set of differently substituted anilines (R^3), alkynes (R^4), and biaryl aldehydes (R^1 and R^2) (Table 3).

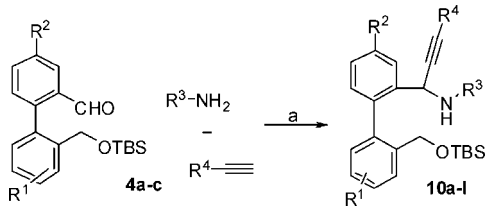
In all cases, except when *n*-butylamine was used (Table 3, entry 2), the A_3-coupling worked well when aldehyde **4a** and phenylacetylene were involved, and the resulting compounds were isolated in good to excellent yields of 73−89% (Table 3, entries 1−8). Interestingly, the steric and electronic demands imposed by the substituents of the anilines did not noticeably influence the outcome of the reaction. In the case of *n*-butylamine, a moderate yield of 42% was obtained as a complex reaction mixture was formed, hampering product isolation (Table 3, entry 2). This was not totally unexpected, as the literature revealed a handful of examples where primary alkyl amines were employed for A_3-coupling,[13f,h,i,x] mostly resulting in low yields. For further increasing diversity, various acetylenes were investigated applying our optimized microwave-assisted A_3-coupling protocol. When **4a** was reacted with 4-fluorophenyl acetylene and 4-fluoroaniline, corresponding propargylamine **10i** was obtained in 82% yield. Upon reaction of trimethylsilylacetylene with aldehyde **4a** and *m*-trifluoromethylaniline, the corresponding propargylamine **10j** was isolated in 82% yield

TABLE 3. A_3-Coupling Reaction with Various Primary Amines for the Generation of Propargylamines 10a−*l*

entry	compd[a]	R^1	R^2	R^3	R^4	temp (°C)	yield (%)[b,c]
1	**10a**	3,4-OMe	H	Ph	Ph	90	89(51:49)
2	**10b**	3,4-OMe	H	*n*-Bu	Ph	90	42(50:50)
3	**10c**	3,4-OMe	H	4-OMe-Ph	Ph	60	73(48:52)
4	**10d**	3,4-OMe	H	4-F-Ph	Ph	90	86(50:50)
5	**10e**	3,4-OMe	H	2-Me-Ph	Ph	90	87(58:42)
6	**10f**	3,4-OMe	H	3,4-di-Cl-Ph	Ph	90	87(46:54)
7	**10g**	3,4-OMe	H	2-pyridine	Ph	90	89(65:35)
8	**10h**	3,4-OMe	H	3-Br-Ph	Ph	120	86(55:45)
9	**10i**	3,4-OMe	H	4-F-Ph	4-F-Ph	90	82(55:45)
10	**10j**	3,4-OMe	H	3-CF_3-Ph	TMS[d]	120	82(49:51)
11	**10k**	3,4,5-OMe	H	Ph	Ph	90	81(51:49)
12	**10l**	3,4,5-OMe	OMe	3-CF_3-Ph	Ph	90	85(50:50)

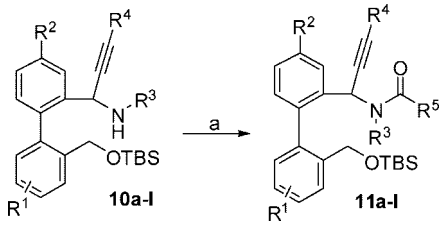
[a] All reactions were carried out upon microwave irradiation (100 W, 15 min) on a 1.0 mmol scale with 3.0 equiv of alkyne, 1.5 equiv of amine, and 5 mol % of CuBr. [b] Yields are isolated yields. [c] Values in parentheses indicate the diastereomeric ratio of the product obtained as determined by NMR; [d] TMS = trimethylsilyl.

SCHEME 6. Generation of a Small Library via A_3-Coupling[a]



[a] Reagents and conditions: (a) alkyne (3.0 equiv), amine (1.5 equiv), CuBr (5 mol %), neat, MW, 15 min, 100 W.

SCHEME 7. Acylation of the Propargylamines 11a−*l*[a]



[a] Reagents and conditions: (a) $(R^5CO)_2O$ (2.5 equiv), MeCN, MW, 150 °C, 30 min, 300 W.

(Table 3, entry 10). For further increasing diversity the aldehydes **4b**,**c** were used (Scheme 6) rendering the desired products **10k** and **10*l*** in 81% and 85% yield, respectively (Table 3, entries 11 and 12).

Next the newly generated propargylamines **10a**−***l*** were protected, in view of decreasing the nucleophilicity of the nitrogen. However, attempts at Boc-protection of propargylamine **10a** resulted in no reaction as all starting material was recovered, presumably owing to the steric bulk of the substrate and reagent. Acylation of **10a** (Scheme 7) with classical conditions as acetic anhydride in the presence of triethylamine, pyridine, or diisopropylethylamine as the base at 0 °C resulted in low yields of the target amide **11a**. Switching to acetyl chloride did not solve the problem. However, microwave-assisted acylation with acetic anhydride (2.5 equiv) in acetonitrile at a ceiling temperature of 150 °C for 30 min at 300 W maximum irradiation power furnished the desired acetamide **11a** in 75% yield (Table 4, entry 1).

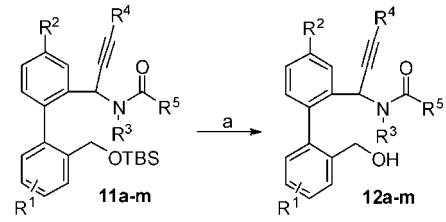
Analogously, all other generated propargylamines **10b**−***l*** yielded the acetamides **11b**−***l*** in yields ranging from 70% to 78% (Table 4, entries 1−12) next to an array of unidentified side compounds.

TABLE 4. Acylation of the Propargylamines 11a−m

entry	compd[a]	R^1	R^2	R^3	R^4	R^5	yield (%)[b]
1	**11a**	3,4-OMe	H	Ph	Ph	Me	75
2	**11b**	3,4-OMe	H	*n*-Bu	Ph	Me	70
3	**11c**	3,4-OMe	H	4-OMe-Ph	Ph	Me	78
4	**11d**	3,4-OMe	H	4-F-Ph	Ph	Me	72
5	**11e**	3,4-OMe	H	2-Me-Ph	Ph	Me	78
6	**11f**	3,4-OMe	H	3,4-diCl-Ph	Ph	Me	75
7	**11g**	3,4-OMe	H	2-pyridine	Ph	Me	76
8	**11h**	3,4-OMe	H	3-Br-Ph	Ph	Me	74
9	**11i**	3,4-OMe	H	3-CF_3-Ph	TMS	Me	73
10	**11j**	3,4-OMe	H	4-F-Ph	4-F-Ph	Me	75
11	**11k**	3,4,5-OMe	H	Ph	Ph	Me	76
12	**11*l***	3,4,5-OMe	OMe	3-CF_3-Ph	Ph	Me	78
13	**11m**	3,4-OMe	H	Ph	Ph	CF_3[c]	96

[a] All reactions were carried out on 1.0 mmol scale in 4 mL of CH_3CN upon microwave irradiation (300 W, 30 min), using 2.5 equiv of acetic anhydride. [b] Yields are isolated yields. [c] TFAA (2.5 equiv), pyridine. TFAA = trifluoroacetic anhydride.

SCHEME 8. Deprotection of the Hydroxyl Group in 11a−m[a]



[a] Reagents and conditions: (a) AcOH, THF, H_2O (3:1:1), rt, 18 h.

TABLE 5. Deprotection of the Hydroxyl Group in 11a−m to Generate 12a−m

entry	compd[a]	R^1	R^2	R^3	R^4	R^5	yield (%)[b]
1	**12a**	3,4-OMe	H	Ph	Ph	Me	75
2	**12b**	3,4-OMe	H	*n*-Bu	Ph	Me	78
3	**12c**	3,4-OMe	H	4-OMe Ph	Ph	Me	90
4	**12d**	3,4-OMe	H	4-F-Ph	Ph	Me	89
5	**12e**	3,4-OMe	H	2-Me-Ph	Ph	Me	87
6	**12f**	3,4-OMe	H	3,4-diCl-Ph	Ph	Me	84
7	**12g**	3,4-OMe	H	2-pyridine	Ph	Me	82
8	**12h**	3,4-OMe	H	3-Br-Ph	Ph	Me	84
9	**12i**	3,4-OMe	H	3-CF_3-Ph	TMS→H[c]	Me	72
10	**12j**	3,4-OMe	H	4-F-Ph	4-F-Ph	Me	87
11	**12k**	3,4,5-OMe	H	Ph	Ph	Me	83
12	**12*l***	3,4,5-OMe	OMe	3-CF_3 Ph	Ph	Me	86
13	**12m**	3,4-OMe	H	Ph	Ph	CF_3	89

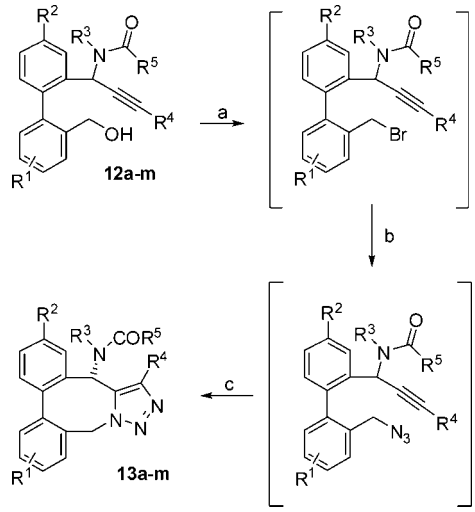
[a] All reactions were carried out on a 1.0 mmol scale in 4 mL of AcOH/THF/H_2O (3:1:1) at rt for 18 h. [b] Yields are isolated yields. [c] 3.0 equiv of TBAF was used to deprotect the hydroxyl group and the acetylene moiety simultaneously.

As acylation could be used to generate diversity in the target aza-analogues, propargylamine **10a** was reacted with trifluoroacetic anhydride in DCM for 2 h at rt with pyridine as base yielding the corresponding trifluoroacetamide **11m** in an excellent yield of 96% (Table 4, entry 13).

The TBS protective group was easily removed upon stirring with AcOH/THF/H_2O (3:1:1) for 18 h at rt, yielding the corresponding alcohols **12a**−**h** and **12j**−**m** in 75−90% yield (Scheme 8, Table 5).

In the case of the TMS-substituted propargylamine **12i**, 3 equiv of tetrabutylammonium fluoride (TBAF) was used to

SCHEME 9. Cyclization of the Intermediates 12a−m to the Target Triazolodibenzo[1,5-*a*]azocines 13a−m[a]



[a] Reagents and conditions: (a) CBr_4 (3.0 equiv), PPh_3 (3.0 equiv), 0 °C to rt, 6 h; (b) NaN_3 (3.0 equiv), DMF, MW, 80 °C, 20 min, 25 W; (c) DMF, MW, 120 °C, 15 min, 50 W.

TABLE 6. Yields of the Cyclized Final Products 13a−m

entry	compd[a]	R^1	R^2	R^3	R^4	R^5	yield (%)[b]
1	**13a**	3,4-OMe	H	Ph	Ph	Me	59
2	**13b**	3,4-OMe	H	*n*-Bu	Ph	Me	47
3	**13c**	3,4-OMe	H	4-OMe-Ph	Ph	Me	50
4	**13d**	3,4-OMe	H	4-F-Ph	Ph	Me	49
5	**13e**	3,4-OMe	H	2-Me-Ph	Ph	Me	48
6	**13f**	3,4-OMe	H	3,4-diCl-Ph	Ph	Me	43
7	**13g**	3,4-OMe	H	2-pyridine	Ph	Me	0
8	**13h**	3,4-OMe	H	3-Br-Ph	Ph	Me	52
9	**13i**	3,4-OMe	H	3-CF_3-Ph	H	Me	51
10	**13j**	3,4-OMe	H	4-F-Ph	4-F-Ph	Me	52
11	**13k**	3,4,5-OMe	H	Ph	Ph	Me	49
12	**13*l***	3,4,5-OMe	OMe	3-CF_3-Ph	Ph	Me	47
13	**13m**	3,4-OMe	H	Ph	Ph	CF_3	50

[a] All reactions were carried out on a 0.1 mmol scale. [b] Yields are calculated over three steps.

deprotect the hydroxyl group and the acetylene moiety simultaneously (Table 5, entry 9).

Thus, having all required key intermediates **12a−m** at hand, we focused our attention on one-pot three-step cyclization for the generation of the target aza-analogues **13a−m** (Scheme 9). Our optimized procedure[10c] was attempted applying alcohol **12a**. Appel bromination of alcohol **12a** with CBr_4 and PPh_3 at rt proceeded smoothly, affording the corresponding benzyl bromide (TLC- and MS-monitoring), which was not isolated. The nucleophilic displacement of the bromo group with azide functionality, using NaN_3 in DMF at 80 °C under microwave irradiation, resulted in the formation of the corresponding azide (TLC- and MS-monitoring). Finally, the intramolecular Huisgen 1,3-dipolar cycloaddition reaction was performed upon microwave irradiation at a ceiling temperature of 120 °C in DMF furnishing the target molecule **13a** in an overall yield of 59% (Table 6, entry 1). The three steps were performed consecutively, without isolation of the intermediates. Interestingly, the ^{1}H NMR spectrum of **13a** indicated the presence of only one diastereoisomer after final cyclization. Analogously, the other alcohols **12b−m** were subjected to this optimized *pseudo* one-pot three-step protocol (Table 6), furnishing the target aza-analogous **13b−m** as single diastereoisomers in overall yields ranging from

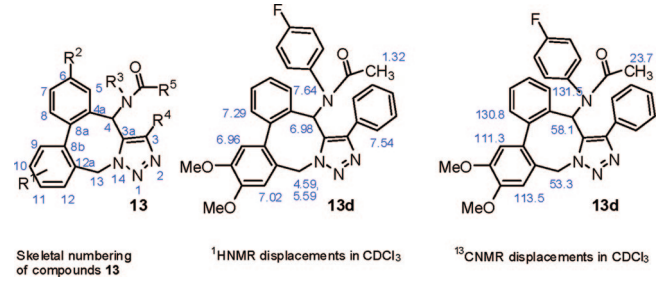


FIGURE 2. Numbering and the key ^{1}H and ^{13}C NMR displacements.

43% to 52%. In the case of compound **12g**, which was generated with 2-aminopyridine during A_3-coupling, no cyclized compound **13g** could be isolated (Table 6, entry 7). Probably, the pyridine nitrogen causes problems during bromination.

Stereochemical Discussion: Surprisingly, in comparison with our previous observations,[10c] the cyclization of the intermediate azides was found to result in the formation of only one of the two possible diastereoisomers of compounds **13a−m**. Therefore, a detailed NMR analysis of compound **13d** was performed. Both protons C-13 (Figure 2) are showing up as only two doublets at δ 4.59 and 5.59 ppm clearly indicating the presence of only one diastereomer.[10c] This high diastereoselectivity during ring closure could probably be explained by the severe steric bulk around the biaryl axis, caused by the densely substituted nitrogen at C-4.

^{1}H, ^{13}C, DEPT, 2D HMBC, HMQC, and NOESY were used to confirm the structure and to assign unambiguously the various ^{1}H and ^{13}C nuclei (see Figure 2). On the basis of ^{1}HNMR, three well-separated singlets (δ 6.96, 6.98, 7.02 ppm) were observed. Two of the three are directly correlated via HMQC with the aromatic carbons, δ 6.96 ppm with δ 111.3 ppm and δ 7.02 ppm with δ 113.5 ppm. The third singlet at δ 6.98 ppm corresponds with the methine carbon at δ 58.1 ppm and is an aliphatic proton. Hence, from the above results, it was seen that the proton signals at δ 6.96 and 7.02 ppm belong to the aromatic protons on the ring C-9 and C-12 while the proton signal at δ = 6.98 ppm belongs to C-4 (Figure 2).

Then NOESY correlation confirms the proposed structure and the assignment of the various protons. The aliphatic proton (δ 6.98 ppm) correlates with the aromatic doublet (δ 7.64 ppm) and with the ortho proton (δ 7.54 ppm) of the phenyl ring. The ^{1}H singlet at δ 6.96 ppm correlates with the aromatic doublet (δ 7.29 ppm) and the ^{1}H singlet at δ 7.02 ppm correlates with the aliphatic methylene protons (δ 4.59 and 5.59 ppm). Finally the most interesting NOESY correlation allows the determination of the obtained diastereomer. It is the correlation between the $-CH_3$ protons (δ 1.32 ppm) of the acetamide and the aromatic proton at (δ 6.96 ppm) revealing a spatial proximity between these two nuclei. Moreover the rather high field chemical shift of the acetamide at δ 1.32 ppm suggests an influence of the magnetic anisotropy of the ring R_1.

To investigate the possibility of the formation of the *R* and *S* diastereomers of **13d**, both were modeled using MOE with the MMFF94 force field (chemical computing group) in the *R* and *S* conformation (Figure 4). We could clearly see a difference in total energy between the *R* (184.8 kcal/mol) and the *S* (164.4 kcal/mol) conformation. This difference can be explained by the higher ring strain of the eight-membered ring in the *R* diastereomer. Furthermore, these models show that the distance between the protons of the acetamide group and the

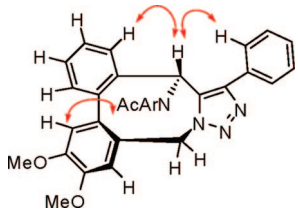


FIGURE 3. Structure of isomer **13**-(*S*) and NOE correlations.

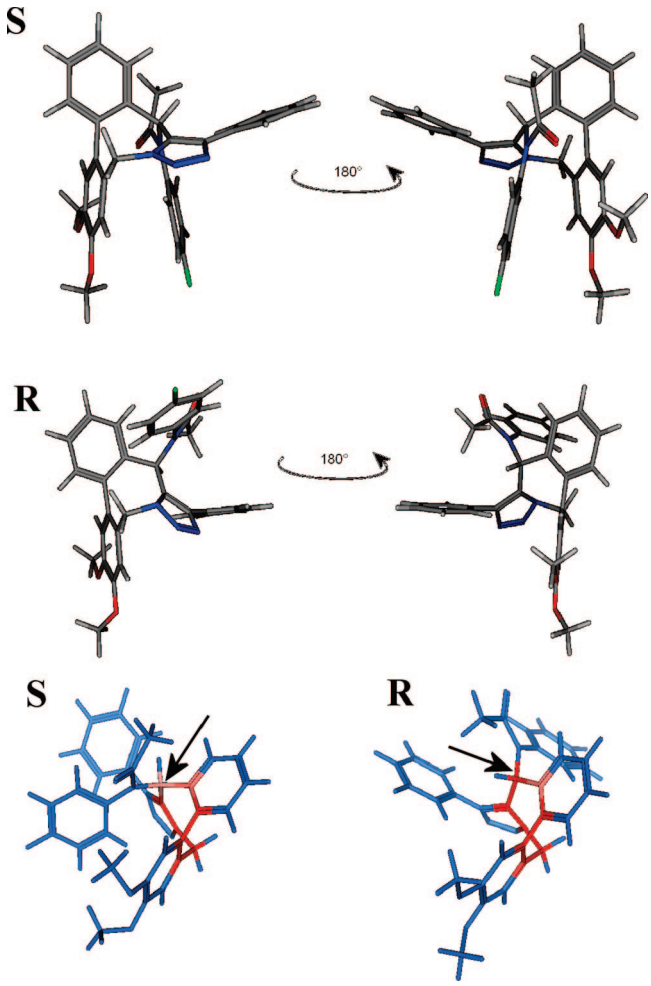


FIGURE 4. MOE models for the molecule **13d**.

proton at C-9 is 5.12 Å for the *R* diastereomer and 4.0 Å for the *S* isomer being in accordance with the observed NOE correlation indicating that only the *S* diastereomer is formed. In Figure 4 the upper part shows the conformation of the **13d** molecule in the ***S*** and ***R*** conformation, while the lower part shows the molecules colored by force (blue to red). We can clearly see that the strain in the *R* conformation is higher (more red) compared to the *S* conformation. Hence we could conclude that the increased steric bulk at the C-4 position is responsible for the high torsional energy observed for the minor **13**-(*R*) isomer and hence this results in the exclusive formation of diastereomer **13**-(*S*) (Figure 3).

Finally, X-ray crystallographic analysis[20] fully confirmed the structure of compound **13d**.

(20) See the Supporting Information for the X-ray structure. CCDC-687382 contains the supplementary crystallographic data for structure **13d**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.com.ac.uk/data_request/cif.

Conclusion

To conclude, we have developed a novel microwave-assisted synthetic protocol for the formation of *hitherto* unknown aza-analogues of (−)-Steganacin. We prepared a small library of diversely functionalized target molecules, starting from cheap and readily available benzyl alcohols, and proved the versatility of this methodology. The key steps of this novel protocol highly benefit from focused microwave irradiation, as the reactions proving to be faster and cleaner. Microwave-assisted A_3-coupling was performed as a handy tool to impart additional diversity to the strategy. Furthermore, the formation of the rigid, medium-sized, and fused ring systems of the title molecules greatly benefited from focused microwave irradiation and the title molecules were generated in high overall yields and purity. Exclusive diastereoselectivity was observed during the cyclization process, furnishing only the **13**-(*S*)-isomer of the target molecules. These compounds are under current investigation to identify their antileukemic and tubulin polymerization inhibitory activities.

Experimental Section

General Procedure for the Synthesis of Propargylamines 10a−*l* via A_3-Coupling. CuBr (7 mg, 5 mol%), alkyne (3.0 mmol, 3.0 equiv), aldehydes **4a**, **4b**, and **4c** (1.0 mmol, 1.0 equiv), and amine (1.5 mmol, 1.5 equiv) were placed in a 10 mL reaction vial containing a stirring bar. The vial was kept under argon for 30 s and then sealed tightly with a Teflon septum and placed into the microwave cavity. It was irradiated at a ceiling temperature of 90 °C, using 100 W maximum power, for 20 min. Then the reaction mixture was rapidly cooled with gas jet cooling to ambient temperature. The crude product was purified by column chromatography [silica gel, heptane/EtOAc (9:1) with 1% TEA] affording the propargylamine **10a−*l*** as a light yellow oil.

Synthesis of {1-[2′-(*tert*-Butyldimethylsilanyloxymethyl)-4′,5′-dimethoxybiphenyl-2-yl]-3-phenylprop-2-ynyl}phenylamine (10a). Compound **10a** was synthesized as described in the general procedure with **4a** as the aldehyde (387 mg, 1 mmol), aniline (140 mg, 1.5 mmol), and phenylacetylene (306 mg, 3.0 mmol) at a ceiling temperature of 90 °C. Column chromatography [silica gel, heptane/EtOAc (9:1) with 1% TEA] afforded propargylamine **10a** (502 mg, 89%) as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (q, 1H, J = 7.3 Hz), 7.53−7.07 (m, 12H), 6.84 (d, 1H, J = 16.6 Hz), 6.73 (q, 1H, J = 7.3 Hz), 6.56 (d, 1H, J = 7.6 Hz), 6.47 (d, 1H, J = 7.6 Hz), 5.30 (d, 1H, J = 5.6 Hz), 4.50 (d,1H, J = 13.2 Hz), 4.44 (d, 1H, J = 13.2 Hz), 3.97, 3.95 (s, 3H), 3.81, 3.48 (s, 3H), 0.91 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.8, 147.7, 146.8, 146.4, 139.5, 139.4, 139.0, 132.1, 132.0, 131.8, 131.2, 130.2, 130.1, 129.5, 129.3, 128.7, 128.6, 128.2, 128.0, 123.3, 123.2, 118.9, 118.8, 114.3, 113.2, 110.9, 90.1, 89.8, 85.1, 84.6, 63.2, 56.4, 56.2, 55.9, 48.6, 48.0, 26.4, 18.8, −4.9; MS (EI): 563 (M^+), 413 (100); HRMS (EI) *m*/*z* calcd for $C_{36}H_{41}O_3NSi$ [M^+] 563.2855, found 563.2852.

General Procedure for the Acetylation of Propargylamines 11a−m. To a solution of compounds **10a−*l*** (1.0 mmol) in acetonitrile (2.5 mL) was added acetic anhydride (255 mg, 2.5 mmol) in a 10 mL reaction glass vial containing a stirring bar. The vial was kept under argon for 30 s and then sealed tightly with a Teflon septum and placed into the microwave cavity. It was irradiated at a ceiling temperature of 150 °C, using 300 W maximum power, for 30 min. Then the reaction mixture was rapidly cooled with gas jet cooling to ambient temperature. The crude mixture was washed with a saturated solution of $NaHCO_3$ (50 mL) and extracted with EtOAc (50 mL). The organic layer was separated and the aqueous layer was further extracted with EtOAc (3 × 15 mL). The combined organic fractions were dried over anhydrous

$MgSO_4$ and then evaporated under reduced pressure to afford crude acetylated product as a pale yellow oil. Column chromatography [silica gel heptane/EtOAc (9:1) with 1% TEA] afforded pure compound **11a**−**m** as a yellow oil.

Synthesis of *N*-{1-[2′-(*tert*-Butyldimethylsilanyloxymethyl)-4′,5′-dimethoxybiphenyl-2-yl]-3-phenylprop-2-ynyl}-*N*-phenylacetamide (11a). Compound **11a** was synthesized from **10a** (564 mg, 1.0 mmol) as described in the general procedure. Column chromatography [silica gel heptane/EtOAc (9:1) with 1% TEA] afforded acetylated product **11a** (454 mg, 75%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−6.8 (m, 16H), 6.72, 6.69 (s, 1H), 4.51 (d, J = 13.2 Hz), 4.35 (d, 1H, J = 13.2 Hz), 3.96, 3.84 (s, 3H), 3.94, 3.84 (s, 3H), 1.67, 1.65 (s, 3H), 0.91, 0.88 (s, 9H), 0.07 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 168.5, 148.9, 148.7, 147.5, 143.0, 140.0, 139.9, 139.5, 135.7, 131.7, 131.5, 130.8, 130.7, 130.4, 130.3, 129.9, 129.8, 128.8, 128.2, 128.0, 127.0, 123.9, 113.2, 113.1, 112.4, 110.7, 110.6, 87.7, 87.5, 86.9, 86.0, 62.8, 62.3, 56.1, 55.8, 48.8, 48.0, 25.9, 22.8, 22.5, 18.3, −5.4; MS (EI) 605 (M^+), 338 (100); HRMS (EI) m/z calcd for $C_{38}H_{43}O_4NSi$ [M^+] 605.2962, found 605.2959.

General Procedure for the Deprotection of the TBDMS Group To Afford the Corresponding Alcohols 12a−m. To the TBS-protected alcohols **11a**−**m** was added a mixture of AcOH:THF:H_2O (3:1:1) (25 mL). The solution was stirred at room temperature for 18 h. The reaction mixture was diluted with water (50 mL), washed with a saturated solution of $NaHCO_3$ (50 mL), and extracted with EtOAc. The organic layer was separated and the aqueous layer was further extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure to yield the crude product as a yellow oil. Column chromatography [silica gel heptane/EtOAc (2:1)] afforded analytically pure products **12a**−**m**.

Synthesis of *N*-[1-(2′-Hydroxymethyl-4′,5′-dimethoxybiphenyl-2-yl)-3-phenylprop-2-ynyl]-*N*-phenylacetamide (12a). Compound **12a** was synthesized from **11a** (606 mg, 1.0 mmol) as described in the general procedure. Column chromatography [silica gel heptane/EtOAc (2:1)] afforded product **12a** (369 mg, 75%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (br s, 4H,), 7.34−7.08 (m, 7H), 6.95 (br s, 3H), 6.77 (d, 2H, J = 13.0 Hz), 6.58 (s, 1H), 4.61 (dd, 2H, J = 11.7, 4.5 Hz), 4.41 (d, 1H, J = 11.7 Hz), 3.98, 3.97, 3.84, 3.79 (s, 6H), 1.73, 1.61 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 148.2, 148.4, 147.8, 140.8, 140.3, 140.0, 139.7, 138.8, 136.0, 132.8, 132.0, 131.7, 131.6, 131.3, 131.1, 130.5, 129.4, 129.2, 129.1, 128.8, 128.6, 128.0, 127.7, 127.6, 124.1, 123.9, 123.1, 122.9, 113.7, 113.3, 112.7, 112.0, 89.5, 87.8, 87.2, 87.1, 62.7, 56.5, 56.4, 56.3, 51.0, 45.3, 23.9; MS (EI) 491 (M^+), 225 (100); HRMS (EI) m/z calcd for $C_{32}H_{29}O_4N$ [M^+] 491.2097, found 491.2103.

General Procedure for the Synthesis of Triazolo[1,5-*a*]azocines (13a−m). To a solution of alcohols **12a**−**m** (0.10 mmol) and CBr_4 (99 mg, 0.30 mmol) in freshly distilled THF (10 mL) at 0 °C was slowly added under stirring a solution of Ph_3P (79 mg, 0.30 mmol) in THF (2 mL). The reaction mixture was allowed to warm to room temperature, and the stirring was continued for an additional 6 h. The colorless precipitate (Ph_3P═O) was then filtered off and the solvent was removed under reduced pressure to furnish the crude bromide. This was dissolved in dry DMF (1 mL) and the solution was placed in a 10 mL reaction vial containing a small magnetic stirring bar. NaN_3 (20 mg, 0.30 mmol) was added and the vial was sealed tightly with a Teflon crimp top. It was irradiated at a ceiling temperature of 80 °C, using 25 W as maximum power, for 20 min. Then the reaction mixture was rapidly cooled with gas jet cooling to ambient temperature. After this irradiation period, the solution of crude azide was additionally irradiated at a ceiling temperature of 120 °C, using 50 W as maximum power, for 15 min. Then the reaction mixture was rapidly cooled with gas jet cooling to ambient temperature. Water (30 mL) was added and the product was extracted with diethyl ether (3 × 30 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure to furnish the crude product as a yellowish oil. Column chromatography [silica gel heptane/EtOAc (2:1)] afforded the products **13a**−**m**.

Synthesis of *N*-(10,11-Dimethoxy-3-phenyl-4,13-dihydrodibenzo-[*d*,*f*][1,2,3]triazolo[1,5-*a*]azocin-4-yl)-*N*-phenylacetamide (13a). Compound **13a** was synthesized from **12a** (49 mg, 0.10 mmol) as described in the general procedure. Column chromatography [silica gel heptane/EtOAc (2:1)] afforded product **13a** (30 mg, 59%, over the 3 steps) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, 1H, J = 7.6 Hz), 7.51−7.47 (m, 7H), 7.27 (dd, 2H, J = 7.6, 1.5 Hz), 7.03−7.00 (m, 1H), 7.00 (d, 2H, J = 10.8 Hz,), 6.94 (s, 1H), 6.84 (br s, 2H), 6.11 (br s, 1H), 5.59 (d, 1H, J = 14.7 Hz), 4.60 (d, 1H, J = 14.7 Hz), 3.97 (s, 3H), 3.93 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 150.3 149.3, 148.3, 140.2, 138.5, 137.6, 137.2, 136.3, 131.6, 131.2, 130.9, 128.9, 128.8, 128.6, 128.3, 127.9, 123.4, 113.6, 111.4, 58.2, 56.5, 56.3, 53.4, 23.8; MS (EI) 516 (M^+), 225 (100); HRMS (EI) m/z calcd for $C_{32}H_{28}O_3N_4$ [M^+] 516.2161, found 516.2154.

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Supporting Information Available: Detailed experimental description, spectral data (NMR, HRMS), and copies of spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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