DOI: 10.1002/adsc.200900287

A New Approach to Pyrrolocoumarin Derivatives by Palladium-Catalyzed Reactions: Expedient Construction of Polycyclic Lamellarin Scaffold

Lei Chen[a] and Ming-Hua Xu[a,b,*]

[a] Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zuchongzhi Road, Shanghai 201203, People's Republic of China
Fax: (+86)-21-5080-7388; e-mail: xumh@mail.shcnc.ac.cn
[b] State key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zuchongzhi Road, Shanghai 201203, People's Republic of China

Received: April 22, 2009; Published online: August 5, 2009

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200900287.

Abstract: A new and efficient protocol for straightforward synthesis of chromeno[3,4-*b*]pyrrol-4(3*H*)-one derivatives by palladium-catalyzed sequential coupling/cyclization reactions has been developed. The key strategy relies on creation of pyrrole ring through palladium-catalyzed intramolecular hydroamination of related acetylenic aminocoumarins. The synthetic utility of the obtained chromeno[3,4-*b*]pyrrol-4(3*H*)-one product has been demonstrated by the expedient synthesis of polycyclic lamellarin scaffold in four steps. It provides a new entry to synthesis of potentially valuable lamellarin analogues.

Keywords: coumarin derivatives; cross-coupling; hydroamination; lamellarin; palladium

Introduction

Coumarin derivatives are known as an important class of compounds and are present in a large number of naturally occurring substances as well as medicinally useful agents. They often exhibit a broad range of biological and pharmacological activities, such as antifungal, antibacterial, antitumor, anti-HIV, antibiotic, antioxidant, and anti-inflammatory.[1] Therefore, the synthesis and screening of coumarin compounds has been the subject of constant interest in the past several decades, and tremendous efforts have been devoted by organic chemists to the development of new methodologies for the synthesis of diverse coumarin derivatives.[2] Among them, the construction of libraries of coumarin compounds that are structurally related to bioactive natural products has received particular attention.[3] Ningalins and lamellarins are two important families of marine alkaloids that both possess an interesting pyrrolocoumarin (chromeno[3,4-*b*]pyrrol-4(3*H*)-one) subunit, as represented by ningalin B and lamellarin D in Figure 1. They have exhibited a variety of potentially valuable biological properties including cytotoxicity, HIV-1 integrase inhibition, multidrug resistance (MDR) reversal, and immunomodulatory activity.[4] Recently, we have become interested in these polyheterocyclic natural products for drug discovery and envisioned the possible structural modification while preserving the common pyrrolocoumarin nucleus to explore the structure-activity relationship (SAR).

Despite numerous studies on the synthesis of coumarin derivatives with broad structural diversity, synthetic methods for the efficient and straightforward construction of chromeno[3,4-*b*]pyrrol-4(3*H*)-one units have been scare. In ningalins and lamellarins syntheses, the strategies employed often involve the

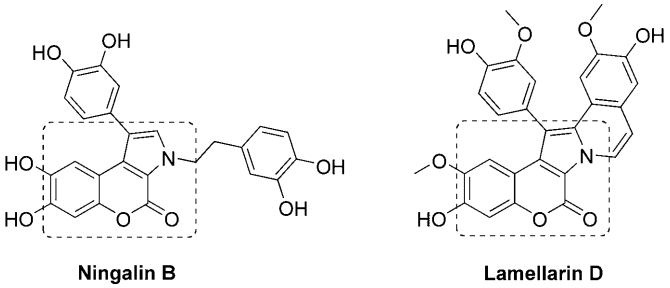


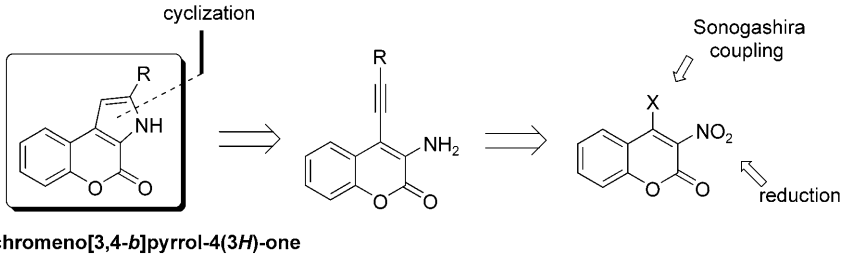
Figure 1. Natural products with chromeno[3,4-*b*]pyrrol-4(3*H*)-one subunit.

multi-step preparation of a highly functionalized pyrrole core followed by lactonization.[5] To the best of our knowledge, there were only two reports employing the strategy of direct formation of the pyrrole ring by classic Fischer indole synthesis[6] and Claisen rearrangement[7] using simple 3-aminocoumarins as the starting point. Unfortunately, both methods suffered from the inaccessibility of highly diversified chromeno[3,4-*b*]pyrrol-4(3*H*)-one products; new approaches with broader reaction generality are greatly desirable. Considering the remarkable development of transition metal-catalyzed coupling reactions on the 3- or 4-position of coumarins in recent years,[8] we envisaged that the direct construction of the pyrrole ring could be expected to be achieved by cyclization of the key intermediate 4-acetylenyl-3-aminocoumarin, whereby this cyclization precursor should be readily accessed after Sonogashira coupling and nitro reduction of the corresponding 3,4-disubstituted coumarin. Thus, diversification on the pyrrole ring could be efficiently realized by easily tuning the starting alkynes in the step of the Sonogashira reaction (Scheme 1). In this paper, we wish to report our successful development of such a new and straightforward approach to the synthesis of chromeno[3,4-*b*]pyrrol-4(3*H*)-one derivatives using a palladium-catalyzed sequential coupling/cyclization strategy.

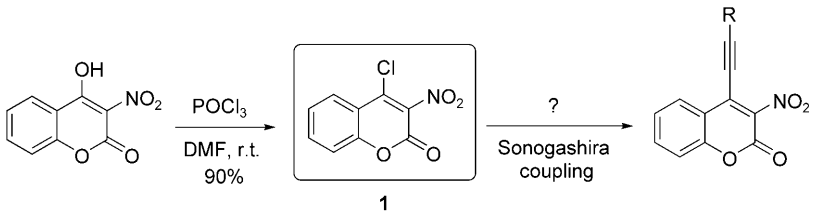
Results and Discussion

Following the above strategy, initial experiments were carried out to synthesize the necessary 4-halogeno-3-nitro- or 4-trifluoromethanesulfonyloxy-3-nitrocoumarin. Under the conditions of 67% HNO_3/HOAc at 80 °C, nitration of the readily available 4-hydroxycoumarin went smoothly to give the corresponding 4-hydroxy-3-nitrocoumarin product in high yield (90%). Unfortunately, triflation of 4-hydroxy-3-nitrocoumarin with trifluoromethanesulfonic anhydride was found to be unsuccessful, mostly probably due to the poor stability of the resulting product containing two strong electron-withdrawing groups. We then decided to convert the 4-hydroxy group into a halogen. Since there are difficulties in preparing 4-bromocoumarins,[9] we turned our attention to 4-chloro-3-nitrocoumarin which could be easily accessed by the reaction of 4-hydroxy-3-nitrocoumarin with $POCl_3$ in DMF at room temperature.[10] In the past ten years, significant progress has been made in the area of transition metal-catalyzed coupling reactions of aryl chlorides.[11] Although aryl chlorides, in general, are poorly reactive, those very electron-deficient ones have been known to serve as suitable substrates for palladium-catalyzed coupling reactions. Accordingly, in our case of 4-chloro-3-nitrocoumarin (**1**), *the C−Cl bond at the C-4 position on the coumarin ring could be activated by the strong electron-withdrawing effect of the neighboring nitro and ester carbonyl groups*, thus enabling the smooth Sonogashira cross-coupling with terminal alkynes (Scheme 2).

Under the conditions of a catalytic amount of $Pd(PPh_3)_2Cl_2$ and CuI, we examined the potential of Sonogashira reaction between 4-chloro-3-nitrocoumarin (**1**) and hexyne in THF at room temperature. With Et_3N as the base, the result is disappointing and no desired product was obtained (Table 1, entry 1). To our delight, when K_2CO_3 was used as base, the coupling reaction proceeded and gave the expected product **2a** in 45% yield in the presence of 20 mol% of $Pd(PPh_3)_2Cl_2$ and CuI (entry 2). Interestingly, a decrease of the catalyst loading to 10 mol% led to a dra-

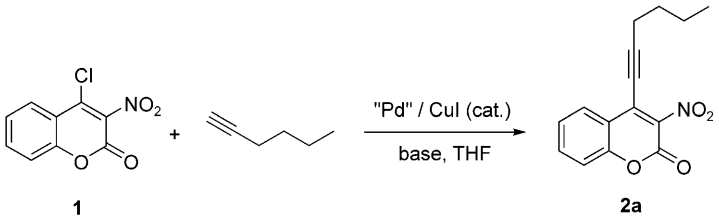


Scheme 1. New strategy for synthesis of chromeno[3,4-*b*]pyrrol-4(3*H*)-ones.



Scheme 2. Synthesis of 4-chloro-3-nitrocoumarin as coupling substrate.

Table 1. Screening of catalytic system for Sonogashira coupling.



1 **2a**

Entry[a]	Catalytic system (mol%)	T [°C]	Base	t [h]	Yield [%][b]
1	$Pd(PPh_3)_2Cl_2$/CuI (20)	r.t.	Et_3N	24	0
2	$Pd(PPh_3)_2Cl_2$/CuI (20)	r.t.	K_2CO_3	24	45
3	$Pd(PPh_3)_2Cl_2$/CuI (10)	r.t.	K_2CO_3	24	79
4	$Pd(PPh_3)_2Cl_2$/CuI (10)	50	K_2CO_3	12	35
5	$Pd(PPh_3)_2Cl_2$/CuI (5)	r.t.	K_2CO_3	48	46
6	$Pd(PPh_3)_2Cl_2$/CuI (10)	r.t.	Cs_2CO_3	24	50
7	$Pd(PPh_3)_4$/CuI (10)	r.t.	K_2CO_3	48	48
8	$Pd(OAc)_2/PPh_3$/CuI (20)	r.t.	K_2CO_3	48	24
9	$Pd(OAc)_2/P(o\text{-Tolyl})_3$/CuI (20)	r.t.	K_2CO_3	48	23
10	$Pd(PhCN)_2Cl_2$/CuI (20)	r.t.	K_2CO_3	48	trace

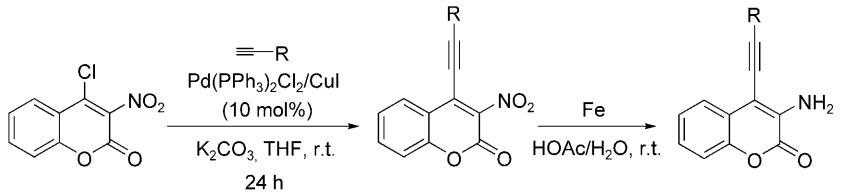
[a] Reaction was carried out with **1** (0.50 mmol) and hexyne (0.60 mmol) in freshly distilled THF (10 mL) under nitrogen atmosphere.
[b] Isolated yield.

matic improvement of the reaction yield to a good level (79%, entry 3). Other attempts including the change of palladium catalysts and increasing the reaction temperature did not afford better results (entries 4–10).

With optimal reaction conditions identified, the scope of the methodology was further investigated by the coupling of coumarin chloride **1** with various alkynes. It was found that aliphatic alkynes including trimethylsilylacetylene could typically work well, but aromatic alkynes are unlikely to be proper substrates probably due to the inefficient transmetallation of aromatic copper(I) acetylide with Pd(0) species. To access the intermediates of 4-acetylenyl-3-aminocoumarins (**3a–d)**, the obtained coupling products **2a–d** were treated with iron powder in $HOAc/H_2O$ at room temperature to undergo a successful reduction (Scheme 3).

In order to extend the substrate generality of 4-acetylenylcoumarins, we decided to check the potential of another Sonogashira coupling of aromatic alkynes with 4-ethynyl-3-aminocoumarin (**4**) that is readily available by desilylation of compound **3d**. Very gratifyingly, the cross-coupling took place smoothly when various aryl iodides were employed under the standard Sonogashira cross-coupling conditions [$Pd(PPh_3)_4$/CuI/Et_3N] in THF at room temperature and was completed in 30 min, leading to a range of 4-arylethynyl-3-aminocoumarins in high yields (Table 2). Notably, no reaction occurred with aryl bromides under similar conditions.

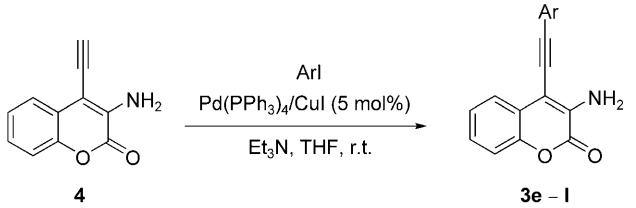
With a variety of 4-acetylenyl-3-aminocoumarin compounds (**3**a–**l**) in hand, we moved on to the key cyclization for constructing the corresponding pyrrolocoumarin framework. Intramolecular hydroamination of alkynes has become a promising method in organic chemistry that allows the straightforward syn-



1 **2a** R = $CH_3(CH_2)_3$, 79%
2b R = $BnO(CH_2)_3$, 60%
2c R = *t*-Bu, 93%
2d R = TMS, 73%
3a – d

Scheme 3. Sonogashira coupling with aliphatic alkynes and reduction.

Table 2. Preparation of 4-arylethynyl-3-aminocoumarins.



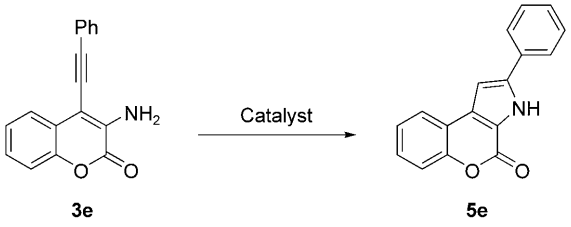
Entry[a]	Ar	3	Yield [%][b]
1	C_6H_5	**3e**	90
2	4-$MeOC_6H_4$	**3f**	90
3	4-$EtO_2CC_6H_4$	**3g**	85
4	2-MeC_6H_4	**3h**	80
5	1-Naphthyl	**3i**	88
6	4-$Me_2NC_6H_4$	**3j**	80
7	4-$AcNHC_6H_4$	**3k**	81
8	4-$PMBNHC_6H_4$	**3l**	75

[a] Reaction was carried out with **4** (1.00 mmol), aryl iodide (1.10 mmol), $Pd(PPh_3)_4$ (0.05 mmol), CuI (0.05 mmol), Et_3N (0.2 mL) in freshly distilled THF (20 mL) under nitrogen atmosphere.
[b] Isolated yield.

thesis of valuable nitrogen-containing heterocycles, especially those indole-like compounds. In recent years, great progress has been made in the development of catalytic hydroaminations of alkynes; various methods have been explored extensively.[12] Concerning intramolecular hydroaminations,[12a,b] however, the palladium catalyst is the most utilized. To find a good reaction system, several different metallic catalysts such as $Pd(PPh_3)_2Cl_2$,[13a,b] $Pd(OAc)_2$,[13c] $PdCl_2$,[13d] CuI,[13e] $InBr_3$,[13f] $In(OTf)_3$[13f] and $Zn(OTf)_2$[13g] were evaluated with 4-phenylacetylenyl-3-aminocoumarin **3e**. As indicated in Table 3, $Pd(PPh_3)_2Cl_2$ emerged as the best catalyst. In the presence of 10 mol% of $Pd(PPh_3)_2Cl_2$ in refluxing DMF, the expected heteroannulation of the acetylenic amine **3e** could be achieved in 60% yield. Other conditions including anionic cyclization[14] with *t*-BuOK, NaH, or KH only resulted in low yield or no reaction.

Upon establishing the reaction conditions of the key cyclization step, we then investigated the substrate scope of the methodology. A series of 4-acetylenyl-3-aminocoumarin precursors (**3a–l**) was subjected to hydroamination to synthesize various chromeno[3,4-*b*]pyrrol-4(3*H*)-one derivatives, the results are summarized in Table 4. In all cases, the desired pyrrolocoumarin products could be obtained in moderate to good yields. For arylacetylenic substrates **3j–l** with strong electron-donating R, it was found that the reaction proceeded very rapidly and was completed in 2 h (entries 9–11). In contrast, for substrate **3i** with the bulky α-naphthyl group attached to the triple bond, hydroamination proceeded very

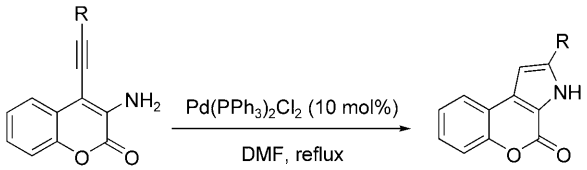
Table 3. Screening of catalyst for intramolecular hydro-amination.



Entry[a]	Catalyst (mol%)	Solvent	*T* [°C]	*t* [h]	Yield [%][b]
1	$Pd(PPh_3)_2Cl_2$ (10)	Toluene	reflux	NR[c]	–
2	$Pd(PPh_3)_2Cl_2$ (10)	DMF	reflux	5	60
3	$Pd(OAc)_2$ (10)	DMF	reflux	8	20
4	$PdCl_2$ (10)	CH_3CN	reflux	5	49
5	CuI (20)	DMF	reflux	8	40
6	$InBr_3$ (20)	Toluene	reflux	8	30
7	$In(OTf)_3$ (20)	Toluene	reflux	NR	–
8	$Zn(OTf)_2$ (20)	Toluene	reflux	NR	–
9	*t*-BuOK	NMP	r.t.	NR	–
10	NaH	NMP	r.t.	NR	–
11	KH	NMP	r.t.	NR	–

[a] Reaction was carried out with **3e** (0.50 mmol) in degassed solvent (5 mL) under nitrogen atmosphere.
[b] Isolated yield.
[c] NR: No Reaction.

Table 4. Synthesis of chromeno[3,4-*b*]pyrrol-4(3*H*)-one derivatives.



Entry[a]	3	R	5	*t* [h]	Yield [%][b]
1	**3a**	$CH_3(CH_2)_3$	**5a**	8	56
2	**3b**	$BnO(CH_2)_3$	**5b**	8	57
3	**3c**	*t*-Bu	**5c**	8	74
4	**3e**	C_6H_5	**5e**	5	60
5	**3f**	4-$MeOC_6H_4$	**5f**	5	83
6	**3g**	4-$EtO_2CC_6H_4$	**5g**	8	80
7	**3h**	2-MeC_6H_4	**5h**	8	75
8[c]	**3i**	1-Naphthyl	**5i**	36	70
9	**3j**	4-$Me_2NC_6H_4$	**5j**	2	73
10	**3k**	4-$AcNHC_6H_4$	**5k**	2	64
11	**3l**	4-$PMBNHC_6H_4$	**5l**	2	75

[a] Reaction was carried out with **3** (0.50 mmol), $Pd(PPh_3)_2Cl_2$ (0.05 mmol) in degassed DMF (5 mL) under nitrogen atmosphere unless otherwise noted.
[b] Isolated yield.
[c] Reaction was carried out with 30% catalyst loading.

slowly even in the presence of 30 mol% of $Pd(PPh_3)_2Cl_2$ catalyst and a prolonged time of 36 h was needed (entry 8). It is interesting to note that the structural X-ray investigation of **5a**[15] indicates that two molecules form intermolecular hydrogen bondings between each carbonyl oxygen and pyrrole N–H (Figure 2).

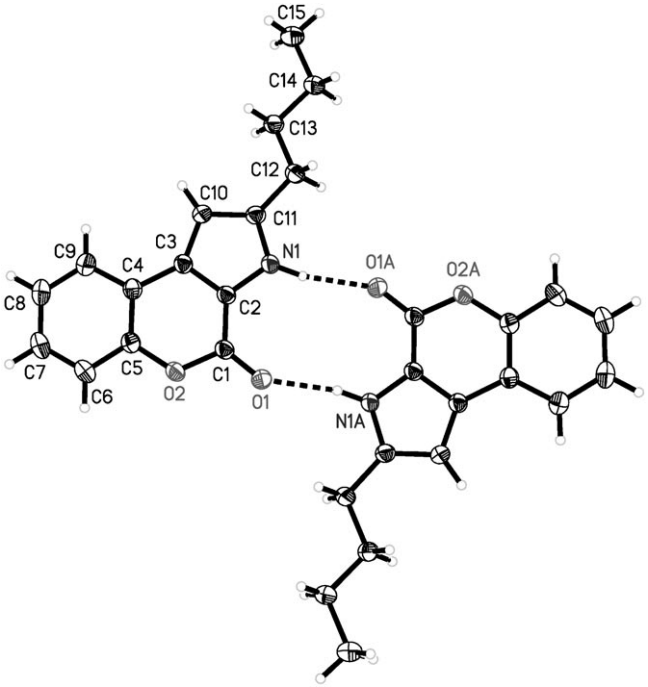
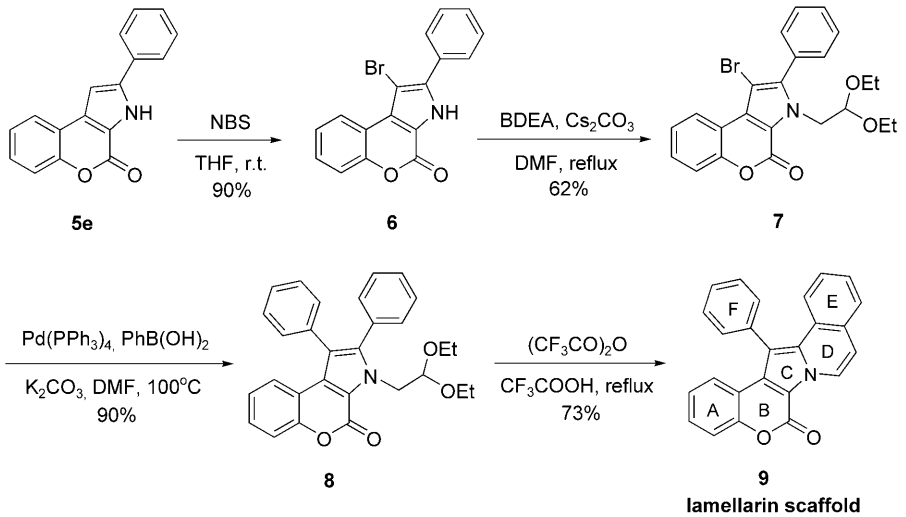


Figure 2. X-ray crystallography of **5a**.

To further demonstrate the synthetic value of this new methodology, we sought to explore the versatility of chromeno[3,4-*b*]pyrrol-4(3*H*)-one **5** for the expedient synthesis of the polycyclic lamellarins[4a] B, D, H, M, N, W, X scaffold (Scheme 4). Selective bromination on the pyrrole ring of 2-phenylchromeno[3,4-*b*]pyrrol-4(3*H*)-one **5e** with NBS at room temperature simply afforded bromide **6** in 90% yield. Condensation of **6** with bromoacetaldehyde diethyl acetal (BDEA) in refluxing DMF gave the corresponding acetal product **7**, which was then efficiently cross-coupled with phenylboronic acid *via* Suzuki coupling to provide **8** in good yield. Ring closure of **8** by treatment with $CF_3COOH/(CF_3CO)_2O$ under reflux according to Nordlander's acetal indolization procedure[16] successfully produced the polycyclic lamellarin scaffold **9** in 73% yield. It is noteworthy that diverse aryl groups for the E and F members could be readily introduced during the preparations of **3** (as in Table 2) and **8** *via* palladium-catalyzed Sonogashira and Suzuki coupling, respectively.

Conclusions

In summary, we have successfully developed a new and efficient protocol for the synthesis of an interesting class of pyrrolocoumarin compounds – chromeno-[3,4-*b*]pyrrol-4(3*H*)-ones. The key strategy relies on the creation of the pyrrole ring through palladium-catalyzed intramolecular hydroamination of related acetylenic aminocoumarins. It has been found that readily available 4-chloro-3-nitrocoumarin could serve as a suitable substrate to undergo smooth Sonogashira cross-coupling with aliphatic alkynes. The preparation of the corresponding arylacetylenylaminocoumarins involves immediate nitro reduction and desilylation of 4-trimethylsilylacetylenyl-3-nitrocoumarin, followed by another Sonogashira cross-coupling with aryl iodides. With the resulting chromeno[3,4-*b*]pyrrol-



Scheme 4. Expedient construction of polycyclic lamellarin scaffold.

4(3*H*)-one product, an expedient construction of polyheterocyclic lamellarin scaffold could be achieved in four steps. The method provides a useful option for the rapid synthesis of potentially valuable lamellarin analogues without pre-preparation of a highly functionalized pyrrole core. Given the abundance of natural products and biologically active compounds that contain the chromeno[3,4-*b*]pyrrol-4(3*H*)-one moiety, this methodology should find wide applications in medicinal chemistry. Access to more lamellarin analogues and evaluation of all these chromeno[3,4-*b*]pyrrol-4(3*H*)-one derivatives for biological effects are currently under way.

Experimental Section

General Procedure for Synthesis of Chromeno[3,4-*b*]pyrrol-4(3*H*)-ones (5)

Under a nitrogen atmosphere, a solution of **3** (0.5 mmol), $Pd(PPh_3)_2Cl_2$ (35 mg, 0.05 mmol) in DMF (5 mL) was stirred at reflux until TLC indicated completion of the reaction. The reaction mixture was cooled to room temperature and diluted with EtOAc. The organic layer was washed with water and dried over Na_2SO_4. After being concentrated under vacuum, the crude product was purified by column chromatography on silica gel to afford **5**.

2-Butylchromeno[3,4-*b*]pyrrol-4(3*H*)-one (5a): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.96$ (t, $J = 7.5$ Hz, 3H), 1.38–1.50 (m, 2H), 1.72–1.82 (m, 2H), 2.88 (t, $J = 7.2$ Hz, 2H), 6.47 (s, 1H), 7.26–7.45 (m, 3H), 7.75 (d, $J = 7.8$ Hz, 1H), 11.22 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.8$, 22.2, 27.7, 31.2, 100.8, 115.6, 117.2, 118.1, 123.2, 124.1, 127.5, 130.9, 146.5, 151.2, 156.0; anal. calcd. for $C_{15}H_{15}NO_2$: C 74.67, H 6.27, N 5.81; found: C 74.64, H 6.31, N 5.44.

2-(3-(Benzyloxy)propyl)chromeno[3,4-*b*]pyrrol-4(3*H*)-one (5b): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.04$–2.13 (m, 2H), 2.97 (t, $J = 7.5$ Hz, 2H), 3.58 (t, $J = 6.0$ Hz, 2H), 4.55 (s, 2H), 6.45 (s, 1H), 7.26–7.42 (m, 8H), 7.74 (d, $J = 7.2$ Hz, 1H), 10.67 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 25.0$, 29.0, 69.1, 73.0, 101.2, 115.9, 117.3, 118.1, 123.2, 124.1, 127.7 (2C), 127.8, 128.4, 130.7, 138.1, 145.1, 151.3, 155.7; HR-MS: $m/z =$ 334.1437, calcd. for $C_{21}H_{20}NO_3$ $[M+H]^+$: 334.1443.

2-*tert*-Butylchromeno[3,4-*b*]pyrrol-4(3*H*)-one (5c): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.46$ (s, 9H), 6.51 (s, 1H), 7.26–7.44 (m, 3H), 7.77 (d, $J = 7.8$ Hz, 1H), 10.42 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 30.1$, 32.5, 98.5, 116.0, 117.2, 118.1, 123.1, 124.1, 127.5, 130.3, 151.3, 154.7, 155.7; anal. calcd. for $C_{15}H_{15}NO_2$: C 74.67, H 6.27, N 5.81; found: C 74.89, H 6.25, N 5.55.

2-Phenylchromeno[3,4-*b*]pyrrol-4(3*H*)-one (5e): ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 7.32$–7.50 (m, 7H), 7.97–8.00 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 100.9$, 116.8, 117.2, 117.5, 123.5, 124.3, 125.8, 128.0, 128.6, 129.0, 129.9, 130.5, 142.3, 150.9, 154.0; HR-MS: $m/z = 261.0791$, calcd. for $C_{17}H_{11}NO_2$: 261.0790.

2-(4-Methoxyphenyl)chromeno[3,4-*b*]pyrrol-4(3*H*)-one (5f): ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 3.79$ (s, 3H), 7.03 (d, $J = 8.7$ Hz, 2H), 7.29–7.45 (m, 4H), 7.91–7.97 (m, 3H), 12.81 (bs, 0.18H); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 55.3$, 99.9, 114.4, 116.4, 116.8, 117.6, 123.1, 123.6, 124.3, 127.4, 128.0, 130.1, 142.4, 150.9, 153.9, 159.7; HR-MS: $m/z =$ 291.0898, calcd. for $C_{18}H_{13}NO_3$: 291.0895.

Ethyl 4-(4-oxo-3,4-dihydrochromeno[3,4-*b*]pyrrol-2-yl) benzoate (5g): ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 1.30$ (d, $J = 6.9$ Hz, 3H), 4.28 (d, $J = 6.9$ Hz, 2H), 7.33–7.47 (m, 4H), 7.92–8.02 (m, 5H), 13.08 (bs, 0.31H); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 14.2$, 60.8, 102.4, 116.8, 117.3, 118.0, 123.5, 124.4, 125.8, 128.1, 129.2, 129.6, 129.7, 134.8, 140.7, 150.9, 153.9, 165.3; HR-MS: $m/z = 334.1074$, calcd. for $C_{20}H_{15}NO_4$ $[M+H]^+$: 334.1079.

2-*o*-Tolylchromeno[3,4-*b*]pyrrol-4(3*H*)-one (5h): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.52$ (s, 3H), 6.81 (s, 1H), 7.26–7.52 (m, 7H), 7.82 (d, $J = 7.2$ Hz, 1H), 9.91 (s, 1H), 12.70 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 20.6$, 103.8, 116.3, 116.8, 117.7, 123.7, 124.3, 126.0, 128.0, 128.8, 129.4, 129.8, 130.8, 131.0, 136.1, 142.1, 150.9, 154.1; HR-MS: $m/z =$ 275.0951, calcd. for $C_{18}H_{13}NO_2$: 275.0946.

2-(Naphthalen-1-yl)chromeno[3,4-*b*]pyrrol-4(3*H*)-one (5i): ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 7.22$ (s, 1H), 7.32–7.75 (m, 3H), 7.58–7.73 (m, 4H), 8.01–8.18 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 104.7$, 116.7, 116.8, 117.7, 123.9, 124.4, 125.2, 125.5, 126.4, 127.1, 128.1 (2C), 128.5, 129.1, 129.2, 129.5, 130.8, 133.4, 141.0, 151.0, 154.1; HR-MS: $m/z =$ 311.0945, calcd. for $C_{21}H_{13}NO_2$: 311.0946.

2-(4-(Dimethylamino)chromeno[3,4-*b*]pyrrol-4(3*H*)-one (5j): ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 2.95$ (s, 6H), 6.77 (d, $J = 8.7$ Hz, 2H), 7.18 (s, 1H), 7.31–7.41 (m, 3H), 7.81 (d, $J = 8.7$ Hz, 2H), 7.95 (d, $J = 8.4$ Hz, 1H), 12.63 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 39.8$, 98.6, 112.1, 115.8, 116.7, 117.6, 118.0, 123.5, 124.1, 126.8, 127.8, 130.2, 143.6, 150.4, 151.0, 153.8; HR-MS: $m/z = 305.1284$, calcd. for $C_{19}H_{17}N_2O_2[M+H]^+$: 305.1290.

***N*-[4-(4-Oxo-3,4-dihydrochromeno[3,4-*b*]pyrrol-2-yl)phenyl]acetamide (5k):** ^{1}H NMR (300 MHz, DMSO-d_6): $\delta =$ 2.06 (s, 3H), 7.32–7.41 (m, 4H), 7.67 (d, $J = 8.7$ Hz, 2H), 7.90–7.97 (m, 3H), 10.10 (s, 1H), 12.85 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 24.1$, 100.2, 116.8, 117.6, 119.1, 123.6, 124.4, 125.2, 126.5, 128.1, 130.1, 139.6, 139.7, 142.3, 151.0, 154.0, 168.6; HR-MS: $m/z = 319.1077$, calcd. for $C_{19}H_{15}N_2O_3[M+H]^+$: 319.1083.

2-[4-(4-Methoxybenzylamino)phenyl]chromeno[3,4-*b*]-pyrrol-4(3*H*)-one (5l): ^{1}H NMR (300 MHz, DMSO-d_6): $\delta =$ 3.70 (s, 3H), 4.23 (d, $J = 5.7$ Hz, 2H), 6.59–6.60 (m, 1H), 6.64 (d, $J = 8.4$ Hz, 2H), 6.88 (d, $J = 8.1$ Hz, 2H), 7.12 (s, 1H), 7.26–7.39 (m, 5H), 7.68 (d, $J = 8.1$ Hz, 2H), 7.93 (d, $J =$ 7.5 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 45.6$, 55.0, 98.3, 112.3, 113.7, 115.7, 116.7, 117.6, 117.9, 123.5, 124.1, 126.9, 127.8, 128.4, 130.2, 131.6, 143.9, 149.2, 150.9, 153.8, 158.2; HR-MS: $m/z = 397.1547$, calcd. for $C_{25}H_{21}N_2O_3$ $[M+H]^+$: 397.1552.

Synthesis of 1-Bromo-2-phenylchromeno[3,4-*b*]-pyrrol-4(3*H*)-one (6)

To a flask was added 2-phenylchromeno[3,4-*b*]pyrrol-4(3*H*)-one **5e** (65 mg, 0.25 mmol), NBS (89 mg, 0.5 mmol) and THF (10 mL). The solution was stirred for 2 h and extracted with EtOAc, washed with water. The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by column chromatography (petroleum ether/acetone, 10/1) on silica gel to afford **6** as a

pale yellow solid; yield: 85 mg (90%); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.38$–7.55 (m, 6H), 7.80 (d, $J = 6.9$ Hz, 2H), 8.74 (d, $J = 7.5$ Hz, 1H), 10.21 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 90.6$, 117.7 (2C), 118.0, 123.1, 124.6, 126.5, 129.0, 129.2, 129.4, 129.9, 130.3, 140.3, 152.1, 153.9; MS (EI): $m/z = 339$ (M^+, 96.5), 341 (M^+, 100).

Synthesis of 1-Bromo-3-(2,2-diethoxyethyl)-2-phenylchromeno[3,4-*b*]pyrrol-4(3*H*)-one (7)

To a flask was added **6** (50 mg, 0.15 mmol), Cs_2CO_3 (325 mg, 1.0 mmol), bromoacetaldehyde diethyl acetal (150 μL, 1.0 mmol) and DMF (5 mL). The solution was stirred at reflux for 48 h until TLC indicated completion of reaction. The mixture was cooled to room temperature and diluted with EtOAc. The organic layer was washed with water and dried over Na_2SO_4. After concentrated under vacuo, the residue was purified by column chromatography (petroleum ether/EtOAc, 40/1) on silica gel to afford **7** as a white solid; yield: 42 mg (62%); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.09$ (t, $J = 6.9$ Hz, 6H), 3.36–3.46 (m, 2H), 3.57–3.67 (m, 2H), 4.46 (d, $J = 5.4$ Hz, 2H), 4.81 (t, $J = 5.4$ Hz, 1H), 7.31–7.57 (m, 8H), 8.72 (d, $J = 7.1$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 15.2$, 49.5, 64.0, 92.4, 102.1, 116.0, 117.1, 117.2, 123.0, 123.9, 126.6, 128.4, 128.5, 128.9, 129.5, 131.3, 144.6, 151.3, 154.5.

Synthesis of 3-(2,2-Diethoxyethyl)-1,2-diphenylchromeno[3,4-*b*]pyrrol-4(3*H*)-one (8)

Under a nitrogen atmosphere, a solution of **7** (26 mg, 0.058 mmol), $Pd(PPh_3)_4$ (12 mg, 0.01 mmol), phenylboronic acid (12 mg, 0.1 mmol) and K_2CO_3 in DMF (5 mL) was stirred at reflux for 1 hour. The reaction mixture was cooled to room temperature and diluted with EtOAc. The organic layer was washed with water and dried over Na_2SO_4. After concentrated under vacuum, the crude product was purified by column chromatography (petroleum ether/EtOAc, 30/1) on silica gel to afford **8** as a white solid; yield: 23 mg (90%); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.12$ (t, $J = 6.9$ Hz, 6H), 3.39–3.49 (m, 2H), 3.60–3.70 (m, 2H), 4.51 (d, $J = 5.4$ Hz, 2H), 4.92 (t, $J = 5.4$ Hz, 1H), 6.99 (t, $J = 7.8$ Hz, 1H), 7.20–7.41 (m, 13H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 15.3$, 48.8, 64.0, 102.5, 115.6, 117.1, 118.1, 119.9, 123.6, 123.7, 127.1, 127.3, 127.6, 128.1, 128.3, 128.5, 129.8, 131.0, 131.4, 134.2, 144.5, 151.4, 155.4.

Synthesis of the Lamellarin Scaffold (9)

A solution of 3-(2,2-diethoxyethyl)-1,2-diphenylchromeno-[3,4-*b*]pyrrol-4(3*H*)-one **8** (23 mg, 0.005 mmol) in $(CF_3CO)_2O$ (1 mL) and CF_3COOH (3 mL) under a nitrogen atmosphere was stirred at reflux for 48 h. The excess anhydride and acid were removed by distillation. The residue was added Et_3N (0.1 mL) and concentrated under vacuum. The crude product was purified by column chromatography (petroleum ether/EtOAc, 20/1) on silica gel to afford **9** as a white solid; yield: 13 mg (73%); ^{1}H NMR [300 MHz, $(CD_3)_2CO$]: $\delta = 6.88$–6.98 (m, 1H), 6.99–7.03 (m, 1H), 7.17–7.23 (m, 1H), 7.25–7.35 (m, 3H), 7.38–7.65 (m, 7H), 7.77 (d, $J = 7.8$ Hz, 1H), 9.19 (d, $J = 7.2$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 109.3$, 113.5, 114.3, 117.4, 117.9, 123.9, 124.1, 124.3, 124.4, 125.0, 127.3, 127.5, 128.2, 128.4, 128.7 (2C), 129.6, 129.9, 130.9, 134.1, 135.6, 151.7, 155.3; HR-MS: $m/z = 361.1101$, calcd. for $C_{25}H_{15}NO_2$: 361.1103.

Acknowledgements

Financial support from the National Natural Science Foundation of China (20721003), the Shanghai Rising-Star Program (08QH14027), the Chinese Academy of Sciences and State key Laboratory of Drug Research, Shanghai Institute of Materia Medica is acknowledged.

References

[1] a) R. O'Kennedy, R. Zhorenes, *Coumarins: Biology, Applications, Mode of Action*; Wiley, Chichester, **1997**; for reviews: b) D. L. Yu, M. Suzuki, L. Xie, S. L. Morris-Natschke, K. H. Lee, *Med. Res. Rev.* **2003**, *23*, 322; c) K. C. Fylaktakidou, D. J. Hadjipavlou-Litina, K. E. Litines, D. N. Nicolaides, *Curr. Pharm. Des.* **2004**, *10*, 3813; d) F. Borges, F. Roleira, N. Mihazes, L. Santana, E. Uriarte, *Curr. Med. Chem.* **2005**, *12*, 887.

[2] For selected examples see: a) D. V. Kadnikov, R. C. Larock, *Org. Lett.* **2000**, *2*, 643; b) B. M. Trost, F. D. Toste, K. Greenman, *J. Am. Chem. Soc.* **2003**, *125*, 4518; c) B. M. Trost, F. D. Toste, *J. Am. Chem. Soc.* **1996**, *118*, 6305; d) C. Jia, D. Piao, J. Oyamada, W. Lu, T. Kitamura, Y. Fujiwara, *Science* **2000**, *287*, 1992; e) C. Jia, W. Lu, J. Oyamada, T. Kitamura, K. Matsuda, M. Irie, Y. Fujiwara, *J. Am. Chem. Soc.* **2000**, *122*, 7252; f) C. Jia, D. Piao, T. Kitamura, Y. Fujiwara, Y. *J. Org. Chem.* **2000**, *65*, 7516–7522; g) Y. Yamamoto, N. Kirai, *Org. Lett.* **2008**, *10*, 5513.

[3] For selected examples see: a) K. Li, Y. Zeng, B. Neuenswander, J. A. Tunge, *J. Org. Chem.* **2005**, *70*, 6515; b) L. Zhang, T. Meng, R. Fan, J. Wu, *J. Org. Chem.* **2007**, ***72***, 7279; c) K. Li, J. A. Tunge, *J. Comb. Chem.* **2008**, *10*, 170; d) X. M. Yu, G. Shen, L. Neckers, H. Blake, J. Holzbeierlein, B. Cronk, B. S. J. Blagg, *J. Am. Chem. Soc.* **2005**, *127*, 12778; e) J. Neyts, E. D. Clercq, R. Singha, Y. H. Chang, A. R. Das, S. K. Chakraborty, S. C. Hong, S.-C. Tsay, M.-H. Hsu and J. R. Hwu, *J. Med. Chem.* **2009**, *52*, 1486; f) A. C. Donnelly, J. R. Mays, J. A. Burlison, J. T. Nelson, G. Vielhauer, J. Holzbeierlein, B. S. J. Blagg, *J. Org. Chem.* **2008**, *73*, 8901.

[4] For a review see: a) H. Fan, J. Peng, M. T. Hamann, J. H. Hu, *Chem. Rev.* **2008**, *108*, 264; b) C. P. Ridley, M. V. R. Reddy, G. Rocha, F. D. Bushman, D. J. Faulknera, *Bioorg. Med. Chem.* **2002**, ***10***, 3285; c) S. M. Reddy, M. Srinivasulu, N. Satyanarayana, A. K. Kondapi, Y. Venkateswarlu, *Tetrahedron* **2005**, *61*, 9242; d) T. Yamaguchi, T. Fukuda, F. Ishibashi, M. Iwao, *Tetrahedron Lett.* **2006**, *47*, 3755; e) C. Tardy, M. Facompré, W. Laine, B. Baldeyrou, D. García-Gravalos, A. Francesch, C. Mateo, A. Pastor, J. A. Jiménez, I. Manzanares, C. Cuevasb, C. Bailly, *Bioorg. Med. Chem.* **2004**, *12*, 1697; f) H. Tao, I. Hwang, D. L. Boger, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5979; g) D. L. Boger, C. W. Boyce, M. A. Labroli, C. A. Sehon, Q. Jin, *J. Am. Chem. Soc.* **1999**, *121*, 54; h) D. L. Boger, D. R. Soenen, C. W. Boyce,

M. P. Hedrick, Q. Jin, *J. Org. Chem.* **2000**, *65*, 2479; i) D. R. Soenen, I. Hwang, M. P. Hedrick, D. L. Boger, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1777; j) D. Pla, A. Marchal, C. A. Olsen, A. Francesch, C. Cuevas, F. Albericio, M. lvarez, *J. Med. Chem.* **2006**, *49*, 3257.

[5] a) S. T. Handy, Y. N. Zhang, H. Bregman, *J. Org. Chem.* **2004**, *69*, 2362; b) D. Pla, A. Marchal, C. A. Olsen, F. Albericio, M. Älvarez, *J. Org. Chem.* **2005**, *70*, 8231; c) M. Iwao, T. Takeuchi, N. Fujikawa, T. Fukuda, F. Ishibashi, *Tetrahedron Lett.* **2003**, *44*, 4443; d) N. Fujikawa, T. Ohta, T. Yamaguchi, T. Fukuda, F. Ishibashi, M. Iwao, *Tetrahedron* **2006**, *62*, 594; e) T. Yamaguchi, T. Fukuda, F. Ishibashi, M. Iwao, *Tetrahedron Lett.* **2006**, *47*, 3755.

[6] M. A. Khan, M. L. de Brito. Morley, *J. Heterocycl. Chem.* **1978**, *15*, 1399.

[7] R. S. Raghu, G. L. D. Krupadanam, G. Srimannarayana, *Synth. Commun.* **1998**, *28*, 2421.

[8] For selected examples see: a) J. Wu, Y. Liao, Z. Yang, *J. Org. Chem.* **2001**, *66*, 3642; b) J. Wu, Z. Yang, *J. Org. Chem.* **2001**, *66*, 7875; c) Q. Zhu, J. Wu, R. Fathi, Z. Yang, *Org. Lett.* **2002**, *4*, 3333; d) M. S. Schiedel, C. A. Briehn, P. Bauerle, *Angew. Chem.* **2001**, *113*, 4813; *Angew. Chem. Int. Ed.* **2001**, *40*, 4677; e) S. Saito, S. Oh-tani, N. Miyaura, *J. Org. Chem.* **1997**, *62*, 8024; f) G. M. Boland, D. M. X. Donnelly, J.-P. Finet, M. D. Rea, *J. Chem. Soc. Perkin Trans. 1* **1996**, 2591; g) A. Elangovan, J.-H. Lin, S.-W. Yang, H.-Y. Hsu, T.-I. Ho, *J. Org. Chem.* **2004**, *69*, 8086; h) D. Conreaux, S. Belot, P. Desbordes, N. Monteiro, G. Balme, *J. Org. Chem.* **2008**, *73*, 8619; i) J. Wu, L.-A. Zhang, H.-G. Xia, *Tetrahedron Lett.* **2006**, *47*, 1525; j) J.-G. Lei, M.-H. Xu, G.-Q. Lin, *Synlett* **2004**, 2364; k) Z.-Y. Tang, Q.-S. Hu, *Adv. Synth. Catal.* **2004**, *346*, 13.

[9] a) R. Tschesche, U. Schacht, G. Legler, *Justus Liebigs Ann. Chem.* **1963**, *662*, 113; b) Y. Kato, S. Okada, K. Tomimoto, T. Mase, *Tetrahedron Lett.* **2001**, *42*, 4849.

[10] a) N. Akhtar, M. A. Munawar, M. Siddiq, *Indian J. Chem. Sect. B* **1992**, *25*, 328; b) S. Govori, V. Rapić, O. Leci, M. Čačić, I. Tabaković, *J. Heterocycl. Chem.* **1996**, *33*, 351.

[11] For reviews see: a) R. Chinchilla, C. Najera, *Chem. Rev.* **2007**, *107*, 874; b) A. F. Littke, G. C. Fu, *Angew. Chem.* **2002**, *114*, 4350; *Angew. Chem. Int. Ed.* **2002**, *41*, 4176.

[12] For reviews see: a) F. Alonso, I. P. Beletskaya, M. Yus, *Chem. Rev.* **2004**, *104*, 3079; b) S. Cacchi, G. Fabrizi, *Chem. Rev.* **2005**, *105*, 2873; c) R. Severin, S. Doye, *Chem. Soc. Rev.* **2007**, *36*, 1407.

[13] Selected examples see: a) T. Sakamoto, Y. Kondo, S. Iwashita, T. Nagano, H. Yamanaka, *Chem. Pharm. Bull.* **1988**, *36*, 1305; b) H.-C. Zhang, H. Ye, A. F. Moretto, K. K. Brumfield, B. E. Maryanoff, *Org. Lett.* **2000**, *2*, 89; c) J. S. Mahanty, M. De, P. Das, N. G. Kundu, *Tetrahedron* **1997**, *53*, 13379; d) K. Iritani, S. Matsubara, K. Utimoto, *Tetrahedron Lett.* **1988**, *29*, 1799; e) C. E. Castro, E. J. Gaughan, D. C. Owsley, *J. Org. Chem.* **1966**, *31*, 4071; f) N. Sakai, K. Annaka and T. Konakahara, *Tetrahedron Lett.* **2006**, *47*, 631; g) T. E. Muller, M. Grosche, E. Herdtweck, A. K. Pleier, E. Walter, Y. K. Yan, *Organometallics* **2000**, *19*, 170.

[14] A. L. Rodriguez, C. Koradin, W. Dohle, *Angew. Chem.* **2000**, *112*, 2607; *Angew. Chem. Int. Ed.* **2000**, *39*, 2488.

[15] Crystallographic data for (**5a**) ($C_{15}H_{15}NO_2$): $T=293$ (2) K; wavelength: 0.71073 Å.; crystal system: monoclinic, space group: $P21/n$; unit cell dimensions: $a=5.3392(6)$ Å, $b=11.0688(13)$ Å, $c=20.905(2)$ Å, $\alpha=90°$, $\beta=90.745$ (2)°, $\gamma=90°$; $V=1235.3$ (2) Å^3; $Z=4$; $\rho_{calcd.}=1.297$ Mg/m^3; $F(000)=512$; final R indices [$I>2\sigma(I)$]: $R_1=0.0563$,$wR_2=0.1444$; R indices (all data), $R_1=0.0690$, $wR_2=0.1525$; 6902 reflections measured, 2560 were unique ($R_{(int)}=0.0607$). CCDC 726962 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.

[16] J. E. Nordlander, D. B. Catalane, K. D. Kotian, R. M. Stevens, J. E. Haky, *J. Org. Chem.* **1981**, *46*, 778.

