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Synthesis of 4-Aminoxanthones by an Uncatalyzed, Multicomponent Reaction

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Abstract: The synthesis of xanthones *via* a multicomponent reaction of isocyanides is described for the first time. In this one-pot process, a tandem [4+1] plus [4+2] cycloaddition leads to polysubstituted 4-aminoxanthones in excellent to quantitative yields at room temperature in a non-catalyzed reaction.

Keywords: biological activity; C–C bond formation; cycloaddition; Diels–Alder reaction; heterocycles; multicomponent reactions

Xanthones are a family of secondary metabolites, naturally occurring in higher plants, fungi, lichens and bacteria. Many natural and synthetic xanthones are able to interact with diverse biological targets, and are therefore privileged structures in drug design.[1] Remarkably, xanthones containing H-bond donating/accepting substituents, such as hydroxyxanthones, have shown to be effective inhibitors of monoamine oxidase (MAO)[2] and different kinases,[3] and to interfere in the cell cycle.[4] Accordingly, hydroxyxanthone derivatives have been proposed as valuable candidates for the development of anti-tumoural and anti-inflamatory drugs.

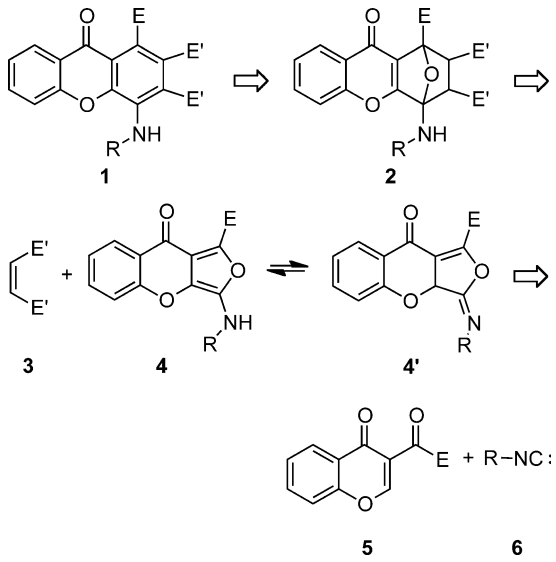
The less explored aminoxanthones are especially interesting, as they can be considered analogues of biologically active hydroxyxanthones with, in some ways, superior pharmacodynamic and pharmacokinetic properties.[5] Protonation of the amino group may allow the interaction with negatively charged sites in the protein target, or the accumulation in certain tissues or cell structures.[5b] Furthermore, aminoxanthones are key intermediates in the synthesis of heterocyclic fused xanthones,[5b,6] which have been proposed as novel chemotherapeutic agents able to overcome adverse multidrug resistance (MDR).[6c] Not less importantly, aminoxanthones have also found utility as fluorescent molecular probes for bioimaging.[6a]

Despite this interest, only few syntheses of aminoxanthones have been reported in the literature. With the exception of a recently described base-promoted addition of acetonitriles to 3-(1-alkynyl)chromones,[7] aminoxanthones are generally obtained through indirect procedures based on the reduction of nitroxanthones.[8] These are in turn obtained by classical synthesis relying on the cyclization of either benzophenones or diaryl ethers.[9] These multistep synthetic procedures often involve harsh reaction conditions and the use of strong acids or transition metals. Consequently, the development of direct and efficient routes to aminoxanthones is highly desirable.

Multicomponent (MCR) reactions are highly convergent processes characterized by the formation of several bonds in a single operation. The experimental simplicity and wide functional group tolerance of MCRs[10] make this type of process a very attractive alternative for the synthesis of xanthones.

In the last years, we have designed new MCRs of isocyanides for the synthesis of chromone derivatives.[11] In a recent work we have also developed a one-pot synthesis of anilines through a tandem [4+1]–[4+2] process, starting from α,β-unsaturated carbonyl compounds, isocyanides and dienophiles in the presence of catalytic $Y(OTf)_3$.[12]

We envisaged that 4-aminoxanthones (**1**) could be readily prepared, using a similar strategy, by a Diels–Alder cycloaddition of dienophiles (**3**) with 3-amino-9*H*-furo[3,4-*b*]chromen-9-ones (**4**). These, in turn, could be obtained *in situ* by the [4+1] cycloaddition of isocyanides (**6**) with electron-deficient 3-carbonylchromones (**5**; Scheme 1). This latter transformation would be predictably facilitated by the presence of strong electron-withdrawing groups on the starting carbonylchromones (**5**). Here we describe the application of this methodology for the efficient and straight-



Scheme 1. Proposed retrosynthesis of 4-aminoxanthones.

forward synthesis of diversified amino-substituted xanthones.

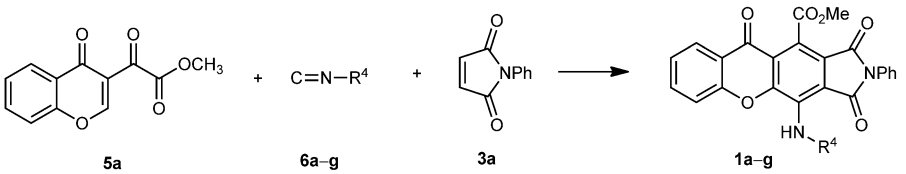
Thus, we investigated the reaction of methyl 2-oxo-2-(4-oxo-4*H*-chromen-2-yl)acetate (**5a**)[13] with cyclohexyl isocyanide (**6a**) and *N*-phenylmaleimide (**3a**) under different conditions. When the reaction was performed in THF at room temperature, a highly fluorescent product began to precipitate from the reaction medium after a few hours. Monitoring the reaction by TLC showed a slow transformation of the starting chromone into this new product. Isolation by simple filtration and characterization by the usual spectroscopic techniques successfully confirmed the structure of this compound as the expected 4-aminoxanthone **1a**. The presence of a highly conjugated push-pull system configured by the oxygen and amino donor groups and the four electron-withdrawing carbonyls results in the product showing an intense fluorescence.

Interestingly, the rate of the reaction was found to be significantly benefited by a moderate increase in the temperature. The solvent was also an important factor. Thus, excellent yields were obtained both in THF and toluene (Table 1, entries 2 and 4), though considerably longer reaction times were required in this latter solvent. Conversely, the reaction in CH_2Cl_2 is characterized by both lower yields and longer reaction times (Table 1, entry 3). Successfully, after some optimizations we were able to obtain quantitative yields of **1a** using equimolar amounts of the three starting reagents at 35 °C in THF.

To explore the scope of this reaction, chromone **5a** was treated with *N*-phenylmaleimide (**3a**) and different isocyanides (**6**) in the optimized reaction conditions (Table 1). Both aliphatic and aromatic isocyanides give the expected aminoxanthones in good to excellent yields. Unsurprisingly, a higher reaction rate is observed with less hindered isocyanides (Table 1, entries 8 and 9).

To further extend the scope of this tandem procedure, we decided to investigate the use of differently substituted 3-carbonylchromones (**5**). Methyl 2-oxo-2-(4-oxo-4*H*-chromen-2-yl)acetate (**5a**) was readily obtained by the reaction of 3-(dimethylamino)-1-(2-hydroxyphenyl)propen-1-one (**9a**) with methyl 2-chloro-2-oxoacetate (**10**) and pyridine, as recently reported

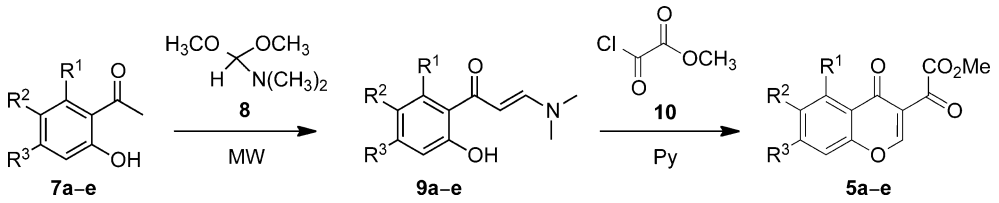
Table 1. Optimization and scope of the reaction with different isocyanides.



Entry	R^4	Solvent	Temperature [°C]	Time [h]	**1** (Yield [%])[a]
1	*c*-C_6H_{11}	THF	25	24	IR[b]
2	*c*-C_6H_{11}	THF	35	96	**1a** (99)
3	*c*-C_6H_{11}	DCM	35	120	**1a** (84)
4	*c*-C_6H_{11}	toluene	35	144	**1a** (97)
5	*t*-Bu	THF	35	96	**1b** (93)
6	2,6-$Me_2C_6H_3$	THF	35	144	**1c** (67)
7	$PHCH_2$	THF	35	78	**1d** (93)
8	C_5H_{11}	THF	35	22	**1e** (97)
9	4-$MeOC_6H_4$	THF	35	22	**1f** (99)
10	CH_2CO_2-*t*-Bu	THF	35	49	**1g** (82)

[a] *General procedure:* 1.1 equiv. of isocyanide and 1.1 equiv. of dienophile were added under nitrogen to a solution of 1 equiv. of chromenone in the specified solvent.
[b] IR = incomplete reaction.

Table 2. Synthesis of 2-oxo-2-(4-oxo-4*H*-chromen-3-yl)acetates (**5**).



Entry	R^1	R^2	R^3	Time [min]	Enaminone **9**[a] (Yield [%])	Time [min]	Chromone **5**[b] (Yield [%])
1	H	H	H	2	**9a** (89)	7	**5a** (85)
2	H	H	OMe	1	**9b** (86)	14	**5b** (67)
3	H	Cl	H	1	**9c** (85)	7	**5c** (81)
4	H	Me	H	1	**9d** (93)	10	**5d** (78)
5	benzo		H	1	**9e** (91)	20	**5e** (30)

[a] *General procedure for the synthesis of enaminones* (**9a–9e**): *ortho*-hydroxyacetophenone **7a–e** (10 mmol) and dimethylformamide dimethyl acetal (10 mmol) were irradiated in a microwave reactor for 1–2 min at 150 °C.

[b] *General procedure for the synthesis of chromenones* (**5a–5e**): a solution of methyl chlorooxoacetate (1.65 mmol), enaminone **9a–9e** (1.5 mmol) and pyridine (3.3 mmol) in 1,2-dichloroethane (1 mL) was irradiated in a microwave reactor for 7–20 min at 100 °C.

by Iaroshenko and Langer.[13] Our modification of this procedure, using microwave irradiation, affords a good yield of **5a** in only 10 min, rather than the 8 h required in the original procedure. Analogously, other carbonylchromones (**5a–e**; Table 2) were conveniently prepared starting from enaminones containing different substituents (**9a–e**).

These enaminones (**9a–e**) were readily prepared by the aldol condensation of *ortho*-hydroxyacetophenones (**7a–e**) with dimethylformamide dimethyl acetal (**8**) under microwave irradiation.[14] The reactions were finished in just 2 min giving excellent yields of virtually pure **9a–e**, which could be directly used in the preparation of chromanones (**5a–e**; Table 2). Both intermediates **9** and **5** crystallize from their respective reaction media, and hence, 2-oxo-2-(4-oxo-4*H*-chromen-3-yl)acetates (**5a–e**) could be easily and efficiently obtained in two steps from commercially available *ortho*-hydroxyacetophenones (**7a–e**), with no need for laborious purifications and in less than 30 min in the overall process (Table 2).

Reactions of chomones **5a–e** with *N*-phenylmaleimide and isocyanides (**6**) have shown to be tolerant to both electron-donor and electron-acceptor substituents on the chromone (Table 3, entries 1–5). However, donor substituents as 7-methoxy (Table 3, entry 1) and 6-methyl (Table 3, entry 3) have a beneficial effect on the reaction rate, considerably reducing the time of the reaction, even when it was performed at room temperature. Conversely, the electron-withdrawing group-containing 6-chlorochromone requires longer reaction times and higher temperatures (Table 3, entries 2 and 5). Unexpectedly, the reaction with benzochromone **5e** is more sluggish, and affords the corresponding pentacyclic aminoxanthone **1k** in only a 30% yield.

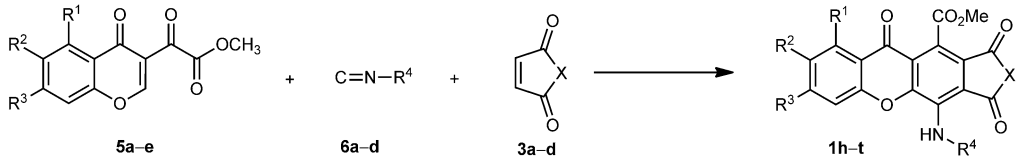
Finally, the reaction has also been performed with different dipolarophiles. *N*-phenyl- (**3a**) and *N*-methylmaleimide (**3b**), maleimide (**3c**), and maleic anhydride (**3d**) were reacted with diverse chromones (**5**) and isocyanides (**6**), affording the corresponding products (**1**) in moderate to excellent yields (Table 3, entries 6–14). In the less favourable case, electron-poor 6-chlorochromone and bulky 2,6-dimethylphenyl isocyanide do not react with maleimide (**3c**) under the usual conditions (Table 3, entry 13); however, refluxing the reaction mixture for 6 h conveniently affords the desired xanthone (**1t**) in a moderate yield (Table 3, entry 14).

Importantly, in all cases the xanthones (**1a–t**) were cleanly isolated by crystallization, with no need for further purification.

In agreement with our initial prediction, the mechanism of the reaction could be explained through a [4+1] cycloaddition of the isocyanide (**6**) with the 3-carbonylchromone (**5**) to give iminolactone intermediate (**4′**). This tautomerizes to aminofuran (**4**), which suffers a [4+2] cycloaddition with the dienophile (**3**), leading to 7-oxabicyclo[2.2.1]heptane (**2**). Then, the nitrogen lone pair assists the *in situ* opening of the oxygen bridge and subsequent dehydration to afford the aromatic 4-aminoxanthone **1** (Scheme 1).

Multistep syntheses of aromatic amines[15] usually require the use of transition metals or strong acids or bases for the dehydration or dehydrogenation of non-aromatic intermediates in a synthetic step independent from the ring formation. In contrast, here all four steps, [4+1] cycloaddition, [4+2] cycloaddition, oxygen ring opening and aromatization, take place smoothly at room temperature in the same pot with no need of catalysts.

Table 3. Scope of the reaction with different chromones, isocyanides and dienophiles.



Entry	R^1	R^2	R^3	R^4	X	Solvent	Temperature [°C]	Time [h]	Product (Yield [%])[a]
1	H	H	OMe	*c*-C_6H_{11}	NC_6H_5	THF	25	24	**1h** (99)
2	H	Cl	H	*c*-C_6H_{11}	NC_6H_5	THF	35	96	**1i** (81)
3	H	Me	H	*c*-C_6H_{11}	NC_6H_5	THF	25	24	**1j** (75)
4	benzo		H	*c*-C_6H_{11}	NC_6H_5	THF	25	140	**1k** (30)[b]
5	H	Cl	H	*t*-Bu	NC_6H_5	THF	35	120	**1l** (85)
6	H	H	H	*c*-C_6H_{11}	NCH_3	THF	35	32	**1m** (94)
7	H	H	OMe	*c*-C_6H_{11}	NCH_3	THF	35	23	**1n** (81)
8	H	H	H	*c*-C_6H_{11}	O	THF	25	96	**1o** (83)
9	H	H	OMe	*c*-C_6H_{11}	O	THF	25	72	**1p** (87)
10	H	H	H	*c*-C_6H_{11}	NH	THF	25	72	**1q** (86)
11	H	H	OMe	$PhCH_2$	NH	THF	25	72	**1r** (30)
12	H	Me	H	*t*-Bu	NH	THF	25	80	**1s** (70)
13	H	Cl	H	2,6-$Me_2C_6H_3$	NH	THF	35	>200	–
14	H	Cl	H	2,6-$Me_2C_6H_3$	NH	THF	85	6	**1t** (53)[c]

[a] *General procedure:* 1.1 equiv. of isocyanide and 1.1 equiv. of dienophile were added under nitrogen to a solution of 1 equiv. of chromenone in THF.
[b] Increasing the temperature to 35 °C or reflux decreased the reaction time but no improved yields were observed.
[c] Reaction was carried out at THF reflux.

In summary, a high yielding and straightforward tandem synthesis of polysubstituted 4-aminoxanthones has been developed from readily accessible 3-carbonylchromones, isocyanides and dienophiles. The reaction is tolerant to a wide range of substituents on the three starting materials, and takes place under mild conditions with no need of catalysts. Importantly, one new single and two new double carbon-carbon bonds are formed in a simple synthetic operation. To the best of our knowledge, this constitutes the first multicomponent synthesis of xanthones reported up to date.

Furthermore, a variety of starting chromones can be readily prepared in a microwave-assisted two-step procedure in less than 30 min. The overall three-step process does not require any chromatographic purification, as both the precursors and the final xanthones can be cleanly isolated by crystallization from the reaction media.

Experimental Section

General Procedure for the Synthesis of Enaminones (9a–9e)

A mixture of *ortho*-hydroxyacetophenone (10 mmol) and dimethylformamide dimethyl acetal (10 mmol) was stirred and irradiated (1–2 min) at 150 °C in a microwave device. The solid obtained was recrystallized from toluene, heating in the microwave reactor during 30 seconds at 150 °C and then cooling at 4 °C. The collected crystals were then washed with hexane.

(*E*)-3-(Dimethylamino)-1-(2-hydroxyphenyl)prop-2-en-1-one (9a): Reaction time 2 min; yield: 89%, obtained as an orange solid; mp 133–137 °C (lit.[14] 123 °C); IR: $\nu = 2920$, 1628, 1548 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 13.94$ (s, 1H, OH), 7.89 (d, $J = 12.1$ Hz, 1H), 7.70 (d, $J = 8.0$ Hz, 1H), 7.35 (t, $J = 8.5$ Hz, 1H), 6.94 (d, $J = 8.3$ Hz, 1H), 6.81 (t, $J = 8.1$ Hz, 1H), 5.79 (d, $J = 12{,}1$ Hz, 1H), 3.18 (s, 3H), 2.96 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 191.7$ (C), 163.2 (C), 154.9 (CH), 134.1 (CH), 128.4 (CH), 120.5 (C), 118.4 (CH), 118.2 (CH), 90.3 (CH), 45.6 (CH_3), 37.6 (CH_3); MS (CI): *m*/*z* (%) = 220 ($M+29$, 79), 193 (M^+, 92), 191 (100), 190 (35), 147 (90), 98 (100).

General Procedure for the Synthesis of Chromenones (5a–5e)

A solution of methyl chlorooxoacetate (1.65 mmol) in 1,2-dichloroethane (1 mL) was added dropwise to an ice-cooled solution of enaminones **9a–9e** (1.5 mmol) and pyridine (3.3 mmol) in 1,2-dichloroethane (1 mL). The resulting mixture was then stirred and irradiated (7–20 min) at 100 °C in a microwave device. The crude material was washed with copper sulfate solution (to eliminate the pyridine) and brine; the organic phase was dried with Na_2SO_4, filtered and evaporated affording a solid, which was filtered and washed with hexane.

Methyl 2-oxo-2-(4-oxo-4*H*-chromen-3-yl)acetate (5a): Reaction time: 7 min; yield: 85%, obtained as a bright brown solid; mp 131–135 °C (lit.[13] 133–135 °C); IR: $\nu = 3063$, 2955, 1731, 1694, 1649 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 8.66$ (s, 1H), 8.25 (d, $J = 7.9$ Hz, 1H), 7.77 (t, $J = 8.5$ Hz, 1H), 7.56 (d, $J = 8.4$ Hz, 1H), 7.52 (t, $J = 7.5$, 1H), 4.00 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 184.7$ (C), 174.8 (C), 164.4 (C), 162.4 (CH), 156.3 (C), 135.2 (CH), 127.1 (CH) 126.5 (CH), 124.9 (C), 120.1 (C), 118.8 (CH), 53.2 (CH_3); MS (CI): *m/z* (%) = 261 (M + 29, 22), 234 (M + 2, 85), 233 (M + 1, 98), 232 (M^+, 99), 217 (69), 121 (22).

General Procedure for the Synthesis of 4-Aminoxanthones

To a solution of chromenone **5a–5e** (0.3 mmol) in dry THF (2 mL), isocyanide **6a–6g** (0.36 mmol) and dienophile **3a–3d** (0.36 mmol) were successively added. The resulting mixture was stirred at room temperature or 35 °C under a nitrogen atmosphere until all the starting chromone had been consumed, as judged by TLC. HCl (1 N) was added to the reaction mixture, the organic phase was extracted with CH_2Cl_2, dried (Na_2SO_4) and concentrated. The resulting solid was filtered and washed with hexane, giving the desired product **1a–1t**.

Methyl 4-(cyclohexylamino)-1,3,10-trioxo-2-phenyl-1,2,3,10-tetrahydrochromeno[2,3-*f*]isoindole-11-carboxylate (1a): Reaction temperature: 35 °C; reaction time: 96 h; yield: 99%, obtained as a yellow solid; mp 250–253 °C (dec.); IR: $\nu = 3331$, 2942, 2842, 1758, 1702, 1661 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 8.31$ (d, $J = 7.9$ Hz, 1H), 7.82 (t, $J = 8.6$ Hz, 1H) 7.51–7.34 (m, 9H), 6.95 (s, 1H), 4.44 (m, 1H), 4.11 (s, 3H), 2.17–1.15 (m, 10H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 175.9$ (C), 168.2 (C), 167.2 (C), 164.7 (C), 155.1 (C), 149.3 (C), 139.1 (C), 135.9 (CH), 131.4 (C), 129.3 (CH), 128.4 (CH), 127.2 (CH), 126.6 (CH), 125.8 (CH), 123.3 (C), 123.0 (C), 121.6 (C), 118.3 (C), 117.9 (CH), 112.2 (C), 54.5 (CH), 53.5 (CH_3), 34.9 (CH_2), 25.6 (CH_2), 24.8 (CH_2); MS (EI): *m/z* (%) = 497 (M^+,20), 496 (M, 62), 453 (92), 421 (35), 383 (52); HR-MS (EI): *m/z* = 496.1626, calcd. for $C_{29}H_{24}N_2O_6$: 496.1634.

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References

[1] a) K.-S. Masters, S. Bräse, *Chem. Rev.* **2012**, *112*, 3717–3776; b) A. Detsi, D. Bouloumbasi, K. C. Prousis, M. Koufaki, G. Athanasellis, G. Melagraki, A. Afantitis, O. Igglessi-Markopoulou, C. Kontogiorgis, D. J. Hadjipavlou-Litina, *J. Med. Chem.* **2007**, *50*, 2450–2458; c) M. M. M. Pinto, M. E. Sousa, M. S. J. Nascimento, *Curr. Med. Chem.* **2005**, *12*, 2517–2538.

[2] A. Urbain, A. Marston, L. S. Grilo, J. Bravo, O. Purev, B. Purevsuren, D. Batsuren, M. Reist, P. A. Carrupt, K. Hostettmann, *J. Nat. Prod.* **2008**, *71*, 895–897.

[3] a) H. Sun, F. Chen, X. Wang, Z. Liu, Q. Yang, X. Zhang, J. Zhu, L. Qiang, Q. Guo, Q. You, *Eur. J. Med. Chem.* **2012**, *51*, 110–123; b) J.-H. Yoo, K. Kang, E. H. Jho, Y.-W. Chin, J. Kim, C. W. Nho, *Food Chem.* **2011**, *129*, 1559–1566; c) L. L. Saraiva, P. Fresco, E. Pinto, E. L. Sousa, M. Pinto, J. Gonçalves, *Bioorg. Med. Chem.* **2003**, *11*, 1215–1225.

[4] K. Matsumoto, Y. Akao, K. Ohguchi, T. Ito, T. Tanaka, M. Iinuma, Y. Nozawa, *Bioorg. Med. Chem.* **2005**, *13*, 6064–6069.

[5] a) Y. Liu, Z. Ke, J. Cui, W. H. Chen, L. Ma, B. Wang, *Bioorg. Med. Chem.* **2008**, *16*, 7185–7192; b) C. Portela, C. M. Afonso, M. M. Pinto, D. Lopes, F. Nogueira, V. do Rosario, *Chem. Biodiversity* **2007**, *4*, 1508–1519.

[6] a) K. K. Ghosh, H. H. Ha, N. Y. Kang, Y. Chandran, Y. T. Chang, *Chem. Commun.* **2011**, *47*, 7488–7490; b) V. Giannouli, I. K. Kostakis, N. Pouli, P. Marakos, O. Kousidou, G. N. Tzanakakis, N. K. Karamanos, *J. Med. Chem.* **2007**, *50*, 1716–1719; c) I. K. Kostakis, N. Pouli, P. Marakos, A. L. Skaltsounis, H. Pratsinis, D. Kletsas, *Bioorg. Med. Chem.* **2006**, *14*, 2910–2934.

[7] Y. Liu, L. Huang, F. Xie, Y. Hu, *J. Org. Chem.* **2010**, *75*, 6304–6307.

[8] a) I. H. Bowen, J. R. Lewis, *J. Chem. Soc. Perkin Trans. 1* **1972**, 683; b) A. A. Goldberg, H. A. Walker, *J. Chem. Soc. (Res)* **1953**, 1348.

[9] M. Pedro, F. Cerqueira, M. E. L. Sousa, M. S. J. Nascimento, M. Pinto, *Bioorg. Med. Chem.* **2002**, *10*, 3725–3730.

[10] a) A. Domling, W. Wang, K. Wang, *Chem. Rev.* **2012**, *112*, 3083–3135; b) E. Ruijter, R. Scheffelaar, R. V. A. Orru, *Angew. Chem.* **2011**, *123*, 6358–6371; *Angew. Chem. Int. Ed.* **2011**, *50*, 6234–6246; c) B. Ganem, *Acc. Chem. Res.* **2009**, *42*, 463–472.

[11] a) A. G. Neo, J. Diaz, S. Marcaccini, C. F. Marcos, *Org. Biomol. Chem.* **2012**, *10*, 3406–3416; b) S. Marcaccini, A. G. Neo, C. F. Marcos, *J. Org. Chem.* **2009**, *74*, 6888–6890; c) A. G. Neo, R. M. Carrillo, S. Barriga, E. Moman, S. Marcaccini, C. F. Marcos, *Synlett* **2007**, 327–329.

[12] A. G. Neo, A. Bornadiego, J. Díaz, S. Marcaccini, C. F. Marcos, *Org. Biomol. Chem.* **2013**, *11*, 6546–6555.

[13] S. Mkrtchyan, V. O. Iaroshenko, S. Dudkin, A. Gevorgyan, M. Vilches-Herrera, G. Ghazaryan, D. M. Volochnyuk, D. Ostrovskyi, Z. Ahmed, A. Villinger, V. Y. Sosnovskikh, P. Langer, *Org. Biomol. Chem.* **2010**, *8*, 5280–5284.

[14] K. Al-Zaydi, R. Borik, *Molecules* **2007**, *12*, 2061–2079.

[15] a) R. Fichtler, J.-M. Neudorfl, A. Jacobi von Wangelin, *Org. Biomol. Chem.* **2011**, *9*, 7224–7236; b) P. Janvier, H. Bienayme, J. P. Zhu, *Angew. Chem.* **2002**, *114*, 4467–4470; *Angew. Chem. Int. Ed.* **2002**, *41*, 4291–4294; c) A. Padwa, M. Dimitroff, A. G. Waterson, T. H. Wu, *J. Org. Chem.* **1997**, *62*, 4088–4096.

