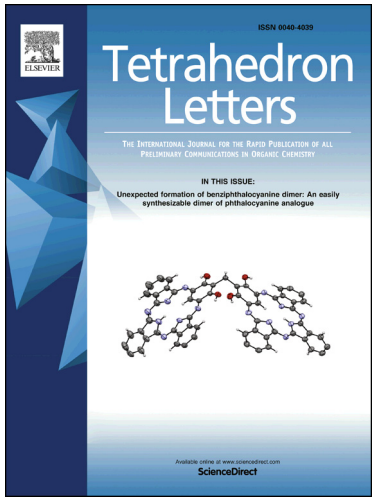

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Graphical Abstract

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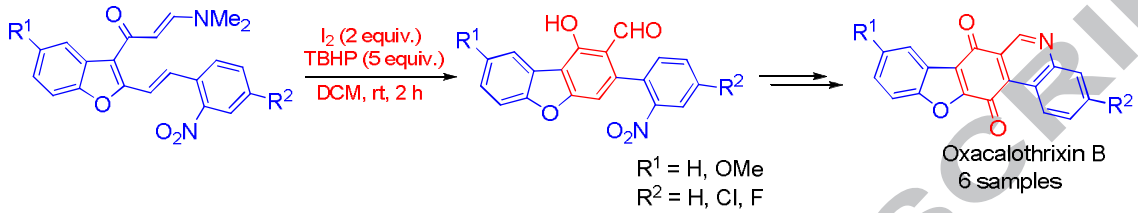

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Synthesis of Oxacalothrixin B and its Analogues Involving Iodine/TBHP-Mediated Electrocyclization

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ABSTRACT

The total synthesis of oxacalothrixins, an isostere of biologically important carbazoloquinone alkaloid, calothrixin B was achieved from 2-acetyl-3-methylbenzofuran. An iodine/TBHP-mediated oxidative cyclization of benzofuranyl-enamine has been employed as a key step to synthesize, the crucial intermediate 1-hydroxy dibenzofurancarbaldehyde. The latter upon reductive cyclization followed by PIDA-mediated oxidation furnished oxacalothrixin B and its analogues.

Calothrixin A **1** and B **2** are novel indolo[3,2-*j*]phenanthridine alkaloids isolated from *calothrix cyanobateria* in 1999.[1] These natural product exhibit important biological activities such as antimalarial, anticancer and they inhibit bacterial RNA polymerase[2] and poison DNA topoisomerase I.[3] Calothrixin A is also known to induce the intracellular formation of reactive oxygen species.[4] The highly promising biological activity of calothrixins led to the development of several synthetic strategies.[5]

The development of more potent as well as more selective analogues of calothrixin may well lead to a suitable clinical candidate. Recently, our group reported a synthesis of thiacalothrixin B **3** involving Lewis acid- mediated domino reaction protocol. Both thia analogues of calothrixin displayed comparable cytotoxicity with that of the parent calothrixin.[6] In a further continuation on the synthesis of calothrixin analogues, oxacalothrixins, the isostere of calothrixin B is planned using an established Lewis acid-mediated domino reaction strategy.[7]

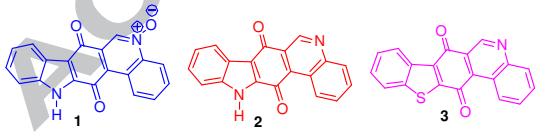
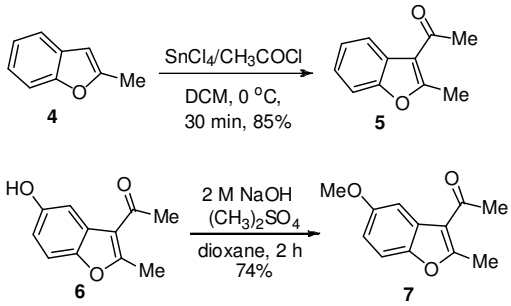


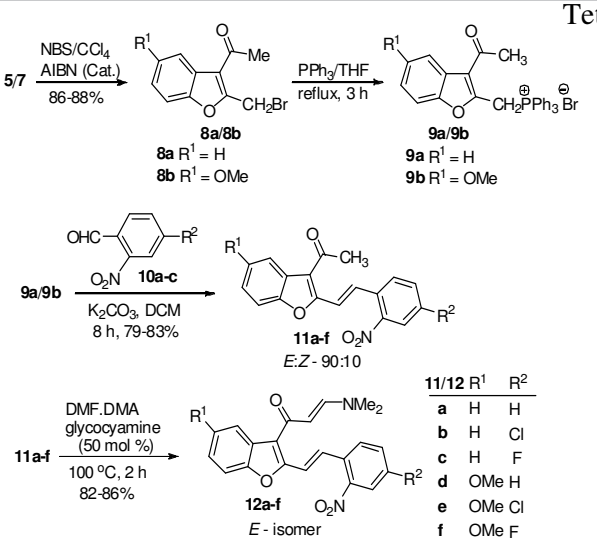
Fig. 1. Bioactive calothrixins and thiacalothrixins B.

The synthetic work started with the preparation of 3-acetyl-2-methylbenzofuran and 5-hydroxy-3-acetyl-2-methylbenzofuran. Friedel-Crafts acylation of 2-methylbenzofuran **4**[8] using CH_3COCl in the presence of $SnCl_4$ in dry DCM at 0 °C for 30 min afforded 3-acetyl-2-methylbenzo[*b*]furan **5** in good yield. Next, a routine *o*-methylation of 5-hydroxy-3-acetyl-2-methylbenzofuran **6**[9] using $(CH_3)_2SO_4$, 2M NaOH in dioxane for 2 h afforded 5-methoxy-3-acetyl-2-methylbenzofuran **7.**



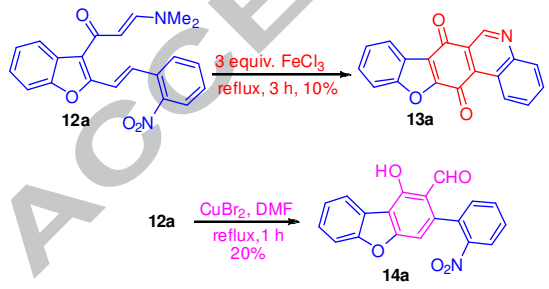
Scheme 1. Synthesis of 2-acetyl-3-methylbenzofurans **5** and **7**.

As expected an allylic bromination of compound **5/7** using NBS and a catalytic amount of AIBN in CCl_4 at reflux for 4 h afforded respective bromo compound **8a/8b** in good yield. Next, the reaction of bromo compound **8a/8b** with PPh_3 in dry THF upon reflux followed by Wittig reaction of resulting phosphonium salt **9a/9b** with 2-nitroarylaldehydes **10a-c** using K_2CO_3 as a base in DCM at room temperature led to the formation of 3-acetyl-2-nitroarylvinyl-benzo[*b*]furan **11a-f** (*E* and *Z* mixture) as yellow-orange/yellow solid in good yields. A subsequent reaction of 3-acetyl-2-nitroarylvinylenes (*E*:*Z*) **11a-f** with DMF.DMA in the presence of 50 mol% glycocyamine as a catalyst at 100 °C for 2 h followed by aqueous workup furnished only *E*-enamines **12a-f** as yellow-orange/yellow solid in 84-86% yields.



Scheme 2. Synthesis of benzofuranyl enamines **12a-f**.

Unfortunately, the reaction of enamine **12a** using established procedure,[6] i.e., with 3 equiv. of $FeCl_3$ in DMF at reflux for 3 h followed by workup and column chromatographic purification afforded oxacalothrixin B **13a** only in a 10% yield. To improve the yield of **13a**, the enamine **12a** was refluxed with 3 equiv. of $FeCl_3$ in DMF for 1 h without any success. Indeed, only a trace amount of product formation could be monitored only by the TLC. Since, the $FeCl_3$-mediated domino reaction of the enamine **12a** was found to be problematic; a slightly detoured route for accessing oxacalothrixin B **13a** *via* 1-hydroxydibenzofuran-2-carbaldehyde **14a** was planned. Unexpectedly, the reaction of enamine **12a** with 1 equiv. of $CuBr_2$ in DMF at reflux for 1 h followed by workup led to the formation of 1-hydroxydibenzofuran-2-carbaldehyde **14a** only in a 20% yield. Reducing the reaction time for 30 min instead of 1 h also afforded the carbaldehyde **14a** in a trace amount. While changing the solvent as 1,2-DCE instead of DMF also failed to give the desired compound **14a** in a reasonable yield. Even though, the corresponding *N*-phenylsulfonylindole enamines were smoothly transformed into the respective 4-hydroxy-2-nitroarylcarbazole-3-carbaldehydes by using $CuBr_2$ in good yields,[7] in the present case, when the similar conditions were employed, transformation of benzofuran based enamine **12a** into the respective aldehyde **14a** was found to be difficult.



Scheme 3. LA-mediated domino reaction of enamine **12a**

It should be noted that the *N*-phenylsulfonylindole as well as benzo[*b*]thiophene based enamines underwent a facile LA-mediated domino reaction to afford the corresponding aldehydes as well as calothrixin analogues in good yields.[7] The obtainment of low yield for LA-mediated transformation of enamine **12a** into oxacalothrixin B **13a**/dibenzofuran-2-carbaldehyde **14a** might be due to the poor co-ordination ability of enamine-carbonyl group. Most likely, the relatively electron withdrawing nature of benzofuran oxygen atom of **12a** compared to the sulfur as well as *N*-phenylsulfonyl units may disfavor the LA-mediated oxidative cyclization reaction.

The formation of 1-hydroxydibenzofuran-2-carboxaldehyde **14a** in low yield prompted us to explore an alternative strategy for conversion of enamine **12a** into the required 1-hydroxydibenzofuran carbaldehyde **14a**. Hence, based on the literature survey, an iodine-mediated cyclization[10] was planned. However, as expected the reaction of enamine **12a** with 1 equiv. of I_2 in DCM at reflux failed to induce any cyclization. Surprisingly, the reaction of **12a** with iodine (0.5 equiv.) in the presence of TBHP (2 equiv.) as co-oxidant in DCM at room temperature for 2 h afforded desired compound **14a** in 30% yield.

Next, we turned our attention to investigate the role of iodine and TBHP-mediated oxidative cyclization of enamine **12a**. As expected, the reaction of the enamine **13a** could be performed with different conditions and the results obtained are summarized in Table 1.

Table 1. Condition optimization on cyclization of enamine **12a**

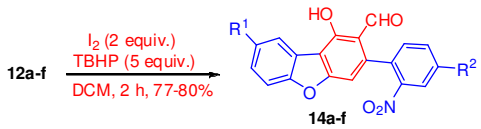
Entry	Catalyst	Oxidant	Solvent	T °C	Time (h)	Yield (%)[a]
1	I_2 (1 equiv.)		DCM	rt	6	NA
2	I_2 (0.5 equiv.)	TBHP (3 equiv.)	DCM	rt	2	30
3	I_2 (1 equiv.)	TBHP (3 equiv.)	DCM	rt	2	52
4	I_2 (2 equiv.)	TBHP (5 equiv.)	DCM	rt	2	80
5	I_2 (2 equiv.)	TBHP (5 equiv.)	ACN	rt	6	72
6	I_2 (2 equiv.)	$K_2S_2O_8$ (5 equiv.)	DCM	50	6	25
7	I_2 (2 equiv.)	*m*-CPBA (5 equiv.)	DCM	rt	6	65
8	NIS (2 equiv.)	TBHP (5 equiv.)	DCM	rt	12	70
9	NaI (2 equiv.)	TBHP (5 equiv.)	ACN	rt	6	NA
10	PIDA (2 equiv.)	TBHP (2 equiv.)	DCM	rt	2	NA

[a] Isolated yields of 1-hydroxydibenzofuran-2-carbaldehyde **14a**

In order to optimize the reaction condition for facile transformation of enamine **12a** into the required aldehyde **14a**, the oxidative cyclization was performed by varying the equivalents of iodine as well as TBHP (Table 1, entries 2-4). An increase in the amount of iodine (2 equiv.) and TBHP (5 equiv.) greatly enhanced the formation of **14a**. When the reaction was performed in acetonitrile (ACN) instead of DCM, resulted in a slightly reduced the yield of **14a** (Table 1, entry 5). Use of other oxidant such as $K_2S_2O_8$ inplace of TBHP furnsihed low yield of dibenzofuran-2-carbaldehyde **14a** (Table 1, entry 6). However, when *m*-CPBA was employed as co-oxidant led to the formation of **14a** in a moderate yield (Table 1, entry 7). The exploration of iodine source as NIS has slightly decreased the yield of **14a** (Table 1, entry 8). However, the replacement of iodine by NaI, failed to induce any cyclization. The replacement I_2-TBHP condition with PIDA/TBHP also failed to produce the expected aldehyde **14a** (Table 1, entry 10), instead a complex mixture was obtained.

The optimised reaction condition for the facile transformation of enamine **13a** into the dibenzofuran aldehyde **14a** was found to involve I_2 (2 equiv.), TBHP (5 equiv.) in DCM at room temperature for 2 h (entry 6).

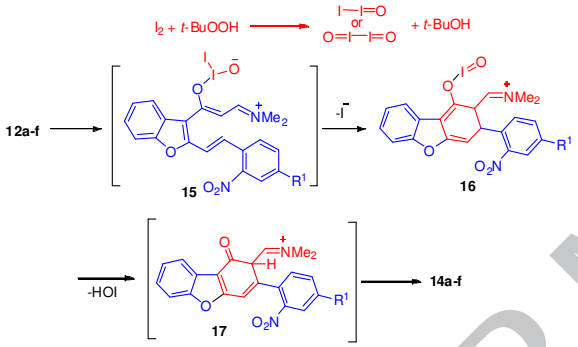
Having established a facile transformation of the enamine **12a** into dibenzofuran aldehyde **14a** using I_2 and TBHP, adopting the similar conditions, rest of the enamines **12b-f** were also converted into the respective 1-hydroxydibenzofuran **14b-f** in excellent yields.



14	R^1	R^2
a	H	H
b	H	Cl
c	H	F
d	OMe	H
e	OMe	Cl
f	OMe	F

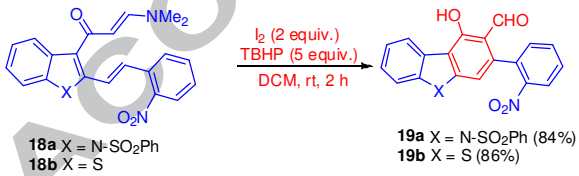
Scheme 4. Synthesis of dibenzofurancarbaldehydes **14a-f**.

The probable mechanism for the smooth transformation of the enamines **12a-f** into the respective aldehydes **14a-f** using I_2 /TBHP is depicted in Scheme 5. The reaction of iodine with TBHP may generate highly reactive trivalent iodine compounds, which upon co-ordination with the enamine carbonyl group led to the formation of triene intermediate **15**. The triene **15** upon electrocyclization followed by aromatization may lead to aldehydes **14a-f**.



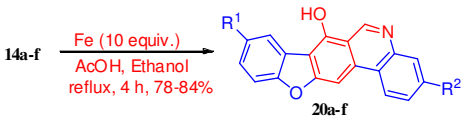
Scheme 5. Mechanistic hypothesis for aldehydes **14a-f**.

To our delight, a representative indole as well as benzo[*b*]thiophene based enamines **18a/18b** could be smoothly transformed into respective carbazole/dibenzo[*b*]thiophene carbaldehyde **19a/19b** using iodine-TBHP protocol in good yields. Thus, this protocol was found to be applicable for smooth transformation of indole as well as benzo[*b*]thiophene based enamines. Upon comparison with Lewis acid-mediated electocyclization of enamine, the iodine/TBHP-mediated oxidative cyclization protocol seems to involve mild reaction condition.



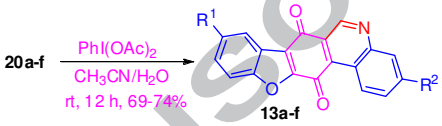
Scheme 6. I_2/TBHP-mediated cyclization of enamines **18a** and **18b**

Initially, the reductive cyclization of 2-nitrophenyldibenzofuran aldehydes **14a-f** using Raney-Ni in THF failed to give the required 13-hydroxyquinodibenzofuran. Subsequently, a smooth reductive cyclization of these compounds **14a-f** was carried out in the presence of Fe (10 equiv.) in acetic acid-ethanol at reflux for 4 h to afford 13-hydroxyquinodibenzofurans **20a-f** in very good yields.



Scheme 7. Synthesis of quinodibenzofurans **20a-f**.

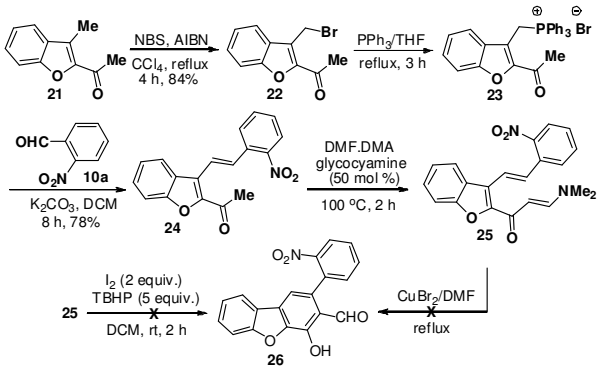
To complete the total synthesis of oxacalaothrixin B, 13-hydroxyquinodibenzofuran **20a** was initially subjected to CAN oxidation[11] in acetone–water mixture to afford product **13a** only in a low yield. Finally, after considerable experimentations, a smooth oxidation of 13-hydroxyquinodibenzofuran **20a** was performed by using 5 equiv. of $PhI(OAc)_2$ in CH_3CN–H_2O at rt for 12 h to furnish oxacalothrixin B **13a** in 74% yield.[11] Adopting the similar conditions, rest of the 13-hydroxyquinodibenzofurans **20b-f** were also converted into the respective oxacalothrixin B **13b-f** in good yields.



13	R^1	R^2
a	H	H
b	H	Cl
c	H	F
d	OMe	H
e	OMe	Cl
f	OMe	F

Scheme 8. Synthesis of oxacalothrixin **B 13a-f**.

After completion of oxacalothrixin B, next, the synthesis of oxaisocalothrixin B is planned from the 2-acetyl-3-methylbenzofuran.[12] As expected, a routine allylic bromination of compound **21** using NBS and a catalytic amount of AIBN in CCl_4 at reflux for 4 h afforded bromo compound **22** in 84% yield. Next, the reaction of bromo compound **22** with PPh_3 in dry THF upon reflux for 3 h followed by the Wittig reaction of resulting phosphonium salt **23** with 2-nitrobenzaldehyde **10a** using K_2CO_3 as a base in DCM at rt gave 2-acetyl-3-nitroarylvinyl-benzo[*b*]furan **24** (*E* and *Z*; 90:10) as a yellow solid in 78% yield. Next, the reaction of 2-acetyl-3-nitroarylvinylene **24** with DMF.DMA in the presence of 50 mol% glycocyamine at 100 °C for 2 h followed by aqueous workup furnished enamine (*E*:*Z*; 80:20) **25** as a yellow solid.



Scheme 9. Attempted oxidative cyclization of enamine **25**.

Unfortunately, the expected oxidative cyclization of the isomeric benzofuran enamine **25** with I_2 (2 equiv.)/TBHP (5 equiv.) conditions in DCM at room temperature failed to give expected dibenzofuran-3-carbaldehyde **26**. Further, the $CuBr_2$-mediated electrocyclization of enamine **25** also failed to give the expected product **26**.

In summary, synthesis of oxacalothrixins and its analogues are achieved involving a novel iodine/TBHP-mediated domino reaction of the enamines as a key step followed by reductive cyclization and PIDA-mediated oxidation. However, the synthesis of oxaisocalothrixin B could not be completed due to the electrocyclization problems encountered with respective enamine using iodine/TBHP as well as $CuBr_2$ conditions. Studies on anticancer activities of oxacalothrixins and their analogues are in progress and the results will be reported in due course.

Acknowledgments

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Supplementary Material

Supplementary data associated with this article can be found, in the online version, at

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Highlights of the Manuscript

- Total synthesis of oxacalothrixins, an isostere of anticancer indole alkaloid, calothrixin B
- Crucial intermediate 1-hydroxy dibenzofurancarbaldehyde achieved through Iodine/TBHP-mediated oxidative cyclization
- PIDA-mediated oxidation of 13-hydroxyquinodibenzofurans led to oxacalothrixins