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Functional group manoeuvring for tuning stability and reactivity: synthesis of cicerfuran, moracins (D, E, M) and chromene-fused benzofuran-based natural products†

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The protecting group manoeuvring as a strategy was applied for tuning the stability and reactivity of 4-(2,2-dibromovinyl)benzene-1,3-diol (**12a**) and 6-(2,2-dibromovinyl)-2,2-dimethylchroman-7-ol (**22**) in the domino synthesis of benzofuran-based natural products (**1–8**). The functional group demands and their impact on the reactivity driven by electronic effects were successfully managed by varying the protecting groups with substituted *gem*-dibromovinylphenols in domino couplings and triarylbismuth reagents under palladium-catalyzed conditions. This approach paved the way for the synthesis of moracin M (**1**) and cicerfuran (**2**), and the first time synthesis of moracin D (**3**) and moracin E (**4**) along with chromene-fused benzofuran-based natural products (**5–8**) in overall good yields.

Introduction

Heterocyclic benzofuran scaffolds are bestowed with abundant biological and medicinal properties. As privileged scaffolds, benzofuran derivatives are associated with anticancer, antimicrobial, immunomodulatory, antioxidant and anti-inflammatory properties.[1a,b] Furthermore, moracins A–Z and their derivatives are the major source for the development of drugs.[1c–n] A few related benzofuran natural products are shown in Fig. 1. Among these, moracin M (**1**) and moracin D (**3**) were isolated from *M. alba* L.,[2a,b] whereas moracin E (**4**) was isolated from the acetone extracts of the cortex and phloem tissues of mulberry shoots infected with *F. solani* f. sp. *mori*.[2c] Furthermore, cicerfuran (**2**) was isolated from the root of the wild species *C. bijugum*.[2d] Gramniphenols F (**8**) and G (**7**) were recently isolated from *Arundina gramnifolia*[2e] and morunigrol C (**5**) was isolated from the bark of *Morus nigra*.[2f] From the structural similarity point of view, this family of benzofuran natural products possesses 6-hydroxy substitutions and related chromene-fused arene scaffolds along with functionalized 2-aryl substitutions. However, a common pool strategy for the synthesis of this family of target skeletons has not been realized so far. A few known methods reported largely focused on the synthesis of individual benzofuran skeletons employing

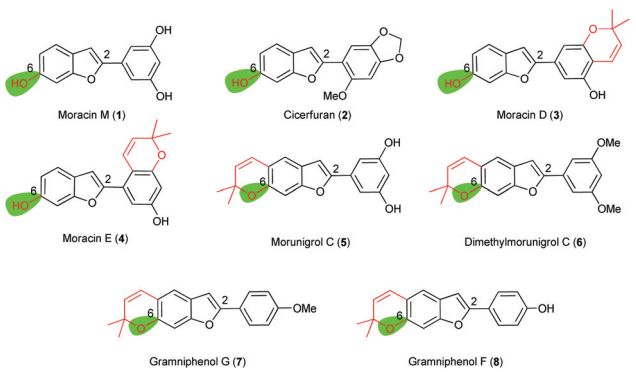

Fig. 1 6-Hydroxy or chromene-fused 2-arylbenzofuran based natural products.

the Wittig-, Sonogashira-, Suzuki- and McMurry-based coupling approaches.[3] For example, Kotschy *et al.* synthesized cicerfuran (**2**) employing the Sonogashira coupling of halogenated phenols. This coupling reaction step became complicated due to the presence of a phenolic group in the coupling partner.

This led to the usage of diacetate derivatives with either 4-bromoresorcinol or aryl alkynes in Sonogashira coupling, and the corresponding aryl acetylenes were obtained although in poor yields [(a), Scheme 1].[3a] Stevenson *et al.* reported Pd-catalyzed coupling of arylacetylenes with 4-iodoresorcinol or its diacetate derivative which also failed to undergo the Sonogashira reaction cleanly under the conditions employed. In this case, the final cicerfuran (**2**) product was identified only by GC-MS

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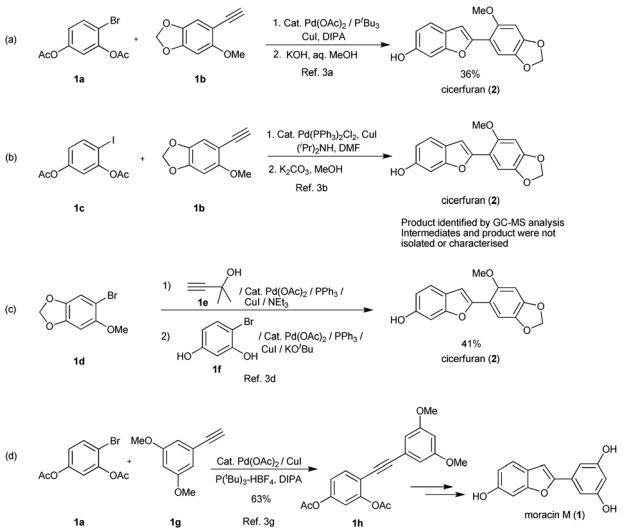


Scheme 1 Application of Sonogashira coupling in synthesis.

[(b), Scheme 1][3b] without isolation. This poor reactivity was attributed to the most probable instability of the Sonogashira coupled acetylenic intermediates. To circumvent this, another approach involving the formation of styrene derivatives through the Wittig reaction was adopted in the synthesis of cicerfuran (**2**).[3b] Furthermore, Duan *et al.* in 2007 reported a two-step sequence using the McMurry cross-coupling of a substituted salicylaldehyde and an aromatic aldehyde followed by oxidative cyclization to obtain a benzofuran core.[3c] Furthermore, Jiang *et al.* showed a one-pot method with propargyl substrates in combination with aryl bromide and 4-bromoresorcinol involving a double Sonogashira reaction for the synthesis of cicerfuran [Scheme 1, (c)].[3d] A few other methods have been reported in the literature utilizing Suzuki[3e] and Wittig[3f] reactions as key transformations in the preparation of cicerfuran (**2**).

Further difficulty in the application of the Sonogashira reaction was also encountered by Jun *et al.* in the synthesis of moracin M [Scheme 1 (d)].[3g] It was carried out initially by the Sonogashira coupling of acetylated 4-bromoresorcinol and an aryl alkyne followed by base mediated cyclization. As this reaction was dictated by electronic constraints, ligand $P(^tBu)_3$-HBF_4 was employed for the Sonogashira coupling of either 4-bromoresorcinol or its acetyl derivative under palladium conditions. A few other methods have also been reported for the synthesis of moracin M (**1**).[3h–o]

This enumeration of the literature approaches clearly highlighted the associated difficulties in the synthesis of benzofuran-based natural products. This motivated us to explore the possibility for new avenues taking a cue from our experience in the development of a concise synthetic strategy for 2,5-disubstituted benzofuran scaffolds (Fig. 2)[4a] and its application in the synthesis of ailanthoidol (**A**), egonol (**B**), homoegonol (**C**), demethoxyegonol (**D**) and demethoxyhomoegonol (**E**).

This led us to plan for a pooled approach for the preparation of the present set of benzofuran-based natural products

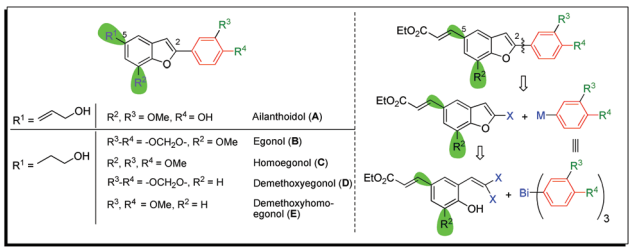


Fig. 2 Strategy for 2-arylbenzofurans with 5- or 5,7-disubstitutions.

(Fig. 1). This strategy mainly revolves around the presence of a 2,6-disubstituted benzofuran core and in turn involves 2-aryl and 6-OH substitutions (Fig. 3). The requirement of 6-OH substitution in the arene part earlier headed to serious difficulties whenever the Sonogashira coupling was employed (*vide supra*). It was addressed in different ways with (i) the use of specialized palladium catalytic protocols and (ii) differently functionalized organometallic coupling reagents (Scheme 1).[3a,b,e,g]

With this background, a pooled approach was conceived to bring out a viable strategy as outlined in Scheme 2. The targeted benzofuran-based natural products (**1–8**) were divided into two different groups (**1–4**) and (**5–8**) to envisage a pooled synthetic strategy using resorcinol (**9**) as a common starting material. The overall process involves the desired functionalizations in the preparation of substituted 2-(2,2-dibromovinyl)-phenols, followed by domino coupling with an appropriate triarylbismuth reagent to generate the benzofuran core.

As is well established, triarylbismuth reagents were chosen as organometallic coupling partners as these reagents provide threefold atom-economical coupling in a one-pot operation with sub-stoichiometric loading of the bismuth reagent.[5]

The success of the proposed strategy heavily depends on the relative stability and reactivity of the 4-(2,2-dibromovinyl) benzene-1,3-diol (**12a**) in domino couplings in the preparation of the first set of benzofuran products (**1–4**). Similarly, the stability and reactivity of the related 6-(2,2-dibromovinyl)-2,2-dimethylchroman-7-ol (**22**) is also crucial in the development of a concise synthetic strategy for the second set of benzofuran products (**5–8**). In fact, this adventure strenuously allowed us to develop a synthetically advantageous pooled approach for the preparation of benzofuran-based natural products (**1–8**) with careful manoeuvring of the functional group and these efforts are described below.

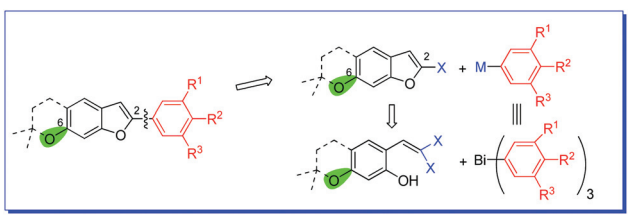
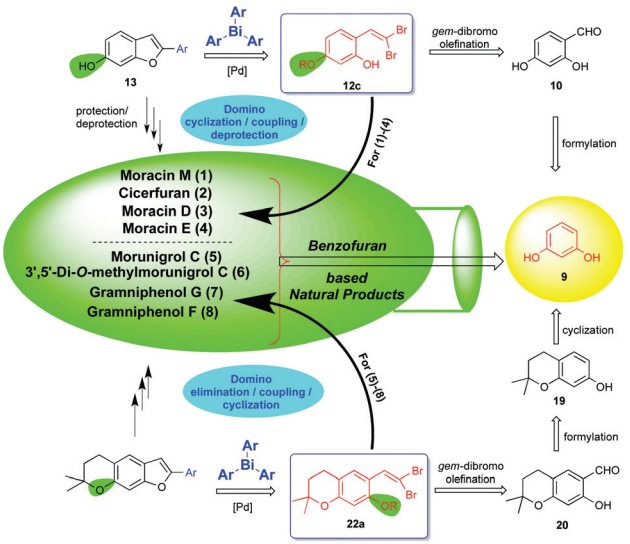


Fig. 3 Strategy for 2-arylbenzofurans with 6 or 5,6-disubstitutions.

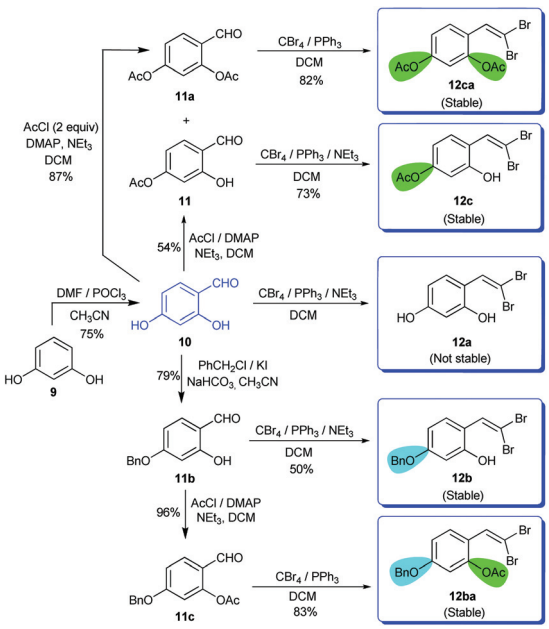


Scheme 2 A pooled synthetic strategy for benzofuran-based natural products (**1–8**).

Results and discussion

Our strategy was commenced with the readily available resorcinol (**9**) as given in Scheme 3. To start with, it was formylated using the Vilsmeier–Haack reaction to obtain 2,4-dihydroxybenzaldehyde (**10**)[6a] and then transformed to the corresponding *gem*-dibromide (**12a**) using Ramirez olefination.[6b–d]

However, this compound **12a** was found to be thermally unstable and decomposed during workup and purification procedures. The possible reason could be due to the presence of free phenolic groups in conjunction with *gem*-dibromide.



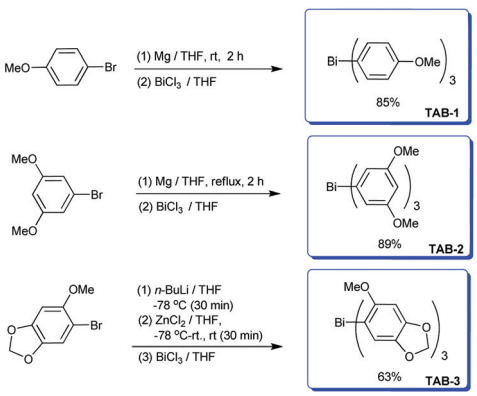
Scheme 3 Synthetic efforts to obtain thermally stable *gem*-bromides.

Hence, the protection of the phenol group with benzyl and/or acetyl groups was invoked to obtain thermally stable *gem*-dibromide suitable for the domino cyclization/coupling protocol. For this, 2,4-dihydroxybenzaldehyde (**10**) was selectively benzylated (**11b**) and converted to the corresponding monobenzylated *gem*-dibromide (**12b**). This benzyl protection gave stability as we could obtain a pure product through routine purification procedures. Furthermore, the acetyl derivative (**11**) and its conversion to dibromide also gave stable monoacetylated *gem*-dibromide (**12c**). Furthermore, we have also prepared bis-protected stable *gem*-dibromides with an acetyl and benzyl combination (**12ba** and **12ca**). This preparation of mono and bis-protected *gem*-dibromides was primarily to check their suitability to generate the benzofuran core under domino coupling conditions in a one-pot operation.

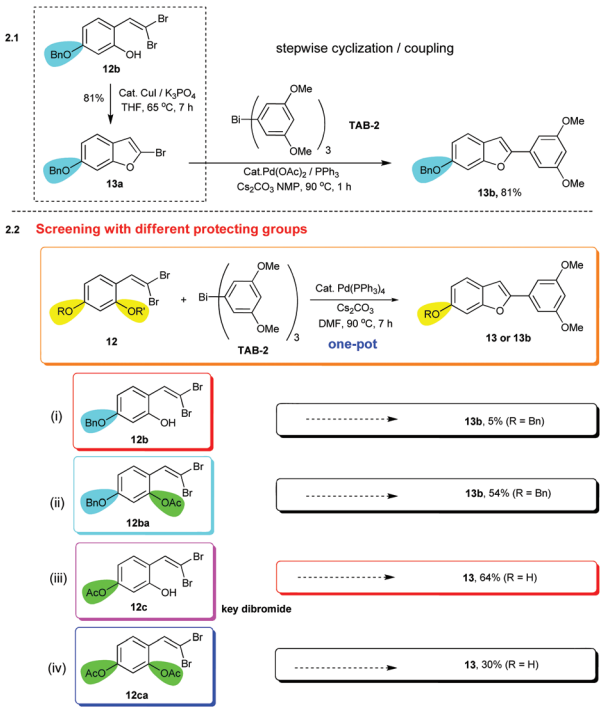
In addition, triarylbismuth reagents (**TAB-1**, **TAB-2** and **TAB-3**) required to carry out domino cross-coupling studies were prepared using literature procedures as given in Scheme 4 and these bismuth reagents were obtained in high yields.[4a,c]

With the availability of various *gem*-dibromides and triarylbismuth reagents in hand, it was time to establish the standardized conditions involving the domino cyclization/coupling reaction. To check the compatibility of *gem*-dibromides for this purpose, a two-step procedure was followed initially for the preparation of benzofurans. The benzyl protected *gem*-dibromide (**12b**) was subjected to copper-catalyzed cyclization[6d] and this afforded 2-bromobenzofuran **13a** in 81% yield (2.1, Scheme 5). It was then cross-coupled with a triarylbismuth reagent (**TAB-2**) under palladium-catalyzed conditions[7a] to afford benzofuran **13b** in 81% yield. This initial attempt under two-step conditions gave the desired benzofuran (**13b**) in 66% overall yield. Encouraged by this, it was decided to check this prospect under one-pot domino coupling conditions. Accordingly, mono- and bis-protected *gem*-dibromides were tested under one-pot domino coupling conditions[4b] with a bismuth reagent (**TAB-2**) (2.2, Scheme 5).

A domino test was carried out with monobenzylated *gem*-dibromide (**12b**) under palladium coupling conditions (2.2, i) and this delivered benzofuran **13b** in 5% poor yield. This was



Scheme 4 Preparation of triarylbismuth reagents.



Scheme 5 Optimization of the key domino step.

disappointing as monobenzylated *gem*-dibromide (**12b**) failed to survive to give the benzofuran product under the conditions employed. An additional test with doubly protected acetyl and benzyl derived *gem*-dibromide (**12ba**) demonstrated much improved reactivity and gave the corresponding benzofuran (**13b**) in 54% yield (2.2, ii). Most probably, the deactivating nature of the acetyl group electronically increased the stability of **12ba** and it survived the reaction course to give the benzofuran product.

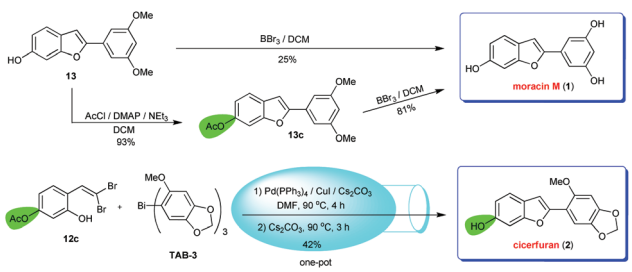
To further fine-tune the reactivity, monoacetylated *gem*-dibromide (**12c**) was tested with acetyl alone as a deactivator, which may further increase the substrate stability in comparison with benzyl and acetyl double protection in **12ba**. Amazingly, this *gem*-dibromide **12c** with monoacetyl protection demonstrated much improved reactivity and directly gave the deacetylated benzofuran (**13**) in 64% yield (2.2, iii). The formation of deacetylated benzofuran is notable as *in situ* acetyl deprotection underwent smoothly without an additional step in a one-pot operation. Furthermore, a curiosity test with bis-acetylated *gem*-dibromide (**12ca**) gave benzofuran (**13**) in 30% yield (2.2, iv). From this, it was realized that the outcome obtained with *gem*-dibromide **12c** is highly useful synthetically as it directly afforded deacetylated benzofuran **13** in good yield. In fact, this benzofuran intermediate **13** is a useful precursor for moracin M (**1**), moracin C[3q] and moracin N.[3g] Overall, (i) the labile acetyl protection (**12c**) served in a better way in comparison with benzyl protection (**12b**), (ii) mono-protection with the acetyl group in **12c** proved to be the best choice in comparison with the bis-protected dibromides (**12ba**, **12ca**), (iii) more labile acetyl did not require an additional deprotection step, as the domino coupling conditions directly gave 6-hydrxoybenzofuran (**13**) in good yield, (iv) the dual role played by acetyl as a stabilizer and labile protecting group proved promising. This investigation helped us to realize that *gem*-dibromide (**12c**) is more suitable to carry out domino coupling to directly generate 6-hydroxybenzofuran (**13**) in a one-pot operation. Note that *gem*-dibromide with a free hydroxyl (**12a**) was found to be unstable initially and this with benzyl protection (**12b**) although found to be thermally stable, but failed to provide an efficient domino coupling process. In such a scenario, the constructive role played by the acetyl group was very positive and synthetically advantageous.

With successful generation of benzofuran **13**, it was directly treated with BBr_3 following the literature procedure[3g,h] and the desired moracin M (**1**) was obtained in 25% yield (Scheme 6).

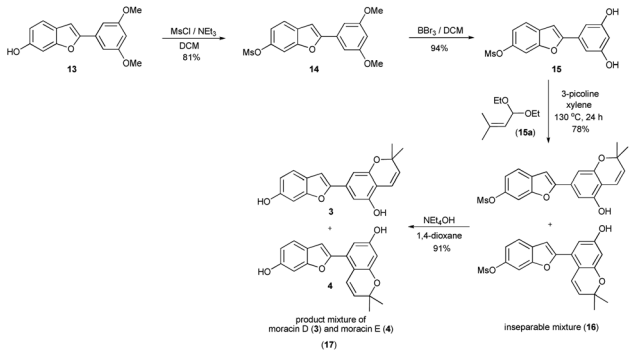
Being not satisfied, further efforts were made to improve this step. To fine-tune the reactivity, the free phenolic group was converted to acetate (**13c**) and then subjected to demethylation using BBr_3. This procedure gave moracin M (**1**) in 75% overall high yield. Our investigation so far assisted us in finding the right combination of protecting groups, and successfully established a domino cyclization/coupling protocol with *gem*-dibromide and its application in the synthesis of moracin M (**1**). It encouraged us to further extend *gem*-dibromide (**12c**) as a key intermediate in the synthesis of the much studied cicerfuran (**2**),[3a–f] a benzofuran-based natural product (Scheme 6). However, this required cross-coupling with an *ortho* substituted sterically congested triarylbismuth reagent (**TAB-3**). This reaction was then carried out in the presence of CuI under palladium coupling conditions[7b] and cicerfuran (**2**) was obtained in a one-pot operation. It involved firstly the domino cyclization/coupling of *gem*-dibromide (**12c**) with the bismuth reagent **TAB-3** under palladium-catalyzed conditions, followed by *in situ* acetyl deprotection in the second step affording cicerfuran (**2**) in 42% yield.

After successfully completing the synthesis of moracin M (**1**) and cicerfuran (**2**), we then focused on the synthesis of moracin D (**3**) and moracin E (**4**). The 6-hydroxybenzofuran (**13**) obtained above was protected with the mesyl group using MsCl and this gave the corresponding derivative **14** in 81% yield (Scheme 7).

Selective demethylation using BBr_3 provided mesyl derivative **15** exclusively in 94% yield. The treatment of this with a masked aldehyde[8a] (**15a**) in the presence of 3-picoline under



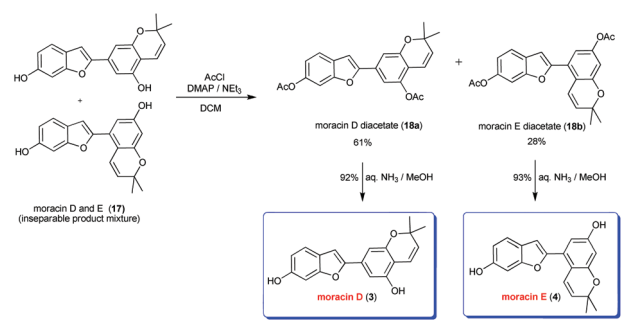
Scheme 6 Synthesis of moracin M (**1**) and cicerfuran (**2**).



Scheme 7 Towards the synthesis of moracin D (**3**) and moracin E (**4**).

heating conditions gave two isomeric chromene derivatives as an inseparable mixture (**16**) in 78% yield. This mixture was subjected to mesyl deprotection[8b] under basic conditions, which gave a mixture (**17**) of moracin D (**3**) and moracin E (**4**) in 91% yield. At this stage, our attempts to separate this mixture through column chromatography and other methods miserably failed. Hence, derivatization with acetyl chloride was carried out to obtain the corresponding acetates **18a** and **18b** (Scheme 8) and this helped us in their separation in 61% and 28% yields, respectively, using silica gel column chromatography. Furthermore, the deprotection of the acetyl group was carried out initially under acidic conditions using methanolic HCl and this gave decomposed products. However, an additional run under mild basic conditions using aqueous ammonia in methanol gave moracin D (**3**) and moracin E (**4**) in 92% and 93% yields, respectively (Scheme 8).

These synthetic efforts have so far successfully delivered moracin M (**1**), cicerfuran (**2**), moracin D (**3**) and moracin E (**4**) in a divergent manner from a common *gem*-dibromide **12c**. Our investigation also gave a few important clues about the stability of *gem*-dibromides (**12a–c**, **12ba** and **12ca**) and their suitability in the domino coupling process. In addition, protection with acetyl group served in a great way to fine-tune electronic properties and stabilize *gem*-dibromide substrates. All these were achieved successfully with a few functional manoeuvrings, which provided a concise and pooled synthetic approach in a facile manner.

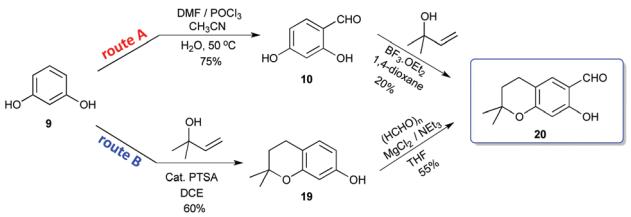


Scheme 8 Separation of moracin D (**3**) and moracin E (**4**).

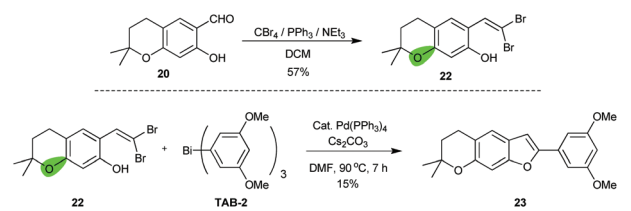
We then continued our efforts towards other set of benzofuran-based natural products, morunigrol C (**5**), 3′,5′-di-*O*-methylmorunigrol C (**6**), gramniphenol G (**7**) and gramniphenol F (**8**) as given in Scheme 2. The substrates required for this were prepared following the known procedures (Scheme 9). The strategy adopted here involved the initial formation of chroman-fused salicylaldehyde (**20**) starting from resorcinol through a simple and straightforward means in two different sequential operations. In route A, resorcinol (**9**) was subjected to Vilsmeier–Haack formylation[6a] to obtain compound **10** in high yield. It was subjected with 2-methyl-3-buten-2-ol in the presence of $BF_3{\cdot}OEt_2$ (2 equiv.) to directly obtain chroman-fused salicylaldehyde (**20**) involving initial prenylation, followed by acid-mediated cyclization. This attempt gave the desired product (**20**) in 20% yield.[8c]

To improve the yield, in route B, firstly acid mediated cyclization[9] of resorcinol (**9**) was carried out to obtain the corresponding chroman-fused derivative **19** in 60% yield. In fact, the formylation of this under Vilsmeier–Haack or Duff's conditions initially gave poor yield. However, the desired formylation underwent smoothly with paraformaldehyde in the presence of $MgCl_2/NEt_3$ [10] and the chroman-fused salicylaldehyde **20** was obtained in 55% yield. Thereafter, it was converted to the corresponding *gem*-dibromide **22** and then subjected to the domino cyclization/coupling protocol with the bismuth reagent **TAB-2**. This attempt afforded the chroman-fused benzofuran **23** in 15% poor yield. The crude product mixture analysis did not show the presence of unreacted *gem*-dibromide (**22**), indicating the most probable unstable nature of the substrate which gave poor yield (Scheme 10).

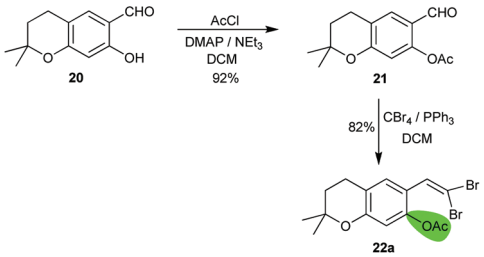
To overcome this problem, it was decided to protect *gem*-dibromide with the acetyl group to stabilize the substrate during the cross-coupling course as the stability accrued in the presence of acetyl led to high domino coupling yield as mentioned above (Scheme 11). The chroman-fused salicylaldehyde



Scheme 9 Synthetic routes for chroman-fused salicylaldehyde **20**.



Scheme 10 Coupling of *gem*-dibromide **22** with bismuth **TAB-2**.



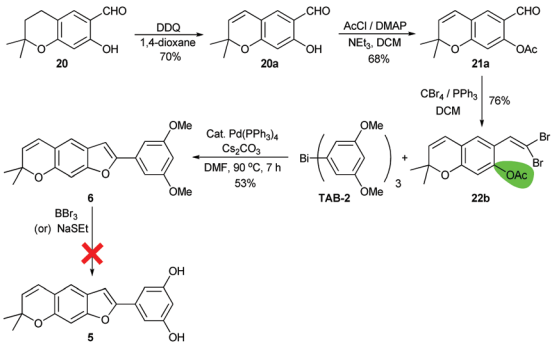
Scheme 11 Preparation of acetyl protected *gem*-dibromide **22a**.

(**20**) was first acetylated (**21**) in 92% yield and it was converted to dibromide (**22a**) in 82% yield following the usual procedures.

The *gem*-dibromide **22a** was subjected to domino cross-couplings with bismuth **TAB-2** under palladium coupling conditions (Scheme 12). Encouragingly, this reaction with acetyl protected *gem*-dibromide (**22a**) afforded benzofuran **23** in 65% yield with much improved reactivity. It was dehydrogenated with DDQ to obtain 3′,5′-di-*O*-methylmorunigrol C (**6**) in 90% yield. The intermediate benzofuran **23** was later demethylated with BBr_3 in DCM to afford intermediate **24** in 85% yield. Further dehydrogenation with 2 equiv. of DDQ afforded morunigrol C (**5**) in 30% yield.

To further improve the yield, an alternate pathway was envisaged through a diacetate followed by dehydrogenation. In the first step, compound **24** was acetylated to obtain diacetate **25** in 95% yield and its dehydrogenation using 1 equiv. of DDQ afforded the acetyl derivative of morunigrol C **26** in 89% yield. This upon hydrolysis using aqueous ammonia in methanol afforded morunigrol C (**5**). Amazingly, this three step procedure afforded morunigrol C (**5**) in 76% overall yield.

It is to be mentioned here that an alternative way of introducing a double bond in an early stage was evidenced to be a futile exercise. As given in Scheme 13, an early stage introduction of a double bond in the chromene (**20a**), followed by acetylation (**21a**), and its conversion to *gem*-dibromide (**22b**) followed by coupling with the bismuth reagent furnished dimethylated morunigrol C (**6**) in overall good yields.

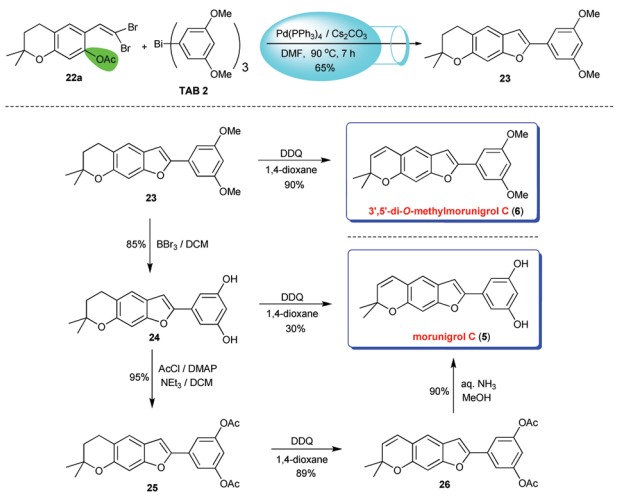


Scheme 13 Attempts for the demethylation of compound **6**.

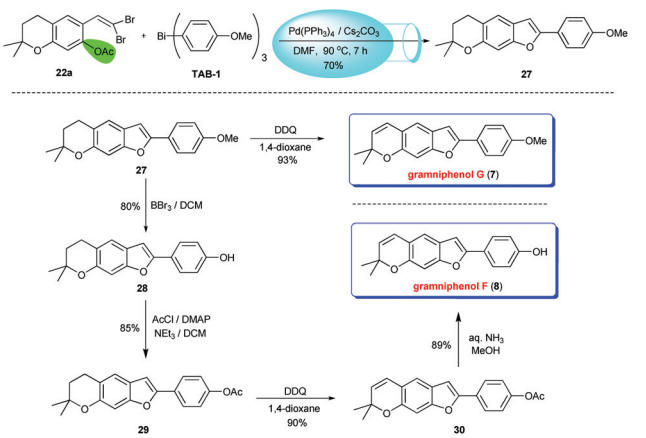
However, our attempts to demethylate compound **6** following literature procedures with either BBr_3 or NaSEt[11] did not provide the desired demethylation in a facile manner. This is in tune with literature observations in the preparation of compound **5**.[3e] In this sense, our attempt with chroman-fused benzofuran **23** successfully gave demethylation product **24** with BBr_3 in high yield. It was indeed achieved more directly without protecting group modifications in organometallic coupling partners.[3e] Evidently, late stage functionalization with a double bond adopted in Scheme 12 evolved as the best synthetic option in this regard.

To achieve other natural products (**7** and **8**) containing the 2-*p*-anisyl group, the *gem*-dibromide **22a** was reacted with tri(*p*-anisyl)bismuth (**TAB-1**) under Pd-catalyzed conditions, which gave the benzofuran intermediate **27** in 70% yield (Scheme 14). From this, the required gramniphenol G (**7**) was readily obtained with direct dehydrogenation using the DDQ reagent in 93% yield.

This concise strategy allowed the synthesis of gramniphenol G (**7**) in a short pathway involving six short steps from resorci-



Scheme 12 Synthesis of morunigrol (**5**) and 3′,5′-di-*O*-methylmorunigrol (**6**).



Scheme 14 Synthesis of gramniphenol G (**7**) and gramniphenol F (**8**).

nol (**9**).[3e,p] Furthermore, gramniphenol F (**8**) was prepared through demethylation, and converted to an acetate derivative (**29**) followed by dehydrogenation and hydrolysis. These steps proceeded very smoothly under the given conditions with high conversion to provide gramniphenol F (**8**) in overall high yield.

Note that Jun *et al.* recently reported the synthesis of benzofuran-based natural products (**5–8**) applying the Suzuki coupling of 2-bromobenzofuran derivatives under Pd-coupling conditions.[3e] Furthermore, Natu *et al.* reported the synthesis of gramniphenol G (**7**) involving the oxidative cyclization of *ortho*-vinylphenol as a key transformation to obtain the corresponding 2-arylbenzofuran.[3p] However, our pooled and concise approach elegantly delivered a series of benzofuran-based natural products, moracin M (**1**) and cicerfuran (**2**), and the first time synthesis of moracin D (**3**) and moracin E (**4**) along with chromene-fused benzofuran-based natural products (**5–8**).

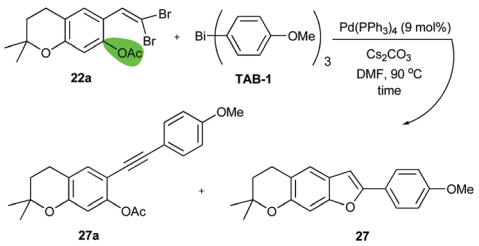
In terms of the reactivity of two *gem*-dibromides (**12c**, **22a**) employed in the coupling process, it was expected that they involve in different ways to give benzofuran, as illustrated in Fig. 4. As is known, in the case of **A**, the presence of a free hydroxyl group allows base mediated *in situ* cyclization to give 2-bromobenzofuran followed by cross-coupling with the bismuth reagent affording 2-arylbenzofuran.[4b] However, this possibility need not be the same in the case of **B**, where free hydroxyl was protected with the acetyl group. It could involve *vide infra* either through the 2-bromobenzofuran/cross-coupling process or the formation of a diarylalkyne intermediate and its cyclization.

To know this, a few control reactions were conducted with different amounts of a base under palladium-catalyzed conditions, as summarized in Table 1.

Firstly, the domino coupling reaction carried out with a base (9 equiv.) for 7 h afforded benzofuran (**27**) exclusively (entry 1, Table 1). Further modifications in the conditions with the amount of base and reaction time gave mixed results. As is given, the formation of the diarylalkyne **27a** gradually increased with decreasing the base amount and reaction time (entries 2–4, Table 1). This investigation thus clearly established the formation of diarylalkyne as an intermediate during the reaction course. Based on this, a probable mechanism is proposed in Scheme 15. The acetyl protected *gem*-dibromide (**p**) undergoes base mediated elimination to give 1-bromoalkyne (**q**). This further involves cross-coupling with the bismuth reagent involving **r** and **s** under palladium coupling conditions to give a diarylalkyne intermediate (**t**).[12] The base mediated *in situ* deprotection of the acetyl group followed by cyclization was expected to deliver benzofuran (**u**) in a one-pot domino process.

Overall, the above synthetic efforts brought out a few important aspects to the fore. For example, (i) the functional group manoeuvring and the dual role of acetyl as a labile protecting group and a stabilizer for 1,1-dibromide delivered fruitful domino cross-coupling reactivity, (ii) the route adopted *via* acetyl protection for efficient demethylations using BBr_3 is another highlight, (iii) the strategic use of mesyl protection and selective demethylations applied in the synthesis of moracin D (**3**) and moracin E (**4**) is notable, (iv) the acetyl derived stability also helped the cross-coupling reactivity of chroman-fused 1,1-dibromide (**22a**) under palladium coupling conditions, (v) acetyl protection also gave facile oxidation using DDQ to obtain morunigrol C (**6**) and gramniphenol F (**8**), (vi) late stage introduction of a double bond evolved as the best synthetic option during demethylation using the BBr_3 reagent, (vii) the presence of a double bond or a free phenolic

Table 1 Screening with different base amounts



Entry	Cs_2CO_3	Time (h)	Product **27a** (%)	Product **27** (%)
1	9 equiv.	7	0	70
2	9 equiv.	4	29	30
3	6 equiv.	4	44	20
4	6 equiv.	2	69	5

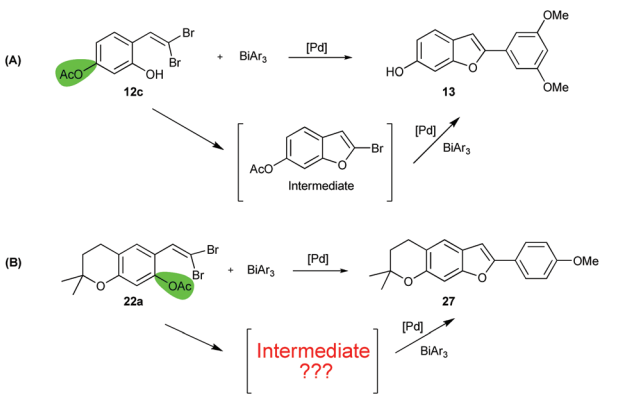
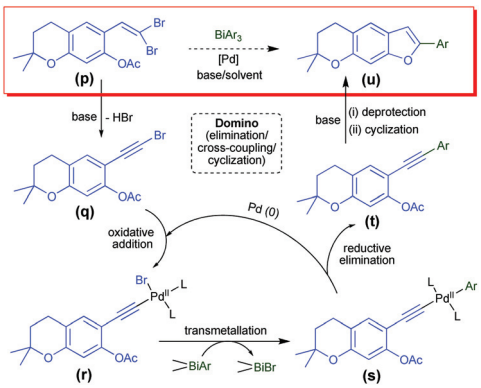


Fig. 4 Pathways for benzofuran formation.



Scheme 15 Domino elimination/coupling/cyclization.

group was demonstrated to be detrimental during BBr_3 mediated demethylations, and (viii) in the formation of chroman-fused 2-arylbenzofurans (**23** and **27**), a domino sequence involving elimination/cross-coupling/deprotection/cyclization was proposed as a probable pathway.

Conclusions

The application of the protecting group manoeuvring as a synthetic strategy was demonstrated in conjunction with the domino coupling process in the synthesis of benzofuran-based natural products (**1–8**). The electronic demands of functional groups and their tuning to derive the desired reactivity were successfully managed by employing acetyl protected 4-(2,2-dibromovinyl)benzene-1,3-diol (**12a**) and 6-(2,2-dibromovinyl)-2,2-dimethylchroman-7-ol (**22**) in domino couplings with triarylbismuth reagents. This approach in short paved the way for the total synthesis of moracin D (**3**) and moracin E (**4**) for the first time along with natural products (**1**, **2** and **5–8**) in good yields.

Conflicts of interest

There are no conflicts to declare.

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