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Weinreb amide based building blocks for convenient access to 1,1-diarylethenes and isocombretastatin analogues

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ABSTRACT

A successful strategy based on the synthetic equivalent containing Weinreb amide functionality for the convenient access to 1,1-diarylethenes in general and for the isocombretastatin analogues in particular has been developed from the commercially available glyoxalic acid. The convenience with which the structural variations can be made in assembling the aryl residues shows generality associated with the developed strategy. The intermediates also provide access to 1,2,2-triarylethanones, represented by the synthesis of advanced intermediate of tamoxifen.

Combretastatin **1**, naturally occurring stilbenoids strongly inhibit tubulin polymerization through binding to the colchicine site of tubulin[1] and have received much attention due to their simple structures. The structure–activity relationships (SARs) have revealed that *Z*-stilbene compounds display remarkable anticancer activities over the *E*-isomers thus making the *cis*-orientation of the two aromatic rings as one of the prerequisite for pronounced biological activity.[2] However, propensity of combretastatins and other *Z*-stilbene analogues to isomerize, either during storage or administration has initiated extensive search for *cis*-restricted analogues.[3] The structure–activity relationship studies revealing that the replacing 1,2-ethylene bridge by 1,1-ethylene bridge between the two aryl rings resulted in the retention of the biological activity which has led to the emergence of a new synthetic analogue called isocombretastain **2**.[4] It was further observed that the trimethoxy phenyl ring is the most essential component for the activity associated with isocombretastain **2** (Fig. 1).[5,6] Freedom to vary aryl ring B in isocombretastain has opened up wide possibility towards several isocombretastain analogues **3**.[5,6] With the emergence of isocombretastatin **2** and its analogues **3** as promising class of compounds, under the broad heading of 1,1-diarylethenes, synthetic efforts towards them become necessary and justified. At present juncture three routes are available in the literature for their synthesis. These routes are based on palladium catalysed Barluenga coupling of *N*-tosylhydrazone derived from acetophenone with aryltriflates,[7] Wittig olefination of di-aryl ketones[5,6] and dehydration in 1,1-diarylethanols as tertiary alcohols.[6]

The importance of isocombretastatin **2** and our continued interest in developing and using the synthetic equivalents based on the Weinreb amide (WA) functionality,[8,9] attracted our attention. In the conceived strategy for **3** as analogues of **2**, the two aryl residues were envisaged to be delivered as nucleophilic component, due to

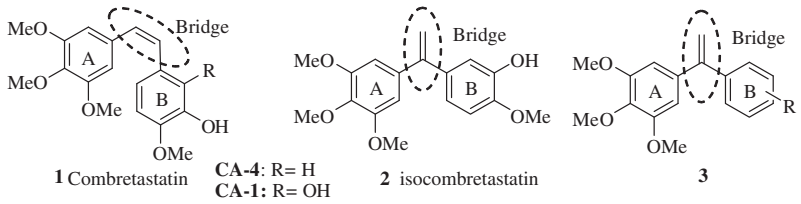

Figure 1. Structure of combretastain, isocombretastatin and novel isocombretastatin analogues.

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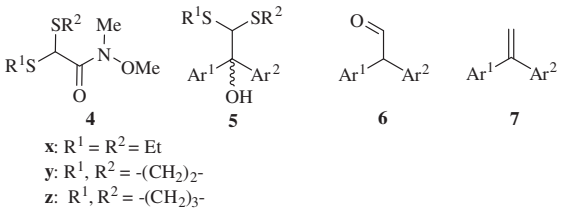
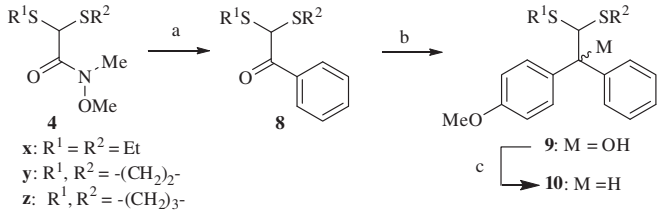


Figure 2. New building blocks for the synthesis of α,α′-diarylacetaldehyde and 1,1-diarylethenes.

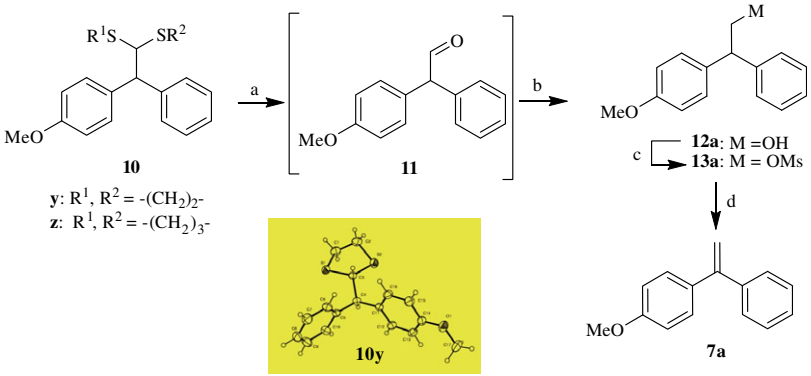


Scheme 1. Reagents and conditions: (a) For **4x** and **4y**: PhMgBr (2.5 equiv), THF, 0–5 °C, 2 h, for **4z** (reverse addition): PhMgBr (2.5 equiv), THF, −30 to −25 °C, 2 h, (**8x**: 70%; **8y**: 78%; **8z**: 68%); (b) *p*-OMePhMgBr (2.5 equiv), THF, 15–20 °C, 2 h, (**9x**: 76%; **9y**: 80%; **9z**: 78%); (c) triethylsilane (5 equiv), TFA (2.0 equiv), DCM (10 V), 0–5 °C, 2 h, 80% for **10y** and **10z**.

convenient availability of ArMgX. Towards the needed electrophilic synthetic equivalent representing the two carbons in ethylene bridge, we banked on potential and promise of WA-based synthetic equivalents. The increasing confidence in the use of WA functionality in industry on kilogram scale[10] further justified its exploration for a strategy towards synthesis of isocombretastatin analogues. Glyoxalic acid derived WA-building blocks **4x–z** were envisaged for quick assembling of the aryl residues and subsequent transformation of the tertiary alcohol **5** to the targeted 1,1-diarylethenes **7** through the intermediacy of α,α′-diarylacetaldehydes **6** (Fig. 2). Incidently the present objective also had an inbuilt additional incentive of paving a way for a new, simple and convenient route for α, α′-diarylacetaldehydes **6** which are synthetically very important.[11]

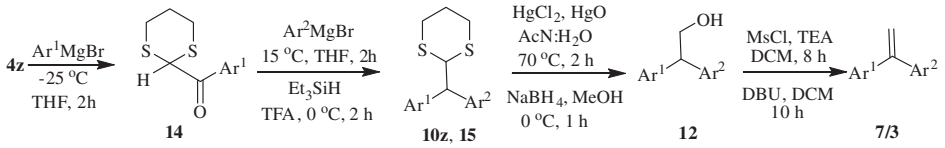
Glyoxalic acid as starting material furnished multi-gram quantities of the proposed building blocks **4x–z** in two simple steps.[12] As a representative example and in an attempt to implement the proposed strategy for 1,1-diarylethenes, the compounds **4x**, **4y** and **4z** were independently added to the preformed phenylmagnesium bromide in THF at 0–5 °C. Clean reaction ensued in each case furnishing the corresponding ketones in good to modest yields, **8x** (70%), **8y** (78%) and **8z** (50%), respectively. Attempts were made to increase the yield of **8z** by varying the reaction temperature and also the mode of addition of the reactants. Much to our delight, better yield of 68% was obtained by adding phenylmagnesium bromide generated in THF to the solution of **4z** in THF at −25 to −30 °C. The anticipated pronounced acidity of the α-proton in the ketones **8x–z** made the subsequent addition of the second arylmagnesium halide onto the ketones challenging and interesting. This was in the context that the Grignard reagent could either act as a base or as a nucleophile. Initial attempts involving addition of 2.5 equiv of *p*-methoxyphenylmagnesium bromide solution in THF to a solution containing **8x**, **8y** and **8z** in THF separately at −5 to 0 °C revealed only 40–50% consumption of the ketones on TLC. Substantial amounts of unreacted ketones were also observed on TLC, even after 2 h of reaction period, indicating possible trapping of the ketones as enolates, which refused any further reaction with the available organometallics. The mild acidic work-up with saturated ammonium chloride solution afforded the corresponding tertiary alcohols **9x**, **9y** and **9z** in 40–50% yields. However, to our satisfaction, the reverse addition comprising of addition of the ketones **8x**, **8y** and **8z** independently to a solution of *p*-methoxyphenylmagnesium bromide (2.5 equiv) in THF at temperature ranging from 15 to 20 °C furnished the corresponding alcohols **9x**, **9y** and **9z** in 76%, 80% and 78%, respectively, along with much reduced quantities (10–15%) of ketones (Scheme 1).

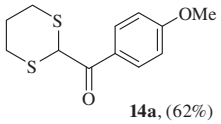
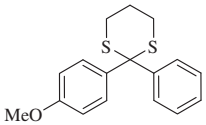
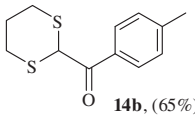
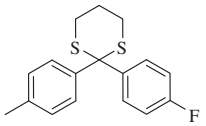
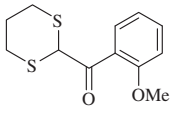
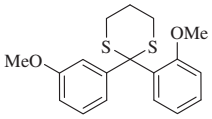
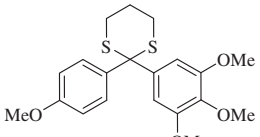
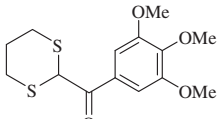
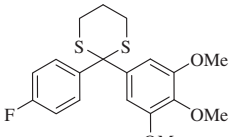
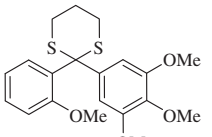
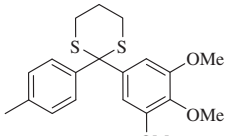
The recovery of ketones is not deleterious as they can be used in the fresh batch of the same reaction to obtain the alcohols **9x–z** or with other arylmagnesium bromides. Having successfully obtained the alcohols **9x-z**, our next aim was to subject these alcohols to deoxygenation and hydrolysis of the thioacetal moiety to arrive at α,α′-diarylacetaldehyde **11**. Tertiary alcohol **9x** failed to furnish the deoxygenated thioacetal **10x** under Et_3SiH/TFA conditions. Even with the change in Lewis acid component (BF_3Et_2O, $SnCl_2$) and reaction conditions, TLC showed only degradation. We focused our attention in evaluating the alcohols **9y** and **9z** towards the same deoxygenation protocol. Indeed alcohols **9y** and **9z** underwent clean deoxygenation with Et_3SiH/TFA conditions at 0–5 °C affording the corresponding alkanes **10y** and **10z** each in good yields (80%). The attempted hydrolysis of the thioacetal moiety in **10y** and **10z** also had contrasting behaviour. The compound **10y** did not undergo hydrolysis and gave only the starting material back under variety of thioketal de-protecting protocols available in literature,[13] whereas the compound **10z** underwent clean hydrolysis using $HgCl_2$/HgO in CH_3CN/H_2O mixture at 70 °C to yield **11**. This sharp contrasting behaviour between **10y** and **10z** raised some doubts on the structural aspect of the compound **10y**. Single crystal X-ray diffraction data[14] of the compound **10y**, confirmed the structure assigned to it. The α,α′-diarylacetaldehyde **11** obtained



Scheme 2. Reagents and conditions: (a) $HgCl_2$ (3.0 equiv), HgO (3.0 equiv), ACN/H_2O (3:1, 10 V), 70 °C, 3 h; (b) $NaBH_4$ (1.1 equiv), MeOH (5 V), 0 °C, 1 h, 75% (2 steps); (c) (i) MsCl (1.25 equiv), TEA (2.1 equiv), DCM (10 V), rt, 8 h; (ii) DBU (3.0 equiv), DCM (10 V), rt, 10 h, 70% (2 steps).

Table 1
1,1-Diaryl ethenes **7a–c** and isocombretastatin analogues **3a–d**

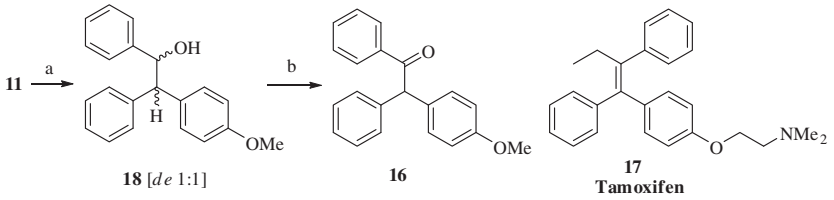


Entry	Aryl ketone **14** (yield)	Dithiane **10Z**, **15** (yield for 2 steps)	Alcohol **12** (yield for 2 steps)	1,1-Diaryl ethenes **7/3** (yield for 2 steps)
1	 **14a**, (62%)	 **10z**, (63%)	**12a** (75%)	**7a** (70%)
2	 **14b**, (65%)	 **15b**, (62%)	**12b** (74%)	**7b** (66%)
3	 **14c**, (63%)	 **15c**, (60%)	**12c** (70%)	**7c** (65%)
4		 **15d**, (64%)	**12d** (70%)	**3a** (64%)
5	 **14d**, (62%)	 **15e**, (62%)	**12e** (68%)	**3b** (65%)
6		 **15f**, (63%)	**12f** (72%)	**3c** (68%)
7		 **15g**, (61%)	**12g** (70%)	**3d** (66%)

through the hydrolysis of **10z** was passed through small filtration column of silica-gel and subjected to reduction with $NaBH_4$ immediately. The primary alcohol **12a** obtained in quantitative yield was converted to the mesylate **13a** and subjected to elimination reaction under DBU conditions to furnish 1,1-diarylethenes **7a** (Scheme 2).

Having realized that amongst the three WA-based building blocks **4x–z**, proposed for arriving at 1,1-diarylethenes through a new strategy, **4z** was the most promising one. Further, successful addition of various arylmagnesium bromide demonstrated the generality associated with the developed new strategy to arrive at **7**, 1,1-diarylethenes class of compounds (Table 1). For the targeted synthesis of isocombretastatin analogues, addition of 3,4,5-trimethoxyarylmagnesium bromide, generated from 3,4,5-trimethoxybromo benzene which can be prepared in two steps from commercially available 2,6-dimethoxy phenol using a literature procedure,[15] onto WA functionality **4z** as one of the arylmagnesium bromide becomes imperative as this aryl residue is most crucial for the biological activity. Successful formation of **3a**, **3b**, **3c** and **3d** (Table 1) as isocombretastatin analogues, illustrates the useful application of developed strategy for 1,1-diarylethene class of compounds. All compounds exhibited satisfactory spectral and analytical details.

Interestingly, α,α′-diarylacetaldehyde **11** also served as a valuable intermediate for the synthesis of 1,2,2-triarylethanone **16**,[16] an advanced precursor for tamoxifen **17** which is a therapeutically



Scheme 3. Reagents and conditions: (a) PhMgBr (1.2 equiv), THF, 0 °C, 1 h, 75%; (b) PCC (2.0 equiv), DCM (10 V), rt, 1 h, 80%.

used drug for the treatment of oestrogen dependent breast cancer (Scheme 3). Addition of preformed phenylmagnesium bromide onto the aldehyde **11** yielded the alcohol **18** in 75% (1:1 de). This alcohol **18** upon oxidation under PCC (Pyridinium chlorochromate) condition yielded the triaryl ethanone **16** in good yields of 80%. Given the fact that 1,2,2-triarylethanones constitutes an important class of compounds, this achievement further illustrates the potential of our new building block **4z** for other synthetic endeavours.

In conclusion, amongst the building blocks **4x**, **4y** and **4z** conceived for the synthesis of 1,1-diarylethenes in general and isocombretastatin analogues in particular, **4z** was found to be the most useful. The developed strategy demonstrates the versatility factor in assembling the aryl residues on the ethylene bridge. All the reactions and conditions en-route synthesis of target molecule are simple, good yielding and amenable for scale-up.

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Supplementary data

Supplementary data (containing experimental procedure, spectral details and ^{1}H and ^{13}C spectra for selected compounds is available) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.03.072.

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