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Cerium(III)-catalyzed regioselective coupling of 2-hydroxychalcones and polyphenols: an efficient domino approach towards synthesis of novel dibenzo-2,8-dioxabicyclo[3.3.1]nonanes

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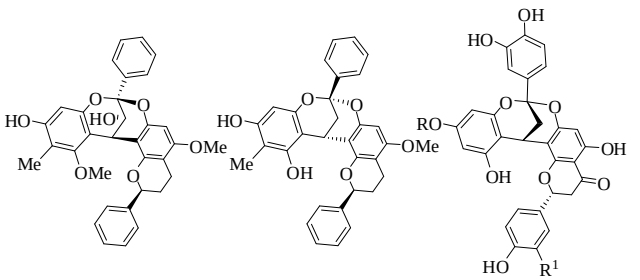
Efficient one-pot construction of functionalized dibenzannulated bicyclic-*O*,*O*-ketals is accomplished by $CeCl_3.7H_2O$-NaI (5 mol% each) catalyzed coupling of 2-hydroxychalcones with resorcinol/phloroglucinol *via* regioselective Michael addition-bicyclization cascade. The enhanced nucleophilicity driven reaction of phloroglucinol with two chalcone partners delivered facile access to unprecedented novel bisbicyclic-*O*,*O*-ketals. Installation of hydrogen donor phenolic function in the conformationally constrained bicyclic-*O*,*O*-ketal core make the designed targets potential anticoagulant candidates.

Introduction

The 2,8-dioxabicyclo[3.3.1]nonane scaffold features in a host of natural and unnatural compounds of diverse biological relevance.[1] It constitutes the core substructure of medicinally valuable dracoflavans, the biflavanoid constituents of resinous exudates of several plants, known as Dragons' Blood.[2a] Significantly, this bicyclic motif linearly annulated with polyphenols are expressed in several plant products endowed with anticancer, antioxidant and antiplatelet aggregation activities. Procyanidin A1,[2c] diinsininol,[2d] diinsinin,[2d] dracoflavan D[2a] represent some members of this class of bioactive compounds (Scheme 1). Several initiatives towards synthesis of compounds embodying this structural bicyclc motif are also documented.[2e-h]



Dracoflavan B Dracoflavan D Diinsininol: R = β-glucose, R^1 = OH
Diinsinin: R = β-glucose, R^1 = H

Scheme 1 Some representative bioactive natural products containing 2,8-dioxabicyclo[3.3.1]nonane subunit.

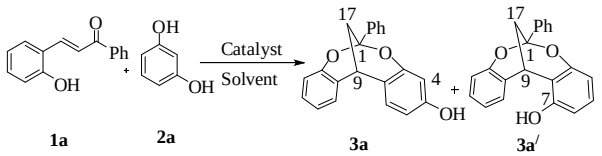
Serious concern about toxicity and side effects of versatile anticoagulants,[3] warfarins and their second generation variants, superwarfarins[4] triggered sustained synthetic initiatives aimed at designing and creating library of structurally diversified anticoagulant candidates for biological screening.[5] The initial forays were based on reactions of 4-hydroxycoumarins with benzalacetone/α,β-enones,[6a] 3-acetylcoumarin[5b] under various acidic and basic conditions. However, these attempts were constrained by failure to arrive at the correct structure of the products. Subsequently, X-ray crystallographic studies[5a] revealed that these products embody a 2,8-dioxabicyclo[3.3.1]nonane core annulated with α-pyrone moiety of the coumarin and benzene. They exhibited moderate vitamin K 2,3-epoxide reductase (VKOR) inhibition activity,[6b, 6c] the lack of crucial enolic hydroxy group notwithstanding. Inasmuch as the hydrogen bond donor activity of 4-OH is critically required for vitamin K antagonism of warfarins, these novel conformationally constrained bicyclic motifs containing *O*,*O*-acetal stregeogenic centre[2h] represent a new paradigm of anticoagulant activity. An attractive synthetic approach towards access of these novel targets is based on domino coupling of various carbon nucleophiles with readily accessibile 2-hydroxychalcones as modular building blocks.[7] Some successful entries include reactions of 2-hydroxychalcone with cyclic 1,3-diones in toluene under refluxing condition,[7a] phenols/naphthols under AgOTf catalysis[7b] and 4-hydroxycoumarin/dimedone in the presence of iodine catalyst.[7c] An elegant $AuBr_3$-catalyzed approach based on reaction of aldehyde-substituted vinylogous carbonates and 1,3-diketones through Knoevenagel-hetero Diels-Alder sequence in aqueous ethanol has been also revealed.[8] Use of expensive reagents and protracted reaction times are limitations of most of these existing protocols. Inspired by the ubiquitous presence of dibenzannulatedbicyclic-*O*,*O*-ketals, particularly those incorporating polyphenols in nature, we felt a need to elaborate similar molecular frameworks from readily accessible simple building blocks. In continuation of our interest in the development of greener synthetic protocols of 2,8-dioxabicyclo[3.3.1]nonanes,[7c] we embarked on the synthesis of targets adorned with methylene bridge and fused with phenolic moiety. The hydrogen bond donor ability of installed phenolic

group would further enable to address VKOR enzyme inhibition process[6b] thereby enlarging anticoagulant activity profile of the designed targets. It was anticipated that 2-hydroxychalcone and polyphenol such as resorcinol/phloroglucinol would constitute competent coupling partners to deliver these targets through one-pot Michael addition-bicyclization domino process. These polyphenols are themselves interlinked in the biogenetic map as they are generated from a common linear tetraketide precursor by divergent cyclization routes.[9] It was previously reported that naphthols reacted sluggishly but selectively with α,β-unsatured cyclic enones *via* Fridel-Crafts-acetallization cascade under iminium ion catalysis.[10a] However, acid-catalyzed reaction of resorcinol with α,β-enones is often unselective involving multiple condensations to give various benzopyrans and chromans depending on the nature of enones and reaction conditions, particularly the acid promoter used.[10b] To address the selectivity issue of the coupling reaction in our case, cerium(III) chloride heptahydrate was identified as an attractive Lewis acid catalyst. It is an inexpensive, nontoxic, water- and air-tolerant lanthanide salt compatible with acetonitrile and a good number of common organic solvents. It is a proven electrophilic activator of carbonyls of broad reactivity levels including α,β-enones and promoter of C-C and C-O bond formation reactions.[11a, 11f-h] It can modulate the reactivity of phenolic hydroxy groups as well by coordination. The catalytic activity of $CeCl_3.7H_2O$ can be further reinforced by addition of iodide.[12] Herein, we reveal an environmentally friendly, straightforward regioselective entry to novel 2,8-dioxabicyclo[3.3.1]nonanes through $CeCl_3.7H_2O$-NaI catalyzed reaction of 2-hydroxychalcones with resorcinol. The protocol has been further extended to similar reaction with phloroglucinol to deliver hitherto unprecedented bisbicyclononanes.

Results and discussion

Initially, we chose 2-hydroxychalcone (**1a**) and resorcinol (**2a**) as reaction partners and allowed them to react in 1:1 millimolar ratio in water under refluxing condition without any catalyst in order to assess their inherent propensity towards coupling. No progress of the reaction was evident after 6 h (TLC monitoring) and **1a** was recovered unchanged in near quantitative yield (entry 1, Table 1). Switching over to polar aprotic solvent acetonitrile was not a success either. These results reflect the unreactive nature of 2-hydroxychalcone as a Michael acceptor[13] primarily due to attenuated electrophilic character of its α,β-enone moiety and unfavourable steric factor associated with nucleophilic attack on its π-face. The Michael addition of chalcones, particularly those bearing electron-releasing substituents at C-2, towards cyclic C-nucleophiles are generally reported to be sluggish and required catalytic assistance.[7a, 7c]. The failure of uncatalyzed reactions prompted us to scout for a suitable catalytic optimized condition for coupling. Exposure of the same mixture in the presence of $CeCl_3.7H_2O$ (10 mol%) in acetonitrile at reflux for 6 h cleanly and exclusively provided **3a** in reasonable 63% yield (entry 3). Its ^{1}H-NMR spectrum showed, in addition to characteristic high field signals of methylene protons at δ 2.37 (d, J = 2.8Hz, 2H, H-17s) and methine proton at δ 4.04 (t, J = 2.8 Hz, 1H, H-9), all twelve required aromatic signals including that due to unique *meta*-coupled proton H-4 in the phenolic moiety at δ 6.52 (d, J = 2.4Hz, 1H). This feature settles the substitution pattern of the resorcinol subunit and, therefore, confirmed the assigned site selectivity of the Michael addition. Addition of 10 mol% of NaI to the above mixture vastly improved the reaction performance delivering **3a** rapidly and efficiently (93%, 2 h) (entry 4). To our gratification, almost identical result was attainable with lower amounts of catalyst combination (5 mol% each; entry 5). The catalytic activity of $CeCl_3.7H_2O$ was also found to be markedly dependent upon the iodide additive used. The organic iodide additive, tetra-*n*-butylammonium iodide (TBAI) was less effective and afforded poorer yield (entry 6). Further lowering of catalyst level (2 mol% each) was not beneficial as the yield dropped off to 71% (entry 7).

Table 1 Optimization experiments for the synthesis of **3a**



1a **2a** **3a** **3a**$^{/}$

Entry	Catalyst (mol%)	Additive (mol%)	Solvent (2 mL)	Time[a] (h)	Yield[b] (%) of **3a**	Yield[b] (%) of **3a**$^{/}$[c]
1	-	-	H_2O	6	-	-
2	-	-	CH_3CN	6	-	-
3	$CeCl_3.7H_2O$ (10)	-	CH_3CN	6	63	-
4	$CeCl_3.7H_2O$ (10)	NaI (10)	CH_3CN	2	93	-
5	$CeCl_3.7H_2O$ (5)	NaI (5)	CH_3CN	2	94	-
6	$CeCl_3.7H_2O$ (5)	TBAI (5)	CH_3CN	2	85	-
7	$CeCl_3.7H_2O$ (2)	NaI (2)	CH_3CN	2	71	-
8	$CeCl_3.7H_2O$ (5)	NaI (5)	THF	8	-	-
9	$CeCl_3.7H_2O$ (5)	NaI (5)	$CHCl_3$	8	5	-
10	$CeCl_3.7H_2O$ (5)	NaI (5)	MeOH	6	49	-
11	$CeCl_3.7H_2O$ (5)	NaI (5)	EtOH	2	75	-
12	$CeCl_3.7H_2O$ (5)	NaI (5)	H_2O	2	65	-
13	I_2 (5)	-	CH_3CN	4	41	-
14	$BiCl_3.2H_2O$ (5)	-	CH_3CN	4	82	-
15	$FeCl_3.6H_2O$ (5)	-	CH_3CN	4	45	-
16	$ZrOCl_2.8H_2O$ (5)	-	CH_3CN	4	62	-
17	$SnCl_2.2H_2O$ (5)	-	CH_3CN	4	81	-

[a] 1 mmol of each starting material was heated at reflux temperature.

[b] Isolated yields after column chromatography.

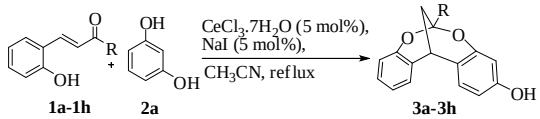
[c] The regioisomer **3a**$^{/}$ was not detected and isolated under these conditions studied.

Several organic solvents such as THF, $CHCl_3$, MeOH, EtOH as well as H_2O were screened but they could not outperform acetonitrile (entries 8-12) and, therefore, latter proved to be the solvent of choice. The poor solubility of $CeCl_3.7H_2O$ in acetonitrile allows attainment of heterogeneity that is crucial for its superior catalytic activity.[11a] A few water-compatible mild Lewis acid catalysts such as I_2, $BiCl_3.2H_2O$, $FeCl_3.6H_2O$, $ZrOCl_2.8H_2O$, $SnCl_2.2H_2O$ were also evaluated as alternative to $CeCl_3.7H_2O$–NaI. Identical regioselectivity was observed when these catalysts were employed at identical catalyst loading; however, **3a** was formed in lower yields and required extended reaction time compared to $CeCl_3.7H_2O$-NaI catalyzed reaction (entries 13-17). AgOTf-catalyzed coupling of resorcinol with 2-

hydroxychalcones led to identical regioselective products (4 examples) in 60-65% yield with resorcinol as substrate, although higher catalyst loading (20 mol%), and longer reaction time (18 h) were required.[7b]

With the satisfactory optimized condition [$CeCl_3.7H_2O$-NaI (5 mol% each), CH_3CN (2 mL), reflux, 2h] in hand, we explored its substrate scope with respect to 2-hydroxychalcone with its carbonyl variously substituted with electron-rich and electron-deficient aryl moieties (entries 1-4, 7, 8; Table 2), α,β-enones bearing ketomethyl and 2-thiophenyl groups (entries 5,6). It proved successful and provided decent yields (87-95%) of **3a-3h** in acceptable reaction times. The benzyloxy, substituted allyloxy and 2-thiophenyl moieties were also well-tolerated under the reaction conditions. These results clearly revealed that presence of electron-releasing as well as electron-withdrawing C-4′ substituents of the chalcone had no perceptible effect on the facility of the reaction.

Table 2 $CeCl_3.7H_2O$-NaI catalyzed coupling of 2-hydroxychalcone/α,β-enone with resorcinol



1a-1h **2a** **3a-3h**

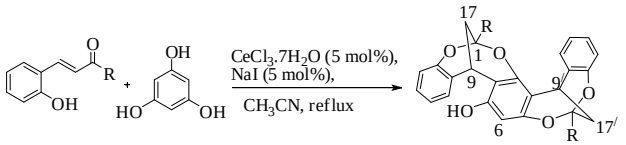
Entry	2-hydroxychalcone/ α,β-enone	R	Product	Time[a] (h)	Yield[b] (%)
1	**1a**	Ph	**3a**	2	94
2	**1b**	4′-Me-C_6H_4	**3b**	3	92
3	**1c**	4′-benzyloxy-C_6H_4	**3c**	3	90
4	**1d**	4′-(2-methylallyloxy)-C_6H_4	**3d**	3	87
5	**1e**	Me	**3e**	4	95
6	**1f**	2-thiophenyl	**3f**	3	92
7	**1g**	4′-Cl-C_6H_4	**3g**	3	94
8	**1h**	4′-F-C_6H_4	**3h**	3	91

[a] Reactions were conducted on 1 mmolar scale.

[b] Isolated yields.

Encouraged by these results, we extended the scope of the protocol to phloroglucinol (**2b**) as nucleophile component. The reaction of a 1:1 mixture of **1a** and **2b** under the optimized reaction conditions was essentially complete within 2 h affording exclusively **4a**, but surprisingly, in low yield (38%). The presence of two dioxabicyclononane substructures was discernible from the high field signals of its ^{1}H-NMR spectrum. It exhibited two distinct triplet peaks at δ 4.45 and 4.42 (J = 2.8Hz, 1H each) corresponding to methine protons (H-9 and 9′) of the bisbicyclic structure. The appearance of two sets of methylene proton at C-17 and C-17′ resonances at δ 2.43, 2.26 (dd, J = 13.2, 3.2Hz, 1 H each) and δ 2.19, 2.16 (dd, J = 13.2, 3.2Hz, 1H each) corroborates this. The appearance of nine aromatic proton signals including one-proton singlet at δ 6.12 due to H-4 of the tetrasubstituted phenolic core is further supportive of the structure **4a**. Significantly, the product **4a** is enriched with six sp^3 centers and four chiral carbons. To improve its yield, the reaction was performed employing **1a** and **2a** in 2:1 ratio under otherwise identical conditions to afford it in 79% yield without compromising selectivity (Table 3, entry 1). Attempt to suppress multiple bicyclizations by stopping the reaction short of completion proved abortive. In fact, the product arising out of first Michael addition-bicyclization cascade defied isolation in all cases presented in Table 3. The presence of 4′-Me, -Cl, -F, -Br substituents in the ketoaryl moiety of chalcones (entries 2-5) slowed down the overall reaction rates. The enhanced reactivity of phloroglucinol (pKa 8.45) may be attributed to its greater nucleophilicity arising out of ionization compared to that of resorcinol (pKa 9.15). Presumably, it tends to react readily as a dienolate which is favored in hydrogen bond accepter solvent, acetonitrile.[14]

Table 3 $CeCl_3.7H_2O$-NaI catalyzed condensation reaction of 2-hydroxychalcone/α,β-enone with phloroglucinol



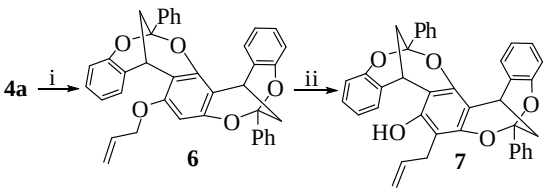
1a, **1b**, **1g-1j** **2b** **4a**, **4b**, **4g-4j**

Entry	2-hydroxychalcone/α,β-enone	R	Product	Time[a] (h)	Yield[b] (%)
1	**1a**	Ph	**4a**	2	79
2	**1b**	4′-Me-C_6H_4	**4b**	4	83
3	**1g**	4′-Cl-C_6H_4	**4g**	4	80
4	**1h**	4′-F-C_6H_4	**4h**	4	81
5	**1i**	4′-Br-C_6H_4	**4i**	4	84
6	**1j**	Et	**4j**	2.5	88

[a] Reactions were conducted with 2-hydroxychalcone/α,β-enone and phloroglucinol in 2:1 molar ratio.

[b] Isolated yields.

The unsymmetrical substitution pattern of **4a** was confirmed by the Claisen rearrangement of its *O*-allylated derivative **6** in 1,2-dichlorobenzene under reflux for 16 h to afford the rearranged *C*-allyl derivative **7** (Scheme 2). This result rules out the alternative symmetrically substituted phloroglucinol core which entails *para*-relationship of the free hydrogen with phenolic group and attests the presence of a free *ortho*-position in the phenol substructure of **4a**.

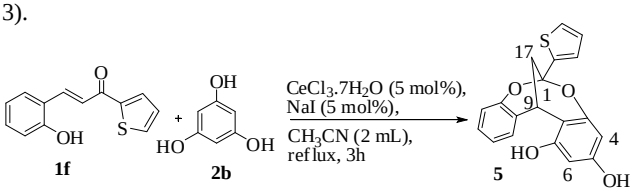


i: allyl bromide, K_2CO_3, acetone, reflux, 10 h, 95%

ii: 1, 2-dichlorobenzene, reflux, 16 h, 85%

Scheme 2 Claisen rearrangement of **6** to *ortho*-allylated phenol **7**

Surprisingly, the reaction of the substrate **1f** bearing 2-thiophenyl moiety at the carbonyl group did not proceed beyond the monobicyclization stage allowing isolation of product **5** (Scheme 3).

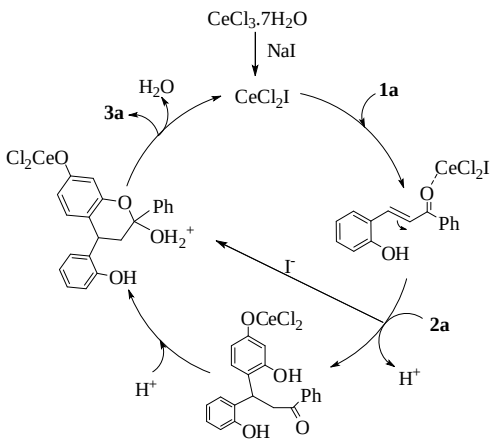


1f **2b** **5**

Scheme 3 $CeCl_3.7H_2O$-NaI catalyzed coupling of **1f** and phloroglucinol (**2b)**

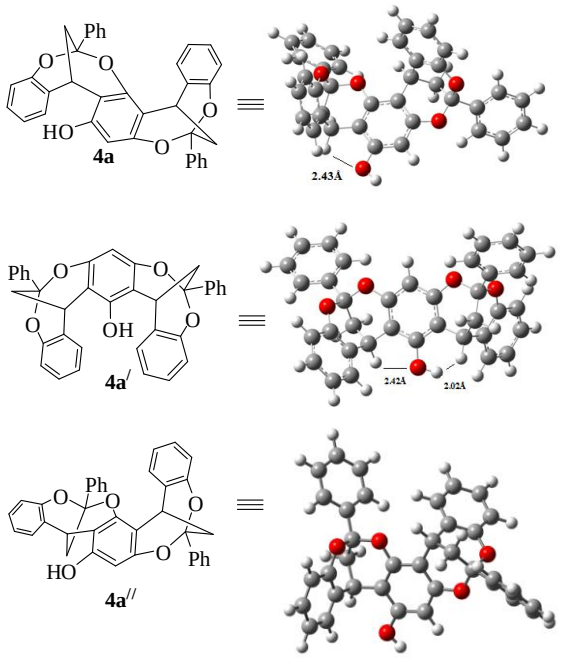
The key C-C bond construction for the bisbyclization event involves highly sterically congested C-4 of **5** and is presumably discouraged due to carbonyl deactivation by strong electron-releasing potential of sulfur of the thienyl moiety. In sharp contrast to **4a**, its ^{1}H-NMR spectrum exhibited three typical methylene bridge proton signals at δ 4.43 (d, J = 2.4Hz, 1H, H-9) and 2.45 (d, J = 2.8Hz, 2H, H-17) confirming the presence of only one bicyclic ring. Apart from thiophenyl proton signals, the appearance of six aromatic proton signals was consistent with the presence of a 1,3-diphenol substructure of which two relatively shielded protons showed them up at δ 6.07 (d, J = 2.4 Hz, 1H, H-4) and 5.82 (d, J = 2 Hz, 1H, H-6) respectively. Its HRMS data also supported the assigned structure **5**. The present protocol provided entry to a small collection of unprecedented novel molecular architectures comprising two bicyclic-*O*,*O*-ketals fused onto a phloroglucinol core.

A plausible catalytic cycle is proposed in Scheme 4. The present protocol relies on regioselective construction of C-C bond by way of Michael addition of polyphenols to the π-face of the α,β-enone moiety of the 2-hydroxychalcone (**1a**). This key initial event removes the conformational restriction of the pendant sidechain allowing its 'folding up' for subsequent bicyclization involving the carbonyl and two phenolic groups of complementary reactivities. The reaction of resorcinol with **1a** occurs selectively at the ring site that is synergistically activated by *ortho*- and *para*-phenolic OH-groups. The alternative possibility of nucleophilic involvement of C-2 is likely to be hindered due to juxtaposition of two bulky *ortho*-hydroxy groups complexed with Ce(III). Analogous steric hindrance of the bulky Ce(III)-complexed hydroxy group in the vicinity of the bicyclization site has been previously reported.[15] In case of phloroglucinol (**2b**) the formation of the initial C-C bond necessarily entails a nucleophilic site *ortho* to two hydroxy groups. The unfavorable steric interaction so encountered is seemingly overcome by strong synergic activation of all phenolic groups. However, the C-C bond formation that follows as a prelude to next bicyclization exhibited preference for the sterically less encumbered ring carbon.



Scheme 4 Plausible catalytic cycle of $CeCl_3.7H_2O$-NaI catalyzed coupling of **1a** and **2a**.

The AM1 calculation showed that the unsymmetrical bicyclic structure **4a** is also energywise favored (E= -36.326 Kcal mol^{-1}) over the corresponding symmetric formulation **4a**$^{/}$ (E= - 35.760 Kcal mol^{-1}) (Scheme 5). AM1 calculation of another possible structure **4a**$^{//}$ that contains different disposition of stereogenic centres has been performed. It was showed to be less stable (E= -36.025 Kcal mol^{-1}) than **4a**.



Scheme 5 AM1 optimized structures of **4a**, **4a**$^{/}$ and **4a**$^{//}$.

Conclusions

In summary, one-pot rapid and efficient access to dibenzannulated-2,8-dioxabicyclo[3.3.1]nonane motif has been accomplished by way of coupling 2-hydroxychalcones with polyphenols (resorcinol, phloroglucinol) under the catalytic influence of combo $CeCl_3.7H_2O$-NaI (5 mol% each) in acetonitrile. The elaboration of the structurally diverse molecular frameworks is based on site-selective C-C bond construction by Michael addition followed by bicyclization through multiple C-O bond formations. The reaction of phloroglucinol (1,3,5-trihydroxybenzene) is particularly intriguing as it engages two chalcone units through repeated cascade sequences to deliver hitherto unprecedented novel bisbicyclic-*O*,*O*-acetals annulated to its core. Installation of hydrogen bond donor phenolic functions in the conformationally constrained *O*,*O*-bicyclic acetal motif adds a critical attribute of VKOR enzyme inhibition activity of versatile anticoagulants, warfarin analogues and, therefore, expected to widen the diverse biological space of the target molecules. The key advantageous features of the present optimized procedure are the use of inexpensive starting materials, low catalyst loading and simplicity of the procedure that does not demand exclusion of air and water. A collection of novel potential anticoagulant targets is achieved in exclusive selectivity in good to excellent yields and essentially free from byproducts.

Experimental

Typical experimental procedure for the synthesis of bicyclononane 3a

To a solution of 3-(2-hydroxyphenyl)-1-phenylprop-2-en-1-one (**1a**) (230 mg, 1.03 mmol) and resorcinol (**2a**) (114 mg, 1.04 mmol) in acetonitrile (2 mL) were added $CeCl_3.7H_2O$ (10 mg, 5 mol%) and NaI (4 mg, 5 mol%) and the resulting red coloured solution was heated at reflux for 2 h. After completion of the reaction (TLC monitoring) the cooled reaction mixture was extracted with EtOAc (3X6 mL), washed with water (2X3 mL) and dried (Na_2SO_4). The crude product obtained after removal of solvent from the combined extract was purified by column chromatography using EtOAc: *n*-hexane (1:19) as eluent to give a white solid **3a** (304 mg, 94%), m.p. 230-232 ^oC (Lit. 231-232 ^oC)[7b]; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 8.4, 1.6 Hz, 2H), 7.48-7.39 (m, 3H), 7.23 (dd, *J* = 8, 1.2 Hz, 1H), 7.14 (dt, *J* = 8.4, 1.6 Hz, 1H), 7.10 (d, *J* = 8 Hz, 1H), 7.03 (d, *J* = 8 Hz, 1H), 6.92 (dt, *J* = 8, 0.8 Hz, 1H), 6.52 (d, *J* = 2.4 Hz, 1H, H-4), 6.41 (dd, *J* = 8, 2.4 Hz, 1H), 4.74 (s, 1H, O**H**, exchangeable with D_2O), 4.04 (t, *J* = 2.8 Hz, 1H, H-9, nonexchangeable with D_2O), 2.37 (d, *J* = 2.8 Hz, 2H, H-17s) ppm; ^1H NMR (400 MHz, DMSO-d_6) δ 9.41 (s, 1H, O**H**), 7.70 (d, *J* = 6.8 Hz, 2H), 7.50-7.44 (m, 3H), 7.38 (d, *J* = 6.8 Hz, 1H), 7.19-7.15 (m, 1H), , 7.13 (t, *J* = 6.8 Hz, 1H), 6.96-6.90 (m, 2H), 6.35 (t, *J* = 2.4 Hz, 2H), 4.14 (s, 1H, H-9), 2.36 (s, 2H, H-17s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 152.8, 151.8, 141.4, 128.8, 128.4, 128.0, 127.1, 126.9, 125.8, 121.5, 119.1, 116.8, 108.8, 103.8, 98.7 (C-1), 33.6 (C-17/C-9) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.1, 152.0, 151.3, 141.2, 128.7, 128.3, 128.0, 127.6 (2C), 127.3, 125.5, 121.3, 117.5, 115.9, 108.8, 102.7, 98.2 (C-1), 32.4 (C-17), 31.9 (C-9) ppm; ^{13}C DEPT NMR (100 MHz, DMSO-d_6) δ **C**H: 128.7, 128.3, 128.1, 127.6, 127.3, 125.5, 121.3, 115.9, 108.8, 102.6, 31.8 (C-9), **C**H_2: 32.4 (C-17) ppm; IR (KBr): 3209, 3033, 2937, 2850, 1604, 1487, 1115, 755 cm^{-1}. HRMS (ESI) m/z: Calcd. for $C_{21}H_{17}O_3$ [M+H]: 317.1177. Found: 317.1172.

Bicyclononane 3b: White solid; m.p. 166-168 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8 Hz, 2H), 7.27-7.21 (m, 3H), 7.16-7.11 (m, 1H), 7.09 (d, *J* = 8 Hz, 1H), 7.01 (d, *J* = 8 Hz, 1H), 6.91 (t, *J* = 7.6 Hz, 1H), 6.51 (d, *J* = 2.4 Hz, 1H), 6.40 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.68 (s, 1H, O**H**), 4.02 (d, *J* = 2.8 Hz, 1H, H-9), 2.40 (s, 3H), 2.36 (d, *J* = 3.2 Hz, 2H, H-17s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 152.8, 151.9, 138.7, 138.5, 129.0, 127.9, 127.1, 126.9, 125.7, 121.5, 119.1, 116.8, 108.8, 103.8, 98.8 (C-1), 33.6 (C-17), 33.5 (C-9), 21.2 ppm; IR (KBr): 3260, 2937, 1629, 1604, 1588, 1485, 1118, 757 cm^{-1}. HRMS (ESI) m/z: Calcd. for $C_{22}H_{19}O_3$ [M+H]: 331.1334. Found: 331.1328.

Bicyclononane 3c: White solid; m.p. 206-208 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.8 Hz, 2H), 7.51-7.44 (m, 2H), 7.39 (t, *J* = 3.6 Hz, 2H), 7.33 (t, *J* = 7.2 Hz, 1H), 7.21 (d, *J* = 6.4 Hz, 1H), 7.15-7.11 (m, 1H), 7.09 (d, *J*= 8.4 Hz, 1H), 7.04 (d, *J*= 8.4 Hz, 2H), 7.00 (d, *J*= 8 Hz, 1H), 6.90 (t, *J*= 7.6 Hz, 1H), 6.50 (d, *J*= 2.4 Hz, 1H), 6.40 (dd, *J*= 8, 2.4 Hz, 1H), 5.11 (s, 2H), 4.83 (s, 1H, O**H**), 4.02 (s, 1H, H-9), 2.40-2.35 (m, 2H, H-17s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 155.4, 152.8, 151.9, 136.9, 133.9, 128.6, 128.0, 127.9, 127.5, 127.2, 127.1, 126.9, 121.5, 119.1, 116.7, 114.6, 108.8, 103.8, 98.7 (C-1), 70.1, 33.7 (C-17), 33.6 (C-9) ppm; IR (KBr): 3402, 2869, 1664, 1599, 1584, 1505, 1231, 999, 751 cm^{-1}. HRMS (ESI) m/z: Calcd. for $C_{28}H_{23}O_4$ [M+H]: 423.1596. Found: 423.1563.

Bicyclononane 3d: Pinkish white solid; m.p. 156-158 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 7.6 Hz, 1H), 7.15-7.11 (m, 1H), 7.09 (d, *J* = 8 Hz, 1H), 7.01-6.97 (m, 3H), 6.91 (t, *J*= 7.6 Hz, 1H), 6.50 (d, *J*= 2.4 Hz, 1H), 6.40 (dd, *J*= 8, 2.4 Hz, 1H), 5.11 (s, 1H), 5.00 (s, 1H), 4.67 (s, 1H, O**H**), 4.48 (s, 2H), 4.02 (s, 1H, H-9), 2.35 (d, *J* = 2.8 Hz, 2H, H-17s), 1.84 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 155.4, 152.9, 151.9, 140.8, 133.7, 127.9, 127.0, 126.9, 121.4, 119.1, 116.7, 114.5, 112.9, 108.7, 103.8, 98.7 (C-1), 71.8, 33.7 (C-17), 33.6 (C-9), 19.4 ppm; IR (KBr): 3526, 3207, 1626, 1612, 1594, 1457, 1233, 1149, 758 cm^{-1}. HRMS (ESI) m/z: Calcd. for $C_{25}H_{22}O_4$ [M+H]: 387.1596. Found: 387.1591.

Bicyclononane 3e: Off-white solid; m.p. 172-174 ^oC; ^1H NMR (400 MHz, $CDCl_3$): *δ* = 7.15 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.09-7.05 (m, 1H), 7.02 (d, *J* = 8.8 Hz, 1H), 6.86-6.83 (m, 2H), 6.35-6.32 (m, 2H), 4.72 (s, 1H, O**H**), 3.93 (t, *J* = 2.8 Hz, 1H, H-9), 2.21 (d, *J* = 3.2 Hz, 2H, H-17s), 1.84 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 152.6, 151.6, 127.9, 127.8, 127.0, 126.9, 121.2, 119.0, 116.4, 108.5, 103.5, 98.1 (C-1), 33.2 (C-17), 31.3 (C-9), 27.3 ppm; IR (KBr): 3480, 3387, 2936, 1619, 1601, 1508, 1485, 1142, 757 cm^{-1}. HRMS (ESI) m/z: Calcd. for $C_{16}H_{15}O_3$ [M+H]: 255.1021. Found: 255.1016.

Bicyclononane 3f: White solid; m.p. 206-208 ^oC (Lit. 218-219 ^oC)[7b]; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 4, 0.8 Hz, 1H), 7.32 (dd, *J* = 4, 1.2 Hz, 1H), 7.22 (dd, *J* = 8, 1.2 Hz, 1H), 7.15-7.11 (m, 1H), 7.09 (d, *J* = 8.4 Hz, 1H), 7.08-7.05 (m, 1H), 6.99 (d, *J* = 8 Hz, 1H), 6.94-6.90 (m, 1H), 6.49 (d, *J* = 2.4 Hz, 1H), 6.41 (dd, *J* = 8, 2.4 Hz, 1H), 4.70 (s, 1H, O**H**), 4.05 (t, *J* = 2.8 Hz, 1H, H-9), 2.52 (d, *J*= 2.8 Hz, 2H, H-17s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 152.4, 151.4, 144.9, 128.0, 127.9, 127.1, 126.9, 126.6, 126.0, 125.0, 121.7, 118.9, 116.8, 109.0, 103.8, 97.7 (C-1), 33.7 (C-17), 33.5 (C-9) ppm; IR (KBr): 3518, 3434, 2938, 1622, 1599, 1486, 1236, 1105, 706 cm^{-1}. HRMS (ESI) m/z: Calcd. for $C_{19}H_{15}O_3S$ [M+H]: 323.0742. Found: 323.0703.

Bicyclononane 3g: White solid; m.p. 150-152 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.8 Hz, 2H), 7.42 (d, *J* = 8.8 Hz, 2H), 7.23 (d, *J* = 7.2 Hz, 1H), 7.17-7.12 (m, 1H), 7.10 (d, *J* = 8 Hz, 1H), 7.01 (d, *J* = 8 Hz, 1H), 6.92 (t, *J* = 7.2 Hz, 1H), 6.50 (d, *J* = 2.4 Hz, 1H), 6.42 (dd, *J* = 8, 2.4 Hz, 1H), 4.86 (s, 1H, O**H**), 4.04 (d, *J* = 2.4 Hz, 1H, H-9), 2.34 (d, *J* = 3.2 Hz, 2H, H-17s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 152.6, 151.6, 140.0, 134.8, 128.5, 128.0 (2C), 127.4, 127.1, 126.7, 121.7, 118.8, 116.7, 109.0, 103.7, 98.3 (C-1), 33.5 (2C) (C-17 & C-9) ppm; IR (KBr): 3237, 2946, 1600, 1586, 1484, 1227, 1152, 729 cm^{-1}. HRMS (ESI) m/z: Calcd. for $C_{21}H_{16}ClO_3$ [M+H]: 351.0788. Found: 351.0732.

Bicyclononane 3h: White solid; m.p. 164-166 ^oC (Lit. 164-1652 ^oC)[7b]; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72-7.69 (m, 2H), 7.23 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.16-7.09 (m, 4H), 7.01 (d, *J* = 7.6 Hz, 1H), 6.94-6.90 (m, 1H), 6.50 (d, *J* = 2.4 Hz, 1H), 6.41 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.75 (s, 1H, O**H**), 4.03 (t, *J* = 2.8 Hz, 1H, H-9), 2.35 (d, *J* = 3.2 Hz, 2H, H-17s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 155.5, 152.6, 151.7, 137.3, 128.0, 127.8 (d, $^3J_{C\text{-}F}$ = 9 Hz), 127.1, 126.7, 121.6, 119.0, 116.7, 115.2 (d, $^2J_{C\text{-}F}$ = 21 Hz), 109.0, 103.7, 98.4 (C-1), 33.7 (C-17), 33.5 (C-9) ppm; IR (KBr): 3530, 3252, 2938, 1605, 1506, 1485, 1227, 1119, 755 cm^{-1}. HRMS (ESI) m/z: Calcd. for $C_{21}H_{16}FO_3$ [M+H]: 335.1083. Found: 335.1007.

Typical experimental procedure for the synthesis of bisbicyclononane 4a

To a solution of 3-(2-hydroxyphenyl)-1-phenylprop-2-en-1-one (**1a**) (450 mg, 2.01 mmol) and phloroglucinol (**2b**) (165 mg, 1.02 mmol) in acetonitrile (2 mL) were added $CeCl_3.7H_2O$ (10 mg, 5 mol%) and NaI (4 mg, 5 mol%) and the red coloured solution was heated at reflux temperature for 2 h. After completion of the reaction (TLC monitoring) the cooled reaction mixture was extracted with EtOAc (3X8 mL), washed with water (2X3 mL), dried (Na_2SO_4) and the combined extract was concentrated under reduced pressure. The crude product was purified by column chromatography using EtOAc:light petrol (1:19) as eluent to give a white solid **4a** (427 mg, 79%), which was further recrystallized from EtOAc-*n*-hexane mixture (m.p. 250-252 ^oC). ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.2 Hz, 2H), 7.65 (d, *J* = 6.4 Hz, 2H), 7.57-7.50 (m, 3H), 7.44-7.35 (m, 4H), 7.25 (d, *J* = 5.6 Hz, 1H), 7.17 (t, *J* = 8 Hz, 2H), 7.11 (d, *J* = 8 Hz, 1H), 7.04 (d, *J* = 8 Hz, 1H), 6.95-6.89 (m, 2H), 6.12 (s, 1H), 4.98 (s, 1H, OH), 4.45 (t, *J* = 2.8 Hz, 1H, H-9/ H-9′), 4.42 (t, *J* = 2.8 Hz, 1H, H-9′/H-9), 2.42 (dd, *J* = 13.2, 3.2 Hz, 1H, H-17/H-17′), 2.26 (dd, *J* =13.2, 3.2 Hz, 1H, H-17/H-17′), 2.20 (dd, *J* = 13.2, 3.2 Hz, 1H, H-17′/ H-17), 2.15 (dd, *J* = 13.2, 3.2 Hz, 1H, H-17′/H-17) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 152.1, 151.5, 151.0, 149.4, 141.4, 141.3, 129.0, 128.7, 128.3, 128.2, 127.7, 127.4, 127.1, 126.1, 125.8, 121.4, 120.9, 116.3, 107.2, 106.9, 99.1 (C-1/C-1′), 98.8 (C-1′/C-1), 96.8, 60.7, 33.4 (C-17/C-17′), 32.8 (C-17′/C-17), 26.7 (C-9/C-9′), 21.2 (C-9′/C-9), 14.2 ppm; IR (KBr): 3411, 3034, 2948, 1614, 1485, 1237, 1111, 1070, 751 cm^{-1}. HRMS (ESI) m/z: Calcd. for $C_{36}H_{27}O_5$ [M+H]: 539.1858. Found: 539.1875.

Bisbicyclononane 4b: White solid; m.p. 256-258 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8 Hz, 2H), 7.53 (d, *J* = 8 Hz, 2H), 7.42 (d, *J* = 7.6 Hz, 1H), 7.35 (d, *J* = 8 Hz, 2H), 7.27 (d, *J* = 7.2 Hz, 1H), 7.21-7.14 (m, 4H), 7.09 (d, *J* = 8 Hz, 1H), 7.02 (d, *J* = 8 Hz, 1H), 6.94-6.89 (m, 2H), 6.10 (s, 1H), 4.88 (s, 1H, O**H**), 4.42 (t, *J* = 2.8 Hz, 2H, H-9 & 9′), 2.47 (s, 3H), 2.36 (s, 3H), 2.42-2.13 (m, 4H, H-17s & 17′s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 152.1, 151.3, 151.1, 149.4, 138.8, 138.6, 138.5 (2C), 129.0, 128.2, 127.7, 127.4, 127.1, 126.0, 125.6, 121.3, 120.8, 116.3, 107.1, 99.1 (C-1/C-1′), 98.8 (C-1′/C-1), 96.7, 33.3 (C-17/C-17′), 32.9 (C-17′/C-17), 26.7, 21.3 (C-9/C-9′), 21.2 (C-9′/C-9) ppm; IR (KBr): 3411, 3031, 2949, 1939, 1606, 1485, 1239, 1182, 1068, 751 cm^{-1}. HRMS (ESI) m/z: Calcd. for $C_{38}H_{30}O_5Na$ [M+Na]: 589.1991. Found 589.1991.

Bisbicyclononane 4g: White solid; m.p. 284-286 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 7.6 Hz, 1H), 7.37 (d, *J* = 8.8 Hz, 2H), 7.20-7.15 (m, 3H), 7.09 (d, *J* = 8.4 Hz, 1H), 7.02 (d, *J* = 8 Hz, 1H), 6.96-6.90 (m, 2H), 6.10 (s, 1H), 5.00 (s, 1H, O**H**), 4.45 (s, 1H, H-9/ H-9′), 4.38 (s, 1H, H-9′/H-9), 2.40-2.10 (m, 4H, H-17 & H-17′s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 151.8, 151.3, 150.9, 149.3, 139.9, 139.8, 135.0, 134.7, 128.5, 128.0, 127.9, 127.8, 127.7 (2C), 127.3, 127.1, 126.8, 121.6, 121.0, 116.3, 107.2, 106.9, 98.7(C-1/C-1′), 98.4 (C-1′/ C-1), 96.8, 33.3 (C-17/C-17′), 32.7 (C-17′/C-17), 26.7 (C-9/C-9′), 26.6 (C-9′/C-9) ppm; IR (KBr): 3315, 3039, 2975, 1627, 1484, 1458, 1234, 1116, 1014, 754 cm^{-1}. HRMS (ESI) m/z: Calcd. for $C_{36}H_{25}O_5Cl_2$ [M+H]: 607.1079. Found: 607.1094.

Bisbicyclononane 4h: White solid; m.p. above 290 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 8.4, 5.6 Hz, 2H), 7.62 (dd, *J* = 8.4, 5.6 Hz, 2H), 7.43 (d, *J* = 7.6 Hz, 1H), 7.24-7.16 (m, 6H), 7.09 (d, *J* = 8.4 Hz, 2H), 7.03 (t, *J* = 8.8 Hz, 1H), 6.96-6.85 (m, 2H), 6.11 (s, 1H), 4.98 (s, 1H, O**H**), 4.45 (s, 1H, H-9/H-9′), 4.39 (s, 1H, H-9′/H-9), 2.40 (dd, *J* = 13.2, 3.2 Hz, 1H, H-17/H-17′), 2.24 (dd, *J* = 13.2, 2.8 Hz, 1H, H-17/H-17′), 2.18 (dd, *J* = 13.6, 3.2 Hz, 1H, H-17′/H-17), 2.13 (dd, *J* = 13.2, 2.8 Hz, 1H, H-17′/H-17) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.4 (d, $^1J_{C\text{-}F}$ = 245 Hz), 162.2 (d, $^1J_{C\text{-}F}$ = 247 Hz), 153.1, 151.7, 151.4, 150.3, 148.4, 137.5, 137.3, 128.0 (d, $^3J_{C\text{-}F}$ = 9Hz), 127.8 (d, $^3J_{C\text{-}F}$ = 9 Hz), 127.6, 127.5, 127.4, 127.0, 121.1, 120.9, 115.8, 115.1 (d, $^2J_{C\text{-}F}$ = 21 Hz), 115.0 (d, $^2J_{C\text{-}F}$ = 22 Hz), 114.9, 107.1, 104.9, 98.3 (C-1/C-1′), 98.0 (C-1′/C-1), 95.7, 32.0 (C-17/C-17′), 31.0 (C-17′/C-17), 25.9 (C-9/C-9′), 25.8 (C-9′/C-9) ppm; IR (KBr): 3315, 3039, 2975, 1627, 1484, 1458, 1234, 1116, 1014, 754 cm^{-1}. HRMS (ESI) m/z: Calcd. for $C_{36}H_{24}O_5F_2$ [M]: 574.1592. Found: 574.1592.

Bisbicyclononane 4i: White solid; m.p. 242-244 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72-7.66 (m, 4H), 7.54-7.52 (m, 4H), 7.42 (d, *J* = 7.6 Hz, 1H), 7.20-7.17 (m, 3H), 7.09 (d, *J* = 8.4 Hz, 1H), 7.02 (d, *J* = 8 Hz, 1H), 6.94 (t, *J* = 7.2 Hz, 2H), 6.11 (s, 1H), 5.02 (s, 1H, **OH**), 4.45 (s, 1H, H-9/H-9′), 4.39 (s, 1H, H-9′/H-9), 2.40-2.13 (m, 4H, H-17s & H-17′s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 152.1, 151.8, 150.7, 148.8, 141.0, 140.8, 132.0, 131.8 (2C), 131.7, 128.6, 128.5, 128.3, 128.1, 128.0, 127.4, 122.9, 122.6, 121.6, 116.3, 107.6, 105.5, 98.9 (C-1/C-1′), 98.8 (C-1′/C-1), 98.5, 96.3, 32.3 (C-17/C-17′), 31.5 (C-17′/C-17), 26.3 (C-9/C-9′) ppm; IR (KBr): 3309, 3038, 2938, 1627, 1485, 1234, 1115, 1071, 1010, 753 cm^{-1}. HRMS (ESI) m/z: Calcd. for $C_{36}H_{25}O_5Br_2$ [M+H]: 695.0068. Found: 695.0063.

Bisbicyclononane 4j: White solid; m.p. 240-242 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (dt, *J* = 7.6, 1.2 Hz, 2H), 7.10-7.05 (m, 2H), 6.90-6.82 (m, 4H), 5.90 (s, 1H), 4.78 (s, 1H, O**H**), 4.39 (t, *J* = 2.8 Hz, 1H, H-9/H-9′), 4.30 (t, *J* = 2.8 Hz, 1H, H-9′/H-9), 2.33-2.18 (m, 2H, H-17/H-17′s), 2.13-1.94 (m, 6H, H-17′/H-17s & four C**H**$_2$CH$_3$ protons), 1.25 (t, *J* = 7.6 Hz, 3H) 1.04 (t, *J* = 7.6Hz, 3H,) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 152.2, 151.0, 149.0, 127.6, 127.5, 127.4, 127.3, 120.8, 120.6, 116.1, 116.0, 107.1, 107.0, 99.9 (2C) **(**C-1 & C-1′**)**, 96.0, 33.3 (C-17/C-17′), 33.0 (C-17′/C-17), 28.4, 28.3, 26.0 (C-9/C-9′), 25.9 (C-9′/C-9), 8.0, 7.9 ppm; IR (KBr): 3409, 2979, 2940, 1623, 1485, 1459, 1234, 1108, 1061, 931, 864, 749 cm^{-1}. HRMS (ESI) m/z: Calcd. for $C_{28}H_{27}O_5$ [M+H]: 443.1858. Found: 443.1875.

Bicyclononane 5: White solid; m.p. 130-132 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.6 Hz, 1H), 7.36 (dd, *J* = 5.2, 0.8 Hz, 1H), 7.31 (d, *J* = 3.6 Hz, 1H), 7.15-7.11 (m, 1H), 7.07-7.04 (m, 1H), 6.99 (d, *J* = 8 Hz, 1H), 6.91 (t, *J* = 7.6 Hz, 1H), 6.07 (d, *J* = 2 Hz, 1H, H-4), 5.82 (d, *J* = 2.4 Hz, 1H, H-6), 5.09 (s, 1H, O**H** of C-5), 4.81 (s, 1H, O**H** of C-7), 4.43 (d, *J* = 2.4 Hz, 1H, H-9), 2.45 (d, *J*= 2.8 Hz, 2H, H-17) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 154.6, 152.8, 151.8, 145.4, 127.9, 127.5, 127.3, 126.8, 125.7, 124.8, 121.1, 116.1, 105.6, 97.7 (C-1), 96.6, 95.3, 33.7 (C-17), 26.5 (C-9) ppm; IR (KBr): 3604, 3533, 3423, 3343, 1619, 1484, 1464, 1230, 1140, 1017, 702 cm^{-1}. HRMS (ESI) m/z: Calcd. for $C_{19}H_{16}O_4S$ [M+H]: 339.0691. Found: 339.0703.

***O*-allylation of the bisbicyclononane 4a to 6**

To a solution of **4a** (150mg, 0.358 mmol) in dry acetone (10 mL) were added allyl bromide (65mg, 0.537 mmol) and K_2CO_3 (200mg, 1.44 mmol). The resulting solution was refluxed in water bath for 10 h (TLC monitoring) and filtered after cooling. The

residual solid was extracted with acetone (2X3 mL) and the combined extract and filtrate was concentrated to give a thick liquid. It was subjected to column chromatography over silica gel (60-120 mesh) using light petrol-ethyl acetate (19:1) as eluent to afford **6** which was further recrystallized from EtOAc-*n*-hexane to give a white crystalline solid (153 mg, 95%), m.p. 204-206 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.2 Hz, 2H), 7.70 (d, *J* = 7.6 Hz, 2H), 7.59-7.51 (m, 3H), 7.46-7.38 (m, 4H), 7.29 (d, *J* = 7.6 Hz, 1H), 7.23-7.18 (m, 2H), 7.13 (d, *J* = 8 Hz, 1H), 7.07 (d, *J* = 8 Hz, 1H), 6.96-6.92 (m, 2H), 6.26 (s, 1H), 6.21-6.12 (m, 1H), 5.52 (d, *J* = 17.2 Hz, 1H), 5.37 (d, *J* = 10.4 Hz, 1H), 4.61-4.55 (m, 2H), 4.54-4.41 (m, 2H, H-9 & 9′), 2.43 (dd, *J* = 13.2, 2.8 Hz, 1H, H-17/H-17′), 2.26 (dd, *J* = 13.2, 2.8 Hz, 1H, H-17/H-17′), 2.23-2.18 (m, 2H, H-17′/H-17s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3, 152.6, 152.1, 151.3, 141.5, 141.3, 133.2, 129.0, 128.7, 128.3, 128.2, 127.7, 127.6, 127.4, 127.1, 126.1, 125.7, 121.3, 120.8, 117.7, 116.3, 108.2, 106.8, 99.0 (C-1/C-1′), 98.8 (C-1′/C-1), 94.0, 69.1, 33.4 (C-17/C-17′), 32.8 (C-17′/C-17), 26.7 (C-9/ C-9′), 26.6 (C-9′/C-9) ppm; IR (KBr): 2936, 1622, 1602, 1484, 1237, 1118, 753 cm^{-1}. HRMS (ESI) m/z: Calcd. for $C_{39}H_{31}O_5$ [M+H]: 579.2171. Found: 579.2413.

Claisen rearrangement of 6

Compound **6** (100 mg, 0.173 mmol) was added to 1,2-dichlorobenzene (2 mL) and heated to reflux for 16 h (TLC monitoring). The reaction mixture was cooled and directly subjected to column chromatography over silica gel (60-120 mesh) using *n*-hexane-ethyl acetate (9:1) as eluent to afford **7** which was recrystallized from EtOAc-*n*-hexane mixture to give a white crystalline solid (85 mg, 85%), m.p. 216-218 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88-7.86 (m, 2H), 7.67-7.65 (m, 2H), 7.59-7.50 (m, 3H), 7.47-7.40 (m, 4H), 7.32-7.30 (m, 1H), 7.22-7.18 (m, 2H), 7.13 (d, *J* = 8 Hz, 1H), 7.06 (d, *J* = 8 Hz, 1H), 6.98-6.92 (m, 2H), 6.04-5.94 (m, 1H), 5.47 (s, 1H, O**H**), 5.31 (d, *J* = 17.2 Hz, 1H), 5.23 (d, *J* = 10 Hz, 1H), 4.49 (s, 1H, H-9/H-9′), 4.49 (s, 1H, H-9′/H-9), 3.64 (dd, *J* = 16.4, 5.6 Hz, 1H), 3.49 (dd, *J* = 16.4, 6.4 Hz, 1H, H-17/H-17′), 2.44 (dd, *J* = 13.2, 3.2 Hz, 1H, H-17/H-17′), 2.27 (dd, *J* = 13.6, 2.8 Hz, 1H, H-17′/H-17), 2.21 (dd, *J* = 13.2, 2.8 Hz, 1H, H-17′/H-17), 2.16 (dd, *J* = 13.2, 3.2 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 152.1, 151.0, 148.3, 147.6, 141.7, 141.4, 136.8, 129.0, 128.7, 128.3 (2C), 127.8, 127.7 (2 C), 127.4, 127.0, 126.1, 125.7, 121.3, 120.9, 116.9, 116.3 (2 C), 107.5, 106.8, 105.0, 99.0 (C-1/C-1′), 98.8 (C-1′/C-1), 33.4 (C-17/C-17′), 32.9 (C-17′/C-17), 28.1, 26.8 (2 C) (C-9 &-9′) ppm; IR (KBr): 3492 (OH), 2940, 1618, 1459, 1232, 1103, 757 cm^{-1}. HRMS (ESI) m/z: Calcd. for $C_{39}H_{31}O_5$ [M+H]: 579.2171. Found: 579.2530.

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Notes and references

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†Electronic Supplementary Information (ESI) available experimental details, spectroscopic data, copies of the ^{1}H NMR and ^{13}C NMR spectra of all final products.

1 (*a*) M. F. Xu, L. Q. Shen and K. W. Wang, *Fitoterapia*, 2009, **80**, 461–464; (*b*) K. I. Nakashima, N. Abe, F. Kamiya, T. Ito, M. Oyama and M. Iinuma, *Helv. Chim. Acta*., 2009, **92**, 1999–2008; (*c*) V. Dumontet, N. van Hung, M. T. Adeline, C. Riche, A. Chiaroni, T. Sévenet and F. Guéritte, *J. Nat. Prod*., 2004, **67**, 858–862.

2 (*a*) A. Arnone, G. Nasini and O. V. de Pava, *J. Nat. Prod*., 1997, **60**, 971–975; (*b*) Part 4. A. Arnone, G. Nasini and L. Merlini, *J. Chem. Soc., Perkin Trans. 1*, 1990, 2637-2640; (*c*) V. Dumontet, N. Van Hung, M. –T. Adeline, C. Riche, A. Chiaroni, T. Sévenet and F. Guéritte, *J. Nat. Prod*., 2004, **67**, 858-862; (*d*) A. Ogundaini, M. Farah, P. Perera, G. Samuelsson and L. Bohlin, *J. Nat. Prod*., 1996, **59**, 587-590; (*e*) C. Seleniski and T. R. R. Pettus, *Tetrahedron,* 2006, **62**, 5298-5307; (*f*) G. A. Kraus, Y. Yuan and A. Kempema, *Molecules*, 2009, **14**, 8807-815; (*g*) F. Wang, F. Chen, M. Qu, T. Li, Y. Liu and M. Shi, *Chem. Commun*., 2013, **49**, 3360-3362; (*h*) M. F. Polat, L. Hettmanczyk, W. Zhang, Z. Szabo and J. Franzen, *ChemCatChem*, 2013, **5**, 1334-1339.

3 (*a*) C. R. Routh, D. A. Triplett, M. J. Murphy, L. J. Felice, J. A. Sadowski and E. G. Bovill, *Am. J. Hematol*, 1991, **36**, 50-54; (*b*) R. Wallin, S. D. Patrick and L. F. Martin, *Int. J. Biochem.*, 1987, **19**, 1063-1068

4 M. R. Hadler and R. S. Shadbolt, *Nature*, 1975, **253**, 275-277.

5 (*a*) I. Manolov, C. Maichle-Moessmer and E. Z. Niquet, *Z. Naturforsch*, 2006, **61b**, 207-212; (*b*) I. Manolov and N. D. Danchev, *Eur. J. Med. Chem.*, 1995, **30**, 531-535.

6 (*a*) M. Ikawa, M. A. Stahmann and K. P. Link, *J. Am. Chem. Soc*., 1944, **66**, 902-906; (*b*) D. –U. Chen, P. –Y. Kuo and D. –Y. Yang, *Bioorg. Med. Chem. Lett*. 2005, **15**, 2665-2668; (*c*) R. B. Silverman and J. S. Oliver, *J. Med. Chem*. 1989, **32**, 2138-2141.

7 (*a*) G. Yin, T. Ren, Y. Rao, Y. Zhou, Z. Li, W. Shu and A. Wu, *J. Org. Chem*., 2013, **78**, 3132−3141; (*b*) Y. Rao and G, Yin, *Org. Biomol. Chem*., 2013, **11**, 6029–6035; (*c*) N. C. Ganguly, P. Mondal and S. Roy, *Tetrahedron Lett*., 2013, **54**, 2386-2390.

8 V. Srinivas and M. Koketsu, *J. Org. Chem*., 2013, **78**, 11612−11617.

9 P. M. Dewick, in *Medicinal Natural Products: A Biosyntheic Approach*, John Wiley & Sons Ltd, Chichester, U. K., 3rd edn., 2009, pp. 39-135.

10 *(a)* E. Paradisi, P. Righi, A. Mazzanti, S. Ranieri and G. Bencivenni, *Chem. Commun*., 2012, **48**, 11178-11180; *(b)* P. Livant and W. Xu, *J. Org. Chem*., 1998, **63**, 636-641.

11 (*a*) G. Bartoli, M. Bosco, A. Giuliani, E. Marcantoni, A. Palmieri, M. Petrini and L. Sambri, *J. Org. Chem*., 2004, **69**, 1290-1297; (*b*) Y. Yamamoto and N. Asao, *Chem. Rev*., 1993, **93**, 2207-2293; (*c*) J. –L. Luche and A. L. Gemal, *Tetrahedron Lett*., 1981, **22**, 4077-4080; (*d*) A. L. Gemal and J. –L. Luche, *J. Am. Chem. Soc*., 1979, **101**, 5848-5849; *(e)* E. Torregiani, G. Seu, A. Minassi and G. Appendino, *Tetrahedron Lett*., 2005, **46**, 2193–2196; (*f*) G. Bartoli, M. Bosco, M. C. Bellucci, E. Marcantoni, L. Sambri and E. Torregiani, *Eur. J. Org. Chem.,* 1999, 617-620; (*g*) G. Bartoli, E. Marcantoni, M. Marcolini and L. Sambri, *Chem. Rev*., 2010, **110**, 6104–6143; (*h*) S. Kobayashi, in *Lanthanides: Chemistry and Use in Organic Synthesis*, Springer-Verlag, Heidelberg, Germany, 1999.

12 (*a*) G. Bartoli, M. Bosco, G. Foglia, A. Giuliani, E. Marcantoni and L. Sambri, *Synthesis*, 2004, 895-900; (*b*) G. Bartoli, M. Bartolacci, M. Bosco, G. Foglia, A. Giuliani, E. Marcantoni, L. Sambri and E. Torregiani, *J. Org. Chem.*, 2003, **68**, 4594-4597.

13 (*a*) L. Liu, Y. Zhu, K. Huang, W. Chang and J. Li, *Eur. J. Org. Chem*., 2013, 2634-2645; (*b*) G. Wang, X. Wang, Z. Ge, T. Cheng and R. Li, *Chem. Commun*., 2010, **46**, 1751-1753.

14 R. J. Highet and I. V. Ekhato, *J. Org. Chem*., 1988, **53**, 2843-2844.

15 M. –C. P. Yeh, W. –J. Yeh, L. –H. Tu and J. –R. Wu, *Tetrahedron*, 2006, **62**, 7466-7470.