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The Application of 2-Benzyl-1,4-naphthoquinones as Pronucleophiles in Aminocatalytic Synthesis of Tricyclic Derivatives

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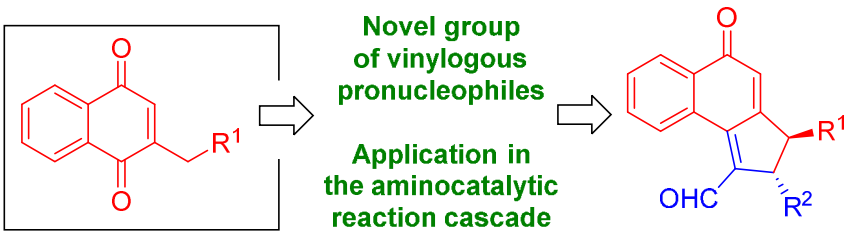
SYNOPSIS TOC



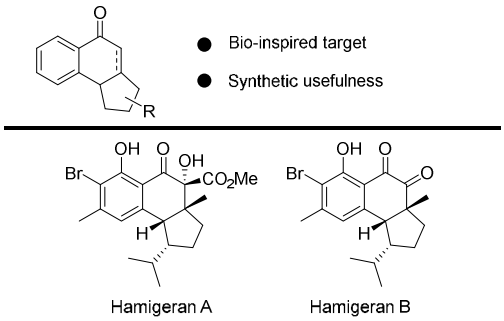
KEYWORDS: Asymmetric catalysis; Vinylogy; 1,4-Naphthoquinones; Naphthalen-1(4*H*)-ones; Remote functionalization.

ABSTRACT: This study demonstrates an unprecedented reactivity of 2-substituted-1,4-naphthoquinones. By applying the principle of vinylogy they have been employed as vinylogous

pronucleophiles in the organocatalytic cascade reaction for the first time. This novel catalytic activation of 1,4-naphthoquinones enables access to carboannulated naphthalen-1(4*H*)-one derivatives of biological importance. The site-selectivity and stereoselectivity of a process proved possible to control by the proper choice of reaction conditions.

Introduction

The development of methods for the facile and efficient construction of complex carbocyclic frameworks constitutes highly relevant goal in the contemporary organic chemistry.[1] In particular, the application of cascade reactivities involving C-C bond-forming event merged with subsequent reactions for the synthesis of bio-inspired products have received considerable interest in the past few years.[2] Among various privileged carbocyclic structures in organic chemistry, α-tetralone and naphthalen-1(4*H*)-one ring systems occupy a prominent position (Scheme 1, top). Due to the presence of a carbonyl group and a double bond within their structure they possess high synthetic usefulness correlated with the functionalization potential of these reactive moieties. Furthermore, such ring systems can be found in nature.[3,4] For instance, Hamigerans are a family of natural products that contains a α-tetralone structural unit merged with additional five-membered cyclopentane ring (Scheme 1, bottom).[4]



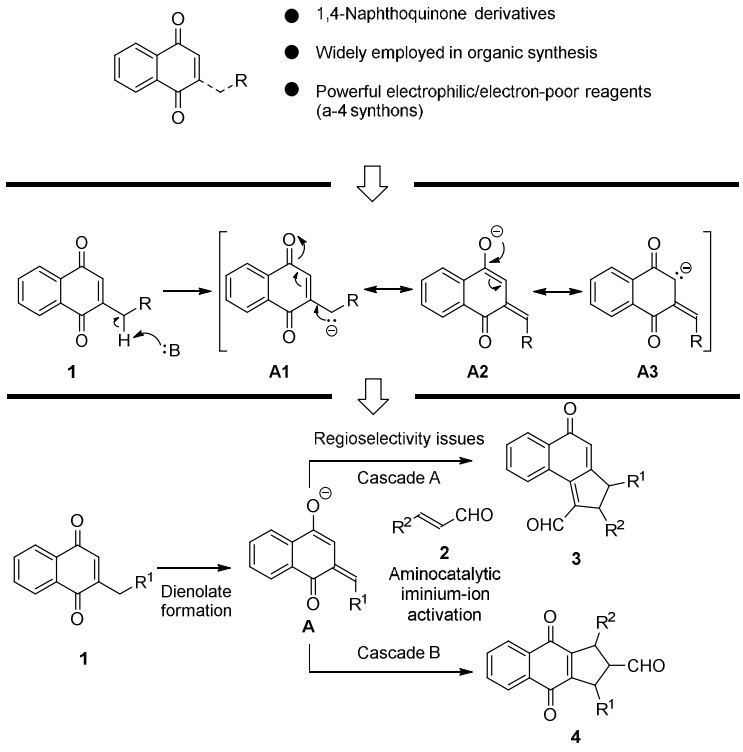
Scheme 1. The importance of α-tetralone and naphthalen-1(4*H*)-one derivatives

1,4-Naphthoquinones and their 2-alkyl-substituted derivatives constitute a useful group of reactants commonly employed in asymmetric synthesis.[5] Due to the presence of a highly electron-deficient double bond they can act as electrophiles in a Michael-type additions.[5b-e] Furthermore, they are employed as electron-poor dienophiles in various cycloaddition reactions.[5f-i] Surprisingly, to the best of our knowledge their potential as vinylogous pronucleophiles in organic synthesis has never before been explored. In the context, it is worth to note that the vinylogous reactivity of organic compounds constitutes a rapidly developing field in the contemporary organic chemistry.[6,7] Due to the presence of conjugated double bond system in vinylogous reactants a transfer of electrophilic or nucleophilic character to a remote reaction site is possible. In the past few years the principle of vinylogy has been successfully implemented in the field of asymmetric organocatalysis.[7,8] In such a manner new reaction pathways have been identified opening access to a variety of optically active products relevant for life-science industry.

Given the importance of carboannulated naphthalen-1(4*H*)-one derivatives and lack of literature precedents on nucleophilic reactivity of 2-substituted-1,4-naphthoquinones **1**, the task of development of such a reactivity for the synthesis of carboannulated naphthalen-1(4*H*)-ones **3** has been undertaken. The novel reactivity concept is based on the application of dienolate **A** readily available via deprotonation of 2-substituted-1,4-naphthoquinones **1** at the C-1' position. We envisioned that deprotonation of **1** should be possible to realize under relatively mild, basic conditions due to the efficient stabilization of **A** through resonance (Scheme 2, middle). It was anticipated that such a system should be capable of participating in the cascade reaction involving Michael addition from the C-1' position of **A** to the iminium-ion-activated enal **2** followed by the intramolecular aldol condensation to give **3** (Scheme 2, bottom, cascade A).

However, it should be noted that due to ambident nature of the nucleophile **A** employed an alternative reaction scenario is also possible (Scheme 2, bottom, cascade B). It can be initiated through the Michael addition of **A** via C-3 nucleophilic position to the iminium-ion-activated enal **1**. Subsequent cyclization via intramolecular Michael addition and re-oxidation should afford undesired **4**.

Herein, we present our studies on the first application of 2-substituted-1,4-naphthoquinones **1** as vinylogous pronucleophiles in asymmetric organocatalysis. Careful optimization of reaction conditions enabled to control the site-selectivity of the cascade providing an efficient and stereoselective access to carboannulated naphthalen-1(4*H*)-ones **3** (Scheme 2, bottom, cascade A).

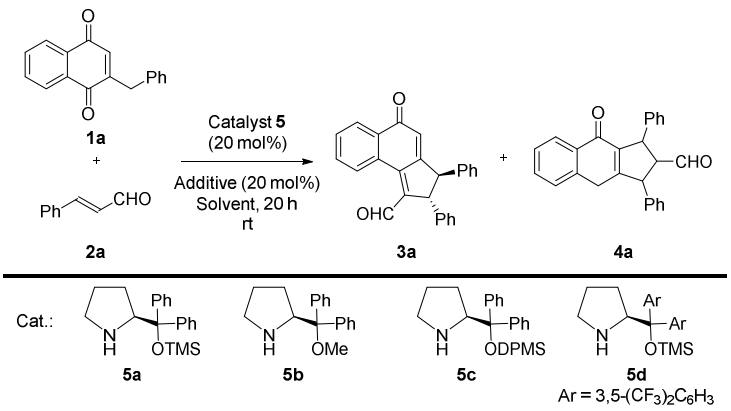


Scheme 2. 2-Substituted-1,4-naphthoquinones **1** in asymmetric organocatalysis and the objectives of our studies

Results and Discussion

Optimization studies were initiated using 2-benzyl-1,4-naphthoquinone **1a** and cinnamaldehyde **2a** as model reagents (Table 1). Initial experiment performed in dichloromethane in the presence of diphenylprolinol trimethylsilyl ether **5a**[9] as aminocatalyst and sodium acetate as basic co-catalyst confirmed the viability of our synthetic hypothesis (Table 1, entry 1). Disappointingly, the conversion to **3a** was low and the formation of the side-product **4a** arising from the alternative reaction mechanism (Scheme 2, cascade B) was observed. To our delight, both diastereoselectivity and enantioselectivity of the process were excellent. In order to improve the conversion and suppress the formation of **4a**, the co-catalyst screening was performed (Table 1, entries 1-5). Among compounds tested the use of amphiprotic additive (4-(dimethylamino)benzoic acid, DMABA) provided the best conversion and limited the formation of **3a** to the highest extend (Table 1, entry 5). In the course of the further studies the influence of various aminocatalyst **5** on the reaction outcome was evaluated (Table 1, entries 5-8) indicating that the alteration of **5** did not improve the results. Similarly, the change of solvent was not beneficial for the developed cascade (Table 1, compare entries 5, 9-11). Therefore, the influence of the relative ratio of reactants and temperature on the reaction was tested (Table 1, entries 12,13). The use of **2a** as limiting factor and performing the reaction at 5 ^{o}C for longer time enabled to increase the conversion with the high chemo- and stereoselectivity of the process being maintained (Table 1, entry 13). Notably, for the convenience of the project the catalyst loading was increased to 30 mol% in order to achieve full conversion within shorter timeframe and similar results were obtained (Table 1, entry 14).

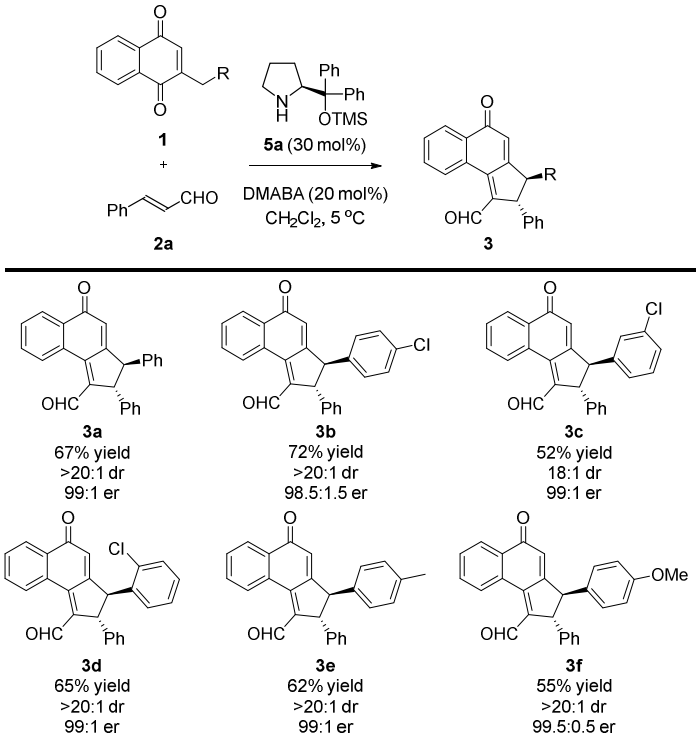
Table 1. 2-Substituted-1,4-naphthoquinones **1** as vinylogous pronucleophiles in asymmetric organocatalysis – optimization studies[a]



	Catalyst (additive)	Solvent	Conv.[b] (yield)	**3a**:**4a**	dr[c]	er[d]
1	**5a** (NaOAc)	CH_2Cl_2	41	3.3:1	>20:1	99:1
2	**5a** (Et_3N)	CH_2Cl_2	18	>20:1	>20:1	n.d.
3	**5a** (Li_2CO_3)	CH_2Cl_2	39	3.3:1	>20:1	n.d.
4	**5a** (K_2CO_3)	CH_2Cl_2	<5	n.d.	n.d.	n.d.
5	**5a** (DMABA)	CH_2Cl_2	50 (34)	11:1	>20:1	99:1
6	**5b** (DMABA)	CH_2Cl_2	34	11:1	>20:1	n.d.
7	**5c** (DMABA)	CH_2Cl_2	33	8:1	>20:1	n.d.
8	**5d** (DMABA)	CH_2Cl_2	<5	n.d.	n.d.	n.d.
9	**5a** (DMABA)	toluene	13	>20:1	>20:1	n.d.
10	**5a** (DMABA)	CCl_4	12	>20:1	>20:1	n.d.
11	**5a** (DMABA)	$CHCl_3$	36	7:1	>20:1	n.d.
12[e]	**5a** (DMABA)	CH_2Cl_2	61	10:1	>20:1	n.d.
13[f]	**5a** (DMABA)	CH_2Cl_2	93 (64)	12:1	>20:1	99:1
14[g]	**5a** (DMABA)	CH_2Cl_2	97 (67)	12:1	>20:1	99:1

[a] Reactions performed on a 0.1 mmol scale employing **1a** (1.0 equiv), **2a** (1.2 equiv), catalyst **5a** (20 mol%) with additive (20 mol%) in 0.4 mL of the solvent at room temperature (for detailed reaction conditions and screening results, see Supporting Information). [b] Conversion was determined by ^{1}H NMR of a crude reaction mixture. Isolated yield is given in parentheses. [c] Determined by ^{1}H NMR of a crude reaction mixture. [d] Determined by chiral stationary phase HPLC. [e] Reaction performed using **1a** (2 equiv) and **2a** (1 equiv). [f] Reaction performed using **1a** (2 equiv) and **2a** (1 equiv) at 5 ^{o}C for 6 days. [g] Reaction performed using **1a** (2 equiv) and **2a** (1 equiv) at 5 ^{o}C using catalyst **5a** (30 mol%) for 3 days.

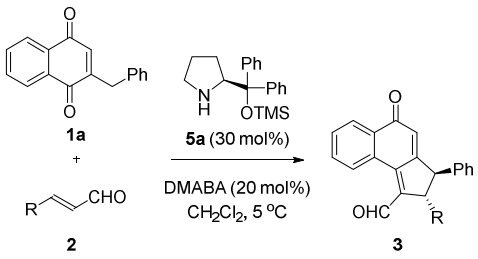
Being successful in accomplishing optimization studies, the scope of developed cascade reactivity was studied (Scheme 3, Table 2). Initially, the performance of various 2-substituted-1,4-naphthoquinones **1** as vinylogous pronucleophiles in the developed cascade was tested (Scheme 3). To our delight, the reaction cascade involving Michael addition followed by the aldol condensation proved unbiased towards the position of groups on the aromatic substituent in the benzyl moiety of **1** (Scheme 3, compare **3b**-**d**). Furthermore, their electronic properties had no significant impact on the cascade outcome (Scheme 3, compare **3b**,**e**,**f**). Notably, in all of the cases the excellent enantio- and diastereoselectivity of the process was fully maintained. Furthermore, chemoselectivity of the cascade was high with the side-reaction initiated through the Michael addition from the C-3 position of the naphthoquinone ring being supressed to high extent. It is worth to stress out that when 1,4-naphthoquinone bearing methyl substituent instead of benzyl group in the 2 position was employed no reaction was observed.



Scheme 3. 2-Substituted-1,4-naphthoquinones **1** as vinylogous pronucleophiles in asymmetric organocatalysis - 2-substituted-1,4-naphthoquinone **1** scope

Subsequently, various α,β-unsaturated aldehydes **2** were evaluated in the developed cascade (Table 2). It was found that the presence of both electron-withdrawing groups (Table 2, entries 2-8) as well as electron-donating groups (Table 2, entries 9-11) on the aromatic substituent in **2** did not affect the cascade providing the target products **3** in a highly enantio- and diastereoselective fashion. The reaction outcome did also not depend from the location of the substituent on the aromatic moiety in **2** (Table 2, entries 6-8 vs. 10,11). Notably, the use of aliphatic, linear enals resulted in sluggish conversion.

Table 2. 2-Substituted-1,4-naphthoquinones **1** as vinylogous pronucleophiles in asymmetric organocatalysis – α,β-unsaturated aldehyde **2** scope[a]



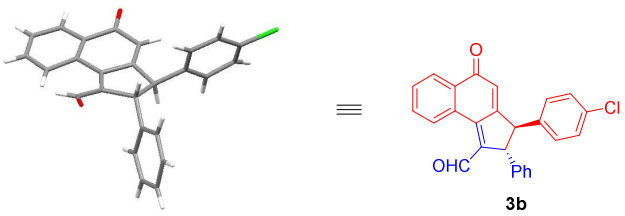
	R	Yield [%]	dr[b]	er[c]
1	Ph (**3a**)	67	>20:1	99:1
2	4-$CF_3C_6H_4$ (**3g**)	54	>20:1	99:1
3	4-$NO_2C_6H_4$ (**3h**)	47	>20:1	99.5:0.5
4	2-$NO_2C_6H_4$ (**3i**)	50	>20:1	99.5:0.5
5	4-BrC_6H_4 (**3j**)	55	>20:1	99:1
6	4-ClC_6H_4 (**3k**)	52	>20:1	99:1
7	3-ClC_6H_4 (**3l**)	56	>20:1	99:1
8	2-ClC_6H_4 (**3m**)	64	>20:1	99.5:0.5

9	4-MeC_6H_4 (**3n**)	61	>20:1	98.5:1.5
10	4-$(MeO)C_6H_4$ (**3o**)	47	>20:1	98.5:1.5
11	2-$(MeO)C_6H_4$ (**3p**)	70	>20:1	>99.5:0.5
12	2,4-$Cl_2C_6H_3$ (**3q**)	62	>20:1	99:1
13[d]	Ph (**3a**)	70	>20:1	99:1

[a] Reactions realized on a 0.1 mmol scale using **1** (2.0 equiv) and **2a** (1.0 equiv) in 0.4 mL of CH_2Cl_2 for 2-6 days. [b] Determined by ^1H NMR of a crude reaction mixture. [c] Determined by a chiral stationary phase HPLC. [d] The reaction performed on a 1 mmol scale.

Furthermore, disubstituted aromatic rings were well-tolerated as presented in the cascade leading to the formation of **3q** (Table 2 ,entry 12). It is worth to note that the developed cascade was also performed in a 10-fold larger scale (Table 2, entry 13) providing **3a** with comparable results to those obtained on a 0.1 mmol scale (Table 2, entry 1), thus increasing the attractiveness of our approach.

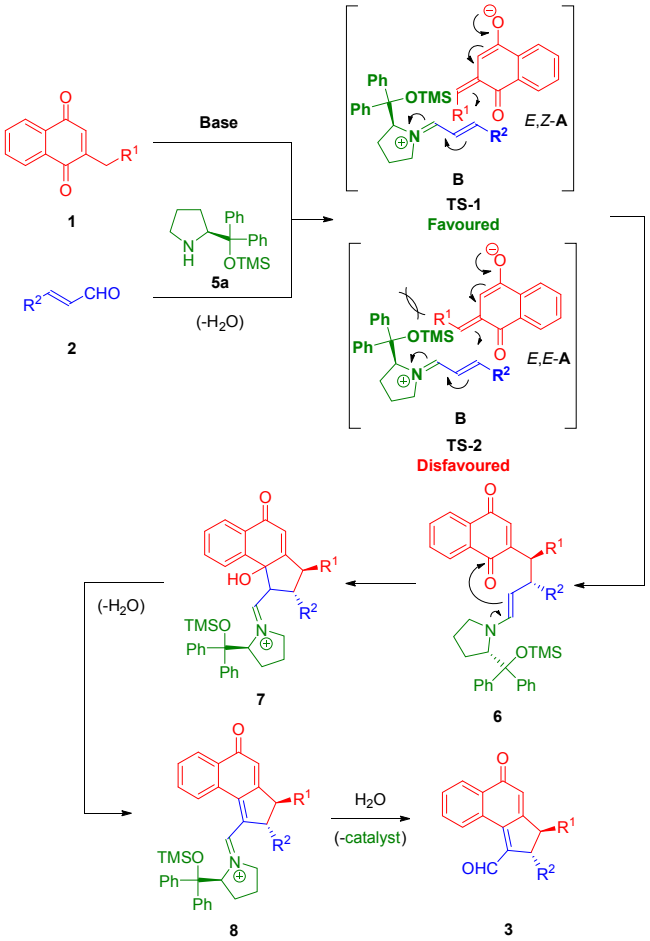
Absolute configuration of the product **3b** was unequivocally confirmed by the single crystal X-ray experiment (Scheme 4).[10] The same absolute configuration was assigned by analogy to the remaining naphthalen-1(4*H*)-ones **3a,c**-**q**.



Scheme 4. 2-Substituted-1,4-naphthoquinones **1** as vinylogous pronucleophiles in asymmetric organocatalysis – absolute configuration assignment

Given the stereochemical assignments, a plausible reaction mechanism was proposed (Scheme 5). It is postulated that the reaction cascade is initiated by two parallel processes. Firstly, 2-substituted-1,4-naphthoquinone **1** is deprotonated to generate the corresponding dienolate **A**. Secondly, enal **2** is activated through the iminium ion **B** formation. Subsequently, the first C-C

bond-forming event takes place. Enantioselectivity of the Michael addition of **1** to **2** is controlled by the bulky substituent present at the C-2 of the pyrrolidine moiety in **B**. Notably, the diastereoselectivity of the addition is a consequence of dienolate **A** reacting in its *E*,*Z*-configuration (Scheme 5, TS-1). Dienolate **A** adopts such a reactive configuration in order to avoid disfavored interactions (between R^2 substituent and the sterically demanding substituent of the iminium ion **B**) that are present in the alternative transition state (Scheme 5, TS-2) proceeding through the *E*,*E*-configured dienolate **A**. The conjugate addition leads to the formation of enamine **6** that undergoes intramolecular aldol reaction to give iminium ion **7**. Subsequent dehydratation and hydrolytic removal of the catalyst affords target product **3**.



Scheme 5. 2-Substituted-1,4-naphthoquinones **1** as vinylogous pronucleophiles in asymmetric organocatalysis – mechanistic considerations

Conclusions

In conclusion, we have demonstrated for the first time that 2-substituted-1,4-naphthoquinones **1** can serve as pronucleophiles thus providing new opportunities for organic synthesis. The reaction between **1** and α,β-unsaturated aldehydes **2** proceeded in a vinylogous fashion providing carboannulated naphthalen-1(4*H*)-ones **3** in a sequence of reaction involving Michael addition followed by the intramolecular aldol condensation. The proper choice of reaction conditions enabled the control of both the site- and stereo-selectivity of the cascade.

Experimental Section

General Information. Unless otherwise noted, analytical grade solvents and commercially available reagents were used without further purification. NMR spectra were acquired on a Bruker Ultra Shield 700 instrument, running at 700 MHz for ^{1}H and 176 MHz for ^{13}C, respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CDCl_3$: 7.26 ppm for ^{1}H NMR, 77.16 ppm for ^{13}C NMR). Mass spectra were recorded on a spectrometer using electrospray ionization (ESI+) using TOF mass analyzer (referenced to the mass of the charged species). Optical rotations were measured on a Perkin-Elmer 241 polarimeter and $[\alpha]_D$ values are given in deg•cm•g^{-1} •dm^{-1}; concentration *c* is listed in g•(100 mL)$^{-1}$. Melting points were determined in open capillaries and are uncorrected. Analytical thin layer chromatography (TLC) was performed using pre-coated aluminum-backed plates (Merck Kieselgel 60 F254) and visualized by ultraviolet irradiation. The enantiomeric ratio (*er*) of the products was determined by chiral stationary phase HPLC (Daicel Chiralpak IA, IC and ID column). For flash chromatography (FC) silica gel (Silica gel 60, 230-400 mesh, Fluka) was used. 2-Substituted-

1,4-naphthoquinones **1a**-**f**[11] and aldehydes **2g-q**[12] were synthetized from the corresponding benzaldehydes according to literature procedures.

*Synthesis of 2- substituted-1,4-naphthoquinone **1** – general procedure*. $AgNO_3$ (1 mmol) and $(NH_4)_2S_2O_8$ (20 mmol) were dissolved in water (40 mL) and a solution of 1,4-naphthoquinone (10 mmol) and 2-phenylacetic acid (20 mmol) in a 1:1 mixture of acetonitrile/dichloromethane (40 mL) was quickly added. The biphasic mixture was refluxed (bath temperature ca. 80 °C) for 2 hours, cooled to ambient temperature, and dichloromethane (40 mL) was added. The aqueous layer was separated and extracted again with dichloromethane (40 mL). The combined organic layers were dried (anhydrous sodium sulphate) and evaporated. Resulting brown oil was purified by column chromatography (hexane:EtOAc 100:1). Pure products were obtained as yellow solids.

2-Benzyl-1,4-naphthoquinone **1a**. Following general procedure, pure product **1a** was isolated by FC on silica (hexane:diethyl ether 100:1) in 71% yield as an yellow solid (mp = 85-86 ˚C). ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.12–8.10 (m, 1H), 8.06-8.03 (m, 1H), 7.73–7.72 (m, 2H), 7.35-7.33 (m, 2H), 7.27–7.25 (m, 3H), 6.61 (t, *J* = 1.6 Hz, 1H), 3.90 (d, *J* = 1.4 Hz, 2H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 185.3, 185.2, 151.0, 136.9, 135.8, 134.0, 133.9, 132.4, 132.2, 129.6 (2C), 129.0 (2C), 127.1, 126.8, 126.3, 35.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{13}O_2$ 249.0910; Found: 249.0913.

2-(4-Chlorobenzyl)-1,4-naphthoquinone **1b**. Following general procedure, pure product **1b** was isolated by FC on silica (hexane:diethyl ether 100:1) in 57% yield as an yellow solid (mp = 98-100 ˚C). ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.10 (ddd, *J* = 4.6, 3.0, 0.5 Hz, 1H), 8.05 (ddd, *J* = 3.9, 3.0, 0.5 Hz, 1H), 7.75–7.71 (m, 2H), 7.32–7.28 (m, 2H), 7.21–7.17 (m, 2H), 6.62 (t, *J* = 1.5

Hz, 1H), 3.87 (d, *J* = 1.4 Hz, 2H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 185.1, 185.0, 150.4, 136.0, 135.4, 134.0, 134.0, 133.1, 132.2, 132.2, 131.0 (2C), 129.1 (2C), 126.8, 126.3, 35.3. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{12}ClO_2$ 283.0520; Found: 283.0526.

2-(3-Chlorobenzyl)-1,4-naphthoquinone **1c**. Following general procedure, pure product **1c** was isolated by FC on silica (hexane:diethyl ether 100:1) in 43% yield as an yellow solid (mp = 75-77 ˚C). ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.11 (ddd, *J* = 4.8, 2.9, 0.5 Hz, 1H), 8.06 (ddd, *J* = 4.1, 2.9, 0.5 Hz, 1H), 7.74 (ddd, *J* = 5.0, 4.5, 3.6 Hz, 2H), 7.29–7.21 (m, 3H), 7.14 (dt, *J* = 7.2, 1.6 Hz, 1H), 6.63 (t, *J* = 1.5 Hz, 1H), 3.87 (d, *J* = 1.3 Hz, 2H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 185.1, 184.9, 150.1, 139.0, 136.0 (2C), 134.8, 134.0, 133.9, 132.2, 130.2, 129.6, 127.7, 127.4, 126.9, 126.3, 35.6. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{12}ClO_2$ 283.0520; Found: 283.0522.

2-(2-Chlorobenzyl)-1,4-naphthoquinone **1d**. Following general procedure, pure product **1d** was isolated by FC on silica (hexane:diethyl ether 100:1) in 68% yield as an yellow solid (mp = 108-110 ˚C). ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.16–8.12 (m, 1H), 8.07–8.03 (m, 1H), 7.75–7.73 (m, 2H), 7.42-7.41 (m, 1H), 7.28–7.23 (m, 3H), 6.44 (t, *J* = 1.7 Hz, 1H), 4.05 (d, *J* = 1.7 Hz, 2H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 185.1, 185.0, 149.3, 135.7, 134.7, 133.9 (2C), 132.3 (2C), 132.0, 130.1, 128.9, 127.4, 126.8 (2C), 126.3, 33.5. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{12}ClO_2$ 283.0520; Found: 283.0517.

2-(p-Tolyl)-1,4-naphthoquinone **1e**. Following general procedure, pure product **1e** was isolated by FC on silica (hexane:diethyl ether 100:1) in 69% yield as an yellow solid (mp = 90-93 ˚C). ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.15–8.11 (m, 1H), 8.09–8.04 (m, 1H), 7.76–7.72 (m, 2H), 7.20–7.17 (m, 2H), 6.91–6.88 (m, 2H), 6.62 (t, *J* = 1.5 Hz, 1H), 3.86 (d, *J* = 1.5 Hz, 2H), 3.82 (s, 3H). ^{13}C

NMR (176 MHz, $CDCl_3$) δ 185.0, 184.9, 150.1, 139.0 (2C), 136.0, 134.8 (2C), 134.0, 133.9, 132.2, 130.2, 129.6, 127.7, 127.4, 126.9, 126.3, 35.5. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{15}O_2$ 263.1067; Found: 263.1062.

2-(4-Methoxybenzyl)-1,4-naphthoquinone **1f**. Following general procedure, pure product **1f** was isolated by FC on silica (hexane:diethyl ether 100:1) in 71% yield as an yellow solid (mp = 74-76 ˚C). ^1H NMR (700 MHz, $CDCl_3$) δ 8.10–8.09 (m, 1H), 8.04–8.03 (m, 1H), 7.72–7.71 (m, 2H), 7.17–7.15 (m, 2H), 6.87–6.86 (m, 2H), 6.60 (t, *J* = 1.5 Hz, 1H), 3.84 (d, *J* = 1.5 Hz, 2H), 3.79 (s, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 185.3, 185.2, 158.7, 151.4, 135.6, 133.9, 133.8, 132.3, 132.2, 130.6 (2C), 128.7, 126.8, 126.2, 114.4 (2C), 55.4, 35.1. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{15}O_3$ 279.1016; Found: 279.1022.

General Procedure for the Synthesis of Compounds **3a-q**. In an ordinary 4 mL glass vial, equipped with a magnetic stirring bar and a screw cap, catalyst **5a** (0.3 equiv, 0.03 mmol, 9.8 mg) and *α,β*-unsaturated aldehyde **2** (1.0 equiv, 0.1 mmol) were dissolved in CH_2Cl_2 (0.2 mL). Subsequently, the mixture was cooled to 5 °C and a solution of the corresponding 2-alkyl-1,4-naphthoquinone **1** (2 equiv, 0.2 mmol) and 4**-**dimethylaminobenzoic acid (0.2 equiv, 0.02 mmol, 3.3 mg) in CH_2Cl_2 (0.2 mL) was added and stirring was continued for 2-6 days at 5 °C. Crude product was purified by the flash chromatography on silica gel.

(2R,3R)-5-Oxo-2,3-diphenyl-3,5-dihydro-2H-cyclopenta[a]naphthalene-1-carbaldehyde **3a**. Following general procedure, pure product **3a** was isolated after 3 days by FC on silica (hexane:diethyl ether 4:1) in 67% yield (24 mg, >20:1 dr, **3a**:**4a** 90:10) as an yellow solid (mp = 88-90 ˚C). ^1H NMR (700 MHz, $CDCl_3$) δ 10.64 (s, 1H), 8.35–8.31 (m, 1H), 8.29–8.22 (m, 1H), 7.78–7.68 (m, 2H), 7.35–7.28 (m, 5H), 7.27-7.25 (m, 1H), 7.17–7.09 (m, 4H), 6.40 (dd, *J* = 2.0,

0.8 Hz, 1H), 4.55 (d, *J* = 2.7 Hz, 1H), 4.18 (t, *J* = 2.4 Hz, 1H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 189.3, 184.6, 166.7, 148.9, 142.1, 141.7, 141.2, 132.5, 131.9, 131.4, 130.2, 129.3 (2C), 129.2 (2C), 128.7, 128.0, 127.8 (2C), 127.7, 127.6, 127.5 (2C), 125.8, 60.5, 57.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{19}O_2$+H^+ 363.1380; Found: 363.1387. The *er* was determined by HPLC using a chiral Chiralpack IA [hexane:*i*-PrOH, 90:10] column; column temperature 30 °C; flow rate 1.0 mL/min; t_{major} = 10.7 min, t_{minor} = 13.4 min (99:1 er); $[\alpha]_D^{20}$ = -254.3 (*c* = 1.0, $CHCl_3$).

(2R,3R)-3-(4-Chlorophenyl)-5-oxo-2-phenyl-3,5-dihydro-2H-cyclopenta[a]naphthalene-1-carbaldehyde **3b**. Following general procedure, pure product **3b** was isolated after 2 days by FC on silica (hexane:diethyl ether 4:1) in 72% yield (29 mg, >20:1 dr, **3b**:**4b** 91:9) as a green solid (mp = 130-132 ˚C). ^{1}H NMR (700 MHz, $CDCl_3$) δ 10.63 (s, 1H), 8.36–8.32 (m, 1H), 8.27–8.22 (m, 1H), 7.77–7.69 (m, 2H), 7.34–7.30 (m, 4H), 7.28–7.26 (m, 1H), 7.15–7.12 (m, 2H), 7.07–7.04 (m, 2H), 6.37 (d, *J* = 1.5 Hz, 1H), 4.48 (d, *J* = 2.8 Hz, 1H), 4.15 (t, *J* = 2.4 Hz, 1H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 189.2, 184.4 , 166.0, 148.6, 142.0, 141.4, 139.6, 133.7, 132.6, 131.8, 131.5, 130.1, 129.5, 129.3, 129.2 (2C), 128.7 (2C), 128.1 (2C), 127.7, 127.4 (2C), 125.8, 60.5, 56.6. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{18}ClO_2$ 397.0990; Found: 397.0991. The *er* was determined by HPLC using a chiral Chiralpack IC [hexane:*i*-PrOH, 80:20] column; column temperature 30 °C; flow rate 1.0 mL/min; t_{major} = 17.9 min, t_{minor} = 22.1 min (98.5:1.5 er); $[\alpha]_D^{20}$ = -256.3 (*c* = 1.0, $CHCl_3$).

(2R,3R)-3-(3-Chlorophenyl)-5-oxo-2-phenyl-3,5-dihydro-2H-cyclopenta[a]naphthalene-1-carbaldehyde **3c**. Following general procedure, pure product **3c** was isolated after 2 days by FC on silica (hexane:diethyl ether 4:1) in 52% yield (21 mg, 18:1 dr, **3c**:**4c** 88:12) as an yellow solid (mp = 118-120 ˚C). ^{1}H NMR (700 MHz, $CDCl_3$) δ 10.63 (s, 1H), 8.36–8.32 (m, 1H), 8.26–8.23

(m, 1H), 7.76–7.71 (m, 2H), 7.34–7.30 (m, 2H), 7.30–7.27 (m, 3H), 7.16–7.12 (m, 2H), 7.12–7.09 (m, 1H), 7.02–6.98 (m, 1H), 6.39 (dd, J = 2.0, 0.6 Hz, 1H), 4.52 (d, J = 2.7 Hz, 1H), 4.16–4.10 (m, 1H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 189.1, 184.4, 165.8, 148.6, 143.2, 141.9, 141.4, 135.2, 132.6, 131.8, 131.6, 130.6, 130.1, 129.3 (2C), 128.7, 128.1, 128.0, 127.9, 127.7, 127.4 (2C), 126.1, 126.0, 60.3, 56.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{18}ClO_2$ 397.0990; found: 397.0999. The *er* was determined by HPLC using a chiral Chiralpack IC [hexane:*i*-PrOH, 80:20] column; column temperature 30 °C; flow rate 1.0 mL/min; t_{major} = 16.0 min, t_{minor} = 18.6 min (99:1 er); $[\alpha]_D^{20}$ = -258.8 (c = 1.0, $CHCl_3$).

(2R,3S)-3-(2-Chlorophenyl)-5-oxo-2-phenyl-3,5-dihydro-2H-cyclopenta[a]naphthalene-1-carbaldehyde **3d**. Following general procedure, pure product **3d** was isolated after 5 days by FC on silica (hexane:diethyl ether 4:1) in 65% yield (26 mg, >20:1 dr, **3d**:**4d** 98:2) as a green amorphous solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ 10.62 (s, 1H), 8.37–8.33 (m, 1H), 8.27–8.23 (m, 1H), 7.75–7.70 (m, 2H), 7.42 (dd, J = 7.9, 1.5 Hz, 1H), 7.31 (dd, J = 10.2, 4.7 Hz, 2H), 7.27–7.23 (m, 3H), 7.21 (td, J = 7.5, 1.5 Hz, 1H), 7.18 (d, J = 7.2 Hz, 2H), 7.05 (dd, J = 7.5, 1.5 Hz, 1H), 6.41 (bs, 1H), 4.66 (bs, 1H), 4.60 (bs, 1H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 189.2, 184.5, 165.8, 149.0, 141.8, 141.6, 134.2, 132.5, 131.9, 131.4, 130.4, 130.2, 129.1 (2C), 129.0 (3C), 128.7, 128.0, 127.6 (4C), 125.4, 59.1, 58.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{18}ClO_2$ 397.0990; Found: 397.0983. The *er* was determined by HPLC using a chiral Chiralpack IC [hexane:*i*-PrOH, 80:20] column; column temperature 30 °C; flow rate 1.0 mL/min; t_{major} = 14.4 min, t_{minor} = 15.8 min (99:1 er); $[\alpha]_D^{20}$ = -181.1 (c = 1.0, $CHCl_3$).

(2R,3R)-5-Oxo-2-phenyl-3-(p-tolyl)-3,5-dihydro-2H-cyclopenta[a]naphthalene-1-carbaldehyde **3e**. Following general procedure, pure product **3e** was isolated after 6 days by FC on silica (hexane:diethyl ether 4:1) in 62% yield (23 mg, >20:1 dr, **3e**:**4e** 88:12) as an yellow

amorphous solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ 10.63 (s, 1H), 8.33 (ddd, *J* = 8.6, 4.1, 3.3 Hz, 1H), 8.26–8.22 (m, 1H), 7.76–7.67 (m, 2H), 7.32–7.29 (m, 2H), 7.28–7.24 (m, 1H), 7.16–7.13 (m, 4H), 7.02–6.99 (m, 2H), 6.39 (dd, *J* = 2.0, 0.7 Hz, 1H), 4.53 (d, *J* = 2.7 Hz, 1H), 4.14 (t, *J* = 2.4 Hz, 1H), 2.34 (s, 3H). ^{13}C NMR (176 MHz, , $CDCl_3$) δ 189.4, 184.6, 166.9, 149.0, 142.0, 141.8, 138.1, 137.4, 132.5, 131.9, 131.4, 130.2, 130.0 (2C), 129.2 (2C), 128.7, 128.0, 127.7 (2C), 127.5, 127.4 (2C), 125.7, 60.5, 56.9, 21.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{27}H_{21}O_2$ 377.1537; Found: 377.1544. The *er* was determined by HPLC using a chiral Chiralpack IC [hexane:*i*-PrOH, 80:20] column; column temperature 30 °C; flow rate 1.0 mL/min; t_{major} = 15.5 min, t_{minor} = 18.0 min (99:1 er); $[\alpha]_D^{20}$=-214.2 (*c* = 1.0, $CHCl_3$).

(2R,3S)-3-(4-Methoxyphenyl)-5-oxo-2-phenyl-3,5-dihydro-2H-cyclopenta[a]naphthalene-1-carbaldehyde **3f**. Following general procedure, pure product **3f** was isolated after 5 days by FC on silica (hexane:diethyl ether 4:1) in 55% yield (22 mg, >20:1 dr, **3f**:**4f** 87:13) as an yellow amorphous solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ 10.62 (s, 1H), 8.35–8.31 (m, 1H), 8.26–8.23 (m, 1H), 7.74–7.69 (m, 2H), 7.33–7.28 (m, 2H), 7.28–7.23 (m, 1H), 7.16–7.12 (m, 2H), 7.05–7.01 (m, 2H), 6.88–6.83 (m, 2H), 6.38 (dd, *J* = 2.0, 0.6 Hz, 1H), 4.50 (d, *J* = 2.8 Hz, 1H), 4.12 (t, *J* = 2.4 Hz, 1H), 3.80 (s, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 189.4, 184.6, 167.0, 159.2, 148.9, 142.0, 141.8, 133.1, 132.5, 131.9, 131.4, 130.2, 129.2 (2C), 128.9 (2C), 128.7, 128.0, 127.5, 127.4 (2C), 125.6, 114.7 (2C), 60.7, 56.6, 55.5. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{27}H_{21}O_3$ 393.1486; Found: 393.1490. The *er* was determined by HPLC using a chiral Chiralpack IC [hexane:*i*-PrOH, 80:20] column; column temperature 30 °C; flow rate 1.0 mL/min; t_{major} = 25.4 min, t_{minor} =28.1 min (99.5:0.5 er); $[\alpha]_D^{20}$ = -256.3 (*c* = 1.0, $CHCl_3$).

(2R,3R)-5-Oxo-3-phenyl-2-(4-(trifluoromethyl)phenyl)-3,5-dihydro-2H-cyclopenta[a]naphthalene-1-carbaldehyde **3g**. Following general procedure, pure product **3g**

was isolated after 3 days by FC on silica (hexane:diethyl ether 4:1) in 54% yield (23 mg, >20:1 dr, **3g**:**4g** 93:7) as an yellow amorphous solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ 10.71 (s, 1H), 8.36–8.32 (m, 1H), 8.23–8.18 (m, 1H), 7.78–7.71 (m, 2H), 7.57 (d, *J* = 8.1 Hz, 2H), 7.36–7.32 (m, 2H), 7.31 (m, 1H), 7.27–7.25 (d, *J* = 8.1 Hz, 2H), 7.12–7.08 (m, 2H), 6.39 (dd, *J* = 2.1, 0.8 Hz, 1H), 4.58 (d, *J* = 3.0 Hz, 1H), 4.13 (dd, *J* = 3.0, 2.1 Hz, 1H). ^{13}C NMR (176 MHz, $CDCl_3$) 188.7, 184.4, 166.0, 147.7, 145.9, 143.6, 140.6, 132.6, 131.9, 131.7, 130.0, 129.8 (q, $J_{C\text{-}F}$ = 32.6 Hz), 129.5 (2C), 128.7, 128.2, 128.0, 127.8 (2C), 127.7 (2C), 126.2 (q, $J_{C\text{-}F}$ = 3.7 Hz, 2C), 126.0, 124.2 (q, $J_{C\text{-}F}$ = 273.0 Hz), 59.9, 57.0. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{27}H_{18}F_3O_2$ 431.1253; Found: 431.1255. The *er* was determined by HPLC using a chiral Chiralpack IC [hexane:*i*-PrOH, 90:10] column; column temperature 30 °C; flow rate 1.0 mL/min; t_{major} = 19.3 min, t_{minor} = 21.0 min (99:1 er); $[\alpha]_D^{20}$ = -211.6 (*c* = 1.0, $CHCl_3$).

(2R,3R)-2-(4-Nitrophenyl)-5-oxo-3-phenyl-3,5-dihydro-2H-cyclopenta[a]naphthalene-1-carbaldehyde **3h**. Following general procedure, pure product **3h** was isolated after 4 days by FC on silica (hexane:diethyl ether 4:1) in 47% yield (19 mg, >20:1 dr, **3h**:**4h** 88:12) as an yellow solid (mp = 123-125 ˚C). ^{1}H NMR (700 MHz, $CDCl_3$) δ 10.75 (s, 1H), 8.36–8.31 (m, 1H), 8.19 (dd, *J* = 7.4, 1.6 Hz, 1H), 8.17 (d, *J* = 8.8 Hz, 2H), 7.77–7.74 (m, 2H), 7.38–7.32 (m, 3H), 7.31 (d, *J* = 8.8 Hz, 2H), 7.13–7.08 (m, 2H), 6.38 (dd, *J* = 2.1, 0.7 Hz, 1H), 4.60 (d, *J* = 3.3 Hz, 1H), 4.12 (dd, *J* = 3.3, 2.1 Hz, 1H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 188.5, 184.3, 165.5, 149.4, 148.9, 147.3, 146.8, 143.8, 140.1, 132.7, 131.9 (4C), 129.8, 129.5, 129.2, 128.7, 128.3, 128.2, 127.9, 126.1, 124.5, 124.4, 59.7, 56.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{18}NO_4$ 408.1230; Found: 408.1237. The *er* was determined by HPLC using a chiral Chiralpack IC [hexane:*i*-PrOH, 80:20] column; column temperature 30 °C; flow rate 1.0 mL/min; t_{major} = 18.0 min, t_{minor} = 20.5 min (>99.5:0.5 er); $[\alpha]_D^{20}$ = -383.8 (*c* = 1.0, $CHCl_3$).

(2R,3R)-2-(2-Nitrophenyl)-5-oxo-3-phenyl-3,5-dihydro-2H-cyclopenta[a]naphthalene-1-carbaldehyde **3i**. Following general procedure, pure product **3i** was isolated after 3 days by FC on silica (hexane:diethyl ether 4:1) in 50% yield (20 mg, >20:1 dr, **3i**:**4i** 82:18) as an yellow amorphous solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ 10.68 (s, 1H), 8.37–8.30 (m, 1H), 8.22–8.15 (m, 1H), 7.85 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.78–7.71 (m, 2H), 7.51 (td, *J* = 7.4, 1.4 Hz, 1H), 7.40 (ddd, *J* = 8.3, 7.4, 1.4 Hz, 1H), 7.36–7.30 (m, 3H), 7.22–7.18 (m, 1H), 7.16–7.11 (m, 2H), 6.38 (d, *J* = 1.6 Hz, 1H), 5.24 (bs, 1H), 4.27 (bs, 1H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 188.4, 184.3, 166.0, 165.5, 149.5, 147.1, 143.3, 140.2, 134.1, 133.3, 132.6, 131.8, 131.7, 129.9, 129.3 (2C), 128.7, 128.3, 128.1, 128.0, 127.9 (2C), 126.1, 125.0, 61.1, 56.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{18}NO_4$ 408.1230; Found: 408.1238. The *er* was determined by HPLC using a chiral Chiralpack IC [hexane:*i*-PrOH, 90:10] column; column temperature 30 °C; flow rate 1.0 mL/min; t_{major} = 24.7min, t_{minor} = 28.4 min (>99.5:0.5 er); $[\alpha]_D^{20}$ = -157.6 (*c* = 1.0, $CHCl_3$).

(2R,3R)-2-(4-Bromophenyl)-5-oxo-3-phenyl-3,5-dihydro-2H-cyclopenta[a]naphthalene-1 carbaldehyde **3j**. Following general procedure, pure product **3j** was isolated after 2 days by FC on silica (hexane:diethyl ether 4:1) in 55% yield (24 mg, >20:1 dr, **3j**:**4j** 92:2) as an yellow solid (mp = 130-132 ˚C). ^{1}H NMR (700 MHz, $CDCl_3$) δ 10.67 (s, 1H), 8.33 (m, 1H), 8.21 (m, 1H), 7.76–7.71 (m, 2H), 7.46–7.40 (m, 2H), 7.35–7.32 (m, 2H), 7.32–7.28 (m, 1H), 7.10 (m, 2H), 7.05–6.99 (m, 2H), 6.38 (dd, *J* = 2.0, 0.6 Hz, 1H), 4.49 (d, *J* = 2.9 Hz, 1H), 4.11–4.10 (m, 1H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 188.9, 184.4, 166.2, 148.0, 143.0, 140.9, 140.7, 132.6, 132.3 (2C), 131.9, 131.6, 130.0, 129.4 (2C), 129.11 (2C), 128.7, 128.1, 127.9, 127.8 (2C), 125.9, 121.4, 59.7, 57.1. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{18}BrO_2$ 441.0485; Found: 441.0477. The *er* was determined by HPLC using a chiral Chiralpack IC [hexane:*i*-PrOH, 80:20]

column; column temperature 30 °C; flow rate 1.0 mL/min; t_{major} = 18.1 min, t_{minor} = 22.8 min (99:1 er); $[\alpha]_D^{20}$ = -285.9 (*c* = 1.0, $CHCl_3$).

(2R,3R)-2-(4-Chlorophenyl)-5-oxo-3-phenyl-3,5-dihydro-2H-cyclopenta[a]naphthalene-1-carbaldehyde **3k**. Following general procedure, pure product **3k** was isolated after 3 days by FC on silica (hexane:diethyl ether 4:1) in 52% yield (21 mg, >20:1 dr, **3k**:**4k** 93:7) as an yellow solid (mp = 118-120 ˚C). ^{1}H NMR (700 MHz, $CDCl_3$) δ 10.67 (s, 1H), 8.34–8.32 (m, 1H), 8.22–8.20 (m, 1H), 7.76–7.71 (m, 2H), 7.37–7.32 (m, 2H), 7.32–7.27 (m, 3H), 7.09 (m, 4H), 6.38 (dd, *J* = 2.0, 0.6 Hz, 1H), 4.50 (d, *J* = 2.9 Hz, 1H), 4.12–4.10 (m, 1H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 189.7, 184.4, 166.2, 148.1, 142.7, 140.7, 140.3, 133.4, 132.6, 131.9, 131.6, 130.1, 129.4 (2C), 129.3 (2C), 128.8 (2C), 128.7, 128.1, 127.9, 127.8 (2C), 125.9, 59.6, 57.1. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{18}ClO_2$ 397.0990; Found: 397.0988. The *er* was determined by HPLC using a chiral Chiralpack IC [hexane:*i*-PrOH, 80:20] column; column temperature 30 °C; flow rate 1.0 mL/min; t_{major} = 17.0 min, t_{minor} = 21.3 min (99:1 er); $[\alpha]_D^{20}$ = -336.8 (*c* = 1.0, $CHCl_3$).

(2R,3R)-2-(3-Chlorophenyl)-5-oxo-3-phenyl-3,5-dihydro-2H-cyclopenta[a]naphthalene-1-carbaldehyde **3l**. Following general procedure, pure product **3l** was isolated after 2 days by FC on silica (hexane:diethyl ether 4:1) in 56% yield (22 mg, >20:1 dr, **3l**:**4l** 88:12) as a green amorphous solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ 10.69 (s, 1H), 8.35–8.33 (m, 1H), 8.23–8.21 (m, 1H), 7.76–7.71 (m, 2H), 7.36–7.33 (m, 2H), 7.32–7.28 (m, 1H), 7.25–7.24 (m, 2H), 7.13–7.10 (m, 3H), 7.06–7.02 (m, 1H), 6.38 (dd, *J* = 2.0, 0.7 Hz, 1H), 4.50 (d, *J* = 2.9 Hz, 1H), 4.15–4.13 (m, 1H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 188.9, 184.4, 166.1, 147.9, 143.9, 142.8, 140.8, 135.0, 132.6, 131.9, 131.6, 130.4, 130.0, 129.4 (2C), 128.7, 128.1, 127.9, 127.8 (2C), 127.7, 127.3, 126.0, 125.8, 59.8, 56.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{18}ClO_2$ 397.0990;

Found: 397.0995. The *er* was determined by HPLC using a chiral Chiralpack IA [hexane:*i*-PrOH, 90:10] column; column temperature 30 °C; flow rate 1.0 mL/min; t_{major} = 11.2 min, t_{minor} = 13.7 min (99:1 er); $[\alpha]_D^{20}$ = -360.3 (*c* = 1.0, $CHCl_3$).

(2R,3R)-2-(2-Chlorophenyl)-5-oxo-3-phenyl-3,5-dihydro-2H-cyclopenta[a]naphthalene-1-carbaldehyde **3m**. Following general procedure, pure product **3m** was isolated after 2 days by FC on silica (hexane:diethyl ether 4:1) in 64% yield (25 mg, >20:1 dr, **3m**:**4m** 91:9) as an yellow solid (mp = 98-100 ˚C). ^{1}H NMR (700 MHz, $CHCl_3$) δ 10.68 (s, 1H), 8.35–8.31 (m, 1H), 8.25 (m, 1H), 7.78–7.68 (m, 2H), 7.38 (m, 1H), 7.35–7.31 (m, 2H), 7.31–7.27 (m, 1H), 7.27–7.17 (m, 2H), 7.17–7.13 (m, 2H), 7.06–7.03 (m, 1H), 6.37 (d, *J* = 2.1 Hz, 1H), 5.09 (bs, 1H), 4.19 (bs, 1H). ^{13}C NMR (176 MHz, $CHCl_3$) δ 188.8, 184.5, 166.4, 148.4, 142.6, 140.8, 133.8, 132.5, 131.8, 131.4 (2C), 130.4, 130.1, 129.2 (2C), 128.7 (2C), 128.6, 128.0, 127.9 (2C), 127.7, 127.5, 125.7, 56.4, 56.1. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{18}ClO_2$ 397.0990; Found: 397.0993. The *er* was determined by HPLC using a chiral Chiralpack IC [hexane:*i*-PrOH, 80:20] column; column temperature 30 °C; flow rate 1.0 mL/min; t_{major} = 16.3 min, t_{minor} = 18.0 min (99.5:0.5 er); $[\alpha]_D^{20}$ = -121.9 (*c* = 1.0, $CHCl_3$).

(2R,3R)-5-Oxo-3-phenyl-2-(p-tolyl)-3,5-dihydro-2H-cyclopenta[a]naphthalene-1-carbaldehyde **3n**. Following general procedure, pure product **3n** was isolated after 3 days by FC on silica (hexane:diethyl ether 4:1) in 61% yield (23 mg, >20:1 dr, **3n**:**4n** 98:2) as a brown amorphous solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ 10.61 (s, 1H), 8.35–8.32 (m, 1H), 8.26–8.24 (m, 1H), 7.75–7.69 (m, 2H), 7.35–7.31 (m, 2H), 7.30–7.27 (m, 1H), 7.14–7.10 (m, 4H), 7.04 (d, *J* = 8.1 Hz, 2H), 6.39 (dd, *J* = 2.0, 0.6 Hz, 1H), 4.52 (d, *J* = 2.6 Hz, 1H), 4.16-4.15 (m, 1H), 2.33 (s, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 189.5, 184.6, 166.8, 149.1, 141.8, 141.2, 138.7, 137.3, 132.3, 131.9, 131.4, 130.3, 129.9 (2C), 129.3 (2C), 128.7, 128.0, 127.8 (2C), 127.7, 127.3 (2C),

125.7, 60.2, 57.3, 21.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{27}H_{21}O_2$ 377.1537; Found: 377.1530. The *er* was determined by HPLC using a chiral Chiralpack IC [hexane:*i*-PrOH, 80:20] column; column temperature 30 °C; flow rate 1.0 mL/min; t_{major} = 15.7 min, t_{minor} = 17.7 min (98.5:1.5 er); $[\alpha]_D^{20}$ = -199.9 (*c* = 1.0, $CHCl_3$).

(2R,3R)-2-(4-Methoxyphenyl)-5-oxo-3-phenyl-3,5-dihydro-2H-cyclopenta[a]naphthalene-1-carbaldehyde **3o**. Following general procedure, pure product **3o** was isolated after 2 days by FC on silica (hexane:diethyl ether 4:1) in 47% yield (18 mg, >20:1 dr, **3o**:**4o** 93:7) as an yellow solid (mp = 100-102 ˚C). ^{1}H NMR (700 MHz, $CDCl_3$) δ 10.60 (s, 1H), 8.35–8.32 (m, 1H), 8.27–8.24 (m, 1H), 7.75–7.69 (m, 2H), 7.34–7.31 (m, 2H), 7.30–7.27 (m, 1H), 7.13–7.09 (m, 2H), 7.09–7.05 (m, 2H), 6.87–6.82 (m, 2H), 6.39 (dd, *J* = 2.0, 0.6 Hz, 1H), 4.50 (d, *J* = 2.7 Hz, 1H), 4.15 (t, *J* = 2.4 Hz, 1H), 3.79 (s, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 189.5, 184.6, 166.7, 159.1, 149.1, 141.6, 141.2, 133.7, 132.5, 131.9, 131.4, 130.3, 129.3 (2C), 128.7, 128.5 (2C), 128.0, 127.8 (2C), 127.7, 125.7, 114.6 (2C), 59.9, 57.4, 55.4. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{27}H_{21}O_3$ 393.1486; Found: 393.1488. The *er* was determined by HPLC using a chiral Chiralpack IA [hexane:*i*-PrOH, 90:10] column; column temperature 30 °C; flow rate 1.0 mL/min; t_{major} = 14.3 min, t_{minor} = 21.5 min (98.5:1.5 er); $[\alpha]_D^{20}$ = -193.7 (*c* = 1.0, $CHCl_3$).

(2R,3R)-2-(2-Methoxyphenyl)-5-oxo-3-phenyl-3,5-dihydro-2H-cyclopenta[a]naphthalene-1-carbaldehyde **3p**. Following general procedure, pure product **3p** was isolated after 4 days by FC on silica (hexane:diethyl ether 4:1) in 70% yield (27 mg, >20:1 dr, **3p**:**4p** 89:11) as an yellow solid (mp = 158-160 ˚C). ^{1}H NMR (700 MHz, $CDCl_3$) δ 10.59 (s, 1H), 8.34–8.32 (m, 1H), 8.28–8.26 (m, 1H), 7.74–7.68 (m, 2H), 7.33–7.30 (m, 2H), 7.28–7.26 (m, 1H), 7.26–7.23 (m, 1H), 7.15–7.13 (m, 2H), 7.00–6.98 (m, 1H), 6.90–6.87 (m, 2H), 6.36 (dd, *J* = 2.0, 0.8 Hz, 1H), 4.82 (d, *J* = 2.8 Hz, 1H), 4.22–4.18 (m, 1H), 3.66 (s, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 189.5,

184.8, 167.2, 157.1, 150.0, 141.6, 141.2, 132.4, 131.8, 131.1, 130.4, 129.3, 129.1, 129.0 (2C), 128.8, 128.6, 128.0 (2C), 127.9, 127.4, 125.1, 121.1, 111.4, 56.2, 55.7, 55.5. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{27}H_{21}O_3$ 393.1486; Found: 393.1481. The *er* was determined by HPLC using a chiral Chiralpack ID [hexane:*i*-PrOH, 90:10] column; column temperature 30 °C; flow rate 1.0 mL/min; t_{major} = 24.1 min, t_{minor} = 25.3 min (>99.5:0.5 er); $[\alpha]_D^{20}$ = -199.9 (*c* = 1.0, $CHCl_3$).

(2S,3R)-2-(2,4-Dichlorophenyl)-5-oxo-3-phenyl-3,5-dihydro-2H-cyclopenta[a]naphthalene-1-carbaldehyde **3q**. Following general procedure, pure product **3q** was isolated after 3 days by FC on silica (hexane:diethyl ether 4:1) in 62% yield (27 mg, >20:1 dr, **3q**:**4q** 99:1) as an yellow amorphous solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ 10.71 (s, 1H), 8.42–8.30 (m, 1H), 8.26–8.15 (m, 1H), 7.76-7.72 (m, 2H), 7.40 (m,1H), 7.35–7.28 (m, 3H), 7.18 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.15–7.12 (m, 2H), 6.98 (d, *J* = 8.3 Hz, 1H), 6.40–6.33 (m, 1H), 5.00 (bs, 1H), 4.14 (bs, 1H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 188.5, 184.4, 165.9, 159.5, 147.9, 143.0, 140.5, 133.8, 132.6, 131.8, 131.6, 130.2, 130.0, 129.5, 129.3 (2C), 128.6, 128.1, 127.9 (2C), 127.9, 127.8, 127.0, 125.9, 62.0, 54.1. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{17}Cl_2O_2$ 431.0600; Found: 431.0609. The *er* was determined by HPLC using a chiral Chiralpack IC [hexane:*i*-PrOH, 80:20] column; column temperature 30 °C; flow rate 1.0 mL/min; t_{major} = 15.1 min, t_{minor} = 17.7 min (99:1 er); $[\alpha]_D^{20}$ = -147.7 (*c* = 1.0, $CHCl_3$).

Supporting Information. Full account of screening results, X-ray structure, copies of ^{1}H and ^{13}C NMR spectra, HPLC traces (PDF).

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