Enantioselective synthesis of highly functionalized octahydro-6-oxo-1-phenylnaphthalene-2-carbaldehydes *via* organocatalytic domino reactions†‡

Bor-Cherng Hong,* Roshan Y. Nimje and Ju-Hsiou Liao

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Organocatalytic double Michael reaction and the subsequent aldol condensation of (*E*)-7-oxooct-5-enal and 3-arylpropenal (*e.g.*, cinnamaldehyde) provided octahydro-6-oxo-1-phenylnaphthalene-2-carbaldehyde in high diastereoselectivity and high enantioselectivity (>99% ee). Structures of the adducts **5a** and **5j** were confirmed unambiguously by X-ray analysis.

Introduction

The synthesis of decalin systems, bicyclo[4.4.0]decanes, has long been of key interest in organic synthesis.[1] Many chiral decalins serve as building blocks for the synthesis of naturally occurring compounds and pharmaceutical drugs.[2] Among the many approaches to decalins, the proline-catalyzed Hajos–Parrish–Eder–Sauer–Wiechert reaction represents an efficient protocol. However, following this pioneering discovery in the 1970s, research into organocatalytic synthesis remained virtually dormant until the turn of this century.[3] Recently, when the study of organocatalysis resumed, the synthetic applications evolved even beyond the decalin system, and soon became a blossoming subject and focal point in the synthetic community.[4] Modern studies into organocatalytic synthesis of the decalin system include the improved Hajos–Parrish–Eder–Sauer–Wiechert reaction,[5] the Diels–Alder reaction,[6] the Michael reaction,[7] and oxidative dearomatization.[8] Other recent successes into organocatalytic synthesis of decalins, by intramolecular Diels–Alder (IMDA) reactions for the total synthesis of solanapyrone D,[9] amaminol B,[10] and UCS1025A,[11] have further demonstrated the range of its synthetic applications.

Despite these impressive achievements, a general and efficient organocatalytic cascade reaction allowing the direct preparation of highly functionalized and enantio-enriched decalins remains elusive. In conjunction with our continuing efforts to explore new organocatalytic annulations, we embarked upon a domino strategy using the tandem Michael–Michael–aldol condensation to attain this objective.[12] Herein, we report the development of a new domino Michael–Michael–aldol condensation process of (*E*)-7-oxooct-5-enal (**1a**) and arylacrylaldehyde (**2**) which provides the highly functionalized decalins, hexahydronaphthalen-2(1*H*)-ones, with the control of four stereocenters in a one-pot, three-bond-formation reaction sequence.

Department of Chemistry and Biochemistry, National Chung Cheng University, Chia-Yi 621, Taiwan, ROC. E-mail: chebch@ccu.edu.tw; Fax: +886 5 272104; Tel: +886 5 2428174

† Dedicated to Professor Teh-Chang Chou on the occasion of his 65th Birthday.

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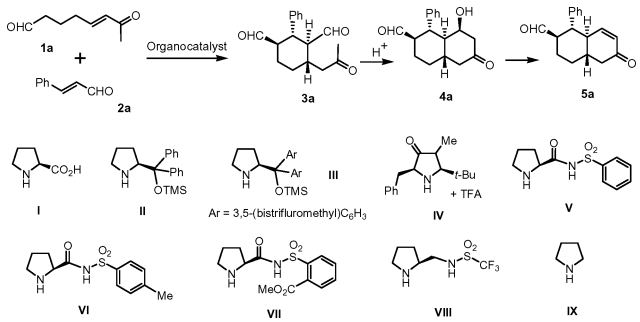
Results and discussion

At the outset of this study, reaction of (*E*)-7-oxooct-5-enal (**1a**)[13] and cinnamaldehyde (**2a**) with 0.2 equiv. of L-proline (**I**) in CH_3CN (4 mL, 0.25 M) at 28 °C for 72 h gave almost no reaction, with recovery of the starting materials (Table 1, entry 1). Conducting the reaction with Et_3N as an additive in an autonomous reaction remained fruitless (Table 1, entry 2). Encouragingly, the same reaction with catalyst **II**[14] and acetic acid (0.2 equiv) in CH_2Cl_2 for 24 h afforded 81% yield of the double Michael adduct **3a** (Table 1, entry 3). The yield increased when the reaction took place in CH_3CN (93% yield; Table 1, entry 4). However, further extension of the reaction time (72 h) did not provide the aldol cyclization product. Noteworthily, a suitable acid additive (*e.g.*, AcOH) was required for the formation of **3a** in CH_3CN or CH_2Cl_2; the reactions with catalyst **II** without an acid additive gave no reaction even after 3 days. Accordingly, a series of solvents was then screened for optimization of yields. However, reactions in polar aprotic solvents (*e.g.*, DMF and DMSO) gave no reaction, and low yields of **3a** were obtained when the reactions proceeded in other, less polar solvents (*e.g.*, 35% yield for the reaction in toluene; Table 1, entries 5–7). Interestingly, the reaction with catalyst **II** in EtOH (a polar protic solvent) without acid additive for 3 days provided a 61% yield of **3a** and a 22% yield of the consequent aldol product **4a** (Table 1, entry 8). We considered the attractive possibility that the synthesis of decalins, which requires three reactions, could be performed as a one-pot synthesis. Furthermore, acceleration of 6-enol*endo* aldolizations[15] by the addition of *p*-TsOH has been reported.[16] In an independent reaction, after the formation of **3a** in CH_2Cl_2 (12 h), *p*-TsOH (1 equiv.) was added to the reaction solution and the resulting mixture was stirred at the same temperature for a further 4 h, leading to the formation of **5a** in 68% yield (>99% ee; Table 1, entry 9). The yield was increased to 86% when reacted in CH_3CN (Table 1, entry 10). With a smaller amount of *p*-TsOH applied in the second-step reaction, the aldol condensation took a longer time for completion. For example, in the reaction with the addition of 0.5 equiv of *p*-TsOH, more than 10 h was required for the complete transformation of **3a** to **5a** (Table 1, entry 11). Unfortunately, replacement of HOAc by *p*-TsOH in the initial step of the reaction in CH_3CN gave no reaction for 16 h (Table 1, entry 12).[17]

Many other pyrrolidine derivatives thereof were tested as potential catalysts. The reactions with catalysts **III**–**VII** and AcOH

Table 1 Screening of the conditions for the domino reaction[a]



Entry	Cat.[b]	Additive[b]	Solvent	t_1/h[c]	t_2/h[d]	Yield (%)[e]	Prod. (ratio)[f]	Ee (%)[g]
1	**I**	—	CH_3CN	72	—	~0[h]	—	n.a.
2	**I**	Et_3N	CH_3CN	72	—	~0[i]	—	n.a.
3	**II**	HOAc	CH_2Cl_2	24	—	81	**3a**	n.d.
4	**II**	HOAc	CH_3CN	12	—	93	**3a**	n.d.
5	**II**	HOAc	DMF	12	—	~0[h]	—	n.a.
6	**II**	HOAc	DMSO	12	—	~0[h]	—	n.a.
7	**II**	HOAc	toluene	12	—	35	**3a**	n.d.
8	**II**	—	EtOH	72	—	83	**3a**/**4a** (2.8 : 1)	n.d.
9	**II**	HOAc	CH_2Cl_2	12	4	68	**5a**	>99
10	**II**	HOAc	CH_3CN	12	4	86	**5a**	>99
11	**II**	HOAc	CH_3CN	12	10[j]	78	**5a**	>99
12	**II**	TsOH	CH_3CN	16	—	~0[h]	—	n.a.
13	**III**	HOAc	CH_3CN	72	—	~0[h]	—	n.a.
14	**IV**	TFA	CH_3CN	72	—	~0[h]	—	n.a.
15	**V**	HOAc	CH_3CN	72	—	~0[h]	—	n.a.
16	**VI**	HOAc	CH_3CN	36	—	~0[h]	—	n.a.
17	**VII**	HOAc	CH_3CN	36	—	~0[h]	—	n.a.
18	**VIII**	—	CH_3CN	16	4	72	**5a**	−54
19	**IX**	HOAc	CH_3CN	16	4	61	**5a**	0

[a] The reactions were performed in 0.25 M of **1** and 1.2 equiv. of cinnamaldehyde at 28 °C. [b] 0.2 equiv. of catalyst and additive, respectively, were applied. [c] First-step reaction time. [d] Unless otherwise specified, reaction time after the addition of *p*-TsOH (1.0 equiv.). [e] Isolated yield. [f] Determined by ^{1}H NMR prior to work up. [g] Enantiomeric excess (ee) of **5a** determined by HPLC with a chiral column (Chiralpak IA). n.d. = not determined; n.a. = not available. [h] No reaction and recovery of starting materials. [i] Complicated mixture with the decomposition of starting materials. [j] Reaction time after the addition of *p*-TsOH (0.5 equiv.).

for 36–72 h gave no reaction in the first-step double Michael reaction. On the other hand, reaction with catalyst **VIII** at ambient temperature for 16 h afforded **3a**; the subsequent addition of *p*-TsOH (1 equiv.) with stirring at the same temperature for 4 h provided a 72% yield of **5a** and 54% ee, but with the inverse enantioselectivity (Table 1, entries 13–18). Reaction with pyrrolidine (**IX**)–AcOH followed by the addition of *p*-TsOH afforded lower yields of **5a** (61% yield; Table 1, entry 19); nevertheless, this racemic product was a suitable standard for HPLC analysis in determining the ee of **5a**, prepared by various catalysts and conditions in Table 1. The structure and relative stereochemistry of **5a** were assigned unambiguously by single-crystal X-ray analysis (Fig. 1).

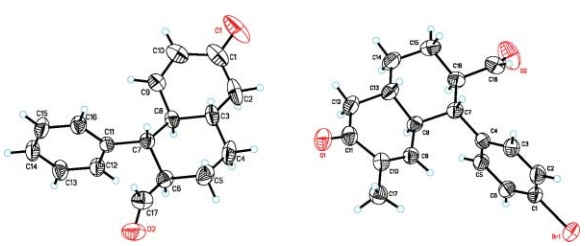
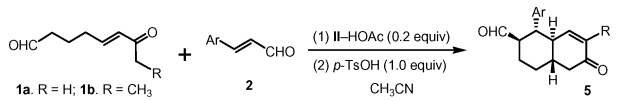


Fig. 1 ORTEP plots for the X-ray crystal structures of **5a** and **5j**.

Although this domino Michael–Michael–aldol condensation could theoretically generate 16 stereoisomers (producing four chiral centers in a three-bond-forming sequence), only one enantiomer was isolated in this reaction.[18] This high stereoselectivity is probably due to the first Michael addition of **1a** to cinnamaldehyde, as it is known that organocatalytic Michael reaction of an aldehyde to α,β-unsaturated aldehydes can proceed with high diastereo- and enantioselectivity,[19] and the resulting product presumably dictates the stereochemistry of the subsequent reactions, including the second Michael reaction and the aldol condensation. A plausible mechanism for the formation of **5a** is shown in Scheme 1. The initial Michael addition of **1a** to cinnamaldehyde is followed by the second Michael reaction in the cyclization to afford **3a**. After the addition of *p*-TsOH, aldol reaction of **3a** produced **4a**, followed by dehydration to provide the hexahydronaphthalenone **5a**.

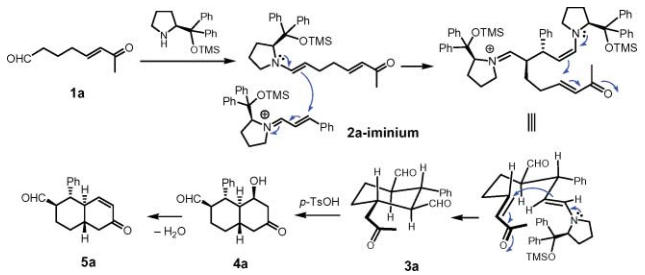
Having established the optimal reaction conditions, a series of arylacrylaldehydes (**2**) were reacted with **1** at ambient temperature in the presence of **II**–AcOH for 11–24 h, followed by the addition of *p*-TsOH in CH_3CN and reacted for an additional 4 h at the same temperature (Table 2). Significantly, regardless of the electron-donating or -withdrawing substituents on **2**, all of the reactions gave **5** in excellent enantioselectivities (>99% ee)[20] and

Table 2 Domino Michael–Michael–Aldol condensation of **1** and **2**[a]



Entry	Product	Time/h[b]	Yield[c] (%)	Ee[d] (%)
1	**5a** R = H, Ar = Ph	12	86	>99
2	**5b** R = H, Ar = (*p*-NO_2)C_6H_4	11	83	99
3	**5c** R = H, Ar = (*p*-OMe)C_6H_4	24	69	>99
4	**5d** R = H, Ar = (*p*-Br)C_6H_4	16	74	99
5	**5e** R = H, Ar = (*p*-Me)C_6H_4	18	72	>99
6	**5f** R = H, Ar = (*o*-NO_2)C_6H_4	16	63	>99
7	**5g** R = H, Ar = Np	24	71	>99
8	**5h** R = CH_3, Ar = Ph	14	84	99
9	**5i** R = CH_3, Ar = (*p*-NO_2)C_6H_4	13	82	99
10	**5j** R = CH_3, Ar = (*p*-Br)C_6H_4	18	75	>99

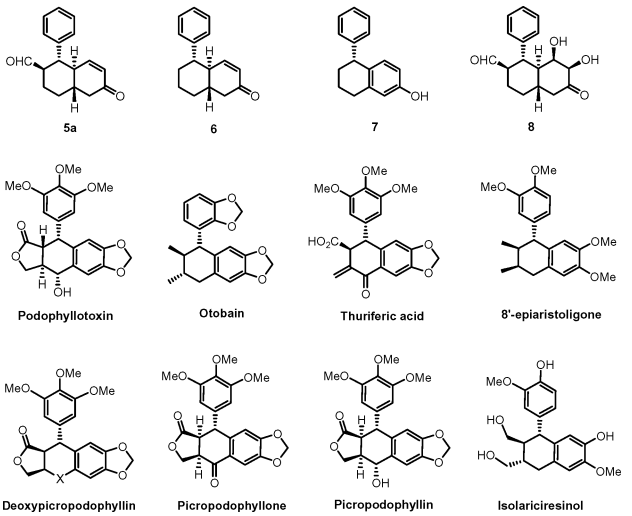
[a] Unless otherwise noted, reactions proceeded in CH_3CN at 25 °C. [b] Reaction time for the first-step (double Michael), before the additional 4 h reaction time after the addition of *p*-TsOH (the second-step aldol condensation). [c] Isolated yield. [d] Enantiomeric excesses (ee) were determined by HPLC with a chiral column (Chiralpak IA).



Scheme 1 Proposed mechanism for the cycloaddition.

diastereoselectivities.[18] However, the first-step Michael reaction of *p*-methoxyacrylaldehyde (**2c**) and of naphthalenylacrylaldehyde (**2g**) were slightly slower than the others (Table 2, entries 3 and 7). The structure and absolute configuration of **5j**, prepared from the reaction with **1b** and **2d**, were assigned unambiguously by X-ray analysis (Fig. 1).

The optically active decaline derivatives obtained from this Michael–Michael–aldol reaction are excellent intermediates for the preparation of many biologically active natural and synthetic compounds. For a simple example, **5a** was converted to antiestrogenic and antiandrogenic agent (*R*)-5-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol (**7**)[21] in two steps (Scheme 2). Decarbonylation of **5a** was achieved using Wilkinson's catalyst [$RhCl(PPh_3)_3$] in refluxing toluene for 5 h, affording 4a,5,6,7,8,8a-hexahydro-5-phenylnaphthalen-2(1*H*)-one (**6**) in 73% yield, followed by aromatization (DDQ, *p*-TsOH, *o*-dichlorobenzene, 170 °C, 7 h; 53% yield) to give **7**. In addition, further functionalization of the decalin system was achieved by dihydroxylation of **5a** with OsO_4–NMO to give **8** (79% yield). More than 300 naturally occurring compounds share the skeleton of tetrahydro-1-phenylnaphthalene, such as podophyllotoxin,[22] picropodophyllotoxin, and etoposide (Scheme 2). Most of them are known for their biological activities and some of them are pharmaceuticals. The successful cascade reactions described herein could provide a useful methodology for the synthesis of these compounds and derivatives.



Scheme 2 Derivatives of the adducts.

Conclusions

In summary, we have developed a highly diastereoselective and enantioselective cascade organocatalytic reaction, constructing three new bonds and four stereocenters, that provides expedited access to highly functionalized and enantiomerically enriched octahydro-6-oxo-1-phenylnaphthalene-2-carbaldehydes (>99% ee). The structures of adducts **5a** and **5j** were confirmed by X-ray analysis. The simple experimental procedures, high diastereoselectivity and enantioselectivity, and great potential of synthetic versatility of the products render this new methodology highly appealing for asymmetric synthesis. Further applications of this methodology toward total synthesis of natural products and pharmaceutical agents are currently under active investigation.

Experimental

General

All solvents were reagent grade. L-proline (99+%) was purchased from Bachem. Other chemicals were purchased from Aldrich or Acros Chemical Co. Reactions were normally carried out under argon atmosphere in flame-dried glassware. Merck silica gel 60 (particle size 0.04–0.063 mm) was employed for flash chromatography. Melting points are uncorrected. ^1H NMR spectra were obtained in $CDCl_3$ unless otherwise noted at 400 MHz (Bruker DPX-400) or 500 MHz (Varian-Unity INOVA-500). ^{13}C NMR spectra were obtained at 100 MHz or 125 MHz. Ee values were measured by HPLC on a chiral column (Chiralpak IA, 0.46 cm ID × 25 cm, particle size 5 μm) by elution with EtOAc–hexane. The flow rate of the indicated elution solvent was maintained at 1 mL min^{-1}, and the retention time of a compound was recorded accordingly. HPLC was equipped with ultraviolet and refractive index detectors. The melting point was recorded on a melting point apparatus (MPA100-Automated melting point system, Stanford Research Systems, Inc.) and is uncorrected. The optical rotation values were recorded with a Jasco-P-2000 digital polarimeter.

Representative procedure for the preparation of 3a and 4a (Table 1, entry 8)

To a solution of (*E*)-7-oxooct-5-enal (70 mg, 0.5 mmol) and *trans*-cinnamaldehyde (79 mg, 0.6 mmol) in EtOH (2 mL) was added dropwise a solution of catalyst **II** (32.5 mg, 0.1 mmol) in EtOH (1 mL). The resulting solution was stirred at ambient temperature for 72 h and diluted with EtOAc (10 mL). The solution was washed with brine (2 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give the crude product. The residue was purified by flash column chromatography with 20% EtOAc–hexane ($R_f = 0.25$ for **3a**, $R_f = 0.18$ for **4a** in 40% EtOAc–hexane) to give **3a** (white solid, 83 mg, 61% yield, m.p. 92–94 °C) and **4a** (white solid, 30 mg, 22% yield, m.p. 118–120 °C).

(1*R*,2*S*,3*S*,4*S*)-4-(2-Oxopropyl)-2-phenylcyclohexane-1,3-dicarbaldehyde (3a). $[\alpha]_D^{25}$ −24 (c 4 $CHCl_3$); IR (neat): 2926, 2722, 1719, 1453, 1358, 1161, 1031, 761, 703 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.18–1.32 (m, 1 H), 1.53 (qd, $J = 12.98$, 3.05 Hz, 1 H), 1.93–2.04 (m, 2 H), 2.06 (s, 3 H), 2.25–2.33 (m, 2 H), 2.33–2.41 (m, 1 H), 2.45–2.53 (m, 1 H), 2.63 (t, $J = 11.84$ Hz, 1 H), 3.12 (t, $J = 11.23$ Hz, 1 H), 7.11–7.20 (m, 3 H), 7.23–7.29 (m, 2 H), 9.26 (d, $J = 4.39$ Hz, 1 H), 9.38 (d, $J = 1.71$ Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 206.9 (C), 203.4 (CH), 202.7 (CH), 139.2 (C), 128.8 (two CH), 127.9 (two CH), 127.7 (CH), 60.5 (CH), 54.4 (CH), 47.5 (CH_2), 45.2 (CH), 32.3 (CH), 30.5 (CH_3) 30.4 (CH_2), 25.9 (CH_2); MS (*m*/*z*, relative intensity): 272 (M^+, 5), 255 (16), 226 (15),186 (26), 168 (68), 129 (39), 115 (43), 91 (100), 77 (26), 55 (14); exact mass calculated for $C_{17}H_{20}O_3$ (M^+): 272.1412; found 272.1415.

(1*R*,2*R*,4a*S*,8*S*,8a*S*)-Decahydro-8-hydroxy-6-oxo-1-phenylnaphthalene-2-carbaldehyde (4a). $[\alpha]_D^{25}$ +22.5 (c 0.6 $CHCl_3$); IR (neat): 3406, 2923, 1708, 1451, 1309, 1154, 1022, 758, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.32–1.43 (m, 1 H), 1.45–1.57 (m, 1 H), 1.72 (t, $J = 10.74$ Hz, 1 H), 1.96 (d, $J = 12.45$ Hz, 2 H), 2.06–2.26 (m, 3 H), 2.31–2.46 (m, 3 H), 2.69 (t, $J = 11.96$ Hz, 1 H), 3.01 (t, $J = 11.47$ Hz, 1 H), 3.76 (br. s., 1 H), 7.18–7.26 (m, 3 H), 7.28–7.34 (m, 2 H), 9.35 (d, $J = 2.20$ Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 209.3 (C), 203.8 (CH), 140.7 (C), 129.0 (two CH), 128.1 (CH), 127.3 (two CH), 68.4 (CH), 55.8 (CH), 50.1 (CH), 49.8 (CH_2), 48.0 (CH_2), 45.2 (CH), 35.2 (CH), 32.6 (CH_2), 25.9 (CH_2).

Representative procedure for the preparation of 5a (Table 2, entry 10)

To a solution of (*E*)-7-oxooct-5-enal (70 mg, 0.5 mmol) and *trans*-cinnamaldehyde (79 mg, 0.6 mmol) in CH_3CN (2 mL) was added dropwise a solution of catalyst **II** (32.5 mg, 0.1 mmol) and acetic acid (6 mg, 0.1 mmol) in CH_3CN (1 mL). The resulting solution was stirred at ambient temperature for 12 h, followed by the addition of *p*-TsOH (80 mg, 0.5 mmol), and stirring for an additional 4 h. The solution was diluted with EtOAc (10 mL), washed with brine (2 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give the crude product. The residue was purified by flash column chromatography with 15% EtOAc–hexane ($R_f = 0.38$ for **5a** in 40% EtOAc–hexane) to give **5a** as a white solid (109 mg, 86% yield), m.p. 161–163 °C.

(1*R*,2*R*,4a*S*,8a*R*)-1,2,3,4,4a,5,6,8a-Octahydro-6-oxo-1-phenylnaphthalene-2-carbaldehyde (5a). $[\alpha]_D^{25}$ +38.8 (c 3 $CHCl_3$); IR (neat): 3030, 2927, 2857, 1722, 1678, 1453, 1389, 1258, 1105, 877, 754, 703 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.41–1.56 (m, 2 H), 1.87–1.97 (m, 2 H), 2.02 (d, $J = 10.99$ Hz, 1 H), 2.14–2.27 (m, 1 H), 2.39 (t, $J = 10.86$ Hz, 1 H), 2.50 (dd, $J = 16.60$, 2.93 Hz, 1 H), 2.63 (t, $J = 11.47$ Hz, 1 H), 2.76 (t, $J = 11.11$ Hz, 1 H), 5.86 (dd, $J = 10.01$, 1.22 Hz, 1 H), 6.43 (d, $J = 10.25$ Hz, 1 H), 7.21–7.30 (m, 3 H), 7.29–7.36 (m, 2 H), 9.37 (d, $J = 2.5$ Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 202.9 (CH), 199.1 (C), 150.7 (CH), 139.8 (C), 129.9 (two CH), 129.1 (two CH), 128.4 (CH), 127.6 (CH), 56.3 (CH), 47.9 (CH), 46.6 (CH), 44.9 (CH_2), 40.9 (CH), 31.2 (CH_2), 25.8 (CH_2); MS (*m*/*z*, relative intensity): 254 (M^+, 90), 226 (10), 183 (15), 157 (15), 128 (48), 120 (84), 108 (82), 91 (100), 77 (42), 55 (26); exact mass calculated for $C_{17}H_{18}O_2$ (M^+): 254.1307; found 254.1305.

Representative one-pot procedure for the preparation of 5b (Table 2, entry 2)

To a solution of (*E*)-7-oxooct-5-enal (70 mg, 0.5 mmol) and (*E*)-3-(4-nitrophenyl)acrylaldehyde (106 mg, 0.6 mmol) in CH_3CN (2 mL) was added dropwise a solution of catalyst **II** (32.5 mg, 0.1 mmol) and acetic acid (6 mg, 0.1 mmol) in CH_3CN (1 mL). The resulting solution was stirred at ambient temperature for 11 h, followed by the addition of *p*-TsOH (80 mg, 0.5 mmol), and stirring for an additional 4 h. The solution was diluted with EtOAc (10 mL), washed with brine (2 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give the crude product. The residue was purified by flash column chromatography with 30% EtOAc–hexane ($R_f = 0.13$ for **5b** in 40% EtOAc–hexane) to give **5b** as a yellow oil (124 mg, 83% yield).

(1*R*,2*R*,4a*S*,8a*R*)-1,2,3,4,4a,5,6,8a-Octahydro-1-(4-nitrophenyl)-6-oxonaphthalene-2-carbaldehyde (5b). $[\alpha]_D^{25}$ +54.3 (c 3.5 $CHCl_3$); IR (neat): 3030, 2928, 2858, 1723, 1680, 1598, 1519, 1346, 1259, 1102, 853, 751, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.41–1.56 (m, 2 H), 1.92–2.00 (m, 2 H), 2.15 (d, $J = 11.96$ Hz, 1 H), 2.23 (t, $J = 15.26$ Hz, 1 H), 2.38–2.46 (m, 1 H), 2.53 (d, $J = 16.36$ Hz, 1 H), 2.81–2.88 (m, 2 H), 5.88 (d, $J = 10.25$ Hz, 1 H), 6.29 (d, $J = 10.01$ Hz, 1 H), 7.43 (d, $J = 7.57$ Hz, 2 H), 8.19 (d, $J = 7.32$ Hz, 2 H), 9.39 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 201.5 (CH), 198.8 (C), 149.5 (CH), 148.5 (C), 147.5 (C), 130.8 (two CH), 129.7 (CH), 124.5 (two CH), 56.6 (CH), 47.4 (CH), 46.4 (CH), 45.0 (CH_2), 41.0 (CH), 34.5 (CH_2), 26.0 (CH_2); MS (*m*/*z*, relative intensity): 299 (M^+, 100), 270 (21), 228 (19), 202 (53), 152 (15), 128 (70), 115 (63), 91 (31), 77 (43), 55 (43); exact mass calculated for $C_{17}H_{17}NO_4$ (M^+): 299.1158; found 299.1156.

(1*R*,2*R*,4a*S*,8a*R*)-1,2,3,4,4a,5,6,8a-Octahydro-1-(4-methoxyphenyl)-6-oxonaphthalene-2-carbaldehyde (5c). $R_f = 0.3$ for **5c** in 40% EtOAc–hexane, yellow solid, m.p. 99–101 °C, 69% yield. Selected spectroscopic data for **5c**: $[\alpha]_D^{25}$ +43.7 (c 2.5 $CHCl_3$); IR (neat): 3030, 2928, 2860, 1719, 1682, 1610, 1513, 1249, 1180, 1032, 820, 772 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.40–1.56 (m, 2 H), 1.86–1.97 (m, 2 H), 2.01 (d, $J = 12.21$ Hz, 1 H), 2.16–2.27 (m, 1 H), 2.33 (t, $J = 10.62$ Hz, 1 H), 2.50 (d, $J = 16.36$ Hz, 1 H), 2.59 (t, $J = 10.86$ Hz, 1 H), 2.66–2.75 (m, 1 H), 3.77 (s, 3 H), 5.87 (d, $J = 10.01$ Hz, 1 H), 6.47 (d, $J = 10.01$ Hz, 1 H), 6.87 (d, $J = 6.84$ Hz, 2 H), 7.13 (d, $J = 6.84$ Hz, 2 H), 9.38 (br. s., 1 H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 203.3 (CH), 199.3 (C), 155.8 (C), 150.9 (CH), 131.7 (C), 129.9 (CH), 129.4 (two CH), 114.5 (two CH), 56.5 (CH), 55.2 (CH_3), 47.1 (CH), 46.8 (CH), 44.9 (CH_2), 41.0 (CH), 31.3 (CH_2), 25.9 (CH_2); MS (*m*/*z*, relative intensity): 284 (M^+, 20), 213 (3), 164 (9), 147 (6), 128 (4), 121 (100), 108 (13), 91 (8), 77 (7), 65 (4); exact mass calculated for $C_{18}H_{20}O_3$ (M^+): 284.1412; found 284.1414.

(1*R*,2*R*,4a*S*,8a*R*)-1-(4-Bromophenyl)-1,2,3,4,4a,5,6,8a-octahydro-6-oxonaphthalene-2-carbaldehyde (5d). $R_f = 0.31$ for **5d** in 40% EtOAc–hexane, white solid, m.p. 146–148 °C, 74% yield. Selected spectroscopic data for **5d**: $[\alpha]_D^{25}$ +19.6 (c 7.5 $CHCl_3$); IR (neat): 3030, 2926, 2857, 1721, 1675, 1489, 1256, 1010, 881, 805, 766 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.41–1.54 (m, 2 H), 1.87–1.97 (m, 2 H), 2.01–2.09 (m, 1 H), 2.17–2.26 (m, 1 H), 2.34 (t, $J = 10.62$ Hz, 1 H), 2.51 (d, $J = 16.60$ Hz, 1 H), 2.60–2.68 (m, 1 H), 2.70–2.78 (m, 1 H), 5.88 (d, $J = 10.01$ Hz, 1 H), 6.40 (d, $J = 10.25$ Hz, 1 H), 7.11 (d, $J = 7.57$ Hz, 2 H), 7.47 (d, $J = 7.57$ Hz, 2 H), 9.38 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 202.3 (CH), 198.9 (C), 150.1 (CH), 147.0 (CH), 139.1 (C), 137.3 (CH), 131.7 (CH), 130.2 (CH), 130.0 (CH), 121.4 (C), 56.3 (CH), 47.1 (CH), 46.3 (CH), 44.8 (CH_2), 40.9 (CH), 31.7 (CH_2), 25.8 (CH_2); MS (*m*/*z*, relative intensity): 332 (M^+, 49), 261 (9), 235 (14), 182 (15), 171 (58), 128 (72), 120 (86), 108 (100), 95 (38), 91 (30), 77 (37), 55 (22); exact mass calculated for $C_{17}H_{17}BrO_2$ (M^+): 332.0412; found 332.0417.

(1*R*,2*R*,4a*S*,8a*R*)-1,2,3,4,4a,5,6,8a-Octahydro-6-oxo-1-*p*-tolylnaphthalene-2-carbaldehyde (5e). $R_f = 0.53$ for **5e** in 40% EtOAc–hexane, white solid, m.p. 106–108 °C, 72% yield. Selected spectroscopic data for **5e**: $[\alpha]_D^{25}$ +39.0 (c 2 $CHCl_3$); IR (neat): 3030, 2925, 2857, 1721, 1683, 1515, 1259, 1103, 809, 771 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.40–1.57 (m, 2 H), 1.86–1.97 (m, 2 H), 2.01 (d, $J = 12.70$ Hz, 1 H), 2.22 (t, $J = 15.14$ Hz, 1 H), 2.31 (s, 3 H), 2.36 (t, $J = 10.74$ Hz, 1 H), 2.51 (d, $J = 16.36$ Hz, 1 H), 2.60 (t, $J = 11.48$ Hz, 1 H), 2.73 (t, $J = 10.99$ Hz, 1 H), 5.86 (d, $J = 10.01$ Hz, 1 H), 6.47 (d, $J = 10.25$ Hz, 1 H), 7.06–7.12 (m, 2 H), 7.12–7.17 (m, 2 H), 9.37 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 203.2 (CH), 199.2 (C), 150.9 (CH), 137.2 (C), 136.7 (C), 129.8 (CH), 129.7 (CH), 129.6 (CH), 128.2 (two CH), 56.4 (CH), 47.6 (CH), 46.6 (CH), 44.9 (CH_2), 41.0 (CH), 31.2 (CH_2), 25.8 (CH_2), 21.0 (CH_3); MS (*m*/*z*, relative intensity): 268 (M^+, 39), 197 (9), 148 (37), 128 (26), 115 (23), 105 (100), 91 (26), 77 (17), 55 (7); exact mass calculated for $C_{18}H_{20}O_2$ (M^+): 268.1463; found 268.1460.

(1*R*,2*R*,4a*S*,8a*R*)-1,2,3,4,4a,5,6,8a-Octahydro-1-(2-nitrophenyl)-6-oxonaphthalene-2-carbaldehyde (5f). $R_f = 0.13$ for **5f** in 40% EtOAc–hexane, yellow oil, 63% yield. Selected spectroscopic data for **5f**: $[\alpha]_D^{25}$ +54.3 (c 5.5 $CHCl_3$); IR (neat): 2925, 2855, 1717, 1683, 1525, 1354, 1258, 853, 745 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.43–1.55 (m, 2 H), 1.92–2.06 (m, 2 H), 2.14 (d, $J = 8.30$ Hz, 1 H), 2.18–2.27 (m, 1 H), 2.45 (t, $J = 10.74$ Hz, 1 H), 2.54 (d, $J = 16.85$ Hz, 1 H), 2.71–2.81 (m, 1 H), 3.39 (t, $J = 11.35$ Hz, 1 H), 5.92 (d, $J = 10.01$ Hz, 1 H), 6.39 (d, $J = 10.25$ Hz, 1 H), 7.35–7.43 (m, 1 H), 7.45 (d, $J = 7.81$ Hz, 1 H), 7.56–7.63 (m, 1 H), 7.77 (d, $J = 8.06$ Hz, 1 H), 9.37 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 201.2 (CH), 198.6 (C), 151.6 (C), 149.9 (CH), 134.9 (C), 133.1 (CH), 130.3 (CH), 128.2 (CH), 128.15 (CH), 124.3 (CH), 57.0 (CH), 46.6 (CH), 44.8 (CH_2), 40.8 (CH), 40.4 (CH), 31.3 (CH_2), 25.7 (CH_2); MS (*m*/*z*, relative intensity): 299 (M^+, 26), 264 (45), 236 (71),180 (36), 146 (46), 130 (60), 120 (100), 115 (72), 91 (67), 77 (78), 55 (88); exact mass calculated for $C_{17}H_{17}NO_4$ (M^+): 299.1158; found 299.1162.

(1*R*,2*R*,4a*S*,8a*R*)-1,2,3,4,4a,5,6,8a-Octahydro-1-(naphthalen-1-yl)-6-oxonaphthalene-2-carbaldehyde (5g). $R_f = 0.43$ for **5g** in 40% EtOAc–hexane, pale yellow oil, 71% yield. Selected spectroscopic data for **5g**: $[\alpha]_D^{25}$ +18.2 (c 3.5 $CHCl_3$); IR (neat): 2926, 2863, 1717, 1683, 1507, 1457, 1260, 1102, 818, 774, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.49–1.66 (m, 2 H), 1.91–2.04 (m, 2 H), 2.04–2.14 (m, 1 H), 2.20–2.31 (m, 1 H), 2.47–2.59 (m, 2 H), 2.78–2.86 (m, 1 H), 2.86–2.95 (m, 1 H), 5.85 (d, $J = 9.77$ Hz, 1 H), 6.46 (d, $J = 10.01$ Hz, 1 H), 7.37 (d, $J = 8.30$ Hz, 1 H), 7.42–7.52 (m, 2 H), 7.68 (br. s., 1 H), 7.74–7.89 (m, 3 H), 9.41 (d, $J = 2.0$ Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 202.9 (CH), 199.2 (C), 150.7 (CH), 137.3 (C), 133.4 (C), 132.8 (C), 130.0 (CH), 129.2 (CH), 127.7 (CH), 127.6 (CH), 126.6 (two CH), 126.1 (two CH), 56.2 (CH), 48.1 (CH), 46.5 (CH), 45.0 (CH_2), 41.0 (CH), 31.3 (CH_2), 25.9 (CH_2); MS (*m*/*z*, relative intensity): 304 (M^+, 89), 276 (6), 233 (7), 184 (20), 165 (27), 141 (100), 128 (31), 115 (13), 95 (15), 69 (12), 55 (24); exact mass calculated for $C_{21}H_{20}O_2$ (M^+): 304.1463; found 304.1469.

(1*R*,2*R*,4a*S*,8a*R*)-1,2,3,4,4a,5,6,8a-Octahydro-7-methyl-6-oxo-1-phenylnaphthalene-2-carbaldehyde (5h). $R_f = 0.6$ for **5h** in 40% EtOAc–hexane, white solid, m.p. 107–109 °C, 84% yield. Selected spectroscopic data for **5h**: $[\alpha]_D^{25}$ +57.4 (c 2 $CHCl_3$); IR (neat): 2925, 2895, 1718, 1671, 1541, 1455, 1259, 1070, 1011, 800, 760, 702 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.36–1.53 (m, 2 H), 1.59 (br. s., 3 H), 1.81–1.92 (m, 2 H), 1.97 (d, $J = 13.43$ Hz, 1 H), 2.17 (t, $J = 15.14$ Hz, 1 H), 2.35 (t, $J = 10.50$ Hz, 1 H), 2.49 (d, $J = 16.36$ Hz, 1 H), 2.59 (t, $J = 11.47$ Hz, 1 H), 2.70 (t, $J = 11.11$ Hz, 1 H), 6.14 (br. s., 1 H), 7.17–7.23 (m, 3 H), 7.28–7.34 (m, 2 H), 9.33 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 203.2 (CH), 199.2 (C), 145.6 (CH), 140.1 (C), 136.0 (C), 129.0 (two CH), 128.5 (CH), 127.4 (two CH), 56.4 (CH), 48.0 (CH), 46.6 (CH), 45.0 (CH_2), 41.2 (CH), 31.0 (CH_2), 25.8 (CH_2), 15.7 (CH_3); MS (*m*/*z*, relative intensity): 268 (M^+, 99), 240 (15), 197 (18), 162 (11), 134 (100), 122 (61), 115 (33), 91 (67), 77 (23), 55 (9); exact mass calculated for $C_{18}H_{20}O_2$ (M^+): 268.1463; found 268.1465.

(1*R*,2*R*,4a*S*,8a*R*)-1,2,3,4,4a,5,6,8a-Octahydro-7-methyl-1-(4-nitrophenyl)-6-oxonaphthalene-2-carbaldehyde (5i). $R_f = 0.25$ for **5i** in 40% EtOAc–hexane, white solid, m.p. 164–166 °C, 82% yield. Selected spectroscopic data for **5i**: $[\alpha]_D^{25}$ +55.8 (c 2.5 $CHCl_3$); IR (neat): 2925, 2858, 1719, 1673, 1519, 1346, 1083, 855, 754, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.48 (br. s., 2 H), 1.63 (br. s., 3 H), 1.94 (br. s., 2 H), 2.14 (br. s., 1 H), 2.17–2.28 (m, 1 H), 2.41 (br. s., 1 H), 2.56 (d, $J = 16.60$ Hz, 1 H), 2.82 (d, $J = 3.17$ Hz, 2 H), 6.02 (br. s., 1 H), 7.44 (br. s., 2 H), 8.22 (br. s., 2 H), 9.40 (d, $J = 3.66$ Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 201.4 (CH), 198.7 (C), 148.5 (C), 147.2 (C), 144.1 (CH), 136.9 (C), 129.4 (two CH), 124.2 (two CH), 56.5 (CH), 47.4 (CH), 46.2 (CH), 44.9 (CH_2), 41.1 (CH), 31.0 (CH_2), 25.7 (CH_2), 15.7 (CH_3); MS (*m*/*z*, relative intensity): 313 (M^+, 100), 271 (15), 242 (21), 216 (11), 165 (11), 141 (26), 134 (44), 115 (42), 91 (27), 69 (42), 55 (15); exact mass calculated for $C_{18}H_{19}NO_4$ (M^+): 313.1314; found 313.1318.

(1*R*,2*R*,4a*S*,8a*R*)-1-(4-Bromophenyl)-1,2,3,4,4a,5,6,8a-octahydro-7-methyl-6-oxonaphthalene-2-carbaldehyde (5j). $R_f = 0.48$ for **5j** in 40% EtOAc–hexane, white solid, m.p. 183–185 °C, 75%

yield. Selected spectroscopic data **5j**: $[\alpha]_D^{25}$ +38.8 (c 3 $CHCl_3$); IR (neat): 2931, 2856, 1716, 1673, 1490, 1258, 1078, 1010, 899, 807, 757 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.38–1.54 (m, 2 H) 1.63 (br. s., 3 H) 1.90 (d, $J = 6.59$ Hz, 2 H) 2.03 (dd, $J = 9.28$, 1.95 Hz, 1 H) 2.14–2.25 (m, 1 H) 2.33 (br. s., 1 H) 2.53 (d, $J = 16.60$ Hz, 1 H) 2.58–2.66 (m, 1 H) 2.69 (d, $J = 9.28$ Hz, 1 H) 6.12 (br. s., 1 H) 7.11 (d, $J = 5.62$ Hz, 2 H) 7.48 (d, $J = 5.62$ Hz, 2 H) 9.37 (d, $J = 2.5$ Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 202.5 (CH), 199.0 (C), 145.0 (CH), 139.4 (C), 136.4 (C), 132.2 (two CH), 130.1 (two CH), 121.3 (C), 56.4 (CH), 47.4 (CH), 46.5 (CH), 45.0 (CH_2), 41.2 (CH), 31.0 (CH_2), 25.8 (CH_2), 15.7 (CH_3); MS (*m*/*z*, relative intensity): 346 (M^+, 26), 277 (5), 196 (3), 169 (24), 134 (100), 122 (58), 115 (24), 91 (16), 77 (15), 55 (7); exact mass calculated for $C_{18}H_{19}BrO_2$ (M^+): 346.0568; found 346.0563.

(4a*R*,5*S*,8a*S*)-4a,5,6,7,8,8a-Hexahydro-5-phenylnaphthalen-2(1*H*)-one (6). To a solution of **5a** (100 mg, 0.4 mmol) in toluene (5 mL) was added Wilkinson's catalyst (182 mg, 0.2 mmol), and the resulting solution was heated to reflux for 5 h. After cooling to room temperature, the solution was diluted with EtOAc (10 mL), filtered over celite, and concentrated in *vacuo* to afford the crude product. The residue was purified by flash column chromatography with 10% EtOAc–hexane ($R_f = 0.43$ for **6** in 20% EtOAc–hexane) to give **6** as a white solid (65 mg, 73%), m.p. 107–109 °C. Selected spectroscopic data for **6**: $[\alpha]_D^{25}$ +57.3 (c 0.7 $CHCl_3$); IR (neat): 3028, 2925, 2854, 1678, 1445, 1385, 1265, 1104, 843, 761, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.30–1.42 (m, 1 H), 1.50 (qd, $J = 12.86$, 2.93 Hz, 1 H), 1.56–1.67 (m, 1 H), 1.78 (d, $J = 12.70$ Hz, 1 H), 1.84–2.00 (m, 3 H), 2.17–2.28 (m, 1 H), 2.27–2.35 (m, 1 H), 2.35–2.43 (m, 1 H), 2.48 (d, $J = 16.60$ Hz, 1 H), 5.84 (d, $J = 10.01$ Hz, 1 H), 6.51 (d, $J = 9.52$ Hz, 1 H), 7.14–7.27 (m, 3 H), 7.28–7.38 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 200.1 (C), 152.8 (CH), 143.9 (C), 129.4 (CH), 128.7 (two CH), 127.8 (two CH), 126.7 (CH), 48.1 (CH), 46.9 (CH), 45.4 (CH_2), 41.7 (CH), 35.9 (CH_2), 32.8 (CH_2), 25.8 (CH_2); MS (*m*/*z*, relative intensity): 227 (M^++1, 16), 226 (M^+, 91), 183 (8), 157 (11), 128 (24), 108 (100), 91 (61); exact mass calculated for $C_{16}H_{18}O$ (M^+): 226.1358; found 226.1359.

(*R*)-5,6,7,8-Tetrahydro-5-phenylnaphthalen-2-ol (7). To a solution of **6** (57 mg, 0.25 mmol) in *o*-dichlorobenzene (3 mL) was added DDQ (86 mg, 0.38 mmol) and catalytic amount of *p*-TsOH (4.5 mg, 0.026 mmol). The resulting solution was heated to 170 °C and stirred for 7 h. After cooling to room temperature, the reaction mixture was directly loaded on to a column and purified by silica gel chromatography with 15% EtOAc–hexane ($R_f = 0.3$ for **7** in 20% EtOAc–hexane) to give **7** as a brown oil (31 mg, 53%). Selected spectroscopic data for **7**: $[\alpha]_D^{25}$ −11.2 (c 0.5 $CHCl_3$); IR (neat): 3550–3100, 2929, 2857, 1607, 1497, 1448, 1254, 940, 822, 754, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.65–1.75 (m, 1 H), 1.77–1.89 (m, 2 H), 2.07–2.15 (m, 1 H), 2.72–2.80 (m, 1 H), 2.80–2.89 (m, 1 H), 4.02 (t, $J = 6.59$ Hz, 1 H), 4.67 (br. s., 1 H), 6.51 (d, $J = 8.30$ Hz, 1 H), 6.59 (br. s., 1 H), 6.68 (d, $J = 8.30$ Hz, 1 H), 7.08 (d, $J = 7.32$ Hz, 2 H), 7.14–7.21 (m, 1 H), 7.22–7.29 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 153.4 (C), 147.7 (C), 139.1 (C), 131.7 (C), 131.3 (CH), 128.7 (two CH), 128.2 (two CH), 125.9 (CH), 114.8 (CH), 113.1 (CH), 44.9 (CH), 33.4 (CH_2), 29.9 (CH_2), 20.8 (CH_2); MS (*m*/*z*, relative intensity): 224 (M^+, 92), 196 (61), 147 (78), 134 (100), 91 (60), 73 (71); exact mass calculated for $C_{16}H_{16}O$ (M^+): 224.1201; found 224.1208.

(1*R*,2*R*,4a*S*,7*R*,8*R*,8a*S*)-Decahydro-7,8-dihydroxy-6-oxo-1-phenylnaphthalene-2-carbaldehyde (8). To a solution of **5a** (25 mg, 0.1 mmol) in THF/*t*-BuOH:H_2O (1 : 3 : 0.5 mL) was added *N*-methylmorpholine *N*-oxide (NMO, 35 mg, 0.3 mmol) and OsO_4 (20 μL, 2.5 wt% in *t*-BuOH), and the solution was stirred for 8 h at ambient temperature. The reaction was quenched by the addition of sodium sulfite (50 mg). The mixture was stirred for 30 min, and extracted with EtOAc (25 mL × 2). The combined organic layers were washed with brine (25 mL), dried over Na_2SO_4, and concentrated *in vacuo* to afford the crude product. The residue was purified by flash column chromatography with 50% EtOAc–hexane ($R_f = 0.20$ for **8** in 50% EtOAc–hexane) to give **8** as a white solid (22 mg, 79%), m.p. 197–199 °C. Selected spectroscopic data for **8**: $[\alpha]_D^{25}$ +65.1 (c 0.5 $CHCl_3$); IR (neat): 3458, 2918, 1639, 1438, 1325, 1258, 1126, 889, 758, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ, 1.34–1.46 (m, 1 H) 1.46–1.57 (m, 1 H) 1.80 (t, $J = 10.01$ Hz, 1 H) 1.93–2.04 (m, 2 H) 2.12–2.23 (m, 2 H) 2.27 (s, 1 H) 2.50–2.61 (m, 1 H) 2.70 (t, $J = 11.96$ Hz, 1 H) 3.10 (t, $J = 11.48$ Hz, 1 H) 3.65–3.75 (m, 2 H) 3.96 (br. s., 1 H) 7.24 (br. s., 3 H) 7.27–7.35 (m, 2 H) 9.36 (d, $J = 1.95$ Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 208.6 (C), 203.7 (CH), 140.3 (C), 129.0 (three CH), 127.3 (two CH), 77.4 (CH), 71.8 (CH), 55.3 (CH), 48.5 (CH), 44.9 (CH_2), 44.8 (CH), 35.8 (CH), 32.2 (CH_2), 25.8 (CH_2); MS (*m*/*z*, relative intensity): 288 (M^+, 60), 241 (12), 215 (38), 197 (21), 169 (42), 129 (24), 115 (30), 91 (100), 77 (18), 55 (20); exact mass calculate for $C_{17}H_{20}O_4$ (M^+): 288.1362; found 288.1363.

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Notes and references

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