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PAPER

An organocatalytic approach to enantiomerically enriched α-arylcyclohexenones and cyclohexanones†‡

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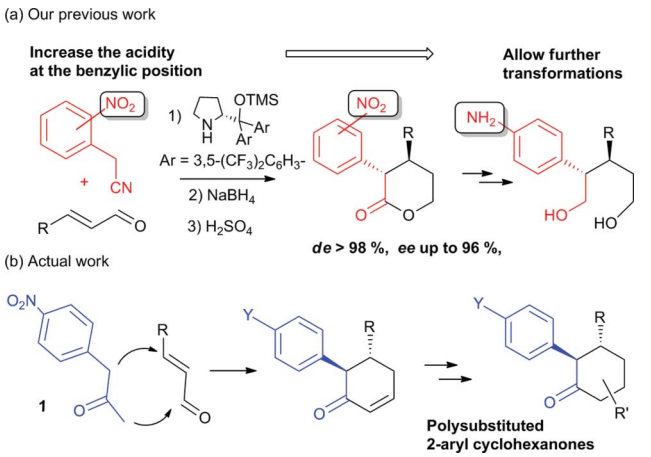
The presence of a *p*-nitrophenyl group converts acetone into an excellent and versatile nucleophile in organocatalytic processes, able to react with α,β-unsaturated aldehydes affording β-substituted α-arylcyclohexenones *via* a Michael reaction/aldol reaction/dehydration sequence, which occurs in good yields, *ee* up to 96% and complete diastereoselectivity. The resulting compounds are excellent synthons for the diastereoselective preparation of a variety of synthetically useful polysubstituted cyclohexanones and derivatives.

Introduction

Optically active cyclohexenones are especially attractive compounds that have found widespread applications in syntheses of target molecules,[1] mainly due to their chemical versatility that allows them to participate in various interesting transformations.[2] Most of the reported procedures for synthesizing these compounds use classical approaches starting from the chiral pool, usually terpenes;[3] but there are also some methods based on asymmetric synthesis,[4] including enantioselective organocatalysis.[5]

The particular case of α-aryl cyclohexenones is interesting as they have been used for the preparation of a wide range of natural products in racemic versions,[6] probably due to the difficulty in obtaining these compounds in enantiomerically pure forms. None of the strategies mentioned above provides a general method for their preparation in an optically pure form, and therefore the search for new strategies leading to a broad range of substitution in 2-aryl cyclohexenones is of interest.[7]

We have recently demonstrated that arylacetonitriles are able to participate in organocatalytic Michael additions to α,β-unsaturated aldehydes by incorporating a nitro group at the phenyl ring.[8,9] The nitro group acts as a versatile temporary activating group in a remote position (Scheme 1, a). In that paper we were able to get the formal diastereoselective α-arylation of lactones by *in situ* reduction of the resulting aldehyde and further intramolecular acylation. On this basis, we envisioned that α,β-disubstituted cyclohexenones could be easily obtained by simple organocatalytic Michael addition of the commercially available ketone **1** to α,β-unsaturated aldehydes,[10] followed by aldol reaction and a dehydration sequence (Scheme 1, b).



Scheme 1 A nitrophenyl moiety as an activating group of monoactivated carbanions.

Taking into account that the presence of the NO_2 group in compounds **5** can be used for introducing other substituents at the aromatic ring and the chemical versatility of the cyclohexenone moiety, these compounds can be considered as appropriated intermediates for synthesizing enantiomerically pure polysubstituted 2-aryl cyclohexanones. It is worth mentioning that the preparation of these compounds by other ways is nontrivial[11] and usually requires umpolung strategies of α-arylation[12,13] or long reaction sequences.[14]

Results and discussion

As a model reaction we studied the addition of ketone **1** to crotonaldehyde (**2a**) looking for the optimal conditions of the Michael addition. This reaction took place in CH_2Cl_2 with the screened pyrrolidine-based catalysts (**I–IV**) affording a mixture of

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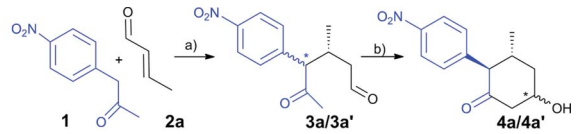
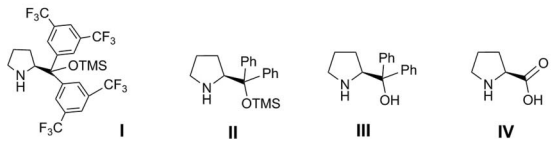
† Dedicated to Amelia Tito on the occasion of her retirement

‡ Electronic supplementary information (ESI) available: Optimization of the Michael addition of **1** to crotonaldehyde and aromatic aldehydes; configurational assignment of **4a** and **4a′**, **8a**, **9a** and **10a**; spectra; chiral HPLC conditions; X-ray crystallographic data of **7a** and computational details. CCDC reference number 838553. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ob06356a

Table 1 Optimization of the sequence Michael addition (**1** to **2a**)/cyclization[a]





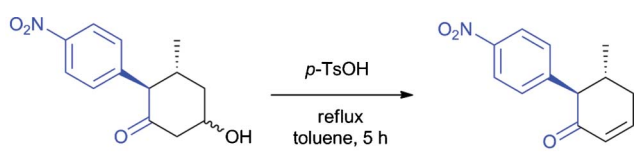
Entry	Cat.	Additive	Solvent	*t* (h)	Conv. step a[b] (%)	*ee* (%)[c] **4a**/**4a′**
1	**I**	—	CH_2Cl_2	24	40	90 : 90
2	**II**	—	CH_2Cl_2	24	95	73 : 70
3	**III**	—	CH_2Cl_2	24	75	<5%
4	**IV**	—	CH_2Cl_2	24	95	10 : 16
5	**I**	—	EtOH	24	90	84 : 88
6	**II**	—	EtOH	24	90	69 : 70
7	**I**	$PhCO_2H$	EtOH	20	100	78 : 80
8	**I**	LiOAc	EtOH	12	100	90 : 90[d]
9	**I**	CsOAc	EtOH	20	100	80 : 78
10	**I**	DABCO	EtOH	20	100	80 : 84

[a] The reactions were carried out on a 0.2 mmol scale with **2a** (1.5 equiv) and [**1**] = 1 M in different solvents. [b] Determined by ^{1}H NMR of the crude of the Michael addition. [c] Determined by HPLC analysis of the alcohols **4a** and **4′a**. [d] Identical *ee* were obtained by decreasing the temperature to 0 °C (24 h).

epimers at the benzylic carbon, **3a** and **3a′** (Table 1, entries 1–4). Their aldol cyclization in the presence of DBU afforded an equimolecular mixture of 3-hydroxycyclohexanones, **4a** and **4a′**, epimers at the hydroxylic center, which indicated that epimerization at the benzylic center towards the presumably most stable *trans* 2,3-substituted diastereoisomer had taken place, due to the high acidity of the benzylic proton. After determining the enantiomeric excesses of **4a** and **4a′** by chiral HPLC we could establish that **I** and **II**[15] were the most promising catalysts (entries 1 and 2). Higher conversions and similar enantioselectivities were obtained by using EtOH as solvent (entries 5–6).

We next investigated the influence of several additives on the reaction times and enantioselectivity of the process using **I** and **II** as catalysts in different solvents. Only the best results have been collected in Table 1 (entries 7–10).[16] The use of EtOH and LiOAc as additives provided the highest levels of conversion and enantioselectivy (entry 8). Unfortunately, *ee* was not improved by decreasing the temperature (see note *d*).

With the optimal conditions for the Michael addition and the aldol reaction established above, the dehydration step was then investigated (Scheme 2). Diastereomerically pure cyclohexenone **5a** was cleanly obtained in high yield, without erosion of the enantioselectivity, after treatment of the mixture **4a**/**4a′** with *p*-TsOH.



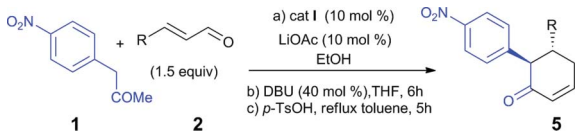
Scheme 2 Dehydration of aldols **4a**/**4a′**.

Fortunately, reaction conditions used in the elimination step could be applied to the crude mixture resulting after aldol reaction and thus, the sequential procedure (Michael addition/aldol reaction/elimination) could be applied directly to **1** affording **5a** in 80% yield (Table 2, entry 1). The application of this procedure only required the elimination of the solvents under vacuum after the first step, filtration through a short pad of silica gel after the aldol reaction and a final chromatographic column. This sequence was scaled up starting from 1 g of product **1** with the same result.

To explore the scope of this protocol a series of α,β-unsaturated aldehydes were subjected to the conditions previously optimized (Table 2). This simple sequence was successfully applied to a series of β-substituted α,β-unsaturated aldehydes with alkyl or alkenyl substituents (entries 1–6). In all these cases, very high *ee* values were obtained (up to 96%). By contrast, reactions of aldehydes bearing aromatic substituents (entries 7–12) also evolved with high reactivity and complete diastereoselectivity, but lower *ee* values were obtained.[17] Additionally, the *ee* values for ketones **5g** and **5h** decreased with time (compare entries 7 and 8 or 9 and 10), and ketone **5g** was even obtained as racemic after 24 h of reaction (entry 10). Finally, reaction of **2h** was more enantioselective in the presence of benzoic acid and that of **2i** in the absence of additives. The variation of the enantioselectivity observed with time could be a consequence of the reversibility of the Michael addition.[18] The equilibration would avoid an asymmetric (kinetic) control allowing a thermodynamic pathway that even in some cases affords racemic products (entry 10).[19]

The lower enantioselectivities found for cinnamaldehyde derivatives had also been observed when arylacetonitriles were used as nucleophiles.[8] In this sense, it is worthwhile to note that these reactions show a complementary behavior to that observed with other related carbon nucleophiles, such as thioesters[18b] or

Table 2 The aldehyde scope of the reaction sequence Michael addition/aldol reaction/dehydration[a]



Entry	R	Step a, *t* (h)	Product	Overall yield (%)	*ee* **5** (%)
1	**2a** (Me)	12	**5a**	80	90
2	**2b** (Et)	15	**5b**	76	91
3	**2c** (*n*-Pr)	26	**5c**	78	96
4	**2d** (*n*-Bu)	48	**5d**	70	92
5	**2e** (^{i}Pr)	50	**5e**	74	80
6	**2f** $(CH_2)_2CH{=}CH(CH_2CH_3)$	30	**5f**	56	94
7	**2g** (Ph)	2.5	**5g**	69	66
8	**2g** (Ph)	48	**5g**	100[d]	46
9	**2h** (*p*-OMe–C_6H_4)	1	**5h**	100[d]	40
10	**2h** (*p*-OMe–C_6H_4)	24	**5h**	100[d]	0
11	**2h** (*p*-OMe–C_6H_4)[b]	16	**5h**	71	75
12	**2i** (*p*-NO_2–C_6H_4)[c]	24	**5i**	75	76

[a] Reactions performed on 0.4 mmol scale. [b] Reaction carried out with 30 mol% of BzOH instead of LiOAc as additive. [c] Reaction carried out without additive. [d] Conversion.

4-*p*-nitrobenzyl pyridines.[9] These nucleophiles exhibit low reactivity and enantioselectivity with α,β-unsaturated aldehydes bearing aliphatic substituents, but better results with aromatic ones. In fact, nucleophile **1** renders the best average enantioselectivities of all these comparable nucleophiles (Fig. 1).

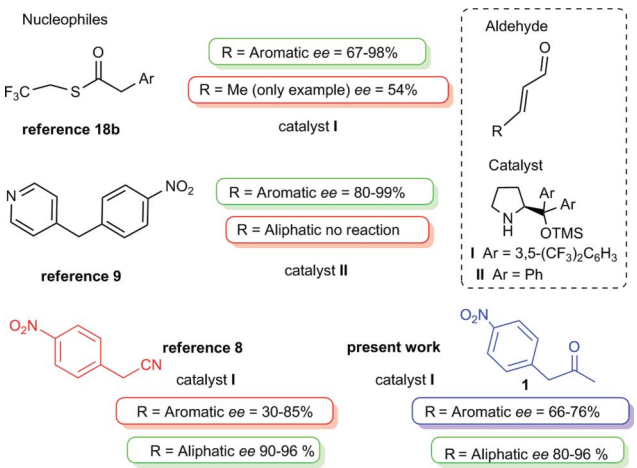
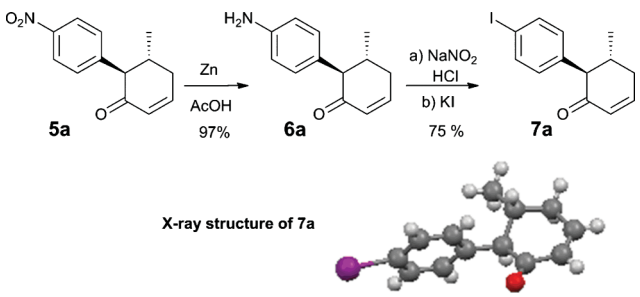


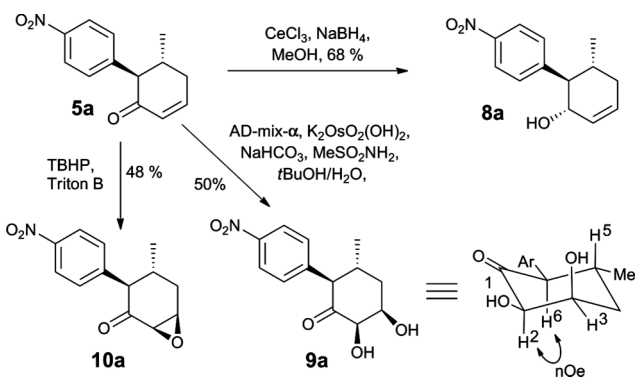
Fig. 1 Comparison of the results obtained in the organocatalytic Michael additions of different nucleophiles to α,β-unsaturated aldehydes bearing aliphatic and aromatic substituents.

Cyclohexenones **5** resulting in these reactions have many synthetic possibilities that we have illustrated by studying the behavior of **5a** under different reaction conditions (Schemes 3 and 4).

First, the presence of the NO_2 group opens the gate to introduce different substituents at the aromatic ring, taking advantage of the diazonium salt's chemistry. Thus, chemoselective Zn/AcOH reduction of the NO_2 group in the presence of the enone moiety afforded amine **6a**, which was easily transformed into the aryliodide **7a**. This compound, that could be employed as the starting material in different coupling reactions, has been used for unequivocally establishing the absolute configuration of the



Scheme 3 Transformations on the aromatic ring and X-ray structure of **7**.



Scheme 4 Chemoselective reactions on C=C and C=O of **5a**.

stereogenic carbons of **5a** (and presumably those of the rest of the cyclohexenones of Table 2) as (5*R*, 6*R*) by X-ray diffraction studies. The (*R*) configuration assigned to C-5 agrees with the predicted one by the models used for explaining the stereochemical course of the organocatalytic Michael additions to β-substituted α,β-unsaturated aldehydes involving iminium intermediates.[20] The (*R*) configuration assigned to C-6 agrees with the expected one by assuming the thermodynamic equilibration of the carbanion generated at C-6.

Chemoselective transformations of the C=O and C=C bonds at compounds **5** can be easily performed (Scheme 4). The selective reduction of the carbonyl group of cyclohexenones is a very interesting transformation because of the high synthetic versatility of the resulting allylic alcohols.[21] Under Luche conditions,[22] **5a** was transformed into **8a** with good stereoinduction (74% *de*, Scheme 4).[23] In order to explain the observed stereoselectivity, we performed theoretical calculations at the DFT (B3LYP) level,[24] by using the Gaussian 09 program,[25] about the most stable structure of **5a**. These studies revealed the scarce steric differentiation of the carbonyl faces (see ESI for details‡), thus suggesting that the observed stereoselectivity must be attributed to the different torsional effects that take place during the hydride attack on each face.[26]

Dihydroxilation and epoxidation reactions of the double bond at **5a** afforded carbocyclic sugar analogs in a highly stereoselective manner (Scheme 4).[27] Compound **9a** was obtained as a single diastereomer under the conditions used in the asymmetric Sharpless dihydroxylation.[28] Its expected stereochemistry and relative configuration were confirmed from the value of the vicinal coupling constants $J_{5,6}$ (11.8 Hz, indicates an anti-periplanar arrangement) and $J_{2,3}$ (3.5 Hz, indicates a *syn* arrangement). Moreover, the NOE between H_2 and H_6 and the absence of NOE between H_3 and H_5 confirm the stereochemistry indicated in Scheme 4. Finally, the comparison of chemical shifts obtained for **9a** with those calculated for the two possible diastereoisomers resulting in the dihydroxylation,[16] reinforces the assignment indicated in Scheme 4.

Epoxidation of **5a** with TBHP[29] yields diastereomerically pure epoxide **10a**. Since NOESY experiments did not allow us to unequivocally establish the configuration of the only detected epoxide **10a**, we performed a calculation, at the DFT (B3LYP) level, of the δ values corresponding to the two possible epoxides (see ESI for details†). Their comparison with those experimentally obtained for **10a** supports the assignment indicated in Scheme 4.[30]

Conclusions

In conclusion, *p*-nitrophenylacetone reacts with a variety of β-substituted α,β-unsaturated aldehydes activated by **I** affording β-substituted α-arylcyclohexenones **5** *via* a Michael addition/aldol reaction/dehydration sequence in a highly enantioselective manner, which is especially successful for aldehydes with alkyl substituents (*ee* = 80–96%). As the diastereomerically pure resulting compounds can be easily converted into α-arylcyclohexanones and derivatives in an efficient and stereoselective manner, this sequence can be considered as a general, efficient and simple procedure for the synthesis of α-aryl cyclohexenones and cyclohexanones. Application of other versatile nucleophiles containing a nitro group as a remote activating moiety is currently ongoing in our laboratory.

Experimental section

More details about the optimization of the Michael addition of **1** to crotonaldehyde are reported in the supporting information.†

Procedure for the Michael/cyclization/dehydration reactions of 1 with crotaonaldehyde step by step (from 1 to 5a)

(3*R*, 4*R* and 3*R*, 4*S*)-3-methyl-4-(4-nitrophenyl)-5-oxohexanal (3a and 3a′). To a solution of (*S*)-α-α-bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether (**I**) (10 mol%, 0.04 mmol) in ethanol (0.4 mL) was added crotonaldehyde (**2a**) (1.5 equiv., 0.6 mmol). After the resulting mixture was stirred at room temperature for 15 min nitrophenylacetone **1** (0.4 mmol, 72 mg) and LiOAc (10 mol%, 0.04 mmol) were sequentially added. After 12 h the reaction mixture was filtered through a plug of silica gel and the solvent was evaporated under vacuum to give a mixture of **3a/3a′** = 2 : 1 in 95%yield. The two diastereomers could be separated by flash chromatography (4 : 1 *n*-hexane : EtOAc). Data of the major diastereomer **3a** ^{1}H NMR (300 MHz): δ 9.55 (s, 1H), 8.18 (d, J = 8.8 Hz, 2H), 7.42 (d, J = 8.8 Hz, 2H), 3.82 (d, J = 10.3 Hz, 1H), 2.95–2.80 (m, 1H), 2.22 (dd, J = 17.2, 3.8 Hz, 1H), 2.13 (s, 3H), 2.04 (ddd, J = 17.2, 10.4, 1.9 Hz, 1H), 1.06 (d, J = 6.6 Hz, 3H). ^{13}C NMR (75 MHz): δ 206.4 (CO), 200.8 (CHO), 147.5 (C), 144.1 (C), 129.6 (2CH), 124.1 (2CH), 64.1 (CH), 47.5 (CH_2), 31.2 (CH_3), 30.8 (CH), 18.8 (CH_3). MS (ESI) *m/z* 304 (M+Na$^+$MeOH, 100), 250 (M+1, 3), 232 (10). HRMS (ESI) calcd. for $C_{13}H_{16}NO_4$ [M+1]: 250.1073; found, 250.1076. $[\alpha]_D^{20}$ +98.0 (*c* 1.0, $CHCl_3$).

(2*R*, 3*R*, 5*R* and 2*R*, 3*R*, 5*S*)-5-hydroxy-3-methyl-2-(4-nitrophenyl) cyclohexanone (4a and 4a′). The mixture of diastereomers **3a/3a′** was placed in a vial with a stirring bar and dissolved in THF (0.5 mL). DBU was added (0.4 equiv., 0.16 mmol), the reaction was stirred at room temperature for 6 h and then filtered through a plug of silica gel. The solvent was eliminated under vacuum to give the aldol **4** as a mixture of diastereomers (95%). ^{1}H NMR (300 MHz) (data obtain from the mixture of diastereomers): δ 8.12 (d, J = 8.7 Hz, $2H_{major}$, $2H_{minor}$), 7.21 (d, J = 8.7 Hz, $2H_{major}$), 7.14 (d, J = 8.7 Hz, $2H_{minor}$) 4.50 (quint, J = 3.0 Hz, $1H_{major}$), 4.02 (m, $1H_{minor}$), 3.32 (d, J = 11.7 Hz, $1H_{major}$), 3.28 (d, J = 11.7 Hz, $1H_{minor}$), 2.95–2.88 (m, $1H_{minor}$), 2.78–2.51 (m, 4H), 2.40–2.30 (m, $1H_{minor}$), 2.23–2.13 (m, $1H_{major}$), 2.09–1.97 (m, $1H_{minor}$), 1.94–1.67 (m, 2H), 0.86 (d, J = 6.6 Hz, $3H_{minor}$), 0.83 (d, J = 6.6 Hz, $3H_{major}$). ^{13}C NMR (75 MHz) (mixture of diastereomers): δ 207.1(C), 205.6 (C), 147.1 (C), 147.0 (C), 145.1 (C), 144.7 (C), 130.4 (2CH), 130.3 (2CH), 123.5 (2CH), 123.4 (2CH), 68.5 (CH), 68.4 (CH), 64.8 (CH), 63.5 (CH), 50.9 (CH_2), 48.9 (CH_2), 43.3 (CH_2), 40.3 (CH_2), 34.6 (CH), 34.5 (CH), 20.6 (CH_3), 20.5 (CH_3). MS (EI) *m/z* 231 (M$^+$, 18), 163 (70), 133 (100), 115 (48). HRMS (EI) calcd. for $C_{13}H_{13}NO_3$ [M$^+$]: 231.0895; found, 231.0903.

(5*R*, 6*R*)-5-methyl-6-(4-nitrophenyl) cyclohex-2-enone (5a). A sealed tube equipped with a magnetic stirring bar was charged with the aldols **4a/4a′** (0.40 mmol), *p*-toluenesulphonic acid (20 mol%) and toluene (2 mL). The sealed tube was capped, placed in a sand bath at 120 °C and the mixture was then vigorously stirred at the same temperature for 5 h. The product can be purified by flash chromatography (4 : 1 to 2 : 1 *n*-hexane : EtOAc) to provide cyclohexenone **5a** as a single diastereomer (white solid, 90% yield). mp = 103–105 °C. ^{1}H NMR (300 MHz): δ 8.20 (d, J = 8.5 Hz, 2H), 7.26 (d, J = 8.5, 2H), 7.06 (ddd, J = 10.0, 5.7, 2.4 Hz, 1H), 6.17 (ddd, J = 10.0, 2.8, 0.9 Hz, 1H), 3.37 (d, J = 12.2 Hz, 1H), 2.60 (dt, J_t = 5.7 Hz, J_d = 18.4 Hz, 1H), 2.52–2.40 (m, 1H), 2.30 (ddt, J_t = 2.4 Hz, J_d = 18.4, 10.0 Hz, 1H), 0.86 (d, J = 6.4 Hz, 3H). ^{13}C NMR (75 MHz) δ 198.1 (C),

149.5 (CH), 147.0 (C), 146.1 (C), 130.1 (2CH), 129.6 (CH), 123.7 (2CH), 61.6 (CH), 36.3 (CH_2), 34.6 (CH), 20.1 (CH_3). MS (ESI) *m/z* 232 (M+1, 100), 150 (16), 149 (59). HRMS (ESI) calcd. for $C_{13}H_{14}NO_3$ [M+1]: 232.0968; found: 232.0967. The enantiomeric excess was determined by HPLC using a Chirapack AD column [hexane/*i*PrOH = 90 : 10]; flow rate 1.0 mL min^{-1}; τ_{major} = 19.1 min, τ_{minor} = 28.5 min (90% *ee*). $[\alpha]_D^{20}$ −49.8 (*c* 1.0, $CHCl_3$). IR (KBr) 1674, 1514, 1342, 742, 706 cm^{-1}.

Sequential procedure for the Michael/cyclization/dehydration reactions of nucleophile 1 with aldehydes 2a–2i. To a solution of (*S*)-α-α-bis [3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether **I** (10 mol%, 0.04 mmol) in ethanol (0.4 mL) the corresponding α,β-unsaturated aldehyde (**2a–i**) (1.5 equiv., 0.6 mmol) was added. After the resulting mixture was stirred at room temperature for 15 min, 4-nitrophenylacetone **1** (0.4 mmol, 72 mg) and LiOAc (10 mol%, 0.04 mmol) were sequentially added. The reactions were followed by TLC (until the disappearance of the 4-nitrophenylacetone **1**), whereupon the solvent was evaporated under vacuum. The residue was dissolved in THF (0.5 mL) and DBU was added (0.4 equiv., 0.16 mmol). The reaction was stirred at room temperature during 6 h, and then filtered through a plug of silica gel. The solvent was evaporated and the crude was placed in a sealed tube and dissolved in toluene. *p*-Toluenesulphonic acid (20 mol%) was added and the reaction mixture was stirred and heated under reflux during 5 h. The residue was directly purified by flash chromatography (6 : 1 to 4 : 1 *n*-hexane : EtOAc) to give the corresponding cyclohexenones **5a–i** in the yields indicated in Table 2.

(5*R*, 6*R*)-5-ethyl-6-(4-nitrophenyl) cyclohex-2-enone (5b). The title compound was obtained as a single diastereomer according to the sequential procedure described above (76% yield). mp = 110–112 °C. ^{1}H NMR (300 MHz): δ 8.20 (d, *J* = 8.7 Hz, 2H), 7.26 (d, *J* = 8.6, 2H), 7.09 (ddd, *J* = 10.0, 6.2, 2.3 Hz, 1H), 6.18 (ddd, *J* = 10.0, 2.7, 1.3 Hz, 1H), 3.48 (d, *J* = 12.0 Hz, 1H), 2.71–2.60 (m, 1H), 2.43–2.21 (m, 2H), 1.34–1.08 (m, 2H), 0.84 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (75 MHz) δ 198.3 (C), 149.4 (CH), 147.1 (C), 146.2 (C), 130.1 (2CH), 129.6 (CH), 123.6 (2CH), 59.7 (CH), 42.0 (CH), 30.8 (CH_2), 26.4 (CH_2), 10.3 (CH_3). MS (ESI) *m/z* 246 (M+1, 100), 150 (11), 149 (49). HRMS (ESI) calcd. for $C_{14}H_{16}NO_3$ [M+1]: 246.1124; found: 246.1130. The enantiomeric excess was determined by HPLC using a Chirapack AD column [hexane/*i*PrOH = 90 : 10]; flow rate 1.0 mL min^{-1}; τ_{major} = 17.4 min, τ_{minor} = 24.5 min (92% *ee*). $[\alpha]_D^{20}$ −21.4 (*c* 1.0, $CHCl_3$). IR (KBr) 1685, 1515, 1342, 742, 704 cm^{-1}.

(5*R*, 6*R*)-6-(4-nitrophenyl)-5-propylcyclohex-2-enone (5c). The title compound was obtained as a single diastereomer according to the sequential procedure described above (78% yield). mp = 125–127. °C. ^{1}H NMR (300 MHz): δ 8.20 (d, *J* = 8.7 Hz, 2H), 7.25 (d, *J* = 8.7, 2H), 7.11–7.04 (m, 1H), 6.18 (dd, *J* = 10.1, 2.6 Hz, 1H), 3.46 (d, *J* = 10.1 Hz, 1H), 2.66 (dt, J_t = 4.7 Hz, J_d = 18.1 Hz, 1H), 2.42–2.33 (m, 1H), 2.32–2.20 (m 1H), 1.35 (m 1H), 1.14–1.30 (m 1H), 1.25 (t, *J* = 6.6 Hz, 1H), 1,14 (m 2H), 0.78 (t, *J* = 6.6 Hz, 3H). ^{13}C NMR (75 MHz) δ 198.3 (C), 149.4 (CH), 147.2 (C), 146.3 (C), 130.2 (2CH), 129.6 (CH), 123.7 (2CH), 60.1 (CH), 40.5 (CH_2), 36.0 (CH_2), 31.4 (CH),19.2 (CH_2), 13.9 (CH_3). MS (ESI) 282 (M+22, 929), *m/z* 260 (M+1, 100), 149 (92), 59 (19). HRMS (ESI) calcd. for $C_{15}H_{18}NO_3$ [M+1]: 260.1281; found: 260.1287. The enantiomeric excess was determined by HPLC using a Chiralpack AD column [hexane/*i*PrOH = 90 : 10]; flow rate 1.0 mL min^{-1}; τ_{major} = 13.9 min, τ_{minor} = 20.5 min (96% *ee*). $[\alpha]_D^{20}$ −37.6 (*c* 1.0, $CHCl_3$). IR (KBr) 1670, 1514, 860, 742, 705 cm^{-1}.

(5*S*, 6*R*)-5-isopropyl-6-(4-nitrophenyl)cyclohex-2-enone (5d). The title compound was obtained as a single diastereomer according to the sequential procedure described above (74% yield). mp = 106–108 °C. ^{1}H NMR (300 MHz): δ 8.21 (d, *J* = 8.8 Hz, 2H), 7.27 (d, *J* = 8.8, 2H), 7.16–7.09 (m, 1H), 6.16 (dd, *J* = 10.0, 2.6 Hz, 1H), 3.61 (d, *J* = 12.1 Hz, 1H), 2.54–2.29 (m, 3H), 1.39 (dsept, J_d = 2.4, J_{sept} = 6.8 Hz, 1H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.79 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (75 MHz) δ 198.8 (C), 149.9 (CH), 147.1 (C), 146.2 (C), 130.3 (2CH), 129.5 (CH), 123.8 (2CH), 58.1 (CH), 46.0 (CH), 27.8 (CH), 25.1 (CH_2), 20.7 (CH_3), 15.3 (CH_3). MS (EI) *m/z* 259 (M^+, 60), 243 (100). MS (EI) calcd. for $C_{15}H_{17}NO_3$ [M^+]: 259.1208; found: 259.1208. The enantiomeric excess was determined by HPLC using a Chiralpack AD column [hexane/*i*PrOH = 90 : 10]; flow rate 1.0 mL min^{-1}; τ_{major} = 15.8 min, τ_{minor} = 20.1 min (80% *ee*). $[\alpha]_D^{20}$ −37.6 (*c* 1.0, $CHCl_3$). IR (KBr) 1677, 1514, 1343, 842 cm^{-1}.

(5*R*, 6*R*)-5-butyl-6-(4-nitrophenyl)cyclohex-2-enone (5e). The title compound was obtained as a single diastereomer according to the sequential procedure described above (70% yield). mp = 130–133 °C. ^{1}H NMR (300 MHz): δ 8.14 (d, *J* = 8.6 Hz, 2H), 7.25 (d, *J* = 8.6, 2H), 7.08 (ddd, *J* = 10.0, 5.9, 2.6 Hz, 1H), 6.18 (d, *J* = 10.0 Hz, 1H), 3.47 (d, *J* = 12.0 Hz, 1H), 2. 67 (dt, J_t = 5.2 Hz, J_d = 18.4 Hz, 1H), 2.45–2.19 (m, 2H), 1.40–1.05 (m, 6H), 0.79 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (75 MHz) δ 198.8 (C), 149.9 (CH), 147.0 (C), 146.2 (C), 130.1 (2CH), 129.6 (CH), 123.7 (2CH), 60.1 (CH), 40.6 (CH), 33.4 (CH_2), 31.3 (CH_2), 28.1 (CH_2), 22.5 (CH_2), 13.8 (CH_3). MS (ESI) *m/z* 274 (M+1, 100), 149 (69). HRMS (ESI) calcd. for $C_{16}H_{19}NO_3$ [M+1]: 274.1437; found: 274.1440. The enantiomeric excess was determined by HPLC using a Chiralpack AD column [hexane/*i*PrOH = 90 : 10]; flow rate 1.0 mL min^{-1}; τ_{major} = 12.8 min, τ_{minor} = 19.2 min (92% *ee*). $[\alpha]_D^{20}$ −46.1 (*c* 1.0, $CHCl_3$). IR (KBr) 1669, 1517, 1347 cm^{-1}.

(5*R*, 6*R*)-5-((*Z*)-hex-3-enyl)-6-(4-nitrophenyl)cyclohex-2-enone (5f). The title compound was obtained as a single diastereomer according to the sequential procedure described above (56% yield). mp = 110–112 °C. ^{1}H NMR (300 MHz): δ 8.20 (d, *J* = 8.8 Hz, 2H), 7.26 (d, *J* = 8.8, 2H), 7.08 (ddd, *J* = 10.0, 5.8, 2.4 Hz, 1H), 6.18 (d, *J* = 10.0 Hz, 1H), 5.39–5.28 (m, 1H), 5.15–5.05 (m, 1H), 3.48 (d, *J* = 11.9 Hz, 1H), 2. 69 (dt, J_t = 4.6 Hz, J_d = 18.4 Hz, 1H), 2.50–2.35 (m, 1H), 2.28 (ddt, J_t = 2.4 Hz, J_d = 18.4, 10.0 Hz, 1H), 2.10–1.88 (m, 4H), 1.23 (q, *J* = 7.5 Hz, 2H), 0.79 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz) δ 198.1 (C), 149.2 (CH), 147.0 (C), 146.1 (C), 132.7 (CH), 130.1 (2CH), 129.6 (CH), 127.4 (CH), 123.7 (2CH), 60.1 (CH), 40.1 (CH), 33.7 (CH_2), 31.3 (CH_2), 23.6 (CH_2), 20.5 (CH_2), 14.2 (CH_3). MS (EI) *m/z* 299 (M^+, 5), 229 (46), 216 (27), 141 (26), 116(67), 115 (77), 68 (100). HRMS (EI) calcd. for $C_{18}H_{21}NO_3$ [M^+]: 299.1521; found: 299.1525. The enantiomeric excess was determined by HPLC using a Chiralpack AD column [hexane/*i*PrOH = 90 : 10]; flow rate 1.0 mL min^{-1}; τ_{major} = 11.2 min, τ_{minor} = 17.2 min (94% *ee*). $[\alpha]_D^{20}$ −23.3 (*c* 1.0, $CHCl_3$). IR (KBr) 1675, 1521, 1346 cm^{-1}.

(5*R*, 6*R*)-6-(4-nitrophenyl)-5-phenylcyclohex-2-enone (5g). The title compound was obtained as a single diastereomer according to the sequential procedure described above (69% yield). mp = 149–152 °C. ^{1}H NMR (300 MHz): δ 7.99 (d, J = 8.5 Hz, 2H), 7.11 (m, 8H), 6.27 (ddd, J = 10.1, 2.4, 1.4 Hz, 1H), 4.00 (d, J = 12.8 Hz, 1H), 3.63–3.53 (m, 1H), 2.90–2.70 (m, 2H). ^{13}C NMR (75 MHz) δ 197.4 (C), 149.0 (CH), 145.5 (2C), 141.0 (C), 130.4 (2CH), 129.8 (CH), 128.7 (2CH), 127.4 (2CH), 127.2 (CH), 123.4 (2CH), 59.9 (CH), 48.3 (CH), 34.9 (CH_2). MS (EI) 282 (M+), m/z 293 (M+, 6), 225 (100), 195 (23), 178 (46). HRMS (EI) calcd. for $C_{18}H_{15}NO_3$ [M+]: 293.1052; found: 293.1046. The enantiomeric excess was determined by HPLC using a Chiralpack IA column [hexane/*i*PrOH = 90 : 10]; flow rate 1.0 mL min^{-1}; τ_{major} = 28.2 min, τ_{minor} = 36.0 min (66% *ee*). $[\alpha]_D^{20}$ –45.6 (*c* 1.0, $CHCl_3$). IR (KBr) 1674, 1514, 1342, 860, 742, 705 cm^{-1}.

(5*R*, 6*R*)-5-(4-methoxyphenyl)-6-(4-nitrophenyl) cyclohex-2-enone (5h). The title compound was obtained as a single diastereomer using 30 mol% of $PhCO_2H$ as additive instead of LiOAc in the Michael addition (71% yield). mp = 196–198 °C. ^{1}H NMR (300 MHz): δ 8.87 (d, J = 8.8 Hz, 2H), 7.16–7.12 (m, 1H), 7.09 (d, J = 8.8 Hz, 2H), 6.96 (d, J = 8.6 Hz, 2H)), 6.70 (d, J = 8.6 Hz, 2H), 6.30–6.23 (m, 1H), 3.96 (d, J = 13.2 Hz, 1H), 3.59–3.48 (m, 1H), 2.81–2.73 (m, 2H). ^{13}C NMR (75 MHz) δ 197.6 (C), 158.5 (C), 149.1 (C), 145.7 (C), 133.0 (CH), 130.3 (2CH), 129.8 (CH),128.3 (2CH), 123.3 (2CH), 114.0 (2CH), 60.4 (CH_3), 55.2 (CH), 47.5 (CH), 35.1 (CH_2). MS (ESI) m/z 324 (M+1, 100), 282 (14), 149 (59), 121 (30). HRMS (ESI) calcd. for $C_{19}H_{18}NO_4$ [M+1]: 324.1229; found: 324.1230. The enantiomeric excess was determined by HPLC using a Chiralpack AD column [hexane/*i*PrOH = 80 : 20]; flow rate 1.0 mL min^{-1}; τ_{major} = 22.9 min, τ_{minor} = 28.5 min (75% *ee*). $[\alpha]_D^{20}$ –42.2 (*c* 1.0, $CHCl_3$). IR (KBr) 1675, 1517, 1349 cm^{-1}.

(5*R*, 6*R*)-5-(4-nitrophenyl)-6-(4-nitrophenyl) cyclohex-2-enone (5i). The title compound was obtained as a single diastereomer according to the sequential procedure described above without using any additive in the Michael addition step (75% yield). mp = 168–170 °C. ^{1}H NMR (300 MHz): δ 8.06 (d, J = 8.7 Hz, 2H), 8.04 (d, J = 8.7 Hz, 2H), 7.26 (d, J = 8.7 Hz, 2H), 7.15 (m,1H), 7.11 (d, J = 8.7 Hz, 2H), 6.32 (bd, J = 10.4 Hz, 1H), 4.03 (d, J = 13.4 Hz, 1H), 3.80–3.71 (m, 1H), 2.85–2.79 (m, 2H). ^{13}C NMR (75 MHz) δ 196.2 (C), 148.1 (C), 148.0 (CH), 147.0 (C), 146.9 (C), 144.4 (C), 130.2 (2CH), 130.0 (CH), 128.3 (2CH), 124.1 (2CH), 123.6 (2CH), 59.1 (CH), 47.9 (CH), 34.4 (CH_2). MS (EI) m/z 338 (M^+, 1), 270 (100), 165 (35), 68 (97). HRMS (EI) calcd. for $C_{18}H_{14}N_2O_5$ [M^+]: 338.0903; found: 338.0899. The enantiomeric excess was determined by HPLC using a Chiralcel OD column [hexane/*i*PrOH = 80 : 20]; flow rate 1.0 mL min^{-1}; τ_{major} = 47.0 min, τ_{minor} = 44.1 min (76% *ee*). $[\alpha]_D^{20}$ –40.8 (*c* 1.0, $CHCl_3$). IR (KBr) 1674, 1514, 1347 cm^{-1}.

(5*R*, 6*R*)-6-(4-aminophenyl)-5-methylcyclohex-2-enone (6a). To a solution of (5*R*,6*R*)-6-(4-nitrophenyl)-5-methylcyclohex-2-enone **5a** (0.20 mmol, 40 mg) in CH_2Cl_2 (2 mL) was added sequentially Zn dust (2.80 mmol, 177 mg) and AcOH (5.6 mmol, 340 µL) at 0 °C. After stirring at room temperature for 10 min, the reaction mixture was filtered through Celite. The filtrate was neutralized with a saturated solution of $NaHCO_3$, the aqueous layer was extracted with ethyl acetate (3 × 5 mL) and the combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was evaporated to give the pure product in 97% yield. mp = 131–134 °C. ^{1}H NMR (300 MHz): δ 6.96 (ddd, J = 2.6, 5.4, 10.1 Hz, 1H), 6.85 (d, J = 8.4 Hz, 2H), 6.64 (d, J = 8.4 Hz, 2H), 6.13 (ddd, J = 10.0, 2.7, 1.1 Hz, 1H), 3.6 (bs, 2H, NH_2), 3.10 (d, J = 11.6 Hz, 1H), 2.51 (dt, J_t = 5.4 Hz, J_d = 18.3 Hz, 1H), 2.43–2.27 (m, 1H), 2.30 (ddt, J_t = 2.6 Hz, J_d = 18.3, 9.8 Hz, 1H), 0.86 (d, J = 6.5 Hz, 3H). ^{13}C NMR (75 MHz) δ 200.3 (C), 148.6 (CH), 145.3 (C), 130.1 (CH), 129.8 (2CH), 128.3 (C), 115.3 (2CH), 60.9 (CH), 36.5 (CH), 34.4 (CH_2), 20.3 (CH_3). MS (EI) m/z 201, 133 (100), 132 (23). HRMS (EI) calcd. for $C_{13}H_{15}NO$ [M^+]: 201.1154; found: 201.1151. IR (KBr) 3450, 3400, 2953, 2923, 1671, 1519, 1283, 1154 cm^{-1}.

(5*R*, 6*R*)-6-(4-iodophenyl)-5-methylcyclohex-2-enone (7a). To a solution of **6a** (0.2 mmol, 26 mg) in HCl 6 N (0.3 mL) cooled to 0 °C, a solution of $NaNO_2$ (1 equiv, 13.8 mg) in water (1 mL) was added dropwise. The resulting solution was added dropwise to a solution of KI (4 equiv, 133 mg) in water (1.5 mL), keeping the bath temperature at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred overnight, then extracted with ethyl acetate. The combined organic layers were washed in sequence with 10% $Na_2S_2O_3$ and brine, then dried over $MgSO_4$ and concentrated under vacuum to give **7a** with 75% yield. ^{1}H NMR (300 MHz): δ 7.66 (d, J = 8.5 Hz, 2H), 7.01 (ddd, J = 2.5, 5.9, 10.0 Hz, 1H), 6.83 (d, J = 8.5, 2H), 6.15 (ddd, J = 0.9, 2.6, 10.0 Hz, 1H), 3.17 (d, J = 11.9 Hz, 1H), 2.55 (dt, J_t = 5.7 Hz, J_d = 18.4 Hz, 1H), 2.46–2.33 (m, 1H), 2.24 (ddt, J_t = 2.5 Hz, J_d = 10.0, 18.4 Hz, 1H), 0.86 (d, J = 6.4 Hz, 3H). ^{13}C NMR (75 MHz) δ 199.0 (C), 149.1 (CH), 138.0 (C), 137.6 (2CH), 131.2 (2CH), 129.9 (CH), 92.5 (C), 61.34 (CH), 36.3 (CH_2), 34.6 (CH), 20.3 (CH_3). MS (EI) m/z 312 (M^+, 60), 243 (100), 117 (20), 115 (27). MS (EI) calcd. for $C_{13}H_{13}IO$ [M^+]: 312.0011; found: 312.0013. $[\alpha]_D^{20}$ –14.1 (*c* 0.3, $CHCl_3$). IR (KBr) 1674, 1386, 1262, 1098, 802, 549 cm^{-1}.

(1*S*, 5*R*, 6*R*)-5-methyl-6-(4-nitrophenyl) cyclohex-2-enol (8a). To a solution of enone **5a** (50 mg, 0.21 mmol) and $CeCl_3 \cdot 7H_2O$ (117 mg, 0.31 mmol) in MeOH (5 mL) at –78 °C $NaBH_4$ (16 mg, 0.42 mmol) was added in one portion. The resulting mixture was stirred for 1 h at –78 °C and slowly warmed up to room temperature during 4 h. The reaction was quenched by addition of 1 mL of acetone and then 1 mL of H_2O. The solvent was evaporated and the residue partitioned between Et_2O (10 mL) and H_2O (5 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (6 : 1 *n*-hexane: EtOAc) gave **8a** as a white solid (68% yield). mp: 108–110 °C. ^{1}H NMR (300 MHz): δ 8.20 (d, J = 8.6 Hz, 2H), 7.38 (d, J = 8.6, 2H), 5.89–5.82 (m, 1H), 5.75 (d, J = 10.1 Hz, 1H), 4.42–4.30 (m, 1H), 2.46 (dd, J = 11.4, 11.6 Hz, 1H), 2.28 (dt, J_t = 2.5 Hz, J_d = 17.9 Hz, 1H), 2.14–2.01 (m, 1H), 1.98–1.84 (m, 1H), 1.44 (d, J = 5.6 Hz, OH), 0.69 (d, J = 6.5 Hz, 3H). ^{13}C NMR (75 MHz) δ 150.6 (C), 146.9 (C), 130.0 (CH), 129.2 (2CH), 128.7 (CH), 123.8 (2CH), 73.3 (CH), 57.1 (CH), 34.6 (CH_2), 32.8 (CH), 19.6 (CH_3). MS (ESI) m/z 256 (M+Na^+, 100), 216 (83), 149 (81). MS (ESI) calcd. for $C_{13}H_{15}NO_3Na$ [M+Na]$^+$: 256.0944; found: 256.0945. $[\alpha]_D^{20}$ –4.1 (*c* 0.3, $CHCl_3$). IR (KBr) 3512, 1530, 1348, 751, 700 cm^{-1}. Representative ^{1}H NMR data of **8a′**: δ 8.19 (d, J =

8.6 Hz, 2H), 7.46 (d, J = 8.6, 2H), 4.08 (m, 1H), 2.69 (dd, J = 11.6, 3.4 Hz, 1H, H_6), 0.79 (d, J = 6.3 Hz, 3H). For more information see supporting information.

(2*R*, 3*R*, 5*R*, 6*R*)-2,3-dihydroxy-5-methyl-6-(4-nitrophenyl)-cyclohexanone (9a). A 5 mL round-bottomed flask was charged with 40 mg of α,β-unsaturated ketone **5a** (1 equiv., 0.158 mmol) and dissolved in 800 μL of *t*-BuOH. Then, 300 mg of AD-mix-α, 40 mg of $NaHCO_3$ (3 equiv, 0.474 mmol), 15 mg of methylsulfonamide (1 equiv., 0.158 mmol), 10 mg of $K_2OsO_2(OH)_2$ (0.16 equiv, 0.027 mmol) and 800 μL of H_2O were subsequently added and the mixture was vigorously stirred at room temperature for 4 days. Whereupon the mixture was transferred to a 25 mL Erlenmeyer flask, diluted with 10 mL of EtOAc and stirred for 1 h with 10 mL of a 40% solution of $NaHSO_3$. The aqueous layer was extracted with EtOAc (15 mL × 4), the combined organic layers were sequentially washed with a 10% solution of NaOH and brine, dried over $MgSO_4$ and the solvent evaporated under vacuum. The crude was purified by flash chromatography (2 : 1 to 1 : 1 *n*-hexane : EtOAc) to afford 23 mg of diastereomerically pure **9a** (50% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.23 (d, J = 8.6 Hz, 2H), 7.28 (d, J = 8.6 Hz, 2H), 4.47 (dd, J = 5.5, 3.5 Hz, 1H), 4.34 (bs, 1H), 3.80 (d, J = 2.0 Hz, OH), 3.38 (d, J = 11.8 Hz), 2.67 (bs, OH), 2.65 (m, 1H), 2.31 (dt, J_d = 14.7 Hz, J_t = 3.8 Hz, 1H), 1.84 (t, J = 14.3 Hz, 1H), 0.86 (d, J = 6.5 Hz, 3H). ^{13}C NMR (75 MHz) (benzene-d_6): δ 206.8(C), 147.6 (C), 143.3 (C), 130.4 (2CH), 123.5 (2CH), 77.1 (CH), 71.8 (CH), 61.6 (CH), 36.8 (CH_2), 34.7 (CH), 19.9 (CH_3). MS (ESI) m/z 248 ($M+1^+$, 75), 149 (81), 74 (61). MS (ESI) calcd. for $C_{13}H_{14}NO_4$ $[M+1]^+$: 248.0917; found: 248.0925. $[\alpha]_D^{20}$ +32.1 (*c* 1.0, $CHCl_3$).

(1*R*, 3*R*, 4*R*, 6*R*)-4-methyl-3-(4-nitrophenyl)-7-oxabicyclo-[4.1.0]heptan-2-one (10a). To a solution of **5a** (50 mg, 0.21 mmol, 1 equiv.) in THF (1 mL) at −78 °C, a solution of *tert*-butylhydroperoxide (TBPH) (5–6 M in decane, 3 equiv) and 4 drops of benzyl trimethylammonium hydroxide (Triton B) (40% in MeOH) were sequentially added. The mixture was stirred at room temperature overnight and then treated with saturated aqueous solution of Na_2SO_3 and extracted with EtOAc. The residue was purified by flash chromatography (*n*-hexane/EtOAc 5 : 1), to give **10a** as colourless oil (48% yield). ^{1}H NMR (500 MHz)(benzene-d_6): δ 7.77 (d, J = 8.8 Hz, 2H), 6.69 (d, J = 8.8, 2H), 3.00 (d, J = 4.0 Hz, 1H), 2.82 (t, J = 3.8 Hz, 1H), 2.15 (d,J = 11.8 Hz, 1H), 2.02–1.92 (m, 1H), 1.66 (dt, J_t = 3.8 Hz, J_d = 15.0 Hz, 1H), 0.87 (dd, J = 15.0, 12.0 Hz, 1H), 0.26 (d, J = 6.5 Hz, 3H). ^{13}C NMR (75 MHz) δ 204.1 (CO), 147.2 (C), 146.1 (C), 130.1 (2CH), 123.9 (2CH), 61.6 (CH), 54.6 (CH), 54.4 (CH), 31.5 (CH_2), 28.7 (CH), 19.5 (CH_3). MS (ESI) m/z 266 ($M+1^+$, 16), 139 (43), 74 (100). MS (ESI) calcd. for $C_{13}H_{15}NO_5Na$ $[M+Na]^+$: 288.0842; found: 288.0837. $[\alpha]_D^{20}$ −9.1 (*c* 0.7, $CHCl_3$).

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