Activation of 1,2- and 1,3-Ketoamides with Thiourea Organocatalyst for the Enantioselective Domino Synthesis of Functionalized Cyclohexanes

Wilfried Raimondi, Maria del Mar Sanchez Duque, Sébastien Goudedranche, Adrien Quintard, Thierry Constantieux, Xavier Bugaut,* Damien Bonne,* Jean Rodriguez

Aix Marseille Université, CNRS, iSm2 UMR 7313, 13397 Marseille, France
Fax +33(491)289187; E-mail: damien.bonne@univ-amu.fr; E-mail: xavier.bugaut@univ-amu.fr

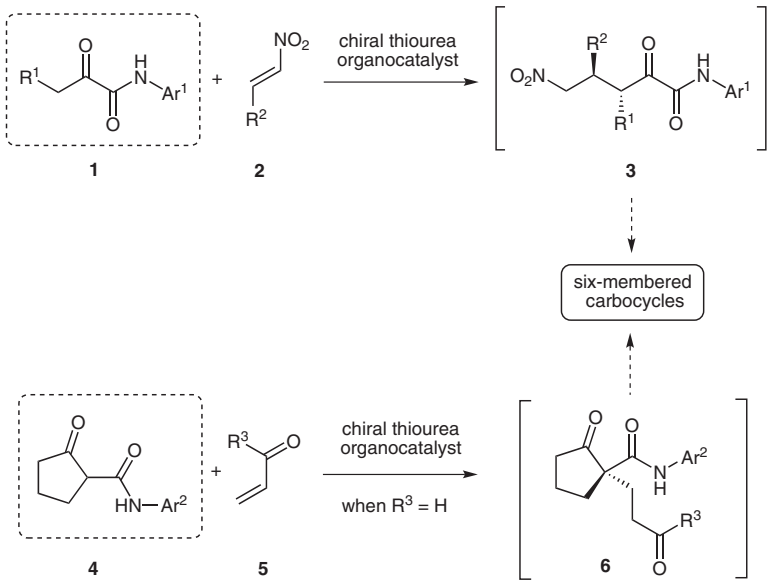
Received: 28.02.2013; Accepted after revision: 03.05.2013

Abstract: Several reactive sites of 1,2- and 1,3-ketoamides were successively exploited in two complementary domino transformations for the synthesis of polysubstituted monocyclic or bridged bicyclic cyclohexanes, with the creation of up to six stereogenic centers. In both cases, a chiral bifunctional thiourea organocatalyst allowed efficient control of chirality in the final carbocycle.

Key words: domino reactions, ketones, amides, cyclizations, cycloalkanes, stereoselectivity, catalysis, thioureas

The development of domino enantioselective organocatalytic methodologies has received intense attention from researchers, as demonstrated by the large number of recent reports on stereoselective constructions of heterocyclic and carbocyclic scaffolds.[1] Among these scaffolds, substituted chiral cyclohexanes are important building blocks for organic synthesis,[2] and many of the reported approaches permit control of the relative and absolute configurations of these versatile molecular architectures.[3,4] These methods have the advantage of permitting efficient assembly of the desired target from easily accessible starting materials, as well as the creation of multiple stereogenic carbon atoms with controlled stereochemistries. Most of these strategies employ simple substrates with multiple reactive sites that are involved in successive formation of several carbon–carbon and/or carbon–heteroatom bonds. In this context, dicarbonyl compounds and, especially, ketoamides are attractive substrates because of their high density of potential reactive sites; these substrates are therefore well suited for use in designing new stereoselective domino transformations for asymmetric syntheses of functionalized six-membered carbocycles.[5]

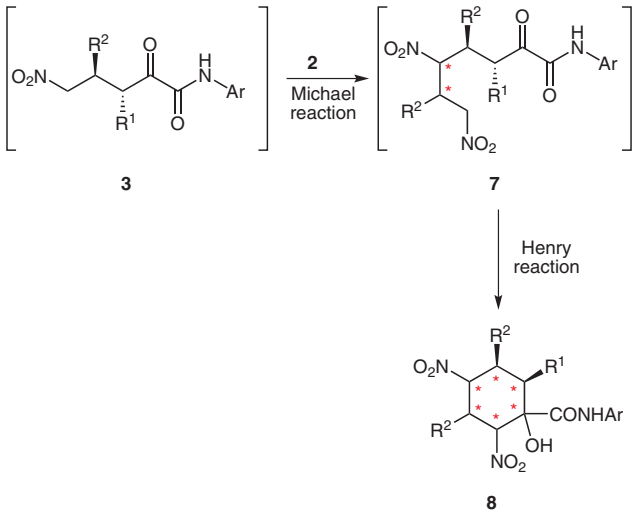
We recently showed that the 1,2- and 1,3-ketoamides **1** and **4**, respectively, can be specifically activated by using a thiourea–tertiary amine bifunctional organocatalyst, and we successfully developed enantioselective Michael additions of these substrates with either nitroalkenes **2** or α,β-unsaturated carbonyl compounds **5** as the electrophilic partners (Scheme 1).[6] We wished to exploit this work by using the Michael adducts **3** and **6** as versatile synthetic platforms for subsequent transformations into more complex molecular frameworks, such as substituted cyclohexanes.



Scheme 1 Access to optically active six-membered carbocycles from 1,2-ketoamides **1** and 1,3-ketoamides **4**

SYNTHESIS 2013, 45, 1659–1666
Advanced online publication: 03.06.2013
DOI: 10.1055/s-0033-1338844; Art ID: SS-2013-C0168-ST

In the case of 1,2-ketoamides **1**, we reasoned that once the Michael adduct **3** is formed (Scheme 2), addition of a second equivalent of a nitroalkene should trigger another conjugate addition leading to intermediate **7**. This should then undergo an intramolecular Henry reaction, completing the domino transformation and affording the desired hexasubstituted cyclohexane **8**.[7]

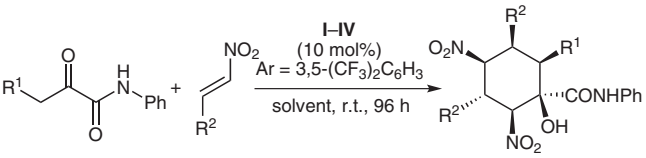


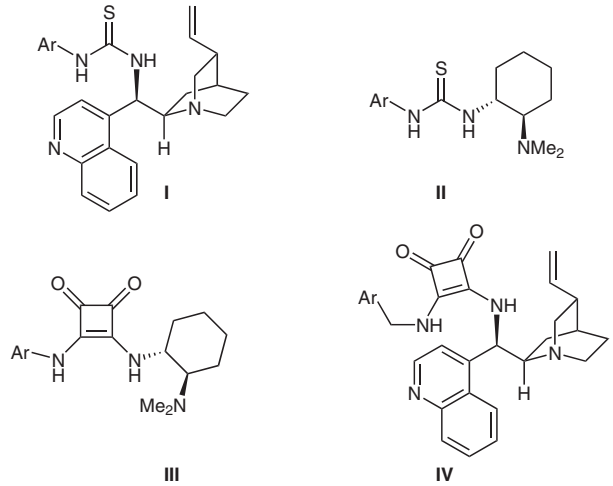
Scheme 2 Strategy for the synthesis of hexasubstituted cyclohexanes **8**

We began our investigations by screening various bifunctional organocatalysts **I**–**IV** bearing either thiourea or squaramide hydrogen-bond donor subunits (Table 1). Catalyst **I**,[8] derived from cinchonine, produced only traces of **8a**, the sequence stopping at the Michael adduct stage (entry 1). However, we were very pleased to find that Takemoto's catalyst **II**[9] was efficient in this domino transformation, affording **8a** in good yield (67%) and very good diastereomeric and enantiomeric ratios (>20:1 and 28:1 respectively) (entry 2). Remarkably, one of the sixty-four possible stereoisomers was obtained predominantly. The use of catalysts **III** and **IV** with squaramide subunits gave poor results (entries 3 and 4),[10] and only traces of cyclohexane **8a** were formed (<5%). The highest yield and stereoselectivity were achieved by using ethyl acetate as solvent (entry 2); switching to dichloromethane led to a lower yields and poorer selectivity of the desired product (entry 5). Other solvents such as dimethyl sulfoxide or methyl *tert*-butyl ether were not suitable, causing decomposition and poor reactivity, respectively (entries 6 and 7).

Having optimized the reaction conditions, we studied the possibility of using a range of ketoamides **1** and nitroalkenes **2** to synthesize various hexasubstituted cyclohexane derivatives **8a**–**e** (Scheme 3). By using Takemoto's catalyst **II** in ethyl acetate at room temperature for four days, we were delighted to obtain cyclohexanes **8** in fair yields and, more importantly, generally very good stereoselectivities. Electron-withdrawing as well as electron-donating groups on the aryl substituent of the ketoamide **1** were well tolerated in this reaction, although

Table 1 Optimization of the Domino Michael–Michael–Henry Reaction





Entry[a]	Catalyst	Solvent	Yield[b] (%) of **8a**	dr[c]	er[d]
1	**I**	EtOAc	<5	n.d.[e]	n.d.
2	**II**	EtOAc	62	>20:1	28:1
3	**III**	EtOAc	<5	n.d.	n.d.
4	**IV**	EtOAc	<5	n.d.	n.d.
5	**II**	CH_2Cl_2	45	1:1.5	n.d.
6	**II**	DMSO	–[f]	–	–
7	**II**	MTBE	<5%	n.d.	n.d.

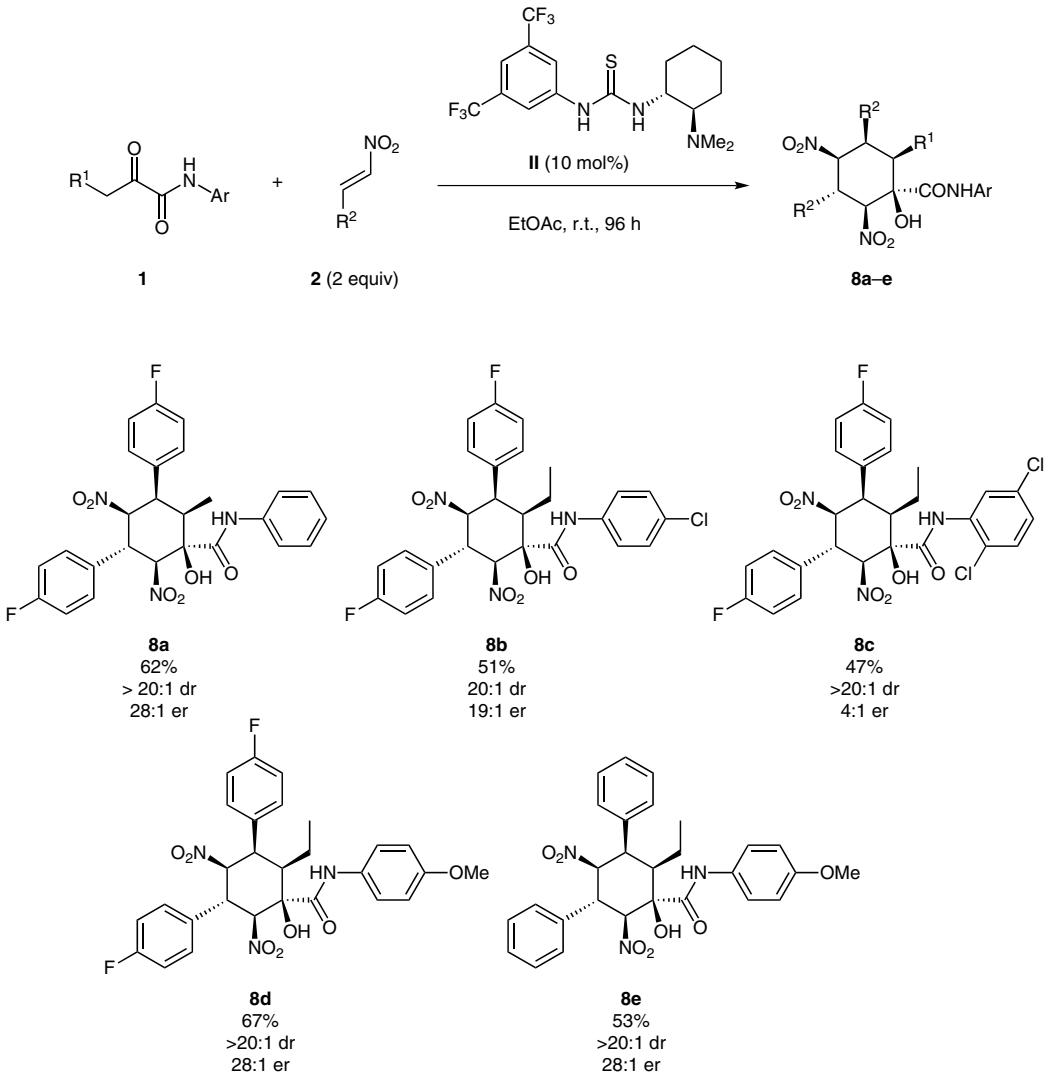
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.42 mmol), solvent (0.4 mL).
[b] Yield of analytically pure isolated product.
[c] Diastereomeric ratios were determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixtures.
[d] Enantiomeric ratios were determined by HPLC analysis on a chiral stationary phase.
[e] n.d. = not determined.
[f] Decomposed.

the use of ketoamide **1c** (R^1 = Et; Ar = 2,5-$Cl_2C_6H_3$), bearing the sterically demanding 2,5-dichlorophenyl substituent, had a negative effect on the enantioselectivity of the domino reaction (**8c**; er = 4:1). With regard to the nitroalkene partner **2**, both phenyl- and (4-fluorophenyl)nitroalkenes are found to be suitable substrates for this reaction.

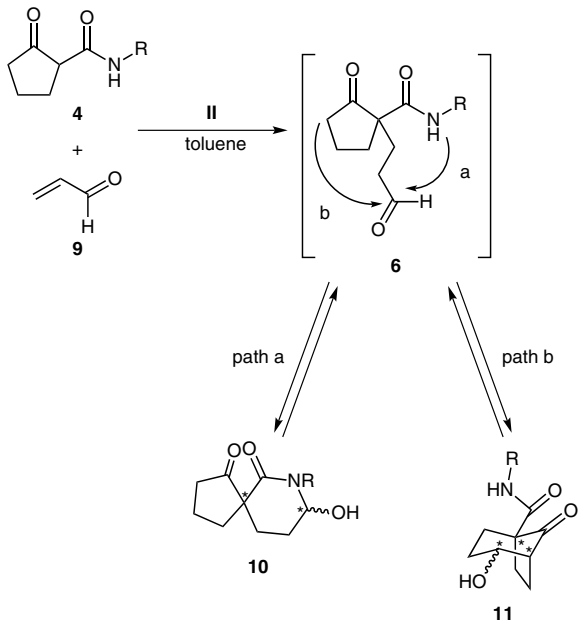
In our earlier studies, we found that Takemoto's catalyst **II** is also an efficient promoter of the enantioselective Michael addition of 1,3-ketoamides **4** to α,β-unsaturated

carbonyl compounds.[6b] If acrolein (**9**) is used as the electrophilic reaction partner, two modes of cyclization can be envisaged for the initial adducts **6** (Scheme 4). The first involves the formation of hemiaminal **10**, which we have already exploited (path a). The second might involve an intramolecular aldol reaction, leading directly to the corresponding bicyclo[3.2.1]octane **11**, which contains a bridged six-membered ring with three stereogenic centers (path b). Given the prevalence of this skeleton in natural products and the challenges associated with its synthesis,[11] new modular enantioselective techniques for accessing this skeleton are of great interest.

In our initial study with an *N*-tosyl ketoamide, the hemiaminal was obtained as the sole product.[6b] However, when we extended this reaction to the *N*-aryl ketoamide **4a**, a spontaneous evolution towards a mixture of the two products **10a** and **11a** occurred (Table 2), indicating that an equilibrium exists between the kinetically favored product **10a** and the thermodynamically favored product **11a**. When the reaction was performed at –20 °C in the presence of catalyst **II** for 48 hours, products **10a** and **11a**, with the hydroxyl group in the axial position, were obtained in a 3.5:1 ratio (entry 1). In attempts to favor the formation of the bicyclic product, we examined the effects of various reaction conditions after the completion of the Michael addition. At room temperature, without the addition of any other reagent, a slow evolution toward a 1.5:1 ratio of **10a** and **11a** occurred after stirring for an additional two days (entry 2). We were able to verify that Takemoto's catalyst **II** is involved in this process, as no interconversion between the products occurred in its absence. As expected, increasing the temperature to 60 °C led to the formation of **11a** as the major product with a 12:1 dr and a 4.7:1 er (entry 3). We then searched for additives that might affect the thermodynamic interconversion of **10a** into **11a**. Whereas the addition of a catalytic amount of L-proline (**V**) had a limited effect (entry 4), the presence of a stoichiometric amount of the N-heterocyclic carbene **VI** (entry 5)[12] or 1,8-diazabicyclo[5.4.0]undec-7-ene (**VII**; DBU) (entry 6) completely shifted the equilibrium towards the desired product **11a**, albeit with very modest diastereoselectivities; in the latter case, the er of the major diastereomer was 4.1:1.



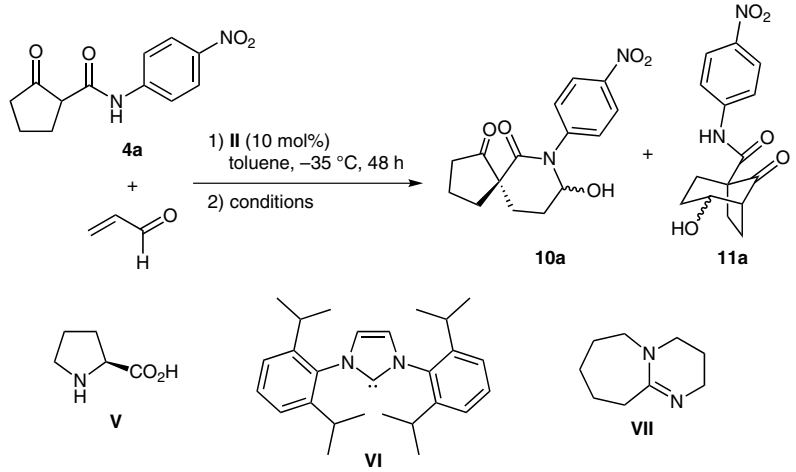
Scheme 3 Scope of the Michael–Michael–Henry reaction leading to cyclohexanes **8**



Scheme 4 Divergent pathways for the cyclization of the adducts of 1,3-ketoamides with acrolein

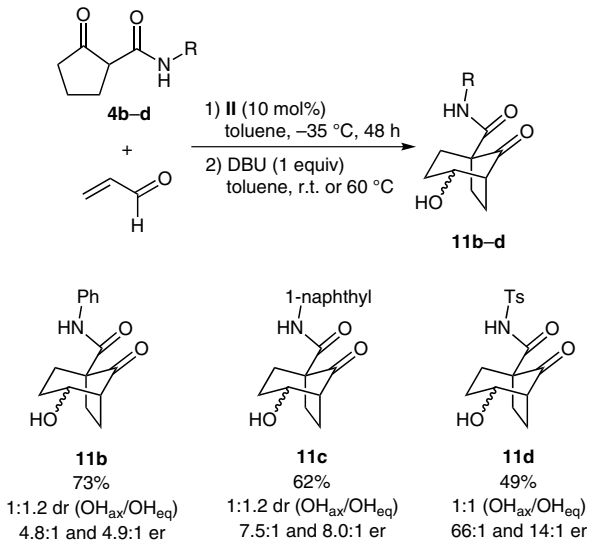
1,8-Diazabicyclo[5.4.0]undec-7-ene was selected as the best promoter of the isomerization, because it allowed an efficient reaction with a short reaction time. We then investigated the behavior of several other 1,3-ketoamides[13] under these reaction conditions (Scheme 5). With the *N*-aryl 1,3-ketoamides **4b** and **4c**, we found that evaporation of the excess acrolein was required before addition of 1,8-diazabicyclo[5.4.0]undec-7-ene to prevent a double Michael addition. Products **11b** and **11c** were obtained in reasonable yields, but moderate stereoselectivities. Interestingly, the *N*-tosyl 1,3-ketoamide **4d** could also be converted into the bicyclic product **11d**. Because of the higher stability of the hemiaminal in this case, the isomerization with 1,8-diazabicyclo[5.4.0]undec-7-ene had to be conducted at 60 °C. Once again, the reaction showed no diastereoselectivity, but both diastereoisomers were obtained with high enantioselectivities (66:1 and 14:1 er, respectively). The differences in the enantiomeric ratios observed between the various cyclization modes[14] clearly indicate that these compounds are prone to racemization. As a result, particular care must be taken to avoid this problem during the cyclization reaction or any later functionalization reactions.

Table 2 Optimization of the Reaction Conditions for the Synthesis of Bicyclo[3.2.1]octane **11a**



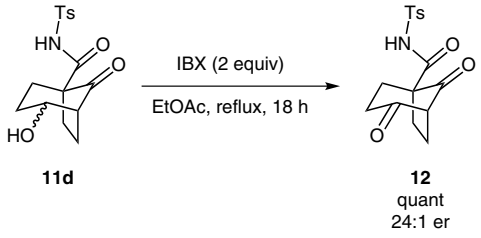
Entry[a]	Post-Michael reaction conditions	**10a**/**11a**[b]	dr (OH_{ax}/OH_{eq})[b]	er[c]
1	–[d]	3.5:1	>20:1	n.d.[e]
2	r.t., 2 d	1.5:1	>20:1	n.d.
3	60 °C, 2 d	1:9.3	12:1	4.7:1
4	**V** (20 mol%), r.t., 2 d	1:1.1	>20:1	n.d.
5	**VI** (1.1 equiv), r.t., 3 d	<1:20	1:2	n.d.
6	**VII** (1 equiv), r.t., 10 min	<1:20[f]	1.4:1	4.1:1 and 3.7:1

[a] Reaction conditions for Michael addition: **4a** (0.2 mmol), **9** (0.4 mmol), solvent (0.4 mL), –35 °C, 48 h.
[b] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.
[c] The er for the major diastereomer of **11a** (OH in axial position) was determined by HPLC analysis on a chiral stationary phase.
[d] Analyses were conducted directly at the end of the Michael addition step.
[e] n.d. = not determined.
[f] 82% yield after purification.



Scheme 5 Study of the scope of substrates for the formation of bicyclo[3.2.1]octanes **11**

Bicyclic alcohol **11d** could also be derivatized by oxidation with 2-iodoxybenzoic acid in refluxing ethyl acetate to give the bicyclo[3.2.1]octanedione **12** quantitatively (Scheme 6). Most importantly, an excellent 24:1 er was observed for the formation of this valuable structure.



Scheme 6 Oxidation of the bicyclic alcohol **11d** with 2-iodoxybenzoic acid (IBX)

In summary, we have demonstrated that 1,2- and 1,3-ketoamides can be specifically activated with thiourea organocatalysts and used in domino transformations for the enantioselective synthesis of polysubstituted cyclohexanes. In the case of 1,2-ketoamides, we exploited their pronucleophilic character[15] and the presence of the ketone moiety as an electrophilic site to permit the synthesis of hexasubstituted cyclohexanes by reaction with nitroalkenes. Amazingly, one of the 64 possible stereoisomers was formed almost exclusively. Alternatively, 1,3-ketoamides where used as efficient C-bisnucleophiles with acrolein as the electrophilic partner to give bicyclo[3.2.1]octanes in optically active forms with formation of two new carbon–carbon bonds and three stereogenic carbon atoms. Further studies are currently under way in our laboratory in attempts to extend the scope of these promising cascade reactions.

All reagents were obtained from commercial sources and used as supplied unless otherwise stated. NMR data were recorded on a Bruker Avance 400 spectrometer in $CDCl_3$, and chemical shifts (δ) are given in ppm relative to the residual nondeuterated solvent signal for ^{1}H NMR ($CHCl_3$, 7.26 ppm) or the deuterated solvent signal for ^{13}C NMR ($CDCl_3$, 77.16 ppm). High-resolution mass spectra were obtained from the Spectropole (http://www.spectropole.u-3mrs.fr/). Optical rotations were measured with a Perkin-Elmer 241 micropolarimeter. Melting points were determined with a Büchi B-450 apparatus and are uncorrected. TLC was performed on silica Merck $60F_{254}$ plates; visualization was performed by illumination with a UVP mineralight UVGL-58 lamp or by developing the plates with phosphomolybdic acid and 4-methoxybenzaldehyde reagents. The products were purified by flash column chromatography on silica gel 60 (Merck 1.09386.9025, 230–400 mesh).

Cyclohexanes 8; General Procedure

1,2-Ketoamide **1** (1.00 equiv), nitroalkene **2** (2.10 equiv), and thiourea catalyst **II** (0.10 equiv) were added successively as solids to a sealed tube and dissolved in EtOAc to form a 0.5 M soln. After 96 h at r.t., the solvent was evaporated and the crude product was purified by flash chromatography [silica gel, EtOAc–PE (30:70 then 50:50)]. The dr of the products was determined by ^{1}H NMR spectroscopy of the crude product and the er was determined by HPLC on a chiral stationary phase.

(1*R*,2*R*,3*R*,4*S*,5*R*,6*S*)-3,5-Bis(4-fluorophenyl)-1-hydroxy-2-methyl-4,6-dinitro-*N*-phenylcyclohexanecarboxamide (8a)

Synthesized according to the general procedure from **1a** (R^1 = Me; Ar = Ph; 36 mg, 0.2 mmol) and **2a** (R^2 = 4-FC_6H_4; 70 mg, 0.42 mmol) as a white solid; yield: 63 mg (62%); mp 181–182 °C; $[\alpha]_D^{30}$ –22.3 (*c* = 1.0, CH_2Cl_2); R_f = 0.30 (EtOAc–PE, 3:7).

Chiral HPLC: ChiralPak AD-H [hexane–*i*-PrOH (9:1), flow rate = 1.0 mL/min], λ = 306 nm; t_{minor} = 24.7 min, t_{major} = 28.0 min, er = 99:1.

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 8.65 (br s, 1 H, NH), 7.62 (br s, 2 H), 7.52 (d, *J* = 8.0 Hz, 2 H), 7.42–7.36 (m, 4 H), 7.20 (d, *J* = 8.0 Hz, 1 H), 7.08 (d, *J* = 8.0 Hz, 2 H), 7.02 (d, *J* = 8.0 Hz, 2 H, ArH), 5.76 (d, *J* = 12.0 Hz, 1 H), 5.60 (dd, *J* = 12.0, 7.2 Hz, 1 H), 4.61 (dd, *J* = 12.0, 12.0 Hz, 1 H), 4.61 (s, 1 H, OH), 4.00 (dd, *J* = 7.2, 7.2 Hz, 1 H), 3.05–2.99 (m, 1 H), 0.98 (d, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, CD_2Cl_2): δ = 169.1, 163.4 (d, *J* = 248 Hz), 163.3 (d, *J* = 248 Hz), 138.8 (d, *J* = 8 Hz, 2 C), 136.7 (2 C), 130.5 (d, *J* = 8 Hz, 2 C), 129.9 (d, *J* = 4 Hz), 129.7, 129.5 (d, *J* = 4 Hz), 126.1, 120.7 (2 C), 116.8 (d, *J* = 17 Hz, 2 C), 115.7 (d, *J* = 17 Hz, 2 C), 92.0, 89.3, 80.1, 49.7, 42.2, 39.3, 14.0.

HRMS (ES+): *m/z* calcd for $C_{26}H_{24}F_2N_3O_6$: 512.1628; found: 512.1619.

(1*R*,2*R*,3*R*,4*S*,5*R*,6*S*)-*N*-(4-Chlorophenyl)-2-ethyl-3,5-bis(4-fluorophenyl)-1-hydroxy-4,6-dinitrocyclohexanecarboxamide (8b)

Synthesized according to the general procedure from **1b** (R^1 = Et, Ar = 4-ClC_6H_4; 45 mg, 0.2 mmol) and **2a** (R^2 = 4-FC_6H_4; 70 mg, 0.42 mmol) as a white solid; yield: 57 mg (51%); mp 248 °C (dec.); R_f = 0.30 (EtOAc–PE, 1:4).

Chiral HPLC: ChiralPak IA [hexane–EtOH–$CHCl_3$ (5:3:2), flow rate = 1.0 mL/min], λ = 254 nm; t_{minor} = 4.0 min, t_{major} = 5.8 min, er = 19:1.

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 8.68 (br s, 1 H, NH), 7.70 (br s, 2 H), 7.50 (d, *J* = 8.9 Hz, 2 H), 7.37–7.31 (m, 4 H), 7.08 (d, *J* = 8.9 Hz, 2 H), 7.03 (d, *J* = 8.9 Hz, 2 H), 5.61 (d, *J* = 12.5 Hz, 1 H), 5.43 (dd, *J* = 12.5, 6.9 Hz, 1 H), 4.65 (s, 1 H, OH), 4.45 (dd, *J* = 12.5, 12.5 Hz, 1 H), 4.16 (dd, *J* = 6.9, 6.9 Hz, 1 H), 2.75–2.70 (m, 1 H), 1.44–1.33 (m, 2 H), 0.87 (d, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, CD_2Cl_2): δ = 169.3, 163.2 (d, *J* = 248 Hz), 163.1 (d, *J* = 248 Hz), 135.3, 133.8 (d, *J* = 8 Hz, 2 C), 130.9, 130.4 (d, *J* = 8 Hz, 2 C), 129.7 (d, *J* = 4 Hz), 129.6 (2 C), 129.0 (d, *J* = 4 Hz), 121.9 (2 C), 116.7 (d, *J* = 22 Hz, 2 C), 115.8 (d, *J* = 22 Hz, 2 C), 92.1, 89.8, 80.2, 46.7, 46.1, 41.6, 20.8, 12.0.

MS (ES+): *m/z* 582 $[M + Na]^+$.

HRMS (ES+): *m/z* calcd for $C_{27}H_{25}ClF_2N_3O_6$: 560.1394; found: 560.1395.

(1*R*,2*R*,3*R*,4*S*,5*R*,6*S*)-*N*-(2,5-Dichlorophenyl)-2-ethyl-3,5-bis(4-fluorophenyl)-1-hydroxy-4,6-dinitrocyclohexanecarboxamide (8c)

Synthesized according to the general procedure from **1c** (R^1 = Et, Ar = 2,5-$Cl_2C_6H_3$; 52 mg, 0.2 mmol) and **2a** (R^2 = 4-FC_6H_4, 70 mg, 0.42 mmol) as a white solid; yield: 57 mg (47%); mp 203–205 °C; $[\alpha]_D^{22}$ –12.9 (*c* = 0.52, CH_2Cl_2); R_f = 0.41 (EtOAc–PE, 1:4).

Chiral HPLC: ChiralPak IA [hexane–EtOH–$CHCl_3$ (3:1:1), flow rate = 1.0 mL/min], λ = 254 nm; t_{minor} = 4.1 min, t_{major} = 5.8 min, er = 4:1.

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 9.21 (br s, 1 H, NH), 8.35 (br s, 1 H), 7.72–7.69 (m, 2 H), 7.38–7.34 (m, 4 H), 7.14–7.04 (m, 4 H), 5.56 (d, *J* = 12.5 Hz, 1 H), 5.39 (dd, *J* = 12.5, 6.8 Hz, 1 H), 4.72 (s, 1 H, OH), 4.46 (dd, *J* = 12.5, 12.5 Hz, 1 H), 4.17 (dd, *J* = 6.8, 6.8 Hz, 1 H), 2.72–2.67 (m, 1 H), 1.55–1.37 (m, 2 H), 0.88 (d, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, CD_2Cl_2): δ = 169.5, 163.3 (d, *J* = 248 Hz), 163.2 (d, *J* = 248 Hz), 134.4, 133.8 (d, *J* = 8 Hz, 2 C), 130.5 (2 C), 130.4 (d, *J* = 8 Hz), 129.6 (d, *J* = 4 Hz), 128.9 (d, *J* = 4 Hz), 126.4, 122.6, 121.8, 116.7 (d, *J* = 22 Hz, 2 C), 115.9 (d, *J* = 22 Hz, 2 C), 92.1, 89.8, 80.5, 46.7, 46.2, 41.6, 20.7, 12.0.

MS (ES+): *m/z* 616 $[M + Na]^+$.

HRMS (ES+): *m/z* calcd for $C_{27}H_{24}Cl_2F_2N_3O_6$: 594.1005; found: 594.1003.

(1*R*,2*R*,3*R*,4*S*,5*R*,6*S*)-2-Ethyl-3,5-bis(4-fluorophenyl)-1-hydroxy-*N*-(4-methoxyphenyl)-4,6-dinitrocyclohexanecarboxamide (8d)

Synthesized according to the general procedure from **1d** (R^1 = Et, Ar = 4-$MeOC_6H_4$; 44 mg, 0.2 mmol) and **2a** (R^2 = 4-FC_6H_4; 70 mg, 0.42 mmol) as a white solid; yield: 74 mg (67%); mp 109–111 °C; $[\alpha]_D^{30}$ +29.5 (*c* = 0.57, CH_2Cl_2); R_f = 0.11 (EtOAc–PE, 1:4).

Chiral HPLC: ChiralPak IB [hexane–EtOH (4:1), flow rate = 1.0 mL/min], λ = 254 nm; t_{minor} = 10.9 min, t_{major} = 6.6 min, er = 28:1.

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 8.60 (br s, 1 H, NH), 7.69–7.66 (m, 2 H), 7.41 (d, *J* = 9.0 Hz, 2 H), 7.34–7.30 (m, 2 H), 7.05 (d, *J* = 9.0 Hz, 2 H), 6.96 (d, *J* = 9.0 Hz, 2 H), 6.88 (d, *J* = 9.0 Hz, 2 H), 5.70 (d, *J* = 12.3 Hz, 1 H), 5.50 (dd, *J* = 12.3, 6.9 Hz, 1 H), 4.69 (s, 1 H, OH), 4.41 (dd, *J* = 12.3, 12.3 Hz, 1 H), 4.11 (dd, *J* = 6.9, 6.9 Hz, 1 H), 3.77 (s, 3 H, OCH_3), 2.82–2.76 (m, 1 H), 1.47–1.36 (m, 2 H), 0.87 (d, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, CD_2Cl_2): δ = 168.7, 162.8 (d, *J* = 248 Hz), 162.7 (d, *J* = 248 Hz), 157.5, 133.2 (d, *J* = 8 Hz, 2 C), 129.9 (d, *J* = 8 Hz, 2 C), 129.0 (d, *J* = 4 Hz), 128.9, 128.5 (d, *J* = 4 Hz), 122.0 (2 C), 116.3 (d, *J* = 22 Hz, 2 C), 115.6 (d, *J* = 22 Hz, 2 C), 114.4 (2 C), 91.7, 89.3, 79.7, 55.5, 46.4, 45.5, 41.2, 20.3, 11.8.

MS (ES+): *m/z* 579 $[M + Na]^+$.

HRMS (ES+): *m/z* calcd for $C_{28}H_{28}F_2N_3O_7$: 556.1890; found: 556.1889.

(1*R*,2*R*,3*R*,4*S*,5*R*,6*S*)-2-Ethyl-1-hydroxy-*N*-(4-methoxyphenyl)-4,6-dinitro-3,5-diphenylcyclohexanecarboxamide (8e)

Synthesized according to the general procedure from **1d** (R^1 = Et, Ar = 4-$MeOC_6H_4$; 44 mg, 0.2 mmol) and **2b** (R^2 = Ph; 63 mg, 0.42 mmol) as a white solid; yield: 55 mg (53%); mp 139–141 °C; R_f = 0.18 (EtOAc–PE, 1:4); $[\alpha]_D^{22}$ +9.7 (*c* = 9.9, CH_2Cl_2).

Chiral HPLC: ChiralPak IB [hexane–EtOH (7:3), flow rate = 1.0 mL/min], λ = 254 nm; t_{minor} = 6.6 min, t_{major} = 5.3 min, er = 28:1.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.59 (br s, 1 H, NH), 7.69 (br s, 2 H), 7.40–7.36 (m, 8 H), 7.34–7.28 (m, 2 H), 6.86 (d, *J* = 9.0 Hz, 2 H), 5.69 (d, *J* = 12.5 Hz, 1 H), 5.48 (dd, *J* = 12.5, 6.7 Hz, 1 H), 4.54 (dd, *J* = 12.5, 12.5 Hz, 1 H), 4.52 (s, 1 H, OH), 4.13 (dd, *J* = 6.7, 6.7 Hz, 1 H), 3.77 (s, 3 H), 2.81–2.76 (m, 1 H), 1.45–1.37 (m, 2 H), 0.91 (d, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.8, 157.3, 133.7, 132.9 (2 C), 131.3 (2 C), 129.2 (2 C), 129.0, 128.7 (2 C), 128.6, 128.2 (2 C), 122.0 (2 C), 114.3 (2 C), 92.0, 89.4, 79.7, 55.5, 47.0, 45.7, 41.9, 20.4, 11.9.

MS (ES+): *m/z* 542 $[M + Na]^+$.

HRMS (ES+): *m/z* calcd for $C_{28}H_{30}N_3O_7$: 520.2078; found: 520.2077.

Bicyclo[3.2.1]octanes 11; General Procedure

A soln of 1,3-ketoamide **4** (0.2 mmol, 1 equiv) and thiourea catalyst **II** (8.3 mg, 0.02 mmol, 0.1 equiv) in dry toluene (4 mL) was cooled to –35 °C, and acrolein (**9**; 27 μL, 0.4 mmol, 2 equiv) was added. The mixture was stirred for 24–48 h until the ketoamide **4** was consumed. DBU (30 μL, 0.2 mmol, 1 equiv) was then added and the mixture was warmed to r.t. and stirred for 1 h then concentrated under reduced pressure. 1 M aq HCl was added and the mixture was extracted with CH_2Cl_2 (2 × 10 mL). The organic phases were combined, washed with brine (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by flash column chromatography (EtOAc–PE).

(1*R*,5*R*)-4-Hydroxy-*N*-(4-nitrophenyl)-8-oxobicyclo[3.2.1]octane-1-carboxamide (11a)

Synthesized according to the general procedure from **4a** (R = 4-$O_2NC_6H_4$; 50 mg, 0.2 mmol) as a pale yellow solid (1.4:1 mixture of diastereomers); yield: 50 mg (82%); mp 137–139 °C; R_f = 0.33 (EtOAc–CH_2Cl_2, 2:3).

Chiral HPLC: Lux-Amylose-2 [hexane–*i*-PrOH (7:3), flow rate = 1.0 mL/min], λ = 220 nm; diastereomer OH_{ax}: t_{minor} = 18.0 min, t_{major} = 21.0 min, er = 4.1:1; diastereomer OH_{eq}: t_{minor} = 10.1 min, t_{major} = 11.3 min, er = 3.7:1.

^{1}H NMR (400 MHz, $CDCl_3$): δ (diastereomer OH_{ax}) = 10.21 (s, 1 H, NH), 8.21 (d, *J* = 9.2 Hz, 2 H), 7.77 (d, *J* = 9.2 Hz, 2 H), 4.45 (s, 1 H), 2.67 (dd, *J* = 7.1, 5.4 Hz, 1 H), 2.46–2.40 (m, 1 H), 2.39–2.31 (m, 2 H), 2.31–2.12 (m, 2 H), 2.03–1.92 (m, 1 H), 1.84–1.71 (m, 2 H); δ (diastereomer OH_{eq}) = 10.07 (s, 1 H, NH), 8.21 (d, *J* = 9.2 Hz, 2 H), 7.77 (d, *J* = 9.2 Hz, 2 H), 4.14 (br s, 1 H), 2.75 (dd, *J* = 7.0, 3.1 Hz, 1 H), 2.46–2.40 (m, 1 H), 2.39–2.31 (m, 2 H), 2.31–2.12 (m, 2 H), 2.03–1.92 (m, 1 H), 1.84–1.71 (m, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ (diastereomer OH_{ax}) = 213.0, 171.0, 145.42, 142.21, 124.88 (2 C), 119.3 (2 C), 76.9, 57.5, 52.3, 34.1, 26.6, 25.4, 18.9; δ (diastereomer OH_{eq}) = 213.1, 170.7, 145.36, 142.23, 124.94 (2 C), 119.2 (2 C), 73.6, 57.7, 54.8, 31.8, 28.2, 26.4, 16.3.

MS (ES+): *m/z* 327 $[M + Na]^+$.

HRMS (ES+): *m/z* calcd for $C_{15}H_{17}N_2O_5$: 305.1132; found: 305.1130.

(1*R*,5*R*)-4-Hydroxy-8-oxo-*N*-phenylbicyclo[3.2.1]octane-1-carboxamide (11b)

Synthesized by an adaptation of the general procedure from **4b** (R = Ph; 41 mg, 0.2 mmol). After full conversion of **4b**, excess of acrolein was eliminated by distillation at a reduced pressure (100 mbar) without evaporation of toluene. DBU (30 μL, 0.2 mmol, 1 equiv) was then added and the mixture was stirred at r.t. for 1 h to give, after workup, a colorless viscous liquid (1:1.2 mixture of diastereomers); yield: 38 mg (73%); R_f = 0.28 (EtOAc–CH_2Cl_2, 2:3).

Chiral HPLC: Chiralcel OD-3 [hexane–*i*-PrOH (9:1), flow rate = 1.0 mL/min], λ = 254 nm; diastereomer OH_{ax}: t_{minor} = 18.9 min, t_{major} = 23.0 min, er = 4.8:1, diastereomer OH_{eq}: t_{minor} = 17.0 min, t_{major} = 20.4 min, er = 4.9:1.

^{1}H NMR (400 MHz, $CDCl_3$): δ (diastereomer OH_{ax}) = 9.79 (s, 1 H, NH), 7.60–7.51 (m, 2 H), 7.32 (t, *J* = 7.9 Hz, 2 H), 7.10 (td, *J* = 7.3, 1.2 Hz, 1 H), 4.42–4.30 (m, 1 H), 2.64–2.57 (m, 1 H), 2.44–2.19 (m, 4 H), 2.16–1.99 (m, 1 H), 1.96–1.64 (m, 3 H); δ (diastereomer OH_{eq}) = 9.67 (s, 1 H, NH), 7.60–7.51 (m, 2 H), 7.32 (t, *J* = 7.9 Hz, 2 H), 7.10 (td, *J* = 7.3, 1.2 Hz, 1 H), 4.18–4.03 (m, 1 H), 2.72 (dd, *J* = 6.9, 3.2 Hz, 1 H), 2.44–2.19 (m, 3 H), 2.16–1.99 (m, 2 H), 1.96–1.64 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (diastereomer OH_{ax}) = 217.9, 170.0, 137.7, 129.1 (2 C), 124.5, 120.3 (2 C), 78.5, 54.4, 53.2, 38.5, 26.3, 25.8, 18.6; δ (diastereomer OH_{eq}) = 216.9, 169.9, 137.6, 129.1 (2 C), 124.6, 120.3 (2 C), 74.7, 55.2, 53.9, 35.6, 27.5, 26.7, 15.5.

MS (ES^+): *m/z* 282 $[M + Na]^+$.

HRMS (ES+): *m/z* calcd for $C_{15}H_{18}NO_3$: 260.1281; found: 260.1284.

(1*R*,5*R*)-4-Hydroxy-*N*-1-naphthyl-8-oxobicyclo[3.2.1]octane-1-carboxamide (11c)

Synthesized by an adaptation of the general procedure from **4c** (R = 1-naphthyl; 51 mg, 0.2 mmol). After full conversion of **4c**, excess of acrolein was eliminated by distillation at reduced pressure (100 mbar) without evaporation of toluene. DBU (30 μL, 0.2 mmol, 1 equiv) was then added and the mixture was stirred at r.t. for 1 h to give, after workup, a viscous liquid (1:1.2 mixture of diastereomers); yield: 38 mg (62%); R_f = 0.30 (EtOAc–CH_2Cl_2, 2:3).

Chiral HPLC: Lux-Amylose-2 [hexane–*i*-PrOH (7:3), flow rate = 1.0 mL/min], λ = 254 nm; diastereomer OH_{ax}: t_{minor} = 10.2 min, t_{major} = 33.5 min, er = 7.5:1; diastereomer OH_{eq}: t_{minor} = 6.9 min, t_{major} = 7.9 min, er = 8.0:1.

^{1}H NMR (400 MHz, $CDCl_3$): δ (diastereomer OH_{ax}) = 10.38 (s, 1 H, NH), 8.18–8.12 (m, 2 H), 7.86 (d, *J* = 7.7 Hz, 1 H), 7.67 (d, *J* = 8.2 Hz, 1 H), 7.61–7.55 (m, 1 H), 7.54–7.44 (m, 2 H), 4.41–4.30 (m, 1 H), 2.64 (dd, *J* = 7.1, 5.2 Hz, 1 H), 2.55–2.21 (m, 4 H), 2.20–2.07 (m, 1 H), 1.88–1.65 (m, 3 H); δ (diastereomer OH_{eq}) = 10.24 (s, 1 H, NH), 8.18–8.12 (m, 1 H), 8.09 (d, *J* = 8.4 Hz, 1 H), 7.87 (d, *J* = 7.8 Hz, 1 H), 7.67 (d, *J* = 8.2 Hz, 1 H), 7.61–7.55 (m, 1 H), 7.54–7.44 (m, 2 H), 4.17–4.04 (m, 1 H), 2.76 (dd, *J* = 6.9, 3.2 Hz, 1 H), 2.55–2.21 (m, 3 H), 2.20–2.07 (m, 1 H), 2.06–1.89 (m, 2 H), 1.88–1.65 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (diastereomer OH_{ax}) = 170.5, 134.2, 132.6, 128.8, 126.6, 126.5, 126.1, 125.8, 125.3, 120.9, 119.3, 78.7, 54.9, 53.2, 38.9, 26.4, 25.9, 18.7; δ (diastereomer OH_{eq}) = 217.6, 170.3, 134.2, 132.5, 128.8, 126.6, 126.5, 126.1, 125.8, 125.3, 120.7, 119.4, 74.8, 55.2, 54.4, 35.9, 27.6, 26.8, 15.6.

MS (ES^+): *m/z* 332 $[M + Na]^+$.

HRMS (ES+): *m/z* calcd for $C_{19}H_{20}NO_3$: 310.1438; found: 310.1443.

(1*R*,5*R*)-4-Hydroxy-8-oxo-*N*-tosylbicyclo[3.2.1]octane-1-carboxamide (11d)

Synthesized by an adaptation of the general procedure from **4d** (R = Ts; 56 mg, 0.2 mmol). After addition of DBU (30 μL, 0.2 mmol, 1 equiv), the mixture was heated to 60 °C for 6 h to give, after workup, a viscous liquid (1:1 mixture of diastereomers); yield: 33 mg (49%); R_f = 0.55 (EtOAc–CH_2Cl_2, 2:3).

Chiral HPLC: Chiralpak IC [hexane–*i*-PrOH–TFA (7:3:0.01), flow rate = 1.0 mL/min], λ = 254 nm; diastereomer OH_{ax}: t_{minor} = 45.6 min, t_{major} = 48.3 min, er = 66:1; diastereomer OH_{eq}: t_{minor} = 26.6 min, t_{major} = 32.6 min, er = 14:1.

^{1}H NMR (400 MHz, $CDCl_3$): δ (diastereomer OH_{ax}) = 10.23 (s, 1 H, NH), 7.93 (d, *J* = 8.4, 2 H), 7.31 (d, *J* = 8.4 Hz, 2 H), 4.36 (d, *J* = 1.7 Hz, 1 H), 2.60 (dd, *J* = 6.9, 5.5 Hz, 1 H), 2.42 (s, 3 H), 2.35–2.26 (m, 1 H), 2.15–1.98 (m, 4 H), 1.92–1.64 (m, 3 H); δ (diastereomer OH_{eq}) = 10.12 (s, 1 H, NH), 7.93 (d, *J* = 8.4, 2 H), 7.31 (d, *J* = 8.4 Hz, 2 H), 4.10–4.07 (m, 1 H), 2.70 (dd, *J* = 6.9, 3.2 Hz, 1 H), 2.42 (s, 3 H), 2.35–2.26 (m, 1 H), 2.15–1.98 (m, 4 H), 1.92–1.64 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (diastereomer OH_{ax}) = 216.0, 169.4, 145.1, 135.8, 129.7 (2 C), 128.5 (2 C), 78.2, 55.5, 52.5, 37.9, 26.4, 25.5, 21.8, 18.6; δ (diastereomer OH_{eq}) = 215.1, 169.4, 145.2, 135.7, 129.7 (2 C), 128.5 (2 C), 74.4, 55.1, 54.5, 35.1, 26.6, 25.4, 21.8, 15.6.

HRMS (ES+): *m/z* calcd for $C_{16}H_{20}NO_5S$: 338.1057; found: 338.1061.

(1*R*,5*R*)-4,8-Dioxo-*N*-tosylbicyclo[3.2.1]octane-1-carboxamide (12)

A soln of **11d** (67.4 mg, 0.2 mmol, 1 equiv) and 2-iodoxybenzoic acid (112 mg, 0.4 mmol, 2 equiv) in EtOAc (1 mL) was refluxed in a sealed tube for 18 h. The mixture was then cooled to r.t., filtered through a short pad of Celite, and concentrated under reduced pressure to afford quantitatively the crude product, which could not be further purified because of its instability on silica gel; yield 67 mg (quant); R_f = 0.22 (EtOAc–PE, 1:3).

Chiral HPLC: Chiralpak IC [hexane–EtOH–TFA (8:2:0.01), flow rate = 1.0 mL/min], λ = 254 nm; t_{major} = 12.1 min, t_{minor} = 13.9 min, er = 24:1.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 8.3 Hz, 2 H), 7.32 (d, *J* = 8.3 Hz, 2 H), 3.35 (d, *J* = 6.8 Hz, 1 H), 2.79 (ddd, *J* = 17.0, 12.6, 9.4 Hz, 1 H), 2.50 (dd, *J* = 17.0, 6.7 Hz, 1 H), 2.45–2.37 (m, 1 H), 2.42 (s, 3 H), 2.28–2.10 (m, 3 H), 1.97 (ddd, *J* = 14.3, 8.0, 3.1 Hz, 1 H), 1.84–1.73 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.0, 203.5, 168.3, 145.3, 135.5, 129.7 (2 C), 128.5 (2 C), 64.9, 56.1, 33.6, 30.4, 26.2, 21.8, 21.2.

MS (ES^+): *m/z* 358 $[M + Na]^+$.

HRMS (ES+): *m/z* calcd for $C_{16}H_{18}NO_5S$: 336.0900; found: 336.0898.

Acknowledgment

Financial support from the Agence Nationale pour la Recherche (ANR-11-BS07-0014), the Centre National de la Recherche Scientifique (CNRS), and the Aix-Marseille Université is gratefully acknowledged.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis. Included are copies of ^{1}H and ^{13}C NMR spectra of all new compounds.

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