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Enantioselective synthesis of bicylco[3.2.1]octan-8-ones using a tandem Michael–Henry reaction

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ABSTRACT

Bicyclo[3.2.1]octan-8-ones have been prepared from a tandem Michael–Henry reaction between cyclohexane-1,2-diones and nitroalkenes using a quinine-derived thiourea as the catalyst. Although four stereogenic centers were created during the reaction, only two diastereomers were obtained in good diastereoselectivity and high enantioselectivity (92–99% ee). When 3-methylcyclohexane-1,2-dione (R^1=Me) was used as the substrate, only the regioisomeric product of the corresponding thermodynamic enolate was obtained.

1. Introduction

Although 1,2-diones are very reactive compounds,[1] they have been rarely studied in organocatalyzed reactions.[2] In 2006, we reported an organocatalyzed direct aldol reaction of 1,2-diones with ketones.[2c] Most recently, Rueping and co-workers reported a tandem Michael-aldol reaction of cyclohexane-1,2-dione and α,β-unsaturated aldehydes.[2d] We also demonstrated that this compound may be used for the synthesis of 8-oxo-5,6,7,8-tetrahydro-4*H*-chromene derivatives through a tandem Michael addition-cyclization reaction with benzylidenemalononitriles.[2e] Although not well studied in organocatalysis, it appears that the dione may behave either as an ene-activator (for a Diels–Alder reaction),[2a] an electrophile,[2b,c] a nucleophile,[2e] or both an electrophile and a nucleophile[2d] in organocatalytic reactions. These multiple capacities warrant many potential applications of these interesting compounds in organocatalytic reactions.

On the other hand, tandem reactions have been the focus of current organic chemistry research because they can assemble complex molecule structures from relatively simple starting materials in a very efficient manner.[3] This approach has also been widely used in organocatalysis in recent years,[4,5a,g] and among the catalyst used for these organocatalyzed tandem reactions, cinchona alkaloid derivatives plays a crucial role.[5] Herein we wish to report a novel tandem Michael–Henry reaction of the 1,2-dione compounds for the highly diastereoselective and enantioselective synthesis of bicylco[3.2.1]octan-8-ones, using a quinine-derived thiourea as the catalyst.

2. Results and discussion

We recently demonstrated that a tandem Michael–Henry reaction may be achieved between 2-mercaptobezaldehydes and *trans*-β-nitrostyrenes,[4a] in which 2-mercaptobezaldehyde acts as both a nucleophile and an electrophile. According to Rueping's results,[2d] such a dual role may also be played by cyclohexane-1,2-dione. Thus, we envisioned that such a dione should be a good substrate for a tandem Michael–Henry reaction with *trans*-β-nitrostyrenes. Thus, cyclohexane-1,2-dione (**1a**) and *trans*-β-nitrostyrene (**2a**) were adopted as the model substrates to test our hypothesis. Since we and others[6] have shown that cinchona alkaloid-derived thioureas[7] are effective catalysts for a tandem Michael-aldol or Michael–Knoevenagel reactions, some thiourea derivatives (**4**–**8**) were adopted as the catalysts (Fig. 1). For comparison purpose, similar catalysts (**9**–**11**) without the thiourea moiety are also included in the screening (Fig. 1). The results of this screening are collected in Table 1.

As shown in Table 1, when quinine-derived thiourea catalyst **4** was applied in toluene at room temperature for 26 h, a bicyclic product was obtained (entry 1). It should be pointed out that only

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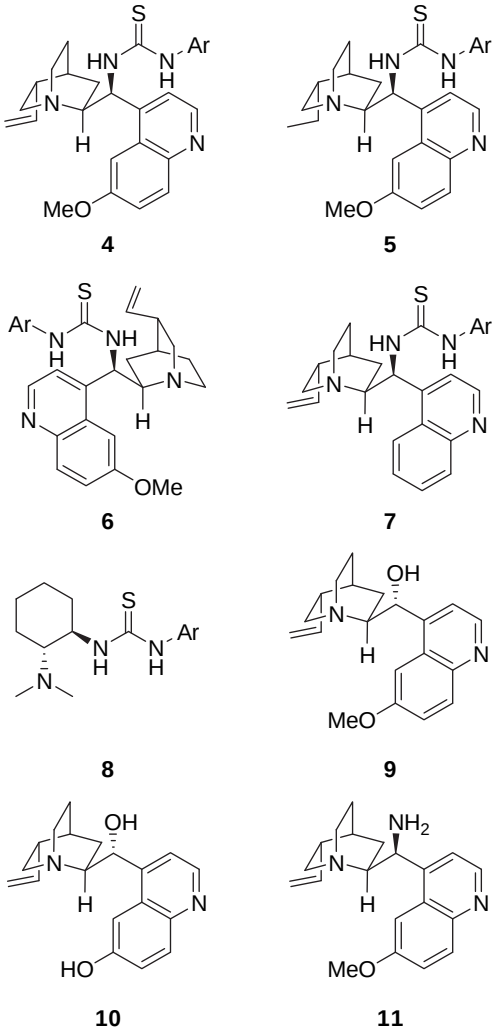
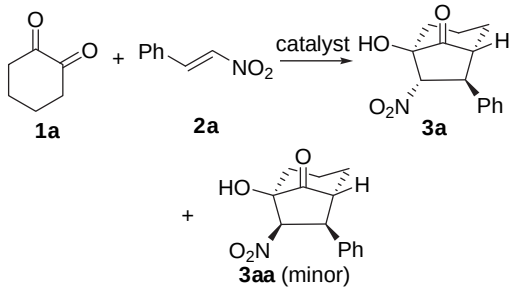


Figure 1. Structure of the catalysts applied in the screening [Ar=3,5-$(CF_3)_2C_6H_3$].

two diastereomers (**3a** and **3aa**) are present in the crude product according to the ^{1}H NMR spectrum, although four stereogenic centers are created during the reaction. The diastereomeric ratio is 88:12. Luckily the minor diastereomer **3aa** may be easily removed by column chromatography, and the major diastereomer **3a** was isolated in 75% yield and 97% ee (entry 1). Similarly, high ee values and good dr values may also be achieved with the other cinchona alkaloid-derived thiourea catalysts **5**, **6**, and **7** (entries 2–4), although the product yields obtained with catalysts **5** and **7** are lower due to the formation of some unidentified products in these cases. A *trans*-cyclohexane-1,2-diamine-derived thiourea catalyst **8** also leads to 59% yield of the product with excellent dr (91:9) and ee value (93%, entry 5). In contrast, similar cinchona alkaloid-derived catalysts without the thiourea moiety (**9**–**11**) all give very low ee values of the product, although the dr values remain high (entries 6–8). These results hint that the thiourea group is indeed essential for maintaining the high enantioselectivity of this reaction, most likely through hydrogen-bonding with *trans*-β-nitrostyrene. It should be pointed out that the major enantiomer obtained with catalysts **6** and **8** is opposite that of the rest of the catalysts.

Because catalyst **4** leads to the highest ee value of the product with a high dr value, it was adopted as the catalyst of choice in our further screening. Besides toluene, several other common organic solvents were screened. In fact, except for acetonitrile (entry 14) and ethanol (entry 15), in which the ee values obtained for the

Table 1
Catalyst screening and reaction condition optimization[a]



Entry	Solvent	Catalyst	Time (h)	dr[b]	Yield[c] (%)	ee[d] (%)
1	Toluene	**4**	26	88:12	75	97
2	Toluene	**5**	30	90:10	48	95
3	Toluene	**6**	36	87:13	71	94[e]
4	Toluene	**7**	28	90:10	60	95
5	Toluene	**8**	25	91:9	59	93[e]
6	Toluene	**9**	30	91:9	77	17
7	Toluene	**10**	40	90:10	63	18
8	Toluene	**11**	144	81:19	45	37
9	THF	**4**	48	74:26	46	97
10	Ether	**4**	48	89:11	49	94
11	CH_2Cl_2	**4**	40	79:21	58	95
12	$CHCl_3$	**4**	36	90:10	74	95
13	EtOAc	**4**	40	78:22	69	94
14	CH_3CN	**4**	40	76:24	41	91
15	EtOH	**4**	32	92:8	72	90

[a] Unless otherwise indicated, all reactions were conducted with *trans*-β-nitrostyrene (0.25 mmol), 1,2-cyclohexanedione (0.30 mmol), and the catalyst (15 mmol %) in the specified solvent (1.5 mL) at room temperature.
[b] Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude mixture.
[c] Yield of the isolated major diastereomer after column chromatography.
[d] Determined by HPLC analysis on a ChiralCel OJ-H column.
[e] The opposite enantiomer was obtained as the major product.

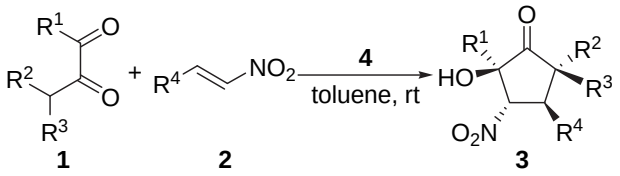
product are slightly lower, all the other solvents (THF, ether, CH_2Cl_2, $CHCl_3$, and EtOAc,) all lead to similar ee values of the product (around 95% ee, entries 9–13), although the yields of the product and/or the dr values are usually inferior to that obtained in toluene (entry 1). Thus, toluene was identified as the best solvent for this reaction.

Next, the scope and limitation of this reaction were studied. The results of this study are summarized in Table 2.

It is clear from the results in Table 2 that high dr values, excellent ee values, and good yields of the desired products may be obtained for the reaction of cyclohexane-1,2-dione and *trans*-β-nitrostyrenes with different substituents on the phenyl ring. For example, both electron-donating and electron-withdrawing groups at the *para* position of the phenyl ring do not lead to major differences in the dr values, the product yields, or the ee values (entries 1–7). Even with the strong electron-withdrawing nitro group, an excellent ee value of 93% and a high dr of 94:6 were obtained (entry 7). Similarly, substituents at the *ortho* (entries 8–9) or *meta* (entry 10) positions show no influence on the enantioselectivity, either. The lower dr value obtained with *ortho*-bromo-substituted nitrostyrene (entry 9) is probably due to steric reasons. A heteroarene-substituted nitroalkene (entry 11) is also a good substrate for this reaction: the reaction of *trans*-2-(2-nitrovinyl)thiophene with cyclohexane-1,2-dione produce the expected product in 89% yield and 99% ee. The original dr value was 92:8 in this case. Excellent ee value (97%), good dr value (88:12) and yield (77%) may also be obtained for a *trans*-nitroalkene with an alkyl substituent (entry 12).

3-Methylcyclohexane-1,2-dione (**1b**) is also a good substrate for this reaction (entry 13). Since this compound is not symmetric, it may enolize both at the less substituted 6-position (to give a kinetic enolate) or the more substituted 3-position (to give

Table 2
Tandem Michael–Henry reaction between 1,2-diones and nitroalkenes[a]



Entry	R^1	R^2	R^3	R^4	dr[b]	Yield (%)[c]	ee[d] (%)
1	$-(CH_2)_3-$		H	Ph(**3a**)	88:12	75	97
2	$-(CH_2)_3-$		H	4-MeC_6H_4(**3b**)	92:8	83	97
3	$-(CH_2)_3-$		H	4-MeO C_6H_4(**3c**)	88:12	82	97
4	$-(CH_2)_3-$		H	4-ClC_6H_4(**3d**)	86:14	68	96
5	$-(CH_2)_3-$		H	4-BrC_6H_4(**3e**)	94:6	89	97
6	$-(CH_2)_3-$		H	4-CNC_6H_4(**3f**)	91:9	79	97[e]
7	$-(CH_2)_3-$		H	4-$NO_2C_6H_4$(**3g**)	94:6	90	93[e]
8	$-(CH_2)_3-$		H	2-MeOC_6H_4(**3h**)	95:5	87	94
9	$-(CH_2)_3-$		H	2-BrC_6H_4(**3i**)	72:28	66	92
10	$-(CH_2)_3-$		H	3-ClC_6H_4(**3j**)	88:12	77	96[e]
11	$-(CH_2)_3-$		H		92:8	89	99[e]
12	$-(CH_2)_3-$		H	*n*-C_6H_{13}(**3l**)	88:12	77	97
13	$-(CH_2)_3-$		Me	Ph (**3m**)	88:12	67[f]	97
14	Me	H	H	Ph	—	0	—
15	$-(CH_2)_2-$		Me	Ph	—	0[g]	—

[a] All reactions were conducted with *trans*-nitroalkenes (0.25 mmol), 1,2-diones (0.30 mmol), and catalyst **4** (15 mmol %) in toluene (1.5 mL) at room temperature for 26 to 32 h (TLC monitoring).
[b] Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude mixture.
[c] Yield of the isolated major diastereomer after column chromatography.
[d] Unless otherwise specified, ee values were determined by HPLC analysis on a ChiralCel OJ-H column.
[e] Determined by HPLC analysis on a ChiralPak AD-H column.
[f] The reaction time was 72 h.
[g] A complex mixture of unidentified products was obtained.

a thermodynamic enolate). However, only the thermodynamic enolate participates in the reaction to give a single regioisomer **3m** with a dr of 88:12 as revealed by the NMR spectrum of the crude product. The major diastereomer may be isolated in 97% ee and 67% yield.

Nevertheless, this reaction seems to be limited to cyclohexane-1,2-diones, because the attempted reactions of both butane-2, 3-dione and 3-methylcyclopentane-1,2-dione failed under the optimized conditions, with the former giving no sign of reaction at all (entry 14) and the latter being too complex to be useful (entry 15).

To determine the absolute configuration of the major enantiomer obtained in this reaction, crystals of compound **3f** were analyzed by X-ray crystallography (Fig. 2).[8] On the basis of the X-ray analysis, its stereochemistry was assigned to be (1*R*,5*R*,6*S*,7*S*). The

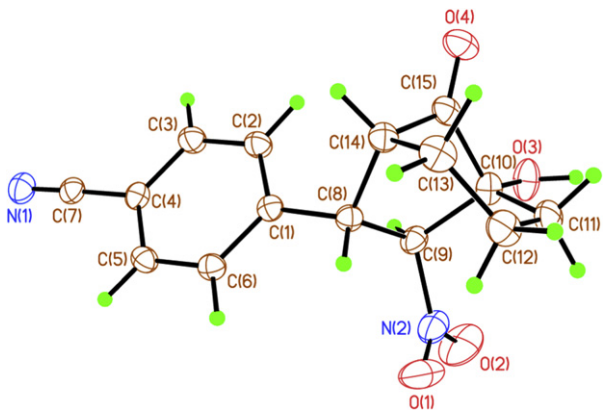
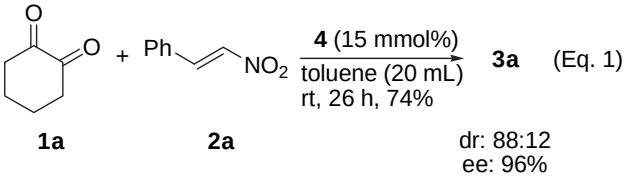


Figure 2. ORTEP drawing of compound **3f**.

stereochemistry of the other products was similarly assigned on the basis of the reaction mechanism.

To show the practical utility of the current method, the reaction of compounds **1a** and **2a** was also carried out with a much larger scale (Eq. 1). As shown in Eq. 1, the reaction with 4 mmol (0.60 g) of **2a** and 4.8 mmol (0.54 g) of **1a** under the optimized conditions gave 0.77 g (74% yield) of **3a** with an ee value of 96%, which is almost identical to the results obtained under the microscale conditions (Table 2, entry 1).



(1)

3. Conclusions

We have demonstrated that bicyclo[3.2.1]otan-8-ones may be prepared in excellent enantioselectivity, high diastereoselectivity, and regioselectivity from a tandem Michael–Henry reaction between cyclohexane-1,2-diones and nitroalkenes by using a quinine-derived thiourea as the catalyst. However, cyclopentan-1,2-diones and enolizable acyclic 1,2-diones fail to give similar products.

4. Experimental

4.1. General

Unless otherwise specified, all compounds used in this study were purchased from commercial sources and were used as received. Catalysts **4**,[9] **5**,[9] **6**,[9] **7**,[9] **10**,[7d] and **11**[9] were prepared by using the reported procedures from quinine or quinidine. THF and ether were freshly distilled from benzophenone and sodium metal. Toluene, CH_2Cl_2, $CHCl_3$, and CH_3CN were distilled from CaH_2. HPLC grade EtOH and EtOAC were used directly. All reactions were carried out at ambient temperature in oven-dried glassware. Optical rotation was measured at room temperature (23 °C).

4.2. General procedure for the tandem Michael–Henry reaction

To a solution of the 1,2-cycloalkanedione (0.30 mmol) and the catalyst (0.038 mmol, 15 mol %) in toluene (1.5 mL) was added the nitroalkene (0.25 mmol). The mixture was stirred at room temperature for the time as indicated in the Tables. The solvent was then removed under reduced pressure and the residue was purified by chromatography on silica gel to afford the product.

*4.2.1. (1R,5R,6S,7S)-1-Hydroxy-7-nitro-6-phenylbicyclo[3.2.1]-octan-8-one (**3a**).* Colorless oil, 75% yield, $[\alpha]_D$ −16.2 (*c* 0.455, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.13–7.16 (m, 2H), 7.24–7.36 (m, 3H), 4.78 (d, *J*=6.0 Hz, 1H), 4.18 (d, *J*=6.0 Hz, 1H), 3.34 (s, 1H), 2.81 (d, *J*=2.7 Hz, 1H), 2.32–2.43 (m, 2H), 1.94–2.14 (m, 3H), 1.76–1.79 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.6, 142.5, 129.6, 128.1, 127.0, 93.9, 82.0, 52.0, 44.3, 40.2, 36.4, 18.4; ν_{max} (cm^{-1}): 3424, 1760, 1545; HRMS calcd for $C_{14}H_{15}NO_4$: 261.1001; found: 261.1006. HPLC conditions: ChiralCel OJ-H column, *i*-PrOH/hexane 20:80, flow rate 1.0 mL/min, UV detection at 240 nm.

*4.2.2. (1R,5R,6S,7S)-1-Hydroxy-6-(4-methylphenyl)-7-nitrobicyclo [3.2.1]octan-8-one (**3b**).* Colorless oil, 83% yield, $[\alpha]_D$ −17.4 (*c* 0.465,

CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$): δ 7.11–7.13 (dd, J_1=6.0 Hz, J_2=1.8 Hz, 2H), 7.01–7.04 (dd, J_1=6.0 Hz, J_2=1.8 Hz, 2H), 4.75 (d, J=5.7 Hz, 1H), 4.13 (d, J=5.7 Hz, 1H), 3.31 (s, 1H), 2.78 (d, J=3.0 Hz, 1H), 2.32–2.42 (m, 2H), 2.30 (s, 3H), 1.95–2.14 (m, 3H), 1.74–1.77 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.7, 139.6, 137.8, 130.2, 126.8, 94.1, 81.9, 52.0, 43.9, 40.2, 36.4, 21.4, 18.3; ν_{max} (cm^{-1}): 3374, 2937, 1758, 1542; HRMS calcd for $C_{15}H_{17}NO_4$: 275.1158; found: 275.1165. HPLC conditions: ChiralCel OJ-H column, *i*-PrOH/hexane 20:80, flow rate 1.0 mL/min, UV detection at 240 nm.

*4.2.3. (1R,5R,6S,7S)-1-Hydroxy-6-(4-methoxyphenyl)-7-nitrobicyclo [3.2.1]octan-8-one (**3c**).* Colorless oil, 82% yield, $[\alpha]_D$ −18.7 (*c* 1.58, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$): δ 7.03–7.08 (dd, J_1=5.1 Hz, J_2=2.7 Hz, 2H), 6.82–6.87 (dd, J_1=5.1 Hz, J_2=2.7 Hz, 2H), 4.73 (d, J=6.0 Hz, 1H), 4.12 (d, J=6.0 Hz, 1H), 3.78 (s, 3H), 3.34 (s, 1H), 2.76 (d, J=2.1 Hz, 1H), 2.31–2.42 (m, 2H), 1.92–2.12 (m, 3H), 1.74–1.77 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.9, 159.3, 135.7, 128.1, 115.0, 94.3, 81.9, 55.6, 52.1, 43.5, 40.0, 36.3, 18.2; ν_{max} (cm^{-1}): 3448, 2962, 1759; HRMS calcd for $C_{15}H_{17}NO_5$: 291.1107; found: 291.1098. HPLC conditions: ChiralCel OJ-H column, *i*-PrOH/hexane 20:80, flow rate 1.0 mL/min, UV detection at 220 nm.

*4.2.4. (1R,5R,6S,7S)-6-(4-Chlorophenyl)-1-hydroxy-7-nitrobicyclo [3.2.1]octan-8-one (**3d**).* Viscous liquid, 68% yield, $[\alpha]_D$ −18.4 (*c* 0.46, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$): δ 7.01–7.08 (dd, J_1=6.6 Hz, J_2=1.8 Hz, 2H), 6.84–6.86 (dd, J_1=6.6 Hz, J_2=1.8 Hz, 2H), 4.46 (d, J=6.0 Hz, 1H), 3.92 (d, J=6.0 Hz, 1H), 3.04 (s, 1H), 2.54 (s, 1H), 2.08–2.20 (m, 2H), 1.68–1.91 (m, 3H), 1.51–1.57 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.2, 140.9, 134.1, 129.7, 128.3, 93.6, 81.9, 51.9, 43.7, 40.1, 36.4, 18.3; ν_{max} (cm^{-1}): 3440, 2938, 1745, 1544; HRMS calcd for $C_{14}H_{14}ClNO_4$: 295.0611; found: 295.0619. HPLC conditions: ChiralCel OJ-H column, *i*-PrOH/hexane 20:80, flow rate 1.0 mL/min, UV detection at 240 nm.

*4.2.5. (1R,5R,6S,7S)-6-(4-Bromophenyl)-1-hydroxy-7-nitrobicyclo [3.2.1]octan-8-one (**3e**).* White solid, 89% yield, mp: 139–140 °C, $[\alpha]_D$ −15.7 (*c* 1.545, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$): δ 7.44–7.48 (m, 2H), 7.01–7.05 (m, 2H), 4.70 (d, J=5.7 Hz, 1H), 4.14 (d, J=5.7 Hz, 1H), 3.29 (s, 1H), 2.77 (d, J=2.1 Hz, 1H), 2.30–2.43 (m, 2H), 2.11–2.17 (m, 1H), 1.91–2.09 (m, 2H), 1.74–1.80 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.2, 141.4, 132.7, 128.7, 122.1, 93.5, 81.9, 51.8, 43.8, 40.1, 36.4, 18.3; ν_{max} (cm^{-1}): 3490, 3387, 1749, 1541; HRMS calcd for $C_{14}H_{14}BrNO_4$: 339.0106; found: 339.0103. HPLC conditions: ChiralCel OJ-H column, *i*-PrOH/hexane 20:80, flow rate 1.0 mL/min, UV detection at 220 nm.

*4.2.6. (1R,5R,6S,7S)-6-(4-Cyanophenyl)-1-hydroxy-7-nitrobicyclo [3.2.1]octan-8-one (**3f**).* White solid, 79% yield, mp: 207–209 °C, $[\alpha]_D$ −16.9 (*c* 0.53, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$): δ 7.66–7.67 (dd, J_1=6.6 Hz, J_2=1.2 Hz, 2H), 7.28–7.32 (dd, J_1=6.6 Hz, J_2=1.2 Hz, 2H), 4.71 (d, J=6.0 Hz, 1H), 4.24 (d, J=6.0 Hz, 1H), 3.33 (s, 1H), 2.80–2.81 (m, 1H), 2.34–2.47 (m, 2H), 2.13–2.19 (m, 1H), 1.90–2.05 (m, 2H), 1.79–1.83 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 211.8, 147.4, 133.5, 128.0, 118.3, 112.3, 92.9, 81.8, 51.5, 44.2, 40.0, 36.2, 18.1; ν_{max} (cm^{-1}): 3517, 2231, 1766, 1609; HRMS calcd for $C_{15}H_{14}N_2O_4$:286.0954; found: 286.0965. HPLC conditions: ChiralPak AD-H column, *i*-PrOH/hexane 35:65, flow rate 1.0 mL/min, UV detection at 254 nm.

*4.2.7. (1R,5R,6S,7S)-1-Hydroxy-7-nitro-6-(4-nitrophenyl)bicyclo [3.2.1]octan-8-one (**3g**).* White solid, 90% yield, mp: 170–171 °C, $[\alpha]_D$ −11.3 (*c* 0.515, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$): δ 8.22–8.24 (dd, J_1=5.4 Hz, J_2=1.5 Hz, 2H), 7.36–7.38 (dd, J_1=5.4 Hz, J_2=1.5 Hz, 2H), 4.72 (d, J=6.0 Hz, 1H), 4.31 (d, J=6.0 Hz, 1H), 3.28 (s, 1H), 2.84 (d, J=2.0 Hz, 1H), 2.45–2.49 (m, 1H), 2.36–2.39 (m, 1H), 2.14–2.21 (m, 1H), 1.90–2.05 (m, 2H), 1.81–1.85 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 211.7, 149.3, 147.8, 128.2, 124.9, 92.8, 81.7, 51.5, 44.0, 40.0, 36.2, 18.2; ν_{max} (cm^{-1}): 1757, 1599, 1546; HRMS calcd for $C_{14}H_{14}N_2O_6$: 306.0852; found: 306.0863. HPLC conditions: ChiralPak AD-H column, *i*-PrOH/hexane 35:65, flow rate 1.0 mL/min, UV detection at 254 nm.

*4.2.8. (1R,5R,6S,7S)-1-Hydroxy-6-(2-methoxyphenyl)-7-nitro-bicyclo[3.2.1]octan-8-one (**3h**).* Colorless oil, 87% yield, $[\alpha]_D$ −13.8 (*c* 0.505, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$): δ7.25–7.30 (m, 2H), 6.84–6.94 (m, 2H), 5.10 (d, J=5.7 Hz, 1H), 4.06 (d, J=5.7 Hz, 1H), 3.67–3.69 (m, 3H), 3.28 (s, 1H), 2.60(d, J=3.9 Hz, 1H), 2.24–2.38 (m, 2H), 1.92–2.08 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.5, 156.0, 130.1, 129.4, 129.1, 120.7, 111.0, 91.9, 81.3, 54.2, 51.3, 43.7, 40.6, 36.5, 17.8; ν_{max} (cm^{-1}): 3451, 2937, 1761, 1543; HRMS calcd for $C_{15}H_{17}NO_5$: 291.1107; found 291.1103. HPLC conditions: ChiralCel OJ-H column, *i*-PrOH/hexane 30:70, flow rate 1.0 mL/min, UV detection at 240 nm.

*4.2.9. (1R,5R,6S,7S)-6-(2-Bromophenyl)-1-hydroxy-7-nitrobicyclo [3.2.1]octan-8-one (**3i**).* Viscous liquid, 66% yield, $[\alpha]_D$ −11.6 (*c* 0.69, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$): δ 7.58–7.61 (m, 1H), 7.28–7.33 (m, 1H), 7.12–7.17 (m, 1H), 6.98–7.02 (m, 1H), 5.08 (d, J=6.0 Hz, 1H), 4.80 (d, J=6.0 Hz, 1H), 3.28 (s, 1H), 2.64 (d, J=3.9 Hz, 1H), 2.41–2.50 (m, 2H), 1.95–2.19 (m, 3H), 1.76–1.81 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.4, 140.9, 133.9, 129.6, 128.8, 128.4, 123.9, 92.1, 82.1, 52.8, 43.5, 40.6, 36.7, 18.3; ν_{max} (cm^{-1}): 3424, 2923, 1746, 1550; HRMS calcd for $C_{14}H_{14}BrNO_4$: 339.0106; found: 339.0120. HPLC conditions: ChiralCel OJ-H column, *i*-PrOH/hexane 20:80, flow rate 1.0 mL/min, UV detection at 220 nm.

*4.2.10. (1R,5R,6S,7S)-6-(3-Chlorophenyl)-1-hydroxy-7-nitrobicyclo [3.2.1]octan-8-one (**3j**).* Colorless oil, 77% yield, $[\alpha]_D$ −12.0 (*c* 0.755, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$): δ 7.24–7.31 (m, 2H), 7.16 (s, 1H), 7.01–7.04 (m, 1H), 4.74 (d, J=6.0 Hz, 1H), 4.16 (d, J=6.0 Hz, 1H), 3.30 (s, 1H), 2.80 (d, J=2.1 Hz, 1H), 2.30–2.45 (m, 2H), 2.10–2.19 (m, 1H), 1.90–2.08 (m, 2H), 1.75–1.81 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.0, 144.2, 135.4, 131.0, 128.4, 127.4, 125.0, 93.4, 81.9, 51.7, 44.0, 40.2, 36.4, 18.3; ν_{max} (cm^{-1}): 3418, 2961, 1759, 1596, 1544; HRMS calcd for $C_{14}H_{14}ClNO_4$: 295.0611; found: 295.0616. HPLC conditions: ChiralPak AD-H column, *i*-PrOH/hexane 35:65, flow rate 1.0 mL/min, UV detection at 254 nm.

*4.2.11. (1R,5R,6R,7S)-1-Hydroxy-7-nitro-6-(thiophen-2-yl)bicyclo-[3.2.1]octan-8-one (**3k**).* Viscous oil, 89% yield, $[\alpha]_D$ −6.2 (*c* 1.30, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$): δ 7.20–7.26 (m, 1H), 6.93–6.96 (m, 1H), 6.86–6.87 (m, 1H), 4.81 (d, J=5.4 Hz, 1H), 4.48 (d, J=5.4 Hz, 1H), 3.29 (s, 1H), 2.91–2.93 (m, 1H), 2.32–2.44 (m, 2H), 2.07–2.18 (m, 1H), 1.94–2.04 (m, 2H), 1.72–1.92 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.4, 144.8, 127.7, 125.3, 124.5, 94.1, 81.7, 52.4, 40.0, 39.7, 36.2, 18.3; ν_{max} (cm^{-1}): 3424, 2948, 1760, 1544; HRMS calcd for $C_{12}H_{13}NO_4S$: 267.0565; found: 267.0556. HPLC conditions: ChiralPak AD-H column, *i*-PrOH/hexane 40:60, flow rate 1.0 mL/min, UV detection at 254 nm.

*4.2.12. (1R,5R,6R,7S)-6-Hexyl-1-hydroxy-7-nitrobicyclo[3.2.1]-octan-8-one (**3l**).* Colorless oil, 77% yield, $[\alpha]_D$ −43.5 (*c* 0.66, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$): δ 4.40 (d, J=5.4 Hz, 1H), 3.22 (s, 1H), 2.91–2.98 (m, 1H), 2.32–2.40 (m, 2H), 2.14–2.18 (m, 1H), 1.70–2.07 (m, 3H), 1.61–1.67 (m, 1H), 1.40–1.50 (m, 2H), 1.20–1.29 (m, 8H), 0.86–0.90 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.6, 92.2, 81.7, 50.0, 40.1, 39.0, 36.2, 36.0, 31.9, 29.3, 26.9, 22.9, 18.4, 14.4; ν_{max} (cm^{-1}): 3420, 2926, 2857, 1760, 1544; HRMS calcd for $C_{14}H_{23}NO_4$: 269.1627; found: 269.1616. HPLC conditions: ChiralCel OJ-H column, *i*-PrOH/hexane 20:80, flow rate 1.0 mL/min, UV detection at 220 nm.

*4.2.13. (1R,5R,6R,7S)-1-Hydroxy-5-methyl-7-nitro-6-phenyl-bicyclo [3.2.1]octan-8-one (**3m**).* Colorless oil, 67% yield, $[\alpha]_D$ −6.5 (*c* 0.94, CH_2Cl_2); ^1H NMR (300 MHz,$CDCl_3$): δ 7.26–7.35 (m, 3H), 6.70–7.03

(m, 2H), 4.99 (d, J=6.0 Hz, 1H), 4.13 (d, J=6.0 Hz, 1H), 3.43 (s, 1H), 2.43–2.47 (m, 1H), 2.14–2.17 (m, 1H), 1.92–2.00 (m, 3H), 1.68–1.74 (m, 1H), 0.73 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ214.0, 139.9, 129.3, 128.6, 128.1, 93.7, 81.3, 51.5, 49.8, 45.5, 39.8, 18.4, 17.4; ν_{max} (cm^{-1}): 3426, 2931, 1756, 1545; HRMS calcd for $C_{15}H_{17}NO_4$: 275.1158; found: 275.1155. HPLC conditions: ChiralCel OJ-H column, *i*-PrOH/hexane 30:70, flow rate 1.0 mL/min, UV detection at 240 nm.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.04.044. These data include MOL files and InChIKeys of the most important compounds described in this article.

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