Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 4767

www.rsc.org/obc

PAPER

New approach to the preparation of bicyclo octane derivatives *via* the enantioselective cascade reaction catalyzed by chiral diamine-Ni(OAc)$_2$ complex†

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Received 18th January 2012, Accepted 17th April 2012
DOI: 10.1039/c2ob25135c

A highly efficient catalyst system assembled from enantiomerically pure diaminocyclohexane and Ni(OAc)$_2$ is, for the first time, used to catalyze the cascade Michael–Henry reaction of various diones and substituted nitroalkenes. A series of polyfunctionalized bicyclo[3.2.1]octane derivatives containing four stereogenic centers are prepared with excellent enantioselectivities (up to >99% ee) and diastereoselectivities (up to 50 : 1 dr) with high yields. In addition, *via* this chiral diamine-Ni(OAc)$_2$ catalyst system, the base-induced epimerization leading to the decrease of stereoselectivity can be prevented.

Introduction

During the past few years, the cascade reaction has represented a flourishing area within organic chemistry. Significant progress has been made in the development of organocatalyzed asymmetric cascade reactions using chiral secondary amines.[1] These straightforward routes—which allow two or more reactions to occur in a single operation under the same reaction conditions—avoid the need for costly protecting-group manipulations, changes in the reaction conditions, or isolation of any intermediates. Moreover, in this way, molecular complexities are often achieved efficiently, accompanied by high levels of stereoselectivity.[2] Therefore, with the significant improvement of synthetic efficiency and the reduction of waste and hazardous by-products, the exploration of catalyzed cascade reactions by employing a single chiral secondary amine catalyst capable of promoting each single step is one of the major topics in current research.[3]

Benzylated diaminocyclohexanes, which belong to vicinal diamines bearing a versatile stereochemical control element, typically combine a flexible and economically feasible synthetic route, strongly binding to the metal centre, together with excellent enantioselectivities for a variety of mechanistically diverse reactions.[4] Research utilizing benzylated diaminocyclohexane-Ni(OAc)$_2$ catalyst system in the asymmetric conjugate addition of nitroalkenes has recently been reported by both Sodeoka's and Yuan's groups separately.[5] Herein, we report our recent effort in the development of Ni(OAc)$_2$-diamine-catalyzed cascade reaction of nitroalkenes with 1,2-diones[6] to provide a series of functionalized bicyclo-[3.2.1]octane derivatives which are important components of neolignan molecules. These natural compounds have been found to exhibit significant biological activities (*e.g.* PAF-antagonistic activity) and have attracted particular interest in synthesis (Fig. 1).[7]

Compared to previous reports,[8] our reaction produced functionalized bicyclo[3.2.1]octane derivatives in a different stereoconfiguration (*S*,*S*,*R*,*S*) with higher yields, diastereo- and enantio-selectivities and shorter reaction times. Some other substituted bicyclo[2.2.1]octane and five-membered cyclic derivatives were also efficiently prepared under our Ni(OAc)$_2$-diamine-catalyzed system. In addition, the decrease in stereoselectivity caused by the base-induced epimerization was prevented in this catalyzed system.

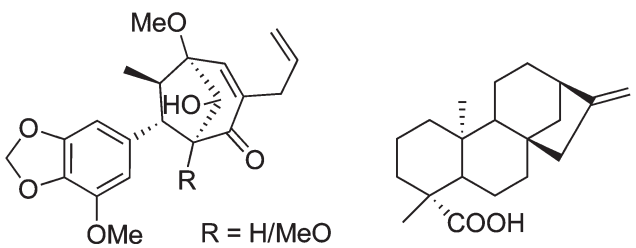

Fig. 1 Natural products with bicyclo[3.2.1]octane core.

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† Electronic supplementary information (ESI) available. CCDC 860005. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob25135c

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Results and discussion

At the outset of the study, we chose the benzylated diaminocyclohexane **3a** as the ligand to catalyze the reaction. To our delight, in the presence of 5 mmol% $Ni(OAc)_2$, the reaction reached completion within 5 h at room temperature to afford the desired product **4a** with 66% ee and 8 : 1 diastereoselectivity in 98% yield (Table 1, entry 1). Subsequently, we examined the reaction at a lower temperature; however, negative effects were observed when the reaction was performed at 0 and −18 °C. Switching the solvents had an obvious effect on the stereoselectivity of the reactions, with tetrahydrofuran proving to be the optimal solvent (Table 1, entry 4). With this promising lead in hand, we next sought to further optimize the reaction conditions. A series of chiral benzylated diaminocyclohexanes ligands **3b–e** were evaluated in the model reaction (Table 1, entries 7–10). Catalyst **3b** exhibited the most effective activity and afforded the product **4a** with a high diastereomeric ratio of 10 : 1 and excellent enantioselectivity of 98%. Replacing the protecting group at the nitrogen atom with a sterically bulky group (2-naphthyl) resulted in an increase of diastereoselectivity but an obvious decrease of enantioselectivity. Some other complexes based on ligand **3b** with various salts, such as $Cu(OAc)_2$ and $Zn(OAc)_2$ showed adverse inductive potential for this reaction (Table 1, entries 11 and 12).

With the optimized reaction conditions in hand, the substrate scope of this cascade reaction was explored by the reaction of 1,2-diones with various substituted nitroalkenes. For the reaction with the nucleophile **1a**, the majority of the reactions proceeded smoothly to furnish the corresponding masked bicyclo[3.2.1]-octane derivatives in high yields with excellent diastereo- and enantio-selectivities. The aromatic ring of aromatic nitroalkenes tolerated both electron-donating and electron-withdrawing functionalities at any other positions, although a 5 : 4 diastereoselective ratio was obtained when there was an *ortho*-bromine substituent at the aromatic ring. The substrate **2b** gave the best result: the corresponding adduct **4b** was offered in excellent yield with a 50 : 1 dr and a >99% ee value. The additions of heteroaromatic nitro-olefin derived from furyl proceeded equally well with excellent enantioselectivity and diastereoselectivity. The more sterically hindered nitroalkene bearing a 2-naphthyl group was also a suitable substrate. In addition, the corresponding adduct **4k** was prepared smoothly when the α-bromonitroalkene **2k** was used in the reaction.

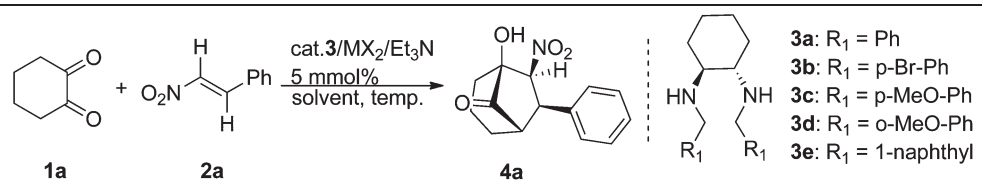
To evaluate the effectiveness of **3b**-$Ni(OAc)_2$ catalyst system in these reactions, several alkyl-substituted nitroalkenes were subjected to the optimized conditions. As shown in Table 2, excellent enantioselectivities with moderate to high diastereoisomeric ratios were obtained for the aliphatic nitroalkenes.

Furthermore, several different diones were evaluated and the 1,2-cyclopentanedione was found to be a good substrate for the present method. A high enantioselectivity (97% ee value) with an excellent diastereoselectivity (29 : 1 dr) was also obtained while the alkyl 3,4-hexanedione was used as a substrate.

It is worth noting that a base-catalyzed isomerization was observed in the Reuping's report: the longer reaction time lasted, the lower the diastereoisomeric ratio was obtained. However, long reaction time had none of adverse effect on the stereoselectivities in the benzylated diaminocyclohexane-$Ni(OAc)_2$ catalyzed system. The stereoselectivity of the reaction was maintained when the reaction time was prolonged from 6 hours to 48 hours. Thus, it suggested that comparing to the strong basicity exhibited by bifunctional thiourea catalyst, the Benzylated diaminocyclohexane-$Ni(OAc)_2$ catalyst system owned weaker basicity.

The relative and absolute configurations of the products were determined by X-ray crystal structure analysis of **4k** (Fig. 2).†

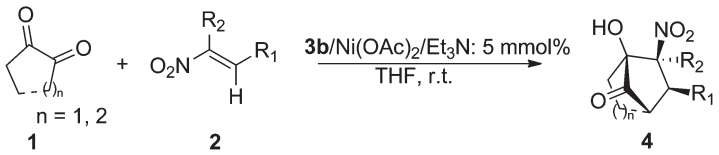
Table 1 Optimization of the initial reaction[a]

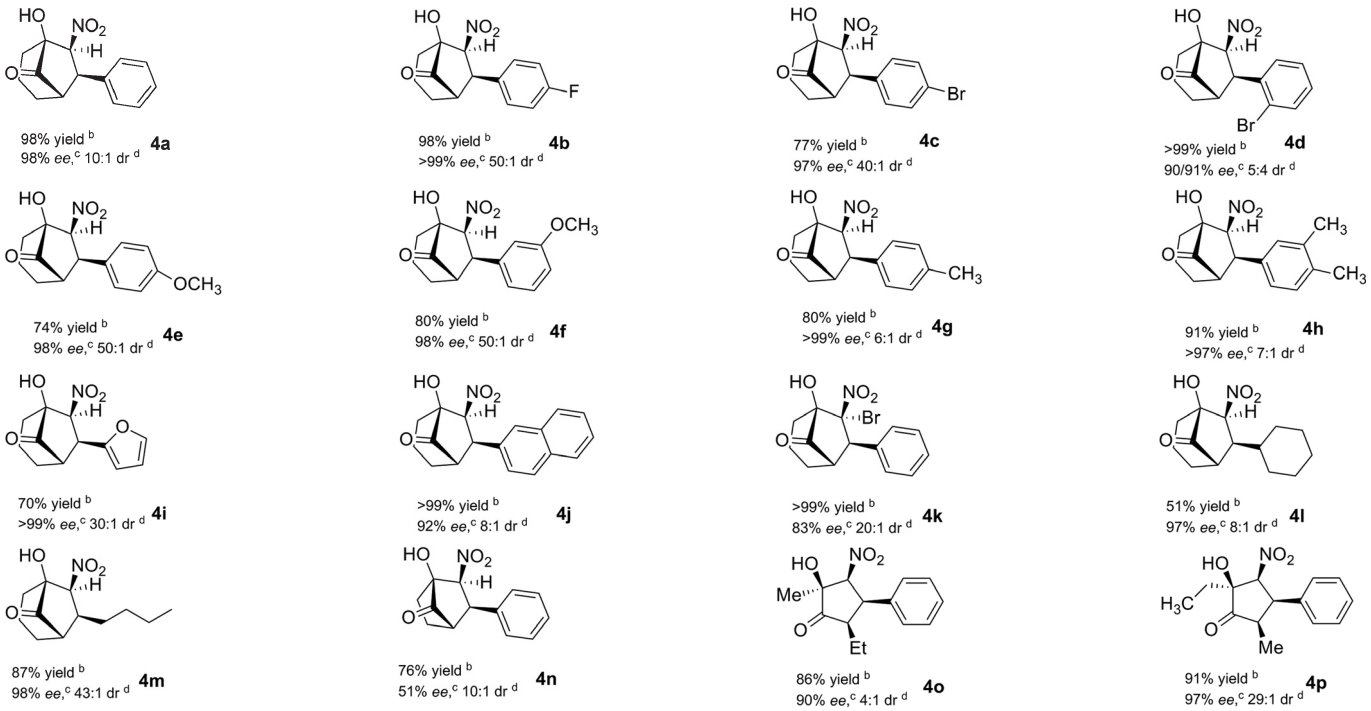


Entry	Cat./MX_2	Solvent	Time (h)	Yield[b] (%)	dr[c]	ee[d] (%)
1	**3a**/$Ni(Oac)_2$	*i*PrOH	5	98	8 : 1	66
2[e]	**3a**/$Ni(Oac)_2$	*i*PrOH	8	86	6 : 1	62
3[f]	**3a**/$Ni(Oac)_2$	*i*PrOH	12	77	7 : 1	46
4	**3a**/$Ni(OAc)_2$	THF	6	78	7 : 1	99
5	**3a**/$Ni(OAc)_2$	Toluene	3	62	5 : 1	85
6	**3a**/$Ni(OAc)_2$	MeOH	3	78	8 : 1	87
7	**3b**/$Ni(OAc)_2$	THF	6	98	10 : 1	98
8	**3c**/$Ni(OAc)_2$	THF	5	73	4 : 1	88
9	**3d**/$Ni(OAc)_2$	THF	6	83	25 : 1	89
10	**3e**/$Ni(OAc)_2$	THF	5	79	25 : 1	87
11	**3e**/$Cu(OAc)_2$	THF	6	—	6 : 1	20
12	**3e**/$Zn(OAc)_2$	THF	6	—	3 : 1	89

[a] Reaction conditions: 0.5 mL solvent, 1,2-cyclohexadione **1** (0.75 mmol), nitroalkene **2** (0.5 mmol), 5 mol% catalyst (cat. : MX_2 : EtN_3 = 1 : 1 : 1) at r.t. [b] Yields were determined after column chromatography. [c] Determined by ^1H NMR spectroscopy. [d] Enantiomeric excess was determined by HPLC. [e] The reaction was performed at 0 °C. [f] The reaction was performed at −18 °C.

Table 2 Scope of the reaction[a]





[a] Reaction conditions: 0.5 mL solvent, 1,2-cyclohexadione 1 (0.75 mmol), nitroalkene **2** (0.5 mmol), 5 mol% catalyst (**3b** : $Ni(OAc)_2$: EtN_3 = 1 : 1 : 1) at r.t. [b] Yields were determined after column chromatography. [c] Determined by ^1H NMR spectroscopy. [d] Enantiomeric excess was determined by HPLC.

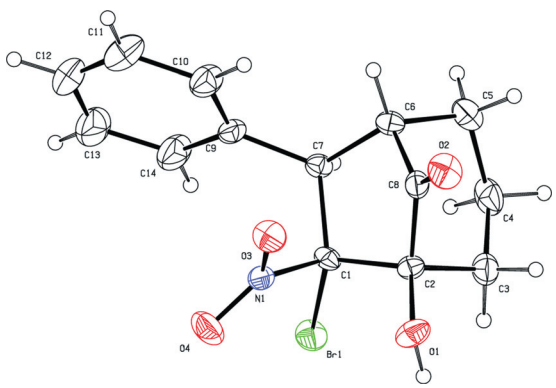
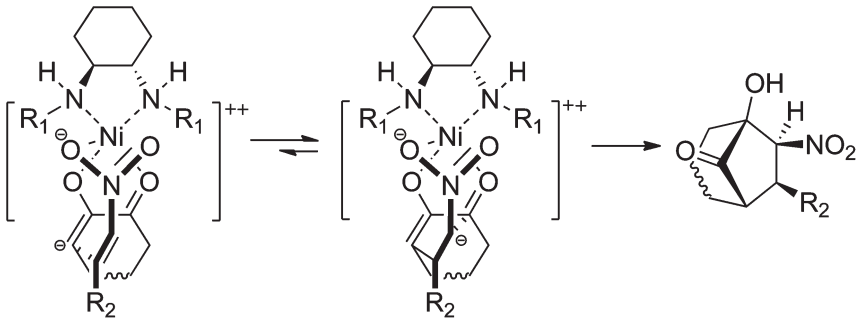


Fig. 2 X-ray Structure of the adduct **4k**.

On the basis of our experimental results and related studies, a possible model to account for the high stereoselectivity of the present reaction is shown in Scheme 1. We assume that at the beginning of the transition state the nitronate anion is stabilized by interaction at the open apical position on the nickel ion. A Michael addition then occurs with the activated metal enolate structure of the 1,2-diones. In the favored transition state, the substituted group of the nitro-olefin is oriented away from the bulky aromatic group of chiral ligand **3b**. The π–π stacking interaction between the enolate structure of the 1,2-dione and the double bond of nitro-olefin probably has a favorable effect on the stereoselectivity of the reaction. The resulting adduct subsequently undergoes an intramolecular Henry reaction to form the target product and is then released. Compared to the hydrogen bond interaction in the bifunctional thiourea catalyst, a strong complexation between the nickel and nitronate anion also induced the high stereoselectivity.

Conclusion

In summary, for the first time we are able to report a simple catalyst system assembled from enantiomerically pure diaminocyclohexane and $Ni(OAc)_2$ which has efficiently catalyzed the cascade Michael–Henry reaction of various 1,2-diones with substituted nitroalkenes. A series of polyfunctionalized bicyclo octane derivatives containing four consecutive stereogenic centers were obtained in excellent enantioselectivities (up to >99% ee) and diastereoselectivities (up to 50 : 1 dr) with high yields. Furthermore, *via* this catalyzed system, the base-induced epimerization leading to the decrease of stereoselectivity can be prevented.



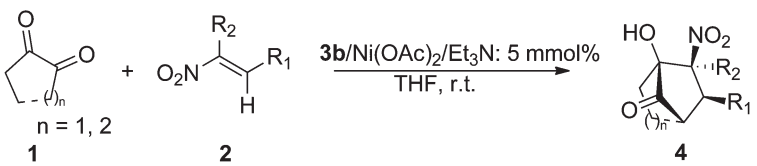
Scheme 1 Proposed reaction transition state.

Experimental

Materials

All reactions were monitored by thin layer chromatography (TLC) and column chromatography purifications were carried out using silica gel. All substrates were prepared according to the literature. ^{1}H NMR and ^{13}C NMR spectra were recorded (300 MHz and 75 MHz, respectively) using tetramethylsilane as internal reference. Data for ^{1}H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, q = quartet, hept = heptet, coupling constant(s) in Hz, integration). Data for ^{13}C NMR are reported in terms of chemical shift (δ, ppm). IR spectra were recorded on a FTIR spectrometer. Optical rotations were reported as follows: $[\alpha]_D^{20}$ (c: g 100 mL^{-1}, in solvent). HR-MS was measured with an APEX II 47e mass spectrometer. The ee value determination was carried out using chiral HPLC with Daicel Chiralcel AD-H, IA, OJ-H, AS column on Waters with a 996 UV-detector.

General procedure for the preparation of 4



Reaction conditions: 0.5 mL solvent, 1,2-cyclohexadione **1** (0.75 mmol), nitroalkene **2** (0.5 mmol), 5 mol% catalyst (**3b** : Ni(OAc)$_2$: EtN_3 = 1 : 1 : 1) at R.T. After the reaction was complete (as determined by TLC); the reaction mixture was concentrated, and the residue was purified by flash chromatography (petroleum ether–ethyl acetate, 5 : 1) to afford the product **4**.

(1*S*,5*S*,6*R*,7*S*)-1-Hydroxy-7-nitro-6-phenylbicyclo[3.2.1]octan-8-one (4a). A single diastereoisomer in 98% yield (diastereomeric ratio = 10 : 1). White solid. m.p. 143–150 °C. H NMR (300 MHz, $CDCl_3$): δ 7.37–7.28 (m, 3H), 7.17–7.14 (m, 2H), 4.77 (d, J = 5.7 Hz, 1H), 4.18 (d, J = 6 Hz, 1H), 3.28 (s, 1H), 2.81 (d, J = 2.1 Hz, 1H), 2.43–2.32 (m, 2H), 2.19–2.05 (m, 1H), 2.01–1.93 (m, 2H), 1.83–1.76 (m, 1H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 212.5, 142.3, 129.4, 127.9, 126.8, 93.7, 81.6, 51.6, 43.9, 39.9, 36.1, 18.0; IR ($CHCl_3$): 3444, 2952, 1763, 1549, 1451, 1370, 1334, 1137, 754, 701, 678 cm^{-1}; HRMS (ESI): $C_{14}H_{15}NO_4$ + NH_4, Calc: 279.1339, Found: 279.1335; $[\alpha]_D^{rt}$ = +16 (c = 1.0 in $CHCl_3$); HPLC: DAICEL CHIRALCEL OJ-H, *n*-hexane/*i*-PrOH = 90/10, flow rate = 1.0 mL min^{-1}, retention time: t_{major} = 17.4, t_{minor} = 22.6, 98% ee.

(1*S*,5*S*,6*R*,7*S*)-6-(4-Fluorophenyl)-1-hydroxy-7-nitrobicyclo-[3.2.1]octan-8-one (4b). A single diastereoisomer in 98% yield (diastereomeric ratio = 50 : 1). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.16–7.12 (m, 2H), 7.06–7.01 (m, 2H), 4.71 (d, J = 6 Hz, 1H), 4.17 (d, J = 6 Hz, 1H), 3.27 (s, 1H), 2.78 (s, 1H), 2.44–2.32 (m, 2H), 2.17–2.08 (m, 1H), 2.01–1.90 (m, 2H), 1.79–1.72 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.3, 138.2 (J_{C-F} = 3.75 Hz), 128.4 (J_{C-F} = 8.25 Hz), 116.3(J_{C-F} = 21.75 Hz), 93.7, 81.6, 51.7, 43.3, 39.8, 36.0, 17.9; IR ($CHCl_3$): 3444, 2954, 2927, 1763, 1550, 1511, 1452, 1370, 1335, 1231, 1138, 1100, 930, 835, 803, 672 cm^{-1}; HRMS (ESI): $C_{14}H_{14}NFO_4$ + NH_4, Calc: 297.1245, Found: 297.1242; $[\alpha]_D^{rt}$ = +9 (c = 1.0 in $CHCl_3$); HPLC: DAICEL CHIRALCEL OJ-H, *n*-hexane/*i*-PrOH = 95/5, flow rate = 1.0 mL min^{-1}, retention time: t_{major} = 60.6, t_{minor} = 70.2, >99% ee.

(1*S*,5*S*,6*R*,7*S*)-6-(4-Bromophenyl)-1-hydroxy-7-nitrobicyclo-[3.2.1]octan-8-one (4c). A single diastereoisomer in 77% yield (diastereomeric ratio = 40 : 1). White solid. m.p. 148–152 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50–7.45 (m, 2H), 7.06–7.02 (m, 2H), 4.70 (d, J = 6 Hz, 1H), 4.14 (d, J = 5.7 Hz, 1H), 3.24 (s, 1H), 2.79–2.76 (m, 1H), 2.45–2.30 (m, 2H), 2.18–2.07 (m, 1H), 2.03–1.86 (m, 2H), 1.81–1.72 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.1, 141.2, 132.5, 128.5, 121.9, 93.3, 81.5, 51.5, 43.4, 39.8, 36.0, 17.9; IR ($CHCl_3$): 3429, 2925, 1763, 1549, 1490, 1371, 1138, 1074, 1010, 825, 732 cm^{-1}; HRMS (ESI): $C_{14}H_{14}NBrO_4$ + NH_4, Calc: 357.0444, Found: 357.0439; $[\alpha]_D^{rt}$ = +12 (c = 1.0 in $CHCl_3$); HPLC: DAICEL CHIRALCEL OJ-H, *n*-hexane/*i*-PrOH = 90/10, flow rate = 1.0 mL min^{-1}, retention time: t_{minor} = 17.3, t_{major} = 22.4, 97% ee.

(1*S*,5*S*,6*R*,7*S*)-6-(2-Bromophenyl)-1-hydroxy-7-nitrobicyclo-[3.2.1]octan-8-one (4d). Both diastereoisomers in 99% yield (diastereomeric ratio = 5 : 4). White solid. m.p. 139–144 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62–7.59 (m, 1H), 7.34–7.29 (m, 1H), 7.18–7.13 (m, 1H), 7.02–6.99 (m, 1H), 5.09 (d, J = 6.3 Hz, 1H), 4.80 (d, J = 6.6 Hz, 1H), 3.31 (s, 1H), 2.63 (d, J = 3.9 Hz, 1H), 2.52–2.42 (m, 2H), 2.18–1.99 (m, 3H), 1.83–1.76 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.4, 140.7, 133.7, 129.4, 128.6, 128.2, 123.7, 91.8, 81.8, 52.5, 43.1, 40.4, 36.4, 17.9; IR ($CHCl_3$): 3428, 2928, 1763, 1551, 1471, 1445, 1369, 1139, 1027, 929, 753 cm^{-1}; HRMS (ESI): $C_{14}H_{14}NBrO_4$ + NH_4, Calc: 357.0444, Found: 357.0434; $[\alpha]_D^{rt}$ = −14 (c = 1.0 in $CHCl_3$); HPLC: DAICEL CHIRALCEL OJ-H, n-hexane/i-PrOH = 90/10, flow rate = 1.0 mL min^{-1}, retention time: t_{major} = 28.7, t_{minor} = 34.1, 90% ee, t_{major} = 58.5, t_{minor} = 79.4, 91% ee.

(1*S*,5*S*,6*R*,7*S*)-1-Hydroxy-6-(4-methoxyphenyl)-7-nitrobicyclo-[3.2.1]octan-8-one (4e). A single diastereoisomer in 74% yield (diastereomeric ratio = 50 : 1). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.10–7.05 (m, 2H), 6.88–6.83 (m, 2H), 4.73 (d, J = 5.7 Hz, 1H), 4.13 (d, J = 5.7 Hz, 1H), 3.79 (s, 3H), 3.27 (s, 1H), 2.77 (d, J = 2.7 Hz, 1H), 2.42–2.32 (m, 2H), 2.16–2.04 (m, 1H), 2.02–1.92 (m, 2H), 1.77–1.75 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.6, 159.1, 134.5, 127.8, 114.7, 94.1, 81.6, 55.3, 51.8, 43.2, 39.8, 36.0, 17.9; IR ($CHCl_3$): 3439, 2925, 1762, 1612, 1549, 1515, 1457, 1070, 1253, 1182, 1030, 831 cm^{-1}; HRMS (ESI): $C_{15}H_{17}NO_4$ + NH_4, Calc: 309.1445, Found: 309.1447; $[\alpha]_D^{rt}$ = +10 (c = 1.0 in $CHCl_3$); HPLC: DAICEL CHIRALCEL AD-H, n-hexane/i-PrOH = 80/20, flow rate = 1.0 mL min^{-1}, retention time: t_{major} = 56.7, t_{minor} = 65.4, 98% ee.

(1*S*,5*S*,6*R*,7*S*)-1-Hydroxy-6-(3-methoxyphenyl)-7-nitrobicyclo-[3.2.1]octan-8-one (4f). A single diastereoisomer in 98% yield (diastereomeric ratio = 50 : 1). White solid. m.p. 144–149 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26 (t, J = 8.1 Hz, 1H), 6.83–6.79 (m, 1H), 6.72–6.70 (m, 2H), 4.78 (d, J = 6 Hz, 1H), 4.15 (d, J = 6 Hz, 1H), 3.79 (s, 3H), 3.27 (s, 1H), 2.81 (d, J = 2.4 Hz, 1H), 2.43–2.32 (m, 2H), 2.17–2.05 (m, 1H), 2.00–1.91 (m, 2H), 1.80–1.73 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.4, 160.2, 143.8, 130.6, 118.7, 112.9, 112.8, 93.5, 81.6, 55.3, 51.5, 43.9, 39.8, 36.0, 17.9; IR ($CHCl_3$): 3439, 2937, 1763, 1602, 1549, 1454, 1370, 1267, 1050, 783, 699 cm^{-1}; HRMS (ESI): $C_{15}H_{17}NO_4$ + NH_4, Calc: 309.1445, Found: 309.1451; $[\alpha]_D^{rt}$ = +10 (c = 1.0 in $CHCl_3$); HPLC: DAICEL CHIRALCEL AD-H, n-hexane/i-PrOH = 80/20, flow rate = 1.0 mL min^{-1}, retention time: t_{major} = 33.6, t_{minor} = 45.2, 98% ee.

(1*S*,5*S*,6*R*,7*S*)-1-Hydroxy-7-nitro-6-p-tolylbicyclo[3.2.1]octan-8-one (4g). A single diastereoisomer in 80% yield (diastereomeric ratio = 6 : 1). Yellow solid. m.p. 135–143 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.14 (d, J = 8.0 Hz, 2H), 7.04 (d, J = 8.1 Hz, 2H), 4.75 (d, J = 5.9 Hz, 1H), 4.14 (d, J = 5.9 Hz, 1H), 3.34 (s, 1H), 2.78 (d, J = 2.5 Hz, 1H), 2.43–2.35 (m, 2H), 2.32 (s, 3H), 2.17–1.92 (m, 3H), 1.77–1.73 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.7, 139.3, 137.6, 130.0, 126.6, 93.8, 81.6, 51.7, 43.5, 39.8, 36.0, 21.0, 17.9; IR ($CHCl_3$): 3358, 2929, 2860, 2024, 1754, 1550, 1369, 1234, 1135, 1057, 930, 814, 672, 572, 513 cm^{-1}; HRMS (ESI): $C_{15}H_{17}NO_4$ + Na, Calc: 298.1050, Found: 298.1055; $[\alpha]_D^{rt}$ = +20 (c = 1.0 in $CHCl_3$); HPLC: DAICEL CHIRALCEL IA, n-hexane/i-PrOH = 90/10, flow rate = 1.0 mL min^{-1}, retention time: t_{major} = 20.4, t_{minor} = 30.0, >99% ee.

(1*S*,5*S*,6*R*,7*S*)-6-(3,4-Dimethylphenyl)-1-hydroxy-7-nitrobicyclo-[3.2.1]octan-8-one (4h). Both diastereoisomers in 91% yield (diastereomeric ratio = 7 : 1). Yellow solid. m.p. 123–126 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.08 (d, J = 7.7 Hz, 1H), 6.91–6.86 (m, 2H), 4.78 (d, J = 5.9 Hz, 1H), 4.11 (d, J = 5.9 Hz, 1H), 3.42 (s, 1H), 2.76 (d, J = 2.8 Hz, 1H), 2.41–2.31 (m, 2H), 2.22 (s, 6H), 2.11–1.93 (m, 3H), 1.81–1.74 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.9, 139.9, 137.8, 136.3, 130.5, 127.8, 124.1, 93.8, 81.7, 51.8, 43.5, 39.8, 36.1, 19.8, 19.4, 17.9; IR ($CHCl_3$): 3381, 2924, 2855, 2023, 1758, 1546, 1455, 1371, 1232, 1135, 1058, 933, 801, 715, 668 cm^{-1}; HRMS (ESI): $C_{15}H_{17}NO_4$ + Na, Calc: 312.1206, Found: 312.1217; $[\alpha]_D^{rt}$ = +12 (c = 1.0 in $CHCl_3$); HPLC: DAICEL CHIRALCEL IA, n-hexane/i-PrOH = 90/10, flow rate = 1.0 mL min^{-1}, retention time: t_{major} = 13.0, t_{minor} = 20.6, >97% ee.

(1*S*,5*S*,6*S*,7*S*)-6-(Furan-2-yl)-1-hydroxy-7-nitrobicyclo[3.2.1]-octan-8-one (4i). Both diastereoisomers in 70% yield (diastereomeric ratio = 30 : 1). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (d, J = 1.2 Hz, 1H), 6.31–6.30 (m, 1H), 6.19 (d, J = 3.3 Hz, 1H), 4.94 (d, J = 6 Hz, 1H), 4.30 (d, J = 5.7 Hz, 1H), 3.28 (s, 1H), 2.83 (d, J = 2.4 Hz, 1H), 2.43–2.29 (m, 2H), 2.15–2.05 (m, 1H), 2.02–1.86 (m, 2H), 1.78–1.70 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.1, 152.7, 143.1, 110.5, 106.5, 90.2, 81.2, 49.5, 39.8, 37.8, 35.5, 17.9; IR ($CHCl_3$): 3431, 2926, 1766, 1551, 1453, 1371, 1335, 1141, 1070, 934, 743 cm^{-1}; HRMS (ESI): $C_{12}H_{13}NO_5$ + NH_4, Calc: 269.1132, Found: 269.1138; $[\alpha]_D^{rt}$ = +48 (c = 1.0 in $CHCl_3$); HPLC: DAICEL CHIRALCEL OJ-H, n-hexane/i-PrOH = 95/5, flow rate = 1.0 mL min^{-1}, retention time: t_{major} = 33.5, t_{minor} = 40.0, >99% ee.

(1*S*,5*S*,6*R*,7*S*)-1-Hydroxy-6-(naphthalen-2-yl)-7-nitrobicyclo-[3.2.1]octan-8-one (4j). As both diastereoisomer in 99% yield (diastereomeric ratio = 8 : 1). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85–7.79 (m, 3H), 7.65 (s, 1H), 7.53–7.46 (m, 2H), 7.23–7.20 (m, 1H), 4.87 (d, J = 5.7 Hz, 1H), 4.36 (d, J = 6 Hz, 1H), 3.32 (s, 1H), 2.92 (d, J = 2.4 Hz, 1H), 2.46–2.37 (m, 2H), 2.21–2.01 (m, 3H), 1.86–1.75 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.5, 139.3, 133.3, 132.6, 129.7, 127.8, 127.7, 126.8, 126.4, 125.7, 124.2, 93.5, 81.7, 51.6, 44.1, 39.9, 36.1, 18.0; IR ($CHCl_3$): 3433, 2928, 1762, 1548, 1451, 1369, 1237, 1136, 1056, 818, 734, 478 cm^{-1}; HRMS (ESI): $C_{18}H_{17}NO_4$ + NH_4, Calc: 329.1496, Found: 329.1492; $[\alpha]_D^{rt}$ = +11 (c = 1.0 in $CHCl_3$); HPLC: DAICEL CHIRALCEL OJ-H, n-hexane/i-PrOH = 90/10, flow rate = 1.0 mL min^{-1}, retention time: t_{major} = 52.3, t_{minor} = 69.6, 92% ee.

(1*R*,5*S*,6*R*,7*R*)-7-Bromo-1-hydroxy-7-nitro-6-phenylbicyclo[3.2.1]-octan-8-one (4k). Both diastereoisomers in 99% yield (diastereomeric ratio = 20 : 1). Yellow solid. m.p. 178–188 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34–7.28 (m, 5H), 4.23 (d, J = 1.5 Hz, 1H), 3.28 (s, 1H), 3.25–3.23 (m, 1H), 2.60–2.55 (m, 1H), 2.27–2.11 (m, 4H), 1.88–1.79 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.8, 134.5, 128.8, 128.6, 128.5, 108.2, 85.2, 57.2, 48.7, 43.9, 36.6, 17.4; IR ($CHCl_3$): 3394, 2957, 1767, 1568, 1447, 1343, 1151, 1087, 1075, 1028, 918, 742, 730, 700 cm^{-1}; HRMS (ESI): $C_{14}H_{14}NBrO_4$ + NH_4, Calc: 357.0444, Found: 357.0439; $[\alpha]_D^{rt}$ = +8 (c = 1.0 in $CHCl_3$); HPLC: DAICEL CHIRALCEL AD-H, n-hexane/i-PrOH = 90/10, flow rate = 1.0 mL min^{-1}, retention time: t_{minor} = 21.1, t_{major} = 24.4, 82% ee.

(1*S*,5*S*,6*S*,7*S*)-6-Cyclohexyl-1-hydroxy-7-nitrobicyclo[3.2.1]-octan-8-one (4l). Both diastereoisomers in 51% yield (diastereomeric ratio = 8 : 1). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.62 (d, J = 6.3 Hz, 1H), 3.18 (s, 1H), 2.85 (t, J = 6.6 Hz, 1H), 2.56 (d, J = 3.9 Hz, 1H), 2.30–2.25 (m, 1H), 2.17–2.03 (m, 2H), 1.96–1.86 (m, 2H), 1.78–1.60 (m, 6H), 1.43–1.31 (m, 1H), 1.25–1.14 (m, 3H), 1.00–0.85 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 213.1, 89.5, 81.5, 47.1, 43.9, 41.7, 39.9, 36.1, 29.8, 29.3, 26.1, 25.9, 17.9; IR ($CHCl_3$): 3429, 2927, 2854, 1763, 1548, 1449, 1369, 1335, 1238, 1137, 1052, 932, 687 cm^{-1}; HRMS (ESI): $C_{14}H_{21}NO_4$ + NH_4, Calc: 285.1809, Found: 285.1817; $[\alpha]_D^{rt}$ = +52 (c = 1.0 in $CHCl_3$); HPLC: DAICEL CHIRALCEL OJ-H, *n*-hexane/*i*-PrOH = 90/10, flow rate = 1.0 mL min^{-1}, retention time: t_{minor} = 12.6, t_{major} = 16.5, 97% ee.

(1*S*,5*S*,6*S*,7*S*)-6-Butyl-1-hydroxy-7-nitrobicyclo[3.2.1]octan-8-one (4m). Both diastereoisomers in 87% yield (diastereomeric ratio = 43 : 1). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.4 (d, J = 5.4 Hz, 1H), 3.15 (s, 1H), 2.95 (q, J = 7.5, 13.5 Hz, 1H), 2.42–2.40 (m, 1H), 2.37–2.33 (m, 1H), 2.21–2.13 (m, 1H), 2.07–1.96 (m, 1H), 1.90–1.85 (m, 2H), 1.71–1.63 (m, 1H), 1.53–1.43 (m, 2H), 1.39–1.29 (m, 4H), 0.90 (t, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.5, 92.0, 81.4, 49.6, 39.8, 38.6, 35.7, 35.5, 28.6, 22.3, 18.1, 13.8; IR ($CHCl_3$): 3426, 2956, 2929, 2862, 1764, 1548, 1453, 1371, 1337, 1239, 1145, 1095, 1055, 678 cm^{-1} ; HRMS (ESI): $C_{12}H_{19}NO_4$ + NH_4, Calc: 259.1652, Found: 259.1648; $[\alpha]_D^{rt}$ = +41 (c = 1.0 in $CHCl_3$); HPLC: DAICEL CHIRALCEL OJ-H, *n*-hexane/*i*-PrOH = 90/10, flow rate = 1.0 mL min^{-1}, retention time: t_{minor} = 12.1, t_{major} = 15.7, 97% ee.

(1*S*,2*S*,3*R*,4*S*)-1-Hydroxy-2-nitro-3-phenylbicyclo[2.2.1]heptan-7-one (4n). Both diastereoisomers in 67% yield (diastereomeric ratio = 10 : 1). White solid. m.p. 170–175 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39–7.26 (m, 5H), 6.57 (s, 1H), 5.31 (dd, J = 13.8, 8.5 Hz, 1H), 4.92 (dd, J = 13.8, 7.4 Hz, 1H), 4.49 (t, J = 8.0 Hz, 1H), 2.50–2.35 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.3, 148.9, 141.8, 136.7, 129.3, 128.3, 127.9, 76.5, 45.4, 31.7, 24.7; IR ($CHCl_3$): 3313, 2919, 1696, 1655, 1546, 1407, 1348, 1304, 1230, 1220, 910, 758, 683 cm^{-1}; HRMS (ESI): $C_{14}H_{21}NO_4$ + Na, Calc: 270.0737, Found: 270.0741; $[\alpha]_D^{rt}$ = +75 (c = 1.0 in $CHCl_3$); HPLC: DAICEL CHIRALCEL IA, *n*-hexane/*i*-PrOH = 90/10, flow rate = 1.0 mL min^{-1}, retention time: t_{minor} = 24.0, t_{major} = 28.9, 50% ee.

(2*S*,3*S*,4*R*,5*R*)-5-Ethyl-2-hydroxy-2-methyl-3-nitro-4-phenylcyclopentanone (4o). Both diastereoisomers in 86% yield (diastereomeric ratio = 4 : 1). White solid. m.p. 164–169 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41–7.31 (m, 5H), 4.86 (d, J = 10.5 Hz, 1H), 4.00 (t, J = 10.8 Hz, 1H), 2.71 (s, 1H), 2.66–2.58 (m, 1H), 1.74 (m, 3H), 1.61 (s, 3H), 0.89 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.7, 137.5, 129.2, 128.1, 127.5 93.8 76.1 53.7, 46.3, 21.8, 20.9, 10.8; IR ($CHCl_3$): 3305,3031, 2920, 2024, 1688, 1653, 1548, 1409, 1377, 1351, 1126, 914, 763, 698, 642 cm^{-1}; HRMS (ESI): $C_{14}H_{21}NO_4$ + Na, Calc: 286.1050, Found: 286.1055; $[\alpha]_D^{rt}$ = +54 (c = 1.0 in $CHCl_3$); HPLC: DAICEL CHIRALCEL IA, *n*-hexane/*i*-PrOH = 90/10, flow rate = 1.0 mL min^{-1}, retention time: t_{minor} = 11.4, t_{major} = 23.5, 90% ee.

(2*S*,3*S*,4*R*,5*R*)-2-Ethyl-2-hydroxy-5-methyl-3-nitro-4-phenylcyclopentanone (4p). Both diastereoisomers in 91% yield (diastereomeric ratio = 29 : 1). White solid. m.p. 166–170 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44–7.30 (m, 5H), 5.05 (d, J = 9.6 Hz, 1H), 3.79 (dd, J = 12.4, 9.6 Hz, 1H), 2.72 (s, 1H), 2.62 (dq, J = 13.4, 6.7 Hz, 1H), 2.05–1.91 (m, 2H), 1.20 (d, J = 6.7 Hz, 3H), 1.03 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.8, 137.2, 129.3, 128.2, 127.3, 90.7, 79.2, 49.1, 47.8, 28.9, 12.2, 7.7; IR ($CHCl_3$): 3499, 2979, 2361, 2022, 1754, 1555, 1457, 1379, 1306, 1116, 753, 699 495 cm^{-1}; HRMS (ESI): $C_{14}H_{21}NO_4$ + Na, Calc: 286.1055, Found: 286.1049; $[\alpha]_D^{rt}$ = +111 (c = 1.0 in $CHCl_3$); HPLC: DAICEL CHIRALCEL AS, *n*-hexane/*i*-PrOH = 90/10, flow rate = 1.0 mL min^{-1}, retention time: t_{minor} = 14.3, t_{major} = 19.2, 97% ee.

Acknowledgements

We are grateful for the grants from the NSFC of China (20932003 and 90813012), the Key National S & T Major Project and Major New Drugs Development of China (2012ZX09504-001-003) and Young Scholar of Distinction for Doctoral Candidate of Lanzhou University.

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