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Diastereo- and enantioselective aldol reaction of granatanone (pseudopelletierine)

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ABSTRACT

Granatanone (granatan-3-one, 9-methyl-9-azabicyclo[3.3.1]nonan-3-one, pseudopelletierine or pseudopelletrierin) undergoes deprotonation with lithium amides giving a lithium enolate, which reacts with aldehydes diastereoselectively giving exclusively *exo* isomers and *anti*/*syn* selectivity up to 98:2. Granatanone can be enantioselectively lithiated by chiral lithium amides and the resulting non-racemic enolate can be reacted with aldehydes giving aldols with enantiomeric excess up to 93% (99% ee after recrystallization). The absolute and relative configuration of the aldol products was determined by NMR spectroscopy and X-ray analysis.

Granatanone; aldol reaction; asymmetric synthesis; enantioselective deprotonation; chiral lithium amide.

1. Introduction

Granatan-3-one or simply granatanone (**1**, 9-methyl-9-azabicyclo[3.3.1]nonan-3-one) known also as pseudopelletierine (or pseudopelletrierin) is an alkaloid from the bark of the pomegranate tree obtained synthetically via a Robinson–Schöpf type procedure.[1,2] The bicyclic skeleton of 9-azabicyclo[3.3.1]nonane is an important substructure of a variety of compounds, which possess anti-Parkinson's,[3] neuroleptic,[4,5] and hypotensive activity.[6] Granatanone and its derivatives were used for synthesis of potential cocaine-binding site ligands.[7] Aldol reaction of tropinone **2**, a homologue of granatanone **1** has been used successfully as a key step in the asymmetric syntheses[8] of several bioactive derivatives including cocaine[9] and some potentially biologically active alkaloids.[10,11] Related to granatanone tropane derivatives make numerous extensively studied ligands for biological receptors.[12,13] Interestingly the aldol reaction of granatanone which can allow for the stereocontrolled construction on the 9-azabicyclo[3.3.1]nonane scaffold was, to the best of our knowledge, not studied or reported. Herein we wish to describe the first diastereoselective and enantioselective directed aldol reactions of granatanone via a lithium enolate.

2. Results and discussion

Granatanone is a C_s symmetrical molecule with distinctly differentiated *exo* and *endo* sides. Thus subjection of granatanone to a deprotonation (lithiation) reaction with lithium amide bases would give a chiral lithium enolate (Scheme 1). Chiral lithium amides, which are capable of enantioselective deprotonation of ketones[14] should in theory give a non-racemic mixture of the lithium enolate. Enantioselective deprotonation of nor-granatanone Cbz derivative with a chiral lithium amide was used for the preparation of chiral silyl enol ethers by Momose.[15] Reaction of preformed chiral enolates with electrophiles should retain the asymmetry of the enolate and give non-racemic products. Such a strategy based on desymmetrization of ketones was successfully used previously for the synthesis of tropane derivatives.[10,16] By analogy to the known reactivity of the tropane analogue[10] electrophiles are expected to approach the granatanone enolate from a pseudo axial direction and give the *exo* products, despite that the *endo* isomers are usually more thermodynamically stable. Approach of electrophiles to cyclic enolates from the axial direction is usually favored stereoelectronically.[17,18]

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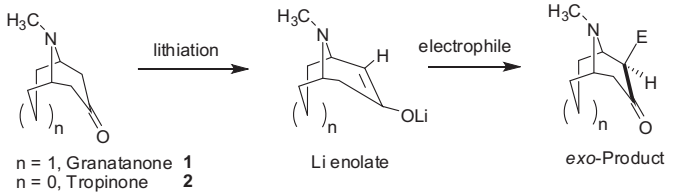
We have tested achievability of such stereocontrolled aldol reactions of granatanone lithium enolate generated with LDA and selected chiral lithium amides.

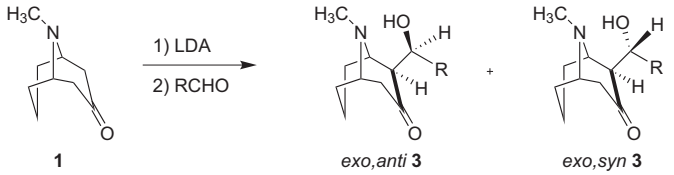


Scheme 1. Formation and reaction of tropinone and granatanone lithium enolates.

2.1. Diastereoselective aldol reaction of granatanone

Reaction of granatanone under standard conditions with LDA gave the lithium enolate which was reacted without isolation with selected aldehydes (Table 1). Such reactions of bicyclic ketones of type **1** or **2** can in principle give four diastereomers. Analysis of the crude product mixtures obtained by reacting aldehydes with the preformed lithium enolate showed high conversion to aldols. To our satisfaction the NMR spectra of the crude products indicated also high diastereomeric purity. The analysis of the spectra suggested the *exo* isomers to be the only detectable products. The assignment of signals was helped by comparison with the known tropane analogues and correlation spectroscopy (^{1}H–^{1}H and ^{1}H–^{13}C).

Table 1
Directed aldol reaction of granatanone via addition of lithium enolate to aldehyde



Entry	R	Yield of aldol **3** (%)	Ratio *exo*, *anti*: *exo*,*syn*	*exo*, *anti* ppm[a] (*J*, Hz)	*exo*, *syn* ppm[a,b] (*J*, Hz)
1	Ph	**3a**, 97	98:2	5.35 (d, 3.9)	5.09 (d, 1.76)
2	4-$NO_2C_6H_4$	**3b**, 98	92:8	5.33 (d, 3.1)	5.15 (d, 1.8)
3	1-Naphthyl	**3c**, 50	97:3	6.05 (d, 2.8)	5.43 (d, 3.7)
4	Me	**3d**, 93	85:15	4.19 (dq, J_1=6.3, J_2=2.6)	4.06 (dq, J_1=6.3, J_2=1.9)
5	*n*-Pentyl	**3e**, 60	89:11	4.02–3.97 multiplet	3.82–3.73 multiplet
6	*i*-Pr	**3f**, 98	96:4	3.51 (dd, J_1=9.5, J_2=2.6)	4.4 (d, J=3.6)
7	*p*-BrPh	**3g**, 94	>99:1	5.20 (d, J=3.3)	No data

[a] Characteristic signals found in ^{1}H NMR spectra of the crude product.
[b] Pure *exo*,*syn* aldols were not isolated.

Ratios of isomers *exo*,*syn* to *exo*,*anti* was inferred from integration of doublets corresponding to the carbinol hydrogens *CH*(OH)-R. The diastereoselectivity of the reaction was excellent in most cases. Slightly lower diastereomeric ratio of crude products was measured for reaction with acetaldehyde and hexanal (Table 1, entries 4 and 5). The aldols were fairly unstable to typical chromatography (decomposition and equilibration of diastereomers was observed). However, purification by precipitation followed by crystallization gave pure crystalline aldols derived from benzaldehyde **3a** and *p*-nitro benzaldehyde **3b**. Overall, the aldols were obtained in excellent yields (>90%) except for aldols derived from hexanal and naphthaldehyde which gave fair yields (50 and 60%, Table 1, entries 3 and 5). The relative configurations assigned based on NMR spectroscopic data were confirmed by X-ray structure determination of the products **3a** and **3b**. The crystal structures of the major aldol product **3a** (Fig. 1) and the

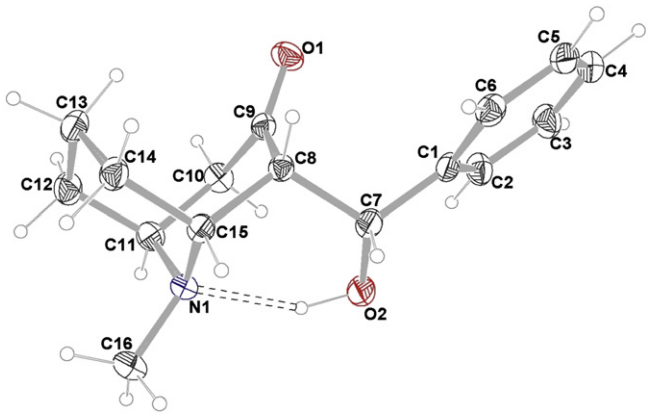


Fig. 1. X-ray structure of the major isomer of aldol synthesized via deprotonation with LDA (**3a**, *exo*,*anti*) showing intramolecular H-bond: N1···O2 2.753(2), N1···H 1.88(3) Å, N1···H–O2 angle 151(2)°. Displacement ellipsoids are drawn at 30% probability level, atoms numbering arbitrary.

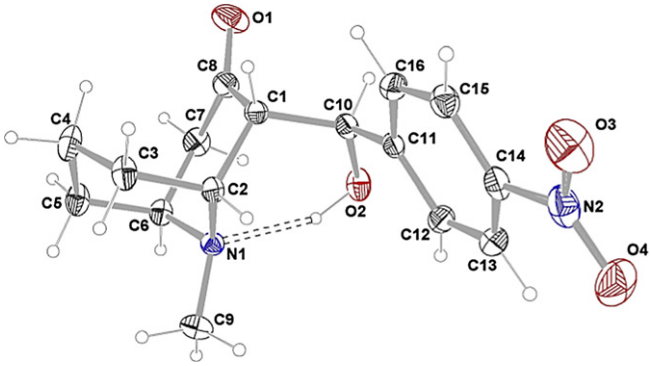
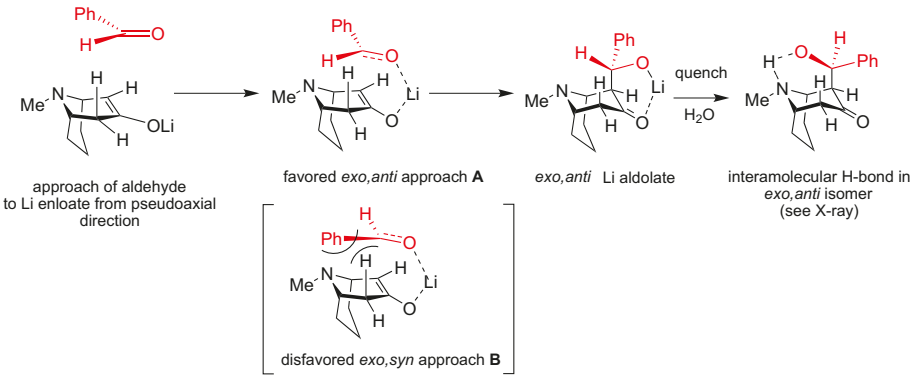


Fig. 2. X-ray structure of the minor isomer of aldol synthesized via deprotonation with LDA (**3b**, *exo*,*syn*) showing intramolecular H-bond: N1···O2 2.775(2), N1···H 1.93(2) Å, N1···H–O2 angle 152(2)°. Displacement ellipsoids are drawn at 30% probability level, atoms numbering arbitrary.

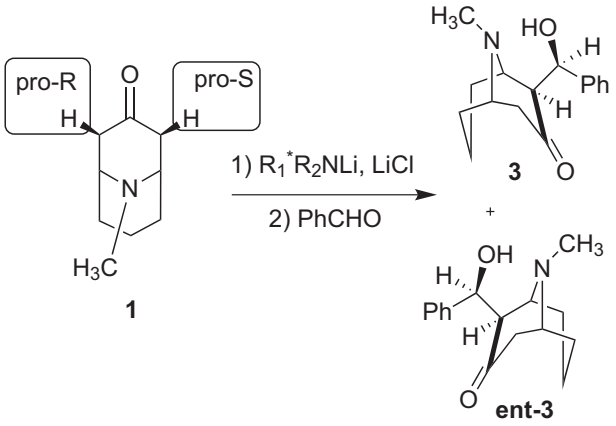
minor **3b** (Fig. 2) evidenced the presence of relatively strong intramolecular hydrogen bonds between the amine nitrogen and the aldol hydroxyl group (for geometry see Figs. 1 and 2). The other studied reactions also showed high *exo*,*anti* selectivity (Table 1). The high *exo* selectivity was expected by analogy to the known reactions of tropinone.[19,10] Accordingly effects such as the stereoelectronic preference of the electrophile for the axial approach to cyclic enolates[17,18,20] and steric hindrance of the *endo* approach may be responsible for the observed pseudo axial attack of the aldehyde on the preformed lithium enolate. To rationalize the observed *anti* selectivity one could consider stability of lithium aldolates directly formed in the reaction with aldehydes (Scheme 2). Owing to stabilizing O–Li–O bonding in aldolates and steric interactions the transition state for formation of the *exo*,*anti* isomers should be lower in energy compared to the *exo*,*syn* counterpart (Scheme 2). Close inspection of models of products **3** reveals possible steric congestion in the *exo*,*syn* isomer of the aldolate and resulting destabilizing steric interactions of the phenyl group with the axial hydrogen on C-4 and the rest of the piperidine ring of the granatanone scaffold (**B** vs **A**). Even though under the applied experimental conditions, the reactions are most likely kinetically controlled the same interactions may influence the stabilities of competing transition states. The transition state leading to *exo*,*anti* lithium aldolate most likely benefits from diminished steric interactions of the R group of the aldehyde with the nitrogen bridge and C-4 hydrogen as shown in favored *exo*,*anti* approach **A** (Scheme 2). This type of interaction in approaching reactants could account for the somewhat lowered diastereoselectivity in case of less sterically demanding aldehydes: acetaldehyde and hexanal.



Scheme 2. Rationalization of observed *anti* diastereoselectivity of the aldol reaction.

2.2. Diastereoselective and enantioselective aldol reaction of granatanone

The reaction with benzaldehyde was studied as a representative example. The enantiomeric excess of aldol product **3a** was measured by NMR spectroscopy in the presence of (*R*)-(-)-2,2,2-trifluoro-1-(9-anthryl)ethanol and was confirmed by HPLC analysis on chiral stationary phase (urethane derivatives of **3a** and **3f**). The enantioselective deprotonation of granatanone (Scheme 3) was probed with four selected, well known chiral lithium amides[14,21–23] (Fig. 3, **4**–**7**). For optimum selectivity lithium chloride, which is known to interact with aggregated lithium amides improving enantioselectivity, was used as an additive.[24] The amount of LiCl used was based on previous optimization studies except for lithium amide **7**, which was not studied before in this capacity. A short optimization of the amount of additive for lithium amide **7** (Table 2, entries 4–7) showed very good results for 0.25–1.0 equiv of LiCl. Using chemical shifts of enantiomers in the presence of chiral solvating agent it was possible to correlate absolute configuration of the major aldol product formed with studied lithium amides. It turned out that lithium amide **7** gave the aldol with opposite absolute configuration to that with lithium amides **4**–**6**.



Scheme 3. Enantioselective aldol reaction of granatanone lithium enolate.

The diastereoselectivity of the aldol reaction remained very high (>95%) with strong preference for *exo*,*anti* isomers with all lithium amides studied. The highest enantioselectivity (93% ee) was obtained with Koga-type bidentate lithium amide **4**. The enantiomeric and diastereomeric excess of products could be boosted by careful crystallization to excellent levels (typically 93–98%). The enantiomeric excess of aldols was unaffected by variation of

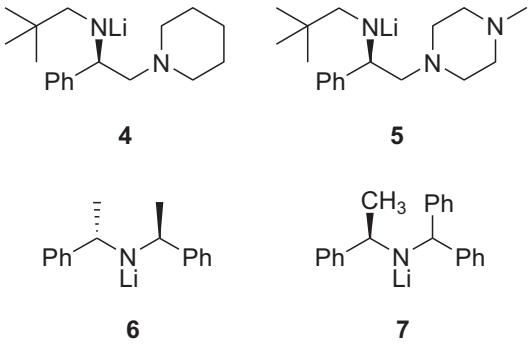


Fig. 3. Chiral lithium amides used for deprotonation of granatanone.

Table 2
Enantioselectivity of aldol reaction resulting from enantioselective deprotonation of granatanone with chiral lithium amides

Entry	Chiral lithium amide	Equiv of LiCl additive	Yield of precipitated product (%)	Major enantiomer	Product % ee
1	**4**	1.0	67	*ent*-**3a**	−93 (98.7[a])
2	**5**	0.5	72	*ent*-**3a**	−87
3	**6**	1.0	81	*ent*-**3a**	−77
4	**7**	1.0	60	**3a**	82
5	**7**	0.5	78	**3a**	83 (93[a,b])
6	**7**	0.25	96	**3a**[b]	80
7	**7**	None	86	**3a**	65
8	**7**	0.5	84	**3g**	89 (99[a,b])

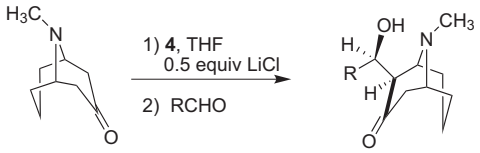
[a] The enantiomeric excess after a single recrystallization.
[b] The absolute structure of this product was determined by X-ray crystallographic analysis.

aldehyde acceptor and remained very high (81–95% ee for crude product, Table 3). The observed lower enantioselectivity of the aldol reaction with acetaldehyde (Table 3, entry 2) is most likely a result of high reactivity of the aldehyde and technical problems (volatility) with controlling the reaction temperature during reagent addition.

2.3. Absolute configuration of deprotonation of granatanone with lithium amides

The absolute configuration and enantiomeric purity of formed aldols of granatanone depended primarily on enantiotopic group selective proton removal from either left or right side of the C_s symmetrical molecules of granatanone (Scheme 3). For granatanone one should expect the same absolute sense of proton abstraction as observed for tropinone and other cyclic ketones

Table 3
Enantioselective and diastereoselective aldol reaction of granatanone with chiral lithium amide **4**



Entry	R	Yield of precipitated product (%)	ee of crude product (%)	ee after single recrystallization (%)
1	Ph	67	93	98.7
2	CH_3	72	81	81
3	1-Naphthyl	75	90	99
4	*i*-Pr	67	93	99

before.[14] The formed chiral enolate reacts with aldehyde in the presence of a chiral amine originally used for preparation of lithium amide. Because of the presence of the chiral amine, in principle, the enantioselection could also operate at the stage of the reaction with electrophile (different rates of reaction of two enantiomeric enolates with aldehydes in the presence of chiral amine). However, under the reaction conditions (excess of aldehyde, high reactivity of aldehydes toward enolates) the preferential reaction of one of the enantiomers of the non-racemic enolate mixtures (kinetic resolution) in the presence of the chiral amine (complexed or not with enolate[25–27]) is not significant and should not affect the overall enantioselectivity.

The absolute sense of deprotonation was inferred from X-ray analysis of the enantiomerically pure product (+)-**3a** (Fig. 4), obtained with chiral amide (*R*)-**7**. Absolute structure of (+)-**3a** was determined via anomalous scattering on the basis of 2263 Friedel pairs measured at 150 K, with refined Flack parameter −0.01(14). Additional proof came from determination of the absolute stereochemistry of a more suitable for crystallography, deprotonation product, the bromine containing aldol (+)-**3g**, which was synthesized in enantiomerically enriched form with help of amide (*R*)-**7** (Table 2, entry 8 and Fig. 5). Flack parameter for (+)-**3g** was 0.074(14), for 2340 Friedel pairs measured at 150 K. It turned out indeed that the preference of deprotonation of granatanone with lithium amides was the same as observed previously for tropinone.[10] In order to rationalize the preference of amide **6** for deprotonation of cyclic ketones a model has been proposed by Majewski and Gleave,[28] later on criticized by Simpkins.[29] As a rationalization of the preference of amide (*R*)-**7** for

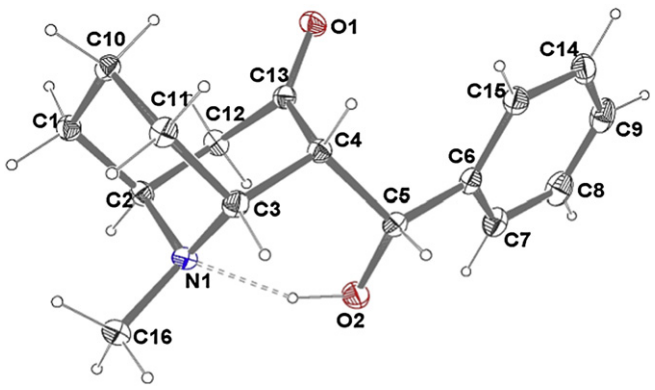


Fig. 4. X-ray structure of aldol (+)-**3a** synthesized via deprotonation of granatanone with lithium amide (*R*)-**7** showing C(4)-*S* and C(5)-*R* configuration. Thermal ellipsoids drawn at 30% probability level, atoms numbering arbitrary.

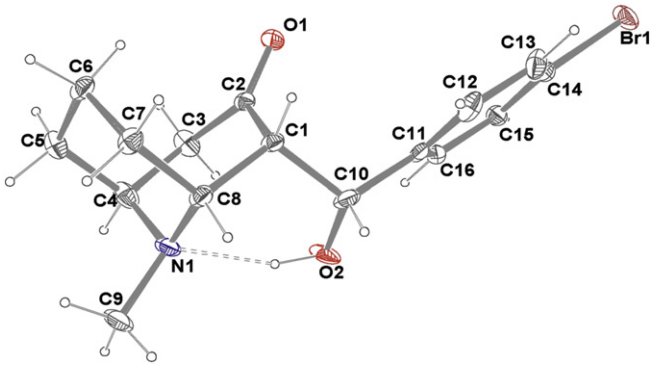


Fig. 5. X-ray structure of aldol (+)-**3g** synthesized via deprotonation of granatanone with lithium amide (*R*)-**7** showing C(1)-*S* and C(10)-*R* configuration. Thermal ellipsoids drawn at 30% probability level, atoms numbering arbitrary.

removal of the pro-R hydrogen of granatanone we propose to consider interactions in the complex of lithium amide with granatanone molecule. Complexation of carbonyl compound with lithium amides prior deprotonation has been observed experimentaly.[25–27] Dissociation of chiral lithium amide dimmer or aggregate with LiCl prior complexation with ketone is implicitly supposed. For simplicity our rational does not take into account interactions with LiCl. These, however, should not make a qualitative difference because in the studied cases addition of LiCl did not change overall absolute sense of proton abstraction. The destabilizing interactions between methyl group at the stereogenic carbon atom of the lithium amide in the R-**7**/pro-S complex which are absent in the competing R-**7**/pro-R complex could be responsible for preference of the latter (Fig. 6). Consequently formation of the favored complex of the chiral amide R-**7** could explain the experimentally observed preferred absolute sense of proton abstraction.

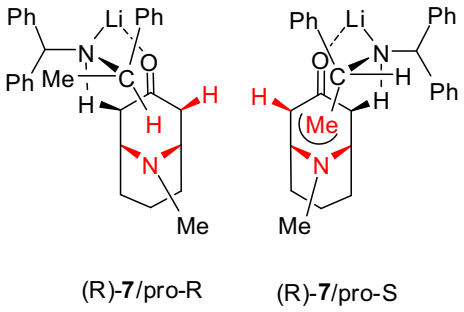


Fig. 6. Favored (left) and disfavored (right) approach of lithium amide reagent (*R*)-7 to granatanone. Sterically interacting groups marked in red.

3. Conclusion

Granatanone (pseudopelletierine) is an interesting scaffold which can be used for stereoselective functionalization and build-up of carbon skeleton through deprotonation with lithium amides. Aldol reaction of granatanone lithium enolates obtained by enantioselective lithiation by chiral lithium amides can provide aldols in high diastereomeric and enantiomeric purity. The preferred diastereomer (*exo*,*anti*) is obtained with great selectivity regardless of lithium amide used. The highest enantioselection is observed with Koga-type bidentate lithium amide **4** (93% ee), however the benzhydryl derivative of commercial phenylethylamine **7** may serve as an economical alternative when work-up is combined with product crystallization. Such economical protocol provided enantiomeric purity of 93–99% ee.

4. Experimental section

4.1. General methods

Thin-layer chromatography (TLC) was performed on pre-coated plates (Merck, silica gel 60, F_{254}). The spots were detected using UV light (254 nm), and phosphomolybdic acid followed by charring. Infrared (IR) spectra of compounds were recorded on a Nicolet Magna-IR 550 FTIR Series II Spectrometer ($CHCl_3$). Only diagnostic peaks are reported (cm^{-1}). Magnetic resonance spectra (^1H NMR and ^{13}C NMR) were recorded on a Bruker AVANCE II 400 spectrometer in $CDCl_3$ at ambient temperature. Chemical shifts are reported in parts per million downfield of tetramethylsilane. Specific rotation was measured with Optical Activity AA-10R Automatic Polarimeter. Reagents were purchased from Aldrich. Granatanone was synthesized as described[2] and sublimed before use. 4-Nitrobenzaldehyde was used without purification. Aldehydes were purified by standard techniques.[30] Crystallographic data were collected with a Bruker–Nonius Apex-X8 CCD-diffractometer with Cu Kα radiation (λ=01.54178 Å) at 150 K. The structures were solved by direct methods and refined using SHELXS97[31] and SHELXL97[31] programs. All non-H atoms were refined anisotropically; all H-atoms bonded to carbon atoms were placed on geometrically calculated positions and refined using a riding model. The hydroxyl H-atoms in three structures were located from $\Delta\rho$ maps and refined isotropically. Anomalous scattering method was used for absolute structure determination.[32]

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 815108, 815107, 815109, and 842429, respectively for compounds **3a**, *exo*,*syn*-**3b**, (+)-**3a** and (+)-**3g**. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.Uk).

4.2. General procedure for diastereoselective aldol reaction (with LDA)

To a cooled to 0 °C, stirred solution of DIPA (0.17 mL, 1.2 mmol) in THF (3 mL) was added *n*-BuLi (0.50 mL, 1.2 mmol, 2.40 M) in hexanes. After 30 min the mixture was cooled to −78 °C and solution of granatanone (0.153 g, 1.0 mmol) in THF (3 mL) was added dropwise. After 1 h aldehyde (1.2 mmol), was added and the reaction mixture was stirred for 15 min. Then the reaction was quenched with aq satd NH_4Cl solution (6 mL). The mixture was warmed up to rt and extracted with dichloromethane (4×10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The resulting crude product was dissolved in small portion of dichloromethane (ca. 1 mL) and treated with hexane until precipitation. The precipitated solid product was dried under vacuum. The crude product **3e**, which was an oil, was vacuum dried only.

4.3. General procedure for diastereoselective and enantioselective aldol reaction (with chiral Li amides 4–7)

To a cooled to 0 °C, stirred solution of chiral amine corresponding to lithium amide **4**–**7** (1.2 mmol) in THF (3 mL) was added *n*-BuLi (0.50 mL, 1.2 mmol, 2.40 M) in hexanes. After 30 min anhydrous LiCl (0.25–1.0 mmol) was added in THF (2 mL) and the mixture was stirred for 10 min. Then the mixture was cooled to −78 °C and solution of granatanone (0.153 g, 1.0 mmol) in THF (3 mL) was added dropwise. After 1 h aldehyde (1.2 mmol), was added and the reaction mixture was stirred for 15 min. Then the reaction was quenched with aq satd NH_4Cl solution (6 mL). The mixture was warmed up to rt and extracted with dichloromethane (4×10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The resulting crude product was dissolved in small portion of dichloromethane (ca. 1 mL) and treated with hexane until precipitation. The precipitated solid product was washed with hexane from remaining chiral amine and dried under vacuum. Yields of precipitated products are given in Tables 2 and 3.

*4.3.1. 2-(Hydroxy(phenyl)methyl)-9-methyl-9-azabicyclo[3.3.1]nonan-3-one (exo,anti-**3a**).* Yield (0.252 g; 97%) after precipitation; analytical sample was recrystallized from diethyl ether; mp: 103–106 °C; R_f 0.38 (10% CH_3OH/CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.72 (br s, 1H), 7.36–7.30 (m, 5H), 5.35 (d, J=3.9 Hz, 1H), 3.45 (d, J=3.9 Hz, 1H), 3.42–3.38 (m, 1H), 3.09 (dd, J_1=6.9 Hz, J_2=16.3 Hz, 1H), 2.82 (s, 3H), 2.61 (d, J=3.8 Hz, 1H), 2.47(d, J=16.3 Hz, 1H), 2.16–2.10 (m, 2H), 1.61–1.57 (m, 2H), 1.42–1.37 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 208.8, 141.5, 128.0, 127.3, 125.4, 77.7, 61.1, 60.5, 54.2, 48.5, 39.8, 22.5, 22.4, 16.5; IR ($CHCl_3$) ν: 3066, 2945, 1703, 1129 cm^{-1}; HRMS (ESI): m/z calcd for ($C_{16}H_{21}NO_2 \cdot Na$): 282.1470, found: 282.1465.

Crystal data for $C_{16}H_{21}NO_2$ (*rac*-**3a**): M_W 259.34, monoclinic, space group $P2_1/c$, a=12.2438(3), b=11.2004(3), c=11.1808(3) Å, β=115.9850(10)°, V=1378.28(6) Å^3, Z=4, D_c=1.250 mg m^{-3}, $F(000)$=560, crystal dimension 0.36×0.30×0.09 mm, radiation Cu Kα (λ=01.54178 Å). 12502 reflections were collected in the range of $-14\leq h\leq 13$, $-12\leq k\leq 12$, $-12\leq l\leq 13$; of these 2329 were independent, R(int)=0.042. The structure was solved and refined using 2096 reflections with $I>2\sigma$. Final R and R_w were 0.0369 and 0.0934, respectively.

Enantiomerically enriched (−)-**3a** prepared with lithium amide **4**: ee=93% [^1H NMR in the presence of (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol] measured on the crude product.

$[\alpha]_D^{20}$ −40.5 (*c* 1.0, $CHCl_3$), Mp 115–117 °C after recrystallization from hexane.

Crystal data for $C_{16}H_{21}NO_2$ (+)-**3a** (prepared with lithium amide **7**): M_W 259.34, orthorhombic, space group $P2_12_12_1$, a=10.2382(2), b=12.1544(2), c=21.9542(4) Å, V=2731.96(9) Å^3, Z=8, D_c=1.261 mg m^{-3}, $F(000)$=1120, crystal dimensions 0.57×0.38×0.34 mm, T=150 K, radiation Cu Kα (λ=1.54178 Å). 21,253 reflections were collected in the range of $-12\leq h\leq 9$, $-14\leq k\leq 14$, $-226\leq l\leq 26$; of these 5096 were independent, R(int)=0.047. The structure was solved and refined using 4997 reflections with $I>2\sigma(I)$. Final R and R_w were 0.0330 and 0.0871, respectively. Absolute structure (Flack) parameter was −0.01(14) for 2163 Friedel pairs.

*4.3.2. 2-(Hydroxy(4-nitrophenyl)methyl)-9-methyl-9-azabicyclo[3.3.1]nonan-3-one (exo,anti-**3b**).* Yield (0.298 g; 98%) after precipitation; analytical sample was recrystallized from mixed solvent (dichloromethane/hexane); mp: 149–152 °C; R_f 0.30 (AcOEt, decomposition); ^1H NMR (400 MHz, $CDCl_3$) δ: 8.16 (d, J=8.8 Hz, 2H), 7.99 (br s, 1H), 7.44 (d, J=8.8 Hz, 2H), 5.33 (d, J=3.1 Hz, 1H), 3.43 (d, J=4.21 Hz, 1H), 3.35–3.28 (m, 1H), 2.87 (dd, J_1=16.4 Hz, J_2=7.0 Hz, 1H), 2.74 (s, 3H), 2.60–2.56 (m, 1H), 2.42 (d, J=16.4 Hz, 1H), 2.22–2.06 (m, 2H), 1.62–1.45 (m, 2H), 2.40–2.27 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 207.9, 149.1, 147.0, 126.3, 123.3, 77.0, 60.8, 60.1, 54.0, 48.6, 39.8, 22.5, 22.4, 16.4; IR ($CHCl_3$) ν: 2946, 2902, 1705, 1522, 1349, 1127 cm^{-1}; HRMS (ESI): m/z calcd for ($C_{16}H_{20}N_2O_4Na$): 327.1321, found: 327.1309.

*4.3.3. exo,syn-2-[Hydroxy(4-nitrophenyl)methyl]-9-methyl-9-azabicyclo[3.3.1]nonan-3-one (exo,syn-**3b**).* Tedious crystallizations from remaining mother liquor gave a fraction of minor isomer of **3b**. Recrystallized from mixed solvent (dichloromethane–hexane), mp 172–174 °C (decomp.); R_f: 0.52 (5% MeOH/DCM); ^1H NMR

($CDCl_3$, 400 MHz): 8.26–8.23 (m, 2H), 7.94 (br s, 1H), 7.64–7.62 (m, 2H), 5.13 (d, J=1.7 Hz, 1H), 3.37–3.29 (m, 1H), 3.16 (dd, J=17.2 Hz, 7.2 Hz, 1H), 2.92 (d, J=4.4 Hz, 1H), 2.65 (s, 3H), 2.58 (d, J=17.2 Hz, 1H), 2.48 (s, 1H), 2.12–2.02 (app tt, J=13.7 Hz, 4.3 Hz, 1H), 2.00–1.89 (app tt, J=14.0 Hz, 4.9 Hz, 1H), 1.65–1.42 (m, 1H) 1.39–1.31 (m, 1H), 1.01–0.96 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): 210.6, 151.4, 147.2, 126.5, 123.7, 75.9, 59.4, 54.1, 53.7, 46.9, 39.8, 22.7, 22.5, 16.3; IR ($CHCl_3$) ν: 2944, 2871, 1705, 1601, 1522, 1470, 1346, 1079, 856 cm^{-1}; HRMS (ESI): calculated for ($C_{16}H_{20}N_2O_4Na$): 327.1321, found: 327.1314.

Crystal data for $C_{16}H_{20}N_2O_4$ (minor isomer *rac*-**3b**): M_W 304.34, triclinic, space group $P(-)1$, a=6.2540(1), b=7.2689(2), c=17.5157(4) Å, α=80.350(1), β=89.170(1), γ=70.369(1)°, V=738.61(3) $Å^3$, Z=2, D_c=1.368 mg m^{-3}, F(000)=324, crystal dimensions 0.45×0.23×0.07 mm, radiation Cu Kα (λ=1.54178 Å). 12667 reflections were collected in the range of $-7\leq h\leq 7$, $-8\leq k\leq 8$, $-20\leq l\leq 20$; of these 2483 were independent, R(int)=0.031. The structure was solved and refined using 2290 reflections with $I>2\sigma$. Final R and R_w were 0.0402 and 0.1079, respectively.

*4.3.4. 2-(Hydroxy(naphthalen-1-yl)methyl)-9-methyl-9-azabicyclo [3.3.1]nonan-3-one (**3c**).* Yield (0.155 g; 50%) after precipitation; analytical sample was recrystallized from mixed solvent (dichloromethane/hexane); mp: 125–128 °C; R_f 0.46 (10% CH_3OH/CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.90–7.86 (m, 2H), 7.78 (d, J=8.2 Hz, 1H), 7.62 (d, J=7.2 Hz, 1H), 7.50–7.47 (m, 3H), 6.05 (d, J=2.8 Hz, 1H), 3.53–3.50 (m, 1H), 3.40–3.30 (m, 1H), 3.05 (dd, J_1=7.0 Hz, J_2=16.2 Hz), 2.84–2.80 (m, 1H), 2.77 (s, 1H), 2.44 (dd, J_1=1.2 Hz, J_2=16.2 Hz), 2.20–2.10 (m, 2H), 1.60–1.50 (m, 2H), 1.40–1.30 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 208.5, 136.9, 133.6, 129.9, 129.2, 127.9, 125.9, 125.3, 125.1, 123.1, 121.9, 74.2, 60.7, 59.6, 54.2, 48.5, 39.9, 22.7, 22.6, 16.6; IR ($CHCl_3$) ν: 3063, 2945, 2820, 1704, 1512, 1128 cm^{-1}; HRMS (ESI): m/z calcd for ($C_{20}H_{23}NO_2Na$): 332,1626, found: 332.1640.

Enantiomerically enriched prepared with lithium amide **4**:

ee=90% [^{1}H NMR in the presence of (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol] measured on the crude product.

$[\alpha]_D^{20}$ −64.1 (c 1.0, $CHCl_3$), Mp 141–144 °C after recrystallization from hexane.

*4.3.5. 2-(1-Hydroxyethyl)-9-methyl-9-azabicyclo[3.3.1]nonan-3-one (exo,anti-**3d**).* Yield (0.183 g; 93%) after precipitation; analytical sample was recrystallized from mixed solvent (dichloromethane/hexane); Mp: 109–111 °C; R_f 0.47 (10% CH_3OH/CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.80 (br s, 1H), 4.22–4.16 (dq, J_1=6.3 Hz, J_2=2.6 Hz, 1H), 3.25–3.20 (m, 1H), 3.18 (d, J=4.2 Hz, 1H), 2.83 (dd, J_1=16.4 Hz, J_2=7 Hz, 1H), 2.66 (s, 3H), 2.41 (d, J=16.4 Hz, 1H), 2.19 (s, 1H), 2.16–2.00 (m, 2H), 1.60–1.52 (m, 2H), 1.30–1.25 (m, 2H), 1.09 (d, J=6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 210.5, 71.8, 61.2, 59.5, 54.0, 48.5, 39.8, 22.6, 22.5, 20.8, 16.7; IR ($CHCl_3$) ν: 2980, 2943, 1698, 1156, 1127 cm^{-1}; MS (EI) m/z: 197 (2), 110 (87), 96 (100), 94 (30), 57 (21), 43 (23), 42 (87), 41 (27); HRMS (ESI): m/z calcd for ($C_{11}H_{19}NO_2Na$): 220.1313, found: 220.1320.

Enantiomerically enriched prepared with lithium amide **4**:

ee=81% [^{1}H NMR in the presence of (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol] measured on the crude product.

$[\alpha]_D^{20}$ +49.4 (c 1.0, $CHCl_3$), Mp 112–114 °C after recrystallization from heptane.

*4.3.6. 2-(1-Hydroxyhexyl)-9-methyl-9-azabicyclo[3.3.1]nonan-3-one (exo,anti-**3e**).* Yield (0.152 g; 60%); R_f 0.50 (10% CH_3OH/CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.04 (br s, 1H), 4.02–3.97 (m, 1H), 3.25–3.21 (m, 1H), 3.19 (d, J=4.0 Hz, 1H), 2.85 (dd, J_1=7.0 Hz, J_2=16.3 Hz), 2.68 (s, 3H), 2.43 (d, J=16.3 Hz, 1H), 2.30 (s, 1H), 2.10–2.02 (m, 2H), 1.60–1.52 (m, 2H), 1.45–1.22 (m, 10H), 0.92–0.83 (t, J=7.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 210.7, 76.1, 61.3, 58.2, 54.2, 48.6, 39.8, 35.0, 31.7, 25.5, 22.6, 22.5, 22.4, 16.8, 14.0; IR ($CHCl_3$) ν: 2935, 2860, 1698, 1153, 1127 cm^{-1}; MS (EI) m/z: 253 (1), 182 (48), 110 (67), 96 (100), 57 (35), 43 (43), 42 (75), 41 (65); HRMS (ESI): m/z calcd for ($C_{15}H_{27}NO_2Na$): 276.1939, found: 276.1925.

*4.3.7. 2-(1-Hydroxy-2-methylpropyl)-9-methyl-9-azabicyclo[3.3.1] nonan-3-one (exo,anti-**3f**).* Yield (0.220 g; 98%) after precipitation; analytical sample was recrystallized from mixed solvent (dichloromethane/hexane); Mp: 77–79 °C; R_f 0.47 (10% CH_3OH/CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33 (br s, 1H), 3.51 (dd, J_1=9.5 Hz, J_2=2.6 Hz, 1H), 3.25–3.19 (m, 1H), 3.14 (d, J=4.0 Hz, 1H), 2.85 (dd, J_1=7.0, J_2=16.2 Hz, 1H), 2.66 (s, 3H), 2.54 (s, 1H), 2.42 (d, J=16.2 Hz, 1H), 2.12–2.00 (m, 2H), 1.60–1.50 (m, 2H), 1.59–1.41 (m, 1H), 1.31–1.25 (m, 2H), 0.97 (d, J=6.6 Hz, 3H), 0.94 (d, J=6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 210.9, 82.3, 61.3, 55.5, 54.1, 48.7, 39.7, 32.0, 22.8, 22.6, 19.4, 18.9, 16.7; IR ($CHCl_3$) ν: 2944, 2870, 1701, 1155, 1125 cm^{-1}; MS (EI) m/z: 225 (1), 182 (30), 153 (22), 110 (65), 96 (100), 94 (29), 43 (67), 42 (63); HRMS (ESI): m/z calcd for ($C_{13}H_{23}NO_2Na$): 248.1626, found: 248.1638.

Enantiomerically enriched prepared with lithium amide **4**:

ee=93% [^{1}H NMR in the presence of (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol] measured on the crude product.

$[\alpha]_D^{20}$ +118.3 (c 1.0, $CHCl_3$), Mp 111–113 °C, after recrystallization from heptane.

*4.3.8. 2-((4-Bromophenyl)(hydroxy)methyl)-9-methyl-9-azabicyclo [3.3.1]nonan-3-one (**3g**).* Yield (0.320 g; 94%) after precipitation; analytical sample was recrystallized from mixed solvent (dichloromethane/hexane); Mp: 132–134 °C; R_f 0.63 (10% CH_3OH/CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.63 (br s, 1H), 7.43 (d, J=8.4 Hz, 1H), 7.15 (d, J=8.4 Hz, 1H), 5.20 (d, J=3.3 Hz, 1H), 3.36 (d, J=4.1 Hz, 1H), 3.30–3.28 (m, 1H), 2.88 (dd, J_1=16.3 Hz, J_2=7.0 Hz, 1H), 2.73 (s, 3H), 2.52 (d, J=3.3 Hz, 1H), 2.42 (d, J=16.3 Hz, 1H), 2.18–2.05 (m, 2H), 1.60–1.45 (m, 2H), 1.35–1.25 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 208.6, 140.7, 131.2, 127.3, 121.1, 77.3, 60.8, 60.7, 54.2, 48.6, 39.9, 22.6, 22.5, 16.6; IR ($CHCl_3$) ν: 2945, 1704, 1228, 1127, 1072 cm^{-1}; HRMS (ESI): m/z calcd for ($C_{16}H_{20}NO_2BrNa$): 360.0575, found: 360.0565.

Enantiomerically enriched (+)-**3g** prepared with lithium amide **7**:

ee=89% [^{1}H NMR in the presence of (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol] measured on the crude product.

$[\alpha]_D^{20}$ +7.1 (c 1.0, $CHCl_3$), Mp 135–137 °C, after recrystallization from ethyl acetate.

Crystal data for $C_{16}H_{20}BrNO_2$ (+)-**3g**: M_W 338.24, orthorhombic, space group $P2_12_12_1$, a=12.2345(2), b=12.8613(2), c=18.9881(4) Å, V=2987.81(9) $Å^3$, Z=8, D_c=1.504 mg m^{-3}, F(000)=1392, crystal dimension 0.57×0.56×0.49 mm, T=150(2) K; radiation Cu Kα (λ=01.54178 Å). 26326 reflections were collected in the range of $-14\leq h\leq 15$, $-14\leq k\leq 15$, $-21\leq l\leq 22$; of these 5524 were independent, R(int)=0.062. The structure was solved and refined using 5488 reflections with $I>2\sigma$. Final R and R_w were 0.0349 and 0.0875, respectively. Absolute structure (Flack) parameter was 0.074(14) for 2340 measured Friedel pairs.

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