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(−)-8-Amino menthol-derived perhydrobenzoxazines as chiral templates and masked aldehydes in the diastereoselective intermolecular Pauson–Khand reaction

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ABSTRACT

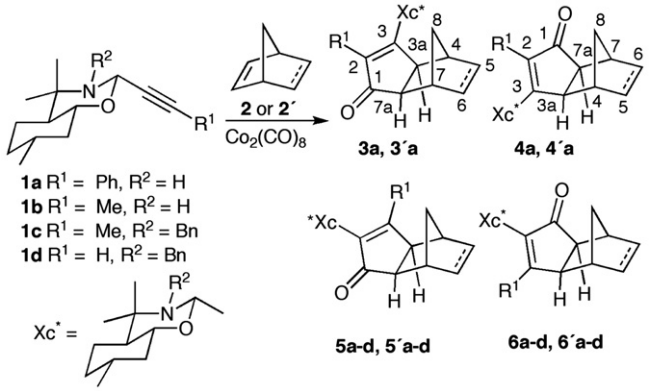
Perhydro-1,3-benzoxazines derived from (−)-8-amino menthol behave as masked aldehydes and chiral templates in diastereoselective intramolecular Pauson–Khand reactions with norbornene and norbornadiene. The regioselectivity is excellent for unsubstituted or methyl-substituted acetylenes and moderate with phenyl-substituted alkynes. The stereoselection is very poor or moderate depending also on the substitution pattern of both the triple bond and the perhydrobenzoxazine nucleus. The hydrolysis of the cycloadducts leads to 2- or 3-formyl–cyclopentenone derivatives.

1. Introduction

Pauson–Khand reaction (PKR) is a powerful reaction in terms of molecular complexity and atom economy leading to 2-cyclopentenone derivatives.[1] The complexity of the resulting cyclopentenone is dependent on the substituents of the alkene and alkyne components of the reaction, and efforts to improve the scope of the reaction have been done by using both functionalized alkynes[2] and alkenes[3] with electron-donating and withdrawing substituents. Interestingly, only few examples on the use of unsaturated ketones have been reported,[4] and no antecedents exist on the use of formyl substituent, probably because it has been demonstrated that aldehydes serve as a carbon monoxide source in Pauson–Khand-like reactions[5] or as the alkene and CO components of the process.[6] On the contrary, ketals have been used as carbonyl protecting groups in some interesting intramolecular PK reactions.[7]

A different and fundamental topic under development is related with the stereoselectivity in the intermolecular PKR in order to prepare enantioenriched cyclopentenone derivatives. In that way, different approaches have been tested,[1] but one of the most extended is based on the use of a chiral auxiliary attached to the olefinic[3] or acetylenic[2g,8] component of the reaction.

Chiral perhydrobenzoxazines, derived from (−)-8-amino menthol, are protected aldehydes as *N,O*-ketals, and more than a decade ago we had demonstrated their ability to promote inter-[9] and intramolecular[10] diastereoselective transformations. Now we consider that these structures could act as chiral inductors in intermolecular PK reactions giving, after hydrolytic work up, formyl cyclopentenone derivatives.[11] To test that hypothesis, we have prepared prehydro-1,3-benzoxazines **1a**–**d** by condensation of (−)-8-amino menthol[12] with propargylic aldehydes, and studied their reactivity with norbornene (**2**) and norbornadiene (**2′**) (Scheme 1).



Scheme 1. Pauson–Khand reaction of perhydrobenzoxazines **1a**–**d** with norbornene and norbornadiene.

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Unsubstituted perhydrobenzoxazine **1a** was used for reaction optimization. First, the catalytic version of the PKR was tested by heating at 60 °C mixtures of **1a** and **2** (10 equiv) with 5 mol % or 10 mol % of dicobalt octacarbonyl in DME and 20 mol % of cyclohexyl amine under CO (1 atm) for 8 h. In both cases the yields of the cyclization products were disappointly low (12% and 10%, respectively). The yields improved to 33% when **1a** was stirred, under nitrogen, with 5 equiv of **2** in the presence of 1.1 equiv of $Co_2(CO)_8$ in DCM and 6 equiv of TMANO,[13] or to 50% in the same reaction conditions but using 10 equiv of **2**. In all these reactions important amounts (10–30%) of the semi-reduction of the triple bond of **1a** were obtained.

A great improvement in the yields was observed when the reactions were carried out in air in the presence of 8 wt. equiv of 3 Å mol sieves.[14] These conditions were chosen as standard for all the reactions, and the results are summarized in Table 1.

Table 1
PKR of perhydrobenzoxazines **1a**–**d** with **2** and **2′** in DCM in the presence of 3 Å mol. sieves and TMANO

Entry	Reagents	Time (h)	Temp (°C)	Yield[a]	Products (ratio)
1	**1a**/**2**	3	25	90	**3a**(61) **4a**(7) **5a**+**6a**(32)
2	**1a**/**2**	8	0	83	**3a**(62) **4a**(7) **5a**+**6a**(31)
3	**1a**/**2′**	3	25	86	**3′a**(52) **4′a**(8) **5′a**+**6′a**(40)
4	**1b**/**2**	3	25	70	**5b**(50) **6b**(50)
5	**1b**/**2′**	3	25	80	**5′b**(50) **6′b**(50)
6	**1c**/**2**	3	25	78	**5c**(79) **6c**(21)
7	**1c**/**2′**	3	25	65	**5′c**(60) **6′c**(40)
8	**1d**/**2**	3	25	88	**5d**(58) **6d**(42)
9	**1d**/**2′**	3	25	75	**5′d**(52) **6′d**(48)

[a] Yields refer to pure and isolated compounds.

The reaction of the phenylpropargyl aldehyde-derived perhydrobenzoxazine (**1a**) with norbornene (**2**) at 25 °C led to a mixture of four isomeric tricyclic cyclopentenones in 90%. When the reaction was carried out at 0 °C similar results were obtained, although at the expense of increased the reaction time (8 h, entry 2 in Table 1). Excellent yields were also obtained in the reaction of **1a** with norbornadiene (**2′**) (entry 3). The multiplicity and coupling constants[15] for protons at C-3a and C-7a indicate that all the compounds are *exo* adducts. Otherwise, the four compounds are grouped as two couples of regioisomers (**3a**/**4a** or **3′a**/**4′a** vs **5a**/**6a** or **5′a**/**6′a**), whereas the members of each couple (**3a** and **4a**; **3′a** and **4′a**; **5a** and **6a**; **5′a** and **6′a**) are diastereoisomers (pseudoenantiomers), which differ at the stereochemistry of the two created stereogenic carbons (C-3a and C-7a).

To our delight, it was possible to determine the absolute stereochemistry for the major compound **3′a** by XR-diffraction analysis[16] as *S* at C-3a, and *R* at C-7a, and consequently to assign configurations *R* at C-3a, and *S* at C-7a for diastereoisomer **4′a** for the nature of the hydrolysis products (vide infra). Unfortunately, it was not possible to establish the stereochemistry for the *exo* regioisomers **5a**–**6a**, and **5′a**–**6′a**, but from the integrals of the ^{1}H NMR signals of their mixtures it was possible to determine 30% and 25% diastereomeric excesses, respectively.

It is interesting to note that, although the diastereoselection of the reaction is good (90:10 dr for **3a**/**4a**, and 87/13 for **3′a**/**4′a**) the regioselectivity is moderate (68/32 for the reaction of **1a** with **2**, and 60/40 for the reaction with **2′**). It is noteworthy that the phenyl group behaves as a bulkier group than the perhydrobenzoxazine substituent because α-phenyl-substituted cyclopentenones **3** and **4** were obtained as the major regioisomers. Looking to improve the regioselectivity, the perhydrobenzoxazine **1b**, with a smaller methyl substituent at the acetylenic terminus, was reacted with norbornene (**2**) and norbonadiene (**2′**) (entries 4 and 5 in Table 1). As expected, only one regioisomer with the bulkiest perhydrobenzoxazine α to the carbonyl group was obtained in those reactions, but as an equimolar mixture of epimers at C-3a- and C-7a. The hydrolysis into the final 2-formyl 2-cyclopentenone derivatives allowed the assignation of the configuration for **5b** and **5′b** as *S* at C-3a and *R* at C-7a, and *R* at C-3a and *S* at C-7a for **6b** and **6′b**.

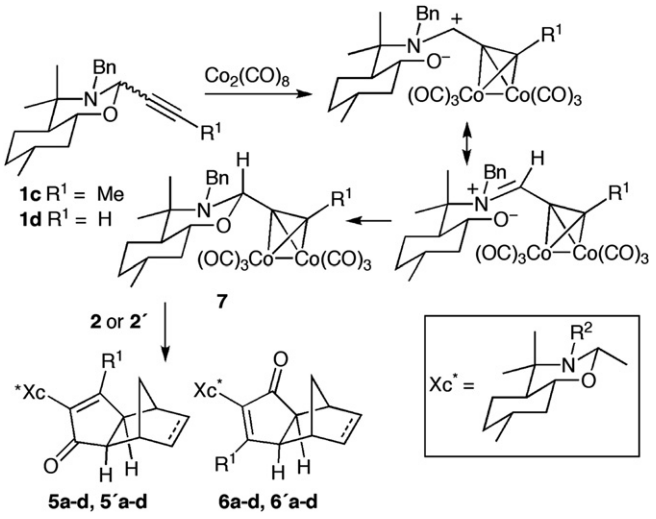
Because the presence of a substituent at the nitrogen atom in the perhydrobenzoxazine could improve the diastereoselection by shielding one of the stereogenic cobalt atoms in the complex, we prepared *N*-benzyl-substituted perhydrobenzoxazines **1c** and **1d** by reaction of **1b** or 2-ethynyl perhydrobenzoxazine with benzyl bromide, respectively. The alkylation yielded the final perhydrobenzoxazines as equimolar mixtures of epimers at C-2 in the heterocycle, and these mixtures were used as starting materials without purification.

The PK reaction of **1c** with **2** yielded a single regioisomer as a mixture (79/21) of *exo*-diastereoisomers **5c** and **6c**, whereas the reaction of **1c** with norbornadiene (**2′**) led to diastereoisomers **5′c** and **6′c** in a ratio 60/40 (entries 6, 7 in Table 1). In the same way, perhydrobenzoxazine **1d** gave cyclopentenone derivatives **5d** and **6d** when reacted with norbornene and a mixture of **5′d** and **6′d** by reaction with norbornadiene in good yield, but very modest diastereoselection (entries 8, 9 in Table 1). Interestingly, all the diastereoisomers have the *S* configuration at the *N*,*O*-acetal carbon in the heterocycle, indicating that previous to the PKR, the complex formed between the cobalt octacarbonyl and the perhydrobenzoxazines **1c** and **1d** isomerized in a Nicholas-like transformation.

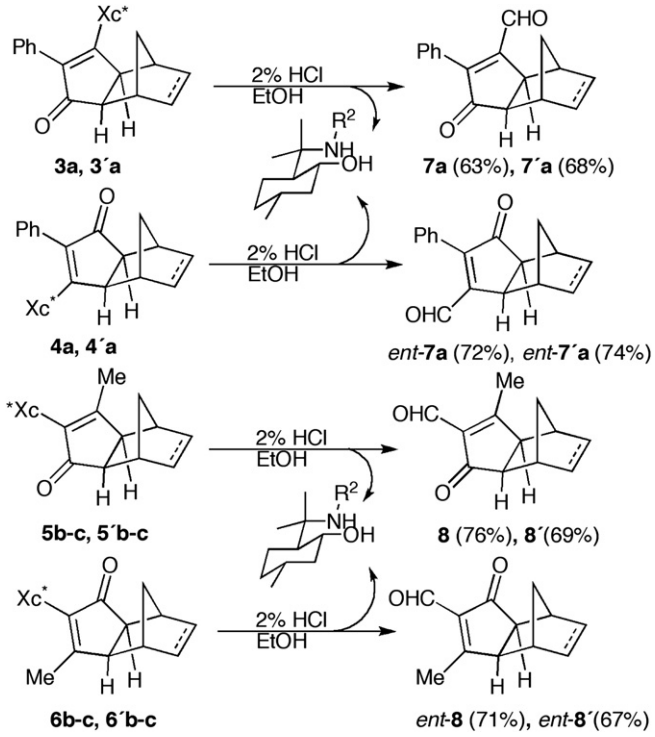
That fact can be explained by accepting that the transformation of **1c**–**d** into the final PK adducts occurs by a tandem intramolecular Nicholas and PK reaction.[17] The coordination of the $Co_2(CO)_8$ to compounds **1c**–**d** leads to cobalt complexes derived from a propargylic alcohol, which evolve to cobalt carbonyl stabilized propargylic cations. That complexes can be intramolecularly captured to the most stable intermediate (**7**) with configuration *S* at C-2 in a Nicholas-like transformation.[18] The subsequent PK reactions on the complexes **7** give the cyclization adducts **5c**–**d** and **6c**–**d** or **5′c**–**d** and **6′c**–**d**, respectively (Schemes 2 and 3).

All these diastereoisomers were separated by flash chromatography, and the XR-diffraction analysis showed a configuration 3a-*S*, 7a-*R* for diastereoisomer **5c**,[16] and consequently 3a-*R*, 7a-*S* for **6c**. The stereochemistry for the other diastereoisomers (**5d**, **5′c**–**d**, **6d**, and **6′c**–**d**) was assigned by analogy.

Once isolated, the major diastereoisomers resulting from the reaction of **1a**–**c** with norbornene **2** or norbornadiene **2′** were transformed into the 2- or 3-formyl cyclopentenone derivatives as summarized in Scheme 2. The reaction was best performed by treatment of the cycloadducts with a 2% solution of HCl in ethanol–water, giving the formyl cyclopentenones in good yields. The hydrolytic cleavage also allowed the recovery of the (−)-8-amino



Scheme 2. Isomerization and PK reaction of compounds **1c**–**d**.



Scheme 3. Hydrolysis of the adducts to 2- or 3-formyl-cyclopentenones.

menthol used as chiral auxiliary and masked aldehyde functionality. That transformation also served to assign the stereochemistry of the cycloadducts formed in the PKR. In fact, the enantiomeric relationship between the ketoaldehydes (**7a**, **7′a**, and *ent*-**7a**, *ent*-**7′a**) obtained from **3a**, **3′a**, and **4a**, **4′a** indicates that those cycloadduts are diastereoisomers, which differ at the configuration of the stereocenters created in the PKR (C-3a, and C-7a). The stereochemistry of compound **5b** was also determined because it gave the same keto aldehyde (**8**) as compound **5c**, whose stereochemistry has been elucidated by XR-diffraction analysis. The diastereomeric relationship between **6b**–**c** and **5b**–**c** was established because they lead to enantiomeric 2-formyl cyclopentenones **8** and *ent*-**8**, respectively. Additionally, to test that the estereochemical integrity of the products is maintained along the elimination process of the chiral template, the enantiomeric purity of the final products was determined for **7a** by chiral HPLC.[19]

It is well documented that the regiochemistry of the PK reaction is dependent on both the size of the substituents on the triple bond and on their electronic nature. In general, the less sterically demanding substituent on the acetylenic bond is found β to the carbonyl group in the formed cyclopentenone,[20] but substituted propiolates always lead to 3-alcoxycarbonyl cyclopentenones as single or major regioisomer,[8g,15a,21] as a consequence of polarization effects of the acetylenic carbons.[22]

In our case, contrary to that described for propiolates and in agreement with the behavior of propargyl alcohols, the reaction of unsubstituted (**1d**) or methyl-substituted (**1b** and **1c**) perhydrobenzoxazines was completely regioselective leading to the masked 1,3-dicarbonyl compounds. The PK reaction of 3-phenyl-substituted perhydrobenzoxazine **1a** was less regioselective, yielding the 1,4-dicarbonyl derivatives as major reigioisomers, probably because the perhydrobenzoxazine moiety is not able to polarize the triple bond, and the regiochemistry is only dictated by steric effects.

A lot of experimental and theoretical[23] studies have been done to explain the stereochemistry associated to the PK reaction. The chiral discrimination of the reaction can be explained assuming that, after the formation of the hexacarbonyl dicobalt complex, the olefin coordinates to the most accessible diastereotopic cobalt atom. It is also generally accepted that the coordination of the norbornene or norbornadiene occurs only from the *exo* face, and that the most stable conformation is that where the methylene bridge points away from the alkyne substituent. Taking into account these assumptions, the observed stereoselection in our case could be explained as a consequence of the coordination of the olefin to the cobalt atom in the side of the nitrogen (Co_N) or to the cobalt at the side of the oxygen atom (Co_O) in the adduct **9** (Fig. 1),

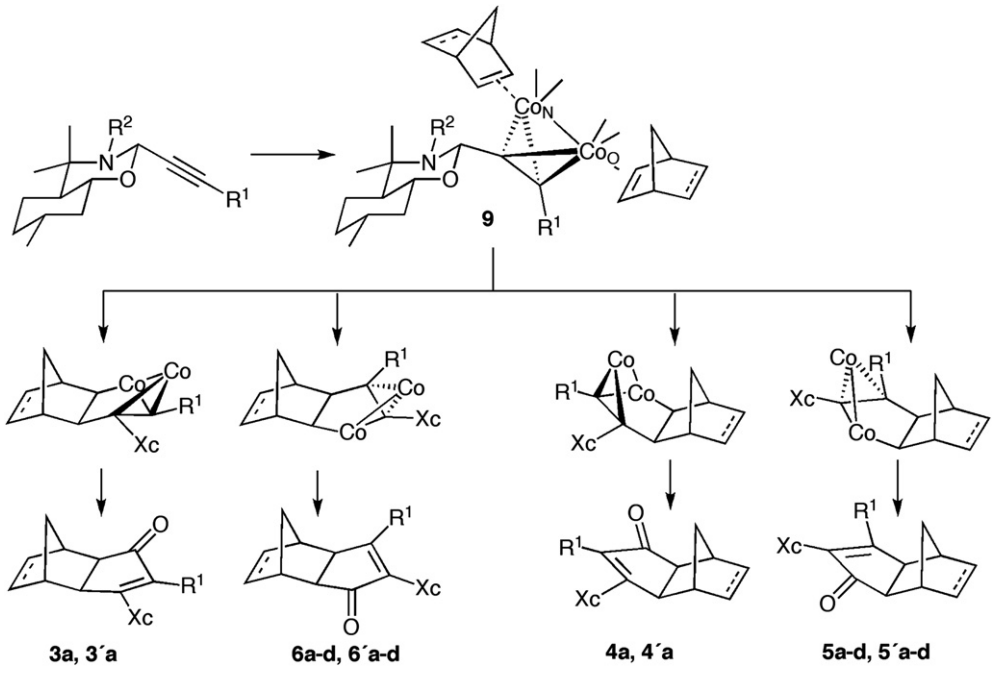


Fig. 1. Schematic representation for the formation of the regio- and diastereoisomers isolated in this work.

and it is dependent on the substitution pattern of the nitrogen atom.

In fact, compounds **1c** and **1d**, with a bulky benzyl substituent at the nitrogen atom lead to **5c** and **5′c** or **5d** and **5′d** as major diastereoisomers because the coordination of the olefins occurs by the less hindered cobalt atom in the side of the oxygen (Co_O). On the contrary, the formation of **3a** or **3′a** as major diastereoisomers from perhydrobenzoxazine **1a**, with a bulk substituent at the triple bond (R^1=Ph) and small at the nitrogen atom (R^2=H) can be explained by the preferred coordination of the olefin to the cobalt atom at the nitrogen face of the complex (Co_N). Perhydrobenzoxazine **1b** with an smaller substituent at the acetylenic bond (R^1=Me) yielded and equimolar mixture of diastereoisomers. On the other hand, compounds **1a** and **1b** are propargyl secondary amines and could establish a hydrogen bond between the NH and the CO substituent of the diastereotopic Co_N in **9**, helping to create a coordination vacant, and facilitating the coordination of the olefin to that cobalt atom.[23c]

In summary, perhydrobenzoxazines derived from (−)-8-amino menthol behave as chiral inductors and masked propargyl aldehydes in diastereoselective intermolecular PKR with norbornene and norbornadiene. Only the *exo*-cycloadducts were formed in high yields and mild conditions, but the diastereoselection varies from negligible to moderate (9:1) depending on the substitution pattern of the triple bond and the nitrogen atom in the heterocycle. The regioselectivity is also dependent on the nature of the substituents at the acetylenic bond. The unsubstituted or methyl-substituted derivatives lead to a single regioisomer, but the phenyl-substituted derivative give a mixture (ca. 2:1) of regioisomeric cycloadducts.

Pure diastereoisomers can be obtained by flash chromatography, and subjected to hydrolysis leading to enantioenriched 2- or 3-formyl-cyclopentenone derivatives.

2. Experimental

2.1. General

^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker AC−300 spectrometer in $CDCl_3$. Chemical shifts for protons are reported in parts per million from tetramethylsilane with the residual $CHCl_3$ resonance as internal reference. Chemical shifts for carbons are reported in ppm from tetramethylsilane and are referenced to the carbon resonance of the solvent. Specific rotations were measured on a Perkin−Elmer digital polarimeter using a 5-mL cell with a 1-dm path length, and a sodium lamp, and concentration is given in gram per 100 mL. Infrared spectra were recorded on a Perkin−Elmer FT−IR spectrometer and are reported in frequency of absorption. Melting points were obtained with open capillary tubes and are uncorrected. Flash chromatography was carried out using silica gel (230−240 mesh). TLC analysis was performed on glass-backed plates coated with silica gel 60 and an F_{254} indicator, and visualized by either UV irradiation or by staining with phosphomolybdic acid solution. Solvents were dried and stored over microwave-activated 4Å molecular sieves. Compounds **1a**, and **1b** have been previously described.[24]

2.2. Synthesis of perhydrobenzoxazines 1c and 1d. General procedure

A mixture of (−)-8-amino menthol[12] (2.61 g, 10 mmol) and the corresponding aldehyde (15 mmol), in toluene (50 ml) was refluxed under nitrogen until the reaction was completed (TLC). The mixture was filtered through a pad of Celite, and the Celite washed with toluene. The solvent was evaporated, and the residue was subjected to *N*-benzylation without further purification. A mixture of potassium carbonate (24 mmol), benzyl bromide (12 mmol), and the corresponding perhydrobenzoxazine (10 mmol) in acetonitrile (15 mL) was placed in a 25 mL flask and stirred at rt until the disappearance of the perhydrobenzoxazine (TLC). The mixture was filtrated and the solids were washed three times with EtOAc. The solvents were eliminated under reduced pressure and the crude of the reactions purified by flash chromatography the benzylated perhydrobenzoxazines **1c** (72%) and **1d** (68%) as equimolar mixtures of epimers at C-2.

*2.2.1. Equimolar mixture of (2R,4aS,7R,8aR)- and (2S,4aS,7R,8aR)-N-benzyl-2-(1′-propinyl)-4,4,7-trimethyloctahydrobenz[e][1,3] oxazine (**1c**).* Yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.89−1.19 (m, 5H); 0.97 (d, 3H, J=6.6 Hz); 0.98 (d, 6H, J=6.6 Hz); 1.23 (s, 3H); 1.26 (s, 6H); 1.29−1.63 (m, 6H); 1.69 (d, 3H, J=1.7 Hz); 1.73−1.77 (m, 3H); 1.93 (d, 3H, J=2.0 Hz); 1.96−2.01 (m, 2H); 3.54 (d, 1H, J=14.4 Hz); 3.58 (dt, 1H, J_1=4.0 Hz, J_2=10.6 Hz); 3.87−3.95 (m, 2H); 4.08 (d, 1H, J=14.4 Hz); 4.55 (d, 1H, J=17.0 Hz); 4.85 (d, 1H, J=2.0 Hz); 5.56 (d, 1H, J=1.7 Hz); 7.17−7.46 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 3.6 (CH_3); 3.7 (CH_3); 16.4 (CH_3); 21.2 (CH_3); 22.2 (CH_3); 22.3 (CH_3); 24.9 (CH_2); 25.1 (CH_2); 27.4 (CH_3); 27.9 (CH_3); 31.2 (CH); 31.4 (CH); 34.8 (CH_2); 35.0 (CH_2); 41.1 (CH_2); 41.3 (CH_2); 44.9 (CH); 48.2 (CH_2); 48.6 (CH_2); 49.9 (CH); 55.7 (C); 56.9 (C); 70.0 (CH); 76.3 (CH); 76.5 (CH); 76.8 (C≡); 76.9 (C≡); 79.6 (CH); 82.1 (C≡); 83.3 (C≡); 125.7 (CH═); 126.8 (CH═); 127.1 (2CH═); 127.8 (2CH═); 128.2 (2CH═); 128.3 (2CH═); 139.6 (C═); 144.4 (C═).

*2.2.2. Equimolar mixture of (2R,4aS,7R,8aR)- and (2S,4aS,7R,8aR)-N-benzyl-2-(ethynyl)-4,4,7-trimethyloctahydrobenz[e][1,3] oxazine (**1d**).* Yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.90−1.21 (m, 5H); 0.97 (d, 3H, J=6.5 Hz); 0.98 (d, 3H, J=6.5 Hz); 1.24 (s, 6H); 1.28 (s, 6H); 1.31−1.67 (m, 6H); 1.74−1.78 (m, 3H); 1.95−2.02 (m, 2H); 2.42 (d, 1H, J=1.5 Hz); 2.56 (d, 1H, J=1.5 Hz); 3.55 (d, 1H, J=14.4 Hz); 3.60 (dt, 1H, J_1=4.0 Hz, J_2=10.5 Hz); 3.92 (dt, 1H, J_1=4.2 Hz, J_2=10.6 Hz); 3.97 (d, 1H, J=17.2 Hz); 4.14 (d, 1H, J=14.4 Hz); 4.57 (d, 1H, J=17.2 Hz); 4.88 (d, 1H, J=2.1 Hz); 5.62 (d, 1H, J=1.5 Hz); 7.18−7.46 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.3 (CH_3); 21.3 (CH_3); 22.2 (CH_3); 22.3 (CH_3); 24.8 (CH_2); 25.0 (CH_2); 27.1 (CH_3); 27.9 (CH_3); 31.2 (CH); 31.4 (CH); 34.7 (CH_2); 35.0 (CH_2); 41.0 (CH_2); 41.2 (CH_2); 44.8 (CH); 48.2 (CH_2); 48.7 (CH_2); 49.8 (CH); 55.9 (C); 57.0 (C); 69.8 (CH); 70.4 (CH); 73.6 (CH≡); 75.5 (CH≡); 76.2 (CH); 79.3 (CH); 80.6 (C≡); 81.6 (C≡); 125.9 (CH═); 126.9 (CH═); 127.0 (2CH═); 127.9 (2CH═); 128.3 (2CH═); 128.4 (CH═); 128.5 (CH═); 139.2 (C═); 143.9 (C═).

2.3. Pauson−Khand reaction. General procedure

A 25 ml flask was charged with 1.0 mmol of perhydrobenzoxazine in 10 ml of dry DCM, eightfold (in weight) of 3 Å mol sieves and 1.1 mmol of $Co_2(CO)_8$ under argon atmosphere and the mixture was stirred for 2 h at rt. Then, the flask was opened to the atmosphere, 10.4 mmol of TMANO were added, and the stirring was continued at rt until the reaction was finished (TLC). The reaction mixture was filtered, the solids were washed 2−3 times with DCM and the solvent was evaporated under vacuum. The residues were purified by flash chromatography and mixtures of EtOAc/hexanes.

*2.3.1. Adduct (**3a**).* White solid. Mp 205−207 °C (from hexane). $[\alpha]_D^{25}$=−33.64 ($CHCl_3$, c=1.10). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.84−1.00 (m, 2H); 0.92 (d, 3H, J=6.5 Hz); 1.02−1.14 (m, 2H); 1.08 (s, 3H); 1.09 (s, 3H); 1.22−1.47 (m, 5H); 1.55−1.80 (m, 4H); 1.86 (m, 1H); 2.00 (m, 1H); 2,31 (d, 1H, J=5.4 Hz); 2.49−2.52 (m, 2H); 2.99 (d, 1H, J=5.4 Hz); 3.39 (dt, 1H, J_1=4.2 Hz, J_2=10.4 Hz); 5.24 (s, 1H); 7.29−7.40 (m, 3H); 7.53−7.57 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 18.9 (CH_3); 22.2 (CH_3); 25.4 (CH_2); 28.5 (CH_2); 29.4 (CH_2); 30.1 (CH_3); 31.3 (CH); 31.4 (CH_2); 34.9 (CH_2); 38.9 (CH); 39.6 (CH); 41.5

(CH_2); 48.0 (CH); 51.7 (CH); 52.0 (C); 53.8 (CH); 75.0 (CH); 81.3 (CH); 127.7 (2CH=); 128.0 (CH=); 129.6 (2CH=); 131.1 (C=); 143.7 (C=); 169.5 (C=); 209.6 (C=O). IR (Nujol dispersion): 3372; 2949; 1697. HRMS for $C_{27}H_{35}NO_2$: calcd 405.2668, found 406.2734 (M^++H).

*2.3.2. Adduct (**4a**).* Yellowish oil. $[\alpha]_D^{25}$=+11.62 ($CHCl_3$, *c*=0.74). ^{1}H NMR ($CDCl_3$) δ: 0.88–1.10 (m, 3H); 0.94 (d, 3H, *J*=6.5 Hz); 1.03 (s, 3H); 1.10 (s, 3H); 1.13–1.48 (m, 6H); 1.55–1.68 (m, 4H); 1.95 (m, 1H); 2.10 (m, 1H); 2.32 (d, 1H, *J*=5.2 Hz); 2.50 (d, 1H, *J*=3.1 Hz); 2.78–2.80 (m, 2H); 3.42 (dt, 1H, J_1=4.1Hz, J_2=10.4 Hz); 5.28 (s, 1H); 7.31–7.43 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 19.1 (CH_3); 22.3 (CH_3); 25.4 (CH_2); 28.5 (CH_2); 29.3 (CH_2); 29.9 (CH_3); 31.3 (CH); 31.5 (CH_2); 34.9 (CH_2); 38.6 (CH); 39.4 (CH); 41.6 (CH_2); 47.3 (CH); 51.8 (C); 51.9 (CH); 53.9 (CH); 75.0 (CH); 80.2 (CH); 127.9 (2CH=); 128.0 (CH=); 129.3 (2CH=); 131.0 (C=); 144.0 (C=); 167.9 (C=); 209.5 (C=O). IR (film): 3304; 3044; 2950; 1702; 1691. HRMS for $C_{27}H_{35}NO_2$: calcd 405.2668, found 406.2726 (M^++H).

*2.3.3. Adduct (**5a**) or adduct (**6a**).* Yellowish oil. $[\alpha]_D^{25}$=+261.23 ($CHCl_3$, *c*=1.46). ^{1}H NMR ($CDCl_3$) δ: 0.85–1.01 (m, 3H); 0.87 (d, 3H, *J*=6.5 Hz); 1.05 (s, 3H); 1.08 (s, 3H); 1.13–1.21 (m, 3H); 1.26–1.36 (m, 3H); 1.57–1.65 (m, 4H); 1.82 (m, 1H); 1.96 (s, 1H); 2.35 (d, 1H,*J*=5.4 Hz); 2.49 (s, 1H); 2.82 (s, 1H); 3.00 (d, 1H, *J*=5.4 Hz); 3.34 (dt, 1H, J_1=4.1 Hz, J_2=10.4 Hz); 5.29 (s, 1H); 7.43–7.46 (m, 3H); 7.50–7.53 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 18.8 (CH_3); 22.2 (CH_3); 25.5 (CH_2); 28.6 (CH_2); 29.0 (CH_2); 29.6 (CH_3); 31.3 (CH); 31.6 (CH_2); 34.8 (CH_2); 37.9 (CH); 39.1 (CH); 41.4 (CH_2); 50.9 (CH); 51.3 (C); 51.5 (CH); 54.2 (CH); 75.1 (CH); 78.0 (CH); 128.1 (2CH=); 128.4 (2CH=); 129.6 (CH=); 135.1 (C=); 140.3 (C=); 172.1 (C=); 209.0 (C=O). IR (film): 3308; 3055; 2952; 1690; 1631. HRMS for $C_{27}H_{35}NO_2$: calcd 405.2668, found 406.2732 (M^++H).

*2.3.4. Adduct (**6a**) or adduct (**5a**).* Yellowish oil. $[\alpha]_D^{25}$=−476.79 ($CHCl_3$, *c*=1.40). ^{1}H NMR ($CDCl_3$) δ: 0.87–1.04 (m, 3H); 0.91 (s, 3H); 0.92 (d, 3H, *J*=7.3 Hz); 1.09 (s, 3H); 1.13–1.39 (m, 5H); 1.48–1.66 (m, 5H); 1.91–1.96 (m, 2H); 2.31 (d, 1H, *J*=5.3 Hz); 2.47 (s, 1H); 3.02 (d, 1H, *J*=5.3 Hz); 3.45 (dt, 1H, J_1=4.2 Hz, J_2=10.4 Hz); 3.70 (broad s, 1H); 5.02 (s, 1H); 7.43–7.48 (m, 3H); 7.51–7.54 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 18.8 (CH_3); 22.2 (CH_3); 25.5 (CH_2); 28.7 (CH_2); 28.8 (CH_2); 29.7 (CH_3); 31.4 (CH); 31.5 (CH_2); 34.9 (CH_2); 37.9 (CH); 39.1 (CH); 41.5 (CH_2); 50.7 (CH); 50.8 (C); 51.0 (CH); 54.3 (CH); 74.8 (CH); 78.8 (CH); 128.0 (2CH=); 128.5 (2CH=); 129.9 (CH=); 134.7 (C=); 138.7 (C=); 173.7 (C=); 210.0 (C=O). IR (film): 3310; 3051; 2953; 1686; 1626. HRMS for $C_{27}H_{35}NO_2$: calcd 405.2668, found 406.2734 (M^++H).

*2.3.5. Adduct (**3′a**).* White solid. Mp 224–225 °C (from hexane). $[\alpha]_D^{25}$=−20.32 ($CHCl_3$, *c*=0.62). ^{1}H NMR ($CDCl_3$) δ: 0.86–0.98 (m, 2H); 0.92 (d, 3H, *J*=6.5 Hz); 1.00–1.17 (m, 2H); 1.08 (s, 3H); 1.10 (s, 3H); 1.42–1.50 (m, 3H); 1.65–1.73 (m, 3H); 1.86 (m, 1H); 2.44 (d, 1H, *J*=5.4 Hz); 3.01 (s, 1H); 3.02 (s, 1H); 3.11 (d, 1H, *J*=5.4 Hz); 3.41 (dt, 1H, J_1=4.1 Hz, J_2=10.4 Hz); 5.25 (s, 1H); 6.26 (dd, 1H, J_1=3.3 Hz, J_2=5.5 Hz); 6.37 (dd, 1H, J_1=3.3 Hz, J_2=5.5 Hz); 7.30–7.41 (m, 3H); 7.54–7.57 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 18.9 (CH_3); 22.3 (CH_3); 25.4 (CH_2); 30.1 (CH_3); 31.3 (CH); 34.9 (CH_2); 41.5 ($2CH_2$); 43.9 (CH); 44.1 (CH); 47.1 (CH); 51.8 (CH); 52.1 (C); 52.8 (CH); 75.1 (CH); 81.2 (CH); 127.8 (2CH=); 128.2 (CH=); 129.5 (2CH=); 130.9 (C=); 137.4 (CH=); 138.4 (CH=); 144.6 (C=); 169.2 (C=); 208.1 (C=O). IR (Nujol dispersion): 3374; 3060; 2925; 1698. HRMS for $C_{27}H_{33}NO_2$: calcd 403.2511, found 404.2580 (M^++H)

*2.3.6. Adduct (**4′a**).* Yellowish oil. $[\alpha]_D^{25}$=+3.36 ($CHCl_3$, *c*=1.1). ^{1}H NMR ($CDCl_3$) δ: 0.88–1.30 (m, 3H); 0.94 (d, 3H, *J*=6.5 Hz); 1.05 (s, 3H); 1.12 (s, 3H); 1.34–1.46 (m, 4H); 1.65–1.69 (m, 2H); 1.95 (m, 1H); 2.43 (d, 1H, *J*=5.2 Hz); 2.60 (broad s, 1H); 2.92 (d, 1H, *J*=5.2 Hz); 3.02 (s, 1H); 3.28 (s, 1H); 3.42 (dt, 1H, J_1=4.1 Hz, J_2=10.4 Hz); 5.30 (s, 1H); 6.24 (dd, 1H, J_1=3.0 Hz, J_2=5.6 Hz); 6.36 (dd, 1H, J_1=3.0 Hz, J_2=5.6 Hz); 7.32–7.56 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 19.1 (CH_3); 22.3 (CH_3); 25.4 (CH_2); 29.9 (CH_3); 31.3 (CH); 34.9 (CH_2); 41.6 ($2CH_2$); 43.9 (CH); 44.1 (CH); 46.5 (CH); 51.9 (CH); 52.0 (C); 52.7 (CH); 75.0 (CH); 80.2 (CH); 128.0 (2CH=); 128.1 (CH=); 129.2 (2CH=); 130.8 (C=); 137.4 (CH=); 138.8 (CH=); 144.7 (C=); 167.8 (C=); 208.2 (C=O). IR (film): 3304; 3059: 2927; 1702. HRMS for $C_{27}H_{33}NO_2$: calcd 403.2511, found 404.2585 (M^++H).

*2.3.7. Adduct (**5′a**) or adduct (**6′a**).* White solid. Mp 82–84 °C (from hexane). $[\alpha]_D^{25}$=+221.66 ($CHCl_3$, *c*=0.90). ^{1}H NMR ($CDCl_3$) δ: 0.80–1.02 (m, 2H); 0.88 (d, 3H, *J*=6.5 Hz); 1.06 (s, 3H); 1.08 (s, 3H); 1.11–1.26 (m, 2H); 1.28–1.42 (m, 3H); 1.60–1.66 (m, 2H); 1.82 (m, 1H); 2.46 (s, 1H); 2.48 (d, 1H, *J*=5.4 Hz); 2.54 (broad s, 1H); 3.01 (s, 1H); 3.16 (d, 1H, *J*=5.4 Hz); 3.34 (dt, 1H, J_1=4.1 Hz, J_2=10.5 Hz); 5.27 (s, 1H); 6.21–6.26 (m, 2H); 7.45–7.48 (m, 3H); 7.50–7.54 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 18.7 (CH_3); 22.2 (CH_3); 25.4 (CH_2); 29.6 (CH_3); 31.3 (CH); 34.8 (CH_2); 41.4 (CH_2); 41.9 (CH_2); 42.9 (CH); 43.8 (CH); 50.9 (CH); 51.2 (CH); 51.4 (C); 53.0 (CH); 75.2 (CH); 78.2 (CH); 128.0 (2CH=); 128.4 (2CH=); 129.7 (CH=); 134.9 (C=); 137.7 (CH=); 138.2 (CH=); 141.5 (C=); 172.3 (C=); 207.8 (C=O). IR (KBr dispersion): 3312; 3050; 2953; 1694; 1633.

*2.3.8. Adduct (**6′a**) or adduct (**5′a**).* Yellowish solid. Mp 90–92 °C (from hexane). $[\alpha]_D^{25}$=−399.76 ($CHCl_3$, *c*=1.26). ^{1}H NMR ($CDCl_3$) δ: 0.82–1.06 (m, 2H); 0.91 (s, 3H); 0.92 (d, 3H, *J*=6.4 Hz); 1.09 (s, 3H); 1.13–1.26 (m, 2H); 1.30–1.44 (m, 2H); 1.48 (m, 1H); 1.66 (m, 2H); 1.94 (m, 1H); 2.39 (d, 1H, *J*=1.1 Hz); 2.42 (d, 1H, *J*=5.3 Hz); 2.98 (d, 1H, *J*=1.1 Hz); 3.17 (d, 1H, *J*=5.3 Hz); 3.45 (dt, 1H, J_1=4.1 Hz, J_2=10.4 Hz); 3.50 (broad s, 1H); 5.01 (s, 1H); 6.19–6.24 (m, 2H); 7.43–7.47 (m, 3H); 7.49–7.55 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 18.8 (CH_3); 22.3 (CH_3); 25.5 (CH_2); 29.7 (CH_3); 31.4 (CH); 34.9 (CH_2); 41.5 (CH_2); 41.9 (CH_2); 42.9 (CH); 43.8 (CH); 50.3 (CH); 50.8 (CH); 51.0 (C); 53.1 (CH); 74.8 (CH); 78.9 (CH); 127.9 (2CH=); 128.6 (2CH=); 130.0 (CH=); 134.5 (C=); 137.7 (CH=); 138.1 (CH=); 139.8 (C=); 173.8 (C=); 208.7 (C=O). IR (film): 3315; 3048; 2955; 1691; 1630.

*2.3.9. Adduct (**5b**).* Yellowish oil. $[\alpha]_D^{25}$=−79.12 ($CHCl_3$, *c*=1.36). ^{1}H NMR ($CDCl_3$) δ: 0.86–0.97 (m, 3H); 0.90 (d, 3H, *J*=6.5 Hz); 1.00–1.20 (m, 2H); 1.12 (s, 6H); 1.21–1.33 (m, 3H); 1.51 (m, 1H); 1.58 (m, 1H); 1.64–1.73 (m, 3H); 1.86 (m, 1H); 2.13 (d, 1H, *J*=3.6 Hz); 2.14 (s, 3H); 2.27 (d, 1H, *J*=4.1 Hz); 2.41–2.43 (m, 2H); 3.01 (broad s, 1H); 3.46 (dt, 1H, J_1=4.2 Hz, J_2=10.4 Hz); 5.19 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 16.0 (CH_3); 18.9 (CH_3); 22.2 (CH_3); 25.4 (CH_2); 28.5 (CH_2); 29.1 (CH_2); 29.7 (CH_3); 31.3 (CH); 31.4 (CH_2); 34.9 (CH_2); 37.3 (CH); 38.7 (CH); 41.4 (CH_2); 51.0 (C); 51.1 (CH); 52.7 (CH); 53.8 (CH); 75.3 (CH); 77.8 (CH); 140.2 (C=); 174.7 (C=); 209.4 (C=O). IR (film): 3296; 2956; 1690; 1646. HRMS for $C_{22}H_{33}NO_2$: calcd 343.2511, found 344.2587 (M^++H).

*2.3.10. Adduct (**6b**).* Yellowish oil. $[\alpha]_D^{25}$=+31.29 ($CHCl_3$, *c*=1.40). ^{1}H NMR ($CDCl_3$) δ: 0.86 (d, 3H, *J*=6.5 Hz); 0.90–1.04 (m, 5H); 1.07 (s, 6H); 1.10–1.29 (m, 3H); 1.46 (m, 1H); 1.55 (m, 1H); 1.60–1.84 (m, 3H); 2.01 (m, 1H); 2.08 (s, 3H); 2.09 (d, 1H, *J*=5.3 Hz); 2.21 (d, 1H, *J*=3.6 Hz); 2.35 (d, 1H, *J*=3.6 Hz); 3.39 (d, 1H, *J*=5.3 Hz); 3.05 (broad s, 1H); 3.43 (dt, 1H, J_1=4.2 Hz, J_2=10.4 Hz); 5.17 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 16.0 (CH_3); 18.8 (CH_3); 22.2 (CH_3); 25.4 (CH_2); 28.4 (CH_2); 29.1 (CH_2); 29.6 (CH_3); 31.3 (CH); 31.6 (CH_2); 34.8 (CH_2); 37.1 (CH); 38.6 (CH); 41.5 (CH_2); 50.9 (C); 51.0 (CH); 52.7 (CH); 54.0 (CH); 75.0 (CH); 78.0 (CH); 139.9 (C=); 174.6 (C=); 209.3 (C=O). IR (film): 3312; 2956; 1690; 1647.

*2.3.11. Adduct (**5′b**).* Yellowish oil. $[\alpha]_D^{25}$=−58.18 ($CHCl_3$, *c*=1.1). ^{1}H NMR ($CDCl_3$) δ: 0.86–0.97 (m, 2H); 0.90 (d, 3H, *J*=6.5 Hz); 1.02–1.26 (m, 2H); 1.12 (s, 6H); 1.28–1.46 (m, 2H); 1.53 (m, 1H); 1.67–1.69 (m,

2H); 1.85 (m, 1H); 2.15 (s, 3H); 2.25 (d, 1H, J=5.2 Hz); 2.57 (d, 1H, J=5.2 Hz); 2.79 (s, 1H); 2.93 (s, 1H); 3.45 (broad s, 1H); 3.46 (dt, 1H, J_1=4.2 Hz, J_2=10.4 Hz); 5.18 (s, 1H); 6.20 (dd, 1H, J_1=3.0 Hz, J_2=5.5 Hz); 6.25 (dd, 1H, J_1=3.0 Hz, J_2=5.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 16.0 (CH_3); 18.9 (CH_3); 22.2 (CH_3); 25.4 (CH_2); 29.7 (CH_3); 31.3 (CH); 34.8 (CH_2); 41.3 CH_2); 41.6 (CH_2); 42.2 (CH); 43.4 (CH); 51.0 (C); 51.1 (CH); 52.1 (CH); 52.6 (CH); 75.3 (CH); 77.7 (CH); 137.6 (CH=); 137.9 (CH=); 141.0 (C=); 174.7 (C=); 208.1 (C=O). IR (film): 3312; 3063; 2927; 1686; 1647. HRMS for $C_{22}H_{31}NO_2$: calcd 341.2355, found 342.2429 (M^++H).

*2.3.12. Adduct (**6′b**).* Yellowish oil. $[\alpha]_D^{25}$=+24.28 ($CHCl_3$, c=0.7). ^{1}H NMR ($CDCl_3$) δ: 0.85–0.98 (m, 1H); 0.90 (d, 3H, J=6.5 Hz); 1.01–1.23 (m, 3H); 1.12 (s, 6H); 1.27–1.38 (m, 2H); 1.46 (m, 1H); 1.67–1.70 (m, 2H); 1.87 (m, 1H); 2.15 (s, 3H); 2.27 (d, 1H, J=5.2 Hz); 2.59 (d, 1H, J=5.2 Hz); 2.77 (s, 1H); 2.92 (s, 1H); 3.38 (broad s, 1H); 3.48 (dt, 1H, J_1=4.2 Hz, J_2=10.4 Hz); 5.21 (s, 1H); 6.20 (dd, 1H, J_1=3.0 Hz, J_2=5.5 Hz); 6.25 (dd, 1H, J_1=3.0 Hz, J_2=5.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 16.1 (CH_3); 18.8 (CH_3); 22.2 (CH_3); 25.4 (CH_2); 29.6 (CH_3); 31.3 (CH); 34.8 (CH_2); 41.5 CH_2); 41.8 (CH_2); 42.1 (CH); 43.3 (CH); 51.0 (CH+C); 52.2 (CH); 52.9 (CH); 75.0 (CH); 78.1 (CH); 137.6 (CH=); 138.0 (CH=); 141.0 (C=); 174.6 (C=); 208.1 (C=O). IR (film): 3311; 3062; 2927; 1686; 1647. HRMS for $C_{22}H_{31}NO_2$: calcd 341.2355, found 342.2425 (M^++H).

*2.3.13. Adduct (**5c**).* White solid. Mp 146.3–147.9 °C (from hexane). $[\alpha]_D^{25}$=+22.61 ($CHCl_3$, c=1.3). ^{1}H NMR ($CDCl_3$) δ: −0.06 (d, 1H, J=10.8 Hz); 0.26 (d, 1H, J=10.8 Hz); 0.94 (d, 3H, J=6.8 Hz); 0.95 (s, 3H); 0.97–1.22 (m, 4H); 1.26 (s, 3H); 1.33–1.59 (m, 5H); 1.65–1.73 (m, 2H); 1.87 (s, 1H); 1.93 (m, 1H); 2.01 (d, 1H, J=5.5 Hz); 2.17 (s, 1H); 2.26 (d, 1H, J=5.5 Hz); 2.32 (s, 3H); 3.52 (dt, 1H, J_1=4.0 Hz, J_2=10.4 Hz); 3.59 (d, 1H, J=18.3 Hz); 3.85 (d, 1H, J=18.3 Hz); 5.49 (s, 1H); 7.06 (m, 1H); 7.15–7.20 (m, 2H); 7.26–7.28 (m, 2H). ^{13}C NMR ($CDCl_3$, 333 K) δ 17.0 (CH_3); 17.4 (CH_3); 22.1 (CH_3); 24.9 (CH_2); 27.0 (CH_3); 28.6 (CH_2); 29.0 (CH_2); 30.5 (CH_2); 31.2 (CH); 35.0 (CH_2); 37.2 (CH); 38.4 (CH); 41.5 (CH_2); 47.3 (CH_2); 48.2 (CH); 53.5 (CH); 53.7 (CH); 57.4 (C); 75.6 (CH); 82.8 (CH); 125.6 (CH=); 126.5 (2CH=); 127.5 (2CH=); 141.2 (C=); 143.5 (C=); 176.6 (C=); 208.5 (C=O). IR (KBr dispersion): 3061; 2955; 1691; 1642. HRMS for $C_{29}H_{39}NO_2$: calcd 433.2981, found 434.3065 (M^++H).

*2.3.14. Adduct (**6c**).* Colorless oil. $[\alpha]_D^{25}$=+149.30 ($CHCl_3$, c=0.72). ^{1}H NMR ($CDCl_3$) δ: 0.75–0.88 (m, 2H); 0.93 (d, 3H, J=6.5 Hz); 0.96–1.22 (m, 3H); 1.16 (s, 3H); 1.18 (s, 3H); 1.25–1.53 (m, 6H); 1.65–1.73 (m, 4H); 1.89 (m, 1H); 2.00 (s, 3H); 2.03 (s, 1H); 2.06 (s, 1H); 3.23 (d, 1H, J=16.7 Hz); 3.44 (dt, 1H, J_1=4.1 Hz, J_2=10.5 Hz); 3.81 (d, 1H, J=16.7 Hz); 5.24 (s, 1H); 7.07–7.16 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 15.0 (CH_3); 17.4 (CH_3); 22.2 (CH_3); 25.1 (CH_2); 27.3 (CH_3); 28.5 (CH_2); 28.9 (CH_2); 31.1 (CH); 31.3 (CH_2); 34.8 (CH_2); 36.9 (CH); 38.5 (CH); 41.4 (CH_2); 47.8 (CH_2); 49.4 (CH); 52.8 (CH); 53.4 (CH); 57.2 (C); 74.9 (CH); 81.7 (CH); 125.6 (CH=); 126.6 (2CH=); 127.5 (2CH=); 141.2 (C=); 143.7 (C=); 179.0 (C=); 209.1 (C=O). IR (film): 3058; 2953; 1686; 1641.

*2.3.15. Adduct (**5′c**).* White solid. Mp 135.9–137.5 °C (from hexane). $[\alpha]_D^{25}$=+39.02 ($CHCl_3$, c=0.82). ^{1}H NMR ($CDCl_3$) δ: 0.17 (d, 1H, J=9.6 Hz); 0.67 (d, 1H, J=9.6 Hz); 0.83–1.20 (m, 3H); 0.94 (d, 3H, J=6.5 Hz); 0.96 (s, 3H); 1.26 (s, 3H); 1.52–1.60 (m, 2H); 1.65–1.73 (m, 2H); 1.93 (s, 1H); 2.12 (d, 1H, J=5.3 Hz); 2.32 (s, 3H); 2.39 (s, 1H); 2.40 (d, 1H, J=5.3 Hz); 2.70 (s, 1H); 3.52 (dt, 1H, J_1=4.1 Hz, J_2=10.5 Hz); 3.60 (d, 1H, J=18.3 Hz); 3.87 (d, 1H, J=18.3 Hz); 5.48 (s, 1H); 6.05–6.10 (m, 2H); 7.05 (m, 1H); 7.16 (m, 2H); 7.27 (m, 2H). ^{13}C NMR ($CDCl_3$, 333 K) δ: 17.0 (CH_3); 17.4 (CH_3); 22.1 (CH_3); 24.9 (CH_2); 27.0 (CH_3); 31.2 (CH); 35.0 (CH_2); 40.8 (CH_2); 41.5 (CH_2); 42.2 (CH); 43.1 (CH); 47.3 (CH_2); 48.2 (CH); 52.5 (CH); 52.8 (CH); 57.4 (C); 75.7 (CH); 82.6 (CH); 125.6 (CH=); 126.5 (2CH=); 127.6 (2CH=); 137.6 (CH=); 137.8 (CH=); 142.5 (C=); 143.4 (C=); 176.3 (C=); 206.9 (C=O). IR (KBr dispersion): 3061; 2927; 1684; 1635. HRMS for $C_{29}H_{37}NO_2$: calcd 431.2824, found 432.2892 (M^++H).

*2.3.16. Adduct (**6′c**).* Colorless oil. $[\alpha]_D^{25}$=+180.49 ($CHCl_3$, c=1.22). ^{1}H NMR ($CDCl_3$) δ: 0.80–0.94 (m, 2H); 0.93 (d, 3H, J=6.5 Hz); 0.95–1.27 (m, 3H); 1.15 (s, 3H); 1.20 (s, 3H); 1.42–1.49 (m, 2H); 1.61 (d, 1H, J=5.1 Hz); 1.70 (s, 1H); 1.73 (s, 1H); 1.78 (d, 1H, J=5.1 Hz); 1.88 (m, 1H); 2.01 (s, 3H); 2.54 (s, 1H); 2.79 (s, 1H); 3.24 (d, 1H, J=16.7 Hz); 3.43 (dt, 1H, J_1=4.2 Hz, J_2=10.5 Hz); 3.83 (d, 1H, J=16.7 Hz); 5.21 (s, 1H); 6.11 (m, 2H); 7.05 (m, 1H); 7.11–7.17 (m, 4H). ^{13}C NMR ($CDCl_3$) δ: 14.7 (CH_3); 17.5 (CH_3); 22.2 (CH_3); 25.1 (CH_2); 27.3 (CH_3); 31.0 (CH); 34.8 (CH_2); 41.4 (CH_2); 41.6 (CH_2); 41.9 (CH); 43.2 (CH); 47.9 (CH_2); 49.5 (CH); 52.1 (2CH_2); 57.2 (C); 74.9 (CH); 81.6 (CH); 125.7 (CH=); 126.7 (2CH=); 127.5 (2CH=); 137.4 (CH=); 137.9 (CH=); 142.5 (C=); 143.6 (C=); 179.0 (C=); 207.8 (C=O). IR (film): 3061; 2927; 1689; 1643. HRMS for $C_{29}H_{37}NO_2$: calcd 431.2824, found 432.2882 (M^++H).

*2.3.17. Adduct (**5d**).* White solid. Mp 104.5–106.3 °C (from hexane). $[\alpha]_D^{25}$=+10.00 ($CHCl_3$, c=0.88). ^{1}H NMR ($CDCl_3$) δ: 0.08 (d, 1H, J=10.8 Hz); 0.31 (d, 1H, J=10.8 Hz); 0.89–0.95 (m, 2H); 0.94 (d, 3H, J=6.6 Hz); 0.96 (s, 3H); 0.97–1.25 (m, 3H); 1.33 (s, 3H); 1.36–1.66 (m, 5H); 1.72 (m, 1H); 1.79 (d, 1H, J=2.5 Hz); 1.92 (m, 1H); 2.08 (d, 1H, J=5.1 Hz); 2.13 (s, 1H); 2.48 (s, 1H); 3.58 (dt, 1H, J_1=3.9 Hz, J_2=10.5 Hz); 3.65 (d, 1H, J=12.2 Hz); 3.96 (d, 1H, J=18.2 Hz); 5.49 (s, 1H); 7.07 (m, 1H); 7.17–7.22 (m, 2H); 7.27–7.30 (m, 2H); 7.48 (d, 1H, J=2.5 Hz). ^{13}C NMR ($CDCl_3$, 333 K) δ: 19.3 (CH_3); 22.1 (CH_3); 24.9 (CH_2); 26.9 (CH_3); 28.4 (CH_2); 29.0 (CH_2); 30.5 (CH_2); 31.3 (CH); 35.0 (CH_2); 37.7 (CH); 38.7 (CH); 41.5 (CH_2); 46.6 (CH+CH_2); 48.3 (CH); 54.3 (CH); 57.3 (C); 76.4 (CH); 81.9 (CH); 125.6 (CH=); 126.7 (2CH=); 127.6 (2CH=); 143.3 (C=); 147.7 (C=); 162.7 (CH=); 208.2 (C=O). IR KBr (dispersion): 3031; 2951; 1698; 1637. HRMS for $C_{28}H_{37}NO_2$: calcd 419.2824, found 420.2897 (M^++H).

*2.3.18. Adduct (**6d**).* White solid. Mp 75.8–77.6 °C (from hexane). $[\alpha]_D^{25}$=+148.78 ($CHCl_3$, c=0.90). ^{1}H NMR ($CDCl_3$) δ: 0.80–0.93 (m, 2H); 0.94 (d, 3H, J=6.5 Hz); 0.98–1.02 (m, 2H); 1.08 (s, 3H); 1.11–1.88 (m, 3H); 1.35 (s, 3H); 1.42–1.59 (m, 5H); 1.64 (m, 1H); 1.72 (m, 1H); 1.93 (m, 1H); 2.04 (s, 1H); 2.08 (d, 1H, J=3.3 Hz); 2.27 (s, 1H); 3.56 (dt, 1H, J_1=4.0 Hz, J_2=10.5 Hz); 3.64 (d, 1H, J=17.2 Hz); 3.89 (d, 1H, J=17.2 Hz); 5.45 (s, 1H); 7.08 (m, 1H); 7.14–7.26 (m, 4H); 7.29 (d, 1H, J=2.3 Hz). ^{13}C NMR ($CDCl_3$) δ: 20.0 (CH_3); 22.3 (CH_3); 25.0 (CH_2); 27.4 (CH_3); 28.1 (CH_2); 29.1 (CH_2); 31.3 (CH+CH_2); 35.0 (CH_2); 37.9 (CH); 38.6 (CH); 41.4 (CH_2); 46.3 (CH_2); 46.6 (CH); 48.3 (CH); 53.9 (CH); 57.0 (C); 76.2 (CH); 81.2 (CH); 125.5 (CH=); 127.1 (2CH=); 127.7 (2CH=); 143.7 (C=); 148.0 (C=); 162.0 (CH=); 208.3 (C=O). IR (KBr dispersion): 3023; 2949; 1697; 1637. HRMS for $C_{28}H_{37}NO_2$: calcd 419.2824, found 420.2903 (M^++H).

*2.3.19. Adduct (**5′d**).* White solid. Mp 152.0–153.9 °C (from hexane). $[\alpha]_D^{25}$=+12.56 ($CHCl_3$, c=1.6). ^{1}H NMR ($CDCl_3$) δ: 0.29 (d, 1H, J=9.7 Hz); 0.71 (d, 1H, J=9.7 Hz); 0.75–1.27 (m, 3H); 0.93 (d, 3H, J=6.5 Hz); 0.96 (s, 3H); 1.32 (s, 3H); 1.39–1.73 (m, 4H); 1.92 (m, 1H); 2.17 (d, 1H, J=5.0 Hz); 2.28 (s, 1H); 2.61 (s, 1H); 2.65 (s, 1H); 3.57 (dt, 1H, J_1=4.1 Hz, J_2=10.4 Hz); 3.63 (d, 1H, J=18.3 Hz); 3.97 (d, 1H, J=18.3 Hz); 5.48 (s, 1H); 6.05 (dd, 1H, J_1=3.0 Hz, J_2=5.5 Hz); 6.12 (dd, 1H, J_1=3.0 Hz, J_2=5.5 Hz); 7.06 (m, 1H); 7.16–7.21 (m, 2H); 7.28 (m, 2H); 7.50 (d, 1H, J=2.4 Hz). ^{13}C NMR ($CDCl_3$, 333 K) δ: 19.2 (CH_3); 22.1 (CH_3); 24.9 (CH_2); 26.8 (CH_3); 31.3 (CH); 35.0 (CH_2); 40.7 (CH_2); 41.5 (CH_2); 42.7 (CH); 43.5 (CH); 46.7 (CH+CH_2); 47.8 (CH); 53.0 (CH); 57.3 (C); 76.4 (CH); 81.6 (CH); 125.6 (CH=); 126.7 (2CH=); 127.7 (2CH=); 137.1 (CH=); 138.3 (CH=); 143.2 (C=); 148.8 (C=); 162.5 (CH=); 206.6 (C=O). IR (KBr dispersion): 3053; 2922; 1698;

1638. HRMS for $C_{28}H_{35}NO_2$: calcd 417.2668, found 418.2735 (M^++H).

*2.3.20. Adduct (**6′d**).* White solid. Mp 141.7–143.3 °C (from hexane). $[\alpha]_D^{25}$=+134.69 ($CHCl_3$, *c*=1.28). ^{1}H NMR ($CDCl_3$) δ: 0.94 (d, 3H, *J*=6.5 Hz); 0.98–1.07 (m, 2H); 1.10 (s, 3H); 1.14–1.28 (m, 3H); 1.34 (s, 3H); 1.41–1.53 (m, 2H); 1.63–1.74 (m, 3H); 1.93 (m, 1H); 2.18 (s, 1H); 2.59 (s, 1H); 2.79 (s, 1H); 3.56 (dt, 1H, J_1=4.0 Hz, J_2=10.5 Hz); 3.66 (d, 1H, *J*=17.1 Hz); 3.93 (d, 1H, *J*=17.1 Hz); 5.42 (s, 1H); 6.06 (dd, 1H, J_1=3.0 Hz, J_2=5.5 Hz); 6.15 (dd, 1H, J_1=3.0 Hz, J_2=5.5 Hz); 7.05 (m, 1H); 7.14–7.26 (m, 4H); 7.33 (d, 1H, *J*=1.9 Hz). ^{13}C NMR ($CDCl_3$) δ: 19.8 (CH_3); 22.3 (CH_3); 25.0 (CH_2); 27.5 (CH_3); 31.3 (CH); 35.0 (CH_2); 41.4 (CH_2); 41.5 (CH_2); 42.8 (CH); 43.3 (CH); 46.4 (CH_2); 46.7 (CH); 47.9 (CH); 52.7 (CH); 57.0 (C); 76.2 (CH); 81.0 (CH); 125.6 (CH=); 127.2 (2CH=); 127.7 (2CH=); 136.9 (CH=); 138.4 (CH=); 143.6 (C=); 149.5 (C=); 162.1 (CH=); 207.3 (C=O). IR (Nujol dispersion): 3027; 2940; 1698. HRMS for $C_{28}H_{35}NO_2$: calcd 417.2668, found 418.2736 (M^++H).

2.4. Hydrolysis of the perhydrobenzoxazines nucleous. Synthesis of 2- or 3-formyl ciclopentenones. general procedure

To a solution of the corresponding adduct (1 mmol) in ethanol (2 mL) was added a 2% HCl solution in water (7.5 mL) and the mixture was refluxed until the reaction was completed (TLC). After cooling, the mixture was extracted with Et_2O (3×25 mL), the organic phase was washed with brine and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated and the oily residues were purified by flash chromatography on silica gel and DCM as a solvent.

*2.4.1. (3aR,4S,7R,7aS)-3-Formyl-2-phenyl-3a,4,5,6,7,7a-hexahydro-4,7-methanoinden-1-one (**7a**).* Yellowish oil (62%). $[\alpha]_D^{25}$=−72.11 ($CHCl_3$, *c*=0.52).^{1}H NMR ($CDCl_3$) δ: 1.01–1.10 (m, 2H); 1.32–1.52 (m, 2H); 1.58–1.80 (m, 2H); 2.46 (d, 1H, *J*=5.6 Hz); 2.49 (d, 1H, *J*=3.8 Hz); 2.56 (d, 1H, *J*=3.8 Hz); 2.99 (d, 1H, *J*=5.6 Hz); 7.36–7.43 (m, 2H); 7.46–7.53 (m, 3H); 10.14 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 28.4 (CH_2); 29.1 (CH_2); 31.7 (CH_2); 38.4 (CH); 40.1 (CH); 45.8 (CH); 54.2 (CH); 128.3 (CH=); 128.5 (2CH=); 129.9 (3CH=); 154.0 (C=); 160.3 (C=); 192.1 (CH=O); 210.5 (C=O). IR (film): 3058; 2960; 1704; 1676. HRMS for $C_{17}H_{16}O_2$: calcd 252.1150, found 307.1295 (M^++MeOH+Na). Chiral HPLC (Chiralpack AD-H, hexane/isopropanol 95:5, 1.0 mL/min, λ=220 nm); t_R=12.1 min) showed ee>99%.[19]

*2.4.2. (3aS,4R,7S,7aR)-3-Formyl-2-phenyl-3a,4,5,6,7,7a-hexahydro-4,7-methanoinden-1-one (ent-**7a**).* Yellowish oil $[\alpha]_D^{25}$=+78.46 ($CHCl_3$, *c*=0.26).

*2.4.3. (3aR,4S,7R,7aS)-3-Formyl-2-phenyl-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one (**7′a**).* Yellowish oil (71%). $[\alpha]_D^{25}$=−37.02 ($CHCl_3$, *c*=1.04). ^{1}H NMR ($CDCl_3$) δ: 1.25 (d, 1H, *J*=9.5 Hz); 1.48 (d, 1H, *J*=9.5 Hz); 2.57 (d, 1H, *J*=5.4 Hz); 2.99 (s, 1H); 3.07 (s, 1H); 3.10 (d, 1H, *J*=5.4 Hz); 6.25 (dd, 1H, J_1=3.1 Hz, J_2=5.6 Hz); 6.40 (dd, 1H, J_1=3.1 Hz, J_2=5.6 Hz); 7.38–7.42 (m, 2H); 7.43–7.52 (m, 3H); 10.13 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 41.7 (CH_2); 43.3 (CH); 44.7 (CH); 45.3 (CH); 53.2 (CH); 128.2 (CH=); 128.6 (2CH=); 129.9 (2CH=); 130.0 (CH=); 136.9 (CH=); 139.3 (CH=); 154.6 (C=); 160.0 (C=); 192.0 (CH=O); 208.9 (C=O). IR (film): 3061; 2983; 1708; 1678. HRMS for $C_{17}H_{14}O_2$: calcd 250.0994, found 305.1136 (M^++MeOH+Na).

*2.4.4. (3aS,4R,7S,7aR)-3-Formyl-2-phenyl-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one (ent-**7′a**).* Yellowish oil (69%) $[\alpha]_D^{25}$=+28.80 ($CHCl_3$, *c*=1.00).

*2.4.5. (3aR,4S,7R,7aS)-2-Formyl-3-methyl-3a,4,5,6,7,7a-hexahydro-4,7-methanoinden-1-one (**8**).* Yellowish oil (76%). $[\alpha]_D^{25}$=−43.33 ($CHCl_3$, *c*=0.30). ^{1}H NMR ($CDCl_3$) δ: 0.97–1.08 (m, 2H); 1.37 (m, 1H); 1.58–1.81 (m, 3H); 2.30 (d, 1H, *J*=5.5 Hz); 2.41 (d, 1H, *J*=4.3 Hz); 2.49 (s, 3H); 2.51 (d, 1H, *J*=4.3 Hz); 2.65 (d, 1H, *J*=5.5 Hz); 9.97 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 17.8 (CH_3); 28.3 (CH_2); 29.3 (CH_2); 31.8 (CH_2); 38.2 (CH); 39.1 (CH); 54.1 (CH); 54.2 (CH); 137.4 (C=); 189.1 (CH=O); 189.2 (C=); 208.0 (C=O). IR (film): 3051; 2953; 1689; 1643. Easily oxidized on standing, and the Mass spectra was registered for the acid. HRMS for $C_{17}H_{14}O_3$: calcd 206.0943, found 229.0829 (M^++Na).

*2.4.6. (3aS,4R,7S,7aR)-2-Formyl-3-methyl-3a,4,5,6,7,7a-hexahydro-4,7-methanoinden-1-one (ent-**8**).* Yellowish oil (64%). $[\alpha]_D^{25}$=+39.33 ($CHCl_3$, *c*=0.60).

*2.4.7. (3aR,4S,7R,7aS)-2-Formyl-3-methyl-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one (**8′**).* Yellowish oil (70%). $[\alpha]_D^{25}$=−63.46 ($CHCl_3$, *c*=0.26). ^{1}H NMR ($CDCl_3$) δ: 1.21 (d, 1H, *J*=9.6 Hz); 1.45 (d, 1H, *J*=9.6 Hz); 2.41 (d, 1H, *J*=5.4 Hz); 2.50 (s, 3H); 2.80 (d, 1H, *J*=5.4 Hz); 2.93 (s, 1H); 3.05 (s, 1H); 6.25–6.34 (m, 2H); 9.96 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 17.8 (CH_3); 41.7 (CH_2); 43.3 (CH); 43.9 (CH); 52.9 (CH); 53.8 (CH); 137.9 (C=); 138.1 (CH=); 138.3 (C=); 188.6 (C=); 189.1 (CH=O); 206.4 (C=O). IR (film): 3060; 2973; 1689; 1653.

*2.4.8. (3aS,4R,7S,7aR)-2-Formyl-3-methyl-3a,4,5,6,7,7a-hexahydro-4,7-methanoinden-1-one (ent-**8′**).* Yellowish oil (60%). $[\alpha]_D^{25}$=+68.75 ($CHCl_3$, *c*=0.32).

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Supplementary data

Supplementary data associated with this article, including copies of ^{1}H NMR and ^{13}C NMR spectra for all new compounds and ORTEP representation of XR structures for compounds **3′a** and **5c** can be found on the online version. Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.tet.2012.08.006.

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