Synthesis of [6,*n*] *cis*-fused ring compounds *via* Cr-mediated dearomatisation–ring-closing metathesis

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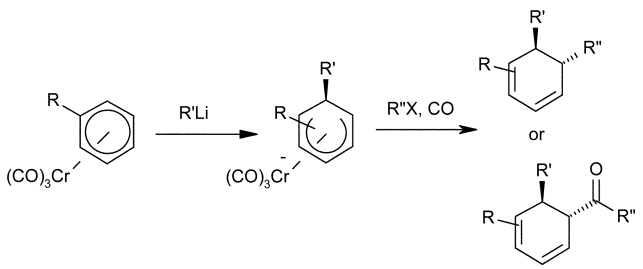
cis-Fused [6,8], [6,7], [6,6] and [6,5] ring systems containing a cyclohexadiene ring unit, a cycloenone ring and a quaternary carbon at the ring junction were obtained in only two steps from [$Cr(CO)_3$(η^6-*p*-methoxyphenyl oxazoline)]. The sequence proceeds *via* diastereoselective addition of three C-substituents across an arene double bond, followed by allylation and ring closing metathesis (RCM). RAMP-hydrazone and (*R*)-isopropyloxazoline were used as chiral auxiliaries to provide, after removal of the auxiliaries, the enantiomerically highly enriched [6,7] *cis*-fused system.

Introduction

The regio- and stereocontrolled addition of substituents across an arene double bond is an efficient route to alicyclic synthetic building blocks containing unmasked functionalities, new carbon–carbon bonds and new stereogenic centers.[1] Our research in this area has focused on $Cr(CO)_3$(arene) complexes.[2] Coordination to the electron withdrawing $Cr(CO)_3$ fragment enables the direct attack of the *exo* face of the arene by nucleophiles.[3] Subsequent alkylation of the anionic cyclohexadienyl complex intermediate at the metal center and reductive elimination gives a *trans* cyclohexadiene.[4] Depending on the nature of the electrophile and the substituents on the arene, the reductive elimination can be preceded by migratory CO insertion. In such a case, enolate chemistry allows the stereospecific introduction of a third substituent (Scheme 1).[5]



Scheme 1

Nucleophilic addition proceeds with generally high regioselectivity. Resonance donor substituents direct *meta*,[6] while bulky substituents and acceptor substituents direct *para*.[7] Finally, functional groups that can efficiently coordinate the incoming organolithium reagent direct *ortho*.[8]

Diasteromerically- or enantiomerically enriched products are accessible from arenes bearing chiral auxiliaries as substituents,[9] from planar chiral arene complexes,[10] from complexes containing a chiral ligand at the metal center,[11] or by using chiral nucleophiles to attack prochiral complexes.[12]

These methods have found applications in the synthesis of natural products and other molecules of interest.[13,14]

In a preliminary communication of this work we have shown that the Cr-mediated dearomatisation sequence could be combined with ring closing metathesis to access *cis*-fused ring systems bearing a Me group at one ring junction.[15] The structural unit of a *cis*-fused ring system with an angular Me group at the ring junction is frequently encountered in natural products.[16] Here we provide a more detailed account of this work, including the synthesis of highly enantiomerically enriched [6,7] ring systems.

Results and discussion

We chose the readily available complex [$Cr(CO)_3$(η^6-*p*-methoxyphenyloxazoline)] (**1**)[8b] as substrate for our initial studies because of the useful and varied functional groups that are implicit in the arene. *In situ* generated vinyllithium was the first nucleophile tested. Selective *ortho*-addition took place presumably because coordination of the reagent to the lone pair of the oxazoline precedes C–C-bond formation. This addition was followed by Cr alkylation with MeI in the presence of [NBu_4][Br],[17] migratory CO insertion and acetyl migration to the less substituted terminus of the cyclohexadienyl ligand (reductive elimination) to give the corresponding cyclohexadiene. The quaternary center was generated *via* enolate formation and diastereoselective introduction of the angular Me group from the less hindered face. The overall yield of 88% in this transformation that involves a dearomatisation with the chemo-, regio- and diastereoselective formation of three C–C bonds and two stereogenic centers attests to the high efficiency of this procedure (Scheme 2).

Next, with a second enolate formation and allylation it was possible to obtain diene **3**.[18] RCM for seven-membered ring formation with the first generation ruthenium carbene complex **8** was sluggish and yields obtained were generally below 40%. This result can be explained by the formation of a stable 7-membered chelate that sequesters the catalyst.[19] Fortunately, the use of the more reactive catalyst **9**[20] circumvented this problem and the [6,7] bicyclic system **4** was obtained in an excellent 88% yield.

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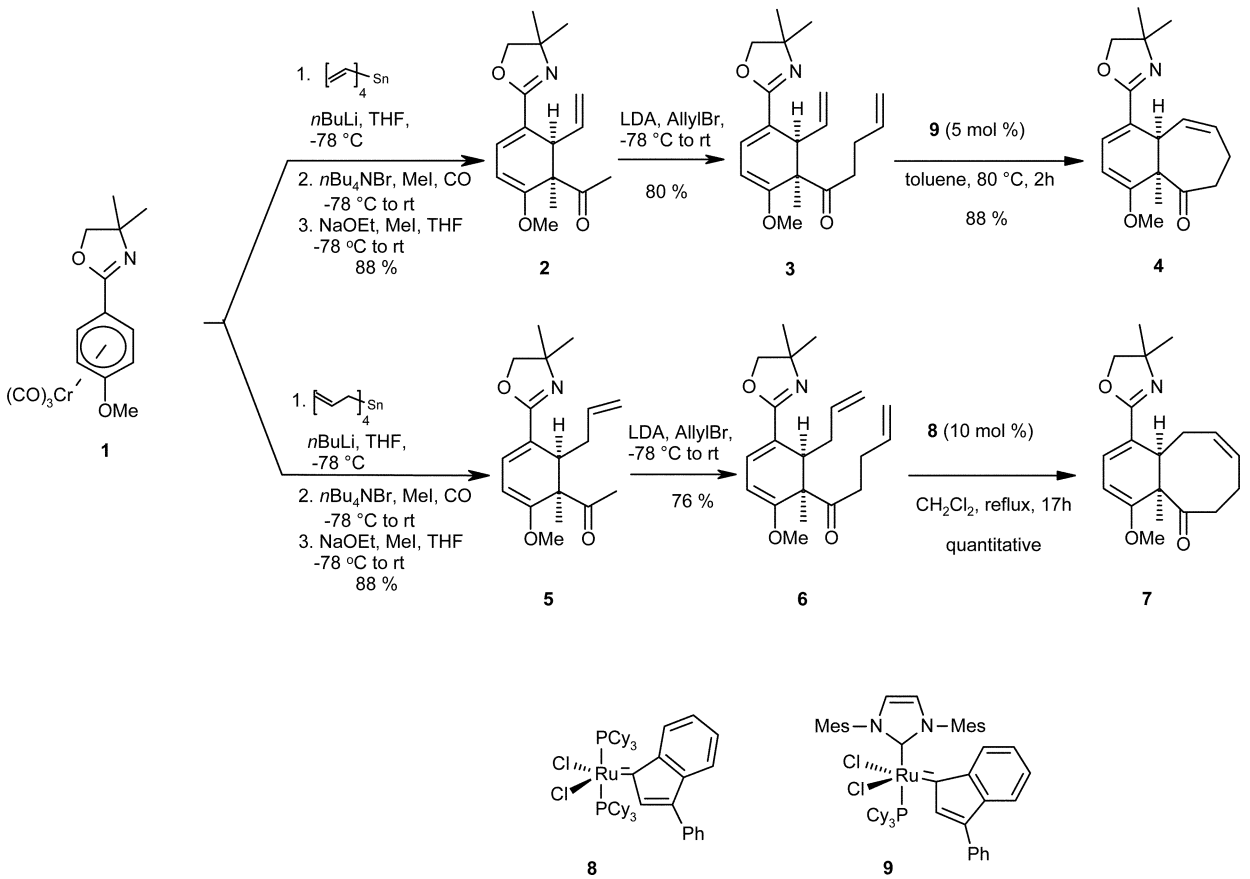
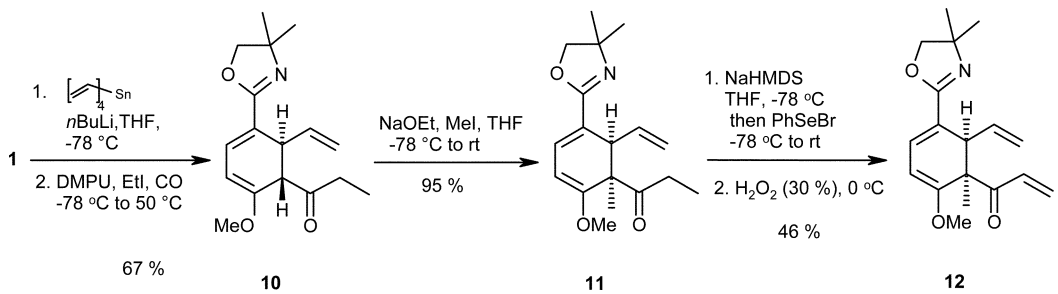


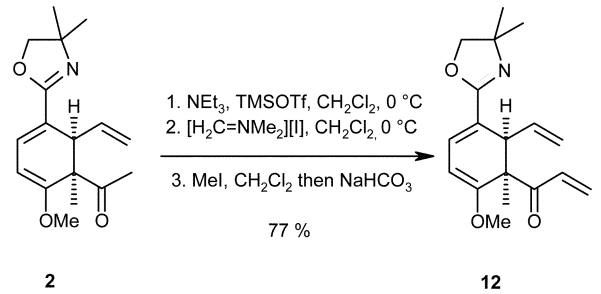
Scheme 2

The same procedure was used to synthesize *cis*-fused [6,8] bicyclic compound **7**. Starting with allyllithium in place of vinyllithium afforded **5** in 88% yield. Allylation afforded diene **6**. In this case RCM with ruthenium catalyst **8** proceeded smoothly giving the [6,8]-*cis*-fused **7** quantitatively (Scheme 2). Access to [6,6] and [6,5] fused rings was investigated next. The most straightforward strategy would involve the use of a vinyl halide as electrophile in the dearomatisation sequence. However, alkylation–carbonylation of the anionic [$Cr(CO)_3$(cyclohexadienyl)] complex intermediate starts with an S_N2 process and halides bound to an sp^2 C-fragment are therefore not suitable electrophiles for this reaction.[21] Moreover, attempts to use acyl electrophiles (acid halides, anhydrides), failed to yield the desired products. We therefore had recourse to stepwise formation of the required RCM precursors **12** and **15**. A first approach comprised vinyllithium addition to **1**, followed by reaction with ethyl iodide and carbonylation to give **10**. Deprotonation and quench with methyl iodide then gave cyclohexadiene **11** and selenation and elimination afforded the desired enone **12** (Scheme 3). This route is interesting because it shows that two different electrophiles can be used in steps 2 and 3 of the sequence. Isolation of **10** proved necessary. Without this step, product **11** was contaminated with its homologue, containing an angular ethyl group. Attempts at separation of the two compounds by FC was not successful.

A second and more efficient approach consisted in the preparation of the enone *via* Mannich reaction. Formation of the silyl enol ether, followed by alkylation with Eschenmoser's salt, N-methylation and elimination of the quaternary amine gave enone **12** in good yield (Scheme 4).

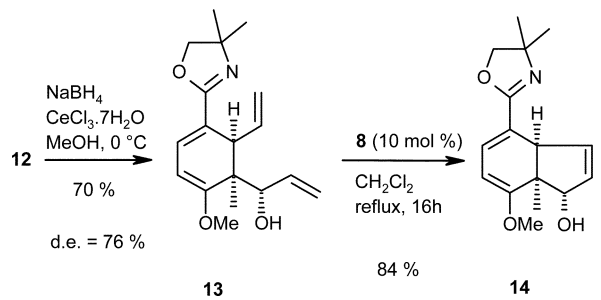


Scheme 3



Scheme 4

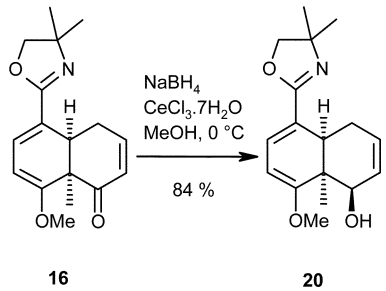
RCM of enone **12** was attempted with the Ru catalyst **9**, but no conversion was observed. This is consistent with the fact that electron poor dienes are less reactive in the metathesis reaction.[22] To avoid this problem enone **12** was diastereoselectively reduced under Luche conditions. The resulting alcohol **13** underwent RCM smoothly with the first generation catalyst **8**, to give the *cis*-fused ring compound **14**. The alcohol's stereochemistry of the major diastereoisomer was assigned by analogy to **19** (*vide infra*) (Scheme 5).



Scheme 5

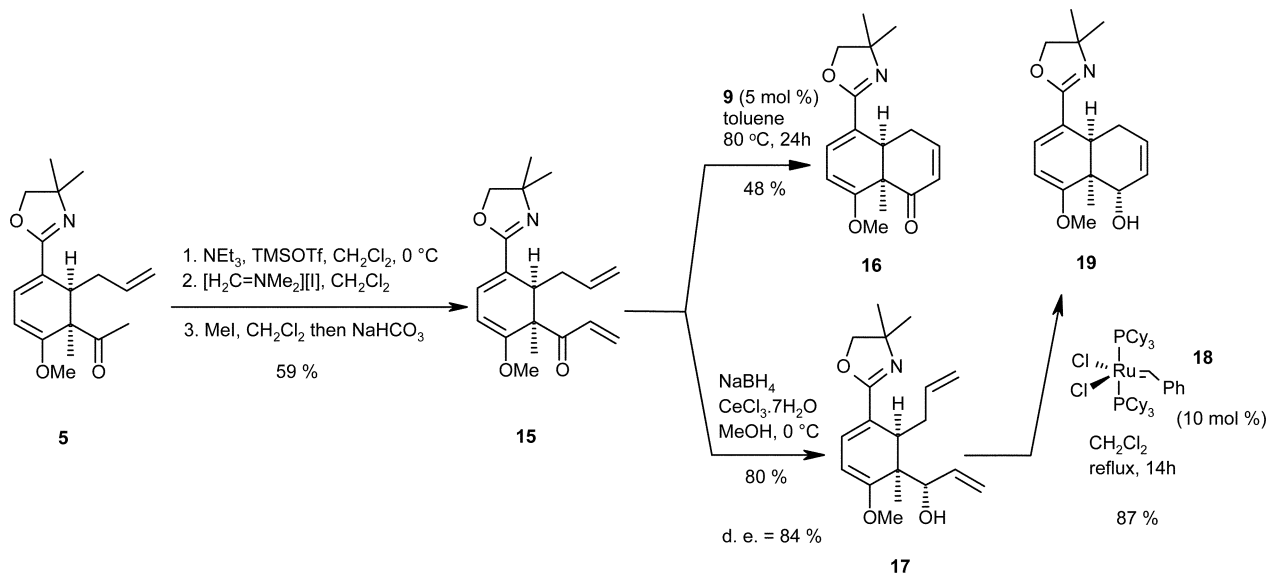
Following the same strategy, enone **15** was obtained starting from methyl ketone **5**. Metathesis was this time possible with catalyst **9**, but the reaction was sluggish and afforded **16** in 48% yield only. Reduction of **15** to the allylic alcohol **17** again resulted in a much more efficient RCM using catalyst **18** to obtain **19** in 87% yield (Scheme 6).

The relative stereochemistry in **19** was assigned by comparison of its NMR spectra with those of its diastereoisomer **20**. Previous work has shown that reduction of **16** to **20** occurs from the less hindered, convex face of the molecule, and this gives the opposite relative stereochemistry than that of allylic alcohol **19** (Scheme 7).[14]

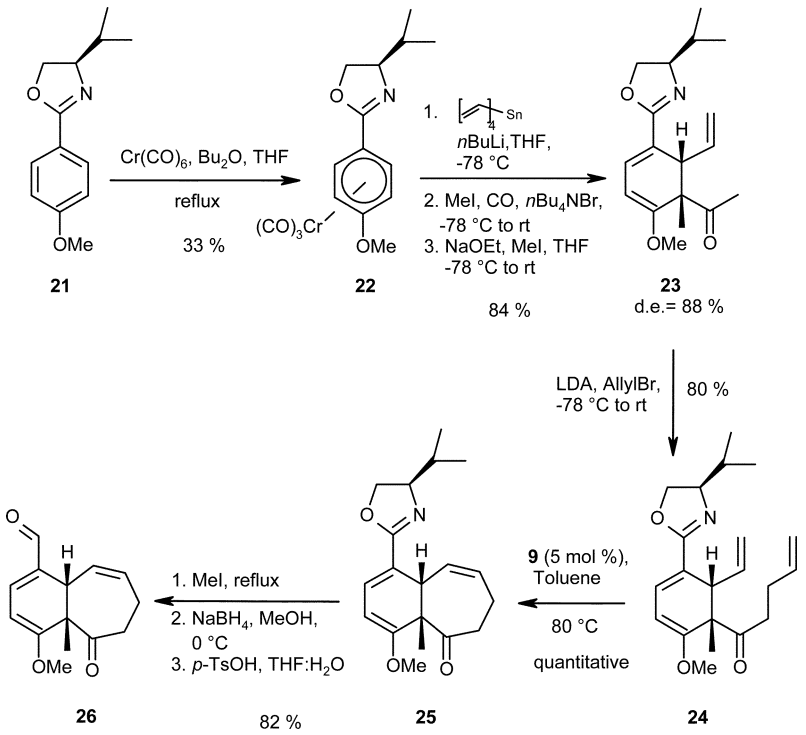


Scheme 7

Having gained efficient access to [6,8], [6,7], [6,6] and [6,5] *cis*-fused rings, the preparation of these compounds in enantiomerically enriched form was considered. In a first approach, complex **22**, bearing a chiral oxazoline, was prepared by thermal complexation.[23] Addition of vinyllithium proceeded with good diastereoselectivity, and trapping with methyl iodide followed by introduction of methyl group, as previously done, gave cyclohexadiene **23** with a diastereoisomeric excess of 88% (Scheme 8). Product stereochemistry reflects a transition state in which the isopropyl substituent of the chiral auxiliary is *syn* to the metal fragment.[8a] Allylation afforded diene **24**. Using the same conditions as for the racemic series afforded the diasteroisomerically enriched ring compound **25**. Finally, cleavage of the chiral oxazoline,[24] gave the enantiomerically enriched aldehyde **26** (Scheme 8).



Scheme 6

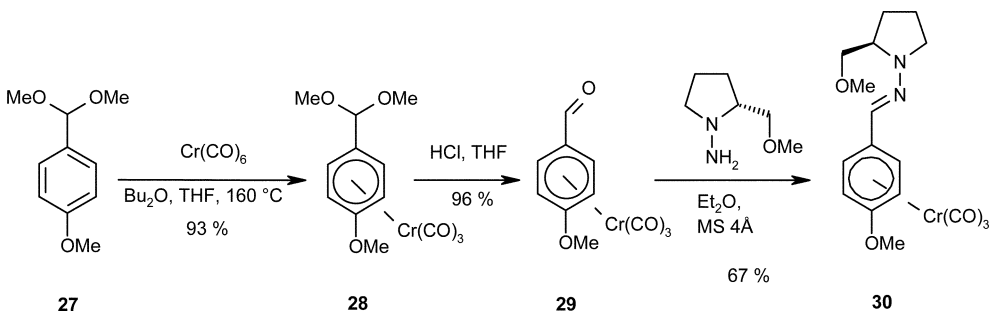


Scheme 8

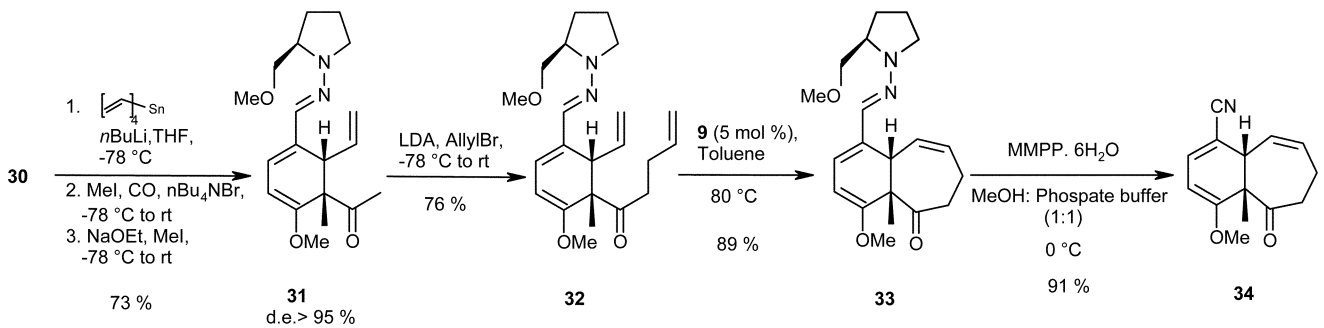
Another possibility involves the use of complex **30** containing RAMP-hydrazone as chiral auxiliary. This complex was synthesized by thermal complexation of anisaldehyde dimethyl acetal, followed by hydrolysis of the acetal **28** and treatment with the RAMP-hydrazone (Scheme 9).

Ring compound **33** was obtained by the same reaction sequence as the one used to obtain **25**. In this case, ^{1}H NMR showed a single diastereoisomer to be formed (de > 95%). Diastereoselectivity is interpreted as arising from the preference of a chair-like transition state over the boat-like transition state during addition of the chelated organolithium reagent.[9] Oxidative cleavage of the hydrazone[25] gave nitrile **34** in good yield (Scheme 10).

It is worth noting that intermediates **23** and **31** should give access to enantiomerically enriched [6,5] *cis*-fused systems by a similar sequence to the one described above.



Scheme 9



Scheme 10

In order to obtain [6,8] and [6,6] *cis*-fused rings, we next turned our attention to allyllithium as incoming nucleophile. Unfortunately, the diastereoselectivities obtained were below 15% starting from complexes **22** and **30**.

In conclusion, an efficient synthesis of highly functionalised *cis*-fused bicyclic [6,8], [6,7], [6,6], and [6,5] ring compounds has been achieved using arene chromium complexes as precursors. The use of chiral auxiliaries gives access to the enantiomerically highly enriched [6,7] bicyclic system. The application of this method to the synthesis of bioactive natural products is currently been studied in our laboratory.

Experimental

Reactions and manipulations were carried out under an atm. of N_2 using a N_2–vacuum double manifold and standard Schlenk techniques, using oven and heat gun-dried glassware. Solvents were distilled prior to use from sodium–benzophenone ketyl (THF), sodium (toluene) or CaH_2 (CH_2Cl_2). Commercially available solid chemicals were used without purification unless indicated; liquids were flash-distilled prior to use. Degassed solns. were obtained *via* three pump–freeze–thaw cycles. Flash chromatography (FC) (silica 60, 40 μm Fluka) was performed in air under pressure (0.2–0.3 bar). IR spectra were measured on a Perkin-Elmer 241 polarimeter with a NaCl cell. NMR spectra were measured on Bruker 400 or 500 MHz, or Varian-XL 200 spectrometers. Chemical shifts were referenced to solvent residual peak and are given in ppm relative to TMS. *J* values are given in Hz. Diastereoisomeric excess was measured by ^{1}H NMR integration. Analytical data always corresponds to the major diastereoisomer. Optical rotations were measured at 22 °C on a Perkin Elmer 241-polarimeter using quartz cell ($l = 10$ cm) with a Na high-pressure lamp ($\lambda = 589$ mm). High resoln. mass spectra were measured on a VG analytical 7070E instrument (data system 11250, resoln. 7000).

1-[5-(4,4-Dimethyl-4,5-dihydro-oxazol-2-yl)-2-methoxy-1-methyl-6-vinyl-cyclohexa-2,4-dienyl]-ethanone (2)

*n*BuLi (1.6 M in hexanes, 3.25 mL, 5.2 mmol) was rapidly added to tetravinyltin (470 μL, 2.6 mmol) at 25 °C. The white suspension was stirred for 2 h and then cooled to −78 °C followed by the addition of THF (32 mL). Complex **1** (1.364 g, 4 mmol) was added in one portion and the resulting orange soln. was stirred at this temp. in the dark for 1 h. nBu$_4$NBr (1.675 g, 5.2 mmol) and MeI (1.2 mL, 20 mmol) were next added and the mixture was placed under an atm. of CO (1.5 Bar) and warmed to rt overnight. Excess CO was vented and volatiles were removed under reduced pressure. The residue was dissolved in THF (40 mL), cooled to −78 °C and sodium ethoxide (2.56 M, 1.5 mL, 6 mmol) was added. The mixture was stirred for 1 h before methyl iodide (750 μL, 12 mmol) was added and the mixture was allowed to warm to rt overnight. The soln. was concentrated under reduced pressure and purified by FC (cyclohexane : AcOEt, 6 : 4) to give **2** (1.021 g, 88%) as a pale yellow solid. Mp = 94–97 °C; ν_{max}/cm^{-1} (CH_2Cl_2) 2970, 1706, 1607, 1571, 1461, 1269, 1203, 1039, 1001; δ_H (200 MHz; C_6D_6) 6.94 (1H, d, $J_{1,3}$ 6.7), 5.98–5.78 (1H, m), 5.34 (1H, dd, $J_{1,2}$ 1.92, $J_{1,3}$ 16.9), 4.95 (1H, dd, $J_{1,2}$ 1.92, $J_{1,3}$ 9.9), 4.72 (1H, d, $J_{1,3}$ 6.7), 3.77 (1H, d, $J_{1,3}$ 9.5), 3.67 (2H, s), 2.95 (3H, s), 2.02 (3H, s), 1.49 (3H, s), 1.18 (3H, s), 1.13 (3H, s); δ_C (50 MHz; C_6D_6) 206.4, 165.0, 161.1, 136.0, 119.1, 117.2, 93.5, 78.5, 67.6, 57.9, 54.8, 50.7, 31.2, 28.5, 28.3, 22.9, 20.6. HRMS (EI) on (M^+) for $C_{17}H_{23}NO_3$ requires 289.1678, found: 289.1670.

1-[5-(4,4-Dimethyl-4,5-dihydro-oxazol-2-yl)-2-methoxy-1-methyl-6-vinyl-cyclohexa-2,4-dienyl]-pent-4-en-1-one (3)

A soln. of **2** (289 mg, 1 mmol) in THF (8 mL) was added to freshly prepared LDA (addition of *n*BuLi (1.6 M, 0.7 mL, 1.12 mmol) to a soln. of diisopropylamine (200 μl, 1.43 mmol) in THF (5 mL) at 0 °C) at −78 °C. The mixture was stirred for 2 h and then allyl bromide (200 μl, 2.31 mmol) was added. The yellow–brown soln. was allowed to warm to rt overnight and then a sat. ammonium chloride soln. was added. The aq. layer was separated and extracted with Et_2O (3 × 10 mL). The organics were combined, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by FC (cyclohexane : Et_2O, 1 : 1) to give **3** (263 mg, 80%) as a pale yellow solid. Mp = 87–89 °C; ν_{max}/cm^{-1} (CH_2Cl_2) 2972, 2939, 1705, 1607, 1571, 1461, 1378, 1263, 1039, 1002, 919; δ_H (200 MHz; C_6D_6) 6.93 (1H, d, $J_{1,3}$ 6.7), 6.18–5.71 (2H, m), 5.53 (1H, dd, $J_{1,3}$ 2, 17), 5.08–4.91 (3H, m), 4.73 (1H, d, $J_{1,3}$ 6.7), 3.78 (1H, d, $J_{1,3}$ 9.6), 3.66 (2H, s), 2.94 (3H, s), 2.61–2.32 (4H, m), 1.49 (3H, s), 1.18 (3H, s), 1.12 (3H, s); δ_C (50 MHz; C_6D_6) 208.1, 164.9, 160.8, 138.2, 135.2, 118.4, 117.1, 114.4, 93.5, 78.2, 67.4, 57.5, 54.5, 50.6, 42.5, 28.5, 28.3, 28.1, 20.4; HRMS (EI) on (M^+) for $C_{20}H_{27}NO_3$ requires 329.1991, found: 329.1970.

1-(4,4-Dimethyl-4,5-dihydro-oxazol-2-yl)-4-methoxy-4a-methyl-4a,6,7,9a-tetrahydro-benzocyclohepten-5-one (4)

A soln. of **3** (120 mg, 0.36 mmol) and **9**[26] (17 mg, 5 mol%) in 40 mL of toluene was degassed and then heated at 80 °C for 2 h. The mixture was then concentrated under reduced pressure and the residue was purified by FC (cyclohexane : AcOEt, 7 : 3) to give **4** (96 mg, 88%) as a brown solid. Mp = 58–59 °C; ν_{max}/cm^{-1} (CH_2Cl_2) 2968, 2953, 1712, 1607, 1577, 1463, 1257, 1204, 1084, 1008; δ_H (200 MHz; C_6D_6) 6.94 (1H, d, $J_{1,3}$ 6.7), 6.18–6.08 (1H, m), 5.75–5.61 (1H, m), 4.65 (1H, d, $J_{1,3}$ 6.7), 3.85 (1H, d, $J_{1,3}$ 4.7 Hz), 3.70 (1H, d, $J_{1,2}$ 7.9), 3.68 (1H, d, $J_{1,2}$ 7.9), 2.90 (3H, s), 2.53 (3H, s), 1.67–1.48 (1H, m), 1.53 (3H, s), 1.16 (3H, s), 1.13 (3H, s); δ_C (50 MHz; C_6D_6) 207.7, 164.9, 161.7, 132.9, 127.1, 120.6, 92.6, 78.7, 67.7, 55.1, 54.7, 47.0, 45.4, 28.6, 28.5, 21.9, 21.7; HRMS (EI) on (M^+) for $C_{18}H_{23}O_3N$ requires 301.1677, found: 301.1670.

1-[6-Allyl-5-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-2-methoxy-1-methyl-cyclohexa-2,4-dienyl]-ethanone (5)

Complex **1** (852 mg, 2.5 mmol) was treated with allyllithium (prepared from *n*BuLi and allyltin) and MeI–CO following the procedure described for the preparation of **2**. Purification by FC (cyclohexane : AcOEt, 1 : 1) afforded **5** (668 mg, 88%) as a pale yellow solid. Mp = 56–58 °C; ν_{max}/cm^{-1} (CH_2Cl_2) 2964, 2932, 1703, 1605, 1572, 1458, 1354, 1245, 1201, 1043, 1000, 913; δ_H (200 MHz; C_6D_6) 6.98 (1H, d, $J_{1,3}$ 6.7), 6.22–6.02 (1H, m), 5.09–4.93 (2H, m), 4.77 (1H, d, $J_{1,3}$ 6.7), 3.71 (2H, d, $J_{1,2}$ 7.9), 3.44 (1H, t, $J_{1,3}$ 6.4), 3.04 (3H, s), 2.47 (2H, t, $J_{1,3}$ 6.4), 2.03 (3H, s), 1.45 (3H, s), 1.23 (3H, s), 1.19 (3H, s); δ_C (50 MHz; $CDCl_3$) 207.3, 165.3, 162.1, 136.7, 119.9, 115.4, 93.3, 78.3, 67.4, 56.6, 54.6, 44.4,

35.7, 30.7, 28.0, 21.6; HRMS (EI) on (M^+) for $C_{18}H_{25}NO_3$ requires 303.1834, found: 303.1823.

1-[5-(4,4-Dimethyl-4,5-dihydro-oxazol-2-yl)-2-methoxy-1-methyl-6-allyl-cyclohexa-2,4-dienyl]-pent-4-en-1-one (6)

Diene **5** (290 mg, 0.96 mmol) was treated with LDA and allylBr following the procedure described for the preparation of **3**. Purification by FC (cyclohexane : AcOEt, 1 : 1) gave **6** (250 mg, 76%) as a pale yellow oil. ν_{max}/cm^{-1} (CH_2Cl_2) 2971, 2934, 1703, 1606, 1572, 1461, 1265, 1247, 1207, 1001, 916; δ_H (200 MHz; C_6D_6) 6.94 (1H, d, $J_{1,3}$ 6.7), 6.22–5.98 (1H, m), 5.87–5.66 (1H, m), 5.09–4.88 (4H, m), 4.74 (1H, d, $J_{1,3}$ 6.7), 3.68 (2H, d, $J_{1,2}$ 7.9), 3.43 (1H, t, $J_{1,3}$ 7.1), 3.02 (3H, s), 2.58–2.29 (6H, m), 1.41 (3H, s), 1.20 (3H, s), 1.15 (3H, s); δ_C (50 MHz; C_6D_6) 209.0, 166.1, 162.6, 138.2, 137.0, 119.9, 115.8, 115.2, 93.8, 78.7, 67.7, 56.9, 54.9, 44.9, 42.1, 36.0, 28.7, 28.4, 21.9; HRMS (EI) on (M^+) for $C_{21}H_{29}NO_3$ requires 343.2147, found: 343.2152.

1-(4,4-Dimethyl-4,5-dihydro-oxazol-2-yl)-4-methoxy-4a-methyl-6,7,10,10a-tetrahydro-4a*H*-benzocycloocten-5-one (7)

A soln. of **6** (150 mg, 0.44 mmol) and **8**[27] (40 mg, 10 mol%) in CH_2Cl_2 (44 mL) was degassed and heated at reflux, under N_2 for 17 h. The mixture was then concentrated and the residue was purified by FC (cyclohexane : Et_2O, 1 : 1) to give **7** as a brown solid. Mp = 127–129 °C; ν_{max}/cm^{-1} (CH_2Cl_2) 2969, 2934, 1703, 1606, 1573, 1455, 1378, 1248, 1204, 1045, 1007, 708; δ_H (200 MHz; C_6D_6) 6.91 (1H, d, $J_{1,3}$ 6.7), 5.88–5.71 (1H, m), 5.58–5.45 (1H, m), 4.75 (1H, d, $J_{1,3}$ 6.7 Hz), 3.69 (1H, d, $J_{1,2}$ 7.9), 3.65 (1H, d, $J_{1,2}$ 7.9), 3.15–2.98 (3H, m), 2.95 (3H, s), 2.72–2.50 (1H, m), 2.38–2.20 (2H, m), 2.18–1.93 (1H, m), 1.46 (3H, s), 1.17 (3H, s), 1.14 (3H, s); δ_C (50 MHz; C_6D_6) 210.2, 165.1, 161.6, 130.8, 126.1, 121.9, 93.1, 78.6, 67.7, 55.6, 54.9, 44.9, 41.2, 29.2, 28.7, 28.5, 26.4, 21.1; HRMS (EI) on (M^+) for $C_{19}H_{25}O_3N$ requires 315.1834, found: 315.1814.

1-[5-(4,4-Dimethyl-4,5-dihydro-oxazol-2-yl)-2-methoxy-6-vinyl-cyclohexa-2,4-dienyl]-propan-1-one (10)

*n*BuLi (1.6 M in hexanes, 750 μL, 1.2 mmol) was rapidly added to tetravinyltin (110 μL, 0.6 mmol) at 25 °C. The white soln. was stirred 2 h and then cooled to −78 °C before addition of THF (8 mL). Complex **1** (341 mg, 1 mmol) was added in one portion and the resulting orange soln. was stirred at this temp. in the dark for 1 h. After this time, DMPU (1.2 mL, 10 mmol) and EtI (800 μL, 10 mmol) were next added and the mixture was placed under CO (1.5 Bar) and warmed up to rt overnight. Then it was stirred at 50 °C for 1 h. Excess CO was vented and the volatiles were removed under reduced pressure. The residue was purified by FC (cyclohexane : Et_2O, 6 : 4) to give the cyclohexadiene **10** (194 mg, 67%) as a pale yellow solid. Mp = 67–69 °C; δ_H (500 MHz; $CDCl_3$) 6.77 (1H, bs), 5.86–5.80 (1H, m), 5.23 (1H, d, $J_{1,3}$ 5.8), 5.05 (1H, d, $J_{1,3}$ 6.4), 5.01 (1H, d, $J_{1,3}$ 10.4), 3.97 (1H, d, $J_{1,3}$ 4.9), 3.95 (1H, d, $J_{1,2}$ 7.9), 3.89 (1H, d, $J_{1,2}$ 7.9), 3.70 (3H, s), 3.06 (1H, s), 2.60–2.47 (2H, m), 1.32 (3H, s), 1.26 (3H, s), 1.01 (3H, t, $J_{1,3}$ 7.2); δ_C (50 MHz; $CDCl_3$) 207.1, 161.5, 158.9, 136.2, 114.2, 94.5, 78.6, 67.1, 55.4, 55.4, 53.2, 39.1, 33.1, 28.3, 28.1, 7.7; HRMS (EI) on (M^+) for $C_{17}H_{23}O_3N$ requires 289.1678, found: 289.1681.

1-[5-(4,4-Dimethyl-4,5-dihydro-oxazol-2-yl)-2-methoxy-1-methyl-6-vinyl-cyclohexa-2,4-dienyl]-propan-1-one (11)

NaOEt in EtOH (2.46 M, 820 μL, 2.01 mmol) was added dropwise to a soln. of **10** (387 mg, 1.34 mmol) in THF (10 mL) at −78 °C. The mixture was stirred for 1 h before MeI (125 μL, 2.01 mmol) was added and the mixture was allowed to warm to rt overnight. The soln. was concentrated under reduced pressure and purified by FC (cyclohexane : Et_2O, 6 : 4) to give **11** (384 mg, 95%) as a colourless oil. ν_{max}/cm^{-1} (CH_2Cl_2) 2974, 2934, 1706, 1654, 1607, 1570, 1456, 1378, 1246, 1039, 1003; δ_H (400 MHz; C_6D_6) 6.84 (1H, d, $J_{1,3}$ 6.7), 5.78 (1H, dt, $J_{1,3}$ 16.9, 9.7), 5.21 (1H, dd, $J_{1,2}$ 2.0, $J_{1,3}$ 16.9), 4.84, (1H, dd, $J_{1,2}$ 2.0, $J_{1,3}$ 9.7), 4.69 (1H, d, $J_{1,3}$ 6.7), 3.65 (1H, d, $J_{1,3}$ 9.7), 3.62–3.57 (2H, m), 2.94 (3H, s), 2.34–2.16 (2H, m), 1.40 (3H, s), 1.10 (3H, s), 1.05 (3H, s), 0.99 (3H, t, $J_{1,3}$ 7.0); δ_C (100 MHz; C_6D_6) 209.3, 164.9, 135.2, 127.1, 118.5, 116.7, 93.3, 78.0, 67.2, 57.4, 54.4, 50.5, 35.9, 28.1, 27.9, 20.2, 7.8; HRMS (EI) on (M^+) for $C_{18}H_{25}O_3N$ requires 302.1756, found 302.1712.

1-[5-(4,4-Dimethyl-4,5-dihydro-oxazol-2-yl)-2-methoxy-1-methyl-6-vinyl-cyclohexa-2,4-dienyl]-propenone (12)

Method A. NaHMDS in THF (1.0 M, 2.3 mL, 2.30 mmol) was added dropwise to a soln. of **11** (348 mg, 1.15 mmol) in THF (16 mL) at −78 °C. The mixture was stirred for 4 h and then PhSeBr (408 mg, 1.73 mmol) was added in one portion. The mixture was warmed to rt overnight. A sat. aq. NH_4Cl soln. was added and the mixture was extracted with Et_2O. The organics were combined, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by FC (cyclohexane : Et_2O, 7 : 3) to give the product of selenation (389 mg) as a mixture of the two diastereoisomers. They were dissolved in 5 mL of CH_2Cl_2 and cooled to −78 °C before dropwise addition of 30% aq. soln. of hydrogen peroxide (200 μL, 1.70 mmol). The mixture was stirred at 0 °C for 3 h and then concentrated and purified by FC (cyclohexane : Et_2O, 7 : 3) to afford **12** (160 mg, 46%) as a white solid.

Method B. TMSOTf (840 μL, 4.7 mmol) was slowly added to a soln. of **2** (908 mg, 3.1 mmol) and NEt_3 (655 μL, 4.7 mmol) in CH_2Cl_2 (30 mL) at 0 °C. The mixture was stirred 1 h and then filtered with ether over a pad of neutral alumina activated with 10% water. Solvents were evaporated and the oil was dissolved in 20 mL of CH_2Cl_2 and added *via* syringe to a suspension of Eschenmosser's salt (1.143 g, 6.2 mmol) in 40 mL of CH_2Cl_2 at 0 °C. The mixture was stirred for 2 h and then NaOH (1 M, 4 mL, 6.2 mmol) was added and the mixture poured onto brine : H_2O (1 : 1) and extracted 3 times with CH_2Cl_2. The combined organic layers were washed with brine and dried with Na_2SO_4. Solvents were evaporated to obtain a grey–green oil which was dissolved in 40 mL of CH_2Cl_2 and MeI (965 μL, 15.5 mmol) was added. After 15 min a precipitate appeared and the mixture was stirred for 1.5 h. Then 40 mL of a sat. $NaHCO_3$ aq. soln. was added and the mixture was extracted 3 times with CH_2Cl_2 and the combined organic layers were washed with brine and dried with Mg_2SO_4. Solvents were evaporated and the residue was purified by FC (cyclohexane : AcOEt, 7 : 3) to give **12** (720 mg, 77%) as a white solid. Mp = 87–89 °C; ν_{max}/cm^{-1} (CH_2Cl_2) 2970, 2934, 1697, 1609, 1573, 1456, 1398, 1246, 1039, 1003; δ_H (400 MHz; C_6D_6) 6.90 (1H, d, $J_{1,3}$ 6.7), 6.23–6.25 (2H, m), 5.77 (1H, dt, $J_{1,3}$

19.2, 9.6), 5.28 (1H, dd, $J_{1,2}$ 1.9, $J_{1,3}$ 16.9), 5.04 (1H, dd, $J_{1,3}$ 6.7, 5.6), 4.92 (1H, dd, $J_{1,2}$ 1.9, $J_{1,3}$ 9.6), 4.69 (1H, d, $J_{1,3}$ 6.7), 3.79 (1H, d, $J_{1,3}$ 9.6), 3.60 (2H, m), 2.89 (3H, s) 1.50 (3H, s), 1.11 (3H, s), 1.04 (3H, s); δ_C (125 MHz; C_6D_6) 197.9, 164.8, 161.1, 136.6, 135.0, 127.5, 123.9, 119.3, 117.9, 93.8, 78.5, 67.7, 55.8, 54.8, 50.9, 28.5, 28.3, 20.4; HRMS (EI) on (M^+) for $C_{18}H_{23}O_3N$ requires 301.1677, found: 301.1646.

1-[5-(4,4-Dimethyl-4,5-dihydro-oxazol-2-yl)-2-methoxy-1-methyl-6-vinyl-cyclohexa-2,4-dienyl]-prop-2-en-1-ol (13)

$NaBH_4$ (12 mg, 0.31 mmol) was added to a soln. of **12** (100 mg, 0.31 mmol) and $CeCl_3{\cdot}7H_2O$ (118 mg, 0.31 mmol) in MeOH (3 mL) at 0 °C. The mixture was stirred for 1 h and then concentrated and purified by FC (cyclohexane : Et_2O, 1 : 1) to give **13** (66 mg, 70%, de = 76%) as a white solid. ν_{max}/cm^{-1} (Et_2O) 3586, 2952, 2825, 1654, 1609, 1574, 1381, 1371, 1130, 1114, 1066; δ_H (400 MHz; C_6D_6) 6.79 (1H, d, $J_{1,3}$ 6.4), 6.20–6.05 (1H, m), 5.91 (1H, dt, $J_{1,3}$ 19.4, 9.3), 5.70 (1H, dt, $J_{1,2}$ 0.9, $J_{1,3}$ 17.0), 5.46 (1H, dd, $J_{1,2}$ 2.2, $J_{1,3}$ 17.6), 5.16 (1H, dt, $J_{1,2}$ 0.9, $J_{1,3}$ 17.0), 5.01 (1H, dd, $J_{1,2}$ 2.2, $J_{1,3}$ 9.1), 4.65–4.63 (1H, m), 4.55 (1H, d, $J_{1,3}$ 6.4), 3.65 (1H, d, $J_{1,3}$ 9.3), 3.61 (1H, d, $J_{1,2}$ 7.8), 3.57 (1H, d, $J_{1,2}$ 7.8), 3.36–3.35 (1H, m), 2.73 (3H, s), 1.32 (3H, s), 1.11 (3H, s), 1.07 (3H, s); δ_C (100 MHz; C_6D_6) 168.2, 161.0, 135.4, 133.4, 120.8, 117.0, 116.8, 93.0, 78.0, 72.7, 67.2, 54.5, 48.6, 45.6, 28.2, 27.9, 26.8, 15.4; HRMS (EI) on (M^+) for $C_{18}H_{25}O_3N$ requires 303.1834, found: 303.1859.

4-(4,4-Dimethyl-4,5-dihydro-oxazol-2-yl)-7-methoxy-7a-methyl-3a,7a-dihydro-1*H*-inden-1-ol (14)

A soln. of **13** (445 mg, 1.46 mmol) and RCM catalyst **8** (10 mol%, 134 mg, 0.15 mmol) in CH_2Cl_2 (100 mL) was degassed and then heated overnight at reflux, under N_2. The mixture was then concentrated to give a brown residue which was purified by FC (cyclohexane : Et_2O, 1 : 1) to give **14** (338 mg, 84%) as a pale yellow solid. Mp = 107–109 °C; ν_{max}/cm^{-1} (CH_2Cl_2) 3586, 2966, 2932, 2869, 1660, 1606, 1578, 1453, 1235, 1093, 1011, 814, 503 cm^{-1}; δ_H (500 MHz; C_6D_6) 6.97 (1H, d, $J_{1,3}$ 6.8) 6.11 (1H, dd, $J_{1,3}$ 5.7, 1.9), 6.01–5.99 (1H, m), 5.10 (1H, s), 4.73 (1H, d, $J_{1,3}$ 6.8), 4.19–4.17 (1H, m), 3.72 (1H, d, $J_{1,2}$ 7.9), 3.70 (1H, dd, $J_{1,3}$ 7.9), 3.02 (3H, s), 1.98 (1H, bs), 1.43 (3H, s), 1.22 (3H, s), 1.21 (3H, s); δ_C (125 MHz; C_6D_6) 167.8, 162.7, 135.9, 132.5, 128.2, 116.2, 91.6, 81.7, 78.5, 67.5, 54.8, 51.9, 50.5, 28.5, 28.4, 20.2; HRMS (EI) on (M^+) for $C_{16}H_{21}NO_3$ requires 275.1521, found: 275.1509.

1-[6-Allyl-5-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-2-methoxy-1-methyl-cyclohexa-2,4-dienyl]-propanone (15)

Compound **5** (303 mg, 1 mmol) was reacted following the procedure described for the preparation of **12** (Method B). Purification by FC (cyclohexane : AcOEt, 6 : 4) gave **15** (185 mg, 59%) as an colourless solid. Mp = 125–126 °C; ν_{max}/cm^{-1} (CH_2Cl_2) 2971, 2934, 1693, 1609, 1573, 1398, 1246, 1048, 1003; δ_H (500 MHz; C_6D_6) 7.0 (1H, d, $J_{1,3}$ 6.7), 6.48 (1H, dd, $J_{1,3}$ 16.9, 10.0), 6.36 (1H, dd, $J_{1,2}$ 2.2, $J_{1,3}$ 16.9), 6.15–6.06 (1H, m), 5.13 (1H, dd, $J_{1,2}$ 2.2, $J_{1,3}$ 10.0), 5.05 (1H, d, $J_{1,3}$ 16.9), 4.97 (1H, d, $J_{1,3}$ 10.0), 4.79 (1H, d, $J_{1,3}$ 6.7), 3.74 (1H, d, $J_{1,2}$ 7.8), 3.67 (1H, d, $J_{1,2}$ 7.8), 3.53 (1H, dd, $J_{1,3}$ 9.0, 4.9), 3.00 (3H, s), 2.59–2.47 (2H, m), 1.58 (3H, s), 1.22 (3H, s), 1.18 (3H, s); δ_C (125 MHz; C_6D_6) 198.9, 165.3, 162.3, 137.1, 136.2, 128.3, 127.6, 124.9, 120.7, 115.6, 93.8, 78.6, 67.7, 55.6, 54.9, 45.2, 36.1, 28.2, 21.4; HRMS (EI) on (M^+) for $C_{19}H_{25}O_3N$ requires 315.1834, found: 315.1877.

1-(4,4-Dimethyl-4,5-dihydro-oxazol-2-yl)-4-methoxy-4a-methyl-4a,6,7,9a-tetrahydro-benzocyclohexen-5-one (16)

Compound **15** (129 mg, 0.41 mmol) was reacted following the procedure described for the preparation of **4** and the residue was purified by FC (cyclohexane : AcOEt, 6 : 4) to give **16** (57 mg, 48%) as a brown solid. Mp = 153–156 °C; ν_{max}/cm^{-1} (CH_2Cl_2) 2971, 2932, 1676, 1602, 1566, 1395, 1344, 1244, 1179, 1079, 1007, 762, 706; δ_H (400 MHz; C_6D_6) 6.90 (1H, d, $J_{1,3}$ 6.4 Hz), 6.27–6.25 (1H, m), 6.07 (1H, dd, $J_{1,3}$ 2.3, 10.2), 4.73 (1H, d, $J_{1,3}$ 6.6), 3.72 (1H, d, $J_{1,2}$ 8.1), 3.71 (1H, d, $J_{1,2}$ 8.1), 3.52 (1H, dd, $J_{1,3}$ 5.5, 10.5), 2.94 (3H, s), 2.49 (1H, ddt, $J_{1,2}$ 19.4, $J_{1,3}$ 0.8, 5.5), 2.30 (1H, ddt, $J_{1,2}$ 19.4, $J_{1,3}$ 2.6, 10.5), 1.57 (3H, s), 1.20 (3H, s), 1.19 (3H, s); δ_C (100 MHz; C_6D_6) 195.0, 163.5, 161.4, 147.9, 129.4, 128.0, 120.9, 92.7, 78.4, 67.3, 55.0, 50.6, 42.7, 28.4, 28.2, 27.9, 18.9; HRMS (EI) on (M^+) for $C_{17}H_{21}NO_3$ requires 287.1521, found: 287.1523.

1-[6-Allyl-5-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-2-methoxy-1-methyl-cyclohexa-2,4-dienyl]-prop-2-en-1-ol (17)

Compound **15** (98 mg, 0.31 mmol) was reacted following the procedure described for the preparation of **13**. Purification by chromatography (cyclohexane : Et_2O, 1 : 1) gave **17** (81 mg, 80%, de = 84%) as a pale yellow oil. ν_{max}/cm^{-1} (CH_2Cl_2) 3575, 3074, 2972, 2930, 1715, 1607, 1573, 1440, 1362, 1296, 1264, 1238, 1208, 1170, 1042, 995; δ_H (500 MHz; $CDCl_3$) 6.68 (1H, d, $J_{1,3}$ 6.4), 6.08–6.01 (1H, m), 5.81–5.73 (1H, m), 5.45 (1H, d, $J_{1,3}$ 17.0), 5.29 (1H, d, $J_{1,3}$ 10.6), 5.05 (1H, d, $J_{1,3}$ 6.5 Hz), 4.85 (1H, d, $J_{1,3}$ 17.0), 4.76 (1H, d, $J_{1,3}$ 9.9), 4.59 (1H, d, $J_{1,3}$ 6.1), 3.90 (1H, d, $J_{1,2}$ 7.8), 3.83 (1H, d, $J_{1,2}$ 7.8), 3.69 (3H, s), 3.29 (1H, d, $J_{1,3}$ 1.6), 2.66 (1H, dd, $J_{1,3}$ 3.9, 9.5), 2.34–2.29 (1H, m), 2.24–2.17 (1H, m), 1.29 (3H, s), 1.22 (3H, s), 1.11 (3H, s); δ_C (125 MHz; C_6D_6) 168.2, 162.4, 136.8, 135.3, 128.1, 121.6, 118.3, 115.0, 93.4, 78.3, 72.9, 67.3, 55.9, 43.3, 42.7, 32.2, 28.0, 27.9, 16.1; HRMS (EI) on (M^+) for $C_{19}H_{27}NO_3$ requires 317.1991, found: 317.1986.

5-(4,4-Dimethyl-4,5-dihydro-oxazol-2-yl)-8-methoxy-8a-methyl-1,4,4a,8a-tetrahydro-naphthalen-1-ol (19)

A soln. of **17** (44 mg, 0.14 mmol) and **18** (10 mol%, 11 mg, 0.014 mmol) in CH_2Cl_2 (30 mL) was degassed and then heated overnight at reflux under N_2. The mixture was then concentrated to give a brown residue which was purified by FC (Et_2O) to give **19** (35 mg, 87%) as a pale yellow oil. ν_{max}/cm^{-1} (CH_2Cl_2) 3593, 3030, 2967, 2931, 1646, 1599, 1560, 1454, 1345, 1223, 1011, 811; δ_H (500 MHz; C_6D_6) 6.95 (1H, d, $J_{1,3}$ 6.4), 6.04–6.01 (1H, m), 5.81–5.77 (1H, m), 4.75 (1H, d, $J_{1,3}$ 6.4), 4.56 (1H, s), 3.73 (1H, d, $J_{1,2}$ 7.9), 3.721 (1H, d, $J_{1,2}$ 7.9), 3.45 (1H, dd, $J_{1,3}$ 10.1, 6.5), 3.02 (3H, s), 2.70–2.62 (1H, m), 2.17–2.08 (1H, m), 1.97 (1H, s), 1.54 (3H, s), 1.24 (3H, s), 1.21 (3H, s); δ_C (125 MHz; C_6D_6) 168.4, 162.6, 131.1, 128.9, 128.3, 123.2, 92.8, 78.5, 67.3, 64.2, 54.9, 42.6, 34.8, 30.1, 28.6, 28.5, 21.5; HRMS (EI) on (M^+) for $C_{17}H_{23}O_3N$ requires 289.1678, found: 289.1693.

5-(4,4-Dimethyl-4,5-dihydro-oxazol-2-yl)-8-methoxy-8a-methyl-1,4,4a,8a-tetrahydro-naphthalen-1-ol (20)

Compound **16** (17 mg, 0.06 mmol) was reacted following the procedure described for the preparation of **13**. Purification by FC (cyclohexane : AcOEt, 1 : 1) afforded **20** (16 mg, 84%) as a pale yellow oil. ν_{max}/cm^{-1} (CH_2Cl_2) 3560, 2927, 29854, 1602, 1566, 1462, 1235, 1181, 968; δ_H (400 MHz; C_6D_6) 6.80 (1H, d, $J_{1,3}$ 6.4), 5.98–5.95 (1H, m), 5.55–5.51 (1H, m), 4.64 (1H, d, $J_{1,3}$ 6.4 Hz), 4.27 (1H, d, $J_{1,3}$ 12.1), 3.69 (1H, d, $J_{1,2}$ 7.9), 3.68 (1H, d, $J_{1,2}$ 7.9), 3.40 (1H, d, $J_{1,3}$ 12.1), 3.32–3.26 (1H, m), 2.78 (3H, s), 2.65–2.58 (1H, m), 2.06–2.00 (1H, m), 1.52 (3H, s), 1.19 (3H, s), 1.17 (3H, s); δ_C (125 MHz; C_6D_6) 169.4, 161.9, 132.6, 128.9, 126.9, 124.0, 94.4, 78.6, 74.9, 67.5, 54.8, 42.8, 32.3, 30.1, 28.6, 28.5, 22.0; HRMS (EI) on (M^+) for $C_{17}H_{23}O_3N$ requires 289.1678, found: 289.1661.

***p*-Methoxyphenyl isopropyloxazoline chromium tricarbonyl complex (22)**

A degassed soln. of oxazoline **21** (3.00 g, 13.7 mmol), $Cr(CO)_6$ (3.00 g, 13.7 mmol), diisobutyl ether (100 mL) and THF was heated at reflux in the dark for 17 h. The mixture was then filtered through Celite and concentrated under reduced pressure to give a brown oil that was purified by FC (cyclohexane : Et_2O, 7 : 3) and then recrystallised in hexanes : Et_2O to give **22** (1.625 g, 33%) as a bright yellow solid. ν_{max}/cm^{-1} (CH_2Cl_2) 1973, 1897; δ_H (500 MHz; C_6D_6) 6.15 (1H, d, $J_{1,3}$ 6.6), 6.04 (1H, d, $J_{1,3}$ 6.6), 4.33–4.30 (2H, m), 3.83–3.68 (3H, m), 2.87 (3H, s), 1.63–1.57 (1H, m), 0.95 (3H, d, $J_{1,3}$ 6.6), 0.84 (3H, d, $J_{1,3}$ 6.6); δ_C (125 MHz; C_6D_6) 232.2, 160.4, 143.8, 94.6, 94.6, 85.3, 76.6, 76.5, 72.7, 70.7, 55.1, 32.9, 18.4, 18.3; HRMS (EI) on (M^+) for $C_{16}H_{17}O_5NCr$ requires 355.0516, found: 355.0512; $[\alpha]_D^{20}$ +89.2 (*c* 0.96 in CH_2Cl_2).

[5-(4-Isopropyl-4,5-dihydro-oxazol-2-yl)-4-methoxy-1-methyl-6-vinyl-cyclohexa-2,4-dienyl]-ethanone (23)

Compound **22** (355 mg, 1 mmol) was reacted following the procedure described for the preparation of **2**. Purification by FC (cyclohexane : AcOEt, 7 : 3) afforded **23** (254 mg, 84%) as a pale yellow oil. ν_{max}/cm^{-1} (CH_2Cl_2) 2963, 2934, 1705, 1610, 1572, 1385, 1353, 1270, 1265, 1044, 1001; δ_H (500 MHz; C_6D_6) 6.95 (1H, d, $J_{1,3}$ 6.4), 5.89 (1H, m), 5.35 (1H, d, $J_{1,3}$ 16.7), 4.97 (1H, d, $J_{1,3}$ 9.8), 4.78 (1H, d, $J_{1,3}$ 6.4), 3.93–3.70 (4H, m), 3.0 (3H, s), 2.0 (3H, s), 1.68–1.62 (1H, m), 1.5 (3H, s), 0.95 (3H, d, $J_{1,3}$ 6.6), 0.79 (3H, d, $J_{1,3}$ 6.6); δ_C (125 MHz; C_6D_6) 206.7, 165.0, 162.6, 135.8, 127.7, 118.9, 117.5, 93.6, 73.1, 69.7, 58.0, 54.9, 50.8, 33.2, 30.1, 20.4, 18.9, 18.4; HRMS (EI) on (M^+) for $C_{18}H_{25}NO_5$ requires 303.1824 found: 303.1834; $[\alpha]_D^{20}$ +159.3 (*c* 1.01 in $CHCl_3$).

1-[5-(4-Isopropyl-4,5-dihydro-oxazol-2-yl)-2-methoxy-1-methyl-6-vinyl-cyclohexa-2,4-dienyl]-pent-4-en-1-one (24)

Compound **23** (161 mg, 0.53 mmol) was reacted following the procedure described for the preparation of **3**. Purification by FC (cyclohexane : Et_2O, 8 : 2) gave **24** (146 mg, 80%) as a pale yellow oil. ν_{max}/cm^{-1} (CH_2Cl_2) 3048, 2963, 2904, 1705, 1605, 1571, 1462, 1384, 1274, 1253, 1158, 1082, 1044, 1002, 920; δ_H (200 MHz; C_6D_6) 6.93 (1H, d, $J_{1,3}$ 6.6), 6.0–5.7 (2H, m), 5.32 (1H, dd, $J_{1,2}$ 2.0, $J_{1,3}$ 17.3), 5.05–4.89 (3H, m), 4.74 (1H, d, $J_{1,3}$ 6.6), 3.92–3.56 (4H, m), 2.96 (3H, s), 2.65–2.30 (4H, m), 1.62 (1H, m), 1.50 (3H, s), 0.95 (3H, d, $J_{1,3}$ 6.6), 0.79 (3H, d, $J_{1,3}$ 6.6); δ_C (100 MHz; C_6D_6) 207.3, 165.6, 163.5, 136.8, 119.7, 115.6, 113.7, 93.4, 73.0, 69.7, 56.6, 54.6, 44.7, 35.7, 33.3, 30.8, 21.7, 18.7. HRMS (EI) on (M^+) for $C_{21}H_{29}NO_5$ requires 343.2143, found: 343.2147; $[\alpha]_D^{20}$ +81.3 (*c* 1.03 in $CHCl_3$).

1-(4-Isopropyl-4,5-dihydro-oxazol-2-yl)-4-methoxy-4a-methyl-4a,6,7,9a-tetrahydro-benzocyclohepten-5-one (25)

Compound **24** (106 mg, 0.31 mmol) was reacted following the procedure described for the preparation of **4**. Purification by FC (cyclohexane : AcOEt, 7 : 3) gave **25** (105 mg, quantitative) as a brown oil. ν_{max}/cm^{-1} (CH_2Cl_2) 2963, 1704, 1609, 1573, 1516, 1381, 1243, 1075, 1006; δ_H (200 MHz; C_6D_6) 6.94 (1H, d, $J_{1,3}$ 6.8), 6.14 (1H, ddd, $J_{1,3}$ 11.8, 4.7, 2.4), 5.73–5.54 (1H, m), 4.69 (1H, d, $J_{1,3}$ 6.8), 3.97–3.67 (4H, m), 2.91 (3H, s), 2.75–2.68 (2H, m), 2.62–2.35 (2H, m), 1.69–1.56 (1H, m), 1.55 (3H, s), 0.95 (3H, d, $J_{1,3}$ 6.7), 0.77 (3H, d, $J_{1,3}$ 6.7); δ_C (125 MHz; C_6D_6) 207.9, 165.2, 163.3, 133.0, 128.3, 127.2, 120.6, 92.8, 73.5, 70.3, 55.3, 54.9, 51.3, 45.6, 33.6, 22.1, 21.7, 19.2, 18.9. HRMS (EI) on (M^+) for $C_{19}H_{25}O_3N$ requires 315.1834, found: 315.1842; $[\alpha]_D^{20}$ +115.3 (*c* 1.06 in $CHCl_3$).

4-Methoxy-4a-methyl-5-oxo-5,6,7,9a-tetrahydro-4a*H*-benzocycloheptene-1-carbaldehyde (26)

A soln. of the chiral oxazoline **25** (70 mg, 0.22 mmol) in 5 mL of MeI was stirred 3 days at reflux. Excess of MeI was then evaporated under reduced pressure. The residue was dissolved in a mixture of THF (1.5 mL), MeOH (0.5 mL) and CH_2Cl_2 (1 mL) and the soln. cooled to 0 °C. $NaBH_4$ (25 mg, 0.66 mmol) was then added and the mixture was stirred for 15 min. H_2O was then added and the soln. was extracted with Et_2O. The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was evaporated and the residue was dissolved in a mixture of THF (2 mL) and H_2O (1 mL) and *p*-toluene sulfonic acid (84 mg, 044 mmol) was added. The soln. was stirred for 1.5 h and then extracted with Et_2O. Organic layers were combined washed with brine and dried over $MgSO_4$. The product was concentrated and purified by FC (cyclohexane : AcOEt, 7 : 3) to afford **26** (42 mg, 82%) as a colourless oil. Mp = 65–68 °C; ν_{max}/cm^{-1} (CH_2Cl_2) 2928, 2854, 1706, 1664, 1553, 1455, 1377, 1184, 1091, 909; δ_H (400 MHz; C_6D_6) 9.32 (1H, s), 6.10 (1H, d, $J_{1,3}$ 6.7), 5.72 (1H, ddd, $J_{1,3}$ 11.6, 4.8, $J_{1,4}$ 2.5), 5.51–5.45 (1H, m), 4.52 (1H, d, $J_{1,3}$ 6.7), 3.59–3.57 (1H, m), 2.81 (3H, s), 2.61 (1H, dd, $J_{1,2}$ 4.6, $J_{1,3}$ 1.8), 2.58 (1H, d, $J_{1,2}$ 4.6), 2.27–2.18 (1H, m), 1.54–1.46 (1H, m), 1.27 (3H, s); δ_C (125 MHz; C_6D_6) 206.6, 189.7, 169.2, 141.8, 133.6, 131.9, 127.6, 93.1, 55.6, 54.8, 45.3, 43.8, 22.0, 21.8; HRMS (EI) on (M^+) for $C_{14}H_{16}O_3$ requires 232.1099, found: 232.1102; $[\alpha]_D^{20}$ +222.5 (*c* 1.05 in $CHCl_3$).

1-Dimethoxymethyl-4-methoxy-benzene chromium tricarbonyl (28)

A soln. of anisaldehyde dimethyl acetal (5.6 mL, 33 mmol), chromium hexacarbonyl (6.6 g, 30 mmol) diisobutyl ether (100 mL) and THF (10 mL) was degassed. The soln. was heated at reflux in the absence of light for 64 h. The mixture was transferred to another flask and concentrated under reduced

pressure to give a brown oil. The residue was dissolved in toluene (3 × 20 mL), filtered through Celite and concentrated to give **28** (8.86 g, 93%) as a bright yellow solid. ν_{max}/cm^{-1} (hexane) 1977, 1908, 746; δ_H (400 MHz; C_6D_6) 5.43 (2H, d, $J_{1,3}$ 6.9), 4.87 (1H, s), 4.45 (2H, d, $J_{1,3}$ 6.9), 3.15 (s, 6H), 2.98 (3H, s); δ_C (100 MHz; C_6D_6) 233.0, 143.0, 101.0, 100.2, 93.4, 76.7, 54.8, 52.8; HRMS (EI) on (M^+) for $C_{13}H_{14}O_6Cr$ requires 318.0196, found: 318.0215.

4-Methoxy-benzaldehyde chromium tricarbonyl (29)

2 M HCl (35 mL) was added to a soln. of **28** (8.65 g, 27 mmol) in THF (35 mL) at rt. The mixture immediately became red and was stirred overnight. The soln. was brought to pH 7 with sat. $NaHCO_3$ soln. The aq. layer was separated and then extracted with Et_2O (3 × 50 mL). The organics were combined, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give **29** (7.07 g, 96%) as a red oil. ν_{max}/cm^{-1} (hexane) 1990, 1932, 1706, 746; δ_H (400 MHz; C_6D_6) 8.89 (1H, s), 5.36 (2H, d, $J_{1,3}$ 6.2), 4.25 (2H, d, $J_{1,3}$ 6.2), 2.93 (3H, s); δ_C (100 MHz; C_6D_6) 230.4, 185.7, 144.2, 94.2, 90.9, 76.4, 54.9; HRMS (EI) on (M^+) for $C_{11}H_8O_5Cr$ requires 271.9776, found: 271.9778.

(4-Methoxy-benzylidene)-(2-methoxymethyl-pyrrolidin-1-yl)-amine chromium tricarbonyl (30)

R-1-Amino-2-(methoxymethyl)pyrrolidine (340 μL, 2.55 mmol) was added to a soln. of **29** (660 mg, 2.43 mmol) in Et_2O (10 mL) and stirred over 4 Å molecular sieves (1.8 g) for 18 h at rt. The mixture was filtered through Celite and concentrated under reduced pressure to give a yellow oil. The residue was crystallised (Et_2O–hexane) to give **30** (623 mg, 67%) as a very fine yellow powder. ν_{max}/cm^{-1} (hexane) 1971, 1903, 746; δ_H (400 MHz; C_6D_6) 6.36 (1H, s), 5.66 (1H, dd, $J_{1,3}$ 6.8, 1.3), 5.59 (1H, dd, $J_{1,3}$ 6.8, 1.3), 4.70 (1H, dd, $J_{1,3}$ 7.0, 2.2), 4.66 (1H, dd, $J_{1,3}$ 7.0, 2.2), 3.76–3.74 (1H, m), 3.66 (1H, d, $J_{1,2}$ 4.6), 3.48 (1H, d, $J_{1,2}$ 4.6), 3.27 (3H, s), 3.05 (3H, s), 2.96–2.87 (1H, m), 2.68–2.60 (1H, m), 1.84–1.68 (3H, m), 1.57–1.44 (1H, m); δ_C (100 MHz; C_6D_6) 233.9, 141.6, 124.1, 90.9, 78.3, 77.8, 74.4, 62.8, 58.6, 54.8, 47.9, 26.7, 21.9; HRMS (EI) on (M^+) for $C_{17}H_{20}O_5N_2Cr$ requires 384.0777, found 384.0780; $[\alpha]_D^{20}$ +7.5 (*c* 0.86 in $CHCl_3$).

1-(2-Methoxy-5-[(2-methoxymethyl-pyrrolidin-1-ylimino)-methyl]-1-methyl-6-vinyl-cyclohexa-2,4-dienyl)-ethanone (31)

Compound **30** (768 mg, 2 mmol) was reacted following the procedure described for the preparation of **2**. Purification by FC (cyclohexane : AcOEt, 7 : 3) afforded **31** (483 mg, 73%) as a pale yellow oil. ν_{max}/cm^{-1} (CH_2Cl_2) 2976, 2931, 1704, 1667, 1634, 1567, 1458, 1352, 1240, 1111, 1002; δ_H (400 MHz; C_6D_6) 6.99 (1H, s), 6.08 (1H, dt, $J_{1,3}$ 18.3, 9.8), 5.92 (1H, d, $J_{1,3}$ 6.6), 5.44 (1H, dd, $J_{1,2}$ 2.2, $J_{1,3}$ 18.3), 5.10 (1H, dd, $J_{1,2}$ 2.2, $J_{1,3}$ 9.8), 5.03 (1H, dd, $J_{1,3}$ 6.6), 3.95 (1H, d, $J_{1,3}$ 9.8), 3.78–3.72 (2H, m), 3.49 (1H, dd, $J_{1,3}$ 9.1, 6.7), 3.24 (3H, s), 3.19 (3H, s), 3.12–3.06 (1H, m), 2.78–2.74 (1H, m), 2.28 (3H, s), 1.86–1.75 (3H, m), 1.67 (3H, s), 1.57–1.49 (1H, m); δ_C (125 MHz; C_6D_6) 207.8, 161.3, 137.4, 132.7, 130.4, 120.2, 116.5, 94.7, 75.1, 63.1, 58.9, 58.1, 54.6, 49.2, 47.1, 31.7, 27.1, 22.3, 20.6; HRMS (EI) on (M^+) for $C_{19}H_{28}O_3N_2$ requires 332.2099, found: 332.2074; $[\alpha]_D^{20}$ +230.8 (*c* 0.57 in $CHCl_3$).

1-(2-Methoxy-5-[(2-methoxymethyl-pyrrolidin-1-ylimino)-methyl]-1-methyl-6-vinyl-cyclohexa-2,4-dienyl)-pent-4-en-1-one (32)

Compound **31** (299 mg, 0.9 mmol) was reacted following the procedure described for the preparation of **3**. Purification by FC (cyclohexane : AcOEt, 7 : 3) afforded **32** (247 mg, 76%) as a pale yellow oil. ν_{max}/cm^{-1} (CH_2Cl_2) 2976, 2932, 1702, 1633, 1565, 1458, 1337, 1240, 1152, 1119, 1005, 918, 812; δ_H (400 MHz; C_6D_6) 6.82 (1H, s), 5.98–5.77 (2H, m), 5.75 (1H, d, $J_{1,3}$ 6.6), 5.25 (1H, dd, $J_{1,2}$ 1.8, $J_{1,3}$ 17.0), 5.01 (1H, dd, $J_{1,2}$ 2.2, $J_{1,3}$ 17.0), 4.92–4.86 (3H, m), 3.78 (1H, d, $J_{1,3}$ 9.8), 3.60–3.50 (2H, m), 3.32 (1H, dd, $J_{1,3}$ 9.1, 6.8), 3.07 (3H, s), 3.03 (3H, s), 2.98–2.89 (1H, m), 2.71–2.40 (m, 5H), 1.74–1.55 (3H, m), 1.51 (3H, s), 1.47–1.36 (1H, m); δ_C (125 MHz; C_6D_6) 209.8, 161.3, 138.8, 137.0, 132.6, 130.4, 120.2, 116.6, 114.6, 114.3, 95.0, 75.1, 63.5, 58.9, 58.0, 54.6, 50.3, 43.1, 28.9, 27.2, 22.3, 20.6; HRMS (EI) on (M^+) for $C_{22}H_{32}O_3N_2$ requires 372.2413, found: 372.2421; $[\alpha]_D^{20}$ +114.4 (*c* 0.70 in $CHCl_3$).

1-(4-Isopropyl-4,5-dihydro-oxazol-2-yl)-4-methoxy-4a-methyl-4a,6,7,9a-tetrahydro-benzocyclohepten-5-one (33)

Compound **32** (78 mg, 0.21 mmol) was reacted following the procedure described for the preparation of **4**. Purification by FC (cyclohexane : AcOEt, 7 : 3) afforded **33** (64 mg, 89%) as a brown oil. ν_{max}/cm^{-1} (CH_2Cl_2) 2978, 2878, 1699, 1635, 1569, 1453, 1376, 1337, 1236, 1172, 1116, 1070, 1010, 744; δ_H (500 MHz; C_6D_6) 6.97 (1H, s), 6.12–6.08 (1H, m), 5.85 (1H, d, $J_{1,3}$ 6.6), 5.75–5.70 (1H, m), 4.92 (1H, d, $J_{1,3}$ 6.6), 3.94–3.93 (1H, m), 3.57–3.54 (1H, m), 3.58 (1H, dd, $J_{1,2}$ 8.8, $J_{1,3}$ 3.4), 3.42 (1H, dd, $J_{1,2}$ 8.8, $J_{1,3}$ 6.6), 3.15 (3H, s), 3.10 (3H, s), 3.04–3.00 (1H, m), 2.88–2.83 (1H, m), 2.80–2.73 (1H, m), 2.69–2.62 (2H, m), 2.46–2.40 (1H, m), 1.75–1.64 (3H, m), 1.72 (3H, s), 1.49–1.43 (1H, m); δ_C (125 MHz; C_6D_6) 208.7, 161.3, 133.3, 131.9, 126.5, 121.0, 93.6, 75.1, 63.2, 58.9, 54.8, 48.6, 46.2, 45.6, 27.2, 27.1, 22.4, 22.2, 21.6; HRMS (EI) on (M^+) for $C_{20}H_{28}O_3N_2$ requires 344.2100, found: 344.2109; $[\alpha]_D^{20}$ +193.4 (*c* 0.67 in $CHCl_3$).

4-Methoxy-4a-methyl-5-oxo-5,6,7,9a-tetrahydro-4a*H*-benzocycloheptene-1-carbonitrile (34)

A soln. of hydrazone **33** (41 mg, 0.12 mmol) in 0.3 mL of a MeOH : phosphate buffer pH 7 (1 : 1) mixture was added dropwise to a soln. of magnesium monoperoxyphthalate hexahydrate (MMPP) (77 mg, 0.16 mmol) in 1 mL of MeOH : phosphate buffer at 0 °C. The mixture was stirred for 15 min and then H_2O was added. The soln. was extracted with Et_2O. The combined organic layers were washed with an aq. soln. of $NaHCO_3$ and dried over $MgSO_4$. **34** (25 mg, 91%) was obtained as a yellow oil after purification by FC (cyclohexane : AcOEt, 7 : 3). ν_{max}/cm^{-1} (CH_2Cl_2) 3062, 2936, 2850, 2203, 1708, 1639, 1563, 1454, 1380, 1275, 1253, 1075, 1005, 907, 808, 762; δ_H (500 MHz; C_6D_6) 6.14 (1H, dd, $J_{1,3}$ 6.6, 3.9), 5.55–5.51 (2H, m), 4.32 (1H, d, $J_{1,3}$ 6.6), 2.81 (3H, s), 2.73–2.69 (1H, m), 2.65 (1H, ddd, $J_{1,2}$ 15.0, $J_{1,3}$ 6.6, $J_{1,4}$ 4.8), 2.42 (1H, ddd, $J_{1,2}$ 15.0, $J_{1,3}$ 10.1, $J_{1,4}$ 4.8), 2.18–1.99 (1H, m), 1.70–1.50 (1H, m), 1.23 (3H, s); δ_C (125 MHz; C_6D_6) 205.8, 164.9, 137.2, 131.1, 128.8, 119.3, 104.2, 92.9, 55.2, 54.9, 45.6, 43.4, 23.1, 21.4; HRMS (EI) on (M^+) for $C_{14}H_{15}NO_2$ requires 229.1106, found: 229.1103; $[\alpha]_D^{20}$ +82.6 (*c* 0.53 in $CHCl_3$).

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