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## Asymmetric Cu-catalyzed 1,2 and 1,4-additions of Grignard reagents

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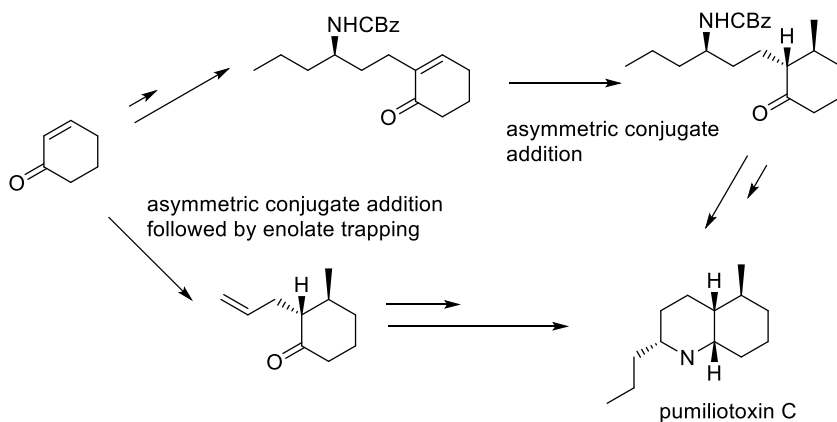
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## Chapter 4: Synthesis of steroid hybrids employing asymmetric catalysis

### Introduction

In the large majority of the studies on (copper)-catalyzed asymmetric conjugate addition reactions of organometallic reagents, the Michael acceptor lacks a substituent at the 2-position. Nevertheless, the development of methodology that allows the use of 2-substituted enones is of critical importance for natural product synthesis. Several years ago, a first report describing the copper catalyzed conjugate addition to 2-methyl cyclohexenone (**1**) originated from Vuagnoux-d'Augustin and Alexakis, and comprized the enantioselective addition of  $\text{Me}_3\text{Al}$  and  $\text{Et}_3\text{Al}$ .<sup>1</sup> This knowledge was subsequently used by Helmchen *et al.* in a synthesis of pumiliotoxin C (Scheme 1).<sup>2</sup>



**Scheme 1.** Two syntheses of pumiliotoxin C based on catalytic asymmetric conjugate addition

(B. C. Calvo and A. J. Minnaard; to be published).

As such, the 2,3-disubstituted ketones that result from of these reactions upon quenching with water, can be obtained equally well by conjugate addition to unsubstituted enones followed by *in situ* alkylation of the resulting enolate. In this connection it is illustrative to compare the Helmchen synthesis of pumiliotoxin C to an earlier synthesis of the same compound by our (Feringa and Minnaard) group.<sup>3</sup> The use of in particular 2-alkyl cyclopentenone and 2-alkyl cyclohexenone, however, leads after conjugate addition *and subsequent in situ alkylation* to building blocks with 2 adjacent chiral centers, one of them being a quaternary center. The stereochemistry of this quaternary center is steered (though not completely) by the initially formed center at the 3-position. Although this chiral induction is a matter of substrate control, in other words leads to a given stereochemical relation between the centers, this is not always a limitation as interchanging the initially present 2-substituent and the electrophile used leads at least in principle to the other stereoisomer. As for most chiral ligands holds that both enantiomers are available, this provides accessibility to all stereoisomers.

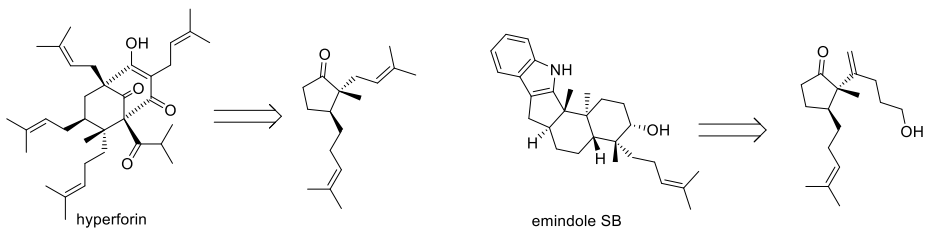
In 2014, two subsequent reports appeared on the use of Grignard reagents in this type of reaction. Mauduit, Alexakis *et al.* reported the successful application of Cu(I)-*N*-heterocyclic carbene complexes in the asymmetric addition of Grignard reagents to 2-methyl cyclopentenone (4) and – hexenone (Scheme 2).<sup>4</sup> The resulting magnesium enolates were subsequently alkylated *in situ* to provide a quaternary stereocenter vicinal to the initially formed stereocenter. From the results it became clear that the reaction performed best with  $\alpha$ -branched Grignard reagents such as isopropylmagnesium bromide

leading to high enantioselectivities. The electrophile added *trans* with respect to the 3-substituent, as expected, and the diastereoselectivity was excellent, probably because of the steric bulk of the isopropyl group. We reported subsequently the asymmetric conjugate addition of Grignard reagents to 2-methyl cyclopentenone with a copper catalyst based on Rev-JosiPhos (L3) and enolate alkylation with a variety of electrophiles (Chapter 2).<sup>5</sup> The catalyst system gave a just moderate enantioselectivity with methylmagnesium bromide and  $\alpha$ -branched Grignard reagents but a high enantioselectivity with  $\beta$ -branched Grignard reagents. This means that the method is complementary to the one of Mauduit and Alexakis.

This work was followed recently by a comprehensive study on the copper-NHC catalyzed conjugate addition of Grignard reagents to 2-substituted cyclopentenone and cyclohexenone by Germain and Alexakis, thereby defining the current state-of-the-art.<sup>6</sup> The scope of Grignard reagents and Michael acceptors was studied and expanded.

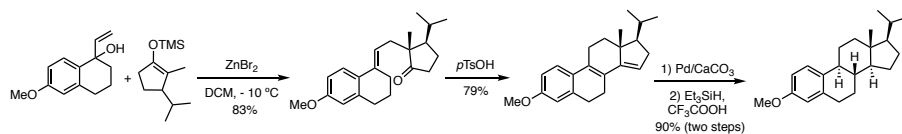
As already precluded upon by the authors of the aforementioned papers, the products of the sequential asymmetric conjugate addition – enolate alkylation are tailor-made for application in natural product synthesis, in particular 2-methyl cyclopentenone and 2-methyl cyclohexenone. This because of the resulting methyl-bearing quaternary stereocenters that can be integrated in bicyclic and polycyclic ring-systems of isoprenoids. This has not been effectuated thus far, however, although several groups explicitly referred to this opportunity in their reports on the total synthesis of natural products that used a non-asymmetric conjugate addition to 2-methyl cyclopentenone. In the synthesis of hyperforin by Ting and Maimone<sup>7</sup> as well as in the synthesis of the

paxilline indole diterpenes by Pronin et al.<sup>8</sup> this approach can readily be used (Scheme 2).

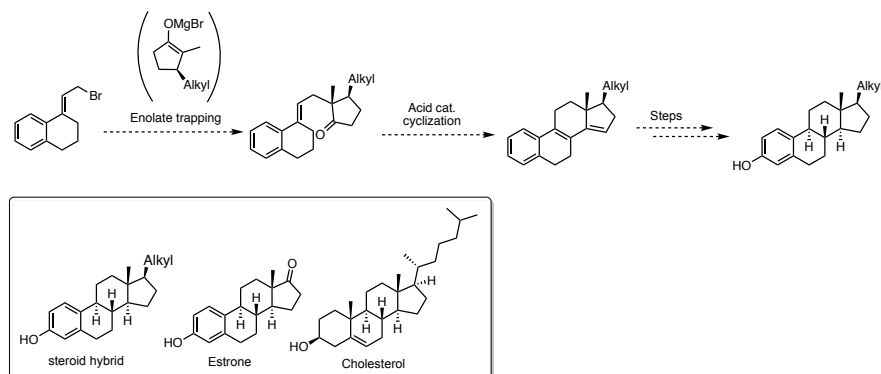


**Scheme 2.** Reported racemic syntheses that could be transformed into enantioselective syntheses using copper-catalyzed enantioselective conjugate addition of organometallics

Elaborating on this, we were inspired by two reports from the group of De Groot et al. more than a decade ago,<sup>9</sup> on the synthesis of steroid hybrids (Scheme 3). Based on the famous Torgov synthesis of estrone,<sup>10</sup> alkylation of a silylenol ether, derived in turn from conjugate addition to 2-methyl cyclopentenone, leads to an intermediate ketone that could be cyclised and step-wise reduced to provide steroids containing an aromatic A ring (that resembles estrone) and an alkyl chain on the D-ring (that resembles cholesterol).



De Groot's route towards steroid hybrids



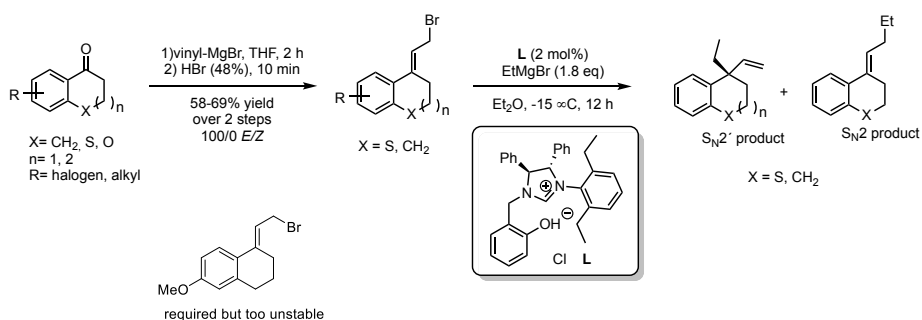
**Scheme 3:** De Groot's synthesis of steroid hybrids vs our approach towards the steroid skeleton.

At the time De Groot reported this strategy, the asymmetric conjugate addition of hard organometallics to enones had hardly been developed, let alone this reaction on  $\alpha$ -substituted enones. We decided to follow-up on this strategy but now with a challenging one-pot asymmetric conjugate addition- $\alpha$ -alkylation with the appropriate electrophile. This would lead in a very short route to the rather complex steroid skeleton (Scheme 3).

## Results and discussion:

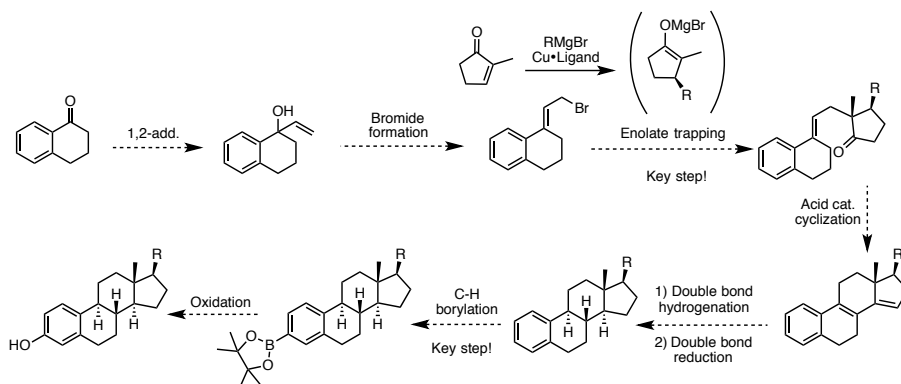
In the Torgov and De Groot syntheses, the cyclopentanone enolate equivalent reacts in an  $S_N1$  reaction with the relatively stable cation formed from the tertiary alcohol. In the current situation we had to prepare a corresponding electrophile in such a way that it could be used

in an  $S_N2$  reaction with the magnesium enolate. Therefore, a suitable vinylogous benzyl bromide had to be prepared but this was not trivial. Preceding our research, the Alexakis group had reported a procedure for the synthesis of this kind of vinylogous benzyl bromides although not precisely the required one (Scheme 4).<sup>11</sup> It turned out that the desired bromide based on methoxy tetralone was very unstable and even escaped isolation. It has been reported that the related *p*-methoxy and *p*-benzyloxy cinnamyl bromides can be prepared and used directly but not stored.<sup>12</sup> A more rigid structure apparently aggravates the problem.



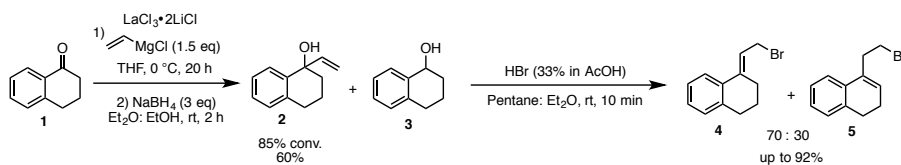
**Scheme 4:** Alexakis' synthesis of allylic bromides, followed by asymmetric allylic alkylation. And the required allylic bromide for our studies.

Therefore, we turned to the unsubstituted analogue starting from tetralone, postponing the introduction of the hydroxyl group in the A-ring of the steroid (Scheme 5).



**Scheme 5:** Proposed synthesis route to steroid hybrids

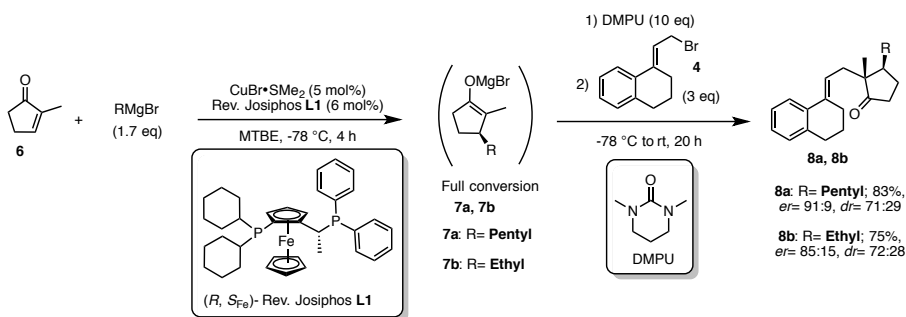
According to known procedures,<sup>13</sup> vinylmagnesium bromide was added to tetralone (1), in presence of the Lewis acid  $\text{LaCl}_3 \cdot 2\text{LiCl}$ . The small amount of remaining 1 was reduced with  $\text{LiAlH}_4$  to facilitate chromatographic purification. Tertiary alcohol (2) underwent bromination to form (4). Unfortunately, the thermodynamically more stable double bond isomer bromide (5), was also formed in considerable amounts. By keeping the temperature of the mixture low, employing an ice-cold phosphate buffer during the quenching and room temperature for the evaporation of the solvent, its formation could be suppressed to 30% (Scheme 6).



**Scheme 6:** The synthesis of bromide (4).



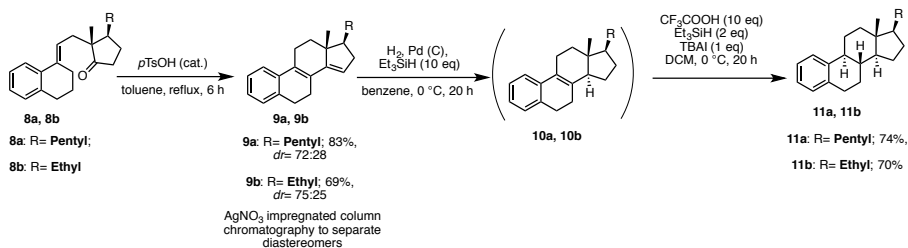
Asymmetric conjugate addition to 1-methylcyclopentenone (**6**) was performed according to chapter 2. In order to demonstrate the scope of the method, ethyl- and pentylmagnesium bromide were used as the nucleophiles. The, *in-situ* formed, enolates (**7a**) and (**7b**) were trapped with the mixture of bromides (**4**) and (**5**) to give compounds (**8a**) and (**8b**) in high yields, good enantioselectivities and moderate diastereoselectivities (Scheme 7).



**Scheme 7:** Sequential asymmetric conjugate addition – enolate trapping to form the intermediates (**8a**) and (**8b**).

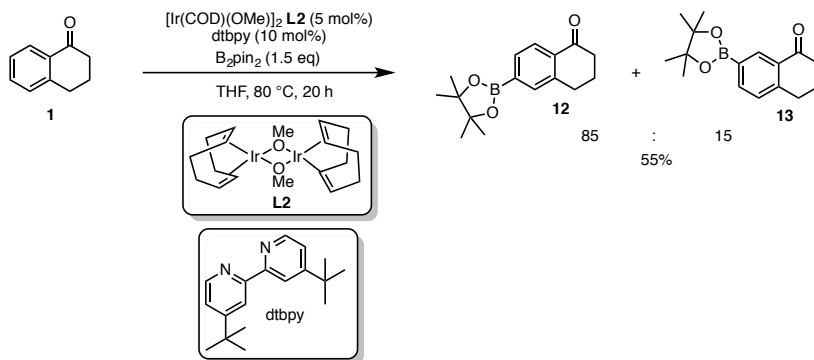
To make the steroids (**11a**) and (**11b**), we followed a procedure reported by Corey and co-workers (in turn based on earlier work) in the synthesis of estrone.<sup>14</sup> Acid catalyzed cyclization of (**8a**) and (**8b**) gave the corresponding dienes (**9a**) and (**9b**). At this point in the synthesis, chromatography with  $\text{AgNO}_3$  impregnated silica separated the diastereomers. This argentation chromatography, mostly used to separate *cis* and *trans* isomers of unsaturated fatty acids and their derivatives, is based on the coordination of  $\text{Ag}^+$  to alkenes which is sensitive to sterics.<sup>15</sup> The pure *trans*-diastereomers (as confirmed by

NOESY) underwent selective *cis* hydrogenation of the trisubstituted double bond followed by a *trans* selective silane reduction of the tetrasubstituted double bond to yield (11a) and (11b) in 70% and 74% yield, respectively (Scheme 8).



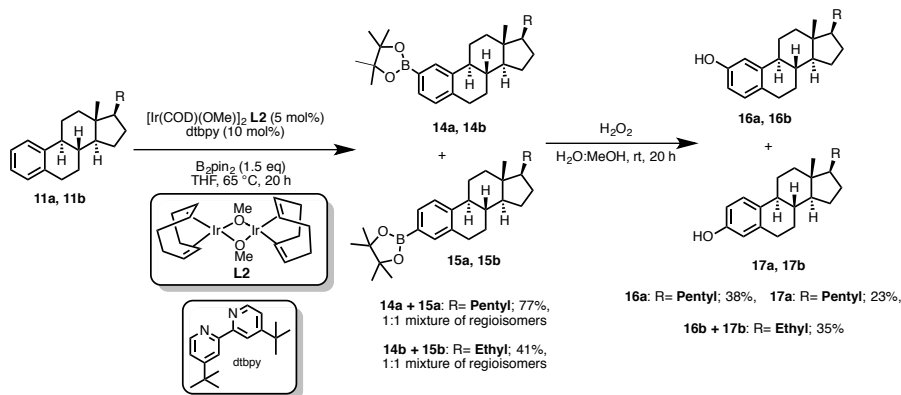
**Scheme 8:** The synthesis of steroid hybrids (11a) and (11b).

The next step was the introduction of the oxygen functionality in the aromatic ring. The planned C-H borylation was first studied on commercially available  $\alpha$ -tetralone (1). This resulted in full conversion to the products (12) and (13) and high selectivities towards the desired regioisomer (12) (Scheme 9). We chose this molecule as the substrate model due to sterics similarity. However, the electronic effects were not the same, since in this substrate there is a ketone present, which increases the ratio of the desired regioisomer.<sup>16</sup>



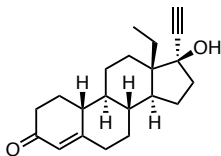
**Scheme 9:** C-H borylation in commercially available tetralone (1).

When the reaction was performed with with (11a) and with (11b), a 1:1 mixture of regioisomers was obtained. Although a better selectivity in the C-H activation was achieved employing  $\alpha$ -tetralone, this reaction could not be performed at the beginning of the synthesis due to incompatibility of the boronate ester with the subsequent reactions. The 1:1 mixtures of the boronate esters (14a) and (14b), and (15a) and (15b), were used for the final step. Oxidation of the boronate esters gave the target hybrid steroids (17a) and (17b), as a mixture with the regioisomeric alcohols (16a) and (16b), inseparable by column chromatography (Scheme 10).



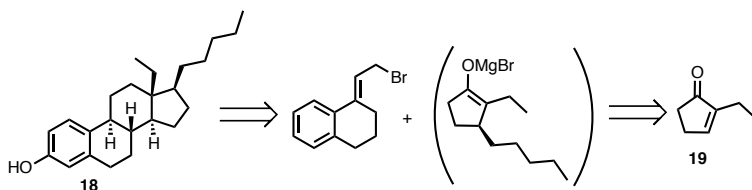
**Scheme 10:** Ir-catalyzed C-H borylation of (11a) and (11b), followed by oxidation.

With our target steroid hybrids in hand, we desired to expand the scope of our synthetic approach. The next goal was to make steroid hybrids like (18), in which an ethyl group is present at the C13 position (steroid numbering). This moiety is present in steroids like desogestrel, a compound used in contraceptive pills (Figure 1).



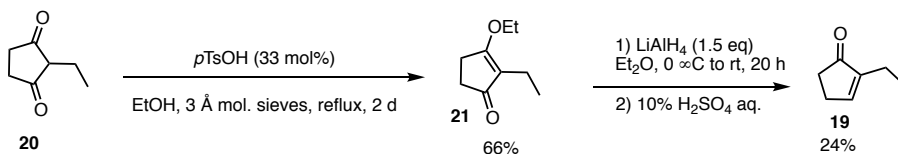
**Figure 1:** Desogestrel.

The only modification required in order to prepare these analogues is to start from 2-ethyl cyclopentenone (19) (Scheme 11).



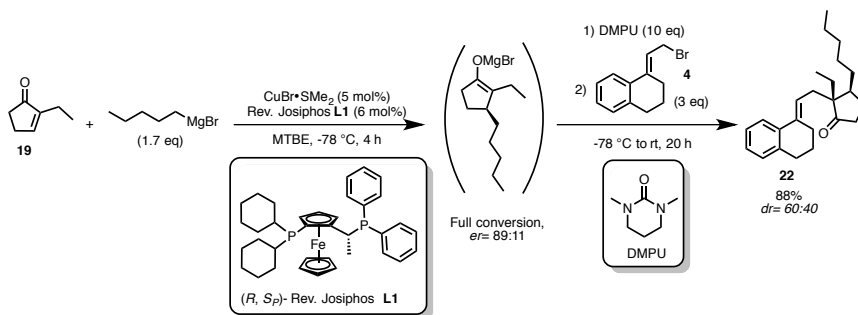
**Scheme 11:** Retrosynthesis of steroid hybrids with an ethyl group at C13.

To make (19), a two-step procedure was carried out.<sup>17,18</sup> Starting with 2-ethylcyclopentane-1,3-dione (20), enol ether (21) was formed in good yield, followed by ketone reduction and acid treatment to afford (19) (Scheme 12). The yield of (19) was decreased due to its volatility.



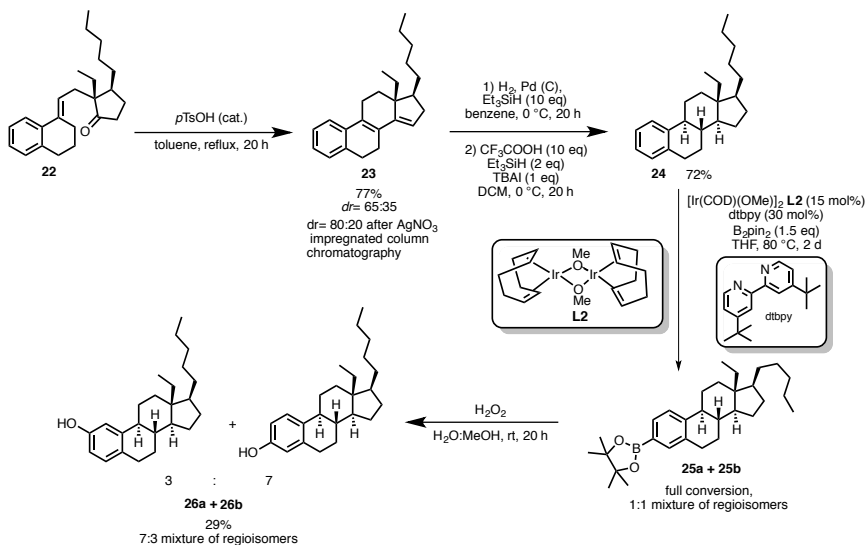
**Scheme 12:** Synthesis of 2-ethyl cyclopentenone (19).

Asymmetric conjugate addition to (19), and subsequent trapping with bromide (4) afforded intermediate (22) in high yield, good enantioselectivity and a slightly lower diastereoselectivity (60:40) compared to methyl substituted cyclopentenone (6) (70:30) (Scheme 13).



**Scheme 13:** Sequential asymmetric conjugate addition – enolate trapping to form intermediate (22).

The remainder of the synthesis was carried out as for the route starting from 2-methyl cyclopentenone (6). Acid catalyzed cyclization gave (23) in good yield. AgNO<sub>3</sub> impregnated silica chromatography gave an 8:2 mixture of diastereomers which underwent stereoselective double bonds reductions to give (24) in 72% yield. C-H borylation followed by oxidation gave alcohols (26a) and (26b) in a 7:3 ratio after column chromatography (Scheme 14).



**Scheme 14:** Synthesis of steroid hybrids (26a) and (26b).

## Conclusions:

It is important to note that the relative stereochemistry in the final product is substrate controlled in the alkylation reaction of the magnesium enolate. The absolute stereochemistry is obviously controlled by the copper catalyst used in the conjugate addition. The *ee* in the conjugate addition reaction is high though not excellent. Improvements in enantioselectivity should come from the development of more selective catalysts or different strategies that lead to the same product. That this is not an easy task is witnessed by the fact that no improvement has been reported along these lines neither by us nor by other groups since the disclosure of our method, which was the first in its kind, in May 2014. As for the diastereoselectivity in the enolate alkylation reaction; there is currently no tool available to either overrule or enforce the substrate control. It is tough to envision an approach at this point.

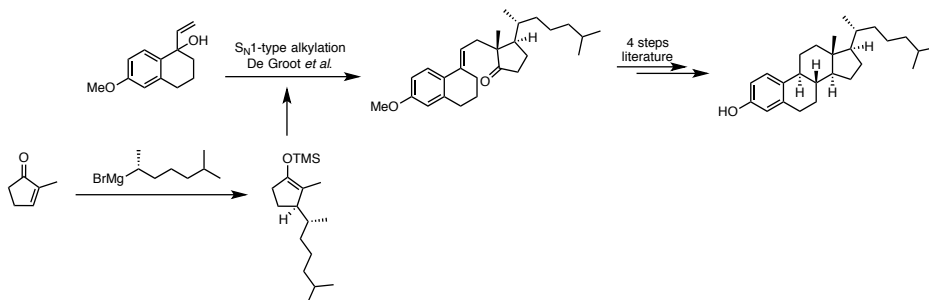
The problem to produce the initially desired allylic bromide with a *p*-methoxy substituent, was circumvented using C-H activation in a later stage. I consider this as a nice illustration of a late stage functionalisation in complex molecule synthesis, and iridium-catalyzed borylation has not been used often in this context. In 2008, C-H borylation was employed by Gaunt and coworkers in the total synthesis of rhazinicine.<sup>19</sup> The complete lack of regioselectivity in this reaction however, takes away part of its elegance. This was not unexpected as there is no obvious driving force for regioselectivity in the substrate.

Looking back, a straightforward combination of the approach by De Groot *et al.* and our approach should lead to a win-win situation. So; asymmetric conjugate addition to 2-alkyl cyclopentenone and trapping of the enolate as its silylenol ether should provide the enantioenriched building block that can then be combined in an S<sub>N</sub>1-type alkylation with Torgov's intermediate according to De Groot. Ringclosure, hydrogenation and de-methoxylation would then provide an efficient route to the steroid hydrides.

Finally, this synthesis uncovers another unmet-need. To mimic more closely cholesterol, one might like to add its sidechain (scheme 15). However, our catalyst system does not allow the successful use of  $\alpha$ -branched Grignard reagents and in addition, this particular Grignard reagent is chiral at the metallated carbon. The first problem might be tackled by application of the Alexakis-Mauduit NHC-catalyst that is known to function well with iso-propylmagnesium bromide.<sup>20</sup> Whether the Grignard reagent can be prepared and used in its enantio-enriched



form or whether the catalyst will also exert an influence on the chirality at that center is currently unknown.



**Scheme 15:** A proposed route to cholesterol-type steroid hybrids.

## **Experimental section:**

### **General Experimental Details**

*t*-BuOMe was taken from an MBraun solvent purification system (SPS-800). All other reagents were purchased from Sigma–Aldrich or Acros Organics and were used without further purification. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded on a Varian AMX400 (400 and 100.59 MHz, respectively) using CDCl<sub>3</sub> as the solvent. Chemical shift values are reported in ppm with the solvent resonance as the internal standard (CHCl<sub>3</sub> : d=7.26 for <sup>1</sup>H, d=77.0 for <sup>13</sup>C). Data are reported as follows: chemical shifts, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, br=broad, m=multiplet), coupling constants (Hz), and integration. High-resolution mass spectra (HRMS) were recorded on an FTMS orbitrap (Thermo Fisher Scientific) mass spectrometer. Optical rotations were measured on a Schmidt + Haensch polarimeter (Polartronic MH8) with a 10 cm cell (c given in g / 100 mL). Enantiomeric excesses were determined by capillary GC analysis (Agilent Technologies 7890, CP-Chiralsil-Dex-CB column (25m x 25 mm x 25 μm)) using a flame ionization detector. Progress and conversion of the reactions were determined by GC-MS (GC, HP6890: MS HP5973) with an HP1 or HP5 column (Agilent Technologies, Palo Alto, CA). Flash chromatography: Merck silica gel type 9385 230–400 mesh. TLC: Merck silica gel 60, 0.25 mm. Compounds were visualized by UV, p-anisaldehyde stain (135 mL abs. ethanol, 5 mL conc. sulfuric acid, 1.5 mL glacial acetic acid and 3.7 mL p-anisaldehyde) and potassium permanganate staining.

### **1-vinyl-1,2,3,4-tetrahydronaphthalen-1-ol (2):**

To a flame-dried 3-necked roundbottom flask under N<sub>2</sub> atmosphere,

containing a magnetic stirring bar,  $\alpha$ -tetralone (3.00 g, 20.5 mmol, 1 eq) was added and dissolved in 60 ml of dry THF. The flask was placed into an ice bath. Vinylmagnesium bromide (5.51 g, 42.0 mmol, 2 eq), was added dropwise and the mixture was left to stir at rt for 3 h. The reaction progress was monitored by  $^1\text{H}$  NMR. Upon >80% conversion, the flask was again placed into an ice bath and the reaction was quenched with 60 ml of sat. aq.  $\text{NH}_4\text{Cl}$ . The mixture was diluted in 90 ml of ether and the layers were separated. The aqueous layer was extracted two times with 40 ml of ether. The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered and the solvent was removed under reduced pressure. The crude material was put in a dried Schlenk flask and dissolved in 15 ml of dry ether/dry methanol (4:1).  $\text{NaBH}_4$  (0.25 g, 3.4 mmol, 0.17 eq) was added slowly and the mixture was stirred at rt for 1 h. Upon completion, the remaining borohydride was quenched with 10 ml of water. The aqueous layer was extracted three times with ether. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude product was purified using column chromatography ( $\text{SiO}_2$ , pentane:ether, 8:2). The product was obtained as a colorless oil in 60% yield.<sup>15</sup>

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.42 – 7.36 (m, 1H), 7.21 – 7.16 (m, 2H), 7.14 – 7.08 (m, 1H), 6.05 (dd,  $J$  = 17.2, 10.6 Hz, 1H), 5.30 (dd,  $J$  = 17.1, 1.5 Hz, 1H), 5.20 (dd,  $J$  = 10.6, 1.5 Hz, 1H), 2.90 – 2.72 (m, 2H), 2.05 – 1.83 (m, 4H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  144.9, 139.7, 137.0, 129.0, 128.0, 127.5, 126.2, 113.1, 77.3, 77.0, 76.7, 73.3, 37.8, 29.7, 19.3.

**(*E*)-1-(2-bromoethylidene)-1,2,3,4-tetrahydronaphthalene (4):**

To a flame-dried Schlenk flask, containing a magnetic stirring bar and under N<sub>2</sub> atmosphere, tertiary alcohol (2) (1.59 g, 9.10 mmol) was added and diluted in 50 ml of a mixture of pentane/ether (9/1). HBr (33% in glacial acetic acid, 1.65 ml, 1.05 eq) was added under vigorous stirring. After exactly 10 min the mixture was poured into 50 ml of ice-cooled phosphate buffer (pH = 7.2) and the layers were separated. The organic phase was washed two times with sat. NaHCO<sub>3</sub> solution, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and the solvent removed under reduced pressure (the water bath of the rotavap at rt). The crude product was obtained as a 70:30 mixture of endocyclic and exocyclic double bond isomers (Scheme 2, page 80) (in favor of the desired one) and not purified further due to instability of the product on basic alumina and silica gel. The product was obtained in 92% yield (1.98 g, 8.35 mmol).<sup>13</sup>

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.23 – 7.13 (m, 4H), 6.30 (t, J = 8.8, 2.0 Hz, 1H), 4.24 (d, J = 8.7 Hz, 2H), 2.80 (t, J = 6.2 Hz, 2H), 2.63 (t, 2H), 1.94 – 1.81 (m, 2H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 133.8, 128.9, 127.9, 127.9, 127.6, 127.0, 126.5, 124.2, 36.6, 31.5, 28.1, 23.1.

**Mixture of diastereomers: (2R,3S)-2-(2-((E)-3,4-dihydronaphthalen-1(2H)-ylidene)ethyl)-2-methyl-3-pentylcyclopentan-1-one (8a):**

To a flame-dried Schlenk tube, containing a magnetic stirring bar and under N<sub>2</sub> atmosphere, CuBr·SMe<sub>2</sub> (18.2 mg, 5 mol%), ligand (L1) (65.5 mg, 6 mol%) and 20 ml of dry *t*-BuOMe were added. The mixture was left to stir for 15 min, after which 2-methylcyclopentenone (172 mg, 1.8 mmol, 1 eq), dissolved in a small amount of dry *t*-BuOMe, was added.

The mixture was cooled to  $-78\text{ }^{\circ}\text{C}$  and left to stir for 30 min. Pentylmagnesium bromide (2 M in  $\text{Et}_2\text{O}$ , 1.5 ml, 1.7 eq) was added dropwise over 15 min and the reaction mixture was left to stir for 3 h at  $-78\text{ }^{\circ}\text{C}$ . Dry DMPU (17.9 mmol, 2.16 ml) was added to the reaction mixture which was left to stir for 10 min at  $-78\text{ }^{\circ}\text{C}$ . The allylic bromide (4) (1.17 g, 2.6 eq) was added (as crude material of the previous reaction). The reaction mixture was allowed to warm up to rt and left to stir for 20 h. The mixture was diluted in 30 ml of  $\text{Et}_2\text{O}$ , 60 ml of  $\text{NH}_4\text{Cl}_{\text{aq}}$  was added and the layers were separated. The aqueous layer was extracted two times with 30 ml of  $\text{Et}_2\text{O}$ . The combined organic layers were dried over  $\text{MgSO}_4$ , filtered and the solvent was removed under reduced pressure. The crude material was purified by using column chromatography ( $\text{SiO}_2$ , pentane:ether (95:5)). Compound (8) was obtained in 82% yield (724 mg) over two steps,  $er = 91 : 9$ ,  $dr = 71 : 29$ .

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.51 – 7.47 (m, 1H), 7.15 – 7.09 (m, 2H), 7.09 – 7.05 (m, 1H), 5.82 (t, 1H), 2.77 (t, 2H), 2.52 – 1.96 (m, 10H), 1.82 (p,  $J = 6.3$  Hz, 2H), 1.52 – 1.16 (m, 10H), 1.08 – 1.05 (m, 1H), 0.92 – 0.86 (m, 5H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  223.9, 137.3, 136.5, 136.2, 128.81, 126.7, 125.9, 123.8, 119.8, 52.2, 42.9, 37.7, 34.5, 32.2, 30.4, 30.1, 26.6, 25.1, 23.3, 22.6, 17.8, 14.1. HRMS calculated for  $\text{C}_{23}\text{H}_{33}\text{O}$   $[\text{M}+\text{H}]^+$ : 325.253, found 325.253.

**(13R,17S)-13-methyl-17-pentyl-7,11,12,13,16,17-hexahydro-6H-cyclopenta[ $\alpha$ ]phenanthrene (9a):**

To a flame-dried Schlenk tube, containing a magnetic stirring bar and under  $\text{N}_2$  atmosphere, compound (8a) (146 mg, 0.453 mmol), dissolved

in 8 ml of toluene, and 5 crystals of *p*-TsOH were added. The reaction mixture was left to stir for 3 days at 40 °C. Subsequently, the reaction was heated to 65 °C and left to stir for an additional 19 h. The reaction was monitored by <sup>1</sup>H NMR and GC-MS to confirm full conversion. The reaction mixture was diluted in Et<sub>2</sub>O and washed with sat. NaHCO<sub>3</sub> solution and brine. The organic layer was dried over MgSO<sub>4</sub>, filtered and the solvent was removed under reduced pressure. The crude product was purified by using column chromatography (SiO<sub>2</sub> impregnated with 10% aqueous AgNO<sub>3</sub>, pentane:ether, 99:1). (9a) was obtained as a bright yellow oil (104 mg, 80% yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.36 (t, 1H), 7.25 (tt, J = 7.5, 4.2 Hz, 1H), 7.18 (d, J = 3.3 Hz, 1H), 7.17 (d, J = 2.6 Hz, 1H), 5.73 (t, J = 5.9, 2.9 Hz, 1H), 2.88 – 2.79 (m, 2H), 2.74 – 2.49 (m, 4H), 2.39 – 2.27 (m, 1H), 2.23 – 2.11 (m, 1H), 2.09 – 2.00 (m, 1H), 1.98 – 1.82 (m, 1H), 1.62 – 1.52 (m, 1H), 1.48 – 1.31 (m, 5H), 0.98 (dt, J = 9.3, 6.2 Hz, 3H), 0.92 – 0.85 (m, 2H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 149.8, 136.5, 136.2, 128.8, 128.3, 127.2, 126.3, 126.2, 122.6, 121.3, 51.8, 45.0, 36.8, 35.1, 32.4, 29.5, 28.5, 28.3, 23.9, 23.6, 22.7, 16.2, 14.1. [α]<sub>D</sub><sup>20</sup> = + 4.6 (c = 1.0, CHCl<sub>3</sub>). HRMS calculated for [C<sub>23</sub>H<sub>30</sub>+H]<sup>+</sup>: 307.242, found 307.241

**(8*S*,9*S*,13*R*,14*S*,17*S*)-13-methyl-17-pentyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopentana[α]phenantrene (11a):**

To a solution of (9a) (74 mg, 0.24 mmol) in 2.4 mL of benzene, was added 10% Pd/C (10 mg) and Et<sub>3</sub>SiH (1.2 mL, 4.8 mmol) at 0 °C. The reaction flask was evacuated and recharged with H<sub>2</sub> for three times by using a H<sub>2</sub> balloon. After 2 d under H<sub>2</sub> atmosphere, GC-MS showed full

conversion and the suspension was filtered through a thin plug of Celite, which was then washed with benzene. The filtrate was concentrated *in vacuo*. *cis* : *trans* ratio = 15 : 85 (analyzed by GC-MS). The residue (62 mg, 0.2 mmol) was diluted in 1 mL of DCM and Et<sub>3</sub>SiH (0.2 mL, 0.4 mmol), TBAI (80 mg, 0.2 mmol) and TFA (0.2 mL, 2 mmol) were added at 0 °C and the mixture was left to stir at the same temperature until CG-MS showed full conversion (4 h). The reaction mixture was concentrated and the residue was purified by column chromatography (SiO<sub>2</sub>, 100% pentane) to afford (11a) in 77% yield over the two steps.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.16 (d, J = 8.3 Hz, 1H), 6.62 (dd, J = 8.5, 2.8 Hz, 1H), 6.55 (d, J = 2.9 Hz, 1H), 4.57 (s, 1H), 2.81 (t, J = 11.9, 11.3 Hz, 2H), 2.30 – 2.19 (m, 1H), 1.93 – 1.79 (m, 4H), 1.77 – 1.66 (m, 1H), 1.48 – 1.11 (m, 16H), 0.89 (t, J = 6.8 Hz, 3H), 0.60 (s, 3H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 153.1, 138.4, 133.3, 126.5, 115.2, 112.5, 54.9, 51.1, 44.2, 38.8, 38.0, 32.4, 30.3, 29.7, 29.7, 28.6, 28.5, 27.8, 26.5, 24.4, 22.7, 14.1, 12.5. [α]<sub>D</sub><sup>20</sup> = + 38.6 (c = 1.0, CHCl<sub>3</sub>). HRMS calculated for [C<sub>23</sub>H<sub>34</sub>+H]<sup>+</sup>: 311.273, found 311.273.

**(8*S*,9*S*,13*R*,14*S*,17*S*)-13-methyl-17-pentyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[α]phenanthren-2-ol (17a):**

In a pressure tube under Ar atmosphere, was added (11a) (73 mg, 0.23 mmol), B<sub>2</sub>pin<sub>2</sub> (0.089 mg, 0.35 mmol), dtbpy (6 mg, 0.023 mmol), Ir[(COD)(OMe)]<sub>2</sub> (8 mg, 0.012 mmol) and 0.2 mL of dry THF. The tube was sealed and the reaction was left to stir at 65 °C for 20 h. CG-MS

confirmed full conversion and the mixture was concentrated *in vacuo*.

The residue was used without further purification for the next step. The boronate ester intermediate (82 mg, 0.19 mmol) was dissolved in 1 mL of MeOH and H<sub>2</sub>O<sub>2</sub> (30% w/w in water) (0.1 mL) was added. The mixture was left to stir at rt for 3 d. The reaction was quenched with Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub>. The aqueous layer was extracted twice with DCM. The combined organic layers were washed with brine, dried and concentrated. Column chromatography (SiO<sub>2</sub>, pentane:Et<sub>2</sub>O (85:15)) gave compound (17a) (single regioisomer) in 23% yield.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.94 (d, J = 8.1 Hz, 1H), 6.79 (d, J = 2.8 Hz, 1H), 6.60 (dd, J = 8.2, 2.6 Hz, 1H), 2.78 (dd, J = 8.6, 4.2 Hz, 2H), 2.27 – 2.18 (m, 1H), 1.94 – 1.80 (m, 3H), 1.73 (t, J = 6.4 Hz, 1H), 1.53 – 1.15 (m, 18H), 0.94 – 0.85 (m, 3H), 0.60 (s, 23H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 153.3, 142.3, 129.9, 129.0, 112.5, 112.1, 55.0, 51.1, 44.7, 42.4, 38.5, 38.0, 32.4, 30.3, 28.8, 28.6, 28.5, 28.0, 26.3, 24.4, 22.7, 14.1, 12.5. [α]<sub>D</sub><sup>20</sup> = + 5.4 (c = 0.15, CHCl<sub>3</sub>). HRMS calculated for [C<sub>23</sub>H<sub>34</sub>O+H]<sup>+</sup>: 327.268, found 327.267.

**Mixture of diastereomers: (2R,3S)-2-(2-((E)-3,4-dihydronaphthalen-1(2H)-ylidene)ethyl)-3-ethyl-2-methylcyclopentan-1-one (8b):**

To a flame-dried Schlenk tube, containing a magnetic stirring bar and under N<sub>2</sub> atmosphere, CuBr·SMe<sub>2</sub> (31 mg, 5 mol%), ligand (L1) (107 mg, 6 mol%) and 30 ml of dry *t*-BuOMe were added. The mixture was left to stir for 15 min, after which 2-methylcyclopentenone (288 mg, 3.0 mmol, 1 eq), dissolved in a small amount of dry *t*-BuOMe, was added. The



mixture was cooled to  $-78\text{ }^{\circ}\text{C}$  and left to stir for 30 min. Ethylmagnesium bromide (1 M in  $\text{Et}_2\text{O}$ , 6 ml, 2 eq) was added dropwise over 15 min and the reaction mixture was left to stir for 3 h at  $-78\text{ }^{\circ}\text{C}$ . Dry DMPU (30 mmol, 3.6 ml) was added to the reaction mixture which was left to stir for 10 min at  $-78\text{ }^{\circ}\text{C}$ . Allylic bromide (4) (2.12 g, 9.0 mmol) was added (as crude material of the previous reaction). The reaction mixture was allowed to warm up to rt and left to stir for 20 h. The mixture was diluted in 40 ml of  $\text{Et}_2\text{O}$ . 70 ml of  $\text{NH}_4\text{Cl}_{\text{aq}}$  was added and the layers were separated. The aqueous layer was extracted two times with 40 ml of  $\text{Et}_2\text{O}$ . The combined organic layers were dried over  $\text{MgSO}_4$ , filtered and the solvent was removed under reduced pressure. The crude material was purified by using column chromatography ( $\text{SiO}_2$ , pentane:ether (95:5)). Compound (8b) was obtained in 75% yield (637 mg) over two steps,  $er= 85 : 15$ ,  $dr= 72 : 28$ .

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.53 – 7.44 (m, 1H), 7.12 (dd,  $J = 5.7, 3.5$  Hz, 2H), 7.08 (t,  $J = 4.7$  Hz, 1H), 5.83 (t, 1H), 2.84 – 2.66 (m, 3H), 2.55 – 2.28 (m, 6H), 2.19 – 1.97 (m, 3H), 1.93 (tdd,  $J = 10.3, 6.2, 3.4$  Hz, 1H), 1.87 – 1.65 (m, 3H), 1.59 (ddd,  $J = 13.7, 7.8, 3.7$  Hz, 1H), 1.47 – 1.17 (m, 3H), 1.10 – 1.05 (m, 3H), 0.98 (td,  $J = 7.4, 5.6$  Hz, 6H), 0.91 (s, 3H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{cdcl}_3$ )  $\delta$  222.4, 221.4, 136.6, 134.7, 127.5, 126.5, 126.4, 125.0, 122.59, 77.3, 77.0, 76.7, 56.2, 54.7, 43.0, 40.7, 38.1, 37.3, 34.7, 32.2, 32.0, 31.70, 29.3, 28.4, 28.0, 27.8, 27.7, 27.0, 26.8, 24.5, 23.6, 23.1, 22.7, 22.6, 20.6, 14.1, 14.0, 11.0, 8.5. HRMS calculated for  $[\text{C}_{20}\text{H}_{26}\text{O} + \text{H}]^+$ : 283.205, found 283.205.

**(13R,17S)-17-ethyl-13-methyl-7,11,12,13,16,17-hexahydro-6H-cyclopenta[a]phenanthrene (9b):**

To a flame-dried Schlenk tube, containing a magnetic stirring bar and under N<sub>2</sub> atmosphere, compound (8b) (637 mg, 2.26 mmol), dissolved in 10 ml of toluene, and *p*-TsOH (0.1 g) were added. The reaction mixture was left to stir for 2 days at 65 °C. The reaction was monitored by <sup>1</sup>H NMR and GC-MS to confirm full conversion. The reaction mixture was diluted in Et<sub>2</sub>O and washed with sat. NaHCO<sub>3</sub> solution and brine. The organic layer was dried over MgSO<sub>4</sub>, filtered and the solvent was removed under reduced pressure. The crude material was purified by using column chromatography (SiO<sub>2</sub>, impregnated with 10% aqueous AgNO<sub>3</sub>, pentane : TBME, 99:1). Steroid (9b) was obtained as a bright yellow oil (280 mg, 69% yield).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.32 (d, J = 7.7 Hz, 1H), 7.24 – 7.17 (m, 1H), 7.14 (d, J = 3.1 Hz, 2H), 5.69 (s, 1H), 2.79 (dd, J = 9.6, 6.0 Hz, 2H), 2.73 – 2.44 (m, 4H), 2.39 – 2.18 (m, 1H), 2.12 (dd, J = 16.7, 10.5 Hz, 1H), 2.01 (ddd, J = 12.6, 5.5, 1.6 Hz, 1H), 1.78 (tdd, J = 10.2, 7.4, 4.9 Hz, 1H), 1.54 (ddp, J = 18.3, 12.6, 5.7 Hz, 3H), 1.47 – 1.36 (m, 1H), 1.35 – 1.25 (m, 1H), 0.99 (t, J = 7.4 Hz, 3H), 0.84 (s, 3H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 149.9, 136.4, 136.2, 128.8, 128.3, 127.2, 126.3, 126.2, 122.6, 121.2, 53.7, 44.9, 36.4, 35.2, 28.3, 23.9, 23.6, 22.4, 16.2, 13.3. [α]<sub>D</sub><sup>20</sup> = +18.2 (c = 1.1, CHCl<sub>3</sub>). HRMS calculated for [C<sub>20</sub>H<sub>24</sub>+H]<sup>+</sup>: 265.195, found 265.158.

**(8*S*,9*S*,13*R*,14*S*,17*S*)-17-ethyl-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[α]phenanthrene (11b):**

To a solution of 9b (88 mg, 0.33 mmol) in 3 mL of benzene, was added 10% Pd/C (76 mg) and Et<sub>3</sub>SiH (1.7 mL, 3.3 mmol) at 0 °C. The reaction

flask was evacuated and recharged with H<sub>2</sub> for three times by using a H<sub>2</sub> balloon. After 2 days under H<sub>2</sub> atmosphere, GC-MS showed full conversion and the suspension was filtered through a thin plug of Celite, which was then washed with benzene. The filtrate was concentrated *in vacuo*. *cis* : *trans* = 15 : 85 based on GC-MS. The residue (80 mg, 0.3 mmol) was diluted in 2 mL of DCM and Et<sub>3</sub>SiH (0.33 mL, 0.6 mmol), TBAI (122 mg, 0.3 mmol) and TFA (0.26 mL, 3 mmol) were added at 0 °C and the mixture was left to stir at the same temperature until CG-MS showed full conversion (4 h). The reaction mixture was concentrated and the residue was purified by column chromatography (SiO<sub>2</sub>, 100% pentane) in 70% yield (62 mg over the two steps).

<sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ 7.39 – 7.33 (m, 1H), 7.22 – 7.09 (m, 3H), 2.98 – 2.84 (m, 2H), 2.34 (tdd, *J* = 16.6, 9.0, 4.6 Hz, 2H), 1.96 (dq, *J* = 11.2, 3.1 Hz, 3H), 1.87 – 1.73 (m, 1H), 1.66 – 1.40 (m, 4H), 1.38 – 1.24 (m, 4H), 1.24 – 1.13 (m, 1H), 0.98 (dt, *J* = 11.3, 7.7 Hz, 4H), 0.86 (d, *J* = 8.1 Hz, 1H), 0.75 (s, 0H), 0.58 (q, *J* = 8.0 Hz, 1H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 140.8, 136.9, 129.0, 125.5, 125.5, 125.3, 55.2, 53.2, 44.8, 42.5, 38.6, 38.1, 29.7, 28.3, 27.9, 26.3, 24.3, 23.2, 13.4, 12.5. [α]<sub>D</sub><sup>20</sup> = + 45.8 (c = 3.15, CHCl<sub>3</sub>). HRMS calculated for [C<sub>20</sub>H<sub>28</sub>+H]<sup>+</sup>: 269.226, found 269.226.

**Mixture of regioisomers: (8*S*,9*S*,13*R*,14*S*,17*S*)-17-ethyl-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[α]phenanthren-3-ol (16b + 17b):**

In a pressure tube under Ar atmosphere, was added (11a) (30 mg, 0.13 mmol), B<sub>2</sub>pin<sub>2</sub> (55.9 mg, 0.22 mmol), dtbpy (10.5 mg, 0.04 mmol), Ir[(COD)(OMe)]<sub>2</sub> (12.6 mg, 0.019 mmol) and 0.2 mL of dry THF. The

tube was sealed and the reaction was left to stir at 65 °C for 20 h. CG-MS confirmed full conversion and the mixture was concentrated *in vacuo*. The residue was used without further purification for the next step. The boronate ester intermediates (20 mg, 0.05 mmol) was dissolved in 1 mL of MeOH and H<sub>2</sub>O<sub>2</sub> (30% w/w in water, 0.1 mL) was added. The mixture was left to stir at rt for 3 d. The reaction was quenched with Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub>. The aqueous layer was extracted twice with DCM. The combined organic layers were washed with brine, dried and concentrated. Column chromatography (SiO<sub>2</sub>, pentane:Et<sub>2</sub>O (85:15)) gave compounds (16b) and (17b) as a mixture in 35% yield (12.9 mg).

<sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ 7.16 (d, *J* = 8.3 Hz, 1H), 6.99 – 6.91 (m, 2H), 6.79 (d, *J* = 2.6 Hz, 2H), 6.68 – 6.53 (m, 4H), 2.79 (dt, *J* = 8.7, 5.1 Hz, 5H), 2.34 (t, *J* = 6.6 Hz, 5H), 2.29 – 2.08 (m, 7H), 1.87 (dq, *J* = 12.9, 6.4 Hz, 14H), 1.73 (q, *J* = 6.0, 5.2 Hz, 5H), 1.58 – 1.46 (m, 5H), 1.40 – 1.33 (m, 2H), 1.33 – 1.09 (m, 21H), 1.12 (dt, *J* = 15.5, 8.0 Hz, 2H), 0.90 (t, *J* = 7.4 Hz, 11H), 0.87 – 0.66 (m, 7H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 153.3, 153.1, 142.32, 138.4, 133.2, 129.9, 129.0, 126.5, 125.5, 115.2, 112.5, 112.5, 112.1, 110.0, 55.1, 54.9, 53.2, 53.1, 51.2, 44.7, 44.2, 42.4, 42.4, 42.0, 38.8, 38.4, 38.0, 30.3, 29.7, 29.7, 28.8, 28.2, 27.9, 27.8, 27.0, 26.5, 26.26, 25.0, 24.3, 24.3, 23.1, 22.8, 22.3, 14.0, 13.7, 13.3, 12.5, 12.5. HRMS calculated for [C<sub>20</sub>H<sub>24</sub>O+H]<sup>+</sup>: 285.221, found 285.221.

### **3-ethoxy-2-ethylcyclopent-2-en-1-one (21):**

To a flame-dried 3 necked roundbottom flask, was added (20) (10 g, 79 mmol), 250 mL of dry ethanol and *p*TsOH (4 g, 26 mmol) and the reaction was left to stir under reflux for 2 d. The mixture was cooled

down to rt, washed with saturated aq. NaHCO<sub>3</sub> solution and the layers were separated. The organic layer was dried and concentrated at reduced pressure. Column chromatography (SiO<sub>2</sub>, pentane: Et<sub>2</sub>O (50:50)) gave the product in 66% yield (8.03 g). The spectral data matched literature.<sup>10</sup> HRMS calculated for [M+H]<sup>+</sup>: 155.106, found 155.106.

### **2-ethylcyclopent-2-en-1-one (19):**

Compound (21) (8.24 g, 52.8 mmol) was dissolved in 80 mL of dry Et<sub>2</sub>O and LiAlH<sub>4</sub> (0.5 g, 13 mmol) was added. The reaction mixture was left to stir overnight at rt. The reaction was quenched by addition of 10% aq. H<sub>2</sub>SO<sub>4</sub>. The layers were separated, the aq. layer was extracted twice with Et<sub>2</sub>O, and the combined organic layers were dried and concentrated at reduced pressure. Column chromatography (SiO<sub>2</sub>, pentane: Et<sub>2</sub>O (30% to 60% Et<sub>2</sub>O)) gave the product in 24% yield (1.39 g). The spectral data matched literature.<sup>18</sup>

### **Mixture of diastereomers: (2R,3S)-2-(2-((E)-3,4-dihydronaphthalen-1(2H)-ylidene)ethyl)-2-ethyl-3-pentylcyclopentan-1-one (22):**

To a flame-dried Schlenk tube, containing a magnetic stirring bar and under N<sub>2</sub> atmosphere, CuBr·SMe<sub>2</sub> (20.6 mg, 0.1 mmol), ligand (L1) (71.3 mg, 0.12 mmol) and 20 ml of dry *t*-BuOMe were added. The mixture was left to stir for 15 min, after which 2-ethylcyclopentenone (0.27 mL, 2 mmol, 1 eq), dissolved in a small amount of dry *t*-BuOMe, was added. The mixture was cooled to -78 °C and left to stir for 30 min. Pentylmagnesium bromide (2 M in Et<sub>2</sub>O, 2 ml, 2 eq) was added

dropwise over 15 min and the reaction mixture was left to stir for 3 h at  $-78\text{ }^{\circ}\text{C}$ . Dry DMPU (20 mmol, 2.4 ml) was added to the reaction mixture which was left to stir for 10 min at  $-78\text{ }^{\circ}\text{C}$ . Allylic bromide (4) (1.42 g, 6 mmol) was added (as crude material of the previous reaction). The reaction mixture was allowed to warm up to rt and left to stir for 20 h. The mixture was diluted in 40 ml of  $\text{Et}_2\text{O}$ . 70 ml of  $\text{NH}_4\text{Cl}_{\text{aq}}$  was added and the layers were separated. The aqueous layer was extracted two times with 40 ml  $\text{Et}_2\text{O}$ . The combined organic layers were dried over  $\text{MgSO}_4$ , filtered and the solvent was removed under reduced pressure. The crude material was purified by column chromatography ( $\text{SiO}_2$ , pentane:ether, 95:5). Compound (22) was obtained in 88% yield (0.576 g) over two steps,  $er= 89 : 11$ ,  $dr= 60 : 40$ . Retention times on chiral GC: 14.8 min and 15.2 min (major *trans* diastereomer), 15.8 min and 16.0 min (minor *cis* diastereomer).

$^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  7.50 (ddd,  $J = 9.8, 6.0, 3.0$  Hz, 2H), 7.09 (ddd,  $J = 20.2, 6.2, 3.6$  Hz, 5H), 5.93 (t,  $J = 7.5$  Hz, 1H), 5.79 (dd,  $J = 9.2, 6.6$  Hz, 1H), 2.76 (dd,  $J = 8.1, 4.2$  Hz, 4H), 2.50 (ddt,  $J = 28.0, 14.0, 6.3$  Hz, 5H), 2.41 – 2.19 (m, 5H), 2.18 – 1.97 (m, 5H), 1.88 – 1.71 (m, 5H), 1.65 (dtd,  $J = 15.7, 7.8, 3.3$  Hz, 1H), 1.60 – 1.37 (m, 6H), 1.37 – 1.21 (m, 13H), 0.98 – 0.82 (m, 11H), 0.77 (t,  $J = 7.4$  Hz, 3H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  222.7, 137.2, 136.3, 135.7, 128.8, 128.7, 126.6, 126.6, 126.0, 125.9, 123.8, 123.8, 120.2, 119.4, 56.2, 55.5, 55.2, 43.6, 42.4, 38.1, 37.6, 37.5, 34.7, 32.2, 32.2, 31.5, 30.4, 30.4, 30.3, 29.7, 29.6, 27.7, 27.7, 27.0, 26.6, 26.6, 26.5, 25.4, 24.8, 24.8, 24.0, 23.3, 23.1, 22.7, 22.6, 20.6, 14.1, 14.0, 14.0, 9.0, 8.7. HRMS calculated for  $[\text{M}+\text{Na}]^+$ : 361,250, found 361,250.

**Mixture of diastereomers: (13*R*,17*S*)-13-ethyl-17-pentyl-7,11,12,13,16,17-hexahydro-6*H*-cyclopenta[ $\alpha$ ]phenanthrene (23):**

To a flame-dried Schlenk tube, containing a magnetic stirring bar and under N<sub>2</sub> atmosphere, compound (22) (523 mg, 1.55 mmol), dissolved in 7 ml of toluene, and *p*-TsOH (0.8 g) were added. The reaction mixture was left to stir for 1 d at 65 °C. The reaction was checked by <sup>1</sup>H NMR and GC-MS to confirm full conversion. The reaction mixture was diluted in Et<sub>2</sub>O and washed with sat. NaHCO<sub>3</sub> solution and brine. The organic layer was dried over MgSO<sub>4</sub>, filtered and the solvent was removed under reduced pressure. The crude material was purified by using column chromatography (SiO<sub>2</sub>, impregnated with 10% aqueous AgNO<sub>3</sub>, pentane : TBME (99:1)). (23) was obtained as a bright yellow oil in 77% yield (0.382 g) as a 80:20 mixture of diastereomers.

<sup>1</sup>H NMR (400 MHz, Chloroform-*d*)  $\delta$  7.28 (d, *J* = 7.7 Hz, 1H), 7.18 (tt, *J* = 8.2, 4.1 Hz, 1H), 7.11 (q, *J* = 2.8, 2.3 Hz, 2H), 5.79 (s, 1H), 5.59 (s, 1H), 2.78 (dd, *J* = 9.9, 6.5 Hz, 2H), 2.59 (ddd, *J* = 36.6, 19.1, 6.9 Hz, 4H), 2.39 – 2.20 (m, 1H), 2.17 – 1.99 (m, 2H), 1.94 – 1.81 (m, 1H), 1.65 (dd, *J* = 20.0, 10.5 Hz, 1H), 1.51 (d, *J* = 7.0 Hz, 2H), 1.48 – 1.12 (m, 6H), 1.05 (d, *J* = 10.5 Hz, 0H), 0.89 (dq, *J* = 11.1, 7.4, 7.0 Hz, 5H), 0.81 (t, *J* = 7.5 Hz, 1H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  147.8, 147.2, 136.4, 136.4, 136.2, 136.1, 129.0, 128.8, 128.7, 128.6, 127.2, 127.2, 126.4, 126.4, 126.3, 126.2, 122.6, 122.6, 122.5, 120.8, 52.7, 49.7, 48.0, 44.1, 38.2, 36.8, 34.5, 32.5, 32.4, 30.8, 29.9, 29.0, 28.4, 28.4, 28.1, 27.5, 25.8, 24.3, 24.0, 24.0, 23.8, 23.7, 22.9, 22.9, 14.3, 10.0, 9.0. HRMS calculated for [M+H]<sup>+</sup>: 321.257, found 321.257

**Mixture of distereomers: (8S,9S,13R,14S,17S)-13-ethyl-17-pentyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[ $\alpha$ ]phenanthrene (24):**

To a solution of (9b) (352 mg, 1.1 mmol) in 12 mL of benzene, was added 10% Pd/C (0.300 g) and Et<sub>3</sub>SiH (5.2 mL, 10 mmol) at 0 °C. The reaction flask was evacuated and recharged with H<sub>2</sub> for three times by using a H<sub>2</sub> balloon. After 2 d under H<sub>2</sub> atmosphere, GC-MS showed full conversion and the suspension was filtered through a thin plug of Celite, which was then washed with benzene. The filtrate was concentrated *in vacuo*. *cis* : *trans* = 15 : 85 based on GC-MS. The residue (322 mg, 1.0 mmol) was diluted in 6 mL of DCM and Et<sub>3</sub>SiH (1.1 mL, 2 mmol), TBAI (0.401 g, 1 mmol) and TFA (0.87 mL, 10 mmol) were added at 0 °C and the mixture was left to stir at the same temperature until CG-MS showed full conversion (4 h). The reaction mixture was concentrated and the residue was purified by column chromatography (SiO<sub>2</sub>, 100% pentane) in 72% yield (0.257 g) over the two steps.

<sup>1</sup>H NMR (400 MHz, Chloroform-*d*)  $\delta$  7.15 (d, *J* = 8.5 Hz, 1H), 6.61 (dd, *J* = 8.4, 2.8 Hz, 1H), 6.55 (d, *J* = 2.9 Hz, 2H), 2.95 – 2.66 (m, 2H), 2.20 (tdd, *J* = 19.3, 9.2, 4.0 Hz, 3H), 1.96 – 1.80 (m, 2H), 1.66 (q, *J* = 8.9, 8.0 Hz, 1H), 1.61 – 1.50 (m, 1H), 1.42 (s, 5H), 1.39 – 1.12 (m, 27H), 1.07 – 0.72 (m, 12H), 0.63 – 0.47 (m, 1H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  153.2, 138.4, 133.3, 126.3, 126.3, 115.2, 112.5, 56.3, 52.5, 43.9, 43.9, 38.8, 33.8, 32.41, 31.7, 29.7, 29.0, 28.7, 27.7, 26.7, 23.6, 22.7, 18.1, 14.1, 9.4. HRMS calculated for [M+H]<sup>+</sup>: 325.288, found 325.149



**Mixture of regioisomers: (8S,9S,13R,14S,17S)-13-ethyl-17-pentyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-ol (26a + 26b):**

In a pressure tube under Ar atmosphere, was added (11a) (45 mg, 0.14 mmol), B<sub>2</sub>pin<sub>2</sub> (55 mg, 0.21 mmol), dtbpy (1 mg, 0.007 mmol), Ir[(COD)(OMe)]<sub>2</sub> (3 mg, 0.0035 mmol) and 0.15 mL of dry THF. The tube was sealed and the reaction was left to stir at 65 °C for 20 h. CG-MS confirmed full conversion and the mixture was concentrated *in vacuo*. The residue was used without further purification for the next step. Boronate ester intermediate (45 mg, 0.1 mmol) was dissolved in 1 mL of MeOH and H<sub>2</sub>O<sub>2</sub> (0.1 mL) was added. The mixture was left to stir at rt for 3 d. The reaction was quenched with Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub>. The aqueous layer was extracted twice with DCM. The combined organic layers were washed with brine, dried and concentrated. Column chromatography (SiO<sub>2</sub>, pentane:Et<sub>2</sub>O, 85:15) gave compounds (26b) and (17b) in 29% yield (9.9 mg) as 7:3 mixture of diastereomers.

<sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ 7.16 (d, *J* = 8.3 Hz, 1H), 6.94 (d, *J* = 8.1 Hz, 2H), 6.79 (d, *J* = 2.7 Hz, 2H), 6.65 – 6.50 (m, 5H), 4.51 (s, 3H), 2.78 (dd, *J* = 8.9, 4.1 Hz, 6H), 2.30 – 2.13 (m, 7H), 2.05 (s, 1H), 1.96 – 1.77 (m, 10H), 1.72 (d, *J* = 8.9 Hz, 2H), 1.66 – 1.46 (m, 9H), 1.45 – 1.03 (m, 69H), 0.88 (q, *J* = 11.1, 8.7 Hz, 14H), 0.78 (s, 2H), 0.67 (s, 1H). HRMS calculated for [M+H]<sup>+</sup>:341.284, found 341.284

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