Enantioselective synthesis of bicyclic compounds via catalytic 1,4-addition-ring closing metathesis
Naasz, R.; Arnold, L.A.; Minnaard, Adriaan; Feringa, B.L.

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tical experimental procedure for the synthesis of (1S,4aR,8aR)-1-ethyl-1,3,4,5,8,8a-hexahydro-4a(2H)-naphthalenol 6a.

Under an Ar atmosphere in flame dried glassware a mixture of 9.4 mg (0.026 mmol) Cu(OTf)₂ and 28 mg (0.052 mmol) of (S,R,R)-3 in 50 mL of toluene was stirred at room temperature for 1 h. The solution was cooled to –30°C and 0.50 mL (5.2 mmol) of cyclohexenone (1a) was added. After the solution was stirred for 10 min Et₂Zn (7.1 mL of a 1.1 M solution in toluene) was added. Following the completion of the reaction (after 3 h as checked by GC) 240 mg (0.21 mmol) of Pd(PPh₃)₄ and 0.59 mL (5.5 mmol) of allyl acetate were added and the reaction mixture was allowed to warm to 0°C and stirred overnight. The reaction mixture was quenched with 50 mL of 1 M HCl and the aqueous layer was extracted with ether (3 x 30 mL). The combined organic layers were washed with brine (50 mL) and dried over Na₂SO₄. Filtration and evaporation of the solvent was followed by column chromatography (silica, hexanes:ether = 4:1) to yield 2a (trans/cis: 9:1, e.e. of trans 2a = 96%) as a colourless oil (763 mg, 4.6 mmol, 88%). ¹H-NMR (CDCl₃, 300 MHz): 0.78 (t, J = 7.3 Hz, 3H), 1.1-2.4 (m, 12H), 4.88 (m, 2H), 5.67 (m, 1H). Trans-2a: ¹³C-
NMR (CDCl$_3$, 300 MHz): 10.41 (q), 24.90 (t), 25.72 (t), 28.36 (t), 31.40 (t), 41.18 (t), 43.18 (d), 54.61 (d), 115.91 (t), 136.45 (d), 212.92 (s).

Under an Ar atmosphere in flame dried glassware 400 mg (2.41 mmol) of 2a was dissolved in 10 mL of dry THF. The solution was cooled to 0°C after which allylmagnesium chloride (1.8 mL of a 2 M solution in THF) was added dropwise and the solution was stirred overnight. The reaction mixture was quenched with 15 mL of 1 M HCl and the aqueous layer was extracted with ether (3 × 20 mL). The combined organic layers were washed with brine (30 mL) and dried over Na$_2$SO$_4$. Filtration and evaporation of the solvent was followed by filtration through a short column (silica, hexanes:ether = 5:1) giving >95% pure 4a as a mixture of isomers as a slightly yellow oil (463 mg, 2.23 mmol, 92%). $^1$H-NMR (CDCl$_3$, 300 MHz): 0.80 (t, 3H), 1.0 - 1.8 (m, 11H), 2.1 - 2.4 (m, 4H), 4.8 - 5.1 (m, 4H), 5.7 - 6.0 (m, 2H). (1R, 2R, 3S)-4a: $^{13}$C-NMR (CDCl$_3$, 300 MHz): 10.53 (q), 20.94 (t), 25.73 (t), 30.92 (t), 31.43 (t), 37.42 (t), 37.38 (d), 46.44 (t), 46.78 (d), 74.75 (s), 115.64 (t), 118.06 (t), 134.11 (d), 139.13 (d).

Under an Ar atmosphere in flame dried glassware 62 mg (0.10 mmol) of 5 was dissolved in 30 mL of dry benzene. 4a (310 mg, 1.49 mmol) was added dropwise and the mixture was stirred overnight. After oxidation of the catalyst by exposing the reaction mixture to air for 24 h and evaporation of the solvent, pure (1$S$, 4a$R$, 8a$S$)-6a (161 mg, 0.89 mmol, 60%, e.e. = 96%) was obtained by column chromatography (silica, hexanes:ether = 6:1). $^1$H-NMR (CDCl$_3$, 300 MHz): 0.78 (t, 3H), 0.8 - 2.3 (m, 15H), 5.54 (m, 1H), 5.68 (m, 1H). $^{13}$C-NMR (CDCl$_3$, 300 MHz): 10.23 (q), 21.23 (t), 24.97 (t), 26.54 (t), 30.78 (t), 38.86 (d), 38.97 (t), 40.86 (t), 42.79 (d), 68.96 (s), 123.74 (d), 127.04 (d). The e.e. of (1$S$, 4a$R$, 8a$S$)-6a was determined by GC on a Chiraldex G-TA column, 50 m x 0.25 mm, He-flow 1.0 mL/min, isothermic 123°C. $T_{ret}$ 53.1 min: (1$S$, 4a$R$, 8a$S$)-6a. $T_{ret}$ 54.4 min: (1$R$, 4a$S$, 8a$S$)-6a.
The configuration of the major isomer of 6a was deduced from the HSQC, COSY and NOESY NMR spectral data of the \( p \)-nitrobenzoate ester of 6a:

All protons could be assigned by COSY and HSQC experiments (*vide infra*). The methyl protons (\( \delta = 0.90 \) ppm, t, 3H) could unambiguously be assigned by their characteristic chemical shift and splitting pattern. A COSY interaction identified the two diastereotopic H\(_7\) neighbour protons at 1.21 and around 1.6 ppm (partial overlap with other proton). Both H\(_7\) protons have a COSY interaction with one other proton: H\(_6\) at 1.55 ppm. H\(_5\) can then be identified by HSQC as the proton connected to the other non-vinylic doublet C which is confirmed by an interaction between this proton (H\(_5\) at 1.46 ppm) and H\(_6\).

Starting from H\(_6\) additional interactions with two other protons are observed. Both protons are attached to the same carbon (HSQC) and are therefore assigned as the two H\(_8\)'s at 1.10 and 1.81 ppm. Both these protons give a COSY interaction with two protons at around 1.35 and 1.6 ppm (both overlap with other signals) which are thus identified as the H\(_9\) protons. The signal at 1.6 ppm couples with a proton at 3.05 ppm (H\(_{10}\)). HSQC identifies the other H\(_{10}\) at around 1.35 ppm.
Starting from H₅ additional COSY interactions with two protons are observed (both H₄’s at 2.07 and 2.38 ppm). Both of these couple with a proton at 5.72 ppm (H₃). This proton couples with its neighbour H₂ at 5.50 ppm which in turn couples with one of the H₁ protons (3.32 ppm). Through HSQC the other H₁ proton is found at 2.09 ppm.

If the two six membered rings are trans fused as is expected from addition of the Grignard reagent trans to the allylic group, NOE interactions should be observed between H₁b and H₁₀b, H₁b and H₅, H₅ and H₁₀b, H₅ and H₈b and H₈b and H₁₀b. Indeed a NOE interaction is observed between H₅ and one of the H₁’s which is therefore H₁b at 2.09 ppm. Also NOE interactions between H₅ and H₈b (1.10 ppm), H₅ and H₁₀b (1.35 ppm) and H₁b and H₁₀b are observed. Especially the presence of both a H₅-H₁b and a H₁b-H₁₀b NOE interaction excludes a cis fused bicycle in a steroid or non-steroid conformation. Since the addition of the ethyl group to 2-cyclohexenone in the presence of (S,R,R)-3 gives the S configuration at carbon 1 (reference 8c in main text) the major isomer of 6a is identified as (1S,4aR,8aR)-1-ethyl-1,3,4,5,8,8a-hexahydro-4a(2H)-naphthalenol as depicted in the figure (vide supra).
500 MHz $^1$H-NMR of $p$-nitrobenzoate ester of $6a$ in CDCl$_3$: 
COSY of p-nitrobenzoate ester of 6a in CDCl₃:
HSQC of \( p \)-nitrobenzoate ester of 6a in CDCl₃:
NOESY of p-nitrobenzoate ester of 6a in CDCl3:
Data for 6a-h:

(4aR, 9S, 9aR)-9-ethyl-1,4,5,6,7,8,9a-octahydro-4aH-benzo[a]cyclohepten-4a-ol (6b)*:

$^1$H-NMR (CDCl$_3$, 300 MHz): 0.79 (t, 3H), 1.16 (m, 2H), 1.37 (m, 5H), 1.6-2.0 (m, 8H), 2.0-2.3 (m, 2H), 5.53 (m, 1H), 5.68 (m, 1H).

$^{13}$C-NMR (CDCl$_3$, 300 MHz): 10.56 (q), 20.71 (t), 25.92 (t), 27.15 (t), 27.91 (t), 33.12 (t), 38.24 (d), 39.87 (t), 42.69 (t), 46.47 (d), 72.38 (s), 124.41 (d), 127.68 (d).

E.e. determination of 6b was performed on a Chiraldex G-TA column, 50 m ¥ 0.25 mm, He flow: 1.0 mL/min, 135 °C isothermic: $T_{ret}$ 53.0 min: (4aR, 9S, 9aR)-6b, $T_{ret}$ 54.3 min: (4aS, 9R, 9aR)-6b. [a]$^{20}_{D}$ + 25.0 (c 0.8, CHCl$_3$).

(4aR, 10S, 10aR)-10-ethyl-1,5,6,7,8,9,10a-octahydrobenzo[a]cycloocten-4a(4H)-ol (6c)*:

$^1$H-NMR (CDCl$_3$, 300 MHz): 0.85 (t, 3H), 1.0-1.4 (m, 4H), 1.4-1.8 (m, 11H), 1.9-1.2 (m, 3H), 2.4 (m, 1H), 5.54 (m, 1H), 5.70 (m, 1H).

$^{13}$C-NMR (CDCl$_3$, 300 MHz): 12.92 (q), 24.98 (t), 25.13 (t), 25.71 (t), 26.48 (t), 27.76 (t), 33.06 (t), 35.96 (d), 39.27 (d), 39.55 (t), 40.01 (t), 73.77 (s), 124.07 (d), 127.39 (d).

E.e. determination of 6c was performed on a Chiraldex G-TA column, 50 m ¥ 0.25 mm, He flow: 1.0 mL/min, 140 °C isothermic: $T_{ret}$ 77.8 min: (4aR, 10S, 10aR)-6c, $T_{ret}$ 79.6 min: (4aS, 10R, 10aR)-6c. [a]$^{20}_{D}$ + 43.3 (c 0.6, CHCl$_3$).

(1R, 4aR, 8aR)-1-ethyl-2,2-dimethyl-1,3,4,5,8,8a-hexahydro-4a(2H)-napthalenol (6d)*:

$^1$H-NMR (CDCl$_3$, 300 MHz): 0.74 (s, 3H), 0.88 (s + t, 6H), 0.9-1.2 (m, 3H), 1.3-1.7 (m, 6H), 1.79 (m, 1H), 1.9-2.3 (m, 3H), 5.54 (m, 1H), 5.71 (m, 1H).

$^{13}$C-NMR (CDCl$_3$, 300 MHz): 16.12 (q), 19.45 (q), 21.59 (t), 30.39 (q), 34.34 (s), 34.60 (t), 36.64 (t), 41.06 (t), 41.11 (d), 48.32 (d), 69.14 (s), 123.72 (d), 127.35 (d).

E.e. determination of 6d was performed on a Chiraldex G-TA column, 50 m ¥ 0.25 mm, He flow: 1.0 mL/min, 125 °C isothermic: $T_{ret}$ 76.1 min: (1S, 4aR, 8aR)-6f, $T_{ret}$ 78.4 min: (1R, 4aS, 8aS)-6d. [a]$^{20}_{D}$ + 43.3 (c 0.6, CHCl$_3$).

(1S, 4aR, 8aR)-1-methyl-1,3,4,5,8,8a-hexahydro-4a(2H)-napthalenol (6e)*:

$^1$H-NMR (CDCl$_3$, 300 MHz): 0.80 (d, 3H), 0.97 (m, 1H), 1.1-1.3 (m, 3H), 1.3-1.5 (m, 2H), 1.5-1.8 (m, 4H), 1.9-2.1 (m, 2H), 2.2 (m, 1H), 5.55 (m, 1H), 5.68 (m, 1H).

$^{13}$C-NMR (CDCl$_3$, 300 MHz): 19.56 (q), 21.31 (t), 26.75 (t), 33.14 (d), 35.42 (t), 38.92 (t), 40.75 (t), 45.51 (d), 68.81 (s), 123.84 (d), 127.04 (d).
E.e. determination was performed with on the \( p \)-nitrobenzoate ester of \( \text{6e} \) by chiral HPLC: Chiralcel OD, heptane/2-propanol: 99/1, 1.0 mL/min, \( \lambda_{\text{det}}: \) 254 nm. \( T_{\text{ret}} \) 6.7 min and \( T_{\text{ret}} \) 7.9 min.

(1S, 4aR, 8aR)-1-butyl-1,3,4,5,8,8a-hexahydro-4a(2H)-naphthalenol (6f)*:

\[ ^1\text{H}-\text{NMR (CDCl}_3, 300 \text{ MHz): 0.83 (t, 3H), 0.9-1.8 (m, 14H), 1.9-2.1 (m, 2H), 2.21 (m, 1H), 5.54 (m, 1H), 5.68 (m, 1H).} \]
\[ ^{13}\text{C}-\text{NMR (CDCl}_3, 300 \text{ MHz): 14.10 (q), 21.82 (t), 23.13 (t), 26.62 (t), 28.23 (t), 31.50 (t), 32.34 (t), 37.64 (d)), 38.96 (t), 40.90 (t), 43.32 (d), 68.98 (s), 123.73 (d), 127.08 (d).} \]

E.e. determination of \( \text{6f} \) was performed on a Chiraldex G-TA column, 50 m \( \times \) 0.25 mm, He flow: 1.0 mL/min, 135 °C isothermic: \( T_{\text{ret}} \) 67.0 min: (1S, 4aR, 8aR)-\( \text{6f} \), \( T_{\text{ret}} \) 68.5 min: (1R, 4aS, 8aS)-\( \text{6f} \). \([\alpha]_D^{20} + 78.6 (c 0.9, \text{CHCl}_3)\).

(1S, 4aR, 9aR)-1-ethyl-1,2,3,4,5,6,9,9a-octahydro-4aH-benzo[a]cyclohepten-4a-ol (6h)*:

\[ ^1\text{H}-\text{NMR (CDCl}_3, 300 \text{ MHz): 0.77 (t, 3H), 0.95 (m, 2H), 1.1-1.7 (m, 10H), 1.8-2.4 (m, 5H), 5.7 (m, 2H).} \]
\[ ^{13}\text{C}-\text{NMR (CDCl}_3, 300 \text{ MHz): 10.11 (q), 21.40 (t), 22.92 (t), 24.59 (t), 26.08 (t), 31.35 (t), 37.07 (d), 40.61 (t), 42.25 (t), 48.14 (d), 74.00 (s), 132.07 (d), 132.23 (d).} \]

E.e. determination of \( \text{6h} \) was performed on a Chiraldex G-TA column, 50 m \( \times \) 0.25 mm, He flow: 1.0 mL/min, 135 °C isothermic: \( T_{\text{ret}} \) 51.9 min: (1S, 4aR, 9aR)-\( \text{6h} \), \( T_{\text{ret}} \) 53.6 min: (1R, 4aS, 9aS)-\( \text{6h} \). \([\alpha]_D^{20} + 41.8 (c 0.7, \text{CHCl}_3)\).

* The absolute configuration was assigned on the basis of analogy with the nitrobenzoate ester of \( \text{6a} \).