Tandem conjugate reduction-aldol cyclization using Stryker's reagent

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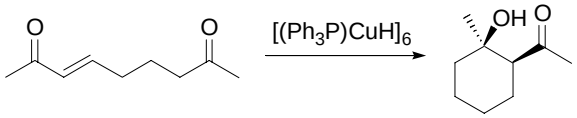
Supporting Information.

General Experimental. Toluene was freshly distilled from CaH_2 under argon. Prior to use in reductions, the toluene was degassed by bubbling in argon for 30 minutes. $[Ph_3PCuH]_6$ Stryker's reagent that was used was both synthesized in our laboratory and also purchased from the Aldrich Chemical Co. The transfer of this reagent was performed inside an argon dry-box. All glassware and syringes used in the reactions were oven-dried at 120°C for at least 4 hrs. Syringes were cooled in a dessicator. Oven-dried glassware were assembled hot and allowed to cool under a stream of dry argon. Solvents and reagents in solution were transferred with syringes and cannulae using standard inert atmosphere techniques. Infrared spectra were recorded on a Bio-Rad FT-IR spectrometer as a solution in CCl_4, from 4000 cm^{-1} to 400 cm^{-1}. All ^1H and ^{13}C NMR spectra were recorded on a Joel DX 270 spectrometer, a Bruker DX300 spectrometer, or a Bruker DX500 spectrometer, operating at 270 MHz, 300 MHz or 500 MHz respectively for ^1H, and at 67.5 MHz, 75 MHz, or 125 MHz respectively for ^{13}C. All the spectra were calibrated at δ 7.26 or δ 0.00 ppm for ^1H spectra (residual $CHCl_3$ or TMS respectively), and δ 77.020 or δ 0.00 ppm for ^{13}C spectra. Spectral features are designated as follows: m=multiplet, q=quartet, t=triplet, d=doublet, s=singlet and br=broad. High resolution mass spectra were recorded on a MAT90 mass spectrometer. For each sample, high resolution mass spectral data was obtained for the molecular ion, or next largest fragment thereof.

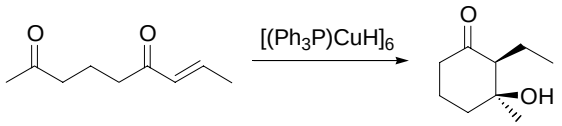
Table 1, entry 1:



General procedure for Tandem conjugate reduction -aldol cyclization using $[Ph_3PCuH]_6$ Stryker's reagent: Stryker's reagent (137.0 mg, 0.070 mmol) was transferred into an oven-dried 5 mL round-bottomed flask in a dry box. The flask was capped with a septum, then removed from the dry-box and cooled to -40°C. 3-Nonene-2,8-dione (21.8 mg, 0.141 mmol), dissolved in 4.5 mL anhydrous and degassed PhMe was added to Stryker's reagent via cannula. The progress of the reaction was followed by TLC. After 1 hour, the reaction was complete as judged by TLC. The reaction was quenched by adding 1 mL of sat. NH_4Cl aqueous solution, and the mixture was stirred for 2 hours, open to air. The resultant mixture was filtered through a silica gel pad and the pad was washed with EtOAc (30 mL). The filtrate was separated, and the aqueous layer was extracted with EtOAc (10 mL x 2). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography of the crude product (10-25% EtOAc in hexane) gave ***(1S*, 2R*)*-1-(2-hydroxy-2-methylcyclohexyl)ethanone** as a colourless oil (17.4 mg, 80%). R_f (50% EtOAc in hexane): 0.86; IR (CCl_4 solution): 3501, 2930, 2865, 1701, 1261, 1179, 1113, 909 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.94 (1H, d, *J*= 2.3Hz), 2.46 (1H, dd, *J*= 10.8, 5.1 Hz), 2.21 (3H, s), 1.65-1.82 (5H, m), 1.48 (1H, dm, *J*= 11.0 Hz), 1.25 (1H, m), 1.18 (1H, m), 1.18 (3H, s) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 216.06, 69.64, 57.32, 38.61, 31.04, 29.68, 29.33, 25.64, 25.40, 21.18 ppm; HRMS (EI): Calculated for $C_9H_{16}O_2$ [M^+]: 156.1150. Found: 156.1146.

Structure determination: Long range ω-coupling of hydroxylic protons are rare because they are typically rapidly exchanging. Hydroxylic protons couple only when they are hydrogen-bonded and are held in place more rigidly than typical hydroxylic protons. Hydrogen bonding between the C=O and OH groups is evidenced by the lowered carbonyl stretching frequency (1701cm^{-1}). The ^1H-^1H cosy correlation (δ_H 3.94 ↔1.18) showed a long range ω-coupling between the hydrogen-bonded hydroxylic proton of the tertiary alcohol and the proton of the adjacent carbon (δ_C 38.6 ppm, δ_H 1.18). This can be possible only if the hydroxyl group is in an axial position. The proton α to the acetyl group (2.46 ppm) has a large coupling (*J*= 10.8 Hz) which is an axial-axial type coupling. This infers that it must be in an axial position. Thus the hydroxyl and the acetyl groups must be *syn*, as shown in the above structure.

Table 1, entry 2:



According to the general procedure for reductive cyclization, ***(2S*, 3S*)*-2-ethyl-3-hydroxy-3-methyl-cyclohexanone** was obtained (31.6 mg, 86% yield): colourless oil; R_f (25% EtOAc in hexane): 0.24; IR (CCl_4 solution): 3473, 2967, 2876, 1717, 1377, 1311, 1066, 995 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.38 (1H, m), 2.29 (1H, m), 2.23 (1H, m), 2.04 (1H, m), 1.87 (4H, m),), 1.68 (1H, br s), 1.60 (1H, m), 1.33 (3H, s), 0.91 (3H, t, *J*= 7.4Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.80, 76.62, 62.76, 40.47, 37.93, 28.62, 21.89, 16.77, 13.18 ppm; HRMS (EI): Calculated for $C_9H_{16}O_2$ [M^+]: 156.1150. Found: 156.1142.

Structure determination: Direct determination of the structure was not possible due to extensive overlapping of NMR signals. 2-Ethyl-3-hydroxy-3-methyl-cyclohexanone (26.6 mg) was reduced with $NaBH_4$ in MeOH. The major alcohol obtained upon workup was the axial alcohol (18.1 mg), and the minor was the equatorial alcohol (6.8 mg). The equatorial alcohol was easily identified by the large axial-axial coupling constant of the -C<u>H</u>OH (δ_H 3.64 ppm, *J*= 10.6, 10.6, 4.4 Hz). The presence of two large axial-axial couplings at δ_H 3.64 ppm infers that -C<u>H</u>Et (δ_H 1.00 ppm) must also be axial. The noe correlations (δ_H 1.33 ↔1.00; 1.33 ↔1.38) show that the Me group must be equatorial. Thus the overall structure of the equatorial alcohol is as shown below, which infers that the original ketone had stereochemistry as shown.

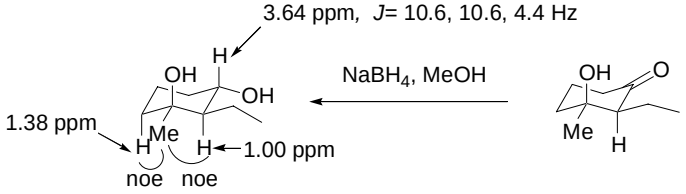
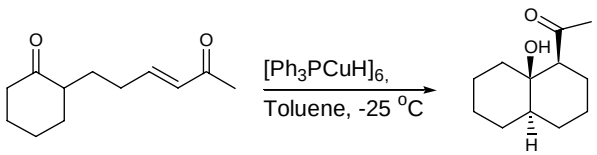


Table 1, entry 3:

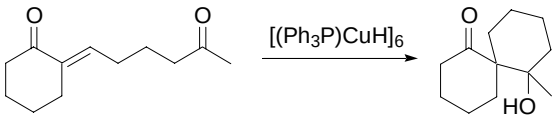


According to the general procedure for reductive cyclization, **(1*S**,4a*R**,8a*R**)-1-(8a-hydroxydecahydro-naphthalen-1-yl)ethanone** was obtained (23.6 mg, 72% yield): colourless oil, R_f (25% EtOAc in hexane): 0.70; IR (CCl_4 solution): 3506, 2933, 2857, 1698, 1447, 1401, 1367, 1355, 1315, 1274, 1221, 1193, 1176,

1143, 1056, 973 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.47 (1H, d, *J*=1.3 Hz), 2.43 (1H, dd, *J*= 12.4, 3.7 Hz), 2.19 (3H, s), 1.81-1.63 (6H, m), 1.55-1.41 (3H, m), 1.33 (1H, dt, *J*=13.10, 3.9 Hz), 1.26 (3H, m), 1.18 (1H, ddd, *J*= 16.3, 16.3, 3.8 Hz), 1.09 (1H, ttd, *J*=12.2, 3.5, 1.2 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 216.39, 71.02, 58.43, 44.42, 37.43, 31.58, 28.10, 27.95, 26.21, 25.74, 25.61, 21.44 ppm; HRMS (EI): Calculated for $C_{12}H_{20}O_2$ [M^+]: 196.1463. Found: 196.1463.

Structure determination: The ^1H-^1H cosy correlation (δ_H 3.47↔1.09) shows a long range ω-coupling between the hydroxylic and the ring junction protons, ie a *trans*-decalin junction. (Long range ω-coupling of hydroxylic protons are rare because they are typically rapidly exchanging. Hydroxylic protons couple only when they are hydrogen-bonded and are held in place more rigidly than typical hydroxylic protons). The lowered carbonyl stretching frequency (1698 cm^{-1}) under high dilution indicated that there is intramolecular hydrogen bonding, which, in a *trans*-decalin framework, was possible only if the hydroxyl group and the acetyl groups were *syn*. This is confirmed by the noe correlation (δ_H 1.09 ↔2.43) of the axial proton at the ring junction with the axial proton α to the acetyl group, which would be impossible if the structure were a *cis*-decalin.

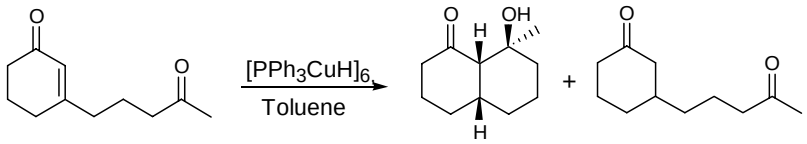
Table 1, entry 4:



According to the general procedure for reductive cyclization, **7-hydroxy-7-methylspiro[5.5]undecan-1-one** was obtained (18.1 mg, 89% yield) as a single diastereomer: pale yellow oil; R_f (25% EtOAc in hexane): 0.65; IR (CCl_4 solution): 3510, 2942, 2866, 1689, 1459, 1324, 1289, 1188, 1131, 1033, 959 cm^{-1}; ^1H NMR (500 MHz, tol-d_8, 80 C) δ 4.14 (1H, br), 2.18 (1H, m), 2.00 (1H, dm, *J*= 14.5 Hz), 1.92 (1H, ddd, *J*= 13.3, 9.6, 4.1 Hz), 1.74 (3H, m), 1.60 (2H, m), 1.44 (1H, m), 1.35 (5H, m), 1.25 (2H, m), 1.15 (3H, s) ppm; ^{13}C NMR (125MHz, tol-d_8, 80 C) δ 218.11, 73.23, 56.05, 39.71, 36.84, 31.42, 29.98, 26.80, 25.30, 22.43, 21.24, 20.75 ppm; HRMS (EI): Calculated for $C_{12}H_{20}O_2$ [M^+]: 196.1463. Found: 196.1468. The NMR spectra at room temperature had very broad and ill-defined peaks; this suggests that there exists more than one stable conformer. When the NMR was obtained at 80°C, the collection of data for a ^1H spectrum was successful to

give more defined signals, but upon prolonged heating to obtain the 2-D spectra, the sample decomposed to give a 1:1 mixture of the original compound plus a new compound. Thus it was not possible to determine the structure of this single diastereomer.

Table 1, entry 5:

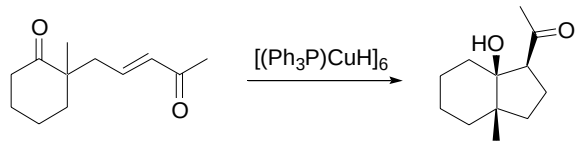


According to the general procedure for reductive cyclization, **(4a*R**, 8*S**, 8a*S**)-8-hydroxy-8-methyl-octahydronaphthalen-1-one** (11.0 mg, 19% yield), **3-(4-oxopentyl)cyclohexanone** (2.9 mg, 5%), and recovered starting material (40.4 mg, 69%) were obtained. **(4a*R**, 8*S**, 8a*S**)-8-hydroxy-8-methyl-octahydronaphthalen-1-one:** white solid; R_f (25% EtOAc in hexane): 0.30; IR (CCl_4 solution): 3617, 2931, 2856, 1742, 1714, 1446, 1372, 1309, 1240, 1134, 1078, 1043, 928 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.71 (1H, dm, *J*= 9.5 Hz), 2.61 (1H, br d, *J*= 4.3 Hz), 2.27 (2H, m), 1.97-1.80 (4H, m), 1.76-1.54 (4H, m), 1.35 (3H, s), 1.20-1.10 (2H, m) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.99, 70.66, 60.56, 43.92, 37.77, 34.06, 31.06, 29.27, 26.44, 24.36, 21.48 ppm; HRMS (EI): Calculated for $C_{11}H_{18}O_2$ [M^+]: 182.1307. Found: 182.1307.

Structure determination: The 2,6-DNP derivative of (4a*R**, 8*S**, 8a*S**)-8-hydroxy-8-methyloctahydro-naphthalen-1-one was synthesized and its crystal structure was obtained.

3-(4-oxopentyl)cyclohexanone: R_f (25% EtOAc in hexane): 0.23; IR (CCl_4 solution): 2957, 2931, 1718, 1360, 1100, 803 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.42 (2H, dd, *J*=7.2 Hz), 2.26 (2H, m), 2.13 (3H, s), 1.96 (3H, m), 1.67 (5H, m), 1.31 (3H, m) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.76, 208.67, 48.05, 43.53, 41.47, 38.91, 35.92, 31.06, 29.95, 25.19, 20.81 ppm; HRMS (EI): Calculated for $C_{11}H_{18}O_2$ [M^+]: 182.1307. Found: 182.1300.

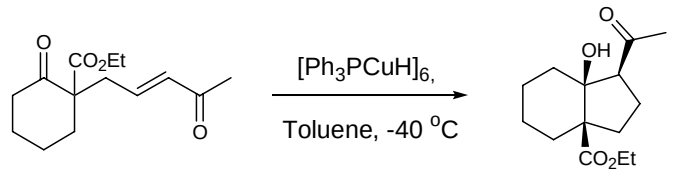
Table 1, entry 6:



According to the general procedure for reductive cyclization, **(*1S**,3a*S**,7a*S**)-1-(7a-hydroxy-3a-methyl-octahydroinden-1-yl)ethanone** (20.3 mg, 66% yield) was obtained: colourless oil; R_f (25 % EtOAc in hexane): 0.51; IR (CCl_4 solution): 3503, 2935, 2863, 1699, 1361, 1174, 988 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.69 (1H, s), 3.34 (1H, t, J =10.2Hz), 2.17 (3H, s), 2.03 (1H, m), 1.90 (1H, m), 1.83 (2H, m), 1.65 (1H, m), 1.52-1.36 (4H, m), 1.35-1.28 (3H, m), 0.99 (3H,s) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 213.79, 82.08, 54.11, 45.81, 37.86, 36.68, 31.98, 31.33, 24.06, 23.79, 21.82, 18.35 ppm; HRMS (EI): Calculated for $C_{12}H_{20}O_2$ [M^+]: 196.1463. Found: 196.1425.

Structure determination: The noe correlation (δ_H 3.69↔0.99) shows the hydroxyl group and the angular methyl group are *syn*, ie. that the ring junction must be *cis*. Furthermore, at least four noe correlations of the proton α to the acetal group are possible only for the diastereomer in which the hydroxyl and the acetyl groups are *cis*. Therefore, the structure of the product is as shown above.

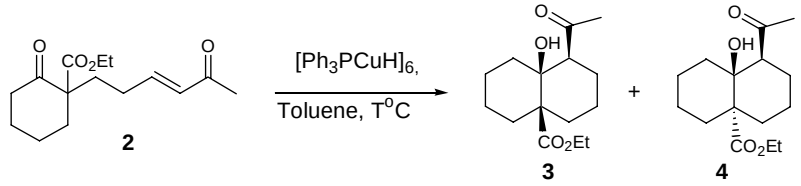
Table 1, entry 7:



According to the general procedure for reductive cyclization, **(*1S**,3a*R**,7a*S**)-1-acetyl-7a-hydroxy-octahydro-indene-3a-carboxylic acid ethyl ester** (27.8 mg, 86% yield) was obtained: pale yellow oil; R_f (10% EtOAc in hexane): 0.40; IR (CCl_4 solution): 3519, 2937, 2861, 1709, 1450, 1369, 1322, 1293, 1230, 1160, 1098, 1027 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.17 (2H, q, *J*= 7.1 Hz), 4.04 (1H, br), 3.13 (1H, m), 2.34 (2H, m), 2.22 (3H, s), 1.66 (10H, m), 1.27 (3H, t, *J*= 7.1 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.62, 176.31, 82.70, 60.68, 56.86, 55.33, 33.38, 33.29, 33.25, 31.06, 23.43, 22.56, 22.46, 14.15 ppm; HRMS (EI): Calculated for $C_{14}H_{22}O_4$ [M^+]: 254.1518. Found: 254.1519.

Structure determination: The structure of the product was unambiguously determined by x-ray crystallography of its 2,4-DNP-derivative.

Table 1, entry 8 and Scheme 2:



According to the general procedure for reductive cyclization, reaction of **1** with substrate **2** –25°C gave the product **3** (36.8 mg, 79%) and **4** (1.5 mg, 3.2%). Reaction of substrate **2** with **1** at –10°C gave products **3** (7.8 mg, 12%) and **4** (38.2 mg, 58%). Reaction of substrate **2** with Stryker's reagent with **1** at –40°C for gave **3** (21.8 mg, 93%) as the only product. **3**: pale yellow oil; R_f (10% EtOAc in hexane): 0.20; IR (CCl_4 solution): 3486, 2942, 2872, 1699, 1456, 1393, 1234, 1197, 1179, 1165, 1135 cm^{-1}; The nmr spectra of this isomer had some very broad peaks, which sharpened when the spectra were obtained at elevated temperatures: ^{1}H NMR (500 MHz, PhMe-d_8, 75°C): δ 4.71 (1H, d, *J*= 1.4 Hz), 3.93(2H, qd, *J*= 7.1, 2.3Hz), 2.72 (1H, ddd, *J*= 10.4, 3.3, 1.8 Hz), 2.12 (3H, s), 2.09 (2H, m), 1.74 (3H, m), 1.62 (2H, m), 1.52-1.36 (4H, m), 1.33-1.16 (3H, m), 0.99 (3H, td, *J*=7.1, 2.3Hz) ppm; ^{13}C NMR (125 MHz, PhMe-d_8, 75°C): δ 209.52, 178.38, 73.09, 60.77, 60.68, 58.82, 54.59, 52.02, 36.32, 32.12, 30.68, 28.96, 24.99, 23.62, 23.47, 20.81, 14.04 ppm; HRMS (CI+): Calculated for $C_{15}H_{25}O_4$ [M^+]: 268.1675. Found: 268.1671.

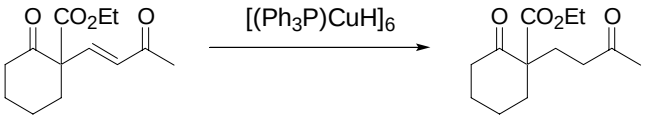
Structure determination: The structure of **3** was unambiguously determined by x-ray crystallography of its 2,4-DNP derivative.

4: a pale yellow oil; R_f (10% EtOAc in hexane): 0.40; IR (CCl_4 solution): 3479, 2933, 2860, 1721, 1695, 1452, 1222, 1148, 1122, 1028 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.13 (2H, q, *J*=7.1 Hz), 3.86 (1H, br), 3.57 (1H, dd, *J*=12.5, 3.9 Hz), 2.19 (3H, s), 1.77 (14H, m), 1.25 (3H, t, *J*=7.1 Hz) ppm ; ^{13}C NMR (75 MHz, $CDCl_3$): δ 217.37, 175.61, 72.22, 60.03, 52.36, 52.10, 32.23, 32.01, 31.12, 31.06, 25.63, 22.91, 22.28, 21.03, 14.18 ppm; HRMS (CI+): Calculated for $C_{15}H_{25}O_4$ [M^+]: 268.1675. Found: 268.1595.

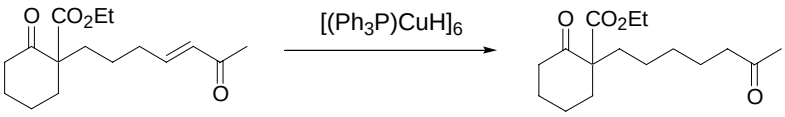
Structure determination: The two distinct C=O stretches in the IR spectrum strongly suggests that the hydroxyl group is not hydrogen-bonding with the ester, thus giving rise to a free ester C=O stretch at 1712 cm^{-1} and a hydrogen-bonded ketone C=O stretch at 1695 cm^{-1}. The proton α to the acetyl group (δ_H 3.57)

has a 12.5 Hz coupling, indicating that it is axial. The only possibility for all of these structural features to be present is if the diastereomer has structure **4** as shown.

Scheme 1.

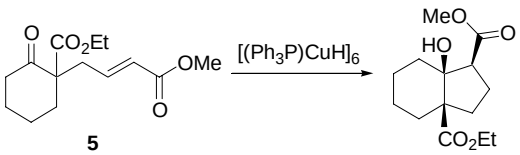


According to the general procedure for reductive cyclization, **2-oxo-1-(3-oxo-butyl)-cyclohexanecarboxylic acid ethyl ester** (21.09 mg, 61% yield) was obtained as a colourless oil: R_f (25 % EtOAc in hexane): 0.40; IR (CCl_4 solution): 2936, 2867, 1718, 1708, 1452, 1355, 1165 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.36 (4H, m), 2.14 (3H, s), 2.01 (1H, m), 1.90-1.76 (5H, m), 1.73-1.60 (2H, m), 1.05 (3H, s) ppm ; ^{13}C NMR (75 MHz, $CDCl_3$): δ 215.51, 208.34, 47.70, 39.43, 38.69, 38.31, 30.98, 29.92, 27.31, 22.50, 20.88 ppm; HRMS (EI): Calculated for $C_{11}H_{18}O_2$ [M^+]: 182.1307. Found: 182.1302.



According to the general procedure for reductive cyclization, **2-oxo-1-(6-oxoheptyl)cyclohexanecarboxylic acid ethyl ester** (30.2 mg, 80% yield) was obtained: colourless oil; R_f (20% EtOAc in hexane): 0.33; IR (CCl_4 solution): 2941, 2866, 1717, 1365, 1160, 1024, 908 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.20 (2H, q, *J*= 7.2Hz), 2.50 (1H, m), 2.42 (4H, m), 2.13 (3H, s), 1.99 (1H, m), 1.82 (2H, m), 1.74-1.41 (7H, m), 1.35-1.19 (3H, m), 1.26 (3H, t, *J*= 7.2Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.06, 208.04, 172.01, 61.05, 60.74, 43.51, 41.06, 36.05, 34.42, 29.81, 29.40, 27.56, 23.92, 23.44, 22.51, 14.10 ppm; HRMS (EI): Calculated for $C_{16}H_{26}O_4$[M^+] 282.1831. Found: 282.1841.

Table 2, entry 1



5 **9**

According to the general procedure for reductive cyclization, substrate **5** (29.8 mg, 0.111 mmol) was treated with Stryker's reagent (178.0 mg, 0.0908 mmol) to give hydroxydiester **9** (22.0 mg, 74% yield).

According to the general procedure for reductive cyclization, substrate **5** (28.5 mg, 0.106 mmol) was treated with Stryker's reagent (70.0 mg, 0.0357 mmol) to give hydroxydiester **9** (23.8 mg, 84% yield).

9: pale yellow oil; R_f (25% EtOAc in hexane): 0.58; IR (CCl_4 solution): 3520, 2949, 2864, 1745, 1716, 1709, 1435, 1230, 1173, 1099 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.18 (2H, pseudo q AB of ABX_3, J= 7.1Hz), 3.97 (1H, br), 3.73 (3H, s), 3.14 (1H, dd, J=10.4, 7.3 Hz), 2.44 (1H, dddd, J= 19.0, 7.6, 7.6, 3.0 Hz), 2.357 (1H, ddd, J= 12.0, 11.6, 7.3 Hz), 2.26 (1H, dm, J= 14.5 Hz), 2.04 (1H, dm, J=14.0 Hz), 1.92(1H, dddd, J= 16.8, 13.4, 9.7, 7.4 Hz), 1.79 (1H, m), 1.76 (1H, m), 1.65 (1H, ddd, J= 12.0, 8.9, 2.4 Hz), 1.58 (1H, dm, J= 12.7 Hz), 1.44 (1H, tt, J= 13.1, 3.6 Hz), 1.36 (1H, td, J= 3.8, 3.4 Hz), 1.26 (3H, t, J= 6.9Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.38, 173.05, 82.64, 60.68, 56.89, 51.76, 47.92, 33.48, 33.39, 32.67, 23.53, 22.65, 22.36, 14.14 ppm; HRMS (EI): Calculated for $C_{14}H_{22}O_5[M^+]$ 270.1467. Found: 270.1469.

Structure determination: The proton α to the carbomethoxy group had noe correlations (δ_H 3.14↔1.44; 3.14↔1.36) with axial protons in the six-membered ring. This interspatial interaction is not possible for isomers with a *trans*-junction, or for the isomer with the *cis*-junction in which the carbomethoxy group is *trans* with respect to the hydroxyl group. Hence, the structure of **9** is assigned as the all *cis*-isomer by the process of elimination.

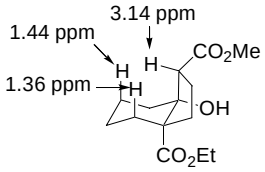
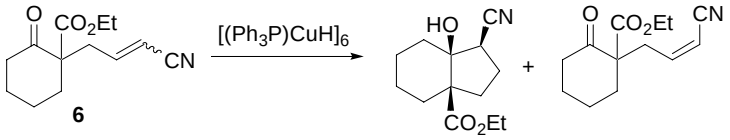


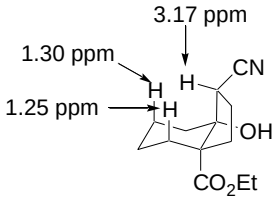
Table 2, entry 2:



According to the general procedure for reductive cyclization, **1-cyano-7a-hydroxyoctahydroindene-3a-carboxylic acid ethyl ester** (15.5 mg, 66%) and **1-(3-cyano-allyl)-2-oxocyclohexanecarboxylic acid ethyl ester** (2.7 mg, 11%) were obtained. ***(1R*, 3aR*, 7aS*)*-1-cyano-7a-hydroxyoctahydroindene-3a-**

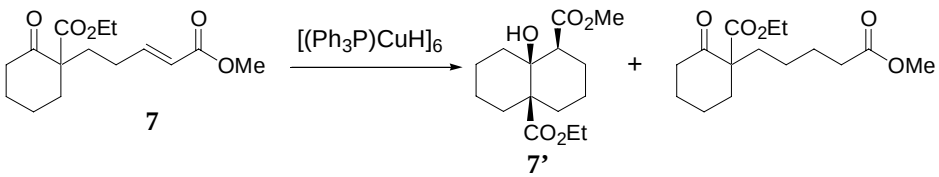
carboxylic acid ethyl ester: a colourless oil; R_f (30% EtOAc in hexane): 0.64; IR (CCl_4 solution): 3536, 2943, 2866, 2246, 1714, 1653, 1451, 1325, 1232, 1160, 1023 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.20 (1H, pseudo q AB of ABX_3, *J*= 7.1 Hz), 4.04 (1H, d, *J*= 2.1 Hz), 3.17 (1H, ddd, *J*= 9.6, 9.5, 2.0Hz), 2.37 (1H, ddd, *J*= 12.8, 11.4, 6.6 Hz), 2.26 (1H, m), 2.23 (1H, m), 2.10 (2H, m), 1.89 (1H, ddd, *J*= 13.2, 13.2, 4.8 Hz), 1.79 (1H, dm, *J*= 13.8 Hz), 1.72 (1H, ddd, *J*= 13.3, 9.0, 4.6 Hz), 1.60 (2H, m), 1.31-1.17 (3H, m), 1.28 (3H, t, *J*= 7.1Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.85, 119.63, 81.39, 61.16, 55.44, 35.42, 34.05, 33.35, 32.36, 24.76, 23.37, 22.41, 14.10 ppm; HRMS (EI): Calculated for $C_{13}H_{19}O_3N$ [M^+] 237.1365. Found: 237.1366.

Structure determination: The proton α to the nitrile group had noe correlations (δ_H 3.17↔1.30, 3.17↔1.25) with axial protons in the six membered ring. The only diastereomer that has a conformation that permits these transannular through space interaction is when all of the substituents are *cis.*



1-(3-cyano-allyl)-2-oxocyclohexanecarboxylic acid ethyl ester: a colourless oil; R_f (30% EtOAc in hexane): 0.70; IR (CCl_4 solution): 2981, 2941, 2687, 2241, 2223, 1718, 1231, 1192, 1022 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.54 (1H, ddd, *J*= 11.0, 8.4, 7.1Hz), 5.39 (1H, dt, *J*= 10.9, 1.3Hz), 4.23 (2H, q, *J*= 7.1Hz), 2.87 (1H, ddd, *J*= 14.6, 7.0, 1.4Hz), 2.75(1H, ddd, *J*= 14.6, 8.5, 1.1Hz), 2.54 (1H, m), 2.50 (2H, m), 2.05 (1H, m), 1.79 (1H, m), 1.62 (2H, m), 1.52 (1H, m), 1.29 (3H, t, *J*= 7.1Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.77, 170.84, 150.02, 115.53, 101.95, 61.84, 60.52, 40.82, 36.81, 36.24, 27.32, 22.38, 14.05 ppm; HRMS (EI): Calculated for $C_{13}H_{17}O_3N$: 235.1208 [M^+]. Found: 235.1205.

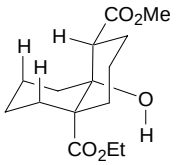
Table 2, entry 3:



7 **7'**

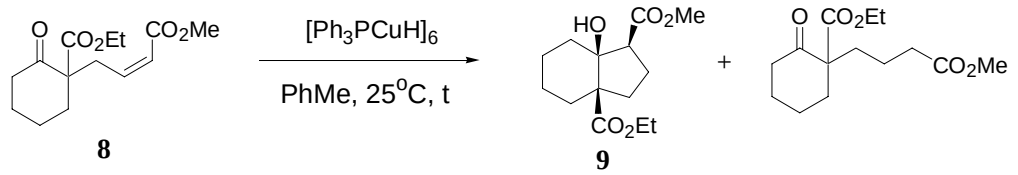
According to the general procedure for reductive cyclization, **7'** (53% yield) and reduced **7** (35% yield) were obtained as an inseparable mixture. To obtain a sample of the analytically pure **7'**, the crude material was treated with sodium borohydride in methanol to give pure **7'** as a white solid upon flash chromatography. **7':** white solid, mp: 61-62°C; R_f: (25% EtOAc in hexane): 0.59; IR (CCl_4 solution): 3506, 2949, 2871, 1747, 1724, 1705, 1457, 1234, 1200, 1143, 1025 cm^{-1}; ^1H NMR (500MHz, PhMe-d_8, 80°C) δ 4.44 (1H, br s), 3.96 (2H, q, *J*= 7.1 Hz), 3.45 (3H, m), 2.76 (1H, dd, *J*= 11.5, 2.7 Hz), 2.24 (1H, dddd, *J*= 12.9, 12.9, 12.9, 3.6 Hz), 2.15 (1H, m), 1.83-2.00 (2H, m), 1.78 (1H, dm, *J*= 13.9 Hz), 1.33-1.67 (8H, m), 1.31 (1H, m), 1.01 (3H, t, *J*= 7.1 Hz); ^{13}C NMR (125MHz, PhMe-d_8, 80°C) δ 177.43, 173.56, 73.05, 60.48, 51.86, 50.73, 46.61, 36.07, 31.62, 30.97, 24.99, 23.58, 23.26, 20.53, 14.09 ppm; HRMS(EI): Calculated for $C_{15}H_{24}O_5[M^+]$ 284.1624. Found:284.1611.

Structure determination: Both the ^1H and ^{13}C NMR spectra at room temperature showed broad signals, which are strongly suggestive of the *cis* decalin system that can exist as two low energy conformers. The NMR spectra obtained at 80°C showed the proton α to the carbomethoxy group (δ_H 2.76) to be an axial proton having a large J value (*J*= 11.5 Hz) typical of an axial-axial coupling. This proton also has a cosy correlation (δ_H $2.76 \leftrightarrow 4.44$) which is a long range ω-coupling with the hydroxyl proton. This is possible only when the carbomethoxy and hydroxylic groups are *cis*. Furthermore, this proton has noe correlations with at least four other protons, which is only possible by through-space interactions with the transannular axial protons in a structure as shown below. Thus the stereochemistry of **7'** is as shown.



1-(4-Methoxycarbonylbutyl)-2-oxocyclohexanecarboxylic acid ethyl ester: R_f: (25% EtOAc in hexane): 0.59; IR (CCl_4 solution): 2959, 2929, 2873, 1741, 1715, 1463, 1367, 1203, 1171, 1086, 1029, 803cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ 4.20 (2H, q, *J*= 7.2Hz), 3.66 (3H, s), 2.45 (3H, m), 2.31 (2H, t, *J*= 7.4Hz), 2.00 (1H, m), 1.86 (1H, m), 1.70-1.56 (6H, m), 1.40 (1H, m), 1.30-1.18 (2H, m), 1.26 (3H, t, *J*=7.1Hz); ^{13}C NMR (75MHz, $CDCl_3$) δ 207.95, 173.95, 171.93, 61.12, 60.68, 51.42, 41.05, 36.00, 34.23, 33.72, 27.55, 25.19, 23.75, 22.51, 14.09 ppm; HRMS(EI): Calculated for $C_{15}H_{24}O_5[M^+]$ 284.1624. Found: 284.1619.

Table 2, entry 4



8 **9**

According to the general procedure for reductive cyclization, recovered **8** (4.1 mg, 24%), **9** (7.9 mg, 41%) and reduction product (0.4 mg, 4%) were obtained. **1-(3-Methoxycarbonyl-propyl)-2-oxocyclohexanecarboxylic acid ethyl ester**: a colourless oil; R_f (20% EtOAc in hexane): 0.43; IR (CCl_4 solution): 2945, 2867, 1741, 1716, 1437, 1173, 1111, 1025, 809 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.22 (2H, q, *J*= 7.0Hz), 3.66 (3H, s), 2.52 (1H, dm, *J*= 13.4Hz), 2.44 (2H, t, *J*= 5.2Hz), 2.31 (2H, t, *J*= 6.8Hz), 2.01 (1H, m), 1.86 (2H, m), 1.68 (3H, m), 1.57 (3H, m), 1.27 (3H, t, *J*= 7.1Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.78, 173.60, 171.77, 61.24, 60.64, 51.48, 41.02, 35.88, 34.17, 33.99, 27.53, 22.49, 19.78, 14.10 ppm; HRMS (EI): Calculated for $C_{14}H_{22}O_5[M^+]$ 270.1467. Found: 270.1441.