Samarium diiodide coupling of enones – a remarkable cascade sequence.

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Electronic supplementary information

CONTENTS

Scheme indicating proofs of stereochemistry for 15 – 20	S2
SmI ₂ mediated cyclodimerisation of enones in THF/MeOH:	
Preparation of tetracycle 13	S3
Preparation of diols 15 and 16	S4
Preparation of diols 17 and 18	S7
Conversion of diol 17 to the <i>p</i> -nitrobenzoyl ester 21	S8
Preparation of diols 19 and 20	S10
Oxidation of diols 19 and 20 to hydroxy ketone 22	S12

Proofs of stereochemistry for **15** – **20**

SCHEME 1 Proof of stereochemistry for **15** - **20**

The stereochemistry of the various diols **15** – **20** was established as outline in Scheme 1. Thus **15** and **16** were established by x-ray crystallography. **17** was converted to the corresponding p -nitrobenzoate **21** and its structure was established by x-ray crystallography. The structure of **18** is assumed by analogy to **15** and **16**. The structure of **20** was established by x-ray crystallography and the structure of **19** was established since both **19** and **20** were converted to a common ketone **22**. Full experimental details are provided in the following pages.

(1R, 5R, 6S, 9R, 10R)-13-(allyloxy)-5,9,10-trimethyl-3-oxatetracyclo[8.2.1.0^{2,6}.0^{2,9}]tridecane-1,6-diol 13

2-(Allyloxy)-3-methylcyclopent-2-en-1-one (100 mg, 0.658 mmol) as a solution in THF (5 ml) was added to a solution of SmI₂ (2.7 mmol) in THF (30 ml) and MeOH (7.5 ml) at -78°C under Ar over 45 min. The reaction mixture was then allowed to warm to 0°C over 2 hrs before the addition of brine (3 ml) and citric acid (128 mg, 0.61 mmol). The aqueous layer was extracted with CH₂Cl₂ (5 x 10 ml), and the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. The crude reaction mixture was purified by flash column chromatography eluting with petrol and gradually increasing the polarity to EtOAc to give diol **13** (67 mg, 0.218 mmol, 67%) as a white solid,

R_f = 0.56 (30% EtOAc-petrol);

m.p.: 116-118°C (recrystallised from EtOAc-petrol);

ν_{max} (cm⁻¹): 3350, 3050, 2950, 2870, 1640;

δ_H (400 MHz, CDCl₃) (assignments were confirmed by 2-D NMR experiments): 5.86 (1H, ddt, *J* = 17, 11, 5 Hz, C=CH), 5.24 (1H, dq, *J* = 17, 2 Hz, C=CH_AH_B), 5.10 (1H, dq, *J* = 10, 2 Hz, C=CH_AH_B), 4.14 (2H, dt, *J* = 5, 2 Hz, OCH₂), 3.89 (1H, dd, *J* = 9, 7 Hz, OCH_AH_BCHCH₃), 3.82 (1H, s, CHOCH₂), 3.11 (1H, dd, *J* = 11, 9 Hz, OCH_AH_BCHCH₃), 2.10 (1H, m, CHCH₃), 1.94 (1H, m, CH_CH_D), 1.83 (1H, dt, *J* = 7, 13 Hz, CH_EH_F), 1.60-1.27 (6H, m, CH_CH_D, CH_EH_F, (CH₂)₂), 0.87 (3H, d, *J* = 7 Hz, CH₃), 0.82 (3H, s, CH₃), 0.71 (3H, s, CH₃);

δ_C (100 MHz, CDCl₃): 135.9 (1), 116.6 (2), 94.2, 93.2, 87.2, 84.6 (1), 72.3 (2), 72.0 (2), 52.3, 47.0, 44.8 (1), 36.8 (2), 29.8 (2), 28.7 (2), 27.2 (2), 14.8 (3), 14.2 (3), 9.0 (3);

^{m/z} (CI⁺): 309 [M + H]⁺ (18%), 291 [M - OH]⁺ (62%), 233 [M - CH₂=CHCH₂O]⁺ (100%);

Microanalysis: Found C, 69.96; H, 9.38. C₁₈H₂₈O₄ requires C, 70.10; H, 9.15%;

Stereochemistry and structure was confirmed by X-ray crystallography (for details see original manuscript).

Tricyclo[6.3.1.0^{2,7}]dodecane-1,3-diols **15 and **16**.**

Cyclohexenone (100 mg, 1.042 mmol) as a solution in THF (5 ml) was added to a solution of SmI_2 (41 mmol) in THF (45 ml) and MeOH (11 ml) at 0°C under Ar over 45 min. The reaction mixture was stirred for 2 h at 0°C before the addition of brine (3 ml) and citric acid. The aqueous layer was then extracted with DCM (5 x 10 ml), and the combined organic extracts were dried over MgSO_4 and concentrated *in vacuo*. The crude reaction mixture was purified using flash column chromatography eluting with petrol and gradually increasing the polarity to EtOAc to give diol **15** (55 mg, 0.281 mmol, 54%) as a white solid and diol **16** (26 mg, 0.133 mmol, 25%) as a pale yellow solid.

Data for tricycle **15**:

R_f = 0.36 (30% EtOAc-petrol);

m.p.: 101-103°C (Recrystallised from EtOAc-petrol);

$\bar{\nu}_{\text{max}}$ (cm^{-1}): 3360, 2920, 2860, 1450;

$\bar{\nu}_H$ (400 MHz, CDCl_3): 4.10 (1H, br s), 2.70 (1H, s, OH), 2.66 (1H, s, OH), 2.13 (1H, m), 1.76-1.17 (15H, m), 1.12 (1H, d, J = 10 Hz);

$\bar{\nu}_C$ (100 MHz, CDCl_3): 81.5, 67.7 (1), 47.5 (1), 43.8 (2), 41.5 (1), 41.0 (2), 40.2 (1), 31.1 (2), 26.4 (2), 24.9 (2), 20.6 (2), 17.4 (2);

m/z (CI^+): 179 [$\text{M} - \text{OH}$] $^+$ (100%);

Microanalysis: Found C, 73.39; H, 10.39. $\text{C}_{12}\text{H}_{20}\text{O}_2$ requires C, 73.43; H, 10.27%.

Stereochemistry and structure was confirmed by X-ray crystallography:

Thermal ellipsoid plot of **15**

Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 234234, data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223-336033 or e-mail: deposit@ccdc.cam.ac.uk]. Crystal data for **15**: C₁₂H₂₀O₂, Mr = 196.28, T = 293(2) K, monoclinic, space group *P*2₁/*c*, *a* = 12.081(2), *b* = 8.9358(18), *c* = 11.019(2) Å, β = 113.24(3), *V* = 1093.0(4) Å³, ρ_{calc} = 1.193 g cm⁻³, μ = 0.079 mm⁻¹, *Z* = 4, reflections collected: 8144, independent reflections: 2485 (*R*_{int} = 0.0778), final *R* indices [*I* > 2σ(*I*): *R*1 = 0.0525, *wR*2 = 0.1076, *R* indices (all data): *R*1 = 0.1316. *wR*2 = 0.1325

Data for tricycle **16**:

*R*_f = 0.19 (30% EtOAc-petrol);

m.p.: 110-112°C (Recrystallised from EtOAc-petrol);

ν_{max} (cm⁻¹): 3345, 2945, 2870, 1465, 1355, 1135;

δ_{H} (400 MHz, CDCl₃): 3.98 (1H, dt, *J* = 5, 12 Hz), 3.50 (1H, s, OH), 2.45 (1H, s, OH), 1.96-1.15 (17H, m);

δ_{C} (100 MHz, CDCl₃): 81.7, 67.3 (1), 51.7 (1), 42.5 (1), 42.1 (2), 41.9 (2), 40.7 (1), 30.8 (2), 27.8 (2), 25.0 (2), 20.3 (2), 19.6 (2);

m/z (CI⁺): 197 [M + H]⁺ (48%), 179 [M - OH]⁺ (100%);

Microanalysis: Found C, 73.11; H, 10.39. C₁₂H₂₀O₂ requires C, 73.43; H, 10.27%;

Stereochemistry and structure was confirmed by X-ray crystallography:

One of the two chemical identical, crystallographically independent molecules of **16**

Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 234235, data can be obtained, free of charge, on application to CCDC, 12 Union Road,

Cambridge CB2 1EZ, UK [fax: +44 (0) 1223-336033 or e-mail: deposit@ccdc.cam.ac.uk]. Crystal data for **16**: C₁₂H₂₀O₂, Mr = 196.28, T = 120(2) K, monoclinic, space group *Cc*, *a* = 22.1999(19), *b* = 5.9517(6), *c* = 16.3776(19) Å, β = 93.251(5), *V* = 2160.4(4) Å³, ρ_{calc} = 1.207 g cm⁻³, μ = 0.080 mm⁻¹, *Z* = 8, reflections collected: 12121, independent reflections: 4680 (*R*_{int} = 0.0668), final *R* indices [*I* > 2σ(*I*): *R*1 = 0.0641, *wR*2 = 0.1539, *R* indices (all data): *R*1 = 0.0863. *wR*2 = 0.1683

Tricyclo[5.2.1.0^{2,6}]decane-1,3-diols **17** and **18**

Cyclopentenone (100 mg, 1.218 mmol) as a solution in THF (5 ml) was added to a solution of SmI₂ (4.9 mmol) in THF (53 ml) and MeOH (13 ml) at -78°C under Ar over 45 min. The reaction mixture was stirred for 2 h at 0°C before the addition of brine (3 ml) and citric acid. The aqueous layer was then extracted with DCM (5 x 10 ml), and the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. The crude reaction mixture was purified by flash column chromatography eluting with petrol and gradually increasing the polarity to EtOAc to give diol **17** (46 mg, 0.273 mmol, 45%) and diol **18** (36 mg, 0.214 mmol, 35%), both as colourless oils.

Data for tricycle **17**:

R_f = 0.25 (30% EtOAc-petrol);

ν_{max} (cm⁻¹): 3330, 2945, 2865, 1460, 1305, 1110;

δ_H (400 MHz, CDCl₃): 4.50 (1H, t, *J* = 5 Hz, CHOH), 3.32 (1H, s, OH), 2.62 (1H, s, OH), 2.01 – 1.16 (13H, m);

δ_C (100 MHz, CDCl₃): 84.7, 76.3 (1), 52.5 (1), 50.1 (1), 39.9 (2), 36.7 (1), 36.5 (2), 36.0 (2), 29.6 (2), 29.4 (2);

m/z (CI+ at T = 150K): 169 [M + H]⁺ (2%);

HRMS [M - OH]⁺ C₁₀H₁₅O required 151.1122 found 151.1123.

Data for tricycle **18**:

R_f = 0.21 (30% EtOAc-petrol);

ν_{max} (cm⁻¹): 3340, 2945, 2870, 1460, 1310, 1125;

δ_H (400 MHz, CDCl₃): 4.35 (1H, dt, *J* = 2, 9 Hz, CHOH), 3.05 (1H, s, OH), 2.88 (1H, s, OH), 2.13 – 1.18 (13H, m);

δ_C (100 MHz, CDCl₃): 84.0 (1), 80.2, 52.5 (1), 49.9 (1), 39.4 (2), 37.3 (1), 36.8 (2), 34.5 (2), 29.7 (2), 29.5 (2);

m/z (CI+ at T = 150K): 169 [M + H]⁺ (3%);

HRMS [M + H]⁺ C₁₀H₁₇O₂ required 169.1228 found 169.1225.

Conversion of diol **17** to the *p*-nitrobenzoyl ester **21**

p-Nitrobenzoyl chloride (175 mg, 0.94 mmol) was added to a solution of diol **17** (59 mg, 0.31 mmol) in DCM (2 mL) and TEA (0.14 mL, 1.0 mmol) at 0 ° and the reaction mixture was stirred for 3 h. Water (30 mL) was added to the reaction mixture and the aqueous layer was extracted with DCM (2 x 20 mL). The combined organic layers were washed with 2M H₂SO₄ (2 x 30 mL) aq. NaHCO₃ (2 x 30 mL) and brine (30 mL), then dried over MgSO₄, filtered and concentrated *in vacuo*. The crude reaction mixture was purified using flash column chromatography (silica, gradient elution, 4-18% ethyl acetate in petrol), to yield ester **21** (58 mg, 0.14 mmol, 45%) as a white solid,

R_f = 0.41 (40% ethyl acetate in petrol)

m.p.: 116-117 °C (recrystallised from CH₂Cl₂)

$\square_H$ (400 MHz, CDCl₃): 8.30 (2H, d, J = 9 Hz, ArH), 8.20 (2H, d, J = 9 Hz, ArH), 5.74 (1H, t, J = 6 Hz, CHOCO), 2.32-2.20 (2H, m), 2.07 (1H, br s, OH), 2.04-1.92 (4H, m), 1.86 (1H, tt, J = 5, 12 Hz), 1.74-1.61 (2H, m), 1.53-1.43 (2H, m), 1.36 (2H, dq, 9, 1.5 Hz).

Stereochemistry and structure was confirmed by X-ray crystallography:

Fig 1. One of the two chemical identical, crystallographically independent molecules of **21**

Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 234233, data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

Crystal data for **21**: C₁₇H₁₉NO₅, Mr = 317.33, T = 120(2) K, monoclinic, space group *P*2₁/*c*, *a* = 7.6129(5), *b* = 18.6167(15), *c* = 21.6505(16) Å, β = 93.835(4), *V* = 3061.6(4) Å³, ρ_{calc} = 1.377 g cm⁻³, μ = 0.102 mm⁻¹, Z = 8, reflections collected: 9852, independent reflections: 5295 (*R*_{int} = 0.0962), final *R* indices [*I* > 2σ(*I*): *R*1 = 0.1343, *wR*2 = 0.3323, *R* indices (all data): *R*1 = 0.2361. *wR*2 = 0.3783

2-(1-hydroxyethyl)-1,3,3,4,4-pentamethyl-1-cyclopentanol **19** and **20**

Dimethyl vinyl ketone (mesityl oxide) (100 mg, 1.020 mmol) as a solution in THF (5 ml) was added to a solution of SmI_2 (4.1 mmol) in THF (46 ml) and MeOH (11.5 ml) at 0°C under Ar over 45 min. The reaction mixture was stirred for 2 h at 0°C before the addition of brine (3 ml) and citric acid. The aqueous layer was then extracted with DCM (5 x 10 ml), and the combined organic extracts were dried over MgSO_4 and concentrated *in vacuo*. The crude reaction mixture was purified using flash column chromatography eluting with petrol and gradually increasing the polarity to EtOAc to give diol **19** (46mg, 0.230 mmol, 45%) as a colourless oil and diol **20** (44mg, 0.220 mmol, 43%) as a white solid

Data for diol **19**:

R_f = 0.25 (30% EtOAc-petrol);

$\bar{\nu}_{\text{max}}$ (cm^{-1}): 3335, 2965, 2865, 1370, 1160;

δ_{H} (400 MHz, CDCl_3): 4.26 (1H, dq, J = 5, 7 Hz), 2.52 (2H, br s, OH), 1.91 (1H, d, J = 14 Hz), 1.66 (1H, d, J = 14 Hz), 1.52 (1H, d, J = 5 Hz), 1.32 (3H, s), 1.31 (3H, d, J = 7 Hz), 1.08 (3H, s), 0.93 (3H, s), 0.79 (3H, s), 0.78 (3H, s);

δ_{C} (100 MHz, CDCl_3): 79.5, 68.0 (1), 61.0 (1), 58.1 (2), 46.6, 42.4, 32.4 (3), 25.8 (3), 25.0 (3), 23.7 (3), 23.2 (3), 21.1 (3);

m/z (CI^+ at $T = 150\text{K}$): 183 $[\text{M} - \text{OH}]^+$ (45%);

HRMS $[\text{M} + \text{H}]^+$ $\text{C}_{12}\text{H}_{25}\text{O}_2$ required 201.1855 found 201.1843.

Data for diol **20**:

R_f = 0.29 (30% EtOAc-petrol);

$\bar{\nu}_{\text{max}}$ (cm^{-1}): 3315, 2700, 2945, 2875, 1365, 1170;

δ_{H} (400 MHz, CDCl_3): 4.08 (1H, dq, J = 9, 6 Hz), 2.24 (2H, br s, OH), 2.00 (1H, d, J = 13 Hz), 1.65 (1H, d, J = 13 Hz), 1.65 (1H, d, J = 9 Hz), 1.50 (3H, s), 1.34 (3H, d, J = 6 Hz), 0.92 (3H, s), 0.90 (3H, s), 0.87 (3H, s), 0.86 (3H, s);

δ_{C} (100 MHz, CDCl_3): 79.4, 68.1 (1), 62.9 (1), 56.8 (2), 45.2, 42.8, 34.9 (3), 25.7 (3), 24.3 (3), 23.8 (3), 23.4 (3), 20.0 (3);

m/z (CI^+ at $T = 150\text{K}$): 183 $[\text{M} - \text{OH}]^+$ (10%);

HRMS $[\text{M} + \text{H}]^+$ $\text{C}_{12}\text{H}_{25}\text{O}_2$ required 201.1855 found 201.1859.

Stereochemistry and structure was confirmed by X-ray crystallography:

One of the two chemical identical, crystallographically independent molecules of **20**.

Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 234236

, data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223-336033 or e-mail:

deposit@ccdc.cam.ac.uk]. Crystal data for **20**: C₁₂H₂₄O₂, Mr = 200.31, T = 120(2) K, monoclinic, space group *P*2₁/*c*, *a* = 10.8507(2), *b* = 14.8374(3), *c* = 14.9670(3) Å, β = 91.428(1), *V* = 2408.88(8) Å³, ρ_{calc} = 1.105 g cm⁻³, μ = 0.072 mm⁻¹, *Z* = 8, reflections collected: 19885, independent reflections: 5503 (*R*_{int} = 0.0457), final *R* indices [*I* > 2σ(*I*): *R*1 = 0.0459, *wR*2 = 0.1068, *R* indices (all data): *R*1 = 0.0584. *wR*2 = 0.1135

Oxidation of diols **19** and **20** to hydroxy ketone **22**

Following the method of Swern,¹² oxalyl chloride (0.30 mL, 4.5 mmol) in CH₂Cl₂ (2.5 mL) was cooled to -78 °C and stirred vigorously. DMSO (0.48 mL, 9.0 mmol) in CH₂Cl₂ (1 mL) and the reaction mixture was stirred for 2 min. Diol **19** or **20** (78 mg, 0.39 mmol) in CH₂Cl₂ (1 mL) was added over 5 min and the reaction was stirred for 45 min. TEA (2.5 mL, 18 mmol) was added and the reaction was stirred for a further 3 h. Water (20 mL) was added to the reaction mixture, and the aqueous layer was extracted with CH₂Cl₂ (2 x 10 mL) and combined organic layers were washed with water (20 mL) and brine (20 mL), then dried over MgSO₄, filtered and concentrated *in vacuo*. The crude reaction mixture was purified using flash column chromatography (silica, gradient elution, 3% ethyl acetate in petrol), to yield ketone **22** (62 mg, 80% from **19**, 55 mg, 70% from **20**) as a pale yellow oil. The samples of **22** obtained from both diols **19** and **20** were identical by ¹H and ¹³C NMR.

R_f = 0.45 (30% ethyl acetate in petrol)

ν_{max} (cm⁻¹): 3430 (br s), 1679 (s).

ν_H (300 MHz, CDCl₃): 2.88 (1H, s), 2.24 (3H, s), 2.03 (1H, d, *J* = 14 Hz), 1.67 (1H, d, *J* = 14 Hz), 1.31 (3H, s), 1.07 (3H, s), 1.02 (3H, s), 0.95 (3H, s), 0.93 (3H, s)

ν_C ppm (75.5 MHz, CDCl₃): 215.4, 78.1, 67.3 (1), 57.0 (2), 48.0, 43.3, 34.0 (3), 32.2 (3), 27.1 (3), 24.4 (3), 23.6 (3), 21.6 (3).

LRMS: *m/z* (CI+ at T = 150K): 181 ([M-OH]⁺, 100%)