Supporting Information for:

Asymmetric Total Synthesis of (+)- and (–)-Clusianone and (+)- and (–)-Clusianone Methyl Enol Ether via ACC Alkylation and Evaluation of their Anti-HIV Activity

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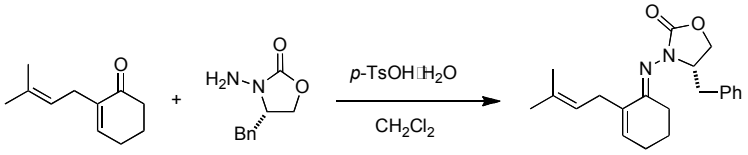
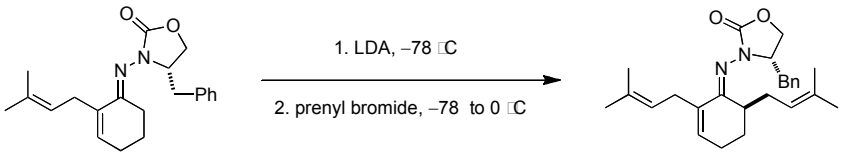
Experimental

General Considerations: Unless stated to the contrary, where applicable, the following conditions apply: Reactions were carried out using dried solvents (see below) and under a slight static pressure of Ar (pre-purified quality) that had been passed through a column (5 x 20 cm) of Drierite. Glassware was dried in an oven at 120 °C for at least 12 h prior to use and then either cooled in a desiccator cabinet over Drierite or assembled quickly while hot, sealed with rubber septa, and allowed to cool under a stream of Ar. Reactions were stirred magnetically using Teflon-coated magnetic stirring bars. Teflon-coated magnetic stirring bars and syringe needles were dried in an oven at 120 °C for at least 12 h prior to use then cooled in a desiccator cabinet over Drierite. Hamilton microsyringes were dried in an oven at 60 °C for at least 24 h prior to use and cooled in the same manner. Commercially available Norm-Ject disposable syringes were used. Dry benzene, toluene, Et_2O, CH_2Cl_2, THF, MeCN, and DME were obtained using an Innovative Technologies solvent purification system. All other dry solvents were of anhydrous quality purchased from Sigma-Aldrich. Commercial grade solvents were used for routine purposes without further purification. Et_3N, pyridine, *i*-Pr_2NEt, 2,6-lutidine, *i*-Pr_2NH, and TMEDA were distilled from CaH_2 under a N_2 atmosphere prior to use. Flash column chromatography was performed on silica gel 60 (32-63μ). ^1H and ^{13}C NMR spectra were recorded on a Varian spectrometer (400 MHz and 100 MHz, respectively) at ambient temperature. All ^1H chemical shifts are reported in ppm (δ) relative to TMS (0.00); ^{13}C shifts are reported in ppm (δ) relative to $CDCl_3$ (77.16). Diastereomer ratios were determined either by ^1H NMR or HPLC analysis of the crude materials. Chiral HPLC was performed on a 4.6 mm x 250 mm Chiralpak AD-H column, using UV detection.

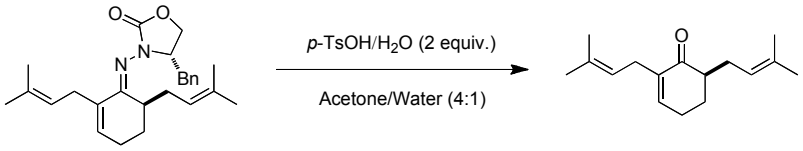


(S,E)-4-benzyl-3-(2-(3-methylbut-2-enyl)cyclohex-2-enylideneamino)oxazolidin-2-one (16). Auxiliary **9** (745 mg, 3.88 mmol) was added to a stirred solution of ketone **15** (763.8 mg, 4.65 mmol) in CH_2Cl_2 (25 mL) (Ar atmosphere). *p*-TsOH·H_2O (147.6 mg, 0.78 mmol) was then added and the stirring was continued at reflux for 10 h and then cooled to rt. Saturated aqueous $NaHCO_3$ (10 mL) was added and the solution was extracted with Et_2O (2 x 50 mL). The combined organic extracts were washed with brine (5 mL), dried over $MgSO_4$, and concentrated *in vacuo* to give a yellow residue. Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave **16** as a clear, colorless oil (1.1 g, 85%). **^1H NMR** ($CDCl_3$, 500 MHz): δ 7.32–7.13 (m, 5 H), 6.24 (apparent t, *J* = 4.0 Hz 1 H), 5.23–5.19 (m, 1 H), 4.38 (apparent dq, *J* = 4.0, 8.5 Hz, 1 H), 4.30 (apparent t, *J* = 8.0 Hz, 1 H), 4.07 (apparent t, *J* = 8.5 Hz, 1 H), 3.13 (dd, *J* = 4.0, 14 Hz, 1 H), 3.00 (dABq, Δν = 32.8 Hz, *J* = 7.0, 16.0, 20.5 Hz, 2 H), 2.83 (dd, *J* = 8.5, 14.0 Hz, 1 H), 2.64 (apparent ddd, *J* = 4.5, 6.5, 16.5 Hz, 1 H), 2.55 (apparent ddd, *J* = 5.0, 10.5, 16.5 Hz, 1 H), 2.31–2.20 (m, 2 H), 1.86–1.79 (m, 1 H), 1.73 (s, 3 H), 1.72–1.65 (m, 1 H), 1.65 (s, 3 H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 170.3, 154.2,

137.2, 135.9, 135.8, 132.8, 129.5, 128.8, 127.2, 122.4, 66.4, 61.1, 38.1, 29.8, 28.3, 26.0, 25.7, 22.2, 17.9; **ESI-MS** *m/z* $[M + Na]^+$ calcd for $C_{21}H_{26}N_2O_2$: 361.4 found: 361.1.



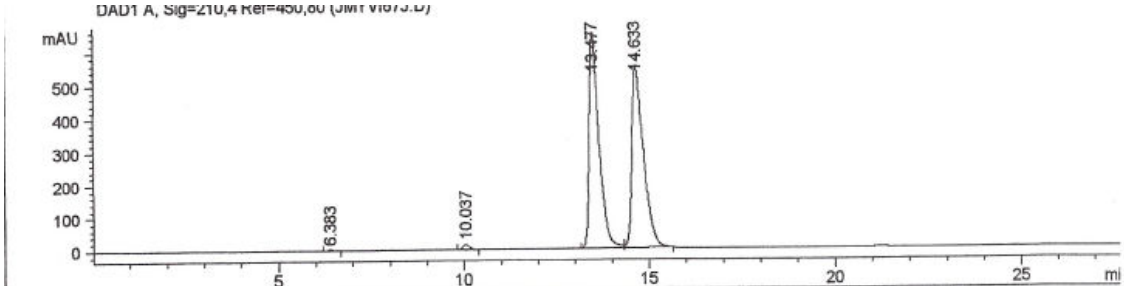
(S)-4-benzyl-3-((E)-((R)-2,6-bis(3-methylbut-2-enyl)cyclohex-2-enylidene)amino)oxazolidin-2-one (17). *n*-BuLi (2.44 M in hexanes, 2.0 mL, 4.9 mmol) was added dropwise over ca. 2 min to a stirred and cooled (–78 °C) solution of *i*-Pr_2NEt (0.73 mL, 5.2 mmol) in THF (20 mL) (Ar atmosphere). The solution was then transferred to an ice–H_2O bath and was stirred for 30 min. This mixture was cooled to –78 °C and a solution of hydrazone **16** (1.10 g, 3.25 mmol) in THF (15 mL) was added dropwise via canula over ca. 3 min. Stirring was continued for 1 h and prenyl bromide (0.563 mL, 4.9 mmol) was added dropwise over ca. 2 min. Stirring was continued for 1 h, and the reaction flask was transferred to an ice–H_2O bath and mixture was stirred for an additional 2.5 h. H_2O (20 mL) was added, the solution was allowed to warm to rt, and it was then extracted with Et_2O (2 x 100 mL). The organic extracts were combined, washed with brine (10 mL), dried over $MgSO_4$, and concentrated *in vacuo* to give a residue. Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave **17** as a light-yellow oil (1.32 g, 90%). **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.34–7.17 (m, 5 H), 6.12 (bs, 1 H), 5.21–5.09 (m, 2 H), 4.44–4.36 (m, 1 H), 4.25 (apparent t, *J* = 8.0 Hz, 1 H), 4.03 (dd, *J* = 9.2, 11.2 Hz, 1 Hz), 3.16 (dd, *J* = 4.0, 13.6 Hz, 1 H), 3.11–2.91 (m, including a dABq, *J* = 6.8, 15.6, 42.0 Hz, Δν = 3.56 Hz, 3 H), 2.59 (dd, *J* = 10.0, 13.2, 1 H), 2.35–1.95 (m, 5 H), 1.87–1.82 (m, 1 H), 1.72 (s, 3 H), 1.70 (s, 3 H), 1.67 (s, 3 H), 1.62 (s, 3 H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 173.9, 155.3, 136.0, 135.6, 134.6, 133.1, 132.6, 129.0, 128.8, 127.2, 122.5, 122.3, 67.8, 61.9, 39.9, 36.3, 30.1, 28.8, 26.0, 25.9, 24.6, 22.1, 17.91, 17.89; **ESI-MS** *m/z* $[M + Na]^+$ calcd for $C_{26}H_{34}N_2O_2$: 429.5, found: 429.2.



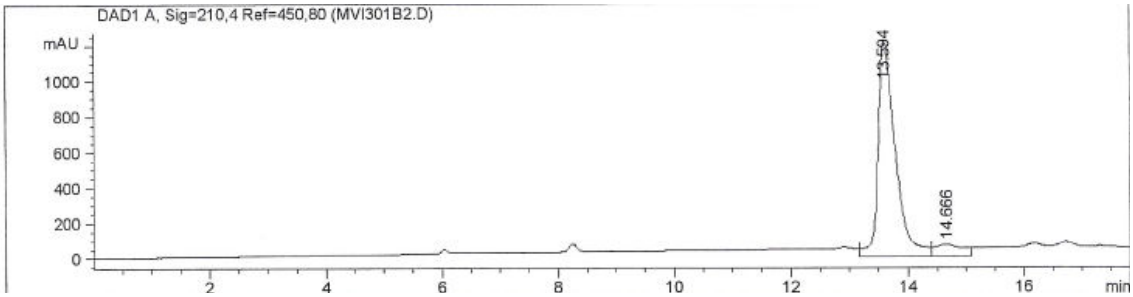
(*R*)-2,6-bis(3-methylbut-2-enyl)cyclohex-2-enone (14). *p*-TsOH•H_2O (424.7 mg, 2.23 mmol) was added to a stirred solution of hydrazone **17** (453.9 mg, 1.11 mmol) in acetone-H_2O (4:1, v/v) (open to air). Stirring was continued for 40 h, saturated aqueous $NaHCO_3$ (3 mL) was added, the mixture was extracted with Et_2O (2 x 20 mL), and the organic extracts were combined, washed with brine (3 mL), dried over $MgSO_4$, and concentrated *in vacuo* to give an oil. Flash chromatography over silica gel using 5:95 EtOAc-hexanes gave **14** as a clear, colorless oil (206.6 mg, 80%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 6.62–6.60 (m, 1 H), 5.14–5.09 (m, 2 H), 2.87 (bd, *J* = 7.2 Hz, 2 H), 2.56–2.50 (m, 1 H), 2.37–2.25 (m, 3 H), 2.12–2.10 (m, 2 H), 1.72 (s, 3 H), 1.71 (s, 3 H), 1.69–1.64 (m, 1 H), 1.61 (s, 6 H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 201.5, 144.0, 138.4, 133.5, 133.3, 122.2,

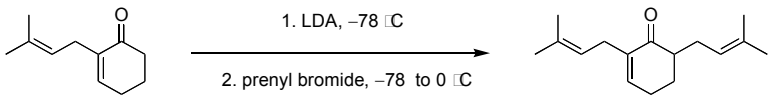
121.5, 47.4, 28.1, 28.0, 27.9, 26.0, 25.9, 25.4, 18.0, 17.8; **ESI-MS** *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{24}O$: 255.2, found: 255.1; **HPLC** (Daicel Chiralpak AD-H, hexane-*i*-PrOH = 97.3/0.3, flow rate 0.5 mL/min, λ = 210 nm): t_R 13.5 min (major enantiomer), 14.6 min (minor enantiomer). major:minor = 98.5:1.5.

HPLC Trace of racemate (see below for synthesis):

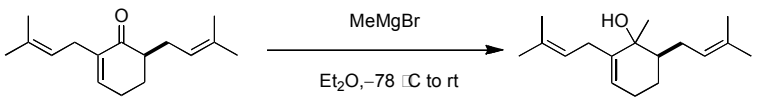


HPLC trace of chiral material:

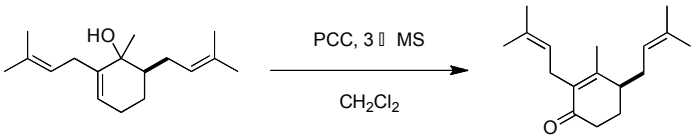




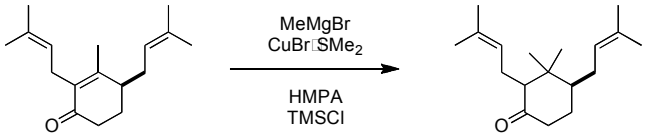
(*R*)-4-benzyl-3-((*E*)-((*S*)-2,6-bis(3-methylbut-2-enyl)cyclohex-2-enylidene)amino)oxazolidin-2-one (±-14). *n*-BuLi (2.5 M in hexanes, 7.3 mL, 18.15 mmol) was added dropwise over ca. 2 min to a stirred and cooled solution (–78 °C) of *i*-Pr_2NEt (2.7 mL, 19.4 mmol) in THF (30 mL) (Ar atmosphere). The solution was then transferred to an ice–H_2O bath and was stirred for 30 min. This mixture was re-cooled to –78 °C and a solution of ketone **15** (2.0 g, 12.1 mmol) in THF (30 mL) was added dropwise via canula over ca. 3 minutes. Stirring was continued for 1 h and the mixture was transferred to an ice–H_2O bath and stirred for an additional 15 min. The solution was cooled to –78 °C and then prenyl bromide (2.2 mL, 19.4 mmol) was added dropwise over ca. 2 min. The mixture was stirred for 1 h, and then allowed to warm to rt over 9 h. The mixture was partitioned between H_2O (30 mL) and Et_2O (200 mL), and the aqueous phase was extracted with Et_2O (200 mL). The organic extracts were combined, washed with brine (15 mL), dried with $MgSO_4$, and concentrated *in vacuo* to give a residue. Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave **±-14** as a colorless oil (1.52 g, 54%). The spectral data are consistent with that obtained above for the enantiomerically enriched material.



(6R)-1-methyl-2,6-bis(3-methylbut-2-enyl)cyclohex-2-enol (18). MeMgBr (3.0 M in Et_2O, 2.6 mL, 7.5 mmol) was added dropwise over ca. 3 min to a stirred and cooled (–78 °C) solution of ketone **14** (584 mg, 2.5 mmol) in Et_2O (13 mL) (Ar atmosphere). Stirring was continued for 20 min, the cooling bath was removed, and the mixture was stirred for an additional 10 h. The mixture was then cooled in an ice–H_2O bath and saturated aqueous NH_4Cl (5 mL) was added dropwise over ca. 5 min (vigorous bubbling). The resulting mixture was extracted with Et_2O (2 x 75 mL), and the combined organic extracts were washed with brine (5 mL), dried with $MgSO_4$, and concentrated *in vacuo* to give a light-yellow oil. Flash chromatography over silica gel using 5:95 EtOAc-hexanes gave **18** as a colorless oil (485.0 mg, 88% yield). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 5.46–5.37 (m, including two bs, 1 H), 5.21–5.16 (m, 2 H), 2.91–2.69 (m, 2 H), 2.37–2.30 (m, 1 H), 2.09–1.81 (m, 5 H), 1.73 (s, 3 H), 1.71 (s, 3 H), 1.63 (s, 3 H), 1.49–1.42 (m, 2 H), 1.34 (s, 3 H), 1.20 (s, 3 H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 142.5, 141.2, 132.7, 132.6, 132.5, 132.4, 124.5, 124.3, 124.0, 123.8, 123.6, 123.2, 74.7, 72.8, 47.6, 45.9, 30.2, 29.0, 28.4, 27.8, 26.0, 25.9, 25.8, 25.4, 25.3, 24.8, 23.9, 21.8, 18.04, 18.00, 17.81, 17.76; **ESI-MS** *m/z* $[M + Na]^+$ calcd for $C_{17}H_{26}O$: 271.2, found: 271.1.

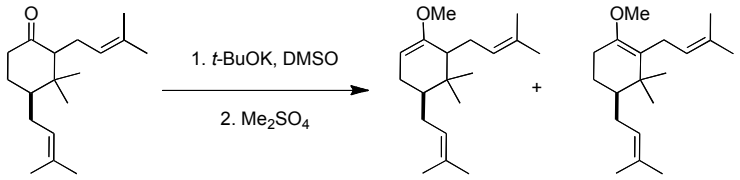


(*R*)-3-methyl-2,4-bis(3-methylbut-2-enyl)cyclohex-2-enone (13). Crushed 3 Å molecular sieves (3.12 g) were added to a solution of alcohol **18** (600 mg, 2.4 mmol) in CH_2Cl_2 (24 mL), followed by PCC (1.56 g, 7.2 mmol) (Ar atmosphere). The mixture was stirred for 1 h, filtered through celite with additional CH_2Cl_2 (10 mL) as a rinse, and concentrated to approximately half volume. The resulting solution was loaded directly onto a silica gel column and eluted with 5:95 EtOAc-hexanes to give **13** as a clear colorless oil (397.5 mg, 67%). The spectral data are consistent with reported values.[1]

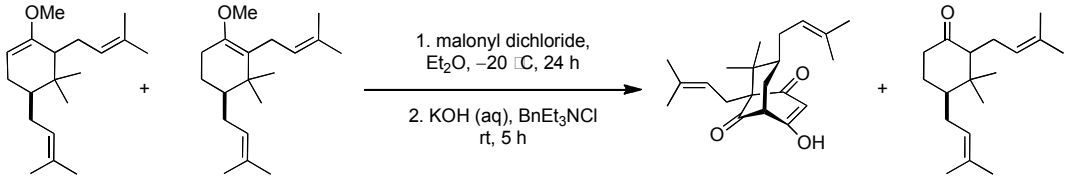


(4*R*)-3,3-dimethyl-2,4-bis(3-methylbut-2-enyl)cyclohexanone (19). MeMgBr (3.0 M in Et_2O, 1.81 mL, 5.43 mmol) was added to a stirred and cooled (–78 °C) suspension of CuBr•SMe_2 (63.7 mg, 0.31 mmol) in THF (20 mL) followed by the addition of HMPA (1.1 mL, 6.2 mmol) (Ar atmosphere). Stirring was continued at –78 °C for 10 min, and then a

solution of ketone **13** (382.6 mg, 1.55 mmol) and TMSCl (0.78 mL, 6.2 mmol) in THF (10 mL) was added dropwise by syringe over ca. 3 min. Additional THF (2 x 2 mL) was used as a rinse. The mixture was warmed to –40 °C over 4 h, carefully quenched with 10% aqueous HCl (10 mL) over ca. 5 min, allowed to warm to rt, and extracted with Et_2O (2 x 75 mL). The organic extracts were washed with brine (10 mL), dried with $MgSO_4$, and concentrated *in vacuo* to give a yellow residue. Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave **19** as a colorless oil (357.7 mg, 88%). The spectral data are consistent with reported values.[1]

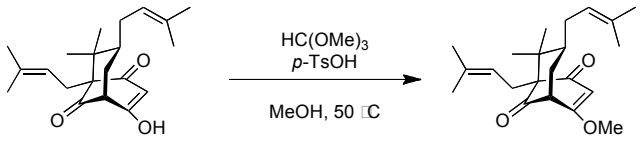


(*R*)-1-methoxy-3,3-dimethyl-2,4-bis(3-methylbut-2-enyl)cyclohex-1-ene and (4*S*)-1-methoxy-5,5-dimethyl-4,6-bis(3-methylbut-2-enyl)cyclohex-1-ene (12 and 20). *t*-BuOK (229.6 mg, 2.05 mmol) was added to a solution of ketone **19** (357.7 mg, 1.36 mmol) in DMSO (3.5 mL) (Ar atmosphere). Stirring was continued for 1 h and then Me_2SO_4 (0.194 mL, 2.05 mmol) was added dropwise over ca. 1 min. Stirring was continuted for 15 min, petroleum ether (20 mL) was added, and stiriing was continued for an additional 5 min. The biphasic solution was then transferred to a separatory funel and the DMSO layer was extracted with petroleum ether (2 x 15 mL) and then 90:10 petroleum ether-Et_2O mixture (20 mL). The combined organic extracts were washed with H_2O (10 mL) and brine (5 mL), dried with $MgSO_4$, and concentrated *in vacuo*. Flash chromatography over silica gel using 98:2 petroleum ether-Et_2O contianing 0.5% Et_3N by volume gave a mixute of **12** and **20** as a colorless residue (235.6 mg, 63%), and **19** as a colorless residue (80 mg). Yield based on recovered **19** was 81%. Spectral data are consistent with literature values.[1]

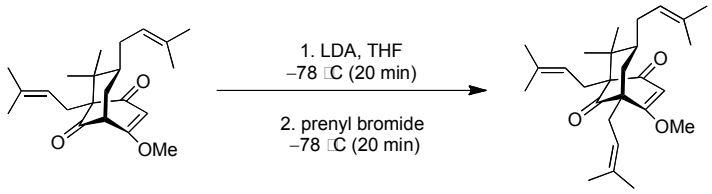


(1R,7S)-4-hydroxy-6,6-dimethyl-5,7-bis(3-methylbut-2-enyl)bicyclo[3.3.1]non-3-ene-2,9-dione (11). Malonyl dichloride (91.3 μL, 0.94 mmol) was added to a stirred and cooled (–20 °C) solution of methyl enol ethers **12** and **20** (235.6 mg, 0.85 mmol) in Et_2O (2 mL) (Ar atmosphere). Stirring was continued for 24 h and $BnEt_3NCl$ (9.7 mg, 0.04 mmol) was added, followed by a solution of KOH (191.4 mg, 3.4 mmol) in H_2O (0.3 mL). The cooling bath was removed and stirring was continued for 5 h. The solution was diluted with H_2O (10 mL) and petroleum ether (10 mL) and the pH was adjusted to 11 with 2 M NaOH. The resulting solution was extracted with petroleum ether (2 x 15 mL) and Et_2O (15 mL) and the combined organic extracts were dried with $MgSO_4$, and concentrated *in vacuo* to give a

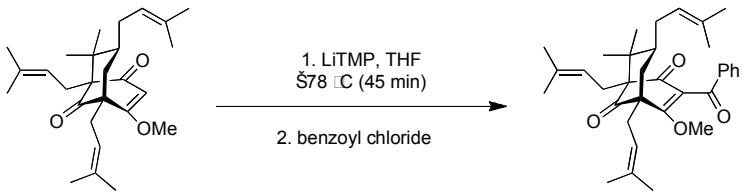
yellow residue. Flash chromatography over silica gel using 10:90 EtOAc–hexanes gave **19** (87.9 mg). The aqueous layer was cooled in an ice–H_2O bath and slowly acidified to approximately pH 2 with 10% aqueous HCl, and extracted with CH_2Cl_2 (2 x 20 mL). The organic extracts were combined, dried with $MgSO_4$ and concentrated *in vacuo* to give **11** as a yellow solid (99.7 mg, 35% or 56.4% based on recovered **19**). Spectral data are consistent with literature values.[1]



(1R,7S)-4-methoxy-6,6-dimethyl-5,7-bis(3-methylbut-2-enyl)bicyclo[3.3.1]non-3-ene-2,9-dione (21). Trimethylorthoformate (0.86 mL, 7.8 mmol) was added to a stirred solution of diketone **11** (99.7 mg, 0.3 mmol) in MeOH (3 mL) (Ar atmosphere). *p*-TsOH•H_2O (4.6 mg, 0.024 mmol) was added and the mixture was heated to 50 °C for 36 h. The mixture was then cooled, four drops of Et_3N were added, and the mixture was concentrated *in vacuo*. Flash chromatography over silica gel using 10:90 EtOAc-petroleum ether gave **21** as a white solid (62.3 mg, 60%). Spectral data are consistent with literature values.[1]

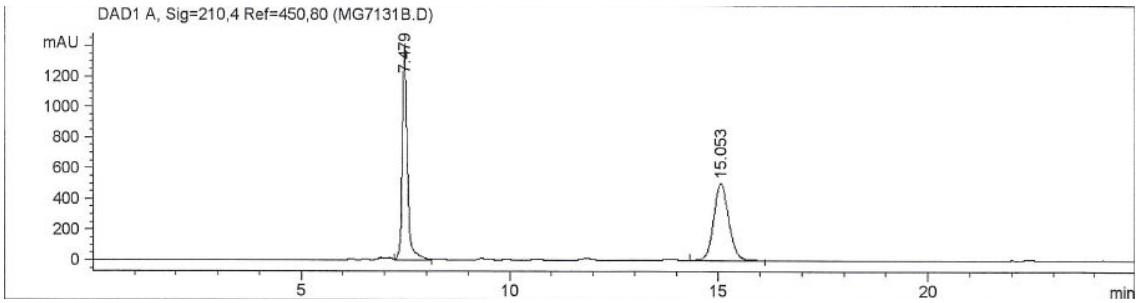


(1R,7S)-4-methoxy-6,6-dimethyl-1,5,7-tris(3-methylbut-2-enyl)bicyclo[3.3.1]non-3-ene-2,9-dione (22). *n*-BuLi (2.5 M in hexane, 0.6 mL, 1.5 mmol) was added dropwise over ca. 2 min to a stirred and cooled (–78 °C) solution of *i*-Pr_2NEt (0.231 mL, 1.65 mmol) in THF (3 mL) (Ar atmosphere). The solution was then transferred to an ice–H_2O bath and was stirred for 30 min. This solution was cooled to –78 °C and an aliquot of the LDA (0.904 mL, 0.452 mmol) was removed via syringe and added dropwise over ca. 2 min to a stirred and cooled (–78 °C) solution of ketone **21** (62.3 mg, 0.181 mmol) in THF (4 mL) (Ar atmosphere). Stirring was continued for 20 min and then the prenyl bromide (0.104 mL, 0.905 mmol) was added. The mixture was stirred for an additional 20 min, quenched with saturated aqueous NH_4Cl (8 mL), and allowed to warm to rt. The mixture was then extracted with Et_2O (2 x 50 mL), washed with brine (5 mL), dried with $MgSO_4$, and concentrated *in vacuo*. Flash chromatography over silica gel using 70:28:2 petroleum ether-CH_2Cl_2-EtOAc gave **22** as a colorless oil (67 mg, 90% yield). Spectral data are consistent with literature values.[1]

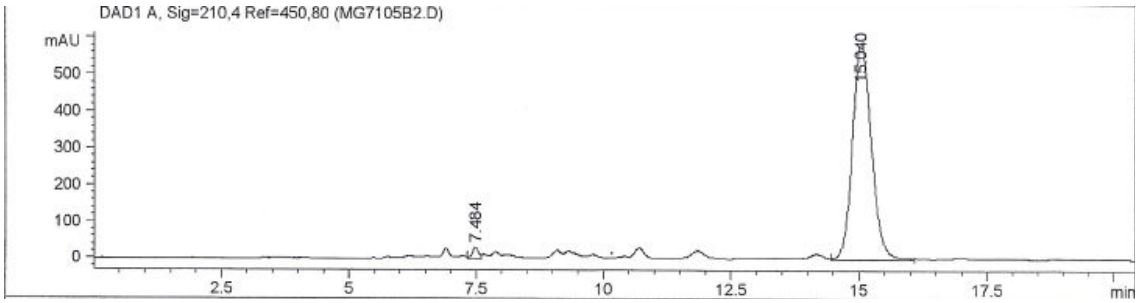


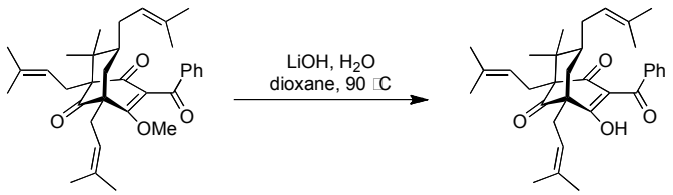
(1S,7S)-3-benzoyl-4-methoxy-6,6-dimethyl-1,5,7-tris(3-methylbut-2-enyl)bicyclo[3.3.1]non-3-ene-2,9-dione (4). *n*-BuLi (2.5 M in hexane, 0.6 mL, 1.5 mmol) was added dropwise over ca. 2 min to a stirred and cooled (–78 °C) solution of TMP (0.280 mL, 1.65 mmol) in THF (3 mL) (Ar atmosphere). The solution was then transferred to an ice–H_2O bath and stirred for 30 min. This solution was cooled to –78 °C and an aliquot of the LiTMP (0.65 mL, 0.32 mmol) was removed via syringe and added dropwise over ca. 2 min to a stirred and cooled (–78 °C) solution of ketone **22** (67 mg, 0.16 mmol) in THF (5 mL) (Ar atmosphere). Stirring was continued for 1 h at –78 °C and then benzoyl chloride (55.7 μL, 0.48 mmol) was added and stirring was continued for an additional 1 h. The mixture was quenched with saturated aqueous NH_4Cl (5 mL), allowed to warm to rt, and extracted with Et_2O (2 x 50 mL). The organic extracts were washed with brine (5 mL), dried with $MgSO_4$, and concentrated *in vacuo*. Flash chromatography over silica gel using 5:95 EtOAc-petroleum ether to 10:90 EtOAc-petroleum ether gave **4** as a white solid (52.3 mg, 62% yield). Spectral data are consistent with literature values.[1] **HPLC** (Daicel Chiralpak AD-H, hexane-*i*-PrOH = 90/10, flow rate 0.5 mL/min, λ = 210 nm): t_R 7.5 min (minor enantiomer), 15.1 min (major enantiomer). major:minor = 98.8:1.2.

HPLC trace of racemate:



HPLC trace of the optically active material:





(–)-Clusianone (2). 10% aqueous LiOH (2.3 mL) was added to a stirred solution of ketone **4** (52.3 mg, 0.101 mmol) in dioxane (2.3 mL). The mixture was heated in a 90 °C oil bath for 3 h, after which it was cooled in an ice–H_2O bath, acidified with 10% aqueous HCl over ca. 2 min, and extracted with Et_2O (2 x 50 mL). The organic extracts were combined, dried with $MgSO_4$, and concentrated *in vacuo* to give **2** as a yellow residue (40.4 mg, 79% yield). Spectral data are consistent with literature values.[1] $[\alpha]^{25}_D = –29.99°$ (*c* 0.673, $CHCl_3$).

References

[1] Rodeschini, V.; Ahmad, N. M.; Simpkins, N.S. *Org. Lett*. **2006**, *8*, 5283–5285.