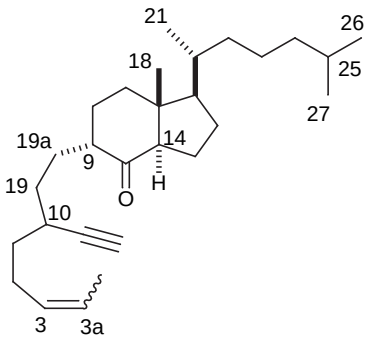
Access to [6.4.0]Carbocyclic Systems by Dienyne Tandem Metathesis. Preliminary Studies on the Synthesis of a PreD$_3$-D$_3$ Transition State Analogue†

Eva M. Codesido, Luis Castedo, Juan R. Granja*

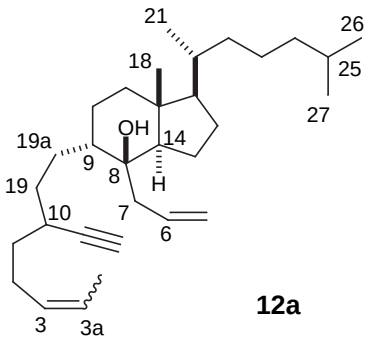
Departamento de Química Orgánica e Unidade Asociada ó C.S.I.C, Facultade de Química, Universidade de Santiago. 15706 Santiago de Compostela, SPAIN.

qojuangg@usc.es

SUPPORTING INFORMATION I

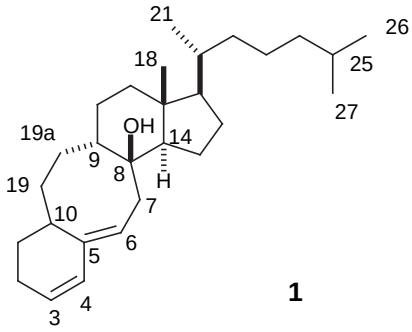


Representative enolate alkylation of 3b. To a solution of KHMDS (0.5 M in toluene, 4.6 ml, 2.3 mmol) in DMF (2 ml) cooled at –78 °C was slowly added a solution of ketone **3b** (305 mg, 1.15 mmol) in DMF (2 ml). The resulting mixture was stirred for 0.5 h, and a solution of iodide **17** (770 mg, 2,3 mmol) in DMF (0.5 ml) was added. After 1 h, a saturated solution of NH_4Cl was added and the aqueous layer was extracted with Et_2O. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting crude mixture was dissolved in THF (6 ml) and treated with TBAF (1 M in THF, 2.3 mL, 2.3 mmol). After stirring for 0.5 h at rt, a saturated solution of NH_4Cl was added and the resulting mixture was extracted with Et_2O. The combined organic extracts were dried, filtered and concentrated in vacuo to give a residue that was flash chromatographed (1 % EtOAc/hexanes) to afford 297 mg of the desired product (65 %, R_f = 0.6 (10 % EtOAc/hexanes), colorless oil). **^{1}H-NMR** ($CDCl_3$, 300 MHz, δ): 5.5-5.3 (2H, m, H-3 and H-3a), 2.58 (1H, dd, *J* = 11.1 Hz and 7.6 Hz, H-14), 2.50 (1H, brs, ≡CH), 1.63 (3H, m, Me-C=), 0.92 (3H, d, *J* = 6.1 Hz, Me-21), 0.85 (6H, 2d, *J* = 6.6 Hz, Me-26 and Me-27), 0.62 (3H, s, CH_3-18). **^{13}C-NMR** ($CDCl_3$, 75 MHz, δ): 215.1 (C), 129.6 (CH), 124.6 (CH), 87.1 (C), 69.8 (CH), 57.9 (CH), 56.7 (CH), 50.1 (C), 49.4 (CH), 39.3 (CH_2), 35.5 (CH), 35.4 (CH_2), 34.6 (CH_2), 32.6 (CH_2), 30.7 (CH), 30.4 (CH_2), 28.1 (CH_2), 28.0 (CH), 27.5 (CH_2), 24.5 (CH_2), 23.7 (CH_2), 22.7 (CH_3), 22.5 (CH_3), 18.9 (CH_2), 18.6 (CH_3), 16.8 (CH_3), 12.7 (CH_3). MS m/z 399 (MH^+, 100), 381 (MH^+-H_2O, 35), 279 (31). HRMS calcd for $C_{28}H_{47}O$ (MH^+) 399,3626, found 399.3610.



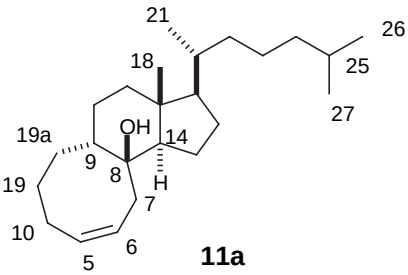
12a

Representative ketone allylation. Preparation of alcohol 12a. A solution of AllylMgBr (1 M in Et_2O, 0.6 ml, 0.6 mmol) was added dropwise to a solution of the previously prepared ketone (120 mg, 0.3 mmol) in THF (4 ml) at –78 °C. After 1 h, a saturated solution of NH_4Cl was added, and the resulting mixture was extracted with Et_2O. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude alcohol was purified by flash chromatography (2 % EtOAc/hexanes) to yield 108 mg of pure **12a** (82 %, R_f = 0.6 (10 % EtOAc/hexanes), colorless oil). **^{1}H-NMR** ($CDCl_3$, 300 MHz, δ): 5.96-5.8 (1H, m, H-6), 5.5-5.3 (2H, m, H-3 and H-3a), 5.1 (2H, m, =CH_2), 1.63 (3H, m, Me-C=), 0.93 (3H, s, Me-18), 0.86 (3H, d, *J* = 6.1 Hz, Me-21), 0.85 (6H, 2d, *J* = 6.6 Hz, Me-26 and Me-27). **^{13}C-NMR** ($CDCl_3$, 75 MHz, δ): 133.3 (CH), 129.7 (CH), 124.6 (CH), 119.2 (CH_2), 87.8 (C), 76.0 (C), 69.3 (C), 57.1 (CH), 51.5 (CH), 43.5 (CH_2), 43.4 (C), 42.2 (CH), 39.5 (CH_2), 35.8 (CH_2), 35.2 (CH), 34.8 (CH_2), 34.7 (CH_2), 33.3 (CH_2), 30.9 (CH), 28.0 (CH), 27.2 (CH_2), 24.9 (CH_2), 24.6 (CH_2), 23.8 (CH_2), 22.8 (CH_3), 22.5 (CH_3), 20.2 (CH_2), 20.0 (CH_2), 18.3 (CH_3), 13.4 (CH_3), 12.8 (CH_3). MS m/z 441 (MH^+, 29), 423 (MH^+-H_2O, 100), 399 (84), 381 (56).



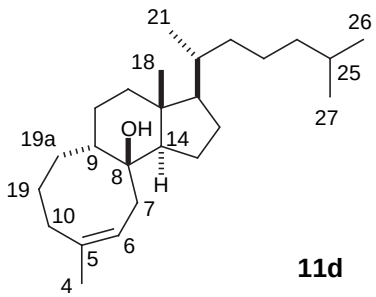
1

Representative procedure for catalytic RCM. Preparation of 1. Ruthenium catalyst **8a** (11 mg, 0.013 mmol) was added to a solution of dienyne **12a** (35 mg, 0.08 mmol) in CH_2Cl_2 (17 ml). The resulting light brown solution was placed in an oil bath at 45 °C. After 20 h, the starting material was completely disappeared on tlc. The solution was concentrated under reduced pressure and purified by flash chromatography (1 % EtOAc/hexanes). The two diastereomeric tetracycle compounds were isolated as colorless oils (13 mg and 2 mg, 48 %, R_f = 0.5 (10% EtOAc/hexanes) and R_f = 0.45 (10 % EtOAc/hexanes) respectively). **(major isomer)**: **^{1}H-NMR** ($CDCl_3$, 500 MHz, δ): 6.03 (1H, d, *J* = 9.7 Hz, H-4), 5.7 (1H, m, H-3), 5.42 (1H, dd, *J* = 10.5 and 6.3 Hz, $=CH_2$), 2.62 (1H, brs, H-10), 2.40 (1H, dd, *J* = 12.9 and 10.9 Hz, H-7), 2.15 (1H, m, H-2), 2.12 (1H, dd, *J* = 12.9 and 6.2 Hz, H-7), 1.98 (2H, m, H-16), 1.84 (1H, m), 0.97 (3H, s, Me-18), 0.87 (3H, d, *J* = 6.1 Hz, Me-21), 0.85 (6H, 2d, *J* = 6.6 Hz, Me-26 and Me-27). **^{13}C-NMR** ($CDCl_3$, 125.8 MHz, δ): 141.4 (C), 129.7 (CH), 127.0 (CH), 123.2 (CH), 79.6 (C), 57.2 (CH), 52.2 (CH), 43.4 (CH), 43.3 (C), 39.5 (CH_2), 37.1 (CH_2), 35.9 (CH_2), 35.8 (CH), 35.6 (CH_2), 35.3 (CH_2), 35.2 (CH), 34.4 (CH_2), 29.6 (CH_2), 28.3 (CH_2), 28.0, 27.2 (CH_2) (CH_2), 23.8 (CH_2), 22.8 (CH_3), 22.5 (CH_3), 21.6 (CH_2), 19.9 (CH_2), 18.4 (CH_3), 12.9 (CH_3). MS m/z 399 (MH^+, 40), 381 (MH^+-H_2O, 100), 365 (30). HRMS calcd for $C_{28}H_{45}$ (MH^+-H_2O) 381,3521, found 399.3505.



11a

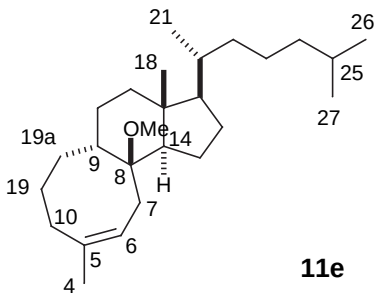
Compound 1 1 a: (86 %, R_f = 0.5 (15% EtOAc/hexanes), colorless oil). **^{1}H-NMR** ($CDCl_3$, 300 MHz, δ): 5.89 (1H, m), 5.58 (1H, m), 2.33 (1H, dd, *J* = 10.1 and 9.9 Hz), 0.9 (3H, s, Me-18), 0.87 (3H, d, *J* = 6.1 Hz, Me-21), 0.85 (6H, 2d, *J* = 6.6 Hz, Me-26 and Me-27). **^{13}C-NMR** ($CDCl_3$, 75 MHz, δ): 133.0 (CH), 126.7 (CH), 78.5 (C), 57.1 (CH), 51.8 (CH), 43.2 (CH), 43.0 (C), 39.5 (CH_2), 36.9 (CH_2), 35.9 (CH_2), 35.2 (CH_2), 34.5 (CH), 30.0 (CH_2), 29.6 (CH_2), 28.1 (CH_2), 28.0 (CH), 27.8 (CH_2), 27.2 (CH_2), 23.7 (CH_2), 22.8 (CH_3), 22.5 (CH_3), 19.9 (CH_2), 18.4 (CH_3), 12.9 (CH_3). MS m/z 346 (M^+, 22), 331 (M^+-CH_3, 18), 277 (26), 264 (17). HRMS calcd for $C_{24}H_{42}O$ (M^+) 346,3236, found 346.3229.



11d

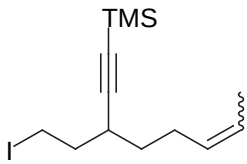
Compound 1 1 d: (92 %, R_f = 0.4 (10 % EtOAc/hexanes), colorless oil). **^{1}H-NMR** ($CDCl_3$, 300 MHz, δ): 5.31 (1H, t, *J* = 7.4 Hz, H-6), 1.75 (3H, s, Me-4), 0.9 (3H, s, Me-18), 0.87 (3H, d, *J* = 6.1 Hz, Me-21), 0.85 (6H, 2d, *J* = 6.6 Hz, Me-26 and M-27). **^{13}C–NMR** ($CDCl_3$, 75 MHz, δ): 140.5 (C), 119.7 (CH), 78.9 (C), 57.2 (CH), 51.8 (CH), 43.2 (CH), 43.0 (C), 39.4 (CH_2), 37.6 (CH_2), 35.9 (CH_2), 35.2 (CH_2), 35.1 (CH), 33.3 (CH_2), 29.6

(CH_2), 29.1 (CH_2), 28.2 (CH_2), 28.0 (CH), 27.2 (CH_2), 25.1 (CH_3), 23.7 (CH_2), 22.7 (CH_3), 22.5 (CH_3), 19.8 (CH_2), 18.4 (CH_3), 12.9 (CH_3). MS m/z 361 (MH^+, 35), 343 (MH^+-H_2O, 100), 327 (41). HRMS calcd for $C_{25}H_{44}O$ (M^+) 360,3392, found 360.3383.



11e

Compound 11e: (89 %, R_f = 0.7 (10 % EtOAc/hexanes), colorless oil). **^{1}H-NMR** ($CDCl_3$, 300 MHz, δ): 5.26 (1H, t, *J* = 8.0 Hz, H-6), 3.34 (3H, s, OMe), 2.47 (1H, dd, *J* = 6.5 Hz, H-7), 1.72 (3H, s, Me-4), 0.93 (3H, s, Me-18), 0.86 (3H, d, *J* = 6.1 Hz, Me-21), 0.85 (6H, 2d, *J* = 6.6 Hz, Me-26 and M-27). MS m/z 375 (MH^+, 53), 343 (100), 341 (90), 327 (41).



Compound 17: (82 %, R_f = 0.8 (10 % EtOAc/hexanes), colorless oil). **^{1}H-NMR** ($CDCl_3$, 300 MHz, δ): 5.53-5.29 (2H, m), 3.39-3.2 (2H, m), 2.53 (1H, m), 2.19 (2H, q, *J* = 7.5 Hz), 1.91 (2H, m), 1.62 (3H, m), 1.48 (2H, m), 0.14 (9H, s). **^{13}C–NMR** ($CDCl_3$, 75 MHz, δ): 129.4 (CH), 124.8 (CH), 108.1 (C), 86.9 (C), 38.6 (CH_2), 34.2 (CH_2), 33.4 (CH), 24.5 (CH_2), 12.8 (CH_3), 3.9 (CH_2), 0.14 (CH_3). MS m/z 319 (M^+-CH_3, 70), 207 (52), 133 (100). HRMS calcd for $C_{12}H_{20}OSiI$ (M^+–CH_3) 319,0379, found 319.0374. “#===END”