A New Approach to Macrocyclization via Alkene Formation in Catalytic Diazo Decomposition. The Synthesis of Patulolide A and B

Michael P. Doyle,* Wenhao Hu, and Iain Phillips

Department of Chemistry, University of Arizona, Tucson, Arizona

mdoyle@u.arizona.edu

Andrew G. H. Wee

Department of Chemistry, University of Regina, Regina, Saskatchewan, Canada, S4S 0A2

Andrew.Wee@uregina.ca

Supplementary Information

General. ^{1}H NMR (250 MHz, 300 MHz or 500MHz) and ^{13}C NMR (62.5 MHz, 75 MHz or 125 MHz) spectra were obtained as solutions in $CDCl_3$, and chemical shifts are reported in parts per million (ppm, δ) downfield from the internal standard, Me_4Si (TMS). Mass spectra were obtained using electron ionization on a quadruapole instrument. Infrared spectra were recorded as indicated, either as a thin film on sodium chloride plates or as solutions; absorptions are reported in wavenumbers (cm^{-1}). Melting points are uncorrected. Elemental analyses were performed at Texas Analytical Laboratories Inc. Retention times are recorded in minutes. Anhydrous THF was distilled over sodium /-benzophenone ketyl, and dichloromethane was doubly distilled over calcium hydride. Methanesulfonyl azide was prepared by reaction of methanesulfonyl chloride with sodium azide and was not distilled.[1] $Cu(PhCOCHCOCH_3)_2$ was purchased from Aldrich. $Cu(MeCN)_4PF_6$,[2] $Rh_2(4S\text{-MEAZ})_4$,[3] $Rh_2(5S\text{-MEPY})_4$,[4] and $Rh_2(pfb)_4$[5] were prepared as previously described.

---

[1] Boyer, J. H.; Mack, C. H.; Goebel, W.; Morgan, L. R. *J. Org. Chem.*, **1959**, *24*, 1051.
[2] Kubas, G. J. *Inorg. Synth*. **1979**, *19*, 90
[3] Doyle, M. P.; Hu, W.; Davies, S. *Org. Lett* **2000**, ASAP.
[4] Doyle, M. P.; Winchester, W. R.; Protopopova, M. N.; Kazala, A. P.; Westrum, L. J. *Org. Synth*. **1996**, *73*, 13.
[5] Doyle, M. P.; Shanklin, M. S. *Organometal*. **1994**, *13*, 1081.

2-{2-[2-(2-{2-[2-(2-Diazoacetoxy)-ethoxy]-ethoxy}-ethoxy)-ethoxy]-ethoxy}ethyl Diazoacetate (1). A solution of hexa(ethyleneglycol) (5.0 g, 17.7 mmol) in 100 mL of THF was treated with triethylamine (0.716 g, 7.0 mmol) and diketene (3.02 g, 36.0 mmol) at 0 °C. The solution was allowed to warm to room temperature and stirred for an additional 20 h. The solution was cooled to 0 °C again, Et_3N (4.29 g, 42.5 mmol) was added, followed by addition of MsN_3 (4.28 g, 35.4 mmol). The reaction solution was allowed to warm to room temperature and stirring was continued for 15 h whereupon the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (200 mL) and then was washed with H_2O (50 mL) and brine (50 mL), and the solvent was evaporated under reduced pressure. The crude bisdiazoacetoacetate was purified by flash column chromatography on silica gel (hexanes:ethyl acetate = 1:2) to give a yellow oil (5.8 g , 11.8 mmol): ^{1}H NMR ($CDCl_3$, 250 MHz) δ 4.41-4.37 (comp, 4H), 3.77-3.72 (comp, 4H), 3.65-3.60 (comp, 16H), 2.48 (s, 6H). The bisdiazoacetoacetate was dissolved in THF (50 mL) and was cooled to 0 °C. To the THF solution was added a solution of LiOH (2.0 g, 83.0 mmol) in 50 mL of H_2O. The reaction mixture was allowed to stir at room temperature for 1 h. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic layer was washed with brine, and the solvent was evaporated under reduced pressure. Purification by column chromatography (hexanes:ethyl acetate = 1:2) yielded product **1** as a yellow oil (3.95 g, 58% yield): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.82 (s, 2H), 4.31-4.29 (comp, 4H), 3.71-3.69 (comp, 4H), 3.68-3.62 (comp, 16H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (C=O not observed), 70.5, 69.1, 63.8, 46.2; IR (neat) 2110 (C=N_2), 1691 (C=O) cm^{-1}.

1,4,7,10,13,16,19-Heptaoxacyclotricos-21-ene-20,23-dione (2). To a refluxing solution of catalyst (1.0 mol %) in CH_2Cl_2 (4 mL) was added **1** (84 mg, 0.20 mmol) in 2 mL of CH_2Cl_2 over 2 h via a syringe pump. The reaction mixture was refluxed for an additional half hour to complete the reaction. After cooling to room temperature, the reaction mixture was subjected to column chromatography on silica gel (hexanes:ethyl acetate = 1:2) to yield a *Z/E* mixture of **2** as a colorless oil. The **2*Z***/**2*E*** ratio was determined by GC analysis on a SPB-5 column, which was confirmed as the same ratio by ^{1}H NMR. The $Cu(CH_3CN)_4PF_6$-catalyzed reaction of **1** yielded coupling product **2** (53 mg, 73% yield). HRMS calcd for $C_{16}H_{27}O_9$: 363.1655, found: 363.1664; IR($CDCl_3$) 1726 (C=O), 1614 (C=C) cm^{-1}; data for **2*Z***:

^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.27 (s, 2H), 4.38-4.35 (comp, 4H), 3.80-3.75 (comp, 4H), 3.70-3.64 (comp, 16H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.0, 129.5, 71.2, 71.1, 70.9, 70.5, 68.8, 64.7; for **2*E***: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.88 (s, 2H), 4.38-4.35 (comp, 4H), 3.74-3.71 (comp, 4H), 3.70-3.64 (comp, 16H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.7, 133.5, 71.2, 71.1, 70.8, 70.4, 68.7, 64.5.

2,3-Dimethyl-1,4,4a,7,8,10,11,13,14,16,17,19,20,22,23,25a-hexadeca-hydro-6,9,12,15,18,21,24-heptaoxabenzocyclotri-cosene-5,25-dione (5). To a 25:75 mixture of the *cis*:*trans* isomers of the macrocycle 2*Z*/2*E* (60 mg, 0.158 mmol) in carbon tetrachloride (25 mL), 2,3-dimethyl-1,3-butadiene (0.179 mL, 130 mg, 1.58 mmol, 10 equiv.) was added and the mixture heated to reflux. After 48 h gas chromatographic analysis showed complete consumption of the *trans*-isomer without any reaction of the *cis*-isomer. The reaction mixture was then evaporated and the resultant oil subjected to column chromatography (EtOAc as eluent) to yield the **5** as a mixture with **2*Z*** (50.2 mg, 75% for 5). ^{1}H NMR analysis showed the mixture to contain a 75:25 mixture of the two products: ^{1}H NMR (500 MHz, $CDCl_3$) for **5**: δ 4.28 (dt, *J* = 12.1, 5.2 Hz, 2 H), 4.22 (dt, *J* = 12.0, 4.8 Hz, 2 H), 3.73 (t, *J* = 4.8 Hz, H_d, 4 H), 3.71-3.64 (comp, 16 H), 2.88-2.85 (comp, 2 H), 2.28-2.21 (comp, 4 H) and 1.62 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) for **5**: δ 174.4, 123.8, 70.8-70.5, 64.0, 62.1, 42.3, 33.9 and 18.6; IR ($CHCl_3$): 1731 (C=O) and 1125 (C–O); HRMS (FAB^+): Calcd. for $C_{22}H_{37}O_9$: 445.2438 (M^{+1}), found 445.2432 (MH^{+1}); calcd. for $C_{22}H_{38}O_9$: 446.2472 (MH_2^{+1}), found: 446.2458 (MH_2^{+1}).

Methyl 8-oxooctanoate (8). *cis*-Cyclooctene (3.15 g, 3.7 mL, 95%) was dissolved in a mixture of dry CH_2Cl_2 (90 mL) and dry methanol (18 mL). Anhydrous Na_2CO_3 (0.82 g) was added and the mixture was cooled to -78 ^{o}C. Ozone was bubbled into the mixture until a faint blue color appeared (~ 20–25 mins). Then argon was bubbled into the mixture until the blue color was discharged. The cooling bath was removed and the mixture was warmed slowly to room temperature. The mixture was filtered and benzene (30 mL) was added. The mixture was concentrated to ~ 20 mL and the resulting viscous liquid was diluted with dry CH_2Cl_2 (80 mL). The solution was cooled to 0 ^{o}C under Ar, and dry Et_3N (5.7 mL) and acetic anhydride (7.2 mL) were added slowly, in sequence. The mixture was stirred at 0 ^{o}C for 20 min and then at room temperature overnight (20 h). The organic phase was washed with 0.1 M aqueous HCl (2 x 60 mL), 10% aqueous NaOH (2 x 60 mL), water (60 mL) and then dried. The filtered solution was evaporated and the residual crude oil was fractionated. The fraction with bp 98-102 ^{o}C at 3

Torr was collected. Yield of aldehyde **8** was 3.12 g (63%): ^{1}H NMR (250 MHz) δ 9.72 (t, *J* = 1.8 Hz, 1H), 3.63 (s, 3H), 2.39 (dt, *J* = 7.3, 1.8 Hz, 2H), 2.26 (t, *J* = 7.5 Hz, 2H), 1.53–1.70 (comp, 4H) 1.26–1.40 (comp, 4H). ^{13}C NMR δ (62.5 MHz): 202.5, 174.0, 51.3, 43.6, 33.8, 28.7, 28.6, 24.5, 21.7.

Methyl 8-Hydroxynonanoate (9). The aldehyde **8** (1.10 g, 6.4 mmol) was dissolved in dry ether (40 mL) under Ar, and the solution was cooled to -30 ^{o}C. MeMgBr (2.6 mL, 7.7 mmol, 3M in ether) was added slowly to the solution. The mixture was stirred at -30 ^{o}C for 45 min and then was quenched at -30 ^{o}C with saturated NH_4Cl (4 mL). The mixture was stirred briefly at -30 ^{o}C, then the cooling bath was removed and the mixture was allowed to warm to room temperature. Brine (10 mL) was added, the aqueous phase was removed and the ethereal layer was washed with brine (10 mL). The combined aqueous phases were re-extracted with ether (20 mL). The combined organic extracts were dried, filtered and evaporated. The residual liquid was purified by chromatography (1:1 hexanes-ether and then 2:1 ether-hexanes) to yield **9** (1.02 g, 83%): 1R: 3605–3142, 1734 cm^{-1}; ^{1}H NMR (250 MHz) δ 3.73–3.86 (m, 1H), 3.68 (s, 3H), 2.32 (t, *J* = 7.0 Hz, 2H), 1.95–2.03 (brs, 1H, OH), 1.56–1.73 (comp, 2H), 1.26–1.50 (comp, 8H), 1.19 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR δ (62.5 MHz): 174.2, 67.8, 51.3, 39.1, 33.9, 29.0, 28.9, 25.4, 24.7, 23.3; FAB-HRMS, calcd for $C_{10}H_{21}O_3$ ($M+H^+$): 189.1491, found: 189.1496.

Methyl 8-(α-Diazoacetoxy)nonanoate (10).m The alcohol **9** (1.02 g, 5.42 mmol) was dissolved in dry CH_2Cl_2 (27 mL) under Ar, and the solution was cooled to 0 ^{o}C. α-(*p*-Toluenesulfonylhydrazone)-glyoxyl chloride (2.55 g, 9.76 mmol) was added and then dry *N*,*N*-dimethylaniline (1.24 mL, 9.76 mmol) was added dropwise to the mixture at 0 ^{o}C. The mixture was stirred at 0 ^{o}C and after 20 min, *N*,*N*-diisopropylethylamine (4.8 mL, 27.6 mmol) was added. Stirring was continued at 0 ^{o}C for 15 min and then at room temperature for 15 min. Then the mixture was diluted with CH_2Cl_2 (10 mL), washed with saturated aqueous citric acid (3 x 10 mL), water (20 mL) and saturated aqueous $NaHCO_3$ (20 mL). The organic phase was dried, filtered and evaporated to leave a reddish-orange oil. Flash chromatography (3:1 hexanes-ether) of the crude oil gave the diazoacetate compound **10** (1.1 g, 79%) as a bright yellow liquid: IR (film) 3123, 3092, 2110 (C=N_2), 1740 (C=O), 1690 cm^{-1}; ^{1}H NMR (250 MHz) δ 4.99 (sextet, *J* = 5.5 Hz, 1H), 4.75 (s, 1H), 3.67 (s, 3H), 2.32 (t, *J* = 7.5 Hz, 2H), 1.41–1.69 (comp, 4H),

1.27–1.41 (comp, 6H), 1.23 (d, J = 6.3 Hz, 3H). ^{13}C NMR (62.5 MHz) δ 174.2, 166.3, 71.4, 51.4, 46.3, 35.7, 33.8, 28.8, 28.7, 24.6, 24.6, 20.0; FAB-HRMS, calcd for $C_{12}H_{20}N_2O_4$: 256.1423, found: 256.1429.

1-Diazo-9-(α-diazoacetoxy)-2-decanone (11). The methyl ester **10** (1.19 g, 4.64 mmol) was dissolved under Ar in acetone, and the solution was cooled to 0 °C. A solution of NaOH (0.223 g, 5.57 mmol, 98.8%) in distilled water (3 mL) was added, and the mixture was stirred at 0 °C for 3 h. Acetone was evaporated in vacuo and then distilled water (10 mL) was added. The basic aqueous mixture was cooled to 0 °C in an ice-bath and then carefully acidified to pH ~ 3 with 0.5 M aqueous HCl (8.2 mL). The mixture was extracted thoroughly with CH_2Cl_2 (4 x 20 mL), then the combined organic extracts were washed with water (20 mL) and dried. The filtered solution was evaporated to leave a yellow liquid which was used, without further purification, in the next step.

The crude carboxylic acid (~1.6 g) was dissolved in dry THF (10 mL) and the solution was cooled to 0 °C. Dry Et_3N (0.97 mL) was added dropwise and the solution was stirred at 0 °C for 15 min. *i*-Butyl chloroformate (0.90 mL) was then added dropwise and the mixture was stirred for 30 min. During the addition of *i*-butylchloroformate, an off-white precipitate was formed). Excess ethereal diazomethane (prepared from 5 g Diazald; ~0.7 mol of CH_2N_2; *CAUTION: see ref. 3, Supplementary Information*) was added and the mixture was stirred at 0 °C to room temperature overnight. Argon was bubbled into the reaction mixture for 15 min and the solvents were evaporated in vacuo. Ethyl acetate (20 mL) and brine (10 mL) were added and the organic layer was separated. The aqueous phase was re-extracted with ethyl acetate (2 x 10 mL) and the combined organic phases were washed with saturated aqueous $NaHCO_3$, dried, filtered and evaporated. The residual crude oil was purified by chromatography (3:1 hexanes-ethyl acetate) to afford **11** as a yellow liquid (451 mg, 36%): 1R (neat) 3091, 2105 (C=N_2), 1700 (C=O), 1633 cm^{-1}; ^{1}H NMR (250 MHz) δ 5.29 (br, 1H), 4.90–5.04 (m, 1H), 4.74 (s, 1H), 2.31 (br t, J = 6.1 Hz, 2H), 1.46–1.68 (comp, 4H), 1.27–1.40 (comp, 6H), 1.23 (d, J = 6 Hz, 3H); ^{13}C NMR (62.5 MHz) δ 195.1, 166.0, 71.4, 54.8, 46.1, 40.7, 35.7, 29.1, 28.9, 28.8, 24.9, 20.0; FAB-HRMS, calcd for $C_{12}H_{19}N_4O_3$ ($M+H^+$): 267.1457, found: 267.1454.

(3*E*)-12-Methyl-oxacyclododec-3-ene-2,5-dione (Patulolide A) (6) and (3*Z*)-12-Methyl-oxacyclododec-3-ene-2,5-dione (Patulolide B) (7). A solution of bis-diazo compound **11** (78 mg) in dry CH_2Cl_2 (5 mL) was added, over a period of 2 h (syringe pump) to a refluxing solution of Cu $(MeCN)_4PF_6$ or $Rh_2(OAc)_4$ (2 mol %) in dry CH_2Cl_2 (5 mL). After addition was complete, the mixture was allowed to reflux for an additional 30 min and then CH_2Cl_2 was evaporated and the crude residue was purified by chromatography (2:1 hexanes-ether) to afford the known[6] macrocyclic lactones **6** and **7**. *trans*-***6***: 1R (film) 3055, 2938, 2870, 1715, 1623 cm^{-1}; ^1H NMR (250 MHz) δ 7.25 (d, *J* = 15.6 Hz, 1H), 6.80 (d, *J* = 15.6 Hz, 1H), 4.82–4.96 (m, 1H), 2.75 (ddd, *J* = 14, 10.4, 4 Hz, 1H), 2.48 (ddd, *J* = 14, 6.4, 3 Hz, 1H), 1.40 (d, 3H, J = 6 Hz, Me), 1.14–1.72 (comp, 13H, CH_2); ^{13}C NMR (125 MHz) δ C=O (not observed) 141.6, 129.7, 74.7, 38.8, 34.7, 25.7, 25.5, 24.4, 22.2, 20.0. *cis*-***7***: 1R (film) 3061, 2938, 2863, 2858, 1721, 1672, 1635 cm^{-1}; ^1H NMR (250 MHz) δ 6.44 (d, *J* = 12.8 Hz, 1H), 6.01 (d, *J* = 12.8 Hz, 1H), 4.91–5.03 (m, 1H), 2.70 (ddd, *J* = 18, 7.5, 4.6 Hz, 1H), 2.54 (ddd, *J* = 18, 7.2, 4.3 Hz, 1H), 1.22–1.84 (comp, 13H), 1.27 (d, *J* = 6 Hz, 3H); ^{13}C NMR (125 MHz) δ 202.8, 165.2, 139.6, 125.8, 74.6, 40.2, 31.8, 24.8, 24.2, 23.3, 20.3, 19.6.

[6] See refs. 15-18 in text