Enantioselective Strategy to the Spirocyclic Core of Palau'amine and Related Bis-guanidine, Marine Alkaloids

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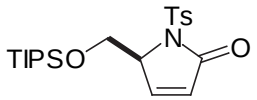
Supporting Information

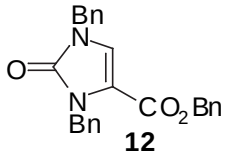
Selected experimental procedures and characterization data (including ^{1}H, GOESY, and ^{13}C NMR spectra) for compounds **9**, **12-14**, **17**, and **20**. This material is available free of charge via the Internet at http://pubs.acs.org



9

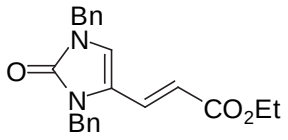
Lactam 9. R_f 0.24 (7:3-Hexanes:Et_2O); $[\alpha]^{25}_D$ -115°(*c* 1.28, $CDCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, *J*=8.4 Hz, 2H), 7.37 (dd, *J*= 1.8, 6.0 Hz, 1H), 7.30 (d, *J*= 8.1 Hz, 2H), 6.02 (dd, *J*=1.5, 6.0 Hz, 1H), 4.82-4.75 (m, 1H), 4.46 (dd, *J*=4.2, 9.6 Hz, 1H), 3.77 (dd, *J*=7.8, 9.6 Hz, 1H), 2.42 (s, 3H), 1.10-0.90 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 151.5, 144.9, 135.9, 129.6, 127.9, 126.1, 65.3, 63.9, 21.6, 17.9, 11.8; IR (thin film) 1731; HRMS (FAB) Calcd for $C_{21}H_{33}NO_4SSi$[M+H]: 424.19778. Found: 424.19683.

The optical purity of dienophile **9** was determined by chiral HPLC on a Chiralpak® AD column eluting with 1% i-PrOH/Hexanes at 1ml/min: t_S= 28 min, t_R=32 min. The enantiomeric excess was determined to be 88% ee but could be increased to >99% ee by a single recrystallization from *i*-PrOH/hexanes. Partial racemization of dienophiles related to lactam **9** during their preparation has been previously observed. [1]



12

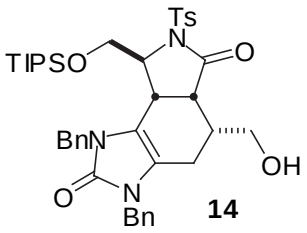
Ester 12. R_f 0.30 (7:3-Hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.25 (m, 15H), 7.0 (s, 1H), 5.25 (s, 2H), 5.15 (s, 2H), 4.87 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 153.5, 137.8, 135.7, 135.4, 129.0, 128.6, 128.4, 128.3, 128.3, 128.2, 128.0, 127.9, 127.8, 127.3, 120.5, 113.6, 66.1, 47.6, 45.6; IR (thin film) 1724, 1695; HRMS (FAB) Calcd for $C_{25}H_{22}N_2O_3$[M+H]: 399.17087. Found: 399.17259.



13

Ester 13. R_f 0.35 (6:4-Hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.19(m, 10H), 7.18 (dd, *J*=0.9, 16.2 Hz, 1H), 6.59 (app s, 1H), 5.92 (dd, *J*=0.6, 15.9 Hz, 1H), 5.05 (s, 2H), 4.85 (s, 2H), 4.13 (q, *J*= 7.2, 14.4 Hz, 2H), 1.22 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.5, 166.5, 153.5, 136.5, 135.9, 129.8, 128.8, 128.7, 128.0, 127.9, 127.5, 126.6, 120.1, 114.4, 114.2, 60.2, 47.3, 45.1, 14.1; IR (thin film) 1687, 1629; HRMS (FAB) Calcd for $C_{22}H_{22}N_2O_3$[M+H]: 363.17087. Found: 363.16909.

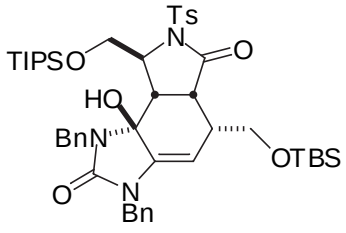
(1) Ohfune, Y.; Tomita, M. *J. Am. Chem. Soc.* **1982**, *104*, 3511-3513.



14

Cycloadduct 14. To a solution of dienophile (2.771 g, 6.550 mmol) in 50.0 ml benzene was added diene (2.805 g, 6.516 mmol) and 460 µl (3.949 mmol) 2,6-lutidine. The reaction mixture was heated to 95 °C in a sealed tube for three days. The mixture was then allowed to cool and additional diene (891.3 mg, 2.785 mmol) was added. After stirring at 95 °C for an additional 24 h, the reaction mixture was concentrated *in vacuo.* Purification by flash chromatography on Si_2O eluting with hexanes:EtOAc (8:2→1:9) gave 3.094 g (64%) Diels-Alder adduct **14** as a yellow solid along with 714.1 mg (15%) of regioisomer **15**: R_f 0.69 (3:7-hexanes:EtOAc); $[\alpha]^{25}_D$ -53 (*c* 2.53, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.1 Hz, 2H), 7.34-7.10 (m, 12H), 5.23 (d, *J* = 16.2 Hz, 1H), 4.91 (d, *J*=16.2 Hz, 1H), 4.62 (d, *J* = 16.2 Hz, 1H), 4.32 (d, *J*=16.2 Hz, 1H), 4.21 (dd, *J* = 2.7, 5.4 Hz, 1H), 4.04 (dd, *J* = 6.9, 10.2 Hz, 1H), 3.92 (dd, *J* = 3.0, 10.8 Hz, 1H), 3.74 (app t, *J* = 3.9 Hz, 2H), 3.41 (dd, *J* = 3.0, 6.9 Hz, 1H), 3.18 (app bd, 6.9 Hz, 1H), 2.40 (s, 3H), 2.00 -1.90 (m, 2H), 1.88-1.80 (m, 1H), 1.05-0.95(m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 154.6, 145.1, 137.0, 137.0, 135.0, 129.4, 128.9, 128.8, 128.5, 128.4, 127.9 127.6, 127.1, 127.0, 120.8, 114.0, 65.2, 64.3, 64.1, 45.6, 45.0, 44.7, 36.4, 35.5, 21.7, 18.9, 17.9, 17.9, 11.8; IR (thin film) 1738, 1680; HRMS (FAB) Calcd for $C_{41}H_{53}N_3O_6SSi$[M+Na]: 766.3322. Found: 766.3311.

In a different run, the optical purity of the Diels-Alder adduct was determined by preparation of the Mosher ester[2] using EDCI, DMAP, and (*S*)-MTPA in CH_2Cl_2. Integration of the diastereomeric methoxy protons by ^{1}H NMR indicated a %ee of >95%. The dienophile (lactam **9**) used in this run was determined to be >99% ee. Recovered dienophile was determined to be 95% ee and thus some racemization of the dienophile occurs under the conditions of the Diels-Alder reaction.

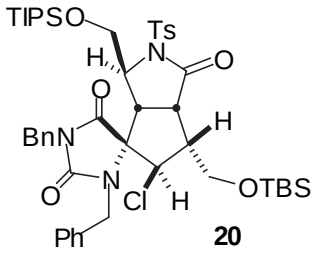


17

Allylic Alcohol 17. To a cooled (-45 °C) solution of silylated Diels-Alder adduct **16** (21.1 mg, 0.0246 mmol) in 300 µl CH_2Cl_2 containing a small quantity of $MgSO_4$ was added 280 µl (0.025 mmol) DMDO in aqueous acetone.[3] Additional DMDO was added after 1h (140 µl, 0.126 mmol), 1.5 h (70 µl**,** 0.0063 mmol), and 2h (70 µl**,** 0.0063 mmol). The reaction was quenched with a few drops of Me_2S at –45 °C. The mixture was allowed to warm to room temperature,

(2) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543-2549.
(3) Murray, R. W.; Ramasubbu, J. *J. Org. Chem.* **1985**, *50*, 2847-2853.

filtered and concentrated *in vacuo* to give 21.5 mg (99%) allylic alcohol **17** yield as an off-white foam: R_f 0.75 (6:4-hexanes:EtOAc); ^{1}H NMR (500 MHz, d_6-acetone) δ 7.80 (d, *J* = 8.5 Hz, 2H), 7.54 (d, *J* = 7.5 Hz, 2H), 7.48 (d, *J*= 8.0 Hz, 2H), 7.42 (app t, *J* = 7.5 Hz), 7.36-7.22 (m, 6H), 5.57 (s, 1H), 4.83 (d, *J* = 15.5 Hz, 1H), 4.76, (d, *J* = 15.5 Hz, 1H), 4.50 (d, *J* = 15.5 Hz, 1H), 4.47 (d, *J* = 3.3 Hz 1H), 4.10 (dd, *J* = 8.0, 9.5 Hz, 1H), 3.97 (app s, 1H), 3.76 (d, *J* = 16.0 Hz, 1H), 3.72 (dd, *J* = 8.0, 9.5 Hz, 1H), 3.53 (dd, *J* = 2.5, 11.0 Hz, 1H), 3.20 (dd, *J* = 4.5, 9.0 Hz, 1H), 3.09-3.03 (m, 1H), 2.89 (d, *J* = 8.5 Hz, 1H), 2.56 (J = 11.0 Hz, 1H), 2.50 (s, 3H), 0.98 (m, 21H), 0.90 (s, 9H), -0.05 (s, 6H); ^{13}C NMR (75MHz, d_6-acetone) δ 173.9, 158.8, 145.8, 141.1, 139.7, 137.7, 130.6, 129.8, 129.4, 128.8, 128.2, 127.6, 98.2, 86.4, 66.0, 63.8, 62.1, 46.5, 45.2, 44.6, 43.8, 38.4, 26.3, 21.7, 18.5, 12.6, -5.0; IR (thin film) 3345, 1731, 1680; HRMS (FAB) Calcd for $C_{47}H_{67}N_3O_7SSi_2$[M+Na]: 896.4136. Found: 896.4138.



20

Spirohydantoin 20. To a cooled (-45 °C) solution of allylic alcohol **17** (19.0 mg, 0.0218 mmol) in 200 µl CH_2Cl_2 was added 11 µl (0.109 mmol) cyclohexene. A cooled (-45 °C) solution of *N*-chlorosuccinimide (9.6 mg, 0.072 mmol) in 100 µl CH_2Cl_2 was added and the resulting reaction mixture was stirred at ambient temperature overnight. Water was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by column chromatography on SiO_2 eluting with hexane:EtOAc (9:1→8:2) and gave 14.7 mg (75%) of spirohydantoin **20** as a white foam: R*f* 0.47 (8:2-Hexanes:EtOAc), ^{1}H NMR (500 MHz, d_6-acetone) δ 8.08 (d, *J*=8.5 Hz, 2H), 7.49 (d, *J* = 8.5 Hz, 2H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.5 Hz, 2H), 7.34-7.30 (m, 6H), 5.32 (d, *J*=16.0 Hz, 1H), 4.68 (dd, *J*=15.0 Hz, 15.5 Hz, 2H), 4.63 (bs, 1H), 4.37 (d, *J*=16.0 Hz, 1H), 4.10 (d, *J*= 12.5 Hz, 1H), 4.05 (dd, *J* = 8.5, 10.0 Hz, 1H), 4.09 (dd, *J* = 3.5, 10.5 Hz, 1H), 3.92 (dd, *J*=1.5, 10.5 Hz, 1H), 3.79 (dd, *J*=4.0, 10.0 Hz, 1H), 3.48 (t, *J*=8.5 Hz, 1H), 3.29 (d, *J*=8.5 Hz, 1H), 3.15-3.07 (m, 1H), 2.44 (s, 3H), 0.98-0.83 (m, 30 H), 0.72 (s, 3 H), 0.069 (s,3H); ^{13}C NMR (75 MHz, d_6-acetone) δ 173.8, 171.9, 157.8, 146.8, 138.4, 137.3, 136.9, 130.8, 129.5, 129.4, 129.4, 129.2, 128.8, 128.7, 128.6, 76.8, 65.7, 61.3, 60.6, 59.7, 48.7, 47.7, 46.9, 46.3, 43.4, 41.0, 26.4, 18.4, 18.3, 12.7, -5.2; IR (thin film) 1716, 1600; HRMS (FAB) Calcd for $C_{47}H_{66}ClN_3O_7SSi_2$[M+Na]: 930.3746. Found: 930.3785.

GOESY experiments were performed on both the spirocycle **20** (pp. S18-S19) and its bis-deprotected derivative since overlapping peaks in the ^{1}H NMR of spirocycle **20** precluded some key nOe's to be observed in this compound. The latter nOe's were more clearly observed in the deprotected derivative (pp. S20-S21).