

Supplementary Material for Organic & Biomolecular Chemistry  
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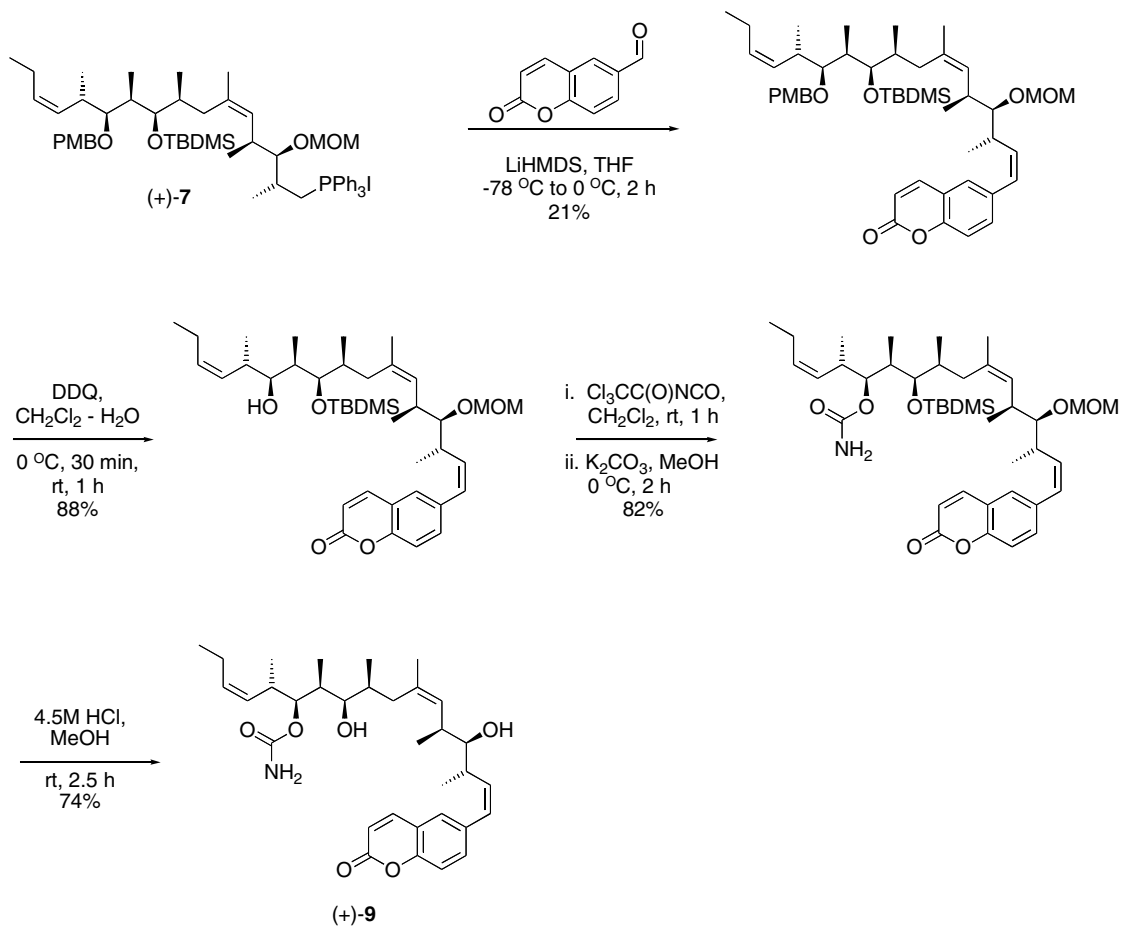
Coumarin-derived discodermolide analogues with equivalent potency – a further  
simplification of the lactone region.

Simon J. Shaw,<sup>\*a</sup> Hugo G. Menzella,<sup>a</sup> David C. Myles,<sup>a</sup> Ming Xian<sup>b</sup> and Amos B. Smith,  
III<sup>\*b</sup>

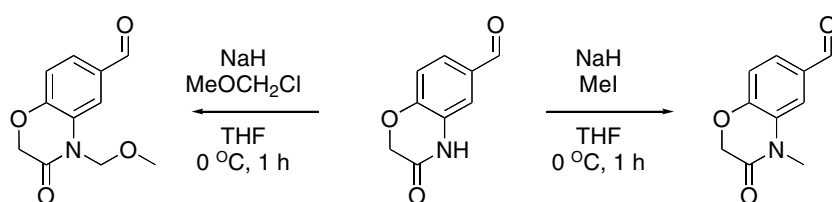
<sup>a</sup> Kosan Biosciences, Inc., 3832 Bay Center Place, Hayward, CA 94545, USA. Fax: 01 510 732 8001; Tel: 01 510 731 5269; E-mail: [shaw@kosan.com](mailto:shaw@kosan.com); <sup>b</sup> Department of Chemistry, University of Pennsylvania, Philadelphia, PA 19104, USA. Fax: 01 215 898 5192; Tel: 01 215 898 4860; E-mail: [smithab@sas.upenn.edu](mailto:smithab@sas.upenn.edu)

Supporting Information

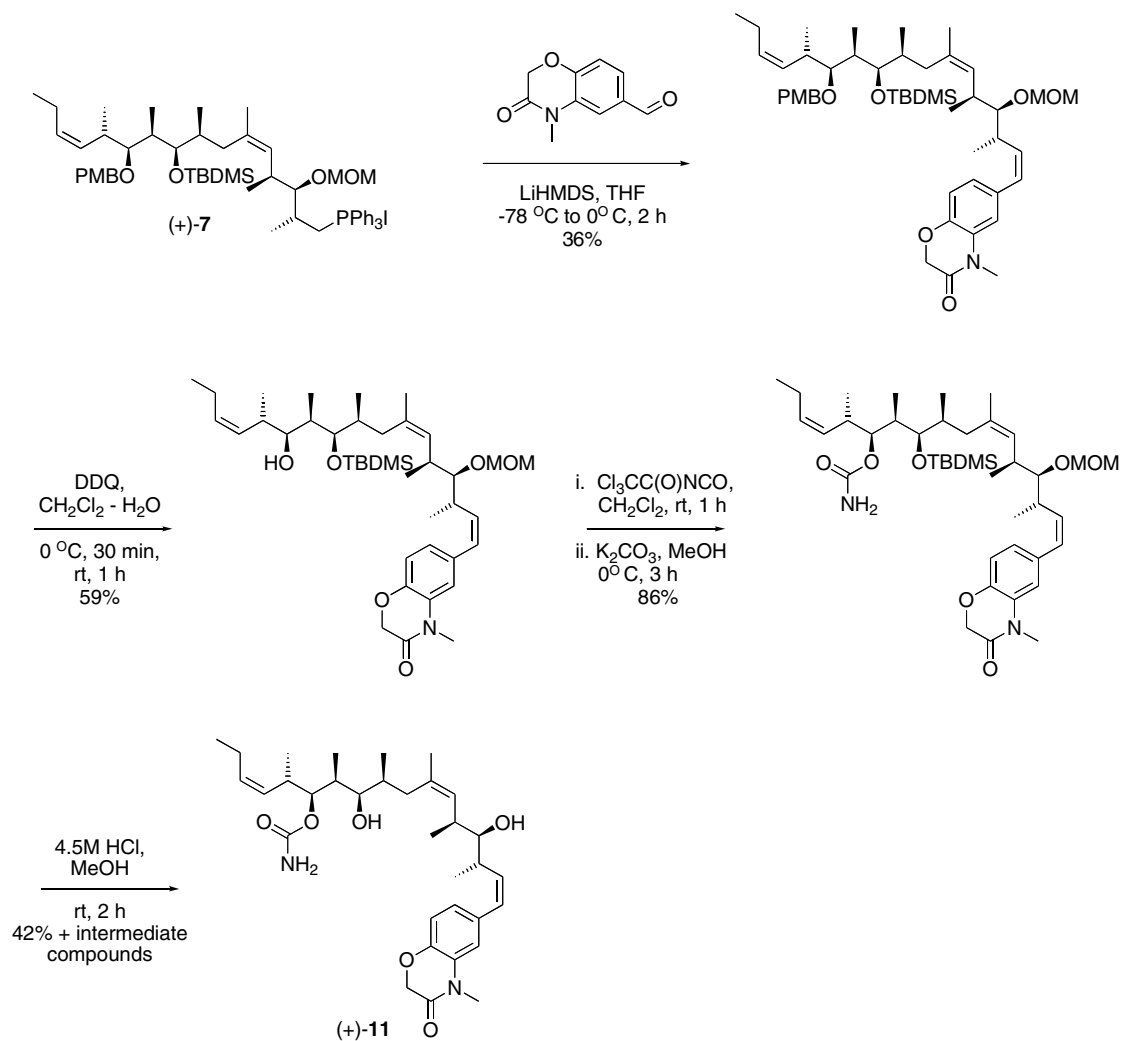
**Scheme S1** Synthesis of the 6-coumarin analogue (+)-9



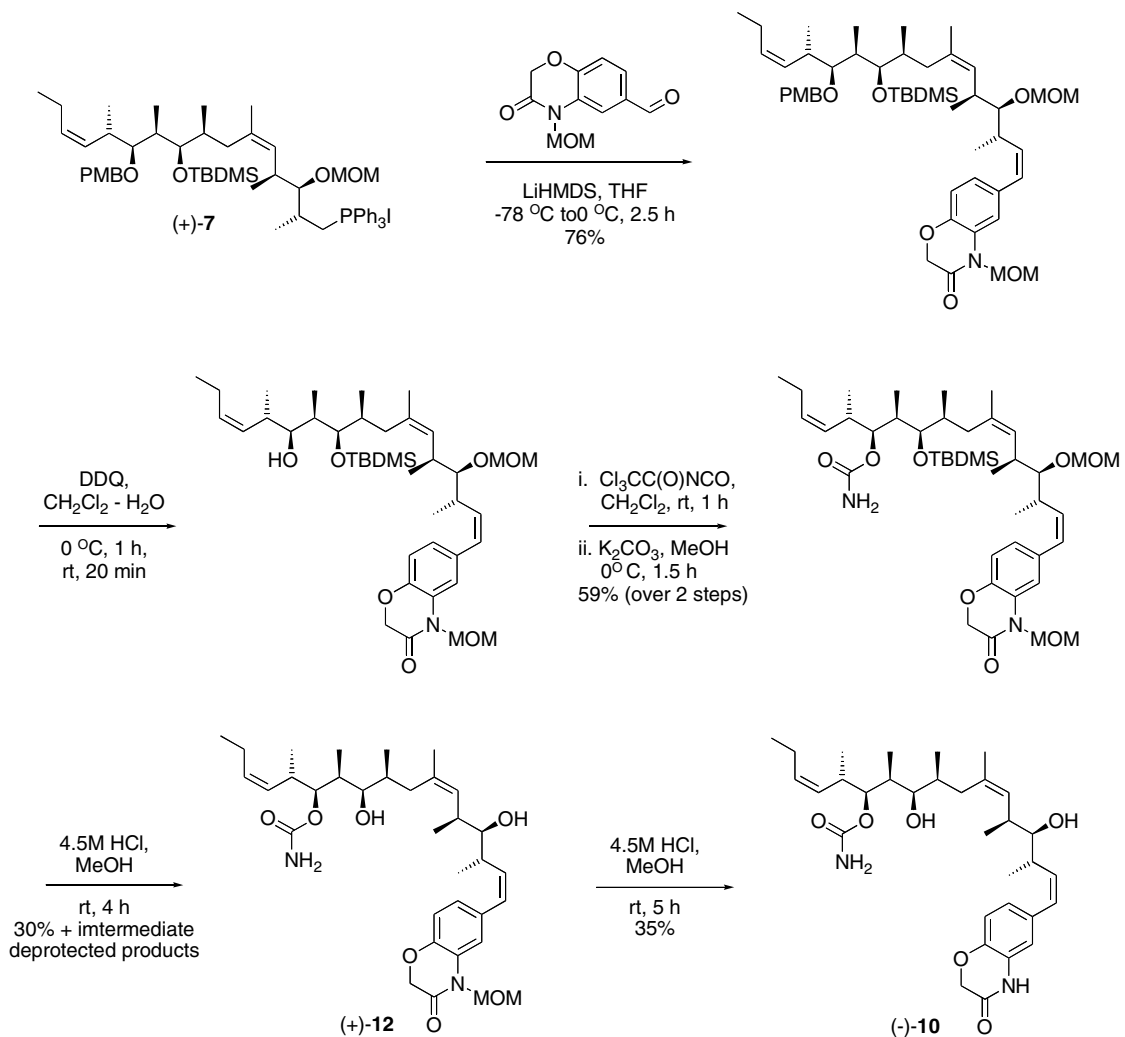
**Scheme S2** Protection of the lactam N-H of the coupling aldehyde



**Scheme S3** Synthesis of the N-methyl lactam analogue (+)-11

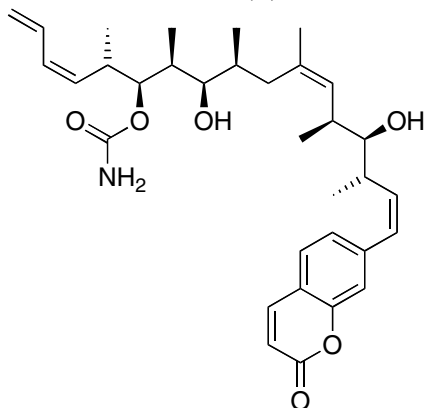


**Scheme S4** Synthesis of the N-methoxymethyl lactam (+)-**12** and the free lactam analogue (-)-**10**



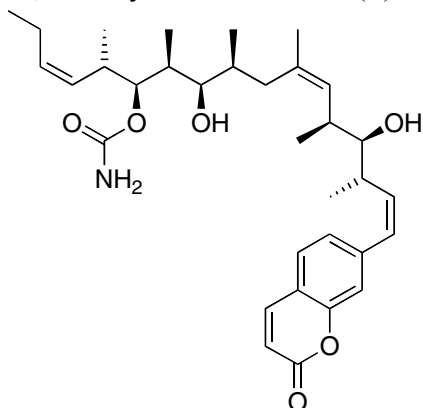
Analytical Data for Final Compounds

7-Coumarin Diene (+)-**6**



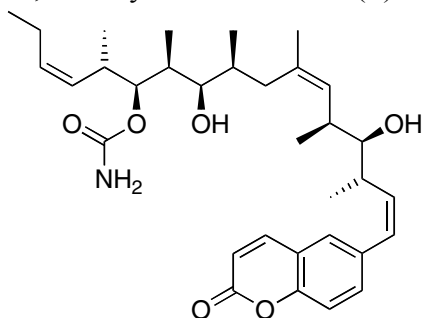
$[\alpha]_{23}^{589} +23.0$  (c 0.30,  $\text{CHCl}_3$ ); IR ( $\text{CH}_2\text{Cl}_2$ ) 3453, 3357, 2965, 2927, 2871, 1713, 1613, 1392, 1325, 1120, 1042, 976, 845  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.69 (1H, d, J 9.5 Hz, H-3 or H-2), 7.40 (1H, d, J 8.0 Hz, H-7b), 7.25 (2H, m, H-7a, H-6), 6.63 (1H, dt, J 16.0, 10.5 Hz, H-23), 6.43 (1H, d, J 12.0 Hz, H-8), 6.38 (1H, d, J 8.5 Hz, H-3 or H-2), 6.11 (1H, dd, J 11.0, 10.5 Hz, H-22), 5.89 (1H, dd, J 12.0, 11.0 Hz, H-9), 5.50 (1H, t, J 10.0 Hz, H-21), 5.24 (1H, d, J 16.0 Hz, H-24trans), 5.15 (1H, d, J 9.5 Hz, H-24cis), 4.90 (1H, d, J 10.0 Hz, H-13), 4.76 (1H, t, J 6.0 Hz, H-19), 3.27 (1H, dd, J 7.5, 3.5 Hz, H-11), 3.20 (1H, dd, J 5.5, 5.0 Hz, H-17), 3.11-3.04 (2H, m, H-20, H-10), 2.40 (1H, m, H-12), 1.77-1.72 (3H, m, H-18, H-16, 1 x H-15), 1.33 (3H, s, H-14'), 1.25 (1H, m, 1 x H-15), 1.17 (3H, d, J 7.0 Hz, H-18'), 1.04 (3H, d, J 7.0 Hz, H-10'), 0.94 (3H, d, J 6.5 Hz, H-20'), 0.81 (3H, d, 7.0 Hz, H-12'), 0.74 (3H, d, J 6.0 Hz, H-16');  $^{13}\text{C}$  nmr (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  161.1, 157.3, 154.0, 143.1, 141.7, 136.9, 133.6, 132.1, 129.9, 129.1, 128.1, 127.8, 127.4, 124.6, 118.0, 117.2, 116.8, 116.0, 80.1, 78.8, 76.1, 37.2, 36.6, 35.5, 35.2, 34.4, 33.2, 22.7, 18.3, 17.6, 17.1, 14.3, 8.3;  $m/z$  574  $[\text{M}+\text{Na}]^+$ , 534  $[\text{M}+\text{H}-\text{H}_2\text{O}]^+$ , 491 (Found:  $[\text{M}+\text{Na}]^+$ , 574.3112).  $\text{C}_{33}\text{H}_{45}\text{NO}_6$  requires  $[\text{M}+\text{Na}]^+$ , 574.3139).

23,24-Dihydro-7-Coumarin (+)-**8**



$[\alpha]_{22}^{589} +20.1$  (c 0.30,  $\text{CHCl}_3$ ); IR ( $\text{CHCl}_3$ ) 3444, 3362, 2962, 2926, 2855, 1711, 1612, 1459, 1378, 1043, 976, 846, 733  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.69 (1H, d, J 9.5 Hz, H-3 or H-2), 7.40 (1H, d, J 8.0 Hz, H-7b), 7.28 (1H, br s, H-6), 7.25 (1H, m, H-7a), 6.43 (1H, d, J 12.0 Hz, H-8), 6.38 (1H, d, J 9.5, H-3 or H-2), 5.89 (1H, d, J 11.5 Hz, H-9), 5.45 (1H, m, H-22), 5.41 (1H, m, H-21), 4.92 (1H, d, J 9.0 Hz, H-13), 4.73 (1H, t, J 6.0 Hz, H-19), 3.28 (1H, dd, J 7.5, 4.0 Hz, H-11), 3.19 (1H, t, J 5.5 Hz, H-17), 3.10 (1H, m, H-10), 2.85 (1H, m, H-12), 2.13-2.01 (2H, m, 2 x H-23), 1.83-1.78 (2H, m, H-18, 1 x H-15), 1.71 (1H, m, H-16), 1.36 (3H, s, H-14'), 1.30 (1H, m, 1 x H-15), 1.17 (3H, d, J 7.0 Hz, H-10'), 1.01 (3H, t, J 7.5 Hz, H-24), 0.99 (3H, d, J 7.0 Hz, H-20'), 0.96 (3H, d, J 6.5 Hz, H-12'), 0.79 (3H, d, J 7.0 Hz, H-18'), 0.76 (3H, d, J 6.0 Hz, H-16');  $^{13}\text{C}$  nmr (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  161.3, 157.4, 154.0, 143.2, 141.5, 136.8, 133.7, 132.3, 130.4, 129.1, 127.8, 127.4, 124.6, 117.2, 116.8, 116.0, 80.0, 79.0, 76.2, 37.3, 36.6, 35.5, 35.3, 33.9, 33.2, 22.8, 20.8, 18.2, 17.9, 17.0, 14.5, 14.4, 8.3;  $m/z$  576  $[\text{M}+\text{Na}]^+$ , 536  $[\text{M}+\text{H}-\text{H}_2\text{O}]^+$ , 493, 475 (Found  $[\text{M}+\text{Na}]^+$ , 576.3310,  $\text{C}_{33}\text{H}_{47}\text{NO}_6$  requires  $[\text{M}+\text{Na}]^+$  576.3296).

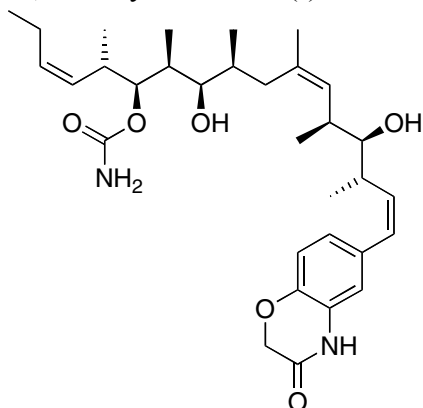
23,24-Dihydro-6-Coumarin (+)-**9**



$[\alpha]_{22}^{589} +27.2$  (c 0.35,  $\text{CHCl}_3$ ); IR ( $\text{CHCl}_3$ ) 3447, 3357, 2960, 2922, 2853, 1716, 1601, 1461, 1377, 1102, 1041, 990  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.68 (1H, d, J 9.5 Hz, H-3 or H-2), 7.50 (1H, dd, J 8.5, 2.0 Hz, H-7), 7.44, (1H, d, J 2.0 Hz, H-7b), 7.28 (1H, d,

J 8.5 Hz, H-6), 6.47 (1H, d, J 12.0 Hz, H-8), 6.43 (1H, d, J 9.5 Hz, H-3 or H-2), 5.74 (1H, dd, J 12.0, 10.5 Hz, H-9), 5.42 (1H, dt, J 11.0, 7.5 Hz, H-22), 5.27 (1H, dd, J 10.5, 9.0 Hz, H-21), 5.06 (1H, d, J 10.0 Hz, H-13), 4.71 (1H, dd, J 6.5, 4.5 Hz, H-19), 4.57 (1H, br s, NH<sub>2</sub>), 3.30 (1H, t, J 5.5 Hz, H-11), 3.19 (1H, t, J 5.5 Hz, H-17), 3.01 (1H, m, H-10), 2.81 (1H, dt, J 9.5, 6.5 Hz, H-20), 2.54 (1H, dt, J 10.0, 6.5 Hz, H-12), 2.13-2.02 (2H, m, 2 x H-23), 1.90-1.85 (3H, H-18, H-16, 1 x H-15), 1.57 (1H, m, 1 x H-15), 1.49 (3H, d, J 1.0 Hz, H-14'), 1.11 (3H, d, J 7.0 Hz, H-10'), 0.98 (3H, t, J 7.5 Hz, H-24), 0.96 (3H, d, J 6.5 Hz, H-20' or H-12'), 0.95 (3H, d, J 6.5 Hz, H-20' or H-12'), 0.91 (3H, d, J 7.0 Hz, H-18'), 0.78 (3H, d, J 6.0 Hz, H-16'); <sup>13</sup>C nmr (100 MHz, CDCl<sub>3</sub>): δ 160.7, 157.0, 152.7, 143.5, 135.2, 134.0, 133.7, 132.4, 132.3, 130.3, 129.4, 127.9, 127.5, 118.5, 116.8, 116.6, 79.6, 79.1, 76.4, 37.3, 35.8 (2C), 34.2, 33.7, 33.0, 23.1, 20.8, 18.2, 17.8, 16.2, 14.5, 13.8, 8.7; *m/z* 576 [M+Na]<sup>+</sup>, 536 [M+H-H<sub>2</sub>O]<sup>+</sup>, 493, 473 (Found [M+Na]<sup>+</sup>, 576.3288, C<sub>33</sub>H<sub>47</sub>NO<sub>6</sub> requires [M+Na]<sup>+</sup> 576.3296).

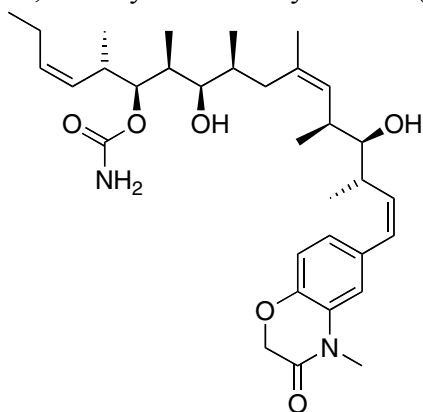
23,24-Dihydro-lactam (-)-10



[α]<sub>20</sub><sup>589</sup> -12.1 (c 0.35, CHCl<sub>3</sub>); IR (CH<sub>2</sub>Cl<sub>2</sub>) 3364, 2964, 2930, 2871, 1694, 1598, 1489, 1457, 1390, 1328, 1044, 991, 968, 734 cm<sup>-1</sup>; <sup>1</sup>H nmr (400 MHz, CDCl<sub>3</sub>): δ 8.31 (1H, s, NH), 6.93 (1H, dd, J 8.5, 1.5 Hz, H-7a), 6.90 (1H, d, J 8.0 Hz, H-7b), 6.80 (1H, d, J 1.5 Hz, H-6), 6.30 (1H, d, J 12.0 Hz, H-8), 5.67 (1H, t, J 12.0 Hz, H-9), 5.52 (1H, dt, J 12.0, 7.0 Hz, H-22), 5.38 (1H, dd, J 12.0, 10.0 Hz, H-21), 4.87 (1H, d, J 10.0 Hz, H-13), 4.81 (1H, t, J 5.0 Hz, H-19), 4.62 (1H, d AB system, J 15.5 Hz, 1 x H-2), 4.56 (1H, d AB system, J 15.5 Hz, 1 x H-2), 3.25 (1H, m, H-17), 3.22 (1H, dd, J 8.0, 3.5 Hz, H-11), 3.00 (1H, m, H-10), 2.90 (1H, dt, J 9.5, 6.5 Hz, H-20), 2.41 (1H, dt, J 9.0, 7.0 Hz, H-12), 2.15-2.06 (2H, m, 2 x H-23), 1.87-1.72 (3H, m, H-18, H-16, 1 x H-15), 1.37 (3H, d, J 1.0 Hz, H-14'), 1.32 (1H, m, 1 x H-15), 1.16 (3H, d, J 7.0 Hz, H-10'), 1.02 (3H, t, J 7.5 Hz, H-24), 1.01 (3H, d, J 7.0 Hz, H-20'), 0.97 (3H, d, J 6.5 Hz, H-12'), 0.87 (3H, d, J 7.0 Hz, H-18'), 0.77 (3H, d, J 6.0 Hz, H-16'); <sup>13</sup>C nmr (100 MHz, CDCl<sub>3</sub>): δ 165.7, 157.7, 142.3,

133.3, 133.1, 132.9, 132.6, 130.4, 129.3, 128.1, 125.5, 123.9, 116.7, 116.4, 80.2, 79.6, 76.0, 67.4, 37.7, 36.9, 35.6, 35.3, 33.8, 33.3, 22.8, 20.9, 18.7, 18.2, 17.5, 14.5, 14.2, 8.6;  $m/z$  579  $[M+Na]^+$ , 539  $[M+H-H_2O]^+$ , 496, 478 (Found,  $[M+Na]^+$  579.3402,  $C_{32}H_{48}N_2O_6$  requires  $[M+Na]^+$  579.3405).

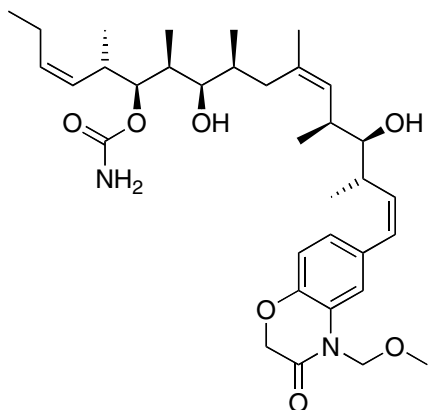
23,24-Dihydro-*N*-methyl-lactam (+)-**11**



$[\alpha]_D^{25} +76.0$  (c 0.20,  $CHCl_3$ ); IR ( $CHCl_3$ ) 3453, 3352, 2962, 2932, 2871, 1712, 1676, 1606, 1477, 1459, 1376, 1322, 1231, 1044, 969  $cm^{-1}$ ;  $^1H$  nmr (400 MHz,  $CDCl_3$ ):  $\delta$  7.02 (1H, d, J 1.5 Hz, H-6), 7.00 (1H, dd, J 8.0, 1.5 Hz, H-7a), 6.92 (1H, d, J 8.0 Hz, H-7b), 6.42 (1H, d, J 12.0 Hz, H-8), 5.60 (1H, dd, J 11.5, 10.5 Hz, H-9), 5.42 (1H, dt, J 11.0, 7.5 Hz, H-22), 5.26 (1H, dd, J 11.0, 10.0 Hz, H-21), 5.10 (1H, d, J 9.5 Hz, H-13), 4.71 (1H, dd, J 6.5, 4.5 Hz, H-19), 4.61 (2H, br s,  $NH_2$ ), 4.61 (2H, s,  $OCH_2CO$ ), 3.37 (3H, s,  $NCH_3$ ), 3.30 (1H, dd, J 6.0, 5.5 Hz, H-17), 3.19 (1H, t, J 5.5 Hz, H-11), 3.07 (1H, dt, J 10.5, 6.5 Hz, H-10), 2.82 (1H, m, H-20), 2.59 (1H, m, H-12), 2.13-2.00 (2H, m, 2 x H-23), 1.87-1.80 (3H, m, H-18, H-16, 1 x H-15), 1.63 (1H, m, 1 x H-15), 1.52 (3H, d, J 1.0 Hz, H-14'), 1.09 (3H, d, J 7.0 Hz, H-10'), 0.98 (3H, t, J 7.5 Hz, H-24), 0.96 (3H, d, J 6.5 Hz, H-12'), 0.95 (3H, d, J 7.0 Hz, H-20'), 0.90 (3H, d, J 7.0 Hz, H-18'), 0.79 (3H, d, J 6.0 Hz, H-16');  $^{13}C$  nmr (100 MHz,  $CDCl_3$ ):  $\delta$  164.6, 157.0, 143.9, 134.1, 133.8, 132.3 (2C), 130.4, 129.2, 129.1, 128.9, 124.1, 116.4, 115.3, 79.8, 78.9, 76.0, 67.6, 37.2, 35.7, 35.6, 34.2, 32.8, 29.7, 28.1, 23.1, 20.8, 18.1, 17.8, 16.3, 14.5, 13.8, 8.8;  $m/z$  593  $[M+Na]^+$ , 571  $[M+H]^+$ , 553  $[M+H-H_2O]^+$ , 510, 492 (Found,  $[M+Na]^+$  593.3565,  $C_{33}H_{50}N_2O_6$  requires  $[M+Na]^+$  593.3561).

23,24-Dihydro-*N*-methoxymethyl-lactam (+)-**12**





$[\alpha]_{21}^{589} +51.2$  (c 0.60,  $\text{CHCl}_3$ ); IR ( $\text{CH}_2\text{Cl}_2$ ) 3452, 3357, 2963, 2932, 2873, 1689, 1607, 1510, 1449, 1373, 1320, 1285, 1080, 1044, 971, 737  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.26 (1H, m, H-6), 7.03 (1H, dd, J 8.5, 2.0 Hz, H-7a), 6.93 (1H, d, J 8.5 Hz, H-7b), 6.41 (1H, d, J 12.0 Hz, H-8), 5.61 (1H, dd, J 11.5, 10.5 Hz, H-9), 5.42 (1H, dt, J 11.0, 7.0 Hz, H-22), 5.31 (2H, s, 2 x H-2), 5.27 (1H, dd, J 11.0, 10.0, H-21), 5.07 (1H, d, J 10.5 Hz, H-13), 4.70 (1H, dd, J 7.0, 4.5 Hz, H-19), 4.62 (2H,  $\text{NCH}_2\text{O}$ ), 4.59 (2H,  $\text{NH}_2$ ), 3.42 (3H, s,  $\text{OCH}_3$ ), 3.29 (1H, dd, J 6.5, 5.5 Hz, H-11), 3.19 (1H, br t, J 5.0 Hz, H-17), 3.04 (1H, dt, J 10.0, 6.5 Hz, H-10), 2.82 (1H, dt, J 10.0, 7.0 Hz, H-20), 2.56 (1H, dt, J 10.0, 6.5, Hz, H-12), 2.09-2.03 (2H, m, 2 x H-23), 1.90-1.81 (3H, H-18, H-16, 1 x H-15), 1.62 (1H, m, 1 x H-15), 1.52 (3H, d, J 1.0 Hz, H-14'), 1.10 (3H, d, J 6.5 Hz, H-10'), 0.98 (3H, t, J 7.5 Hz, H-24), 0.96 (3H, d, J 6.5 Hz, H-20' or H-12'), 0.94 (3H, d, J 6.5 Hz, H-20' or H-12'), 0.92 (3H, d, J 7.0 Hz, H-18'), 0.79 (3H, d, J 6.0 Hz, H-16');  $^{13}\text{C}$  nmr (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  165.5, 157.0, 143.8, 134.1, 133.6, 133.2, 132.6, 130.4, 129.4, 128.7, 127.9, 124.9, 116.5, 116.4, 79.8, 79.0, 76.2, 72.8, 67.6, 56.4, 37.2, 35.6 (3C), 34.2, 32.9, 23.1, 20.8, 17.9, 17.8, 16.2, 14.5, 13.8, 8.8;  $m/z$  623  $[\text{M}+\text{Na}]^+$ , 569, 506 (Found,  $[\text{M}+\text{Na}]^+$  623.3678,  $\text{C}_{34}\text{H}_{52}\text{N}_2\text{O}_7$  requires  $[\text{M}+\text{Na}]^+$  623.3667).