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Thalidomide metabolites and analogs. Part 2: Cyclic derivatives of 2-*N*-phthalimido-2*S*,3*S* (3-hydroxy) ornithine

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Abstract

E-(5-*N*-phthaloyl)-2-pentenoic acid benzyl ester was dihydroxylated by a Sharpless AD-mix protocol followed by mononosylation of the resultant 2*R*,3*S* diol. Azide displacement of the mononosylate followed by protection with the TBDMS group gave the ε-*N*-phthaloyl-substituted-β-*tert*-butyldimethylsilyloxy-α-azidocarboxylic acid benzylester. Hydrazinolysis resulted in removal of the phthalimide group with concomitant lactamization to the 4-silyloxy-3-azidopiperidinones. Staudinger reduction of the azidopiperidinones followed by *N*-phthaloylation and hydrolysis of the silyl group afforded the 4′-hydroxylated-6′-deoxythalidomide derivatives.

Keywords: amino acids and derivatives; azides; hydroxylation; imides; lactams.

The teratogenic and antiangiogenic properties of thalidomide (**1**) may be attributed to a prior metabolic activation step which produces hydroxylated derivatives of either the phthalimide or glutarimide rings.[1] The disposition of **1** and its hydroxylated analogs may also be traced through hydrolytic pathways in vivo which can operate to produce acyclic derivatives, namely the 2-*N*-phthalimidoglutamine, -isoglutamine, -glutamic acid and the carboxybenzamidic (phthalamic acid) derivatives of glutamine, isoglutamine and glutamic acid.[2] The tendency of thalidomide to racemize under physiological conditions[3] together with the sensitivity of the compound and its metabolites toward hydrolysis have complicated the task of identifying the active components and elucidating the pathway of their formation. Moreover, details regarding the molecular mechanism of thalidomide and its putative metabolites have remained elusive. Current studies in our laboratory have involved the synthesis of hydroxylated metabolites and analogs of thalidomide and its hydrolysis products[4] with a particular emphasis on two fronts: (1) stereoselective preparation of hydroxylated products of the glutarimide ring and their analogs; and (2) preparation of deoxygenated analogs in which a carbonyl has been removed from either the glutarimide ring or the phthalimide ring thereby enhancing the biological activity of the molecule as an angiogenesis inhibitor.[1b,5a]

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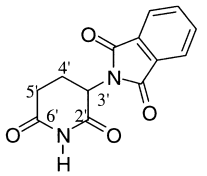
This letter details our progress in the synthesis of hydroxythalidomides **2** and **3**. Analog **2** is a putative metabolic product of 4′-oxidation of the glutarimide ring, or if considering the ultimate hydrolysis products, oxidation of the β-position of glutamine, isoglutamine or glutamic acid. We designed the synthesis of **2** to include the deoxygenated analog **3** since the piperidinone analogs, as in the case of the phthalimidine analog EM-12 (**4**),[5] may offer increased activity due to the resistance of the lactams to hydrolysis in vivo. As in the synthesis of 5′-hydroxythalidomide derivatives (**5**),[6] a subject of previous reports from our laboratory,[7,8] the common objective is the development and evaluation of methods for the stereoselective synthesis of β-and γ-hydroxylated α-amino acids and their derivatives.



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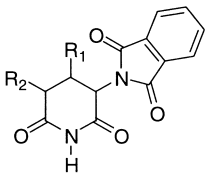
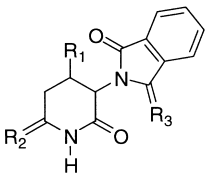
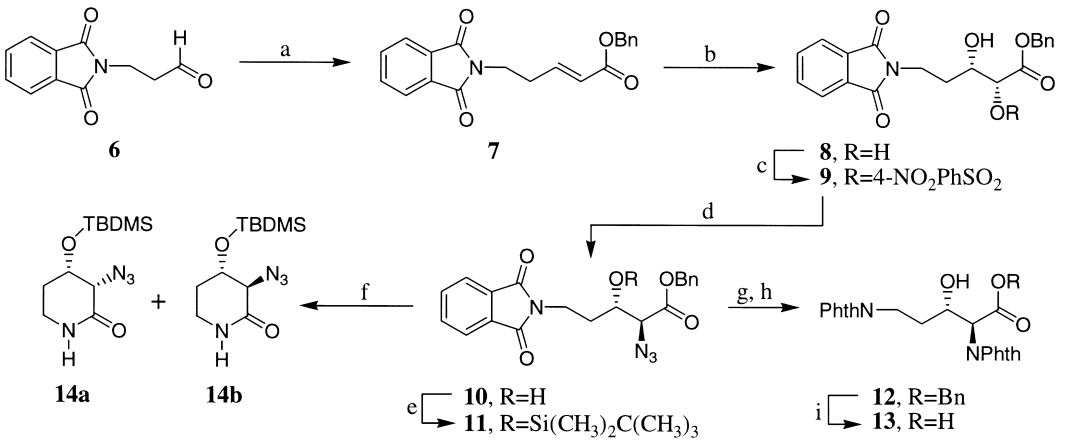


2, R_1=OH, R_2=H
5, R_1=H, R_2=OH



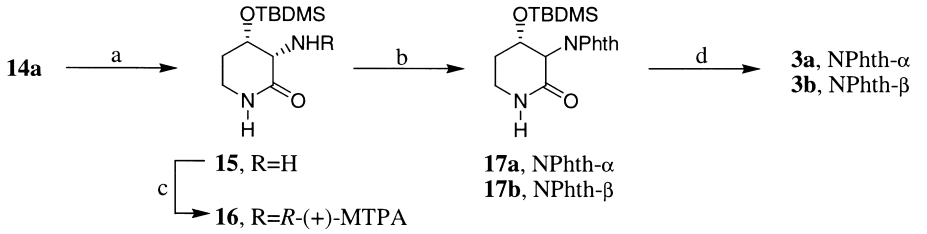
3, R_1=OH, R_2=H_2, R_3=O
4, R_1=H, R_2=O, R_3=H_2

Wittig olefination of 3-(*N*-phthalimido)propionaldehyde **6**[9] with (benzyloxycarbonylmethyl)-triphenylphosphonium bromide in the presence of NaOH/triethylamine in a two-phase system of dichloromethane/H_2O afforded the *E*-5-*N*-phthalimido-α,β-unsaturated benzyl ester **7**[10] in 99% yield (Scheme 1). Sharpless asymmetric dihydroxylation of α,β-unsaturated ester **7**[11] gave the 2*R*,3*S*-diol ester **8**[12] in 82% yield.[13] Azido ester **10** was prepared through a displacement of the sensitive nosylate **9** by a two-step sequence which did not necessitate rigorous purification of intermediate **9**. Treatment of diol ester **8** with 4-nitrobenzenesulfonyl chloride followed by rapid silica gel filtration (hexane/EtOAc) provided the sensitive α-nosyl ester **9** which was immediately exposed to sodium azide in dimethylformamide to afford the 2*S*,3*S*-*N*-phthalimido azido ester **10**.[14,15]



Scheme 1. Conditions: (a) $BnOCOCH_2PPh_3^+Br^-$, NaOH, Et_3N, CH_2Cl_2, H_2O, 12 h, rt (99%); (b) AD mix-α, $CH_3SO_2NH_2$, $(CH_3)_3COH$, H_2O, 48 h, 5°C (82%); (c) 4-NO_2PhSO_2Cl, pyr, CH_2Cl_2, 72 h, 5°C; (d) NaN_3/DMF, 12 h, 60°C (59% from **8**); (e) $(CH_3)_3C(CH_3)_2SiOSO_2CF_3$, 2,4,6-collidine, CH_2Cl_2, 12 h, 5°C (89%); (f) N_2H_4, EtOH, 12 h, rt (90%, **14a**:**14b** = 3:1); (g) PPh_3, THF, H_2O, 16 h, rt; (h) *o*-$C_6H_4(COCl)_2$, DMAP, CH_2Cl_2, 16 h, 0°C (53% from **10**); (i) H_2, Pd-C, EtOH, 7 atm, 72 h, rt (78%)

Staudinger reduction of the azido ester **10** followed by direct *N*-phthaloylation furnished the 2*S*,3*S*-bis-*N*-phthalimido-β-hydroxyester **12** (53% from **10**). Submission of **12** to catalytic hydrogenation with palladium on charcoal facilitated cleavage of the benzyl group thereby affording the bis-*N*-phthalimido-β-hydroxyornithine derivative **13** (78%) (Scheme 2).[16]



Scheme 2. Conditions: (a) PPh_3, CH_3CN, 12 h, rt; then H_2O, Et_3N, 5 h, rt (68%); (b) *o*-$C_6H_4(COCl)_2$, DMAP, CH_2Cl_2, 12 h, 0°C (99%); (c) *R*-(+)-MTPA-Cl, DMAP, CH_2Cl_2, 24 h, 0°C to rt; (d) TFA:H_2O (9:1), CH_2Cl_2, 3 h, 0°C to rt (70%)

The alcohol function of azido ester **10** was silylated with *tert*-butyldimethylsilyl triflate[17] to give the α-azido-β-silyloxy benzyl ester **11** (89%).[18] Hydrazinolysis of the benzyl ester **11** resulted in smooth removal of the phthalimide group and cyclization to provide the epimeric 3-azido-4-silyloxypiperidinones **14a**[19] and **14b** (90% in 3:1 ratio).[20] Staudinger reduction/hydrolysis converted the 3*S*,4*S*-3-azido-4-silyloxypiperidinone **14a** to the corresponding 3-amino-4-silyloxypiperidinone **15**[21] in 68% yield. The enantiomeric composition of the 3-amino-4-silyloxypiperidinone **15** was determined by Mosher amide analysis.[22] Treatment of **15** with *R*-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride provided the chromatographically homogeneous corresponding MTPA amide **16**. ^{19}F NMR analysis of **16** revealed >96% enantiomeric purity [δ 7.13 (major); δ 7.46 (minor), 470 MHz, $CDCl_3$/TFA]. Phthaloylation of the 3-amino-4-silyloxypiperidinone **15** proceeded smoothly to deliver the 6′-deoxy-4′-silyloxythalidomides **17a**[23] and **17b** (99%) as a mixture (**17a**:**17b** = 2:1) of epimers. Desilylation of **17a** and **17b** under acidic conditions[24] provided the 6′-deoxy-4′-hydroxythalidomides 2*S*,3*S*-**3a**[25] and 2*R*,3*S*-**3b** in 70% yield. The oxidation of the 4′-silyloxy-6′deoxythalidomides **17a** and **17b** at C-6′ to afford the corresponding glutarimides is currently under examination. The employment of peroxide/metal oxidants such as *tert*-butylhydroperoxide and Mn^{III}acac systems, although fruitful in many lactam to imide oxidations,[26] have been largely unsuccessful in our application. Recently, Takeuchi[27] has reported the oxidation of 3′-fluoro-6′-deoxythalidomide analog to the corresponding glutarimide using a ruthenium dioxide/metaperiodate system. These new results have given us impetus and encouragement in our pursuit of a suitable oxidation system for the silyloxylactam substrates. In summary we have detailed a novel route to β-hydroxyl-substituted 6′-deoxythalidomide analogs via the lactamization of a pivotal hydroxyornithine derivative. Prior to lactamization to the cycloornithine derivatives, a key functionalization was introduced using the Sharpless asymmetric dihydroxylation method.

References

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10. For **7**: IR (KBr) ν_{max} 3475, 3083, 2921, 2251, 1773, 1687, 1426 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.82–7.81 (m, 2H), 7.34–7.29 (m, 5H), 6.95 (dt, 1H, $J=15.7$, 7.0 Hz), 5.92 (dt, 1H, $J=15.7$, 0.7 Hz), 5.14 (s, 2H), 3.81 (t, 2H, $J=7.0$ Hz), 2.60 (dd, 2H, $J=7.0$, 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.1, 166.1, 144.8, 136.0 134.1, 132.0, 128.6, 128.2, 123.5, 123.4, 109.2, 66.2, 36.3, 31.3. HRMS (EI): calcd for $C_{20}H_{17}O_4$ [M^+]: 335.1157; found: 335.1170.
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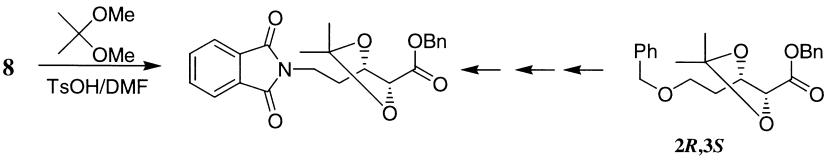
12. For **8**: $[\alpha]_D^{25}$ –29.2 ($c=1.08$, $CHCl_3$); IR (KBr) ν_{max} 3501, 3317, 2940, 2359, 2111, 1715, 1397 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) 7.84–7.82 (m, 2H), 7.72–7.70 (m, 2H), 7.32–7.24 (m, 5H), 5.24–5.19 (m, 2H), 4.12–4.07 (m, 1H), 3.95–3.88 (m, 2H), 3.86–3.78 (m, 1H), 3.04 (d, 1H, $J=11.2$ Hz), 2.88 (d, 1H, $J=7.4$ Hz), 2.4 (m, 1H), 1.88–1.85 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.8, 168.7, 134.1, 132.0, 128.6, 128.5, 128.4, 128.2, 123.4, 73.6, 69.7, 67.6, 34.6, 32.5. HRMS (EI): calcd for $C_{20}H_{19}O_6$ [M^+]: 369.1212; found: 369.1216.
13. Based on the Sharpless model for *E*-olefin enantioselectivity with AD mix-α, the configuration of diol **8** is assumed to be 2*R*,3*S*; however, low ee's have been reported in cases of ε-substituted-*E*-2-pentenoate esters (Ref. 11a) and *E*-olefins bearing carbamate substituents (Shirota, O.; Nakanishi, K.; Berova, N. *Tetrahedron* **1999**, *55*, 13643–13658). For purposes of relating absolute configuration, the isopropylidene derivative of **8** was prepared from the *O*-benzylbenzoate derivative of known (2*R*,3*S*) configuration: Maier, M. E.; Hermann, C. *Tetrahedron* **2000**, *56*, 557–561 (shown below) and the configuration of 2*R*,3*S*-**8** was confirmed. The enantioselectivity of the AD reaction as applied to ε-substituted-*E*-2-pentenoate benzyl esters has been under examination in these laboratories (Ref. 8a). These results will be reported in a separate communication with full experimental details.



14. Attempted derivatization of the β-hydroxyl function of **10**, for assay of chiral purity, with *R*-(+)-MTPA chloride (DMAP/CH_2Cl_2/0°C) resulted in facile elimination to the corresponding α,β-unsaturated ester (β-H, t, 6.23 δ, 500 MHz, $CDCl_3$). See Ref. 22 for the use of *R*-(+)-MTPA chloride.
15. For **10**: $[\alpha]_D^{25}$ –45.11 ($c=1.74$, $CHCl_3$); IR (Kbr) ν_{max} 3466, 3349, 2114, 1769, 1703, 1404, 1199 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.84–7.82 (m, 2H), 7.72–7.70 (m, 2H), 7.32–7.24 (m, 5H), 5.24–5.17 (m, 2H), 4.11–4.09 (m, 1H), 4.02–4.01 (d, 1H, $J=5.5$ Hz), 3.93–3.91 (br m, 1H), 3.82–3.82 (m, 2H), 1.86–1.83 (m, 2H); ^{13}C NMR ($CDCl_3$,

125 MHz) δ 172.8, 168.7, 134.1, 132.0, 128.6, 128.5, 128.4, 128.2, 123.4, 73.6, 69.7, 67.6, 34.6, 32.5. MS: [ES+] m/z 395.3 ([M+1], 100%).

16. Bis-phthalimide **13** was inactive when evaluated for inhibition of angiogenesis in the rat aortic ring and human aortic endothelial cell (HAEC) bioassays (see Ref. 1b).
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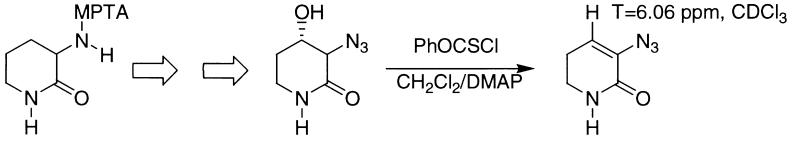
18. For **11**: $[\alpha]_D^{25}$ +8.28 ($c=1.98$, $CHCl_3$); IR (KBr) ν_{max} 3033, 2945, 2858, 2112, 1715, 1443, 1398, 775 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.82–7.80 (m, 2H), 7.70–7.67 (m, 2H), 7.33–7.28 (m, 5H), 5.28–5.11 (m, 2H), 4.19–4.14 (m, 1H), 3.81–3.75 (m, 1H), 3.73–3.66 (m, 1H), 2.08–1.99 (m, 1H), 1.91–1.84 (m, 1H), 0.88 (s, 9H), 0.12 (s, 3H), 0.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.8, 135.2, 134.2, 131.8, 128.8, 123.5, 72.2, 71.3, 67.9, 66.6, 64.6, 34.6, 32.0, 26.0, 18.0. MS: [ES+] m/z 509.4 ([M+1], 100%).
19. For **14a**: $[\alpha]_D^{25}$ –24.06 ($c=1.65$, $CHCl_3$); IR (KBr) ν_{max} 3350, 3311, 3199, 2929, 2247, 2105, 1680, 1255 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) 6.65 (br s, 1H), 4.27 (br m, 1H), 3.72 (d, 1H, $J=2.8$ Hz), 3.59–3.63 (m, 1H), 3.23–3.19 (m, 1H), 1.96 (m, 1H), 1.90 (m, 1H), 0.88 (s, 9H), 0.14 (s, 3H), 0.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.7, 68.4, 63.1, 37.7, 28.6, 25.7, 16.5, –5.0.
20. The hydrazinolysis of **11** to **14a**/**14b** is the most facile conversion of an ornithine derivative to the corresponding δ-valerolactam that we have observed. For example, see: Toshima, H.; Maru, K.; Saito, M.; Ichiara, A. *Tetrahedron* **1999**, *55*, 593–5808. Alternatively, the *N*-phthaloyl-3-azidoalcohol **10** could be lactamized with hydrazine to the corresponding 4-hydroxy-3-azidopiperidinone **18** (below); however, the yields of the cyclization and subsequent silylation of the hydroxyl group to afford **14a** and **14b** were lower. In addition, a remarkable tendency for the 4-hydroxy-3-azidopiperidinone to undergo elimination to the 2-azido-2,3-didehydrocyclo-ornithine **19** (Yonezowa, Y.; Hirosaki, T.; Hayashi, T.; Shin, C. *Synthesis* **2000**, *1*, 144–148) was observed when attempting thionoformylation (below) of the alcohol function (phenylthionochloroformate, DMAP, CH_2Cl_2, 0°C) en route to a *N*-*R*-(+)-MPTA-cycloornithine amide derivative **20**, by a Barton deoxygenation/reduction/MTPA amide derivatization sequence (shown retrosynthetically).



20 **18** **19**

21. For **15**: $[\alpha]_D^{25}$ +12.58 ($c=1.2$, $CHCl_3$); IR (KBr) ν_{max} 3246, 3202, 2973, 2960, 1672, 1488, 1255 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.65 (br s, 1H), 4.27–4.26 (br m, 1H), 3.72 (d, 1H, $J=2.8$ Hz), 3.56 (dt, 1H, $J=4.9$, 6.2, 16.0 Hz), 3.23–3.19 (m, 1H), 1.96–1.92 (m, 1H), 1.90–1.84 (m, 1H), 0.88 (s, 9H), 0.14 (s, 3H), 0.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.7, 68.4, 63.2, 37.7, 28.7, 25.8, 18.1, –5.0. MS: [ES+] m/z 245.3 ([M+1], 100%).
22. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem*. **1969**, *34*, 2543–2549.
23. For **17a**: $[\alpha]_D^{25}$+39.0 ($c=1.1$, $CHCl_3$); IR (KBr) ν_{max} 3219, 3098, 2956, 2860, 1772, 1715, 1687, 1393, 767 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.80 (br s, 2H), 7.67 (dd, 2H, $J=3.0$, 5.3 Hz), 6.79 (br s, 1H), 4.75 (d, 1H, $J=4.5$ Hz), 4.31–4.29 (m, 1H), 3.79–3.73 (m, 1H), 3.25–3.20 (m, 1H), 2.0–1.98 (m, 2H), 0.72 (s, 9H), –0.08 (s, 3H), –0.31 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.0, 134.1, 132.0, 123.4, 67.7, 57.4, 38.3, 32.0, 25.4, 17.6, –4.7, –5.2. MS: m/z 375 $[M]^+$ (82%), 145 (100%).
24. While *tetra*-*N*-butylammonium fluoride (TBAF) facilitated cleavage of the *tert*-butyldimethylsilyl (TBDMS) group, the quaternary ammonium by-products complicated the chromatographic purification of the 6′-deoxythalidomides **3a**/**3b** thereby necessitating the employment of the easily-removable TFA.
25. For **3a**: $[\alpha]_D^{25}$ +16.6 ($c=1.0$, MeOH); IR (KBr) ν_{max} 3346, 2930, 2860, 1713, 1666, 1399, 1082, 717 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.87 (br d, 2H, $J=3.0$ Hz), 7.83 (br d, $J=2.2$ Hz), 4.90 (d, 1H, $J=4.5$ Hz), 4.31 (m, 1H), 3.76–3.70 (m, 1H), 3.32–3.29 (m, 1H), 2.12–2.11 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.2, 169.5, 136.1, 135.5, 133.4, 124.3, 67.7, 58.5, 39.4, 31.9. MS: [ES+] m/z 261.3 ([M+1], 100%).
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