Pergamon

Tetrahedron Letters 41 (2000) 2275–2278

TETRAHEDRON LETTERS

Thalidomide metabolites. Part 1: Derivatives of (+)-2-(*N*-phthalimido)-γ-hydroxyglutamic acid

Frederick A. Luzzio,[a,*] Alexander V. Mayorov [a] and William D. Figg [b]

[a]*Department of Chemistry, University of Louisville, Louisville, Kentucky 40292, USA*
[b]*Medicine Branch, National Cancer Institute, Bethesda, Maryland 20892, USA*

Received 1 December 1999; accepted 15 January 2000

Abstract

A mild version of the Lemieux–Johnson olefin cleavage followed by a peroxide-mediated dialdehyde oxidation and esterification effected the conversion of 1-acyloxy-4-*N*-phthalimido-2-cyclopentenyl esters to γ-oxygenated-*N*-phthalimidoglutamic ester derivatives. © 2000 Elsevier Science Ltd. All rights reserved.

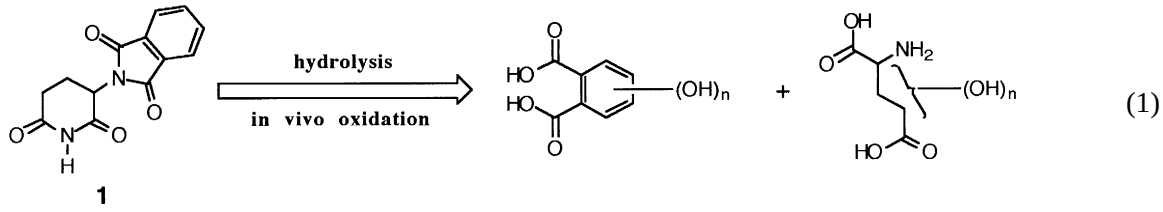
Keywords: amino acids and derivatives; cleavage reactions; imides; osmylation; oxidation.

A resurgence of interest has surrounded thalidomide **(1)**, the development of its analogs and the elucidation of its biological disposition in mammalian systems.[1] Metabolic oxidation of thalidomide and its hydrolysis products has been postulated as the pathway which produces the components responsible for its teratogenic and antiangiogenic effects.[2] Both the phthalimide and the glutarimide domains of **1** may be affected by putative oxidative and hydrolytic pathways in vivo which should ultimately yield hydroxylated derivatives of *o*-phthalic and glutamic acids (Eq. (1)). Intermediate products generated in the *hydrolytic* cascade of thalidomide are a result of partial hydrolysis of either the glutarimide ring or the phthalimide ring and include the *N*-phthaloyl derivatives of glutamine and isoglutamine (glutarimide hydrolysis) and the corresponding carboxybenzamidic acid derivatives of glutamine, isoglutamine and α-aminoglutarimide (phthalimide hydrolysis).[3] The complex hydrolytic pathway exhibited by **1** together with the propensity of **1** to racemize under physiological conditions[4] invokes a number of possible stages in the biological manifold for metabolic activation to occur. Current work in our laboratory has involved the stereospecific synthesis of β- and γ-hydroxy-2-*N*-phthalimido derivatives of glutamic acid and the corresponding γ-functionalized pentanoic acid derivatives with the long-term goal of preparing the putative metabolites of **1** and their analogs for biological evaluation.[5] Previous research in connection with either the natural availability or synthesis of γ-hydroxyglutamic acid, a plausible starting point for our requirements, and its derivatives has been sparse.[6] Moreover, the recent report by Stermitz which described the isolation of an arylamide derivative of L-*threo*-γ-hydroxyglutamic acid from *Justica*

* Corresponding author. Tel: (502) 852-7323; fax: (502) 852-8149; e-mail: faluzz01@athena.louisville.edu (F. A. Luzzio)

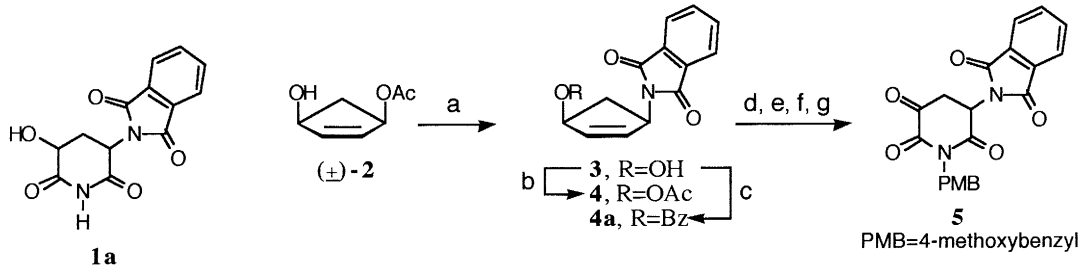
PII: S0040-4039(00)00160-X

ghiesbreghtiana[7] has added further impetus to our studies in the general area of hydroxylated amino acid synthesis. This letter details our progress in the stereospecific synthesis of 5′-hydroxythalidomide **1a**.[8]



1

Our initial studies utilized (±)-4-cyclopentene-1,3-diol-1-acetate **2**[9] (Scheme 1). The (±)-monoacetate **2** was phthalimidated under the conditions [$Pd(PPh_3)_4/PPh_3$/potassium phthalimide/THF/50°C/30 min] reported by Deardorff[10] thereby providing the (±)-*N*-phthalimido alcohol **3** as a crystalline solid in 69% yield. Acetylation of **3** with acetic anhydride/pyridine (rt/16 h) provided the (±)-1-acetoxy-4-*N*-phthalimido-2-cyclopentene **4** in quantitative yield after purification by flash-column chromatography on silica gel. Cyclopentenyl acetate **4** was then submitted to the following sequence of reactions without isolation of the intermediates (e.g., Scheme 1). Oxidative cleavage[11] of **4** with OsO_4/oxochromium-(VI) to the intermediate dicarboxylic acid (d); intermediate glutaric anhydride formation promoted by heating with acetic anhydride (e); intermediate glutamine/isoglutamine formation by reaction with 4-methoxybenzylamine (f);[12] and glutarimide cyclization promoted by heating with acetic anhydride (g). Rather than the expected γ-acetoxy-*N*-phthaloyl-*N*-PMB glutarimide, the γ-keto-*N*-phthaloyl-*N*-PMB glutarimide **5** was the major product isolated (8% overall). Presumably the γ-acetate had hydrolyzed during the oxidative cleavage and the resultant hydroxyl group suffered oxidation to give a ketoacid intermediate.



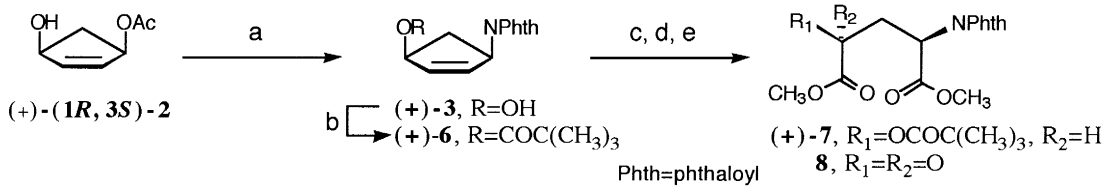
1a

Scheme 1. Conditions: (a) $Pd(PPh_3)_4$, PPh_3, potassium phthalimide, 50°C, THF, 30 min (69%); (b) Ac_2O, pyr, 16 h, rt (99%); (c) PhCOCl, DMAP, CH_2Cl_2, 0°C 1 h (94%); (d) CrO_3, H_2SO_4, OsO_4, acetone, H_2O, 15 h, rt; (e) Ac_2O, 2 h, 100–110°C; (f) 4-methoxybenzylamine, pyr, 4 h, 100–110°C; (g) Ac_2O, 2 h, 110–120°C (8% overall from **4**)

Several combinations/reagent systems composed of potassium metaperiodate/osmium tetraoxide/lead tetraacetate/potassium permanganate/silver oxide and chromium trioxide were used in attempts to mediate the mild oxidative cleavage of substrate **4** so an intermediate recognizable as the corresponding γ-acetoxy dialdehyde or the corresponding dicarboxylic acid may be isolated; however, most of these reagent systems gave intractable products or products in which there was evidence of hydrolysis of the acetoxy group and oxidation to the γ-keto function. The benzoate derivative **4a**, prepared under standard conditions (benzoyl chloride, DMAP, CH_2Cl_2, 0°C, 1 h) in 94% yield, responded in the same fashion as **4**.

In the enantiomeric series pivalate protection of (+)-**2** was explored and was a distinct improvement in response to the oxidative cleavage. By this expedient the intermediate *N*-phthalimidodicarboxylic acid could be isolated as the dimethyl ester (+)-**7** (Scheme 2). Phthalimidation of commercially available (+)-

(1*R*,3*S*)-4-cyclopentene-1,3-diol-1-acetate (+)-**2**, under similar conditions utilized for (±)-**2**, furnished the (+)-(1*S*, 4*R*)-*N*-phthalimido alcohol (+)-**3** as a crystalline solid in 74% yield after purification by flash-column chromatography on silica gel ($[\alpha]_D^{26}$ +253, *c*=1.06, $CHCl_3$). Treatment of (+)-**3** with pivaloyl chloride (DMAP, CH_2Cl_2)[13] for 2 h at 0°C provided the (+)-pivalate ester **6** as a white solid ($[\alpha]_D^{26}$ +100, *c*=1.27, $CHCl_3$) in 96% yield after purification by silica gel flash-column chromatography (hexanes:ethyl acetate, 3:1). The pivalate group of **6** appeared to be hardier to the conditions required for oxidative cleavage and further oxidation to the dicarboxylic acid. The optimal conditions for the cleavage of **6** were found to be osmium tetraoxide (cat.) with KIO_4 in glacial acetic acid (rt, 16 h).[14] The sensitive intermediate dialdehyde, detectable by TLC,[15] was not isolated but directly treated with peracetic acid (38% solution in aqueous acetic acid) for 4 h at 0°C and 32 h at room temperature to provide the intermediate carboxylic acid. As in the case of the intermediate dialdehyde, the dicarboxylic acid was not isolated but directly esterified with acetyl chloride (cat.) in methanol (rt, 12 h) which furnished the (+)-(2*R*, 4*S*)-diester **7** (63% from **6**) after purification by flash-column chromatography on silica gel (hexanes:ethyl acetate, 2:1) $[\alpha]_D^{26}$ +36 (*c*=1.39, $CHCl_3$).[16] Interestingly, replacing the OsO_4/KIO_4/peracetic acid/esterification sequence with $KMnO_4$ (AcOH, H_2O, 0°C, 2 h) resulted in a 46% isolated yield of diester (+)-**7** and ketodiester **8** [(+)-**7**:**8**, 1:1]. In summary, we have developed a straightforward stereospecific route to γ-oxygenated-*N*-phthalimidoglutamate derivatives based on the oxidative cleavage of intermediates procured by established functionalized cyclopentanoid chemistry.[17] The glutamates will provide access to the corresponding oxygenated *N*-phthalimidoglutarimide analogs for evaluation as metabolites and potential angiogenesis inhibitors.

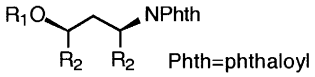


Scheme 2. Conditions: (a) $Pd(PPh_3)_4$, PPh_3, potassium phthalimide, THF, 50°C, 1 h (74%); (b) pivaloyl chloride, DMAP, CH_2Cl_2, 0°C, 2 h (96%); (c) OsO_4, KIO_4, AcOH, H_2O, rt, 16 h; (d) CH_3COOOH (38% in AcOH), AcOH, 0°C, 4 h/rt, 32 h; (e) CH_3OH, AcCl (cat.), 32 h, rt [63% from (+)-**6**]

References

1. Figg, W. D.; Reed, E.; Green, S.; Pluda, J. M. In *Antiangiogenic Agents in Cancer Chemotherapy*; Teicher, B. A., Ed.; Humana Press: New Jersey, 1999; pp. 407–422.
2. Bauer, K. S.; Dixon, S. C.; Figg, W. D. *Biochem. Pharmacol.* **1998**, *55*, 1827–1834. D' Amato, R. J.; Loughnan, M. S.; Flynn, E.; Folkman, J. *J. Proc. Nat. Acad. Sci. USA* **1994**, *91*, 4082–4085.
3. Schumacher, H.; Smith, R. L.; Williams, R. T. *Brit. J. Pharmacol.* **1965**, *25*, 338–351. Czeka, M. J.; Koch, H. P. *J. Chromatog. Biomed App.* **1987**, 413, 181–187.
4. Nishimura, K.; Hashimoto, Y.; Iwasaki, S. *Chem. Pharm. Bull.* **1994**, *42*, 1157–1159.
5. ORGN 164, 218th National Meeting, American Chemical Society, New Orleans, LA, August 23, 1999.
6. Lee, Y. K.; Kaneko, T. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 3494–3498. Kaneko, T.; Lee, Y. K.; Hanafusa, T. *Bull. Chem. Soc. Jpn.* **1962**, *35*, 875–878. Benoiton, L.; Winitz, M.; Birnbaum, S. M.; Greenstein, J. P. *J. Am. Chem. Soc.* **1957**, *79*, 6192–6198.
7. Lorenz, P.; Stermitz, F. R.; Ismail, L. D. *Phytochemistry* **1999**, *52*, 63–66.
8. Eriksson, T.; Björkman, S.; Roth, B. Björk, H.; Höglund, P. *J. Pharm. Pharmacol.* **1998**, 50, 1409–1416.
9. Monoacetate (±)-**2** is readily available on a multi-gram scale by photooxygenation of cyclopentadiene 450W/MeOH/78°C/1 h in the presence of rose bengal and thiourea followed by monoacetylation 1.1 equiv. Ac_2O/pyr/0°C/5 h): Kaneko, C.; Sugimoto, A.; Tanaka, S. *Synthesis* **1974**, 876–877.

10. Deardorff, D. R.; Linde, R. G.; Martin, A. M.; Shulman, M. J. *J. Org. Chem.* **1989**, *54*, 2759–2762.
11. Weinreb, S. M.; Henry, J. M. *J. Org. Chem.* **1993**, *58*, 4785.
12. Luzzio, F. A.; Piatt Zacherl, D.; Figg, W. D. *Tetrahedron Lett.* **1999**, *40*, 2087–2090.
13. Greene, T. W.; Wuts, P. W. *Protective Groups in Organic Synthesis*; 2nd ed.; Wiley: New York, 1991; pp. 98–99.
14. Pappo, R.; Allen Jr., D. S.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478–479.
15. Although the sensitive intermediate dialdehyde appeared to be somewhat stable to TLC detection during the oxidative cleavage, initial concentration prior to workup provided polymeric material thereby requiring an in situ oxidation protocol to provide the corresponding intermediate diacid.



R_1=pivaloyl
Dialdehyde, R_2=R_2=CHO
Dicarboxylic Acid, R_2=R_2=COOH

16. All compounds gave satisfactory spectral analyses (^{1}H NMR, ^{13}C NMR, FTIR, MS).
17. We thank Professor Donald R. Deardorff for helpful discussions and for the ^{1}H and ^{13}C spectra of (+)-**2**.