ORGANIC LETTERS

2006
Vol. 8, No. 24
5625−5628

Efficient Asymmetric Synthesis of Novel 4-Substituted and Configurationally Stable Analogues of Thalidomide

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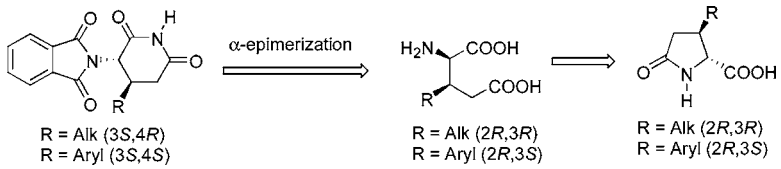
Received September 26, 2006

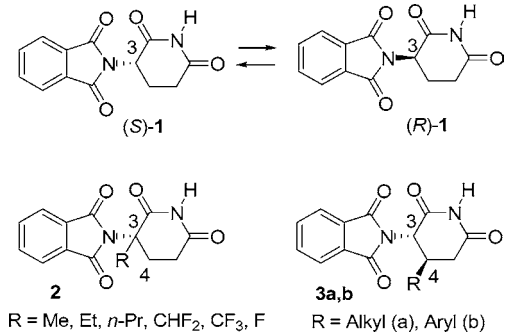
ABSTRACT



The preparation of new thalidomide derivatives 4-methyl-(3*S*,4*R*)-3a and 4-phenyl-(3*S*,4*S*)-3b starting from pyroglutamic acids (2*R*,3*R*)-7a and (2*R*,3*S*)-7b, possessing an inappropriate stereochemistry, was successfully realized due to stereochemically complete epimerization at the α-stereogenic center upon formation of the corresponding *N*-phthaloyl anhydrides 9a,b. The demonstrated conformational stability of these new thalidomide derivatives provides solid experimental evidence for practical feasibility of the approach described here to overcome the inherent problem of configurational instability of thalidomide by introducing an alkyl or aryl group in the C4 position.

Thalidomide (**1**) (Scheme 1) was marketed as a sedative in 1956. However, in 1961, it was withdrawn from the world market due to its serious side effects, i.e., teratogenic activity.[1] However, the recent decade has witnessed a true renaissance in interest in its broad biological activity. In particular, thalidomide (**1**) was reevaluated and attracted significant attention due to its selective inhibitory activity of tumor necrosis factor-α (TNF-a),[2] which is a clinically important activity against serious diseases such as rheumatoid arthritis, Crohn's disease, leprosy, AIDS, and various cancers.[3] The comeback of thalidomide to the legitimate status of a marketed drug came in 1998 when it received FDA approval for the treatment of erythema nodosum leprosum (ENL).[4]

Scheme 1



Thalidomide possesses a single chiral center and was used clinically as a racemate. It has been widely thought that the

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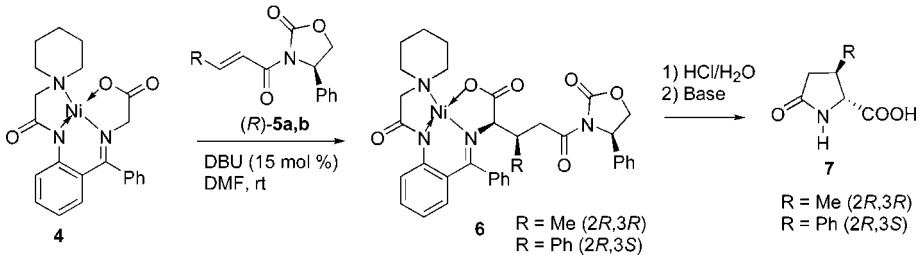
10.1021/ol0623668 CCC: $33.50
Published on Web 10/26/2006

Scheme 2



(*S*)-enantiomer exhibits the teratogenic activity and that the (*R*)-isomer is devoid of this side effect.[5] However, it remained uncertain which enantiomer exhibited the teratogenic effect because optically active thalidomide undergoes quite rapid racemization, via formation of the corresponding enolate, under physiological conditions ($T_{1/2}$ = 8 h at pH 7.1, 37 °C in water).[6] Therefore, it is generally recognized that this inherent configurational instability of thalidomide (**1**) plagues its potentially promising medicinal applications in cases where the use of a single enantiomer is required. As a response to this problem, the design and synthesis of configurationally stable analogues of thalidomide have recently been an important subject in organic and medicinal chemistry. In particular, to prevent the undesired racemization, an approach involving quaternization of the stereogenic center in thalidomide (**1**) was successfully realized. Thus, recently, several groups have reported the synthesis of optically stable thalidomide analogues **2** (Scheme 1) having a C3 substituent such as an alkyl group,[7] a fluoroalkyl group,[8] or a fluorine atom.[7a,9] On the other hand, a conceptually different appraoch that does not alter the geometry of the stereogenic center in thalidomide (**1**) can be realized by introducing a substituent in the β-position (C4). As one can expect, in the compounds **3** (Scheme 1), the stereogenic carbon at C3 might be configurationally stable as its epimerization will lead to the corresponding conformationally unfavorable and unstable cis derivative. However this geometrically alternative approach to stabilize the C3 stereogenic center in thalidomide (**1**) has never been explored.[10]

Here, we report an efficient asymmetric synthesis of 4-alkyl (Me)- (**3a**) and 4-aryl (Ph)- (**3b**) thalidomide derivatives and demonstrate their configurational stability. Our preliminary data convincingly suggest that introduction of a substituent in the β-position of thalidomide is a feasible and useful alternative approach to configurationally stable derivatives of this potent and multibiologically active drug.

Recently, we have developed an operationally convenient methodology for generalized asymmetric synthesis of various types of β-substituted pyroglutamic acids **7** (Scheme 2).[11] One of the methods involves highly diastereoselective, organic base catalyzed Michael addition of achiral glycine Schiff base derivatives **4**[11] with chiral (*R*)- or (*S*)-*N*-(*E*-enoyl)-4-phenyl-1,3-oxazolidine-2-one **5** to give addition products **6** as individual stereoisomers in quantitative chemical yields. Products **6** can be easily hydrolyzed under mild conditions and, upon a workup procedure, transformed to the pyroglutamic acids **7**. We envisioned that β-substituted pyroglutamic acids **7** can be appropriate precursors for the preparation of the corresponding derivatives of 4-substituted thalidomide **3**. However, considering the stereochemical requirements for β-substituted pyroglutamic acids as starting compounds for the preparation of 4-substituted thalidomides **3**, it became clear that the *trans*-pyroglutamic acids **7** available by our method are not stereochemically suitable (Figure 1). The corresponding *cis*-pyroglutamic acids **7**, possessing the correct stereochemistry, are unfortunately very difficult to prepare in optically pure form.[11f] On the other hand, considering our basic idea that cis-4-substituted thalidomides **3** might be conformationally unstable and taking into account that C−H acidity at C3 in 4-substituted **3** might be as high as in the unsubstituted thalidomide (**1**), we assumed that upon the corresponding glutarimide formation the phthalimide group at C3 would undergo epimerization giving rise to the target trans products **3**. On the basis of this stereochemical rationale, thalidomides **3a**,**b** containing 4-methyl and 4-phenyl groups, representing general alkyl and aryl groups, respectively, were chosen as the synthetic targets to examine their 3,4-trans stability and to facilitate their preliminary biological assay. To this end, diastereo- and enantiomerically pure β-substituted pyroglutamates **7a**,**b** and

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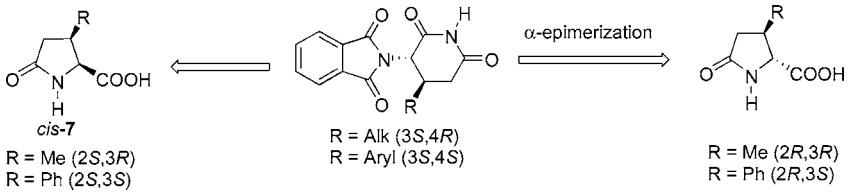


Figure 1. Synthetic approaches to trans-4-substituted thalidomides.

their enantiomers **ent-7a**,**b** (>98% ee) were prepared according to the procedure as shown in Scheme 2.

We chose the synthesis of β-phenyl thalidomide (**3b**) as the first target. Hydrolysis of pyroglutamic acid (2*R*,3*S*)-**7b** with 3 N HCl at reflux afforded (2*R*,3*S*)-3-phenylglutamic acid **8b** in high chemical yield.[12b] The next protocol, transformation of acid **8b** to *N*-phthaloyl anhydride **9b**, was a crucial step in our synthesis as we expected that at this point the corresponding *cis*-**9b** would undergo epimerization at the 3C stereogenic carbon giving rise to the desired *trans*-**9b**. Using the literature protocol,[13] we successfully transformed starting acid **8b** to *N*-phthaloyl anhydride **9b**, which was isolated as a single diastereomer in 67% (two steps) yield. To our delight, determination of the relative stereochemistry in the product **9b** revealed a 3,4-trans relationship, as was evident from the diastereomer (3*S*,4*S*)-**9b** ^{1}H NMR data (J_{3-4} = 12.6 Hz) and NOE experiments. Taking into account that the transformation of **8b** to **9b** is a multistep process, it is difficult to determine at which step the epimerization took place. However, considering the substantial increase in the C−H acidity of C3 in the step of the intermediate *N*-phthaloyl formation, the presence of pyridine, and the high reaction temperature, one can reasonably assume that the desired epimerization at C3 (3*R* to 3*S*) can occur before the cyclization step forming the anhydrate six-membered ring. It is important to note that not a trace of possible *cis*-**9b** was found in the reaction mixture.

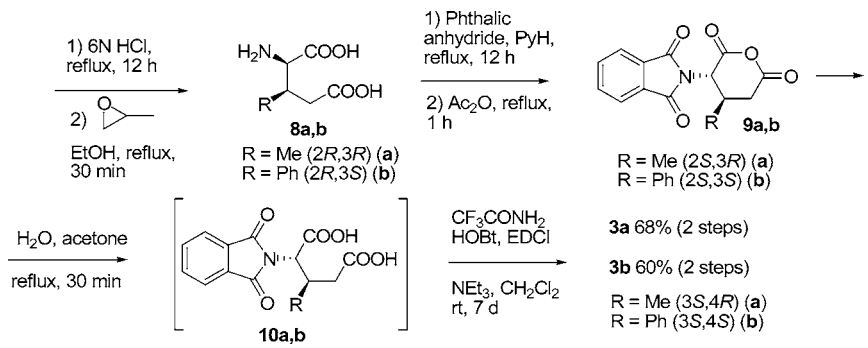
For the final transformation of enantio- and diastereomerically pure **9b** to the target 4-phenyl-substituted thalidomide **3b**, we decided to use a condensation reaction of the intermediate dicarboxylate **10b** with trifluoroacetoamide, reported by Galons et al.[14] After hydrolysis of anhydrate **9a** with water in acetone, the intermediate **10b** was smoothly transformed to (3*S*,4*S*)-**3b**, which was isolated in 68% yield (two steps). The target product (3*S*,4*S*)-**3b** was obtained as a single diastereomer with >98% ee that was evident from its ^{1}H NMR spectrum and chiral HPLC analysis.

With this developed synthetic procedure, we next applied it for the preparation of the alkyl derivative, (3*S*,4*R*)-4-methyl thalidomide **3a**. We found that under the same reaction conditions described for the preparation of **9b** from **7b** transformation of the starting pyroglutamic acid **7a** to **9a** can be conducted in a bit lower 51% overall yield. However, most importantly, the key epimerization at the C3 stereogenic center allows preparation of (3*S*,4*R*)-**3a** starting from (2*R*,3*R*)-**7a** and occurs cleanly and completely, as no cis-configured product was observed in the reaction mixture. The final transformation of **9a** to the target thalidomide **3a** was conducted in noticeably higher (68%) chemical yield as compared to that of the preparation of the 4-phenyl analogue **3b**.

To provide for the systematic study of biological activity of these new derivatives of thalidomide, the enantiomers of (3*S*,4*R*)-**3a** and (3*S*,4*S*)-**3b**, compounds (3*R*,4*S*)-**ent-3a** and (3*R*,4*R*)-**ent-3b**, were prepared according to Scheme 3 and starting from (2*S*,3*S*)-**7a** (2*S*,3*R*)-**7b**, respectively.

The successful and stereochemically complete transformation of (2*R*,3*R*)-**7a** to (3*S*,4*R*)-**3a** and of (2*R*,3*S*)-**7b** to (3*S*,4*S*)-**3b** has convincingly suggested that the thalidomide derivatives (3*S*,4*R*)-**3a** and (3*S*,4*S*)-**3a** are conformationally stable and that the corresponding cis analogues are strongly conformationally disfavored and were not observed in the reaction mixtures. Nevertheless, we decided to additionally examine the configurational stability at the C3 stereogenic

Scheme 3



carbon. To this end, thalidomide (3*S*,4*R*)-**3a** was subjected to deuterium incorporation experiments. Under the neutral or slightly acidic conditions (D_2O, rt, 24 h or 40 °C, 8 h; CD_3OD, 24 h; $CDCl_3$, D_2O, rt, 48 h), no deuterium atom was incorporated to the position C3. This result suggested that the substituent at C4 disfavored the corresponding enolization at C3, contrary to that of unsubstituted thalidomide (**1**). On the other hand, under the basic conditions (CD_3OD, catalytic amounts of Et_3N), C3-H was completely deuterated after 24 h. Formation of some decomposition products was observed under these basic conditions. However, not a trace of the corresponding 3,4-cis isomer was observed by ^1H NMR of the reaction mixture.

In summary, preparation of new thalidomide derivatives 4-methyl-(3*S*,4*R*)-**3a** and 4-phenyl-(3*S*,4*S*)-**3b** starting from pyroglutamic acids (2*R*,3*R*)-**7a** and (2*R*,3*S*)-**7b**, possessing an inappropriate stereochemistry, was successfully realized due to stereochemically complete epimerization at the α-stereogenic center upon formation of the corresponding *N*-phthaloyl anhydrides **9a**,**b**. The demonstrated conformational stability of these new thalidomide derivatives **3a**,**b** provides solid experimental evidence for practical feasibility of the approach described here to overcome the inherent problem of configurational instability of thalidomide. Considering the potent biological activity of thalidomide to various diseases, 4-substituted derivatives **3a**,**b** would be useful as lead compounds for medicinal chemistry. Several biological assays using **3a**,**b** are currently under investigation.

Acknowledgment. This work was supported by JSPS KAKENHI (No. 16201045 and 16073214) and a JSPS Grant from the Research for the Future Program (99L01204) and the Department of Chemistry and Biochemistry, the University of Oklahoma. V.A.S. gratefully acknowledges generous financial support from the Central Glass Company (Tokyo, Japan) and the Ajinomoto Company (Tokyo, Japan).

Supporting Information Available: Experimental Section including the general method and preparation and physical properties for **8a**, **9a**, **3a**, **8b**, **9b**, and **3b**; ^1H NMR of **9a**,**b** and **3a**,**b**; NOESY spectrum of **3b**; and HPLC spectra of **3a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0623668

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