ORGANIC LETTERS

2002
Vol. 4, No. 4
533−536

A β-Lactone Route to Chiral γ-Substituted α-Amino Acids: Application to the Concise Synthesis of (*S*)-α-Azidobutyro Lactone and a Natural Amino Acid

Reginald L. Tennyson,[†] Guillermo S. Cortez, Héctor J. Galicia, Charles R. Kreiman, Christina M. Thompson, and Daniel Romo*

Department of Chemistry, Texas A&M University, P.O. Box 30012, College Station, Texas 77842-3012

romo@mail.chem.tamu.edu

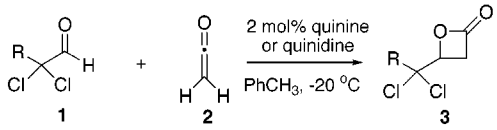
Received November 25, 2001

ABSTRACT

***β*-Lactones are useful synthetic intermediates allowing access to a number of functional arrays. In this report, enantiomerically pure 4-trichloromethyl-2-oxetanone is shown to be a versatile amino acid synthon leading to a variety of γ-substituted α-amino acid precursors. The utility of this methodology was demonstrated by the concise synthesis of a protected homoserine equivalent, α-azidobutyro lactone, and a naturally occurring α-amino acid from the seeds of *Blighia unijugata*.**

β-Lactones are versatile intermediates due to their inherent ring strain and reactivity in addition to their structural analogy to aldol products. Therefore, a renewed interest in their catalytic, asymmetric synthesis has recently occurred.[1] In the early 1980s, Wynberg and co-workers reported the first catalytic, asymmetric approach to β-lactones (Scheme 1).

Scheme 1. Wynberg's Catalytic, Asymmetric β-Lactone Synthesis



This chiral nucleophile-catalyzed process provides a concise approach to chlorinated β-lactones **3** including both enantiomers of 4-trichloromethyl-2-oxetanone (**3**, R = Cl). These compounds are commercially available at reasonable cost and are derived from chloral **1** (R = Cl) and ketene **2** using the cinchona alkaloids, quinidine and quinine, as nucleophilic catalysts.[2]

During our recent studies to expand the utility and scope of the Wynberg process, we developed a method for the use of in situ generated ketene in this process.[1c] In addition, we recently disclosed the first examples of the Wynberg process applied to nonactivated (i.e. non α-chlorinated) aldehydes

[†] Current address: Texas Biotechnology Corp., Houston, TX.

(1) (a) For a review describing routes to optically active β-lactones, see: Yang, H. W.; Romo, D. *Tetrahedron* **1999**, *51*, 6403−6434. (b) For more recent advances in this area, see: Nelson, S. G.; Peelen, T. J.; Wan, Z. *J. Am. Chem. Soc.* **1999**, *121*, 9742−9743. (c) Tennyson, R. L.; Romo, D. *J. Org. Chem.* **2000**, *65*, 7248−7252. (d) Evans, D. A.; Janey, J. M. *Org. Lett.* **2001**, *3*, 2125−2128. (e) Doyle, M. P.; May, E. J. *Synlett* **2001**, 967−969. (f) Cortez, G. S.; Tennyson, R. L.; Romo, D. *J. Am. Chem. Soc.* **2001**, *123*, 7945−7946. (g) Cortez, G. S.; Oh, S. H.; Romo, D. *Synthesis* **2001**, 1731−1736.

(2) Both (*R*)- and (*S*)-3-hydroxy-4,4,4-trichorobutyric-β-lactone (98% ee) are available from Aldrich ($3.12/g and $3.09/g, respectively, 2000−2001 catalog).

10.1021/ol017120b CCC: $22.00
Published on Web 01/24/2002

involving an intramolecular nucleophile catalyzed aldol-lactonization (NCAL) process.[1f,1g]

During the course of these former studies, we recognized that trichlorinated β-lactones **4** could serve as useful precursors to α-amino acids due to the masked trichoromethylcarbinol present in these systems (Figure 1). This is made possible by the procedure of Corey that allows conversion of optically active trichloromethylarbinols to the corresponding α-azido acids.[3] This process, involving treatment with sodium azide under basic conditions, is known to proceed with stereochemical inversion of the initial carbinol center. Thus, commercially available and relatively inexpensive (*R*)- or (*S*)-β-lactones **4** would allow convenient access to both enantiomers of the generalized amino acid synthon **5** that in turn would provide access to a varied array of γ-substituted α-amino acids **6**. The preparation of such synthons derived from enantiopure β-lactones **4** is the subject of this report. Furthermore, the utility of these synthons is demonstrated by concise syntheses of the versatile α-azidobutyro lactone **7**, a protected homoserine lactone, and the naturally occurring γ,δ-unsaturated amino acid **8** found in the seeds of the tropical plant *Blighia unijugata*.[4]

Aldehydes are versatile intermediates allowing conversion to a variety of functional arrays. Thus, we first developed an expedient synthesis of the protected trichloromethylcarbinol **11** bearing a pendant aldehyde (Scheme 2). After alcoholysis of the β-lactone,[5] we protected the trichloromethylcarbinol as the triethylsilyl ether **10**. This protecting group was found to be sufficiently stable for a variety of subsequent transformations but also readily removed before unmasking of the α-amino acid. Reduction to the aldehyde was accomplished with DIBAl-H and provided the aldehyde-containing amino acid synthon **11** in 96% overall yield from β-lactone **4**.

The aldehyde **11** was converted to the versatile vinyl iodide **12** (*E*/*Z*, 8:1) by the procedure of Takai (Scheme 3).[6] In addition, conversion to acetylene **13** was readily accomplished with the Seyferth−Gilbert reagent prepared by the procedure of Brisbois and Hoye.[7] These masked α-amino acid synthons are versatile substrates for a variety of useful transformations including several palladium-mediated reactions such as the Stille, Suzuki, and Sonogashira coupling reactions.

Other simple transformations led to highly versatile amino acid synthons (Scheme 4). For example, simple reduction of ester (*R*)-**10** gave the alcohol **14** useful for substitution reactions including the Mitsunobu coupling process. In addition, substitution gave the iodide **15** suitable for use as an electrophile or conversion to a variety of organometallic reagents.

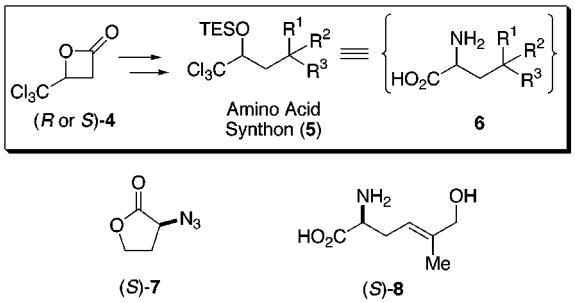
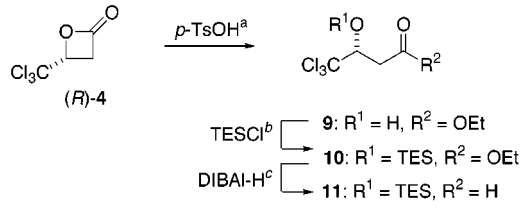


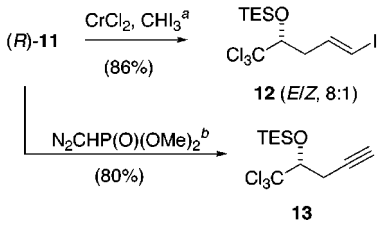
Figure 1. Structures of β-lactone precursors **4**, generalized amino acid synthons **5** and **6**, protected homoserine lactone **7**, and amino acid **8** from the seeds of *B. unijugata*.

Scheme 2. Conversion of β-Lactone (*R*)-**4** to the Versatile Aldehyde-Bearing α-Amino Acid Synthon **11**



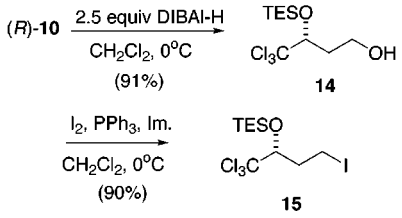
[a] EtOH, reflux (98%) (ref 5). [b]DMAP, Et_3N, CH_2Cl_2, 25 °C (99%). [c]1.15 equiv, CH_2Cl_2, −78 °C (99%).

Scheme 3. Conversion of Aldehyde **11** to a Vinyl Iodide and an Acetylene



[a] THF/dioxane (6:1), 0 → 25 °C. [b]KO-*t*-Bu, THF, −78 → 25 °C.

Scheme 4. Conversion of Ester **10** to Alcohol and Iodide-Bearing α-Amino Acid Synthons, **14** and **15**, Respectively

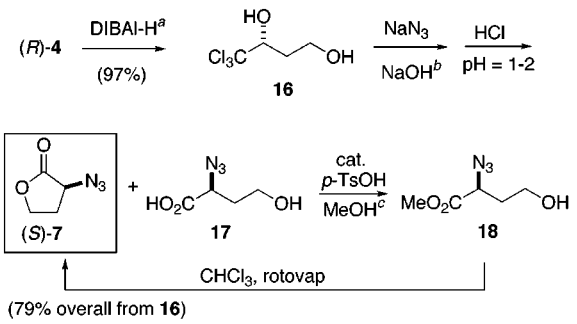


(3) Corey, E. J.; Link, J. O. *J. Am. Chem. Soc.* **1992**, *114*, 1906−1908.
(4) Fowden, L.; MacGibbon, C. M.; Mellon, F. A.; Sheppard, R. C. *Phytochem.* **1972**, *11*, 1105−1110.
(5) Song, C. E.; Lee, J. K.; Lee, S. H.; Lee, S. *Tetrahedron: Asymmetry* **1995**, *6*, 1063−1066.
(6) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408−7410.
(7) Brown, D. G.; Velthulsend, E. J.; Commerford; Brisbois, R.; Hoye, T. R. *J. Org. Chem.* **1996**, *61*, 2540−2541.

We also recognized that β-lactone **4** was a masked version of homoserine lactone, a rather expensive but highly versatile unnatural amino acid.[8] For example, Boc-homoserine lactone was recently employed by Danishefsky and co-workers in their synthesis of 15-aza-epothilones,[9] and this intermediate was also employed by workers at Lilly for the large scale synthesis of the antibiotic nocardicin A.[10] In addition, Berkowitz has shown that Boc-homoserine lactone is a useful precursor to α-vinylglycine.[11]

Thus, we developed an expedient three-step conversion of β-lactone **4** to azido lactone **7**,[12] a direct precursor of homoserine lactone. This entailed reduction of β-lactone **4** to the diol **16** by the procedure of Fujisawa (Scheme 5).[13]

Scheme 5. Concise Synthesis of the Protected Homoserine Synthon, (*S*)-α-Azidobutyrolactone **7**, from (*R*)-β-Lactone **4**



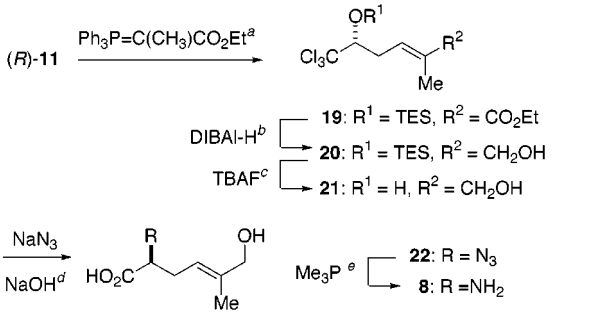
[a] CH_2Cl_2, 25 °C (ref 13). [b]DME/H_2O (4:1), 25 °C. [c]60−65 °C.

Subjecting this diol to Corey's conditions led to conversion to the azido carboxylate and acidification gave a 2:1 mixture of azido lactone **7** and azido acid **17**. Refluxing this mixture with *p*-TsOH in benzene/acetonitrile with a Dean−Stark trap effected complete conversion to the azido lactone; however, this sequence resulted in partial epimerization as the lactone was found to be only 34% ee by chiral GC analysis.

To determine at which point in the sequence racemization was occurring, the azido lactone **7** was isolated after its initial formation upon careful acidification of the crude reaction mixture to pH ∼4. At this stage the α-azido lactone **7** was determined to be 93% ee, indicating that the majority of racemization was occurring during further acidification and subsequent heating to promote complete cyclization. After some experimentation, conditions that minimized racemization were identified for effecting complete conversion to the azidolactone **7**. This entailed careful acidification of the crude mixture of azido lactone **7** and azido acid **17** to pH ∼1−2 followed by gentle heating in methanol to give methyl ester **18** and also promote further conversion to the azido lactone **7**. Complete cyclization to the azido lactone was accomplished upon removal of MeOH from the reaction mixture and successive cycles of $CHCl_3$ addition and removal in vacuo to remove final traces of MeOH. In this way, the azido lactone **7**, obtained in 79% overall yield from diol **16** (31.0 mmol scale), was found to be 93% ee (chiral GC), indicating that under these conditions epimerization is minimal (∼2.5%). Thus, this three-step, two-pot procedure represents a highly efficient and economical approach toward both optical antipodes of α-azidobutyrolactone **7** from commercially available (*R*)- and (*S*)-β-lactones **4**.

To further demonstrate the utility of these synthons for amino acid synthesis, we targeted the total synthesis of α-amino acid **8** isolated from the seeds of the tropical plant *Blighia unijugata*.[4] The synthesis commenced with Wittig olefination of aldehyde (*R*)-**11** (Scheme 6). Reduction

Scheme 6. Enantioselective Synthesis of α-Amino Acid **8** from *B. unijugata* Employing Amino Acid Synthon **11**



[a] PhH, 25 °C (84%). [b]2.2 equiv, CH_2Cl_2, 0 °C (99%). [c]THF, 0 °C (97%). [d]DME/H_2O (1:4), 25 °C (80%). [e]THF, 25 °C (43%).

followed by deprotection of silyl ether **20** gave diol **21**. Conversion to the azido acid **22** was smoothly effected by employing Corey's conditions, and subsequent reduction of the azide with Me_3P gave amino acid **8** in 43% yield after silica gel chromatography (20% H_2O/CH_3CN). Spectral data matched that previously reported for this naturally occurring amino acid. However, since an optical rotation value was not reported for the natural product, we are unable to assign the absolute configuration.

In summary, we have shown that (*R*)- and (*S*)-4-trichloromethyl-β-lactones **4** are useful precursors to a variety of amino acid synthons. This process should be readily extended to the commercially available (*R*)- and (*S*)-4-trichloromethyl-4-methyl oxetanones leading to γ-substituted-α-methyl-α-amino acids. Importantly, the amino acid functionality is masked as a protected trichloromethylcarbinol throughout the sequence and is readily unveiled under very mild conditions. Thus, these synthons are particularly useful since the need for protections and deprotections of the amino acid are avoided. The described methodology should find utility

(8) Both (*R*)- and (*S*)-homoserine are available from Aldrich at high cost ($208/g and $50/g, respectively, 2000−2001 catalog).

(9) Stachel, S. J.; Lee, C. B.; Spassova, M.; Chappell, M. D.; Bornmann, W. G.; Danishefsky, S. J.; Chou, T.-C.; Guan, Y. *J. Org. Chem.* **2001**, *66*, 4369−4378.

(10) Cooper, R. D. G.; Jose, F.; McShane, L.; Koppel, G. A. *Tetrahedron Lett.* **1978**, 2243−2246.

(11) Berkowitz, D. B.; Smith, M. K. *Synthesis* **1996**, 39−41.

(12) For a previous synthesis of optically active azido lactone **7** via resolution, see: Davis, M.; Dudman, N. P. B.; White, H. F. *Aust. J. Chem.* **1985**, *38*, 621−624.

(13) Fujisawa, T.; Ito, T. Nishiura, S.; Shimizu, M. *Tetrahedron Lett.* **1998**, *39*, 9735−9738.

for the expedient and simplified synthesis of γ-substituted-α-amino acids and derivatives.

Acknowledgment. We thank the Robert A. Welch Foundation (A-1280), Zeneca Pharmaceuticals, and the NIH (postdoctoral supplement to G.S.C., GM52964-06) for support of these investigations. D.R. is an Alfred P. Sloan Fellow and a Camille-Henry Dreyfus Teacher-Scholar. H.J.G. was a summer undergraduate research participant supported by the Department of Chemistry, the College of Science and Office of Graduate Studies (Texas A&M). Charles R. Kreiman and Christina M. Thompson are Texas A&M undergraduate research participants. The NSF (CHE-0077917) provided funds for purchase of NMR instrumentation.

Supporting Information Available: Selected experimental procedures and characterization data (including ^{1}H NMR spectra) for compounds **7**−**15**, **19**, and **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL017120B