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Synthesis of Cyclopropene α-Amino Acids via Enantioselective Desymmetrization

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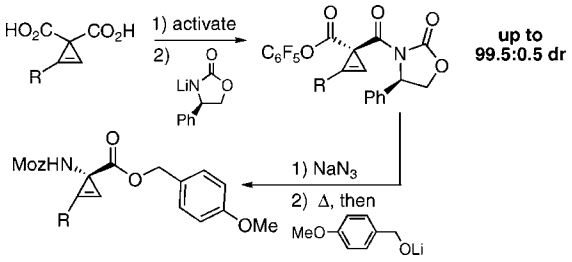
ABSTRACT



The preparation of cyclopropene α-amino acids via the enantioselective desymmetrization of cyclopropene bis-carboxylic acid derivatives is described. The amino acids are stable to harsh reaction conditions, and a derivative has been incorporated into a tripeptide using conventional methods for peptide synthesis.

Small ring analogues of amino acids allow peptide structures to be tuned with exquisite precision because they provide exact control over the orientation of side chains with a minimal change to the remaining structure.[1,2] Despite their geometrical niche for aligning the side chains ~90° relative to the main chain, the chemistry of cyclopropene amino acids is not well developed.[3] In the only report on enantiomerically enriched cyclopropene α-amino acids, Schöllkopf used his elegant bis-lactim ether methodology to access several cyclopropene analogues of phenylalanine.[3a] However, that method has not been extended to other side chains, and cyclopropene α-amino acids have never been incorporated into peptides. We therefore considered a new method that would make these valuable components more broadly available.

Described herein is a concise and highly enantioselective synthesis of cyclopropene α-amino acids (Scheme 1). The key step is the desymmetrization of malonate-derived cyclopropene bis-carboxylic acids. Furthermore, it is demonstrated that cyclopropene α-amino acids and their precursors are stable in the presence of many harsh reagents (e.g., TFA, ethanolic KOH) and can be incorporated into synthetic peptides using conventional coupling strategies.

Chiral oxazolidinones are powerful tools for asymmetric synthesis.[4] In recent years, elegant studies from the labs of Davies, Eames, and Fukuzawa have shown oxazolidinones

(1) (a) Salaun, J. *Top. Curr. Chem.* **2000**, *207*, 1. (b) Stammer, C. H. *Tetrahedron* **1990**, *46*, 2231. (c) Gnad, F.; Reiser, O. *Chem. Rev.* **2003**, *103*, 1603.

(2) Lead examples of secondary structures that are stabilized by cyclopropane α-amino acids: (a) Burgess, K.; Ho, K.-K.; Pettitt, B. M. *J. Am. Chem. Soc.* **1994**, *116*, 799. (b) Burgess, K.; Ho, K.-K.; Pettitt, B. M. *J. Am. Chem. Soc.* **1995**, *117*, 54. (c) Burgess, K.; Ho, K.-K.; Pal, B. *J. Am. Chem. Soc.* **1995**, *117*, 3808. (d) Burgess, K.; Ke, C.-Y. *J. Org. Chem.* **1996**, *61*, 8627. (e) Moye-Sherman, D.; Jin, S.; Li, S.; Welch, M. B.; Reibenspies, J.; Burgess, K. *Chem. Eur. J.* **1999**, *5*, 2730. (f) Jiménez, A. I.; Ballano, G.; Cativiela, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 396. (g) Jiménez, A. I.; Cativiela, C.; Aubry, A.; Marraud, M. *J. Am. Chem. Soc.* **1998**, *120*, 9452.

(3) Cyclopropene α-amino acids: (a) Schöllkopf, U.; Hupfeld, B.; Küper, S.; Egert, E.; Dyrbusch, M. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 433. (b) Wheeler, T. N.; Ray, J. *J. Org. Chem.* **1987**, *52*, 4875. (c) McGregor, S. D.; Jones, W. M. *J. Am. Chem. Soc.* **1968**, *90*, 123. (d) Domnin, I. N.; Zhuravleva, E. F.; Komendantov, M. I.; Ritari, A. É. *Zh. Org. Khim.* **1977**, *13*, 1789; *J. Org. Chem. USSR* **1977**, *13*, 1656. For the synthesis of cyclopropene γ-amino acids, see: (e) Müller, P.; Imogaï, H. *Tetrahedron: Asymmetry* **1998**, *9*, 4419.

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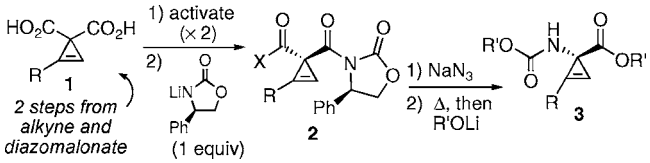
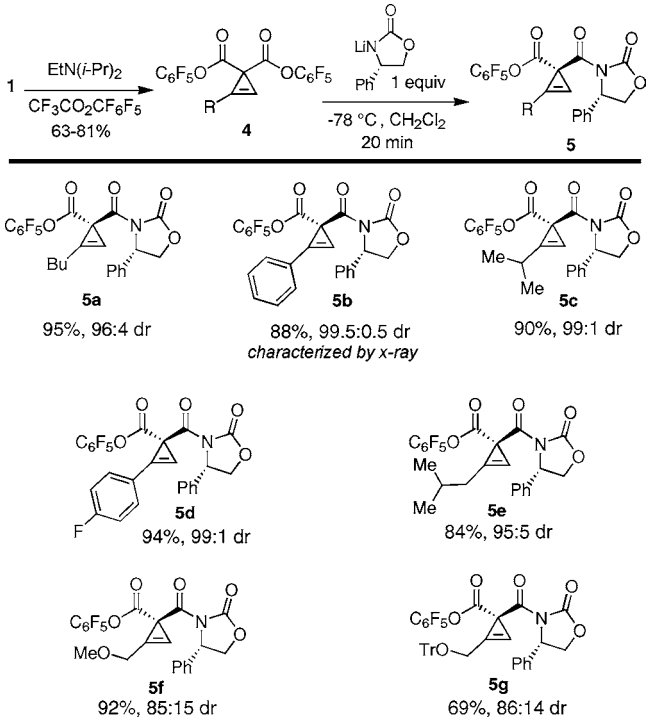
Scheme 1. Enantioselective Desymmetrization Approach to Cyclopropene α-Amino Acids



to be useful tools for the kinetic resolution of chiral carboxylic acid derivatives.[5] We recently described a parallel kinetic resolution strategy for resolving cyclopropene carboxylic acids as quasienantiomeric *N*-acyloxazolidinones.[6] Given the generality of the kinetic resolution, we envisioned the enantioselective desymmetrization[7] approach to nonracemic cyclopropene α-amino acid derivatives **3** shown in Scheme 1. Thus, activation of both acid functions of **1** followed by desymmetrization would provide enantiomerically enriched **2**. A second acyl transfer with azide, subsequent Curtius rearrangement[8] and alcoholysis would provide protected amino acid **3**. This approach would have virtue because it is short and uses an inexpensive[9] oxazolidinone as the source of asymmetry and because diverse types of prochiral cyclopropenes **1** are readily available on large scale from the Rh-catalyzed addition of diazomalonate to alkynes.[10]

It is shown here that high enantioselectivity can indeed be realized by the desymmetrization of bis-pentafluorophenylesters **4**, substances that are available in one step from their corresponding diacids (**1**).[11] Under optimal conditions,[12] bis-pentafluorophenylester **4** is combined with the Li-salt of 4-phenyloxazolidinone at −78 °C in CH_2Cl_2. These conditions were applied for the preparation of a series of derivatives with structure **5** as shown in Scheme 2. High

Scheme 2. Enantioselective Desymmetrization of Bis-pentafluorophenylesters



diastereomer ratios were observed for a range of side chain functionalites. Particularly high selectivities were observed for the phenylalanine analogue **5b** (dr 99.5:0.5), the *p*-fluorophenylalanine analogue **5d** (dr 99:1), and the leucine analogue **5c** (dr 99:1). In each case, the major diastereomer could easily be separated from the minor diastereomer by column chromatography.

Having demonstrated the generality of the enantioselective desymmetrization, we sought to establish a short sequence by which enantiomerically enriched cyclopropenes **5** could be converted into protected amino acids. This was demonstrated for **5a** and **5b** as shown in Scheme 3. Thus, acyl azides **6a** and **6b** were produced in excellent yield upon treatment with NaN_3 and catalytic DMAP in wet THF. Curtius rerrangement and subsequent ester and carbamate formation with *p*-methoxybenzyl alcohol gave the protected amino acids **7a** and **7b**. The modest yields of derivatives **7** from **6** should be considered in the context that three distinct transformations (Curtius rearrangement, ester formation, carbamate formation) take place with only one purification. Multigram quantities of **7a** were prepared by this method, and (4*S*)-4-phenyloxazolidione could be recovered in 75% yield. It is also pointed out that *p*-methoxybenzyl alcohol

(4) (a) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737. (b) Ager, D. J.; Prakash, I.; Schaad, D. R. *Aldrichimica Acta* **1997**, *30*, 3.

(5) (a) Bew, S. P.; Davies, S. G.; Fukuzawa, S.-i. *Chirality* **2000**, *12*, 483. (b) Coumbarides, G. S.; Dingjan, M.; Eames, J.; Flinn, A.; Motevalli, M.; Northen, J.; Yohannes, Y. *Synlett* **2006**, 101. (c) Coumbarides, G. S.; Eames, J.; Flinn, A.; Northen, J.; Yohannes, Y. *Tetrahedron Lett.* **2005**, *46*, 849. (d) Coumbarides, G. S.; Dingjan, M.; Eames, J.; Flinn, A.; Northen, J.; Yohannes, Y. *Tetrahedron Lett.* **2005**, *46*, 2897. (e) Fukuzawa, S.-i.; Chino, Y.; Yokoyama, Y. *Tetrahedron: Asymmetry* **2002**, *13*, 1645. For examples of asymmetric acyl transfer reactions in which oxazolidiones or oxazolidinethiones are leaving groups, see: (f) Notte, G. T.; Sammakia, T. *J. Am. Chem. Soc.* **2006**, *128*, 4230. (g) Nagao, Y.; Inoue, T.; Hashimoto, K.; Hagiwara, Y.; Ochiai, M.; Fujita, E. *J. Chem. Soc., Chem. Commun.* **1985**, 1419. (h) Hashimoto, N.; Ishizuka, T.; Kunieda, T. *Tetrahedron Lett.* **1998**, *39*, 6317.

(6) (a) Liao, L.-a.; Zhang, F.; Dmitrenko, O.; Bach, R. D.; Fox, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 4490. For an earlier study in which cyclopropene carboxylic acids were resolved via their *N*-acyloxazolidinones, see: (b) Liao, L.-a.; Zhang, F.; Yan, N.; Golen, J. A.; Fox, J. M. *Tetrahedron* **2004**, *60*, 1803.

(7) (a) Willis, M. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1765−1784. Enzymatic desymmetrization: (b) Schoffers, E.; Golebiowski, A.; Johnson, C. R. *Tetrahedron* **1996**, *52*, 3769.

(8) The Curtius rearrangment has been applied to the synthesis of the parent cyclopropene amino acid. See ref 3b.

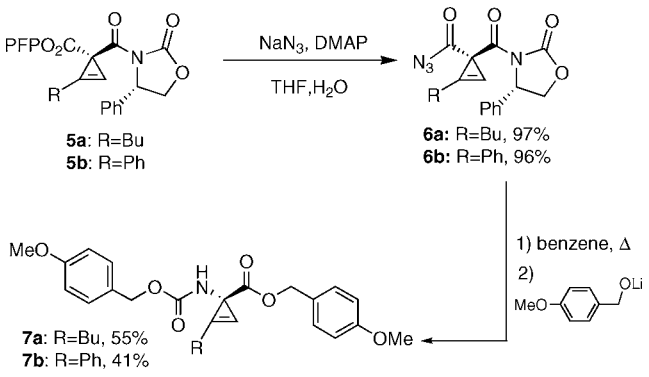
(9) (*S*)-4-Phenyloxazolidinone costs less than $1/g when purchased by the kilogram (Chemicrea Inc, Tokyo, Japan).

(10) See ref 6b and (a) Muller, P.; Granicher, C. *Helv. Chim. Acta* **1993**, *76*, 521. (b) Rubina, M.; Rubin, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2003**, *125*, 7198. (c) Rubin, M.; Gevorgyan, V. *Synthesis* **2004**, 796.

(11) Bis-pentafluorophenylesters were prepared from the corresponding diacids and $CF_3CO_2C_6F_5$. See: Green, M.; Berman, J. *Tetrahedron Lett.* **1990**, *31*, 5851.

(12) Desymmetrization reactions with the bis-acid chloride or bis-ethylcarbonic anhydride of **1** proceeded in very low dr (<2:1). Our efforts to prepare the mixed anhydride of **1** from either *t*-BuCOCl or 1-adamantoyl chloride were unsuccessful. The products of attempted mixed anhydride formation had extremely broad ^{1}H NMR spectra, a possible indication that the materials were polymeric.

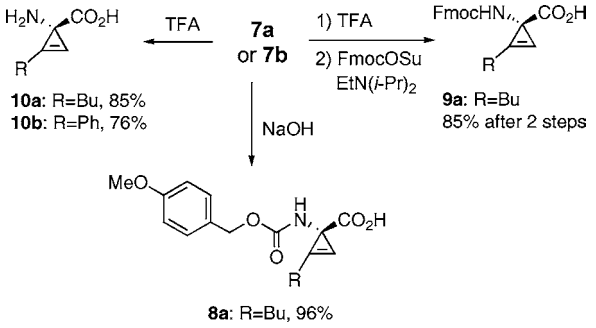
Scheme 3. Synthesis of Protected Cyclopropene α-Amino Acids



was more efficient than *t*-BuOH in trapping the sterically encumbered tertiary isocyanate. Subsequent reactivity parallels Boc chemistry, as Moz[13] carbamates cleave under acidic conditions similar to those used to cleave Boc carbamates.[13]

The bis-*p*-methoxybenzyl-protected cyclopropenes **7** serve as intermediates to a number of useful amino acid derivatives. Thus, the free amino acids **10a** and **10b** were obtained upon simple treatment with 20% TFA in CH_2Cl_2 (Scheme 4).

Scheme 4. Synthesis of Cyclopropene α-Amino Acid Derivatives

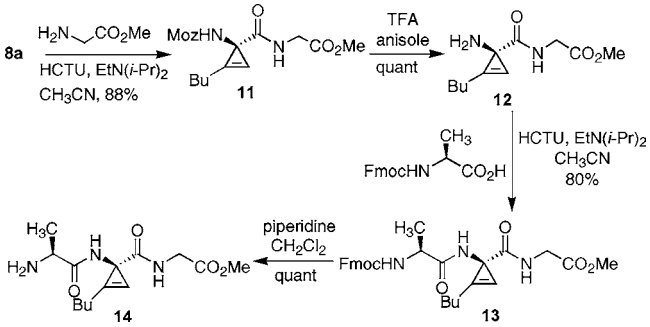


Furthermore, the Fmoc-protected amino acid **9a** was obtained upon sequential treatment of **7a** with TFA and FmocOSu, and the Moz[13]-protected amino acid **8a** was obtained upon saponification of **7a**.

Because of the strain that is inherent to cyclopropenes,[14] there was concern that cyclopropene α-amino acids might be too reactive for applications. Wheeler and Ray had earlier prepared the parent cyclopropene α-amino acid by deprotection of the Boc-protected acid but noted that they were unable to prepare analogues bearing alkyl substituents on the cyclopropene ring.[3b] Schöllkopf prepared methyl 1-amino-2-phenylcyclopropene-1-carboxylate via hydrolysis of the corresponding bis-lactim ether under relatively mild conditions (0.1 M HCl, rt).[3a] However, in a prior study on a cyclopropene γ-amino acid,[3e] protecting group manipulation presented major difficulties. Ultimately, deprotection of a Teoc derivative with TBAF was successful, but alternative strategies (e.g., TFA cleavage of a Boc derivative) were very low yielding.[3e]

Given the uncertainity surrounding the stability of cyclopropene amino acid dervatives, it was notable that the derivatives in Scheme 4 are tolerant of harsh conditions (i.e., KOH/MeOH, 20% TFA in CH_2Cl_2). The residues are also compatible with commonly used conditions for peptide synthesis. Thus, it was possible to incorporate **8a** into tripeptide **14** using HCTU-mediated peptide bond-forming reactions (Scheme 5). A reaction sequence was specifically

Scheme 5. Incorporation of a Cyclopropene α-Amino Acid into a Peptide



chosen to demonstrate compatibility both with piperidine-mediated deprotection of a Fmoc group and with TFA/anisole-mediated deprotection of the Moz group. The latter conditions are also commonly used in the removal of Boc protecting groups.

The sense of asymmetric induction for the formation of **5b** is the reverse of that observed in the parallel kinetic resolution of 1,2-diphenylcycloprop-2-ene-1-carboxylic acid.[6a,15] The major difference in the two procedures is that carboxylic acids were activated as mixed anhydrides in the kinetic resolution, whereas the bis-carboxylic acids in the present study were activated as their pentafluorophenyl esters. In an earlier computational study at the B3LYP/6-31+G(d,p) level of theory,[6a,16] we proposed a transition state for the kinetic resolution in which the carbonyl oxygens of the oxazolidinone and the carboxylate leaving group formed a chelate to the lithium counterion. As the pentafluorophenyl esters cannot form such a chelate, it seems reasonable that the sense of asymmetric induction would differ. Unfortunately, efforts to prepare the mixed anhydrides from **1** and either pivaloyl chloride or 1-adamantoyl chloride were unsuccessful,[12] so a

(13) Moz = *p*-methoxybenzylcarbamate. For cleavage of Moz esters, see: (a) Weygand, F.; Hunger, K. *Chem. Ber.* **1962**, *95*, 1. (b) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3nd ed.; Wiley: New York, 1999; pp 537−538.

(14) (a) Bach, R. D.; Dmitrenko, O. *J. Am. Chem. Soc.* **2004**, *126*, 4444. (b) Wiberg, K. B. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 312.

(15) (4*S*)-4-Phenyl-3-[(1*S*)-1,2-diphenylcycloprop-2-en-1-oyl]oxazolidinone is formed preferentially in the reaction of (4*S*)-4-phenyloxazolidinone with the mixed anhydride from 1,2-diphenylcycloprop-2-ene-1-carboxylic acid and 1-adamantoyl chloride.[6a]

(16) Fox, J. M.; Dmitrenko, O.; Liao, L.-a.; Bach, R. D. *J. Org. Chem.* **2004**, *69*, 7317.

direct comparison to the desymmetrization of bis-pentafluorophenyl esters **4** is not yet possible. In future work, the dependence of asymmetric induction on the nature of the leaving group will be further explored through experiment and computation.

In summary, a new route to enantiomerically enriched cyclopropene α-amino acids is reported. The key step is a highly enantioselective desymmetrization of cyclopropene-bis-carboxylic acids. Derivatives of cyclopropene α-amino acids are shown to be stable to harshly acidic and basic reaction conditions (TFA, NaOH), and one derivative has been incorporated into a tripeptide using conventional methods for peptide synthesis. Efforts to utilize cyclopropene α-amino acids in de novo peptide design are underway.

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Supporting Information Available: Full experimental and characterization details, ^{1}H and ^{13}C NMR spectra, and X-ray data for the stereochemical assignment of **5b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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