ORGANIC LETTERS

2003
Vol. 5, No. 24
4669−4672

Synthesis of β-Cyclopropylalanines by Photolysis of Diacyl Peroxides

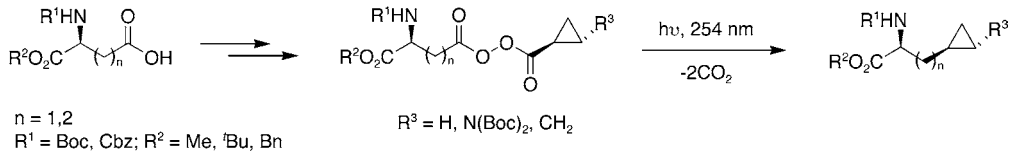
Rajendra P. Jain and John C. Vederas*

Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada T6G 2G2

john.vederas@ualberta.ca

Received September 24, 2003

ABSTRACT



Photolysis at 254 nm of neat (no solvent) unsymmetrical diacyl peroxides derived from cyclopropane carboxylic acids and L-aspartic acid generates protected β-cyclopropylalanines in reasonable yields. Orthogonally protected 3-(*trans*-2-aminocyclopropyl)alanine (21), a key constituent of the antitumor agent belactosin A, as well as protected hypoglycin A (26), a causative agent of Jamaican vomiting sickness, is synthesized by this approach with coupling of the intermediate substituted cyclopropyl radicals proceeding predominantly with retention of configuration (dr ≥ 95:5).

Recently, much attention has focused on amino acids containing conformationally constrained cyclopropane rings due to their important biological activities.[1] For example, β-cyclopropylalanine (**12**, **15,** and **16**, Scheme 3, $n = 1$, $R^1 = R^2 = H$) is a potent antagonist to *E. coli* ATCC 9723[2] and inhibits spore germination of *Pyricularia oryzae* Cav., the causative agent of rice blast disease.[3] The cyclopropane ring can be introduced into amino acids by a number of methods, which include (1) metal-promoted cyclopropanation or carbene addition reactions,[4] (2) glycine enolate alkylation with cyclopropylmethyl halides,[5] and (3) Michael-induced ring closure by glycine enolates.[6]

We have recently reported[7] the low-temperature photolysis of diacyl peroxides in the absence of solvent to generate various functionalized amino acids in a concise manner and with orthogonal protection. We envisaged that recombination of cyclopropane radicals[8,9] with an amino acid derived partner could provide access to various cyclopropane amino acids (Figure 1), but it was not initially obvious whether the special properties of the cyclic radical[10] would interfere in this process.

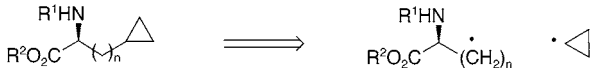


Figure 1. Retrosynthesis of cyclopropane amino acids.

Initial studies focused on the synthesis of protected cyclopropane amino acids **12**−**16**. Two different methods

(1) (a) Williams, R. M. In *Organic Chemistry Series, Volume 7*: *Synthesis of Optically Active* α*-Amino Acids*; Baldwin, J. E., Magnus, P. D., Eds.; Pergamon Press: Oxford, 1989. (b) Stammer, C. H.; *Tetrahedron* **1990**, *46*, 2231−2254. (c) Burgess, K.; Ho, K. K.; Moyesherman, D. *Synlett* **1994**, 575−583. (d) Salaün, J.; Baird, M. S. *Curr. Med. Chem.* **1995**, *2*, 511−542. (e) Salaün, J. *Top. Curr. Chem.* **2000**, *207*, 1−67. (f) Cativiela, C.; Diaz-de-Viellgas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645−732.

(2) Meek, J. S.; Rowe, J. W. *J. Am. Chem. Soc.* **1955**, *77*, 6675−6677.

(3) (a) Ohta, T.; Nakajima, S.; Sato, Z.; Aoki, T.; Hatanaka, S.; Nozoe, S. *Chem. Lett.* **1986**, 511−512. (b) Hamon, C.; Rawlings, B. J. *Synth. Commun.* **1996**, *26*, 1109−1115 and references cited therein.

(4) Rife, J.; Ortuno, R. M.; Lajoie, G. A. *J. Org. Chem.* **1999**, *64*, 8958−8961.

(5) (a) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414−12415. (b) Tzalis, D.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 3685−3688.

(6) Pohlman, M.; Kazmaier, U. *Org. Lett.* **2003**, *5*, 2631−2633.

(7) Spantulescu, M. D.; Jain, R. P.; Derksen, D. J.; Vederas, J. C. *Org. Lett.* **2003**, *5*, 2963−2965.

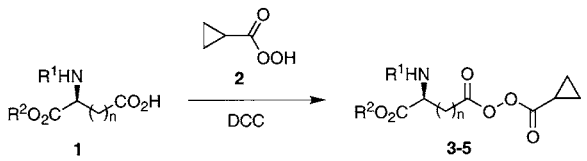
(8) For review on cyclopropane radicals, see: Walborsky, H. M. *Tetrahedron*, **1981**, *37*, 1625−1651.

(9) For other reactions of cyclopropane radicals, see: (a) Stefani, A. P.; Chuang, L.-Y. Y.; Todd, H. E. *J. Am. Chem. Soc.* **1970**, *92*, 4168−4173. (b) Stefani, A. P.; Todd, H. E. *J. Am. Chem. Soc.* **1971**, *93*, 2982−2986. (c) Shono, T.; Nishiguchi, I.; Tetrahedron, **1974**, *30*, 2183−2190. (d) Clerici, A.; Minisci, F.; Porta, O. *J. Chem. Soc., Perkin Trans. 2* **1974**, 1699−1701. (e) Herwig, K.; Lorenz, P.; Rüchardt, C. *Chem. Ber.* **1975**, *108*, 1421−1436.

10.1021/ol035859a CCC: $25.00
Published on Web 10/31/2003

were developed to synthesize the requisite precursor diacyl peroxides **3**−**5** and **10**−**11**. Thus, treatment of suitably protected aspartic and glutamic acids (**1a**−**c**) with an Etheral solution of cyclopropane percarboxylic acid[11] (**2**, obtained from cyclopropane carboxylic acid, concentrated H_2SO_4, and H_2O_2, see the Supporting Information) in the presence of DCC affords the diacyl peroxides **3**−**5** in 83−89% yield (Scheme 1).

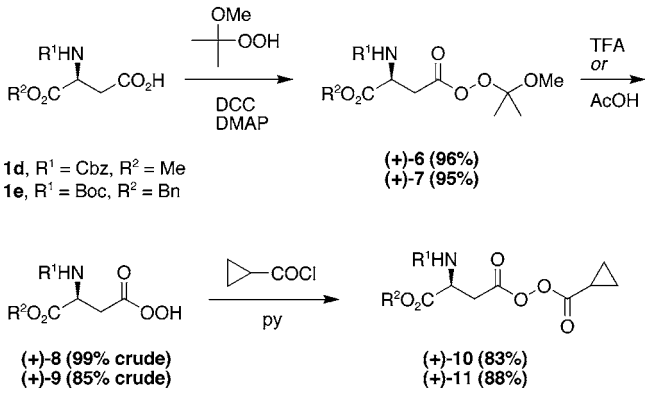
Scheme 1



amino acid (**1**)	diacyl peroxide (% yield)
1a, R^1 = Boc, R^2 = ^{t}Bu, n = 1	(+)-**3** (89)
1b, R^1 = Boc, R^2 = ^{t}Bu, n = 2	(+)-**4** (85)
1c, R^1 = Boc, R^2 = Bn, n = 2	(+)-**5** (83)

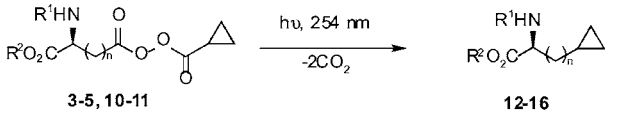
Alternatively, DCC-mediated coupling of the protected L-aspartic acid (**1d** and **1e)** with 2-methoxyprop-2-yl hydroperoxide,[12] acidic deprotection of the resultant peresters **6** and **7** (50% aq TFA/$CHCl_3$ for **6**, 50% aq AcOH for **7**), and acylation of the corresponding peracids **8** and **9** with cyclopropane carbonyl chloride (py/CH_2Cl_2) generates the diacyl peroxides **10** and **11** in good overall yields (Scheme 2). The diacyl peroxides **3**−**5** and **10**−**11** are stable to shock and can be stored in non-nucleophilic organic solvents (EtOAc, $CHCl_3$) for several weeks at −20 °C without decomposition.

Scheme 2



The photolysis reactions of the peroxides **3**−**5** and **10**−**11** are done on neat substrates (solids and oils, no solvent) at −78 °C with a 254 nm UV lamp.[13] Thus, photolysis of **3**, **10**, and **11** produces optically pure β-cyclopropylalanine derivatives[2,3] **12**, **15**, and **16**, respectively, with no detectable crossover products. Similarly, photolysis of **4** and **5** at −78 °C generates one-carbon homologues **13** and **14**, respectively (Scheme 3).

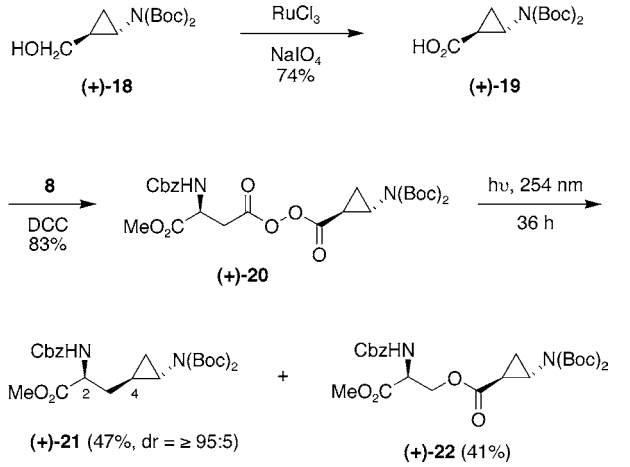
Scheme 3



diacyl peroxide	time (h)	cyclopropane amino acid (% yield)
3, R^1 = Boc, R^2 = ^{t}Bu, n = 1	80	(+)-**12** (58)
4, R^1 = Boc, R^2 = ^{t}Bu, n = 2	80	(+)-**13** (58)
5, R^1 = Boc, R^2 = Bn, n = 2	48	(−)-**14** (53)
10, R^1 = Cbz, R^2 = Me, n = 1	30	(+)-**15** (57)
11, R^1 = Boc, R^2 = Bn, n = 1	30	(−)-**16** (52)

This approach can be extended to the synthesis of the orthogonally protected (2*S*,4*R*)-3-[*trans*-(2*S*)-aminocyclopropyl]alanine (**21**, Scheme 4), a key constituent of the

Scheme 4



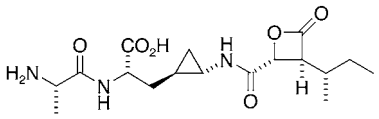
recently isolated metabolite belactosin A (**17**) produced by *Streptomyces* sp. that exhibits antitumor activity.[14] This also provides an opportunity to examine the stereoselectivity of coupling of cyclopropyl radicals (Scheme 4). We have

(10) Mann, D. J.; Hase, W. L. *J. Am. Chem. Soc.* **2002**, *124*, 3208−3209.

(11) The pure peracid was not isolated from its solution due to its high volatility, and to avoid possible explosion hazard, see: Swern, D. *Organic Peroxides*; Wiley-Interscience: New York, 1970; pp 476−498. For characterization purposes, a small aliquot of etheral solution was carefully concentrated under positive pressure of Ar to obtain neat cyclopropanepercarboxylic acid as clear colorless oil.

(12) Dussault, P.; Sahli, A. *J. Org. Chem.* **1992**, *57*, 1009−1012.

recently demonstrated that secondary radicals bearing a methyl substituent generated in this fashion can couple to primary radicals with 5:1 retention of configuration at −196 °C.[7] Earlier syntheses of 3-(*trans*-2-aminocyclopropyl)alanine were reported by the groups of de Meijere[15a] and Armstrong[16] using glycine enolate alkylation of the unstable iodide derived from the alcohol **18**. These routes rely on the generation of C-2 chiral center of 3-(*trans*-2-aminocyclopropyl)alanine either by use of a chiral glycine template[15b] or by chiral phase transfer catalysis.[16] In the present approach, the C-2 chiral center is generated by incorporation of the existing stereocenter of protected aspartic acid **1d** (Scheme 4).



Belactosin A (17)

We followed the Wadsworth−Emmons cyclopropanation protocol on benzyl (*S*)-(+)-glycidyl ether[16] with a slight change (final hydrogenolysis step is modified; 40 psi H_2, 10% Pd−C, EtOAc, rt, 15 h, quant) in order to synthesize requisite (*S*,*S*)-(*trans*-2-aminocyclopropyl)methanol derivative **18** (Scheme 4).

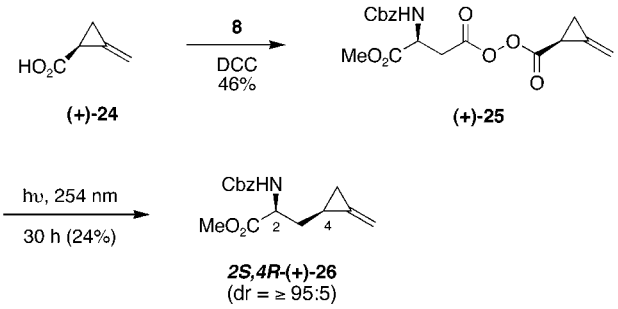
Attempted oxidation of alcohol in **18** either by Jones reagent or PDC could not generate the desired *trans*-*β*-aminocyclopropane carboxylic acid derivative **19** in satisfactory yield, possibly due to cyclopropane ring opening.[17] However, oxidation of **18** with $RuCl_3/NaIO_4$[18] (MeCN/$CHCl_3/H_2O$) cleanly produces **19** in 74% yield.

DCC-mediated coupling of **19** with **8** (R^1 = Cbz, R^2 = Me) forms the diacyl peroxide **20** in 83% yield.

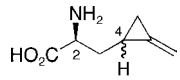
Photolysis of neat **20**[13] at −78 °C (36 h) produces **21** in 47% yield and with ≥95:5 diastereomeric ratio (by ^{1}H NMR analysis in C_6D_6, diastereomers nonseparable by silica gel chromatography), along with monodecarboxylation product **22** (41% yield). The retention of configuration at C-4 of **21** in the photolysis reaction is confirmed by NOE experiments. In contrast to reaction at −78 °C, photolysis of neat **20** at 20 °C (4.5 h) in open atmosphere gives 18% yield of **21** along with **22** (29% yield). Photolysis of **20** at −196 °C is sluggish (<20% conversion of **20** after 36 h).

We next examined the synthesis of protected (*2S*,*4R*)-hypoglycin A (**26**, Scheme 5). Originally isolated from the

Scheme 5



arillus and seeds of unripe fruit of the Jamaican ackee tree (*Blighia sapida*),[19] hypoglycin A (**23**) is the causative agent of Jamaican vomiting sickness.[20] Natural hypoglycin A exists as a mixture of diastereomers at C-4, with 17% diastereomeric excess favoring the (2*S*,4*R*) isomer.[21]



Hypoglycin A (23)

A recent synthesis of optically pure hypoglycin A[21] relies on the generation of C-2 chiral center by use of Schöllkopf bis-lactim ether[22] as chiral glycine template. As in case of **21**, our approach for the synthesis of **26** is based on generation of C-2 chiral center by incorporation of the existing stereocenter of protected aspartic acid **1d** (Scheme 5).

Thus, DCC-mediated coupling (−78 °C, 48 h) of **24**, obtained by modification of reported procedure[23] (see the Supporting Information), with **8** forms the diacyl peroxide **25** in 46% yield. Higher temperatures lower yields in this reaction, probably due to peracid oxidation of the olefin and subsequent decomposition. Photolysis of neat **25** at −78 °C (30 h) produces **26** in 24% yield and with ≥95:5 diastereomeric ratio (by ^{1}H NMR analysis in $CDCl_3$ using $Eu(Hfc)_3$, as well as in DMSO-d_6 at +100 °C, diastereomers inseparable by silica gel chromatography).

Features of the photolytic decarboxylation-coupling reaction that are critical for success are low temperature and absence of solvent, as reported initially for simpler systems by Schäfer and co-workers[24] and extended by us to amino acid derivatives.[7] This reduces the mobility of the radical

(13) All reactions were conducted with a 0.9 Amp UV lamp in 150 × 75 mm crystallizing dish covered with a quartz plate and protected from moisture. Reactions were performed on 0.07−0.93 mmol scale, but larger scales are not problematic in our experience.

(14) Asai, A.; Hasegawa, A.; Ochiai, K.; Yamashita, Y.; Mizukami, T. *J. Antibiot.* **2000** *53*, 81−83.

(15) (a) Brandl, M.; Kozhushkov, S. I.; Loscha, K.; Kokoreva, O. V.; Yufit, D. S.; Howard, J. A. K.; de Meijere, A. *Synlett* **2000**, 1741−1744. (b) Larionov, O. V.; Savel'eva, T. F.; Kochetkov, K. A.; Ikonnokov, N. S.; Kozhushkov, S. I.; Yufit, D. S.; Howard, J. A. K.; Khrustalev, V. N.; Belokon, Y. N.; de Meijere, A. *Eur. J. Org. Chem.* **2003**, 869−877.

(16) Armstrong, A.; Scutt, J. N. *Org. Lett.* **2003**, *5*, 2331−2334.

(17) Cannon, J. G.; Garst, J. E. *J. Org. Chem.* **1975**, *40*, 182−184.

(18) (a) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936−3938. (b) Godier-Marc, E.; Aitken, D. J.; Husson, H.-P. *Tetrahedron Lett.* **1997**, *38*, 4065−4068.

(19) (a) Hassall, C. H.; Reyle, K. *Biochem. J.* **1955**, *60*, 334−339. (b) Fowden, L.; Pratt, H. M. *Phytochemistry* **1973**, *12*, 1677−1681.

(20) (a) Tanaka, K. In *Handbook of Clinical Neurology*; Vinken, P. J., Bruyn. G. W., Eds.; North-Holland: Amsterdam, 1979; Vol. 37, pp 511−539.

(21) Baldwin, J. E.; Adlington, R. M.; Bebbington, D.; Russell, A. T. *Tetrahedron* **1994**, *50*, 12015−12028.

(22) Schöllkopf, U. *Top. Curr. Chem.* **1983**, *109*, 65−84.

(23) Lai, M.-t.; Liu, L.-d.; Liu, H.-w. *J. Am. Chem. Soc.* **1991**, *113*, 7388−7397.

(24) Feldhues, M.; Schäfer, H. J. *Tetrahedron* **1985**, *41*, 4213−4235. (b) Feldhues, M.; Schäfer, H. J. *Tetrahedron* **1986**, *42*, 1285−1290. (c) Lomölder, R.; Schäfer, H. J. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1253−1254.

intermediates, thereby preventing formation of crossover products, minimizing side reactions (e.g. hydrogen abstraction) and enhancing stereochemical control during coupling. It is important to note that the cyclopropyl radical intermediate has a greater propensity to couple with retention of configuration (dr ≥ 95:5 in **21** and **26** at −78 °C) than the more mobile acyclic secondary radicals (4.3:1 at −78 °C; 5:1 at −196 °C) produced in our earlier work.[7] We believe that in both cases the radical intermediates do not necessarily retain their configuration (although cyclopropyl radicals are more prone to do this). Instead, the lack of mobility of the substituents (as well as of the whole molecules) in the frozen matrix forces coupling to occur from the same side as the departing carbon dioxide. Although it may be argued that the bulky bis-(*N*-Boc-amino) substituent in **20** may direct the stereochemical preference, previous work in our laboratory has shown that the effect of a β-chiral center on the stereochemical outcome of the photolysis reaction is often minimal.[7] Whether the cis-amino cyclopropane diastereomer of **21** can be generated with equal selection remains to be determined. However, based on previous work, this method should readily provide access to the C-2 epimer of **21** and **26** in high diastereomeric excess through the use of (*R*)-**8**. The number of steps and overall yields leading to **21** and **26** are favorably competitive to those in the literature, and the unique advantage of the present approach is incorporation of the existing stereocenters and protecting groups of the starting materials into final products.

In conclusion, photolysis of the unsymmetrical diacyl peroxides derived from cyclopropanecarboxylic acids and protected aspartic acid provides an access to various biologically interesting cyclopropylalanines. Current investigations are focused on further extending the applications of the methodology.

Acknowledgment. Financial support from Boehringer Ingelheim Canada, the Natural Sciences and Engineering Research Council of Canada (NSERC), and the Canada Research Chair in Bioorganic and Medicinal Chemistry is gratefully acknowledged.

Supporting Information Available: Experimental procedures and spectroscopic data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL035859A