Simple and Efficient Multigram Scale Synthesis of 1-Aminocyclopent-3-ene-1-carboxylic Acid

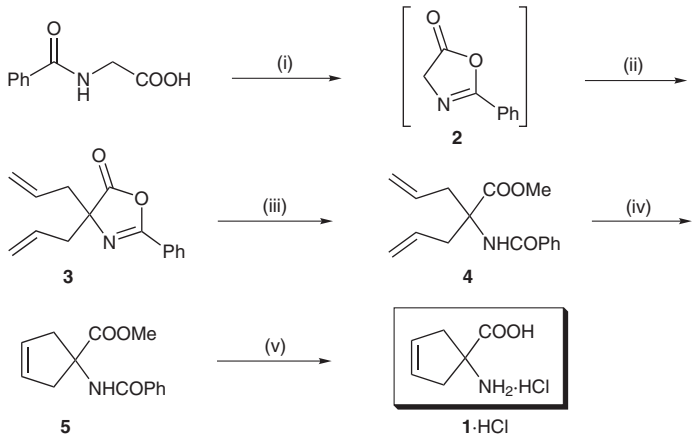
Diego Casabona, Carlos Cativiela*

Departamento de Química Orgánica, Instituto de Ciencia de Materiales de Aragón, Universidad de Zaragoza – CSIC, 50009 Zaragoza, Spain
Fax +34(976)761210; E-mail: cativiela@unizar.es

Received 16 March 2006; revised 30 March 2006

Abstract: A very simple and inexpensive synthesis of the valuable intermediate 1-aminocyclopent-3-ene-1-carboxylic acid on a multigram scale and with a high overall yield (80%) is reported. The efficiency of the procedure relies on the ready accessibility and high reactivity of the glycine equivalent used as the starting material.

Key words: allylations, amino acids, heterocycles, metathesis, ring closure



Scheme 1 *Reagents*: (i) DCC; (ii) DIPEA, NaI, allyl bromide (90% two steps); (iii) MeONa, MeOH (99%); (iv) Grubbs' catalyst (91%); (v) 6 N HCl (99%).

Introduction

The incorporation of quaternary α-amino acids[1] into peptides restricts and controls peptide conformations.[2] In particular, 1-aminocycloalkane-1-carboxylic acids (Ac_nc, Figure 1) stabilize helical and turn conformations.[2b–d,3] A derivative of Ac_5c that is symmetrically disubstituted at γ,δ imparts a helical-screw sense in the absence of chirality at the α-carbon.[4]

Some Ac_5c derivatives exhibit intrinsic biological activity and are potential drugs in the treatment of neurodegenerative pathologies. Glutamic acid is the main excitatory neurotransmitter in the mammalian central nervous system, and its constrained analogue 1-aminocyclopentane-1,3-dicarboxylic acid (ACPD, Figure 1) behaves as a potent ligand for the different glutamate receptors.[5] In the search for highly potent and selective ligands for these receptors, the double bond in 1-aminocyclopent-3-ene-1-carboxylic acid (**1**) (suitably protected in the N- and C-termini) has been subjected to different transformations.[6–9] ACPD itself and other compounds with promising pharmacological profiles have been obtained in this way.

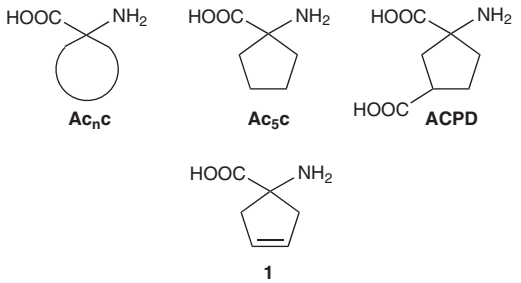


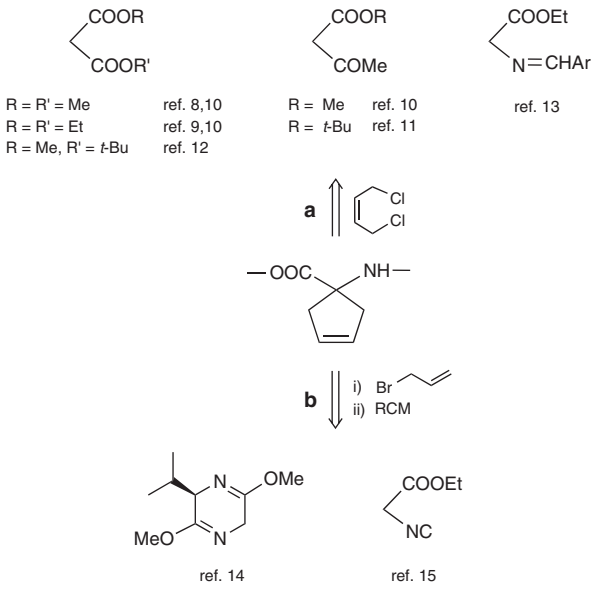
Figure 1 Structure of Ac_nc and some Ac_5c derivatives.

SYNTHESIS 2006, No. 14, pp 2440–2443
Advanced online publication: 07.07.2006
DOI: 10.1055/s-2006-942458; Art ID: P03506SS
© Georg Thieme Verlag Stuttgart · New York

Downloaded by: NYU. Copyrighted material.

Scope and Limitations

The considerations discussed above make protected **1** a versatile and useful intermediate, as evidenced by the significant effort devoted to its synthesis in recent years.[8–15] Two general strategies have been described to prepare precursors of the target compound. The most frequently applied approach (Scheme 2, route a) involves cycloalkylation of a glycine equivalent with a dielectrophile.[8–13] More recently, bis-allylation of a glycine equivalent followed by a ring-closing metathesis (RCM) process (Scheme 2, route b) has emerged as an attractive alternative to prepare derivatives of **1**.[14,15]



Scheme 2 Different strategies reported for the synthesis of protected **1** (the references describing the use of each substrate are indicated).

Several authors have reported the reaction of dimethyl[8,10] or diethyl[9,10] malonate with *cis*-1,4-dichlorobut-2-ene. Hydrolysis of one ester group followed by Curtius rearrangement of the resulting carboxylic acid has led to different *N*-carbamate esters of **1** in about 30% global yield. Acetylacetates[10,11] have been proposed as non-symmetric 1,3-dicarbonyl compounds but did not give a significant improvement in the overall yield (32%), while a huge excess of reagent was needed in the haloform reaction to generate the carboxylic acid prior to Curtius degradation.[11] Among the 1,3-dicarbonyl compounds investigated, only the more expensive *tert*-butyl methyl malonate has provided superior yields (61%).[12] In all cases,[8–12] LiH was used as a base and *cis*-1,4-dichlorobut-2-ene as the dielectrophile.

The Schiff base derived from 4-bromobenzaldehyde and glycine ethyl ester reacted with *cis*-1,4-dichlorobut-2-ene in the presence of excess NaH to afford, after mild acidic hydrolysis, the ethyl ester of **1** in 67% yield.[13] Two other primary glycine synthons were also used to prepare protected **1** according to route b (Scheme 2): the bis-lactim ether developed by Schöllkopf and ethyl isocyanoacetate were bis-alkylated with allyl bromide and subjected to RCM[16] in the presence of the ruthenium(II) Grubbs' catalyst. Whereas the expensive Schöllkopf chiral substrate afforded poor yields of the desired product,[14] ethyl isocyanoacetate led to **1** protected as the *N*-Boc/acetyl ethyl ester in 62–73% global yield.[15] The low stability of the isocyano derivatives reported by the authors[15a] together with the difficulty in handling them (ethyl isocyanoacetate is a potent lachrymator) constitute the main limitations to scaling-up this high-yielding route (to our knowledge, details were not provided about the scale on which these reactions were carried out).

The clear advantage of glycine derivatives bearing a protected unmasked amino group prompted us to explore the synthesis of 1-aminocyclopent-3-ene-1-carboxylic acid (**1**) starting from 2-phenyl-5(4*H*)-oxazolone (**2**, Scheme 1). There were two reasons for this choice: the accessibility of this compound (it is readily obtained from hippuric acid, i.e., *N*-benzoylglycine, an inexpensive commercial glycine derivative) and the high reactivity of the oxazolone moiety in comparison with other amino acid synthons.[17,18]

Treatment of hippuric acid with *N*,*N*′-dicyclohexylcarbodiimide (DCC) led to the formation of 2-phenyl-5(4*H*)-oxazolone (**2**), which was alkylated in situ with allyl bromide to provide 4,4-diallyl-2-phenyl-5(4*H*)-oxazolone (**3**) in good yield (Scheme 1). The high reactivity of the oxazolone moiety[18] is evidenced by the fact that only a slight excess of allylating agent was required and the process was complete in a few hours at room temperature. It is worth noting that a tertiary amine, *N*,*N*-diisopropylethylamine (DIPEA), was used as a base to obtain **3**.

Opening of the heterocyclic ring in **3** was achieved by methanolysis in the presence of a catalytic amount of sodium methoxide. The resulting *N*-benzoyl-α,α-diallyl glycinate (**4**) cyclized by the action of Grubbs' catalyst.[16] The RCM step proceeded smoothly at room temperature and furnished the desired compound **5** in excellent yield. It is interesting to note that when the metathesis process was attempted prior to methanolysis of the oxazolone moiety, the cyclopentene ring was formed much less efficiently, an effect probably associated with the highly strained spirooxazolone formed.

In this way, 10 grams of compound **5** were prepared in a single run. This is, to the best of our knowledge, the largest-scale synthesis reported for an immediate precursor of **1** (in several cases, the scale of work was not mentioned). Moreover, **5** was obtained in 81% overall yield from hippuric acid, which is a much higher yield than those provided by most of the routes described to date for the preparation of similar precursors of **1**, and compares favorably with the most efficient approaches. The final amino acid was obtained as its hydrochloride **1**·HCl from derivative **5** in almost quantitative yield by acid hydrolysis. As far as we know, this is the first time that the free unprotected amino acid has been isolated.

Downloaded by: NYU. Copyrighted material.

In summary, a synthesis of 1-aminocyclopent-3-ene-1-carboxylic acid based on the use of the readily accessible 2-phenyl-5(4*H*)-oxazolone as a glycine equivalent has been developed. The strategy involves simple, high-yielding transformations that are appropriate for large scale synthesis and avoid most of the difficulties associated with previously described methodologies, such as the use of strong air-sensitive bases (LiH, NaH, BuLi), toxic unstable starting materials or large excesses of reagents, as well as the need for rearrangement processes.

4,4-Diallyl-2-phenyl-5(4*H*)-oxazolone (3)

A solution of *N*,*N*′-dicyclohexylcarbodiimide (12.61 g, 61.2 mmol) in anhyd THF (30 mL) was added dropwise to a suspension of hippuric acid (10.74 g, 60 mmol) in anhyd THF (50 mL) at 0 °C under argon. The mixture was stirred overnight at r.t., and then cooled to –30 °C. The white solid was filtered off, and the organic solution was evaporated under reduced pressure to give 2-phenyl-5(4*H*)-oxazolone (**2**) as a yellow solid, which was used without further purification. To a solution of this solid in anhyd DMF under argon, were added successively a spatula tip of NaI, allyl bromide (11.42 mL, 132 mmol) and, dropwise, DIPEA (22.95 mL, 132 mmol) in anhyd DMF (10 mL). The mixture was stirred at r.t. for 6 h. Et_2O (20 mL) and H_2O (20 mL) were added and the resulting biphasic system was vigorously stirred. The layers were separated and the aqueous phase was further extracted with Et_2O (3 × 20 mL). The combined organic phases were washed with 5% aq citric acid and sat. $NaHCO_3$. The organic solution was dried and filtered, and the solvent removed to give a residue, which was chromatographed (eluent: hexanes–EtOAc, 9:1) to yield **3** as an oil; yield: 13.04 g (90% from hippuric acid).

IR (neat): 1817, 1654 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.52 (m, 4 H), 4.99 (m, 2 H), 5.07 (m, 2 H), 5.55 (m, 2 H), 7.32–7.47 (m, 3 H), 7.89 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 40.88, 73.54, 120.35, 125.59, 127.78, 128.59, 130.51, 132.52, 159.85, 178.89.

Methyl 2-Allyl-2-benzamidopent-4-enoate (4)

A 0.1% solution of NaOMe in MeOH (10 mL) was added to a solution of **3** (11.57 g, 48 mmol) in MeOH (20 mL) and the mixture was stirred for 2 h at r.t. The solvent was removed and the oily residue was dissolved in CH_2Cl_2 (100 mL). The CH_2Cl_2 solution was washed with H_2O (20 mL) and dried ($MgSO_4$). The solution was filtered and the solvent evaporated to give **4** as an oil; yield: 12.92 g (99%).

IR (neat): 3276, 1737, 1633 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.62 (dd, *J* = 7.6, 14.0 Hz, 2 H), 3.37 (dd, *J* = 7.2, 14.0 Hz, 2 H), 3.81 (s, 3 H), 5.04–5.13 (m, 4 H), 5.64 (m, 2 H), 7.07 (br s, 1 H), 7.40–7.53 (m, 3 H), 7.77 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.11, 52.82, 64.79, 119.19, 126.79, 128.55, 131.47, 132.17, 134.94, 166.35, 173.66.

Methyl 1-Benzamidocyclopent-3-ene-1-carboxylate (5)

A solution of **4** (12.92 g, 47.5 mmol) in anhyd toluene (80 mL) under argon was treated with benzylidenebis(tricyclohexylphosphine)dichlororuthenium (3.13 g, 3.8 mmol) dissolved in anhyd toluene (20 mL) and the mixture was stirred for 6 h at r.t. The solvent was evaporated and the residue was purified by column chromatography (eluent: hexanes–EtOAc, 7:3) to give **5** as a white solid; yield: 10.62 g (91%); mp 126–127 °C (hexanes–EtOAc).

IR (Nujol): 3314, 1733, 1643 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.82 (br d, *J* = 15.6 Hz, 2 H), 3.16 (br d, *J* = 15.6 Hz, 2 H), 3.78 (s, 3 H), 5.73 (m, 2 H), 6.77 (br s, 1 H), 7.40–7.54 (m, 3 H), 7.79 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.61, 52.85, 64.33, 127.0, 127.89, 128.52, 131.68, 133.92, 166.84, 174.36.

Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.73; H, 6.22; N, 5.59.

1-Aminocyclopent-3-ene-1-carboxylic Acid Hydrochloride (1·HCl)

Compound **5** (10.62 g, 43.2 mmol) was suspended in aq 6 N HCl (150 mL) and refluxed for 24 h. After cooling, the mixture was evaporated to dryness and the residue was partitioned between Et_2O (50 mL) and H_2O (50 mL). The organic layer was discarded and the aqueous phase was washed with an additional portion of Et_2O (20 mL). Final lyophilization furnished pure **1**·HCl as a white solid; yield: 6.99 g (99%).

IR (Nujol): 3300–2350, 1729 cm^{-1}.

^1H NMR (400 MHz, D_2O): δ = 2.59 (br d, *J* = 17.2 Hz, 2 H), 3.03 (br d, *J* = 17.2 Hz, 2 H), 5.65 (m, 2 H).

^{13}C NMR (100 MHz, D_2O): δ = 43.32, 63.61, 127.24, 175.14.

Anal. Calcd for $C_6H_{10}ClNO_2$: C, 44.05; H, 6.16; N, 8.56. Found: C, 44.27; H, 6.24; N, 8.39.

Acknowledgment

Financial support from Ministerio de Educación y Ciencia–FEDER (project CTQ2004-5358) and Diputación General de Aragón (project PIP206/2005, group E40) is gratefully acknowledged. D.C. thanks CSIC for an I3P grant.

References

(1) The selective synthesis of quaternary α-amino acids has been reviewed: (a) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517. (b) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645.

(2) (a) Cowell, S. M.; Lee, Y. S.; Cain, J. P.; Hruby, V. J. *Curr. Med. Chem.* **2004**, *11*, 2785. (b) Toniolo, C.; Crisma, M.; Formaggio, F.; Peggion, C. *Biopolymers (Pept. Sci.)* **2001**, *60*, 396. (c) Venkatraman, J.; Shankaramma, S. C.; Balaram, P. *Chem. Rev.* **2001**, *101*, 3131. (d) Benedetti, E. *Biopolymers (Pept. Sci.)* **1996**, *40*, 3.

(3) Ohwada, T.; Kojima, D.; Kiwada, T.; Futaki, S.; Sugiura, Y.; Yamaguchi, K.; Nishi, Y.; Kobayashi, Y. *Chem. Eur. J.* **2004**, *10*, 617.

(4) Tanaka, M.; Demizu, Y.; Doi, M.; Kurihara, M.; Suemune, H. *Angew. Chem. Int. Ed.* **2004**, *43*, 5360.

(5) (a) Moloney, M. G. *Nat. Prod. Rep.* **2002**, *19*, 597. (b) Monn, J. A.; Schoepp, D. D. *Annu. Rep. Med. Chem.* **2000**, *35*, 1. (c) Pellicciari, R.; Costantino, G. *Curr. Opin. Chem. Biol.* **1999**, *3*, 433.

(6) (a) Conti, P.; De Amici, M.; Bräuner-Osborne, H.; Madsen, U.; Toma, L.; De Micheli, C. *Farmaco* **2002**, *57*, 889. (b) Conti, P.; De Amici, M.; Joppolo-di-Ventimiglia, S.; Stensbol, T. B.; Madsen, U.; Bräuner-Osborne, H.; Russo, E.; De Sarro, G.; Bruno, G.; De Micheli, C. *J. Med. Chem.* **2003**, *46*, 3102. (c) Roda, G.; Conti, P.; De Amici, M.; He, J.; Polavarapu, P. L.; De Micheli, C. *Tetrahedron: Asymmetry* **2004**, *15*, 3079.

(7) Hammer, K.; Wang, J.; Falck-Pedersen, M. L.; Romming, C.; Undheim, K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1691.

Downloaded by: NYU. Copyrighted material.

(8) Amori, L.; Costantino, G.; Marinozzi, M.; Pellicciari, R.; Gasparini, F.; Flor, P. J.; Kuhn, R.; Vranesic, I. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1447.
(9) (a) Hodgson, D. M.; Thompson, A. J.; Wadman, S. *Tetrahedron Lett.* **1998**, *39*, 3357. (b) Hodgson, D. M.; Thompson, A. J.; Wadman, S.; Keats, C. J. *Tetrahedron* **1999**, *55*, 10815.
(10) Deprés, J. P.; Greene, A. E. *J. Org. Chem.* **1984**, *49*, 928.
(11) Larionov, O. V.; Kozhushkov, S. I.; de Meijere, A. *Synthesis* **2005**, 158.
(12) Doller, D.; Chackalamannil, S.; Stamford, A.; McKittrick, B.; Czarniecki, M. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1381.
(13) (a) Park, K.-H.; Olmstead, M. M.; Kurth, M. J. *J. Org. Chem.* **1998**, *63*, 113. (b) Park, K.-H.; Olmstead, M. M.; Kurth, M. J. *J. Org. Chem.* **1998**, *63*, 6579. (c) Park, K.-H.; Kurth, T. M.; Olmstead, M. M.; Kurth, M. J. *Tetrahedron Lett.* **2001**, *42*, 991.
(14) Hammer, K.; Undheim, K. *Tetrahedron* **1997**, *53*, 2309.
(15) (a) Kotha, S.; Sreenivasachary, N. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 257. (b) Kotha, S.; Sreenivasachary, N.; Mohanraja, K.; Durani, S. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1421.
(16) Grubbs, R. H. *Handbook of Metathesis*; Wiley: New York, **2003**.
(17) Cativiela, C.; Díaz-de-Villegas, M. D. *5(2H)-Oxazolones and 5(4H)-Oxazolones,* In *Oxazoles: Synthesis, Reactions and Spectroscopy. The Chemistry of Heterocyclic Compounds*, Part B, Vol. 60; Palmer, D. C., Ed.; Wiley: New York, **2004**, 129–330.
(18) Akashi, H. *Yuki Gosei Kagaku Kyokai Shi* **1975**, *33*, 483; *Chem. Abstr.* **1975**, *83*, 193143.

Downloaded by: NYU. Copyrighted material.