Synthesis of Oxazoles

# Iterative Oxazole Assembly via α-Chloroglycinates: Total Synthesis of (−)-Muscoride A**

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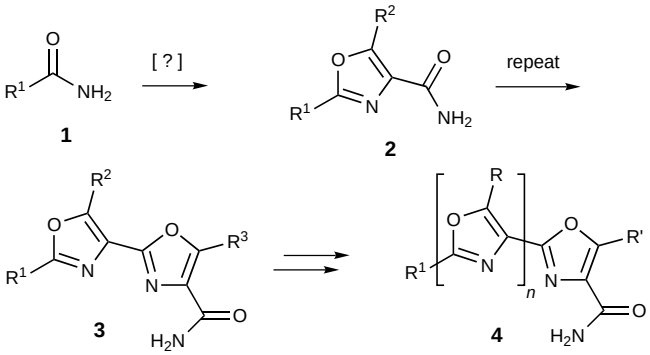
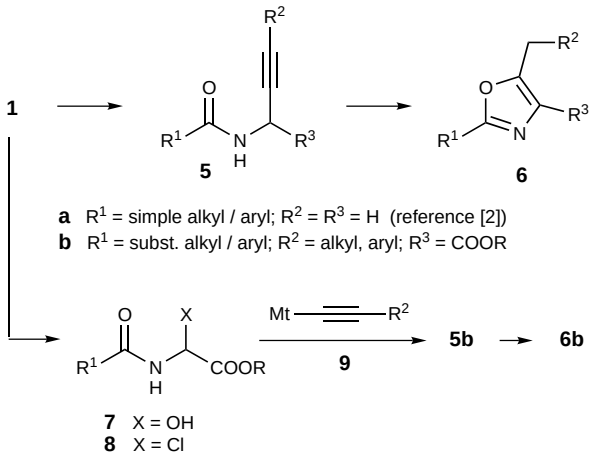
Ongoing work directed toward the synthesis of oxazole-containing natural products revealed the desirability for a mild method for iterative oxazole construction based on the approach shown in Scheme 1.[1] A generic primary amide **1** (possibly derived from an α-amino acid) would be advanced to oxazole-4-carboxamide **2**, which upon subjection to the same reaction sequence leads to bisoxazole **3**. A polyoxazole **4** bearing diverse substituents R would materialize after *n* such iterations.




***Scheme 1.*** Iterative approach to oxazole construction.

The documented cyclization of simple *N*-acyl propargylamines (e.g. **5a**→**6a**, Scheme 2)[2] offered an attractive solution to the issue of oxazole assembly, provided that the transformation could be effected with alkynylglycine-type substrates **5b**, in which $R^1$ may contain potentially labile stereocenters. Furthermore, this logic requires that intermediate **5b** be built de novo from amides **1**. Herein, we provide details of how these principles were translated into practice and we demonstrate an application of the new chemistry to the synthesis of the bisoxazole natural product (−)-muscoride A (**26**, see Scheme 5).




***Scheme 2.*** Cyclization of *N*-acyl propargylamines in oxazole formation.

Alkynyl glycine derivatives can be prepared by the method of Williams and co-workers,[3] which involves the reaction of 1-stannylalkynes (e.g. **9**, Mt = $Bu_3Sn$) with α-chloroglycinates **8**, readily obtained, in turn, by treatment of α-hydroxyglycinates **7** with $SOCl_2$.[4] This approach was readily reproduced, but we found it more practical to use alkynyl dimethylaluminum reagents generated in situ (e.g. **9**, Mt = $AlMe_2$)[5] for the crucial C–C-bond-forming step, especially during large-scale operations.[6,7]

Addition of a primary amide to a glyoxylate ester and dissolution of the resulting α-hydroxyglycinates **7** in $SOCl_2$ resulted in conversion into essentially pure (by NMR spectroscopic analysis) **8**,[8] which reacted rapidly with dimethylaluminum acetylides to form the corresponding alkynyl glycinates **5b**. These intermediates were isolated and characterized in several instances, but we found that prolonged reaction times (> 2 h) induce a considerable degree of in situ cyclization to form oxazoles **6b**. However, complete cyclization may require an inconveniently long contact time, which may also result in side reactions. Fortunately, gentle basic treatment (aqueous $NaHCO_3$) of **5b** was found to induce rapid conversion into **6b**. Complete oxazole formation is thus best achieved during a mild basic workup of the reaction mixture.[9]

Table 1 lists representative oxazoles **10** synthesized by the new procedure. Yields are uniformly good to excellent. Heterocycles **10** often need to be converted into the corresponding free acids as a prelude to subsequent operations. In this case, it is expedient to employ the stronger base LiOH in the workup/cyclization step, whereupon the desired acids are obtained directly (Table 1, **10b**). Treatment of silylated products of the type **10g** (or of their alkynyl glycine forerunners) with LiOH results in loss of the TMS group as well.[10]

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[**] We thank Aventis CropScience and the CNRS (BDI Fellowship to P.-Y.C.), the MENRT, the CNRS, and the Région Rhône-Alpes for support of our research. We are grateful to Ms. Laurence Rousset, Mr. Aymeric Morla, and Dr. Denis Bouchu for the mass spectrometric data. M.A.C. is the recipient of a Merck&Co Academic Development Award.

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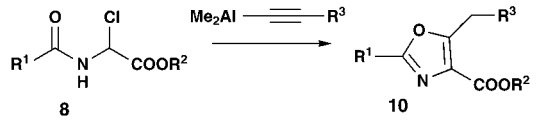
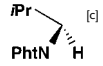
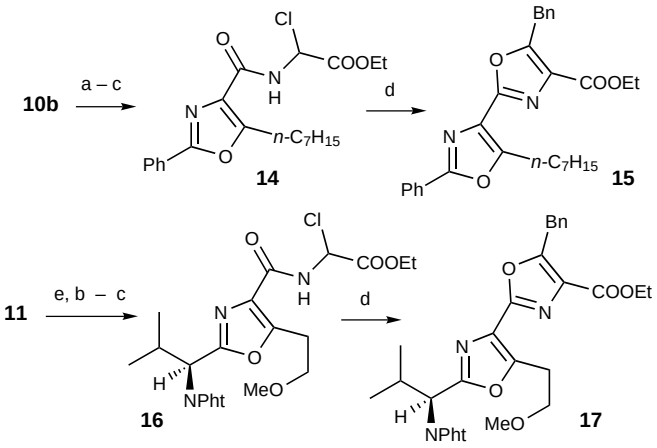
*Table 1:*



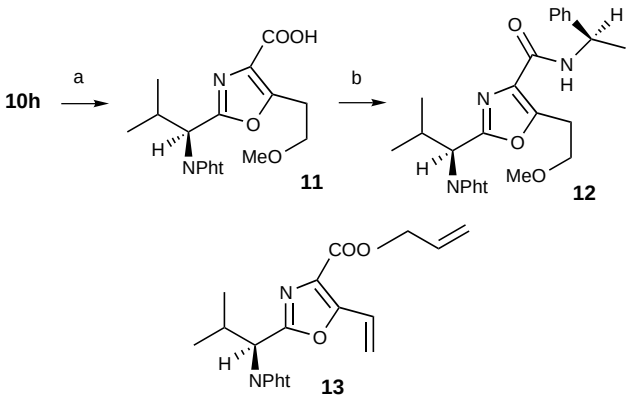
| | $R^1$ | $R^2$ | $R^3$ | Yield [%] |
|---|---|---|---|---|
| **a** | Ph | *n*Bu | *n*-$C_6H_{13}$ | 91 |
| **b** | Ph | H[a] | *n*-$C_6H_{13}$ | 81 |
| **c** | Ph | *n*Bu | Ph | 90 |
| **d** | Ph | Et | *n*-$C_6H_{13}$ | 89 |
| **e** | Me | *n*Bu | Ph | 77 |
| **f** | *cyclo*-$C_6H_{11}$ | *n*Bu | Ph | 84 |
| **g** | *cyclo*-$C_6H_{11}$ | *n*Bu | TMS[c] | 84 |
| **h** |  | allyl | $CH_2OMe$ | 51[b] |

[a] The butyl ester of **8** was used as in this experiment, as in entry **a**; however, the reaction was worked up with aqueous LiOH (see text), resulting in saponification of the ester. [b] The corresponding vinyloxazole resulting from elimination of MeOH was also formed in 21% yield (see text). [c] PhtN = phthalimido, TMS = trimethylsilyl.



***Scheme 4.*** Reagents and conditions: a) $SOCl_2$, reflux, 20 min, then gaseous $NH_3$, room temperature, 71%; b) CHOCOOEt, THF, reflux, 12 h; c) $SOCl_2$, room temperature, 90% (steps b, c for **14**), 68% (steps b, c for **16**); d) PhC≡CAl$Me_2$, $Et_2O$/THF, 0°C→RT, 2 h, 79% (**15**), 65% (**17**); e) EtOOCCl, $Et_3N$, 0°C, then gaseous $NH_3$, room temperature, 44%.

Products **8** derived from α-amino acids behaved normally in the oxazole-forming sequence (e.g. Table 1, with L-valine-derived **8h**). Best results were obtained when the α-amino group of the initial amino acid was blocked as an imide or a tertiary amide, that is, when no N–H bonds remained in the intermediates leading to **10**. Notably, a phthalimide segment (e.g. **8h**) is resistant to the action of the acetylenic organometallic compound. On the other hand, selective ester saponification in oxazoles that bear an *N*-phthalimido group was problematic as a result of competing semihydrolysis of the protecting group and consequent formation of highly polar materials. This difficulty may be circumvented by use of allyl glyoxylate in the synthetic scheme. The emerging allyl esters of the type **10h** are then selectively cleaved under catalysis by $Pd^0$ to form **11** (Scheme 3).[11] This is apparent in the conversion of **10h** into (*R*)-(+)-α-methylbenzylamide **12**, NMR spectra of which revealed the presence of only one diastereomer, indicating no erosion of stereochemical integrity during oxazole formation. Finally, the cyclization of alkynyl glycines derived from propargyl ethers proceeded with partial elimination of a molecule of alcohol to give vinyloxazoles: In the case of **5h**, by-product **13** (21% yield) accompanied oxazole **10h**.[12]



***Scheme 3.*** Reagents and conditions: a) dimedone, $[Pd(PPh_3)_4]$, THF, room temperature, 91%; b) (*R*)-(+)-α-methylbenzylamine, EDCI, DMAP, $CH_2Cl_2$, room temperature, 63%. EDCI = 3-(3-dimethylaminopropyl)-1-ethylcarbodiimide, DMAP = 4-dimethylaminopyridine.

The iterative mode of oxazole construction is exemplified herein with substrates **10b** and **11** (Scheme 4). Overall yields were comparable to those of monooxazoles described in Table 1.

As an application of the new findings, we describe a total synthesis of (−)-muscoride A (**26**),[13] a secondary metabolite of the freshwater cyanobacterium *Nostoc muscorum*, as outlined in Scheme 5. This bisoxazole natural product displays only modest antibiotic activity, but it has served as a useful platform to test methods of oxazole construction.[14] Our synthesis commenced with the reaction of L-*N*-Troc-prolinamide (**18**)[15] with ethyl glyoxylate. Chlorination of the resulting **19** furnished **20**, which upon sequential exposure to the dimethylaluminum derivative of TMS acetylene and aqueous LiOH workup, afforded oxazole carboxylic acid **21** through cyclization, ester hydrolysis, and desilylation.[16] The corresponding amide **22**[17] was subjected to the same sequence. The resulting acid **23** was esterified (prenyl alcohol, BOP), and the Troc group was cleaved with Cd/Pb couple.[18] *N*-Acylation of the emerging **25** with the pentafluorophenyl ester of L-*N*-(3,3-dimethyl-1-propenyl)valine, as described by Wipf and Venkatraman, led to the formation of (−)-muscoride A, $[\alpha]_D^{25} = -80.2$ ($c = 0.5$, MeOH; ref. [13]: −89, $c = 0.7$, MeOH) in 23% yield, consistent with previous work.[14a] The overall yield of **26** from **18** was thus 3.5% over ten steps.

In conclusion, the new oxazole-forming reaction appears to be generally applicable to the preparation of heterocycles

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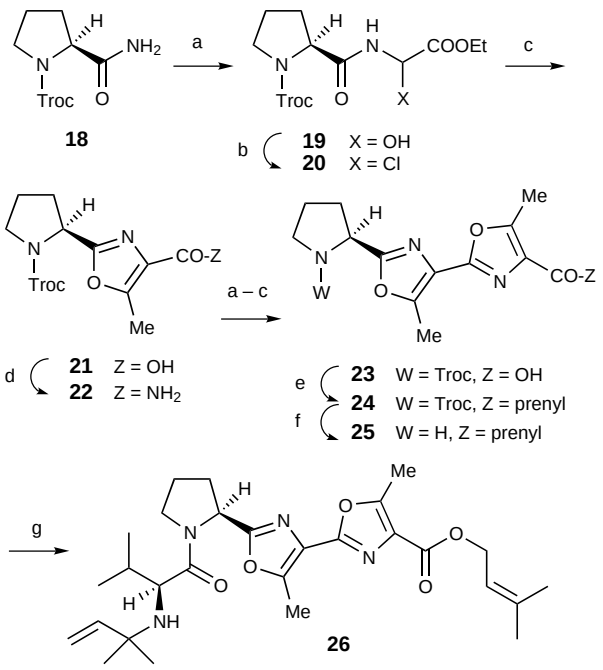


***Scheme 5.*** Reagents and conditions: a) CHOCOOEt (1.2 equiv), THF, reflux, 12 h, 95% (**19**), 75% (**23**); b) $SOCl_2$ (neat), 10 min, room temperature, quant. (crude); c) $Me_2AlC{\equiv}CSiMe_3$ (1 equiv), $Et_2O$/THF, 0 °C→RT, 2 h, then workup with aqueous LiOH (2 equiv), aqueous THF, 72% (**20**, crude), 60% (**24**, crude); d) EtOOCCl (2 equiv), $Et_3N$ (2 equiv), $CH_2Cl_2$, 0 °C, then gaseous $NH_3$, room temperature, 85%; e) prenyl alcohol (2 equiv), BOP (1.5 equiv), $Et_3N$ (3 equiv), $CH_2Cl_2$, room temperature, 12 h, 65%; f) Cd/Pb couple, THF, aqueous $NH_4OAc$ buffer, room temperature, 80%; g) **25** (1.5 equiv relative to the activated valine derivative), DMAP (1 equiv), $CHCl_3$, reflux, 24 h, 23%. Troc = trichloroethoxycarbonyl; BOP = (benzotriazol-1-yloxy)tris-(dimethylamino)phosphonium hexafluorophosphate.[14a]

of type **10**. The technique lends itself to an iterative mode of polyoxazole construction and appears to be fully compatible with multistep synthetic operations.

Received: October 10, 2002 [Z50331]

**Keywords:** alkynes · aluminum · natural products · oxazoles · polyoxazoles

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[5] The use of alkynyl aluminum reagents was inspired by: A. R. Katritzky, D. C. Oniciu, N. M. Yoon, *J. Org. Chem.* **1999**, *64*, 488.

[6] Application of the method of Williams and co-workers[3] was complicated by the poor solubility of several intermediates of the type **8** in $CCl_4$ or other nonpolar solvents, which are required for best results.

[7] Other acetylenic organometallic compounds produced poor results. Thus, we failed to induce conversion of **8** into **5b** with Li or Na acetylides (complex mixtures). Base-promoted formation of the imine corresponding to **8** (see conversion of compound **5** into **3** in: J. Vidal, J.-C. Hannachi, G. Hourdin, J.-C. Mulatier, A. Collet, *Tetrahedron Lett.* **1998**, *39*, 8845) prior to exposure to an alkynyl organometallic compound did not solve the problem. Trimethylsilylacetylenes proved to be unreactive toward **8** under a variety of conditions. The facile reaction of vinylboronic acids with iminium-type electrophiles (see N. A. Petasis, I. A. Zavialov, *J. Am. Chem. Soc.* **1997**, *119*, 7703) prompted us to explore alkynyl boronic acids as acetylide donors. Results were unsatisfactory.

[8] The following modification of the procedure of Ben-Ishai and co-workers[4] was used: α-hydroxyglycinate **7** was dissolved in $SOCl_2$ (30 equiv) and stirred at room temperature for 10 min. The mixture was diluted with an equal volume of $CH_2Cl_2$ and concentrated to afford the crude α-chloroglycinate **8**.

[9] Representative procedure for the preparation of oxazoles: commercial *n*BuLi (1.2 mmol) was added dropwise to a solution

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of 1-octyne (1.2 mmol) in THF (0.9 mL) at −78 °C under Ar. After stirring for 5 min, the mixture was transferred through a cannula into a cold (0 °C) solution of commercial dimethylaluminum chloride (solution in hexane, 1.2 mmol) in diethyl ether (0.9 mL). The mixture was stirred at 0 °C for 1 h and was then transferred dropwise through a cannula into a cold (0 °C) solution of chloroglycinate **8a** (1.2 mmol) in THF (2 mL). The cold bath was removed and the mixture was stirred for 2 h. The mixture was then was carefully concentrated *in vacuo* to about 1/3 of the original volume. Dilution with chloroform (5 mL), filtration through a plug of silica gel (elution with neat EtOAc), concentration, treatment with solid $NaHCO_3$ (2.4 mmol) in THF/$H_2O$ (1:1, 5 mL) for 2 h, extraction with diethyl ether, and concentration provided the crude oxazole. Purification by silica-gel column chromatography with cyclohexane/EtOAc (6:1) gave pure **10a** (1.1 mmol).

[10] Desilylation without ester hydrolysis may be induced in essentially quantitative yield by treatment of, for example, **10g**, with tetrabutylammonium fluoride (TBAF) (2 equiv) in $CH_2Cl_2$ (1 h, room temperature).

[11] For reviews of allyl-type blocking groups, see: a) H. Kunz, *Angew. Chem.* **1987**, *99*, 297; *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 294; b) T. W. Greene, P. G. M. Wuts, *Protective Groups in Organic Synthesis*, Wiley Interscience, New York, NY, **1999**, p. 409, and references therein.

[12] A similar reaction has been described in P. Wipf, L. T. Rahman, S. R. Rector, *J. Org. Chem.* **1998**, *63*, 7132.

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[14] For previous syntheses, see: a) P. Wipf, S. Venkatraman, *J. Org. Chem.* **1996**, *61*, 6517; b) J. C. Muir, G. Pattenden, R. Thomas, *Synthesis* **1998**, 613.

[15] Prepared from *N*-Troc-L-proline (96 mmol) (see S. A. Boys, W. J. Thompson, *J. Org. Chem.* **1987**, *52*, 1790) by reaction with $SOCl_2$ (10 equiv) in $CH_2Cl_2$ (200 mL) at reflux (20 min), concentration to dryness, dissolution into more $CH_2Cl_2$ (200 mL), and treatment with gaseous ammonia (room temperature, 90 min). Partitioning with water (100 mL), washing with brine, and concentration gave an orange residue, which was triturated with diethyl ether to furnish **18** as a white solid, $[\alpha]_D^{25} = -72$ ($c = 2.85$, $CHCl_3$).

[16] Scrutiny of the NMR spectra of the crude (*R*)-(+)-α-methylbenzylamide derivative of **21** revealed the presence of only one diastereomer (1:1 mixture of Troc rotamers) signifying that stereochemical integrity had once again been preserved.

[17] The structure of **22** was confirmed by single-crystal X-ray crystallographic analysis.

[18] Q. Dong, C. A. Anderson, M. A. Ciufolini, *Tetrahedron Lett.* **1995**, *36*, 5681.

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