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Stereoselective Mn-Mediated Coupling of Functionalized Iodides and Hydrazones: A Synthetic Entry to the Tubulysin γ-Amino Acids

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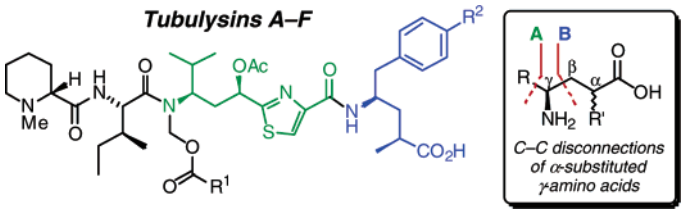
ABSTRACT



Synthesis of γ-amino acids, important building blocks in bioorganic and natural product chemistry, is accomplished using a stereoselective carbon–carbon bond construction of the chiral amine. Alkyl iodides and chiral hydrazones with protected alcohol functionality are coupled via highly diastereoselective photolytic Mn-mediated addition to the C═N bond, providing access to enantiomerically pure multifunctional chiral α-branched amines. Reductive N–N bond cleavage and alcohol oxidation provides α-substituted γ-amino acid building blocks for tubulysin D.

Tubulysins A−F[1] were recently isolated in small quantities (<4 mg/L) from myxobacterial culture broths of *Archangium gephyra* and *Angiococcus disciformis* and were found to be extraordinarily potent antimitotic agents. Cervical cancer cell growth inhibition by tubulysin D (IC_{50} 20 pg/mL[2]) exceeds that of vinblastine and dolastatin-10. Incubation of mammalian cell lines with tubulysin led to disruption of microtubuli, in contrast to the microtubule-stabilizing effects of epothilone or taxol. The extraordinary potency of tubulysin D and its interesting tubulin interactions offer an opportunity to probe the chemical biology of tubulin.[3] A total synthesis, suitable for preparation of unnatural analogues of these targets, is therefore an attractive goal.[4]

Identifiable within tubulysin D are two unusual amino acid subunits unique to the tubulysin family, both of which are α,γ-disubstituted γ-amino acids.[5] Tubuvaline (Figure 1) is comprised of an α-hydroxy-γ-amino acid (**A**, P = H) with the carboxylate masked within a thiazole, while the C-terminal residue tubuphenylalanine (**B**, P = H) is an α-methyl-γ-amino acid. These became the initial focus of our synthetic planning.

Previous methods for syntheses of γ-substituted γ-amino acids have exploited Wittig-type homologation of natural α-amino acids,[6a] addition of enolates to nitroalkenes,[6b] C1-

(1) Sasse, F.; Steinmetz, H.; Heil, J.; Höfle, G.; Reichenbach, H. *J. Antibiot.* **2000**, *53*, 879−885. Höfle, G.; Glaser, N.; Leibold, T.; Karama, U.; Sasse, F.; Steinmetz, H. *Pure Appl. Chem.* **2003**, *75*, 167−178.

(2) Data for human cervical carcinoma DSM ACC 158 (ref 1).

(3) Hung, D. T.; Jamison, T. F.; Schreiber, S. L. *Chem. Biol.* **1996**, *3*, 623−639. Christian, M. C.; Pluda, J. M.; Ho, P. T. C.; Arbuck, S. G.; Murgo, A. J.; Sausville, E. A. *Semin. Oncol.* **1997**, *24*, 219−240. Hamel, E. *Biopolymers* **2002**, *66*, 142−160.

(4) Synthesis: Höfle, G.; Leibold, T.; Steinmetz, H. German Patent DE 10008089, 2001. Also see: Henkel, B.; Beck, B.; Westner, B.; Mejat, B.; Dömling, A. *Tetrahedron Lett.* **2003**, *44*, 8947−8950.

(5) γ-Substituted γ-amino acids have found use in designed mimics of peptide secondary structures. See: Hanessian, S.; Luo, X.; Schaum, R.; Michnick, S. *J. Am. Chem. Soc.* **1998**, *120*, 8569−8570. Seebach, D.; Brenner, M.; Rueping, M.; Jaun, B. *Chem. Eur. J.* **2002**, *8*, 573−584. Baldauf, C.; Günther, R.; Hofmann, H.-J. *Helv. Chim. Acta* **2003**, *86*, 2573−2588. Seebach, D.; Schaeffer, L.; Brenner, M.; Hoyer, D. *Angew. Chem., Int. Ed.* **2003**, *42*, 776−778. Sanjayan, G. J.; Stewart, A.; Hachisu, S.; Gonzalez, R.; Watterson, M. P.; Fleet, G. W. J. *Tetrahedron Lett.* **2003**, *44*, 5847−5851. Watterson, M. P.; Edwards, A. A.; Leach, J. A.; Smith, M. D.; Ichihara, O.; Fleet, G. W. J. *Tetrahedron Lett.* **2003**, *44*, 5853−5857.

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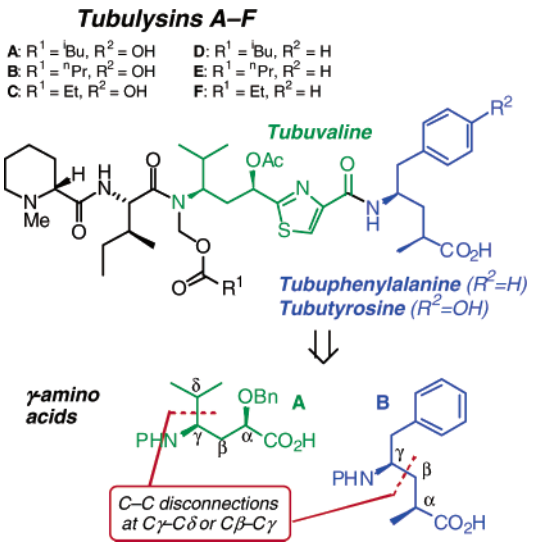

Figure 1. Retrosynthetic analysis of tubulysins A−F, antimitotic agents with picomolar potency, revealing α,γ-disubstituted γ-amino acids as key subgoals.

carboxylate modification of glutamic acid,[6c] allyl addition to sulfinimines,[6d] reaction of enolates with aziridines,[6e] and reductive coupling of nitrones with α,β-unsaturated carbonyl compounds.[6f]

We envisioned a new, general, and versatile synthesis of γ-amino acids involving a C−C bond construction approach to installation of the chiral amine moiety. This plan would obviate the limitations of naturally occurring α-amino acid precursors, facilitating preparation of γ-amino acids bearing unusual functionality or substitution patterns. For versatility, the ideal method would be applicable to strategic construction of either the Cβ-Cγ or Cγ−Cδ bonds (Figure 1) as desired, depending on circumstances such as the availability or reactivity of the proposed precursors, and would be independent of the function or configuration of substituents at the α-position. Here we report application of such strategic bond constructions for preparation of the γ-amino acid subunits of tubulysins.

As part of a program to develop asymmetric C−C bond construction approaches to chiral amines, we have developed stereoselective intermolecular additions of alkyl radicals to C=N bonds[7,8] using chiral *N*-acylhydrazones[9,10] (Figure 2a). One approach exploits photolysis of the Mn−Mn bond,

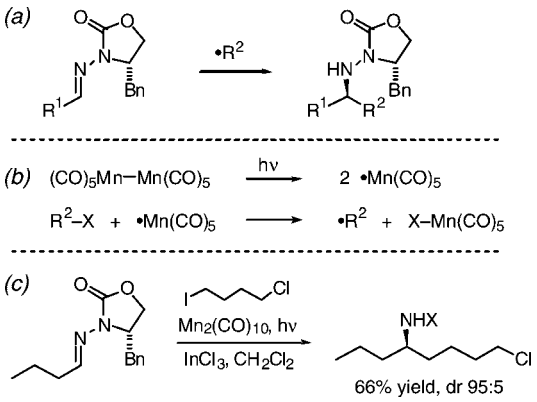

Figure 2. (a) Asymmetric radical addition approach to chiral amines using chiral *N*-acylhydrazones. (b) Photolysis of $Mn_2(CO)_{10}$ producing alkyl radicals from iodides. (c) Mn-mediated coupling of a difunctional iodide and hydrazone.[9]

known to generate alkyl radicals from alkyl halides (Figure 2b),[11] and permits coupling of *N*-acylhydrazones and primary iodides bearing additional halide functionality (e.g., Figure 2c).[9a] The functional group tolerance and nonbasic conditions of this coupling method suggested its potential utility in synthesis of multifunctional amines such as the tubulysin γ-amino acids. Our previous studies had not exploited oxygen-containing iodides or hydrazones, so preparation of **A** and **B** would constitute an important test of the synthetic versatility of the Mn-mediated coupling reactions.

Application of the Mn-mediated coupling to the γ-amino acid progenitor of tubuvaline required enantiocontrolled preparation of chiral β-alkoxyhydrazone **4** (Scheme 1).

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(10) For chiral Lewis acid control in radical addition to C=N bonds, see: (a) Friestad, G. K.; Shen, Y.; Ruggles, E. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 5061−5063. (b) Halland, N.; Jørgensen, K. A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1290−1295. (c) Miyabe, H.; Ushiro, C.; Ueda, M.; Yamakawa, K.; Naito, T. *J. Org. Chem.* **2000**, *65*, 176−185.

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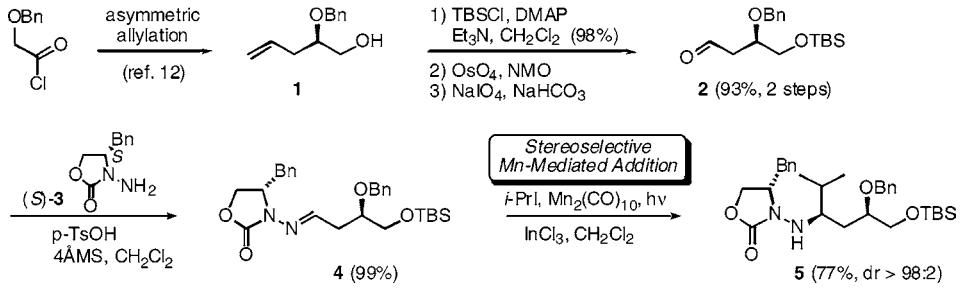
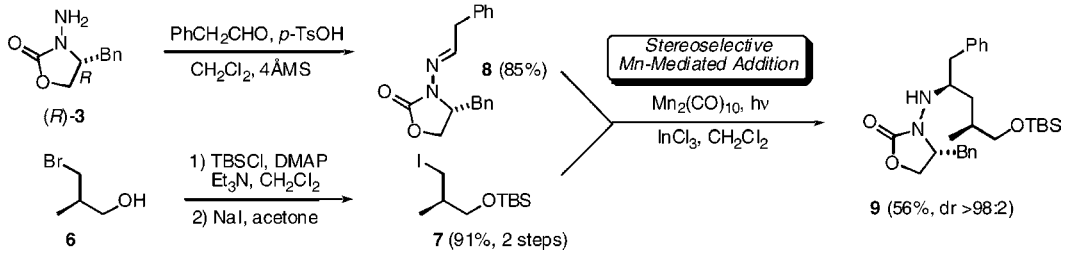
Scheme 1



Scheme 2



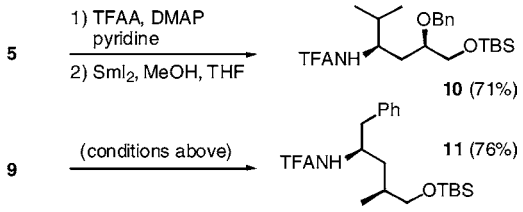
Known alcohol **1**, produced by asymmetric glycolate allylation according to the procedure of Crimmins,[12] was converted to the corresponding TBS ether. The terminal alkene was then oxidized in two steps to afford the corresponding aldehyde **2**.[13] Condensation with *N*-amino oxazolidinone (*S*)-**3**[14] provided hydrazone **4**.

With the required β-alkoxyhydrazone in hand, we proceeded to the key Mn-mediated addition reaction (Scheme 1). Upon photolysis (300 nm, Rayonet) in the presence of $InCl_3$ (2.2 equiv) and $Mn_2(CO)_{10}$ (1 equiv) in CH_2Cl_2, hydrazone **4** underwent addition of isopropyl iodide (5 equiv) providing adduct **5** in 77% isolated yield as a single diastereomer (^{1}H NMR).[15] The configuration was determined after a subsequent step (vide infra). No byproduct from elimination of the β-benzyloxy substituent was detected, a fact that underscores the nonbasic character of these reactions.

Preparation of the iodide and hydrazone components for tubuphenylalanine began with commercial (*R*)-(−)-3-bromo-2-methyl-1-propanol (**6**, Scheme 2) and phenylacetaldehyde. Silylation of the primary alcohol and Finkelstein reaction afforded known iodide **7**[16] in 91% yield after distillation. Phenylacetaldehyde was condensed with *N*-aminooxazolidinone (*R*)-**3**[14] to give *N*-acylhydrazone **8**. Merging the components in the key coupling reaction, Mn-mediated addition of iodide **7** (5 equiv) to hydrazone **8** provided **9**[17] in 56% yield.

Our attention turned to the functional group manipulations required to access the tubulysin building blocks (Scheme 3).

Scheme 3



We recently disclosed a method for facile trifluoroacetyl-activated reductive N−N bond cleavage of hydrazines by SmI_2.[18] This method results in an amine bearing a protecting group suitable for further synthetic manipulations. Treating **5** with TFAA and DMAP in pyridine gave the corresponding trifluoroacetyl derivative,[19] upon which the N−N bond cleavage with SmI_2 proceeded smoothly to provide differentially protected amino diol **10**. By the same transformations, adduct **9** was converted to TFA-protected tubuphenylalanine amino alcohol **11** in good overall yield.[20]

Reinforcing the substantial precedent on the mode of stereocontrol by chiral *N*-acylhydrazones,[9] the configuration

(12) Crimmins, M. T.; Emmitte, K. A.; Katz, J. D. *Org. Lett.* **2000**, *2*, 2165−2167.

(13) Ozonolysis was also effective, but the two-step dihydroxylation and periodate cleavage gave cleaner and more practical conversion to **2**.

(14) Shen, Y.; Friestad, G. K. *J. Org. Chem.* **2002**, *67*, 6236−6239.

(15) Small amount (7%) of unreacted hydrazone was recovered in this experiment. Aged samples of $Mn_2(CO)_{10}$ gave lower yields (ca. 50−60%) due to incomplete conversion in these reactions, but the mass balance was still >80%.

(16) Nakamura, Y.; Mori, K. *Eur. J. Org. Chem.* **2000**, 2745−2753.

(17) Configuration of **9** was assigned by analogy with precedents resting on crystallography and chemical correlation. See ref 9.

(18) Ding, H.; Friestad, G. K. *Org. Lett.* **2004**, *6*, 637−640.

(19) Acylation of tubuphenylalanine precursor **9** as described previously (*n*-BuLi, TFAA) resulted in 69% yield. Similar results were found with tubuvaline precursor **5** (77% yield).

(20) (a) Alternatively, sequential treatment with BH_3·THF and Boc_2O converted **9** to the corresponding Boc-amino alcohol in 74% yield. (b) For examples of N−N cleavage with borane, see refs 9a and 10a. See also: Feuer, H.; Brown, F., Jr. *J. Org. Chem.* **1970**, *35*, 1468. Enders, D.; Lochtman, R.; Meiers, M.; Muller, S.; Lazny, R. *Synlett* **1998**, 1182.

and enantiomeric purity (>96% ee) of **10** were established by ^{1}H NMR analysis using Boc-phenylglycine amide derivatives according to the method of Riguera.[21]

Finally, **10** and **11** were oxidized to γ-amino acids **A** and **B** (Figure 1, P = TFA), respectively, in a two-step process with excellent overall yield. Removal of the TBS protection (TBAF, THF) and oxidation of the resulting primary alcohols with $PhI(OAc)_2$ in the presence of catalytic TEMPO[22] (2,2,6,6-tetramethyl-1-piperidinyloxy) afforded γ-amino acids **A** (96%, two steps) and **B** (81%, two steps).

In conclusion, a new C−C bond construction approach to synthesis of α,γ-disubstituted γ-amino acids has been developed, providing access to enantiomerically pure building blocks for total synthesis of tubulysins. The key step for each is a highly stereoselective Mn-mediated coupling of an alkyl iodide and a hydrazone, methodology extended by this study to incorporate oxygen-containing functionality in either the iodide or hydrazone precursor. Taken together with the scope of our previous Mn-mediated coupling studies,[9a] this work suggests potential access to a broad range of γ-substituted γ-amino acids.

Acknowledgment. We thank NIH (NIGMS, GM-67187-01) for generous support of this work.

Supporting Information Available: Experimental procedures and characterization data for compounds **1**, **2**, **4**, **5**, **8**−**11**, **A**, and **B**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) (a) Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **1999**, *64*, 4669−4675. (b) The amides were prepared via DCC-mediated coupling of the free amines. For spectra used in configuration analysis, see Supporting Information.

(22) For previous applications of TEMPO-catalyzed oxidation to α-alkoxy-acids with remote secondary amide functionality, see: Vescovi, A.; Knoll, A.; Koert, U. *Org. Biomol. Chem.* **2003**, 2983−2997. Yeung, B. K. S.; Hill, D. C.; Janicka, M.; Petillo, P. A. *Org. Lett.* **2000**, *2*, 1279−1282.