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An Intramolecular, Ni(0)-Mediated Approach to the Nonracemic Biaryl Portion of Vancomycin

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Summary. Using a tether derived from tartaric acid to which is attached two halogenated phenylglycine residues, a Ni(0)-induced biaryl coupling can be effected with complete control of axial chirality. © 1999 Elsevier Science Ltd. All rights reserved.

For decades, synthetic chemists have appreciated the challenges posed by the clinically valued antibiotic vancomycin,¹ and only recently have two monumental total syntheses of the aglycon been completed.^{2,3} Several groups have come to focus on the axially chiral biaryl (**A-B**) portion,^{4a-c} for control of this subsection plays a pivotal role in addressing the two additional key issues of planar chirality in this target.⁵ Thus far, the only successful *direct* approach to the natural *S* biaryl isomer has relied on the *unnatural S* stereochemistry at the amino acid 5 site.⁶ Otherwise, constructions of both the inter- and intramolecular variety have been essentially stereorandom or selective for the unnatural *R* biaryl isomer, with levels of efficiency that can be quite variable. We now describe one potential solution which relies on an intramolecular route using a nonracemic tether as a means of inducing the required biaryl asymmetry.



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Phenylglycine derivatives 6 and 7 were prepared as illustrated in Scheme 1 via modification of literature procedures.⁷ Bromination (Br₂, HOAc) of commercially available 1 led to 2 (X = Br), while iodination (ICl, HOAc) afforded the corresponding iodide. Esterification of 2 in acidic methanol led to 3, which could be N-protected using di-*t*-butyldicarbonate to afford Boc derivative 4. Ester reduction gave diol 5, which was readily converted to acetonides 6 and 7, setting the stage for attachment to a nonracemic tether.

Scheme 1. Synthesis of phenylglycine derivatives 6 and 7.



Mitsunobu coupling of 6 (or 7) with inversion in monosilylated tether 8^8 proceeds to give 9 (or 10) (Scheme 2). Desilylation of 9 (or 10) sets the stage for similar attachment of a second phenylglycine equivalent to give tethered intermediates 13-15. Attempted intramolecular coupling *via* the derived cyanocuprate,⁹ used previously with considerable success *en route* to BINOL,⁸ afforded none of the desired biaryl 16 upon oxidation. Switching to group 10 metals, several experiments aimed at effecting a Stille or Negishi cross-coupling under the influence of catalytic Pd(0) (*e.g.*, Pd₂dba₃, Pd(dppf)₂, Pd(PPh₃)₄) failed to produce any of the desired biaryl. Preformed Ni(0) (*i.e.*, two equivalents), prepared from NiCl₂·2PPh₃ + 2PPh₃ + 2*n*-BuLi in THF, remarkably, was totally ineffective on bromoiodide 14a, although complete net reduction of the aryl iodide was noted. Only by utilizing diodide 15 could trace amounts of the critical biaryl bond be formed. Under these cyclization conditions the major by-product was that of double reduction, attributed to the THF medium. Removal of THF *in vacuo* after generation of Ni(0), replacement with dry, deoxygenated DMF (0.01 M), and heating with 15 to 50° C overnight significantly increased the isolated yield of product 16, albeit to only 39%. By increasing the amount of Ni(0) to 2.7 equivalents (added in two equal portions as a slurry in DMF, the second after 2 h), biaryl 16 could be obtained to the extent of 50%.

Although molecular modeling of product ground state structures, as well as precedent in the cuprate route,⁸ strongly suggested that a single (S) diastereomer would be obtained, it was nonetheless gratifying to realize only one isomer using an organonickel intermediate. High field (500 MHz) NMR analysis of the crude



Scheme 2. Attachment of 6 / 7 to a nonracemic tether 8 and intramolecular biaryl coupling to 16.

biaryl reaction mixture showed no indication of the unnatural R isomer. Chiral HPLC analyses under varying conditions of columns and solvent(s) showed the presence of only one compound in each run.¹⁰ Catalytic hydrogenation of **16** afforded debenzylated diol **17**, which displayed a greatly simplified aromatic region in its ¹H NMR spectrum. Again, only signals due to a single biaryl were observed, a finding subsequently corroborated again by chiral HPLC analysis.¹⁰ Comparison data from the CD spectrum for **16** with related compounds in the literature¹¹ were also in full accord with the assignment of *S* stereochemistry.

In sum, a novel, stereospecific, and relatively efficient nickel(0)-induced approach¹² utilizing a tartratederived tether **8** for inducing chirality in a model biaryl (**16**) related to vancomycin aglycon has been demonstrated. Moreover, a tethered intermediate along the lines of **16** may offer the unique feature of serving as a nonracemic biaryl 'protecting group', potentially inhibiting erosion of axial chirality in subsequent synthetic operations. Ongoing efforts aimed at further improvements in the Ni(0)-mediated coupling, extension of this chemistry to the 'real' vancomycin **A-B** unit wherein the A-ring amino acid is differentiated from that in the Bring, and the in-tandem use of both a nonracemic tether *and* dipeptide linkage as control elements in the cyclization, will be reported in due course.



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- 9. Metal-halogen exchange followed by cyanocuprate formation and oxidation affords a single diastereomer, as illustrated below, en route to S-BINOL.⁷



- 10. Chiral HPLC analyses were conducted at Regis Technologies by Dr. Chris Welch, using a conventional analytical column packed with Whelk-O chiral stationary phase (CSP). For a representative reference wherein atropisomers have been separated using this technology, see Wolf, C.; Pirkle, W.H.; Welch, C.J.; Hochmuth, D.H.; König, W.A.; Oleschuk, C.J.; Chee, G.L.; Charlton, J.L. J. Org. Chem. 1997, 62, 5208.
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