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

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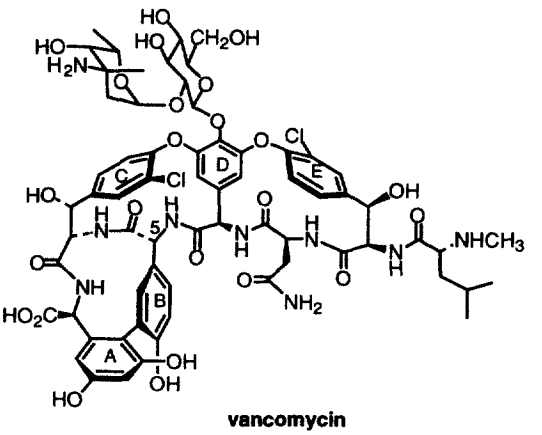
Summary. *Using a tether derived from tartaric acid to which is attached two halogenated phenylglycine residues, a Ni(0)-induced biaryl coupling can be effected with complete control of axial chirality.*

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.



vancomycin

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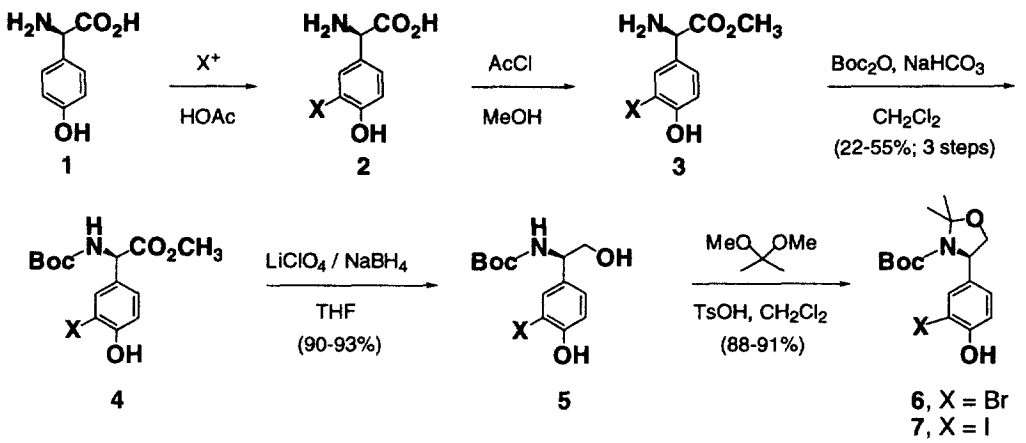
Phenylglycine derivatives **6** and **7** were prepared as illustrated in **Scheme 1** *via* modification of literature procedures.[7] Bromination (Br_2, HOAc) of commercially available **1** led to **2** (X = Br), while iodination (ICl, HOAc) afforded the corresponding iodide. Esterification of **2** 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.

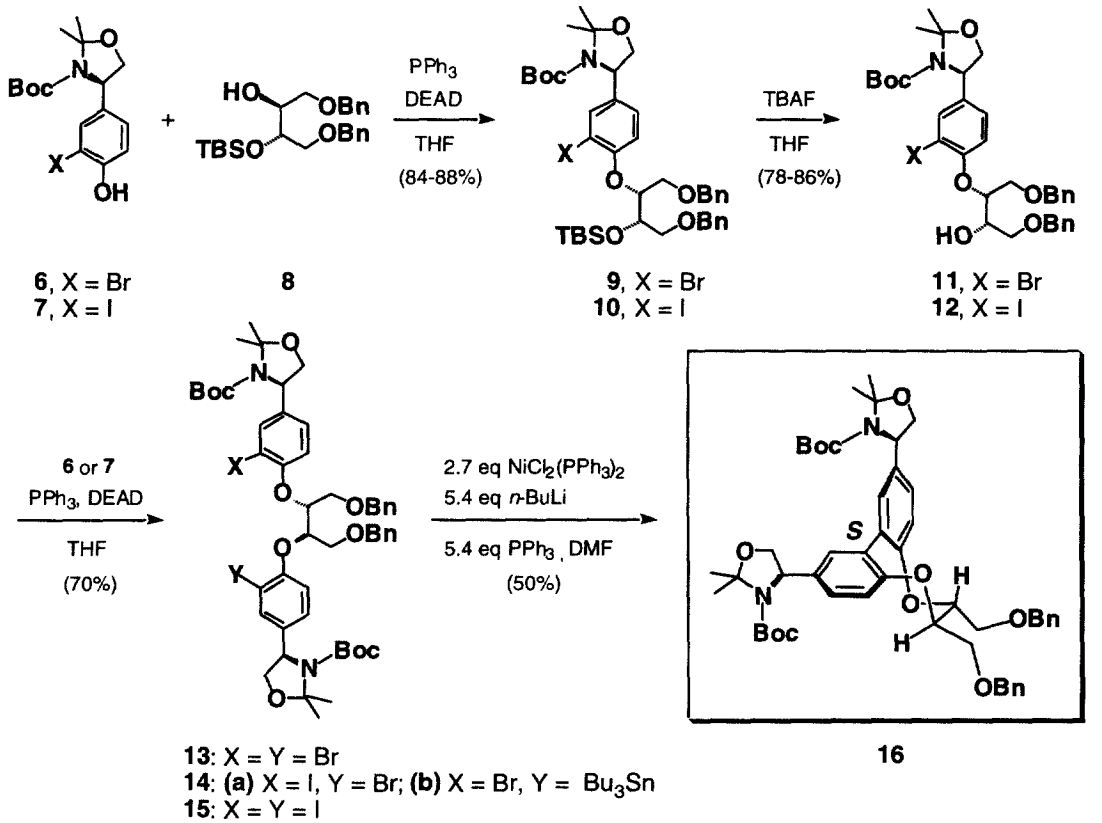
Scheme 1. Synthesis of phenylglycine derivatives **6** and **7**.



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.*, Pd_2dba_3, $Pd(dppf)_2$, $Pd(PPh_3)_4$) failed to produce any of the desired biaryl. Preformed Ni(0) (*i.e.*, two equivalents), prepared from $NiCl_2{\cdot}2PPh_3$ + $2PPh_3$ + 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%.

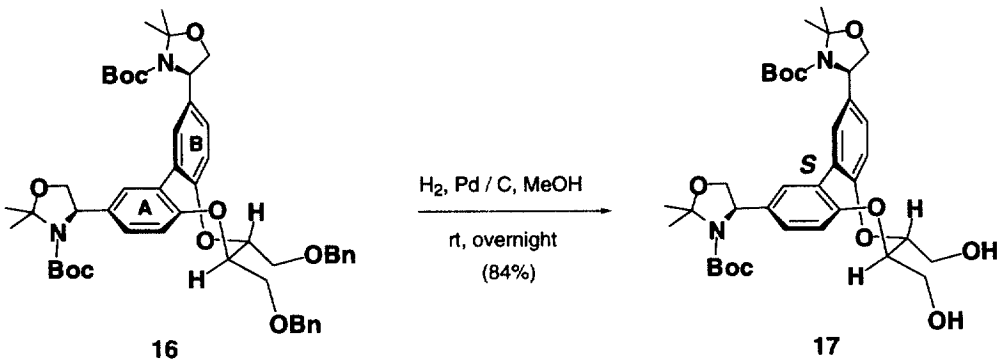
Although molecular modeling of product ground state structures, as well as precedent in the cuprate route,[8] strongly suggested that a single (*S*) diastereomer would be obtained, it was nonetheless gratifying to realize only one isomer using an organonickel intermediate. High field (500 MHz) NMR analysis 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 ^{1}H 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 literature[11] were also in full accord with the assignment of *S* stereochemistry.

In sum, a novel, stereospecific, and relatively efficient nickel(0)-induced approach[12] utilizing a tartrate-derived 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 B-ring, 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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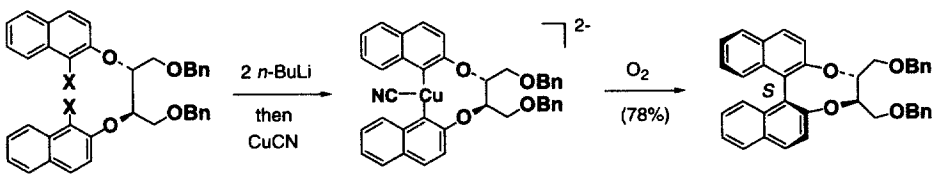
9. Metal-halogen exchange followed by cyanocuprate formation and oxidation affords a single diastereomer, as illustrated below, *en route* to *S*-BINOL.[7]



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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