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INTRAMOLECULAR BIARYL COUPLING: ASYMMETRIC SYNTHESIS OF THE CHIRAL B-RING DIOL UNIT OF PRADIMICINONE

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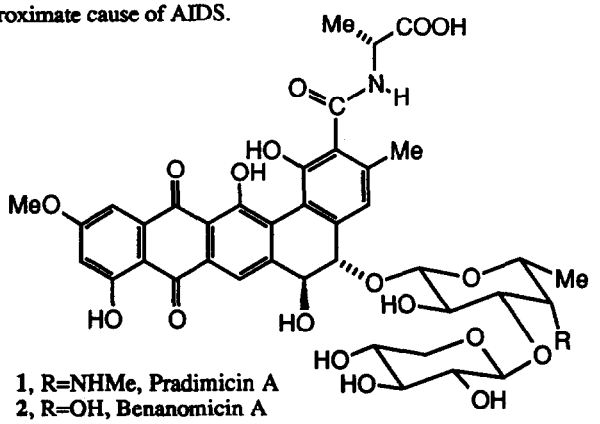
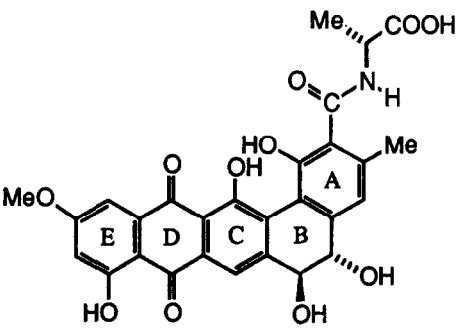
Abstract: *The combination (Equation 1) of palladium-catalyzed intramolecular biaryl coupling with enantioselective dihydroxylation of achiral stilbenes provides an efficient, two-step route to the chiral 9,10-dihydrophenanthrenediol unit of the pradimicins and benanomicins.*

Pradimicin A[1] (**1**), benanomicin A[2] (**2**) and related compounds exhibit potent *in vivo* activity against a variety of potentially fatal systemic fungal infections and are relatively nontoxic. Very recently it was reported[3] that **1**, **2** and some congeners also inhibit initial infection by - and subsequent spreading of - human immunodeficiency virus (HIV), the proximate cause of AIDS.



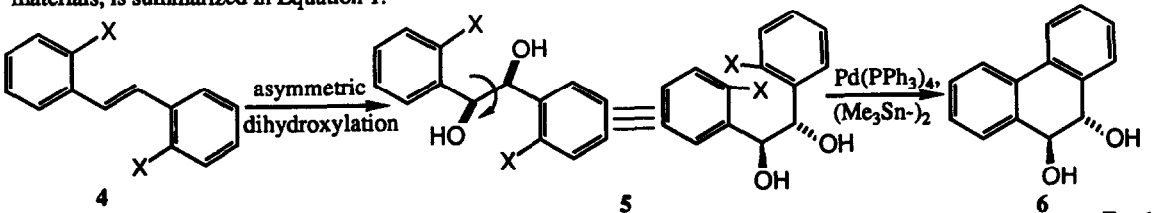
1, R=NHMe, Pradimicin A
2, R=OH, Benanomicin A



3

As one component of a program directed toward the development of an efficient and general synthetic route to **1**, **2**, and analogs thereof, we required a means of constructing the aglycone **3**. To our mind, the principal challenge presented by **3** involves the introduction of the two chiral centers of the B ring, but no method known to us offered a simple solution that addressed both the relative *and* absolute stereochemistry of those two chiral centers.

We now report an efficient, two-step solution to the problem of B-ring construction. The method combines recent discoveries in enantioselective dihydroxylation of olefins[4,5] with a hitherto unreported, *intra*molecular version of palladium-catalyzed biaryl coupling.[6-8] The method, which utilizes easily accessible,[9] achiral *trans*-stilbenes as starting materials, is summarized in Equation 1.



4 **5** **6**

a, X=Br; **b**, X=I; **c**, X=OTf

Eq. 1

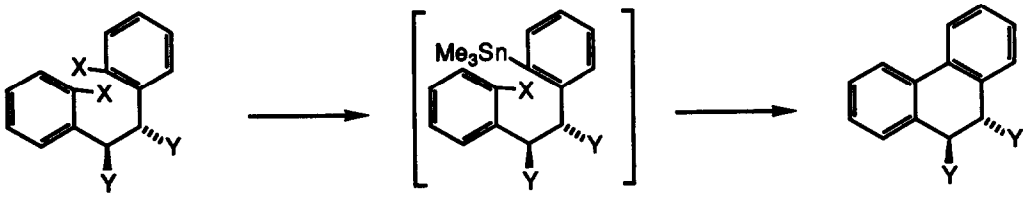
To date we have only explored Sharpless technology[4] for the asymmetric dihydroxylation of **4** to **5** because of the commercial availability (Aldrich) of the Sharpless chiral ligands. Both chemical yields and enantiomeric excess are more than satisfactory (Table 1); even higher ee's may be achievable using other[5] ligands. The intramolecular biaryl coupling of **5** to **6** proceeds (Table 2) well for all three versions of **5** (X = Br, I, OTf) examined to date, as well as for simpler substrates (**7**[15]). Control experiments[16] established that the asymmetry of the two chiral centers in **5** is preserved during the cyclization to **6**.

Table 1. Asymmetric Dihydroxylation of Stilbenes[13]

Substrate	X	Method[a]	Yield (%)[b]	ee (%)[c]	Configuration[d]	Product
4a	Br	A	94	---	-------	**5a**
4a	Br	B	80	95	(S,S)[e]	**5a**
4a	Br	B	83	86	(R,R)[f]	**5a**
4a	Br	C	94	79	(S,S)[e]	**5a**[g]
4a	Br	C	94	72	(R,R)[f]	**5a**
4b	I	A	91	---	-------	**5b**
4b	I	B	82	77	(R,R)[f]	**5b**
4c	OTf	A	96	---	-------	**5c**
4c	OTf	B	70	82	(S,S)[e]	**5c**
4c	OTf	B	70	70	(R,R)[f]	**5c**
4c	OTf	C	80	45	(S,S)[e]	**5c**
4c	OTf	D	97	65	(S,S)[e]	**5c**

(a) Method A[14]: i. OsO_4 (0.02 eq.), *N*-methylmorpholine *N*-oxide (NMO, 1.2 eq.), $PhB(OH)_2$ (1.2 eq.), CH_2Cl_2; ii. excess 20% aq Me_2NH; Method B[4a,d]: i. OsO_4 (1.1 eq.), Dihydroquinine *p*-chlorobenzoate (DHQPCB) or Dihydroquinidine *p*-chlorobenzoate (DHQDPCB) (1.1 eq.), toluene; ii. $LiAlH_4$ (6 eq.), ether; Method C[4b]: OsO_4 (0.01 eq.), DHQPCB or DHQDPCB (0.25 eq.), NMO (1.5 eq.), acetone/water(5/1); Method D: i. OsO_4 (1.1 eq.), DHQPCB (1.1 eq.), $PhB(OH)_2$ (1.1 eq.), CH_2Cl_2, 0 °C; ii. excess 20% aq Me_2NH. (b) isolated yield of chromatographically pure material. (c) ee was determined by HPLC analysis[4d] of bisacetates of diols on a 220x4.6mm ID Pirkle 1A D-phenylglycine column (Regis) using 5% *i*-PrOH in hexane as eluant. (d) assigned using the model proposed by Sharpless et al.[4] (e) DHQPCB was used. (f) DHQDPCB was used. (g) recrystallization twice from CH_2Cl_2 gave enantiomerically pure (*S,S*)-**5a** as colorless needles, mp 105.5-106.0 °C, $[\alpha]_D^{23}$ = +39.9°(c=1.0, EtOH).

That hexamethylditin might induce dihalides and ditriflates **5** and **7** to undergo palladium-catalyzed intramolecular biaryl coupling was initially suggested by the salient observation[17] that $(Me_3Sn\text{-})_2$ fosters *inter*molecular dimerization of aryl halides. We propose that the intramolecular coupling of **5** and **7** proceeds via the intermediacy of monostannanes **8** and **9** (as shown in Equation 2); support for that mechanism is provided by the findings that (i) $Pd(Ph_3P)_4$ alone does not



Eq. 2

5, Y=OH
7, Y=H

8, Y=OH
9, Y=H

6, Y=OH
10, Y=H

a, X=Br; **b**, X=I; **c**, X=OTf

promote the cyclization of **7a** to **10**, (ii) **9a**, prepared independently,[18] cyclizes cleanly (78%) to **10** with $Pd(Ph_3P)_4$ in the absence of $(Me_3Sn\text{-})_2$ (otherwise as in Reaction Condition B of Table 2), and (iii) workup of the $(Me_3Sn\text{-})_2$ mediated

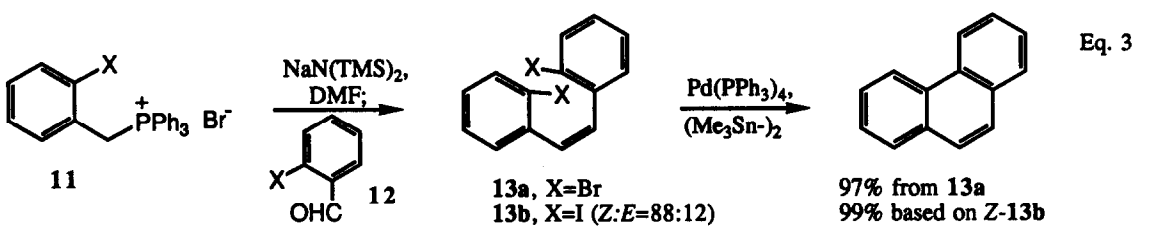
Table 2. Palladium Catalyzed Intramolecular Biaryl Coupling with Hexamethylditin[13]

Substrate	X	Y	Reaction Conditions[a]	Reaction Time (h)	Product	Yield (%)[b]
5a	Br	OH	A	24	**6**	80
5a	Br	OH	B	24	**6**	59
5a	Br	OH	C	48	**6**	48
5b	I	OH	A	24	**6**	87
5c	OTf	OH	D	24	**6**	88
7a	Br	H	A	53	**10**	82
7a	Br	H	B	42	**10**	76
7c	OTf	H	D	24	**10**	95

(a) Condition A: **5** or **7** (0.10 mmol), $Pd(PPh_3)_4$ (5-20 mol %) and $(Me_3Sn\text{-})_2$ (26μl, 1.2 eq.) in 1.0 ml anh dioxane in a sealed tube at 100-105 °C under argon; Condition B: as in A but toluene used as solvent at 110-115 °C; Condition C: as in A except $(Bu_3Sn\text{-})_2$ used in place of $(Me_3Sn\text{-})_2$; Condition D: as in A plus ~5 eq. freshly dried (100 °C / 0.05 torr) LiCl.[7c] (b) isolated yield of chromatographically pure material.

cyclization of **7a** to **10** after only 10 (rather than ~48) hours reveals the presence of substantial amounts of **9a**.

The method described herein, in addition to providing a specific solution to the problem posed by pradimicinone (**3**), also offers a potentially general alternative to more classical methods of intramolecular biaryl coupling (e.g., oxidative coupling[19] and the Pschorr synthesis[20]) in which regiochemical control and/or corrosive reaction conditions sometimes present difficulties. Additionally, we note that in the two cases examined (Equation 3), the palladium catalyzed



Eq. 3

coupling of *cis*[21] stilbenes **13** (the major products from the Wittig reaction of **11** with **12**) achieves the same net result as a stilbene photocyclization. By implication, the results in Equation 3 offer a means for predetermining the regiochemical outcome of cyclizations of unsymmetric stilbenes; such control is not always available in photocyclizations.[22]

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16. (*R,R*)-(-)**5a** (ee=86%) was subjected to condition A (Table 2) to give (*R,R*)-**6**, $[\alpha]_D^{27}$= +68.4° (c=0.25, EtOH) with ee=86% (^{19}F NMR and HPLC of the bis-Mosher ester)
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