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From Axial Chirality to Central Chiralities: Pinacol Cyclization of 2,2′-Biaryldicarbaldehyde to *trans*-9,10-Dihydrophenanthrene-9,10-diol**

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In memory of Vladimir Prelog

We describe herein two salient features of the pinacol cyclization of 2,2′-biaryldicarbaldehydes (Scheme 1): 1) the stereoselectivity to give only the *trans*-diol, and 2) the stereospecificity to transmit the axial chirality (in case the starting
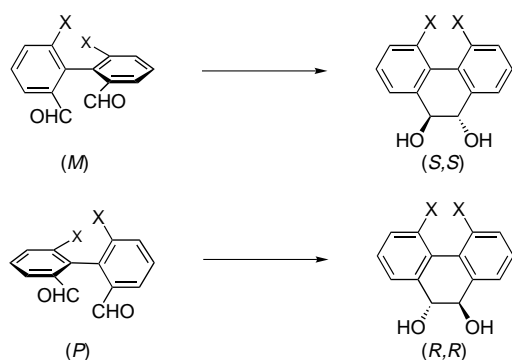

Scheme 1. Chiral transmission.

biphenyl is configurationally stable) onto two stereogenic centers of the product. The accessibility of the *trans*-9,10-dihydrophenanthrene-9,10-diol structure has consequences

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not only to the synthesis of natural products (e.g. **1**),[1] but also to the creation of a new compound such as **2** with potential utility in asymmetric synthesis.[2]

1: pradimicin A   **2**
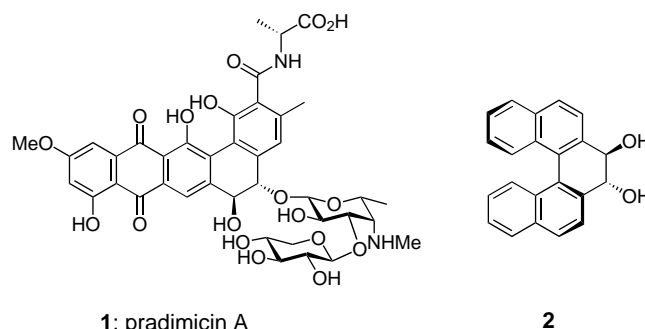
Our initial attempt was centered on the reaction of 2,2′-biphenyldicarbaldehyde (**3**),[3] which upon treatment with SmI$_2$[4] (2 equiv, THF, 0 °C, 5 min) was cleanly converted into the *trans*-diol **4**[5] as the sole product in 99% yield (Table 1, run 1). To our knowledge, the *intramolecular* pinacol coupling of two aromatic aldehydes is unprecedented,[6] as opposed to many *intermolecular* examples.[7] The observed *trans* selectivity stands in contrast to the *cis* selectivity generally seen for aliphatic 1,6-dicarbonyl compounds.[7, 8]

Table 1. Pinacol cyclization of **3** with various reductants.

Run	Reductant	Yield [%]	*trans/cis* of **4**
1	SmI$_2$	99	> 99/1
2	SmI$_2$, HMPA	93	> 99/1
3	[VCl$_3$(THF)$_3$], Zn[a]	93	> 99/1
4	TiCl$_4$, *n*BuLi[b]	80	> 99/1
5	TiCl$_4$, Zn[c]	96	20/1
6	TiCl$_4$, Mg(Hg)[c]	94	16/1
7	Ce, I$_2$	81	16/1

[a] In CH$_2$Cl$_2$. [b] In Et$_2$O. [c] At −10 °C.

It turned out that consistently high selectivities and yields were attained with various reducing agents (Table 1). Especially, SmI$_2$ or [VCl$_3$(THF)$_3$]/Zn[9a] led to perfect *trans* selectivity (runs 1 and 3). Use of a dipolar aprotic cosolvent (hexamethyl phosphoramide, HMPA) did not affect the reaction course (run 2). Use of low-valent titanium or cerium[9b–e] gave a slight decrease in either the selectivity or the yield (runs 4–7).

At this stage, we made an analysis on the origin of the selectivity. Taking the *M* isomer as an example (Scheme 2), emergence of the *trans* selectivity could be traced back to two possible modes of reaction with respect to the mutual relation of two aldehyde faces, both with a *like* topicity, *Re,Re* and/or *Si,Si*. Given that the reaction proceeded uniquely by one of

Scheme 2. Two possible modes of the pinacol cyclization.

these modes, the chiral information due to the atropisomerism can be transmitted to the diol stereogenicities of the product. Of course, prerequisite for such a scenario is the configurational stability of the starting biphenyl (cf. **3**) before participation in the pinacol cyclization.[10]

As a model compound to check out this possibility, chiral dialdehyde **5** [see Eq. (1)] was chosen, considering the relevance to the projected natural product synthesis.[1] Optical resolution was carried out for phenol **7** by esterification ((−)-(1S,4R)-camphanoyl chloride) and separation of the resulting

7   8   9

MOM = methoxymethyl
TBS = *tert*-butyldimethylsilyl
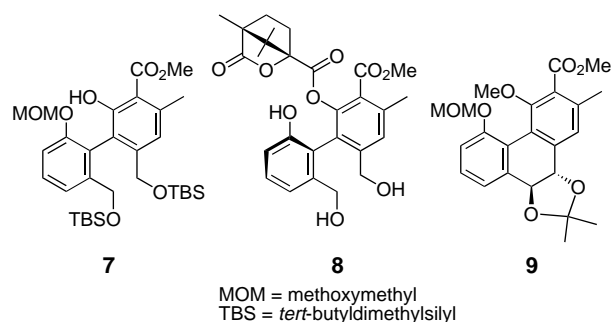
diastereomers by column chromatography (SiO$_2$, hexane/EtOAc 4/1). Subsequent four steps (1. K$_2$CO$_3$/MeOH, 2. MeI, K$_2$CO$_3$, 3. *n*Bu$_4$NF, 4. MnO$_2$) gave the enantiomeric dialdehydes (*P*)-**5** and (*M*)-**5**, which proved to be configurationally stable at room temperature, in line with the general behavior for 2,2′,6,6′-tetrasubstituted biphenyls.[10] The more polar isomer of **7** was converted into the crystalline derivative **8**, which was suitable for an X-ray analysis (Figure 1).[11]

Upon reaction of (*M*)-**5** with SmI$_2$ [Eq. (1)], we observed quantitative formation of the *trans*-diol (*S,S*)-**6**, which proved to be diastereo- and enantiomerically pure.[12] The absolute configuration was determined by the CD spectrum of the
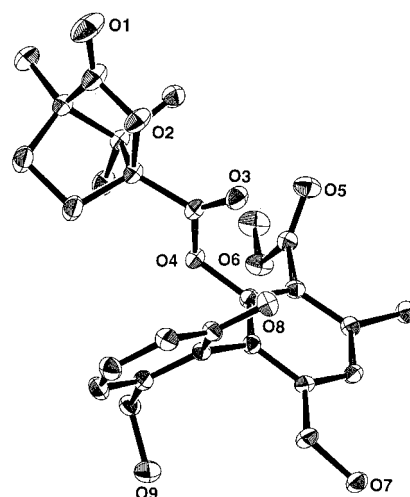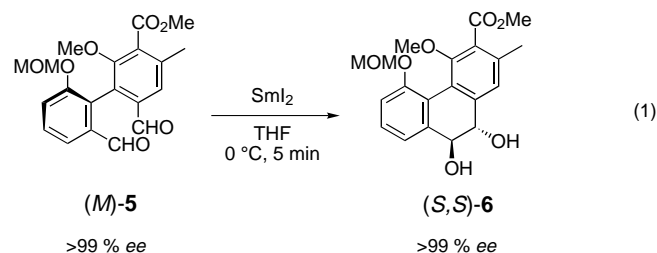
Figure 1. X-ray crystal structure of **8**.

derived acetonide **9**.[13, 14] Thus, among two possible modes of chiral transmission, mode A [(*M*)→(*S,S*)] proved to be uniquely operative (Scheme 2). The same situation was, of course, true for the antipodal series [(*P*)→(*R,R*)].

This outcome implies two points: 1) The reaction proceeds by the *synclinal* mode,[15] and 2) the initial conformation of the cyclized product is diequatorial.[15] However, the latter information is generally lost at the stage of cyclized products, as they undergo a rapid conformational change (diequatorial ⇌ diaxial) due to the pronounced lowering of the rotational barrier of the "2,2′-tethered biphenyl" with a two-atom bridge.[10, 16] Indeed, the diacetate **10** derived from **6** has a low barrier for this interconversion (ca. 15 kcal mol^{-1}), as estimated by variable-temperature NMR spectroscopy (Figure 2).

However, our attempt to snapshoot the "kinetic conformation" of the product was nicely achieved by using a conformationally restricted substrate **11** [racemate; Eq. (2)].[17] Treatment of **11** with SmI$_2$ gave the diequatorial isomer **12a** as the only *trans*-diol, consistent with the above mentioned data.[18]

The synthetic scope of the present process is not restricted to natural product synthesis,[1] but has relevance to asymmetric synthesis: Application of the reaction to the enantiopure dialdehyde **14**, readily obtained from the 2,2′-(*S*)-(−)-binaphthol-derived diester **13**[19] in two steps (1. LiAlH$_4$, 93%,

(*M*)-**5**   (*S,S*)-**6**

>99 % *ee*   >99 % *ee*
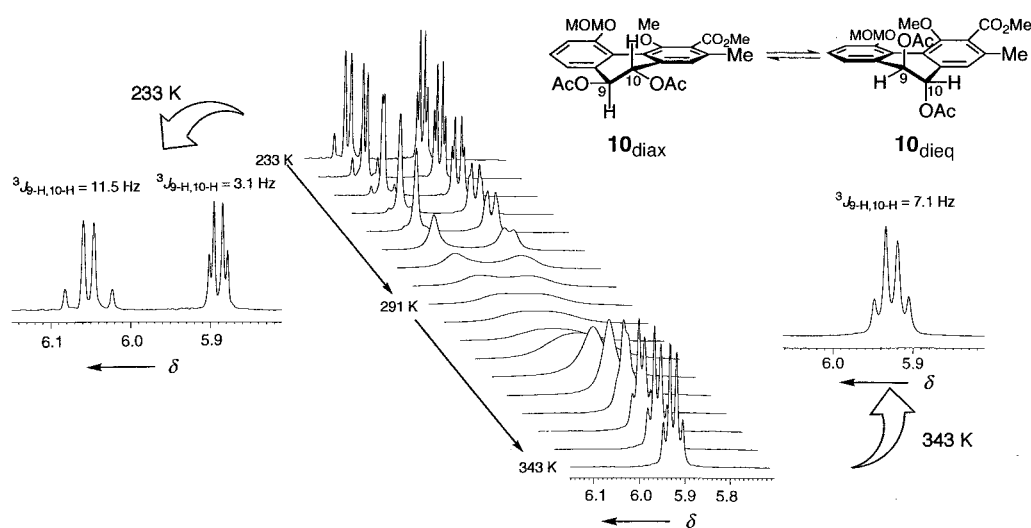
(1)

SmI$_2$
THF
0 °C, 5 min

Figure 2. Variable-temperature NMR spectrum of **10** (500 MHz, CDCl$_3$, sealed tube). At low temperature (233 K), two sets of doublets were observed, assignable to **10$_{dieq}$** ($^3J_{9\text{-H},10\text{-H}}$ = 11.5 Hz) and **10$_{diax}$** ($^3J_{9\text{-H},10\text{-H}}$ = 3.1 Hz), suggesting their slow interconversion. The ratio of **10$_{dieq}$** to **10$_{diax}$** was about 1:1 (233 K). Upon warming, these peaks became closer with broadening and finally coalesced (T_c = 291 K), and further warming (343 K) led to a set of sharp doublets ($^3J_{9\text{-H},10\text{-H}}$ = 7.1 Hz).

2. MnO$_2$, 96 %) gave a novel C_2-symmetric diol **2** in 94 % yield with full stereochemical integrity [*trans*, diequatorial, > 99 % *ee*; Eq. (3)].[20] The utility of **2** and its derivatives in asymmetric reactions is the subject of our current investigation.

(2)

(3)
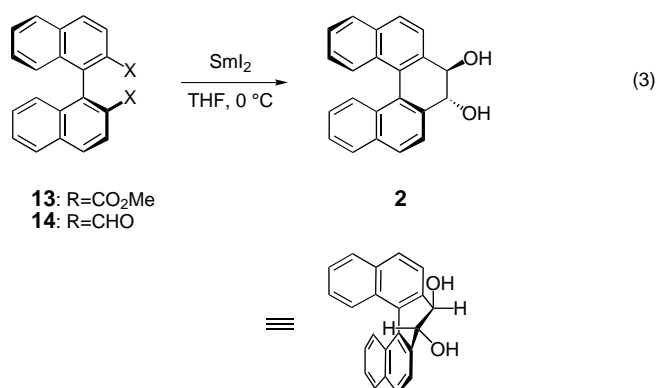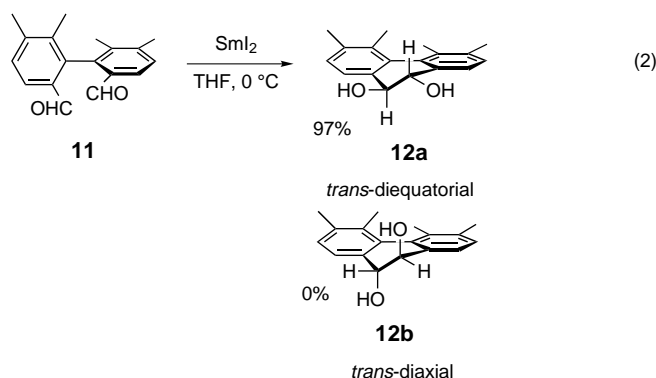
Experimental Section

In a typical experiment for pinacol cyclization, SmI$_2$ (0.1 M in THF, 5.0 mL, 0.50 mmol) was added to a solution of **3** (50.0 mg, 0.238 mmol) in THF (2 mL) at 0 °C. After 5 min of stirring at 0 °C, the reaction was quenched by addition of 1 M HCl, and the mixture was extracted with EtOAc (3 ×). The combined organic extracts were washed with water and brine, dried (Na$_2$SO$_4$), and concentrated in vacuo. The residue was purified by preparative thin-layer chromatography (TLC; hexane/EtOAc 1/1) to afford **4** (49.9 mg, 99 %) as white solid.

2: Colorless needles (EtOAc); R_f = 0.28 (silica gel, EtOAc/hexane 1/1); m.p. 277 – 278 °C (decomp.); $[\alpha]_D^{21}$ = + 689 (c = 1.00, MeOH); IR (KBr): $\tilde{v}$ = 3356 (br), 3055, 1593, 1507, 1359, 1339, 1113, 820, 761, 745 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ = 3.29 (br s, 2 H; O*H*), 4.73 (br s, 2 H; C*H*OH), 7.25 (ddd, 2 H, J = 8.5, 7.0, 1.5 Hz; Ar*H*), 7.45 (ddd, 2 H, J = 8.0, 7.0, 1.0 Hz; Ar*H*), 7.54 (br d, 2 H, J = 8.5 Hz; Ar*H*), 7.89 (br d, 2 H, J = 8.0 Hz; Ar*H*), 7.90 (d, 2 H, J = 8.5 Hz; Ar*H*), 7.94 (d, 2 H, J = 8.5 Hz; Ar*H*); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 136.0, 133.6, 130.0, 128.9, 128.33, 128.29, 127.4, 125.4, 125.2, 121.3, 74.8; HR-MS (EI:) m/z: 312.1155 [M^+] (calcd for C$_{22}$H$_{16}$O$_2$: 312.1150); elemental analysis calcd for C$_{22}$H$_{16}$O$_2$· 0.5 CH$_3$CO$_2$C$_2$H$_5$: C 80.87, H 6.06; found: C 80.88, H 5.66.
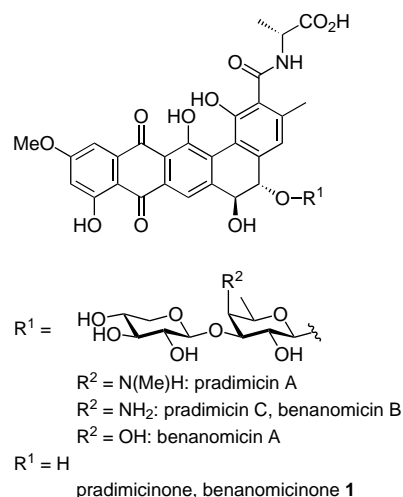
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[11] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-112115. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+ 44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

[12] Both enantiomers of **6** proved to have an enantiomeric excess of greater than 99 % *ee* by derivatization with (*S*)-(+)-methoxy(trifluoromethyl)phenylacetic acid chloride (MTPA-Cl) and assay by ^{1}H NMR spectroscopy (400 MHz) and HPLC (SUMICHIRAL OA-2000): J. A. Dale, D. L. Dull, H. S. Mosher, *J. Org. Chem.* **1969**, *34*, 2543 – 2549.

[13] CD (MeOH): $\lambda_{ext} = 232$ nm ($\Delta \varepsilon = -36$). The acetonide was used to fix the conformation for the CD sample, since the conformational change leads to the opposite helicity for compounds such as **6**. Some examples are known for related compounds where the sign of the CD curve is reversed depending on the solvent.[5] For CD spectra, see N. Harada, K. Nakanishi, *Circular Dichroic Spectroscopy Exciton Coupling in Organic Stereochemistry*, University Science Books, Mill Valley, **1983**.

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[15] Although Scheme 2 is only meant to show the relative topicity during the net two-electron reduction process without referring to the mechanism, we are tempted to note the role of chelation in this stereoselective process. For related work, see a) Z. Hou, X. Jia, M. Hoshino, Y. Wakatsuki, *Angew. Chem.* **1997**, *109*, 1348 – 1350; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1292 – 1294; b) A. Fürstner, B. Bogdanovic, *Angew. Chem.* **1996**, *108*, 2582 – 2609; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2442 – 2469.

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[18] Due to the buttressing effect, the pseudorotation of the expectable products is known to be quite slow.[5a] We thank Professor R. N. Armstrong (Vanderbilt University, Nashville, TN) for valuable information.

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[20] The stereostructure of **2** was analyzed by ^{1}H NMR spectroscopy, by a method similar to that reported in reference [5a]. The *ee* value of **2** proved to be greater than 99 % by the Mosher method (^{1}H NMR, 500 MHz).

Total Synthesis of Pradimicinone, the Common Aglycon of the Pradimicin – Benanomicin Antibiotics**

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The pradimicin – benanomicin antibiotics[1] constitute an emerging class of natural products with a unique structure consisting of a benzo[*a*]naphthacenequinone core, an amino acid, and a disaccharide. The important biological activities shown by these compounds, antifungal and anti-HIV, are attributed to the potentially specific binding to oligosaccharides of fungi or viral surfaces.[1, 2] Stimulated by the unique structure and the significant bioactivities, we initiated a synthetic study of these compounds.[3] Herein, we report the first total synthesis of pradimicinone (benanomicinone, **1**), the common aglycon of these antibiotics, based on the chiral transmission approach.[4]

R² = N(Me)H: pradimicin A
R² = NH₂: pradimicin C, benanomicin B
R² = OH: benanomicin A

R¹ = H

pradimicinone, benanomicinone **1**

Scheme 1 outlines the synthesis plan. Disconnection of the D-alanine moiety from **1** leads to an intact pentacycle, which can presumably be obtained from the simpler tetracyclic haloquinone **II** (X = halogen) by Diels – Alder reaction with siloxydiene **I**.[5] Given that the key pinacol-forming reaction[4] worked well, the diol could be derived from dialdehyde **III**. Formal rotation of the molecule around the biphenyl axis as in **III′** suggests tetracyclic lactone **IV** as a precursor. As another key step, the sterically encumbered biaryl bond could hopefully be formed by the Pd-catalyzed internal C–C bond formation[6] of ester **V**, which in turn could

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