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The Osmium-Catalyzed Asymmetric Dihydroxylation of *cis*-Fused Cyclopenteno-1,2,4-trioxanes

Charles W. Jefford*, Dharmendra Misra, Allan P. Dishington, Géza Timari,[1] Jean-Claude Rossier, and Gérald Bernardinelli

Department of Organic Chemistry, University of Geneva
CH-1211 Geneva 4, Switzerland

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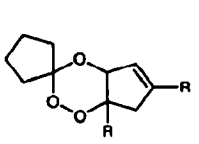
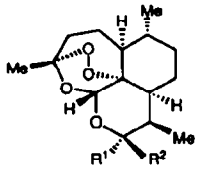
Abstract. Submission of racemic, cis-fused cyclopenteno-1,2,4-trioxanes (1 and 1-ent) to catalytic amounts of K_2OsO_4 and $(DHQD)_2PHAL$ and 1.2 equivalents of N-methylmorpholine N-oxide in aqueous acetone at 20°C (hybrid AD-mix-β) for 2 h gave the (-)-enantiomer, 1-ent (ee 95%) in 30% yield. The same reaction, but with $(DHQ)_2PHAL$, (hybrid AD-mix-α) afforded the (+)-enantiomer, 1 (ee 95%) in 25% yield after 2.7 h reaction. Similar, efficient kinetic resolution of the racemic di-p-fluoro analogues (2 and 2-ent) was also achieved with the same reagents.

The synthetic, racemic *cis*-fused cyclopenteno-1,2,4-trioxanes **1** and **2** display high anti-malarial activities which are commensurate with those of artemisinin (**3**) and its derivative **4**.[2] Evidently, the synthetic and natural trioxanes share a common mode of action.[3] However, in order to define the structure-activity relationship, it was necessary to test both enantiomers. Although chromatographic separation is feasible, we wished to explore the possibility of kinetic resolution. It appears that **1** and **2** are ideal candidates. The styrene portion is encompassed within a concave framework and should exhibit diastereoselectivity towards a chiral electrophile. The obvious reaction to try is osmylation.



1 R = C_6H_5
2 R = C_6H_4F-p



3 R^1, R^2 = O
4 R^1 = H, R^2 = OEt

We now describe the osmium-catalyzed dihydroxylation of **1** and **2** in the presence of cinchona alkaloid-phthalazine ligands. Preliminary experiments were carried out with the AD-mix-β formulation.[4] The racemic olefin, **1** and **1-ent**, was treated with catalytic amounts of potassium osmate and 1,4-bis(dihydroquinidine)phthalazine ($(DHQD)_2PHAL$) together with potassium ferricyanide as co-oxidant in aqueous *t*-butanol as solvent. Surprisingly, dihydroxylation was exceedingly slow (Table 1). Several days were required for 62% completion (entries 1, 2). Enrichment in the (-)-enantiomer of the residual olefin[5] was erratic (entries 2, 3), but increased on progressive dihydroxylation, without reaching full resolution (entries 4-6). The main products were the *exo*-1,2-diols, **5** and **5-ent** (Scheme 1). Their absolute configurations were established by esterification to the dicamphanates **7** and **8**, crystals of which were analyzed by X-ray[6] (Scheme 2). Small amounts (2-6%) of the *endo*-1,2-diols **6** and **6-ent**, were also isolated.[7]

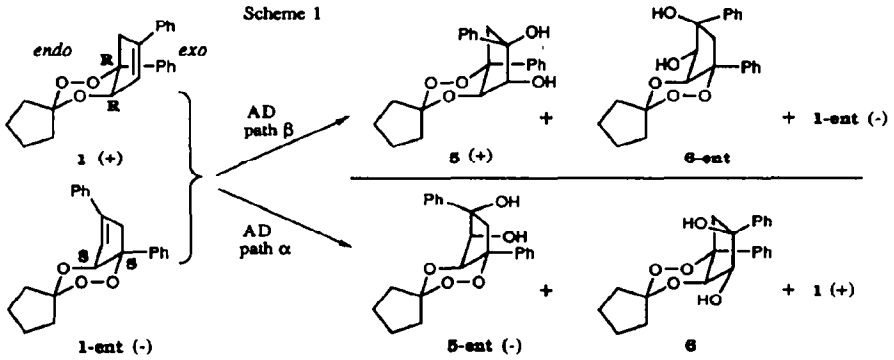
Table 1. Asymmetric dihydroxylation of **1** and **1-ent** by using AD-mix-β

Entry	AD mix[a]	Reaction temp. (°C)	Reaction time (h)	Completion of reaction (%)	Olefin[b] ee (%)
1	A	1	20	26	5
2	A	1	142	62	0
3	A	20	5	71	41
4	B	20	96	23	11
5	B	20	71	49	43
6	B	20	168	78	82

[a]$K_2OsO_4 \cdot 2H_2O$ (0.2 and 0.02 mol % for A and B respectively); $(DHQD)_2PHAL$ (13 and 1 mol % for A and B respectively. The co-oxidant is $K_3Fe(CN)_6$, plus K_2CO_3 (each 3 mmol), and $MeSO_2NH_2$ (1 mmol); olefin (1 mmol) in *t*-BuOH:H_2O (1:1, 10 ml). [b]Enriched in **1-ent**.

Thus it is seen that the chiral reagent discriminates between the *exo* and *endo* faces of the cyclopentene ring, but elicits little diastereoselectivity. However, a dramatic improvement was achieved by changing the co-oxidant and the solvent. Submission of **1** and **1-ent** to catalytic amounts of potassium osmate and $(DHQD)_2PHAL$ as before, but with *N*-methylmorpholine *N*-oxide (NMO) in aqueous acetone, resulted in rapid and total kinetic resolution[8,9] (Table 2). At partial completion, the enantiomeric excess was low (entries 1-3), whereas at more than 70% completion the remaining olefin was essentially the pure (-)-enantiomer (entries 4-6). The configuration of the latter was established as **1-ent** by its non-asymmetric dihydroxylation (NAD) to the (-)-enantiomer, **5-ent**, which was identical to the saponification product[10] obtained from **8** (Scheme 2). In other words, hybrid AD-mix-β brings about asymmetric dihydroxylation (AD) according to path β (Scheme 1). No *endo* diols (**6** or **6-ent**) were detected under these conditions. Moreover, the *exo* diol **5** was always contaminated with minor amounts of **5-ent**.[11]

Scheme 1

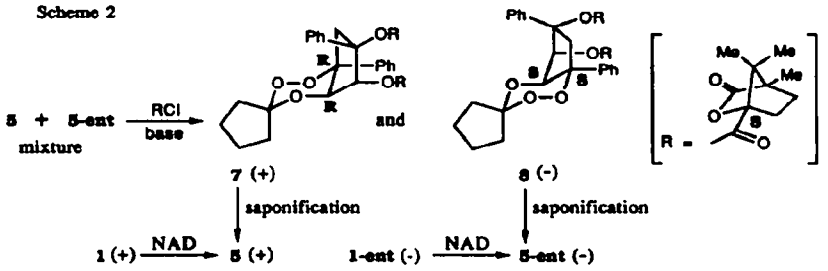


The converse, namely AD by path α, was readily accomplished by employing bis-(dihydroquinine)-phthalazine ($(DHQ)_2PHAL$) and NMO, namely hybrid AD-mix-α. By running the reaction for 1.5-2.0 hours under optimal conditions (*cf.* entries 4-6, Table 2) to 70-75% completion, the (+)-enantiomer, **1**, was fully resolved. This time the *exo* diol, **5-ent**, was the major product together with some **5**.[11] No *endo* diols (**6-ent** or **6**) were observed. In complementary fashion, the configuration of **1** was confirmed by its NAD to the (+)-enantiomer **5**, also obtained from **7** by saponification (Scheme 2).

Table 2. Asymmetric dihydroxylation of **1** and **1-ent** by using hybrid AD-mix-β

Entry	K_2OsO_4[a] [mol %]	Ligand[b] [mol %]	Reaction[c] time (h)	Completion of reaction (%)	Olefin[d] ee (%)
1	0.27	1	4	40	28
2	0.54	5	4	53	44
3	0.65	3	7	62	72
4	0.92	5	2	71	95
5	0.70	5	3.5	75	98
6	3.6	10	1.5	80	>98

[a]Olefin (1 mmol) in acetone:H_2O (5:1, 2 ml); NMO (1.2 mmol) is the co-oxidant). [b]The ligand is $(DHQD)_2PHAL$. [c]Temperature of reaction is 20°C. [d]Enriched in **1-ent**.



The hybrid AD-mixes-β and α were equally effective in resolving **2** and **2-ent**. Pure (ee 95%) **2-ent** (-) and **2** (+) were obtained in 38 and 34% yields after 45 and 90 min. respectively.

In summary, dihydroxylations with the hybrid mixes proceeded efficiently with high double diastereoselectivity and are the first examples of the kinetic resolution of cyclic olefins.[12] They can be rationalized by the predictive model devised for trisubstituted, acyclic olefins.[13] The $(DHQD)_2PHAL$-ligated reagent matches the si,si faces of the C5,C6 atoms of the double bond in **1** and **1-ent**, but this β approach is only kinetically significant in **1** since its *exo* side is more accessible than the *endo* in **1-ent** (Fig. 1). Contrariwise, the $(DHQ)_2PHAL$-ligated reagent selects the re,re faces, but, again for steric reasons, such α-attack succeeds with **1-ent** rather than **1**.

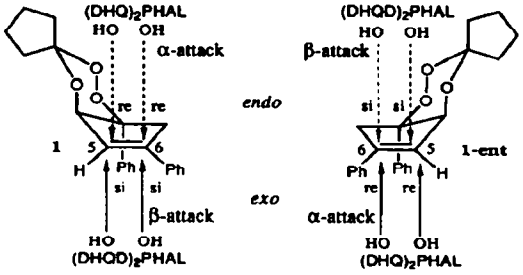


Fig. 1. Attack modes for AD of **1** and **1-ent** controlled by the chiral ligands, $(DHQD)_2PHAL$ and $(DHQ)_2PHAL$

The application of the hybrid mixes for resolving other complex bicyclic olefins should be practicable. The utility of the diols, **5** and **5-ent**, as new chiral ligands for catalysts, will be reported elsewhere.

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5. The optical rotation of the partially resolved olefin was first determined and then the enantiomeric excess (ee) from the diols (**5** and **5-ent**) obtained by NAD. Conversion to Mosher's mono-esters, estimation of the diastereomeric ratio by ^{1}H-NMR at 400 MHz, gave the ee values. For example, the partially resolved olefin (ee 41%) obtained at 71% conversion (entry 3, Table 1), was a colorless solid, m.p. 84-85°C, $[\alpha]_D^{20}$ -38.0° (c 0.25 CH_2Cl_2).
6. A mixture of **5** and **5-ent** was treated with excess (1S)-camphanic acid chloride and 4-dimethylaminopyridine in CH_2Cl_2. Work-up and chromatography (SiO_2, hexanes:AcOEt, 7:1) afforded the crystalline dicamphanates; **7**, m.p. 183-184°C, $[\alpha]_D^{20}$ +43° (c 1.0 $CHCl_3$); **8**, m.p. 179-180°C, $[\alpha]_D^{20}$ -63.3° (c 1.0, $CHCl_3$). Both structures were determined by X-ray.
7. No attempt was made to estimate the enantiomeric ratio of **6** and **6-ent**. The *endo* stereochemistry was deduced from the size of the coupling constant between C(4a)-H and C(5)-H (^3J = 4.3 and 8.9 Hz for **6** and **5** respectively. Although not proven, mechanistic logic dictates that **6** and **6-ent** would be the preferred minor products arising from AD-mix-α and β respectively.
8. We term the new mixture "hybrid", because it incorporates the new improved ligands $(DHQD)_2PHAL$ and $(DHQ)_2PHAL$ (ref. 4) with the old co-oxidant and solvent (ref. 9).
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10. Pure **1-ent** was submitted to NAD (OsO_4, NMO) and gave **5-ent**. Hydrolysis of **8** in aq. THF with 10% aq. KOH also gave **5-ent**. A similar set of correlations was established between **1**, **5** and **7**. Compounds **1-ent**, **5-ent**, **1** and **5** were were fully characterized. **1-ent** and **1** were colorless viscous oils; **5-ent** and **5** were foams. Their $[\alpha]_D^{20}$ values determined in $CHCl_3$ were: -128° (c 1.1), -112° (c 1.0), +129° (c 1.1) and +107° (c 1.0) respectively.
11. The values of ee were 30-40% and were gauged from the optical rotation of the diol mixture compared to that of pure samples of **5** or **5-ent**.
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