Perhydroxylation of Chiral Cycloheptatriene Ring through Stepwise Oxidation under Regio- and Stereocontrol

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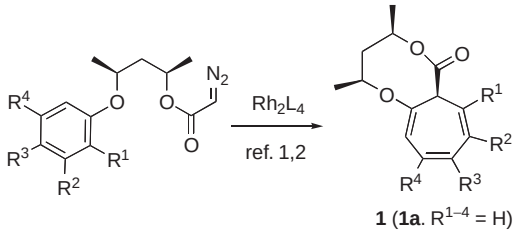
Sequential oxidation of an optically active cycloheptatriene derivative was achieved under regio- and stereocontrol to result in perhydroxylation products.

Optically active cycloheptatrienes became available by a chiral tether-promoted asymmetric Büchner reaction.[1] Diazoacetate and aromatic groups connected by a 2,4-pentanediol tether react in the presence of a rhodium catalyst under strict stereocontrol to produce optically active cycloheptatrienes **1** having different substituents; R = alkyl, alkoxy, alkoxycarbonyl, halogen, etc. (Scheme 1). Formation of regioisomers from the substrate having an *ortho*- or *meta*-substituent at the aromatic group can also sufficiently be controlled.[1b,2] With a variety of **1** in hand, this asymmetric synthesis become more valuable if proper methods for derivation of **1** can be developed.



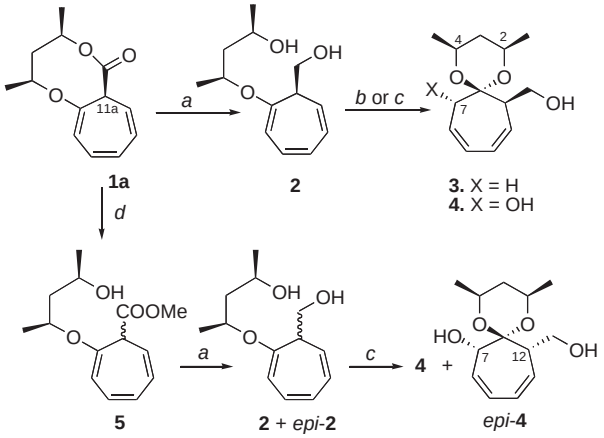
Scheme 1. The PD-tethered Büchner reaction.

Reactions so far studied with **1** are cycloaddition with dienophiles,[3] hydroboration,[4] and thermal[5] and acid-catalyzed[6] rearrangements. Among other possible reactions of **1** aiming at the selective conversion, dihydroxylation (or its equivalent) of double bonds is of particular importance, because a produced vicinal polyhydroxy structure is often included in natural products and the hydroxy group produced can be converted into other functional groups with either inversion or retention of stereochemistry. In addition to the stereocontrol of each dihydroxylation step, the regiochemical control is also important to obtain a single isomer and to suppress the overreaction. The sequence consisting of such well-regulated reactions has an advantage in conversion of a desired hydroxy group into other functional groups. Considering general difficulty in controlling the reaction selectivity of seven-membered ring compounds due to the conformational multiplicity, we herein studied the dihydroxylation of a simple unsubstituted substrate **1a** to disclose the selectivities to extend the versatility of **1** as chiral synthons.

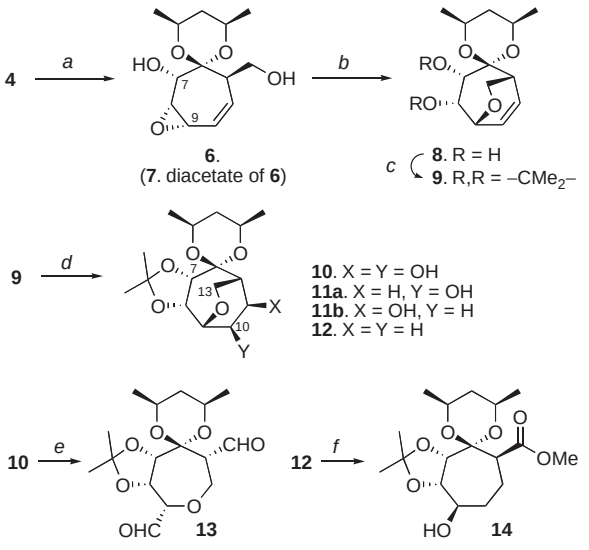
Stereochemically pure **1a** was prepared by the reported method (>99% diastereomeric excess, 81% yield in 4 steps).[1] To avoid the epimerization due to the high kinetic acidity at C-11a,[7] **1a** was first reduced to **2** with $LiAlH_4$ (97% yield, Scheme 2). This process is inevitable so far to keep the stereochemical purity during following reactions. Acid-catalyzed isomerization of **2** (*p*-TsOH·pyridine/THF/rt) proceeded under regio- and stereocontrol to give **3** (70%) as expected from the results of the analogous reaction.[4] When **2** was oxidized with *m*-chloroperbenzoic acid (mcpba) in dichloromethane at −78 °C, the product **4** was again a single isomer (74%).

For determination of the stereochemical properties of the oxidation, a diastereomeric mixture of **2** at C-7 in a 1 to 1 ratio was prepared by the reduction of **5**.[7] The mcpba oxidation of this mixture gave a diastereomeric mixture of **4** in the same 1 to 1 ratio. Under the GLC conditions for separation of these isomers, the reaction mixture obtained from pure **2** showed a single peak, and thus the stereoselectivity was confirmed to be >99%. The unchanged isomer ratio during the reaction indicates that the oxidation of *epi*-**2** must give *epi*-**4** selectively (>90%) stereo-directed by the 2,4-pentanediol part[8] irrespective of the stereochemistry at C-7. Proton NOE experiments indicated close vicinity of H-7 and H-2 (or H-4) for both **4** and *epi*-**4**, and H-7 and H-12 for *epi*-**4**. From these observations, the stereochemistry of **4** was unambiguously assigned.

The oxidation of **3** at the olefinic part was not successful to result in a mixture of 3–4 products with two epoxidation-reagents; mcpba and *tert*-butyl hydroperoxide (TBHP) in the presence of vanadium acetoacetate catalyst.[9] Over-oxidation seems to be a major problem. The oxidation of **4** with mcpba was also slow and sluggish, but proceeded smoothly with TBHP at 0 °C to give **6** as a sole product in 87% yield (Scheme 3). Treatment of **2** with two equivalents of TBHP also directly gave **6** (78% yield). The difference between the two reagents in the oxidation of **4**



Scheme 2. Reagents and conditions. a: $LiAlH_4$ (97% of **2**), b: TsOH·Pyridine (70% of **3**), c: mcpba/CH_2Cl_2/rt (74% of **4**), d: MeOH/K_2CO_3 (100%).



Scheme 3. Reagents and conditions. a: TBHP/$VO(acac)_3$ (87%), b: NaOH/THF-H_2O (ca. 90%), c: 2-methoxypropene/TsOH (86%), d: OsO_4/NMO (57% of **10**), or $ThexBH_2$, then H_2O_2–NaOH (**11a**:**11b** = 2.5:1, 62% of **11a**), or H_2/Pd–C (95% of **12**), e: $NaIO_4$/AcOH (90%), f: $RuCl_3/NaIO_4$ (74%) and K_2CO_3/MeOH (quant.).

can be explained by the conformation of the OH group at C-7; the acetal ring sterically fences mostly at C-7 side and the OH fixed at the axial position.[10,11] Stereochemistry of the produced epoxide was determined to be *cis* to the OH by NOE between H-7 and H-9.

The oxidation of **6** or its diacetate analogue **7** (73% from **6**) was not successful either by the epoxidations nor osmium dihydroxylation to result in complex mixtures. These failures must be due to the instability of the allylic epoxide structure, and **6** should be converted to a more stable derivative prior to oxidation. When **6** was treated with aqueous NaOH (1 mol dm^{-3}) in THF at room temperature, intramolecular substitution took place at C-9 to produce **8** (71% from **4** without purification of **6**). The newly formed tricyclic structure was confirmed by HMBC experiment on NMR. The vicinal diol of **8** was protected as acetonide to give **9** (86%).

Reaction of the remaining olefinic bond in **9** was stereocontrolled as expected from the bridged structure. When **9** was treated with osmium tetraoxide and *N*-methylmorpholine-*N*-oxide, **10** was produced as an only detectable product after extraction (>98% pure, 57%). The deoxy-analogue **11** was also possible to synthesize by the reaction of **9** with thexylborane in THF at rt followed by the oxidation ($NaOH/H_2O_2$). The product was a regioisomeric mixture in a ratio of **11a**:**11b** = 2.5:1 (isolated yield of **11a**, 62%), but did not contain any other stereoisomers. The stereochemistries of **10** and **11a** were determined by NOE between H-10 and one acetonide methyl (the other methyl showed NOE with H-7). A saturated analogue **12** could also be obtained by the hydrogenation of **9** (95%). Hence, **9** is considered to be a good synthetic intermediate.

Finally, two reactions of the oxidation products were demonstrated cleaving the bridged structure to give a cyclic ether and to put it back in a simple ring. When **10** was treated with sodium periodate and acetic acid, the diol part was cleaved to give **13** in 90% yield.[12] The RuO_4 oxidation of **12** with ruthenium chloride and sodium periodate[13] resulted in a selective oxidation at C-13 to convert the ethereal structure to a lactone (74%). Succeeding methanolysis afforded **14** in a quantitative yield.

In this communication, sequential polyhydroxylation under strict regio- and stereocontrol was demonstrated starting with **1a**. Although the reactions presented with **1a** are developed as a model for the reactions with functionalized **1**, the products from **1a** itself can be synthons for macrolides,[14] higher sugars,[15] or more directly for carbaheptoseptanoses.[16]

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