Lipase-mediated Resolution of *cis*-4-Cumyloxy-2-cyclopenten-1-ol and its Utilization for Enantioconvergent Preparation of (–)-Oxabicyclo[3.3.0]-oct-6-en-3-one

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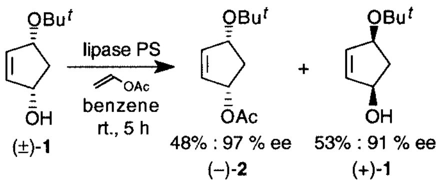
Abstract: Convenient preparation of both enantiomers of *cis*-4-cumyloxy-2-cyclopenten-1-ol from cyclopentadiene employing a lipase-mediated resolution was first established. An efficient enantioconvergent transformation of both enantiomeric products affording (–)-oxabicyclo[3.3.0]oct-6-en-3-one, an important building block of prostaglandin synthesis, was next established.

Key words: chiral building block, prostaglandin building block, kinetic resolution, lipase-mediated kinetic transesterification, enantioconvergent synthesis

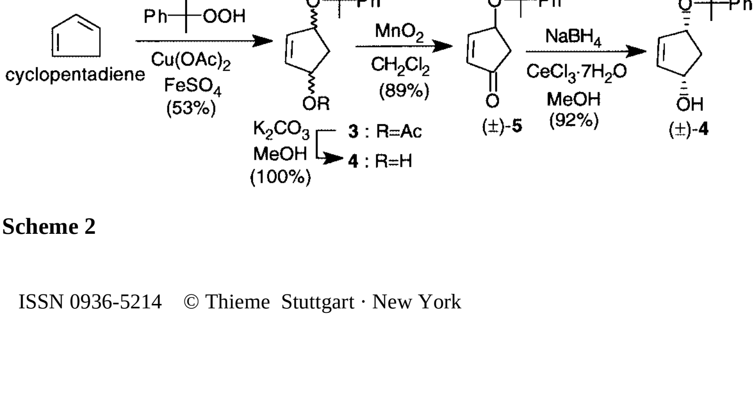
Chiral mono-protected *cis*-1,4-dihydroxy-2-cyclopentenes have proven to be important building blocks for the synthesis of prostaglandins[1,2] and a variety of biologically active compounds.[3] Owing to the 1,4-enediol functionality confined in a five-membered ring having latent *meso* symmetry, these mono-protected chiral alcohols have wide and versatile utility serving as both enantiomers. As a consequence, numerous procedures involving enzymatic and catalytic procedures have been developed. The most widely employed protocols are asymmetric desymmetrization of *meso cis*-1,4-dihydroxy-2-cyclopentene[4,5] and resolution of racemic mono-protected *cis*-1,4-dihydroxy-2-cyclopentene.[6] Efficiency of the synthesis is, therefore, dependent on the availability of the 1,4-*cis*-dihydroxycyclopentene substrates and the enantiospecificity of the chiral procedures.

We have developed an efficient procedure for the preparation of racemic mono-*O*-*tert*butyl-1,4-dihydroxy-2-cyclopentene (±)-**1** starting from cyclopentadiene.[7] This compound was then resolved under kinetic transesterification conditions in the presence of lipase PS-on-Celite (*Pseudomonas* sp., Amano) in benzene solution containing vinyl acetate to give the chiral acetate (–)-**2** and the chiral alcohol (+)-**1** in excellent yields.[6] However, the use of an environmentally unacceptable solvent giving the products with less satisfactory enantiomeric purities, 97% ee for the former and 91% ee for the latter, prompted us to improve our present strategy (Scheme 1). We wish to report here an improved protocol utilizing the racemic substrate[8] (±)-**4** having a *O*-cumyl protecting group which is found to exhibit much better characteristics with respect to resolution and deprotection.



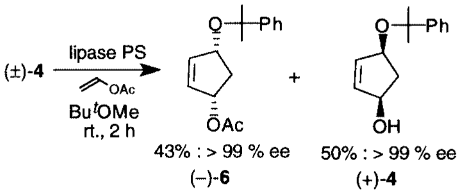
Scheme 1

Cyclopentadiene, generated from dicyclopentadiene by thermolysis, was treated with cumyl hydroperoxide in the presence of copper(II) acetate and iron(II) sulfate in aqueous acetic acid[9] to give a mixture of *cis*- and *trans*-1-acetoxy-4-cumyloxy-2-cyclopentene **3** in acceptable yield in 2.6 mol scale. Alkaline methanolysis of the mixture **3** followed by oxidation of the *cis*- and *trans*-alcohol **4** with manganese(IV) oxide in dichloromethane afforded the racemic 4-cumyloxy-2-cyclopentenone (±)-**5** in 89% yield. Reduction of the enone (±)-**5** with sodium borohydride in the presence of cerium(III) chloride[10] proceeded diastereoselectively to give *cis*-4-cumyloxy-2-cyclopentenol (±)-**4** in 92% yield as a single product (Scheme 2). However, different from the *tert* butyl counterpart,[6] (±)-**4** afforded a 5:1 *cis*/*trans*-mixture on reduction with diisobutylaluminum hydride in toluene.



Scheme 2

We first examined the resolution of the racemic alcohol (±)-**4** under lipase-mediated kinetic transesterification conditions in an organic solvent. Among the tested immobilized lipases, lipase PS-on-Celite gave the best result. Thus, stirring (±)-**4** with lipase PS in *tert* butyl methyl ether containing vinyl acetate[5] brought about clear-cut resolution to give the enantiopure acetate[11] (–)-**6**, $[\alpha]^{29}_D$ –62.03 (*c* 0.98, $CHCl_3$), in 43% yield with 50% recovery yield of the enantiopure alcohol (+)-**4**, $[\alpha]^{31}_D$ +27.52 (*c* 1.11, $CHCl_3$), after 2 h at room temperature. Enantiomeric purities were determined by HPLC using a column with a chiral stationary phase (CHIRALCEL OD, elution with Pr^iOH-hexane 1:200 v/v). Thus, the cumyl ether (±)-**4** was found to be a much more favorable substrate than the *tert* butoxy counterpart (±)-**1** for lipase-mediated resolution (Scheme 3).



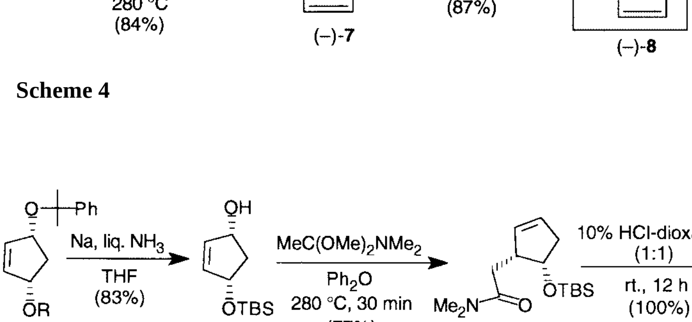
Scheme 3

In order to demonstrate the superiority of the cumyl group over the *tert* butyl group as the protecting group for the prostaglandin synthesis, we next examined the synthesis of (–)-oxabicyclo[3.3.0]oct-6-en-3-one[2,12] (–)-**8** utilizing both resolution products (+)-**4** and (–)-**6** in an enantioconvergent manner.

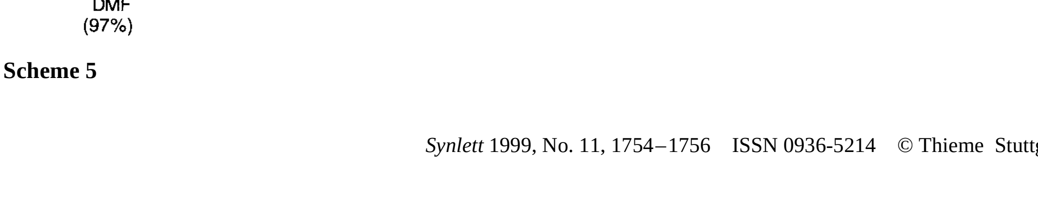
Thus, the alcohol (+)-**4** was heated with 2.5 equiv. of dimethylacetamide dimethyl acetal[13] in refluxing diphenyl ether to afford 3*R*,4*S*-*N*,*N*-dimethyl-4-cumyloxycyclopentenyl-3-acetamide[11] (–)-**7**, $[\alpha]^{28}_D$ –140.57 (*c* 1.08, $CHCl_3$), in 84% yield within 30 min. This Eschenmoser reaction[13] was found to be far superior to the acid-catalyzed Johnson type reaction[14] using triethyl orthoacetate as the latter brought about considerable decomposition. The amide (–)-**7** thus obtained was then stirred in a mixture of 10% hydrochloric acid and dioxane (1:1) at room temperature to give an important prostaglandin intermediate 1*S*,5*R*-oxabicyclo[3.3.0]oct-6-en-3-one (–)-**8**, mp 43-44 °C, $[\alpha]^{29}_D$ –103.21 (*c* 1.02, MeOH) [lit.[12] : mp 42 °C, $[\alpha]^{26}_D$ –102.3 (*c* 0.7, MeOH)], in 87% yield after 12 h (Scheme 4).

On the other hand, the acetate (–)-**6** was exposed to alkaline methanol to give quantitatively the enantiopure alcohol (–)-**4**, $[\alpha]^{31}_D$ –27.43 (*c* 1.01, $CHCl_3$), which was transformed into the *tert*butyldimethylsilyl (TBS) ether (–)-**9**, $[\alpha]_D^{31}$ –47.01 (*c* 1.01, $CHCl_3$), in 97% yield under standard conditions. On the Birch reaction using sodium in ammonia and THF, the *bis*-ether (–)-**9** afforded the allyl alcohol (–)-**10**, $[\alpha]^{30}_D$ –24.53 (1.59, CH_2Cl_2) having 1*R*,4*S*-configuration [lit.[15] : for 1*S*,4*R* enantiomer, $[\alpha]^{20}_D$ +24.29 (*c* 2.47, CH_2Cl_2)], in 83% yield by cleavage at the desired carbon-oxygen bonding. This is worth noting as the cleavage did not occur at another possible allylic carbon-oxygen bonding but selectively at the benzylic carbon-oxygen bonding under these conditions. The Eschenmoser reaction of (–)-**10** under the same conditions as above afforded 3*R*,4*S*-*N*,*N*-dimethyl-4-cumyloxycyclopentenyl-3-acetamide (–)-**11**, $[\alpha]^{27}_D$ –56.55 (*c* 1.01, $CHCl_3$), in 77% yield. This compound, on stirring in a mixture of 10% hydrochloric acid and dioxane (1:1) at room temperature for 12 h, gave the same lactone above (–)-**8**, mp 44 °C, $[\alpha]^{30}_D$ –103.11 (*c* 1.02, MeOH), in quantitative yield (Scheme 5).

Thus, a new route to an important prostaglandin building block (–)-**8** has been established in an enantioconvergent way using both enantiomeric starting materials having a cumyl ether functionality.



Scheme 4



Scheme 5

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(11) Typical procedure: **Resolution** – A solution of (±)-**4** (1.071 g, 4.91 mmol) and vinyl acetate (2.5 ml) in Bu^{t}OMe (30 ml) was stirred with Lipase PS-on-Celite (1.0 g) at room temperature for 2 h. After filtration through a Celite pad, the mixture was evaporated and chromatographed on SiO_2 column (elution with EtOAc-hexane 1:4~1:2) to give (–)-**6** (543 mg, 43%) and (+)-**4** (535 mg, 50%) both as a colorless oil.
Eschenmoser reaction — A mixture of (+)-**4** (2.20 g, 10.08 mmol), dimethylacetamide dimethyl acetal (3.67 ml, 2.51 mmol) in diphenyl ether (20 ml) was refluxed (~280 °C) for 30 min. The mixture was chromatographed on SiO_2 column (elution with EtOAc-hexane 1:4 to remove Ph_2O, then EtOAc-hexane 1:1) to give (–)-**7** (2.44 g, 84%).
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