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Enzymatic resolution of diols derived from *p*-benzoquinones

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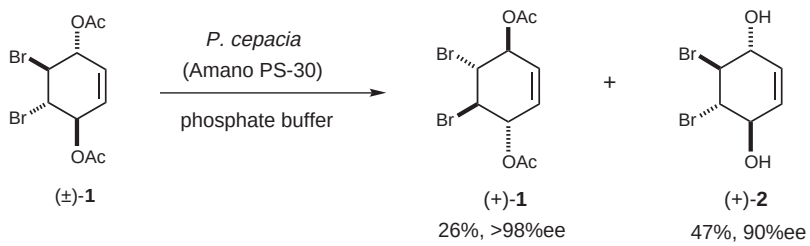
Abstract—An efficient enzymatic resolution of racemic 4-acetoxy-2,3-dibromo-5-cyclohexen-1-ol in organic solvent is described. The methodology is extended to the synthesis of a series of highly functionalized enantiopure intermediates derived from various substituted *p*-benzoquinones. © 2001 Published by Elsevier Science Ltd.

There are many natural products with antibiotic and antitumor activity whose common feature is a densely oxygenated cyclohexene core. Representative examples are molecules such as conduritols,[1] valienamine[2] and gabosine[3] along with family members possessing numerous variations at the asymmetric centers such as bromoxone,[4] epofomin,[5] epiepoxydon,[6] the *Streptomycetes* metabolite LL-C10037α[7] and the manumycins[8] which all have a epoxyquinol core. The synthesis of these compounds has been a topic of considerable interest.

We initiated a program utilizing *p*-benzoquinone as a starting material with bioactive epoxyquinol natural products as targets. Continuation of our efforts has resulted in the synthesis of enantiomerically pure (+)- and (−)-bromoxone,[9] (+)- and (−)-harveynone, (+)-tricholomenyn A,[10] (−)-LL-C100372α[11] and a series of stereochemically defined intermediates with highly functionalized six-membered ring cores.[12] The syntheses started with enzymatic resolution of C_2-symmetric diacetate **1** using *Pseudomonas cepacia* lipase (Amano PS-30) in phosphate buffer at 50°C (Eq. (1)).[9] A modified hydrolytic procedure was reported by Altenbach[13] using porcine pancreatic lipase (PPL) in phosphate buffer in the presence of Et_2O. Nicolosi[14] reported an enzymatic esterification of diol **2** catalyzed by *Mucor miehei* lipase (Lipozyme™) in *tert*-butyl methyl ether.

In this communication we present a more convenient and efficient way to access these enantiopure compounds. Monoacetate **3** derived from NaOMe-mediated mono-deacetylation of (±)-**1** was subjected to enzymatic esterification in organic solvent; this approach was extended to other substituted analogs. The methodology offers advantages in terms of resolution process monitoring and being amenable to large scales. Moreover, differentiation of the acyl groups can be realized through this process, which should prove useful for further elaboration of resulting intermediates.

The monoacetate (±)-**3** is readily available through selective removal of one acetate using a catalytic amount of NaOMe in methanol at 0°C from (±)-**1** (66% yield). Treatment of monoacetate (±)-**3** in hexane/vinyl acetate (4:1) with Amano PS-30 (20% weight) at rt for 16 h afforded diacetate (−)-**1** in 50% yield (≥98% ee) and (−)-**3** in 50% yield (92% ee) (Scheme 1). The latter after recrystallization provided enantiopure material.[15]



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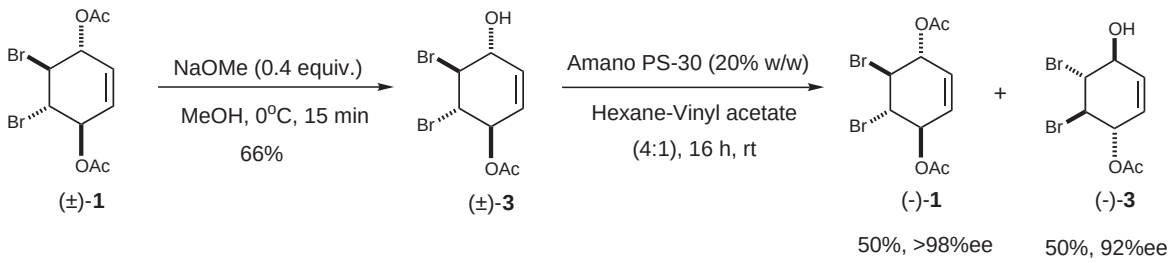
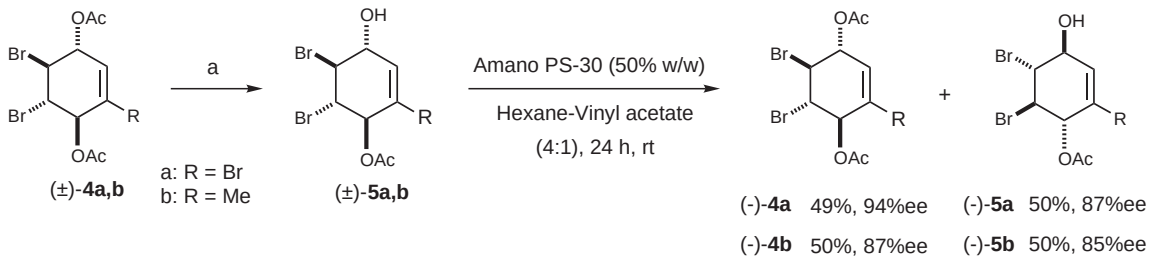
This approach was extended to the production of structural analogs (±)-**4a**,**b** containing bromo or methyl substituents (Scheme 2). The less hindered acetate in (±)-**4a**,**b** was selectively removed using NaOMe in high yield. The resulting monoacetate was then subjected to an enzymatic esterification in hexane with vinyl acetate as the acyl donor. Enzyme screening suggested that Amano PS-30 lipase would afford the most satisfactory results. Resolution of compound **5a** with 50% (w/w) PS-30 provided diacetate (−)-**4a** in 49% yield (94% ee); monoacetate (−)-**5a** was recovered in 50% yield (87% ee). Both enantiomers furnished, after recrystallization from hexane–acetone, enantiomerically pure materials.[16] Enzymatic esterification of **5b** was achieved under similar conditions as for **5a**, with 50% (w/w) PS-30; diacetate (−)-**4b** was obtained in 50% yield (87% ee) and recovered monoacetate (−)-**5b** in 50% yield (85% ee). Recrystallization from hexane–acetone raised both enantiomeric excess to ≥98% according to chiral shift reagent analysis.[17]

The absolute configuration of diacetates (−)-**4a** and (−)-**4b** were determined via X-ray analysis. The monoacetate with the configuration (1*R*,2*S*,3*S*,4*R*) was preferentially acetylated (Scheme 2). The results are consistent with the simple model **6** proposed for *Pseudomonas cepacia* (Amano PS-30) towards secondary alcohols.[18] It is interesting to note that, unlike the diacetate (±)-**1** or diol (±)-**2** which can be enzymatically resolved either by hydrolysis in buffer or esterification in organic solvent,[9,14] neither the diacetate (±)-**4a**,**b**, nor the corresponding diol, are substrates to various lipases such as CRL (*Candida rugosa* lipase), Amano PS-30, PPL, CAL-B (*Candida antarctica* lipase B, Novo SP-435). No hydrolysis or esterification could be observed under various conditions.

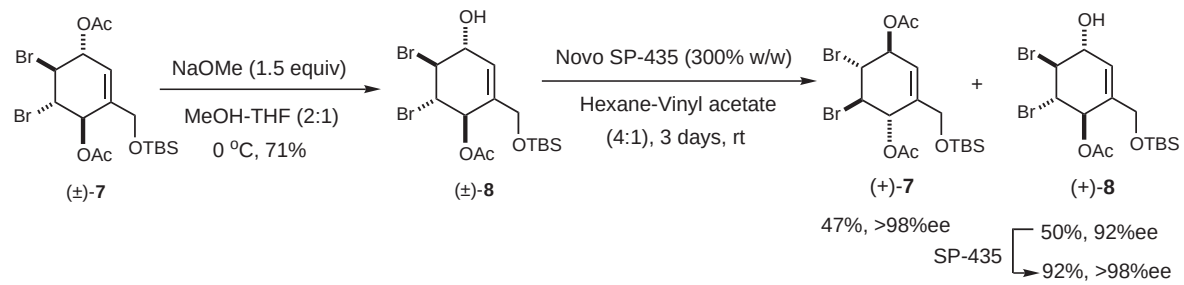
Another compound of interest is **7** which can be quickly obtained in good yield from 2-hydroxy-5-methoxybenzaldehyde. The less hindered acetate group is again regioselectively removed by NaOMe to give monoacetate **8** in 71% yield (Scheme 3). Due to the presence of a bulky TBS protecting group in compound **8**, among many enzymes screened, only lipase from *C.*



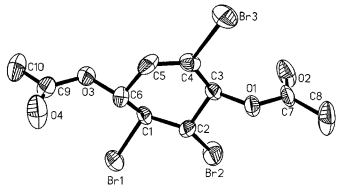
Scheme 1.



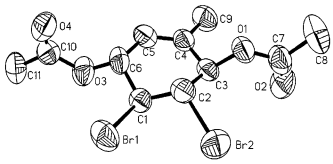
Scheme 2. [a]For **4a**: NaOMe (0.6 equiv.), MeOH–THF (5:2), 0°C, 30 min, 91%; for **4b**: NaOMe (1.2 equiv.), MeOH, 0°C, 45 min, 85%.



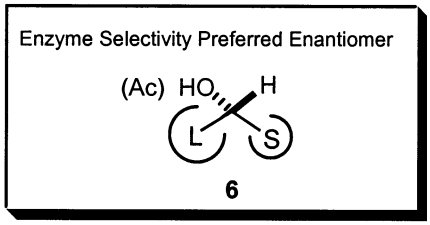
Scheme 3.



(-)-4a



(-)-4b



antarctica (Novo SP-435), which has a more flexible active site showed good activity and enantioselectivity. With lipase SP-435 (300% weight of its immobilized form) and vinyl acetate in hexane, after 3 days, diacetate (+)-**7** was obtained (47% yield, ≥98%ee), monoacetate (+)-**8** was recovered in 50% yield (92% ee). The enantiomerically enriched monoacetate was resubjected to enzymatic esterification with 100% (w/w) SP-435 to bring the ee up to ≥98% in 92% yield.[19] The overall production of enantiopure (+)-**8** from (±)-**8** was 46% (out of a theoretical 50%).

In summary, we have developed an efficient method for the preparation of a series of enantiopure mono- and diacetates of 2,3-dibromo-5-cyclohexen-1,4-diol and their substituted analogs. These highly functionalized intermediates should prove useful in the synthesis of various target molecules. As our preliminary study shows, the bromovinyl functionality in compound (−)-**5a** or (−)-**4a** can participate in Sonogashira or Suzuki cross coupling reactions.

Acknowledgements

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15. Enantiomerically pure (−)-**1**: white crystals (hexane/acetone), mp 107–109°C; $[\alpha]_D=-11.7$ (*c* 1.0, CH_2Cl_2) [lit.[9] mp 107–109°C; $[\alpha]_D=11.7$ (*c* 1.05, CH_2Cl_2) for (+)-**1**]; enantiopure (−)-**3**: white crystals (hexane/acetone), mp 147–148°C; $[\alpha]_D=-36.3$ (*c* 1.0, CH_2Cl_2) [lit.[14] mp 147–148°C, $[\alpha]_D=25.0$ (*c* 1.6, $CHCl_3$) for (+)-**3**].
16. The enantiomeric excess was determined by NMR analysis in the presence of $Eu(hfc)_3$. Enantiopure (−)-**4a**: white crystals (hexane/acetone), mp 132–133°C; $[\alpha]_D=-40.0$ (*c* 1.03, $CHCl_3$). Enantiopure (−)-**5a**: white crystals (hexane/acetone), mp 138–139°C; $[\alpha]_D=-39.8$ (*c* 1.02, $CHCl_3$).
17. Enantiopure (−)-**4b**: white crystals (hexane/acetone), mp 97–99°C; $[\alpha]_D=-2.64$ (*c* 1.0, $CHCl_3$). Enantiopure (−)-**5b**: white crystals (hexane/acetone), mp 102–103°C; $[\alpha]_D=-67.2$ (*c* 1.06, $CHCl_3$).
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19. The absolute configuration of compound (+)-**7** or (+)-**8** has not been assigned unambiguously at this moment as we have been unable to obtain good X-ray crystallographic data. However, based on the stereochemical preference and enantioselectivity of SP-435 observed towards secondary alcohols in six-membered ring systems[20] and the sign of the optical rotation, stereochemistry is assigned tentatively as depicted in Scheme 3. The enantiomeric excess is determined via chiral shift reagent analysis. Enantiopure (+)-**7**: white solid (hexane/ether), mp 63–64°C; $[\alpha]_D=6.0$ (*c* 1.16, $CHCl_3$). Enantiopure (+)-**8**: white solid (hexane/ether), mp 51–52°C; $[\alpha]_D=43.8$ (*c* 1.10, $CHCl_3$).
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