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A Facile Enzyme Assisted Route to Enantiomerically Pure δ - Lactones

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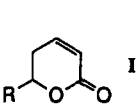
Abstract: *Enantiomerically pure 1,2-epoxyalkanes, obtained via enzymatic resolution of suitable precursors can serve as key building blocks for the preparation of the title compounds. Using a simple and very short synthetic protocol enantiomerically pure δ - lactones are obtained in high yields.*

Chiral 6- substituted 5,6-dihydro-2*H* -pyran-2-ones (α,β – unsaturated δ - lactones) (I) are key structural subunits of widely occurring natural products[1]. Their saturated analogues (II) are important aroma compounds[2], while the 4-methoxy derivatives (III) display a variety of biological activities in compounds like kawa lactone[3] pestalotin[4], or structural moieties of fungal metabolites[5] and toxins[6].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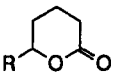
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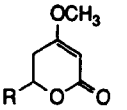
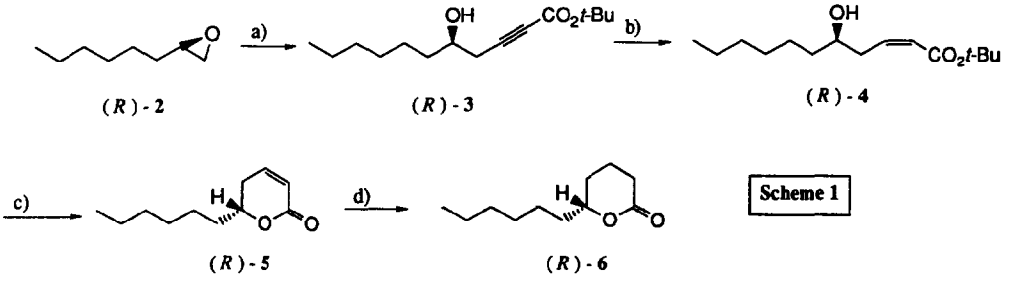

III

Consequently, synthetically useful precursors for these compounds are of considerable interest and numerous routes to these molecules were developed in the past[7]. In connection with our current studies related to the enzyme assisted preparation of enantiomerically pure oxiranes[8] and their application for the synthesis of natural products we wish to report a general and facile route to this whole class of compounds (Scheme 1). As model compound for synthetic studies we chose (*R*) - 1,2-epoxyoctane (*R*) - **2**, which is conveniently accessible in optically pure form *via* enzymatic resolution of 1-*t*-butylthio-2-octanol (*R,S*) - **1**. Regioselective, boron trifluoride assisted ring opening of the oxirane moiety in (*R*)- 1,2-Epoxyoctane (*R*)- **2** [$[\alpha]_D^{20}$ +14.2, (c2.48, EtOH), > 96 % ee] using the carbanion derived from *t*-butylpropiolate[9] led to (*R*)- *t*-butyl 5-hydroxy-2-undecinate (*R*) - **3** [$[\alpha]_D^{20}$ -6.1 (c 0.73 $CHCl_3$), 97.6 % ee] in 73% yield. The optical purity of the starting oxirane was fully retained during this transformation as proven by HPLC on a chiral support (Chiracel OD, n-hexane / 2-propanol 95:5). Partial hydrogenation of (*R*) - **3** in presence of Lindlar catalyst produced, quantitatively, the corresponding (*R*) - *t*-butyl 5-hydroxy-2-Z-undecenate (*R*) - **4** which was cyclized under acidic conditions to (*R*) - 6-hexyl-5,6-dihydro-2*H*-pyran-2-one (*R*) - **5** [$[\alpha]_D^{20}$ -109.4 (c 0.97 $CHCl_3$),96.9 % ee] Hydrogenation of (*R*) - **5** (Pt/C; Et_2O) under atmospheric presure led to



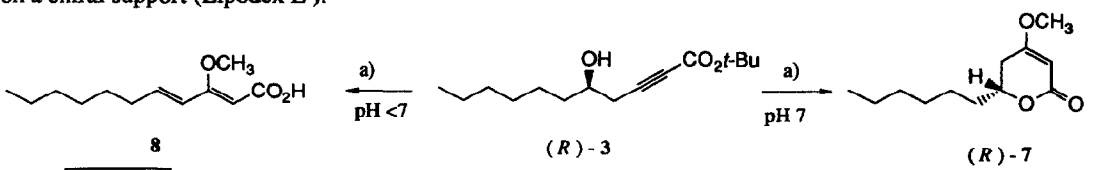
Scheme 1

a)1. $\equiv CO_2t\text{-Bu}$, BuLi, THF, 2. $BF_3{\cdot}Et_2O$, THF; b) Lindlar catalyst, 1 atm H_2, EtOAc; c) p-TsOH, C_6H_6; d) Pt/C, H_2, Et_2O

(*R*) - 6-hexyl-tetrahydro-2*H*- pyran-2-one ((*R*) - 5-undecanolide) (*R*) - **6** [$[\alpha]_D^{20}$ +46.1 (c 0.61 $CHCl_3$) , 98.3 % ee] [10].

Conjugate 1,4- (Michael) addition of sodium methoxide to (*R*) - **3**, followed by careful neutralisation of the resulting reaction mixture with diluted acetic acid to pH 7 led in a clean reaction to (*R*) - 6-hexyl-4-methoxy-5,6-dihydro-2*H* -pyran-2-one (*R*) - **7**, which was isolated after one recrystallisation (n-hexane/EtOAc) in 62% yield [mp. 42 °C; $[\alpha]_D^{20}$ -103.5 (c 0.24 $CHCl_3$); >99 % ee] (Scheme 2). Acidification of the reaction mixture to pH < 7 caused spontaneous elimination of water and the exclusive formation of 3-methoxy-2,4-undecanoic acid **8**.

The enantiomeric purities of (*R*)- **5-7** were conveniently determined by enantioselective GC analysis on a chiral support (Lipodex E).



8 (*R*) - **3** (*R*) - **7**

Scheme 2 a) MeONa, MeOH followed by diluted HOAc

In summary, the above described method provides a rapid and facile access to this whole class of compounds. It should be generally applicable to the synthesis of numerous other δ - lactones with variable substituents R. Corresponding experiments are presently being carried out in our laboratory.

Acnowledgement

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REFERENCES

1. M.T. Davies-Coleman and D.E.A.Rivett, *Fortschr. Chem. Org. Naturst.*1989, **55**, 1
2. G.Ohloff, *Fortschr. Chem. Org. Naturst.* 1978, **35**, 431
3. M.Klohs,"The Chemistry of Kava" In *USPHS Publication No 1645*, 1967, 126; H. Achenbach and W. Regel, *Chem. Ber.* 1973, **106**, 2648 and references cited therein.
4. G. Ellestad, J. McGahren and M.P. Kunstmann, *J. Org. Chem.* 1972, **37**, 2045;Y. Kimura, K. Karagiri and S. Tamura, *Tetrahedron Lett.* **1971**, 3137
5. W.J. McGahren,G.A. Ellestad, G.O. Morton and M.P. Kunstmann, *J. Org. Chem.* 1973, **38**, 3542
6. F.W. Lichtenthaler, J. Dinges and Y. Fukuda, *Angew. Chem.* 1991, **103**, 1385, Int. Edn. 1991, **30**, 1339
7. For the synthesis of chiral
   6-Alkyl-5,6-dihydro-2*H*pyran-2-ones see: K. Mori, T.Otsuka and M. Oda, *Tetrahedron* 1984, **40**, 2929; W.A. Pirkle and P.E. Adams. *J. Org. Chem.* 1980, **45**, 4117; M. Asaoka S. Hayashibe, S. Sonoda and H. Takei , *Tetrahedron Lett.* 1990, **31**, 4761
   6-Alkyl-tetrahydro-pyran-2-ones: S. Servi, *Synthesis* **1990**, 1;
   6-Alkyl-4-methoxy-5,6-dihydro-2*H*-pyran-2-ones: R.M. Carlson and A.R. Oyler, *Tetrahedron Lett.* 1974, **30**, 2615
8. U. Goergens and M.P. Schneider, *J. Chem. Soc, Chem. Commun* **1991**, 1064
   and patent application PCT / EPO 91.01770
9. T.Hoyer, A. Kjaer and J. Lykkesfeldt, *Collect.Czech. Commun.*1991, **56**, 1042
10. P. Ashworth, S.L. Belagali, S. Casson, A. Marczakk and P. Kocienski, *Tetrahedron* 1991, **47**, 9939
    $[\alpha]_D^{20}$ +40.5 (c 0.02 $CHCl_3$)