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ENANTIOTOPOSELECTIVE PLE-CATALYZED HYDROLYSIS OF CIS-5-SUBSTITUTED-1,3-DIACYLOXYCYCLOHEXANES. PREPARATION OF SOME USEFUL CHIRAL BUILDING BLOCKS

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Abstract : PLE-catalyzed hydrolysis of prochiral cis-5-benzyloxymethyl-1,3-diacetoxycyclohexane and cis-5-benzyloxy-1,3-diacetoxycyclohexane proceeds with high enantiotoposelectivity. The preparation of some useful chiral building blocks is described.

In the context of a program directed towards enantioselective total synthesis of natural products containing a cyclohexane ring,[2,3] we decided to study the enzymatic hydrolysis[4] of meso cis-5-substituted-1,3-diacyloxycyclohexanes. In order to obtain versatile chiral building blocks, substrates functionalized at the 5-position or in the 5-side chain were selected for an introductory study.

Cis-1,3,5-cyclohexanetriol (**1**), readily available by hydrogenation of phloroglucinol[5], was selected as the common starting material for the meso substrates **4**, **9**, **10** and **13**. (Scheme 1). For differentiating one of the three hydroxyl groups in **1**, two methods were investigated in parallel. The shorter route involves bis-silylation of **1**, which, in small scale reactions, afforded **2** in 48 % yield.[6] However, during scaling up it was observed that this procedure was rather unreliable, as yields of only 20 % were found. The bis-silylether **2** was transformed into **4** via oxidation and Lombardo-methylenation[7], deprotection and esterification in 50 % overall yield.

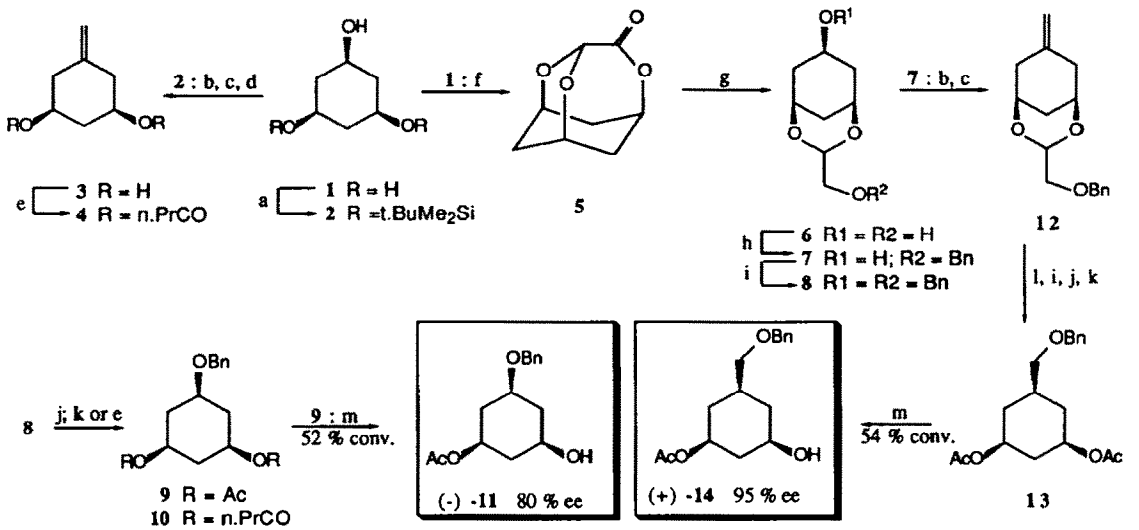
The alternative sequence, suitable for multi-gram preparations, followed the method described by Woodward et al.[8] which gave alcohol **6** in two steps via initial treatment of **1** with glyoxylic acid, followed by reduction. Subsequent benzylation of the free hydroxyl groups (KOt.Bu, benzyl bromide) appeared to be very solvent-dependent : if the reaction was carried out in t.butanol, **7** was obtained (73 %) next to **8** (25 %). Changing to THF as solvent[9] allowed further conversion of **7** into **8**, which was transformed into meso-diesters **9** and **10**.

The fourth substrate **13** was obtained starting from **7**; again methylenation was effected by Lombardo's method.[7] Alternative Wittig reactions invariably resulted in complete decomposition, due to facilitated β-elimination as the β-substituents are locked into an axial position. Hydroboration of **12** occured from the less hindered side affording the all-cis primary alcohol, which was uneventfully transformed in **13** in 41 % overall yield.

The enantiotoposelective hydrolysis of the substrates **4**, **9**, **10** and **13** was studied in the presence of several hydrolases (esterases EC 3.1.1.1 and lipases EC 3.1.1.3). The experiments were carried out in a phosphate buffer (0.1 M) at pH 7 and at 35°C by continuous addition of NaOH (1 M) and monitored by a pH-stat apparatus. The enzymes used are pig liver esterase (PLE; Boehringer), pig pancreatic lipase (PPL; Sigma, type II), Candida cylindracea lipase (Sigma, type VII),and SAM II lipase (Amano Pharm. Co.). It was soon observed that diacetate **13** was an excellent substrate for PLE. The (1R)-alcohol (+)-**14**[13] was obtained in 81 % yield and with 95.5 % ee[10]. Another successful experiment was the PLE-catalyzed hydrolysis of **9** leading to the (1R)-alcohol (-)-**11**[13] in 70 % yield and with 85 % ee[10]. In contrast, no selectivity was observed for PLE nor SAM II towards the

corresponding dibutyrate **10**. Likewise, unselective hydrolysis to the diol **3** occured upon action of PLE and Candida cyl. lipase on substrate **4**. In all other cases, no hydrolysis was observed.

Scheme 1



a : t.BuMe$_2$SiCl, imidazole, DMF, rt, 16 h (48 %); b : $(COCl)_2$, DMSO, CH_2Cl_2, -60°C; NEt_3 (for **3** : 91 %; for **12** : 96 %); c : Zn, CH_2Br_2, $TiCl_4$, THF, CH_2Cl_2, 0°C (for **3** : 79 %; for **12** : 64 %); d : TBAF, THF, rt, 16 h (87 %); e : n.PrCOCl, NEt_3, CH_2Cl_2, DMAP, rt, 2 h; f : HOOCCHO, Amberlyst-15, DME, 85°C, 2 h (84 %); g : $NaBH_4$, EtOH, rt (90 %); h : t.BuOK, t.BuOH, $PhCH_2Br$, 65°C (73 % + 25 % **8**); i : t.BuOK, THF, $PhCH_2Br$, 65°C (**8** : 62 %; for **13** : 86 %); j : 10 % aq.HCl, THF, rt, 18 h (for **9** : 82 %; for **13** : 96 %); k : Ac_2O, Py, DMAP, rt; l : BH_3.THF, THF, rt, NaOH, H_2O_2 (88 %); m : PLE, phosphate buffer (0.1 M, pH 7), NaOH (1 M), 35°C (**11** : 52 %; **14** : 73 %).

In order to prove the absolute configuration of (+)-**14** and (-)-**11** and to gain insight into potential synthetic applications, their elaboration into other chiral building blocks was carried out (Scheme 2). Oxidation of (+)-**14** and subsequent β-elimination gave 5(R)-benzyloxymethyl-2-cyclohexenone (-)-**15**,[13] while (+)-*ent* **15**[13] was obtained in the same way after tosylation and acetate hydrolysis. Hydrogenation of both enantiomers led to cyclohexanones (-)-**16**[13] and (+)-*ent* **16**[13]. The CD-spectra[14] of **15** and **16** established their absolute configuration as depicted in scheme 2.[15]

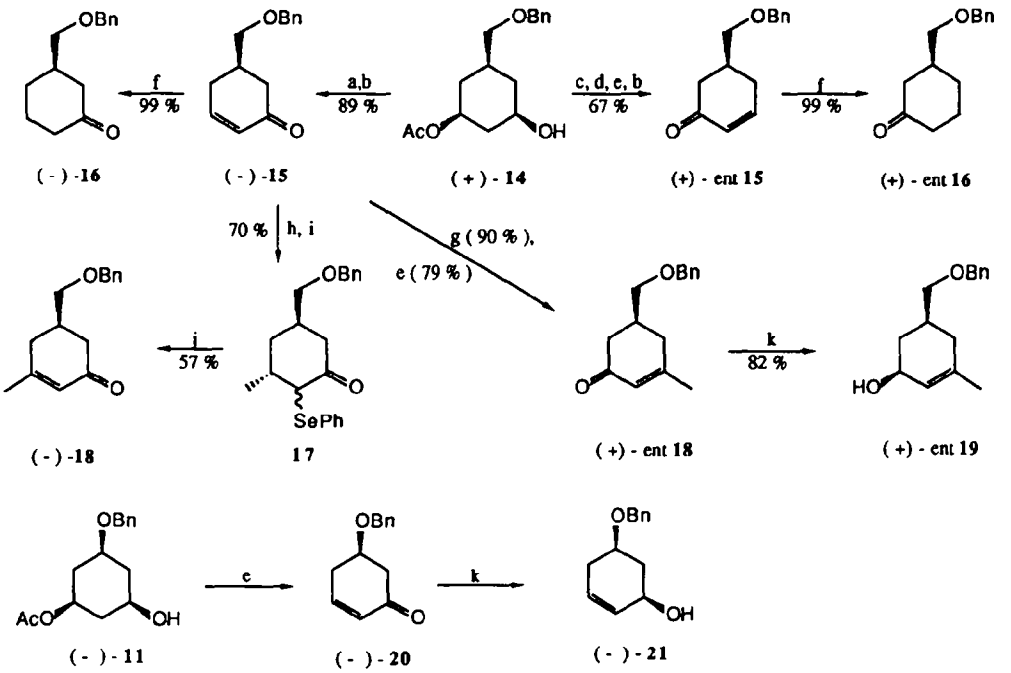
Treatment of (-)-**15** with methyllithium gave the tertiary alcohol, which upon oxidation afforded enone (+)-*ent* **18**[13] in 71 % overall yield. In the same way (-)-**18**[13] is available from (+)-*ent* **15**, or alternatively from (-)-**15** via conjugate addition, trapping of the enolate anion with phenylselenenyl chloride and subsequent oxidative elimination in 40 % overall yield.

On the other hand we were gratified to observe that oxidation of (-)-**11** afforded the ketone (70 %), which upon standing underwent slow β-elimination of only the acetate group to give enone (-)-**20**[13]. This not only allowed to determine the absolute configuration from its CD spectrum (also R)[14] but also opens routes to more elaborate compounds.

As there are many precedents for effective stereocontrol in 5-substituted-2-cyclohexenones during 1,4-additions and cycloadditions, **15**, **18** and **20** are of potential value in enantioselective total synthesis of natural products.[15]

Of special interest is the fact that the cis-allylic alcohols (+)-*ent* **19**[13] and (-)-**21**[13] were obtained almost exclusively upon reduction[12] of (+)-*ent* **18** and (-)-**20** respectively.[15] This broadens the scope for subsequent transformations, as highly stereoselective reactions on allylic alcohols are well-known.

Scheme 2



a : $(COCl)_2$, DMSO, CH_2Cl_2, -60°C; NEt_3; b : DBU, CH_2Cl_2, rt; c : TsCl, NEt_3, DMAP, CH_2Cl_2, rt; d : K_2CO_3, MeOH, rt; e : PCC, CH_2Cl_2, rt; f : Pd/C, H_2 (1 atm), EtOH; g : MeLi, ether, -78 → 0°C; h : Me_2CuLi, ether, 0°C; i : PhSeCl, ether; j : H_2O_2, H_2O, CH_2Cl_2, Py, 0°C; k : $NaBH_4$, $CeCl_3$, MeOH, 0°C.

Applications of these valuable building blocks in total synthesis, especially in the field of pseudo-sugars and vitamin D, are under current investigation.

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9. Direct dibenzylation of diol **6** in THF (benzyl bromide, KOt.Bu) was not successful, because of the low solubility of **6**.
10. The enantiomeric excess (% ee) was determined on the Mosher's ester derivative[11] by ^{1}H NMR spectroscopy at 360 MHz in $CDCl_3$.
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13. Optical rotations ($[\alpha]_D^{20}$) measured in $CHCl_3$:
    (-)-**11** : -5.0° (c=1); (+)-**14** : +14.2° (c=1);
    (-)-**15** : -59.8° (c=1.5) ; (+)-*ent* **15** : +60.4° (c=1.6);
    (-)-**16** : -4.9° (c=1.9); (+)-*ent* **16** : +5.0° (c=0.8);
    (-)-**18** : -69.5° (c=2.2); (+)-*ent* **18** : +74.8° (c=2.8);
    (+)-*ent* **19** : +30° (c=1.9); (-)-**20** : -3.0° (c=1.8);
    (-)-**21** : -39.3° (c=0.6).
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15. All compounds were fully characterized by spectroscopic methods.