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TETRAHEDRON: *ASYMMETRY*

Enzymatic desymmetrization of *meso cis,cis*-2,4,6-substituted tetrahydropyrans

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Abstract

The stereoselective acylation of *meso*-tetrahydropyrans **6** and **7** by enol esters (vinyl acetate or isopropenyl acetate) in the presence of *Candida antarctica* lipase in organic media gave the corresponding (2*R*,4*S*,6*S*)-monoesters **10** and **11** in high enantiomeric purity. The hydrolysis of the corresponding diacetate derivatives **8** and **9** in the presence of the same enzyme provided the opposite enantiomers, (2*S*,4*R*,6*R*)-monoesters **10** and **11**.

The *cis*-2,6-substituted tetrahydropyran ring system is found in many bioactive natural products[1,2] such as phorboxazoles[3] and bryostatins.[4] Synthetic interest in these compounds stems mainly from their biological activities, and in particular, their potential as antineoplastic agents. Recently, Hoffmann et al. reported the enzymatic desymmetrization of 2,4,6-trifunctionalized tetrahydropyrans in studies directed towards the synthesis of bryostatins.[5,6] This report describes new desymmetrizations of tetrahydropyrans.

The substrates were prepared as outlined in Scheme 1. Esterification of chelidonic acid **1** gave diester **2** in 80% yield. Catalytic hydrogenation of **2** over rhodium on alumina gave hydroxy-diester **3** in quantitative yield. Evidence for the stereochemical outcome of the hydrogenation reaction rested on ^{1}H NMR studies. The chemical shifts and coupling constants for H_2, H_4 and H_6 were consistent with an axial configuration and supported the *meso cis,cis* stereochemistry of compound **3**. Protection of the alcohol as the *tert*-butyldimethylsilyl (TBS) ether or the methoxymethyl (MOM) ether provided diesters **4** (80% yield) and **5** (84% yield). Reduction of **4** and **5** with $LiAlH_4$ gave the diols **6** (95% yield) and **7** (80% yield). Diols **6** and **7** were acetylated by acetic anhydride in pyridine in the presence of DMAP to give *meso* diacetates **8** (96% yield) and **9** (95% yield).

Diols **6** and **7** were subjected to enzyme-catalyzed esterification by treatment with *Candida antarctica* lipase (CAL) in vinyl or isopropenyl acetate (solvent and acyl donor) to give optically active esters (2*R*,4*S*,6*S*)-**10** and (2*R*,4*S*,6*S*)-**11** (Table 1). The reactions were monitored by TLC analysis and terminated when all the diol was consumed. The reaction in the presence of CAL was fast and highly

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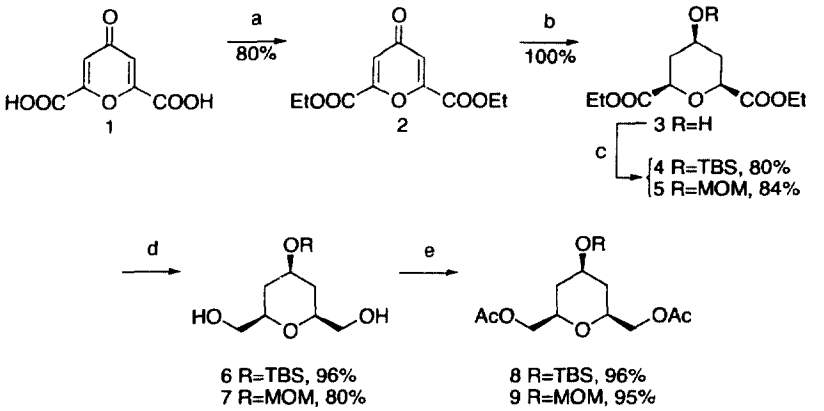
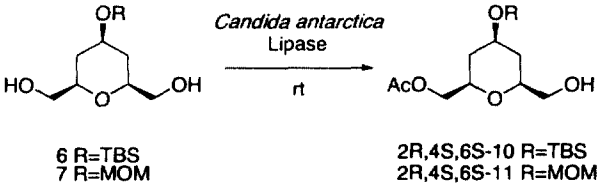


Scheme 1. *Reagents*: (a) EtOH, H_2SO_4, reflux; (b) H_2O, H_2, Rh/Al_2O_3; (c) TBDMSCl, CH_2Cl_2, pyridine, DMAP or MOMCl, CH_2Cl_2; (d) $NaBH_4$, Et_2O, 0°C to rt; (e) pyridine, Ac_2O, DMAP, rt

stereoselective but the yields in monoacetates were moderate, indicating that the monoacetates were also substrates. The starting material was completely converted into the monoacetates **10** and **11** and the corresponding diacetates. The enantiomeric composition was measured by ^{19}F NMR (282 MHz) analysis of the corresponding (+)-α-methoxy-α-trifluoromethyl-α-phenyl acetate (MTPA, Mosher's ester).

Table 1
Enzymatic acylation of diols by *Candida antartica* lipase[a] at room temperature



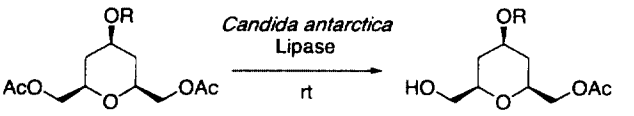
Entry	Diol	Acylating agent	Time (minutes)	Mono-acetate	ee %[b] (yield %)[c]
1	6	vinyl acetate	6	10	94(44)
2	6	isopropenyl acetate	25	10	>98(70)
3	7	vinyl acetate	6	11	90(44)
4	7	isopropenyl acetate	20	11	>95(68)

[a]The reaction was done as described in the text. [b]Enantiomeric excess was determined by ^{19}F NMR of MTPA ester.
[c]Yield based on the starting diol.

The enzymatic hydrolysis of diacetates **8** and **9** was performed in phosphate buffer (pH 7.0) in the presence of *Candida antarctica* lipase and Triton X-100 as surfactant, at room temperature. The hydrolysis was sluggish and incomplete in the absence of a surfactant. In general, the transesterification of *meso* diols and the hydrolysis of the corresponding *meso* diesters are complementary and give the opposite enantiomers. As expected, monoesters (2*S*,4*R*,6*R*)-**10** and (2*S*,4*R*,6*R*)-**11** were obtained in fair yields and high enantioselectivity (Table 2).

The absolute configuration of monoesters **10** and **11** was determined by correlation with compound **15** of known absolute configuration.[6] A sample of compound **10** was transformed into **15** by simple protecting group manipulation in four steps (Scheme 2): protection of the 6-OH group as a *p*-methoxybenzyl ether (**10** → **12**); deprotection of the 4-*O*-*t*-butyldimethylsilyl group by tetrabutylammonium fluoride

Table 2
Enzymatic hydrolysis of diacetates by *Candida antartica* lipase[a] at room temperature in pH 7 buffer with Triton X-100



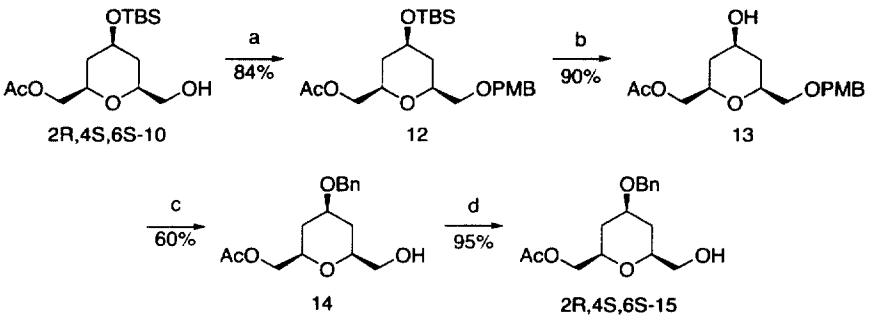
8 R=TBS
9 R=MOM

2S,4R,6R-10 R=TBS
2S,4R,6R-11 R=MOM

Entry	Diacetate	Time (hours)	Mono-acetate	ee %[b] (yield %)[c]
1	8	6	10	>95(70)
2	9	1	11	86 (100)

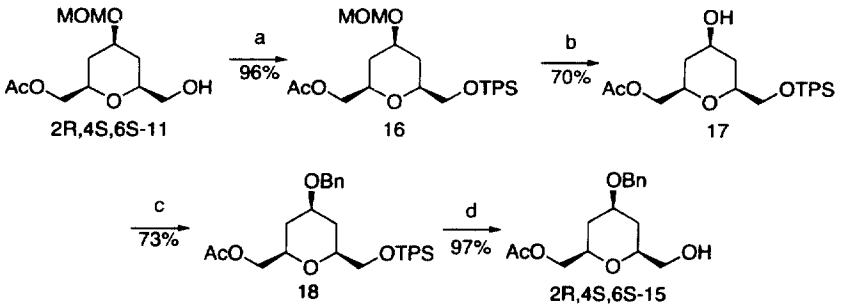
[a]The reaction was done as described in the text. [b]Enantiomeric excess was determined by ^{19}F NMR of MTPA ester. [c]Yield based on the starting diacetates.

(**12** → **13**); protection of the 4-OH group as a benzyl ether (**13** → **14**); and deprotection of the 6-O-PMB group by DDQ (**14** → **15**).



Scheme 2. *Reagents*: (a) *p*-Methoxybenzyl 2,2,2-trichloroacetamidate, Et_2O, TfOH; (b) *n*-Bu_4NF, THF, rt; (c) benzyl 2,2,2-trichloroacetamidate, TfOH, cyclohexane–CH_2Cl_2, rt; (d) DDQ, CH_2Cl_2–H_2O, rt

Similarly, a sample of **11** was transformed into **15** in four steps (Scheme 3): protection of the 6-OH group as a triphenylsilyl ether (**11** → **16**); deprotection of the 4-*O*-methoxymethyl group by Me_3SiBr (**16** → **17**); protection of the 4-OH group as a benzyl ether (**17** → **18**); and deprotection of the 6-OTPS group by tetrabutylammonium fluoride.



Scheme 3. *Reagents*: (a) TPSCl, CH_2Cl_2, pyridine, DMAP, 0°C to rt; (b) Me_3SiBr, CH_2Cl_2, −25°C to 0°C; (c) benzyl 2,2,2-trichloroacetamide, TfOH, cyclohexane–CH_2Cl_2, rt; (d) *n*-Bu_4NF, THF, rt

The current report complements the work of Hoffmann et al.[5,6] in several ways: (1) tetrahydropyrans were prepared by a new method; (2) high enantioselectivity was obtained using a different enzyme; and

(3) both hydrolysis and acylation reactions were highly enantioselective in contrast to previous work in which only hydrolysis gave good results. The enzymatic desymmetrization of *meso* compounds is an efficient approach for the synthesis of enantiomerically pure compounds.[7]

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