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Revision of the enantiotoposelective PLE-catalyzed hydrolysis of *cis*-5-substituted-1,3-diacyloxycyclohexanes

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Abstract : Revision of previous work shows that PLE-catalyzed hydrolysis of **1** *leads to the (S)-alcohol* **5** *and not the (R)-alcohol* **3**. *However the homologue* **2** *gives the (R)-alcohol* **4**.

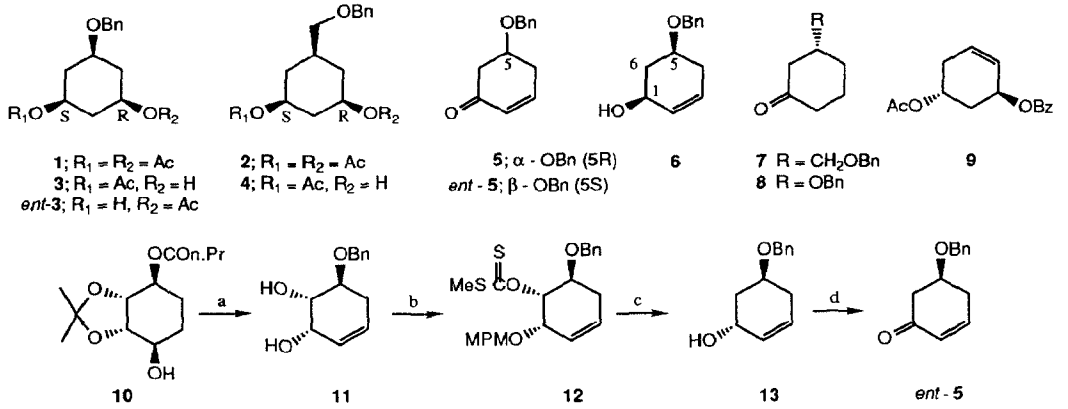
Some time ago we described the enantiotoposelective PLE-catalyzed hydrolysis of the all-*cis* 5-substituted 1,3-diacyloxycyclohexanes **1** and **2** for which we reported the formation of the *(R)*-alcohols **3** and **4**.[1] The assignment of the absolute configuration was based on the CD spectra of the derived ketones **5** and **7** respectively. The correct absolute configuration was obtained for the saturated β-substituted cyclohexanone **7**, whereas some assumptions had to be made about the preferred conformation for the enone **5**. Recently Sakai et al.[2] repeated the hydrolysis of **1** and claimed the formation of the *(S)*-alcohol *ent*-**3**, based on the CD spectrum of the derived benzoate **9**, obtained from *ent*-**3** in an unequivocal way. Furthermore they stated that $NaBH_4$-$CeCl_3$ reduction of *ent*-**5** leads to the *trans* substituted cyclohexene **13**, in contrast to our 1,5-*cis* assignment (**6**).

Presently, we report a revision of our work in relation with the two aforementioned problems.

1. As the assignment of the stereochemical outcome of the enzymatic hydrolysis relied in both cases on CD spectra, we reasoned that an independent chemical proof was needed. At the outset we want to state that our interpretation of the CD spectrum[1] was incorrect; thus, in contrast with our previous paper, we obtained *ent*-**5** and consequently the *(S)*-alcohol *ent*-**3**.
2. Although the ^1H NMR spectrum[3] provides, in our opinion, clearcut evidence for the *cis*-alcohol **6** being formed upon reduction of **5**, the chemical proof was conducted as to leave also no ambiguity for this problem.

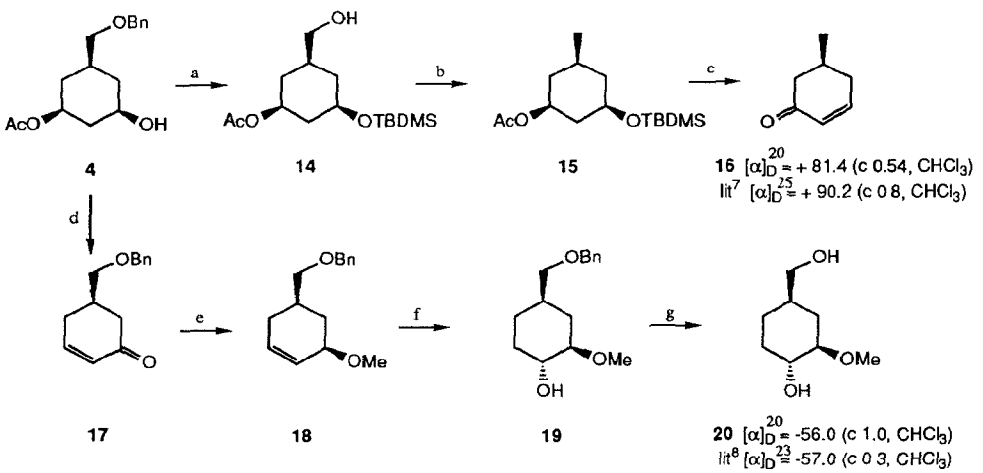
The chemical proof was provided by transformation of **10** into **13** and *ent*-**5** (scheme 1). The absolute configuration of **10**[9] is firmly established, *inter alia*, by correlation with (+)-dihydroconduritol C.[4] Regioselective dehydration[5] followed by ester solvolysis, O-benzylation and solvolysis of the acetonide led to the diol **11**[9]. p.Methoxybenzylation of the allylic alcohol (axial OH) was only moderately selective. The remaining free hydroxyl group was removed by tin hydride reduction of the corresponding methyl xanthate, affording the 3,5-*trans* alcohol **13**[9], which was clearly different from the reduction product **6**[9], obtained from

ent-**5**[9], as shown by its ^1H NMR spectrum[3]. Moreover, in the literature ample precedent is furnished for *syn*-selectivity upon reduction of 5-substituted cyclohexenones.[6] Eventually, formation of *ent*-**5** by oxidation of **6** confirmed our mis-assignment of the absolute configuration.



a : (i) Ph_3P, DEAD, THF (89 %); (ii) K_2CO_3, MeOH (78 %); (iii) BnBr, KO*t*Bu, THF (89 %); (iv) MeOH, pTSA (90 %); b : (i) $MeOPhCH_2OC(NH)CCl_3$, pTSA, CH_2Cl_2 (37 %); (ii) n.BuLi, CS_2, MeI, THF; c : (i) Bu_3SnH, AIBN, PhMe, t↑ (39 %, 2 steps); (ii) DDQ, CH_2Cl_2, H_2O (71 %); d : Collins reagent, CH_2Cl_2 (90 %).

Scheme 1



a : (i) TBDMSCl, DIPEA, DMF (98 %); (ii) $Pd(OH)_2$, EtOAc, H_2 (1 atm) (98 %); b : (i) TCDI, THF, reflux (94 %); (ii) Bu_3SnH, AIBN, PhMe, reflux (57 %); c : (i) K_2CO_3, MeOH (85 %); (ii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2 (58 %); (iii) aq.HCl, THF (22 %); d : (i) PCC, CH_2Cl_2; (ii) DBU, CH_2Cl_2, rt (89 %, 2 steps); e : (i) $NaBH_4$, $CeCl_3$, EtOH, 0°C (100 %); (ii) NaH, MeI, THF (92 %); f : (i) BH_3, THF; (ii) H_2O_2, NaOH (50 %); g : $Pd(OH)_2$, H_2 (1 atm), EtOAc (95 %).

Scheme 2

Subsequently 3(*R*)-benzyloxycyclohexanone **8**[9] was prepared from *ent*-**3**; the CD-spectrum showed positive Cotton effect which is in agreement with its absolute configuration. This is in contrast with the wrong assignment for **5** indicating that CD-data of cyclohexenones have to be interpreted with caution.

Because of the incorrect assignment of the alcohol obtained upon PLE-catalyzed hydrolysis of **1** we felt that our result for the hydrolysis of **2** to the *(R)*-alcohol **4** was compromized and that here also a chemical proof was appropriate. Silylation of the free hydroxyl group in **4** (scheme 2), followed by hydrogenolytic cleavage of the benzyl ether afforded **14**[9]. Reductive removal of the primary hydroxyl function led to **15**[9], which was eventually transformed into the known enone 5(*S*)-**16**[7], thus confirming the CD spectral assignment made earlier.[1] Additional proof was also provided by the transformation of **4** into Schreiber's intermediate **20** for the synthesis of FK-506.[8] (scheme 2). Selective 1,2-reduction of (*R*)-**17**, obtained in two steps from **4**[1], followed by O-methylation led to the methyl ether **18**[9], which upon hydroboration and oxidative work-up afforded the intermediate **19**[9]. Eventually, hydrogenolytic cleavage of the benzyl ether yielded **20**, showing identical optical rotation as described in the literature.[8]

The discrepancy observed during the PLE-catalyzed hydrolysis of respectively **1** (→ *(S)*-alcohol *ent*-**3**) and **2** (→ *(R)*-alcohol **4**) again shows the subtile structure dependence, even for rather similar substrates such as **1** and its homologue **2**. Apparently this observation points towards an electronic effect, rather than a steric one, for the enzyme-substrate interaction. We therefore plan to study the influence of the nature of the 5-substituent in analogues of **1** and **2** in order to gain insight into the active site of the enzyme.

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References

1. Carda, M.; Van der Eycken, J.; Vandewalle, M. *Tetrahedron : Asymmetry* **1990**, *1*, 17.
2. Suemune, H.; Takahashi, M.; Maeda, S.; Xie, Z.F.; Sakai, K. *Tetrahedron . Asymmetry* **1990**, *1*, 425.
3. Alcohol **6** :

   ^{1}H NMR (360 MHz, $CDCl_3$) : δ 7.3 (m, 5H), 5.89 (m, 1H, $^J_{H2,H3}$ = 10.1 Hz, H_2), 5.71 (m, 1H, $J_{H2,H3}$ = 10.1 Hz, H_3), , 4.62 (d, 1H, ^{2}J = 11.9 Hz, *PhCH*), 4.58 (d, 1H, ^{2}J = 11.9 Hz, *PhCH*), 4.15 (m, 1H, J = 1.9, 4.7 and 4.7 Hz, H_1), 3.88 (ddt, 1H, J = 2.7, 4.5, 4.5 and 7.1 Hz, H_5), 2.35 (m, 1H, ^{2}J = 18 Hz, H_4), 2.23 (m, 1H, ^{2}J = 18 Hz, $H_{4'}$), 2.10 (ddd, 1H, J = 4.5, 5.5 and 13.5 Hz + L.R., H_6), 2.03 (ddd, 1H, J = 2.8, 5.2 and 13.5 Hz, $H_{6'}$).

   ^{1}H NMR (360 MHz, CD_3OD) : δ 7.3 (m, 5H), 5.65 (m, 2H, H_2 and H_3), 4.58 (s, 2H, $PhCH_2$), 4.24 (m, 1H, H_1), 3.68 (dddd, 1H, J = 3.1, 5.4, 8.8 and 11.5 Hz, H_5), 2.47-2.34 (m, 2H, H_4 and H_{6eq}), 2.02 (m, 1H, $H_{4'}$), 1.50 (dt, 1H, J = 9.6, 11.5 and 11.5 Hz, H_{6ax}).

   The *cis* relationship in **6** follows from the coupling constants observed for H_{6ax} and H_5 when the spectrum is recorded in CD_3OD, indicating a 1,5-*syn* diequatorial conformation, and is further corroborated by the fact that in the absence of a protic solvent ($CDCl_3$) the molecule adopts a 1,5-*syn* diaxial conformation due to an intramolecular H-bond, as can be seen from the coupling constants of H_5, H_6 and $H_{6'}$.

   Alcohol **13** : ^{1}H NMR (500 MHz, $CDCl_3$) : δ 7.33 (m, 2H), 7.28 (m, 3H), 5.78 (m, 2H, H_2 and H_3), 4.61 (d, 1H, ^{2}J = 11.5 Hz, *PhCH*), 4.58 (d, 1H, ^{2}J = 11.5 Hz, *PhCH*), 4.41 (m, 1H, H_1), 3.87 (m, 1H,

H_5), 2.44 (m, 1H, ^{2}J = 17.6 Hz, H_4), 2.10 (m, 1H, ^{2}J = 17.6 Hz, $H_{4'}$), 2.05 (dt, 1H, J = 4.5, 4.5 and 13.5 Hz, H_{6eq}), 1.90 (ddd, 1H, J = 4.7, 9.8 and 13.5 Hz, H_{6ax}).

4. Dumortier, L.; Van der Eycken, J.; Vandewalle, M. unpublished results.
5. Wojciechowska, H.; Pawiowicz, B.; Andruszkiewics, R.; Grybowska, J. *Tetrahedron Lett.*, **1978**, 4063.
6. Thurkauf, A.; Tius, M.A. *J. Chem. Soc., Chem. Comm.*, **1989**, 1593; Naves, Y.R. *Helv. Chim. Acta* **1964**, *47*, 1617; Gemal, A.L.; Luche, J.L. *J. Am. Chem. Soc.* **1981**, *103*, 5454; Baker, R.; Gibson, C.L.; Swain, C.J.; Tapolczay, D.J. *J. Chem. Soc., Perkin Trans I*, **1985**, 1509.
7. Allinger, N.L.; Riew, C.K. *J. Org. Chem.* **1975**, *40*, 1316; Gorthey, L.A.; Vairamani, M.; Djerassi, C. *J. Org. Chem.* **1985**, *50* (22), 4173.
8. Schreiber, S.L.; Smith, D.B. *J. Org. Chem.* **1989**, *54*, 9.
9. Optical rotations ($[\alpha]_D^{20}$) measured in $CHCl_3$:

ent-**5** :	-5.6	(c 0.9)
6 :	-53.3	(c 0.4)
8 :	+9.45	(c 0.9) (80 % ee)
10 :	+10.8	(c 1.3)
11 :	+167.9	(c 1.2)
13 :	+91.4	(c 1.3)
14 :	-1.9	(c 1.0)
15 :	-9.3	(c 0.64)
18 :	-16.3	(c 1.7)
19 :	-42.7	(c 1.0)