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Optically Active 1,3-Dioxolane-4-methanols. Lipase-Catalysed Acylation of Racemic Ketals and Diastereomeric Acetals

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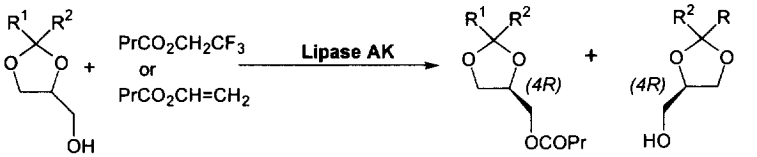
Abstract:. The acylation of 13 different 2-mono- or disubstituted 1,3-dioxolane-4-methanols by lipase AK (lipase from *Pseudomonas sp.*) catalysis in diisopropyl ether has been studied. In the case of monosubstitution, the stereochemical outcome for the acylation of a racemic diastereomeric mixture is considered using graphs which are based on the determined selectivity ratios. The gram-scale separation of the mixture of *cis*- and *trans*-1,2-benzylideneglycerols as well as the mixture of 1,2- and 1,3-benzylideneglycerols, through the lipase AK-catalysed acylation has been described.

Introduction

Many enantiopure C_3 synthons can be regarded as simple derivatives of glycerol and the groups differentiating the synthon from the prochiral triol as protecting groups. In addition to the normal protecting function such groups introduce symmetry elements in these glycerol based derivatives. Thus, monoprotection at the C-1 position or diprotection at the 1,2-positions generate compounds with the C-2 setereocentre.[1,2] On the other hand, blocking the secondary hydroxyl group of glycerol leads to prochiral structures.[3] These derivatives still bear a primary hydroxyl function, the enzymatic reactions at which enabling enantiodiscriminative acyl transfers and the formation of highly enantiopure compounds.

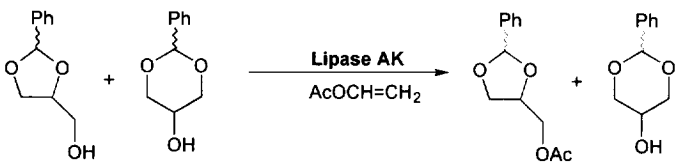
Among the protected glycerol derivatives, 2,2-dimethyl-1,3-dioxolane-4-methanol **3** (trivially called solketal) holds the key position and much synthetic chemistry has been created around it.[4] For the preparation of the enantiomers of solketal, the cheap racemate has served as the starting material in numerous resolution based attempts. Unfortunately, most biocatalytic ways have proceeded at moderate enantioselectivity, the value of the enantiomeric ratio[5] *E* ranging between 2 and 9.[6-15] The lipase AK (from *Pseudomonas sp.*)-catalysed enantioselective acylation (*E* 20-29) of solketal finally made an efficient large-scale preparation of the two enantiomers possible.[2,16] In order to study the resolvability of analogous C_3 synthons and the structural features controlling enzymatic enantioselectivity, the lipase-catalysed acylation of various 1,3-dioxolane-4-methanols was studied in this work. Accordingly, carbonate, ketal and acetal protected glycerol derivatives **1-13** (compounds **8-**

13 as diastereomeric pairs **8+9**, **10+11** and **12+13**) were subjected to the lipase AK-catalysed asymmetric butyrylation (Scheme 1, Tables 1 and 2).[17,18]



Scheme 1.

To the best of our knowledge the enzymatic acylation of 1,2-acetal protected glycerols has not been studied before. One reason for this is certainly the fact that the direct acetalization of glycerol leads to nonchiral *cis*- and *trans*-1,3-dioxan-5-ols in addition to the corresponding 1,3-dioxolane-4-methanols. The separation of these ring isomers by normal chemical means is laborious or even impossible because the isomers have very similar physicochemical properties. On the other hand, the biocatalytic separation of the ring isomers through the acylation of the primary alcohol in the mixture of isomeric alcohols is worth studying. For that purpose, the acetalization[17] mixture consisting of 2-phenyl-1,3-dioxolane-4-methanols and 2-phenyl-1,3-dioxan-5-ols was subjected to acylation in the presence of lipase AK (Scheme 2).



Scheme 2.

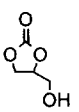
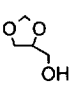
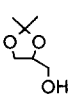
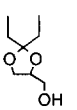
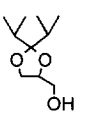
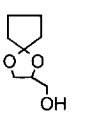
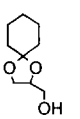
Fortunately the formation of ring isomers can be avoided by relying on a three step synthesis yielding the 2-substituted-1,3-dioxolane-4-methanols **8-13** as a *cis/trans*-mixture.[18] Such a mixture of four stereoisomers affords an opportunity to study the development of enantio- and diastereopurities for substrate and product fractions during enzymatic acylation.

The reactions were followed by the chiral GLC method and if not otherwise stated the stereoisomers were not separated from the reaction mixture.[19] The absolute configuration at the C-2 stereocentre of 2-monosubstituted 1,3-dioxolane-4-methanol is unimportant because it is removed during the subsequent deprotection steps when the C_3 synthon is used for further synthetic purposes. The C-2 centre in glycerol corresponds to the C-4 stereocentre in dioxolanemethanols.

Results and discussion

Enantioselective Acylation. - In our previous work, the butyrylation of solketal in diisopropyl ether in the presence of the lipase AK preparation (8.6% of the lipase and 5.2% of sucrose adsorbed on Celite) at low temperatures (close to 0 °C) achieved practically enantiopure (*R*)-solketal (ee >99%) as the less reactive enantiomer.[2,16] This method was now exploited for the screening of compounds **1-13** towards the enantioselectivity of lipase AK except that part of the screenings were performed at room temperature. Thus, enantioselectivity enhancement is observed at lower temperatures (Tables 1 and 2). 2,2,2-Trifluoroethyl or vinyl butyrate was used as an acyl donor. For the two acyl donors, the *E* values calculated before attaining the 40% conversion were identical indicating that the 2,2,2-trifluoroethyl ester can be regarded as an irreversible acyl donor at low conversions.

Table 1. Enzymatic acylation of 2,2-disubstituted 1,3-dioxolane-4-methanols[a]

Compound	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Structure							
Enzyme preparation (mg ml^{-1})	10	5	10	10	10	10	10
Time (h)	0.3	0.8	1.7	1.2	5.0	1.1	1.0
Conversion (%)	6	32	48	23	10	49	28
E	3	3	13/29[b]	3	8	6	7

[a]Conditions: racemic alcohol (0.1M), 2,2,2-trifluoroethyl butyrate (0.2 M) and the enzyme preparation (10% lipase AK adsorbed on Celite) in diisopropylether were shaken at 23 °C. [b]Acylation with $(PrCO)_2O$ at 0°C see ref. 16.

The *E* values of Table 1 clearly reveal that ketal protective groups in glycerol only slightly affect the enantioselectivity of lipase AK and show solketal **3** to be by far the most appropriate candidate for the preparation of optically active C_3 synthons. Similar structural effects have been detected before for the lipase PS (*Pseudomonas cepacia* lipase)-catalysed hydrolyses of compounds **3**, **4**, **7** and 2,2-diphenyl-1,3-dioxolane-4-methanol with the *E* values 3.5, 1.7, 2.9 and 8.1, respectively.[11] As an exception, the lipase PS-catalysed esterification of compound **5** seems to proceed at considerable enantioselectivity ($E = 23$ as calculated according to the data in ref. 9) in the presence of succinic anhydride in diethyl ether.[9]

The 2-monosubstituted 1,3-dioxolane-4-methanols in the present work are racemic mixtures of *cis*- and *trans*-isomers and accordingly contain two pairs of enantiomers. Before considering the system as such some

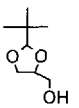
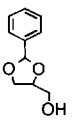
interesting observations can be made concerning enantioselectivity. For the lipase AK-catalysed acylation of acetal protected compounds **8-13**, the structure of the substituent at the position C-2 of 1,3-dioxolane-4-methanol exerts an interesting variation in *E*, exposing the importance of the orientation in space (Table 2). Accordingly, methyl and *tert*-butyl group (at room temperature) when oriented *cis* to the hydroxy methyl group (compounds **8** and **10** in the *cis/trans* mixture) results in the *E* value which is of the same order magnitude as that found for solketal **3** (Table 1). The same substituents in the *trans*-position (compounds **9** and **11**) lead to the reduction of enantioselectivity, the drop of *E* being more pronounced in the case of the more hindered *tert*-butyl group. A phenyl substituent (compounds **12** and **13**) is unfavourable when enantioselectivity is considered. Connecting this information to the enantioselectivity results of Table 1 it is proposed that for the proper enantioselectivity of lipase AK there must be at least one aliphatic substituent (see compound **2**) at the position C-2 of 1,3-dioxolane-4-methanol. Moreover, if this substituent situates *trans*-oriented compared to the asymmetric C-4 centre its size should be restricted to that of the methyl group (see compound **4**).

For the resolution of solketal and solketal butyrate, the (*S*)-selectivity of lipase AK is well documented.[16] That is also the case for the acylation of **1**.[14] As is natural, the more reactive enantiomer of the alcohols **2-13** has also (*S*)-absolute configuration at the C-4 centre (due to priority rules the acylation leads to the formation of the (*R*)-ester, Scheme 1). This was confirmed by preparing an enantiomerically enriched dioxolanemethanol using transacetalization or transketalization between enantiomerically enriched (*R*)-solketal butyrate and the aldehyde or ketone corresponding to the desired dioxolanemethanol. Identification was done by comparing the retention times and relative areas of the enantiomers [area of the (*R*)-butyrate>area of the (S)-butyrate] on chiral GLC to those obtained for the lipase AK-catalysed butyrylation of alcohols **2-13**.[20] The *cis* and *trans* identification of the pairs **8+9** and **12+13** were based on the published ^{1}H NMR data.[21] For the pair **10+11** the assignment is based on the assumed analogy in the GLC elution order and ^{1}H NMR data with the pairs **8+9** and **12+13**.

Enzymatic Acylation of Racemic Diastereomeric Mixtures. - In a conventional kinetic resolution, the constant *E* governs the enantiopurity obtainable for the more and less reactive enantiomers at any degree of conversion.[5] For the resolution of the *cis/trans*-mixture of 1-substituted 1,3-dioxolane-4-methanol [$(A+B)^{cis}$ and $(C+D)^{trans}$], there are two *E* values (E^{cis} and E^{trans}) each corresponding to a single diastereomer.[22] In addition to enantiopurity governed by these two constants diastereopurity can be introduced as a new parameter necessitating the determination of the third analogous ratio now between two enantiomers of different diastereomers ($E^{cis/trans}$; from four possible ratios one suffices for further calculation). With the three ratios, E^{cis}, E^{trans} and $E^{cis/trans}$ the diastereo- and enantiopurities as the function of the total conversion can be visualized by developing the necessary mathematical equations. The graphs with the experimental points for the lipase AK-catalysed acylation of diastereomeric mixtures **8+9**, **10+11** and **12+13** are shown in Figures 1A, B and C, respectively. Due to incomplete GLC-separation, the ee_p points are not shown in Figures 1 B and C. The enzymatic acylation of **8+9**

(Figure 1A) clearly allows the separation of the more reactive *cis*- and *trans*-enantiomers from the less reactive counterparts (Scheme 1). Thus at 60 % conversion the remaining substrate consists of the practically enantiopure mixture of the (*2S,4R*; ◈) and (*2R,4R*; ◆)-alcohols affording the stereogenic C-4 centre with the (*R*) absolute configuration. The efficiency of this kinetic resolution in distinguishing the *4R* and *4S* centres is comparable to that obtained for the resolution of solketal **3**. On the other hand, the acylation of **10**+**11** results in the enantio- and diastereopure (2*S*,4*R*)-isomer (Figure 1B), the acylation of **12**+**13** enabling the enzymatic separation of *cis*- and *trans*-diastereomers (□ and ■, Figure 1 C). The same predictions are possible qualitatively by calculating the relative rates (Table 2) on the basis of the E^{cis}, E^{trans} and $E^{cis/trans}$ values and giving the value 1 to the slowest reacting stereoisomer. Although lipase-catalysed reactions on the mixture of more than two stereoisomers has been reported this kind of a numerical treatment has not been performed before.[23-27]

Table 2. Enzymatic acylation of 2-monosubstituted 1,3-dioxolane-4-methanols as a diastereomeric mixture[a]

Compound	**8** *cis*[b]		**9** *trans*[b]		**10** *cis*[c]		**11** *trans*[c]		**12** *cis*[d]		**13** *trans*[d]	
Structure												
E	13		9		14		1		4		3	
E[e]	23		16		13		1		5		4	
Absolute configuration	*2R4S*	*2S4R*	*2S4S*	*2R4R*	*2R4S*	*2S4R*	*2S4S*	*2R4R*	*2R4S*	*2S4R*	*2S4S*	*2R4R*
Relative rate	13.0	1.0	11.3	1.2	13.7	1.0	7.0	6.7	4.3	1.0	24.1	9.0
Relative rate[e]	23.2	1.0	17.0	1.1	13.5	1.0	6.1	5.8	5.2	1.0	44.1	11.6

[a]Conditions: racemic alcohol (0.2 M), vinyl butyrate (0.4 M) and the enzyme preparation (10-20 mg ml^{-1}, 10% lipase AK adsorbed on Celite) in diisopropylether were shaken at 23 C. [b]Initial *cis/trans* ratio 45/55. [c] Initial *cis/trans* ratio 53/47. [d]Initial *cis/trans* ratio 55/45. [e]Acylation at 0°C.

The separation of *cis/trans*-mixtures by normal physical means is often laborous or even impossible. According to the above results, biocatalysis can be a valuable method for the separation of diastereomeric mixtures. To this end, the preparative scale enzymatic separation of **12** and **13** was performed by acylating the mixture **12**+**13** (10,24 g) with vinyl butyrate (12,98 g) in diisopropyl ether (250 ml) at 0^0C in the presence of the enzyme preparation (2,20 g, containing 10 % of lipase AK).

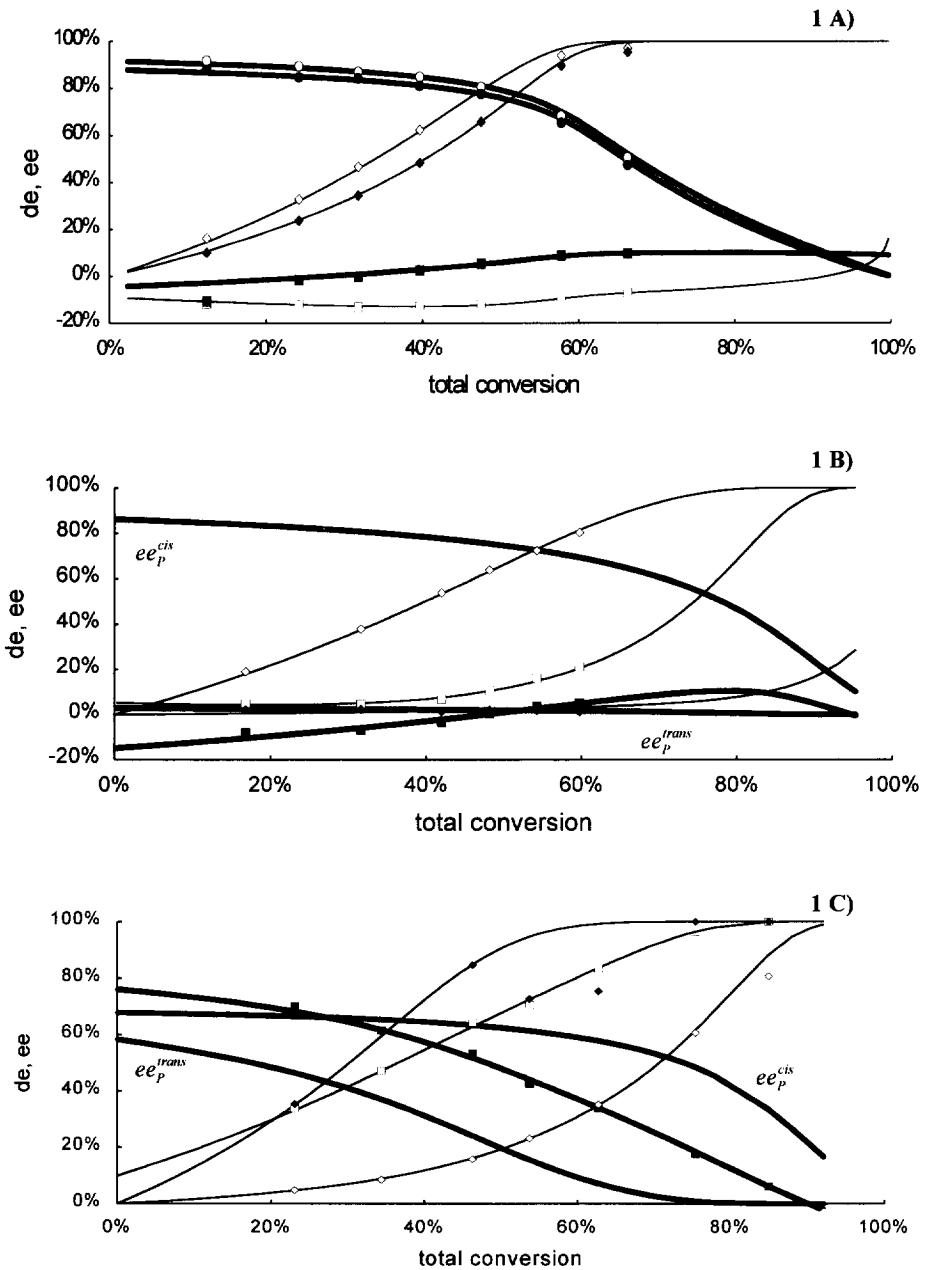


Figure 1. de for *cis* in substrate (□) and trans in product (■) fraction; ee for cis (◈) and trans (◆) in substrate and cis (○) and trans (●) in product fraction *vs.* total conversion in the Lipase AK-catalysed acylation of **8**+**9**, **10**+**11** and **12**+**13** (1 A, 1 B and 1 C, respectively) in diisopropyl ether at 0^0C. Solid lines for the theoretical graphs.

After 18 h the reaction was stopped at 74 % total conversion by filtering off the enzyme. Column chromatography on silica (acetone:hexane 20:80) afforded **13** as the butyrate (10,90 g) at 22 % de^{trans}. Further elution (acetone:hexane 40:60) gave finally alcohol **12** (2,69 g) at 95 % de^{cis} and 50 % ee.

Enzymatic Separation of cis/trans-2-phenyl-1,3-dioxolane-4-methanol from cis/trans-2-phenyl-1,3-dioxan-5-ol by Acylation. - As already mentioned the direct acetalization of glycerol leads to ring isomers.[17] In the case of benzaldehyde the ratio *cis*-1,2-benzylideneglycerol:*trans*-1,2-benzylideneglycerol:1,3-benzylideneglycerols in the acetalization mixture after distillation was 38:27:35. The lipase-catalysed acylation of primary alcohols is significantly favoured over that of secondary alcohols.[1,2] In accordance with this, the initial rate for the lipase AK-catalysed acetylation of dioxolanemethanols was found to be more than 200 times higher than that of the six-membered counterpart in the above mixture. This rate difference was now exploited for the biocatalytic separation of the dioxolanemethanols from the dioxanols (Scheme 2). For that purpose the distilled benzylideneglycerol mixture (13,50 g) was acetylated with vinyl acetate (13,00 g) in diethyl ether (150 ml) at room temperature in the presence of the enzyme preparation (3,00 g, containing 10 % of lipase AK) and triethyl amine (3,00 g). After 4,5 h the reaction was stopped at 50 % total conversion by filtering off the enzyme. Column chromatography on silica (diethyl ether:hexane 50:50) afforded compounds **12** and **13** as the mixture of acetates (7,45 g *cis:trans* 44:56). The amount of dioxanol acetates in the isolated product was less than 1%.[28]

Conclusions

This paper describes useful applications of biocatalysis for the acylation of 2-mono- and 2,2-disubstituted 1,3-dioxolane-4-methanols. We have been able to show that when an alicyclic compound contains two substituents which are *cis* or *trans* to each others the stereochemical outcome of each stereoisomer can be easily studied by determining the selectivity ratios E^{cis}, E^{trans} and $E^{cis/trans}$ at the early stage of the reaction using modern chromatographic methods. The results (either graphs or relative rates of each component in the mixture)[22] can then be used for considering if the system as such is usable for the production of enantio- and/or diastereopure stereoisomers, or if it is more reasonable to do resolution after the separation of the *cis*- and *trans*-isomers.

One of the most valuable applications of the present acylations is the preparation of optically active C_3 synthons for further synthetic purposes. The results of this work address the protected glycerols **3** and **8**+**9** as the most appropriate candidates for the creation of the desired C-2 stereocentre (Tables 1 and 2; Figure 1A). The three-step chemical synthesis used in order to avoid the formation of 1,3-dioxan-5-ols makes the latter case, however, somewhat less favourable compared to the resolution of the ketal protected compound **3**. On the other hand, the reactivity difference between primary and secondary alcohol functions towards enzymatic acylation can sometimes be exploited for the separation of ring isomers.

Acknowledgements. We thank the Technology Development Centre (TEKES) for financial support.

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18. The mixture **8+9** was prepared by condensing paraldehyde with 3-chloropropane-2,3-diol followed by heating with sodium butyrate in DMF. After methanolysis of the butyrates the mixture **8+9** was obtained (ref. 11). **10+11** was prepared in the same way except that the first step consisted of BF_3-catalysed addition of benzaldehyde to epichlorohydrin. Wershofen, S.; Classen, A.; Scharf, H.-D. *Liebigs. Ann. Chem.* **1989**, 9. **12+13** was prepared analogously from pivalaldehyde and epichlorohydrin except that sodium butyrate was replaced by sodium benzoate and the *cis/trans* alcohol was released by saponification of the benzoate ester with NaOH.
19. In most cases, all stereoisomers of the less reactive 1,3-dioxolane-4-methanols (**1-13** as acylated derivatives) and the corresponding butyrylated products can be simultaneously separated using a chiral GLC method on

Chrompack CP-Cyclodextrin-β-2,3,6-M-9 column. In the enzymatic butyrylation of the racemic mixture of the diastereomeric pair $(A+B)^{cis}$ and $(C+D)^{trans}$ the unreacted substrates (A, B, C, and D) and the reaction products (E, F, G and H) can be assigned as follows: The elution order for the derivatized unreacted substrates in the cases of **8**+**9** (as propionates) and **12**+**13** (as acetates) were A, B, D and C. In the case of **10**+**11** (as tert-butyl carbonates) the elution order was B, C, A and D. The produced butyrates came out in the order E, F, H and G for **8**+**9** and **12**+**13** (resolved diastereomerically only), the elution order in the case of **10**+**11** being F, G, E and H (streoisomers F and G coeluted).

$A^{cis} \xrightarrow{\text{fast } v_1} E^{cis}$

$B^{cis} \xrightarrow{\text{slow } v_2} F^{cis}$

$C^{trans} \xrightarrow{\text{fast } v_3} G^{trans}$

$D^{trans} \xrightarrow{\text{slow } v_4} H^{trans}$

20. The acetal and ketal exchange reactions were performed between (*R*)-solketal butyrate (66 % ee) and the carbonyl compound in the presence of acid Amberlyst 15 ion-exchange resin. Acyl migration was insignificant as indicated by only slight racemication.
21. For **8** and **9** see Inch, T. D.; Williams, N. *J. Chem. Soc.* **1970**, 263. For **12** and **13** see Carman, R. M.; Kibby, J. J. *Aust. J. Chem.* **1976**, *29*, 1761.
22. For the enzymatic butyrylation of **8**+**9** (see ref. 19) the three enantiomeric ratios are obtained by equations 1-3, the subscript 0 referring to the initial quantity, the subscripts S and P to the substrate and product respectively, and the letters A-H to the quantities of the stereoisomers. In equation 3, $ee_S = \frac{C-B}{C+B}$, $ee_P = \frac{F-G}{F+G}$ and $ee_0 = \frac{B_0-C_0}{B_0+C_0} = de_0^{cis}$. The total conversion (the x-axis in the graphs, Figure 1) is obtained by equation 4.

$$(1)\quad E^{cis} = \frac{\ln\frac{A}{A_0}}{\ln\frac{B}{B_0}} = \frac{\ln\frac{(ee_P^{cis} - ee_P^{cis}ee_S^{cis})}{(ee_P^{cis} + ee_S^{cis})}}{\ln\frac{(ee_P^{cis} + ee_P^{cis}ee_S^{cis})}{(ee_P^{cis} + ee_S^{cis})}} \qquad (2)\quad E^{trans} = \frac{\ln\frac{C}{C_0}}{\ln\frac{D}{D_0}} = \frac{\ln\frac{(ee_P^{trans} - ee_P^{trans}ee_S^{trans})}{(ee_P^{trans} + ee_S^{trans})}}{\ln\frac{(ee_P^{trans} + ee_P^{trans}ee_S^{trans})}{(ee_P^{trans} + ee_S^{trans})}}$$

$$(3)\quad E^{cis/trans} = \frac{\ln\frac{B}{B_0}}{\ln\frac{C}{C_0}} = \frac{\ln\frac{ee_p - ee_s ee_p + ee_0(ee_s - 1)}{ee_s + ee_p + ee_0(ee_s + ee_p)}}{\ln\frac{ee_p + ee_s ee_p - ee_0(ee_s + 1)}{ee_s + ee_p - ee_0(ee_s + ee_p)}} \qquad (4)\quad c_{total} = \frac{-de_0^{cis} + de_S^{cis}}{de_S^{cis} + de_P^{trans}}$$

For the enzymatic butyrylation of **12**+**13** the three enantiomeric ratios and conversions of the diastereomers are obtained by equations 5-7. In equation 7, $A_0 = B_0 = 0.25 + 0.25 \cdot de_0^{cis}$, $C_0 = D_0 = 0.25 - 0.25 \cdot de_0^{cis}$, $B = (1 - c_{total})(0.5 + 0.5 \cdot de_S^{cis})(0.5 + 0.5 \cdot ee_S^{cis})$ and $C = (1 - c_{total})(0.5 - 0.5 \cdot de_S^{cis})(0.5 - 0.5 \cdot ee_S^{cis})$.

$$(5)\quad E^{cis} = \frac{\ln((1-c_{cis})(1-ee_s^{cis}))}{\ln((1-c_{cis})(1+ee_s^{cis}))} \quad (6)\quad E^{trans} = \frac{\ln((1-c_{trans})(1-ee_s^{trans}))}{\ln((1-c_{trans})(1+ee_s^{trans}))} \qquad (7)\quad E^{cis/trans} = \frac{\ln\frac{[B]}{[B_0]}}{\ln\frac{[C]}{[C_0]}}$$

(8) $c_{cis} = \frac{c_{total}(1 + de_P^{cis})}{(1 + de_0^{cis})}$ (9) $c_{trans} = \frac{c_{total}(1 - de_P^{cis})}{(1 - de_0^{cis})}$

Equations 5-9 were modified for the case of **10+11** due to coeluting E+H. In the modified equations the diastereomeric excess was expressed with respect to E+H for the product and B+C for the substrate.

For the theoretical graphs (Figure 1) equations 10-17, where $A = A_0 \frac{D^{E^{cis}E^{cis/trans}E^{trans}}}{D_0^{E^{cis}E^{cis/trans}E^{trans}}}$, $B = B_0 \frac{D^{E^{cis/trans}E^{trans}}}{D_0^{E^{cis/trans}E^{trans}}}$, $C = C_0 \frac{D^{E^{trans}}}{D_0^{E^{trans}}}$, E=$A_0$-A, F=$B_0$-B, G=$C_0$-C, and H=$D_0$-D were used (see ref. 19).

(10) $ee_S^{cis} = \frac{B - A}{B + A}$ (11) $ee_P^{cis} = \frac{E - F}{E + F}$ (12) $ee_S^{trans} = \frac{D - C}{D + C}$ (13) $ee_P^{trans} = \frac{G - H}{G + H}$

(14) $de_0^{cis} = \frac{A_0 + B_0 - C_0 - D_0}{A_0 + B_0 + C_0 + D_0}$ (15) $de_S^{cis} = \frac{A + B - C - D}{A + B + C + D}$ (16) $de_P^{trans} = \frac{G + H - E - F}{G + H + E + F}$

(17) $c_{total} = \frac{E + F + G + H}{A_0 + B_0 + C_0 + D_0}$

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28. Initial composition and the enzymatic reaction was analyzed by the GLC method after derivatization with acetic and propionic anhydride, respectively (ref. 19). Total conversion was calculated by equation:

$c_{total} = \frac{re_0^{dioxolane} + re_S^{dioxanol}}{re_S^{dioxanol} + re_P^{dioxolane}}$, the term *re* designating ring isomeric excess with respect to the ring isomer cited in the superscript, the subscripts as in ref. 22. It is assumed that the isomers have identical responses in FID-detection.

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