# Synthesis and Lipase-Catalyzed Resolution of 5-(Hydroxymethyl)-1,3-dioxolan-4-ones: Masked Glycerol Analogs as Potential Building Blocks for Pharmaceuticals

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(Hydroxymethyl)-1,3-dioxolan-4-ones from mandelic and lactic acids and 1,5,5-trimethyl-3-phenyloxazolidin-2-one from mandelamide were α-alkylated using benzyl chloromethyl ether. Reductive debenzylation of the products of alkylation unmasked the hydroxymethyl groups. The compounds obtained in this fashion were subsequently subjected to lipase-catalyzed resolution in organic media. Depending on the lipase and substrate employed, enantiomeric ratios up to $E = 200$ were observed. The obtained optically pure compounds can be considered as masked 2-substituted glycerol equivalents, which could be used for the preparation of tertiary (aryloxy)propanolamines, compounds having potential $\beta$-blocking activity.

## Introduction

Functionalized chiral C3-synthons, in particular chiral glycerol derivatives, are of much topical interest. Such compounds are used for the synthesis of several types of pharmacologically active compounds,[1] of which the antihypertensive $\beta$-adrenergic blockers are probably the most important. Several chiral derivatives of (prochiral) glycerol have been developed.

Chiral glycerol synthons can either be prepared by stereoselective synthesis from carbohydrates such as mannitol[2] or by enzymatic resolution procedures.[3] Chiral derivatives of glycerol such as the cyclic carbonate or the acetonide (solketal) have been resolved by enzymatic hydrolysis or acylation procedures.[3] Although these materials can be obtained in optically pure form this way, the chiral recognition (expressed as the enantiomeric ratio E)[4] is only moderate ($E = 5-15$), resulting in low product recovery.

The value of these materials is, however, beyond doubt. It has been shown, for example, that chiral intermediates like solketal are easily converted to the highly valuable $\beta$-blockers,[5] such as (aryloxy)propanolamines like (*S*)-propranolol.[6] The antihypertensive effect of these materials stems from their resemblance to the adrenergenic hormone (*R*)-noradrenaline, which enables them to block adrenergenic receptors.[7] The stereochemistry of these drugs is of utmost importance, and usually the (*S*) enantiomer is by far the most active.[8] The common feature of these active (aryloxy)propanolamines is that, in addition to the aryloxy and amine functionalities, they contain a secondary hydroxyl group at the chiral center. A large variety of aryloxy and amine groups has been used in the development of new $\beta$-blockers.[7] The only position at which no substituent has been introduced is at the chiral center itself where always a secondary hydroxyl group is present.

Previously, we have shown that compounds having a tertiary chiral center can be resolved efficiently by the action of enzymes. For example, we have shown that α-alkylated α-hydroxy esters are resolved by pig liver esterase (PLE) in aqueous media,[8] and that α,α-disubstituted glycols are enantioselectively acylated (at the primary hydroxyl group) by lipases in organic media.[9] We now report the synthesis and enzymatic resolution of chiral masked glycerol derivatives having an additional alkyl substituent at the chiral center. These tertiary compounds might give rise to the synthesis of a new class of (aryloxy)propanolamines having potential $\beta$-blocking properties.

## Results and Discussion

A common building block used by us previously for the synthesis of both α-alkylated α-hydroxy acids and α,α-disubstituted-1,2-diols is dioxolanone **1a**. This compound is easily available from mandelic acid by transacetalization with dimethoxypropane,[9] and can be α-alkylated by deprotonation with LDA followed by trapping of the formed enolate with an electrophile. In principle, the use of formaldehyde as electrophile should lead to (hydroxymethyl)dioxolanone **2a,** which can be considered as a chiral equivalent of 2-phenylglycerol (Scheme 1) in which two of the three hydroxyl groups are masked.

The unmasked primary hydroxyl group in **2a** gives in turn a nice handle with which to perform enantioselective lipase catalyzed acylation.

As far as we are aware, compounds **2** have been described in the literature only once. They were prepared

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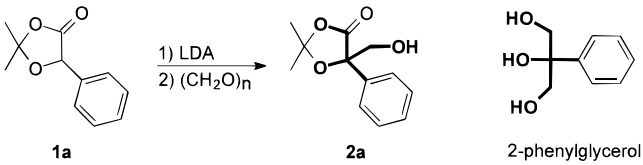
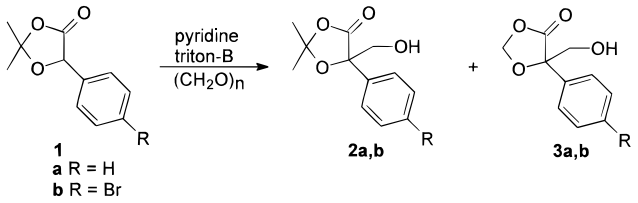
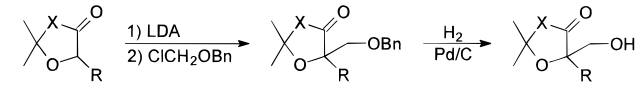
**Scheme 1**




**Scheme 2**




**Scheme 3**




**1a** (X=O; R=Ph)
**4** (X=O; R=Me)
**5** (X=NMe; R=Ph)

**6** (X=O; R=Ph)
**7** (X=O; R=Me)
**8** (X=NMe; R=Ph)

| | X | R | overall yield (%) |
|---|---|---|---|
| **2a** | O | Ph | 91 |
| **9** | O | Me | 98 |
| **10** | NMe | Ph | 76 |

by condensation of dioxolanones **1** and paraformaldehyde in the presence of pyridine and triton-B.[10] Exact repetition of this patent procedure, however, gave only marginal yields (30%) together with a great deal of transacetalized products **3a,b** (Scheme 2).

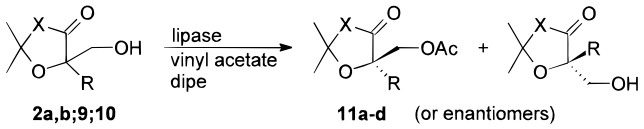
Better results were obtained by generation of the enolate of **1a**, followed by trapping with paraformaldehyde as shown in Scheme 1. Compound **2a** was obtained in higher (44%) yield, but still **3a** was produced as a major side product. An alternative (masked) hydroxymethylating reagent is benzyl chloromethyl ether.[11] Previously, it has been shown to be a powerful masked hydroxymethylating agent.[12] Alkylation of the enolate of **1a** proceeded smoothly using benzyl chloromethyl ether and gave **6** in good yield. This compound can either be purified or directly converted to **2a** by reductive hydrogenation (Scheme 3).

Via this approach, analogs **9** and **10** have been prepared as well. Owing to the fact that it is crystalline, **2b** could be obtained pure by direct condensation of dioxolanone **1b** and paraformaldehyde as shown in Scheme 2.

Resolutions of compounds **2, 9**, and **10** were carried out by lipase-catalyzed acylation in isopropyl ether (ipe) as solvent using the enol ester vinyl acetate as acyl donor (Scheme 4).

A total of six lipases (lipases AKG and PS from Amano, pig pancreatic lipase (PPL), hog pancreatic lipase (HPL), and Candida cylindracae lipase (CCL) from Sigma and Candida antarctica lipase (CAL) from Novo) were screened for reactivity and enantioselectivity. Results are listed in Table 1.

**Scheme 4**




**a** (X=O; R=Ph)
**b** (X=O; R=4-BrPh)
**c** (X=O; R=Me)
**d** (X=NMe; R=Ph)

**Table 1. Lipase-Catalyzed Resolutions of (Hydroxymethyl)dioxolanones 2, 9, and 10**[a]

| entry | substrate | lipase | time (h) | conv[b] (%) | ee (%) alcohol[c] | ee (%) acetate | *E* |
|---|---|---|---|---|---|---|---|
| 1 | **2a** | CCL | 48 | 50 | 66 (*R*) | 66 | 6 |
| 2 | **2a** | CAL | 96 | 32 | 46 (*S*) | >99 | >200 |
| 3 | **2a** | CAL | 240 | 44 | 79 (*S*) | >99 | >200 |
| 4 | **2b** | CCL | 20 | 50 | 80 (*R*) | 60 | 10 |
| 5 | **2b** | CAL | 20 | 38 | 59 (*S*) | 98 | >100 |
| 6 | **9** | CAL | 20 | 60 | >98 (*S*) | 64 | 21 |
| 7 | **9** | CCL | 20 | 76 | >98 (*R*) | 31 | 7 |
| 8 | **9** | HPL | 68 | 31 | 38 (*S*) | 86 | 17 |
| 9 | **9** | HPL | 184 | 47 | 72 (*S*) | 82 | 20 |
| 10 | **9** | PPL | 20 | 29 | 38 (*S*) | 91 | 40 |
| 11 | **9** | PPL | 68 | 46 | 76 (*S*) | 89 | 40 |
| 12 | **10** | CAL | 72 | 54 | >98 (*S*) | 82 | >50 |
| 13 | **10** | CCL | 184 | 80 | 59 (*S*) | 15 | <2 |

[a] Solvent isopropyl ether, temperature 20 °C. [b] Calculated from $c$ = ee (alcohol)/(ee (alcohol)+ee (acetate). [c] See text for a discussion of the establishment of the absolute configurations.

For substrate **2a** lipases AKG, PS, PPL, and HPL gave, even after 17 days, no conversion. Of the two other lipases, CCL gave only moderate enantiodiscrimination ($E$ = 6, entry 1), but CAL was very enantioselective giving, even at conversion approaching 50%, optically pure product **11a** (Table 1, entries 2 and 3). This corresponds to an $E$ value of greater than 200.[13] The chiral discrimination in this kinetic resolution must therefore be nearly absolute, since it is the *product* which is obtained enantiomerically pure. It is also necessary to stress that CCL shows an opposite chiral preference for this substrate compared to CAL. Results analogous to those for **2a** were observed for bromo derivative **2b**. Again, CCL showed only moderate enantiodiscrimination ($E$ = 10, Table 1, entry 4) and its preference was opposite to that of CAL. Enantiodiscrimination by CAL was nearly absolute, and product **11b** was obtained in 98% ee ($E$ = 100, Table 1, entry 5). For lactic acid derivative **9**, not only CAL and CCL catalyzed transacylation, but HPL and PPL as well. This is probably due to less steric repulsion for this substrate, making it more accessible for reaction. As observed more often, the substitution of an aromatic ring by a methyl group increases reactivity, but, unfortunately, decreases chiral discrimination significantly.[9] For example, in 20 h CAL converted **9** to **11c** in 60% yield. In this way the remaining alcohol **9** is obtained enantiomerically pure (Table 1, entry 6), but at the cost of an $E$ ratio of only 21 compared to $E$ > 200 for **2a**.

Also, CCL was more reactive with **9**, and as for **2a**,**b**, the other enantiomer was converted preferentially. Enantiomerically pure **9** was obtained after 76% conversion ($E$ = 7) using this specific lipase (Table 1, entry 7). HPL

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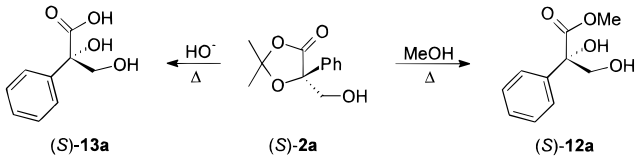
(13) In fact, for such good discriminations the logarithmic formula to calculate $E$ can give bizarre values approaching infinity. It therefore makes no sense to give $E$ values of greater than around 100−200 as a change in determined ee or conversions of less than 0.1% have a dramatic influence on the calculated $E$ value.

**Scheme 5**




and PPL were less reactive (Table 1, entries 8−11), but especially PPL was more enantioselective. After 68 h, a conversion of 46% was achieved combined with an *E* of 40 (Table 1, entry 11).

A compound which is especially interesting to resolve is (hydroxymethyl)oxazolidinone **10**. Oxazolidinones like **10** already have a built-in nitrogen functionality, making them easier, via reduction, to convert to tertiary (aryloxy)propanolamines. Analogously to dioxolanones **2a**,**b**, **10** was resolved smoothly by CAL. At 54% conversion (72 h) the remaining alcohol had an ee of >98%, which corresponds to $E > 50$ (Table 1, entry 12).[14] Resolution by CCL for this specific substrate gave only the barest selectivity since *E* was < 2 (Table 1, entry 13)!

The absolute stereochemistry of compound **2a** was subsequently established by methanolysis to the known methyl ester **12a** (Scheme 5).

This compound had previously been prepared in optically enriched form by asymmetric dihydroxylation. It was shown by Sharpless *et al.*[15] that the enantiomeric excess of **12a** can easily be enriched by a single recrystallization. By correlation of the optical rotation of **12a** with literature values[16] the stereochemistry of **2a** resolved by CAL was established as (*S*). As lipases usually show the same enantiopreference throughout a series of analogous substrates,[16] we expect that also **2b**, **9,** and **10** have the same absolute stereochemistry as **2a**. The stereochemistry of the acetates produced by CAL must therefore be *R*.

Compound (*S*)-**2a** can also be hydrolyzed to phenylglycolic acid (*S*)-**13a** (Scheme 5). This has previously been shown to be the acid moiety in the tropane alkaloid anisodine,[17] an alkaloid showing ganglio blocking properties and used clinically for the treatment of motion sickness, migraine, and vascular spasms of fundus oculi.[18] By modification of synthetic procedures, optically active **2a** might also be used for the preparation of analogs of the antifungal agent Sch 42427.[18] We are currently exploring the possibilities of employing compounds **2**, **9**, and **10** in the syntheses of potentially active pharmaceutical compounds. Such transformations have been achieved and will be described in due course.

## Conclusions and Outlook

We have shown that 5-(hydroxymethyl)1,3-dioxolan-4-ones **2** and **9** and 3-(hydroxymethyl)oxazolidine-2-one **10** are easily prepared from mandelic or lactic acid *via* their acetonides. Alkylation of the acetonide proceeds smoothly and selectively with benzyl chloromethyl ether. By reductive debenzylation compounds **2**, **9**, and **10** are obtained in overall good yields. Compounds **2a**,**b** and **10**, all of which have a phenyl substituent at the chiral center, are efficiently resolved by Candida antarctica lipase with *E* factors of up to 200. For these substrates Candida cylindracae lipase is only marginally enantioselective. Probably due to steric repulsion, four other lipases were shown not to catalyze the acylation of these compounds. The less sterically crowded **9** was also transformed by these other lipases but the enantiomeric ratios observed were somewhat lower. For this substrate the best results were obtained using pig pancreatic lipase ($E = 40$). By conversion of **2a** to the known methyl ester **12a** the stereochemical preference of the lipases toward substrates **2** has been established. Since both PPL and CAL are cheap and readily available lipases, this opens the way to perform resolutions on larger scale. Optimalization and scale up of the synthesis of (aryloxy)propanolamines and other potential drugs are currently in progress.

## Experimental Section

All solvents were reagent grade and were dried and distilled prior to use, following standard procedures. All reagents were purchased from either Acros Chimica (previously Janssen Chimica), Aldrich, Merck, or Fluka and used without purification. Benzyl chloromethyl ether (90%) was obtained from TCI. Melting points are uncorrected. $^1$H NMR spectra were recorded at 200 or 300 MHz. $^{13}$C NMR spectra (APT) were recorded at either 50.32 or 75.48 MHz. Analytical HPLC analysis was carried out using photodiode array detection. Mass spectra were recorded by EI by Mr. A. Kiewiet in our department. Elemental analyses were performed in the microanalytical group of this department by Mr. H. Draaijer, Mr. J. Ebels, and Mr. J. Hommes. Dioxolanones **1a** and **4** were prepared as described previously.[9]

**5-(4-Bromophenyl)-2,2-dimethyl-1,3-dioxolan-4-one (1b)**. A mixture of 4-bromomandelic acid[19] (20.0 g, 86.6 mmol) and acetone (25 g) in 100 mL of benzene containing a catalytic amount of $H_2SO_4$ was azeotropically refluxed for 8 h. After cooling, the mixture was washed three times with a saturated $NaHCO_3$ solution followed by brine. After drying ($Na_2SO_4$) the solution was evaporated to dryness to yield **1b** (13.2 g, 48.9 mmol, 57% yield) mp 62.0−63.0 °C (lit.[20] 65−66 °C): $^1$H-NMR ($CDCl_3$) $\delta$ 1.66 (s, 3H), 1.71 (s, 3H), 5.34 (s, 1H), 7.33−7.37 (m, 2H), 7.50−7.56 (m, 2H); $^{13}$C-NMR ($CDCl_3$) $\delta$ 26.07 (q), 27.19 (q), 75.09 (d), 111.13 (s), 122.82 (s), 127.93 (d), 131.82 (d), 133.52 (s), 172.06 (s).

**1,5,5-Trimethyl-3-phenyloxazolidin-2-one (5)**. Under a nitrogen atmosphere using dried glassware, 5,5-dimethyl-3-phenyloxazolidine-2-one[21] (1.91 g, 10 mmol) was dissolved in 20 mL of dry THF. After the mixture was cooled to −20 °C, KOtBu (1.12 g, 10 mmol) was added. The mixture was stirred for 5 min and methyl iodide (2.13 g, 0.93 mL, 15 mmol) was added. The mixture was stirred for 3 h and quenched with $NH_4Cl$ solution. The reaction mixture was extracted three times with EtOAc, and the combined organic layers were washed with brine. After drying ($Na_2SO_4$) and evaporation a yellow oil (1.97 g, 9.6 mmol, 96% yield) was obtained which was purified by column chromatography (silica, $CH_2Cl_2$) to provide pure **5** (1.50 g, 7.3 mmol, 73% yield): $^1$H-NMR ($CDCl_3$) $\delta$ 1.49 (s, 3H), 1.57 (s, 3H), 2.84 (s, 3H), 5.26 (s, 1H), 7.24−7.48 (m, 5H); $^{13}$C-NMR ($CDCl_3$) $\delta$ 25.2 (q), 25.5 (q), 26.9 (q), 78.1 (d), 93.9 (s), 126.5 (d), 128.3 (d), 128.5 (d), 137.0 (s), 169.4 (s).

**2,2-Dimethyl-5-(hydroxymethyl)-5-phenyl-1,3-dioxolan-4-one (2a) Using Paraformaldehyde**. In a nitrogen atmosphere using dried glassware, diisopropylamine (3.5 mL, 25

(14) The ee determination of **11d** was difficult due to the peak shape of the second eluting minor enantiomer on HPLC. The ee was, therefore, conservatively estimated which results in an *E* of "only" 50.

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(18) Girijavallabhan, V. M.; Ganguly, A. K.; Pinto, P. A.; Sarre, O. Z. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 349.
(19) *(19) Organic Syntheses*; Wiley: New York, 1941; Collect. Vol. I, p 336.
(20) Fuson, R. C.; Rachlin, A. I. *J. Am. Chem. Soc.* **1942**, *64*, 1567.
(21) Fischer, H. O. L.; Dangschat, G.; Stettiner, H. *Ber.* **1932**, *65*, 1032.

mmol) was dissolved in 50 mL of dry THF. After the mixture was cooled to −80 °C, *n*-Buli (14 mL, 1.6 N in hexane, 22 mmol) was added. After being stirred for 15 min the mixture was recooled to −80 °C, and a solution of dioxolanone **1a** (3.84 g, 20 mmol) in dry THF was added dropwise. The mixture was stirred for 15 min and again recooled to −80 °C. Paraformaldehyde (750 mg, 25 mmol) was added, and the mixture was slowly allowed to reach room temperature and allowed to stir overnight. Saturated $NH_4Cl$ solution (50 mL) was added, and the reaction mixture was extracted twice with ether. The combined organic layers were washed with brine, dried ($Na_2SO_4$), and evaporated to give crude **2a** (3.22 g, 14.5 mmol, 73% yield). This material was distilled (125 °C/0.02 mmHg) to give **2a** as a nearly pure yellow oil (1.97g, 8.87 mmol, 44% yield). For physical data see below.

**2,2-Dimethyl-5-(hydroxymethyl)-5-phenyl-1,3-dioxolan-4-one (2a) via the Benzyl Ether 6**. In a nitrogen atmosphere using dried glassware, diisopropylamine (10.5 mL, 75 mmol) was dissolved in 100 mL of dry THF. After the mixture was cooled to −80 °C n-Buli (27 mL, 2.5 N in hexane, 67 mmol) was added. After being stirred for 15 min, the mixture was recooled to −80 °C and a solution of dioxolanone **1a** (11.5 g, 60 mmol) in dry THF was added dropwise. The mixture was stirred for 15 min and again recooled to −80 °C. Benzyl chloromethyl ether (90%) (10.4 mL, 65 mmol) in dry THF was added dropwise, and the mixture was allowed to reach room temperature (3 h) and stirred overnight. Saturated $NH_4Cl$ solution (100 mL) was added, and the reaction mixture was extracted three times with ether. The combined organic layers were washed with brine, dried ($Na_2SO_4$), and evaporated to give crude **6** (19.9 g) containing a small amount of benzyl alcohol. A part of this crude material (13.23 g, 42 mmol) was dissolved in 50 mL of EtOH, and 200 mg of 5% Pd on carbon was added. The mixture was hydrogenated at 40 psi for 48 h in a Parr apparatus, after which time it was filtered and evaporated to give crude **2a** (8.55 g, 38.5 mmol, 91% yield) as an oil. Pure material was obtained by bulb-to-bulb distillation (145 °C/ 0.25 mmHg), giving the title compound **2a** as a colorless oil (7.35 g, 33 mmol, 78% yield). An analytically pure sample was obtained by column chromatography (silica, ether/hexane 1:2): $^1$H-NMR ($CDCl_3$) $\delta$ 1.47 (s, 3H), 1.76 (s, 3H), 2.47 (dd, $J$ = 4.4 and 8.3 Hz, 1H), 3.67 (dd, $J_{AB}$ = 11 HZ, $J_{OH}$ = 4.4 Hz, 1H), 4.01 (dd, $J_{AB}$ = 11 HZ, $J_{OH}$ = 8.3 Hz, 1H), 7.25−7.36 (m, 3H), 7.62−7.66 (m, 2H); $^{13}$C-NMR ($CDCl_3$) $\delta$ 27.56 (q), 27.91 (q), 68.13 (t), 85.23 (s), 110.91 (s), 125.06 (d), 128.56 (d), 136.11 (s). HRMS $m/z$ (− $CH_2O$) calcd 192.079, found 192.079. Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.47; H, 6.32.

The rest of crude **6** was purified by column chromatography (silica ether/hexane 1:25) to provide pure **6**: $^1$H-NMR ($CDCl_3$) $\delta$ 1.53 (s, 3H), 1.78 (s, 3H), 3.62 (d, $J_{AB}$ = 11 Hz, 1H), 3.92 (d, $J_{AB}$ = 11 Hz, 1H), 4.67 (s, 2H), 7.27−7.45 (m, 8H), 7.69−7.75 (m, 2H); $^{13}$C-NMR ($CDCl_3$) $\delta$ 27.44 (q), 28.18 (q), 73.65 (t), 75.14 (t), 84.10 (s), 110.58 (s), 125.20 (d), 127.50 (d), 127.66 (d), 128.36 (d), 128.45 (d), 128.52 (d), 136.18 (s), 137.50 (s); HRMS m/z calcd 312.136, found 312.136.

**2,2-Dimethyl-5-(hydroxymethyl)-5-(4-bromophenyl)-1,3-dioxolan-4-one (2b).**[11] Dioxolanone **1b** (5.42 g, 20 mmol) was dissolved in 35 mL of pyridine, and paraformaldehyde (2.4 g, 80 mmol) and triton-B (2 mL, 40% in MeOH) were added. The mixture was stirred overnight and cooled to −5 °C. Acetic acid was added until the pH reached 6.5−7.0, and the mixture was poured into ice−water. The slurry was extracted three times with $CH_2Cl_2$, and the combined organic layers were dried ($Na_2SO_4$). The organic fraction was evaporated on a rotary evaporator, and subsequently most of the pyridine was evaporated at low pressure (0.01 mm) at 50 °C. The remaining oil was dissolved in ether and stored overnight at 4 °C to give **2b** as white needles (1.33 g, 4.42 mmol, 22% yield): mp 131−132 °C (lit.,[11] mp 123−127 °C): $^1$H-NMR ($CDCl_3$) $\delta$ 1.47 (s, 3H), 1.75 (s, 3H), 2.05 (br, 1H), 3.65 (d, $J_{AB}$ = 12 Hz, 1H), 3.97 (d, $J_{AB}$ = 12 Hz, 1H), 7.54 (s, 4H); $^{13}$C-NMR ($CDCl_3$) 27.54 (q), 27.97 (q), 68.00 (t), 84.60 (s), 110.81 (s), 123.03 (s), 126.87 (d), 131.77 (d), 135.06 (s).

**2,2,5-Trimethyl-5-(hydroxymethyl)-1,3-dioxolan-4-one (9)**. Dioxolanone **4** (2.60 g, 20 mmol) was alkylated with benzyl chloromethyl ether (3.46 mL) analogously to the procedure described above for **1a** to give **7** (5.85g, 100% yield) contaminated with benzyl alcohol. A part of the crude **7** (1.90 g, 7.6 mmol) was dissolved in EtOH and hydrogenated in a Parr apparatus with a catalytic amount of Pd/C (5%) for 48 h. After filtration, crude **9** was obtained (1.19 g, 7.44 mmol, 98% yield) of which a part was purified by column chromatography (silica, EtOAc/hexane 1:9) to give the pure title compound: $^1$H-NMR ($CDCl_3$) $\delta$ 1.35 (s, 3H), 1.56 (s, 3H), 1.58 (s, 3H), 2.93 (br dd, $J$ = 7.4 and 4.7 Hz, 1H), 3.50 (dd, $J_{AB}$ = 12 Hz, $J$ = 4.7 Hz, 1H), 3.68 (dd, $J_{AB}$ = 12 Hz, $J$ = 7.4 Hz, 1H); $^{13}$C-NMR ($CDCl_3$) $\delta$ 20.92 (q), 27.66 (q), 28.73 (q), 66.09 (t), 81.74 (s), 110.81 (s), 174.17 (s); HRMS $m/z$ (− $CH_3$) calcd 145.050, found 145.050.

The rest of crude **7** was purified by column chromatography (silica, EtOAc/hexane 1:9) to give a colorless oil, which solidified upon standing; mp 48−51 °C; $^1$H-NMR ($CDCl_3$) $\delta$ 1.34 (s, 3H), 1.53 (s, 3H), 1.57 (s, 3H), 3.45 (d, $J_{AB}$ = 10 Hz, 1H), 3.57 (d, $J_{AB}$ = 10 Hz, 1H), 7.26 (s, 5H); $^{13}$C-NMR ($CDCl_3$) $\delta$ 21.55 (q), 27.51 (q), 28.99 (q), 73.40 (t), 80.82 (s), 110.18 (s), 127.50 (d), 127.66 (d), 128.36 (d), 137.64 (s), 173.91 (s). HRMS $m/z$ calcd 250.120, found 250.120. Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.09; H, 7.23.

**1,5,5-Trimethyl-3-(hydroxymethyl)-3-phenyloxazolidine-2-one (10).** Using a procedure analogous to **2a** and **9**, oxazolidinone **5** (1.47 g, 7.2 mmol) was alkylated with benzyl chloromethyl ether (1.26 mL). The quantitatively obtained **8** (contaminated with benzyl alcohol) was dissolved in EtOH and hydrogenated in a Parr apparatus (72 h) using a catalytic amount of Pd/C (5%). After filtration and evaporation there remained crude **10** (1.28 g, 5.4 mmol, 76% yield). This was purified by column chromatography (silica, gradient ether/hexane 1:1 to pure ether) to provide the title compound (0.50 g, 2.13 mmol, 30% yield) as an oil which solidified upon standing: mp 87.0−89.3 °C; $^1$H-NMR ($CDCl_3$) $\delta$ 1.39 (s, 3H), 1.82 (s, 3H), 2.60 (br, 1H), 2.83 (s, 3H), 3.60 (dd, $J$ = 12, 4.6 Hz, 1H), 4.02 (dd, $J$ = 12, 8.1 Hz, 1H), 7.27−7.37 (m, 3H), 7.68−7.73 (m, 2H); $^{13}$C-NMR ($CDCl_3$) $\delta$ 25.62 (q), 26.61 (q), 26.90 (q), 67.89 (t), 85.92 (s), 93.70 (s), 125.55 (d), 127.89 (d), 128.15 (d), 138.70 (s). HRMS $m/z$ (− $CH_2O$) calcd 205.110, found 205.109. Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.52; H, 7.27; N, 5.98.

**General Procedure for the Lipase-Catalyzed Resolution of 2.** (Hydroxymethyl)dioxolanone **2** (0.3 mmol) was dissolved in a mixture of 1 mL of isopropyl ether and 0.2 mL of vinyl acetate. Lipase (20 mg) was added, and the mixture was stirred at room temperature. At regular intervals a 0.1 mL sample was taken which was filtered over celite in a Pasteur pipette. The Celite was washed with 1 mL of $CH_2Cl_2$, and the filtrate was evaporated to dryness. The residue was dissolved in 1 mL of isopropanol and analyzed by chiral HPLC (Daicel OJ) or GC (FS-LIPODEX C); see the supporting information for details.

**Preparative Scale Resolution of (*S*)-2a Using CAL.**[22] Alcohol **2a** (573 mg, 2.58 mmol) was dissolved in 10 mL of dipe and 2 mL of vinyl acetate. CAL (300 mg) was added, and the mixture was stirred at room temperature. After 19 days the lipase was removed by filtration and the filtrate was purified by column chromatography (silica ether/hexane 1:2) to yield (*S*)-**2a** (214 mg, 0.96 mmol, 73% ee) and (*R*)-**11a** (203 mg, 0.77 mmol, >99% ee) both as colorless solids.

**(*S*)-2,3-Dihydroxy-2-phenylpropanoic Acid Methyl Ester (12a).** Optically enriched alcohol (*S*)-**2a** (214 mg, 0.96 mmol, 73% ee) was dissolved in 10 mL of MeOH. A catalytic amount of $H_2SO_4$ was added, and the mixture was refluxed for 4 days. Water (10 mL) was added, and the methanol was removed by evaporation. The remaining water layer was washed three times with EtOAc, and the combined organic layers were washed with brine and dried ($Na_2SO_4$). After

(22) This experiment was performed only once to establish the absolute stereochemistry of **8a**. So far, no attempts have been undertaken to improve yields or shorten reaction times.

evaporation there remained (*S*)-**12a** as a colorless oil (163 mg, 0.83 mmol, 87% yield). This material was purified by column chromatography (silica ether/hexane 2:1) to yield (*S*)-**12a** as a white solid (145 mg, 0.74 mmol, 77% yield): $[\alpha]_D = -6.6°$ (*c* 1.50 in EtOH), o.p. 67% (lit.[16] $[\alpha]_D = +8.7°$ (*c* 1.05 in EtOH)) for a sample of the (*R)* enantiomer having an ee of 88%. The ee of the sample was determined as 68% by chiral HPLC (Daicel OJ-column); NMR in accordance with reference NMR.

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**Supporting Information Available:** $^1H$ and $^{13}C$ NMR spectra of **2a**,**b**, **9**, and **10**, tables containing data for chiral HPLC and GC separations of compounds **2a**,**b**, **9** and **10**, **11**, and **12**, and selected HPLC chromatograms (20 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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