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Process Research of (*R*)-Cyclohexyl Lactic Acid and Related Building Blocks: A Comparative Study‡

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Abstract:

(*S*)-Cyclohexyl lactic acid is a component of the selective E-selectin inhibitor 2 ((*S*)-cHexLact-2-*O*-(3-Galβ(1→3)ddGlc-(4→1)αFuc). We describe the evaluation of various synthetic routes to this building block: (*A*) diazotation of phenylalanine followed by phenyl ring hydrogenation; (*B*) phenyl ring hydrogenation of phenyl alanine followed by diazotation; (*C*) acidic hydrolysis of the cyanohydrin derived from phenylacetaldehyde, enantiomeric resolution of the resulting, racemic phenyl lactic acid via diasteromeric salt formation and phenyl ring hydrogenation; (*D*) enantioselective dihydroxylation of a cinnamate ester, followed by hydrogenation of the benzylic hydroxy group and the aromatic nucleus; (*E*) enantioselective biocatalytic reduction of phenylpyruvic acid, followed by phenyl ring hydrogenation. The development of (2*R*)-2-*O*-(4-nitrophenyl)sulfonyl-cyclohexyl lactic acid *p*-bromobenzylester 21 as a buidling block with improved crystallinity and stability is also described.

Introduction

Excessive leukocyte influx from blood vessels into the surrounding tissues has been linked to acute or chronic reactions as observed in reperfusion injuries, psoriasis, stroke, rheumatoid arthritis or respiratory diseases.[1−3] Selectin-dependent leukocyte adhesion is the first step in the cascade of events that leads to the extravasation of leukocytes.[4] In particular, E-Selectin on the surface of the endothelial blood vessel walls recognizes complex glycoprotein ligands on the leukocyte surface via interaction with the common tetrasaccharide epitope sialyl Lewis^x (sLe^x, **1**).[5] Analogues of sialyl Lewis^x have therefore been proposed as potential therapeutics for a host of inflammatory disorders (e.g., ischemia/reperfusion injury following organ transplantation).[6] The sLe^x analogue **2** (Figure 1) was discovered by Thoma et al. at Novartis Pharmaceuticals Corporation.[7] Compared to sLe^x, **2** showed a 30-fold improved affinity in a cell-free E-selectin-ligand binding assay.[8]

As a simplified analogue of SLe^x, **2** features the (*S*)-cyclohexyl lactic acid moiety as a substitute[9] for the structurally more complex *N*-acetylneuraminic acid residue. The former is introduced into the trisaccharide precursor of **2** via nucleophilic displacement reaction of a 2-*O*-sulfonyl substituted (*R*)-cyclohexyl lactic acid building block. Enantiomerically pure (*R*)-cyclohexyl lactic acid[10] is not commercially available. Hence, an efficient synthetic access to this hydroxy acid needed to be elaborated.

Results and Discussion

(A) The Medicinal Chemistry Synthesis. The synthesis (Scheme 1)[7] of the (*R*)-cyclohexyl lactic acid building block **6** started from commercially available (*R*)-3-phenyl lactic acid[10b] (**3**). Hydrogenation of the aromatic nucleus, followed by benzyl ester formation with $CsCO_3$/BnBr and *O*-sulfonylation with triflic anhydride, gave the building block **6** in three steps and 60% total yield after two chromatographies. The triflate **6** proved to be an unstable oil at room temperature and resisted all attempts to crystallization.

‡ Dedicated to Professor Andrea Vasella on the occasion of his 60th birthday.

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(1) Mousa, S. A. *Drugs Fut*. **1996**, *21*, 283.
(2) Mousa, S. A.; Cheresh, D. A. *Drug Discovery Today* **1997**, *2*, 187.
(3) Cines, D. B.; Pollak, E. S.; Buck, C. A.; Loscalzo, J.; Zimmermann, G. A.; McEver, R. P.; Pober, J. S.; Wick, T. M.; Konkle, B. A.; Schwartz, B. S.; Barnathan, E. S.; McCrae, K. R.; Hug, B. A.; Schmidt, A.-M.; Stern, D. M. *Blood* **1998**, *91*, 3527.
(4) Spertini, O.; Luscinskas, F. W.; Gimbrone, M. A.; Tedder, T. F. *J. Exp. Med*. **1992**, *175*, 1789.
(5) Kansas, G. S. *Blood* **1996**, *88*, 3259.
(6) For a review, see: Simanek, E. E.; McGarvey, G. J.; Jablonowsky, J. A.; Wong, C.-H. *Chem. Rev.* **1998**, *98*, 833.
(7) Thoma, G.; Kinzy, W.; Bruns, C.; Patton, J. T.; Magnani, J. L.; Bänteli, R. *J. Med. Chem.* **1999**, *42*, 4909.
(8) Bänteli, R.; Herold, P.; Bruns, C.; Patton, J. T.; Magnani, J. L.; Thoma, G. *Helv. Chim. Acta* **2000**, *83*, 2893.
(9) Kolb, H. C.; Ernst, B. *Chem. Eur. J.* **1997**, 1571.
(10) (a) v. Braun, J.; Nelles, J. *Chem. Ber*. **1933**, *66*, 1464 (racemate). (b) Bajusz, S.; Barabás, E.; Fauszt, I.; Fehér, A.; Horváth, Gy.; Juhász, A.; Szabó, A. G.; Széll, E. *Bioorg. Med. Chem*. **1995**, *3*, 1079 (*R*-enantiomer).

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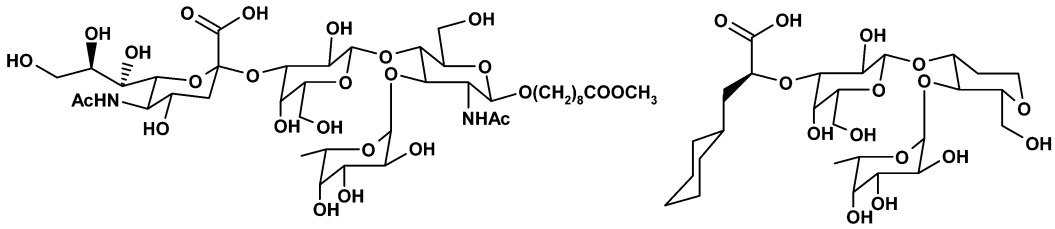
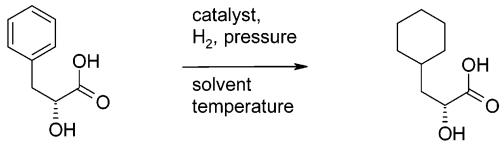


Sialyl Lewis^x **(1)** (Novartis) **(2)**

Figure 1.

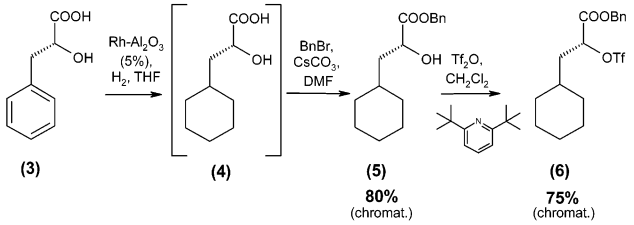
Table 1. **Aromatic ring hydrogenation of phenyl lactic acid: catalyst screening**



3 **4**

entry	(concentration, mmol) batch size (%)	catalyst, H_2 pressure	solvent (%), temperature (°C)	reaction time, h yield (%)/purity (%)
1	12.0 (5)	5% Rh/C (10 wt %/wt) 15 bar	EtOH (94) 50	2 92.9 (GLC) conversion: 99.8
2	300.9 (5)	5% Rh/C (10 wt %/wt) 15 bar	EtOH (94) 50	5 99.6, crude
3	12.0 (5)	10% Ru/C (15 wt %/wt) 15 bar	AcOH 50−70−100	59 h 89.4% (GLC) conversion: 99.9%
4	12.0 (14.3)	5% Rh/C (10 wt %/wt) 15 bar	AcOH/H_2O (8:6) 50−80	108 70.6 (GLC) conversion: 99.9
5	12.0 (13.5)	10% Ru/C (10 wt %/wt) 30 bar	1 M NaOH 60	16 7.0 (GLC) conversion: 13.2

Scheme 1. **Medicinal chemistry synthesis**



(B) Process R&D. Surprisingly, there is only one literature report for the production of (*R*)-cyclohexyl lactic acid (**4**): aromatic ring hydrogenation of D-(+)-3-phenyl lactic acid (**3**) over a platinum oxide catalyst.[10b] Due to the high price and limited availability of **3**, and the unfavorable physicochemical properties combined with the instability of the triflate **6**, we aimed to find a more economic access to **4** and, ultimately, also to replace the triflate **6** by a crystalline, more stable activated building block.

In our first strategy, (*R*)-phenyl alanine (**7**) was chosen as starting material. Two variants were investigated:

(***A***) diazotation of phenylalanine under retention of configuration,[11] followed by hydrogenation of the aromatic nucleus of the resulting phenyl lactic acid over a more economic catalyst: Although literature reports[11−14] had claimed that diazotation of (*R*)-phenyl alanine to (*R*)-phenyl lactic acid **3** proceeds under complete retention of configuration (only optical rotation values were cited as proof of enantiomeric purity), we invariably observed a loss of enantiomeric purity as unequivocally determined by HPLC analysis on a chiral column (2−5%, see Experimental Section). The hydrogenation of the aromatic nucleus in **3** was investigated under various conditions (Table 1). In general, none, or only insignificant loss (<0.1%) of enantiomeric purity was observed (see typical result in Experimental Section).

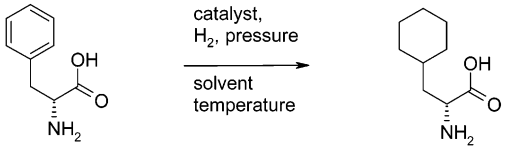
The best overall results of approach ***A*** are summarized in Scheme 2.

(***B***) Hydrogenation of the aromatic nucleus of phenylalanine,[15] followed by diazotation of the resulting cyclohexyl alanine **8** under retention of configuration: The hydrogenation of phenylalanine showed less variability than the corresponding hydrogenation of phenyl lactic acid (Table 2).

(11) Cohen, S. G.; Weinstein, S. Y. *J. Am. Chem. Soc*. **1964**, *86*, 5326.

(12) Yamada, S.-I.; Koga, K.; Juang, T. M.; Achiwa, K. *Chem. Lett.* **1976**, 927.
(13) Terashima, S.; Tseng, C. C.; Koga, K. *Chem. Pharm. Bull*. **1979**, *27*, 747.
(14) Urban, F. J.; Moore, B. S. *J. Heterocycl. Chem*. **1992**, *29*, 431.
(15) Bain, J. D.; Wacker, D. A.; Kuo, E. E.; Chamberlin, A. R. *Tetrahedron* **1991**, *47*, 2389.

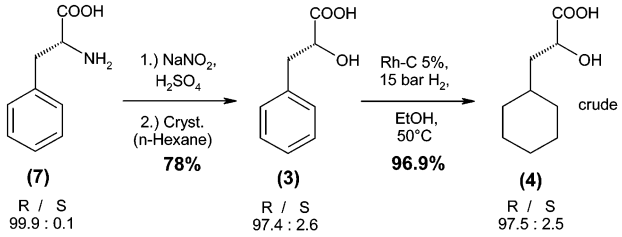
Table 2. **Aromatic ring hydrogenation of phenyl alanine: catalyst screening**



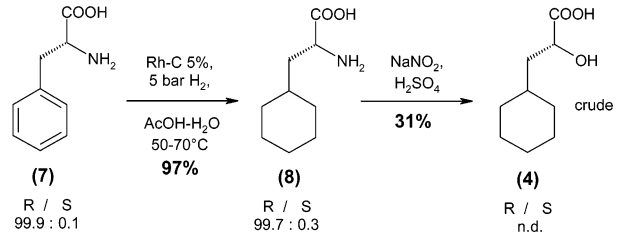
7 **8**

entry	concentration (mmol), batch size (%)	catalyst, H_2 pressure	solvent, temperature (°C)	reaction time, yield/purity
1	12.1 6.7	5% Rh/C (10 wt %/wt) 4 bar	1 M HCl in H_2O 50	3.25 h 96.0% (GLC) conversion: 99.9%
2	12.1 5	5% Rh/C (10 wt %/wt) 15 bar	EtOH (94 5%) 50−100	43 h 94.1% (GLC) conversion: 99.5%
3	12.1 5	10% Ru/C (10 wt %/wt) 15 bar	AcOH 50	19 h no conversion (TLC)
4	12.1 6.7	10% Ru/C (10 wt %/wt) 15 bar	1 M NaOH 60	3 h 90.1% (GLC) conversion: 99.7%
5	12.1 14.3	5% Rh/C (10 wt %/wt) 5 bar	AcOH/H_2O (4:3) 50	17 h 96.9% (GLC) conversion: >99%
6	302.7 14.3	5% Rh/C (10 wt %/wt) 5 bar	AcOH/H_2O (4:3) 50	7 h 100% crude
7	12.1 13.3	10% Ru/C 2.6 wt %/wt) 30 bar	1 M NaOH 60	7 h 91.5% (GLC) conversion: >99.9%

Scheme 2. **Diazotization strategies: approach *A***



Scheme 3. **Diazotization strategies: approach *B***



However, the subsequent diazotation of **8** proceeded only in very poor yields. Hence, approach ***B***, as summarized in Scheme 3, was quickly abandoned.

(***C***) Cyanohydrin reaction of phenylacetaldehyde, followed by acidic hydrolysis to (*R*/*S*)-phenyl lactic acid, resolution of the racemic acid via diastereomeric salt formation and hydrogenolytic reduction of the phenyl ring as in approach (***A***):

Although much progress has recently been achieved with enantioselective cyanohydrin reactions,[16] α-methylene-aldehydes, such as arylacetaldehydes, have proved to be notoriously difficult substrates and, in general, tend to give lower ee[16f,17,18] than their aromatic counterparts. A kinetic resolution of racemic phenylacetaldehyde-cyanohydrin on an analytical scale (no product isolated, no yields given) with a mutant *Pseudomonas* strain to give enantiomerically enriched (ca. 75% ee) (*S*)-(−)-phenyl lactic acid has been reported.[19] One study reporting the synthesis of enantiomerically enriched (88% ee) (*R*)-phenylacetaldehyde-cyanohydrin in 83% yield on a millimolar scale via oxynitrilase-catalyzed transcyanation with acetone cyanohydrin has appeared.[20] However, due to the high substrate dilution, high enzyme concentration (ca. 1000 units/mmol substrate) and the requirement for a special enzyme purification of the commercial enzyme prior to use, this method appeared not practical for preparative scale synthesis.

On the other hand, we obtained racemic phenyl lactic acid (±-PLA) **11** without need for the isolation of the intermediate **10**[21] via cyanohydrin reaction of the bisulfite adduct[22] of **9**

(16) For reviews, see: (a) Groger, H. *Adv. Synth. Catal.* **2001**, *343*, 547. (b) Van Der Gen, A.; Brussee, J. *NATO Sci. Ser. 1: Disarm. Technol.* **2000**, *33*, 365. (c) Gregory, R. J. H. *Chem. Rev.* **1999**, *99*, 3649. (d) Effenberger, F. *Chimia* **1999**, *53*, 3. (e) Johnson, D. V.; Griengl, H. *Chim. Oggi* **1997**, *15*, 9. (f) North, M. *Synlett* **1993**, 807. (g) Kruse, C. G. In *Chirality in Industry*; Collins, A. N., Sheldrake, G. N., Crosby, J., Eds.; Wiley: New York, 1992; Chapter 14, p 279.

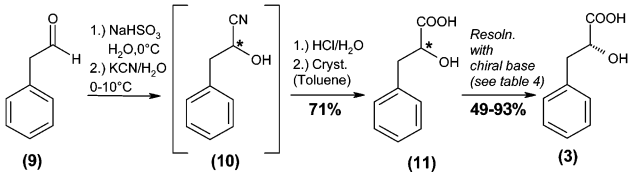
(17) Zandbergen, P.; Van Der Linden, J.; Brussee, J.; Van Der Gen, A. *Synth. Commun.* **1991**, *21*, 1387.

(18) Ziegler, T.; Hörsch, B.; Effenberger, F. *Synthesis* **1990**, 575.

(19) Hashimoto, Y.; Kobayashi, E.; Endo, T.; Nishiyama, M.; Horinouchi, S. *Biosci. Biotechnol. Biochem.* **1996**, *60*, 1279.

(20) Ognyanov, V. I.; Datcheva, V. K.; Kyler, K. S. *J. Am. Chem. Soc.* **1991**, *113*, 6992.

Scheme 4. **Approach *C*: resolution of racemic PLA**



followed by acid-catalyzed hydrolysis in 71% yield after recrystallization of the crude product from toluene (Scheme 4). A variety of readily available optically pure bases were then screened for their potential to form diastereomeric salts[23] (Table 3).

Resolution with the most promising bases, (+)-dehydroabietylamine, (*S*)-phenylglycinol and (*S*)-phenylalaninol was optimized (data not shown); typical results are shown in Table 4.

Especially the resolution via the diastereomeric (*S*)-salt separation with (+)dehydroabietylamine looked very promising, due to the very low cost of the chiral amine. Resolutions with (*S*)-phenylglycinol and (*S*)-phenylalaninol also worked very well, but required recycling of the (expensive) chiral base.

(***D***) Enantioselective dihydroxylation of methyl cinnamate, followed by selective hydrogenolytic removal of the benzylic hydroxy group and hydrogenation of the aromatic nucleus.[24]

Cinnamate esters are very cheap starting materials (Me, Et, Bn: $8−15/kg), and readily scaleable protocols for their enantioselective dihydroxylation to α,*β*-dihydroxy-phenylpropionates in good yield and enantiomeric purity are well established.[25] We aimed at an efficient and selective one pot-reduction process, employing only a noble metal catalyst and hydrogen as the sole reducing agent (Scheme 5).

The methyl and benzyl esters of the corresponding (*2R*,-*3S*)-3-phenyl-2,3-dihydroxypropionate[26] were synthesized as starting materials. The methyl ester is easily purified by recrystallization and can be obtained in very high enantiomeric purity, whereas the benzyl ester has to be purified by chromatography and, in our hands, was routinely obtained in inferior optical purity (Scheme 6).

The subsequent hydrogenolytic removal of the benzylic hydroxy group proceeded in good yield and without significant loss in optical purity, but the benzyl ester apparently was prone to acid-catalyzed transesterification, as the intermediate 3-phenyl lactic acid was isolated as the methyl ester after the reaction (Scheme 7).

Because of this finding and the unfavorable physical properties of the benzyl ester **13B** in combination with the lower ee in the dihydroxylation reaction of benzyl cinnamate, it was decided to focus on the crystalline methyl ester **13A**. Initially, we isolated the intermediate phenyl lactic ester **14** before starting a fresh hydrogenolysis experiment in a separate vessel with the second catalyst. It was then discovered that equivalent results were also obtained by sequential addition of the two catalysts in one pot in the same solvent (Scheme 8). This represents a significant progress over previous methodology for this transformation.[24]

In the sequence from the dihydroxylation product **13A** to (*R*)-cyclohexyl lactic acid **4**, the enantiomeric purity changes only very slightly. The initial osmium impurity in **13A** (200 ppm) dropped to a mere 4 ppm in the final product **4** without any special purification measures. Overall, approach ***D*** delivered a very practical and readily scaleable process based on a cheap and abundant starting material *(*methyl cinnamate).

Finally, we also investigated the enantioselective biocatalytic reduction of phenylpyruvic acid **29** as an alternative access to (*R*)-3-phenyl lactic acid **3**. The enantioselective reduction of 2-oxo carboxylic acids to the corresponding (*R*)-2-hydroxy carboxylic acids by resting cells of *Proteus mirabilis* or *Proteus vulgaris* was reported by H. Simon and collaborators.[27] The stereospecificity is extremely high (ee > 98%)[28] and the substrate specificity very broad. *Proteus* possesses a formate dehydrogenase as well as a hydrogenase, in addition to its specific 2-oxocarboxylate reductase activity. Therefore, the basic principle of the reaction involves the use of formate or hydrogen gas as reducing agents for the 2-oxocarboxylic acids and, of a catalytic amount of viologen (V^{2+}), for example benzyl viologen or methyl viologen, as electron carrier:

$$HCOO^- + 2\ V^{++} \rightarrow H^+ + CO_2 + 2\ V^{\bullet +}$$

$$\text{or: } H_2 + 2\ V^{++} \rightarrow 2\ H^+ + 2\ V^{\bullet +}$$

$$R{-}CO{-}COO^- + 2\ V^{\bullet +} + 2\ H^+ \rightarrow (R)\text{-}R{-}CHOH{-}COO^- + 2\ V^{++}$$

The simplest procedure for the reduction of 2-oxo carboxylic acids is the stirring of the *Proteus* cells together with the substrate, benzyl viologen and formate in phosphate buffer pH 7, at 37 °C under an atmosphere of nitrogen, in a batch-mode process.[29] When oxidised, one molecule of formate delivers two electrons but only one proton. To provide the additional proton necessary for the substrate reduction and to maintain a constante formate concentration, formic acid is continuously added, using an automatic pH control system.The optimal reaction time to obtain a 2-oxo carboxy-

(21) (a) Erlenmeyer, E.; Lipp, A. *Ann. Chem.* **1883**, *219*, 187. (b) Ruggli, P.; Hegedues, B. *Helv. Chim. Acta* **1942**, *25*, 1285.

(22) (a) Biquard, D. *Ann. Chim. (Paris)* **1933**, *10*, 97. (b) Meerpoel, L.; Hoornaert, G. *Synthesis* **1990**, 905. (c) Chesters, N. C. J. E.; O'Hagan, D.; Robins, R. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1159.

(23) The only diastereomeric salt resolution for (D)-(+)-3-phenyl lactic acid we are aware of (base: morphine!) was reported by A. McKenzie and H. Wren (*J. Chem. Soc.* **1910**, *97*, 1358), who later also described the resolution of racemic PLA via its diastereomeric (−)-menthol esters (*J. Chem. Soc.* **1921**, *119*, 801).

(24) To the best of our knowledge, only two selective reductions of α,*β*-dihydroxy-dihydro-cinnnamic esters to 3-aryl lactic acid esters have been reported: (a) Nakajima, M.; Tomioka, K. and Koga, K. *Tetrahedron* **1993**, *49*, 10807 (Et_3SiH/TFA); (b) Rho, H. S.; Ko, B.-S. *Synth. Commun.* **2001**, *31*, *283* (Mg-reduction of the corresponding thionocarbonate derivative). A Mn-catalyzed oxidation of cinnamates in the presence of triphenyl silane also leads to 3-aryl lactic acid esters: Tanaka, M.; Mukaiyama, C.; Mitsuhashi, H.; Maruno, M.; Wakamatsu, T. *J. Org. Chem.* **1995**, *60*, 4339.

(25) For a review, see: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

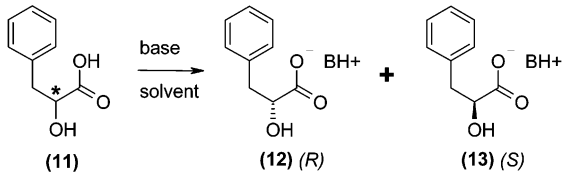
(26) Wang, Z. M.; Kolb, H. C.; Sharpless, K. B. *J. Org. Chem.* **1994**, *59*, 5104.

(27) Simon, H.; Bader, J.; Günther, H.; Neumann, S.; Thanos, J. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 539−553.

(28) Günther, H.; Neumann, S.; Simon, H. *J. Biotechnol.* **1987**, *5*, 53−65.

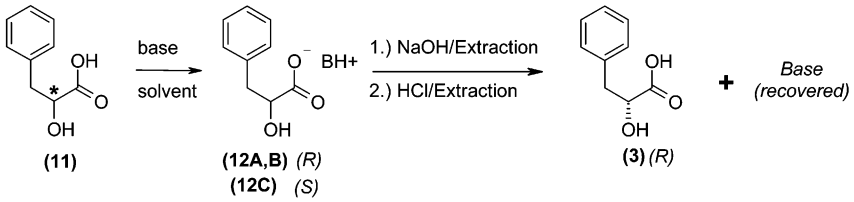
(29) Schummer, A.; Yu, H.; Simon, H. *Tetrahedron* **1991**, *47*, 9019−9034.

Table 3. **Resolution of racemic PLA: base screening**



entry	scale (mmol)	base	solvent	result yield (%)	*R*/*S* crude	*R*/*S* recryst. (yield, %)
1	15	(*R*)-1-phenyl-ethylamine	EtOAc/^{i}PrOH 4:1	(oil)	n.d.	
2	6	cinchonine	EtOAc/^{i}PrOH	(oil)	n.d.	
3	6	cinchonidine	EtOAc/^{i}PrOH	crystals 61	51:49	n.d.
4	6	quinine	EtOAc/^{i}PrOH			
5	6	quinidine	EtOAc/^{i}PrOH	(oil)	n.d.	
6	6	(−)-ephedrine	EtOAc	(oil)	n.d.	
7	6	(+)-pseudoephredine	EtOAc	(oil)	n.d.	
8	6	L-phenylglycinol	EtOAc	crystals, >100	56:44	70:30 (67)
9	6	L-phenylalaninol	EtOAc	crystals, >100	52:48	89:11 (73)
10	6	L-*threo*−2-amino-1-phenyl-1,3-propandiol	EtOAc	crystals, >100	50:50	n.d.
11	6	D-*threo*−2-Amino-1-nitrophenyl-1,3-propandiol	EtOAc	crystals, >100	50:50	n.d.
12	6	(*R*)-2-amino-1-butanol	EtOAc	(oil)	n.d.	
13	6	*N*-methyl-D-glucamine	^{i}PrOH/MeOH	(oil)	n.d.	
14	6	(−)-spartein	EtOAc	(oil)	n.d.	
15	6	(+)-dehydro-abietylamine	EtOAc	crystals, >100	33:67	14:86 (87)

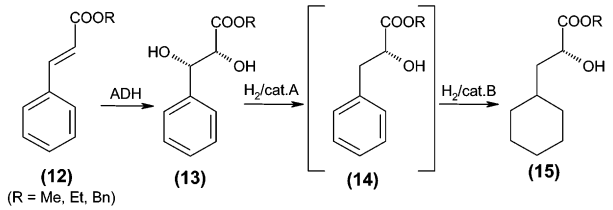
Table 4. **Resolution of racemic PLA by diastereomeric salt formation: optimization**



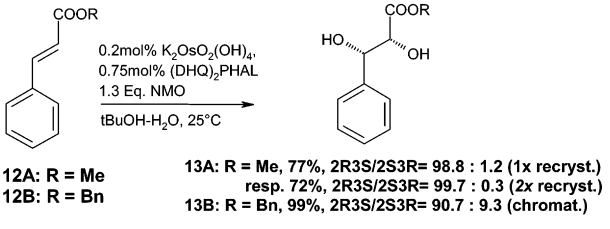
entry	scale (mmol)	base	solvent	yield[a] of diast. salt (%)	yield[a] of recovered acid (%) (*R*/*S*)	base recovery (%)	price of base ($/kg)
A	24	L-phenyl-glycinol	*sec*-butanol	93.8 (*R*)	93.5 ***(99:1)***	79	995
B	24	L-phenyl-alaninol	2-butanone	87.6 (*R*)	52.2 ***(100: 0)***	99	725
C	24	(+)-dehydro-abietylamine	4-methyl-2-pentanone	n.d. (*S*)[b]	73.0 ***(80:20)*** after recryst.: 49.0 ***(100: 0)***	100	20

[a] Based on (*R*)-enantiomer. [b] (*S*)-Salt precipitates out, (*R*)-acid isolated from mother liquor.

Scheme 5. **Approach *D*: asymmetric dihydroxylation/ selective reduction**



Scheme 6. **Approach *D*: starting materials**

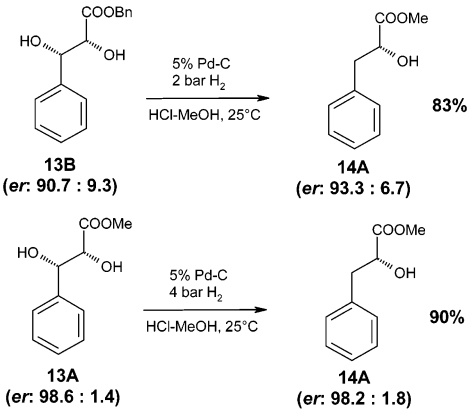


lic acid conversion of about 100% is in the range of 24 h. After removal of the cells by filtration or by centrifugation, the (*R*)-2-hydroxy carboxylic acid produced can be recovered by extraction in ethyl acetate and crystallization by addition of methylcyclohexane or cyclohexane.[30]

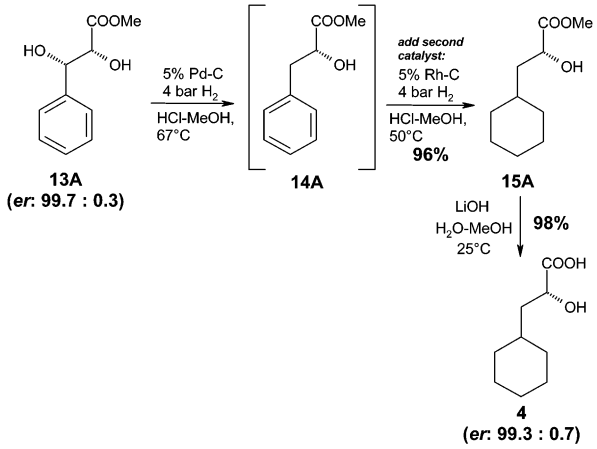
(30) Fauquex, P.; Sedelmeier, G. EP 0371408, 1989.

After optimization of the reaction conditions and of the extraction procedure, we applied this process successfully to the reduction of phenylpyruvic acid (approach ***E***): the product (*R*)-3-phenyl lactic acid was obtained with a conversion of >99.8%, a total yield (bioconversion and recovery) of 87% and an enantiomeric purity (*R*-form) of >99.5% (Scheme 9).

Scheme 7. **Approach *D*: hydrogenation of benzylic hydroxy group**



Scheme 8. **Approach *D*: methyl ester variant**



Scheme 9. **Approach *E*: biocatalytic reduction**

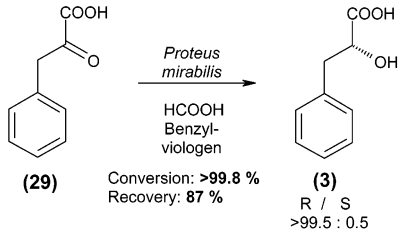


Table 5. **Comparison of different syntheses for (*R*)-3-cyclohexyl lactic acid**

synthesis	starting material (*price*)	number of steps	yield (%)	optical purity *R/S*
(*A*)	D-phenylalanine *(~165 $/kg)*	2	58−75	95:5−98:2
(*C*)	phenylacetaldehyde *(~30 $/kg)*	5 (3 steps "one-pot")	17−32	99:1−100:0
(*D*)	methyl cinnamate *(~10 $/kg)*	4 (2 steps "one pot")	68−72	≥99.3:0.7
(*E*)	phenylpyruvic acid *(≈ 880 $/kg)*	2	80−85	99.5:0.5

Table 5 compares the four processes: the shortest syntheses investigated were processes ***A*** and ***E***, with the latter being much more reliable in terms of the enantiomeric purity.

Scheme 10. **Ester screening for (*R*)-cyclohexyl lactic acid**

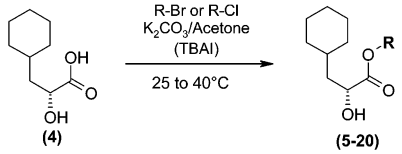


Table 6. **Evaluation of esters of (*R*)-cyclohexyl lactic acid**

ester	R	physical state	melting point (°C)	yield (%) (*chromat.*)	yield (%) (*cryst.*)
5	benzyl	solid	54−56	87	70
16	4-chlorobenzyl	oil	–	50	–
17	2,5-dichlorobenzyl	oil	–	93	–
18	4-bromobenzyl	solid	50−52	88	82
19	4-nitrobenzyl	oil	–	37	–
20	2-naphthyl-methyl	solid	54−55	94	73

However, both ***A*** and ***E*** featured relatively expensive starting materials. On the other hand, with options ***C*** and ***D***, two more sustainable processes were developed, delivering material of acceptable optical purity from cheap starting materials. Overall, process ***D*** was found to be the most attractive option for technical scale manufacture of (*R*)-cyclohexyl lactic acid.

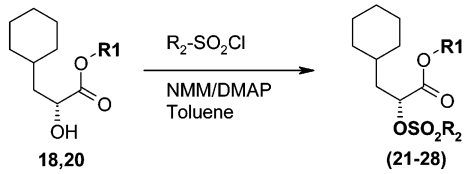
We then initiated a screening process for crystalline esters of (*R*)-cyclohexyl lactic acid. Esters were readily accessible by base-catalyzed, selective *O*-alkylation with the corresponding benzyl halide. The cesium carbonate/DMF-alkylation procedure used in the research synthesis could be replaced by a more convenient (no aqueous workup required) alkylation protocol (anhydrous potassium carbonate in acetone, cat. TBAI) without appreciable loss in yield (Scheme 10). Also, no epimerization was observed under these reaction conditions, as proven by determination of enantiomeric purity in the *p*-bromobenzylester **18** by HPLC on a chiral stationary phase (see Experimental Section).

The best candidates, on basis of their crystalline properties and ease of preparation, were the 4-bromobenzyl (**18**) and the 2-naphthylmethyl (**20**) esters, which were readily accessible on a preparative scale (no chromatography required) (Table 6). Several *O*-sulfonyl derivatives of these two esters—and also of the benzyl ester **5**—were synthesized. Their syntheses and properties are summarized in Table 7. The nosylate of the 4-bromobenzyl ester (**21**) appeared especially attractive. In preliminary experiments with model nucleophiles *(*data not shown), sulfonate **21** displayed electrophilic reactivity comparable to the triflate derivative **6** used in the research synthesis while featuring good crystallinity and improved stability.

Conclusions

In summary, four robust processes amenable for large-scale, chromatography-free preparation of (*R*)-3-cyclohexyl lactic acid were developed from four different starting materials. Asymmetric dihydroxylation of methyl cinnamate, followed by a one-pot catalytic reduction of the benzylic hydroxy group and the aromatic nucleus, and subsequent saponification of the methyl ester proved to be the most sustainable process with regard to price and stability of

Table 7. **Evaluation of different sulfonates**



18,20 (21-28)

ester	R^1	R^2	melting point	yield (%) (*chromat.*)	yield (%) (*cryst.*)
21	4-brom-benzyl	4-nitrophenyl-	71−72 °C	−	60
22	4-brom-benzyl	methyl-	oil	81	−
23	4-brom-benzyl	4-bromophenyl-	68−69 °C	48	52
24	2-naphthyl-methyl	methyl-	oil	79	−
25	2-naphthyl-methyl	4-nitrophenyl-	oil	58	−
26	benzyl	4-nitrophenyl-	oil	80	−
27	benzyl	4-bromophenyl-	oil	63	−
28	benzyl	4-methylphenyl	oil	60	−

starting material, total yield and optical purity of the product (Table 5). As an alternative to the unstable and oily triflate **6**, an activated building block with improved stability and crystallinity (*p*-bromobenzylester nosylate **21**) was found.

Experimental Section

Starting materials, reagents and solvents were obtained from commercial suppliers and were used without further purification. All the melting points are uncorrected and determined on a Buchi apparatus. ^{1}H NMR spectra were recorded at 400 MHz, and ^{13}C NMR spectra were recorded at 100 or 125 MHz on a Bruker DPX 400/500 instrument. IR spectra were measured on a Bruker IFS660 spectrometer. The enantiopurity of **3**, **4**, **5**, **13** and **14** was determined on a Hewlett-Packard Series 1100 HPLC system using a Chiralcel OD or Chiralpak AD column.

(2*R*)-2-Hydroxy-3-phenylpropionic Acid (3) (*A*) (by Diazotation of D-Phenylalanine, Improved Variant of the Procedure of Cohen and Weinstein[11]). A 10-L Buchi reactor was charged with a solution of D-phenylalanine (**7**) (350 g, 2.12 mol, *R*/*S* ≥ 99.5:0.5) in 3245 mL of 0.5 M H_2SO_4. At 5 °C, a solution of sodium nitrite (219.3 g, 3.18 mol) was added over a 3-h period. The reaction temperature was kept between 0 and 10 °C. After the addition was complete, stirring was continued, and the reaction mixture was allowed to reach room temperature overnight. The resulting suspension was cooled to 5 °C, and sulfamic acid (5.2 g, 53.5 mmol) was added portionwise under vigorous stirring until iodine−cadmium reagent paper showed no more nitrite. Upon addition of isopropyl acetate (3000 mL), a clear biphasic mixture formed. The organic phase was separated and washed with water (1000 mL) and 20% aqueous NaCl (750 mL). Collected water phases were extracted with isopropyl acetate (2 × 500 mL) and the combined organic phases dried over MgSO4 and reduced to about 20% of their volume under reduced pressure, just until crystallization started to set in. Hexane was then added, and the suspension was cooled to 0 °C and filtered. The filter cake was washed with 250 mL of cold hexane/isopropyl acetate (1:1-mixture) and 300 mL of cold hexane and dried under reduced pressure at 40 °C (178.8 g, 50.8%). The filtrate was again evaporated under reduced pressure until crystallization started to set in (approximately one-third of the volume), diluted with hexane (300 mL) and allowed to crystallize at 4 °C overnight, which gave a second crop (33 g, 9.4%) of crystals with comparable purity. Total yield of **3**: 211.8 g (60.2%) of a colorless crystalline solid. TLC: R_f = 0.45 (toluene/EtOAc/CH_2Cl_2/HCOOH = 24:40:40:4). MS (EI): *m*/*z* 166 (M^+), 148 ($M^+ - H_2O$), 121, 103, 91, 77, 65.

Enantiomeric purity was determined by HPLC on a chiral column (Chiralpak AD, 25 mm × 4.6 mm, eluent: *n*-hexane/*i*-PrOH/TFA 96:4:0.2, flow: 0.5 mL/min, λ = 210 nm, 40 °C; [*R*]- and [*S*]-enantiomers from Fluka as analytical standards): *R*/*S* = 97.4:2.6. A smaller batch (25-g scale) gave 78% total yield, enantiomeric purity *R*/*S* = 95.5:4.6.

(C) (By Resolution of Racemic PLA via Diastereomeric Salt Separation). A suspension of phenylacetaldehyde (50.0 g, 416.1 mmol) in 228 mL of commercial (38%) aqueous sodium bisulfite solution (832.3 mmol) was stirred in an icebath at 0 °C for 30 min before a solution of potassium cyanide (108.39 g, 1.665 mol) in 200 mL of water was slowly added over 45 min. The reaction mixture was stirred at 5−10 °C for additional 60 min. Water (100 mL) was added, and the mixture was extracted with TBME (2 × 250 mL). Organic phases were dried over sodium sulfate and, after addition of 1 drop of concentrated H_2SO_4, were evaporated under reduced pressure. To the resulting **10**, a yellow oil, was added concentrated aqueous HCl (300 mL), and the mixture was heated under reflux (95 °C) for 60 min. The mixture was allowed to cool to room temperature overnight, and the clear, yellow solution was extracted with TBME (8 × 300 mL) and ethyl acetate (300 mL). Organic phases were dried over sodium sulfate and evaporated under reduced pressure. The crude **11** (65.54 g, 95%), a brown oil, was dissolved in toluene (180 mL) and heated to reflux. Upon cooling, a colorless precipitate formed, which was filtered and dried in a vacuum oven (50 °C). Yield 48.44 g (70.1% based on phenylacetaldehyde) racemic phenyl lactic acid (PLA) **11** as colorless crystals.

(*C1*): Resolution of Racemic PLA with L-(+)-Phenylglycinol. 11 (4.0 g, 24.1 mmol) and L-(+)-phenylglycinol (3.63 g, 26.5 mmol) were dissolved in 2-butanol (80 mL) at

80 °C. The clear solution was heated to 115 °C and slowly cooled to room temperature. At 70 °C, TBME (80 mL) was added. At 50 °C, a few seed crystals of recrystallized (*R*)-salt **12A** from a previous batch were added. The resulting, thick suspension was stirred in an ice bath for several hours and filtered. The filter cake was washed with ice cold TBME (20 mL) and dried in a vacuum oven (35 °C). The crude salt **12A** was dissolved in methylene chloride (40 mL) at room temperature. Aqueous 1 M sodium hydroxide (40 mL) was added, and after stirring vigorously for 5 min, the aqueous phase was separated and extracted with methylene chloride (40 mL) before adjusting the pH to 1 by addition of concentrated aqueous HCl (5 mL). The aqueous phase was then extracted with ethyl acetate (4 × 50 mL). The combined extracts were evaporated to yield crystalline, colorless **3** (1.87 g, 93.5%). Enantiomeric purity (vide supra): *R*/*S* = 99.0:1.0.

(*C2*): Resolution of Racemic PLA with L-Phenylalaninol. 11 (4.56 g, 27.45 mmol) and L-phenylalaninol (4.61 g, 30.5 mmol) were suspended in 2-butanone (180 mL) and heated to 70 °C. After filtration, the clear filtrate was slowly cooled to room temperature. At 30 °C, a few seed crystals of recrystallized (*R*)-salt **12B** from a previous batch were added. The resulting, thick suspension was stirred for another 1.5 h at rt and 1.5 h in an ice bath and filtered. The filter cake was washed with ice-cold TBME (30 mL) and dried in a vacuum oven (35 °C). The resulting salt **12B** (3.82 g, 87.6%) was then suspended in methylene chloride (20 mL) and 1 M sodium hydroxide (20 mL). After stirring vigorously for 5 min, the aqueous phase was separated and extracted with methylene chloride (20 mL). Both methylene chloride phases were washed with aqueous 1 M sodium hydroxide (10 mL). Water phases were combined, and the pH was adjusted to pH 1 by addition of concentrated aqueous HCl (4 mL). The resulting suspension was stirred in an ice bath for 30 min and filtered. The filter cake was dissolved in TBME and evaporated to yield crystalline, colorless **3** (1.19 g, 52.2%). Enantiomeric purity (vide supra): *R*/*S* = 100:0.

(*C3*): Resolution of Racemic PLA with (+)-Dehydroabietylamine. To a solution of **11** (4.0 g, 24.1 mmol) in isobutyl methyl ketone (50 mL) was added a solution of (+)-dehydroabietylamine (Merck, z.S.) (8.22 g, 26.5 mmol) in the same solvent (100 mL). After stirring the initially clear solution at room temperature for approximately 10−15 min, a precipitate formed. The suspension was heated to 95 °C, whereupon a clear yellow solution formed that was slowly cooled to room temperature. At 85−90 °C, a few seed crystals of recrystallized (*S*)-salt **12C** from a previous batch were added. At 70 °C, a thick suspension of (*S*)-salt **12C** formed which was stirred for 1.5 h and filtered. The filter cake was washed with isobutyl methyl ketone (50 mL). The filtrate was evaporated to dryness under reduced pressure, the oily residue taken up in methylene chloride (30 mL), and the clear solution extracted with 1 M sodium hydroxide (3 × 20 mL). The combined water phases were extracted with methylene chloride (20 mL), and the pH of the water phase was adjusted to pH 1−2 by addition of concentrated aqueous HCl (5 mL). The resulting suspension was extracted with ethyl acetate (4 × 30 mL). EtOAc phases were combined and evaporated under reduced pressure to yield crude **3** (1.46 g, 73%). Enantiomeric purity (vide supra): *R*/*S* = 80.4:19.6. A portion of the crude material (1.28 g) was recrystallized from deionized water (7 mL) to give colorless, crystalline **3** (0.86 g, 49.0%). Enantiomeric purity (vide supra): *R*/*S* = 100:0.

(*E*) (By Enantioselective Biocatalytic Reduction of Phenyl Pyruvic Acid). *Proteus mirabilis* DSM 30115 was grown on 5-L scale at 37 °C, under anaerobic conditions (nitrogen flow via sparger) and with pH 6.5 regulation (corrected with a 30% NaOH solution in case of decrease below pH 6.5), in a medium of the following composition: 20 g/L soy peptone, 5 g/L yeast extract, 5 g/L K_2HPO_4, pH 7.2, inoculated with a preculture of 10% volume. During the fermentation a 70% (w/v) glucose monohydrate solution was fed at a constant flow rate of 7.2 mL/h. After 23 h of fermentation, the culture was cooled to 15 °C, and the cells were harvested by centrifugation (Cryofuge 8000, Heraeus, 35 min at 5000 rpm, at 4 °C). The wet cells obtained (about 17 g of wet packed cells/L of culture) were frozen and stored during 2 years at −20 °C.

The reduction of phenyl pyruvic acid was conducted on 100-mL scale in a stirred glas reactor with jacket (Metrohm) at 37 °C, under anaerobic conditions (nitrogen flow subsurface). A mixture was prepared with the following components added (and dissolved) in the same sequence as indicated below: 43 g of purified water, 0.256 g of KH_2PO_4, 0.384 g of K_2HPO_4, 1.36 g of potasium formate, 7 g of phenyl pyruvic acid (Fluka No. 78190, purum, ∼99%), 24 g of poly(ethylene glycol) 4000, ∼5.73 g of a 50% (w/w) KOH solution (to adjust pH 7.0), 11.27 g of purified water, 40 mg of benzyl viologen previously dissolved in 1.5 mL of purified water, 1.5 g of wet packed cells previously suspended in 4 mL of purified water, a drop of antifoam polypropylene glycol 2025, the whole giving a total weight of 100 g (corresponding to a volume of about 90 mL). During the reaction, the pH was controlled and continuously adjusted to pH 7.0 by addition of a 50% (v/v) formic acid solution with an automatic buret (Dosimat Metrohm 665 with a 20-mL buret, Impulsomat Metrohm 614, pH meter Metrohm 632). Samples were taken at different times for determination of the percentage of conversion by HPLC analysis: 20 μL of a 400-fold diluted sample (with 0.1 M KH_2PO_4 pH 3.0) was applied to a 5 μ Nucleosil C18 column (length: 16 cm, diameter: 4.6 mm, mobile phase: 950 mL of 0.05 M KH_2PO_4 pH 3.0 + 500 mL of acetonitrile, flow rate: 1 mL/min, detection at 216 nm). The end of the reaction was reached after 20 h, with a measured phenyl pyruvic acid conversion of >99.8% and a formic acid consumption of 3.16 mL.

The (*R*)-3-phenyl lactic acid was recovered as indicated below. The reaction mixture (about 91 mL) was adjusted to pH 2.0 with 3.69 g of H_2SO_4 96%, and 90 mL of ethyl acetate was added at room temperature under stirring. The mixture was transferred to a separatory funnel for partial phase separation during 30 min and then filtered through a 1-cm thick Hyflo layer (on a Büchner filter of diameter 6.5 cm). The filter was rinsed with 6 mL of ethyl acetate, and the

filtrate was tranfered to a separatory funnel for complete phase separation (during 30−60 min). The aqueous phase was recovered and subjected to a second extraction step at pH 2.0 (adjusted with H_2SO_4 96%) with 90 mL of ethyl acetate, and after phase separation, the organic phase was recovered and added to the organic phase of the first extraction step. The organic pool (168 mL) was subjected to two consecutive wash steps with 0.2 volume of a saturated Na_2SO_4 solution (52 g of Na_2SO_4 per 100 g of purified water) at pH 2.0 (adjusted with H_2SO_4 96%). The recovered, washed organic pool was then concentrated to about 30 mL in a rotavapor. Fresh ethyl acetate (30 mL) was added to the concentrate, and the solution was reduced again to 30 mL. The crystallization of the product was performed by addition of 100 mL methylcyclohexane to the concentrate, and complete removal of ethyl acetate by evaporation in the rotavapor. The product suspension in methylcyclohexane was then cooled to 10 °C and filtered on a paper filter. After two rinse steps with 10 mL of ice cold methylcyclohexane, the final product was recovered and dried at 65 °C, to give white (colorless), crystalline (*R*)-3-phenyl lactic acid (**3**) (6.17 g, 87%). Enantiomeric purity (vide supra): *R/S* > 99.5:0.5.

General Procedure for the Hydrogenation Screening Experiments (Tables 1 and 2). The starting material was placed in stainless steel pressure vessel and dissolved in the solvent indicated, and the moistened catalyst was added. The reaction vessel was closed, flushed twice with nitrogen gas and twice with hydrogen gas. The reactor was pressurized to the hydrogen pressure indicated and stirred at the given temperature for the indicated period of time. The consumption of hydrogen ceased within this period of time. The reactor was cooled to room temperature, the hydrogen pressure released, and the reactor flushed twice with nitrogen gas. The crude reaction mixture was filtered and evaporated to dryness, and the crude product mixture was analyzed by GLC (percent area) after derivatization with AcCl/^{i}PrOH/TFAA.

(2*R*)-2-Hydroxy-3-cyclohexylpropionic acid (4).[10] *(A) From Phenyl Lactic Acid.* A Buchi reactor was charged with a solution of (2*R*)-2-hydroxy-3-phenyl lactic acid (**3**) (50.0 g, 0.3 mol, *R/S* >99.5:0.5, from enantioselective bioreduction with *Proteus mirabilis*; see procedure ***E***) in 94% ethanol (1000 mL) and 5% Rh−C hydrogenation catalyst (5.0 g). The mixture was hydrogenated at 50 °C under 15 bar H_2 pressure under vigorous stirring for 3 h. The suspension was filtered, the clear filtrate was evaporated, and the resulting crystalline solid was dried in a vacuum-drying oven at 50 °C. Yield 50.2 g (96.9%). Enantiomeric purity (vide supra): *R/S* = 99.5:0.5. Mp 92−94 °C. ^{1}H NMR (400 MHz, DMSO) δ 0.75−1.0 (m, 2 H), 1.1−1.3 (m, 3 H), 1.35−1.52 (m, 3 H), 1.55−1.82 (m, 5 H), 3.0−3.8 (br s, 1 H, *H*-O-C(2)), 3.98 (m, 1 H, *H*-C(2)). ^{13}C NMR (100 MHz, DMSO) δ 26.5, 26.8, 27.0 (C(3′), C(4′), C(5′) cHexyl), 32.7/34.4 (C(2′), C(6′) cHexyl), 34.1 (C(1′) cHexyl), 42.4 (C(3), 68.4 (C(2), 177.3 (C(1)). MS(EI) *m/z* 173 (MH^+), 154 ($M^+ - H_2O$), 136, 127, 109, 83, 67, 55.

*(B) From Methyl Dihydroxyphenylpropionate **13A** (vide infra).* To a solution of **13A** (*R/S* = 99.7:0.3) (35.0 g, 178.4 mmol) in methanol (310 mL) was added 98 mL of 2 M methanolic HCl and 5% Pd−C hydrogenation catalyst (10.5 g). Under vigorous stirring in a Buchi glass hydrogenation reactor, the suspension was hydrogenated at 67 °C under 4 bar H_2 pressure for 5 h. The temperature was lowered to 50 °C, and 5% Rh−C hydrogenation catalyst (3.5 g) was added. Hydrogenation was continued at 50 °C for another 17 h before the suspension was filtered, the clear filtrate was evaporated, and the resulting oil (**15**)[33] was dried in a vacuum-drying oven at 35 °C/1 mbar for 1 h. The oil was taken up in methanol (633 mL) and water (211 mL). Lithium hydroxide monohydrate (10.7 g, 255.0 mmol) was added at 30 °C, and the turbid solution was stirred at 25 °C overnight. Amberlyst IR-120 (H^+-form, dry, 60.9 g ≈ 268.1 mEq H^+) was added, the ion-exchange resin was filtered off andwashed with excess methanol and water, and the clear filtrate was evaporated under reduced pressure to yield a crystalline material which was dried in a vacuum drying oven (40 °C, 1 mbar). Yield: 28.95 g (94.2% over three steps) **4** as off-white, crystalline solid. Enantiomeric purity (vide supra): *R/S* = 99.3:0.7. Os-content: 4 ppm (by elemental analysis).

(2*R*,3*S*)-2,3-Dihydroxy-3-phenylpropionic Acid Methyl Ester (13A). According to the procedure of Sharpless et al.,[26] from 41.85 g of methyl cinnamate were obtained 37.72 g (74.5%) **13A**, *R*/S = 98.8:1.2 after first recrystallization from toluene; respectively 35.40 g (69.9%), *R*/S = 99.7:0.3 after second recrystallization from toluene. Os-content: 102 ppm (by elemental analysis).

(2*R*,3*S*)-2,3-Dihydroxy-3-phenylpropionic Acid Benzyl Ester (13B).[31] Following the same procedure,[26] from 15.9 g of benzyl cinnamate was obtained 17.9 g of **13B**, 99% yield, *R*/S = 90.7:9.3 after chromatograpy from toluene/ethyl acetate 5:1. MS(EI) *m/z* 272 (M^+), 197, 166, 148, 107, 91, 79, 65.

(2*R*)-2-Hydroxy-3-phenylpropionic Acid Methyl Ester (14A).[32] (*A) From Hydrogenolysis/Transesterification of the Benzyl Ester Diol*. To a solution of **13B** (*R/S* = 90.7:9.3) (8.7 g, 32.0 mmol) in methanol (100 mL) was added 8.8 mL of 1.1 M methanolic HCl and 5% Pd−C hydrogenation catalyst (870 mg). Under vigorous stirring, the suspension was hydrogenated at 25 °C under 2 bar H_2 pressure for 16 h. The suspension was filtered, the clear filtrate was evaporated, and the resulting crystalline solid was dried in a vacuum-drying oven at 50 °C. Yield 4.805 g (83.3%). Enantiomeric purity (vide supra): *R/S* = 93.3:6.7.

(*B) From Hydrogenolysis of the Methyl Ester Diol*. To a solution of **13A** (*R*/S = 98.6:1.4) (5.7 g, 29.1 mmol) in methanol (50 mL) was added 16 mL of 1.1 M methanolic HCl and 5% Pd−C hydrogenation catalyst (770 mg). Under vigorous stirring, the suspension was hydrogenated at 25 °C under 1.7−4 bar H_2 pressure for 30 h. The suspension was filtered, the clear filtrate was evaporated, and the resulting crystalline solid was dried in a vacuum-drying oven at 50

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(32) (a) Schoofs, A.; Weidmann, R.; Collet, A.; Horeau, A. *Bull. Soc. Chim. Fr*. **1976**, 2031. (b) Mor, G.; Ehret, A.; Cohen, S. G. *Arch. Biochem. Biophys.* **1976**, *174*, 158.
(33) Damon, D. B.; Hoover, D. J. *J. Am. Chem. Soc*. **1990**, *112*, 6439.

°C. Yield 5.22 g (99.0%). Enantiomeric purity (vide supra): *R*/*S* = 98.2:1.8.

General Synthesis Procedure for the Esters 5, and 16−20. Anhydrous potassium carbonate (1.15 equiv) was added to a solution of **4** (10−50 mmol) in dry acetone (80−400 mL). The white suspension was stirred at room temperature for 3 h, whereupon tetrabutylammonium iodide (1.0 equiv) and the corresponding benzyl halide (1.15 equiv) were added, and the suspension was stirred for a further 12−18 h at 40°C, until TLC had indicated complete consumption of the hydroxy acid. After cooling to room temperature, the suspension was filtered over a sand/Celite pad, and the filter cake was washed with acetone. Evaporation under reduced pressure gave the crude product as a colorless-to-yellowish oil, which was further purified or crystallized by the solvent system indicated below with the individual compounds. Following this procedure we obtained:

(2*R*)-2-Hydroxy-3-cyclohexyl-propionic acid benzyl ester (5):[7] 87% yield (chromat. from *n*-hexane/EtOAc 9:1), colorless oil, crystallizes slowly in the refrigerator, mp 54−56 °C, ^{1}H NMR + ^{13}C NMR identical to lit.[7] MS(EI) *m*/*z* 262 (M^+), 181, 166, 153, 127, 109, 91, 83, 67, 55. IR (KBr, cm^{-1}) 3314s/br, 2923s, 2849m, 1751ss, 1742s, 1538m, 1511s, 1463w, 1444w, 1212m, 1192s, 1143s, 1087s, 1078s, 738m, 695m.

(2*R*)-2-Hydroxy-3-cyclohexylpropionic acid *p*-chlorobenzyl ester (16): 50% yield, (chromat. *n*-hexane/EtOAc 9:1), colorless oil, ^{1}H NMR (400 MHz, DMSO) δ 0.79−1.73 (m, 13 H, H_2-C(3) + cHexyl), 4.12 (dt, J = 6.4 Hz, 6.7 Hz, 1 H, *H*-C(2)), 5.12 (AA′, 2 H, ClPh-CH_2), 5.40 (d, 1 H, J = 6.1 Hz, *H*O-C(2)), 7.39−7.47 (AA′BB′, 4 H, ClPh). ^{13}C NMR (100 MHz, DMSO) δ 26.5, 26.7, 26.9, 32.7, 34.0, 34.1, 34.2, 42.3, 65.5, 68.7, 129.3, 129.8, 130.8, 133.6, 135.6, 136.1, 175.3. MS(EI) *m*/*z* 298, 296 (M^+), 171, 153, 127, 125, 109, 89, 83, 81, 67, 55. IR (Film, cm^{-1}) 3479s/br, 2924ss, 2851s, 1736ss, 1494s, 1449m, 1274s, 1198s, 1142s, 1094s, 1017m, 965w, 845w, 809m. Elemental analysis calcd for $C_{16}H_{21}ClO_3$ (296.79): C 64.75%, H 7.13%, Cl 11.95%; found: C 64.84%, H 6.90%, Cl 11.88%.

(2*R*)-2-Hydroxy-3-cyclohexylpropionic acid 2,5-dichlorbenzyl ester (17): 93% yield, (chromat. *n*-hexane/EtOAc 9:1), colorless oil, ^{1}H NMR (400 MHz, DMSO) δ 0.74−1.71 (m, 13 H, H_2-C(3) + cHexyl), 4.10 (br dt, 1 H, *H*-C(2)), 5.31 (AA′, 2 H, Cl_2Ph-CH_2), 5.43 (d, 1 H, J = 6.0 Hz, *H*O-C(2)), 7.42−7.58 (m, 3 H, Cl_2Ph). ^{13}C NMR (100 MHz, DMSO) δ 26.5, 26.7, 26.9, 32.9, 34.0, 34.1, 34.15, 42.5, 61.7, 68.7, 129.6, 131.7, 132.5, 136.9, 175.2. MS(CI) *m*/*z* 331 (MH^+), 285, 171, 159, 125, 79. IR (Film, cm^{-1}) 3477m/br, 2924ss, 2851s, 1738ss, 1583m, 1565m, 1438s, 1248m, 1200s, 1142m, 1096s, 989w, 965w, 779m, 769m. Elemental analysis calcd for $C_{16}H_{20}Cl_2O_3$ (331.24): C 58.02%, H 6.09%, Cl 21.41%; found: C 57.92%, H 6.09%, Cl 21.30%.

(2*R*)-2-Hydroxy-3-cyclohexylpropionic acid *p*-bromobenzyl ester (18): 88% yield (chromat. *n*-hexane/EtOAc 4:1), respectively 82% (recryst. from *n*-hexane), yellowish crystals, mp 50−52 °C, ^{1}H NMR (400 MHz, DMSO) δ 0.77−1.75 (m, 13 H, H_2-C(3) + cHexyl), 4.12 (dt, J = 6.0 Hz, 6.5 Hz, 1 H, *H*-C(2)), 5.11 (AA′, 2 H, BrPh-CH_2), 5.38 (d, 1 H, J = 6.0 Hz, *H*O-C(2)), 7.32−7.53 (AA′BB′, 4 H, ClPh). ^{13}C NMR (100 MHz, DMSO) δ 26.5, 26.7, 26.9, 32.8, 34.0, 34.2, 42.3, 65.5, 68.7, 110.0, 122.1, 131.1, 132.2, 136.5, 175.3. MS(CI): *m*/*z* 367 [M + C_2H_5-gas adduct], 343, 342, 341, 340 (M^+), 339, 295, 293, 277, 211, 198, 171, 169, 127, 125, 109, 83. IR (KBr, cm^{-1}) 3408s/br, 2923s, 2848s, 1752ss, 1728s, 1489m, 1223m, 1209m, 1186m, 1170m, 1142m, 1091m, 1070s, 1012m, 805s. Elemental analysis calcd for $C_{16}H_{21}BrO_3$ (341.24): C 56.32%, H 6.20%, Br 23.42%; found: C 56.31%, H 6.07%, Br 23.30%.

The potential for epimerization during this reaction was checked in two separate batches: *Exp. A*: 3.3 mmol of **4** (*R*/*S* = 98.2:1.8) gave 88% of **18**, *R*/*S* = 99.5/0.5*; Exp. B*: 50 mmol of **4** (*R*/*S* = 99.3:0.7) gave 82% of **18**, *R*/*S* = 99.8:0.2).

(2*R*)-2-Hydroxy-3-cyclohexylpropionic acid *p*-nitrobenzyl ester (19): 37% yield, yellow oil, (chromat. *n*-hexane/EtOAc 4:1), ^{1}H NMR (400 MHz, DMSO) δ 0.80−1.77 (m, 13 H, H_2-C(3) + cHexyl), 4.20 (dt, J = 6.0 Hz, 6.7 Hz, 1 H, *H*-C(2)), 5.28 (A_2, 2 H, NO_2Ph-CH_2), 5.46 (d, 1 H, J = 6.0 Hz, *H*O-C(2)), 7.65, 8.27 (AA′BB′, 4 H, ClPh). ^{13}C NMR (100 MHz, DMSO) δ 25.8, 26.0, 26.2, 32.0, 33.3, 33.5, 41.5, 64.4, 68.0, 123.7, 128.7, 144.1, 147.3, 174.5. MS(EI): *m*/*z* 308, 307 (M^+), 289, 262, 211, 193, 171, 153, 137, 127, 109, 107, 97, 83, 81, 67, 55. IR (Film, cm^{-1}) 3485s/br, 2924ss, 2851s, 1741ss, 1608m, 1524ss, 1449m, 1348ss, 1275s, 1194s, 1142s, 1098s, 1013m, 853w, 738w. Elemental analysis calcd for $C_{16}H_{21}NO_5$ (307.35): C 62.53%, H 6.89%, N 4.56%; found: C 62.79%, H 7.02%, N 4.49%.

(2*R*)-2-Hydroxy-3-cyclohexylpropionic acid 2-naphthylmethyl ester (20): 94% yield, mp 54−55 °C, (chromat. from *n*-hexane/EtOAc 9:1), colorless oil, crystallizes slowly while standing at rt, mp 54−55 °C, ^{1}H NMR (400 MHz, DMSO) δ 0.77−1.74 (m, 13 H, H_2-C(3) + cHexyl), 4.18 (dt, J = 6.2 Hz, 6.8 Hz, 1 H, *H*-C(2)), 5.30 (AA′, 2 H, Naphth-CH_2), 5.42 (d, 1 H, J = 6.2 Hz, *H*O-C(2)), 7.50−7.57 (m, 3 H, Naphth-*H*), 7.90−7.95 (m, 4 H, Naphth-*H*). ^{13}C NMR (100 MHz, DMSO) δ 26.5, 26.7, 26.9, 32.8, 34.0, 34.2, 42.4, 66.5, 68.8, 126.8, 127.2, 127.3, 127.7, 128.5, 128.6, 129.0, 133.5, 133.6, 134.6, 175.4. MS(CI): *m*/*z* 312 (M^+), 281, 141, 109, 83. IR (KBr, cm^{-1}) 3506s, 3483s, 2923s, 2849m, 1708ss, 1742s, 1465w, 1291m, 1258m, 1233w, 1132m, 980m, 823s, 750m. Elemental analysis calcd for $C_{20}H_{24}O_3$ (312.41): C 76.89%, H 7.74%; found: C 76.77%, H 7.75%.

General Synthesis Procedure for the Sulfonates 16−28. Toluene-4-sulfonyl chloride, 4-bromobenzenesulfonyl chloride or 4-nitrobenzenesulfonyl chloride (1.3 equiv) was added to a solution of the corresponding hydroxyester (**5**, **18** or **20**) (1−5 mmol) in dry toluene (5−25 mL) at room temperature. *N*-Methylmorpholine (1.4 equiv) was added, and the suspension was stirred for a further 2−4 h at room temperature and 10−18 h at 50 °C, until TLC had indicated complete consumption of the hydroxy ester. After cooling to room temperature, the suspension was washed with 20% $NaHCO_3$ (2 × 10 mL) and water (2 × 15 mL). Combined water phases were extracted with toluene (1 × 15 mL). Drying of the toluene phases over sodium sulfate and

evaporation under reduced pressure gave the crude product ususally as a yellow oil, which was further purified or crystallized by the solvent system indicated below with the individual compounds.

(2*R*)-2-(4-Nitrophenyl)sulfonyloxy-3-cyclohexyl-propionic acid *p*-brombenzyl ester (21): 60% yield, (crude product recryst. from EtOH), yellowish crystals, mp 71−72 °C, ^{1}H NMR (400 MHz, DMSO) δ 0.67−1.76 (m, 13 H, H_2-C(3) + cHexyl), 4.12 (dt, J = 6.0 Hz, 6.5 Hz, 1 H, *H*-C(2)), 5.09−5.15 (m, 3 H, *H*-C(2) + BrPh-CH_2), 7.28−7.56 (AA′BB′, 4 H, BrPh), 8.20−8.43 (AA′BB′, 4 H, NO_2-Ph). ^{13}C NMR (100 MHz, DMSO) δ 26.1, 26.4, 26.5, 26.6, 32.1, 32.4, 33.6, 33.7, 33.9, 67.0, 77.8, 122.5, 124.2, 125.7, 127.8, 130.4, 131.2, 132.3, 135.4, 141.5, 151.6, 169.1. MS-(EI): *m*/*z* 527 [MH^+], 356, 322 [$M^+ - NO_2PhSO_3H$], 230, 186, 171, 169 [$BrPhCH_2^+$], 138, 94, 83. IR (KBr, cm^{-1}) 3120m, 2926s, 1752s, 1734s, 1535ss, 1372s, 1351s, 1190ss, 1171m, 1166m, 982s, 961s, 858m, 843s, 748m, 617s. Elemental analysis calcd for $C_{22}H_{24}BrNO_7S$ (526.41): C 50.20%, H 4.60%, Br 15.18%, N 2.66%, S 6.09%; found: C 50.17%, H 4.59%, Br 15.05%, N 2.58%, S 6.10%.

(2*R*)-2-Methansulfonyloxy-3-cyclohexyl-propionic acid *p*-brombenzyl ester (22): 81% yield, (crude product chromat. from *n*-Hexane/EtOAc 9:1), colorless oil, ^{1}H NMR (400 MHz, DMSO) δ 0.85−1.79 (m, 13 H, H_2-C(3) + cHexyl), 3.25 (s, 3 H, CH_3SO$_2$), 5.14−5.24 (m, 3 H, *H*-C(2) + BrPh-CH_2), 7.36−7.61 (AA′BB′, 4 H, BrPh). ^{13}C NMR (125 MHz, DMSO) δ 25.9, 26.0, 26.2, 32.1, 33.2, 33.3, 38.3, 66.4, 76.0, 122.1, 130.9, 131.9, 135.2, 169.5. MS(CI): *m*/*z* 421 [MH^+], 420, 419, 418, 417, 339, 337, 323, 321, 249, 171, 138, 94. IR (KBr, cm^{-1}) 3030w, 2926ss, 2852s, 1756ss, 1490m, 1449m, 1361ss, 1277m, 1174ss, 1141m, 1071m, 1010s, 967s, 922m, 858m, 801s.

(2*R*)-2-(4-Bromphenyl)sulfonyloxy-3-cyclohexyl-propionic acid *p*-brombenzyl ester (23): 52% yield (crude product recryst. from EtOH), respectively 48% yield (crude product chromatographed from *n*-hexane/EtOAc 9:1), yellowish crystals, mp 68−69 °C, ^{1}H NMR (400 MHz, DMSO) δ 0.67−1.71 (m, 13 H, H_2-C(3) + cHexyl), 4.94 (dd, J = 3.8 Hz, 9.6 Hz, 1 H, *H*-C(2)), 5.12 (s, 3 H, BrPh-CH_2), 7.29−7.61 (AA′BB′, 4 H, BrBn), 7.88 (s, 4 H, BrPhSO$_2$). ^{13}C NMR (125 MHz, DMSO) δ 25.7, 26.0, 26.1, 31.6, 33.2, 66.5, 76.6, 122.0, 128.2, 129.3, 130.1, 130.8, 131.0, 131.9, 132.0, 133.3, 134.8, 135.0, 168.9. MS(ESI): dec, *m*/*z* 236, 234 [$BrPhSO_3H$]. IR (Film, cm^{-1}) 2924s, 1760ss, 1745sh/s, 1576s, 1490m, 1392s, 1377s, 1278m, 1190s, 1071s, 1012s, 919s, 861m, 823s, 797m, 611s.

(2*R*)-2-Methansulfonyloxy-3-cyclohexyl-propionic acid 2-naphthylmethyl ester (24): 79% yield, (crude product chromat. from *n*-hexane/EtOAc 9:1), slightly yellowish oil, ^{1}H NMR (400 MHz, DMSO) δ 0.88−1.75 (m, 13 H, H_2-C(3) + cHexyl), 3.25 (s, 3 H, CH_3SO$_2$), 5.20 (m, 1 H, *H*-C(2)), 5.40 (Naphth-CH_2), 7.51−7.56 (m, 3 H, Naphth), 7.92−7.95 (m, 4 H, Naphth). ^{13}C NMR (125 MHz, DMSO) δ 25.8, 26.0, 26.2, 32.2, 33.2, 33.3, 38.3, 67.3, 76.2, 126.4, 126.9, 127.7, 128.1, 128.3, 128.6, 133.1, 133.3, 169.6. MS-(CI): *m*/*z* 390 [MH^+], 141 [Naphth-CH_2^+]. IR (Film, cm^{-1}) 3035w, 2925ss, 2852s, 1753ss, 1455m, 1361ss, 1277m, 1175ss, 1142m, 1043m, 1001s, 965s, 922m, 858m, 818m, 797m.

(2*R*)-2-(4-Nitrophenyl)sulfonyloxy-3-cyclohexyl-propionic acid 2-naphthylmethyl ester (25): 58% yield, (crude product chromat. from *n*-hexane/EtOAc 9:1), yellowish oil, ^{1}H NMR (400 MHz, DMSO) δ 0.70−1.52 (m, 11 H, cHexyl), 1.64 (m, 1 H, *H*-C(3)), 1.75 (m, 1 H, *H*′-C(3)), 5.15 (dd, 1 H, J = 4.1, 9.3 Hz, *H*-C(2)), 5.30 (Naphth-CH_2), 7.42−7.56 (m, 3 H, Naphth), 7.87−7.93 (m, 4 H, Naphth), 8.21−8.38 (AA′BB′, NO_2PhSO_2). ^{13}C NMR (125 MHz, DMSO) δ 25.8, 26.0, 26.1, 26.2, 32.0, 33.2, 33.5, 60.2, 67.5, 68.2, 77.5, 81.1, 123.8, 125.2, 126.5, 126.9, 127.0, 127.4, 128.1, 128.2, 128.3, 128.6, 128.8, 130.0, 132.9, 133.0, 133.1, 133.2, 141.1, 147.7, 151.1, 154.8, 168.7, 170.6. MS(CI): *m*/*z* 526 [$M^+ + C_2H_5$ gas adduct], 497 [M^+], 156, 141 [Naphth-CH_2^+]. IR (Film, cm^{-1}) 3100w, 2925s, 2852m, 1757s, 1534ss, 1381m, 1350s, 1278m, 1188ss, 991m, 920w, 853m, 819w, 745m.

(2*R*)-2-(4-Nitrophenyl)sulfonyloxy-3-cyclohexyl-propionic acid benzyl ester (26): 80% yield, (crude product chromat. from *n*-hexane/EtOAc 9:1), yellowish oil, ^{1}H NMR (400 MHz, DMSO) δ 0.72−1.76 (m, 13 H, H_2-C(3) + cHexyl), 5.11−5.14 (m, 3 H, *H*-C(2) + Ph-CH_2), 7.30−7.43 (m, 5 H, Ph), 8.21−8.42 (AA′BB′, NO_2PhSO_2). ^{13}C NMR (100 MHz, DMSO) δ 26.1, 26.4, 26.5, 32.1, 33.2, 33.6, 33.7, 39.4, 67.8, 77.9, 125.7, 129.1, 129.2, 129.3, 130.4, 135.9, 141.5, 147.7, 151.6, 169.1. MS(EI): *m*/*z* 447 [M^+], 356 [$M^+ - PhCH_2^{\bullet}$], 330, 312, 244, 186 [$NO_2PhSO_2+\cdot$], 153, 138, 122, 109, 92, 67, 55. IR (Film, cm^{-1}) 3100w, 2925s, 2852m, 1758s, 1534ss, 1404m, 1381s, 1351s, 1314m, 1278m, 1188ss, 1100m, 920m, 853m, 819w, 745s, 617m.

(2*R*)-2-(4-Bromphenyl)sulfonyloxy-3-cyclohexyl-propionic acid benzyl ester (27): 63% yield, (crude product chromat. from *n*-hexane/EtOAc 9:1), yellowish oil, ^{1}H NMR (500 MHz, DMSO) δ 0.80−1.68 (m, 13 H, H_2-C(3) + cHexyl), 4.91 (dd, 1 H, J = 2.3, 9.7 Hz, *H*-C(2)), 5.11 (s, 2 H, Ph-CH_2), 7.30−7.41 (AA′BB′, 4 H, BrPhSO$_2$), 7.85−7.87 (m, 5 H, Ph). ^{13}C NMR (125 MHz, DMSO) δ 25.7, 26.0, 26.1, 31.6, 33.2, 39.0, 67.3, 76.6, 128.6, 128.8, 128.9, 129.3, 130.2, 133.3, 134.8, 135.6, 168.9. MS(CI): *m*/*z* 481 [M^+], 390 [$M^+ - PhCH_2^{\bullet}$], 244, 220, 181, 153, 138, 91. IR (Film, cm^{-1}) 3100w, 2924s, 2850m, 1759s, 1534ss, 1450m, 1392s, 1378s, 1278m, 1190ss, 1069m, 1012m, 1001m, 919m, 861m, 777w, 749m, 613m. Elemental analysis calcd for $C_{22}H_{25}BrO_5S$ (10% toluene) (442.48): C 55.65%, H 5.31%, S 6.52%; found: C 55.74%, H 5.30%, S 6.57%.

(2*R*)-2-(4-Tolyl)sulfonyloxy-3-cyclohexyl-propionic acid benzyl ester (28): 60% yield, (crude product chromat. from *n*-hexane/EtOAc 9:1), colorless oil, ^{1}H NMR (500 MHz, DMSO) δ 0.60−1.69 (m, 13 H, H_2-C(3) + cHexyl), 2.42 (s, 3 H, CH_3-PhSO$_2$), 4.83 (dd, 1 H, J = 3.6, 9.1 Hz, *H*-C(2)), 5.12 (s, 2 H, Ph-CH_2), 7.32−7.43 (m, 5 H, Ph), 7.46−7.82 (AA′BB′, 4 H, Me*Ph*SO$_2$). ^{13}C NMR (100 MHz, DMSO) δ 26.1, 26.4, 26.5, 32.0, 33.5, 33.6, 39.6, 67.6, 76.4, 128.6, 129.0, 129.2, 129.3, 131.0, 133.0, 136.1, 146.3, 169.5. MS-(CI): *m*/*z* 417 [MH^+], 327, 325, 299, 281, 245, 227, 181, 138, 107, 91. IR (Film, cm^{-1}) 3050w, 2925s, 2852m, 1761s, 1740sh, 1595m, 1498m, 1450m, 1374s, 1278s, 1190ss,

1178ss, 1002s, 918m, 861m, 815m, 698m, 666s, 554m. Elemental analysis calcd for $C_{23}H_{28}O_5S$ (416.54): C 66.32%, H 6.78%, S 7.70%; found: C 66.38%, H 6.75%, S 7.79%.

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