Kinetic Enzymatic Resolution of Cyclopropane Derivatives

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Abstract: The kinetic enzymatic resolution of various cyclopropane derivatives was systematically investigated. The study focused on synthetically useful cyclopropylmethanols (e.g., **18a/j** or **19a/j**) as well as some rarely investigated cyclopropanols (e.g., **24/25** or **27**). The combination of enantioselective catalytic or diastereoselective synthesis of enantiomerically enriched compounds with enzymatic approaches ultimately led to the most convenient route to enantiomerically pure starting materials. Again, this was especially proven for the synthesis of cyclopropanols **18a/j** and **19a/j**. Key to the successful investigation was to rigorously establish an analytical tool for the analysis of enantiomeric composition of reaction mixtures.

Keywords: biotransformations; boron; cyclopropanes; hydrolases; kinetic resolution

Introduction

Even 120 years after the synthesis of the first cyclopropane derivative, the chemistry around this structural element often proves to be special, disregarding the fact that cyclopropanes are regularly found in physiologically active compounds in general and in a number of pharmaceuticals in particular.[1] In this context it is not surprising that despite the well known numerous applications of cyclopropanes and hydrolases[2–8] – and within this group of enzymes especially esterases [EC 3.1.1.1] and lipases [EC 3.1.1.3] – kinetic enzymatic resolutions employing both have scarcely been used.[9] Apart from substances with the cyclopropane unit not being the only stereogenic element,[10–13] *meso*-compounds (Figure 1) are an exception giving presumable the most favorable substrates: yields and selectivities are generally high. This is especially true for dicarboxylic esters **1a**, with the best results obtained when R′ and/or R″ are sterically not demanding.[14–18] Although there have been reports about similar successful results with the corresponding diols and their derivatives **1b**,[17,19–22] these findings would seem somewhat less reliable.[23] By comparison, C_2- or *pseudo*-C_2-symmetric cyclopropanes **2** generally give a decreased selectivity: for different esters **2** E values of $E < 10$ were observed[18] and also the difluorocyclopropane **3** ($E = 11$) gave only slightly better results.[21]

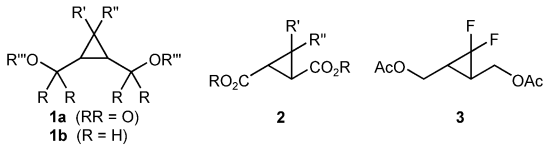

Figure 1. *Meso*-compounds and (*pseudo*)-C_2-symmetric cyclopropanes as substrates for hydrolases.

More generally speaking, with compounds where the cyclopropane moiety is the only stereogenic element, the kinetic resolution using hydrolases provides modest selectivities compared to those observed in the desymmetrization of *meso* compounds: Enantioselectivities (E values[24–28]) greater than 40 are rarely observed (see Figure 2 for some selected examples **4**–**15**[29–40]).[9] A rule for preferred substitution patterns or enzymes cannot be given. For example, the *trans*-chrysanthemic ester **4** was shown to give excellent selectivities[29–31] (more recently also for the polymer-supported ester[32]) whereas the E value for the related *cis*-derivative **5** is distinctively lower.[33] Best results were obtained with different hydrolases. The reverse result was observed for the precursors **7** and **8** of nucleoside analogues[34] and for fluoro-substituted cyclopropanes such as derivative **9**:[36] in both cases the *cis*-configurated cyclopropane is the more suitable substrate. It is interesting to note that in bicyclo[n.1.0]-derivatives 5-membered rings ($n = 3$, e.g., **10**–**12**[37–39]) often show better selectivities than the higher homologues. As pointed out before, if the cyclopropane ring is not the only stereogenic element, E values are often relatively high. Hence, without any (investigated) restrictions for 'R' good results were also obtained for [4.1.0]-compounds **13**,[13] whereas for the related cyclopropane **14** good results were only observed with the *n*-Bu-moiety present.[40] In any case,

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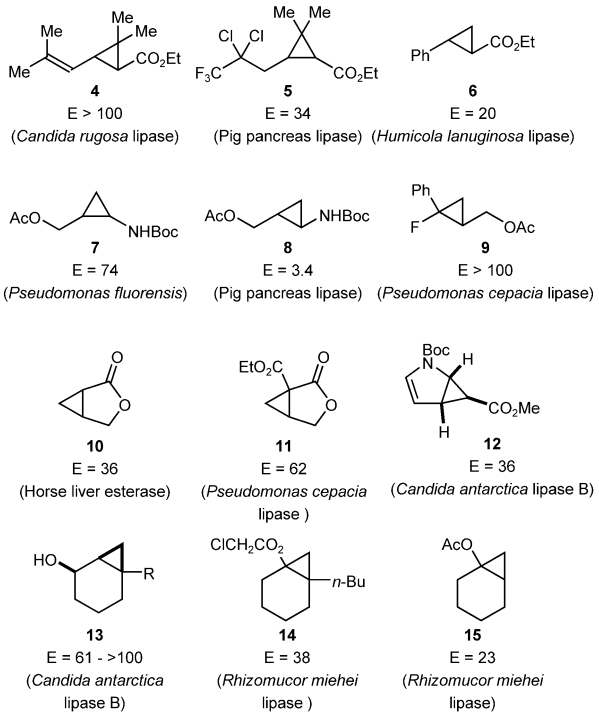


Figure 2. Kinetic enzymatic resolution of selected cyclopropane derivatives (E value: enantioselectivity).

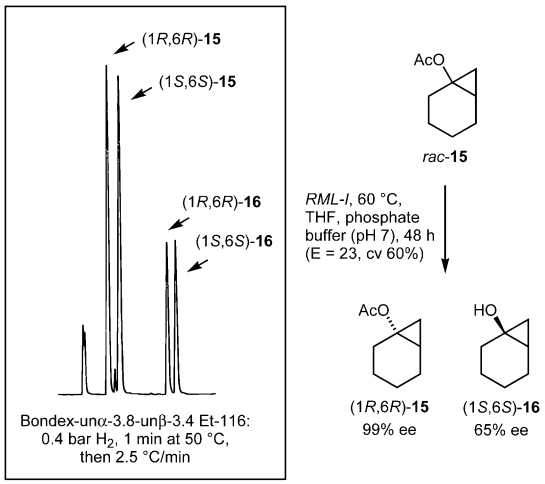


Figure 3. Establishing the analytical separation of enantiomers (cv: calculated conversion).

despite the fact that enzymes have been successfully applied for the large-scale synthesis of the parent cyclopropanol, there are hardly any investigations on kinetic enzymatic resolutions of chiral derivatives of cyclopropanol. As a matter of fact, a first example – prior to our own investigation[41] – has been the bicyclo[4.1.0]heptanyl acetate (**15**),[40] giving modest selectivity in a transesterification reaction with *n*-propanol in the presence of a *Rhizomucor miehei* lipase (*RML*). A more recent, impressive example was disclosed by Westermann and Krebs who synthesized enantiomerically pure cyclopropyl hemiacetals:[42] by changing the enzyme from *Candida antarctica B* lipase (*CAL-B*) to a *Pseudomonas cepacia* lipase (*PCL*; the bacterial species has been renamed to *Burkholderia cepacia*, however, for convenience we continue to use the traditional name), the stereochemical course of the resolution could be reversed.

In view of the reported results, we wanted to investigate two classes of cyclopropane derivatives – cyclopropylmethanols and cyclopropanols – in more detail. Preliminary results in the area have been published;[41] we now wish to report our investigations in full.

Results and Discussion

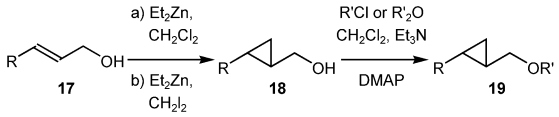
Procedure

Before starting the investigation, it was of ultimate importance to establish a reliable method to analyze the enantiomeric excess. As a matter of fact, we found that to establish the analytical tool – the first step in our procedure – was the most difficult prerequisite: Some of the envisaged investigations failed because we could not find a convenient method to measure the enantiomeric excess of both product and substrate. In only a few cases did we have the ideal situation as shown in Figure 3: For the first model substrate, the known bicyclic derivative **15**,[40] we could not only separate the acetate **15**, but also the products of the enzymatic hydrolysis, alcohols **16**. Next, we looked at both the enzymatic hydrolyses and acylation using a standard protocol with the available enzymes (see "Supporting Information" for a complete list of enzymes with the used abbreviations). Finally, we optimized the reaction conditions by varying the solvent system and the reaction temperature. In the present case we found a moderate E value of E = 23, with *RML* giving the best results in THF at 60 °C. These results are in full agreement with those previously reported.[40]

Cyclopropylmethanols

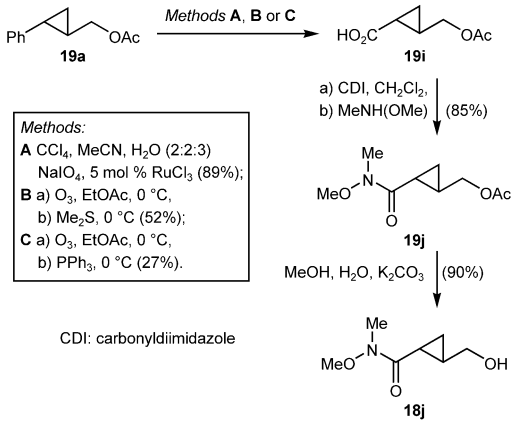
The focus of our first investigation was on cyclopropylmethanol derivatives that were readily synthesized from the corresponding allyl alcohols **17** (Scheme 1). Using a slightly modified Furukawa protocol,[43–45] cyclopropanation with a zinc carbenoid led to the cyclopropanes **18** in good (unoptimized) overall yield. Acylation either with the acid chloride or the anhydride gave the esters **19**.

The cinnamyl alcohol-derived acetate **19a** was also used to provide the synthetically valuable "Weinreb amides" **18j**/**19j** (Scheme 2):[46] Oxidation furnishing the carboxylic acid **19i** could be achieved by ozonolysis, however, most convenient (yield: 89%) was the use of



Entry	R	Yield **18**	R'	Yield **19**
a	Ph	96%	Ac	96%
b	Ph		*n*-PeC(=O)	92%
c	Ph		*n*-C_7H_{15}C(=O)	88%
d	Me	82%	Ac	99%
e	Me		*n*-PeC(=O)	72%
f	Me		*n*-C_7H_{15}C(=O)	92%
g	*n*-Pe	93%	Ac	61%
h	*p*-$MeOC_6H4$	58%	Ac	89%

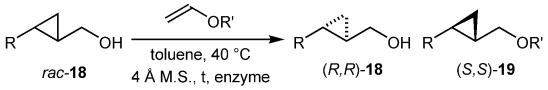
Scheme 1. Synthesis of cyclopropylmethanols **18** and **19**.



Scheme 2. Synthesis of Weinreb amides **18j** and **19j**.

$RuCl_3/NaIO_4$.[47–49] Transformation to the Weinreb amide **19j** by activation with CDI followed by *N*-methoxy-*N*-methylamine was straightforward (85%). Consecutive saponification of the ester yielded the alcohol **18j** (90%). With these compounds in our hands, we separated the enantiomers[50] using direct methods. Most convenient was the GLC analysis with modified cyclodextrins as chiral stationary phases.[51,52] Alternatively, HPLC analysis with a commercially available column was successful. The absolute configurations were established for most compounds *via* correlation with known, available reference substances.[53,54]

First the selective acylation using vinyl esters[55,56] in the presence of different hydrolases was investigated (Scheme 3). As reference conditions, the reactions were performed in toluene at 40 °C. In no case did the acylation give satisfactory results for the investigated resolution of the substrates (**18a – d**): while a conversion could be easily achieved, even with the "best" enzymes only low E values of $E < 10$ were observed. In most cases the enzymes showed no selectivity. In this respect the exemplary results for alcohol **18d** are typical ($E < 2$, entries 6 – 9). Using more lipophilic esters instead of the acetate, did not improve the situation (**18a**: $E = 7.4$; **18b**: $E = 2.4$; **18c**: $E = 1.9$; *PCL-III* – entries 3 – 5). We did not further pursue this approach.

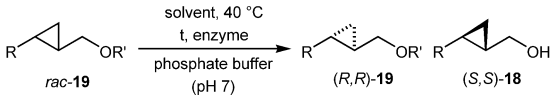


Entry	t [h]	Enzyme	R	R'	ee (*R*,*R*)-**18**	ee (*S*,*S*)-**19**	cv[a]	E[a]
1	1.75	*ACY*	Ph	Ac (**a**)	35%	56%	38%	4.9
2	0.50	*PCL-I*	Ph	Ac (**a**)	67%	38%	64%	4.2
3	0.50	*PCL-III*	Ph	Ac (**a**)	78%	53%	60%	7.4
4	0.50	*PCL-III*	Ph	*n*-PeC(=O) (**b**)	27%	30%	47%	2.4
5	3.00	*PCL-III*	Ph	C_7H_{15}C(=O) (**c**)	17%	24%	41%	1.9
6	5.00	*CRL-I*	Me	Ac (**d**)	6%	10%	38%	<2
7	5.00	*PCL-I*	Me	Ac (**d**)	21%	45%	32%	<2
8	5.00	*RML-I*	Me	Ac (**d**)	37%	72%	34%	<2
9	5.00	*PSL*	Me	Ac (**d**)	20%	60%	25%	<2

Scheme 3. Kinetic enzymatic resolution of cyclopropylmethanols **18** – selective acylation.[50]
[a] Calculated values.[27]

We turned our attention to the selective hydrolysis of esters **19** (Scheme 4). In a phosphate buffer at 40 °C we first examined the phenyl derivative **19a** and used different enzymes in toluene. While most lipases and esterases gave enantioselectivities $E < 2$, the results for *Pseudomonas cepacia* lipase (*PCL-IV*: $E = 2.3$, entry 1) and pig liver esterase I (*PLE-III*: $E = 2.2$, entry 3) were only marginally better. The most promising result was found with *Candida antarctica B* lipase (*CAL-B-I*): An E value of $E = 13$ (entry 2) was observed. With this enzyme we varied the solvent used. In different ethers or pentane the selectivity decreased (entries 5 – 7), however, it was found that dichloromethane was the best solvent for this transformation ($E = 24$, entry 4). Again, changing to more lipophilic esters did not improve the selectivity (compounds **19b/c**, entries 8/9), but dramatically lower E values were observed ($E = 5.3$ and 5.1, respectively). With aliphatic side-chains (compounds **19d – g**, entries 10 – 17) no successful resolutions could be performed, with the E values never exceeding $E = 8.8$ (entry 13). We were surprised to find that changes in the aromatic group have also a strong influence on the selectivity. For the *p*-methoxy derivative **19h** we found that although *CAL-B-I* is the best enzyme for the transformation (entries 18 – 25), the solvent of choice is not dichloromethane, but toluene ($E = 8.7$, entry 18). Finally, we examined the "Weinreb amide" **19j** and were pleased to find that almost all enzymes gave satisfactory transformations in toluene (entries 26 – 30) and some of them even unforeseen high selectivities (*PCL-I*: $E = 25$, entry 26; *PPL-I*: $E = 34$, entry 29; *ASL-I*: $E = 33$, entry 30). We could further improve the results by varying the solvents (entries 31 – 42) and for a number of enzymes enantioselectivity factors $E > 20$ were found. By far the best result was obtained when using *PCL-I* in dioxane ($E = 52$, entry 36).

Obviously, the last example shown is the only preparatively, directly useful substrate. To underline the point, we followed the kinetic resolution of the second best substrate **19a**, taking aliquots after set times



Entry	t [h]	Enzyme	sm[c]	Solvent	ee (*R*,*R*)-**19**	ee (*S*,*S*)-**18**	cv[b]	E[b]
1	3.50	*PCL-IV*	**19a**	toluene	46%	56%	70%	2.3
2	1.00	*CAL-B-I*	**19a**	toluene	86%	38%	57%	13
3	3.50	*PLE-III*	**19a**	toluene	7%	53%	17%	2.2
4	1.75	***CAL-B-I***	**19a**	**CH_2Cl_2**	28%	84%	32%	**24**
5	1.75	*CAL-B-I*	**19a**	Et_2O	56%	35%	62%	3.5
6	1.75	*CAL-B-I*	**19a**	pentane	38%	67%	36%	7.3
7	1.75	*CAL-B-I*	**19a**	THF	27%	61%	31%	5.3
8	5.00	*CAL-B-I*	**19b**	CH_2Cl_2	40%	57%	41%	5.3
9	5.00	*CAL-B-I*	**19c**	CH_2Cl_2	12%	64%	16%	5.1
10	1.00	*CAL-B-I*	**19d**	toluene	15%	40%	27%	2.7
11	1.00	*PCL-I*	**19d**	toluene	13%	65%	17%	5.4
12	24.0	*PPL-I*	**19d**	toluene	50%	55%	48%	5.6
13	18.0	***RML-I***	**19d**	**toluene**	37%	72%	34%	**8.8**
14	1.00	*RML-I*	**19d**	CH_2Cl_2	13%	75%	15%	7.9
15	1.00	*RML-I*	**19e**	toluene	<10%	<20%	~15%	< 5
16	3.00	*RML-I*	**19f**	toluene	<10%	<20%	~15%	< 5
17	5.00	*CAL-B-I*	**19g**	toluene	47%[a]	28%[a]	73%	3.6
18	1.00	***CAL-B-I***	**19h**	**toluene**	44%	70%	39%	**8.7**
19	1.00	*CAL-B-I*	**19h**	CH_2Cl_2	12%	17%	41%	1.6
20	1.00	*CAL-B-I*	**19h**	THF	58%	35%	62%	3.5
21	1.00	*CAL-B-I*	**19h**	*t*-BuOMe	92%	11%	89%	3.0
22	1.00	*CAL-B-I*	**19h**	DMF	71%	17%	81%	2.6
23	1.00	*CAL-B-I*	**19h**	DMSO	56%	19%	75%	2.4
24	1.00	*CAL-B-I*	**19h**	MeCN	96%	10%	91%	3.3
25	1.00	*CAL-B-I*	**19h**	dioxane	80%	20%	80%	3.2
26	0.60	*PCL-I*	**19j**	toluene	65%	86%	43%	25
27	1.50	*CAL-B-I*	**19j**	toluene	71%	57%	57%	8.1
28	3.00	*CRL-I*	**19j**	toluene	57%	32%	64%	3.3
29	1.50	*PPL-I*	**19j**	toluene	95%	81%	54%	34
30	1.50	*ASL-I*	**19j**	toluene	82%	93%	53%	33
31	1.50	*CAL-B-I*	**19j**	Et_2O	90%	36%	71%	6
32	1.50	*CAL-B-I*	**19j**	DME	67%	85%	44%	24
33	1.50	*CAL-B-I*	**19j**	CH_2Cl_2	37%	88%	30%	22
34	1.50	*CAL-B-I*	**19j**	DMF	56%	87%	39%	25
35	1.50	*PCL-I*	**19j**	Et_2O	30%	73%	29%	9
36	1.50	***PCL-I***	**19j**	**dioxane**	72%	92%	44%	**52**
37	1.50	*PCL-I*	**19j**	DME	20%	80%	20%	10
38	5.00	*PPL-I*	**19j**	heptane	>99%	34%	75%	12
39	5.00	*PPL-I*	**19j**	Et_2O	>99%	67%	60%	35
40	5.00	*PPL-I*	**19j**	DMSO	25%	93%	21%	35
41	7.00	*ASL-I*	**19j**	Et_2O	68%	87%	44%	29
42	7.00	*ASL-I*	**19j**	DMSO	63%	80%	44%	17

Scheme 4. Kinetic enzymatic resolution of cyclopropylmethyl esters **19** – selective hydrolyses.[50]
[a] Configuration deduced (by analogy).
[b] Calculated values.[27]
[c] sm = starting material: see Schemes 1 and 2.

(Figure 4). We found a slightly decreased E value that is of no consequence (E = 20), however, there are a number of important observations to be reported:

a) The observed data are in excellent agreement with the theoretical values for the enantioselectivity factor.
b) At no time during the enzymatic hydrolyses is an enantiomerically pure product formed.
c) As a matter of fact, it is only possible to recover enantiomerically pure substrate after approx. 65% conversion.

In other words: The maximum yield of pure **19a** would be 35%. This is the obvious problem especially for

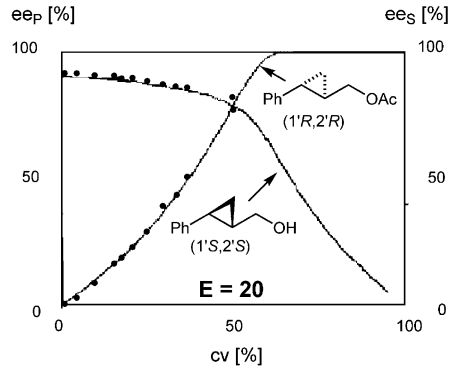
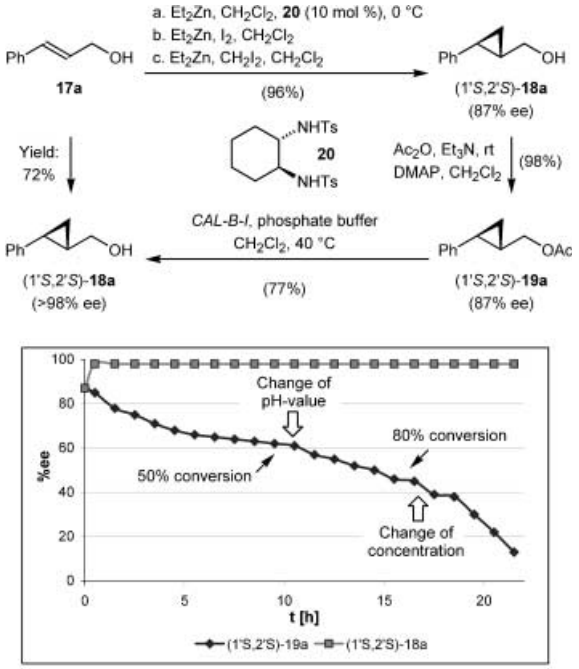


Figure 4. Enantiomeric excess as a function of conversion. Conditions: see entry 4, Scheme 4.

cyclopropane derivatives, since in these cases no re-racemization is possible.

To overcome the problem of low overall yields, an alternative approach was followed (Scheme 5): while the enantiomeric excess of enantioselective catalytic cyclopropanations of cinnamyl alcohol (**17a**) in the presence of bissulfonamide **20** did not exceed 87%, the yield for the transformation according to the Denmark protocol was high (96%).[57] The combination of both processes led to the successful synthesis of enantiomerically pure cyclopropane (1′*S*,2′*S*)-**18a**, a starting material that was just recently used for the total synthesis of the marine oxylipins constanolactone A and B.[58] After the high yielding acetylation (98%), the enantiomerically enriched (1′*S*,2′*S*)-**19a** was subjected to the typical conditions of the kinetic resolution. The reaction was followed by regularly analyzing samples by HPLC. It was important to verify that the enantiomeric excess of the product would always be >98% ee. The pure product (1′*S*,2′*S*)-**18a** was isolated in 77% yield or 72% starting from alcohol **17a**. It is interesting to note that a slightly different protocol for the enzymatic process needed to be followed, since the usual buffer capacity is ideal only for 50% conversion, hence the rate of the reaction decreased under these conditions. It was important to adjust the pH value. At about 80% conversion hardly any transformation could be observed. It was assumed that the substrate concentration was too low for a reasonable rate. Consequently the concentration was increased by slowly distilling the solvent off.

The same concept was successfully applied for the synthesis of enantiomerically pure (1′*S*,2′*S*)-**18j** (Figure 5). The corresponding enriched starting material (1′*S*,2′*S*)-**19j** was synthesized according to the previously described sequence from (1′*S*,2′*S*)-**18a** (87% ee) (see Scheme 2). The enantiomeric products (1′*R*,2′*R*)-**19a** and (1′*R*,2′*R*)-**19j** were synthesized accordingly in 74% and 82% yields, respectively. In these cases the minor enantiomer needed to react predominantly and the starting material was retained in enantiomerically pure



Scheme 5. Enantiomerically pure cyclopropylmethanol (1′*S*,2′*S*)-**18a**.

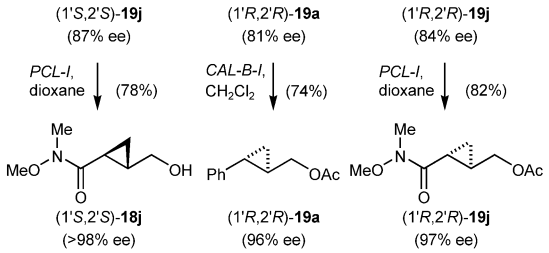
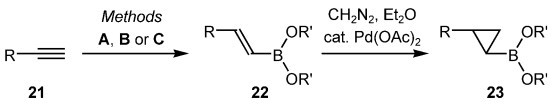


Figure 5. Cyclopropylmethanols (1′*R*,2′*R*)-**18a**, (1′*S*,2′*S*)-**18j** and (1′*R*,2′*R*)-**18j**. Conditions: 40 °C, phosphate buffer.

form (within the experimental error). Obviously, the second process was considerable faster (approx. by a factor of 2), because less substrate needed to be converted. Summing up, for all enantiomers, either alcohols **18a**/**18j** or the corresponding acetates **19a/19j**, a practical approach to pure products could be proposed.

Cyclopropanols

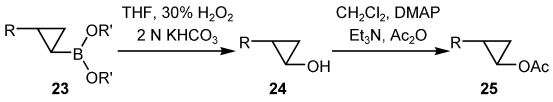
After the primary alcohols **18**, the second group of substrates that we examined were cyclopropanols. The synthesis of the starting materials was established from commercially available alkynes **21** (Scheme 6). First, alkenylboronic esters **22** were synthesized either *via* alkenylboronic acids and consecutive esterification (methods A and B),[59–62] or by direct hydroboration according to Knochel et al.[63] (method C). The overall yields were comparable. The cyclopropanation was



Methods:
A 1. a) $HBBr_2{\cdot}SMe_2$, CH_2Cl_2, 0 °C; b) 10% NaOH; c) sat. NH_4Cl (R' = H); 2. diol, pentane, rt.
B 1. a) Ipc_2BH, THF, -40 °C; b) MeCHO, 0 °C to 40 °C; c) 10% NaOH; 2. diol, pentane, rt.
C pinacolborane, CH_2Cl_2, rt.

Entry	R	Method	'Diol'	Yield **22**	Yield **23**
1	*n*-Pe		R' = H (1.)	78% (**a**)	
2	*n*-Pe	**A**	1,3-propanediol	83% (**b**)	70% (**b**)
3	*n*-Pe		pinacol	70% (**c**)	
4	*n*-Pe	**C**	pinacol	50% (**c**)	83% (**c**)
5	*t*-Bu		R' = H (1.)	63% (**d**)	
6	*t*-Bu	**A**	1,3-propanediol	82% (**e**)	35% (**e**)
7	*t*-Bu		pinacol	84% (**f**)	45% (**f**)
8	Ph		R' = H (1.)	83% (**g**)	
9	Ph	**B**	1,3-propanediol	80% (**h**)	78% (**h**)
10	Ph		pinacol	80% (**i**)	
11	Ph	**C**	pinacol	58% (**i**)	80% (**i**)

Scheme 6. Synthesis of cyclopropylboronic esters **23**.

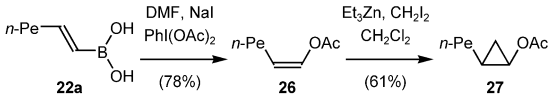


R	sm	Yield **24**	Yield **25**
n-Pe	**23b**	75% (**a**)	76% (**a**)
n-Pe	**23c**	70% (**a**)	
t-Bu	**23e**	'quant' (**b**)	88% (**b**)
t-Bu	**23f**	'quant' (**b**)	
Ph	**23h**	73% (**c**)	69% (**c**)
Ph	**23i**	42% (**c**)	

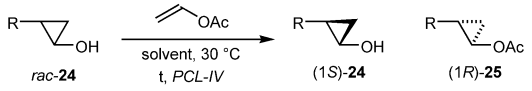
Scheme 7. Synthesis of cyclopropanols **24** and **25**.

most conveniently performed by using diazomethane in the presence of catalytic amounts of $Pd(OAc)_2$.[64,65] The conversion is usually high, however, in order to obtain pure cyclopropylboronic esters **23**, some loss during work-up was acceptable. Oxidation to cyclopropanols **24** and acetylation to **25** using standard conditions was unproblematic (Scheme 7), nevertheless, some loss of material during distillation was observed. The yields were not optimized.

As a single example for a *cis*-1,2-disubstituted cyclopropane, the ester **27** was synthesized (Scheme 8). *E*-Alkenylboronic acid **22a** served as the suitable starting material. Following a procedure of Masuda et al.,[66] the acid was converted in a highly selective manner to the *Z*-enol acetate **26**. Cyclopropanation applying the Furukawa conditions[43–45] furnished the target compound **27** in 61% yield. We also established the analytical tool for *cis*- as well as all *trans*-cyclopropanols **25/28**,[50] correlating the absolute configuration *via* known enantiomerically pure or enriched reference compounds.[67,68]



Scheme 8. Synthesis of cyclopropyl acetates **27**.

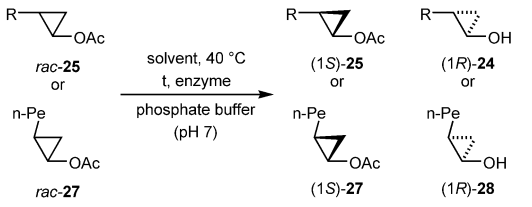


Entry	t [h]	Solvent	R	ee (1*S*)-**24**	ee (1*R*)-**25**	cv[a]	E[a]
1	1.00	pentane	*n*-Pe (**a**)	80%	39%	67%	5.2
2	14.0	CH_2Cl_2	*n*-Pe (**a**)	66%	69%	49%	10
3	2.00	pentane	Ph (**c**)	83%	55%	60%	8.6

Scheme 9. Kinetic enzymatic resolution of cyclopropanols **24**.[50]
[a] Calculated values.[27]

Again, we started by investigating the enzymatic acetylation of cyclopropanols **24** with vinyl acetate (Scheme 9). While we observed a relatively high rate for the secondary alcohols in pentane (entries 1 + 3), even in the best cases only moderate selectivities were observed. As expected, the rate was considerable lower in dichloromethane (entry 2). The lipase of *Pseudomonas cepacia* (*PCL-IV*) gave the highest E values (**24a**: E = 10; **24c**: E = 8.6), however, after our experience with the cyclopropylmethanols **18** it was apparent that better results could be expected for the selective hydrolysis. We did not fully optimize the results for the substrates, because no really practical access to enantiomerically pure cyclopropanol **24** was feasible.

Hydrolysis of esters *rac*-**25**/*rac*-**27** was performed in a two-phase system of an organic solvent and a phosphate buffer on an analytical scale (Scheme 10). Surprisingly low rates were observed at 40 °C even when using toluene as solvent. Enantioselectivities and conversions were usually low after 16 h, hence the data are not expressive. Two exceptions were the phenyl derivative **25c** and the *cis*-pentylcyclopropyne **27**: with different lipases moderate selectivities were observed (**25c**: E = 21, *RML-I* – entry 12; **27**: E = 8.6, *ASL-I* – entry 17). Obviously, the *cis*-derivative **27** was hydrolyzed considerable faster (to **28**) than the *trans*-analogue **25a** (**24a**). Since all transformations were relatively slow, an increase of reaction temperature was tried. While some enzymes denature under these conditions, we found that the immobilized *CAL-B-I* gave satisfactory results in THF. For both *n*-pentyl-derivatives **25a/27** (entries 5/18) good conversions were observed, however, surprisingly only the *trans*-cyclopropane **25a** gave excellent enantioselectivities. The high E value of E = 44 indicated that the resolution might be performed on a preparative scale: Starting material **25a** (87% ee, 42%) and product **24a** (87% ee, 44%) were isolated in good yield; the E value was insignificantly lower (E = 40; 48% conversion). Although the yields were relatively high, they do not (and could not) exceed 50%; only enantiomerically enriched material was isolated. For this reason we followed a similar approach as described for cyclopropylmethanols **18a/j**. Instead of starting from racemic acetate *rac*-**25a**, we decided to use enantiomerically enriched starting material (1*R*)-**24a** that was readily available from enantiomerically pure alkenylboronic ester **29** *via* a diastereoselective cyclopropanation-oxidation sequence (Scheme 11).[69] A moderate (though improved) enantiomeric excess of the product was observed, but the material was available in high yield (92%; 75% ee).[70,71] Acylation and enzymatic resolution gave the enantiomerically pure (within the experimental error) cyclopropanol (1*R*)-**24a**; slightly impure product was obtained in 73%.

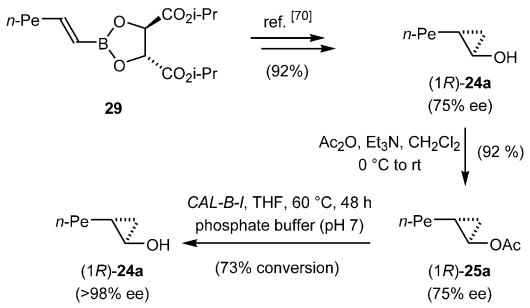


Entry	t [h]	Enzyme	sm[a]	Solvent	ee (1*S*)-**25**	ee (1*R*)-**24**	cv[b]	E[b]
1	16.0	*CRL-I*	**25a**	toluene	5%	38%	12%	2.3
2	16.0	*CAL-A-I*	**25a**	toluene	1%	8%	11%	1.2
3	16.0	*RML-I*	**25a**	toluene	3%	25%	11%	1.7
4	16.0	*ASL-I*	**25a**	toluene	2%	16%	11%	1.4
5	168	***CAL-B-I***	**25a**	**THF (60 °C)**	93%	86%	52%	**44**
6	16.0	*PCL-III*	**25b**	toluene	5%	32%	14%	2.0
7	16.0	*CAL-B-II*	**25b**	toluene	14%	32%	30%	2.2
8	16.0	*RML-I*	**25b**	toluene	4%	32%	11%	2.0
9	16.0	*PCL-III*	**25c**	toluene	42%	84%	67%	6.0
10	16.0	*CRL-I*	**25c**	toluene	9%	49%	16%	3.2
11	16.0	*PPL-I*	**25c**	toluene	10%	58%	15%	4.1
12	16.0	***RML-I***	**25c**	**toluene**	55%	85%	39%	**21**
13	16.0	*ASL-I*	**25c**	toluene	10%	45%	18%	2.9
14	16.0	*PCL-I*	**25c**	toluene	29%	87%	75%	4.5
15	24.0	*PCL-I*	**27**	toluene	37%	84%	31%	16
16	24.0	*CAL-B-II*	**27**	toluene	99%	48%	68%	18
17	24.0	***ASL-I***	**27**	**toluene**	99%	49%	67%	**19**
18	24.0	*CAL-B-I*	**27**	THF (60 °C)	71%	66%	52%	10

Scheme 10. Kinetic enzymatic resolution of cyclopropylmethyl acetates **25** – selective hydrolyses.[50]
[a] sm: starting material (*rac*-**25**).
[b] Calculated values.[27]

Conclusion

Generally speaking, apart from a few examples in the literature, our investigation showed that cyclopropanes are difficult substrates for kinetic enzymatic resolutions, the selectivity often being low. It is a major drawback that every individual example needs to be optimized and that one common procedure cannot be devised. Nevertheless, a number of important results were obtained. First, best selectivities were always found for the enzymatic hydrolysis. Second, compared to the higher



Scheme 11. Enantiomerically pure cyclopropylmethanol (1*R*)-**24a**.

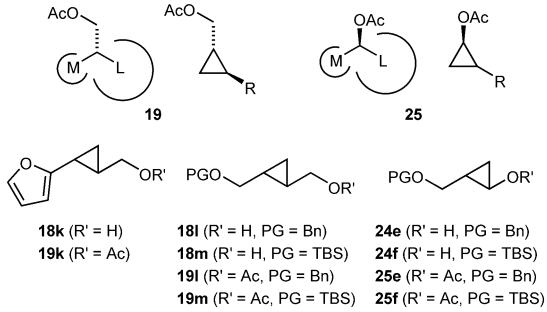


Figure 6. Top: Empirical model for the preferred hydrolyses of primary and secondary esters. Below: Not suitable substrates for kinetic enzymatic resolutions (PG: protecting group; Bn = benzyl, TBS = *t*-BuMe_2Si).

homologues, the simple acetates gave superior results. No clear-cut statements are possible on the steric or electronic requirements for successful separations of cyclopropanes. It is not clear why some compounds, e.g., **24f** and **25f** were in our hands bad substrates. In addition, we found that in several cases the enantiomers (e.g., **18k–m**, **19k–m**, **24e** and **25e**) could not be separated with the available tools. Nevertheless, it is important to note that for all investigated cyclopropane derivatives we observed that the results fit very well with the empirical model for preferred hydrolyses of esters to primary[72] (for *PCL*) or secondary[73] (for *CRL*) alcohols proposed by Kazlauskas et al. (Figure 6). This might serve as an important tool for the prediction of the absolute configuration of unknown cyclopropanes in the future. In addition, we proposed a practical approach to enantiomerically pure cyclopropanes by a combination of enantioselective catalytic or diastereoselective (with labile intermediates) cyclopropanations with enzymatic resolutions.

Experimental Section

General Remarks

All reagents were used as purchased from commercial suppliers without further purification. Enzymes were donations from Roche Diagnostics GmbH, Amano Pharmaceuticals Co., Ltd., and Meito Sangyo Co., Ltd. The following compounds were prepared according to the references given: allyl alcohol **17h**,[74] enantiomerically enriched cyclopropylmethanols **18a, d, g, h**,[57] bissulfonamide **20**,[75] alkyne **21d** (*t*-Bu),[76] alkenylboronic esters **22**[59–63] (known compounds: **22b**,[65] **22h**,[77] and **22i**[63]), cyclopropylboronic esters **23** (known compounds: **23b**[65] and **23h**[77]), cyclopropanols **24** (known compounds **24a**[70] and **24c**[69]), and vinyl acetate **26**.[66] The reactions on a preparative scale were carried out using standard Schlenk techniques under a dry nitrogen atmosphere. Glassware was oven-dried at 150 °C overnight. Solvents were dried and purified by conventional methods prior to use; diethyl ether (Et_2O), 1,2-dimethoxyethane (DME), and tetrahydrofuran (THF) were freshly distilled from sodium/benzophenone. Petroleum ether refers to the fraction with a boiling point between 40–60 °C. Analysis of enantiomeric composition was performed as described in "Supporting Information". Caution: The generation and handling of diazomethane[78–81] requires special precautions.

Flash-column chromatography: *Merck* silica gel 60, 0.040–0.063 mm (230–400 mesh). TLC: Pre-coated sheets, Alugram SIL G/UV_{254} Macherey-Nagel; detection by UV extinction or by cerium molybdenum solution [phosphomolybdic acid (25 g), $Ce(SO_4)_2 \cdot H_2O$ (10 g), conc. H_2SO_4 (60 mL), H_2O (940 mL)]. Preparative MPLC: Gilson (Spectrochrom), with a packed column (49 × 500 mm), LiChroprep, Si60 (15–25 μm), and UV detector (254 nm). ^1H and ^{13}C NMR spectra were recorded – at room temperature in $CDCl_3$ unless otherwise indicated – on a Bruker ARX 500/300. Chemical shifts δ are given in ppm relative to resonances of the solvent (^1H: $CDCl_3$, 7.25 ppm; ^{13}C: $CDCl_3$, 77.0 ppm), coupling constants *J* are given in Hertz; in spectra of higher order δ and *J* values were not corrected. ^{13}C signals were assigned by means of C-H- and H-H-COSY spectra. Microanalysis were performed at the Institut für Organische Chemie, Stuttgart. Melting points (Büchi 510) were not corrected. Specific rotations were measured at 20 °C unless otherwise stated; $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}.

General Procedure for the Synthesis of Cyclopropylmethanols 18

Under an atmosphere of dry nitrogen, allyl alcohol **17** (1.00 equiv.) in dry CH_2Cl_2 (0.33 M) was treated with Et_2Zn (1.25 equivs. of a 1 M solution in hexane) at 0 °C. The suspension was stirred for 30 min. In a second flask, Et_2Zn (1.25 equivs. of a 1 M solution in hexane) was added to CH_2I_2 (2.00 equivs.) in dry CH_2Cl_2 (0.17 M) and stirred for 30 min at 0 °C. The contents of the first flask were transferred into the second flask at 0 °C and the mixture stirred at room temperature until the olefin was completely consumed. The mixture was hydrolyzed with aqueous saturated NH_4Cl solution (11.5 mL/mmol **17**); when an emulsion formed, a minimum amount of 2 N HCl in water was added. The organic layer was separated, and the

aqueous layer extracted with CH_2Cl_2. The combined organic fractions were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Purification of the crude product was achieved either by Kugelrohr distillation or flash column chromatography.

18a: 2.68 g (20.0 mmol) of cinnamyl alcohol (**17a**) was cyclopropanated; after Kugelrohr distillation (80 °C/0.5 Torr) the product **18a** was isolated as a colorless oil; yield: 2.85 g (19.2 mmol, 96%). IR (film): $\tilde{\nu}$ = 3288 (OH), 3026, 2924, 1604, 1497, 1461, 1159, 1091, 1020, 744, 697 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 148 (40) [M$^+$], 130 (20) [M – H_2O^+], 117 (100) [M – CH_3O^+], 104 (40), 91 (30) [$C_7H_7^+$]; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.94 (m, 2H, 3′-H), 1.44 (ddddd, $^3J_{1',3'}$ = 8.4 Hz, $^3J_{1',1a}$ = 7.0 Hz, $^3J_{1',1b}$ = 6.8 Hz, $^3J_{1',3'}$ = 5.7 Hz, $^3J_{1',2'}$ = 4.6 Hz, 1H, 1′-H), 1.80 (ddd, $^3J_{2',3'b}$ = 8.7 Hz, $^3J_{2',1'}$ = 4.6 Hz, $^3J_{2',3'}$ = 4.6 Hz, 1H, 2′-H), 1.99 (b, 1H, OH), 3.60 (m_c, 2H, 1-H), 7.06 (dd, $^3J_{o,m}$ = 8.1 Hz, $^4J_{o,p}$ = 1.3 Hz, 2H, *o*-H), 7.15 (tt, $^3J_{p,m}$ = 7.4 Hz, $^4J_{p,o}$ = 1.3 Hz, 1H, *p*-H), 7.25 (ddd, $^3J_{m,o}$ = 8.1 Hz, $^3J_{m,p}$ = 7.4 Hz, $^4J_{m,m}$ = 1.9 Hz, 2H, *m*-H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.8 (C-3′), 21.2 (C-2′), 25.2 (C-1′), 66.5 (C-1), 125.6 (*p*-C), 125.8 (2 C, *o*-C), 128.3 (2 C, *m*-C), 142.4 (*i*-C); anal. calcd. for $C_{10}H_{12}O$ (148.20 g/mol): C 81.04, H 8.16; found: C 81.03, H 8.21.

18d: 1.44 g (20.0 mmol) of **17d** was cyclopropanated; after chromatographic separation (pentane/Et_2O, 4:3) the product **18d** was isolated as a colorless oil; yield: 1.41 g (16.4 mmol, 82%). IR (film): $\tilde{\nu}$ = 3334 (OH), 3065, 3000, 2952, 2869, 1453, 1413, 1381, 1153, 1064, 1011, 894, 865, 796, 764 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.27 (ddd, $^3J_{3'a,2'}$ = 8.1 Hz, $^3J_{3'a,1'}$ = 4.8 Hz, $^2J_{3'a,3'b}$ = 4.7 Hz, 1H, 3′-H_a), 0.37 (ddd, $^3J_{3'b,1'}$ = 8.4 Hz, $^3J_{3'b,2'}$ = 4.8 Hz, $^2J_{3'b,3'a}$ = 4.7 Hz, 1H, 3′-H_b), 0.64 (dqdd, $^3J_{2',3'b}$ = 8.4 Hz, $^3J_{2',CH_3}$ = 6.0 Hz, $^3J_{2',3'a}$ = 4.8 Hz, $^3J_{2',1'}$ = 4.5 Hz, 1H, 2′-H), 0.82 (ddddd, $^3J_{1',3'a}$ = 8.1 Hz, $^3J_{1',1b}$ = 7.1 Hz, $^3J_{1',1a}$ = 7.1 Hz, $^3J_{1',3'b}$ = 4.8 Hz, $^3J_{1',2'}$ = 4.5 Hz, 1H, 1′-H), 1.06 (d, $^3J_{CH_3,2'}$ = 6.0 Hz, 3 H, CH_3), 1.54 (bs, 1H, OH), 3.41 (dd, $^2J_{1a,1b}$ = 11.2 Hz, $^3J_{1a,1'}$ = 7.1 Hz, 1H, 1-H_a), 3.46 (dd, $^2J_{1b,1a}$ = 11.2 Hz, $^3J_{1b,1'}$ = 7.1 Hz, 1H, 1-H_b); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 11.1 (C-3′), 11.2 (C-2′), 18.5 (C-1′), 22.3 (CH_3), 67.2 (C-1); anal. calcd. for $C_5H_{10}O$ (86.13 g/mol): C 69.72, H 11.70; found: C 67.08, H 11.43.

18g: 600 μL (4.00 mmol) of **17g** was cyclopropanated; after chromatographic separation (petroleum ether/ethyl acetate, 96:4 to 87:13) the product **18g** was isolated as a colorless oil; yield: 0.53 g (3.72 mmol, 93%). IR (film): $\tilde{\nu}$ = 3334 (OH), 3064, 2996, 2956, 2923, 2854, 1459, 1378, 1246, 1153, 1031, 903, 875, 724 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ = 0.30 (ddd, $^3J_{3'a,1'}$ = 8.2 Hz, $^3J_{3'a,2'}$ = 5.2 Hz, $^2J_{3'a,3'b}$ = 4.8 Hz, 1H, 3′-H_a), 0.36 (ddd, $^3J_{3'b,2'}$ = 8.4 Hz, $^3J_{3'b,1'}$ = 4.7 Hz, $^2J_{3'b,3'a}$ = 4.7 Hz, 1H, 3′-H_b), 0.60 (dtddd, $^3J_{2',3'b}$ = 8.4 Hz, $^3J_{2',1''}$ = 6.9 Hz, $^3J_{2',3'a}$ = 5.2 Hz, $^3J_{2',1'}$ = 4.2 Hz, 1H, 2′-H), 0.85 (m, 1H, 1′-H), 0.86 (t, $^3J_{5'',4''}$ = 7.1 Hz, 3H, 5″-H), 1.20 – 1.41 (m, 9H, 1″-H, 2″-H, 3″-H, 4″-H, O*H*), 3.42 (dd, $^2J_{1a,1b}$ = 11.1 Hz, $^3J_{1a,1'}$ = 7.1 Hz, 1H, 1-H_a), 3.46 (dd, $^2J_{1b,1a}$ = 11.1 Hz, $^3J_{1b,1'}$ = 7.1 Hz, 1H, 1-H_b); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 9.9 (C-3′), 14.1 (C-5″), 17.2 (C-1′), 21.2 (C-2′), 22.7 (C-4″), 29.3 (C-2″), 31.7 (C-3″), 33.6 (C-1″), 67.3 (C-1); anal. calcd. for $C_5H_{10}O$ (142.24 g/mol): C 76.00, H 12.76; found: C 75.62, H 12.72.

18h: 0.82 g (5.00 mmol) of **17h** was cyclopropanated; after chromatographic separation (petroleum ether/ethyl acetate, 9:1 to 3:1) the product **18h** was isolated as a colorless oil; yield: 0.52 g (2.90 mmol, 58%). IR (film): $\tilde{\nu}$ = 3363 (OH), 3000, 2935, 2835, 1613, 1582, 1515, 1463, 1293, 1246, 1179, 1113, 1079, 1036, 828 cm^{-1};. MS (EI, 70 eV): *m/z* (%) = 178 (30) [M$^+$], 160 (10) [M – H_2O^+], 147 (100) [M – CH_3O^+], 121 (20), 91 (25) [$C_7H_7^+$], 77 (10) [$C_6H_5^+$]; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.87 (ddd, $^3J_{3'a,2'}$ = 8.8 Hz, $^3J_{3'a,1'}$ = 5.6 Hz, $^2J_{3'a,3'b}$ = 5.1 Hz, 1H, 3′-H_a), 0.87 (ddd, $^3J_{3'b,1'}$ = 8.2 Hz, $^3J_{3'b,2'}$ = 5.4 Hz, $^2J_{3'b,3'a}$ = 5.1 Hz, 1H, 3′-H_b), 1.37 (ddddd, $^3J_{1',3'b}$ = 8.2 Hz, $^3J_{1',1a}$ = 6.8 Hz, $^3J_{1',1b}$ = 6.8 Hz, $^3J_{1',3'a}$ = 5.6 Hz, $^3J_{1',2'}$ = 4.5 HZ, 1H, 1′-H), 1.57 (t, $^3J_{OH,1}$ = 5.0 Hz, 1H, O*H*), 1.78 (ddd, $^3J_{2',3'a}$ = 8.8 Hz, $^3J_{2',3'b}$ = 5.4 Hz, $^3J_{2',1'}$ = 4.5 Hz, 1H, 2′-H), 3.59 (dd, $^2J_{1a,1b}$ = 9.5 Hz, $^3J_{1a,1'}$ = 6.8 Hz, 1H, 1-H_a), 3.60 (dd, $^2J_{1b,1a}$ = 9.5 Hz, $^3J_{1b,1'}$ = 6.8 Hz, 1H, 1-H_b), 3.77 (s, 3H, OCH_3), 6.81 (d, $^3J_{m,o}$ = 8.7 Hz, 2H, *m*-H), 7.00 (d, $^3J_{o,m}$ = 8.7 Hz, 2H, *o*-H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.3 (C-3′), 20.6 (C-2′), 24.8 (C-1′), 55.3 (OCH_3), 66.6 (C-1), 113.8 (2C, *m*-C), 127.0 (2C, *o*-C), 134.4 (*i*-C), 157.8 (*p*-C); anal. calcd. For $C_{11}H_{14}O_2$ (178.23 g/mol): C 74.13, H 7.92; found: C 73.54, H 8.08.

General Procedure for the Synthesis of Cyclopropyl acetates 19

A solution of alcohol **18** (1 equiv.) in CH_2Cl_2 (1 M) was treated with Ac_2O (3 equivs.), Et_3N (3 equivs.), and 4-dimethylaminopyridine (0.1 equivs.) at 0 °C. The mixture was allowed to warm up to room temperature and was stirred until TLC indicated complete consumption of the starting material. The reaction was quenched with saturated aqueous NH_4Cl solution (11.5 mL/mmol **18**), the organic layer separated, and the aqueous layer extracted with CH_2Cl_2. The combined organic fractions were washed with saturated aqueous bicarbonate solution and brine, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Purification of the crude product was achieved either by distillation or flash column chromatography.

19a: 2.80 g (18.9 mmol) of alcohol **18a** was acetylated; after Kugelrohr distillation (80 °C/0.5 Torr) the product **19a** was isolated as a colorless oil; yield: 3.59 g (18.1 mmol, 96%). IR (film): $\tilde{\nu}$ = 3028, 2949, 1740 (C=O), 1605, 1498, 1464, 1376, 1236, 1185, 1094, 1030, 974, 881, 756, 698, 606 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 190 (40) [M$^+$], 149 (15), 130 (100) [M – $C_2H_4O_2^+$], 129 (60), 115 (30), 104 (25) [$C_8H_8^+$], 91 (20) [$C_7H_7^+$], 43 (55) [$C_2H_3O^+$]; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.96 (ddd, $^3J_{3'a,2'}$ = 9.0 Hz, $^3J_{3'a,1'}$ = 5.7 Hz, $^2J_{3'a,3'b}$ = 5.5 Hz, 1H, 3′-H_a), 1.00 (ddd, $^3J_{3'b,1'}$ = 8.4 Hz, $^2J_{3'b,3'a}$ = 5.5 Hz, $^3J_{3'b,2'}$ = 5.3 Hz, 1H, 3′-H_b), 1.46 (ddddd, $^3J_{1',3'b}$ = 8.4 Hz, $^3J_{1',1a}$ = 7.3 Hz, $^3J_{1',1b}$ = 7.0 Hz, $^3J_{1',3'a}$=5.7 Hz, $^3J_{1',2'}$ = 4.6 Hz, 1H, 1′-H), 1.88 (ddd, $^3J_{2',3'a}$ = 9.0 Hz, $^3J_{2',3'b}$ = 5.3 Hz, $^3J_{2',1}$ = 4.6 Hz, 1H, 2′-H), 2.07 (s, 3H, CH_3), 4.04 (dd, $^2J_{1a,1b}$ = 11.5 Hz, $^3J_{1a,1'}$ = 7.3 Hz, 1H, 1-H_a), 4.08 (dd, $^2J_{1b,1a}$ = 11.5 Hz, $^3J_{1b,1'}$ = 7.0 Hz, 1H, 1-H_b), 7.06 – 7.27 (m, 5 H, arom. CH); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.9 (C-3′), 21.0 (C-2′), 21.4 (C-1′), 21.8 (CH_3), 68.0 (C-1), 125.8 (*p*-C), 125.9 (2C, *o*-C), 128.0 (2C, *m*-C), 142.0 (*i*-C), 171.0 ($COCH_3$); anal. calcd. for $C_{12}H_{14}O_2$ (190.24 g/mol): C 75.76, H 7.41; found: C 76.03, H 7.51.

19d: 0.85 g (9.60 mmol) of alcohol **18d** was acetylated; after distillation (bp 111 °C) spectroscopically pure product **19a** was isolated as a colorless liquid; yield: 1.22 g (9.52 mmol, 99%). IR (film): $\tilde{\nu}$ = 3070, 3003, 2955, 2901, 2871, 1741 (C=O), 1454, 1374, 1317, 1238, 1176, 1124, 1069, 1033, 967, 907, 875, 737, 635 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.31 (ddd, $^3J_{3'a,2'}$ = 8.3 Hz, $^3J_{3'a,1'}$ = 5.0 Hz, $^2J_{3'a,3'b}$ = 4.8 Hz, 1H, 3′-H_a), 0.43 (ddd, $^3J_{3'b,1'}$ = 8.8 Hz, $^3J_{3'b,2'}$ = 4.8 Hz, $^2J_{3'b,3'a}$ = 4.8 Hz, 1H, 3′-H_b), 0.68 (dqdd, $^3J_{2',3'b}$ = 8.8 Hz, $^3J_{2',CH_3}$ = 6.0 Hz, $^3J_{2',3'a}$ = 4.8 Hz, $^3J_{2',1'}$ = 4.3 Hz,

1H, 2′-H), 0.83 (ddddd, $^3J_{1',3'a} = 8.3$ Hz, $^3J_{1',1a} = 7.5$ Hz, $^3J_{1',1b} = 7.2$ Hz, $^3J_{1',3'b} = 4.8$ Hz, $^3J_{1',2'} = 4.3$ Hz, 1H, 1′-H), 1.05 (d, $^3J_{CH_3,2'} = 6.0$ Hz, 3H, CH_3), 2.06 (s, 3H, $COCH_3$), 3.86 (dd, $^2J_{1a,1b} = 11.5$ Hz, $^3J_{1a,1'} = 7.5$ Hz, 1H, 1-H_a), 3.93 (dd, $^2J_{1b,1a} = 11.5$ Hz, $^3J_{1b,1'} = 7.2$ Hz, 1H, 1-H_b); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 12.2 (C-3′), 12.4 (C-2′), 18.9 (C-1′), 19.1 ($COCH_3$), 21.9 (CH_3), 69.6 (C-1), 171.3 (C=O).

19g: 0.65 g (4.25 mmol) of alcohol **18g** was acetylated; after chromatographic separation (petroleum ether/ethyl acetate, 100:0 to 99:5) the product **19g** was isolated as a colorless oil; yield: 0.48 g (2.60 mmol, 61%). IR (film): $\tilde{\nu}$ = 3068, 2999, 2957, 2925, 2855, 1742 (C=O), 1460, 1365, 1237, 1030, 968, 885, 725 cm^{-1}; MS (CI, CH_4): *m/z* (%) = 185 (20) [M + H$^+$], 183 (15) [M – H$^+$], 142 (15), 125 (90), 95 (25), 83 (70), 81 (30), 69 (100), 43 (45) [$C_3H_7^+$]; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.30 (ddd, $^3J_{3'a,1'} = 8.2$ Hz, $^3J_{3'a,2'} = 5.0$ Hz, $^2J_{3'a,3'b} = 5.0$ Hz, 1H, 3′-H_a), 0.38 (ddd, $^3J_{3'b,2'} = 8.5$ Hz, $^3J_{3'b,1'} = 4.5$ Hz, $^2J_{3'b,3'a} = 4.5$ Hz, 1H, 3′-H_b), 0.62 (dtddd, $^3J_{2',3'b} = 8.5$ Hz, $^3J_{2',1''} = 6.9$ Hz, $^3J_{2',3'a} = 5.2$ Hz, $^3J_{2',1'} = 4.2$ Hz, 1H, 2′-H), 0.82 (m, 1H, 1′-H), 0.85 (t, $^3J_{5'',4''} = 7.1$ Hz, 3H, 5″-H), 1.09 – 1.35 (m, 8H, 1″-H, 2″-H, 3″-H, 4″-H), 2.03 (s, 3H, $COCH_3$), 3.85 (dd, $^2J_{1a,1b} = 11.4$ Hz, $^3J_{1a,1'} = 7.4$ Hz, 1H, 1-H_a), 3.87 (dd, $^2J_{1b,1a} = 11.4$ Hz, $^3J_{1b,1'} = 7.4$ Hz, 1H, 1-H_b); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 10.4 (C-3′), 14.1 (C-5″), 17.2 (C-1′), 17.6 (C-2′), 21.1 ($COCH_3$), 22.7 (C-4″), 29.1 (C-2″), 31.5 (C-3″), 33.4 (C-1″), 68.9 (C-1), 171.3 ($COCH_3$); anal. calcd. for $C_{11}H_{20}O_2$ (184.28 g/mol): C 71.70, H 10.94; found: C 71.69, H 10.84.

19h: 0.19 g (1.07 mmol) of alcohol **18h** was acetylated; after chromatographic separation (petroleum ether/ethyl acetate, 9:1) the product **19h** was isolated as a colorless oil; yield: 0.21 g (0.95 mmol, 89%); IR (film): $\tilde{\nu}$ = 3000, 2950, 2810, 1738 (C=O), 1613, 1516, 1463, 1375, 1244, 1180, 1034, 829 cm^{-1}; MS (EI, 70 eV): *m/z* (%) =220 (40) [M$^+$], 160 (100) [M – $C_2H_4O_2^+$], 129 (30) [M – $C_7H_7^+$], 91 (30) [$C_7H_7^+$], 43 (55) [$C_3H_7^+$]; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.90 (ddd, $^3J_{3'a,2'} = 8.9$ Hz, $^2J_{3'a,3'b} = 5.5$ Hz, $^3J_{3'a,2'} = 5.3$ Hz, 1H, 3′-H_a), 0.93 (ddd, $^3J_{3'b,1'} = 8.3$ Hz, $^2J_{3'b,3'a} = 5.5$ Hz, $^3J_{3'b,2'} = 5.2$ Hz, 1H, 3′-H_b), 1.39 (ddddd, $^3J_{1',3'b} = 8.3$ Hz, $^3J_{1',1a} = 7.3$ Hz, $^3J_{1',1b} = 7.0$ Hz, $^3J_{1',3'a} = 5.3$ Hz, $^3J_{1',2'} = 4.6$ Hz, 1H, 1′-H), 1.84 (ddd, $^3J_{2',3'a} = 8.9$ Hz, $^3J_{2',3'b} = 5.2$ Hz, $^3J_{2',1'} = 4.6$ Hz, 1H, 2′-H), 2.07 [s, 3H, -C(=O)CH_3], 3.77 (s, 3H, OCH_3), 4.03 (dd, $^2J_{1a,1b} = 11.5$ Hz, $^3J_{1a,1'} = 7.3$ Hz, 1H, 1-H_a), 4.06 (dd, $^2J_{1b,1a} = 11.5$ Hz, $^3J_{1b,2} = 7.0$ Hz, 1H, 1-H_b), 6.81 (d, $^3J_{m,o} = 8.6$ Hz, 2H, *m*-H), 7.00 (d, $^3J_{o,m} = 8.6$ Hz, 2H, *o*-H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.4 (C-3′), 20.9 (C-2′), 21.1 (C-1′), 21.1 [-C(=O)CH_3], 55.3 (OCH_3), 68.1 (C-1), 113.9 (2C, *m*-C), 127.2 (2C, *o*-C), 133.9 (*i*-C), 157.91 (*p*-C), 171.2 [-C(=O)CH_3]; anal. calcd. for $C_{13}H_{16}O_3$ (220.26 g/mol): C 70.89, H 7.32; found: C 70.82, H 7.44.

General Procedure for the Caprylation and Caproylation of Alcohols 18a + d

To a stirred solution of cyclopropylmethanol **18** (1 equiv.) in dry CH_2Cl_2 (0.2 M) was added the required acid chloride (3 equivs.), Et_3N (3 equivs.), and 4-dimethylaminopyridine (0.1 equiv.) at 0 °C. The mixture was allowed to warm up to room temperature and was stirred until TLC indicated complete consumption of the starting material. The reaction was quenched with saturated aqueous NH_4Cl solution (11.5 mL/mmol **17**), the organic layer separated, and the aqueous layer extracted with CH_2Cl_2. The combined organic fractions were washed with saturated aqueous bicarbonate solution and brine, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Purification of the crude product was achieved by flash column chromatography.

19b: 0.30 g (2.02 mmol) of alcohol **18a** was acylated; after chromatographic separation (petroleum ether/ethyl acetate, 95:5) the product **19b** was isolated as a colorless oil; yield: 0.46 g (1.87 mmol, 92%). IR (film): $\tilde{\nu}$ = 3028, 2957, 2872, 1736 (C=O), 1606, 1498, 1465, 1417, 1379, 1244, 1168, 1095, 1032, 994, 878, 746, 698 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 246 (25) [M$^+$], 130 (100) [$C_{10}H_{10}^+$], 115 (15), 99 (45), 77 (< 5) [$C_6H_5^+$], 71 (15) [$C_5H_{11}^+$]; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.88 (t, $^3J_{6,5} = 7.1$ Hz, 3H, 6-H), 0.96 (ddd, $^3J_{3'',1''} = 7.4$ Hz, $^3J_{3''a,2''} = 5.5$ Hz, $^2J_{3''a,3''b} = 5.3$ Hz, 1H, 3″-H_a), 0.99 (ddd, $^3J_{3''b,2''} = 8.8$ Hz, $^3J_{3''b,2''} = 5.6$ Hz, $^2J_{3''b,3''a} = 5.3$ Hz, 1H, 3″-H_b), 1.30 (m, 4H, 5-H, 4-H), 1.49 (ddddd, $^3J_{1'',1'a} = 7.5$ Hz, $^3J_{1'',3''a} = 7.4$ Hz, $^3J_{1'',1'b} = 6.9$ Hz, $^3J_{1'',3''b} = 5.6$ Hz, $^3J_{1'',2''} = 4.4$ Hz, 1H, 1″-H), 1.63 (tt, $^3J_{3,2} = 7.5$ Hz, $^3J_{3,4} = 7.5$ Hz, 2H, 3-H), 1.88 (ddd, $^3J_{2'',3''b} = 8.8$ Hz, $^3J_{2'',3''a} = 5.5$ Hz, $^3J_{2'',1''} = 4.4$ Hz, 1H, 2″-H), 2.31 (t, $^3J_{2,3} = 7.5$ Hz, 2H, 2-H), 4.04 (dd, $^3J_{1'a,1'b} = 11.5$ Hz, $^3J_{1'a,1''} = 7.5$ Hz, 1H, 1′-H_a), 4.09 (dd, $^2J_{1'b,1'a} = 11.5$ Hz, $^3J_{1'b,1''} = 6.9$ Hz, 1H, 1′-H_b), 7.03 – 7.29 (m, 5H, arom. H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 14.2 (C-3″), 14.3 (C-6), 22.0 (C-1″), 22.3 (C-2″), 22.8 (C-5), 25.2 (C-3), 31.8 (C-4), 34.8 (C-2), 68.1 (C-1′), 126.1 (*p*-C), 126.3 (2C, *o*-C), 128.7 (2C, *m*-C), 142.4 (*i*-C), 174.3 (C-1); anal. calcd. for $C_{16}H_{22}O_2$ (246.34 g/mol): C 78.01, H 9.00; found: C 77.84, H 9.03.

19c: 0.30 g (2.02 mmol) of alcohol **18a** was acylated; after chromatographic separation (petroleum ether/ethyl acetate, 9:1 to 3:1) the product **19c** was isolated as a colorless oil; yield: 0.49 g (1.79 mmol, 88%). IR (film): $\tilde{\nu}$ = 2929, 2856, 1736 (C=O), 1606, 1498, 1465, 1379, 1163, 1107, 1032, 980, 746, 697 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 274 [M$^+$] (20), 130 (100), 91 [$C_7H_7^+$] (20), 57 [$C_4H_9^+$] (35); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.87 (t, $^3J_{8,7} = 7.1$ Hz, 3H, 6-H), 0.96 (ddd, $^3J_{3''a,1''} = 8.8$ Hz, $^3J_{3''a,2''} = 5.3$ Hz, $^2J_{3''a,3''b} = 5.3$ Hz, 1H, 3″-H_a), 1.00 (ddd, $^3J_{3''b,2''} = 8.4$ Hz, $^3J_{3''b,2''} = 5.6$ Hz, $^2J_{3''b,3''a} = 5.3$ Hz, 1H, 3″-H_b), 1.22 – 1.32 (m, 8H, 7-H, 6-H, 5-H, 4-H), 1.47 (ddddd, $^3J_{1'',1'a} = 7.5$ Hz, $^3J_{1'',3''a} = 7.4$ Hz, $^3J_{1'',1'b} = 6.9$ Hz, $^3J_{1'',3''b} = 5.6$ Hz, $^3J_{1'',2''} = 4.4$ Hz, 1H, 1″-H), 1.62 (tt, $^3J_{3,2} = 7.6$ Hz, $^3J_{3,4} = 7.6$ Hz, 2H, 3-H), 1.88 (ddd, $^3J_{2'',3''b} = 8.8$ Hz, $^3J_{2'',3''a} = 5.5$ Hz, $^3J_{2'',1''} = 4.4$ Hz, ddd, 1H, 2″-H), 2.32 (t, $^3J_{2,3} = 7.5$ Hz, 2H, 2-H), 4.04 (dd, $^3J_{1'a,1'b} = 11.5$ Hz, $^3J_{1'a,1''} = 7.3$ Hz, 1H, 1′-H_a), 4.09 (dd, $^2J_{1'b,1'a} = 11.5$ Hz, $^3J_{1'b,1''} = 6.9$ Hz, 1H, 1′-H_b), 7.03 – 7.29 (m, 5H, arom. H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.9 (C-3″), 14.1 (C-8), 21.5 (C-1″), 21.8 (C-2″), 22.6 (C-7), 25.0 (C-3), 28.9 (C-4), 29.1 (C-5), 31.6 (C-6), 34.4 (C-2), 67.7 (C-1′), 125.7 (*p*-C), 125.9 (2C, *o*-C), 128.3 (2C, *m*-C), 142.0 (*i*-C), 174.0 (C-1); anal. calcd. for $C_{16}H_{22}O_2$ (274.40 g/mol): C 78.79, H 9.55; found: C 78.84, H 9.62.

19e: 0.16 g (1.80 mmol) of alcohol **18d** was acylated; after chromatographic separation (petroleum ether/ethyl acetate, 97.5:2.5) the spectroscopically product **19e** was isolated as a colorless oil; yield: 0.24 g (1.30 mmol, 72%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.29 (ddd, ^3J = 8.3 Hz, ^3J = 4.9 Hz, ^2J = 4.8 Hz, 1H, 3″-H_a), 0.42 (ddd, ^3J = 8.4 Hz, ^3J = 4.8 Hz, ^2J = 4.8 Hz, 1H, 3″-H_b), 0.68 (m, 1H, 1″-H), 0.84 (m, 1H, 2″-H), 0.9 (t, $^3J_{6,5} = 7.1$ Hz, 3H, 6-H), 1.05 (d, $^3J_{CH_3,2''} = 5.9$ Hz, 3H, CH_3), 1.27 – 1.36 (m, 4H, 4-H, 5-H), 1.63 (m, 2H, 3-H), 2.31 (t, $^3J_{2,3} = 7.6$ Hz, 2H, 2-H), 3.87 (dd, $^2J_{1'a,1'b} = 11.4$ Hz, $^3J_{1'a,1''} = 7.3$ Hz, 1H, 1′-H_a), 3.92 (dd, $^2J_{1'b,1'a} = 11.4$ Hz, $^3J_{1'b,1''} = 7.3$ Hz, 1H, 1′-H_b); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 11.6, 11.7, 14.0, 18.3, 18.4, 22.4, 24.8, 31.3, 34.0, 68.5 (C-1′), 174.1 (C-1).

19f: 160 mg (1.80 mmol) of alcohol **18d** was acylated; after chromatographic separation (petroleum ether/ethyl acetate, 9:1 to 3:1) the spectroscopically product **19f** was isolated as a colorless oil; yield: 0.35 g (1.65 mmol, 97%). IR (film): $\tilde{\nu}$ = 2954, 2926, 2857, 1734 (C=O), 1496, 1455, 1375, 1163, 1106, 1069, 1030, 1004, 875, 736, 696 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 212 [M$^+$] (10), 127 [$C_8H_{15}O^+$] (100), 69 [$C_5H_9^+$] (35); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.30 (ddd, ^3J = 8.3 Hz, ^3J = 5.0 Hz, $^2J_{3''a,3''b}$ = 4.9 Hz, 1H, 3''-H$_a$), 0.42 (ddd, ^3J = 8.4 Hz, ^3J = 5.0 Hz, $^2J_{3''b,3''a}$ = 4.9 Hz, 1H, 3''-H$_b$), 0.68 (m, 1H, 1''-H), 0.82 (m, 1H, 2''-H), 0.88 (t, $^3J_{8,7}$ = 6.9 Hz, 3H, 8-H), 1.05 (d, $^3J_{CH_3,2''}$ = 5.7 Hz, 3H, C*H*$_3$), 1.25 – 1.33 (m, 8H, 4-H, 5-H, 6-H, 7-H), 1.63 (m, 2H, 3-H), 2.31 (t, $^3J_{2,3}$ = 7.5 Hz, 2H, 2-H), 3.86 (dd, $^2J_{1'a,1'b}$ = 11.4 Hz, $^3J_{1'a,1''}$ = 7.2 Hz, 1H, 1'-H$_a$), 3.93 (dd, $^2J_{1'b,1'a}$ = 11.4 Hz, $^3J_{1'b,1''}$ = 7.2 Hz, 1H, 1'-H$_b$); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 11.5, 11.6, 14.1, 18.3, 18.4, 22.6, 25.1, 28.9, 29.1, 31.7, 34.4, 68.5 (C-1'), 174.1 (C-1).

Synthesis of "Weinreb Amide" 18j

Sodium periodate (10.4 g, 48.6 mmol) was added to acetate **19a** (0.65 g, 3.42 mmol) in CCl_4 (30 mL), CH_3CN (30 mL), and water (30 mL) and the mixture was stirred vigorously for 30 min. The suspension was cooled to 0 °C and treated with ruthenium trichloride (40 mg, 0.17 mmol). After TLC indicated complete consumption of starting material (stirring overnight), the reaction mixture was filtered through a pad of celite and the filter thoroughly washed with ethyl acetate. After acidification with 1 N aqueous HCl, the organic layer was separated and the aqueous layer extracted with ethyl acetate; the organic fractions were combined. The solvent was removed under reduced pressure and the black residue was dissolved in saturated aqueous sodium bicarbonate solution. Washing with Et_2O – the organic layer was discarded – was followed by acidification with conc. aqueous HCl. Extraction with ethyl acetate, drying over $MgSO_4$, filtration, and removal of organic solvent under reduced pressure furnished the slightly off-colored product (0.52 g) in spectroscopically pure form. Flash column chromatography (petroleum ether/ethyl acetate 1:1) afforded the acid **19i** as a colorless oil; yield: 0.48 g (3.03 mmol, 89%). Up-scaling of the procedure was possible (12.1 mmol **19a** gave 92% of crude acid **19i**). IR (film): $\tilde{\nu}$ = 2956 (br, COOH), 2538, 1755 (C=O), 1689 (C=O), 1467, 1433, 1369, 1323, 1288, 1222, 1167, 1167, 1087, 1034, 1029, 976, 881, 832, 669, 636, 608 cm^{-1}; MS (CI, CH_4): *m/z* (%) = 159 [M$^+$] (30), 141 [M – OH_2^+] (90), 99 [M – $C_2H_4O_2^+$] (100); HRMS (CI, CH_4); calcd. for $C_7H_{11}O_4$: 159.0657; found: 159.0657; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.98 (ddd, $^3J_{3a,1}$ = 8.4 Hz, $^3J_{3a,2}$ = 6.4 Hz, $^2J_{3a,3b}$ = 4.6 Hz, 1H, 3-H$_a$) 1.31 (ddd, $^3J_{3b,1}$ = 8.9 Hz, $^3J_{3b,2}$ = 4.9 Hz, $^3J_{3b,3a}$ = 4.6 Hz 1H, 3-H$_b$), 1.62 (ddd, $^3J_{1,3a}$ = 8.4 Hz, $^3J_{1,3b}$ = 4.9 Hz, $^3J_{1,2}$ = 4.0 Hz, 1H, 1-H), 1.83 (ddddd, $^3J_{2,3b}$ = 8.9 Hz, $^3J_{2,1'a}$ = 7.5 Hz, $^3J_{2,3a}$ = 6.4 Hz, $^3J_{2,1'b}$ = 6.2 Hz, $^3J_{2,1}$ = 4.0 Hz, 1 H, 2-H), 2.07 [s, 3 H, C(O)C*H*$_3$], 3.88 (dd, $^2J_{1'a,1'b}$ = 11.8 Hz, $^3J_{1'a,2}$ = 7.5 Hz, 1H, 1'-H$_a$), 4.09 (dd, $^2J_{1'b,1'a}$ = 11.8 Hz, $^3J_{1'b,2}$ = 6.2 Hz, 1H, 1'-H$_b$), 11.1 (bs, 1H, COO*H*); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.8 (C-3), 18.6 (C-1), 20.9 [C(O)*C*H$_3$], 21.4 (C-2), 65.7 (C-1'), 171.0 [*C*(O)CH$_3$], 179.5 (*C*OOH); anal. calcd. for $C_7H_{10}O_4$ (158.15 g/mol): C 53.16, H 6.37; found: C 52.17, H 6.40.

Under an atmosphere of dry nitrogen, acid **19i** (0.70 g, 4.43 mmol) in CH_2Cl_2 (40 mL) was treated with carbonyldiimidazole (2.15 g, 13.3 mmol) and stirred for 1 h until no further evolution of gas could be detected. A solution of *N,O*-dimethylhydroxylamine (8.86 mmol) in CH_2Cl_2 (15 mL), synthesized from the corresponding hydrochloride (0.864 g, 8.86 mmol) and Et_3N (1.23 mL, 8.86 mmol), was added. After 18 h the reaction mixture was hydrolyzed with 1 M aqueous HCl (20 mL). The organic layer was separated and washed with 1 M aqueous HCl (20 mL) and water (2 × 20 mL). Drying over $MgSO_4$, filtration, and removal of organic solvent under reduced pressure furnished the crude product (0.83 g). Flash column chromatography (petroleum ether/ethyl acetate, 2:1) afforded the product **19j** as a colorless oil; yield: 0.76 g (3.78 mmol, 85%). IR (film): $\tilde{\nu}$ = 2941, 2822, 1731 (C=O), 1651 (C=O), 1427, 1371, 1236, 1178, 1111, 1030, 996, 900, 872, 847, 765, 723, 606 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.86 (ddd, $^3J_{3a,2}$ = 8.7 Hz, $^3J_{3a,1}$ = 6.0 Hz, $^2J_{3a,3b}$ = 4.2 Hz, 1H, 3-H$_a$), 1.27 (ddd, $^3J_{3b,1}$ = 10.6 Hz, $^3J_{3b,2}$ = 5.1 Hz, $^2J_{3b,3a}$ = 4.2 Hz, 1H, 3-H$_b$), 1.74 (ddddd, $^3J_{2,3a}$ = 8.7 Hz, $^3J_{2,1'a}$ = 7.8 Hz, $^3J_{2,1'b}$ = 6.3 Hz, $^3J_{2,3b}$ = 5.1 Hz, $^3J_{2,1}$ = 4.1 Hz, 1H, 2'-H), 2.06 [s, 2H, C(O)C*H*$_3$], 2.17 (m, 1H, 1-H), 3.21 (s, 3H, NC*H*$_3$), 3.76 (s, 3H, NOC*H*$_3$), 3.91 (dd, $^2J_{1'a,1'b}$ = 11.6 Hz, $^3J_{1'a,1}$ = 7.8 Hz, 1H, 1'-H$_a$), 4.12 (dd, $^2J_{1'b,1'a}$ = 11.6 Hz, $^3J_{1'b,1}$ = 6.3 Hz, 1H, 1'-H$_b$); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 12.6 (C-3), 16.1 (C-1), 20.2 (C-2), 22.9 [C(O)*C*H$_3$], 32.5 (N*C*H$_3$), 61.5 (NO*C*H$_3$), 66.5 (C-1'), 179.9 [1C, *C*(O)CH$_3$]; anal. calcd. for $C_9H_{15}NO_4$ (201.22 g/mol): C 53.72, H 7.51, N 6.96; found: C 53.44, H 7.51, N 6.74.

1.32 g (7.53 mmol) of acetate **19j** was dissolved in MeOH (45 mL) and water (10 mL). Potassium carbonate (80 mg, 0.58 mmol) was added and the mixture stirred for 2 h at room temperature. The reaction mixture was diluted with ethyl acetate and saturated brine was added. Extraction with ethyl acetate was followed by drying over $MgSO_4$, filtration, and removal of organic solvent under reduced pressure. Flash column chromatography (ethyl acetate/petroleum ether, 60:40 to 100:0) gave the product **18j** as a colorless oil; yield: 0.93 g (5.86 mmol, 90%). The whole procedure was repeated with enantiomerically enriched (1'*R*,2'*R*)- and (1'*S*,2'*S*)-**19a**.

18j: IR (film): $\tilde{\nu}$ = 3424 (OH), 3086, 3005, 2939, 2874, 1653 (C=O), 1428, 1389, 1296, 1241, 1179, 1151, 1108, 1036, 987, 956, 892, 762, 718 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 160 (45) [M + H$^+$], 159 (10) [M$^+$], 142 (100) [M – OH_2^+], 99 (85) [M – N(CH$_3$)OCH$_3^+$], 55 (25) [$C_3H_3O^+$]; HRMS (EI, 70 eV); calcd. for $C_7H_{12}NO_3$: 159.0895; found: 159.0895; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.85 (ddd, $^3J_{3a,2}$ = 8.4 Hz, $^3J_{3a,1}$ = 6.1 Hz, $^2J_{3a,3b}$ = 4.0 Hz, 1H, 3-H$_a$), 1.23 (ddd, $^3J_{3b,1}$ = 8.8 Hz, $^3J_{3b,3}$ = 5.0 Hz, $^2J_{3b,3a}$ = 4.0 Hz, 1H, 3-H$_b$), 1.70 (ddddd, $^3J_{2,3b}$ = 8.8 Hz, $^3J_{2,1'a}$ = 7.1 Hz, $^3J_{2,3a}$ = 6.1 Hz, $^3J_{2,1'b}$ = 5.9 Hz, $^3J_{2,1}$ = 4.1 Hz, 1H, 2-H), 1.99 (t, $^3J_{OH,1'}$ = 5.6 Hz, 1H, O*H*), 2.12 (bs, 1H, 1-H), 3.21 (s, 3H, NC*H*$_3$), 3.48 (ddd, $^2J_{1'a,1'b}$ = 11.4 Hz, $^3J_{1'a,2}$ = 7.1 Hz, $^3J_{1',OH}$ = 5.6 Hz, 1H, 1'-H$_a$), 3.68 (ddd, $^2J_{1'b,1'a}$ = 11.4 Hz, $^3J_{1'b,1}$ = 5.9 Hz, $^3J_{1'b,OH}$ = 5.6 Hz, 1H, 1'-H$_b$), 3.77 (s, 3H, NOC*H*$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 12.8 (C-3), 15.9 (C-1), 24.3 (C-2), 32.9 (N*C*H$_3$), 62.0 (NO*C*H$_3$), 65.2 (C-1'), 174.0 (C-1); anal. calcd. for $C_7H_{12}NO_3$ (159.18 g/mol): C 52.82, H 8.23, N 8.80; found: C 52.76, H 8.38, N 8.67.

Synthesis of Alkenylboronic Esters 22

Alkenylboronic esters **22** were prepared from alkynes **21** according to known procedures.[59–63]

22c: Colorless oil, purified by Kugelrohr distillation (90–100 °C/0.1 Torr). IR (film): $\tilde{\nu}$ = 3059, 2928, 1494, 1446, 1387, 1336, 1226, 1181, 1076, 1034, 967, 758, 700 cm^{-1}; MS (FAB): *m/z* (%) = 224 (27) [M$^+$], 209 (64) [M – CH_3^+], 153 (100), 138 (49), 125 (68); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.08 (t, $^3J_{6',7'}$ = 6.8 Hz, 3H, 7′-H), 1.47 [s, 12H, C(CH_3)$_2$], 1.45–1.51 (m, 4H, 5′-H/6′-H), 1.61 (m, 2H, 4′-H), 2.34 (m, 2H, 3′-H), 5.63 (dt, $^3J_{1',2'}$ = 17.9 Hz, $^4J_{1',3'}$ = 1.5 Hz, 1H, 1′-H), 6.84 (dt, $^3J_{1',2'}$ = 17.9 Hz, $^3J_{2',3'}$ = 6.4 Hz, 1H, 2′-H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 14.4 (C-7′), 22.9 (C-6′), 25.1 (C(*C*H$_3$)$_2$), 28.3 (C-4′), 31.8 (C-5′), 36.1 (C-3′), 83.3 (C-4/C-5), 119.0 (C-1′), 155.2 (C-2′); anal. calcd. for $C_{13}H_{25}BO_2$ (224.15 g/mol): C 69.66, H 11.24; found: C 69.56, H 11.14.

22e: Colorless oil. IR (film): $\tilde{\nu}$ = 2956, 1631, 1311, 1235, 1171, 1103, 1001, 937 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 168 (72) [M$^+$], 153 (100) [M – CH_3^+], 67 (68), 41 (75); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.01 [s, 9 H, C(CH_3)$_3$], 1.97 (quint, $^3J_{5,4/6}$ = 5.5 Hz, 2H, 5-H), 4.03 (t, $^3J_{5,4/6}$ = 5.5 Hz, 4H, 4-H, 6-H), 5.24 (d, $^3J_{1',2'}$ = 18.1, 1H, 1′-H), 6.47 (d, $^3J_{1',2'}$ = 18.1, 1H, 2′-H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 27.4 (C-5), 28.9 [C(*C*H$_3$)$_3$], 34.6 [*C*(CH$_3$)$_3$], 61.7 (C-4/C-6), ~119 (br, C-1′), 161.6 (C-2′); anal. calcd. for $C_9H_{17}BO_2$ (168.04): C 64.33, H 10.20; found: C 64.03, H 10.18.

22f: Colorless solid, mp 35 °C. IR (film): $\tilde{\nu}$ = 2960, 2940, 2845, 1625, 1450, 1340, 1250, 1130, 950, 860, 630 cm^{-1}; MS (CI, CH_4): *m/z* (%) = 211 (63) [M + 1$^+$], 195 (27) [M – CH_3^+], 153 (65), 101 (100), 59 (83); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.02 [s, 9H, C(CH_3)$_3$], 1.27 [s, 12H, C(CH_3)$_2$], 5.35 (d, $^3J_{1',2'}$ = 18.3 Hz, 1H, 1′-H), 6.64 (d, $^3J_{1',2'}$ = 18.3 Hz, 1H, 2′-H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 24.8 [C(*C*H$_3$)$_2$], 28.8 [C(*C*H$_3$)$_3$], 35.0 [*C*(CH$_3$)$_3$], 83.0 (C-4/C-5), 129.7 (C-1′), 164.4 (C-2′); anal. calcd. for $C_{12}H_{23}BO_2$ (210.12 g/mol): C 68.59, H 11.03; found: C 68.68, H 10.97.

Synthesis of Cyclopropylboronic Esters 23

Cyclopropylboronic esters **23** were prepared from alkenylboronic esters **22** according to the known procedure by a Pd(II)-catalyzed decomposition of diazomethane.[62,65]

23c: Colorless oil obtained after Kugelrohr distillation (100–110 °C/1.0 Torr). IR (film): $\tilde{\nu}$ = 2993, 2923, 2856, 1476, 1378, 1313, 1221, 1154, 978, 913, 853 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 238 (15) [M$^+$], 181 (34), 110 (29), 84 (100); HRMS (EI, 70 eV): calcd. for $C_{14}H_{27}BO_2$: 238.2104; found: 238.2108; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = –0.43 (ddd, $^3J_{1',3'\text{-}cis}$ = 9.4 Hz, $^3J_{1',3'\text{-}trans}$ = 6.0, $^3J_{1',2'}$ = 5.8 Hz, 1H, 1′-H), 0.38 (ddd, $^3J_{1',3'\text{-}cis}$ = 9.4 Hz, $^3J_{2',3'\text{-}cis}$ = 5.2 Hz, $^2J_{3'\text{-}cis,3'\text{-}trans}$ = 3.3 Hz, 1H, 3′-H$_{cis}$), 0.66 (ddd, $^3J_{2',3'\text{-}trans}$ = 7.8 Hz, $^3J_{1',3'\text{-}trans}$ = 6.0 Hz, $^2J_{3'\text{-}cis,3'\text{-}trans}$ = 3.3 Hz, 1H, 3′-H$_{trans}$), 0.86–0.94 (m, 1H, 2′-H), 0.88 (t, $^3J_{4'',5''}$ = 6.8 Hz, 3H, 5″-H), 1.07–1.12 (m, 1H, 1″-H$_a$), 1.14 [s, 12 H, C(CH_3)$_2$], 1.19–1.25 (m, 5H, 1″-H$_b$, 3″-H and 4″-H), 1.28–1.34 (m, 2H, 2″-H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 11.4 (C-3′), 14.1 (C-5″), 18.3 (C-2′), 22.7 (C-4″), 24.7 [C(*C*H$_3$)$_2$], 29.3 (C-2″), 31.7 (C-3″), 35.2 (C-1″), 82.7 (C-4/C-5), C-1′ not detectable.

23e: Colorless oil obtained after Kugelrohr distillation (60 °C/1.0 Torr). IR (film): $\tilde{\nu}$ = 2972, 2896, 2865, 1486, 1412, 1331, 1276, 1229, 1100, 853, 712 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 182 (12), [M$^+$], 167 (17) [M – CH_3^+], 70 (100); HRMS (EI, 70 eV): calcd. for $C_{10}H_{19}BO_2$: 182.1478; found: 182.1479; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ = –0.42 (m$_c$, 1H, 1′-H), 0.39–0.42 (m, 2H, 3′-H), 0.81 [s, 9H, C(CH_3)$_3$], 0.80–0.84 (m, 1H, 2′-H), 1.91 (quint, ^3J = 5.5 Hz, 2H, 5-H), 3.94 (t, ^3J = 5.5 Hz, 4H, 4-H, 6-H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 6.9 (C-3′), 27.5 (C-2′), 28.3 [C(*C*H$_3$)$_3$], 29.4 (C-5), 29.8 [*C*(CH$_3$)$_3$], 61.6 (C-4/C-6), C-1′ not detectable.

23f: Colorless oil obtained after Kugelrohr distillation (60 °C/0.35 Torr). IR (film): $\tilde{\nu}$ = 2995, 2943, 2867, 1421, 1360, 1313, 1269, 1220, 1153, 980, 856, 716 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 224 (6), [M$^+$], 70.1 (100); HRMS (EI, 70 eV): calcd. for $C_{13}H_{25}BO_2$: 224.1948; found: 224.1947; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = –0.03 (m$_c$, 1H, 1′-H), 0.73–0.77 (m, 2H, 3′-H), 1.06 [s, 9H, C(CH_3)$_3$], 1.16 (m$_c$, 1H, 2′-H), 1.46 [s, 12H, C(CH_3)$_2$]; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = –4.6 (br, C-1′), 7.2 (C-3′), 24.5 [C(*C*H$_3$)$_2$], 28.2 [C(*C*H$_3$)$_3$], 30.1 [*C*(CH$_3$)$_3$], 82.7 (C-4/C-5).

Synthesis of Cyclopropanols 24

Cyclopropanols **24** were prepared from cyclopropylboronic esters **23** according to known procedures.[62,65,70]

24b: Colorless oil with low vapor pressure (impurities: solvents). IR (film): $\tilde{\nu}$ = 3307, 2958, 1467, 1364, 1205, 1150, 1042, 933, 806 cm^{-1}; MS (CI, CH_4): *m/z* (%) = 114 (20) [M$^+$], 97 (100), 81 (13), 70 (39), 57 (82); HRMS (auto-CI): calcd. For $C_7H_{14}O$: 114.1045; found: 114.1046; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.48 (ddd, $^3J_{1,3\text{-}cis}$ = 6.8 Hz, $^3J_{2,3\text{-}cis}$ = 6.8 Hz, $^2J_{3\text{-}trans,3\text{-}cis}$ = 5.8 Hz, 1H, 3-H$_{cis}$), 0.59 (ddd, $^3J_{2,3\text{-}trans}$ = 10.5 Hz, $^2J_{3\text{-}trans,3\text{-}cis}$ = 5.8 Hz, $^3J_{1,3\text{-}trans}$ = 2.9 Hz, 1H, 3-H$_{trans}$), 0.82 [s, 9 H, C(CH_3)$_3$], 0.87 (ddd, $^3J_{2,3\text{-}trans}$ = 10.5 Hz, $^3J_{2,3\text{-}cis}$ = 6.8 Hz, $^3J_{1,2}$ = 2.9 Hz, 1H, 2-H), ~1.78 (br, 1 H, O*H*), 3.36 (ddd, $^3J_{1,3\text{-}cis}$ = 6.8 Hz, $^3J_{1,3\text{-}trans}$ = 2.9 Hz, $^3J_{1,2}$ = 2.9 Hz, 1H, 1-H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 11.0 (C-3), 28.5 [C(*C*H$_3$)$_3$], 30.1 [*C*(CH$_3$)$_3$], 32.5 (C-2), 49.4 (C-1).

Acetylation of Cyclopropanols 24

The same procedure was followed as described for cyclopropyl acetates **19** (*vide supra*).

25a: Obtained as colorless oil from 0.94 g (7.3 mmol) **24a**; yield: 0.94 g (5.6 mmol, 76%). Enantiomerically enriched acetates were obtained following the same sequence, but starting from alkenylboronic ester **26** and *ent*-**26**, respectively. IR (film): $\tilde{\nu}$ = 3080, 3005, 2922, 2855, 1742 (C=O), 1457, 1369, 1231, 1140, 1051, 980, 884, 727 cm^{-1}; MS (CI, CH_4): *m/z* (%) = 171 (22) [M + 1$^+$], 143 (100), 82 (58), 61 (38), 43 (65); HRMS (auto-CI); calcd. for $C_{10}H_{19}O_2$: 171.1385; found: 171.1384; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.50 (m, 1H, 3-H$_a$), 0.78 (m, 1H, 3-H$_b$), 0.89 (t, $^3J_{4',5'}$ = 7.0 Hz, 3H, 5′-H), 1.00 (m, 1H, 2-H), 1.01–1.69 (m, 8H, 1′-H, 2′-H, 3′-H, 4′-H), 2.01 (s, 3H, CH_3CO), 3.81 (m, 1H, 1-H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 12.4 (C-5′), 18.8 (C-3), 21.4 (*C*H$_3$CO), 22.7 (C-2), 23.0 (C-4′), 28.7 (C-3′), 31.7, 31.9 (C-1′, C-2′), 54.9 (C-1), 172.2 (*C*=O).

(1*S*)-**25a:** $[\alpha]_D^{20}$: +23.0 (*c* 0.9, $CHCl_3$); 73% ee.

(1*R*)-**25a:** $[\alpha]_D^{20}$: –23.9 (*c* 1.2, $CHCl_3$); 75% ee).

25b: Obtained as colorless oil from 0.18 g (1.6 mmol) **24b**; yield: 0.22 g (1.4 mmol, 88%). IR (film): $\tilde{\nu}$ = 2962, 2869, 1743, 1472, 1369, 1242, 1144, 1043 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 157 (7) [M + 1$^+$], 156 (2) [M$^+$], 143 (100), 70 (47), 57 (37), 43 [CH_3CO^+] (100); HRMS (auto-CI); calcd. for $C_9H_{16}O_2$: 156.1150; found: 156.1150; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.68–0.71 (m, 2H, 3-H$_{cis}$, 3-H$_{trans}$), 0.87 [s, 9 H, C(CH_3)$_3$], 0.94–

0.99 (m, 1H, 2-H), 2.01 (s, 3H, CH_3), 3.97 (m_c, 1H, 1-H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 8.5 (C-3), 21.0 (*C*H_3CO), 28.3 [C(*C*H_3)$_3$], 28.9 [*C*(CH$_3$)$_3$], 29.8 (C-2), 51.7 (C-1), 171.8 (C=O).

25c: Obtained as colorless oil from 0.48 g (3.5 mmol) **24c**; yield: 0.43 g (2.4 mmol, 68%). IR (film): $\tilde{\nu}$ = 3080, 3029, 1750, 1605, 1500, 1369, 1234, 1140, 1059, 751, 698 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 176 (2.5) [M$^+$], 134 (21) [(M – CH$_3$CO)$^+$], 43 (100) [CH$_3$CO$^+$]; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.20 (ddd, $^3J_{1,3\text{-}cis}$ = 6.8 Hz, $^3J_{2,3\text{-}cis}$ = 6.8 Hz, $^3J_{3\text{-}trans,3\text{-}cis}$ = 6.8 Hz, 1H, 3-H$_{cis}$), 1.31 (ddd, $^3J_{2,3\text{-}trans}$ = 10.5 Hz, $^2J_{3\text{-}trans,3\text{-}cis}$ = 6.6 Hz, $^3J_{1,3\text{-}trans}$ = 3.6 Hz, 1H, 3-H$_{trans}$), 2.07 (s, 3H, CH_3), 2.22 (ddd, $^3J_{2,3\text{-}trans}$ = 10.5 Hz, $^3J_{2,3\text{-}cis}$ = 6.8 Hz, $^3J_{1,2}$ = 2.7 Hz, 1H, 2-H), 4.21 (ddd, $^3J_{1,3\text{-}cis}$ = 6.8 Hz, $^3J_{1,3\text{-}trans}$ = 3.6 Hz, $^3J_{1,2}$ = 2.7 Hz, 1H, 1-H), 7.11 – 7.13 (m, 2H, arom. H), 7.17 – 7.20 (m, 1H, arom. H), 7.25 – 7.28 (m, 2H, arom. H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 14.6 (C-3), 20.9 (*C*H$_3$CO), 22.9 (C-2), 55.9 (C-1), 126.3, 126.6, 128.4 (arom. *C*), 139.6 (*i*-C), 171.5 (*C*=O); anal. calcd. for $C_{11}H_{12}O_2$ (176.21 g/mol): C 74.98, H 6.86; found: C 74.74, H 6.77.

Synthesis of *cis*-Acetate 27

CH_2I_2 (3.30 mL, 40.0 mmol) was dissolved in CH_2Cl_2 (10 mL) and Et_2Zn was added (20 mL of a 1 M solution in hexane) at 0 °C. Vinyl acetate **26** (1.60 g, 10.2 mmol) was slowly added and the mixture was stirred overnight at room temperature. The mixture was hydrolyzed with aqueous saturated NH_4Cl solution. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2. The combined organic fractions were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Purification of the crude product was achieved by flash-column chromatography (pentane/Et_2O, 100:0 to 20:1) furnishing cyclopropane **27** as a colorless oil; yield: 1.05 g (6.18 mmol, 61%). IR (film): $\tilde{\nu}$ = 3080, 3005, 2922, 2855, 1742 (C=O), 1457, 1369, 1231, 1140, 1051, 980, 884, 727 cm^{-1}; MS (auto-CI, 70 eV): *m/z* (%) = 170 (< 1) [M$^+$], 128 (12) [(M – CH$_3$CO)$^+$], 100 (25), 43 (100) [CH$_3$CO$^+$]; HRMS (auto-CI); calcd. for $C_{10}H_{19}O_2$: 171.1385; found: 171.1384; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.34 (m, 1H, 3-H$_a$), 0.84 – 0.93 (m, 5H, 3-H$_b$, 2-H, 5′-H), 1.25 – 1.45 (m, 8H, 1′-H, 2′-H, 3′-H, 4′-H), 2.01 (s, 3H, CH_3CO), 3.81 (m, 1H, 1-H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 10.7 (C-3), 14.1 (C-5′), 16.5 (C-2), 20.9 (*C*H$_3$CO), 22.6 (C-4′), 27.2 (C-1′), 29.1, 31.7 (C-2′, C-3′), 52.7 (C-1), 172.0 (*C*=O); anal. calcd. for $C_{10}H_{18}O_2$ (170.25 g/mol): C 70.55, C 70.55; found: C 70.06, H 10.65.

Enzymatic Acylation with Vinyl Esters (Conditions: See Schemes 3 + 9)

Approx. 10 – 40 mg of the required alcohol, 10 – 40 mg of enzyme and 1 – 4 mL of the appropriate solvent were stirred at the given temperature in a screw-top vial. 0.5 – 0.75 equiv. (for primary alcohols) or 5 equivs. (for secondary alcohols) of the vinyl ester were added along with some 4 Å molecular sieves. When TLC indicated conversion of the alcohol, aliquots were taken and the enantiomeric excess of product and starting material were determined each time either by HPLC or GLC (see Supporting Information).

Enzymatic Hydrolysis of Cyclopropyl Esters (Conditions: See Schemes 4 + 10)

Approx. 5 mg of the required ester, 5 mg of enzyme, 0.5 mL phosphate buffer (pH 7) and 0.5 mL of the appropriate solvent were stirred at the given temperature in a screw-top vial. When TLC indicated conversion to the corresponding alcohol, aliquots were taken and the enantiomeric excess of product and starting material were determined each time either by HPLC or GLC (see Supporting Information).

Kinetic Enzymatic Resolution – Preparative Scale

(1*S*,2*S*)-**18a:** 4.85 g (25.5 mmol) of enantiomerically enriched ester (1*S*,2*S*)-**19a** (87% ee) in CH_2Cl_2 (30 mL) were added to 1.70 g *CAL-B-I* in 40 mL phosphate buffer. The mixture was refluxed, while the pH value was kept at 7 by regularly adding 1 M aqueous NaOH. The reaction was controlled by HPLC. At approx. 85% conversion – the (1*R*,2*R*)-**18a** alcohol could not be detected – the reaction was stopped by separation of the organic layer. The aqueous layer was extracted with CH_2Cl_2, the combined organic fractions dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The colorless oil was purified by flash column chromatography (petroleum ether/ethyl acetate, 9:1 to 3:1); yield of (1*S*,2*S*)-**18a**: 2.90 g (19.6 mmol, 77%, ee >98%); $[\alpha]_D^{20}$: + 86 (*c* 1.0, EtOH).

(1*R*,2*R*)-**19a:** Following the same procedure, (1*S*,2*S*)-**19a** (81% ee) was hydrolyzed in the presence of *CAL-B-I*. Predominantly, the minor enantiomer was converted to the corresponding alcohol (1*S*,2*S*)-**18a** and the major ester (1*R*,2*R*)-**19a** remained unchanged; yield: 74% (ee 96%); $[\alpha]_D^{20}$: – 86 (*c* 1.0, EtOH).

(1*S*,2*S*)-**18j:** 0.46 g (2.29 mmol) of enantiomerically enriched ester (1*S*,2*S*)-**19j** (87% ee) in dioxane (15 mL) were added to 0.13 g *PCL-I* in 15 mL phosphate buffer. The mixture was heated to 40 °C, while the pH value was kept at 7 by regularly adding 1 M aqueous NaOH. The reaction was controlled by GLC. After 14 h – the (1*R*,2*R*)-**18j** alcohol could not be detected – the reaction was stopped by adding ethyl acetate and separation of the organic layer. The aqueous layer was concentrated to dryness, dissolved in ethyl acetate and briefly heated to reflux. The combined organic fractions were dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The colorless oil was purified by flash column chromatography (petroleum ether/ethyl acetate, 1:1 to 0:100); yield of (1*S*,2*S*)-**18j**: 0.29 g (1.79 mmol, 78%, ee >98%); $[\alpha]_D^{20}$: + 36 (*c* 1.0, $CHCl_3$).

(1*R*,2*R*)-**19j:** Following the same procedure, (1*S*,2*S*)-**19j** (84% ee) was hydrolyzed in the presence of *PCL-I*. Predominantly, the minor enantiomer was converted to the corresponding alcohol (1*S*,2*S*)-**18j** and the major ester (1*R*,2*R*)-**19j** remained unchanged; yield: 82% (ee 97%); $[\alpha]_D^{20}$: – 34 (*c* 1.0, $CHCl_3$).

(1*R*)-**24a**/(1*S*)-**25a:** 1.03 g (6.00 mmol) of ester *rac*-**24a** in THF (25 mL) was added to 0.53 g *CAL-B-I* in 25 mL phosphate buffer. The mixture was heated to 60 °C, while pH value was kept at 7 by regularly adding 1 M aqueous NaOH. The reaction was controlled by GLC. At approx. 48% conversion the reaction was stopped by decantation of the solvents from the enzyme and separation of phases. The residue was washed with Et_2O and the aqueous layer extracted with Et_2O. The combined organic fractions were dried over $MgSO_4$, filtered,

and the solvent removed under reduced pressure. The colorless oil was purified by flash column chromatography (pentane/Et_2O, 9:1) to afford cyclopropanol (1*R*)-**24a** (yield 0.34 g, 2.6 mmol, 44%, ee 87%) and acetate (1*S*)-**25a** (yield: 0.43 g, 2.5 mmol, 42%, ee 87%).

(1*S*)-**25a:** $[\alpha]_D^{20}$: +27.7 (*c* 1.2, $CHCl_3$), 87% ee.

(1*R*)-**24a:** $[\alpha]_D^{20}$: −28.3 (*c* 1.0, $CHCl_3$), 87% ee.

Supporting Information

a. Spectroscopic data for **18k – n**, **19k – n**, **24e, f**, and **25e, f** as well as the corresponding synthetic intermediates; b. Tables of enzymes used and the separation of enantiomers **18**, **19**, **24**, **25**, **27**, and **28**; c. A brief discussion of the E value.

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