Synthesis of Enantiomerically Pure *cis*-Cyclopropylboronic Esters

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Dedicated to Professor Dr. Dr. h.c. Franz Effenberger on the occasion of his 70th birthday

Keywords: Boron / Chiral auxiliaries / Cycloadditions / Cyclopropanes / Ring opening

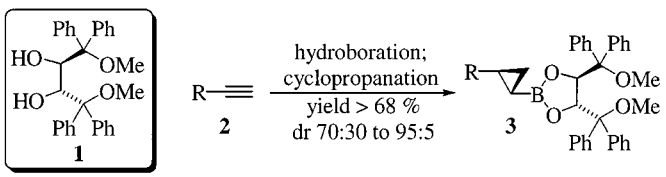
Highly stable, enantiomerically pure cyclopropylboronic esters are desirable building blocks for the preparation of a plethora of different cyclopropane derivatives. Whereas *trans*-configured compounds proved to be readily available, we herein report the first synthesis of the corresponding *cis*-cyclopropanes. The scope and limitation of this process will be discussed. The absolute configuration of the products could be established by means of chemical and spectroscopic correlation.

Introduction

Due to the potential of boronic acids and esters,[1] it is not surprising that an increasing number of reports also deal with their application in cyclopropane chemistry.[2−4] Cyclopropylboronic esters are especially attractive synthetic targets, since on the one hand, the cyclopropane moiety is incorporated into pharmaceuticals and natural products,[5] and on the other hand a general method for obtaining enantiomerically pure compounds is still elusive.[6] With a plethora of transformations possible, enantiomerically pure cyclopropylboronic esters qualify to be considered as universal building blocks. Early work in this area suffered from the relative lability of this class of compounds; the classical advantages of the diastereoselective synthesis, i.e. the separation of diastereomers, could not be profitably exploited.[3] By utilizing diol **1**,[4,7] we demonstrated that highly stable boronic esters can be isolated, conveniently purified and stored. Although we reported a reliable protocol for the transformation of alkynes **2** to the *trans*-1,2-disubstituted cyclopropanes **3** (Scheme 1), neither the corresponding nor other *cis*-configured cyclopropylboronic esters have been synthesized until now. In view of our interest in the synthesis of naturally occurring cyclopropanes containing a *cis*-1,2-disubstituted cyclopropane, e.g. cepaciamides[8] or plakosides,[9] establishing a route to this class of compounds was highly desirable.

Results and Discussion

One problem associated with the synthesis of *cis*-cyclopropylboronic esters is the availability of the starting materials. Whereas the synthesis of (*E*)-alkenylboronic acids and esters is straightforward, routes to the corresponding (*Z*)-products are less direct.[1] The reported alternatives were a) the hydroboration of 1-haloalkynes **4**, followed by reduction/inversion,[10] b) the selective oxidation of (*Z*)-1-alkenylboranes,[11] c) the reaction of (*Z*)-alkenyllithium with borates,[12] d) the *cis*-hydrogenation[13] or hydrozirconation of 1-alkynylboronates,[14] or e) the reaction of lithio(trimethylsilyl)methaneboronic ester with aldehydes (70:30 in favor of the *cis*-isomer).[15] In our hands, using the bulky diol **1**, we could only successfully apply method c (Scheme 2). Following a sequence first reported by Kluge, Untch, and Fried,[16] we synthesized 1-iodoalkyne **4** from 1-alkyne **2**, followed by the diimide reduction (*via* the decomposition of dipotassium azodicarboxylate)[17] to yield



Scheme 1. Synthesis of stable, enantiomerically pure *trans*-cyclopropylboronic esters **3**

(*Z*)-vinyl iodide **5**. Next, lithium-iodide-exchange with *t*BuLi,[18] formation of an ate complex, and direct transesterification gave the alkenylboronic esters **6**. Controlling the reaction temperature is crucial, especially when adding triisopropyl borate, e.g. transformation of **5b** would exclusively give the (*E*)-isomer, when performed at ambient temperature. The last step of this sequence is extremely sluggish

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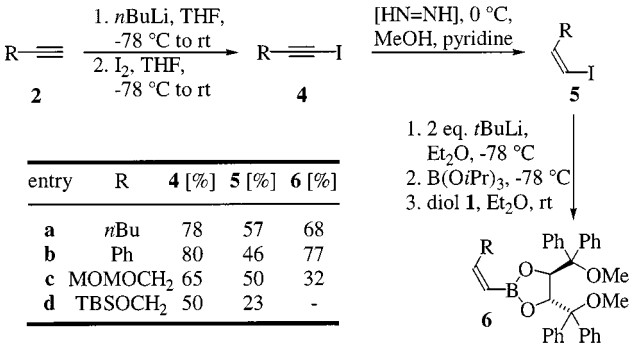
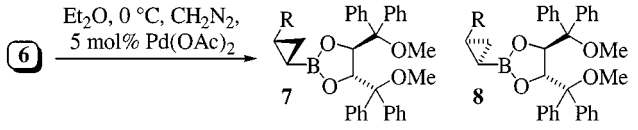


entry	R	4 [%]	5 [%]	6 [%]
a	*n*Bu	78	57	68
b	Ph	80	46	77
c	$MOMOCH_2$	65	50	32
d	$TBSOCH_2$	50	23	-

Scheme 2. Synthesis of *cis*-alkenylboronic esters **6** (MOM = methoxymethyl, TBS = tBuMe$_2$Si)

and with bulky substituents no product was formed (e.g. when starting from silyl-protected alcohol **5d**).

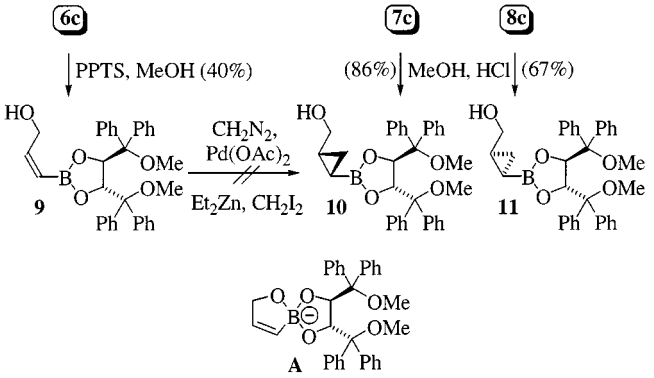
The cyclopropanation of alkenylboronic esters **6** by the Pd^{II}-catalyzed decomposition of diazomethane furnished cyclopropylboronic esters **7** and **8** in high yields (Scheme 3). Although we performed the reaction utilizing our improved protocol,[4] the diastereoselectivity was relatively poor. Nevertheless, the diastereomeric 1,3,2-dioxaborolanes could be separated.[19] In view of the high stability of our boronic esters towards acids, we envisaged deprotection of the MOM-derivative **6c**; the alcohol should have enabled us to perform a Simmons−Smith cyclopropanation. These conditions are known to give complementary diastereoselectivities.[4] We were surprised to find that although the deprotection to give alcohol **9** was possible (Scheme 4), the cyclopropanation step failed. The Pd^{II}-catalyzed reaction led to decomposition, whereas under Simmons−Smith conditions the starting material was re-isolated. While controlling the reaction, TLC indicated that diol **1** was formed. We presume that under basic conditions an intramolecular ate complex **A** promotes the hydrolysis, however, upon workup re-condensation occurs. Finally, the desired building blocks **10** and **11** were synthesized by deprotection of the cyclopropylboronic esters **7c** and **8c**, respectively. The use of HCl/MeOH proved to be superior to PPTS (pyridinium toluene-4-sulfonate) in tBuOH or HCl/NaI/acetone.



entry	yield **7**+**8** [%]	dr **7**:**8**
a	96	87:13
b	90	67:33
c	87	65:35

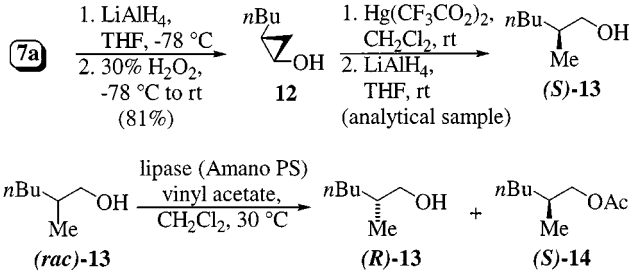
Scheme 3. Diastereoselective cyclopropanation of **6** to yield **7** and **8**

The absolute configuration of the cyclopropylboronic esters **7** and **8** could not be directly determined; neither were we able to obtain an X-ray crystal structure. Also, the corresponding cyclopropanols were not known. For the chemical correlation of cyclopropylboronic ester **7a** (Scheme 5), we first synthesized cyclopropanol **12** (81%).[20] For a ring-opening reaction an analytical sample was treated with



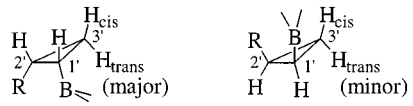
Scheme 4. Synthesis of hydroxymethylcyclopropylboronic esters **10** and **11**

$Hg(CF_3CO_2)_2$ in CH_2Cl_2. In the following step the crude material was directly reduced to the primary alcohol (*S*)-**13**. This result could be correlated by GLC with a reference sample that we obtained after the known lipase-catalyzed acetylation of (*rac*)-**13** with vinyl acetate.[21] In this case, Barth and Effenberger had observed the preferred formation of (*S*)-**14** with the alcohol (*R*)-**14** accumulating. Since one stereogenic center remained untouched during the whole sequence, we proved the configuration of the boronic ester **7a**. With this result in our hands, we could rely on the characteristic NMR data of our cyclopropylboronic ester (Table 1).[4] Again, the chemical shifts for both, proton 3′-H_{trans} and carbon C-3′, follow a distinct pattern for the two diastereomeric series: the major diastereomer shows a downfield shift in all cases (^{1}H: 0.21−0.44 ppm; ^{13}C: 0.12−1.20 ppm), thus allowing us to assign the configuration of all synthesized *cis*-1,2-disubstituted cyclopropylboronic esters.



Scheme 5. Determination of the absolute configuration of cyclopropylboronic ester **7a** by chemical correlation

Table 1. Characteristic NMR data (^{1}H: 500 MHz; ^{13}C: 125 MHz; $CDCl_3$) for diastereomeric cyclopropylboronic esters



R	entry	3′-H_{trans}	C-3′	entry	3′-H_{trans}	C-3′
*n*Bu	**7a**	-0.04	11.71	**8a**	-0.46	11.59
Ph	**7b**	+0.78	10.75	**8b**	+0.57	10.63
$MOMOCH_2$	**7c**	+0.21	11.08	**8c**	-0.23	9.93
$HOCH_2$	**10**	+0.18	9.52	**11**	-0.16	8.32

Conclusion

In summary, we have synthesized *cis*-configured cyclopropylboronic esters for the first time. The stability of the 1,3,2-dioxaborolan unit allowed for the separation of the diastereomers, thus giving enantiomerically pure cyclopropanes, and the acid-catalyzed cleavage of the MOM-protecting group. The absolute configuration of the products were determined by means of chemical correlation and characteristic NMR data. With these new building blocks in our hands, we finally established a general approach to enantiomerically pure 1,2-disubstituted cyclopropanes. We are currently trying to further optimize this sequence and to apply the described method in natural product synthesis.

Experimental Section

General Remarks: All reagents were used as purchased from commercial suppliers without further purification. The vinyl iodides **5** were synthesized as described by Dieck and Heck,[12] the spectroscopic data are in agreement with published data.[12,22,23] The reactions 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 and THF were freshly distilled from sodium/benzophenone. **Caution:** The generation and handling of diazomethane requires special precaution.[24] − 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 molybdenium 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 (259 nm). − ^1H and ^{13}C NMR spectra were recorded at room temp. in $CDCl_3$ unless otherwise indicated on a Bruker A 500. Chemical shifts are given in ppm relative to resonances of the solvent (^1H: $CHCl_3$, 7.25 ppm; ^{13}C: $CDCl_3$, 77.0 ppm), *J* in Hz; in spectra of higher order *δ*s and *J*s were not corrected. ^{13}C signals were assigned by means of C-H- and H-H-COSY spectra. − Microanalysis: Performed at the Institut für Organische Chemie, Stuttgart. − Melting points (Fisher Jones) were not corrected.

Alkenylboronic Esters (6): Under an atmosphere of nitrogen vinyl iodide **5** (1.0 equiv.) was dissolved in diethyl ether (2 mL/mmol olefin) and cooled to −78 °C. After addition of *t*BuLi (1.5 M solution in diethyl ether; 2.0 equiv.) a white precipitate formed. Stirring was continued, and after 2 h triisopropyl borate (1.0 equiv.) was syringed into the mixture, which was then allowed to warm to room temperature. The ate complex was quenched with diol **1** (0.8 equiv.), and the reaction mixture was left at ambient temperature for 18 h. Diethyl ether (10 mL/mmol olefin) was added and the organic layer washed with saturated aqueous NH_4Cl (5 mL/mmol olefin), H_2O (2 × 5 mL/mmol olefin), and brine (5 mL/mmol olefin), and dried over $MgSO_4$. The solution was concentrated under reduced pressure and the residue subjected to flash-column chromatography on silica gel, eluting with pentane/diethyl ether (10:1 to 4:1), yielding product **6**.

6a: Yield 68%, colorless crystals, m.p. 109 °C. − $[\alpha]_D^{20} = -131$ (*c* = 1.6, $CHCl_3$). − IR (film, NaCl): $\tilde{\nu}$ = 3060 cm^{-1}, 3026, 2923, 2849, 1600, 1493, 1453, 1028. − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.75 (t, *J* = 7.0 Hz, 3 H, 6′-H), 1.08 (m_c, 4 H, 4′-H and 5′-H), 1.91 (m_c, 1 H, 3′-H_a), 1.95 (m_c, 1 H, 3′-H_b), 3.00 (s, 6 H, OMe), 4.90 (br d, *J* = 13.5 Hz, 1 H; 1′-H), 5.31 (s, 2 H, 4-H and 5-H), 6.20 (dt, *J* = 13.5 Hz, *J* = 7.6 Hz, 1 H, 2′-H), 7.22−7.39 (m, 20 H, arom.-H). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.9 (q, C-6′), 22.3, 31.5 (t, C-5′/C-4′), 31.6 (t, C-3′), 51.8 (q, OMe), 77.3 (d, C-4/C-5), 83.4 (s, *C*Ph_2OMe), 116.8 (br d, C-1′), 127.14, 127.18, 127.22, 127.3, 127.4, 127.5, 127.7, 127.80, 128.4, 129.7 (d, arom.-CH), 141.22, 141.28, 141.6 (s, arom.-C_{ipso}), 155.2 (d, C-2′). − MS (EI, 70 eV); *m*/*z* (%): 546 (<0.1) [M^+], 514 (1.8) [M − $MeOH^+$], 197 (100) [Ph_2COMe^+]. − $C_{36}H_{39}BO_4$ (546.5): calcd. C 79.12, H 7.19; found C 79.06, H 7.28.

6b: Yield 77%, white foam, softening range 72−77 °C. − $[\alpha]_D^{21}$ = −274 (*c* = 0.90, $CHCl_3$). − IR (film, NaCl): $\tilde{\nu}$ = 3057 cm^{-1}, 2958, 1616, 1197, 1076. − ^1H NMR (500 MHz, $CDCl_3$): δ = 2.98 (s, 6 H, OMe), 5.14 (br d, *J* = 14.9 Hz, 1 H; 1′-H), 5.32 (s, 2 H, 4-H and 5-H), 7.01−7.18 (m, 4 H, 2′-H, arom.-H), 7.20−7.31 (m, 22 H, arom.-H). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = 51.7 (q, OMe), 77.4 (d, C-4/C-5), 83.3 (s, *C*Ph_2OMe), 117.8 (br d, C-1′), 127.2, 127.35, 127.39, 127.6, 127.7, 128.9 (d, arom.-CH), 138.0, 141.2, 141.4 (s, arom.-C_{ipso}), 150.2 (d, C-2′). − MS (FAB, NBA + NaI); *m*/*z* (%): 589 (12) [M + Na^+], 197 (100) [Ph_2COMe^+]. − HRMS: $C_{38}H_{35}{}^{10}BO_4Na$: calcd. 589.2526; found 589.2523. − $C_{38}H_{35}BO_4$ (566.5): calcd. C 80.57, H 6.23; found C 80.18, H 6.31.

6c: Yield 32%, white foam, softening range 55−60 °C. − $[\alpha]_D^{21}$ = −128 (*c* = 3.5, $CHCl_3$). − IR (film, NaCl): $\tilde{\nu}$ = 3063 cm^{-1}, 3039, 3005, 2928, 2815, 1627, 1365, 1298, 1249, 1176, 1090, 1061. − ^1H NMR (500 MHz, $CDCl_3$): δ = 2.92 (s, 6 H, OMe), 3.09 (s, 3 H, OMe), 3.73 (ddd, *J* = 13.6 Hz, *J* = 5.6 Hz, *J* = 1.5 Hz, 1 H, 3′-H_a), 3.91 (ddd, *J* = 13.6 Hz, *J* = 6.7 Hz, *J* = 1.5 Hz, 1 H, 3′-H_b), 5.02 (dt, *J* = 13.9 Hz, *J* = 1.5 Hz, 1 H; 1′-H), 5.27 (s, 2 H, 4-H and 5-H), 6.19 (ddd, *J* = 13.9 Hz, *J* = 6.7 Hz, *J* = 5.6 Hz, 1 H, 2′-H), 7.24−7.28 (m, 20 H, arom.-H). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = 51.9 (q, OMe), 55.0 (q, OMe), 66.8 (t, C-3′), 77.5 (d, C-4/C-5), 83.3 (s, *C*Ph_2OMe), 95.9 (t, −O*C*H_2O−), 118.8 (br d, C-1′), 127.24, 127.29, 127.5, 127.8, 128.3, 129.6 (d, arom.-CH), 141.1, 141.3 (s, arom.-C_{ipso}), 150.0 (d, C-2′). − MS (EI, 70 eV); *m*/*z* (%): 532 (<0.1) [M − $MeOH^+$], 519 (0.1) [M − $C_2H_5O^+$], 197 (100) [Ph_2COMe^+]. − $C_{35}H_{37}BO_6$ (564.5): calcd. C 74.47, H 6.61; found C 74.46, H 6.77.

Cyclopropylboronic Esters 7 and 8: Alkenylboronic ester **6** (1 equiv.) was dissolved in diethyl ether (1 mL/mmol of **6**) and 5 mol-% $Pd(OAc)_2$ was added. The suspension was treated for 2 min in an ultrasonic bath. After the mixture was cooled to 0 °C, diazomethane[24] (50 mL/mmol of **6** of an approximately 0.5 M solution in diethyl ether) was slowly added (2 mL/min) by means of a syringe-pump.[25] Unreacted diazomethane was destroyed by stirring the reaction mixture vigorously. Filtration through celite and evaporation of the solvent under reduced pressure, followed by chromatographic purification, led to analytically pure cyclopropylboronic esters **7** and **8**.

7a and 8a: After flash-column chromatography (pentane/diethyl ether, 10:1), a white foam (yield 96%, *dr* 87:13) was isolated: − IR (film, NaCl): $\tilde{\nu}$ = 3060 cm^{-1}, 2956, 2928, 2852, 1494, 1447, 1417, 1250, 1188, 1077. − MS (EI, 70 eV); *m*/*z* (%): 560 (<0.1) [M^+], 528 (2.2) [M − $MeOH^+$], 197 (100) [Ph_2COMe^+]. − $C_{37}H_{41}BO_4$ (560.5): calcd. C 79.28, H 7.37; found C 79.34, H 7.46. By MPLC (0.4% EtOAc in petroleum ether) the diastereomers **7a** and **8a** could be separated. **7a:** (first eluted, major diastereomer) Softening range 60−65 °C. − $[\alpha]_D^{20} = -123$ (*c* = 1.0, $CHCl_3$). − ^1H NMR (500 MHz, $CDCl_3$): δ = −0.57 (ddd, *J* = 10.0 Hz, *J* = 8.8 Hz, *J* =

6.6 Hz, 1 H, 1′-H), −0.04 (ddd, J = 6.6 Hz, J = 5.6 Hz, J = 3.2 Hz, 1 H, 3′-H_{trans}), 0.50 (ddd, J = 10.0 Hz, J = 7.6 Hz, J = 3.2 Hz, 1 H, 3′-H_{cis}), 0.67 (m_c, 1 H, 2′-H), 0.77 (t, J = 7.3 Hz, 3 H, 4′′-H), 0.72−0.82 (m, 1 H, 1′′-H_a), 0.85−0.94 (m, 2 H, 1′′-H_b, 2′′-H_a), 0.96−1.03 (m, 1 H, 2′′-H_b), 1.12 (qt, J = 7.3 Hz, J = 7.0 Hz, 2 H, 3′′-H), 2.93 (s, 6 H, OMe), 5.19 (s, 2 H, 4-H and 5-H), 7.15−7.28 (m, 20 H, arom.-H). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = ≈ −3 (d, C-1′), 11.7 (t, C-3′), 13.8 (q, C-4′′), 18.1 (d, C-2′), 22.5 (t, C-3′′), 30.0 (t, C-1′′), 31.6 (t, C-2′′), 51.6 (q, OMe), 77.0 (d, C-4/C-5), 83.3 (s, *C*Ph_2OMe), 127.12, 127.14, 127.3, 127.6, 128.4, 129.6 (d, arom.-CH), 141.4, 141.6 (s, arom.-C_{ipso}). − **8a:** (second eluted, minor diastereomer) Softening range 60−65 °C. − $[\alpha]_D^{20}$ = −67.8 (c = 0.7, $CHCl_3$). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = −0.54 (ddd, J = 10.0 Hz, J = 8.7 Hz, J = 6.5 Hz, 1 H, 1′-H), −0.46 (ddd, J = 6.5 Hz, J = 5.9 Hz, J = 3.2 Hz, 1 H, 3′-H_{trans}), 0.45 (ddd, J = 10.0 Hz, J = 7.9 Hz, J = 3.2 Hz, 1 H, 3′-H_{cis}), 0.63 (t, J = 7.3 Hz, 3 H, 4′′-H), 0.68 (m_c, 1 H, 2′-H), 0.87 (m_c, 1 H, 1′′-H_a), 0.97 (m_c, 2 H, 3′′-H), 0.93−1.01 (m, 2 H, 2′′-H), 1.05−1.13 (m, 2 H, 1′′-H_b), 2.91 (s, 6 H, OMe), 5.15 (s, 2 H, 4-H and 5-H), 7.14−7.30 (m, 20 H, arom.-H). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = ≈ −2 (d, C-1′), 11.6 (t, C-3′), 14.0 (q, C-4′′), 18.4 (d, C-2′), 22.4 (t, C-3′′), 30.3 (t, C-1′′), 32.2 (t, C-2′′), 51.7 (q, OMe), 77.4 (d, C-4/C-5), 83.4 (s, *C*Ph_2OMe), 127.18, 127.25, 127.34, 127.7, 128.4, 128.5, 129.7 (d, arom.-CH), 141.4, 141.6 (s, arom.-C_{ipso}).

7b and 8b: After flash-column chromatography (pentane/diethyl ether, 10:1), a white foam (yield 90%, *dr* 67:33) was isolated: − IR (film, NaCl): $\tilde{\nu}$ = 3058 cm^{-1}, 3025, 2958, 2938, 2834, 1494, 1446, 1416, 1375, 1254, 11918, 1076. − MS (EI, 70 eV); *m/z* (%): 580 (<0.3) [M^+], 548 (8) [M − $MeOH^+$], 197 (100) [Ph_2COMe^+]. − $C_{39}H_{37}BO_4$ (580.5): calcd. C 80.69, H 6.42; found C 80.62, H 6.34. By MPLC (0.5−1.0% EtOAc in petroleum ether) the diastereomers **7b** and **8b** could be separated. **7b:** (first eluted, major diastereomer) Softening range 80−85 °C. − $[\alpha]_D^{20}$ = −144 (c = 1.3, $CHCl_3$). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = −0.06 (ddd, J = 10.0 Hz, J = 9.6 Hz, J = 7.1 Hz, 1 H, 1′-H), 0.78 (ddd, J = 7.1 Hz, J = 6.2 Hz, J = 3.8 Hz, 1 H, 3′-H_{trans}), 0.91 (ddd, J = 10.0 Hz, J = 8.0 Hz, J = 3.8 Hz, 1 H, 3′-H_{cis}), 2.04 (ddd, J = 9.6 Hz, J = 8.0 Hz, J = 6.2 Hz, 1 H, 2′-H), 2.83 (s, 6 H, OMe), 5.00 (s, 2 H, 4-H and 5-H), 6.71−6.73 (m, 2 H, arom.-H), 7.00−7.09 (m, 7 H, arom.-H), 7.11−7.23 (m, 16 H, arom.-H). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = ≈ 2 (d, C-1′), 10.8 (t, C-3′), 22.3 (d, C-2′), 51.7 (q, OMe), 77.0 (d, C-4/C-5), 83.2 (s, *C*Ph_2OMe), 125.2, 127.1, 127.19, 127.23, 127.7, 127.8, 128.2, 128.6 (d, arom.-CH), 140.1, 141.5, 141.8 (s, arom.-C_{ipso}). **8b** (second eluted, minor diastereomer): M.p. 164−166 °C. − $[\alpha]_D^{20}$ = −143 (c = 1.6, $CHCl_3$). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = −0.01 (ddd, J = 10.1 Hz, J = 9.6 Hz, J = 7.2 Hz, 1 H, 1′-H), 0.57 (ddd, J = 7.2 Hz, J = 6.6 Hz, J = 4.1 Hz, 1 H, 3′-H_{trans}), 0.82 (ddd, J = 10.1 Hz, J = 8.0 Hz, J = 4.1 Hz, 1 H, 3′-H_{cis}), 2.00 (ddd, J = 9.6 Hz, J = 8.0 Hz, J = 6.6 Hz, 1 H, 2′-H), 2.84 (s, 6 H, OMe), 5.07 (s, 2 H, 4-H and 5-H), 6.59−6.66 (m, 3 H, arom.-H), 6.83−6.87 (m, 6 H, arom.-H), 7.11−7.28 (m, 16 H, arom.-H). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = ≈ 5 (d, C-1′), 10.6 (t, C-3′), 22.9 (d, C-2′), 51.5 (q, OMe), 77.3 (d, C-4/C-5), 83.1 (s, *C*Ph_2OMe), 125.3, 127.0, 127.24, 127.27, 127.4, 127.6, 128.3, 129.6, 129.8 (d, arom.-CH), 139.8, 141.1, 141.2 (s, arom.-C_{ipso}).

7c and 8c: After flash-column chromatography (pentane/diethyl ether, 2:1), a white foam (yield 87%, dr 65:35) was isolated: − IR (film, NaCl): $\tilde{\nu}$ = 3058 cm^{-1}, 3025, 2958, 2939, 2834, 1446, 1418, 1370, 1194, 1076. − MS (FAB, NBA + NaI); *m/z* (%): 601 (35) [M + Na^+], 197 (100) [Ph_2COMe^+]. − HRMS: $C_{36}H_{39}{}^{10}BO_6Na$: calcd. 601.2737; found 601.2742. − $C_{36}H_{39}BO_6$ (578.5): calcd. C 74.74, H 6.80; found C 74.39, H 7.82. By MPLC (4% EtOAc in petroleum ether) the diastereomers **7c** and **8c** could be separated. − **7c:** (second eluted, major diastereomer) Softening range 52−60 °C. − $[\alpha]_D^{21}$ = −125 (c = 0.8, $CHCl_3$). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = −0.40 (ddd, J = 9.6 Hz, J = 9.2 Hz, J = 7.0 Hz, 1 H, 1′-H), 0.21 (ddd, J = 7.0 Hz, J = 5.5 Hz, J = 3.5 Hz, 1 H, 3′-H_{trans}), 0.68 (dddd, J = 9.6 Hz, J = 7.5 Hz, J = 3.5 Hz, J = 1.1 Hz, 1 H, 3′-H_{cis}), 1.06 (ddddd, J = 9.9 Hz, J = 9.2 Hz, J = 7.5 Hz, J = 5.5 Hz, J = 4.6 Hz, 1 H, 2′-H), 2.75 (dd, J = 10.7 Hz, J = 9.9 Hz, 1 H, 1′′-H_a), 2.92 (s, 6 H, OMe), 3.14 (ddd, J = 10.7 Hz, J = 4.6 Hz, J = 1.1 Hz, 1 H, 1′′-H_b), 3.22 (s, 3 H, OMe), 4.43 (d, J = 6.4 Hz, 1 H, −OC$H_a$$H_b$O−), 4.45 (d, J = 6.4 Hz, 1 H, −OC$H_a$$H_b$O−), 5.22 (s, 2 H, 4-H and 5-H), 7.16−7.27 (m, 20 H, arom.-H). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = ≈ −3 (d, C-1′), 11.1 (t, C-3′), 17.1 (d, C-2′), 51.8 (q, OMe), 54.9 (q, OMe), 69.2 (t, C-1′′), 77.4 (d, C-4/C-5), 83.3 (s, *C*Ph_2OMe), 96.1 (t, −O*C*H_2O−), 127.3, 127.5, 127.8, 128.5, 129.6 (d, arom.-CH), 141.3, 141.5 (s, arom.-C_{ipso}). − **8c:** (first eluted, minor diastereomer) Softening range 55−60 °C. − $[\alpha]_D^{20}$ = −67.8 (c = 0.70, $CHCl_3$). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = −0.33 (ddd, J = 9.9 Hz, J = 8.7 Hz, J = 6.8 Hz, 1 H, 1′-H), −0.23 (ddd, J = 6.8 Hz, J = 5.7 Hz, J = 3.5 Hz, 1 H, 3′-H_{trans}), 0.62 (ddd, J = 9.9 Hz, J = 7.7 Hz, J = 3.5 Hz, 1 H, 3′-H_{cis}), 1.12 (m_c, 1 H, 2′-H), 2.97 (s, 6 H, OMe), 3.15 (s, 3 H, OMe), 3.22 (dd, J = 10.2 Hz, J = 8.0 Hz, 1 H, 1′′-H_a), 3.28 (dd, J = 10.2 Hz, J = 6.6 Hz, 1 H, 1′′-H_b), 4.13 (d, J = 6.5 Hz, 1 H, −OC$H_a$$H_b$O−), 4.25 (d, J = 6.5 Hz, 1 H, −OC$H_a$$H_b$O−), 5.22 (s, 2 H, 4-H and 5-H), 7.20−7.39 (m, 20 H, arom.-H). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = ≈ −3 (d, C-1′), 9.9 (t, C-3′), 17.3 (d, C-2′), 51.7 (q, OMe), 55.0 (q, OMe), 69.1 (t, C-1′′), 77.1 (d, C-4/C-5), 83.3 (s, *C*Ph_2OMe), 95.9 (t, −O*C*H_2O−), 127.2, 127.3, 127.5, 127.7, 128.5, 129.7 (d, arom.-CH), 141.26, 141.35 (s, arom.-C_{ipso}).

Alcohols 9−11. − Method A: The protected boronic ester (1.0 equiv. **6c**, **7c** or **8c**) was dissolved in acetone (100 mL/mmol boronic ester), and sodium iodide (5.0 equiv.) and catalytic amounts of HCl_g were added. The mixture was heated under reflux for 2 d, cooled to room temp., diluted with diethyl ether, washed with water, saturated aqueous sodium bicarbonate, and brine, and dried over $MgSO_4$. The solution was concentrated under reduced pressure and the residue subjected to flash-column chromatography on silica gel, eluting with petroleum ether/EtOAc (95:5 to 4:1). − **Method B:** The protected boronic ester (1.0 equiv. **6c**, **7c** or **8c**) was dissolved in *t*BuOH (100 mL/mmol boronic ester), and pyridinium toluene-4-sulfonate (1.0 equiv.) was added. The mixture was heated under reflux for 18 h, cooled to room temp., and worked-up as usual. − **Method C:** The protected boronic ester (1.0 equiv. **6c**, **7c** or **8c**) was dissolved in MeOH (100 mL/mmol boronic ester), and catalytic amounts of conc. $HCl_{aq.}$ were added. The mixture was kept for 2 h at 62 °C, cooled to room temp., and worked-up as usual.

9: The product was isolated as a white foam in 40% yield (method B). − Softening range 55−60 °C. − $[\alpha]_D^{21}$ = −130 (c = 1.8, $CHCl_3$). − IR (film, NaCl): $\tilde{\nu}$ = 3437 cm^{-1}, 3059, 2938, 2835, 1633, 1494, 1447, 1422, 1373, 1308, 1261, 1185, 1077, 1032. − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.51 (t, J = 6.4 Hz, 1 H, OH), 2.97 (s, 6 H, OMe), 3.76−3.80 (m, 2 H, 3′-H), 5.03 (dt, J = 13.9 Hz, J = 1.4 Hz, 1 H; 1′-H), 5.32 (s, 2 H, 4-H and 5-H), 6.30 (dt, J = 13.9 Hz, J = 6.2 Hz, 1 H, 2′-H), 7.19−7.30 (m, 20 H, arom.-H). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = 51.8 (q, OMe), 61.6 (t, C-3′), 77.6 (d, C-4/C-5), 83.3 (s, *C*Ph_2OMe), 119.0 (br d, C-1′), 127.3, 127.5, 127.65, 127.73, 127.79, 127.9, 129.6 (d, arom.-CH), 141.0, 141.1 (s, arom.-C_{ipso}), 152.0 (d, C-2′). − MS (FAB, NBA + NaI);

m/z (%): 543 (18) [M + Na^+], 197 (100) [Ph_2COMe^+]. − HRMS: $C_{33}H_{33}{}^{10}BO_5Na$: calcd. 543.2319; found 543.2310. − $C_{33}H_{33}BO_5$ (520.4): calcd. C 76.16, H 6.39; found C 76.13, H 6.73.

10: The product was isolated as a white foam in 86% yield (method C); the boronic ester could not be obtained in analytically pure form. − Softening range 50−65 °C. − $[\alpha]_D^{20}$ = −116 (*c* = 2.3, $CHCl_3$). − IR (film, NaCl): $\tilde{\nu}$ = 3580 cm^{-1}, 3060, 3009, 2940, 1494, 1446, 1418, 1365, 1251, 1216, 1187, 1077, 1034. − ^1H NMR (500 MHz, $CDCl_3$): δ = −0.45 (ddd, *J* = 9.9 Hz, *J* = 8.6 Hz, *J* = 6.9 Hz, 1 H, 1′-H), 0.18 (ddd, *J* = 6.9 Hz, *J* = 5.5 Hz, *J* = 3.7 Hz, 1 H, 3′-H_{trans}), 0.60 (ddd, *J* = 9.9 Hz, *J* = 7.8 Hz, *J* = 3.7 Hz, 1 H, 3′-H_{cis}), 0.75 (dd, *J* = 9.4 Hz, *J* = 4.7 Hz, 1 H, OH), 1.10 (m, 1 H, 2′-H), 2.94 (m, 1 H, 1′′-H_a), 2.95 (s, 6 H, OMe), 3.34 (ddd, *J* = 11.9 Hz, *J* = 9.4 Hz, *J* = 5.4 Hz, 1 H, 1′′-H_b), 5.26 (s, 2 H, 4-H and 5-H), 7.17−7.34 (m, 20 H, arom.-H). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = ≈ −4 (d, C-1′), 9.5 (t, C-3′), 20.5 (d, C-2′), 51.8 (q, OMe), 64.0 (t, C-1′′), 77.3 (d, C-4/C-5), 83.3 (s, *C*Ph_2OMe), 127.4, 127.5, 127.7, 127.9, 128.5, 129.6 (d, arom.-CH), 141.0, 141.2 (s, arom.-C_{ipso}). − MS (FAB, NBA + NaI); *m/z* (%): 557 (62) [M + Na^+], 197 (100) [Ph_2COMe^+]. − HRMS: $C_{34}H_{35}{}^{10}BO_5Na$: calcd. 557.2475; found 557.2460.

11: The product was isolated as a white foam in 67% yield (method C); the boronic ester could not be obtained in analytically pure form. − Softening range 57−70 °C. − $[\alpha]_D^{20}$ = −116 (*c* = 0.6, $CHCl_3$). − IR (film, NaCl): $\tilde{\nu}$ = 3408 cm^{-1}, 3060, 3006, 2939, 2839, 2834, 1494, 1446, 1417, 1368, 1187, 1087, 1076, 1032. − ^1H NMR (500 MHz, $CDCl_3$): δ = −0.49 (ddd, *J* = 10.3 Hz, *J* = 8.6 Hz, *J* = 6.9 Hz, 1 H, 1′-H), −0.16 (ddd, *J* = 6.9 Hz, *J* = 5.3 Hz, *J* = 3.7 Hz, 1 H, 3′-H_{trans}), 0.50 (ddd, *J* = 10.3 Hz, *J* = 7.7 Hz, *J* = 3.7 Hz, 1 H, 3′-H_{cis}), 1.04 (m_c, 1 H, 2′-H), 1.75 (m, 1 H, OH), 2.77 (dd, *J* = 11.8 Hz, *J* = 8.1 Hz, 1 H, 1′′-H_a), 2.92 (s, 6 H, OMe), 3.40 (dd, *J* = 11.8 Hz, *J* = 5.8 Hz, 1 H, 1′′-H_b), 5.25 (s, 2 H, 4-H and 5-H), 7.18−7.31 (m, 20 H, arom.-H). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = ≈ −4 (d, C-1′), 8.3 (t, C-3′), 19.2 (d, C-2′), 51.7 (q, OMe), 64.4 (t, C-1′′), 77.7 (d, C-4/C-5), 83.4 (s, *C*Ph_2OMe), 127.4, 127.7, 127.9, 128.6, 129.6 (d, arom.-CH), 140.8, 140.9 (s, arom.-C_{ipso}). − MS (FAB, NBA + NaI); *m/z* (%): 557 (19) [M + Na^+], 197 (100) [Ph_2COMe^+]. − HRMS: $C_{34}H_{35}{}^{10}BO_5Na$: calcd. 557.2475; found 557.2460.

2-Butylcyclopropanol (12): Under an atmosphere of nitrogen, the cyclopropylboronic ester **7a** (485 mg, 0.870 mmol) was dissolved in THF (2 mL) and cooled to −78 °C. $LiAlH_4$ (76 mg, 2.0 mmol) was added and the suspension stirred for 2 h while warming to room temp. The resulting mixture was cooled to −78 °C and 30% H_2O_2 (550 μL, 4.85 mmol) was carefully added (for large-scale reactions it is highly recommended to filter the excess $LiAlH_4$ off, before adding H_2O_2). After slowly warming to room temp., TLC indicated the complete conversion into the product after 2 h. The reaction mixture was carefully quenched at 0 °C with brine (5 mL), the aqueous phase was extracted with diethyl ether (4 × 20 mL), the combined organic layers dried over sodium sulfate, filtered, and the solvent evaporated under reduced pressure. Flash column chromatography (pentane/diethyl ether 10:1) yielded diol **1** (380 mg, 0.840 mmol, 97%) and cyclopropanol **12** (80 mg, 0.70 mmol); yield 81%. GLC proved that the product was a 96:2:2 mixture of enantiomers and the corresponding *trans*-cyclopropanol.[26] − $[\alpha]_D^{21}$ = −11.1 (*c* = 0.7, $CHCl_3$). − IR (film, NaCl): $\tilde{\nu}$ = 3326 cm^{-1}, 3072, 2999, 2958, 2929, 2859, 1467, 1342, 1213. − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.08 (m_c, 1 H, 3-H_a), 0.54−0.63 (m, 2 H, 2-H, 3-H_b), 0.84 (t, *J* = 6.8 Hz, 3 H, 4′-H), 1.23−1.43 (m, 6 H, 1′-H, 2′-H, 3′-H), 1.66 (br s, 1 H, OH), 3.43 (td, *J* = 6.6 Hz, *J* = 3.1 Hz, 1 H, 1-H). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.3 (t, C-3), 14.4 (q, C-4′), 18.6 (t, C-2), 23.0, 26.6, 32.6 (t, C-1′, C-2′, C-3′), 50.5 (d, C-1). − MS (EI, 70 eV); *m/z* (%): 114 (2) [M^+], 96 (12) [M − H_2O^+], 57 (100) [$C_4H_9^+/C_3H_5O^+$]. − HRMS: $C_7H_{14}O$: calcd. 114.1045; found 114.1042.

Alcohol 13. − Determination of Configuration: Under an atmosphere of nitrogen an analytical sample of cyclopropanol **12** (35 mg, 0.31 mmol, 60% *ee*) was dissolved in CH_2Cl_2 (1 mL). Mercury trifluoroacetate (185 mg, 0.400 mmol) and MeOH (0.3 mL) were added, and the resulting mixture stirred at room temp. for 18 h. Sodium chloride (2 g) was added, the slurry stirred for 15 min, filtered, washed with CH_2Cl_2, and the solvent evaporated under reduced pressure. The crude product was dissolved in THF (1 mL)and $LiAlH_4$ (180 mg, 5.00 mmol) was added, and the resulting mixture stirred for 6 h. After addition of diethyl ether (5 mL), the reaction was quenched with brine, the layers separated, and the ethereal phase dried over sodium sulfate. The filtered sample was directly subjected to GLC analysis, proving the (*S*)-configuration of the major enantiomer. A racemic reference (*rac*)-**13** had been selectively, lipase-catalyzed (Amano PS) acetylated with vinyl acetate in CH_2Cl_2 as described by Barth and Effenberger,[21] giving predominantly (*S*)-**14** and (*R*)-**13** (47% *ee* after 4 h). − Glc: Bondex-un-α-3,8-un-β-3,4-Et116, 0.6 bar H_2;[27] 50 °C, 3 min iso, 1 °C/min; t_r (*R*)-**13**: 13.45 min; t_r (*S*)-**13**: 13.75 min. − IR (film, NaCl): $\tilde{\nu}$ = 3338 cm^{-1}, 2958, 2928, 2874, 1467, 1379, 1040. − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.1 Hz, 3 H, 6-H), 0.90 (d, *J* = 6.7 Hz, 3 H, Me), 1.09 (m_c, 1 H, 3-H_a), 1.20−1.42 (m, 6 H, OH, 3-H_b, 4-H, 5-H), 1.59 (m_c, 1 H, 2-H), 3.40 (dd, *J* = 10.5 Hz, *J* = 6.6 Hz, 1 H, 1-H_a), 3.50 (dd, *J* = 10.5 Hz, *J* = 5.8 Hz, 1 H, 1-H_b). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1 (q, C-6), 16.6 (q, Me), 23.0, 29.2, 32.8, 35.7 (C-2, C-3, C-4, C-5), 68.4 (t, C-1). − MS (EI, 70 eV); *m/z* (%): 115 (2) [(M − 1)$^+$], 98 (11) [M − H_2O^+], 85 (33) [M − $MeOH^+$], 56 (100) [$C_4H_8^+$]. − $C_7H_{16}O$ (116.2): calcd. C 72.35, H 13.88; found C 72.21, H 13.93.

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