Efficient Asymmetric Synthesis of 2,6-Disubstituted 2*H*-Dihydropyrans *via* a Catalytic Hetero-Diels–Alder/Allylboration Sequence

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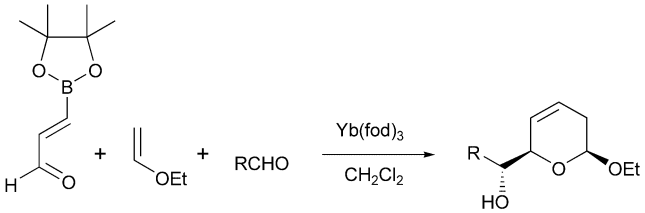
Received: July 31, 2003; Accepted: September 2, 2003

Abstract: [4+2] Cycloaddition of (*E*)-3-borylacrolein **1** with ethyl vinyl ether, catalysed by chromium complex (1*R*,2*S*) or (1*S*,2*R*) **2**, led to the corresponding cycloadducts with high diastereo- and enantioselectivities. Further reaction with aldehydes offers an attractive asymmetric route to synthetically useful substituted 3,4-dihydro-2*H*-pyrans.

Keywords: allylboration; asymmetric catalysis; boronic esters; chromium complex; dihydropyrans; hetero-Diels–Alder



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Scheme 1.

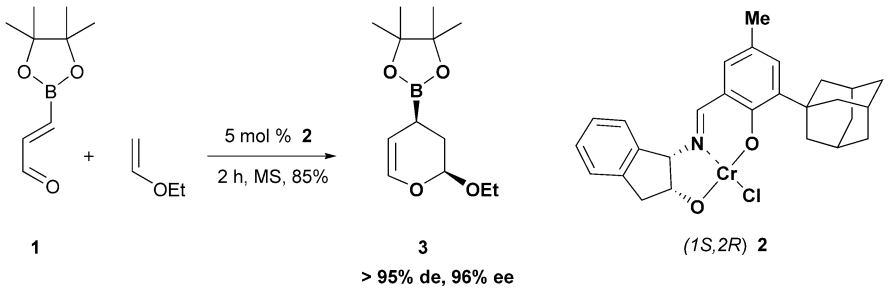
Hetero-Diels–Alder reactions provide a powerful method for the synthesis of oxygen-containing six-membered heterocycles, an important substructure in a large variety of bioactive compounds. This explains the wide range of substrates and catalysts hitherto involved in theses cycloadditions.[1] On the other hand, due to their great versatility, organoboranes have emerged as especially attractive building blocks in organic synthesis.[2,3] Thus, the replacement of the carbon-boron bond by a new carbon-carbon or carbon-heteroatom bond has been largely employed in stereocontrolled syntheses of diversely substituted alkenes, the Suzuki–Miyaura coupling reaction being probably the most attractive process.[4] Cycloadditions involving an alkenyl- or dienyl boronic esters have been also reported, but rarely in asymmetric versions.[5–7] In all cases, stoichiometric amounts of chiral auxiliaries at the borylated moiety or at a proximal position have been employed. We have recently described a new approach for the synthesis of racemic dihydropyrans derivatives, based on a multicomponent reaction: an inverse electron-demand hetero-Diels–Alder reaction of 3-borylacrolein **1**, followed by an allylboration (Scheme 1).[8,9] Recent impressive results obtained by Jacobsen et al. in the field of asymmetric catalysis with chiral chromium(III) complexes[10] led us to study the asymmetric version of our sequence,[11] which would undoubtedly increase the potential of this strategy for further applications in natural products synthesis.

Results and Discussion

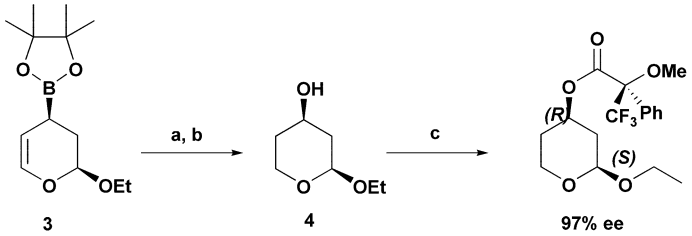
We first examined the [4+2] cycloaddition of the heterodiene **1** to ethyl vinyl ether in the presence of 5 mol % of catalyst **2**, according to Jacobsen's procedure.[10] This reaction was carried out with 4 Å molecular sieves as desiccant and the dienophile as solvent and afforded the expected dihydropyran **3** in good yield (85%) with high diastereo- and enantiomeric excess (> 95% de and 96% ee). The stereoselectivities were measured on the cycloadduct by ^{1}H NMR and GC analysis using a chiral stationary phase, as well as by comparison with a racemic mixture previously prepared in the presence of Yb(fod)$_3$ as catalyst.[9] It is worthy of note that the presence of the boronic ester group significantly increased the rate of the reaction: 100% conversion after 2 h at rt, instead of 24–48 h for the same substrate with a methyl or an aryl substituent.[10] Other vinyl ethers engaged in such cycloadditions with **1** gave unsatisfactory results.

In order to establish the stereochemistry of **3**, oxidation of the cycloadduct by H_2O_2/NaOH or AcONa or by triethylamine *N*-oxide was first tried. This transformation, which was proven to proceed with retention of configuration, was found to give modest yields of the corresponding allylic alcohol and to be unreproducible; this led us to reduce first the double bond of the

 DOI: 10.1002/adsc.200303127

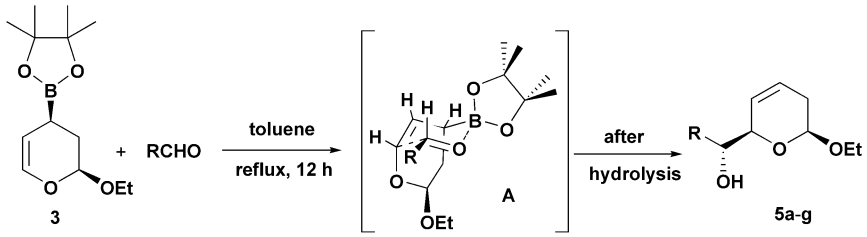


Scheme 2.



a) H_2, Pd/C 10%, AcOEt, 1 h ; b) H_2O_2 35% w/w, NaOH 3 M, THF, 0 °C, 1 h, then K_2CO_3 (95% two steps); c) (*R*)-MTPACl, DMAP, CH_2Cl_2, rt, 1 h, then $NaHCO_3$ (80%).

Scheme 3.



Scheme 4.

cyclohexene ring before achieving the oxidation (Scheme 3). The secondary alcohol **4** was obtained in a 95% yield. Analysis of the Mosher's ester confirmed the isomeric purity of **3** previously measured by chiral gas chromatography and allowed us to determine the absolute configurations by ^{1}H NMR: (2*S*,4*R*)-**4** and therefore (2*S*,4*S*)-**3**.[12] Similar experiments performed with the (1*R*,2*S*)-enantiomer of **2** gave the same results in terms of yield and stereoselectivities. No attempt was made in this preliminary work to decrease the amount of catalyst and to correlate it with the efficiency of the cycloaddition.

Having in hand an efficient asymmetric synthesis of **3**, we next turned our attention to its reactivity towards aldehydes (Scheme 4). Reaction of the cyclic allylborane (2*S*,4*S*)-**3** with benzaldehyde in toluene for 12 h at 70 °C gave after hydrolysis the corresponding homoallylic alcohol **5a** in 85% yield. A >95% diastereoisomeric excess was determined by ^{1}H NMR, while the enantiomeric purity (95% ee) was measured by chiral gas chromatography. Moreover, the stereospecificity of the allylboration process was confirmed by performing the same reaction with the enantiomer (2*R*,4*R*)-**3**. Within the experimental errors, the same purity was measured in both cases, closely paralleling the enantiomeric excess of the starting material. The relative configuration of the stereogenic centres is in full agreement with a cyclic chair-like transition state **A** with the phenyl group of benzaldehyde in an equatorial position, that was currently observed with other cyclic allylboronic esters.[7d,13] The results obtained with other representative aldehydes are collected in Table 1. In all cases, dihydropyrans **5a – g** were obtained in good yields and high stereochemical purities. An X-ray crystal structure determination of **5g** established the absolute configurations of its four stereocentres. (Fig. 1).[14] Unfortunately, attempts to carry out the two steps, cycloaddition/allylboration, in the same pot, gave unsatisfactory results (low yield and ee).[15]

In summary, we have developed an asymmetric version of the hetero-Diels–Alder cycloaddition of (*E*)-3-borylacrolein to ethyl vinyl ether catalysed by a

Table 1. Allylation reactions of (2*S*,4*S*)-**3** using various aldehydes.

Product	R[a]	Yield [%][a]	ee [%][b]	Absolute conf.
5a	Ph	85	95[c]	(2*S*,6*R*,7*R*)
5b	4-MeO-C_6H_4	84	96	(2*S*,6*R*,7*R*)
5c	4-Cl-C_6H_4	77	93	(2*S*,6*R*,7*R*)
5d	4-F-C_6H_4	80	96	(2*S*,6*R*,7*R*)
5e	$PhCH_2$	82	96	(2*S*,6*R*,7*R*)
5f	$PhCH_2CH_2$	87	96 [c]	(2*S*,6*R*,7*R*)
5g	(2*R*)-Ph-CH(OTBDPS)	78	95	(2*S*,6*R*,7*S*,8*R*)

[a] Yields of isolated products after column chromatography.
[b] Determined by chiral GC analysis.
[c] The same reaction performed with (2*R*,4*R*)-**3** gave the opposite enantiomer with the same ee.

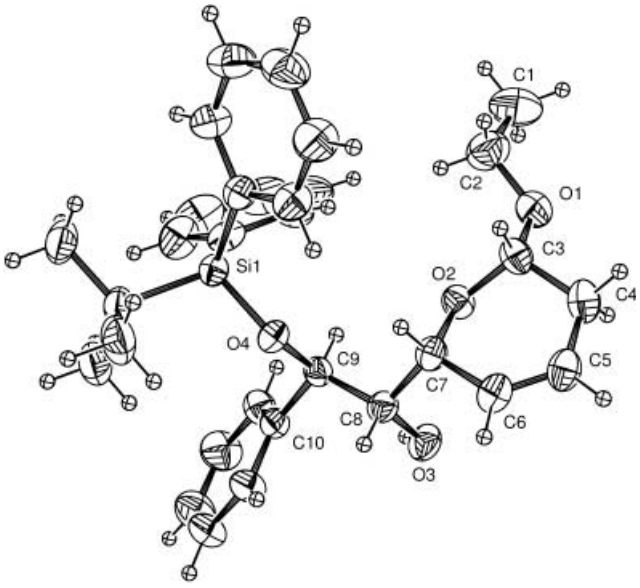


Figure 1. X-ray crystal structure of **5g**.

chiral (Schiff base)chromium(III) complex. Further reactions with aldehydes allow access to a series of 2,6-disubstituted dihydropyrans with a high diastereo- and enantiomeric purity. Studies to expand the scope of this three-components reaction and to apply this strategy in asymmetric synthesis of natural products, particularly in the field of carbohydrate chemistry, are ongoing.

Experimental Section

All chemicals were used as received unless otherwise noted. Catalyst (1*S*,2*R*)-**2** was prepared according to the literature [10], while its enantiomer was kindly donated by Eric N. Jacobsen and D. Chavez. Toluene and ethyl vinyl ether were distilled from sodium/benzophenone. All aldehydes were freshly distilled prior to use. (2*R*)-Phenyl[(trimethylsilyl)oxy]acetaldehyde[16] and 3-borylacrolein **1**[8] were prepared according to literature procedures. 8–12 Mesh 4 Å molecular sieves were dried in a vacuum oven for 12 hours at 160 °C. NMR spectra were recorded with a Brüker spectrometer at 300 (^{1}H NMR) and 75 (^{13}C NMR) MHz. Chemical shifts are reported as δ values downfield from tetramethylsilane. High resolution mass spectra were obtained on an MS/MS ZABSpec TOF Micromass at the Centre Régional de Mesures Physiques de l'Ouest. Optical rotations were recorded using a Perkin Elmer Model 341 polarimeter. Analytical thin layer chromatography was performed on Merck Silica gel 60 F254 aluminium. Column chromatography was performed on Merck silica gel (Geduran 0.063–0.200 mm). Enantiomeric excesses were determined by gas chromatography performed using a Varian CP3380 GC unit equipped with a capillary chiral column Varian WCOT Fused Silica 25 m × 0.25 mm coated CP Chirasil-dex CB DF = 0.25. Chromatography conditions: carrier gas argon; injection temperature 200 °C; detector temperature 250 °C.

(2*S*)-Ethoxy-(4*S*)-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydro-2*H*-pyran (3):

182 mg (1 mmol) of 3-borylacrolein **1**, 150 mg of 4 Å molecular sieves, 24 mg (0.05 mmol, 5 mol %) of dimer (1*S*,2*R*)-catalyst **2** in 960 μL of ethyl vinyl ether were placed in an oven-dried 10-mL round-bottom flask. After stirring for 2 hours at rt, the reaction mixture was diluted with pentane and filtered through a pad of celite. The solvents were removed under vacuum and the product distilled with a Kügelrohr apparatus (oven: 90 °C, 1 mmHg) to afford **3** as a clear oil; yield: 215 mg (0.085 mmol, 85%). ^{1}H NMR ($CDCl_3$): δ = 1.26 (t, 3H, J = 7.1 Hz), 1.30 (s, 12H), 1.81 (m, 1H), 2.19 (m, 2H), 3.64 (dq, 1H, J = 9.9, 7.1 Hz), 3.90 (dq, 1H, J = 9.9, 7.1 Hz), 4.88 (dd, 1H, J = 6.1, 4.5 Hz), 5.04 (dd, 1H, J = 3.5, 3.1 Hz), 6.29 (dd, 1H, H-5, J = 6.2, 2.0 Hz); ^{13}C NMR ($CDCl_3$): δ = 15.7 (CH_3), 25.0 (CH_3), 25.3 (CH_3), 29.1 (CH_2), 63.8 (CH_2), 83.7 (C), 97.1 (CH), 103.1 (CH), 139.4 (CH); HRMS (EI): [M –.OC_2H_5]$^+$ calcd. for $C_{11}H_{18}O_3B$: 209.1349; found: 209.133; $[\alpha]_D^{25}$: +27.3 (*c* 1.41, CH_2Cl_2). Assay of enantiomeric excess: Chiral GC analysis (Chirasil-dex; 80 to 100 °C at 5 °C/min, then 100 to 180 °C at 0.5 °C/min, 15 psi head column pressure; t_R(major) = 63.14 min, t_R(minor) = 64.28 min).

(2*S*)-Ethoxy-(4*R*)-hydroxy-3,4-dihydro-2*H*-pyran (4)

In an oven-dried 10-mL round-bottom flask, 430 mg (1.67 mmol) of (2*S*,4*S*)-(**3**), 170 mg of Pd/C 10% in 10 mL of ethyl acetate were stirred for one hour under hydrogen atmosphere. After filtration through celite and evaporation

of solvent, the residue was taken up in 10 mL of THF. At 0 °C, 676 μL (6.76 mmol) of H_2O_2 35% w/w in water and 2.2 mL (6.76 mmol) of 3 M NaOH were successively added. After stirring for one hour at 0 °C, the mixture was saturated with solid K_2CO_3 and stirred for 30 min. The mixture was extracted with ether and dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by column chromatography (heptane/AcOEt, 1/1) on SiO_2 deactivated with triethylamine to afford **4**; yield: 222 mg (1.59 mmol, 95%). ^{1}H NMR ($CDCl_3$): δ = 1.28 (t, 3H, J = 7.1 Hz), 1.94 (m, 4H), 3.54 (m, 3H), 3.83 (dq, 1H, J = 9.7, 7.1 Hz), 4.07 (m, 2H), 4.81 (t, 1H, J = 3.1 Hz); ^{13}C NMR ($CDCl_3$): δ = 15.5 (CH_3), 33.2 (CH_2), 37.1 (CH_2), 56.2 (CH_2), 64.2 (CH_2), 64.6 (CH), 98.3 (CH); $[\alpha]_D^{25}$: +43.1 (*c* 1.00, $CHCl_3$).

General Procedure for the Allylboration Reactions

A solution of 1 mmol of **3** and 2 mmol of aldehyde in 2 mL of toluene was heated at 70 °C. The reaction was monitored by GC and allowed to stir until complete consumption of **3**. After addition of a saturated solution of NH_4Cl, the aqueous layer was extracted twice with CH_2Cl_2. Combined organic layers were washed with saturated NaCl, dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by column chromatography (heptane/AcOEt, 9/1) on SiO_2 deactivated with triethylamine to yield **5a – g** as indicated in Table 1.

(2*S*,6*R*,7*R*)-3,6-Dihydro-2*H*-pyran (5a): yield: 85% (198 mg, 0.85 mmol). ^{1}H NMR ($CDCl_3$): δ = 1.31 (t, 3H, J = 7.1 Hz), 2.30 (m, 2H), 3.00 (br s, 1H), 3.62 (dq, 1H, J = 9.6, 7.1 Hz), 4.05 (dq, 1H, J = 9.6, 7.1 Hz), 4.39 (m, 1H), 4.61 (d, 1H, J = 7.5 Hz), 4.82 (t, 1H, J = 5.4 Hz), 5.42 (m, 1H), 5.80 (m, 1H), 7.40 (m, 5H); ^{13}C NMR ($CDCl_3$): δ = 15.6 (CH_3), 31.4 (CH_2), 64.9 (CH_2), 77.2 (CH), 79.1 (CH), 98.9 (CH), 125.3 (CH), 125.8 (CH), 127.7 (CH), 128.5 (CH), 128.8 (CH), 140.3 (C); HRMS (EI): $[M-{}^{\bullet}CHOH-Ph]^+$, calcd. for $C_7H_{11}O_2$: 127.0759; found: 127.076; $[\alpha]_D^{25}$: +24.9 (*c* 1.03, $CHCl_3$). Assay of enantiomeric excess: Chiral GC analysis (Chirasil-dex; 80 to 100 °C at 5 °C/min, then 100 to 180 °C at 1 °C/min, 10 psi head column pressure; t_R(major) = 68.37 min, t_R(minor) = 68.74 min).

(2*S*,6*R*,7*R*)-3,6-Dihydro-2*H*-pyran (5b): yield: 84% (221 mg, 0.84 mmol). ^{1}H NMR ($CDCl_3$): δ = 1.28 (t, 3H, J = 7.1 Hz), 2.29 (m, 2H), 3.40 (br s, 1H), 3.64 (dq, 1H, J = 9.5, 7.0 Hz), 3.84 (s, 3H), 4.06 (dq, 1H, J = 9.5, 7.0 Hz), 4.38 (m, 1H), 4.63 (d, 1H, J = 7.8 Hz), 4.83 (t, 1H, J = 5.4 Hz), 5.39 (m, 1H), 5.82 (m, 1H), 6.96 (d, 2H, J = 8.7 Hz), 7.35 (d, 2H, J = 8.7 Hz); ^{13}C NMR ($CDCl_3$): δ = 15.2 (CH_3), 31.1 (CH_2), 64.5 (CH_2), 76.5 (CH), 78.9 (CH), 98.6 (CH), 113.8 (CH_3), 124.8 (CH), 125.5 (CH), 128.6 (CH), 132.0 (C), 159.4 (C); HRMS (EI): $[M]^{+\cdot}$, calcd. for $C_{15}H_{20}O_4$: 264.1362; found: 264.136. $[\alpha]_D^{25}$: +76.4 (*c* 1.02, $CHCl_3$). Assay of enantiomeric excess: Chiral GC analysis (Chirasil-dex; 80 to 100 °C at 5 °C/min, then 100 to 180 °C at 1 °C/min, 10 psi head column pressure; t_R(major) = 75.00 min, t_R(minor) = 74.31 min).

(2*S*,6*R*,7*R*)-3,6-Dihydro-2*H*-pyran (5c): yield: 77% (207 mg, 0.77 mmol). ^{1}H NMR ($CDCl_3$): δ = 1.26 (t, 3H, J = 7.1 Hz), 2.26 (m, 2H), 3.30 (br s, 1H), 3.58 (dq, 1H, J = 9.6, 7.1 Hz), 3.98 (dq, 1H, J = 9.6, 7.1 Hz), 4.32 (m, 1H), 4.61 (d, 1H, J = 7.0 Hz), 4.79 (t, 1H, J = 5.5 Hz), 5.38 (m, 1H), 5.84 (m, 1H), 7.33 (m, 4H); ^{13}C NMR ($CDCl_3$): δ = 15.2 (CH_3), 30.9 (CH_2), 64.5 (CH_2), 76.0 (CH), 78.4 (CH), 98.4 (CH), 125.1 (CH), 125.2 (CH), 128.5 (CH), 128.6 (CH), 133.7 (C), 138.6 (C). Anal calcd. for $C_{14}H_{17}ClO_3$: C 62.57, H 6.38; found: C 62.76, H 6.81. $[\alpha]_D^{25}$: +48.4 (*c* 1.00, $CHCl_3$). Assay of enantiomeric excess: Chiral GC analysis (Chirasil-dex; 80 to 100 °C at 5 °C/min, then 100 to 180 °C at 1 °C/min, 10 psi head column pressure; t_R(major) = 86.62 min, t_R(minor) = 85.58 min).

(2*S*,6*R*,7*R*)-3,6-Dihydro-2*H*-pyran (5d): yield: 80% (202 mg, 0.80 mmol). ^{1}H NMR ($CDCl_3$): δ = 1.30 (t, 3H, J = 7.1 Hz), 2.31 (m, 2H), 3.43 (br d, 1H, J = 2.2 Hz), 3.67 (dq, 1H, J = 9.5, 7.1 Hz), 4.06 (dq, 1H, J = 9.5, 7.1 Hz), 4.36 (m, 1H), 4.65 (dd, 1H, J = 7.3, 2.2 Hz), 4.83 (t, 1H, J = 5.4 Hz), 5.44 (m, 1H), 5.83 (m, 1H), 7.09 (m, 2H), 7.44 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 15.2 (CH_3), 31.0 (CH_2), 64.6 (CH_2), 76.2 (CH), 78.7 (CH), 98.5 (CH), 115.0 (CH), 115.4 (CH), 125.1 (CH), 125.4 (CH), 128.8 (CH), 129.0 (CH), 136.2 (C), 136.3 (C), 160.0 (C), 164.0 (C); HRMS (EI): $[M-{}^{\bullet}OCH_2CH_3]^+$, calcd. for $C_{12}H_{12}FO_2$: 207.0821; found: 207.083. Anal calcd. for $C_{14}H_{17}FO_3$: C 68.16, H 7.63; found: C 68.16, H 7.81. $[\alpha]_D^{25}$: +13.7 (*c* 1.00, $CHCl_3$). Assay of enantiomeric excess: Chiral GC analysis (Chirasil-dex; 80 to 100 °C at 5 °C/min, then 100 to 180 °C at 1 °C/min, 10 psi head column pressure; t_R(major) = 69.88 min, t_R(minor) = 68.70 min).

(2*S*,6*R*,7*R*)-3,6-Dihydro-2*H*-pyran (5e): yield: 82% (203 mg, 0.82 mmol). ^{1}H NMR ($CDCl_3$): δ = 1.25 (t, 3H, J = 7.1 Hz), 2.30 (m, 2H), 2.60 (br d, 1H, J = 6.6 Hz), 3.00 (m, 2H), 3.66 (dq, 1H, J = 9.5, 7.1 Hz), 3.88 (m, 1H), 4.09 (dq, 1H, J = 9.5, 7.1 Hz), 4.20 (m, 1H), 4.80 (t, 1H, J = 5.4 Hz), 5.70 (m, 1H), 5.89 (m, 1H), 7.31 (m, 5H); ^{13}C NMR ($CDCl_3$): δ = 15.7 (CH_3), 31.4 (CH_2), 40.0 (CH_2), 64.9 (CH_2), 74.7 (CH), 75.7 (CH), 98.9 (CH), 125.4 (CH), 126.6 (CH), 126.9 (CH), 128.9 (CH), 129.8 (CH), 138.9 (C); HRMS (EI): $[M-HOC_2H_5]^{1+}$, calcd. for $C_{13}H_{14}O_2$: 202.0994; found: 202.099. $[\alpha]_D^{25}$: +23.7 (*c* 1.00, $CHCl_3$). Assay of enantiomeric excess: Chiral GC analysis (Chirasil-dex; 80 to 100 °C at 5 °C/min, then 100 to 180 °C at 1 °C/min, 10 psi head column pressure; t_R(major) = 75.93 min, t_R(minor) = 76.66 min).

(2*S*,6*R*,7*R*)-3,6-Dihydro-2*H*-pyran (5f): yield: 87% (228 mg, 0.87 mmol). ^{1}H NMR ($CDCl_3$): δ = 1.17 (t, 3H, J = 7.1 Hz), 1.82 (m, 2H), 2.15 (m, 2H), 2.60 (br d, 1H, J = 5.8 Hz), 2.64 (m, 1H), 2.81 (m, 1H), 3.47 (m, 2H), 3.89 (dq, 1H, J = 9.5, 7.1 Hz), 4.08 (m, 1H), 4.66 (dd, 1H, J = 5.4, 6.0 Hz), 5.54 (m, 1H), 5.74 (m, 1H), 7.14 (m, 5H); ^{13}C NMR ($CDCl_3$): δ = 15.2 (CH_3), 31.0 (CH_2), 32.0 (CH_2), 35.0 (CH_2), 64.4 (CH_2), 72.6 (CH), 77.3 (CH), 98.5 (CH), 124.9 (CH), 125.8 (CH), 126.5 (CH), 128.4 (CH), 128.5 (CH), 142.2 (C); HRMS (EI): $[M-HOC_2H_5]^+$, calcd. for $C_{14}H_{16}O_2$: 216.1150; found: 216.115. $[\alpha]_D^{25}$: +70.7 (*c* 1.00, $CHCl_3$). Assay of enantiomeric excess: Chiral GC analysis (Chirasil-dex; 80 to 100 °C at 5 °C/min, then 100 to 180 °C at 1 °C/min, 15 psi head column pressure; t_R(major) = 82.16 min, t_R(minor) = 81.35 min).

(2*S*,6*R*,7*S*,8*R*)-3,6-Dihydro-2*H*-pyran (5g): mp 139 °C; yield: 78% (391 mg, 0.78 mmol). ^{1}H NMR ($CDCl_3$): δ = 1.02 (s, 9H), 1.18 (t, 3H, J = 7.1 Hz), 2.19 (m, 2H), 2.47 (d, 1H, J = 7.9 Hz), 3.30 (dq, 1H, J = 9.5, 7.1 Hz), 3.72 (dq, 1H, J = 9.5, 7.1 Hz), 3.78 (td, 1H, J = 7.8, 2.6 Hz), 4.63 (dd, 1H, J = 6.1, 4.6 Hz), 4.73 (m, 1H), 4.82 (d, 1H, J = 7.6 Hz), 5.63 (m, 1H), 5.80 (m, 1H), 7.40 (m, 13H), 7.68 (dd, 2H, J = 7.8, 1.4 Hz); ^{13}C NMR ($CDCl_3$): δ = 15.5 (CH_3), 19.8 (C), 27.4 (CH_3), 31.2 (CH_2), 64.6 (CH_2), 73.5 (CH), 76.3 (CH), 77.3 (CH), 98.4 (CH), 124.9 (CH), 127.9 (CH), 127.6 (CH), 127.8 (CH), 128.2 (CH), 128.4 (CH), 129.8 (CH), 129.9 (CH), 136.4 (CH), 136.5 (CH), 133.7 (C), 134.4 (C), 141.7 (C). $[\alpha]_D^{25}$: +39.3 (*c* 1.04, $CHCl_3$.

HRMS (EI): $[M-HOC_2H_5 - t\text{-Bu}]^+$, calcd. for $C_{25}H_{23}O_3Si$: 399.1417; found: 399.141.

Acknowledgements

*We are grateful to MJENT for a grant. We thank Prof. E. N. Jacobsen and D. Chavez (Harvard University, Cambridge, USA) for a gift of (1*R,2S*)-**2** and Paul Le Maux (UMR 6509, Rennes France) for his help in chiral GC analysis.*

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