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Stereospecific cyclization of a pseudo-C_2-symmetric unsaturated diol

Bogdan R. Brutiu, Phillip. S. Grant, Daniel Kaiser, and Nuno Maulide*

Institute of Organic Chemistry, University of Vienna, Währinger Straße 38, 1090 Vienna, Austria
Email: nuno.maulide@univie.ac.at

Dedicated fondly to Prof. Léon Ghosez for his pioneering work on chemical reactivity

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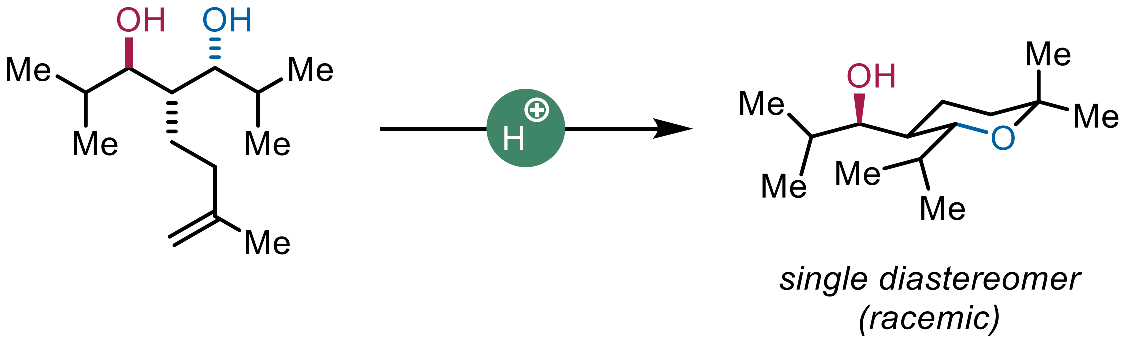
Abstract

The role of chirality in determining molecular functions in biologically active systems, and the importance of investigating single enantiomers of chiral drugs, has resulted in an increasing need for selective synthetic tools for asymmetric synthesis. The efficient desymmetrization of a pseudo-C_2-symmetric 1,3-diol *via* an acid-catalyzed cyclization is described. The process, mediated by TfOH in hexafluoroisopropanol (HFIP), was based on a serendipitous discovery.



Keywords: Asymmetric synthesis, Brønsted acids, hexafluoroisopropanol, tetrahydropyran, cyclization, desymmetrization

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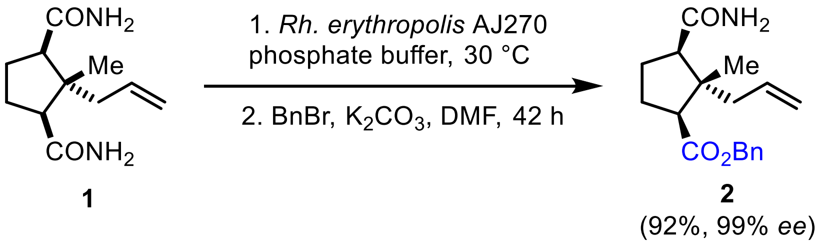
Introduction

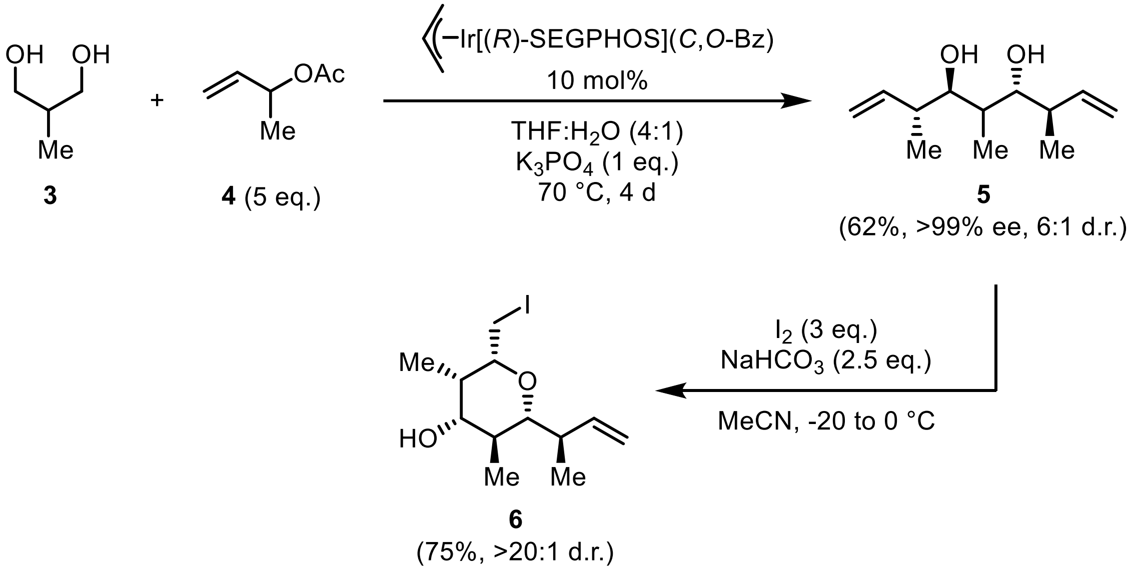
The role of chirality in determining molecular function in biological systems has long been acknowledged. It has, accordingly, become common practice to investigate single enantiomers of chiral drugs, pesticides or fragrances in order to prevent undesired effects in commercial applications.[1] This, in turn, has created an ever-growing need for selective synthetic tools which allow access to single enantiomers of target molecules, and the field of asymmetric synthesis has flourished. Among the many strategies established over the past decades, kinetic resolution,[2] dynamic kinetic resolution and dynamic kinetic asymmetric transformations have all sought to transform racemates into single enantiomeric products.[3]

An alternative strategy, the desymmetrization of *meso*-compounds,[4-8] has also become a widely used tool in the arsenal of enantioselective synthesis. For instance, in a report by Wang *et al.*,[9] *meso*-cyclopentane-1,3-dicarboxamides (**1**) were hydrolytically desymmetrized in biocatalytic fashion (Scheme 1).



Scheme 1. Desymmetrization of *meso*-cyclopentane-1,3-dicarboxamides.[9]

Additionally, Krische *et al.*[10] developed a process for the direct synthesis of polypropionates via iridium-catalyzed double crotylation and effective desymmetrization of 1,3-propanediols [e.g., **3** (Scheme 2)]. In the example shown, iodocyclization of **5** into **6** enabled further stereochemical assignment.

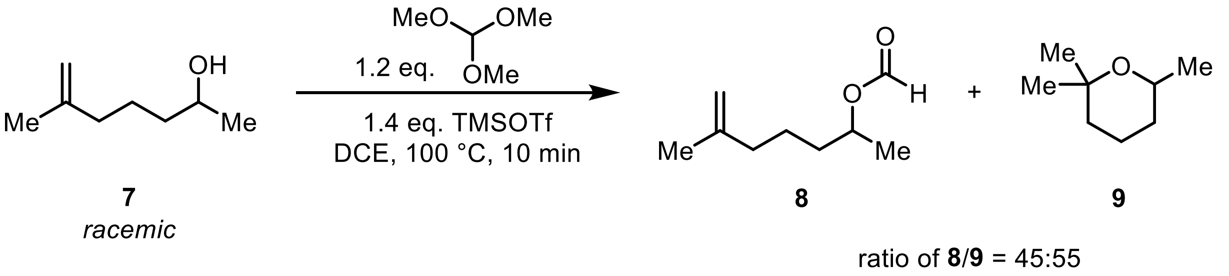


Scheme 2. Selected example of desymmetrization of diol **5**.[10]

Given the similarity between diol **5** and compounds currently investigated in our group, we hypothesized about exploring different cyclization modes which could deploy the stereochemical features of compounds such as **5** to our advantage (*vide infra*).

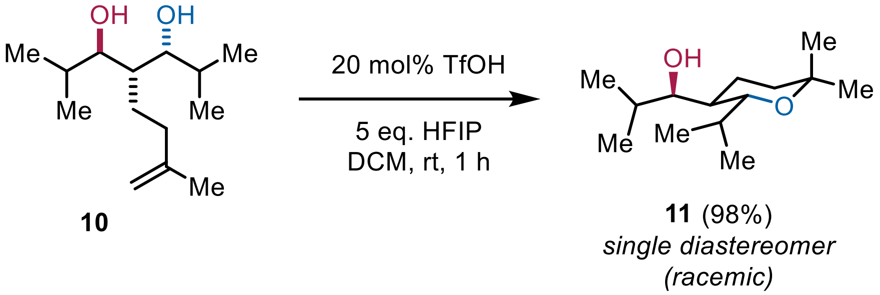
Results and Discussion

During ongoing studies of Lewis acid-promoted reactions involving 1,5-hydride transfer processes,[11, 12] alcohol **7** was treated with 1.4 eq. of trimethylsilyl trifluoromethanesulfonate (TMSOTf) in the presence of a slight excess of trimethylorthoformate. The resulting reaction mixture showed a significant amount of the formate ester **8** and the unanticipated hydroalkoxylation product **9**, with no other products observed (Scheme 3). Further studies on related systems (not shown) revealed that a combination of 20 mol % TfOH and 5 eq. HFIP in DCM at room temperature for 1 hour allows full conversion of alcohol **7** to the tetrahydropyran derivative **9**. Further studies on related compounds are ongoing.



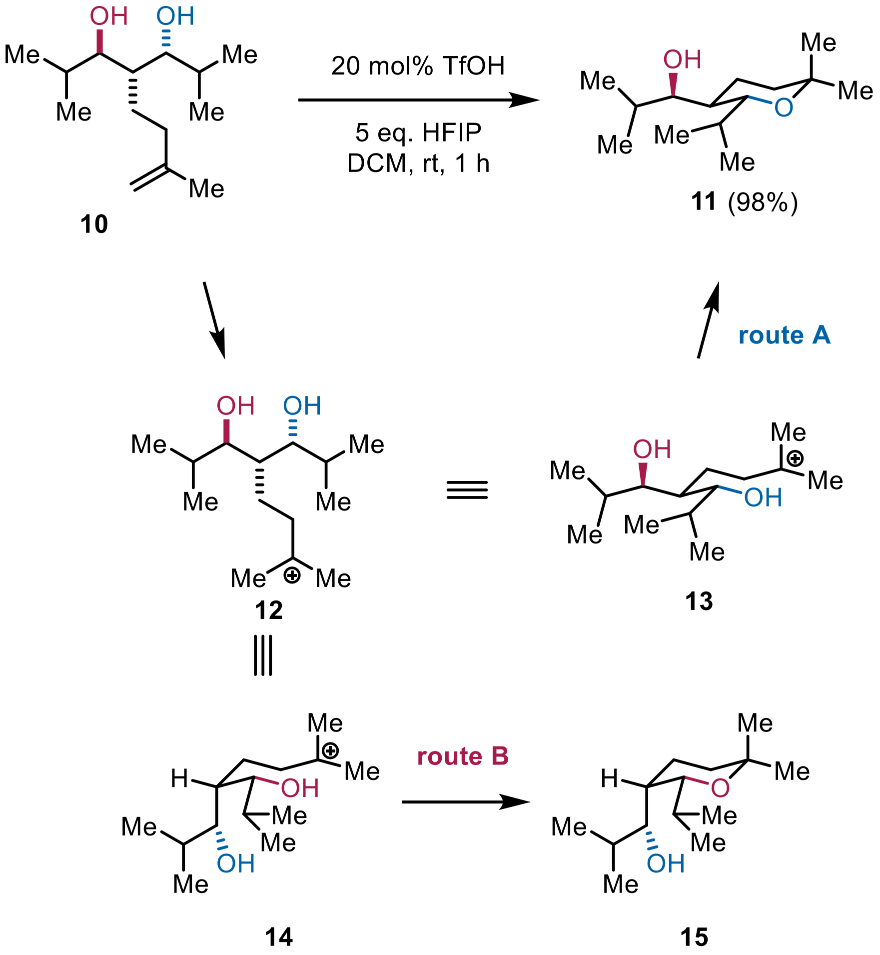
Scheme 3. Serendipitous discovery of Brønsted Acid catalyzed intramolecular hydroalkoxylation of **7**.

With these conditions in hand, we wished to explore a more sophisticated substrate: the pseudo-C_2-symmetric 1,3-diol **10**. Exposure of this compound to the aforementioned optimized conditions led to full conversion within 60 minutes and, following workup and purification, isolation of a single diastereomeric product (**11**, Scheme 4), which has been fully characterized.



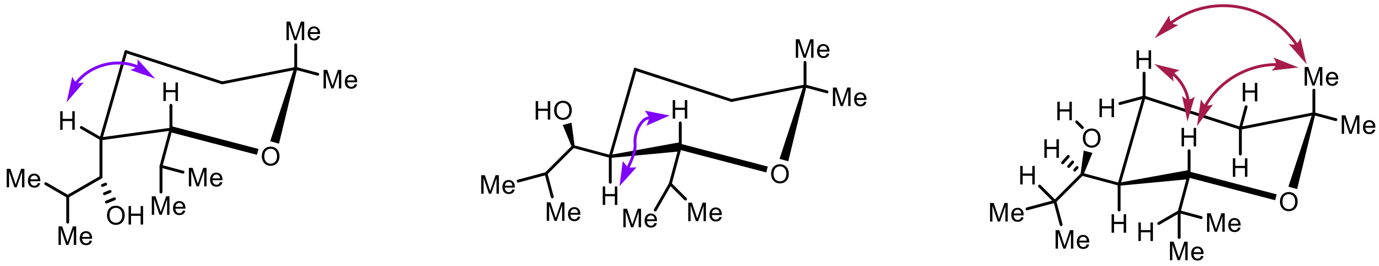
Scheme 4. Intramolecular hydroalkoxylation of pseudo-C_2-symmetric 1,3-diol **10**.

Interestingly, the product obtained is the result of a desymmetrization process where one hydroxyl group appears to have reacted with overwhelming preference. In the first step of the proposed reaction mechanism, protonation of the double bond by the strong Brønsted acid TfOH occurs, generating a tertiary carbocation (**12**) (Scheme 5). At this point, the substrate can evolve through two possible pathways, outlined as route A and route B. These routes differ in the hydroxyl group (red or blue) which cyclizes onto the carbocation. Although one could conceivably expect a mixture of products from this reaction, experiments revealed a clear preference for route A. Indeed, conformational analysis of the cationic intermediate suggests that this route places all substituents of the nascent 6-membered ring in an equatorial orientation (intermediate **13**). Route B, in contrast, would mandate axial orientation of the hydroxyl-bearing isobutyl group (intermediate **14**). While the stereochemical outcome of the reaction can be rationalized by conformational considerations, the remarkable efficiency of this transformation depends heavily on the use of HFIP as a co-solvent. We believe that HFIP acts as a highly efficient mediator for proton-transfer processes, as previously reported by our group and others.[13-15]



Scheme 5. Proposed mechanism.

The conformational rationale for the stereoselectivity of this reaction is in accordance with the 2D NMR analysis (COSY and NOESY) of the obtained product **11**. Indeed, NMR analysis shows a coupling constant (^3J) of 10.1 Hz between the two hydrogens highlighted in Scheme 6 (left and middle structures). This coupling-constant value corresponds to a *trans* (diaxial) orientation and supports the structure assignment. Additionally, the 1,3-diaxial interactions between all three axial substituents on the same face of the tetrahydropyran are detectable in NOESY (Scheme 6, right structure), further confirming our assignment (for additional information and all NMR data, see the Supporting Information).



Karplus value: J = 2-5 Hz

Karplus value: J = 8-15 Hz

is J = 10.1 Hz

most relevant NOESY

Scheme 6. ^{1}H NMR analysis.

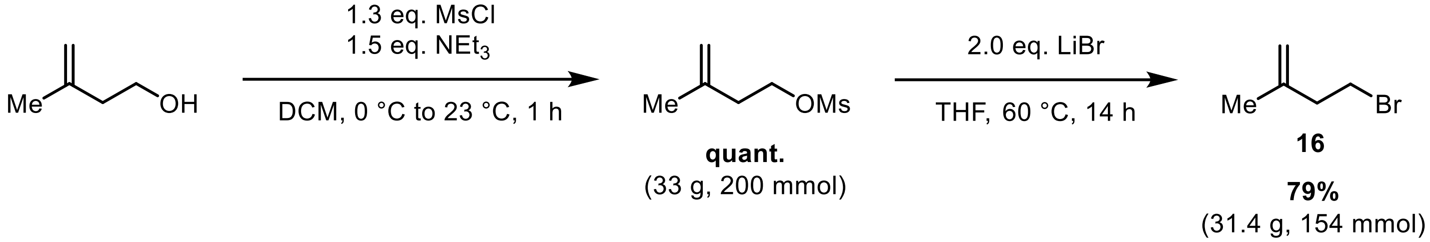
Conclusions

Our ongoing interest in the study of diastereoselective transformations has resulted in the development of a highly diastereoselective, Brønsted acid-catalyzed cyclization of a pseudo-C_2-symmetric 1,3-diol to yield a substituted tetrahydropyran product. Conformational considerations explain the observed stereochemical outcome. We believe that this transformation could be of interest in the synthesis of highly-substituted tetrahydropyran rings.

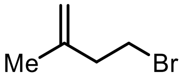
Experimental Section

General. Unless otherwise stated, all glassware was flame-dried before use and all reactions were performed under an atmosphere of argon. All solvents were distilled from appropriate drying agents prior to use or, if purchased in anhydrous form, used as received. All reagents were used as received from commercial suppliers. Reaction progress was monitored by thin-layer chromatography (TLC) performed on aluminium plates coated with silica gel F$_{254}$ with 0.2 mm thickness. Chromatograms were visualized by fluorescence quenching with UV light at 254 nm or by staining using either potassium permanganate or phosphomolybdic acid. Flash-column chromatography was performed using silica gel 60 (230-400 mesh, Merck and co.) or pre-packed columns. Neat infrared spectra were recorded using a Perkin-Elmer Spectrum 100 FT-IR spectrometer. Wavenumbers (ν_{max}) are reported in cm^{-1}. HR-ESI-MS spectra (m/z 50-1900) were obtained in a maXis UHR ESI-Qq-TOF mass spectrometer (Bruker Daltonics, Bremen, Germany) in the positive- and/or negative-ion mode by direct infusion. The sum formulae of the detected ions were determined using Bruker Compass DataAnalysis 4.1 based on the mass accuracy ($\Delta m/z \leq 5$ ppm) and isotopic pattern matching (SmartFormula algorithm). All ^{1}H NMR, ^{13}C DEPTQ-135 NMR and ^{13}C CPD NMR spectra were recorded using a Bruker AV-400, AV-500, AV-600 or AV-700 spectrometer at 300 K. Chemical shifts are given in parts per million (ppm, δ), referenced to the solvent peak of CDCl$_3$, defined at δ = 7.26 ppm (^{1}H NMR) and δ = 77.16 (^{13}C NMR).[16] Coupling constants are quoted in Hz (J). ^{1}H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q) or heptet (hept) as they appeared in the spectrum. If the appearance of a signal differs from the expected splitting pattern, the observed pattern is designated as apparent (app). Splitting patterns that could not be interpreted or easily visualized are designated as multiplet (m) or broad (br).

Procedure 1 - Synthesis of bromo-alkene 16:



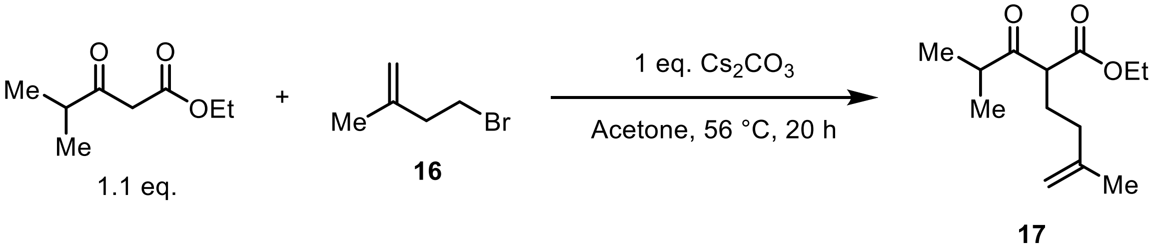
To a 500 mL round-bottom flask equipped with a magnetic stir bar and containing 3-methyl-3-buten-1-ol (1.0 eq., 20.2 mL, 17.2 g, 200 mmol) in DCM (200 mL) at 0 °C, were added methanesulfonyl chloride (1.3 eq., 20.1 mL, 29.8 g, 260 mmol) and triethylamine (1.5 eq., 41.8 mL, 30.4 g, 300 mmol). The reaction mixture was stirred at 0 °C for 1 h, after which 1M HCl (100 mL) was added. The resulting biphasic mixture was transferred to a separation funnel and extracted twice with DCM (50 mL). The organic phase was dried over $MgSO_4$, filtered through a short pad of silica gel and concentrated under reduced pressure. The crude compound was used for the next step without further purification. The crude mesylate was transferred to a 250 mL round-bottom flask, dissolved in anhydrous THF (100 mL), and then LiBr (2.0 eq. 34.7 g, 400 mmol) was added. The reaction mixture was heated to 60 °C and stirred at this temperature for 14 h. After cooling to room temperature, the reaction was stopped by addition of H_2O (40 mL), followed by extraction with pentane (100 mL), and the organic phase was separated. After drying over $MgSO_4$ and filtration, the solvent was carefully removed at 800 mbar and the product (**16**) was isolated as a clear oil after a short vacuum distillation. Spectroscopic data were in accordance with those reported in the literature.[17]



16

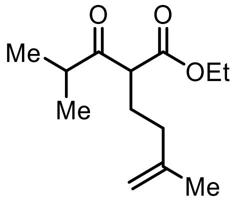
4-Bromo-2-methylbut-1-ene (16): colorless oil (79%, 31.4 g, 154 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.94 – 4.65 (m, 2H), 3.48 (t, *J* = 7.4 Hz, 2H), 2.58 (t, *J* = 7.4 Hz, 2H), 1.75 (s, 3H).

Procedure 2 - Synthesis of keto-ester 17:



To a 250 mL flame-dried flask equipped with a magnetic stir bar and containing ethyl isobutyrylacetate (1.1 eq., 3.55 mL, 3.48 g, 22 mmol) and bromide **16** (1.0 eq., 2.98 g, 20 mmol) in anhydrous acetone (100 mL), was added Cs_2CO_3 (1.0 eq., 6.52 g, 20 mmol). The reaction flask was equipped with a reflux condenser and the reaction mixture was heated at 56 °C for 20 h. Afterwards, the reaction mixture was cooled to room temperature and the reaction was stopped by addition of 1M HCl, which was added until pH 3-4 was reached.

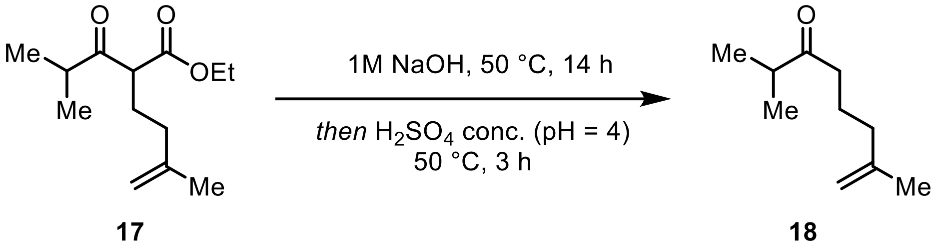
The reaction mixture was transferred to a separation funnel and extracted twice with diethyl ether (50 mL). The combined organic phases were dried over $MgSO_4$, filtered through a cotton plug and carefully concentrated under reduced pressure (P = 800 mbar). The crude product was purified by column chromatography (pentane/diethyl ether = 94:6, R_f = 0.35) to give the desired compound as a colorless oil.



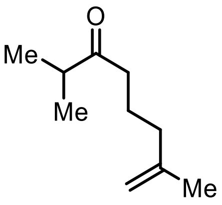
17

Ethyl 2-isobutyryl-5-methylhex-5-enoate (17): colorless oil (38%, 1.70 g, 37.6 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.71 (d, *J* = 27.5 Hz, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.68 – 3.51 (m, 1H), 2.78 (hept, *J* = 6.9 Hz, 1H), 2.01 – 1.95 (m, 4H), 1.70 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.10 (d, *J* = 6.8 Hz, 3H), 1.09 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 209.2, 169.9, 144.5, 111.2, 61.4, 56.4, 40.7, 35.6, 26.2, 22.3, 18.6, 18.2, 14.2; HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{13}H_{22}O_3Na$) requires *m/z* 249.1461, found *m/z* 249.1463; IR (neat) ν_{max}: 3075, 2972, 2936, 2875, 1741, 1713, 1650, 1466, 1447, 1368, 1351, 1208, 1154, 1098, 1026, 889, 863, 770 cm^{-1}.

Procedure 3 – Decarboxylation of 18:



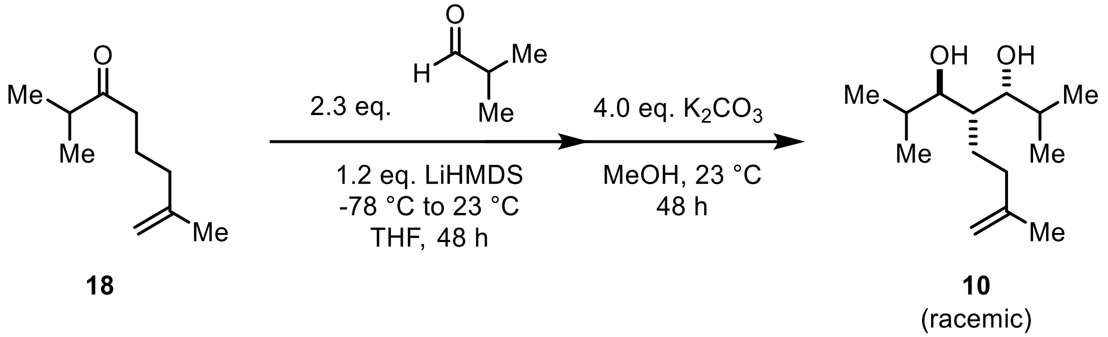
The keto ester **17** was added to a 25 mL round-bottom flask, equipped with a magnetic stir bar and dissolved in 1M NaOH (10 mL). The reaction mixture was subsequently stirred at 50 °C for 14 h, after which it was cooled to 0 °C, followed by addition of conc. H_2SO_4 until pH 3-4 was reached. The reaction mixture was stirred for 1 h at 50 °C and, after cooling to room temperature, diethyl ether (10 mL) was added. The reaction mixture was transferred to a separation funnel and extracted twice with diethyl ether (20 mL). The combined organic phases were dried over $MgSO_4$, filtered through a cotton plug and carefully concentrated under reduced pressure (P = 800 mbar). The highly volatile product was used in the next step without further purification.



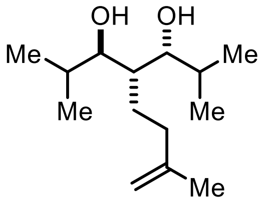
18

2,7-Dimethyloct-7-en-3-one (18): colorless oil (88%, 1.13 g, 2.64 mmol, 36% purity). ^{1}H NMR (400 MHz, CDCl$_3$) *δ*: 4.70 (d, *J* = 20.3 Hz, 2H), 2.71 – 2.52 (m, 1H), 2.44 (t, *J* = 7.3 Hz, 2H), 2.01 (t, *J* = 7.5 Hz, 2H), 1.84 – 1.66 (m, 5H), 1.09 (d, *J* = 6.9 Hz, 6H).

Procedure 4 - Synthesis of the unsaturated pseudo-*C*₂-symmetric diol 10:



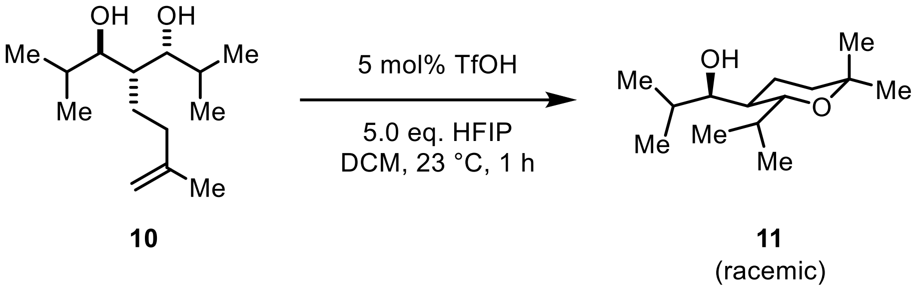
Procedure adapted from a literature report.[18] To an oven-dried Schlenk flask equipped with a magnetic stir bar and containing ketone **18** (1.0 eq., 1.13 g, 2.64 mmol, 36% purity), anhydrous THF (20 mL) was added. The reaction mixture was cooled to –78 °C, and lithium bis(trimethylsilyl)amide (LiHMDS, 1.2 eq., 3.16 mL, 1M in THF, 3.16 mmol) was added dropwise. After 10 min, isobutyraldehyde (2.3 eq., 0.56 mL, 6.1 mmol) was added dropwise and the reaction was allowed warm to room temperature over 48 h. Excess base was then quenched by the addition of sat. aq. NH$_4$Cl (50 mL). The reaction mixture was transferred to a separation funnel and extracted three times with DCM (20 mL). The combined organic phases were dried over MgSO$_4$, filtered through a cotton plug and concentrated under reduced pressure. The resulting crude oil was dissolved in MeOH (20 mL) and potassium carbonate was added (1.46 g, 10.5 mmol, 4.00 eq). The resulting solution was stirred at room temperature for 48 h, then quenched by the addition of 1M HCl (30 mL). The mixture was extracted three times with DCM (30 mL) and the combined organic phases were dried over MgSO$_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (heptanes/ethyl acetate = 90:10, R$_f$ = 0.28) to give the desired compound (**10**) as a colorless oil.



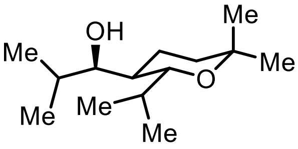
10
(racemic)

***rac*-(3*R**,5*R**)-2,6-Dimethyl-4-(3-methylbut-3-en-1-yl)heptane-3,5-diol (10)**[19]**:** colorless oil (21%, 123 mg, 0.54 mmol). ^{1}H NMR (700 MHz, CDCl$_3$) *δ*: 4.72 (d, *J* = 20.7 Hz, 2H), 3.55 (d, *J* = 9.6 Hz, 1H), 3.35 (d, *J* = 9.4 Hz, 1H), 2.84 (s, 1H), 2.64 (s, 1H), 2.25 – 2.10 (m, 1H), 2.01 – 1.95 (m, 1H), 1.88 (ddd, *J* = 13.2, 6.6, 2.9 Hz, 1H), 1.83 – 1.70 (m, 6H), 1.66 – 1.58 (m, 1H), 1.07 (d, *J* = 6.5 Hz, 3H), 1.02 (d, *J* = 6.5 Hz, 3H), 0.79 (d, *J* = 6.7 Hz, 3H), 0.78 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (176 MHz, CDCl$_3$) *δ*: 146.0, 110.5, 79.3, 77.6, 38.8, 35.8, 31.6, 31.2, 22.5, 21.8, 20.3, 19.9, 19.2, 19.1; HRMS (ESI$^+$): exact mass calculated for [M+Na]$^+$ ($C_{14}H_{28}O_2Na$) requires *m/z* 251.1982, found *m/z* 251.1978; IR (neat) ν_{max}: 3346, 2958, 2930, 2871, 1710, 1649, 1470, 1451, 1384, 1335, 1275, 1210, 1167, 1145, 1116, 1051, 1031, 968, 921, 886, 857, 841, 811, 738 cm^{-1}.

Procedure 5 – Diastereoselective hydroalkylation of 10:



To an oven-dried vial equipped with a magnetic stir bar and containing 0.1 mmol substrate **10** (1 eq., 22.8 mg), HFIP (5 eq., 53 µl) and anhydrous DCM (1 mL), TfOH (20 mol%, 20 µL of a 1M solution in anhydrous DCM) was added, and the reaction was stirred for 1 h at 23 °C. The reaction was stopped by addition of a 1M NaOH solution (0.2 mL). The reaction mixture was transferred to a separation funnel, diluted with DCM (5 mL) and washed twice with a 1M NaOH solution (5 mL each). The organic phase was dried over $MgSO_4$, filtered through a short pad of silica gel and carefully concentrated under reduced pressure to give the title compound (**11**) as a colorless oil.



11

***rac*-(*R**)-1-((2*R**,3*R**)-2-Isopropyl-6,6-dimethyltetrahydro-2H-pyran-3-yl)-2-methylpropan-1-ol (11):** colorless oil (98%, 22.4 mg, 0.10 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.22 (s, 1H), 3.53 (dd, *J* = 9.6, 2.3 Hz, 1H), 3.28 (dd, *J* = 10.1, 2.5 Hz, 1H), 1.99 – 1.87 (m, 3H), 1.77 (ddt, *J* = 13.1, 9.6, 6.6 Hz, 1H), 1.73 – 1.67 (m, 1H), 1.67 – 1.58 (m, 1H), 1.38 – 1.30 (m, 1H), 1.20 (s, 3H), 1.18 (s, 3H), 1.04 (d, *J* = 6.4 Hz, 3H), 0.98 (d, *J* = 6.4 Hz, 3H), 0.85 (d, *J* = 6.7 Hz, 3H), 0.77 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 80.0, 77.8, 73.1, 33.0, 32.5, 31.4, 31.3, 29.5, 22.8, 20.5, 20.3, 20.1, 19.1, 18.8; HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{14}H_{28}O_2Na$) requires *m/z* 251.1982, found *m/z* 251.1979; IR (neat) ν_{max}: 3482, 2957, 2924, 2869, 1714, 1672, 1470, 1421, 1382, 1365, 1327, 1294, 1277, 1250, 1222, 1195, 1148, 1111, 1071, 1043, 993, 964, 932, 895, 856, 830, 800, 767 cm^{-1}.

Acknowledgements

We thank Ass.-Prof. Harry Martin (U. Vienna) for helpful discussions. This research was funded in whole or in part by the Austrian Science Fund (FWF, 10.55776/P35045), the Austrian Academy of Sciences (DOC Fellowship to B.R.B.), and the European Research Council (ERC, CoG VINCAT to N.M.). Generous support by the University of Vienna and by the Vienna Doctoral School in Chemistry (DoSChem) is acknowledged.

Supplementary Material

Copies of ^{1}H and ^{13}C NMR spectra are provided in the Supplementary Material associated with this paper.

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19. The inclusion of asterisks (*) within the stereochemical descriptor of a compound is used to denote *relative* stereochemistry as opposed to *absolute* stereochemistry. Thus, a compound denoted as (*R*,R**) is racemic with either (*R,R*)- or (*S,S*)-configuration.