

Synthesis of Enantiomerically Pure 2,3,4,6-Tetrasubstituted Tetrahydropyrans by Prins-Type Cyclization of Methyl Ricinoleate and Aldehydes

Ursula Biermann,^[a] Arne Lützen,^[a] and Jürgen O. Metzger^{*[a]}

Dedicated to Professor Marcel S. F. Lie Ken Jie on the occasion of his 65th birthday

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The AlCl₃-catalyzed Prins-type cyclization of methyl ricinoleate (**1**), an enantiomerically pure renewable compound, with aldehydes such as heptanal (**2a**), isobutyraldehyde (**2b**), pivaldehyde (**2c**) and benzaldehyde (**2d**) is a simple reaction for the diastereoselective synthesis of enantiomerically pure 2,3,6-trialkyl-substituted 4-chlorotetrahydropyrans. The re-

spective 4-hydroxytetrahydropyrans are obtained e.g. with aldehydes **2a** and **2d** using montmorillonite KSF/O as the catalyst.

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Introduction

Tetrahydropyrans are important compounds that occur as building blocks in many biologically active natural products.^[1] Thus, considerable efforts have been made to develop reliable synthetic procedures to establish these heterocycles. One of them, the reaction of homoallylic alcohols and aldehydes under strongly acidic conditions, was found 50 years ago and is known as the Prins cyclization giving rise to alkyl-substituted tetrahydropyran derivatives.^[2] Since then a number of modifications were published that either varied the substrates or made use of a broad spectrum of Brønsted acids and Lewis acids as promoters.^[3]

However nowadays, the issue of stereoselective synthesis of highly functionalized tetrahydropyrans is becoming more and more important. The reaction of homoallylic alcohols containing an ω -double bond with aldehydes^[3k,3l,4,5] as well as the reaction of suitable derivatives of homoallylic alcohols such as enol ethers^[6] and α -acetoxy ethers,^[7–9] gives – with high diastereoselectivity – *all-cis*-2,6-dialkylsubstituted tetrahydropyrans carrying heteroatom substituents at C-4 such as halide or acetate depending on the acid used. In these cases all three substituents can be found in equatorial positions. This formation of 2,4,6-trisubstituted tetrahydropyrans can be rationalized by assuming a chair-like transition state to give the *all-cis*-configured products.^[8] The formation of the cyclization products via delocalized cationic intermediates is discussed by Alder.^[10] Barry and

co-workers found that the intermediates of the Prins cyclization pathway could be trapped with carbon based nucleophiles such as allylTMS, TMSCN and AlMe₃.^[11]

Reacting homoallylic alcohols containing an internal double bond with formaldehyde gave 2,4,5-trisubstituted tetrahydropyrans with the creation of two new stereocenters with excellent stereocontrol.^[12] The respective products were obtained reacting homoallylic acetals of formaldehyde under acidic conditions.^[13] Reaction of higher aldehydes with homoallylic alcohols with an internal double bond gave 2,3,4,6-tetrasubstituted tetrahydropyrans with remarkable diastereoselectivity forming three new stereocentres, e.g. the reaction of such a homoallylic alcohol with aldehydes in the presence of TFA affords 2,3,6-trialkyl-4-hydroxytetrahydropyrans.^[14] Interestingly, when using (*Z*)-homoallylic alcohols as substrates the *all-cis*-substituted tetrahydropyran with the substituent at C-3 in axial position was obtained. In contrast, the (*E*)-isomer stereoselectively yielded the product with all four substituents in the equatorial position. The respective stereochemical outcome was reported for the acid catalyzed cyclization of homoallylic α -acetoxy ethers.^[15] Enantiomerically pure homoallylic alcohols can give enantiomerically pure tetrahydropyrans with the retention of the stereogenic center.^[14,16] This potential was used recently by Barry et al. for the stereoselective synthesis of the tetrahydropyran core of polycavernoside A, a naturally occurring toxin bearing its substituents in equatorial positions at C-2, C-4 and C-6 and in the axial position at C-3.^[17] Epimerization via the oxonia-Cope rearrangement was also reported.^[8,10] Quite recently Jasti et al. discussed in detail when retention and epimerization of the stereochemistry of the homoallylic alcohol will be ob-

[a] Institute of Pure and Applied Chemistry, University of Oldenburg,
Carl von Ossietzky Strasse 9–11, 26111 Oldenburg, Germany
E-mail: juergen.metzger@uni-oldenburg.de

served.^[18] The oxonia-Cope rearrangement was shown to occur rapidly under typical Prins cyclization conditions when the oxocarbenium ion resulting from the rearrangement is similar to or lower in energy than the starting oxocarbenium ion. Oxonia-Cope rearrangements can be disfavored by destabilizing the resultant oxocarbenium ion or by stabilizing an intermediate tetrahydropyranyl cation.

Methyl ricinoleate [methyl (9*Z*,12*R*)-12-hydroxy-9-octadecenoate] is an enantiomerically pure homoallylic alcohol from the chiral pool. It is commercially available and can easily be obtained in high purity by transesterification from castor oil which is a renewable raw material. It is of increasing importance as an enantiomerically pure building block in organic synthesis.^[19]

We previously reported the aluminium chloride induced addition of formaldehyde to alkenes via homoallylic alcohols as a simple route to alkyl-substituted tetrahydropyrans.^[12] The respective reaction of methyl ricinoleate (**1**) gave the corresponding 2,5-dialkyl-4-chlorotetrahydropyran as a mixture of two diastereomers (ratio: 3.8:1) in 61% yield. In this paper, we report the diastereoselective Prins-type cyclizations of **1** with higher aldehydes, such as heptanal and benzaldehyde in the presence of AlCl₃ or montmorillonite KSF/O, yielding enantiomerically pure 2,3,4,6-tetrasubstituted tetrahydropyrans.

Results

We studied the AlCl₃-induced reaction of methyl ricinoleate (**1**), a homoallylic alcohol with a *cis*-configured double bond, with various aldehydes such as heptanal (**2a**), isobutyraldehyde (**2b**), pivaldehyde (**2c**) and benzaldehyde (**2d**) yielding the respective 2,3,6-trialkyl-substituted 4-chlorotetrahydropyrans **3a–d** (Table 1). The stereochemistry of the major products, which were obtained with high diastereoselectivity, was assigned by analysis of ¹H NMR coupling constants and by NOE measurements.

The reaction of the homoallylic alcohol **1** and aldehyde **2a** gave the 4-chlorotetrahydropyran derivative **3a**, after a reaction time of 3 h at room temperature, as a mixture of three diastereomers (ratio: 86:9:5) with an isolated yield of 76% (Table 1, entry 1). The main diastereomer was separated by column chromatography and identified as the *all-cis* compound (2*S*,3*R*,4*S*,6*R*)-**3a**. The compound was optically active and showed a specific rotation of $[\alpha]_D^{20} = -22.5$ ($c = 3.1$, CHCl₃).

The reaction protocol was expected to be a simple method for the synthesis of a great variety of highly functionalized 4-chloro-tetrahydropyrans by variation of the aldehyde **2**. Isobutyraldehyde (**2b**) was treated with methyl ricinoleate (**1**) giving product **3b** as a mixture of diastereomers in a ratio of 96:2:2. (Table 1, entry 2) The stereochemistry of the main diastereomer, obtained by column chromatography, was clearly identified as (2*S*,3*R*,4*S*,6*R*)-**3b** by NMR spectroscopy.

The AlCl₃-induced cyclization of **1** and benzaldehyde (**2d**) proceeded highly diastereoselectively yielding the enan-

Table 1. AlCl₃-catalyzed Prins-type cyclizations of methyl ricinoleate (**1**) with heptanal (**2a**), isobutyraldehyde (**2b**), pivaldehyde (**2c**) and benzaldehyde (**2d**).

$$\text{R}^1\text{-CH(OH)-CH=CH-R}^2 + \text{R}^3\text{-CHO} \xrightarrow[3\text{ h, r.t.}]{\text{AlCl}_3, \text{CH}_2\text{Cl}_2} \text{R}^1\text{-CH(Cl)-CH(R}^2\text{)-CH(R}^3\text{)-CH}_2\text{-O-CH(R}^1\text{)-CH(R}^2\text$$

[a] Isolated yields were obtained by column chromatography (see Exp. Sect.). [b] Inversion of the absolute configuration at C2 in comparison to **3a**, **b** because of priority rules.

tiomerically pure *all-cis*-(2*R*,3*R*,4*S*,6*R*)-**3d** as the main product together with small amounts of a minor diastereomer (Table 1, entry 4).

In each of the described reactions (Table 1, entries 1, 2 and 4), besides the main diastereomer which was separated by column chromatography, a second diastereomer could be identified by its ¹H and ¹³C NMR spectroscopic data. However, the assignments were made from spectra obtained from mixtures with the respective major products of **3a**, **3b** and **3d**. In all cases the side products had all four substituents in equatorial positions.

The reaction of **1** and pivaldehyde (**2c**) with AlCl₃ proceeded with the formation of tetrahydropyran **3c** (Table 1, entry 3). The product was isolated in 77% yield as a mixture of four diastereomers in a ratio of 60:27:9:4. The diastereomers were distinguishable by GC-MS and two of them were obtained by column chromatography with 91% and 55% enrichment (GC), respectively. The main compound was the *all-equatorial* product (2*R*,3*S*,4*S*,6*R*)-**3c**.

The *all-cis* compound (2*R*,3*R*,4*S*,6*R*)-**3c** was obtained as a side product in 27% yield.

It has to be pointed out that the synthesis of the racemic trialkyl-substituted 4-chlorotetrahydropyran **3a** was possible with methyl 10-undecenoate (**4**) as the starting material. Reaction of **4** with two equivalents of heptanal (**2a**) catalyzed by AlCl₃ after a reaction time of 3 h gave product **3a** in 62% yield (Figure 1). The product was formed by regioselective cyclization as a racemic mixture of two diastereomers (ratio: 2.6:1) with the *all-equatorial* substituted compound *rel*-(2*S*,3*S*,4*S*,6*R*)-**3a** as the main product.

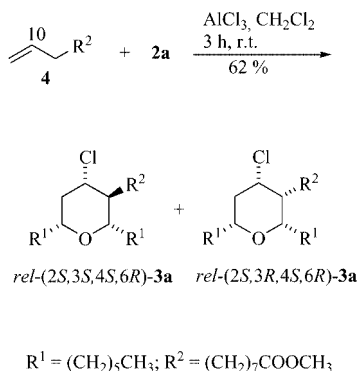


Figure 1. AlCl₃-induced Prins-type cyclization of methyl 10-undecenoate (**4**) with heptanal (**2a**) to give a diastereomeric mixture of *rel*-(2*S*,3*S*,4*S*,6*R*)-**3a** and *rel*-(2*S*,3*R*,4*S*,6*R*)-**3a** in a ratio of 2.6:1. In contrast to the reaction of methyl ricinoleate (**1**) with **2a** a racemic mixture of each diastereomer was obtained which is indicated by the used nomenclature of relative stereochemistry.

2,3,6-Trialkyl-4-hydroxytetrahydropyran **5a** was obtained on reaction of methyl ricinoleate (**1**) and heptanal (**2a**) promoted by montmorillonite KSF/O (Figure 2). The cyclization was performed by heating the reaction mixture for 24 h in refluxing dichloromethane to give product **5a** in 61% yield as a mixture of two diastereomers in a ratio of 73:27. The *all-cis* diastereomer (2*S*,3*S*,4*S*,6*R*)-**5a** was the main and (2*S*,3*R*,4*S*,6*R*)-**5a** the minor product. Under the same reaction conditions, in the presence of montmorillonite clay KSF/O, **1** was treated with benzaldehyde (**2d**) affording product **5d**, however, only in 45% yield. The mixture of three diastereomers in a ratio of 85:10:5 contained the enantiomerically pure *all-cis* diastereomer as the main component. The stereochemistry of (2*R*,3*S*,4*S*,6*R*)-**5d** was assigned by analysis of the ¹H NMR coupling constants and by comparison of the ¹H NMR spectroscopic data with those of compound (2*S*,3*S*,4*S*,6*R*)-**5a**. The minor diastereomer was (2*S*,3*R*,4*S*,6*R*)-**5d**.

All tetrahydropyrans **3** and **5** derived from methyl ricinoleate **1** were optically active. To prove the enantiomeric purity we studied the ¹H NMR spectra of tetrahydropyrans (2*S*,3*S*,4*S*,6*R*)-**5a** and (2*R*,3*S*,4*S*,6*R*)-**5d** by addition of tris[3-(trifluoromethyl-hydroxymethylene)-D-camphorato]europium(III) as a chiral shift reagent. For example, the signal of H-4 was shifted downfield by 4 ppm, however, no splitting was observed. In addition, we esterified both tetrahydropyrans with (1*S*)-(-)-camphanoyl

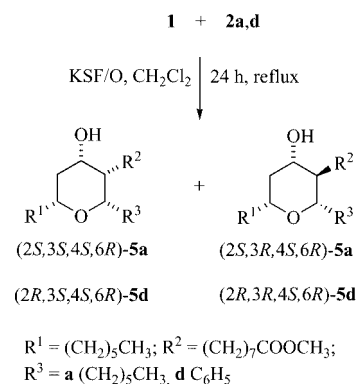


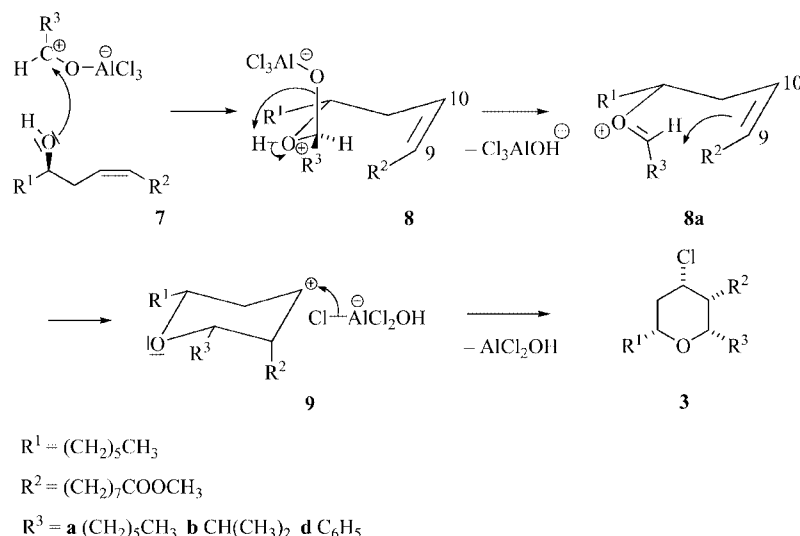
Figure 2. Prins-type cyclization of methyl ricinoleate (**1**) with heptanal (**2a**) and benzaldehyde (**2d**) to give diastereomeric mixtures of 2,3,6-trialkyl-substituted 4-hydroxytetrahydropyrans **5a** and **5d**, respectively, in the presence of montmorillonite clay KSF/O. Ratio of diastereomers: (2*S*,3*S*,4*S*,6*R*)-**5a**: (2*S*,3*R*,4*S*,6*R*)-**5a** = 73:27; (2*R*,3*S*,4*S*,6*R*)-**5d**: (2*R*,3*R*,4*S*,6*R*)-**5d** = 85:10. Inversion of the absolute configuration at C3 in comparison to **3a,d** because of priority rules.

chloride. HPLC analysis of both products showed one single peak giving additional evidence that the tetrahydropyrans were enantiomerically pure compounds.

Discussion

The AlCl₃-induced reaction of methyl ricinoleate (**1**) and aldehydes **2a**, **2b** and **2d** yielded the respective 2,3,4,6-tetraalkyl-substituted tetrahydropyran derivatives **3a**, **3b** and **3d** as mixtures of diastereomers. A high diastereoselectivity was observed (Table 1, entries 1, 2 and 4). Comparable to numerous examples in the literature^[4,5] the major products of all three reactions show the substituents at C-2, C-4 and C-6 in equatorial positions. The axial orientation for the substituent at C-3 was clearly shown by the respective ¹H NMR spectroscopic data and by NOE studies.

The stereochemical outcome of the AlCl₃-induced Prins-type cyclization can be rationalized through a chairlike transition state to give predominantly the *all-cis* products. In the first step of the reaction the aldehyde-AlCl₃ complex **7** is formed and is trapped by the nucleophilic attack of the oxygen of the alcohol function giving, via the adduct **8**, oxocarbenium ion **8a** as the intermediate (Scheme 1). The alkyl group R³ of the aldehyde **2** demands the less hindered position, in the preferred chairlike conformation of the regioselective electrophilic six-ring closure to position C-9 of ricinoleate **1**, giving the cyclic carbenium ion **9**. This is followed by the subsequent transfer of a chloride ion to position C-10. The major product is obtained as the *all-cis* compound, as shown in Scheme 1, with equatorial C-2, C-4 and C-6 and axial C-3 positions. The stereochemistry of the main products obtained from reactions of the (*Z*)-homoallylic alcohol **1** and aldehydes **2a**, **2b**, and **2d**, respectively, is in agreement with those of Barry et al.^[14] who obtained the respective tetrasubstituted tetrahydropyrans with the C-3-substituent in axial position from Lewis acid mediated cy-



Scheme 1. Mechanism of the $AlCl_3$ -catalyzed Prins-type cyclization of methyl ricinoleate (**1**) and heptanal (**2a**), isobutyraldehyde (**2b**) and benzaldehyde (**2d**).

clizations of (*Z*)-homoallylic alcohols with aldehydes, while using (*E*)-homoallylic alcohols as starting materials gave the respective equatorial orientation.

We also performed the synthesis of 2,3,4,6-tetrasubstituted tetrahydropyrans in the presence of $AlCl_3$ using simple alkenes such as methyl 10-undecenoate (**4**) as substrates. However, in this case two equivalents of the aldehyde are necessary to perform the cyclization reaction. The respective reaction of **4** and heptanal (**2a**) proceeds in two steps (Figure 3). Induced by $AlCl_3$ one equivalent of **2a** reacts with the C,C double bond of **4** in an ene reaction to give the respective homoallylic alcohol **10**. The ene adduct is formed as a mixture of the (*E*)- and (*Z*)-isomers, with the (*E*)-isomer as the major compound.^[20,21] Addition of a second equivalent of **2a** to the ene adduct **10** gives the racemic mixtures of the diastereomeric tetrahydropyrans **3a** with *rel*-(2*S*,3*S*,4*S*,6*R*)-**3a** as main product. In agreement with the literature^[8,15] it can be assumed that the formation of the main diastereomer, with the equatorial substituent in 3-position, results from the reaction of the (*E*)-isomer of the ene adduct-intermediate, while the minor diastereomer *rel*-(2*S*,3*R*,4*S*,6*R*)-**3a** with the axial substituent in 3-position is formed by the reaction of the (*Z*)-isomer with **2a**. The outcome of this reaction supports the results of the $AlCl_3$ -induced cyclizations of methyl ricinoleate (**1**) and aldehydes **2a**, **2b** and **2d** to give the main diastereomers with the axial position at C-3.

While cyclizations of **1** with aldehydes **2a** and **2d** showed comparable results concerning the ratios of diastereomers (Table 1, entries 1 and 4) the reaction of **1** with isobutyraldehyde **2b** showed a remarkably higher diastereoselectivity with a ratio of diastereomers of 96:2:2. The predominant formation of (2*S*,3*R*,4*S*,6*R*)-**3b** is probably due to steric effects of the bulky isopropyl group.

The minor diastereomers containing all substituents in equatorial orientation were obtained by all three reactions

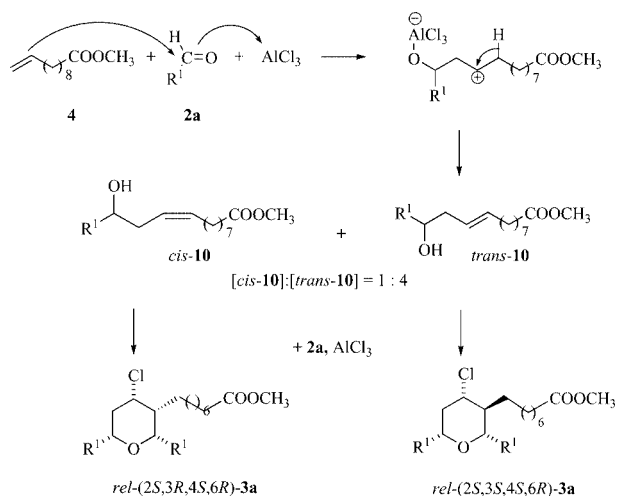


Figure 3. $AlCl_3$ -catalyzed cyclization of methyl 10-undecenoate (**4**) and heptanal (**2a**).

of **1** with **2a**, **2b** and **2d** (Table 1, entries 1, 2 and 4), however, in the case of tetrahydropyran **3b** the respective diastereomer was observed only in traces of 2% (GC). The formation of the *all*-equatorial compounds in cyclization reactions with (*Z*)-alkenes as starting materials is assumed by Rychnovsky and co-workers^[15] to arise from small amounts of the respective (*E*)-alkene which can be already present as an impurity, formed by isomerization of the (*Z*)-alkene or by assuming a competing boat-like transition state in the cyclization.

Rychnovsky and co-workers concluded that the C-2-substituent with the equatorial orientation in the incipient tetrahydropyran ring influences the stereochemical outcome of the newly generated stereogenic centres.^[8] This is in agreement with our results. $AlCl_3$ -induced cyclizations of **1** with higher aldehydes such as **2a**, **2b** and **2d** proceed by creation

of three new stereogenic centres at C-2, C-3, and C-4 to give the respective 2,3,6-trialkyl-substituted 4-chlorotetrahydropyrans, mainly with the axial position of the substituent at C-3 (Table 1, entries 1, 2 and 4). However, the corresponding reaction of **1** with formaldehyde, which gives two new asymmetric centers at C-4 and C-5 (these positions correspond to positions C-4 and C-3 in compounds **2a–2d**), takes place by formation of the respective 2,5-dialkyl-substituted 4-chlorotetrahydropyran with the substituent at C-5 located in an equatorial orientation in the major product.^[12]

With a ratio of diastereomers of 60:27:9:4 of product **3c** the reaction of **1** and pivaldehyde (**2c**) (Table 1, entry 3) showed considerably less diastereoselectivity compared to the corresponding cyclizations with aldehydes **2a**, **2b** and **2d**. It is remarkable that the reaction of (*Z*)-homoallylic alcohol **1** and **2c** yielded the *all*-equatorial diastereomer as the major product. This result shows that the stereochemistry of substituted cyclic products obtained by Prins cyclization reactions is not only influenced by the stereochemistry of the homoallylic alcohol used as starting material, but also by the structure of the reacting aldehyde. Possibly, in this case the cyclization does not occur through a chair-like transition intermediate as a consequence of steric factors caused by the *tert*-butyl group. Maybe the boat-like transition state is preferred to give the *all*-equatorial diastereomer as the major product.

The synthesis of highly functionalized tetrahydropyrans in the presence of heterogeneous catalysts is of interest. These compounds show considerable advantages compared to homogeneous catalysts especially because of their environmental compatibility, their reusability, low cost and simple removal from the reaction mixture by filtration or centrifugation. It is known that in the presence of montmorillonite clay KSF^[4] or Amberlyst-15^[5] homoallylic alcohols with a terminal C=C bond give, on reaction with aldehydes, the respective 2,6-dialkyl-substituted 4-hydroxytetrahydropyrans. Mediated by montmorillonite KSF/O methyl ricinoleate (**1**), a homoallylic alcohol with an internal double bond, reacts with one equivalent of aldehydes **2a** and **2d** to give the 2,3,6-trialkyl-substituted 4-hydroxytetrahydropyrans **5a** and **5d**, respectively (Figure 2). However, the clay promoted cyclizations showed a considerably lower diastereoselectivity compared to the corresponding AlCl₃-catalyzed reactions. As expected, the clay catalyzed cyclizations of (*Z*)-homoallylic alcohol (**1**) yielded, in analogy to the AlCl₃-induced reactions (Table 1, entries 1 and 4), the *all*-*cis* diastereomers (2*S*,3*S*,4*S*,6*R*)-**5a** and (2*R*,3*S*,4*S*,6*R*)-

5d as the main compounds. It has been shown that these compounds are enantiomerically pure. Thus, an oxonia-Cope rearrangement was not observed and is not expected in the systems studied.^[15] The tetrahydropyranyl cation **9** (Scheme 2) will not be able to open to form the rearranged cation **11** because **11** is higher in energy than **9** and much higher in energy than cation **8**.

Conclusion

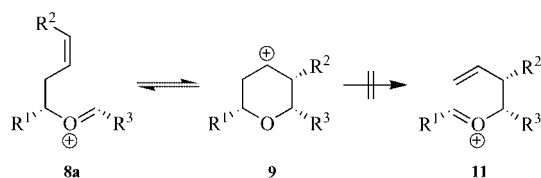
AlCl₃-catalyzed Prins-type cyclizations of methyl ricinoleate and aldehydes give 2,3,6-trialkyl-substituted 4-chlorotetrahydropyrans in good yields. The reactions with heptanal, isobutyraldehyde and benzaldehyde proceed with high diastereoselectivity without epimerization and yield the enantiomerically pure *all*-*cis* products as the main compounds. An exception is pivaldehyde giving the *all*-equatorial diastereomer as main product. 2,3,6-Trialkylsubstituted 4-hydroxytetrahydropyrans can be synthesized using the environmentally benign catalyst montmorillonite KSF/O to give diastereoselectively and the enantiomerically pure *all*-*cis* products.

Experimental Section

General: Methyl ricinoleate (93% purity) was obtained from Cognis, Düsseldorf or by transesterification with methanol from castor oil. The amount of the starting olefin used in the reactions was calculated based on 100% purity. Methyl 10-undecenoate was obtained from Atochem and (1*S*)-(–)-camphanoyl chloride, tris[3-(trifluoromethylhydroxymethylene)-D-camphorato]europium-(III) and AlCl₃ were obtained from Fluka and KSF/O from Süd-Chemie, München, Germany. Heptanal, isobutyraldehyde and pivaldehyde (Aldrich) were used without further purification. Benzaldehyde was freshly distilled. For column chromatography Merck 60 silica gel, 70–230 mesh, was used.

Analytical Equipment: Analytical GC was performed using a Carlo-Erba GC series 4160 with an FID detector and fused silica capillary column DB1, 29 m. Analytical HPLC was performed using a Hitachi L-6250 (Merck) using a silica gel column (Si 60, 5 µm, LiChro 250-4, Merck) and detector RI-71 (Merck). ¹H NMR and ¹³C NMR spectra were recorded in CDCl₃ using a Bruker DRX 500 spectrometer at 300 K using residual non-deuterated solvent (¹H NMR) or CDCl₃ (δ = 77.0 ppm, ¹³C NMR) as internal standards. Assignment of the signals was carried out on the basis of ¹H, ¹³C, H,H-COSY, HMQC, HMBC and *sel*-1D-NOESY spectra. Mass spectra were recorded using a Finnigan MAT 95. All products were unambiguously identified by ¹H NMR and ¹³C NMR and by MS (EI) or GC/MS (EI). Specific rotations [α]_D²⁰ were recorded using a Perkin–Elmer polarimeter 343. Elemental analyses were performed by Mikroanalytisches Labor Beller, 37004 Göttingen, Germany.

Procedure 1: General Procedure for the Synthesis of 2,3,6-Trialkyl-Substituted 4-Chlorotetrahydropyrans **3 with Methyl Ricinoleate (**1**):** A mixture of methyl ricinoleate (**1**) (5 mmol, 1.56 g) and the respective aldehyde **2a–d** (5 mmol) in CH₂Cl₂ (10 mL) was stirred magnetically for 15 min at –15 °C. After addition of AlCl₃ (2.5 mmol, 0.33 g) the sample was stirred for an additional 10 min at –15 °C, then warmed up and stirred for an additional 3 h at room tempera-



Scheme 2. Oxonia-Cope rearrangement of oxocarbenium **8a** was not observed and is not expected because cation **11** is higher in energy than cations **9** and **8a**.^[15]

ture. The reaction was quenched by addition of petroleum ether 60/80 (80 mL) and H₂O (40 mL). 10% HCl was added until the precipitated aluminium salts had dissolved. The organic layer was separated, washed with H₂O (4 × 30 mL) and dried with Na₂SO₄. After filtration the solvent was removed in vacuo. Purification was achieved by kugelrohr distillation or column chromatography [silica gel using petroleum ether/diethyl ether (8:2) as eluent]. Fractions containing the tetrahydropyrans were collected, the solvent was removed in vacuo and the residue was dried at 20 °C/0.01 mbar.

Procedure 2: General Procedure for the Synthesis of 2,3,6-Trialkyl-Substituted 4-Hydroxytetrahydropyrans 5: A mixture of methyl ricinoleate (**1**) (5 mmol, 1.56 g), heptanal (**2a**, 5 mmol, 0.57 g) or benzaldehyde (**2d**, 8 mmol, 0.84 g) and KSF/O (2 g) in CH₂Cl₂ (10 mL) was refluxed for 24 h. The catalyst was removed by filtration and washed with CH₂Cl₂ (4 × 10 mL). The solvent from the combined organic layers was evaporated in vacuo. Purification of the products was achieved by column chromatography as described in procedure 1.

4-Chloro-2,6-dihexyl-5-(7-methoxycarbonylheptyl)tetrahydropyran (3a): Mixture of diastereomers (ratio: 86:9:5), yield: 1.7 g (76%). (2*S*,3*R*,4*S*,6*R*)-(–)-**3a** was obtained by column chromatography (GC), [α]_D²⁰ = –22.5 (*c* = 3.1, CHCl₃). ¹H NMR (500.1 MHz): δ = 4.14 (ddd, *J* = 12.6, 4.4, 4.4 Hz, 1 H), 3.62 (s, 3 H), 3.21 (m, 2 H), 2.26 (t, *J* = 7.4 Hz, 2 H), 1.77 (m, 1 H), 1.65–1.50 (m, 3 H), 1.44–1.20 (m, 31 H), 0.84 (2 t, *J* = 6.6, 6.8 Hz, 6 H) ppm. ¹³C NMR (125.8 MHz): δ = 174.3, 80.7, 77.5, 62.8, 51.4, 45.3, 38.0, 35.8, 34.1, 33.3, 31.8, 31.8, 31.5, 29.7, 29.2, 29.2, 29.1, 29.0, 26.3, 25.5, 24.9, 23.2, 22.6, 14.0 ppm. GC/MS (EI): *m/z* (%) = 408 (1), 359 (40)/361 (13), 323 (100), 294 (24), 291 (23), 263 (25). C₂₆H₄₉ClO₃ (445.13): calcd. C 70.16, H 11.10; found C 70.20, H 10.94.

A mixture of racemic *rel*-(2*S*,3*S*,4*S*,6*R*)-**3a** and racemic *rel*-(2*S*,3*R*,4*S*,6*R*)-**3a** (ratio: 2.6:1, GC) was obtained on reaction of methyl 10-undecenoate (**4**) with heptanal (**2a**): yield: 1.4 g (62%). A mixture of heptanal (**2a**) (10 mmol, 1.14 g) and AlCl₃ (7.5 mmol, 1.0 g) in CH₂Cl₂ (10 mL) was stirred magnetically for 15 min at –15 °C. After the dropwise addition (over 1 h) of methyl 10-undecenoate (**4**) (5 mmol, 1 g) the sample was stirred for an additional 10 min at –15 °C, then warmed up and stirred for an additional 3 h at room temperature. The work-up of the sample and the isolation of the product by column chromatography were performed as described in the general procedure 1. The diastereomeric mixture of racemic **3a** was separated by HPLC with hexane/acetic acetate (95:5) as eluent. *rel*-(2*S*,3*S*,4*S*,6*R*)-**3a**: ¹H NMR (CDCl₃): δ = 3.88 (ddd, *J* = 11.4, 11.2, 4.4 Hz, 1 H), 3.64 (s, 3 H), 3.19 (m, 1 H), 3.06 (ddd, *J* = 9.3, 9.3, 1.6 Hz, 1 H), 2.28 (t, *J* = 7.5 Hz, 2 H), 2.13 (ddd, *J* = 11.4, 9.4, 4.4 Hz, 1 H), 1.60 (m, 5 H), 1.49 (m, 2 H), 1.39 (m, 6 H), 1.27 (m, 21 H), 0.86 (m, 6 H) ppm. ¹³C NMR (125.8 MHz): δ = 174.2, 79.6, 76.4, 62.1, 51.4, 49.2, 43.5, 35.8, 34.1, 33.1, 31.9, 31.6, 30.0, 29.5, 29.4, 29.2, 29.1, 29.0, 28.0, 25.5, 25.3, 25.0, 22.6, 22.5, 14.1, 14.0 ppm.

4-Chloro-6-hexyl-2-isopropyl-3-(7-methoxycarbonylheptyl)tetrahydropyran (3b): Mixture of diastereomers (ratio: 96:2:2), yield: 1.5 g (70%). (2*S*,3*R*,4*S*,6*R*)-(–)-**3b** was obtained by column chromatography (GC), [α]_D²¹ = –30.7 (*c* = 3.2, CHCl₃). ¹H NMR (500.1 MHz): δ = 4.12 (ddd, *J* = 12.4, 4.4, 4.4 Hz, 1 H), 3.63 (s, 3 H), 3.17 (m, 1 H), 2.69 (d, 9.9 Hz, 1 H), 2.26 (t, *J* = 7.4 Hz, 2 H), 1.91 (m, 1 H), 1.79–1.73 (m, 2 H), 1.60–1.55 (m, 3 H), 1.53–1.23 (m, 20 H), 0.95 (d, *J* = 6.6 Hz, 3 H), 0.84 (d, *J* = 6.6 Hz, 3 H), 0.82 (t, *J* = 6.6 Hz, 3 H) ppm. ¹³C NMR (125.8 MHz): δ = 174.2, 87.0, 77.6, 63.1, 51.3, 42.6, 38.0, 35.8, 34.0, 31.8, 31.1, 29.9, 29.8, 29.1, 29.0, 25.5, 24.9, 22.6, 20.1, 19.0, 14.0 ppm. MS/CI (isobutane): *m/z*

(%) = 403 (100)/405 (32) [MH⁺], 367 (2) [MH⁺ – HCl]. C₂₃H₄₃ClO₃ (403.05): calcd. C 68.54, H 10.75; found C 68.60, H 10.70.

2-tert-Butyl-4-chloro-6-hexyl-3-(7-methoxycarbonylheptyl)tetrahydropyran (3c): Mixture of diastereomers (ratio: 60:27:9:4, GC), yield: 1.6 g (77%). The main diastereomers (2*R*,3*S*,4*S*,6*R*)-(–)-**3c** and (2*R*,3*R*,4*S*,6*R*)-(–)-**3c** were obtained by column chromatography with 91% and 55% enrichment (GC), respectively.

(2*R*,3*S*,4*S*,6*R*)-(–)-**3c**: ¹H NMR (500.1 MHz): δ = 3.92–3.80 (m, 2 H), 3.65 (s, 3 H), 3.54 (d, *J* = 3.8 Hz, 1 H), 2.40 (m, 1 H), 2.29 (t, *J* = 6.4 Hz, 2 H), 1.95 (m, 1 H), 1.80 (m, 1 H), 1.67–1.55 (m, 5 H), 1.50 (m, 1 H), 1.45–1.23 (m, 16 H), 0.87 (s, 9 H), 0.86 (t, *J* = 6.6 Hz, 3 H) ppm. ¹³C NMR (125.8 MHz): δ = 174.2, 89.2, 79.3, 67.0, 51.4, 47.8, 35.9, 35.9, 34.8, 34.5, 34.0, 31.8, 29.5, 29.1, 29.0, 28.9, 26.8, 26.3, 25.9, 24.9, 22.6, 14.0 ppm. MS/CI (isobutane): *m/z* (%): 417 (100)/419 (33) [MH⁺], 381 (1) [MH⁺ – HCl]. C₂₄H₄₅ClO₃ (417.07): calcd. C 69.12, H 10.88; found C 68.99, H 10.87.

(2*R*,3*R*,4*S*,6*R*)-(–)-**3c**: ¹H NMR (500.1 MHz): δ = 4.11 (ddd, *J* = 12.1, 4.4, 4.1 Hz, 1 H), 3.64 (m, 1 H), 3.64 (s, 3 H), 2.28 (t, *J* = 7.4 Hz, 2 H), 2.00 (m, 1 H), 1.85 (m, 1 H), 1.77 (m, 1 H), 1.67–1.55 (m, 5 H), 1.50–1.20 (m, 16 H), 0.93 (s, 9 H), 0.86 (t, *J* = 7.4 Hz, 3 H) ppm. ¹³C NMR (125.8 MHz): δ = 174.2, 88.1, 77.9, 64.4, 51.4, 43.0, 38.1, 35.8, 35.2, 34.0, 31.8, 31.3, 29.1, 29.1, 29.0, 27.3, 25.5, 24.9, 23.5, 22.6, 14.0 ppm. MS/CI (isobutane): *m/z* (%): 417 (100)/419 (32) [MH⁺], 381 (4) [MH⁺ – HCl].

4-Chloro-6-hexyl-3-(7-methoxycarbonylheptyl)-2-phenyltetrahydropyran (3d): Mixture of diastereomers (ratio: 95:5), yield: 1.6 g (73%). (2*R*,3*R*,4*S*,6*R*)-(+)-**3d** was obtained by column chromatography with 90% enrichment (GC). ¹H NMR (300.1 MHz): δ = 7.34 (m, 4 H), 7.26 (m, 1 H), 4.55 (m, 1 H), 4.44 (ddd, *J* = 12.4, 4.5, 4.1 Hz, 1 H), 3.68 (s, 3 H), 3.48 (m, 1 H), 2.25 (t, *J* = 7.5 Hz, 2 H), 2.06 (m, 1 H), 1.93 (m, 1 H), 1.71 (m, 2 H), 1.60–1.46 (m, 5 H), 1.40–1.27 (m, 10 H), 1.15–0.97 (m, 5 H), 0.91 (m, 4 H) ppm. ¹³C NMR (75.5 MHz): δ = 174.2, 140.7, 128.3, 127.9, 127.4, 126.8, 125.3, 80.4, 77.4, 62.4, 51.3, 47.2, 37.4, 35.7, 34.0, 31.7, 30.1, 29.3, 29.1, 28.9, 28.8, 28.5, 25.3, 24.8, 22.6, 22.5, 14.0 ppm. MS (EI): *m/z* (%) = 436 (10)/438 (3) [M⁺], 400 (39), 351 (20)/353 (6), 295 (100), 263 (58). C₂₆H₄₁ClO₃ (437.06): calcd. C 71.45, H 9.46; found C 71.52, H 9.37.

2,6-Dihexyl-4-hydroxy-3-(7-methoxycarbonylheptyl)tetrahydropyran (5a): Mixture of diastereomers (ratio: 2.7:1, ¹³C NMR), yield: 1.3 g (61%). (2*S*,3*S*,4*S*,6*R*)-(–)-**5a** was obtained with 90% enrichment (GC) by column chromatography: ¹H NMR (500.1 MHz): δ = 3.80 (ddd, *J* = 11.7, 4.5, 4.4 Hz, 1 H), 3.63 (s, 3 H), 3.15 (m, 2 H), 2.26 (t, *J* = 7.6 Hz, 2 H), 1.61–1.45 (m, 5 H), 1.44–1.20 (m, 31 H), 0.84 (m, 6 H) ppm. ¹³C NMR (125.8 MHz): δ = 79.5, 76.2, 72.2, 51.4, 44.7, 36.3, 36.0, 34.0, 33.0, 31.8, 31.4, 29.3, 29.2, 29.1, 29.1, 26.4, 25.6, 24.9, 22.6, 21.9, 14.0 ppm. MS/CI (isobutane): *m/z* (%): 409 (5) [MH⁺ – HCl]. C₂₆H₅₀O₄ (426.68): calcd. C 73.19, H 11.81; found C 73.20, H 11.75.

(2*S*,3*S*,4*S*,6*R*)-**5a** was treated with the shift reagent tris[3-(trifluoromethylhydroxymethylene)-D-camphorato]europium(III) as described in ref.^[22] The ¹H NMR (500.1 MHz) spectra showed significant shifts of the relevant hydrogen atoms but without any splitting of the signals.

(2*S*,3*S*,4*S*,6*R*)-**5a** was treated with (1*S*)-(–)-camphanil chloride as described in the literature.^[23] The camphanoyl derivative was analyzed by HPLC using hexane/ethyl acetate (8.5:1.5) as the eluent. The chromatogram showed one single peak confirming the enantiomeric purity of the compound.

6-Hexyl-4-hydroxy-3-(7-methoxycarbonylheptyl)-2-phenyltetrahydropyran (5d): Mixture of diastereomers (ratio: 85:10:5), yield:

0.9 g (45%). (2R,3S,4S,6R)-(+)-**5d** was obtained with 91% enrichment (GC) by column chromatography: ^1H NMR (300.1 MHz): δ = 7.23 (m, 4 H), 7.13 (m, 1 H), 4.39 (d, J = 1.9 Hz, 1 H), 4.01 (ddd, J = 12.1, 4.9, 4.5 Hz, 1 H), 3.58 (s, 3 H), 3.37 (m, 1 H), 2.25 (m, 1 H), 2.15 (t, J = 7.5 Hz, 2 H), 1.88 (m, 1 H), 1.60 (m, 2 H), 1.42 (m, 5 H), 1.30–1.12 (m, 11 H), 1.04–0.88 (m, 5 H), 0.81 (m, 4 H) ppm. ^{13}C NMR (75.5 MHz): δ = 174.3, 141.4, 128.3, 127.9, 127.6, 126.5, 125.4, 79.5, 76.1, 72.2, 51.4, 46.7, 36.0, 35.8, 34.0, 31.8, 30.2, 29.4, 29.1, 28.6, 25.4, 24.8, 22.6, 21.3, 14.1 ppm. MS (EI): m/z (%) = 418 (2) [M^+], 400 (26), 243 (18), 198 (26), 166 (20), 107 (100). $\text{C}_{26}\text{H}_{42}\text{O}_4$ (418.62): calcd. C 74.60, H 10.11; found C 74.72, H 10.01.

(2R,3S,4S,6R)-**5d** was treated with the shift reagent tris[3-(trifluoromethylhydroxymethylene)-D-camphorato]europium(III) as described in the literature.^[22] The ^1H NMR (500.1 MHz) spectra showed significant shifts of the relevant hydrogens but without any splitting of the signals.

(2S,3S,4S,6R)-**5d** was treated with (1S)-(-)-camphanoyl chloride as described in the literature.^[23] The camphanoyl derivative was analyzed by HPLC using hexane/ethyl acetate (8.5:1.5) as the eluent. The chromatogram showed one single peak.

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