Chemo-enzymatic routes to enantiopure haloalcohols and epoxides
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Chapter 5
Synthetic applications of enantiopure chloroalcohols

This chapter is centered on the use of chloroalcohols in a variety of reactions with the aim of increasing their functionality and demonstrating their potential as chiral building blocks in synthesis. We focused on rearrangement reactions such as the Achmatowicz, Ireland-Claisen, and Johnson orthoester rearrangements. Initial results are promising, but further research is required to demonstrate the scope and limitations of these transformations.
Chapter 5

5.1 Introduction

Chloroalcohols are often employed as intermediates in organic synthesis, for instance as precursors of epoxides or aminoalcohols. Since we developed a very efficient system to obtain enantiomerically pure chloroalcohols by enzymatic kinetic resolution (see Chapter 3), we became interested in the synthetic applications of these compounds. In particular, we looked into the possible application of enantiopure chloroalcohols in rearrangement reactions such as the Achmatowicz, Ireland-Claisen, and Johnson orthoester rearrangements.

5.2 Achmatowicz rearrangement of 2-chloro-1-(furan-2-yl)ethanol

The Achmatowicz rearrangement (Scheme 5.1), first described in 1971 by Achmatowicz and coworkers, is a useful reaction that converts 2-furanylcarbinols into highly functionalized pyranones. Enantiopure pyranones like 5.2 are building blocks in the synthesis of, for example, carbohydrates, biologically active compounds such as daumone, tirandamycin B, and patuline, as well as other compounds such as functionalized spirocyclic pyrans. Various conditions are described in the literature for this transformation, most importantly via bromination using molecular bromine or NBS or oxidation with m-CPBA, dimethyldioxirane, or PhI(OAc)2-Mg(ClO4)2. Catalytic procedures include the use of t-butyl hydroperoxide / VO(acac)2, and H2O2 / titanium silicalite. The related aza-Achmatowicz rearrangement has been used in the synthesis of naturally occurring alkaloids.

![Scheme 5.1](image)

Scheme 5.1 Achmatowicz rearrangement of 1-(furan-2-yl)ethanol to 6-hydroxy-2-methyl-2H-pyran-3(6H)-one.

In the Achmatowicz rearrangement, the configuration of the alcohol moiety is preserved. As a result, kinetic resolution of 2-furarylcarbinols such as rac-5.1 is possible by using Sharpless asymmetric epoxidation, followed by Achmatowicz rearrangement of the initially formed epoxide.
A recent application is the synthesis of the \( \eta^3 \)-oxopyranyl- and \( \eta^3 \)-oxopyridinylmolybdenum complexes \( \text{TpMo(CO)}_2(\eta^3 \text{-oxopyranyl}) \) and \( \text{TpMo(CO)}_2(\eta^3 \text{-oxopyridinyl}) \) by oxa- and aza-Achmatowicz reactions, both in racemic and enantiomerically pure form.\(^{19,a}\)

Chloroalcohol 5.3 could conceivably be converted into pyranone 5.4 by an Achmatowicz rearrangement (Scheme 5.2).

We looked for suitable reaction conditions using non-chlorinated furanyl carbinol 5.1. The use of bromine\(^3,12\) in acetonitrile or methanol led to black tar, but using NBS in a mixture of THF and water\(^8\) gave 5.2 in 85\% isolated yield as a mixture (65:35) of two diastereomers.

These conditions were then applied to racemic 5.3 (Scheme 5.2) leading, however, to a disappointing yield of 26\%. The product was observed to be unstable on silica gel, as well as upon prolonged standing, but could be crystallized from diethyl ether. However, the reaction turned out not to be reproducible, despite multiple attempts. Also, a subsequent reaction with enantiomerically enriched 5.3 (S-enantiomer, 90\% ee) failed to give 5.4. An alternative procedure using \( m \)-CPBA did not give the product either.\(^9\)

We concluded that that pyranone 5.4 is relatively stable once isolated, but unstable under the conditions of the reaction or the workup, due to the chlorine substituent present in the compound.

Since the reaction failed to work using 5.3, it was attempted to replace chlorine by a benzyloxy substituent and perform the rearrangement subsequently. The substitution of chlorine for benzylationate on vicinal chloroalcohols different from 5.3 was described for example by the groups of Beauchamp\(^{20}\) and Doyle.\(^{21}\) The new approach is outlined in Scheme 5.3.

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\(^{1}\) Tp = hydridotrispyrazolylborato.
Several attempts were made to obtain $\text{5.5}$ from $\text{5.3}$, for instance using PhCH$_2$ONa in DMF at reflux, PhCH$_2$ONa and NaI in THF at room temperature, and PhCH$_2$OH (neat) and NaI at room temperature. In all cases, the reaction resulted in the formation of black tars. Appropriate, mild conditions for this transformation have to be established. Consequently, it has not been tested on the enantiomerically pure chloroalcohol yet.

### 5.3 Ireland-Claisen rearrangement of (E)-1-chloro-4-phenylbut-3-en-2-yl propionate

The ester enolate Claisen rearrangement, or Ireland-Claisen rearrangement, is a variety of the Claisen [3,3]sigmatropic rearrangement developed in the 70's by Ireland and coworkers. It takes place at milder conditions than the regular Claisen rearrangement, is versatile, and exhibits high levels of stereocontrol. By controlling the $E/Z$ stereochemistry of the enolate formed upon deprotonation, the syn/anti stereochemistry of the resulting rearrangement product can be selectively established.

It had been demonstrated that Ireland-Claisen rearrangement reaction was possible on substrates such as (E)-4-phenylbut-3-en-2-yl malonates (Scheme 5.4).

Furthermore, the Ireland-Claisen rearrangement has been applied in the total synthesis of the antitumor alkaloid, (+)-pancratistatin (Scheme 5.5) and it was used in the synthesis of chiral subunits for macrolide synthesis. These and other examples show
the remarkable stereocontrol of this rearrangement, which makes it possible to predict the stereochemical configuration and double bond geometry in the product by examination of the corresponding properties in the starting material.28

Scheme 5.5 Application of the Ireland-Claisen rearrangement in the total synthesis of (+)-pancratistatin.

Furthermore, Sakaitani and Ohfune described the intramolecular ring closure of carbamate-substituted allylic chlorides using silver fluoride (Scheme 5.6).29

Scheme 5.6 Ring closure of carbamate-substituted allylic chloroalcohols using silver fluoride.

Inspired by these previous results, we envisioned the possibility of using allylic chloroacylates 5.7 en route to chiral lactones, as outlined in Scheme 5.7. An Ireland-Claisen rearrangement leading to silyl-protected carboxylic acids 5.8, followed by intramolecular ring closure, would thus provide an enantioselective entry into chiral lactones 5.9. Following the route outlined in Scheme 5.7, a product with three
consecutive stereocenters would be formed from a starting material containing only one.

The esters used as starting material are available in quantitative yield from the corresponding chloroalcohols and the appropriate anhydride, as shown in Scheme 5.8.30

![Scheme 5.8 Synthesis of propyl esters 5.7 from allylic chloroalcohols 5.10.](image)

**Table 5.1** Ireland-Claisen rearrangement of (E)-1-chloro-4-phenylbut-3-en-2-yl propionate (5.7b).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base (equiv.)</th>
<th>Additive</th>
<th>Temp.</th>
<th>Additive</th>
<th>TMSX</th>
<th>Conv. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LDA</td>
<td>HMPA</td>
<td>−80→rt</td>
<td>TMSCl</td>
<td></td>
<td>45 (0)</td>
</tr>
<tr>
<td>2</td>
<td>LDA</td>
<td>HMPA</td>
<td>−80→rt</td>
<td>−</td>
<td>TMSCl</td>
<td>35 (0)</td>
</tr>
<tr>
<td>3</td>
<td>LDA</td>
<td>−</td>
<td>−80→rt</td>
<td>TMSCl</td>
<td></td>
<td>20 (0)</td>
</tr>
<tr>
<td>4</td>
<td>LiHMDS</td>
<td>−</td>
<td>−80→rt</td>
<td>TMSCl</td>
<td></td>
<td>5.7b, 5.11 1:1</td>
</tr>
<tr>
<td>5</td>
<td>LiHMDS</td>
<td>HMPA</td>
<td>−80→rt</td>
<td>TMSCl</td>
<td></td>
<td>5.11 (46), 5.12 (11), 5.7b (43)</td>
</tr>
<tr>
<td>6</td>
<td>LiHMDS</td>
<td>HMPA</td>
<td>−80→Δ'</td>
<td>TMSCl</td>
<td></td>
<td>5.7b and 5.12 only</td>
</tr>
<tr>
<td>7</td>
<td>LiHMDS</td>
<td>−</td>
<td>−80→rt</td>
<td>TMSCl</td>
<td></td>
<td>primarily 5.7b</td>
</tr>
<tr>
<td>8</td>
<td>NaHMDS (1.2 eq)</td>
<td>−</td>
<td>−60→rt</td>
<td>TMSOTf</td>
<td></td>
<td>5.7b</td>
</tr>
<tr>
<td>9</td>
<td>LiHMDS (1.2 eq)</td>
<td>−</td>
<td>−65→rt</td>
<td>TMSOTf</td>
<td></td>
<td>5.7b and 5.12 (trace)</td>
</tr>
<tr>
<td>10</td>
<td>NaHMDS (3 eq)</td>
<td>−</td>
<td>−60→rt</td>
<td>TMSOTf</td>
<td></td>
<td>5.7b and 5.12</td>
</tr>
<tr>
<td>11</td>
<td>LiHMDS (3 eq)</td>
<td>−</td>
<td>−80→rt</td>
<td>TMSOTf</td>
<td></td>
<td>5.7b and 5.12</td>
</tr>
<tr>
<td>12</td>
<td>NaHMDS (3 eq)</td>
<td>HMPA</td>
<td>−80→rt</td>
<td>TMSOTf</td>
<td></td>
<td>n.i.</td>
</tr>
<tr>
<td>13</td>
<td>NaHMDS</td>
<td>HMPA</td>
<td>−80→rt</td>
<td>TBDMSCl</td>
<td></td>
<td>n.i.</td>
</tr>
<tr>
<td>14</td>
<td>LiHMDS</td>
<td>HMPA</td>
<td>−80→rt</td>
<td>TBDMSCl</td>
<td></td>
<td>n.i.</td>
</tr>
</tbody>
</table>

a) Between brackets is the conversion to product 5.11; b) Considerable amount of unidentified byproducts; c) Heated to reflux; d) Additional unidentified byproducts; e) Unidentified mixture of products.
Conditions for the Ireland-Claisen reaction were screened primarily on 5.7b. Various bases (LDA, LiHMDS, NaHMDS) and silylating reagents (TMSCl, TMSOTf, TBDMSCl) were tested, as well as the influence of using HMPA as an additive (Table 5.1). In the end no feasible conditions could be established for this reaction. The best results were obtained using LiHMDS, HMPA, and TMSCl in THF at $-80^\circ C$ → rt: 46% conversion to the product, 43% starting material, and 11% dechlorinated starting material (Table 5.1, entry 5).

For the reactions described in Table 5.1, in entries 13 and 14, a different silylating reagent was used ($t$-butyldimethylsilyl chloride) according to a procedure described by Ko et al.\textsuperscript{26}

Alternative bases, such as NaH, K$_2$CO$_3$, or DIPA, did not give conversion. Some other bases, for instance DBU, $n$-BuLi, or KOH, give partial or complete conversion to unwanted products. Some frequently observed byproducts are $(E)$-4-phenylbut-3-en-2-one (5.13), $(E)$-4-phenylbuta-1,3-dien-2-yl propionate (5.14), and $(1E,3E)$-4-chlorobuta-1,3-dienylbenzene (5.15), shown in Figure 5.1.

![Figure 5.1](image) Side-products observed in [3,3]sigmatropic rearrangement of 5.7b.

Despite extensive efforts, we have been unable to establish reaction conditions which give full conversion of 5.7b to products 5.11 or 5.9. A possible reason for the low conversion to the anticipated products might be direct ring closure of the enolate with chloride as the leaving group, as shown in Scheme 5.9.

![Scheme 5.9](image) Possible explanation for low conversion of 5.7b to product 5.11.

What also remains to be done is the development of the ring closure to butyrolactones 5.9. As already mentioned, there are literature precedents for this reaction, since the ring closure of silyl-protected carboxylic acids\textsuperscript{29} and esters\textsuperscript{31} has been described.
5.4 Johnson orthoester rearrangement of (E)-1-chloro-4-phenylbut-3-en-2-ol

The Johnson orthoester rearrangement, or Johnson-Claisen rearrangement, was published in 1970 by Johnson and coworkers. It involves heating a mixture of an allylic alcohol and an orthoester in the presence of a weak acid, such as propionic acid, after which the resulting ketene acetal undergoes [3,3]sigmatropic rearrangement. In 1993, the synthesis was described of bicyclic lactones via orthoester rearrangement followed by selenolactonization / oxidative elimination. Because of its ease of performance and, generally, high level of stereocontrol, the Johnson rearrangement has been used extensively in the synthesis of natural products.

Johnson orthoester rearrangement has been performed with >97% transfer of chirality on the styryl-substituted alcohols 5.16, 5.17, and 5.18, shown in Figure 5.2.

We anticipated to perform a Johnson orthoester rearrangement using chloroalcohols 5.10 as substrate, followed by ring closure of the initially formed esters 5.19 to highly functionalized enantiopure butyrolactones 5.9. This sequence of reactions is outlined in Scheme 5.10.

Initial reaction of (E)-1-chloro-4-phenylbut-3-en-2-ol (5.10a) with triethyl ortho-propionate in refluxing toluene in the presence of a catalytic amount of propionic acid gave 90% conversion (Table 5.2, entry 1). However, the isolated yield of 5.19a was
only 48% and the two diastereomers were formed in equimolar ratio. Stereocontrol may be improved by using starting materials containing trisubstituted double bonds, as shown in an example from the literature.\textsuperscript{38} We tried to develop a shorter reaction under milder conditions in order to improve stereocontrol. Microwave heating seemed an attractive alternative, however the levels of conversion were similar and the diastereomeric ratio improved only slightly (entries 2 and 3). The use of alternative catalysts such as bentonite clay\textsuperscript{33} or the Lewis acid scandium triflate led to disappointing results (entries 4 and 5).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Orthoester</th>
<th>Product</th>
<th>T</th>
<th>Conv. (%)</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(5.10a)</td>
<td>EtC(OEt)(_3)</td>
<td>(5.19a)</td>
<td>(\Delta)</td>
<td>90</td>
<td>48% isol. y., dr 1:1(^b)</td>
</tr>
<tr>
<td>2</td>
<td>(5.10a)</td>
<td>EtC(OEt)(_3)</td>
<td>(5.19a)</td>
<td>(\Delta, \mu)</td>
<td>80</td>
<td>dr 1:1.5(^b)</td>
</tr>
<tr>
<td>3(^c)</td>
<td>(5.10a)</td>
<td>EtC(OEt)(_3)</td>
<td>(5.19a)</td>
<td>(\Delta, \mu)</td>
<td>90</td>
<td>dr 1:1(^b)</td>
</tr>
<tr>
<td>4</td>
<td>(5.10a)</td>
<td>EtC(OEt)(_3)</td>
<td>(5.19a)</td>
<td>(\Delta, \mu)</td>
<td>black tar</td>
<td>cat: bentonite clay K-10</td>
</tr>
<tr>
<td>5</td>
<td>(5.10a)</td>
<td>EtC(OEt)(_3)</td>
<td>(5.19a)</td>
<td>rt (&gt;98)</td>
<td>no (5.19)</td>
<td>cat: Sc(OTf)(_3)</td>
</tr>
<tr>
<td>6</td>
<td>(5.10a)</td>
<td>MeC(OEt)(_3)</td>
<td>(5.19b)</td>
<td>(\Delta, \mu)</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>7 (\dagger)</td>
<td>(5.10a)</td>
<td>MeC(OEt)(_3)(S)</td>
<td>(5.19b)</td>
<td>(\Delta)</td>
<td>(&gt;98)</td>
<td>ee ((5.19a)) 41%</td>
</tr>
<tr>
<td>8</td>
<td>(5.10b)</td>
<td>EtC(OEt)(_3)</td>
<td>(5.19c)</td>
<td>(\Delta, \mu)</td>
<td>(&gt;98)</td>
<td>dr 56:44(^b)</td>
</tr>
</tbody>
</table>

\(a\) For reaction conditions, see the experimental section; \(b\) Diastereomeric ratio; \(c\) Duplo of entry 2; \(d\) Full conversion to unidentified products.

In an attempt to circumvent the formation of diastereomers, some reactions were also performed using triethyl orthoacetate (Table 5.2, entries 6 and 7). The conversion to product \(5.19b\) was similar compared to the reactions using triethyl orthopropionate. However, a disencouraging result was obtained when using enantiopure starting material. Starting from \((S)-5.10a\) (>99\% ee), product \(5.19b\) was obtained in only 41\% ee (Scheme 5.11), despite complete transfer of chirality (>97\%) on structurally similar substrates such as \(5.16 - 5.18\) (Figure 5.2).\textsuperscript{35,36,37}

It is not clear whether loss of enantiomeric excess stems from racemization of the chloroalcohol prior to rearrangement, or if the rearrangement itself has poor
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stereocontrol. Unfortunately, there was no sufficient time to further test any of these hypotheses or establish more favorable reaction conditions.

![Scheme 5.11](image)

Scheme 5.11 Partial racemization or incomplete transfer of chirality in the Johnson orthoester rearrangement of (S)-5.10a.

Finally, (E)-1-chloropent-3-en-2-ol (5.10c) was subjected to Johnson rearrangement conditions using triethyl orthopropionate (Table 5.2, entry 8). Although full conversion was reached, diastereoselectivity was practically absent, similar to the results with substrate 5.10a.

In conclusion, the functionalization of chiral allylic chloroalcohols by orthoester Claisen rearrangement turned out to be more challenging than expected, despite the progress that has been made. Conversions are excellent, although the diastereoselectivity is unexpectedly low. Possibilities for improvement include the use of alternative catalysts such as a suitable Lewis acid or possibly a transition metal catalyst. Furthermore, suitable conditions have to be established for the ring closure reaction. Considering prior art in this area, this is not expected to pose significant problems.

![Scheme 5.12](image)

Scheme 5.12 Synthesis of chiral butyrolactones from allylic chloroalcohol.

As illustrated in Scheme 5.12, it would still be possible to obtain only one diastereomer of the ring-closed product, despite the lack of diastereoselectivity in the rearrangement reaction. Deprotonation of lactones 5.9, e.g. by DBU, followed by reprotonation, would selectively lead to the more stable trans-substituted butyrolactones.
5.5 Suggestions for further research

Numerous possible applications for chiral chloroalcohols can be envisioned. Here, a number of ideas will be described which have a lot of potential, but could not be completed due to lack of time.

For instance, the hydroxy moiety in enantiopure (E)-1-chloro-4-phenylbut-3-en-2-ol (5.10a) could be converted into a better leaving group in a stereospecific fashion, creating a molecule with two neighbouring leaving group next to a double bond (5.20). A tandem of two consecutive regio- and stereoselective copper-catalyzed allylic substitution reactions would, via intermediate 5.21, lead to highly functionalized enantiopure products 5.22 (Scheme 5.13). Copper-catalyzed asymmetric alkylation\(^\text{39}\) usually show the desired $\gamma$-selectivity, as opposed to catalysts based on e.g. palladium which often give alkylation at the $\alpha$-position.\(^\text{40}\)

Scheme 5.13 Tandem copper-catalyzed allylic alkylation. Nu\(_1\) and Nu\(_2\) are the first and second nucleophile, respectively.

To initiate this chemistry, 5.10a was converted into (E)-(3,4-dichlorobut-1-enyl)benzene (5.20a) using triphenylphosphine in tetrachloromethane.\(^\text{41}\) However, initial allylic alkylation experiments were unsuccessful and there was insufficient time to optimize the reaction conditions.

Related to the previous idea, it could be possible to perform transition-metal catalyzed allylic substitutions on vinyloxiranes under aqueous conditions. Vinyloxiranes 5.23 are the products of enzymatic kinetic resolution of chloroalcohols described in Chapter 3, and there lability to hydrolysis stood in the way of their isolation. However, transforming them \textit{in situ} by way of allylic substitution would yield the much more
stable product 5.24, provided it is possible to do such a transformation in an aqueous environment (Scheme 5.14).

Scheme 5.14  Transition metal catalyzed allylic alkylation of vinyloxiranes under aqueous conditions.

Fortunately, there are indications in the literature that this might be possible. Recently, conditions have been described for Pd/C-mediated allylic substitution in water\(^\text{42}\) and palladium-catalyzed allylic substitution leading to lactones in a water / EtOAc biphasic system.\(^\text{43}\) Both examples use allyl acetates as substrates. Also, palladium-catalyzed allylic substitution using allyl alcohols as allylating agents in aqueous environment has been described.\(^\text{44}\)

5.6 Conclusions

Chloroalcohols 5.3, 5.10a, and 5.10c have been used in Achmatowicz, Ireland-Claisen, and Johnson orthoester rearrangements. Initial results are promising, nevertheless extensive further research has to be done for these reactions to reach their full potential. In the case of the Achmatowicz rearrangement of 5.3, product 5.4 has been obtained in 26\% yield, whereas the yield of the corresponding non-chlorinated compound 5.2 was 85\%. Moreover, 5.4 was found to be significantly less stable than 5.2.

Ireland-Claisen rearrangement of unsaturated chloropropionate 5.7b so far gives a maximum conversion of 46\% to product 5.11, whereas several side-products are observed. Hence, optimum conditions have yet to be established for this transformation. In the case of the Johnson orthoester rearrangement of chloroalcohols 5.10, the conversion to products 5.19 is high (80 – >98\%), but lack of stereocontrol is an issue that still has to be resolved.

5.7 Experimental section

5.7.1 General remarks

For general remarks, see Chapters 2 and 3.
5.7.2 Achmatowicz rearrangement

1-(Furan-2-yl)ethanol (5.1)

Prepared by Grignard addition of \textit{in situ} prepared MeMgI to furfural. Reactions conditions, work-up procedure, and spectral data were in accordance with the literature.\textsuperscript{45}

6-Hydroxy-2-methyl-2H-pyran-3(6H)-one (5.2)\textsuperscript{8}

Synthesized according to a literature procedure\textsuperscript{8} as a 65:35 mixture of diastereoisomers. \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \textdelta 6.92 (d, \(J = 10.3\) Hz, 1H, minor isomer), 6.89 – 6.85 (m, 1H, major isomer), 6.12 (d, \(J = 10.3\) Hz, 1H, minor), 6.07 (d, \(J = 10.3\) Hz, 1H, major), 5.65 (br s, 1H, minor), 5.60 (br d, \(J = 2.2\) Hz, 1H, major), 4.68 (qd, \(J = 7.0, 1.1\) Hz, 1H, major), 4.20 (q, \(J = 6.6\) Hz, 1H, minor), 3.94 (br s, 1H, minor), 3.60 (br s, 1H, major), 1.43 (dd, \(J = 6.6, 1.5\) Hz, 1H, minor), 1.37 (dd, \(J = 7.0, 1.5\) Hz, 1H, major); MS (EI\textsuperscript{+}) m/z = 128 (M\textsuperscript{+}), 111, 84, 55, 43.

2-Chloro-1-(furan-2-yl)ethanol (5.3)

The synthesis of 2-chloro-1-(furan-2-yl)ethanol (5.3) from furfural and chloroiodomethane is described in Chapter 3 (compound 3.6).

2-(Chloromethyl)-6-hydroxy-2H-pyran-3(6H)-one (5.4)

2-Chloro-1-(furan-2-yl)ethanol (5.3, 150 mg, 1.0 mmol) was dissolved in a THF/H\textsubscript{2}O 3:1 (4 mL) after which the mixture was cooled down to 0 °C. Subsequently, NaHCO\textsubscript{3} (170 mg, 2.0 mmol) and NaOAc•3H\textsubscript{2}O (138 mg, 1.0 mmol) were added and the mixture was stirred until all components had dissolved. Then, NBS (180 mg, 1.0 mmol) was added and the mixture, which turned yellow, was allowed to stir at 0 °C for 2 h. The reaction was then quenched by addition of aq. NaHCO\textsubscript{3} sat. (4 mL, the mixture turned red upon addition), extracted with Et\textsubscript{2}O (3 ×), dried over MgSO\textsubscript{4}, filtered and...
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evaporated, yielding a blue powder (154 mg). Subsequent recrystallization yielded light brown crystals (43 mg, 0.265 mmol, 26%). NMR showed a single diastereomer. \(^1\)H NMR (acetone-d\(_6\), \(\delta\) 2.05) \(\delta\) 7.12 (dd, \(J = 10.3\) Hz, 1H), 6.13 (d, \(J = 6.2\) Hz, 1H), 6.07 (d, \(J = 10.3\) Hz, 1H), 5.69 (dd, \(J = 6.2, 3.3\) Hz, 1H), 4.88 (dd, \(J = 5.1, 3.0\) Hz, 1H), 3.98 (d, \(J = 11.7, 5.1\) Hz, 1H), 3.86 (d, \(J = 11.7, 3.0\) Hz, 1H); \(^1\)C NMR (acetone-d\(_6\), C\(_{\text{carbonyl}}\) \(\delta\) 206.2) \(\delta\) 193.9 (s), 148.0 (d), 127.0 (d), 88.4 (d), 74.3 (d), 44.0 (t); MS (EI\(^+\)) m/z = 162 (M\(^+\)), 145, 126, 109, 99, 84, 55, 43; chiral GC: Chiraldex G-TA, 25m x 0.25 mm x 0.25 \(\mu\)m, He-flow: 1.0 mL/min, 50 °C to 150 °C, 3 °C/min, 150 °C to 180 °C, 10 °C/min, hold 10 min, 180 °C to 50 °C, 10 °C/min, stop, \(T_r\) = 38.5 min (first enantiomer), \(T_r\) = 40.7 (second enantiomer).

5.7.3 Ireland-Claisen rearrangement

\((E)\)-1-Chloro-4-phenylbut-3-en-2-y acetate (5.7a)

\[
\begin{align*}
\text{Cl} & \quad \text{O} \\
\text{O} & \quad \text{Cl}
\end{align*}
\]

\((E)\)-1-Chloro-4-phenylbut-3-en-2-ol (5.10a, 0.91 g, 5.0 mmol) was mixed with pyridine (1.0 mL) and acetic anhydride (1.0 mL, 2 eq) at 0 °C. This mixture was allowed to stir overnight, during which the temperature slowly rose to room temperature. Excess reagents were removed by evaporation and the product was purified by flash chromatography over SiO\(_2\) (eluent: \(n\)-pentane / Et\(_2\)O 9:1, \(R_i\) 0.29, quant.). \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.40 \text{−} 7.24 (m, 5H), 6.70 (d, \(J = 16.1\) Hz, 1H), 6.15 (dd, \(J = 15.7, 7.3\) Hz, 1H), 5.61 (dd, \(J = 12.4, 5.9\) Hz, 1H), 3.68 (d, \(J = 6.2\) Hz, 1H), 2.12 (s, 3H); \(^1\)C NMR (CDCl\(_3\)) \(\delta\) 169.9 (s), 135.6 (s), 134.8 (d), 128.6 (d), 128.4 (d), 126.7 (d), 126.7 (d), 123.6 (t), 45.6 (t), 21.0 (q); MS (EI\(^+\)) m/z = 224 (M\(^+\)), 188, 146, 133, 128, 115, 103, 91, 77, 55, 51; HRMS (EI\(^+\)) calcd. for C\(_{12}\)H\(_{13}\)ClO\(_2\): 224.0604, found: 224.0608.

\((E)\)-1-Chloro-4-phenylbut-3-en-2-yl propionate (5.7b)

Prepared analogous to 5.7a, in quantitative yield. Purified by flash chromatography over SiO\(_2\) (eluent: \(n\)-pentane / Et\(_2\)O 9:1, \(R_i\) 0.36). \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.39 \text{−} 7.24 (m, 5H), 6.70 (d, \(J = 15.8\) Hz, 1H), 6.15 (dd, \(J = 16.1, 7.3\) Hz, 1H), (dd, \(J = 12.4, 6.2\) Hz, 1H), 3.68 (d, \(J = 6.2\) Hz, 1H), 2.40 (qd, \(J = 7.3, 1.5\) Hz, 2H), 1.17 (t, \(J = 7.3\) Hz, 3H); \(^1\)C NMR (CDCl\(_3\)) \(\delta\) 173.3 (s), 170.2 (s), 134.6 (d), 128.6 (d), 128.3 (d), 126.7 (d),

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123.7 (d), 73.3 (d), 45.6 (t), 27.6 (t), 9.0 (q); MS (EI+) m/z = 238 (M+), 202, 146, 129, 115, 103, 91, 77, 57, 51; HRMS (EI+) calcd. for C\textsubscript{13}H\textsubscript{15}Cl\textsubscript{3}O\textsubscript{2}: 238.0761, found: 238.0752.

**((E)-1-Chlorooct-3-en-2-yl) propionate (5.7c)**

(E)-1-Chlorooct-3-en-2-ol (5.10b, 0.81 g, 5.0 mmol) was mixed with pyridine (2.5 mL) and acetic anhydride (2.5 mL, 5 eq) at 0 °C. This mixture was stirred overnight, during which the temperature slowly rose to room temperature. The reaction was then quenched with aq. HCl 2M and extracted with Et\textsubscript{2}O (3×). The combined organic fractions were washed with aq. NaHCO\textsubscript{3} and brine, respectively, dried over MgSO\textsubscript{4}, filtered and evaporated, giving 5.7c (1.03 g, 4.74 mmol, 95%). \(^1\)H NMR (CDCl\textsubscript{3}) \(\delta\) 5.86 – 5.76 (m, 1H), 5.45 – 5.38 (m, 2H), 3.56 (br d, \(J = 3.7\) Hz, 2H), 2.34 (q, \(J = 7.7\) Hz, 2H), 2.05 – 1.99 (m, 2H), 1.37 – 1.24 (m, 4H), 1.13 (t, \(J = 7.3\) Hz, 3H), 0.86 (t, \(J = 7.0\) Hz, 3H); \(^13\)C NMR (CDCl\textsubscript{3}) \(\delta\) 173.4 (s), 137.0 (d), 124.6 (d), 73.5 (d), 45.8 (t), 31.9 (t), 30.8 (t), 27.7 (t), 22.1 (t), 13.8 (q), 9.0 (q); MS (EI+) m/z = 218 (M+), 183, 126, 109, 97, 67, 57, 41; HRMS (EI+) calcd. for C\textsubscript{11}H\textsubscript{19}O\textsubscript{2} (M+ – Cl): 183.1385, found: 183.1379.

**General procedure for Ireland-Claisen rearrangement of substrates 5.7**

A flame-dried 50 mL flask under an atmosphere of nitrogen was charged with 5.7a, 5.7b, or 5.7c (0.25 mmol), HMPA (1.5 equiv.), and 2 mL of freshly distilled THF. The reaction mixture was then cooled to –80 °C and a 1.0 M solution of base (typically 0.3 mL) was added, followed after 15 min of stirring by freshly distilled TMSCl (0.1 mL, 0.78 mmol). Subsequently, the reaction mixture was allowed to stir overnight, during which the temperature gradually increased to room temperature. The reaction was then quenched by addition of NH\textsubscript{4}Cl, sat., extracted with Et\textsubscript{2}O (3×), the combined organic fractions washed with aq. NaHCO\textsubscript{3} and brine, respectively, dried over MgSO\textsubscript{4}, filtered and evaporated. Product composition was determined using GC-MS and \(^1\)H NMR.

**((E)-4-Phenylbuta-1,3-dien-2-yl) propionate (5.14)**

(E)-1-Chloro-4-phenylbut-3-en-2-yl propionate (5.7b, 242 mg, 1.0 mmol) was dissolved in THF (5 mL), after which DBU (0.15 mL) was added. The resulting solution was heated at reflux for an hour, after which a white precipitate appeared, which was filtered and washed with freshly distilled THF. The filtrate was
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concentrated in vacuo and the crude product thus obtained was purified by flash chromatography on SiO₂ (eluent: n-pentane / EtOAc gradient 50:1 to 20:1). The main isolated fraction was identified as (E)-4-phenylbuta-1,3-dien-2-yl propionate (129 mg, 0.64 μmol, 64%). ¹H NMR (CDCl₃) δ 7.42 – 7.22 (m, 5H), 6.59 (q, J = 15.8 Hz, 2H), 5.11 (s, 1H), 4.96 (s, 1H), 2.57 (qd, J = 7.3, 1.8 Hz, 2H), 1.26 (td, J = 7.3, 1.8 Hz, 3H); ¹³C NMR (CDCl₃) δ 172.2 (s), 151.8 (s), 136.0 (s), 129.8 (d), 128.9 (d), 128.2 (d), 126.8 (d), 122.7 (d), 106.0 (t), 27.6 (t), 9.2 (q). MS (EI+) m/z = 202 (M⁺), 146, 145, 128, 117, 102, 91, 77, 57, 51.

5.7.4 Johnson orthoester rearrangement

(E)-6-Chloro-2-methyl-3-phenyl-hex-4-enoic acid ethyl ester (5.19a)

(E)-1-Chloro-4-phenylbut-3-en-2-ol (5.10a, 54 mg, 0.3 mmol) was dissolved in 2 mL of freshly distilled toluene, along with triethyl orthopropionate (0.5 mL, 443 mg, 2.5 mmol) and 2 drops of propionic acid. This solution was stirred at reflux for 1 d. Following addition of water, the mixture was extracted with Et₂O (2x), the combined organic fractions washed with aq. NaHCO₃ and brine, respectively, dried over MgSO₄, filtered and the solvent evaporated. The crude product thus obtained was purified by column chromatography over silica, using n-pentane / EtOAc 19:1 as eluent. (E)-Ethyl 6-chloro-2-methyl-3-phenylhex-4-enoate (5.19a) was obtained in 48% yield as an oil, consisting of an equimolar mixture of cis/trans isomers that was not further separated. ¹H NMR (CDCl₃) δ 7.39 – 7.14 (m, 2 × 5H), 5.97 – 5.83 (m, 2 × 1H), 5.75 – 5.59 (m, 2 × 1H), 4.17 – 3.82 (m, 2 × 4H), 3.50 (td, J = 9.5, 2.2 Hz, 1H), 3.44 (m, 1H), 2.85 – 2.74 (m, 2 × 1H), 1.26 (t, J = 7.0 Hz, 3H), 1.25 (t, J = 7.0 Hz, 3H), 0.96 (d, J = 7.0 Hz, 3H), 0.95 (d, J = 7.0 Hz, 3H); ¹³C NMR (CDCl₃) δ 175.4 & 174.9 (s), 141.6 & 140.7 (s), 136.3 & 135.3 (d), 128.7 (d), 128.6 (d), 128.5 (d), 128.03 (d), 127.8 (d), 126.7 (d), 60.4 & 60.1 (t), 52.1 & 52.0 (d), 45.3 & 45.0 (d), 44.7 & 44.6 (t), 15.8 & 15.6 (q), 14.2 & 13.9 (q); MS (EI+) m/z = 267 (M⁺), 231, 165, 157, 129, 115, 102, 91, 77, 65, 51; HRMS (EI+) calcd. for C₁₅H₁₉O₂ (M⁺ – Cl): 231.1385, found: 231.1377.
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(E)-6-Chloro-3-phenyl-hex-4-enoic acid ethyl ester (5.19b)

Prepared analogous to 5.19a. 1H NMR (CDCl₃) δ 7.44 – 7.18 (m, 5H), 5.93 (dd, J = 15.0, 7.3 Hz, 1H), 5.65 (dt, J = 15.0, 7.0, 1.3 Hz, 1H), 4.08 (q, J = 7.0 Hz, 2H), 4.01 (d, J = 7.0, 2H), 3.88 (q, J = 7.3 Hz, 1H), 2.78 – 2.66 (m, 2H), 1.78 (t, J = 7.0 Hz, 3H); ¹³C (CDCl₃) δ 171.5 (s), 141.8 (s), 136.9 (d), 128.6 (d), 127.5 (d), 126.9 (d), 126.4 (d), 60.5 (t), 44.2 (d), 40.4 (t), 14.1 (q); MS (EI+) m/z = 217, 170, 165, 142, 129, 115, 103, 91, 77, 65, 51; HRMS (EI+) calcd. for C₁₄H₁₇O₂ (M+−Cl): 217.1229, found: 217.1220; E.e. determination using chiral HPLC: Chiralcel OD, 40 °C, n-heptane/IPA 99:1, 1.0 mL/min, Tᵣ = 10.2 min (S), 12.9 min (R).

Using (S)-5.10a (>98% ee) as starting material, 5.19b was obtained with 41% ee.

(E)-6-Chloro-2,3-dimethyl-hex-4-enoic acid ethyl ester (5.19c)

Prepared analogous to 5.19a and obtained as a 1:1 mixture of diastereomers. 1H NMR (CDCl₃) δ 5.72 – 5.52 (m, 2H), 4.08 (q, J = 7.3 Hz, 2H), 3.99 (t, J = 6.2, 2H), 2.45 (q, J = 7.0 Hz, 1H), 2.33 (qud, J = 7.3, 7.0, 6.6 Hz, 1H), 1.22 (d, J = 7.0 Hz, 3H), 1.07 (t, J = 6.6 Hz, 3H), 0.99 (d, J = 6.6 Hz, 3H); ¹³C (CDCl₃) δ 138.3 & 137.7 (d), 126.6 & 126.0 (d), 60.6 & 60.3 (t), 45.0 (t), 44.9 & 44.7 (d), 39.4 & 39.1 (d), 18.2 (q), 16.5 (q), 14.5 (q), 14.2 (q), 13.7 (q); MS (EI+) m/z = 169, 159, 153, 141, 131, 123, 113, 103, 958, 85, 74, 67, 55, 41; MS (CI+) m/z = 224 (M+NH₄⁺), 222 (M+NH₄⁺).

Further research

(E)-(3,4-dichlorobut-1-enyl)benzene (5.20a).

Prepared from 5.10a, PPh₃ and CCl₄, according to a literature procedure.¹¹b 1H NMR (CDCl₃) δ 7.47 – 7.24 (m, 5H), 6.71 (d, J = 15.4 Hz, 1H), 6.19 (dd, J = 15.8, 8.8 Hz, 1H), 4.68 (m, 1H), 3.86 (dd, J = 11.0, 5.5 Hz, 1H), 3.76 (dd, J = 11.0, 8.1 Hz, 1H); ¹³C NMR (CDCl₃) δ 135.4 (s), 134.9 (d), 128.7 (d), 128.6 (d), 126.9 (d), 125.8 (d), 61.1 (d), 47.7 (t); Chiral HPLC: Chiralcel OD, 40 °C, n-heptane/IPA 99:1, 1.0 mL/min, Tᵣ = 8.9, 10.5 min.
5.8 Notes and references

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