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# Synthesis of β-hydroxy-δ-trichloromethyl-δ-valerolactones by intramolecular samarium/ytterbium diiodide-mediated Reformatsky reaction

Thies M. Schulze, Jörg Grunenberg, Stefan Schulz *

*Technische Universität Braunschweig, Institut für Organische Chemie, Hagenring 30, 38106 Braunschweig, Germany*

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ABSTRACT

The synthesis of α-methyl-β-hydroxy-δ-trichloromethyl-δ-valerolactone was achieved by an intramolecular Reformatsky reaction. The cyclisation was effected by samarium diiodide or (for the first time) ytterbium diiodide. The diastereoselectivity of the reaction corresponds to earlier investigations by Molander. Consecutive stereoselective reactions during the esterification to the Reformatsky precursor 1,1,1-trichloropent-4-en-2-yl 2-bromopropanoate and in the Reformatsky reaction itself led to (3*RS*,4*RS*,6*SR*)-4-hydroxy-3-methyl-6-(trichloromethyl)tetrahydro-2*H*-pyran-2-one (**3a**) as the major formed diastereomer. The influence of the orientation of the substituents in the transition state is discussed.

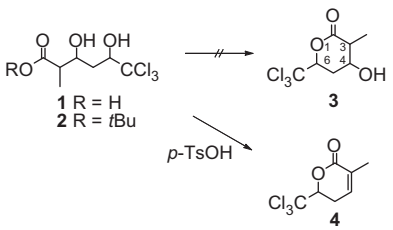


Substituted lactones have been employed as important precursors in the total synthesis of a wide variety of natural products.[1–3] Our recent investigations into the structure and bioactivity of polychlorinated polyketides led us to investigate possible synthetic routes towards β-hydroxy-δ-trichloromethyl-valerolactone **3**, a member of a compound class only rarely investigated. The initial cyclisation approach by intramolecular esterification of the β,δ-dihydroxy acid **1** or transesterification of the corresponding ester **2** was frustrated by the low reactivity of the δ-hydroxyl group, which appears to be caused by the high steric demand and electron-withdrawing properties of the vicinal trichloromethyl group.[4] In addition, the β-hydroxyl group has a high tendency to eliminate, often leading to the formation of the α,β-unsaturated lactone **4** (Scheme 1). While the cyclisation of β,δ-dihydroxycarboxylic acids is a common procedure in the synthesis of β-hydroxylactones,[2,5] it has rarely been described with δ-trichloromethyl substituted hydroxy acids,[6,7] and the high sensitivity of the reaction towards elimination has been noted.[6] In order to circumvent this problem, we revised our approach by use of a C–C bond formation reaction between C-3 and C-4 of the target lactone. A samarium diiodide mediated Reformatsky reaction was used as the key step.[8,9] This type of reaction has already proven its usefulness in a variety of lactonisations,[10] some of which lead to natural products like clavulactone or pederin.[11]

Our synthesis was inspired by a synthetic route reported by Sawant and Jennings for intermediate **7**, needed in the synthesis of diospongins A and B (Scheme 2).[3]

Our approach utilises trichloromethylhomoallyl alcohol **8** that had to be transformed into ester **9** and finally via the intramolecular Reformatsky reaction into lactone **3** (Scheme 3). Intermediate **8** was synthesised as a racemate by the Grignard addition of commercially available allylmagnesium bromide solution to freshly distilled chloral (**10**), a more convenient variation of several previously reported syntheses of alcohol **8** (Scheme 4).[12]

The subsequent esterification with 2-bromopropionyl bromide (**11**) and pyridine[3] exhibited a varying degree of diastereoselectivity, depending on the reaction conditions. Variation of the reaction temperature and the excess of acyl bromide and pyridine used indicated that the reaction is under kinetic control (Table 1). The highest diastereomeric excess of (*RS*)-1,1,1-trichloropent-4-en-2-yl




**Scheme 1.** Direct lactonisation of δ-hydroxycarboxylates **1** or **2**.

* Corresponding author. Tel.: +49 531 391 7353; fax: +49 531 391 5272.
*E-mail address:* stefan.schulz@tu-bs.de (S. Schulz).

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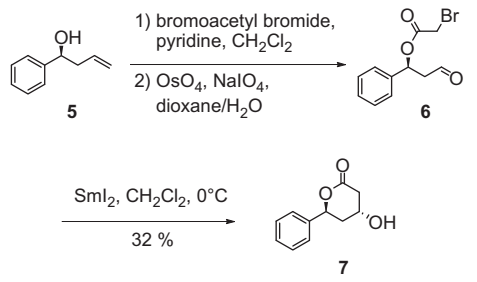
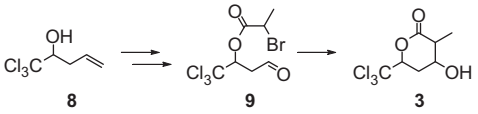
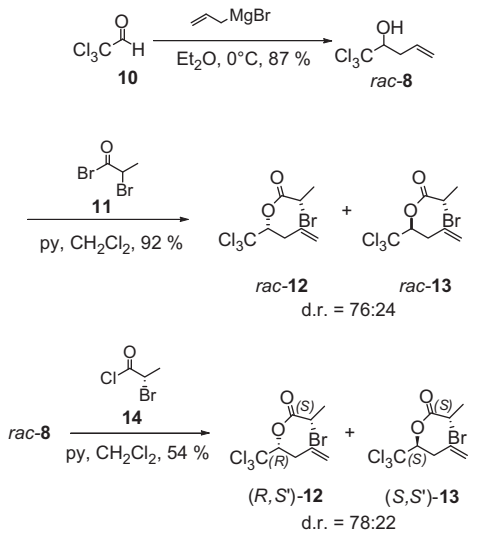



**Scheme 2.** Lactone synthesis by Savant and Jennings.[3]




**Scheme 3.** Synthetic plan to the lactone **3**.




**Scheme 4.** Synthesis of the Reformatsky precursors **12** and **13**.

(*SR*)-2-bromopropanoate (*rac*-**12**) was 53% (dr 76:24), and was achieved with 5 equivalents of acyl bromide and pyridine at −78 °C. Most of the minor diastereomer (*RS*)-1,1,1-trichloropent-4-en-2-yl (*RS*)-2-bromopropanoate (*rac*-**13**) was removed by a single column chromatography, yielding the favoured diastereomer *rac*-**12** in 83% de (Scheme 4). The combined yield over both diastereomers was 92%. This route provided a short and easy access to the favoured enantiomer (*R*,*S*′)-**12** when a substoichiometric amount of enantiomerically pure acyl halide (*S*)-**14** was used, although the yield was lower with chloride **14** than with bromide **11**. Accordingly, (*S*,*R*′)-**12** can be accessed using (*R*)-**14** or **11** instead of the (*S*)-enantiomer. This reaction is an example for the kinetic resolution[13] of alcohol **8** and the counterpart to the previously reported kinetic resolution of *rac*-**11** and *rac*-**14** with different alcohols.[14]

**Table 1**
Stereoselectivity in the esterification of alcohol **8**

| Equiv | Temp (°C) | **13**/**12** |
|---|---|---|
| 2 | 0 | 64:36 |
| 5 | 0 | 67:33 |
| 10 | 0 | 67:33 |
| 5 | −78 | 76:24 |
| 5[a] | −78 | 70:30 |

Equiv: equivalents of compound **11**.
[a] DMAP instead of pyridine.

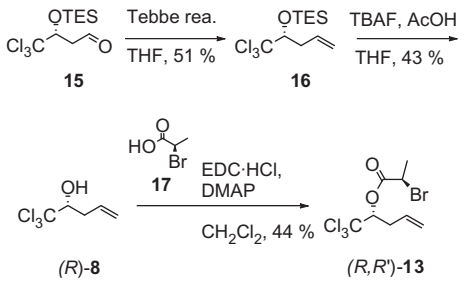
The enantiomers of the kinetically disfavoured diastereomer **13** could potentially be synthesised in the same way, but with decreased yield and purity, only. Consequently, an approach starting from enantiopure **8** was developed.

First, the enantiopure aldehyde **15** was synthesised from commercially available (*R*)-4-(trichloromethyl)oxetan-2-one according to a procedure previously reported by Tennyson.[15] The aldehyde was then methylenated using the Tebbe reagent, because a Wittig-type methylenation proved to be inferior due to the sensitivity of the trichloromethyl group towards strong bases (Scheme 5).[16] Then the triethylsilyl group was cleaved off using acetate-buffered tetrabutylammonium fluoride[17] to yield (*R*)-**8**. The subsequent esterification of (*R*)-**8** to the disfavoured (*R*)-1,1,1-trichloropent-4-en-2-yl (*R*′)-2-bromopropanoate **13** was performed by a modified Steglich esterification[18] using EDC hydrochloride and DMAP in dichloromethane, providing the ester in 44% yield.[19]

The oxidative cleavage of the terminal double bond in **12**/**13** to aldehyde **6** by ozonolysis[20] proceeded smoothly and quantitatively, although subsequent flash chromatography led to partial decomposition of the product to the α,β-unsaturated elimination product **18** (Scheme 6). This problem was reduced by high flow rates and resulting short column retention times, so that largely pure **9** could be isolated in 85% yield. Undesired by-products can alternatively be removed by evaporation under high vacuum, but this led to a less pure product which was detrimental to the yield in the subsequent lactonisation.

The lactonisation was performed in dry tetrahydrofuran using at least 3 equivalents of samarium diiodide.[21] A commercially available stock solution of the reagent in THF was used. The yield, however, was poor at 29%, although similar to the one reported by Savant and Jennings in the synthesis of **7**.[3] Our initial hypothesis was a competing reaction of samarium(II) with the trichloromethyl group, so a less reactive lanthanide was tested. Ytterbium(II) has a lower standard potential than samarium (−1.15 V vs −1.55 V),[22] which led to the assumption that it might be less prone to side reactions. Ytterbium diiodide, freshly prepared from ytterbium chunks and diiodomethane,[8] was then used. While the yield could not be significantly improved, this reaction marks, to the best of our knowledge, the first time that ytterbium has been used as the active reagent in a Reformatsky reaction (Scheme 6).

While stereoselectivity can be induced in the Reformatsky reaction by chiral additives or catalysts,[23] Molander has shown that the intramolecular samarium diiodide-mediated Reformatsky reaction of chiral precursors often exhibits an intrinsic diastereoselectivity.[24] Bulky substituents at C-6 of the target valerolactone favour the formation of the 4,6-*anti* product via the chair-like transition states **19a** and **19b** (Scheme 8). In these cases the substituent at




**Scheme 5.** Synthesis of the disfavored (*R*,*R*′)-**13** enantiomer.