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Large-ring lactones from plant oil†

Cite this: *Green Chem.*, 2013, **15**, 2361

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Received 15th May 2013,

Accepted 11th July 2013

DOI: 10.1039/c3gc40905h

www.rsc.org/greenchem

Large-ring lactones and lactams were prepared utilising the full fatty acid chain of common plant oils as a source of the macrocycle. Ring closure via acyloin condensation does not require large volumes of solvents for dilution. Nonadecalactone (NDL) and tricosalactone (TCL) can be converted to novel polyesters by ring opening.

Lactones are important intermediates in organic synthesis, and they are employed as monomers and used *e.g.* as fragrances. Smaller cycles, such as ϵ -caprolactone, are polymerised to polyesters for medical applications taking advantage of their biodegradability.¹ These small cycles are readily accessible on industrial scales by Baeyer–Villiger oxidation of cyclohexanone. Amongst large-ring lactones, pentadecalactone stands out with an annual volume of around 10^3 metric tons. It is of industrial interest as a fragrance, and used in various cosmetic and non-cosmetic products such as shampoos or household cleaners.² Some large-ring lactones occur naturally, *e.g.* pentadecalactone is a component of *Angelica archangelica* L. root oil. It is in fact isolated from natural sources, rather than being produced synthetically.

An access to even larger ring lactones suffers from a lack of reasonably available starting materials.

In the synthesis of macrocyclic lactones, generation of the cycle is the decisive key step. A general approach to large-ring lactones is provided by cyclisation of ω -hydroxy carboxylic acids (*e.g.* Keck macrolactonisation³ or photochemical routes,⁴ see Scheme S1 in ESI†). However, the high dilution required in these steps is a major limitation. Furthermore, the limited availability of the unsymmetrical α,ω -functionalised starting materials for the ring closure represents a restriction.

We now report a general preparative route to macrocyclic compounds, namely lactones and lactams, based on symmetrical α,ω -diesters from the isomerising alkoxycarbonylation^{5–9} of fatty acid esters from high oleic sun flower and rape seed oil, respectively.^{10,11} Sodium-promoted acyloin condensation^{12–14} results in ring closure. That is, the macrolactone ring of the final nonadecalactone (NDL) and tricosalactone (TCL), respectively, originates from the long-chain methylene sequence of the plant oil¹⁵ starting material.

The synthesis of the macrocyclic lactones employed the four-step protocol depicted in Scheme 1. Starting from methyl oleate or ethyl erucate, respectively, [1,2-bis{(di-*tert*-butylphosphino)-methyl}benzene palladium ditriflate] was used as a catalyst precursor for isomerising alkoxycarbonylation to convert the mono-unsaturated fatty acids into the corresponding saturated long-chain aliphatic α,ω -diesters. This reaction offers the advantage of a full linear incorporation of the aliphatic fatty acid chain segment. Due to the incorporation of carbon monoxide into the newly generated terminal ester moiety, odd carbon-number building blocks are generated from the typically even carbon-number fatty acid chains. The reaction can be conducted conveniently under rather mild conditions (90 °C temperature and 20 bar of CO pressure), allowing for the preparation of diesters using standard laboratory pressure reactors (*cf.* ESI† for detailed experimental procedures and conditions).

Acyloin condensation of the difunctional compounds obtained from isomerising alkoxycarbonylation provided access to macrocycles. To promote the formation of monomeric cycles a low concentration of the diester is required, which was accomplished by slow addition of the starting material. This allowed for working on approximately 20 g scales without the necessity of large volumes of solvents and large reaction vessels. In contrast to cyclisation reactions like the Dieckmann or Thorpe–Ziegler condensation,¹⁶ which exclude one carbon atom from the cycle formed, acyloin condensation incorporates the hydrocarbon chain of the α,ω -diester completely. Although a suitable protocol for purification of the acyloin by recrystallisation had not yet been established, the compound could be isolated by column chromatography.

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†Electronic supplementary information (ESI) available: Experimental procedures, characterisation of products. See DOI: 10.1039/c3gc40905h

Scheme 1 Approach for the synthesis of macrocyclic lactones starting from fatty acid esters.

In this critical cyclisation step, the effective low concentration of diester resulting from a slow rate of addition relative to the acyloin condensation resulted in the selective formation of the desired monomeric macrocycles as evidenced by mass spectrometry (ESI-MS; *cf.* ESI[†]). Dimeric or higher cycles were not observed. Note that for these large ring sizes, the latter would not be distinguishable from the monomeric cycle by NMR spectroscopy. Note that the intermediate macrocyclic cycloketones **4** formed in this synthetic approach (Scheme 1) are also interesting substances in their own right, *e.g.* for fragrances. At the same time the high dilution required for Keck macrolactonisation, involving utilisation of large quantities of halogenated solvents, is avoided.¹⁷

Dehydroxylation of the acyloin was pursued by several protocols, *e.g.* reduction with hydrochloric acid and zinc.¹² However, the application of these standard reagents under different conditions resulted in poor yields (<20%) and a high content of the unfunctionalised cycloalkane. A successful conversion was accomplished by the use of trimethylsilyliodide in good yields (>70%). Purification of the cycloketones by recrystallisation was hampered by their waxy nature; hence column chromatography was used to isolate the pure compounds. A subsequent Baeyer–Villiger oxidation yielded the targeted macrocyclic lactones in good yields. Although the use of standard peroxy acids like *meta*-chloroperoxybenzoic acid (*m*CPBA)¹⁸ resulted in formation of the desired lactones, purification proved difficult with these reagents. Even after column chromatography, minor impurities were still present in the isolated compound (aromatic resonances in the ¹H-NMR spectrum, originating from *m*CPBA); hence alternative routes were investigated. The use of a pH-buffered system, urea/hydrogen peroxide and trifluoroacetic anhydride (TFAA) afforded the desired compound in a pure form and high yields (>70%). The products could be isolated by column chromatography in high purity, as evidenced by GC analysis (*cf.* ESI[†]), thus allowing for polymerisation of the lactones (*vide infra*).

Scheme 2 Synthesis of macrocyclic lactams.

In addition to lactones, macrocyclic lactams are another class of substances of interest. The cycloketone intermediates in the above approach to lactones offer themselves for this purpose. A general route to lactams from cycloketones involves the transformation of an oxime in a Beckmann rearrangement.¹⁹ For the synthesis of the desired macrolactams we employed an *in situ* Beckmann rearrangement^{20,21} starting directly from the cycloketones. The best results were obtained using hydroxylamine-*O*-sulfonic acid and formic acid as reagents promoting the *in situ* conversion of the ketone into an oxime that underwent a Beckmann rearrangement (*cf.* Scheme 2). The lactam could be obtained in a pure form after column chromatography in 48% and 87% yields for the nonadecalactam and tricosalactam, respectively.

Duchateau *et al.* recently reported a ring-opening polymerisation (ROP) of macrocyclic lactones (C₁₅, C₁₆).²² Given that the main driving force for ROP of small cycles, such as ϵ -caprolactone, is the ring strain of the monomer which is expected to be much lower for large cycles, this finding was notable and raises the question of polymerisability of even larger cycles. Preliminary studies of the ROP of our C₁₉- and C₂₃-lactones were performed employing aluminium salen complexes proven to be effective in the ROP of pentadecalactone.²² At 100 °C polymerisation temperature in bulk monomers, indeed poly(nonadecalactone) (PNDL) and poly(tricosalactone) (PTCL) could be obtained (Table 1). Polymer molecular weights determined by quantitative analysis of end groups *via* ¹H-NMR spectroscopy agree

Table 1 ROP of macrocyclic lactones^a

Entry	Ring	Catalyst	Yield /%	T_m ^b /°C	T_c ^b /°C	ΔH_m /J g ⁻¹	$M_{n,NMR}$ /g mol ⁻¹	$M_{n,GPC}$ ^c /g mol ⁻¹	M_w/M_n
1	C ₁₉	R = Et	23	103	84	165	10.3×10^3	6.4×10^3	2.7
2	C ₁₉	R = OBn	17	103	84	164	7.6×10^3	4.9×10^3	2.6
3	C ₂₃	R = Et	4	104	88	190	5.2×10^3	2.2×10^3	2.8
4	C ₂₃	R = OBn	5	104	88	195	4.6×10^3	2.5×10^3	2.3

^a Reaction conditions: 0.24 mol% Al salen catalyst precursor (in case of R = Et 1 equiv. of benzyl alcohol was added), 100 °C, 22 h stirring under an Ar atmosphere. ^b Determined by DSC with a heating/cooling rate of 10 K min⁻¹. ^c GPC at 160 °C in trichlorobenzene versus polyethylene standards.

reasonably well with apparent molecular weights of poly(nona-decalactone) determined by high temperature GPC vs. linear polyethylene standards. This shows that no extensive formation of polymeric cycles occurred. By direct comparison, *ca.* four-fold higher molecular weight ($M_n(NMR) 4 \times 10^4$ g mol⁻¹) poly(pentadecalactone) was formed by ROP of pentadecalactone under otherwise identical conditions in our hands.

The PNDL possesses a melting point (T_m 103 °C) identical to polyester-19,19 synthesised by A₂ + B₂ polycondensation of the corresponding C₁₉ α,ω-diester and α,ω-diol.²³ By comparison, the melting point of PTCL (104 °C) is slightly lower than the corresponding polyester-23,23 (108 °C), probably due to the limited molecular weight of the PTCL reported here.

Conclusions

In conclusion, we have demonstrated a general route to macrocyclic compounds starting from unsaturated fatty acids from plant oils as a convenient source of the macrocycle. Ring closure *via* acyloin condensation does not require large volumes of solvents for dilution. In a four-step synthesis, nonadecalactone and tricosalactone, respectively, were obtained in satisfactory overall yields. Large-ring lactams were accessed by *in situ* Beckmann rearrangement of the intermediate C₁₉ and C₂₃ cycloketones. Preliminary studies show that it is still possible to use ring-opening polymerisation of these large-ring lactones to form aliphatic polyesters with exceptionally high melting points exceeding 100 °C. Beyond their utilisation as monomers, the macrocycles prepared are also interesting starting materials for ring-opening to *e.g.* the corresponding ω-hydroxy carboxylic acid or ω-amino carboxylic acid, which can be useful as a building block in organic chemistry. Such unsymmetrical α,ω-difunctionalised long-chain compounds are not easily accessible through conventional routes.

Acknowledgements

Financial support from BASF SE is gratefully acknowledged. We thank Lars Bolk for DSC and GPC measurements.

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