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Unexpected formation of a chiral δ-lactone by reduction of the 1,3-dicarbonylic cyclopentanoid derivatives

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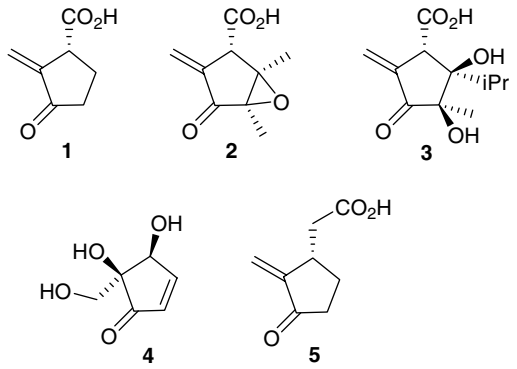
Abstract—We have described the synthesis of highly functionalized chiral cyclopentanoids, which are important building units for synthesis of biological active compounds. The (−)- or (+)-7,7-dimethoxy-1,4,5,6-tetrachlorobicyclo[2.2.1]hept-5-en-2-*endo*-yl acetate, obtained from the enzyme catalyzed transesterification of the racemate, was converted to α-diketone chiral. The α-diketone was treated with H_2O_2/NaOH and esterified with CH_2N_2 to furnish a mixture of the compounds (+)- or (−)-**10** and (+)- or (−)-**11**. The reduction of the (+)- or (−)-**10** and/or (+)- or (−)-**11** with BH_3·THF furnished the lactone (+)- or (−)-**13** with excellent yield. The α-diketone was reduced with indium metal in the presence of NH_4Cl furnishing the acyloin (+)-**14** in 67% of yield. The treatment of acyloin (+)-**14** with $Pb(OAc)_4$ furnished the aldehyde (+)-**15** with 80% of yield. The reduction of the aldehyde (+)-**15** with $NaBH_4$ has again produced the lactone (+)-**13**.

Cyclopentanoids products are a biologically important class of compounds, constituting structural part of prostaglandins[1] and there are several examples of this class of compounds acting as antitumor agents.[2] Since many natural products and synthetic materials of biological importance have cyclopentyl skeletons, in the last few years there has been intense development of synthetic methods to construct such moieties.[3] Aminocyclopentanoids have been reported to be potent glycosidase inhibitors.[4] Some examples of antitumor agents[2] are the sarkomycin **1**, the methylenomycin **2**, the xanthocidin **3**, the pentenomycin **4**, and the homosarkomycin **5**.



Several methodologies of asymmetric synthesis of the chiral building blocks with cyclopentane ring have been developed.[5] Khan et al.[6] described an efficient synthetic methodology employing catalytic $RuCl_3 \cdot 3H_2O$ and $NaIO_4$ as stoichiometric cooxidants to get α-diketones from the vicinal dihaloalkenes. α-Diketones were cleaved using $Pb(OAc)_4$ or alkaline H_2O_2 to give cyclopentanoids derivatives in their racemic form.

A convenient method for obtaining enantiopure materials is catalyzed acylation.[7] The enzyme catalyzed transesterification using vinyl acetate was applied for resolution of 7,7-disubstituted-1,4,5,6-tetrachlorobicyclo[2.2.1]hept-5-en-2-ols using lipase from *Candida rugosa*.[8]

In the last years, enzymatic resolution has been used by our group to obtain enantiopure alcohols and their derivatives,[9] and, recently, we described an efficient synthesis of enantiopure 1,2-[10] and 1,3-amino alcohols[11] from the 7,7-dimethoxy-1,4,5,6-tetrachlorobicyclo[2.2.1]-hept-5-en-2-endo-ol (**6**), which were obtained by enzymatic procedure using the lipase from *Candida rugosa*

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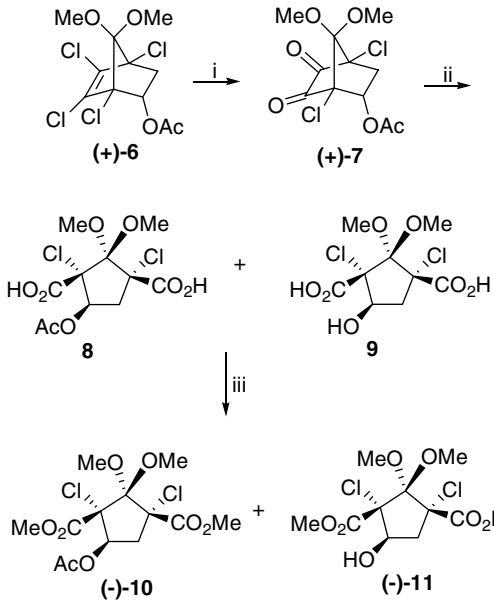
in vinyl acetate. We now report the asymmetric synthesis of the interesting chirals cyclopentanoids synthons **8** and **9** from the enantiopure acetate (+)- and (−)-**6**.

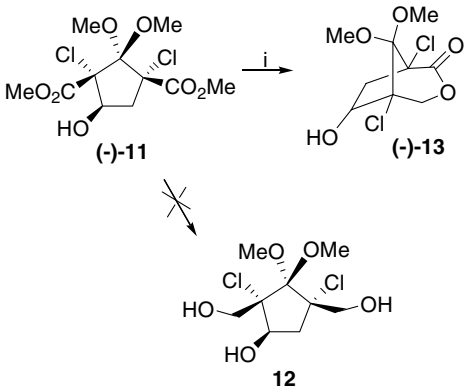
(±)-7,7-Dimethoxy-1,4,5,6-tetrachlorobicyclo[2.2.1]hept-5-en-2-endo-ol, obtained from the Diels–Alder reaction of 1,2,3,4-tetrachloro-5,5-dimethoxycyclopentadiene and vinyl acetate followed by acid hydrolysis (sulfuric acid/methanol), was subjected to transesterification[8] with vinyl acetate and lipase from *Candida rugosa*, over 7 days.

The enantiomeric purity of the products was determined by chiral gas chromatography (alcohol: ee 98%; acetate: ee 99%). The alcohol was acetylated (acetic anhydride, DMAP) to furnish the corresponding acetate (+)-**6**.

Using the Khan[6b] procedure, the acetate (+)-**6** was subjected to an oxidative cleavage reaction using a catalytic amount of $RuCl_3$ anhydrous in the presence of $NaIO_4$ to give α-diketone (+)-**7** in excellent yield (Scheme 1). We subsequently examined the H_2O_2/NaOH mediated cleavage reaction of α-diketone (+)-**7**. When this reaction was employed, a mixture of **8** and **9** was obtained. This mixture was esterified to the dimethyl ester (−)-**10** and (−)-**11**, purified by flash chromatography furnishing acetate (−)-**10**[12] and alcohol (−)-**11**[13] in a ratio of 4:1 in quantitative yield. However, the reduction of this mixture with $LiAlH_4$ was unsuccessful due to its lower yield. The reduction of the alcohol (−)-**11**, protected with THP, with $LiAlH_4$ also gave lower yield. Therefore, with a purpose to obtain the triol **12**, the compound (−)-**11** was subjected to reduction with BH_3·THF at room temperature.[14] Surprisingly, this reduction furnished just the lactone (−)-**13**, instead of the alcohol **12** (Scheme 2). Carboxylic acids can be reduced with boranes more easily than with esters, so, we subject the mixture of **8** and **9**



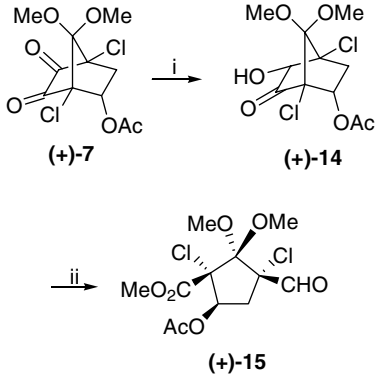
Scheme 1. Reagents and conditions: (i) $RuCl_3$, $NaIO_4$, MeCN/H_2O (6:1), rt, 10 min, 99%; (ii) H_2O_2/NaOH, MeOH, rt, 2 h; (iii) CH_2N_2, Et_2O, 0 °C, 15 min, 90%.



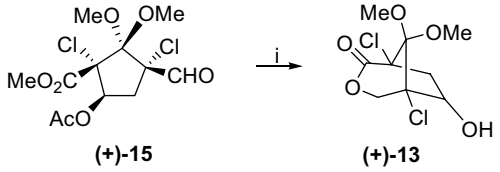
Scheme 2. Reagents and conditions: (i) BH_3·THF, 24 h, rt, 90%.

to a reduction with BH_3·THF or BH_3·SMe_2, in the same reaction conditions; however, always the lactone (−)-**13**, was obtained with high yields.

Since the attempted reduction of **8**, **9**, **10**, or **11** furnish always of the lactone **13**, we have decided to make use of the Khan[15] methodology to obtain cyclopentane carboxaldehydes. The α-diketone (+)-**7** was reduced with indium metal in MeOH/H_2O (4:1) in the presence of NH_4Cl furnishing the acyloin (+)-**14** in 67% of yield.[16] It is important to use dry MeOH even though water is also used as a cosolvent, because it is crucial for the solvent ratio MeOH/H_2O (4:1). The treatment of acyloin (+)-**14** with $Pb(OAc)_4$ in MeOH/PhH (3:1) furnished the aldehyde[17] (+)-**15** with 80% of yield (Scheme 3). Surprisingly, the reduction of the aldehydes (+)-**15** with $NaBH_4$ in MeOH has again produced the same lactone (+)-**13** (Scheme 4).



Scheme 3. Reagents and conditions: (i) In, NH_4Cl, MeOH/H_2O (4:1), 23 h, reflux, 67%; (ii) $Pb(OAc)_4$, MeOH/PhH (3:1), 4.5 h, rt, 80%.



Scheme 4. Reagents and conditions: (i) $NaBH_4$, MeOH, 8 h, rt, 89%.

In conclusion, we have described the synthesis of chiral highly functionalized cyclopentanoids, which are potential building blocks in organic synthesis. The obtainment of the lactone from the α-chloro diester and α-chloro diacid was achieved with excellent yields.

Acknowledgments

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12. $[\alpha]_D^{20}$ −8 (*c* 5.0, AcOEt). IR (film): *v* (cm^{-1}): 1746. ^1H RMN (300 MHz, $CDCl_3$): δ 2.01 (s, 3H), 2.53 (dd, $J = 14.3$, 6.4 Hz, 1H), 3.18 (s, 3H), 3.83 (dd, $J = 14.3$, 10.5 Hz, 1H), 3.61 (s, 3H), 3.76 (s, 3H), 3.78 (s, 3H), 5.56 (dd, $J = 10.5$, 6.4 Hz, 1H). ^{13}C RMN (75 MHz, $CDCl_3$): δ 20.7, 41.5, 52.5, 53.2, 53.4, 53.5, 75.8, 77.7, 78.7, 108.3, 165.9, 167.5, 169.4.
13. $[\alpha]_D^{20}$ −6 (*c* 2.2, AcOEt), mp = 78–80 °C. IR (film): *v* (cm^{-1}): 3507 (OH), 1743 (C=O). ^1H RMN (300 MHz, $CDCl_3$): δ 2.61 (dd, $J = 14.7$, 8.2 Hz, 1H), 3.28 (dd, $J = 14.7$, 8.2 Hz, 1H), 3.31 (s, 3H), 3.58 (d, $J = 9.1$ Hz, OH), 3.73 (s, 3H), 3.84 (s, 3H), 3.85 (s, 3H), 4.65 (m, 1H). ^{13}C RMN (75 MHz, $CDCl_3$): δ 44.2, 52.4, 53.4, 53.6, 53.7, 74.7, 76.2, 79.2, 109.5, 167.8, 168.3.
14. General procedure for obtainment of the lactone: To a solution of the acetate (−)-**10** (250 mg, 0.67 mmol) in dry THF (5 mL) and under argon, BH_3·THF (5 mL, 5 mmol, 1 M) was slowly added. The mixture was stirred at room temperature for 24 h and then was added MeOH (50 mL). The solution was stirred for 1 h and the solvent evaporated under reduced pressure. The crude product was purified by flash chromatography (silica, cyclohex/AcOEt 85:15) yielding 164 mg (0.605 mmol, 90%) of (−)-**13** as a white solid. Mp = 195–197 °C, $[\alpha]_D^{20}$ −9 (*c* 1.5, AcOEt). IR (film): *v* (cm^{-1}): 3406, 1738. ^1H RMN (300 MHz, $CDCl_3$): δ 2.34 (dd, $J = 14.8$, 4.4 Hz, 1H), 2.79 (dd, $J = 14.8$, 10.9 Hz, 1H), 3.63 (s, 3H), 3.75 (s, 3H), 4.25 (dd, $J = 10.4$, 1.1 Hz, 1H), 4.61 (d, $J = 10.4$ Hz, 1H), 4.66 (dd, $J = 10.9$, 4.4 Hz, 1H). ^{13}C RMN (75 MHz, $CDCl_3$): δ 44.6 (CH_2), 52.4 (CH_3), 52.9 (CH_3), 66.9 (CH_2), 72.6 (C), 72.7 (C), 72.9 (CH), 101.2 (C), 167.8 (C=O). HRMS found: $m/z =$ 271.0140; calcd for $C_9H_{12}Cl_2O_5$ $[M]^+$: 271.0177.
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16. General procedure for reduction of α-diketone: A mixture of α-diketone (0.3 mmol), indium metal (0.6 mmol, cut into small pieces) and NH_4Cl (0.9 mmol) in dry MeOH (4 mL) and water (1 mL) was refluxed for 23 h. It is important to use very small pieces of indium metal, with very good stirring and most crucial is the solvent ratio MeOH/H_2O (4:1). The reaction mixture was quenched with 3 mL of 5% HCl and extracted with ethyl acetate. The crude product was purified by flash chromatography gave the acyloin with 67% of yield. Mp = 98–100 °C, $[\alpha]_D^{20}$ +10 (*c* 1.25, AcOEt); more details related to the spectroscopy data are available in the literature.[15]
17. Aldehyde (+)-**15**: $[\alpha]_D^{20}$ +12 (*c* 1.02, AcOEt); more details related to the spectroscopy data are available in the literature.[15]