Pergamon

Tetrahedron Letters 41 (2000) 4959–4963

TETRAHEDRON LETTERS

Synthesis and asymmetric hydrogenation of 3,5-dioxoheptanedioates. Preparation of enantiomerically pure substituted δ-valerolactones

Jarosław Kiegiel,[a,*] Julita Jóźwik,[a] Krzysztof Woźniak[a] and Janusz Jurczak[a,b]

[a]*University of Warsaw, Chemistry Department, Pasteura 1, 02-093 Warsaw, Poland*
[b]*Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland*

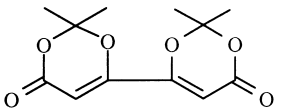
Received 29 February 2000; accepted 8 May 2000

Abstract

The synthesis of 3,5-dioxoheptanedioic acid derivatives based on the reaction of ketene with malonyl chloride was developed. Resulting diketones were subjected to Ru–(*S*)-BINAP-catalyzed asymmetric hydrogenation. The products were transformed into enantiomerically pure 3,5-substituted-δ-valerolactones.

Substituted tetrahydropyrans are common constituents of many natural products such as mevinic acids,[1] spongistatins,[2] milbemycins,[3] avermectins[4] and phorboxazoles.[5] We wish to report a novel short approach leading to enantiomerically pure substituted δ-valerolactones which are potentially useful in the synthesis of these natural products.[6]

It appeared to us that Ru–BINAP[7] catalyzed asymmetric hydrogenation of 3,5-dioxoheptanedioates could be a route to synthesize enantiomerically pure δ-valerolactones and might reveal some interesting features. In order to examine this possibility we were prompted to find an effective procedure for the synthesis of 3,5-dioxoheptanedioates.



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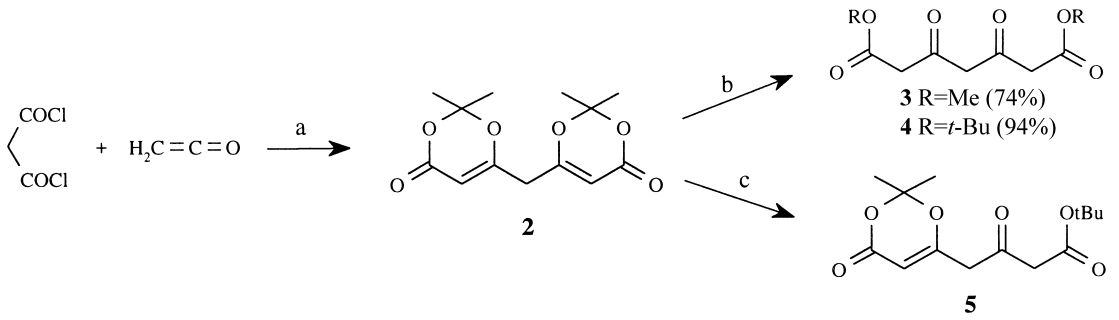
An inspiration came from the work of Stachel[8] who obtained bisdioxinone **1** by the action of ketene on oxalyl chloride in the presence of acetone and the product was used as the substrate for 3,4-dioxohexanedioates.[9] A few attempts to carry out a similar reaction with malonyl chloride

* Corresponding author.

0040-4039/00/$ - see front matter
PII: S0040-4039(00)00747-4

have been reported[10] showing that only one chlorocarbonyl group reacted. We found that both chlorocarbonyl groups could react with ketene, providing that the intermediate acyl chloride was trapped by the acetone used as a solvent. After work-up and crystallization the resulting bis-dioxinone **2** was obtained in 60% yield (Scheme 1).

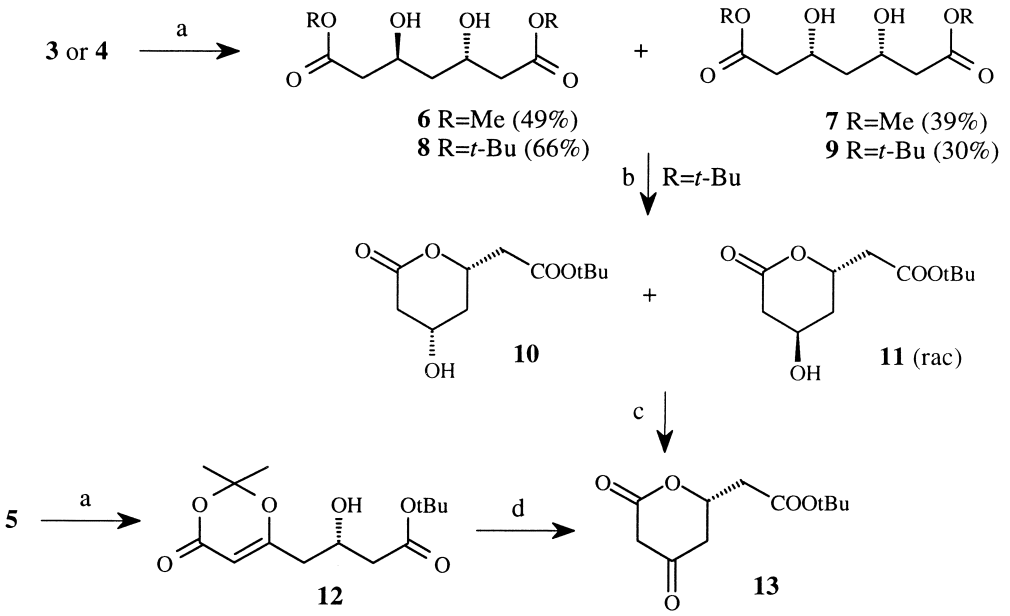


Scheme 1. (a) acetone, –50°C (60%); (b) ROH, 130°C, sealed tube, 1 h; (c) *t*-BuOH, 65°C, 12 h (57%)

Dioxinones are excellent stable sources of ketenes and upon heating they react with alcohols, amines and other nucleophiles.[11] Thus, by heating compound **2** in methanol or *t*-butanol at 130°C we obtained dimethyl (**3**) and di-*t*-butyl 3,5-dioxoheptanedioate (**4**) in 74 and 94% yields, respectively. We also discovered that if the reaction was carried out under controlled conditions mono-*t*-butyl ester **5** could be obtained in 57% yield. Next, we turned our attention to the asymmetric hydrogenation of ketones **3** and **4**. Diketone **3** gave a mixture of two products: *anti*-diol **6** and *syn*-diol **7** (*meso*) in 88% overall yield and the ratio 5:4, respectively (Scheme 2). The enantiomeric excess of the *anti*-diol **6** could be estimated by ^{1}H NMR spectroscopy through the use of the chiral shift reagent [Eu(hfc)$_3$] and amounted to 48%. Similarly, asymmetric hydrogenation of diketone **4** produced an inseparable mixture of diols *anti*-**8** and *syn*-**9** (*meso*) in the ratio 20:9. Though operating with a mixture of diastereoisomers we were also able to estimate the enantiomeric excess of **8** using a chiral shift reagent. The *t*-Bu group singlets clearly split into two equal singlets of *meso*-diol **9** and two singlets reflecting the ratio (82:18, 64% ee) of enantiomers for *anti*-diol **8**.

The results of the asymmetric hydrogenation of diketones **3** and **4** were unsatisfactory due to significant yields of the *meso*-diols and only modest enantiomeric excesses. Mono-*t*-butyl ester **5** containing only one 3-oxoester group promised to give better results. By applying the asymmetric hydrogenation conditions to compound **5**, alcohol **12** was obtained in 97% yield and 87% ee as judged from a ^{1}H NMR experiment with the chiral shift reagent (the shift of the *t*-butyl group singlet was observed). Crystallization of compound **12** from 2-propanol enhanced the enantiomeric purity to $>98\%$ ee. The latter was transformed into ketolactone **13** by heating in *t*-butanol at 100°C. The same compound was obtained by lactonization of the mixture of diols **8** and **9** and subsequent oxidation of the resulting inseparable mixture of hydroxylactones **10** and **11**. The ketolactone **13** obtained in this manner showed the same sign of specific rotation as the one obtained from **12**, evidence for the same configuration of products **8** and **12**.[12]

However, the problem arose of the absolute configuration of the prevailing enantiomers of compounds **6**, **8** and **12**. Our initial prediction was that asymmetric hydrogenation of **3** and **4** followed the 3,5-diketone rather than the 3-oxoester catalyst coordination pattern and should produce the (*R*,*R*)-diols as the major products. This prediction was supported by the findings of



Scheme 2. (a) H_2, 100 atm, 0.5% $RuCl_2$[(*S*)-BINAP](*p*-cymene), *t*-BuOH, 50°C, 16 h; (b) *p*-TsOH, CH_2Cl_2, reflux, 1 h (92%); (c) Jones' reagent, acetone, 15 min (82%); (d) *t*-BuOH, 100°C, 6 h (88%)

Saburi et al.[13] dealing with asymmetric hydrogenation of methyl 3,5-dioxohexanoate. They obtained the product of 3,5-diketone catalyst chelation in 78% ee. To solve this problem we synthesized the chiral nonracemic diimide **14** in 63% yield by heating bisdioxinone **2** and (1*S*)-bornane-10,2-sultam[14] in toluene at 55°C. Then we attempted to reduce it under various non-chiral conditions in order to obtain a well-defined diastereoisomer for correlation with diol **6**. However, due to the lability of the imide bond, only a few methods proved to be effective for the reduction of **14**. All of these gave mixtures of diastereomers and were not practical. Interestingly, application of (*S*)-Ru–BINAP-catalyzed hydrogenation to compound **14** produced diol **15** in high yield (92%) and high diastereomeric excess (96% de). By crystallization from 2-propanol diastereomerically pure **15** was obtained (Scheme 3). The (3*S*,5*S*) absolute configuration was established by an X-ray diffraction experiment (Fig. 1).

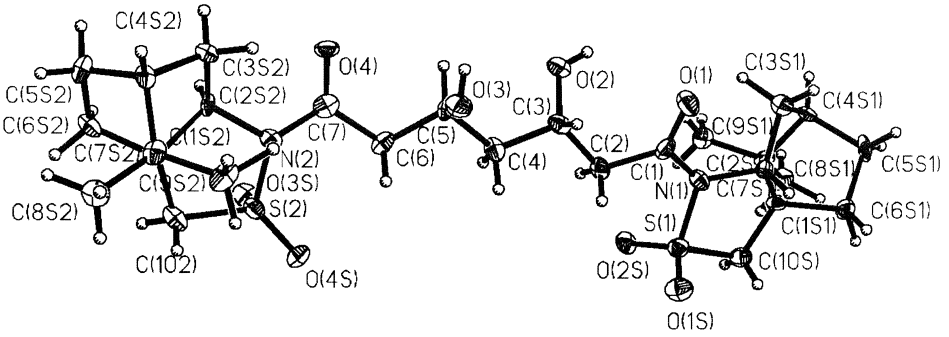
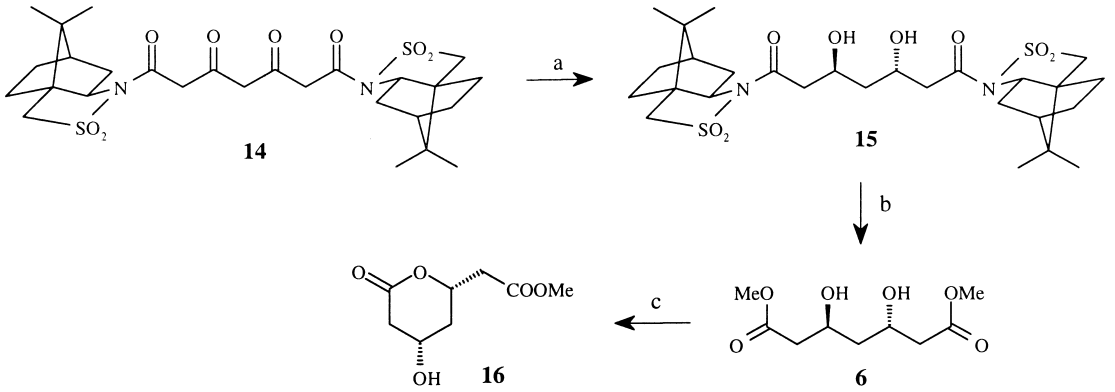


Figure 1. ORTEP representation of **15**



Scheme 3. (a) H_2, 100 atm, 0.5% $RuCl_2$[(*S*)-BINAP](*p*-cymene), CH_2Cl_2, 50°C, 16 h (92%, 96% de); (b) $NaHCO_3$, MeOH, rt, 24 h (88%); (c) PPTS, benzene, reflux, 15 min (84%)

The stereochemical outcome of the hydrogenation of **14** raised the question as to whether the face selectivity could be reversed by applying the (*R*)-BINAP catalyst. In fact, reversal of face selectivity took place, but the (3*R*,5*R*) equivalent of **15** was obtained in only 78% de. This result suggests that the chiral auxiliary plays an important, but not a crucial, role in the asymmetric induction. Apparently, a matched double asymmetric induction occurs for the (*S*)-BINAP-catalyzed hydrogenation of **14**, while a mismatched situation takes place for the (*R*)-BINAP-catalyzed reaction. The absence of a *syn* hydrogenation product is also an interesting point. We believe that the participation of a nitrogen atom of **14** in chelation of the catalyst is mainly responsible for the stereochemical outcome of the hydrogenation of **14**, but to date it is not quite clear and requires more in depth investigation.

Diol **15** was then transformed into enantiomerically pure dimethyl ester **6** by applying mild methanolysis in the presence of $NaHCO_3$. Diols **6** obtained from **3** and **14** showed the same sign of specific rotation.[15] This correlation established the (*S*,*S*)-configuration for the major enantiomers of diols **6** and **8** and the (*S*)-configuration for compound **12**. In contrast to our earlier predictions this was proof that the major products of the asymmetric hydrogenation of 3,5-dioxoheptanedioates were formed as a result of catalyst chelation to the 3-oxoester rather than to the 3,5-diketone.

Finally, upon refluxing in benzene in the presence of pyridinium *p*-toluenesulfonate compound **6** furnished enantiomerically pure lactone **16**.[16] This compound had been prepared in racemic form by Langlois and Bac[17] for the synthesis of the spiroketal part of milbemycins and avermectins.

In summary, we have developed a short and practical synthesis of 3,5-dioxoheptanedioates and used these compounds in an enantioselective approach to 3,5-disubstituted-δ-lactones **13** and **16**. Studies aimed to explain all aspects of the asymmetric hydrogenation of 3,5-dioxoheptanedioates are being pursued.

Acknowledgements

The authors thank the State Committee for Scientific Research of Poland for supporting this work (Grant No. 3 T09A 020 13).

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12. **13** (> 98% ee from **12**): $[\alpha]_D^{22}$ –74.8 (*c* 1.0, $CHCl_3$). **13** (from the mixture **10**+**11**): $[\alpha]_D^{22}$ –27.3 (*c* 1.0, $CHCl_3$).
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15. Compound **6** (enantiomerically pure from **15**): $[\alpha]_D^{22}$ 21.8 (*c* 1.0, $CHCl_3$); (from **3**): $[\alpha]_D^{22}$ 10.3 (*c* 1.0, $CHCl_3$).
16. Compound **16**: mp 85–87°C (Et_2O/hexane); $[\alpha]_D^{22}$ 33.7 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.65–1.72 (m, 1H), 2.35–2.41 (m, 1H), 2.48–2.54 (m, 1H), 2.63–2.68 (m, 1H), 2.81–2.87 (m, 1H), 2.89–2.95 (m, 1H), 3.73 (s, 3H), 4.29–4.36 (m, 1H), 4.65–4.71 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 37.2, 39.3, 40.0, 52.1, 63.6, 73.2, 169.8, 170.1.
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