Pergamon

Tetrahedron Letters, Vol. 37, No. 29, pp. 5069-5072, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01019-2

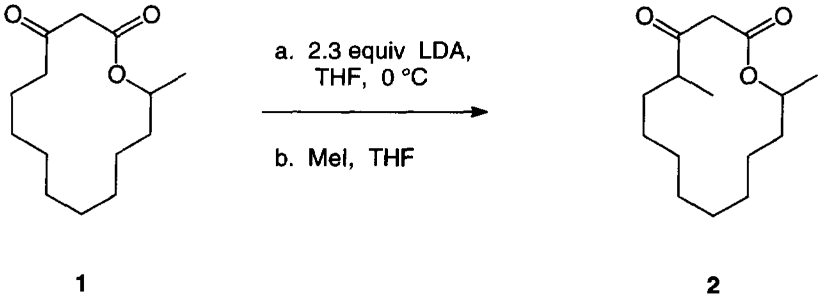
Alkylation of the Dianion of 3-Oxo-13-tetradecanolide

Edward G. Neeland, Anurag Sharadendu and Larry Weiler*

Department of Chemistry, University of British Columbia, Vancouver, British Columbia, CANADA V6T 1Z1

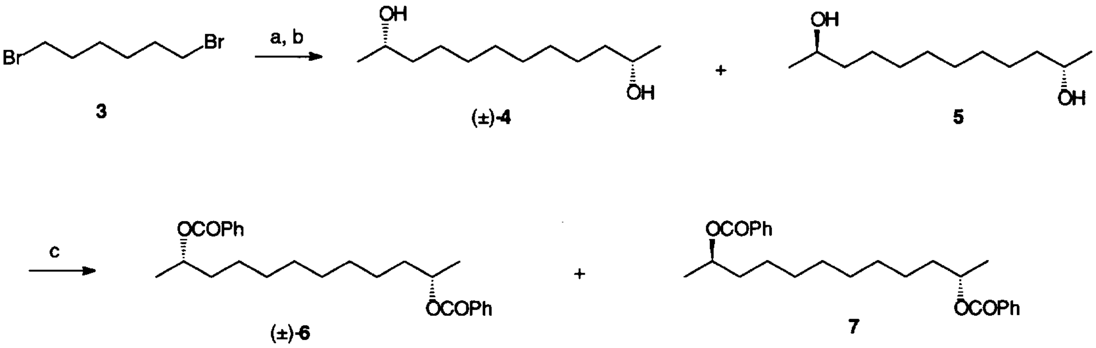
Abstract: Alkylation of the dianion of 3-oxo-13-tetradecanolide(**1**) was carried out in high stereoselectivity and chemical yield. The relative stereochemistry of the two distant chiral centers were determined by chemical transformation of **2** to dibenzoates **6** and **7**, whose relative stereochemistry was determined using chiral HPLC.

The chemistry of large carbocyclic rings continues to interest the synthetic chemist. Recently we reported the synthesis and conformational analysis of 14-membered β-keto lactones.[1] In particular the reduction of lactone **1** was highly stereoselective. We were intrigued about the possibility of preparing the dianion[2] of **1** and investigating its chemistry. The dianion of 3-oxo-13-tetradecanolide (**1**)[1] was generated using slightly more than two equivalents of LDA. A D_2O quench demonstrated that the dianion had been generated in over 95% yield. Alkylation of dianion **1** with one equivalent of methyl iodide gave the monoalkylated product **2** in 88% isolated yield. Chromatographic (TLC and GC), and ^1H and ^{13}C NMR data suggested that the alkylation was very stereoselective, with only one of the two possible diastereomeric products being obtained.[3] However, we were unable to determine the relative stereochemistry of the two stereogenic centers in **2** using any spectroscopic techniques.



As a result we turned to chemical correlations to unravel this stereochemical problem. One possibility might be a direct Baeyer-Villiger oxidation of **2**, followed by hydrolysis to yield the diol.

The Baeyer-Villiger oxidation is known to proceed with retention of stereochemistry.[4] However, earlier studies on the Baeyer-Villiger oxidation of simple β-keto esters is known to give 2-hydroxy-3-keto esters, presumably by epoxidation of the enol.[5] Since there was no evidence for the enolized form of the β-keto lactone **2** from its ^{1}H NMR and IR spectra, it was decided to pursue the possible Baeyer-Villiger oxidation of **2** and identification of the resulting diol. First we investigated the possibility of separating and identifying the (±)- and meso-2,11-dodecanediols **4** and **5**. The synthesis of these diols is shown in Scheme 1.



Scheme 1. (a) Mg, I_2, Et_2O, 30 min; (b) propylene oxide, 18 h; (c) PhCOCl, py, 30 min.

The separation of diastereomers **4** and **5** turned out to be quite a formidable task. They were inseparable by TLC, GC, normal-, and reverse-phase HPLC as well they could not be distinguished by their ^{1}H NMR, ^{13}C NMR or IR spectra. The diols were subsequently esterified to give (±)-**6** and meso-**7**. However, they also were inseparable or indistinguishable by any of the above physical techniques. Next, the attention was shifted to their separation on chiral HPLC columns, in particular, Chiralcel OD and Chiralpak OP(+) columns. The dibenzoate esters **6** and **7** were resolved on the Chiralpak OP(+) column into three peaks in a ratio of 1:2:1 with a retention time of 9.1, 9.9, and 10.5 minutes respectively at a flow rate of 0.6 mL/min with methanol as eluent (Figure 1). The peak areas corresponded to a 1:1 mixture of the two diastereomers. The peak at 9.9 minutes was assigned to the meso compound **7**. When this mixture of diastereomers was co-injected with the enantiomerically pure (2*S*,11*S*)-**6** dibenzoate, synthesized from (S)-propylene oxide following the same route as in Scheme 1, it was found that the peak at 9.1 min was from the enantiomer (2*S*,11*S*)-**6**. Thus the peak at 10.5 min was assigned to (2*R*,11*R*)-**6**.

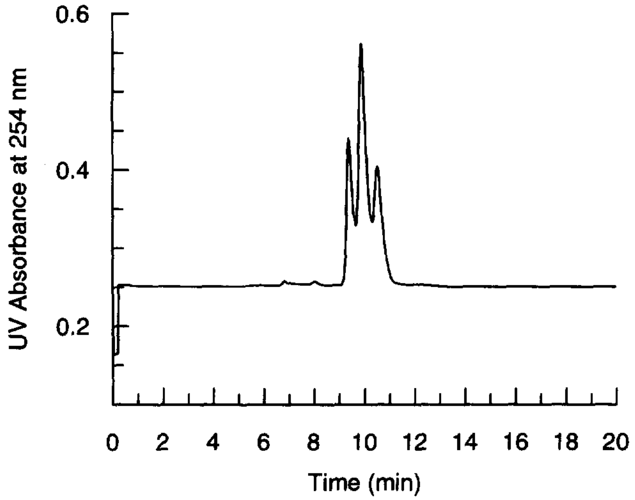
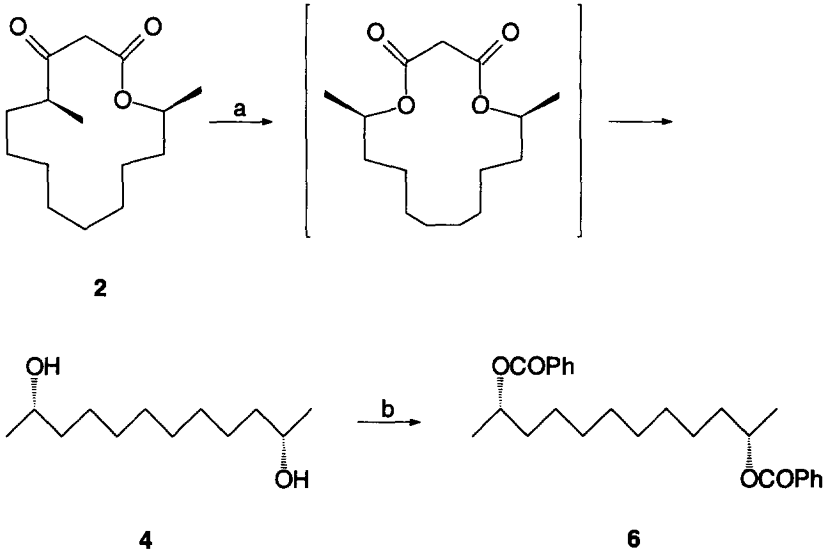


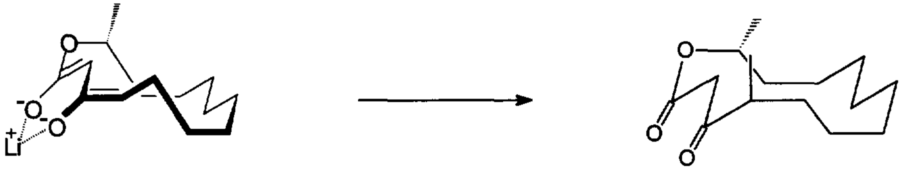
Figure 1: HPLC trace of the dibenzoate esters **6** and **7** of 2,11-dodecanediol on Chiralpak OP (+) column.

Peroxytrifluoroacetic acid[6] treatment of the β-keto lactone **2** gave 2,11-dodecanediol in 60% purified yield from **2**. None of the dilactone could be detected (Scheme 2), nor could any of another diol. The diol was converted into its dibenzoate ester, and HPLC analysis showed only the peaks at 9.1 and 10.5 min due to the racemic (2*S**,11*S**)-**6**. This was confirmed by co-injection of the dibenzoate from **2** with authentic (2*S*,11*S*)-**6**. Hence, the relative stereochemistry of the dianion alkylation product was determined to be (4*S**,13*S**).



Scheme 2: (a) $(NH_2)_2CO.H_2O_2$, Na_2HPO_4, $(CF_3CO)_2O$, CH_2Cl_2, 12 h; (b) PhCOCl, py, 1 h.

This stereoselectivity could arise from the dianion enolate with the conformation shown in **8**. Attack from the more open 3-re, 4-re face of **8** by an electrophile would produce the observed 4S*,13S* stereochemistry. A MacroModel search[7] using the MM2* force-field parameters suggested that the global minimum energy conformation of the dianion did, in fact, have the distorted [3434] conformation **8** with chelation of the metal ion possible.



8 **2**

Enzymes have been used to separate symmetric meso and racemic diols where the hydroxyl groups are separated by two or three methylene units, or a benzene ring.[8] These results demonstrate that meso and racemic diols insulated by a long carbon chain can also be separated, and the diols used in structure proof.[9]

References and notes

1. (a) Lermer, L.; Neeland, E. G.; Ounsworth, J. P.; Sims, R. J.; Tischler, S. A.; Weiler, L. *Can. J. Chem.* **1992**, *70*, 1427; (b) Neeland, E. G.; Ounsworth, J. P.; Sims, R. J.; Weiler, L. *J. Org. Chem.* **1994**, *59*, 7383.
2. (a) Weiler, L. *J. Am. Chem. Soc.* **1970**, *92*, 6702; (b) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082.
3. For example, there were only 14 peaks in the ^{13}C NMR with the carbonyl peak for the lactone being absent, and in the ^{1}H NMR spectrum, the signals due to the methyl groups were clean doublets.
4. House H.O. Modern Synthetic Reactions; 2nd edition, Benjamin: New York, 1972; pp 321-329.
5. Karrer, P.; Kebrle, J.; Thakkar, R. M. Helv. Chim. Acta 1950, 33, 1711.
6. Cooper, M. S.; Heany, H.; Newbold, A. J.; Sanderson, W. R. Synlett. 1990, 533.
7. Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. J. Comput. Chem. 1990, 11, 440.
8. (a) Chênevert, R.; Desjardins, M. J. Org. Chem. 1996, 61, 1219; (b) Caron, G.; Kazlauskas, R. J. Tetrahedron Asymmetry, 1994, 5, 657; (c) Wallace, J. S.; Baldwin, B. W.; Morrow, C. J. J. Org. Chem. 1992, 57, 5231; (d) Takemura, T.; Saito, K.; Nakazawa, S.; Mori, N. Tetrahedron Lett. 1992, 33, 6335.
9. We are grateful to the Natural Sciences and Engineering Council of Canada for financial support.

(*Received in USA* 17 *April* 1996; *accepted* 22 *May* 1996)