Tetrahedron Letters, Vol. 34, No. 7, pp. 1149-1150, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Stereoselective Ester Dienolate Carroll Rearrangement: a New Approach to the Prelog-Djerassi Lactone Framework

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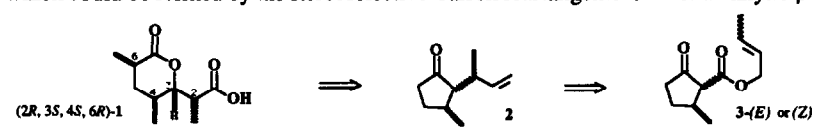
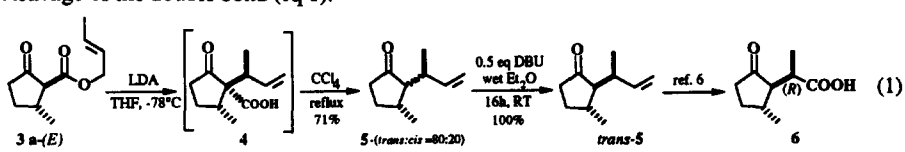
Abstract: *The stereoselective ester dienolate Carroll rearrangement of (E) and (Z)-allylic β-ketoesters has been studied and found to be a new attractive approach to the synthesis of the Prelog-Djerassi lactone and related compounds. The synthesis of the optically active lactone (-)-(2R, 3R, 4R, 6S)-***1** *as well as the formal synthesis of its natural occurring isomer are described.*

The Prelog-Djerassi lactone is an important synthon for the preparation of several macrolide antibiotics as it constitutes a key degradation product of various aglycons like methynolide and narbonolide.[1] Since the first preparation by Masamune in 1975, considerable attention has been given to the preparation of **1**. Our own interest for the stereoselective synthesis of **1**[2] is based on the preparation of a substituted γ,δ-ethylenic ketone **2** as a key intermediate, which could be formed by the stereoselective Carroll rearrangement[3a-e] of an allylic β-ketoester **3**.

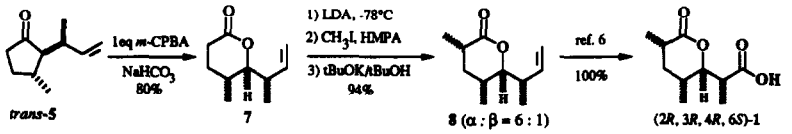


Although a number of recent works have demonstrated the synthetic potentiality of [3,3] sigmatropic rearrangements,[3f] only few reports on the stereoselective Carroll rearrangement have been published recently.[3d,e] Herein, we wish to report our preliminary results on the stereoselective synthesis of (2*R*, 3*R*, 4*R*, 6*S*)-**1** by using the ester dienolate Carroll rearrangement of the (*E*)-β-ketoester **3a** as a new efficient approach to the Prelog-Djerassi lactone and related compounds. The optically active (2*S*, 3*R*)-β-ketoesters **3a** and **3b** serve as model compounds for our study and are easily prepared by transesterification[4] of the corresponding methyl ester[2] in quantitative yield. The correct (2*R*, 3*S*) enantiomer can be formed in good yield from (*S*)-(-)-pulegone.[2]

Treatment of **3a** (45.0 mmol, 8.8g) with 2.5 equiv of LDA in THF at -78 °C followed by decarboxylation[3b] of the crude rearranged β-ketoacid **4** leads to the γ,δ-ethylenic ketone **5** as a mixture of *trans* and *cis* isomers in the ratio 80/20, which upon epimerization gives rise to pure *trans*-**5** in 71% overall yield.[5] The configuration of *trans*-**5** was confirmed by an X-Ray structural determination of the ketoacid **6** obtained by oxidative cleavage of the double bond (eq 1).[6]

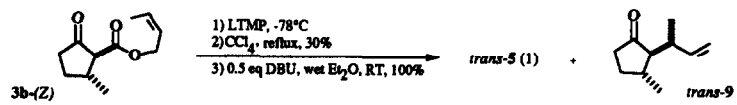


The synthesis was completed by the regio- and chemoselective Baeyer-Villiger oxidation of **5** (8.3 mmol, 1.26g) to the δ-lactone **7** which was alkylated and subjected to thermodynamically equilibrated conditions to give predominantly **8** bearing α-Me with a ratio of α:β=6:1 easily purified by medium pressure chromatography on silica gel (76% overall).[7] RuO_4 oxidation[6] yielded quantitatively (2*R*, 3*R*, 4*R*, 6*S*)-**1**[8] (eq 2).



(2)

The synthesis of unnatural (2*S*, 3*R*, 4*R*, 6*S*)-**1** was similarly attempted starting from the (Z)-(2*S*, 3*R*)-β-ketoester **3b**. However, in this case, the rearrangement of the dilithium dienolate (LDA, -78 °C) proceeds with only moderate diastereoselectivity at the newly created asymmetric center (c.a. 40%). An improved selectivity has been obtained with lithium 2,2,6,6-tetramethylpiperidine (LTMP) at -78 °C leading after decarboxylation and epimerization to a mixture of *trans*-**5** and *trans*-**9** in the ratio 1/9 with 30% overall yield providing a formal stereoselective synthesis of natural occurring **1** (eq 3).



(3)

The synthetic sequence based on the stereoselective ester dienolate Carroll rearrangement giving rise to (2*R*, 3*R*, 4*R*, 6*S*)-**1** associated to the diastereoselective preparation of the key intermediate **9** constitutes a new interesting approach to the synthesis of **1** and related compounds. Works aimed at the completion of the synthesis of the natural occurring Prelog-Djerassi lactone as well as the study of the scope and limitation of this approach are under active investigations.

Acknowledgment. We gratefully acknowledge the generous support of Rhône-Poulenc-Rorer (Vitry) and we are particularly grateful to Dr. J. C. Barrière (Rhône-Poulenc-Rorer) for helpful discussions.

References and notes

1 - For a recent review, see : Martin, S.F.; Guinn, D.E. *Synthesis*, **1991**, 245-262.

2 - For previous works from our laboratory, see : Hacini, S.; Santelli, M. *Tetrahedron*, **1990**, *46*, 7787-7792.

3 - (a) Carroll, M.F. *J. Chem. Soc.*, **1941**, 507-511. (b) Wilson, S.R.; Price, M.F. *J. Org. Chem.*, **1984**, *49*, 722-725. (c) Snider, B. B.; Beal, R.B. *J. Org. Chem.*, **1988**, *53*, 4508-4515. (d) Gilbert, J.C.; Kelly, T.A.*Tetrahedron*, **1988**, *44*, 7587-7600. (e) Echavarren, A.M.; de Mendoza, J.; Prados, P.; Zapata A. *Tetrahedron Lett.*, **1991**, *32*, 6421-6424. (f) Ziegler, F.E. *Chem. Rev.*, **1988**, *88*, 1423-1452.

4- Gilbert, J. C.; Kelly, T.A. *J. Org. Chem.*, **1988**, *53*, 449-450.

5 - *trans*-**5**: colorless oil, R_f = 0.42, ether/pentane: 1/9; $[\alpha]_{578}^{22}$ = +128.8 ($CHCl_3$, c = 2); IR (CCl_4) 3080, 1745, 1640 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 0.98 (d, *J* = 7.1 Hz, 3H), 1.02 (d, *J* = 6.0 Hz, 3H), 1.26 (m, 1H), 1.63 (dm, *J* = 10.3 Hz, 1H), 1.96 (m, 3H), 2.19 (dd, *J* = 16.4, 7.1 Hz, 1H), 2.59 (m, 1H), 4.89 (d, *J* = 10.0, Hz, 1H), 4.92 (d, *J* = 17.1, 1H), 5.71 (ddd, *J* = 17.1, 10.0, 7.3 Hz, 1H); ^{13}C-NMR δ = 16.28, 20.24, 29.58, 33.68, 36.42, 38.77, 60.88, 114.00, 141.69, 219.74; Anal. Calcd. for $C_{10}H_{16}O$: C, 78.95; H, 10.53. Found: C, 78.80; H, 10.63.

6 - Carlsen, H.J.; Katsuki, T.; Martin, V.S.; Sharpless, K.B. *J. Org. Chem.*, **1981**, *46*, 3936-3938.

7 - Suzuki, K.; Tomooka, K.; Katayama, E.; Matsumoto, T.; Tsuchihashi, G. *J. Am. Chem. Soc.*, **1986**, *108*, 5221-5229.

8 - (2*S*, 4*R*, 5*R*, 6*R*)-**1**: greenish cristals, m.p. = 90 °C; R_f = 0.32: ether; $[\alpha]_{578}^{26}$ = -12.86 (c = 1.5 $CHCl_3$); IR (CCl_4) 3300-3180 (broad), 1740, 1720, 1240, 1010 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 0.97 (d, *J* = 6.6 Hz, 3H), 1.23 (d, *J* = 7.1 Hz, 3H),.1.29 (d, *J* = 7.2 Hz, 3H), 1.30 (q, *J* = 13.0 Hz, 1H), 1.87 (ddd, *J* = 3.4, 6.0, 13.4 Hz, 1H), 2.16 (m, 1H), 2.51 (dquint., *J* = 6.0, 13.0 Hz, 1H), 2.84 (dq, *J* = 2.6, 7.2 Hz, 1H), 4.10 (dd, *J* = 2.6, 10.4 Hz, 1H), 8.80 (m, 1H); ^{13}C-NMR δ = 13.19, 17.10, 17.41, 31.41, 36.07, 37.28, 41.94, 87.77, 174.51, 177.95; HRMS calcd. for $C_{10}H_{16}O_4$: 200.1048. Found: 200.1047.

(Received in France 2 November 1992)