Pergamon

Tetrahedron Letters, Vol. 35, No. 45, pp. 8381-8384, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01810-3

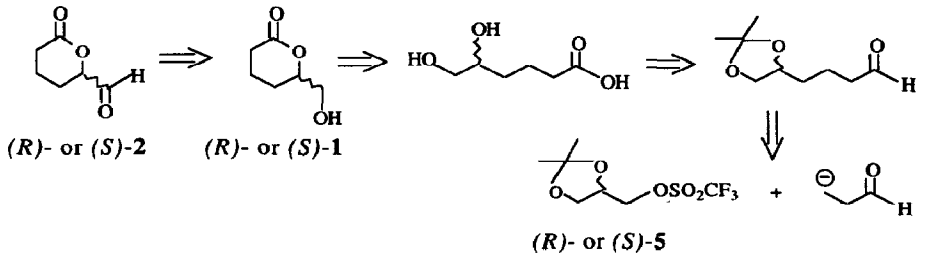
5-Formyl-δ–Valerolactone : A Useful Synthon for the Chiral Synthesis of the *Vespa Orientalis* Pheromone and the Mosquito Oviposition Attractant Pheromone

Ph. Coutrot*, C. Grison, C. Bômont

Institut Nancéien de Chimie Moléculaire, Laboratoire de Chimie Organique II, associé au CNRS, Université Henri Poincaré, Nancy 1, BP 239, 54506 Vandoeuvre-lès-Nancy, France

Abstract : A synthetic scheme starting from the reaction between the lithiated N-allyl-N-methyl-(bisdimethylamino)phosphoramide anion and the triflate derivative of *(R)*-(-)- or *(S)*-(+)-2,3-*O*-isopropylideneglycerol is described to prepare the key chiral synthon *(R)*-5- or *(S)*-5-formyl-δ-valerolactone that leads to the title compounds.

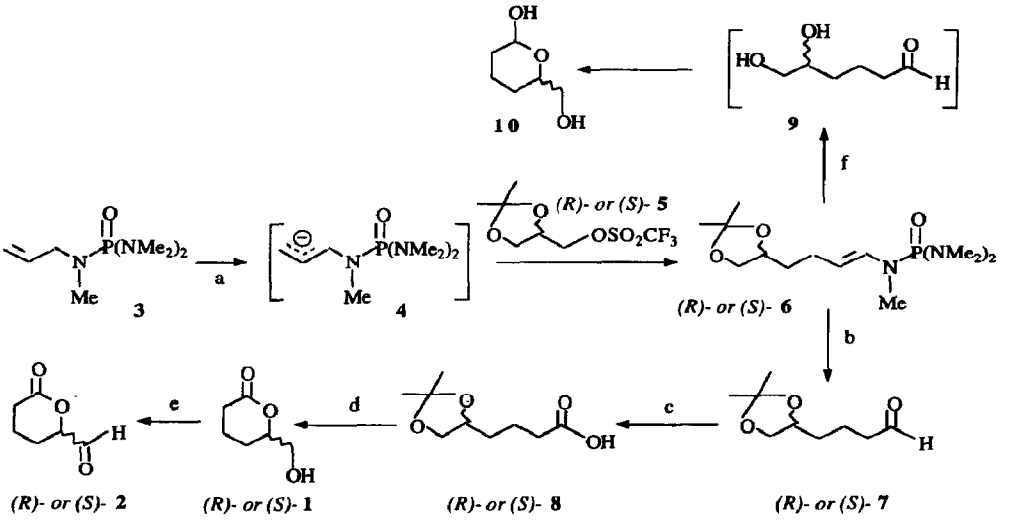
Chiral functionalized γ– and δ-lactones are useful intermediates in the synthesis of natural products. Many of them are also biologically active compounds.[1] 5-hydroxymethyl δ-valerolactone **1**, for example, is an important synthetic building block that has been prepared by various methods in racemic and enantiomerically pure form.[2] It has been employed as a key intermediate for the total synthesis of leucotriene LTB5[3] . However the access to this enantiomerically pure δ-lactone is not always easy. We report here a novel access to the enantiomerically pure 5-hydroxymethyl δ-valerolactone, **1**, and its oxidation product, 5-formyl δ-valerolactone, **2**, based on the consideration that these molecules can result of a coupling between the *(R)*-(-)- or *(S)*-(+)- 2,3-*O*-isopropylideneglycerol triflate and an homoenolate anion equivalent :



(R)- or *(S)*-**2** *(R)*- or *(S)*-**1** *(R)*- or *(S)*-**5**

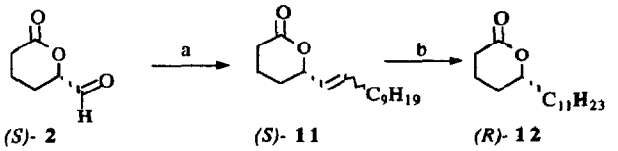
As previously reported, the lithiated N-allyl-N-methyl-(bisdimethylamino)phosphoramide anion **4** is an excellent homoenolate synthetic equivalent.[4] We show now that this anion **4** allows the introduction of the propanal moiety on the chiral glyceryl backbone of **5** and leads, after a series of transformations, to the chiral δ-lactones **1** and **2**, as depicted in Scheme 1. The treatment of N-allyl-N-methyl-(bisdimethylamino)

Scheme 1



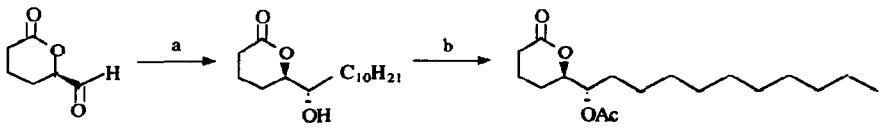
a) nBuLi, THF, -50°C, 1.5h, then **5**, -50°C, 1h, 98%. b) H_2SO_4, H_2O, ether, pH = 2.5, 87%. c) $AgNO_3$,NaOH, 5°C, 1h ; then saturated $(COOH)_2$, H_2O to pH 3.7, 70%. d) Amberlyst 15 ; 4 Å molecular sieves, 20°C, 6h, 75% (34-36% overall yield from commercially available *(R)*- or *(S)*-2,3-*O*- isopropylideneglycerol). e) PDC (pyridinium dichromate), 4 Å molecular sieves, 20°C, 2h, 60% yield in crude product (20% overall yield from commercially available *(R)*- or *(S)*-2,3-*O*- isopropylideneglycerol). f) H_2SO_4 2N, ether (90% yield for *(R,S)*-**6** → *(R,S)*-**10**).

Scheme 2



a) $Ph_3\overset{\oplus}{P}C_{10}H_{21}\ \overset{\ominus}{Br}$, tBuOK,THF, 0°C, then 1h 20°c, 47%. b) H_2 , 5% Pd, 98% (11% overall yield from commercially available (S)-(+)- 2,3-O-isopropylideneglycerol)

Scheme 3



a) $C_{10}H_{21}MgBr$, Et_2O, 55% (5R, 6S : 5R, 6R = 85 : 15), then prep TLC and recrystallisation from n-hexane
b) Ac_2O, DMAP, CH_2Cl_2, 90% (13% overall yield from*(R)*-(+)- 2,3-*O*-isopropylideneglycerol)

phosphoramide **3** with n-butyllithium at -50°C during 1h 30 mn in THF gave the ambident anion **4**, which upon addition of *(R)*-(-)- or *(S)*-(+)-2,3-*O*-isopropylideneglycerol triflate derivative, **5**, yielded the enephosphoramide **6** (98% yield). It is worth noting that the ambident lithiated allylic anion **4** reacted only at the γ-position with the triflate **5** as in similar previously reported reactions with alkyl halides.[5] The sensitivity of **6** towards acids can be compared with that of enamines for the enephosphoramide function and with that of acetals for the dioxolane protective group. With a 2N aqueous-ether solution of chlorhydric or sulfuric acid, both dioxolane and enephosphoramide functions were hydrolysed involving a direct cyclisation of the intermediate dihydroxyaldehyde **9** into the lactol **10**.

An accurate study of the hydrolysis of **6** determinated the conditions of the chemioselective cleavage of the nitrogen-carbon bond at pH 2.5 and led to the aldehyde **7** (87% yield). Subsequent mild oxidation (AgNO3-NaOH)[6] followed by a filtrate acidification at pH 3.7 with a saturated solution of oxalic acid and blue of bromophenol as indicator gave the carboxylic acid **8** (70% yield). After examining several inorganic and organic acids as releasing catalysts, we found amberlyst 15 in the presence of 4 Å molecular sieves to be most effective for the smooth deprotection of the α-diol of **8**. In these conditions a simultaneous internal esterification occured that afforded the δ-lactone **1** (45% overall yield from **5**) .We noted that this last compound was relatively unstable and degraded beyond 24 h at -20°C. Immediate oxidation of the lactone **1** with Corey's procedure[3] led to the expected 5-formyl δ-valerolactone **2** that is also a very sensitive compound that has to be used immediately after a rapid purification (26% overall yield in crude product from **5**).[7]

The flexibility of this method is illustrated by the synthesis of the two natural products, 5-hexadecanolide, **12**, the *Vespa orientalis* pheromone,[8] and 6-acetoxy-5-hexadecanolide, **14**, the Mosquito oviposition attractant pheromone,[1a, 9] which both present the δ-valerolactone moiety in their backbone.

The enantiomers of 5-hydroxymethyl δ-valerolactone, *(R)*-**1** ($[\alpha]_D^{25}$ = -32 (c 1.3 , $CHCl_3$), 34% overall yield from *(R)*-(-)-2,3-*O*-isopropylideneglycerol) and *(S)*-**1** ($[\alpha]_D^{25}$=+33 (c 1.3, $CHCl_3$), 36% overall yield from *(S)*-(+)-2,3-*O*-isopropylideneglycerol)[3] were previously obtained in 5 steps by the enephosphoramide method from the respectively commercially available *(R)*-(-)- and *(S)*-(+)-2,3-*O*-isopropylideneglycerols, as described in scheme 1. Subsequent oxidation of respectively *(R)*-**1** and *(S)*-**1** led to the expected enantiomers *(R)*-**2** (20% overall yield in crude product from *(R)*-(-)-2,3-*O*-isopropylideneglycerol) and *(S)*-**2** (20% overall yield in crude product from *(S)*-(+)-2,3-*O*-isopropylideneglycerol).[7]

The synthesis of the *Vespa orientalis* pheromone, *(R)*-**12** (m.p. 36-37°C, $[\alpha]_D^{25}$ = +38 (c 1.8, THF)), is based on the reaction between the lactone *(S)*-**2**, and the Wittig reagent derived from decyl triphenylphosphonium bromide (47% yield) followed by an hydrogenation reaction (98% yield), as depicted in scheme 2. The overall yield of*(R)*-**12** from *(S)*-(+)-2,3-*O*-isopropylideneglycerol was 11% in 8 steps.The same sequence applied to the lactone *(R)*-**2** afforded *(S)*-**12** (m.p. 36-37°C, $[\alpha]_D^{25}$ = -38 (c 1.8, THF)). The overall yield of *(S)*-**12** from *(S)*-(+)-2,3-*O*-isopropylideneglycerol was 13% in 8 steps.[8d, 10]

The synthesis of (*5R, 6S*)-6-hydroxy-5-hexadecanolide **13** was attempted from the reaction between n-

decylmagnesium bromide and *(R)*-5-formyl-δ-valerolactone, *(R)* **-2**, as described in scheme 3. The reaction was entirely chemoselective on the aldehyde without attack of the lactone and gave the adduct (*5R, 6S*)-**13**, in *ca.* 85 : 15 ratio with diastereomer (*5R, 6R*)-**13**. Preparative TLC afforded the crude lactone (*5R, 6S*)-**13**. After recrystallisation from n-hexane the pure lactone (*5R, 6S*)-**13** (m.p. 67°C, $[\alpha]_D^{25}$=-13 (c 1.0, $CHCl_3$)) was then acetylated (Ac_2O, pyridine) and yielded the expected pheromone, (*5R, 6S*)-6-acetoxy-5-hexadecanolide, (*5R, 6S*)-**14** (13% overall yield from *(R)*-(-)-2,3-*O*-isopropylideneglycerol).[9c] In a similar way the same sequence applied to *(S)*-5-formyl-δ-valerolactone, *(S)* **-2**, led to the major diastereomer (*5S, 6R*)-**13** , in *ca.* 91 : 9 ratio with diastereomer (*5S, 6S*)-**13**.

In conclusion we have described a new and versatile method to obtain the enantiomers of 5-formyl δ-valerolactone, **2**, via the reaction between the homoenolate anion equivalent derived from N-allyl-N-methyl-(bisdimethylamino)phosphoramide and the triflate derivative of *(R)*-(-)- and *(S)*-(+)-2,3-*O*-isopropylidene glycerol. The method was illustrated by the synthesis of the enantiomers of 5-hexadecanolide, the *Vespa orientalis* pheromone, and (*5R, 6S*)-6-acetoxy-5-hexadecanolide, the major component of the oviposition attractant pheromone *Culex pipiens fatigans*.

References

1. a) Gravier-Pelletier, C. ; Sanière, M. ; Charvet, I. ; Le Merrer, Y. ; Depezay, J.C. *Tetrahedron Lett.* **1994**, *35*, 115-118. b) Sakamoto, A. ; Yamamoto, Y. ; Oda, J. *J. Am. Chem. Soc.* **1987**, *109*, 7188 -7189. c) Chattopadhyay, S. ; Mamdapur, V.R. ; Chadha, M.S. *Synth. Commun.* **1990**, *20* , 1299 -1303 and references cited therein.
2. a) Blaser, F. ; Deschenaux, P.F. ; Kallimopoulos,T. ; Jacot-Guillarmod, A. *Helv. Chim. Acta* **1991**,*74*, 141-145. b) Gerth, D.B. ; Giese, B. *J. Org. Chem.* **1986**, *51*, (19), 3726-3729. c) Pianetti, P. ; Pougny, J.R. *J. Carbohydr. Chem.* **1988**, *7*, 811-815. d) Taylor, R.J.K. ; Wiggins, K. ; Robinson, D.H. *Synthesis* **1990**, 589-590. e) Murahashi, S.I. ; Naota, T. ; Ito, K. ; Maeda, Y. ; Taki, H. *J. Org. Chem.* **1987**, *52* , 4319-4327 and references cited therein.
3. Corey, E.J. ; Pyne, S.G. ; Su, W.*Tetrahedron Lett.* **1983**, *24* , 4883-4886.
4. Coutrot, P. ; Dormoy, J.R. ; Moukimou, A. *J. Organomet. Chem.* **1983**, *258*, C25-C28.
5. Coutrot, P. ; Savignac, P. *J. Chem. Res. (S)* **1977**, 308 *J. Chem. Res. (M)* **1977**, 3401-3416.
6. a) Leggeri, P. ; Azzolina, O. ; Pirillo, D. ; Traverso, G. *Il Farmaco* **1989**, *44* , 303-313. b) Lee, T. J. ; Holz, W.J. ; Smith, R.L. *J. Org. Chem.* **1982**, *47*, 4750-4757.
7. Crude product. IR (CH_2Cl_2) : 1729 cm^{-1} ; ^1H NMR ($CDCl_3$, 250 MHz) : 1.5-2.0 (m,4H) ; 2.2-2.7 (m, 2H) ; 4.8-5.2 (m, 1H) ; 9.7 (br s, 1H) ; ^{13}C NMR ($CDCl_3$) : 191.3 (C6), 170.6 (C1), 80.2(C5), 32.6 (C2), 23.7 (C4), 18.0 (C3).
8. a) Larchevêque, M. ; Lalande, J. *Tetrahedron* **1984**,*40*, 1061-1065. b) Solladié, G. ; Matloubi-Moghadam, F. *J. Org. Chem.* **1982**, *47*, 91-94. c) Kosugi, H. ; Konta, H. ; Uda, H. *J. Chem. Soc., Chem. Commun.* **1985**, 211-213. d) Mori, K. ; Otsuka, T. *Tetrahedron* **1985**, *41*, 547-551. e) Taber, D.F. ; Deker, P. B. ; Gaul, M.D.*J. Am. Chem. Soc.* **1987**,*109*, 7488-7494. f) Mori, A. ; Yamamoto, H. *J. Org. Chem.* **1985**, *50*, 5444-5446. e) Servi, S.*Tetrahedron Lett.* **1983**, *24*, 2023-2024 and references cited therein.
9. a) Fuganti, C. ; Grasselli, P. ; Servi, S. *J. Chem. Soc., Chem. Commun.* **1982**, 1285-1286. b) Ramaswamy, S. ; Oehlschlager, A.C. *Tetrahedron* **1991**, *47*, 1145-1156. c) Mori, K. ; Otsuka, T. *Tetrahedron* **1983**, *39*, 3267-3269. d) Ko, K.Y. ; Eliel, E.L. *J. Org. Chem.* **1986**, *51*, 5353-5362. e) Sato, T. ; Watanabe, M. ; Honda, N. ; Fujisawa, T. *Chem. Lett.* **1984**, 1175-1176. f) Laurence, B.R. ; Mori, K. ; Otsuka, T. ; Pickett, J.A. ; Wadhams, L.J. *J. Chem. Ecology* **1985**, *11*, 643-648. g) Masaki,Y. ; Nagata, K. ; Kaji, K. *Chem. Lett.* **1983**, 1835-1836. h) Guo-qiang, L. ; Hai-jian, X. ; Bi-chi, W.*Tetrahedron Lett.* **1985**, *26*, 1233-1236. i) Barua, N.C. ; Schmidt, R.R. *Tetrahedron* **1986**, *42*, 4471-4474. j) Machiya, K. ; Ichimoto, I. ; Kirihata, M. ; Ueda, H. *Agriculture Biological Chemistry* **1985**, *49*, 643-649.
10. Satisfactory analytical and spectroscopic data were obtained in good agreement with reported values.

(*Received in France* 20 *July* 1994; *accepted* 12 *September* 1994)