Tetrahedron Letters, Vol. 33, No. 52, pp. 8035-8038, 1992
Printed in Great Britain

0040-4039/92 \$5.00 + .00
Pergamon Press Ltd

A Convenient Stereoselective Synthesis of a (-)-Vertinolide Precursor[1]

Apurba Datta, Dinah Datta, and Richard R. Schmidt*

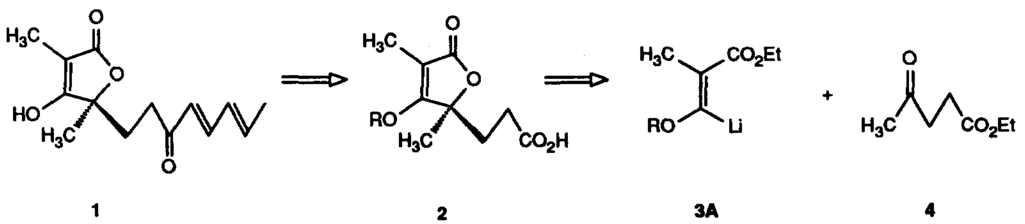
Fakultät für Chemie, Universität Konstanz,

Postfach 5560, D-7750 Konstanz, Germany

Abstract: **A short practical method for the enantioselective synthesis of (-)-vertinolide precursor 2 is described. The readily available chiral β-alkoxy substituted acrylate 7 has been reacted with ethyl levulinate to form the tetronic acid nucleus 8, which in three subsequent steps was converted to the known precursor 2 in high overall yield.**

Vertinolide (1), a tetronic acid derivative of fungal origin, was isolated from *Verticulium intertextum*[2] and its chemical structure determined by X-ray analysis[3]. Three total syntheses have since been reported confirming the assigned structure and establishing the 5-(S)-configuration[4,5,6]. However, considering the diverse biological properties exhibited by tetronic acids and derivatives[7], it remains worthwhile to develop new methods for the synthesis of these compounds in optically pure form. Recent work from this laboratory[8,9] has established a simple route for the stereoselective synthesis of various substituted tetronic acid derivatives, utilizing the readily available β-C-lithiated acrylates as a C_3 building unit[10,11]. In continuation, we planned to utilize the above mentioned pathway for a short enantioselective synthesis of the known (-)-vertinolide precursor 2 which can be readily converted into 1[5,6]. The results of our work are described herein.

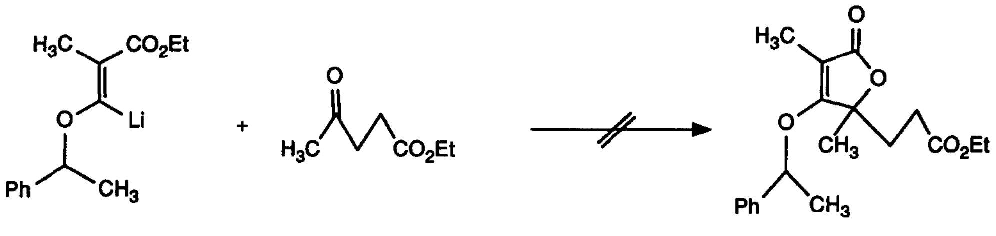
From the retrosynthetic perspective, it is evident that a properly substituted β-lithioacrylate 3A, on reacting with a levulinic acid derivative 4, should afford the fully substituted tetronic acid derivative 2 (Scheme 1), a key intermediate in two of the reported total syntheses[5,6] of (-)-vertinolide.



Scheme 1

Induction of the desired stereochemistry in the product was expected to be achieved by using a proper chiral β-alkoxy substituent in the starting acrylate.

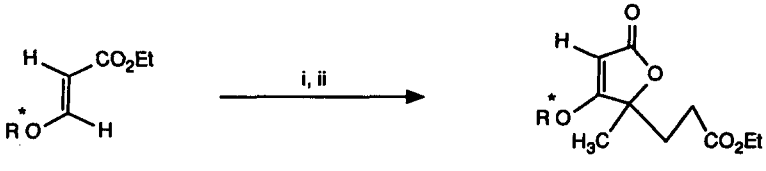
However, to our dismay, attempted reactions of ethyl β-lithio-2-methyl-3(1-phenylethoxy)propenoate (**5A**)[9] with ethyl levulinate (**4**) failed to form the expected product **6** (Scheme 2), and the starting material was recovered unchanged. This probably was due to the low nucleophilicity of the vinyl carbanion **5A** which instead underwent proton exchange with the added levulinate.



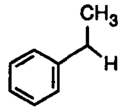
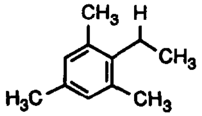
5A **4** **6**

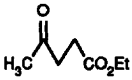
Scheme 2

To circumvent this problem, we then reacted the vinyllithium derivative **7aA** of 2-unsubstituted ethyl 3-(1-phenylethoxy)acrylate (**7a**)[8] with ethyl levulinate (**4**) which underwent smooth addition to give the expected 5,5-disubstituted tetronate **8a** (Scheme 3) in good yield[12]; however, presumably due to similar steric demand of the substituents in ketone **4** diastereoselectivity was not observed.



7 **8**

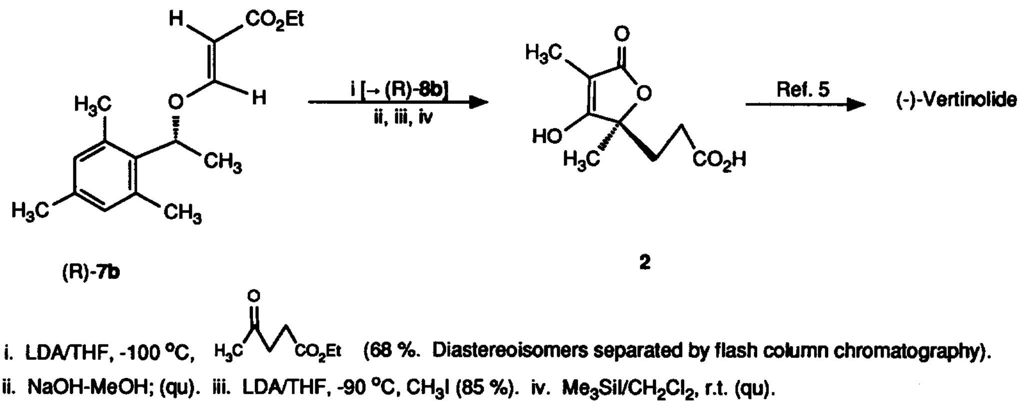
7, 8	R* (±)	Yield (%) +	Diastereomer ratio
a		70 (77)	1 : 1
b		68 (76)	4.5 : 1

i. LDA/THF, -100 °C, 45 min (→ **7aA**, **7bA**); ii.  /THF, -100 ° - -60 °C, 1 h.

\+ yields in parentheses are based on 7 consumed

Scheme 3

In order to achieve better stereocontrol, the more bulky 1-mesitylethoxy group was then introduced as chiral auxiliary in the starting acrylate (→ **7b**). Generation of **7bA** and reaction with **4** improved the selectivity satisfactorily and the product **8b** (Scheme 3) was obtained in equally good yield. To complete the proposed synthesis and in order to assign the stereochemistry, enantiomerically pure (R)-**7b** was reacted as above to yield the tetronate (RS)- and (RR)-**8b** (Scheme 4); the minor diastereoisomer [(RR)-**8b**] was separeted by flash column chromatography. The major isomer [(RS)-**8b**], a white crystalline solid (m.p. 119°C), was then converted to the corresponding acid under standard reaction conditions. Introduction of the methyl group at 2-position was done following a previously reported procedure[13]. Trimethylsilyl iodide assisted O-deprotection then afforded the pivotal vertinolide intermediate **2**[14]. This, on the basis of its spectral and analytical data and comparison of its optical rotation ($[\alpha]_D^{25} = +5.8°$, c = 0.6, EtOH) with the reported compound ($[\alpha]_D = +5.2°$, c = 1.73, EtOH)[15], was assigned the (*S*)-configuration, thus achieving the intended synthesis of **2** in high overall yield.



i. LDA/THF, -100 °C, $H_3CCOCH_2CH_2CO_2Et$ (68 %. Diastereoisomers separated by flash column chromatography).
ii. NaOH-MeOH; (qu). iii. LDA/THF, -90 °C, CH_3I (85 %). iv. Me_3SiI/CH_2Cl_2, r.t. (qu).

Scheme 4

In conclusion, the present method offers a short and enantioselective approach for the construction of a key intermediate in the synthesis of (-)-vertinolide, using easily available and well established starting materials; thus, it should prove to be a method of choice for the synthesis of this important structural unit.

Acknowledgements

This work was supported by the Schwerpunktprogramm des Landes Baden-Württemberg and the Fonds der Chemischen Industrie. - A.D. thanks the Alexander von Humboldt-Foundation for a postdoctoral fellowship.

References and Notes

1. Vinyl carbanions, Part 46. For part 45, see ref. 9.
2. Trifonov, L; Dreiding, A. S.; Hoesch, L.; Rast, D. M., *Helv. Chim. Acta* **1981**, *64*, 1843-1846.
3. Trifonov, L.; Bieri, J. H.; Prewo, R.; Dreiding, A. S., *Tetrahedron* **1982**, *38*, 397-403.
4. Wrobel, J. E.; Ganem, B. J.; *J. Org. Chem.* **1983**, *48*, 3761-3764.
5. Takaiwa, A.; Yamashita, K., *Agri. Biol. Chem.* **1984**, *48*, 961-963.
6. Desmaele, D., *Tetrahedron*, **1992**, *48*, 2925-2934.
7. Haynes, L. J.; Plimmer, J. R., *Quart. Rev.* **1960**, *14*, 292-315.

8. Jatzke, H.; Evertz, U.; Schmidt, R. R., *Synlett*, **1990**, 191-194.

9. Datta, A.; Schmidt, R. R., *Synlett*, **1992**, 429-430.

10. Schmidt, R. R., *Bull. Soc. Chim. Belg.*, **1983**, *92*, 825-836.

11. Hirsenkorn, R.; Schmidt, R. R.; *Liebigs Ann. Chem.* **1990**, 883-899, and references cited therein.

12. Preparation of **8**: To a solution of LDA (5.2 mmol) in dry THF (15 mL) at -100 °C and under N_2 atmosphere, **7** (5 mmol) in THF (10 mL) is added dropwise with stirring. After 45 min a solution of **4** (5 mmol) in THF (5 mL) is injected to the reaction mixture and the temp. allowed to warm up to -60 °C within 1 h. The reaction is quenched by addition of 25 mL of aq. saturated NH_4Cl. Extraction with ether (3 x 50 mL), drying (Na_2SO_4) and removal of solvent gave the crude product as a yellow oil. Purification by flash chromatography (petroleumether/ethylacetate, 7:1) yielded the pure products. **8b** (major isomer): White crystalline solid ($CHCl_3$/petroleum ether), m.p. 119 °C. ^1H NMR (250 MHz, $CDCl_3$): δ 1.27 (t, J = 7.1 Hz, 3 H), 1.47 (s, 3 H), 1.69 (d, J = 6.8 Hz, 3 H), 2.08-2.39 (m, 13 H), 4.14 (q, J = 7.1 Hz, 2 H), 4.62 (s, 1 H), 5.48 (q, J = 6.8 Hz, 1 H), 6.84 (s, 2 H). **8b** (minor isomer): White crystalline solid ($CHCl_3$/petroleum ether), m.p. 75 °C. ^1H NMR (250 MHz, $CDCl_3$): δ 1.21 (t, J = 7.1 Hz, 3 H), 1.50 (s, 3 H), 1.67 (d, J = 6.8 Hz, 3 H), 1.94-2.28 (m, 7 H), 2.33 (s, 6 H), 4.07 (q, J = 7.1 Hz, 2 H), 4.67 (s, 1 H), 5.49 (q, J = 6.8 Hz, 1 H), 6.81 (s, 2 H).

13. a) Miyata, O.; Schmidt, R.R., *Tetrahedron Lett.* **1982**, *23*, 1793-1796.

    b) Clemo, N. G.; Pattenden, G., *Tetrahedron Lett.* **1982**, *23*, 581-584.

14. The spectral and analytical data of all the compounds prepared are consistent with the assigned structures.

15. Takaiwa, A.; Yamashita, K., *Agri. Biol. Chem.* **1983**, 429-430.

(Received in Germany 26 August 1992)