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Chiral β-C-Lithiated β-Alkoxy Acrylates: Efficient Synthons for Highly Functionalized Cyclopentenones[1]

Apurba Datta and Richard R. Schmidt*

Fakultät für Chemie, Universität Konstanz

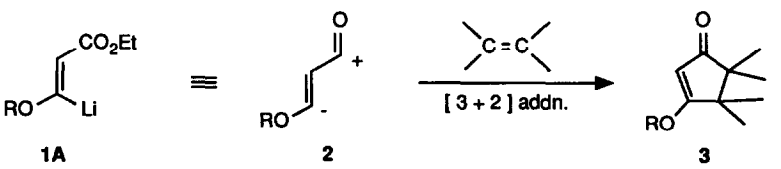
Postfach 5560, D-7750 Konstanz, Germany

Abstract: A one step synthesis of highly functionalized cyclopentenones has been developed by the Michael addition of the readily available β-lithiated acrylate **1A** with suitable acceptors.

The occurrence of prostaglandins as cyclopentane derivatives, as well as the discovery of a wide array of cyclopentanoid natural products, such as jasmonoids, hirsutane sesquiterpenes, pentaleno-lactones to name a few, intitiated a flurry of activities towards devising methodologies for the synthesis of such cyclopentane based products. This resulted in the development of a number of new and interesting strategies for the construction of cyclopentanoids and polycondensed cyclopentanoids[2]. In spite of this, the widespread occurrence of this skeleton in many biologically important natural products continues to attract interest in developing new methods and the design of new pathways for cyclopentane ring forming reactions remains challenging and worthwhile[3,4].

These facts, alongwith the expectation that β-C-metallated acrylates **1A** (Scheme 1), formal three-carbon zwitterionic species of type **2**[5], should afford on reaction with CC-double bond systems in a [3 + 2]-manner directly cyclopentenones **3**, were a stimulus for our investigations.

Scheme 1



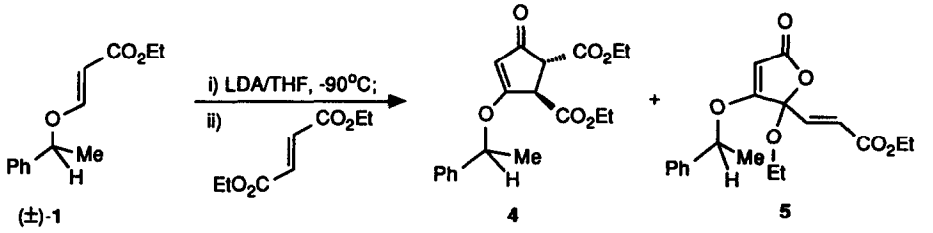
1A **2** **3**

Surprisingly, but for a couple of isolated reports[5,6], the Michael addition of β-metalloacrylates to suitable acceptors and subsequent ring closure to cyclopentenones has remained virtually unexplored. Recent work from this laboratory has shown that acrylates possessing a chiral auxiliary group at β-position react in a center-face interaction diastereoselectively with carbonyl compounds, forming tetronates with moderate to high

enantiomeric excess[7,8,9]. Therefore, in carrying out our present strategy, we decided to undertake the proposed Michael addition studies using a chiral β-alkoxy acrylate as the C_3 fragment, which also is expected to impart stereoselectivity in the products formed. The results of our preliminary studies are reported herein.

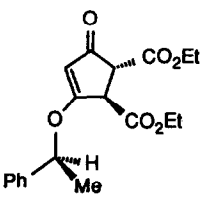
Attempted reactions of ethyl 3-(1-phenylethoxy)acrylate (±)-**1** (Scheme 2) in the pesence of a strong base with Michael acceptors having only one electron withdrawing group failed to afford either the initial adduct or the cyclized product. Changes in solvent (THF, Et_2O), base (LDA, LHMDS) or even the addition of further activating reagents (HMPT, $BF_3{\cdot}Et_2O$, $CuBr{\cdot}Me_2S$) also failed to effect the expected addition. However, when acrylate **1** was reacted with the stronger Michael acceptor diethyl fumarate[10], work-up and subsequent purification of the reaction mixture showed the presence of two products along with the recovery of some unreacted starting material (~10%). Spectral and analytical studies confirmed the major product (62%) to be the expected cyclopentenone derivative **4** having exclusively *trans*-geometry between the two substituents at 4 and 5 positions. The minor product was found to be the tetronate derivative **5** (14%), obtained via a formal 1,2-addition of a carbonyl group of the substrate.

Scheme 2



(62%, diast. ratio = 2 : 1) (14%)

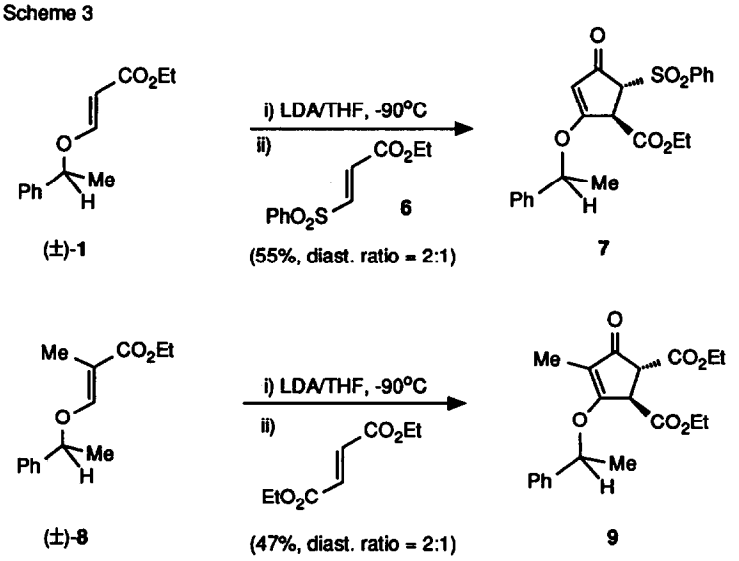
The effect of the chiral auxiliary in the starting acrylate, however was not very pronounced in inducing selectivity in the derived cyclopentenone, which was formed in a 2:1 diastereoisomer ratio. Substituting the chiral group by more bulky 1-mesitylethoxy or 1-(9-anthracenyl)ethoxy groups did not result in better stereocontrol. However, gratifyingly the major isomer was found to crystallize out as a white solid[11] from the isomeric mixture, making possible further structural studies. In order to assign the stereochemistry, in one experiment the reaction of enantiomerically pure (*S*)-**1** with diethyl fumarate was carried out as above, and the major isomer (-)-**4**[12] obtained as crystals was subjected to X-ray analysis[13], which confirmed the *trans*-relationship between the two ethoxycarbonyl groups, as well as the absolute (*4R,5R*) configuration:



(-)-4

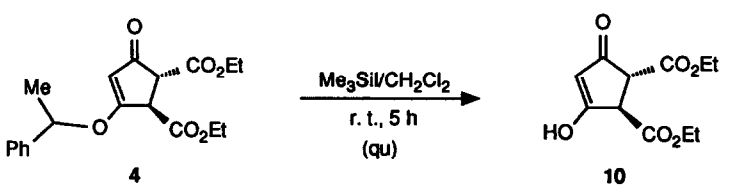
To further utilize the present reaction for synthesizing variously substituted cyclopentenones, the acrylate (±)-**1** was next reacted with ethyl 3-phenylsulphonylacrylate (**6**) (Scheme 3), forming the expected 5-phenylsulphonyl substituted cyclopentenone **7** in comparable yield (55%). Similarly, when the acrylate (±)-**8**, with an additional methyl group at 2-position, was reacted with diethyl fumarate, the 2-methyl substituted cyclopentenone **9** was obtained in 47% yield[14].

Scheme 3



The versatility and broad potential of the present method for synthesizing structurally useful building blocks was further demonstrated by carrying out selective O-deprotection of the cyclopentenone **4** to afford the corresponding 3-hydroxy derivative **10** (Scheme 4).

Scheme 4



In conclusion, the present strategy for the synthesis of highly functionalized cyclopentenones should prove to be a useful addition to the existing methodologies. It is also expected that the compounds thus synthesized can be used as important building blocks for obtaining a diverse array of biologically useful cyclopentanoids.

Acknowledgements

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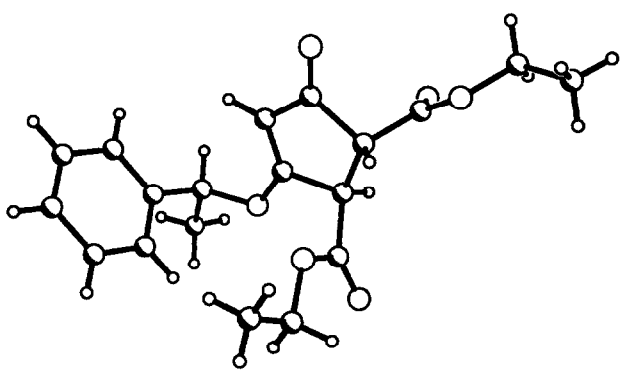
10. *Procedure*: To a solution of LDA (5 mmol) in dry THF (15 mL) at -90°C and under N_2 atmosphere, **1** (5 mmol) in dry THF (10 mL) is added dropwise with stirring. After 45 min a solution of diethyl fumarate (5 mmol) in dry THF (10 mL) is injected to the reaction mixture and after stirring for 30 min, the reaction is brought up to room temp. and stirred for another 8 h. The reaction is then quenched by adding 25 mL of aq. saturated NH_4Cl. Extraction with ether (4 x 50 mL), drying (Na_2SO_4) and removal of solvent followed by flash chromatography purification (petroleum ether/ethyl acetate, 4:1) yielded the pure products.
11. **4** (major isomer): White solid ($CHCl_3$-petroleum ether), m.p. 92°C. ^1H NMR (250 MHz, $CDCl_3$): δ 1.24-1.33 (m, 6 H), 1.67 (d, J = 6.5 Hz, 3 H), 3.65 (d, J = 3.2 Hz, 1 H), 4.15-4.29 (m, 5 H), 5.14 (d, J = 1.2 Hz, 1 H), 5.22 (q, J = 6.5 Hz, 1 H), 7.23-7.38 (m, 5 H).
12. $[\alpha]_D^{20}$ -1.17 (c 0.6, EtOH).
13. The atomic co-ordinates of (-)-**4** are available on request from the Fachinformationszentrum Karlsruhe, D-7514 Eggenstein-Leopoldshafen 2, Germany, referring to No. CSD - 57221 and the full literature citation for this communication



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

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