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# An Alternative Enantioselective Synthesis of (+)-Tricyclodecadienone

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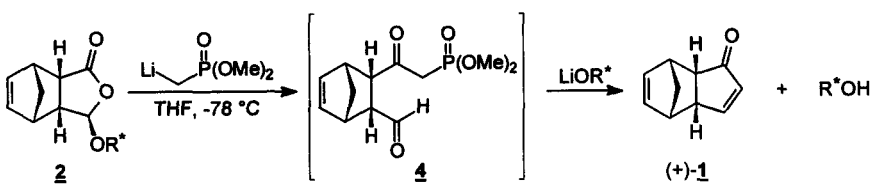
***Abstract:*** The enantiomerically pure *endo*-cycloadduct **2**, obtained from the thermal Diels-Alder reaction of 5*R*-(*l*-menthyloxy)-2(5H)-furanone with cyclopentadiene is converted into (+)-tricyclo[5.2.1.$0^{2,6}$]decadi-4,8-en-3-one ((+)-**1**) in a one-pot procedure via ring-opening with lithium methyl dimethylphosphonate followed by an intramolecular Wittig-Horner-Emmons reaction in THF. The use of LiBr as additive in this step is highly beneficial to the formation of **1**. © 1997 Published by Elsevier Science Ltd.

Optically active tricyclo[5.2.1.$0^{2,6}$]decadi-4,8-en-3-one (**1**) has been recognized as an important starting material for the synthesis of a wide variety of natural products in enantiomerically pure form.[1] Recent literature reports offer a number of useful synthetic methodologies for the preparation of enantiomerically pure **1**, several of which are based on enzymatic resolution.[2] We now report an alternative enantioselective route to tricyclodecadienone **1**.

Starting point of this investigation formed the known enantiomerically pure *endo*-cycloadduct **2**[3] which is easily accessible in multigram quantities from the thermal Diels-Alder reaction of 5*R*-(*l*-menthyloxy)-2(5H)-furanone[4] with cyclopentadiene according to a procedure developed in our laboratories.[5] We envisaged that tricyclodecadienone (+)-**1** would be obtained by the ring-opening reaction of **2** with the lithium salt of methyl dimethylphosphonate and subsequent Wittig-Horner-Emmons (WHE) cyclization[6] of the intermediate β-keto-phosphonate **4** (Scheme 1).

Scheme 1.

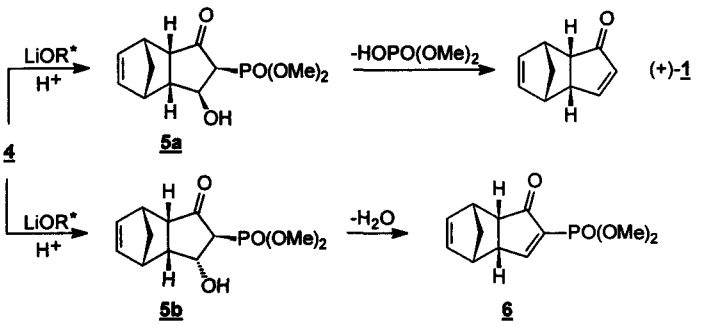



**2** **4** (+)-**1**

R* = *l*-menthyl

Initial reactions of **2** with equimolar amounts of phosphonate anion in THF at -78 °C, followed by warming to RT and quenching with water, afforded a mixture of products which contained unreacted **2** (~15-25%), (+)-**1** and Knoevenagel product **6**[7] (scheme 2) after extractive workup. The observation that both **1**, and Knoevenagel product **6** are formed during the reaction indicates that the cyclization of **4** yields two diastereomeric β-hydroxy-phosphonates which follow distinctly different routes of product formation. The *cis*-β-hydroxy-phosphonate **5a** is expected to undergo irreversible cycloelimination with formation of the product **1** of WHE cyclization, while the epimeric *trans*-β-hydroxy-phosphonate **5b** can undergo dehydration to yield Knoevenagel product **6**.

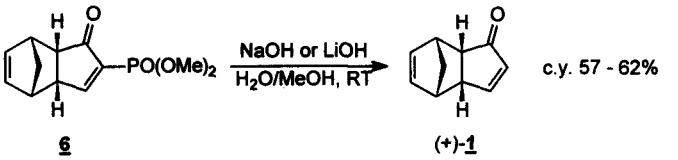
Scheme 2.




The formation of **6** could not be prevented by adjusting reaction parameters such as temperature and concentration of the reactants[8] and isolated yields of (+)-**1** remained moderate.

A key aspect proved to be the finding that Knoevenagel product **6** could be transformed into the WHE product **1** by exposure of **6** to an aqueous alkaline medium (NaOH or LiOH in $H_2O$/MeOH) which clearly indicates that the dehydration step leading to **6** is reversible (scheme 3).[9] This observation supports the recent work of Mikolajczyk *et al.* dealing with similar transformations of Knoevenagel products into WHE products.[6c,e]

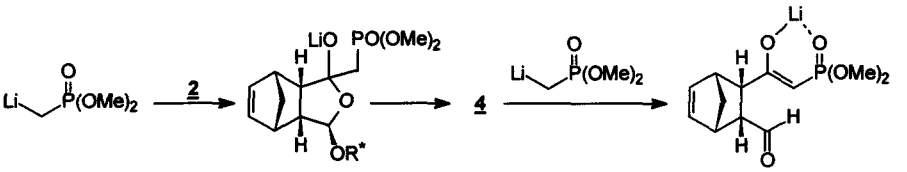
Scheme 3.




In order to utilize this phenomenon in a more elegant fashion we employed continuous extraction with hexane after aqueous quenching and removal of THF. This procedure allows the facile extraction of the hexane-soluble components ((+)-**1**, unreacted **2** and chiral auxiliary *l*-(-)-menthol) from the reaction mixture, while hexane-insoluble **6** is simultaneously converted into (+)-**1** in the aqueous phase. In this way we were able to obtain enantiomerically pure (+)-**1** in satisfactory and reproducible yields (c.y. 70-75% from **2**)[10] with efficient recovery of the chiral auxiliary *l*-(-)-menthol (≥ 85%) after chromatographic purification.

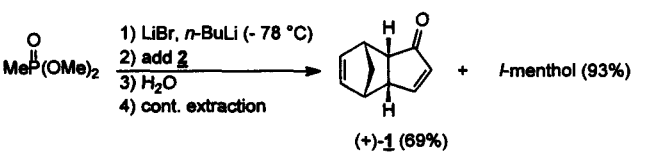
The second problem which was addressed involved the incomplete conversion of **2** when 1 equivalent of lithium methyl dimethylphosphonate was used. It turned out that the incomplete conversion of **2** was hardly affected by employing larger amounts of phosphonate anion at different temperatures and concentrations. We speculate that incomplete conversion originates from the fact that the initial 1,2-addition process of $LiCH_2PO(OMe)_2$ to **2** is relatively slow as compared to the ring-opening of **3** into β-keto-phosphonate **4** (scheme 4). The latter compound could in turn act as an acidic scavanger for unreacted $LiCH_2PO(OMe)_2$.

Scheme 4.




In search for a method that would facilitate the formation of the intermediate 1,2-addition adduct **3** we examined the effect of lithium salts as additive. It was expected that additional amounts of lithium salts would have a stabilizing effect on **3** via formation of a chelate.[11] Satisfactory results were obtained when an equimolar amount of lithium bromide was added prior to the addition of **2** to the reaction mixture. In this way the stoichiometric reaction (1 eq. $LiCH_2PO(OMe)_2$) gave 95% conversion which allowed the isolation of (+)-**1** in 69% yield with recovery of *l*-menthol in 93% yield (scheme 5).[12]

Scheme 5.




We believe that the present methodology is especially attractive since it utilizes a short two-step procedure from readily available enantiomerically pure 5*R*-(*l*-menthyloxy)-2(5H)-furanone via *endo*-cycloadduct **2** with efficient recovery of the chiral auxiliary. This procedure would of course allow an equally easy synthesis of (-)-**1**, since *ent*-**2** is available via the use of *d*-(+)-menthol.[4]

**Acknowledgements**

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7. Spectroscopic data of 6: $^{31}$P-NMR (80.95 MHz, $CDCl_3$) δ +12.28; $^1$H-NMR (200 MHz, $CDCl_3$) δ 1.63 (d, $J$ = 8.8 Hz, 1H), 1.76 (d, $J$ = 8.8 Hz, 1H), 2.97 (t, $J$ = 5.1 Hz, 1H), 3.07 (br. s, 1H), 3.27 (br. s, 1H), 3.51 (m, 1H),3.68 (d, $J_{H,P}$ = 11.4 Hz, 3H), 3.74 (d, $J_{H,P}$ = 11.4 Hz, 3H), 5.82 (dd, $J$ = 5.3, 2.9 Hz, 1H), 5.98 (dd, $J$ = 5.3, 2.9Hz, 1H), 8.06 (dd, $J_{H,P}$ = 10.6 Hz; $J_{H,H}$ = 2.6 Hz, 1H); HRMS calcd for $C_{12}H_{15}O_4P$: 254.071. Found: 254.071.
8. The amount of Knoevenagel product was increased when reaction mixtures were left at room temperature for prolonged periods. This illustrates that the dehydration process leading to 6 is a relatively slow process.
9. Typical procedure: A solution of 6 (300 mg, 1.18 mmol) in methanol (2 mL) and water (2 mL) containing LiOH or NaOH (1.77 mmol) was stirred at room temperature for 24 h. Methanol was evaporated and the resulting aqueous mixture was neutralized with dilute HCl and extracted with ethyl acetate. The combined extracts were dried ($Na_2SO_4$), filtered and evaporated to yield a ~75/25 mixture of (+)-1 and 6 according to $^1$H-NMR. Filtration over silica gel (diethyl ether) afforded pure (+)-1 (57 - 62%, based on recovered 6) as a white solid.
10. (a) Purification was performed by chromatography on silica gel (hexane, 30% diethyl ether) which readily separated 2 ($R_f$ = 0.7), *l*-menthol ($R_f$ = 0.5) and (+)-1 ($R_f$ = 0.35). Isolated yields are based on recovery of 2. (b) Purified (+)-1 showed the following data: mp: 76.7-78.2 °C (lit.[2d] mp: 76-76.5 °C); $[\alpha]_D^{RT}$ +136.7 ° ($c$ = 1.1, MeOH) (lit.[2d] $[\alpha]_D^{28}$ +138.4 ° ($c$ = 0.81, MeOH); e.e. > 99% according to HPLC analysis (Daicel OB, eluent hexane/*i*PrOH 9/1).
11. Additionally, lithium salts might also function as weak Lewis acids for the activation of 2.
12. Typical experimental procedure: To a stirred and cooled (-78 °C) solution of dimethyl methylphosphonate (595 mg, 4.8 mmol) and anhydrous lithium bromide (417 mg, 4.8 mmol) in dry THF (20 mL) was added *n*-butyllithium (3 mL of a 1.6 M solution in hexanes, 4.8 mmol) over a period of ± 2 min. The resulting clear solution was stirred at -78 °C for 30 min after which a solution of 2 (1.45 g, 4.8 mmol) in dry THF (5 mL) was added at once. Stirring was continued for an additional period of 2 h at -78 °C and the mixture was allowed to reach room temperature in 3½ h. After addition of water (10 mL) and evaporation of THF in vacuo the resulting aqueous residue was continuously extracted with hexane (100 mL) for 20 h. Evaporation of the solvent in vacuo yielded a slightly yellow oil which was purified by column chromatography (see ref. 10) to yield pure *l*-(-)-menthol (661 mg, 93%) and (+)-1 (459 mg, 69%).


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