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Novel Asymmetric Synthesis of a Bicyclo[3.1.0]hexane Derivative by an Efficient Retro-Diels-Alder Strategy.

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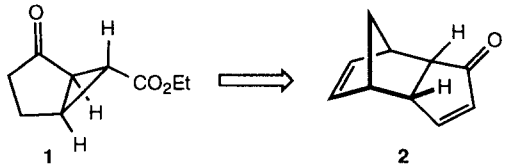
Abstract: The first preparation of enantiomerically pure bicyclo[3.1.0]hexane-2-one-6-carboxylic acid ethyl ester (1), a valuable synthetic intermediate, is described. The synthesis features a retro-Diels-Alder reaction as a key step. Conditions which allow for a high yielding thermal conversion of **3** to **4** are described.

Intensive excitatory amino acid (*eg. L*-glutamate) research is fueled by the need to find novel therapeutic agents capable of ion (Ca^{2+}, K^+, Na^+) channel regulation in nerve cells. Efforts in this area have shown promise in preventing physical and mental impairment resulting from ischemic stroke.[1] The pharmacological effects of excitatory amino acids are mediated by ligand-gated ionotropic glutamate receptors and G-protein coupled metabotropic glutamate receptors.[2] As a result of our research program aimed at identifying new lead structures exhibiting glutamate receptor affinity, we required access to enantiomerically pure bicyclo[3.1.0]hexane-2-one-6-carboxylic acid ethyl ester (**1**).[3] Keto-ester **1**, while readily available as a racemate,[3,4] has not been previously prepared as a single enantiomer. We imagined an attractive approach toward the synthesis of **1** starting with (+)-dicyclopentadienone **2** as part of a retro-Diels-Alder[5] strategy (eq. 1).



1 **2** (eq. 1)

The [4π+2π] cycloreversion reaction, while finding limited application when compared to the forward cycloaddition process, has been incorporated into numerous synthetic sequences.[5,6] The dicyclopentadiene derived substrates have been particularly popular due to the fact that manipulations of the rigid tricyclic core prior to cycloreversion are highly diastereoselective. Thermal[6] and Lewis acid[7] mediated methods have been realized

for ready removal of the covalently bound adjuvant which obviate the need for employing traditional flash vacuum pyrolysis (FVP) techniques.[8] The retro-Diels-Alder route to **1** was, however, undertaken with a certain degree of reservation since within the direct product of the reaction, cyclopentenone **4** (*vide infra*), is incorporated a vinylcyclopropane moiety. It is well known that vinylcyclopropanes suffer rearrangement under thermolytic as well as Lewis acidic conditions.[9]

Preparation of the requisite norbornene derivative **3** necessitated cyclopropanation of (+)-enone **2**, readily available in high optical purity *via* enzyme based technology.[10] Transition metal-catalyzed addition of diazoesters to double bonds is a common means for cyclopropane installation with rhodium(II) being the most effective promoter, particularly in terms of diastereoselectivity.[11] Typically, electron deficient olefins are poor substrates for metal-catalyzed cyclopropanations since the 1,3-dipolar cycloaddition pathway effectively competes.[12] As a result of this undesired reactivity mode in conjunction with an effort to avoid using expensive and toxic metals, an alternative means of cyclopropanation of **2** was utilized.

The preparation of **3** follows from a modification of Payne's sulphur ylid methodology.[4] Thus, exposure of **2** to ethyl (dimethylsulfuranylidene)acetate, formed *in situ*[3] upon reaction of carboethoxymethyl dimethylsulfonium bromide[4] with DBU, afforded tetracycle **3**[13] {$[\alpha]_D^{25}$ +112° (c 1.39, MeOH), >99% ee by HPLC[14]} in 88% yield as a single diastereomer (eq. 2). The desired exo-orientation of the carboethoxy substituent was confirmed by an n.O.e. difference experiment where irradiation of H_A resulted in enhancement of the signals due to H_B and H_C.

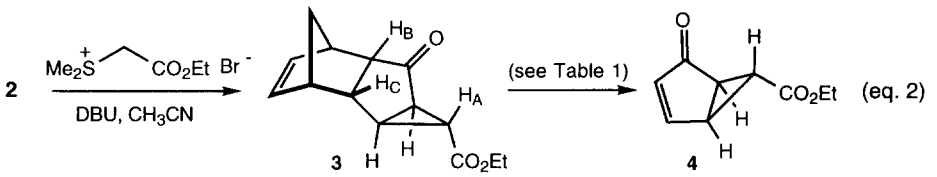


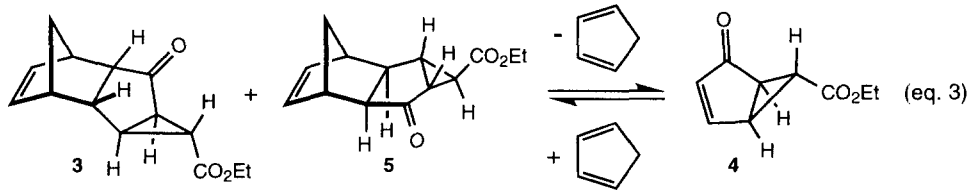
Table 1. Thermolysis of Norbornene **3**.

Entry	Conditions	Time	Chromatographed Yield
1	1,2-dichlorobenzene, reflux, N_2 blanket	23 h	55%
2	1,2-dichlorobenzene, reflux, N_2 purge	25 h	82%
3	DMSO, reflux, N_2 purge	8 h	78%
4	$MeAlCl_2$, maleic anhydride	12 h	-----

Fortunately, thermolytic conversion of **3** to cyclopentenone **4**[13] {mp 96-98 °C, $[\alpha]_D^{25}$ +251° (c 1.12, MeOH), >99% ee by HPLC[14]} (eqn. 2) could be carried out under a variety of conditions (see Table 1) in good yield. Initially the cycloreversion was conducted in refluxing 1,2-dichlorobenzene (bp 180 °C) under a blanket of nitrogen (entry 1) giving rise to **4** in moderate yield. However, the reaction failed to go to completion even upon prolonged heating and after 28 h HPLC analysis[15] revealed the presence of **4** along with remaining **3**

(10%) and an unknown component (33%). The new component was identified as tetracycle **5**,[13] the thermodynamic product of Diels-Alder recapture of cyclopentadiene by **4** (eqn. 3).

To suppress the formation of **5** and concomitantly drive the reaction forward, liberated cyclopentadiene was purged from the reaction mixture and head space by gently bubbling a stream of nitrogen through the heated reaction solution (entry 2) providing **4** in 82% isolated yield. The reaction could be carried out in a more rapid fashion with only a slight decrease in efficiency using dimethylsulfoxide (bp 189 °C) as solvent (entry 3), a medium readily removed by partitioning between methyl *tert*-butylether and water. Unfortunately, **3** remained unchanged upon exposure to methylaluminum dichloride in the presence of the diene scavanger maleic anhydride.[7] Cyclopentenone **4** was converted (10% Pd-C, 1 atm H_2, EtOH) to cyclopentanone **1**[16] in 97% isolated yield.



In summary, the first synthesis of enantiomerically pure bicycle **1** is reported. The preparation employs a retro-Diels-Alder reaction as a key transformation and takes place in three steps to provide **1** in 70% overall yield from optically pure dicyclopentadienone **2**. Conditions allowing for a practical and efficient retro-Diels-Alder reaction are described which should find future application in synthesis.

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13. All isolated compounds displayed ^{1}H NMR, ^{13}C NMR, and IR spectra consistent with their assigned structure. All intermediates have exhibited satisfactory (± 0.4%) elemental analysis.
14. Chiralpak® AD column (4.6 mm X 250 mm) eluting with 30% *n*-PrOH/hexanes at a flow rate of 1 ml/min and UV detection at 220 or 230 nm.
15. Zorbax® SB-Phenyl column (4.6 mm X 250 mm) eluting with 40% acetonitrile/0.1 M sodium phosphate monobasic buffer (pH =2) at a flow rate of 1.5 ml/min with UV detection at 210 nm.
16. mp 63-65 °C; $[\alpha]_D^{25}$ -60° (c 1.34, MeOH); >99% ee by HPLC[14]; Rf 0.49 (hexanes:ethyl acetate/2:1); IR (KBr) 2987 (w), 1722 (s), 1410 (m), 1193 (s), 1009 (m), 827 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.16 (q, 2H, J = 7.1 Hz), 2.52 (q, 1H, J = 4.9 Hz), 2.29-2.22 (m, 2H), 2.17-2.00 (m, 4H), 1.28 (t, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 212.07, 170.80, 61.64, 36.17, 32.30, 29.59, 26.91, 22.87, 14.56. Anal. calcd. for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.10; H, 7.31.

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