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FACILE ENANTIOSELECTIVE SYNTHESIS OF TWO NEW BICYCLIC CHIRAL TEMPLATES

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Abstract: Optically active bicyclic dienes, **4** and **5** have been enantioselectively prepared in three and four steps, respectively. Mixtures of predominantly either the *R* or *S* enantiomer were obtained via an asymmetric alkylation of a chiral enamine.

The bicyclo[4.4.0]octane ring system (decalin) is prevalent in many natural products possessing a variety of biological activities. Perhaps the most common occurrence of this ring system appears as the A and B rings of steroidal compounds, though it is also a part of many other compounds. Functionalized decalin derivatives are also valuable intermediates in the synthesis of many important natural products, e.g., bicyclic enones in the syntheses of Vernolepin[1] and Ambrox®.[2] Thus, new, functionalized chiral decalin derivatives are expected to be useful as chiral templates in the synthesis of novel biologically active compounds, both natural and unnatural.

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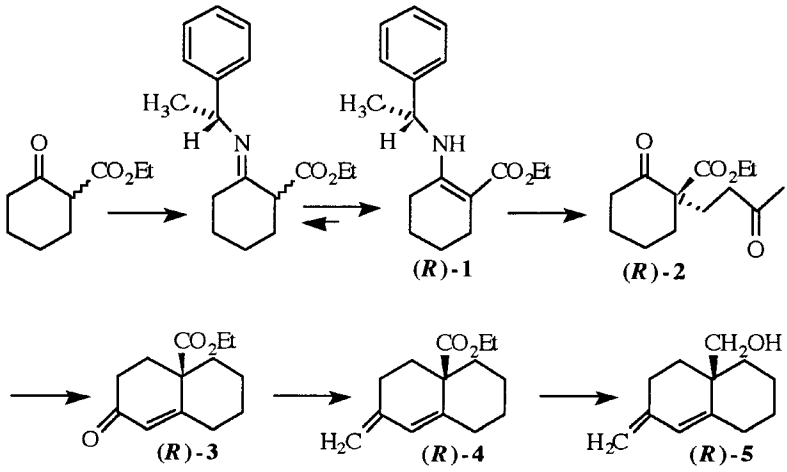
In the present communication, we report a straightforward, efficient enantioselective synthesis of two multifunctionalized bicyclic dienes, (*R*) and (*S*)-ethyl-3,4,5,6,7,8-hexahydro-2-methylene-4a(2H)-naphthalenecarboxylate (**4**) and (*R*) and (*S*)-3,4,5,6,7,8-hexahydro-4a-hydroxymethyl-2(2H)-methylenenaphthalene (**5**), via the asymmetric alkylation of a chiral enamine. Especially attractive is the ease of recovery of the chiral auxiliary for reuse. The reported procedure is efficient and easily scaled up. Furthermore, the strategy reported herein has the advantage in that it is extremely versatile, allowing the synthesis of racemic, predominantly *R* or predominantly *S* bicyclic dienes **4** and **5** from the same methodology. These previously unreported compounds should serve as useful chiral templates for further elaboration such as asymmetric Diels-Alder reactions or epoxidation.



The synthesis of the chiral enamine **1** was accomplished by treatment of ethyl 2-cyclohexanonecarboxylatc with α-methylbenzylamine, followed by refluxing in benzene using a Dean-Stark trap to remove water.[3] One-pot alkylation of the enamine was achieved with 3-buten-2-one. Hydrolysis of the resulting imine with acetic acid afforded the diketoester alkylation product **2**. Depending on which

enantiomer is desired in product **2**, the corresponding enantiomer of α-methylbenzylamine was used. The asymmetric alkylation reaction proceeded enantioselectively, producing a product in 71 - 72% ee, as determined directly by chiral capillary GC on a Macherey-Nagel FS-LIPODEX E® fused-silica column.[4] The use of racemic α-methylbenzylamine resulted in formation of racemate **2**. Treatment of **2** with NaOEt/EtOH effected ring closure to form the bicyclic enone **3** in 65% yield, after purification, from ethyl 2-cyclohexanonecarboxylate. Wittig reaction using methyltriphenylphosphonium bromide converted **3** to the acid labile diene ester **4** in 67% yield. Chiral capillary GC resolutions allowed the direct determination of the enantiomeric excesses for bicyclic esters **3** and **4**. Optical purities and specific rotations are listed in the Table. Obvious from these results is that either enantiomer of α-methylbenzylamine reproducibly directs the alkylation with the same degree of enantioselectivity.

Quantitative regiospecific reduction of the ester functionality in **4** was accomplished using $LiAlH_4$. The hydroxy diene **5** was thus obtained cleanly in 98% yield from **4**. Both new bicyclic dienes, **4** and **5**, were completely characterized spectroscopically (NMR, IR, high resolution MS).

In summary, we have developed a practical enantioselective synthesis of **4** and **5**, two potentially useful chiral synthons, in three and four steps, respectively, from commercially available ethyl 2-cyclohexanonecarboxylate.

EXPERIMENTAL

(*R*)-Ethyl-3,4,5,6,7,8-hexahydro-2-oxo-4a(2H)-naphthalene carboxylate (3) was prepared by first forming the corresponding enamine[3] from 48.47 g of (*R*)-(+)-1-phenylethylamine (0.40 mol), 68.0 g of ethyl 2-cyclohexanone carboxylate (0.40 mol), and 50 mL of benzene by refluxing using a Dean-Stark trap for 24 h. The resulting solution was then cooled to 0 °C and 43.3

Table

Enantiomeric Purities and Optical Rotations of Optically Active Esters.

Compound[a]	% ee by Chiral GC	$[\alpha]_D$ (g/mL, CCl_4)[b]
2(***S***)	72	- 67.6 ° (8.98×10^{-3})
2(***R***)	71	+ 60.5 ° (21.70×10^{-3})
3(***S***)	72	- 157.5 ° (17.66×10^{-3})
3(***R***)	71	+ 157.2 ° (21.07×10^{-3})
4(***S***)	72	- 211.6 ° (21.73×10^{-3})
4(***R***)	71	+ 203.2 ° (20.92×10^{-3})

[a] Tentative assignment of the absolute configuration of the predominant enantiomer is indicated.

[b] Rotations were secured using a JASCO Model DIP-370 polarimeter.

mL of 3-buten-2-one (0.52 mol) was added. This was heated to 40 °C for 24 h. After hydrolysis with aqueous AcOH, the reaction mixture was worked up, resulting in an orange liquid. A small amount of this product (***R***)-**2** was purified by column chromatography for characterization (see Table). Ethanol (30 mL) was then added to the remainder of crude (***R***)-**2**. A 25 wt % NaOEt/EtOH solution was added dropwise at room temperature until a red color developed. The reaction mixture was heated at 60 °C for 10 h then cooled, neutralized with AcOH, and worked up. A red oily material resulted which was distilled under reduced pressure (bp 110 - 140 °C, 0.25 - 0.6 mmHg) to afford 58 g of a colorless liquid (65% yield). A second vacuum fractional distillation provided 53.1 g of colorless liquid (bp 97 - 105 °C, 0.05 mmHg) having a GC purity of 97%. The optical rotation and

% ee data are listed in Table 1. ^{1}H NMR δ 5.92 (s, 1H), 4.22 (q, 2H), 2.42-2.46 (brm, 3H), 2.29-2.38 (brm, 3H), 1.85-1.97 (brm, 2H), 1.72-1.76 (brm, 1H), 1.38-1.51 (brm, 2H), 1.33-1.39 (brm, 1H), 1.28 (t, 3H). GC/MS m/e 222 (M^+).

(*R*)-(+)-Ethyl-3,4,5,6,7,8-hexahydro-2-methylene-4a(2H)-naphthalene carboxylate (4) was prepared by reacting 25 g of **(*R*)-3** (0.112 mol) in 125 mL THF with 80.4 mL of 2.5 M n-BuLi in hexane (0.201 mol) and 66.5 g of methyltriphenylphosphonium bromide in 500 mL THF at 0 °C.[4] The reaction mixture was allowed to stir at room temperature for 17 h. Concentration on a rotovap afforded a brown gummy residue which was extracted repeatedly with hexane. The combined organic extracts were dried over K_2CO_3 and concentrated, affording 20 g of yellow liquid. The first vacuum distillation provided 16.55 g (67% yield) of colorless liquid (bp 63 - 65 °C, 0.07 - 0.10 mmHg). A second vacuum fractional distillation resulted in 14.86 g of product **(*R*)-4** (bp 73 - 77 °C, 0.15 - 0.20 mmHg) with a purity of 98%, determined by capillary GC. ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.03 (s, C=CH, 1H), 4.77 (s, exocyclic =CH, 1H), 4.70 (s, exocyclic =CH, 1H), 4.17 (q, 2H), 2.37-2.09 (br m, 6H), 1.78-1.39 (br m, 6H), 1.25 (t, 3H); high-resolution MS (EI, 70 eV) *m/z* 220.1459 [(M^+); calcd for $C_{14}H_{20}O_2$: 220.1463].

(*R*)-3,4,5,6,7,8-Hexahydro-4a-hydroxymethyl-2(2H)-methylenenaphthalene (5) was prepared by the slow addition of a solution of 10.22 g **(*R*)-4** (46.19 mmol) in 40 mL Et_2O to a stirred suspension of 1.98 g $LiAlH_4$ (52.17 mmol) in 80 mL Et_2O at room temperature. After being stirred at room temperature for 30 min, the mixture was refluxed overnight. The reaction mixture was then decomposed by adding H_2O, stirring for 4 h, and filtering. The residue was washed with Et_2O. The combined ethereal extract was washed dried over Na_2SO_4 and concentrated with a rotovap affording 8.03 g of a white compound that solidified upon refrigeration (98% yield with a GC purity of 98%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.98 (s, =CH, 1H), 4.74 (s, $=CH_2$, 1H), 4.68 (s,

$=CH_2$, 1H), 3.65 (q, OCH_2, 2H), complex absorptions 0.98-2.50 (brm, CH_2, 12H); FT-IR (cm^{-1}) 3358 (OH), 2928, 2856 (C-H), 880 ($=CH_2$); high-resolution MS (EI, 70 eV) *m/z* 178.1350 [(M^+); calcd for $C_{12}H_{18}O$: 178.1358].

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