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Enantioselective Synthesis of Homologous Methyl-Substituted Bicyclic Enones Through Michael-Type Alkylation of Chiral Imines

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ENANTIOSELECTIVE SYNTHESIS OF HOMOLOGOUS METHYL-SUBSTITUTED BICYCLIC ENONES THROUGH MICHAEL-TYPE ALKYLATION OF CHIRAL IMINES

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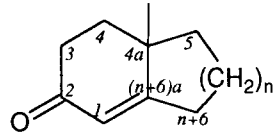
ABSTRACT: The preparation of 4a-methyl-substituted bicyclic enones in high enantiomeric purity is described, involving a Michael alkylation of (*R*)- or (*S*)-1-phenylethyl imines of the corresponding (±)-2-methylcyclopentanone, 2-methylcyclohexanone, 2-methylcycloheptanone, and 2-methylcyclooctanone with methyl vinyl ketone .

Optically pure methyl-substituted bicyclic enones **1** [1] and their microbial hydroxylation products [2-6] may constitute pivotal intermediates in the total synthesis of terpenoids [7-10] and steroids [11,12].



1 (n= 1-4)

The key step in the synthesis of such enones is based on a new type of *"deracemizing alkylation"* of 2-monosubstituted cycloalkanones **2**, first reported by Pfau *et al.* [1].This process involves a Michael-type reaction of a chiral ketimine **3** (*Scheme 1*), reacting under its enamine tautomeric form [13,14], with an electrophilic olefin such as methyl vinyl ketone. An inexpensive auxiliary chiral amine, such as 1-phenylethylamine, commercially available in both enantiomeric forms, has been

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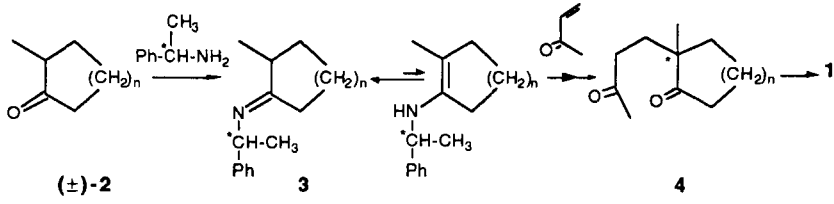
routinely used and can be recovered without optical purity loss. This reaction has been the subject of theoretical studies for its reactivity aspect [15], as well as its enantioselectivity [16]. Since the original examples with 2-methylcyclopentanone (**1**, n= 1) [1] and 2-methylcyclohexanone (**1**, n= 2) [1,17], the reaction has been successfully applied to several other cyclanones [10-12,18-23], including heterocyclic (thio or aza) analogs [24,25], and leading in high yields and high enantiomeric excesses to the corresponding 2,2-disubstituted cyclanones **4**. In a second step, a base-induced cyclization of the enantiomeric diketones **4** gives access to the desired optically active bicyclic enones **1**, bearing a quaternary chiral center.



Scheme 1

We want to report herein a practical extension of this synthesis, using homologous (±)-2-methylcycloalkanones **2** (n = 1-4), in order to compare the yield and enantioselectivity of the process with previously described data, and to obtain new homologous enantiomeric bicyclic enones substrates for microbial hydroxylation studies [3-6].

Using slightly modified experimental conditions compared to those initially described for (±)-2-methylcyclohexanone [1,17] (see a typical procedure in the experimental part), the results obtained in one-pot reactions from commercial or easily prepared homologous (±)-2-methyl-cycloalkanones **2** (n= 1-4) are given in Tables 1 and 2. Commercial 96% ee (*R*) or (*S*)-1-phenylethylamine were used throughout and recovered from the reaction mixtures in about 60% yield, without any loss of optical purity. Enantiomeric excess of the bicyclic enones was determined by chiral HPLC, both on the crude distilled products and after one additional crystallization at low temperature.

Very similar results were obtained in the different steps of the synthesis for n=1 to 4. However, some difficulties were encountered with n=4, particularly in the imine formation and hydrolysis steps. This is probably responsible for the lower yield observed, and the higher recovery of the starting 2-methylcyclo-octanone. An increased amount of a 2,6-dialkylated regioisomer [17] was observed

Table 1: Enantiomeric products obtained from (*S*)-1-phenylethylimines **3**

	1 (crude)			**1** (after crystallization)		Recovered
n	Yield (%)	ee (%)	$[\alpha]_D^{20}$ (EtOH)	ee (%)	$[\alpha]_D^{20}$ (EtOH)	methylketone[a] (%)
1	68[b]	76(R)[c]	– 87 (c 1.06)	94	–113 (c 1.06)	-
2	68[b]	85(R)[d]	–169 (c 0.99)	94	–209 (c 1.02)[e]	-
3	54[b]	80(R)	–146 (c 1.09)	92	–162 (c 1.22)	3
4	44[f]	76(R)	–185 (c 1.05)	99	–232 (c 1.14)	14

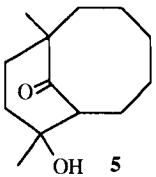
[a] from the distillation head-fractions. [b] after distillation (≥95% pure). [c] reported [1]: 90% ee $[\alpha]_D^{20}$ –108 (c 3.5, EtOH). [d] reported [1,17]: 91% ee. [e] lit. –207 (c 1, EtOH) [26], –216 (c 0.321, MeOH) [9],–219 (c 1, EtOH) [17]. [f] after distillation (86% pure).

Table 2: Enantiomeric products obtained from (*R*)-1-phenylethylimines **3**

	1 (crude)			**1** (after crystallization)		Recovered
n	Yield (%)	ee (%)	$[\alpha]_D^{20}$ (EtOH)	ee (%)	$[\alpha]_D^{20}$ (EtOH)	methylketone[a] (%)
1	57[b]	76(S)	+ 85 (c 0.95)	94	+111 (c 1.04)	-
2	69[b]	85(S)	+168 (c 1.08)	95	+214 (c 1.03)[c]	-
3	64[b]	80(S)	+140 (c 1.13)	92	+166 (c 1.06)	7
4	46[d]	76(S)	+188 (c 1)	99	+229 (c 1.01)	19

[a] from the distillation head-fractions. [b] after distillation (≥95% pure). [c] lit. +208.3 (c 1, EtOH) [26], +219 (c 0.1, MeOH) [27], +198 (c 0.8, EtOH) [28]. [d] after distillation (83% pure).

by GC in the alkylation reaction with higher n values (10% for n=3, 13% for n=4), but this by-product did not affect the final purity of the corresponding distilled (and crystallized) enones. On the other hand, the cyclization of the 2,2-dialkylated cyclooctanone was more difficult, necessitating higher heating, in more alkaline conditions. In that case, one observed a small amount of different cyclization products and derivatives, which could be assigned to an alternative aldolisation process, leading to a putative initial structure of a bicyclo[5.3.1] compound **5**. This is not unexpected, since such cyclized compounds [11,12] have already been observed. It has also been noted that an extension of the cycloalkanone ring do favour such a cyclization mode [14].



5

With 1-phenylethylamine of 96% e.e., the enantiomeric purity of the crude enones was in the 75-85% range and did not justify the use of a more purified chiral auxiliary. A single crystallization at low temperature allowed in all cases to reach a 95-99% enantiomeric excess.

Experimental

General. (±)-2-methylcyclopentanone, 2-methylcyclohexanone, cyclohexanone, and cycloheptanone were purchased from Aldrich. 2-Carbethoxy-cycloheptanone and 2-carbethoxycyclooctanone were obtained by diazoacetate homologation of cyclohexanone and cycloheptanone respectively, in the presence[29,30] of BF_3-etherate. (±)-2-methylcycloheptanone (b.p 92-96°C/34 mm Hg), and (±)-2-methylcyclooctanone (104-106°C/30 mm Hg) were prepared by alkylation of the corresponding 2-carbethoxycycloalkanones with ICH_3/NaOH in ethanol solution, followed by alkaline hydrolysis and decarboxylation. Methyl vinyl ketone (Aldrich) was dried upon K_2CO_3, distilled under nitrogen, and collected on a few crystals of hydroquinone. *(R)-* and *(S)*-phenylethylamine (96% ee) were purchased from Fluka.

General procedure for the final crystallization of enones. Oily distilled bicyclic enones were dissolved at room temperature under magnetic stirring in a 50-100 ml round-bottomed flask with a 10-25 mL volume of solvent (pentane or heptane). After dissolving, the flask was immersed in liquid nitrogen until total solidification, then removed from the cold bath and left at room temperature, under magnetic stirring, until only a few crystals remain. At that time, the flask was immersed in an acetone cold bath which was slowly brought to –10 to –50°C by dry ice addition, and left 15 min at this temperature, inducing crystallization. Magnetic stirring was stopped and the supernatant cautiously removed with the assistance of a glass stick. Still in the cold, the crystals were washed by stirring 5 min with a small amount of cold solvent (1-3 mL), then filtered again. The washing operation was repeated 2-3 more times. Crystals (or the resulting oil at room temperature) were dried *in vacuo* (1 mm Hg). Specific details are given below for each one of the prepared enones.

(R)- and (S)-4,4a,5,6-tetrahydro-4a-methyl-2(3H)-indenone (= 1,2-dehydro-3-oxo-6-methyl-bicyclo[4.3.0]nonane) (**1**, n= 1) were prepared from 2-methyl cyclopentanone-phenylethylimines as described for n= 2 [1,17] (b.p.110-120° C / 10 mm Hg). From a distilled oily enone (96-97% pure by GC, 76% ee by HPLC on a Chiralpak AD column, solvent: heptane-iPrOH, 99:1), a 99% pure sample (20-25% yield) of each enantiomer (94% ee) was obtained by a single crystallization in

heptane (12-13.5 g in 25 mL of heptane) at – 48° C. The remaining enone (95 % pure, about 65% ee) was recovered from the mother liquors. ^{1}H-NMR (250 MHz, $CDCl_3$), δ ppm, J Hz: 5.76 (1H, t, J= 2.2, H-1), 2.68 (1H, ddm, J= 18 and 9, H-7β), 2.54 (1H, ddd, J= 18, 14.5 and 5, H-3ax), 2.40 (1H, m, H-7α), 2.31 (1H, dddd, J= 18, 5.2, 2.2 and 1, H-3eq), 1.98 (1H, ddd, J= 13.2, 5.4 and 2.2, H-4eq), 1.7-1.9 (4H, m, H-4ax, H-5β, H-6α and H-6β), 1.45 (dt, J= 8 and 11.5, H-5α), 1.14 (3H, s, CH_3-4a). ^{13}C-NMR (62.9 MHz, $CDCl_3$), δ ppm: 199.43 (CO), 178.51 (C-7a), 121.16 (CH-1), 42.59 (C-4a), 40.73, 35.96, 33.69, 30.63, and 21.05 (5 CH_2), 22.28 (CH_3). MS (EI), m/z (relative abundance): 150(35) $[M]^+$, 135(5) $[M-CH_3]^+$, 122(100) $[M-CO]^+$, 108(45), 93(20), 79(31). HRMS (EI): calc. for $C_{10}H_{14}O$, 150.1045; found, 150.1056.

(R)- and (S)-4,4a,5,6,7,8-hexahydro-4a-methyl-2(3H)-naphthalenone (= 1,2-dehydro-3-oxo-6-methyl-bicyclo[4.4.0]decane) (**1**, n= 2) were prepared from 2-methylcyclohexanone-phenylethylimines as previously described [1,17] (b.p. 140-146° C / 14 mm Hg). From a distilled oily enone (94-95% pure by GC, 70-85% ee by HPLC on a Chiralpak AD column, solvent: heptane-iPrOH, 98:2), a 99% pure sample (60-63% yield) of each enantiomer (95% ee) was obtained by a single crystallization (14 g in 25 mL of pentane) at – 35° C. The remaining enone (87 % pure, 52% ee) was recovered from the mother liquors. ^{1}H-NMR (250 MHz, $CDCl_3$), δ ppm, J Hz: 5,75 (1H, br.s, H-1), 2.50 (1H, ddd, J= 17, 14.5 and 5, H-3ax), 2.30 (1H, ddd, J= 17, 4 and 3, H-3eq), 2.2-2.4 (2H, m, H-8), 1.35-1.9 (8H, m, CH_2), 1.23 (3H, s, CH_3). ^{13}C-NMR (62.9 MHz, $CDCl_3$) δ ppm: 199.42 (CO), 170.43 (C-8a), 124.05 (C-1), 35.88 (C-4a), 41.50, 37.99, 33.94, 32.72, 27.13, and 21.71 (6 CH_2), 22.01 (CH_3).MS (EI), m/z (relative abundance): 164(88) $[M]^+$, 149(16) $[M-CH_3]^+$, 136(80) $[M-CO]^+$, 122(100), 107(59), 93(36), 79(46). HRMS (EI): calc. for $C_{11}H_{16}O$, 164.1202; found, 164.1204.

(S)-1,11-dehydro-10-oxo-7-methyl-bicyclo[5.4.0]undecane (**1**, n= 3). *(R)*-1-phenylethylamine (9.62 g, 0.079 mol) and (±)-2-methylcycloheptanone (10 g, 0.079 mol) in toluene (10 mL) were refluxed with continuous azeotropic removal of water during 24 h under a nitrogen atmosphere (GC indicated 95% formation of the imine). The reaction mixture was cooled in an ice-bath, and methyl vinyl ketone (6.8 mL, 0.084 mol) was added with a syringe under a nitrogen atmosphere. The mixture was heated at 40° C during 26 h. After cooling in an ice-bath, acetic acid (6.35 mL, 0.111 mol) and water (5 mL) were added and the mixture was hydrolyzed at room temperature under nitrogen during 26 h. Water (16 mL) and water saturated with NaCl (10 mL) were added and the mixture was thoroughly extracted with ether. After washing with diluted HCl and brine, the combined ethereal extracts were dried on Na_2SO_4, then evaporated *in vacuo* to give 16.3 g of oily disubstituted ketone. An analytical pure sample of *(S)*-2-methyl-2-(3'-oxobutyl)cycloheptanone was obtained by flash chromatography (cyclohexane-EtOAc, 9:1). ^{1}H-NMR (250 MHz, $CDCl_3$), δ ppm, J Hz: 2.66 (1H, dt, J= 11.3 and 2.0, H-7a), 2.35 (1H, ddd, J= 11.3, 9.2, and 6.2, H-7b), 2.20-2.45 (2H, m,

H-2'), 2.10 (3H, s, 4'-CH_3), 1.20-1.90 (10H, m, CH_2), 0.99 (3H, s, 2-CH_3). ^{13}C-NMR (62.9 MHz, $CDCl_3$) δ ppm: 217.19 and 208.17 (2CO), 50.07 (C-2), 40.24, 38.47, 38.32, 33.09, 30.56, 26.56, 24.45 (7 CH_2), 29.97 (4'-CH_3), 21.16 (2-CH_3). MS (EI): 196(2) $[M]^+$, 178(4) $[M-H_2O]^+$, 168(6) $[M-CO]^+$, 153(9), 139(24), 126(76), 110(100), 95(73), 81(49), 69(82).

The crude oil precedently obtained was dissolved in methanol (60 mL) and 25% NaOMe in methanol (25 mL) was added under nitrogen. After stirring at 60° C during 48 h, the mixture was cooled in an ice-bath, and acetic acid (30 mL) was slowly added. The mixture was concentrated by evaporation *in vacuo*, then water (30 mL) was added. Extraction with ether afforded, after usual work-up, a brown oily residue (15.9 g) which was distilled to give 0.66 g of cycloheptanone (7%), b.p. 46-50° C/ 4 mm Hg, then 8.96 g of (*S*)-enone (64%), b.p. 128° C/ 4 mm Hg (96% pure by GC). The distilled oily enone (80% ee by HPLC on a Chiralpak AD column, solvent: heptane-iPrOH, 98:2), was submitted to a single crystallization in pentane (25 mL) at -50° C to give a 99% pure sample (38% yield, 92% ee). The remaining enone (95 % pure, 76% ee) was recovered from the mother liquors. ^{1}H-NMR (250 MHz, $CDCl_3$), δ ppm, J Hz: 5.81 (1H, s, H-1), 2.55 (1H, ddd, J= 17.5, 14.3, and 5.5, H-3ax), 2.37 (1H, ddd, J= 17.5, 5.5, and 2.5, H-3eq), 2.25 (1H, dm, H-9), 1.20-2.20 (11H, m, CH_2), 1.15 (3H, s, CH_3). ^{13}C-NMR (62.9 MHz, $CDCl_3$) δ ppm: 199.36 (CO), 174.96 (C-9a), 127.42 (CH-1), 38.98 (C-4a), 41.15, 35.56, 34.14, 33.89, 30.84, 30.66, 25.51 (7CH_2), 25.69 (CH_3). MS (EI): 178(91) $[M]^+$, 163(17) $[M-CH_3]^+$, 150(29) $[M-CO]^+$, 136(100), 121(71), 107 (41), 93(42), 79(46). HRMS (EI): calc.for $C_{12}H_{18}O$, 178.1358; found, 178.1348. The *(R)*-enantiomer was similarly obtained from *(S)*-1-phenyl-ethylamine.

(R)- and (S)-1,12-dehydro-11-oxo-8-methyl-bicyclo[6.4.0]dodecane (**1**, n = 4). 2-Methylcyclooctanone-phenylethylimines were formed in only 80-85% yield (GC determination) after 72 h refluxing 2-methylcyclooctanone with the respective *(R)*- or *(S)*-phenylethylamine in toluene. *(R)*- or *(S)*-2-methyl-2-(3'-oxobutyl) cyclooctanone were obtained after reaction of the imine with methyl vinyl ketone during 31 h, then hydrolysis with acetic acid at 80° C during 72 h. Analytical samples were obtained by flash chromatography (cyclohexane-EtOAc, 9:1). ^{1}H-NMR (250 MHz, $CDCl_3$), δ ppm, J Hz: 2.67 (1H, dt, J= 10.8 and 3.6, H-8a), 2.37 (1H, ddd, J= 17.8, 10.5, and 5.6, H-8b), 2.10 (3H, s, 4'-CH_3), 0.8-2.5 (14H, CH_2), 0.98 (3H, s, 2-CH_3). ^{13}C-NMR (62.9 MHz, $CDCl_3$) δ ppm: 220.27 and 207.99 (2CO), 49.33 (C-2), 38.39, 36.71, 34.90, 31.71, 30.33, 25.95, 24.84, 24.30 (8 CH_2), 29.95 (4'-CH_3), 18.53 (2-CH_3). MS (EI): 210(4) $[M]^+$, 192(8) $[M-H_2O]^+$, 182(7) $[M-CO]^+$, 167(5), 153(15), 135(22), 124(83), 109(37), 95(68), 81(52), 55(100).

The crude enantiomeric 2,2-disubstituted ketones were cyclized in the presence of 3M KOH in ethanol during 22 h at 110° C and distilled to give the enone (b.p.96° C/ 0.05 mm Hg), 83-86% pure by GC, 76% ee by HPLC on a Chiralpak AD column, solvent: hexane-iPrOH, 98:2. A 96% pure sample (35-37% yield) of

each enantiomer (99% ee) was obtained by a single crystallization (2.7-2.8 g in 10 mL of pentane) at – 10° C. M.p. 58° C. The remaining enone (about 80% pure, 56% ee) was recovered from the mother liquors. ^{1}H-NMR (250 MHz, $CDCl_3$), δ ppm, J Hz: 5.84 (1H, s, H-1), 2.57 (1H, ddd, J= 17.2, 14.6, and 5.1, H-3ax), 2.38 (1H, ddd, J= 17.2, 4.9, and 2.9, H-3eq), 1.20-2.32 (14H, m, CH_2), 1.11 (3H, s, CH_3). ^{13}C-NMR (62.9 MHz, $CDCl_3$) δ ppm: 198.67 (CO), 176.39 (C-10a), 126.60 (CH-1), 37.76 (C-4a), 35.21, 33.75, 32.38, 32.13, 31.41, 26.14, 24.79, 24.11 (8 CH_2), 26.41 (CH_3). MS (EI): 192(100) $[M]^+$, 177(10) $[M-CH_3]^+$, 164(16) $[M-CO]^+$, 150(55), 135(53), 122(42), 107(50), 93(39), 79(50). HRMS (EI): calc. for $C_{13}H_{20}O$, 192.1515; found, 192.1521.

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