Synthesis of 2,3-Disubstituted 5,6,7,8-Tetrahydronaphthyls and Related Structures via Diels–Alder Reaction

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This paper is dedicated to Daniel Bellus on the occasion of his 65th birthday.

Abstract: A variety of 2,3-disubstituted 5,6,7,8-tetrahydronaphthyl analogues have been synthesized via vinylation of cyclic ketones, subsequent lactonisation and thermally induced, inverse electron demand hetero Diels–Alder reaction. The diversity of the obtained products derives from the multiplicity of cyclic ketones and from the variety of dienophiles of the Diels–Alder reaction.

Key words: condensation, ketones, lactones, bicyclic compounds, Diels–Alder reaction

Imidazolines have been proven to act as insulin secretagogues in a glucose dependent manner,1 which is potentially interesting for the treatment of type II diabetes. With imidazoline 1 being identified as an interesting structure,1 we were looking for synthetic approaches for modification of its precursor 2 in order to synthesize analogues of 1. It was envisioned that tetrahydronaphthyl platform 2 could be modified regarding ring size and substitution pattern of the saturated ring (Scheme 1). The targeted synthesis should thus provide access to various ring sizes and substitution patterns of the saturated ring, allow for facile introduction of the side chain, and enable ready access to various imidazolines. The latter would be achieved by introduction of an ester group at this position as in 2 that could be transformed into imidazolines according to known procedures.1

Scheme 1  Synthetic objective

A two step procedure consisting of a condensation of a cyclic ketone 3 with methoxymethylene dimethyl malonate (4) followed by an intermolecular Diels–Alder reaction of the resulting pyrone 6 and a ketene acetal enabled us to meet these objectives (Scheme 2).2 Mechanistically, the enolate of cyclic ketone 3 displaces the terminal methoxy group of methoxymethylene dimethyl malonate (4) via addition and elimination. In a second reaction step, the resulting product 5 forms pyrone 6 via lactonisation. The thermally induced Diels–Alder reaction (of 6 with ketene acetals) under inverse electron demand led to a primary unstable adduct 7, which could not be isolated, but rapidly eliminated carbon dioxide and alcohol to afford aromatic compound 8.

In order to synthesize a variety of pyrones, we condensed different commercially available cyclic ketones with methoxymethylene dimethyl malonate (4) in the presence of lithium di-isopropyl amide (LDA) between −50 °C and room temperature. A list of six cyclic ketones, the resulting pyrones, and yields can be seen in Table 1.

Scheme 2  General scheme
The condensation of cyclic ketones 8, 12 and 14 proceeded smoothly towards pyrones 9, 13 and 15 with LDA (1.2 equiv) in tetrahydrofuran within 10 hours, while other condensation reactions gave predominantly the primary 1,4-addition–elimination products analogous to compound 5 under these conditions. In the case of ketones 10 and 16, additional heating to 150 °C in dimethyl formamide of the predominantly formed primary 1,4-addition–elimination products was found to be optimal to achieve higher yields of lactonisation. In order to obtain heterocyclic analog 19, heating of the primary 1,4-addition–elimination product in toluene in the presence of p-toluenesulfonic acid for 4 hours was beneficial.3

In initial attempts to introduce a small set of side chains we used ketene acetals 204 and 235 for the thermally induced Diels–Alder reactions (Scheme 3). Tetrahydronaphthyl derivative 21 was synthesized in 35% yield by heating pyrone 226 and 2.5 equivalents 1,1-bisethoxyethene 20 in xylene to 145 °C for 8 hours. Pyrone 22 underwent Diels–Alder reaction with ketene acetal 23 (2.5 equiv) in refluxing xylene to afford 24 in 26% yield. Note that in this case the alcohol eliminating from the intermediate analogous to structure 7 remains in the side chain of bis-substituted tetrahydronaphthyl derivative 24, suitable for further elaboration.

We found compounds having the ethoxy methoxy side chain as in 2 particularly interesting. Although cleavage of an ethoxy group as in 21 and subsequent alkylation of the resulting phenol could have given access to the desired side chain, we preferred introducing the side chain via Diels–Alder reaction, thus saving two steps. To introduce this side chain via a ketene acetal serving as a dienophile in a Diels–Alder reaction, bromoacetaldehyde diethyl acetal (25) was treated with 2-methoxyethanol to form acetal 26 (Scheme 3). Elimination of HBr from acetal 26 required the presence of tetrabutylammonium bromide7 to form ketene acetal 27.

Table 1 Cyclic Ketones and Condensation Products (Pyrones)

<table>
<thead>
<tr>
<th>Ketone</th>
<th>Pyrone</th>
<th>Yield (%)</th>
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<tbody>
<tr>
<td></td>
<td>8</td>
<td>56</td>
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<tr>
<td></td>
<td>10</td>
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</tr>
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<td></td>
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<td>49</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>50</td>
</tr>
</tbody>
</table>

Scheme 3  Diels–Alder reaction and synthesis of ketene acetal 27
The Diels–Alder reaction generally proceeded in refluxing xylene within 8 hours in the presence of the ketene acetal (2.5 equiv). In order to optimize the reaction conditions, the purity of the ketene acetal had a great influence. Diels–Alder reactions with ketene acetal worked best when the ketene acetal was purified via distillation. Afterwards it could be stored at −20 °C for weeks. It solidified under these conditions. With the purified ketene acetal, satisfactory yields in the Diels–Alder reaction could be achieved as summarized in Scheme 4.

Even though the overall yield over two steps is moderate, we found this route to be the method of choice since starting materials are readily available, and the route is convenient and flexible, allowing straightforward modification of ring sizes and substitution patterns of the saturated ring and side chain of 2,3-disubstituted 5,6,7,8-tetrahydronaphthyl analogues.

All reagents were obtained either from Aldrich Chemical Co. or from Fisher Scientific Co. and used without further purification. 
1H NMR spectra were recorded on a Bruker 300 MHz or on a 500 MHz using CDCl₃ as solvent and residual CHCl₃ as reference. For mass spectroscopy the electrospray ionisation (ESI) spectra were obtained from a Perkin–Elmer Sciex API 150 MCA, and for electron impact (EI) a Finnegan SSQ 700 solid probe was used at 70 eV (positive charge).

Condensation of Cyclic Ketones with 2-Methoxymethylene Dimethyl Malonate

To a solution of freshly prepared LDA (1.2 equiv) in THF (2 mL/mmol) was added at −50 °C the cyclic ketone (1.0 equiv) in THF (1 mL/mmol). The solution was warmed to −30 °C within 1.5 h, treated with 2-methoxymethylene dimethyl malonate (1.2 equiv), and warmed to r.t. within 10 h. The mixture was poured into aq HCl (5%; 10 mL/mmol) and extracted with tert-butyl methyl ether (10 mL/mmol). After removal of the solvent, the product was either re-crystallized or purified by column chromatography (silica gel).

Methyl 8-Methyl-2-oxo-2,5,6,7,8-pentahydro-2H-benzo[b]pyran-3-ylcarboxylate (9)

From 2-methylcyclohexanone (3.0 g, 26.5 mmol); purified by re-crystallization from tert-butylmethyl ether. Yield: 3.30 g (56%).

1H NMR (500 MHz, CDCl₃): δ = 1.25 (d, J = 7.0 Hz), 1.45–1.55 (m, 1 H), 1.60–1.65 (m, 1 H), 1.70–1.75 (m, 1 H), 1.80–1.95 (m, 1 H), 2.35–2.45 (m, 2 H), 2.65–2.75 (m, 1 H), 3.85 (s, 3 H), 7.95 (s, 1 H).

13C NMR (75.7 MHz, CDCl₃): δ = 18.8 (CH₃), 19.9 (CH₃), 26.1 (CH₂), 30.2 (CH₃), 33.0 (CH₂), 52.9 (CH₃), 112.9 (C), 114.4 (C), 152.6 (CH), 158.9 (C), 164.7 (C), 169.8 (C).

MS: m/z (%) = 222 (60) [M⁺], 191 (20), 179 (50), 162 (36), 135 (100).

HRMS: m/z calcd for C₁₉H₁₈O₄ [M + H⁺]: 223.0970; found: 223.0967.

Methyl 2-Oxo-2,5,6,7-tetrahydrocyclopenta[b]pyran-3-ylcarboxylate (11)

From cyclopentanone (1.00 g, 11.89 mmol). After aqueous workup the primary condensation product was dissolved in DMF and heated to 150 °C for 2 h. Afterwards the solvent was removed in vacuo and the remaining oil was purified via chromatography (silica gel; EtOAc–hexane).

Yield: 0.78 g (34%).

1H NMR (500 MHz, CDCl₃): δ = 2.10–2.15 (m, 2 H), 2.70–2.75 (m, 2 H), 2.80–2.85 (m, 2 H), 3.85 (s, 3 H, 1 H).

13C NMR (75.7 MHz, CDCl₃): δ = 26.0 (CH₂), 32.2 (CH₂), 33.9 (CH₂), 52.1 (CH₂), 119.1 (C), 127.4 (CH), 136.8 (C), 151.0 (C), 158.2 (C), 167.4 (C).

MS: m/z (%) = 194 (90) [M⁺], 162 (92), 134 (100), 106 (53), 79 (46), 59 (23).

HRMS: m/z calcd for C₁₀H₁₀O₄ [M + Na⁺]: 217.0477; found: 217.0471.

Methyl 2-Oxo-2,5,6,7,8,9-hexahydrocyclohepta[b]pyran-3-ylcarboxylate (13)

From cycloheptanone (1.10 g, 4.95 mmol); purification via chromatography (silica gel; EtOAc–hexane).

Yield: 0.85 g (62%).

1H NMR (500 MHz, CDCl₃): δ = 1.25–1.95 (m, 6 H), 2.50–2.55 (m, 2 H, 2.80–2.85 (m, 2 H), 3.85 (s, 3 H), 1.85 (s, 1 H).

13C NMR (75.7 MHz, CDCl₃): δ = 24.9 (CH₂), 27.1 (CH₂), 31.5 (CH₂), 31.8 (CH₂), 35.2 (CH₂), 52.9 (CH₂), 112.8 (C), 118.5 (C), 154.3 (CH), 158.9 (C), 164.9 (C), 172.5 (C).

MS: m/z (%) = 222 (70) [M⁺], 194 (88), 152 (33), 135 (100).

HRMS: m/z calcd for C₁₂H₁₄O₄ [M + H⁺]: 223.0966; found: 223.0966.

Anal. Calcd for C₁₂H₁₄O₄: C, 64.85; H, 6.35. Found: C, 64.70; H, 6.39.

**Scheme 4**

Diels–Alder reaction and products
Methyl 2-Oxo-2,5,6,7,8,9,10-heptahydrocycloocta[b]pyran-3-ylcarboxylate (15)
From cyclooctanone (0.69 g, 5.45 mmol); purification via chromatography (silica gel; EtOAc–hexane).
Yield: 0.74 g (57%).

1H NMR (500 MHz, CDCl3): δ = 1.25–1.90 (m, 8 H), 2.45–2.50 (m, 2 H), 2.60–2.65 (m, 2 H), 3.85 (s, 3 H), 8.00 (s, 1 H).

13C NMR (125 MHz, CDCl3): δ = 15.2 (CH3), 28.3 (CH2), 39.9 (CH2), 42.6 (CH2), 53.1 (CH2), 62.5 (CH2), 110.7 (C), 115.4 (C), 148.8 (CH15), 155.5 (C), 157.8 (C), 164.2 (C), 177.4 (C).

MS: m/z (%) = 234 (12) [M+], 203 (100), 145 (35).


Yield: 128.5 g (98%); colorless oil.

1H NMR (300 MHz, CDCl3): δ = 3.40 (s, 6 H), 3.43 (d, J = 8.0 Hz, 2 H), 3.55–3.85 (m, 8 H), 4.83 (t, J = 8.0 Hz, 1 H).

13C NMR (75.7 MHz, CDCl3): δ = 31.7 (CH2), 59.3 (CH2), 66.0 (CH2), 72.1 (CH2), 102.2 (CH).

MS: m/z (%) = 181 (14) [M – O(CH2)2OCH3]+, 163 (14), 59 (100).


1,1-Bis-(2-methoxyethoxy)ethene (27)
A solution of 2-bromo-1,1-bis-(2-methoxyethoxy)ethane (50 g, 0.18 mol) in xylene (50 mL) was treated with tetrabutylammonium tert-butoxide (24.2 g, 216 mmol) added in six equal portions over 30 minutes at r.t. The slurry was heated to 110 °C for 3 h, cooled to r.t., and filtered. The solvent was removed from reduced pressure, and the remaining red oil was distilled in vacuo to afford the title acetate.
Yield: 16.2 g (51%); colorless oil that solidified at −20 °C; bp 75 °C (9 mmbar).

1H NMR (300 MHz, CDCl3): δ = 3.20 (s, 2 H), 3.40 (s, 6 H), 3.60–3.70 (m, 4 H), 3.85–3.90 (m, 2 H).

13C NMR (75.7 MHz, CDCl3): δ = 57.3 (CH2), 59.4 (CH2), 67.7 (CH2), 70.9 (CH2), 165.2 (CH).

MS: m/z (%) = 177 (20) [MH]+, 59 (100).

HRMS: m/z calcd for C10H10O4 [M + H]+: 177.1127; found: 177.1118.


Diels–Alder Reaction; General Preparation B
A solution of pyrone (1.0 equiv) with ketene acetal (2.5 equiv) in xylene (2 mL/mmol pyrone) was refluxed for 8 h. After removal of the solvent in vacuo the remaining oil was purified via chromatography (silica gel; with EtOAc–hexane).

Methyl 3-Ethoxy-5,6,7,8-tetrahydrophthaloyl-3,1-oxo-2,3-dihydrophthaloyl-2-yl-carboxylate (21)
From methyl 8-ethoxy-2-oxo-2,5,6,7,8-pentahydro-2H-benzo[b]pyran-3-ylcarboxylate (2.0 g, 5.4 mmol) and 1,1-bismethoxyethane (2.99 g, 13.5 mmol); purified by chromatography (silica gel; with EtOAc–hexane).
Yield: 444 mg (35%).

1H NMR (300 MHz, CDCl3): δ = 1.35 (t, J = 8.0 Hz, 3 H); 2.70–2.75 (m, 2 H); 3.75–3.80 (m, 2 H); 3.95 (s, 3 H); 4.20 (q, J = 8.0 Hz, 2 H); 4.35–4.40 (m, 2 H); 8.05 (s, 1 H).

13C NMR (125 MHz, CDCl3): δ = 15.0 (CH3), 28.3 (CH3), 39.9 (CH2), 42.6 (CH2), 53.1 (CH2), 62.5 (CH2), 110.7 (C), 115.4 (C), 148.8 (CH15), 155.5 (C), 157.8 (C), 164.2 (C), 177.4 (C).

MS: m/z (%) = 281 (12) [M]+, 252 (100), 149 (35).


2-Bromo-1,1-bis-(2-methoxyethoxy)ethane (26)
A solution of 2-bromoacetaldehyde methyl acetal (100 g, 0.51 mol) and 2-methoxyethanol (200 g, 2.62 mol) in a distillation apparatus was treated with p-toluensulfonic acid (550 mg, 2.76 mmol). The reaction mixture was heated to 150 °C. Within 4 h EtOH (41.6 g, 0.91 mol) distilled off at r.t. The remaining solvents were removed in vacuo (14 mbar, 70 °C). The resulting 2-bromoacetaldehyde bis-(2-methoxyethoxy) acetal (26) was dissolved in anhyd toluene (200 mL) and vigorously stirred with NaHCO3 (585 mg, 5.5 mmol). The suspension was filtered and the filtrate concentrated under reduced pressure to afford 2-bromo-1,1-bis-(2-methoxyethoxy)ethane.

Yield: 128.5 g (98%); colorless oil.

1H NMR (300 MHz, CDCl3): δ = 3.40 (s, 6 H), 3.43 (d, J = 8.0 Hz, 2 H), 3.55–3.85 (m, 8 H), 4.83 (t, J = 8.0 Hz, 1 H).

13C NMR (75.7 MHz, CDCl3): δ = 31.7 (CH2), 59.3 (CH2), 66.0 (CH2), 72.1 (CH2), 102.2 (CH).

MS: m/z (%) = 181 (14) [M – O(CH2)2OCH3]+, 163 (14), 59 (100).


2-Bromo-1,1-bis-(2-methoxyethoxy)ethane (26)
From methyl 2-oxo-2,5,6,7,8-pentahydro-2H-benzo[b]pyran-3-ylcarboxylate (1.20 g, 5.4 mmol) and 1,1-bismethoxyethane (2.99 g, 13.5 mmol); purified by chromatography (silica gel; with EtOAc–hexane).

Yield: 444 mg (35%).

1H NMR (300 MHz, CDCl3): δ = 1.28 (d, J = 8.0 Hz, 3 H), 1.65–1.78 (m, 4 H), 2.58–2.72 (m, 4 H), 3.83 (s, 3 H), 3.98 (q, J = 8.0 Hz, 2 H), 6.59 (s, 1 H), 7.48 (s, 1 H).

13C NMR (75.7 MHz, CDCl3): δ = 15.2 (CH3), 23.2 (CH3), 23.6 (CH3), 28.7 (CH3), 30.3 (CH3), 52.1 (CH3), 65.2 (CH2), 114.5 (CH), 118.2 (C), 129.4 (C), 132.6 (CH), 143.6 (C), 156.8 (C), 167.3 (C).

MS: m/z (%) = 234 (36) [M]+, 203 (12), 187 (28), 174 (100).

Yield: 1.18 g (54%).

1H NMR (500 MHz, CDC13): δ = 1.70–1.80 (m, 4 H), 2.65–2.80 (m, 4 H), 3.80–3.90 (m, 5 H), 4.18–4.23 (m, 2 H), 6.70 (s, 1 H), 7.53 (s, 1 H).

13C NMR (75.7 MHz, CDC13): δ = 21.7 (CH), 22.1 (CH), 27.4 (CH2), 28.8 (CH2), 51.0 (CH), 60.0 (CH2), 71.3 (CH), 115.3 (C), 117.0 (CH), 129.3 (C), 131.2 (CH2), 142.9 (C), 155.9 (C), 165.8 (C).

MS: m/z (%) = 250 (23) [M+], 174 (100).

HRMS: m/z calc for C16H22O4 [M + Na+] = 301.1416; found: 315.1566.

Methyl 2-(2-Methoxyethoxy)-5-methyl-5,6,7,8-tetrahydro-2-oxo-2,5,6,7,8-pentahydro-2H-benzo[b]pyran-3-ylcarboxylate (31)

From methyl 2-(2-methoxyethoxy)-5-methyl-5,6,7,8-tetrahydro-2H-benzo[b]pyran-3-ylcarboxylate (1.20 g, 5.4 mmol) and 1,1-bis-(2-methoxyethoxy)ethene (2.99 g, 13.5 mmol); purification via chromatography (silica gel; EtOAc–hexane).

Yield: 974 mg (62%).

1H NMR (500 MHz, CDC13): δ = 1.35–1.40 (m, 4 H), 1.60–1.75 (m, 4 H), 2.65–2.80 (m, 4 H), 3.80–3.85 (m, 2 H), 3.90 (s, 3 H), 4.20–4.25 (m, 2 H), 6.80 (s, 1 H), 7.55 (s, 1 H).

13C NMR (75.7 MHz, CDC13): δ = 26.1 (CH2), 26.3 (CH2), 31.8 (CH), 32.4 (CH2), 36.2 (CH2), 33.0 (CH), 52.1 (CH), 59.8 (CH2), 69.6 (CH), 71.5 (CH2), 115.4 (CH), 118.7 (C), 132.7 (CH), 133.4 (C), 148.0 (C), 157.5 (C), 167.2 (C).

MS: m/z (%) = 292 (10) [M+], 234 (10), 202 (100), 91 (18), 59 (88).

HRMS: m/z calc for C17H22O6 [M + H+] = 323.1494; found: 323.1490.

Methyl 2-(2-Methoxyethoxy)-5,6,7,8,9,10-hexahydrobenzo[c]-1,3-dioxolene-3-carboxylate (32)

From methyl 2-oxo-2,5,6,7,8,9,10-heptahydrocycloocta[b]pyran-3-ylcarboxylate (1.20 g, 5.4 mmol) and 1,1-bis-(2-methoxyethoxy)ethene (2.99 g, 13.5 mmol); purification via chromatography (silica gel; EtOAc–hexane).

Yield: 886 mg (51%).

1H NMR (500 MHz, CDC13): δ = 1.90–1.95 (m, 2 H), 3.00–3.05 (m, 2 H), 3.55–3.60 (m, 2 H), 3.80–3.85 (m, 2 H), 3.90 (s, 3 H), 4.00–4.10 (m, 4 H), 4.20–4.25 (m, 2 H), 6.75 (s, 1 H), 7.55 (s, 1 H).

13C NMR (75.7 MHz, CDC13): δ = 28.9 (CH2), 31.8 (CH2), 38.5 (CH), 52.1 (CH), 59.7 (CH), 65.3 (CH2), 65.8 (CH2), 69.6 (CH), 71.4 (CH2), 108.4 (C), 114.7 (CH), 119.0 (C), 127.2 (C), 133.0 (C), 141.9 (C), 157.2 (C), 166.9 (C).

MS: m/z (%) = 322 (16) [M+], 290 (10), 232 (17), 178 (26), 146 (40), 59 (100).

HRMS: m/z calc for C31H22O8 [M + Na+] = 560.1267; found: 560.1267.

Methyl 2-Ethoxy-6-aza-6-ethylcarboxy-2-oxo-2,5,6,7,8-pentahydro-2H-naphth-7-ylcarboxylate (33)

From methyl 2-ethoxy-6-aza-6-ethylcarboxy-2,5,6,7,8-pentahydro-2H-benzo[b]pyran-3-ylcarboxylate (1.20 g, 5.4 mmol) and 1,1-bis-(2-methoxyethoxy)ethene (2.99 g, 13.5 mmol); purification via chromatography (silica gel; EtOAc–hexane).

Yield: 891 mg (51%).

1H NMR (500 MHz, CDC13): δ = 2.05–2.15 (m, 2 H), 2.80–2.95 (m, 4 H), 3.80–3.85 (m, 2 H), 3.90 (s, 3 H), 4.20–4.25 (m, 2 H), 6.85 (s, 1 H), 7.65 (s, 1 H).

13C NMR (75.7 MHz, CDC13): δ = 26.0 (CH2), 32.2 (CH2), 33.9 (CH2), 52.1 (CH2), 59.7 (CH), 69.8 (CH), 71.5 (CH), 111.3 (CH), 119.1 (C), 127.4 (CH), 136.8 (C), 151.0 (C), 158.2 (C), 167.4 (C).

MS: m/z (%) = 250 (10) [M+], 219 (6), 177 (44), 160 (96), 105 (23), 59 (100).

HRMS: m/z calc for C16H19O4 [M + Na+] = 273.1103; found: 273.1109.


Methyl 2-(2-Methoxyethoxy)-5,6,7,8,9-tetrahydro-5H-benzo[c]-1,3-dioxolene-3-carboxylate (30)

From methyl 2-oxo-2,5,6,7,8,9-hexahydrocyclohepta[b]pyran-3-ylcarboxylate (1.20 g, 5.4 mmol) and 1,1-bis-(2-methoxyethoxy)ethene (2.99 g, 13.5 mmol); purification via chromatography (silica gel; EtOAc–hexane).

Yield: 1.28 g (85%).
71.4 (CH₂), 114.7 (CH), 119.4 (C), 130.1 (CH), 141.0 (C), 156.0 (C), 157.4 (C), 166.7 (C), 185.9 (C).

**MS: m/z (%) = 337 (5) [M+], 308 (62), 218 (100), 174 (22), 59 (100).**

**HRMS: m/z calcd for C₁₇H₂₃NO₆ [M + H+]: 338.1603; found: 338.1590.**

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(4) Commercially available from Fluka.

