Asymmetric Synthesis of Tetrahydrobenzofurans and Annulated Dihydropyrans via Cooperative One-Pot Organo- and Silver-Catalysis

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In memory of Professor Jean Normant

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Abstract A low catalyst loading of a squaramide (0.5 mol%) and a silver(I) salt (1 mol%) efficiently catalyzes a one-pot asymmetric Michael addition/hydroalkoxylation reaction between 1,3-diketones and alkynetethered nitroalkenes. Depending on the 1,3-dicarbonyl substrate this cooperative catalytic approach opens access to tetrahydrobenzofurans or annulated dihydropyrans in moderate to excellent yields and very good to excellent enantioselectivities.

Key words asymmetric synthesis, organocatalysis, one-pot synthesis, silver catalysis, annulation

Benzofuran and its partially hydrogenated analogues are important heterocyclic building blocks and very common structures in natural products with interesting biological and pharmaceutical properties. This is also true for structurally isomeric annulated dihydropyrans. Natural products such as the furanomonterpene evodone (I), which has been isolated from Evodia hortensis, exhibits significant inhibitory activity on the seed germination of certain species. Curzerenone (II) and bisabolangelone (III) are other natural products with antibacterial and anti-inflammatory activities, respectively, whereas the diterpenoid maecrystal V (IV) is a potent selective HeLa cell inhibitor. The dihydropyran-type natural product crolubulin (V) and the pharmaceutical HA14-1 (VI) show anticancer properties (Figure 1).

Figure 1 Bioactive natural products and pharmaceuticals containing the partially hydrogenated benzofuran and dihydropyran moieties

Recently, much effort has been invested in the synthesis of tetrahydrobenzofuran and dihydropyran core structures. Singh and co-workers developed a silver-catalyzed interrupted Feist–Bénary reaction between ynones and β-diketones to provide dihydrofurans in moderate to good yields and good to excellent enantioselectivities (Scheme 1). Feng and co-workers reported an asymmetric domino Michael addition/O-alkylation reaction between cyclohexane-1,3-dione derivatives and bromonitrostyrenes catalyzed by a bifunctional N,N′-dioxide organocatalyst to afford polysubstituted bicyclic dihydrofurans. Calter’s group published another interesting synthesis of highly substituted bicyclic dihydrofurans via an organocatalytic asymmetric aldol/oxa-Michael addition sequence between 2-ene-1,4-diketones and dimedone in the presence of a bis(cinchona alkaloid)-pyrimidine catalyst. The Schneider group developed an interesting enantioselective phosphoric acid-catalyzed syn-
thesis of 4-aryl-4H-chromenes via a conjugate addition of 1,3-diketones to in situ generated ortho-quinone methides followed by a cyclodehydration reaction. The coinage metals (Cu, Ag and Au) bond metathesis or cloisomerization, or hydrofunctionalization. Activation reactions such as alkynylation, cycloaddition, cytoxic synthesis. Particularly cooperative, relay, synergistic, and dual catalysis variations, where all reactants and catal-ysts are present from the beginning, is challenging and re-quire high compatibility of the combined catalysts.15

In search of new methods for acquiring valuable bioactive heterocyclic compounds and our interest in the combination of organocatalysts and silver(I) salts, we investigated an asymmetric Michael addition/hydroalkoxylation sequence between 1,3-diketones and alkyne-tethered nitroalkenes catalyzed by a bifunctional squaramide17 and a silver(I) salt to provide the desired tetrahydrobenzofurans. We began our investigation by choosing dimedone (1) and nitroalkene 2a as model substrates. To our delight, the one-pot reaction of 1 and 2a in CH2Cl2 at room temperature catalyzed by squaramide A and Ag2O afforded the desired 5-exo-dig cyclization product 3a in 98% yield and 94% enantioselectivity (Scheme 2). Inspired by these excellent results, the reaction was carried out with different squaramide and thiourea catalysts A-1 along with Ag2O as silver(I) salt. All squaramide catalysts as well as thiourea catalysts provided the tetrahydrobenzofuran in high yields and mod-erate to very good enantioselectivities. The best result was obtained with squaramide A, which gave 98% yield and 94% ee.

The activation of alkynes for subsequent transforma-tions has become an important tool in organic chemistry to develop new and valuable reactions. Alkyne functionalization can be achieved in two crucial routes: σ-activation (σ-bond metathesis or σ-coordination) and π-activation (π-complex formation). The coinage metals (Cu, Ag and Au) are suitable candidates for alkyne functionalization due to their good alkynophilicity. Especially, silver(I) salts have emerged as powerful activators of alkynes. The advantages of stability, nontoxicity, low price, or catalyst compatibility with organocatalysts favor the choice of silver in C=C bond activation reactions such as alkynylation, cycloaddition, cy-cloisomerization, or hydrofunctionalization.

Merging organocatalysis and metal catalysis enables multiple unique transformations in one-pot and this catalytic approach has become a powerful strategy in asymmetric synthesis. Particularly cooperative, relay, synergistic, and dual catalysis variations, where all reactants and catal-ysts are present from the beginning, is challenging and re-quire high compatibility of the combined catalysts.15

In search of new methods for acquiring valuable bioactive heterocyclic compounds and our interest in the combination of organocatalysts and silver(I) salts, we investigated an asymmetric Michael addition/hydroalkoxylation sequence between 1,3-diketones and alkyne-tethered nitroalkenes catalyzed by a bifunctional squaramide and a silver(I) salt to provide the desired tetrahydrobenzofurans. We began our investigation by choosing dimedone (1) and nitroalkene 2a as model substrates. To our delight, the one-pot reaction of 1 and 2a in CH2Cl2 at room temperature catalyzed by squaramide A and Ag2O afforded the desired 5-exo-dig cyclization product 3a in 98% yield and 94% enantioselectivity (Scheme 2). Inspired by these excellent results, the reaction was carried out with different squaramide and thiourea catalysts A-1 along with Ag2O as silver(I) salt. All squaramide catalysts as well as thiourea catalysts provided the tetrahydrobenzofuran in high yields and moderate to very good enantioselectivities. The best result was obtained with squaramide A, which gave 98% yield and 94% ee.

The reaction conditions were optimized further by varying the solvent (Table 1). The solvent screening indicated that the chlorinated solvents and Et2O gave very good results. The best yields were obtained with CH2Cl2 and CHCl3. We chose CH2Cl2 over CHCl3 on the basis of its lower toxici-
ty. Further optimization studies were carried out by screening transition metal catalysts for the hydroalkoxylation reaction. \( \text{Ag}_2\text{CO}_3 \) provided the annulated product with 99% yield and 95% ee. The cost aspect led to our decision to use \( \text{Ag}_2\text{O} \) instead of \( \text{Ag}_2\text{CO}_3 \). After carrying out the reaction at different temperatures and catalyst loadings of the squaramide and the silver(I) salt, we determined the optimal reaction conditions, these being 0.5 mol% of the squaramide and 1 mol% of \( \text{Ag}_2\text{O} \), and \( \text{CH}_2\text{Cl}_2 \) as solvent at room temperature.

Table 1: Further Optimization Studies

<table>
<thead>
<tr>
<th>Entry</th>
<th>M-catalyst</th>
<th>Solvent</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
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<tr>
<td>1</td>
<td>( \text{Ag}_2\text{O} )</td>
<td>toluene</td>
<td>90</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>( \text{Ag}_2\text{O} )</td>
<td>( \text{Et}_2\text{O} )</td>
<td>99</td>
<td>92</td>
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<tr>
<td>3</td>
<td>( \text{Ag}_2\text{O} )</td>
<td>( \text{CHCl}_3 )</td>
<td>99</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>( \text{Ag}_2\text{O} )</td>
<td>DCE</td>
<td>99</td>
<td>94</td>
</tr>
<tr>
<td>5</td>
<td>( \text{Ag}_2\text{O} )</td>
<td>( \text{CH}_2\text{Cl}_2 )</td>
<td>99</td>
<td>95</td>
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<tr>
<td>6</td>
<td>( \text{PtCl}_2 )</td>
<td>( \text{CH}_2\text{Cl}_2 )</td>
<td>traces</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>( \text{CuCl} )</td>
<td>( \text{CH}_2\text{Cl}_2 )</td>
<td>37</td>
<td>94</td>
</tr>
<tr>
<td>8</td>
<td>( \text{AgOTf} )</td>
<td>( \text{CH}_2\text{Cl}_2 )</td>
<td>25</td>
<td>22</td>
</tr>
<tr>
<td>9</td>
<td>( \text{AgBF}_3 )</td>
<td>( \text{CH}_2\text{Cl}_2 )</td>
<td>20</td>
<td>47</td>
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<tr>
<td>10</td>
<td>( \text{Ag}_2\text{CO}_3 )</td>
<td>( \text{CH}_2\text{Cl}_2 )</td>
<td>99</td>
<td>95</td>
</tr>
<tr>
<td>11</td>
<td>( \text{AuClPPh}_3 )</td>
<td>( \text{CH}_2\text{Cl}_2 )</td>
<td>n.d.</td>
<td>–</td>
</tr>
<tr>
<td>12</td>
<td>( \text{Ag}_2\text{O} )</td>
<td>( \text{CH}_2\text{Cl}_2 )</td>
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<td>96</td>
</tr>
<tr>
<td>13</td>
<td>( \text{Ag}_2\text{O} )</td>
<td>( \text{CH}_2\text{Cl}_2 )</td>
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<tr>
<td>14</td>
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<td>( \text{CH}_2\text{Cl}_2 )</td>
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<tr>
<td>15</td>
<td>( \text{Ag}_2\text{O} )</td>
<td>( \text{CH}_2\text{Cl}_2 )</td>
<td>99</td>
<td>97</td>
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</table>

\* Reaction conditions: Dimedone (1; 0.25 mmol), nitroalkene 2a (1.1 equiv), cat. A (1 mol%), \( \text{Ag}_2\text{O} \) (10 mol%), solvent (2.5 mL, 0.1 M).
\& Yield of 3a after flash chromatography.
\% The enantiomeric excess was determined by HPLC on a chiral stationary phase.

The substrate scope of the cooperative organo- and silver-catalyzed asymmetric one-pot reaction was then explored for the reaction of dimedone (1) with various alkynete-tethered nitroalkenes 2 under optimal reaction conditions (Table 2). The nitroalkenes with electron-withdrawing and electron-donating groups worked smoothly under the cooperative catalysis condition to provide tetrahydrobenzofuran 3b–f in excellent yields and very good enantioselectivities. The sterically encumbered 1-naphthyl- and 2-naphthyl-substituted nitroalkenes led to the formation of the desired tetrahydrobenzofuran 3g,h in very good yields and excellent enantiomeric excesses (Table 2). Furthermore, the one-pot Michael addition/hydroalkoxylation sequence with heteroaryl-substituted nitroalkenes provided the desired annulated product 3i in excellent yields and enantioselectivity.

Table 2: Substrate Scope

<table>
<thead>
<tr>
<th>3</th>
<th>R</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Ph</td>
<td>99</td>
<td>96</td>
</tr>
<tr>
<td>b</td>
<td>3-MeOC\text{C}_2\text{H}_4</td>
<td>98</td>
<td>96</td>
</tr>
<tr>
<td>c</td>
<td>2-CIC\text{C}_2\text{H}_4</td>
<td>97</td>
<td>95</td>
</tr>
<tr>
<td>d</td>
<td>4-F\text{C}_6\text{C}_2\text{H}_4</td>
<td>93</td>
<td>94</td>
</tr>
<tr>
<td>e</td>
<td>3-MeC\text{C}_2\text{H}_4</td>
<td>97</td>
<td>95</td>
</tr>
<tr>
<td>f</td>
<td>3,4-(OCH\text{H}_2)O\text{C}_6\text{H}_4</td>
<td>97</td>
<td>95</td>
</tr>
<tr>
<td>g</td>
<td>2-naphthyl</td>
<td>94</td>
<td>97</td>
</tr>
<tr>
<td>h</td>
<td>1-naphthyl</td>
<td>90</td>
<td>95</td>
</tr>
<tr>
<td>i</td>
<td>2-furanyl</td>
<td>96</td>
<td>96</td>
</tr>
</tbody>
</table>

\( a \) Reaction conditions: Dimedone (1; 0.25 mmol), nitroalkene 2 (1.1 equiv), cat. A (0.5 mol%), \( \text{Ag}_2\text{O} \) (1 mol%), solvent (2.5 mL, 0.1 M).
\b Yield of 3a after flash chromatography.
\c The enantiomeric excess was determined by HPLC on a chiral stationary phase.

An extended substrate scope was investigated using different cyclic 1,3-diketones based on five- and six-membered rings. The reaction with 1,3-cyclohexanedione led to the tetrahydrobenzofuran product in good yield and excellent enantioselectivity (Scheme 3, 5a) Interestingly, a dihydropyran derivative 5b could be obtained in moderate yield and good enantiomeric excess using 1,3-cyclopentanedi-one. The substrate scope of the cooperative catalytic reaction was extended further to 1,3-diketones bearing heteroatoms, which also provided dihydropyran derivatives in moderate to very good yields and high enantioselectivities (Scheme 3, 5c, d).

The developed one-pot asymmetric transformation was also conducted with various 5-substituted 1,3-cyclohexanediones to introduce another stereocenter via desymmetrization. The desired tetrahydrobenzofurans could be obtained in very good yields and enantioselectivities, but the diastereomeric ratio was virtually 1:1 in all attempts (Scheme 4, 7a–d).

To evaluate the efficiency and synthetic utility of the current Michael addition/hydroalkoxylation strategy, tetrahydrobenzofuran 3a was prepared on a gram-scale maintaining the excellent yield and ee value (Scheme 5).
The absolute configuration of the tetrahydrobenzofurans was determined by X-ray crystal structure analysis of compound 5a (Figure 2)\textsuperscript{18} in combination with a CD measurement and calculation (Figure 3).

The absolute configuration of the dihydropyran derivatives is based on an X-ray crystallographic analysis of compound 5d (Figure 4).\textsuperscript{18}

This one-pot Michael addition/hydroalkoxylation protocol is proposed to proceed via two catalytic cycles (Scheme 6). The first organocatalytic cycle involves the synergistic activation of the 1,3-diketone 1 and the nitroalkene 2 by the bifunctional squaramide A, where the squaramide moiety activates the nitroalkene 2 through the formation of hydrogen bonds to the nitro group and simultaneously the 1,3-diketone undergoes activation by the tertiary amine to promote the Michael addition from the \( \text{Re} \)-face. In the second catalytic cycle the silver forms a \( \pi \)-complex for the electrophilic activation of the internal alkyne to facilitate a 5-\( \text{exo} \)-dig or a 6-\( \text{endo} \)-dig annulation reaction leading to the vinylsilver intermediate. The latter undergoes a fast protodeargentation to provide the desired product 3, 5 and 7.

In conclusion, we have developed a one-pot asymmetric Michael addition/hydroalkoxylation protocol by merging a bifunctional squaramide and a silver(1) salt at a very low...
Tetrahydrobenzofurans and Annotated Dihydropryan; General Procedure

A mixture of 1,3-diketones 1,4, or 6 (0.25 mmol), nitroalkene 2 (0.275 mmol, 1.1 equiv), catalyst A (0.5 mol%), and Ag₂O (1 mol%) in CH₂Cl₂ (2.5 mL, 0.1 M) was stirred at r.t. until the intermediate Michael adduct was completely converted as indicated by TLC. The crude product was directly subjected to flash chromatography on silica (n-pentane/Et₂O or n-pentane(CH₂Cl₂) to afford the corresponding product 3, 5, or 7.

(R)-Z-2-Benzylidene-6,6-dimethyl-3-(nitromethyl)-3,5,6,7-tetrahydrobenzofuran-4(2H)-one (3a)

Compound 3a was isolated after flash chromatography (n-pentane/Et₂O, 1:1); yield: 75 mg (96%); colorless solid; mp 127–129 °C; 1H NMR (600 MHz, C₆D₆): δ = 7.37 (t, J = 7.6 Hz, 1 H, ArH), 7.06 (t, J = 7.6 Hz, 1 H, ArH), 5.42 (d, J = 2.0 Hz, 1 H, OC=CH), 4.36 (dd, J = 13.1, 6.3 Hz, 1 H, CH₂(CH₂O₂)), 4.17 (dd, J = 13.1, 4.7 Hz, 1 H, CH₂(NO₂)), 3.92 (s, 1 H, CH₂), 1.85 (d, J = 16.0 Hz, 1 H, CH₃), 1.66 (d, J = 17.9 Hz, 1 H, CH₃), 1.58 (d, J = 17.9 Hz, 1 H, CH₃), 0.64 (s, 3 H, CH₃), 0.58 (s, 3 H, CH₃).

IR (ATR): 2934, 2293, 2090, 1891, 1649, 1566, 1399, 1232, 1015, 840, 755, 694 cm⁻¹.

MS (EI, 70 eV): m/z (%) = 313.1 (1, [M]+), 267.1 (17, [M – NO₂]+), 253.0 (7, [M – CH₂NO₂]+), 246.0 (100), 239.0 (100), 221.0 (44), 213.0 (44), 195.0 (44), 177.0 (44), 161.0 (17), 143.0 (17), 125.0 (17), 107.0 (17), 99.0 (17), 81.0 (17), 63.0 (17), 45.0 (17), 27.0 (17), 19.0 (17).

1H NMR (600 MHz, CDCl3): δ = 7.25 (m, 1 H, ArH), 7.11 (m, 2 H, ArH), 6.83–6.78 (m, 1 H, ArH), 5.71 (d, J = 2.2 Hz, 1 H, OC=CH), 4.89 (dd, J = 13.3, 3.9 Hz, 1 H, CH(NO2)), 4.73 (dd, J = 13.3, 7.1 Hz, 1 H, CH(NO2)), 4.58–4.53 (m, 1 H, CH2), 3.82 (s, 3 H, OCH3), 2.54 (m, 2 H, CH2), 2.31 (m, 2 H, CH2), 1.17 (s, 3 H, CH3), 1.16 (s, 3 H, CH3).

13C NMR (151 MHz, CDCl3): δ = 193.6 (C=O), 175.0 (Cq), 159.6 (Cq), 153.3 (Cq), 134.5 (ArC), 129.4 (Arc), 121.3 (Arc), 114.2 (Arc), 112.8 (Arc), 111.3 (Cq), 106.7 (OC=CH), 75.7 (CH2NO2), 55.2 (OCH3), 51.0 (CH3), 41.7 (CH2), 37.2 (CH2), 34.4 [CH(CH3)], 29.0 (CH3), 28.3 (CH3).

MS (EI, 70 eV): m/z (%): 343.3 (5, [M]+), 297.3 (34, [M – NO2]–), 283.3 (12, [M – CH2NO2]–).


(R)-Z)-2-(2-Chlorobenzylidene)-6,6-dimethyl-3-(nitromethyl)-3,5,6,7-tetrahydrobenzofuran-4(2H)-one (3e)

Compound 3e was isolated after flash chromatography (n-pentane/EtO, 1:1); yield: 79 mg (97%); colorless solid; mp 138–140 ºC; Rf = 0.26 (n-pentane/EtO, 1:1); [α]D24 +71.2 (c = 0.4, benzene).

HPLC: Daicel Chiralpak IB, n-heptane/i-ProH (7:3). 0.7 mL/min, λ = 254 nm, τ(peak) (minor) = 11.0 min, τ(peak) (major) = 10.0 min; 95% ee.

IR (ATR): 2957, 2290, 2086, 1644, 1547, 1474, 1403, 1328, 1280, 1214, 1171, 1093, 1006, 891, 748, 781, 697 cm⁻¹.

1H NMR (600 MHz, CDCl3): δ = 7.37 (dd, J = 7.8 Hz, 1 H, ArH), 7.32 (s, 1 H, ArH), 7.23 (t, J = 7.7 Hz, 1 H, ArH), 7.06 (d, J = 7.5 Hz, 1 H, ArH), 5.70 (d, J = 2.2 Hz, 1 H, OC=CH), 4.89 (dd, J = 13.3, 3.9 Hz, 1 H, CH(NO2)), 4.73 (dd, J = 13.3, 7.1 Hz, 1 H, CH(NO2)), 4.55 (m, 1 H, CH2CH3), 2.55 (m, 2 H, CH2), 2.35 (m, 2 H, CH2), 2.32 (m, 2 H, CH2), 1.17 (s, 3 H, CH3), 1.16 (s, 3 H, CH3).

13C NMR (151 MHz, CDCl3): δ = 111.4 (Cq), 110.9 (Cq), 110.8 (Cq), 110.5 (Cq), 111.1 (Cq), 106.9 (OC=CH), 75.7 (CH2NO2), 55.2 (OCH3), 51.0 (CH3), 41.9 (CH2), 37.2 (CH2), 34.4 [CH(CH3)], 28.9 (CH3), 28.2 (CH3).

Compound 3g was isolated after flash chromatography (n-pentane/Et2O, 1:2); yield: 85 mg (94%); colorless solid; mp 133–135 °C; Rf = 0.24 (n-pentane/EtO, 1:1); [α]D24 49.3° (c = 0.4, benzene).

HPLC: Daicel Chiralpak IA, n-heptane/i-PrOH (7:3), 0.7 mL/min, λ = 254 nm, tR (minor) = 11.1 min, tR (major) = 11.7 min; 96% ee.

IR (ATR): 3075, 2922, 2308, 2096, 1902, 1665, 1543, 1393, 1234, 991, 796 cm⁻¹.


Compound 3h was isolated after flash chromatography (n-pentane/Et2O, 1:1); yield: 82 mg (90%); colorless solid; mp 165–167 °C; Rf = 0.23 (n-pentane/EtO, 1:1); [α]D24 41.1° (c = 0.4, benzene).

HPLC: Daicel Chiralpak IB, n-heptane/EtOH (7:3), 0.5 mL/min, λ = 230 nm, tR (minor) = 15.9 min, tR (major) = 16.9 min; 95% ee.

IR (ATR): 3056, 2959, 1648, 1550, 1398, 1248, 1218, 1172, 1141, 1089, 1019, 975, 915, 838, 780, 699 cm⁻¹.


Compound 3i was isolated after flash chromatography (n-pentane/Et2O, 1:1); yield: 82 mg (90%); colorless solid; mp 165–167 °C; Rf = 0.23 (n-pentane/EtO, 1:1); [α]D24 41.1° (c = 0.4, benzene).

HPLC: Daicel Chiralpak IB, n-heptane/EtOH (7:3), 0.5 mL/min, λ = 230 nm, tR (minor) = 15.9 min, tR (major) = 16.9 min; 95% ee.

IR (ATR): 3056, 2959, 1648, 1550, 1398, 1248, 1218, 1172, 1141, 1089, 1019, 975, 915, 838, 780, 699 cm⁻¹.


Compound 3j was isolated after flash chromatography (n-pentane/Et2O, 1:1); yield: 73 mg (96%); colorless solid; mp 103–105 °C; Rf = 0.31 (n-pentane/EtO, 1:1); [α]D24 85.7° (c = 0.4, benzene).

HPLC: Daicel Chiralpak IB, n-heptane/EtOH (7:3), 0.7 mL/min, λ = 254 nm, tR (minor) = 9.3 min, tR (major) = 10.3 min; 96% ee.

IR (ATR): 2960, 2878, 2081, 1888, 1649, 1554, 1466, 1374, 1292, 1228, 1167, 1089, 1049, 1016, 989, 920, 884, 816, 747, 700, 671 cm⁻¹.

1H NMR (600 MHz, CDCl3): δ = 7.05 (d, J = 1.6 Hz, 1 H, OCH), 6.59 (d, J = 3.3 Hz, 1 H, CH), 6.19 (dd, J = 3.3, 1.8 Hz, 1 H, CH), 5.61 (d, J = 2.3 Hz, 1 H, OC=CH), 4.29 (dd, J = 13.2, 6.1 Hz, 1 H, CHNO2), 4.04 (dd, J = 13.2, 3.7 Hz, 1 H, CHNO2), 3.79 (s, 1 H, CH2CH2), 1.90 (d, J = 16.0 Hz, 1 H, CH), 1.82 (d, J = 16.0 Hz, 1 H, CH), 1.71 (d, J = 17.8 Hz, 1 H, CH3), 1.63 (d, J = 17.8 Hz, 1 H, CH3), 0.62 (s, 3 H, CH3), 0.57 (s, 3 H, CH3).

13C NMR (151 MHz, CD2Cl2): δ = 191.6 (C=O), 173.2 (Cα), 152.1 (Cγ), 149.1 (Cβ), 141.2 (OCH), 111.6 (CH), 111.3 (Cβ), 109.5 (CH), 96.2 (OC=CH), 74.8 (CH2NO2), 50.5 (CH2), 41.4 (CH2CH2), 36.2 (CH2), 33.2 (CH2), 28.3 (CH2), 27.2 (CH2).


HRMS (ESI\(^+\)): \([m/z \ [M + Na\]^+] \) calcd for C\(_{17}\)H\(_{17}\)NO\(_4\)Na: 322.1050; found: 322.1049.

**HRMS (ESI\(^+\))**: \([m/z \ [M + Na\]^+] \) calcd for C\(_{21}\)H\(_{28}\)NO\(_4\)Na: 350.1362; found: 350.1359.

**HRMS (ESI\(^+\))**: \([m/z \ [M + Na\]^+] \) calcd for C\(_{19}\)H\(_{17}\)NO\(_4\)Na: 335.1216; found: 335.1216.

**HRMS (ESI\(^+\))**: \([m/z \ [M + Na\]^+] \) calcd for C\(_{21}\)H\(_{25}\)NO\(_4\)Na: 349.1438; found: 349.1438.

**HRMS (ESI\(^+\))**: \([m/z \ [M + Na\]^+] \) calcd for C\(_{22}\)H\(_{27}\)NO\(_4\)Na: 363.1659; found: 363.1659.

**HRMS (ESI\(^+\))**: \([m/z \ [M + Na\]^+] \) calcd for C\(_{24}\)H\(_{29}\)NO\(_4\)Na: 377.1879; found: 377.1879.

**HRMS (ESI\(^+\))**: \([m/z \ [M + Na\]^+] \) calcd for C\(_{26}\)H\(_{31}\)NO\(_4\)Na: 391.2098; found: 391.2098.

**HRMS (ESI\(^+\))**: \([m/z \ [M + Na\]^+] \) calcd for C\(_{28}\)H\(_{33}\)NO\(_4\)Na: 405.2317; found: 405.2317.

**HRMS (ESI\(^+\))**: \([m/z \ [M + Na\]^+] \) calcd for C\(_{30}\)H\(_{35}\)NO\(_4\)Na: 420.2527; found: 420.2527.

**HRMS (ESI\(^+\))**: \([m/z \ [M + Na\]^+] \) calcd for C\(_{32}\)H\(_{37}\)NO\(_4\)Na: 436.2748; found: 436.2748.

**HRMS (ESI\(^+\))**: \([m/z \ [M + Na\]^+] \) calcd for C\(_{34}\)H\(_{39}\)NO\(_4\)Na: 450.2967; found: 450.2967.

**HRMS (ESI\(^+\))**: \([m/z \ [M + Na\]^+] \) calcd for C\(_{36}\)H\(_{41}\)NO\(_4\)Na: 465.3188; found: 465.3188.

**HRMS (ESI\(^+\))**: \([m/z \ [M + Na\]^+] \) calcd for C\(_{38}\)H\(_{43}\)NO\(_4\)Na: 480.3407; found: 480.3407.

**HRMS (ESI\(^+\))**: \([m/z \ [M + Na\]^+] \) calcd for C\(_{40}\)H\(_{45}\)NO\(_4\)Na: 495.3627; found: 495.3627.

**HRMS (ESI\(^+\))**: \([m/z \ [M + Na\]^+] \) calcd for C\(_{42}\)H\(_{47}\)NO\(_4\)Na: 510.3846; found: 510.3846.

**HRMS (ESI\(^+\))**: \([m/z \ [M + Na\]^+] \) calcd for C\(_{44}\)H\(_{49}\)NO\(_4\)Na: 525.4066; found: 525.4066.

**HRMS (ESI\(^+\))**: \([m/z \ [M + Na\]^+] \) calcd for C\(_{46}\)H\(_{51}\)NO\(_4\)Na: 540.4286; found: 540.4286.

**HRMS (ESI\(^+\))**: \([m/z \ [M + Na\]^+] \) calcd for C\(_{48}\)H\(_{53}\)NO\(_4\)Na: 555.4487; found: 555.4487.

**HRMS (ESI\(^+\))**: \([m/z \ [M + Na\]^+] \) calcd for C\(_{50}\)H\(_{55}\)NO\(_4\)Na: 570.4687; found: 570.4687.

**HRMS (ESI\(^+\))**: \([m/z \ [M + Na\]^+] \) calcd for C\(_{52}\)H\(_{57}\)NO\(_4\)Na: 585.4887; found: 585.4887.

**HRMS (ESI\(^+\))**: \([m/z \ [M + Na\]^+] \) calcd for C\(_{54}\)H\(_{59}\)NO\(_4\)Na: 600.5086; found: 600.5086.

**HRMS (ESI\(^+\))**: \([m/z \ [M + Na\]^+] \) calcd for C\(_{56}\)H\(_{61}\)NO\(_4\)Na: 615.5286; found: 615.5286.

**HRMS (ESI\(^+\))**: \([m/z \ [M + Na\]^+] \) calcd for C\(_{58}\)H\(_{63}\)NO\(_4\)Na: 630.5486; found: 630.5486.

**HRMS (ESI\(^+\))**: \([m/z \ [M + Na\]^+] \) calcd for C\(_{60}\)H\(_{65}\)NO\(_4\)Na: 645.5686; found: 645.5686.

**HRMS (ESI\(^+\))**: \([m/z \ [M + Na\]^+] \) calcd for C\(_{62}\)H\(_{67}\)NO\(_4\)Na: 660.5886; found: 660.5886.

**HRMS (ESI\(^+\))**: \([m/z \ [M + Na\]^+] \) calcd for C\(_{64}\)H\(_{69}\)NO\(_4\)Na: 675.6086; found: 675.6086.

**HRMS (ESI\(^+\))**: \([m/z \ [M + Na\]^+] \) calcd for C\(_{66}\)H\(_{71}\)NO\(_4\)Na: 690.6286; found: 690.6286.

**HRMS (ESI\(^+\))**: \([m/z \ [M + Na\]^+] \) calcd for C\(_{68}\)H\(_{73}\)NO\(_4\)Na: 705.6486; found: 705.6486.

**HRMS (ESI\(^+\))**: \([m/z \ [M + Na\]^+] \) calcd for C\(_{70}\)H\(_{75}\)NO\(_4\)Na: 720.6686; found: 720.6686.

**HRMS (ESI\(^+\))**: \([m/z \ [M + Na\]^+] \) calcd for C\(_{72}\)H\(_{77}\)NO\(_4\)Na: 735.6886; found: 735.6886.

**HRMS (ESI\(^+\))**: \([m/z \ [M + Na\]^+] \) calcd for C\(_{74}\)H\(_{79}\)NO\(_4\)Na: 750.7086; found: 750.7086.
Compound 7c was isolated after flash chromatography (n-pentane/EtO, 1:1); yield: 86 mg (98%); colorless solid; mp 143–145 °C; [α]D 25 4°, 182 nm. 
HPLC: Daicel Chiralpak AD, n-heptane/MeOH (1:1), 1.0 mL/min, λ = 254 nm, tR (minor) 1 = 9.2 min, tR (major) 1 = 17.1 min; tR (minor) 2 = 11.0 min, tR (major) 2 = 13.9 min; 94% ee, dr = 1:1.
IR (ATR): 2914, 2327, 2098, 1647, 1547, 1393, 1201, 1009, 849, 752 cm⁻¹.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561468.

References


(18) CCDC 1474771 (5a) and CCDC 1474975 (5d) contain the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.
