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An asymmetric synthesis of trans-fused butyrolactones from endoperoxides

Joshua Priest, Mark. R. Longland, Mark R. J. Elsegood and Marc C. Kimber*

Department of Chemistry, Loughborough University, Leicestershire, LE11 3TU, UK

M.C.Kimber@lboro.ac.uk.

Abstract

The intermolecular addition of 1,3-dicarbonyl equivalents to endoperoxides in the presence of an organocatalyst yields trans-fused butyrolactones in high yield and enantioselectivities. This methodology expands the synthetic utility of endoperoxides and further underlines their potential as sources of oxygen functionality for natural and non-natural product target synthesis.
The oxidation of dienes to yield endoperoxides represents a selective and green chemical method for introducing oxygen functionality within a substrate. However, conversion of these endoperoxide products into useful asymmetric building blocks for natural and non-natural product target synthesis, without the use of toxic transition metals, has yet to be fully exploited. For example, Taylor and co-workers in 2002 reported the conversion of endoperoxides (1) into useful butyrolactones (2) via an intermediary cis-γ-hydroxy-enone (3) (Scheme 1); however, they were only able to achieve this in an enantioselective fashion using a Co(II) catalyst and no asymmetric examples of bicyclic endoperoxides were included in their study, presumably due to the reactivity of bicyclic endoperoxides with Co(II) salts which traditionally delivers the bis-epoxide products. In 2006, Toste and co-workers successfully desymmetrised bicyclic endoperoxides (4) using an organocatalytic Kornblum-De La Mare rearrangement; however, the synthetic use of these highly enantio-enriched hydroxyenone products (5) has been limited.

In a project aimed at investigating the anti-inflammatory activity of trans-fused xanthanolide natural product analogues, we recently required access to enantioenriched trans-fused butyrolactones (7) which we envisaged could be obtained from endoperoxides (6) (Scheme 1). While enantioselective routes toward cis-fused butyrolactones exist in general synthetic routes toward trans-fused butyrolactones are less common; e.g. in Shishido’s first asymmetric synthesis of the anti-inflammatory natural product xanthatin, they had to convert a key cis-lactone precursor into the trans-lactone using a 3-step procedure which included a Mitsunobu inversion of the crucial hydroxyl group.

Scheme 1. Planned route toward trans-fused butyrolactones.

Key to this approach is the trapping of a cyclic hydroxyenone, a result of the based catalysed rearrangement of endoperoxides, by a 1,3-dicarbonyl equivalent which we envisaged would occur via an intermolecular 1,4-conjugate addition pathway. Furthermore, since hydroxy enones such as 5 can be obtained via an organocatalysed Kornblum-De La Mare rearrangement of endoperoxides this approach would represent an asymmetric protocol for generating complex trans-fused butyrolactone scaffolds from endoperoxides, which in turn can be obtained from simple ¹⁸O₂ oxidation of dienes.

After initial optimisation studies we found treatment of endoperoxide 4 in THF in the presence of 10 mol% of catalyst 8a for a 16h period followed by addition diethylsodiomalonate gave the desired lactone (-)-9a in an isolated yield of 76% and ee of 92% (Scheme 1 and Table 1; entry 1). While the rearrangement of 4 with catalyst 8b with subsequent addition of diethylsodiomalonate gave lactone (+)-9a in a yield of 78% and ee of 94% (entry 2).

Scheme 2. Lactone optimisation.
With optimal conditions for lactone formation determined we then looked at the scope of this sequence using other 1,3-dicarbonyls and endoperoxides in the presence of both catalysts 8a and 8b (Scheme 2 and Table 1). Undertaking the reaction with dimethylsodium maleonate and using catalyst 8a gave lactone (−)-9b in a comparable isolated yield and ee (entry 3). The use of ethyl sodioacetate failed to deliver the butyrolactone but instead only yielded the alkoxy Michael addition product 10 as an inseparable mixture of diastereoisomers (entry 4); however, the addition of ethyl sodio benzoyl acetate gave the lactone (−)-9d using catalyst 8a in an isolated yield of 82% and an ee of 94% (entry 5). The endoperoxide 11, obtained in 87% yield from cycloheptadiene,\(^{12}\) was also exposed to the optimised reaction conditions with catalyst 8a delivering (−)-13 in 82% yield and ee of 78%, while the antipode (+)-13 was obtained in an ee of 76% and a comparable isolated yield using catalyst 8b (entries 6 and 7, respectively). When the OTBS protected seven membered endoperoxide 12, derived from commercially available tropone,\(^{13}\) was treated with catalyst 8a under the optimised conditions the lactone (−)-14 was isolated in a good yield of 74% and an excellent ee of 94%, while catalyst 8b gave the antipode (+)-14 in 70% yield and an ee of 92% (entries 8 and 9, respectively).

### Table 1. Asymmetric butyrolactone formation and scope.\(^{a,b}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Endoperoxide</th>
<th>R</th>
<th>Product</th>
<th>Yield [%](^c)</th>
<th>ee (^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>CO(_2)Et</td>
<td>(−)-9a</td>
<td>76</td>
<td>92</td>
</tr>
<tr>
<td>2(^e)</td>
<td>4</td>
<td>CO(_2)Et</td>
<td>(+)-9a</td>
<td>78</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>CO(_2)Me</td>
<td>(−)-9b</td>
<td>76</td>
<td>92</td>
</tr>
<tr>
<td>4(^f)</td>
<td>4</td>
<td>C(O)Me</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>C(O)Ph</td>
<td>(−)-9d</td>
<td>82</td>
<td>94</td>
</tr>
<tr>
<td>6</td>
<td>11</td>
<td>CO(_2)Et</td>
<td>(−)-13</td>
<td>82</td>
<td>78</td>
</tr>
<tr>
<td>7(^e)</td>
<td>11</td>
<td>CO(_2)Et</td>
<td>(+)-13</td>
<td>82</td>
<td>76</td>
</tr>
<tr>
<td>8</td>
<td>12</td>
<td>CO(_2)Et</td>
<td>(−)-14</td>
<td>74</td>
<td>94</td>
</tr>
<tr>
<td>9(^e)</td>
<td>12</td>
<td>CO(_2)Et</td>
<td>(+)-14</td>
<td>70</td>
<td>92</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>CO(_2)Et</td>
<td>(+)-2</td>
<td>44</td>
<td>10</td>
</tr>
</tbody>
</table>

\(^a\)See the general experimental procedure. \(^b\)10 mol% of catalyst 8a used unless otherwise stated. \(^c\)Isolated yields. \(^d\)Determined by chiral HPLC. \(^e\)10 mol% of catalyst 8b. \(^f\)10 was isolated as an inseparable mixture of diastereoisomers.
While the absolute stereochemistry of this later lactone can be deduced from the work of Toste,\textsuperscript{4} the relative stereochemistry of (±)-14 was definitively assigned via X-ray crystallography.\textsuperscript{14} Importantly, the enantioselective synthesis of lactones containing a trans-fused 5,7-ring system gives us access to scaffolds ideal for investigating the biologically active xanthanolide class of natural products.\textsuperscript{5a,b} Finally, endoperoxide 1 was exposed to the lactonisation conditions, but gave the known lactone (+)-2 in a disappointing ee of 10% (entry 10).

Next we explored the installation of a methyl group at the alpha position of the trans-fused butyrolactone, as many natural product classes possess this substitution pattern (Scheme 3). Desymmetrisation of 4 using catalyst 8b followed by addition of diethylsodiomalonate gave the intermediate sodium salt 15 which upon treatment with iodomethane followed by acid mediated decarboxylation, gave the alpha methyl substituted lactone (+)-19 as the major diastereoisomer in 66% yield.\textsuperscript{15} Alternatively, the rearranged endoperoxide 4 could be treated with alpha-methyldiethylsodiomalonate giving lactone 17 which upon decarboxylation gave (+)-19 in a comparable chemical yield and diastereoselectivity. These two processes were also performed upon the seven membered endoperoxide 11 using catalyst 8a in this case, giving the desired alpha methyl substituted lactone (-)-20 in good chemical yield and diastereoselectivity.\textsuperscript{16}

Scheme 3. Direct installation of an α-methyl group.

The trans-stereochemistry of the butyrolactone is installed via the mechanism shown below in Scheme 4. The hydroxynone 23 undergoes conjugate addition anti to the hydroxyl group, as depicted in 25, to deliver the addition product 24. This undergoes lactonisation to deliver the trans-fused product 26, which can then be protonated or trapped by an appropriate electrophile therefore giving 27.\textsuperscript{17}

Scheme 4. Trans-fused lactone formation.

Finally, in reference to accessing xanthanolide analogues, we investigated the use of the ketone contained within the fused carbocycle as a synthetic handle (Scheme 5). Accordingly, we were able to selectively install an exo-methylene group using the conditions of Connell and co-workers\textsuperscript{18} on lactone (-)-20 giving 28. This compound proved to be unstable and was directly reduced under Luche conditions\textsuperscript{19} to yield the allylic alcohol. Subsequent exposure of this alcohol to trimethyl orthoacetate, gave the Claisen rearrangement product (-)-29 in a yield 51%
over 3-steps from (-)-20. Therefore using this approach we have a convenient asymmetric route to trans-fused xanthanolide analogues in just 5-steps and from readily available endoperoxides.

**Scheme 5. Synthesis of xanthanolide analogue (-)-29.**

![Chemical structure of xanthanolide analogue (-)-29]

In summary, we have developed a convenient and single pot method for the synthesis of highly enantioenriched trans-fused butyrolactones from endoperoxides. Importantly, this process gives the desired products without the use of transition metals and also showcases the use of endoperoxides as environmentally sustainable sources of oxygen functionality. The use of this methodology in the total synthesis of xanthanolide sesquiterpenoids and analogues for evaluation of their inflammatory activity is currently being pursued and will be reported on in due course.

**Experimental**

**General experimental procedure for enantio-enriched lactone formation.**

To a solution of the endoperoxide (1mmol) in dry THF (5mL) was added the catalyst (0.1mmol, 8a or 8b as indicated below) and the resultant reaction mixture stirred at room temperature for 16h under N₂. After this period a solution of the desired nucleophile (1.0mmol) [prepared in THF (3mL) by the addition of NaOEt or NaOMe (2.2mL, 0.5M, 1.1mmol) to the required malonate derivative (1.0mmol)] was added dropwise to the reaction mixture at 0°C, and the resultant solution allowed to warm to room temperature and stirred for a further 16h under N₂. The reaction mixture was then cooled to 0°C and quenched by the addition of 1M HCl, after which it was partitioned between EtOAc (50mL) and H₂O (50mL), and the aqueous layer extracted with further portions of EtOAc (2x20mL). The organic layers were then combined, washed with brine, dried (Na₂SO₄), filtered and the solvent removed in vacuo. The crude products were then purified by chromatography. Using this procedure then following compound were obtained:

(-)-(3R, 3aS, 9aR)-Ethyl-2,5-dioxodecahydrocycloocta[b]furan-3-carboxylate ((-)9a). Prepared using catalyst 8a (193 mg, 76%; R₂ 0.50 in 3:2 petroleum ether:ethyl acetate); [α]D²⁰ = -41.2 (c 1.00, CHCl₃); HRMS (ESI-orbitrap): MNa⁺, C₁₂H₁₆O₃, found 277.1039, requires MNa⁺ 277.1052; IR (solution, CHCl₃) 3032, 3019, 2946, 1785, 1743, 1708, 1216, 1209, 1159 cm⁻¹; ¹H NMR (400 MHz; CDCl₃) δ 4.30 (dq, J = 2.4, 7.2 Hz, 2H), 4.19 (ddd, J = 3.2, 8.8, 10.0 Hz, 1H), 3.41 (d, J = 12.4 Hz, 1H), 3.19 (ddt, J = 3.6, 10.0, 11.6 Hz, 1H), 2.78 – 2.68 (m, 2H), 2.43 (dd, J = 11.6, 14.4 Hz, 1H), 2.35 (dt, J = 5.6, 12.8 Hz, 1H), 2.23 – 2.16 (m, 1H), 1.90 – 1.70 (m, 4H), 1.48 – 1.40 (m, 1H), 1.31 (t, J = 7.2 Hz, 3H); ¹³C NMR (100 MHz;CDCl₃) δ 211.6, 169.5, 167.0, 84.1, 62.5, 53.9, 45.4, 43.9, 39.0, 31.1, 26.0, 22.1, 14.1. 3S, 3aR, 9aS)-Ethyl-2,5-dioxodecahydrocycloocta[b]furan-3-carboxylate ((+)9a). Prepared using catalyst 8b (196mg, 78%); [α]D¹⁸ = +45.2 (c 1.00, CHCl₃).

(-)-(3R, 3aS, 9aR)-Methyl-2,5-dioxodecahydrocycloocta[b]furan-3-carboxylate ((-)9b). Prepared using catalyst 8a (182mg, 76%; R₂ 0.20 in 1:1 petroleum ether/ethyl acetate; MP 70.0 – 71.5 °C); [α]D²⁰ = -58.0 (c 1.00, CHCl₃); HRMS (ESI-orbitrap): MNa⁺, C₁₂H₁₆O₃, found 263.0883, requires MNa⁺ 263.0895; IR (solution, CHCl₃) 3033, 3019, 2946, 1785, 1743, 1708, 1216, 1209, 1159 cm⁻¹; ¹H NMR (400 MHz; CDCl₃) δ 4.18 (ddd, J = 3.2, 8.8, 11.2 Hz, 1H), 3.86 (s, 3H), 3.42 (d, J = 12.0 Hz, 1H), 3.25 – 3.18 (m, 1H), 2.80 – 2.71 (m, 1H), 2.75 (dd, J =
General methylation conditions. Method A: To a solution of the endoperoxide 4 or 11 (1.0mmol) in dry THF (10mL) was added the catalyst 8a or 8b (0.1mmol) and the resultant reaction mixture stirred at room temperature for 16h under N2. After this period a solution of Na(OEt)2 (1.1mmol; prepared from Na2CO3 (393mg, 1.1mmol) and 2M HCl) was added dropwise to the reaction mixture at 0°C, and the resultant solution allowed to warm to room temperature and stirred for a further 16h under N2.

(-)-(3S,3aS,9aR)-tert-Butyl 2,5-dioxodecahydrocycloocta[b]furran-3-carboxylate ((-)9c). Prepared using catalyst 8a (181mg, 68%; Rf 0.65 in 1:1 petroleum ether/ethyl acetate; MP 87 – 89 °C); [α]D26 = -29.6 (c 1.00, CHCl3); HRMS (ESI-orbitrap): MNa+, C13H22O4Na, found 305.1353, requires MNa+ 305.1365; IR (solution, CHCl3) δ 2983, 1789, 1717, 1619, 1549, 1371, 1220 cm−1; 1H NMR (400 MHz; CDCl3) δ 4.11 (ddd, J = 3.2, 8.4, 11.6 Hz, 1H), 3.26 (d, J = 12.4 Hz, 1H), 3.12 (ddt, J = 3.6, 10.0, 14.0 Hz, 1H), 2.77 – 2.70 (m, 1H), 2.68 (dd, J = 4.0, 14.8 Hz, 1H), 2.41 (dd, J = 12.0, 14.8 Hz, 1H), 2.33 (dt, J = 5.2, 12.8 Hz, 1H), 2.19 – 2.12 (m, 1H), 1.90 – 1.69 (m, 5H), 1.49 (s, 9H); 13C NMR (100 MHz; CDCl3) δ 211.8, 169.8, 165.7, 83.8, 83.4, 54.6, 45.5, 43.7, 39.0, 31.0, 28.0, 26.1, 22.0.

(-)-(3R,3aS,9aR)-3-Benzoylhexahydrocycloocta[b]furran-2,5(3H,6H)-dione ((-)9d). Prepared using catalyst 8a (234mg, 82%; Rf 0.55 in 1:1 petroleum ether/ethyl acetate; MP 103 - 105 °C); [α]D26 = -122.8 (c 1.00, CHCl3); HRMS (ESI-orbitrap): MNa+, C13H12O4Na, found 309.1091, requires MNa+ 309.1103; IR (solution, CHCl3) 2939, 1773, 1706, 1685, 1449, 1270 cm−1; 1H NMR (400 MHz; CDCl3) δ 8.05 – 8.03 (m, 2H), 7.67 – 7.63 (m, 1H), 7.55 – 7.51 (m, 2H), 4.38 (d, J = 12.0 Hz, 1H), 4.27 (ddd, J = 3.6, 8.4, 10.0 Hz, 1H), 3.71 – 3.62 (m, 1H), 2.94 – 2.88 (m 1H), 2.68 (dd, J = 4.0, 14.8 Hz, 1H), 2.39 – 2.33 (m, 1H), 2.23 – 2.19 (m, 1H), 1.96 – 1.84 (m, 4H), 1.52 – 1.48 (m, 1H); 13C NMR (100 MHz; CDCl3) δ 211.9, 191.7, 170.0, 135.8, 134.4, 129.6, 128.9, 84.1, 55.5, 45.8, 41.9, 38.6, 31.2, 26.3, 21.7.

(-)-(3S,3aS,8aR)-ethyl 2,5-dioxoctahydro-2H-cyclohepta[b]furran-3-carboxylate ((-)13). Prepared using catalyst 8a (193mg, 82%; Rf 0.30 in 1:1 petroleum ether/ethyl acetate; MP 64.0 – 66.0 °C); [α]D26 = -25.6 (c 1.00, CHCl3); HRMS (ESI-orbitrap): MNa+, C13H22O4Na, found 263.1130, requires MNa+ 263.0895; IR (solution, CHCl3) 3029, 2957, 2931, 2859, 1789, 1736, 1709, 1016 cm−1; 1H NMR (400 MHz; CDCl3) δ 4.26 (dq, J = 1.6, 7.2 Hz, 2H), 4.09 – 4.01 (m, 1H), 3.34 (d, J = 12.4 Hz, 1H), 3.04 (ddt, J = 4.4, 10.4, 12.0 Hz, 1H), 2.78 (dd, J = 4.0, 18.0 Hz, 1H), 2.63 (dt, J = 2.4, 13.2 Hz, 1H), 2.58 – 2.52 (m, 1H), 2.50 – 2.43 (m, 1H), 2.37 (dd, J = 12.0, 18.0 Hz, 1H), 2.11 – 2.02 (m, 1H), 1.80 – 1.71 (m, 1H), 1.58 – 1.48 (m, 1H), 1.28 (t, J = 7.6 Hz, 3H); 13C NMR (100 MHz; CDCl3) δ 209.4, 169.9, 166.7, 83.6, 62.5, 53.1, 43.3, 43.1, 42.1, 34.0, 20.7, 14.1. (+)-(3S,3aR,8aS)-ethyl 2,5-dioxoctahydro-2H-cyclohepta[b]furran-3-carboxylate ((+)-13). Prepared using catalyst 8b (188mg, 81%); [α]D21 = +29.6 (c 1.00, CHCl3).

(-)-(3S,3aS,7S,8aR)-Ethyl 7-(tert-butyldimethylsilyloxy)-2,5-dioxoctahydro-2H-cyclohepta[b]furran-3-carboxylate ((-)14). Using the general method but on a 0.40 mmol scale and prepared using catalyst 8a (107mg, 74%; Rf 0.45 in 3:1 petroleum ether/ethyl acetate; MP 102.0 – 103.5 °C); [α]D19 = -35.8 (c 1.00, CHCl3); HRMS (ESI-orbitrap): MNa+, C13H25O3Si, found 393.1696, requires MNa+ 393.1709; IR (solution, CHCl3) 2957, 2931, 2858, 1789, 1736, 1708, 1260, 1016 cm−1; 1H NMR (400 MHz; CDCl3) δ 4.28 (dq, J = 2.8, 7.2 Hz, 2H), 4.10 (dd, J = 3.6, 10.0, 11.6 Hz, 1H), 3.93 – 3.87 (m, 1H), 3.30 (d, J = 13.2 Hz, 1H), 3.30 – 3.19 (m, 1H), 3.04 (dd, J = 11.2, 12.0 Hz, 1H), 2.87 (dd, J = 4.8, 17.6 Hz, 1H), 2.68 – 2.64 (m, 2H), 2.29 (dd, J = 11.6, 17.6 Hz, 1H), 2.03 – 1.95 (m, 1H), 1.32 (t, J = 7.2 Hz, 3H), 0.87 (s, 9H), 0.08 (s, 6H); 13C NMR (100 MHz; CDCl3) δ 205.7, 169.4, 166.4, 79.0, 66.1, 62.6, 53.3, 44.8, 43.8, 41.4, 31.0, 25.6, 18.0, 14.1, -4.9. (+)-(3S,3aR,7R,8aS)-Ethyl 7-(tert-butyldimethylsilyloxy)-2,5-dioxoctahydro-2H-cyclohepta[b]furran-3-carboxylate ((+)-14). Using the general method and prepared using catalyst 8b (102mg, 70%); [α]D18 = +32.6 (c 1.00, CHCl3).
The reaction mixture was then cooled to 0°C and iodomethane (94μL, 1.5mmol) was added after which the reaction mixture was stirred for a further 16h at room temperature. A sat. solution of NH₄Cl (10mL) was then added and the solution then partitioned between CH₂Cl₂ (50mL) and H₂O (50mL), and the aqueous layer extracted with further portions of CH₂Cl₂ (2x40mL). The organic layers were then combined, washed with brine (50mL), dried (Na₂SO₄), filtered and the solvent removed in vacuo. The crude material was then dissolved in 50% AcOH (10mL) and refluxed overnight. After this period, the reaction was cooled, carefully basified with NaHCO₃ and the aqueous layer extracted with dichloromethane (2x40mL). The combined organic extracts were then dried (Na₂SO₄), filtered, and the solvent was removed in vacuo. The crude product was then purified by column chromatography.

Method B: To a solution of the endoperoxide 4 or 11 (1.0mmol) in dry THF (8mL) was added the catalyst 8a or 8b (35mg, 0.1mmol) and the resultant reaction mixture stirred at room temperature for 16h under N₂. After this period a solution of NaCMe(CO₂Et)₂ [1.1mmol; prepared from HCMe(CO₂Et)₂ (193mg, 1.10mmol) and NaOEt (2.30mL, 0.5M soln., 1.15mmol) THF (5mL)] was added dropwise to the reaction mixture at 0°C, and the resultant solution allowed to warm to room temperature and stirred for a further 16h under N₂. The reaction mixture was then cooled to 0°C and a sat. soln. of NH₄Cl (10mL) added, partitioned between CH₂Cl₂ (50mL) and H₂O (50mL), and the aqueous layer extracted with further portions of CH₂Cl₂ (2x30mL). The organic layers were then combined, washed with brine (50mL), dried (Na₂SO₄), filtered and the solvent removed in vacuo. The crude material was then dissolved in 50% AcOH (10mL) and refluxed overnight. After this period, the reaction was cooled, carefully basified with NaHCO₃ and the aqueous layer extracted with CH₂Cl₂ (2x40mL). The combined organic extracts were then dried (Na₂SO₄), filtered, and the solvent was removed in vacuo. The crude product was then purified by column chromatography. Using these methods the following compounds were obtained.

(+)-(3R, 3aR, 9aS)-3-Methylhexahydrocycloocta[b]furan-2,5(3H,6H)-dione (++)-19. Obtained as a colourless oil (Method A 130mg, 66%; Method B 123mg, 63%; Rf 0.18 in 3:2 petroleum ether/ethyl acetate); [α]D²⁰ = +26.4 (c 1.00, CHCl₃); HRMS (ESI-orbitrap): MNa⁺, C₁₁H₁₆O₃, found 219.0992, requires MNa⁺ 219.0997; IR (solution, CHCl₃) 3029, 2938, 1774, 1705, 991 cm⁻¹; ¹H NMR (400 MHz; CDCl₃) δ 4.22 (dt, J = 3.2, 9.2 Hz, 1H), 2.68 – 2.61 (m, 1H), 2.45 (dd, J = 11.6, 14.0 Hz, 1H), 2.40 – 2.35 (m, 1H), 2.34 (q, J = 6.8 Hz, 1H), 2.27 – 2.19 (m, 2H), 1.95 – 1.85 (m, 1H), 1.85 – 1.72 (m, 2H), 1.68 – 1.59 (m, 1H), 1.54 – 1.46 (m, 1H), 1.26 (d, J = 6.8 Hz, 3H); ¹³C NMR (100 MHz;CDCl₃) δ 212.8, 177.1, 84.0, 49.0, 45.3, 42.6, 39.9, 31.4, 25.8, 22.9, 12.8.

(-)-(3S, 3aS, 8aR)-3-Methylhydroxy-2H-cyclohepta[b]furan-2,5(3H)-dione (-)-20. Obtained as a waxy solid (Method A (performed on a 2mmol scale) 298mg, 79%; Method B 124mg, 68%; Rf 0.35 in 1:1 petroleum ether/ethyl acetate; MP 28 – 31°C); [α]D²⁰ = -92 (c 1.00, CHCl₃); HRMS (ESI-orbitrap): MNa⁺, C₁₀H₁₄O₂, found 205.0836, requires MNa⁺ 205.0841; IR (solution, CHCl₃) 3029, 3019, 2936, 1776, 1703, 1208 cm⁻¹; ¹H NMR (400 MHz; CDCl₃) δ 3.97 (ddd, J = 3.2, 9.6, 10.8 Hz, 1H), 2.78 (dd, J = 4.0, 18.0 Hz, 1H), 2.51 – 2.47 (m, 2H), 2.36 – 2.28 (m, 1H), 2.20 – 2.15 (m, 2H), 2.12 – 2.08 (m, 1H), 2.07 – 2.03 (m, 1H), 1.72 – 1.53 (m, 2H), 1.26 (d, J = 7.6 Hz, 3H); ¹³C NMR (100 MHz;CDCl₃) δ 210.3, 177.4, 83.6, 46.2, 43.5, 43.4, 41.9, 34.3, 20.8, 12.9.

(+)-(3aR, 9aS)-Hexahydrocycloocta[b]furan-2,5(3H,6H)-dione (++)-21. Lactone (+)-9a (0.36g, 1.4mmol) was dissolved ethanol (15mL) and 2M KOH (15mL) and the resultant solution stirred at room temperature for 16h. After this period the reaction mixture was carefully acidified with 5M HCl, extracted with CH₂Cl₂ (2x30mL), and the combined organic layers dried (Na₂SO₄), filtered and the solvent removed in vacuo. The crude acid was then dissolved in toluene (25mL) and refluxed for overnight. The solvent was then removed in vacuo and the crude solid purified by column chromatography (Rf 0.13, 3:2 petroleum ether/ethyl acetate) to yield the title compound as a colourless solid (194mg, 76%; MP 74 – 76 °C); [α]D²⁰ = +21.2 (c 1.00, CHCl₃); HRMS (ESI-orbitrap): MNa⁺, C₁₀H₁₄O₂, found 205.0836, requires MNa⁺ 205.0841; IR (solution, CHCl₃) 3011, 3027, 2942, 1780, 1705, 1016 cm⁻¹; ¹H NMR (400 MHz; CDCl₃) δ 4.22 (dt, J = 3.2, 9.2 Hz, 1H), 2.77 – 2.64 (m, 4H), 2.48 (dd, J = 11.2, 13.6 Hz, 1H), 2.42 – 2.34 (m, 2H), 2.27 – 2.21 (m, 1H), 1.93 – 1.76 (m, 3H), 1.72 – 1.63 (m, 1H), 1.54 – 1.46 (m, 1H); ¹³C NMR (100 MHz;CDCl₃) δ 21.4, 174.4, 86.0, 46.4, 41.1, 39.7, 37.1, 31.6, 25.7, 22.8.
(-)-(3aS,8aR)-hexahydro-2H-cyclohepta[b]furan-2,5(3H)-dione ((-)22). Lactone (-)-13 (241mg, 1.00mmol) was dissolved in 50% AcOH (10mL) and refluxed overnight. After this period, the reaction was cooled, basified with NaHCO₃ and the aqueous layer extracted with dichloromethane (2x30mL). The combined organic extracts were then dried (Na₂SO₄), filtered, and the solvent was removed in vacuo. The crude product was then purified by chromatography giving the title compound as a colourless solid (130mg, 78%; MP 69.0 – 70.5 °C; [α]D³ = -59.6 (c 1.00, CHCl₃); HRMS (ESI-orbitrap): MNa⁺, C₉H₁₂O₅, found 251.0679, requires MNa⁺ 251.0684; IR (solution, CHCl₃) 3019, 2950, 1782, 1704, 1211 cm⁻¹; ¹H NMR (400 MHz; CDCl₃) δ 4.03 (dd, J = 3.6, 5.2, 9.6 Hz, 1H), 2.80 (dd, J = 3.6, 18.0 Hz, 1H), 2.74 – 2.52 (m, 4H), 2.48 (dq, J = 3.6, 12.8 Hz, 1H), 2.40 – 2.30 (m, 2H), 2.12 – 2.04 (m, 1H), 1.72 (ddt, J = 4.0, 11.2, 13.2 Hz, 1H), 1.61 – 1.50 (m, 1H); ¹³C NMR (100 MHz;CDCl₃) δ 210.3, 175.0, 85.6, 44.1, 43.3, 38.6, 35.9, 34.2, 20.8.

(-)-Methyl 3-((3S,3aS,8aR)-3-methyl-2-oxo-3, 3a, 4, 7, 8, 8a-hexahydro-2H-cyclohepta[b]furan-6-yl)propanoate ((-)29). To a mixture of (-)-20 (282mg, 1.55mmol) and paraformaldehyde (94mg, 3.10mmol) in dry THF (2mL) was added (Pr)₂NH.TFA (334mg, 1.55mmol) and TFA (12μL, 0.16mmol). The reaction mixture was then refluxed for 2h, after which it was cooled to room temperature and another portion of paraformaldehyde (94mg, 3.10mmol) added and the reaction mixture refluxed for a further 6h. After this period the reaction mixture was cooled, the solvent removed in vacuo and the residue dissolved in CH₂Cl₂ (40mL) and washed sequentially with 1M HCl (30mL), NaHCO₃ (30mL) and finally brine (30mL). The combined organic layers were then dried (Na₂SO₄), filtered and the solvent removed in vacuo. The crude oil was then purified by chromatography (Rf: 0.4 in 3:1 ethyl acetate/petroleum ether) to give the desired methenylated compound as a colourless oil (182mg, 61%) which was used without further purification. The methenylated compound (160mg, 0.825mmol) was dissolved in methanol (6mL) and to this solution was added CeCl₃.9H₂O (308mg, 0.825mmol). The reaction mixture was cooled to 0°C and to the stirring solution was added NaBH₄ (102mg, 2.68mmol) in portions over 20min. After the addition the reaction mixture was then monitored by tlc until the disappearance of the starting material was detected. After approx. 1h the reaction was cooled once again cooled to 0°C and carefully quenched with a sat. solution of NH₄Cl. The reaction mixture was then transferred to a separating funnel and the aqueous extracted with ethyl acetate (3x20mL), and the resultant combined organic extracts dried (Na₂SO₄), filtered and the solvent finally removed in vacuo. The crude product was then immediately dissolovd in trimethyl orthoacetate (1.00mL) and to this mixture was added a propionic acid (1drop). This solution was then heated for 16h at reflux under a N₂ atmosphere. After this period the reaction mixture was cooled and the residual trimethyl orthoacetate removed in vacuo and the crude product purified by column chromatography (Rf: 0.55 in 5:3 ethyl acetate/petroleum ether) giving the title compound ((-)29 as a colourless oil (172mg, 83% over 2-steps); [α]D²⁰ = -50.4 (c 1.00, CHCl₃); HRMS (ESI-orbitrap): MNa⁺, C₁₅H₂₀O₅, found 275.1256, requires MNa⁺ 275.1259; IR (solution, CHCl₃) 2900, 1765, 1733, 1440 cm⁻¹; ¹H NMR (400 MHz; CDCl₃) δ 2.81 (dd, J = 4.0, 10.0, 11.2 Hz, 1H), 2.25 (s, 3H), 2.86 (m, 1H), 2.19 (q, J = 6.8 Hz, 1H), 1.96 (d, J = 4.0, 11.2 Hz, 1H), 1.92 – 1.60 (m, 1H), 1.31 (d, J = 6.8 Hz, 3H); ¹³C NMR (100 MHz;CDCl₃) δ 178.5, 173.2, 136.2, 130.0, 79.0, 52.7, 51.8, 38.0, 37.1, 32.8, 27.4, 26.7, 24.0, 15.7.

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Supporting Information: General experimental conditions; optimisation table for the formation of (−)-9a; spectral data for all new compounds and chiral HPLC traces for (−)-9a, (+)-9b, (−)-9b, (−)-9d, (−)-13, (+)-13, (−)-14, (+)-14, (−)2; crystallographic data or (±)14; and is available free of charge via Internet at http://pubs.acs.org.

References


Toste reported that CH$_2$Cl$_2$ was the optimum solvent as it exhibited an enhanced rate for the rearrangement (6h) as compared to other solvents.

As lactone 9a contains an acidic proton the dr for this product was determined to be 9:1 by $^1$H NMR. It must be noted that these diastereoisomers readily interconvert due to this acidity and that the observed dr is a reflection of the thermodynamic product.

See the Supporting information for optimization studies.


(14) See the supporting information. Crystal data for (±)-14: C_{18}H_{30}O_{6}Si, M = 370.51, monoclinic, C2, a = 57.606(17), b = 6.594(2), c = 10.648(3) Å, β = 95.468(4), V = 4026(2) Å³, Z = 8, μ(Mo-Kα) = 0.145 mm⁻¹, 20441 reflections measured, 9762 unique, R_{int} = 0.0520, R_{1}([F^2 > 2σ(F^2)]) = 0.0667, wR_{2} (all data) = 0.1841. Flack parameter x = 0.41(13); both enantiomers present in the asymmetric unit. Space group C2/c was tried but gave a disordered structure. CCDC 907291 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(15) The crude ¹H NMR of the alkylated salt indicated an approximate 4:1 diastereomeric mixture.

(16) Direct deprotonation of lactones (+)-21 or (-)-22 followed by treatment with iodomethane failed to deliver (+)-19 or (-)-20.

