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An asymmetric synthesis of *trans*-fused butyrolactones from endoperoxides

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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.¹ However, conversion of these endoperoxide products into useful asymmetric building blocks^{1c,2} 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,^{2g} presumably due to the reactivity of bicyclic endoperoxides with Co(II) salts which traditionally delivers the bis-epoxide products.³ In 2006, Toste and co-workers successfully desymmetrised bicyclic endoperoxides (**4**) using an organocatalytic Kornblum-De La Mare rearrangement;⁴ however, the synthetic use of these highly enantio-enriched hydroxyenone products (**5**) has been limited.⁵ In a project aimed at investigating the *anti*-inflammatory activity of *trans*-fused xanthanolide natural product analogues,⁶ 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^{6c-i} 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,^{6j} they had to convert a key *cis*-lactone precursor^{6k} 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.^{2g} Furthermore, since hydroxy enones such as **5** can be obtained *via* an organocatalysed Kornblum-De La Mare^{4,7} 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 ¹O₂ oxidation of dienes.

After initial optimisation studies⁹ we found treatment of endoperoxide **4**⁸ in THF⁹ in the presence of 10 mol% of catalyst **8a** for a 16h period followed by addition diethylsodiummalonate gave the desired lactone (**-**)-**9a** in an isolated yield of 76% and *ee* of 92% (Scheme 1 and Table 1; entry 1).^{10,11} While the rearrangement of **4** with catalyst **8b** with subsequent addition of diethylsodiummalonate 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 dimethylsodiummalonate and using catalyst **8a** gave lactone **(-)-9b** in a comparable isolated yield and ee (entry 3). The use of ethyl sodioacetoacetate 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}

Entry	Endo-peroxide	R	Product	Yield [%] ^c	ee ^d
1	4	CO ₂ Et	(-)-9a	76	92
2 ^e	4	CO ₂ Et	(+)-9a	78	94
3	4	CO ₂ Me	(-)-9b	76	92
4 ^f	4	C(O)Me	-	-	-
5	4	C(O)Ph	(-)-9d	82	94
6	11	CO ₂ Et	(-)-13	82	78
7 ^e	11	CO ₂ Et	(+)-13	82	76
8	12	CO ₂ Et	(-)-14	74	94
9 ^e	12	CO ₂ Et	(+)-14	70	92
10	1	CO ₂ Et	(+)-2	44	10

^aSee the general experimental procedure. ^b10 mol% of catalyst **8a** used unless otherwise stated. ^cIsolated yields. ^dDetermined by chiral HPLC. ^e10 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,⁴ the relative stereochemistry of **(±)**-**14** was definitively assigned *via* X-ray crystallography.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 xanthanolid class of natural products.^{6a,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 diethylsodiummalonate 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.¹⁵ Alternatively, the rearranged endoperoxide **4** could be treated with *alpha*-methyldiethylsodiummalonate 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.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 hydroxyenone **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**.¹⁷

Scheme 4. *Trans*-fused lactone formation.

Finally, in reference to accessing xanthanolid 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-workers¹⁸ on lactone **(-)**-**20** giving **28**. This compound proved to be unstable and was directly reduced under Luche conditions¹⁹ 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**.

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 N_2 . 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 N_2 . 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 H_2O (50mL), and the aqueous layer extracted with further portions of EtOAc (2x20mL). The organic layers were then combined, washed with brine, dried (Na_2SO_4), 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%; R_f 0.50 in 3:2 petroleum ether:ethyl acetate); $[\alpha]_D^{20} = -41.2$ (c 1.00, CHCl_3); HRMS (ESI-orbitrap): MNa^+ , $\text{C}_{12}\text{H}_{16}\text{O}_5$, found 277.1039, requires MNa^+ 277.1052; IR (solution, CHCl_3) 3032, 3019, 2942, 1784, 1734, 1708, 1209, 1159 cm^{-1} ; ^1H NMR (400 MHz; CDCl_3) 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); ^{13}C NMR (100 MHz; CDCl_3) 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%); $[\alpha]_D^{18} = +45.2$ (c 1.00, CHCl_3).

(-)-(3R, 3aS, 9aR)-Methyl-2,5-dioxodecahydrocycloocta[b]furan-3-carboxylate ((-)-9b). Prepared using catalyst **8a** (182mg, 76%; R_f 0.20 in 1:1 petroleum ether/ethyl acetate; MP $70.0 - 71.5^\circ\text{C}$); $[\alpha]_D^{20} = -58.0$ (c 1.00, CHCl_3); HRMS (ESI-orbitrap): MNa^+ , $\text{C}_{12}\text{H}_{16}\text{O}_5$, found 263.0883, requires MNa^+ 263.0895; IR (solution, CHCl_3) 3033, 3019, 2946, 1785, 1743, 1708, 1216, 1209, 1159 cm^{-1} ; ^1H NMR (400 MHz; CDCl_3) 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, $J =$

4.0, 14.8 Hz, 1H), 2.43 (dd, $J = 11.6, 14.4$ Hz, 1H), 2.36 (dt, $J = 5.2, 12.8$ Hz, 1H), 2.24 – 2.16 (m, 1H), 1.95 – 1.72 (m, 4H), 1.50 – 1.41 (m, 1H); ^{13}C NMR (100 MHz; CDCl_3) δ 211.4, 169.3, 167.0, 84.1, 53.8, 53.3, 45.5, 43.9, 39.0, 31.1, 26.0, 22.1.

(-)-(3S,3aS,9aR)-tert-Butyl 2,5-dioxodecahydrocycloocta[b]furan-3-carboxylate ((-)-9c). Prepared using catalyst **8a** (191mg, 68%; R_f 0.65 in 1:1 petroleum ether/ethyl acetate; MP 87 – 89 °C); $[\alpha]_D^{26} = -29.6$ (c 1.00, CHCl_3); HRMS (ESI-orbitrap): MNa^+ , $\text{C}_{15}\text{H}_{22}\text{O}_5$, found 305.1353, requires MNa^+ 305.1365; IR (solution, CHCl_3) 2938, 1783, 1727, 1709, 1459, 1371, 1221 cm^{-1} ; ^1H NMR (400 MHz; CDCl_3) 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); ^{13}C NMR (100 MHz; CDCl_3) 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]furan-2,5(3H,6H)-dione ((-)-9d). Prepared using catalyst **8a** (234mg, 82%; R_f 0.55 in 1:1 petroleum ether/ethyl acetate; MP 103 – 105 °C); $[\alpha]_D^{26} = -122.8$ (c 1.00, CHCl_3); HRMS (ESI-orbitrap): MNa^+ , $\text{C}_{17}\text{H}_{18}\text{O}_4$, found 309.1091, requires MNa^+ 309.1103; IR (solution, CHCl_3) 2939, 1773, 1706, 1685, 1449, 1270 cm^{-1} ; ^1H NMR (400 MHz; CDCl_3) 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); ^{13}C NMR (100 MHz; CDCl_3) 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.

(-)-((3R, 3aS, 8aR)-ethyl 2,5-dioxooctahydro-2H-cyclohepta[b]furan-3-carboxylate ((-)-13). Prepared using catalyst **8a** (193mg, 82%; R_f 0.30 in 1:1 petroleum ether/ethyl acetate; MP 64.0 – 66.0 °C); $[\alpha]_D^{19} = -25.6$ (c 1.00, CHCl_3); HRMS (ESI-orbitrap): MNa^+ , $\text{C}_{12}\text{H}_{16}\text{O}_5$, found 263.1130, requires MNa^+ 263.0895; IR (solution, CHCl_3) 3029, 2957, 2931, 2859, 1789, 1736, 1709, 1016 cm^{-1} ; ^1H NMR (400 MHz; CDCl_3) 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); ^{13}C NMR (100 MHz; CDCl_3) 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-dioxooctahydro-2H-cyclohepta[b]furan-3-carboxylate ((+)-13).** Prepared using catalyst **8b** (188mg, 81%); $[\alpha]_D^{21} = +29.6$ (c 1.00, CHCl_3).

(-)-(3R, 3aS, 7S, 8aR)-Ethyl 7-(tert-butyldimethylsilyloxy)-2,5-dioxooctahydro-2H-cyclohepta[b]furan-3-carboxylate ((-)-14). Using the general method but on a 0.40 mmol scale and prepared using catalyst **8a** (107mg, 74%; R_f 0.45 in 3:1 petroleum ether/ethyl acetate; MP 102.0 – 103.5 °C); $[\alpha]_D^{19} = -35.8$ (c 1.00, CHCl_3); HRMS (ESI-orbitrap): MNa^+ , $\text{C}_{18}\text{H}_{30}\text{O}_6\text{Si}$, found 393.1696, requires MNa^+ 393.1709; IR (solution, CHCl_3) 2957, 2931, 2858, 1789, 1736, 1708, 1260, 1016 cm^{-1} ; ^1H NMR (400 MHz; CDCl_3) δ 4.28 (dq, $J = 2.8, 7.2$ Hz, 2H), 4.10 (ddd, $J = 3.6, 10.0, 11.6$ 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); ^{13}C NMR (100 MHz; CDCl_3) 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-dioxooctahydro-2H-cyclohepta[b]furan-3-carboxylate ((+)-14).** Using the general method and prepared using catalyst **8b** (102mg, 70%); $[\alpha]_D^{18} = +32.6$ (c 1.00, CHCl_3).

General methylation conditions. Method A: To a solution of the endoperoxide **4** or **11** (1.00mmol) 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 N_2 . After this period a solution of $\text{NaCH}(\text{CO}_2\text{Et})_2$ [1.1mmol; prepared from $\text{H}_2\text{C}(\text{CO}_2\text{Et})_2$ (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 N_2 .

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%; R_f 0.18 in 3:2 petroleum ether/ ethyl acetate); [α]_D¹⁹ = +26.4 (c 1.00, CHCl₃); HRMS (ESI-orbitrap): MNa⁺, C₁₁H₁₆O₃, found 219.0992, requires MNa⁺ 219.0997; IR (solution, CHCl₃) 3025, 2938, 1774, 1705, 991 cm⁻¹; ¹H NMR (400 MHz; CDCl₃) δ 4.11 (dt, *J* = 3.2, 9.2 Hz, 1H), 2.66 (dd, 3.6, 10.4 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-Methylhexahydro-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%; R_f 0.35 in 1:1 petroleum ether/ethyl acetate; MP 28 – 31°C); [α]_D¹⁹ = -92 (c 1.00, CHCl₃); HRMS (ESI-orbitrap): MNa⁺, C₁₀H₁₄O₃, 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 (R_f 0.13, 3:2 petroleum ether/ethyl acetate) to yield the title compound as a colourless solid (194mg, 76%; MP 74 – 76 °C); [α]_D¹⁹ = +21.2 (c 1.00, CHCl₃); HRMS (ESI-orbitrap): MNa⁺, C₁₀H₁₄O₃, 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 were then purified by chromatography giving the title compound as a colourless solid (130mg, 78%; MP 69.0 – 70.5 °C); [α]_D¹⁹ = -59.6 (c 1.00, CHCl₃); HRMS (ESI-orbitrap): MNa⁺, C₉H₁₂O₃, found 191.0679, requires MNa⁺ 191.0684; IR (solution, CHCl₃) 3019, 2950, 1782, 1704, 1211 cm⁻¹; ¹H NMR (400 MHz; CDCl₃) δ 4.03 (ddd, *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 (iPr)₂NH.TFA (334mg, 1.55mmol) and TFA (12 μ L, 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 (R_f 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 dissolved 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 (R_f 0.55 in 5:3 ethyl acetate/petroleum ether) giving the title compound **(-)-29** as a colourless oil (172mg, 83% over 2-steps); [α]_D²¹ = -50.4 (c 1.00, CHCl₃); HRMS (ESI-orbitrap): MNa⁺, C₁₄H₂₀O₄, found 275.1256, requires MNa⁺ 275.1259; IR (solution, CHCl₃) 2900, 1765, 1733, 1440 cm⁻¹; ¹H NMR (400 MHz; CDCl₃) δ 5.77 – 5.73 (m, 1H), 3.83 (ddd, *J* = 4.0, 10.0, 11.2 Hz, 1H), 3.67 (s, 3H), 2.91 – 2.86 (m, 1H), 2.79 (q, *J* = 6.8 Hz, 1H), 2.52 – 2.41 (m, 4H), 2.39 – 2.35 (m, 2H), 2.24 – 2.16 (m, 1H), 2.11 – 2.01 (m, 1H), 1.81 – 1.75 (m, 1H), 1.71 – 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>.

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