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An Asymmetric Synthesis of *trans*-Fused Butyrolactones from Endoperoxides

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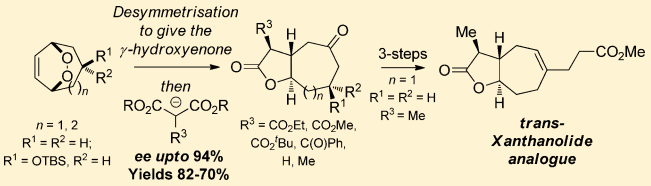
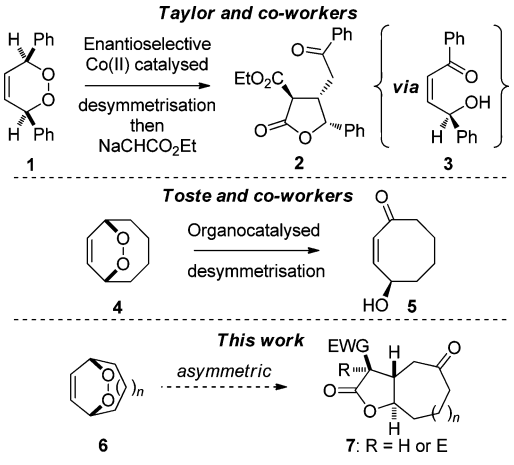
Supporting Information

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 desymmetrized 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]

Scheme 1. Planned Route toward *trans*-Fused Butyrolactones



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. For example, 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 that included a Mitsunobu inversion of the crucial hydroxyl group.

Key to this approach is the trapping of a cyclic hydroxyenone, a result of the base-catalyzed 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 organocatalyzed 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 $^1O_2$ oxidation of dienes.

After initial optimization studies[9] we found treatment of endoperoxide **4**[8] in THF[9] in the presence of 10 mol % of catalyst **8a** for a 16 h period followed by addition of diethylsodiomalonate gave the desired lactone (−)-**9a** in an isolated yield of 76% and ee of 92% (Scheme 2 and Table 1; entry 1),[10] 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). Lactones (−)- and (+)-**9a** contain an acidic proton between the 1,3-dicarbonyl unit and therefore exist as an inseparable mixture of diastereomers with the major diastereoisomer, as determined

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Scheme 2. Lactone Optimization

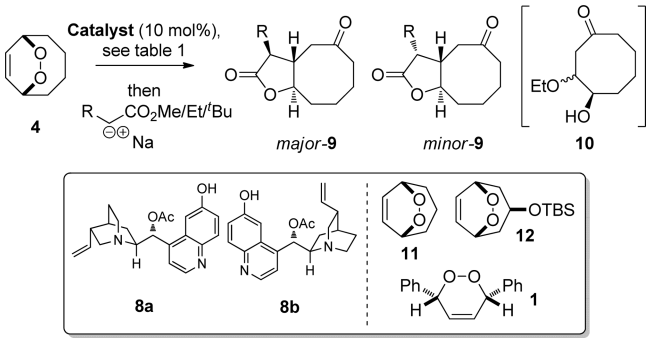
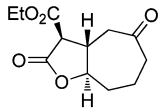
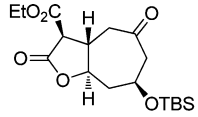
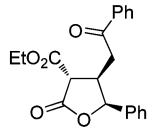


Table 1. Asymmetric Butyrolactone Formation and Scope[a,b]

Entry	Endo-peroxide	R	Product	Yield [%][c]	ee[d]
1	**4**	CO_2Et	**(-)-9a**	76	92
2[e]	**4**	CO_2Et	**(+)-9a**	78	94
3	**4**	CO_2Me	**(-)-9b**	76	92
4[f]	**4**	C(O)Me	**10**	62	-
5	**4**	C(O)Ph	**(-)-9d**	82	94
6	**11**	CO_2Et	 **(-)-13**	82	78
7[e]	**11**	CO_2Et	**(+)-13**	82	76
8	**12**	CO_2Et	 **(-)-14**	74	94
9[e]	**12**	CO_2Et	**(+)-14**	70	92
10	**1**	CO_2Et	 **(+)-2**	44	10

[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]Isolated as an inseparable mixture of diastereoisomers.

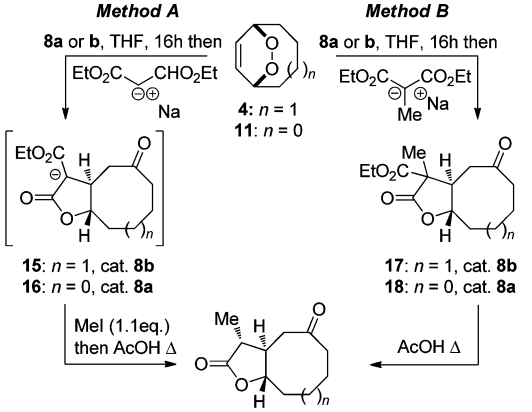
via NOE, as depicted in Scheme 2. The dr for (−)- and (+)-**9a** was determined to be approximately 9:1 as assigned *via* ^{1}H NMR analysis.

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 dimethylsodiomalonate and using catalyst **8a** gave lactone (−)-**9b** in a comparable isolated yield and ee (entry 3). Surprisingly, ethyl sodioacetoacetate failed to deliver the butyrolactone but instead yielded only the alkoxy Michael addition product **10** as an inseparable mixture of diastereoisomers (entry 4); however, the addition of ethyl sodiobenzoyl 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,[11] was also exposed to the optimized reaction conditions with catalyst **8a** delivering (−)-**13** in 82% yield and ee of 78%, while the enantiomer (+)-**13** was obtained in an ee of 76% and a comparable isolated yield using catalyst **8b** (entries 6 and 7, respectively). As with lactones (−)- and (+)-**9a**, (−)- and (+)-**13** were isolated in a dr of 8:1. When the OTBS-protected seven-membered endoperoxide **12**, derived from commercially available tropone,[12] was treated with catalyst **8a** under the optimized conditions, the lactone (−)-**14** was isolated in a good yield of 74% and an excellent ee of 94%, while catalyst **8b** gave the enantiomer (+)-**14** in 70% yield and an ee of 92% (entries 8 and 9, respectively). Once again, due to the acidity of the proton between the 1,3-dicarbonyl unit, (−)- and (+)-**14** were each isolated as an inseparable mixture of diastereoisomers in a dr of 8:1.

While the absolute stereochemistry of this latter lactone can be deduced from the work of Toste,[4] the relative stereochemistry of (±)-**14** was definitively assigned *via* X-ray crystallography.[13] 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.[6a,b] Finally, endoperoxide **1** was exposed to the lactonization 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).

Scheme 3. Direct Installation of the α-Methyl Group



Desymmetrization 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 α-methyl-substituted lactone (+)-**19** in a diastereomeric ratio of 4:1 in 66% yield.[14] Alternatively, the rearranged endoperoxide **4** could be treated with α-methyldiethylsodiomalonate giving lactone **17**, which upon decarboxylation gave (+)-**19** in a comparable chemical yield and a similar diastereomeric ratio of 4:1. Additionally, as these two processes rely on the decarboxylation of a common intermediate the stereochemical outcome was the same in both cases. These two processes were also performed upon the seven membered endoperoxide **11** using catalyst **8a** in

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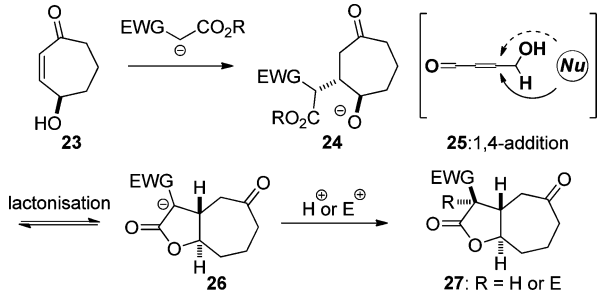
this case, giving the desired α-methyl-substituted lactone (−)-**20** in good chemical yield and diastereoselectivity.[15]

The *trans* stereochemistry of the butyrolactone is installed *via* the mechanism shown below in Scheme 4. The hydroxyenone

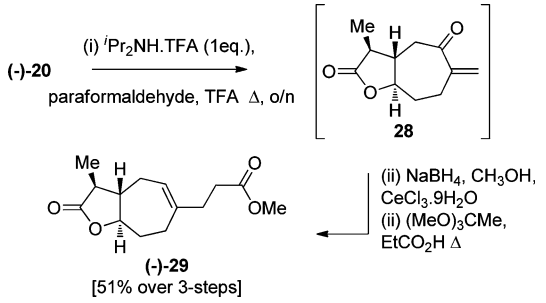
Scheme 4. *trans*-Fused Lactone Formation



23 undergoes conjugate addition *anti* to the hydroxyl group, as depicted in **25**, to deliver the addition product **24**. This undergoes lactonization to deliver the *trans*-fused product **26**, which can then be protonated or trapped by an appropriate electrophile, therefore giving **27**.[16]

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

Scheme 5. Synthesis of Xanthanolide Analogue (−)-29



were able to selectively install an exomethylene group using the conditions of Connell and co-workers[17] on lactone (−)-**20**, giving **28**. This compound proved to be unstable and was directly reduced under Luche conditions[18] to yield the allylic alcohol. Subsequent exposure of this alcohol to trimethyl orthoacetate gave the Claisen rearrangement product (−)-**29** in a yield of 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.

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 transitions metals and also showcases the use of endoperoxides as environmentally sustainable sources of oxygen functionality.

EXPERIMENTAL SECTION

General Experimental Procedure for Racemic Lactone Formation. To a solution of the endoperoxide (1.0 mmol) in dry THF (5 mL) was added a solution of the desired nucleophile (1.0 mmol) [prepared in THF (3.0 mL) by the addition of NaOEt or NaOMe (2.2 mL, 0.5M, 1.1 mmol) to the required malonate derivative (1.0 mmol)] dropwise at 0 °C, and the resultant solution allowed to warm to room temperature and stirred for 16 h under N_2. The reaction mixture was then cooled to 0 °C and quenched by the addition of 1 M HCl, after which it was partitioned between ethyl acetate (50 mL) and H_2O (50 mL), and the aqueous layer was extracted with further portions of ethyl acetate (2 × 20 mL). The organic layers were then combined, washed with brine, dried (Na_2SO_4), and filtered, and the solvent was removed *in vacuo*. The crude products were then purified by chromatography. The ^{1}H NMR, ^{13}C NMR, IR, and MS physical data for **9a**,[2g] **9b**, **9c**, **9d**, **13**, **14**, and **2**[2g] matched that for the enantio-enriched examples.

General Experimental Procedure for Enantio-enriched Lactone Formation. To a solution of the endoperoxide (1.0 mmol) in dry THF (5.0 mL) was added the catalyst (0.1 mmol, **8a** or **8b** as indicated below), and the resultant reaction mixture was stirred at room temperature for 16 h under N_2. After this period a solution of the desired nucleophile (1.0 mmol) [prepared in THF (3.0 mL) by the addition of NaOEt or NaOMe (2.2 mL, 0.5M, 1.1 mmol) to the required malonate derivative (1.0 mmol)] 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 16 h under N_2. The reaction mixture was then cooled to 0 °C and quenched by the addition of 1 M HCl, after which it was partitioned between EtOAc (50 mL) and H_2O (50 mL), and the aqueous layer was extracted with further portions of ethyl acetate (2 × 20 mL). The organic layers were then combined, washed with brine, dried (Na_2SO_4), and filtered, and the solvent was removed *in vacuo*. The crude products were then purified by chromatography. *Using this procedure the following compounds were obtained:*

(−)-(3*R*,3a*S*,9a*R*)-Ethyl 2,5-Dioxodecahydrocycloocta[*b*]-furan-3-carboxylate ((−)-9a). Prepared using catalyst **8a** and obtained as a colorless viscous oil (193 mg, 76%; R_f 0.50 in 3:2 petroleum ether/ethyl acetate); $[\alpha]^{20}_D$ = −41.2 (*c* 1.00, $CHCl_3$); IR (solution, $CHCl_3$) 3032, 3019, 2942, 1784, 1734, 1708, 1209, 1159 cm^{-1}; ^{1}H 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; HRMS (ESI-orbitrap) *m*/*z*: [M + Na]$^+$ calcd for $C_{13}H_{18}O_5Na$ for 277.1052, found 277.1039.

(+)-(3*S*,3a*R*,9a*S*)-Ethyl 2,5-Dioxodecahydrocycloocta[*b*]furan-3-carboxylate ((+)-9a). Prepared using catalyst **8b** and obtained as a colorless viscous oil (196 mg, 78%); $[\alpha]^{18}_D$ = +45.2 (*c* 1.00, $CHCl_3$); ^{1}H and ^{13}C NMR matched that for (−)-**9a**; HRMS (ESI-orbitrap) *m*/*z*: [M + Na]$^+$ calcd for $C_{13}H_{18}O_5Na$ for 277.1052, found 277.1041.

(−)-(3*R*,3a*S*,9a*R*)-Methyl 2,5-Dioxodecahydrocycloocta[*b*]-furan-3-carboxylate ((−)-9b). Prepared using catalyst **8a** and obtained as a colorless crystalline solid (182 mg, 76%; R_f 0.20 in 1:1 petroleum ether/ethyl acetate; mp 70.0−71.5 °C); $[\alpha]^{20}_D$ = −58.0 (*c* 1.00, $CHCl_3$); IR (solution, $CHCl_3$) 3033, 3019, 2946, 1785, 1743, 1708, 1216, 1209, 1159 cm^{-1}; ^{1}H 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; HRMS (ESI-orbitrap) *m*/*z*: [M + Na]$^+$ calcd for $C_{12}H_{16}O_5Na$ for 263.0895, found 263.0883.

(−)-(3*S*,3a*S*,9a*R*)-*tert*-Butyl 2,5-dioxodecahydrocycloocta[*b*]-furan-3-carboxylate ((−)-9c). Prepared using catalyst **8a** and obtained as a colorless crystalline solid (191 mg, 68%; R_f 0.65 in 1:1 petroleum ether/ethyl acetate; mp 87−89 °C); $[\alpha]^{26}_D$ = −29.6 (*c* 1.00, $CHCl_3$); IR (solution, $CHCl_3$) 2938, 1783, 1727, 1709, 1459, 1371, 1221 cm^{-1}; ^{1}H 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,

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28.0, 26.1, 22.0; HRMS (ESI-orbitrap) m/z: $[M + Na]^+$ calcd for $C_{15}H_{22}O_5Na$ for 305.1365, found 305.1353.

(−)-(3*R*,3a*S*,9a*R*)-3-Benzoylhexahydrocycloocta[*b*]furan-2,5-(3*H*,6*H*)-dione ((−)-9d). Prepared using catalyst **8a** and obtained as colorless needles (234 mg, 82%; R_f 0.55 in 1:1 petroleum ether/ethyl acetate; mp 103−105 °C); $[\alpha]^{26}_D$ = −122.8 (*c* 1.00, $CHCl_3$); 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; HRMS (ESI-orbitrap) m/z: $[M + Na]^+$ calcd for $C_{17}H_{18}O_4Na$ for 309.1103, found 309.1091.

(−)-((3*R*,3a*S*,8a*R*)-Ethyl 2,5-Dioxooctahydro-2*H*-cyclohepta-[*b*]furan-3-carboxylate ((−)-13). Prepared using catalyst **8a** and obtained as a colorless crystalline solid (193 mg, 82%; R_f 0.30 in 1:1 petroleum ether/ethyl acetate; mp 64.0−66.0 °C); $[\alpha]^{19}_D$ = −25.6 (*c* 1.00, $CHCl_3$); 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; HRMS (ESI-orbitrap) m/z: $[M + Na]^+$ calcd for $C_{12}H_{16}O_5Na$ for 263.0895, found 263.0883. **(+)-(3*S*,3a*R*,8a*S*)-Ethyl 2,5-Dioxooctahydro-2*H*-cyclohepta[*b*]furan-3-carboxylate ((+)-13).** Prepared using catalyst **8b** (188 mg, 81%); $[\alpha]^{21}_D$ = +29.6 (*c* 1.00, $CHCl_3$); ^1H and ^{13}C NMR matched that for (−)-**13**. HRMS (ESI-orbitrap) m/z: $[M + Na]^+$ calcd for $C_{12}H_{16}O_5Na$ for 263.0895, found 263.0885.

(−)-(3*R*,3a*S*,7*S*,8a*R*)-Ethyl 7-(*tert*-Butyldimethylsilyloxy)-2,5-dioxooctahydro-2*H*-cyclohepta[*b*]furan-3-carboxylate ((−)-14). Using the general method but on a 0.4 mmol scale, prepared using catalyst **8a** and obtained as colorless needles (107 mg, 74%; R_f 0.45 in 3:1 petroleum ether/ethyl acetate; mp 102.0−103.5 °C); $[\alpha]^{19}_D$ = −35.8 (*c* 1.00, $CHCl_3$); 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; HRMS (ESI-orbitrap) m/z: $[M + Na]^+$ calcd for $C_{18}H_{30}O_6SiNa$ for 393.1709, found 393.1696. **(+)-(3*S*,3a*R*,7*R*,8a*S*)-Ethyl 7-(*tert*-Butyldimethylsilyloxy)-2,5-dioxooctahydro-2H-cyclohepta[*b*]furan-3-carboxylate ((+)-14).** Using the general method and prepared using catalyst **8b** (102 mg, 70%); $[\alpha]^{18}_D$ = +32.6 (*c* 1.00, $CHCl_3$). ^1H and ^{13}C NMR matched that for (−)-**14**. HRMS (ESI-orbitrap) m/z: $[M + Na]^+$ calcd for $C_{18}H_{30}O_6SiNa$ for 393.1709, found 393.1698.

General Methylation Conditions. Method A: To a solution of the endoperoxide **4** or **11** (1.0 mmol) in dry THF (10 mL) was added the catalyst **8a** or **8b** (0.1 mmol), and the resultant reaction mixture was stirred at room temperature for 16 h under N_2. After this period a solution of $NaCH(CO_2Et)_2$ [1.1 mmol; prepared from $H_2C(CO_2Et)_2$ (193 mg, 1.1 mmol) and NaOEt (2.2 mL, 0.50 M solution, 1.1 mmol) THF (5.0 mL)] was added dropwise to the reaction mixture at 0 °C, and the resultant solution was allowed to warm to room temperature and stirred for a further 16 h under N_2. The reaction mixture was then cooled to 0 °C, and iodomethane (94 μL, 1.5 mmol) was added, after which the reaction mixture was stirred for a further 16 h at room temperature. A satd solution of NH_4Cl (10 mL) was then added, the solution then partitioned between CH_2Cl_2 (50 mL) and H_2O (50 mL), and the aqueous layer extracted with further portions of CH_2Cl_2 (2 × 40 mL). The organic layers were then combined, washed with brine (50 mL), dried (Na_2SO_4), and filtered, and the solvent was removed *in vacuo*. The crude material was then dissolved in 50% acetic acid (10 mL) and refluxed overnight. After this period, the reaction was cooled and carefully basified with $NaHCO_3$, and the aqueous layer was extracted with dichloromethane (2 × 40 mL). The combined organic extracts were then dried (Na_2SO_4) and 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** (1.0 mmol) in dry THF (8 mL) was added the catalyst **8a** or **8b** (35 mg, 0.1 mmol), and the resultant reaction mixture was stirred at room temperature for 16 h under N_2. After this period a solution of $NaCMe(CO_2Et)_2$ [1.1 mmol; prepared from $HCMe(CO_2Et)_2$ (193 mg, 1.1 mmol) and NaOEt (2.2 mL, 0.5 M solution, 1.1 mmol) THF (5.0 mL)] 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 16 h under N_2. The reaction mixture was then cooled to 0 °C, and a satd solution of NH_4Cl (10 mL) was added, partitioned between CH_2Cl_2 (50 mL) and H_2O (50 mL), and the aqueous layer was extracted with further portions of CH_2Cl_2 (2 × 30 mL). The organic layers were then combined, washed with brine (50 mL), dried (Na_2SO_4), and filtered, and the solvent was removed *in vacuo*. The crude material was then dissolved in 50% acetic acid (10 mL) and refluxed overnight. After this period, the reaction was cooled and carefully basified with $NaHCO_3$, and the aqueous layer was extracted with CH_2Cl_2 (2 × 40 mL). The combined organic extracts were then dried (Na_2SO_4) and 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:*.

(+)-(3*R*,3a*R*,9a*S*)-3-Methylhexahydrocycloocta[*b*]furan-2,5-(3*H*,6*H*)-dione ((+)-19). Obtained as a colorless oil (**Method A**; 130 mg, 66%; **Method B**; 123 mg, 63%; R_f 0.18 in 3:2 petroleum ether/ethyl acetate); $[\alpha]^{19}_D$ = +26.4 (*c* 1.00, $CHCl_3$); IR (solution, $CHCl_3$) 3025, 2938, 1774, 1705, 991 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) 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); ^{13}C NMR (100 MHz; $CDCl_3$) δ 212.8, 177.1, 84.0, 49.0, 45.3, 42.6, 39.9, 31.4, 25.8, 22.9, 12.8; HRMS (ESI-orbitrap) m/z: $[M + Na]^+$ calcd for $C_{11}H_{16}O_3Na$ for 219.0997, found 219.0992.

(−)-(3*S*,3a*S*,8a*R*)-3-Methylhexahydro-2*H*-cyclohepta[*b*]-furan-2,5(3*H*)-dione ((−)-20). Obtained as a waxy solid (**Method A** (performed on a 2.0 mmol scale) 298 mg, 79%; **Method B**; 124 mg, 68%; R_f 0.35 in 1:1 petroleum ether/ethyl acetate; mp 28−31 °C); $[\alpha]^{19}_D$ = −92 (*c* 1.00, $CHCl_3$); IR (solution, $CHCl_3$) 3029, 3019, 2936, 1776, 1703, 1208 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) 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); ^{13}C NMR (100 MHz; $CDCl_3$) δ 210.3, 177.4, 83.6, 46.2, 43.5, 43.4, 41.9, 34.3, 20.8, 12.9; HRMS (ESI-orbitrap) m/z: $[M + Na]^+$ calcd for $C_{10}H_{14}O_3Na$ for 205.0841, found 205.0836.

(+)-(3a*R*,9a*S*)-Hexahydrocycloocta[*b*]furan-2,5(3*H*,6*H*)-dione ((+)-21). Lactone (+)-**9a** (0.36g, 1.40 mmol) was dissolved in ethanol (15 mL) and 2 M KOH (15 mL), and the resultant solution was stirred at room temperature for 16 h. After this period the reaction mixture was carefully acidified with 5 M HCl and extracted with CH_2Cl_2 (2 × 30 mL), the combined organic layers were dried (Na_2SO_4) and filtered, and the solvent was removed *in vacuo*. The crude acid was then dissolved in toluene (25 mL) and refluxed for overnight. The solvent was then removed *in vacuo*, and the crude solid was purified by column chromatography (R_f 0.13, 3:2 petroleum ether/ethyl acetate) to yield the title compound as a colorless solid (194 mg, 76%; mp 74−76 °C); $[\alpha]^{19}_D$ = +21.2 (*c* 1.00, $CHCl_3$); IR (solution, $CHCl_3$) 3011, 3027, 2942, 1780, 1705, 1016 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) 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); ^{13}C NMR (100 MHz; $CDCl_3$) δ 21.4, 174.4, 86.0, 46.4, 41.1,

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39.7, 37.1, 31.6, 25.7, 22.8; HRMS (ESI-orbitrap) m/z: $[M + Na]^+$ calcd for $C_{10}H_{14}O_3Na$ for 205.0841, found 205.0836.

(−)-(3a*S*,8a*R*)-Hexahydro-2*H*-cyclohepta[*b*]furan-2,5(3*H*)-dione ((−)-22). Lactone (−)-**13** (241 mg, 1.0 mmol) was dissolved in 50% acetic acid (10 mL) and refluxed overnight. After this period, the reaction was cooled and basified with $NaHCO_3$, and the aqueous layer was extracted with dichloromethane (2 × 30 mL). The combined organic extracts were then dried (Na_2SO_4) and filtered, and the solvent was removed *in vacuo*. The crude product were then purified by chromatography giving the title compound as a colorless solid (130 mg, 78%; mp 69.0−70.5 °C); $[\alpha]^{19}_D$ = −59.6 (*c* 1.00, $CHCl_3$); IR (solution, $CHCl_3$) 3019, 2950, 1782, 1704, 1211 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) 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); ^{13}C NMR (100 MHz; $CDCl_3$) δ 210.3, 175.0, 85.6, 44.1, 43.3, 38.6, 35.9, 34.2, 20.8; HRMS (ESI-orbitrap) m/z: $[M + Na]^+$ calcd for $C_9H_{12}O_3Na$ for 191.0684, found 191.0679.

(−)-Methyl 3-((3*S*,3a*S*,8a*R*)-3-Methyl-2-oxo-3,3a,4,7,8,8a-hexahydro-2*H*-cyclohepta[*b*]furan-6-yl)propanoate ((−)-29). To a mixture of (−)-**20** (282 mg, 1.55 mmol) and paraformaldehyde (96 mg, 3.10 mmol) in dry THF (2 mL) were added $(^iPr)_2NH.TFA$ (334 mg, 1.55 mmol) and TFA (12 μL, 0.16 mmol). The reaction mixture was then refluxed for 2 h, after which it was cooled to room temperature. Another portion of paraformaldehyde (94 mg, 3.10 mmol) added, and the reaction mixture refluxed for a further 6 h. After this period the reaction mixture was cooled, the solvent was removed *in vacuo*, and the residue was dissolved in CH_2Cl_2 (40 mL) and washed sequentially with 1 M HCl (30 mL), $NaHCO_3$ (30 mL), and finally brine (30 mL). The combined organic layers were then dried (Na_2SO_4) and filtered, and the solvent was 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 colorless oil (182 mg, 61%), which was used without further purification. The methenylated compound (160 mg, 0.83 mmol) was dissolved in methanol (6 mL), and to this solution was added $CeCl_3{\cdot}9H_2O$ (308 mg, 0.83 mmol). The reaction mixture was cooled to 0 °C, and to the stirring solution was added $NaBH_4$ (102 mg, 2.68 mmol) in portions over 20 min. After this addition the reaction mixture was then monitored by TLC until the disappearance of the starting material was detected. After approximately 1 h the reaction was once again cooled to 0 °C and carefully quenched with a satd solution of NH_4Cl. The reaction mixture was then transferred to a separating funnel, and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The resultant combined organic extracts were dried (Na_2SO_4) and filtered, and the solvent finally was removed *in vacuo*. The crude product was then immediately dissolved in trimethyl orthoacetate (1.00 mL), and to this mixture was added a propionic acid (1 drop). This solution was then heated for 16 h at reflux under a N_2 atmosphere. After this period the reaction mixture was cooled, the residual trimethyl orthoacetate was removed *in vacuo*, and the crude product was purified by column chromatography (R_f 0.55 in 5:3 ethyl acetate/petroleum ether) giving the title compound (−)-**29** as a colorless oil (172 mg, 83% over 2 steps); $[\alpha]^{21}_D$ = −50.4 (*c* 1.00, $CHCl_3$); IR (solution, $CHCl_3$) 2900, 1765, 1733, 1440 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) 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); ^{13}C NMR (100 MHz; $CDCl_3$) 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; HRMS (ESI-orbitrap) m/z: $[M + Na]^+$ calcd for $C_{14}H_{20}O_4Na$ for 275.1259, found 275.1256.

■ ASSOCIATED CONTENT

Supporting Information

General experimental conditions; optimization 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**; crystallographic data or (±)-**14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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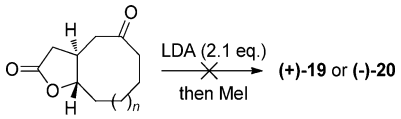
(13) See the Supporting Information. Crystal data for (±)-**14**: $C_{18}H_{30}O_6Si$, M = 370.51, monoclinic, $C2$, a = 57.606(17), b = 6.594(2), c = 10.648(3) Å, β = 95.468(4)°, V = 4026(2) Å^3, Z = 8, μ(Mo Kα) = 0.145 mm^{-1}, 20441 reflections measured, 9762 unique, R_{int} = 0.0520, $R_1[F^2 > 2\sigma(F^2)]$ = 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.

(14) This dr was assigned *via* ^{1}H NMR of the crude decarboxylated material, and the stereochemistry of the methyl group within (−)-**19** and (+)-**20** was assigned using NOE.

(15) An attempt to directly methylate lactones (+)-**21** and (−)-**22** was also trialed. This involved treatment of the lactone with 2.1 equiv of LDA, first effecting deprotonation alpha to the ketone and second alpha to the lactone. However, subsequent addition of 1.0 equiv of iodomethane failed to deliver (+)-**19** or (−)-**20**, and only generated a complex mixture in each case.



(+)-21: n = 1, cat. **8b**
(-)-22: n = 0, cat. **8a**

(16) In context, this sequence should be seen as an intermolecular conjugate addition route to the *trans*-fused lactones, complementary to the intramolecular conjugate addition approach which exclusively give *cis*-fused lactones; see (a) Burns, A. R.; McAllister, G. D.; Shanahan, S. E.; Taylor, R. J. K. *Angew. Chem., Int. Ed.* **2010**, *49*, 5574. (b) Kitson, R. R. A; Taylor, R. J. K.; Wood, J. L. *Org. Lett.* **2009**, *11*, 5338. (c) Edwards, M. G.; Kenworthy, M. N.; Kitson, R. R. A.; Perry, A.; Scott, M. S.; Whitwood, A. C.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2008**, 4769. (d) Edwards, M. G.; Kenworthy, M. N.; Kitson, R. R. A.; Scott, M. S.; Taylor, R. J. K. *Angew. Chem., Int. Ed.* **2008**, *47*, 1935.

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