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2,6-Disubstituted Tetrahydropyrans by Tandem Cross-Metathesis/ Iodocyclisation

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A new approach to 2,6-disubstituted tetrahydropyrans by a tandem cross-metathesis/iodocyclisation reaction has been developed. The stereochemical outcome of the cyclisation reactions has been studied for different substrates. This sequence has allowed the preparation of a series of *cis*- and *trans*-2,6-disubstituted analogues of the tetrahydropyran subunit of bistramide A.

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Introduction

The tetrahydropyran subunit is present in numerous natural products and many strategies have been developed over the years to build this heterocycle.[1] The most widely used methods in natural product synthesis are the hetero-Diels–Alder cyclisation,[2] the Prins and related cyclisation reactions,[3] intramolecular oxo-Michael additions[4] and ring-closing metathesis.[5,6] Other strategies include the cyclisation of non-activated hydroxy alkenes promoted by an electrophilic species. Thus, the tetrahydropyran core structure of different synthetic targets can be obtained by the oxypalladation of allylic acetates[7] or terminal alkenes,[8] but also by alkene activation with selenonium[9] or iodonium ions.[10]

Bistramide A is a marine metabolite containing substituted tetrahydropyran and spiroketal subunits linked by a γ-amino acid (Figure 1). This molecule was initially isolated in 1988 from the marine ascidian *Lissoclinum bistratum*[11] and four other members of the bistramide family (bistramides B, C, D and K) have been identified to date.[12] Bistramides exhibit significant biological properties, in particular, antiproliferative,[13] neurotoxic[14] and cytotoxic[12] activities. More specifically, the potent antiproliferative profile of bistramide A was initially attributed to a highly selective activation of protein kinase C-δ.[15] Recent studies have called into question this mode of action and instead reported actin to be the primary cellular receptor of bistramide A.[16] Since the first total synthesis of bistramide A by Kozmin and co-workers, which provided the full structural assignment of this complex molecule,[5] two other syntheses have been achieved.[17,18]

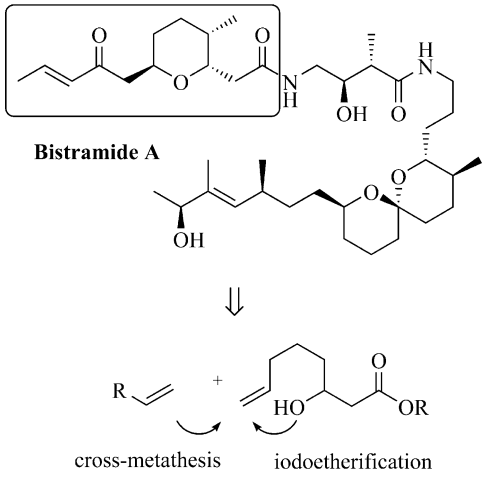

Figure 1. Strategic route to 2,6-disubstituted tetrahydropyran analogues of the north part of bistramide A.

We are interested in the synthesis of analogues of the north part of bistramide A (the tetrahydropyran subunit) as part of a research program devoted to the discovery of new modulators of protein kinases in order to investigate the potential role of this subunit in actin- and kinase-mediated effects. In connection with our work on tandem processes involving metathesis reactions,[19] we envisaged a rapid access to various 2,6-disubstituted tetrahydropyranyl ester analogues by a cross-metathesis of a common hydroxy alkene precursor followed by iodocyclisation to form the tetrahydropyran ring (Figure 1). These two reactions have previously been closely associated with the synthesis of bis(tetrahydrofuran) acetogenin derivatives[20] (THF fragments obtained by iodocyclisation and assembled after further functionalisation by a cross-metathesis reaction) and with the synthesis of spiroketal-containing bioactive compounds such as attenol A[21] (iodoetherification used as a protection method for a 1,5-alkenol subunit before a sili-

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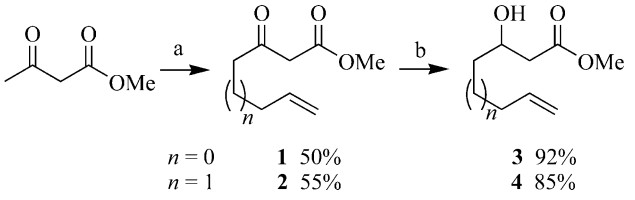
con-tether-aided coupling metathesis step). However, neither of these approaches was reported to involve a tandem process of these two reactions. Herein, we wish to report our results based on this strategy.

Results and Discussion

First, we performed cross-metathesis reactions on a common δ- or ε-unsaturated alcohol precursor easily prepared in two steps. Next, we optimised the electrophile-mediated cyclisation step by testing different activating agents and the resulting cycloadducts were submitted to hydrogenolysis in order to determine the regio- and stereochemical outcome of the haloetherification step. Finally, the cross-metathesis and iodocyclisation reactions were combined in a tandem process to rapidly access the target 2,6-disubstituted tetrahydropyranyl ester analogues.

Cross-Metathesis Reactions

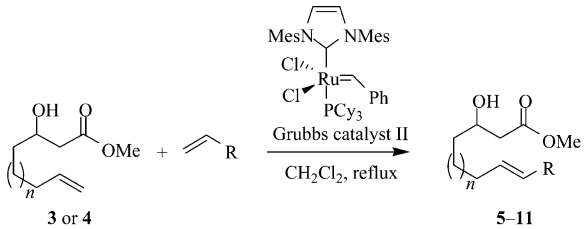
The initial attempt at the cross-metathesis reaction was performed on unsaturated β-keto ester **2**, prepared by γ-alkylation of methyl acetoacetate with 4-bromobut-1-ene (Scheme 1). The next step involved the reduction of the ketone to the alcohol and, considering that the presence of a free hydroxy group has been shown to favour cross-metathesis reactions,[22] we performed cross-metathesis reactions on β-hydroxy esters **3** and **4**, prepared by selective reduction of **1** and **2** with sodium borohydride.



Scheme 1. Synthesis of β-hydroxy esters **3** and **4**. Reagents and conditions: (a) NaH, BuLi, alkyl bromide, THF; (b) $NaBH_4$, MeOH, room temp.

The results of the cross-metathesis reactions between unsaturated β-keto ester **2** or unsaturated β-hydroxy esters **3** and **4** and various olefins are reported in Table 1. The reactions were performed by using the second-generation Grubbs reagent as the catalyst (2 mol-%) and 5 equivalents of olefin in refluxing dichloromethane. The functionalised products **5**–**12** were isolated in good to high yields (61–83%), the *E* isomer being the major product in all cases, reflecting the reversibility of the process. The cross-metathesis product of unsaturated β-keto ester **2** with 1-hexene was obtained in good yield (78%, entry 3) and the same reaction with unsaturated β-hydroxy ester **4** (entry 4) delivered in slightly better yield the corresponding butyl-substituted product **8** (82%). When the chain length of the olefin was increased (R = C_4H_9 or R = C_8H_{17}, entries 4 and 5), we observed similar yields of products, but a quite different *E*/*Z* selectivity: the *E*/*Z* ratio dropped from 9:1 with 1-hexene to 1.2:1 with 1-decene.

Table 1. Cross-metathesis of β-hydroxy esters **3** or **4** with various olefins.



Entry	*n*	Olefin	Product	Yield (%)	*E*/*Z*[b]
1	0		**5**	70	9:1
2	0	TBDPSO	**6**	61	1.5:1
3[a]	1		**7**	78	>19:1
4	1		**8**	82	9:1
5	1	C_6H_{13}	**9**	76	1.2:1
6	1	Br	**10**	83	9:1
7	1	Ph	**11**	75	>19:1
8	1	O, BnO	**12**	69	5.7:1[c]

[a] This reaction was performed on β-keto ester **2**. [b] Approximate ratio determined by ^1H and ^{13}C NMR signal intensity. [c] Exact value determined by ^1H NMR signal integration.

Cyclisation Reactions

Optimisation of Conditions

Different activating agents for the cyclisation of butyl-substituted hydroxy alkene **8** were examined in order to find suitable conditions for the haloetherification step (Table 2, entries 1–3). *N*-Bromo- and *N*-iodosuccinimide (1.5 equiv.) in acetone/water (10:1) gave, respectively, traces or a low yield (37%, method A) of cyclised products. In both cases, the starting material was primarily recovered. The cyclisation promoted by iodine (3 equiv.) in the presence of sodium hydrogen carbonate (3.2 equiv.) occurred to give a good yield of 78% (entry 2). Finally, the best conditions were found by using bis(*sym*-collidine)iodine(I) hexafluorophosphate as the iodonium ion source[23] which gave a higher 93% yield of cycloadducts (entry 3).

Cyclisation of All Substrates

Next, the unsubstituted hydroxy alkene **4** and the remaining cross-metathesis products **5** and **9**–**12** were cyclised with bis(*sym*-collidine)iodine(I) hexafluorophosphate as the iodonium ion source (Table 2, method C). In some cases, the cyclisation was also tested with iodine and sodium hydrogen carbonate (method B) to compare the efficiency of the two methods. In general, better yields of cyclised products were obtained with bis(*sym*-collidine)iodine(I) hexafluorophosphate (75–99%). However, the iodocyclisation of phenyl-substituted hydroxy alkene **11** was more complete with iodine (67 vs. 49%, entries 9 and 10).

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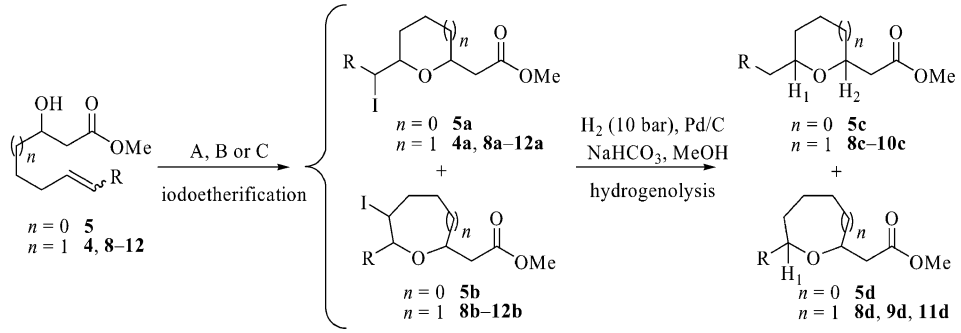
Table 2. Iodoetherification and hydrogenolysis of compounds **4**, **5** and **8**–**12**.



Entry	*n*	SM (*E*/*Z*)	Method[a]	Combined yield (%)[b]	Combined yield (%)[c]	**c**/**d**	**c**[d] *cis*/*trans*	**d** *dr*[e]
1	1	**8** (9:1)	A	37	77	3.5:1	67:33	≈50:50
2	1	**8** (9:1)	B	78	94	4:1	63:37	≈50:50
3	1	**8** (9:1)	C	93	85	4:1	68:32	≈50:50
4	0	**5** (9:1)	C	75	84	9:1	70:30	*cis* only
5	1	**4**	B	76	–	1:0[f]	67:33[g]	–
6	1	**4**	C	99	–	1:0[f]	73:27[g]	–
7	1	**9** (1.2:1)	C	87	87	1.8:1	75:25	64:36
8	1	**10** (9:1)	C	93	42	1:0	100:0	–
9	1	**11** (>19:1)	C	49	92	0:1	–	76:24[h]
10	1	**11** (>19:1)	B	67	–	–	–	–
11	1	**12** (5.7:1)	C	55	–	–	–	–

[a] Conditions: A) NIS (1.5 equiv.), acetone/H_2O (1:0.1); B) I_2 (3 equiv.), $NaHCO_3$ (3.2 equiv.), CH_3CN; C) bis(collidine)I·PF_6 (1.2 equiv.), CH_2Cl_2. [b] Yield of iodoetherification. [c] Yield of hydrogenolysis. [d] The *cis* and *trans* isomers of tetrahydropyrans **c** were isolated. [e] Diastereomeric ratio of the isolated mixture of *cis*- and *trans*-oxepanes **d** were determined by NMR spectroscopy. [f] These values refer to the **4a**/**4b** ratio. [g] These values refer to the *cis*/*trans* ratio of **4a**. [h] The *cis* and *trans* isomers were isolated.

Hydrogenolysis of the Iodocycloadducts: Regio- and Stereochemical Outcome of the Cyclisation Reactions

The stereochemical outcome of iodine-mediated intramolecular cyclisations has been studied for a diverse range of substituted substrates.[10,24] In our case, the regio- and stereoselectivities of ring closure is essentially governed by the *E*/*Z* ratio and the nature of the substitution of the olefin as there is no substitution between the alcohol and the olefin functions. In order to determine the structures and relative ratios of the cyclised products, the isolated mixtures of the iodinated cycloadducts (**a** and **b**) were submitted to hydrogenolysis over Pd/C under 10 bars of hydrogen to reduce the carbon–iodine bonds. The hydrogenolysis reactions proceeded in high yields (77–94%, Table 2) except with the mixture of bromo-substituted compounds **10a** and **10b**: *cis*-**10c** was the only isomer recovered and this in a low yield of 42% (entry 8). The competitive hydrogenolysis of the C–Br bond along with the C–I bond may explain the low yield in this case. The dehalogenated products were separated by flash chromatography and in the case of six-membered ring derivatives, the *cis* and *trans* isomers could be isolated. Only the *cis*- and *trans*-oxepanes **11d** could also be separated. The structures of the cycloadducts (ring size and *cis* or *trans* relationship of the tetrahydrofuran and tetrahydropyran derivatives) were determined by HMBC, HSQC and NOESY experiments and by comparison of the NMR spectra and the relative chemical shifts of the protons next to the ring oxygen atom (H_1 and H_2) with the literature data.[10,24,25] For the tetrahydropyran compounds, the relative chemical shifts are: δ H_2-*trans* (4.30–4.20 ppm) > δ H_2-*cis* (3.80–3.70 ppm) > δ H_1-*trans* (3.75–3.70 ppm) > δ H_1-*cis* (3.30–3.20 ppm).

Except for compound **10**, the relative ratio of **c** and **d** obtained after deiodination can be correlated to the relative ratio of cycloadducts **a** and **b**. In agreement with Baldwin's rules,[26] the iodocyclisation of compound **5** (*n* = 0) led with high regioselectivity to tetrahydrofuran **5a** in preference to tetrahydropyran **5b** (5-*exo*-*trig* favoured over 6-*endo*-*trig* ring closure, Scheme 2). In the case of compounds **4**, **8**–**10** and **12** (*n* = 1), the regioselective formation of the corresponding tetrahydropyrans (6-*exo* adduct) was also favoured over oxepane (7-*endo* adduct) formation. A 4:1 mixture of tetrahydropyran **8a** and oxepane **8b** was obtained from butyl-substituted hydroxy alkene **8** whatever the method of cyclisation used. In contrast, the only cycloadduct obtained from the phenyl-substituted olefin **11** was the oxepane (*endo* cyclisation) but in a low yield of 49% (for 55% conversion, entry 9). As the iodocyclisation occurs under kinetic control,[27] this could be explained by a higher stabilisation of a partial positive charge next to the phenyl group in the transition state and hence a lower energy barrier for the *endo* attack of the alcohol function on this site. Interestingly, no oxepane adduct was observed when the olefin was terminal (entries 5 and 6, tetrahydropyran **4a** only). Unlike compound **11**, the *endo* attack is not observed as a partial positive charge on the terminal site of the olefin would not be stabilised. The exclusive formation of the *exo*

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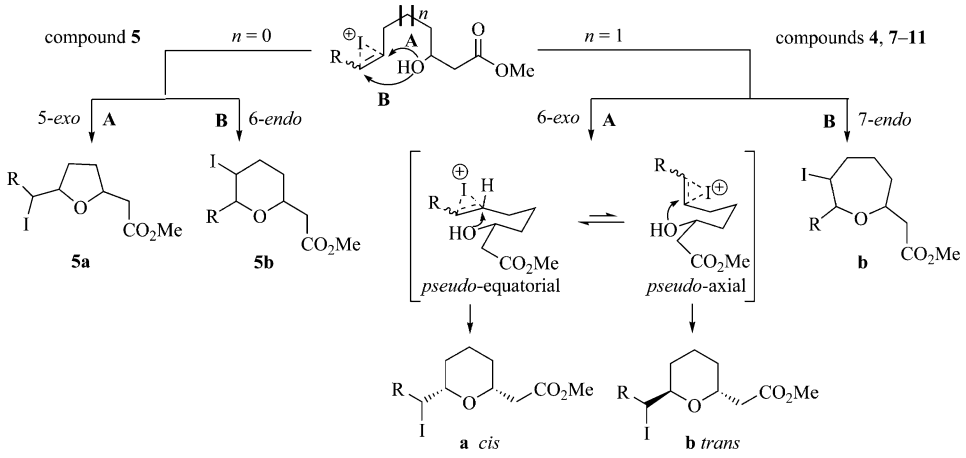
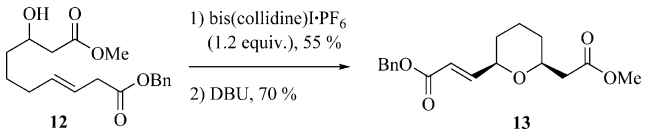


Scheme 2. Different modes of iodine-promoted cyclisation of compounds **4**–**12**.

cycloadduct from terminal hydroxy alkenes has been reported with similar substrates[21,24a] and for the synthesis of oxepanes[25] (7-*exo* vs. 8-*endo*) and oxocanes[28] (8-*exo* vs. 9-*endo*).

It is also worth noting that the *E*/*Z* ratio of the starting hydroxy alkene has more effect on the regioselectivity of the cyclisation (path **A** or path **B**, Scheme 2) than on the relative *cis*/*trans* relationship of the resulting major cycloadduct, which remains constant (around 7:3 in favour of the *cis* isomer) whatever the geometry (*E*/*Z* ratio) of the starting substrate. This selectivity was also observed with similar substrates by other groups.[21,29] In the case of these unsaturated β-hydroxy ester substrates, the main factor that governs the *exo*-type cyclisation step is therefore the position of the activated olefin, either in the favoured pseudo-equatorial or the disfavoured pseudo-axial position, whatever the double bond configuration (cf. Scheme 2), whereas the *E* or *Z* stereochemistry and the stabilisation of the activated double bond (nature of the R group) have an impact on the type of cyclisation.

In the case of compound **12**, the hydrogenolysis reaction of the cycloadducts could not be carried out because of the benzyl ester. An attempt at dehalogenation by radical chemistry (Bu_3SnH, AIBN) gave 70% yield of tin-contaminated products. Finally, an elimination reaction promoted by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) performed directly on the cycloadducts allowed us to isolate compound **13** in 70% yield (Scheme 3). The *cis*-tetrahydropyranyl structure of this major cycloadduct was easily determined by NMR spectroscopy.

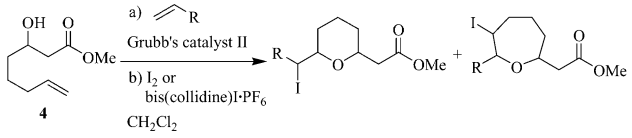


Scheme 3. Synthesis of analogue **13**.

Tandem Cross-Metathesis/Iodoetherification Reactions

Finally, the possibility of a tandem cross-metathesis/iodoetherification process was also studied. Starting from ε-unsaturated alcohol **4**, the sequence was first tested with only 2 equivalents (instead of 5 equivalents) of 1-hexene for the cross-metathesis reaction in order to use a minimum of the relatively expensive bis(*sym*-collidine)iodine(I) hexafluorophosphate in the second iodocyclisation step (Table 3, entry 1). The resulting yield of the cyclised products by this sequential process was only 48% as against 76% after the two separate steps. In order to improve the yield, we next focused on iodine which, as a cheaper activating agent, can be used in large excess. As in preliminary experiments, the cross-metathesis step was then performed with 5 equivalents of olefin and after the disappearance of **4**, iodine (4 equiv.) and sodium hydrogen carbonate (4.3 equiv.) were added to the reaction mixture. Although the cyclisation step usually gave slightly lower yields with iodine, the overall tandem process gave comparatively higher yields than with bis(*sym*-collidine)iodine(I) hexafluorophosphate. Thus, the results obtained by tandem cross-metathesis and iodine-promoted iodocyclisation (35–66% of cyclised products) were closer to those obtained after two separate steps. Moreover, this

Table 3. Tandem cross-metathesis/iodoetherification reactions.



Entry	Olefin	(equiv.)	Iodonium ion source	(equiv.)	Yield[a] (%)
1		(2)	bis(collidine)I·PF_6	(1.2)	48% (76)
2		(5)	I_2, $NaHCO_3$	(4 / 4.3)	58% (64)
3	Br	(5)	I_2, $NaHCO_3$	(4 / 4.3)	66% (77)[b]
4	Ph	(5)	I_2, $NaHCO_3$	(4 / 4.3)	35% (50)

[a] Isolated mixture of iodinated tetrahydropyrans and oxepanes after the tandem process (in parentheses, yield calculated from two separate steps). [b] Yield calculated from the reaction carried out by using bis(collidine)I·PF_6 for the cyclisation step.

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sequential process eliminates the need for an intermediate purification step, which is non-negligible in library synthesis as it is time- and solvent-consuming.

Conclusions

In conclusion, we have developed a new approach to 2,6-disubstituted tetrahydropyrans that involves a cross-metathesis and an iodocyclisation reaction. Both *cis* and *trans* isomers could be obtained and isolated. We have also shown that the competitive formation of 6-*exo*- and 7-*endo*-type cycloadducts can be modulated by the geometry (*E*/*Z* ratio) of the substrate and the substitution on the reacting double bond. Finally, we have demonstrated that the target cycloadducts could be obtained more rapidly by a tandem cross-metathesis/iodine-promoted cyclisation process. This methodology has allowed us to prepare a series of *cis*- and *trans*-2,6-disubstituted tetrahydropyran analogues of the north part of bistramide A, which will be tested against protein kinase C-δ.

Experimental Section

General: ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AM 300 MHz NMR spectrometer which provided all the necessary data for the full assignment of each compound. Chemicals shifts are reported in ppm. High-resolution mass spectrometry (HRMS) analyses were conducted by using a ThermoFinigan-MAT 95 XL instrument. IR spectra were measured with a Perkin-Elmer Spectrum One FT-IR spectrometer. Melting points were measured with a B-540 Büchi apparatus. TLC analyses were performed on plates (layer thickness 0.25mm) and were visualised with UV light, phosphomolybdic acid or *p*-anisaldehyde solution. Column chromatography was performed on silica gel (40–63 μm) by using ethyl acetate (EtOAc) and hexanes as eluents. When appropriate, solvents and reagents were dried by distillation over the appropriate drying agents prior to use. Diethyl ether and tetrahydrofuran were distilled from Na/benzophenone and used fresh. Dichloromethane was distilled from CaH_2.

General Procedure for Cross-Metathesis Reactions (Table 1, entries 1–7): Methyl 3-hydroxyhept-6-enoate (**3**) (1 mmol) or methyl 3-hydroxyoct-7-enoate (**4**) (1 mmol) and olefin (5 mmol) were diluted in dichloromethane (10 mL). The solution was degassed with nitrogen and the 2nd-generation Grubbs catalyst (2 mol-%) was added. The mixture was heated under reflux until reaction completion (4–12 h). After evaporation of the solvent, the residue was purified by flash chromatography to yield the (*E*)-olefin as the major isomer (**5**–**12**).

Methyl 3-Hydroxyundec-6-enoate (5): Purification with EtOAc/hexanes, 10:90. Brown oil (70%), *E*/*Z* = 90:10. *E* isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, J = 7.2 Hz, 3 H, CH_3), 1.28–1.33 (m, 4 H), 1.40–1.65 (m, 2 H), 1.94–2.23 (m, 4 H), 2.41 (dd, J_{AB} = 16.4, J = 8.9 Hz, 1 H, CH_AH$_B$CO$_2$Me), 2.51 (dd, J_{AB} = 16.4, J = 3.4 Hz, 1 H, CH$_A$$H_BCO_2$Me), 2.86 (br. s, 1 H, OH), 3.71 (s, 3 H, OCH_3), 3.98–4.07 (m, 1 H, C*H*OH), 5.33–5.48 (m, 2 H, C*H*=C*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 22.5, 28.9, 32.0, 32.5, 36.6, 41.4, 52.0, 67.8, 129.4, 131.6, 173.6 ppm.

Methyl 9-(*tert*-Butyldiphenylsilyloxy)-3-hydroxynon-6-enoate (6): Purification with EtOAc/hexanes, 5:95. Grey oil (61%), *E*/*Z* = 60:40. *E* isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.04 (s, 9 H, 3×CH_3), 1.56–2.55 (m, 7 H), 2.76–2.84 (m, 1 H), 3.64–3.70 (m, 2 H), 3.70 (s, 3 H, OCH_3), 3.98–4.07 (m, 1 H, C*H*OH), 5.40–5.53 (m, 2 H, C*H*=C*H*), 7.35–7.42 (m, 5 H), 7.65–7.68 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.4, 27.1 (3 C), 28.9, 36.3, 36.5, 41.4, 51.9, 63.9, 68.1, 127.6 (2 C), 127.8 (3 C), 127.9, 129.8, 131.1, 131.7, 134.2, 135.8 (4 C), 173.4 ppm.

Methyl 3-Oxododec-7-enoate (7): Purification with ethyl acetate/petroleum ether, 15:95. Red oil (78%), *E*/*Z* = >95:5. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84–0.88 (m, 3 H, CH_3), 1.269–1.35 (m, 4 H), 1.63 (quint, J = 7.4 Hz, 2 H, CO-CH_2-CH_2), 1.92–2.04 (m, 4 H, CH_2-CH=CH-CH_2), 2.50 (t, J = 7.4 Hz, 2 H, CH_2-CO), 3.42 (s, 2 H, CH_2-COOMe), 3.71 (s, 3 H, O-CH_3), 5.25–5.44 (m, 2 H, C*H*=C*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 22.5, 22.5, 23.5, 32.0, 32.5, 42.5, 49.3, 52.6, 129.1, 132.0, 168.0, 203.0 ppm. IR (film): $\tilde{\nu}_{max}$ = 2956, 2928, 2873, 2857, 1750, 1719, 1654, 1631, 1449, 1438, 1407, 1320, 1260, 1150, 1090, 1015, 968, 801 cm^{-1}.

Methyl 3-Hydroxydodec-7-enoate (8): Purification with EtOAc/hexanes, 10:90. Brown oil (82%), *E*/*Z* = 90:10. *E* isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, J = 6.8 Hz, 3 H, CH_3), 1.24–1.55 (m, 8 H), 1.91–2.03 (m, 4 H), 2.39 (dd, J_{AB} = 16.4, J = 8.7 Hz, 1 H, CH_AH$_B$CO$_2$Me), 2.50 (dd, J_{AB} = 16.4, J = 3.4 Hz, 1 H, CH$_A$$H_B$-CO$_2$Me), 2.89 (br. s, 1 H, OH), 3.69 (s, 3 H, OCH_3), 4.00 (m, 1 H, C*H*OH), 5.28–5.45 (m, 2 H, C*H*=C*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.3, 22.5, 25.7, 32.1, 32.5, 32.6, 36.2, 41.4, 52.0, 68.2, 129.9, 131.3, 173.8 ppm. IR (film): $\tilde{\nu}_{max}$ = 3700 (–3100), 2956, 2928, 1739, 1438, 1261, 1174, 1089, 969 cm^{-1}. MS (ESI): *m*/*z* = 229 (54) [MH]$^+$, 251 (69) [M + Na]$^+$, 313 (56), 355.2 (54), 362.3 (87), 478.9 (93) [2M + Na]$^+$, 541 (100).

Methyl 3-Hydroxyhexadec-7-enoate (9): Purification with EtOAc/hexanes, 10:90. Orange oil (76%), *E*/*Z* = 55:45. *E* isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, J = 7.0 Hz, 3 H, CH_3), 1.25–1.60 (m, 16 H), 1.93–2.20 (m, 4 H), 2.43 (dd, J_{AB} = 16.5, J = 8.6 Hz, 1 H, CH_AH$_B$CO$_2$Me), 2.51 (dd, J_{AB} = 16.5, J = 3.4 Hz, 1 H, CH$_A$$H_BCO_2$Me), 2.89 (br. s, 1 H, OH), 3.70 (s, 3 H, OCH_3), 3.95–4.07 (m, 1 H, C*H*OH), 5.34–5.44 (m, 2 H, C*H*=C*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4, 23.0, 25.4, 29.5, 29.8, 28.9, 29.9, 32.2, 32.7, 32.9, 36.3, 41.4, 52.1, 68.2, 129.9, 131.3, 173.8 ppm. IR (film): $\tilde{\nu}_{max}$ = 3680 (–3200), 2925, 2851, 1739, 1456, 1438, 1262, 1172, 1078, 966 cm^{-1}. MS (ESI): *m*/*z* = 284 [M]$^{+\cdot}$, 129 (64), 116 (90), 103 (80), 96 (72), 81 (83), 71 (52), 69 (60), 55 (100), 43 (83), 41 (75).

Methyl 11-Bromo-3-hydroxyundec-7-enoate (10): Purification with EtOAc/hexanes, 20:80. Colourless oil (83%), *E*/*Z* = 90:10. *E* isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40–1.54 (m, 4 H), 1.89 (quint, J = 6.8 Hz, 2 H), 2.00 (q, J = 6.4 Hz, 2 H), 2.07–2.20 (m, 2 H), 2.40 (dd, J_{AB} = 16.4, J = 8.9 Hz, 1 H, CH_AH$_B$CO$_2$Me), 2.50 (dd, J_{AB} = 16.4, J = 3.4 Hz, 1 H, CH$_A$$H_BCO_2$Me), 2.91 (br. s, 1 H, OH), 3.39 (t, J = 6.7 Hz, 2 H, CH_2Br), 3.70 (s, 3 H, OCH_3), 3.98–4.10 (m, 1 H, C*H*OH), 5.29–5.51 (m, 2 H, C*H*=C*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.6, 31.1, 32.6, 32.7, 33.7, 36.2, 41.4, 52.1, 68.2, 128.8, 131.9, 173.8 ppm. IR (film): $\tilde{\nu}_{max}$ = 3692 (–3071), 3005, 2934, 2852, 1733, 1438, 1261, 1201, 1168, 1086 cm^{-1}. MS (ESI): *m*/*z* = 293 (96) [MH]$^+$, 295 (67), 315 (95) [MNa]$^+$, 317 (100), 326 (62).

Methyl 3-Hydroxy-8-phenyloct-7-enoate (11): Purification with EtOAc/hexanes, 20:80. Grey oil (75%), *E*/*Z* = >95:5. *E* isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42–1.63 (m, 4 H, CH_2CH_2OH), 2.17 (q, J = 6.8 Hz, 2 H, CH_2CH=), 2.35 (dd, J_{AB} = 16.4, J = 8.9 Hz, 1 H, CH_AH$_B$CO$_2$Me), 2.47 (dd, J_{AB} = 16.4, J = 3.4 Hz, 1

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H, $CH_AH_BCO_2Me$), 3.64 (s, 3 H, OCH_3), 3.86–4.05 (m, 1 H, C*H*OH), 6.13 (dt, J = 15.8, 6.8 Hz, 1 H,=C*H*CH_2), 6.32 (d, J = 15.8 Hz, 1 H, PhCH=), 7.12–7.28 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.5, 33.1, 36.3, 41.4, 52.1, 68.2, 126.3 (2 C), 127.2, 128.8 (2 C), 130.6, 130.7, 133.5, 173.8 ppm. IR (film): $\tilde{\nu}_{max}$ = 3700 (–3100), 2962, 2856, 1732, 1438, 1414, 1261, 1092, 1070, 1044, 1019 cm^{-1}. HRMS (EI): calcd. for $C_{15}H_{20}O_3$ $[M]^+$ 248.1412; found 248.1417.

Benzyl 8-Hydroxy-9-(methoxycarbonyl)non-3-enoate (12): Purification with EtOAc/hexanes, 20:80. Orange oil (69%), *E*/*Z* = 85:15. *E* isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37–1.59 (m, 4 H, CH_2CH_2OH), 2.04–2.07 (m, 2 H, CH_2CH=), 2.39 (dd, J_{AB} = 16.4, J = 8.9 Hz, 1 H, CH_AH$_B$CO$_2$Me), 2.49 (dd, J_{AB} = 16.4, J = 3.4 Hz, 1 H, $CH_AH_BCO_2Me$), 3.07 (dd, J = 3.4, 1.1 Hz, 2 H, =CHCH_2CO), *Z* isomer (d, J = 5.6 Hz, 2 H, =CHCH_2CO), 3.71 (s, 3 H, OCH_3), 3.95–4.03 (m, 1 H, C*H*OH), 5.12 (s, 2 H, OCH_2-Ph), 5.53–5.59 (m, 2 H, C*H*=C*H*), 7.34–7.36 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.3, 32.5, 36.2, 38.3, 41.4, 52.1, 66.7, 68.1, 122.2, 128.5 (3 C), 128.9 (2 C), 133.4, 134.7, 172.3, 173.8 ppm. IR (film): $\tilde{\nu}_{max}$ = 3703 (–3137), 3033, 2940, 2863, 1731, 1498, 1451, 1438, 1377, 1262, 1161, 974 cm^{-1}. MS (ESI): *m*/*z* = 321 (100) $[MH]^+$, 343 (65) $[MNa]^+$.

General Procedures for Iodoetherification

Method A (with NIS): *N*-Iodosuccinimide (1.5 mmol) was added to a solution of unsaturated alcohol (1 mmol) in acetone (50 mL) and water (5 mL) at 0 °C and the mixture was warmed to room temperature and stirred in the dark for 24 h. The solvents were evaporated and the residue partitioned between dichloromethane (20 mL) and an aqueous solution of sodium thiosulfate (5%, 20 mL). After extraction with dichloromethane, the organic phase was washed with brine, dried with $MgSO_4$ and concentrated. The crude residue was purified by flash chromatography to give the iodinated cyclised products.

Method B (with I_2): Iodine (3 mmol) was added in one portion to a solution of unsaturated alcohol (1 mmol) and sodium hydrogen carbonate (3.16 mmol) in acetonitrile (25 mL) at room temp. The mixture was stirred in the dark for 24 h before quenching with an aqueous saturated solution of sodium thiosulfate (20 mL). The acetonitrile was removed under reduced pressure and the residue partitioned between ethyl acetate (20 mL) and water (20 mL). The aqueous phase was further extracted with ethyl acetate and the combined organic extracts dried with $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography to give the iodinated cyclised products.

Method C [with bis(collidine)I·PF_6]: A solution of unsaturated alcohol (1 mmol) in dichloromethane (5 mL) was added over 1 h at room temp. to a solution of bis(*sym*-collidine)iodine(I) hexafluorophosphate (1.22 mmol) in dichloromethane (15 mL). The resulting mixture was stirred for an additional 1 h and silica gel (2 g) was added. The solvent was evaporated under reduced pressure and the resulting residue purified by chromatography (EtOAc/hexanes) to give the iodinated cyclised products.

General Procedure for the Iodoetherification/Hydrogenolysis of Compounds 4, 5 and 8–12 (Table 3, entries 1–10): Compounds **4**, **5** and **8**–**12** were cyclised by iodoetherification following method A, B or C. Pd/C (10%, w/w) and sodium hydrogen carbonate (0.86 mmol) were added to the isolated mixture of iodinated products **a** and/or **b** (0.75 mmol) in methanol (6 mL). The mixture was hydrogenated under pressure (10 atm) for 24 h at room temperature. The catalyst was filtered through Celite and washed with diethyl ether. The filtrate was concentrated under reduced pressure and purified by flash chromatography (EtOAc/hexanes) to give compounds **c** and/or **d**.

Methyl 2-(6-Iodomethyltetrahydropyran-2-yl)ethanoate (4a): Purification with EtOAc/hexanes, 2:98. ***cis* isomer:** yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.10–1.15 (m, 2 H), 1.48–1.62 (m, 2 H), 1.80–1.87 (m, 2 H), 2.41 (dd, J_{AB} = 14.9, J = 5.5 Hz, 1 H, CH_AH$_B$CO$_2$Me), 2.56 (dd, J_{AB} = 14.9, J = 7.9 Hz, 1 H, $CH_AH_BCO_2Me$), 3.13 (d, J = 6.2 Hz, 2 H, CH_2I), 3.35–3.40 (m, 1 H, OC*H*CH_2I), 3.69 (s, 3 H, OCH_3), 3.76–3.84 (m, 1 H, OC*H*CH_2-CO_2Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.7, 23.4, 31.0, 31.2, 41.6, 52.1, 75.2, 77.6, 172.0 ppm. IR (film): $\tilde{\nu}_{max}$ = 2938, 2861, 1739, 1435, 1371, 1343, 1287, 1255, 1200, 1176, 1129, 1087, 1051, 1015 cm^{-1}. HRMS (EI): calcd. for $C_9H_{15}IO_3$ $[M]^+$ 298.0066; found: 298.0066. ***trans* isomer:** yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23–1.41 (m, 2 H), 1.56–1.79 (m, 4 H), 2.43 (dd, J_{AB} = 14.7, J = 5.6 Hz, 1 H, CH_AH$_B$CO$_2$Me), 2.68 (dd, J_{AB} = 14.7, J = 8.5 Hz, 1 H, $CH_AH_BCO_2Me$), 3.26 (dd, J_{AB} = 10.2, J = 6.4 Hz, 1 H, CH_AH$_B$I), 3.31 (dd, J_{AB} = 10.2, J = 7.0 Hz, 1 H, CH_AH_BI), 3.71 (s, 3 H, OCH_3), 3.83–3.91 (m, 1 H, OC*H*CH_2I), 4.19–4.27 (m, 1 H, OC*H*CH_2CO_2Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 8.3, 18.3, 29.0, 29.6, 39.2, 52.1, 68.9, 72.0, 171.9 ppm. IR (film): $\tilde{\nu}_{max}$ = 2938, 2861, 1739, 1435, 1371, 1343, 1287, 1256, 1200, 1176, 1129, 1088, 1051, 1043, 1015 cm^{-1}. HRMS (ESI): calcd. for $C_9H_{15}IO_3Na$ [MNa] requires 320.9964; found 320.9961.

Methyl 2-(5-Pentyltetrahydrofuran-2-yl)ethanoate (5c): Purification with EtOAc/hexanes, 5:95. Colourless oil. Mixture of isomers (70:30): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, J = 6.8 Hz, 3 H, CH_3), 1.28–1.64 (m, 11 H), 1.90–1.92 (m, 1 H), 2.42 (dd, J_{AB} = 15.1, J = 6.4 Hz, 1 H, CH_AH$_B$CO$_2$Me), 2.62 (dd, J_{AB} = 15.1, J = 6.8 Hz, 1 H, $CH_AH_BCO_2Me$) [minor isomer: 2.63 (dd, J_{AB} = 15.1, J = 6.6 Hz, 1 H, $CH_AH_BCO_2Me$)], 3.67 (s, 3 H, OCH_3) [minor isomer: 3.82 (quint, J = 6.2 Hz, 1 H, OCH)], 3.94 (quint, J = 6.2 Hz, 1 H, OCH) [minor isomer: 4.23 (quint, J = 6.6 Hz, 1 H, OCH)], 4.35 (quint, J = 6.6 Hz, 1 H, OCH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): [major isomer] δ = 14.3, 22.9, 26.0, 31.3, 32.1, 32.2, 36.1, 41.0, 51.8, 74.9, 79.4, 172.0 ppm. IR (film): $\tilde{\nu}_{max}$ = 2956, 2923, 2851, 1731, 1632, 1454, 1434, 1264, 1091, 1018 cm^{-1}. HRMS (EI): calcd. for $C_{12}H_{22}O_3$ $[M]^+$ requires 214.1569; found 214.1569.

Methyl 2-(6-Butyltetrahydropyran-2-yl)ethanoate (5d): Purification with EtOAc/hexanes, 5:95. Yellow oil. ***cis* isomer:** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, J = 6.0 Hz, 3 H, CH_3), 1.08–1.64 (m, 11 H), 1.80–1.85 (m, 1 H), 2.39 (dd, J_{AB} = 14.7, J = 5.7 Hz, 1 H, CH_AH$_B$CO$_2$Me), 2.54 (dd, J_{AB} = 14.7, J = 7.9 Hz, 1 H, $CH_AH_BCO_2Me$), 3.24–3.31 (m, 1 H, OC*H*CH_2), 3.68 (s, 3 H, OCH_3), 3.69–3.78 (m, 1 H, OC*H*CH_2CO_2Me) ppm.

Methyl 2-(6-Butyltetrahydropyran-2-yl)ethanoate (8c): Purification with EtOAc/hexanes, 2:98. ***cis* isomer:** yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, J = 6.6 Hz, 3 H, CH_3), 1.12–1.64 (m, 13 H), 1.78–1.85 (m, 1 H), 2.39 (dd, J_{AB} = 14.7, J = 5.5 Hz, 1 H, CH_AH$_B$CO$_2$Me), 2.54 (dd, J_{AB} = 14.7, J = 7.9 Hz, 1 H, $CH_AH_BCO_2Me$), 3.23–3.30 (m, 1 H, OC*H*CH_2), 3.67 (s, 3 H, OCH_3), 3.70–3.78 (m, 1 H, OC*H*CH_2CO_2Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.3, 22.9, 23.8, 25.5, 31.6, 31.6, 32.1, 36.6, 41.9, 51.8, 74.7, 78.4, 172.3 ppm. IR (film): $\tilde{\nu}_{max}$ = 2934, 2857, 1744, 1457, 1438, 1369, 1344, 1287, 1254, 1196, 1075 cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{25}O_3$ $[M]^+$ 228.1725; found 228.1727. ***trans* isomer:** colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, J = 6.6 Hz, 3 H, CH_3), 1.23–1.37 (m, 10 H), 1.54–1.77 (m, 4 H), 2.40 (dd, J_{AB} = 14.5, J = 5.5 Hz, 1 H, CH_AH$_B$CO$_2$Me), 2.66 (dd, J_{AB} = 14.5, J = 8.7 Hz, 1 H, $CH_AH_BCO_2Me$), 3.67 (s, 3 H, OCH_3), 3.68–3.75 (m, 1 H, OC*H*CH_2), 4.15–4.24 (m, 1 H, OC*H*CH_2-CO_2Me) ppm.^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4, 18.8, 23.0,

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25.7, 30.0, 30.2, 32.1, 33.3, 39.5, 51.9, 68.2, 71.9, 172.3 ppm. IR (film): $\tilde{\nu}_{max}$ = 2933, 2863, 1744, 1457, 1436, 1377, 1358, 1287, 1259, 1207, 1165, 1091, 1045 cm^{-1}. HRMS (EI): calcd. for $C_{13}H_{25}O_3$ $[M]^+$ 228.1725; found 228.1726.

Methyl 2-(7-Butyloxepan-2-yl)ethanoate (8d): Purification with EtOAc/hexanes, 2:98. Colourless oil. Mixture of *cis* and *trans* isomers (*dr* = 50:50). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, J = 7.0 Hz, 3 H, CH_3), 1.25–1.67 (m, 12 H), 1.90–2.17 (m, 2 H), 2.43 (dd, J_{AB} = 15.1, J = 6.4 Hz, 1 H, CH_AH$_B$CO$_2$Me), 2.62 (dd, J_{AB} = 15.1, J = 7.8 Hz, 1 H, CH$_A$$H_BCO_2$Me) [other isomer: 2.63 (dd, J_{AB} = 15.1, J = 7.8 Hz, 1 H, CH$_A$$H_BCO_2$Me)], 3.68 (s, 3 H, OCH_3), 3.82 (quint, J = 6.8 Hz, 1 H, OCH) [other isomer: 3.92 (quint, J = 6.6 Hz, 1 H, OCH)], 4.22 (quint, J = 6.8 Hz, 1 H, OCH) [other isomer: 4.35 (quint, J = 6.6 Hz, 1 H, OCH)] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): [*cis* and *trans* isomers] δ = 14.3, 22.9, 23.1, 26.1, 28.6, 31.1, 31.3, 32.0, 32.2, 36.1, 41.1, 43.3, 51.9, 74.9, 75.4 79.5, 80.2, 172.1 ppm. IR (film): $\tilde{\nu}_{max}$ = 2956, 2931, 2863, 1743, 1460, 1435, 1380, 1196, 1161, 1070 cm^{-1}.

Methyl 2-(6-Octyltetrahydropyran-2-yl)ethanoate (9c): Purification with EtOAc/hexanes, 2:98. ***cis* isomer:** colourless oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, J = 6.4 Hz, 3 H, CH_3), 1.12–1.64 (m, 21 H), 1.64–1.85 (m, 1 H), 2.38 (dd, J_{AB} = 14.8, J = 5.5 Hz, 1 H, CH_AH$_B$CO$_2$Me), 2.54 (dd, J_{AB} = 14.8, J = 7.9 Hz, 1 H, CH$_A$$H_BCO_2$Me), 3.23–3.30 (m, 1 H, OCHCH$_2$), 3.69 (s, 3 H, OCH_3), 3.71–3.78 (m, 1 H, OCHCH$_2$CO$_2$Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4, 23.0, 23.8, 25.9, 29.7, 29.9 (3 C), 31.6, 31.7, 32.2, 36.7, 42.0, 51.9, 74.8, 78.5, 172.4 ppm. IR (film): $\tilde{\nu}_{max}$ = 2929, 2856, 1745, 1457, 1437, 1371, 1344, 1287, 1251, 1198, 1177, 1089, 1073 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{32}O_3$ $[M]^+$ 284.2351; found 284.2355. ***trans* isomer:** colourless oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, J = 5.5 Hz, 3 H, CH_3), 1.25–1.34 (m, 17 H), 1.58–1.71 (m, 5 H), 2.40 (dd, J_{AB} = 14.5, J = 5.6 Hz, 1 H, CH_AH$_B$CO$_2$Me), 2.66 (dd, J_{AB} = 14.5, J = 8.7 Hz, 1 H, CH$_A$$H_BCO_2$Me), 3.68 (s, 3 H, OCH_3), 3.68–3.70 (m, 1 H, OCHCH$_2$), 4.15–4.21 (m, 1 H, OCHCH$_2$CO$_2$Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4, 18.8, 23.0, 26.0, 29.7, 30.0 (3 C), 30.1, 30.2, 32.2, 33.4, 39.6, 51.9, 68.2, 71.9, 172.3 ppm. IR (film): $\tilde{\nu}_{max}$ = 2928, 2855, 1744, 1460, 1437, 1289, 1259, 1204, 1170, 1092, 1045 cm^{-1}. HRMS (EI): calcd. for $C_{17}H_{32}O_3$ $[M]^+$ 284.2351; found 284.2350.

Methyl 2-(7-Octyloxepan-2-yl)ethanoate (9d): Purification with EtOAc/hexanes, 2:98. Colourless oil. Mixture of *cis* and *trans* isomers (*dr* = 64:36). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, J = 7.0 Hz, 3 H, CH_3), 1.25–1.67 (m, 20 H), 1.90–2.17 (m, 2 H), 2.43 (dd, J_{AB} = 15.1, J = 6.4 Hz, 1 H, CH_AH$_B$CO$_2$Me), 2.62–2.63 (dd, J_{AB} = 15.1, J = 7.8 Hz, 1 H, CH$_A$$H_BCO_2$Me) [minor isomer: 2.63 (dd, J_{AB} = 15.1, J = 7.8 Hz, 1 H, CH$_A$$H_BCO_2$Me)], 3.68 (s, 3 H, OCH_3) [minor isomer: 3.82 (quint, J = 6.6 Hz, 1 H, OCH)], 3.92 (quint, J = 6.4 Hz, 1 H, OCH) [minor isomer: 4.22 (quint, J = 6.6 Hz, 1 H, OCH)], 4.35 (quint, J = 6.4 Hz, 1 H, OCH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) [*cis* and *trans* isomers]: δ = 14.4, 23.0, 26.4, 29.6, 29.7, 29.9 (2 C), 30.1, 31.1, 32.1, 32.2, 36.2, 36.4, 41.1, 43.3, 51.9, 75.0, 79.5, 172.2 ppm. IR (film): $\tilde{\nu}_{max}$ = 2927, 2856, 1743, 1462, 1437, 1377, 1278, 1257, 1196, 1172, 1068 cm^{-1}.

Methyl 2-[6-(3-Bromopropyl)tetrahydropyran-2-yl]ethanoate (10c): Purification with EtOAc/hexanes, 2:98. Pale yellow oil. ***cis* isomer:** ^1H NMR (300 MHz, $CDCl_3$): δ = 1.14–1.87 (m, 12 H), 2.39 (dd, J_{AB} = 14.9, J = 5.5 Hz, 1 H, CH_AH$_B$CO$_2$Me), 2.52 (dd, J_{AB} = 14.9, J = 8.1 Hz, 1 H, CH$_A$$H_BCO_2$Me), 3.25–3.32 (m, 1 H, OCHCH$_2$), 3.39 (t, J = 6.8 Hz, 2 H, CH_2Br), 3.68 (s, 3 H, OCH_3), 3.70–3.79 (m, 1 H, OCHCH$_2$CO$_2$Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.8, 24.6, 31.6, 31.6, 33.0, 34.3, 35.7, 41.9, 51.9, 74.8, 78.1, 172.3 ppm. IR (film): $\tilde{\nu}_{max}$ = 2934, 2860, 1739, 1435, 1373, 1346, 1286, 1257, 1199, 1741, 1088, 1040 cm^{-1}. HRMS (ESI): calcd. for $C_{12}H_{21}O_3Br$ $[M]^+$ 315.0572; found 315.0571.

Methyl 2-(7-Phenyloxepan-2-yl)ethanoate (11d): Purification with EtOAc/hexanes, 2:98. **Less polar isomer:** colourless oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.57–1.89 (m, 7 H), 2.02–2.15 (m, 1 H), 2.46 (dd, J_{AB} = 15.2, J = 4.9 Hz, 1 H, CH_AH$_B$CO$_2$Me), 2.64 (dd, J_{AB} = 15.2, J = 8.9 Hz, 1 H, CH$_A$$H_BCO_2$Me), 3.62 (s, 3 H, OCH_3), 4.16–4.23 (m, 1 H, OCHCH$_2$CO$_2$Me), 4.62 (dd, J = 8.3, 3.9 Hz, 1 H, OCHPh), 7.30–7.31 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.1, 25.4, 36.0, 38.2, 42.3, 51.7, 76.7, 81.7, 125.9, 126.9 (2 C), 128.2 (2 C), 144.4, 172.3 ppm. IR (film): $\tilde{\nu}_{max}$ = 3066, 3027, 2927, 2860, 1738, 1634, 1445, 1434, 1260, 1196, 1106, 1021 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{20}O_3$ $[M]^+$ 248.1412; found 248.1410. **More polar isomer:** colourless oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.51–2.07 (m, 8 H), 2.40 (dd, J_{AB} = 14.5, J = 5.6 Hz, 1 H, CH_AH$_B$CO$_2$Me), 2.58 (dd, J_{AB} = 14.5, J = 7.9 Hz, 1 H, CH$_A$$H_BCO_2$Me), 3.45 (s, 3 H, OCH_3), 4.26–4.33 (m, 1 H, OCHCH$_2$CO$_2$Me), 4.69 (dd, J = 11.0, 2.5 Hz, 1 H, OCHPh), 7.28–7.38 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.1, 28.4, 36.2, 37.1, 41.8, 51.7, 73.0, 76.6, 126.4 (2 C), 127.3, 128.4 (2 C), 144.3, 172.1 ppm. IR (film): $\tilde{\nu}_{max}$ = 2930, 2857, 1739, 1437, 1290, 1200, 1151, 1102, 1026 cm^{-1}. HRMS (EI): calcd. for $C_{15}H_{20}O_3$ $[M]^+$ 248.1412; found 248.1412 (,).

Benzyl *cis*-(*E*)-3-[6-(Methoxycarbonylmethyl)tetrahydropyran-2-yl]-propenoate (13): 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.18 mmol) was added to a solution of benzyl *cis*-3-iodo-3-[6-(methoxycarbonylmethyl)tetrahydropyran-2-yl]propanoate (**12a**) (0.18 mmol) in dichloromethane (5 mL) at room temp. The mixture was stirred for 24 h before quenching with an aqueous saturated solution of sodium thiosulfate (5 mL). The aqueous phase was extracted with dichloromethane (3 × 5 mL) and the combined organic extracts dried with $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography to give **12** as a colourless oil (40 mg, 0.13 mmol, 70%). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.19–1.32 (m, 2 H), 1.62–1.72 (m, 3 H), 1.87–1.91 (m, 1 H), 2.42 (dd, J_{AB} = 15.2, J = 5.5 Hz, 1 H, CH_AH$_B$CO$_2$Me), 2.57 (dd, J_{AB} = 15.2, J = 7.5 Hz, 1 H, CH$_A$$H_BCO_2$Me), 3.68 (s, 3 H, OCH_3), 3.81–3.89 (m, 1 H), 4.00–4.06 (m, 1 H), 5.14 (d, J_{AB} = 12.4 Hz, 1 H, CH_AH$_B$Ph), 5.19 (d, J_{AB} = 12.4 Hz, 1 H, CH$_A$$H_B$Ph), 6.04 (dd, J = 15.7, 1.7 Hz, 1 H, COCH=), 6.91 (dd, J = 15.7, 3.8 Hz, 1 H, COCH=CH), 7.30–7.36 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.6, 30.9, 30.9, 41.6, 52.0, 66.5, 74.6, 76.4, 119.9, 128.5, 128.5, 128.8, 136.3, 148.7, 166.8, 171.9 ppm. IR (film): $\tilde{\nu}_{max}$ = 3034, 2942, 2861, 1722, 1660, 1498, 1456, 1438, 1377, 1296, 1269, 1199, 1167, 1114, 1080, 1022 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{22}O_5$ $[M]^+$ 341.1365; found 341.1368.

General Procedure for Tandem Cross-Metathesis/Iodoetherification: Methyl 3-hydroxyoct-7-enoate (**4**) (0.5 mmol) and olefin (2.5 mmol) were diluted in dichloromethane (5 mL). The solution was degassed with nitrogen and the second-generation Grubbs catalyst (2 mol-%) was added. The mixture was heated under reflux until reaction completion (4–12 h) and then cooled to room temperature. The reaction mixture was diluted with dichloromethane (10 mL) and iodine (2 mmol) and sodium hydrogen carbonate (2.15 mmol) were added in one portion. The mixture was stirred in the dark for 24 h before quenching with an aqueous saturated solution of sodium thiosulfate (20 mL). The aqueous phase was separated and extracted with dichloromethane (3 × 10 mL). The organic phases were dried with $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography to give the iodocycloadducts.

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Supporting Information (see also the footnote on the first page of this article): Experimental procedures and spectroscopic data for compounds **1**–**4**, ^{1}H and ^{13}C NMR spectra of cycloadducts **4a**, **5d**, **8c**, **9c**, **10c**, **11d** and **13**.

Acknowledgments

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