Toward the total synthesis of lophotoxin — New methodologies and synthetic strategies[1]

Peter Wipf and Michel Grenon

Abstract: Our recent progress toward the synthesis of the furanocembranolide lophotoxin (**1**) is disclosed. Strategies for the stereoselective incorporation of the C_{13} stereocenter by a catalytic desymmetrization of a cyclic *meso*-anhydride, as well as a novel 1,6-addition reaction of organocuprates to unsaturated [1,3]dioxin-4-ones are discussed. Preliminary results on the development of a rhodium-catalyzed asymmetric 1,6-addition reaction are also mentioned. Finally, modifications of a previously reported transition-metal-catalyzed cyclization reaction involving α-propargyl β-keto esters allow furan ring formation either under thermal conditions or by microwave irradiation.

Key words: 1,6-addition, organocuprates, catalytic desymmetrization, furan cyclization, microwave.

Résumé : Nos plus récents progrès concernant la synthèse totale du furanocembranolide lophotoxine (**1**) sont décrits. Des stratégies pour l'incorporation stéréosélective du substituant en C_{13} par la désymétrisation catalytique d'un anhydride cyclique *meso*, ainsi qu'une nouvelle réaction d'addition 1,6-conjuguée d'organocuprates sur des [1,3]dioxin-4-ones insaturées sont discutées. Des résultats préliminaires sur le dévelopement d'une réaction d'addition 1,6-conjugée asymétrique catalysée par le rhodium sont aussi mentionnés. Finalement, la modification d'une réaction de cyclisation catalysée par un métal de transition et mettant en jeu l'α-propargyl β-céto ester permet la formation d'un furane soit sous certaines conditions thermiques ou par irradiation aux micro-ondes.

Mots clés : addition 1,6-, organocuprates, désymétrisation catalytique, cyclisation de furane, microonde.

Introduction

Lophotoxin (**1**) is a member of the furanocembranolides (1), a growing class of natural products that comprise a number of highly functionalized cyclic diterpenes (Fig. 1). This compound is found in a number of marine invertebrates (gorgonian octocorals) located in tropical and subtropical waters (2). Lophotoxin acts as a potent neurotoxin by binding selectively and irreversibly to the Tyr^{190} residue present in the α-subunit of nicotinic acetylcholine receptors, leading to respiratory depression, paralysis, asphyxia, and ultimately death (3). SAR studies have demonstrated that the key structural elements responsible for this unique biological activity can be attributed to the C_7–C_8 epoxide and the lactone oxygens, allowing for a direct structural correlation of the pharmacophore in **1** with acetylcholine (4).

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Dedicated to Dr. Alfred Bader, in recognition of his spirit for entrepreneurship, and his appreciation for the legacy of human accomplishment!

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The presence of a 2,3,5-trisubstituted furan ring adjacent to a trans-trisubstituted epoxide, along with an epoxidized butenolide imbedded in a strained 14-membered macrocycle are the most prominent structural features of this molecule. In addition to the interesting biological activity displayed by this compound, the synthetic challenge offered to organic chemists has prompted a number of research groups to develop strategies aimed at the total synthesis of lophotoxin (5, 6) and other furanocembranolides (7–10).

Our research group has been interested in this class of molecules for a few years and we have recently disclosed a method to construct the 2-alkenyl-3,5-trisubstituted furan (**2**) from the simple acyclic α-propargyl β-keto ester (**3**) (Fig. 1) (11). This method is based on a general strategy for the construction of five-membered heterocycles (12) and features the use of a palladium catalyst and an inorganic base to induce the 5-exo-dig cyclization and concomitant aromatization to the furan ring. High levels of selectivity for the (*Z*)-isomer **2** were obtained as a result of the facial-selective protonation of an allene intermediate. With the furan in hand, the vinylsilane moiety was further elaborated to the C_{19} methyl group attached to the trans-trisubstituted epoxide in lophotoxin.

Some issues that were not addressed in our previous communication concern the installation of the C_{13} acetate group as well as a method to introduce the C_1 isopropenyl group in a stereoselective way. Previous synthetic work by others has either exploited the chiral pool (8, 9), a diastereoselective alkylation (5), or an intramolecular Nozaki–Hiyama–Kishi reaction (7) to introduce the isopropenyl group, whereas the

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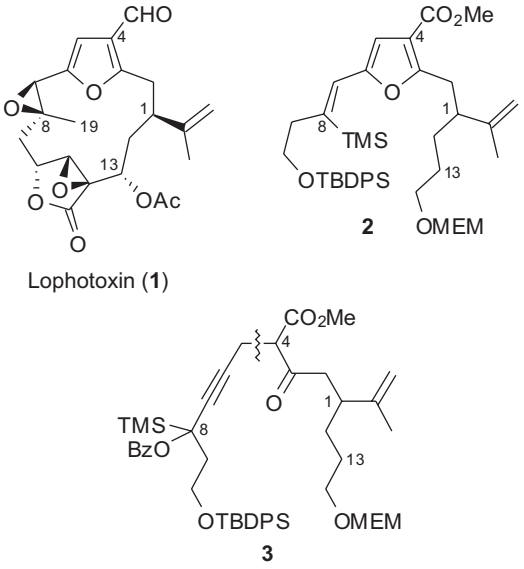
Fig. 1. Lophotoxin and the structures of synthetic intermediates.



configuration of the C_{13} substituent was not addressed (5, 6) or of no concern (7–9). In this paper, we wish to report on our findings for the stereoselective introduction of these two stereogenic carbons. A modification of our initial set of conditions, which uses microwave irradiation for the furan cyclization reaction, is also disclosed.

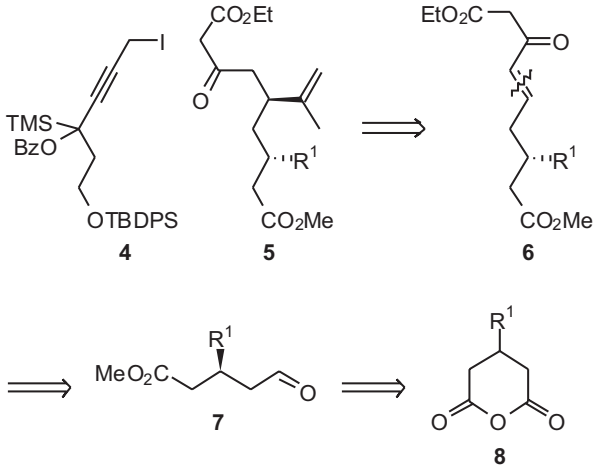
Results and discussions

β-Keto esters, such as **3**, are rapidly constructed by an alkylation reaction with propargylic iodide (**4**) (11) (Scheme 1). Segment **5** would need to be constructed in a stereocontrolled fashion. Further simplification of **5** provides **6**, which can be assembled from aldehyde **7** and an appropriate phosphonate by a Horner–Wadsworth–Emmons olefination. Finally, the highly symmetrical nature of aldehyde **7** led us to consider the use of a catalytic desymmetrization reaction of cyclic *meso*-anhydride (**8**) with an alcohol (13) to create the stereocenter at C_{13}.

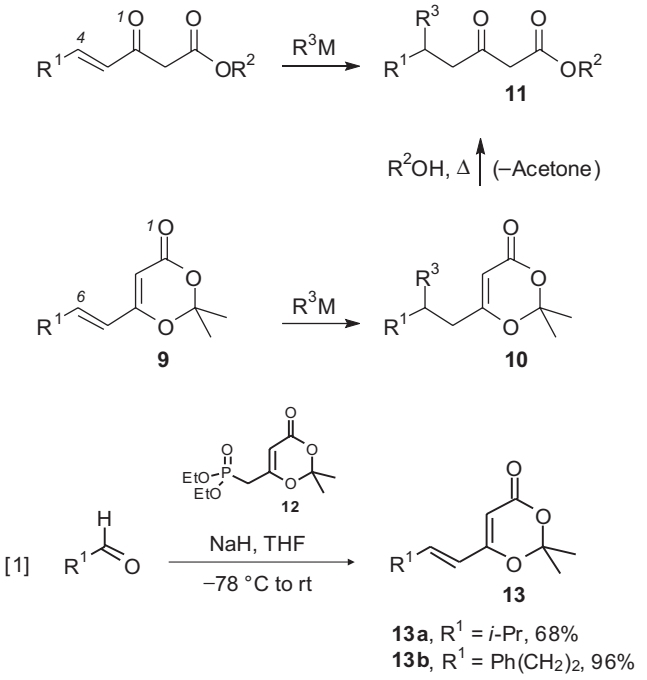
We initially envisioned that a conjugate 1,4-addition of an isopropenyl group to the unsaturated β-keto ester would be a straightforward means to introduce the C_1 side chain in **6**. However, owing to the ease of enolization of this particular type of substrate, we opted for an indirect route in which the 1,3-dicarbonyl unit would be revealed at a later stage (Scheme 2). We further anticipated that confinement of the β-keto ester to a [1,3]dioxin-4-one ring system, such as in **9**, would solve the problem, however, instead of a conjugate 1,4-addition, this required an extended 1,6-additon reaction. Thermolysis of adduct **10** in the presence of an alcohol (R^2OH) would then provide a number of different β-keto esters **11**, and an even greater number of derivatives could be obtained if other heteronucleophiles such as thiols or amines were to be used instead.

To test the feasibility of this route, [1,3]dioxin-4-ones (**13**) were prepared from phosphonate (**12**) (14) and either isobutyraldehyde or hydrocinnamaldehyde according to a literature procedure (15) and used as model substrates (eq. [1]).

Scheme 1. Strategy for the incorporation of the C_{13} stereogenic carbon center.

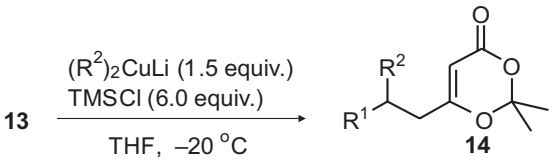


Scheme 2. Strategy for the incorporation of the C_1 stereogenic carbon center.



After some optimization of the reaction conditions, it was found that the addition of these extended Michael acceptors to solutions of Gillman-type organocuprates (R_2CuLi) containing chlorotrimethylsilane (16) at low temperature cleanly afforded the desired 1,6-addition products in high yields (Table 1). A small survey of different organocuprates revealed that simple alkyl groups were readily added (Table 1, entries 1–4), as were aromatic (Table 1, entries 5 and 6) and even silicon-based groups (17) (Table 1, entries 7 and 8). The addition of sterically encumbered organocuprates such as $(t\text{-Bu})_2CuLi$ also proceeded to afford the 1,6-addition adduct, albeit in low yields (Table 1, entries 9 and 10). However, the low yields observed were not because of a lack of reactivity during the 1,6-addition, but rather the result of a

Table 1. 1,6-Addition of organocuprates to [1,3]dioxin-4-ones **13**.



Entry	Substrate	$(R^2)_2CuLi$	Yield (%)
1	**13a**	Me_2CuLi	91
2	**13b**	Me_2CuLi	77
3	**13a**	Et_2CuLi	88
4	**13b**	Et_2CuLi	92
5	**13a**	Ph_2CuLi	79
6	**13b**	Ph_2CuLi	66
7	**13a**	$(PhMe_2Si)_2CuLi$	60
8	**13b**	$(PhMe_2Si)_2CuLi$	61
9	**13a**	*t*-Bu_2CuLi	17
10	**13b**	*t*-Bu_2CuLi	43

nonselective protonation step of the intermediate extended silyl enol ether formed after the 1,6-addition. No reaction occured when less reactive sp-hybridized organocopper reagents (RC≡CCu) or organocuprates [$(RC{\equiv}C)_2CuLi$] were used. It should be pointed out that in all cases studied using these sets of conditions, no adducts derived from 1,4- or 1,2-addition were isolated (18).

Having established that the extended conjugate addition reaction was possible, we next turned our attention toward the preparation of fragment **5** for our synthesis of lophotoxin. As we discussed previously, we planned on introducing the stereocenter at C_{13} by a catalytic desymmetrization reaction on cyclic *meso*-anhydrides **8** (Scheme 3). These were conveniently prepared according to a literature procedure (19) from commercially available diethyl 3-hydroxyglutarate by protection of the free hydroxyl group as a silyl ether to give **15**, followed by exhaustive saponification and dehydration of the resulting disodium acid salt with acetic anhydride. The TBDMS-protected cyclic anhydride **8a** was obtained as an off-white solid upon recrystallization of the crude material after the dehydration step, whereas the TBDPS-protected anhydride **8b** had to be filtered rapidly over a pad of silica gel pretreated with acetic anhydride to remove silanes before recrystallization was successful.[3]

Although there are a number of reported procedures to effect the desymmetrization of the cyclic anhydride **8a** (20–22), we opted for a method recently developed by Deng and co-workers (23) that employs modified cinchona alkaloids, initially adapted for the catalytic asymmetric dihydroxylation of alkenes (24) (Table 2). Using substoichiometric amounts (30 mol%) of $(DHQD)_2AQN$ in the presence of an excess of methanol at low temperature, Deng and co-workers (23) converted cyclic *meso*-anhydrides **8** (R^1 = Me, *i*-Pr) to acids **16** in good yields and high values of ee (Table 2, entries 1 and 2). When these optimized conditions were applied to the TBDMS-protected cyclic anhydride **8a**, a similar conversion to the desired acid was obtained (Table 2, entry 3). Longer reaction times resulted in higher conversions (Table 2, entry 4), however extensive desilylation of the product in both cases precluded the use of this substrate. Fortunately, when the TBDPS-protected cyclic anhydride **8b** was submitted to the desymmetrization reaction, conversions of 75%–85% were obtained, and more importantly, ^{1}H NMR analysis of the crude mixture indicated that no desilylation of **16** had occurred (Table 2, entry 5). An aliquot of the crude acid, accumulated from seven desymmetrizations under identical conditions, was reduced to the corresponding alcohol and treated with dil. HCl to provide the cyclic lactone **18** (Scheme 4) (25). Comparison of the chiral HPLC trace of this material with the racemic material prepared using quinuclidine as the organocatalyst (Table 2, entry 7) showed that the desymmetrization reaction occurred with a high level of enantioselectivity (95% ee). Finally, conducting the desymmetrization of **8b** at a higher temperature (–20 °C, Table 2, entry 6) resulted in a com-

Scheme 3. Preparation of cyclic anhydrides **8**. Reagents and conditions: (*a*) chlorosilane, imidazole, CH_2Cl_2, rt (**15a**, R^1 = OTBDMS, 92%; **15b**, R^1 = OTBDPS, 96%); (*b*) NaOH, MeOH, rt, 24–40 h; (*c*) Ac_2O, C_6H_6, Δ, 1.5 h (**8a**, R^1 = OTBDMS, 80%; **8b**, R^1 = OTBDPS, 46%).

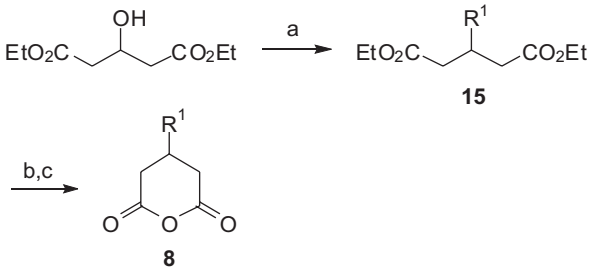
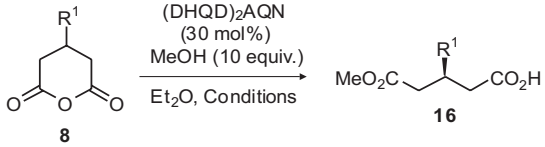


Table 2. Catalytic desymmetrization of cyclic *meso*-anhydrides **8** with $(DHQD)_2AQN$.

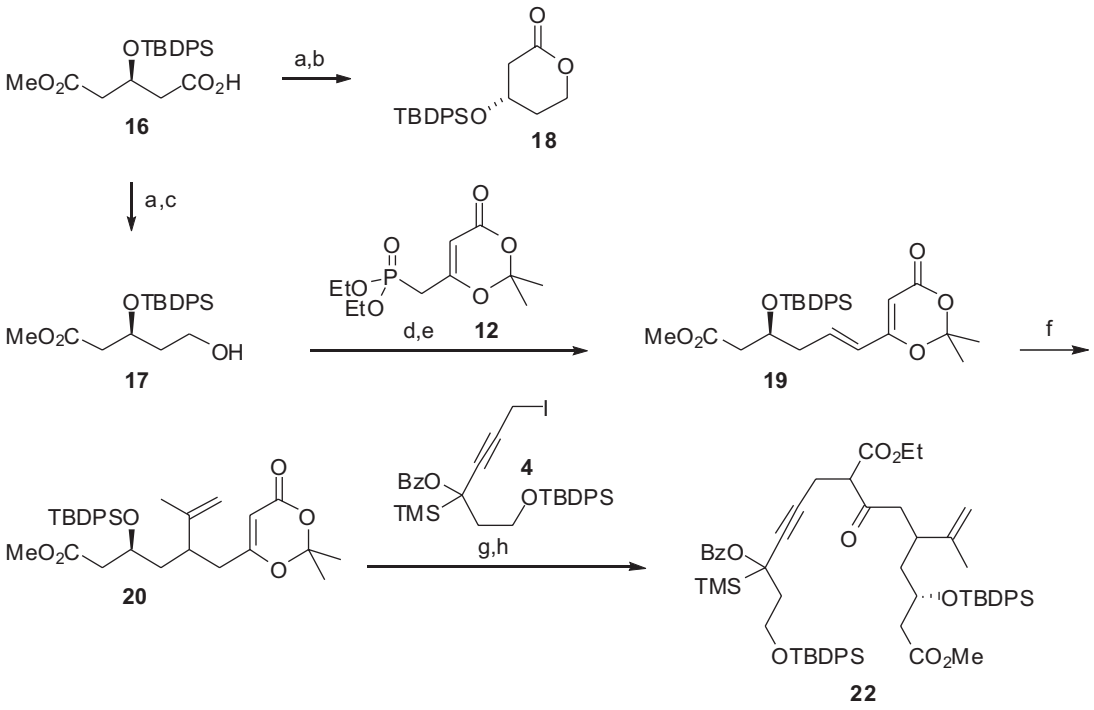


Entry	R^1	Conditions (°C, h)	Conversion (%)	ee (%)
1[a]	Me	–40, 43[a]	70[a,b]	91
2[a]	*i*-Pr	–40, 43[a]	72[a,b]	90
3	OTBDMS (**8a**)	–40, 41	65[c]	Nd[d]
4	OTBDMS (**8a**)	–40, 70	90–95[c]	Nd
5	OTBDPS (**8b**)	–40, 70	75–85[e]	95
6	OTBDPS (**8b**)	–20, 70	100	88
7	OTBDPS (**8b**)	–40, 70	96[f]	—

[a]Data from ref. 23.
[b]Isolated yield.
[c]Extensive desilylation of the product was observed.
[d]Nd (not determined).
[e]Conversions from seven desymmetrizations under identical conditions.
[f]Quinuclidine was used as a catalyst.

[3] Extensive desilylation occurs during the two-step sequence leading to lower yields of **8b**.

Scheme 4. Preparation of furan cyclization precursor **22**. Reagents and conditions: (*a*) BH_3·DMS, THF, rt, 15–17 h; (*b*) 10% HCl, rt, 1 h (38% from **8b**); (*c*) satd. aq. $NaHCO_3$, rt, 20 min (71% from **8b**); (*d*) TPAP (5 mol%), NMO, 4 Å MS, MeCN–CH_2Cl_2 (1:9), 30 min; (*e*) **12**, NaH, THF, –78 °C to rt, 1 h (49%, two steps); (*f*) CuI, 2-lithiopropene, TMSCl, THF, –20 °C, 16 h (94%, 1:1 dr); (*g*) EtOH, toluene, Δ; (*h*) NaH, **4**, THF, 0 °C to rt (77%, two steps).



plete conversion to the acid, albeit with lower selectivity (88% ee).

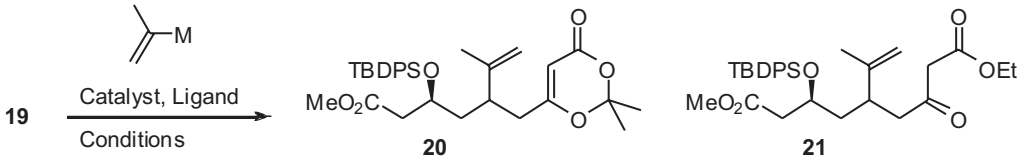
With an efficient and stereoselective solution for introducing the protected alcohol at C_{13}, we proceeded with our synthesis of fragment **5**. Reduction of the acid function in **16** with the borane – dimethyl sulfide complex followed by basic aqueous work up gave the alcohol **17** in good overall yield from cyclic *meso*-anhydride **8b**. Ley–Griffith oxidation of this alcohol to the aldehyde (26) followed by a Horner–Wadsworth–Emmons olefination with the stabilized phosphonate **12** (15) provided the 1,6-addition precursor **19** as a single isomer. Using 3 equiv. of the organocuprate derived from 2-lithiopropene, addition to the extended Michael acceptor occurred smoothly to provide **20** in high yield as a 1:1 mixture of diastereomers. Thermolysis of the [1,3]dioxin-4-one ring with ethanol in refluxing toluene revealed the β-keto ester (**21**) (see Table 3) that was then alkylated with the previously reported iodide **4** (11) to give the furan cyclization precursor **22** in good yield as a mixture of stereoisomers.

We were not surprised by the lack of stereocontrol obtained for the 1,6-addition of the organocuprate to [1,3]dioxin-4-one (**19**) (Scheme 4). By analogy to the diastereoselective 1,4-addition of copper-based organometallic reagents to Michael acceptors possessing a stereogenic center at the δ position under substrate control (27), we anticipated low levels of selectivity for the 1,6-addition. This gave us the opportunity to develop a catalytic asymmetric variant of the 1,6-addition reaction, and since stoichiometric copper-based reagents were effective, we initially screened for copper catalysts (Table 3). These studies proved quite disappointing; indeed, using conditions optimized for the catalytic asymmetric 1,4-addition of diorganozincs to enones (28), no reaction occurred and the starting material was recovered unchanged (Table 3, entry 1). The addition of chlorotrimethylsilane had no effect on the outcome of the reaction and even the use of Et_2Zn, which is often employed as a nucleophile in catalytic asymmetric conjugate additions, failed as well.

Over the past decade, rhodium catalysts have received increasing attention as alternatives to copper catalysts for the catalytic asymmetric 1,4-addition reaction, especially since the pioneering work by the research groups of Miyaura and Hayashi (29). However, a serious concern arises when considering the experimental conditions employed; most of the procedures involve heating at elevated temperatures in a binary solvent mixture composed of water and a cosolvent. We feared that thermal fragmentation of the [1,3]dioxin-4-one ring would lead to the α,β-unsaturated methyl ketone derived from **19** by a sequence that involves addition of 1 equiv. of water to an acyl ketene intermediate, followed by intramolecular decarboxylation of the resulting β-keto acid. As shown in Table 3 (entry 2), these concerns were confirmed when an addition of lithium 2-propenylborate in the presence of 1 equiv. of water (30) resulted in hydrolysis of **19** and isolation of the α,β-unsatured ester (65%).

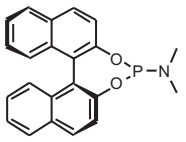
Recent findings by Feringa and co-workers (31) and Genêt and co-workers (32) have shown that potassium organotrifluoroborates (RBF_3K), a class of air- and moisture-stable organometallic reagents, can be used as substitutes for boronic acids in the rhodium-catalyzed asymmetric 1,4-addition to enones using phosporamidites or

Table 3. Catalytic asymmetric 1,6-addition to [1,3]dioxin-4-one **19**.

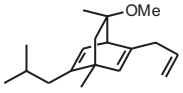


Entry	Substrate	M	Catalyst (mol%), Ligand (mol%)	Conditions	Yield **20**,**21** (%)	dr[a]
1	**19**	$(\text{Zn})_2$	$Cu(OTf)_2$ (5), **L_1** (10)	Toluene, –20 °C	0	—
2	**19**	$B(OMe)_3Li$	$Rh(acac)(eth)_2$ (4), Binap (6.5)	Dioxane H_2O (1 equiv.), Δ	0	—
3	**19**	BF_3K	$Rh(acac)(eth)_2$ (4), **L_1** (13)	EtOH, 83 °C	23,41	1.7:1
4	**19**		$Rh(acac)(eth)_2$ (4), **L_2** (6)	EtOH, 82 °C	21,38	4.0:1
5	**24**[b]		$Rh(acac)(eth)_2$ (4), **L_2** (6)	EtOH, 78 °C	27,32	3.7:1

[a] Diastereomeric ratio determined by ^{1}H NMR.
[b] Reaction performed on the acetate-protected derivative.



L_1 (MonoPhos™)



L_2 (Carreira's diene)

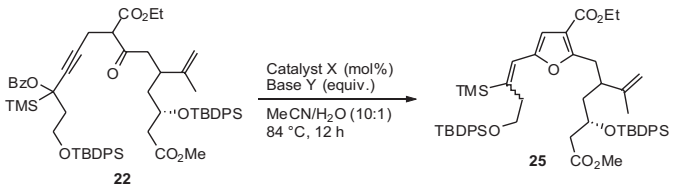
bidentate phosphines as chiral ligands. Of particular interest to us was the fact that these reactions can be performed in the absence of water (pure EtOH) and at lower temperatures (70 °C) (31), so that addition could occur before any significant cleavage of the [1,3]dioxin-4-one ring could take place. Gratifyingly, on our first try with Monophos™ (**L_1**, see bottom of Table 3) in a heated ethanolic solution, we obtained a mixture of 1,6-addition products **20** and **21** in a moderate combined yield, albeit in low diastereoselectivity (Table 3, entry 3). We then turned our attention to chiral bidentate phosphine ligands such as (*R*)-Binap, (*R*,*R*)-Me-Duphos, and (*S*,*S*)-Chiraphos, however, the use of these ligands seemed to considerably diminish the activity of the catalytic system and only starting material was recovered.

Another class of promising chiral ligands for the catalytic asymmetric 1,4-addition are chiral dienes (33), which have been disclosed recently by Hayashi et al. (34) and Carreira and co-workers (35). We chose to prepare Carreira's diene (see **L_2**, bottom of Table 3) from commercially available carvone. After heating **19** with the organotrifluoroborate in the presence of a rhodium catalyst, we were able to isolate the addition products **20** and **21** in a moderate combined yield as a 4:1 mixture of isomers (Table 3, entry 4) (36). Performing the reaction with a different neutral rhodium catalyst, $\{[RhCl(eth)_2]_2\}$ gave similar results (64% combined yield, 3.1:1 dr), whereas lower temperatures (57–60 °C) resulted in lower conversions.[4] We also attempted the reaction with the acetate-protected derivative **24** (Table 3, entry 5) as well as the free-hydroxyl derivative **23**, however, no increase in selectivity was observed with the former and the latter appeared to be unreactive.

Since we were unable to prepare the 1,6-addition products **20** and (or) **21** with high levels of stereoselectivity, we decided to resume our synthesis of lophotoxin with the 1:1 mixture of diastereomers obtained in high yield from the organocuprate addition (Scheme 4). The stage was now set for the key cyclization step that would produce the 2,3,5-trisubstituted furan ring and stereoselectively generate the olefin with the appropriate geometry, all in a single transition-metal-catalyzed event. Unfortunately, treatment of the α-propargyl β-keto ester **22** under our previously optimized conditions (11) gave only trace amounts of furan **25** (Table 4, entry 1). Although the starting material had been completely consumed, as judged by ^{1}H NMR analysis, no identifiable products could be isolated from the crude reaction mixture. After a number of unsuccessful attempts, we decided to conduct control experiments and we were quite surprised to see that treatment of **22** with only K_2CO_3, present under otherwise identical reaction conditions, resulted in rapid desilylation (TMS group) of the starting material (ca. 1 h, Table 4, entry 2). In light of this result, we decided to screen for other catalyst–base combinations and we were pleased to see that the use of $Pd(PPh_3)_4$ and $NaOAc{\cdot}3H_2O$ provided a reasonable yield of furan **25** as a 6.8:1 mixture of isomers (Table 4, entry 3). The addition of more base (Table 4, entry 4) or the use of related bases (Table 4, entries 5

[4] Comparable diastereomeric ratios (3.9:1) were obtained.

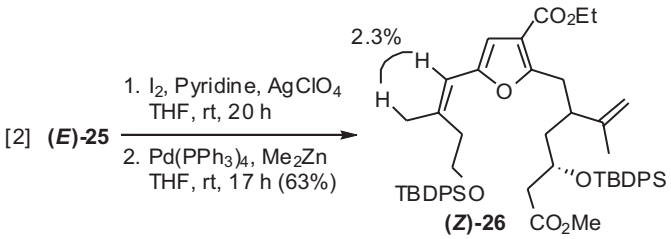
Table 4. Transition-metal-catalyzed cyclization of α-propargyl β-keto ester **22**.



Entry	Catalyst X (mol%)	Base Y (equiv.)	*E*/*Z* (ratio)[a]	Yield (%)
1	$Pd(OAc)_2$ (5), dppf (6)	K_2CO_3 (1.1)	—	Nd[b]
2	none	K_2CO_3 (1.1)	—	0
3	$Pd(PPh_3)_4$ (15)	$NaOAc{\cdot}3H_2O$ (1.1)	6.8:1	49
4	$Pd(PPh_3)_4$ (15)	$NaOAc{\cdot}3H_2O$ (5.0)	6.8:1	51
5	$Pd(PPh_3)_4$ (15)	NaOBz (1.1)	5.4:1	44
6	$Pd(PPh_3)_4$ (15)	$NaOPiv{\cdot}H_2O$ (1.1)	5.5:1	53
7	$Pd(PPh_3)_4$ (15)	$NaOAc{\cdot}3H_2O$ (1.1), 2,6-lutidine (1.1)	6.6:1	56

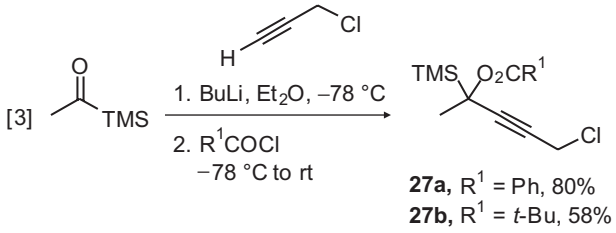
and 6) led to almost identical results, as did the combination of $NaOAc{\cdot}3H_2O$ and an organic base (Entry 7).

Comparison of the ^1H NMR spectra of **25** with our previously described furan **2** (Fig. 1) indicated that the major isomer formed during the reaction was the undesired (*E*)-isomer.[5] To verify the olefin configuration, we converted the vinylsilane moiety to the corresponding iodide and performed a Negishi cross-coupling reaction with dimethylzinc that yielded furan **26** (eq. [2]). A 1D-nOe analysis allowed us to assign the stereochemistry of the major isomer as **(*Z*)-26** since an nOe enhancement was observed between the hydrogen atoms of the newly introduced methyl group and the hydrogen atom of the alkene, establishing that the TMS group in **25** was located *trans* to the furan ring.



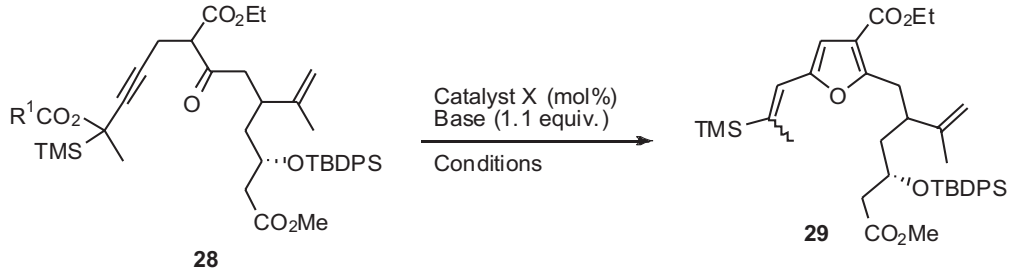
Our inability to gain access to **(*Z*)-25** forced a reconsideration of our strategy to close the macrocyclic ring in lophotoxin. Instead of relying on the furan cyclization reaction to set the stereochemistry as shown in **(*Z*)-25** and then attach the C_{19} methyl group, we decided to prepare furan **(*E*)-29** (Table 5) that already had an attached C_{19} methyl group and to use the vinylsilane moiety for further transformations. In addition to being more convergent, this approach gave us the opportunity to focus on a different bond disconnection in which C_8 and C_9 would be joined together by a transition-metal-catalyzed intramolecular cross-coupling reaction. In any event, we prepared the α-propargyl β-keto esters **28** from β-keto ester **21** and the appropriate halides **27** (eq. [3]).

When substrate **28a** (R^1 = Ph) was subjected to the original cyclization conditions, virtually no furan was formed and the starting material decomposed (Table 5, entry 1). Using the modified set of conditions [$Pd(PPh_3)_4$–$NaOAc{\cdot}3H_2O$] we were pleased to see that cyclization had occured, although we were alarmed by the much lower isolated yield (Table 5, entry 2). Another product, possibly arising from migration of the benzoate group across the alkyne, was recovered from this reaction in ca. 32% yield. Since the benzoate might be too readily eliminated, we prepared the pivaloate derivative **28b** (R^1 = *t*-Bu) and were relieved to see that under the new set of conditions, the desired furan **29** was formed once again in moderate yield (Table 5, entry 3). To decrease the reaction times and possibly minimize side reactions, we next turned our attention to the use of microwave irradiation to promote the cyclization reaction. Gratifyingly, heating **28b** for only 40 min in the microwave under otherwise identical reaction conditions led to furan **29** in a comparable yield and high selectivity (Table 5, entry 4). While screening for other transition-metal catalysts, we were pleased to find that the allylpalladium chloride dimer was also an effective catalyst for the cyclization. In this case, both pivalate and benzoate derivatives could be used and the furan was obtained in acceptable yields (Table 5, entries 5 and 6). Although the (*E*/*Z*) selectivity was severely diminished, isomerization of the furan mixture with a catalytic amount (5–10 mol%) of $(PhSe)_2$ in THF at reflux produced pure **(*E*)-29** in high yield (Table 5, entry 5). With a more practical route to this furan in hand, we are currently exploring a strategy that involves further modification of the protected β-hydroxy ester fragment followed by an intramolecular transition-metal-



[5] The ^1H NMR chemical shift of the TMS group is particularly diagnostic. Indeed, in **2** the TMS group has a δ of 0.11 ppm, whereas the major isomer in **25** has a δ of 0.00 ppm and the minor isomer has a δ of 0.09 ppm.

Table 5. Transition-metal-catalyzed cyclization of α-propargyl β-keto esters **28**.



28 **29**

Entry	R^1	Catalyst X (mol%)	Base (1.1 equiv.)	Conditions[a]	E/Z (ratio)[b]	Yield (%)
1	Ph (**28a**)	$Pd(OAc)_2$ (5), dppf (6)	K_2CO_3	A	—	Nd[c]
2	Ph (**28a**)	$Pd(PPh_3)_4$ (15)	$NaOAc{\cdot}3H_2O$	A	5.1:1	30
3	*t*-Bu (**28b**)	$Pd(PPh_3)_4$ (15)	$NaOAc{\cdot}3H_2O$	A	6.6:1	53
4	*t*-Bu (**28b**)	$Pd(PPh_3)_4$ (15)	$NaOAc{\cdot}3H_2O$	B	8.6:1	51
5	*t*-Bu (**28b**)	$[(\eta^3\text{-}C_3H_5)PdCl]_2$ (7.5), dppf (15)	None	C	1.4:1	59 (50[d])
6	Ph (**28a**)	$[(\eta^3\text{-}C_3H_5)PdCl]_2$ (7.5), dppf (15)	None	C	1.5:1	54

[a]Reagents and conditions: (A) MeCN–H_2O (10:1); (B) MeCN–H_2O (10:1), 100 °C, μW, 40 min; (C) THF, 100 °C, μW, 20 min.
[b]Isomeric ratio determined by ^1H NMR.
[c]Nd (not determined).
[d]Yield of pure (***E*)-29** from **28** after isomerization with $(PhSe)_2$.

catalyzed cross-coupling reaction with the vinylsilane moiety. These results will be disclosed in due course.

Conclusion

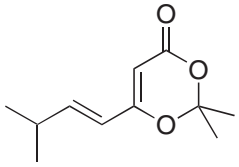
We have shown that a catalytic desymmetrization reaction using a modified cinchona alkaloid allows for the stereoselective incorporation of the C_{13} substituent present in lophotoxin from a simple prochiral cyclic anhydride. A newly developed, highly regioselective 1,6-addition reaction of organocuprates to unsaturated [1,3]dioxin-4-ones provided a means to introduce the C_1 isopropenyl group, and encouraging preliminary results have established that a rhodium-catalyzed asymmetric 1,6-addition reaction provides moderate levels of diastereocontrol. Problems encountered with the transition-metal catalyzed furan cyclization reaction have led to modifications of our original thermal procedure and to the development of a microwave-assisted variant. We are currently applying these modifications toward the total synthesis of lophotoxin and other members of the furanocembranolide family of natural products.

Experimental

General methods

All moisture-sensitive reactions were performed under an atmosphere of N_2 and glassware was flame-dried under vacuum prior to use. Et_2O and THF were dried by distillation over Na–benzophenone. Distilled hexane and ethyl acetate were used for chromatographic purifications. Toluene and CH_2Cl_2 were purified by filtration through activated alumina. TMSCl was distilled over CaH_2 and kept in a dessicator. $(DHQD)_2AQN$ was prepared according to a literature procedure (24). Unless otherwise stated, all other reagents and solvents were used as received. Analytical thin layer chromatography (TLC) was performed on precoated silica gel 60 F-254 plates (particle size 0.040–0.055 mm, 230–400 mesh) and visualization was accomplished with a 254 nm UV light and (or) by staining with a basic $KMnO_4$ solution (1.5 g of $KMnO_4$ and 1.5 g of K_2CO_3 in 100 mL of a 0.1% aq. NaOH solution). NMR spectra were recorded at 300 MHz and 76 MHz for ^1H NMR and ^{13}C NMR, respectively, using a Bruker AVANCE 300 MHz spectrometer at 21 °C in $CDCl_3$ unless stated otherwise. Chemical shifts (δ) are reported as follows: chemical shift, multiplicity (singlet (s), doublet (d), triplet (t), quartet (q), quintet (qn), hextet (hex), multiplet (m), broad (b)), coupling constants, and integration. IR spectra were obtained on a Nicolet AVATAR 360 FT-IR ESP spectrometer. Mass spectra were obtained on a Micromass Autospec double focusing instrument. Optical rotations were measured on a PerkinElmer 241 polarimeter. Microwave reactions were run on a CEM Discover instrument.

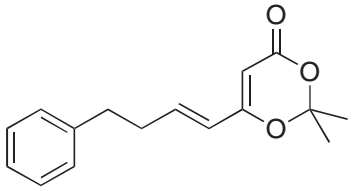
2,2-Dimethyl-6-(3-methylbut-1-enyl)[1,3]dioxin-4-one (13a)



To a solution of phosphonate **12** (1.11 g, 3.99 mmol) in THF (20 mL) cooled to 0 °C was added NaH (192 mg of a 60% mineral dispersion, 4.80 mmol). The ice bath was removed and the reaction mixture was stirred at rt for 30 min, cooled to –78 °C, and treated with isobutyraldehyde (400 μL, 4.4 mmol). The solution was allowed to gradually warm to rt and stirred for 1 h. One drop of satd. aq. $NaHCO_3$ was added and the mixture was stirred for 5 min (to complete the deprotonation step). After adding satd. aq. $NaHCO_3$ (50 mL), the reaction was transferred to a separatory funnel and extracted with Et_2O (3 × 50 mL). The organic layers were combined, dried (Na_2SO_4), filtered,

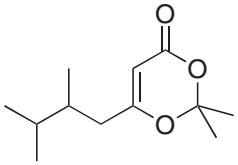
concentrated under reduced pressure, and purified by chromatography on SiO_2 to afford 532 mg of **13a** (68%) as a colourless oil. R_f 0.26 (20% EtOAc–hexane). FT-IR (neat, cm^{-1}): 2963, 2872, 1731, 1653, 1592, 1391, 1374, 1273, 1206, 1018. ^1H NMR ($CDCl_3$) δ: 6.54 (dd, J = 15.6, 6.8 Hz, 1H), 5.85 (dd, J = 15.6, 1.4 Hz, 1H), 5.26 (s, 1H), 2.46 (hexd, J = 6.8, 1.4 Hz, 1H), 1.72 (s, 6H), 1.08 (d, J = 6.8 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ: 163.5, 161.8, 148.5, 119.6, 106.0, 93.1, 31.1, 24.8 (2), 21.3 (2). HR-MS (EI) *m/e* calcd. for $C_{11}H_{16}O_3$: 196.1099; found: 196.1102.

2,2-Dimethyl-6-(4-phenylbut-1-enyl)[1,3]dioxin-4-one (13b)



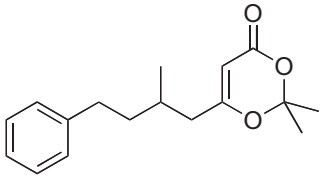
To a solution of phosphonate **12** (1.95 g, 7.01 mmol) in THF (50 mL) cooled to 0 °C was added NaH (240 mg of a 60% mineral dispersion, 6.00 mmol). The ice bath was removed and the reaction mixture was stirred at rt for 30 min, cooled to –78 °C, and treated with hydrocinnamaldehyde (730 μL, 5.0 mmol). The solution was allowed to gradually warm to rt and stirred for 1 h. One drop of satd. aq. $NaHCO_3$ was added and the mixture was stirred for 5 min (to complete the deprotonation step). After adding satd. aq. $NaHCO_3$ (50 mL), the reaction was transferred to a separatory funnel and extracted with Et_2O (4 × 50 mL). The organic layers were combined, dried (Na_2SO_4), filtered, concentrated under reduced pressure, and purified by chromatography on SiO_2 to afford 1.23 g of **13b** (96%) as a colourless oil. R_f 0.20 (20% EtOAc–hexane). FT-IR (neat, cm^{-1}): 2999, 2941, 1725, 1653, 1592, 1390, 1274, 1205, 1020. ^1H NMR ($CDCl_3$) δ: 7.34–7.18 (m, 5H), 6.61 (dt, J = 15.5, 7.1 Hz, 1H), 5.93 (dt, J = 15.6, 1.4 Hz, 1H), 5.25 (s, 1H), 2.82–2.76 (m, 2H), 2.58–2.50 (m, 2H), 1.72 (s, 6H). ^{13}C NMR ($CDCl_3$) δ: 163.1, 161.9, 141.2, 140.6, 128.4 (2), 128.2 (2), 126.1, 122.9, 106.2, 93.4, 34.6, 34.4, 24.9 (2). HR-MS (EI) *m/e* calcd. for $C_{16}H_{18}O_3$: 258.1256; found; 258.1254.

6-(2,3-Dimethylbutyl)-2,2-dimethyl[1,3]dioxin-4-one (14a)



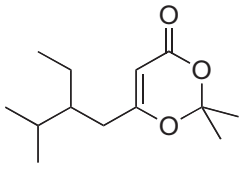
To a suspension of CuI (143 mg, 0.751 mmol) in THF (2.5 mL) cooled to –78 °C was added dropwise a solution of MeLi in Et_2O (1.6 mol/L, 940 μL, 1.5 mmol). The cold bath was removed and the mixture was stirred at rt for 30 min. The resulting colourless solution was then cooled to –78 °C and TMSCl (380 μL, 3.0 mmol) was added. After stirring for ca. 5 min, a solution of **13a** (98.8 mg, 0.503 mmol) in THF (1.5 mL, 1.0 mL rinse) was added. The mixture was stirred at –78 °C for 30 min, then at –20 °C for ca. 18 h. The reaction was stopped by adding satd. aq. $NaHCO_3$ (30 mL) at –20 °C, then warmed to rt, transferred to a separatory funnel, and extracted with Et_2O (4 × 30 mL). The organic layers were combined, dried (Na_2SO_4), filtered, concentrated under reduced pressure, and purified by chromatography on SiO_2 to afford 97 mg of **14a** (91%) as a colourless oil. R_f 0.36 (20% EtOAc–hexane). FT-IR (neat, cm^{-1}): 2961, 2876, 1735, 1633, 1390, 1272, 1205, 1013. ^1H NMR ($CDCl_3$) δ: 5.23 (s, 1H), 2.29 (dd, J = 14.1, 5.0 Hz, 1H), 1.96 (dd, J = 14.1, 9.4 Hz, 1H), 1.75–1.70 (m, 1H), 1.70 (s, 3H), 1.69 (s, 3H), 1.65–1.59 (m, 1H), 0.91 (d, J = 6.8 Hz, 3H), 0.87 (d, J = 6.8 Hz, 3H), 0.86 (d, J = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 171.7, 161.2, 106.1, 94.0, 38.5, 36.0, 31.8, 25.2, 24.7, 19.8, 17.7, 15.0. HR-MS (ESI–POS) *m/e* calcd. for $C_{12}H_{20}O_3Na$: 235.1310 [M + Na]; found: 235.1299.

2,2-Dimethyl-6-(2-methyl-4-phenylbutyl)[1,3]dioxin-4-one (14b)



Following the previous procedure for the 1,6-addition of Me_2CuLi, [1,3]dioxin-4-one **13b** (124 mg, 0.480 mmol) gave 101 mg (77%) of **14b** as a colourless oil. R_f 0.29 (20% EtOAc–hexane). FT-IR (neat, cm^{-1}): 2998, 2929, 1732, 1633, 1390, 1272, 1204, 1014. ^1H NMR ($CDCl_3$) δ: 7.32–7.27 (m, 2H), 7.22–7.15 (m, 3H), 5.22 (s, 1H), 2.73–2.67 (m, 1H), 2.63–2.57 (m, 1H), 2.28 (dd, J = 14.2, 6.1 Hz, 1H), 2.07 (dd, J = 14.2, 7.9 Hz, 1H), 1.86 (hex, J = 6.4 Hz, 1H), 1.73–1.67 (m, 1H), 1.67 (s, 3H), 1.66 (s, 3H), 1.56–1.47 (m, 1H), 1.02 (d, J = 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 170.8, 161.1, 141.9, 128.3 (2), 128.2 (2), 125.8, 106.1, 94.2, 41.0, 38.3, 33.1, 30.1, 25.0, 24.9, 19.3. HR-MS (ESI–POS) *m/e* calcd. for $C_{17}H_{22}O_3Na$ [M + Na]: 297.1467; found: 297.1447.

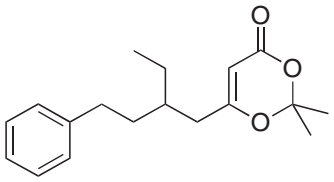
6-(2-Ethyl-3-methylbutyl)-2,2-dimethyl[1,3]dioxin-4-one (14c)



To a suspension of CuI (143 mg, 0.751 mmol) in THF (2.0 mL) cooled to 0 °C was added dropwise a 0.39 mol/L solution of EtLi in benzene–cyclohexane (90:10, 3.8 μL, 1.5 mmol) and the mixture was stirred at 0 °C for 30 min. The resulting dark black solution was then cooled to –78 °C and TMSCl (380 μL, 3.0 mmol) was added. After stirring for ca. 5 min, a solution of **13a** (97.6 mg, 0.497 mmol) in THF (1.5 mL, 1.0 mL rinse) was added. The mixture was stirred at –78 °C for 30 min, then at –20 °C for ca. 17 h. The reaction was stopped by adding satd. aq. $NaHCO_3$ (30 mL) at –20 °C, then warmed to rt, transferred to a separatory funnel, and extracted with Et_2O (3 × 30 mL). The organic layers were combined, dried (Na_2SO_4), filtered, concentrated under

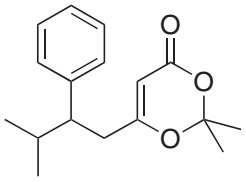
reduced pressure, and purified by chromatography on SiO_2 to afford 99 mg of **14c** (88%) as a colourless oil. R_f 0.35 (20% EtOAc–hexane). FT-IR (neat, cm^{-1}): 2961, 2876, 1735, 1632, 1464, 1389, 1272, 1205, 1015. ^1H NMR ($CDCl_3$) δ: 5.24 (s, 1H), 2.21 (dd, *J* = 14.4, 6.0 Hz, 1H), 2.06 (dd, *J* = 14.4, 7.7 Hz, 1H), 1.82–1.72 (m, 1H), 1.69 (s, 6H), 1.53–1.42 (m, 1H), 1.42–1.17 (m, 2H), 0.89 (t, *J* = 7.5 Hz, 3H), 0.88 (d, *J* = 7.3 Hz, 3H), 0.86 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 172.3, 161.3, 106.1, 94.0, 42.8, 34.9, 28.6, 25.1, 24.9, 22.8, 19.0, 18.6, 11.6. HR-MS (EI) *m/e* calcd. for $C_{10}H_{16}O_2$: 168.1150 [M – CH_3COCH_3]; found: 168.1148.

6-(2-Ethyl-4-phenylbutyl)-2,2-dimethyl[1,3]dioxin-4-one (14d)



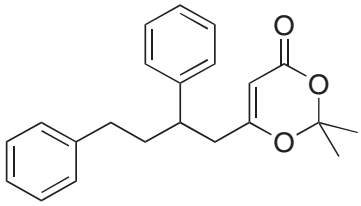
Following the previous procedure for the 1,6-addition of Et_2CuLi, [1,3]dioxin-4-one **13b** (131 mg, 0.507 mmol) gave 134 mg (92%) of **14d** as a colourless oil. R_f 0.28 (20% EtOAc–hexane). FT-IR (neat, cm^{-1}): 2998, 2935, 1731, 1631, 1455, 1390, 1272, 1204, 1014. ^1H NMR ($CDCl_3$) δ: 7.32–7.26 (m, 2H), 7.22–7.14 (m, 3H), 5.23 (s, 1H), 2.67–2.57 (m, 2H), 2.26–2.19 (m, 2H), 1.73–1.60 (m, 3H), 1.67 (s, 3H), 1.65 (s, 3H), 1.49–1.36 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 171.2, 161.2, 142.0, 128.3 (2), 128.2 (2), 125.8, 106.2, 94.2, 37.7, 36.1, 34.7, 32.7, 25.5, 25.0, 24.9, 10.4. HR-MS (EI) *m/e* calcd. for $C_{18}H_{24}O_3$: 288.1725; found: 288.1727.

2,2-Dimethyl-6-(3-methyl-2-phenylbutyl)-[1,3]dioxin-4-one (14e)



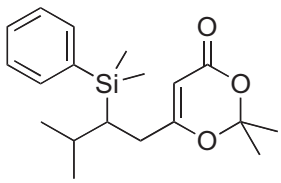
To a suspension of CuI (143 mg, 0.751 mmol) in THF (2.5 mL) cooled to 0 °C was added dropwise a solution of PhLi (1.0 mol/L) in cyclohexane–Et_2O (70:30, 1.5 mL, 1.5 mmol). After stirring at 0 °C for 30 min, the mixture was cooled to –78 °C, at which point a dense precipitate formed. TMSCl (380 μL, 3.0 mmol) was added and after ca. 5 min a solution of **13a** (99.2 mg, 0.506 mmol) in THF (1.5 mL, 1.0 mL rinse) was added. The mixture was stirred at –78 °C for 30 min, then at –20 °C for ca. 18 h. The reaction was stopped by adding satd. aq. $NaHCO_3$ (30 mL) at –20 °C, then warmed to rt, transferred to a separatory funnel, and extracted with Et_2O (4 × 30 mL). The organic layers were combined, dried (Na_2SO_4), filtered, concentrated under reduced pressure, and purified by chromatography on SiO_2 to afford 110 mg of **14e** (79%) as a colourless oil. R_f 0.31 (20% EtOAc–hexane). FT-IR (neat, cm^{-1}): 2960, 2873, 1731, 1633, 1454, 1390, 1272, 1204, 1014. ^1H NMR ($CDCl_3$) δ: 7.29–7.24 (m, 2H), 7.22–7.17 (m, 1H), 7.10–7.06 (m, 2H), 5.05 (s, 1H), 2.76 (dd, *J* = 14.2, 4.3 Hz, 1H), 2.73–2.66 (m, 1H), 2.52 (dd, *J* = 14.2, 11.1 Hz, 1H), 1.84 (apparent hex, *J* = 6.8 Hz, 1H), 1.51 (s, 3H), 1.32 (s, 3H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.77 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 170.7, 161.2, 141.4, 128.4 (2), 128.1 (2), 126.6, 106.2, 94.5, 49.5, 36.9, 33.6, 25.4, 24.0, 20.6, 20.1. HR-MS (EI) *m/e* calcd. for $C_{14}H_{16}O_2$: 216.1150 [M – CH_3COCH_3]; found: 216.1150.

6-(2,4-Diphenylbutyl)-2,2-dimethyl[1,3]dioxin-4-one (14f)



Following the previous procedure for the 1,6-addition of Ph_2CuLi, [1,3]dioxin-4-one **13b** (128 mg, 0.496 mmol) gave 110 mg (66%) of **14f** as a colourless oil. R_f 0.24 (20% EtOAc–hexane). FT-IR (neat, cm^{-1}): 3027, 2999, 2939, 2858, 1728, 1632, 1495, 1454, 1390, 1272, 1204, 1014. ^1H NMR ($CDCl_3$) δ: 7.36–7.31 (m, 2H), 7.29–7.23 (m, 3H), 7.21–7.15 (m, 3H), 7.12–7.07 (m, 2H), 5.07 (s, 1H), 2.97–2.89 (m, 1H), 2.60 (dd, *J* = 14.5, 6.4 Hz, 1H), 2.56–2.40 (m, 3H), 2.05–1.88 (m, 2H), 1.53 (s, 3H), 1.46 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 169.8, 161.0, 142.6, 141.6, 128.6 (2), 128.29 (2), 128.26 (2), 127.5 (2), 126.8, 125.8, 106.3, 94.5, 42.3, 40.7, 38.1, 33.3, 25.0, 24.6. HR-MS (EI) *m/e* calcd. for $C_{19}H_{18}O_2$: 278.1307 [M – CH_3COCH_3]; found: 278.1303.

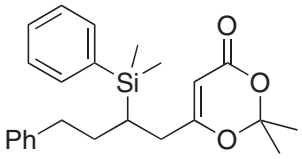
6-[2-(Dimethylphenylsilanyl)-3-methylbutyl]-2,2-dimethyl[1,3]dioxin-4-one (14g)



To a suspension of CuI (143 mg, 0.751 mmol) in THF (1.0 mL) cooled to –20 °C was added dropwise a solution of $PhMe_2SiLi$ in THF (0.40 mol/L, 3.8 μL, 1.5 mmol), and the mixture was stirred at –20 °C for 4 h. TMSCl (380 μL, 3.0 mmol) was added and the mixture was stirred for ca. 5 min after which a solution of **13a** (95.4 mg, 0.486 mmol) in THF (1.5 mL, 1.0 mL rinse) was added. The reaction mixture was stirred at –20 °C for ca. 15 h, stopped by adding satd. aq. $NaHCO_3$ (30 mL) at –20 °C, then warmed to rt, transferred to a separatory funnel, and extracted with Et_2O (4 × 30 mL). The organic layers were combined, dried (Na_2SO_4), filtered, concentrated under reduced pressure, and purified by chromatography on SiO_2 to afford 97 mg of **14g** (60%) as a colourless oil. R_f 0.42 (20% EtOAc–hexane). FT-IR (neat, cm^{-1}): 2998, 2957, 2872, 1732, 1630, 1427, 1389, 1271, 1205, 1111, 1016. ^1H NMR ($CDCl_3$) δ: 7.54–7.47 (m,

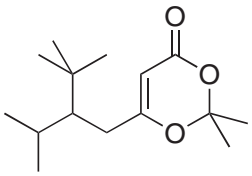
2H), 7.39–7.33 (m, 3H), 5.17 (s, 1H), 2.30–2.22 (m, 2H), 1.98–1.92 (m, 1H), 1.63 (s, 3H), 1.60 (s, 3H), 1.31–1.26 (m, 1H), 0.95 (d, J = 6.9 Hz, 3H), 0.88 (d, J = 7.0 Hz, 3H), 0.36 (s, 6H). ^{13}C NMR ($CDCl_3$) δ: 172.6, 161.2, 138.3, 133.7 (2), 129.0, 127.8 (2), 106.1, 93.5, 31.4, 29.8, 28.7, 25.2, 24.6, 22.0, 21.3, –2.2, –3.1. HR-MS (EI) *m/e* calcd. for $C_{18}H_{25}O_3Si$: 317.1573 [M – CH_3]; found: 317.1557.

6-(2-(Dimethyl(phenyl)silyl)-4-phenylbutyl)-2,2-dimethyl-4H-1,3-dioxin-4-one (14h)



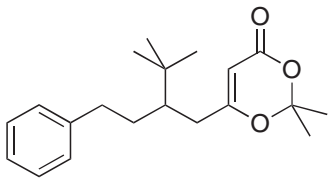
Following the previous procedure for the 1,6-addition of $(PhMe_2Si)_2CuLi$, [1,3]dioxin-4-one **13b** (129 mg, 0.499 mmol) gave 121 mg (61%) of **14h** as a colourless oil. R_f 0.26 (20% EtOAc–hexane). FT-IR (neat, cm^{-1}): 2999, 2950, 2859, 1729, 1629, 1389, 1272, 1204, 1112, 1014. ^{1}H NMR ($CDCl_3$) δ: 7.53–7.48 (m, 2H), 7.42–7.36 (m, 3H), 7.28–7.23 (m, 2H), 7.20–7.16 (m, 1H), 7.05–7.01 (m, 2H), 5.19 (s, 1H), 2.61–2.53 (m, 1H), 2.53–2.46 (m, 1H), 2.38 (dd, J = 14.9, 4.5 Hz, 1H), 2.16 (dd, J = 14.9, 9.6 Hz, 1H), 1.83–1.75 (m, 1H), 1.67–1.59 (m, 1H, hidden under two s), 1.65 (s, 3H), 1.64 (s, 3H), 1.32–1.25 (m, 1H), 0.363 (s, 3H), 0.360 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 171.9, 161.0, 141.8, 137.2, 133.8 (2), 129.3, 128.3 (2), 128.1 (2), 127.9 (2), 125.8, 106.2, 93.8, 35.2, 34.3, 31.9, 25.1, 24.7, 22.1, –4.1, –4.2. HR-MS (EI) *m/e* calcd. for $C_{24}H_{30}O_3Si$: 394.1964; found: 394.1953.

6-(2-Isopropyl-3,3-dimethylbutyl)-2,2-dimethyl[1,3]dioxin-4-one (14i)



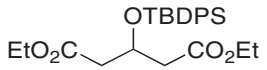
To a suspension of CuI (143 mg, 0.751 mmol) in THF (2.5 mL) cooled to –78 °C was added dropwise a solution of *t*-BuLi in pentane (1.4 mol/L, 1.1 µL, 1.5 mmol). The mixture was stirred at –78 °C for 30 min and then TMSCl (380 µL, 3.0 mmol) was added. After stirring for ca. 5 min, a solution of **13a** (101 mg, 0.515 mmol) in THF (1.5 mL, 1.0 mL rinse) was added. The mixture was stirred at –78 °C for 30 min, then at –20 °C for ca. 15 h. The reaction was stopped by adding satd. aq. $NaHCO_3$ (30 mL) at –20 °C, then warmed to rt, transferred to a separatory funnel, and extracted with Et_2O (3 × 30 mL). The organic layers were combined, dried (Na_2SO_4), filtered, concentrated under reduced pressure, and purified by chromatography on SiO_2 to afford 22 mg of **14i** (17%) as a colourless oil. R_f 0.53 (20% EtOAc–hexane). FT-IR (neat, cm^{-1}): 2960, 1733, 1630, 1389, 1271, 1205, 1016. ^{1}H NMR ($CDCl_3$) δ: 5.29 (s, 1H), 2.22 (d, J = 5.6 Hz, 2H), 2.11–2.06 (m, 1H), 1.69 (s, 6H), 1.50 (td, J = 5.7, 1.9 Hz, 1H), 0.93–0.92 (m, 12H), 0.87 (d, J = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 174.1, 161.5, 106.1, 93.2, 49.9, 34.9, 30.4, 28.6 (3), 27.7, 25.2, 25.0, 24.4, 18.3. HR-MS (EI) *m/e* calcd. for $C_{15}H_{27}O_3$: 255.1960 [M + H]; found: 255.1964.

6-(3,3-Dimethyl-2-phenethylbutyl)-2,2-dimethyl[1,3]dioxin-4-one (14j)



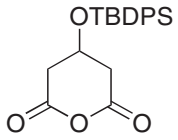
Following the previous procedure for the 1,6-addition of $(t\text{-Bu})_2CuLi$, [1,3]dioxin-4-one **13b** (130 mg, 0.503 mmol) gave 68 mg (43%) of **14j** as a colourless oil. R_f 0.33 (20% EtOAc–hexane). FT-IR (neat, cm^{-1}): 3026, 2960, 1732, 1630, 1454, 1389, 1272, 1204, 1014. ^{1}H NMR ($CDCl_3$) δ: 7.32–7.25 (m, 2H), 7.22–7.13 (m, 3H), 5.32 (s, 1H), 2.74–2.67 (m, 1H), 2.58–2.51 (m, 1H), 2.47 (dd, J = 15.0, 4.2 Hz, 1H), 2.07 (dd, J = 15.0, 7.5 Hz, 1H), 1.90–1.82 (m, 1H), 1.71 (s, 6H), 1.53–1.48 (m, 1H), 1.46–1.37 (m, 1H), 0.91 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 172.7, 161.2, 142.1, 128.4 (2), 128.2 (2), 125.9, 106.2, 93.8, 45.1, 35.9, 35.6, 33.9, 33.4, 27.5 (3), 25.3, 24.9. HR-MS (EI) *m/e* calcd. for $C_{17}H_{22}O_2$: 258.1620 [M – $(CH_3)_2CO$]; found: 258.1616.

3-(tert-Butyldiphenylsilanyloxy)pentanedioic acid diethyl ester (15, R^1 = OTBDPS)



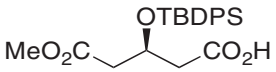
To a solution of imidazole (1.36 g, 20.0 mmol) in CH_2Cl_2 (20 mL) at rt was added TBDPSCl (2.47 mL, 9.50 mmol). After stirring for 10 min at rt, a solution of diethyl 3-hydroxyglutarate (2.04 g, 10.0 mmol) in CH_2Cl_2 (5, 2, and 1 mL rinses) was added to the white suspension. The reaction was stirred at rt for 16 h after which it was stopped by the addition of water (25 mL) and diluted with Et_2O (125 mL). The mixture was then transferred to a separatory funnel, extracted, the layers separated, and the organic layer was washed with brine (25 mL). The aqueous layers were combined and extracted with Et_2O (50 mL). The organic layers were combined, dried (Na_2SO_4), filtered, concentrated under reduced pressure, and purified by chromatography on SiO_2 to afford 4.05 g of **15** (96%) as a white solid; mp 44–46 °C. R_f 0.48 (20% EtOAc–hexane). FT-IR (KBr, cm^{-1}): 2966, 1740, 1378, 1268, 1227, 1145, 1107, 1026. ^{1}H NMR ($CDCl_3$) δ: 7.70–7.66 (m, 4H), 7.47–7.35 (m, 6H), 4.55 (qn, J = 6.0 Hz, 1H), 4.08–3.97 (m, 4H), 2.60 and 2.54 (AB of ABX, J = 15.2, 6.3 and 15.2, 5.9 Hz, 4H), 1.19 (t, J = 7.1 Hz, 6H), 1.03 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 170.8 (2), 135.8 (4), 133.5 (2), 129.7 (2), 127.6 (4), 67.2, 60.3 (2), 41.8 (2), 26.8 (3), 19.2, 14.1 (2). HR-MS (EI) *m/e* calcd. for $C_{24}H_{31}O_5Si$: 427.1941 [M – CH_3]; found: 427.1931.

3-[(*tert*-Butyldiphenylsilyl)oxy]pentanedioic anhydride (8b, R^1 = OTBDPS)



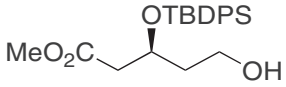
To a solution of diester **15** (8.85 g, 20.0 mmol) in MeOH (30 mL) was added NaOH pellets (2.00 g, 50.0 mmol) and the mixture was stirred vigorously at rt for 38 h. The resulting yellowish suspension was concentrated under reduced pressure and kept under high vacuum. The flaky solid was then crushed into smaller pieces, suspended in a mixture of benzene (40 mL) and Ac_2O (30 mL) and heated to reflux for 1.5 h. During this time, the colour changed to a deep purple. After cooling to rt, the reaction was stopped by the addition of brine (200 mL) and the mixture was transferred to a separatory funnel with $CHCl_3$ (400 mL). After extraction, the layers were separated and the organic layer was washed with satd. aq. $NaHCO_3$ (3 × 200 mL). The organic layer was then dried ($MgSO_4$), filtered, concentrated under reduced pressure, and purified by chromatography on SiO_2 [pretreated with hexane containing 1% Ac_2O, solvent gradient from pure hexane (+1% Ac_2O) to 20% EtOAc–hexane (+1% Ac_2O)] to afford 3.40 g of **8b** (46%) as a white solid. Recrystallization from a hot mixture of hexane–EtOAc (20:1) provided white needles; mp 107 to 108 °C (hexane–EtOAc 20:1). R_f 0.27 (20% EtOAc–hexane containing 1% Ac_2O). FT-IR (KBr, cm^{-1}): 2932, 1817, 1765, 1429, 1348, 1262, 1191, 1111, 1070, 1044. ^{1}H NMR ($CDCl_3$) δ: 7.71–7.56 (m, 4H), 7.55–7.35 (m, 6H), 4.31 (qn, *J* = 3.2 Hz, 1H), 2.86 (dd, *J* = 16.0, 3.6 Hz, 2H), 2.58 (dd, *J* = 16.0, 2.4 Hz, 2H), 1.05 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 165.3 (2), 135.8 (4), 132.4 (2), 130.6 (2), 128.3 (4), 62.9, 38.9 (2), 26.9 (3), 19.2. HR-MS (EI) *m/e* calcd. for $C_{17}H_{15}O_4Si$: 311.0740 [M – C_4H_9]; found: 311.0744.

(S)-((3-*tert*-Butyldiphenylsilyl)oxy)pentanedioic acid monomethyl ester (16)



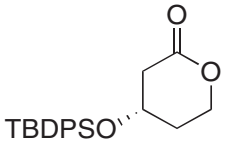
To a previously dried flask containing cyclic anhydride **8b** (1.09 g, 2.96 mmol) was added Et_2O (100 mL). The solution was cooled to –40 °C, $(DHQD)_2AQN$ (760 mg, 0.887 mmol) was added and the mixture was stirred for about 20 min. MeOH (1.20 mL, 29.6 mmol) was then added and the reaction was stirred at –40 °C for 70–72 h, stopped by the addition of 10% aq. HCl (90 mL) at –40 °C, and allowed to warm to rt. After transferring to a separatory funnel, the mixture was extracted, the layers were separated, and the aqueous layer was reextracted with EtOAc (2 × 100 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to provide 1.25 g of the crude acid **16** as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ: 7.70–7.65 (m, 4H), 7.48–7.35 (m, 6H), 4.51 (qn, *J* = 6.1 Hz, 1H), 3.56 (s, 3H), 2.69–2.53 (m, 4H), 1.03 (s, 9H). The ^{1}H NMR spectra was identical with the one reported in ref. 25. This material was combined with other crude desymmetrized material to provide 7.29 g of product. The catalyst was recovered by basifying the acidic aqueous layer with KOH pellets (a yellow precipitate formed). The aqueous layer was then extracted with Et_2O until the organic layer remained colourless. The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The recovered catalyst was purified by chromatography on SiO_2 with 5% MeOH–$CHCl_3$ containing 0.5% aq. NH_4OH before being reused.

(S)-3-((*tert*-Butyldiphenylsilyl)oxy)-5-hydroxypentanoic acid, methyl ester (17)



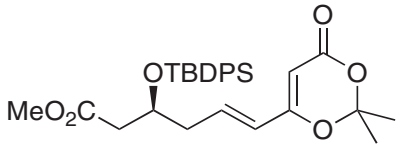
To a solution of crude acid **16** (7.29 g, 19.8 mmol) in THF (100 mL) at rt was added a solution of BH_3·DMS in THF (2.0 mol/L, 30 mL, 60 mmol) and the mixture was stirred for 15 h. The reaction was stopped by slowly adding satd. aq. $NaHCO_3$ (350 mL) and stirred vigorously for 20 min. The mixture was then transferred to a separatory funnel and extracted with Et_2O (3 × 300 mL). The organic layers were combined, dried (Na_2SO_4), filtered, concentrated under reduced pressure, and purified by chromatography on SiO_2 to afford 5.41 g of **17** (71%) as a colourless oil. ^{1}H NMR ($CDCl_3$) δ: 7.74–7.65 (m, 4H), 7.48–7.37 (m, 6H), 4.38 (qn, *J* = 5.9 Hz, 1H), 3.70–3.61 (m, 2H), 3.54 (s, 3H), 2.55 (d, *J* = 6.4 Hz, 2H), 1.86–1.80 (m, 1H), 1.78–1.72 (m, 1H), 1.62 (bt, *J* = 5.5 and 5.2 Hz, 1H), 1.06 (s, 9H). The ^{1}H NMR spectra was identical with the one reported in ref. 25.

(S)-3-((*tert*-Butyldiphenylsilyl)oxy)-5-hydroxypentanoic acid lactone (18)



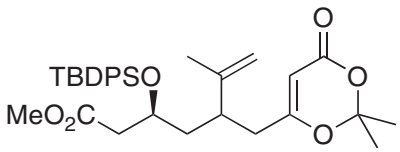
To a solution of crude acid **16** (115 mg, 0.287 mmol) in THF (2.0 mL) at rt was added a solution of BH_3·DMS in THF (2.0 mol/L, 430 μL, 0.86 mmol) and the mixture was stirred for 17 h. The reaction was stopped by slowly adding 10% HCl (3.5 mL) and stirred vigorously for 1 h. The mixture was then transferred to a separatory funnel and extracted with Et_2O (3 × 5 mL). The organic layers were combined, dried (Na_2SO_4), filtered, concentrated under reduced pressure, and purified by chromatography on SiO_2 to afford 38 mg of **18** (38%) as a colourless oil. $[\alpha]_D$ –12.3 (*c* 7.55, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 7.67–7.62 (m, 4H), 7.50–7.37 (m, 6H), 4.63 (ddd, *J* = 11.3, 8.6, 4.5 Hz, 1H), 4.28–4.18 (m, 2H), 2.59 (d, *J* = 4.9 Hz, 2H), 1.94–1.75 (m, 2H), 1.08 (s, 9H). The ^{1}H NMR spectra was identical with the one reported in ref. 25. The enantiomeric excess was determined by chiral HPLC (Chiralcel OD) using *i*-PrOH–hexane (1.0%) at a flow rate of 1.0 mL/min (R_t minor = 22.8 min, R_t major = 24.5 min).

3-(tert-Butyldiphenylsilanyloxy)-6-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)hex-5-enoic acid methyl ester (19)



To a stirred solution of alcohol **17** (5.41 g, 14.0 mmol) in a mixture of CH_2Cl_2 (63 mL) and CH_3CN (7 mL) at rt was added NMO (2.46 g, 21.0 mmol) and 4 Å molecular sieves (7.0 g). TPAP (246 mg, 0.700 mmol) was added in three portions over a period of 20 min and the resulting mixture was stirred for 30 min at rt. The dark black mixture was then filtered over Celite with CH_2Cl_2 and the filtrate was concentrated under reduced pressure. The resulting oil was rapidly purified by chromatography on SiO_2 with EtOAc–hexanes (20%) to afford 4.23 g of the corresponding aldehyde (79%) as a colourless oil. A solution of phosphonate **12** (4.28 g, 15.4 mmol) in THF (100 mL) cooled to 0 °C was treated with 95% NaH (317 mg, 13.2 mmol). The cold bath was removed and the mixture was stirred at rt for 20 min. After cooling to –78 °C, a solution of the aldehyde (4.23 g, 11.0 mmol) in THF (5 mL, 5 mL rinse) was added, the bath was removed, and the reaction was allowed to gradually warm to rt and was stirred at that temperature for 1 h. One drop of satd. aq. $NaHCO_3$ was added and the mixture was stirred for 5 min (to complete the deprotonation step). After adding additional satd. aq. $NaHCO_3$ (300 mL), the mixture was transferred to a separatory funnel and extracted with Et_2O (3 × 300 mL). The organic layers were combined, dried (Na_2SO_4), filtered, concentrated under reduced pressure, and purified by chromatography on SiO_2 to afford 3.50 g of **19** (49% from alcohol) as a colourless oil. $[\alpha]_D$ 58.0 (*c* 0.21, $CHCl_3$). R_f 0.33 (30% EtOAc–hexane). FT-IR (neat, cm^{-1}): 2932, 2858, 1728, 1655, 1592, 1428, 1390, 1274, 1206, 1111, 1020. ^1H NMR ($CDCl_3$) δ: 7.76–7.60 (m, 4H), 7.52–7.33 (m, 6H), 6.44 (dt, *J* = 15.5, 7.5 Hz, 1H), 5.78 (d, *J* = 15.6 Hz, 1H), 5.18 (s, 1H), 4.29 (qn, *J* = 6.0 Hz, 1H), 3.57 (s, 3H), 2.54 (A of ABX, J_{AB} = 15.2, J_{AX} = 6.4 Hz, 1H), 2.48–2.36 (m, 3H), 1.67 (s, 6H), 1.04 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 171.3, 162.7, 161.9, 137.4, 135.81 (2), 135.78 (2), 133.4, 133.3, 129.8 (2), 127.6 (4), 125.2, 106.2, 93.8, 69.5, 51.5, 41.7, 40.2, 26.8 (3), 24.9 (2), 19.2. HR-MS (EI) *m/e* calcd. for $C_{25}H_{27}O_6Si$: 451.1577 [M – C_4H_9]; found: 451.1575.

(3S)-Methyl 3-(tert-butyldiphenylsilyloxy)-5-((2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)methyl)-6-methylhept-6-enoate (20)

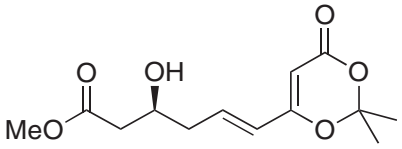


A solution of *t*-BuLi in pentane (1.2 mol/L, 33 mL, 40 mmol) cooled to –78 °C was diluted with THF (33 mL) and 2-bromopropene (1.78 mL, 20.0 mmol) was added dropwise. The mixture was stirred at –78 °C for 30 min, then at 0 °C for 30–45 min. To a suspension of CuI (1.10 g, 5.78 mmol) in THF (20 mL) cooled to –78 °C was added the solution of 2-lithiopropene (39 mL, 12 mmol). The dark black mixture was stirred at –78 °C for 30 min and then TMSCl (3.0 mL, 24 mmol) was added. After stirring for ca. 5 min, a solution of **19** (981 mg, 1.93 mmol) in THF (6.0 mL, 2 × 2.0 mL rinse) was added. The mixture was stirred at –78 °C for 30 min, then at –20 °C for ca. 16 h. The reaction was stopped by adding satd. aq. $NaHCO_3$ (100 mL) at –20 °C, then warmed to rt, transferred to a separatory funnel, and extracted with Et_2O (4 × 100 mL). The organic layers were combined, dried (Na_2SO_4), filtered, concentrated under reduced pressure, and purified by chromatography on SiO_2 to afford 999 mg of **20** (94%) as a colourless oil. R_f 0.38 (30% EtOAc–hexane). FT-IR (neat, cm^{-1}): 2933, 2858, 1732, 1633, 1428, 1390, 1272, 1205, 1111, 1015. ^1H NMR ($CDCl_3$) δ: 7.75–7.62 (m, 4H), 7.51–7.34 (m, 6H), 5.08 and 5.05 (s, 1H), 4.66–4.62 (m, 1H), 4.54 and 4.41 (br s, 1H), 4.14–4.03 (m, 1H), 3.59 and 3.54 (s, 3H), 2.65–2.26 (m, 3H), 2.11–1.97 (m, 2H), 1.67–1.47 (m, 2H), 1.65 and 1.64 (s, 3H), 1.60 and 1.58 (s, 3H), 1.49 and 1.21 (s, 3H), 1.04 and 1.02 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 171.6 [171.3], 170.0 [169.8], 161.16 [161.09], 144.4 [144.3], 135.9 (8), 133.9 [133.7], 133.6 [133.5], 129.8 (4), 127.6 (8), 113.9 [113.3], 106.3 (2), 94.2 [94.1], 68.6 [68.4], 51.41 [51.36], 42.6 [41.2], 40.8 [40.7], 40.8 [40.4], 37.8 [37.4], 26.9 (3) [26.8 (3)], 25.40 [25.36], 25.0 [24.9], 19.3 [19.2], 17.6 [17.3]. HR-MS (ESI–POS) *m/e* calcd. for $C_{32}H_{42}O_6NaSi$: 573.2648 [M + Na]; found: 573.2642.

Rhodium-catalyzed asymmetric 1,6-addition of potassium isopropenyl organotrifluoroborate to 19 in the presence of Carreira's diene

To a dry sealed tube was added the diene ligand (3.6 mg, 0.014 mmol), $Rh(acac)(eth)_2$ (3 mg, 0.01 mmol), and EtOH (0.5 mL) and the mixture was stirred at rt for 15 min. A solution of **19** (117 mg, 0.230 mmol) in EtOH (0.75 mL, 0.75 mL rinse) was then added, followed by potassium isopropenyl organotrifluoroborate (37) (102 mg, 0.689 mmol). The reaction mixture was stirred at 82 °C for 24 h, cooled to rt, and treated with satd. aq. $NaHCO_3$ (15 mL). The mixture was transferred to a separatory funnel and extracted with Et_2O (3 × 15 mL). The organic layers were combined, dried (Na_2SO_4), filtered, concentrated under reduced pressure, and purified by chromatography on SiO_2 to afford 27.2 mg (21%) of **20** and 47.5 mg of **21** (38%).

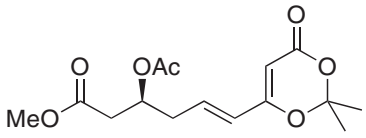
6-(2,2-Dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-3-hydroxyhex-5-enoic acid methyl ester (23)



To a solution of **19** (234 mg, 0.460 mmol) in THF (5.5 mL) in a plastic tube was added HF·pyridine (600 µL, 23 mmol) and the mixture was stirred vigorously at rt for 3 days. The reaction was stopped by dropwise addition to

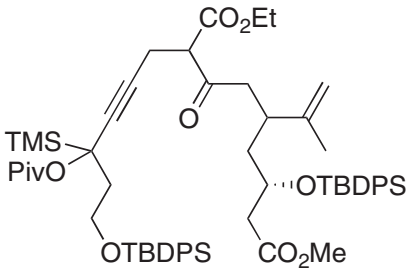
satd. aq. $NaHCO_3$ (75 mL). After adding solid $NaHCO_3$ to the aqueous solution, the mixture was transferred to a separatory funnel and extracted with Et_2O (4 × 30 mL). The organic layers were combined, dried (Na_2SO_4), filtered, concentrated under reduced pressure, and purified by chromatography on SiO_2 to afford 34 mg (15%) of starting material **19** and 101 mg of **23** (81%) as a colourless oil. $[\alpha]_D$ 5.9 (*c* 2.38, CH_2Cl_2). R_f 0.17 (50% EtOAc–hexane). FT-IR (neat, cm^{-1}): 3454, 2999, 2952, 1728, 1651, 1592, 1392, 1276, 1204, 1067, 1020. ^1H NMR ($CDCl_3$) δ: 6.59 (dt, *J* = 15.6, 7.6 Hz, 1H), 6.01 (d, *J* = 15.6 Hz, 1H), 5.28 (s, 1H), 4.23–4.13 (m, 1H), 3.74 (s, 3H), 3.10 (d, *J* = 3.6 Hz, 1H), 2.54 (A of ABX, J_{AB} = 16.7, J_{AX} = 3.4 Hz, 1H), 2.51–2.40 (m, 3H), 1.72 (s, 6H). ^{13}C NMR ($CDCl_3$) δ: 172.8, 162.7, 161.9, 137.2, 125.1, 106.4, 93.9, 66.9, 51.8, 40.6, 39.4, 24.9 (2). HR-MS (EI) *m/e* calcd. for $C_{13}H_{16}O_5$: 252.0998 [M – H_2O]; found: 252.0999.

(S,E)-Methyl 3-acetoxy-6-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)hex-5-enoate (24)



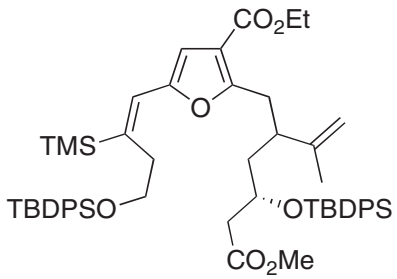
To a solution of **23** (51.2 mg, 0.189 mmol) in pyridine (1.56 mL, 19.3 mmol) was added Ac_2O (910 μL, 9.6 mmol) and the mixture was stirred at rt for 6.5 h. After concentrating under reduced pressure, the resulting mixture was purified by chromatography on SiO_2 to afford 56.4 mg (95%) of **24** as a colourless oil. $[\alpha]_D$ 11.9 (*c* 1.96, CH_2Cl_2). R_f 0.37 (50% EtOAc–hexane). FT-IR (neat, cm^{-1}): 2999, 2954, 1732, 1656, 1594, 1438, 1376, 1244, 1020. ^1H NMR ($CDCl_3$) δ: 6.45 (dt, *J* = 15.5, 7.5 Hz, 1H), 5.98 (dt, *J* = 15.6, 1.3 Hz, 1H), 5.36–5.27 (m, 1H), 5.28 (s, 1H), 3.69 (s, 3H), 2.64 (A of ABX, J_{AB} = 15.8, J_{AX} = 7.3 Hz, 1H), 2.59–2.52 (m, 2H), 2.04 (s, 3H), 1.71 (s, 6H). ^{13}C NMR ($CDCl_3$) δ: 170.3, 170.1, 162.5, 161.9, 135.6, 125.8, 106.5, 94.3, 68.8, 51.9, 38.2, 37.0, 25.0, 24.9, 20.9. HR-MS (EI) *m/e* calcd. for $C_{13}H_{16}O_5$: 252.0998 [M – CH_3CO_2H]; found: 252.0998.

(7S)-Dimethyl 2-(4-(benzoyloxy)-6-(tert-butyldiphenylsilyloxy)-4-(trimethylsilyl)hex-2-ynyl)-7-(tert-butyldiphenylsilyloxy)-3-oxo-5-(prop-1-en-2-yl)nonanedioate (22)



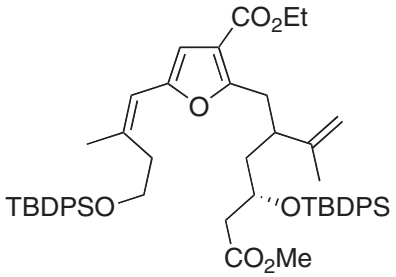
To a solution of [1,3]dioxin-4-one **20** (999 mg, 1.81 mmol) in toluene (20 mL) was added EtOH (530 μL, 9.1 mmol). The solution was heated at reflux for ca. 1.5 h until TLC analysis showed complete consumption of the starting material. The solution was then concentrated under reduced pressure and kept under high vacuum. The crude β-keto ester was redissolved in THF (20 mL) and cooled to 0 °C. The septum was temporarily removed to allow the quick introduction of 98% NaH (52 mg, 2.2 mmol) and the mixture was stirred at 0 °C for ca. 20 min. Afterwards, a solution of iodide **4** [prepared from the corresponding chloride (1.86 g, 3.30 mmol) and NaI (679 mg, 4.53 mmol) in refluxing acetone (15 mL)] in THF (6.0 mL, 6.0 mL rinse) was added and the reaction was gradually warmed to rt, while maintaining the flask in the cold bath. After stirring overnight, the reaction mixture was concentrated under reduced pressure and filtered over a pad of SiO_2 with EtOAc–hexane (20%). This material was then purified by chromatography on SiO_2 to afford 1.50 g of **22** (77%, two steps) as a colourless oil. Since this α-propargyl β-keto ester exists as a mixture of up to four different diastereomers, it was not characterized.

Ethyl 5-((E)-4-(tert-butyldiphenylsilyloxy)-2-(trimethylsilyl)but-1-enyl)-2-((4S)-4-(tert-butyldiphenylsilyloxy)-6-methoxy-6-oxo-2-(prop-1-en-2-yl)hexyl)furan-3-carboxylate (25)



A solution of α-propargyl β-keto ester **22** (76.0 mg, 0.0713 mmol) in a mixture of MeCN (1.0 mL) and H_2O (100 μL) was subjected to three freeze–pump–thaw cycles. Afterwards, $NaOAc{\cdot}3H_2O$ (10.7 mg, 0.0784 mmol) and $Pd(PPh_3)_4$ (12 mg, 0.010 mmol) were added and the mixture was stirred at 87 °C for 2 h. After cooling to rt, the crude mixture was filtered over a pad of SiO_2 with 20% EtOAc–hexane and concentrated under reduced pressure. This material was then purified by chromatography on SiO_2 to afford 33.2 mg of **25** (49%, 6.8:1 mixture of (*E*)–(*Z*)-isomers) as a colourless oil. R_f 0.28 (10% EtOAc–hexane). FT-IR (neat, cm^{-1}): 3071, 2931, 2857, 1741, 1716, 1590, 1428, 1388, 1230, 1111. ^1H NMR ($CDCl_3$) δ: 7.75–7.59 (m, 8H), 7.46–7.31 (m, 12H), 6.75 and 6.71 (s, 1H), 6.45 and 6.42 (s, 1H), 4.58 and 4.46 (brs, 1H), 4.46 and 4.41 (brs, 1H), 4.32–4.20 (m, 2H), 4.18–4.03 (m, 1H), 3.71–3.61 (m, 2H), 3.55 and 3.49 (s, 3H), 2.94–2.72 (m, 4H), 2.61–2.33 (m, 2H), 1.75–1.48 (m, 3H), 1.57 and 1.21 (s, 3H), 1.33 and 1.30 (t, *J* = 7.2 Hz, 3H), 1.063 and 1.056 (s, 9H), 1.00 (s, 9H), –0.003 and –0.004 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 172.0 [171.5], 163.8 [163.7], 160.0 [159.7], 151.1 [151.0], 145.7 [144.9], 140.04 [139.99], 135.94, 135.88, 135.8, 135.6, 135.2, 134.8, 134.2, 133.8, 133.62, 133.58, 129.5, 127.7, 127.6, 127.5, 127.4, 126.6 [126.4], 115.6, 112.85 [112.80], 110.0, 69.0 [68.9], 62.5, 60.1, 51.33 [51.27], 43.2, 43.0, 42.5 41.0, 40.1, 39.6, 34.7, 32.4 [32.3], 26.9, 26.8, 26.5, 19.2, 19.1, 19.0, 18.0, 16.9, 14.33 [14.28], 0.14, –1.8.

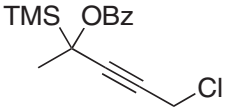
Ethyl 5-((Z)-4-(*tert*-butyldiphenylsilyloxy)-2-methylbut-1-enyl)-2-((4S)-4-(*tert*-butyldiphenylsilyloxy)-6-methoxy-6-oxo-2-(prop-1-en-2-yl)hexyl)furan-3-carboxylate (26)



To a solution of I_2 (105 mg, 0.414 mmol) in THF (0.5 mL) was added pyridine (50 μL, 0.62 mmol) followed by $AgClO_4$ (85 mg, 0.41 mmol). The mixture was stirred at rt for 15 min, then a solution of furan **25** (97.4 mg, 0.103 mmol) in THF (1.0 mL, 2 × 0.5 mL rinse) was added. After stirring at rt for 19 h, the crude reaction mixture was filtered over a pad of Celite with Et_2O (25 mL). The solution was transferred to a separatory funnel and extracted with a mixture of 10% aq. $Na_2S_2O_3$ (10 mL) and satd. aq. $NaHCO_3$ (10 mL). The layers were separated and the aqueous layer was extracted again with Et_2O (2 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford 113 mg of crude vinyl iodide. The iodide was redissolved in THF (1.0 mL) and subjected to two freeze–pump–thaw cycles. The degassed solution was then cooled to 0 °C and $Pd(PPh_3)_4$ (6.0 mg, 0.0052 mmol) was added, followed by a 2.0 mol/L solution of Me_2Zn in toluene (160 μL, 0.32 mmol). The cold bath was removed and the reaction was stirred at rt for ca. 17 h, stopped by adding H_2O (5 mL), and transferred to a separatory funnel. The aqueous layer was extracted with Et_2O (3 × 5 mL), the organic layers were combined, washed with brine (10 mL), dried (Na_2SO_4), filtered, concentrated under reduced pressure, and purified by chromatography on SiO_2 to afford 57.5 mg of **26** (63%, 4.7:1 mixture of (*Z*)–(*E*)-isomers) as a colourless oil. R_f 0.28 (10% EtOAc–hexane). FT-IR (neat, cm^{-1}): 3071, 2931, 2857, 1740, 1715, 1600, 1428, 1385, 1227, 1111. ^1H NMR ($CDCl_3$) δ: 7.74–7.61 (m, 8H), 7.45–7.33 (m, 12H), 6.47 and 6.45 (s, 1H), 6.02 and 6.00 (s, 1H), 4.54 and 4.43 (brs, 1H), 4.43 and 4.37 (brs, 1H), 4.31–4.20 (m, 2H), 4.16–4.04 (m, 1H), 3.87–3.79 (m, 2H), 3.55 and 3.50 (s, 3H), 2.98–2.77 (m, 2H), 2.77–2.59 (m, 2H), 2.55–2.35 (m, 2H), 1.86 and 1.85 (s, 3H), 1.71–1.50 (m, 3H), 1.56 and 1.09 (s, 3H), 1.32 and 1.30 (t, J = 7.2 Hz, 3H), 1.041 and 1.038 (s, 9H), 1.01 and 1.00 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 172.0 [171.5], 163.93 [163.90], 159.2 [158.9], 151.05 [150.97], 145.8 [145.0], 137.43 [137.38], 135.91, 135.88, 135.81, 135.6, 135.2, 134.8, 134.2, 133.9, 133.7, 133.6, 133.5, 129.5, 127.7, 127.6, 127.5, 127.4, 115.37 [115.24], 115.15 [115.08], 112.7, 107.7 [107.6], 69.0 [68.9], 62.3, 60.0, 51.31 [51.25], 43.3, 43.0, 42.4, 41.0, 40.3, 39.7, 36.6, 32.3 [32.2], 26.9, 26.8, 26.5, 25.2, 19.2, 19.1, 18.4, 18.0, 17.0, 14.4 [14.3].

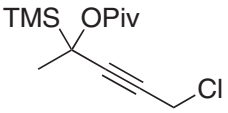
5-Chloro-2-(trimethylsilyl)pent-3-yn-2-yl benzoate (27a)

A solution of *n*-BuLi (1.6 mol/L, 4.4 mL, 7.0 mmol) in Et_2O (40 mL) was cooled to –78 °C and treated with propargyl chloride (540 μL, 7.5 mmol). After stirring at



–78 °C for 20 min, acetyltrimethylsilane (720 μL, 5.0 mmol) was added dropwise. The mixture was stirred at –78 °C for 30 min and benzoyl chloride (870 μL, 7.8 mmol) was added. The reaction was allowed to gradually warm up to rt, while maintained in the cold bath and stirred overnight. The reaction was stopped by adding H_2O (50 mL) and the mixture was transferred to a separatory funnel. After extraction, the organic layer was separated and the aqueous layer was extracted once more with Et_2O (50 mL). The organic layers were combined, dried (Na_2SO_4), filtered, concentrated under reduced pressure, and purified by chromatography on SiO_2 to afford 1.2 g of **27a** (80%) as a yellow-orange oil. For the full spectral characterization of this compound, see ref. 11.

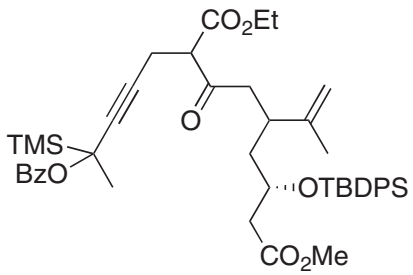
5-Chloro-2-(trimethylsilyl)pent-3-yn-2-yl pivalate (27b)



A solution of *n*-BuLi (1.6 mol/L, 8.8 mL, 14 mmol) in Et_2O (80 mL) cooled to –78 °C was treated with propargyl chloride (1.09 mL, 15.0 mmol). After stirring at –78 °C for 20 min, acetyltrimethylsilane (1.43 mL, 9.98 mmol) was added dropwise. The mixture was stirred at –78 °C for 30 min and trimethylacetyl chloride (1.85 mL, 15.0 mmol) was added. The reaction mixture was allowed to gradually warm up to rt, while maintained in the cold bath and stirred overnight. The reaction was stopped by adding H_2O (100 mL) and transferred to a separatory funnel. After extraction, the organic layer was separated and the aqueous layer was extracted once more with Et_2O (100 mL). The organic layers were combined, dried (Na_2SO_4), filtered, concentrated under reduced pressure, and purified by chromatography on SiO_2 to afford 1.59 g of **27b** (58%) as a yellow-orange oil. R_f 0.22 (5% EtOAc–hexane). FT-IR (neat, cm^{-1}): 2970, 1737, 1479, 1367, 1262, 1144, 1060. ^1H NMR ($CDCl_3$) δ: 4.24 (s, 2H), 1.62 (s, 3H), 1.19 (s, 9H), 0.19 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 177.1, 87.6, 82.4, 67.2, 39.2, 31.3, 27.1 (3), 21.1, –4.2. HR-MS (EI) *m/e* calcd. for $C_{13}H_{23}O_2SiCl$: 274.1156; found: 274.1154.

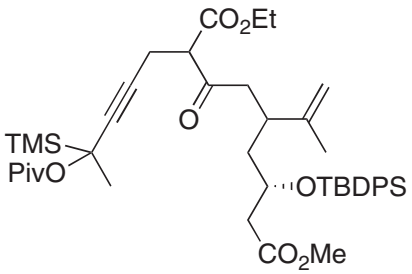
(7S)-1-Ethyl 9-methyl 2-(4-(benzoyloxy)-4-(trimethylsilyl)pent-2-ynyl)-7-(*tert*-butyldiphenylsilyloxy)-3-oxo-5-(prop-1-en-2-yl)nonanedioate (28a)

Following the same procedure as for the preparation of α-propargyl β-keto ester **22**, the alkylation of β-keto ester **21**



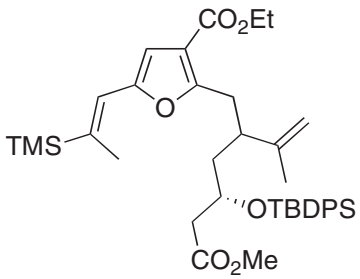
[prepared from [1,3]dioxin-4-one **20** (422 mg, 0.765 mmol)] with the iodide derived from **27a** (406 mg, 1.38 mmol) gave 580 mg (95%, two steps) of **28a** as a colourless oil. Since this α-propargyl β-keto ester exists as a mixture of up to four different diastereomers, it was not characterized.

(7S)-1-Ethyl 9-methyl 7-(tert-butyldiphenylsilyloxy)-3-oxo-2-(4-(pivaloyloxy)-4-(trimethylsilyl)pent-2-ynyl)-5-(prop-1-en-2-yl)nonanedioate (28b)



Following the same procedure as for the preparation of α-propargyl β-keto ester **22**, the alkylation of β-keto ester **21** [prepared from [1,3]dioxin-4-one **20** (387 mg, 0.703 mmol)] with the iodide derived from **27b** (349 mg, 1.27 mmol) gave 350 mg (64%, two steps) of **28b** as a colourless oil. Since this α-propargyl β-keto ester exists as a mixture of up to four different diastereomers, it was not characterized.

Ethyl 2-((4S)-4-(tert-butyldiphenylsilyloxy)-6-methoxy-6-oxo-2-(prop-1-en-2-yl)hexyl)-5-((E)-2-(trimethylsilyl)prop-1-enyl)furan-3-carboxylate (29)



In a microwave tube, a solution of **28b** (84.3 mg, 0.108 mmol) in THF (500 μL) was subjected to three freeze–pump–thaw cycles. To the degassed solution was then added allylpalladium chloride dimer (3.0 mg, 0.0082 mmol) and dppf (9.0 mg, 0.016 mmol) and the mixture was stirred vigorously at rt for ca. 5 min (during this time a voluminous precipitate formed). The microwave tube was then heated with stirring in the microwave reactor for 20 min (100 °C, 300 W) and then cooled to rt. The crude, wine-red reaction mixture was filtered over a pad of SiO_2 with 20% EtOAc–hexane. This material was then purified by chromatography on SiO_2 to afford 43.5 mg of **29** (59%) as a colourless oil. The diastereomeric mixture of furans was dissolved in THF (500 μL) and $(PhSe)_2$ (1.0 mg, 0.0032 mmol) was added. The solution was heated at 70 °C for 16 h in a sealed tube, then cooled to rt, and concentrated under reduced pressure. This material was purified by chromatography on SiO_2 to afford 36.8 mg of pure ***E*-29** (50% from **28b**) as a colourless oil. R_f 0.55 (20% EtOAc–hexane). FT-IR (neat, cm^{-1}): 3072, 2954, 2857, 1742, 1715, 1597, 1428, 1229, 1111. ^1H NMR ($CDCl_3$) δ: 7.73–7.60 (m, 4H), 7.45–7.31 (m, 6H), 6.55 and 6.54 (s, 1H), 6.44 and 6.37 (apparent q, J = 1.5 and 1.6 Hz, 1H), 4.59 and 4.48 (bs, 1H), 4.46 and 4.43 (bs, 1H), 4.31–4.19 (m, 2H), 4.18–4.04 (m, 1H), 3.56 and 3.50 (s, 3H), 3.00–2.75 (m, 2H), 2.63–2.36 (m, 2H), 2.01 and 2.00 (d, J = 1.6 and 1.6 Hz, 3H), 1.75–1.49 (m, 3H), 1.56 and 1.16 (s, 3H), 1.34 and 1.31 (t, J = 7.1 and 7.1 Hz, 3H), 1.00 (s, 9H), 0.14 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 171.9 [171.5], 163.9 [163.8], 159.4 [159.1], 151.83 [151.79], 145.7 [145.1], 140.2 [140.0], 135.92 (2) [135.88 (2)], 135.85 (2) [135.77 (2)], 134.2 [133.8], 133.6 (2), 129.6 (3), 129.5, 127.5 (6), 127.4 (2), 124.3 [124.2], 115.5 (2), 112.8 [112.6], 109.74 [109.71], 69.0 [68.8], 60.0 (2), 51.3 [51.2], 43.0 [42.9], 42.5 [41.0], 40.1 [39.6], 32.3 (2), 26.9 (3) [26.8 (3)], 19.2 (2), 18.0 [17.1], 17.1 (2), 14.34 [14.28], –2.3 (6). HR-MS (ESI–POS) *m/e* calcd. for $C_{39}H_{54}O_6NaSi_2$: 697.3357 [M + Na]; found: 697.3303.

Acknowledgements

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