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Chiral enolates for highly stereoselective aldol reactions—Scope and limitations

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ABSTRACT

Enantioselective approaches to the formation of α,β-disubstituted ketones through aldol reactions are compared. A one-pot ACA/aldol domino process is lower yielding than alternative procedures involving enantiomerically pure β-substituted silyl enol ethers. The use of chiral acetals derived from hydrobenzoin provides access to *syn* and *anti* diols in moderate to good yields and high diastereoselectivities. A novel synthesis of functionalized β,γ-unsaturated acetals is also described.

1. Introduction

In the last decade, extensive studies have contributed to the development of highly enantioselective copper(I)-catalyzed asymmetric conjugate addition (ACA) reactions of diorganozinc reagents using phosphoramidite ligands. These have been recently reviewed.[1] However, beyond the possibility of adding sp^3 or sp^2 carbon nucleophiles with high enantioselectivities, these developments have also opened the way for use of the chiral enolates resulting from these reactions. Indeed, the chiral Zn-enolate products are interesting reactive species in their own right, which can be used for further functionalization through tandem reactions rather than simple protonation. Consequently, a number of disperate studies on the formation of products containing several stereogenic centers with high enantio- and diastereoselectivities have appeared from such proceses over the past few years.[2] These have been summarized by Ma and Guo.[3] Despite this situation very few systematic comparisons of the scope and limitations of such enolate trapping protocols have appeared, which lead us to disclose the results here.

2. Results and discussion

2.1. Developments in the ACA/aldol domino reaction

In the late 1990s it was found that zinc enolates resulting from ACA reactions could be used for subsequent aldol reactions in variable, often low, yields.[4,5] Among the most interesting synthetic use for chiral zinc enolates, we were attracted by an elegant conjugate addition/aldol domino[6] and the preparation of chiral silyl enol ethers by Alexakis and Knopff.[7] This study on the use of chiral acetals for the preparation of *trans/syn* and *trans/anti* aldol compounds showed promising preliminary results. However, this study was limited to the use of $ZnEt_2$ as a nucleophile, and only two chiral acetals and to the best of our knowledge no further details have appeared. We have extended this work and defined its scope and limitations with respect to other nucleophiles, and functionalized chiral acetals.

Most chiral acetals required for this scope study were prepared in good yields from commercially available aldehydes (Table 1). Additionally, we describe here an unprecedented synthetic pathway to the preparation of chiral acetals of β,γ-unsaturated aldehydes. (Scheme 2, see later). Initial investigations indicated difficulties in extending the literature precedent[6] (Table 2, entry 1 vs 2). Although benzaldehyde reacted under TMSOTf catalysis, simple alkyl acetal systems proved less reactive and failed to react under conditions similar to those used by Alexakis et al.[6] This could be due to lower reactivity in the alkyl acetals used, but also due to the lower reactivity of $ZnMe_2$ compared to $ZnEt_2$. Therefore alternative conditions were tested, and strongly Lewis acidic $TiCl_4$ was found to be an effective activator of all acetals used, giving the desired products with excellent diastereomeric ratios (entries 4–10).

The moderate yields obtained for these domino reactions were quite limiting and this convinced us to investigate the use of silyl enol ethers in a Mukaiyama-type reaction[9] instead of Zn enolates as the nucleophiles. A range of aggregated species is likely to be present in domino aldol reaction and that this might be a cause of

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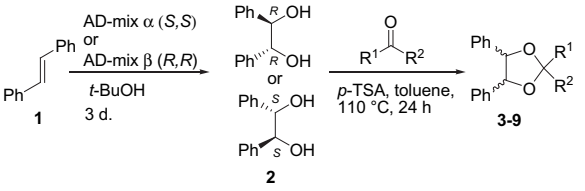
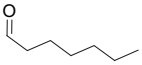
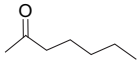
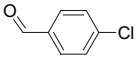
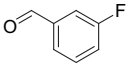
Table 1
Preparation of chiral acetals



Entry	Diol config.	Aldehyde	Product	Yield[a]
1	*S*,*S*[b]		**3**	81%
2	*R*,*R*[c]		**4**	93%
3	*R*,*R*		**5**	65%
4	*R*,*R*		**6**	56%
5	*R*,*R*		**7**	85%
6	*R*,*R*		**8**	80%
7	*R*,*R*		**9**	61%

[a] Isolated yield after column chromatography.
[b] (*S*,*S*)-Diol **2** prepared from stilbene diol in 99% ee.[8]
[c] (*R*,*R*)-Diol was purchased from Sigma–Aldrich.

the limited yields. Therefore isolating a TMS enol ether after the ACA reaction should result in an improvement of the efficiency of the aldol reaction.

2.2. Developments of a Mukaiyama asymmetric aldol reaction using chiral acetals

Examples of Mukaiyama aldol reactions where an existing chiral center β to the carbonyl is used to also induce a *trans* stereochemistry are not common (Scheme 1). Our concept is to first install the stereochemistry on carbon *C*1 via a highly stereoselective 1,4-conjugate addition and trap the enolate with TMSOTf in order to isolate the chiral TMS enol ether.[7] These compounds were prepared in good yields using the known methodology. They are stable and can easily be stored for weeks in a refrigerator (Scheme 1).

This enol ether will then undergo a Mukaiyama reaction, which would lead to the introduction of the desired stereochemistry at centers *C*1, *C*2, and *C*3 with complete control.[6,10] It was assumed that the methyl and alkyl chain at centers *C*1 and *C*2 would be preferentially in the thermodynamically more stable *trans* configuration, while the configuration at center *C*3 should not depend on the configuration of center *C*2, but should be fully controlled by the acetal.[6,11] This would give access to both *trans*/*threo* and *trans*/*erythro* diastereomers.

A study was performed using the same substrates as for the domino reaction; the results are reported in Table 3. An appreciable enhancement in the yields can be noticed when compared with the domino reaction (Table 2). However, $TiCl_4$ is still needed for these transformations. Other Lewis acids were inefficient when used in this reaction (entries 2,3).

The reaction did not work with ketals (entry 4). Both cyclopropyl and halogenated aryl acetals gave satisfying results (entries 7–10). The products were in most cases isolated as single diastereomers. The use of the (*S*,*S*)-enantiomer of **6** also produced a single diastereomer, therefore confirming that the *threo*/*erythro* selectivity of the aldol reaction can be totally controlled by the configuration of the acetal moiety.

Indeed, adduct **12** was crystalline and an X-ray structure (Fig. 1) confirmed the absolute configuration of the compound. It corresponded to the expected results from proposed transition states and from comparison with literature results.[6,11]

We then sought to investigate the possibility of constructing and using more complex and functionalized acetals. Therefore a new route toward difunctional complex acetals has been developed (Scheme 2). Satisfyingly, the desymmetrization[12] of malonaldehyde dimethyl acetal was very efficient and **24** was isolated in 66% yield. We were pleased to see that, whereas a standard Wittig–Horner reaction on aldehyde **26** afforded (*E*)-**27** as a 94:6 mixture, the Still–Gennari modification[13] allowed us to completely reverse the selectivity and afforded (*Z*)-**27** as the only geometrical isomer. Finally, acetal **10** reacted cleanly with TMS enol ether **21** in good, but not perfect, selectivity (Table 3, entry 12, *d.r.* 7:1).

2.3. Removal of the chiral auxiliary

As the results of Table 3 show, even complex acetals can lead to good to excellent diastereocontrol of aldol reactions from chiral enolates, providing either *trans*/*threo* or *trans*/*erythro* aldol adducts as required. However, the main limitation of this approach resides in the fact that the aldol product is not obtained directly, but that a further step is required for the removal of the chiral auxiliary. In 2001, Alexakis[6] used a multistep procedure for the removal of the auxiliary: treatment with acidic Amberlyst-15 removed the TMS group and the auxiliary was then removed in a further two steps, via PDC oxidations and treatment with Zn, and acetic acid.

Alternatively we report here that the auxiliary can be simply removed in a more user-friendly single step using cerium(IV) ammonium nitrate (CAN).[14] The results of this reaction on some substrates are presented in Table 4. The alcohols can be attained in good yields using this methodology.

3. Conclusion

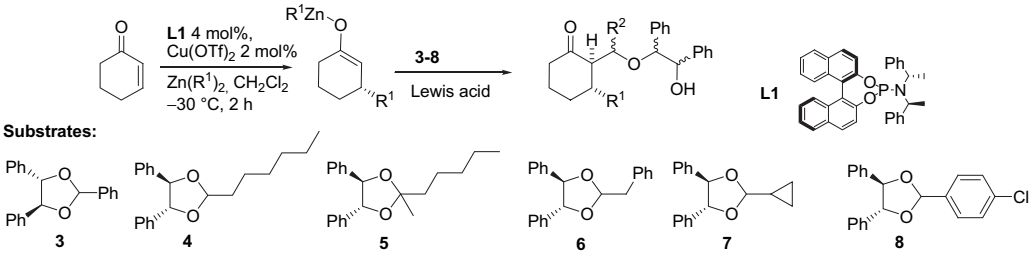
In conclusion, the scope and limitations of two different methods to produce rapidly and with high stereoselectivity complex compounds containing three chiral centers were compared. An ACA/aldol domino approach while intellectually attractive, has limitations due to its low yielding nature. A two-step procedure, where a chiral zinc enolate is first trapped as a silyl enol ether and later subjected to Mukaiyama conditions, showed significant advantages. Not only the enol ether can be stored for weeks without degradation, but also this reaction proceeds in higher yields and with excellent diastereocontrol of the new chiral centers. In this latter case useful difunctionalized acetals derived from β,γ-unsaturated aldehydes react in good yields and selectivities with good functional group tolerance. The utility of this latter method is also significantly inproved by single-step oxidative cleavage of the chiral auxiliary.

4. Experimental section

4.1. General methods

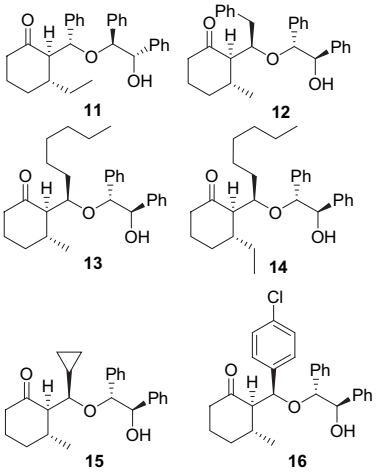
Infrared spectra were recorded by using a Perkin–Elmer 983 G infrared spectrophotometer and a Perkin–Elmer 882 infrared

Table 2
ACA/aldol domino reaction with chiral acetals

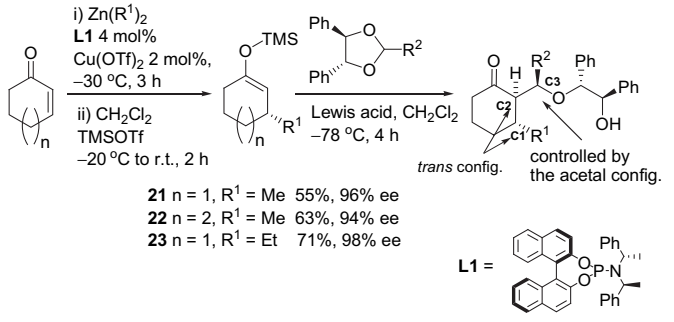


Entry	Substr.	R^1	Lewis acid	Yield[d]	Prod. (selectivity)	Products
1	3	Et	TMSOTf[a]	25%	**11** (Single diaster.)	
2	4	Me	TMSOTf[b]	0%	/	
3	4	Me	$Ti(O^iPr)_4$or $BF_3\cdot Et_2O$[c]	0%	/	
4	4	Me	$TiCl_4$[c]	44%[f]	**13** (86:14)[e]	
5	4	Et	$TiCl_4$	32%[f]	**14** (91:9)[e]	
6	4[f]	Me	$TiCl_4$[c]	6%[f]	**13** (80:20)[e]	
7	5	Me	$TiCl_4$[c]	0%	/	
8	6	Me	$TiCl_4$[c]	34%	**12** (Single diaster.)	
9	7	Me	$TiCl_4$[c]	46%	**15** (Single diaster.)	
10	8	Me	$TiCl_4$[c]	41%	**16** (Single diaster.)	

Products:



[a] Conditions: Lewis acid 1.5 equiv, Acetal 1.5 equiv, −20 °C–0 °C, 2 h.
[b] Conditions: Acetal 1.5 equiv, −20 °C to room temperature, overnight °C, 2 h.
[c] Typical conditions for the ACA/$Cu(OTf)_2$ 2 mol %, L1 4 mol %, $Zn(Me)_2$ 1.3 equiv, CH_2Cl_2, −40 °C, 1 h. Typical conditions for the trapping step: see general procedure B in Experimental section.
[d] Isolated yield.
[e] Determined by ^1H NMR on the benzylic protons signals.
[f] Reaction performed with MeMgBr as the nucleophile, typical conditions for the ACA/MeMgBr 1.15 equiv, CuCl 5 mol %, TaniaPhos 6 mol %, Et_2O, 0 °C, 20 min.



Scheme 1. Chiral TMS enol ethers preparation for use in step-wise Mukaiyama protocols.

spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on either Jeol (JNM GX270) or Bruker (DPX400, AV400) spectrometers (using tetramethylsilane as a standard). All spectra were recorded at ambient temperature unless otherwise noted. Mass spectra were obtained on FinniganMAT 1020 or Autospec VG (electron impact ionisation, EI) Finnigan QMS (electrospray ionisation, ES) machines. Elemental analyses were performed by using a Fisons Instrument EA 1108 CHN elemental analyser. Optical rotations were measured using a Bellingham Stanley ADP440 digital polarimeter at ambient temperature in units of 10^{-1} cm^2 g^{-1} (*c* in g/100 cm^3). GC analyses were performed on a Varian 3380 gas chromatography. Light petroleum refers to that fraction with bp 40–60 °C.

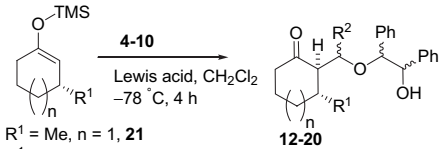
Ligand **L1**,[5a] (*S*,*S*)(−)-hydrobenzoin **2**[8] and silyl enol ethers **21**,[7] and **23**[7] were obtained by literature procedures.

4.2. General procedures

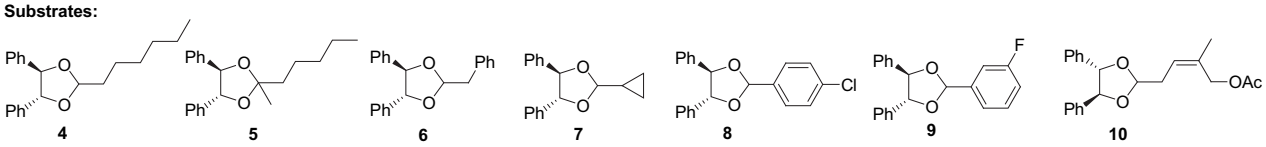
4.2.1. General procedure A. Preparation of chiral acetals: In a 3-neck flask equipped with a Dean–Stark apparatus, (*R*,*R*)-(+)- or (*S*,*S*)-(−)-hydrobenzoin **2** (1 equiv) and the aldehyde (1 equiv) were dissolved in toluene (5 mL/mmol). To this solution was added a catalytic amount of p-TSA (2 mol %) and the resulting solution was heated at reflux overnight. After 20 h the reaction was monitored by TLC (Petrol/Et_2O 2:1), which showed no trace of diol. The reaction mixture was then allowed to cool to room temperature. Solid Na_2CO_3 was added (200 mg/mmol) and the suspension was filtered. Solvent was then removed in vacuo and the resulting crude acetal purified by column chromatography (Petrol/Et_2O 2:1), to afford the desired products.

4.2.2. General procedure B for 1,4-conjugate addition/aldol domino reaction. A suspension of $Cu(OTf)_2$ (3.6 mg, 2.0 mol %) and (*R*,*S*,*S*)-Feringa ligand **L1** (10.8 mg, 4.00 mol %) in CH_2Cl_2 (1 mL) was stirred under argon at room temperature for 15 min. The suspension was

Table 3
Mukaiyama reaction on model chiral acetals

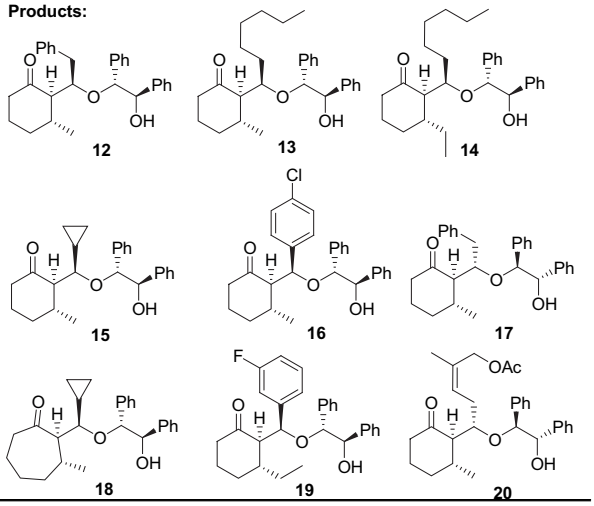


Substrates:



Run	Sub.	R^1, n	Lewis acid[d]	Yield[a]	Selectivity[b] (prod.)	Products
1	**4**	Me, 1	$TiCl_4$	72%	96:4[b] (**13**)	
2	**6**	Me, 1	TMSOTf	0%[c]	—	
3	**6**	Me, 1	$Ti(O^iPr)_4$ *or* $BF_3{\bullet}Et_2O$	0%[c]	—	
4	**5**	Me, 1	$TiCl_4$	0%	—	
5	**6**	Me, 1	$TiCl_4$	47%	Single diast.[b] (**12**)	
6	(***S,S***)–**6**[e]	Me, 1	$TiCl_4$	58%	Single diast.[b] (**17**)	
7	**8**	Me, 1	$TiCl_4$	60%	Single diast.[b] (**16**)	
8	**7**	Me, 1	$TiCl_4$	62%	Single diast.[b] (**15**)	
9	**7**	Me, 2	$TiCl_4$	65%	Single diast.[b] (**18**)	
10	**9**	Et, 1	$TiCl_4$	68%	Single diast.[b] (**19**)	
11	**4**	Et, 1	$TiCl_4$	66%	Single diast.[b] (**14**)	
12	**10**	Me, 1	$TiCl_4$	61%	7:1.[b] (**20**)	

Products:



Typical conditions: see general procedure C in Experimental section.
[a] Isolated yield after column chromatography.
[b] Determined by ^1H NMR spectroscopy using the signals of the benzylic protons.
[c] Starting material was recovered.
[d] 1.5 equiv.
[e] The (*S,S*)-enantiomer of acetal **6** was used.

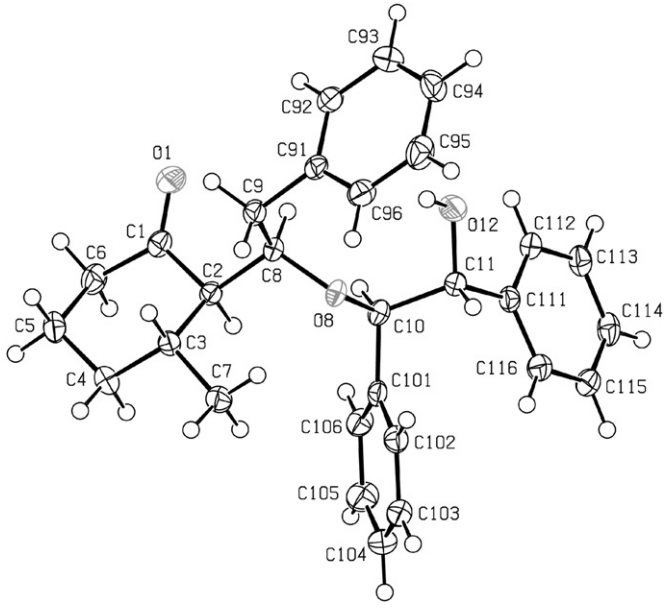
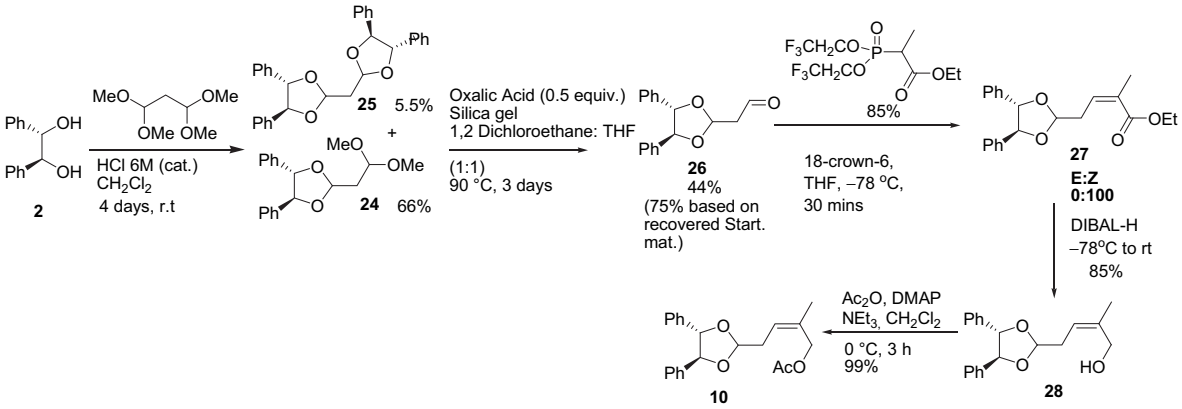


Fig. 1. Structure of aldol adduct (1′*R*,2′*R*,3′*R*,2*R*,3*R*)-12.

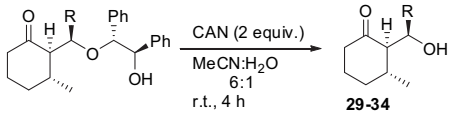
then cooled to −40 °C, $ZnMe_2$ (1 M in hexanes, 0.65 mL) was added. After 20 min cyclohexenone (48 μL, 0.5 mmol) was added to the reaction mixture. The yellow solution was left to warm to −20 °C over 1 h until completion of the reaction. A previously prepared solution of the acetal (0.75 mmol) and $TiCl_4$ (1 M in CH_2Cl_2, 0.75 mL) in 1 mL CH_2Cl_2 was added at −50 °C. The resulting dark red/brown solution was then stirred at −50 °C for 1 h and left to warm to room temperature over 1–2 h. The reaction mixture was then treated with saturated $NH_4Cl_{(aq)}$ (10 mL) and then extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude material was then purified by silica column chromatography (light petroleum/Et_2O 2:1).

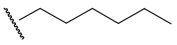
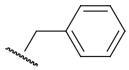
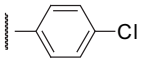
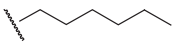
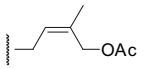
4.2.3. General procedure C for the asymmetric Mukaiyama reaction. A solution of the chiral acetal (1.0 mmol) in freshly distilled CH_2Cl_2 (1 mL) was prepared and cooled to −78 °C. A solution of $TiCl_4$ (1 M in CH_2Cl_2, 1.1 mL, 1.1 mmol) was slowly added at −78 °C. To the dark red solution was immediately added a solution of the TMS enol ether in 1 mL CH_2Cl_2 and the solution was then stirred at −78 °C for 4 h. The reaction completion was followed by TLC (light petroleum/Et_2O 2:1). After 4 h at −78 °C, the reaction mixture was treated with an aqueous solution saturated with NH_4Cl



Scheme 2. Synthesis of functionalized acetal 10.

Table 4
Auxiliary removal



Entry	R	Isolated yield	Product
1		81%	29
2		82%	30
3		83%	31
4		86%	32
5		88% ($ZnEt_2$ used[a])	33
6[b]		78%	34

[a] $ZnEt_2$ used in initial ACA reaction.
[b] b: acetal 10 used for aldol reaction-the opposite configuration of the alcohol is obtained in this case.

(10 mL). The product was extracted with CH_2Cl_2 (3×10 mL), combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude material was then purified by silica column chromatography (light petroleum/Et_2O 2:1).

4.3. Compound preparations and data

*4.3.1. (S,S)-Hydrobenzoin (**2**)*[8]. Prepared using the literature method;[7] R_f (cyclohexane/EtOAc 1:1) 0.57; $[\alpha]_D^{25}$ −93.2 (*c* 1.0, $CHCl_3$); ν_{max} ($CHCl_3$, solution) 3612 (OH), 2895, 1454, 1388, 1319, 1046, 913 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.05–7.35 (10H, m, C*H*$_{ar.}$), 4.71 (2H, s, C*H*–C*H*), 2.91 (2H, s, O*H*); δ_C (100.6 MHz, $CDCl_3$) 139.9 (2C), 128.2 (4C), 128.0 (2C), 127.0 (4C), 79.2 (2C, COH); HRMS (ES^+): MNa^+, found 237.0886. $C_{14}H_{14}O_2Na$ requires 237.0886; mp 142–145 °C. The spectral data was in accordance with the literature.[8]

*4.3.2. (4S,5S)-2,4,5-Triphenyl-1,3-dioxolane (**3**).* Prepared following *general procedure A*, using heptane instead of toluene. The reaction was performed with benzaldehyde dimethyl acetal (693 μL, 4.66 mmol) and (*S*,*S*)-hydrobenzoin **2** (1.00 g, 4.66 mmol). After 40 h the crude was purified by column chromatography (light petroleum/Et_2O 2:1) to afford the desired product as a light yellow solid (1.13 g, 81% yield); R_f (cyclohexane/EtOAc 2:1) 0.77; $[\alpha]_D^{25}$ −20.1 (*c* 1.0, $CHCl_3$); ν_{max} ($CHCl_3$, solution) 2887, 1723, 1495, 1454, 1359, 1095, 1067, 1026, 1001 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.25–7.80 (15H, m, C*H*$_{ar}$), 6.44 (1H, s, C*H*), 5.00 (2H, s, PhC*H*–C*H*Ph); δ_C (100.6 MHz, $CDCl_3$) 138.1, 136.2, 128.7, 128.7 (4C), 128.6 (2C), 127.0 (2C), 126.8 (2C), 126.5 (2C), 104.8, 87.3, 85.4; *m*/*z* (ES^+) 197.1 (23), 325.1 (49, M+Na^+), 341.1 (100), 659.2 (44%); HRMS (ES^+): MNa^+, found 325.1210. $C_{21}H_{18}O_2Na$ requires 325.1199; mp 64–65 °C.

*4.3.3. (4R,5R)-2-Hexyl-4,5-diphenyl-1,3-dioxolane (**4**).* Prepared following *general procedure A*. The reaction was performed with heptanal (1.96 mL, 14.0 mmol) and (*R*,*R*)-(+)-hydrobenzoin **2** (3.00 g, 14.0 mmol). After 20 h the crude was purified by column chromatography (light petroleum/Et_2O 2:1) to afford the desired product as a yellow solid (4.03 g, 93% yield); [found: C, 81.27; H, 8.48. $C_{21}H_{26}O_2$ requires C, 81.25; H, 8.44%]; R_f (light petroleum/Et_2O 2:1) 0.75; $[\alpha]_D^{24}$ +42.0 (*c* 1.0, $CHCl_3$); ν_{max} ($CHCl_3$, solution) 3067, 3009, 2930, 2860, 1733, 1605, 1497, 1455, 1361, 1288, 1241, 1140, 1118, 1025, 916, 863 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.42–7.17 (10H, m, C*H*$_{ar}$), 5.55 (1H, t, *J* 4.6 Hz, C*H*(OR)$_2$), 4.80 (1H, d, *J* 7.6 Hz, C*H*–Ph), 4.76 (1H, d, *J* 7.6 Hz, C*H*–Ph), 1.94 (2H, m, C*H*$_2$), 1.67–1.57 (2H, m, C*H*$_2$); 1.50–1.40 (2H, m, C*H*$_2$), 1.40–1.34 (4H, m, C*H*$_2$C*H*$_2$), 0.94 (3H, t, *J* 7.2 Hz, C*H*$_3$); δ_C (100.6 MHz, $CDCl_3$) 138.8, 137.2, 128.7 (2C), 128.6 (2C), 128.5, 128.2, 126.9 (2C), 126.5 (2C), 106.0, 86.9, 85.0, 34.9, 32.0, 29.5, 23.9, 22.7, 14.2; *m*/*z* (ES^+) 333.2 (13, M+Na^+), 349.2 (100), 350.2 (20), 675.4 (54), 676.4 (22%); mp: 55 °C.

*4.3.4. (4R,5R)-2-Methyl-2-pentyl-4,5-diphenyl-1,3-dioxolane (**5**).* Prepared following *general procedure A*. The reaction was performed with (*R*,*R*)-(+)-hydrobenzoin **2** (2.20 g, 10.3 mmol) and 2-heptanone (1.43 mL, 10.3 mmol). Purification by column chromatography (light petroleum/Et_2O 2:1) afforded the desired compound as a yellow oil (2.07 g, 65% yield); [found: C, 81.17; H, 8.23. $C_{21}H_{26}O_2$ requires C, 81.25; H, 8.44%]; R_f (light petroleum/Et_2O 2:1) 0.72; $[\alpha]_D^{24}$ +46.4 (*c* 1.0, $CHCl_3$); ν_{max} ($CHCl_3$, solution) 3068, 3009, 2985, 2935, 2872, 1605, 1497, 1455, 1378, 1308, 1241, 1141, 1099, 1064, 1040, 1026, 907, 867, 649 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.38–7.20 (10H, m, C*H*$_{ar}$), 4.79 (1H, d, *J* 8.4 Hz, C*H*–Ph), 4.74 (1H, d, *J* 8.4 Hz, C*H*–Ph), 1.98–1.92 (2H, m, C*H*$_2$), 1.72–1.60 (2H, m, C*H*$_2$), 1.67 (3H, s, C*H*$_3$), 1.45–1.38 (4H, m, C*H*$_2$), 0.97 (3H, t, *J* 7.2 Hz, C*H*$_3$CH$_2$); δ_C (100.6 MHz, $CDCl_3$) 137.2, 136.6, 128.5 (4C), 128.4, 128.3, 126.7 (2C), 126.6 (2C), 111.0, 85.9, 85.1, 40.5, 32.1, 25.4, 23.7, 22.7, 14.1; *m*/*z* (ES^+) 333.2 (63, M+Na^+), 334.2 (15), 415.2 (100), 431.1 (47), 610.2 (18),

643.4 (45%); HRMS (ES^+): MNa^+, found 333.1817. $C_{21}H_{26}O_2Na$ requires 333.1825.

*4.3.5. (4R,5R)-2-Benzyl-4,5-diphenyl-1,3-dioxolane (**6**).* Prepared following *general procedure A*. The reaction was performed with (*R*,*R*)-(+)-hydrobenzoin **2** (3.00 g, 14.0 mmol) and 2-phenylacetaldehyde (1.68 g, 14.0 mmol). Purification by column chromatography (light petroleum/Et_2O 2:1) afforded the desired compound as a white solid (2.48 g, 56% yield); [found: C, 83.40; H, 6.39. $C_{22}H_{20}O_2$ requires C, 83.51; H, 6.37%]; R_f (light petroleum/Et_2O 2:1) 0.70; $[\alpha]_D^{24}$ +21.5 (*c* 0.5, $CHCl_3$); ν_{max} ($CHCl_3$, solution) 3067, 3009, 2886, 1604, 1496, 1455, 1406, 1244, 1133, 1080, 1009, 912. 855 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.44–7.27 (11H, m, C*H*$_{ar}$), 7.22–7.13 (4H, m, C*H*$_{ar}$), 5.74 (1H, t, *J* 4.2 Hz, C*H*(OR)$_2$), 4.74 (1H, d, *J* 8.0 Hz, PhC*H*–OR), 4.61 (1H, d, *J* 8.0 Hz, PhC*H*–OR), 3.23 (2H, dd, *J* 4.2, 2.3 Hz, C*H*$_2$); δ_C (100.6 MHz, $CDCl_3$) 138.2, 136.7, 135.8, 130.2 (2C), 128.5 (4C), 128.2, 128.2 (2C), 128.1, 126.8 (2C), 126.6, 126.3 (2C), 105.4, 86.8, 85.0, 41.3; *m*/*z* (ES^+) 317.2 (6, $M+H^+$), 334.2 (12, $M+NH_4^+$), 339.1 (100, $M+Na^+$), 340.1 (24), 445.3 (18%); HRMS (ES^+): MNa^+, found 339.1345. $C_{22}H_{20}O_2Na$ requires 339.1356; mp 99 °C.

*4.3.6. (4R,5R)-2-Cyclopropyl-4,5-diphenyl-1,3-dioxolane (**7**).* Prepared following *general procedure A*. The reaction was performed with (*R*,*R*)-(+)-hydrobenzoin **2** (2.10 g, 10.0 mmol) and cyclopropane carboxaldehyde (0.700 g, 10.0 mmol). Purification by column chromatography (light petroleum/Et_2O 2:1) afforded the desired compound as a yellow oil (2.25 g, 85% yield); R_f (light petroleum/Et_2O 2:1) 0.80; $[\alpha]_D^{22}$ +18.7 (*c* 1.0, $CHCl_3$); ν_{max} ($CHCl_3$, solution) 3068, 3011, 2889, 2821, 1699, 1598, 1584, 1453, 1287, 1168, 1097, 1072 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.40–7.30 (8H, m, C*H*$_{ar.}$), 7.28–7.18 (2H, m, C*H*$_{ar.}$), 5.04 (1H, d, *J* 6.0 Hz, C*H*(OR)$_2$), 4.79 (1H, d, *J* 8.0 Hz, C*H*–Ph), 4.75 (1H, d, *J* 8.0 Hz, C*H*–Ph), 1.36 (1H, m, C*H*$_{cyclopr.}$), 0.69 (2H, m, C*H*$_{2cyclopr.}$), 0.62 (2H, m, C*H*$_{2cyclopr.}$); δ_C (100.6 MHz, $CDCl_3$) 138.4, 136.8, 133.7, 130.2, 128.5 (4C), 126.7 (2C), 126.3 (2C), 108.6, 86.5, 84.9, 14.0, 1.4, 1.3; *m*/*z* (ES^+) 213.1 (51), 289.1 (25, $M+Na^+$), 303.1 (72), 403.1 (57), 487.2 (100%); HRMS (ES^+): MNa^+, found 289.1174. $C_{18}H_{18}O_2Na$ requires 289.1199.

*4.3.7. (4R,5R)-2-(4-Chlorophenyl)-4,5-diphenyl-1,3-dioxolane (**8**).* Prepared following *general procedure A*. The reaction was performed with (*R*,*R*)-(+)-hydrobenzoin **2** (3.00 g, 14.0 mmol) and 4-chlorobenzaldehyde (2.00 g, 14.0 mmol). Purification by column chromatography (light petroleum/Et_2O 2:1) afforded the desired compound as a yellow oil (4.05 g, 80% yield); R_f (light petroleum/Et_2O 2:1) 0.75; $[\alpha]_D^{23}$ +3.3 (*c* 1.0, $CHCl_3$); ν_{max} ($CHCl_3$, solution) 3068, 3009, 2891, 1702, 1602, 1494, 1454, 1422, 1363, 1239, 1089, 1015, 824 cm^{-1}; d_H (400 MHz, $CDCl_3$) 7.66 (2H, d, *J* 8.4 Hz, C*H*$_{ar}$), 7.48 (2H, d, *J* 8.4 Hz, C*H*$_{ar}$), 7.42–7.33 (10H, m, C*H*$_{ar}$), 6.43 (1H, s, C*H*(OR)$_2$), 5.02 (1H, d, *J* 8.0 Hz, C*H*–Ph), 4.97 (1H, d, *J* 8.0 Hz, C*H*–Ph); δ_C (100.6 MHz, $CDCl_3$) 137.8, 136.8, 136.2, 135.1, 128.7 (2C), 128.6 (4C), 128.3 (2C), 128.0 (2C), 126.8 (2C), 126.4 (2C), 103.9, 87.2, 85.2; *m*/*z* (ES^+) 219.1 (98), 263.1 (100), 359.1 (50, $M+Na^+$), 410.2 (39), 415.2 (61), 695.2 (94%); HRMS (ES^+): MNa^+, found 359.0832. $C_{21}H_{17}^{35}ClO_2Na$ requires 359.0809.

*4.3.8. (4R,5R)-2-(3-Fluorophenyl)-4,5-diphenyl-1,3-dioxolane (**9**).* Prepared following *general procedure A*. The reaction was performed with (*R*,*R*)-(+)-hydrobenzoin **2** (3.45 g, 16.1 mmol) and 3-fluorobenzaldehyde (2.00 g, 16.1 mmol). Purification by column chromatography (light petroleum/Et_2O 2:1) afforded the desired compound as a yellow oil (3.13 g, 61% yield); R_f (light petroleum/Et_2O 2:1) 0.76; $[\alpha]_D^{25}$ +11.8 (*c* 1.0, $CHCl_3$); ν_{max} ($CHCl_3$, solution) 3068, 3009, 2896, 1596, 1495, 1454, 1402, 1361, 1268, 1166, 1046 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.50–7.35 (13H, m, C*H*$_{ar}$), 7.17 (1H, m, C*H*$_{ar}$), 6.44 (1H, s, C*H*(OR)$_2$), 5.02 (1H, d, *J* 8.0 Hz, C*H*–Ph), 4.97 (1H, d, *J* 8.0 Hz, C*H*–Ph); δ_C (100.6 MHz, $CDCl_3$) 162.8 (d, *J* 246 Hz), 140.9 (d, *J* 6.9 Hz), 137.7, 136.1, 130.1 (d, *J* 7.6 Hz), 128.6 (5C), 128.3, 126.9 (2C), 126.4 (2C), 122.3 (d, *J* 3.0 Hz), 116.2 (d, *J* 21.5 Hz), 113.5 (d, *J* 22.2 Hz), 103.6, 87.1, 85.2; *m*/*z* (ES^+) 304.2 (14), 325.1 (18), 343.1 (100, $M+Na^+$), 344.1 (22), 413.3 (58), 414.3 (15%); HRMS (ES^+): MNa^+, found 343.1098. $C_{21}H_{17}FO_2Na$ requires 343.1105.

*4.3.9. (2R,3R)-3-ethyl-2-((R)-((1S,2S)-2-hydroxy-1,2-diphenylethoxy)(phenyl)methyl)cyclohexanone (**11**).* In a flame-dried Schlenk tube was introduced under argon $Cu(OTf)_2$ (3.6 mg, 2.0 mol %) and (*R*,*S*,*S*)-Feringa ligand **L1** (10.8 mg, 4.00 mol %). The suspension was stirred in CH_2Cl_2 (1 mL) at room temperature for 15 min. Then the mixture was cooled to −20 °C, and diethylzinc (1 M in hexanes, 0.65 mL, 1.3 equiv) was added dropwise. After 30 min at −20 °C, 2-cyclohexenone (48 μL, 0.50 mmol) dissolved in 0.5 mL of CH_2Cl_2 was added and the mixture stirred at −20 °C for 30 min. Monitoring by TLC (light petroleum/Et_2O 4:1; R_f=0.3) and GC (Lipodex A, isothermal, 60 °C, Flow rate=2 mL/min, retention times: (+)-enantioner: 8.45 min, (−)-enantiomer: 8.65 min, 98% ee), showed complete conversion and acetal **3** (227 mg, 0.750 mmol) was added in a single portion at −20 °C, followed by TMSOTf (0.150 mL, 0.750 mmol). This solution was stirred for 15 min at −20 °C, and then heated up to 0 °C and stirred for 2 h, until TLC analysis showed no starting material. The reaction was then quenched with NH_4Cl saturated, and the aqueous layer extracted with CH_2Cl_2 and Et_2O. The organic layer was dried over Na_2SO_4 and solvents evaporated under vacuum. The crude was dissolved in 10 mL MeOH, a=with Amberlyst-15 (100 mg) for 1 h at room temperature. The solution was then filtered, and poured into water (20 mL). An extractive work up was performed to afford the crude oil, which was purified by column chromatography (light petroleum/Et_2O 7:3), to afford the pure desired compound as a colorless oil (48 mg, 25% yield). The absolute stereochemistry was assigned by analogy with previous studies[6] and the diastereoselectivity was measured by ^1H NMR on the benzylic proton signal; R_f (light petroleum/Et_2O 7:3) 0.51; $[\alpha]_D^{23}$ +39.2 (*c* 1.0, $CHCl_3$); ν_{max} ($CHCl_3$, solution) 3564 (OH), 2931, 2874, 1704 (C=O), 1455, 1383, 1308, 1051, 909 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.25–7.38 (6H, m, C*H*$_{ar}$), 7.05–7.20 (5H, m, C*H*$_{ar}$), 6.95 (2H, m, C*H*$_{ar}$), 6.89 (2H, m, C*H*$_{ar}$), 4.79 (1H, d, *J* 8.1 Hz, COCHCH–Ph), 4.52 (1H, d, *J* 9.7 Hz, CH–Ph), 4.09 (1H, d, *J* 8.1 Hz, C*H*–Ph), 3.28 (1H, d, *J* 1.6 Hz), 2.77 (1H, d, *J* 9.7 Hz), 2.50 (1H, s, O*H*), 2.04 (2H, m), 1.50–1.80 (3H, m), 1.10–1.40 (3H, m), 0.84 (3H, t, *J* 5.4 Hz, C*H*$_3$); δ_C (68 MHz, $CDCl_3$) 211.2, 139.2, 137.1, 128.9, 128.8, 128.5, 128.4, 127.8, 127.7, 127.7, 127.6, 127.2, 83.4, 78.1, 77.6, 63.4, 41.1, 38.9, 25.3, 23.7, 22.2, 12.0; HRMS (ES^+): MNa^+, found 451.2236. $C_{29}H_{32}O_3Na$ requires 451.2249.

*4.3.10. (2R,3R)-2-((R)-1-((1R,2R)-2-Hydroxy-1,2-diphenylethoxy)-2-phenylethyl)-3-methylcyclohexanone (**12**).* Prepared following *general procedure C*, starting from acetal **6** (0.465 g, 1.50 mmol) and TMS enol ether **21** (184 mg, 1.00 mmol). The crude material was purified by silica column chromatography (light petroleum/Et_2O 2:1), to afford the desired compound as a white solid (201 mg, 47% yield, single isomer); [found: C, 80.95; H, 7.49. $C_{29}H_{32}O_3$ requires C, 81.27; H, 7.53%]; R_f (light petroleum/Et_2O 2:1) 0.27; $[\alpha]_D^{23}$ −16.7 (*c* 1.0, $CHCl_3$); ν_{max} ($CHCl_3$, solution) 3532 (OH), 3066, 3009, 2932, 1703 (C=O), 1603, 1495, 1455, 1383, 1342, 1320, 1264, 1194, 1074, 1047, 1023, 915, 852 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.35–7.30 (2H, m, C*H*$_{ar}$), 7.27–7.22 (3H, m, C*H*$_{ar}$), 7.20–7.14 (3H, m, C*H*$_{ar}$), 7.11–7.07 (3H, m, C*H*$_{ar}$), 6.95–6.88 (4H, m, C*H*$_{ar}$), 4.62 (1H, d, *J* 8.8 Hz, Ph–C*H*), 4.15 (1H, d, *J* 8.8 Hz, Ph–C*H*), 4.08 (1H, td, *J* 6.6, 1.7 Hz, C*H*–OR), 3.09 (2H, d, *J* 6.6 Hz), 2.27 (1H, dt, *J* 13.6, 4.8 Hz), 2.10 (1H, m), 2.05–1.95 (3H, m), 1.95–1.86 (1H, m), 1.81–1.71 (1H, m), 1.70–1.62 (1H, m), 1.26 (1H, t, *J* 7.2 Hz), 0.81 (3H, d, *J* 6.0 Hz, C*H*$_3$); δ_C (100.6 MHz, $CDCl_3$) 211.5, 139.3, 139.2, 138.0, 129.3 (2C), 128.7 (2C), 128.3 (2C), 128.1, 128.0 (2C), 127.7 (2C), 127.5, 127.2 (2C), 126.5, 86.0, 78.2, 77.6, 59.0, 42.1, 37.7, 35.1, 33.3, 24.9, 20.4; *m*/*z* (ES^+) 429.24 (2, $M+H^+$),

446.27 (3; M+NH_4^+), 451.22 (76, M+Na^+), 452.23 (23), 879.46 (100, 2M+Na^+), 880.46 (63%); HRMS (ES^+): MNa^+, found 451.2231. $C_{29}H_{32}O_3Na$ requires 451.2244; mp 142–144 °C.

*4.3.11. (2R,3R)-2-((R)-1-((1R,2R)-2-Hydroxy-1,2-diphenylethoxy) heptyl)-3-methylcyclohexanone (**13**).* Prepared following *general procedure C*, starting from acetal **4** (0.310 g, 1.00 mmol) and TMS enol ether **21**. The crude material was purified by silica column chromatography (light petroleum/Et_2O 2:1), to afford the desired compound as a colorless oil (303 mg, 72% yield, 96:4 mixture of isomers, d.r. measured by ^1H NMR on the benzylic protons signal); R_f (light petroleum/Et_2O 2:1) 0.38; $[\alpha]_D^{25}$ −13.0 (*c* 1.0, $CHCl_3$); ν_{max} ($CHCl_3$, solution) 3559 (OH), 3065, 3009, 2958, 2930, 2872, 1704 (C=O), 1454, 1383, 1194, 1074, 1047, 1023 cm^{-1}; δ_H (400 MHz, $CDCl_3$) data for the mixture: 7.22–7.17 (3H, m, C*H*$_{ar}$), 7.15–7.11 (3H, m, C*H*$_{ar}$), 7.04–6.98 (4H, m, C*H*$_{ar}$), 4.72 (1H, d, *J* 8.3 Hz, C*H*–Ph, minor isomer), 4.67 (1H, d, *J* 8.3 Hz, C*H*–Ph, Major isomer), 4.27 (1H, d, *J* 8.3 Hz, C*H*–Ph), 4.20 (1H, d, *J* 8.3 Hz, C*H*–Ph, minor isomer), 3.74 (1H, q, *J* 5.5 Hz, C*H*–OR), 2.15 (1H, t, *J* 5.5 Hz, C*H*–CO), 2.08 (2H, t, *J* 6.8 Hz), 1.89–1.62 (4H, m), 1.36–1.23 (10H, m), 0.93–0.81 (8H, m); δ_C (100.6 MHz, $CDCl_3$), major isomer: 212.0, 139.4, 138.0, 128.4 (2C), 128.2, 128.1 (2C), 127.8 (2C), 127.6, 127.2 (2C), 85.0, 78.0, 75.5, 59.9, 41.1, 34.2, 31.7, 31.2, 30.2, 29.5, 25.1, 23.9, 22.6, 20.1, 14.1, minor isomer: 213.7, 139.8, 138.7, 128.5 (2C), 128.1, 128.0 (2C), 127.9 (2C), 127.7, 127.5 (2C), 86.1, 78.5, 76.7, 57.8, 41.6, 34.6, 31.9, 29.1, 27.8, 26.4, 23.9, 22.7, 21.3, 20.7, 14.5; *m*/*z* (ES^+) 423.29 (2, M+H^+), 440.31 (1, M+NH_4^+), 445.27 (100, M+Na^+), 446.27 (28), 867.55 (31, 2M+Na^+), 868.56 (19%); HRMS (ES^+): MNa^+, found 445.2697. $C_{28}H_{38}O_3Na$ requires 445.2713.

*4.3.12. (2R,3R)-3-Ethyl-2-((R)-1-((1R,2R)-2-hydroxy-1,2-diphenylethoxy)heptyl)cyclohexanone (**14**).* Prepared following *general procedure B*, starting from acetal **4** (232 mg, 0.750 mmol), 2-cyclohexenone (48 μL, 0.50 mmol), and $ZnEt_2$ (1.0 M in hexanes, 0.65 mL). The crude material was purified by silica column chromatography (light petroleum/Et_2O 2:1), to afford the desired compound as a colorless oil (70 mg, 32% yield, 91:9 mixture of diastereomers, d.r. ratio measured on the benzylic proton signal); $[\alpha]_D^{24}$ −6.8 (*c* 0.5, $CHCl_3$); ν_{max} ($CHCl_3$, solution) 3493 (OH), 3066, 3006, 2933, 2874, 1703 (C=O), 1601, 1494, 1452, 1408, 1342, 1049 cm^{-1}; δ_H (400 MHz, $CDCl_3$) data for the mixture: 7.23–7.18 (3H, m, C*H*$_{ar}$), 7.15–7.11 (3H, m, C*H*$_{ar}$), 7.03–6.98 (4H, m, C*H*$_{ar}$), 4.73 (1H, d, *J* 8.4 Hz, C*H*OH, minor isomer), 4.68 (1H, d, *J* 8.4 Hz, C*H*OH, major isomer), 4.28 (1H, d, *J* 8.4 Hz, C*H*CHOH, major isomer), 4.21 (1H, d, *J* 8.4 Hz, C*H*CHOH, minor isomer), 3.75 (1H, ddd, *J* 7.6, 5.2, 3.6, C*H*–OR), 3.65 (1H, s, O*H*), 2.37 (1H, dd, *J* 6.8, 5.2 Hz, C(O)C*H*R_2), 2.08–1.95 (2H, m), 1.85–1.60 (5H, m), 1.40–1.10 (12H, m), 0.91 (3H, t, *J* 7.2 Hz, C*H*$_3$), 0.83 (3H, t, *J* 7.6 Hz, C*H*$_3$); δ_C (100.6 MHz, $CDCl_3$) 212.8, 139.3, 137.7, 128.4 (2C), 128.2, 128.0 (2C), 127.7 (2C), 127.5 (2C), 127.0, 84.4, 77.9, 75.1, 58.1, 40.2, 40.1, 31.7, 29.6, 29.3, 26.1, 25.6, 23.7, 23.0, 22.6, 14.0, 11.4; *m*/*z* (ES^+) 226.1 (33), 451.2 (55), 459.3 (100, M+Na^+), 460.3 (31%); HRMS (ES^+): MNa^+, found 459.2865. $C_{29}H_{40}O_3Na$ requires 459.2870.

*4.3.13. (2R,3R)-2-((R)-Cyclopropyl((1R,2R)-2-hydroxy-1,2-diphenylethoxy)methyl)-3-methylcyclohexanone (**15**).* Prepared following *general procedure C*, starting from acetal **7** (400 mg, 1.50 mmol) and TMS enol ether **21** (275 mg, 1.50 mmol). The crude material was purified by silica column chromatography (light petroleum/Et_2O 2:1), to afford the desired compound as a colorless oil (351 mg, 62% yield); R_f (light petroleum/Et_2O 2:1) 0.22; $[\alpha]_D^{22}$ +21.1 (*c* 2.5, $CHCl_3$); ν_{max} ($CHCl_3$, solution) 3465 (OH), 3066, 3009, 2932, 2872, 1704 (C=O), 1494, 1429, 1321, 1264, 1192, 1081, 1022 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.22–7.12 (6H, m, C*H*$_{ar.}$), 7.05 (2H, m, C*H*$_{ar}$), 6.96 (2H, m, C*H*$_{ar}$), 4.92 (1H, d, *J* 8.8 Hz, C*H*–Ph), 4.61 (1H, d, *J* 8.8 Hz, C*H*–Ph), 4.5 (1H, br s, O*H*), 2.75 (1H, dd, *J* 9.6, 2.0 Hz), 2.40–2.23 (4H, m), 2.00 (1H, m), 1.87 (1H, dd, *J* 13.4, 3.2 Hz), 1.76 (1H, m), 1.43 (2H, m), 0.86 (3H, d, *J* 6.2 Hz, CH_3), 0.80 (1H, m), 0.44 (1H, m), 0.16 (1H, sext, *J* 4.8 Hz, C*H*$_{cyclopr.}$), −0.15 (1H, sext, *J* 4.8 Hz, C*H*$_{cyclopr.}$); δ_C (100.6 MHz, $CDCl_3$) 211.4, 139.5, 137.9, 127.9 (2C), 127.8 (2C), 127.7, 127.6 (2C), 127.4, 127.3 (2C), 82.7, 78.7, 78.4, 61.8, 42.7, 35.5, 33.5, 25.4, 20.1, 11.9, 7.2, 0.5; *m*/*z* (ES^+) 401.2 (21, M+Na^+), 402.2 (5), 779.4 (100), 780.4 (55%); HRMS (ES^+): MNa^+, found 401.2089. $C_{25}H_{30}O_3Na$ requires 401.2087.

*4.3.14. (2R,3R)-2-((S)-(4-chlorophenyl)((1R,2R)-2-hydroxy-1,2-diphenylethoxy)methyl)-3-methylcyclohexanone (**16**).* Prepared following *general procedure C*, starting from acetal **8** (0.50 g, 1.50 mmol) and enol ether **21** (275 mg, 1.50 mmol). The crude material was purified by silica column chromatography (light petroleum/Et_2O 2:1), to afford the desired compound as a colorless oil (404 mg, 60% yield); R_f (light petroleum/Et_2O 2:1) 0.30; $[\alpha]_D^{23}$ −126.3 (*c* 1.0, $CHCl_3$); ν_{max} ($CHCl_3$, solution) 3572 (OH), 3064, 3009, 2963, 1710 (C=O), 1490, 1454, 1363, 1239, 1091, 1047 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.36 (2H, d, *J* 8.8 Hz, C*H*$_{ar}$), 7.28–7.20 (3H, m, C*H*$_{ar}$), 7.15 (2H, d, *J* 8.8 Hz, C*H*$_{ar}$), 7.12–7.05 (3H, m, C*H*$_{ar}$), 6.92 (2H, dd, *J* 7.6, 1.8 Hz, C*H*$_{ar}$), 6.87 (2H, dd, *J* 7.6, 1.8 Hz, C*H*$_{ar}$), 4.70 (1H, d, *J* 8.0 Hz, C*H*–Ph), 4.51 (1H, d, *J* 10.0 Hz, C*H*–Ar), 3.95 (1H, d, *J* 8.0 Hz, C*H*–Ph), 3.34 (1H, br s, O*H*), 2.51 (1H, d, *J* 10.0 Hz), 2.23–2.08 (2H, m), 1.88–1.55 (4H, m), 1.26 (1H, m), 0.82 (3H, d, *J* 7.2 Hz, C*H*$_3$); δ_C (100.6 MHz, $CDCl_3$) 211.8, 139.1, 136.9, 134.4, 129.2 (2C), 129.1 (2C), 128.5, 128.3 (2C), 128.2 (2C), 128.1, 127.8 (2C), 127.5, 126.9 (2C), 83.6, 78.0, 77.7, 64.3, 39.3, 32.8, 27.1, 22.6, 19.0; *m*/*z* (ES^+) 471.2 (51, M+Na^+), 472.2 (15), 473.2 (18), 919.4 (100), 920.4 (61), 921.4 (83%); HRMS (ES^+): MNa^+, found 471.1708. $C_{28}H_{29}^{35}ClO_3Na$ requires 471.1697.

*4.3.15. (2R,3R)-3-Ethyl-2-((S)-(3-fluorophenyl)((1R,2R)-2-hydroxy-1,2-diphenylethoxy)methyl)cyclohexanone (**19**).* Prepared following *general procedure C*, starting from acetal **9** (0.256 mg, 0.8 mmol) and enol ether **23**. The crude material was purified by silica column chromatography (light petroleum/Et_2O 2:1), to afford the desired compound as a colorless oil (242 mg, 68% yield); R_f (light petroleum/Et_2O 2:1) 0.28; $[\alpha]_D^{23}$ −74.4 (*c* 1.0, $CHCl_3$); ν_{max} ($CHCl_3$, solution) 3574 (OH), 3066, 3011, 2964, 2938, 1706 (C=O), 1592, 1488, 1453, 1385, 1253, 1050 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.40 (1H, m, C*H*$_{ar}$), 7.30–7.23 (3H, m, C*H*$_{ar}$), 7.13–7.02 (5H, m, C*H*$_{ar}$), 6.98–6.92 (3H, m, C*H*$_{ar}$), 6.89 (2H, dd, *J* 7.4, 1.6 Hz, C*H*$_{ar}$), 4.73 (1H, d, *J* 7.8 Hz, C*H*–Ph), 4.55 (1H, d, *J* 10.5 Hz, C*H*–Ar), 3.99 (1H, d, *J* 7.8 Hz, C*H*–Ph), 3.10 (1H, br s, O*H*), 2.70 (1H, d, *J* 10.5 Hz, C(O)–C*H*–CH–Ar), 2.25–2.08 (2H, m), 1.76 (2H, m), 1.62 (1H, m), 1.41 (1H, m), 1.35–1.15 (3H, m), 0.69 (3H, t, *J* 7.3 Hz, C*H*$_3$); δ_C (100.6 MHz, $CDCl_3$) 212.0, 163.1 (d, *J* 248 Hz), 141.0 (d, *J* 6.4 Hz), 139.1, 137.0, 130.6 (d, *J* 8.4 Hz), 128.5, 128.3 (4C), 127.7 (2C), 127.5, 126.9 (2C), 123.3 (d, *J* 3.0 Hz), 115.8 (d, *J* 21.5 Hz), 114.6 (d, *J* 21.5 Hz), 83.8, 78.3, 77.6, 62.3, 39.6, 39.2, 24.9, 24.4, 22.5, 11.3; *m*/*z* (ES^+) 469.2 (52, M+Na^+), 470.2 (16), 915.4 (100), 916.4 (64%); HRMS (ES^+): MNa^+, found 469.2145. $C_{29}H_{31}FO_3Na$ requires 469.2149.

*4.3.16. (R)-Trimethyl(3-methylcyclohex-1-enyloxy)silane (**21**).*[7]. In a flame-dried Schlenk tube flushed with argon, we dissolved Cu$(OTf)_2$ (72 mg, 2.0 mol %) and (*R*,*S*,*S*)-Feringa phosphoramidite ligand **L1** (216 mg, 4.00 mol %) in dry CH_2Cl_2 (8 mL). The resulting suspension was stirred at room temperature for 30 min before cooling to −40 °C. Dimethylzinc in toluene (13 mmol of a 1.81 M solution) was then added and the mixture stirred 2 min at −40 °C, after which time 2-cyclohexenone (0.96 mL, 10 mmol) was added. The mixture was stirred at −40 °C for 1 h, until TLC indicated complete conversion. To the zinc enolate a previously prepared solution of TMSOTf (2.18 mL, 12.0 mmol) and dimethylzinc (0.5 mL) was added at −20 °C. The resulting solution was then allowed to warm to room temperature and stirred for 2 h. The reaction was

then diluted with Et_2O (20 mL) and filtered through deactivated silica gel using (previously deactivated by addition of 2.5 mL triethylamine to the top of the silica before the addition of the silyl enol ether) using Et_2O. The solvent was removed in vacuo. Impurities were separated by a fast column filtration on similar NEt_3 deactivated silica gel using pentane to afford the desired compound as a colorless liquid (1.01 g, 55% yield).; GC: performed on 3-methylcyclohexanone, ee=96% (Lipodex A, isothermal, 75 °C, flow rate=1 mL/min, retention times: (+)-enantioner: 11.3 min, (−)-enantiomer: 10.9 min); ν_{max} ($CHCl_3$, solution) 3009, 2957, 2928, 2867, 1663, 1455, 1364, 1324, 1253, 1181, 1131, 1046, 1015, 989, 960, 887, 849 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.73 (1H, dd, C*H*=C, *J* 1.7, 1.1 Hz), 2.22 (1H, m), 2.02–1.92 (2H, m, CH_2), 1.80–1.65 (2H, m, CH_2), 1.60–1.50 (1H, m, C*H*); 1.06–1.00 (1H, m, C*H*), 0.93 (3H, d, CH_3, *J* 6.8 Hz), 0.16 (9H, s, SiCH_3); δ_C (100.6 MHz, $CDCl_3$) 150.0, 111.2, 31.1, 29.8, 29.5, 22.5, 21.8, 0.3 (3C); HRMS (EI): M^+, found 184.1256. $C_{10}H_{20}OSi$ requires 184.1283. The spectral data was in accordance with the literature.[7]

*4.3.17. (R)-Trimethyl(3-methylcyclohept-1-enyloxy)silane (**22**).* Prepared following the procedure described for silyl enol ether **21**, using 2-cycloheptanone (668 μL, 6.00 mmol) as the Michael acceptor. The desired product was obtained as a colorless liquid (747 mg, 63% yield); $[\alpha]_D^{23}$ +3.0 (*c* 1.0, $CHCl_3$); GC: performed on 3-methylcycloheptanone, ee=94% (Lipodex A, isothermal, 60 °C, Flow rate=1 mL/min, retention times: (+)-enantiomer: 10.4 min, (−)-enantiomer: 10.0 min); ν_{max} ($CHCl_3$, solution) 3008, 2958, 2924, 2850, 1658, 1456, 1366, 1252, 1182, 1130, 874 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.74 (1H, d, *J* 4.0 Hz, C*H*=C), 2.40–2.20 (2H, m), 2.10 (1H, m), 1.83 (1H, m), 1.70–1.20 (5H, m), 0.98 (3H, d, CH_3, *J* 7.0 Hz), 0.17 (9H, s, SiCH_3); δ_C (100.6 MHz, $CDCl_3$) 154.1, 116.1, 36.3, 35.3, 31.0, 30.0, 25.1, 23.8, 0.3 (3C); *m*/*z* (EI): 73, 75, 169, 183, 198 (M^+); HRMS (EI): M^+, found 198.1438. $C_{11}H_{22}OSi$ requires 198.1440.

*4.3.18. (R)-Trimethyl(3-ethylcyclohex-1-enyloxy)silane (**23**).*[7]. Prepared following the procedure described for silyl enol ether **21**, using 2-cyclohexanone (960 μL, 10.0 mmol) as the Michael acceptor and diethylzinc (13.0 mmol, 1.1 M solution). The desired product was obtained as a colorless liquid (1.39 g, 71% yield); $[\alpha]_D^{23}$ +5.2 (*c* 1.0, $CHCl_3$); GC: performed on 3-ethylcyclohexanone, ee=98% (Lipodex A, isothermal, 60 °C, Flow rate=2 mL/min, retention times: (+)-enantioner: 8.45 min, (−)-enantiomer: 8.65 min); ν_{max} ($CHCl_3$, solution) 3008, 2961, 2933, 2858, 1663, 1456, 1366, 1252, 1180, 1130, 848 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.80 (1H, d, *J* 1.4 Hz, C*H*=C), 2.05–1.92 (3H, m), 1.80–1.62 (2H, m), 1.58–1.48 (1H, m), 1.33–1.23 (2H, m), 1.07 (1H, m), 0.88 (3H, t, CH_3, *J* 7.4 Hz), 0.17 (9H, s, SiCH_3); δ_C (100.6 MHz, $CDCl_3$) 150.3, 109.5, 36.3, 30.0, 29.6, 28.4, 21.8, 11.4, 0.3 (3C); *m*/*z* (EI): 73.0 (71), 75.0 (20), 169.1 (100), 170.1 (10), 198 (M^+, 7%); HRMS (EI): M^+, found 198.1433. $C_{11}H_{22}OSi$ requires 198.1440. The spectral data was in accordance with the literature.[7]

*4.3.19. (2R,3R)-2-((S)-1-((1S,2S)-2-Hydroxy-1,2-diphenylethoxy)-2-phenylethyl)-3-methylcyclohexanone (**17**).* Prepared following *general procedure C*, starting from (*S*,*S*)-**6** (310 mg, 1.00 mmol) and TMS enol ether **21** (184 mg, 1.00 mmol). The crude material was purified by silica column chromatography (light petroleum/Et_2O 2:1), to afford the desired compound as a white solid (248 mg, 58% yield); R_f (light petroleum/Et_2O 2:1) 0.30; $[\alpha]_D^{24}$ −1.3 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.43–7.27 (5H, m, CH_{ar}), 7.22–7.17 (3H, m, CH_{ar}), 7.14–7.07 (3H, m, CH_{ar}), 6.95–6.85 (4H, m, CH_{ar}), 4.60 (1H, d, *J* 8.8 Hz, CH–Ph), 4.08 (1H, d, *J* 8.8 Hz, CH–Ph), 4.04 (1H, td, *J* 4.8, 0.7 Hz, CH–OR), 3.44 (1H, dd, *J* 14.2, 8.7 Hz), 2.87 (1H, dd, *J* 14.2, 4.0 Hz), 2.21 (1H, dd, *J* 8.8, 4.8 Hz), 2.10–1.97 (2H, m), 1.87–1.77 (2H, m), 1.65–1.53 (2H, m), 1.25–1.18 (1H, m), 1.04 (3H, t, *J* 6.6 Hz, CH_3), 0.91 (1H, d, *J* 6.6 Hz); δ_C (100.6 MHz, $CDCl_3$) 211.1, 139.5, 139.0, 138.6, 129.5 (2C), 128.8 (2C), 128.1 (2C), 128.0 (3C), 127.7 (2C), 127.5, 127.3 (2C), 126.7, 87.5, 78.7, 78.5, 60.6, 42.0, 37.7, 35.2, 32.4, 24.9, 20.1; mp 136–138 °C.

*4.3.20. (2R,3R)-2-((R)-Cyclopropyl((1R,2R)-2-hydroxy-1,2-diphenylethoxy)methyl)-3-methylcycloheptanone (**18**).* Prepared following *general procedure C*, starting from acetal **7** (400 mg, 1.50 mmol) and TMS enol ether **22** (198 mg, 1.00 mmol). The crude material was purified by silica column chromatography (light petroleum/Et_2O 2:1), to afford the desired compound as a colorless oil (252 mg, 65% yield); R_f (light petroleum/Et_2O 2:1) 0.28; $[\alpha]_D^{22}$ +67.5 (*c* 0.8, $CHCl_3$); ν_{max} ($CHCl_3$, solution) 3535 (OH), 3066, 3008, 2962, 2939, 1691 (C=O), 1454, 1382, 1321, 1192, 1054, 1026 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.25–7.21 (3H, m, C$H_{ar.}$), 7.20–7.15 (3H, m, C$H_{ar.}$), 7.04 (4H, m, CH_{ar}), 4.89 (1H, d, *J* 8.4 Hz, C*H*–Ph), 4.74 (1H, d, *J* 8.4 Hz, C*H*–Ph), 2.97 (1H, td, *J* 12.0, 3.0 Hz), 2.73 (1H, dd, *J* 9.6, 2.5 Hz), 2.51 (1H, m), 2.22 (1H, dd, *J* 10.5, 2.5 Hz), 2.03–0.80 (9H, m), 0.81 (1H, m, C$H_{cyclopr.}$), 0.74 (3H, d, *J* 6.8 Hz, CH_3), 0.58 (1H, m, C$H_{cyclopr.}$), 0.24 (1H, sext., *J* 4.8 Hz, C$H_{cyclopr.}$), −0.12 (1H, sext, *J* 4.8 Hz, C$H_{cyclopr.}$); δ_C (100.6 MHz, $CDCl_3$) 215.6, 139.2, 137.1, 128.3, 128.1 (2C), 128.0 (2C), 127.8 (2C), 127.6, 127.2 (2C), 83.4, 80.3, 78.6, 65.7, 44.2, 37.0, 31.4, 29.4, 27.3, 21.5, 12.9, 7.5, 0.6; *m*/*z* (ES^+) 259.2 (11), 415.2 (100, M+Na^+), 416.2 (28%); HRMS (ES^+): MNa^+, found 415.2250. $C_{26}H_{32}O_3Na$ requires 415.2244.

*4.3.21. (2R,3R)-2-((R)-1-Hydroxyheptyl)-3-methylcyclohexanone (**29**).* Cerium(IV) ammonium nitrate (CAN, 328 mg, 0.600 mmol) was added in a single portion to a solution of **13** (125 mg, 0.300 mmol) in MeCN (3 mL) and water (0.5 mL). The resulting yellow mixture was then stirred at room temperature under an air atmosphere for 4 h. After that time K_2CO_3 (400 mg) was added, the suspension stirred for 10 more minutes and filtered. Diethyl ether was added and the mixture was dried over $MgSO_4$. Solvent was then removed under vacuum and the crude oil purified by column chromatography (light petroleum/Et_2O 1:1) to afford the desired product as a yellow oil (55 mg, 81% yield); $[\alpha]_D^{25}$ +90.0 (*c* 0.5, $CHCl_3$); ν_{max} ($CHCl_3$, solution) 3541 (OH), 3007, 2930, 2857, 1695 (C=O), 1457, 1406, 1380, 1362, 1240, 1125, 1063 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.71 (1H, br s, O*H*), 2.82 (1H, d, *J* 10.0 Hz), 2.36 (2H, m), 2.20–2.00 (3H, m), 1.92 (1H, m), 1.79–1.65 (2H, m), 1.52–1.40 (3H, m), 1.31 (7H, m), 1.13 (3H, d, *J* 6.4 Hz, CH_3), 0.91 (3H, t, *J* 6.8 Hz, CH_3); δ_C (100.6 MHz, $CDCl_3$) 215.9, 70.1, 61.2, 43.2, 37.3, 36.4, 34.0, 31.8, 29.2, 26.7, 26.6, 22.6, 20.4, 14.0; *m*/*z* (ES^+): 249.2 (39, M+Na^+), 475.4 (100), 476.4 (32%); HRMS (ES^+): MNa^+, found 249.1779. $C_{14}H_{26}O_2Na$ requires 249.1825.

*4.3.22. (2R,3R)-2-(R)-(1-Hydroxy-2-phenylethyl)-3-methyl cyclohexanone (**30**).* Prepared as described for **29**, using **12** (98 mg, 0.23 mmol) and cerium(IV) ammonium nitrate (CAN, 252 mg, 0.460 mmol) and yielding the desired product as a yellow oil after column chromatography (44 mg, 82% yield); $[\alpha]_D^{23}$ +11.8 (*c* 2.0, $CHCl_3$); ν_{max} ($CHCl_3$, solution) 3537 (OH), 3064, 3009, 2933, 2871, 1695 (C=O), 1495, 1454, 1239, 1080, 1024, 909 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.35–7.15 (5H, m, CH_{ar}), 4.01 (1H, s, O*H*), 3.15 (1H, dd, *J* 18.6, 7.2 Hz), 2.93 (1H, dd, *J* 13.4, 7.2 Hz), 2.43–2.32 (2H, m), 2.20–2.00 (3H, m), 1.89 (1H, ddd, *J* 13.4, 3.6, 1.2 Hz), 1.74 (2H, m), 1.42 (1H, m), 1.05 (3H, d, *J* 6.4 Hz, CH_3); δ_C (100.6 MHz, $CDCl_3$) 215.9, 139.0, 129.0 (2C), 128.6 (2C), 126.3, 71.2, 59.3, 43.1, 42.5, 37.2, 33.9, 26.6, 20.1; *m*/*z* (ES^+) 255.1 (39, M+Na^+), 451.2 (87), 487.3 (64), 683.4 (42) 879.5 (100%); HRMS (ES^+): MNa^+, found 255.1357. $C_{15}H_{20}O_2Na$ requires 255.1356.

*4.3.23. (2R,3R)-2-((S)-(4-Chlorophenyl)(hydroxy)methyl)-3-methyl cyclohexanone (**31**).* Prepared as described for **29** using **16** (300 mg, 0.670 mmol) and cerium(IV) ammonium nitrate (CAN, 734 mg, 1.33 mmol) and yielding the desired product as a yellow oil after column chromatography (140 mg, 83% yield); $[\alpha]_D^{22}$ −18.2 (*c* 1.0, $CHCl_3$); ν_{max} ($CHCl_3$, solution) 3523 (OH), 3008, 2933, 2871, 1697 (C=O), 1599, 1492, 1454, 1413, 1239, 1092, 1079, 1049, 1014 cm^{-1}; δ_H

(400 MHz, $CDCl_3$) 7.28 (4H, s, CH_{ar}), 4.8 (1H, d, *J* 3.6 Hz, C*H*–OH), 3.74 (1H, br s, O*H*), 2.51 (1H, dd, *J* 9.5, 3.6 Hz, C*H*–CH–OH), 2.31 (2H, m), 2.18–1.90 (3H, m), 1.75 (1H, m), 1.50 (1H, m), 1.13 (3H, d, *J* 6.6 Hz, CH_3); δ_C (100.6 MHz, $CDCl_3$) 215.0, 142.2, 132.6, 128.3 (2C), 127.1 (2C), 71.2, 63.1, 42.5, 36.9, 33.1, 26.1, 20.4; *m*/*z* (ES^+) 275.1 (100, M+Na^+), 277.1 (33), 471.2 (66), 473.2 (24), 919.3 (15%); HRMS (ES^+): MNa^+, found 275.0800. $C_{14}H_{17}^{35}ClO_2Na$ requires 275.0809.

*4.3.24. (2R,3R)-2-((R)-Cyclopropyl(hydroxy)methyl)-3-methyl cyclohexanone (**32**).* Prepared as described for **29**, using **15** (264 mg, 0.700 mmol) and cerium(IV) ammonium nitrate (CAN, 767 mg, 1.40 mmol) and yielding the desired product as a yellow oil after column chromatography (110 mg, 86% yield); $[\alpha]_d^{21}$ + 42.0 (*c* 0.5, $CHCl_3$); ν_{max} ($CHCl_3$, solution) 3547 (OH), 3081, 3008, 2932, 1695 (C=O), 1454, 1431, 1379, 1239, 1091, 1075, 1023 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.77 (1H, dd, *J* 9.4, 2.3 Hz, C*H*–OH), 2.37 (2H, m), 2.25 (1H, m), 2.15–2.01 (2H, m), 1.86 (1H, m), 1.71 (1H, m), 1.53–1.40 (1H, m), 1.30–1.20 (2H, m), 1.05 (3H, d, *J* 6.4 Hz, CH_3), 0.61–0.55 (1H, m, C$H_{2cyclopr.}$), 0.50–0.36 (2H, m, C$H_{2cyclopr.}$), 0.05 (1H, m, C$H_{2cyclopr.}$); δ_C (100.6 MHz, $CDCl_3$) 215.7, 75.5, 61.8, 43.0, 36.8, 33.8, 26.4, 20.3, 16.5, 4.2, 3.3; *m*/*z* (ES^+) 205.1 (17, M+Na^+), 387.2 (100), 388.2 (24); HRMS (ES^+): MNa^+, found 205.1182. $C_{11}H_{18}O_2Na$ requires 205.1199.

*4.3.25. (2R,3R)-3-Ethyl-2-((R)-1-hydroxyheptyl)cyclohexanone (**33**).* Prepared as described for **29**, using **14** (145 mg, 0.33 mmol) and cerium(IV) ammonium nitrate (CAN, 395 mg, 0.72 mmol) and yielding the desired product as a yellow oil after column chromatography (70 mg, 88% yield); $[\alpha]_D^{21}$ +58.2 (*c* 0.5, $CHCl_3$); ν_{max} ($CHCl_3$, solution) 3538 (OH), 3008, 2931, 2859, 1694 (C=O), 1461, 1408, 1365, 1239, 1183, 1065 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.70 (1H, t, *J* 9.2 Hz), 2.66 (1H, d, *J* 10.5 Hz, C*H*–OH), 2.34 (2H, m), 2.18 (1H, m), 2.06–1.85 (3H, m), 1.74–1.58 (3H, m), 1.52–1.25 (11H, m), 0.92 (3H, t, *J* 7.4 Hz, CH_3), 0.87 (3H, t, *J* 7.0 Hz, CH_3); δ_C (100.6 MHz, $CDCl_3$) 216.2, 70.0, 59.2, 42.8, 42.5, 36.5, 31.8, 29.2, 29.1, 26.4, 26.0, 25.8, 22.6, 14.1, 10.3; *m*/*z* (ES^+) 263.2 (73, M+Na^+), 459.3 (100), 503.4 (26), 895.6 (29%); HRMS (ES^+): MNa^+, found 263.1971. $C_{15}H_{28}O_2Na$ requires 263.1982.

*4.3.26. (Z)-4-((4S,5S)-4,5-Diphenyl-1,3-dioxolan-2-yl)-2-methylbut-2-enyl acetate (**10**).* A solution of alcohol **28** (0.81 g, 2.6 mmol) in dry CH_2Cl_2 (25 mL) was cooled to 0 °C. To the solution was added successively DMAP (10 mg), NEt_3 (1.1 mL, 7.9 mmol) and acetic anhydride (0.52 mL, 5.5 mmol). The reaction was then allowed to warm and stirred at room temperature for 3 h. After that time a saturated solution of NH_4Cl was added (10 mL) and the product extracted with CH_2Cl_2 (10 mL), and Et_2O (2×10 mL). The combined organic fractions were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was then purified by column chromatography (light petroleum/Et_2O 2:1) to afford the desired product as a colorless oil. (99% yield, 915 mg); R_f (light petroleum/Et_2O 2:1) 0.45; $[\alpha]_D^{25}$ −26.4 (*c* 1.0, $CHCl_3$); ν_{max} ($CHCl_3$, solution) 3067, 3011, 2888, 1731 (C=O), 1496, 1454, 1368, 1241, 1135, 1024 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.40–7.22 (10H, m, C$H_{ar.}$), 5.70 (1H, t, *J* 7.6 Hz, C*H*=C) 5.59 (1H, t, *J* 4.4 Hz, C*H*($OR)_2$), 4.79 (2H, s, C*H*–Ph), 4.73 (2H, s, CH_2OH), 2.78 (2H, dd, *J* 7.6, 4.4 Hz, CH_2CH=C), 2.07 (3H, s, CH_3), 1.93 (3H, d, *J* 1.2 Hz, CH_3); δ_C (100.6 MHz, $CDCl_3$) 170.7, 138.0, 136.5, 133.5, 128.3 (4C), 128.2, 128.0, 126.6 (2C), 126.2 (2C), 123.3, 104.6, 86.6, 85.9, 63.0, 33.3, 21.5, 20.7; *m*/*z* (ES^+) 370.0 (20, M+NH_4^+), 375.2 (100, M+Na^+), 376.2 (22); 633.3 (18%); HRMS (ES^+): MNH_4^+, found 370.2013. $C_{22}H_{28}O_4N$ requires 370.2013.

*4.3.27. (S,Z)-5-((1S,2S)-2-Hydroxy-1,2-diphenylethoxy)-2-methyl-5-((1R,2R)-2-methyl-6-oxocyclohexenyl)pent-2-enyl acetate (**20**).* Prepared following *general procedure C*. The reaction was performed with enol ether **21** (82 mg, 0.44 mmol) and acetal **10** (150 mg, 0.44 mmol). The crude was purified by column chromatography (light petroleum/Et_2O 2:1) to afford the desired product as a yellow oil (120 mg, 61% yield); $[\alpha]_D^{25}$ +12.9 (*c* 1.0, $CHCl_3$); ν_{max} ($CHCl_3$, solution) 3564 (OH), 3070, 3009, 2942, 1730 (C=O), 1454, 1385, 1240, 1070, 1046, 1024, 909 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.10–6.85 (10H, m, CH_{ar}), 5.52 (1H, t, *J* 7.2 Hz, C*H*=C), 4.66 (2H, dd, *J* 15.3, 9.0 Hz), 4.64 (1H, d, *J* 8.0 Hz, C*H*–Ph), 4.31 (1H, d, *J* 8.0 Hz, C*H*–Ph), 3.80 (1H, m), 3.16 (1H, s, O*H*), 2.60 (1H, m), 2.40 (1H, m), 2.20 (1H, m), 2.15–2.02 (2H, m), 2.08 (3H, s, CH_3), 1.81 (3H, d, CH_3, *J* 1.2 Hz), 1.60–1.25 (3H, m), 1.15 (1H, m), 0.93 (3H, d, *J* 6.4 Hz, CH_3), 0.84 (1H, m); δ_C (100.6 MHz, $CDCl_3$) 211.5, 171.0, 140.0, 139.0, 138.0, 133.2, 128.1, 127.9 (2C), 127.7 (2C), 127.1 (2C), 127.0 (2C), 126.0, 86.5, 79.0, 78.4, 75.6, 63.1, 60.6, 41.4, 33.8, 30.3, 29.3, 23.9, 22.6, 21.6, 20.9, 19.8; *m*/*z* (ES^+) 355.0 (22), 369.0 (10), 473.2 (99), 487.2 (100, M+Na^+), 951.5 (19%); HRMS (ES^+): MNa^+, found 487.2241. $C_{29}H_{36}O_5Na$ requires 487.2460.

*4.3.28. (4S,5S)-2-(2,2-Dimethoxyethyl)-4,5-diphenyl-1,3-dioxolane (**24**).* To a flame-dried flask flushed with argon was added (*S*,*S*)-hydrobenzoin **2** (2.00 g, 9.31 mmol) in CH_2Cl_2 (25 mL). To this stirred solution at room temperature was added (1,1,3,3)-tetramethoxypropane (1.53 mL, 9.31 mmol) and HCl 6 M (0.08 mL). The resulting solution was left to stir at room temperature for 4 days. After that period almost all the starting material has been consumed, and Na_2CO_3 was added (1 g). The resulting suspension was filtered and the crude mixture of mono- and diacetal (12:1) was purified by flash chromatography (light petroleum/Et_2O 2:1) to give the desired product as an air stable colorless oil (1.93 g, 66% yield); [found: C, 72.79; H, 7.10. $C_{19}H_{22}O_4$ requires C, 72.59; H, 7.05%]; R_f (light petroleum/Et_2O 2:1) 0.75; $[\alpha]_D^{25}$ −37.7 (*c* 1.0, $CHCl_3$); ν_{max} ($CHCl_3$, solution) 2901, 2835, 2357, 1455, 1367, 1119, 1072, 899 cm^{-1}; d_H (400 MHz, $CDCl_3$) 7.39–7.25 (10H, m, CH_{ar}), 5.62 (1H, t, *J* 5.2 Hz, C*H*$CH_2CH(OMe)_2$), 4.82 (1H, t, *J* 5.6 Hz, C*H*($OMe)_2$), 4.80 (2H, s), 3.42 (6H, d, *J* 3.2 Hz, CH_3OR), 2.28 (2H, t, *J* 5.6 Hz, C$H_2CH(OMe)_2$); d_C (100.6 MHz, $CDCl_3$) 138.2, 136.7, 128.5 (2C), 128.5 (2C), 127.8 (2C), 126.8 (2C), 126.3 (2C), 102.9, 101.3, 86.9, 84.8, 53.1, 52.8, 38.2; HRMS (ES^+): MNa^+, found 337.1395. $C_{19}H_{22}O_4Na$ requires 337.1416.

*4.3.29. 2-((4S,5S)-4,5-Diphenyl-1,3-dioxolan-2-yl)acetaldehyde (**26**).* To a flame-dried flask equipped with a condenser and flushed with argon was added **24** (2.14 g, 6.79 mmol) in a THF/1,2-dichloroethane 1:1 mixture (50 mL). To this stirred solution was added silica gel (0.340 g) and oxalic acid (0.340 g, 3.78 mmol). The resulting suspension was heated to 90 °C for 3 days. After that period some starting material remained but the reaction was stopped as some side products began to appear (monitored by TLC light petroleum/Et_2O 2:1). The reaction mixture was cooled down to room temperature, and $NaCO_3$ was added (1 g). The resulting suspension was filtered and the crude mixture was purified by flash chromatography (light petroleum/Et_2O 2:1) to give the desired product in a 44% yield as an air stable colorless oil and a fraction of recovered starting material as a colorless oil (0.750 g, 41%); R_f (light petroleum/Et_2O 2:1) 0.37; $[\alpha]_D^{25}$ −34.3 (c 1.0, $CHCl_3$); ν_{max} ($CHCl_3$, solution) 2901, 2834, 2356, 1455, 1367, 1119, 1072, 899 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 10.03 (1H, t, *J* 2.4 Hz, C*H*O) 7.41–7.24 (10H, m, CH_{ar}), 5.95 (1H, t, *J* 4.4 Hz, C*H*CH_2CHO), 4.84 (2H, dd, *J* 11.2, 8.0 Hz, C*H*–Ph), 3.05 (2H, m, CH_2CHO); δ_C (100.6 MHz, $CDCl_3$) 199.0, 137.7, 136.0, 128.7 (5C), 128.5, 126.7 (2C), 126.2 (2C), 101.3, 87.0, 85.2, 48.1; HRMS (ES^+): MNa^+, found 291.0757. $C_{17}H_{16}O_3Na$ requires 291.0997.

*4.3.30. (Z)-Ethyl-4-((4S,5S)-4,5-diphenyl-1,3-dioxolan-2-yl)-2-methylbut-2-enoate (**27**).* To a solution of 18-crown-6 (15.9 g, 60.2 mmol) and ethyl 2-(bis(2,2,2-trifluoroethoxy) phosphoryl) propanoate (415 mg, 12.0 mmol) in THF (150 mL) a solution of KHMDS (15% in toluene, 18.2 mL, 12.0 mmol) was added under argon at −78 °C. The resulting slightly green mixture was stirred for 20 min at −78 °C. After that time a solution of **26** (3.22 g, 12.0 mmol) in 10 mL THF was added at −78 °C. The resulting yellow

solution was then stirred for 2 h at −78 °C. The reaction mixture was treated with an aqueous solution saturated with NH_4Cl and then extracted with CH_2Cl_2 (3×60 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude mixture was purified by column chromatography (2:1 light petroleum/Et_2O) to give the pure compound as a yellow oil (3.59 g, 85% yield); [found: C, 74.68; H, 6.80. $C_{22}H_{24}O_4$ requires C, 74.98; H, 6.86%]; R_f(light petroleum/Et_2O 2:1) 0.68; $[\alpha]_D^{25}$ −16.5 (*c* 1.0, $CHCl_3$); ν_{max} ($CHCl_3$, solution) 3011, 2897, 1706 (C=O), 1497, 1455, 1374, 1240, 1131, 1020, 898 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.40–7.23 (10H, m, C*H*$_{ar}$), 6.23 (1H, td, *J* 7.2, 1.5 Hz, C*H*=C), 5.63 (1H, t, *J* 4.6 Hz, C*H*(OR)$_2$), 4.80 (2H, d, *J* 1.5 Hz, C*H*–Ph,), 4.25 (2H, q, *J* 7.2 Hz, C*H*$_2$CH$_3$), 3.17 (2H, m, C*H*$_2$CH=C), 2.00 (3H, d, *J* 1.5 Hz, C*H*$_3$); 1.34 (3H, t, *J* 7.2 Hz, C*H*$_3$); δ_C (100.6 MHz, $CDCl_3$) 167.8, 138.2, 136.7, 135.2, 130.1, 128.6 (2C), 128.5 (2C), 128.5, 128.2, 126.8 (2C), 126.4 (2C), 104.7, 86.8, 85.1, 60.3, 35.2, 20.8, 14.3; *m*/*z* (EI+) 375.1 (100, M+Na^+), 376.1 (17%); HRMS (ES^+): MNa^+, found 375.1248. $C_{22}H_{24}O_4Na$ requires 375.15668.

*4.3.31. (Z)-4-((4S,5S)-4,5-Diphenyl-1,3-dioxolan-2-yl)-2-methylbut-2-en-1-ol (**28**).* A solution of ester **27** (1.00 g, 2.83 mmol) in dry THF (50 mL) was cooled to −78 °C. DIBAL-H (1.7 M in toluene, 5.00 mL, 8.51 mmol) was then added slowly and the reaction was allowed to warm to room temperature over 2 h. After complete disappearance of the starting material, hydrolysis was effected by addition of 20 mL of wet diethyl ether, followed by 2 mL of water, 2 mL of 10% aqueous NaOH solution and 3 g of Na_2SO_4. The resulting suspension was stirred for 30 min, filtered through Celite and washed with diethyl ether. The filtrate was dried with Na_2SO_4, filtered, and the solvent was evaporated in vacuo. Purification by column chromatography (light petroleum/Et_2O 1:1) afforded the allylic alcohol as a colorless oil (770 mg, 88% yield); R_f (light petroleum/Et_2O 2:1) 0.10; $[\alpha]_D^{25}$ −29.4 (*c* 1.0, $CHCl_3$); ν_{max} ($CHCl_3$, solution) 3504 (OH), 3068, 3007, 2886, 1605, 1496, 1454, 1407, 1306, 1288, 1240, 1131, 1003, 943, 861 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.40–7.20 (10H, m, C*H*$_{ar}$), 5.58 (1H, dt, *J* 8.0, 1.3 Hz, C*H*=C) 5.56 (1H, t, *J* 4.2 Hz, C*H*(OR)$_2$), 4.80 (2H, s, C*H*–Ph), 4.17 (2H, s, C*H*$_2$OH), 2.76 (2H, dd, *J* 8.0, 4.2 Hz, C*H*$_2$CH=C), 1.94 (3H, d, *J* 1.3 Hz, C*H*$_3$); δ_C (100.6 MHz, $CDCl_3$) 139.8, 138.0, 136.3, 128.7 (2C), 128.6 (2C), 128.2, 126.9 (2C), 126.3 (2C), 120.7, 104.5, 86.9, 85.1, 61.6, 33.1, 22.3; *m*/*z* (ES^+) 333.1 (100, M+Na^+), 334.1 (19); 412.7 (12%); HRMS (ES^+): MNa^+, found 333.1162. $C_{20}H_{22}O_3Na$ requires 333.1461.

*4.3.32. (S,Z)-5-Hydroxy-2-methyl-5-((1R,2R)-2-methyl-6-oxocyclohexyl)pent-2-enyl acetate (**34**).* Prepared following the procedure described for compound **29**. The reaction was performed using **20** (235 mg, 0.500 mmol) and cerium(IV) ammonium nitrate (CAN, 548 mg, 1.00 mmol). This afforded the allylic acetate after column chromatography (105 mg, 78% yield); $[\alpha]_D^{22}$ −18.2 (*c* 1.00, $CHCl_3$); ν_{max} ($CHCl_3$, solution) 3530 (OH), 3009, 2937, 1729 (C=O), 1695 (C=O), 1454, 1368, 1240, 1130, 1026, 909 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.53 (1H, t, *J* 7.8 Hz, C*H*=C), 4.56 (2H, d, *J* 5.7 Hz, C*H*$_2$OAc), 3.78 (1H, s, O*H*), 2.51–2.20 (5H, m), 2.11–1.85 (4H, m), 2.03 (3H, s, C*H*$_3$), 1.75 (3H, d, *J* 1.2 Hz, C*H*$_3$), 1.75–1.65 (1H, m), 1.46 (1H, m), 1.01 (3H, d, *J* 7.6 Hz, C*H*$_3$); δ_C (100.6 MHz, $CDCl_3$) 214.4, 171.1, 132.0, 127.5, 70.4, 63.3, 61.5, 41.9, 35.0, 32.7, 31.0, 24.4, 21.5, 21.0, 19.9; *m*/*z* (ES^+) 291.2 (86, M+Na^+), 292.2 (14), 559.3 (100), 671.3 (15%); HRMS (ES^+): MNa^+, found 291.1567. $C_{15}H_{24}O_4Na$ requires 291.1567.

5. Supplementary data

Crystallographic data for compound **12** is available from the Cambridge Crystallographic Data Centre (reference number: 783764). This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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References and notes

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