Lewis Acid Catalysed [4+2] Heterocycloadditions between Ketone Enol Ethers and β-Ethylenic α-Oxo Esters

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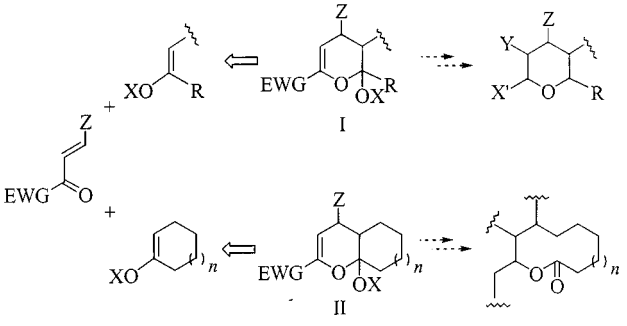
The [4+2] heterocycloaddition reaction between (*E*)-γ-substituted β-unsaturated α-oxo esters **1a**–**d** and cyclic and acyclic ketone enol ethers **2a**–**l** afforded heteroadducts **3**–**5** in high yields when either [Eu(fod)$_3$] or $SnCl_4$ were used as the catalyst. With methyl (*E*)-benzylidenepyruvate (**1a**), the two catalytic modes displayed divergent stereoselectivities. In the case of the heterocycloaddition of silyl enol ether **2h**, X-ray investigations established the relative configurations of the bicyclic adducts **3h** and **5h**, each obtained as the major isomer with [Eu(fod)$_3$] and with $SnCl_4$, respectively. These assignments provided valuable information concerning the concerted vs. nonconcerted mechanism of these acid-catalysed reactions. With methyl (*E*)-*tert*-butoxymethylenepyruvate (**1d**), the scope of the reaction proved to be restricted to alkyl enol ethers as the dienophiles. In this case, the stereochemical process followed a different pathway, exemplified by the X-ray structure of the adduct **4q**, obtained with total stereoselectivity from **1d** and 1-methoxycyclohexene (**2f**) when $SnCl_4$ was the catalyst.

Introduction

In the last decade, Lewis acid catalysed hetero-Diels−Alder reactions between 1-oxabutadienes bearing oxygenated electron-withdrawing groups (EWGs) at the C-2 position and electron-rich olefins have received growing attention,[1] the latest advances being the impressive results obtained by Evans's[2] and Jorgensen's[3] groups [EWG = $PO(OR)_2$, CO_2R] with the use of Cu^{II}−BOX asymmetric catalysts.

In this context, cycloadducts deriving from ketone enol ethers display specific synthetic potential, especially towards targets such as: a) C-glycosides obtainable by functionalization and ketal reduction of adducts I (Scheme 1), and b) macrolactones obtainable by functionalization and ring-expansion reactions[4] of bicycloadducts II. Extensive studies with cyclic and acyclic ketone enol ethers **2** as dienophiles under various Lewis acid conditions have been performed by our group and extended to various (*E*)-γ-substituted β-unsaturated α-oxo esters **1**. We have found that [Eu(fod)$_3$] and $SnCl_4$ are especially efficient and complementary catalysts for such reactions and that both can provide valuable and divergent stereoselectivities.[5] Our aim is to present a survey of these results, and − from stereochemical assignment of representative structures − to deduce a set of significant arguments concerning the concerted vs. nonconcerted mechanisms that can be ascribed to [Eu(fod)$_3$]- vs. $SnCl_4$-catalysed reactions.



Scheme 1

Results and Discussion

Cycloadditions between Ketone Enol Ethers and Methyl (*E*)-Benzylidenepyruvate (1a)

In view of the results previously obtained with vinyl ethers and heterodiene **1a** with use of Danishefsky's catalyst [Eu(fod)$_3$],[6] similar conditions were applied to various ketone enol ethers **2**. Heterocycloaddition again occurred smoothly and in high yields, even in the case of bulky dienophiles. With dienophiles **2a**−**e**, deriving from methyl ketones (Scheme 2, Table 1), "*endo*" selectivities (with the al-

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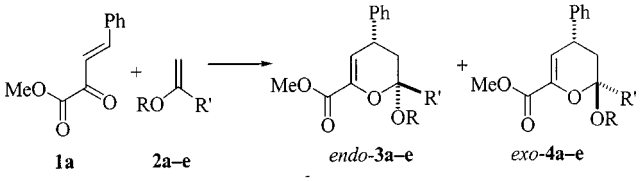
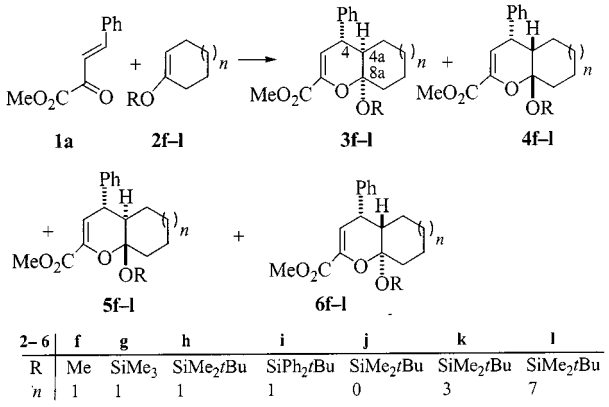
koxy substituent considered to be the *endo* directing group) were found to be only moderate. Notably, this *endo*/*exo* selectivity proved to be highly temperature-dependent with α-methoxyvinylarenes such as **2c**, varying from 10:1 at 20 °C in hexane to 1:8 at 140 °C in xylene (Table 1, Entries 4−5).[7a] This last fact suggests that a thermally induced C-2 epimerization must occur in aromatic solvents, although this was not observed in previously reported [Eu(fod)$_3$]-catalysed heterocycloadditions of vinylic[6] and styrenic[8] dienophiles.



2–4	a	b	c	d	e
R	Me	Me	Me	Me	SiMe$_2$*t*Bu
R'	Me	Ph	4-MeO-C$_6$H$_4$	2-Napht	2-Napht

Scheme 2. Conditions: Eu(fod)$_3$ (5 mol %), reflux

With 1-methoxycyclohexene (**2f**) (Scheme 3, Conditions A; Table 2, Entry 1), [Eu(fod)$_3$] catalysis afforded a high degree of "*endo*" selectivity (up to 32:1). In order to widen the scope of this heterocycloaddition methodology, we considered using as dienophiles the corresponding silyl enol ethers **2g**−**i**, more readily available than their alkyl counterparts. The expected bicyclic adducts were obtained in all cases, the best selectivities being observed with the *tert*-butyldimethylsilyl and *tert*-butyldiphenylsilyl enol ethers **2h** and **2i**. Indeed, whereas the heterodiene **1a** did not react with the *tert*-butyldimethylsilyl enol ether **2h** in the absence of catalyst, heterocycloaddition smoothly occurred in the presence of catalytic amounts (5 mol %) of [Eu(fod)$_3$] (Table 2, Entry 3), thus selectively producing the crystalline major *endo* adduct **3h**. Use of chloroform as a cosolvent enhanced the yield to a large extent, but brought about some epimerization at C-8a (Table 2, Entry 4). Indeed, X-ray crystallographic studies of this *endo* isomer (Figure 1) identified a *cis* pseudoequatorial position of both phenyl and siloxy groups (relative to the dihydropyran ring), consistent with a *trans*-1,2-diaxial relationship between protons 4-H and 4a-H, as established by ^{1}H NMR ($^3J_{4-4a}$ = 9 Hz).



2–6	f	g	h	i	j	k	l
R	Me	SiMe$_3$	SiMe$_2$*t*Bu	SiPh$_2$*t*Bu	SiMe$_2$*t*Bu	SiMe$_2$*t*Bu	SiMe$_2$*t*Bu
n	1	1	1	1	0	3	7

Scheme 3. Conditions: A: Eu(fod)$_3$ (5 mol %), reflux; B: catalyst, CH_2Cl_2, −78 °C, 0.5−1 h

With *tert*-butyldimethylsilyl enol ethers of five-, eight- and twelve-membered ring cycloalkanones **2j**−**l**, both cycloadducts were readily obtained, but the diastereoselectivity was significantly lower than that in the cyclohexanone series (Entries 6−8).

Cycloaddition between the heterodiene **1a** and 1-*tert*-butyldimethylsilyl enol ether **2h** was investigated with other Lewis acids (Scheme 3, Conditions B; Table 3). Use of catalytic amounts of $SnCl_4$ in CH_2Cl_2 at −78 °C efficiently provided the cycloaddition product (Table 3, Entries 3−4). It should be mentioned that the quantities of $SnCl_4$ required here are unusually low in view of the few literature precedents.[9,10] Use of 5% of this Lewis acid quantitatively provided the "abnormal" adduct **5h**, together with small amounts of the *exo* adduct **4h**. The unexpected *trans* ring junction of the cyclohexyl moiety in the crystalline product **5h** was established by X-ray crystallographic studies (Figure 2), which showed that the phenyl substituent and the siloxy group were pseudoequatorial and pseudoaxial, respectively. This structure is consistent with the *trans*-diaxial relationship exhibited by the vicinal protons 4-H and 4a-H ($^3J_{4-4a}$ = 11.2 Hz).

In contrast, the corresponding coupling constant has a lower value ($^3J_{4-4a}$ = 5.9 Hz) for the minor adduct. The existence of a ^4J coupling between 4a-H and the vinylic proton 3-H in the spectrum of the adduct **4h** ($^4J_{3-4a}$ = 2.5 Hz) strongly suggests a pseudoequatorial position of 4a-

Table 1. [Eu(fod)$_3$]-catalysed heterocycloadditions between methyl benzylidenepyruvate (**1a**) and enol ethers **2a**−**e**

Entry	R	R′	**2**	Conditions (solvent, time)	Major adduct[ref]	Ratio (%) **3**	**4**	Yield (%)
1	Me	Me	**2a**	hexane, 3 d	**3a**[7b]	80	20	83
2	Me	Me	**2a**	CH_2Cl_2, 2 d	**3a**[7b]	80	20	92
3	Me	Ph	**2b**	hexane, 12 h	**3b**[7a]	80	20	82
4	Me	4-MeO-C$_6$H$_4$	**2c**	hexane, 3 d[a]	**3c**[7a]	91	9	60
5	Me	4-MeO-C$_6$H$_4$	**2c**	xylene, 2 h	**4c**[7a]	11	89	91
6	Me	2-naphthyl	**2d**	hexane, 5 d	**3d**[7b]	80	20	98
7	SiMe$_2$*t*Bu	2-naphthyl	**2e**	hexane/toluene, 5 d	**3e**[7b]	75	25	96

[a] Room temperature.

Table 2. [Eu(fod)$_3$]-cataysed heterocycloadditions between methyl benzylidenepyruvate (**1a**) and enol ethers **2f**−**l**

Entry	R	*n*	**2**	Conditions	Major adduct	Diastereomeric ratio (%) **3**	**4**	**5**	**6**	Yield (%)
1	Me	1	**2f**	[a]	**3f**	97	3	0	0	84
2	$SiMe_3$	1	**2g**	[b]	**3g**	89	4	5	2	93
3	$SiMe_2tBu$	1	**2h**	[a]	**3h**	97	3	0	0	62
4	$SiMe_2tBu$	1	**2h**	[b]	**3h**	93	3	4	0	92
5	$SiMe_2tBu$	1	**2i**	[b]	**3i**	98	0	2	0	80
6	$SiMe_2tBu$	0	**2j**	[a]	**3j**	84	10	6	0	92
7	$SiMe_2tBu$	3	**2k**	[b]	**3k**	49	36	15	0	88
8	$SiMe_2tBu$	7	**2l**	[b]	**3l**	13	0	11	76	83

[a] Petroleum ether, 60 °C, 60 h. [b] Petroleum ether/$CHCl_3$ (6:1), 60 °C, 3−7 d.

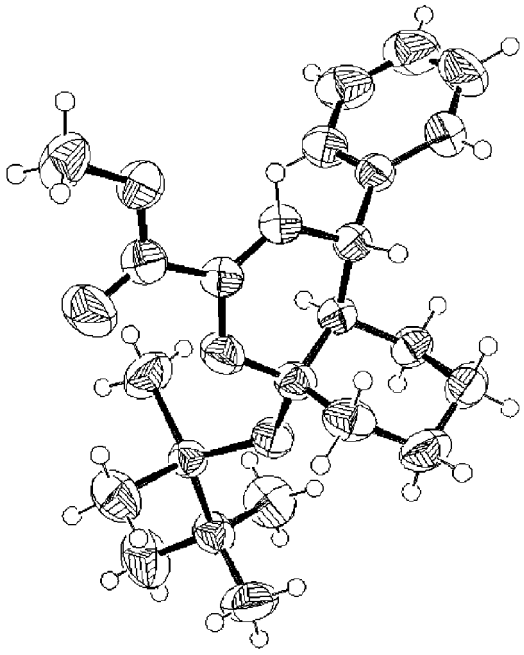


Figure 1. X-ray crystal structure analysis of adduct **3h**

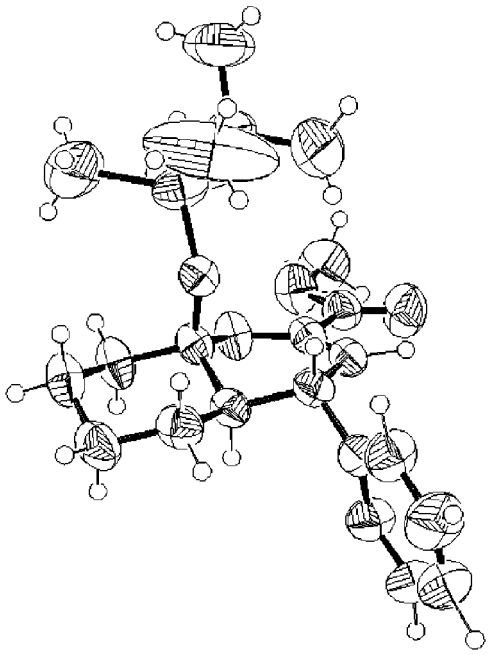


Figure 2. X-ray crystal analysis of adduct **5h**

Table 3. $SnCl_4$-catalysed heterocycloadditions between methyl benzylidenepyruvate (**1a**) and enol ethers **2f**−**l**

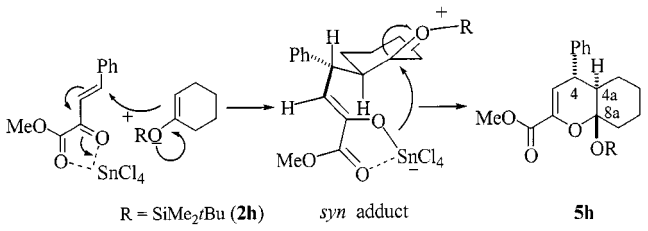
Entry	R	*n*	**2**	Catalyst	Major adduct	Diastereomeric ratio (%) **3**	**4**	**5**	**6**	Yield (%)
1	Me	1	**2f**	20% $SnCl_4$	**5f**	0	5	95	0	86
2	$SiMe_3$	1	**2g**	1% $SnCl_4$	**5g**	9	12	49	30	63[a]
3	$SiMe_2tBu$	1	**2h**	1% $SnCl_4$	**5h**	0	11	89	0	95
4	$SiMe_2tBu$	1	**2h**	5% $SnCl_4$	**5h**	0	11	89	0	99
5	$SiMe_2tBu$	1	**2h**	1.5 equiv. $SnCl_4$	**5h**	0	5	95	0	88
6	$SiMe_2tBu$	1	**2h**	1% $TiCl_4$	**5h**	8	13	79	0	10
7	$SiMe_2tBu$	1	**2i**	1% $SnCl_4$	**3i**	74	5	21	0	85
8	$SiMe_2tBu$	0	**2j**	5% $SnCl_4$	**3j**	50	18	32	0	67
9	$SiMe_2tBu$	3	**2k**	5% $SnCl_4$	**5k**	0	11	89	0	81
10	$SiMe_2tBu$	7	**2l**	5% $SnCl_4$	**5l**	0	46	54	0	94

[a] Some other unstable products, mainly Michael-type monocyclic adduct **7** (up to 30% yield), were obtained in this reaction.

H, which rules out a *trans* ring junction and thus implies a "normal" *exo* cycloaddition.

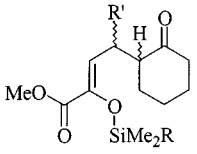
As a supplementary proof of the structural assignment, the *endo* adduct **3h** was treated with 5 mol % $SnCl_4$ under the conditions used for the above cycloaddition reaction. This afforded the adduct **5h**, clearly resulting from epimerization of **3h** at C-8a. Thus, contrary to some previous observations with other types of cycloreactants,[10] $SnCl_4$ does

not act as an *exo*-directing catalyst in the current case. In order to explain the almost exclusive formation of **5h**, a concerted mechanism, which would involve the *endo*-selective formation of **3h** with ultimate epimerization at C-8a, appears to be less likely than a stepwise sequence of two stereocontrolled reactions, as previously suggested in relevant cases,[9] the first step being a Mukaiyama−Michael addition of the silyl vinyl ether **2h** to the Michael acceptor **1a**, followed by the ring-closing *O*-attack of the transient enolate on the intermediate oxonium species (Scheme 4). Conjugate addition would be *syn*-selective and ring closure would exclusively afford the thermodynamically favoured *trans* ring junction. It should be mentioned that use of stoichiometric amounts of $SnCl_4$ enhanced this stereocontrol (Table 3, Entry 5). Attempts to effect the cycloaddition of **1a** with **2h** with $TiCl_4$ as a catalyst resulted in very low yields (ca. 10%; Entry 6) of mixtures of four products, which were not further examined.



Scheme 4

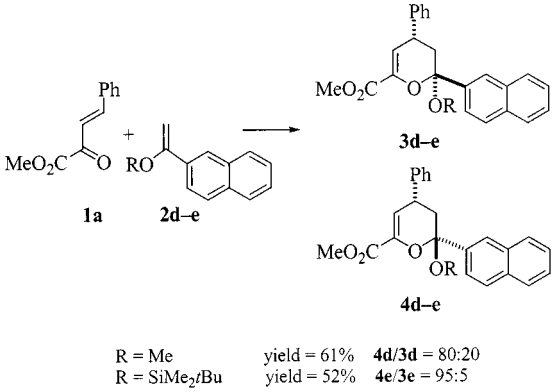
Some variations of the dienophile were studied next. Under the same Lewis acid catalysed conditions ($SnCl_4$ 5 mol %, CH_2Cl_2, −78 °C), an unexpected reversal of selectivity between **5** and **3** forms was observed when the *tert*-butyldiphenylsilyl derivative **2i** was used in place of **2h** (Entry 7), indicating that the nature of the siloxy group must interfere strongly with the stereochemical course of the cyclisation process. The trimethylsilyl enol ether **2g** gave somewhat lower yields and lower selectivities (Entry 2), the main by-products being unstable Michael-type acyclic adducts **7**, in which migration of the silyl group had occurred (Scheme 5). With *tert*-butyldimethylsilyl enol ethers of five-, eight- and twelve-membered ring cycloalkanones **2j**−**l**, both cycloadducts were readily obtained, but the diastereoselectivity was only significant in the cyclooctanone series (Entry 9). The isomeric distribution of the cyclopentane adduct (Entry 8) reflected a moderate *syn* selectivity (82:18) for the presumed first step (Michael-type addition) and a lack of selectivity in the ring-closing step of the *syn* adduct. This last fact is not surprising if we take into account that the relative rigidity of the five-membered ring results more easily in a *cis* ring junction in the following cyclisation than in the *trans* ring junction, the latter being favoured in the case of larger rings. However, some epimerization occurred in both catalysed processes. The twelve-membered ring enol ether **2l** used in this study was obtained as an isomeric mixture [(*Z*)/(*E*) = 3:1], and so the isomeric composition of the corresponding adduct can hardly reflect any stereocontrol.



7 : R = Me, R' = Ph
8 : R = *t*Bu, R' = *t*BuO

Scheme 5

Finally, application of $SnCl_4$ catalysis to dienophiles **2d**−**e** at 0 °C (Scheme 6) resulted mainly in the adducts **4d**−**e**, the formation of which may arise either from an *exo*-concerted transition state (with respect to the alkoxy substituent) or from a stepwise mechanism analogous to that proposed for **5h**. Under the same conditions, Sera and coworkers[11] previously demonstrated that the selective formation of the *trans* cycloadduct from heterodiene **1a** and styrene resulted from both mechanisms, with a predominance of the *exo*-concerted pathway. In the current case, we can consider that the highly polarized double bond of the enol ether moiety is nucleophilic enough mainly to undergo an ionic process with the Sn^{IV}-coordinated benzylidenepyruvate **1a**.



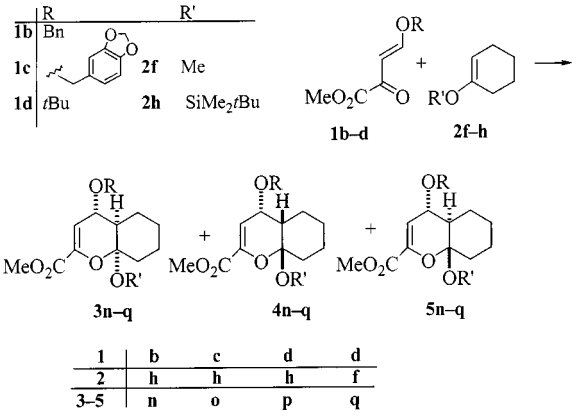
Scheme 6. Conditions: $SnCl_4$ (9 mol %), CH_2Cl_2, 0 °C, 3 h

Cycloadditions of Ketone Enol Ethers with (*E*)-(Alkoxymethylene)pyruvates

From a synthetic point of view, application of such heterocycloadditions to (*E*)-(alkoxymethylene)pyruvates seemed particularly promising. We thus investigated the acid-catalysed reaction of enol ethers **2** with heterodienes variously bearing at the C-4 position a benzyloxy group (**1b**), a (3,4-methylenedioxy)benzyloxy group (**1c**) or a *tert*-butoxy group (**1d**). This study was extensively performed with methyl enol ethers **2d** and **2f** and with *tert*-butyldimethylsilyloxy enol ethers **2e** and **2h**.

Despite all our attempts, application of [Eu(fod)$_3$] or $SnCl_4$ catalysis conditions to silyl enol ether **2e** gave no results with any of the three *O*-substituted heterodienes **1b**−**d**.

With silyl enol ether **2h**, only low yields of cycloadducts were obtained when [Eu(fod)$_3$] was used with **1b−c** (Scheme 7, Table 4, Entries 1 and 3), with no reaction occurring when it was applied to the bulkier heterodiene **1d** (Entry 5). With $SnCl_4$ as the catalyst, results remained unsatisfactory. We were surprised to observe a low selectivity in the reaction between **2h** and **1c**, relative to that observed in the reaction between **2h** and **1b** (Entry 4 vs. 2), probably due to secondary complexation between the Lewis acid and the methylenedioxy group in the cyclisation step. The reaction conducted with **2h** and the heterodiene **1d** furnished as main products a diastereomeric mixture of Michael-type adducts **8** (Entry 5, Scheme 5).



Scheme 7. Conditions: A: Eu(fod)$_3$ (5 mol %), reflux; B: $SnCl_4$ (5 mol %), CH_2Cl_2, −78 °C, 1−2 h

In contrast, positive results were obtained with **1d** and the corresponding methyl enol ether **2f** (Entries 7−8) and particularly when $SnCl_4$ was used as the catalyst at −50 °C (20 mol %; Entry 8). In this case, the desired cycloadduct was obtained in up to 90% yield as a single isomer. The [Eu(fod)$_3$]-catalysed reaction between **1d** and **2f** required unusually harsh conditions (60 h at 114 °C) and again provided a single isomer in 56% yield (Entry 7). Surprisingly, comparison of the two ^{1}H NMR spectra clearly indicated that the same isomer was obtained in both reactions. This adduct clearly shows a ^4J coupling constant between 3-H and 4a-H, fully consistent with the *exo* configuration. The structure of this crystalline adduct was established by X-ray crystallographic studies (Figure 3) as being **4q** of *exo* configuration.

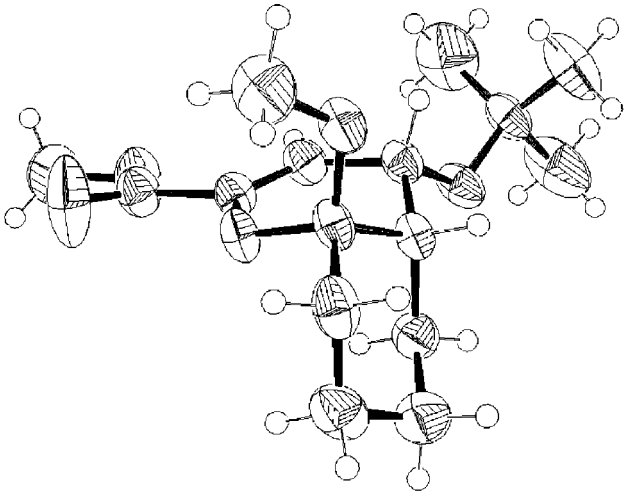
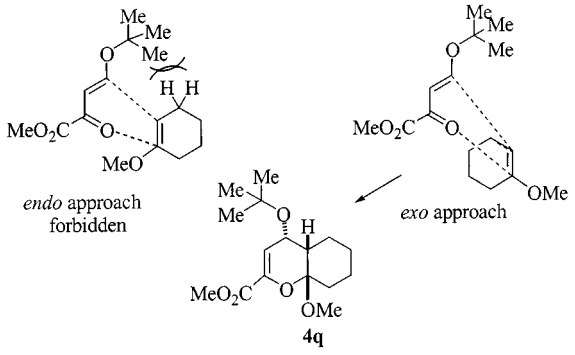


Figure 3. X-ray crystal analysis of adduct **4q**

This *exo* selectivity was particularly unexpected in the context of the [Eu(fod)$_3$] catalysis, in which high levels of *endo* selectivity are classically observed. If we assume a preferred *s-trans* conformation of the enol ether moiety of the heterodiene,[12] this stereochemical outcome could be explained as the consequence of major steric interactions between the *tert*-butyl group and the dienophilic ring in the *endo*-concerted transition state (Scheme 8). Thus, only the *exo* approach would be permitted, but would require more drastic conditions (refluxing toluene).



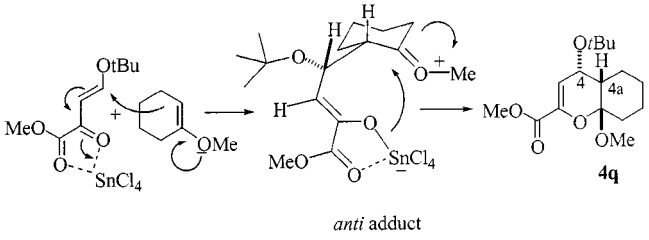
Scheme 8

Table 4. Heterocycloadditions between cyclic enol ethers **2f** and **2h** and alkoxy heterodienes **1b−d**

Entry[a]	R	1	2	Catalyst	Major adduct	Diastereomeric ratio (%) 3	4	5	6	Yield (%)
1	Bn	**1b**	**2h**	[Eu(fod)$_3$]	**3n**	87	13	0	0	19
2	Bn	**1b**	**2h**	$SnCl_4$	**5n**	0	11	89	0	35
3	Piperonyl	**1c**	**2h**	[Eu(fod)$_3$]	**3o**	86	14	0	0	38
4	Piperonyl	**1c**	**2h**	$SnCl_4$	**5o**	32	18	50	0	51
5	*t*Bu	**1d**	**2h**	[Eu(fod)$_3$]	−	−	−	−	−	0
6	*t*Bu	**1d**	**2h**	$SnCl_4$	**4/5p**	13	50	37	0	21
7	*t*Bu	**1d**	**2f**	[Eu(fod)$_3$][b]	**4q**	0	100	0	0	56
8	*t*Bu	**1d**	**2f**	$SnCl_4$[c]	**4q**	0	100	0	0	90

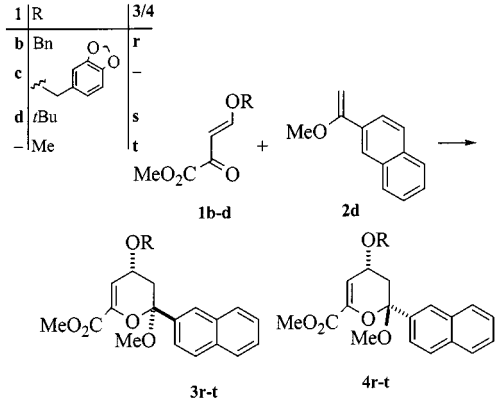
[a] + 44% yield of Michael-type monocyclic adduct **8**. [b] Solvent: (refluxing) toluene. [c] 20 mol % of catalyst, −50 °C.

The stepwise pathway suggested with $SnCl_4$ as the catalyst can fit in well with the unique formation of **4q**, if we now consider that the primary Mukaiyama−Michael addition of the nucleophile to **1d** is *anti*-stereocontrolled, contrary to the *syn* attack preferred when **1a** is the electrophile (Scheme 9). The ring closure is univocally controlled by the imposed pseudoequatorial position of the *tert*-butoxy group.



Scheme 9

In the same way, the methyl enol ether **2d** of 2-acetylnaphthalene, unlike its bulky silyl analogue **2e**, gave satisfactory results when the reaction was conducted with the 4-*tert*-butoxy-1-oxabutadiene **1d**, and particularly so when $SnCl_4$ was used as the catalyst at 0 °C (Scheme 10, Table 5, Entry 6). In this case, adduct **4s** was obtained as a single isomer in 75% yield. The *cis*-bis(pseudoequatorial) relationship of *tert*-butoxy and naphthyl substituents of **4s** was established by ^1H NMR NOE measurements (Figure 4) and comparison with relevant data from phosphonated analogues.[2] Indeed, the absence of a reciprocal NOE effect between one or both *ortho*-naphthalenic proton(s) and the allylic proton of the dihydropyran ring is not in favour of the opposite relative configuration, in which the aromatic substituent should be pseudoaxial.



Scheme 10. Conditions: A: $Eu(fod)_3$ (5 mol %), reflux; B: $SnCl_4$ (5 mol %), CH_2Cl_2, −78 °C, 1−2 h

It must be mentioned that $[Eu(fod)_3]$ catalysis with the same reactants gave no substantial selectivity (Table 5, Entry 5) and nearly the same result was obtained with 4-benzyloxy-1-oxabutadiene **1b** (Entry 1). Benzyloxy and 3,4-methylenedioxybenzyloxy heterodienes **1b**−**c** appear to be unstable in the presence of $SnCl_4$ at 0 °C (Entries 2−4). Thus, in this last study, the heterodiene **1d** again proved to be the reagent of choice for $SnCl_4$-catalysed heterocycloaddition of the methyl enol ethers of methyl aryl ketones. As a minor drawback of these last conditions, the cycloaddition process resulted in some amounts of adducts **3t/4t** as by-products. The unexpected formation of this 4-methoxy analogue of **4s** is reasonably attributable to the in situ generation of methyl (*E*)-methoxymethylenepyruvate, probably through the mixed acetal resulting from acid-catalysed addition of methanol to **1d**.

The above study on heterocycloadditions of ketone enol ethers, and particularly of cyclic ketones, makes it possible to understand the mechanisms of this reaction and the results obtained.

Firstly, the formation of the adducts **7** and **8** strongly supports the multistep mechanism proposed for the $SnCl_4$-catalysed reaction. These species, resulting from the migration of the silyl group during the reaction, are probably formed for the following reasons. In the case of **6**, the trimethylsilyl group on the intermediate oxonium ion is not sufficiently stable and migrates during the reaction. In the case of **7**, the presence of bulky groups significantly slows the kinetics of the second step of the cyclisation, thus allowing for migration of the silyl group.

If limited epimerization may in some cases be observed in $[Eu(fod)_3]$-catalysed reactions, the mechanism of the cycloaddition is unambiguously concerted. This phenomenon only occurred thermally in polar (CH_2Cl_2, $CHCl_3$) or aromatic solvents and not in hydrocarbons. Thus, we suppose that epimerization can occur through opening of the dihydropyran ring, with an intermediate probably similar to the transient Mukaiyama adduct expected in the $SnCl_4$-catalysed heterocycloaddition. This zwitterion open form is not stable enough in nonpolar solvents, explaining why epimerization does not occur in petroleum ether or hexane, and this may account for the surprising results obtained (Table 1, Entries 4 and 5). However, with cyclic enol ethers, addition of small amounts of $CHCl_3$ has permitted the yield to be increased significantly with limited epimerization.

Conclusion

This study demonstrates that $[Eu(fod)_3]$ and $SnCl_4$ are efficient and complementary catalysts for heterocycloadditions between cyclic and acyclic ketone enol ethers and (*E*)-γ-substituted β-unsaturated α-oxo esters. These two Lewis acid catalysed pathways gave rise to high yields together with valuable and divergent stereoselectivities. The stereostructures of representative bicyclic adducts thus obtained have been fully elucidated by X-ray and NMR analyses and are in good agreement with the concerted and nonconcerted mechanisms that may be ascribed to $[Eu(fod)_3]$- and $SnCl_4$-catalysed reactions, respectively.

As shown by the selective formation of **4q** and **5h**, the relationship between the substituents at C-4 and C-4a appears to be more due to simple steric interactions between

Table 5. Heterocycloadditions between enol ether **2d** and alkoxy heterodienes **1b−d**

Entry	R	1	Catalyst	Major adduct	Diastereomeric ratio (%) 3	4	Yield (%)
1	Bn	**1b**	$[Eu(fod)_3]$[a]	**3r**	60	40	52
2	Bn	**1b**	$SnCl_4$[b]	–	–	–	0
3	Piperonyl	**1c**	$[Eu(fod)_3]$[a]	–	–	–	0
4	Piperonyl	**1c**	$SnCl_4$ [b]	–	–	–	0
5	*t*Bu	**1d**	$[Eu(fod)_3]$[a]	**3s/4s**	45	55	75
6	*t*Bu	**1d**	$SnCl_4$ [b]	**4s**	0	100	75[c]

[a] 5 mol %, petroleum ether, 60 °C, 18 h. [b] 9 mol %, CH_2Cl_2, 0 °C, 3 h. [c] + 25% yield of adduct **3t/4t.**

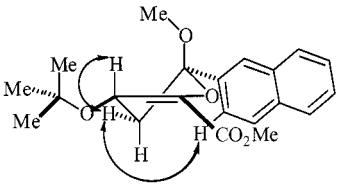


Figure 4. Observed NOE enhancements for **4s**

the heterodiene and the enol ether than really controlled by the catalyst. In contrast, the second step of the nonconcerted reaction and the C-8a epimerization (which can occur with both mechanisms) are largely dependent upon the catalyst, the solvent, the temperature, the substituents and all other secondary interactions between the intermediate and the Lewis acid catalyst. These facts may explain the stereodivergent results obtained in the case of vinyl enol ethers vs. enol ethers deriving from methyl ketones.

Considering the important epimerisation capability of hard Lewis acids such as $SnCl_4$, the good selectivity obtained when bulky substituents are present may be explained by the respective stabilities of the adducts formed (for example, Table 5, Entry 6). Thus, in this last case, the energy gap between the diastereomers, due to the presence of the *tert*-butoxy group, may be responsible for the total selectivity observed.

Catalysts other than those described here have also been examined, but resulted in the degradation of the starting products or in side reactions that significantly reduced the yield of the cycloaddition. $SnCl_4$ or $[Eu(fod)_3]$ are not only the best catalysts we have tested, they are also complementary. This choice of cycloaddition reaction modes, proceeding by two different mechanisms, can increase either the selectivity or the yield.

Finally, extension of the heterocycloadditions proposed here on enol ethers deriving from ketones is potentially valuable for access to various targets. Apart from our current work on the syntheses of macrolactones and C-arylglycosides, this reaction could be considered as an alternative to a Mukaiyama−Michael reaction. This strategy can provide better selectivity and allow selective modifications on the adduct, due to the protected carbonyl groups.

Experimental Section

General: IR: Genesis (Mattson). NMR: Bruker AC 400 (400 MHz for ^1H; 100 MHz for ^{13}C). $CDCl_3$ was used as solvent and TMS as internal standard. High resolution mass spectra were performed with a Varian MAT 311 at the C.R.M.P.O. (Rennes). Heterodienes **1a**, **1b** and **1d** were prepared according to reported procedures.[6] Methyl enol ether **2a** was used as purchased from commercial sources without further purification. Methyl enol ethers **2b−d** and **2f** were prepared according to reported procedures.[13,14] The silyl enol ethers **2e**,[7b] **2g**, **2h**, **2j**, **2k** and **2l**[15] were prepared by Duboudin's modified procedure[16] starting from the appropriate chlorosilane and ketone (NaI/Et_3N/MeCN/20 °C). Spectroscopic data of adducts **3a/4a**, **3d/4d** and **3e/4e** were described in a previous paper by our group.[7b]

Methyl (*E*)-(1,3-Benzodioxol-5-ylmethoxy)methylenepyruvate (1c): 3,4-Methylenedioxybenzyl vinyl ether (1.78 g, 10 mmol) was added dropwise at − 20 °C to vigorously stirred oxalyl chloride (2.3 g, 18 mmol). After stirring at −20 °C overnight, the resulting dark yellow oil was transferred dropwise with a syringe into an ice-cooled solution of methanol (1.25 mL) and triethylamine (15 mL) in diethyl ether (100 mL). The viscous white suspension thus obtained was quickly filtered and the white solid was removed. After evaporation of volatile materials, the yellow crude product was rapidly chromatographed (Et_2O/cyclohexane, from 3:7 to 1:0), giving **1c** (white solid, 2.12 g, 80%); m.p. 90−91 °C. IR (neat): $\tilde{\nu}$ = 1747 (C=O), 1670, 1600 (C=C) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.87 (s, 3 H), 4.92 (s, 2 H), 5.98 (s, 2 H), 6.29 (d, *J* = 12.5 Hz, 1 H), 6.82 (m, 3 H), 7.95 (d, *J* = 12.5 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.9,; 74.2, 101.3, 102.6, 108.4, 108.5, 122.0, 128.0, 148.1, 148.2, 162.6, 166.7, 181.6. $C_{13}H_{12}O_6$ (264.24): calcd. C 59.09, H 4.58; O 36.33. found C 58.87, H 4.58; O 36.55.

1-*tert*-Butyldiphenylsiloxy-1-cyclohexene (2i): A solution of sodium iodide (0.96 g, 1.25 equiv.) in freshly distilled anhydrous acetonitrile (6 mL) was added dropwise at −20 °C to a vigorously stirred mixture of cyclohexanone (0.51 g, 5.1 mmol), *tert*-butyldimethylsilyl chloride (1.75 g, 1.25 equiv.) and freshly distilled triethylamine (0.89 mL, 1.25 equiv.). After stirring under reflux for 48 h, the resulting mixture was quickly filtered and extracted with petroleum ether (3 × 10 mL). After evaporation of volatile materials, the crude product was distilled under reduced pressure, b.p. 136 °C at 0.1 Torr, giving pure **2i** (colourless oil, 1.45 g, 84%). IR (neat): $\tilde{\nu}$: 1675 (C=C) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.05 (s, 9 H); 1.39 (m, 2 H), 1.55 (m, 2 H), 1.83 (m, 2 H), 2.00 (m, 2 H), 4.74 (t, 1 H), 7.4 (m, 6 H), 7.73 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.2, 22.2, 23.1, 23.7, 26.7, 29.8, 105.0, 127.5, 129.5, 133.5,

134.0, 150.3. $C_{22}H_{28}OSi$ (264.24): calcd. C 78.52, H 8.39, Si. 8.35; found C 78.71, H 8.38, Si. 8.40.

[Eu(fod)$_3$]-Catalyzed Cycloadditions (Procedure 1)

Procedure 1A: The heterodiene, the dienophile, the catalyst [Eu(fod)$_3$] (5 mol % with respect to the heterodiene) and petroleum ether (10 mL/mmol of heterodiene) were placed in a round flask equipped with a magnetic stirrer and a reflux condenser fitted with a silica gel drying tube. The mixture was heated under reflux until the heterodiene had totally disappeared (NMR). After cooling, the solvent was evaporated and the residue was chromatographed on silica gel with a cyclohexane/EtOAc mixture as eluent. The various fractions were checked by TLC.

Procedure 1B: Same as Procedure 1A, but with a mixture of petroleum ether and $CHCl_3$ (6:1) instead of petroleum ether as the reaction solvent.

Procedure 1C: Same as Procedure 1A, but with toluene instead of petroleum ether as the reaction solvent.

Procedure 1D: Same as Procedure 1A, but with xylene instead of petroleum ether as the reaction solvent.

$SnCl_4$-Catalyzed Cycloadditions (Procedure 2)

Procedure 2A: The heterodiene and the enol ether (1.1 equiv.) were dissolved in dichloromethane (7 mL/mmol of heterodiene) in a round flask equipped with a magnetic stirrer, maintained under argon and placed in a cooling bath at −78 °C. A 1 M solution of $SnCl_4$ in dichloromethane (1−20 mol % proportions) was added dropwise, and the resulting mixture was kept at −78 °C for 1 h. The reaction medium was hydrolysed by straightforward addition of a saturated aqueous solution of $NaHCO_3$ (5 mL/mmol of heterodiene). The aqueous phase was separated and extracted twice with ether. The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure, and the oily residue was chromatographed on silica gel, with a mixture of cyclohexane and EtOAc as eluent.

Procedure 2B: Same as Procedure 2A, but the reaction was conducted at 0 °C for 3 h with 9 mol % of $SnCl_4$.

3,4-Dihydro-2,4-diphenyl-2-methoxy-6-methoxycarbonyl-2*H*-pyran (3b/4b): A mixture of diastereomers **3b/4b** (80:20, 267 mg, 82%) was obtained as a viscous yellow oil, R_f = 0.57 (cyclohexane/EtOAc, 6:4) by Procedure 1A (eluent cyclohexane/EtOAc, 9:1), from heterodiene **1a** (190 mg, 1 mmol) and dienophile **2b** (200 mg, 1.5 equiv.). IR (film): $\tilde{\nu}$ = 1733 (C=O, ester) cm^{-1}, 1654 (C=C, conjugated alkene). ^{1}H NMR (400 MHz, $CDCl_3$): **3b:** δ = 2.31 (dd, J = 13.7, J = 7.9 Hz, 1 H, 3-H), 2.48 (dd, J = 13.7, J = 6.9 Hz, 1 H, 3-H), 3.13 (s, 3 H), 3.30 (ddd, J = 7.9, J = 6.9, J = 3.2 Hz, 1 H, 4-H), 3.88 (s, 3 H), 6.25 (d, J = 3.2 Hz, 1 H, 5-H), 7.20−7.60 (m, 10 H); **4b** (selected signals): δ = 1.74 (dd, J = 13.6, J = 12.4 Hz, 1 H, 3-H), 2.41 (ddd, J = 13.6, J = 6.2, J = 1.2 Hz, 1 H, 3-H), 3.16 (s, 3 H), 3.29 (ddd, J = 12.4, J = 6.2, J = 3.2 Hz, 1 H, 4-H), 3.88 (s, 3 H), 6.25 (dd, J = 3.2, J = 1.2 Hz, 1 H, 5-H), 7.20−7.60 (m, 10 H). ^{13}C NMR (100 MHz, $CDCl_3$): **3b:** δ = 36.9, 41.2, 50.2, 52.2, 102.8, 115.0, 126.2, 126.3, 126.7, 128.3, 128.4, 128.5, 139.2, 142.3, 143.0, 163.1; **4b** (characteristic signals): δ = 36.3, 42.9, 50.4, 52.1, 101.3, 116.2, 142.8, 163.1. HRMS (EI) ($C_{20}H_{20}O_4$): calcd. 324.13615; found 324.1367.

3,4-Dihydro-2-methoxy-6-methoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-2*H*-pyran (3c/4c): A mixture of diastereomers **3c/4c** (91:9, 53 mg, 60%) was obtained as a viscous yellow oil, R_f = 0.54 (cyclohexane/EtOAc, 6:4), by Procedure 1A (eluent cyclohexane/EtOAc, 9:1), from heterodiene **1a** (48 mg, 0.25 mmol) and dienophile **2c** (64 mg, 1.5 equiv.). The diastereomers **3c/4c** (11:89, 85 mg, 96%) were also obtained as a viscous yellow oil, R_f = 0.54 (cyclohexane/EtOAc, 6:4), by Procedure 1D (eluent cyclohexane/EtOAc, 9:1), from heterodiene **1a** (48 mg, 0.25 mmol) and dienophile **2c** (64 mg, 1.5 equiv.). IR (film): $\tilde{\nu}$ = 1733 (C=O, ester) cm^{-1}, 1648 (C=C, conjugated alkene), 1610. ^{1}H NMR (400 MHz, $CDCl_3$): **3c:** δ = 2.28 (dd, J = 13.7, J = 8.4 Hz, 1 H, 3-H), 2.46 (dd, J = 13.7, J = 6.9 Hz, 1 H, 3-H), 3.13 (s, 3 H), 3.30 (ddd, J = 8.4, J = 6.9, J = 3.3 Hz, 1 H, 4-H), 3.82 (s, 3 H), 3.88 (s, 3 H), 6.25 (d, J = 3.3 Hz, 1 H, 5-H), 6.92 (d, J = 8.7 Hz, 2 H), 7.20−7.30 (m, 5 H), 7.37 (d, J = 8.7 Hz, 2 H); **4c:** δ = 1.72 (dd, J = 13.2, J = 12.9 Hz, 1 H, 3-H), 2.41 (ddd, J = 13.2, J = 7.4, J = 1.0 Hz, 1 H, 3-H), 3.15 (s, 3 H), 3.81 (s, 3 H), 3.86 (s, 3 H), 3.94 (ddd, J = 12.9, J = 7.4, J = 2.3 Hz, 1 H, 4-H), 6.34 (dd, J = 2.3, J = 1.0 Hz, 1 H, 5-H), 6.92 (d, J = 8.7 Hz, 2 H), 7.20−7.30 (m, 5 H), 7.50 (d, J = 8.7 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): **3c:** δ = 37.1, 41.2, 50.1, 52.2, 55.3, 102.9, 113.8, 115.0, 126.7, 127.6, 127.8, 128.5, 131.2, 142.4, 143.0, 159.7, 163.2; **4c:** δ = 36.6, 43.2, 50.6, 52.4, 55.5, 101.5, 114.0, 116.5, 127.1, 127.8−128.0, 129.0, 132.4, 141.3, 143.1, 159.9, 163.7. $C_{21}H_{22}O_5$ (354.147): calcd. C 71.17, H 6.60; found C 70.92, H 6.33.

Methyl (4*R,4a*S**,8a*S**)-8a-Methoxy-4-phenyl-4a,5,6,7,8,8a-hexahydro-4*H*-chromene-2-carboxylate (3f):** A mixture of diastereomers **3f/4f** (97:3, 358 mg, 88%) was obtained as a viscous colourless oil, R_f = 0.59 (cyclohexane/EtOAc, 6:4), by Procedure 1A (eluent: cyclohexane/EtOAc, 9:1), from heterodiene **1a** (256 mg, 1.35 mmol) and dienophile **2f** (302 mg, 2 equiv.). IR (film): $\tilde{\nu}$ = 1734 (C=O, ester) cm^{-1}, 1654 (C=C, conjugated alkene), 1604. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.2−1.8 (m, 7 H), 2.06 (ddd, 1 H, 2 × J = 3.4, J = 10.4 Hz), 2.26 (m, 1 H), 3.17 (s, 3 H, OMe), 3.28 (dd, 2 × J = 3.6 Hz, 4-H), 3.86 (s, 3 H, CO_2Me), 6.32 (d, J = 4.1 Hz, 1 H, 3-H), 7.18 (m, 1 H), 7.25 (d, J = 4.8 Hz, 4 H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.7, 23.8, 30.1, 31.4, 43.1, 44.3, 47.4, 51.8, 101.2, 113.6, 126.0, 127.9, 140.3, 143.6, 163.1. HRMS ($C_{18}H_{22}O_4$): calcd. 302.15180; found 302.1513.

Methyl (4*R,4a*S**,8a*R**)-8a-Methoxy-4-phenyl-4a,5,6,7,8,8a-hexahydro-4*H*-chromene-2-carboxylate (5f):** The diastereomers **5f/4f** (95:5, 260 mg, 86%) were obtained as a viscous colourless oil by Procedure 2A, cat. 20 mol % (eluent cyclohexane /EtOAc, 9:1), from heterodiene **1a** (191 mg, 1.0 mmol) and dienophile **2f** (224 mg, 2 equiv.). R_f = 0.63 (cyclohexane/EtOAc, 6:4). IR (film): $\tilde{\nu}$ = 1720 (C=O, ester) cm^{-1}, 1643 (C=C, conjugated alkene). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.10−2.40 (m, 9 H), 3.29 (s, 3 H, OMe), 3.30 (dd, J = 11.1, J = 2.4 Hz, 1 H, 4-H), 3.79 (s, 3 H, CO_2Me), 6.16 (d, J = 2.4 Hz, 1 H, 3-H), 7.15−7.34 (m, 5 H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.3, 25.1, 26.6, 30.8, 41.4, 45.9, 48.1, 51.9, 100.3, 117.3, 126.6, 128.3, 128.4, 139.8, 142.0, 163.3. HRMS ($C_{18}H_{22}O_4$): calcd. 302.15180; found 302.1513. The minor isomer **(4*S**,4a*S**,8a*S**)-4f** was detected by ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.10−2.40 (m, 9 H), 3.36 (s, 3 H, OMe), 3.83 (s, 3 H, CO_2Me), 4.21 (dd, J = 6.4, J = 2.5 Hz, 1 H, 4-H), 6.30 (d, J = 2.5 Hz, 1 H, J = 1.5 Hz, 3-H), 7.15−7.34 (m, 5 H, Ph).

Methyl 4-Phenyl-8a-trimethylsiloxy-4a,5,6,7,8,8a-hexahydro-4*H*-chromene-2-carboxylate (3g/4g/5g/6g): A mixture of diastereomers **3g/4g/5g/6g** (89:4:5:2, 347 mg, 93%) was obtained as a viscous colourless oil by Procedure 1B (eluent cyclohexane/EtOAc, 98:2), from heterodiene **1a** (197 mg, 1.04 mmol) and dienophile **2g** (220 mg, 1.25 equiv.). The diastereomers **3g/4g/5g** (3:30:67, 50 mg, 30%) were also obtained as a viscous colourless oil by Procedure 2A, cat. 1 mol % (eluent cyclohexane/EtOAc, 98:2), from heterodiene **1a** (90 mg, 0.47 mmol) and dienophile **2g** (89 mg, 1.1 equiv.). IR (film): $\tilde{\nu}$ = 1736 (C=O, ester) cm^{-1}, 1654.6 (C=C, conjugated al-

kene). **(4*R**,4a*S**,8a*R**)-3g:** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.17 (s, 9 H, $SiMe_3$), 1.3−1.85 (m, 8 H), 2.26 (m, 1 H, 4a-H), 3.82 (s, 3 H, CO_2Me), 4.16 (dd, *J* = 2.2, *J* = 6.0 Hz, 1 H, 4-H), 6.28 (dd, *J* = 2.2, *J* = 1.5 Hz, 1 H, 3-H), 7.15−7.35 (m, 5 H, Ph). R_f = 0.56 (cyclohexane/EtOAc, 8:2).). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 1.6, 22.7, 23.4, 28.6, 36.3, 41.9, 46.0, 51.9, 100.9, 112.3, 126.1, 127.9, 128.1, 140.9, 143.5, 163.4. **(4*S**,4a*S**,8a*R**)-4g:** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.05 (s, 9 H, $SiMe_3$), 1.3−1.75 (m, 7 H), 2.00 (m, 2 H), 3.35 (dd, *J* = 3.8, *J* = 4.6 Hz, 1 H, 4-H), 3.81 (s, 3 H, CO_2Me), 6.22 (d, *J* = 3.8 Hz, 1 H, 3-H), 7.15−7.35 (m, 5 H, Ph). R_f = 0.56 (cyclohexane/EtOAc, 8:2).). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 1.6, 23.3, 23.6, 24.7, 38.9, 41.2, 43.9, 52.0, 100.2, 112.7, 126.7, 128.2, 128.5, 141.1, 142.3, 163.3. **(4*R**,4a*S**,8a*S**)-5g:** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.17 (s, 9 H, $SiMe_3$), 0.85−1.85 (m, 8 H), 2.14 (m, 1 H, 8-H), 3.18 (dd, *J* = 2.3, *J* = 11.0 Hz, 1 H, 4-H), 3.79 (s, 3 H, CO_2Me), 6.13 (d, *J* = 2.3 Hz, 1 H, 3-H), 7.15−7.35 (m, 5 H, Ph).). R_f = 0.56 (cyclohexane/EtOAc, 8:2).). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 1.3, 23.1, 25.4, 26.9, 37.6, 41.4, 46.8, 52.0, 100.1, 116.4, 126.7, 128.4, 128.6, 140.5, 141.3, 163.5. **(4*S**,4a*S**,8a*S**)-6g:** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.13 (s, 9 H, $SiMe_3$), 0.95 (m, 1 H), 1.3 (m, 2 H), 1.64 (m, 4 H), 2.03 (ddd, 1 H, *J* = 7.9, *J* = 12.8, *J* = 3.4, 4a-H), 2.14 (m, 1 H), 3.47 (dd, *J* = 4.9, *J* = 7.9 Hz, 1 H, 4-H), 3.83 (s, 3 H, CO_2Me), 6.36 (d, *J* = 4.9 Hz, 1 H, 3-H), 7.15−7.32 (m, 5 H, Ph). R_f = 0.52 (cyclohexane/EtOAc, 8:2) − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 1.7, 22.8, 25.9, 27.3, 38.0, 40.3, 44.1, 52.0, 99.9, 115.3, 126.2, 127.1, 130.8, 139.3, 141.3, 163.7. **Methyl 4-(2-Oxocyclohexyl)-4-phenyl-2-trimethylsiloxy-2-butenoate (7):** This compound was obtained as a by-product in Procedure 2A. The major isomer of the three was identified by the following signals: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.19 (s, 9 H, $SiMe_3$), 1.1−2.5 (m, 8 H), 2.76 (m, 1 H), 3.71 (s, 3 H, CO_2Me), 4.13 (dd, *J* = 9.8, *J* = 9.4, 1 H), 6.24 (d, *J* = 9.8 Hz, 1 H), 7.14−7.35 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 0.5, 23.6, 24.8, 27.9, 31.4, 41.6, 51.7, 56.1, 123.7, 126.4, 128.2, 128.3, 140.0, 141.3, 161.1, 211.6. IR (neat): $\tilde{\nu}$ = 1716 (C=O) cm^{-1}, 1643 (C=C, conjugated alkene).

Methyl (4*R,4a*S**,8a*R**)-8a-*tert*-Butyldimethylsiloxy-4-phenyl-4a,5,6,7,8,8a-hexahydro-4*H*-chromene-2-carboxylate (3h):** A mixture of diastereomers **3h/4h/5h** (93:3:4, 366 mg, 92.0%) was obtained by Procedure 1B (eluent: cyclohexane/EtOAc, 98:2), from heterodiene **1a** (188 mg, 0.99 mmol) and dienophile **2h** (420 mg, 2 equiv.). The diastereomers **3h/4h** (97:3, 190 mg, 62.0%), R_f = 0.59 (cyclohexane/EtOAc, 8:2), were obtained by Procedure 1A (eluent: cyclohexane/EtOAc, 98:2), from heterodiene **1a** (99 mg, 0.52 mmol) and dienophile **2h** (122.1 mg, 1.1 equiv.). Pure **3h** was isolated as colourless crystals, m.p. 110 °C (pentane). IR (KBr): $\tilde{\nu}$ = 1735 (C=O, ester) cm^{-1}, 1650 (C=C, conjugated alkene). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.10 (s, 3 H, Me), 0.24 (s, 3 H, Me), 0.83 (s, 9 H, *t*Bu), 1.35−1.95 (m, 9 H), 3.50 (dd, *J* = 2.7, *J* = 9.5 Hz, 1 H, 4-H), 3.78 (s, 3 H, CO_2Me), 6.05 (d, *J* = 2.7 Hz, 1 H, 3-H), 7.15−7.35 (m, 5 H, Ph).). ^{13}C NMR (100 MHz, $CDCl_3$): δ = −3.1, −3.2, 17.8, 20.5, 25.4, 25.7, 33.9, 40.6, 45.5, 51.9, 101.8, 112.6, 126.5, 128.0, 128.4, 141.1, 142.8, 163.2.). $C_{23}H_{34}O_4Si$ (402.6): calcd. C 68.62, H 8.51, Si 6.98; found C 68.45, H 8.38, Si 6.90.

Methyl (4*S,4a*S**,8a*R**)-8a-*tert*-Butyldimethylsiloxy-4-phenyl-4a,5,6,7,8,8a-hexahydro-4*H*-chromene-2-carboxylate (4h):** R_f = 0.59 (cyclohexane/EtOAc, 8:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.10 (s, 3 H, Me), 0.22 (s, 3 H, Me), 0.88 (s, 9 H, *t*Bu), 1.35−1.95 (m, 8 H), 2.25 (m, 8 H), 3.50 (dd, *J* = 2.7, *J* = 9.5 Hz, 1 H, 4-H), 3.78 (s, 3 H, CO_2Me), 6.05 (d, *J* = 2.7 Hz, 1 H, 3-H), 7.15−7.35 (m, 5 H, Ph).

Methyl (4*R,4a*S**,8a*S**)-8a-*tert*-Butyldimethylsiloxy-4-phenyl-4a,5,6,7,8,8a-hexahydro-4*H*-chromene-2-carboxylate (5h):** A mixture of diastereomers **5h/4h** (89:11, 185 mg, 95%), R_f = 0.54 (cyclohexane/EtOAc, 8:2), was obtained by Procedure 2A ($SnCl_4$: 1%; eluent: cyclohexane/EtOAc, 98:2), from heterodiene **1a** (92.5 mg, 0.49 mmol) and dienophile **2h** (114 mg, 1.1 equiv.). The diastereomers **5h/4h** (89:11, 202 mg, 100%) were also obtained by Procedure 2A ($SnCl_4$: 5%; eluent: cyclohexane/EtOAc, 98:2), from heterodiene **1a** (95 mg, 0.50 mmol) and dienophile **2h** (122 mg, 1.1 equiv.). By Procedure 2A ($SnCl_4$: 1.5 equiv.; eluent: cyclohexane/EtOAc, 98:2), the diastereomers **5h/4h** (95:5, 349 mg, 88%) were also obtained from heterodiene **1a** (188 mg, 0.99 mmol) and dienophile **2h** (420 mg, 2 equiv.). Pure **5h** was isolated as colourless crystals, m.p. 126 °C (pentane). IR (KBr): $\tilde{\nu}$ = 1725 (C=O, ester) cm^{-1}, 1650 (C=C, conjugated alkene).). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.05 (s, 3 H, Me), 0.22 (s, 3 H, Me), 0.93 (s, 9 H, *t*Bu), 1.0−1.7 (m, 8 H), 2.14 (m, 1 H, 8-H), 3.22 (dd, *J* = 2.2, *J* = 11.2 Hz, 1 H, 4-H), 3.78 (s, 3 H, CO_2Me), 6.12 (d, *J* = 2.2 Hz, 1 H, 3-H), 7.10−7.36 (m, 5 H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$): δ = −2.8, −3.9, 18.4, 23.0, 25.4, 25.9, 26.9, 37.6, 41.5, 47.2, 52.0, 100.0, 116.3, 126.7, 128.4, 128.6, 140.6, 142.2, 163.5.). $C_{23}H_{34}O_4Si$ (402.6): calcd. C 68.62, H 8.51, Si 6.98; found C 68.45, H 8.38, Si 6.90.

Methyl (4*R,4a*S**,8a*R**)-8a-(*tert*-Butyldiphenylsiloxy-4-phenyl-4a,5,6,7,8,8a-hexahydro-4*H*-chromene-2-carboxylate (3i):** A mixture of the two diastereomers **3i/5i** (98:2, 454 mg, 80%) was obtained as a viscous colourless oil by Procedure 1B (eluent: cyclohexane/EtOAc, 98:2), from heterodiene **1a** (203 mg, 1.07 mmol) and dienophile **2i** (449 mg, 1.1 equiv.). The diastereomers **3i/4i/5i** (74:5:21, 435 mg, 85%) were obtained as a viscous colourless oil by Procedure 2A ($SnCl_4$: 1%; eluent: cyclohexane/EtOAc, 98:2), from heterodiene **1a** (187 mg, 0.98 mmol) and dienophile **2i** (364 mg, 1.1 equiv.). IR (film): $\tilde{\nu}$ = 1735 (C=O, ester) cm^{-1}, 1655 (C=C, conjugated alkene). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11 (s, 9 H, *t*Bu), 1.28 (m, 1 H), 1.48 (m, 2 H), 1.65−1.85 (m, 5 H), 3.37 (dd, *J* = 2.5, *J* = 10.6 Hz, 1 H, 4-H), 3.57 (s, 3 H, CO_2Me), 5.71 (d, *J* = 2.5 Hz, 1 H, 3-H), 6.67 (m, 2 H), 7.1−7.5 (m, 9 H), 7.54 (m, 4 H).). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 19.3, 19.5, 22.2, 23.4, 23.9, 27.4, 33.1, 40.1, 44.1, 51.5, 102.9, 112.4, 126.6, 126.72, 126.8, 128.4, 128.6, 129.2, 134.9, 136.2, 136.3, 140.9, 142.4, 163.0. HRMS [($C_{33}H_{38}O_4Si$) − *t*Bu]: calcd. 469.1835; found 469.1837. R_f = 0.56 (cyclohexane/EtOAc, 8:2).

Methyl (4*S,4a*S**,8a*R**)-8a-*tert*-Butyldiphenylsiloxy-4-phenyl-4a,5,6,7,8,8a-hexahydro-4*H*-chromene-2-carboxylate (4i):** ^{1}H NMR (400 MHz, $CDCl_3$) (selected signals): δ = 1.15 (s, 9 H, *t*Bu), 3.79 (s, 3 H, CO_2Me), 4.47 (dd, *J* = 2.5, *J* = 5.9 Hz, 1 H, 4-H),6.34 (d, *J* = 2.5 Hz, 1 H, 3-H). **Methyl (4*R**,4a*S**,8a*S**)-8a-*tert*-Butyldiphenylsiloxy-4-phenyl-4a,5,6,7,8,8a-hexahydro-4*H*-chromene-2-carboxylate (5i):** ^{1}H NMR (400 MHz, $CDCl_3$), selected signals: δ = 1.07 (s, 9 H, *t*Bu), 3.39 (m, 1 H, 4-H), 3.51(s, 3 H, CO_2Me), 6.05 (d, *J* = 2.5 Hz, 1 H, 3-H).

Methyl 7a-*tert*-Butyldimethylsiloxy-4-phenyl-4,4a,5,6,7,7a-hexahydrocyclopenta[*b*]pyran-2-carboxylate (3−5j): A mixture of diastereomers **3j/4j/5j** (84:10:6, 376 mg, 92.2%) was obtained as a viscous colourless oil by Procedure 1B (eluent: cyclohexane/EtOAc, 95:5), from heterodiene **1a** (200 mg, 1.05 mmol) and dienophile **2j** (261 mg, 1.25 equiv.). The diastereomers **3j/4j/5j** (50:18:32, 256 mg, 67.0%) were also obtained as a viscous colourless oil by Procedure 2A ($SnCl_4$: 5%; eluent: cyclohexane/EtOAc, 95:5), from heterodiene **1a** (187 mg, 0.98 mmol) and dienophile **2j** (215 mg, 1.1 equiv.). IR (film): $\tilde{\nu}$ =1741 (C=O, ester) cm^{-1}, 1655 (C=C, conjugated alkene). HRMS ($C_{22}H_{32}O_4Si$): calcd. 388.20697; found 388.2069. **(4*R**,4a*S**,7a*R**)-3j:** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.04 (s, 3

H, Me), 0.07 (s, 3 H, Me), 0.72 (s, 9 H, *t*Bu), 1.40−2.35 (m, 7 H), 3.35 (dd, J = 3.6, J = 4.0 Hz, 1 H, 4-H), 3.82 (s, 3 H, CO_2Me), 6.29 (dd, J = 4.0, J = 0.7 Hz, 1 H, 3-H), 7.15−7.35 (m, 5 H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$): δ = −3.6, −3.5, 17.5, 18.7, 25.5, 28.9, 37.8, 40.4, 48.2, 52.0, 106.9, 112.9, 126.1, 127.7, 128.1, 141.0, 143.3, 163.3. R_f = 0.52 (cyclohexane/EtOAc, 8:2). **(4*S**,4a*R**,7a*R**)-4j:** ^1H NMR (400 MHz, $CDCl_3$): δ = 0.07 (s, 3 H, Me), 0.23 (s, 1 H, Me), 0.89 (s, 9 H, *t*Bu), 1.20−2.30 (m, 7 H), 3.45 (dd, J = 11.5, J = 2.1, 4-H), 3.81 (s, 3 H, CO_2Me), 6.22 (d, J = 2.1 Hz, 1 H, 3-H), 7.15−7.35 (m, 5 H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$): δ = −4.0, −3.6, 17.9, 18.7, 25.1, 25.4, 35.2, 41.4, 49.8, 51.9, 105.4, 116.4, 126.5, 128.0, 128.4, 142.3, 142.4, 163.3. R_f = 0.55 (cyclohexane/EtOAc, 8:2). **(4*S**,4a*S**,7a*R**)-5j:** ^1H NMR (400 MHz, $CDCl_3$): δ = 0.11 (s, 3 H, Me), 0.21 (s, 3 H, Me), 0.89 (s, 9 H, *t*Bu), 1.00−2.30 (m, 7 H), 3.81 (s, 3 H, CO_2Me), 3.83 (dd, J = 6.3, J = 2.4 Hz, 1 H, 4-H), 6.22 (d, J = 2.4 Hz, 1 H, J = 1.4 Hz, 3-H), 7.15−7.35 (m, 5 H, Ph). R_f = 0.55 (cyclohexane/EtOAc, 8:2). ^{13}C NMR (100 MHz, $CDCl_3$): δ = −4.0, −3.6, 17.9, 18.7, 25.1, 25.4, 35.2, 41.4, 49.8, 51.9, 105.4, 116.4, 126.5, 128.0, 128.4, 142.3, 142.4, 163.3.

Methyl 10a-*tert*-Butyldimethylsiloxy-4-phenyl-4a,5,6,7,8,9,10,10a-octahydro-4*H*-cyclooct[*b*]pyran-2-carboxylate (3−5k): A mixture of diastereomers **3k/4k/5k** (53:16:31, 450 mg, 98%) was obtained as a viscous colourless oil by Procedure 1B (eluent: cyclohexane/EtOAc, 98:2), from heterodiene **1a** (205 mg, 1.07 mmol) and dienophile **2k** (324 mg, 1.25 equiv.). The diastereomers **4k/5k** (11:89, 395 mg, 81%) were obtained as a viscous colourless oil by Procedure 2A (eluent: cyclohexane/EtOAc, 98:2), from heterodiene **1a** (217 mg, 1.14 mmol) and dienophile **2k** (300 mg, 1.1 equiv.). IR (film): $\tilde{\nu}$ = 1741 (C=O, ester) cm^{-1}, 1655 (C=C, conjugated alkene). HRMS ($C_{25}H_{38}O_4Si$): calcd. 430.25392; found 430.2543. **(4*R**,4a*S**,10a*R**)-3k:** ^1H NMR (400 MHz, $CDCl_3$): δ = 0.11 (s, 3 H, Me), 0.25 (s, 3 H, Me), 0.84 (s, 9 H, *t*Bu), 1.25−2.25 (m, 13 H), 3.54 (dd, J = 9.7, J = 3.0 Hz, 1 H, 4-H), 3.78 (s, 3 H, CO_2Me), 6.04 (d, J = 3.0 Hz, 1 H, 3-H), 7.18−7.35 (m, 5 H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$): δ = −3.0, −2.9, 18.1, 23.1, 23.2, 25.9, 28.2, 35.7, 42.1, 47.3, 51.7, 104.8, 113.6, 126.5, 127.8, 128.4, 141.0, 142.3, 163.1. R_f = 0.59 (cyclohexane/EtOAc, 8:2). **(4*S**,4a*S**,10a*R**)-4k:** ^1H NMR (400 MHz, $CDCl_3$): δ = 0.05 (s, 3 H, Me), 0.21 (s, 3 H, Me), 0.90 (s, 9 H, *t*Bu), 1.00−2.10 (m, 13 H), 3.25 (dd, J = 11.2, J = 2.3 Hz, 1 H, 4-H), 3.76 (s, 3 H, CO_2Me), 6.02 (d, J = 2.3 Hz, 1 H, 3-H), 7.15−7.35 (m, 5 H, Ph). R_f = 0.55 (cyclohexane/EtOAc, 8:2). **(4*R**,4a*S**,10a*S**)-5k:** ^1H NMR (400 MHz, $CDCl_3$): δ = 0.05 (s, 3 H, Me), 0.22 (s, 3 H, Me), 0.91 (s, 9 H, *t*Bu), 1.0−2.3 (m, 13 H), 3.82 (s, 3 H, CO_2Me), 4.18 (dd, J = 5.6, J = 2.5 Hz, 1 H, 4-H), 6.36 (dd, J = 2.5, J = 1.6 Hz, 1 H, 3-H), 7.15−7.35 (m, 5 H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$): δ = −4.0, −2.7, 18.2, 22.0, 24.5, 25.7, 26.9, 27.2, 28.1, 38.1, 42.6, 43.6, 51.7, 103.2, 116.1, 126.6, 128.4, 128.7, 140.4, 142.6, 163.4. R_f = 0.53 (cyclohexane/EtOAc, 8:2).

Methyl 14a-*tert*-Butyldimethylsiloxy-4-phenyl-4a,5,6,7,8,9,10,11,12,13,14,14a-dodecahydro-4*H*-cyclododeca[*b*]pyran-2-carboxylate (3−6l): A mixture of diastereomers **3l/5l/6l** (13:11:76, 438 mg, 83%) was obtained by Procedure 1B (eluent: cyclohexane/EtOAc, 98:2), from heterodiene **1a** (207 mg, 1.09 mmol) and dienophile **2l** (404 mg, 1.25 equiv.). The diastereomers **4l/5l** (46:54, 479 mg, 94%) were obtained by Procedure 2A ($SnCl_4$: 5%; eluent: cyclohexane/EtOAc, 98:2), from heterodiene **1a** (200 mg, 1.05 mmol) and dienophile **2l** (343 mg, 1.1 equiv.). IR (film): $\tilde{\nu}$ = 1741 (C=O, ester) cm^{-1}, 1655 (C=C, conjugated alkene). $C_{29}H_{46}O_4Si$ (486.8): calcd. C 71.56, H 9.53, Si 5.77; found C 71.52, H 9.69, Si 6.90. **(4*R**,4a*S**,14a*R**)-3l:** ^1H NMR (400 MHz, $CDCl_3$) (selected signals): δ = 0.05 (s, 3 H, Me), 0.20 (s, 3 H, Me), 0.80 (s, 9 H, *t*Bu), 3.82 (s, 3 H, CO_2Me), 6.35 (d, J = 4.1 Hz, 1 H, 3-H), 7.10−7.35 (m, 5 H, Ph). **(4*S**,4a*S**,14a*R**)-4l:** ^1H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 3 H, Me), 0.14 (m, 1 H), 0.23 (s, 3 H, Me), 0.52 (m, 1 H), 0.90 (s, 9 H, *t*Bu), 0.75−1.7 (m, 17 H), 1.97 (dd, J = 5.2, J = 6.9 Hz, 1 H, 4a-H), 2.25 (ddd, 1 H, J = 14.7, J = 12.3, J = 2.9, 14-H), 3.83 (s, 3 H, CO_2Me), 4.23 (dd, J = 5.2, J = 1.7 Hz, 1 H, 4-H), 6.35 (dd, J = 1.7, J = 1.7 Hz, 1 H, 3-H), 7.15−7.35 (m, 5 H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$): δ = −3.87, −2.85, 18.3, 20.0, 21.3, 22.0, 22.5, 24.0, 24.4, 25.4, 26.2, 26.0, 26.9, 35.7, 39.5, 42.3, 52.1, 104.6, 113.7, 126.4, 128.4, 128.6, 141.9, 142.2, 163.3. R_f = 0.59 (cyclohexane/EtOAc, 8:2). **(4*R**,4a*S**,14a*S**) -5l:** ^1H NMR (400 MHz, $CDCl_3$): δ = 0.06 (s, 3 H, Me), 0.21 (s, 3 H, Me), 0.42 (m, 1 H), 0.90 (s, 9 H, *t*Bu), 0.75−2.1 (m, 20 H), 3.33 (dd, J = 10.8, J = 2.3 Hz, 1 H, 4-H), 3.76 (s, 3 H, CO_2Me), 6.00 (d, J = 2.3 Hz, 1 H, 3-H), 7.15−7.35 (m, 5 H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$): δ = −3.77, −2.53, 18.2, 20.3, 22.9, 23.0, 23.4, 24.0, 25.3, 25.4, 26.6, 27.4, 25.8, 38.0, 41.7, 44.6, 52.1, 104.0, 116.1, 126.8, 128.4, 128.6, 140.4, 143.3, 163.5. R_f = 0.65 (cyclohexane/EtOAc, 8:2). **(4*S**,4a*S**,14a*S**)-6l:** ^1H NMR (400 MHz, $CDCl_3$); (selected signals): δ = 0.09 (s, 3 H, Me), 0.23 (s, 3 H, Me), 0.80 (s, 9 H, *t*Bu), 3.66 (dd, J = 8.2, J = 4.8 Hz, 1 H, 4-H), 3.79 (s, 3 H, CO_2Me), 6.22 (t, J = 4.1 Hz, 1 H, 3-H), 7.10−7.35 (m, 5 H, Ph).

Methyl 4-Benzyloxy-8a-*tert*-butyldimethylsiloxy-4a,5,6,7,8,8a-hexahydro-4*H*-chromene-2-carboxylate (3n−5n): A mixture of diastereomers **3n/4n** (87:13, 93 mg, 19%) was obtained by Procedure 1A, from heterodiene **1b** (246 mg, 1.12 mmol) and dienophile **2h** (297 mg, 1.25 equiv.). A mixture of diastereomers **4n/5n** (11:89, 112 mg, 35%) was obtained by Procedure 2A ($SnCl_4$: 5%), from heterodiene **1b** (160 mg, 0.73 mmol) and dienophile **2h** (169 mg, 1.1 equiv.). IR (film): $\tilde{\nu}$ = 1741 (C=O, ester), 1654 (C=C, conjugated alkene). HRMS ($C_{24}H_{36}O_5Si$): calcd. 432.23318; found 432.2319. **(4*R**,4a*S**,8a*R**)-3n:** ^1H NMR (400 MHz, $CDCl_3$): δ = 0.11 (s, 3 H), 0.19 (s, 3 H), 0.8' (s, 9 H), 0.80−2.10 (m, 9 H), 3.78 (dd, J = 3.9, J = 3.5 Hz, 1 H, 4-H), 3.88 (s, 3 H), 4.53 (d, J = 11.8 Hz, 1 H), 4.64 (d, J = 11.8 Hz, 1 H), 6.33 (d, J = 3.9 Hz, 1 H, 3-H), 7.25−7.40 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = −3.2, −2.7, 18.0, 23.0, 25.7, 29.7, 33.9, 44.9, 52.5, 70.3, 72.2, 101.0, 109.1, 127.5, 127.9, 128.2, 138.3, 141.8, 163.7. **(4*R**,4a*S**,8a*S**)-5n:** ^1H NMR (400 MHz, $CDCl_3$): δ = 0.07 (s, 3 H), 0.16 (s, 3 H), 0.83 (s, 9 H), 1.20−1.70 (m, 7 H), 2.00 (m, 2 H, 4a-H and 8-H), 3.70 (m, 1 H, 4-H), 3.81 (s, 3 H), 4.52 (d, J = 11.8 Hz, 1 H), 4.63 (d, J = 11.8 Hz, 1 H), 6.24 (d, J = 3.8 Hz, 1 H, 3-H), 7.25−7.40 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = −2.7, −3.4, 18.0, 23.2, 23.0, 25.6, 27.0, 37.0, 43.9, 52.0, 70.3, 72.0.100.5 (8a-C), 108.6 (3-C); 127.9, 128.2, 128.3, 138.3, 141.5, 163.4. **(4*S**,4a*S**,8a*R**)-4n:** ^1H NMR (400 MHz, $CDCl_3$): δ = 0.01 (s, 3 H), 0.14 (s, 3 H), 0.77 (s, 9 H), 1.10−1.90 (m, 9 H), 3.78 (s, 3 H), 4.56 (m, 2 H), 4.68 (d, 1 H), 6.08 (dd, J = 2.1, J = 1.4, 1 H), 7.25−7.40 (m, 5 H). IR (neat): $\tilde{\nu}$ = 1728 (C=O) cm^{-1}, 1643 (C=C, conjugated alkene).

Methyl 4-(1,3-Benzodioxol-5-ylmethoxy)-8a-*tert*-butyldimethylsiloxy-4a,5,6,7,8,8a-hexahydro-4*H*-chromene-2-carboxylate (3−5o): A mixture of diastereomers **3o/4o** (86:14, 46 mg, 38%) was obtained by Procedure 1B, from heterodiene **1c** (67 mg, 0.254 mmol) and dienophile **2h** (68 mg, 1.25 equiv.). The diastereomers **3o/4o/5o** (32:18:50, 150 mg, 51%) were obtained by Procedure 2A ($SnCl_4$: 5%), from heterodiene **1c** (164 mg, 0.62 mmol) and dienophile **2h** (145 mg, 1.1 equiv.). IR (film): $\tilde{\nu}$ = 1741 (C=O, ester) cm^{-1}, 1654 (C=C, conjugated alkene). HRMS ($C_{25}H_{38}O_4Si$): calcd. 476.22301; found 476.2217. **(4*R**,4a*S**,8a*R**)-3o:** ^1H NMR (400 MHz, $CDCl_3$): δ = 0.10 (s, 3 H, $SiMe_2$), 0.19 (s, 3 H), 0.86 (s, 9 H, *t*Bu), 1.00−2.40 (m, 9 H), 3.77 (dd, J = 3.8, J = 3.4, 1 H), 3.83 (s, 3 H,

OMe), 4.16 (d, J = 10.6 Hz, 1 H), 4.31 (d, J = 10.6 Hz, 1 H), 5.97 (s, 2 H), 6.23 (d, J = 1.8 Hz, 1 H, 3-H), 6.7−6.9 (m, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = −3.3, −2.7, 18.0, 23.2, 23.0, 25.6, 27.0, 37.0, 43.9, 52.0, 70.3, 72.0, 100.5, 108.6, 127.9, 128.2, 128.3, 138.3, 141.5, 163.4. **(4*S**,4a*S**,8a*R**)-4o:** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.04 (s, 3 H), 0.17 (s, 3 H), 0.80 (s, 9 H, *t*Bu), 1.00−2.40 (m, 9 H), 3.80 (s, 3 H, OMe), 4.48 (d, J = 10.9 Hz, 1 H), 4.62 (d, J = 10.9 Hz, 1 H), 4.56 (m, 1 H), 5.97 (s, 2 H), 6.07 (dd, J = 1.6, J = 1.2 Hz, 1 H, 3-H), 6.7−6.9 (m, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = −3.8, −2.6, 17.8, 21.4, 23.1, 25.5, 27.8, 30.3, 43.8, 52.0, 70.5, 71.7, 100.5, 100.9, 108.1, 108.5, 108.6, 120.5, 132.1, 140.3, 147.0, 147.7, 162.9. **(4*R**,4a*S**,8a*S**)-5o:** ^{1}H NMR (400 MHz, $CDCl_3$): δ = −0.01 (s, 3 H, $SiMe_2$), 0.17 (s, 3 H), 0.83 (s, 9 H, *t*Bu), 1.00−2.10 (m, 9 H), 3.81 (s, 3 H, OMe), 3.90 (dd, J = 1.9, J = 10.2 Hz, 1 H), 4.38 (d, J = 11.1 Hz, 1 H), 4.60 (d, J = 11.1 Hz, 1 H), 5.95 (s, 2 H), 6.25 (d, J = 1.8 Hz, 1 H, 3-H), 6.7−6.9 (m, 3 H).

Methyl 4-*tert*-Butoxy-8a-*tert*-butyldimethylsiloxy-4a,5,6,7,8,8a-hexahydro-4*H*-chromene-2-carboxylate (3−5p): A mixture of diastereomers **3p/4p/5p** (13:50:37, 48 mg, 21%) was obtained by Procedure 2A ($SnCl_4$ 5%), from heterodiene **1d** (105 mg, 0.57 mmol) and dienophile **2h** (132 mg, 1.1 equiv.). IR (film): $\tilde{\nu}$ = 1733 (C=O, ester) cm^{-1}, 1648 (C=C, conjugated alkene). **(4*R**,4a*S**,8a*R**)-3p:** ^{1}H NMR (400 MHz, $CDCl_3$) (selected signals): δ = 0.06 (s, 3 H), 0.15 (s, 3 H), 0.86 (s, 9 H, *t*Bu), 1.20 (s, 9 H, *t*Bu), 3.77 (s, 3 H, OMe), 3.78 (m, 1 H, 4-H), 5.99 (d, J = 3.9 Hz, 1 H, 3-H). R_f = 0.47 (cyclohexane/EtOAc, 8:2). **(4*S**,4a*S**,8a*R**)-4p**: ^{1}H NMR (400 MHz, $CDCl_3$) (selected signals): δ = 0.05 (s, 3 H), 0.15 (s, 3 H), 0.85 (s, 9 H, *t*Bu), 1.20 (s, 9 H, *t*Bu), 3.75 (s, 3 H, OMe), 4.71 (dd, J = 6.4, J = 2.0 Hz, 1 H, 4-H), 5.88 (dd, J = 2.0, J = 1.5 Hz, 1 H, 3-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = −3.8, −2.6, 17.9, 22.3, 23.1, 24.4, 25.6, 28.1, 38.7, 44.1, 51.9, 64.0, 74.2, 101.7, 114.5, 139.2, 162.9. R_f = 0.50 (cyclohexane/EtOAc, 8:2). **(4*R**,4a*S**,8a*S**)-5p:** ^{1}H NMR (400 MHz, $CDCl_3$) (selected signals): δ = 0.00 (s, 3 H), 0.17 (s, 3 H), 0.88 (s, 9 H, *t*Bu), 1.21 (s, 9 H, *t*Bu), 3.76 (s, 3 H, OMe), 4.01 (dd, J = 10.3, J = 2.0 Hz, 1 H, 4-H), 6.03 (d, J = 2.0 Hz, 1 H, 3-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = −4.0, −2.9, 18.3, 22.9, 23.2, 25.3, 25.8, 28.4, 37.7, 45.8, 52.0, 65.6, 74.2, 101.9, 116.8, 140.1, 163.2. R_f = 0.50 (cyclohexane/EtOAc, 8:2).

Methyl 4-*tert*-Butoxy-2-(*tert*-butyldimethylsilyl)oxy-4-(2-oxocyclohexyl)-2-butenoate (8): This compound was obtained as a by-product of **3−5p** (95 mg, 42%, three isomers: 93:4:3), R_f = 0.50 (cyclohexane/EtOAc, 8:2). The major isomer was detected by the following signals. ^{1}H NMR (400 MHz, $CDCl_3$) (selected signals): δ = 0.18 (s, 3 H), 0.19 (s, 3 H), 0.90 (s, 9 H, *t*Bu), 1.15 (s, 9 H, *t*Bu), 3.72 (s, 3 H, OMe), 4.95 (dd, J = 8.4, J = 3.9 Hz, 1 H, 4-H), 6.02 (d, J = 8.4 Hz, 1 H, 3-H).). ^{13}C NMR (100 MHz, $CDCl_3$): δ = −4.1, −4.1, 18.6, 24.1, 25.9, 26.3, 27.1, 28.6, 41.9, 51.9, 5.5, 64.7, 74.0, 135.8, 138.2, 165.0, 209.9.

Methyl (4*S,4a*S**,8a*S**)-4-*tert*-Butoxy-8a-methoxy-4a,5,6,7,8,8a-hexahydro-4*H*-chromene-2-carboxylate (4q):** The heterodiene **1d** (2.76 g, 14.8 mmol) and the dienophile **2f** (1.83 g, 1.1 equiv.) were dissolved in dichloromethane (100 mL) in a round flask equipped with a magnetic stirrer, maintained under argon and placed in a cooling bath at −50 °C. A 1 M solution of $SnCl_4$ in dichloromethane (20 mol % proportions) was added dropwise and the resulting mixture was kept at −50 °C for 1 h. The reaction medium was hydrolysed by straightforward addition of a saturated aqueous solution of $NaHCO_3$ (20 mL). The aqueous phase was separated and extracted twice with ether. The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure, and the oily residue was chromatographed on silica gel with a 95:5 mixture of cyclohexane and EtOAc for the elution, and thus afforded the purified adduct **4q** (4.10 g, 93%), m.p. 74.5−75 °C (MeOH/H_2O, 1:1), as a single diastereomer. R_f = 0.55 (cyclohexane/EtOAc, 6:4). IR (KBr): $\tilde{\nu}$ = 1739 (C=O, ester) cm^{-1}, 1648 (C=C, conjugated alkene). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.05 (m, 1 H), 1.16 (m, 1 H), 1.22 (s, 9 H, *t*Bu), 1.26 (dd, J = 4.4, J = 13.3 Hz, 1 H, 8-H), 1.49 (m, 1 H), 1.64−1.79 (m, 3 H), 1.90 (m, 1 H, 5-H), 2.38 (m, 1 H, 8-H), 3.27 (s, 3 H, OMe), 3.77 (s, 3 H, CO_2Me), 4.66 (dd, J = 2.0, J = 6.9 Hz, 1 H, 4-H), 5.90 (dd, J = 1.5, J = 2.0 Hz, 1 H, 3-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.3, 22.4, 24.4, 28.0, 32.4, 41.9, 48.2, 51.8, 63.5, 74.1, 102.6, 115.4, 139.2, 162.8. $C_{16}H_{26}O_5$ (240.3): calcd. C 64.40, H 8.78; found C 64.35, H 8.76.

Methyl 4-Benzyloxy-2-methoxy-2-(2-naphthyl)-3,4-dihydro-2*H*-pyran-6-carboxylate (3r/4r): A mixture of diastereomers **3r/4r** (60:40, 48 mg, 52%) was obtained as a viscous yellow oil, R_f = 0.46 (cyclohexane/EtOAc, 7:3), by Procedure 1A (eluent: cyclohexane/EtOAc, 19:1), from heterodiene **1b** (50 mg, 0.23 mmol) and dienophile **2d** (48 mg, 1.1 equiv.). IR (film): $\tilde{\nu}$ = 1731 (C=O, ester) cm^{-1}, 1650 (C=C, conjugated alkene). HRMS (EI) ($C_{19}H_{21}O_5$): calcd. 328.1311; found 328.1315. ^{1}H NMR (400 MHz, $CDCl_3$): **3r:** δ = 2.13 (dd, J = 14.8, J = 6.5 Hz, 1 H, 3-H), 2.61 (ddd, J = 14.8, J = 2.8, J = 1.2 Hz, 1 H, 3-H), 3.16 (s, 3 H), 3.89 (s, 3 H), 3.98 (m, 1 H, 4-H), 4.68 (s, 2 H), 6.43 (dd, J = 4.0, J = 0.8 Hz, 1 H, 5-H), 7.27−8.05 (m, 12 H); **4r:** δ = 1.89 (dd, J = 13.3, J = 10.8 Hz, 1 H, 3-H), 2.66 (ddd, J = 13.2, J = 6.8, J = 1.6 Hz, 1 H, 3-H), 3.09 (s, 3 H), 3.89 (s, 3 H), 3.89 (m, 1 H, 4-H), 4.59 (d, J = 11.6 Hz, 1 H), 4.64 (d, J = 11.6 Hz, 1 H), 6.39 (t, 1 H, J = 1.9, 5-H), 7.22−8.10 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): **3r**: δ: 40.3, 50.9, 52.4, 66.1, 70.4, 101.3, 111.5, 123.6−128.5, 133.0, 137.1, 138.2, 142.0, 163.2; **4r:** δ: 38.3, 49.5, 51.3, 67.9, 69.7, 102.4, 112.1, 121.0−129.2, 132.0, 132.1, 132.2, 135.8, 137.0, 140.2, 162.1.

Methyl 4-*tert*-Butoxy-2-methoxy-2-(2-naphthyl)-3,4-dihydro-2*H*-pyran-6-carboxylate (4s): A mixture of diastereomers **3s/4s** (45:55, 279 mg, 75%) was obtained as a viscous, yellow oil by Procedure 1A (eluent: cyclohexane/EtOAc, 4:1), from heterodiene **1d** (200 mg, 1 mmol) and dienophile **2d** (205 mg, 1.25 equiv.). The adduct **4s** (279 mg, 75%) was obtained as a single isomer by Procedure 2B (eluent: cyclohexane/EtOAc, 4:1), from heterodiene **1d** (200 mg, 1 mmol) and dienophile **2d** (368 mg, 2 equiv.). R_f = 0.43 (cyclohexane/EtOAc, 8:2). IR (film): $\tilde{\nu}$ = 1733 (C=O, ester) cm^{-1}, 1648 (C=C, conjugated alkene). HRMS (EI) ($C_{19}H_{21}O_5$): calcd. 370.1780; found 370.1779. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25 (s, 9 H), 1.83 (dd, J = 13.6, J = 10.5 Hz, 1 H, 3-H), 2.42 (ddd, J = 13.6, J = 6.9, J = 1.5 Hz, 1 H, 3-H), 3.11 (s, 3 H), 3.86 (s, 3 H), 4.66 (ddd, J = 10.4, J = 6.9, J = 2.2 Hz, 1 H, 4-H), 6.43 (t, J = 1.9 Hz, 1 H, 5-H); 7.40−8.00 (m, 7 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.1, 41.7, 50.5, 52.1, 61.8, 74.4, 103.5, 116.4, 123.6−142.4, 163.1. **3s:** ^{1}H NMR (400 MHz, $CDCl_3$); δ = 1.20 (s, 9 H), 2.34 (dd, J = 14.2, J = 6.6 Hz, 1 H, 3-H), 2.43 (dd, J = 14.2, J = 6.6 Hz, 1 H, 3-H), 3.16 (s, 3 H), 3.87 (s, 3 H), 3.98 (m, 1 H, 4-H), 6.16 (d, J = 3.6 Hz, 1 H, 5-H); 7.25−8.00 (m, 7 H). ^{13}C NMR (100 MHz, $CDCl_3$), δ = 28.0, 42.5, 50.8, 52.3, 60.7, 74.7 102.1, 115.2, 123.5−141.5, 163.1.

Methyl 2,4-Dimethoxy-2-(2-naphthyl)-3,4-dihydro-2*H*-pyran-6-carboxylate (3t/4t): This compound (83 mg, 25%) was isolated as a by-product of **4s** in Procedure 2B. R_f = 0.31 (cyclohexane/EtOAc, 8:2), IR (film): $\tilde{\nu}$ = 1731 (C=O, ester) cm^{-1}, 1654 (C=C, conjugated alkene). HRMS (EI) ($C_{19}H_{20}O_5$): calcd. 328.1311; found 328.1311. **3t:** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.13 (dd, J = 15.0, J = 6.5 Hz, 1 H, 3-H), 2.58 (ddd, J = 15.0, J = 2.3, J = 1.4 Hz, 1 H, 3-H), 3.14 (s, 3 H), 3.47 (s, 3 H), 3.80 (m, 1 H, 4-H), 3.89 (s, 3 H), 6.49 (dd, J = 4.1, J = 1.3 Hz, 1 H, 5-H); 7.26−8.03 (m, 7 H). ^{13}C

Table 6. X-ray crystallographic data for compounds **3h**, **5h** and **4q**

Compound	**3h**	**5h**	**4q**
Empirical formula	$C_{16}H_{26}0_5$	$C_{23}H_{34}0_4Si$	$C_{23}H_{34}0_4Si$
Formula mass [g·mol^{-1}]	298.37	402.59	402.59
Unit cell dimensions			
a [Å]	13.781(1)	28.084(3)	9.459(2)
b [Å]	29.081(5)	8.3502(7)	11.159(2)
c [Å]	8.430(1)	20.303(2)	12.489(2)
α [°]	90	90	89.41(1)
β [°]	90	98.37(2)	72.02(1)
γ [°]	90	90	70.12(1)
V [Å^3], *Z*	3378.5(7), 8	4710.5(9), 8	1172.5(2), 2
Calculated density [g·cm^{-3}]	1.173	1.135	1.140
Crystal system, space group	orthorhombic, *Pccn*	monoclinic, *C*2/*c*	triclinic, $P\bar{1}$
T [K], scan method	293, ω	293, 2θ/ω	293, 2θ/ω
2θ range for data collection [°]	2−50	2−60	2−50
$(h,k,l)_{min}$; $(h,k,kl)_{max}$	−16,−34,−10; 16,34,10	−39,−11,−28; 39,11,28	−10,−13,0; 10,13,14
Absorption correction, μ [mm^{-1}]	not applied, 0.09	not applied, 0.12	not applied, 0.12
Reflection and refined numbers	2965, 196	6914, 276	3845, 285
Goodness of fit (F^2)	1.028	1.029	1.063
R_1 [$I > 2\sigma(I)$], wR_2 (all data)	0.0535, 0.1375	0.0536, 0.1809	0.0783, 0.2423

NMR (100 MHz, $CDCl_3$): δ = 40.2, 50.9, 52.4, 56.8, 69.0, 101.5, 110.7, 123.5−141.7, 163.2. **4t:** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.77 (dd, *J* = 13.2, *J* = 10.7 Hz, 1 H, 3-H), 2.63 (ddd, 1 H, *J* = 13.2, *J* = 6.8, 3-H), 3.10 (s, 3 H), 3.41 (s, 3 H), 3.88 (s, 3 H), 4.41 (ddd, *J* = 12.8, *J* = 6.7, *J* = 2.0 Hz, 1 H, 4-H), 6.34 (t, *J* = 1.9 Hz, 1 H, 5-H), 7.47−8.07 (m, 7 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 38.1, 49.7, 51.5, 55.3, 69.7, 102.6, 118.8, 122.7−140.3, 162.2.

X-ray Crystal Structure Determination of 3h, 5h and 4q: A single crystal, selected with the aid of an optical microscope, was mounted on a glass fibre. The crystal cell parameters were obtained by a random reflection search, and X-ray diffraction data were collected with a Siemens AED 2 four-circle diffractometer equipped with graphite-monochromated Mo-$K_{\alpha 1}$ radiation (λ = 0.71073 Å). The intensities of the reflections were corrected for Lorentz and polarisation effects but no absorption correction was applied. The scattering factors and the anomalous dispersions corrections for all atoms were taken from the "International Tables for X-ray Crystallography". The crystallographic data and information about data collection are given in Table 6. The space group was deduced from the observed systematic extinctions. The structure was solved by direct methods with the SHELXS-86 program and successive refinements and difference Fourier maps with the SHELXL-97 program. The location of the hydrogen atoms was performed by applying the geometrical constraints using AFIX and DFIX option in the SHELXL-97 program. Crystallographic data of the structures have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-165571 (**3h**), -165572 (**5h**), -165573 (**4q**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: (internat.) +44−1223/336−033; E-mail: deposit@ccdc.cam.ac.uk).

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