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Tandem Mukaiyama Michael–aldol reactions catalysed by samarium diiodide

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Dedicated to Professor H. B. Kagan on the occasion of his 70th birthday

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Abstract—Samarium diiodide is an efficient precatalyst for tandem Michael–aldol reactions, which allow the formation of two carbon–carbon bonds by successive additions of a ketene silyl acetal and an aldehyde on cyclic α,β-unsaturated ketones. The adducts are isolated as silyl ethers, in good yields, and in some cases with high diastereoselectivities when the reactions are performed at low temperatures. Comparative study of the activities of other lanthanide iodides for the same tandem reactions is presented. A key step for a formal synthesis of $PGF_{2\alpha}$ has been performed by a tandem Michael–aldol samarium-catalysed sequence.

1. Introduction

The realization of successive reactions leading to the formation of several bonds by one-pot procedures affords useful methodologies for the preparation of complex molecules. The minimization of the number of steps not only provides more efficient syntheses but also allows the reduction of waste production and the diminution of costs. The so-called domino, cascade or tandem reactions have been the focus of several reviews.[1] Amongst the large panel of transformations described up to now, a major part concerns radical or anionic processes and/or intramolecular reactions leading to the formation of one or several cycles.[2] The use of metal catalysts in tandem reactions has been recently investigated, although the possibility to control the stereo and/or enantioselectivity in the formation of several stereogenic centres offers a promising area.[3] Three-component reactions, leading to the successive formation of two bonds using a single catalyst are currently studied, and Lewis acid catalysed reactions have been reported.[4–6] Lanthanide and scandium triflates activate imines and are efficient catalysts for a large range of three-component reactions involving the in situ formation of an imine followed by carbon–carbon bond formation.[5a–j] Similar examples of three-component coupling reactions catalysed by lanthanide halides have been recently described.[6] Lanthanide triflates catalyse a sequence of allylation and acylation reactions,[7] and bismuth chloride catalyse tandem aldolization–halogenation reactions.[8] However, the successive formation of two carbon–carbon bonds by Lewis acids catalysed reactions is poorly documented.[4g]

The fixation of two carbon chains in α,β-position of enones by three-component couplings is frequently used in synthesis, especially for prostaglandins.[9] They involve a Michael addition of an organometallic derivative on the enone followed by an alkylation reaction. Two groups have performed enantioselective catalysis of cascades of Michael–aldol reaction.[10] Feringa studied an enantioselective Michael addition of an organometallic on an enone catalysed by $Cu(OTf)_2$ in the presence of a chiral phosphorus ligand, the intermediate being trapped by an aldehyde.[10a] By catalysis with heterobimetallic binaphthoxides, Shibasaki realized three-component couplings, resulting in a direct Michael reaction followed by an aldol reaction on one hand[10b] and tandem inter-intramolecular nitroaldol reactions on the other hand.[10c]

An alternative route to realize the formation of two carbon–carbon bonds on enones by a one-pot process is a Michael reaction of a silyl derivative on an α,β-unsaturated ketone followed by an aldol reaction of the in situ formed enoxysilane with a carbonyl compound. To the best of our knowledge, trityl salts are the sole catalysts reported for these tandem Mukaiyama Michael–aldol reactions,[†] as well as for two tandem Michael additions.[11] A similar intermolecular Mukaiyama–Michael/Michael/aldol sequence promoted by $TiCl_3(O\text{-}i\text{Pr})$ has been carried out for the

Keywords: samarium diiodide; catalysis; tandem reactions; Michael reactions; aldol reactions.

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[†] Recently, Mukaiyama aldol and Michael reactions catalysed by iridium complexes have been reported, with one example of tandem Michael–aldol reaction.[11h]

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Table 1. Tandem Mukaiyama Michael–aldol reactions catalysed by samarium diiodide

Entry	α,β-Unsaturated ketone	Aldehyde[a]	Ketene silyl acetal	*T* (°C)	Product	**4/5**[b]	Yield[c] (%)
1	Cyclohexen-2-one	Benzaldehyde	**2a**	rt	**4a**+**5a**+**6a**	44/39/17	73[d]
2	Cyclohexen-2-one	Benzaldehyde	**2a**	−60	**4a**+**5a**	98/2	70
3	Cyclohexen-2-one	*p*-Trifluorobenzaldehyde	**2a**	−10	**4b**+**5b**	60/40	45
4	Cyclohexen-2-one	*p*-Trifluorobenzaldehyde	**2a**	−60	**4b**+**5b**	95/5	67
5	Cyclohexen-2-one	Crotonaldehyde[e]	**2a**	0	**4c**+**5c**+**6c**	40/40/20[f]	30
6	Cyclohexen-2-one	Benzaldehyde	**2b**	−60	**4d**+**5d**	95/5	42
7	Cyclohexen-2-one	Benzaldehyde	**2c**	−60	**4e**+**4e**	90/10	85[g]
8	Cyclopenten-2-one	Benzaldehyde	**2a**	−30	**4f**+**5f**	80/20	77
9	Cyclopenten-2-one	Benzaldehyde	**2a**	−60	**4f**+**5f**	100/0	88
10	Cyclopenten-2-one	Cinnamaldehyde	**2a**	−60	**4g**+**5g**	95/5	72
11	Cyclopenten-2-one	*trans*-Octen-2-al	**2a**	rt	**4h**+**5h**	n.d.	5[d,h]
12	Cyclopenten-2-one	*trans*-Octen-2-al	**2a**	−20	**4h**+**5h**	n.d.	40[d]
13	Cyclopenten-2-one	*trans*-Octen-2-al	**2a**	−40	**4h**+**5h**	n.d.	70[d]
14	Cyclopenten-2-one	*trans*-Octen-2-al	**2a**	−60	**4h**+**5h**	95/5	74
15	Cyclopenten-2-one	Benzaldehyde	**2b**	−30	**4i**+**5i**	83/17	71
16	Cyclopenten-2-one	Benzaldehyde	**2b**	−60	**4i**+**5i**	92/8	82
17	Cyclopenten-2-one	Cinnamaldehyde	**2b**	rt	**4j**+**5j**	n.d.	83[d]
18	Cyclopenten-2-one	Cinnamaldehyde	**2b**	−60	**4j**+**5j**	60/40	63
19	Cyclopenten-2-one	*trans*-Octen-2-al	**2b**	−60	**4k**+**5k**	59/41[i]	72

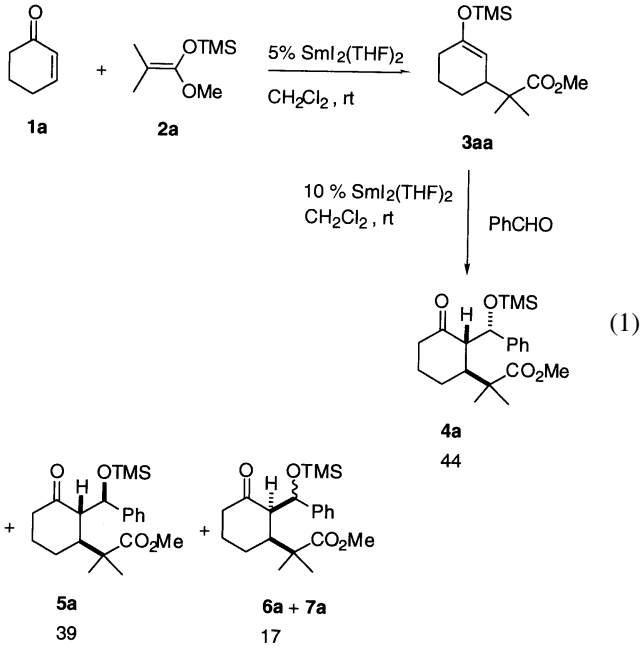
[a] 10% $SmI_2(THF)_2$ in 10 mL CH_2Cl_2; ratio **1/2**: 1/1.5.
[b] Diastereoisomer ratios measured by GC and ^1H NMR.
[c] Isolated yield, %.
[d] Yield in crude product, %.
[e] 5 equiv. Crotonaldehyde.
[f] Diastereoisomer ratios measured by GC on the crude product: 58/26/10/6.
[g] Yield in crude product.
[h] Formation of 1-trimethylsilyloxy-1,3-octadiene **9** as the major product.
[i] The four diastereomers are observed in the crude product, GC ratio: 47/33/12/8.

synthesis of pentasubstituted arenes, however, it requires four equivalents of the Lewis acid. Otherwise, a one pot tandem Michael–imino aldol reaction needs two different catalysts for the sequential Michael–aldol reactions.[12]

In the course of our investigations concerning the properties of samarium diiodide and lanthanide iodides as Lewis acids, we found that these compounds are the precursors of efficient catalysts for various reactions including Mukaiyama aldol and Michael reactions.[13] Particularly, the use of samarium diiodide allows to perform selective 1,4-addition of ketene silyl acetals onto ketones and to isolate the adducts as enoxysilanes. Similarly, aldol reactions of carbonyl compounds with ketene silyl acetals, but also with enoxysilanes, are catalysed by samarium diiodide and various lanthanide iodides. This prompted us to study the catalysis of a sequence of Michael addition and aldol reaction by a one-pot procedure. We have already reported our first results concerning the use of samarium diiodide as a catalyst precursor for tandem Mukaiyama-aldol reactions on cyclic α,β unsaturated ketones.[14] We wish to present now our extensive study including a comparison with other lanthanide derivatives and an application to a formal synthesis of the prostaglandin $PGF_{2\alpha}$.

2. Results

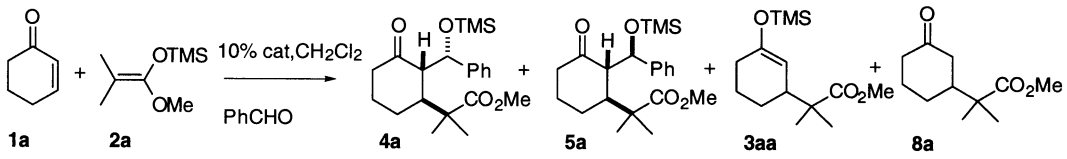
In a preliminary study, we have examined the catalytic activity of samarium diiodide for the sequential addition of silyl ketene acetal **2a** and benzaldehyde on cyclohexen-2-one, and optimized the conditions for this tandem reaction. We first prepared the desired product by a stepwise procedure (Eq. (1)). Reaction of **2a** with cyclohexen-2-one using 5 mol% $SmI_2(THF)_2$ as catalyst in methylene chloride at room temperature, led to the enoxysilane **3aa** isolated according to the previously described procedure.[13c] The reaction of this enoxysilane **3aa** with benzaldehyde in the presence of a catalytic amount of samarium diiodide (10 mol%) in methylene chloride at room temperature afforded the aldol products in moderate yield (76% in crude product), as a mixture of diastereoisomers **4a**, **5a**, **6a** or **7a** (44/39/17).



(1)

The same adduct could be obtained in a one-pot procedure

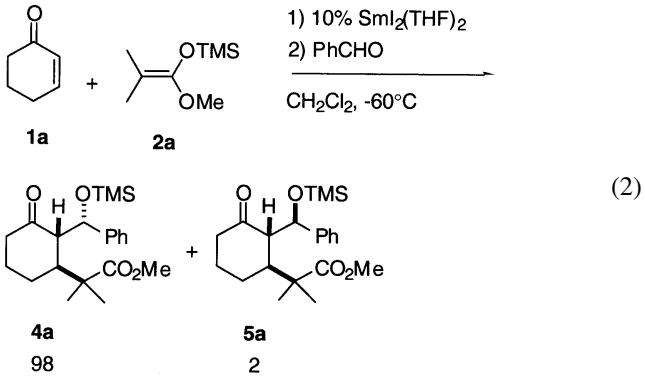
Table 2. Influence of the catalyst on a Mukaiyama–aldol tandem reaction



Entry	Catalyst	Temperature (°C)	Time (h)	4a+5a[a]	3aa/8a	4a/5a
1	$SmI_2(THF)_2$	−60	36	100		95:5
2	$SmI_3(THF)_3$	−60	20	20	30:70	55:45
3	$SmI_2(OtBu)(THF)_3$	−60	20	19	30:70	76:24
4	$YbI_2(THF)_2$	−60	20	81		78:22
5	$YbI_3(THF)_3$	−60	28	93		97:3
6	$LaI_3(DME)_2$	−60	28	100		97:3
7	$Yb(OTf)_3$	−60	22	6	100:0	
8		rt	28	8	82:18	
9	$Sc(OTf)_3$	−60	22	100[b]		93:7
10		−30	2	87[b]		80:20
11		rt	1	90[b]		55:45
12	BiI_3	−60	36	0	100:0	
13		−20	6	0	100:0	

[a] Yield % in adducts **4**+**5** in the crude product determined by GC/MS.
[b] Determined on an aliquot by GC/MS.

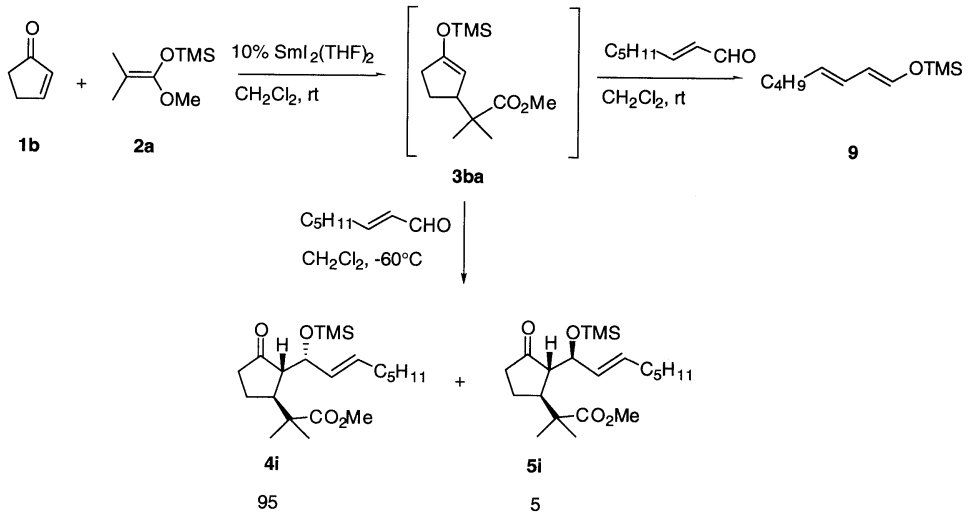
by successive additions of ketene silyl acetal **2a**, cyclohexen-2-one and benzaldehyde on 10 mol% $SmI_2(THF)_2$ suspended in methylene chloride at room temperature (Table 1, entry 1). The yield in the tandem product (73% in crude material) and the diastereoselectivity (44/37/19) are close to those found in the stepwise procedure. We have shown, in our previous studies, that a decrease of reaction temperature afforded better yields for aldolizations catalysed by samarium diiodide involving 1-trimethylsilyloxycyclohexene, which was explained by the suppression of crotonization reactions.[13c] We were pleased to find that performing the tandem reactions at −60°C permitted to improve not only the yield in adducts **4a**+**5a** but also the diastereoselectivity (Eq. (2)). Only the two diastereoisomers **4a** and **5a** with the two chains linked to the cycle in *trans* positions are isolated as the silyl ethers, in the ratio **4/5** of 98/2 (see below for structure assignment). Surprisingly, at low temperature, the stepwise reaction did not furnish the tandem adducts. After reacting **3aa** and benzaldehyde for 36 h at −60°C in the presence of 10 mol% $SmI_2(THF)_2$, a GC analysis of an aliquot showed the presence of the enoxysilane **3aa** and of the corresponding ketone **8a**. When the reaction mixture was allowed to stand up slowly to room temperature, the aldol reaction occurred and **3aa** was transformed into the tandem product as a mixture of three diastereomers with a ratio close to that found for the stepwise reaction at room temperature (36/42/21).



(2)

Influence of the reaction temperature was also studied on the tandem reaction involving cyclopenten-2-one **1b**, ketenesilyl acetal **2a**, and *E*-octen-2-al (Eq. (3), Table 1, entries 11–14). When the reaction was realized through a one-pot sequence at room temperature, GC/MS analyses of the crude product indicated the presence of tandem addducts in trace amounts while *E*-octen-2-al was converted in 1-trimethylsilyloxy-1-3-octadiene **9**. The formation of **9** can be explained by an enolization reaction of *E*-octen-2-al by the enoxysilane **3ba** (resulting from Michael addition of ketenesilyl acetal **2a** to cyclopenten-2-one **1b**). This reaction is similar to the transformation of ketones in enoxysilanes with ketenesilyl acetal **2a** catalysed by samarium diiodide that we have previously reported.[15] A decrease of the reaction temperature has more pronounced effect on the rate of enolization of *E*-octen-2-al than on the rate of the aldol reaction. The tandem product is selectively obtained at −60°C. Addition of *E*-octen-2-al on the intermediate enoxysilane **3ba** is 1,2-regioselective as was previously observed for the reaction of *E*-octen-2-al with **2b** catalysed by samarium diiodide.[13c] In the tandem reactions above, after addition of α,β-unsaturated ketone **1a** or **b**, the blue colour characteristic of samarium diiodide disappears and the reaction mixture keeps a pale yellow colour until the end of the reaction. Therefore, the true catalyst is trivalent and samarium diiodide is not the active species as for other reactions using samarium diiodide as a precatalyst.[13]

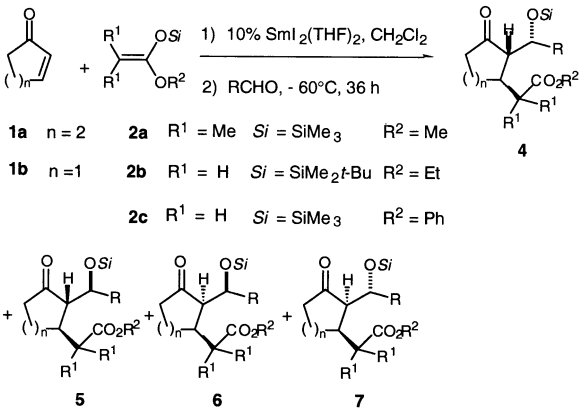
After optimization of the tandem reaction catalysed by $SmI_2(THF)_2$ leading to adduct **4a** we have evaluated the catalytic activity of other lanthanide derivatives under the same experimental conditions (Table 2). We have first studied the behaviour of some lanthanide iodides that we have previously found to catalyse efficiently several reactions including aldolizations.[13] By the use of trivalent samarium iodides in catalytic amounts (10 mol%), we obtained only products resulting from the Michael addition, as a mixture of the enoxysilane **3aa** and of the corresponding ketone **8a** (entries 2 and 3). The divalent ytterbium iodide (entry 4) allowed to carry out the tandem sequence



(3)

but the diastereoselectivity of the aldolization was lower than that provided by samarium diiodide. On the contrary, trivalent ytterbium and lanthanum iodides led to the tandem adducts in good yields and with high diastereoselectivities (entries 5 and 6). Amongst the numerous Lewis acid catalysts, ytterbium and scandium triflates are now well known for their high efficiency in a wide range of reactions.[16] Recently, it has been reported that $BiCl_3$-metallic iodides systems, leading to in situ formation of BiI_3, catalyse Mukaiyama and Michael reactions.[17] The catalytic activities displayed by these three compounds and by lanthanide iodides have been compared for the same tandem reaction. Ytterbium triflate (entries 7 and 8) at low temperature or room temperature afforded only the intermediate enoxysilane **3aa** (with only a small amount of ketone **8a**), as did also bismuth iodide (entry 12). These two derivatives are unable to perform successively the Michael and the aldol reactions. To the best of our knowledge, no three-component reaction catalysed by ytterbium triflate, involving the formation of two carbon–carbon bonds has been reported yet. In the case of scandium triflate, monitoring the reaction by GC/MS on aliquots, indicated a higher rate of the tandem reaction than with other catalysts (entries 9–11). As with samarium diiodide, higher diastereoselectivity is displayed at low temperature. Yet, several procedures have been tested for quenching the reaction mixtures, which led, in all cases, to decomposition without isolation of the tandem product. This can be explained by the higher acidity of scandium triflate compared to that of lanthanide iodides and by the liberation of triflic acid during hydrolysis which reacts with the very sensitive tandem adducts. The results gathered in Table 2 indicate that samarium diiodide, as well as ytterbium and lanthanum triiodides have similar activities and allow to prepare tandem adducts with high diastereoselectivity. However, samarium diiodide being commercially available, and more easily prepared[18] than ytterbium or lanthanum triiodides[19] was selected in our further investigations.

A variety of tandem Michael–aldol reactions on cyclohexen-2-one or cyclopenten-2-one catalysed by samarium diiodide have been successfully performed with ketene silyl acetals **2a**, **b** or **c** and different aromatic and α,β-unsaturated aldehydes (Eq. (4), Table 1, Fig. 1). In all cases, regioselective 1,4 addition on the ketone is observed in the first step, and, with α,β-conjugated aldehydes, regioselective 1,2 addition in the second step. The tandem adducts are isolated as silyl ethers in good yields in all the reactions proceeding at low temperature.

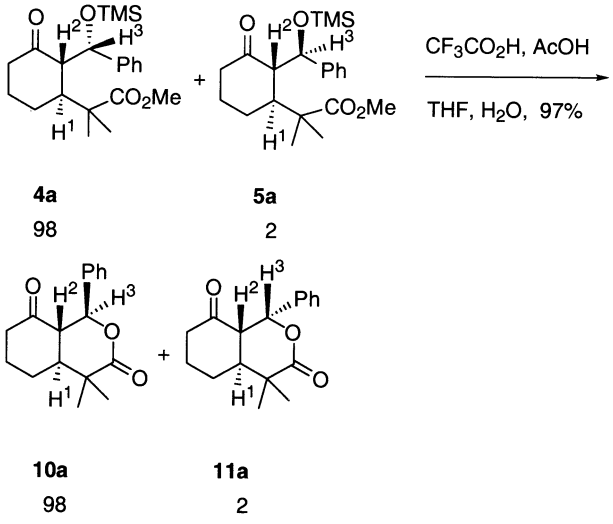


(4)

The selectivity for aldolization versus Michael reaction in the second step is consistent with our previous results for aldol reactions catalysed by samarium diiodide.[13c] We reported that reactions involving α,β-unsaturated aldehydes in most cases led to mixtures of 1,2- and 1,4-additions. Products were isolated as silyl ethers, with aldols as major products and selectivity depending on the silyl substrates. Higher ratios of aldol products were found with the less bulky ketene silyl acetals. A regioselective 1,2-addition was observed in the reaction of 1-trimethylsilylcyclohexene with cinnamaldehyde, which is close to the aldol step of the tandem reaction.

The structure of the major diastereoisomer has been established as **4**. This isomer results from the *trans* attachment of the two chains on the cycle, and a *syn* stereochemistry arising from the second step. This structure was assigned on the basis of the values of coupling constants measured in the ^1H NMR spectra of the major diastereomer **4a** and of the corresponding lactone **10a** (Eq. (5)). Coupling constants J (H^1–H^2)=12.3 Hz and J (H^2–H^3)=10.8 Hz for the lactone

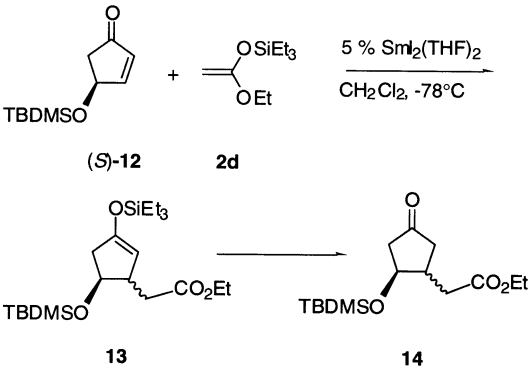
10a are indicative of a *trans–trans* stereochemistry. The two chains are in *trans* configuration in the adduct **4a**. The coupling constant J (H^2–H^3)=5.1 Hz for adduct **4a** indicates the *syn* position of these two protons.[13c]



(5)

The diastereoselectivities of tandem reactions depend on the substrates and can be very high in some cases (Table 1, entries 2, 4, 6, 10, 14 and 16). For most adducts, only two diastereomers were isolated: they result from the fixation of the two chains in *trans* positions on the enone. The two chiral carbons ligating the second bond formed in the tandem process are always in a *syn* relationship in the major isomer. Similarly, aldol reaction between 1-trimethylsilylcyclohexene and *p*-anisaldehyde catalysed by samarium diiodide afforded a mixture of diastereoisomers with the *syn* isomer favoured.[13c] The diastereoselectivity of the aldol step in tandem reactions increases at low temperature as was shown above, but depends also on the ketene silyl acetal. Reactions involving the silyl derivative **2a** afforded higher ratios **4**:**5** than those involving **2b** (compare entries 9 and 16, 10 and 18, 14 and 19). This can be explained by the difference of steric hindrance of the intermediate enoxysilanes **3ba** and **3bb**. The bulkiness due to methyl substituents increases the diastereofacial selectivity in the reaction of aldehydes on enoxysilanes. Similarly, Mukaiyama observed high diastereoselectivities for the tandem Michael–aldol reactions on cyclic ketones catalysed by trityl perchlorate with the same major diastereomer. In these reactions, only a bulky ketenesilyl acetal similar to **2a** (TBDMS instead of TMS) has been tested.[11b]

The tandem Michael–aldol reaction catalysed by samarium diiodide is a staightforward method for introducing two chains in α and β position of a cyclic α,β-unsaturated ketone and we planned to apply this methodology to a synthesis of a molecule of biological interest. As a key step in the synthesis of $PGF_{2\alpha}$, Danishefsky has proposed a new route involving the Michael addition of ketene acetal **2d** on the enantiopure substituted cyclopentenone **12**, followed by an aldol reaction on the resulting enoxysilane **13**.[20] The first reaction is catalysed by HgI_2 and the second promoted by $TiCl_4$. We anticipated that this reaction could be realized with samarium diiodide in a one-pot procedure. The substrate (*S*)-**12** was prepared according to published methods, by oxidation of cyclopentadiene to *cis*-3,5-diacetoxyclopentene.[21] This compound is hydrolysed by acetyl chlolinesterase in the corresponding enantiopure monoacetate (3*R*)-acetoxy,(5*S*)-hydroxycyclopent-1-ene.[22] This latter compound is transformed in ketone (*S*)-**12** by a described procedure.[23] We first examined the diastereoselectivity of the Michael reaction catalysed by samarium diiodide leading to enoxysilane **13** (Eq. (6)). As in studies described above, we found that both the chemoselectivity and the stereoselectivity of the Michael addition were improved by lowering temperature. At −78°C, enolization of ketone (*S*)-**12** did not occur and we found by GC a 85/15 ratio for the diastereoisomers of ketone **14** produced by hydrolysis of enoxysilane **13**. We could not attribute the stereochemistry to each of these isomers. Otera has studied the stereoselectivity of Michael additions on enone **12** catalysed by several Lewis acids and found a preference for the *syn* diastereomer in reactions involving unsubstituted ketene silyl acetals.[24] This allows to suppose that the *syn* isomer of enoxysilane **13** is the major one, as will be confirmed below.



(6)

Then we performed a tandem Michael–aldol reaction catalysed by samarium diiodide by an addition of ketene silyl acetal **2d** on ketone (*S*)-**12** for the Michael step and of *E*-octen-2-al for the aldol reaction (Eq. (7)). The tandem product **15** was isolated as a triethylsilyl ether, while in the described procedure, the crude product resulting from the addition of *E*-octen-2-al was directly transformed in allylic acetate.[20] In the samarium-catalysed tandem sequence, the addition of *E*-octen-2-al is 1,2-regioselective as found with other enoxysilanes, and leads to only one diastereomer. The structure of compound **15** was established by 2D NMR COSY and NOESY experiments. This allowed us to establish a *cis* relationship for protons H^1 and H^2, *trans* for H^2 and H^3 and *syn* for H^3 and H^4. The *cis* relationship between H^1 and H^2 indicates a *syn* configuration for the major isomer of enoxysilane **13**. Thus stereoselectivity of the Michael addition of ketenesilyl acetal **2d** on ketone (*S*)-**12** is similar with samarium diiodide and with other Lewis acids.[24] The isolation of only one diastereomer for adduct **15** can be explained either by a lower reactivity of the minor isomer of **13** towards *E*-octen-2-al, or by degradation of the minor stereoisomers of **15** during purification. Comparison of the NMR spectra of crude product and product **15** after chromatography on silica confirms the second hypothesis. The diastereoisomer formed by aldolization on *syn*-**13**, results of a *trans* addition on the cycle and

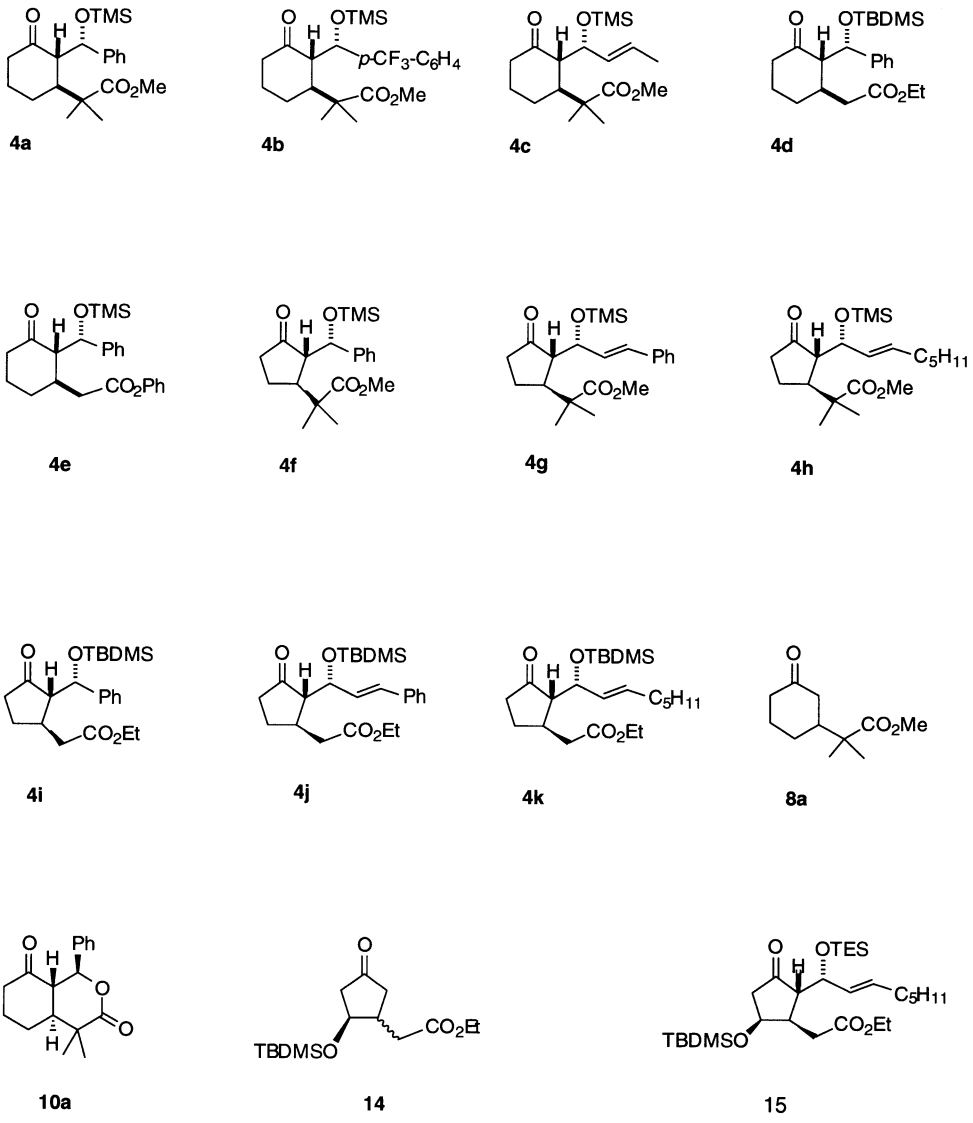
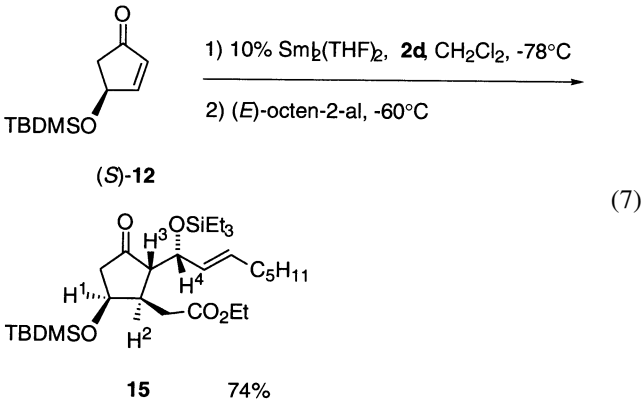


Figure 1.



(7)

displays *syn* stereochemistry of the carbons of the second bond, similarly to the major stereoisomer in all tandem reactions. In sequences involving cyclopenten-2-one and *E*-octen-2-al (Table 1, entries 14 and 19), higher selectivity was obtained with ketenesilyl acetal **2a** than with **b**. Thus, the high selectivity observed in the aldol reaction providing **15** can be due either to the steric hindrance introduced by the *tert*-butyldimethylsilyloxy group, or to the size of the silyl group of the acetal. We have found that catalysis by samarium diiodide of Michael–aldol reaction on ketone (*S*)-**12** furnishes similar results to sequential reactions described by Danishefsky. The desired product is obtained with the same stereochemistry and yield. Thus, we have improved the previously reported method for the formal synthesis of $PGF_{2\alpha}$, by performing tandem reactions with a catalytic amount of samarium diiodide.

3. Conclusion

We have shown that samarium diiodide is a highly efficient precatalyst for tandem Mukaiyama Michael–aldol reaction. The process requires only small amounts of catalyst and leads to the fixation of two chains in α and β positions of an α,β-unsaturated ketone. The stereoselectivity can be controlled on the three formed stereogenic centres. The potential of the procedure is highlighted by a successful application on a key step of synthesis of $PGF^{2\alpha}$. The use of samarium diiodide as a Lewis acid catalyst provides a

new attractive methodology for the formation of two carbon–carbon bonds by a one-pot procedure. We are currently studying in our laboratory other tandem sequences catalysed by samarium diiodide.

4. Experimental

4.1. General

All manipulations were carried out under an argon atmosphere using standard Schlenk or glovebox techniques. THF was distilled from sodium benzophenone ketyl, methylene dichloride (stabilized with amylene) from calcium hydride and all solvents were degassed immediately prior to use. Silyl ketene acetal **2a** was purchased from Aldrich. **2b** and **c** were prepared according to Tamura's procedure[25] and **2d** to Rousseau's procedure.[26] The method for preparing $SmI_2(THF)_2$, $YbI_2(THF)_2$[18] and *t*BuOS$mI_2(THF)_3$,[27] has been previously described by us as well as $LaI_3(DME)_2$ and $YbI_3(DME)_2$ which were prepared from La or Yb powder and iodine.[19]

Bruker AM 250 and AM 400 spectrometers, operating at 250 and 400 MHz for ^1H, 62.9 and 100.8 MHz for ^{13}C were used for the NMR spectra. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane for spectra in $CDCl_3$. Infrared spectra were recorded as Nujol mulls using NaCl plates on a Perkin–Elmer 883 spectrometer (FTIR) and are reported in cm^{-1}. Mass spectra (MS) (70 eV) data were determined on a Ribermag R-10 GC/MS and high-resolution mass spectra and electrospray mass spectra on a Varian 3400 GC-LC/MS. Flash chromatography was realized using 230–400 mesh silica gel desactivated by Et_3N.

4.2. Typical procedure for the synthesis of tandem products

A solution of SmI_2 in THF (0.2 M, 2.0 mL, 0.2 mmol) was carefully evaporated in vacuo to give $SmI_2(THF)_2$ as a blue powder and suspended in CH_2Cl_2 (5 mL), then 1-methoxy-2-methyl-1-trimethylsilyloxypropene (406 μL, 2 mmol) and cyclohexen-2-one (193 μL, 2 mmol) were added. After 0.5 h at room temperature, the yellow solution was cooled at −78°C and a solution of benzaldehyde (302 μL, 3 mmol) in 5 mL CH_2Cl_2 was added at the same temperature. The reaction mixture was allowed to stand at −60°C during 36 h. The reaction was quenched by the addition of hexane (20 mL), which precipitates the samarium salts. After filtration through celite, the solvents were removed under reduced pressure and the residue was purified by flash chromatography on deactivated silica gel (hexane/ethyl acetate, 90/10) (527 mg, 70% yield).

4.2.1. 2-Methyl-2-[3-oxo-2-{1-(trimethylsilyloxy)-1-(phenylmethyl)}-cyclohexyl] propionic acid methyl ester (4a). ^1H NMR (250 MHz, $CDCl_3$) δ 7.27 (m, 5H), 5.0 (d, *J*=5.1 Hz, 1H), 3.65 (s, 3H), 2.63 (d, *J*=5.1 Hz, 1H), 2.40–2.20 (m, 3H), 1.95 (m, 2H), 1.70 (m, 1H), 1.50 (m, 1H), 0.86 (s, 3H), 0.75 (s, 3H), −0.02 (s, 9H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 216.10, 177.80, 142.95, 128.05, 127.55, 125.40, 77.30, 58.75, 51.40, 45.70, 41.40, 40.15, 24.50, 24.30, 22.60, 20.80, −0.20; FTIR (NaCl) 1730, 1703 cm^{-1}; HRMS calcd for $C_{21}H_{32}O_4Si$ (M^+) 376.2069, found 376.2070. Anal. calcd for $C_{21}H_{32}O_4Si$: C, 66.98; H, 8.57. Found: C, 67.25; H, 8.55.

4.2.2. 2-Methyl-2-[3-oxo-2-{1-(trimethylsilyloxy)-1-(4-(trifluoromethyl) phenylmethyl)}-cyclohexyl] propionic acid methyl ester (4b). ^1H NMR (250 MHz, $CDCl_3$) δ 7.50 (m, 4H), 5.19 (d, *J*=6.1 Hz, 1H), 3.64 (s, 3H), 2.63 (m, 1H), 2.40–1.50 (m, 7H), 1.18 (s, 3H), 1.12 (s, 3H), −0.02 (s, 9H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 209.65, 177.15, 146.70, 129.35 (q, CF_3), 127.35, 126.50, 124.85, 71.75, 58.55, 51.80, 47.00, 45.30, 28.10, 26.45, 24.70, 22.20, 21.70, −0.05; FTIR (NaCl) 1732, 1618 cm^{-1}; HRMS calcd for $C_{22}H_{31}F_3O_4Si$ (M^+) 444.1944, observed 444.1932. Anal. calcd for $C_{22}H_{31}F_3O_4Si$: C, 59.44; H, 7.03. Found: C, 59.67; H, 6.88.

4.2.3. 2-Methyl-2-[3-oxo-2-{1-(trimethylsilyloxy)-1-((*E*)-but-2-enyl)}-cyclohexyl] propionic acid methyl ester (mixture of diastereomers) (4c+5c+6c). ^1H NMR (250 MHz, $CDCl_3$,) δ 5.75–4.85 (m, 2H), 4,55 (m, 1H), [3.69, (s), 3.68 (s), 3.67 (s); 3H], 2.50–1.90 (m, 7H), 1.80 (m, 1H), 1.66 (m, 3H), 1.18–1.14 (m, 6H); 0.13–0.07 (m, 9H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 210.37, 210.31, 177.39, 177.36, 132.87, 131.16, 126.60, 125.40, 70.85, 70.12, 56.88, 56.43, 51.82, 46.73, 46.43, 45.87, 45.23, 43.97, 43.90, 43.31, 41.21, 27.34, 26.89, 26.53, 26.42, 26.35, 25.11, 22.27, 22.15, 21.79, 21.70, 17.62, 0.99, 0.28, 0.23; FTIR (NaCl) 1734 cm^{-1}; HRMS calcd for $C_{21}H_{32}O_4Si$ ($M+Na^+$) 363.1969, found 363.1967.

4.2.4. 2-[3-Oxo-2-{1-(*tertio*butyldimethylsilyloxy)-1-(phenylmethyl)}-cyclohexyl] acetic acid ethyl ester (4d). ^1H NMR (250 MHz, $CDCl_3$) δ 7.40–7.20 (m, 5H), 5.12 (d, *J*=3.9 Hz, 1H), 4.10 (q, *J*=7.3 Hz, 2H), 2.85 (m, 2H), 2.55 (m, 1H), 2.34 (d, 2H, *J*=5.9 Hz), 1.80 (m, 2H), 1.28 (t, *J*=7.3 Hz, 3H), 1.00 (s, 9H), 1.10–0.80 (m, 3H), 1.00 (s, 9H), 0.20 (s, 3H), 0.21 (s, 3H); ^{13}C RMN (62.9 MHz, $CDCl_3$) δ 218.50, 172.40, 129.24, 128.05, 126.39, 123.18, 112.87, 60.34, 40.88, 32.40, 28.98, 25.92, 25.57, 18.35, 14.29, 1.00, −4.40, −4.54. IR (NaCl) ν_{max}: 1758, 1716 cm^{-1}; HRMS (IE^+) calcd for $C_{27}H_{44}O_5Si_2Na$: (M^++Na) 527.2625, found 527.2625.

4.2.5. 2-[3-Oxo-2-{1-(trimethylsilyloxy)-1-(phenylmethyl)}-cyclohexyl] acetic acid phenyl ester (4e). ^1H RMN (250 MHz, $CDCl_3$) δ 7.40–6.90 (m, 10H), 5.35 (d, *J*=4.7 Hz, 1H), 2.86 (m, 2H), 2.55 (m, 1H), 2.4–1.80 (m, 7H), 0.03 (s, 9H); ^{13}C RMN (62.9 MHz, $CDCl_3$) δ 210.66, 170.27, 156.02, 150.34, 129.44, 129.40, 128.41, 126.85, 126.76, 121.38, 120.10, 115.26, 73.58, 47.26, 40.96, 40.73, 35.50, 30.70, 24.67, −0.07. IR (NaCl) ν_{max}: MS (IE^+) calcd for $C_{24}H_{30}O_4SiNa$: (M^++Na, 433).

4.2.6. 2-[3-Oxo-2-{1-(trimethylsilyloxy)-1-{phenylmethyl)}-cyclopentyl] propionic acid methyl ester (4f). ^1H NMR (250 MHz, $CDCl_3$,) δ 7.34–7.22 (m, 5H), 5.34 (d, *J*=2 Hz, *syn*), 3.47 (s, 3H), 2.60–1.00 (m, 6H,), 0.70 (s, 3H), 0.64 (s, 3H), 0.03 (s, 9H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 222.10, 177.50, 142.60, 128.05, 127.10, 125.80, 75.35, 58.70, 51.55, 45.40, 42.80, 38.00, 24.00, 23.70, 21.95, −0.20; FTIR (NaCl) 2955, 1733, 1473, 1452, 1434, 1369, 1252, 1190,

1167, 1141, 1118, 1091, 1065, 1027, 1002, 954, 896, 843, 754, 703; HRMS calcd for $C_{19}H_{27}O_4Si$ (M^+-CH_3): 347.1693, found 347.1694.

4.2.7. 2-Methyl-2-[3-oxo-2-{1-(trimethylsilyloxy)-1-((*E*)-3-phenylprop-2-enyl)}-cyclopentyl] propionic acid methyl ester (4g). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.35 (m, 5H), 6.55 (d, J=13.4 Hz, 1H), 6.10 (dd, J=13.4, 5.8 Hz, 1H), 4.85 (d, J=5.8 Hz, 1H), 3.50 (s, 3H), 2.70 (bs, 1H), 2.20–1.80 (m, 5H), 1.05 (s, 6H); 0.05 (s, 9H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 221.97, 177.58, 136.56, 130.93, 130.01, 128.55, 127.5, 126.38, 74.70, 56.57, 51.74, 47.75, 43.41, 37.95, 23.81, 23.00, 0.01; FTIR (NaCl) 1739 cm^{-1}; HRMS calcd for $C_{22}H_{32}O_4Si$ (M^+) 388.2070, found 388.2081.

4.2.8. 2-Methyl-2-[3-oxo-2-{1-(trimethylsilyloxy)-1-((*E*)-oct-2-enyl)}-cyclopentyl] propionic acid methyl ester (4h). ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.58 (m, 1H), 5.35 (dd, J=14.5, 4.5 Hz, 1H), 4.60 (d, J=4.5, 1H), 3.57 (s, 3H), 2.65 (m, 1H), 2.20–1.70 (m, 8H), 1.45–1.10 (m, 5H), 1.10 (s, 3H) 1.05 (s, 3H); 0.85 (m, 3H), 0.10 (s, 9H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 222.40, 177.65, 131.85, 131.00, 74.80, 56.80, 51.65, 45.70, 43.45, 37.90, 32.05, 31.40, 28.80, 24.00, 23.80, 22.70, 22.45, 14.00, 0.05; FTIR (NaCl) 1736 cm^{-1}. Anal. calcd for $C_{21}H_{38}O_4Si$: C, 65.92; H, 10.01. Found: C, 65.78; H, 9.85.

4.2.9. 2-[3-Oxo-2-{1-(*tertio*butyldimethylsilyloxy)-1-(phenylmethyl)}-cyclopentyl] acetic acid ethyl ester (4i+5i). ^{1}H NMR (250 MHz, $CDCl_3$,) δ 7.37–7.10 (m, 5H, *syn*+*anti*), 5.62 (bs, 0.1H, *anti*), 5.49 (bs, 0.9H, *syn*), 4.10 (q, J=7.0 Hz, 0.3H, *anti*), 3.90 (q, J=7.0 Hz, 1.7H, *syn*), 2.45 (bs, 1H, *syn*+*anti*), 2.25–1.63 (m, 7H, *syn*+*anti*), 1.07 (s, 9H, *syn*+*anti*), 0.96 (t, J=7.0 Hz, 3H, *syn*+*anti*), 0.58 (s, 3H *anti*), 0.25 (s, 2.7H *syn*), 0.15 (s, 0.3H, *anti*), 0.01 (s, 2.7H, *syn*); 0.01 (s, 3H, *syn*); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ *syn* 218.50, 172.20, 142.95, 128.40, 127.35, 125.65, 72.95, 61.25, 60.25, 39.60, 39.10, 32.20, 27.70, 26.00, 14.35, −4.35, −5.30; FTIR (NaCl) 1737 cm^{-1}; HRMS calcd for $C_{20}H_{31}O_4Si$ (M^+-Me) 375.1974, observed 375.1975. Anal. calcd for $C_{22}H_{34}O_4Si$: C, 67.65; H, 8.77. Found: C, 67.83; H, 8.51.

4.2.10. 2-[3-Oxo-2-{1-(*tertio*butyldimethylsilyloxy)-1-((*E*)-3-phenylprop-2-enyl)}-cyclopentyl] acetic acid ethyl ester (4j+5j). ^{1}H NMR (250MHz, $CDCl_3$) δ 7.5 (m, 5H, *syn*+*anti*), 6.58 (d, J=15.8 Hz, 1H, *syn*+*anti*); 6.15 (dd, J=5.5, 15.8 Hz, 1H, *syn*+*anti*), 4.90 (dd, J=5.0, 5.55 Hz, 1H, *syn*+*anti*), 4.15 (q, J=7.3 Hz, 0.8H, *anti*), 4.05 (q, J=7.3 Hz, 1.2H, *syn*), 2.91 (dd, J=5.0, 14.0 Hz, 1H, *syn*+*anti*), 2.65–2.00 (m, 7H, *syn*+*anti*), 1.25 (t, J=7.3 Hz, 1.2H, *anti*), 1.15 (t, J=7.3 Hz, 1.8H, *syn*), 0.89 (s, 3.6H, *anti*), 0.87 (s, 5.4H, *syn*), 0.09 and 0.06 (2s, 2.4H, *anti*), 0.00 and −0.01 (2s, 3.6H, *syn*); ^{13}C (62.9 MHz, $CDCl_3$) δ *syn*+*anti* 218.40, 172.15, 172.08, 136.58, 138.52, 131.21, 130.82, 129.56, 129.30, 128.55, 128.48, 128.26, 127.53, 127.40, 126.29, 73.06, 71.93, 60.49, 60.26, 60.20, 59.29, 39.95, 39.43, 38.82, 38.67, 34.89, 32.44, 27.34, 27.06, 25.83, 25.79, 25.60, 18.10, 14.19, 14.07, −4.29, −4.48, −5.55, −5.69; FTIR (NaCl), 1737 cm^{-1}. Anal. calcd for $C_{24}H_{36}O_4Si$: C, 69.19; H, 8.71. Found: C, 69.21; H, 8.65.

4.2.11. 2-[3-Oxo-2-{1-(*tertio*butyldimethylsilyloxy)-1-((*E*)-oct-2-enyl)}-cyclopentyl] acetic acid ethyl ester (4k+5k). ^{1}H NMR (250 MHz, $CDCl_3$,) δ 5.63 (m, 1H, *syn*+*anti*), 5.39 (m, 1H, *syn*+*anti*), 4.80 (dd, J=10.2, 11.7 Hz, 0.40H *anti*), 4.65 (d, J=6.8 Hz, 0.60H *syn*), 4.15 (m, 2H, *syn*+*anti*), 2.85 (m, 1H, *syn*+*anti*), 2.60–1.15 (m, 20H, *syn*+*anti*), 0.88 (s, 5.3H, *syn*), 0.82 (s, 3.7H, *anti*), 0.10 (s, 1.8H, *syn*), 0.08 (s, 1.8H, *syn*), −0.04 (s, 1.2H, *anti*), −0.6 (s, 1.2H, *anti*); ^{13}C NMR (62.9 MHz, CDCl3) δ *syn*+*anti*, 219.55, 218.85, 172.20, 172.05, 141.95, 131.20, 111.90, 111.25, 72.15, 60.45, 60.25, 59.55, 58.90, 40.25, 39.25, 39.05, 38.75, 38.20, 38.00, 34.75, 33.65, 32.00, 31.50, 31.25, 30.90, 28.75, 27.65, 27.45, 27.25, 27.15, 25.80, 25.65, 22.60, 22.40, 18.30, 18.05, 14.10, 14.00, −4.22, −5.30, −5.35; FTIR (NaCl), 1738. Anal. calcd for $C_{23}H_{42}O_4Si$: C, 67.27; H, 10.31. Found: C, 66.74; H, 10.34.

4.2.12. Lactone of 2-methyl-2-[3-oxo-2-phenylmethyl)-cyclohexyl] propanoic acid (10a). To a solution of the tandem product **4** (500 mg, 1.32 mmol) in THF (2 mL) were successively added H_2O (2 mL), acetic acid (10 mL) and trifluoroacetic acid (2 mL), and reaction mixture was stirred at room temperature during 12 h. After addition of Na_2CO_3 until PH 7, the reaction mixture was extracted with ether, washed with brine and dried over $MgSO_4$. After evaporation of solvents, the crude product was purified by column chromatography on silica gel (heptane/ethyl acetate, 90/10). The product was isolated as a white powder (349 mg, 97% yield), which after recrystallization in ether/toluene, 75/25 at −30°C gave white crystals (F= 169°C).

^{1}H NMR (250 MHz, $CDCl_3$,) δ 7.30 (m, 5H), 5.78 (d, J=10.2 Hz, 1H), 2.98 (dd, J_a=12.8 Hz, J_b=10.3 Hz, 1H), 2.40–1.80 (m, 5H), 1.80–1.50 (m, 2H), 1.42 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 208.02, 175.65, 140.17, 128.40, 128.26, 126.77, 79.89, 52.87, 47.87, 42.04, 41.25, 26.50, 25.21, 24.36, 21.02; FTIR (NaCl), 1712; LRMS (EI$^+$) m/z: 272 (M^+; 100). Anal. calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.78; H, 7.47.

4.2.13. 2-[(1*S*,5*S*)-{3-Oxo}-5-*tertio*butyldimethylsilyloxy}-cyclopentyl] acetic acid ethyl ester (14). To a suspension of $SmI_2(THF)_2$ (0.1 mmol) in CH_2Cl_2 (5 mL) at −78°C were successively added 1-ethoxy-1-triethylsilyloxyethene **2d** (202 mg, 1 mmol) and (4*S*)-4-*tert*-butyldimethylsilyloxy-cyclopenten-2-one **12** (212 mg, 1 mmol) and the reaction mixture was allowed to stand at the same temperature during 24 h. The reaction was quenched with hexane (20 mL), the samarium salts filtrated on celite and solvents evaporated. The spectral data of the crude product **13** are identical to those reported in literature.[20] This product was dissolved in THF (20 mL) and stirred with a mixture MeOH (20 mL) /HCl 1N (10 mL) during 30 min. After neutralization with $NaHCO_3$, extraction by ether, drying on $MgSO_4$, solvents were evaporated. The residue was purified by flash chromatography on silica gel (pentane/ether, 90/10) (199 mg, 66% yield).

^{1}H NMR (250 MHz, $CDCl_3$) δ 4.51 (m, 1H, *cis*+*trans*), 4.15 (q, J=7.1 Hz, 2H, *cis*+*trans*), 2.68–1.89 (m, 7H, *cis*+*trans*), 1.26 (t, J=7.1 Hz, 3H, *cis*+*trans*), [0.88 (s)

(*trans*) and 0.86 (s) (*cis*), 9H], [0.05 (s) ((*trans*) and −0.03 (s) (*cis*), 6H]; ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 216.50, 172.45, 71.10, 60.45, 49.05, 40.60, 38.90, 34.25, 25.65, 17.90, 14.20, −4.70, −5.20; FTIR (NaCl): 1734; HRMS) calcd for $C_{14}H_{25}O_4Si$ (M^+-CH_3): 285.1523, observed 285.1522. $[\alpha]_D^{20}=-11.3$ (c=1, $CHCl_3$).

4.2.14. 2-[(1*S*,2*S*,5*R*)-2-{{3-Oxo-2{(1*S*)-1-(triethylsilyloxy)-(*E*)-oct-2-enyl}-5-*tert*-butyldimethylsilyloxy}-cyclopentyl] acetic acid ethyl ester (15). To a suspension of $SmI_2(THF)_2$ (0.1 mmol) in CH_2Cl_2 (5 mL) at −78°C were successively added 1-ethoxy-1-triethylsilyloxyethene **2d** (202 mg, 1 mmol) and (4*S*)-4-*tert*-butyldimethylsilyloxy-cyclopenten-2-one **12** (212 mg, 1 mmol) and the reaction mixture was allowed to stand at the same temperature during 24 h. Then a solution of *E*-octen-2-al (189 mg, 1.5 mmol) in CH_2Cl_2 (5 mL) was added and temperature was raised to −60°C and maintained during 36 h. The reaction was quenched with hexane (20 mL), the samarium salts filtrated on celite and solvents evaporated. The residue was purified by flash chromatography on deactivated silica gel (hexane/ethyl acetate, 95/5) (400 mg, 74% yield).

^{1}H NMR (250 MHz, $CDCl_3$) δ 5.65 (dt, J_1=15.4 Hz, J_2=8.2 Hz, 1H), 5.41 (dd, J_1=15.4, J_2=6.3 Hz, 1H), 4.70 (m, 1H), 4.57 (m, 1H), 4.12 (q, J=7.1 Hz, 2H), 2.93 (m, 1H), 2.60 (dd, J_1=10.3, J_2=3.8 Hz, 1H), 2.50 (dd, J_1=15 Hz, J_2=10.3 Hz, 1H), 2.27 (d, J=2.8 Hz, 2H), 2.00 (m, 3H), 1.35 (m, 2H), 1.25 (m, 7H), 0.90 (m, 12H), 0.83 (s, 9H), 0.52 (q, J=6.0 Hz, 6H), [0.01 and −0.01 (6H); 0.01 (s, 3H), −0.01 (s, 3H)]; ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 216.90, 172.65, 131.20, 131.05, 76.70, 72.05, 69.40, 60.15, 56.55, 49.30, 37.85, 33.90, 32.00, 31.40, 28.75, 25.70, 22.45, 17.90, 14.20, 6.80, 4.80, -4.65, -5.35; FTIR (NaCl): 1736; LRMS (EI^+) m/z 483 ($M^+-C(CH_3)_3$; 3), 379 (26), 241 (10), 103 (27), 75 (100), 45 (13); HRMS (electrospray) calcd for $C_{29}H_{56}O_5Si_2K$ (M^++K): 579.3303, observed 579.3312. $[\alpha]_D^{20}=-4.8$ (c=1, $CHCl_3$).

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