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A short multigram asymmetric synthesis of prostanoid scaffolds

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Dedicated to Professor K. C. Nicolaou for his outstanding contribution to chemistry and his friendship

Abstract—Enantiomerically pure polysubstituted cyclopentanes which can be regarded as prostanoid scaffolds have been prepared by an efficient synthetic sequence readily applicable to the preparation of multigram quantities. The first key reaction is the diastereoselective allylmetallation of oxoamide **4** which is readily prepared from γ-butyrolactone and an enantiomerically pure 2,5-dimethylpyrrolidine. The second key-step is an intramolecular [2+2] cycloaddition of a keteneiminium salt leading to bicylo[3.2.0] heptanones. These intermediates have been easily transformed into a variety of prostanoid scaffolds of high enantiomeric purities.
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1. Introduction

As a class of compounds of considerable therapeutic interest, the prostaglandin family of natural products has provided one of the most dramatic areas of chemistry of our generation.[1] Natural prostaglandins exist in such minute concentrations that extraction of commercial amounts from natural sources is unpractical. A first total synthesis was published by Corey et al. in 1969.[2] Since then, many research groups have been involved in synthetic studies of these important natural products.[1,3] However, as a result of the metabolic instability and non-discriminating biological properties of the natural prostaglandins, it soon became clear that the synthesis of analogs with higher metabolic stability and well-defined biological profile was highly desirable. This stimulated a vast synthetic programme aiming at the discovery of pharmacologically interesting analogs of the natural prostaglandins. It also stimulated the search for practical methods of synthesis of enantiomerically pure polysubstituted cylopentane rings, an essential element of prostanoid structures.

For several years, our laboratory has been involved in this synthetic endeavour.[4] We had shown that intramolecular [2+2] cycloadditions of ketenes or keteneiminium salts to carbon–carbon double bonds offered an easy access to various polycyclic systems.[5] During the course of this venture, we also showed that cycloaddition of olefins to keteniminium salts derived from chiral amides took place with a high level of stereoselectivity.[6] It became soon obvious to us that these highly selective asymmetric [2+2] cycloadditions could provide a short route to a wide variety of enantiopure prostanoid scaffolds which should be useful to medicinal chemists. We present here a detailed description of these studies which eventually led to multigram syntheses of enantiopure polysubstituted cyclopentanes.[7]

2. Strategy

Our synthetic strategy is outlined in Scheme 1. As first target, we selected the bicyclic lactone **1** carrying a protected hydroxyl group and a vinyl substituent which should be easily transformed into 1- or 2-carbon side-chains. We were rather confident that conditions should be found to generate regioselectively the lactone ring by a Baeyer–Villiger oxidation of cyclobutanone **2**.

From the outset, it was anticipated that the control of the absolute configuration of the three stereogenic centers would not be possible with the help of a single chiral inductor: we neither expected the secondary hydroxyl group to dictate the stereochemical outcome of the cycloaddition reaction nor the chiral pyrrolidine to control the facial selectivity of the allylmetallation reaction. Thus, to deal with the establishment of the desired configuration of the three stereogenic centers, we expected to need: (1) a chiral auxiliary for the stereoselective construction of the bridgehead stereogenic centers by an intramolecular [2+2] cycloaddition reaction of a keteniminium salt **3**, (2) a chiral

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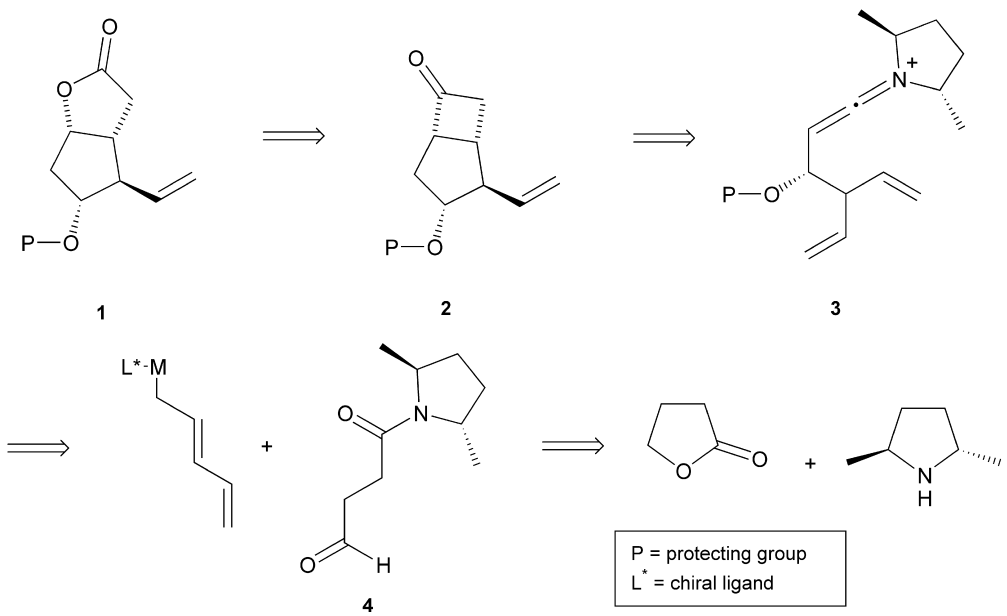


Scheme 1.

ligand for the diastereoselective allylmetallation of 4-oxoamide **4**. This strategy could give access to compounds with the configuration of the natural prostaglandins but also to their enantiomers or diastereomers.

3. Results and discussion

3.1. Synthesis and allylmetallation of 4-oxoamide 4

The inexpensive γ-butyrolactone was converted in 93% yield into 3-oxoamide **4** by treatment with (2*S*,5*S*)-dimethylpyrrolidine[8] followed by Swern oxidation of the intermediate alcohol **5** (Scheme 2). After aqueous work-up and removal of the volatile products, the crude 3-oxoamide **4** was sufficiently pure to be directly used in the allylmetallation step.

The reaction of **4** with pentadienylzinc bromide generated from zinc dust and pentadienyl bromide[9] yielded a quasi-equimolecular (**6**–**7**=1.1:1) mixture of diastereomeric adducts. This observation experimentally confirmed the inability of the chiral pyrrolidine to control the facial selectivity of the allylmetallation reaction. After much trial and error in order to improve the selectivity of formation of **6** using pentadienylzinc derivatives carrying various chiral ligands,[10] we turned to the class of chiral organotitanate compounds developed by Hafner et al.[11] The pentadienyltitanate reagent was prepared in situ from pentadienyllithium and the corresponding (*R*,*R*)-chlorotitanate derivative. The crude alcohol **6** was obtained in 95% yield with a diastereomeric excess of 94%. A single recrystallization gave enantiomerically pure **6** in 74% yield. Its epimer **7** was similarly obtained from the (*S*,*S*)-chlorotitanate. The enantiomerically pure alcohols **6** and **7** were transformed into derivatives **8**–**11** by standard procedures (Scheme 3).

The structure and configuration of **7** and **10** were confirmed by an X-ray diffraction analysis.[12]

The short sequence of Scheme 2 was applied to the preparation of up to 73 g of protected alcohols. The TADDOL ligand could be recovered after chromatography.

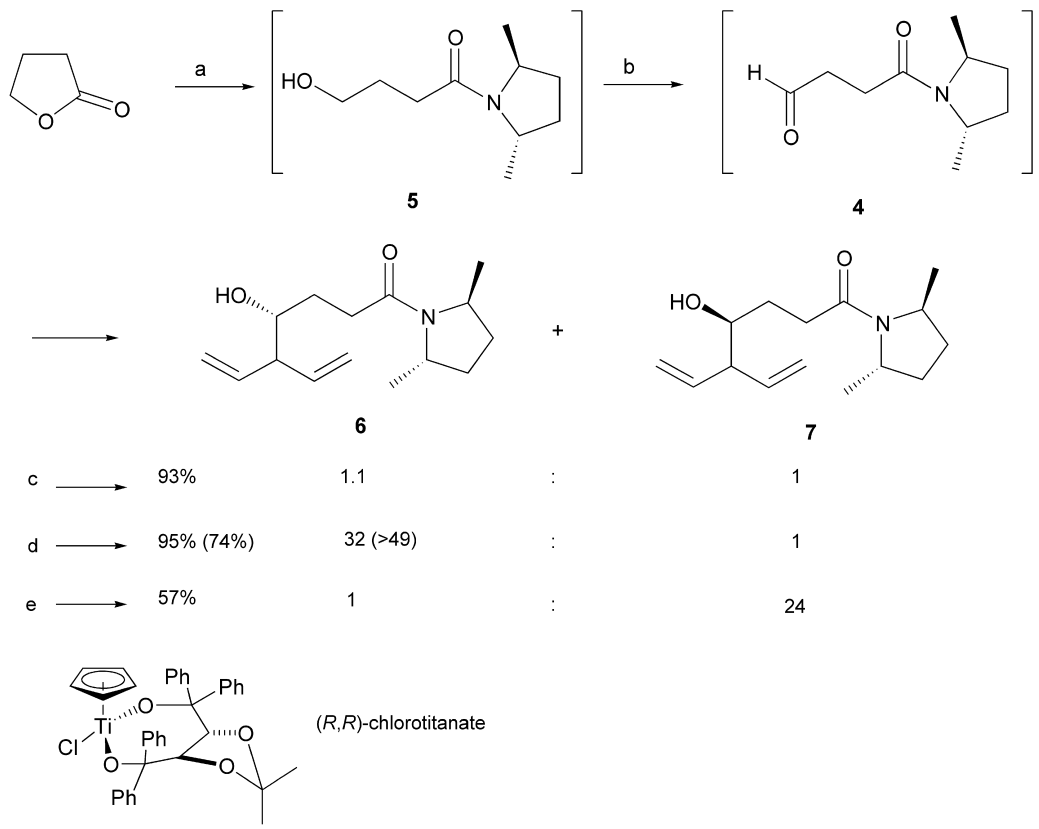
3.2. Cycloaddition reactions

The slow addition of triflic anhydride to a solution of amide **8** and 2,6-di-*t*-butyl-4-methylpyridine in 1,2-dichloroethane (DCE) at room temperature generated the corresponding keteneiminium salt **12** which underwent the intramolecular cycloaddition reaction to give, after hydrolysis, the epimeric cyclobutanones **13a** and **13b** (Scheme 4). The separation of the epimeric cyclobutanones was effected by MPLC. Both di-*t*-butyl-4-methylpyridine and 2,5-dimethylpyrrolidine could be recovered after aqueous work-up (ca. >95% and 80–85%, respectively). Similarly, the [2+2] cycloaddition starting from **11** gave good yields of epimeric cyclobutanones **14a** and **14b** which could be readily separated by flash chromatography.

Under the same conditions, amide **9** gave cyclobutanones **15a** and **15b** (Scheme 5). The two cyclobutanones were also easily separated by flash chromatography.

The enantiomeric purity of cyclobutanones **13a**,**13b**, **14a**,**14b** and **15a**,**15b** was measured by HPLC (Chiralpak AD) using racemic standards of each diastereoisomer obtained by preparative HPLC. The relative configurations were assigned on the basis of the $^{3}J_{H-H}$ coupling constants (Scheme 6).[13]

Thus, in the case of **13a** and **14a**, the low $^{3}J_{H\text{-}1,H\text{-}2}$ values (0–3 Hz) correspond to dihedral angles between 90 and 110° in agreement with an *exo* stereochemistry for the vinyl group. This coupling constant was higher (7.5–7.6 Hz) for compounds **13b** and **14b** indicating a dihedral angle around 30° between the two nuclei. This angle was that expected for an *endo* stereochemistry of the vinyl substituent. Similar analyses of the values of $J_{H\text{-}2,H\text{-}3}$ and $J_{H\text{-}3,H\text{-}4}$ allowed us to assign the configuration of the silyloxy group. Since the absolute configurations of the carbon atom bearing the silyloxy group



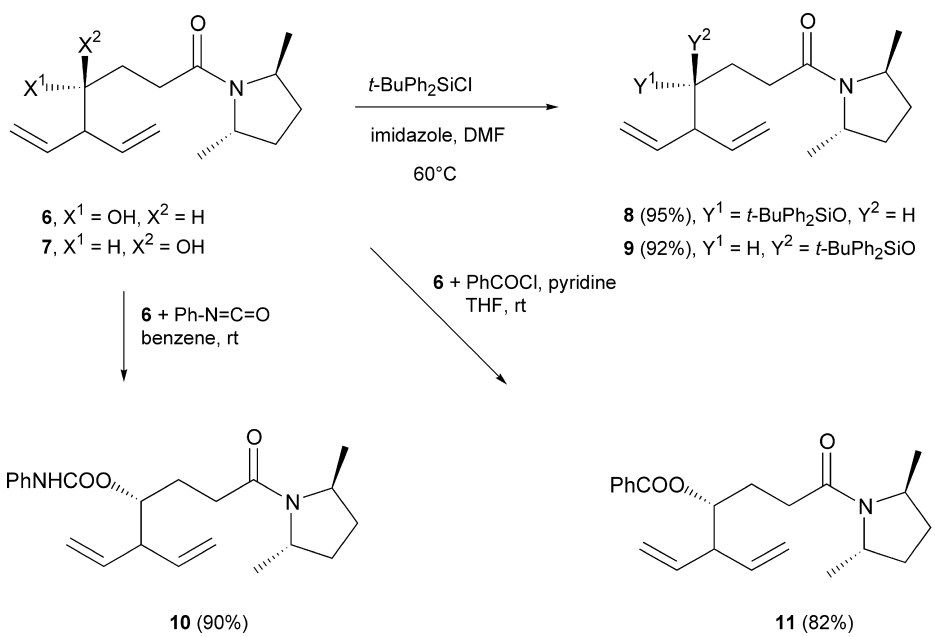
Scheme 2. *Conditions*: (a) (2*S*,5*S*)-dimethylpyrrolidine, Et_3N, Δ, 95% crude; (b) oxalyl chloride, DMSO in DCM, −78°C then **5**, Et_3N, −78°C to room temperature, 99% crude; (c) $CH_2{=}CH{-}CH{=}CH{-}CH_2Br$, Zn powder, THF, 50°C, 93%; (d) 1,4-pendadiene, *n*-BuLi in THF, −78°C to room temperature, then (*R*,*R*)-chorotitanate in THF–ether, −78 to 0°C, then **4**, NH_4F, −78°C to room temperature; (e) same as (d) but with (*S*,*S*)-chlorotitanate.

were known from the X-ray diffraction studies of **7** and **10**, these studies also established the absolute configuration of the other asymmetric centers of the bicyclic systems.

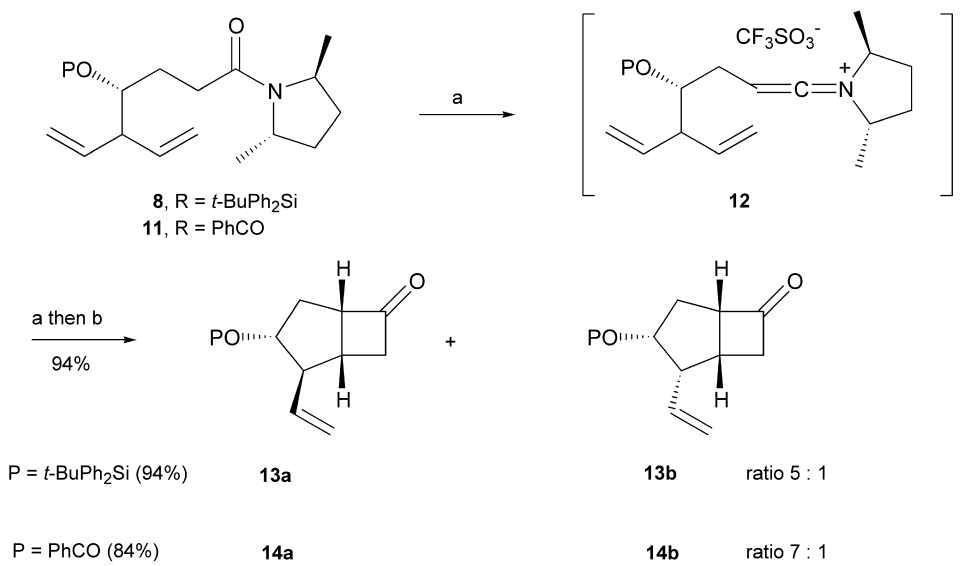
In conclusion, through these two key reactions, we had achieved our goal to construct four bonds attached to the five-membered ring in a stereocontrolled fashion.

3.3. Baeyer–Villiger oxidations

Our next task was to transform the bicyclic cyclobutanones into prostanoid synthons. The first subgoal involved the insertion of an oxygen atom between the carbonyl group and the vicinal bridgehead carbon atom through a Baeyer–Villiger oxidation reaction. No problem of stereochemical



Scheme 3.

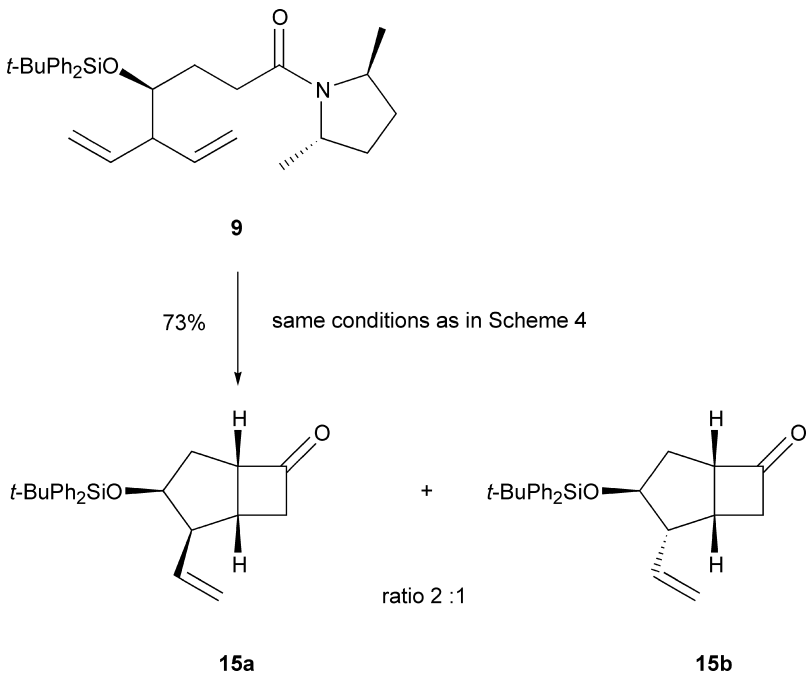


Scheme 4. *Conditions*: (a) triflic anhydride, 2,6-di-*t*-Bu-4-methylpyridine, 1,2-DCE, room temperature; (b) CCl_4–H_2O, Δ.

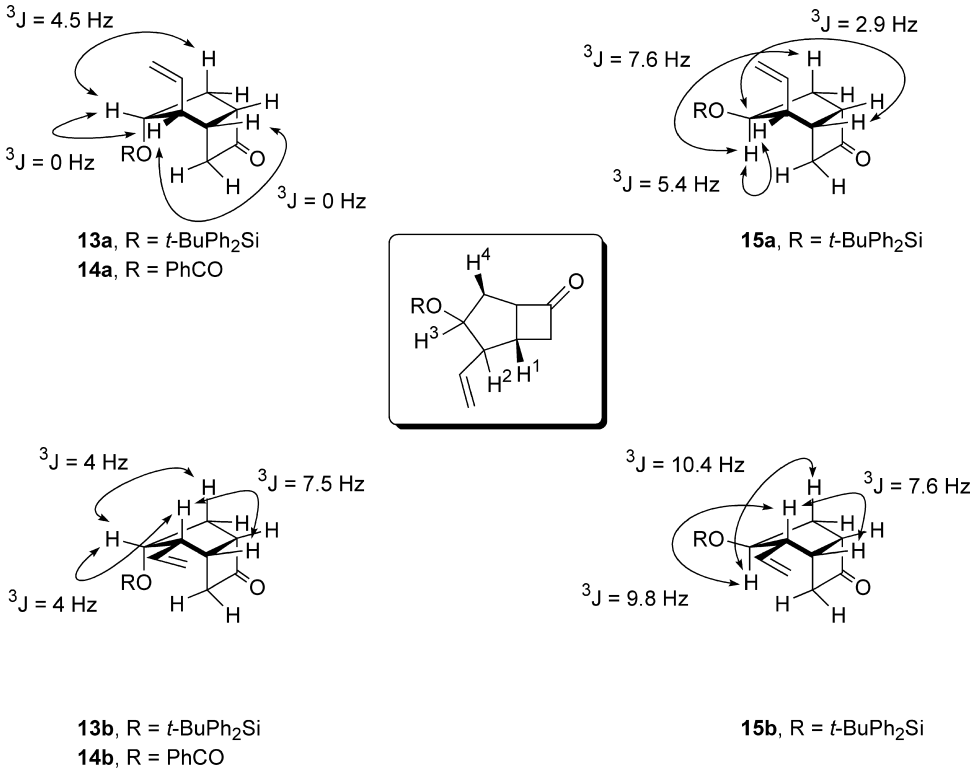
nature was expected here since these oxidations are known to proceed with retention of configuration.[14] On the other hand, we were mindful that the insertion of the oxygen atom might not occur with acceptable levels of regioselectivity. The results are shown in Table 1.

Our initial studies were performed on compound **13a**. The reaction with *m*CPBA in the presence of sodium hydrogen carbonate (entry 1), gave a mixture of lactone **16a** and the corresponding regioisomer **17a** in almost quantitative yields but with disappointingly low selectivity.[13,15] The oxidation by bis(trimethylsilyl)peroxide (entry 2) was even less selective though this reagent had been reported to oxidize the parent bicycloheptanone with the exclusive formation of the type of γ-lactone we were interested in.[16] The best selectivity was obtained with hydrogen peroxide in trifluoroethanol (entry 3), but the reaction took several days.[17] The use of a bulkier reagent (entry 4) further decreased the reaction rate without increasing the selectivity. We then applied the best conditions (H_2O_2–trifluoroethanol) to the other bicyclic ketones. The selectivity was somewhat lower for **13b**, **14a** and **14b** (entries 5, 6, 7). Interestingly, the oxidation of **15a**,**15b** carrying an *exo* *t*-butyldiphenylsilyloxy substituent was completely selective in favour of the formation of the desired lactone with both hydrogen peroxide (entries 8, 10) and *m*CPBA (entry 9).[18]

In each case the desired lactones were readily purified by recrystallization. X-Ray diffraction analyses on lactones **16a**, **16b** and **16e** confirmed the structural and stereochemical assignments.[19–21]



Scheme 5.



Scheme 6.

3.4. Transformations of the bicyclic lactones

Our final task was to demonstrate that the enantiomerically pure bicyclic lactones **16a**–**16f** could be readily transformed into a wide variety of prostanoid scaffolds. The study was performed on compound **16a**.

3.4.1. Oxidative cleavage of the vinyl substituent. Compound **16a** was converted in good yields into **18** after ozonolysis and reductive treatment of the corresponding ozonide with the borane–DMS complex (Scheme 7, reaction a).[22] Treatment of the intermediate ozonide with DMS only gave aldehyde **19**. Under the same conditions, a 2.1:1 mixture of **16a** and **16b** gave **19** and enal **20** (ratio≈2.5:1).

The formation of enal **20** probably resulted from a E_2 elimination of *t*-butyldiphenylsilanol from the minor aldehyde in which the acidic hydrogen α to the aldehyde group and the silyloxygroup are in a *trans* relationship.

3.4.2. Epoxidation of the vinyl substituent. A 4:1 mixture of diastereomeric epoxides **21a** and **21b** was quantitatively formed from the reaction of **16a** with *m*CPBA (Scheme 8). They were readily separated by flash chromatography on silica gel. Both epoxides gave crystals which were submitted to X-ray diffraction analyses.[23]

3.4.3. Hydroboration. Hydroboration of **16a** using bromoborane–DMS complex[24] followed by chromatography on silica gel with ethyl acetate as eluent, gave a mixture of alcohol **22** and the corresponding acetate **23** in 60 and 21% yields, respectively (Scheme 9).

The acetate probably originated from a silicagel-catalysed *trans*-acetylation of alcohol **22** with ethyl acetate used for the chromatographic separation. Treatment of the crude alcohol with acetic anhydride in pyridine quantitatively converted **22** into **23**.

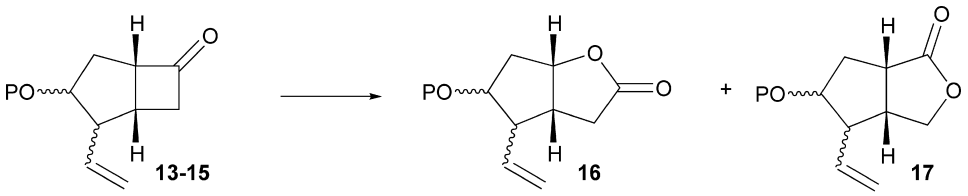
3.4.4. Wacker oxidation. When reacted under the conditions of the Wacker oxidation,[25,26] compound **16a** gave the enantiomerically pure ketone **24** in 76% yield together with a small amount (17%) of aldehyde **25** (Scheme 10).

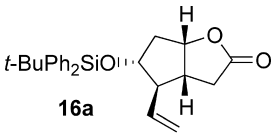
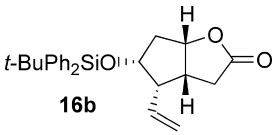
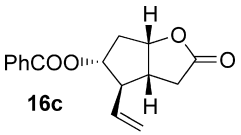
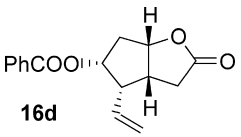
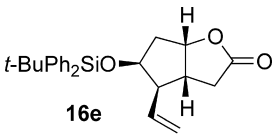
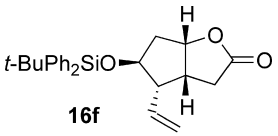
3.5. Syntheses of precursors of 13-aza- or 13-oxaprostanoids

The vinyl group of **16a** was readily transformed into a carboxyl group by treatment with Jone's reagent in the presence of catalytic amount of osmium tetroxide.[27] A Curtius rearrangement of acid **26** provided an easy access to an advanced precursor of the class of 13-azaprostaglandins. Carbamate **27** was obtained in excellent yield from the reaction of carboxylic acid **26** with diphenylphosphoryl azide[28] in the presence of benzyl alcohol. As a result of the orthogonal protections, selective transformations of the various functional groups embedded in **27** should be quite easy. Indeed hydrogenolysis selectively cleaved the benzyl carbamate group to give the free amine **28** in 98% yield.

Our initial attempts to convert carboxylic acid **26** into a precursor of the class of 13-oxaprostaglandins were less successful: oxidative decarboxylation of **26** with lead tetraacetate under many different conditions always led to complex mixtures containing no alcohol **30** or its acetate.[29] Fortunately, Barton's radical oxidative decarboxylation

Table 1. Baeyer–Villiger oxidations



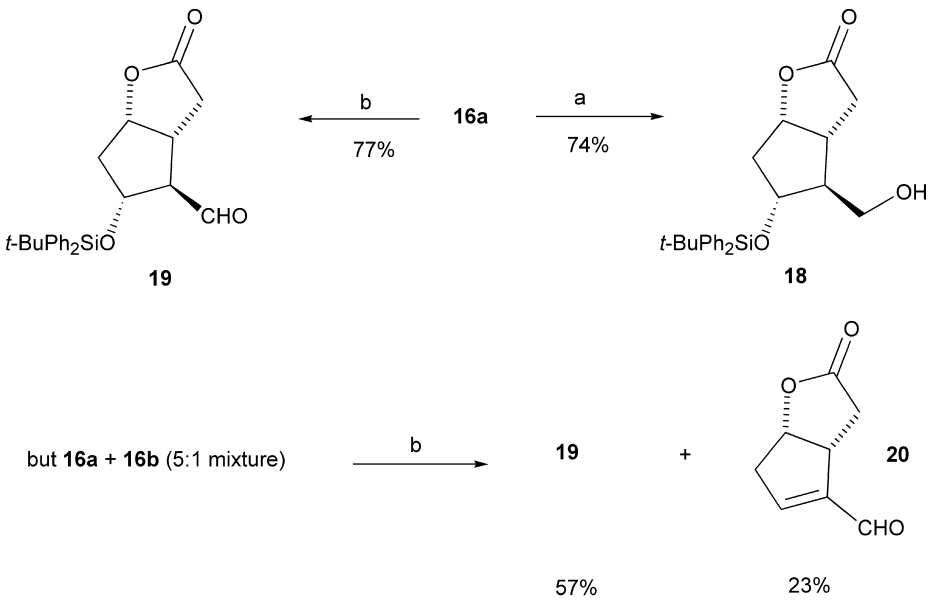
Entry	Ketone	Conditions	Major product	Yield (%)	Regioisomer ratio **16**–**17**
1	**13a**	*m*CPBA, $NaHCO_3$, DCM, 0°C, 30 min	 **16a**	96	3.4:1
2		$(TMS)_2O$, TMSOTf (cat), DCM, −15°C, 15 h		82	1.5:1
3		H_2O_2, CF_3CH_2OH, 5°C, 4–7 days		89	13.3:1
4		*t*BuOOH, CF_3CH_2OH, 5°C, 11 days		52	13.3:1
5	**13b**	H_2O_2, CF_3CH_2OH, 5°C, 4–7 days	 **16b**	69	5.6:1
6	**14a**	H_2O_2, CF_3CH_2OH, 5°C, 4–7 days	 **16c**	83	8.1:1
7	**14b**	H_2O_2, CF_3CH_2OH, 5°C, 4–7 days	 **16d**	87	6.7:1
8	**15a**	H_2O_2, CF_3CH_2OH, 5°C, 4–7 days	 **16e**	94	Only one isomer
9		*m*CPBA, $NaHCO_3$, DCM, 0°C, 30 min		94	
10	**15b**	H_2O_2, CF_3CH_2OH, 5°C, 4–7 days	 **16f**	>98	Only one isomer

reaction[30] provided us with a practical though not perfect route towards alcohol **30**. Acid **26** was first converted into the activated ester **29** which was photolyzed in the presence of oxygen and *t*-butylthiol to give an intermediate hydroperoxide which was reduced in situ with trimethylphosphite. Alcohol **30** was obtained with a moderate 45% yield. When the decomposition of ester **29** was carried out thermally, yield dropped to 29% and a sulfide **31** (21%) was obtained as a by-product. The sulfide probably originated from a radical recombination in a solvent cage as previously reported in other instances (Scheme 11).[31]

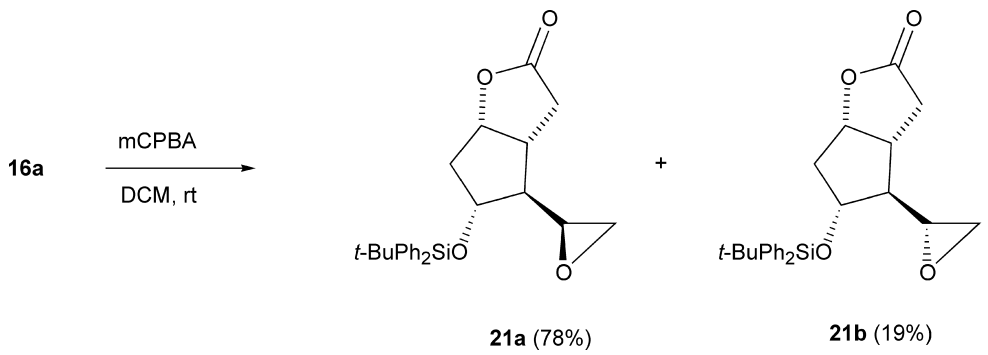
The configuration of the carbon bearing the carbamoyl substituent in **27** was assumed to be the same as in **26** since the Curtius rearrangement is known to occur with retention of configuration. The proposed configuration of the alcohol in **30** was supported by the fact that ^1H and ^{13}C NMR spectra of **30** were found to be identical to those of the alcohol resulting from the Baeyer–Villiger rearrangement of **24**.

4. Conclusion

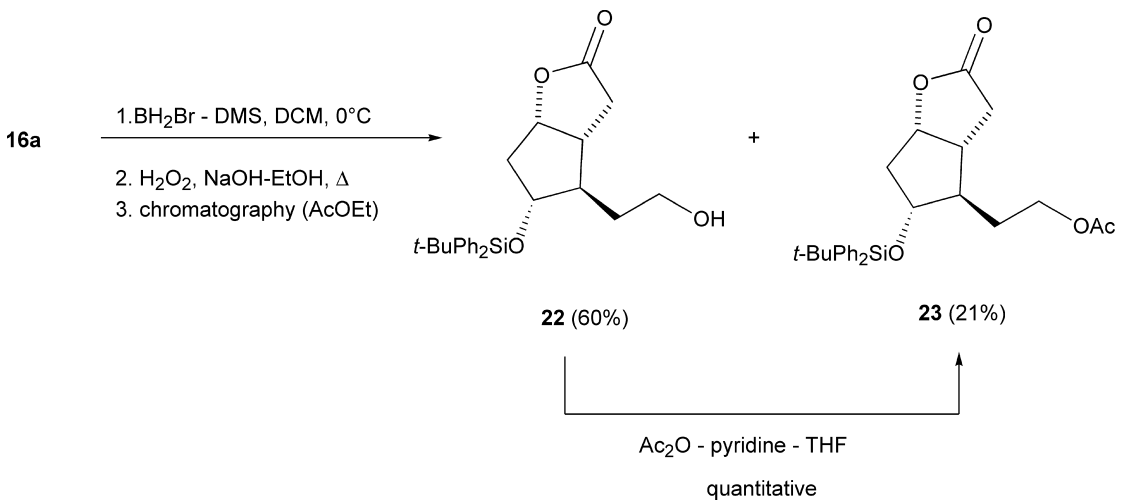
The synthetic strategy using an asymmetric allylmetallation of a functionalised aldehyde and an intramolecular [2+2] cycloaddition of a keteniminium salt provides a framework for the enantiospecific access to polycyclic compounds. This paper provides an illustration of the power of this strategy. A short sequence of reactions which can easily be scaled up led to a wide variety of prostanoid scaffolds in enantiopure form. A proper choice of the chiral auxiliaries



Scheme 7. *Conditions*: (a) O_3, DCM, −78°C then H_3B–DMS, −78°C to room temperature; (b) O_3, DCM, −78°C then DMS.

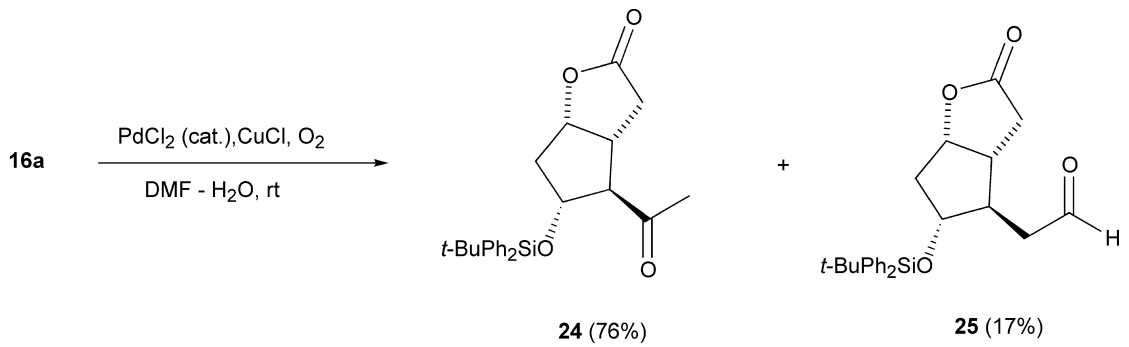


Scheme 8.

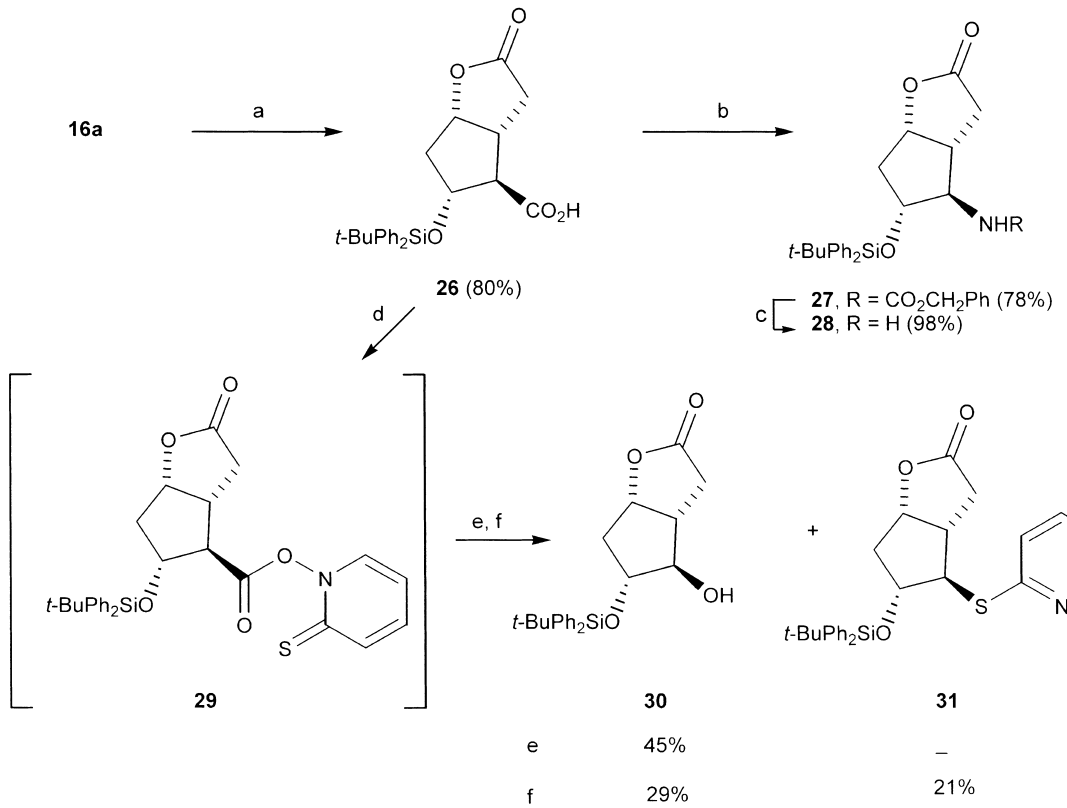


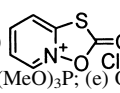
Scheme 9.

should allow the preparation of all diastereomeric lactones **16**. The main drawback of the present sequence is that it requires two chiral auxiliaries to establish the desired configurations of the stereogenic centers. In particular, it would be desirable to avoid the use of the rather expensive 2,5-dimethylpyrrolidine. We have recently shown that this was indeed possible.[32] Further applications of this synthetic strategy are presently under way.



Scheme 10.



Scheme 11. *Conditions*: (a) Jones reagent, OsO_4 (cat), acetone, room temperature; (b) $(PhO)_2P(O)N_3$, Et_3N, $PhCH_2OH$, benzene, Δ; (c)  **31**, Et_3N, toluene, room temperature (protected from light), filtration; (d) O_2, *t*-BuSH, toluene, 500 W halogen lamp, room temperature then $(MeO)_3P$; (e) O_2, *t*-BuSH, toluene, 80°C then $P(OMe)_3$.

5. Experimental

5.1. General

^1H and ^{13}C NMR spectra were recorded in deuteriochloroform on Varian Gemini-200, Varian Gemini-300 and Brucker AM-500 spectrometers. ^{13}C NMR spectra were recorded in $CDCl_3$ at 50, 75 or 125 MHz. Chemical shifts are reported in ppm relative to tetramethylsilane or $CDCl_3$. Mass spectra (electron impact 70 eV) were recorded on a Varian Mat-44 and on Finnigan Mat-TSQ 70 spectrometers. Infra-red (IR) spectra were recorded on a Perkin–Elmer 1710 Fourier transform spectrometer. Absorption frequencies are reported in cm^{-1}. High resolution mass spectra (HRMS, electronic impact) were recorded by Professor R. Flammang, Université de Mons-Hainaut, Belgium. Elemental analyses were performed in the laboratory of Mr Stone at University College London, UK. Gas chromatography (GC) analyses were performed on a Carlo-Erba Fractovap 4160 chromatograph fitted with a Heliflex AT-1 (30 m×0.25 mm int. ∅) or a Permabond SE-52 (25 m×0.25 mm int. ∅) capillary column and a flame ionisation detector using N_2 as carrier gas. HPLC analyses were performed on a Waters 600-E system fitted with a column oven Merck Lichrojet and a variable-wavelength UV detector set up at 220 nm. Chiralpak AD refers to a Chiralpak AD column, 250 mm×4 mm int. ∅ from Diacel. Lichrospher Si60 refers to a Merck Lichrospher Si60 4 μm column, 250×4.6 mm. Novapak C18 refers to a Novapak C18 4 μm column, 300×3.9 mm int. ∅ from Waters.

Hypersil Phenyl refers to a Hypersil Phenyl 3 mm, 150×4.6 mm int. ∅ from Chandon. Flash chromatography separations were performed with silica gel Merck 60 230–400 mesh. Preparative MPLC separations were performed on a Prochrom LC-80 system with silica gel Merck 60 15–40 μm. Solvents for reaction, extraction and chromatography were of technical grade and distilled. Solvents for reaction under anhydrous conditions were further distilled on an appropriate drying agent.

5.1.1. (2*S*,5*S*)-1-(4-Hydroxybutanoyl)-2,5-dimethylpyrrolidine 5. A mixture of 17.4 ml (227 mmol) γ-butyrolactone, 45 g (454 mmol) (2*S*,5*S*)-dimethylpyrrolidine and 63 ml (907 mmol) triethylamine was refluxed for 2 days. Then an additional portion (17.4 ml, 227 mmol) of γ-butyrolactone was added and the reflux was maintained until complete conversion of the lactone. The mixture was concentrated in vacuo to yield 81.0 g of **5** (96%, colourless oil). ^{1}H NMR (200 MHz) 4.23 (1H, m, *J*=6.5 Hz), 4.04 (1H, m, *J*=6.7 Hz), 3.71 (2H, t, *J*=5.6 Hz), 3.9 (1H, br), 2.52 (1H, d, *J*=6.3 Hz), 2.51 (1H, d, *J*=6.3 Hz), 2.23 (2H, m), 1.91 (2H, m, *J*=5.9 Hz), 1.60 (2H, m), 1.19 (3H, d, *J*=6.2 Hz), 1.17 (3H, d, *J*=6.6 Hz). ^{13}C NMR (50 MHz) 172.2, 62.7, 53.9, 53.2, 32.6, 30.8, 29.0, 27.9, 21.5, 19.0. IR ν_{max} (thin film) 3403 (O–H), 1615 (C═O), 1422 (C–N amide). MS *m/z* 185 ($M^{+\circ}$), 141, 84. Calculated for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.33; N, 7.56. Found: C, 64.90; H, 10.68; N, 7.59. $[\alpha]_D^{20}$=40.3° (*c*: 1.06; $CHCl_3$).

5.1.2. (2*S*,5*S*)-1-(4-Oxobutanoyl)-2,5-dimethylpyrrolidine 4. 30.5 ml (430 mmol) dry DMSO dissolved in 100 ml dichloromethane were added to a cold (−70°C) solution of oxalyl chloride (18.7 ml, 214 mmol) in 600 ml dry dichloromethane over a period of 30 min and the resulting mixture was stirred for 15 min at −70°C. Then, a solution of **5** (39.8 g, 201 mmol) in 70 ml dichloromethane was added in 5 min. After 20 min at −70°C, triethylamine (137 ml, 988 mmol) was added and the reaction mixture was allowed to warm up to room temperature. The reaction mixture was worked-up with 700 ml water. The organic layer was dried over magnesium sulphate, filtered and concentrated in vacuo to give **4** (37.88 g, 96%, pale brown liquid). Crude **4** was used without further purification. ^{1}H NMR (200 MHz) 9.87 (1H, s), 4.20 (1H, m, *J*=6.7 Hz), 4.08 (1H, m, *J*=6.5 Hz), 2.85 (2H, m, *J*=6 Hz), 2.63 (2H, m, *J*=6 Hz), 2.02–2.32 (2H, m), 1.49–1.66 (2H, m), 1.21 (3H, d, *J*=6.4 Hz), 1.15 (3H, d, *J*=6.4 Hz). ^{13}C NMR (50 MHz) 201.2, 169.3, 53.4, 53.1, 38.8, 30.7, 28.9, 27.2, 21.3, 18.9. IR ν_{max} (thin film) 1723 (C═O aldehyde), 1636 (C═O amide), 1425. MS *m/z* 184 ($[M+H]^+$), 183 ($M^{+\circ}$), 155, 84. HRMS (EI) calculated for $C_{10}H_{17}NO_2$: 183.125925. Found, 183.126454. $[\alpha]_D^{20}$=44.30° (*c*: 1.34; $CHCl_3$).

5.1.3. (2*S*,5*S*)-1-(4-Hydroxy-5-vinylhept-6-enoyl)-2,5-dimethylpyrrolidine (6+7). A solution of **4** (366 mg, 2 mmol) and 5-bromo-penta-1,3-diene (735 mg, 5 mmol) in 8 ml THF was added dropwise in 30 min to a warm (60°C) suspension of 405 mg (6.2 mmol) zinc dust in 8 ml THF. After 3 h at 60°C, the reaction mixture was treated with 10 ml 1 M aqueous HCl and 2.5 ml ether. The dried organic layer was concentrated in vacuo to give a residue which was purified by flash chromatography (ether) to give 467 mg of a mixture of **6** and **7** (93%, d.e. 7% in favour of **6**, colourless solid). The isomer ratio was measured by HPLC (Chiralpak AD 250×4.6 mm, hexane–isopropanol 25:1, flow 1 ml/min, R_t 14.27 min (**6**), 17.10 min (**7**).

(2*S*,5*S*)-1-[(4*R*)-4-*Hydroxy*-5-*vinylhept*-6-*enoyl*]-2,5-*dimethylpyrrolidine* **6**. 84 ml (210 mmol) of a 2.5 M solution of *n*-butyllithium in hexanes were added to a solution (−75°C) of 1,4-pentadiene (26.8 ml, 260 mmol) in 800 ml dry THF. The resulting solution was allowed to warm up to 0°C (1 h). It was transferred at −50°C to a well stirred suspension of 141 g (230 mmol) (*R*,*R*)-chlorotitanate in 3.4 l dry ether. The reaction mixture was allowed to warm up to −20°C (appearance of a brown colour) then cooled back to −75°C. 36.6 g (200 mmol) of **4** in 200 ml dry ether were added and the mixture was allowed to react for 5 h at −75°C. The resulting mixture was quenched with 1.85 l of 45% aqueous NH_4F and allowed to warm up to room temperature. The suspension was filtered through Celite and the biphasic filtrate was decanted. The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over magnesium sulphate and concentrated in vacuo. The residue (160 g) was divided into 5 portions and filtered through 1 kg silica (ether then ethyl alcohol–ether 1:19) to give 48.1 g **6** (95% yield, 94% d.e., white solid). Recrystallization from ethyl acetate gave 37.1 g **6** with d.e. >98% (colourless plates). TLC (ether) R_f 0.29. Mp 77–78°C. $[\alpha]_D^{20}$=27.0 (*c*: 1.0; $CHCl_3$). Chiral-phase HPLC (Chiralpak AD, 2-propanol–hexane 4:96, 1 ml/min, 20°C) R_t 14.3 min. ^{1}H NMR (300 MHz) 5.88 (m, 2H), 5.14 (m, 4H), 4.21 (quint, 1H, *J*=6.7 Hz), 4.02 (quint, 1H, *J*=6.6 Hz), 3.59 (ddd, 1H, *J*=9.4, 6.3, 2.9 Hz), 3.20 (br, 1H), 2.82 (q, 1H, *J*=7 Hz), 2.51 (m, 2H), 2.04–2.26 (m, 2H), 1.92 (m, 1H), 1.73 (m, 1H), 1.50–1.63 (m, 2H), 1.18 (d, 3H, *J*=4.4 Hz), 1.16 (d, 3H, *J*=4.4 Hz). ^{13}C NMR (75 MHz) 172.1, 137.7, 137.4, 116.9, 116.5, 73.6, 55.2, 53.7, 53.2, 31.7, 30.8, 29.4, 29.0, 21.5, 19.0. IR ν_{max} (KBr) 3226 (O–H), 1635 (C═C), 1599 (C═O), 1469, 1430. MS *m/z* 251 ($M^{+\circ}$), 233 ($[M-H_2O]^{+\circ}$), 184 ($[M-C_5H_7]^+$). Calculated for $C_{15}H_{25}NO_2$: C, 71.67; H, 10.02; N, 5.57. Found: C, 71.74; H, 10.22; N, 5.53.

(2*S*,5*S*)-1-[(4*S*)-4-*Hydroxy*-5-*vinylhept*-6-*enoyl*]-2,5-*dimethylpyrrolidine* **7**. Same procedure as for **6** starting from 1,4-pentadiene (0.88 ml, 8.53 mmol), 2.5 M *n*-butyllithium (2.75 ml, 5.88 mmol) in hexanes, 4.81 g (7.85 mmol) (*S*,*S*)-chlorotitanate and 1.20 g (6.55 mmol) **4**. Purification by flash chromatography (ether, then ether–ethyl alcohol 9:1) gave 937 mg of **7** (57%, 92% d.e., white solid). Recrystallization from ether–pentane gave **7** with d.e. >99% (colourless crystals). TLC (ether) R_f 0.29. Mp 87–87.5°C. $[\alpha]_D^{20}$=41.9° (*c*: 0.98; $CHCl_3$). Chiral-phase HPLC (Chiralpak AD, 2-propanol–hexane 4:96, 1 ml/min, 20°C) R_t 17.1 min. ^{1}H NMR (300 MHz) 5.81–5.97 (m, 2H), 5.08–5.19 (m, 4H), 4.22 (quint, 1H, *J*=6.6 Hz), 4.04 (quint, 1H, *J*=6.5 Hz), 3.68 (d, 1H, *J*=4.0 Hz), 3.6 (m, 1H), 2.83 (q, 1H, *J*=7.2 Hz), 2.40–2.62 (m, 2H), 2.04–2.27 (m, 2H), 1.92 (m, 1H), 1.49–1.77 (m, 3H), 1.17 (d, 3H, *J*=6.4 Hz), 1.16 (d, 3H, *J*=6.5 Hz). ^{13}C NMR (75 MHz) 172.2, 137.7, 137.5, 116.9, 116.6, 73.6, 54.2, 53.9, 53.3, 31.7, 30.9, 29.7, 29.1, 21.6, 19.2. IR ν_{max} (KBr) 3227 (O–H), 1635 (C═C), 1599 (C═O), 1469, 1430. MS *m/z* 252.2 ($[M+H]^+$), 251 ($M^{+\circ}$), 233 ($[M-H_2O]^{+\circ}$), 184 ($[M-C_5H_7]^+$). Calculated for $C_{15}H_{25}NO_2$: C, 71.67; H, 10.02; N, 5.57. Found: C, 71.75; H, 10.01; N, 5.46.

5.1.4. (2*S*,5*S*)-1-[(4*R*)-4-(*tert*-Butyldiphenylsilyloxy)-5-vinylhept-6-enoyl]-2,5-dimethylpyrrolidine 8. A solution of **6** (37.71 g, 150 mmol), *tert*-butyldiphenylsilyl chloride (42.9 ml, 165 mmol) and imidazole (22.47 g, 330 mmol) in 700 ml DMF was stirred at 60°C until complete conversion of **6** (ca. 3 days). DMF was removed in vacuo and the residue was treated with dichloromethane (1.9 l). The resulting precipitate was filtered off through Celite and the filtrate was concentrated under vacuum. The residue was filtered through silica (ethyl acetate–petroleum ether 1:4) to give 81 g of an oil. Removal of volatile impurities by bulb-to-bulb distillation (70°C/0.02 mbar) yielded 73.8 g pure **8** (100%, colourless to pale yellow oil). TLC (ethyl acetate–petroleum ether 1:3) R_f 0.4. $[\alpha]_D^{20}=10.5°$ (*c*: 1.13; CH_2Cl_2). ^{1}H NMR (300 MHz) 7.70 (m, 4H), 7.26–7.40 (m, 6H), 6.01 (ddd, 1H, *J*=17.2, 10.5, 6.7 Hz), 5.83 (ddd, 1H, *J*=17.8, 9.7, 7.5 Hz), 4.89–5.12 (m, 4H), 3.79 (dt, 1H, *J*=7.6, 3.7 Hz), 4.10 (quint, 1H, *J*=6.5 Hz), 3.47 (quint, 1H, *J*=6.5 Hz), 2.90 (m, 1H), 2.27 (m, 1H), 2.01 (m, 2H), 1.68–1.90 (m, 3H), 1.46 (m, 2H), 1.06 (s, 9H), 1.08 (d, 3H, *J*=6.3 Hz), 0.89 (d, 3H, *J*=6.4 Hz). ^{13}C NMR (75 MHz) 171.0, 137.8, 136.9, 136.0, 135.9, 134.4, 133.6, 129.7, 129.5, 127.5, 127.4, 116.9, 116.2, 76.7, 53.8, 53.2, 52.7, 31.7, 30.7, 29.9, 29.0, 27.0, 21.4, 19.6, 19.2. IR ν_{max} (thin film) 1646 (C=O), 1462, 1426. MS *m*/*z* 489 ($M^{+\circ}$), 432 ($[M-t\text{-Bu}]^+$). Calculated for $C_{31}H_{43}NO_2Si$: C, 76.02; H, 8.84; N, 2.85. Found: C, 75.75; H, 8.90; N, 2.89.

5.1.5. (2*S*,5*S*)-1-[(4*S*)-4-(*tert*-Butyldiphenylsilyloxy)-5-vinylhept-6-enoyl]-2,5-dimethylpyrrolidine 9. Same procedure as for the synthesis of **8** starting with 377 mg (1.5 mmol) of **7**, 0.39 ml (1.5 mmol) of *tert*-butyldiphenylsilyl chloride and 224 mg (3.3 mmol) of imidazole. Yield: 677 mg of **9** (92%, colourless oil). TLC (ethyl acetate–petroleum ether 1:3) R_f 0.43. $[\alpha]_D^{20}=3.26°$ (*c*: 1.35; $CHCl_3$). ^{1}H NMR (300 MHz) 7.67–7.79 (m, 4H), 7.33–7.43 (m, 6H), 5.98 (ddd, 1H, *J*=17.2, 10.5, 6.7 Hz), 5.82 (ddd, 1H, *J*=17.3, 10.2, 8 Hz), 4.86–5.10 (m, 4H), 3.81 (dt, 1H, *J*=7.1, 4.3 Hz), 4.11 (quint, 1H, *J*=6.7 Hz), 3.63 (quint, 1H, *J*=6.4 Hz), 2.90 (m, 1H), 2.26 (m, 1H), 1.99 (m, 2H), 1.67–1.87 (m, 3H), 1.46 (m, 2H), 1.06 (s, 9H), 1.05 (d, 3H, *J*=6.7 Hz), 0.92 (d, 3H, *J*=6.3 Hz). ^{13}C NMR (75 MHz) 171.0, 137.7, 137.3, 136.1, 136.0, 134.8, 134.6, 129.6, 129.5, 127.5, 116.7, 116.2, 76.6, 53.6, 53.3, 52.9, 31.3, 30.9, 29.1, 27.2, 21.5, 19.6, 19.4. IR ν_{max} (thin film) 1634 (C=O), 1427. MS *m*/*z* 432 ($[M-t\text{-Bu}]^+$), 199 ($[Ph_2SiOH]^+$). Calculated for $C_{31}H_{43}NO_2Si$: C, 76.02; H, 8.84; N, 2.85. Found: C, 75.70; H, 8.88; N, 2.96.

5.1.6. (2*S*,5*S*)-1-[(4*R*)-4-Anilinocarbonyloxy-5-vinylhept-6-enoyl]-2,5-dimethylpyrrolidine 10. 0.11 ml (1 mmol) of phenyl isocyanate was added to a solution of 126 mg (0.5 mmol) of **6** in 1 ml benzene. The reaction mixture was stirred at room temperature for 2 days. Volatile products were removed in vacuo. The residue was treated with ethyl acetate–aqueous 0.5 M HCl (3 ml+1 ml). The biphasic mixture was vigorously stirred at room temperature for 1 h. The organic layer was dried over potassium carbonate, filtered and concentrated in vacuo. The residue was purified by filtration through a plug of silicagel (ethyl acetate–pentane 3:7) to give 166 mg of **10** (90%, white powder). Colourless needles suitable for X-ray diffraction analysis were obtained by recrystallization from ether–pentane. TLC (ethyl acetate–pentane 3:7) R_f 0.25. Mp (ether–pentane) 113°C. $[\alpha]_D^{20}=41.7$ (*c*: 1.05; $CHCl_3$). ^{1}H NMR (200 MHz) 7.30–7.42 (m, 4H), 7.06 (tt, 1H, *J*=7, 1.5 Hz), 6.70 (br, 1H), 5.74–5.93 (m, 2H), 5.08–5.17 (m, 4H), 4.95 (m, 1H, *J*=8.5, 6, 4.1 Hz), 4.19 (quint, 1H, *J*=6.6 Hz), 3.97 (quint, 1H, *J*=6.4 Hz), 3.05 (m, 1H, *J*=7.7, 5.8 Hz), 2.38 (m, 2H), 1.89–2.14 (m, 4H), 1.43–1.58 (m, 2H), 1.13 (d, 3H, *J*=6.4 Hz), 1.12 (d, 3H, *J*=6.3 Hz). ^{13}C NMR (50 MHz) 170.6, 153.4, 138.0, 136.5, 136.1, 129.1, 123.4, 118.6, 117.5, 117.3, 76.5, 53.5, 53.0, 52.8, 31.1, 30.8, 29.0, 21.5, 19.2, 17.7. IR ν_{max} (KBr) 3240 (N–H), 3068, 2970, 1720 (C=O carbonate), 1617 (C=O amide), 1549, 1503, 1447, 1225. MS *m*/*z* 370 ($M^{+\circ}$), 303 ($[M-C_5H_7]^+$), 184 ($[M-PhNCO-C_5H_7]^+$). Calculated for $C_{22}H_{30}N_2O_3$: C, 71.32; H, 8.16; N, 7.56. Found: C, 71.10; H, 8.19; N, 7.76.

5.1.7. (2*S*,5*S*)-1-[(4*R*)-4-Benzoyloxy-5-vinylhept-6-enoyl]-2,5-dimethylpyrrolidine 11. A solution 21.37 g (85 mmol) of **6**, 19.7 ml (170 mmol) benzoyl chloride and 17.2 ml (212 mmol) pyridine in 140 ml THF was stirred at room temperature for 3 days then poured into 250 ml 1 M aqueous HCl. The organic layer was washed with 140 ml 2 M aqueous NaOH and 140 ml of water, then dried over magnesium sulphate, filtered and concentrated under vacuum. The residue was purified by flash chromatography (ethyl acetate–petroleum ether 1:3) to give 24.6 g **11** (81%, pale yellow liquid). TLC (ethyl acetate–petroleum ether 3:1) R_f 0.38. $[\alpha]_D^{20}=44.3°$ (*c*: 1.29; $CHCl_3$). ^{1}H NMR (300 MHz) 8.04 (dd, 2H, *J*=8.5, 1.4 Hz), 7.57 (tt, 1H, *J*=7.4, 1.4 Hz), 7.44 (m, 2H, *J*=7.5 Hz), 5.81–5.94 (m, 2H), 5.26 (ddd, 1H, *J*=9.5, 5.9, 3.5 Hz), 5.09–5.18 (m, 4H), 3.14 (q, 1H, *J*=7.2 Hz), 3.17 (quint, 1H, *J*=6.6 Hz), 3.10 (quint, 1H, *J*=6.4 Hz), 2.36 (t, 2H, *J*=7.7 Hz), 1.98–2.31 (m, 4H), 1.50 (m, 2H), 1.08 (d, 6H, *J*=6.4 Hz). ^{13}C NMR (75 MHz) 170.4, 166.3, 136.5, 136.0, 132.9, 130.4, 129.6, 128.3, 117.5, 117.3, 76.0, 53.5, 53.0, 52.7, 31.1, 30.8, 29.0, 27.8, 21.5, 19.2. IR ν_{max} (thin film) 1718 (C=O ester), 1636 (C=O amide), 1451, 1418. MS *m*/*z* 355 ($M^{+\circ}$), 288 ($[M-C_5H_7]^+$), 105 ($[PhCO]^+$). Calculated for $C_{22}H_{29}NO_3$: C, 74.33; H, 8.22; N, 3.94. Found: C, 74.27; H, 8.32; N, 3.88.

5.2. Intramolecular [2+2] cycloaddition reactions—general procedure

Triflic anhydride (1.05 equiv. of a 0.66 M solution in DCE) was added at room temperature over a period of 12 h to a well stirred 0.06 M solution of amide **8**, **9** or **11** in DCE containing 1.20 equiv. of di-*tert*-butyl-methylpyridine. The reaction mixture was stirred at room temperature for 24 h then concentrated under vacuum. The residue was refluxed in a biphasic mixture of water and CCl_4 (2×11.5 l/mol) for 5 h to hydrolyse the intermediate cyclobutaneiminium salts. Addition of 1.06 equiv. 1 M aqueous HCl, separation and concentration of the organic layer left a residue which was dissolved in ether (11.5 l/mol). The pyridium salts were filtered off. The filtrate was dried over magnesium sulphate and concentrated in vacuo. The crude product was purified by flash chromatography or by MPLC to give the corresponding cyclobutanones.

Recovery of 2,5-dimethylpyrrolidine. The aqueous layer from the hydrolysis step was brought up to pH=14 by

adding sodium hydroxide at 0°C. The resulting emulsion was extracted with ether. The organic layer was dried over potassium hydroxide. A stream of gaseous HCl was passed at 0°C through the solution to give the dimethylpyrrolidine as its hydrochloride salt (ca. 83%).

5.2.1. [2+2] Cycloaddition from 7. 1.20 g (2.13 mmol) of **7** gave after flash chromatography (ethyl acetate–petroleum ether 1:9) 783 mg (94%, colourless gel) of a mixture of **13a** and **13b** (**13a**–**13b**: 84:16 measured on MERCK LICHROSPHER SiO_2 4 μm, 250×4.6 mm, hexane–isopropanol, 99.7:0.3, flow 1 ml/min, R_t 10.24 min (**13a**) and 11.2 min (**13b**). The separation of **13a** and **13b** was performed by MPLC (ethyl acetate–petroleum ether 7:93). When the reaction was carried out from 70 g (143 mmol) **7**, 57.8 g of a mixture of cyclobutanones were obtained. The separation by MPLC gave 28.0 g **13a** (50%, colourless gel), 3.18 g **13b** (6%, colourless gel), 4.58 g of **13a** and **13b** as a mixture (8%), and 450 mg *ent*-**15a** (1%, colourless gel). No *ent*-**15b** was isolated.

(1*R*,2*R*,3*R*,5*S*)-3-(*tert-Butyldiphenylsilyloxy*)-2-*vinyl-bicyclo*[3.2.0]*heptan*-6-*one* **13a**. TLC (ethyl acetate–hexane 1:19) R_f 0.31. $[\alpha]_D^{20}$=46.5° (*c*: 1.0; $CHCl_3$). HPLC (Lichrospher Si60, 2-propanol–hexane 0.3:99.7, 1 ml/min, 20°C) R_t 10.1 min. Chiral-phase HPLC (Chiralpak AD, 2-propanol–hexane 0.2:99.8, 0.5 ml/min, 20°C) $R_{t\,ent\text{-}\mathbf{13a}}$ 19.2 min, $R_{t\mathbf{13a}}$ 22.8 min. ^{1}H NMR (500 MHz) 7.62–7.70 (m, 4H), 7.40 (m, 6H), 5.44 (ddd, 1H, *J*=17.3, 10.5, 7.6 Hz), 4.86 (d, 1H, *J*=10.5 Hz), 4.78 (d, 1H, *J*=17.3 Hz), 4.20 (d, 1H, *J*=3.7 Hz), 3.63 (m, 1H, *J*=9.5, 6.8 Hz), 3.28 ((AB)MX, 2H, *J*=18, 9.7, 3, 2.9, 1.6 Hz), 2.76 (m, 1H, *J*=6.6 Hz), 2.71 (d, 1H, *J*=7.7 Hz), 2.17 (d, 1H, *J*=14.1 Hz), 1.85 (ddd, 1H, *J*=14.1, 9.6, 4.1 Hz), 1.50 (s, 9H). ^{13}C NMR (125 MHz) 212.9, 138.9, 135.9, 135.8, 133.6, 133.3, 129.6, 127.6, 127.5, 114.6, 81.8, 63.5, 57.0, 52.5, 38.4, 33.4, 26.7, 18.8. IR ν_{max} (thin film) 1785 (C=O). MS *m/z* 390 ($M^{+\circ}$), 333 ($[M-t\text{-Bu}]^+$). Calculated for $C_{25}H_{30}O_2Si$: C, 76.87; H, 7.74. Found: C, 76.74; H, 7.82.

(1*R*,2*S*,3*R*,5*S*)-3-(*tert-Butyldiphenylsilyloxy*)-2-*vinyl-bicyclo*[3.2.0]*heptan*-6-*one* **13b**. TLC (ethyl acetate–hexane 1:19) R_f 0.24. $[\alpha]_D^{20}$=72.4° (*c*: 1.0; $CHCl_3$). HPLC (Lichrospher Si60, 2-propanol–hexane 0.3:99.7, 1 ml/min, 20°C) R_t 10.9 min. Chiral-phase HPLC (Chiralpak AD, 2-propanol–hexane 0.2:99.8, 0.5 ml/min, 20°C) $R_{t\,ent\text{-}\mathbf{13b}}$ 18.8 min, $R_{t\mathbf{13b}}$ 20.8 min. ^{1}H NMR (500 MHz) 7.61–7.70 (m, 4H), 7.42 (m, 6H), 6.10 (ddd, 1H, *J*=18.1, 10.3, 7.8 Hz), 5.13 (d, 1H, *J*=10.3 Hz), 5.07 (d, 1H, *J*=18.1 Hz), 4.38 (t, 1H, *J*=3.9 Hz), 3.55 (m, 1H), 3.53 (m, 1H, *J*=3.9 Hz), 3.06 (m, 1H, *J*=18.1, 10.0, 4.2 Hz), 2.90 (m, 1H, *J*=6.5 Hz), 2.62 (td, 1H, *J*=7.8, 7.6, 3.9 Hz), 2.04 (d, 1H, *J*=13.7 Hz), 1.65 (ddd, 1H, *J*=13.7, 9.4, 3.9 Hz), 1.05 (s, 9H). ^{13}C NMR (125 MHz) 213.1, 136.2, 135.8, 133.6, 133.0, 129.6, 129.5, 127.5, 127.4 (2×), 127.3, 116.8, 78.9, 63.2, 52.1, 48.9, 39.4, 32.9, 26.9, 19.0. IR ν_{max} (thin film) 1780 (C=O). MS *m/z* 390 ($M^{+\circ}$), 333 ($[M-t\text{-Bu}]^+$), 205. Calculated for $C_{25}H_{30}O_2Si$: C, 76.87; H, 7.74. Found: C, 76.52; H, 7.80.

5.2.2. [2+2] Cycloaddition from 8. 556 mg (0.99 mmol) of **8** gave after filtration through silicagel (ethyl acetate–hexane 1:19) 350 mg (73%, colourless gel) of a mixture of **15a** and **15b** (**15a**–**15b**=67:33). **15a** and **15b** were separated by flash chromatography (ethyl acetate–hexane 3:97).

(1*R*,2*R*,3*S*,5*S*)-3-(*tert-Butyldiphenylsilyloxy*)-2-*vinyl-bicyclo*[3.2.0]*heptan*-6-*one* **15a**. TLC (ethyl acetate–hexane 1:19) R_f 0.40. $[\alpha]_D^{20}$=47.8° (*c*: 1.08; $CHCl_3$). HPLC (Lichrospher Si60, 2-propanol–hexane 0.3:99.7, 1 ml/min, 20°C) R_t 7.7 min. Chiral-phase HPLC (Chiralpak AD, 2-propanol–hexane 0.2:99.8, 0.4 ml/min, 20°C) $R_{t\,ent\text{-}\mathbf{15a}}$ 19.8 min, $R_{t\mathbf{15a}}$ 21.4 min. ^{1}H NMR (500 MHz) 7.62–7.70 (m, 4H), 7.42 (m, 6H), 6.07 (ddd, 1H, *J*=17.3, 10.5, 7.6 Hz), 5.14 (d, 1H, *J*=10.5 Hz), 5.05 (d, 1H, *J*=17.3 Hz), 4.43 (dt, 1H, *J*=7.8, 5.4 Hz), 3.55 (m, 1H, *J*=7.8, 2.7 Hz), 3.14 (ddd, 1H, *J*=18.3, 9.3 Hz, 4), 2.81 (m, 1H, *J*=2.8 Hz), 2.46 (m, 1H, *J*=18.3, 3.7 Hz), 2.41 (m, 1H), 1.92 (ddd, 1H, *J*=13.1, 5.5, 2.8 Hz), 1.85 (ddd, 1H, *J*=13.1, 9.8, 7.6 Hz), 1.05 (s, 9H). ^{13}C NMR (125 MHz) 212.3, 137.2, 135.7, 135.5, 133.9 (2×), 129.7, 127.5 (2×), 115.6, 76.8, 61.5, 53.9, 51.0, 34.9, 32.3, 26.8, 19.1. IR ν_{max} (thin film) 1785 (C=O). MS *m/z* 333 ($[M-t\text{-Bu}]^+$). Calculated for $C_{25}H_{30}O_2Si$: C, 76.87; H, 7.74. Found: C, 76.58; H, 7.71.

(1*R*,2*S*,3*S*,5*S*)-3-(*tert-Butyldiphenylsilyloxy*)-2-*vinyl-bicyclo*[3.2.0]*heptan*-6-*one* **15b**. TLC (ethyl acetate–hexane 1:19) R_f 0.33. $[\alpha]_D^{20}$=55.0° (*c*: 1.08; $CHCl_3$). HPLC (Lichrospher Si60, 2-propanol–hexane 0.3:99.7, 1 ml/min, 20°C) R_t 8.7 min. Chiral-phase HPLC (Chiralpak AD, 2-propanol–hexane 0.2:99.8, 0.5 ml/min, 20°C) $R_{t\mathbf{15b}}$ 15.8 min, $R_{t\,ent\text{-}\mathbf{15b}}$ 18.7 min. ^{1}H NMR (500 MHz) 7.60–7.70 (m, 4H), 7.30–7.50 (m, 6H), 5.68 (ddd, 1H, *J*=18.4, 9.1, 7.6 Hz), 5.12 (m, 2H), 4.07 (m, 1H, *J*=10.4, 9.8, 6.1 Hz), 3.44 (m, 1H), 2.91 (ddd, 1H, *J*=18.3, 9.2, 4.6 Hz), 2.82 (m, 1H), 2.75 (m, 1H, *J*=9.8, 7.6 Hz), 2.64 (ddd, 1H, *J*=18.3, 4.3, 3.1 Hz), 1.92 (ddd, 1H, *J*=13.1, 6.1, 0.9 Hz), 1.71 (dt, 1H, *J*=13.1, 10.4 Hz), 1.04 (s, 9H). ^{13}C NMR (125 MHz) 212.1, 136.0, 135.9, 135.7, 134.0, 133.4, 129.6, 127.4, 117.5, 75.5, 60.5, 54.0, 47.5, 36.5, 30.5, 26.9, 19.1. IR ν_{max} (thin film) 1780 (C=O). MS *m/z* 333 ($[M-t\text{-Bu}]^+$). Calculated for $C_{25}H_{30}O_2Si$: C, 76.87; H, 7.74. Found: C, 76.47; H, 7.73.

5.2.3. [2+2] Cycloaddition from 11. 20 g (56.3 mmol) **11** gave after flash chromatography (ethyl acetate–petroleum ether 15:85) 10.34 g **14a** (72%, pale yellow liquid) and 1.80 g **14b** (13%, pale yellow solid).

(1*R*,2*R*,3*R*,5*S*)-3-*Benzoyloxy*-2-*vinyl-bicyclo*[3.2.0]*heptan*-6-*one* **14a**. TLC (ethyl acetate–petroleum ether 15:85) R_f 0.72. $[\alpha]_D^{20}$=21.3 (*c*: 1.0; $CHCl_3$). HPLC (Lichrospher Si60, 2-propanol–hexane 0.8:99.2, 1 ml/min, 20°C) R_t 15.3 min. ^{1}H NMR (500 MHz) 7.93 (d, 2H), 7.56 (t, 1H), 7.44 (t, 2H), 5.82 (ddd, 1H, *J*=17.3, 10.5, 7 Hz), 5.44 (d, 1H, *J*=4.6 Hz), 5.20 (d, 1H, *J*=10.5 Hz), 5.16 (d, 1H, *J*=17.3 Hz), 3.80 (m, 1H), 3.37 (ddd, 1H, *J*=17.6, 9.7, 4.5 Hz), 3.02 (d, 1H, *J*=7 Hz), 3.02 (m, 1H, *J*=4.1 Hz), 2.98 (m, 1H), 2.38 (d, 1H, *J*=14.7 Hz), 2.20 (ddd, 1H, *J*=14.7, 9.6, 4.6 Hz). ^{13}C NMR (125 MHz) 212.1, 165.5, 137.6, 133.0, 129.8, 129.5, 128.4, 115.8, 82.4, 63.7, 54.1, 52.6, 35.5, 43.3. IR ν_{max} (thin film) 1779 (C=O cyclobutanone), 1717 (C=O ester). MS *m/z* 256 ($M^{+\circ}$), 105 ($[PhCO]^+$). Calculated for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.86; H, 6.16.

(1*R*,2*S*,3*R*,5*S*)-3-*Benzoyloxy*-2-*vinyl-bicyclo*[3.2.0]*heptan*-6-*one* **14b**. TLC (ethyl acetate–petroleum ether 15:85) R_f

0.47. Mp 133.4°C. $[\alpha]_D^{20}$=77.2 (*c*: 1.0; $CHCl_3$). HPLC (Lichrospher Si60, 2-propanol–hexane 0.8:99.2, 1 ml/min, 20°C) R_t 35.3 min. ^{1}H NMR (500 MHz) 7.90 (d, 2H), 7.55 (t, 1H), 7.44 (t, 2H), 5.95 (ddd, 1H, *J*=18.4, 9.1, 7 Hz), 5.72 (t, 1H, *J*=4.3 Hz), 5.19 (m, 2H), 3.77 (m, 1H), 3.34 (dt, 1H, *J*=18.3, 4.0 Hz), 3.20 (ddd, 1H, *J*=18.3, 9.8, 4.0 Hz), 3.11 (m, 1H), 3.06 (m, 1H, *J*=7.3 Hz), 2.40 (d, 1H, *J*=14.7 Hz), 2.14 (ddd, 1H, *J*=14.7, 9.5, 4.3 Hz). ^{13}C NMR (125 MHz) 212.2, 165.6, 133.1, 132.9, 129.7, 129.4, 128.4, 118.2, 79.4, 63.3, 49.9, 48.8, 37.0, 32.5. IR ν_{max} (KBr) 1773 (C=O cyclobutanone), 1719 (C=O ester). MS *m*/*z* 256 ($M^{+\circ}$), 105 ($[PhCO]^+$). Calculated for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.75; H, 6.24.

5.3. Baeyer–Villiger oxidations—general procedure

Aqueous 35% hydrogen peroxide (4 equiv.) was added at 0°C to a 0.4 M solution of cyclobutanone **13**–**15** in trifluoroethanol. The resulting reaction mixture was then stirred at 0°C until complete conversion of the starting material (ca. 4–7 days). The solvent was removed under vacuum and the residue was dissolved in ether and extracted with 1 M aqueous $Na_2S_2O_3$ (2×2.7 l/mol). The organic layer was dried over magnesium sulphate, concentrated in vacuo. The crude product was purified by flash chromatography then recrystallized to give pure lactones **16a**–**16f**.

5.3.1. (1*S*,5*R*,6*R*,7*R*)-7-(*tert*-Butyldiphenylsilyloxy)-6-vinyl-2-oxabicyclo[3.3.0]octan-3-one 16a. 17.0 g (43.5 mmol) **13a** gave after filtration through a plug of silicagel 15.64 g (88%, colourless gel, which solidified after a few hours) of a mixture of **16a** and **17a** (**16a**–**17a**=91:8). A recrystallization (ethyl acetate–hexane) gave pure **16a**. TLC (ethyl acetate–petroleum ether 1:4) R_f 0.44. Mp (ethyl acetate–hexane) 66°C. $[\alpha]_D^{20}$=−11.0° (*c*: 1.36; $CHCl_3$). HPLC (Novapak C18, methanol–water 80:20, 0.4 ml/min, 20°C) $R_{t\mathbf{17a}}$ 45.8 min, $R_{t\mathbf{16a}}$ 47.8 min. ^{1}H NMR (300 MHz) 7.66 (m, 4H), 7.35–7.47 (m, 6H), 5.43 (ddd, 1H, *J*=17, 10.4, 7.7 Hz), 4.99 (d, 1H, *J*=10.5 Hz), 4.97 (d, 1H, *J*=17 Hz), 4.83 (m, 1H, *J*=6.9, 5.9, 3.4 Hz), 3.98 (q, 1H, *J*=5.6 Hz), 2.75 (dd, 1H, *J*=18.8, 10.6 Hz), 2.45–2.62 (m, 3H), 2.02 (m, 2H), 1.05 (s, 9H). ^{13}C NMR (75 MHz) 176.9, 137.5, 136, 135.9, 133.6, 133.4, 129.8, 127.6 (2×), 116.8, 83.3, 78.5, 58.1, 41.7, 40.4, 34.8, 26.9, 19. IR ν_{max} (thin film) 1774 (C=O), 1640, 1589, 1473, 1428. MS *m*/*z* 406 ($[M]^{+\circ}$), 349 ($[M-t\text{-Bu}]^+$). Calculated for $C_{25}H_{30}O_3Si$: C, 73.85; H, 7.43. Found: C, 73.64; H, 7.37.

5.3.2. (1*S*,5*R*,6*S*,7*R*)-7-(*tert*-Butyldiphenylsilyloxy)-6-vinyl-2-oxabicyclo[3.3.0]octan-3-one 16b. 1.24 g (3.17 mmol) **13b** gave 865 mg (65%, colourless gel which solidified after a few hours) of a mixture of **16b** and **17b** (**16b**–**17b**=85:15). Recrystallization (ethyl acetate–hexane 1:2) gave pure **16b** (colourless crystals). TLC (ethyl acetate–petroleum ether 1:4) R_f 0.33. Mp (ethyl acetate–hexane) 99–99.5°C. $[\alpha]_D^{20}$=19.5° (*c*: 1.23; $CHCl_3$). HPLC (Novapak C18, methanol–water 80:20, 0.4 ml/min, 20°C) $R_{t\mathbf{16b}}$ 38.7 min, $R_{t\mathbf{17b}}$ 43.1 min. ^{1}H NMR (300 MHz) 7.68 (m, 4H), 7.34–7.46 (m, 6H), 6.06 (ddd, 1H, *J*=17.2, 10.3, 8.5 Hz), 5.19 (d, 1H, *J*=10.4 Hz), 5.08 (d, 1H, *J*=17.2 Hz), 5.01 (t, 1H, *J*=6.9, 6.8 Hz), 4.24 (m, 1H, *J*=3.6 Hz), 2.96–3.11 (m, 2H), 2.55–2.65 (m, 1H), 2.46 (m, 1H, *J*=8.3, 3.5 Hz), 2.09 (d, 1H, *J*=15.5, 1.5 Hz), 1.73 (ddd, 1H, *J*=15.5, 6.9, 4.2 Hz), 1.05 (s, 9H). ^{13}C NMR (75 MHz) 177.6, 136.2, 134.7, 133.5, 132.9, 129.8, 129.7, 127.6, 127.5, 118.5, 84.5, 77.2, 52.1, 41.6, 41.4, 31.2, 27, 19.1. IR ν_{max} (thin film) 1766 (C=O). MS *m*/*z* 349 ($[M-t\text{-Bu}]^+$). Calculated for $C_{25}H_{30}O_3Si$: C, 73.85; H, 7.43. Found: C, 73.65; H, 7.49.

5.3.3. (1*S*,5*R*,6*R*,7*R*)-7-(Benzoyloxy)-6-vinyl-2-oxabicyclo[3.3.0]octan-3-one 16c. 8.0 g (31.2 mmol) **14a** gave 7.03 g (83%, colourless solid) of a mixture of **16c** and **17c** (**16c**–**17c**=89:11). Recrystallization (ethyl acetate–hexane 1:2) gave pure **16c** (colourless crystals). TLC (ethyl acetate–petroleum ether 1:1) R_f 0.78. Mp (ethyl acetate–hexane) 69.6°C. $[\alpha]_D^{20}$=−28.7° (*c*: 1.00; $CHCl_3$). HPLC (Hypersil Phenyl, acetonitrile–water 40:60, 0.5 ml/min, 20°C) $R_{t\mathbf{17c}}$ 9.7 min, $R_{t\mathbf{16c}}$ 15.6 min. ^{1}H NMR (300 MHz) 8.01 (dd, 2H, *J*=8.7, 1.5 Hz), 7.57 (tt, 1H, *J*=7.4, 1.6 Hz), 7.45 (t, 2H, *J*=7.5 Hz), 5.76 (ddd, 1H, *J*=17.6, 10, 7.2 Hz), 5.28 (m, 1H, *J*=6.3, 5.6 Hz), 5.19 (d, 1H, *J*=17.1 Hz), 5.17 (d, 1H, *J*=10.4 Hz), 5.07 (td, 1H, *J*=5.6, 1.9 Hz), 2.80–2.93 (m, 2H), 2.76 (q, 1H, *J*=5.5 Hz), 2.60 (dt, 1H, *J*=15.5, 6.5, 6 Hz), 2.53 (m, 1H, *J*=15.9 Hz), 2.24 (ddd, 1H, *J*=15.6, 4.7, 1.7 Hz). ^{13}C NMR (75 MHz) 176.4, 166.0, 136.3, 133.3, 129.8, 129.6, 128.5, 117.5, 83.3, 78.9, 55.1, 42.2, 37.5, 34.9. IR ν_{max} (thin film) 1773 (C=O lactone), 1712 (C=O benzoate). MS *m*/*z* 272 ($M^{+\circ}$). Calculated for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.30; H, 5.79.

5.3.4. (1*S*,5*R*,6*S*,7*R*)-7-(Benzoyloxy)-6-vinyl-2-oxabicyclo[3.3.0]octan-3-one 16d. 1.0 g (3.9 mmol) **14b** gave 920 mg (87%, colourless solid) of a mixture of **16d** and **17d** (**16d**–**17d**=87:13). Recrystallization (ethyl acetate–hexane 1:2) gave pure **16d** (colourless crystals). TLC (ethyl acetate–petroleum ether 1:1) R_f 0.7. Mp (ethyl acetate–hexane) 133.4°C. $[\alpha]_D^{20}$=−40.1° (*c*: 0.99; $CHCl_3$). HPLC (Novapak C18, methanol–water 50:50, 0.5 ml/min, 20°C) $R_{t\mathbf{16d}}$ 27.8 min, $R_{t\mathbf{17d}}$ 32.2 min. ^{1}H NMR (300 MHz) 7.95 (dd, 2H), 7.56 (tt, 1H, *J*=7.3, 1.6 Hz), 7.45 (t, 2H, *J*=7.6 Hz), 5.89 (ddd, 1H, *J*=17.3, 10.2, 7.5 Hz), 5.60 (t, 1H, *J*=4.9, 4.1 Hz), 5.26 (d, 1H, *J*=10.5 Hz), 5.22 (d, 1H, *J*=17 Hz), 5.19 (t, 1H, *J*=7 Hz), 3.29 (m, 1H, *J*=11.5, 8.9, 4.4 Hz), 2.96 (m, 1H), 2.89 (dd, 1H, *J*=18.9, 4.4 Hz), 2.70 (dd, 1H, *J*=18.9, 11.5 Hz), 2.47 (d, 1H, *J*=15.9 Hz), 2.23 (ddd, 1H, *J*=16.1, 6.5, 4.3 Hz). ^{13}C NMR (75 MHz) 176.9, 165.9, 133.2, 132.3, 129.6, 128.5, 119.8, 84.1, 77.8, 50.0, 41.4, 39.7, 30.9. IR ν_{max} (thin film) 1753 (C=O lactone), 1718 (C=O benzoate). MS *m*/*z* 272 ($M^{+\circ}$). Calculated for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.47; H, 5.72.

5.3.5. (1*S*,5*R*,6*R*,7*S*)-7-(*tert*-Butyldiphenylsilyloxy)-6-vinyl-2-oxabicyclo[3.3.0]octan-3-one 16e. 126 mg (0.32 mmol) **15a** gave 125 mg **16e** (94%, colourless crystals). TLC (ethyl acetate–petroleum ether 1:4) R_f 0.58. $[\alpha]_D^{20}$=6.2° (*c*: 1.00; $CHCl_3$). ^{1}H NMR (300 MHz) 7.62 (m, 4H), 7.34–7.46 (m, 6H), 5.99 (ddd, 1H, *J*=17.5, 10.1, 8.5 Hz), 5.06–5.14 (m, 2H), 5.01 (m, 1H, *J*=7.1, 7, 3.6 Hz), 4.43 (t, 1H, *J*=3.8, 3.4 Hz), 3.02 (m, 1H, *J*=9.8, 8.9, 1 Hz), 2.75 (dd, 1H, *J*=18.1, 9.3 Hz), 2.33 (dd, 1H, *J*=18.3, 1.3 Hz), 2.14 (m, 1H, *J*=8.8, 3.3 Hz), 2.10 (ddd, 1H, *J*=15.6, 6.8, 1.1 Hz), 1.76 (dt, 1H, *J*=15.2, 4.3, 3.5 Hz), 1.06 (s, 9H). ^{13}C NMR (75 MHz) 176.9, 135.9, 135.7, 134.1, 133.2, 129.8, 127.7, 127.6, 117.4, 84.2, 77.7, 55.9, 42.4, 42.2, 33.3, 27.0, 19.4. IR ν_{max} (thin film) 1772 (C=O).

MS *m/z* 349 ([M−*t*-Bu]$^+$). Calculated for $C_{25}H_{30}O_3Si$: C, 73.85; H, 7.43. Found: C, 73.89; H, 7.43.

5.3.6. (1*S*,5*R*,6*S*,7*S*)-7-(*tert*-Butyldiphenylsilyloxy)-6-vinyl-2-oxabicyclo[3.3.0]octan-3-one 16f. 63 mg (0.15 mmol) **15b** gave 66 mg **16f** (100%, colourless gel which solidified after a few hours). TLC (ethyl acetate–petroleum ether 1:9) R_f 0.49. $[\alpha]_D^{20}=-28.7°$ (*c*: 1.00; $CHCl_3$). ^{1}H NMR (300 MHz) 7.61 (m, 4H), 7.34–7.47 (m, 6H), 5.37 (ddd, 1H, *J*=17.5, 10.9, 8.4 Hz), 5.08 (dd, 1H, *J*=10.3, 1.4 Hz), 5.02 (ddd, 1H, *J*=7.5, 5.7, 3.5 Hz), 4.97 (dd, 1H, *J*=16.9, 1.9 Hz), 4.17 (m, 1H, *J*=5.6, 5.5 Hz), 3.17 (m, 1H), 2.66 (td, 1H, *J*=8.7, 8.3, 5.6 Hz), 2.54 (dd, 1H, *J*=18.7, 10.4 Hz), 2.36 (dd, 1H, *J*=18.6, 3.7 Hz), 1.99–2.05 ((AB)MX, 2H, *J*=14.7, 5.6, 5.7, 3.4, 5.6 Hz), 1.06 (s, 9H). ^{13}C NMR (75 MHz) 177.0, 135.8, 135.7, 134.7, 133.8, 133.5, 129.8, 127.7, 119.5, 83.7, 77.2, 54.7, 40.1, 39.9, 30.6, 27.0, 19.1. IR ν_{max} (thin film) 1772 (C=O). MS *m/z* 349 ([M−*t*-Bu]$^+$). Calculated for $C_{25}H_{30}O_3Si$: C, 73.85; H, 7.43. Found: C, 73.65; H, 7.21.

5.3.7. (1*S*,5*R*,6*S*,7*R*)-7-(*tert*-Butyldiphenylsilyloxy)-6-hydroxymethyl-2-oxabicyclo[3.3.0]octan-3-one 18. A stream of ozone was passed through a solution of **16a** (900 mg, 2.21 mmol) in 80 ml dichloromethane at −78°C until the apparition of a blue colour. Excess ozone was removed with a stream of argon and the solution of ozonide was quenched with 0.80 ml (8.84 mmol) borane–dimethyl sulphide complex then warmed up to room temperature. Addition of 1 ml 1 M aqueous HCl, stirring at room temperature for 1 h and neutralization with $NaHCO_3$ gave a crude residue which was purified by flash chromatography (ethyl acetate–cyclohexane 3:7) to give 667 mg of **18** (74%, white solid). TLC (ethyl acetate–cyclohexane 1:1) R_f 0.34. Mp 166.2°C. $[\alpha]_D^{20}=-32.5°$ (*c*: 1.23; $CHCl_3$). ^{1}H NMR (300 MHz) 7.67 (m, 4H), 7.36–7.48 (m, 6H), 4.84 (dt, 1H, *J*=6.9, 4.4 Hz), 4.10 (q, 1H, *J*=5.5 Hz), 3.37 (t, 2H, *J*=4.9 Hz), 2.80 (dd, 1H, *J*=17.6, 9.9 Hz), 2.65 (m, 1H), 2.57 (dd, 1H, *J*=17.6, 2.6 Hz), 2.08 (t, 2H, *J*=5.5 Hz), 2.01 (m, 1H, *J*=5.8, 5.6, 5.4 Hz), 1.05 (s, 9H). ^{13}C NMR (75 MHz) 177.0, 135.9, 135.8, 133.6, 133.4, 129.9 (2×), 127.8, 127.7, 83.8, 75.3, 61.8, 56.5, 40.8, 38.8, 35.5, 26.9, 19.0. IR ν_{max} (KBr) 3488 (O–H), 1757 (C=O lactone). MS *m/z* 353 ([M−*t*-Bu]$^+$). Calculated for $C_{24}H_{30}O_4Si$: C, 70.20; H, 7.36. Found: C, 69.97; H, 7.32.

5.3.8. (1*S*,5*R*,6*R*,7*R*)-7-(*tert*-Butyldiphenylsilyloxy)-6-formyl-2-oxabicyclo[3.3.0]octan-3-one 19. Same as for the synthesis of **18** using 1.76 ml (24 mmol) of dimethyl sulphide to quench the ozonide. Purification by flash chromatography (ethyl acetate–petroleum ether 1:1) yielded 1.88 g **19** (77%, unstable colourless gel, becomes yellow after a few hours). TLC (ethyl acetate–petroleum ether 1:1) R_f 0.64. $[\alpha]_D^{20}=-50.5°$ (*c*: 1.4; $CHCl_3$).^{1}H NMR (300 MHz) 9.30 (s, 1H), 7.68 (m, 4H), 7.39–7.47 (m, 6H), 5.00 (t, 1H, *J*=6.7 Hz), 4.52 (m, 1H), 3.32 (m, 1H), 2.92 (dd, 1H, *J*=18.4, 11.2 Hz), 2.89 (br, 1H), 2.57 (dd, 1H, *J*=18.4, 3.3 Hz), 2.23 (d, 1H, *J*=15.4 Hz), 1.68 (ddd, 1H, *J*=15.3, 6.3, 5.1 Hz), 1.07 (s, 9H). ^{13}C NMR (75 MHz) 198.6, 176.4, 135.9, 135.8, 132.9, 130.2, 130.1, 128.0, 127.9, 84.6, 74.6, 68.1, 40.7, 36.3, 35.8, 26.8, 18.9. IR ν_{max} (thin film) 1772 (C=O lactone), 1724 (C=O aldehyde). MS *m/z* 351 ([M−*t*-Bu]$^+$). HRMS (EI) calculated for $C_{20}H_{19}O_4Si$ ([M−*t*-Bu]$^+$): 351.105263. Found, 351.105927.

The reaction with 700 mg (1.72 mmol) of a mixture of **16a** and **16b** gave 399 mg **19** (57%) and 61 mg **20** (23%, unstable colourless gel, spectroscopic data identical to that of literature[33]).

5.3.9. Epoxidation reaction. 1.63 g (4 mmol) **16a** and 2.21 g (8 mmol) *m*CPBA (technical grade) were dissolved in 10 ml dichloromethane and the resulting mixture was stirred overnight at room temperature then treated with 8 ml 1 M aqueous sodium thiosulphate. The aqueous layer was dried over magnesium sulphate and concentrated in vacuo. The crude product was purified by flash chromatography (ethyl acetate–petroleum ether 4:6) to give 1.31 g **21a** (78%, colourless needles) and 326 mg **21b** (19%, colourless crystals).

(1*S*,5*R*,6*S*,7*R*)-7-(*tert-Butyldiphenyl-silyloxy*)-6-[(*S*)-*oxiran*-2-*yl*]-2-*oxabicyclo*[3.3.0]*octan*-3-*one* **21a**. TLC (ethyl acetate–pentane 1:1) R_f 0.73. Mp 87.4°C. $[\alpha]_D^{20}=-27.3°$ (*c*: 1.19; $CHCl_3$). ^{1}H NMR (300 MHz) 7.66 (m, 4H), 7.37–7.48 (m, 6H), 4.87 (td, 1H, *J*=6.8, 2.7 Hz), 4.17 (m, 1H, *J*=5.1, 4.9 Hz), 2.81 (dd, 1H, *J*=18.8, 11.2 Hz), 2.51–2.66 (m, 4H), 2.29 (dd, 1H, *J*=4.6, 2.7 Hz), 2.09 (m, 1H, *J*=15, 4.7, 2.4 Hz), 2.03 (m, 1H, *J*=15.1, 6.1, 5.5 Hz), 1.85 (m, 1H, *J*=5.6, 5.2 Hz), 1.06 (s, 9H). ^{13}C NMR (75 MHz) 176.8, 135.9, 135.8, 133.2, 130.0, 129.9, 127.8, 127.7, 83.6, 76.8, 56.2, 52.2, 45.8, 41.0, 38.5, 35.4, 26.7, 18.9. IR ν_{max} (KBr) 1773 (C=O lactone). MS *m/z* 365 ([M−*t*-Bu]$^+$). Calculated for $C_{25}H_{30}O_4Si$: C, 71.05; H, 7.15. Found: C, 70.86; H, 7.27.

(1*S*,5*R*,6*S*,7*R*)-7-(*tert-Butyldiphenyl-silyloxy*)-6-[(*R*)-*oxiran*-2-*yl*]-2-*oxabicyclo*[3.3.0]*octan*-3-*one* **21b**. TLC (ethyl acetate–pentane 1:1) R_f 0.52. Mp 101.4°C. $[\alpha]_D^{20}=-29.9°$ (*c*: 0.99; $CHCl_3$). ^{1}H NMR (300 MHz) 7.67 (m, 4H), 7.36–7.48 (m, 6H), 4.95 (m, 1H, *J*=7.1, 6.5 Hz), 4.18 (dt, 1H, *J*=5.3, 2.6 Hz), 2.88 (dd, 1H, *J*=18.8, 11.7 Hz), 2.55–2.68 (m, 4H), 2.24 (dd, 1H, *J*=4.5, 2.8 Hz), 2.13–2.21 (m, 2H), 1.91 (m, 1H, *J*=15.4, 6.3, 5.2 Hz), 1.05 (s, 9H). ^{13}C NMR (75 MHz) 176.8, 135.9 (×2), 133.3, 133.2, 129.9 (×2), 127.8 (×2), 84.5, 76.6, 56.1, 51.8, 44.9, 41.0, 38.8, 36.1, 26.8, 18.9. IR ν_{max} (KBr) 1759 (C=O lactone). MS *m/z* 365 ([M−*t*-Bu]$^+$). Calculated for $C_{25}H_{30}O_4Si$: C, 71.05; H, 7.15. Found: C, 70.76; H, 7.21.

5.3.10. Hydroboration reaction. 203 mg (0.5 mmol) of **16a** were added to 0.25 ml (0.25 mmol) of a 1 M solution of BH_2Br–DMS complex in dichloromethane at 0°C. After 2 h at room temperature, 0.5 ml (3 mmol) of 6 M aqueous sodium hydroxide, 0.5 ml ethyl alcohol and 0.11 ml (1 mmol) of 30% hydrogen peroxide were successively added. The resulting biphasic mixture was stirred at room temperature for 1 h, then acidified with 6 M aqueous HCl and extracted with ethyl acetate. The organic layer was dried over magnesium sulphate and concentrated in vacuo. The residue (276 mg, yellow oil) was purified by flash chromatography (ethyl acetate–hexane 1:4 to 1:2) to give 47 mg **23** (21%, white solid) and 126 mg **22** (60%, white solid). Acetylation of **22**: 250 mg (0.59 mmol) **22**, 0.11 ml (1.18 mmol) acetic anhydride and 0.1 ml (1.18 mmol) pyridine were stirred overnight at room temperature in

1 ml THF. The reaction mixture was then diluted with ethyl acetate (5 ml) and poured into 2 ml aqueous 1 M HCl. The organic layer was dried over sodium carbonate and concentrated under vacuum to give 260 mg crude **23** (100% pale yellow crystals) which did not require further purification.

(1*S*,5*R*,6*R*,7*R*)-7-(*tert-Butyldiphenylsilyloxy*)-6-(2-*hydroxyethyl*)-2-*oxabicyclo*[3.3.0]*octan*-3-*one* **22**. TLC (ethyl acetate–petroleum ether 3:2) R_f 0.23. Mp 95–95.5°C. $[\alpha]_D^{20}=-27.2°$ (*c*: 1.93; $CHCl_3$). ^1H NMR (300 MHz) 7.68 (m, 4H), 7.37–7.49 (m, 6H), 4.92 (m, 1H, *J*=7.4, 6.4, 1.8 Hz), 3.98 (m, 1H), 3.41–3.43 (m, 2H), 2.85 (dd, 1H, *J*=18.4, 10.9 Hz), 2.67 (dd, 1H, *J*=18.4, 3.6 Hz), 2.55 (m, 1H, *J*=10.9, 3.9 Hz), 2.09 (dd, 1H, *J*=14.9, 3.1 Hz), 2.03 (m, 1H), 1.95 (ddd, 1H, *J*=15.1, 6.6, 5.2 Hz), 1.29–1.37 (m, 3H), 1.05 (s, 9H). ^{13}C NMR (75 MHz) 177.4, 135.9, 133.5, 133.4, 129.9, 129.8, 127.8, 127.7, 84.1, 78.8, 60.7, 51.7, 42.9, 40.2, 36.2, 35.8, 26.8, 19.0. IR ν_{max} (KBr) 3557 (O–H), 3439 (O–H), 1768 (C=O lactone). MS *m/z* 367 ([M−*t*-Bu]$^+$). Calculated for $C_{25}H_{32}O_4Si$: C, 70.71; H, 7.59. Found: C, 70.44; H, 7.57.

(1*S*,5*R*,6*R*,7*R*)-6-(2-*Acetoxyethyl*)-7-(*tert-butyldiphenylsilyloxy*)-2-*oxabicyclo*[3.3.0]*octan*-3-*one* **23**. TLC (ethyl acetate–petroleum ether 1:1) R_f 0.72. Mp (ethyl ether–pentane) 108.5–109.5°C. $[\alpha]_D^{20}=-9.6°$ (*c*: 0.99; $CHCl_3$). ^1H NMR (300 MHz) 7.65 (m, 4H), 7.36–7.47 (m, 6H), 4.92 (td, 1H, *J*=7.1, 2.1 Hz), 3.96 (q, 1H, *J*=4.1 Hz), 3.87 (t, 2H, *J*=6.6 Hz), 2.86 (dd, 1H, *J*=18.3, 11 Hz), 2.62 (dd, 1H, *J*=18.1, 3.6 Hz), 2.55 (m, 1H), 2.08 ((A)BMX, 1H, *J*=15.1, 3.8, 1.7 Hz), 1.99 (m, 1H), 1.99 (s, 3H), 1.94 (A(B)MX, 1H, *J*=15.1, 6.8, 5.1 Hz), 1.50 (m, 1H), 1.31 (m, 1H), 1.05 (s, 9H). ^{13}C NMR (75 MHz) 176.8, 170.6, 136.0, 135.9, 133.5, 129.9 (2×), 127.8, 127.7, 83.9, 78.9, 62.4, 52.1, 42.8, 40.4, 36.1, 32.0, 26.9, 20.8, 19.0. IR ν_{max} (KBr) 1763 (C=O lactone), 1736 (C=O acetate). MS *m/z* 409 ([M−*t*-Bu]$^+$). Calculated for $C_{27}H_{34}O_5Si$: C, 69.49; H, 7.34. Found: C, 69.20; H, 7.39.

5.3.11. Wacker oxidation. A suspension of 72 mg (0.4 mmol) palladium diacetate and 442 mg (4.46 mmol) cuprous chloride in DMF water (2.8 ml+0.8 ml was vigorously stirred at room temperature under an oxygen atmosphere for 90 min. The suspension became greenish due to the oxidation of Cu(I) to Cu(II). Then 1.65 g (4.06 mmol) **16a** in 2 ml DMF was added and the reaction mixture was stirred at room temperature until complete conversion (ca. 2 days). Addition of 12 ml of 1 M aqueous HCl and 12 ml ethyl acetate followed by separation of the organic layer which was concentrated in vacuo. The residue was purified by flash chromatography (ethyl acetate–petroleum ether 3:7 then 4:6) to give 1.30 g **24** (76%, white solid) and 290 mg **25** (17%, colourless gel).

(1*S*,5*R*,6*R*,7*R*)-6-*Acetyl*-7-(*tert-butyldiphenylsilyloxy*)-2-*oxabicyclo*[3.3.0]*octan*-3-*one* **24**. TLC (ethyl acetate–petroleum ether 3:7) R_f 0.19. Mp 80–81°C. $[\alpha]_D^{20}=-76.3°$ (*c*: 1.58; $CHCl_3$). GC (Permabond SE-52, 100–290°C, 10°C/min) R_t 26.6 min. ^1H NMR (300 MHz) 7.69 (m, 4H), 7.38–7.50 (m, 6H), 5.07 (t, 1H, *J*=7.5, 6.3 Hz), 4.34 (m, 1H, *J*=4.3, 1.5 Hz), 3.24 (m, 1H, *J*=11, 3.1, 7 Hz), 3.05 (br, 1H), 2.90 (dd, 1H, *J*=18.4, 11.5 Hz), 2.58 (dd, 1H, *J*=18.4, 3.6 Hz), 2.22 (d, 1H, *J*=15.3 Hz), 1.76 (ddd, 1H, *J*=15, 4.7, 6.3 Hz), 1.73 (s, 3H), 1.07 (s, 9H). ^{13}C NMR (75 MHz) 206.9, 176.7, 135.9, 133.0, 132.7, 130.2, 130.0, 128.0, 127.9, 85.3, 77.2, 68.6, 40.6, 38.7, 35.9, 29.3, 26.8, 19.0. IR ν_{max} (KBr) 1775 (C=O lactone), 1710 (C=O ketone). MS *m/z* 365 ([M−*t*-Bu]$^+$). Calculated for $C_{25}H_{30}O_4Si$: C, 71.05; H, 7.15. Found: C, 70.81; H, 7.13.

(1*S*,5*R*,6*R*,7*R*)-7-(*tert-Butyldiphenylsilyloxy*)-6-*formylmethyl*-2-*oxabicyclo*[3.3.0]*octan*-3-*one* **25**. TLC (ethyl acetate–petroleum ether 3:7) R_f 0.1. $[\alpha]_D^{20}=-17.4°$ (*c*: 1.41; $CHCl_3$). GC (Permabond SE-52, 100–290°C, 10°C/min) R_t 28.7 min. ^1H NMR (300 MHz) 9.48 (t, 1H, *J*=1.3 Hz), 7.66 (m, 4H), 7.37–7.48 (m, 6H), 4.88 (td, 1H, *J*=7, 2.7 Hz), 3.91 (q, 1H, *J*=4.8 Hz), 2.84 (dd, 1H, *J*=18.6, 10.4 Hz), 2.71 (dd, 1H, *J*=18.5, 3.5 Hz), 2.49 (m, 1H), 2.28–2.41 (m, 2H, *J*=5.2, 1.3 Hz), 2.15 (ddd, 1H, *J*=17.1, 8.3, 1.5 Hz), 2.08 (m, 1H, *J*=16.4 Hz), 1.98 (m, 1H, *J*=15.1, 6.6, 5.4 Hz), 1.05 (s, 9H). ^{13}C NMR (75 MHz) 200.0, 176.8, 135.9, 135.8, 133.2, 129.9, 127.8, 127.7, 83.4, 78.2, 48.8, 46.5, 42.5, 40.2, 35.7, 26.8, 19.0. IR ν_{max} (thin film) 1768 (C=O lactone), 1727 (C=O aldehyde). MS *m/z* 365 ([M−*t*-Bu]$^+$). HRMS (EI) calculated for $C_{21}H_{21}O_4Si$ ([M−*t*-Bu]$^+$): 365.120913. Found, 365.120386.

5.3.12. (1*S*,5*R*,6*R*,7*R*)-7-(*tert*-butyldiphenylsilyloxy)-3-oxo-2-oxabicyclo[3.3.0]octane-6-carboxylic acid 26. 13.5 ml (36 mmol) of 2.67 M Jones reagent and 1.22 ml (0.2 mmol) of a 4% aqueous solution of OsO_4 were added to 4.07 g (10 mmol) of **16a** in 50 ml acetone. The reaction mixture was stirred at room temperature for 24 h. Addition of 5 ml 2-propanol and 3 g sodium hydrogen sulphite then of 100 ml water gave an homogeneous green solution after 90 min. Extraction with ethyl acetate and concentration of the organic solution in vacuo gave a residue (4 g) which was recrystallized from ethyl acetate–cyclohexane (3:10) to give 3.39 g **26** (80%, white needles). Mp 144–145°C. $[\alpha]_D^{20}=-35.2°$ (*c*: 1.22; $CHCl_3$). ^1H NMR (300 MHz) 10.91 (br, 1H), 7.65 (m, 4H), 7.34–7.44 (m, 6H), 5.01 (t, 1H, *J*=7.6 Hz), 4.52 (m, 1H, *J*=3 Hz), 3.19 (m, 1H, *J*=11, 3.8 Hz), 2.90 (m, 1H, *J*=3 Hz), 2.89 ((A)BX, 1H, *J*=18.4, 11.3 Hz), 2.66 (A(B)X, 1H, *J*=18.4, 3.8 Hz), 2.25 (d, 1H, *J*=14.7 Hz), 1.04 (s, 9H), 1.04 (dt, 1H, *J*=14.7, 6.5, 5.1 Hz). ^{13}C NMR (75 MHz) 177.5, 176.4, 135.9, 135.8, 132.8, 132.7, 130.0, 129.9, 127.8, 84.5, 77.6, 59.6, 40.8, 40.4, 35.6, 26.7, 18.9. IR ν_{max} (KBr) 3100 (O–H), 1746 (C=O). MS *m/z* 367 ([M−*t*-Bu]$^+$). Calculated for $C_{24}H_{28}O_5Si$: C, 67.89; H, 6.64. Found: C, 67.74; H, 6.83.

5.3.13. (1*S*,5*R*,6*R*,7*R*)-7-(*tert*-Butyldiphenylsilyloxy)-6-benzyloxycarbonylamino-2-oxabicyclo[3.3.0]octan-3-one 27. A solution of 424 mg (1 mmol) of **26**, 0.15 ml (1.1 mmol) triethylamine, 0.41 ml benzyl alcohol and 0.24 ml (1.1 mmol) diphenylphosphoryl azide in 2 ml benzene was refluxed for 24 h. Addition of 15 ml ethyl acetate followed successively by 5 ml 1 M aqueous HCl, 5 ml 1 M aqueous NaOH and 5 ml water led to **27** (835 mg) which was purified by flash chromatography (ethyl acetate–petroleum ether 1:3 to 1:1). Yield: 415 mg (78%, colourless solid). TLC (ethyl acetate–petroleum ether 1:3) R_f 0.24. Mp 126.5–127°C. $[\alpha]_D^{20}=25.5°$ (*c*: 1.89; $CHCl_3$). ^1H NMR (300 MHz) 7.64 (m, 4H), 7.26–7.46 (m, 11H), 5.00–5.03 (AB, 2H, *J*=12.3 Hz), 4.84 (m, 1H, *J*=7.2, 4.6 Hz), 4.47 (br,

1H), 3.99 (q, 1H, *J*=5.1 Hz), 3.87 (m, 1H, *J*=6.9, 4.9 Hz), 2.67–2.81 (m, 3H), 2.04 (br, 2H), 1.03 (s, 9H). ^{13}C NMR (75 MHz) 176.5, 155.5, 136.1, 135.9, 133.1, 132.8, 130.0, 128.5, 128.3, 128.1, 127.8 (2×), 81.7, 77.2, 66.9, 64.9, 43.2, 39.1, 34.2, 26.7, 19.0. IR ν_{max} (KBr) 3340 (N–H), 1744 (C=O lactone), 1711 (C=O carbonate). MS *m/z* 472 ([M−*t*-Bu]$^+$). Calculated for $C_{31}H_{35}NO_5Si$: C, 70.29; H, 6.66; N, 2.64. Found: C, 69.93; H, 6.71; N, 2.62.

5.3.14. (1*S*,5*R*,6*R*,7*R*)-6-Amino-7-(*tert*-butyldiphenylsilyloxy)-2-oxabicyclo[3.3.0]octan-3-one 28. A solution of 100 mg (0.19 mmol) of **27** in 2 ml of methanol and 1 ml of THF was hydrogenated at room temperature in the presence of 10 mg of 10% dry Pd/C catalyst. After completion of the reaction (3 h), the catalyst was filtered off and the solvents were removed under vacuum to give 73 mg of **28** (98%—colourless film). ^{1}H NMR (200 MHz) 7.64–7.69 (m, 4H), 7.37–7.45 (m, 11H), 4.95 (dt, 1H, *J*=7.1, 2.0 Hz), 3.83 (m, 1H, *J*=4.8, 4.2 Hz), 3.18 (t, 1H, *J*=4.0 Hz), 2.65–2.78 ((AB)X, 2H, *J*=18.4, 10.4, 4.0 Hz), 2.48 (m, 1H), 2.20 (ddd, 1H, *J*=15.0, 6.6, 5.6 Hz), 2.03 (dm, 1H, *J*=15.1 Hz), 1.36 (br, 2H), 1.03 (s, 9H). ^{13}C NMR (50 MHz) 177.1, 135.8, 135.7, 133.4, 133.2, 129.9 (2×), 127.8, 127.7, 83.5, 80.6, 65.6, 45.0, 39.1, 34.1, 26.7, 18.9. IR ν_{max} (KBr) 3377 (N–H), 1770 (C=O lactone). MS *m/z* 396 ([M+H]$^+$).

5.3.15. Barton reaction on 26. 425 mg (1 mmol) of **26** and 0.24 ml (1 mmol) of triethylamine were successively added at room temperature in the dark to a well stirred suspension of 209 mg (1.1 mmol) of **32** in 10 ml toluene. After complete conversion of **26** (ca. 45 min in the dark, reaction followed by TLC), the precipitate was filtered off. The resulting clear solution of **29** and a solution of 1 ml (9 mmol) of *tert*-butyl thiol in 10 ml toluene were added simultaneously into a reactor containing 10 ml toluene through which an oxygen stream was passed. During the addition, the reactor was either warmed up to 80°C or irradiated at room temperature with a 500-W halogen lamp. The stream of oxygen was passed through the reaction mixture for an additional hour after the end of the addition of **29** and thiol. The reaction mixture was quenched with 0.25 ml (2.1 mmol) of trimethyl phosphite and stirred at room temperature for 24 h. Volatile products were removed under vacuum and the residue was purified by flash chromatography (ethyl acetate–petroleum ether 15:85 to 40:60). Thermal reaction: 103 mg **31** (21%, colourless gel) and 113 mg **30** (29%, white solid). Photochemical reaction: 190 mg **30** (45%, white solid).

(1*S*,5*S*,6*R*,7*R*)-7-(*tert-Butyldiphenylsilyloxy*)-6-*hydroxy*-2-*oxabicyclo*[3.3.0]*octan*-3-*one* **30**. TLC (ethyl acetate–petroleum ether 2:3) R_f 0.31. Mp 132.7°C. $[\alpha]_D^{20}=-13.2°$ (*c*: 1.00; $CHCl_3$). ^{1}H NMR (300 MHz) 7.67 (m, 4H), 7.36–7.45 (m, 6H), 5.04 (m, 1H, *J*=6.7, 3.8 Hz), 4.04 (m, 1H, *J*=3.2, 2.1 Hz), 4.00 (br, 1H), 2.64–2.87 (m, 3H), 2.10 (m, 2H), 1.71 (br, 1H), 1.05 (s, 9H). ^{13}C NMR (75 MHz) 177.0, 135.9, 135.7, 133.4, 133.0, 129.9, 127.8 (2×), 83.9, 83.4, 79.9, 45.3, 38.8, 33.4, 26.8, 19.0. IR ν_{max} (KBr) 3406 (O–H), 1741 (C=O). MS *m/z* 339 ([M−*t*-Bu]$^+$). Calculated for $C_{23}H_{28}O_4Si$: C, 69.66; H, 7.11. Found: C, 69.35; H, 7.12.

(1*S*,5*S*,6*R*,7*R*)-7-(*tert-Butyldiphenylsilyloxy*)-6-(2-*pyridinylthio*)-2-*oxabicyclo*[3.3.0]*octan*-3-*one* **31**. TLC (ethyl acetate–petroleum ether 2:3) R_f 0.76. $[\alpha]_D^{20}=70.6°$ (*c*: 1.00; $CHCl_3$). ^{1}H NMR (300 MHz) 8.24 (dm, 1H, *J*=4.9, 1.8, 0.9 Hz), 7.67 (m, 4H), 7.26–7.44 (m, 7H), 7.01 (d, 1H, *J*=8 Hz), 6.97 (dd, 1H, *J*=7.2, 5 Hz), 5.06 (m, 1H, *J*=7.4, 3.7 Hz), 4.30 (m, 2H), 2.95–3.08 (m, 3H), 2.12 (t, 2H, *J*=3.6 Hz), 1.05 (s, 9H). ^{13}C NMR (75 MHz) 176.7, 157.3, 149.5, 136.0 (2×), 135.9, 133.2, 133.1, 129.8, 129.6, 127.6, 127.5, 122.5, 119.8, 84.3, 79.4, 56.9, 44.9, 40.2, 36.2, 26.8, 19.0. IR ν_{max} (thin film) 1771 (C=O). MS *m/z* 432 ([M−*t*-Bu]$^+$). HRMS (EI) calculated for $C_{24}H_{22}NO_3SSi$ ([M−*t*-Bu]$^+$): 432.108969. Found, 432.108825.

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