Application of [5+2] cycloaddition toward the functionalized bicyclo[4.3.1]decane ring system: synthetic study of phomoidride B (CP-263,114)†

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Received (in Cambridge, UK) 19th November 2001, Accepted 25th January 2002
First published as an Advance Article on the web 19th February 2002

Oxidopyrylium–alkene [5+2] cycloaddition was utilized in combination with an intramolecular aldol reaction to construct the bicyclo[4.3.1]decane ring system of phomoidride B (CP-263,114).

Introduction

Phomoidride B (CP-263,114 **1**) has attracted considerable interest since the original report of its isolation by a Pfizer group.[1] Phomoidride B possesses potent inhibitory activity against both farnesyl transferase[2] and squalene synthase[3] with IC_{50}-values in the micromolar range. The structural features of this compound lie in the anti-Bredt bridgehead double bond, a maleic anhydride moiety, a quaternary carbon center adjacent to the anti-Bredt bridgehead and most importantly this compound bears two hydrophobic moieties attached to the highly functionalized hydrophilic core. This ambiphilic structural nature is believed to be the key to its biological activities. Prompted by the promising biological activities as well as the fascinating structural features, numerous chemists have embarked on the total synthesis of phomoidride B[4] and so far four groups have completed the total synthesis of compound **1**.[5]

[5+2] Cycloaddition reaction between oxidopyrylium ylide and an alkene offers a suitably functionalized seven-membered ring in a relatively easy (heating of the reaction mixture or base-assisted) way[6] and has been applied to the synthesis of some seven-membered ring containing natural products.[7,8] Among them, Wender successfully applied this approach to the synthesis of phorbol[8a] and resiniferatoxin[8b] in which the [5+2] reaction was employed in an intramolecular fashion. Although there had been relatively few precedents of the utilization of intermolecular oxidopyrylium [5+2] cycloaddition to the synthesis of natural products, we anticipated that the bicyclo-[4.3.1]decane ring system, the core cyclic system of phomoidride B, could be constructed based on the [5+2] cycloaddition strategy followed by some further manipulations.

In this article we report our utilization of the [5+2] cycloaddition approach towards the highly substituted bicyclo-[4.3.1]decane ring system of **1**.

Results and discussion

Arising from our interest in the evaluation of the hydrophobic side chains of ambiphilic natural products,[9] we decided on an approach that would allow us to introduce the hydrophobic side chains (and possibly some variants) at a late stage of the synthesis. Thus, as illustrated in Scheme 1, our disconnection left us with bicycle **2** as our primal target, which could be envisaged as being derived from suitably functionalized oxabicyclic compound **3**. Compound **3** in turn could be viewed as the product from the reaction between oxidopyrylium ylide and a fumarate ester or its variant, thus providing an easy access to the maleic anhydride moiety of **1**.

On the basis of this retrosynthetic plan, we began the synthesis with but-2-ene-1,4-diol. After *tert*-butyldimethylsilyl (TBS) protection of the diol, the alkenic moiety was cleaved by means of ozonolysis to give 2 equiv. of aldehyde **6**. 2-Furyllithium prepared from furan and *n*-BuLi was added to this aldehyde to deliver furan adduct **7**. Treatment of **7** with *m*-CPBA followed by acetylation of the resultant lactol provided oxidopyrylium ylide precursor **8** (39% from but-2-enediol, diastereomeric ratio dr ≈ 2 : 1). We were pleased to find that treating **8** with dimethyl fumarate in the presence of triethylamine at the reflux temperature of acetonitrile delivered oxabicyclic compounds **9a** and **9b** in 65–77 % yield in a high diastereomeric ratio (dr ≈ 13 : 1, Scheme 2). Surprisingly, with other activated alkenes such as dimethyl maleate and maleic anhydride, we observed no desired reaction and only recovery or decomposition of the oxidopyrylium precursor, or, in the case of dimethyl maleate, isomerization of the maleate to the more stable fumarate ester. While the reason for this reactivity is unclear, this demonstrates the very subtle reactivity associated with intermolecular oxidopyrylium cycloaddition compared with the intramolecular one. The major product in this reaction can be rationalized to arise from the transition state in which the steric repulsion created by the sterically demanding $TBSOCH_2$- and one of the methoxycarbonyl groups on dimethyl fumarate is avoided as shown in Fig. 1.[10]

With the oxabicycles in hand we then decided on the construction of the bicyclo[4.3.1]decane ring system lacking the quaternary carbon center adjacent to a bridgehead as a model study. To this end, the alkenic moiety of compound **9a** was first reduced by hydrogenation in the presence of Pd on carbon to give compound **11**. Removal of TBS was done with aqueous HCl followed by iodination of the alcohol **12** to give iodide **13** in 64% yield (3 steps). Among several conditions we employed, the use of Zn proved to be the most effective in the subsequent reductive opening of the bridging ether of bicycle **13**, yielding exocyclic enone **14** in 96% yield.

Our initial focus was tuned to the introduction of the additional carbon chain for the construction of the desired bicyclo[4.3.1]decane ring system by the inverse-electron-demand Diels–Alder (IEDDA) reaction.[11] This was under the assumption that product **16** from the IEDDA reaction with certain silyl enol ethers would give rise to the bicyclo[4.3.1]decane ring

† Preliminary communication: N. Ohmori, *Chem. Commun.*, 2001, 1552.

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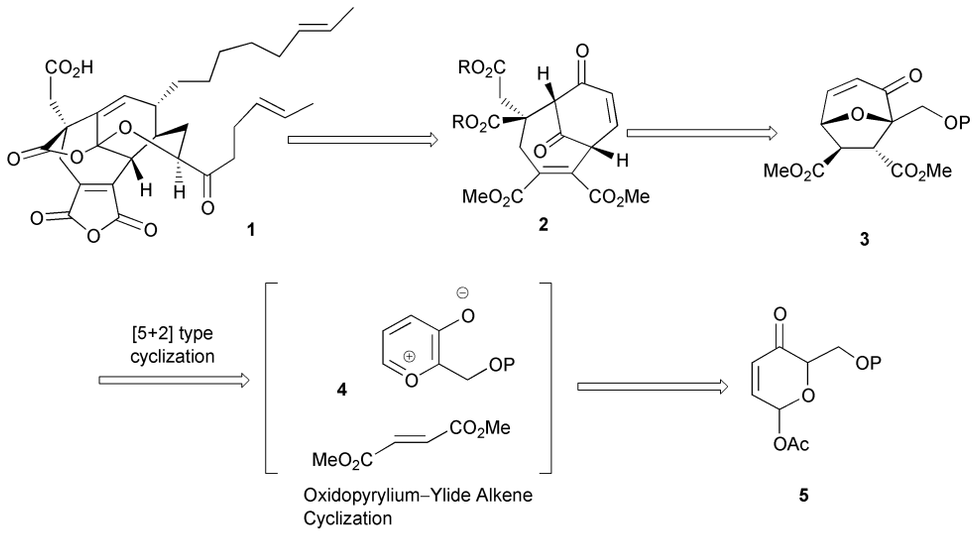
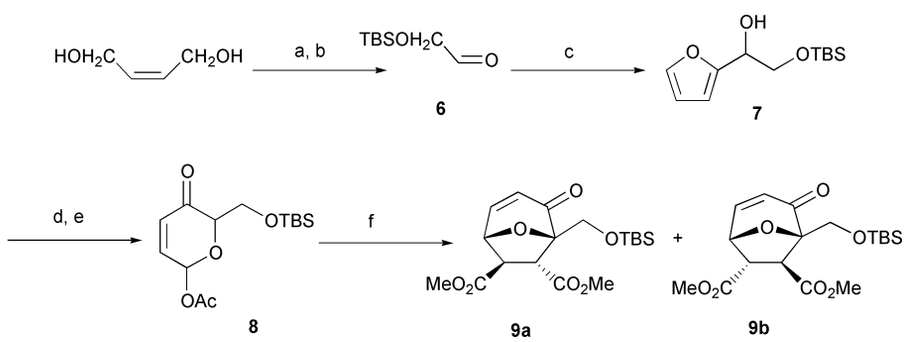
DOI: 10.1039/b110607b



Scheme 1 Strategy for the total synthesis of phomoidride B **1**.



Scheme 2 *Reagents and conditions (and yields)*: (a) TBSCl, Et_3N, DMAP, THF, rt; (b) O_3, MeOH, −78 °C; then $NaHCO_3$, Me_2S, −78 °C to rt; (c) 2-furyllithium, Et_2O, −78 °C to rt; (d) *m*-CPBA, CH_2Cl_2, 0 °C to rt; (e) Ac_2O, pyridine, rt (39% in 5 steps); (f) dimethyl fumarate, Et_3N, CH_3CN, reflux (77% **9a** : **9b**, 13 : 1).

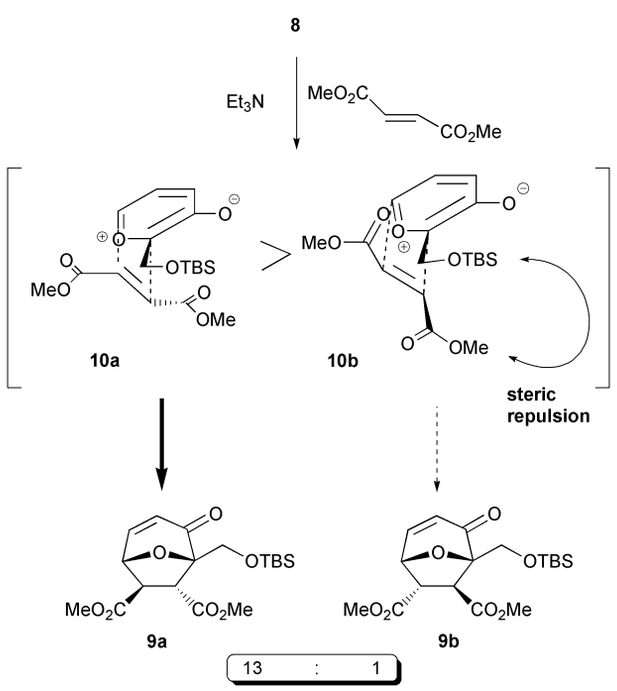
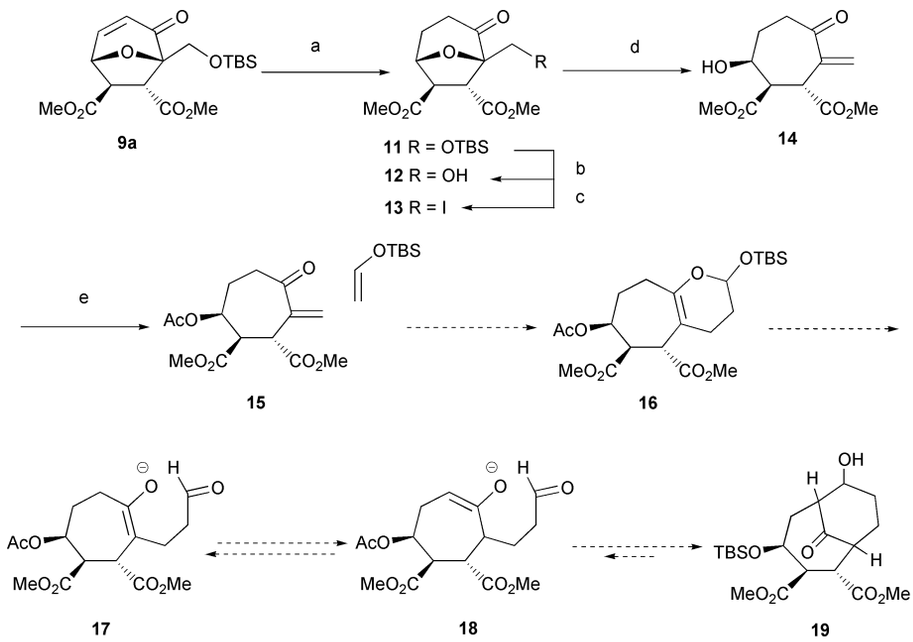


Fig. 1 Origin of stereoselectivity.

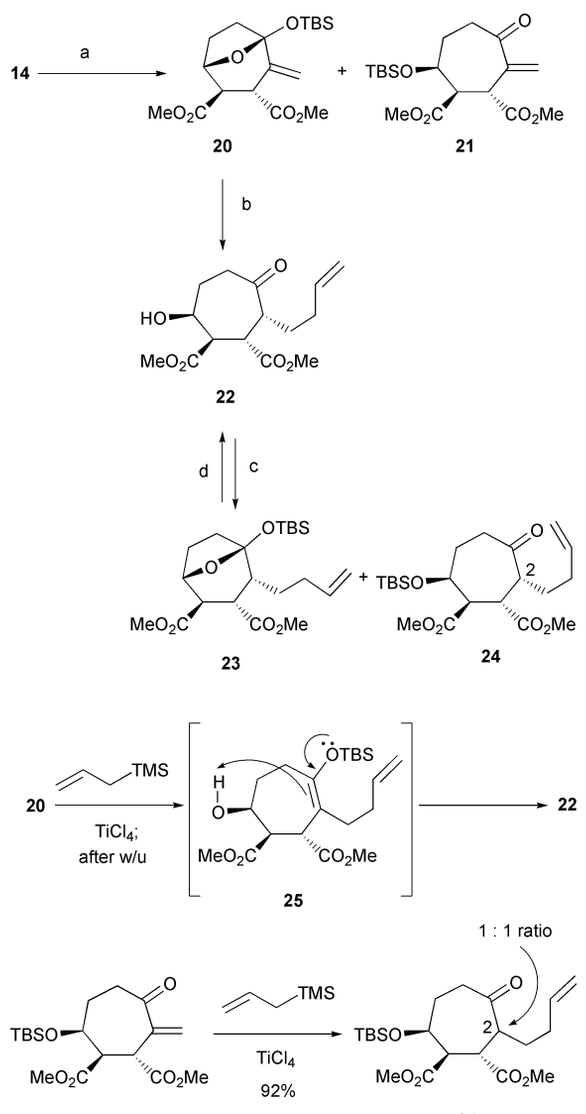
system upon treatment with fluoride *via* a thermodynamically driven ring-reconstruction.[12] However, enone **15**, protected with an acetyl group, turned out to be totally unreactive towards the IEDDA reaction with silyl enol ether even under sealed-tube (120 °C) conditions, resulting in only recovery of starting material (Scheme 3).

Having failed with the above strategy, we then attempted to install the two-carbon unit required for the construction of the bicyclic system by allylation followed by oxidative cleavage of the terminal alkene. To this end, the secondary hydroxy group of **14** was protected with TBSOTf in the presence of 2,6-dimethylpyridine (2,6-lutidine) to give ketal **20** (61%) along with exocyclic enone **21** (21%) as a minor component. Ketal **20** was treated with allyltrimethylsilane in the presence of $TiCl_4$ to give allylated product **22** with concomitant loss of the TBS group (82%). Compound **22** was obtained exclusively with no presence of the isomer based on the C2 stereocenter. The direct proton transfer from the hydroxy group in the intermediate silyl enol ether **25** formed upon work-up seems to be operative, thus leading to the observed selectivity since almost 1 : 1 selectivity was obtained with exocyclic enone **21** in the same transformation (Scheme 4).[13] The liberated free hydroxy group in compound **22** was once again protected with TBSOTf in the presence of 2,6-lutidine to give compound **24** (42%) along with the undesired ketal **23** (58%). Compound **23** could be recycled by TBS deprotection (87%) followed by reprotection to reproduce mixtures of **23** and **24**.[14] After three deprotection–protection sequences, compound **24** was obtained in a total yield of ≈ 60%, sufficient for further transformations.

By means of ozonolysis of **24**, the terminal alkene was cleaved to give a keto aldehyde (structure not shown; Scheme 5). Intramolecular aldol reaction under basic conditions[15] gave a crude aldol adduct, which was used directly without purification. Pyridinium chlorochromate (PCC) oxidation of this crude aldol adduct provided diones **26a** (66%) and **26b** (16%) bearing the desired bicyclo[4.3.1]decane ring system. To install the two hydrophobic side chains of phomoidride B, the major product **26a** needed to be converted to the corresponding enone. For this purpose, the Saegusa reaction was employed,

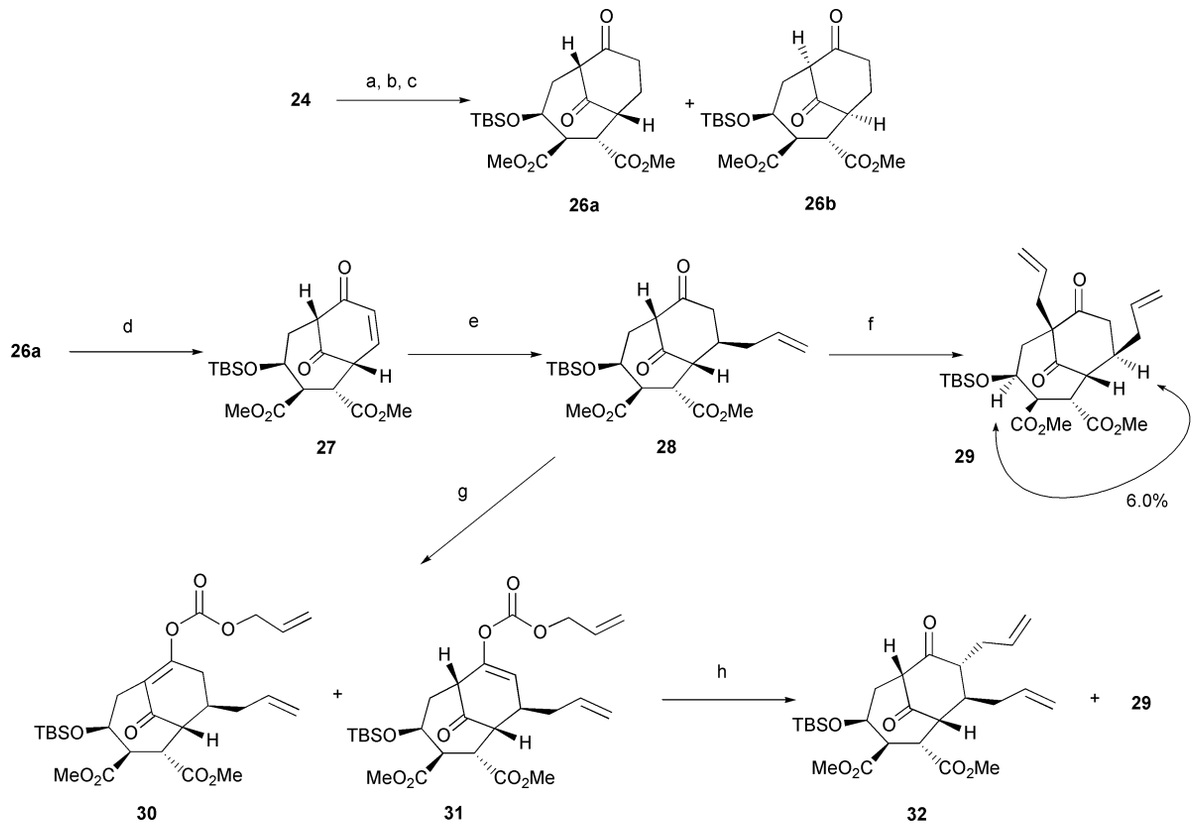


Scheme 3 IEDDA route to the bicyclo[4.3.1]decane core: *Reagents and conditions (and yields)*: (a) H_2, Pd/C, MeOH, rt; (b) aq. HCl, rt; (c) I_2, PPh_3, imidazole, benzene, reflux, (64% in 3 steps); (d) Zn, MeOH, reflux (96%); (e) Ac_2O, pyridine, 0 °C to rt (86%).

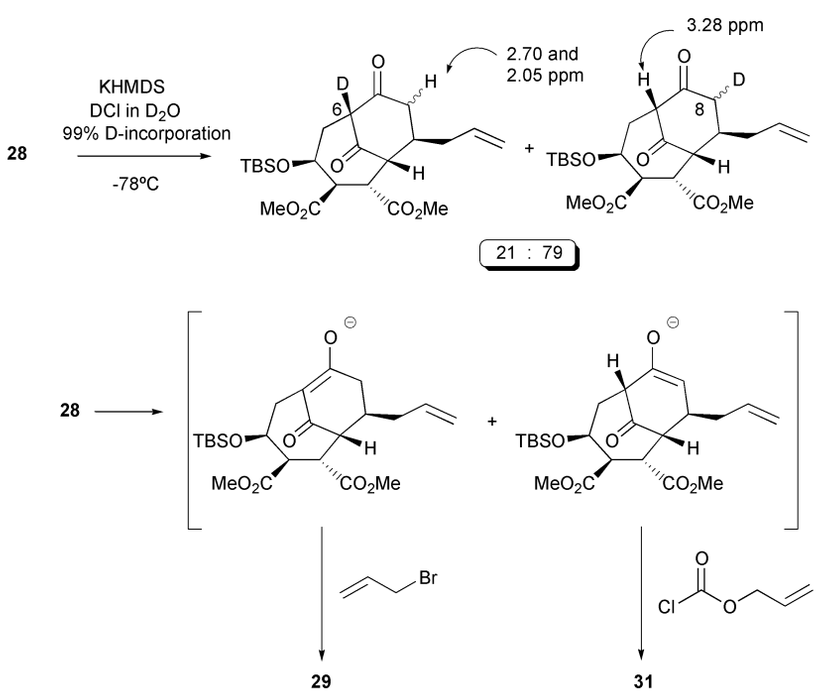


Scheme 4 *Reagents and conditions (and yields)*: (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C (82% **20** : **21**, 3 : 1); (b) allyltrimethylsilane, $TiCl_4$, CH_2Cl_2, −78 °C (82%); (c) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt (**23**, 58%; **24**, 42%); (d) TBAF, THF, rt (87%).

yielding enone **27** in rather low yield (35%).[16] An improved yield was achieved by employing the recently developed Nicolaou method using 2-iodosylbenzoic acid (IBX), providing enone (30%) along with starting material (42% recovery).[17] The recovered starting material was re-treated with IBX and this process was repeated twice to give a sufficient amount of enone **27** (42%, 52% based on consumed starting material) for further studies. 1,4-Addition of an allyl group under Lewis acidic conditions gave compound **28**, a product from convex-face attack of the enone as the sole stereoisomer in 57% yield. The diastereomeric identity of **28** was established upon carrying out NOE measurements on the product of the ensuing reaction (**29**). Attempts to introduce substituents α to the carbonyl group in a one-pot procedure met with failure and thus we decided to look into a stepwise method. To incorporate an additional allyl group at the α position of the ketone, compound **28** was treated with potassium hexamethyldisilazide (KHMDS) followed by allyl bromide. To our surprise, this allylation protocol proved to be disappointing and the compound we obtained was only the bridgehead-allylated material **29** (57%, 76% based on consumed starting material). To obtain further knowledge about this unique reactivity, a deuterium-exchange experiment was performed on **28** and mono-deuterated material was obtained upon treatment with 1.3 eq. of KHMDS at −78 °C followed by the addition of deuterium chloride in deuterium oxide at the same temperature (Scheme 6). This experiment resulted in incorporation of deuterium (99% deuterium incorporation) at C-6 and C-8 in the ratio 21 : 79. This result, in conjunction with results from the allylation experiment, suggested that an equilibration of anions between C-6 and C-8 takes place and that the allyl group can access only from the supposedly less hindered bridgehead position. Also, the reactivity of this anion seems to be highly dependent on the nature of electrophile, and in the case of allyl chloroformate as the electrophile the reaction proceeded preferencially *via* the C8 anion to provide the carbonate **31** as a 4 : 1 (63%) mixture with a minor product that we believe to be **30**. Palladium-mediated allyl migration[18] using this mixture provided diallyl species **32** and **29** in a 2 : 1 ratio (81%).[19] Thus, we established a protocol to obtain the fully functionalized bicyclo[4.3.1]decane ring system minus the quaternary center (C5) adjacent to a bridgehead. Since the introduction of the two hydrophobic side chains was planned after functionalization of C5, we envisaged that steric factors would make the C6 site less accessible and drive the



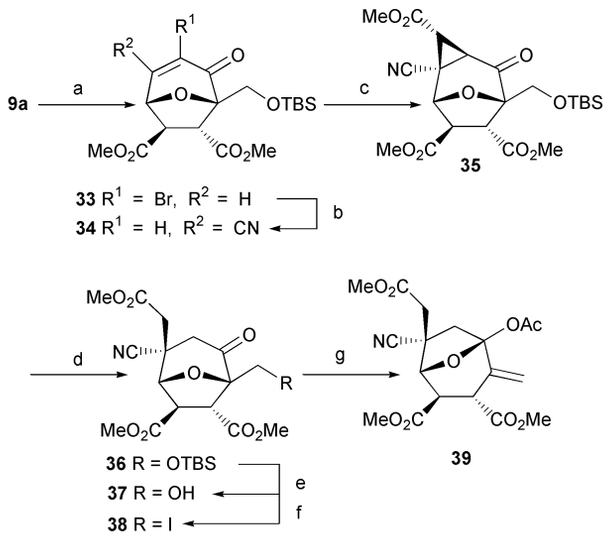
Scheme 5 *Reagents and conditions (and yields)*: (a) O_3, MeOH; then $NaHCO_3$, Me_2S, −78 °C to rt, (78%); (b) DBU, CH_2Cl_2; (c) PCC, CH_2Cl_2, 4 Å MS, rt (82% in 2 steps) (**26a** : **26b**, 4 : 1); (d) IBX, DMSO–toluene (1 : 2), 80 °C (52%); (e) allyltrimethylsilane, $TiCl_4$, CH_2Cl_2, −78 °C (57%); (f) KHMDS, allyl bromide, THF, −78 °C (57%); (g) KHMDS, allyl chloroformate, THF, −78 °C (63% **30** : **31**, 1 : 4); (h) $Pd_2(dba)_3{\cdot}CHCl_3$, PPh_3, THF, rt (81% **32** : **29**, 2 : 1).



Scheme 6 Deuterium-exchange experiment and equilibration of the anion.

selectivities towards the desired diastereomers in the actual total synthesis and make these processes more favourable.

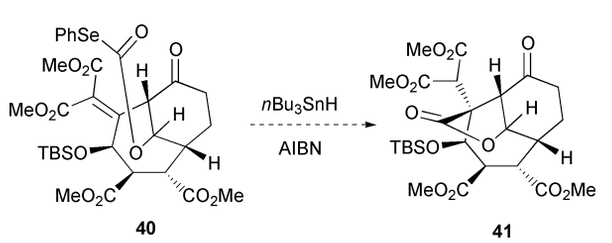
Having succeeded in obtaining the bicyclo[4.3.1]decane core in the model system, we then focused on the installation of the quaternary carbon center adjacent to a bridgehead. Our strategy to install the quaternary carbon center lay in cyclopropane formation followed by regioselective cleavage of the cyclopropane ring (Scheme 7). We envisaged that if we could cleave the cyclopropane ring in a regioselective fashion it would be a simple procedure for incorporating a quaternary carbon in the desired position. According to this strategy, compound **9a** was dibrominated followed by elimination of HBr to give



Scheme 7 *Reagents and conditions (and yields)*: (a) Br_2, CH_2Cl_2, −40 °C, then Et_3N, −40 °C to rt (99%); (b) NaCN, Bu_4NI, CH_2Cl_2–H_2O, rt, then Et_3N, rt (97%); (c) $Me_2S{=}CHCO_2Me$, THF, 0 °C to rt (61%); (d) SmI_2, THF, −78 °C (79%); (e) aq. HCl 0 °C to rt; (f) I_2, PPh_3, imidazole, benzene, reflux (65% in 2 steps); (g) Zn, Ac_2O, 50 °C (25%).

bromo enone **33**. This was next treated with NaCN and subsequent elimination of HBr gave a β-cyanized compound **34** in 96% yield (2 steps).[20] With nitrile **34** in hand, cyclopropanation was examined and a sulfonium ylide turned out to be most effective for this transformation of electron-deficient enone **34**, providing the desired cyclopropane compound **35** (61%) as a single isomer. This cyclopropanation occurred by way of the less hindered *exo*-face of the oxabicycle. With the cyclopropane in hand, the next critical regioselective cyclopropane opening was performed. Among the reaction conditions we employed (Zn, Na–naphthalene), samarium diiodide[21] most efficiently met our requirement and provided compound **36** (79%) bearing the stereochemically defined quaternary carbon center in the desired position as the sole reductive cleavage product. This completely regioselective reduction was rather surprising since electron-stabilizing groups are appended on all three carbon centers in the cyclopropane ring. To reductively cleave the bridging ether in the oxabicycle, the TBS group was removed by means of aqueous HCl, and subsequent iodination of the alcohol **37** gave iodide **38** in 65% yield (2 steps). Zn reduction in Ac_2O was next performed to give compound **39** in 25% yield (Scheme 7). Although the yield here was somewhat low, we were able to establish a diastereoselective route to a fully functionalized seven-membered-ring analog of **20**.

As an alternative strategy for the construction of the fully functionalized bicyclic system, we envisaged that radical reaction would be useful for the installation of a quaternary carbon center such as with compound **40** (Scheme 8). Previous liter-

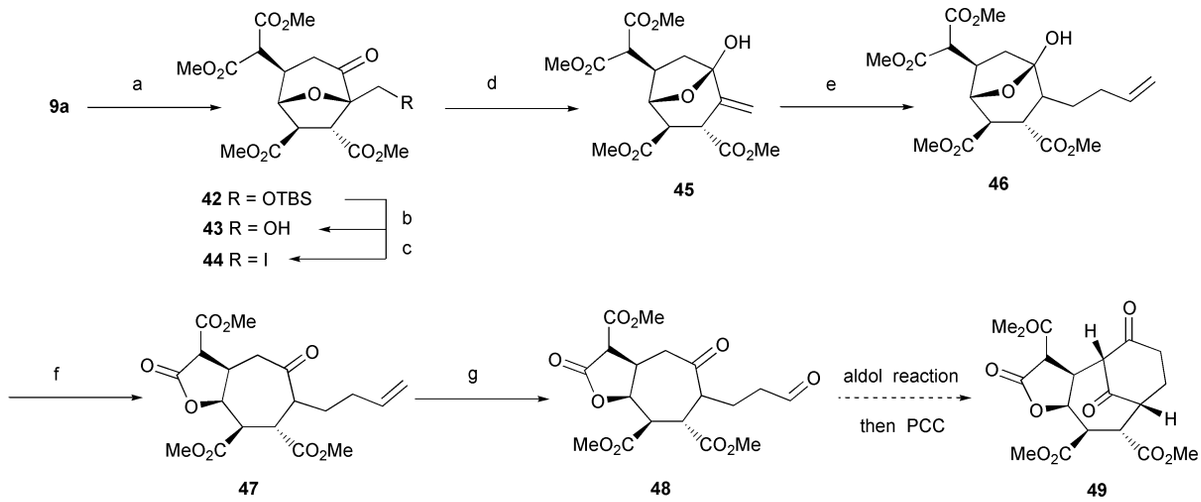


Scheme 8 Plausible strategy to install the quaternary carbon center by a 5-*exo*-*trig* pathway.

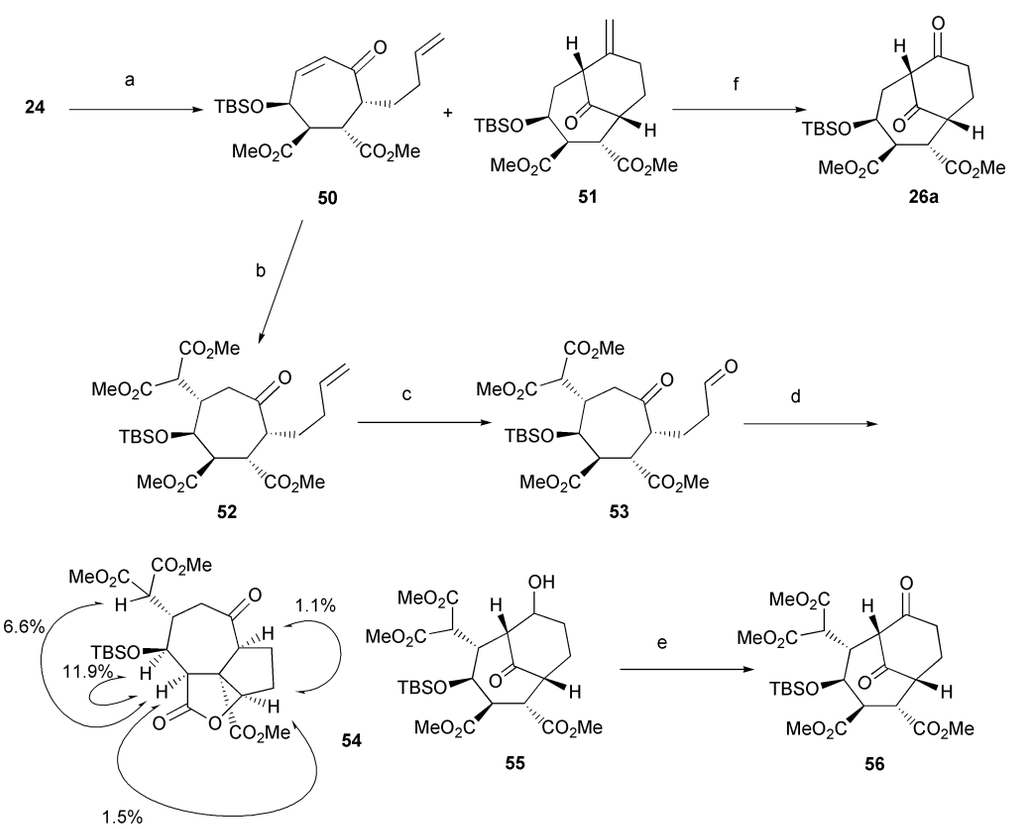
ature precedence has shown that various γ-lactones were relatively easily prepared by acyl radical 5-*exo*-*trig* cyclization and that this cyclization is normally favoured over plausible decarboxylation.[22] To this end, compound **9a** was treated with the anion of dimethyl malonate to give bicycle **42** in 83% yield. TBS deprotection by means of aqueous HCl followed by iodination of the alcohol **43** gave iodide **44** in 82% yield (2 steps). Subsequent zinc-mediated cleavage gave cyclic hemiketal **45** in 59% yield. Without protecting the lactol, allylation was carried out with allyltrimethylsilane in the presence of $TiCl_4$ to give allylated hemiketal **46** in 46% yield as the sole isomer, which was used for the next step without elucidating the stereochemistry at C2. To expose the ketone carbonyl group masked as a hemiketal, compound **46** was treated with sodium methoxide to liberate the secondary alkoxide, which immediately reacted further to give lactone **47**. Attempts to perform ozonolytic cleavage of the terminal alkene turned out to be problematic due to the decomposition of the aldehyde **48** during attempted purification. Since the subsequent base-promoted aldol reaction using a crude mixture of the aldehyde (containing aldehyde, PPh_3, $O=PPh_3$) didn't give any signals indicating the presence of the desired material, utilization of this compound was abandoned (Scheme 9). Following the failure to utilize **48** to gain access to **40**, a modified approach was next pursued (Scheme 10). Since the cause of the instability of aldehyde **48** seemed to lie in the lability of the lactone group due to a possible β-elimination leading to the opening of the lactone, we next focused upon compound **53**, which lacks the lactone moiety. By introducing a dimethyl malonate group into enone **50**, we thought we could overcome the complications associated with the instability of **48**. To this end compound **24** was subjected to the Saegusa oxidation protocol. Treatment of **24** with KHMDS followed by trapping of the resulting enolate with TMSCl gave a silyl enol ether and this silyl enol ether was used in the next reaction with $Pd(OAc)_2$ without purification. From this reaction we obtained the desired enone **50** (35%) as well as oxidatively cyclized compound **51** (<30%). The mechanism of the reaction yielding **51** can be considered to be as in Scheme 11.[23] According to the proposal by Kende[23b] in a similar system, compound **51** seemed to have formed by initial coordination of Pd to exocyclic olefin (**59**) followed by the attack of the enol ether upon the Pd-coordinated olefin. Oxidative cleavage of this terminal alkene provided an additional access to **26a** (14%, 2 steps). The malonate addition of **50** proceeded uneventfully in refluxing THF to give **52** (61%) as the sole product, which was next subjected to ozonolysis to give aldehyde **53**. As expected, this aldehyde bore sufficient stability against silica gel column chromatography and could be easily purified. With **53** in hand, we performed a base-promoted intramolecular aldol reaction and obtained two products. The major constituent turned out to be a tricyclic compound **54** (29% yield, 2 steps). The structure of this material was unambiguously established by means of DEPT, H–H COSY, NOE, *etc*. The minor one turned out to be the desired bicyclo[4.3.1]decane compound **55** (7% yield, 2 steps). This was oxidized with PCC to give dione **56** (77%), a suitable candidate for further studies. Thus, we could secure a pathway to the bicyclic core functionalized at the C5 center.

Conclusions and outlook

The chemistry presented in this article includes the efficient utilization of oxidopyrylium [5+2] cycloaddition combined with an intramolecular aldol reaction to construct the bicyclo-[4.3.1]decane ring system of phomoidride B. During the course of this study some less precedented observations were made, such as the unique reactivity of the anions of **28** and the completely selective cleavage of a cyclopropane ring bearing electron-withdrawing groups on all three carbon atoms. Efforts to utilize diester **39** for further studies, to improve the yield of compound **55**, and to develop a strategy for suitably introducing the actual side chains of phomoidride B are now ongoing.



Scheme 9 *Reagents and conditions (and yields)*: (a) NaH, dimethyl malonate, THF, 0 °C to rt (83%); (b) aq. HCl rt; (c) I_2, PPh_3, imidazole, benzene, reflux (82% in 2 steps); (d) Zn, MeOH, reflux (59%); (e) allyltrimethylsilane, $TiCl_4$, CH_2Cl_2, −78 °C (46%); (f) NaOMe, THF, rt (66%); (g) O_3, MeOH; then $NaHCO_3$, Me_2S, −78 °C to rt.



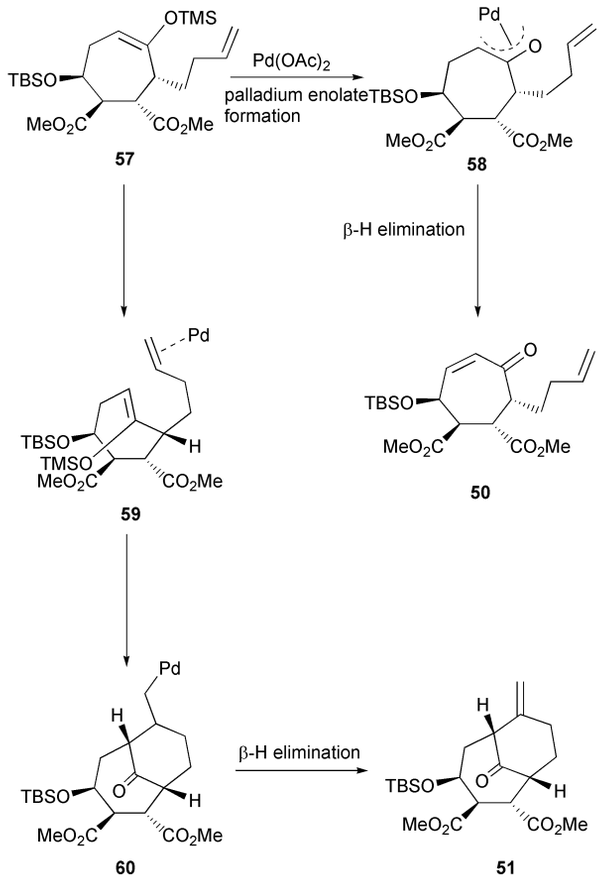
Scheme 10 *Reagents and conditions (and yields)*: (a) KHMDS, TMSCl, THF, −78 °C; then $Pd(OAc)_2$, CH_3CN, rt (**50** 35%, **51** ≈ 30%); (b) NaH, dimethyl malonate, THF, rt to reflux (61%); (c) O_3, MeOH, then $NaHCO_3$, Me_2S, −78 °C to rt; (d) K_2CO_3, MeOH, rt (**54** 29% in 2 steps; **55** 7% in 2 steps); (e) PCC, CH_2Cl_2, 4 Å MS, rt (77%); (f) O_3, MeOH, then $NaHCO_3$, Me_2S, −78 °C to rt (14% from **24**).

Experimental

All reactions were carried out under N_2 unless otherwise noted. THF and Et_2O were distilled after refluxing over Na–benzophenone prior to use. CH_2Cl_2, Et_3N, CH_3CN, DMSO, HMPA, benzene and toluene were distilled over CaH_2 before use. Silica gel $60F_{254}$ was used for preparative thin-layer chromatography (PLC). NMR spectra were recorded on JNM-LA500 and JNM-ECP500 instruments. ^1H and ^{13}C NMR spectra were observed in $CDCl_3$ solutions with tetramethylsilane (TMS) as the internal reference. *J*-values are given in Hz. IR spectra were recorded on a JASCO IRA-1H instrument. MS spectra were recorded on a JEOL JMS-SX102A instrument. FAB spectra were obtained with glycerol as a matrix and EI data were obtained at 70 eV. Melting points were recorded on a Yanagimoto melting-point apparatus and are uncorrected. Elemental analyses were performed on a Perkin-Elmer 2400-CHN elemental analyzer.

(1*R**,5*S**,6*R**,7*R**)-1-*tert*-Butyldimethylsilyloxymethyl-6,7-bis(methoxycarbonyl)-8-oxabicyclo[3.2.1]oct-3-en-2-one (9a) and (1*R**,5*S**,6*S**,7*S**)-1-*tert*-butyldimethylsilyloxymethyl-6,7-bis(methoxycarbonyl)-8-oxabicyclo[3.2.1]oct-3-en-2-one (9b)

To a solution of compound **8**[24] (16 mg, 0.053 mmol) in CH_3CN (0.5 ml) was added dimethyl fumarate (35 mg, 0.24 mmol) followed by Et_3N (0.010 ml, 0.072 mmol). The mixture was refluxed for 2 d and then treated with CH_2Cl_2 and H_2O. The separated aqueous layer was extracted with CH_2Cl_2. The combined organic solutions were dried ($MgSO_4$), filtered and



Scheme 11 Plausible mechanism of Pd-catalyzed oxidative cyclization.

concentrated. Chromatography of the residue on silica gel (elution with EtOAc–hexane–CH_2Cl_2, 1 : 12 : 1) gave diastereomers **9a** and **9b** in 13 : 1 ratio (15.8 mg, 0.041 mmol, 77%) as white solids.

For compounds **9a**, $R_f = 0.40$ (silica gel; EtOAc–hexane, 1 : 2); mp 92–94 °C (CH_2Cl_2); ν_{max}(neat)/cm^{-1} 2955, 2930, 2855, 1740 and 1695; δ_H (500 MHz, $CDCl_3$) 7.34 (dd, *J* 9.7, 4.6, 1 H), 6.02 (d, *J* 9.7, 1 H), 5.20 (d, *J* 4.6, 1 H), 4.25 (d, *J* 12, 1 H), 4.22 (d, *J* 4.3, 1 H), 4.01 (d, *J* 12, 1 H), 3.76 (s, 3 H), 3.66 (s, 3 H), 3.61 (d, *J* 4.3, 1 H), 0.90 (s, 9 H), 0.11 (s, 3 H) and 0.07 (s, 3 H); δ_C (125 MHz, $CDCl_3$) 193.6, 171.0, 170.3, 150.7, 127.0, 91.7, 75.9, 60.3, 52.6, 52.4, 50.6, 46.6, 25.6(× 3), 18.1, −5.5 and −5.7; MS (EI) *m*/*z* 384 (M^+); HRMS (EI) Calc. for $C_{18}H_{28}O_7Si$ (*M*): 384.1604. Found: M^+, 384.1588; Calc. for $C_{18}H_{28}O_7Si$: C, 56.23, H, 7.34. Found: C, 56.13; H, 7.43%.

For **9b**, R_f = 0.39 (silica gel; EtOAc–hexane, 1 : 2); δ_H (500 MHz, $CDCl_3$) 7.21 (dd, *J* 9.7, 4.3, 1 H), 6.03 (d, *J* 9.7, 1 H), 5.10 (dd, *J* 7.3, 4.3, 1 H), 4.16 (d, *J* 7.3, 1 H), 4.14 (d, *J* 12, 1 H), 4.04 (d, *J* 12, 1 H), 3.75 (s, 3 H), 3.70 (s, 3 H), 3.21 (d, *J* 7.3, 1 H), 0.86 (s, 9 H), 0.04 (s, 3 H) and 0.03 (s, 3 H).

(1*R**,5*S**,6*R**,7*R**)-1-*tert*-Butyldimethylsilyloxymethyl-6,7-bis(methoxycarbonyl)-8-oxabicyclo[3.2.1]octan-2-one (11)

To a solution of enone **9a** (2.5 g, 6.5 mmol) in MeOH (70 ml) was added 5% Pd/C (0.3 g). The mixture was stirred under a hydrogen atmosphere for 3 h at room temperature, then filtered and concentrated. Chromatography of the residue on silica gel (elution with EtOAc–hexane, 1 : 4) gave compound **11** (2.3 g, 6.0 mmol, 92%) as a colourless oil; $R_f = 0.33$ (silica gel; EtOAc–hexane, 1 : 4); ν_{max}(neat)/cm^{-1} 2955, 2930, 2855 and 1740; δ_H (500 MHz, $CDCl_3$) 4.84 (d, *J* 4.9, 1 H), 4.11 (d, *J* 5.8, 1 H), 4.09 (d, *J* 12, 1 H), 3.93 (d, *J* 12, 1 H), 3.75 (s, 1 H), 3.70 (s, 3 H), 3.60 (dd, *J* 5.8, 1.8, 3 H), 2.50–2.40 (m, 2 H), 2.43–2.35 (m, 1 H), 2.10–2.04 (m, 1 H), 0.90 (s, 9 H), 0.09 (s, 3 H) and 0.06 (s, 3 H); δ_C (125 MHz, $CDCl_3$) 204.6, 172.4, 170.5, 91.1, 77.3, 60.5, 52.6, 52.5, 51.0, 49.5, 33.5, 31.0, 25.7(× 3), 18.2, −5.4 and −5.6; MS (EI) *m*/*z* 387 (M^+ + H), 355 (M^+ − OCH_3), 329, 297, 269; HRMS (EI) Calc. for $C_{14}H_{21}O_7Si$ (M − *t*Bu): *m*/*z*, 329.1057. Found: *m*/*z*, 329.1070.

(1*R**,5*S**,6*R**,7*R**)-1-Hydroxymethyl-6,7-bis(methoxycarbonyl)-8-oxabicyclo[3.2.1]octan-2-one (12)

To a solution of silyl ether **11** (2.1 g, 5.4 mmol) in THF (40 ml) were added H_2O (20 ml), AcOH (20 ml) and 12 M HCl (4 ml). The mixture was stirred for 1 h at room temperature, then neutralized with saturated aq. $NaHCO_3$. The aqueous solution was extracted with EtOAc and the combined organic solutions were dried ($MgSO_4$), filtered and concentrated. Chromatography of the residue on silica gel (elution with EtOAc–hexane, 2 : 1) gave the alcohol **12** (1.2 g, 4.5 mmol, 83%) as a colourless oil; $R_f = 0.13$ (silica gel; EtOAc–hexane, 1 : 2); ν_{max}(neat)/cm^{-1} 3515, 2955 and 1710; δ_H (500 MHz, $CDCl_3$) 4.83 (d, *J* 4.3, 1 H), 4.05 (d, *J* 13, 1 H), 4.00–3.89 (m, 2 H), 3.78 (s, 3 H), 3.71 (s, 3 H), 3.63 (dd, *J* 6.4, 1.5, 1 H), 2.60–2.48 (m, 2 H), 2.44–2.36 (m, 1 H), 2.15–2.09 (m, 1 H) and 2.01 (br s, 1 H); δ_C (125 MHz, $CDCl_3$) 204.7, 172.5, 170.1, 90.4, 78.0, 61.4, 52.9, 52.8, 50.9, 50.8, 33.4 and 31.0; MS (EI) *m*/*z* 272 (M^+), 240, 226, 212, 194; HRMS (EI) Calc. for $C_{12}H_{16}O_7$ (*M*): 272.0896. Found: M^+, 272.0896.

(1*R**,5*R**,6*S**,7*S**)-1-Iodomethyl-6,7-bis(methoxycarbonyl)-8-oxabicyclo[3.2.1]octan-2-one (13)

To a solution of alcohol **12** (1.4 g, 5.1 mmol) in benzene (130 ml) were added PPh_3 (3.7 g, 14 mmol), imidazole (0.93 g, 14 mmol) and I_2 (2.9 g, 11 mmol). The mixture was refluxed for 3 h and then quenched with saturated aq. $Na_2S_2O_3$. The separated aqueous solution was extracted with CH_2Cl_2 and the combined organic solutions were dried ($MgSO_4$), filtered and concentrated. Chromatography of the residue on silica gel (elution with EtOAc–hexane, 1 : 6) gave iodide **13** (1.63 g, 4.3 mmol, 84%) as a yellow oil; $R_f = 0.40$ (silica gel; EtOAc–hexane, 1 : 2); ν_{max}(neat)/cm^{-1} 2955, 1745, 1740 and 1435; δ_H (500 MHz, $CDCl_3$) 4.85 (d, *J* 4.9, 1 H), 3.89 (d, *J* 6.4, 1 H), 3.80 (d, *J* 11, 1 H), 3.79 (s, 3 H), 3.72 (s, 3 H), 3.67 (dd, *J* 6.4, 1.5, 1 H), 3.65 (d, *J* 11, 1 H), 2.60–2.40 (m, 3 H) and 2.13–2.07 (m, 1 H); δ_C (125 MHz, $CDCl_3$) 202.4, 172.0, 169.5, 88.7, 77.8, 54.5, 53.0, 52.9, 51.2, 33.3, 30.9 and 6.0; MS (EI) *m*/*z* 382 (M^+), 351 (M^+ − OCH_3), 255, 223, 195; HRMS (EI) Calc. for $C_{12}H_{15}IO_6$ (*M*): 381.9913. Found: M^+, 381.9906.

(3*R**,4*R**,5*S**)-5-Hydroxy-3,4-bis(methoxycarbonyl)-2-methylenecycloheptanone (14)

To a solution of iodide **13** (1.2 g, 3.1 mmol) in MeOH (100 ml) was added activated Zn (by means of successive washing with saturated aq. NH_4Cl, H_2O, EtOH and Et_2O, 900 mg, 14 mmol). The mixture was refluxed for 30 min, quenched with solid NH_4Cl at room temperature, filtered and concentrated. Chromatography of the residue on silica gel (elution with EtOAc–hexane, 1 : 1) gave enone **14** (770 mg, 3.0 mmol, 96%) as a colourless oil; R_f = 0.11 (silica gel; EtOAc–hexane, 1 : 2); ν_{max}(neat)/cm^{-1} 3470, 2955, 2850, 1735, 1695, 1610 and 1435; δ_H (500 MHz, $CDCl_3$) 6.16 (s, 1 H), 5.38 (s, 1 H), 4.21–4.15 (m, 2 H), 3.78–3.70 (m, 7 H), 3.32–3.28 (m, 1 H), 3.00 (dd, *J* 15, 10, 1 H), 2.39 (dd, *J* 15, 9.1, 1 H), 2.22–2.15 (m, 1 H) and 1.91–1.84 (m, 1 H); δ_C (125 MHz, $CDCl_3$) 200.8, 173.4, 172.2, 143.4, 125.9, 68.7, 53.2, 52.7, 52.5, 45.5, 35.6 and 29.4; MS (EI) *m*/*z* 256 (M^+), 324, 329, 197, 179, 165; HRMS (EI) Calc. for $C_{12}H_{16}O_6$ (M): 256.0947. Found: M^+, 256.0940.

(1*R**,3*S**,4*S**,5*R**)-1-*tert*-Butyldimethylsilyloxy-2-methylene-3,4-bis(methoxycarbonyl)-8-oxabicyclo[3.2.1]octane (20) and (3*R**,4*R**,5*S**)-5-*tert*-butyldimethylsilyloxy-2-methylene-3,4-bis(methoxycarbonyl)cycloheptanone (21)

To a solution of enone **14** (3.0 g, 12 mmol) in CH_2Cl_2 (3 ml) at

−78 °C were added 2,6-lutidine (1.75 ml, 15 mmol) and TBSOTf (3.0 ml, 13 mmol). The mixture was stirred at this temperature for 1 h, then quenched with saturated aq. NH_4Cl. The separated aqueous solution was extracted with CH_2Cl_2 and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated. Chromatography of the residue on silica gel (elution with EtOAc–hexane, 1 : 8) gave silyl ether isomers **20** (2.7 g, 7.3 mmol, 61%) and **21** (0.94 g, 2.5 mmol, 21%) as colourless oils.

For isomer **20**, R_f = 0.33 (silica gel; EtOAc–hexane, 1 : 5); ν_{max}(neat)/cm^{-1} 2925, 2855, 1735, 1465 and 1250; δ_H (500 MHz, $CDCl_3$) 5.50 (s, 1 H), 5.00 (s, 1 H), 4.89 (d, *J* 7.9, 1 H), 4.09 (s, 1 H), 3.72 (s, 6 H), 3.18 (s, 1 H), 2.20–2.10 (m, 1 H), 2.00–1.94 (m, 1 H), 1.82–1.74 (m, 2 H), 0.89 (s, 9 H), 0.09 (s, 3 H) and 0.07 (s, 3 H); δ_C (125 MHz, $CDCl_3$) 173.4, 172.5, 143.6, 112.6, 104.7, 75.6, 52.6, 52.3, 48.5, 45.3, 36.1, 27.0, 25.9(× 3), 18.0, −3.0 and −3.2; MS (EI) *m*/*z* 370 (M^+), 339 ($M^+ - OCH_3$), 313 ($M^+ - t$Bu), 281, 253; HRMS (EI) Calc. for $C_{18}H_{30}O_6Si$ (M): 370.1812. Found: M^+, 370.1797.

For isomer **21**, R_f = 0.17 (silica gel; EtOAc–hexane, 1 : 5); ν_{max}(neat)/cm^{-1} 2950, 1700, 1435 and 1160; δ_H (500 MHz, $CDCl_3$) 6.00 (s, 1 H), 5.39 (s, 1 H), 4.45–4.47 (m, 1 H), 3.99 (d, *J* 10.4, 1 H), 3.69 (s, 3 H), 3.67 (s, 3 H), 3.09 (ddd, *J* 16, 12, 1.8, 1 H), 3.01 (dd, *J* 10, 2.7, 1 H), 2.30 (ddd, *J* 16, 7.9, 1.5, 1 H), 2.09–2.02 (m, 1 H), 1.82–1.75 (m, 1 H), 0.87 (s, 9 H), 0.03 (s, 3 H) and −0.01 (s, 3 H); δ_C (125 MHz, $CDCl_3$) 202.1, 172.9, 172.1, 144.7, 123.8, 69.1, 55.8, 52.2, 51.9, 43.8, 33.8, 30.2, 25.6(× 3), 17.9, −4.5 and −5.5; MS (EI) *m*/*z* 370 (M^+), 339 ($M^+ - OCH_3$), 313 ($M^+ - t$Bu), 281, 253; HRMS (EI) Calc. for $C_{18}H_{30}O_6Si$ (M): 370.1812. Found: M^+, 370.1815.

(2*R**,3*S**,4*R**,5*S**)-2-(But-3-enyl)-5-hydroxy-3,4-bis(methoxycarbonyl)cycloheptanone (22)

To a solution of bicycle **20** (2.6 g, 7.0 mmol) in CH_2Cl_2 (50 ml) at −78 °C were added allyltrimethylsilane (1.8 ml, 11 mmol) and $TiCl_4$ (0.6 ml, 5.5 mmol). The mixture was stirred at this temperature for 30 min, then quenched with saturated aq. $NaHCO_3$. The separated aqueous solution was extracted with CH_2Cl_2 and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated. Chromatography of the residue on silica gel (elution with EtOAc–hexane, 1 : 1) gave compound **22** (1.7 g, 5.8 mmol, 82%) as a colourless oil; R_f = 0.33 (silica gel; EtOAc–hexane, 1 : 1); ν_{max}(neat)/cm^{-1} 3450, 2950, 1735, 1435 and 1170; δ_H (500 MHz, $CDCl_3$) 5.77–5.70 (m, 1 H), 5.04–4.96 (m, 2 H), 4.18 (br s, 1 H), 3.78 (s, 3 H), 3.70 (s, 3 H), 3.47 (dd, *J* 7.0, 2.7, 1 H), 3.32 (dd, *J* 7.0, 3.1, 1 H), 2.83 (br s, 1 H), 2.72 (ddd, *J* 18, 9.1, 3.7, 1 H), 2.44 (ddd, *J* 18, 9.1, 3.1, 1 H), 2.30–2.21 (m, 1 H), 2.10–1.94 (m, 4 H) and 1.50–1.48 (m, 1 H), O*H* not observed; δ_C (125 MHz, $CDCl_3$) 210.9, 174.4, 173.8, 137.9, 115.5, 70.1, 52.8, 52.4, 52.1, 49.6, 43.7, 38.6, 32.7, 28.9 and 26.3; MS (EI) *m*/*z* 298 (M^+), 280, 266, 212, 152; HRMS (EI) Calc. for $C_{15}H_{22}O_6$ (M): 298.1416. Found: M^+, 298.1408.

(1*R**,2*S**,3*R**,4*S**,5*R**)-2-(But-3-enyl)-1-*tert*-butyldimethylsilyloxy-3,4-bis(methoxycarbonyl)-8-oxabicyclo[3.2.1]octane (23) and (2*R**,3*S**,4*R**,5*S**)-2-(but-3-enyl)-5-*tert*-butyldimethylsilyloxy-3,4-bis(methoxycarbonyl)cycloheptanone (24)

To a solution of hydroxy ketone **22** (1.1 g, 3.7 mmol) in CH_2Cl_2 (50 ml) were added 2,6-lutidine (0.9 ml, 7.7 mmol) and TBSOTf (1.4 ml, 6.1 mmol) at room temperature. The mixture was stirred at this temperature for 1 h, then quenched with saturated aq. NH_4Cl. The separated aqueous solution was extracted with CH_2Cl_2 and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated. Chromatography of the residue on silica gel (elution with EtOAc–hexane, 1 : 6) gave bicycle **23** (880 mg, 2.1 mmol, 58%) along with its isomer **24** (640 mg, 1.6 mmol, 42%) as colourless oils.

The bicycle **23** was treated with TBAF (1.2 eq.) in THF at room temperature to afford compound **22** (550 mg, 87%).

Compound **22** was subjected to the above conditions to give **23** and **24** again. This procedure was repeated once again to give a final total of 110 mg **23** (7%) and 860 mg of **24** (57%) as colourless oils.

For bicycle **23**, R_f = 0.56 (silica gel; EtOAc–hexane, 1 : 3); ν_{max}(neat)/cm^{-1} 2950, 1735, 1435 and 1195; δ_H (500 MHz, $CDCl_3$) 5.82 (m, 1 H), 5.03 (dq, *J* 17, 1.5, 1 H), 4.99–4.95 (m, 1 H), 4.78 (br s, 1 H), 3.75 (s, 3 H), 3.67 (s, 3 H), 3.52 (br d, 1 H), 2.88 (t, *J* 1.8 Hz, 1 H), 2.36–2.29 (m, 1 H), 2.22–2.09 (m, 3 H), 2.08–1.99 (m, 1 H), 1.91–1.83 (m, 1 H), 1.78–1.64 (m, 2 H), 1.49 (ddt, *J* 13, 4.9, 1.8, 1 H), 0.86 (s, 9 H), 0.08 (s, 3 H) and 0.07 (s, 3 H); δ_C (125 MHz, $CDCl_3$) 174.0, 172.9, 138.8, 114.6, 107.4, 75.6, 52.4, 51.7, 48.0, 45.2, 40.0, 31.6, 31.3, 27.6, 26.5, 26.0(× 3), 18.0, −2.9 and −2.9; MS (EI) *m*/*z* 412 (M^+), 355 ($M^+ - t$Bu), 272, 169; HRMS (EI) Calc. for $C_{21}H_{36}O_6Si$ (M): 412.2281. Found: M^+, 412.2276.

For isomer **24**, R_f = 0.41 (silica gel; EtOAc–hexane, 1 : 2); ν_{max}(neat)/cm^{-1} 2950, 2930, 1730, 1435 and 1165; δ_H (500 MHz, $CDCl_3$) 5.75–5.67 (m, 1 H), 5.02–4.95 (m, 2 H), 4.56 (dt, *J* 7.3, 2.3, 1 H), 3.70 (s, 3 H), 3.68 (s, 3 H), 3.31 (dd, *J* 9.9, 3.9, 1 H), 3.15 (dt, *J* 10, 3.9, 1 H), 3.09 (dd, *J* 9.9, 2.3, 1 H), 2.66 (ddd, *J* 17, 10, 5.5, 1 H), 2.42 (dt, *J* 17, 5.5, 1 H), 2.18–2.10 (m, 1 H), 2.09–1.93 (m, 3 H), 1.88–1.80 (m, 1 H), 1.60–1.52 (m, 1 H), 0.86 (s, 9 H), 0.04 (s, 3 H) and −0.03 (s, 3 H); δ_C (125 MHz, $CDCl_3$) 210.9, 173.8, 173.1, 137.4, 115.8, 70.2, 52.1, 52.0, 51.2, 51.0, 42.8, 37.7, 32.1, 29.8, 26.4, 25.7(× 3), 18.0, −4.6 and −5.5; MS (EI) *m*/*z* 412 (M^+), 381 ($M^+ - OCH_3$), 355 ($M^+ - t$Bu), 323, 295; HRMS (EI) Calc. for $C_{17}H_{27}O_6Si$ (M − *t*Bu): 355.1577. Found: *m*/*z*, 355.1570.

Ozonolysis of compound 24

Compound **24** (72 mg, 0.18 mmol) in MeOH (3 ml) was ozonolyzed at −78 °C for 12 h. After removal of excess of ozone by bubbling oxygen through the solution for 10 min, sodium bicarbonate (20 mg) was introduced followed by the addition of dimethyl sulfide (0.1 ml). This mixture was allowed to warm to room temperature, then was stirred overnight. The reaction mixture was filtered and the filtrate was concentrated. Chromatography of the residue on silica gel (elution with EtOAc–hexane, 1 : 2) gave the expected aldehyde (59 mg, 0.14 mmol, 78%) as a colourless oil.

(1*R**,2*S**,3*R**,4*S**,6*R**)-4-*tert*-Butyldimethylsilyloxy-2,3-bis(methoxycarbonyl)bicyclo[4.3.1]decane-7,10-dione (26a) and (1*R**,2*R**,3*S**,4*R**,6*R**)-4-*tert*-butyldimethylsilyloxy-2,3-bis(methoxycarbonyl)bicyclo[4.3.1]decane-7,10-dione (26b)

To a solution of the foregoing aldehyde (10.2 mg, 24 μmol) in CH_2Cl_2 (1 ml) was added DBU (0.01 ml, 67 μmol) at room temperature. This mixture was stirred overnight and then quenched with saturated aq. NH_4Cl. The separated aqueous solution was extracted with CH_2Cl_2 and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated.

To a solution of this material in CH_2Cl_2 (1 ml) were added PCC (8 mg, 37 μmol) and 4 Å MS (20 mg) at room temperature. The mixture was stirred at room temperature for 3 h, then filtered and concentrated. Chromatography of the residue on silica gel (elution with EtOAc–hexane, 1 : 2) gave stereoisomers **26a** and **26b** in 4 : 1 ratio (8.3 mg, 20 μmol, 82%) as white solids.

For isomer **26a**, R_f = 0.40 (silica gel; EtOAc–hexane, 1 : 1); mp 142–143 °C (CH_2Cl_2); ν_{max}(neat)/cm^{-1} 2950, 1740, 1445 and 1180; δ_H (500 MHz, $CDCl_3$) 4.72 (d, *J* 6.7, 1 H), 3.74 (s, 3 H), 3.69 (s, 3 H), 3.52 (dd, *J* 12, 3.4, 1 H), 3.32 (dd, *J* 12, 7.9, 1 H), 3.27–3.21 (m, 2 H), 2.67 (dt, *J* 18, 3.0, 1 H), 2.58–2.51 (m, 1 H), 2.28–2.20 (m, 1 H), 2.13–2.03 (m, 1 H), 1.93 (dd, *J* 16, 7.9, 1 H), 1.91–1.83 (m, 1 H), 0.84 (s, 9 H), 0.05 (s, 3 H) and −0.06 (s, 3 H); δ_C (125 MHz, $CDCl_3$) 206.2, 204.3, 173.5, 172.5, 70.6, 61.2, 52.6, 52.4, 51.0, 48.0, 42.1, 37.5, 33.1, 25.5(× 3), 18.0,

17.9, −4.7 and −5.7; MS (EI) *m*/*z* 355 (M^+ − *t*Bu), 211, 159, 138; HRMS (EI) Calc. for $C_{16}H_{23}O_7Si$ (M − *t*Bu): 355.1213. Found: *m*/*z*, 355.1214; Calc. for $C_{20}H_{32}O_7Si$: C, 58.23, H, 7.82. Found: C, 57.63; H, 7.83%.

For isomer **26b**, R_f = 0.53 (silica gel; EtOAc–hexane, 1 : 1); mp 92–95 °C (CH_2Cl_2); ν_{max}(neat)/cm^{-1} 2950, 2930, 1740, 1435 and 1160; δ_H (500 MHz, $CDCl_3$) 4.47 (t, *J* 2.7, 1 H), 3.73 (s, 3 H), 3.66 (s, 3 H), 3.38 (dd, *J* 12, 5.5, 1 H), 3.28 (dd, *J* 14, 6.1, 1 H), 3.26–3.22 (m, 1 H), 2.94–2.90 (m, 1 H), 2.84 (d, *J* 12, 1 H), 2.54–2.47 (m, 2 H), 2.44–2.37 (m, 1 H), 2.05 (ddd, *J* 15, 6.1, 3.0, 1 H), 2.02–1.95 (m, 1 H), 0.87 (s, 9 H), 0.01 (s, 3 H) and −0.03 (s, 3 H); δ_C (125 MHz, $CDCl_3$) 209.1, 207.6, 174.9, 172.9, 71.3, 61.8, 52.6, 52.3, 51.6, 49.0, 41.4, 38.7, 34.1, 25.8(× 3), 23.7, 18.1, −4.9 and −5.7; MS (EI) *m*/*z* 355 (M^+ − *t*Bu), 323, 159; HRMS (EI) Calc. for $C_{16}H_{23}O_7Si$ (M − *t*Bu): 355.1213. Found: *m*/*z*, 355.1216; Calc. for $C_{20}H_{32}O_7Si$: C, 58.23; H, 7.82. Found: C 58.90: H, 8.12%.

(1*R**,2*S**,3*R**,4*S**,6*R**)-4-*tert*-Butyldimethylsilyloxy-2,3-bis(methoxycarbonyl)bicyclo[4.3.1]dec-8-ene-7,10-dione (27)

A solution of ketone **26a** (160 mg, 0.39 mmol) in toluene (6 ml) and DMSO (3 ml) was treated with IBX (430 mg, 1.5 mmol), stirred at 80 °C for 3 h, then quenched with saturated aq. $NaHCO_3$. The separated aqueous solution was extracted with EtOAc and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated. Chromatography of the residue on silica gel (elution with EtOAc–hexane, 1 : 4) gave enone **27** (47 mg, 0.12 mmol, 30%) along with starting material (66 mg, 0.16 mmol, 41% recovery). This procedure was repeated once again to provide a final total of 68 mg (43%) of **27** as a white solid along with 30 mg (19%) recovery of starting material (52% yield based on consumed starting material); R_f = 0.43 (silica gel; EtOAc–hexane, 1 : 1); mp 131–134 °C (CH_2Cl_2); ν_{max}(neat)/cm^{-1} 2955, 2925, 2855, 1725 and 1685; δ_H (500 MHz, $CDCl_3$) 6.81 (dd, *J* 10, 4.3, 1 H), 6.30 (d, *J* 10, 1 H), 4.54 (d, *J* 5.5, 1 H), 3.79 (s, 3 H), 3.72–3.65 (m, 5 H), 3.55 (dd, *J* 12, 4.6, 1 H), 3.0 (d, *J* 11, 1 H), 2.66–2.59 (m, 1 H), 1.88–1.83 (m, 1 H), 0.86 (s, 9 H), 0.04 (s, 3 H) and −0.06 (s, 3 H); δ_C (125 MHz, $CDCl_3$) 199.9, 196.9, 172.7, 172.6, 144.7, 129.9, 71.2, 60.7, 52.8, 52.4, 51.5, 50.9, 43.2, 36.9, 25.5(× 3), 18.0, −4.8 and −5.6; MS (EI) *m*/*z* 396, 353 (M^+ − *t*Bu), 229, 209; HRMS (EI) Calc. for $C_{16}H_{21}O_7Si$ (M − *t*Bu): 353.1057, Found: *m*/*z*, 353.1047.

(1*R**,2*S**,3*R**,4*S**,6*R**,9*R**)-9-Allyl-4-*tert*-butyldimethylsilyloxy-2,3-bis(methoxycarbonyl)bicyclo[4.3.1]decane-7,10-dione (28)

To a solution of enone **27** (11.0 mg, 27 μmol) in CH_2Cl_2 (1 ml) at −78 °C were added allyltrimethylsilane (10 μl, 63 μmol) and $TiCl_4$ (5 μl, 46 μmol). The mixture was stirred at this temperature for 30 min, then quenched with saturated aq. $NaHCO_3$. The separated aqueous solution was extracted with CH_2Cl_2 and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated. Chromatography of the residue on silica gel (elution with EtOAc–hexane, 1 : 6) gave compound **28** (6.9 mg, 15 μmol, 57%) as a colourless oil; R_f = 0.32 (silica gel; EtOAc–hexane, 1 : 4); ν_{max}(neat)/cm^{-1} 2925, 1740, 1710 and 1435; δ_H (500 MHz, $CDCl_3$) 5.67–5.59 (m, 1 H), 5.16 (m, 1 H), 5.04 (d, *J* 17, 1 H), 4.62 (d, *J* 6.4, 1 H), 3.74 (s, 3 H), 3.69 (s, 3 H), 3.52 (dd, *J* 12, 3.4, 1 H), 3.28 (dd, *J* 11, 7.6, 1 H), 3.2 (d, *J* 12, 1 H), 3.06–3.03 (m, 1 H), 2.70 (dd, *J* 17, 4.0, 1 H), 2.50 (ddd, *J* 15, 11.3, 6.4, 1 H), 2.37–2.29 (m, 1 H), 2.10–2.03 (m, 2 H), 1.96 (dd, *J* 15, 7.6, 1 H), 1.87–1.79 (m, 1 H), 0.84 (s, 9 H), 0.04 (s, 3 H) and −0.07 (s, 3 H); δ_C (125 MHz, $CDCl_3$) 206.6, 205.6, 174.1, 172.7, 133.5, 119.2, 70.4, 60.3, 53.7, 52.4, 52.4, 51.2, 43.5, 41.4, 39.1, 33.8, 30.0, 25.5(× 3), 17.9, −4.7 and −5.7; MS (EI) *m*/*z* 452 (M^+), 437 (M^+ − CH_3), 396, 362, 251; HRMS (EI) Calc. for $C_{23}H_{36}O_7Si$ (M): 452.2230. Found: M^+, 452.2218.

(1*R**,2*S**,3*R**,4*S**,6*R**,9*R**)-6,9-Diallyl-4-*tert*-butyldimethylsilyloxy-2,3-bis(methoxycarbonyl)bicyclo[4.3.1]decane-7,10-dione (29)

To a solution of compound **28** (14 mg, 32 μmol) in THF (1 ml) at −78 °C, was added KHMDS (0.5 M in toluene, 40 μmol), then the mixture was stirred for 10 min. To this solution was added at this temperature, allyl bromide (0.01 ml, 120 μmol) and the resulting solution was stirred for 30 min. Saturated aq. NH_4Cl and Et_2O were added and the organic layer was separated. The aqueous layer was extracted with Et_2O then the combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated. Purification by means of chromatography on silica gel (elution with EtOAc–hexane, 1 : 6) gave compound **29** (9.0 mg, 18 μmol, 57%, 76% based on consumed starting material) as a colourless oil along with recovered starting material (3.5 mg, 7.7 μmol); R_f = 0.43 (silica gel; EtOAc–hexane, 1 : 4); ν_{max}(neat)/cm^{-1} 3455, 3415, 1735 and 1700; δ_H (500 MHz, $CDCl_3$) 5.74–5.57 (m, 2 H), 5.10 (d, *J* 9.5, 1 H), 5.05 (d, *J* 7.9, 1 H), 5.03–5.00 (m, 2 H), 4.39 (t, *J* 3.4, 1 H), 3.71 (s, 3 H), 3.66 (s, 3 H), 3.60 (dd, *J* 12, 4.6, 1 H), 3.10 (dd, *J* 6.4, 4.6, 1 H), 2.98 (d, *J* 12, 1 H), 2.70 (dd, *J* 14, 5.2, 1 H), 2.65 (dd, *J* 14, 3.7, 1 H), 2.43–2.37 (m, 2 H), 2.12–1.82 (m, 5 H), 0.88 (s, 9 H), 0.02 (s, 3 H) and −0.11 (s, 3 H); δ_C (125 MHz, $CDCl_3$) 209.1, 205.0, 173.8, 173.1, 133.6, 133.3, 119.3, 119.0, 70.0, 63.0, 53.9, 52.3(× 2), 49.7, 44.7, 43.0, 41.6, 40.7, 39.9, 30.1, 25.7(× 3), 17.9, −4.2 and −5.6; MS (EI) *m*/*z* 435 (M^+ − *t*Bu), 403, 375, 343; HRMS (EI) Calc. for $C_{22}H_{31}O_7Si$ (M − *t*Bu): 435.1839. Found: *m*/*z*, 435.1834.

(1*R**,2*S**,3*R**,4*S**,6*R**,9*R**)-9-(Allyl)-7-allyloxycarbonyloxy-4-*tert*-butyldimethylsilyloxy-2,3-bis(methoxycarbonyl)bicyclo-[4.3.1]dec-7-en-10-one (31)

To a solution of dione **28** (7.1 mg, 16 μmol) in THF (1 ml) at −78 °C was added KHMDS (0.5 M in toluene; 50 μl, 25 μmol). The mixture was stirred at this temperature for 30 min, then allyl chloroformate (5 ml, 47 μmol) was to the mixture added at −78 °C. The resulting material was further stirred for 3 h at −78 °C and then quenched with saturated aq. NH_4Cl. The separated aqueous solution was extracted with EtOAc and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated. Chromatography of the residue on silica gel (elution with EtOAc–hexane, 1 : 6) gave the mixed enol carbonates **30** and **31** in a 1 : 4 ratio (5.0 mg, 9.8 μmol, 63%) as colourless oils.

For isomer **31**, R_f = 0.40 (silica gel; EtOAc–hexane, 1 : 4); ν_{max}(neat)/cm^{-1} 2950, 2855 and 1735; δ_H (500 MHz, $CDCl_3$) 6.00–5.90 (m, 1H), 5.72 (d, *J* 6.1, 1 H), 5.66–5.56 (m, 1 H), 5.40 (d, *J* 17, 1 H), 5.32 (d, *J* 10, 1 H), 5.10–5.01 (m, 2 H), 4.67 (d, *J* 5.5, 2 H), 4.39–4.37 (m, 1 H), 3.70 (s, 3 H), 3.65 (s, 3 H), 3.62 (dd, *J* 12, 5.5, 1 H), 3.53 (d, *J* 12, 1 H), 3.19 (d, *J* 9.7, 1 H), 3.08 (d, *J* 5.5, 1 H), 2.49 (dd, *J* 12, 6.1, 1 H), 2.23–2.17 (m, 1 H), 2.12–2.05 (m, 2 H), 2.00–1.92 (m, 1 H), 0.86 (s, 9 H), 0.00 (s, 3 H) and −0.09 (s, 3 H); δ_C (125 MHz, $CDCl_3$) 204.5, 174.0, 173.8, 152.8, 146.9, 134.2, 131.0, 119.7, 118.6, 118.0, 70.8, 69.3, 52.2, 52.1, 51.2, 48.0, 47.3, 41.9, 40.3, 36.2, 35.4, 25.6(× 3), 17.9, −4.7 and −5.5; MS (EI) *m*/*z* 480 (M^+ + H − *t*Bu), 435, 390, 386, 257; HRMS (EI) Calc. for $C_{23}H_{31}O_9Si$ (M − *t*Bu): 479.1737, Found: *m*/*z*, 479.1752.

(1*R**,2*S**,3*R**,4*S**,6*R**,8*R**,9*R**)-8,9-Diallyl-4-*tert*-butyldimethylsilyloxy-2,3-bis(methoxycarbonyl)bicyclo[4.3.1]decane-7,10-dione (32)

To a solution of double-bond isomers **30** and **31** (1 : 4, 5.0 mg, 9.8 μmol) in THF were added $Pd_2(dba)_3$·$CHCl_3$§ (0.5 mg) and PPh_3 (1.0 mg, 3.8 μmol). The mixture was stirred at room temperature for 2 h and then concentrated. Chromatography of

§ $Pd_2(dba)_3$ is tris(dibenzylideneacetone)dipalladium.

the residue on silica gel (elution with EtOAc–hexane, 1 : 6) gave isomers **32** and **29** in a 2 : 1 ratio (3.9 mg, 7.9 μmol, 81%) as colourless oils.

For isomer **32**, R_f = 0.43 (silica gel; EtOAc–hexane, 1 : 4); ν_{max}(neat)/cm^{-1} 2925, 2855, 1735, 1700 and 1435; δ_H (500 MHz, $CDCl_3$) 5.73–5.49 (m, 2 H), 5.12–5.00 (m, 4 H), 4.58 (d, *J* 5.0, 1 H), 3.73 (s, 3 H), 3.69 (s, 3 H), 3.62 (dd, *J* 12, 4.4, 1 H), 3.41 (dd, *J* 13, 3.2, 1 H), 3.33 (d, *J* 12, 1 H), 3.26 (t, *J* 4.4, 1 H), 3.03–2.98 (m, 1 H), 2.54 (ddd, *J* 16, 13, 5.0, 1 H), 2.36–2.29 (m, 1 H), 2.26–2.19 (m, 1 H), 2.12–1.82 (m, 4 H), 0.85 (s, 9 H), 0.03 (s, 3 H) and −0.07 (s, 3 H); δ_C (125 MHz, $CDCl_3$) 206.5, 203.1, 173.7, 173.5, 134.6, 134.2, 118.6, 117.6, 70.8, 61.6, 52.6, 52.4, 52.3, 51.1, 47.9, 41.4, 35.4(× 2), 32.9, 29.7, 25.5(× 3), 17.9, −4.7 and −5.6; MS (EI) *m*/*z* 435 (M^+ − *t*Bu), 403, 374, 341; HRMS (EI) Calc. for $C_{22}H_{31}O_7Si$ (M − *t*Bu): 435.1839. Found: *m*/*z*, 435.1861.

(1*R**,5*R**,6*R**,7*R**)-3-Bromo-1-*tert*-butyldimethylsilyloxymethyl-6,7-bis(methoxycarbonyl)-8-oxabicyclo[3.2.1]oct-3-en-2-one (33)

To a solution of enone **9a** (7.4 g, 19 mmol) in CH_2Cl_2 (300 ml) at −40 °C was added Br_2 (2.4 ml, 45 mmol). The mixture was stirred at this temperature for 30 min, followed by the addition of Et_3N (16 ml, 110 mmol). The resulting solution was allowed to warm to room temperature, then was stirred for 10 min. The solvent was evaporated and chromatography of the residue on silica gel (elution with EtOAc–hexane, 1 : 4) gave bromide **33** (8.7 g, 19 mmol, 99%) as a yellow oil; R_f = 0.42 (silica gel; EtOAc–hexane, 1 : 2); ν_{max}(neat)/cm^{-1} 2955, 2930, 2855, 1740, 1710, 1600 and 1435; δ_H (500 MHz, $CDCl_3$) 7.66 (d, *J* 5.2, 1 H), 5.20 (d, *J* 5.2, 1 H), 4.26 (d, *J* 12, 1 H), 4.21 (d, *J* 4.3, 1 H), 4.04 (d, *J* 12, 1 H), 3.76 (s, 3 H), 3.67 (s, 3 H), 3.62 (d, *J* 4.3, 1 H), 0.90 (s, 9 H), 0.11 (s, 3 H) and 0.07 (s, 3 H); δ_C (125 MHz, $CDCl_3$) 186.9, 170.5, 169.8, 150.3, 122.4, 92.1, 77.6, 60.7, 52.8, 52.7, 50.5, 47.0, 25.7(× 3), 18.2, −5.5 and −5.6; MS (EI) *m*/*z* 407 (M^+ − *t*Bu), 405 (M^+ − *t*Bu), 263, 261; HRMS (EI) Calc. for $C_{14}H_{18}{}^{79}BrO_7Si$ (M − *t*Bu): 405.0005. Found: *m*/*z*, 405.0009; Calc. for $C_{18}H_{27}BrO_2Si$: C, 46.65; H, 5.87. Found: C, 46.72, H, 5.70%.

(1*R**,5*R**,6*R**,7*R**)-1-*tert*-Butyldimethylsilyloxymethyl-4-cyano-6,7-bis(methoxycarbonyl)-8-oxabicyclo[3.2.1]oct-3-en-2-one (34)

To a solution of bromide **33** (8.7 g, 19 mmol) in CH_2Cl_2 (300 ml) and H_2O (100 ml) were added *n*-BuN_4I (100 mg) and NaCN (1.0 g, 20 mmol) at room temperature. The mixture was stirred vigorously for 1 h, then the organic phase was separated. Et_3N (4.9 ml, 35 mmol) was added, and the resulting solution was stirred for 30 min. The solvent was evaporated off and chromatography of the residue on silica gel (elution with EtOAc–hexane, 1 : 4) gave nitrile **34** (7.5 g, 18 mmol, 97%) as a yellow oil; R_f = 0.46 (silica gel; EtOAc–hexane, 1 : 2); ν_{max}(neat)/cm^{-1} 2955, 2930, 2230, 1740, 1705 and 1440; δ_H (500 MHz, $CDCl_3$) 6.51 (s, 1 H), 5.28 (s, 1 H), 4.23 (d, *J* 4.3, 1 H), 4.18 (d, *J* 12, 1 H), 4.00 (d, *J* 12, 1 H), 3.80 (s, 3 H), 3.71 (d, *J* 4.3, 1 H), 3.68 (s, 3 H), 0.89 (s, 9 H), 0.10 (s, 3 H) and 0.06 (s, 3 H); δ_C (125 MHz, $CDCl_3$) 190.8, 169.8(× 2), 136.4, 133.5, 113.6, 92.1, 77.3, 60.1, 53.1, 53.0, 51.5, 47.4, 25.7(× 3), 18.2, −5.5 and −5.6; MS (EI) *m*/*z* 394 (M^+ − CH_3), 378 (M^+ − OCH_3), 352 (M^+ − *t*Bu), 294, 234, 208; HRMS (EI) Calc. for $C_{15}H_{18}NO_7Si$ (M − *t*Bu): 352.0853. Found: *m*/*z*, 352.0869; Calc. for $C_{19}H_{27}NO_2Si$: C, 55.73, H, 6.65, N, 3.42. Found: C, 55.67, H, 6.86, N, 3.22%.

(1*R**,2*R**,3*R**,4*R**,6*R**,7*R**,8*R**)-6-*tert*-Butyldimethylsilyloxymethyl-2-cyano-3,7,8-tris(methoxycarbonyl)-9-oxatricyclo-[4.2.1.0^{2,4}]nonan-5-one (35)

To a suspension of NaH (60%, prewashed with hexane; 100 mg, 2.5 mmol) in THF (10 ml) was added the sulfonium salt (210 mg, 0.98 mmol) in HMPA (10 ml) at 0 °C. After stirring of the mixture for 30 min at room temperature, a solution of nitrile **34** (320 mg, 0.78 mmol) in THF (10 ml) was added to the suspension at 0 °C. The mixture was stirred at room temperature for 1 h, then quenched with saturated aq. NH_4Cl and Et_2O. The separated aqueous solution was extracted with Et_2O and the combined organic extracts were washed with H_2O, dried ($MgSO_4$), filtered and concentrated. Chromatography of the residue on silica gel (elution with EtOAc–hexane, 1 : 6) gave tricycle **35** (231 mg, 0.48 mmol, 61%) as a colourless oil; R_f = 0.33 (silica gel; EtOAc–hexane, 1 : 2); ν_{max}(neat)/cm^{-1} 2955, 2930, 2250 and 1740; δ_H (500 MHz, $CDCl_3$) 5.16 (s, 1 H), 4.00 (dd, *J* 5.5, 0.9, 1 H), 3.96 (d, *J* 12, 1 H), 3.91 (d, *J* 12, 1 H), 3.84 (d, *J* 5.5, 1 H), 3.83 (s, 3 H), 3.79 (s, 3 H), 3.74 (s, 3 H), 3.03 (d, *J* 5.5, 1 H), 2.87 (dd, *J* 5.5, 0.60, 1 H), 0.86 (s, 9 H), 0.06 (s, 3 H) and 0.03 (s, 3 H); δ_C (125 MHz, $CDCl_3$) 194.9, 170.3, 169.2, 166.5, 114.4, 92.6, 75.7, 60.9, 53.3, 53.1(× 2), 51.0, 50.7, 34.7, 27.9, 25.6(× 3), 22.7, 18.1 and −5.6(× 2); MS (EI) *m*/*z* 466 (M^+ − CH_3), 450 (M^+ − OCH_3), 424 (M^+ − *t*Bu), 392, 364; HRMS (EI) Calc. for $C_{18}H_{22}NO_9Si$ (M^+ − *t*Bu): 424.1064. Found: *m*/*z*, 424.1075.

Methyl {(1*R**,2*R**,5*R**,6*R**,7*R**)-5-*tert*-butyldimethylsilyloxymethyl-2-cyano-6,7-bis(methoxycarbonyl)-4-oxo-8-oxabicyclo-[3.2.1]octan-2-yl}acetate (36)

To a solution of tricycle **35** (1.2 g, 2.6 mmol) in THF (10 ml) at −78 °C was added SmI_2 (0.1 M in THF; 57 ml). The resulting solution was stirred for 1 h prior to the addition of saturated aq. $NaHCO_3$ and EtOAc. The separated aqueous solution was further extracted with EtOAc and the combined organic extracts were washed with H_2O, dried ($MgSO_4$), filtered and concentrated. Chromatography of the residue on silica gel (elution with EtOAc–hexane, 1 : 6) gave compound **36** (991 mg, 2.1 mmol, 79%) as a colourless oil; R_f = 0.33 (silica gel; EtOAc–hexane, 1 : 2); ν_{max}(neat)/cm^{-1} 2955, 2930, 2250, 1740 and 1440; δ_H (500 MHz, $CDCl_3$) 4.95 (s, 1 H), 4.18 (d, *J* 7.0, 1 H), 4.06 (d, *J* 12, 1 H), 4.05 (dd, *J* 7.0, 1.8, 1 H), 3.86 (d, *J* 12, 1 H), 3.82 (s, 3 H), 3.75 (s, 3 H), 3.72 (s, 3 H), 3.04–2.84 (m, 4 H), 0.89 (s, 9 H), 0.08 (s, 3 H) and 0.06 (s, 3 H); δ_C (125 MHz, $CDCl_3$) 197.8, 170.9, 169.7, 168.9, 119.0, 91.5, 80.9, 59.7, 53.3, 53.1, 52.4, 49.4, 49.1, 42.8, 41.7, 40.0, 25.8(× 3), 18.3, −5.3 and −5.5; MS (EI) *m*/*z* 452 (M^+ − OCH_3), 426 (M^+ − *t*Bu), 394, 366, 241; HRMS (EI) Calc. for $C_{18}H_{24}NO_9Si$ (M^+ − *t*Bu): 426.1220. Found: *m*/*z*, 426.1230.

Methyl {(1*R**,2*R**,5*R**,6*R**,7*R**)-2-cyano-5-hydroxymethyl-6,7-bis(methoxycarbonyl)-4-oxo-8-oxabicyclo[3.2.1]octan-2-yl}-acetate (37)

With the procedure as described for the alcohol **12**, silyl ether **36** (103 mg, 0.21 mmol) was desilylated to give alcohol **37** (70 mg, 0.19 mmol, 89%) as a colourless oil; R_f = 0.10 (silica gel; EtOAc–hexane, 1 : 2); ν_{max}(neat)/cm^{-1} 3505, 2925, 2855, 2245, 1720 and 1435; δ_H (500 MHz, $CDCl_3$) 5.00 (t, *J* 1.8, 1 H), 4.06 (dd, *J* 7.0, 1.8, 1 H), 4.01–3.93 (m, 3 H), 3.84 (s, 3 H), 3.76 (s, 3 H), 3.74 (s, 3 H), 3.07 (d, *J* 18, 1 H) and 2.96–2.86 (m, 3 H), O*H* not observed; δ_C (125 MHz, $CDCl_3$) 198.1, 170.9, 169.2, 168.8, 118.7, 90.9, 80.9, 60.5, 53.3, 53.2, 52.4, 50.4, 49.3, 42.7, 41.4 and 39.8; MS (FAB^+) *m*/*z* 370 (M^+ + H), 338 (M^+ − OCH_3), 306, 185; HRMS (FAB^+) Calc. for $C_{16}H_{20}NO_9$ (M + H): 370.1138. Found: *m*/*z*, 370.1129.

Methyl {(1*R**,2*R**,5*S**,6*R**,7*R**)-2-cyano-5-iodomethyl-6,7-bis-(methoxycarbonyl)-4-oxo-oxabicyclo[3.2.1]octan-2-yl}acetate (38)

Alcohol **37** (21.2 mg, 56 μmol) was iodinated with the procedure as described previously for iodide **13** to give iodide **38** (20 mg, 42 μmol, 73%) as a pale yellow oil; R_f = 0.29 (silica gel; EtOAc–hexane, 1 : 2); ν_{max}(neat)/cm^{-1} 2955, 2250, 1735 and

1440; δ_H (500 MHz, $CDCl_3$) 4.99 (t, *J* 1.8, 1 H), 4.13 (dd, *J* 6.7, 1.8, 1 H), 3.96 (d, *J* 6.7, 1 H), 3.86 (s, 3 H), 3.77 (s, 3 H), 3.74 (s, 3 H), 3.71 (d, *J* 12, 1 H), 3.59 (d, *J* 12, 1 H) and 3.03–2.86 (m, 4 H); δ_C (125 MHz, $CDCl_3$) 195.7, 170.6, 168.9, 168.6, 118.7, 89.4, 80.9, 54.0, 53.6, 53.6, 52.5, 49.7, 42.7, 41.6, 39.9 and 3.7; MS (EI) *m*/*z* 448 ($M^+ - OCH_3$), 352 ($M^+ - I$), 320, 292, 250; HRMS (EI) Calc. for $C_{16}H_{18}NO_8$ (M − I): 352.1032. Found: *m*/*z*, 352.1035.

Methyl {(1*S,3*R**,4*R**,5*R**,6*R**)-1-acetoxy-6-cyano-2-methylene-3,4-bis(methoxycarbonyl)-8-oxabicyclo[3.2.1]octan-6-yl}acetate (39)**

To a solution of iodide **38** (20 mg, 42 μmol) in Ac_2O was added activated Zn. The mixture was stirred at 50 °C for 3 h and then saturated aq. $NaHCO_3$ and CH_2Cl_2 were added. The separated aqueous solution was extracted with CH_2Cl_2 and the combined organic solutions were dried ($MgSO_4$), filtered and concentrated. Chromatography of the residue on silica gel (elution with EtOAc–hexane, 1 : 4) gave compound **39** (4.1 mg, 10 μmol, 25%) as a colourless oil; R_f = 0.52 (silica gel; EtOAc–hexane, 1 : 1); ν_{max}(neat)/cm^{-1} 2955, 1740 and 1440; δ_H (500 MHz, $CDCl_3$) 5.59 (br s, 1 H), 5.09 (s, 1 H), 4.99 (s, 1 H), 4.23 (d, *J* 7.0, 1 H), 3.81 (s, 3 H), 3.79 (s, 3 H), 3.77 (s, 3 H), 3.66 (dd, *J* 7.0, 1.8, 1 H), 3.08 (d, *J* 17, 1 H), 3.00 (d, *J* 17, 1 H), 2.89 (d, *J* 14, 1 H), 2.62 (d, *J* 14, 1 H) and 2.11 (s, 3 H); δ_C (125 MHz, $CDCl_3$) 171.8, 171.5, 169.4, 167.6, 141.4, 119.8, 113.3, 104.9, 80.9, 53.1, 52.8, 52.3, 45.9, 45.5, 44.6, 43.1, 40.9 and 21.6; MS (EI) *m*/*z* 396 (M^+ + H), 363, 353, 322, 275; HRMS (EI) Calc. for $C_{18}H_{21}NO_9$ (M): 395.1216. Found: M^+, 395.1212.

Dimethyl {(1*R,2*S**,5*S**,6*S**,7*S**)-5-*tert*-butyldimethylsilyloxymethyl-6,7-bis(methoxycarbonyl)-4-oxo-8-oxabicyclo[3.2.1]octan-2-yl}malonate (42)**

To a solution of NaH (60%, prewashed with hexane; 100 mg, 2.5 mmol) in THF (5 ml) at 0 °C was added dimethyl malonate (0.25 ml, 2.2 mmol) in THF (10 ml). The resulting solution was stirred for 20 min at room temperature. Then a solution of compound **9a** (700 mg, 1.8 mmol) in THF (15 ml) was added to this solution at 0 °C, then the mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with Et_2O, then saturated aq. NH_4Cl was added. The organic layer was separated, the aqueous phase was extracted with ether and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated. Purification with chromatography on silica gel (elution with EtOAc–hexane, 1 : 3) gave compound **42** (780 mg, 1.5 mmol, 83%) as a white solid; R_f = 0.17 (silica gel; EtOAc–hexane, 1 : 2); mp 103–106 °C (CH_2Cl_2); ν_{max}(neat)/cm^{-1} 2950, 2860, 1735 and 1435; δ_H (500 MHz, $CDCl_3$) 4.76 (br s, 1 H), 4.04 (d, *J* 12, 1 H), 3.96 (d, *J* 6.7, 1 H), 3.90 (d, *J* 12, 1 H), 3.76 (s, 3 H), 3.75 (s, 3 H), 3.73 (s, 3 H), 3.70 (s, 3 H), 3.65 (d, *J* 8.2, 1 H), 3.63 (dd, *J* 6.7, 1.8, 1 H), 2.94 (tdd, *J* 8.2, 4.3, 1.2, 1 H), 2.62 (dd, *J* 17, 8.2, 1 H), 2.44 (dd, *J* 17, 4.3, 1 H), 0.89 (s, 9 H), 0.07 (s, 3 H) and 0.05 (s, 3 H); δ_C (125 MHz, $CDCl_3$) 204.1, 171.8, 170.1, 168.2, 168.0, 91.8, 79.4, 60.6, 54.9, 52.8, 52.7(×2), 52.6, 51.9, 49.7, 40.8, 37.2, 25.7(×3), 18.2, −5.5 and −5.6; MS (FAB^+) *m*/*z* 517 (M^+ + H), 485, 427, 385; HRMS (FAB^+) Calc. for $C_{23}H_{37}O_{11}Si$ (M + H): 517.2105. Found: *m*/*z* 517.2108; Calc. for $C_{23}H_{36}O_{11}Si$: C, 53.47; H, 7.02. Found: C, 53.33; H, 7.07%.

Dimethyl {(1*R,2*S**,5*S**,6*S**,7*S**)-5-hydroxymethyl-6,7-bis(methoxycarbonyl)-4-oxo-8-oxabicyclo[3.2.1]octan-2-yl}malonate (43)**

With the procedure as described for alcohol **12**, the silyl ether **42** (600 mg, 1.2 mmol) was desilylated to give alcohol **43** (450 mg, 1.1 mmol, 97%) as a white solid; R_f = 0.27 (silica gel; EtOAc–hexane, 2 : 1); mp 105–110 °C (CH_2Cl_2); ν_{max}(neat)/cm^{-1} 3520, 2960, 1730 and 1440; δ_H (500 MHz, $CDCl_3$) 4.80 (br s, 1 H), 3.99 (dd, *J* 13, 4.9, 1 H), 3.93 (dd, *J* 13, 9.1, 1 H), 3.82 (d, *J* 6.7, 1 H), 3.78 (s, 3 H), 3.76 (s, 3 H), 3.74 (s, 3 H), 3.72 (s, 3 H), 3.69 (dd, *J* 6.7, 1.8, 1 H), 3.65 (d, *J* 7.6, 1 H), 2.99 (tdd, *J* 7.6, 3.0, 1.2, 1 H), 2.73 (dd, *J* 18, 7.6, 1 H), 2.53 (ddd, *J* 18, 3.1, 1.5, 1 H) and 1.91 (dd, *J* 9.1, 4.8, 1 H); δ_C (125 MHz, $CDCl_3$) 203.8, 171.9, 169.9, 168.3, 168.1, 91.0, 79.9, 61.2, 54.6, 53.0, 52.9(×2), 52.7, 51.7, 50.9, 40.8 and 37.2; HRMS (FAB^+) Calc. for $C_{17}H_{23}O_{11}$ (M + H): 403.1240. Found: *m*/*z*, 403.1255; Calc. for $C_{17}H_{22}O_{11}$: C, 50.75; H, 5.51. Found: C, 51.10; H, 5.81%.

Dimethyl {(1*R,2*S**,5*R**,6*S**,7*S**)-5-iodomethyl-6,7-bis(methoxycarbonyl)-4-oxo-8-oxabicyclo[3.2.1]octan-2-yl}malonate (44)**

Alcohol **43** (26 mg, 65 μmol) was iodinated with the procedure as described previously for iodide **13** to give iodide **44** (28 mg, 55 μmol, 84%) as a colourless oil; R_f = 0.3 (silica gel; EtOAc–hexane, 1 : 2); ν_{max}(neat)/cm^{-1} 2955, 1730 and 1440; δ_H (500 MHz, $CDCl_3$) 4.79 (br s, 1 H), 3.79 (s, 3 H), 3.78–3.76 (m, 1 H), 3.77 (s, 3 H), 3.75 (s, 3 H), 3.72 (s, 3 H), 3.73–3.69 (m, 2 H), 3.66 (d, *J* 7.9, 1 H), 3.61 (d, *J* 12, 1 H), 2.96 (tdd, *J* 7.9, 4.0, 1.2, 1 H), 2.67 (dd, *J* 17, 7.9, 1 H) and 2.53 (ddd, *J* 17, 4.0, 1.2, 1 H); δ_C (125 MHz, $CDCl_3$) 202.2, 171.5, 169.1, 168.2, 167.9, 89.1, 79.6, 54.6, 54.4, 53.1, 52.9(×2), 52.8, 52.1, 40.8, 37.1 and 4.8; MS (EI) *m*/*z* 513 (M^+ + H), 385 ($M^+ - I$); HRMS (EI) Calc. for $C_{17}H_{21}O_{10}$ (M − I): 385.1135. Found: *m*/*z*, 385.1146.

Dimethyl {(1*R,3*R**,4*R**,5*S**,6*R**)-1-hydroxy-2-methylene-3,4-bis(methoxycarbonyl)-8-oxabicyclo[3.2.1]octan-6-yl}malonate (45)**

Iodide **44** (352 mg, 0.69 mmol) in MeOH (15 ml) was treated with activated Zn as described for enone **14**. Chromatography on silica gel (elution with EtOAc–hexane, 1 : 1) gave hemiketal **45** (158 mg, 0.41 mmol, 59%) as a colourless oil; R_f = 0.09 (silica gel; EtOAc–hexane, 1 : 2); δ_H (500 MHz, $CDCl_3$) 5.53 (br s, 1 H), 5.15 (d, *J* 1.2, 1 H), 4.75 (br s, 1 H), 4.20 (br s, 1 H), 3.78 (s, 3 H), 3.77 (s, 3 H), 3.75 (s, 6 H), 3.55 (d, *J* 9.1, 1 H), 3.37 (t, *J* 5.3, 1 H), 3.10 (br s, 1 H), 2.90 (tdd, *J* 9.1, 5.8, 1.5, 1 H), 2.28 (dd, *J* 9.1, 1.3, 1 H) and 1.78 (dd, *J* 13, 5.8, 1 H); MS (EI) *m*/*z* 386 (M^+), 337, 250; HRMS (EI) Calc. for $C_{17}H_{22}O_{10}$ (M): 386.1213. Found: M^+, 386.1216.

Dimethyl {(1*R,3*S**,4*R**,5*S**,6*R**)-2-(but-3-enyl)-1-hydroxy-3,4-bis(methoxycarbonyl)-8-oxabicyclo[3.2.1]octan-6-yl}malonate (46)**

To a solution of alkene **45** (158 mg, 0.41 mmol) in CH_2Cl_2 (5 ml) at −78 °C were added allyltrimethylsilane (0.12 ml, 0.76 mmol) and $TiCl_4$ (0.05 ml, 0.46 mmol). The mixture was stirred at this temperature for 30 min, then quenched with saturated aq. $NaHCO_3$. The separated aqueous solution was extracted with CH_2Cl_2 and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated. Chromatography of the residue on silica gel (elution with EtOAc–hexane, 1 : 2) gave compound **46** (80 mg, 0.19 mmol, 46%) as a colourless oil; R_f = 0.31 (silica gel; EtOAc–hexane, 1 : 1); ν_{max}(neat)/cm^{-1} 3575, 2954, 1725 and 1440; δ_H (500 MHz, $CDCl_3$) 5.84–5.74 (m, 1 H), 5.02 (d, *J* 17, 1 H), 4.95 (d, *J* 10, 1 H), 4.57 (br s, 1 H), 3.74 (s, 3 H), 3.73 (s, 3 H), 3.72 (s, 3 H), 3.69 (s, 3 H), 3.61 (d, *J* 7.6, 1 H), 3.50 (d, *J* 9.4, 1 H), 3.01 (s, 1 H), 2.82 (dt, *J* 9.4, 5.2, 1 H), 2.69 (dd, *J* 13, 9.4, 1 H), 2.19–2.09 (m, 2 H), 2.09–1.99 (m, 1 H), 1.86–1.77 (m, 1 H), 1.71–1.62 (m, 1 H) and 1.39 (dd, *J* 13, 5.2, 1 H), O*H* not observed; δ_C (125 MHz, $CDCl_3$) 173.5, 172.2, 168.9, 168.8, 138.2, 114.9, 106.5, 78.8, 56.0, 52.7(×2), 52.6, 51.9, 47.0, 42.9, 41.0, 40.2, 35.3, 31.5 and 26.4; MS (EI) *m*/*z* 385 (M^+ − allyl), 353, 288, 225; HRMS (EI) Calc. for $C_{20}H_{28}O_{10}$ (M): 428.1682. Found: M^+, 428.1697.

(1*R,5*S**,6*R**,7*S**)-4-(But-3-enyl)-5,6,10-tris(methoxycarbonyl)-8-oxabicyclo[5.3.0]decane-3,9-dione (47)**

To a solution of hemiketal **46** (59 mg, 0.14 mmol) in THF (5 ml) at room temperature was added NaOMe (45 mg, 0.83 mmol)

during 2 h. Saturated aq. $NaHCO_3$ was added and the organic phase was extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated. Chromatography on silica gel (elution with EtOAc–hexane, 1 : 2) gave bicycle **47** (36 mg, 0.091 mmol, 66%) as a colourless oil; R_f = 0.29 (silica gel; EtOAc–hexane, 1 : 1); ν_{max}(neat)/cm^{-1} 2950, 2925, 1785, 1735 and 1435; δ_H (500 MHz, $CDCl_3$) 5.71–5.62 (m, 1 H), 5.06 (d, *J* 17, 1 H), 5.01–4.96 (m, 2 H), 3.80 (s, 3 H), 3.78 (s, 3 H), 3.71 (s, 3 H), 3.66 (d, *J* 7.6, 1 H), 3.58 (dd, *J* 6.4, 3.4, 1 H), 3.51 (dd, *J* 6.4, 5.8, 1 H), 3.47–3.39 (m, 1 H), 2.81–2.71 (m, 1 H), 2.57 (dt, *J* 7.6, 5.5, 1 H), 2.10–1.88 (m, 3 H) and 1.39–1.31 (m, 1 H), O*H* not observed; δ_C (125 MHz, $CDCl_3$) 205.3, 171.0, 170.8, 169.9, 167.5, 137.1, 115.9, 78.0, 53.3, 53.0, 52.8, 52.5, 50.5, 46.4, 44.3, 44.1, 36.1, 31.2 and 26.7; MS (EI) *m*/*z* 397 (M^+ + H), 353 (M^+ − allyl), 225; HRMS (EI) Calc. for $C_{19}H_{24}O_9$ (M): 396.1420. Found: M^+, 396.1412.

(4*R**,5*S**,6*R**,7*S**)-7-(But-3-enyl)-4-*tert*-butyldimethylsilyloxy-5,6-bis(methoxycarbonyl)cyclohept-2-enone (50) and (1*R**,2*S**,3*R**,4*S**,6*R**)-4-*tert*-butyldimethylsilyloxy-7-methylene-2,3-bis(methoxycarbonyl)bicyclo[4.3.1]decan-10-one (51)

To a solution of the cycloheptanone **24** (200 mg, 0.46 mmol) in THF (10 ml) at −78 °C was added KHMDS (0.5 M solution in toluene, 0.55 mmol) and then the resulting mixture was stirred for 15 min. To this solution at −78 °C was added TMSCl (0.08 ml, 0.63 mmol) and then the solution was stirred for 30 min. Saturated aq. $NaHCO_3$ was added and the aqueous phase was extracted with Et_2O. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated.

To the above material in CH_3CN (10 ml) at room temperature was added $Pd(OAc)_2$ (170 mg, 0.75 mmol). The resulting solution was stirred for 3 h at this temperature and the solvent was evaporated. Purification with PLC (EtOAc–hexane, 1 : 7, twice) gave enone **50** (70 mg, 0.17 mmol, 35%) and bicycle **51** along with starting material (60 mg, 4 : 1), which could not be separated.

For compound **50**, R_f = 0.43 (silica gel; EtOAc–hexane, 1 : 3); ν_{max}(neat)/cm^{-1} 2950, 2930, 1735 and 1685; δ_H (500 MHz, $CDCl_3$) 6.61 (dd, *J* 12, 7.0, 1 H), 6.06 (d, *J* 12, 1 H), 5.83–5.74 (m, 1 H), 5.01 (dq, *J* 17, 1.8, 1 H), 4.97–4.93 (m, 2 H), 3.73 (s, 3 H), 3.67 (d, *J* 4.26, 1 H), 3.67 (s, 3 H), 3.50 (dd, *J* 7.0, 4.3, 1 H), 3.45 (dd, *J* 7.0, 2.7, 1 H), 2.19–2.12 (m, 2 H), 2.10–2.02 (m, 1 H), 1.59–1.50 (m, 1 H), 0.84 (s, 9 H), 0.04 (s, 3 H) and 0.04 (s, 3 H); δ_C (125 MHz, $CDCl_3$) 201.9, 173.3, 172.0, 142.4, 138.0, 134.8, 115.3, 68.0, 52.3, 52.1, 51.1, 48.5, 43.7, 31.7, 28.0, 25.5(×3), 17.8, −4.4 and −5.5; MS (EI) *m*/*z* 410 (M^+), 353 (M^+ − *t*Bu); HRMS (FAB$^+$) Calc. for $C_{17}H_{26}O_6Si$ (M + H − *t*Bu): 354.1499. Found: *m*/*z*, 354.1490.

For compound **51**, R_f = 0.46 (silica gel; EtOAc–hexane, 1 : 3); δ_H (500 MHz, $CDCl_3$) 4.76 (s, 1 H), 4.75 (s, 1 H), 4.57 (d, *J* 6.1, 1 H), 3.71 (s, 3 H), 3.68 (s, 3 H), 3.48 (dd, *J* 12, 4.0, 1 H), 3.28–3.23 (m, 2 H), 3.08–3.03 (m, 1 H), 2.53–2.46 (m, 2 H), 2.22–2.17 (m, 1 H), 2.00–1.93 (m, 1 H), 1.82 (d, *J* 15, 5.5, 1 H), 1.73–1.65 (m, 1 H), 0.85 (s, 9 H), 0.05 (s, 3 H) and −0.07 (s, 3 H).

Dimethyl [(1*R**,2*R**,3*S**,4*R**,5*S**)-5-(but-3-enyl)-2-*tert*-butyldimethylsilyloxy-3,4-bis(methoxycarbonyl)-6-oxocycloheptyl]malonate (52)

To a solution of NaH (60%, prewashed with hexane; 15 mg, 0.38 mmol) in THF (1 ml) at 0 °C was added dimethyl malonate (0.05 ml, 0.44 mmol) in THF (2 ml). The resulting solution was stirred for 20 min at room temperature. A solution of enone **50** (70 mg, 0.17 mmol) in THF 15 min was added to this solution at 0 °C, then the mixture was stirred at reflux temperature for 1 d. The reaction mixture was diluted with Et_2O, then saturated aq. NH_4Cl was added. The organic layer was separated and the aqueous phase was extracted with ether. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated. Purification with chromatography on silica gel (elution with EtOAc–hexane, 1 : 4) gave compound **52** (56 mg, 0.10 mmol, 61%) as a colourless oil; R_f = 0.11 (silica gel; EtOAc–hexane, 1 : 3); ν_{max}(neat)/cm^{-1} 2955, 2860, 1740 and 1435; δ_H (500 MHz, $CDCl_3$) 5.77–5.68 (m, 1 H), 4.99 (d, *J* 17, 1 H), 4.96 (d, *J* 8.8, 1 H), 4.55 (br s, 1 H), 3.77 (s, 3 H), 3.75 (s, 3 H), 3.69 (s, 6 H), 3.73–3.68 (m, 1 H), 3.39–3.28 (m, 2 H), 3.22 (d, *J* 10, 1 H), 2.93–2.79 (br s, 1 H), 2.74–2.63 (m, 2 H), 2.04 (sept, *J* 7.6, 2 H), 1.86 (sept, *J* 6.7, 1 H), 1.50–1.41 (m, 1 H), 0.88 (s, 9 H), 0.11 (s, 3 H) and 0.03 (s, 3 H); δ_C (125 MHz, $CDCl_3$) 208.7, 172.7, 172.6, 168.5, 168.1, 137.8, 115.5, 73.4, 52.8(×2), 52.6(×2), 52.3, 52.0, 48.7, 47.1, 42.3, 41.1, 31.7, 27.1, 25.6(×3), 17.9, −4.8 and −5.0; MS (EI) *m*/*z* 485 (M^+ − *t*Bu), 454 (M^+ − *t*Bu − OMe); HRMS (EI) Calc. for $C_{22}H_{33}O_{10}Si$ (M − *t*Bu): 485.1843. Found: *m*/*z*, 485.1843.

Dimethyl [(1*R**,2*R**,3*S**,4*R**,5*S**)-2-*tert*-butyldimethylsilyloxy-5-(2-formylethyl)-3,4-bis(methoxycarbonyl)-6-oxocycloheptyl]malonate (53)

The olefin **52** (36 mg, 66 μmol) in MeOH (3 ml) was ozonolyzed at −78 °C for 30 min. After removal of excess of ozone by bubbling oxygen through the solution for 10 min, sodium bicarbonate (5 mg) was introduced followed by the addition of dimethyl sulfide (0.3 ml). This mixture was allowed to warm to room temperature, then was stirred overnight. The reaction mixture was filtered and concentrated. Chromatography of the residue on silica gel (elution with EtOAc–hexane, 1 : 1) gave the aldehyde **53** as a colourless oil.

Dimethyl {(1*R**,4*R**,7*S**,10*S**,11*S**,12*S**)-11-*tert*-butyldimethylsilyloxy-12-methoxycarbonyl-2,10-dioxo-3-oxatricyclo[5.4.1.0^{4,12}]dodecan-10-yl}malonate (54) and dimethyl {(1*R**,2*S**,3*S**,4*R**,5*S**,6*R**)-3-*tert*-butyldimethylsilyloxy-9-hydroxy-4,5-bis(methoxycarbonyl)-10-oxobicyclo[4.3.1]decan-2-yl}malonate (55)

To a solution of aldehyde **53** in MeOH (2 ml) was added solid K_2CO_3 at room temperature, then the resulting mixture was stirred for 1.5 h. Saturated aq. NH_4Cl and EtOAc were added, then the organic layer was separated. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated. Purification by means of chromatography on silica gel (elution with EtOAc–hexane 1 : 4) gave tricycle **54** (9.9 mg, 19 μmol, 29%, 2 steps) along with bicycle **55** (2.7 mg, 4.9 μmol, 7%, 2 steps) as colourless oils.

For compound **54**, R_f = 0.37 (silica gel; EtOAc–hexane, 1 : 2); ν_{max}(neat)/cm^{-1} 2955, 2930, 2855 and 1735; δ_H (500 MHz, $CDCl_3$) 4.93 (d, *J* 5.5, 1 H), 4.49 (t, *J* 2.7, 1 H), 3.89 (s, 3 H), 3.83 (d, *J* 2.7, 1 H), 3.80 (s, 3 H), 3.74 (s, 3 H), 3.62 (d, *J* 11, 1 H), 3.42 (dd, *J* 11, 6.7, 1 H), 3.00 (q, *J* 10, 1 H), 2.55 (dd, *J* 12, 9.1, 1 H), 2.37–2.30 (m, 1 H), 2.29–2.15 (m, 3 H), 1.97–1.88 (m, 1 H), 0.86 (s, 9 H), 0.17 (s, 3 H) and 0.09 (s, 3 H); δ_C (125 MHz, $CDCl_3$) 202.9, 175.5(×2), 167.9, 167.4, 88.3, 72.5, 62.1, 57.5, 54.4, 54.1, 53.0, 52.9, 48.2, 40.9, 40.5, 32.2, 27.2, 25.9(×3), 18.3, −5.0 and −5.3; MS (EI) *m*/*z* 455 (M^+ − tBu), 395, 303, 275; HRMS (EI) calc. for $C_{20}H_{27}O_{10}Si$ (M − *t*Bu): 455.1374. Found: *m*/*z*, 455.1364.

For compound **55** (major isomer), R_f = 0.22 (silica gel; EtOAc–hexane, 1 : 2); δ_H (500 MHz, $CDCl_3$) 4.43 (br s, 1 H), 4.18 (s, 1 H), 3.79 (s, 3 H), 3.78–3.76 (m, 4 H), 3.68 (s, 3 H), 3.62 (s, 3 H), 3.23 (dd, *J* 12, 5.2, 1 H), 2.94 (dt, *J* 12, 2.4, 1 H), 2.87–2.80 (m, 1 H), 2.74 (d, *J* 12, 1 H), 2.65 (br s, 1 H), 2.44 (br s, 1 H), 2.31–2.21 (m, 1 H), 2.07–2.01 (m, 1 H), 1.66–1.62 (m, 1 H), 0.93 (s, 9 H), 0.16 (s, 3 H) and −0.04 (s, 3 H), O*H* not observed.

Dimethyl {(1*R**,2*S**,3*S**,4*R**,5*S**,6*R**)-3-*tert*-butyldimethylsilyloxy-4,5-bis(methoxycarbonyl)-9,10-dioxobicyclo[4.3.1]decan-2-yl}malonate (56)

To a solution of the alcohol **55** (2.6 mg, 4.8 μmol) in CH_2Cl_2

(1 ml) were added PCC (10 mg, 46 μmol) and 4 Å MS at room temperature. The mixture was stirred at room temperature for 2 d, then filtered and concentrated. Chromatography of the residue on silica gel (elution with EtOAc–hexane, 1 : 3) gave dione **56** (2.0 mg, 3.7 μmol, 77%) as a colourless oil; $R_f = 0.37$ (silica gel; EtOAc–hexane, 1 : 2); ν_{max}(neat)/cm^{-1} 2955, 2930, 2855, 1735 and 1445; δ_H (500 MHz, $CDCl_3$) 4.21 (d, *J* 2.7, 1 H), 3.80 (s, 3 H), 3.78 (s, 3 H), 3.72 (s, 3 H), 3.65 (s, 3 H), 3.53 (d, *J* 12, 1 H), 3.40 (dd, *J* 12, 5.8, 1 H), 3.34 (dt, *J* 12, 2.7, 1 H), 3.26 (br s, 1 H), 3.19 (ddd, *J* 18, 12, 7.3, 1 H), 2.90 (br s, 1 H), 2.83 (d, *J* 12, 1 H), 2.53 (d, *J* 18, 1 H), 2.41–2.35 (m, 1 H), 2.02–1.94 (m, 1 H), 0.88 (s, 9 H), 0.12 (s, 3 H) and −0.06 (s, 3 H): δ_C (125 MHz, $CDCl_3$) 206.9, 206.6, 174.6, 172.5, 168.1, 167.1, 73.0, 62.1, 53.3, 53.0, 52.6, 52.4, 51.6, 49.1, 48.2, 47.5, 38.9, 34.3, 25.9(×3), 23.5, 18.0, −4.9 and −6.0; MS (FAB$^+$) *m*/*z* 543 (M^+ + H), 512 (M^+ − OCH_3), 475, 206, 185; HRMS (FAB$^+$) Calc. for $C_{25}H_{39}O_{11}Si$ (M^+ + H): 543.2261. Found: *m*/*z*, 543.2278.

Acknowledgements

The author is grateful to Prof K. Ohkata for his valuable advice and to Dr S. Kojima for prereading the manuscript. He is also grateful to Drs Y. Hiraga and R. Takagi for assistance in NMR. He thanks Dr M. Sawada for support of elemental analysis. The Instrument Center for Chemical Analysis of Hiroshima University and the Hiroshima Prefectural Institute of Industrial Science and Technology are heartily acknowledged for providing machine time on NMR and MS.

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