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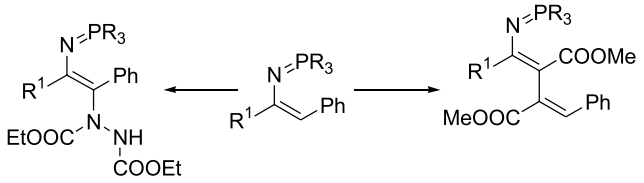
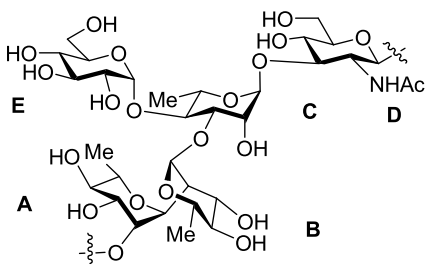
Contents

REPORT

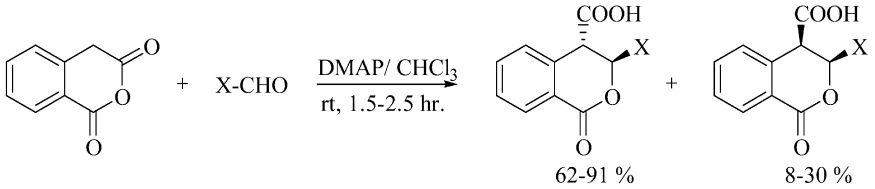
This review evaluates the advantages, disadvantages, and effectiveness of newly developed peptide coupling reagents used in organic synthesis. Each reagent is classified into one of eight types including phosphonium, uronium, immonium, carbodiimide, imidazolium, organophosphorous, acid halogenating and other coupling reagents, according to the structural similarity.

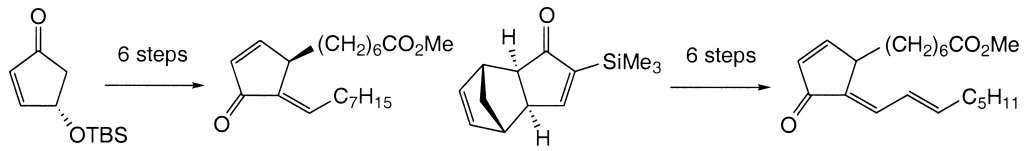
ARTICLES



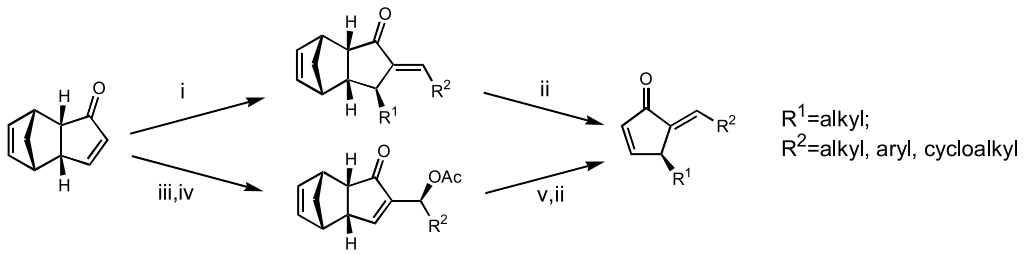


The synthesis of the methyl glycosides of fragments **B(E)CD**, **AB(E)CD**, and **ECDAB** is described.

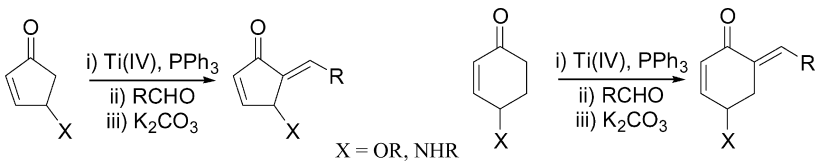




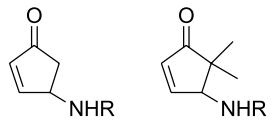
The syntheses of $\Delta^{12,14}$-15-deoxy-PG-J_1 methyl ester and _epi_-Δ^{12}-15-deoxy-PG-J_1, using as key steps a one-pot conjugate addition–Peterson olefination and Noyori-type three-component coupling approach, respectively, are described.



(i) Conjugate addition/aldehyde quench/dehydration; (ii) _retro_ Diels-Alder; (iii) Baylis-Hillman; (iv) acetylation; (v) conjugate addition/elimination.

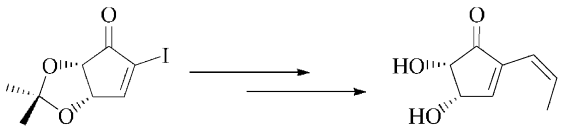


The conversion of substituted cyclopent-2-enones and cyclohex-2-enones into corresponding α'-_exo_-alkylidene compounds using Ti(IV) catalysis, with PPh_3 and an aldehyde, is described.



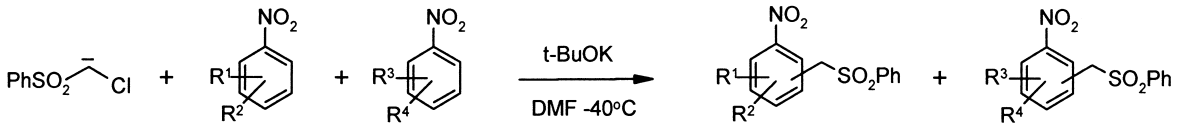
R = alkyl, aryl or protecting group

Three different methods are reported for the preparation of 4-azacyclopent-2-enones, two of which allow the preparation of the compounds in optically active form. In addition, a facile route to 4-aza-5,5-dimethylcyclopent-2-enones is disclosed.



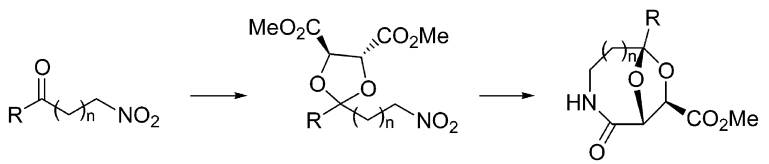
5 **(-)-10**

Stille-type reactions were employed to prepare and revise the stereochemistry of a natural product isolated from ascomycete strain A23-98.

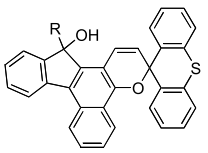


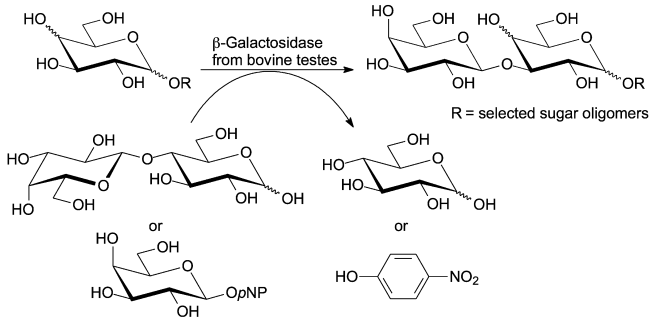
R^1 - R^4 = H, Cl, Br *ortho* and / or *para*

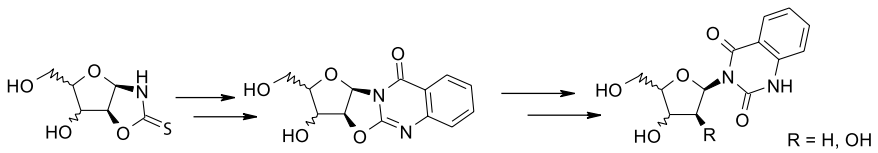
Relative reactivities of substituted nitrobenzenes were estimated in competitive Vicarious Nucleophilic Substitution reactions.

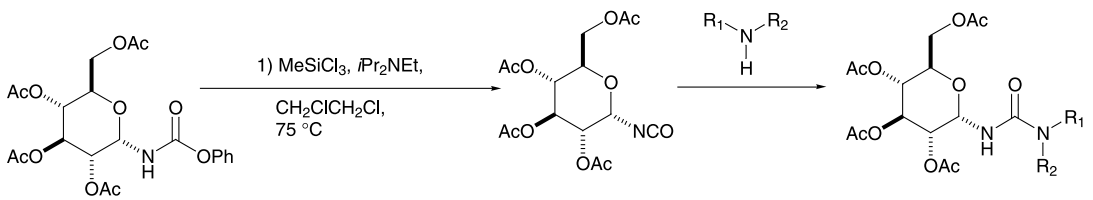


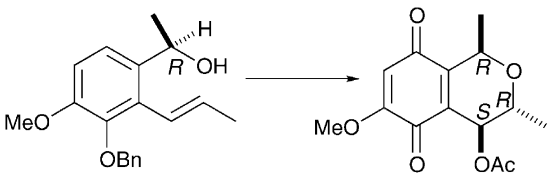
n = 1 R = Et, Ph, 4-ClC_6H_4
n = 2 R = Me, Ph, 4-$OMeC_6H_4$

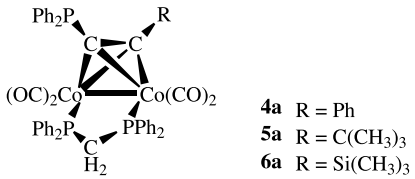






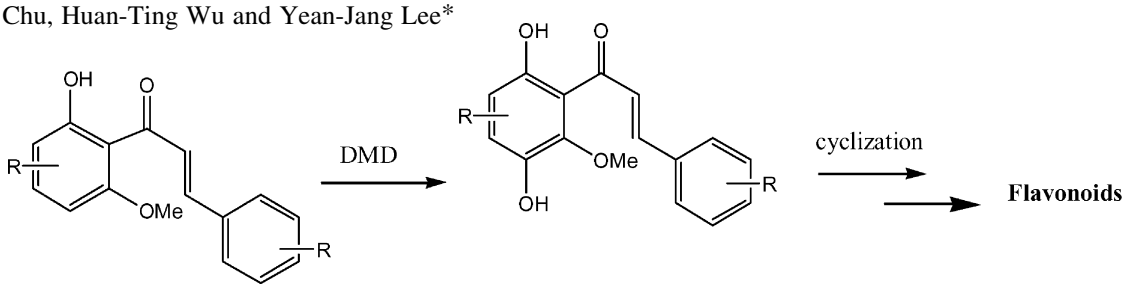




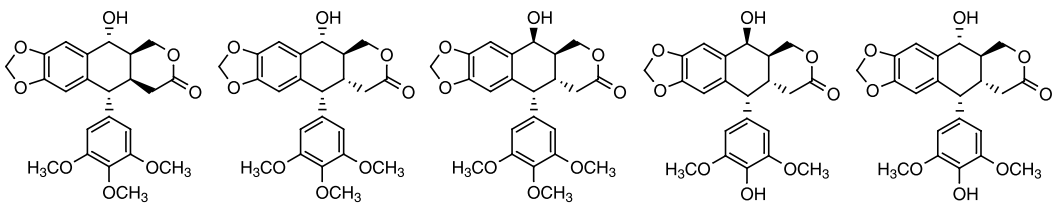


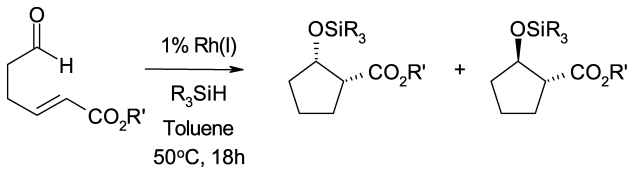
4a R = Ph
5a R = $C(CH_3)_3$
6a R = $Si(CH_3)_3$

Three bulky mono-dentate alkyne-bridged dicobalt-phosphine complexes, **4a**, **5a** and **6a** were prepared and took part in the Suzuki type cross-coupling reactions as effective, authentic mono-dentate phosphine ligands.



The novel regioselective hydroxylation of 2-hydroxychalcones with DMD is described. Based upon this methodology, the polymethoxylated flavonoids are synthesized.





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Recent development of peptide coupling reagents in organic synthesis

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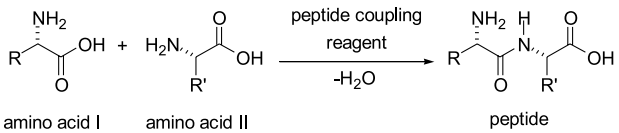
Contents

1. Introduction

In recent years, peptide coupling reactions have been significantly advanced in accord with the development of new peptide coupling reagents in organic synthesis. Even though a number of valuable reviews have been published in this area,[1] the development of new peptide coupling reagents has been steadily accelerated in the past few years. Moreover, tremendously expanded applications have been possible to new and broad synthetic challenges. This report focuses on the major advances in coupling reagents that have had a great impact in the field. Among many, coupling reagents responsible for the formation of azide, mixed anhydride, and acid halide intermediates have gained substantial popularity in peptide coupling reactions. DCC as a peptide-coupling reagent has particularly attracted organic chemists in their synthesis of complex molecules. Moreover, the development of onium-type coupling reagents has made the incorporation of non-coded or sterically hindered amino acids including *N*-methylated and α,α-dialkylated amino acids smoothly into the corresponding peptides possible. In a typical peptide coupling reaction, the carboxylic acid moiety of the amino acid I is first activated by an appropriate peptide coupling reagent, and then reacted with the amine moiety of the amino acid II to produce a desired peptide as illustrated in Scheme 1.



Scheme 1.

Another significant development in the field of peptide coupling reactions is the discovery of the racemisation suppressants. Racemisation can occur at the C-terminal amino acid residue in the course of a coupling reaction due to the ionisation of the α-hydrogen and the formation of an oxazolone intermediate (Scheme 2). A peptide coupling reagent with an appropriate racemisation suppressing agent assures suppression of the undesired racemisation and other side reactions, and thus minimises the loss of the optical integrity at the chiral centre.[2] In some cases, racemisation suppressants are also used as additives to the peptide coupling reagent. In there examples, the additive plays a role as not only a racemisation suppressor but also as a rate enhancer.

Keywords: Peptide coupling reagent; Amino acid; Racemisation suppressant; Enantiomeric excess.

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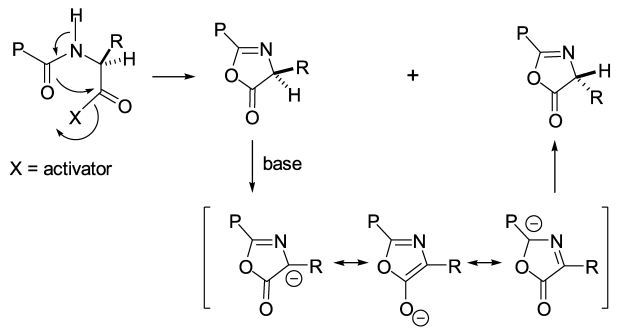
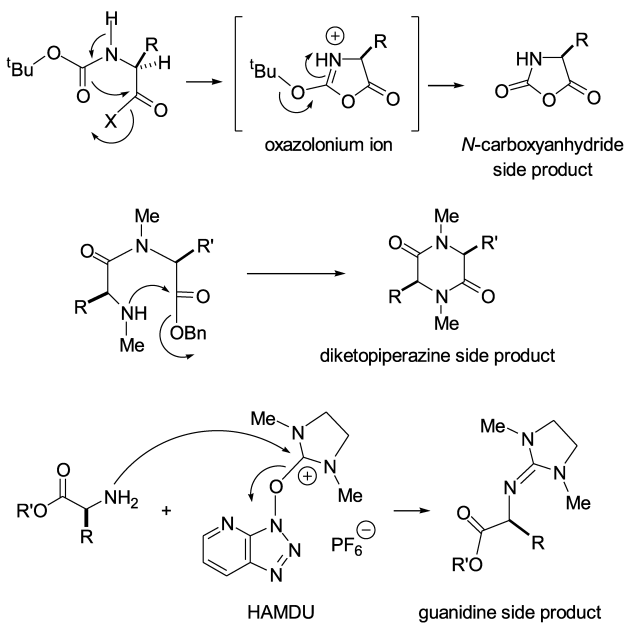


Scheme 2.

Immediate side reactions in peptide coupling reactions are the formation of *N*-carboxyanhydride, diketopiperazine and guanidine (Scheme 3).[3,4] A guanidine side product is often produced when the uronium coupling reagent is directly connected to the amine moiety of the amino acid residue.



Scheme 3.

Several techniques have been developed to overcome such side reactions during peptide coupling reactions. One aspect is the use of appropriate protecting groups (Fmoc, Trt, Cbz, etc.) on the nitrogen atom. Vedejs introduced arenesulfonyl protecting groups such as Bts and Ths in 1996 (Fig. 1). The *N*-Bts protected acid chloride gave a greater reactivity without any detectable racemisation than the *N*-Cbz protected acid fluoride (Bts-Phg-Aib-OCH_3, 0.1% racemisation; Cbz-Phg-Aib-OCH_3, <1% racemisation). Bts- and Ths-protected amines were easily deprotected by Zn/HOAc-EtOH or 50% H_3PO_2.[5]

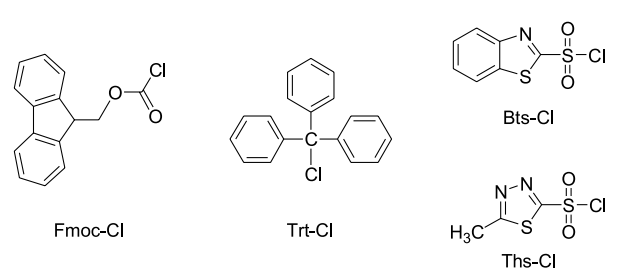
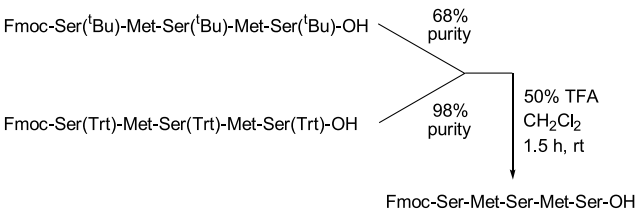


Figure 1.

Barlos showed that protecting groups influenced the purity of the peptides (Scheme 4).[6] For example, the purity of Fmoc-pentapeptide obtained from *N*-Fmoc-*O*-Trt protected peptide was 98%, while *N*-Fmoc-*O*-^{t}Bu protected peptide gave only 68% due to the undesired *tert*-butylation of the nucleophilic side chain of Met and Trp. In addition, the Trt group of Fmoc-amino acids could be removed more easily than the ^{t}Bu group under very mild condition such as diluted TFA.



Scheme 4.

The choice of base is also important in peptide coupling reactions (Fig. 2). Tertiary amines such as DIEA and NMM have been considered as practically useful bases in peptide synthesis due to the non-nucleophilic property of the base itself. More recently, collidine, TEMP, and DBDMAP were recommended by Carpino.[7] For example, coupling of Fmoc-Leu-OH with H-Pro-PAL-PEG-PS in DMF using TFFH/DIEA produced 0.8% of undesired epimer, while TFFH/DBDMAP reduced the epimerisation to 0.2%. The best result was obtained when collidine or TEMP was used as a base (0.1% of epimer).

This review evaluates advantages, disadvantages, and effectiveness of newly developed peptide coupling reagents. Each reagent is classified into one of eight types including phosphonium, uronium, immonium, carbodiimide, imidazolium, organophosphorous, acid halogenating and other coupling reagents, according to the structural similarity. Solid phase peptide synthesis is beyond the scope of this review.

2. Phosphonium reagents

In the early 1970s, Castro introduced ClopP[8] and BropP[9] as peptide coupling reagents with noticeable racemisation in Young's test (Fig. 3). After HOBt was discovered as a

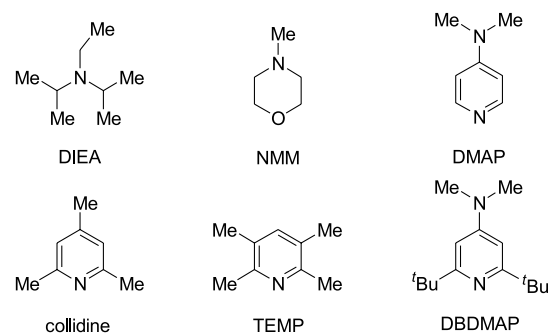


Figure 2.

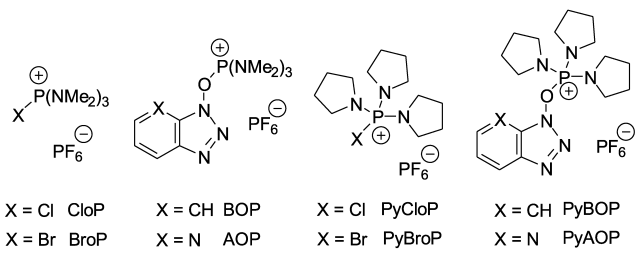
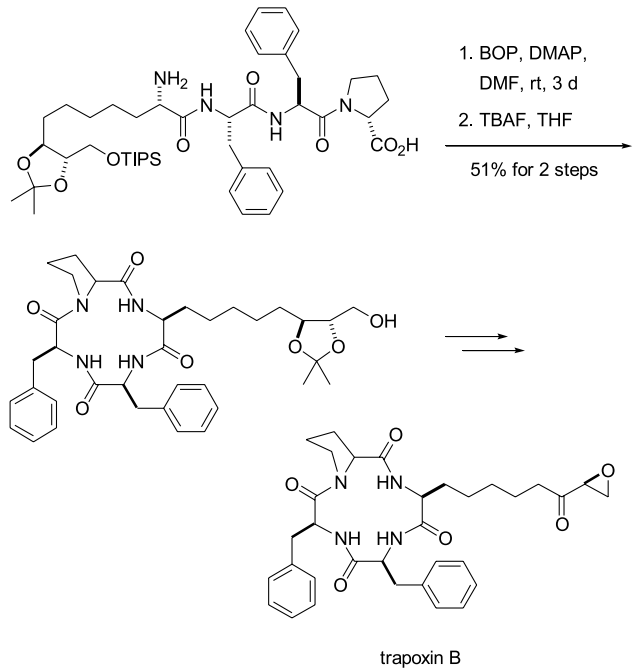


Figure 3.

racemisation suppressant, a new CloP-HOBt combined coupling reagent, known as BOP, was introduced in 1975.[10] BOP is a non-hygroscopic crystalline compound which can easily be prepared in large quantities.

Schreiber reported the use of BOP in the ring closure of 12-membered tetrapeptides such as trapoxin B. Schmidt's pentafluorophenyl ester protocol gave unsatisfactory results in this case (Scheme 5).[11]



Scheme 5.

Later, PyCloP, PyBroP, and PyBOP were introduced, where the dimethylamine moiety was replaced by pyrrolidine (Fig. 3).[12] These reagents could avoid the generation of poisonous hexamethylphosphoramide (HMPA) by-product.

In a following investigation, Coste reported that halogenophosphonium reagents often gave better results than other phosphonium-HOBt reagents in *N*-methylated amino acid cases.[13] For example, PyBroP and PyCloP gave 70–85% yields in the synthesis of Boc-Pro-MeVal-OMe and Cbz-Val-MeVal-OMe, whereas PyBOP gave only 11–26% yields. HBPyU and PyClU uronium reagents also displayed a similar tendency. The formation of a stable benzotriazole activated ester intermediate lowered the reactivity and the yield. Similarly, the standard procedure such as the DCC/HOBt method gave a poor result due to the formation of

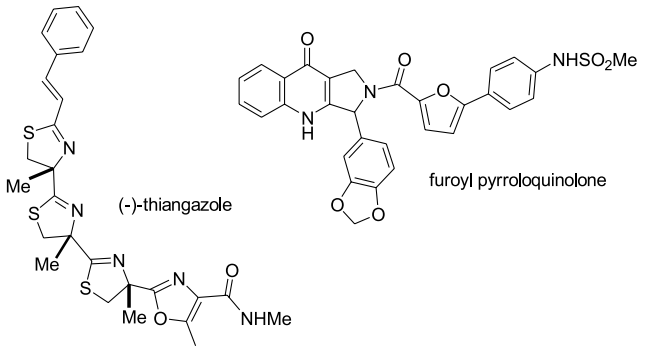
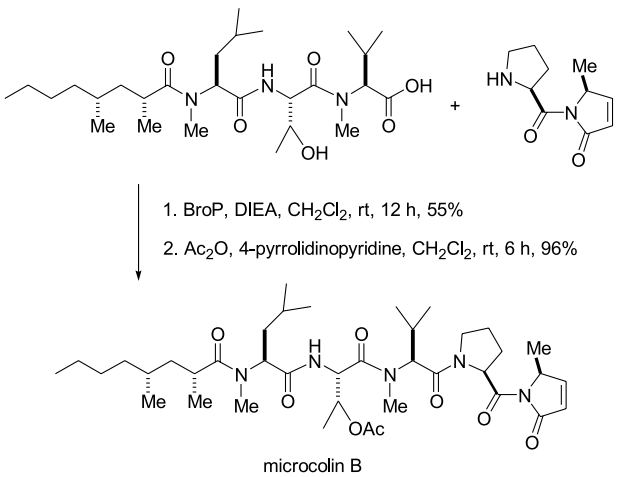


Figure 4.

HOBt ester and the *N*-acylurea as by-products. Coste also demonstrated that Fmoc or Cbz protected *N*-methyl amino acids were more prone to coupling reactions than Boc when PyBroP or PyCloP was used as the peptide coupling reagent. The loss of the *tert*-butyl cation caused the formation of *N*-carboxyanhydride through a Boc-oxazolonium ion intermediate and lowered the reactivity (Scheme 3).[14] The efficiency of PyBroP was confirmed in the synthesis of (−)-thiangazole, destruxin B, and furoyl pyrroloquinolone (Fig. 4).[15]

Andrus reported the synthesis of a potent new immunosuppressant, microcolin B, using BroP as a peptide coupling reagent (Scheme 6).[16]



Scheme 6.

Since the discovery of HOBt-attached coupling reagents was successful, many racemisation suppressants have been exploited as a part of compositions of new peptide coupling reagents (Fig. 5). For example, AOP, PyAOP, PyTOP, and PyDOP (Figs. 3 and 5) were prepared in this regard. Additional electron-withdrawing substituents on the benzotriazole ring were introduced to form CF_3-BOP, CF_3-PyBOP, and CF_3-NO_2-PyBOP. They served as efficient peptide coupling reagents for the synthesis of dipeptides bearing *N*-methyl amino acids.[17]

Høeg–Jensen reported the formation of the thioamide as major and the amide as minor products when a monothio acid was reacted with an amine and phosphonium (BOP,

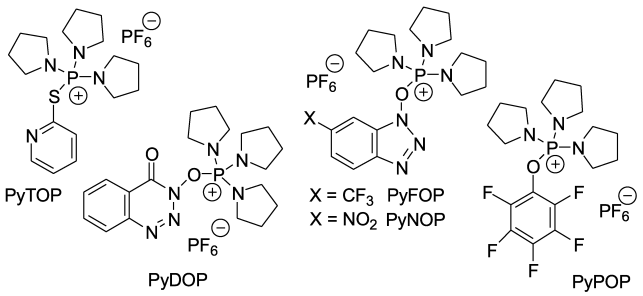
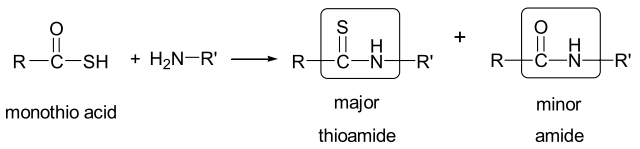


Figure 5.

NOP, PyBOP, PyNOP, PyBroP, PyCloP, PyFOP, PyTOP, PyPOP, and PyDOP) and organophosphorous reagents (BOP-Cl and ENDPP) as coupling reagents (Scheme 7). This was based upon the fact that phosphorus formed a stronger bond to oxygen than to sulfur for O/S-selectivity. PyNOP and PyFOP gave the best results for thioamide formation, while PyBroP gave the amide as the major product.[18]



Scheme 7.

3. Uronium reagents

Gross introduced HBTU as the progenitor of uronium reagents in 1978 (Fig. 6).[19] Since then, various analogues of HBTU have been prepared and investigated by Knorr.[20] The tetrafluoroborate or hexafluorophosphate anion is generally used as the non-nucleophilic counterion in uronium reagents. A comparison study between HBTU and TBTU showed that the counterion had no significant influence on the coupling rate or racemisation. Carpino disclosed the true structure of the active HBTU and its family as the *N*-guanidium rather than the *O*-uronium salt in his elegant study.[21]

TSTU and TNTU were recognised as useful peptide coupling reagents in aqueous reactions. The hematoregula-

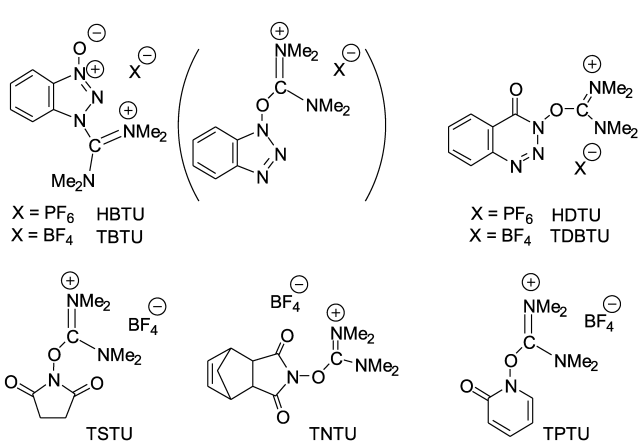
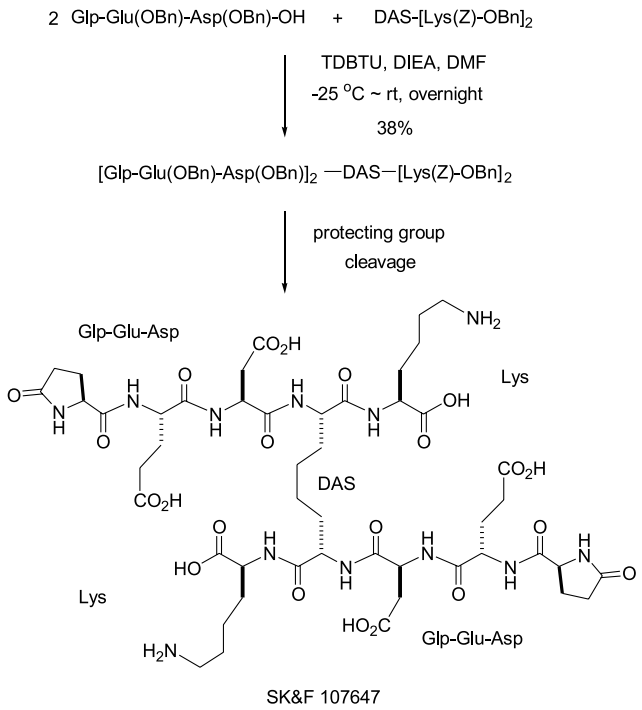


Figure 6.

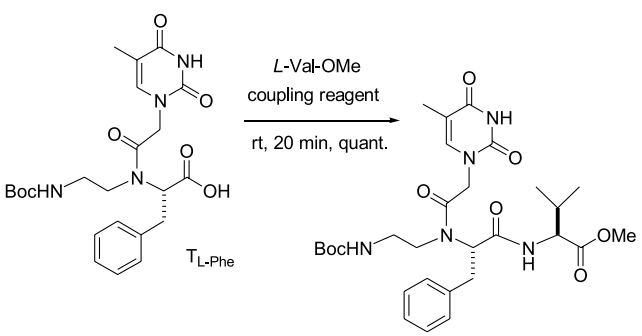


Scheme 8.

tory non-apeptide SK&F 107647 was synthesised from the corresponding Glp-Glu(OBn)-Asp(OBn)-OH and DAS-[Lys(Z)-OBn]$_2$ by using TDBTU as the peptide coupling reagent in a purity of >97% in a Kg-scale synthesis (Scheme 8). Other coupling reagents were not as effective as TDBTU. DIEA was more efficient than NMM or collidine as a base in peptide coupling reactions.[22]

Since Nielsen first introduced PNA (peptide nucleic acid), in which the sugar-phosphate backbone was replaced by a polyamide chain composed of aminoethylglycine covalently linked to DNA bases,[23] several peptide coupling reagents have been employed in the synthesis of PNAs as DNA mimics.[24] As an example, the coupling reaction between $T_{L\text{-Phe}}$ and *L*-Val-OMe using TDBTU, DEPBT, HBTU, or HATU produced the chiral PNA monomer with good enantiomeric purity (DEPBT/DIEA, 95.8% ee; TDBTU/DIEA, 91.8% ee; HBTU/DIEA, 83.6% ee; HATU/DIEA, 77.2% ee) (Scheme 9).[24a]

The structural modification of HBTU provided several new peptide coupling reagents of same types with good activity.[4,25]



Scheme 9.

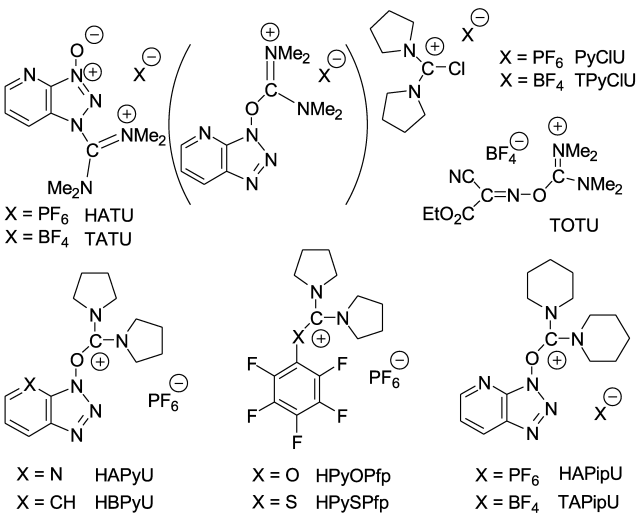
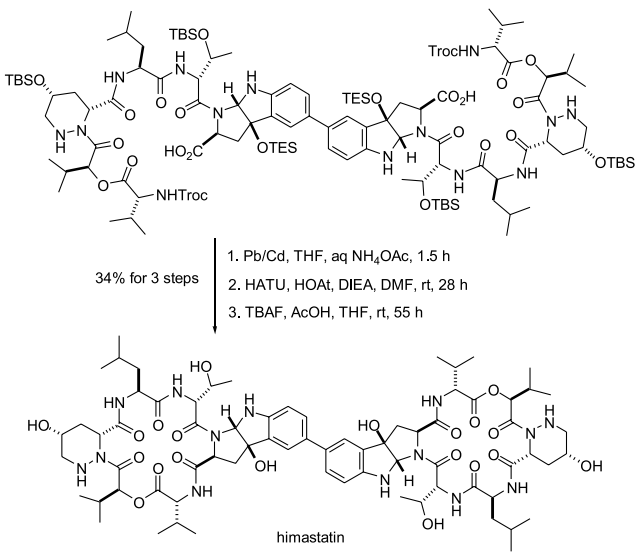


Figure 7.

Firstly, alteration on the HOBt moiety generated HATU, TATU, and TOTU (Fig. 7). Secondly, alteration on the *O*-uronium moiety gave HBPyU. Thirdly, alteration on both HOBt and *O*-uronium moieties resulted in PyClU, TPyClU, HAPyU, HPyOPfp, HPySPfp, HAPipU, and TAPipU.

HATU, the *N*-guanidium salt of HOAt, has been recently utilised in the macrocyclisation of complicated molecules.[26] For example, Danishefsky reported the total synthesis of himastatin, which structurally consisted of the biaryl linkage connecting the two identical subunits (Scheme 10).[27] Bismacrocyclisation on each end of the linear precursor was simultaneously achieved by the use of HATU/HOAt/DIEA.

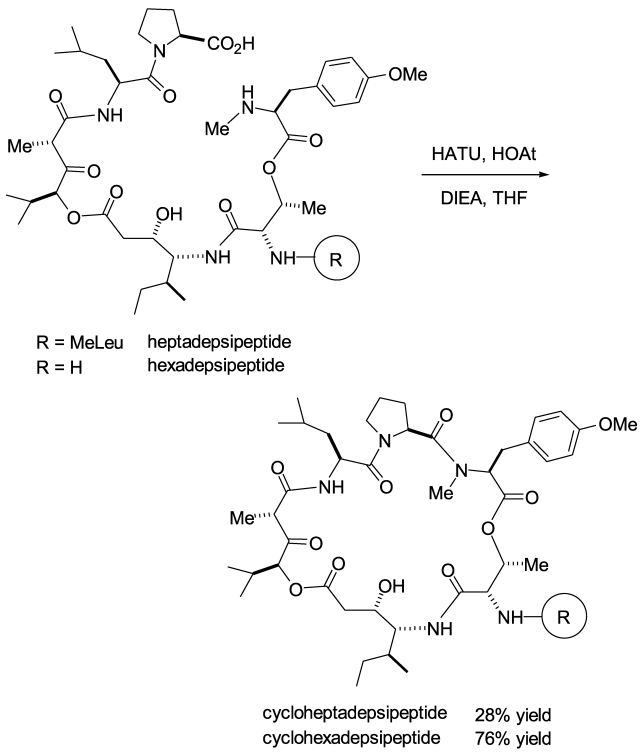
The cyclisation of all-L-tetrapeptides or all-L-pentapeptides was investigated by Ehrlich.[26b] It needed caution during the reaction to avoid side reactions such as cyclodimerisation or epimerisation at the C-terminal residue. HOAt-based reagents such as HATU, HAPyU, and TAPipU were more effective than TBTU or BOP. Notably, α-configuration



Scheme 10.

alternation of the linear precursor ensured the efficient cyclisation. Marchelli reported a successful optimisation of the coupling condition using HATU/collidine in the synthesis of PNA analogues both in solution and in the solid phase.[24b]

Giralt and Lloyd-Williams applied HATU and improved the synthetic procedure of dehydrodidemnin B (Scheme 11), based on an earlier total synthesis of didemnins (Fig. 8).[28]



Scheme 11.

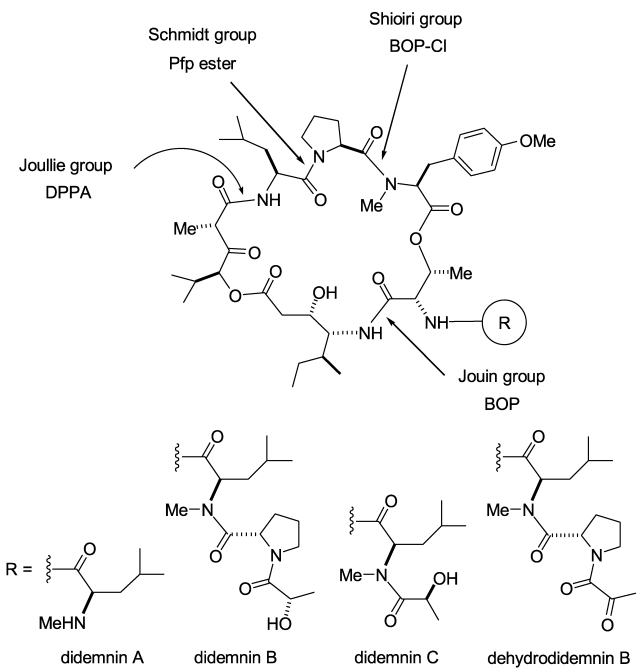
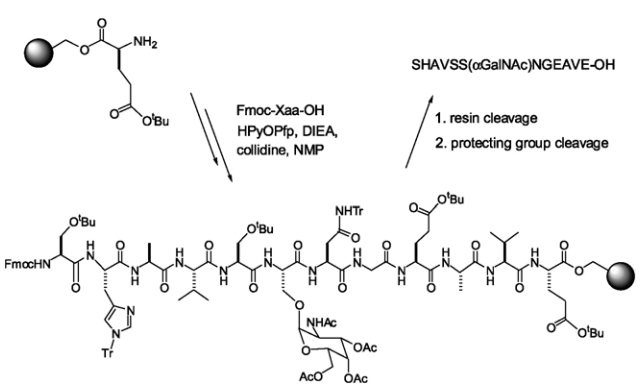


Figure 8.

Two routes were pursued for the synthesis of dehydrodidemnin B.[29] Firstly, the peptide coupling reaction with HATU/HOAt was undertaken between the carboxylic acid moiety of proline and the amine moiety of MeTyr-OMe, at the same cyclisation site with Shioiri's method in Figure 8, with the MeLeu side-chain already attached to the linear precursor to afford the desired macrocycle in 28% yield. The second route involved the synthesis of the macrocycle from the MeLeu side-chain-free linear hexadepsipeptide (HATU/HOAt, 76%; PyAOP/HOAt, 70%; PyBroP/HOAt, 37%). The side-chain was connected to the macrocycle afterwards in latter route.

More recently, Kunz introduced HPyOPfp (PfPyU), which has a pentafluorophenyl (Pfp) residue as the leaving group, in 1998. HPyOPfp was first utilised in the synthesis of a glycopeptide from the homophilic recognition domain of mouse epithelial cadherin 1 in a solid-phase synthesis, and the result was compared with those of TBTU and Pfp-activated ester methods (Scheme 12).[30]



Scheme 12.

Carpino also investigated the ability of HPyOPfp to cyclise the linear Ala-Ala-MeAla-Ala-Ala peptide (0.001 M DMF, DIEA, 60 min). HPyOPfp (10%) and HPySPfp (11%) were less effective in yield compared with other reagents (HAPyU, 55%; HATU, 53%; PyAOP, 54%). However, when HOAt was applied together with HPyOPfp to the cyclisation, the product was obtained in much higher yield (56%) than with HPyOPfp alone. This result suggested that the racemisation suppressant could also take a part in the reaction rate enhancement.[31]

New thiouronium reagents were reported by Nájera (Fig. 9).[32,33] These reagents commonly consisted of 2-mercaptopyridine-1-oxide which was also used as a racemisation suppressant. Structurally, HOTT and TOTT were derived from TMU (1,1,3,3-tetramethylurea), whereas HODT and TODT were derived from DMPU (1,3-dimethylpropyleneurea).

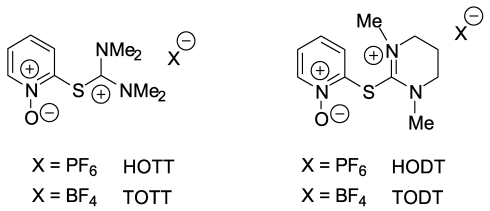
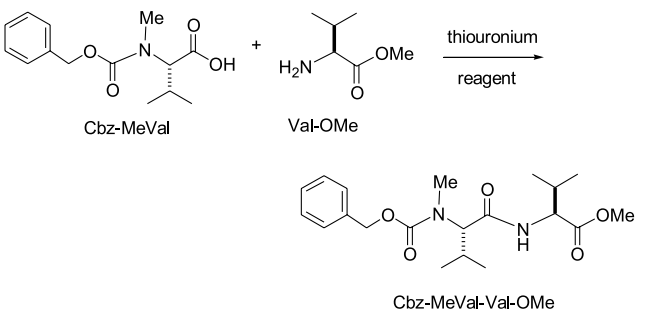


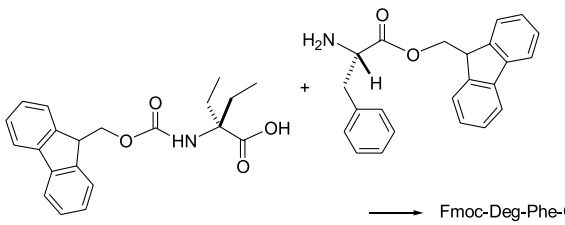
Figure 9.



Scheme 13.

When HOTT, TOTT, HODT, and TODT were applied to the solution synthesis of Cbz-MeVal-Val-OMe, similar yields were obtained (75–82%) (Scheme 13). In contrast, HODT and TODT showed a higher efficiency in both yield and racemisation inhibition in solid-phase synthesis, compared with HOTT and TOTT.

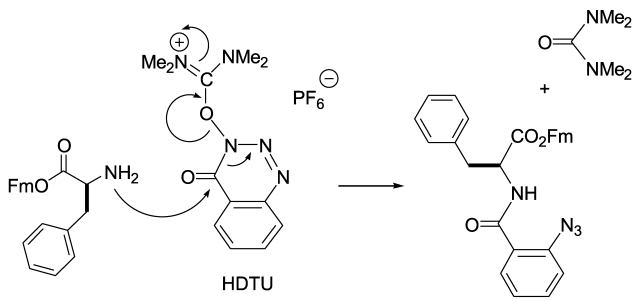
Albericio and Kates investigated the onium salt-based coupling reagents.[4] Uronium reagents were generally more stable than phosphonium reagents, while phosphonium reagents were more stable in the presence of base. It is particularly interesting to note that uronium and phosphonium reagents derived from HOAt were more efficient than the corresponding HOBt-based reagents. The difference in activities of these compounds could be explained by the hydrogen bond from the additional nitrogen atom of HOAt, stabilising the activated ester intermediate via the anchimeric assistance effect.[34] The reactivity pattern of these reagents was confirmed during the synthesis of a dipeptide, Fmoc-Deg-Phe-OFm (Scheme 14).



coupling reagent	HPLC yield (%)	coupling reagent	HPLC yield (%)
HATU	94	PyAOP	96
HBTU	85	PyBOP	89
HAPyU	92	AOP	94
HAMDU	57	BOP	85
HDTU	64		

Scheme 14.

HAMDU and HDTU are considered as inefficient reagents due to their instability by fast decomposition before achieving the activation of the carboxylic acid, as shown in Scheme 15. HAMDU decomposes to guanidine (Scheme 3), while HDTU decomposes to the side-product by the direct attack of the amine moiety of the amino acid on the carbonyl carbon of HDTU (Scheme 15).[18,20]



Scheme 15.

4. Immonium reagents

Xu designed new immonium reagents by modifying known uronium reagents.[35] The structural distinction of immonium reagents is the replacement of the amino group of the central carbon atom in uronium reagents with a hydrogen, an alkyl, or an aryl group. BOMI was shown to be the *N*-guanidine derivative instead of the *O*-uronium compound by an X-ray single crystal analysis. Some representative immonium reagents are shown in Figure 10.

BOMI and BDMP showed a higher reactivity than other immonium reagents such as AOMP, FOMP, DOMP, BPMP, and SOMP for the synthesis of a tripeptide (Scheme 16).[36] Interestingly, immonium reagents gave better results than uronium compounds such as HAPyU and HBPyU, presumably due to the fact that resonance stabilisation of uronium reagents from the amine substituent on the central carbon atom contributed to the retardation of reactivity and

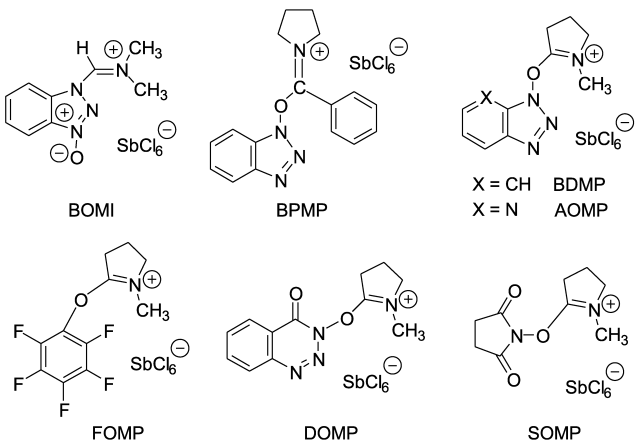
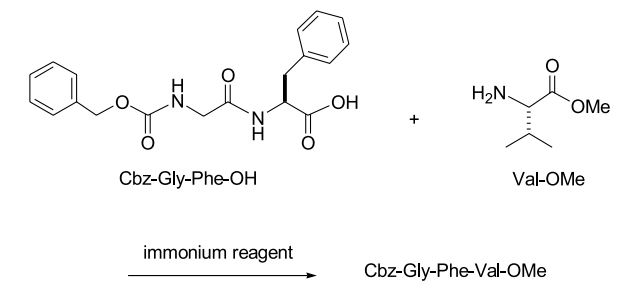


Figure 10.



Scheme 16.

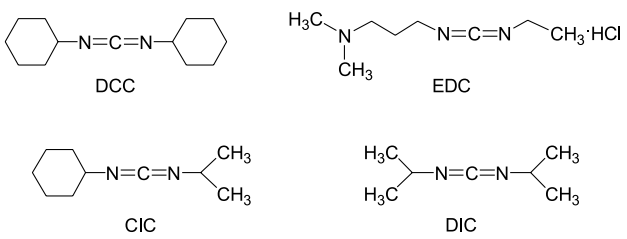


Figure 11.

such a nitrogen atom was not available in the immonium reagents.

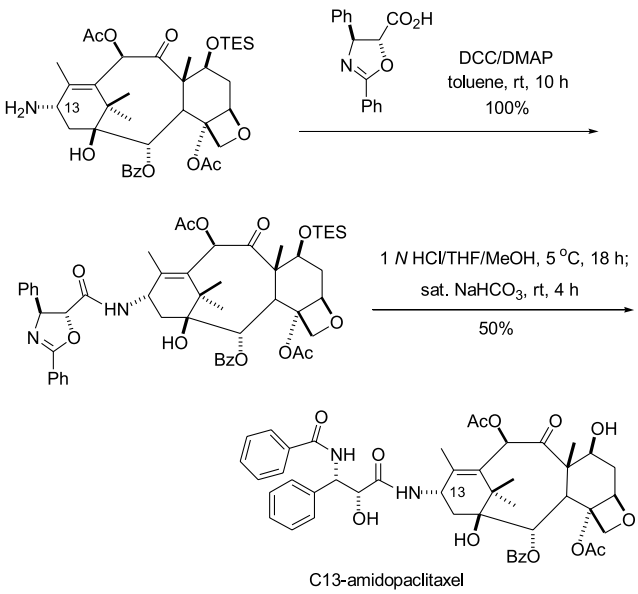
A suitable base for the immonium reagents was found to be 2,6-lutidine in THF or MeCN. BOMI was applied to the synthesis of an oligopeptide, Leu-enkephalin, both in solution and in the solid phase.[36b]

5. Carbodiimide reagents

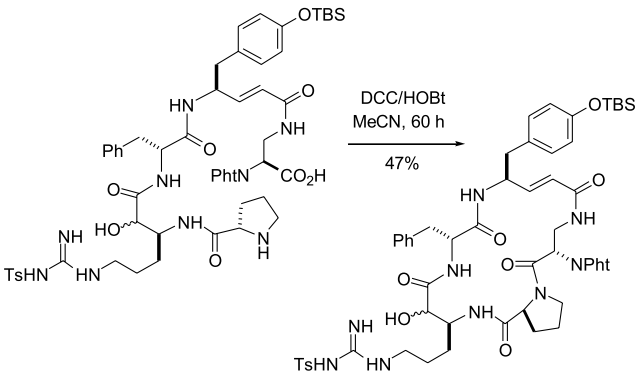
Carbodiimide reagents have been widely used in peptide synthesis because they show a moderate activity and they are reasonably cheap (Fig. 11). DCC was first reported by Sheehan in 1955.[37] The by-product was insoluble in most solvents and hence was easily separable from the product. Since the successful launch of DCC/HOBt in peptide synthesis,[38] carbodiimides have dramatically expanded their scope with the aid of various additives such as HOPO, HOAt, HODhbt and more recently HOCt. These additives have complemented the weakness of coupling reagents by enhancing the reaction rate and reducing the racemisation.

Chen reported the synthesis of C-13 amide-linked paclitaxel analogues (Scheme 17).[39] The coupling reaction between the C13-aminobaccatin and oxazoline was achieved by using DCC/DMAP to provide the desired product in good yield.

Maryanoff successfully constructed the macrocycle in a cyclic pentapeptide, cyclotheonamide A, employing



Scheme 17.

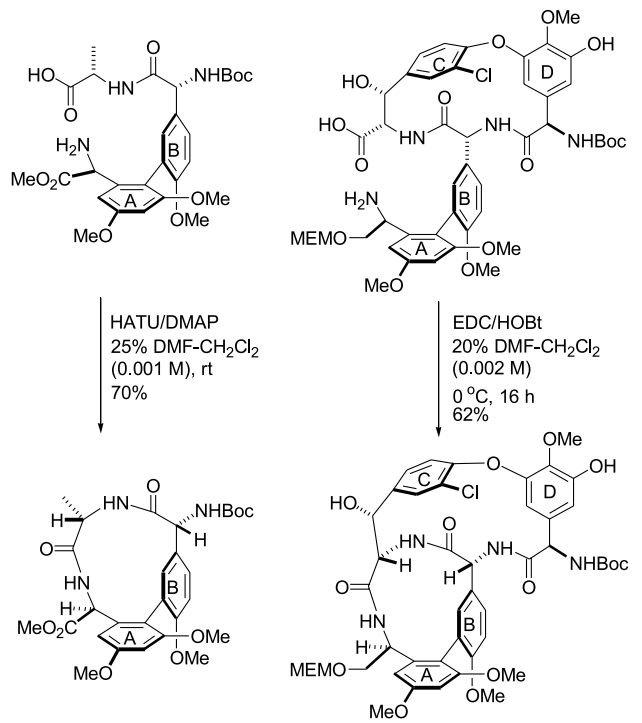


Scheme 18.

DCC/HOBt, in 47% yield (Scheme 18).[40] Cyclisation of the unprotected hydroxyl function produced the undesired 15-membered lactone as the side-product.

Some examples have been reported using EDC/HOBt, as compared to other types of reagents. Boger applied EDC/HOBt to the synthesis of the vancomycin aglycon AB ring system (Scheme 19).[41a] For the formation of the monocycle in a model study, HATU/DMAP gave a better result than PyBOP/DMAP or EDC/HOBt. However, the best condition in the natural bicyclo system of the vancomycin aglycon was EDC/HOBt for 16 h at 0 °C (62% yield). Joullié further adapted the same macrocyclisation condition elegantly for the synthesis of a cyclic depsipeptide containing a chiral tertiary-alkyl-aryl ether, ustiloxin D.[41b]

Carbodiimide reagents were designed to prevent the formation of the undesired *N*-acylurea and to facilitate easy separation from the by-products. The insolubility of the



Scheme 19.

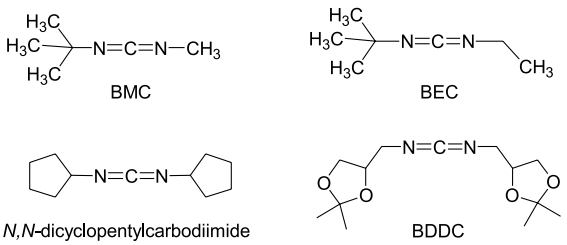


Figure 12.

by-product occasionally caused problems for the synthesis of polypeptides. Since the ureas from DIC and CIC were relatively soluble in CH_2Cl_2, these reagents were more suitable for solid-phase peptide synthesis than DCC. The solubilities of *N*-cyclohexyl-*N*′-isopropylurea, *N*,*N*′-diisopropylurea, and *N*,*N*′-dicyclohexylurea were 30, 5.2 and 1.5 g/L in CH_2Cl_2, respectively.[42] In Fmoc solid-phase peptide synthesis, the DIC/additive method was investigated in various conditions by changing the additive, base, and solvent. Carpino demonstrated that DIC/HOAt was superior to DIC/other additives.[43] Further variations of the carbodiimide such as BMC, BEC, and *N*,*N*′-dicyclopentylcarbodiimide were reported (Fig. 12).[44] Rapoport developed the hydrophilic side-chain-containing carbodiimide, BDDC, in 1994.[45] BDDC in THF, DMF, or toluene gave a reasonable yield for the coupling reaction with a Boc-protected amino acid and the by-product was easily removed by an acid wash.

A combination method using carbodiimides with appropriate activators has been widely applied in peptide coupling reactions since the pioneering work by Bodanszky with *p*-nitrophenol.[46] Active esters can be produced from activators such as *N*-hydroxyphthalimide,[47] and *N*-hydroxysuccinimide[48] (Fig. 13).

As an example, the HOSu/DCC method was used in the synthesis of the peptidyl nucleoside antibiotic, polyoxin J (Scheme 20). The polyoxamic acid derivative was converted to the *N*-hydroxysuccinimide active ester and then coupled with the unprotected thymine, polyoxin C, providing the sugar analogue in 58% yield.[49]

Kovacs and Balasubramanian have explored the electron-withdrawing effect of chlorine atoms in the pentachlorophenyl (Pcp) activated esters.[50] More recently, it was found that the Pfp activated ester was more reactive than the Pcp ester due to the steric hindrance of chlorine atoms. Although the Pfp ester should be isolated and purified prior to

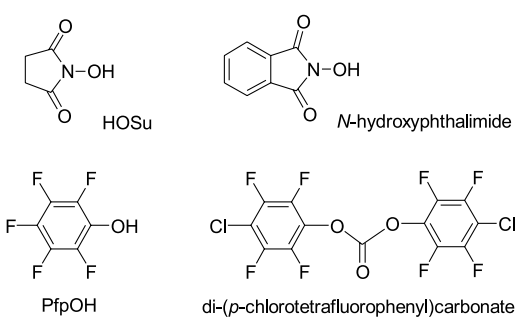
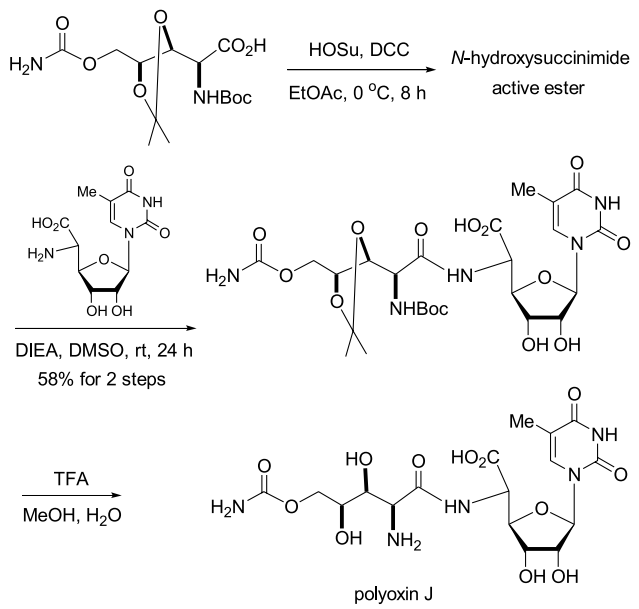


Figure 13.

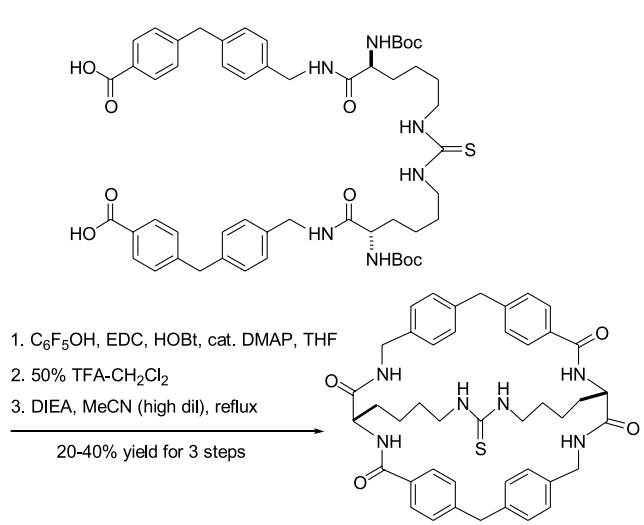


Scheme 20.

coupling with amines, the efficiency of the Pfp ester method in peptide coupling reaction has popularised its use in macrolactamisations. For example, the total synthesis of cyclopeptide alkaloids such as frangulanine and nummularine F was successfully achieved via the corresponding Pfp ester intermediates.[51] The Pfp active ester method was also applied to the synthesis of cyclopeptolides containing the tripeptolide, H-Leu-HOMeVal-(*R*)-HMP-OH, as a building block. Interestingly, aureobasidin A was only formed with PyBroP, whereas the Pfp ester afforded the epimeric [(*R*)-Pro9]-aureobasidin.[52]

Kilburn and Mortishire-Smith elegantly synthesised a macrobicycle via the Pfp active ester, as shown in Scheme 21. Intramolecular cyclisation between the *bis*-carboxylic acid and the *bis*-amine via the *bis*-Pfp active ester smoothly afforded the desired macrobicycle.[53]

Kretsinger suggested that the *p*-chlorotetrafluorophenyl (Tfc) esters obtained from protected amino acids with di-



Scheme 21.

(*p*-chlorotetrafluorophenyl)carbonate (Fig. 13) or *p*-chlorotetrafluorophenyl trifluoroacetate showed a similar or better reactivity than the Pfp esters in peptide coupling reactions.[54] For example, the hexadecameric tandem repeat H-(AlaAlaLysPro)$_4$-OH was synthesised in good yield from the corresponding Tfc esters using di-Tfc-carbonate, thus obviating the need to use DCC.

6. Imidazolium reagents

Some representative imidazolium reagents used in peptide coupling reactions are shown in Figure 14. The search for better coupling reagents based on DCC led to the development of CDI.[55] The mechanism may involve nucleophilic attack of the carboxylate at the carbonyl carbon of CDI, followed by either intramolecular rearrangement of the anhydride-type intermediate or nucleophilic attack of the counteranion of imidazole on the carbonyl carbon to form the active imidazolide.

Recently, Kato has reported the synthesis of analogues of a gastroprokinetic agent, mosapride, using CDI (Scheme 22). When EDC was used in place of CDI, a lower reactivity was observed.[56]

Rapoport introduced a new imidazolium reagent, CBMIT, by bismethylating CDI with methyl triflate.[57] CBMIT is particularly useful in peptide coupling reactions with sterically hindered amino acids such as Val or Aib, and showed no sign of racemisation in the presence of $CuCl_2$ or $Cu(OTf)_2$. CBMIT is moisture sensitive and should be handled in the air for a very short period of time. Due to the polarity of CBMIT, the choice of solvent is restricted to polar solvents such as nitromethane.[58]

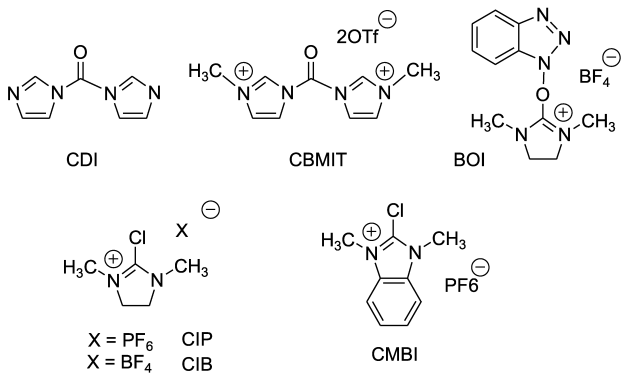
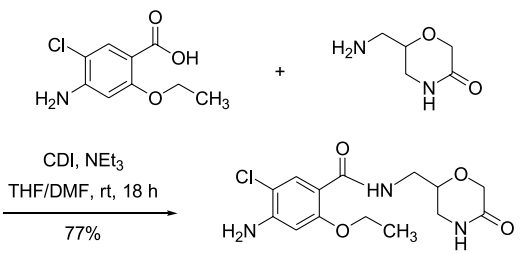
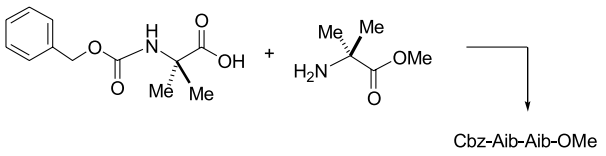


Figure 14.



Scheme 22.

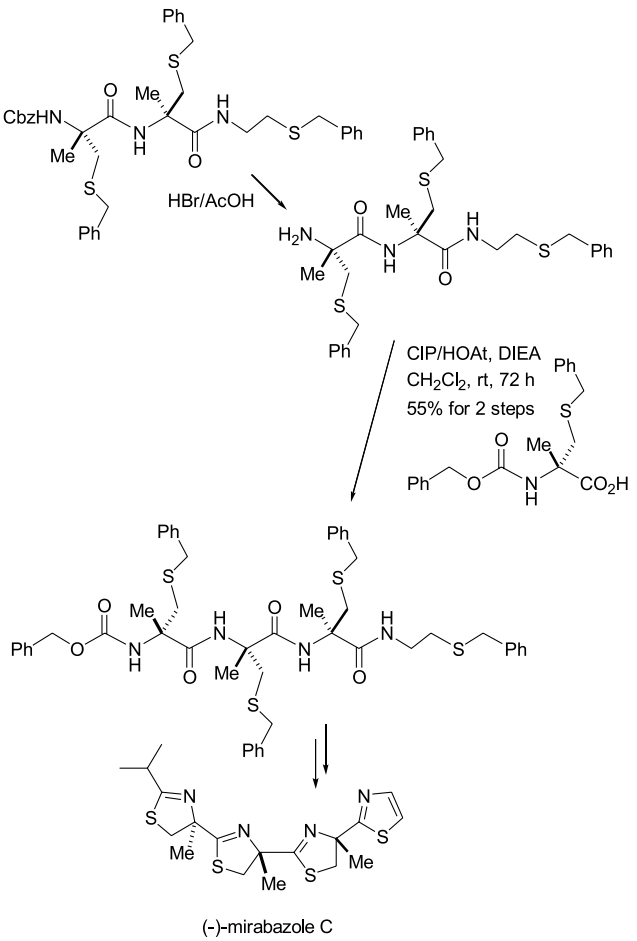


coupling reagent	CIP	CIP/HOAt	PyBroP	TOTT	TODT
yield (%)	11	82	17	68	74

Scheme 23.

Kiso developed modified imidazolium reagents, BOI, and its precursor, CIP, as new peptide coupling reagents and, later, as new esterification reagents to avoid the toxic HMPA by-product of the BOP reagent.[59] The efficiency of CIP was also evaluated in peptide coupling reactions between sterically hindered α,α-dialkylated amino acids (Scheme 23). The CIP/HOAt combined coupling reagents showed the best result in the formation of a dipeptide, Cbz-Aib-Aib-OMe, compared with PyBroP, TODT, TOTT, and CIP alone.[33] HOAt as the additive to CIP gave the highest catalytic enhancement with the trend of activity in the order: HOAt>HODhbt>DMAP>HOBt.

In addition, Kiso successfully applied the CIP/HOAt combination to the synthesis of (−)-mirabazole C (Scheme 24).[60] After removal of the Cbz protecting group with HBr/AcOH, the resulting amine was coupled with *N*-Cbz-*S*-benzyl-(*R*)-2-methylcysteine using CIP/HOAt in 55% yield for 2 steps. The demasked tetrathiol unit of (*R*)-2-methylcysteine underwent $TiCl_4$-mediated cyclo-dehydration to establish the thiazole ring moiety in (−)-mirabazole C.



Scheme 24.

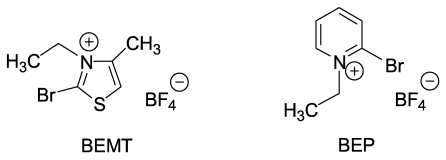


Figure 15.

Recently, Xu developed CMBI (Fig. 14) a benzene ring-fused derivative of CIP, as a new peptide coupling reagent during the synthesis of a pentadepsipeptide intermediate of an anticancer drug, actinomycin D.[61]

Xu also introduced a thiazolium-type reagent, BEMT, as shown in Figure 15[62] The mechanism of BEMT may involve the sequential conversion of a carboxylic acid of an amino acid into the corresponding acyloxythiazolium salt and then to the acid bromide, leaving *N*-ethyl-4-methylthiazolidone as the by-product. For the synthesis of the tripeptide, Z-Gly-Phe-Val-OMe, BEMT gave 46% yield and 2.7% racemisation, while a halogenouronium reagent, PyClU, gave 12% yield and 25% racemisation after 2 min.

The efficacy of BEMT and BEP was elegantly demonstrated in fragment coupling reactions containing *N*-alkylated amino acids during the synthesis of the immunosuppressive cyclosporin O (Fig. 16).[63]

More recently, Wischnat has introduced the crystalline and non-hygroscopic BMTB as a new peptide coupling reagent (Scheme 25). BMTB was produced by alkylation of its

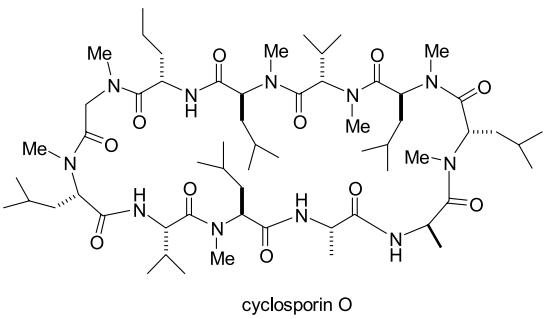
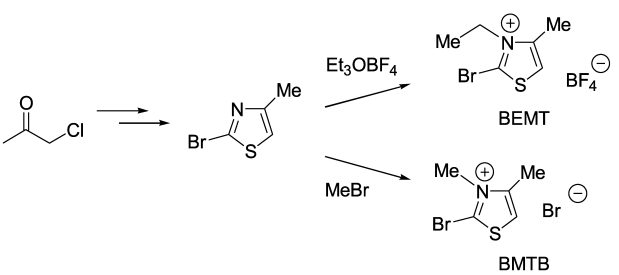


Figure 16.



Scheme 25.

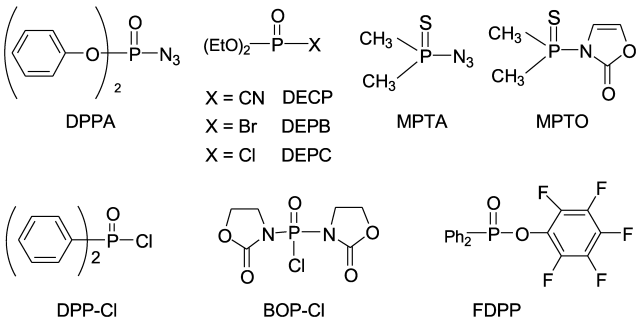


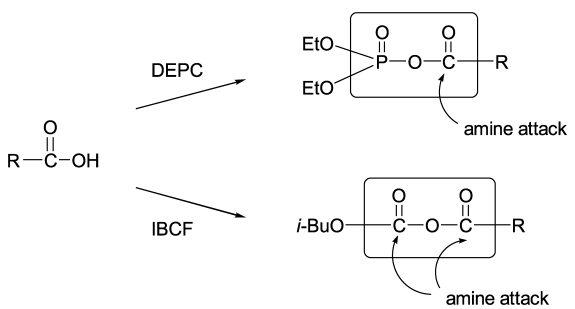
Figure 17.

precursor with methyl bromide (MeBr), while BEMT was prepared with triethyloxonium tetrafluoroborate (Et_3OBF_4) from the common intermediate.[64]

7. Organophosphorous reagents

Since the mixed carboxylic-phosphoric anhydride method was first proposed in peptide chemistry by Yamada in 1972 using DPPA from diphenylphosphorochloridate and sodium azide,[65] various organophosphorous compounds have been developed as new peptide coupling reagents (Fig. 17).

This method usually gave a higher regioselectivity towards nucleophilic attack by the amine component than a mixed carbonic anhydride method (Scheme 26).[66]

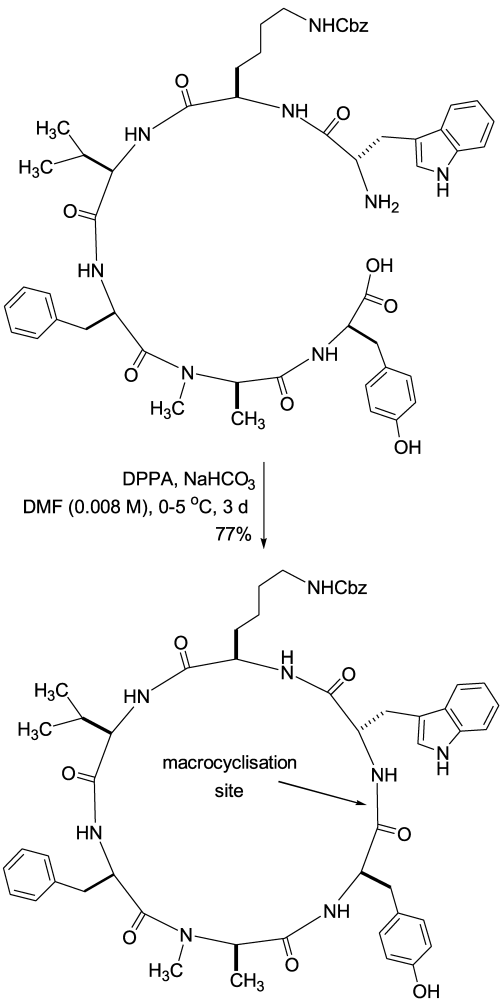


Scheme 26.

Brady applied an improved DPPA technique, in which the triethylamine base was replaced by sodium bicarbonate, in the macrocyclisation step during the synthesis of a cyclic hexapeptide analogue of somatostatin (DPPA/$NaHCO_3$, 90% monomer; DPPA/Et_3N, 75% monomer, as determined by analytical gel filtration) (Scheme 27).[67]

The DPPA/$NaHCO_3$ method was also employed for the 32-membered macrocyclisation of (−)-sandramycin.[68] The key advantage of the use of this method relied on the insolubility of $NaHCO_3$ in the reaction medium, where a mild reaction condition was required.

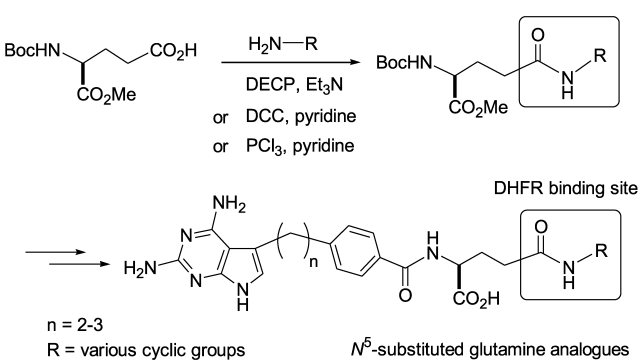
DECP (Fig. 17) was easily prepared by the reaction of triethyl phosphite with cyanogen bromide.[69] Itoh reported the synthesis of N^5-substituted glutamine analogues, which displayed potent antitumour activities against MTX-resistant tumours by inhibition of dihydrofolate reductase, using several coupling reagents including DECP and compared



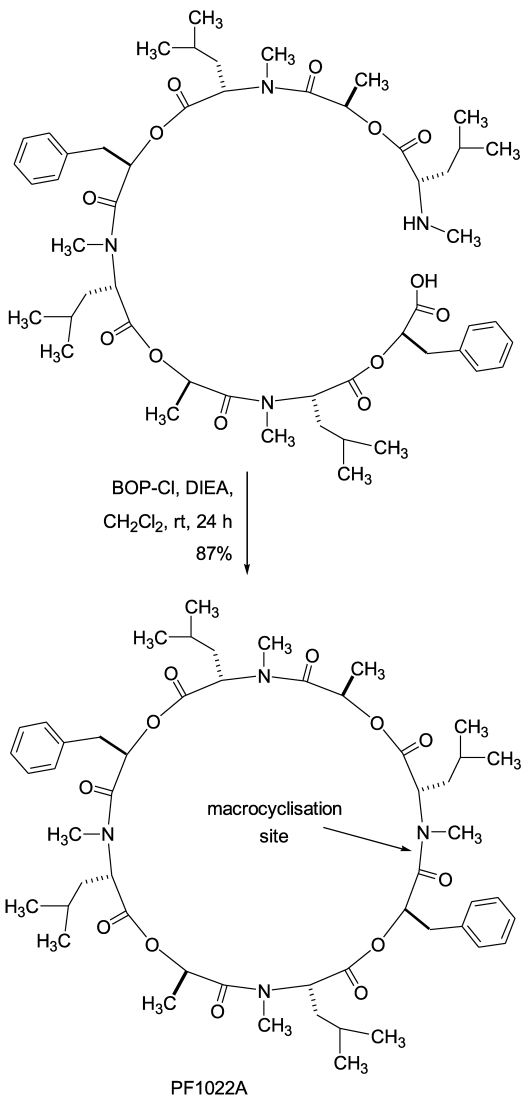
Scheme 27.

their results (Scheme 28).[70] The use of traditional carbodiimide reagents such as DCC was effective for coupling reactions between Boc-Glu-OMe and regular amines. On the other hand, DECP was useful for more nucleophilic amines containing electron-donating substituents in an aromatic ring, whereas phosphorus trichloride was effective for less nucleophilic amines.

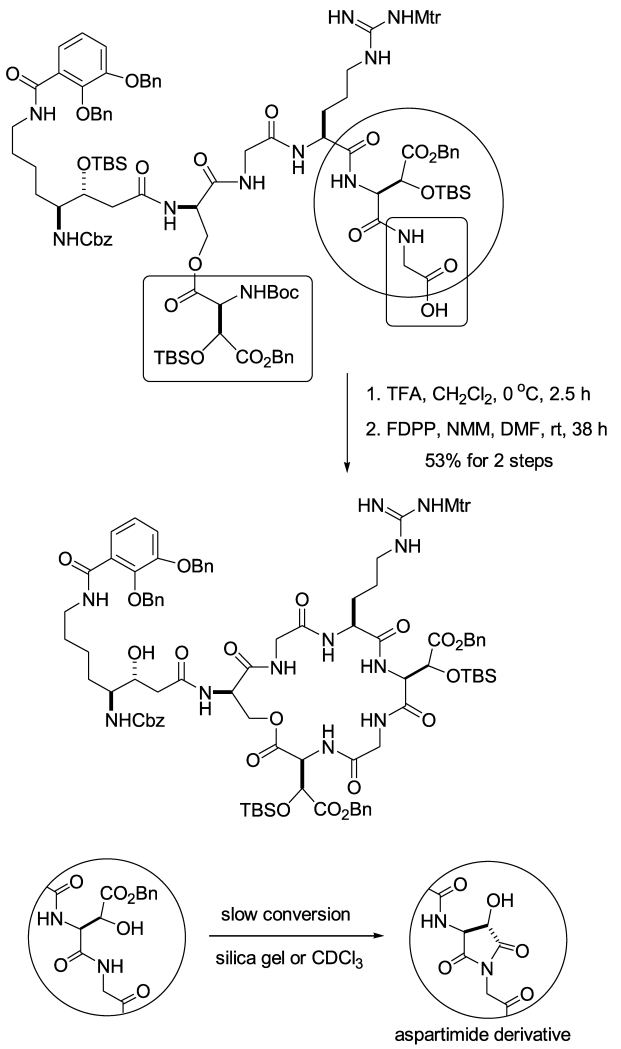
One of the notable variations in organophosphorous reagents was the development of the phosphinic acid derivatives. DPP-Cl was first introduced in 1976.[65b,71]



Scheme 28.



Scheme 29.



Scheme 30.

Shortly after, Palomo-Coll developed BOP-Cl (Fig. 17) in 1980[72] and it quickly became popular in practical applications. BOP-Cl was well known as a powerful reagent for peptide coupling reactions involving *N*-alkylamino acids. In the macrocyclisation step during the synthesis of the cyclooctadepsipeptide, PF1022A (Scheme 29), BOP-Cl gave a high yield (87%) with negligible racemisation, whereas the Pfp active ester or EDC/HOBt method gave only moderate yields (28 and 59%, respectively).[73]

FDPP has been widely used as a new coupling reagent in macrocyclisation since its development in 1991 (Fig. 17).[74] Shioiri employed FDPP for the synthesis of a cyclic depsipeptide, alterobactin A, containing two types of non-coded amino acids such as L-*threo*-β-hydroxyaspartic acid and (3*R*,4*S*)-4,8-diamino-3-hydroxyoctanoic acid (Scheme 30). Cyclisation between Gly and β-OH-Asp was accomplished with FDPP in 53% yield for 2 steps. The choice of glycine as the C-terminal residue in the macrocyclisation gave the synthetic advantages of non-epimerisation and non-steric hindrance.[75] When the hydroxyl group of the eastern hemisphere was not protected prior to the macrocyclisation, an aspartimide derivative was formed as the by-product.

Modification of DPPA led to the development of thiophosphinic-type coupling reagents such as MPTA and MPTO (Fig. 17).[76] As DPPA is an oil, these reagents are crystalline and stable for long-term storage. Since MPTA generated a carbamoyl azide or urea derivative as the by-product, Ueki introduced MPTO, in which the azide group of MTPA was replaced by a 2-oxazolone group. When the coupling conditions were compared for the cyclisation of H-D-Trp-D-Glu(OBn)-Ala-D-Val-Leu-OH, MPTA/HOBt/ DIEA gave 84% yield (<0.1% of epimer) in 8 h and MPTO/HOBt/ DIEA gave 78% yield (<0.1% of epimer) in 3 h, whereas DPPA/HOBt/DIEA gave only 66% yield in 3 days (6.0% of epimer).

In addition to the earlier development of organophosphorous reagents, a great deal of effort has been focused on creating various coupling reagents of a similar kind. For example, NDPP,[77] Cpt-Cl,[78] BMP-Cl,[79] DEBP,[80] BDP,[81] bis(*o*-nitrophenyl)phenyl phosphonate,[82] (5-nitro-pyridyl)-diphenyl phosphinate,[83] diphenyl 2-oxo-3-oxazolinyl phosphonate,[84] and 1,2-benzisoxazol-3-yl diphenyl phosphate[85] were prepared by various research groups (Fig. 18).

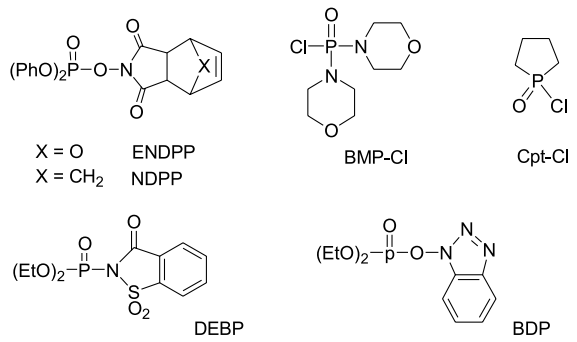


Figure 18.

More recently, Ye developed DEPBO, DOPBO, DOPBT, and DEPBT (Fig. 19).[86] DEPBT derived from DEPC and HODhbt was evaluated against other peptide coupling reagents and gave good results in segment coupling reactions.[87] Even though HODhbt was superior to HOBt for racemisation-suppressing ability, its utility was limited due to the side reactions. Thus, the reaction conditions were optimised to use 2 equivalents of DEPBT and DIEA in THF.

DEPBT was efficient for the synthesis of *N*-protected peptide alcohols and *N*-glycopeptides (Scheme 31).[88] When DEPBT was used as the coupling reagent, the carboxylic group selectively reacted with the amino group in the presence of unprotected hydroxyl functional groups.

8. Acid halogenating reagents

The acid halide technique is frequently recommended in

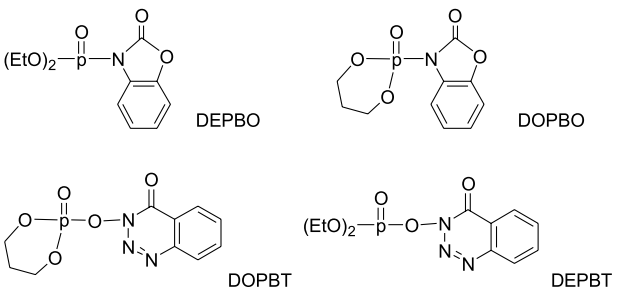
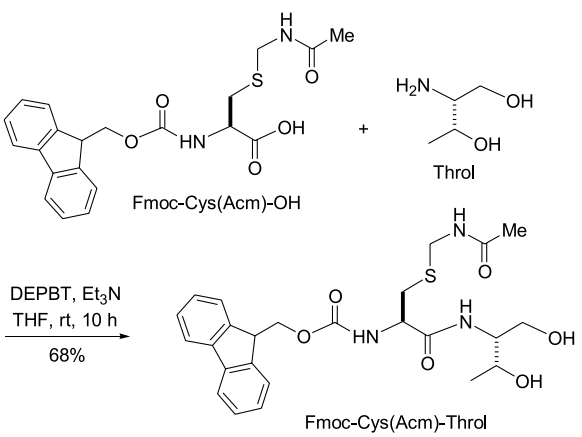


Figure 19.

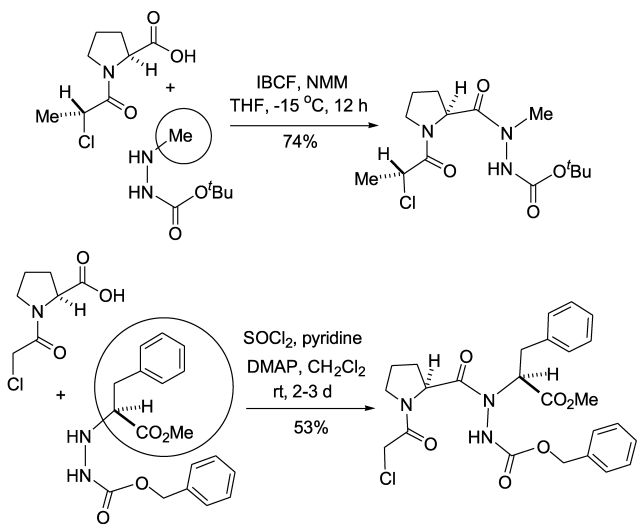


Scheme 31.

peptide coupling reactions of extremely hindered amino acids. Nonetheless, an amino acid chloride-bearing acid-labile protecting group can be easily racemised to the oxazolone so that the practical application of the acid chloride is restricted, despite its high reactivity and low cost.

The acid chloride method was first introduced to peptide chemistry by Fisher in 1903.[89] Since then, chlorination of amino acids was carried out with various chlorinating reagents such as pivaloyl chloride,[90] phthaloyl dichloride,[91] thionyl chloride,[92] oxalic chloride,[93] etc.

Gani reported the synthesis of *cis*-peptidyl prolyl peptide mimetics (Scheme 32). The coupling reaction between proline and methyl hydrazide was achieved with IBCF in 74% yield. However, when the steric bulkiness of the *N*-substituent in the hydrazide was increased, a more powerful activation of the carboxylic acid was required. Thionyl chloride in pyridine was applied to the coupling reactions for this purpose.[92c]



Scheme 32.

Other useful acid halogenating reagents are cyanuric chloride[94] and CDMT[95] (Fig. 20). Due to the weak basicity of the triazine moiety, the by-product and excess coupling reagent were easily removed by washing with dilute acid.

Gilon has recently reported the use of BTC (Fig. 20) as a chlorinating reagent in solid-phase peptide synthesis.[96] Coupling reactions mediated by BTC gave good results for Fmoc-amino acids containing acid-labile side-chains. Since NMP reacted with BTC to form the chloroiminium ion and led to racemisation, inert solvents such as THF or dioxane were required.

Since amino acid fluorides showed a better stability towards

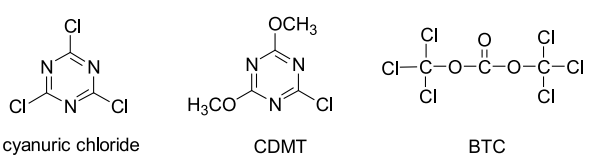


Figure 20.

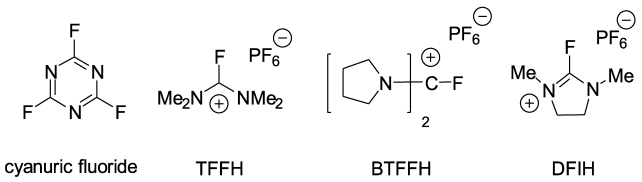
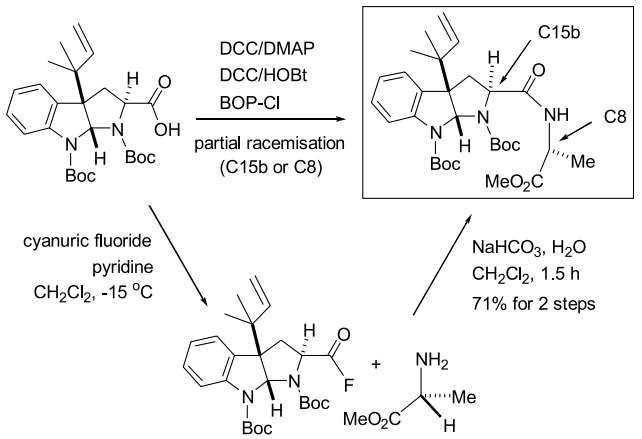


Figure 21.

moisture and acid-labile functional groups than amino acid chlorides, several acid fluorinating reagents were developed, as shown in Figure 21[97] Cyanuric fluoride easily converted amino acids into the corresponding acid fluorides.[98] For sterically hindered amino acids, such as Deg, MeAib and Iva, the acid fluoride method gave excellent yields in peptide coupling reactions.[99]

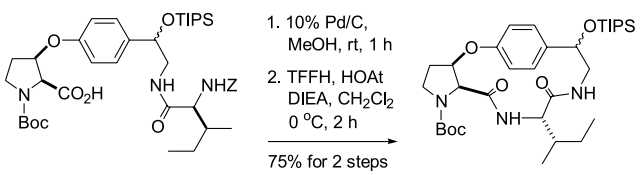
Danishefsky elegantly applied the acid fluoride method to the peptide coupling reaction in the crucial chain-elongation step during the synthesis of a potential MDR reversal agent, 5-*N*-acetylardeemin. Other attempts with BOP-Cl, DCC/HOBt and DCC/DMAP were inefficient, due to partial racemisation (Scheme 33).[100]



Scheme 33.

The most notable advance in acid halogenations has been the development of fluoroformamidinium salts. Carpino reported TFFH, BTFFH, and DFIH as new acid fluorinating reagents which act by in situ generating amino acid fluorides in peptide coupling reactions (Fig. 21).[101] These fluorinating reagents are especially useful for His and Arg because the corresponding amino acid fluoride intermediates are not stable on shelf storage. BTFFH may be more useful than TFFH due to its lack of toxic by-product forming ability.[102]

Han applied the acid fluoride method to the synthesis of a 14-membered cyclic enamide, the key intermediate of C3-epimauritine D (Scheme 34).[103] The in situ-generated acid



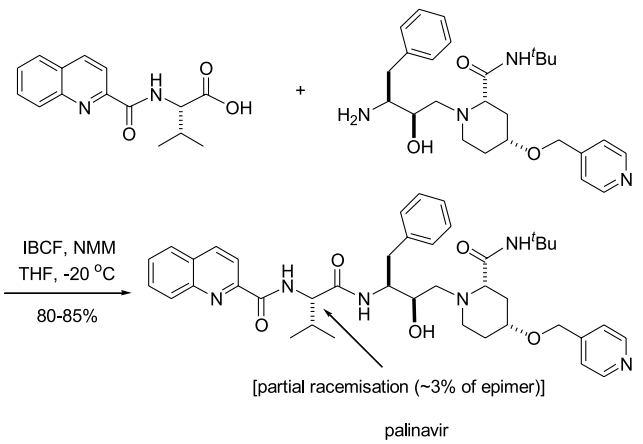
Scheme 34.

fluoride with TFFH in the presence of HOAt successfully afforded the desired macrolactam in 75% yield for 2 steps, while the corresponding Pfp activated ester gave none of the product.

9. Chloroformate, pyridinium and other coupling reagents

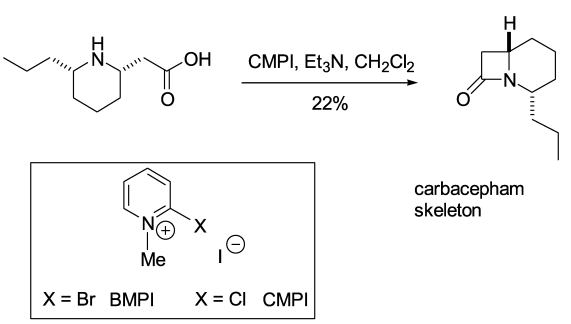
Chloroformates have been used in peptide coupling reactions via mixed carbonic anhydride intermediates. A well-known side reaction with chloroformate is the second acylation of the amine at the carbonate carbonyl carbon (Scheme 26). IBCF was mainly used in peptide synthesis among chloroformate reagents such as IPCF, $^{i}PrO_2CCl$, EtO_2CCl, and PhO_2CCl because the bulky *tert*-butyl group decreased the side reaction.[104]

Beaulieu applied IBCF to the synthesis of a peptidomimetic HIV protease inhibitor, palinavir (Scheme 35).[104b] The coupling reaction was successful by the use of IBCF/NMM with little racemisation. Lower temperatures (−20 °C) minimised the epimerisation compared with room temperature. Attempts to form palinavir using other coupling reagents such as BOP, TBTU, DCC/HOBt, or pivaloyl chloride gave poorer results.

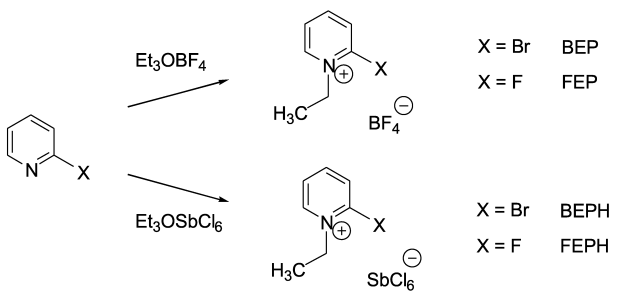


Scheme 35.

Mukaiyama introduced pyridinium reagents such as BMPI and CMPI to peptide chemistry in 1979.[105] CMPI was applied to the synthesis of a β-lactam carbacepham skeleton (Scheme 36).



Scheme 36.

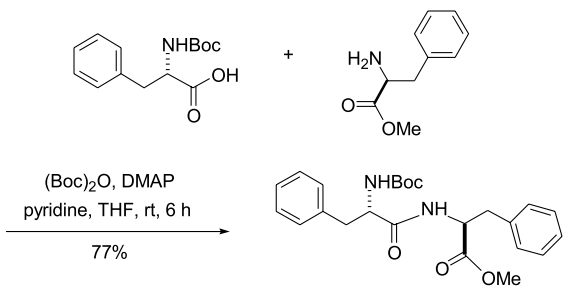


Scheme 37.

Recently, Xu reported novel pyridinium reagents such as BEP, FEP, BEPH, and FEPH (Scheme 37).[106] Tetrafluoroborate or hexachloroantimonate was chosen as the non-nucleophilic counterion to improve the solubility of the pyridinium reagents, compared to Mukaiyama's reagents.[105] BEP was applied in the synthesis of a tetrapeptide fragment of cyclosporin A and a pentapeptide moiety of dolastatin 15.

Datta applied $(Boc)_2O$/DMAP to peptide coupling reactions in the presence of pyridine.[107] For the proposed mechanism, 1-*tert*-butoxycarbonyl-4-dimethylaminopyridinium *tert*-butyl carbonate (Fig. 22) was first induced by condensation between $(Boc)_2O$ and DMAP, and then attacked by an oxygen nucleophile of a carboxylic acid to form an activated ester species.

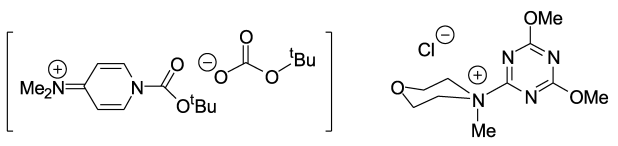
The $(Boc)_2O$-mediated coupling reaction gave the dipeptide in good yield with very little racemisation comparable to DCC/HOBt method (Scheme 38). This method was efficient in terms of its low cost, non-toxicity, and stability on storage compared with other coupling reagents.



Scheme 38.

Taddei reported DMTMM (Fig. 22), which was derived from CDMT and NMM, as a new coupling reagent, and has applied it to solid-phase synthesis.[108]

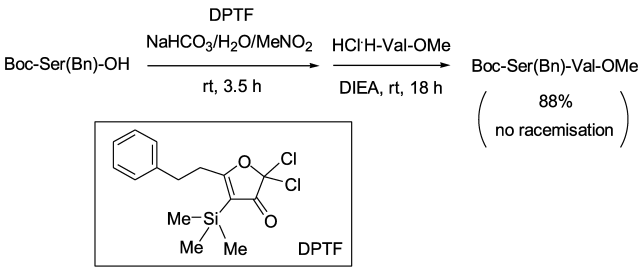
Murakami and Ito reported a water-compatible reagent, DPTF. The coupling reaction was processed via step-wise



1-*tert*-butoxycarbonyl-4-dimethylaminopyridinium *tert*-butyl carbonate

DMTMM

Figure 22.



Scheme 39.

dehydration in a multisolvent system composed of water and organic solvent (Scheme 39).[109]

10. Racemisation suppressants

In 1970, König and Geiger first reported the use of HOBt as a racemisation suppressant in peptide coupling reactions with carbodiimide coupling reagents (Fig. 23).[38] With this technique, additives such as HOBt, HOAt, HODhbt, *N*-hydroxytetrazole, HOCt, and PTF have roles in not only suppressing racemisation, but also enhancing the reactivity.

HODhbt has been limited in its widespread adoption due to the side reaction of ring opening. HOAt has been reported to be more efficient than HOBt because of an anchimeric assistance effect caused by the pyridine ring.[34] Later, *N*-hydroxytriazoles and *N*-hydroxytetrazoles were examined for their coupling efficiency.[110a] Ramage reported the coupling reaction of dipeptides with DIC and the newly designed HOCt for a racemisation study. Racemisation with DIC/HOCt activation was negligible for all amino acids except histidine.[110b,c] More recently, Carpino and Henklein reported polyhydrogen fluoride additives, $Py(HF)_n$.[111] For example, the efficiency of the coupling reaction for HBTU combinated with PTF (Fig. 23) was as good as HATU. Unfortunately, PTF was unsuitable for phosphonium or organophosphorous reagents due to the high strength of the P–F linkage.

For inorganic additives, the lowest level of racemisation was occasionally found in the presence of $CuCl_2$ combined with various coupling reagents.[58,112] However, the improvement in yield was not sufficient by addition of $CuCl_2$. In addition, the Cu(II)-based complexes, $Cu(OBt)_2$ and $Cu(OAt)_2$ also showed the ability to function as racemisation suppressants.[113]

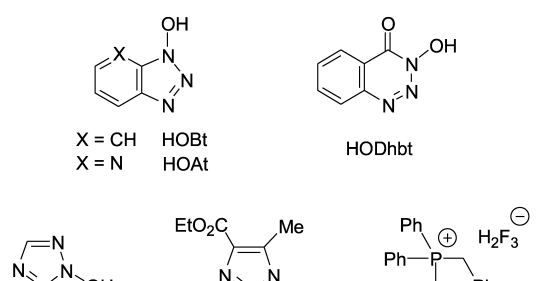


Figure 23.

11. Conclusions

This review has presented an overview of the recent development of peptide coupling reagents including racemisation suppressants. For coded amino acids, the standard coupling method using a carbodiimide/additive method produces peptides in good yield. However, a number of organic and natural products with interesting biological activities have been discovered and they usually contain highly functionalised or non-coded amino acids as building blocks, which may not be easily constructed by the traditional peptide coupling reagents. For this reason, the development of new peptide coupling reagents and reactions has become a most fascinating field of research for many organic chemists with various backgrounds.

Since Fischer introduced the acid chloride method into peptide coupling reactions in 1903, the development of diverse peptide coupling reagents has made many difficult peptide coupling reactions possible. Perhaps one of the most significant advances in peptide coupling reagents was the emergence of the onium or fluoroformamidinium salts. Moreover, the discovery of racemisation suppressants has reinforced the coupling reagents by enhancing the reactivity as well as reducing racemisation and side reactions. In addition, both difficult fragment coupling reactions and macrocyclisation are often influenced by other reaction parameters such as solvent systems, temperature, disconnection sites, etc. It is believed that this review presents a systematic overview of recent advances in peptide coupling reagents and serves as an excellent guideline for the organic synthesis of bioactive molecules bearing peptide linkages.

Abbreviations

Aib	α-aminoisobutyric acid
AOMP	5-(7-azabenzotriazol-1-yloxy)-3,4-dihydro-1-methyl 2*H*-pyrrolium hexachloroantimonate
AOP	(7-azabenzotriazol-1-yl)oxytris-(dimethylamino)phosphonium hexafluorophosphate
BDDC	bis[[4-(2,2-dimethyl-1,3-dioxolyl)]-methyl]carbodiimide
BDMP	5-(1*H*-benzotriazol-1-yloxy)-3,4-dihydro-1-methyl 2*H*-pyrrolium hexachloroantimonate
BDP	benzotriazol-1-yl diethylphosphate
BEC	*N*-*tert*-butyl-*N*′-ethylcarbodiimide
BEMT	2-bromo-3-ethyl-4-methyl thiazolium tetrafluoroborate
BEP	2-bromo-1-ethyl pyridinium tetrafluoroborate
BEPH	2-bromo-1-ethyl pyridinium hexachloroantimonate
BMC	*N*-*tert*-butyl-*N*′-methylcarbodiimide
BMP-Cl	*N*,*N*′-bismorpholinophosphinic chloride
BMPI	2-bromo-1-methylpyridinium iodide
BMTB	2-bromo-3-methyl-4-methyl thiazolium bromide
BOI	2-(benzotriazol-1-yl)oxy-1,3-dimethyl-imidazolidinium hexafluorophosphate
BOMI	benzotriazol-1-yloxy-*N*,*N*-dimethyl-methaniminium hexachloroantimonate
BOP	benzotriazol-1-yloxytris(dimethyl-amino)-phosphonium hexafluorophosphate
BOP-Cl	*N*,*N*′-bis(2-oxo-3-oxazolidinyl)-phosphinic chloride
BPMP	1-(1*H*-benzotriazol-1-yloxy)phenyl-methylene pyrrolidinium hexachloroantimonate
BroP	bromotris(dimethylamino)phosphonium hexafluorophosphate
BTC	bis(trichloromethyl)carbonate
BTFFH	bis(tetramethylene)fluoroformamidinium hexafluorophosphate
Bts-Cl	benzothiazol-2-sulfonyl chloride
CBMIT	1,1′-carbonylbis(3-methyl-imidazolium)-triflate
CDI	1,1′-carbonyldiimidazole
CDMT	2-chloro-4,6-dimethoxy-1,3,5-triazine
CIC	*N*-cyclohexyl-*N*′-isopropylcarbodiimide
CIP	2-chloro-1,3-dimethylimidazolidinium hexafluorophosphate
CMBI	2-chloro-1,3-dimethyl 1*H*-benzimidazolium hexafluorophosphate
CMPI	2-chloro-1-methylpyridinium iodide
Cpt-Cl	1-oxo-chlorophospholane
DBDMAP	2,6-di-*tert*-butyl-4-(dimethylamino)pyridine
DCC	*N*,*N*′-dicyclohexylcarbodiimide
DEBP	diethyl 2-(3-oxo-2,3-dihydro-1,2-benzisosulfonazolyl)phosphonate
DECP	diethylcyanophosphonate
Deg	α,α-diethylglycine
DEPB	diethyl phosphorobromidate
DEPBO	*N*-diethoxyphosphoryl benzoxazolone
DEPBT	3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one
DEPC	diphenyl phosphorochloridate
DFIH	1,3-dimethyl-2-fluoro-4,5-dihydro-1*H*-imidazolium hexafluorophosphate
DIC	*N*,*N*′-diisopropylcarbodiimide
DIEA(DIPEA)	diisopropylethylamine
DMTMM	4-(4,6-dimethoxy[1,3,5]triazin-2-yl)-4-methylmorpholinium chloride
DOMP	5-(3′,4′-dihydro-4′-oxo-1′,2′,3′-benzotriazin-3′-yloxy)-3,4-dihydro-1-methyl 2*H*-pyrrolium hexachloroantimonate
DOPBO	*N*-(2-oxo-1,3,2-dioxaphosphorinanyl)-benzoxazolone
DOPBT	3-[*O*-(2-oxo-1,3,2-dioxaphosphorinanyl)-oxy]-1,2,3-benzotriazin-4(3*H*)-one
DPP-Cl	diphenylphosphinic chloride
DPPA	diphenylphosphoryl azide
DPTF	2,2-dichloro-5-(2-phenylethyl)-4-(trimethylsilyl)-3-furanone
EDC	1-[3-(dimethylamino)propyl]-3-ethyl-carbodiimide hydrochloride
FDPP	pentafluorophenyl diphenyl phosphinate
FEP	2-fluoro-1-ethyl pyridinium tetrafluoroborate
FEPH	2-fluoro-1-ethyl pyridinium hexachloroantimonate
FOMP	5-(pentafluorophenyloxy)-3,4-dihydro-1-methyl 2*H* pyrrolium hexachloroantimonate
HAMDU	*O*-(7-azabenzotriazol-1-yl)-1,3-dimethyl-

	1,3-dimethyleneuronium hexafluorophosphate
HAPipU	*O*-(7-azabenzotriazol-1-yl)-1,1,3,3-bis(pentamethylene)uronium hexafluorophosphate
HATU	*O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HBPyU	*O*-(benzotriazol-1-yl)oxybis-(pyrrolidino)-uronium hexafluorophosphate
HBTU	*O*-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HDTU	*O*-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HIP	α-(α-hydroxyisovaleryl)propionic acid
HOAt	1-hydroxy-7-azabenzotriazole
HOBt	1-hydroxybenzotriazole
HOCt	ethyl-1-hydroxy-1*H*-1,2,3-triazole-4-carboxylate
HODhbt	3,4-dihydro-3-hydroxy-4-oxo-1,2,3-benzotriazine
HODT	*S*-(1-oxido-2-pyridinyl)-1,3-dimethyl-1,3-trimethylenethiouronium hexafluorophosphate
HOSu	*N*-hydroxysuccinimide
HOTT	*S*-(1-oxido-2-pyridinyl)-1,1,3,3-tetramethylthiouronium hexafluorophosphate
HPyOPfp	*N*,*N*,*N*′,*N*′-bis(tetramethylene)-*O*-pentafluorophenyluronium hexafluorophosphate
IBCF	isobutyl chloroformate
Iva	isovaline
MPTA	dimethylphosphinothioyl azide
MPTO	3-dimethylphosphinothioyl-2(3*H*)-oxazolone
NDPP	norborn-5-ene-2,3-dicarboximidodiphenylphosphate
PTF	benzyltriphenylphosphonium dihydrogen trifluoride
PyAOP	[(7-azabenzotriazol-1-yl)oxy]tris-(pyrrolidino)phosphonium hexafluorophosphate
PyBOP	benzotriazol-1-yloxytri(pyrrolidino)-phosphonium hexafluorophosphate
PyBroP	bromotri(pyrrolidino)phosphonium hexafluorophosphate
PyCloP	chlorotri(pyrrolidino)phosphonium hexafluorophosphate
PyClU	chloro-1,1,3,3-bis(tetramethylene)-formamidinium hexafluorophosphate
PyDOP	[(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)oxy]tris-(pyrrolidino)phosphonium hexafluorophosphate
PyFOP	[[6-(trifluoromethyl)benzotriazol-1-yl]oxy]-tris(pyrrolidino)phosphonium hexafluorophosphate
PyNOP	[(6-nitrobenzotriazol-1-yl)oxy]tris-(pyrrolidino)phosphonium hexafluorophosphate
PyTOP	(pyridyl-2-thio)tris(pyrrolidino)-phosphonium hexafluorophosphate
SOMP	5-(succinimidyloxy)-3,4-dihydro-1-methyl 2*H*-pyrrolium hexachloroantimonate
TATU	*O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate
TBTU	*O*-benzotriazol-1-yl-1,1,3,3-tetramethyluronium tetrafluoroborate
TDBTU	2-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate
TEMP	2,3,5,6-tetramethylpyridine
TFFH	tetramethylfluoroformamidinium hexafluorophosphate
Ths-Cl	5-methyl-1,3,4-thiadiazole-2-sulfonyl chloride
TNTU	2-(5-norbornene-2,3-dicarboximido)-1,1,3,3-tetramethyluronium tetrafluoroborate
TODT	*S*-(1-oxido-2-pyridinyl)-1,3-dimethyl-1,3-trimethylenethiouronium tetrafluoroborate
TOTT	*S*-(1-oxido-2-pyridinyl)-1,1,3,3-tetramethylthiouronium tetrafluoroborate
TOTU	*O*-[cyano(ethoxycarbonyl)methyleneamino]-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate
TSTU	2-succinimido-1,1,3,3-tetramethyluronium tetrafluoroborate

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Biographical sketch

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Reactions of *N*-vinylic phosphazenes with azodicarboxylic and acetylenic esters

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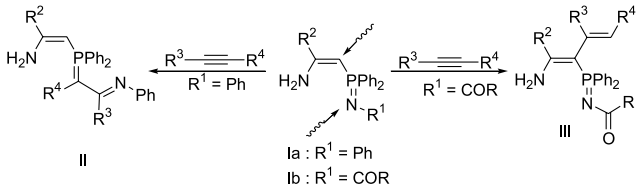
Abstract—*N*-Vinylic phosphazenes react as enamines (1,4-addition) with azodicarboxylic esters, whereas different behavior is observed when these phosphazenes react with dimethyl acetylenedicarboxylate (3,4-addition). A [2+2] cycloaddition reaction of the vinyl moiety of vinylic phosphazenes with the acetylenic triple bond of the acetylenic esters followed by a ring opening leads to the formation of functionalized conjugated phosphazenes.

1. Introduction

Phosphazenes[1,2] have been extensively used as useful tools for the construction of carbon–nitrogen double bonds (Aza-Wittig reaction)[1,3] and they are versatile precursors of acyclic[4] and heterocyclic compounds,[5] but as far as we know no reaction of phosphazenes with azodicarboxylic derivatives has been described,[1] and few examples of their reaction with acetylenic derivatives such as propargylic phosphonium salts[6] or acetylenedicarboxylic acid esters[7] are reported.

We have previously studied the [2+2] cycloaddition reaction of simple phosphazenes with acetylenic esters involving a formal insertion of the triple bond into the phosphazene linkage (1,2-addition).[7] However, when P-functionalized phosphazenes such as β-enamino phosphazenes **I** were used, the presence of a new functional group offered new reactive centres towards the acetylenic triple bond and the reaction may have taken place either through the phosphazene linkage or through the enamine moiety, depending on the reactivity of the phosphazene. *N*-Aryl β-enamino phosphazenes **Ia** (R^1=Ph) reacted with acetylenic esters through the phosphazene group to give conjugated phosphorus ylides **II**.[8a] However, when the reactivity of the phosphazene group decreased with the introduction of electron-withdrawing substituent in the nitrogen atom such as *N*-benzoyl-[8b] **Ib** (R^1=COPh) or *N*-ethoxycarbonyl β-enamino phosphazenes[8c] **Ib** (R^1=COOR) the reaction with acetylenic esters took place through the enamine moiety to give functionalized enamines **III** (Scheme 1), without altering the phosphazene group. Following on from our previous studies on the reactivity and the synthetic utility of phosphazenes, here, we aim to explore the reaction of *N*-vinylic phosphazenes with well known electrophilic reagents widely used in cycloaddition reactions[9] such as azodicarboxylic and acetylenic esters, in order to test whether the introduction in the nitrogen atom of a new functional group (a double bond) conjugated with the phosphazene group could drive the process through the vinyl carbon atom.



Scheme 1.

2. Results and discussion

2.1. Reaction of *N*-vinylic phosphazenes with diethyl azodicarboxylate

N-Vinylic phosphazenes **1** were easily obtained by reaction of phosphorus ylides and nitriles.[10] The treatment of phosphazene **1** (R=Ph), derived from triphenylphosphine, with diethyl azodicarboxylate **2** in $CHCl_3$ at room temperature gave functionalized hydrazino derivatives **3**, in good yields (Scheme 2, Table 1, entries 1–5). Compounds **3** were characterized on the basis of spectroscopic data. A ^{31}P NMR spectrum of compound **3a** showed

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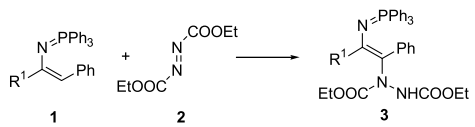


Scheme 2.

Table 1. Conjugated phosphazenes **3** obtained

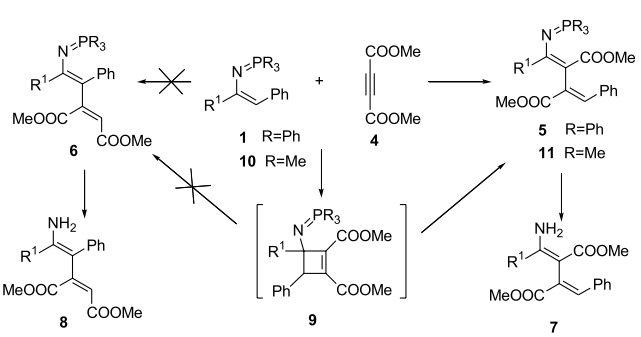
Entry	Compound	R^1	Yield (%)[a]	Mp (°C)
1	**3a**	2-Pyridyl	85	149–150
2	**3b**	Ph	80	180–181
3	**3c**	2-Furyl	67	59–60
4	**3d**	2-Thienyl	87	128–129
5	**3e**	3-Pyridyl	81	103–105

[a] Yield after purification by flash chromatography.

absorption at δ_P=8.09 ppm, while ^{13}C NMR displayed singlets at δ_C=148.2 ppm for the enamine double carbon atom attached to the azo substituent and δ_C=157.8 and 158.2 ppm for the carboxylate esters. The GC–MS spectrometry of **3a** shows the molecular ion peak (*m*/*z* 630, 24%) which is in agreement with the structure of compounds **3**. The formation of conjugated phosphazenes **3** could be explained by conjugative addition of the γ-C-atom (1,4-addition) of phosphazenes **1** to the azo moiety of diethyl azodicarboxylate **2** in a similar way to that observed of *N*-vinylic phosphazenes to simple[3c,d] and unsaturated carbonyl compounds.[11] A similar way was observed when enamines react with diethyl azodicarboxylate.[12]

2.2. Reaction of *N*-vinylic phosphazenes with acetylenic esters

Different behavior is observed in the reaction of *N*-vinylic phosphazenes with acetylenic compounds. Treatment of phosphazene **1a**, derived from triphenylphosphine (R=Ph, R^1=2-pyridyl), with dimethyl acetylenedicarboxylate **4** in $HCCl_3$ at room temperature gave an 1:1 adduct in good yield (Scheme 3). This adduct was characterized on the basis of spectroscopic data and the structure could be initially consistent with both conjugated phosphazenes **5a** or **6a**. Mass spectrometry showed the molecular ion peak (*m*/*z* 599, 50%). A ^{31}P NMR spectrum of adduct **5a** or **6a** showed absorption at δ_P=7.52 ppm, characteristic of conjugated phosphazenes.[3] ^1H NMR showed absorptions in the region of 6.45–7.60 ppm for the aromatic and the vinyl protons and two singlets at 3.74 and 3.77 ppm for the methoxy groups of carboxylic esters, while the ^{13}C NMR displayed



Scheme 3.

singlets at δ_C=147.5 ppm for the enamine carbon bonded to the nitrogen atom and at δ_C=168.2 and 170.5 ppm for carboxylate esters. However, given that the vinyl proton signal appeared with the aromatic protons, it is not easy to use NMR experiments (NOE, HMBC…) in order to distinguish between both structures **5a** and **6a**, the hydrolysis of the phosphazene linkage of the adduct **5a** or **6a** was carried out to give primary enamines **7a** or **8a** (Scheme 3, Table 2, entry 4). The primary enamine obtained (**7a** or **8a**) shows a vinylic proton separated from the aromatic signals which could be used to establish whether the phenyl group in **7a** or the carboxylate group in **8a** is vicinal to the vinyl proton by NMR experiments.

Table 2. Compounds **5** and **7** obtained

Entry	Compound	R^1	Yield (%)[a]
1	**5a**	2-Pyridyl	60
2	**5b**	Ph	93[b]
3	**5c**	2-Furyl	80[c]
4	**7a**	2-Pyridyl	86[d]
5	**7b**	Ph	93[b]/88[e]
6	**7c**	2-Furyl	80[c]/79[e]
7	**7d**	2-Thienyl	54

[a] Yield after purification by flash-chromatography.
[b] Proportion **5b/7b**, 67:33.
[c] Proportion **5c/7c**, 90:10.
[d] Obtained from phosphazenes **5**.
[e] Obtained from phosphazenes **10**.

HMBC experiments corroborated the structure **7a** and, therefore, the formation of compound **5a** with exclusion of the other possible structure **6a**. A correlation between the olefinic proton and aromatic =CH indicated that the phenyl group was the substituent more closely situated to the olefinic proton. In addition, in the case of conjugated β-enamino ester **7a** the presence of an ester group would stabilize the primary enamine, since it is known that primary enamines are very unstable unless conjugated with an electron-withdrawing group in the β-carbon atom.[13]

The formation of conjugated phosphazene **5a** (Scheme 3, Table 2, entry 1) could be explained by [2+2] cycloaddition reaction of the vinyl moiety of the phosphazene with the triple carbon–carbon bond of the acetylenic ester after redistribution of bonds in the four-membered intermediate cycle **9**, although a different cleavage of the same intermediate **9** could also explain the formation of isomeric **6a**. When the reaction was performed with phosphazenes **1b** (R^1=Ph) and **1c** (R^1=2-furyl), not only conjugated phosphazenes **5b**,**c** but also primary enamines **7b**,**c**, as minor components (Scheme 3, Table 2, entries 2, 3, 5, and 6) were isolated, due to the easy hydrolysis of the phosphazene, and in the case of phosphazene **1d** (R^1=2-thienyl) only primary enamine **7d** (Scheme 3, Table 2, entry 7) was obtained. An X-ray diffraction analysis for primary enamine **7d** (R^1=2-thienyl) was performed and confirmed the structure proposed for **7d** (Fig. 1).[14]

In order to test whether the reaction of *N*-vinylic phosphazenes with dimethyl acetylenedicarboxylate could be driven to the phosphazene linkage in a similar way to that observed in simple phosphazenes,[15] *N*-vinylic phosphazenes **10** (R=Me), derived from trimethylphosphine were

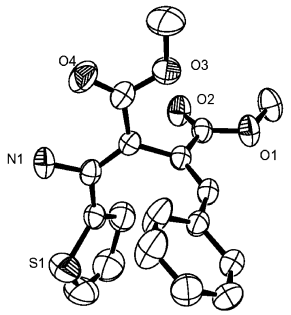


Figure 1. ORTEP for compound **7d**.

prepared, given that it is known that the substitution in the phosphorus atom of phosphazenes of aryl by alkyl substituents increases the reactivity of the phosphazene in a similar way to that observed in the isosteric phosphorus ylides.[3c,d,15] However, a similar result was obtained when *N*-vinylic phosphazenes **10** (R=Me), derived from aliphatic phosphines, were treated with dimethyl acetylenedicarboxylate **4**, affording in this case the enamine derivatives **7** exclusively (Scheme 3, Table 2, entries 5 and 6), without detection of conjugated phosphazene intermediate **11** derived from trimethylphosphine. The higher hydrolysis sensibility to the nucleophilic attack of water to the phosphazene derived from trimethylphosphine, more reactive than that derived from triphenylphosphine, could favor the formation of the primary enamine **7**. As before, the formation of conjugated enamines **7** could be explained by [2+2] cycloaddition reaction followed by ring opening of intermediate **9** and subsequent hydrolysis of the unstable phosphazenes derived from trimethylphosphine **11**.

3. Conclusion

In conclusion, the presence of an olefinic group in conjugation with the phosphazene group in *N*-vinylic phosphazenes opens new synthetic pathways. *N*-Vinylic phosphazenes derived from triphenyl phosphine react like enamines (1,4-addition) with diethylazodicarboxylate. However, different behavior is observed in the reaction with acetylenic esters. *N*-Vinylic phosphazenes derived from triphenyl **1** or trimethyl phosphine **10** gave [2+2] cycloaddition reaction through the vinylic double bond with diacetylenic esters such as dimethyl acetylendicarboxylic ester to afford conjugated phosphazenes **5** and **11**.

4. Experimental

4.1. General

Chemicals were purchased from Aldrich Chemical Company. Solvents for extraction and chromatography were technical grade. All solvents used in reactions were freshly distilled from appropriate drying agents before use. All other reagents were recrystallized or distilled as necessary. All reactions were performed under an atmosphere of dry nitrogen. Analytical TLC was performed with Merck silica gel 60 F_{254} plates. Visualization was accomplished by UV light. Flash chromatography was carried out using Merck silica gel 60 (230–400 mesh ASTM). Melting points were determined with an Electrothermal IA9100 Digital Melting Point Apparatus and are uncorrected. ^{1}H (400, 300, 250 MHz), ^{13}C (100, 75 MHz) and ^{31}P NMR (120 MHz) spectra were recorded on a Bruker Avance 400 MHz, a Varian VXR 300 MHz and a Bruker AC 250 MHz spectrometer using $CDCl_3$ or CD_3OD solutions with TMS as an internal reference (δ=0.00 ppm) for ^{1}H and ^{13}C NMR spectra and phosphoric acid (85%) (δ=0.0 ppm) for ^{31}P NMR spectra. Chemical shifts (δ) are reported in ppm. Coupling constants (J) are reported in Hertz. Low-resolution mass spectra (MS) were obtained at 50–70 eV by electron impact (EIMS) on a Hewlett–Packard 5971 or 5973 spectrometer. Data are reported in the form m/z (intensity relative to base=100). Infrared spectra (IR) were taken on a Nicolet IRFT Magna 550 spectrometer, and were obtained as solids in KBr or as neat oils. Peaks are reported in cm^{-1}. Elemental analyses were performed in a LECO CHNS-932 apparatus.

4.2. General procedure for the reaction of *N*-vinylic phosphazenes and diethylazodicarboxylate

To a 0 °C solution of *N*-vinylic phosphazene (5 mmol) in $CHCl_3$ under a nitrogen atmosphere, diethylazodicarboxylate (0.8 ml, 5 mmol) was added. The mixture was stirring at room temperature until TLC indicated the disappearance of phosphazene. Evaporation of solvent under reduced pressure and chromatographic purification by flash column chromatography with hexane/AcOEt afforded the corresponding derivatives.

4.2.1. 1,1,1,4-Tetraphenyl-3-(2-pyridyl)-2-aza-4-(*N*,*N*′-diethoxycarbonylhydrazono)-1,λ^5-phosphabuta-1,3-diene (3a). The general procedure was followed using 1,1,1,4-tetraphenyl-3-(2-pyridyl)-2-aza-1,λ^5-phosphabuta-1,3-diene (2.28 g, 5 mmol) and the mixture was stirred at room temperature for 1 h. Chromatographic purification (1:1, hexane/diethyl ether) gave 2.680 g (85%) of compound **3a**; mp 149–150 °C (ethyl acetate); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.01–1.24 (m, 6H), 1.52 (s, 1H), 4.06–4.15 (m, 4H), 6.63–7.80 (m, 24H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.4, 14.5, 61.2, 62.0, 121.0–135.2 (m), 138.5, 148.2, 157.8, 158.2; ^{31}P NMR (120 MHz, $CDCl_3$): δ 8.09; IR (KBr) ν_{max} 3355, 1740, 1719, 1367; MS (EI): m/z 630 (M^+, 24). Anal. Calcd for $C_{37}H_{35}N_4O_4P$: C, 70.46; H, 5.59; N, 8.88. Found: C, 70.31; H, 5.52; N, 8.81.

4.2.2. 1,1,1,3,4-Penthaphenyl-2-aza-4-(*N*,*N*′-diethoxycarbonylhydrazono)-1,λ^5-phosphabuta-1,3-diene (3b). The general procedure was followed using 1,1,1,3,4-pentaphenyl-2-aza-1,λ^5-phosphabuta-1,3-diene (2.28 g, 5 mmol) and the mixture was stirred at room temperature for 1 h. Chromatographic purification (1:1, hexane/ethyl acetate) gave 2.517 g (80%) of compound **3b**; mp 180–181 °C (ethyl acetate); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.03–1.24 (m, 6H), 4.00–4.12 (m, 4H), 5.82 (s, 1H), 6.73–7.57 (m, 25H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.4, 14.8, 61.5, 62.2, 124.0–132.6 (m), 138.0, 141.3, 156.8; ^{31}P NMR (120 MHz, $CDCl_3$): δ 3.9; IR (KBr) ν_{max} 3361, 1765, 1729, 1394; MS (EI): m/z 629 (M^+, 100). Anal. Calcd for $C_{38}H_{36}N_3O_4P$: C, 72.48; H, 5.76; N, 6.67. Found: C, 71.99; H, 5.70; N, 6.63.

4.2.3. 1,1,1,4-Tetraphenyl-3-(2-furyl)-2-aza-4-(*N*,*N*′-diethoxycarbonylhydrazono)-1,λ^5-phosphabuta-1,3-diene (3c). The general procedure was followed using 1,1,1,4-tetraphenyl-3-(2-furyl)-2-aza-1,λ^5-phosphabuta-1,3-diene (2.22 g, 5 mmol) and the mixture was stirred at room temperature for 30 min. Chromatographic purification (4:1, hexane/diethyl ether) gave 2.076 g (67%) of compound **3c**; mp 59–60 °C (ethyl acetate); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.09–1.29 (m, 6H), 4.04–4.20 (m, 4H),5.50 (d, $^3J_{HH}$=2.9 Hz, 1H), 5.80 (s, 1H) 6.69–7.63 (m, 22H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.4, 14.5, 61.3, 62.1, 109.8, 110.6, 125.1–132.7 (m), 140.2, 158.0; ^{31}P NMR (120 MHz, $CDCl_3$): δ 8.56; IR (KBr) ν_{max} 3247, 1720, 1328; MS (EI): *m*/*z* 620 (M^+, 100). Anal. Calcd for $C_{36}H_{34}N_3O_5P$: C, 69.78; H, 5.53; N, 6.78. Found: C, 70.00; H, 5.48; N, 6.80.

4.2.4. 1,1,1,4-Tetraphenyl-3-(2-thienyl)-2-aza-4-(*N*,*N*′-diethoxycarbonylhydrazono)-1,λ^5-phosphabuta-1,3-diene (3d). The general procedure was followed using 1,1,1,4-tetraphenyl-3-(2-thienyl)-2-aza-1,λ^5-phosphabuta-1,3-diene (2.30 g, 5 mmol) and the mixture was stirred at room temperature for 30 min. Chromatographic purification (1:1, hexane/diethyl ether) gave 2.765 g (87%) of compound **3d**; mp 128–129 °C (ethyl acetate); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.06–1.30 (m, 6H), 4.06–4.18 (m, 4H), 6.26–7.63 (m, 23H), 8.25 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.5, 14.7, 62.1, 62.3, 124.6–132.6 (m), 138.5, 142.6, 156.0, 156.7; ^{31}P NMR (120 MHz, $CDCl_3$): δ 4.51; IR (KBr) ν_{max} 3356, 1725, 1723, 1335; MS (EI): *m*/*z* 636 (M^+, 10). Anal. Calcd for $C_{36}H_{34}N_3O_4PS$: C, 68.02; H, 5.39; N, 6.61. Found: C, 67.89; H, 5.32; N, 6.59.

4.2.5. 1,1,1,4-Tetraphenyl-3-(3-pyridyl)-2-aza-4-(*N*,*N*′-diethoxycarbonylhydrazono)-1,λ^5-phosphabuta-1,3-diene (3e). The general procedure was followed using 1,1,1,4-tetraphenyl-3-(3-pyridyl)-2-aza-1,λ^5-phosphabuta-1,3-diene (2.28 g, 5 mmol) and the mixture was stirred at room temperature for 3 h. Chromatographic purification (1:10, hexane/diethyl ether) gave 2.552 g (81%) of compound **3e**; mp 103–105 °C (ethyl acetate); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.11–1.25 (m, 6H), 1.75 (s, 1H), 4.00–4.12 (m, 4H), 6.51–7.56 (m, 22H) 8.05–8.18 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 14.3, 61.6, 62.1, 122.5, 127.2–132.4 (m), 137.0, 141.8, 147.1, 149.0, 157.2; ^{31}P NMR (120 MHz, $CDCl_3$): δ 4.55; IR (KBr) ν_{max} 3361, 1767, 1716, 1329; MS (EI): *m*/*z* 630 (M^+, 43). Anal. Calcd for $C_{37}H_{35}N_4O_4P$: C, 70.46; H, 5.59; N, 8.88. Found: C, 70.36; H, 5.51; N, 8.86.

4.3. General procedure for the reaction of phosphazenes 1, 10 and acetylenic ester 4

To a solution of phosphazene **1** or **10** (5 mmol) in chloroform (20 ml) was added dimethyl acetylendicarboxylate (0.67 ml, 5 mmol), and the mixture was stirred at room temperature in an atmosphere of nitrogen until TLC indicated the disappearance of phosphazene. Evaporation of solvent under reduced pressure afforded an oil that was chromatographied on silica gel to give compounds **5** and/or **7**.

4.3.1. 4,5-Bis(methoxycarbonyl)-1,1,1,6-tetraphenyl-3-(2-pyridyl)-2-aza-1,λ^5-phosphahexa-1,3,5-triene (5a). The general procedure was followed using 1,1,1,4-tetraphenyl-3-(2-pyridyl)-2-aza-1,λ^5-phosphabuta-1,3-diene **1a** (2.28 g) for 20 h. Chromatographic separation (1:1, hexane/ethyl acetate) gave **5a** (1.80 g, 60%) as a yellow solid; mp 171–172 °C (hexane/dichloromethane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.74 (s, 3H), 3.77 (s, 3H), 6.45–6.97 (m, 3H), 7.18 (s, 1H), 7.20–7.60 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 50.7, 53.0, 122.0 (d, J_{PC}=75 Hz), 127.8–134.4 (m), 136.4, 139.7, 147.5, 157.6, 162.3, 168.2, 170.5; ^{31}P NMR (120 MHz, $CDCl_3$): δ 7.52; IR (KBr) ν_{max} 1694, 1241. MS (EI): *m*/*z* 599 (M^+, 50). Anal. Calcd for $C_{37}H_{31}N_2O_4P$: C, 74.24; H, 5.22; N, 4.68. Found: C, 74.33; H, 5.28; N, 4.63.

4.3.2. 1-Amino-2,3-dimethoxycarbonyl-4-phenyl-1-(2-pyridyl)buta-1,3-diene (7a). To a solution of phosphazene **5a** (1 mmol) in toluene (20 ml), HCl 6 N (2 ml) was added and the mixture was stirred at reflux temperature under inert atmosphere. The reaction was monitored by ^{31}P NMR and after 24 h the total disappearance of phosphazene was observed. Evaporation under reduced pressure afforded a solid which was chromatographied (5:1, hexane/ethyl acetate) giving **7a** (0.29 g, 86%) as a yellow solid; mp 137–138 °C (hexane/dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.52 (s, 3H), 3.94 (s, 9H), 7.29–7.48 (m, 7H), 7.60 (s, 2H), 7.72 (dd, *J*=4.2, 1.7 Hz, 1H), 8.81 (d, *J*=8.5, 1.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.7, 52.0, 101.4, 123.9–149.1 (m), 167.7, 169.4.; IR (KBr) ν_{max} 3456, 3330, 1732, 1679, 1235. MS (EI): *m*/*z* 338 (M^+, 15). Anal. Calcd for $C_{19}H_{18}N_2O_4$: C, 67.44; H, 5.36; N, 8.28. Found: C, 67.33; H, 5.28; N, 8.43.

4.3.3. 4,5-Bis(methoxycarbonyl)-1,1,1,3,6-pentaphenyl-2-aza-1,λ^5-phosphahexa-1,3,5-triene (5b) and 1-amino-2,3-dimethoxycarbonyl-1,4-diphenyl-buta-1,3-diene (7b). The general procedure was followed using 1,1,1,3,4-pentaphenyl-2-aza-1,λ^5-phosphabuta-1,3-diene **1b** (2.28 g) for 7.5 h. Chromatographic separation (5:1, hexane/ethyl acetate) gave **5b** (1.67 g, 56%) as a yellow solid; mp 107–108 °C (hexane/dichloromethane) and **7b** (0.62 g, 37%) as a yellow solid; mp 120–121 °C (hexane/dichloromethane). For compound **5b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.33 (s, 3H), 3.81 (s, 3H), 6.75–7.83 (m, 26H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 50.4, 52.0, 126.2–132.8 (m), 137.1, 138.4, 142.7, 168.1, 170.2; ^{31}P NMR (120 MHz, $CDCl_3$): δ 7.78; IR (KBr) ν_{max} 1705, 1407; MS (EI): *m*/*z* 597 (M^+, 100). Anal. Calcd for: $C_{38}H_{32}NO_4P$: C, 76.37; H, 5.40; N, 2.34. Found: C, 76.33; H, 5.38; N, 2.33. For **7b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.65 (s, 3H), 3.73 (s, 3H), 4.75 (s, 2H, NH_2), 6.86–7.26 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 50.9, 52.0, 91.4, 127.0–140.5 (m), 161.1, 169.9, 170.1; IR (KBr) ν_{max} 3424, 1710, 1690; MS (EI): *m*/*z* 337 (M^+, 100). Anal. Calcd for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15; Found: C, 71.33; H, 5.70; N, 4.13.

When the general procedure was followed using 1,1,1-trimethyl-3,4-phenyl-2-aza-1,λ^5-phosphabuta-1,3-diene **10b** (5 mmol) generated 'in situ',[7a] the mixture was stirred at room temperature for 3 h. Chromatographic separation (5:1, hexane/ethyl acetate) gave **7b** (1.47 g, 88%).

4.3.4. 4,5-Bis(methoxycarbonyl)-3-(2-furyl)-1,1,1,6-tetraphenyl-2-aza-1,λ^5-phosphahexa-1,3,5-triene (5c) and

1-amino-2,3-dimethoxycarbonyl-1-(2-furyl)-4-phenyl-buta-1,3-diene (7c). The general procedure was followed using 1,1,1,4-tetraphenyl-3-(2-furyl)-2-aza-1,λ^5-phospha-buta-1,3-diene **1c** (2.22 g) for 18 h. Chromatographic separation (5:1, hexane/ethyl acetate) gave **5c** (2.05 g, 70%) as a yellow solid; mp 128–129 °C (hexane/dichloro-methane) and **7c** (0.16 g, 10%) as a yellow solid; mp 143–144 °C (hexane/dichloromethane). For compound **5c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.35 (s, 3H), 3.61 (s, 3H), 5.90 (s, 2H), 6.82 (s, 1H), 7.22–7.74 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 50.7, 51.9, 109.3, 110.3, 128.0–140.4 (m), 152.4, 168.0, 170.0; ^{31}P NMR (120 MHz, $CDCl_3$): δ 8.59; IR (KBr) ν_{max} 1694, 1406; MS (EI): *m/z* 587 (M^+, 100). Anal. Calcd for $C_{36}H_{30}NO_5P$: C, 73.58; H, 5.15; N, 2.38. Found: C, 73.53; H, 5.18; N, 2.33. For compound **7c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.54 (s, 3H), 3.72 (s, 3H), 6.33 (dd, J_{HH}=1.7, 3.5 Hz, 1H), 6.69 (d, J_{HH}=3.5 Hz, 1H), 7.25–7.77 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 50.7, 51.9, 109.3, 110.3, 128.0–148.1 (m), 169.5, 169.8; IR (KBr) ν_{max} 3509, 1705, 1665; MS (EI): *m/z* 327 (M^+, 100). Anal. Calcd for $C_{18}H_{17}NO_5$: C, 66.05; H, 5.23; N, 4.28. Found: C, 66.10; H, 5.20; N, 4.20.

When the general procedure was followed using 1,1,1-trimethyl-4-phenyl-3-(2-furyl)-2-aza-1,λ^5-phosphabuta-1,3-diene **10c** (5 mmol) generated in situ,[7a] the mixture was stirred at room temperature for 2 h. Chromatographic separation (5:1, hexane/ethyl acetate) gave **7c** (1.29 g, 79%).

4.3.5. 1-Amino-2,3-dimethoxycarbonyl-4-phenyl-1-(2-thienyl)buta-1,3-diene (7d). The general procedure was followed using 1,1,1,4-tetraphenyl-3-(2-thienyl)-2-aza-1,λ^5-phosphabuta-1,3-diene **1d** (2.30 g) for 22.5 h. Chromatographic separation (5:1, hexane/ethyl acetate) gave **7d** (0.93 g, 54%) as a brown solid; mp 122–124 °C (hexane/dichloromethane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.60 (s, 3H), 3.72 (s, 3H), 6.80–7.49 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 51.1, 52.2, 92.4, 126.8–141.7 (m), 153.4, 169.6, 169.8; IR (KBr) ν_{max} 3425, 1711, 1680; MS (EI): *m/z* 343 (M^+, 100). Anal. Calcd for $C_{18}H_{17}NO_4S$: C, 62.96; H, 4.99; N, 4.08. Found: C, 63.02; H, 5.00; N, 4.10.

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Total synthesis of a tetra- and two pentasaccharide fragments of the O-specific polysaccharide of *Shigella flexneri* serotype 2a☆

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Abstract—The synthesis of the methyl glycoside of the branched pentasaccharide biological repeating unit of the O-antigen of *Shigella flexneri* serotype 2a is described together with that of the methyl glycoside of the corresponding tetrasaccharide and frame-shifted linear pentasaccharide. All the strategies disclosed herein involve a key disaccharide corresponding to the branching point and otherwise appropriate monosaccharide building blocks activated as their trichloroacetimidate. Our data suggest partial lack of conformational flexibility at the branched residue.

1. Introduction

Shigellosis, also known as bacillary dysentery, is a major enteric disease which accounts for some 165 million annual episodes, among which 1.1 million deaths, occurring mostly in developing countries.[12] Young children and immunocompromised individuals are the main victims. Some 15 years ago, vaccination was defined as a priority by the WHO in its program on enteric diseases. However, there is still no license vaccine against this bacterial infection although intensive research is ongoing in the field.[11] *Shigellae* are Gram negative bacteria. As for other bacterial pathogens, their lipopolysaccharide (LPS) is an important virulence factor. It is also a major target of the host's protective immunity against infection.

Shigella flexneri 2a is the prevalent serotype in developing countries, where it is responsible for the endemic form of the disease.[12] Based on the early hypothesis that a critical level of serum IgG antibodies specific for the O-specific polysaccharide (O-SP) moiety of the LPS was sufficient to confer protection against homologous infections,[26,27] several *S. flexneri* 2a O-SP-protein conjugates were prepared. They were found safe and immunogenic in both adults and children.[2,22]

Allowing a better control of the various structural parameters possibly involved in the immunogenicity of glycoconjugate vaccines, oligosaccharide-protein conjugates were proposed as alternatives to polysaccharide–protein conjugate vaccines against bacteria.[24] Indeed, such constructs were found immunogenic on several occasions, including examples whereby the oligosaccharide portion was made of one repeating unit only.[5,18] We reasoned that glycoconjugates incorporating chemically synthesized oligosaccharides, appropriately selected for their ability to mimic the native O-SP in terms of both antigenicity and solution conformation, may offer an alternative to the *S. flexneri* 2a O-SP-protein conjugates currently under study. Our approach relies on a rational basis. Indeed, in order to select the best oligosaccharide mimic, we have undertaken the characterization of the antigenic determinants of *S. flexneri* 2a O-SP recognized by serotype-specific protective monoclonal antibodies. A panel of methyl glycosides representative of fragments of *S. flexneri* 2a O-SP was thus synthesized to be used as probes in the study of antibody recognition.

A **B** **E** **C** **D**

2)-α-L-Rha*p*-(1→2)-α-L-Rha*p*-(1→3)-[α-D-Glc*p*-(1→4)]-α-L-Rha*p*-(1→3)-β-D-GlcNAc*p*(1→

I

The O-SP of *S. flexneri* 2a is a heteropolysaccharide defined by the pentasaccharide repeating unit **I**.[15,29] It features a linear tetrasaccharide backbone, which is common to all *S. flexneri* O-antigens and comprises a *N*-acetyl

☆ See Ref. 1.

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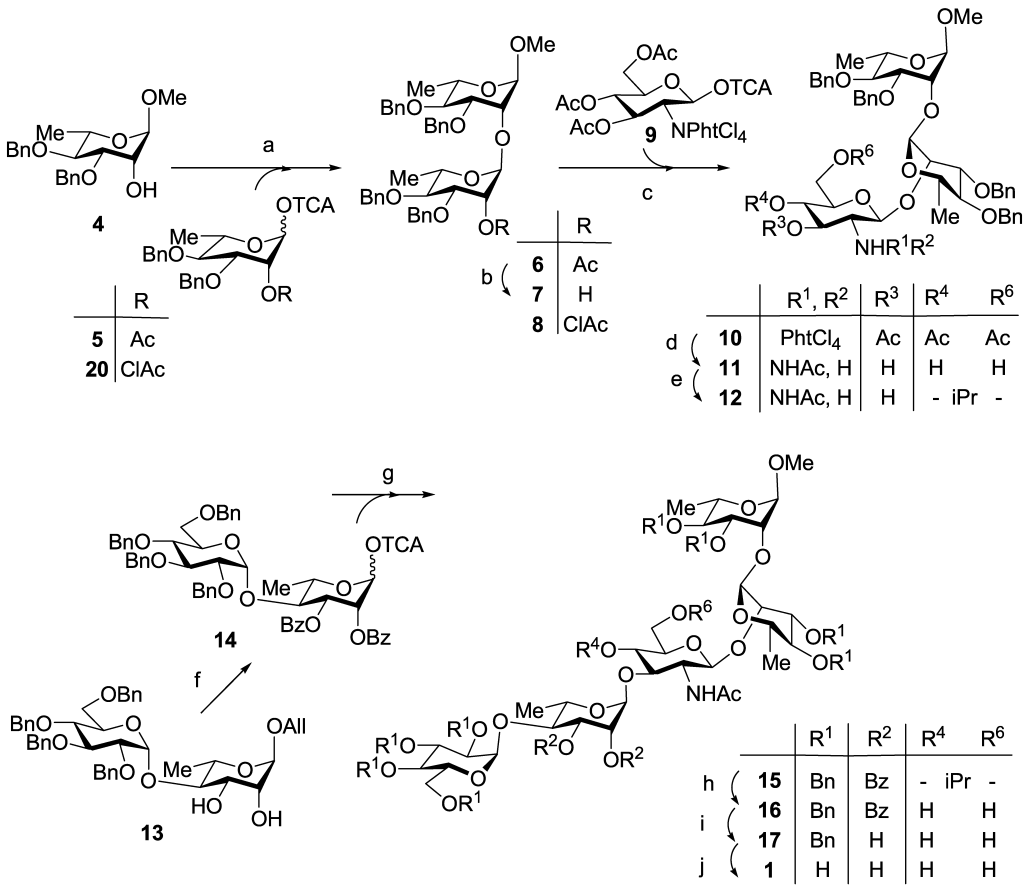
glucosamine and three rhamnose residues, together with an α-D-glucopyranose residue branched at position 4 of one of the rhamnoses. We have already reported on the synthesis of the methyl glycosides of various fragments of the O-SP, including the known **EC** disaccharide,[6,16,19] the **ECD**[19] and **B(E)C**[19] trisaccharides, the **ECDA**[28] and **AB(E)C**[9] tetrasaccharides, the **B(E)CDA**[28] and **DAB(E)C**[9] pentasaccharides, the **B′(E′)C′DAB(E)C** octasaccharide[3] and more recently the **D′A′B′(E′)C′DAB(E)C** decasaccharide.[4] However, in order to complete the full set of frame-shifted fragments of the repeating unit, the methyl glycosides of the **ECDAB**, **AB(E)CD** pentasaccharides and that of the **B(E)CD** tetrasaccharide, **1**, **2** and **3**, respectively, were missing. Their synthesis is reported in the following.

2. Results and discussion

Analysis of the targets shows that all the glycosylation reactions to set up involve 1,2-*trans* glycosidic linkages except for that at the **E**–**C** junction which is 1,2-*cis*. Consequently, the syntheses described herein rely on key **EC** disaccharide building blocks as well as on appropriate **A**, **B** and **D** monosaccharide synthons.

2.1. Synthesis of the linear ECDAB-OMe pentasaccharide 1

Earlier findings in the series have demonstrated that the **C**–**D** linkage was an appropriate disconnection site.[3,4,28] Consequently, the synthesis of **1** was designed (Scheme 1) based on the glycosylation of the known **EC** trichloroacetimidate donor **14**,[19] obtained in three steps (69%) from the key diol **13**,[28] and the **DAB** trisaccharide acceptor **12**. The latter was obtained by the stepwise condensation of known monosaccharide precursors, readily available by selective protection, deprotection and activation sequences. Thus, TMSOTf-catalysed condensation of the rhamnopyranoside acceptor **4**[25] with the trichloroacetimidate donor **5**[7] in diethyl ether to give the fully protected rhamnobioside **6**,[23] and subsequent de-*O*-acetylation gave the **AB** disaccharide acceptor **7**[25] in 91% overall yield, which compares favourably with the previously described preparation using the corresponding 1-*O*-acetyl donor.[25] Analogously to previous work in a related series,[4] the known glucosaminyl trichloroacetimidate donor **9**,[8] was chosen as the precursor to residue **D**. Conventional glycosylation of **7** with **9** was best performed in acetonitrile using tin trifluoromethanesulfonate ($Sn(OTf)_2$) as the catalyst[17] to give the fully protected trisaccharide **10** in 72% yield (extracted from the ^1H NMR spectrum). When TMSOTf was used instead of $Sn(OTf)_2$, **10** was formed in lower yield (52%) outlining the sensitivity of the tetrachlorophtaloyl group to these stronger conditions, as previously noted.[14] A three step process including heating **10** with ethylenediamine in dry ethanol,[10] ensuing *N*-acetylation with acetic anhydride, and de-*O*-acetylation under Zemplén conditions, furnished the triol **11** (51% from **7**). It



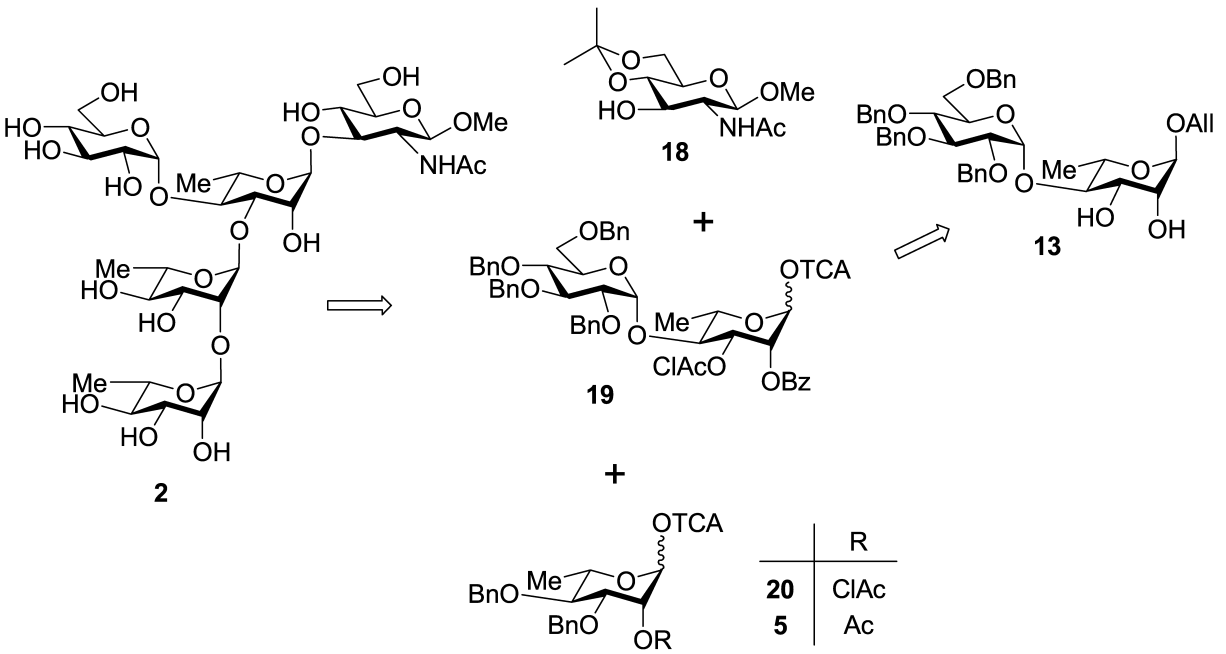
Scheme 1. (a) **6** from **5**, **8** from **20**, TMSOTf, Et_2O, −35 °C→rt; (b) cat. MeONa, MeOH–CH_2Cl_2, rt; (c) from **7**, $Sn(OTf)_2$, CH_3CN, rt; (d) (i) $H_2NCH_2CH_2NH_2$, EtOH, 60 °C, (ii) Ac_2O, EtOH; (iii) MeONa, MeOH–CH_2Cl_2, rt; (e) $Me_2C(OMe)_2$, PTSA, acetone, rt; (f) see Ref. 19; (g) 4 Å molecular sieves, TfOH, CH_2Cl_2, −15 °C→rt; (h) 90% aq. TFA, 0 °C; (i) cat. MeONa, MeOH–CH_2Cl_2, rt; (j) H_2, 10% Pd/C, EtOH–AcOH, rt.

was next protected at positions 4_D and 6_D by regioselective introduction of an isopropylidene acetal upon reaction with 2,2-dimethoxypropane under acid-catalysis to give **12** (96%). The latter acetal-protecting group was selected based on data previously obtained when synthesizing shorter fragments in the series which had outlined the interest of using 4,6-*O*-isopropylidene–glucosaminyl intermediates instead of the more common benzylidene analogues.[19] Once the two key building blocks were made available, their condensation was performed in dichloromethane in the presence of a catalytic amount of triflic acid to give the fully protected pentasaccharide **15** (84%). Conventional stepwise deprotection involving (i) acidic hydrolysis of the isopropylidene acetal using 90% aq. TFA to give diol **16** (95%), (ii) conversion of the latter into the corresponding tetraol **17** under Zemplén conditions (86%), and (iii) final hydrogenolysis of the benzyl protecting groups, gave the linear pentasaccharide target **1** in 81% yield.

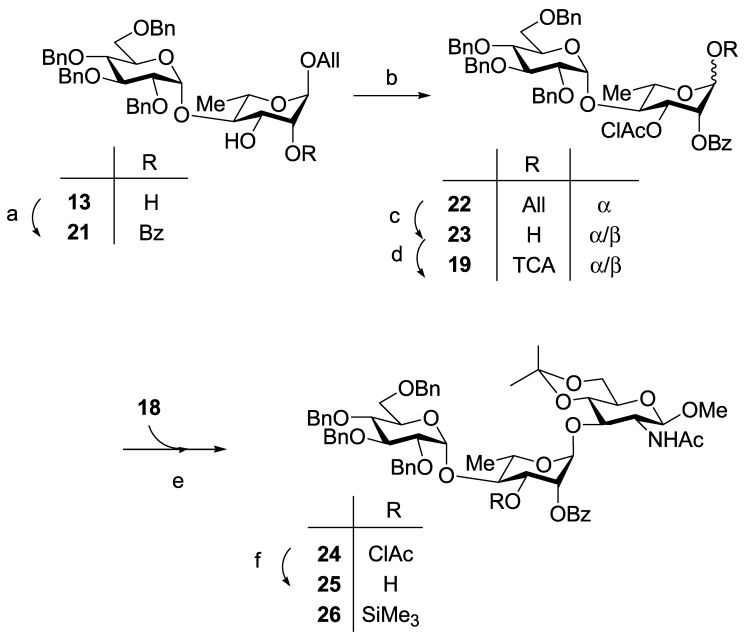
2.2. Synthesis of the AB(E)CD pentasaccharide 2 and of the B(E)CD tetrasaccharide 3

For reasons mentioned above, the glucosaminyl acceptor **18**,[19] protected at its 4 and 6 hydroxyl groups by an isopropylidene acetal was the precursor of choice for residue **D** (Scheme 2). In the past, introduction of residue **B** at position 3_C was performed on a 2_C-*O*-benzoylated **EC** acceptor resulting from the regioselective acidic hydrolysis of the corresponding 2,3-orthoester intermediate.[9,28] It rapidly occurred to us that opening of the intermediate phenyl orthoester was not compatible with the presence of the 4_D,6_D-*O*-isopropylidene acetal. For that reason, the trichloroacetimidate donor **19**, suitably benzoylated at position 2_C and orthogonally protected by a chloroacetyl group at position 3_C was used as the **EC** building block instead of the previously used **14**. Protection at the 2-OH of the rhamnosyl precursor to residue **B** was also crucial in the synthesis of **2**. Indeed, most of our previous work in the series relied on the use of the known 2-*O*-acetyl rhamnopyranosyl donor **5**. In the reported syntheses,[9] selective de-*O*-acetylation at position 2_B in the presence of a 2_C-*O*-benzoate was best performed by treatment with methanolic $HBF_4{\cdot}OEt_2$ for 5 days. Clearly, such de-*O*-acetylation conditions are not compatible with the presence of an isopropylidene acetal on the molecule. To overcome this limitation, the corresponding 2-*O*-chloroacetyl rhamnopyranosyl trichloroacetimidate **20** was selected as an alternate donor. In theory, the latter could also serve as an appropriate precursor to residue **A**.

Regioselective conversion of diol **13** into its 2-*O*-benzoylated counterpart **21** was performed as described (Scheme 3).[28] Treatment of the latter with chloroacetic anhydride and pyridine gave the orthogonally protected **22** (95%), which was smoothly de-*O*-allylated to yield the corresponding hemiacetal **23** (91%) by a two-step process, involving (i) iridium (I)-promoted isomerisation[21] of the allyl glycoside and (ii) subsequent hydrolysis in the presence of iodine.[20] The selected trichloroacetimidate leaving group was successfully introduced by treatment of **23** with trichloroacetonitrile in the presence of 1,8-diazabicyclo[4.3.0]undec-7-ene (DBU), which resulted in the formation of **19** (84%) together with the recovery of some starting hemiacetal (14%) since partial hydrolysis during column chromatography could not be avoided. TMSOTf-mediated glycosylation of donor **19** and acceptor **18** furnished the fully protected **ECD** trisaccharide (**24**, 80%), which was readily converted to the required acceptor **25** upon selective deblocking of the chloroacetyl protecting group with thiourea (97%). Following the two-step protocol described above for the preparation of **19**, the known allyl rhamnopyranoside **27**,[33] bearing a 2-*O*-chloroacetyl protecting group, was converted to the hemiacetal **28** (85%) (Scheme 4). Next, treatment of the latter with trichloroacetonitrile and a slight amount of DBU gave at best donor **20**

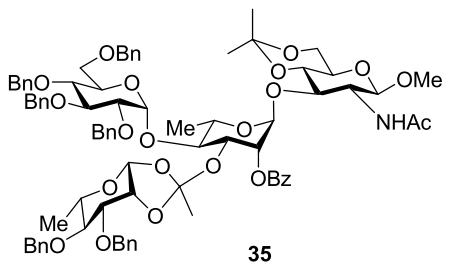


Scheme 2. Retrosynthetic analysis of pentasaccharide **2**.



Scheme 3. (a) see Ref. 28; (b) $(ClAc)_2O$, Pyridine–CH_2Cl_2, 0 °C; (c) (i) $(COD)Ir^+(P(MePh_2)_2)PF_6^-$, THF; (ii) I_2, THF/H_2O, rt; (d) CCl_3CN, DBU, CH_2Cl_2, 0 °C; (e) 4 Å molecular sieves, TMSOTf, CH_2Cl_2, −60 °C→rt; (f) thiourea, MeOH–pyridine, 65 °C.

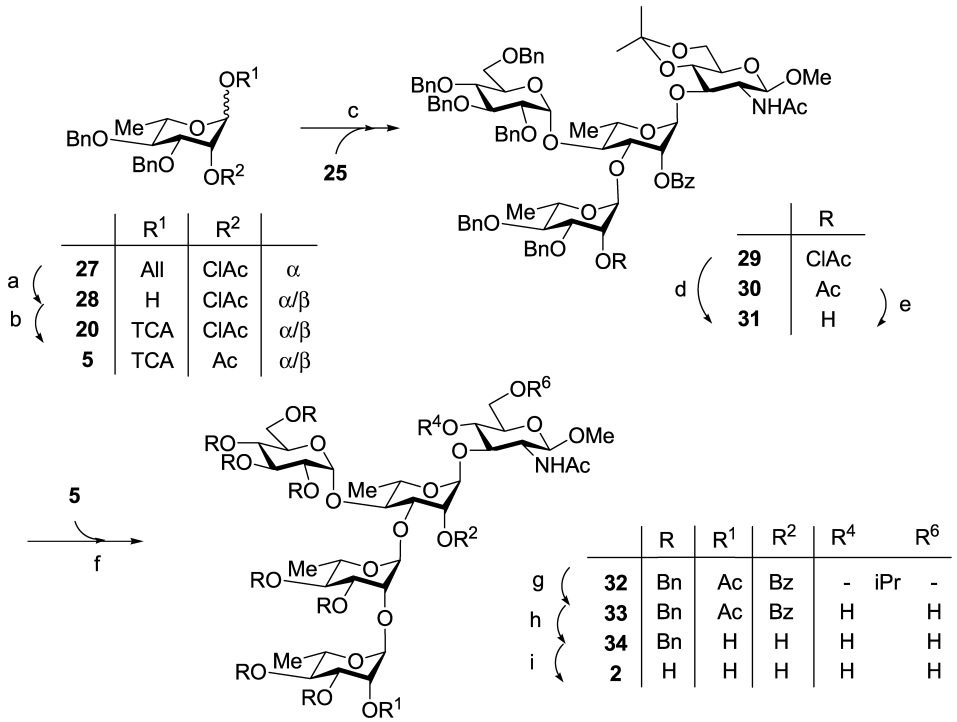
in a yield of 73%. Although the isolated yield of **20** was not better (72%), running the activation step in the presence of K_2CO_3 instead of DBU resulted in a more reproducible isolated yield of the activated donor. Glycosylation of the **ECD** acceptor **25** and the **B** donor **20** was attempted under various conditions of solvent and catalyst. Whatever the conditions, hardly separable mixtures of compounds were obtained, among which the yield of the target tetrasaccharide reached 45–50%. Running the condensation in Et_2O in the presence of TMSOTf as the promoter were the best conditions tested, although the expected tetrasaccharide **29** was often slightly contaminated with glycosylation intermediates such as the silylated **26** or the orthoester **35**, as suggested from mass spectroscopy analysis and NMR data. In fact, the nature of the latter was fully ascertained at the next step in the synthesis. Indeed, full recovery of the starting material was observed upon treatment of **35** with thiourea (Fig. 1). On the contrary, treatment of a mixture of the condensation products **29** and supposedly **26** under the same conditions led to the expected tetrasaccharide acceptor **31** and the trisaccharide acceptor **25** (not described). The β**B**-tetrasaccharide isomer could not be detected at this stage, indicating that the corresponding chloroacetylated β**B**-anomer was probably not part of the initial mixture. Formation of the starting **25** during the dechloroacetylation step was not unexpected, since loss of a trimethylsilyl group under similar treatment was observed for a model compound (not described). Although the fluoride analog corresponding to donor **20** has been used successfully in a prior report,[33] the poor yield of **29** may be, in part, associated to the sensitivity of the chloroacetyl group to the glycosylation conditions. Thus, in order to investigate the poor outcome of the condensation reaction, the donor properties of the chloroacetylated **20** were compared to that of the more common acetylated **5**. When methyl rhamnopyranoside **4** was condensed with **20** as described for the preparation of **6**, the rhamnobioside **8** was isolated in 67% yield. This result tends to suggest that indeed the acetylated **5** is a more powerful donor than **20**.



35

Figure 1.

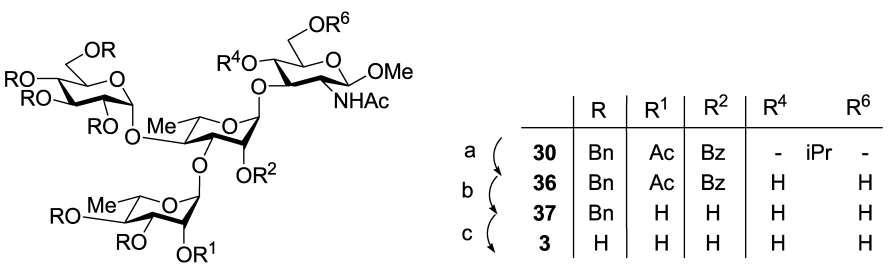
Starting from **20** and **25**, the isolated yield of the tetrasaccharide acceptor **31** was 34%, which encouraged us to reconsider the use of **5** as a precursor to residues **B** and **A** in the synthesis of **2**. Condensation of **5** and **25** in CH_2Cl_2 using TMSOTf as the promoter furnished the corresponding tetrasaccharide **30** (72%). However, even though the yield of **30** was better than that of **29**, slight contamination by the silylated side-product **26** was again apparent, outlining the somewhat poor reactivity of the **ECD** acceptor. Subsequent treatment of **30** with a 4 mM ethanolic solution of guanidine[13] resulted, as expected, in selective 2_B-*O*-deacetylation to give **31** in a satisfactory 83% yield, which outlined the interest of the method. However, previous experience in other closely related series has shown that the selectivity of the method was highly dependent on the nature of the substrate. Nevertheless, the 2-*O*-acetylated donor **5** was clearly preferred to the chloroacetate analogue **20**. Condensation of the tetrasaccharide acceptor **31** and donor **5** in the presence of TMSOTf gave the fully protected pentasaccharide **32** in a yield of 52%. TFA-mediated hydrolysis of the isopropylidene acetal followed by transesterification of the ester groups and subsequent conventional hydrogenolysis of the benzyl ethers finally gave the target pentasaccharide **2** (88%).



Scheme 4. (a) (i) $(COD)Ir^{+}(P(MePh_2)_2)PF_6^{-}$, THF; (ii) I_2, THF/H_2O, rt; (b) CCl_3CN, K_2CO_3, CH_2Cl_2, 0 °C; (c) **29** from **20**, **30** from **5**, TMSOTf, Et_2O, −60 °C→0 °C; (d) thiourea, MeOH–pyridine, 65 °C; (e) guanidine, EtOH–CH_2Cl_2, rt; (f) 4 Å molecular sieves, TMSOTf, Et_2O, −60 °C→rt; (g) 50% aq. TFA, CH_2Cl_2, 0 °C; (h) 0.5% MeONa, MeOH, 55 °C; (i) 10% Pd/C, EtOH–AcOEt, 1 N aq. HCl, rt.

Alternatively, the fully protected tetrasaccharide **30** was converted to the diol **36** by acidic removal of the isopropylidene acetal (85%), and subsequently to the corresponding tetraol **37** upon transesterification (83%). Final hydrogenolysis of the benzyl groups furnished the target tetrasaccharide **3** (71%) (Scheme 5).

Noteworthy, in the case of intermediates **33** and **36**, successful sodium methoxide-mediated transesterification of the acyl groups required heating of the reaction mixture.[31] Isolation of the esters to be cleaved may best explain the phenomenon. Indeed, the above-mentioned procedure may be seen as an alternative to the use of K_2CO_3 in dioxane/methanol[30] or that of *t*BuOK in methanol,[32] which were found appropriate in related cases. Steric hindrance may account for the poor outcome of the condensation of the **ECD** acceptor **25** with the **B** donors **20** and **5**. Interestingly, ^{13}C NMR data support this hypothesis. Although no altered signals could be seen in the ^{13}C NMR spectrum of the **ECD** acceptor **25** or in the ^{13}C NMR spectra of the fully protected precursor **24**, significant disturbance of several signals in the ^{13}C NMR spectra of the tetra- and pentasaccharides were observed repeatedly. At the protected and partially protected stage, major altered signals are those tentatively assigned to C-3_C and C-4_C. Besides, signals assigned to C-2_D, C-3_D as well as to C-1_B are significantly broader than expected. Loss of conformational flexibility at the **C** ring is not totally unexpected especially since the carbons involved are those corresponding to the branching points. Of particular interest, however, was the observation that residue **D**, the *N*-acetyl-glucosaminyl residue, was also partially constrained. Full conformational freedom of residue **D** is recovered when the **B(E)CD** and **AB(E)CD** oligosaccharides are in their free form. However, this observation does not stand true for residue **C** since characteristic broad signals for C-3_C and C-4_C as well for C-1_B and C-1_E are still present in the ^{13}C NMR spectra of compounds **2** and **3**, respectively. Overall, these observations suggest a somewhat compact organisation at the branching point of the **B(E)CD** structure. It is worth mentioning that none of these disturbed signals are seen in the ^{13}C NMR spectra of the oligosaccharides corresponding to the linear **ECDAB** fragment.



Scheme 5. (a) 50% aq. TFA, CH_2Cl_2, 0 °C; (b) 0.1% MeONa, MeOH, 55 °C; (c) 10% Pd/C, EtOH–AcOEt, 1 N aq. HCl, rt.

3. Conclusion

The synthesis of the methyl glycoside (**2**) of the repeating unit **I** of the *S. flexneri* 2a O-SP, together with that of the corresponding frame-shifted pentasaccharide **1** and tetrasaccharide **3** were described. All the methyl glycosides of the di- to pentasaccharides obtained by circular permutation of the monosaccharide residues partaking in the linear backbone of **I**, and comprising the **EC** portion, are now available in the laboratory. Their binding to a set of protective monoclonal IgG antibodies will be reported elsewhere.

4. Experimental

4.1. General methods

Melting points were determined in capillary tubes with an electrothermal apparatus and are uncorrected. Optical rotations were measured for $CHCl_3$ solutions at 25 °C, except where indicated otherwise, with a Perkin–Elmer automatic polarimeter, Model 241 MC. TLC on precoated slides of Silica Gel 60 F_{254} (Merck) was performed with solvent mixtures of appropriately adjusted polarity consisting of *A*, dichloromethane–methanol; *B*, cyclohexane–ethyl acetate, *C*, cyclohexane–acetone, *D*, water–acetonitrile, *E*, *iso*-propanol–ammonia–water; *F*, 0.01 M aq. TFA–acetonitrile. Detection was effected when applicable, with UV light, and/or by charring with orcinol (35 mM) in 4 N aq. H_2SO_4. Preparative chromatography was performed by elution from columns of Silica Gel 60 (particle size 40–63 μm). RP-HPLC (215 nm) used a Kromasil 5 μm C18 100 Å 4.6×250 mm analytical column (1 mL min^{-1}). The NMR spectra were recorded at 20 °C for solution in $CDCl_3$, unless stated otherwise, on a Brucker Avance 400 spectrometer (400 MHz for ^1H, 100 MHz for ^{13}C). External references: for solutions in $CDCl_3$, TMS (0.00 ppm for both ^1H and ^{13}C); for solutions in D_2O, dioxane (67.4 ppm for ^{13}C) and trimethylsilyl-3-propionic acid sodium salt (0.00 ppm for ^1H). Proton signal assignments were made by first-order analysis of the spectra, as well as analysis of two-dimensional $^1H-^1H$ correlation maps (COSY) and selective TOCSY experiments. Of the two magnetically non-equivalent geminal protons at C-6, the one resonating at lower field is denoted H-6a and the one at higher field is denoted H-6b. The ^{13}C NMR assignments were supported by two-dimensional $^{13}C-^1H$ correlation maps (HETCOR). Interchangeable assignments are marked with an asterisk in the listing of signal assignments. Sugar residues in oligosaccharides are serially lettered according to the lettering of the repeating unit of the O-SP and identified by a subscript in the listing of signal assignments. Low-resolution mass spectra were obtained by either chemical ionisation (CIMS) using NH_3 as the ionising gas, by electrospray mass spectrometry (ESMS), or by fast atom bombardment mass spectrometry (FABMS). HRMS were obtained by Matrix Assisted Laser Desorption Ionisation Mass Spectrometry (MALDIMS).

4.1.1. Methyl (3,4-di-*O*-benzyl-2-*O*-chloroacetyl-α-L-rhamnopyranosyl)-(1→2)-3,4-di-*O*-benzyl-α-L-rhamnopyranoside (8). Activated powered 4 Å molecular sieves (200 mg) was added to a solution of alcohol[25] **4** (60 mg, 167 μmol) and trichloroacetimidate donor **20** (113 mg, 0.2 mmol) in dry Et_2O (2 mL) and the solution was stirred at rt for 30 min then cooled to −40 °C. TMSOTf (9 μL, 50 μmol) was added and the mixture was stirred for 1 h at −30 °C, then for 2 h while the bath temperature was coming back to rt. TLC (solvent B, 4:1) showed the presence of a major product less polar than **4**. The mixture was neutralized by addition of Et_3N, and filtered on a pad of Celite. Concentration of the filtrate and column chromatography of the residue (solvent B, 4:1) gave 86 mg of **8** as a colourless oil (67%). $[\alpha]_D$ −13.6 (*c* 1.0); ^1H NMR δ 7.42–7.32 (m, 20H, Ph), 5.64 (dd, 1H, $J_{1,2}$=1.9 Hz, $J_{2,3}$=3.2 Hz, H-2_A), 5.07 (d, 1H, H-1_A), 4.98–4.93 (m, 2H, OCH_2), 4.83–4.61 (m, 6H, OCH_2), 4.64 (brs, 1H, H-1_B), 4.18 (d, 1H, *J*=15.2 Hz, CH_2Cl), 4.13 (d, 1H, OCH_2Cl), 3.90 (dd, 1H, $J_{3,4}$=9.3 Hz, H-3_B), 3.89 (m, 1H, partially overlapped, $J_{5,6}$=6.3 Hz, H-5_A), 3.73 (dq, 1H, $J_{4,5}$=9.5 Hz, $J_{5,6}$=6.2 Hz, H-5_B), 3.48 (pt, 1H, $J_{3,4}$=9.4 Hz, H-4_B), 3.45 (pt, 1H, $J_{3,4}$=$J_{4,5}$=9.4 Hz, H-4_A), 3.36 (s, 3H, OCH_3), 1.37 (d, 3H, H-6_A), 1.35 (d, 3H, H-6_B); ^{13}C NMR δ 165.5 (C=O), 137.4–126.4 (Ph), 100.2 (C-1_A), 99.2 (C-1_B), 80.4, 80.3, 80.2 (3C, C-4_A, 4_B, 3_B), 77.9 (C-3_A), 75.8, 75.7 (2C, OCH_2), 74.8 (C-2_B), 72.6, 72.5 (2C, OCH_2), 71.2 (C-2_A), 68.7 (C-5_A), 68.2 (C-5_B), 55.0 (OCH_3), 41.4 (CH_2Cl), 18.4 (2C, C-6_A, 6_B). FABMS for $C_{43}H_{49}ClNO_{10}$ (M, 760.3) *m/z* 783.3 $[M+Na]^+$. Anal. calcd for $C_{43}H_{49}ClNO_{10}$: C, 67.84; H, 6.49%. Found: C, 68.03; H, 7.02.

4.1.2. Methyl (3,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-(1→2)-3,4-di-*O*-benzyl-α-L-rhamnopyranoside (7). Activated powered 4 Å molecular sieves was added to a solution of alcohol **4** (322 mg, 0.90 mmol) and trichloroacetimidate donor[7] **5** (573 mg, 1.08 mmol) in dry Et_2O (9 mL) and the solution was stirred at rt for 30 min then cooled to −35 °C. TMSOTf (48 μL, 266 μmol) was added and the mixture was stirred for 4 h, while the bath temperature was coming back to rt. TLC (solvent B, 23:2) showed that only little starting material remained and the mixture was neutralized by addition of Et_3N, and filtered on a pad of Celite. Concentration of the filtrate and column chromatography of the residue (solvent B, 9:1) gave 647 mg of slightly contaminated **6**. The later (626 mg) was dissolved in a mixture of CH_2Cl_2 (2 mL) and MeOH (5 mL), and 1 M methanolic sodium methoxide (300 μL) was added. The mixture was stirred overnight, neutralized with Amberlite IR 120 (H^+), filtered and concentrated. Chromatography of the residue (solvent G, 89:11) gave syrupy **7** (554 mg, 91% from **4**). Analytical data were as described.[25]

4.1.3. Methyl (3,4,6-tri-*O*-acetyl-2-deoxy-2-tetrachlorophtalimido-β-D-glucopyranosyl)-(1→2)-(3,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-(1→2)-3,4-di-*O*-benzyl-α-L-rhamnopyranoside (10). A solution of disaccharide **7** (179 mg, 0.26 mmol) and trichloroacetimidate donor[8] **9** (436 mg, 0.60 mmol) in dry CH_3CN (9 mL) was stirred at rt for 30 min in the presence of activated 4 Å molecular sieves (1.2 g). Tin(II) trifluoromethanesulfonate $[Sn(OTf)_2]$ (75 mg, 180 μmol) was added and the mixture was stirred at rt for 4 h, then neutralized with Et_3N. Filtration on a pad of Celite, concentration of the filtrate and column chromatography of the residue (solvent B, 87:13) gave **10** (324 mg) as a slightly contaminated white foam (72% as

estimated from the ^{1}H NMR spectrum). An analytical sample had $[\alpha]_D$ +23.3 (*c* 1.0); ^{1}H NMR δ 7.43–7.17 (m, 20H, Ph), 5.92 (d, 1H, *J*=9.2, 10.5 Hz, H-3$_D$), 5.24 (d, 1H, $J_{1,2}$=8.4 Hz, H-1$_D$), 5.14 (dd, 1H, *J*=9.7, 9.4 Hz, H-4$_D$), 5.00 (brs, 1H, H-1$_A$), 4.79 (d, 1H, *J*=10.8 Hz, OCH$_2$), 4.65 (s, 2H, OCH$_2$), 4.55 (d, 1H, *J*=11.2 Hz, OCH$_2$), 4.53 (brs, 1H, H-1$_B$), 4.46–4.36 (m, 3H, H-2$_D$, OCH$_2$), 4.28 (d, 1H, *J*=12.4 Hz, OCH$_2$), 4.26 (d, 1H, *J*=10.6 Hz, OCH$_2$), 4.06 (dd, 1H, $J_{6a,6b}$=12.5 Hz, $J_{5,6a}$=6.8 Hz, H-6a$_D$), 3.91 (brs, 1H, H-2$_B$), 3.85–3.69 (m, 5H, H-2$_A$, 3$_B$, 3$_A$, 6b$_D$, 5$^*_A$), 3.59 (dq, 1H, $J_{4,5}$=9.4 Hz, $J_{5,6}$=6.2 Hz, H-5$^*_B$), 3.40 (m, 1H, H-5$_D$), 3.27 (s, 3H, OCH$_3$), 3.18 (m, 2H, H-4$_A$, 4$_B$), 2.03, 2.01, 1.94 (3s, 9H, C(O)CH$_3$), 1.27, 1.25 (2d, 6H, H-6$_A$, 6$_B$); ^{13}C NMR δ 170.5, 170.4, 170.3, 163.8, 162.6 (5C, C=O), 140.3–128.0 (Ph), 101.1 (C-1$_A$), 100.0 (C-1$_D$), 99.8 (C-1$_B$), 80.7 (2C, C-4$_A$, 4$_B$), 79.7 (C-2$_A$), 78.9 (C-3$_B$), 78.1 (C-3$_A$), 76.2 (C-2$_B$), 75.3, 75.2, 72.7, 71.4 (4C, OCH$_2$), 71.3 (C-5$_D$), 70.1 (C-3$_D$), 68.5 (C-5$^*_A$), 68.4 (C-4$_D$), 67.4 (C-5$^*_B$), 61.3 (C-6$_D$), 55.4 (C-2$_D$), 54.6 (OCH$_3$), 20.7, 20.6 (3C, C(O)CH$_3$), 18.0, 17.7 (2C, C-6$_A$, 6$_B$). FABMS for $C_{61}H_{63}Cl_4NO_{18}$ (M, 1237.3) *m/z* 1259.9 [M+Na]$^+$. Anal. calcd for $C_{61}H_{63}Cl_4NO_{18}\cdot H_2O$: C, 58.24; H, 5.21; N, 1.11%. Found: C, 58.21; H, 4.91; N, 1.01%.

4.1.4. Methyl (2-acetamido-2-deoxy-β-D-glucopyranosyl)-(1→2)-(3,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-(1→2)-3,4-di-*O*-benzyl-α-L-rhamnopyranoside (11). A solution of disaccharide **7** (179 mg, 0.26 mmol) and trichloroacetimidate donor **9** (436 mg, 0.60 mmol) in dry CH_3CN (9 mL) was stirred at rt for 30 min in the presence of activated 4 Å molecular sieves (1.2 g). Tin(II) trifluoromethanesulfonate [Sn(OTf)$_2$] (75 mg, 180 μmol) was added and the mixture was stirred at rt for 4 h, then neutralized with Et_3N. Filtration on a pad of Celite, concentration of the filtrate and column chromatography of the residue (solvent B, 87:13) gave **10** (324 mg) as a slightly contaminated product. The latter was solubilized in dry ethanol (13 mL) and diethylamine (200 μL, 3.0 mmol) was added and the mixture was stirred overnight at 60 °C. The mixture was cooled to rt and acetic anhydride (1.0 mL, 10.6 mmol) was added and the mixture was stirred at this temperature for 2 h. The suspension was filtered and volatiles were evaporated and co-evaporated repeatedly with toluene and cyclohexane. The crude residue was taken up in a minimum of CH_2Cl_2 and MeOH (10 mL). 1 N methanolic sodium methoxide was added until the pH was 10 and the solution was stirred overnight at rt, neutralized with IR 120 (H$^+$), filtered and concentrated. Chromatography of the residue (solvent A, 24:1) gave foamy **11** (135 mg, 51% from **7**). $[\alpha]_D$ −15.0 (*c* 1.0); ^{1}H NMR δ 7.44–7.28 (m, 20H, Ph), 8.88 (brs, 1H, NH$_D$), 5.28 (brs, 1H, H-1$_A$), 4.93–4.61 (m, 8H, OCH$_2$), 4.59 (s, 1H, $J_{1,2}$=1.3 Hz, H-1$_B$), 4.41 (d, 1H, $J_{1,2}$=8.3 Hz, H-1$_D$), 4.06 (m, 2H, H-2$_A$, 2$_B$), 4.00 (dd, 1H, $J_{2,3}$=3.3 Hz, $J_{3,4}$=9.4 Hz, H-3$_A$), 3.86 (dd, 1H, $J_{2,3}$=2.9 Hz, $J_{3,4}$=9.4 Hz, H-3$_B$), 3.79 (dq, 1H, $J_{4,5}$=9.4 Hz, $J_{5,6}$=6.2 Hz, H-5$^*_A$), 3.67 (m, 2H, H-5$^*_B$, 6a$_D$), 3.51 (m, 1H, H-2$_D$), 3.49–3.38 (m, 6H, H-6b$_D$, 4$_D$, 3$_D$, 4$_B$, 4$_A$), 3.31 (s, 3H, OCH$_3$), 3.29 (m, 1H, H-5$_D$), 1.55 (s, 3H, C(O)CH$_3$), 1.35 (d, 6H, H-6$_A$, 6$_B$); ^{13}C NMR δ 173.6 (C=O), 138.5–127.6 (Ph), 103.2 (C-1$_D$), 100.2 (C-1$_A$), 99.9 (C-1$_B$), 81.3, 80.7 (2C, C-4$_A$, 4$_B$), 79.9 (2C, C-3$_A$, 3$_B$), 79.0 (C-2$_A$), 77.2 (C-3$_D$), 75.8 (C-5$_D$), 75.7, 75.2, 74.6 (3C, OCH$_2$), 73.4 (C-2$_B$), 72.3 (OCH$_2$), 71.8 (C-4$_D$), 68.2, 67.7 (2C, C-5$_A$, 5$_B$), 62.5 (C-6$_D$), 58.9 (C-2$_D$), 54.6 (OCH$_3$), 22.3 (C(O)CH$_3$), 17.9, 17.7 (2C, C-6$_A$, 6$_B$). FABMS for $C_{49}H_{61}NO_{14}$ (M, 887.44) *m/z* 910.1 [M+Na]$^+$. Anal. calcd for $C_{49}H_{61}NO_{14}H_2O$: C, 64.96; H, 7.01; N, 1.55%. Found: C, 65.19; H, 6.83; N, 1.51%.

4.1.5. Methyl (2-acetamido-2-deoxy-4,6-*O*-isopropylidene-β-D-glucopyranosyl)-(1→2)-(3,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-(1→2)-3,4-di-*O*-benzyl-α-L-rhamnopyranoside (12). 2,2-Dimethoxypropane (4.9 mL, 39.8 mmol) and *para*-toluenesulfonic acid (18 mg, 95 μmol) were added to a solution of the triol **11** (964 mg, 1.09 mmol) in acetone (3 mL) and the mixture was stirred at rt for 1 h. Et_3N was added, and volatiles were evaporated. Column chromatography of the residue (solvent A, 99:1) gave the acceptor **12** as a white solid (969 mg, 96%) which could be crystallized from AcOEt/iPr_2O; mp 164–165 °C $[\alpha]_D$ −25.9 (*c* 1.0); ^{1}H NMR δ 7.45–7.31 (m, 20H, Ph), 6.98 (d, 1H, $J_{NH,2}$=2.4 Hz, NH), 6.37 (brs, 1H, OH), 5.07 (d, 1H, $J_{1,2}$=1.9 Hz, H-1$_A$), 4.90 (d, 1H, *J*=10.8 Hz, OCH$_2$), 4.85 (d, 1H, *J*=10.1 Hz, OCH$_2$), 4.84 (d, 1H, *J*=10.8 Hz, OCH$_2$), 4.76 (d, 1H, OCH$_2$), 4.69 (d, 1H, OCH$_2$), 4.68 (s, 2H, OCH$_2$), 4.65 (d, 1H, OCH$_2$), 4.61 (d, 1H, $J_{1,2}$=1.6 Hz, H-1$_B$), 4.48 (d, 1H, $J_{1,2}$=8.3 Hz, H-1$_D$), 4.09 (dd, 1H, H-2$_A$), 4.01 (dd, 1H, $J_{2,3}$=3.2 Hz, $J_{3,4}$=9.4 Hz, H-3$_A$), 3.91 (dd, 1H, H-2$_B$), 3.89–3.84 (m, 2H, $J_{5,6}$=6.3 Hz, $J_{4,5}$=9.4 Hz, $J_{2',3'}$=3.3 Hz, $J_{3',4'}$=9.4 Hz, H-5$_A$, 3$_B$), 3.68 (dq, partially overlapped, $J_{5,6}$=6.2 Hz, $J_{4,5}$=9.5 Hz, H-5$_B$), 3.66–3.58 (m, 5H, H-6a$_D$, 6b$_D$, 2$_D$, 3$_D$, 4$_D$), 3.44 (pt, 1H, H-4$_A$), 3.41 (pt, 1H, H-4$_B$), 3.32 (s, 3H, OCH$_3$), 3.16 (m, 1H, H-5$_D$), 1.60 (s, 3H, C(O)CH$_3$), 1.54, 1.48 (2s, 6H, C(CH$_3$)$_2$), 1.35 (d, 6H, H-6$_A$, 6$_B$); ^{13}C NMR δ 173.9 (C=O), 138.8–128.0 (Ph), 103.7 (C-1$_D$), 101.3 (C-1$_A$), 100.3 (C(CH$_3$)$_2$), 100.2 (C-1$_B$), 81.9 (C-4$_A$), 80.8 (C-4$_B$), 80.5 (C-3$_A$), 79.7 (C-3$_B$), 79.4 (C-2$_A$), 76.2 (OCH$_2$), 76.0 (C-2$_B$), 75.6, 75.1 (2C, OCH$_2$), 74.7 (C-4$_D$), 74.4 (C-3$_D$), 72.6 (OCH$_2$), 68.6 (C-5$_A$), 68.0, 67.9 (2C, C-5$_B$, 5$_D$), 62.2 (C-6$_D$), 60.6 (C-2$_D$), 55.1 (OCH$_3$), 29.5 (C(CH$_3$)$_2$), 22.7 (C(O)CH$_3$), 19.4 (C(CH$_3$)$_2$), 18.5, 18.2 (2C, C-6$_A$, 6$_B$). FAB-MS for $C_{52}H_{65}NO_{14}$ (M, 927.44) *m/z* 950.1 [M+Na]$^+$. Anal. calcd for $C_{52}H_{65}NO_{14}$: C, 67.30; H, 7.06; N, 1.51%. Found: C, 67.12; H, 6.98; N, 1.44%.

4.1.6. Methyl (2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-(2,3-di-*O*-benzoyl-α-L-rhamnopyranosyl)-(1→3)-(2-acetamido-2-deoxy-4,6-*O*-isopropylidene-β-D-glucopyranosyl)-(1→2)-(3,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-(1→2)-3,4-di-*O*-benzyl-α-L-rhamnopyranoside (15). Activated powdered 4 Å molecular sieves were added to a solution of the trisaccharide acceptor **12** (202 mg, 0.22 mmol) and the disaccharide donor **14**[19] (263 mg, 0.25 mmol) in anhydrous CH_2Cl_2 (5 mL) and the suspension was stirred for 30 min at −15 °C. TfOH (7 μL, 34 μmol) was added and the mixture was stirred for 2 h while the bath temperature was slowly coming back to 10 °C. TLC (solvent D, 49:1) showed that no **12** remained. Et_3N was added and after 30 min, the suspension was filtered through a pad of Celite. Concentration of the filtrate and chromatography of the residue (solvent *B*, 9:1→17:5) gave the fully protected pentasaccharide **15** (330 mg, 84%) as a white foam; $[\alpha]_D$ +63.3 (*c* 1.0); ^{1}H NMR δ 8.07–6.96 (m, 50H, Ph), 5.82 (d, 1H, $J_{NH,2}$=7.4 Hz, NH), 5.63 (dd, 1H, $J_{2,3}$=3.5 Hz, $J_{3,4}$=9.5 Hz, H-3$_C$), 5.43 (dd, 1H, $J_{1,2}$=1.6 Hz,

H-2_C), 5.09 (brs, 1H, H-1_A), 5.02 (d, 1H, $J_{1,2}$=3.4 Hz, H-1_E), 4.99 (d, 1H, $J_{1,2}$=8.3 Hz, H-1_D), 4.95 (d, 1H, $J_{1,2}$=1.1 Hz, H-1_C), 4.94–4.63 (m, 13H, OCH_2), 4.63 (s, 1H, H-1_B), 4.37 (d, 1H, J=11.0 Hz, OCH_2), 4.29 (dq, 1H, $J_{4,5}$=9.5 Hz, $J_{5,6}$=6.2 Hz, H-5_C), 4.25 (d, 1H, J=9.5 Hz, OCH_2), 4.23 (pt, 1H, $J_{3,4}$=$J_{4,5}$=9.5 Hz, H-3_D), 4.01 (m, 1H, H-2_A), 3.97–3.86 (m, 5H, H-3_A, 2_B, 3_E, 4_C, OCH_2), 3.82 (m, 1H, H-3_B, 5_A), 3.71–3.57 (m, 6H, H-5_D, 4_E, 5_B, 4_D, $6a_D$, $6b_D$), 3.54–3.41 (m, 3H, H-2_E, 4_A, 2_D) 3.38–3.31 (m, 2H, H-4_B, $6a_E$), 3.31 (s, 3H, OCH_3), 3.17 (m, 1H, H-5_D), 3.08 (d, 1H, $J_{6a,6b}$=10.1 Hz, H-$6b_E$), 1.84 (s, 3H, C(O)CH_3), 1.46 (s, 3H, C(CH_3)$_2$), 1.45 (d, 3H, $J_{5,6}$=5.9 Hz, H-6_C), 1.35 (m, 6H, $J_{5,6}$=5.9 Hz, H-6_A, C(CH_3)$_2$), 1.31 (d, 3H, $J_{5,6}$=6.2 Hz, H-6_B); ^{13}C NMR δ 171.7, 165.9, 165.8 (3C, C=O), 138.9–127.9 (Ph), 102.3 (C-1_D, J=167 Hz), 101.5 (C-1_A, J=170 Hz), 100.3 (C-1_B, J=170 Hz), 99.8 (C(CH_3)$_2$), 99.6 (C-1_E, J=172 Hz), 98.2 (C-1_C, J=172 Hz), 82.0 (C-3_E), 81.2, 80.9, 80.7 (3C, C-4_A, 4_B, 2_E), 80.0, 79.7, 79.3 (3C, C-3_B, 3_A, 4_C), 78.1, 77.8, 77.4 (3C, C-2_A, 4_E, 3_D), 75.9, 75.8, 75.6 (3C, OCH_2), 75.5 (C-2_B), 75.0, 74.4, 73.7 (3C, OCH_2), 73.2 (2C, C-4_D, OCH_2), 72.2 (OCH_2), 71.7, 71.6 (3C, C-2_C, 3_C, 5_E), 68.8 (C-5_B), 68.0 (C-6_E), 68.0 (2C, C-5_A, 5_B), 67.6 (C-5_D), 62.5 (C-6_D), 58.9 (C-2_D), 55.0 (OCH_3), 29.5 (C(CH_3)$_2$), 23.8 (C(O)CH_3), 19.8 (C(CH_3)$_2$), 18.6 (C-6_C), 18.5 (C-6_A), 18.3 (C-6_B). FAB-MS for $C_{106}H_{117}NO_{25}$ (M, 1803.79) *m/z* 1826.4 $[M+H]^+$. Anal. calcd for $C_{106}H_{117}NO_{25}\cdot H_2O$: C, 69.83; H, 6.58; N, 0.77%. Found: C, 69.86; H, 6.33; N, 0.71%.

4.1.7. Methyl (2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-(2,3-di-*O*-benzoyl-α-L-rhamnopyranosyl)-(1→3)-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-(1→2)-(3,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-(1→2)-3,4-di-*O*-benzyl-α-L-rhamnopyranoside (16). Aq. TFA (750 μL) was added at 0 °C to a solution of the fully protected **15** (588 mg, 326 μmol) in CH_2Cl_2 (6.7 mL) and the mixture was stirred at this temperature for 1 h TLC (solvent *B*, 1.5:1) showed that no **15** remained. Volatiles were evaporated by repeated addition of toluene. Chromatography of the residue (solvent *B*, 4:1→1:1) gave **16** (544 mg, 95%) as a white foam; $[\alpha]_D$ +58.8 (*c* 1.0); ^{1}H NMR δ 8.06–7.06 (m, 50H, Ph), 5.82 (d, 1H, $J_{NH,2}$=7.1 Hz, NH), 5.65 (dd, 1H, $J_{2,3}$=3.8 Hz, $J_{3,4}$=9.0 Hz, H-3_C), 5.53 (m, 1H, H-2_C), 5.34 (brs, 1H, H-1_A), 5.04 (d, 1H, $J_{1,2}$=8.3 Hz, H-1_D), 5.00 (m, 2H, H-1_C, 1_E), 4.97–4.63 (m, 13H, OCH_2), 4.48 (brs, 1H, H-1_B), 4.40 (d, 1H, J=8.4 Hz, OCH_2), 4.29 (d, 1H, J=8.0 Hz, OCH_2), 4.28–4.21 (m, 2H, H-3_D, 5_C), 4.10 (m, 1H, H-2_B), 4.04 (m, 1H, H-2_A), 3.99 (d, 1H, OCH_2), 3.95–3.89 (m, 3H, H-3_A, 3_E, 4_C), 3.87 (dd, 1H, $J_{2,3}$=2.7 Hz, $J_{3,4}$=9.7 Hz, H-3_B), 3.81–3.64 (m, 5H, H-5_E, 5_A, $6a_D$, 4_E, 5_B), 3.54 (dd, 1H, $J_{1,2}$=3.2 Hz, $J_{2,3}$=9.7 Hz, H-2_E), 3.51 (pt, 1H, $J_{3,4}$=$J_{4,5}$=9.5 Hz, H-4_A), 3.45–3.37 (m, 4H, H-4_B, 4_D, $6a_E$, 2_D), 3.33 (m, 5H, H-5_D, $6b_D$, OCH_3), 3.12 (d, 1H, $J_{6a,6b}$=10.6 Hz, H-$6b_E$), 2.28 (brs, 1H, OH),1.97 (brs, 1H, OH), 1.84 (s, 3H, C(O)CH_3), 1.54 (d, 3H, $J_{5,6}$=6.1 Hz, H-6_C), 1.37 (m, 6H, H-6_B, 6_A); ^{13}C NMR δ 171.5, 165.8, 165.6 (3C, C=O), 138.8–127.9 (Ph), 101.6 (C-1_D), 100.8 (C-1_A), 100.5 (C-1_B), 100.1 (C-1_E^*), 99.9 (C-1_C^*), 84.9 (C-3_D), 82.1 (C-3_E), 80.9, 80.7, 80.6, 80.5 (4C, C-4_B, 3_B, 4_A, 2_E), 79.7 (C-4_C), 79.3 (C-3_A), 77.8 (2C, C-2_A, 4_E), 76.0, 75.9 (2C, OCH_2), 75.8 (C-5_D), 75.6, 75.1, 74.6, 73.7, 73.1 (5C, OCH_2), 72.8 (C-2_B), 72.6 (OCH_2), 71.8 (C-5_E), 71.6 (C-4_D), 71.3 (C-3_C), 71.1 (C-2_C), 69.4 (C-5_C), 68.8 (C-5_A), 68.3 (C-5_B), 68.1 (C-6_E), 63.0 (C-6_D), 57.6 (C-2_D), 55.0 (OCH_3), 23.8 (C(O)CH_3), 18.8 (C-6_C), 18.6, 18.5 (2C, C-6_A, 6_B). FAB-MS for $C_{103}H_{113}NO_{25}$ (M, 1763.76) *m/z* 1786.2 $[M+H]^+$. Anal. calcd for $C_{103}H_{113}NO_{25}\cdot 2H_2O$: C, 68.69; H, 6.55; N, 0.78%. Found: C, 68.74; H, 6.45; N, 0.65%.

4.1.8. Methyl (2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-α-L-rhamnopyranosyl-(1→3)-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-(1→2)-(3,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-(1→2)-3,4-di-*O*-benzyl-α-L-rhamnopyranoside (17). 1 M Methanolic sodium methoxide was added to a solution of **16** (277 mg, 157 μmol) in a 1:1 mixture of CH_2Cl_2 and MeOH (6 mL) until the pH was 10. The mixture was stirred overnight at rt and neutralized with Amberlite IR-120 (H^+). The crude material was chromatographed (solvent *A*, 49:1) to give **17** (211 mg, 86%) as a white foam; $[\alpha]_D$ +23.8 (*c* 1.0); ^{1}H NMR δ 7.33–7.16 (m, 40H, Ph), 5.34 (d, 1H, $J_{NH,2}$=7.6 Hz, NH), 5.18 (brs, 1H, H-1_A), 4.79 (d, partially overlapped, 1H, H-1_E), 4.67 (brs, 1H, H-1_C), 4.50 (d, partially overlapped, 1H, H-1_D), 4.49 (brs, 1H, H-1_B), 4.88–4.33 (m, 16H, OCH_2), 3.98–3.81 (m, 6H, H-2_A, 2_B, 5_E, 3_A, 3_E, 5_B^*), 3.77–3.70 (m, 3H, H-3_B, 2_C, 5_C^*), 3.65 (dq, 1H, $J_{4,5}$=9.4 Hz, $J_{5,6}$=6.2 Hz, H-5_A^*), 3.62–3.51 (m, 4H, H-2_D, $6a_D$, $6a_E$, $6b_E$), 3.48–3.27 (m, 7H, H-2_E, 4_E, 3_D, 4_A, 4_B, 3_C, 4_C), 3.23–3.12 (m, 6H, H-4_D, $6b_D$, 5_D, OCH_3), 2.76 (brs, 1H, OH), 1.72 (brs, 3H, OH), 1.65 (s, 3H, NHAc), 1.32, 1.25 (2d, 9H, H-6_C, 6_B, 6_A); ^{13}C NMR δ 170.6 (C=O), 138.5–128.0 (Ph), 103.0 (C-1_D), 101.8 (C-1_C), 100.7 (C-1_A), 100.4 (C-1_B), 99.6 (C-1_E), 87.3 (C-3_D), 85.0 (C-4_C^*), 82.0 (C-3_E), 81.2, 80.7, 80.5, 80.2, 79.7, 78.1, 77.9 (7C, C-2_B, 3_A, 3_B, 4_A, 4_B, 2_E, 4_E), 76.2 (C-5_D), 76.1, 75.9, 75.6, 75.4, 74.0, 73.9, 73.6 (7C, OCH_2), 73.0 (C-2_A), 72.8 (OCH_2), 71.7, 71.2, 71.1, 69.8 (4C, C-4_D, 5_E, 2_C, 3_C), 68.8, 68.2 (3C, C-5_A, 5_B, 5_C), 63.1 (C-6_D), 55.6 (C-2_D), 55.0 (OCH_3), 23.7 (C(O)CH_3), 18.6, 18.3, 18.1 (3C, C-6_A, 6_B, 6_C). FAB-MS for $C_{89}H_{105}NO_{23}$ (M, 1555.71) *m/z* 1578.2 $[M+H]^+$. Anal. calcd for $C_{89}H_{105}NO_{23}$: C, 68.66; H, 6.80; N, 0.90%. Found: C, 68.41; H, 6.78; N, 0.61%.

4.1.9. Methyl α-D-glucopyranosyl-(1→4)-α-L-rhamnopyranosyl-(1→3)-2-acetamido-2-deoxy-β-D-glucopyranosyl-(1→2)-α-L-rhamnopyranosyl-(1→2)-α-L-rhamnopyranoside (1). The benzylated tetrasaccharide **17** (352 mg, 226 μmol) was dissolved in a mixture of ethanol (14 mL) and AcOH (1 mL), treated with 10% Pd–C catalyst (200 mg), and the suspension was stirred for 5 days at rt. TLC (solvent A, 1:1) showed that the starting material had been transformed into a more polar product. The suspension was filtered on a pad of Celite. The filtrate was concentrated and co-evaporated repeatedly with cyclohexane. Reverse phase chromatography of the residue (solvent D, 100:0→49:1), followed by freeze-drying, gave the target tetrasaccharide **1** as an amorphous powder (153 mg, 81%). RP-HPLC gave a single product eluting at rt: 15.21 min (solvent F, 1:0→80:20 over 20 min); $[\alpha]_D$ −3.2 (*c* 1.0, methanol); ^{1}H NMR (D_2O) δ 5.08 (d, 1H, $J_{1,2}$=1.2 Hz, H-1_A), 4.97 (d, 1H, $J_{1,2}$=3.9 Hz, H-1_E), 4.79 (d, 1H, $J_{1,2}$=1.3 Hz, H-1_C), 4.69 (m, 2H, H-1_B, 1_D), 4.07 (dd, 1H, $J_{2,3}$=3.3 Hz, H-2_A), 4.02 (dq, 1H, $J_{4,5}$=9.3 Hz, $J_{5,6}$=6.2 Hz, H-5_C), 3.93 (m, 1H, H-5_E), 3.86 (m, 2H, H-2_B, 3_A), 3.82–3.73 (m, 7H, H-3_C, 2_D, $6a_E$, $6b_E$, 3_B, 2_C, $6a_D$), 3.70–3.59 (m, 4H, H-5_A, 3_E, $6b_D$, 5_B), 3.56 (pt, 1H, $J_{3,4}$=$J_{4,5}$=9.4 Hz,

H-3_D), 3.49 (dd, 1H, $J_{2,3}$=9.6 Hz, H-2_E), 3.46–3.38 (m, 5H, H-4_C, 4_B, 4_D, 5_D, 4_E), 3.32 (s, 3H, OCH_3), 3.24 (pt, 1H, $J_{3,4}$=$J_{4,5}$=9.6 Hz, H-4_A), 2.00 (s, 3H, C(O)CH_3), 1.25 (d, 3H, partially overlapped, H-6_C), 1.23 (d, 3H, partially overlapped, H-6_B), 1.18 (d, 3H, $J_{5,6}$=6.2 Hz, H-6_A); ^{13}C NMR (D_2O) δ 175.0 (C=O), 102.3 (C-1_D, J=162 Hz), 101.5 (C-1_C, J=170 Hz), 101.3 (C-1_A, J=173 Hz), 100.0 (C-1_E, J=170 Hz), 99.9 (C-1_B, J=172 Hz), 81.9 (C-3_D), 81.4 (C-4_C), 79.2 (C-2_A), 79.0 (C-2_B), 76.2, 73.1, 72.6, 72.2, 72.0, 71.4, 70.4, 70.0, 69.8, 69.7, 69.6, 69.3, 68.9, 68.7 (14C, 3_A, 4_A, 5_A, 3_B, 4_B, 5_B, 2_C, 3_C, 4_D, 5_D, 2_E, 3_E, 4_E, 5_E), 68.4 (C-5_C), 60.5 (2C, C-6_D, 6_E), 56.0 (C-2_D), 55.3 (OCH_3), 22.6 (C(O)CH_3), 17.0 (3C, C-6_A, 6_B, 6_C). HRMS (MALDI) calcd for $C_{27}H_{47}NO_{19}$ +Na: 858.3214. Found: 858.3206.

4.1.10. 3,4-Di-*O*-benzyl-2-*O*-chloroacetyl-α/β-L-rhamnopyranose (28). 1,5-Cyclooctadiene-bis(methyldiphenylphosphine)iridium hexafluorophosphate (Ir(I), 25 mg) was dissolved in dry THF (5 mL) and the resulting red solution was degassed in an argon stream. Hydrogen was then bubbled through the solution, causing the colour to change to yellow. The solution was then degassed again in an argon stream. A solution of rhamnopyranoside[33] **27** (3.28 g, 7.12 mmol) in THF (30 mL) was degassed and added. The mixture was stirred overnight at rt, and a solution of iodine (3.6 g, 14.2 mmol) in a mixture of THF (70 mL) and water (20 mL) was added. The mixture was stirred at rt for 1 h, then concentrated. The residue was taken up in CH_2Cl_2 and washed twice with 5% aq. $NaHSO_4$. The organic phase was dried and concentrated. The residue was purified by column chromatography (solvent B, 9:1) to give **28** (2.53 g, 85%). ^{1}H NMR δ 7.40–7.28 (m, 10H, Ph), 5.57 (brd, 0.2H, H-2β), 5.45 (dd, 0.8H, $J_{1,2}$=2.0 Hz, H-2α), 5.13 (brd, 0.8H, H-1α), 4.92 (d, 1H, J=10.9 Hz, OCH_2α, OCH_2β), 4.79 (d, 0.2H, J=11.2 Hz, OCH_2β), 4.74 (d, 1H, J=11.2 Hz, OCH_2α, H-1β), 4.65 (d, 0.8H, OCH_2α), 4.64 (d, 0.2H, OCH_2β), 4.58 (d, 0.8H, OCH_2α), 4.54 (d, 0.2H, OCH_2β), 4.30 (d, 0.2H, J=15.1 Hz, CH_2Clβ), 4.26 (d, 0.2H, CH_2Clβ), 4.20 (s, 1.6H, CH_2Clα), 4.08 (dd, 0.8H, $J_{2,3}$=3.3 Hz, $J_{3,4}$=9.6 Hz, H-3α), 4.04 (dq, 0.8H, $J_{4,5}$=9.5 Hz, H-5α), 3.66 (dd, 0.2H, $J_{2,3}$=3.2 Hz, $J_{3,4}$=8.7 Hz, H-3β), 3.44 (pt, 2H, H-4α, 5β, OH-1α, 1β), 3.38 (pt, 0.2H, $J_{4,5}$=9.5 Hz, H-4β), 1.37 (d, 0.6H, $J_{5,6}$=5.7 Hz, H-6β), 1.34 (d, 2.4H, $J_{5,6}$=6.2 Hz, H-6α); ^{13}C NMR δ 167.8 (C=Oβ), 167.4 (C=Oα), 138.6–128.2 (Ph), 93.0 (C-1β), 92.4 (C-1α), 80.3 (C-4α), 80.2 (C-3β), 79.6 (C-4β), 77.8(C-3α), 75.9 (OCH_2β), 75.8 (OCH_2α), 72.5 (OCH_2α), 72.3 (0.4C, C-5β, OCH_2β), 71.9 (C-2-β), 71.7 (C-2α), 68.2(C-5α), 41.3 (CH_2Clα, CH_2Clβ), 18.3 (C-6α, 6β); FAB-MS for $C_{22}H_{25}ClO_6$ (M, 420.5) *m/z* 443.1 $[M+Na]^+$. Anal. calcd for $C_{22}H_{25}ClO_6$: C, 62.78; H, 5.94%. Found: C, 62.92; H, 6.11%.

4.1.11. 3,4-Di-*O*-benzyl-2-*O*-chloroacetyl-α/β-L-rhamnopyranosyl trichloroacetimidate (20). (a) The hemiacetal **28** (700 mg, 1.66 mmol) was dissolved in CH_2Cl_2 (6 mL) and the solution was cooled to 0 °C. Trichloroacetonitrile (1.7 mL) and DBU (26 μL) were added. The mixture was stirred at rt for 2 h. Toluene was added, and co-evaporated twice from the residue. The crude material was purified by flash chromatography (solvent *B* 4:1+0.1% Et_3N) to give **20** as a white foam (687 mg, 73%, α/β: 4:1).

(b) The hemiacetal **28** (858 mg, 2.04 mmol) was dissolved in CH_2Cl_2 (11 mL) and freshly activated K_2CO_3 (1.1 g, 8.0 mmol) was added. The suspension was cooled to 0 °C, and trichloroacetonitrile (1.0 mL) was added. The mixture was stirred vigorously at rt for 5 h. The suspension was filtered on a pad of Celite, and concentrated. The crude material was purified by flash chromatography (solvent *B*, 9:1+0.1% Et_3N) to give **20** as a white foam (840 mg, 72%, α/β: 9:1 from the ^{1}H NMR spectrum). ^{1}H NMR (α-anomer) δ 8.71 (s, 1H, NH), 7.40–7.30 (m, 10H, Ph), 6.24 (d, 1H, $J_{1,2}$=1.8 Hz, H-1), 5.57 (dd, 1H, H-2), 4.94 (d, 1H, J=10.8 Hz, OCH_2), 4.76 (d, 1H, J=11.2 Hz, OCH_2), 4.67 (d, 1H, OCH_2), 4.62 (d, 1H, OCH_2), 4.22 (s, 2H, CH_2Cl), 4.04 (dd, 1H, $J_{2,3}$=3.2 Hz, H-3), 3.99 (dq, 1H, $J_{4,5}$=9.6 Hz, H-5), 3.53 (pt, 1H, H-4), 1.37 (d, 3H, $J_{5,6}$=6.2 Hz, H-6); ^{13}C NMR (α-anomer) δ 166.9 (C=O), 160.4 (C=NH), 138.4–128.3 (Ph), 95.2 (C-1), 91.1 (CCl_3), 79.5 (C-4), 77.6 (C-3), 76.1, 72.9 (2C, OCH_2), 71.2 (C-5), 69.8 (C-2), 41.1 (CH_2Cl), 18.3 (C-6).

4.1.12. Allyl (2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-2-*O*-benzoyl-3-*O*-chloroacetyl-α-L-rhamnopyranoside (22). To a solution of the known **21**[28] (7.10 g, 8.55 mmol) in a mixture of CH_2Cl_2 (40 mL) and pyridine (5 mL) at 0 °C was added chloroacetic anhydride (3.65 g, 21.3 mmol), and the mixture was stirred at this temperature for 2 h. TLC (solvent C, 9:1) showed the complete disappearance of the starting material. MeOH (10 mL) was added, and after 30 min, volatiles were evaporated. Column chromatography (solvent *B*, 1:0→4:1) of the crude yellow oil afforded **22** as a colourless foam (7.34 g, 95%). $[\alpha]_D$ +47.5 (*c* 1.0); ^{1}H NMR δ 8.12–7.13 (m, 25H, Ph), 5.95 (m, 1H, CH=), 5.50–5.42 (m, 2H, $J_{2,3}$=3.6 Hz, H-2_C, 3_C), 5.37 (m, 1H, =CH_2), 5.28 (m, 1H, =CH_2), 4.96 (d, 1H, J=11.0 Hz, OCH_2), 4.93 (d, 1H, $J_{1,2}$=1.5 Hz, H-1_C), 4.90 (d, 1H, $J_{1,2}$=3.3 Hz, H-1_E), 4.87–4.81 (m, 3H, OCH_2), 4.67 (d, 1H, J=12.1 Hz, OCH_2), 4.64 (d, 1H, J=12.8 Hz, OCH_2), 4.47 (d, 1H, J=10.8 Hz, OCH_2), 4.43 (d, 1H, J=12.0 Hz, OCH_2), 4.25 (m, 2H, OCH_2), 4.09 (d, 1H, J=15.5 Hz, CH_2Cl), 3.99–3.93 (m, 3H, CH_2Cl, H-5_C, 3_C), 3.84 (m, 1H, H-5_E), 3.78–3.74 (m, 2H, H-$6a_E$, 4_E), 3.70 (pt, 1H, $J_{4,5}$=$J_{3,4}$=9.3 Hz, H-4_C), 3.58–3.54 (m, 2H, H-$6b_E$, 2_E), 1.50 (d, 3H, $J_{5,6}$=6.2 Hz, H-6_C); ^{13}C NMR δ 167.0, 166.0 (2C, C=O), 139.1–128.0 (Ph, All), 118.5 (All), 99.5 (C-1_E), 96.8 (C-1_C), 81.9 (C-3_E), 81.0 (C-2_E), 79.7 (C-4_C), 77.7 (C-4_E), 76.0, 75.4, 74.1, 73.8 (4C, OCH_2), 73.5 (C-3_C), 71.8 (C-5_E), 70.9 (C-2_C), 68.8 (OCH_2), 68.1 (C-6_E), 67.7 (C-5_C), 41.5 (CH_2Cl), 18.6 (C-6_C); FAB-MS for $C_{52}H_{55}O_{12}$ (M, 906.5) *m/z* 929.3 $[M+Na]^+$. Anal. calcd for $C_{52}H_{55}ClO_{12}$: C, 68.83; H, 6.11%. Found: C, 68.74; H, 6.19%.

4.1.13. (2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-2-*O*-benzoyl-3-*O*-chloroacetyl-α/β-L-rhamnopyranose (23). A solution of **22** (7.21 g, 7.95 mmol) in THF (80 mL) containing activated iridium complex (60 mg) was treated as described for the preparation of **28**. The mixture was stirred at rt for 3 h, at which point a solution of iodine (4.0 g, 15.7 mmol) in a mixture of THF (90 mL) and water (24 mL) was added. The mixture was stirred at rt for 30 min, then concentrated. The residue was taken up in CH_2Cl_2 and washed twice with 5% aq. $NaHSO_4$, then with brine. The organic phase was dried and concentrated. The residue was purified by column chromatography (solvent *B*, 4:1) to give

23 (6.7 g, 97%) as a slightly yellow foam. ^{1}H NMR δ 8.10–7.09 (m, 25H, Ph), 5.47 (dd, 1H, $J_{2,3}$=3.5 Hz, $J_{3,4}$=9.3 Hz, H-3$_C$), 5.41 (brs, 1H, H-2$_C$), 5.03 (brs, 1H, H-1$_C$), 4.94 (d, 1H, J=10.9 Hz, OCH$_2$), 4.87 (d, 1H, $J_{1,2}$=3.4 Hz, H-1$_E$), 4.85 (d, 1H, OCH$_2$), 4.80 (m, 2H, OCH$_2$), 4.64 (m, 2H, OCH$_2$), 4.45 (d, 1H, J=10.7 Hz, OCH$_2$), 4.41 (d, 1H, J=12.1 Hz, OCH$_2$), 4.16 (dq, 1H, $J_{4,5}$=9.3 Hz, H-5$_C$), 4.09 (d, 1H, J=15.6 Hz, CH$_2$Cl), 3.96 (d, 1H, CH$_2$Cl), 3.93 (pt, 1H, H-3$_E$), 3.83 (m, 1H, H-5$_E$), 3.77–3.68 (m, 2H, H-4$_E$, 6a$_E$), 3.65 (pt, 1H, H-4$_C$), 3.54 (m, 2H, H-6b$_E$, 2$_E$), 1.48 (d, 3H, $J_{5,6}$=6.2 Hz, H-6$_C$); ^{13}C NMR δ 167.0, 166.0 (2C, C=O), 139.1–127.9 (Ph), 99.5 (C-1$_E$), 92.3 (C-1$_C$), 81.9 (C-3$_E$), 81.0 (C-2$_E$), 79.9 (C-4$_C$), 77.6 (C-4$_E$), 76.0, 75.6, 74.2, 74.1 (4C, OCH$_2$), 72.1 (C-3$_C$), 71.7 (C-4$_E$), 71.1 (C-2$_C$), 68.0 (C-6$_E$), 67.5 (C-5$_C$), 41.5 (CH$_2$Cl), 18.9 (C-6$_C$); FAB-MS for $C_{49}H_{51}ClO_{12}$ (M, 866.3) *m/z* 889.3 [M+Na]$^+$. Anal. calcd for $C_{49}H_{51}ClO_{12}$: C, 67.85; H, 5.93%. Found: C, 67.72; H, 6.00%.

4.1.14. (2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-2-*O*-benzoyl-3-*O*-chloroacetyl-α-L-rhamnopyranosyl trichloroacetimidate (19). Trichloroacetonitrile (1.1 mL, 10.9 mmol) and DBU (17 μL) were added to a solution of the hemiacetal **23** (950 mg, 1.09 mmol) in dry CH_2Cl_2 (8 mL), and the mixture was stirred at 0 °C for 1.5 h. Toluene was added, and volatiles were evaporated. The residue was purified by flash chromatography (solvent *B*, 3:2 containing 0.1% Et_3N) to give **19** (930 mg, 84%) as a colourless foam. Further elution gave some remaining starting material **23** (136 mg, 14%). $[\alpha]_D$ +39.3 (*c* 1.0); ^{1}H NMR δ 8.76 (s, 1H, NH), 8.12–7.17 (m, 25H, Ph), 6.34 (d, 1H, $J_{1,2}$=1.5 Hz, H-1$_C$), 5.67 (dd, 1H, H-2$_C$), 5.54 (dd, 1H, $J_{2,3}$=3.4 Hz, $J_{3,4}$=8.8 Hz, H-3$_C$), 4.98 (d, 1H, OCH$_2$), 4.88 (d, 1H, $J_{1,2}$=3.4 Hz, H-1$_E$), 4.84 (d, 1H, J=11.1 Hz, OCH$_2$), 4.82 (d, 1H, J=11.2 Hz, OCH$_2$), 4.65 (d, 1H, OCH$_2$), 4.62 (d, 1H, OCH$_2$), 4.44 (d, 1H, J=11.4 Hz, OCH$_2$), 4.41 (d, 1H, J=11.8 Hz, OCH$_2$), 4.14 (dq, 1H, $J_{4,5}$=9.5 Hz, H-5$_C$), 4.11 (d, 1H, J=15.5 Hz, CH$_2$Cl), 3.98 (d, 1H, CH$_2$Cl), 3.94 (pt, 1H, H-3$_E$), 3.83–3.71 (m, 4H, H-5$_E$, 6a$_E$, 4$_E$, 4$_C$), 3.56–3.51 (m, 2H, H-6b$_E$, 2$_E$), 1.51 (d, 3H, $J_{5,6}$=6.2 Hz, H-6$_C$); ^{13}C NMR δ 167.1, 165.7, 160.6 (3C, C=), 139.0–127.9 (Ph), 99.9 (C-1$_E$), 95.2 (C-1$_C$), 82.1 (C-3$_E$), 80.9 (C-2$_E$), 79.0 (C-4$_C$), 77.6 (C-4$_E$), 76.0, 75.6, 74.2, 73.8 (4C, OCH$_2$), 73.0 (C-3$_C$), 71.9 (C-5$_E$), 70.7 (C-5$_C$), 69.2 (C-2$_C$), 68.0 (C-6$_E$), 67.7 (C-5$_C$), 41.4 (CH$_2$Cl), 18.6 (C-6$_C$). Anal. calcd for $C_{51}H_{51}Cl_4NO_{12}$: C, 60.54; H, 5.08; N, 1.38%. Found: C, 60.49; H, 5.01; N, 1.34%.

4.1.15. Methyl (2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-(2-*O*-benzoyl-3-*O*-chloroacetyl-α-L-rhamnopyranosyl)-(1→3)-2-acetamido-2-deoxy-4,6-*O*-isopropylidene-β-D-glucopyranoside (24). The acceptor[19] **18** (500 mg, 1.82 mmol) was dissolved in CH_2Cl_2 (5.5 mL) and 4 Å molecular sieves (300 mg) were added. The mixture was cooled to −60 °C and stirred for 15 min. TMSOTf (35 μL, mmol) and a solution of the disaccharide donor **19** (2.39 g, 2.36 mmol) in CH_2Cl_2 (7.5 mL) were added. The mixture was stirred for 45 min while the cooling bath was coming back to rt, and for more 3 h at rt. The mixture was then heated at 65 °C for 1 h 30 min. Et_3N was added and the mixture was stirred at rt for 20 min, then diluted with CH_2Cl_2 and filtered through a pad of Celite. The filtrate was concentrated and purified by column chromatography (solvent *B*, 85:15→1:1) to give **24** (1.64 g, 80%) as a white powder. $[\alpha]_D$ +55.1 (*c* 1.0); ^{1}H NMR δ 8.06–6.93 (m, 25H, Ph), 6.18 (d, 1H, $J_{NH,2}$=7.3 Hz, NH$_D$), 5.40 (dd, 1H, $J_{2,3}$=3.5 Hz, H-3$_C$), 5.38 (brs, 1H, H-2$_C$), 4.98 (d, 1H, $J_{1,2}$=8.3 Hz, H-1$_D$), 4.94 (brs, 1H, H-1$_C$), 4.94 (d, 1H, OCH$_2$), 4.93 (d, 1H, $J_{1,2}$=3.4 Hz, H-1$_E$), 4.83 (d, 2H, J=10.7 Hz, OCH$_2$), 4.81 (d, 1H, J=10.6 Hz, OCH$_2$), 4.67 (d, 1H, J=11.7 Hz, OCH$_2$), 4.62 (d, 1H, J=11.4 Hz, OCH$_2$), 4.47 (m, 3H, H-3$_D$, OCH$_2$), 4.22 (dq, 1H, $J_{4,5}$=9.4 Hz, $J_{5,6}$=6.2 Hz, H-5$_C$), 4.10 (d, 1H, J=15.5 Hz, CH$_2$Cl), 3.96 (m, 2H, H-6a$_D$, CH$_2$Cl), 3.91 (pt, 1H, H-3$_E$), 3.82 (m, 2H, H-5$_E$, 6b$_D$), 3.72 (m, 3H, H-6a$_E$, 4$_E$, 4$_C$), 3.62 (pt, 1H, $J_{3,4}$=$J_{4,5}$=9.4 Hz, H-4$_D$), 3.55 (m, 2H, H-6b$_E$, 2$_E$), 3.51 (s, 3H, OCH$_3$), 3.41 (m, 1H, H-5$_D$), 3.15 (m, 1H, H-2$_D$), 2.04 (s, 3H, C(O)CH$_3$), 1.51 (s, 3H, C(CH$_3$)$_2$), 1.42 (m, 6H, H-6$_C$, C(CH$_3$)$_2$), 1.51 (d, 3H, $J_{5,6}$=6.2 Hz, H-6$_C$); ^{13}C NMR δ 171.8, 167.3, 166.1 (3C, C=O), 139.0–128.0 (Ph), 101.1 (C-1$_D$, J_{CH}<164 Hz), 99.9 (C(CH$_3$)$_2$), 99.4 (C-1$_E$, J_{CH}>165 Hz), 98.2 (C-1$_C$, J_{CH}=172 Hz), 81.8 (C-3$_E$), 80.9 (C-2$_E$), 79.0 (C-4$^*_C$), 77.7 (C-4$^*_E$), 76.7 (C-3$_D$), 75.9, 75.3, 74.2, 73.9 (4C, OCH$_2$), 73.7 (C-4$_D$), 73.4 (C-3$_C$), 71.9 (C-5$_E$), 71.2 (C-2$_C$), 68.2 (C-6$_E$), 67.8 (C-5$_C$), 67.4 (C-5$_D$), 62.7 (C-6$_D$), 59.6 (C-2$_D$), 57.6 (OCH$_3$), 41.5 (CH$_2$Cl), 29.5 (C(CH$_3$)$_2$), 27.3 (C(O)CH$_3$), 19.7 (C(CH$_3$)$_2$), 18.6 (C-6$_C$); FAB-MS for $C_{61}H_{70}ClNO_{17}$ (M, 1123.4) *m/z* 1146.5 [M+Na]$^+$. Anal. calcd for $C_{61}H_{70}ClNO_{17}$: C, 65.15; H, 6.27; N, 1.25%. Found: C, 65.13; H, 6.23; N, 1.22%.

4.1.16. Methyl (2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-(2-*O*-benzoyl-α-L-rhamnopyranosyl)-(1→3)-2-acetamido-2-deoxy-4,6-*O*-isopropylidene-β-D-glucopyranoside (25). To a solution of the fully protected **24** (1.40 g, 1.25 mmol) in a mixture of methanol (18 mL) and pyridine (18 mL) was added thiourea (951 mg, 12.5 mmol). The mixture was stirred at 65 °C for 5 h, at which time TLC (solvent C, 4:1) showed that no starting material remained. Evaporation of the volatiles and co-evaporation of petroleum ether from the residue resulted in a crude solid, which was taken up in a minimum of methanol. A large excess of CH_2Cl_2 was added and the mixture was left to stand at 0 °C for 1 h. The precipitate was filtrated on a pad of Celite and the filtrate was concentrated. Column chromatography of the residue (solvent C, 4:1) gave the trisaccharide acceptor **25** (1.28 g, 97%) as a white powder. $[\alpha]_D$ +33.5 (*c* 1.0); ^{1}H NMR δ 8.10–6.96 (m, 25H, Ph), 6.09 (d, 1H, $J_{NH,2}$=7.9 Hz, NH$_D$), 5.26 (dd, 1H, $J_{1,2}$=1.6 Hz, $J_{2,3}$=3.4 Hz, H-2$_C$), 4.97 (m, 3H, H-1$_C$, 1$_E$, OCH$_2$), 4.86 (m, 3H, H-1$_D$, OCH$_2$), 4.81 (d, 1H, OCH$_2$), 4.72 (d, 1H, OCH$_2$), 4.58 (d, 1H, J=12.2 Hz, OCH$_2$), 4.51 (d, 1H, J=10.9 Hz, OCH$_2$), 4.48 (d, 1H, J=12.2 Hz, OCH$_2$), 4.23 (pt, 1H, $J_{2,3}$=$J_{3,4}$=9.4 Hz, H-3$_D$), 4.18–4.10 (m, 2H, H-5$_C$, 5$_E$), 4.06–3.95 (m, 3H, H-3$_C$, 3$_E$, 6a$_D$), 3.80 (pt, 1H, $J_{5,6b}$=$J_{6a,6b}$=10.4 Hz, H-6b$_D$), 3.66 (m, 2H, H-6a$_E$, 6b$_E$), 3.62 (dd, 1H, $J_{2,3}$=9.8 Hz, $J_{1,2}$=4.1 Hz, H-2$_E$), 3.59 (pt, 1H, $J_{3,4}$=$J_{4,5}$=8.9 Hz, H-4$_E$), 3.55 (pt, 1H, $J_{3,4}$=$J_{4,5}$=9.2 Hz, H-4$_D$), 3.51 (pt, 1H, $J_{3,4}$=$J_{4,5}$=9.3 Hz, H-4$_C$), 3.49 (s, 3H, OCH$_3$), 2.22 (s, 3H, C(O)CH$_3$), 1.90 (brs, 1H, OH), 1.49 (s, 3H, CMe$_2$), 1.43 (s, 3H, CMe$_2$), 1.40 (s, 3H, $J_{5,6}$=6.2 Hz, H-6$_C$); ^{13}C NMR δ 171.8, 166.6 (2C, C=O), 138.9–128.1 (Ph), 101.6 (C-1$_D$), 99.8 (C(CH$_3$)$_2$), 98.6 (C-1$^*_E$), 98.3 (C-1$^*_C$), 85.4 (C-4$_C$), 82.0 (C-3$_E$), 80.4 (C-2$_E$), 78.2 (C-4$_E$), 77.1 (C-3$_D$), 75.9, 75.5, 74.2, 73.9 (4C, OCH$_2$), 73.6 (C-4$^*_D$), 73.5 (C-2$^*_C$), 71.7 (C-5$_E$), 69.0 (C-6$_E$), 68.3 (C-3$_C$), 67.5

(C-5_D), 66.9 (C-5_C), 62.7 (C-6_D), 58.9 (C-2_D), 57.5 (OCH_3), 29.5 ($C(CH_3)_2$), 24.0 ($C(O)CH_3$), 19.7 ($C(CH_3)_2$), 18.2 (C-6_C); FAB-MS for $C_{59}H_{69}NO_{16}$ (M, 1047.5) *m/z* 1070.4 $[M+Na]^+$. Anal. calcd for $C_{70}H_{76}O_{16}$: C, 67.61; H, 6.64; N, 1.34%. Found: C, 67.46; H, 6.78; N, 1.24%.

4.1.17. Methyl (3,4-di-*O*-benzyl-2-*O*-chloroacetyl-α-L-rhamnopyranosyl)-(1→3)-[2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl-(1→4)]-(2-*O*-benzoyl-α-L-rhamnopyranosyl)-(1→3)-2-acetamido-2-deoxy-4,6-*O*-isopropylidene-β-D-glucopyranoside (29). (a) The trisaccharide acceptor **25** (615 mg, 0.58 mmol) was dissolved in Et_2O (10 mL) and the solution was cooled to −60 °C. TMSOTf (32 μL) and donor **20** (497 mg, 0.88 mmol) in Et_2O (12 mL) were added, and the mixture was stirred for 1 h while the bath was slowly coming back to −20 °C. The mixture was stirred for 4 h at this temperature, then at 0 °C overnight. More **20** (50 mg, 88 μmol) was added, and the mixture was stirred at rt for 3 h more at 0 °C. Et_3N was added, and the mixture was concentrated. Column chromatography of the residue (solvent B, 9:1→1:1) gave the orthoester **35** (44 mg, 5%) then the fully protected **29** (445 mg, 52%) contaminated with the trimethylsilyl side product **26** (**29/26**: 9:1) together with a mixture of **29** and **35** (65 mg, 8%), and the starting **25** (27 mg, 4%). An analytical sample of compound **29** had $[\alpha]_D$ +17.9 (*c* 1.0); ^1H NMR δ 8.07–7.12 (m, 35H, Ph), 5.96 (d, 1H, $J_{NH,2}$=7.9 Hz, NH), 5.82 (m, 1H, H-2_B), 5.33 (dd, 1H, $J_{1,2}$=1.8 Hz, $J_{2,3}$=3.2 Hz, H-2_C), 5.07 (d, 1H, $J_{1,2}$=3.2 Hz, H-1_E), 5.05 (d, 1H, $J_{1,2}$=1.7 Hz, H-1_B), 4.98 (d, 1H, OCH_2), 4.97 (brs, 1H, H-1_C), 4.91–4.78 (m, 5H, H-1_D, OCH_2), 4.64 (d, 1H, *J*=11.6 Hz, OCH_2), 4.60–4.45 (m, 5H, OCH_2), 4.36 (d, 1H, *J*=11.9 Hz, OCH_2), 4.26 (pt, 1H, $J_{2,3}$=$J_{3,4}$=9.5 Hz, H-3_D), 4.17 (dd, 1H, $J_{2,3}$=3.4 Hz, H-3_C), 4.16 (d, 1H, *J*=15.1 Hz, CH_2Cl), 4.11 (d, 1H, CH_2Cl), 4.10 (dq, 1H, $J_{4,5}$=9.1 Hz, $J_{5,6}$=6.3 Hz, H-5_C), 4.06 (m, 1H, H-5_E), 4.00 (pt, 1H, $J_{3,4}$=$J_{2,3}$=9.4 Hz, H-3_E), 3.97 (dd, 1H, $J_{5,6a}$=5.3 Hz, $J_{6a,6b}$=10.8 Hz, H-$6a_D$), 3.89 (m, 1H, H-$6a_E$), 3.88–3.68 (m, 4H, H-$6b_E$, $6b_D$, 4_C, 3_B), 3.67 (m, 1H, H-5_B), 3.58 (pt, 1H, $J_{3,4}$=$J_{4,5}$=9.4 Hz, H-4_D), 3.52 (dd, 1H, $J_{1,2}$=3.3 Hz, $J_{2,3}$=9.8 Hz, H-2_E), 3.49 (s, 3H, OCH_3), 3.39 (m, 1H, H-5_D), 3.30 (m, 2H, H-2_D, 4_B), 2.12 (s, 3H, $C(O)CH_3$), 1.52 (s, 3H, $C(CH_3)_2$), 1.42 (s, 3H, $C(CH_3)_2$), 1.33, 0.96 (2d, 6H, $J_{5,6}$=6.2 Hz, H-6_B, 6_C); ^{13}C NMR δ 171.9, 167.0, 166.3 (3C, C=O), 138.8–128.0 (Ph), 101.4 (C-1_D, J_{CH}=164 Hz), 99.9 ($C(CH_3)_2$), 99.3 (C-1_C, J_{CH}=168 Hz), 98.3 (C-1_E, J_{CH}=168 Hz), 97.9 (C-1_B, J_{CH}=171 Hz), 82.1 (C-3_E), 81.8 (C-2_E), 80.4 (brs, C-3_B), 80.0 (C-4_C), 78.8 (brs, C-4^*_E), 78.3 (C-4^*_B), 77.7 (C-3^*_C), 76.9 (C-3_D), 75.9, 75.5, 75.3, 74.3 (4C, OCH_2), 73.4 (C-4_D), 73.2 (OCH_2), 72.7 (C-2_B), 72.1 (C-5_E), 69.1 (C-5_C), 67.7 (C-5^*_D), 67.6 (C-5^*_B), 62.7 (C-6_D), 59.1 (C-2_D), 57.5 (OCH_3), 41.4 (CH_2Cl), 29.5 ($C(CH_3)_2$), 24.0 ($C(O)CH_3$), 19.7 ($C(CH_3)_2$), 18.8, 18.2 (2C, C-6_B, 6_C); FAB-MS for $C_{81}H_{92}NClO_{21}$ (M, 1449.5) *m/z* 1472.7 $[M+Na]^+$. Anal. calcd for $C_{81}H_{92}NClO_{21}$: C, 67.05; H, 6.39; N, 0.97%. Found: C, 66.21; H, 6.46; N, 1.01%.

Compound **35** had $[\alpha]_D$ +26.7 (*c* 0.8); ^1H NMR δ 8.07–7.15 (m, 35H, Ph), 5.47 (d, 1H, $J_{NH,2}$=7.4 Hz, NH_D), 5.45 (brs, 1H, H-2_C), 5.42 (d, 1H, $J_{1,2}$=2.3 Hz, H-1_B), 5.24 (d, 1H, $J_{1,2}$=3.4 Hz, H-1_E), 4.94 (d, 1H, $J_{1,2}$=8.2 Hz, H-1_D), 4.91–4.82 (m, 7H, H-1_C, OCH_2), 4.80 (d, 1H, *J*=11.0 Hz, OCH_2), 4.75 (d, 1H, *J*=11.6 Hz, OCH_2), 4.68 (dd, 1H, $J_{1,2}$=2.4 Hz, $J_{2,3}$=4.0 Hz, H-2_B), 4.65–4.47 (m, 4H, OCH_2), 4.44–4.32 (m, 4H, H-5_E, 3_D, 3_C, OCH_2), 4.15 (m, 1H, H-5_C), 4.05 (pt, 1H, $J_{2,3}$=$J_{3,4}$=9.5 Hz, H-3_E), 4.03 (pt, 1H, $J_{3,4}$=$J_{4,5}$=9.4 Hz, H-4_C), 3.94 (dd, 1H, $J_{5,6a}$=5.3 Hz, $J_{6a,6b}$=10.7 Hz, H-$6a_D$), 3.83–3.75 (m, 4H, H-$6a_E$, $6b_D$, CH_2Cl), 3.74–3.70 (m, 3H, H-4_E, 6_E, 3_B), 3.65 (dd, 1H, $J_{1,2}$=3.4 Hz, $J_{2,3}$=9.4 Hz, H-2_E), 3.48 (pt, 2H, H-4_B, 4_D), 3.46 (s, 3H, OCH_3), 3.38 (m, 1H, H-5_D), 3.22 (dq, 1H, $J_{4,5}$=9.5 Hz, $J_{5,6}$=6.2 Hz, H-5_B), 2.88 (m, 1H, H-2_D), 1.90 (s, 3H, $C(O)CH_3$), 1.42 (s, 3H, $C(CH_3)_2$), 1.36 (s, 6H, $C(CH_3)_2$, H-6_C), 1.30 (d, 3H, $J_{5,6}$=6.3 Hz, H-6_B); ^{13}C NMR δ 171.8, 166.4 (2C, C=O), 139.1–122.5 (Ph), 101.0 (C-1_D, J_{CH}=165 Hz), 99.7 ($C(CH_3)_2$), 98.3 (C-1_C, J_{CH}=172 Hz), 97.8 (brs, C-1_E, J_{CH}=170 Hz), 97.5 (C-1_B, J_{CH}=176 Hz), 82.2 (C-3_E), 80.7 (C-2_E), 79.3 (brs, C-4_B), 78.8 (C-3_B), 78.1 (brs, C-4_E), 77.3 (C-2_B), 76.2 (brs, C-3_C), 75.8, 75.6, 74.9, 74.6, 73.9 (6C, C-4_C, OCH_2), 73.5 (2C, C-4_D, 2_C), 71.4 (OCH_2), 71.0 (C-3_D), 70.7 (2C, C-5_E, 5_B), 69.0 (C-5_C), 68.8 (C-6_E), 67.2 (C-5_D), 62.5 (C-6_D), 60.0 (C-2_D), 57.6 (OCH_3), 46.9 (CH_2Cl), 29.5 ($C(CH_3)_2$), 23.9 ($C(O)CH_3$), 19.7 ($C(CH_3)_2$), 19.0 (C-6_B), 18.4 (C-6_C); FAB-MS for $C_{81}H_{92}NClO_{21}$ (M, 1449.5) *m/z* 1472.7 $[M+Na]^+$. Anal. calcd for $C_{81}H_{92}NClO_{21}\cdot H_2O$: C, 66.23; H, 6.34; N, 0.96%. Found: C, 66.11; H, 6.62; N, 0.85%.

4.1.18. Methyl (2-*O*-acetyl-3,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-(1→3)-[2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl-(1→4)]-(2-*O*-benzoyl-α-L-rhamnopyranosyl)-(1→3)-2-acetamido-2-deoxy-4,6-*O*-isopropylidene-β-D-glucopyranoside (30). The trisaccharide acceptor **25** (500 mg, 0.47 mmol) was dissolved in CH_2Cl_2 (5 mL) and the solution was cooled to −40 °C. TMSOTf (21 μL) and donor **5** (328 mg, 0.62 mmol) were added and the mixture was left under stirring while the bath was slowly coming back to rt. After 5 h, more **5** (50 mg, 94 μmol) was added and the mixture was stirred at rt for 1 h more. Et_3N was added and the mixture was concentrated. Column chromatography of the residue (solvent B, 4:1→1:1) gave the fully protected **30** (484 mg, 72%) slightly contaminated with the corresponding trimethylsilyl side product **26**. The **30/26** ratio was estimated to be 85:15 from the ^1H NMR spectrum. Eluting next was some residual starting **25** (45 mg, 9%). Thus, based on the consumed acceptor, the estimated yield of contaminated **30** was 79%. An analytical sample of **30** had $[\alpha]_D$ +15.9 (*c* 0.8); ^1H NMR δ 8.09–7.14 (m, 35H, Ph), 6.04 (brs, 1H, NH_D), 5.76 (m, 1H, H-2_B), 5.37 (dd, 1H, $J_{1,2}$=1.9 Hz, $J_{2,3}$=2.8 Hz, H-2_C), 5.11 (d, 1H, $J_{1,2}$=3.1 Hz, H-1_E), 5.06 (d, 1H, H-1_B), 4.96 (brs, 1H, H-1_C), 5.02–4.82 (m, 7H, H-1_D, OCH_2), 4.69–4.37 (m, 6H, OCH_2), 4.28 (pt, 1H, $J_{2,3}$=$J_{3,4}$=9.5 Hz, H-3_D), 4.15 (dd, 1H, $J_{2,3}$=3.3 Hz, $J_{3,4}$=9.4 Hz, H-3_C), 4.13–3.93 (m, 5H, H-5_E, $6a_E$, 3_E, 5_C, $6a_D$), 3.87–3.76 (m, 5H, H-4_E, $6b_E$, 3_B, 4_C, $6b_D$), 3.68 (dq, 1H, $J_{4,5}$=9.5 Hz, H-5_B), 3.57 (pt, 1H, $J_{3,4}$=$J_{4,5}$=9.4 Hz, H-4_D), 3.54 (dd, 1H, $J_{2,3}$=3.2 Hz, H-2_E), 3.48 (s, 3H, OCH_3), 3.40 (m, 1H, H-5_D), 3.34 (pt, 1H, $J_{3,4}$=9.7 Hz, H-4_B), 3.27 (m, 1H, H-2_D), 2.18, 2.13 (2s, 6H, $C(O)CH_3$), 1.51, 1.42 (2s, 6H, $C(CH_3)_2$), 1.33 (d, 3H, $J_{5,6}$=6.2 Hz, H-6_C), 0.98 (d, 3H, $J_{5,6}$=6.2 Hz, H-6_B); ^{13}C NMR δ 171.9, 170.5, 166.3 (3C, C=O), 139.3–127.7 (Ph), 101.3 (C-1_D), 99.9 ($C(CH_3)_2$), 99.6 (C-1_B), 98.4 (C-1_E), 98.0 (C-1_C), 82.1 (C-3_E), 81.8 (C-2_E), 80.3 (2C, C-3_C, 4_B), 78.7 (brs, C-4_C), 78.2 (C-3^*_B), 77.7 (C-4^*_E), 76.9 (brs, C-3_D), 75.9, 75.4, 75.3, 74.3 (4C, OCH_2), 73.4 (C-4_D), 73.3 (OCH_2), 72.7 (C-2_C),

72.1 (C-5_E), 70.9 (OCH_2), 69.0 (3C, C-2_B, 5_B, 6_E), 67.8 (C-5_C), 67.6 (C-5_D), 62.7 (C-6_D), 59.2 (C-2_D), 57.5 (OCH_3), 29.5 ($C(CH_3)_2$), 24.0, 21.6 (2C, $C(O)CH_3$), 19.7 ($C(CH_3)_2$), 18.9 (C-6_C), 18.2 (C-6_B). FAB-MS for $C_{81}H_{93}NO_{21}$ (M, 1415) *m/z* 1438.6 $[M+Na]^+$.

4.1.19. Methyl (3,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-(1→3)-[2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl-(1→4)]-(2-*O*-benzoyl-α-L-rhamnopyranosyl)-(1→3)-2-acetamido-2-deoxy-4,6-*O*-isopropylidene-β-D-glucopyranoside (31). (a) Thiourea (22 mg, 0.29 mmol) was added to the chloroacetylated **29** (83 mg, 57 μmol) in MeOH/pyridine (1:1, 2.8 mL), and the mixture was heated overnight at 65 °C. Volatiles were evaporated, and the solid residue thus obtained was taken up in the minimum of MeOH. CH_2Cl_2 was added, and the suspension was left standing at 0 °C for 1 h. The precipitate was filtered on a pad of Celite, and the filtrate was concentrated. Column chromatography of the residue (solvent B, 9:1→1:1) gave the tetrasaccharide acceptor **31** (74 mg, 94%).

(b) The monoacetylated **30** (52 mg, 37 μmol) was dissolved in a mixture of EtOH (10 mL) and CH_2Cl_2 (100 μL). A freshly prepared 0.4 M ethanolic solution of guanidine (92 μL, 37 μmol) was added and the mixture was stirred at rt overnight. Volatiles were evaporated, and the residue taken up in CH_2Cl_2 was washed with water. The organic phase was dried and concentrated. Column chromatography of the crude product gave **31** (42 mg, 83%) as a glassy solid. Compound **31** had $[\alpha]_D$ +27.3 (*c* 1.0); ^{1}H NMR δ 8.24–6.88 (m, 35H, Ph), 5.90 (brs, 1H, NH_D), 5.29 (brs, 1H, H-2_C), 5.14 (d, 1H, $J_{1,2}$=3.0 Hz, H-1_E), 5.06 (d, 1H, $J_{1,2}$=1.6 Hz, H-1_B), 5.00–4.95 (m, 3H, H-1_D, 1_C, OCH_2), 4.88–4.46 (m, 9H, OCH_2), 4.31 (pt, 1H, $J_{2,3}$=$J_{3,4}$=9.4 Hz, H-3_D), 4.24 (brs, 1H, H-2_B), 4.14–3.08 (m, 3H, H-3_C, 5_C, 5_E), 4.02 (pt, 1H, $J_{2,3}$=$J_{3,4}$=9.3 Hz, H-3_E), 3.97 (dd, 1H, $J_{5,6a}$=5.2 Hz, $J_{6a,6b}$=10.7 Hz, H-$6a_D$), 3.80 (m, 2H, H-4_C, $6b_D$), 3.71 (m, 2H, H-$6a_E$, $6b_E$), 3.66 (pt, 1H, $J_{4,5}$=9.5 Hz, H-4_E), 3.61–3.55 (m, 4H, H-3_B, 2_E, 5_B, 4_D), 3.50 (s, 3H, OCH_3), 3.42–3.36 (m, 2H, H-5_D, 4_B), 3.20 (m, 1H, H-2_D), 2.85 (brs, 1H, OH), 2.10 (s, 3H, $C(O)CH_3$), 1.51, 1.41 (2s, 6H, $C(CH_3)_2$), 1.33 (d, 3H, $J_{5,6}$=6.2 Hz, H-6_C), 1.15 (s, 3H, $J_{5,6}$=6.2 Hz, H-6_B); ^{13}C NMR δ 171.7, 166.3 (2C, C=O), 139.0–127.8 (Ph), 103.1 (C-1_B), 101.2 (C-1_D), 99.8 ($C(CH_3)_2$), 98.2, 98.1 (2C, C-1_E, 1_C), 82.0 (C-3_E), 81.5 (C-3_B^*), 80.6 (C-4_B), 79.4 (C-2_E^*), 79.1 (2C, C-4_C, 3_C), 78.2 (C-4_B), 76.8 (C-3_D), 76.0, 75.5, 74.5, 74.2 (4C, OCH_2), 73.9 (C-2_C), 73.7 (OCH_2), 73.5 (C-4_D), 72.1 (OCH_2), 71.6 (C-5_E), 69.0 (C-6_E), 68.7 (2C, C-2_B, 5_B), 67.9 (C-5_C), 67.5 (C-5_D), 62.7 (C-6_D), 59.4 (C-2_D), 57.5 (OCH_3), 29.5 ($C(CH_3)_2$), 24.0 ($C(O)CH_3$), 19.7 ($C(CH_3)_2$), 19.0 (C-6_C), 18.3 (C-6_B); FAB-MS for $C_{79}H_{91}NO_{20}$ (M, 1373) *m/z* 1396.5 $[M+Na]^+$. Anal. calcd for $C_{79}H_{91}NO_{20}0.5H_2O$: C, 68.56; H, 6.65; N, 1.01%. Found: C, 68.53; H, 6.71; N, 1.01%.

4.1.20. Methyl (2-*O*-acetyl-3,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-(1→2)-(3,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-(1→3)-[2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl-(1→4)]-(2-*O*-benzoyl-α-L-rhamnopyranosyl)-(1→3)-2-acetamido-2-deoxy-4,6-*O*-isopropylidene-β-D-glucopyranoside (32). Activated 4 Å molecular sieves and TMSOTf (16 μL) were added to a solution of the tetrasaccharide acceptor **31** (406 mg, 0.29 mmol) in Et_2O (10 mL), and the mixture was stirred at −60 °C for 30 min. The donor **5** (234 mg, 0.44 mmol) in CH_2Cl_2 (7 mL) was added, and the mixture was stirred for 1 h while the bath temperature was reaching rt. After a further 1 h at this temperature, more **5** (50 mg, 94 μmol) was added, and the mixture was stirred for 1 h before Et_3N was added. Filtration through a pad of Celite and evaporation of the volatiles gave a residue which was column chromatographed twice (solvent B, 4:1; then solvent A, 17:3) to give **32** (262 mg, 52%) as a white powder. $[\alpha]_D$ +25.9 (*c* 1.0); ^{1}H NMR δ 8.07–7.13 (m, 45H, Ph), 6.03 (brs, 1H, NH_D), 5.59 (brs, 1H, H-2_A), 5.35 (brs, 1H, H-2_C), 5.16 (brs, 1H, H-1_E), 5.13 (brs, 1H, H-1_A), 5.06 (brs, 1H, H-1_B), 5.02–4.97 (m, 4H, H-1_D, 1_C, OCH_2), 4.91–4.50 (m, 12H, OCH_2), 4.44–4.32 (m, 4H, H-2_B, 3_D, OCH_2), 4.20–3.96 (m, 7H, H-5_E, 5_A, 3_C, 3_E, $6a_D$, 5_C, 3_A), 3.87–3.68 (m, 6H, H-4_E, $6a_E$, $6b_E$, $6b_D$, 4_C, 3_B), 3.64–3.47 (m, 7H, H-5_B, 4_D, 2_E, 4_A, OCH_3), 3.42 (m, 1H, H-5_D), 3.34 (pt, 1H, $J_{3,4}$=$J_{4,5}$=9.3 Hz, H-4_B), 3.17 (m, 1H, H-2_D), 2.13 (s, 3H, $C(O)CH_3$), 1.49 (s, 3H, $C(CH_3)_2$), 1.43 (s, 6H, $C(CH_3)_2$, H-6_C), 1.33 (d, 3H, $J_{5,6}$=6.1 Hz, H-6_A), 1.01 (d, 3H, $J_{5,6}$=5.8 Hz, H-6_B); ^{13}C NMR δ 171.9, 170.3, 166.3 (3C, C=O), 139.2–127.6 (Ph), 101.5 (brs, C-1_B, J_{CH}=171 Hz), 101.2 (C-1_D, J_{CH}=163 Hz), 99.8 ($C(CH_3)_2$), 99.7 (C-1_A, J_{CH}=171 Hz), 97.9 (2C, C-1_E, 1_C, J_{CH}=172, 169 Hz), 82.4 (C-3_E), 82.1 (C-2_E), 80.5 (C-4_A), 80.2 (brs, C-3_C), 80.1 (C-4_B), 79.4, 78.1, 78.0 (4C, C-3_B, 4_E, 3_A, 4_C), 76.6 (brs, C-3_D), 75.9, 75.8, 75.4 (3C, OCH_2), 74.8 (2C, C-2_B, OCH_2), 73.5 (C-4_D), 73.4 (OCH_2), 73.2 (C-2_C), 72.1 (OCH_2), 71.8 (C-5_A), 71.2 (OCH_2), 69.4 (C-2_A), 69.2 (C-5_B), 68.9 (C-6_E), 68.7 (C-5_C), 67.8 (C-5_E), 67.5 (C-5_D), 62.7 (C-6_D), 59.6 (brs, C-2_D), 57.6 (OCH_3), 29.5 ($C(CH_3)_2$), 24.0, 21.4 (2C, $C(O)CH_3$), 19.7 ($C(CH_3)_2$), 19.1 (C-6_A), 18.8 (C-6_C), 18.2 (C-6_B); FAB-MS for $C_{101}H_{115}NO_{25}$ (M, 1741.7) *m/z* 1765.9 $[M+Na]^+$. Anal. calcd for $C_{101}H_{115}NO_{25}$: C, 69.60; H, 6.65; N, 0.80%. Found: C, 69.56; H, 6.75; N, 0.73%.

4.1.21. Methyl α-L-rhamnopyranosyl-(1→2)-α-L-rhamnopyranosyl-(1→3)-[α-D-glucopyranosyl-(1→4)]-α-L-rhamnopyranosyl-(1→3)-2-acetamido-2-deoxy-β-D-glucopyranoside (2). 50% aq. TFA (1 mL) was added at 0 °C to a solution of the fully protected pentasaccharide **32** (155 mg, 89 μmol) dissolved in CH_2Cl_2 (4 mL) After 1 h at this temperature, volatiles were evaporated. The residue, containing diol **33**, was taken up in 0.5% methanolic sodium methoxide (8 mL) and the mixture was heated overnight at 55 °C. Neutralisation with Dowex X8 (H^+), evaporation of the volatiles and column chromatography of the residue gave **34** (121 mg, 98%). Compound **34** (111 mg, 81 μmol) was dissolved in a mixture of ethanol (13 mL) and ethyl acetate (2.6 mL) containing 1 N aq. HCl (130 μL). Palladium on charcoal (130 mg) was added, and the suspension was stirred under a hydrogen atmosphere for 2 h. Filtration of the catalyst and reverse phase chromatography gave the target pentasaccharide (60 mg, 88%) as a slightly yellow foam. RP-HPLC purification followed by freeze-drying gave pure **2** (36 mg). Compound **2** had rt: 9.63 min (solvent F, 100:0→80:20 over 20 min); $[\alpha]_D$ −18.6 (*c* 1.0, methanol); ^{1}H NMR δ 5.13 (d, 1H, $J_{1,2}$=3.7 Hz, H-1_E), 4.98 (brs, 1H, H-1_B), 4.90 (d, 1H, $J_{1,2}$=1.4 Hz, H-1_A), 4.72 (d, 1H, $J_{1,2}$=1.4 Hz, H-1_C), 4.39 (d, 1H, $J_{1,2}$=8.6 Hz, H-1_D), 4.09 (dq, 1H, $J_{4,5}$=9.2 Hz, H-5_C), 4.00 (m, 2H, H-2_B, 2_A), 3.94–3.79 (m, 7H, H-5_E, 2_C,

3_C, $6a_E$, $6a_D$, 2_D, 3_A), 3.76–3.65 (m, 7H, H-4_C, 3_E, $6b_E$, $6b_D$, 5_A, 5_B, 3_B), 3.52 (pt, 1H, $J_{3,4}$=8.8 Hz, H-3_D), 3.49–3.33 (m, 9H, H-4_D, 2_E, 4_A, 4_B, 5_D, 4_E, OCH_3), 1.98 (s, 3H, $C(O)CH_3$), 1.27 (d, 3H, $J_{5,6}$=6.3 Hz, H-6_C), 1.24, 1.23 (d, 6H, H-6_A, 6_B); ^{13}C NMR δ 172.3 (C=O), 100.7 (C-1_A, J_{CH}=171 Hz), 99.6 (2C, C-1_D, 1_B, J_{CH}=163, 170 Hz), 99.2 (C-1_C, J_{CH}=170 Hz), 95.7 (brs, C-1_E, J_{CH}=170 Hz), 82.0 (C-3_D), 79.1 (C-2_B), 79.4 (brs, C-3_C), 76.4 (C-5_D^*), 75.4 (brs, C-4_C), 73.0 (C-3_E), 72.4 (2C, C-4_A, 4_B), 72.2 (C-5_E), 71.7 (C-2_E), 71.1 (C-2_C), 70.4, 70.1, 70.0 (4C, C-2_A, 3_A, 3_B, 4_E), 69.7, 69.6, 69.3 (3C, C-5_A, 5_B, 5_C), 68.8 (C-4_D), 61.2, 61.0 (2C, C-6_D, 6_E), 57.4 (OCH_3), 55.4 (C-2_D), 22.6 ($C(O)CH_3$), 18.2 (C-6_C), 17.2, 17.0 (2C, C-6_A, 6_B); HRMS (MALDI) calcd for $C_{33}H_{57}NO_{23}$ +Na: 858.3219. Found: 858.3089.

4.1.22. Methyl (2-*O*-acetyl-3,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-(1→3)-[2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl-(1→4)]-(2-*O*-benzoyl-α-L-rhamnopyranosyl)-(1→3)-2-acetamido-2-deoxy-β-D-glucopyranoside (36). 50% aq. TFA (400 μL) was added to a solution of the fully protected tetrasaccharide **30** (57 mg, 40 μmol) in CH_2Cl_2 (1 mL) at 0 °C, and the mixture was stirred overnight at this temperature. Volatiles were evaporated and the residue was purified by column chromatography (solvent B, 1:1) to give diol **36** (47 mg, 85%). $[\alpha]_D$ +19.5 (*c* 0.9); ^1H NMR δ 8.10–7.16 (m, 35H, Ph), 5.80 (d, 1H, *J*=8.8 Hz, NH_D), 5.66 (m, 1H, H-2_B), 5.39 (pt, 1H, $J_{1,2}$=2.8 Hz, H-2_C), 5.01 (m, 2H, H-1_B, 1_E), 4.96 (m, 2H, H-1_C, OCH_2), 4.90–4.81 (m, 5H, H-1_D, OCH_2), 4.66–4.41 (m, 7H, OCH_2), 4.18 (dd, 1H, $J_{2,3}$=2.9 Hz, $J_{3,4}$=7.4 Hz, H-3_C), 4.10 (pt, 1H, H-3_D), 4.08–3.95 (m, 5H, H-5_E, 3_E, 5_C), 3.89–3.64 (m, 8H, H-$6a_D$, $6b_D$, $6a_E$, $6b_E$, 3_B, 4_C, 4_E, 5_B), 3.54–3.49 (m, 5H, H-2_E, 4_D, OCH_3), 3.45 (m, 1H, H-5_D), 3.33 (pt, 1H, $J_{3,4}$=$J_{4,5}$=9.4 Hz, H-4_B), 3.27 (m, 1H, H-2_D), 2.26 (brs, 1H, OH), 2.17 (s, 6H, $C(O)CH_3$), 1.99 (brs, 1H, OH), 1.39 (d, 3H, $J_{5,6}$=6.2 Hz, H-6_C), 0.95 (d, 3H, $J_{5,6}$=6.1 Hz, H-6_B); ^{13}C NMR δ 171.5, 170.4, 166.1 (3C, C=O), 139.1–127.8 (Ph), 100.9 (C-1_D), 99.7 (2C, C-1_B^*, 1_C), 99.2 (brs, C-1_E), 85.0 (C-3_D), 82.1 (C-3_E), 81.3 (brs, C-3_E), 80.1 (C-4_B), 78.0, 77.8 (4C, C-3_C, 4_C, 3_B, 4_E), 76.0 (OCH_2), 75.6 (C-5_D), 75.3, 75.2, 74.4, 73.4 (4C, OCH_2), 72.3 (C-2_C), 72.1 (C-5_C^*), 71.3 (C-4_D), 71.2 (OCH_2), 69.2 (C-5_B), 69.0 (C-5_E, 2_B), 68.4 (C-6_E), 63.2 (C-6_D), 57.4 (2C, C-2_D, OCH_3), 23.9, 21.0 (2C, $C(O)CH_3$), 19.1 (C-6_C), 18.0 (C-6_B). FAB-MS for $C_{78}H_{89}NO_{21}$ (M, 1375.6) *m/z* 1398.6 $[M+Na]^+$. Anal. calcd for $C_{78}H_{89}NO_{21}$: C, 68.06; H, 6.52; N, 1.02%. Found: C, 68.10; H, 6.62; N, 0.98%.

4.1.23. Methyl α-L-rhamnopyranosyl-(1→3)-[α-D-glucopyranosyl-(1→4)]-α-L-rhamnopyranosyl-(1→3)-2-acetamido-2-deoxy-β-D-glucopyranoside (3). 1% Methanolic sodium methoxide (255 μL) was added to a suspension of diol **36** (68 mg, 49 μmol) in MeOH (2 mL) and the mixture was heated overnight at 55 °C TLC (solvent A, 19:1) showed that the starting material had been converted to a more polar product. Neutralisation with Dowex X8 (H^+), evaporation of the volatiles, and column chromatography (solvent A, 24:1) gave tetraol **37** (52 mg, 85%). The latter (48 mg, 39 μmol) was dissolved in a mixture of ethanol (5 mL) and ethyl acetate (2 mL) containing 1 N aq. HCl (50 μL). Palladium on charcoal (50 mg) was added and the suspension was stirred under a hydrogen atmosphere overnight. TLC (solvent E, 4:1:2) showed the presence of a single product. Filtration of the catalyst and reverse phase chromatography, followed by RP-HPLC purification and freeze-drying gave pure **3** (19 mg, 71%). Rt: 9.35 min (solvent F, 100:0→80:20 over 20 min); $[\alpha]_D$ +12.5 (*c* 0.8, methanol); ^1H NMR δ 5.09 (d, 1H, $J_{1,2}$=3.7 Hz, H-1_E), 4.89 (brs, 1H, H-1_B), 4.71 (d, 1H, $J_{1,2}$=1.1 Hz, H-1_C), 4.39 (d, 1H, $J_{1,2}$=8.6 Hz, H-1_D), 4.08 (dq, 1H, $J_{4,5}$=9.3 Hz, H-5_C), 3.96 (dd, 1H, $J_{1,2}$=1.4 Hz, $J_{2,3}$=3.2 Hz, H-2_B), 3.88–3.80 (m, 4H, H-2_C, 3_C, $6a_E$, $6b_E$, 5_D), 3.77–3.62 (m, 6H, H-$6a_D$, $6b_D$, 3_B, 5_B, 2_D, 4_C), 3.59 (pt, 1H, $J_{3,4}$=$J_{4,5}$=9.4 Hz, H-3_E), 3.50 (pt, 1H, $J_{3,4}$=$J_{4,5}$=9.4 Hz, H-3_E), 3.50 (pt, 1H, $J_{3,4}$=$J_{4,5}$=8.7 Hz, H-3_D), 3.47–3.34 (m, 8H, H-2_E, 4_E, 4_B, 4_D, 5_E, OCH_3), 1.98 (s, 3H, $C(O)CH_3$), 1.27 (d, 3H, $J_{5,6}$=6.3 Hz, H-6_C), 1.21 (d, 3H, $J_{5,6}$=6.3 Hz, H-6_B); ^{13}C NMR δ 174.5 (C=O), 103.2 (brs, C-1_B, J_{CH}=172 Hz), 101.8 (C-1_D, J_{CH}=160 Hz), 101.5 (C-1_C, J_{CH}=170 Hz), 98.0 (C-1_E, J_{CH}=170 Hz), 82.2 (C-3_D), 79.1 (brs, C-3_C), 76.6 (brs, C-4_C), 76.4 (C-4_B^*), 72.9 (C-3_E), 72.3, 72.2 (2C, C-4_D, 5_D), 71.87 (C-2_E), 71.1 (brs, C-2_C), 70.6 (2C, C-2_B, 3_B), 69.7, 69.6 (2C, C-5_E, 5_B), 69.2, 68.9 (2C, C-6_D, 6_E), 57.4 (OCH_3), 55.4 (C-2_D), 22.6 ($C(O)CH_3$), 18.0 (C-6_C), 17.0 (C-6_B). HRMS (MALDI) calcd for $C_{27}H_{47}NO_{19}$ +Na: 712.2635. Found: 712.2635.

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Tetrahedron

Celogentin K, a new cyclic peptide from the seeds of *Celosia argentea* and X-ray structure of moroidin

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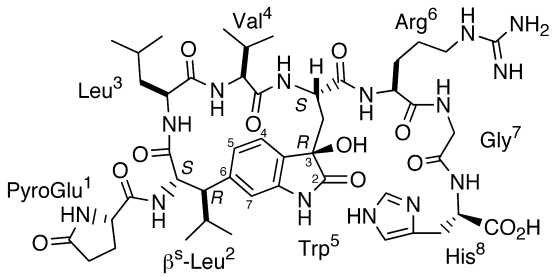
Abstract—A new cyclic peptide with a 3-hydroxyoxindole ring, celogentin K (**1**), has been isolated from the seeds of *Celosia argentea* and the structure including its absolute stereochemistry was assigned by using extensive NMR, MS/MS, and CD spectra. The stereostructure of a known related bicyclic peptide, moroidin (**2**), was confirmed by a single crystal X-ray diffraction analysis.

A series of celogentins A–H and J[1,2] as well as moroidin (**2**)[3,4] isolated from the seeds of *Celosia argentea* (Amaranthaceae) are unique cyclic peptides containing a bicyclic ring system, an unusual C–N bond formed by Trp and His residues, and an unusual amino acid, β-substituted Leu (β^s-Leu). Among them, celogentin C showed a potent inhibition of tubulin polymerization comparable to that of vinbrastine.[1] These unusual ring systems have attracted great interest as targets for biosynthetic and synthetic studies.[5] During our continuous search for structurally unique and biogenetically interesting peptides from *C. argentea*, we isolated a new cyclic peptide with a 3-hydroxyoxindole ring, celogentin K (**1**). In addition, the stereostructure of a known related bicyclic peptide, moroidin (**2**), was established by a single crystal X-ray diffraction analysis. Here we describe the isolation and structure elucidation of celogentin K (**1**) and the X-ray structure of moroidin (**2**).



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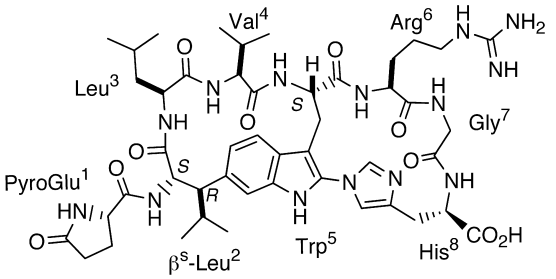
1. Isolation of celogentin K

The seeds of *C. argentea* were extracted with MeOH, and the MeOH extract was in turn partitioned with hexane, EtOAc, and *n*-BuOH. *n*-BuOH-soluble materials were subjected to a Diaion HP-20 column (MeOH/H_2O, 0:1→1:0), in which a fraction eluted with 60% MeOH was purified by an amino silica gel column ($CHCl_3$/MeOH/H_2O, 7:3:0.5→6:4:1) followed by C_{18} HPLC (17% CH_3CN/0.1% CF_3CO_2H) to afford celogentin K (**1**, 0.00002% yield) as colorless solids together with moroidin (**2**)[4] and celogentins A–H and J.[1,2]

2. Structure elucidation of celogentin K (1)

FABMS data of celogentin K (**1**) {$[\alpha]_D^{24}=-51°$ (*c* 0.5, 50% MeOH)} showed the pseudomolecular ion at *m/z* 1021 $(M+H)^+$, and the molecular formula, $C_{50}H_{69}N_{14}O_{10}$, was established by HRFABMS [*m/z* 1021.5221, $(M+H)^+$, Δ +0.2 mmu]. IR absorptions implied the presence of hydroxyl (3400 cm^{-1}) and amide carbonyl groups



2

Keywords: Cyclic peptide; Celogentin K; Moroidin; NMR; MS/MS; CD; X-ray.
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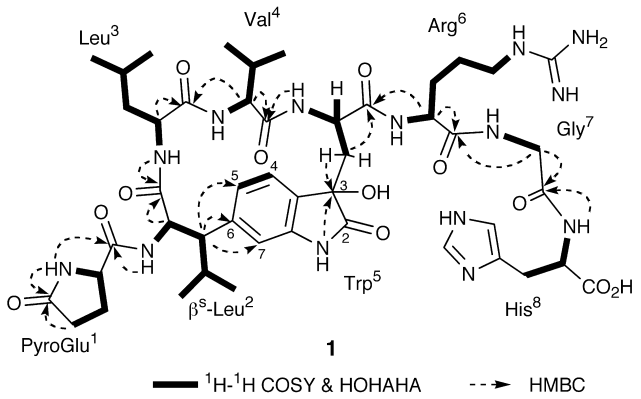

Figure 1. Selected 2D NMR correlations for celogentin K (**1**).

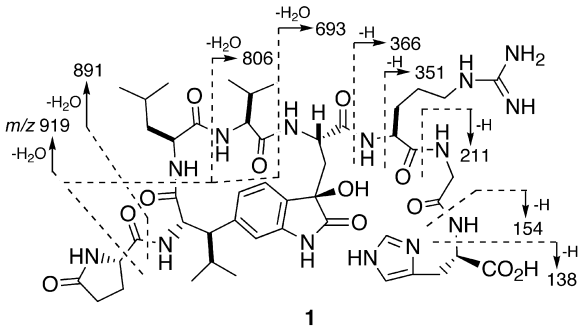

Figure 2. Fragmentation patterns observed in negative ion FABMS/MS spectrum of celogentin K (**1**) (precursor ion; *m/z* 1019.5).

(1660 cm^{-1}). Standard amino acid analysis of the hydrolysates of **1** showed the presence of each 1 mol of glutamic acid (Glu), leucine (Leu), valine (Val), arginine (Arg), glycine (Gly), and histidine (His). The ^1H NMR (Table 1) spectrum of **1** in DMSO-d_6 at 310 K showed eight proton resonances (δ 3.74–5.05), which were indicative of α-protons of amino acid residues. The presence of six methyl groups, nine methylenes, 16 methines, one sp^3 quaternary carbon, and six olefins was indicated by the ^{13}C NMR (Table 1) spectrum. Among them, one quaternary carbon (δ_C 73.50) was ascribed to that bearing an oxygen. The unusual amino acids, β-substituted Leu (β^s-Leu) and 2,6-substituted Trp (Trp), were revealed by analysis of the ^1H and ^{13}C NMR data (Table 1) using ^1H–^1H COSY, HOHAHA, HMQC, and HMBC experiments. The carbonyl signal (δ 179.34) was assigned as C-2 in an oxindole ring of Trp^5. The presence of the oxindole ring with a hydroxyl at C-3 of Trp^5 was implied by HMBC cross-peaks for H-β1 and NH to C-3 (Fig. 1). The UV absorption (ε 1760) at 268 nm different from that (283 nm, ε 4600) of moroidin (**2**) with an indole ring supported the presence of an oxindole ring. These data combined with observation of ten carbonyl signals (δ 168.55–179.34) including a PyroGlu residue in the ^{13}C NMR spectrum suggested that **1** was an octapeptide.

The cyclic peptide nature, which was different from the bicyclic ring system of moroidin (**2**), and the sequence (PyroGlu^1-β^s-Leu^2-Leu^3-Val^4-Trp^5-Arg^6-Gly^7-His^8) of celogentin K (**1**) were elucidated by detailed analysis of HMBC correlations as shown in Figure 1. The connection between Cβ of β^s-Leu^2 and C-6 of Trp^5 was deduced from HMBC correlations for H-β of β^s-Leu^2 to C-5, 6, and 7 of Trp^5. The HMBC correlations of Hα and NH to carbonyl carbon in each residue revealed the whole sequence of celogentin K to be **1** (Fig. 1).

Further evidence supporting the proposed structure of **1** was provided by tandem mass spectrometry through examination of the collision-induced dissociation (CID) mass spectrum of the $(M+H)^+$ions.[6] Negative ion FABMS/MS spectra of **1** showed characteristic patterns for charge-remote fragmentation, probably due to the presence of the carboxylate group of His.[7] Product ion peaks generated by fissions of amide bonds were prominently observed (Fig. 2).

The relative stereochemistry around β^s-Leu^2 and Trp^5 in **1** were deduced from NOESY correlations and $^3J_{H-H}$ coupling constants as shown in computer-generated 3D drawing (Fig. 3). The absolute configurations of the PyroGlu^1, Leu^3, Val^4, Arg^6, and His^7 residues in celogentin K (**1**) were assigned as all L-configurations by chiral HPLC analysis of the hydrolysates of **1**. The absolute configurations of Cα and Cβ of the β^s-Leu^2 and Cα of the Trp^5 residue were assigned from NOESY correlations (Fig. 4), which showed relation with L-Leu^3 and L-Val^4. The ring conformation deduced from such NOESY relations was consistent with those of moroidin[3] and celogentins A–H and J.[1,2] The absolute stereochemistry of C-3 of Trp^5 was elucidated to be *R* by the CD spectrum showing positive curves at 264 ([θ]+10000) and 294 nm ([θ]+2200) and a negative one at 238 nm ([θ] −33000) (Fig. 5).[8] Therefore, the stereostructure of celogentin K was concluded to be **1**.

Biogenetically, celogentin K (**1**) might be derived from moroidin (**2**), by oxidation of Trp^5 followed by C–N bond cleavage between C-2 of Trp^5 and imidazol ring of His^8.

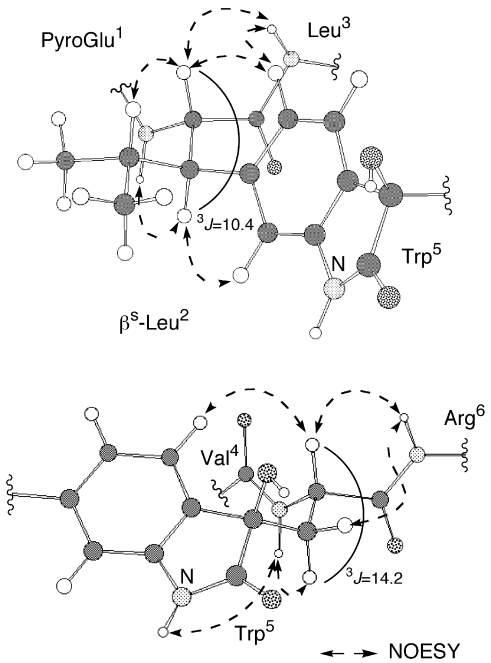

Figure 3. Selected NOESY correlations, $^3J_{H-H}$ couplings and relative stereochemistry for two units around Trp^5 in celogentin K (**1**).

Table 1. ^{1}H and ^{13}C NMR data of celogentin K (**1**) in DMSO-d_6 at 310 K

	δ_H [int. mult, J (Hz)]		δ_C	NOE relationship
PyroGlu[1]				
α	4.08 (1H, m)	α	55.07	PyroGlu[1]: Hγ; β[s]-Leu[2]: Hα, β, NH
β	1.69 and 2.25 (2H, m)	β	25.40	PyroGlu[1]: NH; β[s]-Leu[2]: Hα, β, NH
γ	2.09 (2H, t, 8.3)	γ	28.99	PyroGlu[1]: NH;
NH	7.87 (1H, s)	δ	177.41	β[s]-Leu[2]: Hα, β, NH
		C=O	172.28	
β[s]-Leu[2]				
α	4.86 (1H, t, 10.4)	α	53.36	β[s]-Leu[2]: Hγ, δ; Leu[3]: Hα, β, NH; Val[4]: Hα; Trp[5]: Hα, H4, 5, 7
β	2.97 (1H, m)	β	50.16	β[s]-Leu[2]: Hδ, NH; Trp[5]: H4, 5, 7, NH1
γ	2.05 (1H, m)	γ	26.26	β[s]-Leu[2]: NH; Leu[3]: NH; Trp[5]: H4, 5, 7, NH1
δ	0.63 (3H, d, 6.2)	δ	16.31	Leu[3]: NH; Trp[5]: α, H4, 5, 7, NH1
	0.73 (3H, m)		21.51	
NH	8.62 (1H, d, 9.0)	C=O	169.35	Trp[5]: NH1
Leu[3]				
α	4.12 (1H, m)	α	51.88	Leu[3]: Hγ, δ; Val[4]: Hα, NH
β	1.32 and 1.47 (1H, m)	β	42.13	Leu[3]: NH; Val[4]: Hα, β, NH
γ	1.45 (1H, m)	γ	24.72	
δ	0.71 (3H, m)	δ	20.69	
	0.80 (3H, m)		23.15	
NH	8.30 (1H, d, 10.3)	C=O	172.28	Val[4]: Hα, β, NH; Trp[5]: H4, 5, 7
Val[4]				
α	4.10 (1H, dd, 4.7, 8.6)	α	57.70	Val[4]: Hγ; Trp[5]: NH, Hα, β, H4, 5
β	1.96 (1H, m)	β	30.54	Val[4]: NH; Arg[6]: NH
γ	0.78 (6H, m)	γ	18.10	Val[4]: NH; Trp[5]: H5
			19.36	
NH	7.30 (1H, m)	C=O	169.21	Trp[5]: NH, H5
Trp[5]				
α	5.05 (1H, brt, 8.0)	α	47.18	Trp[5]: H4, 5; Arg[6]: Hα, β, γ, NH; Gly[7]: NH
β	1.47 (1H, m)	β	40.10	Trp[5]: H4, 5, NH, NH1; Arg[6]: Hα, NH; Gly[7]: NH
	2.32 (1H, brd, 14.2)	C2	179.34	
NH1	10.28 (1H, s)	C3	73.50	Trp[5]: H7
H4	6.81 (1H, d, 8.0)	C4	123.55	Trp[5]: H7; Arg[6]: NH
H5	7.35 (1H, d, 8.0)	C5	120.60	Trp[5]: H7; Arg[6]: NH
H7	6.42 (1H, s)	C6	138.10	
NH	8.24 (1H, m)	C7	112.68	
		C8	140.30	
		C9	128.43	
		C=O	172.13	
Arg[6]				
α	4.32 (1H, q, 7.0)	α	52.18	Arg[6]: Hγ, NHε; Gly[7]: Hα, NH; His[8]: NH, H2
β	1.54 (1H, m)	β	29.73	Arg[6]: NH; Gly[7]: Hα, NH
	1.69 (1H, m)	γ	23.89	
γ	1.48 (2H, m)	δ	40.34	
δ	3.10 (2H, m)	ε	156.89	
ε(NH)	7.81 (1H, br t, 5.4)	C=O	171.77	
NH	7.50 (1H, m)			
Gly[7]				
α	3.74 (2H, m)	α	41.68	His[8]: Hα, β, NH, H2
NH	8.46 (1H, t, 6.4)	C=O	168.55	His[8]: Hα, β, NH
His[8]				
α	4.50 (1H, q, 7.5)	α	51.58	His[8]: H2:
β	2.99 (1H, m)	β	27.04	His[8]: H2, NH
	3.11 (1H, m)	C1	130.34	
H2	7.22 (1H, m)	C2	116.87	
H4	8.60 (1H, m)	C4	133.93	His[8]: NH:
NH	8.24 (1H, m)	C=O	171.41	

Celogentin K (**1**) exhibited a weak inhibitory effect on polymerization of tubulin (20% inhibition at 100 μM) as compared to that of moroidin (**2**, IC_{50} 3.0 μM).

3. X-ray structure of moroidin (2)

Moroidin (**2**) isolated from *C. argentea* was crystallized from methanol–water as colorless needles, dec. 280 °C. The asymmetric unit contains two molecules (**A** and **B**) of **2** and 14 water molecules, giving a calculated density of 1.179 g cm^{-3}. The ORTEP drawings of conformers **A** and **B** were shown in Figures 6 and 7, respectively. The configurations at seven chiral centers in **2** obtained from X-ray analysis corresponded well to those proposed previously.[3,4]

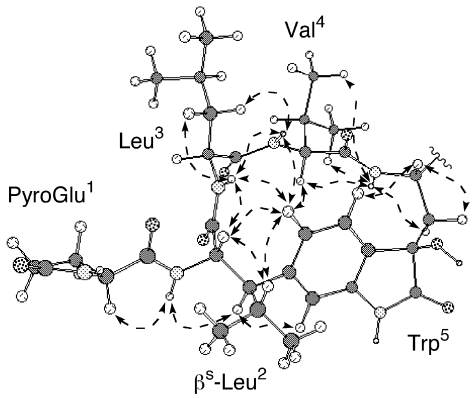

Figure 4. The ring conformation with selected NOESY correlations in celogentin K (**1**).

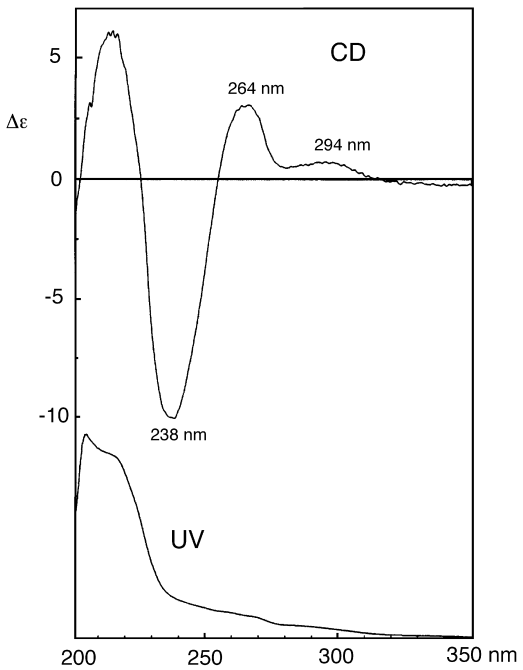

Figure 5. CD and UV spectra of celogentin K (**1**) in MeOH.

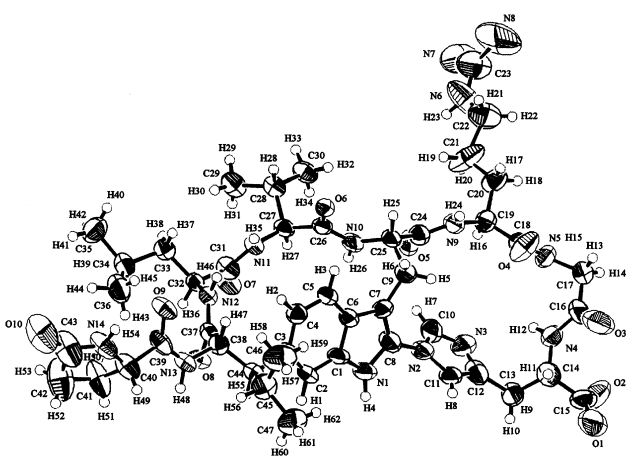

Figure 6. ORTEP drawing for conformer **A** of moroidin (**2**).

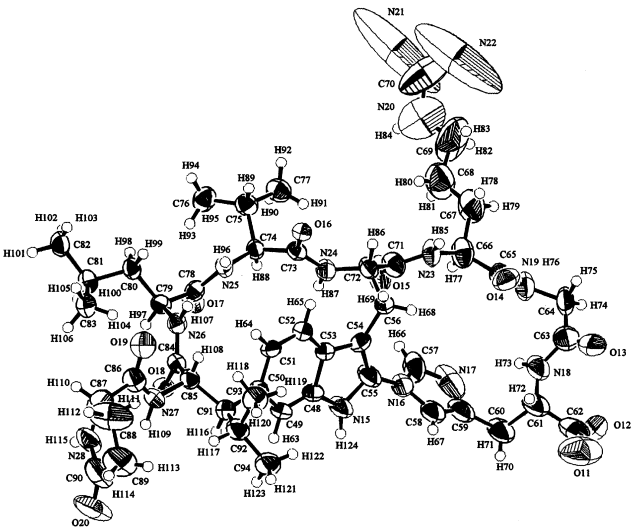

Figure 7. ORTEP drawing for conformer **B** of moroidin (**2**).

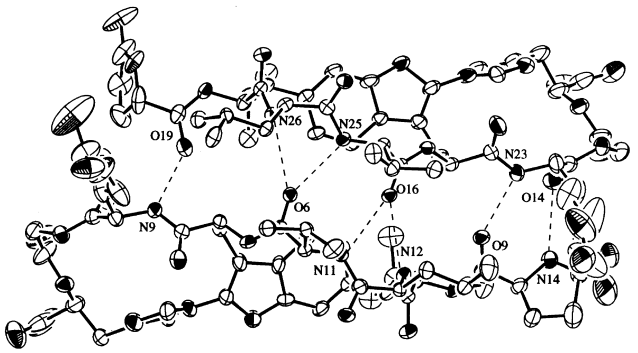

Figure 8. Two conformationally different molecules in the asymmetric unit. Broken lines show H-bonded contacts between conformers **A** and **B** for moroidin (**2**).

The ϕ and ψ-angles of the backbone of conformers **A** and **B** of moroidin (**2**) are summarized in Table 1, which shows that all (ϕ,ψ)-values lie in the β-region allowed for L-amino acids with the exception of the (ϕ,ψ)-value for Leu^3 and Gly^7. The conformation of the two respective moroidin molecule is essentially the same except for pyroGlu^1 residue. There are differences in the (ϕ,ψ)-values of pyroGlu^1 residue. The slightly twisting ω value of Arg^6 and (ϕ,ψ)-value for Gly^7 in the left handed α-helix region is considered to be caused by the highly constrained 14-membered ring system including the imidazol ring. Cyclic peptides are constrained as they contain turns in the backbones and these turns are often stabilized by intramolecular hydrogen bonds. There are no intramolecular hydrogen bonds in both conformers. The asymmetric unit consists of a pair of moroidin molecules, each of which forms seven hydrogen bonds linking N9, N11, N12, N14, N23, N25, and N26 of each molecule to the opposite CO moiety (see Fig. 8 and hydrogen-bond parameters listed in Table 3). Two molecules of **2** are also involved in peptide–water interactions with eight water molecules.

Table 2. Parts of torsion angles (°) along each peptide backbone of conformers **A** and **B** for moroidin (**2**)

Residue or angles	A			B		
	ϕ	ψ	ω	ϕ	ψ	ω
PyroGlu[1]	138 (2)	176 (1)	180 (1)	108 (2)	−8 (2)	−176 (1)
β^s-Leu[2]	−98 (1)	114.3 (8)	−173.8 (7)	−103 (1)	115.1 (9)	−174.5 (8)
Leu[3]	−106.8 (8)	−48 (1)	−173.7 (8)	−103.7 (9)	−52 (1)	−174 (1)
Val[4]	−142.1 (9)	126.8 (9)	172.5 (9)	−140 (1)	124.3 (9)	168 (1)
Trp[5]	−143 (1)	166.1 (8)	174.9 (8)	−140 (1)	163 (1)	172 (1)
Arg[6]	−128 (1)	157.0 (8)	170.1 (8)	−127 (1)	163.3 (9)	169 (1)
Gly[7]	79 (2)	29 (3)	−179 (1)	65 (2)	32 (2)	−178 (1)
His[8]	−69 (2)			−57 (2)		
C4–C3–C44–C38	45 (2)		C51–C50–C91–C85	42 (1)		
C3–C44–C38–C37	56 (1)		C50–C91–C85–C84	57.5 (8)		
C6–C7–C9–C25	−87 (2)		C53–C54–C56–C72	−86 (1)		
N10–C25–C9–C7	17 (1)		N24–C72–C56–C54	25 (1)		
N4–C14–C13–C12	−55 (2)		N18–C61–C60–C59	−61 (2)		
N3–C12–C13–C14	88 (2)		N17–C59–C60–C61	80 (2)		
C7–C8–N2–C10	−65 (2)		C54–C55–N16–C57	−62 (3)		

Table 3. Hydrogen bonds for moroidin (**2**)

A[a]	D[a]	H[a]	Distance (Å) A···D	A···H	Angle (°), A···H–D
O(1)	N(28)$^{(1)}$	115	2.83(2)	1.9	175
O(6)	N(25)	96	2.953(9)	2.1	166
O(6)	N(26)	107	2.986(9)	2.2	148
O(7)	N(15)$^{(4)}$	124	2.88(1)	2.0	161
O(9)	N(23)	85	2.90(1)	2.0	166
O(10)	N(5)$^{(5)}$	15	2.92(2)	2.3	130
O(14)	N(14)	54	2.85(1)	2.0	163
O(16)	N(11)	35	2.97(1)	2.1	161
O(16)	N(12)	46	2.967(8)	2.2	148
O(17)	N(1)$^{(8)}$	4	2.97(1)	2.1	174
O(19)	N(9)	24	2.86(2)	2.0	165
O(2)	N(22)$^{(2)}$	[b]	3.31(4)		
O(3)	N(7)$^{(3)}$	[b]	3.06(3)		
O(3)	N(22)$^{(2)}$	[b]	3.17(4)		
O(11)	N(8)$^{(6)}$	[b]	2.99(5)		
O(12)	N(8)$^{(6)}$	[b]	3.24(4)		
O(13)	N(7)$^{(6)}$	[b]	2.87(3)		
A	D (water)				
O(1)	O(32)$^{(1)}$		3.12(9)		
O(1)	O(34)$^{(2)}$		2.82(4)		
O(2)	O(23)		2.99(3)		
O(2)	O(28)		2.71(2)		
O(2)	O(33)		2.80(6)		
O(5)	O(21)$^{(4)}$		2.92(2)		
O(8)	O(24)		2.68(2)		
O(11)	O(27)		2.72(3)		
O(12)	O(25)		2.79(2)		
O(15)	O(31)		3.11(4)		
O(18)	O(22)		2.77(3)		
O(18)	O(32)		3.19(9)		
O(20)	O(26)$^{(7)}$		2.78(3)		
O(20)	O(32)		3.48(7)		
O(20)	O(34)$^{(9)}$		3.20(4)		

Symmetry operators: (1) $+1+X, -1+Y, +Z$; (2) $+1+X, +Y, -1+Z$; (3) $+1+X, +Y, +Z$; (4) $+X, -1+Y, +Z$; (5) $+X, +Y, +1+Z$; (6) $+1+X, +Y, +1+Z$; (7) $+X, +1+Y, +Z$; (8) $-1+X, +1+Y, +Z$; (9) $+X, +1+Y, -1+Z$; (10) $+X, +Y, -1+Z$; (11) $-1+X, +1+Y, +1+Z$; (12) $+1+X, -1+Y, -1+Z$; (13) $-1+X, +Y, +1+Z$; (14) $+X, -1+Y, +1+Z$; (15) $-1+X, +Y, +Z$; (16) $-1+X, +Y, -1+Z$.

[a] A=proton acceptor, D=proton donor, H=number of hydrogen atom.

[b] Hydrogen atoms could not be detected.

4. Experimental

4.1. General methods

^{1}H spectra were recorded in DMSO-d_6 on a 600 MHz spectrometers (Bruker AMX600) using 2.5 mm micro cells (Shigemi Co. Ltd.) at 310 K, while ^{13}C NMR spectra were measured on a 150 MHz spectrometer. The NMR sample of celogentin K (**1**) was prepared by dissolving 2.0 mg in 30 μL of DMSO-d_6 and chemical shifts were reported using residual DMSO-d_6 (δ_H 2.50 and δ_C 39.5) as internal standards. Standard pulse sequences were employed for the 2D NMR experiments. COSY, HOHAHA, and NOESY spectra were measured with spectral widths of both dimensions of 4800 Hz, and 32 scans with two dummy scans were accumulated into 1K data points for each of 256 t_1 increments. NOESY and HOHAHA spectra in the phase sensitive mode were measured with a mixing time of 800 and 30 ms, respectively. For HMQC spectra in the phase sensitive mode and HMBC spectra, a total of 256 increments of 1K data points were collected. For HMBC spectra with *Z*-axis PFG, a 50 ms delay time was used for long-range C–H coupling. Zero-filling to 1K for F_1 and multiplication with squared cosine-bell windows shifted in both dimensions were performed prior to 2D Fourier transformation. FABMS was measured on a JEOL JMS-HX110 by using glycerol as matrix.

4.2. Material

The seeds of *Celosia argentea* were purchased from Uchida Wakannyaku Co. in 1996. The botanical identification was made by Mr. N. Yoshida, Health Sciences University of Hokkaido. A voucher specimen has been deposited in the herbarium of Hokkaido University.

4.3. Extraction and isolation

The seeds (13.5 kg) of *C. argentea* were crashed and extracted with MeOH (18 L×3), and the MeOH extract was in turn partitioned with hexane, EtOAc, and *n*-BuOH. The *n*-BuOH-soluble materials were subjected to a Diaion

HP-20 column (MeOH/H_2O, 0:1→1:0), in which a fraction eluted with 60% MeOH was purified by an amino silica gel column ($CHCl_3$/MeOH/H_2O, 7:3:0.5→6:4:1) followed by C_{18} HPLC [CAPCELL PAK AQ, 5 μm, Shiseido Fine Chemicals, 10×250 mm; eluent, CH_3CN/0.1% CF_3CO_2H, (17:83); flow rate, 2 mL/min; UV detection at 210 nm] to afford celogentin K (**1**, 0.00002% yield) together with moroidin (**2**)[4] and celogentins A–H and J.[1,2]

4.3.1. Celogentin K (1). Colorless solid; $[\alpha]_D^{24}=-51°$ (*c* 0.5, 50% MeOH); UV (MeOH) λ_{max} (ε): 268 (1760) nm; IR (KBr) ν_{max} 3400, 2960, 1660, and 1545 cm^{-1}; ^1H and ^{13}C NMR (Table 1); FABMS *m/z* 1021 $(M+H)^+$; HRFABMS *m/z* 1021.5221 (M+H; calcd for $C_{50}H_{70}N_{14}O_{10}$, 1021.5219); CD (MeOH) λ_{max} (θ): 264 ([θ]+10000), 294 ([θ]+2200), and 238 nm ([θ]−33000).

4.4. Amino acid analysis of 1

Solution of **1** (0.05 mg) in 6 N HCl was heated at 110 °C for 24 h in a sealed tube. After cooling, solution was concentrated to dryness. The hydrolysate was dissolved in 0.02 N HCl and subjected to amino acid analyzer.

4.5. Absolute configurations of amino acids

Solution of **1** (0.1 mg) in 6 N HCl (0.2 mL) was heated at 110° for 24 h. The solution was concentrated to dryness. The residue was dissolved in H_2O (50 μL) and chiral HPLC analyses were carried out using a SUMICHIRAL OA-5000 column (Sumitomo Chemical Industry; 150 mm; 25 °C, detection at 254 nm). Retention times (min) of authentic amino acids were as follows: L-Glu (19.2), D-Glu (24.2), L-Val (6.1), D-Val (9.0), L-Arg (2.2), D-Arg (2.4), L-His (9.4), D-His (7.8), L-Leu (13.6), D-Leu (20.2) [eluent: MeOH/H_2O (15:85) containing 2.0 mM $CuSO_4$, flow rate 1.0 mL/min]; Retention times of the hydrolysate were as follows: L-Glu (19.2), L-Val (6.1), L-Arg (2.2), L-His (9.4), and L-Leu (13.6).

4.6. Microtubule assembly assay

Microtubule assembly was monitored spectroscopically by using a spectrophotometer equipped with a thermostatically regulated liquid circulator. The temperature was held at 37 °C and changes in turbidity were monitored at 400 nm. For the drug–protein studies, 10 μM of drug dissolved in 1% DMSO concentration. The turbidity changes were monitored throughout the incubation time.

4.7. X-ray analysis of moroidin (2)

Moroidin (**2**) was crystallized from MeOH–H_2O to give colorless needles (dec. 280 °C). Crystal data: $C_{47}H_{80}N_{14}O_{17}$, crystal dimensions 0.35×0.20×0.10 mm, space group *P*1 (#1), *a*=12.040 (5), *b*=13.422 (6), *c*=22.19 (1) Å, α=77.11(4)°, β=86.81(4)°, γ=63.85(4)°, *V*=3134(2) $Å^3$, *Z*=2, D_{calc}=1.179 g/cm^3. A crystal was coated with liquid paraffin and mounted in a loop. All measurements were made on a Rigaku RAXIS RAPID imaging plate area detector with graphite monochromated Mo Kα radiation (λ=0.71075 Å). Indexing was performed from 10° oscillations that were exposed for 1800 s. The crystal-to-detector distance was 127.40 mm. Cell constants and an orientation matrix for data collection as shown above corresponded to a primitive triclinic cell. Based on a statistical analysis of intensity distribution, and the successful solution and refinement of the structure, the space group was determined to be *P*1 (#1). The data were collected at a temperature of −180±1 °C in the range of 20.0°<2θ<50.7°. A total of 40 oscillation images were collected. A sweep of data was done using ω scans from 130.0 to 190.0° in 5.0° step, at χ=45.0° and ϕ=0.0°. The exposure rate was 360.0 [sec./°]. A second sweep was performed using ω scans from 0.0 to 140.0° in 5.0° step, at χ=45.0° and ϕ=180.0°. The exposure rate was 360.0 [sec./°]. The crystal-to-detector distance was 127.40 mm. Readout was performed in the 0.100 mm pixel mode. Of the 22704 reflections that were collected, 10479 were unique (R_{int}=0.041); equivalent reflections were merged. The linear absorption coefficient, μ, for Mo Kα radiation is 0.9 cm^{-1}. The data were corrected for Lorentz and polarization effects.

The structure was solved by direct methods and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms except for guanidino moiety of Arg[6] and water were included but not refines. The final cycle of full-matrix least-squares refinement on F^2 was based on 10456 observed reflections and 1406 variable parameters and converged (largest parameter shift was 0.01 times its esd) with unweighted and weighted agreement factors of $R1=\sum||F_o|-|F_c||/\sum w|F_o|=0.122[I>2.00\sigma(I)]$ and $wR2=[\sum w(F_o^2-F_c^2)^2/\sum w(F_o^2)^2]^{1/2}=0.348$ [$I>-3.00\sigma(I)$]. The standard deviation of an observation of unit weight was 1.10. Unit weights were used. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.69 and −0.41$e^-/Å^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber.[9] Anomalous dispersion effects were included in F_c; the values for $\Delta f'$ and $\Delta f''$ were those of Creagh and McAuley.[10] The values for the mass attenuation coefficients are those of Creagh and Hubbell.[11] All calculations were performed using the CrystalStructure crystallographic software package[12] except for refinement, which was performed using SHELXL-97. The refined fractional atomic coordinates, bond lengths, bond angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC).

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New entry to the Pauson–Khand reaction: trimethylgermyl group at the triple bond terminus as a latent functional group

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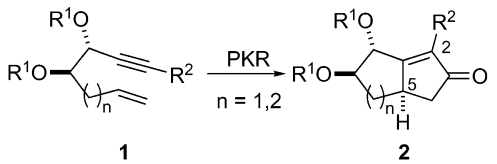
Abstract—The Pauson–Khand reaction of enynes possessing a trimethylgermyl group at the alkyne terminus afforded the corresponding bicyclo[3.3.0]octenone and bicyclo[4.3.0]nonenone skeletons in a stereoselective manner. The resulting trimethylgermyl group of the bicyclic compounds was then converted to the iodo group, which was used for further elaboration. Thus, the trimethylgermyl group at the triple bond terminus was shown to be a precursor for other appendages.

1. Introduction

The $Co_2(CO)_6$-mediated Pauson–Khand reaction (PKR)[1] is recognized as one of the most convenient and straightforward methods for the construction of bicyclo[3.3.0] as well as bicyclo[4.3.0] ring systems. Recent efforts from this laboratory[2,3] have led to the development of the highly stereoselective Pauson–Khand reaction of the enynes *ent*-**1** leading to the formation of the bicyclo[3.3.0]octenone and the bicyclo[4.3.0]nonenone derivatives *ent*-**2**[2,3] possessing two distinguishable hydroxyl groups. In particular, the exclusive formation of *ent*-**2a** (n=1,2) was observed when both substituents (R^1 and R^2) were sterically bulky silyl groups (R^1=TBDMS and R^2=TMS). However, upon exposure of the enyne **1b** (n=1) to PKR conditions, the ring-closed product **2b** (n=1) was obtained nonselectively.[2] Similarly, a decrease in stereoselectivity[3] was observed in the formation of the homologated **2b** (n=2). In addition, during the course of our program[4] directed toward the application of the newly developed stereoselective PKR to the total synthesis of bioactive compounds, the bicyclo[3.3.0]octenone derivatives **2** (n=1) with a suitable carbon appendage at the C_2-position were required as a core carbon framework. However, the PKR of the corresponding **1** (n=1) gave only a mixture of **2** (n=1) and its C_5-epimer in a moderately stereoselective manner, or nonstereoelectively (Scheme 1).[5]



a : R^1 = TBDMS, R^2 = TMS
b : R^1 = TBDMS, R^2 = H

Scheme 1.

Thus, the stereoselectivity recorded in the PKR of **1** appeared to depend in part on the bulkiness of the substituent at the triple bond terminus. In order to improve the low stereoselectivity encountered in the formation of **2b** (n=1,2)[2,3] and **2**[5] with a carbon side chain at the C_2-position, we concentrated on the silyl group at the triple bond terminus, since a bulky silyl group at the triple bond terminus might not only govern the diastereoselectivity in the PKR,[6] but could also be replaced under electrophilic substitution. Therefore, the terminal silyl moiety can be considered as a latent functional group. As a result, compound **2a** (n=1),[2] obtained from **1a** in a stereocontrolled manner, would become a versatile intermediate for the stereoselective preparation of several bicyclo[3.3.0] and bicyclo[4.3.0] skeletons **2** possessing a useful substituent at the α-position of the carbonyl functionality if efficient transformation of the vinylic TMS group into the suitable carbon tethers and hydrogen atom could be realized. However, treatment of **2a** (n=1) under typical conditions using I_2[7] or NIS,[8] showed no reaction at all and the starting **2a** (n=1) was completely recovered intact. Negishi's procedure[9] with ICl or the ICl–$AlCl_3$ system also was found not to be effective in this case. Consequently, we examined the PKR of **1** having a stannyl or germyl group instead of a silyl group at the triple bond terminus and the further transformation of the resulting **2** into the corresponding target compounds. In this paper,[10] we describe in detail the results of (i) the highly stereoselective PKR of

Keywords: Pauson–Khand reaction; Enyne; Trimethylgermyl group; Latent functional group; NIS.
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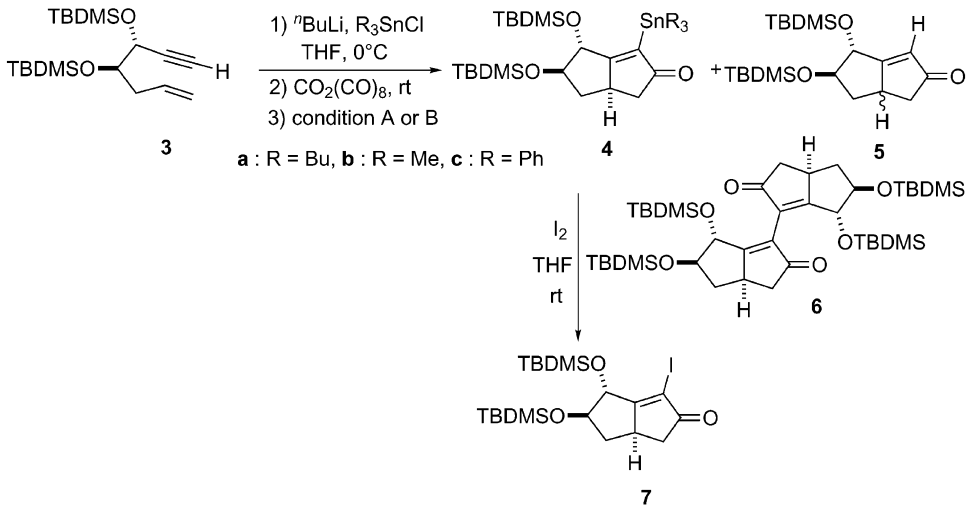
Table 1.



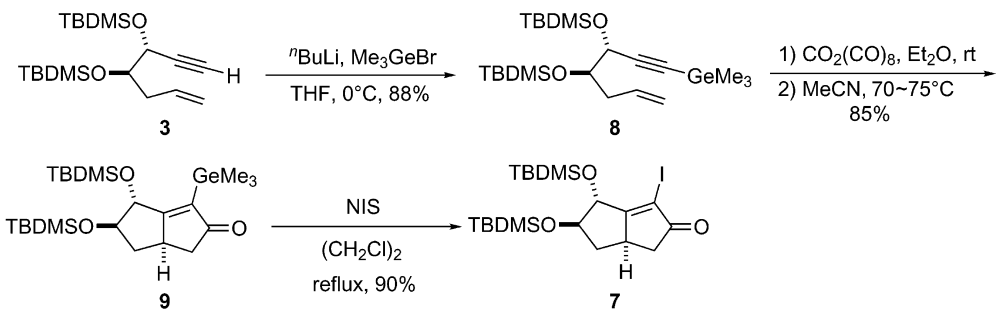
Entry	R	Condition	Yield (%)		
			4	**5**	**6**
1	Bu	A	47	14	—
2	Bu	B	65	—	—
3	Me	A	26	21	8
4	Me	B	24	24	9
5	Ph	A	27	17	—
6	Ph	B	48	Trace	—

Condition A: heated in CH_3CN at 50–55 °C. Condition B: heated in CH_3CN at 50–55 °C in the presence of 4 Å MS.

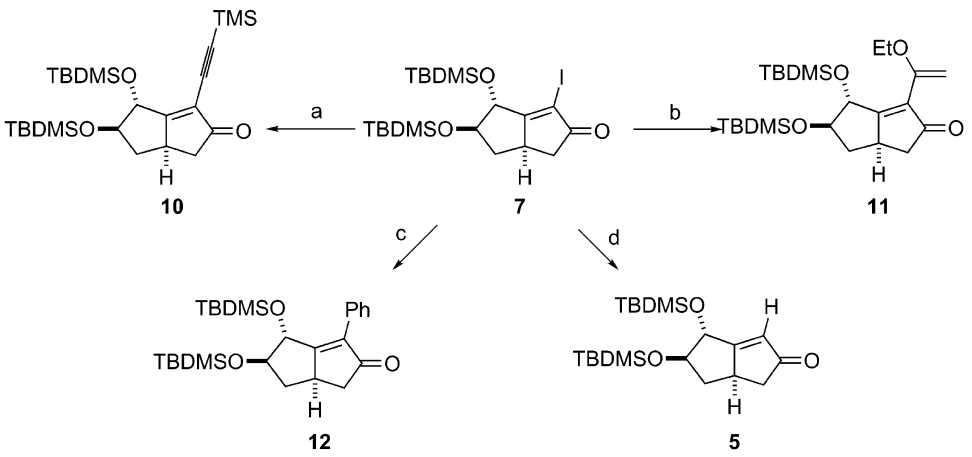
enynes having a trimethylgermyl group at the triple bond terminus and (ii) the successful transformation of the trimethylgermyl group into the desired functionalities.

We started out this study by investigating the PKR of the stannyl compounds, derived from compound **3**.[2] Treatment of the acetylide of **3** with tributyltin chloride afforded the corresponding enyne with the tributylstannyl functionality at the triple bond terminus. Because of its instability, the stannylated enyne was directly converted to the cobalt complex, which was then heated at 50–55 °C in acetonitrile[11] to provide **4a** in 47% yield in a stereoselective manner along with the nonstereoselective formation of **5** (50:50).[2b] The bicyclic compound **4a** was stable enough under PKR conditions, so that the formation of **5** could be rationalized by destannylation before the ring-closing reaction occurred. When the ring-closing reaction was carried out in the presence of 4 Å molecular sieves, **4a** was obtained in 65% yield as the sole product without detection of **5** (Table 1, entry 2). Changing the tributyl group on the tin atom to the trimethyl and triphenyl groups did not improve the chemical yield of **4** (entries 3–6). In the PKR of the trimethylstannylated derivative (entries 3 and 4), a small amount of the dimer **6** was observed. These results are summarized in Table 1. In contrast to compound **2a** with the TMS group, conversion of **4a** with the tributylstannyl group into the corresponding iodo derivative **7** (97%) was easily realized by simple treatment with I_2[7] in THF at rt.

Although the transformation of **3** into the iodide **7**, a key compound for various transformations, proceeded in a completely stereocontrolled manner via the corresponding stannylated **3** (Table 1, entry 2), this procedure (exclusive formation of **4a** without detection of **5** and **6**) could not be reproduced easily due to facile destannylation under PKR conditions. Therefore, a more reliable and reproducible method was required. To this end, we introduced a trimethylgermyl group instead of the tributylstannyl group at the alkyne terminus of **3** with the expectation that (i) the germyl group would be more reactive toward electrophilic



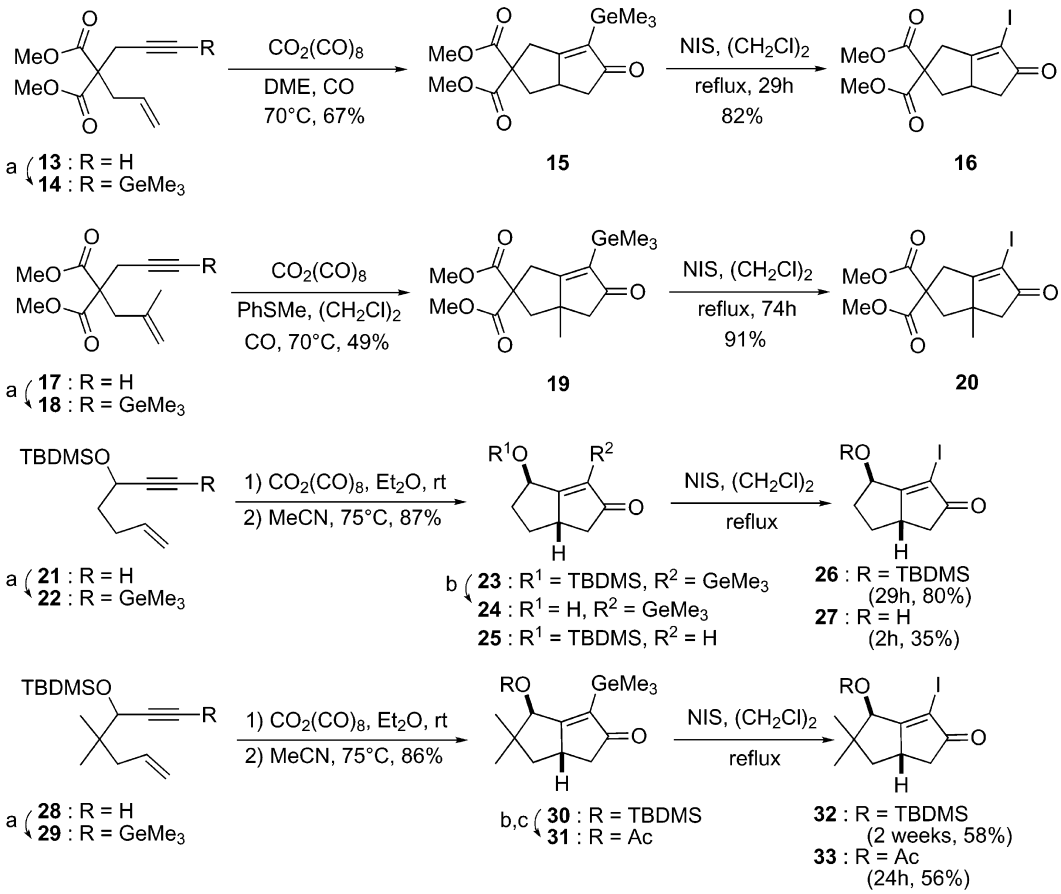
Scheme 2.



Scheme 3. Reagents and conditions: (a) $Pd(PPh_3)_2Cl_2$, TMSC≡CH, $^iPr_2NH$, CuI, THF, rt, 98%; (b) $Pd(PPh_3)_2Cl_2$, (α-ethoxyvinyl)$SnMe_3$, THF, 65 °C, 84%; (c) $Pd(PPh_3)_2Cl_2$, $PhSnBu_3$, THF, reflux, 76%; (d) Bu_3SnH, THF, 55 °C, 83%.

substitution than the silyl group, and (ii) that the C–Ge bond would be stronger than the C–Sn bond and could tolerate the PKR conditions (Scheme 2). Thus, the acetylide, generated from **3**, was trapped by treatment with trimethylgermyl bromide to give **8** in 88% yield, which was subsequently exposed to $Co_2(CO)_8$. The resulting cobalt complex was heated in acetonitrile[11] to produce exclusively **9** in 85% overall yield. No formation of **5** or **6** could be detected in the reaction mixture. The 4 Å molecular sieves were not necessary in this case (Table 1, entry 2). Compound **9** was treated with NIS[8] in refluxing 1,2-dichloroethane for 36 h to furnish **7** in 90% yield. It could be predicted that the conversion of **9** to **7** required a higher reaction temperature compared to the transformation of the stannylated compound **4a** to **7**. It should be noted that the transformation of **8** to **7** via **9** under these conditions was reproduced several times.

With the iodo derivative **7** in hand, we next examined the conversion of the iodo group on the vinyl moiety of **7** to



Scheme 4. Reagents and conditions: (a) ^{n}BuLi, Me_3GeBr, THF, −78 °C, **14** (90%), **18** (81%), **22** (91%), **29** (97%); (b) TBAF, AcOH, THF, 0 °C, **24** (85%),; (c) Ac_2O, DMAP, CH_2Cl_2, 0 °C, (72%).

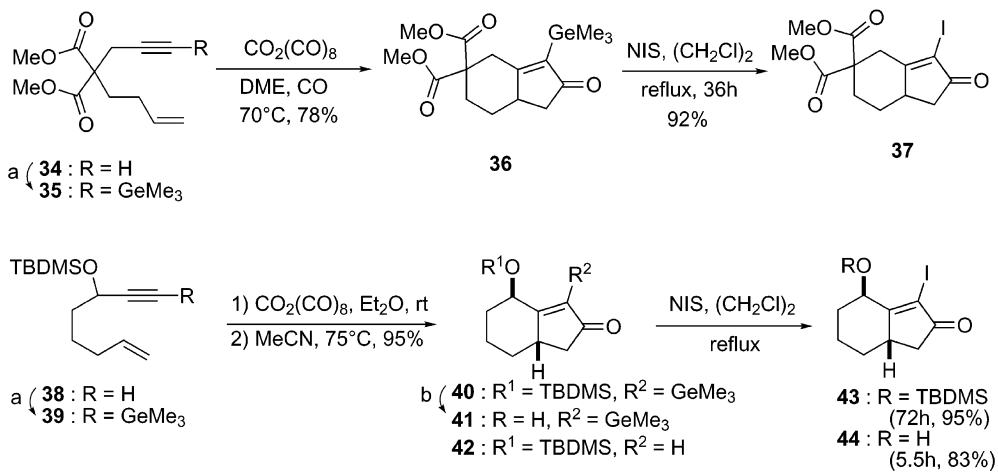
suitable functionalities (Scheme 3). Introduction of carbon side chains to the C_2-position was realized by palladium-catalyzed coupling[12] with trimethylsilylacetylene, α-(ethoxyvinyl)trimethylstannane and tributylphenylstannane to produce the corresponding coupling products **10**, **11**, and **12** in 98, 84, and 76% yield, respectively. The C_2-unsubstituted bicyclo[3.3.0]octenone derivative **5**, which had previously been nonstereoselectively obtained in 83% yield by the PKR of **3**,[2] could now be formed exclusively upon exposure of **7** to Bu_3SnH (Scheme 2).

We next investigated the PKR of several other enynes having trimethylgermyl functionality at the triple bond terminus to confirm the generality of this newly developed procedure. Scheme 4 summarizes our preparation of several bicyclo[3.3.0]octenone derivatives. The PKR[13] of the simple malonate derivative **14** possessing the trimethylgermyl functionality provided, in 67% yield, the corresponding bicyclic compound **15**, which was subsequently converted to the iodo derivative **16** in 82% yield. Under PKR conditions,[14] the enyne derivative **18** with a methyl group on the olefin moiety produced the desired **19**, although the yield (49%) was somewhat lower. Prolonged treatment of **19** with NIS furnished **20** in 91% yield, indicating tolerance of the 1,1-disubstituted olefin functionality in this transformation. Exclusive formation of **23** was realized by the PKR[11] of **22**, similar to the case of compound **9**. The enyne **21** without a terminal trimethylgermyl group was submitted to the PKR conditions[11] as a control experiment to afford a mixture of **25** along with its epimer in 79% yield in a ratio of 72 to 28. Thus, trimethylgermyl group was again found to govern the stereochemical outcome in this ring-closing reaction. Conversion of **23** into **26** under standard conditions required a relatively longer reaction time. In order to make the reaction time shorter, **23** was first desilylated to give **24**, which was subjected to the standard iodination conditions. Complete consumption of the starting material **24** was achieved within 2 h, but the yield was poor (35%).[15] Exclusive construction of **30** (86%)[11] from **29** was followed by conversion of the trimethylgermyl group to the iodo moiety to produce **32** in good yield (58%). A prolonged reaction time was required to complete the transformation of **30** into **32** under standard conditions (two weeks). Thus, adjustment of the protecting group of **30** from the bulky silyl group to the less sterically hindered acetyl group (compound **31**)[16] shortened its reaction time (24 h) and gave a similar yield.

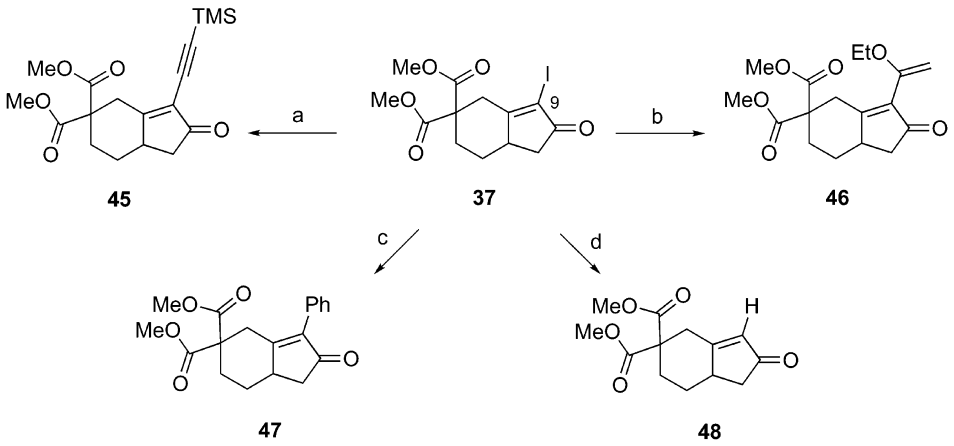
The final phase of this study was the successful application of this procedure to the synthesis of the bicyclo[4.3.0] skeleton. The homologated enyne **35** possessing the trimethylgermyl group underwent the ring-closing reaction[13] to provide the bicyclo[4.3.0]nonenone derivative **36**, which was then transformed to the corresponding iodo derivative **37** in 92% yield. On the basis of the above-mentioned preparation of compounds **9**, **23**, and **30**, it is therefore not surprising that the PKR[11] of **39** produced **40** exclusively in 95% yield. A control experiment using the unsubstituted enyne **38** produced a mixture of **42** and its epimer in 77% yield in a ratio of 92 to 8. The bicyclic derivative **40** was converted to the iodo derivative **43** in 95% yield when heated with NIS in dichloroethane for 72 h. Treatment of the alcohol (compound **41**), prepared by removal of the bulky silyl group, shortened the reaction to less than one tenth the time (5.5 h), although the yield was somewhat lower (**44**, 83%) (Scheme 5).

According to the procedure described in Scheme 3, the introduction of various carbon units at the C_9-position of **37** was achieved in the presence of a palladium catalyst[12] to furnish compounds **45**, **46**, and **47** in high yields. Reduction of **37** to **48** was also realized in 87% yield, as shown in Scheme 6.

In summary, we have developed the PKR of enynes having a trimethylgermyl group at the alkyne terminus where the stereoselective construction of the bicyclic compounds was achieved. The trimethylgermyl moiety at the α position to the carbonyl functionality of the resulting bicyclo[3.3.0]-octenone and bicyclo[4.3.0]nonenone frameworks could be converted into an iodo functionality by simple treatment with NIS in refluxing 1,2-dichloroethane. Thus, this procedure provides a new utilization of the trimethylgermyl group in PKR as a latent functional group. Further elaboration is still required and is underway in our laboratory.



Scheme 5. Reagents and conditions: (a) ^{n}BuLi, Me_3GeBr, THF, −78 °C, **35** (80%), **39** (93%); (b) TBAF, AcOH, THF, 0 °C, (87%).



Scheme 6. Reagents and conditions: (a) $Pd(PPh_3)_2Cl_2$, TMSC≡CH, $^iPr_2NH$, CuI, THF, rt, 99%; (b) $Pd(PPh_3)_2Cl_2$, (α-ethoxyvinyl)$SnMe_3$, THF, 65 °C, 87%; (c) $Pd(PPh_3)_2Cl_2$, $PhSnBu_3$, THF, reflux, 88%; (d) Bu_3SnH, THF, 55 °C, 87%.

2. Experimental

Infrared spectra were measured with a Shimazu IR-460 spectrometer in $CHCl_3$, mass spectra with a Hitachi M-80 and JEOL GC mate mass spectrometers, ^1H NMR spectra with JEOL JNM-EX270 and JNM-GSX500 spectrometers for samples in $CDCl_3$, using either tetramethylsilane (for compounds without a silyl group) or $CHCl_3$ (7.26 ppm) (for compounds with a silyl group) as an internal standard, and ^{13}C NMR spectra with JEOL JNM-EX270 and JNM-GSX500 spectrometers in $CDCl_3$ with $CDCl_3$ (77.00 ppm) as an internal reference. All reactions were carried out under a nitrogen atmosphere otherwise stated. Silica gel (Silica gel 60, 230–400 mesh, Merck) was used for chromatography. Organic extracts were dried over anhydrous Na_2SO_4.

2.1. General procedure for PKR of stannylated enynes

Conditions A. To a solution of enyne **3** in dry THF (0.1 M) was dropwise added *n*-BuLi in hexane (1.5 equiv.) at 0 °C. After stirring for 1 h, R_3SnCl (2.0 equiv.) was added to the reaction, which was stirred at the same temperature for 1 h. The reaction was quenched by addition of saturated aqueous NH_4Cl, extracted with Et_2O, which was then washed with H_2O and brine, dried and concentrated to dryness. The residue was directly used for the next PKR without further purification. To a solution of the crude residue in Et_2O (0.1 M) was added $Co_2(CO)_8$ (1.5 equiv.) at rt and the mixture was stirred for 1 h. Et_2O was evaporated and the residue was passed through a short pad of silica gel with hexane to give the cobalt complexed enyne derivative. A solution of the cobalt complex in acetonitrile (0.05 M) was heated at 50–55 °C for 1 h. The reaction mixture was filtered through a short pad of celite, washed with AcOEt, and concentrated to dryness. Chromatography of the residue with 2–5% AcOEt in hexane afforded **4**, **5**,[2b] and **6**.

Conditions B. The PKR of the stannylated enynes was carried out in the presence of 4Å-MS. The results were summarized in Table 1.

2.1.1. (5*R*,7*R*,8*R*)-7,8-Bis(*tert*-butyldimethylsiloxy)-2-(tributylstannyl)bicyclo[3.3.0]oct-1-en-3-one (4a). Colorless oil; $[\alpha]_D^{29}$=+78.9 (*c* 0.64, $CHCl_3$); IR 1682, 1612 cm^{-1}; ^1H NMR δ 4.34–4.31 (1H, m), 4.17 (1H, dd, *J*=6.8, 2.9 Hz), 3.32–3.24 (1H, m), 2.67 (1H, dd, *J*=17.6, 6.8 Hz), 2.57 (1H, ddd, *J*=13.2, 10.3, 6.4 Hz), 2.05 (1H, dd, *J*=17.6, 3.4 Hz),1.53–1.45 (6H, m), 1.31 (6H, sex, *J*=7.3 Hz), 1.11 (1H, ddd, *J*=13.2, 8.3, 2.9 Hz), 1.04 (6H, t, *J*=7.3 Hz), 0.88 (9H, t, *J*=7.3 Hz), 0.87 (9H, s), 0.83 (9H, s), 0.13 (3H, s), 0.07 (3H, s), 0.05(3H, s), 0.03 (3H, s); ^{13}C NMR δ 216.5, 193.8, 139.7, 80.3, 77.0, 44.5, 42.8, 39.6, 29.1, 27.3, 25.8, 25.6, 18.0, 17.9, 13.6, 9.8, −4.2, −4.3, −4.6, −4.8; MS *m/z* 672 (M^+, 0.46). HRMS calcd for $C_{32}H_{64}O_3Si_2Sn$ 672.3416, Found 672.3431.

2.1.2. (5*R*,7*R*,8*R*)-7,8-Bis(*tert*-butyldimethylsiloxy)-2-(trimethylstannyl)bicyclo[3.3.0]oct-1-en-3-one (4b). Colorless oil; $[\alpha]_D^{28}$=+85.0 (*c* 0.32, $CHCl_3$); IR 1682, 1614 cm^{-1}; ^1H NMR δ 4.37–4.33 (1H, m), 4.20–4.14 (1H, m), 3.31–3.24 (1H, m), 2.69 (1H, dd, *J*=17.6, 6.8 Hz), 2.57 (1H, ddd, *J*=13.2, 10.3, 6.4 Hz), 2.06 (1H, dd, *J*=17.6, 3.4 Hz), 1.15 (1H, ddd, *J*=13.2, 7.3, 2.0 Hz), 0.87 (9H, s), 0.82 (9H, s), 0.27 (9H, s), 0.12 (3H, s), 0.05 (3H, s), 0.04 (3H, s), 0.03 (3H, s); ^{13}C NMR δ 239.5, 216.3, 194.1, 139.4, 80.1, 76.5, 44.6, 42.5, 39.2, 25.7, 25.6, 18.0, 17.8, −4.3, −4.4, −4.6, −4.7; MS *m/z* 542 (M^+, 13.7). HRMS calcd for $C_{23}H_{46}O_3Si_2Sn$ 542.2007, Found 542.1977.

2.1.3. (5*R*,7*R*,8*R*)-7,8-Bis(*tert*-butyldimethylsiloxy)-2-(triphenylstannyl)bicyclo[3.3.0]oct-1-en-3-one (4c). Colorless oil; $[\alpha]_D^{26}$=+90.9 (*c* 0.3, $CHCl_3$); IR 1686, 1616 cm^{-1}; ^1H NMR δ 7.62–7.60 (6H, m), 7.37–7.35 (9H, m), 4.29–4.25 (1H, m), 4.11 (1H, dd, *J*=6.4, 2.0 Hz), 3.48–3.42 (1H, m), 2.80 (1H, dd, *J*=18.1, 6.8 Hz), 2.62 (1H, ddd, *J*=13.2, 10.3, 6.4 Hz), 2.20 (1H, dd, *J*=18.1, 3.4 Hz), 1.21 (1H, ddd, *J*=13.2, 7.3, 2.0 Hz), 0.80 (9H, s), 0.75 (9H, s), 0.02 (6H, s), −0.32 (3H, s), −0.33 (3H, s); ^{13}C NMR δ 215.5, 196.6, 137.8, 137.4, 137.3, 137.2, 129.1, 128.9, 128.1, 80.3, 75.6, 44.2, 4.6, 39.5, 25.8, 25.5, 17.9, 17.7, −4.6, −4.7, −4.8; MS *m/z* 732 (M^+, 32.6). HRMS calcd for $C_{38}H_{52}O_3Si_2Sn$ 732.2477, Found 732.2482.

2.1.4. Dimer 6. Colorless oil; IR 1703, 1614 cm^{-1}; ^1H NMR δ 4.96 (2H, d, *J*=2.9 Hz), 4.28 (2H, ddd, *J*=8.3, 6.8, 2.9 Hz), 3.15–3.08 (2H, m), 2.68 (2H, dd, *J*=18.1, 6.8 Hz), 2.50 (2H, dt, *J*=12.2, 6.8 Hz), 2.18 (2H, dd, *J*=18.1, 3.4 Hz), 1.24 (2H, dt, *J*=12.2, 8.3 Hz), 0.90 (18H, s), 0.81

(18H, s), 0.10 (6H, s), 0.08 (6H, s), 0.06 (6H, s), −0.07 (6H, s); ^{13}C NMR δ 207.1, 182.0, 129.1, 83.6, 76.6, 41.8, 40.9, 39.0, 25.9, 25.7, 17.97, 17.92, −3.9, −4.5, −4.6, −4.7; MS *m/z* 762 (M^+, 12.6). FABHRMS calcd for $C_{40}H_{75}O_6Si_4$ 763.4641, Found 763.4606.

2.1.5. (5*R*,7*R*,8*R*)-7,8-Bis(*tert*-butyldimethylsiloxy)-2-iodobicyclo[3.3.0]oct-1-en-3-one (7). *From compound* **4a**. A solution of **4a** (175 mg, 2.61×10^{-1} mmol) and I_2 (133 mg, 5.24×10^{-1} mmol) in dry THF (1.3 mL) was stirred at rt overnight. The reaction mixture was diluted with Et_2O, washed with saturated aqueous $Na_2S_2O_3$ and brine, dried, and concentrated to dryness. Chromatography of the residue with hexane–AcOEt (32:1) gave **7** (133 mg, quant.) as a colorless oil: $[\alpha]_D^{28}$=+138.3 (*c* 0.43, $CHCl_3$); IR 1715, 1632 cm^{-1}; ^{1}H NMR δ 4.40–4.35 (1H, m), 4.24 (1H, ddd, *J*=6.4, 4.4, 2.0 Hz), 3.31–3.26 (1H, m), 2.92 (1H, dd, *J*=18.1, 6.8 Hz), 2.61 (1H, ddd, *J*=13.2, 9.8, 6.4 Hz), 2.23 (1H, dd, *J*=18.1, 2.9 Hz), 1.23 (1H, ddd, *J*=13.2, 8.8, 4.4 Hz), 0.89 (9H, s), 0.85 (9H, s), 0.20 (3H, s), 0.14 (3H, s), 0.08 (3H, s), 0.05 (3H, s); ^{13}C NMR δ 204.8, 187.8, 96.3, 80.8, 78.2, 42.2, 41.5, 39.2, 25.7, 18.0, 17.8, −4.1, −4.5, −4.6, −4.8; FABMS *m/z* 509 (M^++1, 12.5). FABHRMS calcd for $C_{20}H_{38}IO_3Si_2$ 509.1404, Found 509.1409 (M^++1).

From compound **9**. A solution of **9** (6.8 mg, 1.36×10^{-2} mmol) and *N*-iodosuccinimide (4.6 mg, 2.04×10^{-2} mmol) in 1,2-dichroloethane (0.3 mL) was refluxed for 36 h in the dark. The reaction mixture was quenched by addition of water, extracted with CH_2Cl_2, which was washed with water and brine, dried and concentrated to dryness. Chromatography of the residue gave **7** (6.2 mg, 90%).

2.1.6. (4*R*,5*R*)-4,5-Bis(*tert*-butyldimethylsiloxy)-7-(trimethylgermyl)hep-1-en-6-yne (8). To a solution of **3** (50.0 mg, 1.41×10^{-1} mmol) in THF (1.4 mL) was added *n*-BuLi in hexane (1.30 M, 0.16 mL, 2.11×10^{-1} mmol) at 0 °C and the reaction mixture was stirred for 1 h at the same temperature. Me_3GeBr (0.04 mL, 2.82×10^{-1} mmol) was then added to a solution of the acetylide in THF and stirring was continued for 30 min at 0 °C. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl, extracted with Et_2O, washed with water and brine, dried, and concentrated to dryness. Chromatography of the residue with hexane gave **8** (58.4 mg, 88%) as a colorless oil: $[\alpha]_D^{26}$=−0.20 (*c* 0.5, $CHCl_3$); IR 2170, 1639 cm^{-1}; ^{1}H NMR^{1}H NMR δ 5.87 (1H, ddt, *J*=17.6, 10.3, 7.3 Hz), 5.09–5.01 (2H, m), 4.29 (1H, d, *J*=5.4 Hz), 3.63 (1H, ddd, *J*=6.8, 5.4, 4.4 Hz), 2.48–2.33 (2H, m), 0.91 (9H, s), 0.90 (9H, s), 0.33 (9H, s), 0.14 (3H, s), 0.10 (3H, s), 0.07 (3H, s), 0.06 (3H, s); ^{13}C NMR δ 135.7, 116.7, 104.2, 90.2, 75.1, 67.1, 37.3, 25.93, 25.88, 18.3, 18.1, −0.4, −4.3, −4.42, −4.43, −4.6; MS *m/z* 472 (M^+, 41.0). HRMS calcd for $C_{22}H_{46}GeO_2Si_2$ 472.2248, Found 472.2244.

2.1.7. (5*R*,7*R*,8*R*)-7,8-Bis(*tert*-butyldimethylsiloxy)-2-(trimethylgermyl)bicyclo[3.3.0]oct-1-en-3-one (9). According to the general procedure for PKR (Conditions A), **8** (58.0 mg, 1.23×10^{-1} mmol) was treated with $Co_2(CO)_8$ (63.0 mg, 1.85×10^{-1} mmol). The resulting cobalt complex was heated at 70–75 °C in acetonitrile (1.2 mL) for 3 h. Work-up and chromatography of the residue with hexane–AcOEt (50:1) gave **9** (51.5 mg, 85%) as a colorless oil: $[\alpha]_D^{25}$=+95.9 (*c* 0.5, $CHCl_3$); IR 1686, 1622 cm^{-1}; ^{1}H NMR δ: 4.48–4.44 (1H, m), 4.16 (1H, d, *J*=5.9 Hz), 3.24–3.19 (1H, m), 3.63 (1H, dd, *J*=17.6, 6.8 Hz), 2.55 (1H, ddd, *J*=13.2, 10.3, 5.9 Hz), 3.63 (1H, dd, *J*=17.6, 3.9 Hz), 1.13 (1H, ddd, *J*=13.2, 7.3, 2.0 Hz), 0.87 (9H, s), 0.82 (9H, s), 0.36 (9H, s), 0.13 (3H, s), 0.07 (3H, s), 0.04 (3H, s), 0.02 (3H, s); ^{13}C NMR δ 215.0, 191.2, 138.7, 80.0, 75.7, 45.0, 41.4, 38.9, 25.7, 25.6, 17.9, 17.8, −1.2, −4.3, −4.6, −4.7; MS *m/z* 500 (M^+, 27.0). HRMS calcd for $C_{23}H_{46}GeO_3Si_2$ 500.2197, Found 500.2195.

2.1.8. (5*R*,7*R*,8*R*)-7,8-Bis(*tert*-butyldimethylsiloxy)-2-[2-(trimethylsilyl)ethyn-1-yl]bicyclo[3.3.0]oct-1-en-3-one (10). To a solution of **7** (20.0 mg, 3.93×10^{-2} mmol), (trimethylsilyl)acetylene (0.8×10^{-2} mL, 5.90×10^{-2} mmol), $Pd(PPh_3)_2Cl_2$ (1.7 mg, 2.36×10^{-3} mmol), and CuI (0.23 mg, 1.18×10^{-3} mmol) in THF (0.4 mL) was added *i*-Pr_2NH (0.06 mL, 3.93×10^{-1} mmol) at rt. The reaction mixture was stirred for 2 h, passed through a short pad of celite, and concentrated to dryness. Chromatography of the residue with hexane–AcOEt (5:1) gave **10** (18.5 mg, 98%) as a colorless oil: $[\alpha]_D^{28}$=+130.7 (*c* 0.26, $CHCl_3$); IR 2158, 1717, 1639 cm^{-1}; ^{1}H NMR δ 4.58–4.51 (1H, m), 4.28–4.25 (1H, m), 3.20–3.15 (1H, m), 2.77 (1H, dd, *J*=18.6, 6.8 Hz), 2.55 (1H, ddd, *J*=12.7, 9.3, 6.3 Hz), 2.15 (1H, dd, *J*=18.6, 3.4 Hz), 1.13 (1H, ddd, *J*=12.7, 9.3, 4.9 Hz), 0.89 (9H, s), 0.85 (9H, s), 0.22 (9H, s), 0.18 (3H, s), 0.11 (3H, s), 0.08 (3H, s), 0.05 (3H, s); ^{13}C NMR δ 206.2, 186.4, 122.7, 103.9, 94.7, 82.1, 75.7, 43.1, 39.3, 39.1, 25.73, 25.70, 18.0, 17.9, −0.2, −4.4, −4.6, −4.8, −4.9; FABMS *m/z* 479 (M^++1, 3.7). FABHRMS calcd for $C_{25}H_{47}O_3Si_3$ 479.2833, Found 479.2846.

2.1.9. (5*R*,7*R*,8*R*)-7,8-Bis(*tert*-butyldimethylsiloxy)-2-(1-ethoxyethen-1-yl)bicyclo[3.3.0]oct-1-en-3-one (11). A solution of **7** (99.2 mg, 1.95×10^{-1} mmol), $Pd(PPh_3)_2Cl_2$ (13.7 mg, 1.95×10^{-2} mmol) and (α-ethoxyvinyl)trimethyltin (183 mg, 7.80×10^{-1} mmol) in THF (1.0 mL) was heated at 65 °C for 6.5 h. The reaction mixture was diluted with AcOEt, which was washed with water and brine, dried, and concentrated to dryness. Chromatography of the residue with hexane–AcOEt (50:1) gave **11** (74.1 mg, 84%) as a colorless oil: $[\alpha]_D^{28}$=+114 (*c* 0.28, $CHCl_3$); IR 1701, 1651 cm^{-1}; ^{1}H NMR δ 5.24 (1H, d, *J*=2.4 Hz), 5.03–4.96 (1H, m), 4.37 (1H, d, *J*=2.4 Hz), 4.20 (1H, dd, *J*=6.3, 2.4 Hz), 3.88–3.78 (2H, m), 3.14–3.08 (1H, m), 2.78 (1H, dd, *J*=17.6, 6.8 Hz), 2.58 (1H, ddd, *J*=13.7, 10.3, 6.3 Hz), 2.17 (1H, dd, *J*=17.6, 3.4 Hz), 1.37 (3H, t, *J*=7.3 Hz), 1.14 (1H, ddd, *J*=13.7, 7.8, 2.4 Hz), 0.86 (9H, s), 0.81 (9H, s), 0.11 (3H, s), 0.04 (3H, s), 0.03 (3H, s), 0.00 (3H, s); ^{13}C NMR δ 205.6, 177.9, 153.5, 130.9, 89.0, 81.7, 76.2, 62.0, 44.7, 39.0, 37.7, 25.9, 25.8, 18.1, 18.0, 14.6, −4.4, −4.6, −4.7; FABMS *m/z* 453 (M^++1, 4.1). FABHRMS calcd for $C_{24}H_{45}O_4Si_2$ 453.2856, Found 453.2858.

2.1.10. (5*R*,7*R*,8*R*)-7,8-Bis(*tert*-butyldimethylsiloxy)-2-phenylbicyclo[3.3.0]oct-1-en-3-one (12). A solution of **7** (17.6 mg, 3.46×10^{-2} mmol), $Pd(PPh_3)_2Cl_2$ (2.5 mg, 3.46×10^{-3} mmol) and Bu_3SnPh (45 μL, 1.38×10^{-1} mmol) in THF (0.3 mL) was refluxed for 5 h. The reaction mixture was diluted with AcOEt, which was washed with water and brine, dried, and concentrated to dryness.

Chromatography of the residue with hexane–AcOEt (26:1) gave **12** (12.0 mg, 76%) as a colorless oil: $[\alpha]_D^{26}$= +88.6 (*c* 0.42, $CHCl_3$). FABHRMS calcd for $C_{26}H_{43}O_3Si_2$ 459.2750, Found 459.2762. Spectral data were shown in ref 2b.

2.1.11. (5*R*,7*R*,8*R*)-7,8-Bis(*tert*-butyldimethylsiloxy)bicyclo[3.3.0]oct-1-en-3-one (5). A solution of **7** (51.0 mg, 1.00×10^{-1} mmol), Bu_3SnH (0.13 mL, 5.01×10^{-1} mmol) and AIBN (a catalytic amount) in THF (0.2 mL) was heated at 55 °C for 1 h. The reaction mixture was diluted with AcOEt, which was washed with water and brine, dried, and concentrated to dryness. Chromatography of the residue with hexane–AcOEt (20:1) gave **5** (32.0 mg, 83%) as a colorless oil: $[\alpha]_D^{26}$=+102.5 (*c* 0.3, $CHCl_3$). FABHRMS calcd for $C_{20}H_{39}O_3Si_2$ 383.2437, Found 383.2432. Spectral data are shown in Ref. 2b.

2.1.12. Dimethyl 2-allyl-2-[3-(trimethylgermyl)-2-propyn-1-yl]malonate (14). According to the procedure described for preparation of **8** from **3**, **14** (1.07 g, 90%) was obtained from **13**[17] (794 mg, 3.78 mmol) a colorless oil: IR 2174, 1736, 1641 cm^{-1}; ^1H NMR δ 5.63 (1H, ddt, *J*=10, 17, 7.6 Hz), 5.19–5.09 (2H, m), 3.72 (6H, s), 2.81–2.78 (4H, m), 0.31 (9H, s); ^{13}C NMR δ 170.2, 131.9, 119.5, 99.5, 88.0, 57.1, 52.5, 36.5, 23.9, −0.3; FABMS *m*/*z* 329 (M^++1, 10.1). FABHRMS calcd for $C_{14}H_{23}GeO_4$ 329.0808, Found 329.0814.

2.1.13. 7,7-Bis(methoxycarbonyl)-2-(trimethylgermyl)-bicyclo[3.3.0]oct-1-en-3-one (15). To a solution of enyne **14** (32.8 mg, 1.00×10^{-1} mmol) in DME (1.0 mL) was added $Co_2(CO)_8$ (41.2 mg, 1.20×10^{-1} mmol). The reaction mixture was heated at 70 °C under an atmosphere of CO for 24 h, passed through a short pad of celite, and concentrated to dryness. Chromatography of the residue with hexane–AcOEt (10:1) gave **15** (23.9 mg, 67%) as colorless plates: mp 70–71 °C (hexane–Et_2O); IR 1732, 1686, 1614 cm^{-1}; ^1H NMR δ: 3.79 (3H, s), 3.75 (3H, s), 3.28, 3.16 (2H, AB-q, *J*=19 Hz), 3.10–2.98 (1H, m), 2.89–2.75 (1H, m), 2.59 (1H, dd, *J*=6.6, 17 Hz), 2.07 (1H, dd, *J*=4.0, 17 Hz), 1.68 (1H, t, *J*=13 Hz), 0.34 (9H, s); ^{13}C NMR δ 212.6, 190.7, 171.9, 171.3, 137.8, 60.6, 53.1, 52.9, 46.4, 42.5, 38.6, 35.9, −1.8; FABMS *m*/*z* 357 (M^++1, 21.8). FABHRMS calcd for $C_{15}H_{23}GeO_5$ 357.0757, Found 357.0758.

2.1.14. 2-Iodo-7,7-bis(methoxycarbonyl)bicyclo[3.3.0]-oct-1-en-3-one (16). According to the procedure described for preparation of **7** from **9**, **16** (14.0 mg, 82%) was obtained from **15** (17.4 mg, 4.78×10^{-2} mmol) as colorless needles: mp 90–91 °C (hexane–Et_2O); IR 1732, 1720, 1634 cm^{-1}; ^1H NMR δ 3.80 (3H, s), 3.77 (3H, s), 3.39, 3.13 (2H, AB-q, *J*=20 Hz), 3.26–3.12 (1H, m), 2.93–2.80 (2H, m), 2.25 (1H, dd, *J*=3.0, 18 Hz), 1.80 (1H, t, *J*=13 Hz); ^{13}C NMR δ 203.2, 188.1, 171.5, 170.7, 94.7, 59.7, 53.4, 53.2, 46.4, 39.9, 39.2, 37.3; MS *m*/*z* 364 (M^+, 20.5). Anal. Calcd for $C_{12}H_{13}IO_5$: C, 39.58; H, 3.60. Found: C, 39.57; H, 3.61.

2.1.15. Dimethyl 2-(2-methyl-2-propen-1-yl)-2-[3-(trimethylgermyl)-2-propyn-1-yl]malonate (18). According to the procedure described for preparation of **8** from **3**, **18** (742 mg, 81%) was obtained from **17**[18] (605 mg, 2.70 mmol) as a colorless oil: IR 2174, 1740, 1645 cm^{-1}; ^1H NMR δ 4.90–4.83 (2H, m), 3.72 (6H, s), 2.84 (2H, s), 2.83 (2H, s), 1.65 (3H, s), 0.30 (9H, s); ^{13}C NMR δ 170.5, 139.8, 116.0, 100.0, 88.2, 56.7, 52.5, 39.4, 23.8, 23.1, −0.4. FABMS *m*/*z* 343 (M^++1, 3.7). FABHRMS calcd for $C_{15}H_{25}GeO_4$ 343.0964, Found 343.0967.

2.1.16. 7,7-Bis(methoxycarbonyl)-5-methyl-2-(trimethylgermyl)bicyclo[3.3.0]oct-1-en-3-one (19). To a solution of enyne **18** (32.4 mg, 9.50×10^{-2} mmol) in DME (1.0 mL) was added $Co_2(CO)_8$ (39.0 mg, 1.14×10^{-1} mmol). The reaction mixture was stirred at rt for 15 min, to which PhSMe (0.04 mL, 3.33×10^{-1} mmol) was added. After being stirred for 24 h at 70 °C, the reaction mixture was passed through a short pad of celite and concentrated to dryness. Chromatography of the residue with hexane–AcOEt (10:1) gave **19** (17.1 mg, 49%) as colorless needles: mp 67–68 °C (hexane–Et_2O): IR 1732, 1693, 1618 cm^{-1}; ^1H NMR δ 3.79 (3H, s), 3.71 (3H, s), 3.41, 3.23 (2H, AB-q, *J*=17 Hz), 2.60 (1H, d, *J*=14 Hz), 2.34 (2H, s), 2.13 (1H, d, *J*=14 Hz), 1.11 (3H, s), 0.33 (9H, s); ^{13}C NMR δ 212.5, 193.7, 172.2, 172.0, 59.8, 53.3, 53.2, 52.5, 50.9, 44.3, 34.8, 27.0, −1.5; FABMS *m*/*z* 371 (M^++1, 25.4). FABHRMS calcd for $C_{16}H_{25}GeO_5$ 371.0914, Found 371.0939.

2.1.17. 2-Iodo-7,7-bis(methoxycarbonyl)-5-methylbicyclo-[3.3.0]oct-1-en-3-one (20). According to the procedure described for preparation of **7** from **9**, **20** (74.8 mg, 91%) was obtained from **19** (80.1 mg, 2.17×10^{-1} mmol) as colorless needles: mp 116–117 °C (hexane–Et_2O): IR 1732, 1720, 1636 cm^{-1}; ^1H NMR δ 3.80 (3H, s), 3.73 (3H, s), 3.56 (1H, d, *J*=18 Hz), 3.13 (1H, d, *J*=18 Hz), 2.66 (1H, d, *J*=14 Hz), 2.59, 2.47 (2H, AB-q, *J*=18 Hz), 2.27 (1H, d, *J*=14 Hz), 1.15 (3H, s); ^{13}C NMR δ 202.9, 191.0, 171.7, 171.3, 94.0, 58.8, 53.44, 53.41, 51.5, 49.5, 44.8, 36.4, 26.7; MS *m*/*z* 378 (M^+, 41.4). Anal. Calcd for $C_{13}H_{15}IO_5$: C, 41.29; H, 4.00. Found: C, 41.49; H, 4.13.

2.1.18. 5-(*tert*-Butyldimethysiloxy)hept-1-en-6-yne (21). A solution of DMSO (9.9 mL, 139 mmol) in CH_2Cl_2 (30 mL) was gradually added to a solution of oxalyl chloride (6.1 mL, 69.7 mmol) in CH_2Cl_2 (40 mL) at −78 °C. After stirring of the CH_2Cl_2 solution for 15 min, a solution of 4-penten-1-ol (3.00 g, 34.8 mmol) in CH_2Cl_2 (30 mL) was added and the reaction was stirred at −78 °C for 1 h. Et_3N (29.1 mL, 209 mmol) was added to the reaction mixture, which was then gradually warmed to rt and diluted with CH_2Cl_2. The CH_2Cl_2 solution was washed successively with water and brine, dried and concentrated to leave the crude aldehyde. *n*-BuLi in hexane (1.23 M, 42.5 mL, 52.2 mmol) was added to a solution of (trimethylsilyl)acetylene (7.4 mL, 52.2 mmol) in THF (180 mL) at −78 °C and the solution was stirred for additional 1 h. A solution of the crude aldehyde derived from 4-penten-1-ol in THF (60 mL) was then added to a solution of the acetylide in THF at −78 °C and stirring was continued for 1 h at the same temperature. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl and extracted with AcOEt, which was washed successively with water and brine, dried and concentrated to dryness. Chromatography of the residue with hexane–AcOEt (10:1) gave the alcohol (5.27 g, 83%) as a pale yellow oil. To a solution of the crude alcohol (1.00 g, 5.48 mmol) and Et_3N (2.3 mL, 16.5 mmol) in CH_2Cl_2 (50 mL) was added TBSOTf (1.9 mL,

8.23 mmol) at 0 °C. The reaction mixture was stirred for 30 min at rt, quenched by addition of water, and extracted with CH_2Cl_2. The extract was washed successively with water and brine, dried and concentrated to dryness. Chromatography of the residue with hexane gave the silyl ether (1.17 g, 72%). To a solution of the silyl ether (605 mg, 2.04 mmol) in MeOH (20 mL) was added K_2CO_3 (282 mg, 2.04 mmol) at rt. The reaction mixture was stirred for 5 h at the same temperature. MeOH was evaporated off, and the residue was diluted with Et_2O, washed with water and brine, dried and concentrated to dryness. Chromatography of the residue with hexane gave **21** (380 mg, 83%) as a colorless oil: IR 3306, 1639 cm^{-1}; ^1H NMR δ 5.82 (1H, ddt, J=10, 17, 6.6 Hz), 5.08–4.95 (1H, m), 4.36 (1H, dt, J=6.6, 2.0 Hz), 2.39 (1H, d, J=2.0 Hz), 2.24–2.16 (2H, m), 1.81–1.73 (2H, m), 0.91 (9H, s), 0.14 (3H, s), 0.11 (3H, s); ^{13}C NMR δ 137.8, 115.0, 85.4, 72.2, 62.1, 37.7, 29.3, 25.8, 18.2, −4.5, −5.1. This crude **21** was directly converted into compound **22**.

2.1.19. 5-(*tert*-Butyldimethysiloxy)-7-(trimethylgermyl)-hept-1-en-6-yne (22). According to the procedure described for preparation of **8** from **3**, **22** (512 mg, 91%) was obtained from **21** (371 mg, 1.65 mmol) as a colorless oil: IR 2166, 1639 cm^{-1}; ^1H NMR δ 5.82 (1H, ddt, J=17, 10, 6.6 Hz), 5.08–4.93 (2H, m), 4.35 (1H, t, J=6.6 Hz), 2.23–2.13 (2H, m), 1.86–1.68 (2H, m), 0.91 (9H, s), 0.33 (9H, s), 0.13 (3H, s), 0.11 (3H, s); ^{13}C NMR δ 138.1, 114.8, 106.4, 88.7, 62.8, 37.8, 29.5, 25.9, 18.3, −0.3, −4.4, −4.9; FABMS m/z 343 (M^++1, 1.5). FABHRMS calcd for $C_{16}H_{33}GeOSi$ 343.1512, Found 343.1525.

2.1.20. (5*R* *,8*R* *)-8-(*tert*-Butyldimethylsiloxy)-2-(trimethylgermyl)bicyclo[3.3.0]oct-1-en-3-one (23). According to the procedure described for preparation of **9** from **8**, **23** (320 mg, 87%) was obtained from **22** (341 mg, 1.00 mmol) as a colorless oil: IR 1686, 1616 cm^{-1}; ^1H NMR δ 4.81 (1H, dd, J=3.3, 5.6 Hz), 3.25–3.14 (1H, m), 2.64 (1H, dd, J=6.9, 18 Hz), 2.27–2.09 (2H, m), 2.04–1.82 (2H, m), 1.16–0.97 (1H, m), 0.88 (9H, s), 0.36 (9H, s), 0.12 (3H, s), 0.10 (3H, s); ^{13}C NMR δ 215.1, 193.4, 137.1, 68.9, 43.5, 43.4, 36.6, 28.0, 25.7, 17.9, −1.3, −3.8, −4.3; FABMS m/z 371 (M^++1, 8.3). FABHRMS calcd for $C_{17}H_{33}GeO_2Si$ 371.1461, Found 371.1463.

2.1.21. (5*R* *,8*R* *)-8-Hydroxy-2-(trimethylgermyl)bicyclo[3.3.0]oct-1-en-3-one (24). A mixture of TBAF in THF (1.00 M, 1.43 mL, 1.43 mmol) and AcOH (3 drops) was added to a solution of **23** (440 mg, 1.19 mmol) in THF (0.6 mL) at 0 °C. The reaction mixture was stirred for 30 h at the same temperature, quenched by addition of saturated aqueous NH_4Cl, and extracted with Et_2O. The extract was washed with water and brine, dried, and concentrated to dryness. Chromatography of the residue with hexane–AcOEt (4:1) gave **24** (257 mg, 85%) as a colorless oil: IR 3422, 1690, 1616 cm^{-1}; ^1H NMR δ 4.83 (1H, t, J=5.6 Hz), 3.22–3.07 (1H, m), 2.65 (1H, dd, J=6.3, 18 Hz), 2.50–2.38 (1H, m), 2.29–2.17 (1H, m), 2.04 (1H, dd, J=3.3, 18 Hz), 1.96–1.81 (1H, m), 1.25 (1H, s), 1.17–1.00 (1H, m), 0.89 (9H, s); ^{13}C NMR δ 215.1, 193.5, 138.2, 68.0, 44.5, 43.2, 36.3, 28.6, −1.5; FABMS m/z 257 (M^++1, 31.2). FABHRMS calcd for $C_{11}H_{19}GeO_2$ 257.0597, Found 257.0604.

2.1.22. (5*R* *,8*R* *)-8-(*tert*-Butyldimethylsiloxy)bicyclo[3.3.0]oct-1-en-3-one (25). According to the procedure described for preparation of **9** from **8**, **25** (96.1 mg, 74%) was obtained along with its stereoisomer (**25**: epimer= 72:28) from **21** (116 mg, 5.17×10^{-1} mmol). Compound **25** was a colorless oil: IR 1703, 1636 cm^{-1}; ^1H NMR δ 5.92 (1H, d, J=2.3 Hz), 4.75 (1H, dd, J=5.5, 5.6 Hz), 3.25–3.15 (1H, m), 2.67 (1H, dd, J=6.6, 18 Hz), 2.37–2.16 (2H, m), 2.06 (1H, dd, J=3.0, 18 Hz), 1.97–1.83 (1H, m), 1.17–1.04 (1H, m), 0.89 (9H, s), 0.11 (3H, s), 0.07 (3H, s); ^{13}C NMR δ 211.3, 188.4, 125.0, 68.4, 42.9, 42.8, 36.9, 28.4, 25.7, 18.1, −4.6, −4.8; MS m/z 252 (M^+, 6.7). Anal. Calcd for $C_{14}H_{24}O_2Si$: C, 66.61; H, 9.58. Found: C, 66.34; H, 9.82. Epimer of **25** was a colorless oil: IR 1701, 1636 cm^{-1}; ^1H NMR δ 6.02 (1H, s), 4.96 (1H, dd, J=4.9, 9.3 Hz), 2.96–2.89 (1H, m), 2.64 (1H, dd, J=6.3, 18 Hz), 2.40–2.31 (1H, m), 2.16–2.08 (2H, m), 1.88–1.81 (1H, m), 1.57–1.42 (1H, m), 0.92 (9H, s), 0.12 (3H, s), 0.11 (3H, s); ^{13}C NMR δ 210.2, 192.3, 124.4, 70.5, 43.5, 41.7, 35.4, 29.0, 25.7, 18.2, −4.8,-4.9; MS m/z 252 (M^+, 2.5). Anal. Calcd for $C_{14}H_{24}O_2Si$: C, 66.61; H, 9.58. Found: C, 66.33; H, 9.81.

2.1.23. (5*R* *,8*R* *)-8-(*tert*-Butyldimethylsiloxy)-2-iodobicyclo[3.3.0]oct-1-en-3-one (26). According to the procedure described for preparation of **7** from **9**, **26** (17.2 mg, 80%) was obtained from **23** (21.0 mg, 5.69×10^{-2} mmol) as a colorless oil: IR 1715, 1628 cm^{-1}; ^1H NMR δ 4.69–4.65 (1H, m), 3.34–3.24 (1H, m), 2.89 (1H, dd, J=6.6, 18 Hz), 2.43–2.14 (3H, m), 1.99–1.85 (1H, m), 1.25–1.04 (1H, m), 0.91 (9H, s), 0.18 (6H, s); ^{13}C NMR δ 205.1, 189.8, 95.2, 70.4, 44.9, 40.4, 36.6, 28.6, 25.8, 18.0, −4.2, −4.3; MS m/z 378 (M^+, 0.3). Anal. Calcd for $C_{14}H_{23}IO_2Si$: C, 44.45; H, 6.13. Found: C, 44.56; H, 6.34.

2.1.24. (5*R* *,8*R* *)-8-Hydroxy-2-iodobicyclo[3.3.0]oct-1-en-3-one (27). According to the procedure described for preparation of **7** from **9**, **27** (18.7 mg, 35%) was obtained from **24** (52.0 mg, 2.04×10^{-1} mmol) as colorless needles: mp 96–97 °C (hexane–Et_2O); IR 3418, 1715, 1628 cm^{-1}; ^1H NMR δ 4.33 (1H, t, J=6.3 Hz), 3.32–3.21 (1H, m), 2.91 (1H, dd, J=6.3, 18 Hz), 2.58–2.46 (1H, m), 2.35–2.17 (3H, m), 2.04–1.88 (1H, m), 1.25–1.05 (1H, m); ^{13}C NMR δ 204.8, 189.5, 96.0, 65.7, 45.5, 40.5, 35.2, 28.9; MS m/z 264 (M^+, 20.2). Anal. Calcd for $C_8H_9IO_2$: C, 36.39; H, 3.44. Found: C, 36.41; H, 3.57.

2.1.25. 5-(*tert*-Butyldimethysiloxy)-4,4-dimethyl-7-(trimethylgermyl)hept-1-en-6-yne (29). According to the procedure described for preparation of **8** from **3**, **29** (284 mg, 97%) was obtained from **28**[6] (200 mg, 7.92×10^{-1} mmol) as a colorless oil: IR 2166, 1638 cm^{-1}; ^1H NMR δ 5.82 (1H, ddt, J=6.3, 9.2, 17 Hz), 5.09–4.96 (2H, m), 4.00 (1H, s), 2.15–2.05 (2H, m), 0.91 (6H, s), 0.90 (9H, s), 0.33 (9H, s), 0.14 (3H, s), 0.09 (3H, s); ^{13}C NMR δ 135.5, 117.0, 105.1, 89.9, 71.0, 42.6, 39.0, 25.9, 22.7, 22.6, 18.3, −0.3, −4.2, −5.1; FABMS m/z 371 (M^++1, 1.4). FABHRMS calcd for $C_{18}H_{37}GeOSi$ 371.1825, Found 371.1862.

2.1.26. (5*R* *,8*R* *)-8-(*tert*-Butyldimethylsiloxy)-7,7-dimethyl-2-(trimethylgermyl)bicyclo[3.3.0]oct-1-en-3-one (30). According to the procedure described for preparation of **9** from **8**, **30** (656 mg, 86%) was obtained from **29**

(707 mg, 1.92 mmol) as a colorless oil: IR 1686, 1616 cm^{-1}; ^1H NMR δ 4.13 (1H, s), 3.43–3.35 (1H, m), 2.68 (1H, dd, J=6.8, 18 Hz), 2.03 (1H, t, J=12 Hz), 1.98 (1H, dd, J=3.4, 18 Hz), 1.13 (3H, s), 1.06 (1H, dd, J=5.9, 13 Hz), 0.89 (9H, s), 0.76 (3H, s), 0.36 (9H, s), 0.11 (3H, s), 0.02 (3H, s); ^{13}C NMR δ 214.9, 193.6, 136.9, 77.3, 45.6, 44.1, 42.3, 42.2, 28.5, 25.6, 24.0, 18.1, −1.3, −4.2, −4.8; FABMS m/z 397 (M^++1, 4.2). FABHRMS calcd for $C_{19}H_{37}GeO_2Si$ 397.1774, Found 397.1790.

2.1.27. (5*R* *,8*R* *)-8-Acetoxy-7,7-dimethyl-2-(trimethylgermyl)bicyclo[3.3.0]oct-1-en-3-one (31). According to the procedure described for preparation of **24** from **23**, **30** (216 mg, 5.43×10^{-1} mmol) was converted into the corresponding hydroxyl compound (118 mg, 77%). To a solution of the crude alcohol (68.6 mg, 2.42×10^{-1} mmol) and DMAP (5.9 mg, 4.85×10^{-1} mmol) in CH_2Cl_2 (2.4 mL) was added acetic anhydride (0.05 mg, 4.84×10^{-1} mmol) at 0 °C. The reaction mixture was stirred for 40 min, quenched by addition of saturated aqueous $NaHCO_3$, extracted with CH_2Cl_2. The extract was washed with water and brine, dried, and concentrated to dryness. Chromatography of the residue with hexane–AcOEt (50:1) gave **31** (74.0 mg, 94%) as a colorless oil: IR 1734, 1692, 1622 cm^{-1}; ^1H NMR δ 5.35 (1H, s), 3.34–3.20 (1H, m), 2.66 (1H, dd, J=6.6, 17 Hz), 2.09 (3H, s), 2.10–1.98 (2H, m), 1.16–1.11 (1H, m), 1.07 (3H, s), 1.05 (3H, s), 0.34 (9H, s); ^{13}C NMR δ 213.8, 188.4, 170.0, 141.3, 78.0, 44.5, 44.2, 43.9, 43.6, 29.4, 23.5, 20.8, −1.5; FABMS m/z 327 (M^++1, 8.3). FABHRMS calcd for $C_{15}H_{25}GeO_3$ 327.1015, Found 327.1006.

2.1.28. (5*R* *,8*R* *)-8-(*tert*-Butyldimethylsiloxy)-2-iodo-7,7-dimethylbicyclo[3.3.0]oct-1-en-3-one (32). According to the procedure described for preparation of **7** from **9**, **32** (3.0 mg, 58%) was obtained from **30** (5.1 mg, 1.28×10^{-2} mmol) as a colorless oil: IR 1715, 1626 cm^{-1}; ^1H NMR δ 4.06 (1H, s), 3.52–3.41 (1H, m), 2.93 (1H, dd, J=6.9, 18 Hz), 2.18–2.06 (2H, m), 1.23–1.13 (1H, m), 1.13 (3H, s), 0.89 (9H, s), 0.84 (3H, s), 0.17 (3H, s), 0.10 (3H, s); ^{13}C NMR δ 205.0, 190.6, 94.3, 79.1, 44.6, 43.1, 43.0, 42.4, 28.4, 25.7, 23.8, 18.1, −4.0, −4.8; FABMS m/z 407 (M^++1, 54.2). FABHRMS calcd for $C_{16}H_{28}IO_2Si$ 407.0903, Found 407.0903.

2.1.29. (5*R* *,8*R* *)-8-Acetoxy-2-iodo-7,7-dimethylbicyclo[3.3.0]oct-1-en-3-one (33). According to the procedure described for preparation of **7** from **9**, **33** (13.7 mg, 56%) was obtained from **31** (23.7 mg, 7.29×10^{-2} mmol) as a colorless oil: IR 1740, 1720, 1634 cm^{-1}; ^1H NMR δ 5.33 (1H, s), 3.42–3.32 (1H, m), 2.96–2.88 (1H, m), 2.24–2.05 (2H, m), 2.13 (3H, s), 1.26–1.10 (1H, m), 1.13 (3H, s), 1.10 (3H, s); ^{13}C NMR δ 204.0, 185.9, 169.9, 97.9, 78.6, 44.4, 44.3, 44.0, 41.4, 28.8, 23.1, 20.6; MS m/z 334 (M^+, 21.0). HRMS calcd for $C_{12}H_{15}IO_3$ 334.0066, Found 334.0062.

2.1.30. Dimethyl 2-(3-buten-1-yl)-2-[3-(trimethylgermyl)-2-propyn-1-yl]malonate (35). According to the procedure described for preparation of **8** from **3**, **35** (273 mg, 80%) was obtained from **34** (234 mg, 1.04 mmol) as a colorless oil: IR 2174, 1732, 1641 cm^{-1}; ^1H NMR δ 5.78 (1H, ddt, J=9.9, 17, 6.3 Hz), 5.10–4.30 (2H, m), 3.72 (6H, s), 2.85 (2H, s), 2.20–1.88 (4H, m), 0.30 (9H, s); $^{13}C^{13}C$ NMR δ 170.6, 137.3, 115.0, 99.5, 88.0, 56.8, 52.5, 31.2, 28.3, 24.1, −0.3; FABMS m/z 343 (M^++1, 12.7). FABHRMS calcd for $C_{15}H_{25}GeO_4$ 343.0964, Found 343.0939.

2.1.31. 3,3-Bis(methoxycarbonyl)-9-(trimethylgermyl)-bicyclo[4.3.0]non-1(9)-en-8-one (36). According to the procedure described for preparation of **15** from **14**, **36** (410 mg, 78%) was obtained from **35** (484 mg, 1.42 mmol) as colorless needles: mp 74–75 °C (hexane–Et_2O); IR 1732, 1686, 1603 cm^{-1}; ^1H NMR δ 3.76 (3H, s), 3.70 (3H, s), 3.60 (1H, dd, J=1.7, 14 Hz), 2.70–2.44 (4H, m), 2.20–2.06 (1H, m), 2.00–1.84 (2H, m), 1.40–1.20 (1H, m), 0.38 (9H, s); ^{13}C NMR δ 211.6, 182.8, 171.6, 170.1, 141.6, 56.7, 53.0, 52.6, 42.4, 41.8, 35.2, 30.9, 30.6, −0.9; FABMS m/z 371 (M^++1, 16.6). FABHRMS calcd for $C_{16}H_{25}GeO_5$ 371.0914, Found 371.0901.

2.1.32. 9-Iodo-3,3-bis(methoxycarbonyl)bicyclo[4.3.0]-non-1(9)-en-8-one (37). According to the procedure described for preparation of **7** from **9**, **37** (70.3 mg, 92%) was obtained from **36** (74.4 mg, 2.02×10^{-1} mmol) as colorless needles: mp 119–120 °C (hexane–Et_2O); IR 1734, 1709, 1612 cm^{-1}; ^1H NMR δ 3.78 (3H, s), 3.72 (3H, s), 3.65 (1H, dd, J=2.3, 14 Hz), 2.87–2.63 (3H, m), 2.53 (1H, ddd, J=3.0, 5.6, 14 Hz), 2.20–2.02 (2H, m), 1.96 (1H, dd, J=4.0, 14 Hz), 1.38–1.16 (1H, m); ^{13}C NMR δ 201.9, 179.7, 170.9, 169.8, 102.0, 56.4, 53.2, 52.8, 42.9, 39.1, 37.4, 31.0, 30.5; MS m/z 378 (M^+, 58.6). Anal. Calcd for $C_{13}H_{15}IO_5$: C, 41.29 H, 4.00. Found: C, 41.15; H, 3.99.

2.1.33. 6-(*tert*-Butyldimethysiloxy)oct-1-en-7-yne (38). According to the procedure described for preparation of **21** from 4-penten-1-ol, **38** (495 mg, 54%) was obtained from 5-hexen-1-ol (383 mg, 3.82 mmol) as a colorless oil: IR 3308, 1639 cm^{-1}; ^1H NMR δ 5.81 (1H, ddt, J=6.6, 9.9, 17 Hz), 5.05–4.93 (2H, m), 4.35 (1H, dt, J=2.0, 6.3 Hz), 2.37 (1H, d, J=2.0 Hz), 2.12–2.04 (2H, m), 1.74–1.48 (4H, m), 0.90 (9H, s), 0.13 (3H, s), 0.11 (3H, s); ^{13}C NMR δ 138.5, 114.6, 85.5, 72.0, 62.6, 37.9, 33.3, 25.7, 24.3, 18.2, −4.6, −5.1; FABMS m/z 239 (M^++1, 1.5). FABHRMS calcd for $C_{14}H_{27}OSi$ 239.1831, Found 239.1829.

2.1.34. 6-(*tert*-Butyldimethysiloxy)-8-(trimethylgermyl)-oct-1-en-7-yne (39). According to the procedure described for preparation of **8** from **3**, **39** (147 mg, 93%) was obtained from **38** (107 mg, 4.47×10^{-1} mmol) as a colorless oil: IR 2166, 1639 cm^{-1}; ^1H NMR δ 5.81 (1H, ddt, J=6.6, 10, 17 Hz), 5.05–4.93 (2H, m), 4.33 (1H, t, J=6.6 Hz), 2.11–2.03 (2H, m), 1.72–1.45 (4H, m), 0.90 (9H, s), 0.33 (9H, s), 0.13 (3H, s), 0.11 (3H, s); ^{13}C NMR δ 138.7, 114.5, 106.6, 88.4, 63.3, 38.1, 33.3, 25.8, 24.6, 18.3, −0.3, −4.4, −4.9; FABMS m/z 355 (M^++1, 0.9). FABHRMS calcd for $C_{17}H_{35}GeOSi$ 355.1669, Found 355.1679.

2.1.35. (2*R* *,6*R* *)-2-(*tert*-Butyldimethylsiloxy)-9-(trimethylgermyl)bicyclo[4.3.0]non-1(9)-en-8-one (40). According to the procedure described for preparation of **9** from **8**, **40** (705 mg, 95%) was obtained from **39** (692 mg, 1.95 mmol) as a colorless oil: IR 1680, 1599 cm^{-1}; ^1H NMR δ 4.89 (1H, t, J=2.6 Hz), 3.16–3.07 (1H, m), 2.49 (1H, d, J=6.6, 19 Hz), 2.17–2.11 (1H, m), 2.02–1.84 (3H, m), 1.53–1.40 (2H, m), 1.26–1.08 (1H, m), 0.89 (9H, s), 0.36 (9H, s), 0.09 (3H, s), 0.01 (3H, s); ^{13}C NMR δ 213.0,

189.5, 138.6, 66.9, 42.1, 38.9, 36.6, 35.7, 25.6, 19.1, 17.9, −0.7, −4.6, −4.7; FABMS *m/z* 385 (M^++1, 9.3). FABHRMS calcd for $C_{18}H_{35}GeO_2Si$ 385.1618, Found 385.1624.

2.1.36. (2*R,6*R**)-2-Hydroxy-9-(trimethylgermyl)bicyclo[4.3.0]non-1(9)-en-8-one (41).** According to the procedure described for preparation of **24** from **23**, **41** (74.6 mg, 87%) was obtained from **40** (122 mg, 3.18×10^{-1} mmol) as colorless needles: mp 88–90 °C (hexane–Et_2O); IR 3420, 1682, 1597 cm^{-1}; ^1H NMR δ 4.91 (1H, t, *J*=2.6 Hz), 3.15–3.05 (1H, m), 2.52 (1H, dd, *J*=6.6, 19 Hz), 2.19–1.85 (6H, m), 1.64–1.49 (1H, m), 1.33–0.88 (1H, m), 0.36 (9H, s); ^{13}C NMR δ 212.9, 187.9, 139.4, 66.1, 42.3, 38.9, 35.6, 34.4, 19.1, −0.6; FABMS *m/z*: 271 (M^++1, 27.8). Anal. Calcd for $C_{12}H_{20}GeO_2$: C, 53.60; H, 7.50. Found: C, 53.49; H, 7.70.

2.1.37. (2*R,6*R**)-2-(*tert*-Butyldimethylsiloxy)bicyclo[4.3.0]non-1(9)-en-8-one (42).** According to the procedure described for preparation of **9** from **8**, **42** (81.0 mg, 71%) and its epimer (6.6 mg, 6%) were obtained from **38** (102 mg, 4.27×10^{-1} mmol). Compound **42** was a colorless oil: IR 1703, 1628 cm^{-1}; ^1H NMR δ 5.82 (1H, d, *J*=1.3 Hz), 4.73 (1H, t, *J*=2.3 Hz), 3.11–3.01 (1H, m), 2.57 (1H, dd, *J*=6.6, 19 Hz), 2.21–2.10 (1H, m), 2.04–1.86 (3H, m), 1.59–1.42 (2H, m), 1.14–0.98 (1H, m), 0.88 (9H, s), 0.07 (3H, s), 0.00 (3H, s); ^{13}C NMR δ 209.3, 183.8, 125.6, 66.7, 42.1, 37.4, 35.4, 35.3, 25.6, 19.1, 18.0, −4.9, −5.1; MS *m/z* 266 (M^+, 3.8). Anal. Calcd for $C_{15}H_{26}O_2Si$: C, 67.61 H, 9.84. Found: C, 67.27; H, 10.13. Epimer of **42** was a colorless oil: IR 1699, 1624 cm^{-1}; ^1H NMR δ 6.07 (1H, s), 4.38–4.31 (1H, m), 2.75–2.56 (2H, m), 2.17–2.01 (3H, m), 1.88–1.81 (1H, m), 1.53–1.42 (2H, m), 1.14–1.02 (1H, m), 0.91 (9H, s), 0.08 (9H, s); ^{13}C NMR δ 208.0, 186.8, 125.4, 71.6, 42.3, 40.8, 36.9, 34.4, 25.7, 23.4, 18.2, −4.8, −5.0; MS *m/z* 266 (M^+, 2.6). Anal. Calcd for $C_{15}H_{26}O_2Si$: C, 67.61 H, 9.84. Found: C, 67.37; H, 10.16.

2.1.38. (2*R,6*R**)-2-(*tert*-Butyldimethylsiloxy)-9-iodobicyclo[4.3.0]non-1(9)-en-8-one (43).** According to the procedure described for preparation of **7** from **9**, **43** (151 mg, 95%) was obtained from **40** (155 mg, 4.05×10^{-1} mmol) as a colorless oil: IR 1703, 1609 cm^{-1}; ^1H NMR δ 4.83 (1H, t, *J*=2.3 Hz), 3.24–3.14 (1H, m), 2.74 (1H, dd, *J*=6.6, 19 Hz), 2.15–1.92 (4H, m), 1.62–1.42 (2H, m), 1.25–0.98 (1H, m), 0.89 (9H, s), 0.14 (3H, s), 0.04 (3H, s); ^{13}C NMR δ 203.0, 184.4, 97.0, 69.0, 40.5, 39.4, 35.9, 35.0, 25.7, 19.3, 17.9, −4.3, −4.8; MS *m/z* 392 (M^+, 0.7). Anal. Calcd for $C_{15}H_{25}IO_2Si$: C, 45.92 H, 6.42. Found: C, 45.94; H, 6.59.

2.1.39. (2*R,6*R**)-2-Hydroxy-9-iodobicyclo[4.3.0]non-1(9)-en-8-one (44).** According to the procedure described for preparation of **7** from **9**, **44** (19.2 mg, 83%) was obtained from **41** (22.3 mg, 8.29×10^{-2} mmol) as a colorless oil: IR 3412, 1709, 1607 cm^{-1}; ^1H NMR δ 4.95–4.90 (1H, m), 3.31–3.18 (1H, m), 2.77 (1H, dd, *J*=6.6, 19 Hz), 2.18–1.90 (5H, m), 1.71–1.52 (2H, m), 1.26–1.02 (1H, m); ^{13}C NMR δ 202.9, 183.1, 98.7, 68.4, 40.5, 39.4, 35.3, 33.7, 19.4; MS *m/z* 278 (M^+, 35.9). HRMS calcd for $C_9H_{11}IO_2$ 277.9804, Found 277.9807.

2.1.40. 3,3-Bis(methoxycarbonyl)-9-[2-(trimethylsilyl)-propyn-1-yl]bicyclo[4.3.0]non-1(9)-en-8-one (45). According to the procedure described for preparation of **10** from **7**, **45** (26.6 mg, 99%) was obtained from **37** (29.1 mg, 7.70×10^{-2} mmol) as a colorless oil: IR 2160, 1732, 1713, 1624 cm^{-1}; ^1H NMR δ 3.77 (3H, s), 3.77 (1H, dd, *J*=2.3, 14 Hz), 3.71 (3H, s), 2.72–2.47 (4H, m), 2.22–1.83 (3H, m), 1.43–1.23 (1H, m), 0.22 (9H, s); ^{13}C NMR δ 203.6, 179.9, 171.3, 169.7, 125.2, 103.6, 94.0, 56.6, 53.2, 52.7, 41.1, 39.4, 34.6, 30.9, 30.8, −0.1; MS *m/z* 348 (M^+, 79.2). HRMS calcd for $C_{18}H_{24}O_5Si$ 348.1393, Found 348.1395.

2.1.41. 9-(1-Ethoxy-ethen-1-yl)-3,3-bis(methoxycarbonyl)bicyclo[4.3.0]non-1(9)-en-8-one (46). According to the procedure described for preparation of **11** from **7**, **46** (22.9 mg, 87%) was obtained from **37** (30.9 mg, 8.17×10^{-2} mm) as a colorless oil: IR 1732, 1707, 1686, 1616 cm^{-1}; ^1H NMR δ 4.10 (1H, dd, *J*=2.3, 15 Hz), 3.79–3.66 (2H, m), 3.73 (3H, s), 3.66 (3H, s), 2.73–2.39 (8H, m), 2.31–2.16 (1H, m), 2.11–1.98 (2H, m), 1.41–1.18 (2H, m); ^{13}C NMR δ 203.8, 197.4, 183.2, 170.9, 170.1, 139.4, 56.6, 53.0, 52.7, 41.6, 39.6, 34.0, 30.5, 30.4, 30.3; MS *m/z* 322 (M^+, 15.4). HRMS calcd for $C_{17}H_{22}O_6$ 322.1416, Found 322.1417.

2.1.42. 3,3-Bis(methoxycarbonyl)-9-phenylbicyclo[4.3.0]-non-1(9)-en-8-one (47). According to the procedure described for preparation of **12** from **7**, **47** (22.7 mg, 88%) was obtained from **37** (29.7 mg, 7.85×10^{-2} mmol) as colorless needles: mp 114–115 °C (hexane–Et_2O); IR 1732, 1697, 1645 cm^{-1}; ^1H NMR δ7.45–7.24 (5H, m), 3.72 (3H, s), 3.67 (1H, dd, *J*=2.3, 14 Hz), 3.53 (3H, s), 2.80–2.49 (4H, m), 2.28–1.95 (3H, m), 1.52–1.25 (1H, m); ^{13}C NMR δ 205.8, 171.4, 171.1, 170.1, 140.2, 131.0, 128.9, 128.2, 127.8, 56.2, 53.0, 52.4, 41.4, 39.0, 33.5, 30.8, 30.3; MS *m/z* 328 (M^+, 38.6). HRMS calcd for $C_{19}H_{20}O_5$ 328.1311, Found 328.1315.

2.1.43. 3,3-Bis(methoxycarbonyl)bicyclo[4.3.0]non-1(9)-en-8-one (48). According to the procedure described for preparation of **5** from **7**, **48**[19] (19.7 mg, 87%) was obtained from **37** (33.9 mg, 8.96×10^{-2} mmol).

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Dendritic octa-CMPO derivatives of calix[4]arenes

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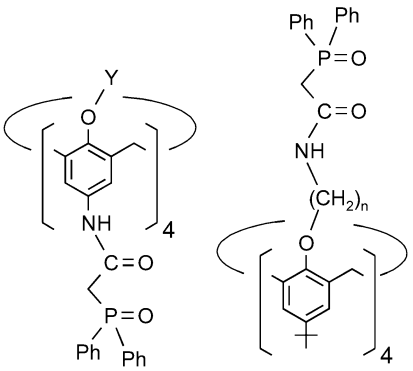
Abstract—Calix[4]arenes substituted at the narrow or wide rim by eight carbamoylmethyl-phosphine oxide (=CMPO) functions in a dendritic manner were synthesised and studied in extraction of Eu^{3+} and Am^{3+} from aqueous nitric acid into *o*-nitrophenylhexyl ether. ^1H NMR relaxivity titrations for a wide rim octa-CMPO reveal the clear formation of a solvent-free 1:2 ligand/metal complex, while the wide rim tetra-CMPO formed oligomeric complexes under similar conditions.

1. Introduction

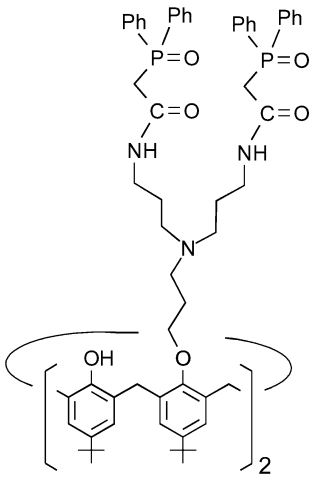
Calix[4]arenes bearing at their wide[1] or at their narrow rim[2] four CMPO functions (general formulas **1** and **2**) are much better extractants for lanthanides and actinides than *N*,*N*-diisobutyl carbamoylmethyl-(octyl)phenyl phosphine oxide, the extractant technically used in the so-called TRUEX process.[3] Distribution coefficients higher by several orders of magnitude (depending on the conditions and on the cation[4] to be extracted) are convincing evidence that it is advantageous to preorganise several CMPO-functions by covalent attachment to a basic platform.[5]



1 **2**

2. Syntheses

Since it could well be that merely a high local concentration of CMPO-functions is responsible for the beneficial extraction properties of **1** and **2**, we decided to increase the number of CMPO functions attached to the calix[4]arene skeleton, using structural principles well-known from dendrimers.[6] Compounds **6a**,**b** with eight CMPO groups at the narrow rim were prepared from the known aminoalkoxy calix[4]arenes **3** by Michael addition of acrylonitrile, followed by reduction and acylation with the active *p*-nitrophenyl ester **7** (Scheme 1). The tetra-CMPO derivative **8** in which the two remaining phenolic hydroxyl groups could be used in principle for the attachment of additional



8

Keywords: Calix[4]arenes; Dendrimers; CMPO; Extraction; NMR relaxation.
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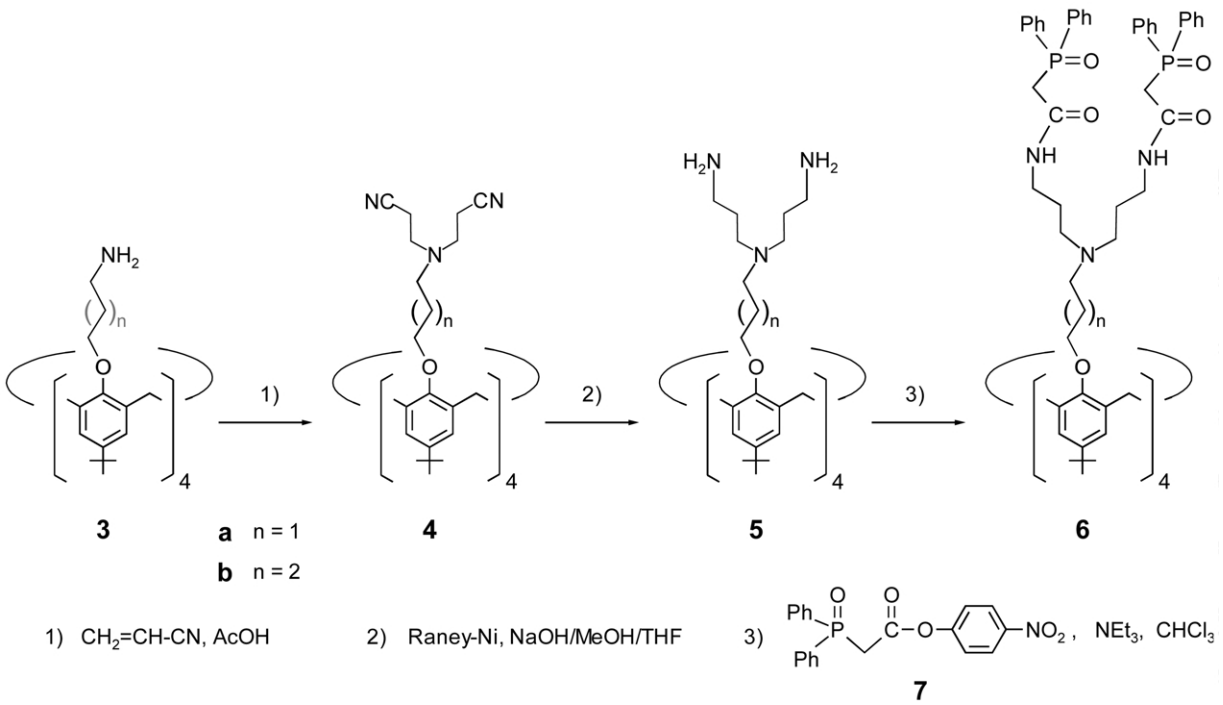


Scheme 1.

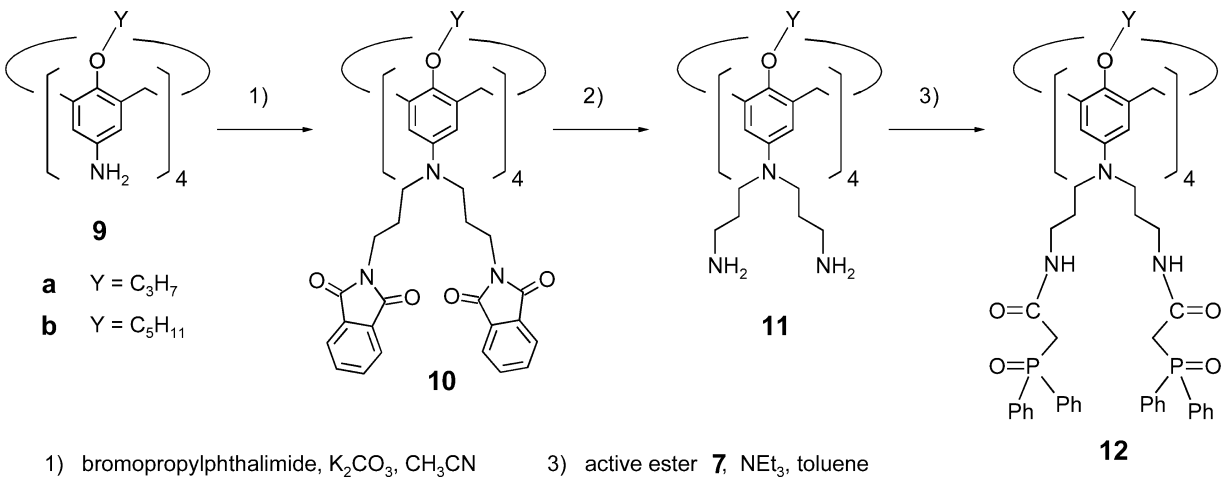
functional groups was prepared analogously starting with the respective 1,3-diamine.

Addition of acrylonitrile was not successful with wide rim tetraamine **9** due to the lower nucleophilicity of the amino groups. Mixtures of compounds containing less than one nitrile residue per amino group were formed. However, an exhaustive alkylation with bromopropylphthalimide led to the tertiary amine **10**. Cleavage of the phthalimide groups by hydrazine and subsequent acylation with **7** furnished the octa-CMPO derivative **12**; see Scheme 2.

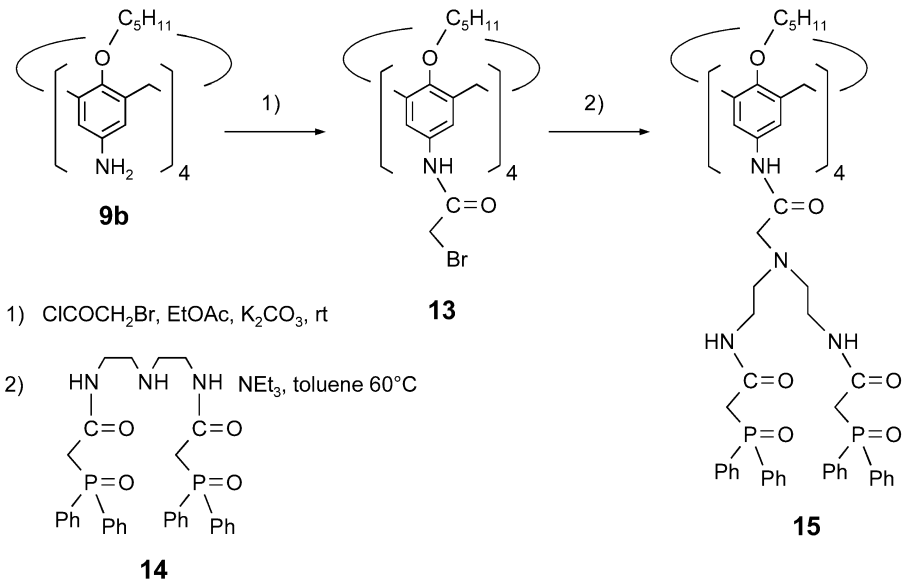
Yet another strategy was used for the synthesis of **15** (Scheme 3): wide rim tetra-amine **9** was acylated with bromoacetyl chloride to prepare **13** that was subsequently reacted with the di-CMPO-derivative **14**. The latter was obtained by mild acylation of diethylene triamine with the active ester **7**.

3. Liquid–liquid extraction and complexation studies

The separation of trivalent actinides from lanthanides remains a challenging problem because of the close similarity of these ions. This is especially true if Am^{3+} has to be separated from Eu^{3+} by extraction from strongly acidic media as it is required in the reprocessing of nuclear fuels.[3] Calixarenes **1** and **2** proved to be efficient extracting agents and the extraction properties of their dendritic analogues **6**, **8** and **12** were analyzed under the conditions



Scheme 2.



Scheme 3.

used previously (concentrated nitric acid as aqueous phase, *o*-nitrophenylhexylether, NPHE, as organic solvent). In addition, nuclear magnetic relaxation studies were performed on **12b**, the dendritic analogue of **1** which is the most promising calixarene extracting agent found so far.[1,2] As reported earlier,[7] NMR relaxation studies require only very small amounts of material and yield information that are not easily obtained by other methods.

As shown by the values collected in Table 1, the extraction efficiency of the dendritic CMPO calixarenes is distinctly lower in comparison with **1** and **2**. This phenomenon is observed whether the CMPO units are located on the wide or on the narrow rim of the calixarene units. In addition, the Am^{3+}/Eu^{3+} separation coefficients are lower and complications arise due to precipitation and to the formation of a third liquid phase during the extractions. The solubility problem could probably be alleviated by the introduction of more lipophilic residues (e.g. the ether group Y in **12**). However, the extraction results suggest that the simple accumulation of CMPO functions is not an appropriate way of improving the extraction properties.

Table 1. Distribution coefficients D for the extraction of Eu^{3+} and Am^{3+} for various calix[4]arenes bearing CMPO units ([L]=10^{-3} M in NPHE) as a function of the nitric acid concentration in the aqueous phase

Ligand		[HNO_3] (M)					
		0.01	0.1	1	2	3	4
1[a] (Y=C_5H_{11})	D_{Am}		19	195	275	150	100
	D_{Eu}		2.3	30	52	37	19
12b	D_{Am}	0.001	0.12	[b]	[b]	[b]	[b]
	D_{Eu}	0.001	0.07	[b]	[b]	[b]	[b]
2[c] (n=4)	D_{Am}		48	51	61	63	
	D_{Eu}		28	33	44	48	
6b[d]	D_{Am}	0.05	0.14	2.1	4.8	7.5	8.4
	D_{Eu}	0.02	0.11	0.7	1.9	2.4	2.8
8	D_{Am}	11×10^{-3}	0.02	0.57	1.45	0.88	
	D_{Eu}	6×10^{-3}	7×10^{-3}	0.22	0.59	0.38	

[a] Compare Ref. 7b.
[b] Precipitation.
[c] Compare Ref. 2.
[d] Partly third phase formation.

NMR relaxation studies shed some light on the origin of the striking differences between the extraction properties of the simple and the dendritic CMPO calixarenes. This technique takes advantage of the relaxation properties of the Gd^{3+} ion to establish the stoichiometry of lanthanide complexes as well as their solvation and dynamic behaviour. It has already been showed that calix[4]arenes substituted on the narrow rim such as **2** exclusively form monomeric 1:1 Gd^{3+} perchlorate complexes in anhydrous acetonitrile while their analogues substituted on the wide rim such as **1** occur as oligomeric species in a large range of [ligand]/[Gd^{3+}] concentration ratios.[7] As shown in Figure 1(a), the progressive complexation of the metal ions by **2** brings about the removal of solvent molecules from the paramagnetic centres and thus a decrease of $1/T_1$ as the relaxation of solvent protons takes place in the bulk of the solution rather than close to the unpaired electronic spins. A relaxivity plateau is reached for a ~1 [ligand]/[metal] ratio when the Gd^{3+} complex is fully formed. By contrast, aggregation phenomena at low [ligand **1**]/[Gd^{3+}] ratios cause an increase in relaxation rates because of the decreased rotational mobility of the oligomeric species[7,8] and a range of complexes of different stoichiometries are formed in solution. Contrary to all expectations, ligand **12b** forms a monomeric Gd^{3+} complex of well-defined 2:1 metal/ligand stoichiometry even though this calixarene is substituted by CMPO groups on the wide rim.

The differences between calix[4]arenes **1**, **2** and **12b** are also shown in Figure 1(b) that shows the dispersion of the nuclear magnetic relaxation with the resonance frequency. A relaxivity maximum is observed at 40 MHz for the complex with ligand **1** because it forms oligomers.[7] By contrast, the relaxivity of the $(Gd^{3+})_2$·**12b** complex is much lower than that of uncomplexed Gd^{3+} and of the complex

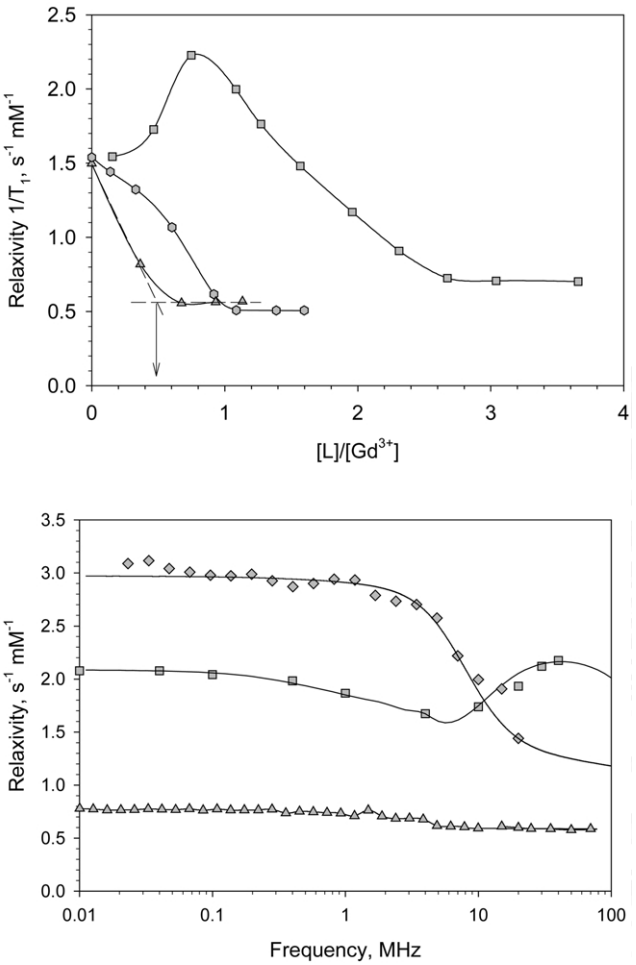


Figure 1. (a) (Top) Relaxivity titration curves of Gd^{3+} by calix[4]arenes **1** (■), **2** (●) and **12b** (▲) in anhydrous acetonitrile. (b) (Bottom) Nuclear magnetic relaxation dispersion curves of anhydrous acetonitrile solutions of uncomplexed Gd^{3+} (◆), Gd^{3+}·**1** (■, concentration ratio [**1**]/[Gd^{3+}]=1) and Gd^{3+}·**12b** (▲, concentration ratio [**12b**]/[Gd^{3+}]=1.3).

with **1** at all frequencies. This low relaxivity is ascribed to essentially outer-sphere effects due to solvent molecules in the second co-ordination sphere of the metal complexes (note: the relaxation rate of pure acetonitrile[9] is 6.2×10^{-2} s^{-1}). It thus seems that **12b** forms exclusively a monomeric 2:1 metal/ligand complex in which the two Gd^{3+} ions are totally encapsulated by the CMPO and amino coordinating groups and are essentially unsolvated. The extraction of trivalent lanthanides and actinides would thus proceed as

$$2\mathrm{Me}(\mathrm{H_2O})n^{3+} + 6\mathrm{NO_3^{3-}} + \overline{\mathbf{12b}} \rightarrow \overline{\mathrm{Me_2}(\mathbf{12b})(\mathrm{NO_3})_6} + n\mathrm{H_2O}$$

where n=8 or 9[8] and where a bar over a symbol designates the organic phase species.

The dendritic calixarenes appear to be a class of ligands in their own right because of the unusual stoichiometry of their complexes and because of their monomeric behaviour in solution. Their poor extraction efficacy could be related to these unusual features. However, the correct preorganisation needed to achieve high extraction coefficients and a high selectivity is not yet understood in details and remains a crucial factor to be controlled.

4. Experimental

4.1. Reagents and methods

Tetraamino calix[4]arenes **3**,[2] **9**,[10] **13**,[7b] and *p*-nitrophenyl (diphenyl-phosphoryl)-acetate **7**[10] were prepared according to known procedures. Melting points, determined with a MEL TEMP 2 capillary melting point apparatus, are uncorrected. ^{1}H NMR spectra were monitored on Bruker 200 and 400 MHz spectrometers. FD and ESI mass spectra were recorded in a positive mode with a Finnigan MAT 90 (5 kV/10 mA/min) and a QTof ULTIMA3 (Micromass), respectively.

NMRD measurements were conducted as reported previously[7] at 20 MHz on a Minispec 120 (Bruker Optics) and between 0.01 and 80 MHz on a Stelar relaxometer equipped with a 1.88 T electromagnet. Samples of Gd^{3+} complexes were prepared as reported earlier.[7]

4.2. Narrow Rim CMPO-derivatives

4.2.1. Octanitrile 4a. A solution of tetraamine **3a** (1.2 g) and acetic acid (328 mg) in acrylonitrile (25 ml) was refluxed for 2.5 days. The excess of acrylonitrile was removed by distillation under vacuum and the residue was dissolved in chloroform. After filtration the solution was washed three times with conc. ammonia, then water, dried over $MgSO_4$ and evaporated. The oily residue was purified by column chromatography (chloroform/methanol 20/1). Colourless oil, yield 87%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (s, 8H, Ar*H*), 4.41 (d, J=12.3 Hz, 4H, ArCH_2Ar), 4.07 (t, J=7.1 Hz, 8H, OCH_2), 3.21 (d, J=12.5 Hz, 4H, ArCH_2Ar), 2.86 (t, J=6.5 Hz, 16H, CNCH_2), 2.65 (t, J=7.5 Hz, 8H, NCH_2), 2.40 (t, J=6.8 Hz, 16H, NCH_2), 2.17–2.10 (m, 8H, CH_2), 1.09 (s, 36H, *t*-Bu); FD-MS m/z=1301.2 (M^+, 100%). Anal. calcd for $C_{80}H_{108}N_{12}O_4$ (1301.8) C 73.81, H 8.36, N 12.91. Found C 73.38, H 8.12, N 12.39.

4.2.2. Octanitrile 4b. The title compound was prepared as described for **4a**. Colourless oil, yield 54%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75 (s, 8H, Ar*H*), 4.35 (d, J=12.5 Hz, 4H, ArCH_2Ar), 3.89 (t, J=7.8 Hz, 8H, OCH_2), 3.10 (d, J=12.5 Hz, 4H, ArCH_2Ar), 2.85 (t, J=6.7 Hz, 16H, CNCH_2), 2.62 (t, J=7.5 Hz, 8H, NCH_2), 2.44 (t, J=6.7 Hz, 16H, NCH_2), 2.01–1.94 (m, 8H, CH_2), 1.60–1.52 (m, 8H, CH_2), 1.05 (s, 36H, *t*-Bu); FD-MS m/z=1357.8 (M^+, 100%). Anal. calcd for $C_{84}H_{116}N_{12}O_4$ (1357.9) C 74.30, H 8.61, N 12.38. Found C 75.88, H 8.42, N 12.19.

4.2.3. Octaamine 5a. NaOH (0.33 g in 3 ml water) was added to a suspension of octanitrile **4a** (0.5 g) in a mixture of methanol (20 ml) and THF (10 ml) and the solution was stirred at room temperature for 1 h. Raney-nickel (0.8 g) was added and the reaction mixture was stirred under hydrogen at room temperature overnight. The catalyst was filtered off, the solvents were removed in vacuum and the obtained residue was dissolved in a mixture of CH_2Cl_2 and water. The aqueous layer was washed three times with CH_2Cl_2 and the combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated to give a colourless oil, yield 55%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (s, 8H,

ArH), 4.31 (d, J=12.5 Hz, 4H, ArCH_2Ar), 3.90 (t, J=7.1 Hz, 8H, OCH_2), 3.38 (br s, 16H, NH_2), 3.08 (d, J=12.2 Hz, 4H, ArCH_2Ar), 2.65 (t, J=6.2 Hz, 16H, NH_2CH_2), 2.56 (t, J=7.5 Hz, 8H, NCH_2), 2.43 (t, J=6.8 Hz, 16H, NCH_2), 1.94–2.11 (m, 8H, CH_2), 1.58 (br, 16H, CH_2), 1.03 (s, 36H, *t*-Bu).

4.2.4. Octaamine 5. The title compound was prepared as described for **5a**. Colourless oil, yield 51%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (s, 8H, ArH), 4.39 (d, J=12.7 Hz, 4H, ArCH_2Ar), 3.91 (t, J=7.5 Hz, 8H, OCH_2), 3.36 (br. s, 16H, NH_2), 3.16 (d, J=12.4 Hz, 4H, ArCH_2Ar), 2.89 (t, J=7.2 Hz, 16H, NH_2CH_2), 2.66 (t, J=7.1 Hz, 8H, NCH_2), 2.50 (t, J=6.8 Hz, 16H, NCH_2), 2.02–1.94 (m, 8H, CH_2), 1.59–1.51 (m, 8H, CH_2), 1.34 (br, 16H, CH_2), 1.09 (s, 36H, *t*-Bu).

4.2.5. Octa-CMPO 6a. Active ester **7** (0.531 g) was added to a solution of octaamine **5a** (0.2 g) and triethylamine (0.1 g) in chloroform (30 ml) and the mixture was stirred at room temperature overnight. Additional chloroform (20 ml) was added and the solution was washed repeatedly with 5% aq. NaOH, then water, and dried ($MgSO_4$). Evaporation of the solvent afforded a residue which was reprecipitated from chloroform/hexane to give the desired compound as a pale yellow powder, yield 80%; mp 255–259 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 (br s, 8H, ArNH), 7.83–7.66 (m, 32H, PPh_2), 7.55–7.36 (m, 48H, PPh_2), 6.78 (s, 8H, ArH), 4.37 (d, 4H, ArCH_2Ar), 3.96 (br t, 8H, OCH_2), 3.42–3.16 (m, 20H, ArCH_2Ar+POCH_2CO), 3.04–2.98 (m, 16H, CONHCH_2), 2.58–2.53 (m, 8H, NCH_2), 2.33 (br, 16H, CH_2N), 2.02–1.96 (m, 8H, CH_2), 1.35–1.29 (m, 16H, CH_2), 0.99 (s, 36H, *t*-Bu); ESI-MS *m*/*z*=3271.5 (MH^+, 42%).

4.2.6. Octa-CMPO 6b. The title compound was prepared as described for **6a**. Colourless powder, yield 51%; mp 237–239 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (s, 8H, NH), 7.73–7.69 (m, 32H, PPh_2), 7.42–7.36 (m, 48H, PPh_2), 6.71 (s, 8H, ArH), 4.3 (d, 4H, ArCH_2Ar), 3.80 (t, 8H, OCH_2), 3.57 (d, 16H, POCH_2CO), 3.20 (br, 16H, CONHCH_2), 3.09 (d, 4H, ArCH_2Ar), 2.97–2.90 (m, 8H, CH_2N), 2.32 (br, 16H, NCH_2), 1.86–1.82 (m, 8H, CH_2), 1.50 (br, 8H, CH_2), 1.45–1.39 (br, 16H, CH_2), 0.99 (s, 36H, *t*-Bu); ESI-MS *m*/*z*=3327.8 (MH^+, 22%).

4.2.7. 1,3-Tetra-CMPO calix[4]arene 8. *Addition of acrylonitrile*. A solution of the 1,3-di(aminopropyl)calix[4]-arene (500 mg) in acrylonitrile (10 ml) was heated to reflux, acetic acid (140 mg) was added, and refluxing was continued for 12 h. The excess of acrylonitrile was removed by distillation and the residue dissolved in chloroform. Some insoluble material was filtered off and the solution was washed three times with conc. ammonia. The organic layer was dried over $MgSO_4$ and the solvent evaporated. Addition of hexane gave the desired tetranitrile as a white powder, yield 70%; mp 120–121 °C. Found C 76.48, H 8.62, N 8.39, $C_{62}H_{82}N_6O_4$ (975.4) requires C 76.35, H 8.47, N 8.62; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.19 (s, 2H, ArOH), 7.06 (s, 4H, ArH), 6.75 (s, 4H, ArH), 4.21 (d, J=13.2 Hz, 4H, ArCH_2Ar), 4.05 (t, J=5.9 Hz, 4H, OCH_2), 3.32 (d, J=13.2 Hz, 4H, ArCH_2Ar), 2.95 (m, 12H, NCH_2), 2.55 (t, J=6.8 Hz, 8H, CH_2), 2.12 (t, J=5.9 Hz, 4H, CH_2), 1.28 (s, 18H, *t*-Bu), 0.91 (s, 18H, *t*-Bu).

Reduction of the nitrile groups. To a stirred suspension of the tetranitrile (400 mg) and $CoCl_2$ (800 mg) in methanol (40 ml) was added sodium-borohydride (2.4 g) in small portions over 1 h. After 5 h conc. HCl (40 ml) was added cautiously and the methanol was evaporated. The remaining aqueous solution was mixed with conc. ammonia (100 ml) and extracted with chloroform (3×50 ml). The organic phase was dried ($MgSO_4$), concentrated and the tetraamine was precipitated by the addition of hexane as a white powder, yield 32%; mp 231–233 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.03 (s, 4H, ArH), 6.73 (s, 4H, ArH), 4.24 (d, J=13.2 Hz, 4H, ArCH_2Ar), 3.99 (s, 4H, OCH_2), 3.5 (br s, 8H, NH_2), 3.27 (d, J=13.2 Hz, 4H, ArCH_2Ar), 2.77 (br t, 12H, CH_2), 2.53 (br, 8H, CH_2), 2.10 (br, 4H, CH_2), 1.66 (br, 8H, CH_2), 1.27 (s, 18H, *t*-Bu), 0.91 (s, 18H, *t*-Bu).

N-Acylation. To a solution of the tetraamino calix[4]arene (130 mg) and triethylamine (1 ml) in chloroform (10 ml) was added the active ester **7** (300 mg). The mixture was stirred at room temperature for 24 h. Usual work up gave **8** as white powder, mp 210–211 °C, yield 83%; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.80–7.60 (m, 16H, PPh_2), 7.50–7.30 (m, 24H, PPh_2), 7.00 (s, 4H, ArH), 6.17 (s, 4H, ArH), 4.19 (d, J=12.2 Hz, 4H, ArCH_2Ar), 3.90 (br s, 4H, OCH_2), 3.4–3.1 (m, 20H, ArCH_2Ar, PCH_2 and NCH_2), 2.56 (br, 4H, CH_2), 2.35–1.90 (br m, 20H, CH_2), 1.50 (br, 8H, CH_2) 1.24 (s, 18H, *t*-Bu), 0.90 (s, 18H, *t*-Bu); FD-MS *m*/*z*=1960.8 (22%), ESI-MS *m*/*z*=1961.9 (MH^+, 73%).

4.3. Wide rim CMPO-derivatives

4.3.1. N-Alkylation by *N*-(3-bromopropyl)phthalimide. *Compound* **10a**. A suspension of tetraamine **9a** (0.37 g, 0.48 mmol) and K_2CO_3 (0.67 g, 4.8 mmol) in acetonitrile (40 ml) was refluxed for 1 h. *N*-(3-bromopropyl)phthalimide (1.30 g, 4.8 mmol) was added and the reaction mixture was stirred for 1.5 days. After cooling to room temperature, the solid was filtered and the solvent was evaporated. The remaining oil was extracted with chloroform/water and washed with brine. The organic layer was dried ($MgSO_4$). Column chromatography (chloroform) and reprecipitation from chloroform/hexane gave the octaphthalimido derivative **10a** as a pale yellow powder, yield 75%; mp 143–145 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.63–7.60 (m, 32H, Pht), 6.14 (s, 8H, ArH), 4.31 (d, J=13.2 Hz, 4H, ArCH_2Ar), 3.73 (t, J=6.2 Hz, 8H, OCH_2), 3.62 (t, J=6.4 Hz, 16H, PhtCH_2), 3.07 (t, J=6.2 Hz, 16H, NCH_2), 2.92 (d, J= 13.3 Hz, 4H, ArCH_2Ar), 1.93 (m, 8H, CH_2), 1.77 (m, 16H, CH_2), 0.94 (t, J=6.3 Hz, 12H, CH_3). Anal. calcd for $C_{128}H_{124}N_{12}O_{20}$ (2150.5) C 71.49, H 5.81, N 7.82. Found C 71.24, H 5.65, N 7.54.

Compound **10b** was prepared as described for **10a**, yield 86%; pale yellow powder, mp 156–157 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.60 (m, 32H, Pht), 6.14 (s, 8H, ArH), 4.31 (d, J=13.1 Hz, 4H, ArCH_2Ar), 3.76 (t, J=6.1 Hz, 8H, OCH_2), 3.61 (t, J=6.4 Hz, 16H, Pht-CH_2), 3.07 (t, J=6.2 Hz, 16H, NCH_2), 2.92 (d, J=13.4 Hz, 4H, ArCH_2Ar), 1.90 (m, 8H, CH_2), 1.77 (m, 16H, CH_2), 1.36 (m, 16H, CH_2), 0.93 (t, J=6.1 Hz, 12H, CH_3). Anal. calcd for $C_{136}H_{140}N_{12}O_{20}$ (2262.7) C 72.19, H 6.24, N 7.43. Found C 70.94, H 6.55, N 7.34.

Octaamine **11a**. Hydrazine hydrate (8 ml) was added to a solution of octaphthalimido-calix[4]arene **10a** (0.9 g, mmol) in ethanol (25 ml). After 2 h of reflux, the solvent was evaporated and the obtained residue was dissolved in a mixture of CH_2Cl_2 and water. The aqueous layer was washed three times with CH_2Cl_2, the combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated to give a yellow oil, yield 65%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 6.09 (s, 8H, Ar*H*), 4.26 (d, J=13.4 Hz, 4H, ArCH_2Ar), 3.65 (t, J=6.5 Hz, 8H, OCH_2), 3.00 (m, 16H, NCH_2), 2.85 (m, 20H, NH_2CH_2 and ArCH_2Ar), 2.54 (t, J=6.6 Hz, 16H, NH_2), 1.90 (m, 8H, CH_2), 1.46 (m, 16H, CH_2), 0.93 (t, J=6.4 Hz, 12H, CH_3).

Octaamine **11b** was prepared as described for **11a**. Pale yellow oil, yield 90%; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.13 (s, 8H, Ar*H*), 4.38 (br d, J=13.4 Hz, 4H, ArCH_2Ar), 3.76 (m, 8H, OCH_2), 3.01 (m, 20H, NCH_2 and ArCH_2Ar), 2.63 (br, 16H, NH_2CH_2), 2.19 (b, 16H, NH_2), 1.90 (br, 8H, CH_2), 1.53 (b, 16H, CH_2), 1.36 (br, 16H, CH_2), 0.92 (t, J=6.6 Hz, 12H, CH_3).

Octa-CMPO **12a**. Active ester **7** (0.6 g, 1.15 mmol) was added to a stirred solution of octaamine **11a** (0.2 g,) and triethylamine (0.1 g) in chloroform (25 ml). The mixture was stirred at room temperature overnight and the solution was washed repeatedly with 10% aq. NaOH and dried ($MgSO_4$). Evaporation of the solvent afforded a residue which was passed through a chromatography column (chloroform/methanol 9/1) and reprecipitated from chloroform/hexane to give the desired octa-CMPO derivative **12a** as a pale yellow powder, yield 80%; mp 220–222 °C; ^{1}H NMR (400 MHz, DMSO-d_6, 120 °C) δ 8.16 (s, 8H, CO*NH*), 7.73 (m, 32H, PPh_2), 7.44 (m, 48H, PPh_2), 6.03 (s, 8H, Ar*H*), 4.22 (d, 4H, ArCH_2Ar), 3.64 (br, 24H, $POCH_2CO$+OCH_2), 2.92 (m, 36H, $NHCH_2$, NCH_2 and ArCH_2Ar), 1.84 (br, 8H, CH_2), 1.38–1.32 (m, 16H, CH_2), 0.92 (t, 12H, CH_3); FD-MS m/z=3044.5 (M^+, 35%).

Octa-CMPO **12b** was prepared as described for **12a**. Pale yellow powder, yield 82%; mp 239–242 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.08 (s, 8H, CO*NH*), 7.71–7.66 (m, 32H, PPh_2), 7.44–7.33 (m, 48H, PPh_2), 5.98 (s, 8H, Ar*H*), 4.14 (d, J=13.4 Hz, 4H, ArCH_2Ar), 3.61 (t, 8H, OCH_2), 3.49 (d, J=14.3 Hz, 16H, $POCH_2CO$), 3.20–2.88 (m, 36H, $NHCH_2$, NCH_2 and ArCH_2Ar), 1.88 (br, 8H, CH_2), 1.33 (br, 32H, CH_2), 0.89 (t, J=6.5 Hz, 12H, CH_3). FD-MS m/z=3158.7 (M^+, 100%).

Di-CMPO-diethylenetriamine **14**. To a solution of diethylenetriamine (27 mg) and triethylamine (0.2 ml) in chloroform (20 ml) was added dropwise a solution of active ester **7** (200 mg) in chloroform (20 ml). The mixture was stirred at room temperature overnight. The solution was washed repeatedly with 10% aq. NaOH and dried ($MgSO_4$). Evaporation of the solvent afforded a residue which was reprecipitated from chloroform/hexane to give the desired compound as a white powder, yield 58%; mp 157–158 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.52 (br s, 2H, N*H*), 7.7–7.3 (m, 20H, Ar*H*), 3.45 (d, J=13.6 Hz, 4H, PCH_2), 3.30 (m, 4H, NCH_2), 2.62 (t, J=5.4 Hz, 4H, NCH_2); FD-MS m/z=588.6 (MH^+, 100%).

5,11,17,23-Octa-CMPO-25,26,27,28-tetrapentyloxycalix-[4]-arene **15**. To a stirred solution of tetra-bromoacetamide **13** (1.0 g) and triethylamine (1 ml) in toluene (30 ml) was added dropwise a solution of **14** (2.5 g) in toluene (10 ml). The mixture was kept at 60 °C for 2 days and worked up as usual. Reprecipitation from chloroform/hexane afforded the desired compound as a white powder, yield 58%; mp 212–213 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 (s, 4H, CON*H*), 7.78–7.44 (m, 80H, PPh_2), 6.35 (s, 8H, Ar*H*), 4.22 (d, J=12.5 Hz, 4H, ArCH_2Ar), 3.83 (m, 16H, $COCH_2$ and OCH_2), 3.60 (d, J=13.5 Hz, 16H, PCH_2), 3.11 (m, 20H, NCH_2 and ArCH_2Ar), 2.62 (t, J=5.6 Hz, 16H, NCH_2CH_2), 1.84 (m, 8H, CH_2), 1.36 (m, 16H, CH_2), 0.91 (m, 12H, CH_3). ESI-MS m/z=3274.2 (MH^+, 65%).

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Structure and cytotoxicity of new metabolites from the sponge *Mycale cecilia*

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Abstract—The chemical study of the sponge *Mycale cecilia* has led to the isolation of 14 new pyrrole-containing metabolites. Mycalazals 3–13 are pyrrole-2-carbaldehydes possessing at C-5 hydrocarbon side chains of different length and/or number of unsaturations. Mycalenitriles 1–3 are 5-cyanoalkylpyrrole-2-carbaldehydes. The structures of the new compounds were established mainly by NMR and MS spectroscopic analysis. The location of the double bond in mycalazal-4, -8, and -11 was determined by MS analysis of the corresponding bis(methylthio) derivatives. Mycalazals have shown activity as growth inhibitors of several tumor cell lines, in particular the LNcaP cell line, being mycalazal-8 the most active metabolite.

1. Introduction

Although heterocyclic compounds are widely distributed in nature, those containing a simple pyrrole nucleus are among the less frequently found, despite that pyrrole is a structurally simple five-membered ring. Other than tetrapyrrole pigments, pyrrole-containing natural products have scarcely been encountered in the marine environment, with distribution limited principally to specific species of algae, sponges, bryozoans, tunicates and mollusca.[1] Furthermore, the enormous reactivity of pyrroles in electrophilic substitution reactions, has been claimed to explain the high incidence of halogenated derivatives among marine pyrroles.[2]

Sponges of the *Mycale* genus have been source of novel nitrogenous metabolites belonging to very diverse structural types. Thus, while one of the first accounts on this genus describes the isolation of the nucleosides mycalisines,[3] likely of symbiotic origin, other species are characterized by containing highly cytotoxic compounds of the mycalamides family.[4–6] Another relevant group of *Mycale* metabolites is formed by macrocyclic compounds as the mycalolides,[7–11] thiomycalolides,[12] pateamine[13] and peluroside,[14] all of them also displaying a potent cytotoxic activity. On the other hand, several species of this genus have shown to contain complex mixtures of pyrrole-containing metabolites.[15–17]

In our continuing search for cytotoxic metabolites from marine invertebrates, we have studied specimens of the sponge *Mycale cecilia*, collected along the coasts of Sinaloa in the Gulf of California (Mexico). Bioassay guided isolation yielded fourteen new metabolites, the mycalazals 3–13 (**1**–**11**) and mycalenitriles 1–3 (**12**–**14**), together with the known compounds **15**–**17**,[16] **18**,[18] **19**,[16] **20** and **21**,[19] and **22**.[16]

2. Results and discussion

Specimens of *M. cecilia* were collected by hand using SCUBA, lyophilized and exhaustively extracted with acetone. After evaporation of the solvent under reduced pressure the residue was partitioned between H_2O and Et_2O and the organic extract subjected to column chromatography. Fractions eluted with hexane/Et_2O (8:2) and hexane/Et_2O (7:3) showed cytotoxicity against P-388, A-549 and HT-29 tumor cell lines, and were subjected to repeated separations on reversed phase HPLC to yield, in order of elution, mycalazals 3–13 (**1**–**11**) and mycalenitriles 1–3 (**12**–**14**).

Keywords: Natural products; Sponges; Pyrroles; Structure determination; Cytotoxicity.
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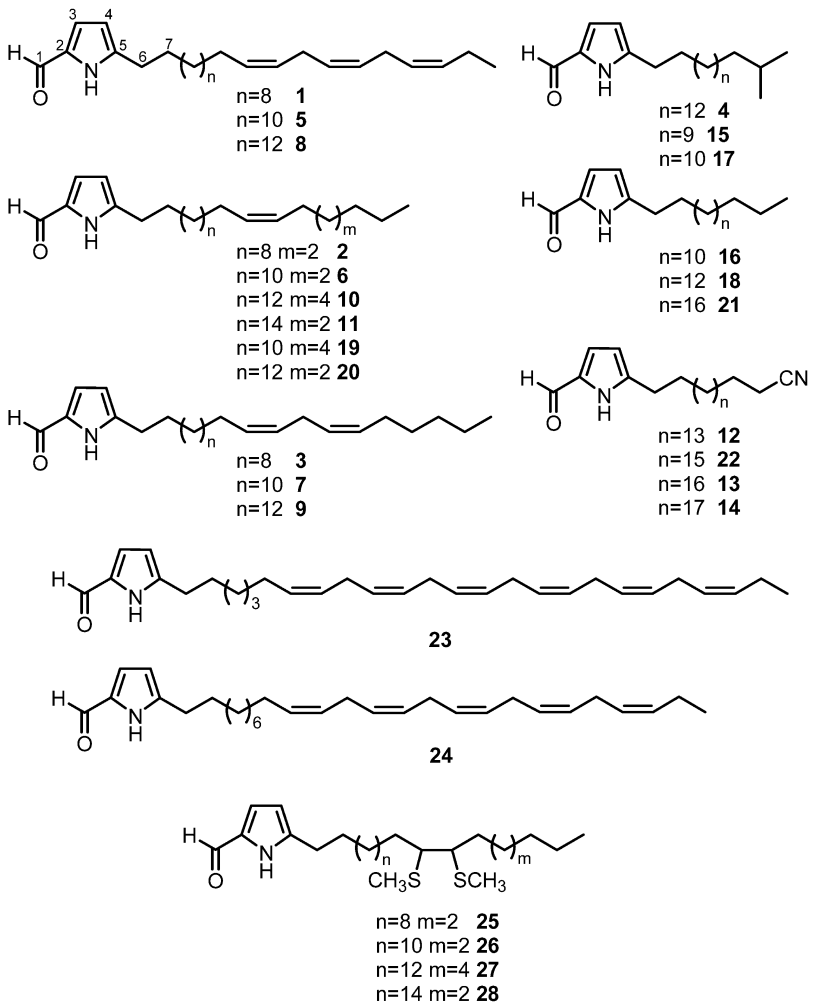

The metabolites **1**–**14** displayed NMR spectra closely similar to those of mycalazals 1 and 2 (**23** and **24**),[15] indicating that all the new compounds possessed a pyrrole-2-carbaldehyde nucleus, but substituted at C-5 with different side chains. For the sake of clarity, in the following discussion compounds have been grouped by the number of unsaturations in the side chain.

2.1. Compounds 1, 5, and 8

Mycalazal-3 (**1**) was isolated as a colorless oil whose molecular formula $C_{26}H_{41}NO$ was established by HRMS. The ^1H and ^{13}C NMR spectra showed, in addition to the signals of the 2,5-disubstituted pyrrole and the formyl group (Table 1), signals attributable to an unbranched polyolefinic chain. In particular, the ^1H NMR multiplet centered at 5.36 as well as six doublets in the ^{13}C NMR spectrum at δ 132.2, 130.6, 128.5, 128.4, 127.9, and 127.3, were assigned to three disubstituted double bonds. These data, together with two ^1H NMR multiplets at δ 2.06 (4H) and 2.81 (4H) attributable to two allylic and two bis-allylic methylenes, respectively, were in agreement with a sequence of three methylene interrupted double bonds. An all-*cis* geometry was proposed for the olefinic system based on the chemical shift of the bis-allylic carbon signals in the ^{13}C NMR spectrum at δ 25.6 and 25.5. Furthermore, the chemical shift of one of the allylic methylenes at δ 20.5 indicated that the series of three methylene interrupted double bonds started at ω-3.[20] Finally, taking into account the molecular formula of **1**, it was deduced that the olefinic system had to be connected to C-5 of the pyrrole nucleus through a sequence of ten methylenes. These gave rise to the ^1H NMR signals at δ 2.64 (t, 2H, J=7.7 Hz, H-6), 1.65 (q, 2H, J=7.4 Hz, H-7), and 1.25 (bs, 16H, H-8 to H-15). It was therefore proposed structure **1** for mycalazal-3.

Mycalazal-7 (**5**) and mycalazal-10 (**8**) displayed NMR spectra almost identical to those previously described for mycalazal-3 (**1**), which indicated that compounds **5** and **8** also were pyrrole-2-carbaldehydes possessing a side chain with a sequence of three methylene interrupted double bonds that started at ω-3. This structural assignment was further confirmed by the cross peak observed in the HMBC spectrum of **5** between the olefinic carbon signal at δ 131.9 and the signal at δ 0.97 (t, 3H, J=7.5 Hz), due to the methyl at the end of the chain. These data, together with the molecular formulae $C_{28}H_{45}NO$ and $C_{30}H_{49}NO$ obtained from HRMS of compounds **5** and **8**, respectively, indicated that the side chain of each compound was elongated in two and four methylenes, respectively, with respect to that of **1**.

2.2. Compounds 3, 7, and 9

Mycalazal-5 (**3**) was isolated as a colorless oil of molecular

Table 1. NMR data for compounds **1**–**3** and **5**–**11**[a–c]

	1		**2**		**3**[d]		**5**[d]		**6**		**7**[d]		**8**		**9**[d]		**10/11**	
	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H
1	178.1	9.37	178.1	9.37	178.1	9.37	178.1	9.35	178.1	9.37	178.1	9.36	178.1	9.35	178.1	9.36	177.9	9.37
2	131.8	—	131.8	—	131.8	—	131.8	—	131.8	—	131.8	—	131.8	—	131.8	—	131.8	—
3	122.3	6.89	122.4	6.89	122.3	6.89	122.6	6.89	122.7	6.89	122.7	6.89	122.8	6.89	122.6	6.89	122.5	6.89
4	109.4	6.07	109.4	6.07	109.4	6.07	109.4	6.07	109.4	6.07	109.5	6.07	109.6	6.07	109.5	6.07	109.5	6.07
5	142.8	—	142.9	—	142.9	—	143.1	—	143.3	—	143.2	—	143.3	—	143.2	—	143.0	—
6	27.9	2.64	27.9	2.64	28.2	2.64	27.9	2.65	27.9	2.65	27.9	2.65	27.9	2.65	27.8	2.65	27.9	2.64
7	28.9	1.65	28.9	1.65	29.1	1.64	28.9	1.65	28.9	1.65	28.9	1.64	28.9	1.64	28.9	1.64	29.0/28.9	1.65
8–15	29.6–28.9	1.25	29.8–29.0	1.25	29.9–29.5	1.25	29.7–29.2	1.25	29.8–29.2	1.25	29.8–29.2	1.25	29.7–29.2	1.25	29.2–29.7	1.25	29.8–29.2	1.25
16	27.2	2.06	27.2	2.02	27.6[e]	2.03	29.7–29.2	1.25	29.8–29.2	1.25	29.8–29.2	1.25	29.7–29.2	1.25	29.2–29.7	1.25	29.8–29.2	1.25
17	127.9	5.36	129.9	5.35	128.3	5.35	29.7–29.2	1.25	29.8–29.2	1.25	29.8–29.2	1.25	29.7–29.2	1.25	29.2–29.7	1.25	29.8–29.2	1.25
18	130.6	5.36	129.9	5.35	130.5	5.35	27.2	2.06	27.2	2.02	27.2	2.03	29.7–29.2	1.25	29.2–29.7	1.25	29.8–29.2	1.25
19	25.6	2.81	27.2	2.02	25.9	2.77	127.6	5.35	129.9	5.35	127.9	5.36	29.7–29.2	1.25	29.2–29.7	1.25	29.8–29.2	1.25
20	128.5[e]	5.36	29.8–29.0	1.25	128.3	5.35	130.4	5.35	129.9	5.35	130.2	5.36	27.2	2.07	27.2	2.03	27.2/29.8–29.2	2.01/1.25
21	128.4[e]	5.36	29.8–29.0	1.25	130.5	5.35	25.6[e]	2.80	27.2	2.02	25.6	2.77	127.6	5.34	127.9	5.35	129.9/29.8–29.2	5.35/1.25
22	25.6	2.81	31.8	1.25	27.5[e]	2.03	128.2[f]	5.35	29.8–29.2	1.25	127.9	5.36	130.4	5.34	130.2	5.35	129.9/27.2	5.35/2.01
23	127.3	5.36	22.6	1.25	29.5–29.9	1.25	128.3[f]	5.35	29.8–29.2	1.25	130.2	5.36	25.6[e]	2.80	25.6	2.77	27.2/129.9	2.01/5.35
24	132.2	5.36	14.1	0.88	31.8	1.25	25.5[e]	2.80	31.8	1.25	27.2	2.03	128.2[f]	5.34	127.9	5.35	29.8–29.2/129.9	1.25/5.35
25	20.5	2.06			22.9	1.25	127.1	5.35	22.6	1.25	29.8–29.2	1.25	128.3[f]	5.34	130.2	5.35	29.8–29.2/27.2	1.25/2.01
26	14.3	0.98			14.4	0.88	131.9	5.35	14.1	0.88	31.5	1.25	25.5[e]	2.80	27.2	2.03	29.8–29.2	1.25
27							20.5	2.06			22.6	1.25	127.1	5.34	29.2–29.7	1.25	29.8–29.2	1.25
28							14.3	0.97			14.1	0.89	131.9	5.34	31.5	1.25	31.9/31.8	1.25
29													20.5	2.07	22.6	1.25	22.7	1.25
30													14.3	0.97	14.1	0.89	14.1	0.88
NH		9.10		9.30		9.08		9.48		9.47		9.57		9.40		9.50		9.19

[a] ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 400 MHz and 100 MHz, respectively.
[b] Assignments were aided by gHSQC experiments.
[c] Multiplicity and coupling constant: H-3 (dd, J=3.8, 2.5 Hz), H-4 (dd, J=3.8, 2.5 Hz), H-6 (t, J=7.7 Hz), H-7 (q, J=7.4 Hz), CH_3 at the end of the chain (t, J=7.5 Hz for **1**, **5**, **8**; J=6.8 Hz for **2**, **3**, **6**, **7**, **9**, **10/11**).
[d] Assignments were aided by gHMBC experiments.
[e,f]Values with the same superscripts in the same column may be interchanged.

formula $C_{26}H_{43}NO$, as determined by HRMS. Since the pyrrole-2-carbaldehyde moiety accounted for five carbons, four unsaturations, and all the heteroatoms of the molecular formula, it was concluded that compound **3** contained a C_{21} diunsaturated hydrocarbon side chain. The double bonds gave rise to a ^1H NMR multiplet centered at δ 5.35 that was correlated in the HSQC spectrum with the olefinic carbon signals at δ_C 130.5 (2C, d) and 128.3 (2C, d). Furthermore, it was readily inferred that the two double bonds were separated by a methylene upon observation of the NMR signals at δ_H 2.77 and δ_C 25.9, this latter chemical shift being typical of a *cis* configuration of the double bonds. Finally, the analysis of the HMBC spectrum allowed to establish the location of the olefinic system in the chain. In particular, the proton signal at δ 0.88 (t, 3H, J=6.8 Hz) showed two and three bonds correlations with the methylene carbon signals at δ 22.9 and 31.8, respectively, while this latter signal, in turn, was correlated with the allylic protons signal at δ 2.03 (Fig. 1). It was therefore concluded that the olefinic system started at ω-6 and structure **3** was proposed for mycalazal-5.

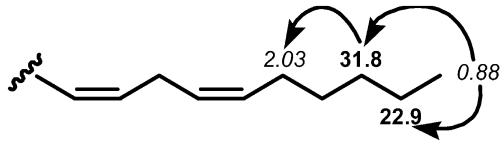

Figure 1. Selected HMBC correlations observed for compound **3**.

The molecular formulae $C_{28}H_{47}NO$ and $C_{30}H_{51}NO$ established for mycalazal-9 (**7**) and mycalazal-11 (**9**), respectively, together with the close similarity of their NMR data with those of the previously described mycalazal-5 (**3**), clearly indicated that the three compounds were members of the same homologous series and that differed in the number of methylenes linking the pyrrole nucleus and the olefinic system. Therefore, structures **7** and **9** were proposed for mycalazal-9 and mycalazal-11, respectively.

2.3. Compounds 2, 6, and 10/11

The NMR spectra of mycalazal-4 (**2**) indicated that it was another pyrrole-2-carbaldehyde metabolite containing a linear unsaturated side chain. In particular, from the molecular formula $C_{24}H_{41}NO$, established by HRMS, it was inferred the presence of nineteen carbon atoms and one double bond in the side chain. However, none of the NMR data allowed to assign the position of this unsaturation along the chain. Furthermore, the fragments observed in the low-resolution mass spectra did not provide unambiguous information, due to double bond migration in the ionization process. It was therefore decided to perform an oxidative cleavage of the double bond with $HIO_4/RuCl_3$ as described by Sharpless[21] with the aim to characterize the two resulting carboxylic acids. Although this procedure has been previously employed by us with good results,[22] in this occasion all attempts to perform the reaction were unfruitful. At room temperature an untreatable complex mixture of compounds were obtained, while lowering temperature led to the recovery of the starting material together with minor amounts of the corresponding diol and α-hydroxyketo derivatives. Finally, the location of the double bond in compound **2** could be deduced from the bis(methylthio) derivative **25** obtained by treatment of **2** with Me_2S_2.[23] The ^1H NMR spectrum of **25** was closely similar to that of compound **2**, except by the absence of the signals due to olefinic and allylic protons, appearing in turn the signals attributable to the methylthio groups (δ 2.10, s, 6H) and their geminal protons (δ 2.69, m, 2H). The low resolution mass spectrum of **25** showed the molecular ion peak at m/z 453 $(C_{26}H_{47}NOS_2)^+$ and two intense peaks at m/z 308 and 145 due to fragments resulting from the easy cleavage of the bond between carbons bearing the methylthio groups. The peak at m/z 308 was due to the fragment containing the pyrrole nucleus $(C_{18}H_{30}NOS)^+$ while the peak at m/z 145 arose from the fragment containing the methyl group at the end of the chain $(C_8H_{17}S)^+$ (Fig. 2). These data unambiguously established that the methylthio groups in **25** were attached to C-17 and C-18 and therefore it was concluded that the double bond in **2** was located at Δ^{17}.

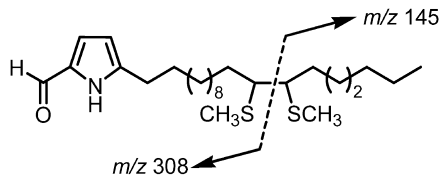

Figure 2. MS fragmentation of compound **25**.

An inspection of the NMR data of mycalazal-8 (**6**) together with its molecular formula $C_{26}H_{45}NO$ were consistent with the presence of a monounsaturated side chain elongated in two methylenes with respect to that of mycalazal-4 (**2**). Derivatization of **6** with Me_2S_2 and subsequent analysis of the corresponding bis(methylthio) derivative **26** by mass spectrometry, as described above, allowed to locate the double bond in **6** at Δ^{19}.

Mycalazal-12 (**10**) and mycalazal-13 (**11**) were obtained as an inseparable mixture. In fact, this mixture showed a single peak in GC–MS analysis and all the spectroscopic data accounted for a single compound possessing a C_{25} monounsaturated hydrocarbon side chain. However, when the procedure to locate the double bond was applied, the presence of two isomeric bis(methylthio) derivatives, **27** and **28**, became apparent during the GC–MS analysis (t_R 57.3 and 57.9 min, respectively). It was deduced that the methylthio groups in **27** were linked to C-21 and C-22 upon observation in its mass spectrum of two peaks at m/z 364 and 173 attributed to the fragments $(C_{22}H_{38}NOS)^+$ and $(C_{10}H_{21}S)^+$, respectively. On the other hand, the mass spectrum of **28** showed peaks at m/z 392 $(C_{24}H_{42}NOS)^+$ and 145 $(C_8H_{17}S)^+$. Following a similar rationale to that employed for compound **2**, it was determined that mycalazal-12 (**10**) and mycalazal-13 (**11**) were constitutional isomers which differed in the position of the double bond, Δ^{21} for **10** and Δ^{23} for **11**.

2.4. Compound 4

Two distinctive features of the ^1H NMR spectrum of mycalazal-6 (**4**) were the absence of signals due to olefinic protons and the presence of a doublet at δ 0.86 which integrated for 6H. These data indicated that in compound **4**

the pyrrole-2-carbaldehyde nucleus was substituted at C-5 with an aliphatic chain possessing a terminal isopropyl group. These data together with the molecular formula $C_{23}H_{41}NO$, established by HRMS, allowed to characterize mycalazal-6 (**4**) as the 5-(16-methylheptadecyl)pyrrole-2-carbaldehyde.

2.5. Compounds 12–14

Mycalenitrile-1 (**12**) was isolated as a colorless oil whose molecular formula, $C_{23}H_{38}N_2O$, indicated the presence of an additional nitrogen atom in the structure. The presence of the pyrrole-2-carbaldehyde nucleus was confirmed upon observation of the NMR signals at δ_H 9.33 (CHO), 9.20 (NH), 6.90 (dd, J=3.9, 2.3 Hz, H-3), 6.08 (dd, J=3.9, 2.3 Hz, H-4), and δ_C 177.5 (CHO), 142.9 (C-2), 131.8 (C-5), 123.1(C-3), and 109.8 (C-4). The remaining signals of the ^{1}H NMR spectrum were attributable to a series of methylenes within an aliphatic chain, although no signal could be found due to a methyl or an isopropyl group at the end of the chain. In fact, the ^{13}C NMR spectrum showed a downfield signal at δ 119.9 (s) that together with the IR absorption 2246 cm^{-1} were assigned to a nitrile group located at the end of the side chain. All these data led us to propose structure **12** for mycalenitrile-1.

Mycalenitrile-2 (**13**) and mycalenitrile-3 (**14**) possessed IR and NMR spectra almost superimposable with those of mycalenitrile-1 (**12**) above described, indicating that the three compounds had to differ only in the length of the chain. Thus, the molecular formulae obtained from HRMS allowed to establish that compound **13** ($C_{26}H_{44}N_2O$) possessed a side chain elongated in three methylenes with respect to that of **12** while in compound **14** ($C_{27}H_{46}N_2O$) the side chain contained four additional methylenes with respect to that of **12**.

From a biosynthetic point of view, different precursors and mechanisms have been proposed to explain the formation of a pyrrole nucleus in marine metabolites. Thus, while the central pyrrole ring present in a series of marine alkaloids could arise from the condensation of DOPA or tyrosine units,[24] the origin of the pyrrole system in stevensine has been traced to the amino acids ornithine and proline.[25] The structures of mycalazols,[15] mycalazals and mycalenitriles, combine a pyrrole moiety with long hydrocarbon chains reminiscent of those of fatty acids. These features suggest a mixed biogenesis pathway in which pyrrole-2-carboxylic acid (or equivalent), derived from ornithine and/or proline,[25] could be acylated at C-5 with different long chain acyl units.

2.6. Cytotoxic activity

All the metabolites isolated from *M. cecilia* were tested against a panel of tumor cell lines in bioassays directed to detect in vitro cytotoxicity (see Section 3). In general, all the metabolites showed activity as growth inhibitors of various cell lines. The more significant GI_{50} values (<5 μg/mL) are presented in Table 2. The cell lines LNcaP, IGROV, and SK-MEL28 were affected by most of the compounds of the class of mycalazals. These results could suggest a general selectivity of mycalazals as growth inhibitors of the cell lines above mentioned. Furthermore, the higher levels of activity for all the tested compounds were observed against the LNcaP cell line, being compound **6** the most active (GI_{50}=0.2 μg/mL). In addition, compounds **1**, **2**, **5**, **15**, **16**, and **17** showed a significant cytostatic effect on this cell line with TGI (total growth inhibition) values of 3.3, 2.6, 2.8, 3.1, 2.9, and 3.0 μg/mL, respectively. On the other hand, compounds of the mycalenitrile class showed a mild but highly selective activity against the cell lines PANC1, LOVO and HELA cell lines (Table 2).

The high number of metabolites isolated prompted us to analyze possible relationships between the structural features of the side chain of mycalazals (length, number of double bonds, and/or position of the unsaturations) and the observed activity, in particular concerning to the growth inhibition effect of mycalazals on the LNcaP line. A comparison of the activity of compounds **1**, **3**, **6**, and **21**, all of them possessing a C_{21} side chain, showed that the higher

Table 2. Cytotoxicity assay results for the compounds isolated from *Mycale cecilia* (GI_{50} values in μg/mL)

GI_{50}	A	B	C	D	E	F	G	H	I
1	1.8	4.8		3.8					
2	1.3	3.0		2.7		5.0			
3		3.9	4.1	3.9			3.1	2.0	3.6
4			4.8	3.5			3.6	3.2	4.1
5	1.5	3.0		2.9	3.6			4.2	
6	0.2	2.7		3.2			4.5		
7	3.0	4.5		4.2					
8	1.5	3.2		3.8					
9	3.8	4.8							
10/11	4.2								
12							4.8	2.4	
13								3.9	4.7
14									4.3
15	1.6			3.9		3.2		4.2	
16	1.6			2.3				3.6	
17	1.6			4.1		3.3		4.4	
18			4.7	4.1		4.3	3.9	2.1	3.9
19/20	2.8	4.8							
21									4.4
22								4.5	4.4

A: LN-caP, B: IGROV, C: SK-BR3; D: SK-MEL-28, E: A-549, F: K-562, G: PANC1, H: LOVO, I: HELA.

activity is associated to the presence of one double bond at ω-7 (compound **6**). When three double bonds are present (**1**) the activity decreases and it is lost for compounds possessing two (**3**) or no (**21**) double bond. The higher level of activity showed by compounds **5** and **8** with respect to **7** and **9** again points out that compounds with triunsaturated side chains are more active than the corresponding diunsaturated ones. The GI_{50} values observed for compounds **1**, **5**, **8**, displaying C_{21}, C_{23}, and C_{25} triolefinic side chains, respectively, were closely similar without regard of the length of the chain. However, this trend was not observed for the remaining mycalazals.

3. Experimental

3.1. General experimental procedures

IR spectra were recorded with a Genesis Series FT IR Mattson spectrophotometer, and UV spectra were registered on a Philips PU 8710 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively, on a Varian INOVA 400 spectrometer using $CDCl_3$ as solvent. Proton chemical shifts were referenced to the residual $CHCl_3$ signal at δ 7.26. ^{13}C NMR spectra were referenced to the central peak of $CDCl_3$ at δ 77.0. $^1H-^1H$-COSY, HMQC and HMBC were performed using standard VARIAN pulse sequences. Low resolution mass spectra were recorded on an Finningan Voyager GC8000^{top} spectrometer. High resolution electronic impact mass spectra were recorded on a VG Autospec spectrometer. Column chromatography was carried out using Merck Silica gel 60 (70–230 mesh). HPLC separations were performed on a LaChrom-Hitachi apparatus equipped with LiChrosorb RP-18 (Merck) column using a differential refractometer RI-71. All solvents were spectral grade or distilled prior to use.

3.2. Collection, extraction and isolation procedure

The sponge *Mycale cecilia* was collected by hand using SCUBA in the Gulf of California and liophylized (298.84 g). The material was extracted with acetone (9 L) and the solvent concentrated under reduced pressure to give a residue that was partitioned between H_2O and Et_2O. The Et_2O extract (7 g) was chromatographed on a silica gel column using solvents of increasing polarities from hexane to Et_2O and, subsequently $CHCl_3$/MeOH (8:2) and MeOH. The fraction eluted with hexane/Et_2O (8:2) was subjected to repeated reversed HPLC separations using MeOH as eluent to afford 5-(13′-methyltetradecyl)pyrrole-2-carbaldehyde (**15**, 13.1 mg, 0.0044%), 5-pentadecylpyrrole-2-carbaldehyde (**16**, 57.9 mg, 0.019%), 5-(14′-methylpentadecyl)-pyrrole-2-carbaldehyde (**17**, 5.8, 0.002%), 5-heptadecylpyrrole-2-carbaldehyde (**18**, 1.5 mg, 4.92×10^{-4}%), mycalazal-3 (**1**, 5.1 mg, 0.0017%), mycalazal-4 (**2**, 7.4 mg, 0.0025%), mycalazal-5 (**3**, 1.9 mg, 6.29×10^{-4}%), mycalazal-6 (**4**, 1.5 mg, 5.02×10^{-4}%), mycalazal-7 (**5**, 10.1 mg, 0.0034%), mycalazal-8 (**6**, 16.0 mg, 0.0054%), mycalazal-9 (**7**, 8.5 mg, 0.0028%), mycalazal-10 (**8**, 9.2 mg, 0.0032%), a mixture of (14′*Z*)-5-tricos-14′-enylpyrrole-2-carbaldehyde and (16′*Z*)-5-tricos-16′-enylpyrrole-2-carbaldehyde (**19/20**, 46.5 mg, 0.016%), 5-heneicosylpyrrole-2-carbaldehyde (**21**, 1.0 mg, 0.0003%), mycalazal-11 (**9**, 8.3 mg, 0.0029%),and a mixture of mycalazal-12 and mycalazal-13 (**10/11**, 15.7 mg, 0.0053%). Fractions from the general chromatography eluted with hexane/Et_2O (7:3) yielded, after purification on HPLC eluting with CH_3CN/MeOH (7:3), mycalenitrile-1 (**12**, 6.5 mg; 0.0022%), 5-(19′-cyanononadecyl)pyrrole-2-carbaldehyde (**22**, 26.8 mg, 0.009%), mycalenitrile-2 (**13**, 4.8 mg; 0.0016%), and mycalenitrile-3 (**14**, 8.2 mg, 0.0028%). Final purification of all these compounds was accomplished by HPLC on reversed phase mode using solvents of various proportions of either H_2O in MeOH or H_2O in CH_3CN.

3.2.1. Mycalazal-3 (1). Colorless oil, IR (film) 3257, 2924, 2850, 1666, 1496, 770 cm^{-1}; UV (MeOH) 204 (ε 14,688), 248 (ε 3437), 300 (ε 15,397) nm; ^1H and ^{13}C NMR (see Table 1); EIMS (70 eV) *m*/*z* (rel. int.) 383 (9.5), 354 (8.3), 150 (19.1), 136 (11.5), 122 (77.4), 108 (100), 94 (54.4); HREIMS Obsd. *m*/*z*=383.3188 $(M)^+$, $C_{26}H_{41}NO$ requires *m*/*z*=383.3187.

3.2.2. Mycalazal-4 (2). Amorphous powder, IR (film) 3255, 2920, 2850, 1664, 1496, 770 cm^{-1}; UV (MeOH) 202 (ε 7585), 249 (ε 2344), 300 (ε 11,764) nm; ^1H and ^{13}C NMR (see Table 1); EIMS (70 eV) *m*/*z* (rel. int.) 359 (38.0), 330 (24.1), 316 (9.9), 288 (10.0), 274 (11.7), 260 (13.8), 150 (42.5), 136 (29.6), 122 (45.2), 108 (100), 94 (43.5); HREIMS Obsd. *m*/*z*=359.3183 $(M)^+$, $C_{24}H_{41}NO$ requires *m*/*z*=359.3188

3.2.3. Mycalazal-5 (3). Colorless oil, IR (film) 3262, 2924, 2852, 1644, 1496, 770 cm^{-1}; UV (MeOH) 204 (ε 9254), 248 (ε 2392), 300 (ε 11,150) nm; ^1H and ^{13}C NMR (see Table 1); EIMS (70 eV) *m*/*z* (rel. int.) 385 (31.5), 356 (20.5), 342 (8.2), 328 (11.0), 314 (11.0), 150 (39.7), 122 (97.3), 108 (100), 94 (54.8); HREIMS Obsd. *m*/*z*=385.3342 $(M)^+$, $C_{26}H_{43}NO$ requires *m*/*z*=385.3345

3.2.4. Mycalazal-6 (4). Amorphous powder, IR (film) 3248, 2920, 2850, 1633, 774 cm^{-1}; UV (MeOH) 203 (ε 6260), 249 (ε 2078), 300 (ε 9786) nm; ^1H NMR δ 9.36 (s, 1H, H-1), 9.20 (s, 1H, NH), 6.89 (dd, *J*=3.8, 2.5 Hz, 1H, H-3), 6.07 (dd, *J*=3.8, 2.5 Hz, 1H, H-4), 2.65 (t, *J*=7.7 Hz, 2H, H-6), 1.65 (q, *J*=7.4 Hz, 2H, H-7), 1.51 (sept, *J*=6.6 Hz, 1H, H-21), 1.25 (broad signal, 24H, H-8, H-9, H-10, H-11, H-12, H-13, H-14, H-15, H-16, H-17, H-18 and H-19), 1.13 (m, 2H, H-20), 0.86 (d, *J*=6.5 Hz, 6H, H-22 and H-23); EIMS (70 eV) *m*/*z* (rel. int.) 347 (45.5), 304 (34.0), 150 (43.5), 136 (25.5), 122 (74.9), 108 (100), 94 (43.4); HREIMS Obsd. *m*/*z*=347.3182 $(M)^+$, $C_{23}H_{41}NO$ requires *m*/*z*=347.3188.

3.2.5. Mycalazal-7 (5). Colorless oil, IR (film) 3263, 2924, 2853, 1645, 1496, 770 cm^{-1}; UV (MeOH) 204 (ε 9254), 248 (ε 2392), 300 (ε 11,150) nm; ^1H and ^{13}C NMR (see Table 1); EIMS (70 eV) *m*/*z* (rel. int.) 411 (16.6), 382 (13.7), 150 (11.3), 136 (10.7), 122 (64.9), 108 (83.4), 94 (100); HREIMS Obsd. *m*/*z*=411.3501 $(M)^+$, $C_{28}H_{45}NO$ requires *m*/*z*=411.3499.

3.2.6. Mycalazal-8 (6). Amorphous powder, IR (film) 3248, 2920, 2850, 1644, 1496, 773 cm^{-1}; UV (MeOH) 202 (ε 7803), 248 (ε 2317), 300 (ε 11,290) nm; ^1H and ^{13}C NMR (see Table 1); EIMS (70 eV) *m*/*z* (rel. int.) 387 (38.3), 358

(18.9), 344 (22.2), 330 (26.0), 150 (53.0), 136 (21.9), 122 (59.5), 108 (100), 94 (52.0); HREIMS Obsd. *m/z*=387.3501 $(M)^+$, $C_{26}H_{45}NO$ requires *m/z*=387.3500.

3.2.7. Mycalazal-9 (7). Colorless oil, IR (film) 3259, 2924, 2853, 1644, 1496, 717 cm^{-1}; UV (MeOH) 201 (ε 14,167), 248 (ε 4056), 300 (ε 21,159) nm; ^1H and ^{13}C NMR (see Table 1); EIMS (70 eV) *m/z* (rel. int.) 413 (62.7), 384 (37.3), 150 (44.0), 136 (34.7), 122 (100), 108 (97.3), 94 (96.0); HREIMS Obsd. *m/z*=413.3658 $(M)^+$, $C_{28}H_{47}NO$ requires *m/z*=413.3653.

3.2.8. Mycalazal-10 (8). Colorless oil, IR (film) 3252, 2922, 2850, 1661, 1496, 772 cm^{-1}; UV (MeOH) 204 (ε 11,921), 248 (ε 3692), 300 (ε 16,903) nm; ^1H and ^{13}C NMR (see Table 1); EIMS (70 eV) *m/z* (rel. int.) 439 (20.8), 410 (15.5), 150 (43.0), 136 (29.6), 122 (75.1), 108 (99.8), 94 (100); HREIMS Obsd. *m/z*=439.3814 $(M)^+$, $C_{30}H_{49}NO$ requires *m/z*=439.3803.

3.2.9. Mycalazal-11 (9). Colorless oil, IR (film) 3263, 2923, 2852, 1644, 1496, 772 cm^{-1}; UV (MeOH) 202 (ε 6044), 248 (ε 1796), 301 (ε 7633) nm; ^1H and ^{13}C NMR (see Table 1); EIMS (70 eV) *m/z* (rel. int.) 441 (39.5), 412 (23.3), 398 (9.3), 384 (11.6), 150 (35.0), 136 (14.0), 122 (90.7), 108 (100), 94 (51.2); HREIMS Obsd. *m/z*=441.3971 $(M)^+$, $C_{30}H_{51}NO$ requires *m/z*=441.3943.

3.2.10. Mycalazal-12/13 (10/11). Amorphous powder, IR (film) 3251, 2953, 2850, 1639, 1457, 770 cm^{-1}; UV (MeOH) 202 (ε 7458), 248 (ε 2750), 301 (ε 12,728) nm; ^1H and ^{13}C NMR (see Table 1); EIMS (70 eV) *m/z* (rel. int.) 443 (40.5), 400 (9.0), 386 (9.2), 150 (50.9), 136 (22.1), 122 (61.0), 108 (100); HREIMS Obsd. *m/z*=443.4127 $(M)^+$, $C_{30}H_{53}NO$ requires *m/z*=443.4124.

3.2.11. Mycalenitrile-1 (12). Colorless oil, IR (film) 3250, 2246, 1644, 1490, 780 cm^{-1}; UV (MeOH) 204 (ε 6025), 248 (ε 2544), 300 (ε 10,125) nm; ^1H NMR δ 9.33 (s, 1H, H-1), 9.20 (s, 1H, NH), 6.90 (dd, *J*=3.9, 2.3 Hz, 1H, H-3), 6.08 (dd, *J*=3.9 and 2.3 Hz, 1H, H-4), 2.64 (t, *J*=7.7 Hz, 2H, H-6), 2.33 (t, *J*=7.1 Hz, 2H, H-22), 1.65 (m, 4H, H-7 and H-21), 1.43 (m, 2H, H-20), 1.25 (broad signal, 24H, H-8, H-9, H-10, H-11, H-12, H-13, H-14, H-15, H-16, H-17, H-18 and H-19); ^{13}C NMR δ 177.5 (s, C-1), 142.9 (s, C-2), 131.8 (s, C-5), 123.1 (d, C-3), 119.9 (s, C-23), 109.8 (d, C-4), 28.7 and 29.1-29.7 (t, C-8, C-9, C-10, C-11, C-12, C-13, C-14, C-15, C-16, C-17, C-18, C-19), 28.8 (t, C-7), 28.6 (t, C-20), 27.9 (t, C-6); 25.3 (t, C-21), 17.1 (t, C-22); EIMS (70 eV) *m/z* (rel. int.) 358 (35.6), 329 (15.5), 150 (41.5), 136 (20.0), 122 (56.1), 108 (100), 94 (43.5); HREIMS Obsd. *m/z*=358.2978 $(M)^+$, $C_{23}H_{38}N_2O$ requires *m/z*=358.2984.

3.2.12. Mycalenitrile-2 (13). Colorless oil, IR (film) 3255, 2246, 1660, 1490, 780 cm^{-1}; UV (MeOH) 204 (ε 6028), 248 (ε 2714), 300 (ε 11,788) nm; ^1H NMR δ 9.38 (s, 1H, H-1), 6.88 (dd, *J*=3.8, 2.5 Hz, 1H, H-3), 6.07 (dd, *J*=3.8, 2.5 Hz, 1H, H-4), 2.63 (t, *J*=7.8 Hz, 2H, H-6), 2.33 (t, *J*=7.2 Hz, 2H, H-25), 1.65 (m, 4H, H-7 and H-24), 1.43 (m, 2H, H-23), 1.25 (broad signal, 30H, H-8, H-9, H-10, H-11, H-12, H-13, H-14, H-15, H-16, H-17, H-18, H-19, H-20, H-21 and H-22); ^{13}C NMR δ 178.1 (s, C-1), 142.9 (s, C-2), 131.8 (s, C-5), 122.9 (d, C-3), 119.9 (s, C-26), 109.4 (d, C-4), 28.7 and 29.1-29.7 (t, C-8, C-9, C-10, C-11, C-12, C-13, C-14, C-15, C-16, C-17, C-18, C-19, C-20, C-21, C-22), 28.9 (t, C-7), 28.6 (t, C-23), 27.9 (t, C-6); 25.4 (t, C-24), 17.1 (t, C-25); EIMS (70 eV) *m/z* (rel. int.) 400 (16.9), 371 (15.5), 150 (43.0), 136 (29.6), 122 (75.1), 108 (99.8), 94 (100); HREIMS Obsd. *m/z*=400.3460 $(M)^+$, $C_{26}H_{44}N_2O$ requires *m/z*=400.3453.

3.2.13. Mycalenitrile-3 (14). Colorless oil, IR (film) 3250, 2920, 2848, 2242, 1646, 1490, 780 cm^{-1}; UV (MeOH) 203 (ε 5950), 248 (ε 2512), 300 (ε 10,000) nm; ^1H NMR δ 9.36 (s, 1H, H-1), 9.20 (s, 1H, NH), 6.89 (dd, *J*=3.8, 2.5 Hz, 1H, H-3), 6.07 (dd, *J*=3.8, 2.5 Hz, 1H, H-4), 2.64 (t, *J*=7.7 Hz, 2H, H-6), 2.33 (t, *J*=7.1 Hz, 2H, H-26), 1.65 (m, 4H, H-7 and H-25), 1.43 (m, 2H, H-24), 1.25 (broad signal, 32H, H-8, H-9, H-10, H-11, H-12, H-13, H-14, H-15, H-16, H-17, H-18, H-19, H-20, H-21, H-22 and H-23); ^{13}C NMR δ 178.1 (s, C-1), 142.9 (s, C-2), 131.8 (s, C-5), 122.9 (d, C-3), 119.9 (s, C-27), 109.4 (d, C-4), 28.7 and 29.1-29.7 (t, C-8, C-9, C-10, C-11, C-12, C-13, C-14, C-15, C-16, C-17, C-18, C-19, C-20, C-21, C-22, C-23), 28.9 (t, C-7), 28.6 (t, C-24), 27.9 (t, C-6); 25.4 (t, C-25), 17.1 (t, C-26); EIMS (70 eV) *m/z* (rel. int.) 439 (20.8), 410 (15.5), 150 (43.0), 136 (29.6), 122 (75.1), 108 (99.8), 94 (100); HREIMS Obsd. *m/z*=414.3610 $(M)^+$, $C_{27}H_{46}N_2O$ requires *m/z*=414.3591.

3.3. Location of the double bond in compounds 2, 6 and 10/11

To a solution of mycalazal-5 (**2**, 1.1 mg, 3.06×10^{-3} mmol) in dimethyl disulfide (0.5 mL) was added iodine (4.7 mg, 0.019 mmol) at room temperature. After 3.5 h of stirring the reaction was quenched with 5% $Na_2S_2O_3$ (1 mL) and extracted with n-hexane (3×1 mL). The combined extracts were concentrated under reduced pressure yielding 0.8 mg (1.77×10^{-3} mmol) of the bis(methylthio) derivative **25**.

3.3.1. Compound 25. Amorphous powder, ^1H NMR δ 9.36 (s, 1H, H-1), 9.21 (s, 1H, NH), 6.88 (dd, *J*=3.5, 2.3 Hz, 1H, H-3), 6.07 (dd, *J*=3.5, 2.3 Hz, 1H, H-4), 2.69 (m, 2H, H-17, H-18), 2.64 (t, *J*=7.6 Hz, 2H, H-6), 2.10 (s, 6H, 2×SCH_3), 1.63 (m, 6H, H-7, H-16 and H-19), 1.25 (broad signal, 24H, H-8, H-9, H-10, H-11, H-12, H-13, H-14, H-15, H-20, H-21, H-22 and H-23), 0.86 (d, *J*=6.4 Hz, 3H, H-24); EIMS (70 eV) *m/z* (rel. int.) 453 (8.5), 308 (81.4), 232 (84.3), 145 (85.7), 108 (88.5), 94 (35.5), 80 (100).

Application of this procedure to 4.6 mg (0.012 mmol) of mycalazal-8 (**6**) yielded 5.19 mg (0.011 mmol) of the bis(methylthio) derivative **26**.

3.3.2. Compound 26. Amorphous powder, ^1H NMR δ 9.36 (s, 1H, H-1), 9.21 (s, 1H, NH), 6.88 (dd, *J*=3.5, 2.3 Hz, 1H, H-3), 6.07 (dd, *J*=3.5, 2.3 Hz, 1H, H-4), 2.69 (m, 2H, H-19, H-20), 2.64 (t, *J*=7.6 Hz, 2H, H-6), 2.10 (s, 6H, 2×SCH_3), 1.63 (m, 6H, H-7, H-18 and H-21), 1.25 (broad signal, 28H, H-8, H-9, H-10, H-11, H-12, H-13, H-14, H-15, H-16, H-17, H-22, H-23, H-24 and H-25), 0.86 (d, *J*=6.4 Hz, 3H, H-26); EIMS (70 eV) *m/z* (rel. int.) 481 (0.2), 336 (79.7), 260 (92.0), 145 (47.7), 108 (91.3), 94 (42.2), 80 (100).

Application of this same experimental procedure to the

mixture of mycalazal-12 and mycalazal-13 (**10/11**) (3.8 mg, 8.58×10^{-3} mmol) yielded the corresponding mixture of the bismethylthio derivatives **27** and **28**.

3.3.3. Compounds 27 and 28. Amorphous powder, ^{1}H NMR δ 9.37 (s, 2H, H-1), 9.14 (s, 2H, NH), 6.88 (dd, J=3.5, 2.3 Hz, 2H, H-3), 6.07 (dd, J=3.5, 2.3 Hz, 2H, H-4), 2.69 (m, 4H, H-21 and H-22/H-23 and H-24), 2.64 (t, J=7.6 Hz, 4H, H-6), 2.10 (s, 12H, 4×SCH_3), 1.63 (m, 12H, H-7, H-20 and H-23/H-7, H-22 and H-25), 1.25 (broad signal, 56H, H-8, H-9, H-10, H-11, H-12, H-13, H-14, H-15, H-16, H-17, H-22, H-23, H-24 and H-25/H-8, H-9, H-10, H-11, H-12, H-13, H-14, H-15, H-16, H-17, H-18, H-19, H-20, H-21, H-26, H-27, H-28 and H-29), 0.86 (d, J=6.4 Hz, 6H, H-26).

The reaction mixture was analyzed by CG–MS and the results were as follows:

Compound **27**: t_R [min]=57.3, EIMS (70 eV) *m/z* (rel. int.) 364 (40.0, $(C_{22}H_{38}NOS)^+$), 288 (45.7), 173 (57.1, $(C_{10}H_{21}S)^+$), 108 (67.1), 94 (41.4), 80 (100).

Compound **28**: t_R [min]=57.9, EIMS (70 eV) *m/z* (rel. int.) 392 (40.0, $(C_{24}H_{42}NOS)^+$), 316 (51.0), 145 (64.3, $(C_8H_{17}S)^+$), 108 (70.1), 94 (37.1), 80 (100).

3.4. Cytotoxicity assays

All the compounds isolated from *M. cecilia* were tested against the following human tumor cell lines: DU-145 (prostate carcinoma), LN-caP (prostate carcinoma), IGROV (ovarian adenocarcinoma), SK-BR3 (breast adenocarcinoma), SK-MEL-28 (melanoma), A-549 (lung adenocarcinoma), K-562 (chronic myelogenous leukemia), PANC-1 (pancreas carcinoma), HT-29 (colon adenocarcinoma), LOVO (colon adenocarcinoma), LOVO-DOX (colon adenocarcinoma resistant to doxorubicin), and HELA (cervix epithelial adenocarcinoma).

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cis/trans-Isochromanones. DMAP induced cycloaddition of homophthalic anhydride and aldehydes

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Abstract—Homophthalic anhydride (**1**) reacts with wide variety of aromatic aldehydes, in the presence of chloroform and DMAP (*N*,*N*-dimethyl-4-amino-pyridine) at room temperature, to give in high yields *cis*- and *trans*-1-oxo-isochroman-4-carboxylic acids. Under these conditions, the *trans*-isomer is predominant and formation of Perkin-type products was not observed in contrast to the reaction carried out in the presence of pyridine. The unexpected *trans*-6-oxo-11-thiophen-2-yl-11,12-dihydro-6*H*-dibenzo[*c*,*h*]chromene-12-carboxylic acid methyl ester (**8**) was isolated when the reaction between **1** and thiophene-2-carbaldehyde was carried out in pyridine.

1. Introduction

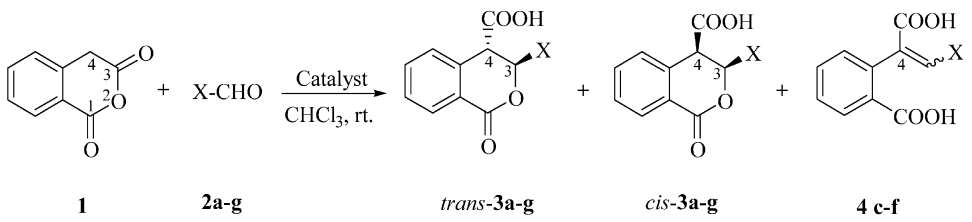
Until now, the reaction between homophthalic anhydride (**1**) and aldehydes has been performed under different reaction conditions[1–7] affording the corresponding thermodynamically controlled C-4 methylene condensed products of type **4** or the kinetically controlled cycloadducts *trans*-**3**[2] (Scheme 1). This reaction has been performed both in basic and acidic media (Table 1). The best results for benzaldehyde have been observed in the presence of strong base at low temperature[2] (entry 3). In contrast, under the same catalyst, but at room temperature[2] (entry 4), the reaction is considered as thermodynamically controlled yielding a mixture of acid *trans*-**3a** and the C-4 methylene condensed product **4a**, the latter being predominant. When the reaction is carried out in the presence of a Lewis acid ($BF_3{\cdot}Et_2O$ complex, entry 5),[3] the reaction gives the cycloadducts *cis*- and *trans*-**3a** and formation of **4a** is not observed. It is clear that there is some contradiction as to which is the thermodynamically favored diastereomer. In the analogous reaction between **1** and acyclic imines,[8,9] the *trans* is the thermodynamically preferred diastereomer.

Table 1. Ratios among products in the reaction of homophthalic anhydride (**1**) and benzaldehyde (**2a**) under different reaction conditions

Entry	Catalyst	Reaction conditions		Ratios (%)		
		t (°C)	Time (h)	*cis*-**3a**	*trans*-**3a**	**4a**
1	Na/liq. NH_3[1]	rt	14	—	61	—
2	Na_2CO_3[2]	rt	24	—	35[a]	43[a]
3	NaH[2]	0-rt	24	—	83[a]	—
4	NaH[2]	rt	33	—	5[a]	82[a]
5	$BF_3{\cdot}Et_2O$[3]	rt	5	38	43	—

[a] Isolated as a methyl esters after treatment of acidic residue with diazomethane.

4-Dimethylaminopyridine (DMAP) is known to be an excellent catalyst for a variety of synthetic transformations under mild conditions, such as alkylation, acylation, silylation, esterification, polymerisation and



1 **2a-g** *trans*-**3a-g** *cis*-**3a-g** **4 c-f**

X= Ar or HetAr (see Table 2)

Scheme 1.

Keywords: Homophthalic anhydride; Aldehydes; Cycloaddition; DMAP; Pyridine; Isochroman-4-carboxylic acids.
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rearrangements.[10] This paper presents a study on the reaction of homophthalic anhydride (**1**) with different aromatic or heteroaromatic aldehydes in the presence of DMAP at mild conditions: room temperature and duration of 1.5–2.5 h. Thus, we demonstrated that under these conditions **1** reacted with benzaldehyde to give cycloadducts *cis*-**3a** and *trans*-**3a** only. This procedure gives excellent results and was extended to a wide variety of aromatic aldehydes. A comparison with the reaction in the presence of pyridine is done.

2. Results and discussion

2.1. Small scale syntheses of 3-aryl-1-oxo-isochroman-4-carboxylic acids 3a–g

Scheme 1 shows that the reaction between **1** and aldehydes **2a–g**, including benzaldehyde (**2a**), lead always to cycloadducts **3**, while the C-4 methylene condensed by-products **4** are obtained in cases **c–f** only. To establish the ratios among *cis*-**3**, *trans*-**3** and **4** in the presence of DMAP, the reaction between **1** and aldehydes **2a–g** was performed on a small scale (by 0.54–0.77 mmol of **1**) under mild conditions (Table 2). The aprotic solvent used was chloroform. Such studies on the reaction of **1** with aldehydes are not known. The reaction is stereoselective towards the *trans*-isomer. The ratios among *cis*-**3**, *trans*-**3** and **4** were determined by ^{1}H NMR spectroscopy from the integrals of relevant protons. The signals for the protons at C-3 and C-4 were used[1–6] for any isomer of type **3**. In the case of products **4c–f**, the olefinic proton was taken into account. The results are summarized in Table 2. The configuration of each isomer was determined on the basis of $J_{3,4}$.[1–6] *trans* Configuration was as to the isomer with greater $J_{3,4}$ ($J_{3,4}>5.6$ Hz) and *cis* configuration as to the isomer with smaller $J_{3,4}$ ($J_{3,4}<4$ Hz). It is clear that the quantities of **3** (both isomers) vary from 70 to 100% when **1** is not present at the end of the reaction (TLC). When benzaldehyde or substituted benzaldehydes are used, the total yield of cycloadducts **3a–d,g** (both isomers) is 95%. In the cases when the aldehyde is substituted with a heterocyclic ring, such as furan-2-yl and thiophen-2-yl (**2e,f**), the C-4 methylene condensed products **4e,f** were detected in quantities 9–30%. It is known that the reaction of **1** with furfural in the presence of sodium carbonate[6] gives the C-4 methylene condensed product **4f** only. **4e** is known, but is prepared in another way.[11] It is clear that cycloaddition is the preferred reaction when DMAP is used as a base. The formation of the C-4 methylene condensed by-products **4** depends on the type of the aromatic or heteroaromatic substituent on the aldehyde. Formation of **4** is avoided if the substituent X does not deactivate or even activates the aldehyde group to nucleophilic addition (entries a, b, g). It is worth noting that the nitrogen atom in 9-methyl-carbazole-3-carbaldehyde (**2g**) influences slightly the aldehyde group. Thus, aldehyde **2g** behaves in a similar manner to **2a** in the reaction studied. The presence of electron-donating group in **2c–f** deactivates the aldehyde group and always leads to formation of **4** along with adducts **3**.

2.2. Large scale preparation of acids 3a–g

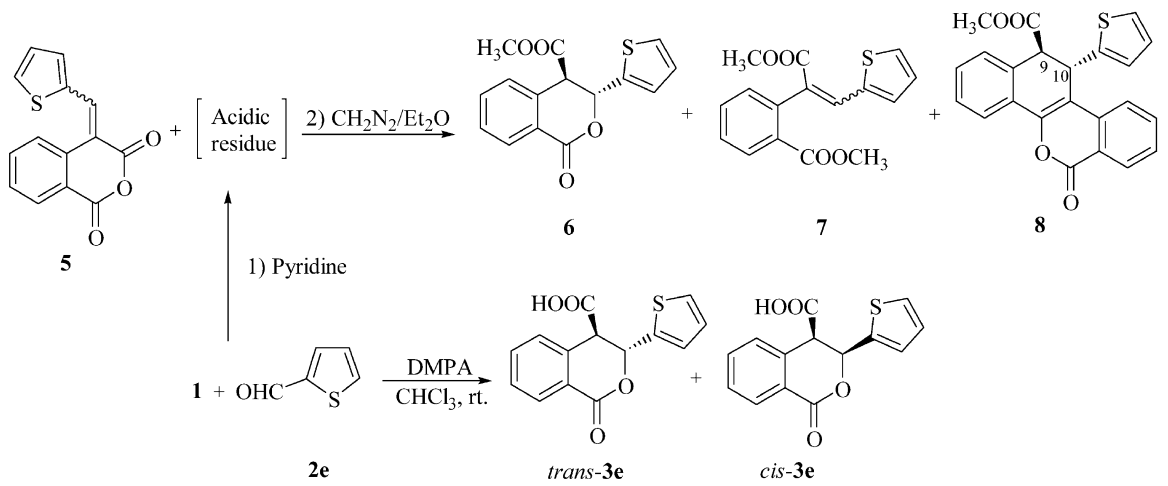
For the isolation and characterization of acids **3a–g**, we carried out the reactions between **1** and **2a–g**, on 2.7–3.9 mmol of substrate, in the presence of DMAP–chloroform. In all cases, both diastereomeric cycloadducts were formed. The diastereomers of **3a,b** were separated by fractional crystallization. In case **2d**, column chromatography lead to isolation of **4d** only, while *cis*- and *trans*-**3d** crystallized as a diastereomeric mixture. **3c,e,f** and **g** were isolated as *trans*-isomers only, since the quantity of the relevant *cis*-isomers was small. All isolated compounds gave the expected spectroscopic data (IR, ^{1}H NMR) and microanalyses.

2.2.1. Preparation of acid *trans*-3e and the methyl esters 6, 7 and 8. Comparison between two basic catalysts. The reaction between **1** and thiophene-2-carbaldehyde **2e** was performed also on larger scales (18–36 mmol of substrate) both in DMAP–chloroform and in pyridine. These experiments aimed to compare of DMAP with another basic catalyst. Significant differences were established, as shown in Scheme 2. When the reaction was carried out in pyridine, the unsaturated anhydride **5** was isolated in 27% yield. Compound **5** is known[11] but is prepared in another way. Having isolated **5**, the acidic residue was treated with diazomethane giving a mixture of compounds **6**, **7** and **8** (TLC) separated by column chromatography of the crude reaction mixture. The presence of **6** and **7** is well understood, but the presence of **8** is unexpected. There is no literature procedure for the preparation of compounds of this type in a reaction between **1** and carbonyl compounds. The structure of compound **8** was confirmed by spectral data

Table 2. Ratios among products in the reaction of homophthalic anhydride and aromatic aldehydes in the presence of DMAP at room temperature

2	X–CHO	Reaction time (h)[a]	Total yield (%)[b]	Ratio (%)[c]		
				3-*cis*	**3**-*trans*	**4**
2a	Benzaldehyde	2	100	30	70	—
2b	4-Nitro-benzaldehyde	2	98	23	77	—
2c	4-Methoxy-benzaldehyde	2.5	98	16	80	4
2d	Benzo[1,3]dioxole-5-carbaldehyde[d]	2	100	16	79	5
2e	Thiophene-2-carbaldehyde	1.5	100	9	82	9
2f	Furan-2-carbaldehyde	1.5	100	8	62	30
2g	9-Methyl-9*H*-carbazole-3-carbaldehyde	2	80	9	91	—

[a] The complete consumption of **1** was determined by TLC.
[b] Yields of the obtained acidic residue before recrystallization.
[c] The ratio was determined by ^{1}H NMR integrals of the obtained acidic residue (see text).
[d] Pipperonal.



Scheme 2.

(^{1}H, ^{13}C NMR, MS, IR) and microanalysis. In general, the lower value of $J_{9,10}$ (J=1.3 Hz) in ^{1}H NMR spectrum suggests the *cis*-configuration of **8** and a conformation with equatorial thiophenyl and axial methoxycarbonyl group,[1] but X-ray crystallography of **8**[12] showed the configuration to be *trans* and that the substituents at C-9 and C-10 are diaxial. The torsion angle H9–C9–C10–H10 is 78°. (Fig. 1). This angle agrees with the smaller value of the coupling constant $J_{9,10}$. The presence of the parent acid of **8** can be rationalized by lactam ring opening in *trans*-**3e** and subsequent interaction with an equimolar quantity of homophthalic anhydride.

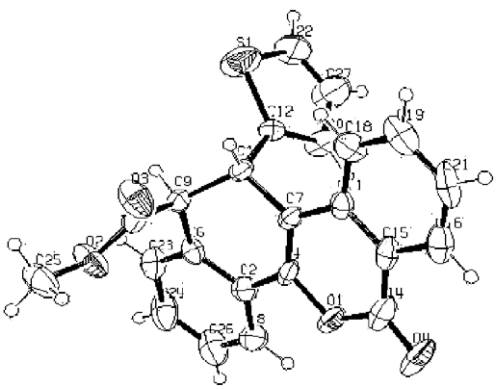


Figure 1. Configuration and conformation of *trans*-**8**.

The reaction between **1** and thiophene-2-carbaldehyde **2e** in the presence of DMAP on larger scale proceeded similarly to the smaller-scale cases and by-products **5** (Perkin-type) and **8** were not observed. Under these conditions, we were able to isolate also acid *cis*-**3e**. The conversion of *trans*-**3e** to the methyl ester was accomplished by treatment with diazomethane in diethylether solution. The direct esterification of acid **3e** or its treatment with iodomethane in the presence of potassium carbonate leads to α,β-unsaturated product **7**.

3. Conclusions

We have presented an optimized method for synthesis of 1-oxo-isochroman-4-carboxylic acid derivatives by the cyclo-addition reaction of homophthalic anhydride with aldehydes, catalyzed by DMAP. The reaction occurs under mild conditions and has been extended to a wide variety of aldehydes. The reaction is highly stereoselective towards the *trans*-cycloadducts in cases **3a–g**. This method has been compared with the analogous reaction in pyridine and has proved to be preferable.

4. Experimental

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. The IR spectra were recorded on a Specord 75. Nujol was used for all acidic products and chloroform for all other compounds. The ^{1}H NMR spectra were obtained on a Bruker AM300 NMR spectrometer at 300.13 MHz and Bruker Avance DRX-250 spectrometer at 250.13 MHz. The ^{13}C NMR spectra were obtained on a Bruker AM300 NMR spectrometer at 75 MHz in $CDCl_3$. The chemical shift is given in ppm (δ) relative to tetramethylsilane as internal standard. The integrals in the ^{1}H NMR spectra show that any compound was isolated in purity more than 98%. Mass spectra were recorded on a Hewlett Packard MS 5973 using electron impact of 30 eV. The microanalyses were done in the relevant laboratories at the Faculty of Chemistry, University of Sofia. TLC was done on precoated 0.2 mm Merck silica gel 60F_{254} plates. Merck silica gel 60 (0.040–0.063 mm) was used for chromatographic filtration and column chromatography.

4.1. General procedure for determination of the ratios of the products obtained from 1 and aldehydes 2a–g in the small scale experiments

To a mixture of **1** (0.54–0.77 mmol) and 1.1 equiv. of corresponding aldehyde (see Table 2) in dry chloroform (1 ml), DMAP (1 equiv.) was added. The reaction mixture was stirred at room temperature for 1.5–2.5 h. At the end of the reaction, presence of **1** was not established (TLC). The obtained carboxylic acids were extracted with 10% sodium hydrogen carbonate and the aqueous layer was acidified (pH=3) with 10% hydrochloric acid and extracted with ethyl acetate. The organic layer was dried (sodium sulfate), filtered and the solvent was then evaporated. The ratios of

all products (*cis*-**3**/*trans*-**3**/**4**) were determined, as described above, by ^{1}H NMR (300 MHz) integrations. The data obtained are summarized in Table 2.

4.2. General procedure for synthesis of 1-oxo-isochroman-4-carboxylic acids on large scales

To a mixture of **1** (2.69–3.87 mmol) and 1.1 equiv. of corresponding aldehyde **2** in dry chloroform (5 ml) DMAP (1 equiv.) was added. The reaction mixture was stirred at room temperature for 1.5–2.5 h. At the end of the reaction, when **1** was shown to have been consumed (TLC), the obtained carboxylic acids were extracted with 10% sodium hydrogen carbonate. The aqueous layer was acidified (pH=3) with 10% hydrochloric acid and extracted with ethyl acetate. The organic layer was dried (sodium sulfate), filtered and the solvent was then evaporated under reduced pressure. The products were obtained by precipitation or fractional crystallization of the residue.

4.2.1. 3-Phenyl-1-oxo-isochroman-4-carboxylic acids (3a). *cis-Diastereomer*. The residue was treated with dichloromethane until precipitation. Yield: 0.14 g (14%), mp 179–180 °C, (lit.[3] mp 189–190 °C); IR (Nujol): (CO) 1735, 1710 cm^{-1}; ^{1}H NMR (250 MHz, dimethyl sulfoxide-d_6): δ=4.14 (1H, d, J=3.5 Hz, *H*-4), 5.80 (1H, d, J=3.5 Hz, *H*-3), 7.38–7.46 (4H, m, phenyl protons), 7.53–7.59 (3H, m, phenyl protons), 7.65 (1H, dt, J=1.5, 7.5 Hz, phenyl proton), 8.18 (1H, dd, J=1.4, 7.8 Hz, phenyl proton), 13.01 (1H, s, COOH). Anal. Calcd for $C_{16}H_{12}O_4$: C, 71.64%; H, 4.51%; Found: C, 71.36%; H, 4.32%.

trans-Diastereomer. The dichloromethane filtrate was distilled under reduced pressure and the product was recrystallized from ethyl acetate giving colorless prisms. Yield: 0.61 g (61%), mp 169–170 °C, (lit.[3] mp 180–181 °C); IR (Nujol): (CO) 1735, 1715 cm^{-1}; ^{1}H NMR (250 MHz, dimethyl sulfoxide-d_6): δ=4.36 (1H, d, J=7.5 Hz, *H*-4), 5.92 (1H, d, J=7.5 Hz, *H*-3), 7.29–7.39 (6H, m, phenyl protons), 7.50 (1H, t, J=7.5 Hz, phenyl proton), 7.62 (1H, dt, J=1.5, 7.5 Hz, phenyl proton), 8.18 (1H, dd, J=1.5, 7.8 Hz, phenyl proton), 12.75 (1H, s, COOH). Anal. Calcd for $C_{16}H_{12}O_4$: C, 71.64%; H, 4.51%; Found: C, 71.88%; H, 4.11%.

4.2.2. 3-(4-Nitro-phenyl)-1-oxo-isochroman-4-carboxylic acids (3b). *cis-Diastereomer*. The residue was treated with dichloromethane until precipitation. Yield: 0.18 g (18%), mp 199–201 °C; IR (Nujol): (CO) 1740, 1710 cm^{-1}; ^{1}H NMR (250 MHz, dimethyl sulfoxide-d_6): δ=4.48 (1H, d, J=3.5 Hz, *H*-4), 6.19 (1H, d, J=3.5 Hz, *H*-3), 7.53–7.62 (2H, m, phenyl protons), 7.74 (1H, dt, J=1.5, 7.5 Hz, phenyl proton), 7.83 (2H, d, J=8.5 Hz, phenyl protons), 8.06 (1H, dd, J=1.3, 7.8 Hz, phenyl proton), 8.32–8.36 (2H, m, phenyl protons), 12.86 (1H, s, COOH). Anal. Calcd for $C_{16}H_{11}NO_6$: C, 61.35%; H, 3.54%; Found: C, 61.41%; H, 3.44%.

trans-Diastereomer. After isolation of the *cis*-isomer, the solvent was removed under reduced pressure and the product was crystallized from ethanol–water (1:1) as colorless prisms. Yield: 0.70 g (70%), mp 163–165 °C; IR (Nujol): (CO) 1740, 1715 cm^{-1}; ^{1}H NMR (250 MHz, dimethyl sulfoxide-d_6): δ=4.35 (1H, d, J=7.5 Hz, *H*-4), 6.06 (1H, d, J=7.5 Hz, *H*-3), 7.38 (1H, d, J=7.8 Hz, phenyl proton), 7.50 (1H, t, J=7.5 Hz, phenyl proton), 7.61–7.69 (3H, m, phenyl protons), 8.11 (1H, dd, J=1.3, 7.8 Hz, phenyl proton), 8.19–8.23 (2H, m, phenyl protons), 13.21 (1H, s, COOH). Anal. Calcd for $C_{16}H_{11}NO_6$: C, 61.35%; H, 3.54%; Found: C, 61.51%; H, 3.54%.

4.2.3. 3-(4-Methoxy-phenyl)-1-oxo-isochroman-4-carboxylic acid (3c). *trans-Diastereomer*. The residue crystallized as white crystals (from ethyl acetate). Yield: 0.60 g (60%), mp 149–151 °C; IR (Nujol): (CO) 1740, 1715 cm^{-1}; ^{1}H NMR (250 MHz, dimethyl sulfoxide-d_6): δ=3.73 (3H, s, OCH_3), 4.61 (1H, d, J=7.2 Hz, *H*-4), 5.86 (1H, d, J=7.2 Hz, *H*-3), 6.89–6.95 (2H, m, phenyl protons), 7.32–7.39 (3H, m, phenyl protons), 7.51 (1H, dt, J=1.0, 7.5 Hz, phenyl proton), 7.69 (1H, dt, J=1.5, 7.5 Hz, phenyl proton), 7.97 (1H, dd, J=1.3, 7.8 Hz, phenyl proton), 13.22 (1H, s, COOH). Anal. Calcd for $C_{17}H_{14}O_5$: C, 68.45%; H, 4.73%; Found: C, 68.68%; H, 4.68%.

4.2.4. 3-Benzo[1,3]dioxol-5-yl-1-oxo-isochroman-4-carboxylic acids (3d) and 2-(2-benzo[1,3]dioxol-5-yl-1-carboxyvinyl)-benzoic acid (4d). A precipitate being a mixture of *cis*- and *trans*-diastereomers **3d** (from ethyl acetate, after column chromatography) was obtained. Yield: 0.76 g (76%), mp 139–141 °C; IR (Nujol): (CO) 1740, 1700 cm^{-1}; ^{1}H NMR (250 MHz, dimethyl sulfoxide-d_6).

cis-Diastereomer. δ=4.08 (1H, d, J=3.6 Hz, *H*-4), 5.69 (1H, d, J=3.6 Hz, *H*-3).

trans-Diastereomer. δ=4.30 (1H, d, J=8.0 Hz, *H*-4), 5.77 (1H, d, J=8.0 Hz, *H*-3), other signals for both diastereomers: δ=5.95 (2H, s, $-OCH_2O-$), 6.73 (1H, d, J=8.0 Hz, phenyl proton), 6.80–6.89 (2H, m, phenyl protons), 7.29 (1H, d, J=8 Hz, phenyl proton), 7.45 (1H, t, J=7.4 Hz, phenyl proton), 7.61 (1H, dt, J=1.5, 7.6 Hz, phenyl proton), 8.17 (1H, dd, J=1.3, 7.6 Hz, phenyl proton). Anal. Calcd for $C_{17}H_{12}O_6$: C, 65.39%; H, 3.87%; Found: C, 64.98%; H, 4.05%.

By-product **4d** was obtained from the filtrate of **3d** as colorless prisms (from ethyl acetate, after column chromatography). Yield: 0.04 g (4%), mp 177–179 °C; IR (Nujol): (CO) 1745, 1715 cm^{-1}; ^{1}H NMR (250 MHz, dimethyl sulfoxide-d_6): δ=5.94 (2H, s, $-OCH_2O-$), 6.24 (1H, d, J=1.5 Hz, phenyl proton), 6.69 (1H, dd, J=1.8, 8.3 Hz, phenyl proton), 6.79 (1H, d, J=8.0 Hz, phenyl proton), 7.09 (1H, dd, J=1.8, 7.0 Hz, phenyl proton), 7.45–7.57 (2H, m, phenyl protons), 7.56 (1H, s, H-olefinic), 8.01 (1H, dd, J=2.0, 7.0 Hz, phenyl proton), 12.57 (2H, s, COOH).

4.2.5. 3-Thiophen-2-yl-1-oxo-isochroman-4-carboxylic acid (3e). *trans-Diastereomer*. This compound was obtained as colorless prisms (from ethyl acetate). Yield: 0.75 g (75%), mp 122–124 °C; IR (Nujol): (CO) 1740, 1685 cm^{-1}; ^{1}H NMR (250 MHz, dimethyl sulfoxide-d_6) δ=4.28 (1H, d, J=5.7 Hz, *H*-4), 6.23 (1H, d, J=5.7 Hz, *H*-3), 6.92 (1H, dd, J=3.6, 5.0 Hz, thienyl proton), 7.03–7.09 (1H, m, thienyl proton), 7.25 (1H, dd, J=3.6, 5.0 Hz, thienyl proton), 7.40–7.45 (1H, m, phenyl proton), 7.48–7.52 (1H, m, phenyl proton), 7.63 (1H, dt, J=1.6,

7.7 Hz, phenyl proton), 8.12 (1H, dd, *J*=1.5, 7.8 Hz, H-8). Anal. Calcd for $C_{14}H_{10}O_4S$: C, 61.30%; H, 3.67%; Found: C, 61.50%; H, 3.51%.

4.2.6. 3-Furan-2-yl-1-oxo-isochroman-4-carboxylic acid (3f). *trans-Diastereomer*. This compound was obtained as white crystals (from ethyl acetate). Yield: 0.54 g (54%), mp 152–154 °C; IR (Nujol): (CO) 1730, 1710 cm^{-1}; ^1H NMR (250 MHz, dimethyl sulfoxide-d_6): δ=4.59 (1H, d, *J*=4.8 Hz, *H*-4), 6.07 (1H, d, *J*=4.8 Hz, *H*-3), 6.31 (1H, d, *J*=3.3 Hz, furyl proton), 6.40 (1H, dd, *J*=2.0, 3.5 Hz, furyl proton), 7.49–7.55 (2H, m, phenyl protons), 7.64 (1H, dd, *J*=0.8, 2.0 Hz, furyl proton), 7.72 (1H, dt, *J*=1.5, 7.8 Hz, phenyl proton), 7.95 (1H, d, *J*=7.8 Hz, phenyl proton), 13.40 (1H, s, COOH). Anal. Calcd for $C_{14}H_{10}O_5$: C, 65.12%; H, 3.90%; Found: C, 64.97%; H, 3.88%.

4.2.7. 3-(9-Methyl-9*H*-carbazol-3-yl)-1-oxo-isochroman-4-carboxylic acid (3g). *trans-Diastereomer*. This compound was precipitated in water, purified by recrystallization and isolated as white crystals (from DMF). Yield: 0.78 g (78%), mp 206–208 °C; IR (Nujol): (CO) 1740, 1715 cm^{-1}; ^1H NMR (250 MHz, dimethyl sulfoxide-d_6): δ=3.87 (3H, s, $-NCH_3$), 4.79 (1H, d, *J*=8.0 Hz, *H*-4), 6.07 (1H, d, *J*=8.0 Hz, *H*-3), 7.22 (1H, t, *J*=7 Hz, phenyl proton), 7.39–7.62 (6H, m, phenyl protons), 7.71 (1H, dt, *J*=1.5, 7.8 Hz, phenyl proton), 8.03 (1H, dd, *J*=1.0, 7.5 Hz, phenyl proton), 8.13 (1H, d, *J*=7.8 Hz, phenyl proton), 8.26 (1H, s, phenyl proton), 13.26 (1H, s, COOH). Anal. Calcd for $C_{23}H_{17}NO_4$: C, 74.38%; H, 4.61%; Found: C, 73.99%; H, 4.52%.

4.3. Reaction between homophthalic anhydride and thiophene-2-carbaldehide (2e) performed on larger scales and subsequent transformations

4.3.1. Reaction in DMAP–chloroform. 1-Oxo-3-thiophen-2-yl-isochroman-4-carboxylic acid (**3e**). To a stirring mixture of 3.00 g (18.52 mmol) homophthalic anhydride and 1.7 ml (18.25 mmol) 2-thiophene carbaldehyde in dry chloroform (20 ml) was added DMAP 3.34 g (27.37 mmol). After stirring for 1.5 h. at room temperature, TLC analysis showed the absence of homophthalic anhydride. The reaction mixture was then extracted with 10% sodium hydrogen carbonate three times. The hydrogen carbonate layers were washed once with ethyl acetate, acidified with 10% hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and dried (sodium sulfate). The solvent was removed under reduced pressure. Crystallization of the residue gave:

trans-Diastereomer. This compound was obtained as colorless prisms (from hexane–ethyl acetate). Yield: 3.74 g (74%), mp 122–124 °C (see Section 4.2.5).

cis-Diastereomer. This compound was obtained as colorless needless (from ethyl acetate) after isolation of the *trans*-diastereomer. Yield: 0.35 g (7%), mp 160–162 °C; IR (Nujol): (CO) 1740, 1690 cm^{-1}; ^1H NMR (300 MHz, dimethyl sulfoxide-d_6): δ=4.37 (1H, d, *J*=3.5 Hz, *H*-4), 6.23 (1H, d, *J*=3.5 Hz, *H*-3), 7.09 (1H, dd, *J*=3.5, 5.0 Hz, thienyl proton), 7.24 (1H, d, *J*=3.5 Hz, thienyl proton), 7.52–7.60 (3H, m, thienyl and phenyl protons), 7.72 (1H, dt, *J*=1.5, 7.5 Hz, phenyl proton), 8.03 (1H, dd, *J*=1.5, 7.7 Hz, phenyl proton), 12.95 (1H, s, COOH). Anal. Calcd for $C_{14}H_{10}O_4S$: C, 61.30%; H, 3.67%; Found: C, 61.28%; H, 3.67%.

4.3.2. Reaction in pyridine. 4-Thiophen-2-yl-methylene-isochroman-1,3-dione (**5**), *trans*-1-oxo-3-thiophen-2-yl-isochroman-4-carboxylic acid methyl ester (**6**), 2-(1-methoxycarbonyl-2-thiophen-2-yl-vinyl)-benzoic acid methyl ester (**7**) and *trans*-6-oxo-11-thiophen-2-yl-11,12-dihydro-6*H*-dibenzo [*c*,*h*]chromene-12-carboxylic acid methyl ester (**8**)

To a mixture of 5.91 g (36.5 mmol) homophthalic anhydride and 5 ml (57.74 mmol) 2-thiophene carbaldehyde, 35 ml pyridine was added. After stirring for 5 h. at room temperature, the reaction mixture was filtered to give orange crystals of **5** (2.67 g) in 27% yield. The filtrate was diluted with water and extracted with chloroform. The chloroform layer was washed with diluted hydrochloric acid once and extracted with 10% sodium hydrogen carbonate. The hydrogen carbonate extract was washed once with ethyl acetate, acidified (pH=3) with 10% hydrochloric acid and extracted three times with ethyl acetate (100 ml). The organic layers were washed with water, dried (sodium sulfate) and the solvent was removed under reduced pressure to give 6.74 g an oil. The residue, containing acidic compounds was diluted with chloroform and treated with diazomethane. The mixture was stirred at room temperature for 2 h. The excess diazomethane and chloroform was removed under reduced pressure giving an oil (6.80 g). The residue was purified by column chromatography on silica gel to give the esterified products *trans*-**6** (2.34 g, 34%), *trans*-**8** (1.00 g, 15%) along with 1.70 g (25%) of **7**.

Compound **5** was obtained as orange needles (from pyridine). Yield: 2.67 g (27%). After recrystallization from DMF: mp 232 °C, (lit.[11] mp 232 °C); IR: (CO–O–CO) 1755, 1715 cm^{-1}; ^1H NMR (250 MHz, TFA): δ=7.25 (1H, t, *J*=4 Hz, thienyl proton), 7.53 (1H, t, *J*=7.5 Hz, phenyl proton), 7.80–7.96 (4H, m, thienyl and phenyl protons), 8.27 (1H, d, *J*=8 Hz, phenyl proton), 8.60 (1H, s, H-olefinic). Anal. Calcd for $C_{14}H_8O_3S$: C, 65.61%; H, 3.15%; Found: C, 65.59%; H, 3.15%.

Compound **6** was obtained as colorless prisms after column chromatography (from hexane–ethyl acetate). Yield: 2.34 g (34%), mp 126–128 °C; IR: (CO) 1750, 1730 cm^{-1}; ^1H NMR (300 MHz, deuteriochloroform): δ=3.75 (3H, s, OCH_3), 4.34 (1H, d, *J*=6.3 Hz, *H*-4), 6.18 (1H, d, *J*=6.3 Hz, *H*-3), 6.23 (1H, dd, *J*=3.6, 5.0 Hz, thienyl proton), 7.04–7.07 (1H, m, thienyl proton), 7.26 (1H, dd, *J*=1.5, 5.1 Hz, thienyl proton), 7.29 (1H, dm, *J*=7.6 Hz, phenyl proton), 7.49 (1H, t, *J*=7.6 Hz, phenyl proton), 7.63 (1H, dt, *J*=1.5, 7.6 Hz, phenyl proton), 8.15 (1H, dd, *J*=1.5, 7.8 Hz, phenyl proton); ^{13}C NMR (75 MHz): δ=169.71, 163.28, 139.62, 135.45, 134.40, 130.65, 129.07, 127.67, 127.20, 126.79, 126.66, 124.74, 76.32, 52.93, 50.41; MS *m*/*z*: 288 (molecular ion), 229 $(M-COOCH_3)^+$. Anal. Calcd for $C_{15}H_{12}O_4S$: C, 62.49%; H, 4.20%; Found: C, 62.18%; H, 3.80%.

Compound **7** was obtained as colorless prisms after column

chromatography (from hexane–ethyl acetate). Yield: 1.70 g (25%), mp 90–92 °C, (lit.[11] mp 90 °C); IR: (CO) 1730, 1710 cm^{-1}; ^1H NMR (300 MHz, deuteriochloroform): δ=3.75 (3H, s, -OCH_3), 3.78 (3H, s, -OCH_3), 6.88 (1H, dd, *J*=3.6, 8.8 Hz, thienyl proton), 7.06–7.08 (1H, m, thienyl proton), 7.15–7.19 (1H, m, phenyl proton), 7.30 (1H, dd, *J*=1.4, 8.8 Hz, thienyl proton), 7.51–7.62 (2H, m, phenyl protons), 7.98 (1H, s, H-olefinic), 8.16 (1H, dd, *J*=1.5, 7.7 Hz, phenyl proton); ^{13}C NMR (75 MHz): δ=167.59, 166.55, 138.61, 137.05, 133.16, 132.87, 131.98, 131.33, 131.31, 130.38, 130.06, 129.95, 128.81, 126.76, 52.21, 52.03; MS *m*/*z*: 302 (molecular ion), 243 $(M-COOCH_3)^+$. Anal. Calcd for $C_{16}H_{14}O_4S$: C, 63.56%; H, 4.67%; Found: C, 63.27%; H, 4.93%.

Compound **8** was obtained as colorless prisms after column chromatography (from hexane–ethyl acetate). Yield: 1.00 g (15%), mp 220–222 °C; IR: (CO) 1740, 1730 cm^{-1}; ^1H NMR (300 MHz, deuteriochloroform) δ=3.61 (3H, s, OCH_3), 4.12 (1H, d, *J*=1.3 Hz, *H*-4), 5.33 (1H, d, *J*=1.3 Hz, *H*-3), 6.73–6.79 (2H, m, thienyl protons), 7.01 (1H, dd, *J*=1.5, 4.8 Hz, thienyl proton), 7.29 (1H, dd, *J*=1.7, 7.4 Hz, thienyl proton), 7.35 (1H, dt, *J*=1.3, 7.4 Hz, phenyl proton), 7.41–7.51 (2H, m, phenyl protons), 7.65–7.75 (2H, m, phenyl protons), 7.99 (1H, dd, *J*=1.3, 7.6 Hz, phenyl proton), 8.36 (1H, dm, *J*=7.6 Hz, phenyl proton); ^{13}C NMR (75 MHz): δ=171.59, 161.64, 147.78, 143.32, 136.33, 135.10, 130.97, 130.74, 130.36, 129.93, 128.73, 128.09, 127.83, 126.85, 125.19, 124.47, 123.31, 122.57, 121.37, 111.31, 52.80, 52.18, 35.86; MS *m*/*z*: 388 (molecular ion), 329 $(M-COOCH_3)^+$. Anal. Calcd for $C_{23}H_{16}O_4S$: C, 71.12%; H, 4.15%; Found: C, 71.02%; H, 4.07%.

4.4. Methyl ester 6 of acid *trans*-3e

The reaction was attempted in three modes.

(1) To a stirring solution of *trans*-**3e** (0.71 g, 2.59 mmol) in 3.5 ml methanol, H_2SO_4 (0.2 ml, 3.8 mmol) was added dropwise. The reaction mixture was refluxed for 3 h. and left over night. The colorless crystals were filtered and washed with water/methanol yielding 0.55 g (74%) of **7**, mp 90–92 °C.

(2) To a mixture of potassium carbonate (0.24 g, 1.74 mmol) and acid *trans*-**3e** (0.48 g, 1.74 mmol) in DMF (3 ml), iodomethane (0.2 ml, 3.47 mmol) was added dropwise. The reaction mixture was stirred for 3 h. added to water and extracted with ethyl acetate. The organic layer was washed with water, dried (sodium sulfate) and evaporated giving an oil. The later afforded **7** as colorless crystals (from ethyl acetate) in yield 76% (0.38 g), mp 90–92 °C.

(3) A stirring solution of trans-**3e** (1.00 g, 3.65 mmol) in 5 ml chloroform was treated with diazomethane. The mixture was stirred at room temperature for 2 h. The excess diazomethane and chloroform was removed under reduced pressure giving an oil. The later afforded *trans*-**6** as colorless crystals (from ethyl acetate) in yield 85% (0.85 g), mp 126–128 °C.

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Synthesis of $\Delta^{12,14}$-15-deoxy-PG-J_1 methyl ester and *epi*-Δ^{12}-15-deoxy-PG-J_1

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Abstract—The synthesis of racemic $\Delta^{12,14}$-15-deoxy-PG-J_1 is readily achieved in six steps employing as the key transformation a one-pot conjugate addition–Peterson olefination sequence using *exo*-2-trimethylsilyl-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one. Additionally a Noyori-type three-component coupling approach is employed for the synthesis of enantioenriched *epi*-Δ^{12}-15-deoxy-PG-J_1 from 4(*S*)-*tert*-butyldimethylsilyloxycyclopent-2-enone.

1. Introduction

The prostaglandin family of arachidonic acid-derived C-20 natural products, for example PG-D_2 **1**, control a myriad of complex, seemingly diverse biological functions.[1] More recently it has been demonstrated that the cyclopentenone prostanoids, for example PG-J_2 **2**, putative end products of the arachidonic acid-cyclooxygenase cascade, possess distinct and important activities.[2] Interestingly, these activities sometimes counter those of the earlier products of the cascade, suggesting the intriguing possibility of a regulatory-feedback system. For example PG-$F_{2\alpha}$ has been shown to cause the contraction of smooth muscle, whereas, PG-A_1 is a smooth muscle relaxant.[2b] Amongst the cyclopentenone prostanoids and related compounds those possessing the so-called cross-conjugated dienone structural motif **3**–**6** appear to demonstrate the most interesting and potent biological activities (Fig. 1).

Currently the complex mechanisms by which these compounds confer their biological activities are not entirely clear. However, it was recently reported that $\Delta^{12,14}$-15-deoxy-PG-J_2 **3** was a potent inhibitor of influenza A viral replication, a property linked to the induction of cytoprotective, heat shock protein synthesis.[3] Additionally, $\Delta^{12,14}$-15-deoxy-PG-J_2 **3** was found to be a high affinity ligand for the PPAR-γ nuclear receptor.[2,4] In a series of papers Noyori, Suzuki and co-workers have reported structure-activity optimisation studies of cross-conjugated cyclopentenone prostaglandin analogues, aimed at identifying a clinical candidate for the treatment of cancer. These efforts culminated in the development of **4**.[5] The possibility that

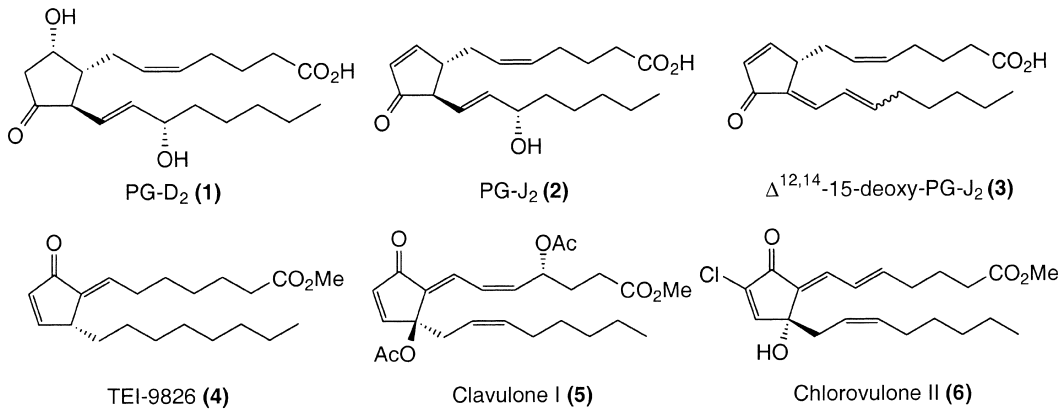

Figure 1.

Keywords: $\Delta^{12,14}$-15-Deoxy-PG-J_1 methyl ester; Conjugate addition–Peterson olefination; *epi*-Δ^{12}-15-Deoxy-PG-J_1; Cross-conjugated cyclopenteone.
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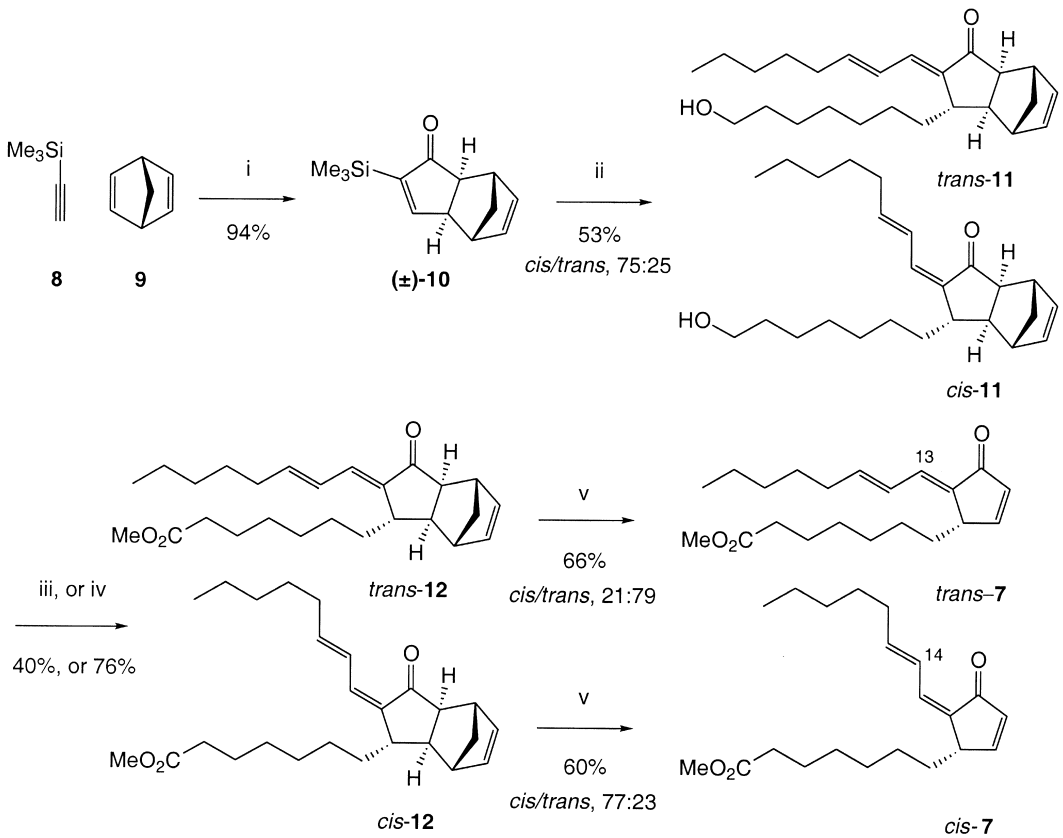
$\Delta^{12,14}$-15-deoxy-PG-J_2 **3** is formed from PG-D_2 **1** post extraction has been speculated upon, since **2** has been detected only rarely in vivo.[6] Apparently part of the reason for this may be the reactive nature of the prostanoid, undergoing conjugation rapidly with cellular nucleophilic species such as glutathione, and consequently removing these compounds from circulation as water soluble metabolites.[6,7]

2. Results and discussion

The PG-D_1 and PG-J_1 series of prostaglandins, lacking unsaturation in the α-side-chain, have yet to be discovered from a natural source, unlike PG-E_1 and A_1.[1,2] Although there has been one previous synthesis of optically active PG-J_1[8] to the best of our knowledge the preparation of $\Delta^{12,14}$-15-deoxy-PG-J_1 has not been reported.

The three-component coupling protocol developed by Noyori has emerged as the most efficient means for the synthesis of cyclopentenone prostanoids.[9] We have recently reported a variation of this method, namely the conjugate addition–Peterson olefination reaction, for the construction of cross-conjugated compounds and have employed this method for the preparation of (±)-TEI-9826 **4**.[10] Now we report that, using a similar protocol, the synthesis of both *cis*- and *trans*-$\Delta^{12,14}$-15-deoxy-PG-J_1 **7** has been achieved (see Scheme 1). The availability of both stereoisomers is potentially of interest, since recently it was reported that *cis*-$\Delta^{12,14}$-15-deoxy-PG-J_2 **3** was a more potent PPAR-γ ligand than its *trans*- counterpart.[11]

The masked cyclopentenone building block **10** was readily available following the Pauson–Khand cycloaddition between trimethysilylacetylene **8** and norbornadiene **9**. Optimum yields for this transformation were achieved under thermal microwave promoted conditions, with one equivalent of $Co_2(CO)_8$.[12] One-pot conjugate addition of the silyl protected Grignard reagent, under copper(I) catalysis, followed by addition of *trans*-oct-2-enal gave an isomeric mixture of the corresponding adducts (*cis*/*trans*, 75:25 by ^{1}H NMR spectroscopy). Separation of the crude reaction mixture proved problematic, consequently direct removal of the silicon protecting group under proteolysis was necessary. This gave a separable mixture of *cis*-**11** and *trans*-**11** in a combined yield of 53% for the three steps. However, during this deprotection some isomerisation of the dienone was observed (*cis*/*trans*, 60:40). Functional group interconversion of the hydroxyl group into the methyl ester moiety was achieved in two ways. Initially an unseparated mixture of alkene geometrical isomers (*cis*/*trans*, 60:40) was directly oxidised into the carboxylic acid using Jones reagent. The crude acid, following aqueous work-up, was then converted into the *cis*- and *trans*-methyl esters **12** on treatment with (trimethylsilyl)diazomethane in 40% combined yield. More efficient conversion was achieved using a three-step protocol in which *trans*-**11**



Scheme 1. Synthesis of *trans*-$\Delta^{12,14}$-15-deoxy-PG-J_1 and *cis*-$\Delta^{12,14}$-15-deoxy-PG-J_1. Reagents and conditions: (i) $Co_2(CO)_8$, DCE, μ-wave, 90 °C, 20 min; (ii) (a) $BrMg(CH_2)_7OTBS$, CuI (13 mol%), Et_2O, −78 to −20 °C, 1 h; (b) oct-2-enal, −20 °C to rt, 15 h; (c) AcOH/H_2O/THF (6:3:4), rt, 15 h; (iii) (a) CrO_3–H_2SO_4, acetone, 0 °C, 1 h; (b) $Me_3SiCH_2N_2$, PhH, MeOH, rt, 0.5 h; (iv) (a) Dess–Martin Periodinane, DCM, rt, 3 h; (b) $NaClO_2$, NaH_2PO_4, ^{t}BuOH, Me_2CCMe_2, rt, 15 h; (c) Me_3SiCHN_2, PhH, MeOH, rt, 1.5 h; (v) $MeAlCl_2$, maleic anhydride (10 equiv.), DCM, μ-wave, 100 °C, 200 s.

was oxidised, initially with the Dess–Martin periodinane, then sodium chlorite and finally the acid was converted without purification into the *trans*-methyl ester **12** in 76% overall yield. Isomer separation, by flash column chromatography, and subsequent Lewis acid mediated *retro*-Diels–Alder reaction,[13] in the presence of maleic anhydride (MA), afforded both geometrical isomeric cross-conjugated cyclopentenones. Optimum results for this thermal process were obtained following short bursts of microwave irradiation.[14] Interestingly, in contrast to the longer periods under standard conductive heating,[10] these short-intense reaction periods gave only limited double bond isomerisation. Thus, *cis*-**12** gave mainly *cis*-**7** in 60% yield (*cis*/*trans*, 77:23) and similarly *trans*-**12** gave *trans*-**7** in 66% yield (*cis*/*trans*, 21:79). These isomeric mixtures proved readily separable by flash column chromatography.

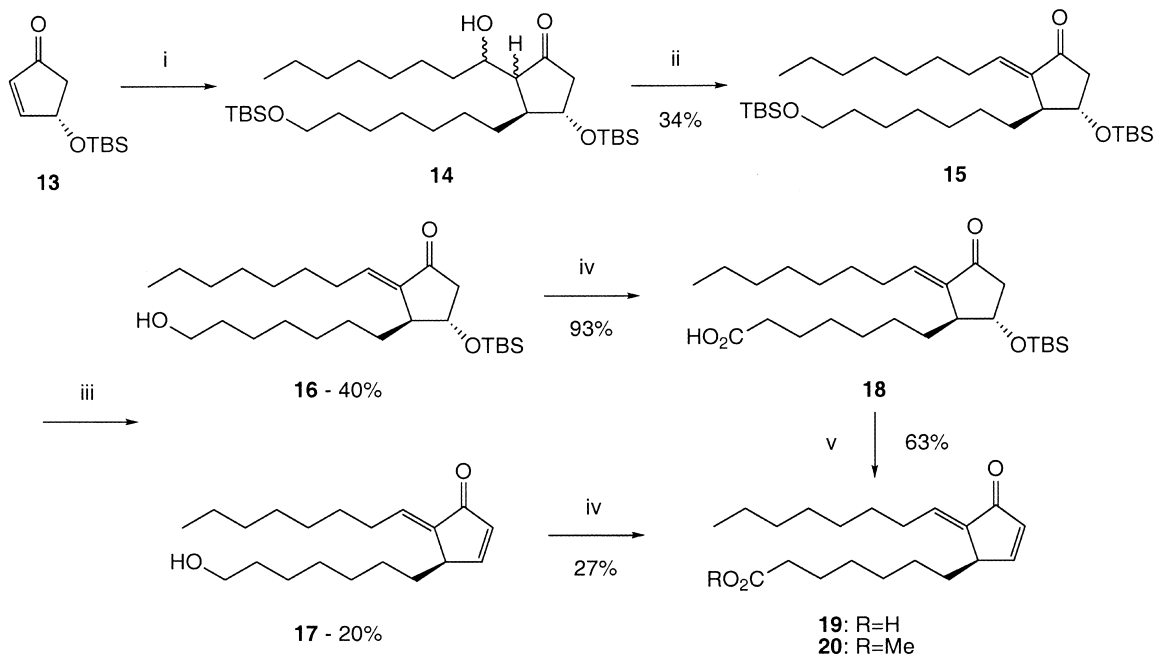
Generally proton NMR spectroscopy proved to be important as a diagnostic tool, enabling the conformation of the exocyclic-alkylidene double bond to be determined, since significant anisotropic effects are observed when either proton in the 13- or 14-position is *syn*-orientated to the carbonyl moiety. For example, *cis*-**7**: 6.37 ppm (13-H), 7.69 ppm (14-H); *trans*-**7**: 6.93 ppm (13-H), 6.17–6.32 ppm (14-H).[15]

In view of the current interest in Δ^{12}-15-deoxy-PG-J's,[2,11] we adopted a second strategy, based on the traditional three-component coupling methodology of Noyori[9] (as used in the synthesis of Δ^{7}-PGA-type systems), for the production of some other novel cross-conjugated compounds. Although this sequence is a less efficient method for accessing the cross-conjugated cyclopentenone system than the conjugate addition–Peterson olefination sequence described, it enables homochiral material to be prepared more efficiently. Studies indicate that compounds possessing the natural PG stereochemistry at the single stereocentre are recognised by metabolic enzymes more readily than the corresponding epimeric compounds. For example, Noyori has shown that *epi*-PG-A analogues of this type exhibit considerably longer half-lives in rat serum than their naturally configured counterparts.[6a] Hence we targeted the preparation of an 8-*epi*-PG-J_1 analogue in order to explore the synthetic strategy.

Thus, 4(*S*)-*tert*-butyldimethylsilyloxycyclopent-2-enone **13**[16] reacted with the Grignard reagent derived from 1-*tert*-butyldimethylsilyloxy-7-bromoheptane in ether containing copper(I) iodide at −78 °C for 30 min. Octanal was then added and the reaction was stirred at low temperature (−78 °C) overnight. Work-up furnished the crude alcohol **14** as a mixture of diastereoisomers, which was immediately converted into the corresponding mesylate and treated with *N*,*N*-dimethylaminopyridine to afford the unsaturated ketone **15** in 34% yield over the two steps (Scheme 2).

Deprotection of the bis-silylated compound **15** was effected using aqueous acetic acid to give a readily separated mixture of the alcohol **16** (40%) and the dienone **17** (20%). The former compound was readily converted into acid **18** (93% yield) which on treatment initially with (trimethylsilyl)-diazomethane, then aqueous base gave 8(*R*)-Δ^{12}-15-deoxy-PG-J_1 methyl ester **20** (63% yield). The more sensitive dienone **17** gave the carboxylic acid **19** in a lower-yielding two-step procedure.

In conclusion, we have developed an efficient method for the synthesis of both geometrical stereoisomers of racemic $\Delta^{12,14}$-15-deoxy-PG-J_1. Significantly the conjugate addition reaction proceeds with very high diastereoselectivity; consequently in order to generate enantioenriched, or homochiral material the corresponding enantioenriched, or



Scheme 2. Synthesis of *epi*-8(*R*)- Δ^{12}-15-deoxy-PG-J_1. Reagents and conditions: (i) (a) $BrMg(CH_2)_7OTBS$, CuI (10 mol%), Et_2O, −78 °C to −20 °C, 1 h; (b) octanal, −78 °C, 16 h; (ii) MsCl, DMAP, DCM, rt, 16 h; (iii) AcOH/H_2O/THF (3:1:1), rt, 4 days; (iv) (a) Dess–Martin Periodinane, DCM, rt, 3 h; (b) $NaClO_2$, NaH_2PO_4, ^{t}BuOH, Me_2CCMe_2, rt, 15 h; (v) (a) Me_3SiCHN_2, PhH, MeOH, rt, 1.5 h; (b) Na_2CO_3, MeOH, 0 °C to rt, 2 h.

homochiral Pauson–Khand adduct could be employed.[17] A related three-component coupling method enabled the enantioselective synthesis of *epi*-Δ^{12}-15-deoxy-PG-J_1.

3. Experimental

3.1. General

Starting materials were purchased from commercial sources and were used without further purification. Anhydrous Et_2O was distilled under nitrogen from the sodium-benzophenone ketyl radical, DCM was distilled from CaH_2. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded using a Bruker AMX400 spectrometer. Infrared spectroscopy was performed on a Perkin–Elmer Paragon 1000 FTIR spectrometer. Optical rotation measurements were recorded using a Optical Activity, Polaar 2001 polarimeter at 589 nm and are quoted in units of 10^{-1}deg cm^2g^{-1}. Flash column chromatography, under moderate pressure was performed using silica gel-ICN 32-63, 60 Å. Focused microwave irradiation used in this study was generated by a Coherent Synthesis-Smith Workstation package (Personal Chemistry AB, Sweden).

3.1.1. 1-*tert*-Butyldimethylsilyloxy-7-bromoheptane.[18] A solution of 7-bromoheptanol (3.48 g, 17.8 mmol, 1 equiv.) in DCM (50 cm^3) was cooled to 0 °C and treated with TBSCl (2.96 g, 19.6 mmol, 1.1 equiv.) and TEA (3.1 cm^3, 22.2 mmol, 1.25 equiv.). A catalytic amount of DMAP (ca.10 mg) was added and stirring was continued for 15 h during which period room temperature was reached. The solvent was removed in vacuo before Et_2O (50 cm^3) and H_2O (50 cm^3) were added. The resultant aqueous phase was further extracted with Et_2O (3×50 cm^3) and the combined organic extracts were dried over $MgSO_4$. Filtration followed by solvent removal under reduced pressure and purification by flash column chromatography (Hex–Et_2O; 19:1) gave 1-*tert*-butyldimethylsilyloxy-7-bromoheptane (4.30 g, 78%) as a colourless liquid. R_f=0.6 (Hex–Et_2O; 19:1); *m/z* (CI) 311 (MH^+, 100%, ^{81}Br), 309 (MH^+, 100%, ^{79}Br); δ_H (400 MHz, $CDCl_3$) 0.04 (6H, s, CH_3), 0.90 (9H, s, CH_3), 1.28–1.37 (4H, m, CH_2), 1.39–1.45 (2H, m, CH_2), 1.46–1.55 (2H, m, CH_2), 1.85 (2H, pent, J=7.5 Hz, CH_2), 3.41 (2H, t, J=7.0 Hz, CH_2), 3.62 (2H, t, J=6.5 Hz, CH_2); δ_C (100 MHz, $CDCl_3$) −5.3, 18.4, 25.6, 26.0, 28.2, 28.6, 32.8, 34.0, 63.1.

3.1.2. *exo*-2-Trimethylsilyl-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one 10.[12] At room temperature $Co_2(CO)_8$ (352 mg, 1.03 mmol, 1 equiv.) was added to a solution of trimethylsilylacetylene **8** (0.15 cm^3, 1.06 mmol, 1 equiv.) in DCE (4 cm^3). Stirring was continued for 1 h. Norbornadiene **9** (0.55 cm^3, 5.0 mmol, 5 equiv.) was added and the mixture was heated in the microwave (Smith Creator, 300 W) at 90 °C for 20 min. Silica (ca. 2 g) was added to the crude reaction mixture and the solvent was removed under reduced pressure. Purification by flash column chromatography (Hex→Hex–EtOAc; 9:1) afforded the title compound **10** (218 mg, 94%) as a colourless solid, mp 94–95 °C (Hex). R_f *exo*-**10**=0.25 [*endo*-**10**=0.2] (Hex–EtOAc; 9:1); ν_{max} ($CDCl_3$/cm^{-1}) 3062, 2972, 1689, 1570, 1247; *m/z* (CI) 219 (MH^+, 100%); found 219.12086, $C_{13}H_{18}OSi{\cdot}H$ requires 219.12053 (+1.5 ppm); δ_H (400 MHz, $CDCl_3$) −0.17 (9H, s, CH_3), 1.05 (1H, d, J=11.25 Hz, CH_2), 1.22 (1H, d, J=11.25 Hz, CH_2), 2.01 (1H, d, J=6.25 Hz, CH), 2.52 (1H, s, CH), 2.72–2.74 (1H, m, CH), 2.80 (1H, s, CH), 6.21–6.30 (2H, m, 2×CH), 7.65 (1H, d, J=2.5 Hz, CH); δ_C (100 MHz, $CDCl_3$) −2.1, 41.1, 42.8, 43.7, 51.9, 53.2, 137.2, 138.1, 152.0, 172.7, 213.0; Found C, 71.50; H, 8.31%, $C_{13}H_{18}OSi$ requires C, 71.60; H, 8.30%.

3.1.3. (±)-3-(7-Hydroxylheptyl)-2-[*trans*-oct-2-en-*cis*/*trans*-ylidene]-2,3,3a,4,7,7a-hexahydro-4,7-methanoinden-1-one 11. Under N_2, at room temperature 1-*tert*-butyldimethylsilyloxy-8-bromoheptane (580 mg, 1.88 mmol, 1.3 equiv.) was added dropwise over 0.25 h to a rapidly stirred mixture of magnesium (200 mg, 8.23 mmol, 5.9 equiv.) and a catalytic amount of iodine (ca. 5 mg) in THF (10 cm^3). The resultant Grignard reagent was stirred at room temperature for 2 h before TLC analysis (Hex–Et_2O; 19:1) indicated consumption of starting material. This reagent was added via cannula to a slurry of CuI (36 mg, 0.19 mmol, 0.13 equiv.) in Et_2O (10 cm^3) at −50 °C [washed with Et_2O (5 cm^3)]. The mixture was stirred for 0.25 h before cooling to −78 °C and addition of enone **10** (307 mg, 1.41 mmol, 1 equiv.) in Et_2O (10 m^3) [washed with Et_2O (5 cm^3)]. Stirring was continued for 1 h during which period the temperature was raised to −20 °C. With stirring freshly distilled *trans*-oct-2-enal (0.4 cm^3, 2.81 mmol, 2 equiv.) was added and the reaction mixture was allowed to reach room temperature over a 15 h period. A saturated solution of NH_4Cl (50 cm^3) was added and the mixture was extracted with Et_2O (3×50 cm^3). The combined organic extracts were dried over $MgSO_4$. Filtration followed by solvent removal afforded the crude products of the conjugate addition–Peterson olefination process. This mixture was dissolved in THF (4 cm^3) and at room temperature a solution of acetic acid (12 cm^3) in H_2O (6 cm^3) was added dropwise. The mixture was stirred at room temperature for 15 h before EtOAc (50 cm^3) and a saturated solution of $NaHCO_3$ (100 cm^3) were added. The resultant aqueous layer was further extracted with EtOAc (3×50 cm^3) and the combined organic extracts were dried over $MgSO_4$. Filtration followed by addition of silica (ca. 15 g), solvent removal in vacuo and purification by flash column chromatography (Hex–EtOAc; 9:1→3:1) afforded initially *cis*-**11** (130 mg, 25%) as a viscous yellow oil. R_f=0.15 (Hex–EtOAc; 3:1); ν_{max} (neat/cm^{-1}) 3404, 3059, 2928, 2855, 1731, 1708, 1623, 1590, 1459; *m/z* (ES) 409 (MK^+, 100%), 393 (MNa^+, 50%); found 393.2774, $C_{25}H_{38}O_2{\cdot}Na$ requires 393.2770 (+1.1 ppm); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, J=7.0 Hz, CH_3), 1.25–1.48 (17H, m, CH_2), 1.48–1.60 (3H, m, CH_2), 1.84 (1H, d, J=8.0 Hz, CH), 2.18 (2H, q, J=7.25 Hz, CH_2), 2.32 (1H, d, J=8.0 Hz, CH), 2.33–2.40 (1H, m, CH), 2.70 (1H, s, CH), 3.06 (1H, s, CH), 3.63 (2H, t, J=7.0 Hz, CH_2), 6.02 (1H, dt, J=7.25, 15.25 Hz, CH), 6.16–6.22 (2H, m, CH), 6.24 (1H, dd, J=1.0, 11.25 Hz, CH), 7.53 (1H, ddt, J=1.25, 11.25, 15.25 Hz, CH); δ_C (100 MHz, $CDCl_3$) 14.0, 22.5, 25.8, 26.4, 28.7, 29.4, 29.8, 31.5, 32.8, 33.0, 38.7, 43.4, 45.8, 46.1, 47.9, 49.4, 55.8, 63.0, 127.0, 137.6, 137.8, 138.6, 140.6, 145.4, 208.8. Further elution gave *trans*-**11** (148 mg, 28%) as a pale yellow oil. R_f=0.1 (Hex–EtOAc; 3:1); *m/z* (ES) 393 (MNa^+, 100%); found 393.2787, $C_{25}H_{38}O_2{\cdot}Na$ requires 393.2770 (+4.4 ppm); ν_{max} (neat/cm^{-1}) 3429, 3059, 2927, 2855, 1700, 1624, 1623, 1598, 1460; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t,

J=7.0 Hz, CH_3), 1.24–1.50 (17H, m, CH_2), 1.54–1.60 (3H, m, CH_2), 1.91 (1H, d, J=7.5 Hz, CH), 2.19 (2H, q, J=7.0 Hz, CH_2), 2.39 (1H, d, J=7.5 Hz, CH), 2.65–2.69 (1H, m, CH), 2.73 (1H, s, CH), 3.02 (1H, s, CH), 3.64 (2H, t, J=6.5 Hz, CH_2), 6.16–6.24 (4H, m, CH), 6.84–6.88 (1H, m, CH); δ_C (100 MHz, $CDCl_3$) 14.0, 22.5, 25.7, 26.5, 28.4, 29.4, 29.8, 31.4, 32.8, 33.5, 37.5, 43.2, 43.3, 46.4, 48.1, 49.6, 54.6, 63.0, 126.3, 133.4, 137.6, 138.8, 142.6, 146.9, 208.8.

3.1.4. (±)-7-{2-[*trans*-Oct-2-en-*cis*/*trans*-ylidene]-3-oxo-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoinden-1-yl}heptanoic acid methyl ester 12. At 0 °C a mixture of *cis*-**11** and *trans*-**11** (1.636 g, 4.42 mmol, 1 equiv.) [*cis*/*trans*; 60:40] in acetone (30 cm^3) was treated with a 1.28 mol dm^{-3} solution of chromic acid (7.3 cm^3, 9.34 mmol, 2.1 equiv.) in a dropwise fashion. Stirring was continued for 1 h at room temperature. Et_2O (50 cm^3) and H_2O (50 cm^3) were added and the resultant aqueous phase was further extracted with Et_2O (3×50 cm^3). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. At room temperature the crude mixture of the isomeric carboxylic acids was dissolved in benzene (20 cm^3) and methanol (5 cm^3). A 2.0 mol dm^{-3} solution of (trimethylsilyl)diazomethane in hexane (3.0 cm^3, 5.94 mmol, 1.3 equiv.) was added and stirring was continued for 0.5 h. Silica (ca. 10 g) was added and the solvents were removed in vacuo. The crude mixture was then purified by flash column chromatography (Hex–EtOAc; 19:1→9:1) affording *cis*-**12** (425 mg, 24%) as a yellow oil. R_f=0.35 (Hex–EtOAc; 9:1); ν_{max} (neat/cm^{-1}) 2930, 2857, 1731, 1685, 1622, 1588, 1460; *m*/*z* (ES) 421 (MNa^+, 100%); found 421.2721, $C_{26}H_{38}O_3$·Na requires 421.2791 (+0.6 ppm); δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, J=7.0 Hz, CH_3), 1.25–1.36 (11H, m, CH_2), 1.37–1.46 (4H, m, CH_2), 1.47–1.57 (1H, m, CH_2), 1.58–1.77 (2H, m, CH_2), 1.83 (1H, d, J=8.0 Hz, CH), 2.18 (2H, q, J=7.25 Hz, CH_2), 2.31 (2H, t, J=7.5 Hz, CH_2), 2.33 (1H, d, J=8.0 Hz, CH), 2.33–2.38 (1H, m, CH), 2.70 (1H, s, CH), 3.07 (1H, s, CH), 3.66 (3H, s, CH_3), 6.02 (1H, dt, J=7.25, 15.0 Hz, CH), 6.15–6.21 (2H, m, CH), 6.24 (1H, dd, J=1.0, 11.25 Hz, CH), 7.52 (1H, ddt, J=1.25, 11.25, 15.0 Hz, CH); δ_C (100 MHz, $CDCl_3$) 14.0, 22.5, 24.9, 26.3, 28.6, 29.1, 29.4, 31.5, 33.0, 34.0, 38.6, 43.3, 45.8, 46.1, 47.9, 49.4, 51.4, 55.8, 126.9, 137.6, 137.8, 138.5, 140.5, 145.4, 174.1, 208.8. Further elution afforded *trans*-**12** (283 mg, 16%) as a pale yellow oil. R_f=0.25 (Hex–EtOAc; 9:1); ν_{max} (neat/cm^{-1}) 2931, 2857, 1730, 1691, 1624, 1598, 1460, 1437; *m*/*z* (ES) 437 (MK^+, 100%), 421 (MNa^+, 10%); found 421.2709, $C_{26}H_{38}O_3$·Na requires 421.2719 (−2.3 ppm); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, J=7.0 Hz, CH_3), 1.23–1.38 (11H, m, CH_2), 1.40–1.48 (2H, m, CH_2), 1.53–1.66 (3H, m, CH_2), 1.91 (1H, d, J=7.5 Hz, CH), 2.21 (2H, q, J=7.0 Hz, CH_2), 2.29 (2H, t, J=7.5 Hz, CH_2), 2.37 (1H, d, J=7.5 Hz, CH), 2.64–2.68 (1H, m, CH), 2.74 (1H, s, CH), 3.05 (1H, s, CH), 3.68 (3H, s, CH_3), 6.17–6.24 (4H, m, CH), 6.84–6.88 (1H, m, CH); δ_C (100 MHz, $CDCl_3$) 14.0, 22.4, 24.9, 26.3, 28.4, 29.1, 29.4, 31.4, 33.5, 34.0, 37.5, 43.2, 43.3, 46.3, 48.1, 49.6, 51.4, 54.6, 126.3, 133.4, 137.5, 138.7, 142.5, 146.9, 174.1, 208.8.

3.1.5. (±)-7-{2-[*trans*-Oct-2-en-*trans*-ylidene]-3-oxo-2,3,3a,4,7,7a-hexahydro-1H-4,7-methano inden-1-yl} heptanoic acid methyl ester 12. At room temperature, alcohol **11** (100 mg, 0.27 mmol, 1 equiv.) in DCM (6 cm^3) was treated with Dess–Martin's periodinane (149 mg, 0.35 mmol, 1.3 equiv.) and stirring was continued for 3 h. Et_2O (20 cm^3), saturated $NaHCO_3$ (10 cm^3) and Na_2SO_3 (10 cm^3) were added and the resultant aqueous layer was further extracted with Et_2O (4×10 cm^3). The combined extracts were dried over $MgSO_4$ and filtration, solvent removal under reduced pressure gave the aldehyde [R_f=0.45 (Hex–EtOAc; 3:1)]. At room temperature the crude aldehyde (ca. 0.27 mmol, 1 equiv.) was dissolved in a mixture of ^{t}BuOH (6 cm^3) and 2,3-dimethylbut-2-ene (4.0 cm^3) and a solution of $NaClO_2$ (450 mg, 4.98 mmol, 18 equiv.) and NaH_2PO_4 (450 mg, 3.75 mmol, 14 equiv.) in H_2O (5 cm^3) was added dropwise. Stirring was continued for 1.5 h before the volatile materials were removed under reduced pressure and the residue was dissolved in Et_2O (5 cm^3) and H_2O (5 cm^3). This mixture was acidified with 1.0 M HCl solution (ca. p*H* 3) and the resultant aqueous layer was further extracted with Et_2O (5×10 cm^3). The combined extracts were dried over $MgSO_4$. Filtration and solvent removal in vacuo gave the crude acid (ca.0.27 mmol, 1 equiv.), which was dissolved in PhH (18 cm^3) and MeOH (5 cm^3). A 2.0 M solution of (trimethylsilyl)diazomethane in hexane (0.14 cm^3, 0.28 mmol, 1.05 equiv.) was added. After stirring at room temperature for 1.5 h the solvent was removed under reduced pressure and the residue was purified by flash column chromatography (Hex–EtOAc; 19:1→9:1). Thus, *trans*-**12** (82 mg, 76%) was isolated as a pale yellow oil, whose data corresponded with that described above.

3.1.6. 7-{5-[(*trans*)-Oct-2-en-(*cis*)-ylidene]-4-oxocyclopen-2-enyl}heptanoic acid methyl ester [*cis*-$\Delta^{12,14}$-15-deoxy-PG-J_1] 7. Under N_2 a solution of *cis*-**12** (277 mg, 0.696 mmol, 1 equiv.) and maleic anhydride (682 mg, 6.96 mmol, 10 equiv.) in DCM (8 cm^3) was treated with a 1.0 M solution of $MeAlCl_2$ in hexane (0.7 cm^3, 0.7 mmol, 1 equiv.). The solution was then split into two dry microwavable vials under a nitrogen atmosphere. Each vial was irradiated (Smith Creator, 300 W) at 110 °C for two bursts of 100 s. The reaction mixture was then poured into a rapidly stirred saturated solution of $NaHCO_3$ (25 cm^3) and Et_2O (25 cm^3). This mixture was partitioned for 1 h before extraction and subsequent re-extraction of the aqueous phase with Et_2O (5×25 cm^3). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed in vacuo. Purification by flash column chromatography (Hex–EtOAc; 9:1→3:1) gave *cis*-**7** (107 mg, 46%) as a viscous pale yellow oil. Further elution afforded *trans*-**7** (32 mg, 14%). R_f=0.3 (Hex–EtOAc; 4:1); ν_{max} (neat/cm^{-1}) 3054, 2930, 2858, 1732, 1682, 1630, 1608, 1582, 1436, 1370; *m*/*z* (ES) 355 (MNa^+, 100%); found 355.2252, $C_{21}H_{32}O_3$·Na requires 355.2249 (+0.8 ppm); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, J=7.0 Hz, CH_3), 1.26–1.37 (10H, m, CH_2), 1.42–1.53 (3H, m, CH_2), 1.57–1.66 (2H, m, CH_2), 1.68–1.77 (1H, m, CH_2), 2.22 (2H, dq, J=1.25, 7.0 Hz, CH_2), 2.30 (2H, t, J=7.5 Hz, CH_2), 3.28–3.35 (1H, m, CH), 3.67 (3H, s, CH_3), 6.06 (1H, dt, J=7.0, 15.25 Hz, CH), 6.28 (1H, dd, J=2.0, 6.0 Hz, CH), 6.37 (1H, d, J=11.0 Hz, CH), 7.43 (1H, dd, J=2.5, 6.0 Hz, CH), 7.69 (1H, ddt, J=1.25, 11.0, 15.25, CH); δ_C (100 MHz, $CDCl_3$) 14.0, 22.5, 24.8, 26.1, 28.7, 28.9, 29.4, 31.5, 33.0, 33.3, 34.0, 45.6, 51.4, 126.3, 134.2, 135.8, 136.5, 145.6, 159.7, 174.1, 197.5.

3.1.7. 7-{5-[(*trans*)-Oct-2-en-(*trans*)-ylidene]-4-oxocyclopen-2-enyl}heptanoic acid methyl ester [*trans*-$\Delta^{12,14}$-15-deoxy-PG-J_1] 7. Following the procedure outlined above: under N_2, a solution of *trans*-**12** (252 mg, 0.633 mmol, 1 equiv.) in DCM (8 cm^3) was initially treated with a 1.0 M solution of $MeAlCl_2$ in hexane (0.65 cm^3, 0.65 mmol, 1 equiv.) then split into two dry microwavable vials. Each vial was irradiated (Smith Creator, 300 W) at 110 °C for two bursts of 100 s. The reaction mixture was then poured into a rapidly stirred saturated solution of $NaHCO_3$ (25 cm^3) and Et_2O (25 cm^3). This mixture was partitioned for 0.5 h before extraction and subsequent re-extraction of the aqueous phase with Et_2O (5×25 cm^3). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed in vacuo. Purification by flash column chromatography (Hex–EtOAc; 9:1→3:1) gave initially *cis*-**7** (30 mg, 14%), then *trans*-**7** (110 mg, 52%) as viscous yellow oils. R_f=0.2 (Hex–EtOAc; 4:1); ν_{max} (neat/cm^{-1}) 3054, 2931, 2858, 1734, 1690, 1631, 1579, 1437; *m/z* (CI) 333 (MH^+, 25%), 265 (100%); found 333.24347, $C_{21}H_{32}O_3$·H requires 333.24298 (+1.6 ppm); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J*=7.0 Hz, CH_3), 1.27–1.36 (10H, m, CH_2), 1.45 (2H, pent, *J*=7.0 Hz, CH_2), 1.53–1.65 (3H, m, CH_2), 1.81–1.92 (1H, m, CH_2), 2.22 (2H, q, *J*=7.0 Hz, CH_2), 2.29 (2H, t, *J*=7.5 Hz, CH_2), 3.51–3.57 (1H, m, CH), 3.65 (3H, s, CH_3), 6.17–6.32 (2H, m, CH), 6.35 (1H, dd, *J*=2.0, 6.0 Hz, CH), 6.93 (1H, d, *J*=11.0 Hz, CH), 7.52 (1H, ddd, *J*=1.0, 2.5, 6.0 Hz, CH); δ_C (100 MHz, $CDCl_3$) 14.0, 22.5, 24.8, 25.8, 28.5, 29.0, 29.4, 31.4, 32.9, 33.4, 34.0, 43.5, 51.4, 125.7, 131.3, 135.2, 135.6, 146.5, 160.9, 174.1, 197.5.

3.1.8. (3*S*,4*S*)-4-(*tert*-Butyldimethylsilyloxy)-3-[7-(*tert*-butyldimethylsilyloxy)heptyl]-2-[*trans*-octylidene]cyclopentanone 15. Under N_2, a stirred mixture of magnesium turnings (372 mg, 15.31 mmol, 2.2 equiv.) and a spatula tip of I_2 in Et_2O (15 cm^3) was treated dropwise with 1-*tert*-butyldimethylsilyloxy-7-bromoheptane (2.36 g, 7.62 mmol, 1.08 equiv.) at room temperature. The resultant mixture was stirred at room temperature for 3 h. The resultant Grignard reagent was transferred to a pre-cooled mixture of CuI (116 mg, 0.61 mmol, 0.1 equiv.) in Et_2O (8 cm^3) at −78 °C and this mixture was allowed to warm gradually to 0 °C over 1 h. The resultant mixture was then re-cooled to −78 °C, and a solution of **13**[16] (1.58 g, 7.06 mmol, 1 equiv.) in Et_2O (6 cm^3) was added dropwise. After stirring at −78 °C for 30 min, neat octanal (1.10 g, 8.47 mmol, 1.2 equiv.) was introduced and the mixture was stirred at −78 °C overnight. The reaction was quenched with addition of a 1:4 mixture of conc. ammonia to sat. ammonium chloride (20 cm^3) and stirred until the organic phase had clearly separated. The organic layer was separated and the aqueous layer was extracted using EtOAc (3×50 cm^3). The combined organic extracts were washed with sat. NaCl solution, dried over $MgSO_4$ and concentrated to affording the crude alcohol **14** (4.29 g), which was used in the next reaction directly. To a stirred mixture of the alcohol **14** (4.29 g, 7.06 mmol, 1 equiv.) and *N*,*N*-dimethylaminopyridine (4.31 g, 35.3 mmol, 5 equiv.) in dichloromethane (30 cm^3) was added slowly methanesulfonyl chloride (0.90 g, 7.77 mmol, 1.1 equiv.) at room temperature. The reaction mixture was stirred overnight before dilution with Et_2O (50 cm^3) and 2 M dilute HCl (20 cm^3). The organic layer was separated and the aqueous layer was extracted using ether (3×50 cm^3). The combined organic layers were washed with saturated NaCl solution, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography (Hex–Et_2O 19:1→9:1) to yield the ketone **15** (1.35 g, 34%) as a viscous oil. $[\alpha]_D$=−31.8 (*c*=4.4, $CHCl_3$); ν_{max} (neat/cm^{-1}) 2927, 2855, 1726, 1651, 1471, 1255, 1098, 1071; *m/z* (ES) 575 (MNa^+, 100%), 379 (50%), 291 (38%); found 575.4301, $C_{32}H_{64}O_3Si_2$·Na requires 575.4292 (+1.6 ppm); δ_H (400 MHz, $CDCl_3$) 0.06 (12H, s, CH_3), 0.84 (9H, s, CH_3), 0.89–0.92 (12H, m, CH_3), 1.60–1.26 (22H, m, CH_2), 2.12–2.16 (2H, m, CH_2), 2.20 (1H, d, *J*=18.0 Hz, 5-CH_2), 2.55 (1H, dd, *J*=5.0, 18.0 Hz, 5-CH_2), 2.78 (1H, m, 3-CH), 3.60 (2H, t, *J*=6.5 Hz, CH_2), 4.24 (1H, d, *J*=5.0 Hz, 4-CH), 6.60 (1H, dt, *J*=1.5, 8.0 Hz, CH); δ_C (100 MHz, $CDCl_3$) −5.0, −4.95, −4.4, −4.35, 14.3, 18.1, 18.6, 22.9, 25.95, 26.0, 26.05, 26.1, 26.25, 26.3, 26.35, 27.9, 29.0, 29.4, 29.6, 29.65, 29.7, 30.0, 31.9, 33.1, 33.5, 46.6, 49.5, 63.5, 72.0, 138.0, 140.6, 216.6.

3.1.9. (3*S*,4*S*)-4-(*tert*-Butyldimethylsilyloxy)-3-(7-hydroxyheptyl)-2-[*trans*-octylidene] cyclopentanone 16 and (4*R*)-4-(7-hydroxyheptyl)-5-[*trans*-octylidene]cyclopent-2-enone 17. To a stirred mixture of the ketone **15** (218 mg, 0.394 mmol) in THF (0.5 cm^3) was added H_2O (0.5 cm^3) and then AcOH (1.5 cm^3) at room temperature. The resultant mixture was stirred at rt for 4 days until TLC analysis indicated that the reaction was complete. The reaction was quenched on addition of sat. $NaHCO_3$ solution (15 cm^3) and the resulting mixture was extracted with EtOAc (3×15 cm^3). The combined organic layers were washed with brine (15 cm^3), dried over $MgSO_4$ and concentrated in vacuo, whereupon the residue was purified by column chromatography (Hex–Et_2O; 9:1→1:1) thus yielding the hydroxyketone **16** (70 mg, 40%) as a colourless oil. $[\alpha]_D$=−30.9 (*c*=6.9, $CHCl_3$); ν_{max} (neat/cm^{-1}) 3443, 2926, 2854, 1724, 1650; *m/z* (ES) 461 (MNa^+, 100%); found 461.3431, $C_{26}H_{50}O_3Si$·Na requires 461.3427 (+0.9 ppm); δ_H (400 MHz, $CDCl_3$) 0.06 (3H, s, CH_3), 0.07 (3H, s, CH_3), 0.85 (9H, s, CH_3), 0.89 (3H, t, *J*=7.0 Hz, CH_3), 1.60–1.20 (23H, m, OH, CH_2), 2.12–2.18 (2H, m, CH_2), 2.26 (1H, d, *J*=18.0 Hz, 5-CH_2), 2.56 (1H, dd, *J*=5.0, 18.0 Hz, 5-CH_2), 2.70–2.78 (1H, m, 3-CH), 3.65 (2H, t, *J*=6.5 Hz, CH_2), 4.24 (1H, d, *J*=5.0 Hz, 4-CH), 6.61 (1H, dt, *J*=1.5, 7.5 Hz, CH); δ_C (100 MHz, $CDCl_3$) −4.45, −4.4, 14.2, 18.1, 22.8, 25.75, 25.8, 25.85, 25.9, 27.8, 28.9, 29.3, 29.5, 29.55, 29.6, 29.9, 31.9, 32.9, 33.2, 46.5, 49.4, 63.1, 74.9, 138.0, 140.4, 205.8. Further elution gave **17** (24 mg, 20%) as a colourless oil. $[\alpha]_D$=−145 (*c*=4.15, $CHCl_3$); ν_{max} (neat/cm^{-1}) 3429, 2926, 2855, 1696, 1650; *m/z* (CI) 307 (MH^+, 100%); found 307.2642, $C_{20}H_{35}O_2$ requires 307.2637 (+2.0 ppm); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J*=7.0 Hz, CH_3), 1.47 (1H, s, OH), 1.20–1.90 (22H, m, CH_2), 2.18–2.30 (2H, m, CH_2), 3.44–3.50 (1H, m, 4-CH), 3.63 (2H, t, *J*=7.0 Hz, CH_2), 6.32 (1H, dd, *J*=2.0, 6.0 Hz, 2-CH), 6.55 (1H, t, *J*=7.5 Hz, CH), 7.52 (1H, dd, *J*=2.5, 6.0 Hz, 3-CH); δ_C (100 MHz, $CDCl_3$) 22.8, 25.7, 25.8, 28.7, 29.1, 29.2, 29.3, 29.5, 29.8, 30.4, 31.7, 32.5, 32.8, 43.5, 63.1, 135.0, 136.0, 138.0, 162.0, 197.2.

3.1.10. (3*S*,4*S*)-4-(*tert*-Butyldimethylsilyloxy)-3-(6-carboxyhexyl)-2-[*trans*-octylidene] cyclopentanone 18. To a solution of the alcohol **16** (102 mg, 0.23 mmol, 1 equiv.) in

dichloromethane (2.5 cm^3) was added Dess–Martin's periodinane (128 mg, 0.30 mmol, 1.3 equiv.) at room temperature. The resulting mixture was stirred for 1 h. Saturated aqueous solutions of Na_2CO_3 (3 cm^3) and Na_2SO_3 (3 cm^3) were added to quench the reaction, and the resultant mixture was extracted with Et_2O (3×10 cm^3); the combined organic layers were dried over $MgSO_4$, filtered and concentrated to yield the crude aldehyde which was used directly in the next step without further purification. To a mixture of the aldehyde (ca. 0.23 mmol, 1 equiv.), *tert*-butyl alcohol (5.0 cm^3) and 2,3-dimethylbut-2-ene (3.1 cm^3), H_2O (3.0 cm^3), NaH_2PO_4 (388 mg, 3.2 mmol, 14 equiv.) and $NaClO_2$ (388 mg, 4.3 mmol, 19 equiv.) were added sequentially. The resulting mixture was stirred at room temperature for 16 h. Aqueous 2 M HCl was added to acidify the mixture, followed by extraction with Et_2O (30 cm^3). The extract was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (Hex–Et_2O–AcOH; 3:1:0.01) to yield the carboxylic acid **18** (97 mg, 93%) as a pale oil. $[\alpha]_D$=−25.4 (c=4.25, $CHCl_3$); ν_{max} (neat/cm^{-1}) 3000, 2927, 2856, 1710, 1647; *m/z* (ES) 453 (MH^+, 100%), 371 (22%), 321 (32%); found 453.3402, $C_{26}H_{49}O_4Si$ requires 453.3400 (+0.4 ppm); δ_H (400 MHz, $CDCl_3$) 0.05 (3H, s, CH_3), 0.06 (3H, s, CH_3), 0.84 (9H, s, CH_3), 0.88 (3H, t, J=7.5 Hz, CH_3), 1.19–1.88 (20H, m, CH_2), 2.09–2.15 (2H, m, CH_2), 2.24 (1H, d, J=18.5 Hz, 5-CH_2), 2.34 (2H, t, J=7.5 Hz, CH_2), 2.55 (1H, dd, J=5.0, 18.5 Hz, 5-CH_2), 2.77–2.81 (1H, m, 3-CH), 4.24 (1H, d, J=5.0 Hz, 4-CH), 6.61 (1H, dt, J=1.5, 7.0 Hz, CH), 6.80–7.01 (1H, s(br), CO_2H); δ_C (100 MHz, $CDCl_3$) −4.45, −4.4, 14.8, 18.6, 22.9, 25.0, 25.95, 26.0, 26.05, 27.8, 29.0, 29.4, 29.5, 29.6, 29.7, 29.8, 32.0, 33.4, 34.5, 46.6, 49.5, 72.0, 138.2, 140.5, 179.3, 206.0.

3.1.11. (4*R*)-4-(6-Carboxyhexyl)-5-[*trans*-octylidene]-cyclopent-2-enone [*epi*-8*R*-Δ^{12}-15-deoxy-PG-J_1] 19. To a solution of the alcohol **17** (99 mg, 0.32 mmol, 1 equiv.) in DCM (2.2 cm^3) was added Dess–Martin's periodinane (178 mg, 0.42 mmol, 1.3 equiv.) at room temperature. The resulting mixture was stirred until TLC analysis indicated that the reaction was complete. Then sat. aqueous Na_2CO_3 (3 cm^3) and sat. aqueous Na_2SO_3 (3 cm^3) were added and the resultant mixture was extracted with Et_2O (3×10 cm^3). The combined organic solutions were dried over $MgSO_4$, filtered and concentrated to yield the crude aldehyde, which was used directly in the next step without further purification. To a mixture of the aldehyde (0.75 mmol, 1 equiv.), *tert*-butyl alcohol (6.8 cm^3) and 2,3-dimethylbut-2-ene (4.3 cm^3) was added sequentially H_2O (4.0 cm^3), NaH_2PO_4 (533 mg, 4.4 mmol, 14 equiv.) and $NaClO_2$ (533 mg, 5.9 mmol, 18 equiv.) at room temperature. The resulting mixture was stirred for 16 h. Work-up as described above gave the crude product, which was purified by flash column chromatography (Hex–Et_2O–AcOH; 3:1:0.01) to yield the carboxylic acid **19** (27 mg, 27%) as a pale oil. $[\alpha]_D$=−96.8 (c=2.2, $CHCl_3$); ν_{max} (neat/cm^{-1}) 3000, 2927, 2885, 1720, 1709, 1647; *m/z* (ES) 343 (MNa^+, 63%); found 343.2234, $C_{20}H_{32}O_3Na$ requires 343.2249 (−4.4 ppm); δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, J=7.0 Hz, CH_3), 1.10–1.85 (20H, m, CH_2), 2.24 (2H, t, J=7.5 Hz, CH_2), 2.34 (2H, t, J=7.5 Hz, CH_2), 3.45–3.52 (1H, m, 4-CH), 6.34 (1H, dd, J=2.0, 6.0 Hz, 2-CH), 6.56 (1H, t, J=7.5 Hz, CH), 7.50–7.56 (1H, m, 3-CH); δ_C (100 MHz, $CDCl_3$) 14.3, 22.9, 24.8, 25.9, 28.9, 29.2, 29.3, 29.4, 29.45, 29.7, 32.0, 32.6, 34.1, 43.6, 135.1, 136.3, 138.1, 162.1, 179.3, 197.3.

3.1.12. (4*R*)-4-(6-Carboxyhexyl)-5-[*trans*-octylidene]-cyclopent-2-enone methyl ester [*epi*-8*R*-Δ^{12}-15-deoxy-PG-J_1 methyl ester] 20. At room temperature a solution of **18** (60 mg, 0.13 mmol, 1 equiv.) in a mixture of benzene (10 cm^3) and MeOH (3 cm^3) was treated with a 2.0 M solution of (trimethylsilyl)diazomethane in hexane (0.1 cm^3, 0.2 mmol, 1.5 equiv.). Stirring was continued for 0.5 h before the solvent was removed under reduced pressure. Purification by flash column chromatography (Hex–Et_2O; 9:1) gave the methyl ester (50.5 mg, 81%) as a colourless oil. At 0 °C a solution of the methyl ester (16 mg, 0.03 mmol) in MeOH (2.5 cm^3) was treated with a 10% solution of Na_2CO_3 (2.5 cm^3). The reaction was warmed to room temperature over 2 h before a 1 M aqueous solution of HCl (2 cm^3) and water (5 cm^3) were added. The resultant solution was extracted with Et_2O (4×10 cm^3) and the combined organic extracts were dried over $MgSO_4$. Filtration, solvent removal in vacuo and purification by flash column chromatography (Hex–EtOAc; 4:1) gave **20** (9 mg, 78%) as a pale yellow oil. $[\alpha]_D$=−110 (c=0.9, $CDCl_3$); ν_{max} (neat/cm^{-1}) 2926, 2855, 1740, 1701, 1654; *m/z* (CI) 352 (MNH_4^+, 10%), 335 (MH^+, 100%); found 335.25857, $C_{21}H_{34}O_3{\cdot}H$ requires 335.25861 (−0.1 ppm); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, J=7.0 Hz, CH_3), 1.20–1.85 (14H, m, CH_2), 1.42–1.65 (5H, m, CH_2), 1.75–1.87 (1H, m, CH_2), 2.26 (2H, pent, J=7.5 Hz, CH_2), 2.29 (2H, t, J=7.5 Hz, CH_2), 3.44–3.52 (1H, m, 4-CH), 3.66 (3H, s, CH_3), 6.32 (1H, dd, J=1.75, 6.0 Hz, 2-CH), 6.56 (1H, t, J=7.5 Hz, CH), 7.52 (1H, ddd, J=0.75, 2.5, 6.0 Hz, 3-CH); δ_C (100 MHz, $CDCl_3$) 14.0, 22.6, 24.8, 25.7, 28.7, 29.0, 29.1, 29.15, 29.4, 29.45, 31.7, 32.4, 34.0, 43.3, 51.4, 134.9, 135.8, 137.8, 161.7, 174.1, 196.9.

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Preparation of optically pure cross-conjugated cyclopentadienones

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Abstract—The synthesis of optically pure cross-conjugated cyclopentadienones is readily achieved in two steps via a one-pot alkylcuprate addition/aldol condensation/dehydration sequence using racemic or enantioenriched *endo*-3a,4,7,7a-tetrahydro-1*H*-4,7-methano-inden-1-ones followed by microwave-mediated Lewis acid-catalysed *retro* Diels–Alder reaction. An alternative route involving a modified Baylis–Hillman protocol followed by conjugate addition with alkylcuprates and a retro Diels–Alder reaction was also investigated.

1. Introduction

Recent reports of the potent biological properties exhibited by many prostanoid compounds containing a cross-conjugated cyclopentadienone unit has heightened our interest in the synthesis of this important structural motif.[1]

The clavulone series of marine natural products **1**,[2] the unsaturated prostaglandin (PG) $\Delta^{12,14}$-15-deoxy-PG-J_2 **2**,[3] the related C-18 chromomoric acid **3**[4] and the potential anticancer agent TEI-9826 **4**[5] all contain the 5-alkylidene-cyclopent-2-enone unit (Fig. 1). In addition, similar compounds have recently been implicated in the development and progression of atherosclerosis.[6]

In general there exists a number of approaches to cross-conjugated dienone-containing ring structures **D** from enones **A** that involve the formation of a β-hydroxy alkylated species **C**, their further derivatisation and subsequent β-elimination (Scheme 1).

In many of these cases, the β-hydroxy alkylated moiety of **C** can be obtained by either trapping the enolate **B** (resulting from conjugate addition) with a suitable aldehyde[6b,7] or through conjugate addition to an α-alkoxy alkylated enone **F** (derived from seleno enolate **E**) using alkylcuprates, as reported by Noyori.[8]

Although the enolate trapping route has enjoyed considerable popularity in the synthesis of structures of type **C**, Noyori's pathway has not been employed to the same extent, probably due to the greater number of steps involved, as well as the potential hazards from handling toxic selenide reagents and intermediates. Interestingly, Noyori's procedure had notable mechanistic similarities with the Baylis–Hillman reaction and, in particular, with a recently reported variant involving mild cooperative catalysis (from tributylphosphine as a Lewis base with phenol as a Brønsted acid) to give α-methylene-β-hydroxy enones **F** via enolate **G** and adduct **H** (Scheme 2).[9]

We surmised that a novel synthetic sequence that comprised a mechanistically similar and higher yielding Baylis–Hillman reaction as its key step, circumventing the disadvantages of Noyori's method, might offer a more efficient approach to cross-conjugated cyclopentadienones.

2. Results and discussion

We chose to conduct the modified Baylis–Hillman reaction on racemic *endo*-3a,4,7,7a-tetrahydro-1*H*-4,7-methano-inden-1-one **5**[10] to give β-hydroxy alkylated enones which we wished to derivatise (e.g. by acetoxylation) and finally perform an alkylcuprate conjugate addition to give an exocyclic alkene, after spontaneous β-elimination. Lewis acid-catalysed *retro* Diels–Alder would then release the corresponding cross-conjugated cyclopentadienone (Scheme 3).

Keywords: Microwave-promoted reactions; *retro*-Diels–Alder reaction; 4-Alkyl 5-alkyli-denecyclopent-2-enones; Baylis–Hillman reaction.
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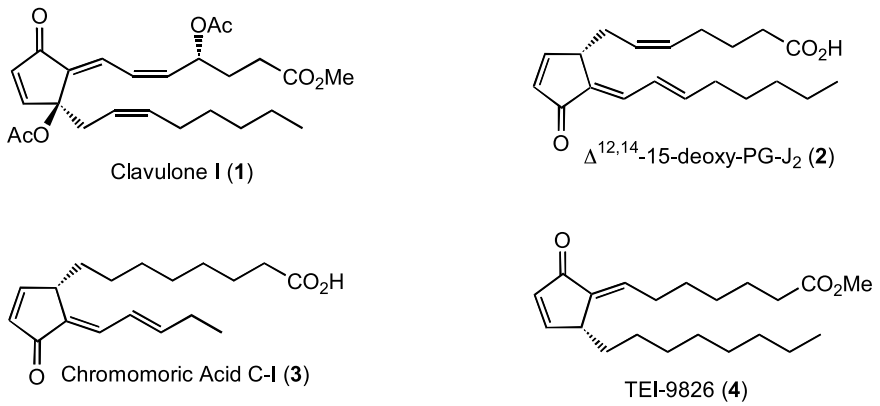


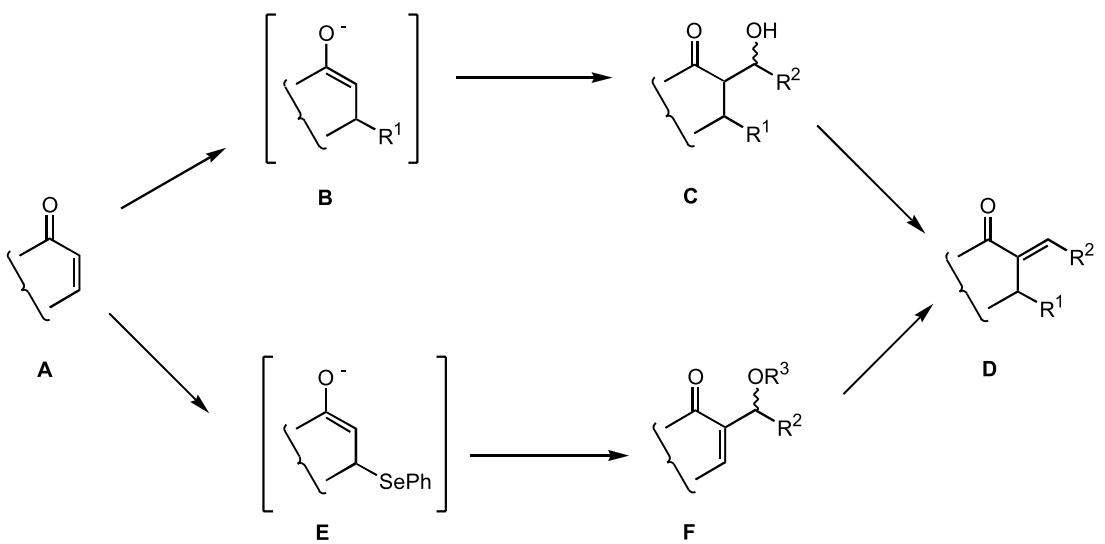
Figure 1. Alkylidenecyclopentenones of biological interest.

The Baylis–Hillman adducts **6**–**10** were easily prepared, usually in high yield (87–93%) after stirring a mixture of racemic enone, phenol, tributylphosphine and aldehyde in THF at room temperature for 24 h. The corresponding acetates **11**–**15** were prepared in the standard manner (47–97% yield).

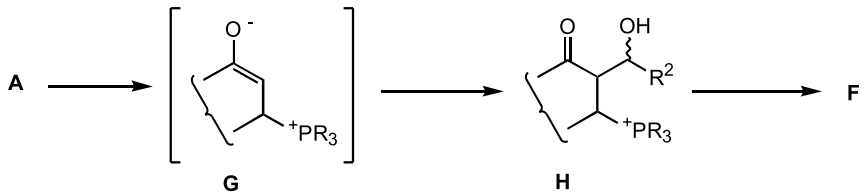
The key conjugate addition/elimination tandem reaction worked well for the isopropyl compound **11**, furnishing the alkylated products **16** and **17** as the only isolable compounds in 57 and 59% yield, respectively. However, the procedure was not as satisfactory for other substrates. For example, when the compound **12** was used as starting material in a reaction with dimethylcuprate, the desired compound **18** was formed (34%) in admixture with the bis-alkylated product **25** (28%). Reaction of **12** with butylcyanocuprate was even more complex furnishing the bis-alkylated product **26** (7%) as well as the required product **19** which was not separated from the isomer **27** (42% yield; ratio **19**:**27** 9:1 by NMR spectroscopy). Similarly addition of methylcyanocuprate to the acetoxy-enone **13** was not regioselective, the desired product **20** (61%) being contaminated with the (separable) isomer **28** (19%).

Clearly continuing with this strategy with its unpredictable overall yields and, more significantly, the often-observed poor regioselectivity, was not appealing. Our attention turned to a one-pot alkylcuprate addition/aldol condensation/dehydration procedure which had literature precedent[4d] and, we felt, could be applied with more confidence to racemic and enantioenriched *endo*-3a,4,7,7a-tetrahydro-4,7-methano-inden-1-one **5** in order to access a range of target compounds. Indeed cross-conjugated cyclopentenedione precursors have been obtained from **5** previously.[11] However the required intermediate was obtained only after isolation of the aldol and subsequent acid-catalysed rearrangement, generating a mixture of *Z*- and *E*-geometrical isomers (Scheme 4). More recently cross-conjugated cyclopentadienones have been accessed from enone **29** using a one-pot conjugate addition/Peterson olefination sequence followed by a *retro* Diels–Alder reaction.[12]

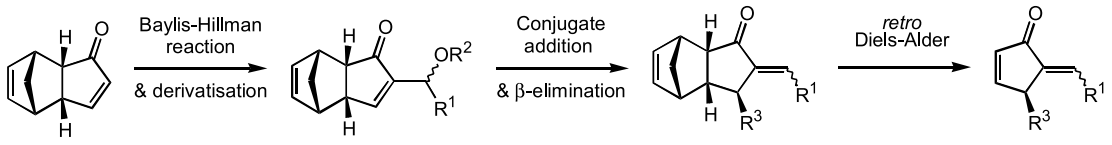
Both enantioenriched (+)-**5** and (−)-**5** were available in high yield and on a multi-gram scale.[13] The enantiomers underwent facile chemo- and diastereoselective 1,4-conjugate addition with an alkylcuprate; aldehyde quench of the intermediate enolate and spontaneous dehydration upon



Scheme 1. Approaches towards β-hydroxy alkylated species.



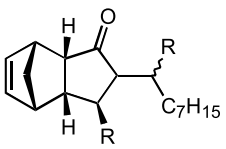
Scheme 2. An approach comprising the modified Baylis–Hillman reaction.

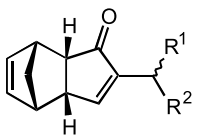


6 R^1=$CHMe_2$; R^2=H
7 R^1=C_7H_{15}; R^2=H
8 R^1=$CH(CH_2)_2$; R^2=H
9 R^1=Ph; R^2=H
10 R^1=CH_2Ph; R^2=H
11 R^1=$CHMe_2$; R^2=Ac
12 R^1=C_7H_{15}; R^2 = Ac
13 R^1=$CH(CH_2)_2$; R^2=Ac
14 R^1=Ph; R^2=Ac
15 R^1=Bn; R^2=Ac

16 R^1=$CHMe_2$; R^3=Me
17 R^1=$CHMe_2$; R^3=C_4H_9
18 R^1=C_7H_{15}; R^3=Me
19 R^1=C_7H_{15}; R^3=C_4H_9
20 R^1=$CH(CH_2)$; R^3=Me
21 R^1=$CHMe_2$; R^3=C_8H_{17}
22 R^1=Ph; R^3=Me
23 R^1=Ph; R^3=C_8H_{17}
24 R^1=*p*-F.C_6H_4; R^3=Me

Scheme 3. Baylis–Hillman adducts and cross-conjugated cyclopentadienones derived from (±)-*endo* enone **5**.



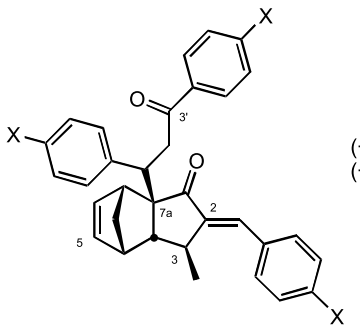


25 R=Me
26 R=C_4H_9

27 R^1=C_4H_9; R^2=C_7H_{15}
28 R^1=Me; R^2=$CH(CH_2)_2$

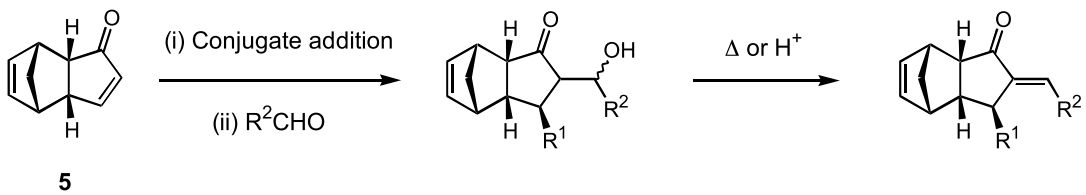
work-up furnished the desired products (Table 1). Generally, the one-pot three component coupling proceeded smoothly giving good or very good yields of *exo*-cyclic enones. Entries 1–4 and 10, demonstrated that the reaction exhibited exclusively *E*-selectivity, whilst the remainder (entries 5–8) provided the same isomer in very high purity (>95%). It is possible that the small contamination by the *Z*-isomer may have been due to photolytic and or thermally induced isomerisation. Differentiation between *E*- and *Z*-isomers of compounds **32**–**36** was possible using ^{1}H NMR spectroscopic techniques and was in accordance with literature precedent.[4d]

In a few cases the one-pot strategy provided some unexpected by-products. In addition to the desired *exo*-cyclic enones (+)-**22** and (+)-**24** (entries 5 and 10 respectively), more polar compounds were also isolated (15% yield in each case). After NMR spectroscopic and high resolution mass spectrometric analysis the compounds were assigned the structures of the tri-aryl species (+)-**30** and (+)-**31**.



(+) **30** (X= H)
(+) **31** (X= F)

Previously, it has been reported that Lewis acid-catalysed *retro* Diels–Alder reactions involving *exo*-cyclic enones similar to **16**, **21**–**24** were achievable only with reaction times of between 1 and 24 h duration.[12] It was found that a



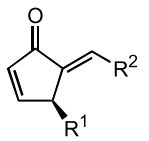
Scheme 4. Synthesis of cross-conjugated cyclopentadienone precursors.

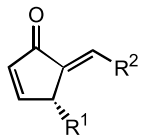
Table 1. Synthesis of some *exo*-cyclic enones by one-pot conjugate addition/aldol condensation/dehydration

Entry	Substrate	Cuprate reagent	Aldehyde	Product (yield, %)[a] (*E*/*Z* ratio)[b]
1	(+)-**5**	Me_2CuLi	Me_2CHCHO	(+)-**16** (76) (100:0)
2	(−)-**5**	Me_2CuLi	Me_2CHCHO	(−)-**16** (60) (100:0)
3	(+)-**5**	Oct_2CuLi	Me_2CHCHO	(+)-**21** (61) (100:0)
4	(−)-**5**	Oct_2CuLi	Me_2CHCHO	(−)-**21** (54) (100:0)
5	(+)-**5**	Me_2CuLi	PhCHO	(+)-**22** (64) (97:3)
6	(−)-**5**	Me_2CuLi	PhCHO	(−)-**22** (75) (92:8)
7	(+)-**5**	Oct_2CuLi	PhCHO	(+)-**23** (57) (92:8)
8	(−)-**5**	Oct_2CuLi	PhCHO	(−)-**23** (83) (99:2)
9	(±)-**5**	Me_2CuLi	*p*-F.C_6H_4CHO	(±)-**24** (83) (99:1)
10	(+)-**5**	Me_2CuLi	*p*-F.C_6H_4CHO	(+)-**24** (55) (100:0)

[a] Yield following purification by flash column chromatography.
[b] Ratio determined by ^{1}H NMR spectroscopy of the crude reaction mixture.

considerable enhancement of the reaction rate was possible, for the *exo*-cyclic enones **16**, **21**–**24**, when the [4+2]-cycloreversion step was carried out in a microwave reactor (SmithCreator, ~20 W).





(+)-**32** R^1=Me; R^2=$CHMe_2$ (-)-**32** R^1=Me; R^2=$CHMe_2$
(+)-**33** R^1=C_8H_{17}; R^2=$CHMe_2$ (-)-**33** R^1=C_8H_{17}; R^2=$CHMe_2$
(-)-**34** R^1=Me; R^2=Ph (+)-**34** R^1=Me; R^2=Ph
(+)-**35** R^1=C_8H_{17}; R^2=Ph (-)-**35** R^1=C_8H_{17}; R^2=Ph
(-)-**36** R^1=Me; R^2=*p*-F.C_6H_4 (+)-**36** R^1=Me; R^2=*p*-F.C_6H_4

Thus microwave-mediated reactions of *exo*-cyclic enones **16**, **21**–**24** were performed in DCM in sealed glass vials at 60 °C with $MeAlCl_2$ as Lewis acid catalyst and an excess of maleic anhydride as a cyclopentadiene trap.[13] In most cases, the reaction was stopped after 25 min. Continued irradiation eroded the yields of products **32**–**36** which were generally very respectable (Table 2). In contrast to earlier reports,[12] little significant change in the *E*/*Z* isomer ratios was observed.

Table 2. Synthesis of some optically active cross-conjugated cyclopentadienones **32**–**36**

Entry	Substrate	Product (yield %)[a] (*E*/*Z* ratio)[b]
1	(+)-**16**	(+)-**32** (63)* (98:2)
2	(−)-**16**	(−)-**32** (83)* (97:3)
3	(+)-**21**	(+)-**33** (84)* (100:0)
4	(−)-**21**	(−)-**33** (65)* (94:6)
5	(+)-**22**	(−)-**34** (74) (97:3)
6	(−)-**22**	(+)-**34** (69) (97:3)
7	(+)-**23**	(+)-**35** (82)* (99:1)
8	(−)-**23**	(−)-**35** (62)* (98:2)
9	(±)-**24**	(±)-**36** (83) (96:4)
10	(+)-**24**	(−)-**36** (91) (100:0)

[a] Yield following purification by flash column chromatography and taking into account recovered starting material (10–20%) where indicated (*).
[b] Estimated by ^{1}H NMR spectroscopy.

3. Conclusions

We have combined a one-pot three-component coupling procedure on racemic and enantioenriched substrate **5** with a facile microwave-mediated *retro* Diels–Alder reaction to give optically pure cross-conjugated cyclopentadienones in two steps. Significantly the initial alkylcuprate conjugate addition reaction proceeds with high diastereoselectivity and the condensation with very high *E*-selectivity; the overall yield for the whole process is 50% or greater in the vast majority of the cases studied.

4. Experimental

4.1. General

Starting materials were purchased from commercial sources and were used without further purification. ^{1}HNMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded using a Bruker AMX400 spectrometer. ^{13}C NMR assignments were made using DEPT experiments. Infra red spectroscopy was performed on a Perkin–Elmer Paragon 1000 FT1R machine. Optical rotation measurements were recorded using an Optical Activity, Polar 2001 polarimeter at 589 nm and are quoted in units of 10^{-1} deg cm^2 g^{-1}. Flash column chromatography was performed using silica gel-ICN 32-63, 60 Å.

4.2. Baylis–Hillman reaction representative procedure

4.2.1. (±)-2-(1-Hydroxy-octyl)-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one 7. Phenol (0.2 equiv.) and *n*-tributylphosphine (0.4 equiv.) was added to a stirring solution of enone **5** (1.0 g, 6.91 mmol) and *n*-octylaldehyde (1.5 equiv.) in anhydrous THF (6.2 cm^3) at room temperature under nitrogen stream. After 5–8 days at this temperature, flash silica (4.5 g) was added and the solvent removed in vacuo to afford crude product, pre-absorbed on silica. Purification using flash column chromatography (SiO_2), eluting with *n*-hexane/2-butanone, (9:1) afforded the allylic alcohol **7** (1.63 g, 86%) as a transparent pale yellow oil; R_f 0.24 (SiO_2, *n*-hexane/diethyl ether, 2:1); δ_H (400 MHz, $CDCl_3$) 7.10 (1H, d, *J*=2.6 Hz, H_3), 5.91 (1H, dd, *J*=5.6, 2.9 Hz, $H_{5/6}$), 5.79 (1H, m, $H_{6/5}$), 4.20 (1H, s, 2C*H*(OH) *n*-hep), 3.27 (2H, m), 2.91 (2H, m), 1.75 (1H, m), 1.75 (1H, d, *J*=8.5 Hz, 4-C*H*H-7), 1.62 (1H, d, *J*=8.5 Hz, 4-CH*H*-7), 1.26 (1H, s, 1CH(OH)(CH_2)$_6$Me), 0.87 (3H, t, *J*=6.7 Hz, 1CH(OH)(CH_2)$_6$*Me*); δ_C (100 MHz, $CDCl_3$) 210.9 (s, C_1), 158.1 (d, C_3), 150.9 (s, C_2), 133.0 (d, $C_{5/6}$), 132.7 ($C_{6/5}$), 68.7 (2*C*H(OH) *n*-hep), 53.1 (t, 4-CH_2-7), 52.0 (d), 45.89, 45.5, 44.5, 36.6 (t, 2CH(OH)(*C*H_2)$_6$Me), 32.1, 29.7, 29.6, 25.8, 23.0, 14.4 (q, 2CH(OH)(CH_2)$_6$*Me*); *m*/*z* (CI/NH_3) 275 (MH^+, 100%), 257 ([$MH-H_2O$]$^+$, 97), 144 (29); (HRMS: found MH^+, 275.2011. $C_{18}H_{27}O_2^+$ requires 275.2018).

4.2.2. (±)-2-(1-Hydroxy-2-methylpropyl)-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one 6. (1.32 g, 87%), a transparent pale yellow oil; R_f 0.25 (SiO_2, *n*-hexane/2-butanone, 4:1); δ_H (400 MHz, $CDCl_3$) 7.07 (1H, d, *J*=2.5 Hz, H_3), 5.94 (1H, dd, *J*=5.5, 2.8 Hz, $H_{5/6}$), 5.80 (1H, dd, *J*=5.5, 3.0 Hz, $H_{6/5}$), 3.99 (1H, d, *J*=5.8 Hz, 2C*H*(OH) *i*-prop), 3.34 (1H, m), 3.22 (1H, m), 2.97 (1H, m),

2.88 (1H, t, J=4.8 Hz), 1.87–1.75 (1H, m), 1.64–1.57 (1H, m), 0.89 (3H, d, J=6.8 Hz, 2CH(OH)CH*Me*Me), 0.83 (3H, d, J=6.8 Hz, 2CH(OH)CHMe*Me*); δ_C (100 MHz, $CDCl_3$) 211.1 (s, C_1), 159.5 (d, C_3), 149.3 (s, C_2), 133.2 (d, $C_{5/6}$), 133.0 ($C_{6/5}$), 74.9 (2*C*H(OH) *i*-prop), 53.2 (t, 4-CH_2–7), 52.0 (d), 46.1, 45.5, 44.6, 33.6, 19.3 (q, 2CH(OH)CH-*Me*Me), 17.9 (2CH(OH)CHMe*Me*); *m/z* (CI/NH_3) 219 (MH^+, 100%), 201 ($[MH-H_2O]^+$, 75), 137 (42.3); (HRMS: found MH^+, 219.1393. $C_{14}H_{19}O_2^+$ requires 219.1385).

4.2.3. (±)-2-(Cyclopropyl-hydroxy-methyl)-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one 8. (3.44 g, 93%), a transparent yellow oil; R_f 0.17 (SiO_2, *n*-hexane/2-butanone, 4:1); δ_H (400 MHz, $CDCl_3$) 7.20 (1H, d, J=2.6 Hz, H_3), 5.92 (1H, dd, J=5.3, 2.7 Hz, H_6), 5.80 (1H, dd, J=5.3, 3.0 Hz, H_5), 3.67 (1H, d, J=8.1 Hz, 2C*H*(OH) cycloprop), 3.33 (1H, m, H_{3a}), 3.22 (1H, m, H_7), 3.12 (1H, br. s, 2CH(OH) cycloprop), 2.97 (1H, m, H_4), 2.89 (1H, t, J=5.12 Hz, H_{7a}), 1.75 (1H, dd, J=8.4, 1.4 Hz, 4-C*H*H-7), 1.62 (1H, d, J=8.4 Hz, 4-CH*H*-7), 1.07–0.94 (1H, m, 2CH(OH) *cycloprop*), 0.57–0.42 (2H, m, 2CH(OH) *cycloprop*), 0.38–0.33 (1H, m, 2CH(OH) *cycloprop*), 0.27–0.21 (1H, m, 2CH(OH) *cycloprop*); δ_C (100 MHz, $CDCl_3$) 210.9 (s, C_1), 158.4 (d, C_3), 150.3 (s, C_2), 132.9 (d, C_6), 132.7 (C_5), 72.2 (2*C*H(OH) cycloprop), 51.9 (C_{7a}), 45.9 (C_{3a}), 45.5 (C_7), 44.4 (C_4), 17.0 (2CH(OH) *cycloprop*), 3.5 (t, 2CH(OH) *cycloprop*), 2.5 (2CH(OH) *cycloprop*); *m/z* (CI/NH_3) 234 ($[MH+NH_3]^+$, 3.7%), 216 ($[MH+NH_3-H_2O]^+$, 74.4), 199 (100); (HRMS: found $MH+NH_3^+$, 234.1498. $C_{14}H_{20}NO_2^+$ requires 234.1494).

4.2.4. (±)-2-(1-Hydroxy-phenyl-methyl)-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one 9. (0.73 g, 89%), an off-white crystalline solid; R_f 0.28 (SiO_2, *n*-hexane/diethyl ether, 1:1); ν_{max} (film)/cm^{-1} 3355 (OH), 1664.9 (CO); δ_H (400 MHz, $CDCl_3$) 7.34–7.31 (5H, m, 2CH(OH)*Ph*), 6.94 (1H, d, J=1.9 Hz, H_3), 5.90 (1H, dd, J=5.6, 2.9 Hz, $H_{5/6}$), 5.76 (1H, dd, J=5.6, 3.0 Hz, $H_{6/5}$), 5.42 (1H, s, 2C*H*(OH)Ph), 3.45 (1H, s, 2CH(*OH*)Ph), 3.29 (1H, m, H_{3a}), 3.22 (1H, m, $H_{4/7}$), 2.93 (1H, m, $H_{7/4}$), 2.89 (1H, t, J=5.1 Hz, H_{7a}), 1.74 (1H, dt, J=8.5, 1.7 Hz, 4-C*H*H-7), 1.60 (1H, d, J=8.5 Hz, 4-CH*H*-7); δ_C (100 MHz, $CDCl_3$) 210.7 (s, C_1), 159.7 (d, C_3), 150.7 (s, C_2), 141.9 (2CH(OH)*Ph*), 133.0 (d, C_6), 132.9 (C_5), 128.8 (2d, 2CH(OH)*Ph*), 128.1 (d, 2CH(OH)*Ph*), 126.8 (2d, 2CH(OH)*Ph*), 70.6 (d, 2*C*H(OH)Ph), 53.1 (t, 4-CH_2-7), 52.0 (d, C_{3a}), 45.9 (C_{7a}), 45.6 (C_4), 44.5 (C_7); *m/z* (CI/NH_3) 504 (7.0%), 487 (8.8), 270 ($[MH+NH_3]^+$, 7.9), 252 (44.8), 235 (100), 207 (35.7), 169 (13.8); (HRMS: found $MH+NH_3^+$, 270.1498. $C_{17}H_{20}NO_2^+$ requires 270.1501).

4.2.5. (±)-2-(1-Hydroxy-2-phenyl-ethyl)-3a,4,7,7a-tetrahydro-4,7-methano inden-1-one 10. (0.51 g, 56%), a yellow crystalline solid; R_f 0.24 (SiO_2, *n*-hexane/diethyl ether, 1:1); δ_H (250 MHz, $CDCl_3$) 7.27–7.16 (6H, m, 2CH(OH)CH_2*Ph*, H_3), 5.83 (1H, dd, J=5.5, 3.1 Hz, $H_{5/6}$), 5.66 (1H, dd, J=5.5, 3.1 Hz, $H_{6/5}$), 4.44 (1H, m, 2C*H*(OH)CH_2Ph), 4.30 (1H, br. s, 2CH(O*H*)CH_2Ph), 3.22 (1H, m, H_{3a}), 3.15 (1H, m, $H_{4/7}$), 2.96 (1H, dd, J=13.7, 4.1 Hz, 2CH(OH)C*H*HPh), 2.90 (1H, m, $H_{7/4}$), 2.83 (1H, t, J=5.1 Hz, H_{7a}), 2.68 (1H, dd, J=13.7, 8.2 Hz, 2CH(OH)CH*H*Ph), 1.69 (1H, d, J=8.6 Hz, 4-C*H*H-7), 1.59 (1H, m, 4-CH*H*-7); δ_C (100 MHz, $CDCl_3$) 213.9 (s, C_1), 163.4 (d, C_3), 155.9 (s), 143.4, 137.5 (d, $C_{5/6}$), 136.9 ($C_{6/5}$), 134.4 (2d, 2CH(OH)CH_2*Ph*), 132.8, 130.9 (d, 2CH(OH)CH_2*Ph*), 72.7 (2*C*H(OH)CH_2Ph), 57.3 (t, 4-CH_2-7), 56.5 (d), 56.5, 50.1, 49.7, 48.7, 47.2 (t, 1CH(OH)*C*H_2Ph); *m/z* (CI/NH_3) 387 (100%), 369 (58.1), 351 (18.0), 266 ($[MH+NH_3-H_2O]^+$, 7.3), 249 ($[MH-H_2O]^+$, 26.9), 194 (17.4), 91 (26.4); (HRMS: found MH^+, 267.1391. $C_{18}H_{19}O_2^+$ requires 267.1385).

4.3. Acetylation of Baylis–Hillman products representative procedure

4.3.1. (±)-Acetic acid 1-(1-oxo-3a,4,7,7a-tetrahydro-1*H*-4,7-methano-inden-2-yl)-octyl ester 12. Acetic anhydride (11 equiv.) was added to a solution of allylic alcohol **7** (0.25 g, 0.91 mmol) in freshly distilled pyridine (1.6 cm^3) and stirred at room temperature for 17 h under nitrogen atmosphere. Water (8 cm^3) and ethyl acetate (8 cm^3) were added, the aqueous layer separated and extracted further with ethyl acetate (3×8 cm^3). The combined organic layers were washed with 10% $NaHCO_3$ solution (8 cm^3), water (8 cm^3), dried ($MgSO_4$) and solvent removed in vacuo to afford crude acetate. Purification using flash column chromatography (SiO_2), eluting with *n*-hexane/2-butanone (9:1) gave allylic acetate **12** (0.21 g, 72%) as a transparent amber oil; R_f 0.46 (SiO_2, *n*-hexane/2-butanone, 4:1); δ_H (400 MHz, $CDCl_3$) 7.11 (1H, d, J=2.5 Hz, H_3), 5.91 (1H, m, $H_{5/6}$), 5.71 (1H, m, $H_{6/5}$), 5.34 (1H, m, 2C*H*(OAc) *n*-hep), 3.31–3.28 (1H, m), 3.21 (1H, m), 2.94 (1H, m), 2.84 (1H, m), 2.03 (3H, s, 2CH(OCO*Me*) *n*-hep), 1.74–1.58 (4H, m, 2CH(OAc)(CH_2)$_6$Me), 1.24 (10H, m, 2CH(OAc)(CH_2)$_6$-Me), 0.86 (3H, m, 2CH(OAc)(CH_2)$_6$*Me*); δ_C (100 MHz, $CDCl_3$) 207.5 (s, C_1), 169.9 (2CH(O*CO*Me) *n*-hep), 158.8 (d, C_3), 148.0 (s, C_2), 132.7 (d, $C_{5/6}$), 132.3 ($C_{6/5}$), 69.7 (2*C*H(OAc) *n*-hep), 52.5 (t, 4-CH_2-7), 53.0 (d), 45.5, 45.2, 44.2, 33.0 (t, 2CH(OAc)(CH_2)$_6$Me), 31.8, 29.2, 29.1, 25.2, 22.6, 21.1 (q, 2CH(OCO*Me*) *n*-hep), 14.1 (2CH(OAc)(CH_2)$_6$*Me*); *m/z* (CI/NH_3) 334 ($[MH+NH_3]^+$, 30.7%), 317 (MH^+, 93.4), 274 (3.3), 257 (100), 144 (21.9); (HRMS: found MH^+, 317.2116. $C_{20}H_{29}O_3^+$ requires 317.2117).

4.3.2. (±)-Acetic acid 2-methyl-1-(1-oxo-3a,4,7,7a-tetrahydro-1*H*-4,7-methano-inden-2-yl)-propyl ester 11. (0.25 g, 83%), a transparent pale yellow oil; R_f 0.49 (SiO_2, *n*-hexane/2-butanone, 4:1); ν_{max} (film)/cm^{-1} 3061, 2966, 2934, 2873, 1738, 1703, 1627; δ_H (400 MHz, $CDCl_3$) 7.11 (1H, d, J=2.5 Hz, H_3), 5.91 (1H, m, $H_{5/6}$), 5.70 (1H, m, $H_{6/5}$), 5.15 (1H, d, J=6.3 Hz, 2C*H*(OAc) *i*-prop), 3.31 (1H, m), 3.22 (1H, m), 2.94 (1H, m), 2.85 (1H, m), 2.12 (1H, m, 2CH(OAc)C*H*Me_2), 2.03 (3H, s, 2CH(OAc) *i*-prop), 1.75 (1H, m, 4-C*H*H-7), 1.60 (1H, m, 4-CH*H*-7), 0.84 (3H, s, 2CH(OH)CH*Me*Me), 0.83 (3H, 2CH(OH)CHMe*Me*); δ_C (100 MHz, $CDCl_3$) 207.5 (s, C_1), 170.0 (2CH(O*CO*Me) *i*-prop), 160.0 (d, C_3), 147.1 (s, C_2), 132.9 (d, $C_{5/6}$), 132.4 ($C_{6/5}$), 74.1 (2*C*H(OAc) *i*-prop), 52.5 (t, 4-CH_2-7), 51.6 (d), 45.6, 45.2, 44.2, 30.3 (2CH(OAc)*C*HMe_2), 21.0 (q, 2CH(OCO*Me*) *i*-prop), 18.7 (2CH(OH)CH*Me*Me), 17.5 (2CH(OH)CHMe*Me*); *m/z* (CI/NH_3) 278 ($[MH+NH_3]^+$, 16.1%), 261 (MH^+, 71.4), 201 (100); (HRMS: found MH^+, 261.1485. $C_{16}H_{21}O_3^+$ requires 261.1491); Found: C, 73.7; H, 7.8%, $C_{16}H_{20}O_3$ requires C, 73.8; H, 7.7%.

4.3.3. (±)-Acetic acid cyclopropyl-(1-oxo-3a,4,7,7a-tetrahydro-1*H*-4,7-methano-inden-2-yl)-methyl ester 13. (4.56 g, 97%), a transparent pale brown oil; R_f 0.35 (SiO_2, *n*-hexane/Et_2O, 1:1); δ_H (400 MHz, $CDCl_3$) 7.19 (1H, d, *J*=2.6 Hz, H_3), 5.90 (1H, dd, *J*=5.6, 2.9 Hz, $H_{5/6}$), 5.72 (1H, dd, *J*=5.6, 3.0 Hz, $H_{6/5}$), 4.78 (1H, d, *J*=8.9 Hz, 2C*H*(OAc) cycloprop), 3.31 (1H, m), 3.22 (1H, m), 2.96 (1H, m), 2.86 (1H, t, *J*=5.0 Hz), 2.03 (3H, s, 2CH(OCO*Me*) cycloprop), 1.74 (1H, dt, *J*=8.4, 1.7 Hz, 4-C*H*H-7), 1.60 (1H, d, *J*=8.4 Hz, 4-CH*H*-7), 1.24–1.16 (1H, m, 2CH(OAc) *cycloprop*), 0.55–0.44 (2H, m, 2CH(OAc) *cycloprop*), 0.39–0.28 (2H, m, 2CH(OAc) *cycloprop*); δ_C (100 MHz, $CDCl_3$) 207.7 (s, C_1), 170.3 (2CH(O*CO*Me) cycloprop), 159.4 (C_2), 148.0 (d, C_3), 133.0 ($C_{5/6}$), 132.6 ($C_{6/5}$), 73.1 (t, 2CH(OAc) cycloprop), 52.8 (4-CH_2-7), 51.7 (d), 45.9, 45.6, 44.9, 21.5 (2CH(OAc) *cycloprop*), 14.6 (q, 2CH(OCO*Me*) cycloprop), 4.3 (t, 2CH(OAc) *cycloprop*), 2.9 (2CH(OAc) *cycloprop*); *m/z* (CI/NH_3) 276 ([MH+NH_3]$^+$, 11.0%), 259 (MH^+, 13.3), 216 (100), 199 (94.5), 164 (16.4), 147 (20.3), 135 (9.6); (HRMS: found MH^+, 259.1329. $C_{16}H_{18}O_3^+$ requires 259.1334).

4.3.4. (±)-Acetic acid (1-oxo-3a,4,7,7a-tetrahydro-1*H*-4,7-methano-inden-2-yl)-phenyl-methyl ester 14. (0.74 g, 93%), an off-white crystalline solid; R_f 0.34 (SiO_2, *n*-hexane/diethyl ether, 1:1); δ_H (400 MHz, $CDCl_3$) 7.33–7.22 (5H, m, 2CH(OCOMe)*Ph*), 7.19 (1H, m, H_3), 6.38 (1H, dd, *J*=5.2, 2.9 Hz, $H_{5/6}$), 5.91 (1H, dd, *J*=5.2, 2.5 Hz, $H_{6/5}$), 3.30–3.27 (1H, m, $H_{3a/7a}$), 3.18 (1H, m, $H_{4/7}$), 2.95 (1H, m, $H_{7/4}$), 2.80 (1H, t, *J*=4.9 Hz, $H_{7a/3a}$), 2.05 (3H, s, 2CH(OCO*Me*)Ph), 1.71 (1H, d, *J*=8.4 Hz, 4-C*H*H-7), 1.56 (1H, d, *J*=8.4 Hz, 4-CH*H*-7); δ_C (100 MHz, $CDCl_3$) 207.0 (s, C_1), 169.8 (2CH(O*CO*Me)Ph), 159.1 (d, C_3), 148.4 (s, C_2), 138.6 (2CH(OCOMe)*Ph*), 133.0 (d, $C_{5/6}$), 132.7 ($C_{6/5}$), 128.8 (2d, 2CH(OCOMe)*Ph*), 128.5, 127.4 (d, 2CH(OCOMe)*Ph*), 70.7 (2*C*H(OCOMe)Ph), 52.9 (t, 4-CH_2-7), 51.8 (d, $C_{3a/7a}$), 46.0 ($C_{4/7}$), 45.6 ($C_{7/4}$), 44.6 ($C_{7a/3a}$), 21.4 (q, 2CH(OCO*Me*)Ph); *m/z* (ES$^+$) 413 (5.0%), 408 (5.0), 333 ([M+K]$^+$, 5.6), 317 ([M+Na]$^+$, 100), 301 (29.4), 251 (36.9); (HRMS: found M+Na^+, 317.1160. $C_{19}H_{18}O_3^{23}Na$ requires 317.1154); Found: C, 77.5; H, 6.2%, $C_{19}H_{18}O_3$ requires C, 77.5; H, 6.2%.

4.3.5. (±)-Acetic acid-1-(1-oxo-3a,4,7,7a-tetrahydro-1*H*-4,7-methano-inden-2-yl)-2-phenyl-ethyl ester 15. (0.27 g, 47%), a transparent pale yellow oil; R_f 0.22 (SiO_2, *n*-hexane/diethyl ether, 2:1); ν_{max} (film)/cm^{-1} 3469, 3062, 3029, 2979, 2936, 2869, 1742, 1698; δ_H (400 MHz, $CDCl_3$) 7.27–7.12 (5H, m, 2CH(OAc)CH_2*Ph*), 7.01 (1H, d, *J*=2.4 Hz, H_3), 5.86 (1H, dd, *J*=5.6, 2.8 Hz, $H_{5/6}$), 5.61 (1H, m, 2C*H*(OAc)CH_2Ph), 5.54 (1H, dd, *J*=5.6, 2.9 Hz, $H_{6/5}$), 3.24–3.20 (2H, m), 3.10 (1H, dd, *J*=14.0, 5.5 Hz, 2CH(OAc)C*H*HPh), 2.92 (1H, m, 2CH(OAc)CH*H*Ph), 2.88 (1H, m), 2.84 (1H, t, *J*=5.1 Hz), 1.98 (3H, s, 2CH(OCO*Me*)CH_2Ph), 1.70 (1H, dt, *J*=8.4, 1.6 Hz, 4-C*H*H-7), 1.56 (1H, d, *J*=8.4 Hz, 4-CH*H*-7); δ_C (100 MHz, $CDCl_3$) 207.8 (s, C_1), 170.0 (2CH(O*CO*Me)Ph), 160.1 (d, C_3), 147.2 (s, C_2), 137.3 (2CH(OCOMe)CH_2*Ph*), 133.0 (d, $C_{5/6}$), 132.6 ($C_{6/5}$), 129.9 (2d, 2CH(OCOMe)CH_2*Ph*), 128.5, 126.9 (d, 2CH(OCOMe)*Ph*), 70.5 (2*C*H(OCOMe)CH_2Ph), 52.8 (t, 4-CH_2-7), 52.0 (d, $C_{3a/7a}$), 45.9 ($C_{4/7}$), 45.5 ($C_{7/4}$), 44.4 ($C_{7a/3a}$), 39.3 (t, 2CH(OAc)*C*H_2Ph), 21.3 (q, 2CH(OCO*Me*)CH_2Ph); *m/z* (CI/NH_3) 326 ([MH+NH_3]$^+$, 15.1%), 309 ([MH]$^+$, 48.8), 249 (100); (HRMS: found MH^+, 309.1491. $C_{20}H_{21}O_3^+$ requires 309.1491) as well as its elimination product (0.23 g, 48%) as white crystalline solid; R_f 0.54 (SiO_2, *n*-hexane/diethyl ether, 1:1); ν_{max} (film)/cm^{-1} 3061, 3028, 2978, 2940, 2869, 1748, 1697, 910, 734; δ_H (400 MHz, $CDCl_3$) 7.45–7.30 (2H, m, 2C*H*CH*Ph*), 7.29–7.16 (5H, m, H_3, 2CHCH*Ph*), 6.65 (1H, d, *J*=16.4 Hz, 2CHC*H*Ph), 5.94 (1H, dd, *J*=5.6, 3.0 Hz, $H_{5/6}$), 5.80 (1H, dd, *J*=5.6, 2.8 Hz, $H_{6/5}$), 3.33 (1H, m, $H_{3a/7a}$), 3.26 (1H, m, $H_{4/7}$), 2.98 (1H, m, $H_{7/4}$), 2.94 (1H, t, *J*=5.1 Hz, $H_{7a/3a}$), 1.76 (1H, dt, *J*=8.4, 1.7 Hz, 4-C*H*H-7), 1.62 (1H, d, *J*=8.4 Hz, 4-CH*H*-7); δ_C (100 MHz, $CDCl_3$) 208.7 (CO, C_1), 158.8 (CH, C_3), 144.0 (R_4C, C_2), 137.6 (2CHCH*Ph*), 133.1 (CH), 133.0, 128.9, 128.3, 127.0, 118.7 (2CH*C*HPh), 53.1 (R_2CH_2, 4-CH_2-7), 52.4 (R_3CH), 45.9 (2R_3CH), 45.1; *m/z* (CI/NH_3) 266 ([MH+NH_3]$^+$, 22.9%), 249 ([MH]$^+$, 100); (HRMS: found MH^+, 249.1275. $C_{18}H_{17}O^+$ requires 249.1279).

4.4. Alkylcuprate addition and acetate elimination representative procedure

4.4.1. (±)-2-(*E*)-Octylidene-3-methyl-2,3,3a,4,7,7a-hexahydro-4,7-methanoinden-1-one 18 and (±)-2-(1-methyloctyl)-3-methyl-2,3,3a,4,7,7a-hexahydro-4,7-methanoinden-1-one 25. 1.4 M Methyllithium in diethyl ether (3.3 equiv.) was added to a suspension of anhydrous copper (I) iodide (1.7 equiv.) in diethyl ether (1.6 cm^3) at −78 °C under nitrogen atmosphere. The reaction mixture was allowed to warm to −40 °C and stirred for 30 min. The alkylcuprate reagent was added dropwise to a stirring solution of acetate **12** (53 mg, 0.17 mmol) in anhydrous diethyl ether (0.17 cm^3) at −78 °C and the reaction allowed to warm to room temperature. After 12.5 h at room temperature, saturated aqueous NH_4Cl solution (0.75 cm^3) was added and the reaction mixture extracted with diethyl ether (3×0.75 cm^3). The combined organic layers were dried ($MgSO_4$) and the solvent removed in vacuo to afford crude product. Preparative thin layer chromatography (SiO_2) eluting with *n*-hexane/2-butanone (5:1) gave the methylated adduct **18** (15.8 mg, 34%) as a pale yellow transparent oil; R_f 0.56 (SiO_2, *n*-hexane/2-butanone, 4:1); δ_H (400 MHz, $CDCl_3$) 6.94 (1H, d, *J*=2.7 Hz, 2C*Hn*-hep), 5.87 (1H, dd, *J*=5.5, 2.7 Hz, $H_{5/6}$), 5.73 (1H, dd, *J*=5.5, 2.9 Hz, $H_{6/5}$), 3.25–3.22 (1H, m), 3.20 (1H, m), 2.92 (1H, m), 2.89 (1H, t, *J*=5.1 Hz), 2.38 (1H, m, H_3), 1.74–1.71 (1H, dt, *J*=8.3, 1.8 Hz, 4-C*H*H-7), 1.61–1.59 (1H, m, 4-CH*H*-7), 1.41–1.09 (12H, m, 2CH(CH_2)$_6$Me), 0.98 (3H, d, *J*=6.9 Hz, 3*Me*), 0.87 (3H, t, *J*=6.8 Hz, 2CH(CH_2)$_3$*Me*); δ_C (100 MHz, $CDCl_3$) 209.6 (s, C_1), 155.9 (d, 2*C*H *n*-hep), 154.7 (s, C_2), 132.5 (d, $C_{5/6}$), 132.4 ($C_{6/5}$), 52.6 (t, 4-CH_2-7), 51.1 (d), 49.0, 45.2, 44.2, 35.9 (t, 2CH(*C*H_2)$_6$Me), 31.9, 31.8, 29.6, 29.3, 27.1, 22.1, 19.6 (q, 3Me), 14.1 (2CH(CH_2)$_6$*Me*); *m/z* (CI/NH_3) 303 (0.5%), 290 ([MH+NH_3]$^+$, 0.9), 273 (MH^+, 100), 173 (26.4); (HRMS: found MH^+, 273.2224. $C_{19}H_{19}O^+$ requires 273.2218) and the bis-alkylated adduct **25** (13.9 mg, 28%) as a pale yellow transparent oil; R_f 0.66 (SiO_2, *n*-hexane/2-butanone, 4:1); δ_H (400 MHz, $CDCl_3$) 6.14 (1H, dd, *J*=5.6, 3.0 Hz, $H_{5/6}$), 6.04 (1H, dd, *J*=5.6, 3.0 Hz, $H_{6/5}$), 3.13 (1H, m), 3.03 (1H, m), 2.97–2.92 (1H, m), 2.48–2.43 (1H, m), 1.95 (1H, dt, *J*=11.8, 2.8 Hz), 1.67–1.55 (3H, m), 1.40 (1H, d, *J*=8.1 Hz), 1.29–1.20 (12H, m, 2CHMe(CH_2)$_6$Me), 1.17 (3H, d, *J*=6.6 Hz, 2CH*Men*-hep), 0.87 (3H, t, *J*=6.6 Hz, 2CHMe(CH_2)$_3$*Me*), 0.83 (3H, d, *J*=6.8 Hz, 3*Me*); δ_C

(100 MHz, $CDCl_3$) 218.3 (s, C_1), 137.1 (d, $C_{5/6}$), 135.7 ($C_{6/5}$), 65.1 (d), 55.1, 52.3 (t, 4-CH_2-7), 48.0 (d), 45.5, 44.7, 35.7, 34.5, 31.9 (t, 2CH(CH_2)$_6$Me), 31.6, 29.8, 29.4, 28.0, 22.7, 21.8 (q), 16.8, 14.1; *m/z* (CI/NH_3) 306 ([MH+NH_3]$^+$, 20.7%), 289 (MH^+, 6.3), 240 (37.6), 223 (100), 96 (20), 60 (15.5); (HRMS: found MH+NH_3^+, 306.2799. $C_{20}H_{36}NO^+$ requires 306.2797).

4.4.2. (±)-2-(2-(*E*)-Methylpropylidene)-3-methyl-2,3,3a,4,7,7a-hexahydro-4,7-methano-inden-1-one 16. (50.7 mg, 57%), a pale yellow transparent oil; R_f 0.50 (SiO_2, *n*-hexane/2-butanone, 4:1); δ_H (400 MHz, $CDCl_3$) 6.06 (1H, dd, *J*=10.5, 2.1 Hz, 2C*Hi*-prop), 5.95 (2H, m, H_5, H_6), 3.23 (1H, m), 3.06 (1H, m), 3.00 (1H, m), 2.52 (1H, m), 1.47 (1H, dt, *J*=8.3, 1.7 Hz, 4-C*H*H-7), 1.37 (1H, d, *J*=8.3 Hz, 4-CH*H*-7), 1.11 (3H, d, *J*=7.3 Hz, 3Me), 1.00 (3H, d, *J*=7.3 Hz, 2CHCH*Me*Me), 0.95 (3H, d, *J*=6.6 Hz, 2CHCHMe*Me*); δ_C (100 MHz, $CDCl_3$) 209.7 (s, C_1), 143.2 (C_2), 142.8 (d), 136.1, 133.0, 53.3 (d),51.4 (t, 4-CH_2-7), 47.4 (d), 47.1, 46.9, 35.0, 28.5, 23.4 (q, 3Me), 22.1 (2CHCH*Me*Me), 21.9 (2CHCHMe*Me*); *m/z* (CI/NH_3) 234 ([MH+NH_3]$^+$, 3.1%), 217 (MH^+, 16.8), 168 (23.7), 151 (100); (HRMS: found MH^+, 217.1595. $C_{15}H_{21}O^+$ requires 217.1592).

4.4.3. (±)-2-(2-(*E*)-Methylpropylidene)-3-butyl-2,3,3a,4,7,7a-hexahydro-4,7-methano-inden-1-one 17. (28.2 mg, 59%) as a transparent pale yellow oil; R_f 0.54 (SiO_2, *n*-hexane/2-butanone, 4:1); δ_H (400 MHz, $CDCl_3$) 6.07 (1H, dd, *J*=10.7, 2.1 Hz, 2C*Hi*-prop), 5.95 (2H, m, H_5, H_6), 3.23 (1H, m), 3.00 (1H, m), 2.96 (1H, m), 2.51 (1H, m), 2.43–2.34 (2H, m), 1.41–1.31 (8H, m, 4-CH_2-7 and 3(CH_2)$_3$Me), 1.00 (3H, d, *J*=6.6 Hz, 2CH(OH)CH*Me*Me), 0.95 (3H, d, *J*=6.5 Hz, 2CH(OH)CHMe*Me*), 0.90 (3H, t, *J*=6.6 Hz, 3(CH_2)$_3$*Me*); δ_C (100 MHz, $CDCl_3$) 210.4 (s, C_1), 143.3 (d, 2*C*H *i*-prop), 142.5 (s, C_2), 136.3 (d, $C_{5/6}$), 133.8 ($C_{6/5}$), 54.2, 51.9 (t, 4-CH_2-7), 47.9 (d), 44.6, 40.8, 37.4 (t), 29.4, 29.0 (d), 23.3 (t), 22.3 (2q, 2CH*Me*$_2$), 14.5 (q, 3(CH_2)$_3$*Me*); *m/z* (CI/NH_3) 278 (3.6%), 259 (MH^+, 11.3), 210 (25.2), 193 (100); (HRMS: found MH^+, 259.2060. $C_{18}H_{27}O^+$ requires 259.2062).

4.5. Alkyl cyanocuprate addition and elimination representative procedure

4.5.1. (±)-2-(*E*)-Octylidene-3-butyl-2,3,3a,4,7,7a-hexahydro-4,7-methano-inden-1-one 19 and (±)-2-(1-butyl-octyl)-3-butyl-2,3,3a,4,7,7a-hexahydro-4,7-methano-inden-1-one 26. 2.5 M *n*-Butyllithium in diethyl ether (1.2 equiv.) was added to a suspension of anhydrous copper (I) cyanide (1.2 equiv.) in diethyl ether (3.1 cm^3) at −78 °C under nitrogen atmosphere. The reaction mixture was allowed to warm to −40 °C and stirred for 40 min. The alkyl cyanocuprate reagent was added dropwise to a stirring solution of acetate **12** (0.5 g, 1.58 mmol) in anhydrous diethyl ether (1.6 cm^3) at −78 °C. After 45 min at this temperature, saturated aqueous NH_4Cl solution (2.5 cm^3) was added and the reaction mixture extracted with diethyl ether (3×4 cm^3). The combined organic layers were dried ($MgSO_4$) and the solvent removed in vacuo to afford a yellow opalescent oil. Purification by flash column chromatography (SiO_2), eluting with *n*-hexane/diethyl ether (9:1 and 4:1), gave an inseparable mixture (9:1) of the 3-butylated adduct **19** and its *exo*-butylated regioisomer **27** (0.21 g, 42%) as a transparent pale yellow oil; R_f 0.43 (SiO_2, *n*-hexane/diethyl ether, 4:1); ν_{max} (film)/cm^{-1} 2958, 2927, 2857, 1712, 1639; δ_H (400 MHz, $CDCl_3$) 6.31 (1H, m, 2C*Hn*-hep), 5.98 (2H, m, H_5, H_6), 3.26 (1H, m), 3.04 (1H, m), 2.99 (1H, m), 2.55 (1H, m), 2.43 (1H, m), 2.08 (2H, m), 1.51 (1H, m, 4-C*H*H-7), 1.43 (1H, d, *J*=8.1 Hz, 4-CH*H*-7), 1.39–1.25 (15H, m, 2CH(CH_2)$_6$Me, 3(CH_2)$_3$Me), 0.95–0.89 (6H, m, 2CH(CH_2)$_6$*Me*, 3(CH_2)$_3$*Me*); δ_C (100 MHz, $CDCl_3$) 209.8 (s, C_1), 143.9 (C_2), 137.6 (d, 2*C*H *n*-hep), 136.2 ($C_{5/6}$), 133.9 ($C_{6/5}$), 54.2, 51.9 (t, 4-*C*H_2-7), 47.9 (d), 47.8, 44.6, 40.8, 36.8 (t), 32.2, 29.8, 29.7, 29.5, 29.4, 29.0, 23.3, 23.0, 14.5 (q, 2CH(CH)$_6$*Me*), 14.5 (3(CH_2)$_3$*Me*); *m/z* (CI/NH_3) 315 (MH^+, 19.4%), 249 (100); (HRMS: found MH^+, 315.2681. $C_{22}H_{35}O^+$ requires 315.2688) as well as the bis-alkylated adduct **26** (38.3 mg, 7%) as a transparent pale yellow oil; R_f 0.59 (SiO_2, *n*-hexane/diethyl ether, 4:1); ν_{max} (film)/cm^{-1} 2924, 2854, 1733, 1466, 1229, 731; δ_H (400 MHz, $CDCl_3$) 6.13 (1H, dd, *J*=5.5, 2.9 Hz, $H_{5/6}$), 6.04 (1H, dd, *J*=5.5, 2.9 Hz, $H_{6/5}$), 3.13 (1H, m), 2.99 (1H, m), 2.97–2.92 (1H, m), 2.54–2.49 (1H, m), 2.15 (1H, dt, *J*=11.8, 2.4 Hz), 1.67–1.61 (1H, m), 1.59–1.50 (3H, m), 1.45–1.09 (24H, m), 0.95 (3H, t, *J*=6.8 Hz), 0.89 (6H, m); δ_C (75.5 MHz, $CDCl_3$) 218.9 (s, C_1), 137.3 (d, $C_{5/6}$), 135.8 ($C_{6/5}$), 61.0, 55.1, 52.59 (t, 4-CH_2-7), 47.4 (d), 46.2, 44.5, 40.5, 36.9, 36.65 (t), 32.2, 31.8, 31.5, 30.5, 29.9, 29.8, 29.2, 28.1, 22.8, 22.7, 14.0 (q), 13.9, 13.89; *m/z* (CI/NH_3) 390 (MH+NH_3^+, 18.2%), 373 (MH^+, 14.2), 324 (21.0), 138 (26.2); (HRMS: found MH^+, 373.3462. $C_{26}H_{45}O^+$ requires 373.3470).

4.5.2. (±)-2-(*E*)-Cyclopropylmethylene-3-methyl-2,3,3a,4,7,7a-hexahydro-4,7-methano-inden-1-one 20 and 2-(1-cyclopropyl-ethyl)-3a,4,7,7a-tetrahydro-4,7-methano-inden-1-one 28. Methylated enone **20** (0.25 g, 61%), a pale yellow transparent oil; R_f 0.36 (SiO_2, *n*-hexane/Et_2O, 2:1); δ_H (400 MHz, $CDCl_3$) 6.02 (1H, dd, *J*=5.7, 3.0 Hz, H_6), 5.96 (1H, dd, *J*=5.7, 2.9 Hz, H_5), 5.71 (1H, dd, *J*=11.0, 2.2 Hz, 2C*H* cycloprop), 3.23 (1H, m, H_4), 3.08 (1H, m, H_7), 3.01 (1H, m, H_{3a}), 2.61 (1H, m, H_3), 2.43 (1H, m, H_{7a}), 1.48 (1H, dt, *J*=8.3, 1.8 Hz, 4-C*H*H-7), 1.44–1.36 (2H, m, 4-CH*H*-7, 2CH *cycloprop*), 1.20 (3H, d, *J*=7.3 Hz, 3*Me*), 0.99–0.90 (2H, m, 2CH *cycloprop*), 0.63–0.58 (2H, m, 2CH *cycloprop*); δ_C (100 MHz, $CDCl_3$) 208.1 (s, C_1), 143.6 (C_2), 142.3 (d, 2*C*H cycloprop), 136.0 (C_5), 133.5 (C_6), 53.8 (d, C_{3a}), 51.4 (t, 4-CH_2-7), 47.2 (d, C_4), 46.9 (C_7), 46.9 (C_{7a}), 35.2 (C_3), 22.3 (q, 3*Me*), 12.3 (d, 2CH *cycloprop*), 9.5 (t, 2CH *cycloprop*), 8.8 (2CH *cycloprop*); *m/z* (CI/NH_3) 429 (2.4%), 363 (4.7), 232 ([MH+NH_3]$^+$, 1.3), 215 (MH^+, 34.6), 149 (100); (HRMS: found MH^+, 215.1441. $C_{15}H_{19}O_3^+$ requires 215.1436); and its regioisomer **28** (77.3 mg, 19%) as a pale yellow transparent oil; R_f 0.49 (SiO_2, *n*-hexane/diethyl ether, 2:1); ν_{max} (film)/cm^{-1} 3062, 2962, 2931, 2870, 1698, 1621; δ_H (400 MHz, $CDCl_3$) 7.04 (1H, d, *J*=2.6 Hz, H_3), 5.84 (1H, dd, *J*=5.5, 2.9 Hz, $H_{5/6}$), 5.72 (1H, dd, *J*=5.5, 2.9 Hz, $H_{6/5}$), 3.23 (1H, m), 3.18 (1H, m), 2.90 (1H, m), 2.79 (1H, t, *J*=5.1 Hz), 1.71 (1H, d, *J*=8.4 Hz, 4-C*H*H-7), 1.58 (1H, d, *J*=8.4 Hz, 4-CH*H*-7), 1.05 (3H, d, *J*=7.0 Hz, 2CHCH*Me* cycloprop), 0.66 (1H, m, 2CHCHMe *cycloprop*), 0.39 (1H, m), 0.20 (1H, m), 0.03-(-0.02) (2H, m); *m/z* (CI/NH_3) 232 ([MH+NH_3]$^+$, 0.6%), 215 (MH^+, 100); (HRMS: found MH^+, 215.1441. $C_{15}H_{19}O^+$ requires 215.1436).

4.6. Alkyl cuprate addition/aldol condensation/dehydration representative procedure

4.6.1. (+)-2-(*E*)-Isobutylidene)-3(*S*)-methyl-2,3,3a,4,7,7a-hexahydro-4,7-methanoinden-1-one (+)-16. 1.6 M Methyl lithium in diethyl ether (2.4 equiv.) was added to a stirring suspension of copper (I) iodide (1.2 equiv.) in anhydrous diethyl ether (6 cm^3) at −78 °C under nitrogen stream. After 3.0 h stirring at this temperature, a solution of (+)-enone (+)-**5** (0.2 g, 0.37 mmol) in diethyl ether (3 cm^3) was added dropwise over 5 min at −78 °C and stirred for 1.5 h. Whereupon, a solution of freshly distilled isobutyraldehyde (3.0 equiv.) was added, the reaction mixture stirred at −78 °C for 2 h and then allowed to warm to 0 °C overnight. The reaction was quenched with saturated aqueous NH_4Cl (9 cm^3), aqueous ammonia (2–3 drops) added and the reaction mixture extracted with diethyl ether (3×15 cm^3). The combined organic layers were washed with saturated aqueous NaCl (3×7 cm^3), dried ($MgSO_4$) and the solvent removed in vacuo to afford crude enone as a dark green transparent oil. Purification using flash column chromatography (SiO_2), eluting with *n*-hexane/acetone, (38:1) afforded the (+)-**16** (0.23 g, 76%) as a transparent pale yellow oil; R_f 0.50 (SiO_2, *n*-hexane/acetone, 4:1); $[\alpha]_D^{24}$ 2.89 (*c* 2.27 $CHCl_3$); δ_H (400 MHz, CD_2Cl_2) 5.91 (1H, d, *J*=2.1 Hz, 2C*Hi*-prop), 5.88 (1H, m, H_6), 5.81 (1H, dd, *J*=5.7, 2.9 Hz, H_5), 3.08 (1H, m, H_4), 2.97 (1H, br. s, H_7), 2.87 (1H, dd, *J*=8.8, 4.8 Hz, H_{3a}), 2.47–2.41 (1H, m, H_3), 2.39–2.29 (2H, m, H_{7a}, 2CHC*H*Me_2), 1.36 (1H, dt, *J*=8.1, 1.8 Hz, 4-C*H*H-7), 1.29 (1H, d, *J*=8.1, 1.4 Hz, 4-CH*H*-7), 1.02 (3H, d, *J*=7.2 Hz, 3Me), 0.91 (3H, d, *J*=6.7 Hz, 2CHCH*Me*Me), 0.87 (3H, d, *J*=6.5 Hz, 2CHCHMe*Me*); δ_C (100 MHz, CD_2Cl_2) 209.5 (s, C_1), 144.2 (C_2), 142.9 (d, 2*C*H *i*-prop), 136.6 (C_5), 134.2 (C_6), 54.2 (C_{3a}), 52.0 (t, 4-CH_2-7), 48.1 (d, C_4), 47.9 (C_7), 47.6 (2CH*C*HMe$_2$), 35.7 (C_3), 29.1 (C_{7a}), 23.9 (q, 3Me), 22.6 (2CHCH*Me*Me), 22.4 (2CHCHMe*Me*); *m/z* (CI/NH_3) 234 ($[MH+NH_3]^+$, 2.6%), 217 (MH^+, 8.9), 168 ($[MH+NH_3-C_5H_6]^+$, 15.3), 151 ($[MH-C_5H_6]^+$, 100.0), 66 (C_5H_6, 5.8); (HRMS: found MH^+, 217.1592. $C_{15}H_{21}O^+$ requires 217.1597).

4.6.2. (−)-2-(*E*)-Isobutylidene)-3(*R*)-methyl-2,3,3a,4,7,7a-hexahydro-4,7-methanoinden-1-one (−)-16. (0.14 g, 60%), a transparent pale brown oil; R_f 0.55 (SiO_2, *n*-hexane/acetone, 4:1); $[\alpha]_D^{22}=-3.13$ (*c* 6.90 $CHCl_3$); δ_H (400 MHz, CD_2Cl_2) 6.03 (1H, d, *J*=2.1 Hz, 2C*Hi*-prop), 6.00 (1H, m, H_6), 5.93 (1H, dd, *J*=5.6, 2.8 Hz, H_5), 3.20 (1H, m, H_4), 3.08 (1H, m, H_7), 2.98 (1H, dd, *J*=8.6, 4.8 Hz, H_{3a}), 2.55 (1H, m, H_3), 2.51–2.40 (2H, m, H_{7a}, 2CHC*H*Me_2), 1.47 (1H, dt, *J*=8.2, 1.6 Hz, 4-C*H*H-7), 1.40 (1H, d, *J*=8.2 Hz, 4-CH*H*-7), 1.14 (3H, d, *J*=7.3 Hz, 3Me), 1.03 (3H, d, *J*=6.7 Hz, 2CHCH*Me*Me), 0.95 (3H, d, *J*=6.7 Hz, 2CHCHMe*Me*); δ_C (100 MHz, CD_2Cl_2) 209.5 (s, C_1), 144.2 (C_2), 142.8 (d, 2*C*H *i*-prop), 136.6 (C_5), 134.2 (C_6), 54.2 (C_{3a}), 52.0 (t, 4-CH_2-7), 48.1 (d, C_4), 47.9 (C_7), 47.6 (2CH*C*HMe$_2$), 35.7 (C_3), 29.1 (C_{7a}), 23.9 (q, 3Me), 22.6 (2CHCH*Me*Me), 22.4 (2CHCHMe*Me*); *m/z* (CI/NH_3) 234 ($[MH+NH_3]^+$, 1.0%), 217 (MH^+, 5.4), 168 ($[MH+NH_3-C_5H_6]^+$, 6.7), 151 ($[MH-C_5H_6]^+$, 100), 91 (6.7), 66 (C_5H_6, 13.7); (HRMS: found MH^+, 217.1602. $C_{15}H_{21}O^+$ requires 217.1592).

4.6.3. (+)-2-(*E*)-Isobutylidene-3(*S*)-octyl-2,3,3a,4,7,7a-hexahydro-4,7-methano-inden-1-one (+)-21. (0.26 g, 61%) as a very pale yellow transparent oil; R_f 0.38 (SiO_2, *n*-hexane/ethyl acetate, 9:1); $[\alpha]_D^{21}$ 2.39 (*c* 8.49 $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 6.07 (1H, dd, *J*=10.7, 2.1 Hz, 2C*Hi*-prop), 5.97 (1H, d, *J*=5.6, 3.0 Hz, $H_{5/6}$), 5.93 (1H, dd, *J*=5.6, 2.9 Hz, $H_{6/5}$), 3.32 (1H, m, $H_{4/7}$), 3.01 (1H, br. s, $H_{7/4}$), 2.96 (1H, dd, *J*=8.7, 4.8 Hz, $H_{3a/7a}$), 2.51 (1H, ddd, *J*=8.7, 4.1, 1.4 Hz, $H_{7a/3a}$), 2.43–2.36 (2H, m, H_3, 2CHC*H*Me_2), 1.47 (1H, d, *J*=8.2 Hz, 4-C*H*H-7), 1.40 (1H, d, *J*=8.2 Hz, 4-CH*H*-7), 1.37–1.27 (14H, m, 3(CH_2)$_7$Me), 1.00 (3H, d, *J*=6.6 Hz, 2CHCH*Me*Me), 0.96 (3H, d, *J*=6.6 Hz, 2CHCHMe*Me*), 0.88 (3H, t, *J*=6.7 Hz, 3(CH_2)$_7$*Me*); δ_C (100 MHz, CD_2Cl_2) 210.5 (s, C_1), 143.3 (d, 2*C*H *i*-prop), 142.5 (s, C_2), 136.3 (d, C_6), 133.8 (C_5), 54.2 (C_{7a}), 51.9 (t, 4-CH_2-7), 47.9 (2d, C_4, C_7), 44.6 (C_{3a}), 40.8 (C_3), 37.7 (t, 3(*C*H_2)$_7$Me), 32.3, 30.2, 29.6, 29.7, 29.0 (d, 2CH*C*HMe$_2$), 27.2 (t, 3(CH_2)$_7$Me), 23.0, 22.3 (2q, 2CHCH*Me*$_2$), 14.5 (q, 3(CH_2)$_7$*Me*); *m/z* (CI/NH_3) 332 ($[MH+NH_3]^+$, 0.5%), 315 (MH^+, 4.0), 287 (0.3), 266 (4.1), 249 ($[MH+NH_3-C_5H_6]^+$, 100), 150 (4.0), 66 (C_5H_6, 3.7); (HRMS: found MH^+, 315.2689. $C_{22}H_{35}O^+$ requires 315.2688).

4.6.4. (−)-2-(*E*)-Isobutylidene)-3(*R*)-octyl-2,3,3a,4,7,7a-hexahydro-4,7-methanoinden-1-one (−)-21. (0.23 g, 54%), a very pale yellow transparent oil; R_f 0.38 (SiO_2, *n*-hexane/ethyl acetate, 9:1); $[\alpha]_D^{27}$ −2.27 (*c* 8.34 $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 6.06 (1H, dd, *J*=10.6, 2.0 Hz, 2C*Hi*-prop), 5.96 (1H, d, *J*=5.6, 3.0 Hz, $H_{5/6}$), 5.93 (1H, dd, *J*=5.6, 2.8 Hz, $H_{6/5}$), 3.22 (1H, m, $H_{4/7}$), 3.00 (1H, m, $H_{7/4}$), 2.95 (1H, dd, *J*=8.7, 4.8 Hz, $H_{3a/7a}$), 2.50 (1H, ddd, *J*=8.7, 4.1, 1.8 Hz, $H_{7a/3a}$), 2.43–2.34 (2H, m, H_3, 2CHC*H*Me_2), 1.48 (1H, dt, *J*=8.3, 1.6 Hz, 4-C*H*H-7), 1.39 (1H, m, 4-CH*H*-7), 1.43–1.21 (14H, m, 3(*C*H_2)$_7$Me), 1.00 (3H, d, *J*=6.5 Hz, 2CHCH*Me*Me), 0.96 (3H, d, *J*=6.7 Hz, 2CHCHMe*Me*), 0.88 (3H, t, *J*=6.7 Hz, 3(CH_2)$_7$*Me*); δ_C (100 MHz, $CDCl_3$) 210.3 (s, C_1), 143.3 (d, 2*C*H *i*-prop), 142.5 (s, C_2), 136.3 (d, C_6), 133.7 (C_5), 54.2 (C_{7a}), 51.8 (t, 4-CH_2-7), 47.9 (d, C_4), 47.8 (C_7), 44.7 (C_{3a}), 40.8 (C_3), 37.7 (t, 3(*C*H_2)$_7$Me), 32.3, 30.2, 29.9, 26.6, 29.0 (d, 2CH*C*HMe$_2$), 27.1 (t, 3(*C*H_2)$_7$Me), 23.0, 22.30 (q, 2CHCH*Me*Me), 22.98 (2CHCHMe*Me*), 14.3 (q, 3(CH_2)$_7$*Me*); *m/z* (CI/NH_3) 315 (MH^+, 3.9%), 266 ($[MH+NH_3-C_5H_6]^+$, 4.8), 249 ($[MH-C_5H_6]^+$, 100), 163 (7.4), 150 (10), 135 (7.4), 121 (3.5), 107 (5.7), 91 (7.1), 66 (C_5H_6, 15.8); (HRMS: found MH^+, 315.2692. $C_{22}H_{35}O^+$ requires 315.2688).

4.6.5. (+)-2-(*E*)-Benzylidene-3(*S*)-methyl-2,3,3a,4,7,7a-hexahydro-4,7-methanoinden-1-one (+)-(22) and (+)-7a(*S*)-(1,3-bisphenyl-3-oxo-propyl)-2-(*E*)-benzylidene-3(*S*)-methyl-2,3,3a,4,7,7a-hexahydro-4,7-methano-inden-1-one (+)-30. Methylated enone (+)-**22** (0.22 g, 64%), a pale yellow crystalline solid; R_f 0.43 (SiO_2, *n*-hexane:diethyl ether, 2:1); δ_H (400 MHz, $CDCl_3$) 7.50 (2H, d, *J*=7.3 Hz, 2CH*Ph*), 7.38–7.29 (3H, m, 2CH*Ph*), 7.07 (1H, d, *J*=1.9 Hz, 2C*H*Ph), 5.98 (2H, m, H_5, H_6), 3.30 (1H, m, H_4), 3.11 (1H, m, H_7), 3.08–3.02 (2H, m, H_3, H_{3a}), 2.56 (1H, ddd, *J*=8.7, 4.1, 1.3 Hz, H_{7a}), 1.50 (1H, m, 4-C*H*H-7), 1.42 (1H, d, *J*=8.2 Hz, 4-CH*H*-7), 1.18 (3H, d, *J*=7.1 Hz, 3*Me*); δ_C (100 MHz, $CDCl_3$) 210.3 (s, C_1), 144.8 (2CH*Ph*), 136.7 (d, $C_{5/6}$), 135.4 (s, C_2), 133.8 (d, $C_{6/5}$),

132.7 (2C*H*Ph), 130.8 (2CH*Ph*), 129.5 (2CH*Ph*), 129.1 (2CH*Ph*), 52.9 (C_{3a}), 51.8 (t, 4-CH_2-7), 48.0 (d, C_4), 47.5 ($C_{7/7a}$), 47.5 ($C_{7a/7}$), 36.64 (C_3), 21.2 (q, 3Me); *m/z* (CI/NH_3) 502 (3.0%), 435 (4.2), 268 ($[MH+NH_3]^+$, 2.4), 251 (MH^+, 36.1), 222 (5.6), 202 ($[MH+NH_3-C_5H_6]^+$, 6.1), 185($[MH-C_5H_6]^+$, 100), 156 (7.9), 141 (4.3), 115 (3.2), 91 (4.1), 66 (C_5H_6, 4.3); (HRMS: found MH^+, 251.1434. $C_{18}H_{19}O^+$ requires 251.1436), and the 7a(*S*)-alkylated by-product, (+)-**30** (108 mg, 15%) as a transparent pale yellow oil; R_f 0.18 (SiO_2, *n*-hexane/acetone, 9:1); δ_H (400 MHz, $CDCl_3$) 7.84 (2H, d, *J*=7.2 Hz, 2CH*Ph*), 7.51 (2H, m, 1′/3′*Ph*), 7.43–7.48 (3H, m, 1′/3′*Ph*), 7.30–7.39 (4H, m, 1′/3′*Ph*), 7.25 (2H, m, 1′/3′*Ph*), 7.16 (2H, m, 2C*H*Ph, 1′/3′*Ph*), 6.07 (1H, dd, *J*=5.6, 2.7 Hz, H_6), 5.97 (1H, dd, *J*=5.6, 3.0 Hz, H_5), 3.91 (1H, dd, *J*=10.3, 3.2 Hz, $H_{1'}$), 3.79 (1H, dd, *J*=10.5, 4.9 Hz, 1′C*H*HCOPh), 3.54 (1H, dd, *J*=16.7, 3.3 Hz, 1′CH*H*COPh), 3.03 (1H, br. s, H_4), 3.00 (1H, m, H_3), 2.91 (1H, br. s, H_7), 2.44 (1H, dd, *J*=3.8, 1.0 Hz, H_{3a}), 1.61 (1H, d, *J*=8.6 Hz, 4-C*H*H-7), 1.36 (1H, d, *J*=8.6 Hz, 4-CH*H*-7), 1.16 (3H, d, *J*=7.2 Hz, 3*Me*); δ_C (100 MHz, $CDCl_3$) 211.0 (s, C_1), 198.8 ($C_{3'}$), 145.1 (2CH*Ph*), 141.8 (3′CO*Ph*), 138.6 (d, C_5), 137.7 (s, 1′*Ph*), 135.9 (d, C_6), 135.4 (s, C_2), 133.7 (d, 2*C*HPh), 133.2 (1′/3′*Ph*), 131.0 (2d, 2CH*Ph*), 130.4 (d, 1′/3′*Ph*), 129.7 (2CH*Ph*), 129.1 (2d, 2CH*Ph*), 128.9 (1′/3′*Ph*), 128.5, 128.4, 127.1 (d, 1′/3′*Ph*), 64.9 (s, C_{7a}), 54.6 (d, C_{3a}), 51.2 (C_7), 4.3 (t, 4-CH_2-7), 48.5 (d, C_4), 47.4 ($C_{1'}$), 41.4 (t, $C_{2'}$), 36.4 (d, C_3), 20.6 (q, 3Me); *m/z* (ES^+) 939 ($[2M+Na]^+$, 57.8%), 518 (10.2), 481 ($[M+Na]^+$, 100), 415 (9.6); (HRMS: found $M+Na^+$, 481.216. $C_{33}H_{30}O_2Na^+$ requires 481.2144).

4.6.6. (−)-2-(*E*)-Benzylidene-3(*R*)-methyl-2,3,3a,4,7,7a-hexahydro-4,7-methanoinden-1-one (−)-22. (0.13 g, 75%) as a transparent pale yellow oil; R_f 0.51 (SiO_2, *n*-hexane/Et_2O, 2:1); δ_H (400 MHz, $CDCl_3$) 7.51 (2H, d, *J*=7.2 Hz, 2CH*Ph*), 7.40–7.30 (3H, m, 2CH*Ph*), 7.08 (1H, d, *J*=2.1 Hz, 2C*H*Ph), 5.99 (2H, m, H_5, H_6), 3.30 (1H, m, H_4), 3.13 (1H, m, H_7), 3.08 (1H, dd, *J*=8.6, 4.8 Hz, H_{3a}), 3.06 (1H, m, H_3), 2.57 (1H, ddd, *J*=8.6, 4.0, 1.3 Hz, H_{7a}), 1.51 (1H, dt, *J*=8.2, 1.6 Hz, 4-C*H*H-7), 1.43 (1H, d, *J*=8.2 Hz, 4-CH*H*-7), 1.18 (3H, d, *J*=7.3 Hz, 3*Me*); δ_C (100 MHz, $CDCl_3$) 210.6 (s, C_1), 144.7 (2CH*Ph*), 136.7 (d, $C_{5/6}$), 135.4 (s, C_2), 133.8 (d, $C_{6/5}$), 132.7 (2C*H*Ph), 130.9 (2CH*Ph*), 129.6 (2CH*Ph*), 129.1 (2CH*Ph*), 52.9 (C_{3a}), 51.8 (t, 4-CH_2-7), 48.0 (d, C_4), 47.5 ($C_{7/7a}$), 47.5 ($C_{7a/7}$), 36.7 (C_3), 21.2 (q, 3Me); *m/z* (EI) 250 (M^+, 53.2%), 222 (8.6), 185 (88.5), 183 (100), 165 (16.3), 156 (33.6), 147 (37.9), 129 (25.5), 128 (32.3), 115 (57.5), 91 ($[M-PhCH_2]^+$, 47.2), 66 (92.8); (HRMS: found M^+, 250.1360. $C_{18}H_{19}O^+$ requires 250.1358).

4.6.7. (+)-2-(*E*)-Benzylidene-3(*S*)-octyl-2,3,3a,4,7,7a-hexahydro-4,7-methano-inden-1-one (+)-23. (0.27 g, 57%) as a transparent yellow oil; R_f 0.36 (SiO_2, *n*-hexane/ethyl acetate, 9:1); $[\alpha]_D^{22}$ 1.13 (*c* 8.33 $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.48 (2H, dd, *J*=7.3, 1.4 Hz, 2CH*Ph*), 7.39–7.30 (3H, m, 2CH*Ph*), 7.09 (1H, d, *J*=2.1 Hz, 2C*H*Ph), 5.98 (2H, m, H_5, H_6), 3.30 (1H, m, H_7), 3.07 (1H, m, H_4), 3.03 (1H, dd, *J*=8.6, 4.8 Hz, H_{7a}), 2.89 (1H, d, *J*=8.1 Hz, H_3), 2.67 (1H, ddd, *J*=8.1, 4.0, 1.3 Hz, H_{3a}), 1.52 (1H, m, 4-C*H*H-7), 1.47 (1H, m, 4-CH*H*-7), 1.50–1.24 (12H, m, 3(CH_2)$_7$Me), 0.87 (3H, t, *J*=6.8 Hz, 3(CH_2)$_7$*Me*); δ_C (100 MHz, $CDCl_3$) 210.6 (s, C_1), 143.9 (C_2), 136.6 (d, C_6), 135.6 (s, 2CH*Ph*), 133.9 (d, C_5), 132.8 (2*C*HPh), 130.8 (2d, 2CH*Ph*), 129.50 (d, 2CH*Ph*), 129.0 (2d, 2CH*Ph*), 53.4 (C_{7a}), 51.9 (t, 4-CH_2-7), 48.1 (d, C_7), 48.0 (C_4), 45.0 (C_{3a}), 42.3 (C_3), 34.8 (t, 3(*C*H_2)$_7$Me), 32.2, 30.0, 29.9, 29.6, 27.6, 23.0, 14.5 (q, 3(CH_2)$_7$*Me*); *m/z* (CI/NH_3) 349 (MH^+, 9.7%), 320 (1.3), 283 ($[MH-C_5H_6]^+$, 48.9), 169 (4.1), 141 (10.4), 128 (3.3), 115 (9.8), 91 (11.1), 66 (C_5H_6, 100), 55 (5.5); (HRMS: found MH^+, 349.25394. $C_{25}H_{33}O^+$ requires 349.25314).

4.6.8. (−)-2-(*E*)-Benzylidene-3(*R*)-octyl-2,3,3a,4,7,7a-hexahydro-4,7-methano-inden-1-one (−)-23. (0.40 g, 83%) as a transparent pale yellow oil; R_f 0.31 (SiO_2, *n*-hexane/ethyl acetate, 9:1); $[\alpha]_D^{24}$ −0.87 (*c* 12.09 $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.48 (2H, dd, *J*=8.6, 1.5 Hz, 2CH*Ph*), 7.39–7.32 (3H, m, 2CH*Ph*), 7.09 (1H, d, *J*=2.2 Hz, 2C*H*Ph), 5.99 (2H, m, H_5, H_6), 3.30 (1H, m, H_7), 3.07–3.06 (1H, m, H_4), 3.03 (1H, dd, *J*=8.7, 4.8 Hz, H_{7a}), 2.90 (1H, d, *J*=8.1 Hz, H_3), 2.67 (1H, ddd, *J*=8.1, 4.0, 1.3 Hz, H_{3a}), 1.62–1.18 (12H, m, 3(CH_2)$_7$Me), 1.52 (1H, m, 4-C*H*H-7), 1.47 (1H, m, 4-CH*H*-7), 0.88 (3H, t, *J*=6.7 Hz, 3(CH_2)$_7$*Me*); δ_C (100 MHz, $CDCl_3$) 210.5 (s, C_1), 143.9 (C_2), 136.6 (d, C_6), 135.6 (s, 2CH*Ph*), 133.9 (d, C_5), 132.8 (2*C*HPh), 130.8 (2d, 2CH*Ph*), 129.50 (d, 2CH*Ph*), 129.0 (2d, 2CH*Ph*), 53.4 (C_{7a}), 51.9 (t, 4-CH_2-7), 48.1 (d, C_7), 48.0 (C_4), 45.1 (C_{3a}), 42.3 (C_3), 34.8 (t, 3(*C*H_2)$_7$Me), 32.2, 30.0, 29.9, 29.6, 27.6, 23.0, 14.5 (q, 3(CH_2)$_7$*Me*); *m/z* (CI/NH_3) 349 (MH^+, 11.4%), 320 (2.9), 300 (9.3), 284 ($[MH-C_5H_6]^+$, 70.9), 169 (16.9), 155 (10.8), 141 (22.9), 115 (12.8), 91 (12.6), 66 (C_5H_6, 16.3); (HRMS: found MH^+, 349.25362. $C_{25}H_{33}O^+$ requires 349.25314).

4.6.9. (±)-2-(4-(*E*)-Fluorobenzylidene)-3(*R*/*S*)-methyl-2,3,3a,4,7,7a-hexahydro-4,7-methanoinden-1-one (±)-24. (0.15 g, 83%), a pale yellow crystalline solid; R_f 0.47 (SiO_2, *n*-hexane/Et_2O, 2:1); δ_H (400 MHz, CD_2Cl_2) 7.42 (2H, m, 2CH*Ph*·*p*-F), 6.99 (2H, m, 2CH*Ph*·*p*-F), 6.89 (1H, d, *J*=2.1 Hz, 2C*H*Ph·*p*-F), 5.89 (1H, dd, *J*=5.6, 2.8 Hz, H_6), 5.85 (1H, dd, *J*=5.6, 2.7 Hz, H_5), 3.15 (1H, m, H_4), 3.02 (1H, m, H_7), 2.94 (1H, m, H_{3a}), 2.90 (1H, dd, *J*=14.3, 7.1 Hz, H_3), 2.47 (1H, ddd, *J*=8.6, 4.0, 1.4 Hz, H_{7a}), 1.39 (1H, m, 4-C*H*H-7), 1.34 (1H, m, 4-CH*H*-7), 1.07 (3H, d, *J*=7.1 Hz, 3*Me*); δ_C (100 MHz, CD_2Cl_2) 209.9 (s, C_1), 163.7 (sd, $J_{C,F}$=249.0 Hz, 2CH*Ph*·*p*-F), 145.1 (sd, $J_{C,F}$=2.3 Hz, C_2), 136.9 (d, C_5), 134.2 (C_6), 133.1 (dd, $J_{C,F}$=8.3 Hz, 2CH*Ph*·*p*-F), 132.2 (sd, $J_{C,F}$=3.2 Hz, 2CH*Ph*·*p*-F), 131.2 (d, 2*C*HPh·*p*-F), 116.4 (dd, $J_{C,F}$=21.7 Hz, 2CH*Ph*·*p*-F), 53.2 (C_{3a}), 52.6 (t, 4-CH_2-7), 48.4 (d, C_4), 48.0 (C_7), 47.9 (C_{7a}), 36.8 (C_3), 21.2 (q, 3Me); *m/z* (CI/NH_4) 286 ($[MH+NH_4]^+$, 1.5%), 269 (MH^+, 31.2), 240 (3.9), 220 (7.7), 203 ($[MH-C_5H_6]^+$, 100); (HRMS: found MH^+, 269.1333. $C_{18}H_{18}OF^+$ requires 269.1342).

4.6.10. (+)-2-(4-(*E*)-Fluorobenzylidene)-3(*S*)-methyl-2,3,3a,4,7,7a-hexahydro-4,7-methanoinden-1-one (+)-24 and (+)-7a(*S*)-[1,3-bis-(4-fluoro-phenyl)-3-oxo-propyl]-2-(4-(*E*)-fluorobenzylidene)-3(*S*)-methyl-2,3,3a,4,7,7a-hexahydro-4,7-methano-inden-1-one (+)-31. Methylated enone (+)-**24** (0.20 g, 55%) as a transparent pale yellow oil; R_f 0.29 (SiO_2, *n*-hexane/acetone, 9:1); $[\alpha]_D^{20}$ 0.89 (*c* 8.50, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.49 (2H, m, 2CH*Ph*·*p*-F), 7.06 (2H, m, 2CH*Ph*·*p*-F), 7.03 (1H, d, *J*=2.0 Hz, 2C*H*Ph·*p*-F), 5.99 (2H, m, H_6, H_5), 3.30 (1H, m, H_4), 3.12 (1H, m, H_7), 3.07 (1H, dd, *J*=8.6, 4.8 Hz, H_{3a}), 3.00 (1H, m, H_3), 2.57 (1H, ddd,

J=8.7, 4.1, 1.4 Hz, H_{7a}), 1.51 (1H, m, 4-C*H*H-7), 1.43 (1H, m, 4-CH*H*-7), 1.17 (3H, d, J=7.3 Hz, 3*Me*); δ_C (100 MHz, $CDCl_3$) 210.1 (s, C_1), 163.3 (sd, $J_{C,F}$=250.0 Hz, 2CH*Ph·p*-F), 144.3 ($J_{C,F}$=2.9 Hz, C_2), 136.7 (d, C_5), 133.7 (C_6), 132.7 (dd, $J_{C,F}$=8.1 Hz, 2CH*Ph·p*-F), 131.6 (sd, $J_{C,F}$=3.6 Hz, 2CH*Ph·p*-F), 131.4 (d, 2C*H*Ph·*p*-F), 116.3 (dd, $J_{C,F}$=21.2 Hz, 2CH*Ph·p*-F), 52.9 (d, C_{3a}), 51.8 (t, 4-CH_2-7), 48.0 (d, C_4), 47.5 (C_7, C_{7a}), 36.5 (C_3), 21.0 (q, 3Me); *m/z* (CI/NH_4) 286 ($[MH+NH_4]^+$, 1.5%), 269 (MH^+, 34.7), 240 (6.5), 220 (6.1), 203 ($[MH-C_5H_6]^+$, 100), 174 (10.5), 66 (7.5); (HRMS: found MH^+, 269.1343. $C_{18}H_{18}OF^+$ requires 269.1342), and the 7a(*S*)-alkylated by-product (+)-**31** (108 mg, 15%) as a transparent pale yellow oil; R_f 0.18 (SiO_2, *n*-hexane/acetone, 9:1); $[\alpha]_D^{18}$ 0.44 (*c* 6.65, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.85 (2H, m, 3′*Ph·p*-F), 7.51 (2H, m, *Ph·p*-F), 7.43 (2H, m, *Ph·p*-F), 7.14 (1H, d, J=2.2 Hz, 2C*H*Ph·*p*-F), 7.11–7.02 (4H, m, *Ph·p*-F), 6.95 (2H, m, *Ph·p*-F), 6.08 (1H, dd, J=5.6, 2.9 Hz, $H_{5/6}$), 5.97 (1H, dd, J=5.6, 3.0 Hz, $H_{6/5}$), 3.85 (1H, dd, J=10.6, 3.3 Hz, $H_{1'}$), 3.66 (1H, m, 1′C*H*HCOPh·*p*-F), 3.42 (1H, dd, J=16.7, 3.3 Hz, 1′CH*H*COPh.p-F), 3.08 (1H, br. s, H_4), 2.96 (1H, dd, J=14.3, 7.3 Hz, H_3), 2.84 (1H, br. s, H_7), 2.41 (1H, dd, J=4.0, 1.3 Hz, H_{3a}), 1.63 (1H, m, 4-C*H*H-7), 1.39 (1H, m, 4-CH*H*-7), 1.17 (3H, d, J=7.3 Hz, 3*Me*); δ_C (100 MHz, $CDCl_3$) 210.4 (s, C_1), 196.7 ($C_{3'}$), 165.7 (sd, $J_{C,F}$=253.4 Hz, *Ph·p*-F), 163.3 ($J_{C,F}$=250.4 Hz, *Ph·p*-F), 161.8 ($J_{C,F}$=244.4 Hz, *Ph·p*-F), 144.2 ($J_{C,F}$=2.3 Hz, *Ph·p*-F), 138.0 (d, $C_{5/6}$), 137.7 (sd, $J_{C,F}$=12.7 Hz, *Ph·p*-F), 135.7 (d, $C_{6/5}$), 133.6 (sd, $J_{C,F}$=9.6 Hz, *Ph·p*-F), 132.6 (dd, $J_{C,F}$=8.8 Hz, *Ph·p*-F), 132.4 (d, 2*C*HPh·*p*-F), 131.4 (dd, $J_{C,F}$=7.2 Hz, *Ph·p*-F), 131.1 (sd, $J_{C,F}$=12.7 Hz, *Ph·p*-F), 130.6 (dd, $J_{C,F}$=8.8 Hz, *Ph·p*-F), 115.9 ($J_{C,F}$=21.6 Hz, *Ph·p*-F), 115.6, 115.0 ($J_{C,F}$=20.8 Hz, *Ph·p*-F), 64.5 (s, C_{7a}), 54.7 (d, C_{3a}), 50.9 (C_7), 48.8 (t, 4-CH_2-7), 47.6 (d, C_4), 46.7 ($C_{1'}$), 41.1 (t, $C_{2'}$), 35.9 (d, C_3), 20.2 (q, 3Me); δ_F (376 MHz, $CDCl_3$) −105.7 (Ph·*p*-*F*), −110.4, −116.5; *m/z* (ES$^+$) 1047 ($[2M+Na]^+$, 3.7%), 551 (4.4), 535 ($[M+Na]^+$, 100), 469 ($[M-C_5H_6]^+$, 87.0), 449 (3.1), 413 (4.4), 331 (3.4); (HRMS: found $M+Na^+$, 535.1843. $C_{33}H_{27}O_2F_3Na^+$ requires 535.1861).

4.7. Microwave assisted *retro* Diels–Alder reaction: representative procedure

4.7.1. (+)-5-(*E*)-Isobutylidene-4(*S*)-methyl-cyclopent-2-enone (+)-32. To a stirring solution of (+)-**16** (0.22 g, 1.02 mmol) and maleic anhydride (5.0 equiv.) in anhydrous DCM (5.1 cm^3) was added 1.0 M methyl aluminiumdichloride in hexanes (0.5 equiv.) at room temperature under a nitrogen stream. The mixture was heated at 60 °C for 30 min in a microwave (Smith-Creator), and cooled to room temperature under a nitrogen stream. Flash silica (0.94 g) was added and the solvent removed in vacuo to afford pre-absorbed crude product. Purification by flash column chromatography (SiO_2), eluting with *n*-hexane/diethyl ether (5:1), gave recovered enone (+)-**16** (32 mg, 14%) as a pale yellow transparent oil and an inseparable mixture (98:2) of *E*- and *Z*-isomers of dienone (+)-**32** (81.8 mg, 54%) as a transparent yellow oil; R_f 0.31 (SiO_2, *n*-hexane/diethyl ether, 2:1); δ_H (400 MHz, CD_2Cl_2) 7.37 (1H, dd, J=5.9, 2.6 Hz, H_3), 6.19 (1H, d, J=10.7 Hz 5C*Hi*-prop), 6.13 (1H, dd, J=5.9, 1.7 Hz, H_2), 3.40 (1H, m, H_4), 2.59 (1H, m, 5CHC*H*Me_2), 1.18 (3H, d, J=7.2 Hz, 4Me), 1.00 (3H, d, J=6.7 Hz, 5CHCH*Me*Me), 0.98 (3H, d, J=6.6 Hz, 5CHCHMe*Me*); δ_C (100 MHz, CD_2Cl_2) 197.4 (s, C_1), 164.2 (d, C_3), 142.0 (5*C*H *i*-prop), 137.7 (s, C_5), 134.5 (d, C_2), 39.0 (d, C_4), 29.3 (5CHC*H*Me_2), 22.6 (q, 5CHCH*Me*Me), 22.6 (5CHCHMe*Me*), 19.4 (4*Me*); *m/z* (CI/NH_3) 233 (5.2%), 220 (12.3), 205 (19.9), 168 ($[MH+NH_3]^+$, 7.0), 151 (MH^+, 100); (HRMS: found MH^+, 151.1120. $C_{10}H_{15}O^+$ requires 151.1123).

4.7.2. (−)-5-(*E*)-Isobutylidene-4(*R*)-methyl-cyclopent-2-enone (−)-32. (69.7 mg, 73%), a transparent yellow oil; R_f 0.32 (SiO_2, *n*-hexane/diethyl ether, 2:1); $[\alpha]_D^{22}$ −10.52 (*c* 4.44 $CHCl_3$); δ_H (250 MHz, CD_2Cl_2) 7.40 (1H, ddd, J=5.8, 2.4, 1.1 Hz, H_3), 6.25 (1H, dt, J=10.6, 1.0 Hz 5C*Hi*-prop), 6.19 (1H, dd, J=5.8, 1.7 Hz, H_2), 3.47 (1H, m, H_4), 2.65 (1H, m, 5CHC*H*Me_2), 1.23 (3H, d, J=7.2 Hz, 4Me), 1.05 (3H, d, J=6.5 Hz, 5CHCH*Me*Me), 1.03 (3H, d, J=6.5 Hz, 5CHCHMe*Me*); δ_C (100 MHz, CD_2Cl_2) 197.4 (s, C_1), 164.2 (d, C_3), 142.0 (5*C*H *i*-prop), 136.7 (s, C_5), 134.5 (d, C_2), 39.0 (C_4), 28.7 (5CHC*H*Me_2), 22.7 (q, 5CHCH*Me*Me), 22.6 (5CHCHMe*Me*), 19.4 (4*Me*); *m/z* (CI/NH_3) 168 ($[MH+NH_3]^+$, 7.4%), 151 (MH^+, 100); (HRMS: found MH^+, 151.1123. $C_{10}H_{15}O^+$ requires 151.1123).

4.7.3. (+)-5-(*E*)-Isobutylidene-4(*S*)-octyl-cyclopent-2-enone (+)-33. (94.2 mg, 74%) a transparent pale yellow oil; R_f 0.28 (SiO_2, *n*-hexane/ethyl acetate, 9:1); $[\alpha]_D^{22}$ 1.70 (*c* 4.65 $CHCl_3$); δ_H (400 MHz, CD_2Cl_2) 7.46 (1H, dd, J=6.0, 2.5 Hz, H_3), 6.19 (1H, m, H_2), 6.17 (1H, dd, J=1.4 Hz, 5CH *i*-prop), 3.42 (1H, m, H_4), 2.58 (1H, m, 5CHC*H*Me_2), 1.75 (1H, m, 4C*H*H$(CH_2)_6$Me), 1.45 (1H, m, 4CH*H*$(CH_2)_6$Me), 1.26–1.12 (12H, m, 4CH_2(C$H_2)_6$Me), 0.98 (6H, m, 5CHCHMe_2), 0.79 (3H, t, J=6.5 Hz, 4$(CH_2)_7$*Me*); δ_C (100 MHz, CD_2Cl_2) 197.8 (s, C_1), 162.8 (d, C_3), 141.9 (5*C*H *i*-prop), 136.4 (s, C_5), 135.3 (d, C_2), 44.0 (C_4), 33.7 (t, 4*C*$H_2(CH_2)_6$Me), 32.6 (4CH_2(*C*$H_2)_6$Me), 30.6, 30.2, 29.3 (d, 5CH*C*HMe_2), 26.6 (t, 4CH_2(*C*$H_2)_6$Me), 23.4, 22.7 (q, 5CHCH*Me*Me), 22.5 (5CHCHMe*Me*), 14.7 (4$(CH_2)_7$*Me*); *m/z* (CI/NH_3) 266 ($[MH+NH_3]^+$, 2.0%), 249 (MH^+, 100), 163 (4.0), 150 (5.8), 135 (3.7), 121 (2.3), 107 (3.7), 91 (2.2); (HRMS: found MH^+, 249.2222. $C_{17}H_{29}O^+$ requires 249.2218).

4.7.4. (−)-5-(*E*)-Isobutylidene-4(*R*)-octyl-cyclopent-2-enone (−)-33. (95 mg, 60%) a transparent pale yellow oil; R_f 0.28 (SiO_2, *n*-hexane/ethyl acetate, 9:1); $[\alpha]_D^{24}$ −1.76 (*c* 4.35 $CHCl_3$); δ_H (400 MHz, CD_2Cl_2) 7.56 (1H, ddd, J=6.0, 2.7, 1.0 Hz, H_3), 7.47 (0.06H, dd, J=6.0, 2.6 Hz, *Z*-isomer H_3), 6.31–6.27 (2H, m, H_2, 5C*Hi*-prop), 6.23 (0.06H, m, *Z*-isomer H_2), 5.83 (0.06H, d, J=9.8 Hz, *Z*-isomer 5C*Hi*-prop), 3.93 (0.06H, m, *Z*-isomer H_4), 3.53 (1H, m, H_4), 3.28 (0.06H, m, *Z*-isomer 5CHC*H*Me_2), 2.69 (1H, m, 5CHC*H*Me_2), 1.86 (1H, m, 4C*H*H$(CH_2)_6$Me), 1.55 (1H, m, 4CH*H*$(CH_2)_6$Me), 1.29 (12H, m, 4CH_2(C$H_2)_6$Me), 1.10 (3H, d, J=6.7 Hz, 5CHCH*Me*Me), 1.08 (3H, d, J=6.8 Hz, 5CHCHMe*Me*), 1.03 (0.18 Hz, d, J=2.1 Hz, *Z*-isomer 5CHCH*Me*Me), 1.02 (0.18 Hz, d, J=2.1 Hz, *Z*-isomer 5CHCHMe*Me*), 0.90 (3H, t, J=6.8 Hz, 4$(CH_2)_7$*Me*); δ_C (100 MHz, CD_2Cl_2) 197.65 (s, C_1), 162.7 (d, C_3), 161.3 (*Z*-isomer C_3), 147.1 (*Z*-isomer 5*C*H *i*-prop), 141.9 (5*C*H *i*-prop), 136.7 (*Z*-isomer C_2), 136.4 (s, C_5), 135.3 (d, C_2), 46.2 (*Z*-isomer C_4), 44.0 (C_4), 34.3 (t, *Z*-isomer 4*C*$H_2(CH_2)_6$Me), 33.7 (4*C*$H_2(CH_2)_6$Me), 32.6 (4CH_2(*C*$H_2)_6$Me), 30.5, 30.5 (*Z*-isomer 4CH_2(*C*$H_2)_6$Me), 30.2 (4CH_2(*C*$H_2)_6$Me), 30.0,

29.2 (d, 5CH*C*HMe$_2$), 26.6 (t, 4CH$_2$(*C*H$_2$)$_6$Me), 26.3 (d, *Z*-isomer 5CHC*H*Me$_2$), 23.4 (t, 4(*C*H$_2$)$_7$Me), 23.0 (q, *Z*-isomer 5CHCH*Me*Me), 22.9 (*Z*-isomer 5CHCHMe*Me*), 22.7 (q, 5CHCH*Me*Me), 22.4 (5CHCHMe*Me*), 14.6 (4(CH$_2$)$_7$*Me*); *m/z* (CI/NH$_3$) 266 ([MH+NH$_3$]$^+$, 3.8%), 249 (MH$^+$, 100), 163 (4.3), 149 (6.1), 135 (4.6), 121 (3.0), 107 (4.8), 91 (3.0); (HRMS: found MH$^+$, 249.2219. $C_{17}H_{29}O^+$ requires 249.2218).

4.7.5. (−)-5-(*E*)-Benzylidene-4(*S*)-methyl-cyclopent-2-enone (−)-34. (54.5 mg, 74%) as a transparent pale yellow oil; R_f 0.34 (SiO$_2$, *n*-hexane/ethyl acetate, 3:1); $[\alpha]_D^{21}$ −0.61 (*c* 5.34 CHCl$_3$); δ_H (400 MHz, CD$_2$Cl$_2$) 7.53 (1H, ddd, *J*=5.9, 2.7, 1.0 Hz, H$_3$), 7.48 (2H, d, *J*=7.2 Hz 5CH*Ph*), 7.34–7.25 (3H, m, 5CH*Ph*), 7.21 (1H, m, 5C*H*Ph), 6.27 (1H, dd, *J*=5.9, 1.9 Hz, H$_2$), 3.86 (1H, m, H$_4$), 1.10 (3H, d, *J*=7.2 Hz, 4Me); δ_C (100 MHz, CD$_2$Cl$_2$) 197.7 (s, C$_1$), 164.9 (d, C$_3$), 139.4 (s, 5CH*Ph*), 135.6 (C$_5$), 134.1 (d, C$_2$), 131.8 (5*C*HPh), 131.4 (2d, 5CH*Ph*), 129.9 (d, 5CH*Ph*), 129.5 (2d, 5CH*Ph*), 39.6 (d, C$_4$), 16.9 (q, 4Me); *m/z* (CI/NH$_3$) 185 (MH$^+$, 100%), 202 ([MH+NH$_3$]$^+$, 2.4); (HRMS: found MH$^+$, 185.0969. $C_{13}H_{13}O^+$ requires 185.0967).

4.7.6. (+)-5-(*E*)-Benzylidene-4(*R*)-methyl-cyclopent-2-enone (+)-34. (62.0 mg, 69%) as a transparent pale yellow oil; R_f 0.33 (SiO$_2$, *n*-hexane/ethyl acetate, 3:1); $[\alpha]_D^{18}$ 0.88 (*c* 5.02 CHCl$_3$); δ_H (400 MHz, CD$_2$Cl$_2$) 7.53 (1H, ddd, *J*=5.9, 2.6, 0.8 Hz, H$_3$), 7.47 (2H, d, *J*=7.3 Hz, 5CH*Ph*), 7.34 (2H, t, *J*=7.0 Hz, 5CH*Ph*), 7.29 (1H, d, *J*=7.1 Hz, 5CH*Ph*), 7.35 (1H, br. s, 5C*H*Ph), 6.27 (1H, dd, *J*=5.9, 1.9 Hz, H$_2$), 3.85 (1H, m, H$_4$), 1.10 (3H, d, *J*=7.2 Hz, 4Me); δ_C (100 MHz, CD$_2$Cl$_2$) 197.7 (s, C$_1$), 164.9 (d, C$_3$), 139.4 (s, 5CH*Ph*), 135.6 (C$_5$), 134.1 (d, C$_2$), 131.8 (5*C*HPh), 131.4 (2d, 5CH*Ph*), 130.0 (d, 5CH*Ph*), 129.5 (2d, 5CH*Ph*), 39.6 (d, C$_4$), 16.9 (q, 4Me); *m/z* (CI/NH$_3$) 202 ([MH+NH$_3$]$^+$, 3.0%), 185 (MH$^+$, 100); (HRMS: found MH$^+$, 185.0967. $C_{13}H_{13}O^+$ requires 185.0967).

4.7.7. (+)-5-(*E*)-Benzylidene-4(*S*)-octyl-cyclopent-2-enone (+)-35. (91 mg, 56%) as a transparent pale yellow oil; *E*-isomer; R_f 0.26 (SiO$_2$, *n*-hexane/ethyl acetate, 9:1); $[\alpha]_D^{22}$ 0.61 (*c* 6.07 CHCl$_3$); δ_H (400 MHz, CD$_2$Cl$_2$) 7.63 (1H, ddd, *J*=6.0, 2.7, 1.0 Hz, H$_3$), 7.47–7.44 (2H, m, 5CH*Ph*), 7.36–7.25 (4H, m, 5CH*Ph*, 5C*H*Ph), 6.31 (1H, dd, *J*=6.0, 1.9 Hz, H$_2$), 3.84 (1H, m, H$_4$), 1.79–1.70 (1H, m, 4C*H*H(CH$_2$)$_6$Me), 1.33–1.25 (1H, m, 4CH*H*(CH$_2$)$_6$Me), 1.23–1.05 (12H, m, 4CH$_2$(C*H*$_2$)$_6$Me), 0.77 (3H, t, *J*=7.0 Hz, 4(CH$_2$)$_7$Me); δ_C (100 MHz, CD$_2$Cl$_2$) 197.7 (s, C$_1$), 163.2 (d, C$_3$), 138.3 (s, 5CH*Ph*), 135.8 (C$_5$), 134.9 (d, C$_2$), 131.7 (5*C*HPh), 131.2 (2d, 5CH*Ph*), 129.9 (d, 5CH*Ph*), 129.4 (2d, 5CH*Ph*), 44.7 (d, C$_4$), 32.6 (t, 4(*C*H$_2$)$_7$Me), 31.0, 30.3, 30.1, 29.9, 26.8, 23.4, 14.6 (q, 4(CH$_2$)$_7$*Me*); *m/z* (CI/NH$_3$) 300 ([MH+NH$_3$]$^+$, 11.5%), 283 (MH$^+$, 100), 195 (6.2), 186 (8.3), 169 (4.7), 156 (5.9), 141 (8.6), 128 (5.0), 115 (5.8), 91 (6.9); (HRMS: found MH$^+$, 283.2070. $C_{20}H_{27}O^+$ requires 283.2062); *Z*-isomer; R_f 0.36 (SiO$_2$, *n*-hexane/ethyl acetate, 9:1); δ_H (400 MHz, CDCl$_3$) 7.98 (2H, dd, *J*=8.3, 1.6 Hz, 5CH*Ph*), 7.48 (1H, dd, *J*=6.0, 2.6 Hz, H$_3$), 7.44–7.32 (3H, m, 5CH*Ph*), 6.76 (1H, br. s, 5CH*Ph*), 6.34 (1H, dd, *J*=6.0, 1.8 Hz, H$_2$), 3.47 (1H, m, H$_4$), 1.89–1.81 (1H, m, 4C*H*H(CH$_2$)$_6$Me), 1.66–1.56 (1H, m, 4CH*H*(CH$_2$)$_6$Me), 1.43–1.23 (12H, m, 4CH$_2$(C*H*$_2$)$_6$Me), 0.88 (3H, t, *J*=6.5 Hz, 4(CH$_2$)$_7$Me); δ_C (100 MHz, CDCl$_3$) 196.0 (s, C$_1$), 160.1 (d, C$_3$), 138.0 (s, C$_5$), 137.2 (d, C$_2$), 136.5 (5*C*HPh), 134.8 (s, 5CH*Ph*), 131.2 (2d, 5CH*Ph*), 129.8 (d, 5CH*Ph*), 128.4 (2d, 5CH*Ph*), 47.7 (d, C$_4$), 34.4 (t, 4(*C*H$_2$)$_7$Me), 32.2, 30.2, 29.8, 29.6, 26.6, 23.0, 14.4 (q, 4(CH$_2$)$_7$*Me*); *m/z* (CI/NH$_3$) 300 ([MH+NH$_3$]$^+$, 1.4%), 283 (MH$^+$, 100), 225 (6.7), 211 (9.5), 199 (6.7), 183 (20.6), 169 (32.5), 156 (35.0), 141 (60.8), 128 (24.6), 115 (36.5), 91 (26.2), 55 (11.2); (HRMS: found MH$^+$, 283.2065. $C_{20}H_{27}O^+$ requires 283.2062).

4.7.8. (−)-5-(*E*)-Benzylidene-4(*R*)-octyl-cyclopent-2-enone (−)-35. (0.15 g, 54%) as a transparent pale yellow oil; R_f 0.23 (SiO$_2$, *n*-hexane/ethyl acetate, 9:1); $[\alpha]_D^{22}$ −0.48 (*c* 4.67 CHCl$_3$); δ_H (400 MHz, CDCl$_3$) 7.69 (1H, ddd, *J*=6.0, 2.7, 0.8 Hz, H$_3$), 7.52 (2H, dd, *J*=7.2, 1.4 Hz, 5CH*Ph*), 7.43–7.34 (4H, m, 5CH*Ph*, 5C*H*Ph), 6.45 (1H, dd, *J*=6.0, 1.9 Hz, H$_2$), 3.92 (1H, m, H$_4$), 1.87–1.79 (1H, m, 4C*H*H(CH$_2$)$_6$Me), 1.43–1.33 (1H, m, 4CH*H*(CH$_2$)$_6$Me), 1.31–1.08 (12H, m, 4CH$_2$(C*H*$_2$)$_6$Me), 0.86 (3H, t, *J*=6.8 Hz, 4(CH$_2$)$_7$Me); δ_C (100 MHz, CDCl$_3$) 197.9 (s, C$_1$), 162.8 (d, C$_3$), 137.6 (s, 5CH*Ph*), 135.2 (C$_5$), 134.8 (d, C$_2$), 132.0 (5*C*HPh), 130.8 (2d, 5CH*Ph*), 129.6 (d, 5CH*Ph*), 129.1 (2d, 5CH*Ph*), 44.7 (d, C$_4$), 32.2 (t, 4(*C*H$_2$)$_7$Me), 30.6, 29.8, 29.6, 29.5, 26.4, 23.0, 14.4 (q, 4(CH$_2$)$_7$*Me*); *m/z* (CI/NH$_3$) 300 ([MH+NH$_3$]$^+$, 5.7%), 283 (MH$^+$, 100), 186 (3.0), 169 (4.5), 156 (3.5), 141 (6.7), 128 (2.9), 115 (4.5), 91 (4.3); (HRMS: found MH$^+$, 283.2070. $C_{20}H_{27}O^+$ requires 283.2062).

4.7.9. (±)-5-(4-(*E*)-Fluorobenzylidene)-4(*R*/*S*)-methyl-cyclopent-2-enone (±)-36. (96.9 mg, 86%) as a transparent pale yellow oil; R_f 0.35 (SiO$_2$, *n*-hexane/ethyl acetate, 3:1); δ_H (400 MHz, CD$_2$Cl$_2$) 7.52 (1H, ddd, *J*=5.9, 2.5, 0.8 Hz, H$_3$), 7.47 (2H, m, 5CH*Ph*·*p*-F), 7.21 (1H, m, 5C*H*Ph·*p*-F), 7.04 (2H, m, 5CH*Ph*·*p*-F), 6.27 (1H, dd, *J*=5.9, 1.9 Hz, H$_2$), 3.81 (1H, m, H$_4$), 1.10 (3H, d, *J*=7.2 Hz, 4Me); δ_C (100 MHz, CD$_2$Cl$_2$) 197.5 (s, C$_1$), 164.6 (d, C$_3$), 163.8 (sd, $J_{C,F}$=250.0 Hz, 5CH*Ph*·*p*-F), 139.1 ($J_{C,F}$=1.6 Hz, C$_5$), 134.1 (d, C$_2$), 133.23 (dd, $J_{C,F}$=8.4 Hz, 5CH*Ph*·*p*-F), 131.9 (sd, $J_{C,F}$=3.2 Hz, 5CH*Ph*·*p*-F), 130.5 (d, 5*C*HPh·*p*-F), 116.5 (dd, $J_{C,F}$=21.6 Hz, 5CH*Ph*·*p*-F), 39.5 (C$_4$), 16.9 (q, 4Me); *m/z* (CI/NH$_3$) 220 ([MH+NH$_3$]$^+$, 3.7%), 203 (MH$^+$, 100); (HRMS: found MH$^+$, 203.0873. $C_{13}H_{12}OF^+$ requires 203.0872).

4.7.10. (−)-5-(4-(*E*)-Fluorobenzylidene)-4(*S*)-methyl-cyclopent-2-enone (−)-36. (0.14 g, 91%) as a transparent yellow oil; R_f 0.31 (SiO$_2$, *n*-hexane/ethyl acetate, 3:1); $[\alpha]_D^{22}$ −0.87 (*c* 7.50, CHCl$_3$); δ_H (400 MHz, CD$_2$Cl$_2$) 7.51 (1H, m, H$_3$), 7.45 (2H, m, 5CH*Ph*·*p*-F), 7.21 (1H, br. s, 5C*H*Ph·*p*-F), 7.03 (2H, m, 5CH*Ph*·*p*-F), 6.26 (1H, dd, *J*=5.9, 1.8 Hz, H$_2$), 3.80 (1H, m, H$_4$), 1.08 (3H, d, *J*=7.2 Hz, 4Me); δ_C (100 MHz, CD$_2$Cl$_2$) 197.5 (s, C$_1$), 164.6 (d, C$_3$), 163.8 (sd, $J_{C,F}$=250.0 Hz, 5CH*Ph*·*p*-F), 139.1 ($J_{C,F}$=2.4 Hz, C$_5$), 134.1 (d, C$_2$), 133.2 (dd, $J_{C,F}$=8.8 Hz, 5CH*Ph*·*p*-F), 131.9 (sd, $J_{C,F}$=3.2 Hz, 5CH*Ph*·*p*-F), 130.5 (d, 5*C*HPh·*p*-F), 116.5 (dd, $J_{C,F}$=3.2 Hz, 5CH*Ph*·*p*-F), 39.4 (d, C$_4$), 16.9 (q, 4Me); *m/z* (CI/NH$_3$) 220 ([MH+NH$_3$]$^+$, 3.7%), 203 (MH$^+$, 100), 174 (9.4), 159 (6.6), 133 (4.9); (HRMS: found MH$^+$, 203.0877. $C_{13}H_{12}OF^+$ requires 203.0872).

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Titanium mediated alkylidenation of substituted cycloalkenones: scope and limitations

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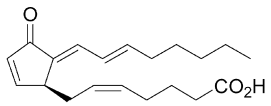
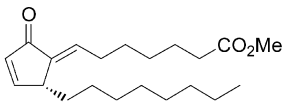
Abstract—The conversion of the cyclopent-2-enone **5** and cyclohex-2-enones **11a**, **c**-**e** into corresponding α'-*exo*-alkylidene compounds using Ti(IV) catalysis, with PPh_3 and an aldehyde, is described.

1. Introduction

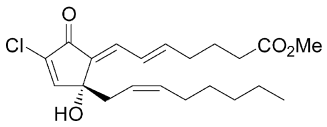
The cross-conjugated dienone unit is present in many natural products of significant biological interest.[1] The unsaturated prostaglandin $\delta^{12,14}$-15-deoxy-PG-J_2 **1**,[2] has been implicated in the control of various medical conditions,[3] and TEI-9826 **2**, a related analogue of PG-A_2, is currently in pre-clinical trials as an anti-tumour agent.[4] Also, 12-oxy-prostaglandins, the clavulones[5] and the chlorovulones[6] such as chlorovulone II **3**, have been isolated from the marine environment. Unnatural 12-amino prostaglandins, such as **4**, have been synthesised and have shown high cytotoxicity.[7]



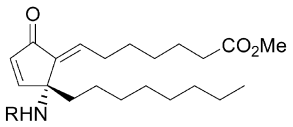
$\Delta^{12,14}$-15-deoxy-PG-J_2 (**1**)



TEI-9826 (**2**)



Chlorovulone II (**3**)



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There are a number of strategies for converting 4-alkylcyclopentenones into the corresponding cross-conjugated dienones. One tactic is to perform an aldol reaction on the cyclopentenone, followed by activation of the alcohol (usually as a sulfonate ester) and elimination.[8] Often preparing the enolate of cyclopentenones can prove problematic and in any case a 3-step protocol for this transformation is not ideal, although a good overall yield can be obtained. Other strategies involve masking the cyclic enone in some manner. Noyori et al. has utilised this approach in a three-component coupling reaction using 4-silyloxycyclopentenones, followed by elimination of the silyloxy group to reveal the cyclic enone.[9] A more recent example involves protecting the *endo*-cyclic carbon–carbon double bond as a norbornene unit, from which cyclopentadiene can be removed in a *retro*-Diels–Alder reaction.[10]

However, we were intrigued by the communication of Suda et al.[11] which reported a one-pot sequence to convert cyclopentenone to a cross-conjugated dienone. A number of examples were reported, but the only substrates investigated were cyclopentenone and cyclohexenone and no further reports have alluded to any extension in this methodology. We wanted to investigate whether this protocol could be extended to substituted cyclopentenones and cyclohexenones.

2. Results and discussion

Initially, we studied the reaction of the 4-aza-cyclopentenone **5**,[12] under similar conditions to those reported. The enone **5** and an equivalent of triphenylphosphine were dissolved in dichloromethane and cooled to −50 °C, whereupon 0.5 equiv. of titanium (IV) isopropoxide, then titanium (IV) chloride were added. At this stage an intense red colour indicated the formation of the enolate, which could be quenched with a variety of aldehydes. Finally, stirring with aqueous potassium carbonate solution released the desired dienones **6a**-**e** (Table 1).

Unlike the reaction with cyclopentenone, these reactions did

Keywords: 5-Alkylidene-cyclopent-2-enones; 6-Alkylidene-cyclohex-2-enones; Titanium enolate chemistry; 4-Aza cycloalk-2-enones.
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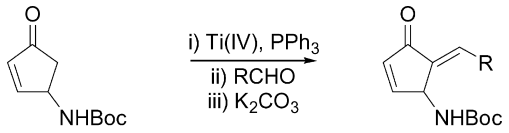
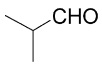
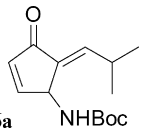
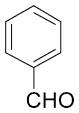
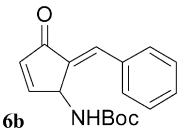
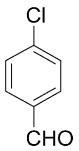
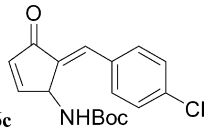
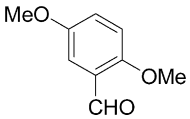
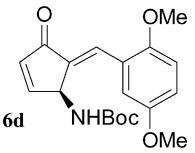
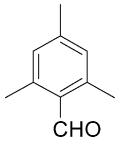
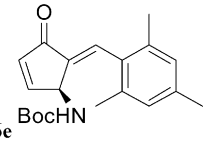
Table 1. Reaction of enone **5** with Ti(IV), PPh_3 and an aldehyde



5 **6a-e**

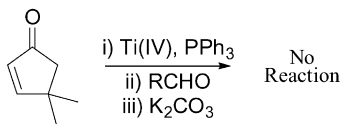
Entry	Aldehyde	Product	Yield (%)[a] [*E*:*Z*][b]	Recovered **5**[a] (%)	Yield based on recovered SM (%)
1[c]		 **6a**	39 [7.3:1]	48	74
2[c]		 **6b**	48[d]	45	87
3[c]		 **6c**	52[d]	37	82
4[e]		 **6d**	60[d]	25	80
5[e]		 **6e**	24[d]	67	73

[a] Yields following purification by flash chromatography.
[b] Ratio determined by amounts of isolated product.
[c] Racemic enone **5** used.
[d] Only (*E*)-isomer detected.
[e] (*R*) enantiomer of **5** used.[12]

not go to completion, with only moderate yields of dienone being isolated. However, as there was a significant recovery of **5**, the yield based on starting material consumed was good and compares well with the other methods for this transformation, especially as the Suda protocol involves a one-pot operation.

Also, this reaction gives a single geometric isomer when aromatic aldehydes are used, and the small *Z*-isomer impurity in the preparation of **6a** could well be due to light-induced isomerisation rather than a lack of selectivity.[13] A range of aromatic aldehydes could be tolerated, with the more electron-rich 2,5-dimethoxybenzaldehyde actually resulting in the highest conversion. The sterically crowded product **6e** could also be formed, albeit in lower yield, but attempts to use 2-pyridinecarboxaldehyde as the electrophile resulted in no cross-conjugated dienone being formed.

The more demanding enones **7** and **8** were examined. However, the geminally disubstituted enone **7** did not result in any reaction and subjecting the 4-oxa enone **8** to the reaction conditions only resulted in a complex mixture.[14]



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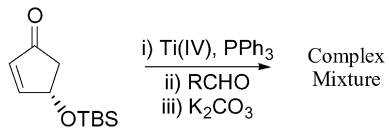
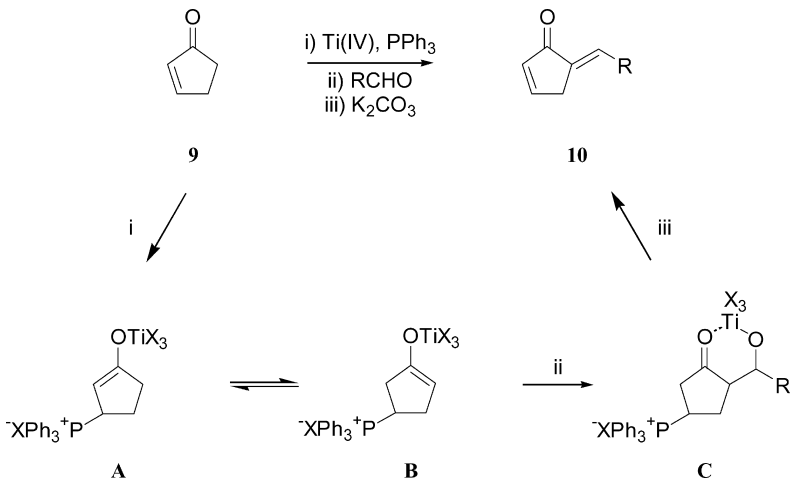


8

Suda et al. has proposed a mechanism for this reaction,[11] which is illustrated for cyclopentenone **9** in Scheme 1. Reaction of **9** with triphenylphosphine and the titanium (IV) complex results in the titanium enolate **A**, which isomerises to a regioisomeric enolate **B**. Reacting this equilibrium



Scheme 1.

mixture of enolates **A** and **B** with an aldehyde then gives the aldol product **C** that is transformed into the dienone product **10** by treatment with base.

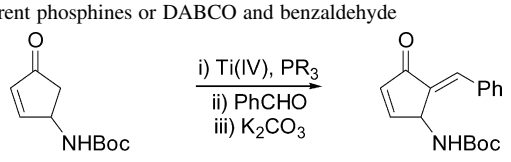
The rates of reaction of the two enolates **A** and **B** are quite different. It is suggested that the steric bulk of the phosphonium substituent in **A** would greatly reduce the reactivity of this enolate, leaving enolate **B** to react and give the product. However, this distinction is partially or completely nullified by adding substituents in the 4-position of the cyclopentenone ring. The addition of a single substituent, such as in **5**, makes it much less clear cut as to which enolate would be the more sterically accessible. Reaction of the aldehyde with **A** would give an aldol product that would regenerate the starting enone on addition of aqueous base on work-up. This material would not be available to proceed along the pathway through **B** to the desired product. Hence, a mixture of starting material and product is obtained in the reactions involving **6a**-**e**.

This mechanistic analysis can also rationalise the results observed for enones **7** and **8**. The decomposition of enone **8** can be explained, as the enolate **B** in this case is likely to be unstable. We believe that the silyloxy-group would be eliminated under these conditions, generating the very reactive cyclopentadienone. The lack of reactivity of **7** can be explained on the grounds of steric arguments. Either the geminal methyl groups inhibit the initial addition of the phosphine, or the two substituents can now shut down the reactivity of enolate **B** completely, allowing only the 'non-productive' enolate **A** to react with aldehyde.

In order to try to increase the level of reactivity in these reactions, other phosphines were investigated (Table 2). The use of tri(*ortho*-tolyl) phosphine did not result in greater productivity. Perhaps, the greater size of the phosphine led to less favourable addition initially, accounting for the lower yield. Disappointingly, reducing the size or altering the electronic properties of the phosphine also led to less favourable results, demonstrating the subtle kinetic effects in this reaction. On the positive side, initial results replacing phosphines with an amine have shown some promise. Using DABCO in this reaction instead of a phosphine gave a 10% yield of the product **6b** along with unreacted enone **5**.

In the course of this work we have made a number of observations that are crucial to obtaining the best results from this reaction. Azeotropic drying of the phosphine prior to use enhances the final yield; adding titanium (IV) isopropoxide, then titanium (IV) chloride allows the maximum tolerance of acid sensitive substrates and, after addition of aqueous potassium carbonate, a extensive period of vigorous stirring (usually over an hour) allows the maximum recovery of both product and starting material.

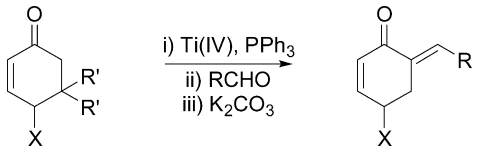
Table 2. Reaction of enone **5** with Ti(IV), different phosphines or DABCO and benzaldehyde



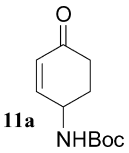
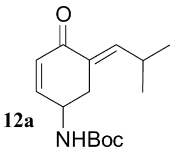
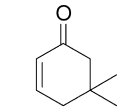
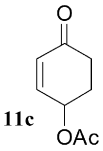
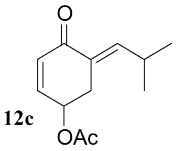
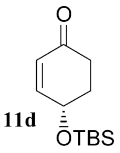
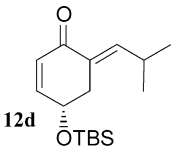
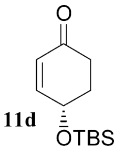
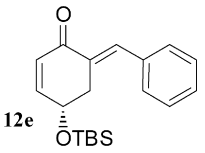
Entry	Phosphine/amine	Yield[a]	Recovered **5**[a] (%)	Yield based on recovered SM
1	PPh_3	48%	45	87%
2	P(*o*-Tol)$_3$	24%	70	80%
3	$P(OPh)_3$	None	71	n/a
4	P(*n*-C_4H_9)$_3$	None	94	n/a
5	P(*t*-C_4H_9)$_3$	None	91	n/a
6	DABCO	10%	55	22%

[a] Yields following purification by flash chromatography.

Table 3. Reaction of substituted cyclohexenones **11a-d** with Ti(IV), PPh_3 and an aldehyde



11a-d **12a-e**

Entry	Substrate	Product	Yield (%)[a,b]	Recovered **11**[a]	Yield based on recovered SM (%)
1	 **11a**	 **12a**	49	33%	73
2	 **11b**	No product	—	—	—
3	 **11c**	 **12c**	87	—	87
4	 **11d**	 **12d**	40	None	40
5	 **11d**	 **12e**	62	None	62

[a] Yields following purification by flash chromatography.
[b] Only isomer shown isolated.

Finally, aqueous extraction can be accompanied with troublesome emulsions, which can be greatly minimised by the filtering of the reaction mixture through a short pad of Celite®, while noting that care needs to be taken to wash the Celite® thoroughly, especially on a larger scale.

This methodology can also be extended to substituted cyclohexenones. For example, the 4-aza substituted enone **11a**,[15] gave a similar yield to that obtained for the corresponding cyclopentenone (Table 3).

As expected the geminally substituted enone **11b** gave no product. In this case, after addition of the phosphine, the aldol reaction can take place at C-2, but not at C-6 due to steric hindrance. This C-2 adduct then regenerates starting material on work-up. Finally, 4-oxacyclohexenones are suitable substrates for the reaction, as these cannot undergo elimination-type processes that plagued the cyclopentenone **8**. The acetate **11c**,[16] performs particularly well and the stability of silyl protecting groups under these conditions is demonstrated by the formation of **12d** and **12e**.

In conclusion, we have successfully applied the Suda reaction to more demanding substrates. Some limitations of this approach have been identified, a mechanistic rational for these observations has been proposed and improvements to the method have been outlined. The method compares well with other methods for this transformation, allowing the conversion of cycloalkenones to cross-conjugated dienones to be performed in a single operation.

3. Experimental

3.1. General

Starting materials were purchased from commercial sources and were used without further purification, except for the phosphines that were azeotropically dried with toluene. Dichloromethane was distilled from CaH_2. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded using a Bruker AMX400 spectrometer. Optical rotation measurements were recorded using an Optical Activity,

Polaar 2001 polarimeter at 589 nm and quoted in units of 10^{-1} deg cm^2 g^{-1}. Flash column chromatography was performed under moderate pressure using silica gel—ICN 32-63, 60 Å. Analytical HPLC measurements were performed on a Gilson HPLC machine using a Synergi Max RP column (Phenomenex).

3.1.1. (5-*iso*-Butylidene-4-oxocyclopent-2-enyl)-carbamic acid *tert*-butyl ester (6a). Triphenylphosphine (1.33 g, 5.07 mmol) was added to a stirred solution of the enone **5** (1.00 g, 5.07 mmol) in dichloromethane (25 cm^3) at room temperature, under an atmosphere of argon. The resulting mixture was then cooled to 50 °C and titanium (IV) *iso*-propoxide (0.75 cm^3, 2.54 mmol) and then titanium (IV) chloride (0.28 cm^3, 2.55 mmol) were added dropwise over 3 min each. The mixture was stirred at −50 °C for a further 15 min, then *iso*-butyraldehyde (1.38 cm^3, 15.2 mmol) was added over 3 min. The mixture was then allowed to warm to room temperature over 15 h. An aqueous solution of potassium carbonate (10% aq., 25 cm^3) was added, the biphasic mixture was stirred for 90 min, then filtered through a short pad of Celite® washing with dichloromethane (50 cm^3) and diethyl ether (50 cm^3). The organic phase of the filtrate was separated and the aqueous phase was extracted with diethyl ether (4×25 cm^3). The combined organics were dried over anhydrous magnesium sulfate and evaporated in vacuo. Flash chromatography (SiO_2, 15%, then 20% ethyl acetate in hexane) gave the starting enone **5** (475 mg, 2.41 mmol, 48% recovery) as a white solid, after giving the less polar (*Z*)-dienone (60 mg, 0.24 mmol, 4.7% (9.0% based on recovery)) and the (*E*)-dienone **6a** (435 mg, 1.73 mmol, 34% (65% based on recovery)) also as white solid; mp 141–142 °C (Et_2O); δ_H (400 MHz, $CDCl_3$) 7.40 (1H, ddd, *J*=6.0, 2.5, 0.8 Hz, C*H*=CHC=O), 6.49 (1H, d, *J*=10.7 Hz, C=C*H*), 6.38 (1H, dd, *J*=6.0, 1.7 Hz, CH=C*H*C=O), 5.47 (1H, br. d, *J*=8.7 Hz, N*H*), 4.56 (1H, br. d, *J*=8.7 Hz, C*H*NH), 2.75 (1H, dsept, *J*=10.7, 6.7 Hz, C*H*$(CH_3)_2$), 1.48 (9H, s, $CO_2C(CH_3)_3$), 1.09 (3H, d, *J*=6.7 Hz, CHC*H*$_3$), 1.07 (3H, d, *J*=6.7 Hz, CHC*H*$_3$); δ_C (100 MHz, $CDCl_3$) 195.2 (s), 156.9 (d), 154.9 (s), 145.2 (d), 136.2 (d), 132.9 (s), 80.3 (s), 51.5 (d), 28.5 (d), 28.3 (q), 22.0 (q), 21.9 (q); *m*/*z* (CI). Found $[MH]^+$ 252.1596 ($[MH]^+$ $C_{14}H_{22}NO_3$ requires 252.1600).

3.1.2. ((*E*)-5-Benzylidene-4-oxo-cyclopent-2-enyl)-carbamic acid *tert*-butyl ester (6b). Triphenylphosphine (333 mg, 1.27 mmol) and the enone **5** (250 mg, 1.27 mmol) in dichloromethane (6 cm^3) was treated, in an analogous manner to that for the preparation of **6a**, with titanium (IV) *iso*-propoxide (0.19 cm^3, 0.64 mmol), titanium (IV) chloride (70 μl, 0.64 mmol) and benzaldehyde (0.39 cm^3, 3.84 mmol). After work-up, flash chromatography (SiO_2, 20%, then 35% ethyl acetate in hexane) gave the starting enone **5** (98 mg, 0.50 mmol, 39% recovery) as a white solid, after giving the less polar dienone **6b** (180 mg, 0.63 mmol, 50% (82% based on recovery)) also as a white solid; mp 148–149 °C (Et_2O); δ_H (400 MHz, $CDCl_3$) 7.62–7.56 (3H, m, C*H*=CHC=O+Ar*H*), 7.49 (1H, br. s, C=C*H*Ar), 7.44–7.39 (3H, m, Ar*H*), 6.50 (1H, dd, *J*=5.9, 1.6 Hz, CH=C*H*C=O), 5.81 (1H, br. d, *J*=7.2 Hz, N*H*), 4.42 (1H, br. d, *J*=7.2 Hz, C*H*NH), 1.44 (9H, s, $CO_2C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 195.5 (s), 157.7 (d), 155.3 (s), 135.4 (d), 134.3 (d), 133.1 (s), 132.2 (s), 131.4 (d), 130.1 (d), 128.7 (d), 80.4 (s), 52.1 (d), 28.3 (q); *m*/*z* (ES) 309 ($[MHNa]^+$, 17%), 308 ($[MNa]^+$, 100). Found $[MNa]^+$ 308.1267 ($[MNa]^+$ $C_{17}H_{19}NO_3Na$ requires 308.1263).

3.1.3. [(*E*)-5-(4-Chlorobenzylidene)-4-oxo-cyclopent-2-enyl]-carbamic acid *tert*-butyl ester (6c). Triphenylphosphine (333 mg, 1.27 mmol) and the enone **5** (250 mg, 1.27 mmol) in dichloromethane (6 cm^3) was treated, in an analogous manner to that for the preparation of **6a**, with titanium (IV) *iso*-propoxide (0.19 cm^3, 0.64 mmol), titanium (IV) chloride (70 μl, 0.64 mmol) and chlorobenzaldehyde (535 mg, 3.81 mmol). After work-up, flash chromatography (SiO_2, 20%, then 35% ethyl acetate in hexane) gave the starting enone **5** (93 mg, 0.47 mmol, 37% recovery) as a white solid, after giving the less polar dienone **6c** (210 mg, 0.66 mmol, 52% (82% based on recovery)) also as a white solid; mp 187–188 °C (Et_2O); δ_H (400 MHz, $CDCl_3$) 7.58 (1H, ddd, *J*=5.9, 2.4, 0.7 Hz, C*H*=CHC=O), 7.51 (2H, dt, *J*=8.6, 1.9 Hz, Ar*H*), 7.43 (1H, br. s, C=C*H*Ar), 7.38 (2H, dt, *J*=8.6, 1.9 Hz, Ar*H*), 6.51 (1H, dd, *J*=5.9, 1.7 Hz, CH=C*H*C=O), 5.79 (1H, br. d, *J*=8.0 Hz, N*H*), 4.41 (1H, br. d, *J*=8.0 Hz, C*H*NH), 1.45 (9H, s, $CO_2C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 195.2 (s), 157.7 (d), 155.3 (s), 136.3 (s), 135.6 (s), 135.5 (d), 132.8 (d), 132.5 (d), 131.6 (s), 129.0 (d), 80.6 (s), 52.0 (d), 28.3 (q); *m*/*z* (ES) 344 ($[M(^{37}Cl)Na]^+$, 32%), 342 ($[M(^{35}Cl)Na]^+$, 100). Found $[MNa]^+$ 342.0890 ($[MNa]^+$ $C_{17}H_{18}NO_3NaCl$ requires 342.0873).

3.1.4. (1*S*)-[(*E*)-5-(2,5-Dimethoxybenzylidene)-4-oxo-cyclopent-2-enyl]-carbamic acid *tert*-butyl ester (6d). Triphenylphosphine (267 mg, 1.02 mmol) and the (*R*)-enantiomer of the enone **5** (201 mg, 1.02 mmol) in dichloromethane (5 cm^3) was treated, in an analogous manner to that for the preparation of **6a**, with titanium (IV) *iso*-propoxide (0.15 cm^3, 0.51 mmol), titanium (IV) chloride (56 μl, 0.51 mmol) and 2,5-dimethoxybenzaldehyde (508 mg, 3.06 mmol). After work-up, flash chromatography (SiO_2, 20%, then 35% ethyl acetate in hexane) gave the starting enone **5** (51 mg, 0.26 mmol, 25% recovery) as a white solid, after giving the less polar dienone **6d** (210 mg, 0.61 mmol, 60% (80% based on recovery)) as a yellow solid; mp 122–124 °C (Et_2O); $[\alpha]_D$=+18.8 (*c* 2.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.87 (1H, s, C=C*H*Ar), 7.57 (1H, dd, *J*=5.9, 2.0 Hz, C*H*=CHC=O), 7.09 (1H, d, *J*=2.9 Hz, *o*-Ar*H*), 6.93 (1H, dd, *J*=9.1, 2.9 Hz, *p*-Ar*H*), 6.86 (1H, d, *J*=9.1 Hz, *m*-Ar*H*), 6.49 (1H, dd, *J*=5.9, 1.6 Hz, CH=C*H*C=O), 5.77 (1H, br. d, *J*=7.0 Hz, N*H*), 4.41 (1H, br. d, *J*=7.0 Hz, C*H*NH), 3.85 (3H, s, OC*H*$_3$), 3.80 (3H, s, OC*H*$_3$), 1.38 (9H, s, $CO_2C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 195.4 (s), 157.5 (d), 153.4 (s), 138.5 (s), 135.5 (d), 132.6 (s), 129.1 (d), 122.7 (d), 118.1 (s), 115.8 (s), 114.6 (d), 112.0 (d), 80.2 (s), 56.1 (q), 55.6 (q), 52.3 (d), 28.2 (q); *m*/*z* (ES) 369 ($[MHNa]^+$, 22%), 368 ($[MNa]^+$, 100). Found $[MNa]^+$ 368.1463 ($[MNa]^+$ $C_{19}H_{23}NO_5Na$ requires 368.1474).

3.1.5. (1*S*)-[4-Oxo-(*E*)-5-(2,4,6-trimethylbenzylidene)-cyclopent-2-enyl]-carbamic acid *tert*-butyl ester (6e). Triphenylphosphine (267 mg, 1.02 mmol) and the (*R*)-enantiomer of the enone **5** (201 mg, 1.02 mmol) in dichloromethane (6 cm^3) was treated, in an analogous manner to that for the preparation of **6a**, with titanium

(IV) *iso*-propoxide (0.15 cm^3, 0.51 mmol), titanium (IV) chloride (56 μl, 0.51 mmol) and mesitaldehyde (0.45 cm^3, 3.05 mmol). After work-up, flash chromatography (SiO_2, 20%, then 35% ethyl acetate in hexane) gave the starting enone **5** (135 mg, 0.68 mmol, 67% recovery) as a white solid, after giving the less polar dienone **6e** (80 mg, 0.24 mmol, 24% (73% based on recovery)) also as a white solid; mp 147–149 °C (Et_2O); $[\alpha]_D=-62.4$ (*c* 2.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.57 (1H, s, C═C*H*Ar), 7.44 (1H, dd, *J*=6.2, 2.2 Hz, C*H*═CHC═O), 6.87 (2H, s, Ar*H*), 6.48 (1H, dd, *J*=6.2, 1.9 Hz, CH═C*H*C═O), 5.33 (1H, br. d, *J*=5.6 Hz, N*H*), 4.10 (1H, br. d, *J*=5.6 Hz, C*H*NH), 2.26 (3H, s, *p*-ArCH_3), 2.20 (6H, s, *o*-Ar(CH_3)$_2$), 1.22 (9H, s, $CO_2C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 194.4 (s), 158.1 (d), 154.3 (s), 137.6 (s), 137.5 (s), 135.9 (d), 135.1 (s), 134.3 (d), 130.4 (s), 128.4 (d), 79.7 (s), 52.6 (d), 28.1 (q), 20.9 (q), 20.2 (q); *m/z* (ES) 351 ([MHNa]$^+$, 22%), 350 ([MNa]$^+$, 100). Found [MNa]$^+$ 350.1719 ([MNa]$^+$ $C_{20}H_{25}NO_3Na$ requires 350.1732).

3.1.6. (*E*)-(5-*iso*-Butylidene-4-oxocyclohex-2-enyl)-carbamic acid *tert*-butyl ester (12a). Triphenylphosphine (525 mg, 2.00 mmol) and the enone **11a** (422 mg, 2.00 mmol) in dichloromethane (12 cm^3) was treated, in an analogous manner to that for the preparation of **6a**, with titanium (IV) *iso*-propoxide (0.30 cm^3, 1.02 mmol), titanium (IV) chloride (110 μl, 1.00 mmol) and *iso*-butyraldehyde (0.55 cm^3, 6.06 mmol). After work-up, flash chromatography (SiO_2, 20% ethyl acetate in petrol) gave the starting enone **11a** (140 mg, 0.66 mmol, 33% recovery) as a white solid, after giving the less polar dienone **12a** (260 mg, 0.98 mmol, 49% (73% based on recovery)) also as a white solid; mp 93–94 °C (Et_2O); δ_H (400 MHz, $CDCl_3$) 6.85 (1H, dd, *J*=10.0, 3.3 Hz, C*H*═CHC═O), 6.59 (1H, d, *J*=9.9 Hz, C═C*H*), 6.15 (1H, dd, *J*=10.0, 1.8 Hz, CH═C*H*C═O), 4.67 (1H, br. s, N*H*), 4.50 (1H, br. s, C*H*NH), 3.01 (1H, dd, *J*=14.3, 5.2 Hz, C*H*H), 2.65 (1H, dsept, *J*=9.9, 6.6 Hz, C*H*(CH_3)$_2$), 2.60 (1H, dd, *J*=14.3, 7.8 Hz, CH*H*), 1.47 (9H, s, $CO_2C(CH_3)_3$), 1.06 (3H, d, *J*=6.6 Hz, CHCH_3), 1.04 (3H, d, *J*=6.6 Hz, CHCH_3); δ_C (100 MHz, $CDCl_3$) 187.9 (s), 154.9 (s), 148.8 (d), 147.3 (d), 131.4 (s), 129.0 (d), 80.1 (s), 46.5 (d), 32.4 (t), 28.3 (q), 27.0 (d), 22.3 (q), 22.1 (q); *m/z* (ES) 289 ([MHNa]$^+$, 20%), 288 ([MNa]$^+$, 100). Found [MNa]$^+$ 288.1573 ([MNa]$^+$ $C_{15}H_{23}NO_3Na$ requires 288.1576).

3.1.7. (*E*)-Acetic acid 5-*iso*-butylidene-4-oxocyclohex-2-enyl ester (12c). Triphenylphosphine (672 mg, 2.53 mmol) and the enone **11c** (390 mg, 2.53 mmol) in dichloromethane (12 cm^3) was treated, in an analogous manner to that for the preparation of **6a**, with titanium (IV) *iso*-propoxide (0.38 cm^3, 1.29 mmol), titanium (IV) chloride (0.14 cm^3, 1.28 mmol) and *iso*-butyraldehyde (0.92 cm^3, 10.1 mmol). After work-up, flash chromatography (SiO_2, 20% ethyl acetate in hexane) gave the dienone **12c** (460 mg, 2.21 mmol, 87%) as a colourless oil; δ_H (400 MHz, $CDCl_3$) 6.85 (1H, ddd, *J*=10.2, 3.0, 1.2 Hz, C*H*═CHC═O), 6.55 (1H, br. d, *J*=10.0 Hz, C═C*H*), 6.11 (1H, dd, *J*=10.2, 1.6 Hz, CH═C*H*C═O), 5.45 (1H, m, C*H*OAc), 3.05 (1H, ddt, *J*=14.0, 5.5, 1.2 Hz, C*H*HCHOAc), 2.68 (1H, ddd, *J*=14.0, 8.5, 2.2 Hz, CH*H*CHOAc), 2.62–2.56 (1H, m, C*H*(CH_3)$_2$), 2.03 (3H, s, O_2CCH_3), 1.00 (3H, d, *J*=6.6 Hz, CHCH_3), 0.97 (3H, d, *J*=6.6 Hz, CHCH_3); δ_C (100 MHz, $CDCl_3$) 186.4 (s), 169.3 (s), 146.7 (d), 145.2 (d), 131.0 (d), 126.9 (s), 66.8 (d), 30.2 (t), 26.1 (d), 21.3 (q), 21.0 (q), 20.0 (q); *m/z* (CI) 209 ([MH]$^+$, 100%), 149 ([MH−AcOH]$^+$, 21), 148 ([M−AcOH]$^+$, 56). Found [MH]$^+$ 209.1183 ([MH]$^+$ $C_{12}H_{17}O_3$ requires 209.1178).

3.1.8. (4*S*)-(*E*)-4-(*tert*-Butyldimethylsilanyloxy)-6-*iso*-butylidenecyclohex-2-enone (12d). Triphenylphosphine (217 mg, 0.83 mmol) and the enone **11d** (187 mg, 0.83 mmol) in dichloromethane (5 cm^3) was treated, in an analogous manner to that for the preparation of **6a**, with titanium (IV) *iso*-propoxide (0.12 cm^3, 0.41 mmol), titanium (IV) chloride (45 μl, 0.41 mmol) and *iso*-butyraldehyde (0.23 cm^3, 2.53 mmol). After work-up, flash chromatography (SiO_2) gave the dienone **12d** (93 mg, 0.33 mmol, 40%) as a colourless oil; $[\alpha]_D=-95.0$ (*c* 2.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 6.84 (1H, dt, *J*=10.3, 1.8 Hz, C*H*═CHC═O), 6.55 (1H, dd, *J*=9.7, 2.3 Hz, C═C*H*), 6.06 (1H, dd, *J*=10.3, 1.8 Hz, CH═C*H*C═O), 4.52 (1H, ddt, *J*=9.4, 5.4, 2.0 Hz, C*H*OTBS), 3.00 (1H, dd, *J*=14.0, 5.4 Hz, C*H*HCHOTBS), 2.70–2.59 (1H, m, C*H*(CH_3)$_2$), 2.55 (1H, ddd, *J*=14.0, 9.4, 2.4 Hz, CH*H*CHOTBS), 1.07 (3H, d, *J*=5.7 Hz, CHCH_3), 1.05 (3H, d, *J*=5.7 Hz, CHCH_3), 0.94 (9H, s, $SiC(CH_3)_3$), 0.14 (6H, s, Si(CH_3)$_2$); δ_C (100 MHz, $CDCl_3$) 188.2 (s), 153.1 (d), 146.2 (d), 129.5 (d), 129.4 (s), 67.2 (d), 35.8 (t), 27.1 (d), 25.8 (q), 22.6 (q), 22.0 (q), 18.1 (s), −4.6 (q), −4.8 (q); *m/z* (CI) 281.1941 ([MH]$^+$ $C_{16}H_{29}O_2Si$ requires 281.1937).

3.1.9. (4*S*)-(*E*)-6-Benzylidene-4-(*tert*-butyldimethylsilanyloxy)-cyclohex-2-enone (12e). Triphenylphosphine (225 mg, 0.86 mmol) and the enone **11d** (194 mg, 0.86 mmol) in dichloromethane (5 cm^3) was treated, in an analogous manner to that for the preparation of **6a**, with titanium (IV) *iso*-propoxide (0.13 cm^3, 0.44 mmol), titanium (IV) chloride (47 μl, 0.43 mmol) and benzaldehyde (0.26 cm^3, 2.56 mmol). After work-up, flash chromatography (SiO_2) gave the dienone **12e** (166 mg, 0.53 mmol, 62%) as a white solid; mp 40–42 °C (Et_2O); $[\alpha]_D=-179.1$ (*c* 1.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.65 (1H, d, *J*=2.6 Hz, C═C*H*Ar), 7.49–7.28 (5H, m, Ar*H*), 6.89 (1H, dt, *J*=10.2, 1.9 Hz, C*H*═CHC═O), 6.16 (1H, dd, *J*=10.2, 1.9 Hz, CH═C*H*C═O), 4.56 (1H, ddt, *J*=9.1, 5.4, 1.9 Hz, C*H*OTBS), 3.39 (1H, dd, *J*=14.4, 5.4 Hz, C*H*HCHOTBS), 2.83 (1H, ddd, *J*=14.4, 9.1, 2.6 Hz, CH*H*CHOTBS), 0.90 (9H, s, $SiC(CH_3)_3$), 0.10 (3H, s, SiCH_3), 0.07 (3H, s, SiCH_3); δ_C (100 MHz, $CDCl_3$) 188.1 (s), 152.9 (d), 136.5 (d), 129.6 (d), 129.5 (s), 129.4 (d), 128.6 (d), 128.5 (d), 127.9 (s), 66.8 (d), 36.9 (t), 25.7 (q), 18.1 (s), −4.6 (q), −4.8 (q); *m/z* (CI) 315.1788 ([MH]$^+$ $C_{19}H_{27}O_2Si$ requires 315.1780).

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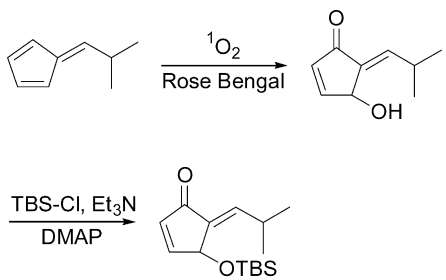
14. 4-Oxy-5-alkylidene cyclopentenones can be prepared utilising the procedures described in (a) Kawamoto, A.; Kosugi, H.; Uda, H. *Chem. Lett.* **1972**, 807. (b) Roberts, S. M.; Santoro, M. G.; Änggård, E. E. PCT Pat. Appl. WO 01 44254. (c) Snape, T. J. PhD Thesis, University of Liverpool, 2003; as follows:



($\pm$)-4-[*tert*-Butyldimethylsilanyloxy]-5-[2-methylprop-(*E*)-ylidene]-cyclopent-2-enone. A solution of 6-*iso*-propylfulvene (1.00 g, 8.32 mmol) and a catalytic amount of Rose Bengal in methanol (200 cm^3) was stirred at room temperature with a steady stream of oxygen bubbling through it for 20 min. The solution was irradiated (500W IR lamp), with continuation of the stream of oxygen, for 13 h. The irradiation and oxygen flow were ceased and the methanol removed in vacuo. Flash chromatography (SiO_2, 40% ethyl acetate in hexane) gave an inseparable mixture of the (*E*) and (*Z*)-isomers of the alcohol (320 mg, 2.10 mmol, 25%) as an orange oil. This mixture of alcohols (2.48 g, 16.3 mmol) in dry dichloromethane (24 cm^3) was added dropwise to a stirred solution of *tert*-butyldimethylsilylchloride (3.19 g, 21.2 mmol), triethylamine (8.0 cm^3, 57.0 mmol) and a catalytic amount of dimethylaminopyridine (0.26 g, 2.13 mmol) in dichloromethane (24 cm^3) at 0 °C, under an atmosphere of nitrogen. The reaction mixture was allowed to warm to room temperature over 16 h. Water (60 cm^3) was added, the phases separated and the aqueous phase was extracted with dichloromethane (3×50 cm^3). The combined organics were dried over anhydrous magnesium sulfate and evaporated in vacuo. Flash chromatography (SiO_2, 10% ethyl acetate in petrol) gave the (*Z*)-isomer of the title compound (392 mg, 1.47 mmol, 9.0%) as a yellow oil, followed by the (*E*)-isomer (1.27 g, 4.77 mmol, 29%) also as a yellow oil; δ_H (400 MHz, $CDCl_3$) 7.36 (1H, dd, *J*=6.0, 2.3 Hz, C*H*=CHC=O), 6.45 (1H, d, *J*=10.4 Hz, C=C*H*), 6.37 (1H, d, *J*=6.0 Hz, CH=C*H*C=O), 5.36 (1H, m, C*H*OTBS), 2.94–2.78 (1H, m, C*H*$(CH_3)_2$), 1.08 (3H, d, *J*=6.7 Hz, CHCH_3), 1.07 (3H, d, *J*=6.7 Hz, CHCH_3), 0.91 (9H, s, SiC$(CH_3)_3$), 0.17 (3H, s, SiCH_3), 0.15 (3H, s, SiCH_3); δ_C (100 MHz, $CDCl_3$) 195.4 (s), 158.1 (d), 144.9 (d), 136.5 (d), 134.8 (s), 71.1 (d), 28.6 (d), 26.1 (q), 22.4 (q), 22.3 (q), 18.3 (s), −3.3 (q), −4.0 (q); *m/z* (EI) 266 ($[M]^+$, 1%), 209 ($[M-C_4H_9]^+$, 100). Found $[M]^+$ 266.1701 ($[M]^+$ $C_{15}H_{26}O_2Si$ requires 266.1702). Found: C, 67.7; H, 9.9, $C_{15}H_{26}O_2Si$ requires C, 67.6; H, 9.8%.

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Synthesis of 4-azacyclopent-2-enones and 5,5-dialkyl-4-azacyclopent-2-enones

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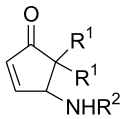
Abstract—Three different methods are reported for the preparation of 4-azacyclo-2-enones **1**, two of which allow the preparation of the compounds in optically active form. In addition, a facile route to 4-aza-5,5-dimethylcyclopent-2-enones **2** is disclosed.

1. Introduction

4-Aza-cyclopentenones **1** and **2** are potentially interesting scaffolds for parallel synthesis/combinatorial chemistry and are possibly useful building blocks for the construction of carbocyclic nucleosides.[1] Paradoxically, little work has been reported in the literature concerning the synthesis of such compounds.[2] In our laboratories we were keen to access these materials in racemic and optically active form in connection with our studies concerning the anti-viral activity of simple cyclopentenones.[3]



(**1**) R^1 = H; R^2 = alkyl, aryl or protecting group
(**2**) R^1 = CH_3; R^2 = alkyl, aryl or protecting group

2. Results and discussion

Initially, the earlier studies of Harris attracted our attention.[4] Harris showed that 4-hydroxycyclopent-2-enone **3** could be converted into the urethane **4** which itself was transformed into the 4-anilino-compound **8** (with loss of CO_2) on treatment with triethylamine (Scheme 1). We found that the same two-step transformation could be applied more broadly and, for example, was accomplished by reacting hydroxyketone **3** with *N*-tosylisocyanate to afford compound **5** (44%), which was converted into the desired product **9** (68%) on treatment with base. Similarly the compound **10** was prepared in 42% overall yield through the intermediate formation of urethane **6**.

The synthesis of the phenoxycarbonyl compound **11** suffered from a low yield (27%) in the first step, although the rearrangement/decarboxylation of **7** proceeded in almost quantitative yield. Interestingly, reaction of the alcohol **3** with chloroacetyl isocyanate gave the rearranged product **12** directly in 40% yield.

Overall, this pathway suffered from some drawbacks. First, the overall yields were only modest to good. In addition, the decarboxylative rearrangements of some other intermediates (for example those derived by reaction of **3** with cyclohexyl- or *tert*-butyl-isocyanate) were capricious and none of the desired product could be detected. One of our target compounds, 4-*tert*-butoxycarbonylaminocyclopent-2-enone **13** could not be obtained. Finally, the hydroxyketone **3** is not readily available in optically active form,[5] and therefore access to optically active compounds was not facile.

The second methodology investigated, specifically to prepare compound **13**, involved, in the first step, the cycloaddition of the nitroso-compound derived from **14** and cyclopentadiene (Scheme 2) to furnish the bicyclic compound **15**. This proceeded as reported previously,[6,7] as

Keywords: 4-Aza-cyclopentenones; 4-Aza-cyclopent-2-en-1-ols; Asymmetric synthesis of aminocyclopentenols; Lipase resolution.
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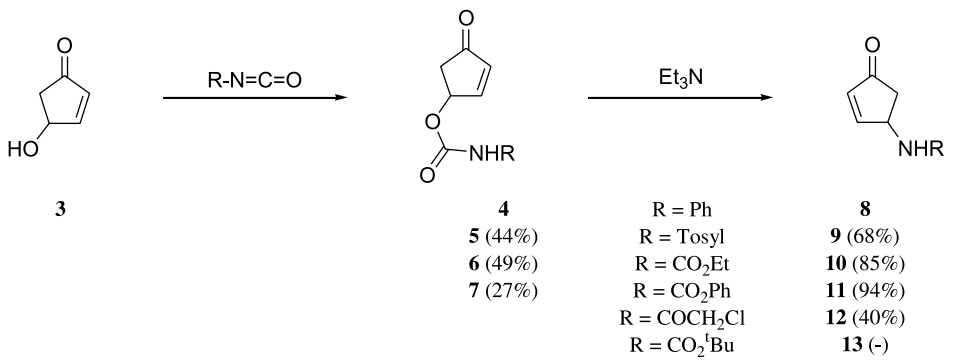
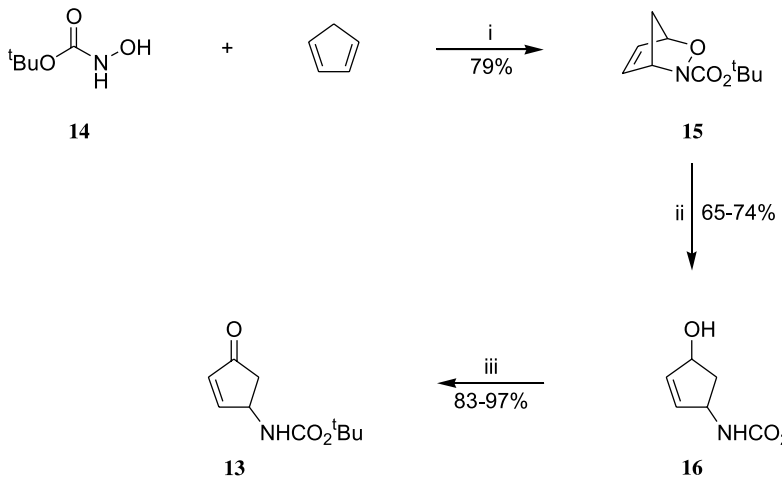


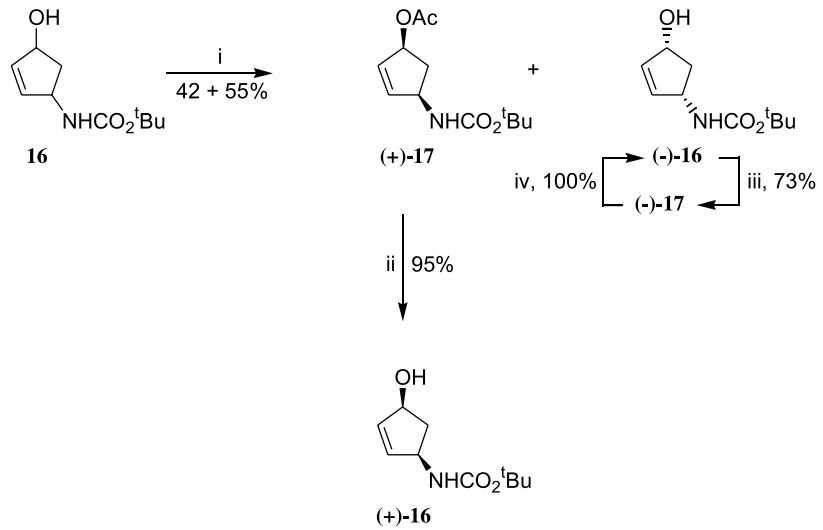
Scheme 1.



Scheme 2. Reagents and conditions: (i) $(n\text{-Bu})_4NIO_4$, CH_2Cl_2, 1 h, 79%; (ii) $Mo(CO)_6$, CH_3CN, H_2O, then $NaBH_4$, reflux, 3 h, 65%; OR Na/Hg, Na_2HPO_4, C_2H_5OH, 0 °C, 1.5 h, 74%; (iii) PCC, CH_2Cl_2, 4 Å mol. sieve, 2 h, 83%; OR TEMPO, H_5IO_6, CH_2Cl_2, 2.5 h, 97%.

did the N–O bond cleavage using $Mo(CO)_6$.[6] However, we were anxious to find a replacement for the latter reagent and we found that sodium amalgam was a suitable alternative,[8] leading to a cleaner reaction providing the protected amino alcohol **16** in 74% yield in a protocol more suitable for scale-up. Oxidation of the alcohol **16** to the enone **13** proceeded smoothly using pyridinium chlorochromate, or periodate and a catalytic amount of TEMPO.[9]

The intermediacy of alcohol **16** in this pathway suggested this might be a suitable substrate for enzyme-controlled kinetic resolution.[10] Incubation with Amano PS-C II lipase



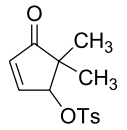
Scheme 3. Reagents and conditions: (i) Amano PS-C II lipase, CH_2CHOAc, CH_2Cl_2, 35 °C, 72 h, 42% of (+)-**17** and 55% of (−)-**16**; (ii) LiOH, C_2H_5OH, H_2O, 4 h, 95%; (iii) CH_3COCl, CH_2Cl_2, 0 °C, 18 h, 84%; Amano PS-C II lipase, $(CH_3)_2CO$, pH 7.4 buffer, 35 °C, 54 h, 73% of (−)-**17** and 20% of (+)-**16**; (iv) LiOH, C_2H_5OH, H_2O, 100%.

in dichloromethane containing vinyl acetate gave the acetate (+)-**17** (42%) and recovered alcohol (−)-**16** (55%) after the biotransformation, followed by work-up in a conventional manner (Scheme 3). The recovered alcohol (−)-**16** was acetylated and this acetate (−)-**17** was hydrolysed in phosphate buffer using Amano PS-C II lipase to give optically enriched (−)-**17** (73%) and alcohol (+)-**16** (20%). The acetate (+)- and (−)-**17** were readily hydrolysed to the alcohols (+)- and (−)-**16**, respectively. The optical purities were measured as 92 and 99% ee by GC employing a chiral column after oxidation to (+)- and (−)-**13**, respectively.

To circumvent the loss of material at the stage of the kinetic resolution a new method was sought to provide optically active **16** that was less wasteful in material. The initial findings of this initiative are reported here but full details will be reported elsewhere. First, the readily available *meso*-diacetate **18** could be mono-substituted by using $HN(CO_2^tBu)_2$ and a palladium catalyst to give the racemic acetate **19**.[11] Treatment of **19** with TFA then gave the acetate **17** is very short order.

Furthermore, the monoacetate **20** could be prepared from the corresponding *meso*-diacetate **18** using an enzyme-catalysed hydrolysis.[12] This hydroxyester **20** was then directly converted into the bis-protected amine **21** using similar conditions.[13] Mono-deprotection of **21** was then effected, to provide the protected amine **16** with a enantiomeric excess of 98% in only 3 high yielding transformations (Scheme 4).

The preparation of compounds of type **2** involved another novel transformation in the key step. 2-Methylcyclopentane-1,3-dione was converted into 4-hydroxy-5,5-dimethylcyclopent-2-enone as prescribed by Yamada et al.[14] and reaction of this alcohol with *para*-toluenesulfonyl chloride gave the tosylate **22**. Reaction of **22** with the appropriate amine gave the amines **23**-**25** directly in 65–74% yield. It is likely that the reaction proceeds through conjugate addition of the amine to the enone and secondary rearrangement through an aziridinium species, rather than direct attack at the neopentyl centre. In accord with this postulate, reaction of tosylate **22** with hexanethiol gave, under mild conditions, the conjugate addition products **28** and **30** and the enone **26** (ratio 1:1:2). Heating the major conjugate adduct **28** (*trans*-stereochemistry) furnished the enone **26** in high yield, but the *cis*-isomer **30** remained unchanged after prolonged heating under the same conditions. In a similar manner, under the appropriate reaction conditions, octanethiol and the tosylate **22** gave a mixture of Michael adducts **29** and **31** as well as the enone **27** in a ratio of 5:4:8. Heating **29** in dichloromethane for 1 h afforded **27** in 89% yield whereas, **31** was stable under these conditions.



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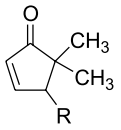
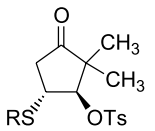
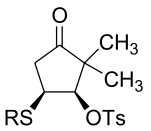


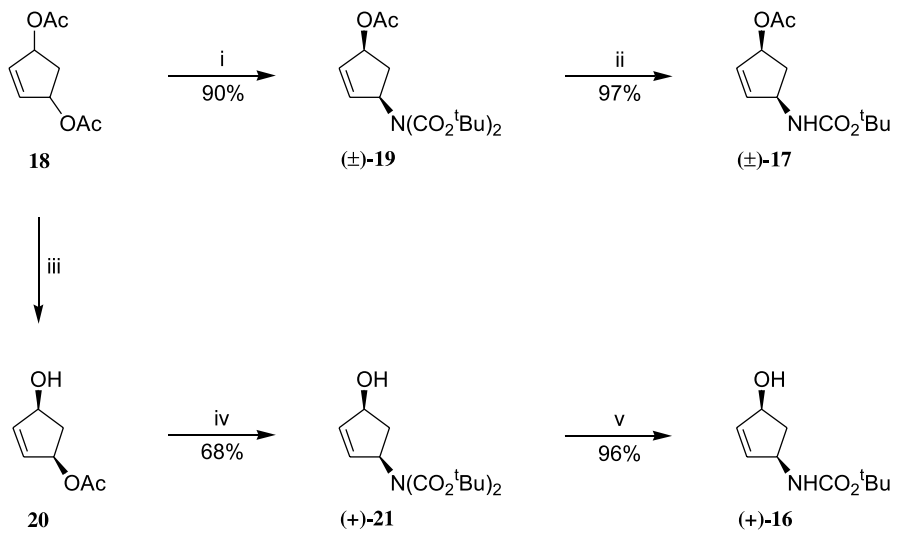
(**23**) R = $N(CH_3)CH_2Ph$
(**24**) R = $N[CH_2CH_2]_2O$
(**25**) R = $N[CH_2CH_2]_2NC_6H_4F$
(**26**) R = SC_6H_{13}
(**27**) R = SC_8H_{17}





28 R = C_6H_{13} **30**
29 R = C_8H_{17} **31**

In conclusion, the preparation of 4-azacyclopentenones according to the method of Harris has been used to access compounds **8**-**12**. The route does not allow the preparation of the *N*-Boc derivative **13**. However, this compound can be made from the alcohol **16**, kinetic resolution of **16** using a lipase allows access to optically active material. However, the preferred route to optically active **13** involves conversion of the monoester **20** into the diprotected amine **21** in the



Scheme 4. Reagents and conditions: (i) $Pd_2(dba)_3$, dppf, $NH(Boc)_2$, BSA, THF, 50 °C, 12 h, 90%; (ii) TFA, CH_2Cl_2, 20 h, 97%; (iii) see Ref. 12; (iv) $Pd_2(dba)_3$, dppf, $NH(Boc)_2$, BSA, THF, 45 °C, 3 h, 68%; (v) TFA, CH_2Cl_2, 20 h, 96%.

key step. The scope of the latter transformation is under active investigation.

3. Experimental

3.1. General

Starting materials were purchased from commercial sources and were used without further purification. Dichloromethane was distilled from calcium hydride and tetrahydrofuran was distilled from sodium benzophenone ketyl. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded using a Bruker AMX400 spectrometer. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded using a Varian Gemini 2000 spectrometer. Optical rotation measurements were recorded using an Optical Activity, Polaar 2001 polarimeter at 589 nm and quoted in units of 10^{-1} deg cm^2 g^{-1}. Flash column chromatography was performed under moderate pressure using silica gel—ICN 32-63, 60 Å. Analytical HPLC measurements were performed on a Gilson HPLC machine using an OD column and GC measurements were performed on a Shimadzu GC-14AH machine using a Lipodex E (Macherey-Nagel) column.

3.1.1. 3-(4-Oxocyclopent-2-enyl)-4-methylphenylsulfonyl carbamic acid (9).[15] *p*-Tolylsulfonyl isocyanate (2.94 g, 14.9 mmol) was added to a solution of the enone **3** (1.46 g, 14.9 mmol) in dry dichloromethane (10 mL) under a nitrogen atmosphere and the reaction mixture was stirred at room temperature for 5 h. The dichloromethane was removed in vacuo and the crude product was purified by flash chromatography (SiO_2, 40% ethyl acetate in hexane) to afford the compound **5** (1.93 g, 6.54 mmol, 44%) as a light yellow solid; R_f 0.25 (50% ethyl acetate in hexane); δ_H (400 MHz, $CDCl_3$) 7.87–7.76 (2H, m, Ar*H*), 7.39–7.32 (3H, m, C*H*=CHC=O, Ar*H*), 6.20 (1H, dd, *J*=5.6, 1.8 Hz, CH=C*H*C=O), 4.96 (1H, d, *J*=9.1 Hz, N*H*), 4.63 (1H, m, C*H*OR), 2.58 (1H, dd, *J*=18.8, 6.7 Hz, C*H*H), 2.45 (3H, s, ArCH_3), 1.98 (1H, dd, *J*=18.8, 2.5 Hz, CH*H*); δ_C (100 MHz, $CDCl_3$) 205.3 (s), 160.9 (d), 145.7 (s), 144.3 (s), 137.2 (s), 136.0 (d), 130.1 (d), 127.2 (d), 53.6 (d), 42.1 (t), 21.6 (q).

A catalytic amount of triethylamine (3–4 drops) was added to a solution of the enone **5** (148 mg, 0.50 mmol) in dry chloroform (5 mL) under a nitrogen atmosphere and the reaction mixture was stirred at room temperature for 4 h. The chloroform was removed in vacuo and the crude product was purified by flash chromatography (SiO_2, 40% ethyl acetate in hexane) to afford the title compound **9** (86 mg, 0.34 mmol, 68%) as a white crystalline solid; δ_H (400 MHz, $CDCl_3$) 7.75 (2H, d, *J*=8.2 Hz, Ar*H*), 7.37 (1H, dd, *J*=5.7, 2.4 Hz, C*H*=CHC=O), 7.35 (2H, d, *J*=8.2 Hz, Ar*H*), 6.20 (1H, dd, *J*=5.7, 1.8 Hz, CH=C*H*C=O), 4.80 (1H, d, *J*=9.2 Hz, N*H*), 4.60 (1H, m, C*H*NH), 2.55 (1H, dd, *J*=18.8, 6.7 Hz, C*H*H), 2.45 (3H, s, ArCH_3), 1.95 (1H, dd, *J*=18.8, 2.6 Hz, CH*H*); δ_C (100 MHz, $CDCl_3$) 205.1 (s), 160.7 (d), 144.3 (s), 137.3 (s), 136.1 (d), 130.1 (d), 127.2 (d), 53.6 (d), 42.2 (t), 21.6 (q); *m*/*z* (CI) 269 ([MNH_4]$^+$, 100%), 252 ([MH]$^+$, 20). Found [MH]$^+$ 252.0699 ([MH]$^+$ $C_{12}H_{14}NO_3S$ requires 252.0694).

3.1.2. (4-Oxocyclopent-2-enyl)-carbamic acid ethyl ester (10). Ethoxycarbonyl isocyanate (0.90 mL, 8.72 mmol) was added to a solution of the enone **3** (1.08 g, 11.0 mmol) in dry dichloromethane (20 mL) under a nitrogen atmosphere and the reaction mixture was stirred at room temperature for 5 h. The dichloromethane was removed in vacuo, then filtered through a short pad of silica eluting with a 2:1 mixture of dichloromethane and petrol to give the crude product **6** (1.16 g, 5.45 mmol, 49%) as a brown oil, which was taken on without further purification.

Triethylamine (0.84 mL, 6.03 mmol) was added to a solution of the crude enone **6** (1.16 g, 5.45 mmol) in dry chloroform (20 mL) under a nitrogen atmosphere and the reaction mixture was stirred at room temperature for 3 h. The chloroform was removed in vacuo and the crude product was purified by flash chromatography (SiO_2, 50% ethyl acetate in hexane) to afford the title compound **10** (0.78 g, 4.62 mmol, 85%) as a white crystalline solid; R_f 0.3 (50% ethyl acetate in hexane); δ_H (400 MHz, $CDCl_3$) 7.53 (1H, m, C*H*=CHC=O), 6.25 (1H, m, CH=C*H*C=O), 5.00 (1H, br. s, N*H*), 4.91 (1H, br. s, C*H*NH), 4.15 (2H, q, *J*=7.1 Hz, CH_2CH$_3$), 2.86 (1H, dd, *J*=18.7, 6.5 Hz, C*H*H), 2.18 (1H, dd, *J*=18.7, 2.4 Hz, CH*H*), 1.26 (3H, t, *J*=7.1 Hz, CH$_2$CH_3); δ_C (100 MHz, $CDCl_3$) 206.2 (s), 161.7 (d), 155.9 (s), 135.4 (d), 61.4 (t), 51.4 (d), 42.3 (t), 14.5 (q); *m*/*z* (CI) 187 ([MNH_4]$^+$, 100%), 170 ([MH]$^+$, 92), 169 ([M]$^+$, 14). Found [MH]$^+$ 170.0814 ([MH]$^+$ $C_8H_{12}NO_3$ requires 170.0817).

3.1.3. (4-Oxocyclopent-2-enyl)-carbamic acid phenyl ester (11). Phenoxycarbonyl isocyanate (1.60 mL, 12.1 mmol) was added to a solution of the enone **3** (1.18 g, 12.0 mmol) in dry dichloromethane (15 mL) under a nitrogen atmosphere and the reaction mixture was stirred at room temperature for 24 h. The dichloromethane was removed in vacuo and the crude product was purified by flash chromatography (SiO_2, 20% ethyl acetate in hexane) to afford the compound **7** (0.85 g, 3.26 mmol, 27%) as a white solid; R_f 0.4 (50% ethyl acetate in hexane); δ_H (400 MHz, $CDCl_3$) 7.60 (1H, dd, *J*=5.7, 2.4 Hz, C*H*=CHC=O), 7.38 (2H, t, *J*=7.9 Hz, Ar*H*), 7.23 (1H, t, *J*=7.5 Hz, Ar*H*), 7.14 (2H, m, Ar*H*), 6.30 (1H, dd, *J*=5.7, 1.7 Hz, CH=C*H*C=O), 5.33 (1H, m, N*H*), 5.07 (1H, m, C*H*OR), 2.93 (1H, dd, *J*=18.8, 6.8 Hz, C*H*H), 2.28 (1H, dd, *J*=18.8, 2.5 Hz, CH*H*); δ_C (100 MHz, $CDCl_3$) 205.8 (s), 161.2 (d), 154.0 (s), 150.7 (s), 135.8 (d), 129.4 (d), 125.7 (d), 121.4 (d), 120.5 (s), 51.6 (d), 42.0 (t).

Triethylamine (0.23 mL, 1.65 mmol) was added to a solution of the enone **7** (0.41 g, 1.57 mmol) in dry chloroform (10 mL) under a nitrogen atmosphere and the reaction mixture was stirred at room temperature for 4 h. The solvent was removed in vacuo to afford the title compound **11** (0.32 g, 1.47 mmol, 94%) as a copper coloured solid; R_f 0.4 (50% ethyl acetate in hexane); mp 111–112 °C (EtOAc/hexane); δ_H (400 MHz, $CDCl_3$) 7.58 (1H, dd, *J*=5.6, 2.4 Hz, C*H*=CHC=O), 7.40–7.33 (2H, m, Ar*H*), 7.247.19 (1H, m, Ar*H*), 7.15–7.10 (2H, m, Ar*H*), 6.29 (1H, dd, *J*=5.6, 1.8 Hz, CH=C*H*C=O), 5.28 (1H, br. s, N*H*), 5.09–5.01 (1H, m, C*H*NH), 2.91 (1H, dd, *J*=18.6, 6.8 Hz, C*H*H), 2.27 (1H, dd, *J*=18.6, 2.2 Hz, CH*H*); δ_C (100 MHz, $CDCl_3$) 205.7 (s), 161.1 (d), 153.9 (s), 150.7 (s),

135.8 (d), 129.4 (d), 125.7 (d), 121.4 (d), 51.6 (d), 42.0 (t); *m/z* (CI) 235 ($[MNH_4]^+$, 100%), 218 ($[MH]^+$, 16), 217 ($[M]^+$, 0.3). Found $[MH]^+$ 218.0824 ($[MH]^+$ $C_{12}H_{12}NO_3$ requires 218.0817).

3.1.4. 2-Chloro-*N*-(4-oxocyclopent-2-enyl)-acetamide (12). Chloroacetyl isocyanate (0.84 g, 9.86 mmol) was added to a solution of the enone **3** (0.96 g, 9.80 mmol) in dry dichloromethane (10 mL) under a nitrogen atmosphere and the reaction mixture was stirred at room temperature for 20 h. The dichloromethane was removed in vacuo and the crude product was purified by flash chromatography (SiO_2, 20% ethyl acetate in hexane) to afford the title compound **12** (0.68 g, 3.92 mmol, 40%) as a white solid; R_f 0.5 (ethyl acetate); mp 99–100 °C (EtOAc/hexane); δ_H (400 MHz, $CDCl_3$) 7.53 (1H, dd, *J*=5.6, 2.4 Hz, C*H*═CHC═O), 6.71 (1H, s, N*H*), 6.33 (1H, dd, *J*=5.6, 1.8 Hz, CH═C*H*C═O), 5.31–5.23 (1H, m, C*H*NH), 4.09 (2H, s, CH_2Cl), 2.91 (1H, dd, *J*=18.8, 6.8 Hz, C*H*H), 2.22 (1H, dd, *J*=18.8, 2.7 Hz, CH*H*); δ_C (100 MHz, $CDCl_3$) 205.5 (s), 165.8 (s), 160.6 (d), 136.2 (d), 50.0 (d), 42.4 (t), 41.7 (t); *m/z* (CI) 191 ($[MNH_4]^+$, 100%), 174 ($[MH]^+$, 39), 173 ($[M]^+$, 3.7). Found $[MH]^+$ 174.0321 ($[MH]^+$ $C_7H_9NO_2Cl$ requires 174.0322).

3.1.5. 2-Oxa-3-azabicyclo[2.2.1]hept-5-ene-3-carboxylic acid *tert*-butyl ester (15).[6] Water (5 mL) and sodium carbonate (23.9 g, 0.23 mol) were added to a suspension of hydroxylamine hydrochloride (24.0 g, 0.35 mol) in diethyl ether (150 mL). The suspension was stirred at room temperature for 1 h, then cooled to 0 °C. Subsequently, a solution of di-*tert*-butyl dicarbonate (50.2 g, 0.23 mol) in diethyl ether (50 mL) was added dropwise over 30 min and the suspension was allowed to warm up to room temperature, then stirred for 3 h. Upon completion of reaction, the mixture was filtered and washed with ether (2×100 mL). The filtrate was evaporated to dryness to yield a colourless oil. Upon addition of cyclohexane, compound **14** was crystallised as colourless needles (27.2 g, 0.20 mol, 89%, 2 crops).

Tetra-*n*-butylammonium periodate (2.0 g, 4.67 mmol) was added to a solution of freshly cracked cyclopentadiene (0.46 g, 6.97 mmol) in dichloromethane (15 mL). *tert*-Butyl-*N*-hydroxycarbamate **14** (0.62 g, 4.67 mmol) was added portionwise over 5 min and the solution was stirred for 1 h at room temperature. Upon completion of reaction, the organic solution was washed successively with sodium thiosulfate (10% aq. soln., 2×50 mL) and sodium hydrogen carbonate (sat'd. aq., 80 mL), then dried over anhydrous magnesium sulfate, filtered and concentrated to give a crude black oil. Flash chromatography (SiO_2, 20% ethyl acetate in petrol) gave the bicyclic adduct **15** (0.73 g, 3.71 mmol, 79%) as a yellow oil, which solidified upon standing in the freezer; δ_H (400 MHz, $CDCl_3$) 6.41 (2H, m, C*H*═C*H*), 5.20 (1H, m, C*H*NBoc), 4.98 (1H, m, C*H*ON), 1.98 (1H, dt, *J*=8.5, 1.9 Hz, C*H*H), 1.73 (1H, m, CH*H*), 1.46 (9H, s, $CO_2C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 158.6 (s), 134.1 (d), 132.9 (d), 83.5 (d), 81.8 (s), 65.0 (d), 48.1 (t), 28.2 (q).

3.1.6. (4-Hydroxycyclopent-2-enyl)-carbamic acid *tert*-butyl ester (16). *Method A*.[6] Molybdenum hexacarbonyl (1.46 g, 5.53 mmol) was added to a solution of the bicycle **15** (0.70 g, 3.55 mmol) in a 7:1 mixture of acetonitrile and water (24 mL). The suspension was stirred for 10 min at room temperature, then sodium borohydride (0.07 g, 1.85 mmol) was added and the suspension was heated under reflux for 3 h. Upon completion of reaction, the mixture was allowed to cool to room temperature, filtered through a celite® plug, and evaporated to dryness to give a dark oil. Flash chromatography (SiO_2, 50% ethyl acetate in petrol) gave the alcohol **16** (0.46 g, 2.31 mmol, 65%) as a colourless oil; δ_H (400 MHz, $CDCl_3$) 6.02–5.96 (1H, m, C*H*═CH), 5.85 (1H, dd, *J*=5.5, 1.2 Hz, CH═C*H*), 4.82–4.67 (2H, m), 4.47–4.39 (1H, m), 2.75 (1H, dt, *J*=14.4, 7.7 Hz, C*H*H), 2.63–2.57 (1H, m, CH*H*), 1.56–1.50 (1H, m, O*H*), 1.45 (9H, s, $CO_2C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 155.2 (s), 136.1 (d), 134.2 (d), 79.6 (s), 75.3 (d), 55.0 (d), 41.5 (t), 28.4 (q); *m/z* (CI). Found $[MH]^+$ 200.1285 ($[MH]^+$ $C_{10}H_{18}NO_3$ requires 200.1287).

Method B. Disodium hydrogen phosphate (42.3 g, 0.30 mol) was added to a solution of the bicycle **15** (16.9 g, 85.7 mmol) in ethanol (230 mL). After cooling to 0 °C, freshly prepared and pulverised sodium amalgam (150 g, 5% sodium, 0.33 mol) was added in one portion (CAUTION: EXOTHERM). However, after stirring for 1 h at 0 °C some starting material remained, so further amalgam (50 g, 0.11 mol) was added. Further stirring at 0 °C for 30 min allowed full consumption of starting material, so the reaction mixture was then filtered through a celite® plug. The filtrate was then diluted with water (350 mL) and extracted with dichloromethane (3×100 mL). The combined organic extracts were then dried over anhydrous magnesium sulfate, and evaporated in vacuo to give the alcohol **16** (12.7 g, 63.7 mmol, 74%) as a pale yellow oil of suitable purity to be taken on and with identical data to the material prepared via the previous method.

3.1.7. (4-Oxocyclopent-2-enyl)-carbamic acid *tert*-butyl ester (13). *Method A*. 4 Å powdered, activated, molecular sieves (0.50 g) and pyridinium chlorochromate (0.60 g, 2.78 mmol) were successively added to a solution of the alcohol **16** (0.46 g, 2.31 mmol) in anhydrous dichloromethane (20 mL). The suspension was stirred for 2 h at room temperature. Upon completion of reaction, the mixture was filtered over a short silica gel column (50% ethyl acetate in petrol) to give the ketone **13** (0.38 g, 1.93 mmol, 83%) as a white solid; δ_H (400 MHz, $CDCl_3$) 7.51 (1H, m, C*H*═CHC═O), 6.21 (1H, dd, *J*=5.7, 0.7 Hz, CH═C*H*C═O), 4.94 (2H, m, N*H*+C*H*NH), 2.83 (1H, m, C*H*H), 2.17 (1H, m, CH*H*), 1.45 (9H, s, $CO_2C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 206.9 (s), 162.6 (d), 155.5 (s), 135.5 (d), 80.6 (s), 51.5 (d), 42.7 (t), 28.7 (q); *m/z* (EI). Found $[M]^+$ 197.1057 ($[M]^+$ $C_{10}H_{15}NO_3$ requires 197.1052).

Method B. TEMPO (91 mg, 0.58 mmol) and periodic acid (14.6 g, 64.0 mmol) were successively added to a solution of the alcohol **16** (11.5 g, 57.7 mmol) in dichloromethane (250 mL). The suspension was stirred for 2.5 h at room temperature. The reaction mixture was poured onto sodium thiosulfate (sat'd. aq., 300 mL) (CAUTION: EXOTHERM), the phases separated and the aqueous phase extracted with dichloromethane (3×500 mL). The combined organic extracts were then dried over anhydrous magnesium sulfate, and evaporated in vacuo to give the ketone **13** (11.0 g,

55.8 mmol, 97%) as a white solid of suitable purity to be taken on and with identical data to the material prepared via the previous method.

3.1.8. (2*S*,4*R*)-Acetic acid 4-*tert*-butoxycarbonylamino-cyclopent-2-enyl ester ((+)-17) and (2*S*,4*R*)-(4-hydroxycyclopent-2-enyl)-carbamic acid *tert*-butyl ester ((−)-16).[10] Vinyl acetate (7.0 mL, 76 mmol) and PS-C II Amano lipase (1.51 g) were successively added to a solution of the racemic alcohol (±)-**16** (1.51 g, 7.59 mmol) in anhydrous dichloromethane (40 mL) and the slurry was stirred for 72 h at 35 °C. The mixture was filtered and evaporated to dryness to give a yellow oil. Flash chromatography (SiO_2, 50% ethyl acetate in petrol) gave the optically active acetate (+)-**17** (0.76 g, 3.15 mmol, 42%) and the optically enriched alcohol (−)-**16** (0.82 g, 4.12 mmol, 55% recovery). Crystallisation from petroleum ether afforded the optically active acetate (+)-**17** (0.64 g) as white orthorhombic crystals, whose stereochemistry was elucidated by obtaining an X-ray structure; δ_H (400 MHz, $CDCl_3$) 5.97 (1H, d, J=5.6 Hz, C*H*=CH), 5.92 (1H, d, J=5.6 Hz, CH=C*H*), 5.54–5.48 (1H, m, C*H*OAc), 4.66 (2H, br. s, N*H*+C*H*NH), 2.81 (1H, dt, J=14.5, 7.3 Hz, C*H*H), 2.02 (3H, s, O_2CCH_3), 1.51 (1H, dt, J=14.5, 4.0 Hz, CH*H*), 1.44 (9H, s, $CO_2C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 170.5 (s), 155.0 (s), 136.9 (d), 132.0 (d), 79.5 (s), 77.4 (d), 54.3 (d), 38.6 (t), 28.3 (q), 21.1 (q); *m*/*z* (CI) 242 ($[MH]^+$, 15%), 182 ($[MH-AcOH]^+$, 34), 142 ($[MH_2-CO_2C(CH_3)_3]^+$, 77), 126 ($[MH-NHBoc]^+$, 100). Found $[MH]^+$ 242.1394 ($[MH]^+$ $C_{12}H_{20}NO_4$ requires 242.1392).

3.1.9. (2*R*,4*S*)-(4-Hydroxycyclopent-2-enyl)-carbamic acid *tert*-butyl ester ((+)-16). Lithium hydroxide monohydrate (0.17 g, 4.05 mmol) was added to a solution of the optically active acetate (+)-**17** (0.64 g, 2.66 mmol) in 75% aqueous ethanol (40 mL). The solution was stirred for 4 h at room temperature. Upon completion of reaction, the mixture was partitioned between water (40 mL) and ethyl acetate (40 mL), and the aqueous layer was further extracted with ethyl acetate (2×30 mL). The combined organic layers were washed successively with sodium hydrogen carbonate (sat'd. aq., 40 mL), water (40 mL) and brine (40 mL), then dried over anhydrous magnesium sulfate and evaporated to give the optically active alcohol (+)-**16** (0.50 g, 2.51 mmol, 95%) as a light yellow oil, which solidified upon standing at room temperature; $[\alpha]_D$=+64.0 (*c* 1.0, $CHCl_3$); and gave identical data to the racemic material described in Section 3.1.6.

3.1.10. (2*R*)-(4-Oxocyclopent-2-enyl)-carbamic acid *tert*-butyl ester ((+)-13). 4 Å powdered, activated, molecular sieves (0.50 g) and pyridinium chlorochromate (0.65 g, 3.02 mmol) were successively added to a solution of the optically active alcohol (+)-**16** (0.50 g, 2.54 mmol) in anhydrous dichloromethane (20 mL). The suspension was stirred for 1.5 h at room temperature. Upon completion of reaction, the mixture was filtered over a short silica gel column (50% ethyl acetate in petrol) to give the optically active cyclopentenone (+)-**13** (0.40 g, 2.03 mmol, 80%) as a white solid; ee=92% (determined by chiral GC (Lipodex; 140 °C; t_R (+)-**13**=19.0 min)); $[\alpha]_D$=+71.0 (*c* 1.0, $CHCl_3$); which gave identical data to the racemic material described in Section 3.1.7.

3.1.11. (2*R*,4*S*)-Acetic acid 4-*tert*-butoxycarbonylamino-cyclopent-2-enyl ester ((−)-17). A solution of acetyl chloride (0.53 mL, 7.45 mmol) in anhydrous dichloromethane (10 mL) was added slowly to a solution of the enriched alcohol (−)-**16** (1.13 g, 5.68 mmol) in a mixture of pyridine (10 mL) and anhydrous dichloromethane (10 mL), cooled to 0 °C. The mixture was stirred overnight at 0 °C. Upon completion of reaction, the mixture was evaporated and diluted with ethyl acetate (200 mL), then washed with citric acid (10% aq. soln., 200 mL). The aqueous layer was then extracted with ethyl acetate (150 mL). The combined organic layers were washed with brine (200 mL), dried over anhydrous magnesium sulfate, filtered and evaporated to give a yellow oil. Flash chromatography (SiO_2, 50% ethyl acetate in petrol) gave the optically enriched acetate (−)-**17** (1.15 g, 4.77 mmol, 84%) as a yellow oil, which showed identical spectroscopic data to its enantiomer (+)-**17** as described in Section 3.1.8.

PS-C II Amano lipase (1.15 g) was added to an emulsion of the enriched acetate (−)-**17** (1.15 g, 4.77 mmol) in a mixture of acetone (20 mL) and phosphate buffer (c=0.1 M, pH=7.4, 20 mL). The slurry was stirred for 54 h at 35 °C. The mixture was filtered and evaporated to dryness to give a yellow oil. Flash chromatography (SiO_2, 50% ethyl acetate in petrol) gave in the order of elution, the optically active acetate (−)-**17** (0.84 g, 3.49 mmol, 73% recovery), and the optically enriched alcohol (+)-**16** (0.19 g, 0.95 mmol, 20%).

3.1.12. (2*S*,4*R*)-(4-Hydroxycyclopent-2-enyl)-carbamic acid *tert*-butyl ester ((−)-16). Lithium hydroxide monohydrate (0.22 g, 5.24 mmol) was added to a solution of the optically active acetate (−)-**17** (0.84 g, 3.49 mmol) in 75% aqueous ethanol (48 mL). The solution was stirred overnight at room temperature. Upon completion of reaction, the mixture was partitioned between water (50 mL) and ethyl acetate (50 mL), and the aqueous layer was further extracted with ethyl acetate (2×50 mL). The combined organic layers were washed successively with sodium hydrogen carbonate (sat'd. aq., 50 mL), water (50 mL) and brine (50 mL), then dried over anhydrous magnesium sulfate and evaporated to give the optically active alcohol (−)-**16** (0.70 g, 100%) as a light yellow oil, which solidified upon standing at room temperature; $[\alpha]_D$=−67.0 (*c* 1.0, $CHCl_3$); and gave identical data to the racemic material described in Section 3.1.6.

3.1.13. (2*S*)-(4-Oxocyclopent-2-enyl)-carbamic acid *tert*-butyl ester ((−)-13). 4 Å powdered, activated, molecular sieves (0.75 g) and pyridinium chlorochromate (0.91 g, 4.22 mmol) were successively added to a solution of the optically active alcohol (−)-**16** (0.70 g, 3.52 mmol) in anhydrous dichloromethane (30 mL). The suspension was stirred for 1 h at room temperature. Upon completion of reaction, the mixture was filtered over a short silica gel column (50% ethyl acetate in petrol) to give the optically active cyclopentenone (−)-**13** (0.55 g, 2.79 mmol, 79%) as a white solid; ee=99% (determined by chiral GC (Lipodex; 140 °C; t_R (−)-**13**=18.4 min)); $[\alpha]_D$=−72.0 (*c* 1.0, $CHCl_3$); which gave identical data to the racemic material described in Section 3.1.7.

3.1.14. (2*RS*,4*SR*)-Acetic acid 4-*tert*-butoxycarbonylaminocyclopent-2-enyl ester ((±)-17). 1,1′-Bis(diphenylphosphino)ferrocene (1.43 g, 2.28 mmol), tris(dibenzylideneacetone)dipalladium (554 mg, 0.61 mmol) and anhydrous, oxygen-free tetrahydrofuran (90 mL) were added to dry reaction vessel, under an atmosphere of nitrogen, to give a very dark purple solution. After stirring for 20 min at room temperature, the solution turned dark orange/brown. Di-*tert*-butyl iminodicarboxylate (22.4 g, 0.10 mol) and the *meso*-diacetate **18** (19.0 g, 0.10 mol) were added and the resulting mixture was quickly degassed by placing under reduced pressure, then backfilling with nitrogen. *N*, *O*-Bis(trimethylsilyl)acetamide (21.0 g, 0.10 mol) was then added and a further 3 degassing cycles carried out. The resulting solution was heated to 50 °C for 12 h, when tlc analysis showed the reaction to be complete. Diethyl ether (200 mL) was then added and the mixture was poured onto ammonium chloride (sat'd., aq., 100 mL). The phases were then separated and the aqueous phase was extracted with dichloromethane (3×20 mL). The combined organic extracts were then dried over anhydrous magnesium sulfate and evaporated in vacuo. Flash chromatography (SiO_2, 12% ethyl acetate in hexane) gave the mono-substituted product **19** (31.7 g, 92.8 mmol, 90%) as a white solid; δ_H (400 MHz, $CDCl_3$) 5.98 (1H, dt, J=5.6, 1.7 Hz, C*H*=CH), 5.82 (1H, dt, J=5.6, 2.2 Hz, CH=C*H*), 5.59–5.53 (1H, m, C*H*OAc), 5.14–5.08 (1H, m, C*H*N), 2.84 (1H, dt, J=13.3, 8.0 Hz, C*H*H), 2.04 (3H, s, O_2CCH_3), 1.93 (1H, dt, J=13.3, 6.6 Hz, CH*H*), 1.49 (18H, s, $N[CO_2C(CH_3)_3]_2$); which was taken on without further characterisation.

Trifluoroacetic acid (15.3 g, 0.13 mol) was added to a solution of this product **19** (31.3 g, 91.7 mmol) in dichloromethane (450 mL) at 0 °C. The mixture was then stirred for 20 h. Sodium hydrogen carbonate (sat'd., aq., 400 mL) was then added, the phases separated and the aqueous phase extracted with dichloromethane (3×20 mL). The combined organic extracts were then dried over anhydrous magnesium sulfate and evaporated in vacuo. Flash chromatography (SiO_2, 25% ethyl acetate in hexane) gave the mono-Boc product (±)-**17** (21.5 g, 89.1 mmol, 97%) as a pale yellow oil, which gave identical data to the enantiomerically enriched material prepared by the method in Section 3.1.8.

3.1.15. (2*R*,4*S*)-(4-Hydroxycyclopent-2-enyl)-carbamic acid *tert*-butyl ester ((+)-16). 1,1′-Bis(diphenylphosphino)ferrocene (80 mg, 0.14 mmol), tris(dibenzylideneacetone)dipalladium (32 mg, 35 μmol) and anhydrous, oxygen-free tetrahydrofuran (4 mL) were added to dry reaction vessel, under an atmosphere of nitrogen, to give a very dark purple solution. After stirring for 15 min at room temperature, the solution turned dark orange/brown. This solution was added, via cannula, to a solution of di-*tert*-butyl iminodicarboxylate (0.75 g, 3.45 mmol) and the mono-acetate **20** (0.50 g, 3.42 mmol) in anhydrous, oxygen-free tetrahydrofuran (4 mL) and the resulting mixture was quickly degassed by placing under reduced pressure, then backfilling with nitrogen. *N*, *O*-Bis(trimethylsilyl)acetamide (0.84 g, 4.14 mmol) was then added and a further 2 degassing cycles carried out. The resulting solution was heated to 45 °C for 3 h, when tlc analysis showed the reaction to be complete. This was then filtered through a short pad of silica and the filtrate was treated with a solution of tetrabutylammonium fluoride in tetrahydrofuran and washed with brine. The organics were then dried over anhydrous magnesium sulfate and evaporated in vacuo. Flash chromatography (SiO_2, 25% ethyl acetate in hexane) gave the mono-substituted product **21** (714 mg, 2.39 mmol, 68%) as a white solid; mp 54–55 °C (EtOAc/hexane); δ_H (400 MHz, $CDCl_3$) 6.04 (1H, dt, J=5.4, 2.3 Hz, C*H*=CH), 5.76 (1H, dd, J=5.4, 2.3 Hz, CH=C*H*), 5.09 (1H, app. dq, J=9.3, 2.3 Hz, C*H*N), 4.60 (1H, m, C*H*OH), 3.53 (1H, br. d, J=11.0 Hz, O*H*), 2.68 (1H, ddd, J=15.1, 9.3, 7.9 Hz, C*H*H), 1.85 (1H, dt, J=15.1, 2.3 Hz, CH*H*), 1.49 (18H, s, $N[CO_2C(CH_3)_3]_2$); δ_C (100 MHz, $CDCl_3$) 153.3 (s), 136.8 (d), 131.4 (d), 82.8 (s), 75.7 (d), 60.2 (d), 38.8 (t), 28.0 (q); *m*/*z* (CI). Found $[MNa]^+$ 322.1642 ($[MNa]^+$ $C_{15}H_{25}NO_5Na$ requires 322.1630). Found: C, 60.4; H, 8.6; N, 4.4, $C_{15}H_{25}NO_5$ requires C, 60.2; H, 8.4; N, 4.7%.

Trifluoroacetic acid (0.41 g, 3.60 mol) was added to a solution of this product **21** (0.71 g, 2.37 mmol) in dichloromethane (12 mL) at 0 °C. The mixture was then stirred for 20 h. Sodium hydrogen carbonate (sat'd., aq., 12 mL) was then added, the phases separated and the aqueous phase extracted with dichloromethane (3×20 mL). The combined organic extracts were then dried over anhydrous magnesium sulfate and evaporated in vacuo. Flash chromatography (SiO_2, 50% ethyl acetate in hexane) gave the mono-Boc product (+)-**16** (452 mg, 2.27 mmol, 96%) as a pale yellow oil; ee=98% (determined by chiral HPLC (OD; 5% ethanol in hexane; t_R (+)-**16**=8.1 min; t_R (−)-**16**=7.3 min)); which gave identical data to the racemic material prepared by the method in Section 3.1.6.

3.1.16. Toluene-4-sulfonic acid 5,5-dimethyl-4-oxocyclopent-2-enyl ester (22). *p*-Toluenesulfonyl chloride (477 mg 2.50 mmol) was added to a solution of 4-hydroxy-5,5-dimethylcyclopent-2-enone (252 mg, 2.00 mmol) and 4-dimethylaminopyridine (366 mg, 3.00 mmol) in dichloromethane (6 mL) and the reaction mixture was stirred at room temperature for 2 h. The solvent was removed in vacuo and the residue was purified by flash chromatography (Si_2O, dichloromethane) to give the tosylate **22** (500 mg, 1.78 mmol, 89%) as a white solid; mp 74–75 °C (Et_2O/hexane); ν_{max}(film)/cm^{-1} 2976, 1727, 1598; δ_H (400 MHz, $CDCl_3$) 7.85 (2H, d, J=8.1 Hz, Ar*H*), 7.40 (2H, d, J=8.1 Hz, Ar*H*), 7.28 (1H, dd, J=6.0, 2.3 Hz, C*H*=CHC=O), 6.27 (1H, dd, J=6.0, 1.4 Hz, CH=C*H*C=O), 5.20–5.19 (1H, m, C*H*OTs), 2.48 (3H, s, ArCH_3), 1.04 (3H, s, CCH_3), 1.03 (3H, s, CCH_3); δ_C (100 MHz, $CDCl_3$) 208.5 (s), 155.5 (d), 145.5 (s), 134.9 (d), 133.3 (s), 130.1 (d), 127.9 (d), 86.2 (d), 47.3 (s), 22.3 (q), 21.7 (q), 20.7 (q); *m*/*z* (CI) 298 ($[MNH_4]^+$, 43%). Found $[MNH_4]^+$ 298.1113 ($[MNH_4]^+$ $C_{14}H_{20}NO_4S$ requires 298.1113). Found: C, 60.0; H, 5.7, $C_{14}H_{16}O_4S$ requires C, 60.0; H, 5.8%.

3.1.17. 4-(Benzylmethylamino)-5,5-dimethylcyclopent-2-enone (23). Benzyl methylamine (34 μL, 0.26 mmol) was added to a solution of tosylate **22** (33 mg, 0.12 mmol) in ethanol (12 mL) and the reaction was heated at reflux for 48 h. The reaction was allowed to cool and the solvent removed in vacuo. The crude product was dissolved in

diethyl ether (10 mL) and $NaHCO_3$ (sat'd., aq., 10 mL) added. The layers were separated and the aqueous layer was extracted with diethyl ether (3×5 mL). The combined organic layers were dried over anhydrous magnesium sulfate and evaporated in vacuo. Flash chromatography (SiO_2, 10% ethyl acetate in hexane) gave the title compound **23** (20 mg, 87 μmol, 74%) as a colourless oil; ν_{max}(film)/cm^{-1} 1712; δ_H (400 MHz, $CDCl_3$) 7.66 (1H, dd, *J*=6.0, 2.4 Hz, C*H*=CHC=O), 7.37–7.25 (5H, m, Ar*H*), 6.24 (1H, dd, *J*=6.0, 1.9 Hz, CH=C*H*C=O), 3.72 (2H, s, CH_2Ar), 3.62 (1H, t, *J*=2.2 Hz, C*H*N), 2.30 (3H, s, NCH_3), 1.19 (3H, s, CCH_3), 1.08 (3H, s, CCH_3); δ_C (100 MHz, $CDCl_3$) 213.1 (s), 160.6 (d), 139.4 (s), 132.8 (d), 128.4 (d), 128.3 (d), 127.1 (d), 74.3 (d), 60.2 (t), 48.2 (s), 40.3 (q), 26.4 (q), 20.1 (q); *m*/*z* (CI) 230 ([MH]$^+$, 100%). Found [MH]$^+$ 230.1553 ([MH]$^+$ $C_{15}H_{20}NO$ requires 230.1545).

3.1.18. 5,5-Dimethyl-4-morpholin-4-yl-cyclopent-2-enone (24). Morpholine (35 μL, 0.40 mmol) was added to a solution of tosylate **22** (50 mg, 0.18 mmol) in ethanol (18 mL) and the reaction was heated at reflux for 48 h. The reaction was allowed to cool and the solvent removed in vacuo. The crude product was dissolved in diethyl ether (5 mL) and $NaHCO_3$ (sat'd., aq., 5 mL) added. The layers were separated and the aqueous layer was extracted with diethyl ether (2×5 mL). The combined organic layers were dried over anhydrous magnesium sulfate and evaporated in vacuo. Flash chromatography (SiO_2, 50% ethyl acetate in hexane) gave the title compound **24** (23 mg, 0.12 mmol, 66%) as a pale orange oil; ν_{max}(film)/cm^{-1} 1713; δ_H (400 MHz, $CDCl_3$) 7.65 (1H, dd, *J*=6.0, 2.4 Hz, C*H*=CHC=O), 6.24 (1H, dd, *J*=6.0, 1.9 Hz, CH=C*H*C=O), 3.75–3.65 (4H, m, 2×CH_2), 3.35 (1H, t, *J*=2.2 Hz, C*H*N), 2.63 (4H, t, *J*=4.6 Hz, 2×CH_2), 1.15 (3H, s, CCH_3), 1.11 (3H, s, CCH_3); δ_C (100 MHz, $CDCl_3$) 213.0 (s), 159.4 (d), 133.3 (d), 76.1 (d), 67.6 (t), 52.9 (t), 48.3 (s), 26.6 (q), 20.6 (q); *m*/*z* (CI) 196 ([MH]$^+$, 100%). Found [MH]$^+$ 196.1340 ([MH]$^+$ $C_{11}H_{18}NO_2$ requires 196.1337).

3.1.19. 4-[4-(4-Fluorophenyl)-piperazin-1-yl]-5,5-dimethylcyclopent-2-enone (25). 1-(4-Fluorophenyl)-piperazine (83 mg, 0.46 mmol) was added to a solution of tosylate **22** (60 mg, 0.21 mmol) in ethanol (20 mL) and the reaction was heated at reflux for 19 h. The reaction was allowed to cool and the solvent removed in vacuo. The crude product was dissolved in diethyl ether (5 mL) and $NaHCO_3$ (sat'd., aq., 5 mL) added. The layers were separated and the aqueous layer was extracted with diethyl ether (2×5 mL). The combined organic layers were dried over anhydrous magnesium sulfate and evaporated in vacuo. Flash chromatography (SiO_2, 25% ethyl acetate in hexane) gave the title compound **25** (41 mg, 0.14 mmol, 65%) as a colourless oil; ν_{max}(film)/cm^{-1} 1712, 1510, 1236; δ_H (400 MHz, $CDCl_3$) 7.68 (1H, dd, *J*=6.0, 2.5 Hz, C*H*=CHC=O), 6.99–6.93 (2H, m, Ar*H*), 6.89–6.84 (2H, m, Ar*H*), 6.25 (1H, dd, *J*=6.0, 1.8 Hz, CH=C*H*C=O), 3.44 (1H, t, *J*=2.2 Hz, C*H*N), 3.15–3.06 (4H, m, 2×CH_2), 2.83–2.74 (4H, m, 2×CH_2), 1.17 (3H, s, CCH_3), 1.13 (3H, s, CCH_3); δ_C (100 MHz, $CDCl_3$) 213.2 (s), 159.7 (d), 158.8 (s), 148.3 (s), 133.3 (d), 118.3 (d), 115.9 (d), 75.7 (d), 52.2 (t), 51.0 (t), 48.3 (s), 26.8 (q), 20.5 (q); *m*/*z* (CI) 289 ([MH]$^+$, 100%). Found [MH]$^+$ 289.1720 ([MH]$^+$ $C_{17}H_{22}FN_2O$ requires 289.1716).

3.1.20. 4-Hexylsulfanyl-5,5-dimethylcyclopent-2-enone (26), *trans*-2,2-dimethyl-4-hexylsulfanyl-3-*O*-*para*-toluenesulfonylcyclopentanone (28) and *cis*-2,2-dimethyl-4-hexylsulfanyl-3-*O*-*para*-toluenesulfonyl-cyclopentanone (30). A solution of DBU (0.16 mL, 1.07 mmol) and hexanethiol (0.15 mL, 1.07 mmol) in dry tetrahydrofuran (1 mL) was added to a solution of tosylate **22** (300 mg, 1.07 mmol) in dry tetrahydrofuran (2 mL). The reaction mixture was stirred for 1 min before solvent was removed at 0 °C. Flash chromatography of the residue (SiO_2, 2%, then 5% ethyl acetate in hexane) afforded the enone **26** (104 mg, 0.46 mmol, 43%) as a yellow viscous oil; ν_{max}(film)/cm^{-1} 1709; δ_H (300 MHz, $CDCl_3$) 7.50 (1H, dd, *J*=5.8, 2.5 Hz, C*H*=CHC=O), 6.16 (1H, dd, *J*=5.8, 1.9 Hz, CH=C*H*C=O), 3.66 (1H, dd, *J*=2.5, 1.9 Hz, C*H*S), 2.57 (2H, t, *J*=7.4 Hz, SCH_2), 1.64–1.55 (2H, m, SCH$_2$CH_2), 1.47–1.20 (6H, m, (CH_2)$_3$CH$_3$), 1.18 (3H, s, CCH_3), 1.16 (3H, s, CCH_3), 0.90 (3H, t, *J*=6.7 Hz, CH$_2$CH_3); δ_C (75 MHz, $CDCl_3$) 215.5 (s), 161.2 (d), 131.0 (d), 57.6 (d), 47.6 (s), 32.4 (t), 31.4 (t), 29.7 (t), 28.5 (t), 25.2 (t), 22.5 (q), 22.2 (q), 13.9 (q); *m*/*z* (EI) 226 ([M]$^+$, 5%), 109 ([M−SC$_6$H$_{13}$]$^+$, 100). Found [M]$^+$ 226.1392 ([M]$^+$ $C_{13}H_{22}OS$ requires 226.1391); then the *trans*-3,4-disubstituted cyclopentanone **28** (98 mg, 0.25 mmol, 23%) as a white solid; mp 34–35 °C (EtOAc/hexane); ν_{max}(film)/cm^{-1} 1747; δ_H (300 MHz, $CDCl_3$) 7.88–7.84 (2H, m, Ar*H*), 7.40–7.35 (2H, m, Ar*H*), 4.75 (1H, d, *J*=6.0 Hz, C*H*OTs), 3.35 (1H, m, C*H*S), 2.92 (1H, dd, *J*=19.2, 9.0 Hz, C*H*HC=O), 2.52–2.40 (5H, m, SCH_2, ArCH_3), 2.29 (1H, dd, *J*=19.2, 8.1 Hz, CH*H*C=O), 1.57–1.41 (2H, m, SCH$_2$CH_2), 1.40–1.21 (6H, m, (CH_2)$_3$CH$_3$), 1.20 (3H, s, CCH_3), 1.00 (3H, s, CCH_3), 0.89 (3H, t, *J*=6.9 Hz, CH$_2$CH_3); δ_C (75 MHz, $CDCl_3$) 215.3 (s), 145.2 (s), 134.0 (s), 129.9 (d), 128.1 (d), 90.6 (d), 49.9 (s), 42.8 (d), 42.0 (t), 31.8 (t), 31.3 (t), 29.3 (t), 28.4 (t), 23.4 (t), 22.4 (q), 21.5 (q), 19.2 (q), 13.9 (q). Found: C, 60.3; H, 7.7, $C_{20}H_{30}O_4S_2$ requires C, 60.3; H, 7.6%; and finally, the corresponding *cis*-iosmer **30** (90 mg, 0.23 mmol, 21%) as a white solid; mp 37–38 °C (diethyl ether/hexane); ν_{max}(film)/cm^{-1} 1746; δ_H (300 MHz, $CDCl_3$) 7.88–7.84 (2H, m, Ar*H*), 7.35–7.32 (2H, m, Ar*H*), 5.00 (1H, d, *J*=4.4 Hz, C*H*OTs), 3.56–3.48 (1H, m, C*H*S), 2.69 (1H, dd, *J*=18.7, 8.1 Hz, C*H*HC=O), 2.53–2.37 (6H, m, SCH_2, ArCH_3, CH*H*C=O), 1.55–1.41 (2H, m, SCH$_2$CH_2), 1.40–1.20 (6H, m, (CH_2)$_3$CH$_3$), 1.10 (3H, s, CCH_3), 1.07 (3H, s, CCH_3), 0.89 (3H, t, *J*=6.8 Hz, CH$_2$CH_3); δ_C (75 MHz, $CDCl_3$) 215.9 (s), 144.9 (s), 134.2 (s), 129.6 (d), 128.2 (d), 88.4 (d), 51.0 (s), 42.5 (d), 42.0 (t), 32.0 (t), 31.4 (t), 29.4 (t), 28.5 (t), 23.6 (t), 22.5 (q), 21.6 (q), 19.4 (q), 14.0 (q); *m*/*z* (EI) 398 ([M]$^+$, 8%), 226 ([M−TsOH]$^+$, 24), 171 ([TsO]$^+$, 33), 155 ([Ts]$^+$, 29), 109 ([M−TsOHSC$_6$H$_{13}$]$^+$, 27). Found [M]$^+$ 398.1582 ([M]$^+$ $C_{20}H_{30}O_4S_2$ requires 398.1586). Found: C, 60.4; H, 7.6, $C_{20}H_{30}O_4S_2$ requires C, 60.3; H, 7.6%.

3.1.21. Conversion of *trans*-2,2-dimethyl-4-hexylsulfanyl-3-*O*-*p*-toluenesulfonyl-cyclopentanone (28) to 4-hexylsulfanyl-5,5-dimethylcyclopent-2-enone (26). A solution of **28** (15.8 mg, 40 μmol) in dichloromethane (1 mL) was refluxed for 1 h. The solvent was removed in vacuo and flash chromatography (SiO_2, 2.5% ethyl acetate in hexane) of the residue afforded enone **26** (8.3 mg, 37 μmol, 93%) as a yellow viscous oil; which showed identical spectroscopic data to the material obtained by the

procedure described above in Section 3.1.20. Thiol adduct **30** remained unchanged even after prolonged refluxing (10 h) under the same conditions.

3.1.22. 4-Octylsulfanyl-5,5-dimethylcyclopent-2-enone (27), *trans*-2,2-dimethyl-4-octylsulfanyl-3-*O*-*para*-toluenesulfonylcyclopentanone (29) and *cis*-2,2-dimethyl-4-octylsulfanyl-3-*O*-*para*-toluenesulfonylcyclopentanone (31). A solution of DBU (0.16 mL, 1.07 mmol) and *n*-octanethiol (0.19 mL, 1.07 mmol) in dry tetrahydrofuran (1 mL) was added to a solution of tosylate **22** (300 mg, 1.07 mmol) in dry tetrahydrofuran (2 mL). The reaction mixture was stirred for 10 min, then evaporated in vacuo. Flash chromatography of the residue (SiO_2, 2%, then 5% ethyl acetate in hexane) afforded the enone **27** (0.11 g, 0.43 mmol, 40%) as a yellow viscous oil; ν_{max}(film)/cm^{-1} 1709; δ_H (300 MHz, $CDCl_3$) 7.50 (1H, dd, J=5.8, 2.5 Hz, C*H*=CHC=O), 6.15 (1H, dd, J=5.8, 1.9 Hz, CH=C*H*C=O), 3.66 (1H, dd, J=2.5, 1.9 Hz, C*H*S), 2.56 (2H, t, J=7.4 Hz, SCH_2), 1.67–1.55 (2H, m, SCH_2CH_2), 1.45–1.20 (10H, m, $(CH_2)_5CH_3$), 1.18 (3H, s, CCH_3), 1.16 (3H, s, CCH_3), 0.88 (3H, t, J=6.7 Hz, CH_2CH_3); δ_C (75 MHz, $CDCl_3$) 212.6 (s), 161.3 (d), 131.1 (d), 57.6 (d), 47.5 (s), 32.3 (t), 31.7 (t), 29.7 (t), 29.1 (t), 29.0 (t), 28.8 (t), 25.2 (t), 22.5 (q), 22.1 (q), 13.9 (q); *m*/*z* (EI) 254 ($[M]^+$, 2%), 109 ($[M-SC_8H_{17}]^+$, 100). Found $[M]^+$ 254.1703 ($[M]^+$ $C_{15}H_{26}OS$ requires 254.1704); then the *trans*-3,4-disubstituted cyclopentanone **29** (0.12 g, 0.28 mmol, 26%) as a white solid; mp 58–59 °C (EtOAc/hexane); ν_{max}(film)/cm^{-1} 1748; δ_H (300 MHz, $CDCl_3$) 7.88–7.84 (2H, m, Ar*H*), 7.39–7.35 (2H, m, Ar*H*), 4.75 (1H, d, J=6.0 Hz, C*H*OTs), 3.35 (1H, m, C*H*S), 2.92 (1H, dd, J=19.1, 9.0 Hz, C*H*HC=O), 2.60–2.40 (5H, m, SCH_2, ArCH_3), 2.30 (1H, dd, J=19.1, 8.0 Hz, CH*H*C=O), 1.60–1.41 (2H, m, SCH_2CH_2), 1.40–1.21 (10H, m, $(CH_2)_5CH_3$), 1.20 (3H, s, CCH_3), 1.00 (3H, s, CCH_3), 0.89 (3H, t, J=6.7 Hz, CH_2CH_3); δ_C (75 MHz, $CDCl_3$) 215.2 (s), 145.1 (s), 133.9 (s), 129.9 (d), 128.1 (d), 90.6 (d), 49.9 (s), 42.8 (d), 42.0 (t), 31.9 (t), 31.8 (t), 29.4 (t), 29.1 (t), 28.8 (t), 23.5 (t), 22.6 (q), 21.6 (q), 19.2 (q), 14.0 (q). Found: C, 61.8; H, 8.1, $C_{22}H_{34}O_4S_2$ requires C, 61.9; H, 8.0%; and finally, the corresponding *cis*-iosmer **31** (96 mg, 0.23 mmol, 21%) as a white solid; mp 50–51 °C (diethyl ether/hexane); ν_{max}(film)/cm^{-1} 1747; δ_H (300 MHz, $CDCl_3$) 7.87–7.84 (2H, m, Ar*H*), 7.36–7.32 (2H, m, Ar*H*), 5.00 (1H, d, J=4.3 Hz, C*H*OTs), 3.56–3.48 (1H, m, C*H*S), 2.68 (1H, dd, J=18.7, 8.1 Hz, C*H*HC=O), 2.53–2.37 (6H, m, SCH_2, ArCH_3, CH*H*C=O), 1.60–1.41 (2H, m, SCH_2CH_2), 1.40–1.18 (10H, m, $(CH_2)_5CH_3$), 1.10 (3H, s, CCH_3), 1.07 (3H, s, CCH_3), 0.89 (3H, t, J=6.7 Hz, CH_2CH_3); δ_C (75 MHz, $CDCl_3$) 215.9 (s), 144.9 (s), 134.2 (s), 129.6 (d), 128.2 (d), 88.4 (d), 51.0 (s), 42.5 (d), 42.0 (t), 32.1 (t), 31.8 (t), 29.5 (t), 29.2 (t), 28.9 (t), 23.7 (t), 22.6 (q), 21.6 (q), 19.5 (q), 14.0 (q); *m*/*z* (EI) 426 ($[M]^+$, 5%), 254 ($[M-TsOH]^+$, 7), 155 ($[Ts]^+$, 28), 109 ($[M-TsOHSC_8H_{17}]^+$, 46). Found $[M]^+$ 426.1895 ($[M]^+$ $C_{22}H_{34}O_4S_2$ requires 426.1899). Found: C, 61.9; H, 8.1, $C_{22}H_{34}O_4S_2$ requires C, 61.9; H, 8.0%.

3.1.23. Conversion of *trans*-2,2-dimethyl-4-octylsulfanyl-3-*O*-*p*-toluenesulfonyl-cyclopentanone (29) to 4-octylsulfanyl-5,5-dimethylcyclopent-2-enone (27). A solution of **29** (17 mg, 40 μmol) in dichloromethane (1 mL) was refluxed for 1 h. The solvent was removed in vacuo and flash chromatography (SiO_2, 2.5% ethyl acetate in hexane) of the residue afforded enone **27** (9 mg, 35 μmol, 89%) as a yellow viscous oil; which showed identical spectroscopic data to the material obtained by the procedure described above in Section 3.1.22. Thiol adduct **31** remained unchanged even after prolonged refluxing (10 h) under the same conditions.

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Synthesis and revision of the stereochemistry of a cyclopentenone natural product isolated from ascomycete strain A23-98

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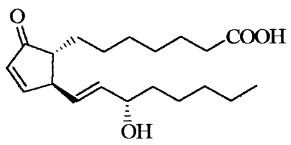
Abstract—The 2-propenyl-4,5-dihydroxycyclopent-2-enones **4**, **10** and **14** have been synthesised in optically active form. NMR data suggest the compounds **10** and **14** (but not **4**) correspond to compounds isolated from ascomycete strain A23-98.

1. Introduction and background information

The cyclopentenone prostaglandins, for example, prostaglandin A_1 **1** display anti-viral and anti-inflammatory properties in vitro and in vivo as well as anti-cancer activity in vitro.[1] These properties have been linked to the ability of prostaglandins -A and -J to activate heat shock factors (HSFs) and thus to potentiate the production of heat shock proteins (HSPs; in particular HSP-70) and to inhibit the formation of nuclear transcription factor NF-κB.[2]



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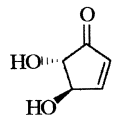
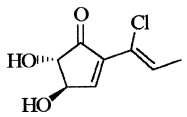


2

It has also been shown that cyclopentenone[3] itself and the dihydroxy compound **2**[4] activate HSF and/or inhibit NF-κB with weak to modest potency, respectively.

More recently, ((*Z*)-1-chloro-propenyl)-4,5-dihydroxy-cyclopent-2-enone **3** was isolated from ascomycete strain A23-98 and shown to possess NF-κB inhibitory activity.[5] A dechloro compound was also isolated and given the structure **4**, based on NMR evidence. It is noteworthy that compound **4** comprised a mixture of *syn*- and *anti*-C(4) epimers and was reported to possess NF-κB inhibitory activity.



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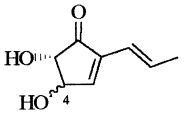

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The NMR evidence regarding the geometry of the *exo*-cyclic alkene unit in **4** was based on the lack of a NOESY correlation between H-C(3) and the methyl group. The coupling constant between the alkene protons could not be observed because of overlapping peaks in the ^{1}H NMR spectrum.

We set out to synthesise *syn*-**4** and *anti*-**4** (i.e., the *cis*- and *trans*-diols) in order to confirm the structure of the compounds.

2. Results and discussion

Retrosynthetic analysis suggested cleavage of the C(2) bond as shown (Fig. 1). It was envisaged that, in the forward sense this bond could be made via a palladium-catalysed Stille-type reaction between a stannane and vinyl iodide **5**.[6]

Further retrosynthesis reveals the cyclopentenone **6**; the dextrorotatory enantiomer is available in 6 steps from D-ribose **7** while (−)-**6** is prepared from D-ribose **7** by varying the order of the steps (Scheme 1).[7] In our hands D-ribose **7** was converted into (+)-**6** in 40% overall yield, while (−)-**6** was prepared from **7** in 29% overall yield. Halogenation of (+)-**6** using iodine in a mixture of pyridine and carbon tetrachloride, furnished the 2-iodo-compound **5** (Scheme 2).

Palladium-catalysed Stille reaction between vinyl iodide **5**

Keywords: 2-Alkenyl-4,5-dihydroxycyclopent-2-enones; Stille-type reaction; *cis*-Tributylpropenyl Stannane.
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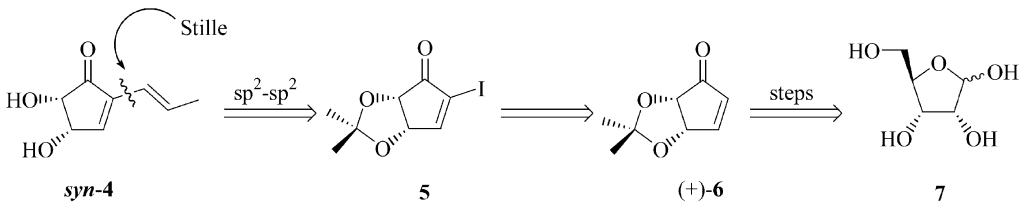


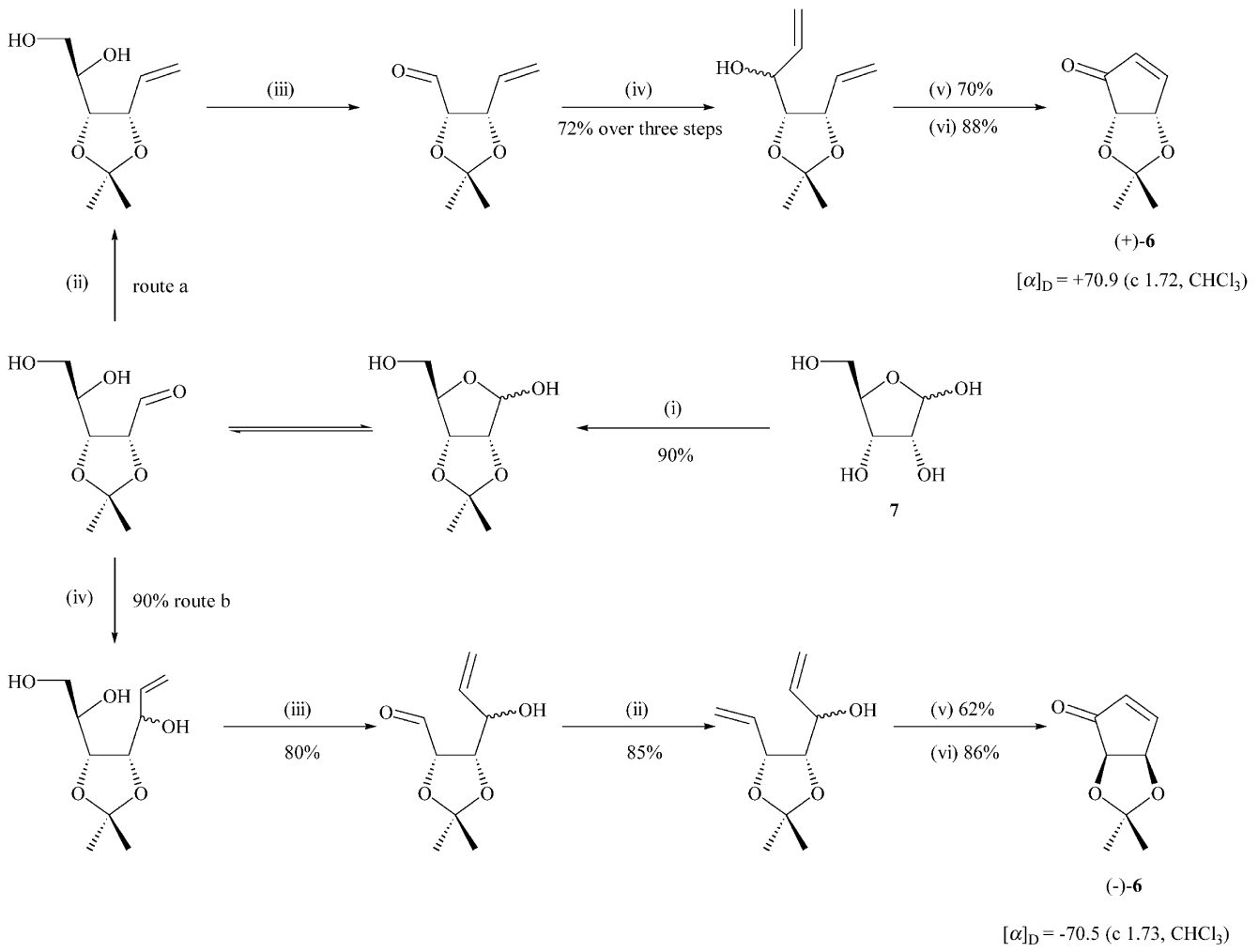
Figure 1.

and *trans*-tributylpropenylstannane[8] gave a crude sample of the compound **8**. Deprotection of **8** with PPTS in methanol gave (+)-*syn*-**4**. The ^{1}H NMR spectrum of **4** showed two distinct signals for the *exo*-cyclic alkene protons in contrast to the literature data for the natural compound which stipulated these protons produced an AA′ spin system centred at 6.05 ppm.

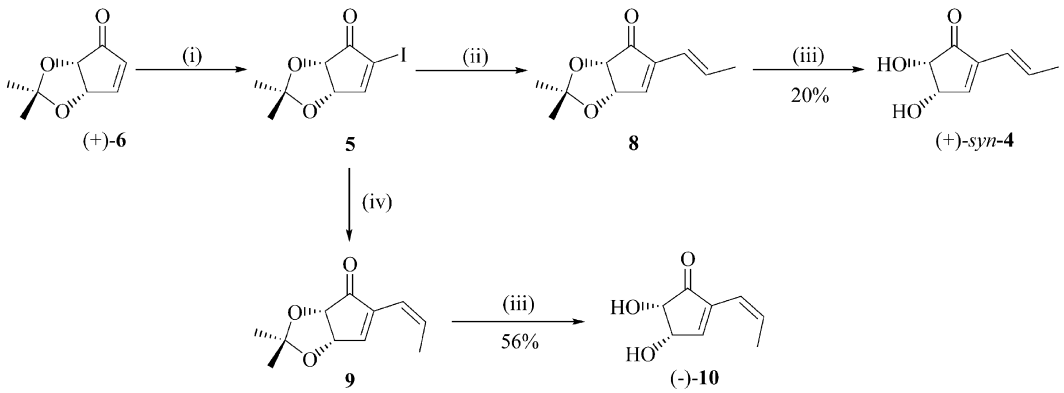
Employing *cis*-tributylpropenyl stannane[9] in the Stille coupling reaction gave the corresponding (*Z*)-propenyl-cyclopent-2-enone **9** in 93% yield. Deprotection with PPTS in methanol gave the diol (−)-**10**, the structure of which was confirmed by X-ray crystallography (Fig. 2).[10]

(+)-Cyclopentenone **10** was obtained from (−)-**6** using the same methodology in an overall yield of 38%. The diol **10** gave an NMR spectrum that was identical to that described for the natural product;[5] to illustrate the point the distinctive alkene signals for **4** and **10** are shown in Figure 3.

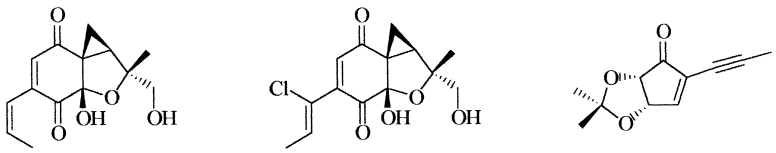
Interestingly, by way of an analogy, Smith et al. have shown previously that the alkenyl side-chain of dechloromikrolin **11** possessed a (*Z*)-alkene unit and not an (*E*)-alkene side-chain as predicted by NMR studies and correlation with mikrolin **12**. This led to a revision of the proposed biosynthetic pathway, in particular the step at which chlorination took place.[11]



Scheme 1. Reagents and conditions: (i) acetone, H_2SO_4, rt, 90%; (ii) CH_3PPh_3Br, NaH/DMSO, THF, rt (route a) or CH_3PPh_3Br, *t*BuOK, THF, reflux (route b); (iii) $NaIO_4$, DCM, H_2O, rt; (iv) vinylmagnesium bromide, THF −78 °C; (v) Grubbs' catalyst, $CHCl_3$, rt; (vi) PDC, DCM, rt.



Scheme 2. Reagents and conditions: (i) I_2, pyr./CCl_4, 97%; (ii) $(PhCN)_2PdCl_2$, CuI, $AsPh_3$, *trans*-tributylpropenyl stannane, 73%; (iii) PPTS, MeOH, reflux; (iv) $(PhCN)_2PdCl_2$, CuI, $AsPh_3$, *cis*-tributylpropenyl stannane, 93%.



11 **12** **13**

Palladium-catalysed Sonogashira coupling of the iodide **5** and propyne gave the alkyne **13**. Unfortunately, attempted reduction of **13** to the alkene **9** using Lindlar's catalyst was unsuccessful.

In view of the revision of the structure of the natural product, we changed our second target structure to that of the *anti*-diol **14** (Scheme 3) and styled the approach on the strategy of Takahashi and co-workers.[12] Thus, Weitz–Scheffer oxidation of 4-silanyloxycyclopentenone **15** gave the epoxide **16** (41%) which was converted into the tertiary alcohol **17** in a highly satisfactory 88% yield. Treatment of **17** with Tf_2O in 2,6-lutidine at −78 °C gave a mixture of the desired product **18** in admixture with a second compound, which was tentatively ascribed the structure of the triflate derivative of compound **17**. Treatment of this mixture with Pd(0) and benzoic acid gave rise to two pairs of diastereoisomers **19** and **20**. Protection of the free hydroxyl group as the *tert*-butyldimethylsilyl derivative simplified the situation, furnishing one pair of diastereoisomers **21**.

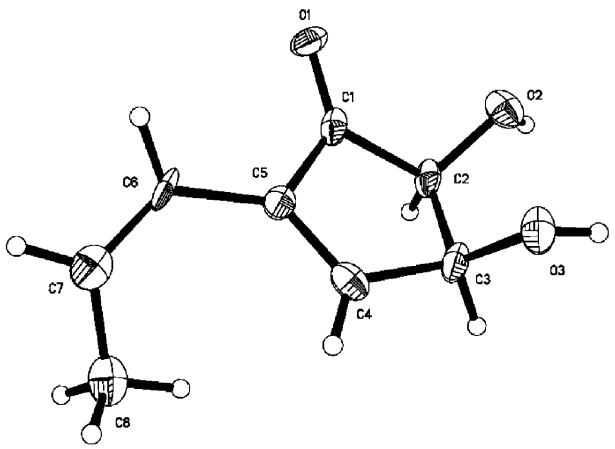


Figure 2. X-ray crystal structure of (−)-**10**.

Reduction of the alkyne moiety proceeded exceedingly well on this occasion, affording diene **22** in 90% yield. Removal of the benzoyl group using DIBAL and oxidation employing PDC furnished compound **23**, whereupon acid-catalysed removal of the silyl protecting groups gave the diol **14** (31% yield for the last three steps). The NMR spectrum of compound **14** showed a coupling constant of 2.8 Hz between H–C(4) and H–C(5) (cf. 5.5 Hz for the *cis*-diol). The *exo*-cyclic alkene protons gave an AA′ signal centred at 6.03 ppm.

3. Conclusions

The non-halogenated compounds isolated from ascomycete strain A23-98 are not *syn*- and *anti*-diols **4**. Instead, the reported physical data fit better to the measurements obtained for the *cis*-alkenes **10** and **14**. While the absolute configurations of the natural products were not ascertained and optical rotations were not reported, $[\alpha]_D$ values are now available for (+)-**10**, (−)-**10** and (+)-**14**, should further information for the natural compounds become available.

The biological activity of the cyclopentenone derivatives described herein will be reported in a separate publication.

4. Experimental

4.1. General

Starting materials were purchased from commercial sources and were used without further purification. Anhydrous THF was distilled under nitrogen from the sodium-benzophenone

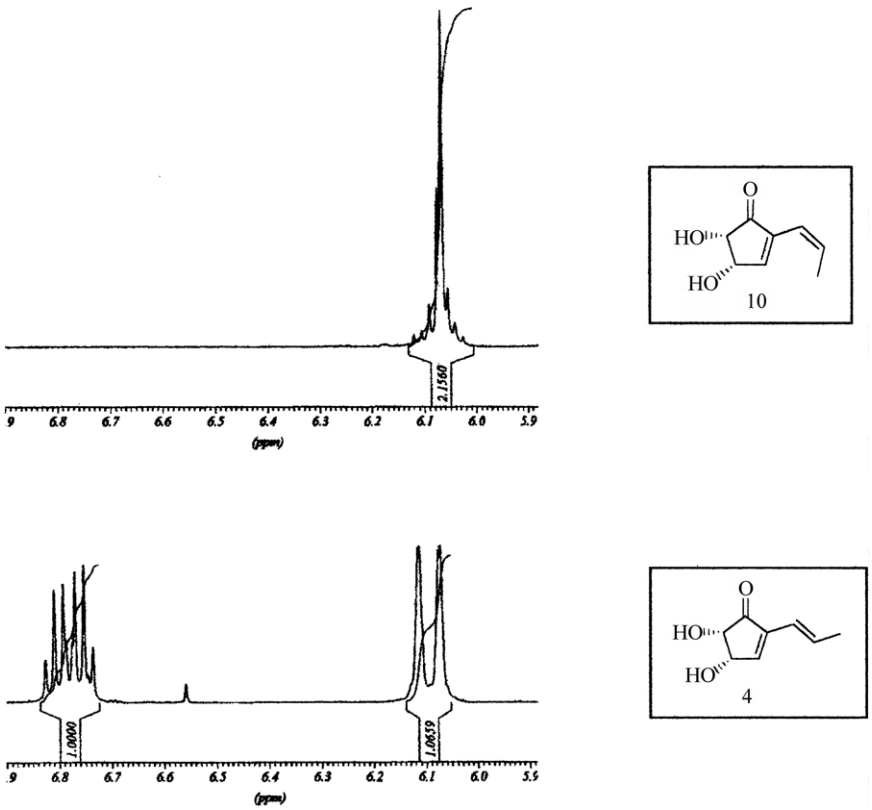


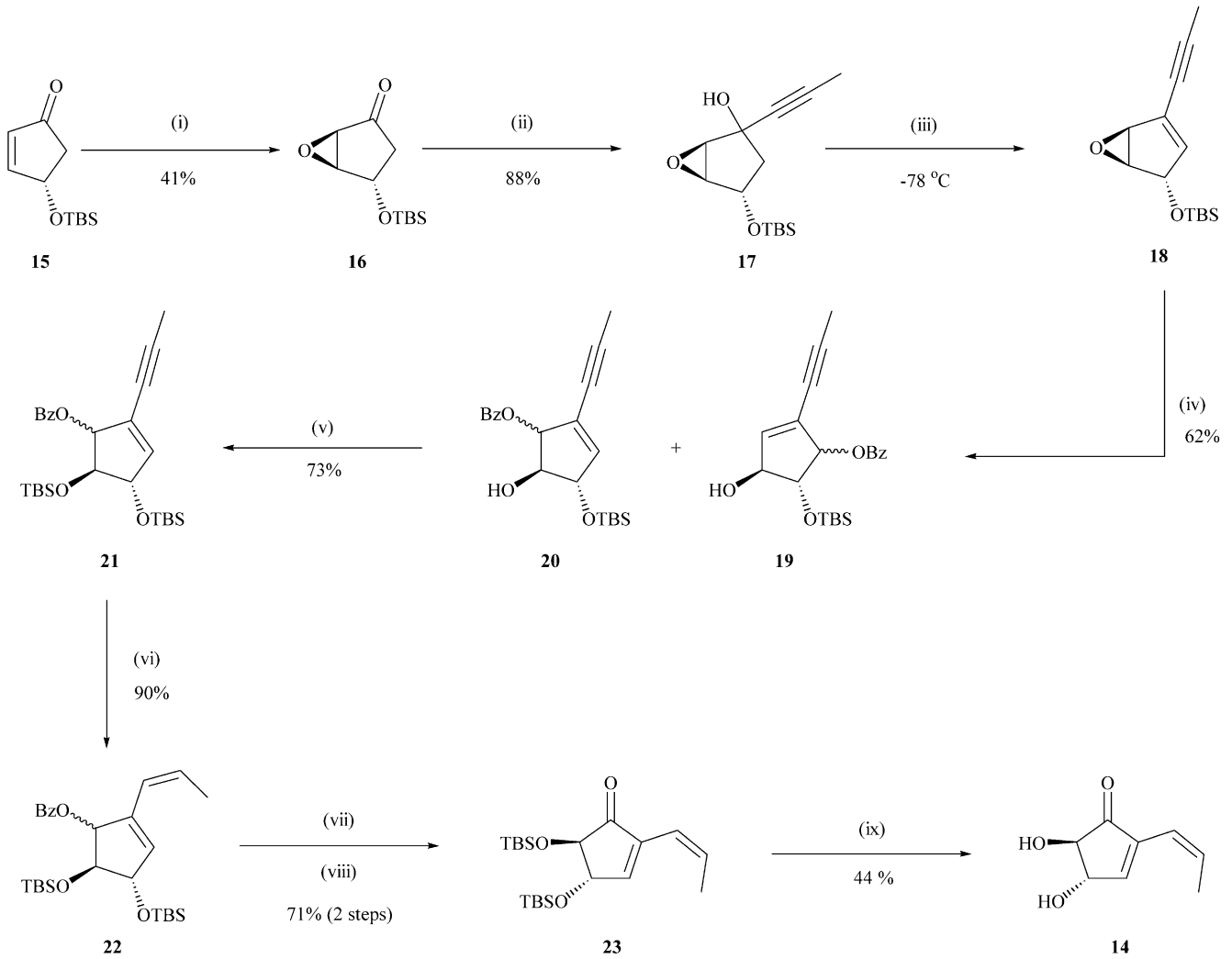
Figure 3.

ketyl radical, DCM was distilled from CaH_2. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded using a Bruker AMX400 spectrometer. Infrared spectroscopy was performed on a Perkin–Elmer Paragon 1000 FTIR spectrometer. Optical rotation measurements were recorded using an Optical Activity, Polar 2001 polarimeter at 589 nm and are quoted in units of 10^{-1} deg cm^2 g^{-1}. Melting points are uncorrected. Flash column chromatography, under moderate pressure, was performed using silica gel-ICN 32-63, 60 Å.

4.1.1. (3a*S*,6a*S*)-5-Iodo-2,2-dimethyl-3a,6a-dihydrocyclopenta[1,3]dioxol-4-one (5). To a solution of enone (+)-**6** (100 mg, 0.65 mmol) in carbon tetrachloride–pyridine (2.5 ml, 1:1) at 0 °C was added iodine (0.65 g, 2.6 mmol) in carbon tetrachloride–pyridine (2.5 ml, 1:1) dropwise and the reaction stirred for 2.5 h at room temperature under an atmosphere of nitrogen. The reaction was diluted with diethyl ether (25 ml) and water (25 ml) and the layers separated. The aqueous layer was washed with diethyl ether (3×25 ml) and the combined organic layers washed with sat. aq. $Na_2S_2O_3$ (2×50 ml), dried ($MgSO_4$) and the solvent removed in vacuo. The product was purified by flash column chromatography (SiO_2; EtOAc–*n*-hexane, 1:4) to yield the title compound **5** (116 mg, 64%) as a white solid; ν_{max}(film)/cm^{-1} 1380, 1568, 1732, 2356, 2939, 2997; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.39 (3H, s, CH_3), 1.42 (3H, s, CH_3), 4.53 (1H, d, J=5.6 Hz, C(3a)H), 5.22 (1H, dd, J=2.6, 5.6 Hz, C(6a)H), 7.97 (1H, d, J=2.6 Hz, C(6)H); δ_C (100 MHz, $CDCl_3$, Me_4Si) 26.5, 27.4 (CH_3), 73.8, 79.7 (CH), 105.8, 115.9 (C), 164.8 (CH), 197.4 (C); *m*/*z* (CI) 298 ([M+NH_4]$^+$, 100%); Found: [M+NH_4]$^+$, 297.99380. $C_8H_{13}INO_3$ requires [M+NH_4]$^+$, 297.99405.

4.1.2. *trans*-Tributyl-propenyl-stannane. To a solution of *trans*-1-bromopropene (1.0 g, 8.3 mmol) in anhydrous diethyl ether (23 ml) at −78 °C was added *t*-BuLi (1.7 M in pentane, 10.8 ml, 18.3 mmol) slowly and the reaction stirred for 1 h under an atmosphere of argon. Tributyltin chloride (2.25 ml, 8.3 mmol) was added and the reaction allowed to warm to room temperature over 16 h. The reaction was quenched with methanol (1 ml) and water (50 ml) was added. The product was extracted with ethyl acetate (2×50 ml) and the combined organic layers dried ($MgSO_4$) and the solvent removed in vacuo. The product was purified by high vacuum distillation (125 °C, 0.1 mm Hg) to yield the title compound (2.69 g, quant.) as a colourless oil; ν_{max}(film)/cm^{-1} 874, 982, 1376, 1418, 1442, 1464, 1602, 2956; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.88 (9H, t, J=7.2 Hz, 3×CH_3), 1.26–1.57 (18H, m, 9×CH_2), 1.84 (3H, d, J=5.4 Hz, CH_3), 5.87–6.03 (2H, m, 2×CH); δ_C (100 MHz, $CDCl_3$, Me_4Si) 9.8 (CH_2), 14.0, 23.9 (CH_3), 27.6, 29.5 (CH_2), 129.3, 144.6 (CH).

4.1.3. (3a*S*,6a*S*)-2,2-Dimethyl-5-prop-(*E*)-enyl-3a,6a-dihydro-cyclopenta[1,3]dioxol-4-one (8). To a solution of vinyliodide **5** (150 mg, 0.54 mmol) in degassed 1-methyl-2-pyrrolidinone (4.0 ml) was added bis(benzonitrile)dichloropalladium(II) (11.5 mg, 0.03 mmol), copper iodide (9.5 mg, 0.05 mmol) and triphenylarsine (15.3 mg, 0.05 mmol). A solution of *trans*-tributyl-propenyl-stannane (0.20 g, 0.6 mmol) in 1-methyl-2-pyrrolidinone (1.0 ml)



Scheme 3. Reagents and conditions: (i) H_2O_2, NaOH, MeOH, 41%; (ii) propynylmagnesium bromide, THF, −78 °C, 88%; (iii) trifluoromethanesulfonic anhydride, 2,6-lutidene, 4 Å molecular sieves, DCM; (iv) $Pd(PPh_3)_4$, benzoic acid, THF, 62%; (v) TBSCl, imid., DMF, 73%; (vi) H_2, Lindlar's cat., quinoline, EtOAc, 90%; (vii) DIBAL, toluene, −78 °C; (viii) PDC, 4 Å molecular sieves, DCM; (ix) acetic acid–water–THF (3:1:1), 60 °C, 44%.

was added and the reaction stirred for 16 h at room temperature under an atmosphere of nitrogen. The reaction was diluted with ethyl acetate (5 ml) and the product washed with aqueous KF (2×5 ml). The combined organic layers were washed with water (10 ml) and the combined aqueous layers back extracted with ethyl acetate (10 ml). The combined organic layers were dried ($MgSO_4$) and the solvent removed in vacuo. The product was purified by flash column chromatography (SiO_2; EtOAc–*n*-hexane, 1:9) to yield the title compound **8** (76 mg, 73%) as a yellow solid; ν_{max}(film)/cm^{-1} 1345, 1374, 1456, 1653, 1717, 2936; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.38 (3H, s, CH_3), 1.41 (3H, s, CH_3), 1.84 (3H, dd, J=1.4, 6.8 Hz, CH_3) 4.50 (1H, d, J=5.6 Hz, C(3a)H), 5.19 (1H, dd, J=2.6, 5.6 Hz, C(6a)H), 6.08 (1H, dd, J=1.4, 15.7 Hz, C(1′)H), 6.80 (1H, dq, J=6.8, 15.7 Hz, C(2′)H), 7.18 (1H, d, J=2.6 Hz, C(6)H); δ_C (100 MHz, $CDCl_3$, Me_4Si) 19.1, 26.3, 27.6 (CH_3), 76.6, 78.2 (CH), 115.1 (C), 120.5, 135.2 (CH), 141.2 (C), 150.0 (CH), 201.8 (C); *m/z* (CI) 212 ([M+NH_4]$^+$, 30%), 154 ([M−C_3H_6O+NH_4]$^+$, 40), 137 ([M−C_3H_6O+H]$^+$, 100); Found: [M+NH_4]$^+$, 212.12849. $C_{11}H_{18}NO_3$ requires [M+NH_4]$^+$, 212.12866.

4.1.4. (3a*S*,6a*S*)-4,5-Dihydroxy-2-prop-(*E*)-enyl-cyclopent-2-enone (*syn*-4). To a solution of acetonide **8** (75 mg, 0.39 mmol) in methanol (3.5 ml) was added pyridinium *p*-toluenesulfonate (15 mg, 0.06 mmol) and the reaction was heated at reflux for 6.5 h. The solvent was removed in vacuo and the product was purified by flash column chromatography (SiO_2; EtOAc–*n*-hexane, 1:1) to yield the title compound *syn*-**4** (12 mg, 20%) as a pale yellow solid; mp 97–99 °C; $[\alpha]_D$=+38.8 (*c* 1.0, MeOH); ν_{max}(film)/cm^{-1} 983, 1158, 1652, 1708, 2956, 3250 br., 3452 br.; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.85 (3H, dd, J=1.4, 6.8 Hz, CH_3) 2.71 (1H, br.s, −OH), 2.99 (1H, br.s, −OH), 4.17 (1H, d, J=5.6 Hz, C(5)H), 4.82–4.84 (1H, m, C(4)H), 6.10 (1H, d, J=16.0 Hz, C(1′)H), 6.74–6.83 (1H, dq, J=6.8, 16.0 Hz, C(2′)H), 7.24 (1H, d, J=3.2 Hz, C(3)H); δ_C (100 MHz, $CDCl_3$, Me_4Si) 19.2 (CH_3), 67.3, 72.6, 120.5, 135.3 (CH), 140.9 (C), 150.7 (CH), 205.2 (C); *m/z* (CI) 172 ([M+NH_4]$^+$, 100%), 154 ([M]$^+$, 23); Found: [M+NH_4]$^+$, 172.09704. $C_8H_{14}NO_3$ requires [M+NH_4]$^+$, 172.09737.

4.1.5. *cis*-Tributyl-propenyl-stannane. To a solution of

tributyl(propynyl)stannane (500 mg, 1.5 mmol) in anhydrous tetrahydrofuran (35 ml) was added bis(cyclopentadienyl)zirconium chloride hydride (0.77 g, 3 mmol) and the reaction stirred for 30 min. under an atmosphere of nitrogen. The reaction was quenched with water (1 ml) and the reaction mixture stirred for 30 min. Pentane (5 ml) was added and the mixture filtered through a silica plug and the solvent removed in vacuo. The product was purified by high vacuum distillation (125 °C, 0.1 mm Hg) to yield the title compound (0.5 g, 99%) as a pale yellow oil; ν_{max}(film)/cm^{-1} 960, 1072, 1376, 1464, 1601, 2854, 2923, 2958; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.87–0.94 (9H, m, 3×CH_3), 1.27–1.54 (18H, m, 9×CH_2), 1.76 (3H, dd, J=1.3, 6.4 Hz, CH_3), 5.80 (1H, dq, J=1.3, 12.4 Hz, CH), 6.59 (1H, dq, J=6.4, 12.4 Hz, CH); δ_C (100 MHz, $CDCl_3$, Me_4Si) 10.5 (CH_2), 14.0, 22.3 (CH_3), 27.7, 29.6 (CH_2), 129.5, 143.6 (CH).

4.1.6. (3a*S*,6a*S*)-2,2-Dimethyl-5-prop-(*Z*)-enyl-3a,6a-dihydro-cyclopenta[1,3]dioxol-4-one ((−)-9). To a solution of vinyliodide **5** (150 mg, 0.54 mmol) in degassed 1-methyl-2-pyrrolidinone (4.0 ml) was added bis(benzonitrile)dichloropalladium(II) (11.5 mg, 0.03 mmol), copper iodide (9.5 mg, 0.05 mmol) and triphenylarsine (15.3 mg, 0.05 mmol). A solution of *cis*-tributyl-propenyl-stannane (0.27 g, 0.81 mmol) in 1-methyl-2-pyrrolidinone (1.0 ml) was added and the reaction stirred for 16 h at room temperature under an atmosphere of nitrogen. Work-up and chromatography as described above afforded the title compound (−)-**9** (97 mg, 93%) as a yellow solid; mp 32–34 °C; $[\alpha]_D$=−73.7 (*c* 1.5, $CHCl_3$); ν_{max}(film)/cm^{-1} 1202, 1373, 1637, 1725, 2937, 2990; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.40 (3H, s, CH_3), 1.42 (3H, s, CH_3), 1.87 (3H, d, J=5.4 Hz, CH_3) 4.50 (1H, d, J=5.6 Hz, C(3a)H), 5.28 (1H, dd, J=2.7, 5.6 Hz, C(6a)H), 6.05–6.12, (2H, m, C(1′)H and C(2′)H), 7.38 (1H, d, J=2.7 Hz, C(6)H); δ_C (100 MHz, $CDCl_3$, Me_4Si) 16.1, 26.6, 28.0 (CH_3), 76.9, 77.6 (CH), 115.6 (C), 118.1, 134.8 (CH), 141.3 (C), 152.3 (CH), 202.5 (C); *m*/*z* (CI) 212 ([M+NH_4]$^+$, 51%), 154 ([M−C_3H_6O+NH_4]$^+$, 29), 137 ([M−C_3H_6O+H]$^+$, 100); Found: [M+NH_4]$^+$, 212.12812. $C_{11}H_{18}NO_3$ requires [M+NH_4]$^+$, 212.12866.

4.1.7. (3a*S*,6a*S*)-4,5-Dihydroxy-2-prop-(*Z*)-enyl-cyclopent-2-enone ((−)-10). To a solution of acetonide (−)-**9** (60 mg, 0.31 mmol) in methanol (3.0 ml) was added pyridinium *p*-toluenesulfonate (12 mg, 0.05 mmol) and the reaction heated at reflux for 5.5 h. The solvent was removed in vacuo and the product was purified by flash column chromatography (SiO_2; EtOAc–*n*-hexane, 2:3) to yield the title compound (−)-**10** (27 mg, 56%) as a white solid; mp 108–109 °C; $[\alpha]_D$=−17.6 (*c* 1.0, MeOH); ν_{max}(film)/cm^{-1} 983, 1153, 1292, 1712, 2939, 3283 br., 3431 br.; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.88 (3H, d, J=5.2 Hz, CH_3), 2.90 (1H, br.s, −OH), 3.16 (1H, br.s, −OH), 4.18 (1H, d, J=5.5 Hz, C(5)H), 4.90 (1H, dd, J=3.2, 5.5 Hz, C(4)H), 6.02–6.12 (2H, m, C(1′)H and C(2′)H), 7.45 (1H, d, J=3.2 Hz, C(3)H); δ_C (100 MHz, $CDCl_3$, Me_4Si) 15.8 (CH_3), 67.8, 71.2, 117.6, 134.6 (CH), 140.6 (C), 153.3 (CH), 205.7 (C); *m*/*z* (CI) 172 ([M+NH_4]$^+$, 100%), 155 ([M+H]$^+$, 23), 154 ([M]$^+$, 28), 137 ([M−OH]$^+$, 57); Found: [M+NH_4]$^+$, 172.09704. $C_8H_{14}NO_3$ requires [M+NH_4]$^+$, 172.09737.

4.1.8. (3a*R*,6a*R*)-5-Iodo-2,2-dimethyl-3a,6a-dihydro-cyclopenta[1,3]dioxol-4-one (*ent*-5). To a solution of enone (−)-**6** (0.53 g, 3.4 mmol) in carbon tetrachloride–pyridine (12.5 ml, 1:1) at 0 °C was added iodine (3.45 g, 13.6 mmol) in carbon tetrachloride–pyridine (12.5 ml, 1:1) dropwise and the reaction stirred for 1.5 h at room temperature under an atmosphere of nitrogen. Work-up and chromatography as described above furnished the title compound *ent*-**5** (0.69 g, 73%) as a white solid; Found: C, 34.45; H, 3.22. $C_8H_9IO_3$ requires C, 34.31; H, 3.24%; Found: [M+NH_4]$^+$, 297.99408. $C_8H_{13}INO_3$ requires [M+NH_4]$^+$, 297.99405.

4.1.9. (3a*R*,6a*R*)-2,2-Dimethyl-5-prop-(*Z*)-enyl-3a,6a-dihydro-cyclopenta[1,3]dioxol-4-one ((+)-9). To a solution of vinyliodide *ent*-**5** (150 mg, 0.54 mmol) in degassed 1-methyl-2-pyrrolidinone (4.0 ml) was added bis(benzonitrile)dichloropalladium(II) (11.5 mg, 0.03 mmol), copper iodide (9.5 mg, 0.05 mmol) and triphenylarsine (15.3 mg, 0.05 mmol). A solution of *cis*-tributyl-propenyl-stannane (0.27 g, 0.81 mmol) in 1-methyl-2-pyrrolidinone (1.0 ml) was added and the reaction stirred for 16 h at room temperature under an atmosphere of nitrogen. Work-up and chromatography as described above furnished the title compound (+)-**9** (78 mg, 75%) as a yellow solid; mp 32–34 °C; $[\alpha]_D$=+85.6 (*c* 1.4, $CHCl_3$); Found: [M+NH_4]$^+$, 212.12848. $C_{11}H_{18}NO_3$ requires [M+NH_4]$^+$, 212.12866.

4.1.10. (3a*R*,6a*R*)-4,5-Dihydroxy-2-prop-(*Z*)-enyl-cyclopent-2-enone ((+)-10). To a solution of acetonide (+)-**9** (65 mg, 0.34 mmol) in methanol (3.0 ml) was added pyridinium *p*-toluenesulfonate (13 mg, 0.05 mmol) and the reaction heated at reflux for 6.5 h. The solvent was removed in vacuo and the product was purified by flash column chromatography (SiO_2; EtOAc–*n*-hexane, 2:3) to yield the title compound (+)-**10** (36 mg, 69%) as a white solid; mp 106–108 °C; $[\alpha]_D$=+25.0 (*c* 1.0, MeOH); Found: [M+NH_4]$^+$, 172.09753. $C_8H_{14}NO_3$ requires [M+NH_4]$^+$, 172.09737.

4.1.11. (3a*S*,6a*S*)-2,2-Dimethyl-5-prop-1-ynyl-3a,6a-dihydro-cyclopenta[1,3]dioxol-4-one (13). To a solution of vinyliodide **5** (150 mg, 0.54 mmol) in degassed dimethylformamide (3.0 ml) was added tetrakis(triphenylphosphine)palladium (62 mg, 0.05 mmol), copper iodide (21 mg, 0.1 mmol) and triethylamine (0.15 ml, 1.08 mmol). Propyne was bubbled through the solution for 10 min. and the reaction stirred for 4 h at room temperature under an atmosphere of propyne. The reaction was diluted with water (2 ml) and the product was extracted with diethyl ether (3×10 ml). The combined organic layers were dried ($MgSO_4$) and the solvent removed in vacuo. The product was purified by flash column chromatography (SiO_2; EtOAc–petrol, 1:10) to yield the title compound **13** (60 mg, 58%) as a yellow solid; mp 74–76 °C; $[\alpha]_D$=+33.0 (*c* 1.1, $CHCl_3$); ν_{max}(film)/cm^{-1} 1375, 1603, 1732, 2241, 2936, 2991; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.39 (3H, s, CH_3), 1.41 (3H, s, CH_3), 2.06 (3H, s, CH_3) 4.51 (1H, d, J=5.6 Hz, C(3a)H), 5.24 (1H, dd, J=2.2, 5.6 Hz, C(6a)H), 7.48 (1H, d, J=2.2 Hz, C(6)H); δ_C (100 MHz, $CDCl_3$, Me_4Si) 5.0, 26.6, 27.9 (CH_3), 70.1 (C), 76.9, 77.2 (CH), 96.5, 115.8, 131.1 (C), 157.8 (CH), 199.9 (C); *m*/*z* (CI) 210 ([M+NH_4]$^+$, 100%), 152 ([M−C_3H_6O+NH_4]$^+$,

58), 135 ([M−C_3H_6O+H]$^+$, 71); Found: [M+NH_4]$^+$, 210.11328. $C_{11}H_{16}NO_3$ requires [M+NH_4]$^+$, 210.11301.

4.1.12. (1*R*,4*S*,5*S*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-6-oxa-bicyclo[3.1.0]hexan-2-one (16). To a solution of 4-(*tert*-butyl-dimethyl-silanyloxy)-cyclopent-2-enone **15** (5.0 g, 23.6 mmol) in methanol (100 ml) at 0 °C was added 30% aqueous hydrogen peroxide (11.5 ml, 113 mmol). Sodium hydroxide (0.4 M, 61 ml, 24.4 mmol) was added dropwise over 10 min., and the reaction stirred at 0 °C for 30 min. The reaction was quenched with sat. aq. Na_2SO_3 (100 ml) and diluted with diethyl ether (100 ml). The layers were separated and the aqueous layer extracted with diethyl ether (3×100 ml), the organic layers were combined, dried ($MgSO_4$) and the solvent removed in vacuo. The product was purified by flash column chromatography (SiO_2; Et_2O–*n*-hexane, 1:6) to yield the title compound **16** (2.21 g, 41%) as a colourless oil; $[\alpha]_D$=+21.7 (*c* 0.9, $CHCl_3$); Found: C, 58.12; H, 9.07. $C_{11}H_{20}O_3Si$ requires C, 57.85; H, 8.83%; ν_{max}(film)/cm^{-1} 1260, 1472, 1759, 2858, 2930, 2956; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.10 (3H, s, $SiCH_3$), 0.12 (3H, s, $SiCH_3$), 0.89 (9H, s, $SiC(CH_3)_3$), 1.95 (1H, d, *J*=18.1 Hz, C*H*H), 2.59 (1H, dd, *J*=5.7, 18.1 Hz, CH*H*), 3.39 (1H, d, *J*=2.2 Hz, C(5)H), 3.78 (1H, d, *J*=2.2 Hz, C(1)H), 4.59 (1H, d, *J*=5.7 Hz, C(4)H); δ_C (100 MHz, $CDCl_3$, Me_4Si) −4.8, −4.76 (CH_3), 18.0 (C), 25.7 (CH_3), 42.3 (CH_2), 54.2, 60.8, 67.7 (CH), 207.9 (C); *m*/*z* (CI) 246 ([M+NH_4]$^+$, 29%), 171 ([M−$C(CH_3)_3$]$^+$, 24); Found: [M+NH_4]$^+$, 246.15305. $C_{11}H_{24}NO_3Si$ requires [M+NH_4]$^+$, 246.15254.

4.1.13. (1*R*,4*S*,5*S*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-2-prop-1-ynyl-6-oxa-bicyclo[3.1.0]hexan-2-ol (17). To a solution of 4-(*tert*-butyl-dimethyl-silanyloxy)-6-oxa-bicyclo[3.1.0]hexan-2-one **16** (3.2 g, 14.0 mmol) in anhydrous tetrahydrofuran (140 ml) at −78 °C was added propynylmagnesium bromide (0.5 M in tetrahydrofuran, 42.1 ml, 21.0 mmol) slowly over 15 min. and the reaction stirred at −78 °C for 20 h. The reaction was quenched with sat. aq. NH_4Cl (100 ml) and the reaction mixture diluted with ethyl acetate (100 ml). The layers were separated and the aqueous layer extracted with ethyl acetate (3×100 ml), the organic layers were combined, dried ($MgSO_4$) and the solvent removed in vacuo. The product was purified by flash column chromatography (SiO_2; Et_2O–*n*-hexane, 4:5) to yield the title compound **17** (3.31 g, 88%) as a colourless oil; ν_{max}(film)/cm^{-1} 1258, 1351, 1473, 2360, 2857, 2929, 2955, 3419 br.; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.08 (3H, s, $SiCH_3$), 0.09 (3H, s, $SiCH_3$), 0.90 (9H, s, $SiC(CH_3)_3$), 1.83 (1H, dd, *J*=5.3, 13.7 Hz, C*H*H), 1.85 (3H, s, CH_3), 2.09 (1H, d, *J*=13.7 Hz, CH*H*), 3.41 (1H, d, *J*=2.5 Hz, C(5)H), 3.58 (1H, d, *J*=2.5 Hz, C(1)H), 4.38 (1H, d, *J*=5.3 Hz, C(4)H); δ_C (100 MHz, $CDCl_3$, Me_4Si) −4.5, −4.4, 4.0 (CH_3), 18.3 (C), 25.9 (CH_3), 46.6 (CH_2), 59.6, 62.1, 71.7 (CH), 73.4, 79.6, 83.3 (C); *m*/*z* (CI) 286 ([M+NH_4]$^+$, 49%), 269 ([M+H]$^+$, 28), 268 ([M]$^+$, 43), 251 ([M−OH]$^+$, 70); Found: [M+NH_4]$^+$, 286.18363. $C_{14}H_{28}NO_3Si$ requires [M+NH_4]$^+$, 286.18387.

4.1.14. (4*S*,5*S*)-Benzoic acid 4,5-bis-(*tert*-butyl-dimethyl-silanyloxy)-2-prop-1-ynyl-cyclopent-2-enyl ester (21). A solution of 4-(*tert*-butyl-dimethyl-silanyloxy)-2-prop-1-ynyl-6-oxa-bicyclo[3.1.0]hexan-2-ol **17** (1.0 g, 3.73 mmol) and 4 Å molecular sieves (1.0 g) in anhydrous dichloromethane (40 ml) at −78 °C was stirred for 1 h under an atmosphere of nitrogen. 2,6-Lutidene (2.17 ml, 18.6 mmol) was added to the solution followed by trifluoromethanesulfonic anhydride (0.92 ml, 5.5 mmol) and the reaction stirred at −78 °C for 1 h. The reaction was quenched with water (10 ml) and the reaction mixture filtered through Celite. The product was extracted with dichloromethane (3×10 ml) and the organic layers combined, dried ($MgSO_4$) and the solvent removed in vacuo. The product was purified by flash column chromatography (SiO_2; Et_2O–*n*-hexane, 1:6) to yield the eliminated alcohol **18** along with an unseparable, unidentified product (687 mg) as a pale yellow oil (~3:1 in favour of the eliminated alcohol). The mixture was taken onto the next step without further characterisation. A solution of this mixture (425 mg, 1.7 mmol) in anhydrous tetrahydrofuran (0.5 ml) was added to a stirred solution of tetrakis(triphenylphosphine)palladium (98 mg, 0.09 mmol) and benzoic acid (azeotropically dried with toluene, 0.23 g, 1.9 mmol) in anhydrous tetrahydrofuran (2 ml) at 0 °C, under an atmosphere of nitrogen. The reaction was stirred at 0 °C for ten min. followed by 1 h at room temperature. The reaction mixture was passed through a plug of silica and flushed through with diethyl ether and the solvent removed in vacuo. The product was purified by flash column chromatography (SiO_2; Et_2O–*n*-hexane, 1:10) to yield a mixture of regio- and diastereoisomers of the products **19** and **20** (392 mg, 62% over 2 steps) as a yellow oil. The mixture was taken onto the next step without further characterisation. To a solution of the mixture of alcohols (392 mg, 1.05 mmol) in anhydrous dimethylformamide (10 ml) was added imidazole (143 mg, 2.1 mmol) followed by *tert*-butyldimethylsilyl chloride (191 mg, 1.3 mmol) and the reaction stirred at room temperature for 18 h. The reaction was quenched with water (20 ml) and the product extracted with diethyl ether (30 ml). The organic layer was washed with brine (20 ml), dried ($MgSO_4$) and the solvent removed in vacuo. The product was purified by flash column chromatography (SiO_2; Et_2O–*n*-hexane, 1:10) to yield the title compound **21** (358 mg, 70%) as a colourless oil; ν_{max}(film)/cm^{-1} 1728, 2233, 2856, 2886, 2929, 2954; δ_H (400 MHz; $CDCl_3$; Me_4Si) −0.02 (3H, s, $SiCH_3$), 0.07 (3H, s, $SiCH_3$), 0.11 (3H, s, $SiCH_3$), 0.12 (3H, s, $SiCH_3$), 0.85 (9H, s, $SiC(CH_3)_3$), 0.92 (9H, s, $SiC(CH_3)_3$), 1.81 (3H, s, CH_3), 4.29 (1H, t, *J*=5.0 Hz, C(5)H), 4.57 (1H, m, C(4)H), 5.82 (1H, d, *J*=5.0 Hz, C(1)H), 5.95 (1H, s, C(3)H), 7.45 (2H, dd, *J*=7.5, Ph), 7.57 (1H, tt, *J*=1.5, 7.5 Hz, Ph), 8.10 (2H, d, *J*=7.5 Hz, Ph); δ_C (100 MHz, $CDCl_3$, Me_4Si) −4.2, −4.15, −4.1, 4.7 (CH_3), 18.3, 18.4 (C), 26.1, 26.2 (CH_3), 73.8 (C), 80.3, 82.3, 86.7 (CH), 90.9, 125.3 (C), 128.7, 130.2 (CH), 130.6 (C), 133.3, 138.6 (CH), 166.1 (C); *m*/*z* (ES+) 509 ([M+^{23}Na]$^+$, 100%); Found: [M+^{23}Na]$^+$, 509.2514. $C_{27}H_{42}^{23}NaO_4Si_2$ requires [M+^{23}Na]$^+$, 509.2519.

4.1.15. (4*S*,5*S*)-Benzoic acid 4,5-bis-(*tert*-butyl-dimethyl-silanyloxy)-2-prop-(*Z*)-enyl-cyclopent-2-enyl ester (22). To a solution of alkyne **21** (271 mg, 0.56 mmol) in ethyl acetate (11 ml) was added a solution of quinoline (0.1 M solution in ethyl acetate, 2.8 ml, 0.28 mmol) followed by Lindlar's catalyst (379 mg). The solution was evacuated and backfilled 4 times with hydrogen and the reaction stirred for 40 min. under a balloon of hydrogen. The reaction mixture was filtered through a plug of silica and the solvent removed

in vacuo. The product was purified by flash column chromatography (SiO_2; Et_2O–*n*-hexane, 1:15) to yield the title compound **22** (245 mg, 90%) as a colourless oil; ν_{max}(film)/cm^{-1} 1724, 2343, 2360, 2857, 2894, 2929, 2955; δ_H (400 MHz; $CDCl_3$; Me_4Si) −0.01 (3H, s, $SiCH_3$), 0.08 (3H, s, $SiCH_3$), 0.14 (3H, s, $SiCH_3$), 0.15 (3H, s, $SiCH_3$), 0.86 (9H, s, $SiC(CH_3)_3$), 0.94 (9H, s, $SiC(CH_3)_3$), 1.80 (3H, d, J=5.7 Hz, C(3′)H), 4.33 (1H, t, J=4.8 Hz, C(5)H), 4.61 (1H, m, C(4)H), 5.68–5.78 (3H, m, C(1)H, C(1′)H and C(2′)H), 5.90 (1H, d, J=4.8 Hz, C(3)H), 7.44 (2H, dd, J=7.5 Hz, Ar), 7.56 (1H, tt, J=1.5, 7.5 Hz, Ar), 8.07 (2H, dd, J=1.5, 7.5 Hz, Ar); δ_C (100 MHz, $CDCl_3$, Me_4Si) −4.2, −4.15, −4.04, −4.01, 15.5 (CH_3), 18.3, 18.5 (C), 26.1, 26.3 (CH_3), 80.8, 83.4, 86.7, 122.4, 128.7, 130.1 (CH), 130.5 (C), 131.3, 132.6, 133.3 (CH), 138.2, 166.5 (C); *m/z* (ES+) 511 ([M+^{23}Na]$^+$, 100%); Found: [M+^{23}Na]$^+$, 511.2698. $C_{27}H_{44}^{23}NaO_4Si_2$ requires [M+^{23}Na]$^+$, 511.2676.

4.1.16. (4*S*,5*R*)-4,5-Bis-(*tert*-butyl-dimethyl-silanyloxy)-2-prop-(*Z*)-enyl-cyclopent-2-enone (23). To a solution of benzoate **22** (365 mg, 0.75 mmol) in anhydrous toluene (8 ml) at −78 °C under an atmosphere of nitrogen was added diisobutylaluminium hydride (1 M solution in hexanes, 1.65 ml, 1.65 mmol) slowly and the reaction stirred for 90 min. The reaction mixture was allowed to warm to room temperature then cooled to −78 °C and quenched with methanol (1 ml) and water (5 ml). The product was extracted with diethyl ether (3×10 ml) and the combined organic layers dried ($MgSO_4$) and the solvent removed in vacuo to yield 350 mg of a crude colourless oil. The crude alcohol (350 mg) was dissolved in dichloromethane (8 ml) and 4 Å molecular sieves (350 mg) added. After 45 min. at room temperature pyridinium dichromate (0.71 g, 1.88 mmol) was added and the reaction was stirred for 16 h. The reaction was filtered through a plug of silica and the solvent removed in vacuo. The product was purified by flash column chromatography (SiO_2; Et_2O–*n*-hexane, 1:15) to yield the title compound **23** (202 mg, 71% over two steps) as a colourless oil; $[\alpha]_D$=+86.2 (*c* 1.2, $CHCl_3$); ν_{max}(film)/cm^{-1} 1472, 1732, 2359, 2857, 2885, 2929, 2955; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.15 (3H, s, $SiCH_3$), 0.17 (3H, s, $SiCH_3$), 0.18 (3H, s, $SiCH_3$), 0.20 (3H, s, $SiCH_3$), 0.94 (18H, s, 2×$SiC(CH_3)_3$), 1.84 (3H, d, J=5.7 Hz, CH_3), 4.18 (1H, d, J=2.7 Hz, C(5)H), 4.70 (1H, m, C(4)H), 5.94–6.03 (2H, m, C(1′)H and C(2′)H), 7.00 (1H, d, J=1.8 Hz, C(3)H); δ_C (100 MHz, $CDCl_3$, Me_4Si) −4.6, −4.19, −4.18, −3.9, 16.0 (CH_3), 18.4, 18.7 (C), 26.15, 26.18 (CH_3), 77.4, 83.0, 118.3, 133.5 (CH), 139.3 (C), 152.7 (CH), 202.6 (C); *m/z* (CI) 383 ([M+H]$^+$, 100%), 325 ([M−C$(CH_3)_3$]$^+$, 49), 268 ([M−2×C$(CH_3)_3$]$^+$, 47); Found: [M+H]$^+$, 383.24393. $C_{20}H_{39}O_3Si_2$ requires [M+H]$^+$, 383.24377.

4.1.17. (4*S*,5*R*)-4,5-Dihydroxy-2-prop-(*Z*)-enyl-cyclopent-2-enone (14). A solution of *bis*-silylether **23** (200 mg, 0.52 mmol) in acetic acid–water–tetrahydrfuran (2 ml, 3:1:1) was heated at 60 °C for 4 h. Ethyl acetate (10 ml) was added to the cooled reaction mixture and the solution washed with sat. aq. $NaHCO_3$ (5 ml) and brine (5 ml). The aqueous layers were combined and washed with ethyl acetate (3×10 ml) and the organic layers combined, dried ($MgSO_4$) and the solvent removed in vacuo. The product was purified by flash column chromatography (SiO_2; EtOAc–*n*-hexane, 7:3) to yield the title compound **14** (36 mg, 44%) as a white solid; mp 52–56 °C; $[\alpha]_D$=+22.6 (*c* 0.9, MeOH); ν_{max}(film)/cm^{-1} 1050, 1132, 1292, 1417, 1715, 2361, 2921, 3372 br.; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.86 (3H, d, J=4.8 Hz, CH_3), 4.28 (1H, d, J=2.8 Hz, C(5)H), 4.82 (1H, m, C(4)H), 5.98–6.08 (2H, m, C(1′)H and C(2′)H), 7.25 (1H, d, J=2.2 Hz, C(3)H); δ_C (100 MHz, $CDCl_3$, Me_4Si) 15.8 (CH_3), 75.6, 81.6, 117.3, 134.2 (CH), 139.2 (C), 153.2 (CH), 203.6 (C); *m/z* (CI) 172 ([M+NH_4]$^+$, 100%), 155 ([M+H]$^+$, 79), 154 ([M]$^+$, 20); Found: [M+H]$^+$, 155.07109. $C_8H_{11}O_3$ requires [M+H]$^+$, 155.07082.

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Effect of halogens on the activity of halonitrobenzenes in reactions with carbanions

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Abstract—On the basis of competition experiments using a model VNS reaction of chloromethyl phenyl sulfone with halonitrobenzenes it was shown that halogen substituents activate electron-deficient nitroarenes for the addition of carbanions whereas they protect the positions they occupy against the addition.

1. Introduction

It is well documented, that the addition of nucleophiles to nitroaromatic rings proceeds faster at positions occupied with hydrogen than at the analogous positions occupied with halogen, thus reactions proceeding via σ^H adducts such as vicarious,[1] oxidative[2] and other type of nucleophilic substitution of hydrogen are favored over conventional aromatic nucleophilic substitution of halogen (S_NAr). A similar situation is observed for other electron-deficient arenes: transition metal complexes of arenes,[3] quinone derivatives[4] and even electron-deficient alkenes.[5] Since this is a general rule and numerous qualitative observations indicate that rate of the formation of σ^H adducts is substantially higher than of σ^X adducts one can consider that a halogen in a given position of electron-deficient π-systems protects that position against nucleophilic attack. This statement, although contradicting the common opinions, is entirely correct. On the other hand, halogens being in general electron-withdrawing substituents per nature, should increase total electron-deficiency of the system and accelerate the addition of nucleophilic agents to electron deficient arenes.[6] Thus, a general effect of ring halogens on reactions of electron-deficient arenes with nucleophiles should be somewhat controversial—general activation of the ring, namely acceleration of the addition in positions occupied with hydrogen, but deceleration of the addition in positions they occupy. Such a clear-cut situation was already observed for the reactions of 1,4-naphthoquinone derivatives with carbanions.[4] In simple competitive experiments, it was shown that carbanions of methyl acetoacetate and malonate add to 2-chloro-1,4-naphthoquinone exclusively in the 3-position, occupied by hydrogen, and that this reaction proceeds much faster than addition to 1,4-naphthoquinone itself. On the other hand, the reaction of these carbanions with 2,3-dichloro-1,4-naphthoquinone proceeds much more slowly than with 1,4-naphthoquinone. Thus the chloro substituent activates the electron-deficient π-system of 1,4-naphthoquinone in reactions with nucleophilic agents, but protects positions they occupy against nucleophilic attack. It is therefore of substantial interest to confirm this hypothesis and collect semi-quantitative data concerning the effect of halogen substituents on reactions of carbanions with nitrobenzene derivatives.

2. Results and discussion

In order to estimate the effect of halogens on the activity of halonitrobenzenes with carbanions we have studied relations of rates of nucleophilic addition of carbanionic nucleophiles to nitrobenzene (**2**), 2-chloronitrobenzene (**3**), 4-chloronitrobenzene, (**4**), 2,4-dichloronitrobenzene (**5**), 2,4,6-trichloronitrobenzene (**6**), 2-bromonitrobenzene (**7**) and 4-bromonitrobenzene (**8**). As the model reaction, we chose vicarious nucleophilic substitution, VNS with the carbanion of chloromethyl phenyl sulfone (**1**) carried out in the presence of an excess of *t*-BuOK. The relationship of rates of the reactions of various halonitroarenes with this carbanion was estimated on the basis of competitive experiments in which a pair of different nitroarenes **A** and **B** was treated with sub-equimolar amount of **1** and excess of *t*-BuOK. After acidification of the reaction mixture, the ratio of the VNS products was determined by GC. These experiments are presented in Scheme 1.

Keywords: Carbanions; Halonitrobenzenes; Vicarious substitution.
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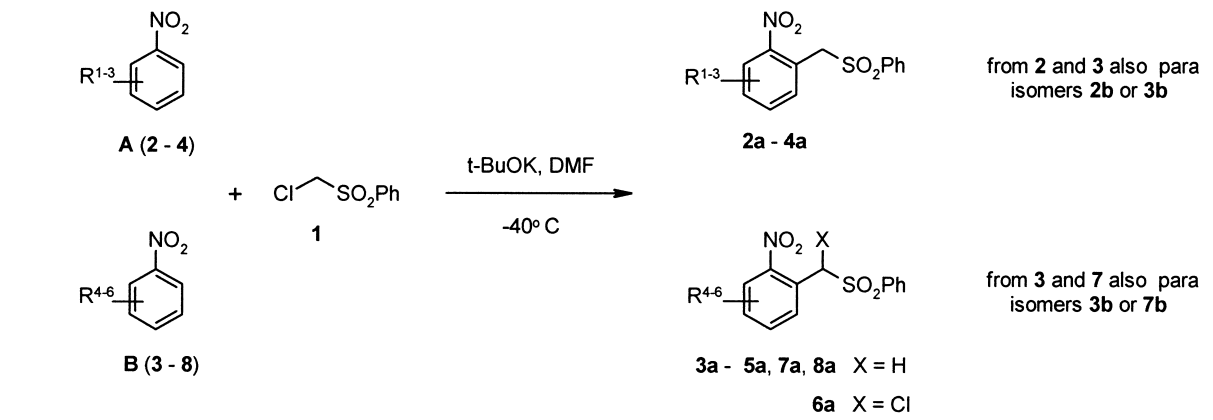
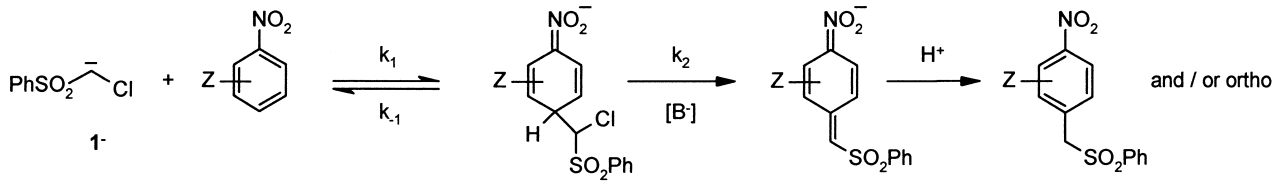


Scheme 1.



Scheme 2.

The goal of this study required that the VNS reactions should proceed under kinetic control, namely the conditions should assure high rate of conversion of the intermediate σ^H adducts into products of the VNS reaction. According to the mechanism of this reaction shown in Scheme 2[1d] value of $k_2[B^-]$ should be very high, hence the kinetic equation of VNS (Eq. 1) can be simplified (Eq. 2).

$$\text{rate}_{VNS} = k_1k_2[\text{nitroarene}][\mathbf{1}^-][\text{base}]/(k_{-1} + k_2[\text{base}]) \quad (1)$$

$$\text{rate}_{VNS} = k_1[\text{nitroarene}][\mathbf{1}^-] \quad (2)$$

According to the results of our earlier study, the VNS reaction is kinetically controlled, namely the rate of the overall process is determined by the rate of the addition, when the process is carried out in the presence of strong base (*t*-BuOK) used in sufficiently high concentration, in aprotic dipolar solvent (DMF) at low temperature (−40 °C).[1e,f] However, under such conditions some chloronitroarenes, especially those containing more than one chloro substituent, are of limited stability, thus the concentration ratio of the competing nitroarenes becomes not constant. After some experimentation we have found procedures, which assure both the kinetic control of the process and reproducible results of the competition experiments. Observation that the orientation (*ortho*/*para* ratio) for **2** and **3** is not affected when the base concentration was substantially varied, and the value of the kinetic isotope effect KIE, found in 2-D-4-chloronitrobenzene under the conditions applied for the competitive reactions is close to unity, have confirmed the assumed kinetic scheme.

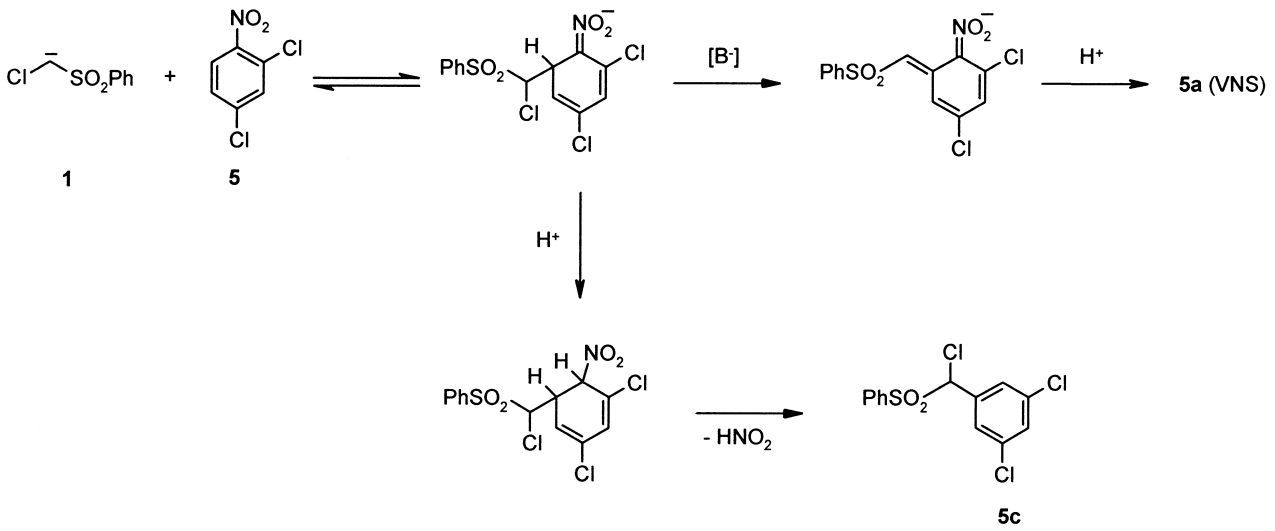
In the competitive experiments of **5** with **3** or **4** we have made a peculiar observation that the ratio of the products depends to some extend on the reaction time. When the reaction mixture was acidified after a very short time (5 s), **5a** was formed in a relatively smaller quantity whereas another product **5c** was also detected in the reaction mixture. Longer reaction time (10–15 s) assured the absence of **5c** and a higher yield of **5a**. The unexpected product **5c** was isolated in a separate experiment and identified as chloro(3,5-dichlorophenyl)methyl phenyl sulfone—a product of the *cine* substitution of the nitro group—formed during the work-up of the reaction mixture containing some amount of σ^H-adducts (Scheme 3). Apparently, addition of the carbanion to the highly electrophilic aromatic ring of **5** produces the σ-adduct which can attain a noticeable concentration due to the relatively hindered β-elimination step.

This situation seems to contradict our requirements concerning the kinetic scheme of the reaction. However, a closer inspection of the reaction course suggests that under the applied conditions, formation of σ-adducts is an irreversible process, thus the relationship of k_1 observed for a particular pair of nitroarenes after a time when the adducts are completely transformed into the VNS products reflects the genuine relation of the addition rates.[7]

Assuming equal, and constant during the course of the reaction, concentration of the both starting nitroarenes **A** and **B** ($[A]_0=[B]_0$) the observed ratio of the respective products is equal to ratio of the rates of the competing VNS reactions, which directly reflect relative rate constants of the nucleophilic addition step (Eq. 3)

$$\text{rate}^B_{VNS}/\text{rate}^A_{VNS} = [P_B]/[P_A] = k_1^B/k_1^A \quad (3)$$

In our experiments, in order to maintain comparable concentrations of the products, starting concentrations of the particular competing nitroarenes were chosen appropriately to their relative reactivity. Moreover, the molar excess of each nitroarene over **1** was usually only 2- to 6-fold, so the requirements for Eq. 3 were not met. Therefore the k_1^B/k_1^A ratio was calculated using appropriate mathematics (see Section 3) and the final results are presented in Table 1.



Scheme 3.

Table 1. Rate constants ratio in competitive reactions of nitroarenes **A** and **B** with **1**[a]

Nitroarene **A**[b]		Nitroarene **B**[b]		k_1^B/k_1^A (compared positions)
No	R_{1-3}	No	R_{4-6}	
2	H	**3**	2-Cl	8.5 (o/o), 12.6 (p/p)
2	H	**4**	4-Cl	130 (o/o)
2	H	**6**	2,4,6-Cl_3[c]	1.6 (o/o)
3	2-Cl	**4**	4-Cl	14 (o/o)
3	2-Cl	**5**	2,4-Cl_2	75 (o/o)
4	4-Cl	**5**	2,4-Cl_2	6.2 (o/o)
3	2-Cl	**7**	2-Br	0.8 (o/o), 0.7 (p/p)
4	4-Cl	**8**	4-Br	1.2 (o/o)

[a] Calculated on the basis of the observed products ratio, starting nitroarenes concentrations and number of reacting positions (see Section 3).
[b] Description according to Scheme 2.
[c] Nucleophilic substitution of 2-chlorine occurs. Substitution of chlorine in *para* position was not observed.

In the case of **6**, which was found to be exceptionally unstable in the presence of strong base, such that its concentration dropped quickly during the reaction course, another procedure was applied. The reaction was carried out for a very short time in order to achieve low conversion. The use of both nitroarenes in 1:1 proportion in considerable excess over the carbanion allows us to consider the observed product ratio directly as k_1^B/k_1^A.

The results were then re-calculated to reflect the reactivity of particular positions in the aromatic rings of nitroarenes **2**–**8** in relation to that of the *ortho* position in nitrobenzene and are presented in Figure 1. In the cases of **4**, **5** and **8** the relative rates are shown as a range of values as they were calculated from reactions of different pairs of competing nitroarenes.

For compound **4**, there is satisfactory agreement of the results obtained in direct competition of **4**+**2** and of that calculated from competition **4**+**3** then **3**+**2**. In the case of **5**, the results of direct competition were not reliable due to the large difference in reactivity of **2** and **5**. The range of values shown comprises those calculated from results of three competition sequences: **5**+**4** then **4**+**2**, **5**+**3** then **3**+**2** and also **5**+**4** then **4**+**3** then **3**+**2**.

The results in Figure 1 clearly demonstrate the expected influence of the chloro substituents on the reactivity of the nitrobenzene ring at the activated positions *ortho* and *para* to the nitro group. Activation of positions 2- and 6- by 4-Cl is substantial and much higher than that of position 4- and 6- by 2-Cl. Much weaker activation in the latter case is apparently due to a secondary steric effect, i.e., partial loss of activating effect of the nitro group caused by the bulky *ortho* substituent. Although one could not expect strict additivity of the effects in **5**, the observed reactivity of the position 6-activated by two chloro substituents seems to be in a reasonably good relation to that of **3** and **4**. Of great importance in that respect is the relative reactivity of position 2-substituted by chlorine in **6**. Although activation of this position by two other chloro substituents should be similar to that in **5**, the observed reactivity, i.e. rate constant of the addition at this position is *ca*. 400–500 times smaller than in **5**. Thus, the formulated earlier supposition concerning the deactivating effect of a halogen substituent on the position which it occupies seems to be justified. Effects of bromo substituents in 2-bromo- and

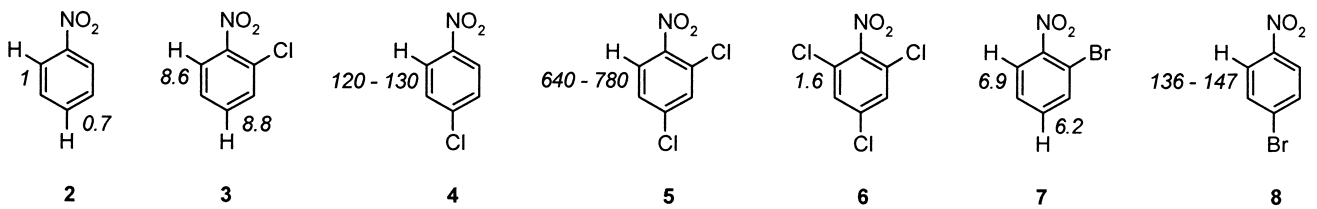


Figure 1.

4-bromonitrobenzenes **7** and **8** were similar to those of chloro substituents. The secondary steric effect in **7** was somewhat stronger than in **3**, but less than one might expect.

3. Experimental

3.1. General

Melting points are uncorrected. ^{1}H NMR spectra were recorded on a Varian Mercury 400 (400 MHz) or a Brucker DRX 500 (500 MHz) instruments. Chemical shifts are expressed in ppm referred to TMS, coupling constants in Hertz. Mass spectra were obtained on an AMD-604 spectrometer. GC analyses were performed on a HP 6890 chromatograph with HP-5 capillary column. Silica gel Merck 60 (230–400 mesh) was used for column chromatography.

All starting materials and reagents were commercially available. Authentic samples of the VNS products of nitroarenes **1**–**5** and **8** were obtained according to the published procedures.[8,9] The products of the VNS in **7** (**7a** and **7b**) were obtained analogously in reaction of **7** with **1** in the KOH/DMSO system.[9] A sample of **6a** was isolated from the competitive reaction mixture by column chromatography (SiO_2, hexane/AcOEt).

3.2. General procedure for competition reactions of nitroarenes 2–5, 7 and 8 with 1

To a solution of chlorosulfone **1** (0.12 mmol) and a mixture of two nitroarenes (0.15–1.3 mmol each) in DMF (7 mL) cooled to −40±0.1 °C under argon, was added rapidly a solution of *tert*-BuOK (0.5 mmol) in DMF (1 mL) from a stock solution kept at −40 °C. After 15 s. the reaction mixture was quenched at −40 °C with aqueous HCl (1:10, 2 mL), then diluted with water and extracted with CH_2Cl_2. Combined extracts were washed with water, dried with Na_2SO_4 and analyzed by GC using internal standards and calibration curve prepared for authentic samples of the products. In all instances, conversion of **1** was over 90%. The reactions were repeated 3–5 times for each pair of nitroarenes, and the results were averaged.

The relative reactivity for particular pairs of nitroarenes (Table 1) were calculated from the observed products ratios by combining integrated kinetic equation 4, with 5 and 6 involving some simplifications derived from the fact of almost complete (>90%) conversion of **1**. Further calculations according to equations 7 and 8 provided ratios of rate constants for *ortho* and *para* substitution, which were then re-calculated to obtain relative rate constants referred to that of the VNS *ortho* substitution in nitrobenzene, shown in Figure 1:

$$(k_1^{oB} + k_1^{pB})/(k_1^{oA} + k_1^{pA}) = \ln(1 - ([P^{oB}] + [P^{pB}])/[\mathbf{B}]_0)/\ln(1 - ([P^{oA}] + [P^{pA}])/[\mathbf{A}]_0) \quad (4)$$

$$[P^{oA}] + [P^{pA}] = [\mathbf{1}]_0/(1 + ([P^{oB}] + [P^{pB}])/([P^{oA}] + [P^{pA}])) \quad (5)$$

$$[P^{oB}] + [P^{pB}] = [\mathbf{1}]_0 - [\mathbf{1}]_0/(1 + ([P^{oB}] + [P^{pB}])/([P^{oA}] + [P^{pA}])) \quad (6)$$

$$k_1^{oB}/k_1^{oAB} = ((k_1^{oB} + k_1^{pB})/(k_1^{oA} + k_1^{pA}))(((1 + (p/o)^A)n^A)/(1 + (p/o)^B)n^B)) \quad (7)$$

$$k_1^{pB}/k_1^{pA} = ((k_1^{oB} + k_1^{pB})/(k_1^{oA} + k_1^{pA}))((1 + 1/(p/o)^A)/(1 + 1/(p/o)^B)) \quad (8)$$

where: $[\mathbf{A}]_0$ and $[\mathbf{B}]_0$ are starting concentrations of nitroarenes; $[P^{oA}]$, $[P^{pA}]$, $[P^{oB}]$, and $[P^{pB}]$ are concentrations of *ortho* and *para* reaction products of nitroarenes **A** and **B** respectively; $(p/o)^A$ and $(p/o)^B$ are ratios of *ortho* and *para* isomeric products observed in the reactions; n^A and n^B are numbers of reactive *ortho* positions in nitroarenes **A** and **B**.

3.1.1. (3-Bromo-2-nitrophenyl)methyl phenyl sulfone 7a. White crystals, mp 140–141 °C (EtOH), ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.38 (s, 2H), 7.38 (t, J=7.9 Hz, 1H), 7.50–7.55 (m, 2H), 7.59 (dd, J=7.9 Hz, 1.0, 1H), 7.66–7.71 (m, 4H). MS (EI) *m*/*z* 357 (1), 355 (2), 311 (20), 309 (19), 216 (99), 214 (100), 158 (31), 156 (32), 77 (68); HRMS (EI) calcd for $C_{13}H_{10}O_4NS^{79}Br$ 354.9514. Found 354.9526.

3.1.2. (3-Bromo-4-nitrophenyl)methyl phenyl sulfone 7b. White solid, mp 173 °C (EtOH), ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.32 (s, 2H), 7.23 (dd, J=8.3 Hz, 1.8, 1H), 7.46 (d, J=1.8 Hz, 1H), 7.52–7.57 (m, 2H), 7.67–7.73 (m, 3H), 7.77 (d, J=8.3 Hz, 1H). MS (EI) *m*/*z* 357 (28), 355 (27), 216 (97), 214 (100), 186 (35), 184 (35), 141 (40), 89 (40), 77 (68); HRMS calcd for $C_{13}H_{10}O_4NS^{79}Br$ 354.9514. Found 354.9516.

3.1.3. Chloro(3,5-dichloro-2-nitrophenyl)methyl phenyl sulfone 6a. White crystals, mp 174–176 °C (EtOH), ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (s, 1H), 7.59–7.65 (m, 3H), 7.75–7.80 (m, 1H), 7.83 (d, J=2.2 Hz, 1H), 7.87–7.91 (m, 2H). MS (EI) *m*/*z* 240 (97), 238 (100), 212 (30), 210 (32), 141 (30), 77 (34). HRMS (EI) calcd for $C_7H_3O_2N^{35}Cl_3$ (M^+−$PhSO_2$) 237.9229. Found 237.9232.

3.3. Competitive reactions of nitroarenes 6 and 2 with 1

To a solution of **6** (0.38–0.40 mmol) and **2** (0.43–0.47 mmol) in DMF (7 mL) cooled to −40±0.1 °C under argon, was added a stock solution (1 mL) containing carbanion of **1** (0.2 mmol) and *tert*-BuOK (0.4 mmol) in DMF. The reaction was quenched after 4–5 s with dilute HCl_{aq} (1:10), and extracted with CH_2Cl_2. Combined extracts were washed with water, dried with Na_2SO_4 and analysed by GC using internal standards as indicated earlier. Conversion of **1** was always under 20%, which means *ca* 5% conversion of the nitroarenes. The regular product of S_NAr in **6** (**6a**) was accompanied by a small amount of its dechlorinated derivative, identical to **5a**. Since the latter was formed under the reaction conditions directly from **6a** in a subsequent process, both products were counted as products of the chlorine substitution in **6**.

3.3.1. Chloro(3,5-dichlorophenyl)methyl phenyl sulfone (5c). To a solution of **5** (440 mg, 2.3 mmol) in DMF (5 mL) cooled to -40 ± 0.1 °C under argon, was added a stock solution (2 mL) containing carbanion of **1** (0.54 mmol) in DMF, prepared by addition of **1** in DMF to a solution of equimolar amount of *tert*-BuOK in DMF at -40 °C under argon. The reaction was quenched after 5 s with aqueous HCl_{aq} (1:10), diluted with water and extracted with CH_2Cl_2. Combined extracts were thoroughly washed with water, dried with Na_2SO_4 and the solvent was evaporated. The crude mixture of starting reagents, the VNS product, and **5c** were separated by column chromatography on SiO_2 using hexane/AcOEt to give **5c**, 51 mg (28%).

White crystals, mp 157–158 °C (EtOH), ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.54 (s, 3H), 5.56 (s, 1H), 7.28 (d, J=1.9 Hz, 1H), 7.42 (t, J=1.9 Hz, 2H), 7.55–7.59 (m, 2H), 7.71–7.75 (m, 1H), 7.77–7.81 (m, 2H); MS (EI) m/z 334 (M^+, 1), 195 (96), 193 (100), 159 (6), 123 (7), 77 (11); HRMS (EI) calcd for $C_{13}H_9O_2S^{35}Cl_3$ 333.9389. Found 333.9374.

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Synthesis of new molecular scaffolds: 3-aza-7,9-dioxa-bicyclo[4.2.1]nonane (8-*exo* BTKa) and 3-aza-8,10-dioxa-bicyclo[5.2.1]decane (9-*exo* BTKa) carboxylic acids

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Abstract—Two classes of enantiopure molecular scaffolds were prepared, whose lactam structure formally derives from the coupling between tartaric acid and β- or γ-ketoamines. We labelled these compounds as 8-*exo* and 9-*exo* BTKa, indicating the lactam size (8- and 9-membered ring, respectively). Starting from β- and γ-nitroketones, the synthesis involves the ketal formation by (*R*,*R*)-dimethyl tartrate. The subsequent amide bond formation occurs during the hydrogenation of the nitro group over Raney-Ni and no expected open chain amine was observed.

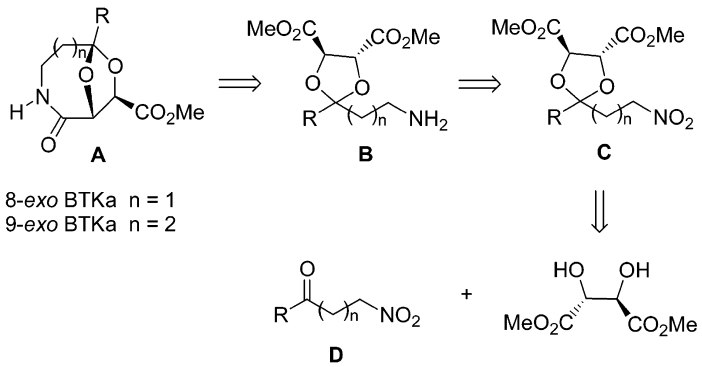
1. Introduction

We recently reported on the synthesis of two new classes of conformationally restricted dipeptide isosteres, whose synthesis is based on the combination of a tartaric acid derivative and either α-amino aldehydes[1] or α-amino-ketones.[1b,2] For the sake of simplicity, we named these compounds BTAa[3] (**1a**–**b**) and BTKa[4] (**2a**–**b**), respectively. Their general structure is reported in Figure 1.

$R_1 = H$	7-exo BTAa, **1a**	7-endo BTAa, **1b**
$R_1 \neq H$	7-exo BTKa, **2a**	7-endo BTKa, **2b**

Figure 1. General structure of peptide isosteres BTAa and BTKa.

Both classes of compounds have some interesting features, commonly required in designing new peptide isosteres: the synthesis starts from commercially available enantiopure precursors; the stereochemistry can be controlled by choosing the suitable α-amino acid or tartaric acid derivative; they are compatible with solid phase synthesis techniques.[5] The 7-*endo* BTAa isosteres (**1b**) proved to be efficient reverse turn inducers in a peptide chain.[1b,5,6] Furthermore, these compounds found an application as monomers for the generation of oligomers[7] and as chiral auxiliares.[8]



Scheme 1. Retrosynthetic analysis of 8-*exo* and 9-*exo* BTKa.

Keywords: Ketal; Nitroketone; Peptidomimetic; Tartaric acid.
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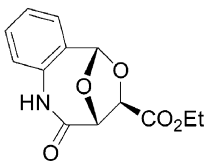
With the aim to extend the methodology to new structures of the BTKa family by ring enlargement from 7-membered one (**2a**–**b**) up to the size of 8 and 9, we envisaged a retrosynthetic approach (Scheme 1), where the formation of the ketal (**B**) between the tartaric moiety and an amino-ketone precedes the ring closure through the amide bond (**A**).

To avoid the formation of Schiff bases and facilitate the ketalisation process, the amino group needs to be protected. Therefore, β- and γ-nitroketones (**D**) were used as starting materials, where the nitro group masks the amine function needed for the amide bond formation.

Furthermore, we were encouraged on the possible success of the envisaged strategy by an analogue example reported by Levine et al.[9] In their paper, the authors used *o*-nitro-benzaldehyde as starting material to be coupled with (*R*,*R*)-diethyl tartrate to obtain the cyclic compound **3** (Fig. 2).



3

Figure 2. Structure of the compound synthesised by Levine and co-workers.[9]

However, there is an important difference with our case: we used ketones instead of aldehydes and the nitro group was bound to an aliphatic chain. Probably due to these differences in substrates, during the synthesis we encountered a few problems that did not occur to Levine et al. These will be reported in details in the next section.

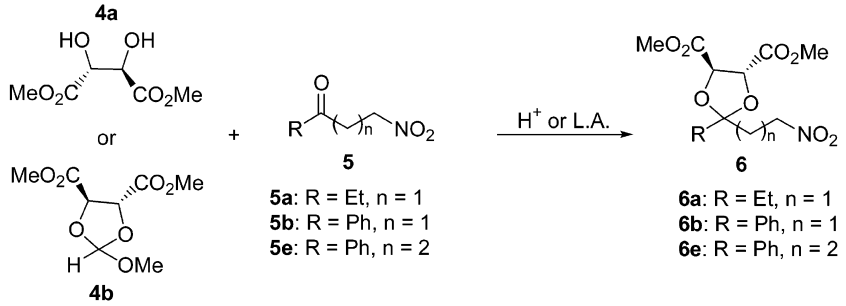
2. Results and discussion

With respect to the previously published methodology,[1a,2] we inverted the order of the two key steps of the synthesis, i.e. the formation first of the ketal with the tartaric moiety and then of the amide bond to close the ring.

Although the preparation of ketals with tartaric acid is extensively reported, the ketalisation of β- or γ-nitroketones is not as straightforward as one would expect it to be.

The reaction, reported in Scheme 2, has been performed under many conditions, summarised in Table 1.

The classical ketalisation reaction, employing **4a** as a diol and **5b** as a substrate,[9] was performed under acidic catalysis and Dean–Stark azeotropic distillation, affording the unreacted starting material (entry 1). Because of this unexpected result, we experimented alternative methods, employing trimethyl orthoformate as dehydrating agent (entry 2).[10] Starting from **4a** and **5b** in a 2:1 ratio, in the presence of 2 equiv. of $HC(OMe)_3$ under MsOH catalysis at 100 °C for 3 h, unreacted **5b** was recovered, whereas the dimethyl tartrate **4a** was transformed into **4b**. This activated form of tartaric acid has been used in *trans*-ketalisation reactions, as exemplified by the synthesis reported by Giordano et al.,[11] where, in order to obtain a cyclic ketals with dimethyl tartrate, **4a** was first converted into **4b** and then added to the substrate. Performing the reaction under



Scheme 2. Ketalisation with (*R*,*R*)-dimethyl tartrate or its derivative. The reaction conditions are reported in Table 1.

Table 1. Ketal formation with (*R*,*R*)-dimethyl tartrate or its derivative under acidic catalysis

Entry	Substrate	(*R*,*R*)-**4** (eq)	Eq $HC(OMe)_3$	Solvent	Temp. (°C)	Time (h)	H^+ or L.A. (%)	Products (%)
1	**5b**	**4a** (1)	None	Benzene	Reflux	30	*p*-TsOH (5)	nr[a]
2		**4a** (2)	2	None	100	3	MsOH (7)	**4b**
3		**4b** (1)	None	DCM	25	48	H_2SO_4 (30)	**6b** (35)
4		**4b** (1.2)	2	DCM	25	88	H_2SO_4 (23)	**6b** (25)
5		**4b** (1.3)	4	DCM	25	136	H_2SO_4 (23)	**6b** (35)
6		**4b** (1)	2	DCM	25	60	MsOH (10)	**4a**
7		**4b** (1)	None	DCM	25	60	Amberlyst15 (25 w/w)	nr[a]
8	**5a**	**4b** (1.3)	None	DM	25	36	H_2SO_4 (23)	**6a** (36)
9	**5e**	**4b** (1.5)	None	DCM	25	24	H_2SO_4 (23)	**6e** (44)
10		**4b** (1.3)	None	DCM	25	48	H_2SO_4 (23)	**6e** (74)
11	**5a**	**4a** (1.2)	1.2	ACN	25	19	$Sc(OTf)_3$ (10)	**6a** (60)
12	**5b**	**4a** (1.2)	1.2	ACN	25	48	$Sc(OTf)_3$ (10)	**6b** (22)
13		**4a** (1.1)	None	DCM	25	48	$In(Otf)_3$ (10)	nr[a]

[a] No reaction.

the reported conditions[11] on **5b** in DCM at room temperature and under H_2SO_4 catalysis, **6b** was eventually obtained in 35% yield after 48 h, together with unreacted **5b** (entry 3). Based on this result, we tried to increase the reaction conversion by increasing the **4b**:**5b** ratio, the reaction time and the amount of $HC(OMe)_3$ in the reaction mixture (entries 4 and 5). In both cases the conversion never exceeded 35%.

The change of acid catalyst from H_2SO_4 to MsOH (entry 6) or to the sulphonic resin Amberlyst15 (entry 7) proved to be inefficient towards the *trans*-ketalisation and resulted in the hydrolysis of **4b** or no reaction at all, respectively.

The reaction performed under the best conditions found so far (entry 3) on the aliphatic substrate **5a**, afforded **6a** in 36% yield (entry 8). This unreactivity cannot be attributed only to the reluctance of the substrate **5b** to break the conjugation of its enone moiety, since the same behaviour was found in the case of the aliphatic nitroketone **5a**. Furthermore, the reaction proved much more efficient on the aromatic substrate **5e**, affording **6e** in 44% yield (entry 9). Conversion increased up to 74% (entry 10), simply by extending the reaction time from 24 to 48 h.

Since the use of protic acids as catalysts afforded unsatisfying results, at least in the case of β-nitroketones **5a** and **5b**, we decided to explore the use of Lewis acids instead.

Scandium triflate and scandium triflimide promote ketalisation and *trans*-ketalisation reactions, under very mild conditions and in very good yields.[12]

In their paper, Ishihara et al.[12] report that $Sc(OTf)_3$ gives better results in the reaction of ketones with diethyl tartrate. In our case, we had to increase the amount of catalyst up to 10% (using the advised 1% quantity gave no result; data not shown) and the conversion, if fairly good in the case of aliphatic ketone **5a** (60%, Entry 11), was disappointing in the case of aromatic **5b** (22%, entry 12). The last attempt using $In(OTf)_3$ as catalyst resulted in the recovery of the starting material **5b** (entry 13), as actually expected since this method has in fact been reported for thio- and *trans*-thioketalisations.[13]

Unfortunately, when we repeated the reaction under the best conditions found for each substrate, we always got different results. Since the reaction represented in Scheme 1 is an equilibrium and we did not find a way to shift it towards the products, we must, therefore, assume that minimal variations of the reaction conditions, normally unperceptable by the operator, have great influence on the outcome of the reaction.

Thus, the real obstacle to the formation of the ketal could be the proximity of the nitro group to the carbonyl. This is probably due to the keto–enol and nitro–isonitro tautomerisms contemporarily present in the substrates (i.e., β-nitroketones) that form an extended conjugate species that does not easily undergo the ketalisation. The effect is increased in aromatic substrates. This hypothesis seems to be confirmed when α-nitroacetophenone is used as substrate (this would afford 7-*exo* BTKa, **2a**), since in all cases the unreacted starting material is recovered (data not shown). Furthermore, in the case of γ-nitroketones, the presence of an additional methylene unity between the carbonyl and the nitro group (from **5b** to **5e**) breaks the extended conjugation of the substrate, resulting in much higher conversion (from 35 to 74%).

Therefore, considering that in all cases the carbonyl group must be activated in some way towards the attack by the hydroxyls belonging to the tartaric acid derivative, we decided to synthesise and isolate first the dimethyl ketal of each substrate on which to perform a *trans*-ketalisation reaction.

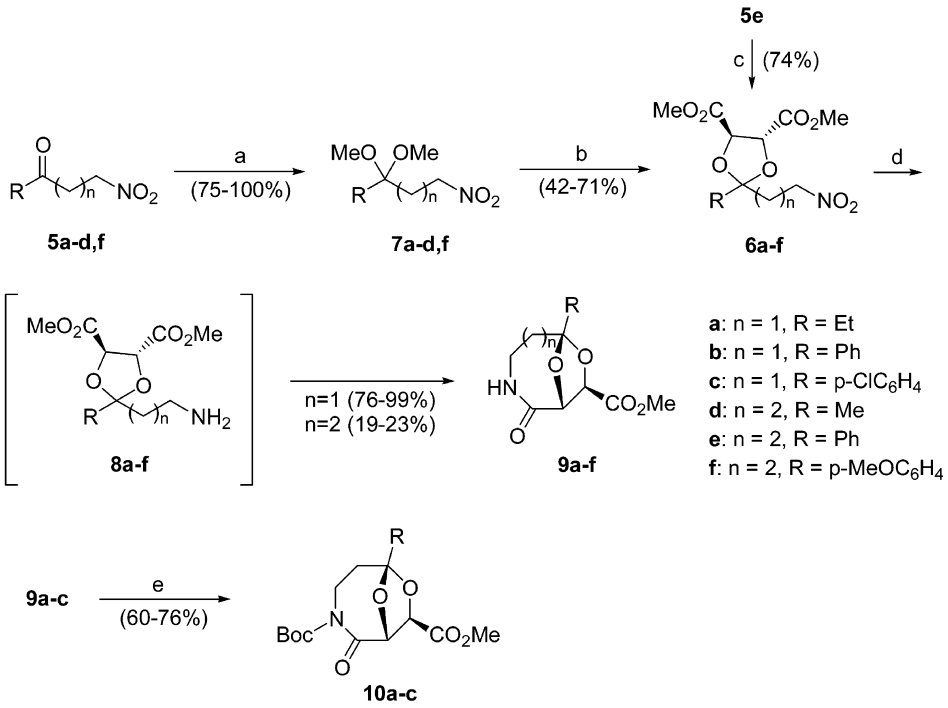
This proved to be the successful method to afford the target compounds and the final synthesis is reported in Scheme 3.

Ketones **5a**–**d** and **5f** were converted into their corresponding dimethyl ketals by treatment with an excess of trimethyl ortoformate in methanol under *p*-TsOH catalysis.[14] Depending on the substrate, the reaction was left 72 h at room temperature (**5a** and **5f**) or refluxed for 5 h (**5b**–**d**) affording **7a**–**d** and **7f** in very good yields (75% to quantitative). Apart from ketones **5b** and **5c**, conversions were always quantitative and the product recovered after the usual work-up could be used without further purification in the next step. *Trans*-ketalisations using dimethyl (*R*,*R*)-tartrate (**4a**) was performed under the conditions reported by Seebach et al.[15] for aromatic aldehydes. The use of 2 equiv. of $BF_3{\cdot}Et_2O$ in anhydrous ethyl acetate at 0 °C allowed the *trans*-ketalisation of **7a**–**d** and **7f** into **6a**–**d** and **6f**, yields ranging from 42 to 71% after purification. In all cases, starting β- or γ-nitroketones (20–30%) are re-formed during the reaction and they can be recovered by chromatographic purification, allowing material recycling when repeating the first step of the synthesis. Tartaric ketal **6e** was synthesised starting from γ-nitroketone **5e** under the conditions reported in Table 1 (entry 10).

Reduction of the nitro group to amino was obtained by hydrogenation on Raney-Ni of **7a**–**f** in methanol at room temperature in 16 h.[16] Surprisingly, in the case of substrates **7a**–**f**, we did not recover the corresponding amines **8a**–**f**, as we expected in analogy with the synthesis of **3**.[9] In our case, the amide formation that allows the ring closure is spontaneous during the reduction, so that cyclic 8-membered amides **9a**–**c** were obtained in good yields (76–99%) and high purity after filtration from the catalyst. On the other hand, in the case of substrates **7d**–**f**, cyclic 9-membered amides **9d**–**f** was obtained as main products, together with unidentified by-products. After chromatographic purification, pure **9d**–**f** were obtained in 19–24% yields and in the MeOH fraction we recovered a complex mixture of by-products, where amines **8d**–**f** were probably also present but could not be isolated.

Since compounds **9a**–**c** are more readily accessible, we decided to prepare their *N*-*tert*-butoxycarbonyl derivatives, as an example of amide protection that could be useful in the subsequent functional group transformation.

Amides **9a**–**c** were protected as *N*-Boc derivatives by



Scheme 3. (a) $HC(OMe)_3$, *p*-TsOH cat., MeOH, reflux or rt, 5 or 48 h; (b) **4a**, BF_3:Et_2O, EtOAc, 0 °C, 4 h; (c) **4b**, DCM, H_2SO_4 cat., rt, 48 h; (d) Raney-Ni, H_2, MeOH, rt, 16 h; (e) Boc_2O, Et_3N, DMAP cat., DCM, reflux, 18 h.

treatment in refluxing CH_2Cl_2 with Boc_2O and Et_3N in the presence of a catalytic amount of DMAP.[17] After 18 h, **10a–c** were recovered in fair yields (60–76%).

In this way we realised the synthesis of two new classes of BTKa, where the cyclic amide consists in a 8- or 9-membered ring and the substituent on the bridgehead carbon that derives from the ketone moiety is an aliphatic chain (**9a**, **9d**) or a phenyl group (**9b**, **9e**) or a *p*-substituted aromatic ring (**9c**, **9e**).

There are a few advantages in this approach: first, since the formation of the amide bond spontaneously occurs after the reduction of the nitro group, there is no need to use expensive peptide coupling reagents nor, in most cases, to purify the product; then, the isostere is obtained as the free amide that can be suitably protected, depending on the subsequent use of the substrate.

The aim of the present work was to obtain the ring enlargement of the rigid *exo* BTKa scaffolds and it also seemed interesting to evaluate how this modification would affect the conformational freedom of these compounds that represent a new class of dipeptide isosteres.

We, therefore, performed a complete conformational analysis on amides **9a**, **9b**, **9d** and **9e**.

As expected, these compounds are less rigid than their 7-membered counterparts and the 8-*exo* and 9-*exo* BTKa are more prone to take different conformations. Molecular modeling calculations revealed that the most interesting feature lies in the distance between the aromatic ring and the carbomethoxy group. This is found to decrease as the ring enlarges: in compounds **9b** and **9e**, the average distance is 3.4 and 3.0 Å, respectively, and it averages 3.8 Å in the 7-*exo* BTKa. This observation is confirmed by the experimental ^1H NMR data: the shielding effect of the aromatic ring increases and the OCH_3 group resonates at 3.75 (7-*exo* BTKa,[2] **2a**), 3.70 (8-*exo* BTKa, **9b**) and 3.37 ppm (9-*exo* BTKa, **9e**).

3. Conclusions

In this work, we prepared two classes of modified BTKa, where the ring size was increased from 7- up to 8- and 9-members.

As starting materials we used β- and γ-nitroketones. The synthesis presents the two key steps in reversed order with respect to the previously reported methodology: first the carbonyl is protected as ketal, and then the amide bond is formed. The presence of the nitro group seems to influence the reactivity of the carbonyl and the ketalisation using (*R*,*R*)-dimethyl tartaric ester as a partner diol was thus extensively studied, since the well known reaction conditions failed on these substrates. When tartaric ketals were obtained, the subsequent hydrogenation on Raney-Ni of the nitro group surprisingly afforded directly the 8-membered cyclic compounds, whereas in the case of 9-membered cyclic amides the reaction afforded a complex mixture of compounds, including the target lactames.

As expected by considering the ring dimensions, conformational analysis performed on these molecules revealed an increased flexibility with respect to 7-*exo* BTKa. However, an interesting feature of these compounds consists in the distance between the carbomethoxy group and the aromatic ring on the bridgehead carbon that decreases as the ring

enlarges. This explains the experimental upfield shift of the OCH_3 group observed in the ^1H NMR when passing from the 7-*exo* BTKa to the 8- and 9-*exo* ones. This structural characteristic could be useful in further applications.

4. Experimental

4.1. General

Melting points are uncorrected. Chromatographic separations were performed under pressure on silica gel by flash-column techniques; R_f values refer to TLC carried out on 25-mm silica gel plates (Merck F254), with the same eluent as indicated for the column chromatography. IR spectra were recorded with a Perkin–Elmer 881 spectrophotometer in $CHCl_3$ solution. ^1H NMR (200 MHz) and ^{13}C NMR (50.33 MHz) spectra were recorded with a Varian XL 200 instrument in $CDCl_3$ solution. Mass spectra were carried out by EI at 70 eV, unless otherwise stated, on 5790A–5970A Hewlett–Packard and QMD 1000 Carlo Erba instruments. Microanalyses were carried out with a Perkin–Elmer 2400/2 elemental analyser. Optical rotations were determined with a JASCO DIP-370 instrument. Molecular modeling was carried out by using the MM2* force field implemented in MacroModel v6.5 using the default values of the software for all calculations. (4*R*,5*R*)-2-Methoxy-[1,3]dioxolane-4,5-dicarboxylic acid dimethyl ester **4b**,[18] β-nitroketone **5a**,[19] and γ-nitroketones **5d–f**[16] were synthesised as reported.

4.1.1. 1-Phenyl-3-nitro-1-propanone (5b). Synthesised as reported for **5a**,[19] starting from 1-phenylpropenone (2.10 g, 15.9 mmol). After chromatografic purification (eluent: CH_2Cl_2–petroleum ether, 1:1, R_f=0.13), pure **5b** (1.37 g, 48%) was obtained as white solid.

Compound **5b**. Mp 77–78 °C. ^1H NMR δ (ppm): 7.99–7.95 (m, 2H), 7.65–7.45 (m, 3H), 4.82 (t, *J*=6.2 Hz, 2H), 3.65 (t, *J*=6.2 Hz, 2H). ^{13}C NMR δ (ppm): 195.4 (s), 138.6 (s), 129.4 (d), 129.3 (d, 2C), 128.7 (d, 2C), 69.8 (t), 35.4 (t). MS *m*/*z* (%): 105 ($M^+-(CH_2)_2NO_2$, 100), 77 (65). IR ($CDCl_3$): 1708, 1689, 1555 and 1364 cm^{-1}. Anal. Calcd for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.52; H, 5.05; N, 7.58.

4.1.2. 1-(4-Chlorophenyl)-3-nitro-1-propanone (5c). Synthesised as reported,[20] starting from 3-chloro-1-(4-chlorophenyl)-1-propanone (2.00 g, 9.85 mmol). After crystallisation from hexane, pure **5c** (1.68 g, 80%) was obtained as pale yellow solid.

Compound **5c**. Mp 71–72 °C (lit.[20b] 79–80 °C). ^1H NMR δ (ppm): 7.91 (d, *J*=8.4 Hz, 2H), 7.47 (d, *J*=8.4 Hz, 2H), 4.82 (t, *J*=5.8 Hz, 2H), 3.62 (t, *J*=5.8 Hz, 2H). ^{13}C NMR δ (ppm): 193.8 (s), 140.3 (s), 133.8 (s), 129.4 (d, 2C), 129.0 (d, 2C), 69.0 (t), 34.7 (t). MS *m*/*z* (%): 213 (M^+, 1), 167 (M^+-NO_2, 18), 139 ($M^+-(CH_2)_2NO_2$, 100). IR ($CDCl_3$): 1691, 1560, 1374 cm^{-1}.

4.1.3. 3,3-Dimethoxy-1-nitro-pentane (7a). To a solution of **5a** (686 mg, 5.23 mmol) in MeOH (8 mL), trimethyl ortoformate (8 mL) and a catalytic amount of *p*-TsOH were added. The solution was left under magnetic stirring at room temperature. After 72 h, satd $NaHCO_3$ was added (10 mL), the product extracted with CH_2Cl_2 (3×10 mL) and the organic layer dried over Na_2SO_4. After filtration and evaporation of the solvent, crude **7a** was obtained in quantitative yield and used in the next step without further purification.

Compound **7a**. ^1H NMR δ (ppm): 4.34 (m, 2H, CH_2NO_2), 3.15 (s, 6H, OCH_3), 2.33 (m, 2H, $CH_2CH_2NO_2$), 1.56 (q, *J*=7.7 Hz, 2H, CH_2CH_3), 0.86 (t, *J*=7.7 Hz, 3H, CH_3). ^{13}C NMR δ (ppm): 101.6 (s), 71.5 (t), 48.0 (q, 2C), 29.8 (t), 25.9 (t), 7.9 (q). MS *m*/*z* (%): 178 (M^++1, 1.2), 113 ($M^+-(CH_2)_2NO_2$, 10), 103 (53), 71 (57), 57 (100).

4.1.4. (1,1-Dimethoxy-3-nitro-propyl)-benzene (7b). Prepared as described for **7a**, starting from **5b** (506 mg, 2.83 mmol) but refluxing the solution for 5 h. Crude **7b**, isolated after the work up in 80% yield, was used in the next step without further purification.

Compound **7b**. ^1H NMR δ (ppm): 7.39–7.22 (m, 5H, Ph), 4.00 (m, 2H, CH_2NO_2), 3.12 (s, 6H, OCH_3), 2.57 (m, 2H, $CH_2CH_2NO_2$). ^{13}C NMR δ (ppm): 138.8 (s), 128.8 (d), 128.4 (d, 2C), 126.5 (d, 2C), 101.4 (s), 71.3 (t), 48.9 (q, 2C), 34.6 (t). MS *m*/*z* (%): 225 (M^+, 1), 178 (8), 151 (21), 105 (100), 77 (54).

4.1.5. 1-Chloro-4-(1,1-dimethoxy-3-nitro-propyl)-benzene (7c). Prepared as described for **7a**, starting from **5c** (285 mg, 1.33 mmol) but refluxing the solution for 5 h. Crude **7c**, isolated after the work up in 75% yield, was used in the next step without further purification.

Compound **7c**. ^1H NMR δ (ppm): 7.34–7.26 (m, 4H, C_6H_4), 3.97 (m, 2H, CH_2NO_2), 3.08 (s, 6H, OCH_3), 2.54 (m, 2H, $CH_2CH_2NO_2$). ^{13}C NMR δ (ppm): 144.8 (s), 137.5 (s), 128.6 (d, 2C), 128.1 (d, 2C), 101.1 (s), 71.1 (t), 48.9 (q, 2C), 34.5 (t). MS (30 eV) *m*/*z* (%): 185 ($M^+-(CH_2)_2NO_2$, 19), 139 (100).

4.1.6. 4,4-Dimethoxy-1-nitro-pentane (7d). Prepared as described for **7a**, starting from **5d** (651 mg, 4.96 mmol) but refluxing the solution for 5 h. Crude **7d**, isolated after the work up in quantitative yield, was used in the next step without further purification.

Compound **7d**. ^1H NMR δ (ppm): 4.38 (t, *J*=7.0 Hz, 2H, CH_2NO_2), 3.15 (s, 6H, OCH_3), 2.14–1.96 (m, 2H, $CH_2CH_2CH_2NO_2$), 1.70–1.61 (m, 2H, $CH_2CH_2CH_2NO_2$), 1.27 (s, 3H, CH_3). ^{13}C NMR δ (ppm): 100.6 (s), 75.2 (d), 47.7 (q, 2C), 32.8 (t), 22.2 (t), 20.5 (q). MS *m*/*z* (%) 177 (M^+, 1), 89 ($M^+-(CH_2)_3NO_2$, 100).

4.1.7. 1-(1,1-Dimethoxy-3-nitro-butyl)-4-methoxy-benzene (7f). Prepared as described for **7a**, starting from **5f** (1.01 g, 4.53 mmol). Crude **7f**, isolated after the work up in quantitative yield, was used in the next step without further purification.

Compound **7f**. ^1H NMR δ (ppm): 7.34 (d, *J*=8.8 Hz, 2H, Ph), 6.86 (d, *J*=8.8 Hz, 2H, Ph), 4.17 (t, *J*=7.0 Hz, 2H, CH_2NO_2), 3.80 (s, 3H, $C_6H_4OCH_3$), 3.12 (s, 6H, OCH_3),

1.96–1.90 (m, 2H, $CH_2CH_2CH_2NO_2$), 1.89–1.63 (m, 2H, $CH_2CH_2CH_2NO_2$). ^{13}C NMR δ (ppm): 159.2 (s), 131.9 (s), 127.9 (d, 2C), 113.4 (d, 2C), 102.7 (s), 75.1 (t), 55.2 (q), 48.6 (q, 2C), 33.7 (t), 21.8 (t). MS *m/z* (%) 181 ($M^+-(CH_2)_3NO_2$, 73), 135 (100).

4.1.8. (4*R*,5*R*)-2-Ethyl-2-(2-nitro-ethyl)-[1,3]dioxolane-4,5-dicarboxylic acid dimethyl ester (6a). To a solution of **7a** (927 mg, 5.23 mmol) and (*R*,*R*)-dimethyl tartrate **4a** (1.86 g, 10.46 mmol) in anhydrous EtOAc (10 mL), cooled at 0 °C, BF_3:Et_2O (2 equiv., 1.23 mL) was added. After 4 h, the solution was diluted with EtOAc (10 mL) and $NaHCO_3$ satd (10 mL) added; the resulting mixture was left under vigorous stirring for 10 min. After separation of the phases, the organic layer was dried over Na_2SO_4. After filtration and evaporation of the solvent, crude **6a** was obtained and purification by chromatography (eluent: EtOAc–petroleum ether, 1:3, R_f=0.20) afforded pure **6a** (637 mg, 42%) as colourless oil.

Compound **6a**. $[\alpha]_D^{25}=-12.1$ (*c* 0.3, $CHCl_3$). ^{1}H NMR δ (ppm): 4.78 (d, *J*=6.2 Hz, 1H, C*H*CO_2Me), 4.64 (d, *J*=6.2 Hz, 1H, C*H*CO_2Me), 4.57–4.48 (m, 2H, CH_2NO_2), 3.83 (s, 3H, CO_2CH_3), 3.80 (s, 3H, CO_2CH_3), 2.54–2.45 (m, 2H, $CH_2CH_2NO_2$), 1.70 (q, *J*=7.4 Hz, 2H, CH_2CH_3), 0.96 (t, *J*=7.4 Hz, 3H, CH_2CH_3). ^{13}C NMR δ (ppm): 169.5 (s), 169.2 (s), 115.2 (s), 77.5 (d), 76.9 (d), 70.3 (t), 52.9 (q, 2C), 33.1 (t), 30.6 (t), 7.9 (q). MS *m/z* (%) 291 (M^+, 0.12), 244 (1), 217 (48), 215 (84), 55 (100). IR ($CHCl_3$) 1751, 1557 and 1383, 1439 cm^{-1}. Anal. Calcd for $C_{11}H_{17}NO_8$: C, 45.36; H, 5.88; N, 4.81. Found: C, 45.81; H, 6.05; N, 4.25.

4.1.9. (4*R*,5*R*)-2-(2-Nitro-ethyl)-2-phenyl-[1,3]dioxolane-4,5-dicarboxylic acid dimethyl ester (6b). Prepared as described for **6a**, starting from **7b** (630 mg, 2.83 mmol) and obtaining **6b** (600 mg, 63%) after chromatographic purification (eluent: EtOAc–petroleum ether, 1:4, R_f=0.19) as yellow oil.

Compound **6b**. $[\alpha]_D^{25}=+7.91$ (*c* 0.6, $CHCl_3$). ^{1}H NMR δ (ppm): 7.48–7.42 (m, 2H, Ph), 7.36–7.28 (m, 3H, Ph), 4.87 (d, *J*=5.1 Hz, 1H, C*H*CO_2Me), 4.73 (d, *J*=5.1 Hz, 1H, C*H*CO_2Me), 4.69–4.47 (m, 2H, CH_2NO_2), 3.84 (s, 3H, CO_2CH_3), 3.47 (s, 3H, CO_2CH_3), 2.86–2.57 (m, 2H, $CH_2CH_2NO_2$). ^{13}C NMR δ (ppm): 168.9 (s), 168.7 (s), 139.1 (s), 129.2 (d), 128.2 (d, 2C), 125.6 (d, 2C), 112.4 (s), 77.5 (d), 76.1 (d), 70.1 (t), 52.9 (q), 52.4 (q), 37.2 (t). MS *m/z* (%) 292 (M^+-HNO_2, 0.6), 265 (100), 232 (6), 155 (1), 105 (27), 77 (14). IR ($CHCl_3$) 1752, 1557 and 1383, 1439 cm^{-1}. Anal. Calcd for $C_{15}H_{17}NO_8$: C, 53.10; H, 5.05; N, 4.13. Found: C, 53.24; H, 5.08; N, 4.30.

4.1.10. (4*R*,5*R*)-2-(4-Chloro-phenyl)-2-(2-nitro-ethyl)-[1,3]dioxolane-4,5-dicarboxylic acid dimethyl ester (6c). Prepared as described for **6a**, starting from **7c** (276 mg, 1.06 mmol) and obtaining **6c** (175 mg, 44%) after chromatographic purification (eluent: CH_2Cl_2, R_f=0.38) as dark yellow oil.

Compound **6c**. $[\alpha]_D^{25}=+12.4$ (*c* 0.1, $CHCl_3$). ^{1}H NMR δ (ppm): 7.35 (d, *J*=8.6 Hz, 2H, Ph), 7.24 (d, *J*=8.6 Hz, 2H, Ph), 4.76 (d, *J*=5.5 Hz, 1H, C*H*CO_2Me), 4.67 (d, *J*=5.5 Hz, 1H, C*H*CO_2Me), 4.64–4.39 (m, 2H, CH_2NO_2), 3.77 (s, 3H, CO_2CH_3), 3.45 (s, 3H, CO_2CH_3), 2.75–2.47 (m, 2H, $CH_2CH_2NO_2$). ^{13}C NMR δ (ppm): 168.5 (s), 168.4 (s), 137.8 (s), 135.1 (s), 128.4 (d, 2C), 127.1 (d, 2C), 112.0 (s), 77.6 (d), 76.2 (d), 70.0 (t), 53.0 (q), 52.5 (q), 37.2 (t). MS *m/z* (%): 299 ($M^+-(CH_2)_2NO_2$, 95), 139 (100), 111 (40). IR ($CDCl_3$): 3151, 1601, 1560 and 1381 cm^{-1}. Anal. Calcd for $C_{15}H_{16}ClNO_8$: C, 48.20; H, 4.32; N, 3.75. Found: C, 48.60; H, 4.49; N, 3.69.

4.1.11. (4*R*,5*R*)-2-Methyl-2-(3-nitro-propyl)-[1,3]dioxolane-4,5-dicarboxylic acid dimethyl ester (6d). Prepared as described for **6a**, starting from **7d** (400 mg, 2.25 mmol) and obtaining **6d** (467 mg, 71%) after chromatographic purification (eluent: EtOAc–petroleum ether, 1:3, R_f=0.26) as colourless oil.

Compound **6d**. $[\alpha]_D^{25}=-23.5$ (*c* 1.0, $CHCl_3$). ^{1}H NMR δ (ppm): 4.80 (d, *J*=5.9 Hz, 1H, C*H*CO_2Me), 4.69 (d, *J*=5.9 Hz, 1H, C*H*CO_2Me), 4.43 (t, *J*=7.3 Hz, 2H, CH_2NO_2), 3.80 (s, 6H, CO_2CH_3), 2.23–2.12 (m, 2H, $CH_2CH_2CH_2NO_2$), 1.87–1.79 (m, 2H, $CH_2CH_2CH_2NO_2$), 1.42 (s, 3H, CH_3). ^{13}C NMR δ (ppm): 169.8 (s), 169.4 (s), 114.5 (s), 77.4 (d), 76.9 (d), 75.3 (t), 52.9 (q, 2C), 35.6 (t), 24.5 (q), 21.8 (t). MS *m/z* (%): 276 (M^+-CH_3, 20), 232 (M^+-CO_2Me, 6), 203 ($M^+-(CH_2)_3NO_2$, 100). IR ($CDCl_3$): 1755, 1554 and 1383 cm^{-1}. Anal. Calcd for $C_{11}H_{17}NO_8$: C, 45.36; H, 5.88; N, 4.81. Found: C, 45.40; H, 5.89; N, 4.44.

4.1.12. (4*R*,5*R*)-2-(2-Nitro-propyl)-2-phenyl-[1,3]dioxolane-4,5-dicarboxylic acid dimethyl ester (6e). To a solution of **5e** (100 mg, 0.52 mmol) and **4b** (150 mg, 0.68 mmol) in CH_2Cl_2 (2 mL), H_2SO_4 (50 μL) is added. After 48 h solvent is removed and 10% $NaHCO_3$ solution (5 mL) is added and the product extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were dried on Na_2SO_4 and filtration and evaporation of the solvent afforded crude **6e**. This was purified by flash chromatography (eluent: EtOAc–petroleum ether, 1:3, R_f=0.24), obtaining pure **6e** (135 mg, 74%) as yellow oil.

Compound **6e**. $[\alpha]_D^{25}=+13.6$ (*c* 1.0, $CHCl_3$). ^{1}H NMR δ (ppm): 7.46–7.41 (m, 2H, Ph), 7.34–7.29 (m, 3H, Ph), 4.87 (d, *J*=5.4 Hz, 1H, C*H*CO_2Me), 4.76 (d, *J*=5.4 Hz, 1H, C*H*CO_2Me), 4.48–4.41 (m, 2H, CH_2NO_2), 3.83 (s, 3H, CO_2CH_3), 3.49 (s, 3H, CO_2CH_3), 2.21–2.00 (m, 4H, $CH_2CH_2CH_2NO_2$). ^{13}C NMR δ (ppm): 162.9 (s), 169.0 (s), 139.8 (s), 128.8 (d), 128.1 (d, 2C), 125.7 (d, 2C), 113.9 (s), 77.4 (d), 76.1 (d), 75.1 (t), 52.9 (q), 52.4 (q), 36.8 (t), 21.4 (t). MS *m/z* (%): 265 ($M^+-(CH_2)_3NO_2$, 100), 105 (25), 77 (11). IR ($CHCl_3$): 1751, 1554 and 1371, 1438 cm^{-1}. Anal. Calcd for $C_{16}H_{19}NO_8$: C, 54.39; H, 5.42; N, 3.96. Found: C, 54.34; H, 5.56; N, 4.27.

4.1.13. (4*R*,5*R*)-2-(4-Methoxy-phenyl)-2-(2-nitro-propyl)-[1,3]dioxolane-4,5-dicarboxylic acid dimethyl ester (6f). Prepared as described for **6a**, starting from **7f** (500 mg, 1.85 mmol) and obtaining **6f** (285 mg, 45%) after chromatographic purification (eluent: EtOAc–petroleum ether, 1:3, R_f=0.25) as colourless oil.

Compound **6f**. $[\alpha]_D^{25}=+12.1$ (*c* 0.3, $CHCl_3$). ^{1}H NMR δ (ppm): 7.35 (d, *J*=8.8 Hz, 2H, Ph), 6.82 (d, *J*=8.8 Hz, 2H, Ph), 4.85 (d, *J*=5.5 Hz, 1H, C*H*CO_2Me), 4.73 (d, *J*=5.5 Hz,

1H, C*H*CO_2Me), 4.44–4.40 (m, 2H, CH_2NO_2), 3.82 (s, 3H, CO_2CH_3), 3.77 (s, 3H, OCH_3), 3.52 (s, 3H, CO_2CH_3), 2.17–2.02 (m, 4H, $CH_2CH_2CH_2NO_2$). ^{13}C NMR δ (ppm): 169.0 (s), 168.8 (s), 159.6 (s), 131.7 (s), 126.9 (d, 2C), 113.7 (s), 113.2 (d, 2C), 77.2 (d), 75.9 (d), 75.0 (t), 55.0 (q), 52.6 (q), 52.2 (q), 36.8 (t), 21.4 (t). MS *m/z* (%) 295 ($M^+-(CH_2)_3NO_2$, 100), 135 (79), 107 (6). IR ($CDCl_3$): 1751, 1553 and 1372 cm^{-1}. Anal. Calcd for $C_{17}H_{21}NO_9$: C, 53.26; H, 5.52; N, 3.65. Found: C, 53.38; H, 5.49; N, 3.58.

4.1.14. (1*R*,6*S*,8*R*)-6-Ethyl-2-oxo-7,9-dioxa-3-aza-bicyclo-[4.2.1]nonane-8-carboxylic acid methyl ester (9a). A solution of **7a** (637 mg, 2.19 mmol) in MeOH (20 mL) was added under stirring to a prehydrogenated suspension of wet Raney-Ni (924 mg, washed three times with 5 mL of MeOH before the addition of the solution of **7a**) in the same solvent (10 mL). The mixture was left under hydrogen atmosphere for 16 h at room temperature and then filtered twice on a Celite layer and finally evaporated to give pure **9a** (491 mg, 99%) as pale yellow solid.

Compound **9a**. Mp 66–67 °C. $[\alpha]_D^{25}=-75.6$ (*c* 0.8, $CHCl_3$). ^{1}H NMR δ (ppm): 6.26 (s br, 1H, N*H*), 4.90 (br s, 1H, C*H*$CHCO_2CH_3$), 4.76 (d, *J*=1.8 Hz, 1H, C*H*CO_2CH_3), 3.78 (s, 3H, CO_2CH_3), 3.33–3.25 (m, 2H, CH_2NHC=O), 2.08–2.02 (m, 2H, CH_2CH_2NHC=O), 1.88 (q, *J*=7.4 Hz, 2H, CH_2CH_3), 0.99 (t, *J*=7.2 Hz, 3H, CH_2CH_3). ^{13}C NMR δ (ppm): 174.9 (s), 169.8 (s), 115.2 (s), 81.6 (d), 77.1 (d), 52.6 (q), 38.6 (t), 37.5 (t), 32.0 (t), 7.4 (q). MS *m/z* (%) 229 (M^+, 17), 170 (40), 113 (79), 97 (80), 56 (100). IR ($CHCl_3$) 3405, 1760, 1671, 1357 cm^{-1}. Anal. Calcd for $C_{10}H_{15}NO_5$: C, 52.40; H, 6.60; N, 6.11. Found: C, 52.63; H, 6.46; N, 5.99.

4.1.15. (1*R*,6*R*,8*R*)-2-Oxo-6-phenyl-7,9-dioxa-3-aza-bicyclo[4.2.1]nonane-8-carboxylic acid methyl ester (9b). Prepared as described for **9a**, starting from **7b** (400 mg, 1.18 mmol) and obtaining pure **9b** (279 mg, 85%) as pale yellow solid.

Compound **9b**. Mp 95–96 °C. $[\alpha]_D^{25}=-32.8$ (*c* 0.5, $CHCl_3$). ^{1}H NMR δ (ppm): 7.63–7.58 (m, 2H, Ph), 7.43–7.29 (m, 3H, Ph), 6.30 (br s, 1H, N*H*), 5.05 (s, 1H, C*H*$CHCO_2CH_3$), 4.95 (d, *J*=2.2 Hz, 1H, C*H*CO_2CH_3), 3.70 (s, 3H, CO_2CH_3), 3.51–3.42 (m, 2H, CH_2NHC=O), 2.42–2.33 (m, 2H, CH_2CH_2NHC=O). ^{13}C NMR δ (ppm): 174.8 (s), 169.5 (s), 140.6 (s), 128.6 (d), 128.2 (d, 2C), 124.8 (d, 2C), 113.7 (s), 82.0 (d), 77.3 (d), 52.6 (q), 40.9 (t), 37.5 (t). MS *m/z* (%) 277 (M^+, 2), 218 (22), 147 (26), 104 (100), 77 (92). IR ($CHCl_3$) 3405, 1761, 1710, 1673 cm^{-1}. Anal. Calcd for $C_{14}H_{15}NO_5$: C, 60.64; H, 5.45; N, 5.05. Found: C: 60.21; H, 5.56; N, 4.61.

4.1.16. (1*R*,6*R*,8*R*)-6-(4-Chloro-phenyl)-2-oxo-7,9-dioxa-3-aza-bicyclo[4.2.1]nonane-8-carboxylic acid methyl ester (9c). Prepared as described for **9a**, starting from **7c** (150 mg, 0.40 mmol) and obtaining pure **9c** (95 mg, 76%) as yellow oil.

Compound **9c**. $[\alpha]_D^{25}=-23.6$ (*c* 0.3, $CHCl_3$). ^{1}H NMR δ (ppm): 7.54 (d, *J*=8.4 Hz, 2H, Ph), 7.33 (d, *J*=8.4 Hz, 2H, Ph), 6.75 (br s, 1H, N*H*), 5.01 (s, 1H, C*H*$CHCO_2CH_3$), 4.94 (br s, 1H, C*H*CO_2CH_3), 3.69 (s, 3H, CO_2CH_3), 3.52–3.34 (m, 2H, CH_2NHC=O), 2.40–2.22 (m, 2H, CH_2CH_2-NHC=O). ^{13}C NMR δ (ppm): 174.4 (s), 169.3 (s), 139.2 (s), 134.6 (s), 128.3 (d, 2C), 126.3 (d, 2C), 113.2 (s), 82.0 (d), 77.4 (d), 52.7 (q), 41.1 (t), 37.6 (t). MS *m/z* (%) 252 (M^+-CO_2Me, 19), 139 (100), 111 (46). IR ($CDCl_3$): 1763, 1674 cm^{-1}. Anal. Calcd for $C_{14}H_{14}ClNO_5\cdot H_2O$: C, 50.10; H, 4.89; N, 4.25. Found: C: 50.00; H, 4.69; N, 4.19.

4.1.17. (1*R*,7*S*,9*R*)-7-Methyl-2-oxo-8,10-dioxa-3-aza-bicyclo[5.2.1]decane-9-carboxylic acid methyl ester (9d). Prepared as described for **9a**, starting from **7d** (445 mg, 1.53 mmol) and obtaining crude **9d**. After chromatografic purification (eluent: EtOAc–petroleum ether, 3:1, R_f=0.36) pure **9d** (68 mg, 19%) as white solid.

Compound **9d**. Mp 149–150 °C. $[\alpha]_D^{25}=-69.8$ (*c* 0.2, $CHCl_3$). ^{1}H NMR δ (ppm): 6.53 (br s, 1H, N*H*), 5.00 (d, *J*=2.6 Hz, 1H, C*H*$CHCO_2CH_3$), 4.86 (d, *J*=2.6 Hz, 1H, C*H*CO_2CH_3), 4.12–3.95 (m, 1H, CH_aH_bNHC=O), 3.79 (s, 3H, CO_2CH_3), 3.20–3.04 (m, 1H, CH_aH_bNHC=O), 1.89–1.67 (m, 4H, $CH_2CH_2CH_2$NHC=O), 1.51 (s, 3H, CH_3). ^{13}C NMR δ (ppm): 174.2 (s), 170.5 (s), 115.1 (s), 79.3 (d), 78.9 (d), 52.8 (q), 41.1 (t), 33.6 (t), 25.1 (t), 24.8 (q). IR ($CDCl_3$): 1751, 1653 cm^{-1}. MS (30 eV) *m/z* (%): 230 (M^++1, 11), 214 (M^+-CH_3, 3), 187 (51), 84 (100). Anal. Calcd for $C_{10}H_{15}NO_5$: C, 52.40; H, 6.60; N, 6.11. Found: C: 52.23; H, 6.43; N, 5.95.

4.1.18. (1*R*,7*R*,9*R*)-2-Oxo-7-phenyl-8,10-dioxa-3-aza-bicyclo[5.2.1]decane-9-carboxylic acid methyl ester (9e). Prepared as described for **9a**, starting from **7e** (90 mg, 0.26 mmol) and obtaining crude **9e**. After chromatografic purification (eluent: EtOAc–petroleum ether, 1:3, 1% Et_3N, R_f=0.16) pure **9e** (17 mg, 24%) as yellow oil.

Compound **9e**. $[\alpha]_D^{25}=-32.8$ (*c*0.5, $CHCl_3$). ^{1}H NMR δ (ppm): 7.51–7.46 (m, 2H, Ph), 7.40–7.27 (m, 3H, Ph), 6.35 (br s, 1H, N*H*), 5.31 (d, *J*=1.8 Hz, 1H, C*H*$CHCO_2CH_3$), 4.93 (d, *J*=1.8 Hz, 1H, C*H*CO_2CH_3), 4.15–4.07 (m, 1H, CH_aH_bNHC=O), 3.37 (s, 3H, CO_2CH_3), 3.25–3.16 (m, 1H, CH_aH_bNHC=O), 2.24–1.82 (m, 4H, $CH_2CH_2CH_2$-NHC=O). ^{13}C NMR δ (ppm): 173.8 (s), 169.3 (s), 141.5 (s), 128.3 (d), 127.8 (d, 2C), 125.3 (d, 2C), 114.7 (s), 79.6 (d), 78.8 (d), 52.3 (q), 42.2 (t), 36.7 (t), 25.8 (t). MS *m/z* (%): 291 (M^+, 2), 105 (24), 104 (100). IR ($CDCl_3$): 3400, 1745, 1655 cm^{-1}. Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 60.62; H, 5.92; N, 4.76.

4.1.19. (1*R*,7*R*,9*R*)-7-(4-Methoxy-phenyl)-2-oxo-8,10-dioxa-3-aza-bicyclo[5.2.1]decane-9-carboxylic acid methyl ester (9f). Prepared as described for **9a**, starting from **7f** (150 mg, 0.39 mmol) and obtaining crude **9f**. After chromatografic purification (eluent: EtOAc, R_f=0.52) pure **9f** (29 mg, 23%) as yellowish solid.

Compound **9f**. Mp 124–125 °C. $[\alpha]_D^{25}=-25.7$ (*c*0.3, $CHCl_3$). ^{1}H NMR δ (ppm): 7.41 (d, *J*=8.8 Hz, 2H, Ph), 6.83 (d, *J*=8.8 Hz, 2H, Ph), 6.58 (br s, 1H, N*H*), 5.28 (d, *J*=1.5 Hz, 1H, C*H*$CHCO_2CH_3$), 4.91 (d, *J*=1.5 Hz, 1H, C*H*CO_2CH_3), 4.13–4.03 (m, 1H, CH_aH_bNHC=O), 3.78 (s, 3H, OCH_3), 3.43 (s, 3H, CO_2CH_3), 3.27–3.13 (m, 1H, CH_aH_bNHC=O), 2.22–1.86 (m, 4H, $CH_2CH_2CH_2$-NHC=O). ^{13}C NMR δ (ppm): 173.9 (s), 169.3 (s), 159.5 (s), 133.5 (s), 126.7 (d, 2C), 114.7 (s), 113.1 (d, 2C), 79.5

(d), 78.7 (d), 55.2 (q), 52.4 (q), 42.1 (t), 36.3 (t), 25.8 (t). MS *m/z* (%): 321 (M^+, 3), 262 (13), 177 (19), 135 (100). IR ($CDCl_3$): 1747, 1653 cm^{-1}. Anal. Calcd for $C_{16}H_{19}NO_6 \cdot H_2O$: C, 56.63; H, 6.24; N, 4.13. Found: C, 57.09; H, 6.08; N, 3.93.

4.1.20. (1*R*,6*S*,8*R*)-6-Ethyl-2-oxo-7,9-dioxa-3-aza-bicyclo-[4.2.1]nonane-3,8-dicarboxylic acid 3-*tert*-butyl ester 8-methyl ester (10a). To a solution of **9a** (350 mg, 1.55 mmol) in anhydrous CH_2Cl_2 (10 mL) Boc_2O (690 mg, 3.10 mmol), Et_3N (325 μL, 2.32 mmol) and catalytic DMAP (18 mg, 0.16 mmol) were added under nitrogen atmosphere. The resulting solution was refluxed for 6 h; a second portion of Boc_2O (690 mg, 3.10 mmol) was added after this period and the mixture refluxed for further 16 h. After cooling to rt, H_2O (10 mL) was added and the phases separated. The organic layer was washed with 5% $KHSO_4$ (2×10 mL), satd $NaHCO_3$ (2×10 mL), brine (2×10 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvent, crude **10a** was obtained. Chromatographic purification (eluent: petroleum ether–EtOAc, 6:1, R_f=0.33) afforded pure **10a** (388 mg, 76%) as yellow oil.

Compound **10a**. $[\alpha]_D^{25}=-47.8$ (*c*1.0, $CHCl_3$). ^1H NMR (1.6:1 mixture of rotamers) δ (ppm): 4.92 (d, *J*=2.2 Hz, 1H major rotamer, C*H*CO_2Me), 4.71 (d, *J*=2.2 Hz, 1H minor rotamer, C*H*CO_2Me), 4.69 (bs s, 1H minor rotamer, C*H*$CHCO_2$Me), 4.48 (br s, 1H major rotamer, C*H*$CHCO_2$-Me), 4.12 (dt, *J*=15.8, 4.0 Hz, 1H major rotamer, CH_aH_bN), 3.71 (s, 3H major rotamer, CO_2CH_3), 3.70 (s, 3H minor rotamer, CO_2CH_3), 3.70–3.64 (m, 1H minor rotamer, CH_aH_bN), 3.41–3.04 (m, 1H, CH_aH_bN), 2.05–1.82 (m, 2H, CH_2CH_2N), 1.77 (q, *J*=7.3 Hz, 2H, major rotamer, CH_2CH_3), 1.60 (q, *J*=7.3 Hz, 2H minor rotamer, CH_2CH_3), 1.39 (s, 9H major rotamer, *t*-Bu), 1.38 (s, 9H minor rotamer, *t*-Bu), 0.89 (t, *J*=7.3 Hz, 3H major rotamer, CH_2CH_3), 0.83 (t, *J*=7.3 Hz, 3H minor rotamer, CH_2CH_3). ^{13}C NMR δ (ppm): 174.0 and 169.4 (s), 169.8 and 168.1 (s), 116.9 and 116.3 (s), 83.4 and 83.1 (s), 82.5 and 77.6 (d), 77.4 and 76.9 (d), 52.7 and 52.6 (q), 39.2 and 37.2 (t), 35.6 and 35.4 (t), 31.3 and 30.5 (t), 28.4 and 27.9 (q, 3C), 7.9 and 7.4 (q). MS *m/z* (%): 228 (M^+−Boc, 7), 203 (95), 201 (32). IR ($CDCl_3$): 1753, 1711 cm^{-1}. Anal. Calcd for $C_{15}H_{23}NO_7$: C, 54.70; H, 7.04; N, 4.25. Found: C: 54.57; H, 7.24; N, 4.18.

4.1.21. (1*R*,6*R*,8*R*)-2-Oxo-6-phenyl-7,9-dioxa-3-aza-bicyclo[4.2.1]nonane-3,8-dicarboxylic acid 3-*tert*-butyl ester 8-methyl ester (10b). Prepared as described for **10a**, starting from **9b** (200 mg, 0.72 mmol) and obtaining, after chromatographic purification (eluent: petroleum ether–EtOAc, 6:1, R_f=0.38) pure **10b** (163 mg, 60%) as yellow oil.

Compound **10b**. $[\alpha]_D^{25}=-114.2$ (*c*0.5, $CHCl_3$). ^1H NMR δ (ppm): 7.63–7.58 (m, 2H, Ph), 7.40–7.30 (m, 3H, Ph), 5.17 (d, *J*=2.2 Hz, 1H, C*H*$CHCO_2CH_3$), 4.96 (d, *J*=2.2 Hz, 1H, C*H*CO_2CH_3), 4.36 (dt, *J*=15.8, 4.0 Hz, 1H, CH_aH_bN), 3.72 (s, 3H, CO_2CH_3), 3.53–3.40 (m, 1H, CH_aH_bN), 2.49–2.32 (m, 1H, C$H_aH_bCH_2$N), 2.26–2.12 (m, 1H, $CH_aH_bCH_2$N), 1.51 (s, 9H, Boc). ^{13}C NMR δ (ppm): 174.0 (s), 169.1 (s), 153.0 (s), 139.6 (s), 128.8 (d), 128.2 (d, 2C), 124.9 (d, 2C), 114.8 (s), 83.6 (s), 82.8 (d), 77.9 (d), 52.8 (q), 39.9 (t), 39.3 (t), 28.0 (q, 3C). MS *m/z* (%): 320 (M^+−*t*Bu, 1), 279 (M^+−Boc, 4), 105 (100). IR ($CDCl_3$): 1763, 1718 cm^{-1}. Anal. Calcd for $C_{19}H_{23}NO_7$: C, 60.47; H, 6.14; N, 3.71. Found: C: 60.28; H, 6.00; N, 3.53.

4.1.22. (1*R*,6*R*,8*R*)-6-(4-Chloro-phenyl)-2-oxo-7,9-dioxa-3-aza-bicyclo[4.2.1]nonane-3,8-dicarboxylic acid 3-*tert*-butyl ester 8-methyl ester (10c). Prepared as described for **10a**, starting from **9c** (90 mg, 0.29 mmol) and obtaining, after chromatographic purification (eluent: petroleum ether–EtOAc, 7:1, R_f=0.23) pure **10c** (88 mg, 74%) as yellow oil.

Compound **10c**. $[\alpha]_D^{25}=-102.5$ (*c*0.8, $CHCl_3$). ^1H NMR δ (ppm): 7.44 (d, *J*=8.6 Hz, 2H, Ph), 7.31 (d, *J*=8.6 Hz, 2H, Ph), 5.15 (d, *J*=2.2 Hz, 1H, C*H*$CHCO_2CH_3$), 4.95 (d, *J*=2.2 Hz, 1H, C*H*CO_2CH_3), 4.43–4.27 (m, 1H, CH_aH_bN), 3.73 (s, 3H, CO_2CH_3), 3.55–3.38 (m, 1H, CH_aH_bN), 2.32–2.18 (m, 2H, CH_2CH_2N), 1.51 (s, 9H, Boc). ^{13}C NMR δ (ppm): 173.8 (s), 169.1 (s), 153.0 (s), 138.9 (s), 134.7 (s), 128.4 (d, 2C), 126.6 (d, 2C), 114.4 (s), 83.3 (s), 82.9 (d), 78.0 (d), 52.9 (q), 39.9 (t), 39.2 (t), 28.0 (q, 3C). MS (30 eV) *m/z* (%): 358 (M^+−*t*Bu, 3), 314 (M^+−Boc, 2), 254 (7), 139 (94), 57 (100). IR ($CDCl_3$): 1744, 1718 cm^{-1}. Anal. Calcd for $C_9H_{22}ClNO_7$: C, 55.41; H, 5.38; N, 3.40. Found: C: 55.59; H, 5.22; N, 3.19.

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The effect of a sulphur bridge on the photochromic properties of indeno-fused naphthopyrans

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Abstract—The synthesis of four new 2,2-diphenyl-2*H*-naphtho[1,2-*b*]pyrans with a fused indeno group at the *f* face and a sulphur junction between the 2,2-phenyl groups is described. The photochromic properties in solution of these novel compounds were investigated under continuous irradiation. Compared to known indeno-fused naphthopyrans, these new compounds showed a significant bathochromic shift in the spectra of the open forms, faster ring closure kinetics and an expected decrease in the colourabilities.

1. Introduction

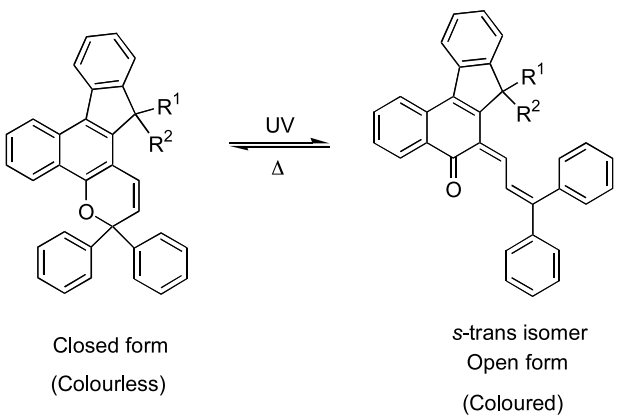
Naphthopyrans are one of the most studied classes of photochromic compounds due to their use in plastic lenses. When exposed to sunlight, in solution or in polymer matrices, these molecules exhibit colours from orange to blue/gray. [1] When the irradiation ceases the solution returns to its original colourless state, normally via a thermal electrocyclic ring closure. The change in the visible absorption spectrum of these compounds is due to the photoinduced reversible opening of the pyran ring leading to the formation of an 'open form' with an extensively conjugated π system (Scheme 1). The photochromic properties of naphthopyrans are strongly dependent on structural features. [1–3] The fusion of an indeno group to the 5,6 positions (*f* face) of 2,2-diphenyl-2*H*-naphtho[1,2-*b*]pyrans is a well known strategy to improve the photochromic properties because it effectively extends the π-system conjugation and introduces important nonbonding interactions in the open forms, without affecting the process that leads to the coloured forms. [1] The net result are readily obtained coloured forms with an observable bathochromic shift in the visible spectra and interesting bleaching kinetics due to the increased instability of the open forms. These indeno-fused naphthopyrans exhibit a wide range of colours, a high molar absortivity in the near-UV and interesting discolouration kinetics (Scheme 1). [4–8]

The set of isomers that constitute the open form of the 2,2-diphenyl-2*H*-naphtho[1,2-*b*]pyrans, obtained upon UV irradiation, are not completely planar, due to the steric hindrance between the two phenyl groups. In recent studies it was showed that in some naphthopyrans the linkage of the two phenyl sp^3-substituents through a sulphur bridge results in the increase of the maximum wavelength of absorption and in a very significant increase of the discolouration rate. [9] In order to study this effect on indeno-fused naphthopyrans we decided to prepare some new indeno-fused spiro[thioxanthene-naphthopyrans]. In this paper, we report the synthesis and photochromic behaviour of these novel compounds.

2. Results and discussion

2.1. Synthesis

Naphthopyrans are usually prepared in fair to good yield by reaction of phenols with propynols. This reaction is quite general and a large variety of substituted or fused naphthols



Scheme 1.

Keywords: Photochromism; Naphthopyrans; Spectrokinetics; Heterocycles; Spiro[thioxanthene-naphthopyrans].
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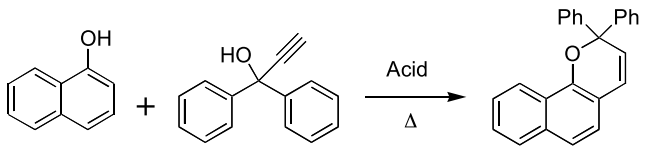
can be used. Several different aromatic propynols have also been used (Scheme 2). [10]

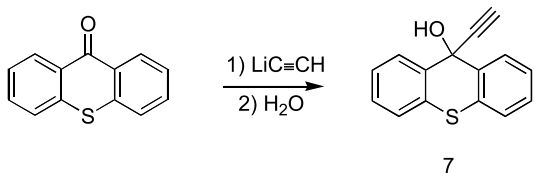


Scheme 2.

For the synthesis of indeno-fused spiro[thioxantene-naphthopyrans] we needed indeno-fused naphthols and the propynol derived from thioxanthone. Indeno-fused naphthol **6** was prepared in five steps from commercially available 1,4-dihydroxy-2-naphthoic acid **1**. This acid was converted into the 1,4-dimethoxy-2-naphthoic acid **2** by methylation followed by basic hydrolysis. In order to introduce a phenyl group in position 1 the acid **2** was converted into the 4,5-dihydrooxazole **3**. The activating effect of the 4,5-dihydrooxazole ring allows the nucleophilic substitution of the methoxy group by an alkyl/aryl group through reaction with Grignard reagents at room temperature. [11] The 4,5-dihydrooxazole **4** was then hydrolysed to the corresponding acid and treated for 5 min with concentrated sulphuric acid affording methoxybenzofluorenone **5**. Finally, heating a solution of methoxybenzofluorenone in HBr/HOAc gave the naphthol **6** in good yield (Scheme 3).

Diaryl propynols are usually prepared through reaction of diarylketones with lithium or sodium acetylide (Scheme 4). The reaction is incomplete and gives a diol as secondary product. Due to the presence of this by-product and a significant amount of the unreacted ketone, column chromatography purification is usually necessary. [12]

The reaction of thioxanthone with lithium acetylide gave the expected products but the purification of the propynol **7** proved to be very difficult since an extended decomposition is observed upon silica or alumina column chromatography. However, an almost pure sample of this alcohol was obtained through silica gel flash chromatography. Although limited to small amounts the use of this technique allowed the preparation of several grams of alcohol **7** in approximately 67% overall yield (Scheme 5).

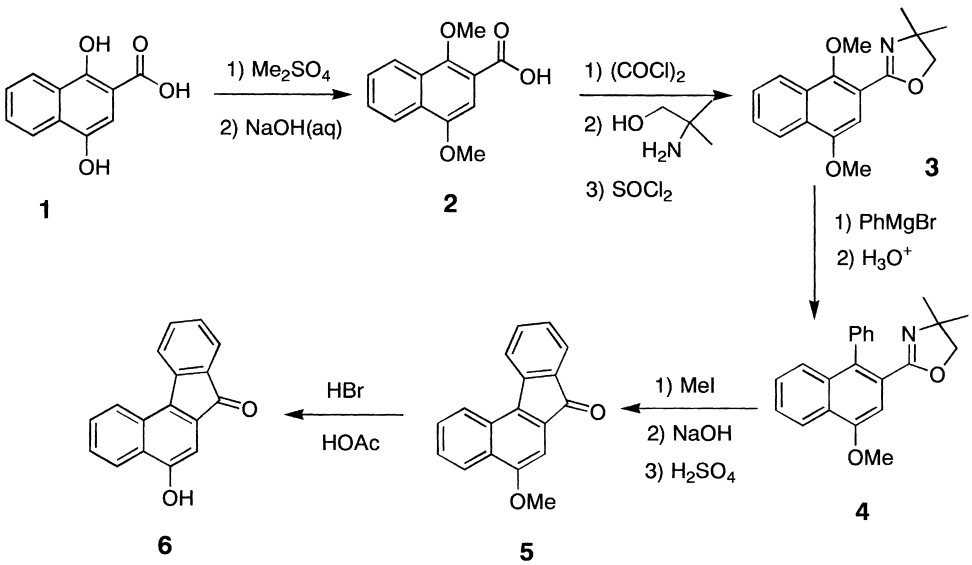


Scheme 5.

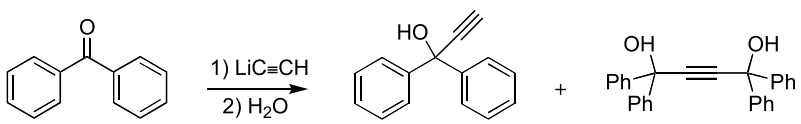
Heating a chloroform solution of naphthol **6** with propynol **7** in the presence of a catalytic amount of PPTS gave spiro[thioxanthene-naphthopyran] **8** in 62% yield. This compound is not photochromic (Scheme 6). [13] Treatment of **8** with the Grignard reagents derived from methyliodide, *tert*-butylcloride, bromobenzene and 2-bromothiophene gave, after hydrolysis, the photochromic spiro[thioxanthene-naphthopyran] **9a–d** in low to good yield (24–84%).

2.2. Photochromic properties

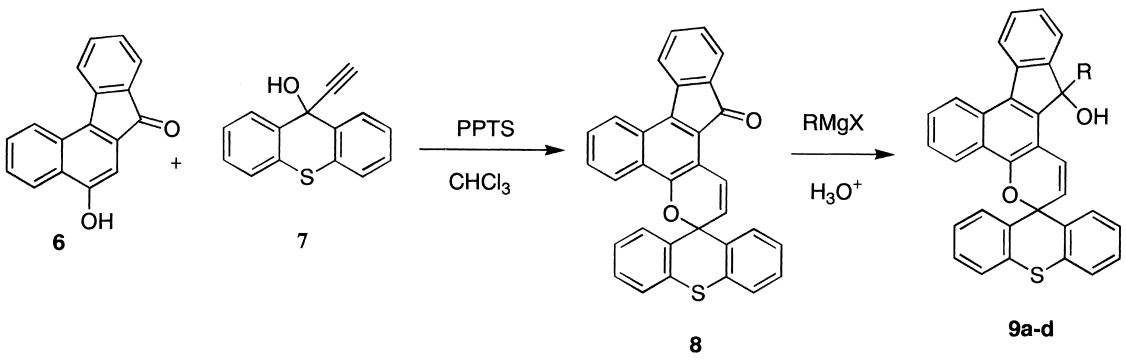
The photochromic behaviour of compounds **9a–d** was studied in toluene solutions under continuous near-UV irradiation. Three spectrokinetic parameters namely, the maximum wavelength of absorption of the open form



Scheme 3.

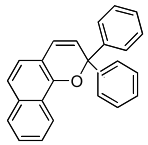
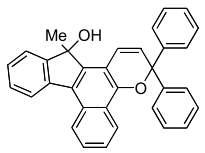
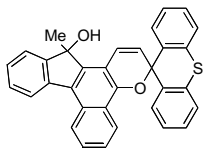
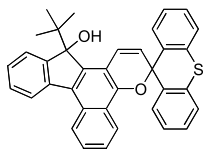
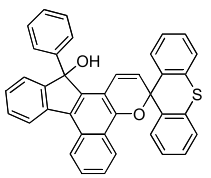
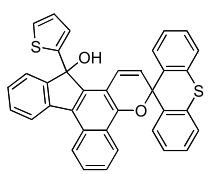


Scheme 4.



Scheme 6.

Table 1. Spectrokinetic properties under continuous irradiation: maxima wavelengths of the coloured form (λ_{max}), colourability (A_{eq} is the absorbance after photostationary equilibrium at λ_{max}), thermal bleaching rate (k_{Δ}) of compounds **9a**–**d**, and two reference compounds in toluene solutions: **10** (2,2-diphenyl-2*H*-naphtho[1,2-*b*]pyran), **11** (13-hydroxy-13-methyl-3,3-diphenyl-indeno[2,1-*f*]naphtho[1,2-*b*]pyran)

Compound		λ_{max} (nm)	A_{eq}	k_{Δ} (s^{-1})
10		469	0.72	0.0006 (98) 0.0003 (2)
11		530	1.2	0.004 (98) 0.0001 (2)
9a		552	0.66	0.047 (90) <0.0001 (10)
9b		557	0.27	0.047 (90) <0.0001 (10)
9c		558	0.49	0.10 (91) 0.0001 (9)
9d		556	0.44	0.11 (83) <0.0001 (17)

(λ_{max}), the thermal bleaching rate, (k_{Δ}) and the colourability or absorbance of the solution after reaching photostationary equilibrium (A_{eq}) were evaluated. The data are summarised in Table 1. For comparison purposes the same parameters were obtained, under identical experimental conditions, for two known naphthopyrans: the compound without any substituents 2,2-diphenyl-2*H*-naphtho[1,2-*b*]pyran **10** and the known indeno-fused naphthopyran without the sulphur bridge, 3,3-diphenyl-13-hydroxy-13-methyl-indeno[2,1-*f*]naphtho[1,2-*b*]pyran **11**.

All of the new naphthopyrans, **9a**–**d**, exhibited photochromic behaviour at room temperature in toluene solutions. Compared to the reference naphthopyran **10** the absorption wavelength in the visible range obtained after irradiation, λ_{max}, show, as expected, substantial bathochromic shifts for all the new indeno-fused derivatives. From the data presented in Table 1, it can be observed that the extension of the π-conjugation is due to not only the indeno moiety but results also from the presence of the sulphur bridge: similarly substituted indeno-fused naphthopyrans (**9a** and **11**) exhibit significantly different λ_{max} (+22 nm) confirming that the introduction of a sulphur bridge linking the 2,2-diphenyl groups is an efficient way to increase the participation of each phenyl nucleus in the π-conjugation of the open forms. [9]

On the other hand, all of the new compounds exhibit absorption localised at ca. 555 nm indicating that the nature of the substituents at the indeno sp^3-carbon atom have only a minor influence in the conjugation of the open forms.

With regard to the ring closure kinetics, the new described compounds exhibit two phases kinetics with similar amplitudes. It is apparent that the open forms of the compounds with the sulphur bridge are thermally less stable than the reference compounds (rate of ring closure 10–20 times faster than **11**). The same was already observed with spiro[thioxanthene-naphthopyrans] [9] and is probably due to some strain in the planar open forms promoted by the sulphur bridge. The first rate constant, 0.047–0.11 s^{-1}, is higher than that observed for the reference compounds with an amplitude a little lower, around 90%. The second rate constant is very slow, as for the reference compounds, and is responsible for the persistence of a residual colour even after several minutes after the removal of the source of the

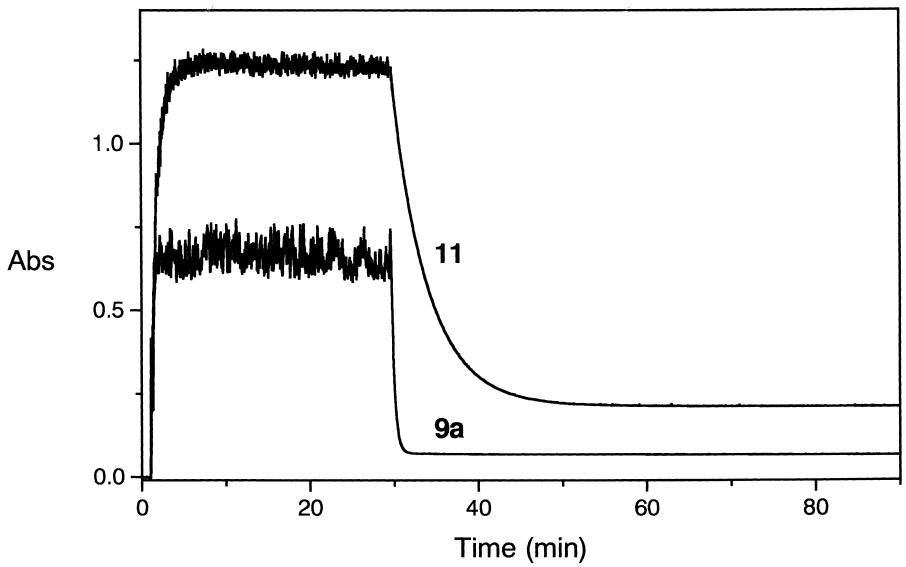


Figure 1. Variation of the absorbance at λ_{max} of **11** and **9a** (toluene solution, 1×10^{-4} M) under continuous UV irradiation (150 W Xe lamp, 30 min) and then when the irradiation is stopped (20 °C).

activating light. However, as can be shown in Figure 1, the spiro[thioxantene-naphthopyran] **9a** is much faster (almost 6 times) than **11**: naphthopyran **9a** reaches one half the highest absorbance attained in 39 s; **11** takes 246 s to reach one half of its maximum absorbance. The residual colour of **9a** is also significantly lower (0.07 after 30 min in the dark) than for **11** (0.21 in the same time). The observed kinetics make the novel compounds more acceptable compounds for application in variable optical transmission materials.

The presence of an aromatic group at the indeno sp^3-carbon atom (compounds **9c** and **9d**) contributes to the instability of the coloured forms leading to two-fold increase in the first kinetic rate constant. This does not seem to be a steric effect as compounds **9a** and **9b** differ markedly in the size of the substituent group and exhibit similar rates of ring closure.

The colourabilities of all the new described compounds are variable and lower than the observed for the reference compounds. This can be related to the faster thermal fading rates. Under continuous irradiation at low concentration, the colourability is proportional to both the quantum yield of photocolouration and the molar absortivity of the coloured form, but inversely proportional to the fading-rate constant. Faster bleaching kinetics are normally accompanied by lower colourabilities due to the lower concentration of coloured products at the photostationary state (Fig. 1).

3. Conclusion

Four new photochromic indeno-fused naphthopyrans were synthesised in good yield. Spiro[thioxanthene-naphthopyrans] **9a**–**d** showed a general significant bathochromic shift in the spectra of the open forms, higher ring closure rates and an expected decrease in the colourabilities when compared to a similar known indeno-fused naphthopyran (**11**). Although all compounds showed a residual colour even after several minutes in the dark, the absorbance is considerably lower than that observed for the reference compound without the sulphur bridge (**11**). The linkage of the two C-sp^3 phenyl groups in diphenyl indeno-fused naphthopyrans through a sulphur bridge increases the participation of each phenyl nucleus in the π-conjugation of the open forms and constitutes an effective way to extend the chromophore and to accelerate the ring closure kinetics. The nature of the substituents at the C-sp^3 of the indeno group seems to have little effect on the π-conjugation of the open forms. Bulky substituents at this atom do not have a marked effect on the thermal stability of the open forms but aromatic substituents promote some instability. These indeno-fused spiro[thioxanthene-naphthopyrans] would appear to be promising compounds for application in ophthalmic photochromic lenses.

4. Experimental

4.1. Spectrokinetic studies under continuous irradiation

For measurements of λ_{max}, A_{eq} and k_{Δ} under continuous irradiation, 1×10^{-4} M toluene solutions were used. Irradiation experiments were made using a CARY 50 Varian spectrometer coupled to a 150 W Ozone free Xenon lamp (6255 Oriel Instruments). The light from the UV lamp was filtered using a water filter (61945 Oriel Instruments) and then carried to the spectrophotometer holder at the right angle to the monitoring beam using a fiber-optic system (77654 Oriel Instruments). A light flux of 40 W m^{-2}, measured with a Goldilux Photometer with a UV-A probe was used. A thermostated (20 °C) 10 mm quartz cell, containing the sample solution (3.5 ml), equipped with magnetic stirring was used. In a preliminary experiment, the visible absorption spectrum of the closed form and the λ_{max} of the open form were determined. In a second experiment the absorbance at photostationary equilibrium, A_{eq}, was measured at λ_{max} and then the decrease in the absorbance with the time was monitored. The rate constants were calculated using a multi exponential model.

4.2. General remarks

^{1}H spectra were recorded in $CDCl_3$ on a Varian Unity Plus at 300 MHz. ^{13}C spectra were recorded in $CDCl_3$ on a Varian Unity Plus at 75.4 MHz. IR spectra were recorded on a Perkin–Elmer FTIR 1600 spectrometer, wave numbers in cm^{-1}. Mass spectra were measured on an AutoSpecE spectrometer. Melting points are uncorrected. Column chromatography was performed on silica gel 60 (70–230 mesh). All new compounds were determined to be >95% pure by ^{1}H NMR spectroscopy. Compounds **10** and **11** were prepared from 1-naphthol and 5-hydroxy-7*H*-benzo[*c*] fluoren-7-one, respectively, using standard procedures.[1,4] The melting points of photochromic naphthopyrans **9a–d** were not measured because thermochromism was observed at high temperatures.

4.2.1. 1,4-Dimethoxynaphthoic acid 2. A mixture of 1,4-dihydroxynaphthoic acid (10.0 g, 0.0490 mol), K_2CO_3 (61 g, 0.44 mol), dimethyl sulphate (14 ml, 0.15 mol) and acetone (100 ml) was heated for 2 days at reflux under argon atmosphere. After return to room temperature the mixture was filtered and the filtrate evaporated to give the crude 1,4-dimethoxynaphthoic methyl ester. 100 ml of aqueous NaOH (20%) was added to the crude ester and the solution heated under reflux for 3 h. After return to room temperature the aqueous solution was extracted with CH_2Cl_2 and the organic phase discarded. The aqueous phase was acidified with HCl (10%) and extracted with Et_2O (3×100 ml). The combined organic layers were dried (Na_2SO_4) and concentrated to give pure 1,4-dimethoxynaphthoic acid **2** (10.80 g, 0.0466 mmol) as a light brown solid. Yield: 95%. Mp 68.3–69.2 (lit. [14] 57–59). IR: 3200–2400 broad band, 1675, 1367, 1110; ^{1}H NMR: 11.5 (s, 1H, COOH), 8.32 (m, 1H), 8.11 (m, 1H), 7.66 (m, 2H), 7.39 (s, 1H), 4.13 (s, 2H, OCH_3), 4.06 (s, 2H, OCH_3). Exact mass for $C_{13}H_{12}O_4$: 232.0736. Found 232.0735.

4.2.2. 2-(1′,4′-Dimethoxynaphth-2-yl)-4,4-dimethyl-4,5-dihydrooxazole 3. A mixture of 1,4-dimethoxynaphthoic acid (1.00 g, 4.31 mmol), CH_2Cl_2 (60 ml) and oxalyl chloride (0.60 ml, 5.6 mmol) was stirred at room temperature for 24 h. The solvent and the oxalyl chloride excess were removed by rotary evaporation. 1,2-Dichloroethane (15 ml) was added followed by additional rotary evaporation in order to remove any residual oxalyl chloride. The crude acyl chloride was then dissolved in 1,2-dichloroethane (30 ml) and treated successively with triethylamine (0.80 ml, 5.76 mmol) and 2-amino-2-methyl-1-propanol (574 mg, 6.44 mmol) at 0 °C and stirred overnight at room temperature. Aq. sat. NH_4Cl (15 ml) and water (15 ml) was added and then the entire mixture was transferred to a separatory funnel and extracted with Et_2O (3×100 ml). The combined organic layers were dried (Na_2SO_4) and concentrated to give the crude hydroxy amide which was redissolved in CH_2Cl_2 (120 ml) and benzene (20 ml) and placed at 0 °C. Thionyl chloride (2.0 ml, 27.5 mmol) was added and the mixture stirred 4 h at room temperature. After solvent evaporation, ether (260 ml), aq. sat. $NaHCO_3$ (24 ml), water (24 ml) and NaOH (2 N, 24 ml) were added. The mixture was stirred 30 min and then the organic layer removed and the aqueous layer re-extracted with ether (2×100 ml). The combined organic layers were dried, concentrated and the product purified by column chromatography (0–20% ethyl acetate/light petroleum) to give pure 4,5-dihydrooxazole **3** (1.027 g, 3.60 mmol) as a yellow oil. [15] Yield: 84%. IR: 2961, 1650, 1370, 1261, 1106; ^{1}H NMR: 8.21 (m, 2H), 7.56 (m, 2H), 7.14 (s, 1H), 4.19 (s, 2H, CH_2O), 4.03 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 1.45 (s, 6H, 2×CH_3). MS: *m*/*z* (%): 285 (45), 232 (48), 215 (100), 149 (75), 58 (90). Exact mass for $C_{17}H_{19}O_3N$: 285.1365. Found 285.1354.

4.2.3. 2-(1′-Phenyl-4′-methoxynaphth-2-yl)-4,4-dimethyl-4,5-dihydrooxazole 4. A solution of phenylmagnesium bromide (prepared from bromobenzene (2.84 g, 18.1 mmol) and magnesium (0.435 g, 18.1 mmol) in 20 ml of dry ethyl ether) was slowly added to a solution of 4,5-dihydrooxazole **3** (1.00 g, 3.02 mmol) in ethyl ether (15 ml). After stirring at room temperature for 24 h, the solution was quenched in aq. sat. NH_4Cl, extracted with Et_2O (3×40 ml), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by CC (0–30% ethyl acetate/light petroleum) to give pure 4,5-dihydrooxazole **4** (0.740 g, 2.24 mmol) as a yellow oil. Yield: 75%. IR: 2969, 2877, 1658, 1592, 1457, 1145; ^{1}H NMR: 8.33 (d, *J*=8.4 Hz, 1H), 7.62 (d, *J*=8.0 Hz, 1H), 7.52 (dt, *J*=8.4 Hz, 1.5, 1H), 7.48–7.30 (m, 6H), 7.11 (s, 1H), 4.10 (s, 3H, OCH_3), 3.72 (s, OCH_2, 2H), 1.23 (s, 6H, 2×CH_3). MS: *m*/*z* (%): 331 (55), 330 (100), 316 (25), 245 (24), 189 (24), 77 (14). Exact mass for $C_{22}H_{21}O_2N$: 331.1572. Found 331.1568.

4.2.4. 5-Methoxy-7*H*-benzo[*c*]fluoren-7-one 5. A solution of 4,5-dihydrooxazole **4** (0.690 g, 2.08 mmol) in MeI (10 ml) was stirred at room temperature overnight and the excess of MeI removed under reduced pressure. To the crude methyl iodide salt, were added methanol (12 ml) and NaOH 20% (12 ml) and the mixture heated to reflux for 12 h. The solution was extracted with Et_2O and the organic layer discarded. The aqueous layer was acidified with HCl (aq.), extracted with Et_2O, dried (Na_2SO_4) and concentrated to give the 4-methoxy-1-phenylnaphthoic acid. Without further purification, H_2SO_4 (5 ml) was added. After stirring for 5 min at room temperature the resulting dark coloured solution was poured into ice (50 g) and then extracted with Et_2O (3×50 ml). The organic layer was dried (Na_2SO_4) and the solvent was evaporated under reduced pressure to give pure ketone **5** (0.340 g, 1.31 mmol) as a red solid. Yield: 63%. Mp 142.0–143.3 (lit. [16] 155–156). IR: 2930, 1718, 1270, 1122; ^{1}H NMR: 8.43 (d, *J*=7.8 Hz, 1H), 8.34 (d, *J*=8.1 Hz, 1H), 7.91 (d, *J*=7.8 Hz, 1H), 7.70–7.55 (m, 3H), 7.48 (dt, *J*=1.2 Hz, 7.5, 1H), 7.22 (dt, *J*=1.0 Hz, 7.5, 1H), 7.13 (s, 1H), 4.08 (s, 3H, OCH_3). MS: *m*/*z* (%): 260 (55), 245 (37), 217 (22), 189 (20), 167 (45), 149 (100). Exact mass for $C_{18}H_{12}O_2$: 260.0837. Found 260.0827.

4.2.5. 5-Hydroxy-7*H*-benzo[*c*]fluoren-7-one 6. A mixture of ketone **5** (0.340 g, 1.31 mmol), acetic acid (2.5 ml) and HBr 47% (5 ml) was heated under reflux for 5 h. After cooling the reaction mixture was poured into 100 ml of water and extracted with ethyl ether (3×50 ml). The combined organic layers were extracted 3 times with NaOH (5%, 20 ml) and the organic phase discarded. The aqueous phase was acidified with HCl 10%, and extracted with ether (3×50 ml). The combined organic layers were dried (Na_2SO_4) and the solvent evaporated under reduced

pressure giving the pure hydroxybenzofluorenone **6** (0.212 g, 0.86 mmol) as a red solid. Yield: 66%. Mp 252.2–253.3 (lit.[16] above 235). IR: 3397, 1714, 1579, 1351; ^{1}H NMR (acetone-d_6): 9.78 (s, 1H, OH), 8.60 (d, *J*=8.5 Hz, 1H), 8.36 (d, *J*=8.4 Hz, 1H), 8.11 (d, *J*=7.8 Hz, 1H), 7.72 (t, *J*=7.5 Hz, 1H), 7.64 (t, *J*=7.5 Hz, 1H), 7.57 (m, 2H), 7.28 (t, *J*=7.5 Hz, 1H), 7.16 (s, 1H). MS: *m*/*z* (%): 246 (100), 217 (6), 189 (40), 149 (7), 95 (14). Exact mass for $C_{17}H_{10}O_2$: 246.0681. Found 246.0680.

4.2.6. Spiro[13-oxoindeno[2,1-*f*]naphtho[1,2-*b*]pyran-3,9′-thioxanthene] 8. A suspension of thioxanthone (2.00 g, 9.43 mmol), and lithium acetylide ethylene diamine complex (3.00 g, 29.4 mmol) in dry THF (250 ml) was stirred under an argon atmosphere for 24 h. The suspension was treated with water (200 ml) and the aqueous phase extracted with ethyl ether (3×100 ml). The organic phase was dried over anhydrous Na_2SO_4 and the solvent evaporated leaving the crude 9-hydroxy-9-ethynyl-9*H*-thioxanthene. The crude product was further divided into four fractions each one was submitted to flash column chromatography (10% ethyl acetate/hexane) (not more than 30 min) affording almost pure 9-hydroxy-9-ethynyl-9*H*-thioxanthene **7** (1.5 g, 67% yield); [17] ^{1}H NMR: 8.15 (dd, *J*=7.8 Hz, 2.1, 2H), 7.52 (dd, *J*=7.2 Hz, 2.1, 2H), 7.37 (ddd, *J*=7.5 Hz, 7.5, 1.8, 2H), 7.33 (ddd, *J*=7.5 Hz, 7.5, 1.8, 2H), 2.94 (s, 2H).

A solution of 9-hydroxy-9-ethynyl-9*H*-thioxanthene **7** (0.800 mg, 3.36 mmol), 5-hydroxy-7*H*-benzo[*c*]fluoren-7-one **6** (0.174 g, 0.707 mmol) *p*-toluenosulphonic acid (50 mg) and $CHCl_3$ (60 ml) was refluxed for 4 h under an argon atmosphere. Solvent evaporation gave a brown oil which was purified by silica gel column chromatography (3% ethyl acetate/hexane). Recrystallisation from $CHCl_3$/pentane gave a crystalline red compound (0.240 g, 0.515 mmol). Yield: 73%. Mp 234–235 °C. IR: 3052, 2921, 1698, 1641, 1270, 1068; ^{1}H NMR: 8.46 (dd, *J*=7.8 Hz, 1.2, 1H), 8.38 (dd, *J*=7.8 Hz, 1.2, 1H), 7.95 (d, *J*=7.5 Hz, 1H), 7.81 (d, *J*=10.2 Hz, 1H), 7.76–7.68 (m, 2H), 7.68–7.46 (m, 6H), 7.36–7.20 (m, 5H), 6.37 (d, *J*=10.2 Hz, 1H). ^{13}C NMR 195.70; 148.95; 144.83; 137.52; 135.48; 134.56; 134.45; 129.90; 129.61; 128.16; 128.06; 127.80; 127.64; 127.09; 126.92 (two carbons overlapped); 126.50; 126.10; 124.80; 124.24; 123.76; 123.53; 122.36; 117.63; 111.56; 80.53. MS: *m*/*z* (%): 466 (100), 449 (20), 330 (26), 233 (45), 221 (90), 210 (35).

4.3. Procedure for the reaction of naphthopyran 8 with Grignard reagents

A solution of the Grignard reagent prepared in ethyl ether (2.0 ml, 2.0 mmol) was added to a solution of the naphthopyran **8** (0.100 mg, 0.215 mmol) dissolved in THF (10 ml) at 0 °C. After stirring at room temperature for 4 h, the solution was quenched in aq. sat. NH_4Cl, extracted with Et_2O (3×40 ml) and the combined organic layers dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by CC (3% ethyl acetate/light petroleum) to give the pure naphthopyrans **9a**–**d**.

4.3.1. 13-Hydroxy-13-methyl-spiro[indeno[2,1-*f*]naphtho[1,2-*b*]pyran-3,9′-thioxanthene] 9a. Light yellow solid. Yield: 44%. IR: 3386, 3058, 2950, 1457, 1268, 1112. UV/Vis (closed form): 372 (ε 7800), 392 (ε 4700); ^{1}H NMR: 8.64 (dd, *J*=8.4 Hz, 1H), 8.48 (dd, *J*=8.4 Hz, 1.0, 1H), 8.15 (d, *J*=7.8 Hz, 1H), 7.80–7.72 (m, 2H), 7.67 (dt, *J*=8.4 Hz, 1.5, 1H), 7.60 (dd, *J*=7.5 Hz, 1.0, 1H), 7.57–7.50 (m, 2H), 7.44 (dt, *J*=7.8 Hz, 1.2, 1H), 7.40–7.20 (m, 7H), 6.30 (d, *J*=10.2 Hz, 1H), 1.80 (s, CH_3, 3H). ^{13}C NMR: 151.14, 148.59, 143.96, 139.47, 138.44, 138.32, 130.86, 130.13, 129.69, 129.46, 128.97, 127.64, 127.62, 127.54, 126.99, 126.92, 126.87, 126.44, 126.31, 126.26, 126.18, 125.72, 124.58, 124.08, 123.20, 122.44, 122.12, 122.02, 118.35, 110.88, 80.78, 80.21, 26.59. MS: *m*/*z* (%): 482 (50), 464 (33), 449 (100), 221 (35), 197 (46). Exact mass for $C_{33}H_{22}O_2S$: 482.1341. Found 482.1349.

4.3.2. 13-*tert*-Butyl-13-hydroxy-spiro[indeno[2,1-*f*]naphtho[1,2-*b*]pyran-3,9′-thioxanthene] 9b. Light yellow solid. Yield: 28%. IR: 3410, 3050, 2982, 1620. UV/Vis (closed form): 366 (ε 3500); ^{1}H NMR: 8.64 (d, *J*=8.1 Hz, 1H), 8.48 (d, *J*=8.2 Hz, 1H), 8.11 (d, *J*=7.9 Hz, 1H), 7.80–7.78 (m, 1H), 7.73–7.71 (m, 4H), 7.66–7.63 (t, *J*=7.5 Hz, 1H), 7.55–7.50 (m, 3H), 7.40–7.38 (t, *J*=7.5 Hz, 1H), 7.30–7.20 (m, 4H), 6.20 (d, *J*=10.3 Hz, 1H), 0.92 (s, CH_3, 9H). MS: *m*/*z* (%): 524 (20), 467 (42), 450 (10), 271 (17), 221 (40), 210 (45), 197 (57), 149 (100). Exact mass for $C_{36}H_{28}O_2S$: 524.1810. Found 524.1827.

4.3.3. 13-Hydroxy-13-phenyl-spiro[indeno[2,1-*f*]naphtho[1,2-*b*]pyran-3,9′-thioxanthene] 9c. Light blue solid. Yield: 81%. IR: 3457, 3058, 2923, 1457, 1268, 1162. UV/Vis (closed form): 372 (ε 12300), 393 (ε 7400); ^{1}H NMR: 8.67 (d, *J*=8.7 Hz, 1H), 8.43 (d, *J*=8.4 Hz, 1H), 8.15 (d, *J*=7.8 Hz, 1H), 7.74–7.15 (m, 18H), 6.75 (d, *J*=10.2 Hz, 1H), 6.07 (d, *J*=10.2 Hz, 1H). MS: *m*/*z* (%): 544 (1), 526 (1), 444 (4), 347 (5), 287 (28), 273 (15), 213 (100), 184 (31), 77 (31). Exact mass for $C_{38}H_{24}O_2S$: 544.1497. Found 544.1498.

4.3.4. 13-Hydroxy-13-thiophen-2-yl-spiro[indeno[2,1-*f*]naphtho[1,2-*b*]pyran-3,9′-thioxanthene] 9d. Light brown solid. Yield: 84%. IR: 3519, 3062, 2915, 1562, 1455, 1365, 1268, 1110. UV/Vis (closed form): 368 (ε 11000); ^{1}H NMR: 8.64 (d, *J*=8.4 Hz, 1H), 8.45 (d, *J*=8.1 Hz, 1H), 8.13 (d, *J*=7.5 Hz, 1H), 7.76–7.70 (m, 2H), 7.67 (dt, *J*=7.5 Hz, 1.2, 1H), 7.57 (dt, *J*=7.5 Hz, 1.2, 1H) 7.54–7.46 (m, 2H), 7.40 (dt, *J*=7.5 Hz, 1.2, 1H), 7.30–7.20 (m, 6H), 7.19 (dd, *J*=4.5 Hz, 1.0, 1H), 6.93 (d, *J*=10.2 Hz, 1H), 6.83 (dd, *J*=4.5 Hz, 4.8, 1H), 6.68 (dd, *J*=4.5 Hz, 1.0, 1H), 6.15 (d, *J*=10.2 Hz, 1H). ^{13}C NMR: 150.50; 148.83; 147.00; 142.84; 139.32; 137.77; 137.22; 130.10; 129.87; 129.25; 127.70; 127.65; 127.50; 126.88; 126.84; 126.77; 126.69; 126.61; 126.58; 126.02; 125.27; 124.48, 124.18; 123.74; 123.35; 122.30; 122.01; 119.30; 111.58; 82.59; 80.09. MS: *m*/*z* (%): 550 (98), 532 (82), 466 (42), 449 (43), 221 (55), 197 (100). Exact mass for $C_{36}H_{22}O_2S_2$: 550.1061. Found 550.1050.

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Synthesis of oligosaccharides as potential novel food components and upscaled enzymatic reaction employing the β-galactosidase from bovine testes

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Abstract—The β-galactosidase from bovine testes (EC 3.2.1.23) promotes the transfer of a galactose unit to glucose or galactose-containing residues in manifold derivatives, establishing β1→3 linkages.The synthesis of several potentially biologically important oligosaccharides β-D-Gal*p*-(1→3)-α-D-Glc*p*-(1→2)-β-D-Fru*f* **2**, β-D-Gal*p*-(1→3)-β-D-Gal*p*-(1→4)-α,β-D-Glc*p* **4**, β-D-Gal*p*-(1→3)-α-D-Glc*p*-(1→4)-D-Glc*p*-ol/Man*p*-ol **6**, β-D-Gal*p*-(1→3)-α-D-Glc*p*-(1→6)-β-D-Fru*f* **8**, β-D-Gal*p*-(1→3)-α-D-Glc*p*-(1→6)-[α-D-Glc*p*-(1↔2)]-β-D-Fru*f* **10**, α-D-Gal*p*-(1→6)-[β-D-Gal*p*-(1→3)]-α-D-Glc*p*-(1↔2)-β-D-Fru*f* **12**, β-D-Gal*p*-(1→3)-α-D-Glc*p*-(1↔2)-β-D-Fru*f*-(1↔2)-β-D-Fru*f* **14** has been reached in yields between 7 and 44% by implementation of this specific enzyme. In addition, we found that it is feasible to gain high yields without an enzyme-specific buffer and even making upscaled preparation on a gram scale.

1. Introduction

Oligosaccharides participate in a wide range of biological processes. Commencing with incidents such as cell recognition and communication, leading over to growth regulation and antibody interactions,[1] oligosaccharides play an important role in proper nutrition. Thus, in recent years, health-food additives became increasingly relevant.[2]

The right balance of the intestinal bacterial flora is related to human health. In particular, the growth of Bifidobacterium to dominate the pathogenic germs and thus invigorate human health is facilitated by special oligosaccharides.[3–6] Furthermore, it is known that diseases and ageing cause decay or a significant decrease of the intestinal Bifidobacteria flora. Based on these facts, in recent years a lively interest in food additives that enhance human health commenced. In this case, some articles are denoted that deal with the presence of specific oligosaccharides in human or animal nourishment that improve health by encouraging the growth of Bifidobacterium and so positively affecting on the intestinal cells and the immune system.[7–9]

In light of these facts, certain oligosaccharides such as galactosyllactose, galacto-, isomalto-, and xylooligosaccharides show these favoured characteristics.[6] Especially, the important role of undigestible β-(1-3) linked galactosyl-structures should be emphasised.

Determining factors in industrial production of new products in this case are the availability of large and cheap sources of the basic material followed by access to good and effective methods of converting the basic material to the favoured product. The synthesis of oligosaccharides by classical chemical methods has been developed in recent years. However, it is not facile to adopt these classical multistep approaches including protection and deprotection steps for larger scale production. As an alternative, synthetic strategies utilising enzymes as catalyst have been developed.[10–13] At first glance, glycosyltranferases seem to be promising for this purpose, but their cofactors as well as the nucleotide sugar donors are not accessable on an industrial scale and are very expensive.

Another option is using glycoside hydrolases (glycosidases) for synthesis of the desired oligomers, as these hydrolases show marked transglycosylation qualities.[14–17] The advantages of hydrolases are their stereospecificity, which contrasts, however with their low regioselectivity. Increasingly transglycosylations are described with rather improved regioselectivity which in turn allow preparative

Keywords: Novel food components; Regioselective galactosylation; Enzyme; Bovine testes; Upscaled enzymatic reaction devoid of buffer.
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approaches. Under these conditions donor substrates with improved leaving groups exhibit an altered kinetic of the binding of the enzyme and thus hydrolases show stereospecific and often regiospecific properties in transfering a sugar unit to a specific acceptor. Further more glycosidases are available in larger quantities and are able to be used with simple donor substrates.

2. Results and discussion

2.1. Enzymatic galactosylation with β-galactosidase from bovine testes of an acceptor series utilising lactose as donor substrate

The β-galactosidase from bovine testes is commercially available but too expensive for upscaled synthesis. Thus, Hedbys et al.[18] developed a method based on the work of Distler and Jourdian[19] to gain and purify the β-galactosidase from fresh bovine testes, that satisfies the preparative approach. β-Galactosidase from bovine testes cleaves in vivo β-(1→3)-, β-(1→4)- and β-(1→6)-bound galactose from *N*acetyllactosamine derivatives and isomers.[18]

Under transglycosidation conditions, the enzyme shows a preference for establishing β-(1→3) linkages. The selectivity of the enzyme was examined and previously described by Gambert et al. with a variety of *N*-acetylglucosamine acceptors.[20]

Here we report the implementation of the β-galactosidase from bovine testes with sucrose (**1**), lactose (**3**), isomalt (**5**), isomaltulose (**7**), isomelezitose (**9**), raffinose (**11**) and 1-kestose (**13**) in enzymatic synthesis to give the resulting tri- and tetrasaccharides: β-D-Gal*p*-(1→3)-α-D-Glc*p*-(1↔2)-β-D-Fru*f* **2**, β-D-Gal*p*-(1→3)-β-D-Gal*p*-(1→4)-α,β-D-Glc*p* **4**, β-D-Gal*p*-(1→3)-α-D-Glc*p*-(1→6)-D-Glc-ol/Man-ol **6**, β-D-Gal*p*-(1→3)-α-D-Glc*p*-(1→6)-α/β-D-Fru*f* **8**, β-D-Gal*p*-(1→3)-α-D-Glc*p*-(1→6)-[α-D-Glc*p*-(1↔2)]-β-D-Fru*f* **10**, α-D-Gal*p*-(1→6)-[β-D-Gal*p*-(1→3)]-α-D-Glc*p*-(1↔2)-β-D-Fru*f* **12**, β-D-Gal*p*-(1→3)-α-D-Glc*p*-(1↔2)-β-D-Fru*f*-(1↔2)-β-D-Fru*f* **14**.

For the purpose of synthesizing new carbohydrates with characteristics that may be suitable for food additives, a series of di- and trisaccharides have been chosen to act as acceptor substrate. The chosen acceptors sucrose (**1**), lactose (**3**), isomalt (**5**), isomaltulose (**7**), isomelezitose (**9**), raffinose (**11**) and 1-kestose (**13**) are already known substances of content in food. Furthermore it is of prime importance that no toxic compounds are involved in the synthetic pathways. From this follows that the generally used *p*-nitrophenyl β-galactopyranoside does not satisfy the demands of food additives because the poisonous *p*-nitrophenol is released during the reaction. Lactose is predestined to be applied as donor substrate, since it is a natural substrate of β-galactosidases and is available in large scale.

The results of the transglycosylations are summarised in Table 1. The itemised acceptors could all be regioselectively galactosylated at the C-3 position of the terminal non-reducing saccharide unit. This does not only apply to the disaccharides (Scheme 1) but also to the more complex trisaccharide acceptors (Scheme 2). It is remarkable that only the C-3 glucosyl unit of raffinose (**11**), isomelezitose (**9**) and 1-kestose (**13**) are selectively galactosylated. These facts indicate the high substrate specificity of the bovine testes hydrolase.

Table 1. Summarised yields of transglycosylation with β-galactosidase from bovine testes on various acceptors

Acceptor	Product(s)	Yield (%)
Succrose (**1**)	**2**	9
Lactose (**3**)	**4**	44
Isomalt (**5**)	**6**	17
Isomaltulose (**7**)	**8**	17
Isomelezitose (**9**)	**10**	23
Raffinose (**11**)	**12**	10
1-Kestose (**13**)	**14**	7

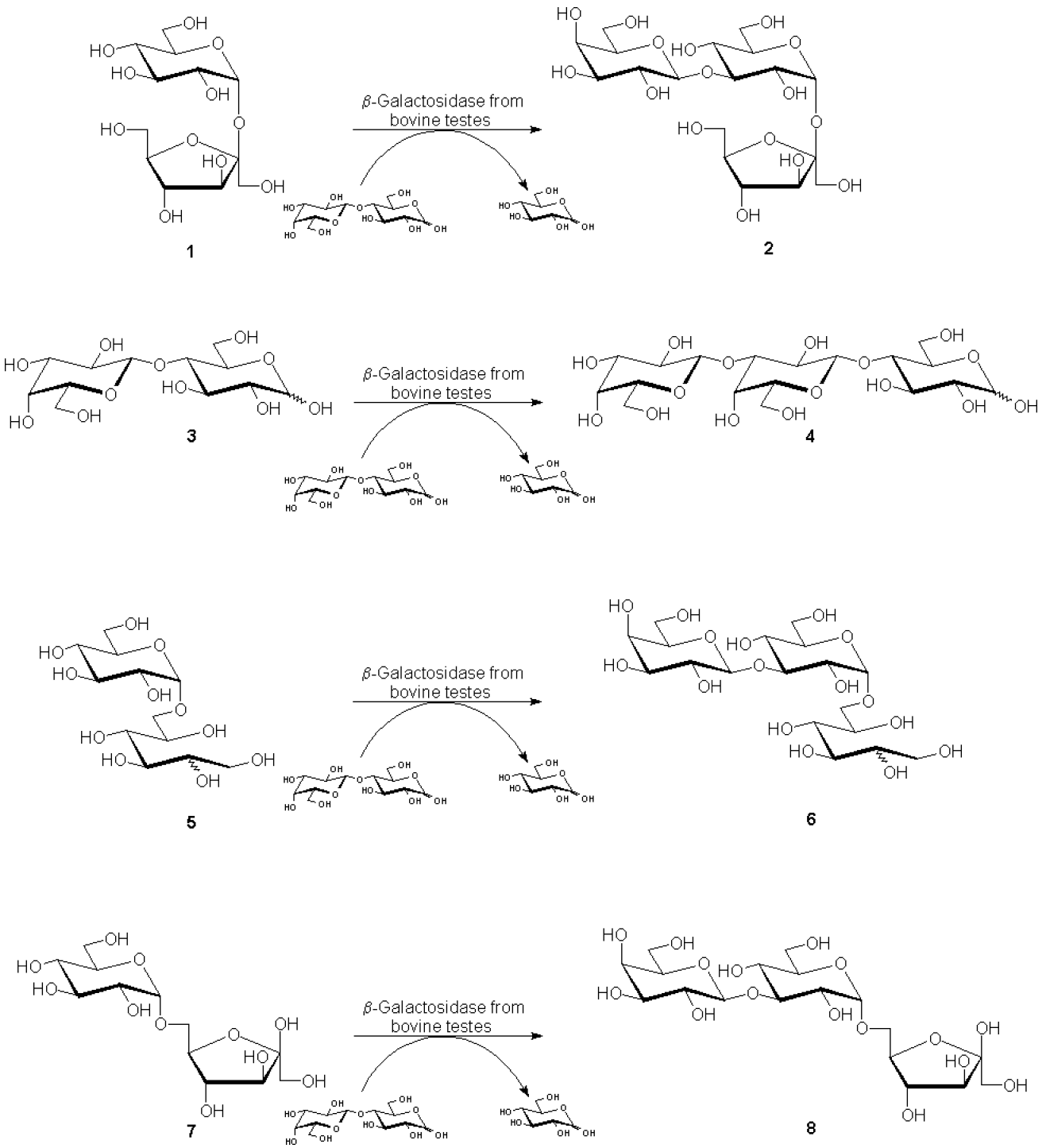
Regarding these results, the trend is obvious that neither furanosyl nor glycitol structures represent a suitable acceptor substrate for the β-galactosidase of bovine testes. Otherwise terminal pyranosyl units with free C-3 position are preferred transglycosylation targets; again a gluco-terminal is favoured over a galacto-residue as shown in Scheme 2 in the examples of isomelezitose (**9**), raffinose (**11**) and 1-kestose (**13**). As shown in Table 1, the yields were in the range of 7–44%. In the case of lactose acting as donor as well as acceptor, the yield is given on the basis of a donor-acceptor ratio of 1:4.

2.2. Enzymatic galactosylation with β-galactosidase from bovine testes of methyl α-D-glucopyranoside utilising various donor substrates

The different donor characteristics of the four β-galactosides *p*-nitrophenyl β-D-galactopyranoside (*p*NP-Gal, **17**), lactose (**3**), lactulose (**18**) and lactitol (**20**) were investigated. To simplify matters, methyl α-D-glucopyranoside (**15**) was chosen as model acceptor (Scheme 3). With *p*NP-Gal (**17**) and lactose (**3**) as donor, the disaccharide β-D-Gal-(1→3)α-D-GlcOMe (**16**) was obtained as the only product in 22 and 23% yield, respectively. By increasing the donor-acceptor ratio from 1:2 to 1:10, the yield with *p*NP-Gal (**17**) as donor could be significantly raised to 53%.

The use of lactulose (**18**) and lactitol (**20**) showed that a competitive self-transgalactosylation took place. On the basis of ^{1}H NMR signal integration it could be observed that besides the expected β-D-Gal-(1→3)α-D-GlcOMe (**16**), the trisaccharide β-D-Gal-(1→3)α-D-Glcp-(1→4)-Glc-ol (**21**) was also generated (ratio 10:7). The overall yield of 8% is composed of 5% compound (**16**) and 3% compound (**21**). The data of the reactions with methyl α-D-glucopyranoside (**15**) as model acceptor are summarised in Table 2.

In the reaction with lactulose as donor, it was not possible to calculate the yield since the signals overlaid and did not allow an explicit integration.

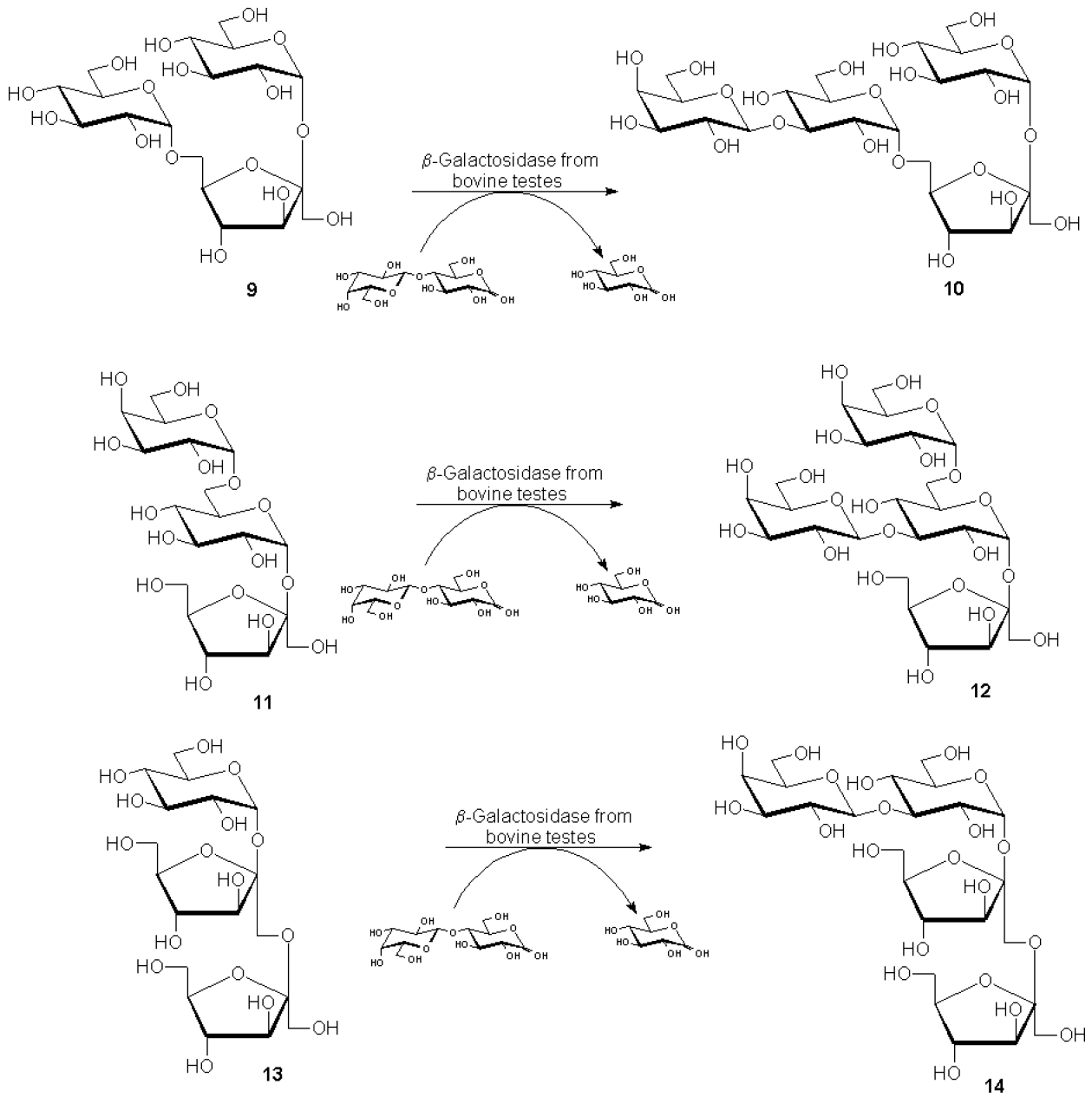


Scheme 1. Reagents and conditions: Lactose (4 mmol) as donor and sucrose, lactose or isomaltulose (1 mmol) as acceptor substrate was suspended in McIlvane buffer (50 mM, $NaH_2PO_4 \cdot 12H_2O$/citric acid, pH=4.3) and incubated with galactosidase from bovine testes (2.3 U/mmol acceptor) at 37 °C for 48 h to 72 h.

2.3. Larger scale enzymatic reaction with β-galactosidase from bovine testes devoid of buffer solution

Since yields are often decreased by running large preparations a common problem of chemical and enzymatic reactions is upscaling. To overcome this problem here, the work was performed with such a high concentration of donor and acceptor substrates that only a minor part of the reaction components were dissolved, and thus the solution was like a thick syrup. Typically 30–40 g of sugar substrates could be reacted in 50 ml aqueous 'solution'.

Furthermore, the salt charge of the buffer solution became a problem during processing, and so a pH=4.3 adjusted



Scheme 2. Reagents and conditions: Lactose (4 mmol) as donor and sucrose, lactose or isomaltulose (1 mmol) as acceptor substrate was suspended in McIlvane buffer (50 mM, $NaH_2PO_4{\cdot}12H_2O$/citric acid, pH=4.3) and incubated with galactosidase from bovine testes (2.3 U/mmol acceptor) at 37 °C for 48 h.

aqueous solution was used for the upscaled reaction. Lactose (**3**) as donor and sucrose (**1**) and isomalt (**5**) as acceptors were employed, and this approach have resulted in yields of 16% of compound (**2**) and 17% compound (**6**), respectively (Scheme 4).

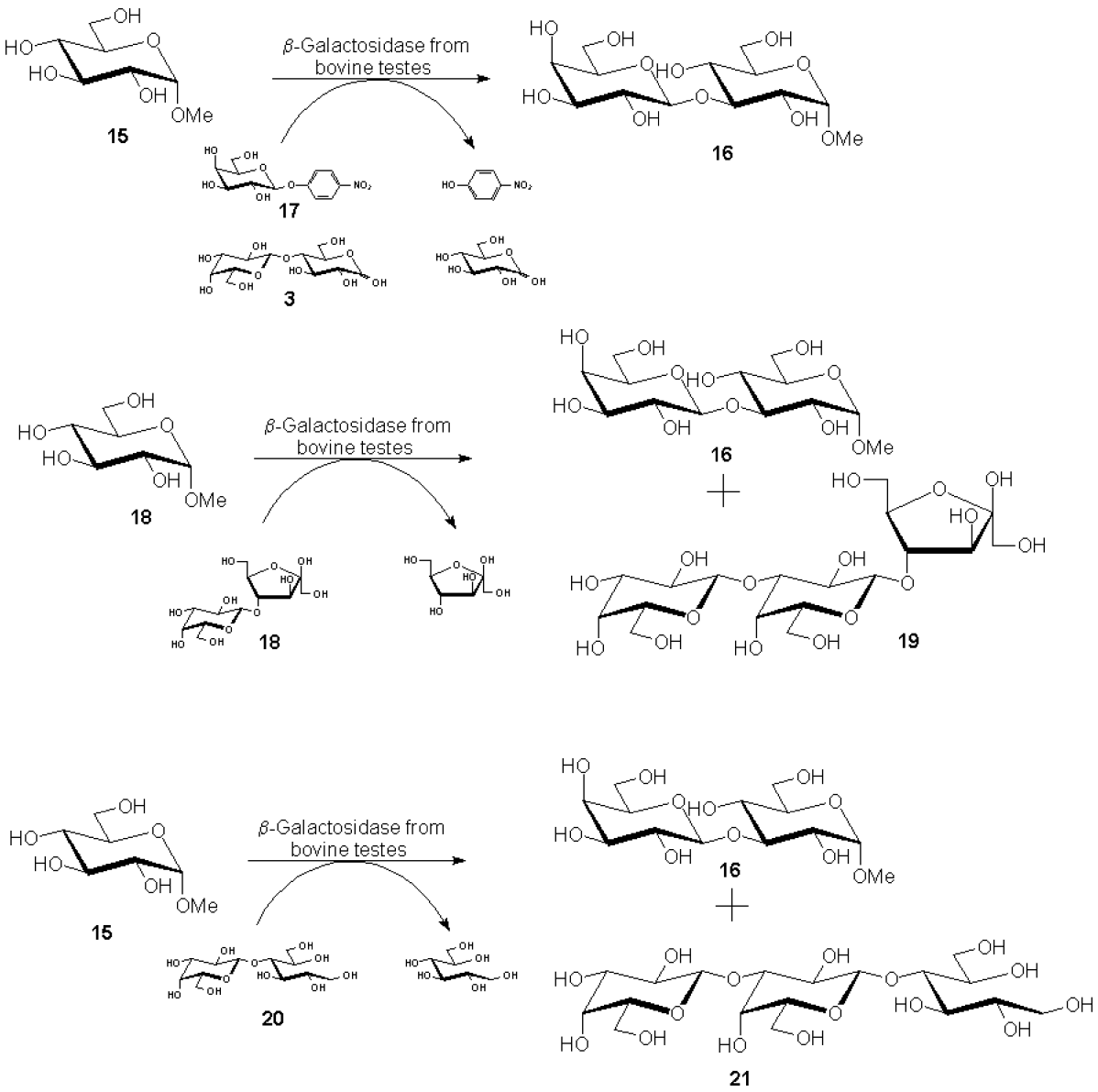
3. Conclusion

In summarising, an efficient synthetic pathway for the production of novel β(1→3) galacto-oligosaccharides derived from established food di- and trisaccharides was developed. Further, upscaling reactions could be effected without the use of specific buffers.

4. Experimental

4.1. General

The reactions were monitored by TLC analysis using silica gel plates (Kieselgel 60 F_{254}, Merck) and HPLC (Merck-Hitachi LaChrom® 7000Series; used coloumn: Polysphere® CH NA, eluent water, T=90 °C). Compounds were visualised by spraying with 20% sulfuric acid in ethanol, followed by charring at 150 °C and/or UV irradiation.-Column chromatography was performed on Biogel P2 (BioRad-Pharmacia) with water as eluent.-Optical rotations were determined at room temperature with a Perkin–Elmer 241 and 341 polarimeter. NMR spectra were recorded with a Bruker AMX 400 spectrometer. Chemical shifts are given in



Scheme 3. Reagents and conditions: Methyl α-D-glucopyranoside as acceptor and *p*NP-β-D-Ga1, lactose, lactulose and lacitol as donor substrate was suspended in McIlvane buffer (50 mM, $Na_2H_2PO_4{\cdot}12H_2O$/citric acid, pH=4.3) and incubated with β-galactosidase from bovine testes (2.3 U/mmol acceptor) at 37 °C for 48 h.

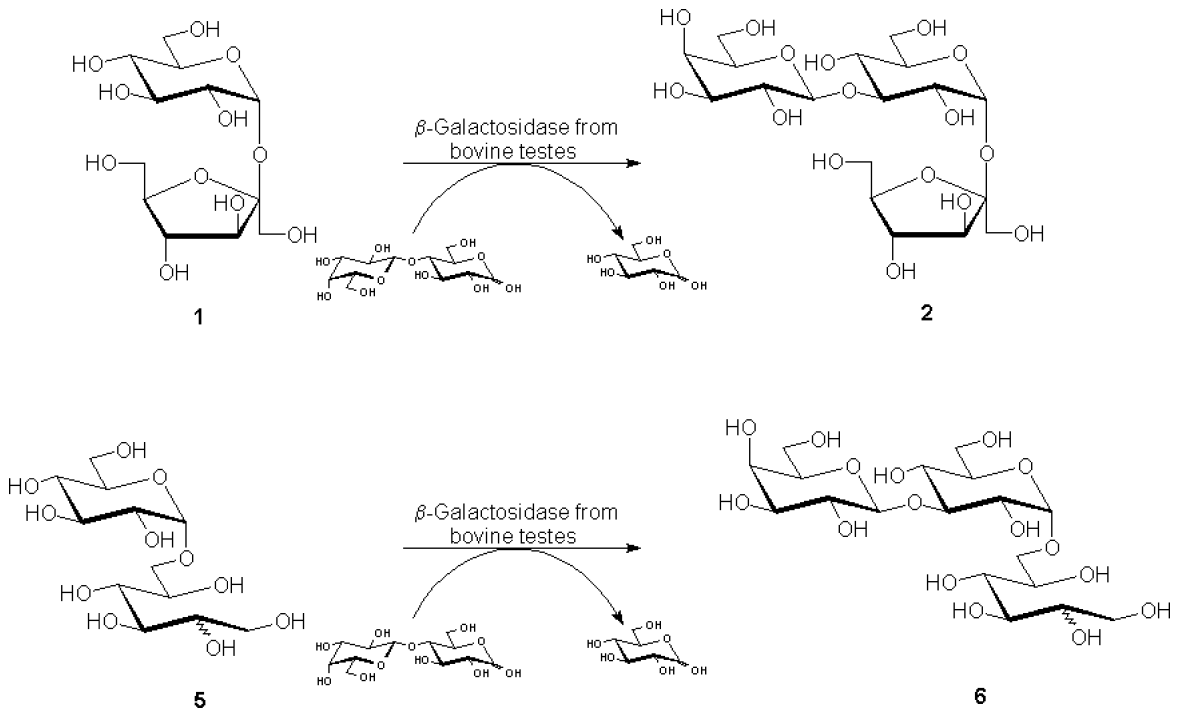
ppm (δ). For the improved interpretation of products the chemical shifts of the acceptor substrates are summerised in Table 3. Mass spectra were recorded with a Bruker MALDI-TOF mass spectrometer (with N_2 laser operating at 337 nm and 5 μl of 2,5-dihydroxybenzoic acid as matrix).

4.1.1. General galactosylation procedure A. To lactose monohydrate (1.33 mmol, 4 equiv.) **3** as donor and raffinose pentahydrate (0.33 mmol, 1 equiv.) **11** or 1-kestose (0.33 mmol, 1 equiv.) **13** as acceptor solubilised in McIlvane buffer (50 ml, $Na_2H_2PO_4{\cdot}12H_2O$/citric acid, pH=4.3), and β-galactosidase from bovine testes (2.3 U/mmol acceptor) solubilised in 100 μl McIlvane buffer is added. The mixture is incubated for 48 h at 37 °C. Subsequently, the reaction was terminated by heating to 90 °C for 5 min. The separation of the starting material from the product and desalination was carried out by column chromatography (Biogel P2, water). The structures of the products were confirmed by ^1H and ^{13}C NMR spectroscopy and MALDI-TOF mass spectrometry.

Table 2. Enzymatic galactosylations employing different donors to GlcpαOMe as model acceptor

Donor	Product	Yield (%)
*p*NP-β-D-Gal*p*(**17**)	**16**	53
Lactose (**3**)	**16**	22
Lactulose (**18**)	**16**+**19**	4
Lactitol (**20**)	**16**+**21**	2.2

4.1.2. β-D-Galactopyranosyl-(1→3)-α-D-glucopyranosyl-(1↔2)-β-D-fructofuranoside [β-D-Gal*p*-(1→3)-α-D-Glc*p*-(1↔2)-β-D-Fru*f*] (2). Sucrose (396 mg, 1.1 mmol) **1** and lactose (180 mg, 0.5 mmol) **3** were solubilised in 3.5 ml McIlvane buffer (50 mM, pH=4.3) together with β-galactosidase from bovine testes (0.75 U) suspended in 100 μl



Scheme 4. Reagents and conditions: (1) lactose (30 mmol) as donor and sucrose (50 mmol) as acceptor; or (2) lactose (60 mmol) as donor and isomalt (50 mmol) as acceptor; was suspended in pH=4.3 adjusted water and incubated with galactosidase from bovine testes (25 U for (1) and 37.5 U for (2)) at 37 °C.

McIlvane buffer. After incubation for 48 h at 37 °C the reaction was terminated by heating to 90 °C for 5 min. The mixture was concentrated under vacuo and separated by column chromatography on Biogel P2, to give 23 mg (0.045 mmol, 9%) of a white amorphic solid. $[\alpha]_D$=+45 (c=0.5 in H_2O). ^{1}H NMR (400 MHz, D_2O) δ=5.5 (d, 1H, H-1), 4.72 (d, 1H, H-1″), 4.28 (d, 1H, H-3′), 4.03 (t, 1H, H-4′), 3.98 (t, 1H, H-3). $J_{1,2}$=4.1 Hz, $J_{1'',2''}$=7.6 Hz, $J_{3',4'}$=8.7 Hz, $J_{3,4}$=9.7 Hz. ^{13}C NMR (100.67 MHz, D_2O) δ=104.03 (C-2′), 103.52 (C-1″), 92.47 (C-1), 82.07 (C-3), 81.73 (C-5′), 76.86 (C-3′), 75.63 (C-5″), 74.34 (C-4′), 72.96 (C-3″), 72.45 (C-5), 71.60 (C-2), 70.89 (C-2″), 68.96–68.16 (C-4/4″), 62.71 (C-6′), 61.78 (C-1′), 61.43 (C-6′), 60.47 (C-6). MALDI-TOF m/z calculated for $C_{18}H_{32}O_{16}$, 504.44 found, 526.91 $[M+Na]^+$, 542.89 $[M+K]^+$.

4.1.3. β-D-Galactopyranosyl-(1→3)-β-D-galactopyranosyl-(1→4)-α/β-D-glucopyranose [β-D-Gal*p*-(1→3)-β-D-Gal*p*-(1→4)-α,β-D-Glc*p*] (4). Lactose monohydrate (360 mg, 1 mmol) **3** was solubilised in 2 ml McIlvane

Table 3. ^{13}C NMR chemical data of the glycosyl acceptors in D_2O solution

Compound	Residue	Chemical shifts (δ)					
		C-1	C-2	C-3	C-4	C-5	C-6
1	Glc*p*-(1↔2)	92.52	71.41	72.91	69.56	72.74	60.46
	Fru*f*	61.68	104.02	76.75	74.33	81.71	62.70
3	Gal*p*-(1→4)	103.27	71.32	72.88	68.91	75.71	61.39
	α-Glc*p*	92.17	70.46	71.51	78.66	71.77	60.44
	β-Glc*p*	96.11	74.16	74.72	78.79	75.16	60.31
5	Glc*p*-(1→6)	98.55/	71.67	73.28	69.80	72.23	60.86
	Glc*p*-ol	98.51	—[a]	—[a]	—[a]	—[a]	68.90
	Man*p*-ol	63.63	—[a]	—[a]	—[a]	—[a]	69.16
		62.79					
7	Glc*p*-(1→6)	98.63	71.76	73.41	69.93	72.26	60.96
	β-Fru*f*	63.02	102.10	75.64	74.87	79.29	68.16
9	Gal*p*-(1→6)	98.82	68.83	69.80	69.56	71.30	61.47
	Glc*p*-(1↔2)	92.45	71.38	73.01	69.74	71.74	66.24
	Fru*f*	61.75	104.14	76.68	74.33	81.68	62.81
11	Glc*p*-(1→6)	98.61	71.67	73.30	69.80	72.23	60.83
	Glc*p*-(1↔2)	92.20	71.46	73.01	69.73	72.69	60.66
	Fru*f*	61.88	104.11	76.43	74.64	79.77	69.07
13	Glc*p*-(1↔2)	92.83	71.48	72.93	69.56	72.76	60.45
	Fru*f*-(1↔2)	60.76	104.07	76.97	74.81	81.55	62.67
	Fru*f*	61.24	103.59	76.97	74.19	81.46	62.52

[a] Not distinguishable from other signals.

buffer (50 mM, pH=4.3) together with β-galactosidase from bovine testes (0.75 U) suspended in 100 μl of the same buffer. After incubation for 72 h at 37 °C, the reaction was terminated by heating to 90 °C for 5 min. The mixture was concentrated under vacuum and separated by column chromatography on Biogel P2, to afford 44 mg (0.087 mmol, 44%, based on 0.2 mmol acceptor (theoretical donor-acceptor ratio of 4:1), 9% based on 1 mmol donor, donor=acceptor) of a white amorphic solid. $[\alpha]_D$=+32 (*c* 0.1 in H_2O). ^{1}H NMR (400 MHz, D_2O): δ=5.00 (d, 1H, H-1α), 4.44 (d, 1H, H-1β), 4.39 (d, 1H, H-1″), 4.29 (d, 1H, H-1′), 3.97 (d, 1H, H-4′), 3.70 (d, 1H, H-4″), 3.06 (t, 1H, H-2). $J_{1\alpha,2\alpha}$=3.6 Hz, $J_{1\beta,2\beta}=J_{1'',2''}$=8.1 Hz, $J_{1',2'}$=7.6 Hz, $J_{3',4'}=J_{3'',4''}$=3.6 Hz. ^{13}C NMR (100.67 MHz, D_2O): δ=104.71 (C-1″), 102.94 (C-1′), 96.17 (C-1β), 82.28 (C-3′), 78.56 (C-4β), 75.38 (C-5′/5″), 74.76 (C-3β), 74.22 (C-2β), 72.91 (C-3″), 71.42 (C-2″), 70.60 (C-2′), 68.97 (C-4″), 68.81 (C-4′), 61.38 (C-6′), 61.33 (C-6″), 60.49 (C-6β). MALDI-TOF *m*/*z* calculated for $C_{18}H_{32}O_{16}$ 504.44, found 527.56, $[M+Na]^+$, 543.51 $[M+K]^+$.

4.1.4. β-D-Galactopyranosyl-(1→3)-α-D-glucopyranosyl-(1→6)-D-glucitol/mannitol [β-D-Gal*p*-(1→3)-α-D-Glc*p*-(1→6)-D-Glc-ol/Man-ol] (6). Isomalt monohydrate (180 mg, 0.5 mmol) **5** and lactose monohydrate (400 mg, 1.33 mmol) **3** were solubilised in 2 ml McIlvane buffer (50 mM, pH=4.3) together with β-galactosidase from bovine testes (0.75 U) suspended in 100 μl of the same buffer. After incubation for 48 h at 37 °C, the reaction was terminated by heating to 90 °C for 5 min. The mixture was concentrated under vacuum and separated by column chromatography on Biogel P2, to afford 27.8 mg (0.055 mmol, 17%) of a white amorphic solid. $[\alpha]_D$=+52 (*c* 0.6 in H_2O). ^{1}H NMR (400 MHz, D_2O) δ=4.84 (d, 1H, H-1), 4.51 (d, 1H, H-1″) $J_{1,2}$=3.1 Hz, $J_{1'',2''}$=8.1 Hz. ^{13}C NMR (100.67 MHz, D_2O) δ=103.70 (C-1″), 98.50 (C-1), 82.65 (C-3), 75.69 (C-5″), 73.30 (C-2′, Glc-ol), 72.98 (C-3″), 71.89 (C-2), 71.35 (C-2″), 69.21–69.43 (C-6′), 68.97–68.53 (C-4/4″), 63.62 (C-1′, Man-ol), 62.78 (C-1′, Glc-ol), 61.44 (C-6″), 60.88 (C-6). MALDI-TOF *m*/*z* calculated for $C_{18}H_{34}O_{16}$, 506.46; found 529.67 $[M+Na]^+$, 545.56 $[M+K]^+$.

4.1.5. β-D-Galactopyranosyl-(1→3)-α-D-glucopyranosyl-(1→6)-β-D-fructofuranose [β-D-Gal*p*-(1→3)-α-D-Glc*p*-(1→6)-β-D-Fru*f*] (8). Isomaltulose (684 mg, 2 mmol) **7** and lactose monohydrate (69 mg, 0.2 mmol) **3** were solubilised in 2 ml McIlvane buffer (50 mM, pH=4.3) together with β-galactosidase from bovine testes (0.75 U) suspended in 100 μl of the same buffer. After incubation for 48 h at 37 °C, the reaction was terminated by heating to 90 °C for 5 min. The mixture was concentrated under vacuum and separated by column chromatography on Biogel P2, to give 17.3 mg (0.034 mmol, 17%) of a white amorphic solid. $[\alpha]_D$=+43 (*c* 1.2 in H_2O). ^{1}H NMR (400 MHz, D_2O) δ=5.12 (d, 1H, H-1), 4.76 (d, 1H, H-1″), 4.28 (d, 1H, H-3′). $J_{1,2}$=4.1 Hz, $J_{1'',2''}$=7.6 Hz, $J_{3',4'}$= 8.7 Hz. ^{13}C NMR (100.67 MHz, D_2O) δ=103.71 (C-1″), 102.11 (C-2′), 98.58 (C-1), 82.55 (C-3), 79.30 (C-5′), 76.50 (C-3′), 75.67 (C-5″), 74.91 (C-4′), 72.96 (C-3″), 72.30 (C-5), 71.77 (C-2), 71.20 (C-2″), 69.95 (C-4), 68.95 (C-4″), 68.37 (C-6′), 63.02 (C-1′), 61.39 (C-6″), 60.94 (C-6). MALDI-TOF *m*/*z* calculated for $C_{18}H_{32}O_{16}$, 504.44; found 527.63 $[M+Na]^+$, 543.54 $[M+K]^+$.

4.1.6. β-D-Galactopyranosyl-(1→3)-α-D-glucopyranosyl-(1→6)-[α-D-glucopyranosyl-(1↔2)]-β-D-fructofuranoside [β-D-Gal*p*-(1→3)-α-D-Glc*p*-(1→6)-[α-D-Glc*p*-(1↔2)]-β-D-Fru*f*] (10). Isomelezitose dihydrate (120 mg, 0.22 mmol) **9** and lactose monohydrate (400 mg, 0.2 mmol) **3** were solubilised in 2 ml McIlvane buffer (50 mM, pH=4.3) together with β-galactosidase from bovine testes (0.75 U) suspended in 100 μl of the same buffer. After incubation for 48 h at 37 °C, the reaction was terminated by heating to 90 °C for 5 min. The mixture was concentrated under vacuum and separated by column chromatography on Biogel P2, to give 33.2 mg (0.049 mmol, 23%) of a white amorphic solid. $[\alpha]_D$=+101 (*c* 0.6 in H_2O). ^{1}H NMR (400 MHz, D_2O) δ=5.27 (d, 1H, H-1), 4.82 (d, 1H, H-1″), 4.46 (d, 1H, H-1‴), 4.04 (d, 1H, H-3′), 3.28 (dd, 1H, H-2‴). $J_{1,2}$=4.1 Hz, $J_{1'',2''}$=3.6 Hz, $J_{1''',2'''}$=7.6 Hz, $J_{3',4'}$=8.7 Hz, $J_{2''',3'''}$=9.2 Hz. ^{13}C NMR (100.67 MHz, D_2O) δ=104.09 (C-2′), 103.82 (C-1‴), 98.49 (C-1″), 92.20 (C-1), 82.95 (C-3″), 79.77 (C-5′), 76.42 (C-3′), 75.68 (C-5‴), 74.58 (C-4′), 73.03 (C-3), 72.94 (C-3‴), 72.69 (C-5), 71.93 (C-5″), 71.58 (C-2″), 71.47 (C-2), 71.02 (C-4″), 70.08 (C-2‴), 69.86 (C-6′), 68.90 (C-4‴), 68.34 (C-4), 61.88 (C-1′), 61. 34 (C-6‴), 60.87 (C-6″), 60.61 (C-6). MALDI-TOF *m*/*z* calculated for $C_{24}H_{42}O_{21}$, 666.58; found 689.57 $[M+Na]^+$, 705.54 $[M+K]^+$.

4.1.7. α-D-Galactopyranosyl-(1→6)[-β-D-galactopyranosyl-(1→3)]-α-D-glucopyranosyl-(1↔2)-β-D-fructofuranoside [α-D-Gal*p*-(1→6)-[β-D-Gal*p*-(1→3)]-α-D-Glc*p*-(1↔2)-β-D-Fru*f*] (12). Prepared from raffinose pentahydrate (198 mg, 0.33 mmol) **11** and lactose monohydrate (400 mg, 1.33 mmol) **3** according to General Procedure A; yield: 21.4 mg (0.032 mmol, 10%); white amorphic solid. $[\alpha]_D$=+90 (*c* 0.9 in H_2O). ^{1}H NMR (400 MHz, D_2O) δ=5.35 (d, 1H, H-1), 4.90 (d, 1H, H-1″), 4.57 (d, 1H, H-1‴), 4.14 (d, 1H, H-3′), 3.97 (dd, 1H, H-4′). $J_{1,2}$=4.1 Hz, $J_{1'',2''}$=3.6 Hz, $J_{1''',2'''}$=7.6 Hz, $J_{3',4'}$=8.6 Hz. ^{13}C NMR (100.67 MHz, D_2O) δ=104.15 (C-2′), 103.55 (C-1‴), 98.65 (C-1″), 92.42 (C-1), 82.10 (C-3), 81.70 (C-5′), 76.78 (C-3′), 75.61 (C-5‴), 74.33 (C-4′), 72.94 (C-3‴), 71.63 (C-5), 71.47 (C-2), 71.28 (C-5″), 70.85 (C-2‴), 69.80 (C-3″), 69.52 (C-4), 68.94 (C-4″), 68.85 (C-2″), 68.17 (C-4‴), 66.26 (C-6), 62.79 (C-6′), 61.80 (C-1′), 61.44 (C-6‴), 61.39 (C-6″). MALDI-TOF *m*/*z* calaculated for $C_{24}H_{42}O_{21}$, 666.58; found, 689.63 $[M+Na]^+$, 705.59 $[M+K]^+$.

4.1.8. β-D-Galactopyranosyl-(1→3)-α-D-glucopyranosyl-(1↔2)-β-D-fructofuranosyl-(1↔2)-β-D-fructofuranoside [β-D-Gal*p*-(1→3)-α-D-Glc*p*-(1↔2)-β-D-Fru*f*-(1↔2)-β-D-Fru*f*] (14). Prepared from 1-kestose (168 mg, 0.33 mmol) **13** and lactose (400 mg, 1.33 mmol) **3** according to General Procedure A; yield: 15.6 mg (0.023 mmol, 7%); white amorphic solid. $[\alpha]_D$=+48 (*c* 0.1 in H_2O). ^{1}H NMR (400 MHz, D_2O) δ=5.32 (d, 1H, H-1), 4.52 (d, 1H, H-1‴), 4.15 (d, 1H, H-3′), 4.08 (d, 1H, H-3″). $J_{1,2}$=4.1 Hz, $J_{1''',2'''}$=8.1 Hz, $J_{3',4'}$=8.7 Hz, $J_{3'',4''}$=8.7 Hz. ^{13}C NMR (100.67 MHz, D_2O) δ=104.12 (C-2′), 103.53 (C-1‴), 103.54 (C-2″), 92. 81 (C-1), 81.97 (C-3), 81.68–81.52 (C-5′/5″), 77.23–77.04 (C-3′/3″), 75.68 (C-5‴), 74.86–74.28 (C-4′/4″), 73.01 (C-3‴), 72.53 (C-5), 71.65 (C-2), 71.07 (C-2‴), 69.01–68.23 (C-4/4‴), 62.76 (C-6′), 62.56 (C-6″), 61. 48 (C-1″), 61.45 (C-6‴), 60.79 (C-1′), 60.53

(C-6). MALDI-TOF *m/z* calculated for $C_{24}H_{42}O_{21}$, 666.58; found 689.44 $[M+Na]^+$, 705.42 $[M+K]^+$.

4.1.9. Methyl β-D-galactopyranosyl-(1→3)-α-D-glucopyranoside (16). Prepared from methyl α-D-glucopyranoside (64.7 mg, 0.33 mmol) **15** and the following donors: (a) *p*NP-β-D-Gal (52.3 mg, 0.17 mmol) **17**, (b) lactose (480.0 mg, 1.33 mmol) **3**, (c) lactulose (455.0 mg, 1.33 mmol) **18**, (d) lactitol (455.0 mg, 1.33 mmol) **20** according to General Procedure A; yield: (a) 13.3 mg (0.037 mmol, 22%) **16**, (b) 27.3 mg (0.077 mmol, 23%) **16**, (c) 19.5 mg (0.054 mmol, 4%) **16**, (d) 10.6 mg (0.029 mmol, 2.2%) **16**. $[\alpha]_D$=+90 (*c* 1.6 in H_2O). ^1H NMR (400 MHz, D_2O) δ=4.68 (d, 1H, H-1), 4.47 (d, 1H, H-1′), 3.25 (s, 3H, OCH_3) $J_{1,2}$=3.6 Hz, $J_{1',2'}$=8.1 Hz. ^{13}C NMR (100.67 MHz, D_2O) δ=103.74 (C-1′), 99.52 (C-1), 82.94 (C-3), 75.69 (C-5′), 72.95 (C-3′), 71.68 (C-5), 71.61–71.02 (C-2/2′), 68.94 (C-4′), 68.50 (C-4), 61.40 (C-6′), 60.89 (C-6), 55.37 (OCH_3). MALDI-TOF *m/z* calculated for $C_{13}H_{24}O_{11}$, 356.32; found 379.47 $[M+Na]^+$, 395.41 $[M+K]^+$. (c) Additional $C_{18}H_{32}O_{16}$ (504.44). MALDI-TOF: *m/z* 526.79 $[M+Na]^+$. d) additional $C_{18}H_{34}O_{16}$ (506.46). MALDI-TOF: *m/z* 528.79 $[M+Na]^+$, 544.76 $[M+K]^+$.

4.1.10. Upscaled formation of β-D-Gal*p*-(1→3)-α-D-Glc*p*-(1→6)-D-Glc-ol/Man-ol (6) devoid of buffer solution. Lactose (20.7 g, 60 mmol) and isomalt (17.2 g, 50 mmol) were solubilised in 50 ml pH=4.3 adjusted deionised water and β-galactosidase from bovine testes (37.5 U) was added. After incubation at 37 °C for 5 d the reaction was terminated by heating to 90 °C for 5 min. The mixture was freeze-dried and separated on an industrial scale GPC-column to give 4.6 g (9.1 mmol, 16%) of the desired product **2**.

The analytical data matched with the data under Section 4.1.2.

4.1.11. Upscaled formation of β-D-Galp-(1→3)-α-D-Glcp-(1↔2)-β-D-Fruf (2) devoid of buffer solution. Lactose (10.8 g, 30 mmol) and sucrose (17.1 g, 50 mmol) were solubilised in 50 ml pH=4.3 adjusted deionised water and β-galactosidase from bovine testes (25 U) was added. After incubation at 37 °C for 5 d the reaction was terminated by heating to 90 °C for 5 min. The mixture was freeze-dried and separated on an industrial scale GPC-column to give 2.7 g (5.3 mmol, 17%) of the desired product **4**.

The analytical data matched with the data under Section 4.1.3.

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Small libraries of fused quinazolinone-sugars. Access to quinazolinedione nucleosides

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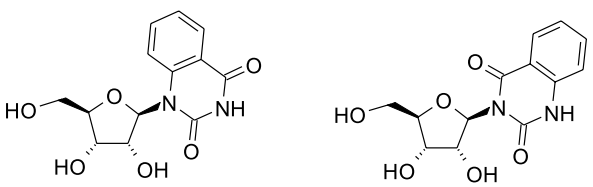
Abstract—Unprotected carbohydrates can readily be converted into base-modified nucleosides and deoxynucleosides through a short sequence involving the condensation of anthranilic acid derivatives with a suitably protected sugar-derived 2-alkylthio-1,3-oxazoline.

1. Introduction

Over the past thirty years, natural as well as synthetic nucleosides and nucleotides have been the cornerstone of antiviral therapies against hepatitis virus (HBV), herpes virus (VZV) and human immunodeficiency virus (HIV).[1] Many of those compounds exhibit antiproliferative, antibiotic and antifungal activities and some have been used as probes for DNA damages,[2] as well as in the anti-sense approach and DNA-probe technology with fluorescence properties.[3] Investigations were also undertaken on the physico-chemical parts of DNA base-to-base interactions (hydrogen bonding and stacking).[4,5] It is also well admitted that introducing diversity either into the carbohydrate or into the heterocyclic moiety of nucleosides—from natural modified nucleosides, methylated bases in the bacteria world or in RNA duplex[6] as well as new antibiotic analogues like oxanosine[7] or modified purines or pyrimidines[8] but also pyrazoles, imidazoles, phthalimides, pteridines and lumazines[9]-leads to promising molecules with a therapeutical potential. In a search for novel structural features, we have turned our attention to the quinazolinedione moiety.

To construct such bases, two general methods for nucleoside preparation could be applied from the literature, one using the glycosylation method,[10] which may lead to anomeric selectivity problems, and the other based on a multistep process to assemble entirely the base onto the carbohydrate template.[11] Our study was based on an old reaction between carbohydrates and thiocyanic acid giving 1,3-oxazolidine-2-thione (OZT) fused with a carbohydrate furan ring. OZT was the basic structure to develop a convergent preparation of fused quinazolinone-sugars and quinazolinedione nucleosides. Earlier approaches performed to obtain quinazolinedione nucleosides involve condensation of an activated ribo- or 2-deoxyribo-donor with quinazoline derivatives.[12] We herein develop a new flexible approach to what can be called *iso*-quinazolinedione nucleosides (Scheme 1).

Our convergent approach to synthesize benzopyrimidine-modified nucleosides involves a sugar derived OZT and anthranilic acid. Condensation reactions of anthranilic acid derivatives have already been explored.[13] Within the frame of a research program centered on the preparation and reactivity of chiral natural OZT, such reactions were explored.[14,15] Application of the process of anthranilic acid condensation with per-benzylated OZT led to new homochiral quinazolinone derivatives. Extension of the cyclocondensation process to sugar-derived OZT constitutes a promising extension of this reaction to new base-modified nucleosides and nucleotides.[16]



Scheme 1. Quinazolinedione nucleoside and its *iso* derivative.

Keywords: 1,3-Oxazolidine-2-thione; Nucleoside; Quinazolinone; Quinazolinedione; Anthranilic acid.
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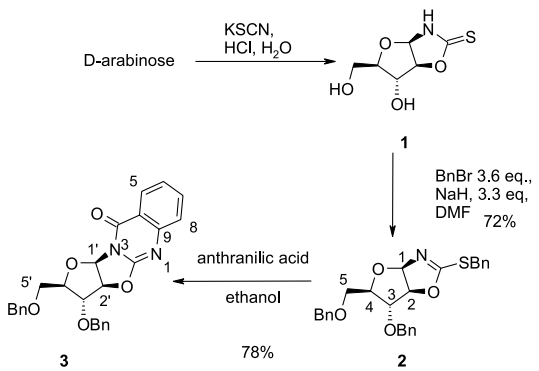


Scheme 2. The cyclocondensation process to quinazolinone via a benzylthiooxazoline intermediate in the D-arabino series.

2. Results and discussion

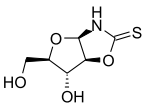
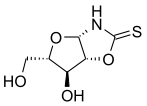
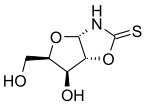
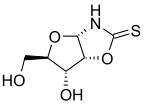
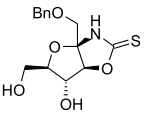
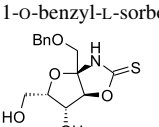
2.1. Quinazolinones preparation

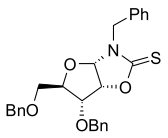
Our approach is illustrated in Scheme 2 with D-arabinose. Scheme 2: the cyclocondensation process to quinazolinone via a benzylthiooxazoline intermediate in the D-arabino series.

The preparation of the D-arabino derived OZT **1** is straightforward.[17] Standard conditions were applied to various series of sugars: D- and L-arabinose, D-xylose, D-ribose (aldopentose series) as well as D-fructose and L-sorbose (hexoketose series). On pentoses and partially protected hexoketoses (1-*O*-benzyl-D-fructose and 1-*O*-benzyl-L-sorbose), the OZT were prepared in one step using potassium thiocyanate under acidic conditions. This reaction allowed us to produce diverse OZT in which the configuration of the sugar ring was unambigously defined. A furano-conformation and an anomeric configuration controlled by the location of the hydroxyl group on C-2 was observed. In addition, in D-fructo- and L-sorbo-derivatives, known to usually give mixtures of furanose or pyranose OZT, the benzyl protection on the first primary position determined the formation of only one isomer out of the seven that could be expected from an unprotected ketohexoses.

Prior to cyclocondensation, the OZT **1** has to be activated through *S*-alkylation. This sequence furnishes the per-*O*- and -*S*-benzylated compound **2** in reasonable yields for a two-step sequence (Table 1). Alkylation of the other OZT (**4**–**8**) afforded the 2-benzylthiooxazolines (**9**–**13**) with yields ranging from 38 to 73%. For most of the compounds *N*-alkylation was not observed except with the D-ribo OZT **6**, for which 24% of *N*-benzylation was obtained (Scheme 3).

Table 1. Application of the procedure previously described for miscellaneous aldoses and ketoses

OZT		Alkylthiooxazoline (two step yields)	Quinazolinone EtOH, m.s. 3 Å (*t*BuOH, CSA, m.s 3 Å)
1	D-arabino 	**2** 38%	**3** 78% (92%)
4	L-arabino 	**9** 41%	**14** 79%
5	D-xylo 	**10** 50%	**15** 75%
6	D-ribo 	**11** 42%	**16** 65%
7	1-O-benzyl-D-fructo 	**12** 64%	**17** 14% (50%)
8	1-O-benzyl-L-sorbo 	**13** 38%	**18** 16% (70%)



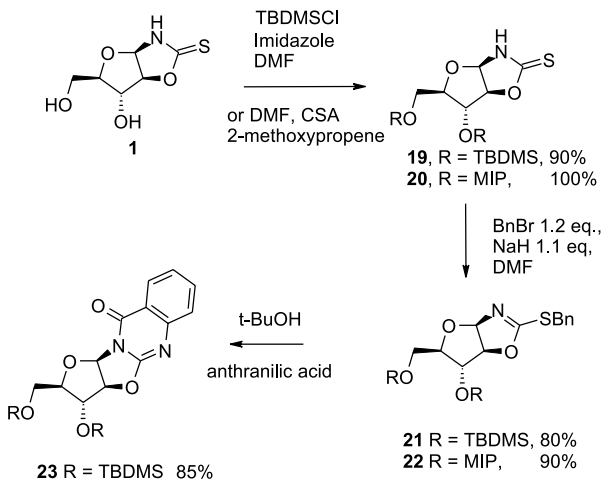
11a

Scheme 3. *N*-benzyl derivative isolated from D-ribo OZT.

Condensation of 2-benzylthio-1,3-oxazoline **2** with anthranilic acid in dry ethanol offers an efficient access to the D-arabino derived quinazolinone **3** in good yield. Application of the process to other alkylthiooxazolines (**9**–**11**) generated the quinazolinones (**14**–**16**) in similar yields. In the case of D-fructo **12** and L-sorbo **13** derivatives however, yields were poor and non-reproducible. Those results might be explained by a steric hindrance of the benzyloxymethyl group attached to the anomeric carbon. Moreover, a competing nucleophilic attack of ethanol providing the corresponding 2-ethoxy-1,3-oxazoline analogues was observed.

Improvement of the conditions was investigated using various solvents such as DMF or *tert*-butanol. In aprotic media (DMF), no condensation was detected whereas in *tert*-butanol only a slow reaction occurred. Activation was performed through addition of two equivalents of camphorsulfonic acid. In such conditions, cyclocondensations occurred in reasonable yield for D-fructo **17** and L-sorbo **18** derivatives (57 and 70%, respectively). When applied to the D-arabino derivative **2**, the above conditions resulted in much improved yields (92%).

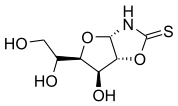
Discrimination of hydroxyls versus the OZT moiety allowed a more flexible approach to cyclocondensations. Selective protection of hydroxyls was performed either with TBDMS group or with mixed acetals, thus allowing selective activation of the OZT as benzylthiooxazoline intermediates (Scheme 4). Mixed acetal (methoxyisopropylidene, MIP) did not appear stable enough for an efficient cyclocondensation. In contrast, silyl derivatives gave the cycloadducts in 70% yield albeit together with some O-deprotection. Skipping the acidic catalysis resulted in an increased yield of 85%.



Scheme 4. The alternative approach to quinazolinone.

Table 2. Application on silylated OZT of cyclocondensation

OZT	Silylated alkylthiooxazoline	Quinazolinone *t*BuOH
D-Arabino **1**	**21** 72%	**23** 85%
L-Arabino **4**	**24** 75%	**27** 83%
D-Xylo **5**	**25** 79%	**28** 95%
D-Gluco	**26** 48%	**29** 59%



This sequence of reaction has been successfully applied to other carbohydrate series—namely L-arabino, D-xylo and D-gluco (Table 2). The silylation–thioalkylation sequence led to the formation of alkylthiooxazoline derivatives in much better yields than through direct per-alkylation. Even with a more complex structure, such as for the D-gluco derivative **26**, the process is still competitive.

Applying the cyclocondensation conditions with anthranilic acid on the *O*-silylated benzylthiooxazolines **21**, **24**, **25** gave similar yields as with the perbenzylated derivatives. With the more complex D-gluco-alkylthiooxazoline **26**, a somewhat lower yield was observed, maybe for hindrance reason.

2.2. The limits of cyclocondensation

A panel of 1,2-aminoaromatic acids was condensed with the D-arabino per-benzylated alkylthiooxazoline **2** as a model. Using the first procedure developed, results (Table 3) showed that the presence of a withdrawing group hampered to some extent the reaction. Replacing in anthranilic acid of the benzene ring by pyridine (2-aminonicotinic acid) expectedly did not allow the transformation into the desired compound.

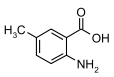
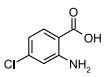
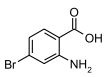
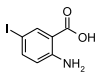
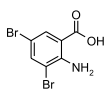
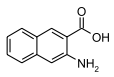
Applying the conditions developed for hindered compounds led to dramatic improvement of the yields most significantly with withdrawing groups (chloro-, bromo- and iodoanthranilic acid). However, those conditions remained inefficient in condensing aminonicotinic acid and dibromoanthranilic acid.

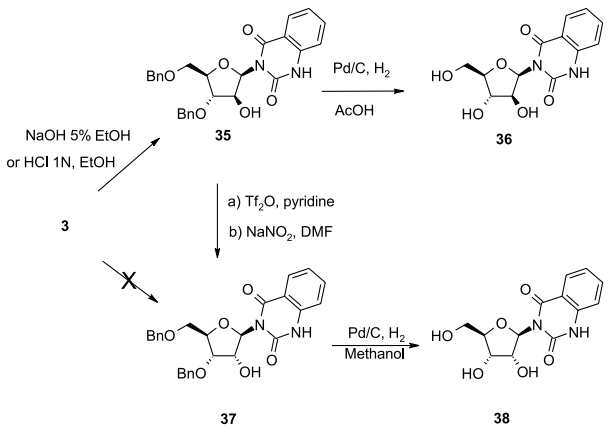
2.3. Nucleosides synthesis

Having in hand an efficient and short three steps protocol to generate new base modified 2,2′-anhydronucleosides, we have explored the ability of the newly formed heterocycles to generate the corresponding nucleosides and deoxynucleosides. To validate our approach to base-modified nucleosides, we have investigated the ring-cleavage of quinazolinones on the D-arabino model (Scheme 5). Inspired by the well-documented 2,2′-anhydronucleoside chemistry, we have reacted the D-arabino derivative **3** under basic and acidic conditions. In both cases hydrolysis of the anhydro ring was effected with good yields—67 and 73%, respectively—and complete configuration retention at the 2′-hydroxylated position.

All our attempts to induce a direct inversion aimed at producing the D-ribo-configuration failed. Thus, we obtained a D-arabino compound **35** which incorporates a

Table 3. Extension to diverse amino-aromatic acids

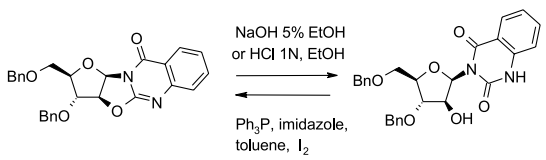
Amino acids								
EtOH, ms 4 Å	75% **3**	78% **30**	38% **31**	40% **32**	—	—	—	0%
*t*BuOH, ms 4 Å	92%	89%	86%	94%	78% **33**	0%	65% **34**	0%



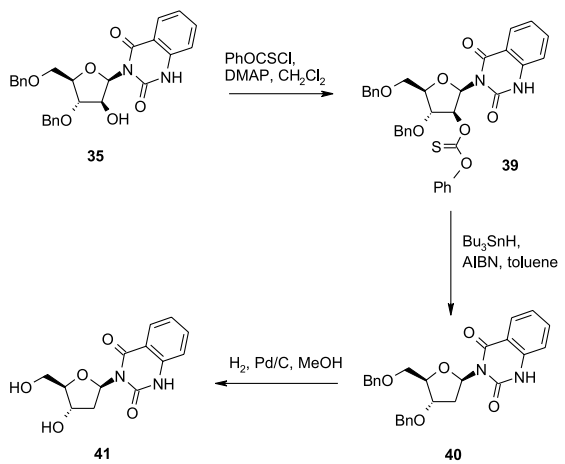
Scheme 5. Routes to base-modified nucleosides in the D-arabino series.

quinazolinedione system as the base. Further hydrogenolysis of benzyl groups (H_2 and Pd/C) afforded the D-arabino-nucleoside analogue **36** with 74% yield.

To obtain the natural carbohydrate analogue, inversion of configuration was required: among the diverse methods applied, the most efficient in our hands was the two steps process involving triflic anhydride activation of the alcohol followed by inversion with sodium nitrite. An interesting aspect of our investigations was the clean intramolecular cyclisation to the anhydro derivative, observed under standard Garegg conditions (Scheme 6).



Scheme 6. 2,2′-Anhydro formation under Garegg conditions.



Scheme 7. Deoxynucleoside formation.

Finally, the deoxynucleoside analogue was prepared through a Barton–McCombie process (Scheme 7).

The thionocarbonate **39** was prepared (85%) under basic conditions, then deoxygenated with tributylstannane to the deoxynucloside **40** in 62% yield. The fully deprotected structure **41** was obtained (62% yield) through Pd-catalysed hydrogenolysis.

3. Conclusion

In summary, a concise (5–8 steps) and practical synthesis of base-modified nucleosides has been disclosed starting from native carbohydrates through OZT derivatives. This procedure constitutes an original application of cyclo-condensations involving anthranilic acid and analogues. The reaction has been extended with success to different sugar series (pentoses and hexoses) and also to diverse heterocyclic systems (halogenoanthranilic acid and amino-naphtalenic acid), leading to a small library of base-modified anhydronucleosides.

4. Experimental

4.1. General methods

Melting points were determined on a Köfler hot-stage apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX250 at 250 MHz and 62.89 MHz, respectively. The chemical shifts (δ) are reported in ppm downfield from TMS as the internal standard. Coupling constants (J) are reported in Hz. Specific rotations were measured at 20 °C using a Perkin–Elmer polarimeter 141. HR-ESI-TOF-mass spectra were recorded on a Micromass LC TOF spectrometer. Evaporation was conducted in vacuo with a Büchi rotary evaporator. Analytical TLC was carried out on precoated silica gel 60F-254 plates (E. Merck) and spots were detected by UV light (254 nm) and by heat treatment with a 10/85/5 mixture of sulfuric acid, ethanol and water. Flash column chromatography was performed on Kieselgel 60 (230–400 mesh) silica gel (E. Merck).

4.2. Chemical procedure

4.2.1. General protocol for the per-benzylation of sugar-OZT. The sugar OZT (1 equiv.) was dissolved in DMF and cooled in an ice-bath. NaH (4 equiv.) was added portionwise then benzyl bromide (4 equiv.). The reaction was brought to room temperature and stirred until completion (few hours). Ice-cold water was poured in and the mixture was extracted with AcOEt (3×50 mL). Organic phases were collected and

washed thoroughly with water, then brine and dried over $MgSO_4$. Per-benzylated compounds were purified by column chromatography using petroleum ether–ethyl acetate eluents.

4.2.2. 2-Benzylthio-4,5-dihydro-(3′,5′-di-*O*-benzyl-1′,2′-dideoxy-β-D-arabinofuranoso) [1,2-*d*]-oxazole 2. Eluent: petroleum ether–ethyl acetate 80/20, yellow oil (1.83 g, 76%); $[\alpha]_D$=−71 (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 3.20 (dd, 1H, $J_{5a,4}$=7.0 Hz, $J_{5a,5b}$=10.2 Hz, *H-5a*); 3.40 (dd, 1H, $J_{5b,4}$=5.3 Hz, *H-5b*); 4.00–4.11 (m, 1H, *H-3*); 4.15–4.28 (m, 3H, *H-4*, SCH_2-Ph); 4.36 (d, 1H, *J*=12.1 Hz, CH_2-Ph); 4.43 (d, 1H, CH_2-Ph); 4.49 (d, 1H, *J*=12.1 Hz, CH_2-Ph); 4.55 (d, 1H, CH_2-Ph); 4.85 (dd, 1H, $J_{2,1}$=6.0 Hz, $J_{2,3}$= 1.0 Hz, *H-2*); 6.01 (d, 1H, *H-1*), 7.10–7.30 (m, 15H, CH_{Ar}); ^{13}C NMR ($CDCl_3$): δ 36.1 (S-*C*H_2-Ph); 69.4 (*C*-5); 76.1 (*C*H_2-Ph); 73.1 (*C*H_2-Ph); 81.9 (*C-4*); 85.4 (*C-3*); 88.1 (*C-2*); 100.7 (*C-1*); 126.4; 126.7; 127.0; 127.5; 127.7; 127.8; 128.2; 128.3; 128.4; 128.9 (*C*H_{Ar}); 137.5; 137.8; 138.8 (*Cq*); 169.2 (*C*-S); IR (NaCl): 1608 cm^{-1} (C═N); MS IS *m*/*z* =462.0 [M+H$^+$]; HRMS: calcd for $C_{21}H_{23}NO_4$ (353.1627), found (353.1632).

4.2.3. 2-Benzylthio-4,5-dihydro-(3′,5′-di-*O*-benzyl-1′,2′-dideoxy-β-L-arabinofuranoso) [1,2-*d*]-oxazole 9. Eluent: petroleum ether–ethyl acetate 80/20, yellow oil (0.99 g, 48%); $[\alpha]_D$=+72 (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 3.23 (dd, 1H, $J_{5a,4}$=7.1 Hz, $J_{5a,5b}$=10.2 Hz, *H-5a*); 3.41 (dd, 1H, $J_{5b,4}$=5.5 Hz, *H-5b*); 4.05 (d, 1H, $J_{3,4}$=2.2 Hz, *H-3*); 4.16–4.28 (m, 3H, *H-4*, SCH_2-Ph); 4.39 (d, 1H, *J*=12.3 Hz, CH_2-Ph); 4.45 (d, 1H, CH_2-Ph); 4.52 (d, 1H, *J*=11.9 Hz, CH_2-Ph); 4.57 (d, 1H, CH_2-Ph); 4.88 (dd, 1H, $J_{2,1}$=6.0 Hz, $J_{2,3}$=0.9 Hz, *H-2*); 6.03 (d, 1H, *H-1*), 7.15–7.38 (m, 15H, CH_{Ar}); ^{13}C NMR ($CDCl_3$): δ 36.2 (S*C*H_2-Ph); 69.5 (*C-5*); 71.8; 73.2 (*C*H_2-Ph); 81.7 (*C-4*); 83.9 (*C-3*); 88.3 (*C-2*); 100.8 (*C-1*); 127.6; 127.7; 127.8; 127.9; 128.0; 128.1; 128.3; 128.4; 128.5; 128,6; 129.0 (*C*H_{Ar}); 136.3; 137.0; 137.9 (*Cq*); 169.4 (*C-S*); IR (NaCl): 1608 cm^{-1} (C═N); MS IS *m*/*z*=462.5 [M+H$^+$]; HRMS: calcd for $C_{27}H_{27}NO_4S$ (461.1660), found (461.1669).

4.2.4. 2-Benzylthio-4,5-dihydro-(3′,5′-di-*O*-benzyl-1′,2′-dideoxy-β-D-xylofuranoso) [1,2-*d*]-oxazole 10. Eluent: petroleum ether–ethyl acetate 80/20, yellow oil (1.52 g, 50%); $[\alpha]_D$=+37 (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 3.82–3.88 (m, 2H, *H-5*); 3.92–3.97 (m, 1H, *H-4*); 4.06 (d, 1H, $J_{3,4}$=3.2 Hz, *H-3*); 4.31 (d, 1H, *J*=13.2 Hz, SCH_2-Ph); 4.37 (d, 1H, *J*=13.2 Hz, SCH_2-Ph); 4.56 (d, 1H, *J*=11.9 Hz, CH_2-Ph); 4.58 (d, 1H, *J*=11.9 Hz, CH_2-Ph); 4.65 (d, 1H, *J*=11.9 Hz, CH_2-Ph); 4.72 (d, 1H, *J*=11.9 Hz, CH_2-Ph); 4.89 (d, 1H, $J_{2,1}$=5.5 Hz, *H-2*); 6.19 (d, 1H, *H-1*), 7.28–7.44 (m, 15H, CH_{Ar}); ^{13}C NMR ($CDCl_3$): δ 36.5 (S*C*H_2-Ph); 67.0 (*C-5*); 72.2; 73.5 (*C*H_2-Ph); 77.5 (*C-4*); 81.0 (*C-3*); 85.5 (*C-2*); 99.9 (*C-1*); 127.7; 127.8; 128.0; 128.3; 128.4; 128.5; 128.6; 129.0 (*C*H_{Ar}); 136.2; 137.2; 138.2 (*Cq*); 165.5 (*C*-S); IR (NaCl): 1606 cm^{-1} (C═N); MS IS *m*/*z*=462.5 [M+H$^+$]; HRMS: calcd for $C_{27}H_{27}NO_4S$ (461.1660), found (461.1665).

4.2.5. 2-Benzylthio-4,5-dihydro-(3′,5′-di-*O*-benzyl-1,2-dideoxy-β-D-ribofuranoso) [1,2-*d*]-oxazole 11. Eluent: petroleum ether–ethyl acetate 80/20, white solid (3.5 g; 73%); $[\alpha]_D$=+34 (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 3.62 (dd, 1H, $J_{5a,4}$=3.6 Hz, $J_{5a,5b}$=10.9 Hz, *H-5a*); 3.66–3.76(m, 1H, *H-4*); 3.80 (dd, 1H, $J_{5b,4}$=1.9 Hz, *H-5b*); 4.01 (dd, 1H, $J_{3,2}$=5.1 Hz, $J_{3,4}$=8.9 Hz, *H-3*); 4.27 (d, 1H, *J*=13.2 Hz, SCH_2-Ph); 4.34 (d, 1H, SCH_2-Ph); 4.51 (d, 1H, *J*=12.0 Hz, CH_2-Ph); 4.52 (d, 1H, *J*=11.5 Hz, CH_2-Ph); 4.82 (dd, 1H, $J_{2,3}$=$J_{2,1}$=5.3 Hz, *H-2*); 6.03 (d, 1H, *H-1*), 7.22–7.42 (m, 15H, CH_{Ar}); ^{13}C NMR ($CDCl_3$): δ 37.0 (S*C*H_2-Ph); 67.7 (*C-5*); 72.8 (*C*H_2-Ph); 73.9 (*C*H_2-Ph); 77.0 (*C-4*); 78.0 (*C-3*); 80.9 (*C-2*); 100.1 (*C-1*); 128.1; 128.1; 128.4; 128.5; 128.8; 128.9; 129.0; 129.5 (*C*H_{Ar}); 136.6; 137.7; 138.4 (*Cq*); 171.5 (*C*-S); IR (NaCl): 1605 cm^{-1} (C═N); MS IS *m*/*z*=462.0 [M+H$^+$]; 484.0 [M+Na$^+$]; HRMS: calcd for $C_{27}H_{27}NO_4S$ (461.1660), found (461.1662).

4.2.6. 1-*N*-Benzyl-3,5-di-*O*-benzyl-1-*N*,2-*O*-thiocarbonyl-β-D-ribofuranosylamine 11a. Eluent: petroleum ether–ethyl acetate 80/20, oil (1.18 g; 24%); $[\alpha]_D$=+128 (*c* 1.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 3.56 (dd, 1H, $J_{5a,4}$=3.8 Hz, $J_{5a,5b}$=11.3 Hz, *H*-5a); 3.75 (dd, 1H, $J_{5b,4}$=1.9 Hz, *H-5b*); 3.85 (ddd, 1H, $J_{4,3}$=9.1 Hz, *H-4*); 4.99 (dd, 1H, $J_{3,2}$=5.3 Hz, *H-3*); 4.42 (d, 1H, *J*=14.8 Hz, NCH_2-Ph); 4.44 (d, 1H, *J*=11.9 Hz, CH_2-Ph); 4.51 (d, 1H, *J*=11.6 Hz, CH_2-Ph); 4.53 (d, 1H, CH_2-Ph); 4.75 (d, 1H, CH_2-Ph); 4.85 (dd, 1H, $J_{2,1}$=5.3 Hz, *H-2*); 5.31 (d, 1H, NCH_2-Ph); 5.50 (d, 1H, *H-1*), 7.22–7.41 (m, 15H, CH_{Ar}); ^{13}C NMR ($CDCl_3$): δ 48.0 (N*C*H_2-Ph); 66.1 (*C-5*); 71.7 (*C*H_2-Ph); 72.6 (*C*H_2-Ph); 76.1; 76.6; 77.4 (*C-4*, *C-3*, *C-2*); 89.2 (*C-1*); 126.8; 126.9; 127.0; 127.3; 127.4; 127.5; 127.6; 127.7; 127.9 (*C*H_{Ar}); 133.7; 136.0; 136.7 (*Cq*); 187.6 (*C*═S); MS IS *m*/*z*=462,0 [M+H$^+$]; 484,0 [M+Na$^+$]; HRMS: calcd $C_{27}H_{27}NO_4S$ (461.1660), found (461.1665).

4.2.7. 2-Benzylthio-4,5-dihydro-(1′,4′,6′-tri-*O*-benzyl-2′,3′-dideoxy-β-D-fructofuranoso) [2,3-*d*]-oxazole 12. Eluent: petroleum ether–ethyl acetate 80/20, oil (0.75 g; 64%); $[\alpha]_D$=−37 (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 3.36 (dd, 1H, $J_{6a,6b}$=10.3 Hz, $J_{6a,5}$=6.1 Hz, *H*-6a); 3.47 (dd, 1H, $J_{6b,5}$=5.3 Hz, *H-6b*); 3.70 (d, 1H, $J_{1a,1b}$=10.6 Hz, *H-1a*); 3.78 (d, 1H, *H-1b*); 4.06 (dd, 1H, $J_{4,3}$=1.9 Hz, $J_{4,5}$=4.4 Hz, *H-4*); 4.20–4.34 (m, 3H, SCH_2-Ph, *H-5*); 4.45–4.65 (m, 6H, CH_2-Ph); 4.96 (d, 1H, *H-3*); 7.19–7.38 (m, 20H, CH_{Ar}); ^{13}C NMR ($CDCl_3$): δ 36.3 (S*C*H_2); 69.6 (*C-6*); 71.8; 73.4; 73.6 (*C*H_2-Ph); 72.1 (*C-1*); 82.1 (*C-5*); 84.6 (*C-4*); 89.0 (*C-3*); 110.0 (*C-2*); 127.6; 127.7; 127.8; 127.9; 128.4; 128.5; 128.6; 129.1; 136.5 (*C*H_{Ar}); 137.2; 138.0; 138.1 (*C*q_{Ar}); 168.6 (*C*-S); IR (NaCl): 1596 cm^{-1} (C═N); MS IS *m*/*z*=582.5 [M+H$^+$]; HRMS: calcd for $C_{35}H_{35}NO_5S$ (581.2235), found (581.2244).

4.2.8. 2-Benzylthio-4,5-dihydro-(1′,4′,6′-tri-*O*-benzyl-2′,3′-dideoxy-*a*-L-sorbofuranoso) [2,3-*d*]-oxazole 13. Eluent: petroleum ether–ethyl acetate 80/20, oil (0.17 g; 42%); $[\alpha]_D$=−32 (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 3.73–3.88 (m, 2H, *H-6*, *H-1*); 3.92–4.00 (m, 2H, *H-5*, *H-4*); 4.23 (d, 1H, *J*=13.2 Hz, SCH_2-Ph); 4.31 (d, 1H, SCH_2-Ph); 4.44 (d, 1H, *J*=11.9 Hz; CH_2-Ph); 4.46 (d, 1H, CH_2-Ph); 4.52–4.65 (m, 4H, CH_2-Ph); 4.83 (s, 1H, *H-3*); 7.12–7.40 (m, 20H, CH_{Ar}); ^{13}C NMR ($CDCl_3$): δ 36.5 (S*C*H_2); 67.0 (*C-6*); 71.5 (*C-1*); 71.8; 73.5; 73.7 (*C*H_2-Ph); 78.6; 81.2 (*C-4*, *C-5*); 85.7 (*C-3*); 109.4 (*C-2*); 127.6; 127.7; 127.8; 127.9; 128.3; 128.4; 128.5; 128.6; 129.1 (*C*H_{Ar}); 136.3; 137.4; 138.0; 138.2 (*C*q_{Ar}); 188.8 (*C*═S); IR (NaCl): 1600 cm^{-1} (C═N); MS IS *m*/*z*=582.5 [M+H$^+$];; HRMS: calcd for $C_{35}H_{35}NO_5S$ (581.2235), found (581.2231).

4.2.9. 2-Benzylthio-4,5-dihydro-(3′,5′-bis-*O*-(1-methoxy-1-methylethyl)-1′,2′-dideoxy-β-D-arabinofuranoso) [1,2-*d*]-oxazole 22. The sugar OZT **1** (0.1 g, 0.52 mmol) was dissolved in DMF under Ar and cooled in an ice-bath. 2-Methoxypropene (5 equiv.) then CSA (0.1 equiv.) were added. The reaction was run at room temperature for 16 h. At completion, the solution was basified with Et_3N, diluted with water, then extracted with AcOEt. The organic phases obtained were collected and washed thoroughly with water then brine. After evaporation, the residue was dissolved in DMF and after cooling in an ice bath, NaH (2 equiv.) was added portionwise then benzyl bromide (2 equiv.). The reaction was brought to room temperature and stirred until completion of the reaction (2 h). Ice-cold water was poured in then the mixture was extracted with AcOEt (3×50 mL). Organic phases were collected and washed thoroughly with water, then brine. Purification was effected by column chromatography with eluents of petroleum ether–ethyl acetate, yielding **22**; eluent: petroleum ether–ethyl acetate 95/5, oil (0.22 g; 94%); $[\alpha]_D=-115$ (*c* 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.29; 1.31; 1.37; 1.41 (4 s, 12H, $(CH_3)_2C$); 3.18; 3.22 (2 s, 6H, CH_3O); 3.22–3.32 (m, 1H, *H-5a*); 3;39 (dd, 1H, $J_{5b,4}=8.2$ Hz, $J_{5b,5a}=9.7$ Hz, *H-5b*); 4.15 (ddd, 1H, $J_{4,5a}=6.0$ Hz, *H-4*); 4.28 (s, 2H, SCH_2-Ph); 4.42 (d, 1H, $J_{3,4}=2.2$ Hz, *H-3*); 4.87 (d, 1H, $J_{2,1}=6.0$ Hz, *H-2*); 6.08 (d, 1H, *H-1*); 7.25–7.45 (m, 5H, CH_{Ar}); ^{13}C NMR ($CDCl_3$): δ 24.3; 24.4; 24.8; 25.3 ($(CH_3)_2C$); 36.4 (SCH_2-Ph); 48.7; 49.1 (CH_3O); 60.8 (*C-5*); 75.8 (*C-3*); 84.2 (*C-4*); 90.1 (*C-2*); 100.9 (*C-1*); 101.1; 101.7 (*Cq*); 127.7; 128.7; 129.1 (CH_{Ar}); 136.7 (*Cq*); 169.1 (*C*-S); IR (NaCl): 1603 cm^{-1} (C=N); MS IS *m*/*z*=426.0 $[M+H^+]$; 448.0 $[M+Na^+]$; HRMS: calcd for $C_{21}H_{31}NO_6S$ (425.1872), found (425.1876).

4.2.10. General protocol for the silylation/benzylation of sugar-OZTs. The sugar-OZT (1 equiv.) was dissolved in DMF (0.2 M) under Ar and cooled in an ice-bath. Imidazole, then TBDMSCl (1.2 equiv./OH group) were added. The reaction was kept at room temperature until completion, then extracted with AcOEt and water. The organic phases were collected and washed with water (4–5 times) and brine, then dried over $MgSO_4$. After evaporation, the silylated OZT was purified by column chromatography with petroleum ether-AcOEt solvent mixtures. The purified OZT was dissolved in DMF, cooled in an ice-bath, NaH (1.2 equiv.) was added portionwise then benzyl bromide (1.2 equiv.). The reaction was brought to room temperature and stirred until completion of the reaction (few hours). Ice-cold water was poured in then the mixture was extracted with AcOEt (3×50 mL). Organic phases were collected and washed thoroughly with water, then brine and dried over $MgSO_4$. The benzylated compounds were purified by column chromatography with eluents of petroleum ether–ethyl acetate.

4.2.11. 2-Benzylthio-4,5-dihydro-(3′,5′-di-*O*-*tert*butyldimethylsilyl-1′,2′-dideoxy-β-D-arabinofuranoso) [1,2-*d*]-oxazole 21. Eluent: petroleum ether–ethyl acetate 90/10, oil (0.23 g; 95%); $[\alpha]_D=-51$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 0.05; 0.12; 0.13; 0.15 (4s, 12H, CH_3Si); 0.90; 0.93 (2s, 18H, $(CH_3)C$); 3.33 (dd, 1H, $J_{5a,5b}=10.6$ Hz, *H-5a*); 3.61 (dd, 1H, *H-5b*); 3.97 (ddd, 1H, $J_{4,3}=2.8$ Hz, $J_{4,5a}=4.7$ Hz, $J_{4,5b}=8.5$ Hz, *H-4*); 4.29 (d, 1H, *J*=13.2 Hz, SCH_2-Ph); 4.33 (d, 1H, SCH_2-Ph); 4.42 (sl, 1H, *H-3*); 4.77 (dd, 1H, $J_{2,1}=6.0$ Hz, $J_{2,3}=1.1$ Hz, *H-2*); 6.07 (d, 1H, *H-1*); 7.23–7.42 (m, 5H, CH_{Ar}); ^{13}C NMR ($CDCl_3$): δ −5.3; −4.8 (CH_3Si); 18.1; 18.4 ($(CH_3)_3C$); 25.8; 26.0 ($(CH_3)_3C$); 36.4 (SCH_2-Ph); 62.3 (*C-5*); 76.6 (*C-3*); 86.4 (*C-4*); 91.0 (*C-2*); 100.6 (*C-1*); 127.7; 128.7; 129.1 (CH_{Ar}); 136.5 (*Cq*); 169.6 (*C*-S); IR (NaCl): 1609 cm^{-1} (C=N); MS IS *m*/*z*=510.0 $[M+H^+]$; HRMS: calcd for $C_{25}H_{43}NO_4SSi_2$ (509.2451), found (509.2458).

4.2.12. 2-Benzylthio-4,5-dihydro-(3′,5′-di-*O*-*tert*butyldimethylsilyl-1′,2′-dideoxy-α-L-arabinofuranoso) [1,2-*d*]-oxazole 24. Eluent: petroleum ether–ethyl acetate 90/10, white foam (2.42 g; 80%); $[\alpha]_D=+51$ (*c* 1.1, CH_2Cl_2); ^1H NMR ($CDCl_3$): δ −0.07; 0.02; 0.03 (3 s, 12H, CH_3Si); 0.78; 0.80 (2 s, 18H, $(CH_3)C$); 3.21 (dd, 1H, $J_{5a,5b}=10.5$ Hz, $J_{5b,4}=8.8$ Hz, *H-5b*); 3.49 (dd, 1H, $J_{5a,4}=4.9$ Hz, *H-5b*); 3.86 (m, 1H, *H-4*); 4.21 (d, 1H, *J*=13.2 Hz, SCH_2-Ph); 4.24 (d, 1H, SCH_2-Ph); 4.30 (s, 1H, *H-3*); 4.67 (d, 1H, $J_{2,1}=5.8$ Hz, *H-2*); 5.96 (d, 1H, *H-1*); 7.16–7.29 (m, 5H, CH_{Ar}); ^{13}C NMR ($CDCl_3$): δ −5.1; −4.6 (CH_3Si); 18.2; 18.5 ($(CH_3)_3C$); 25.9; 26.0; 26.1; 26.2 ($(CH_3)_3C$); 36.6 (SCH_2-Ph); 62.5 (*C-5*); 77.1 (*C-3*); 86.6 (*C-4*); 91.2 (*C-2*); 100.7 (*C-1*); 127.9; 128.9; 129.3 (CH_{Ar}); 136.9 (*Cq*); 169.8 (*C*-S); IR (NaCl): 1609 cm^{-1} (C=N); MS IS *m*/*z*=510.5 $[M+H^+]$; HRMS: calcd for $C_{25}H_{43}NO_4SSi_2$ (509.2451), found (509.2455).

4.2.13. 2-Benzylthio-4,5-dihydro-(3′,5′-di-*O*-*tert*butyldimethylsilyl-1′,2′-dideoxy-β-D-xylofuranoso) [1,2-*d*]-oxazole 25. Eluent: petroleum ether–ethyl acetate 90/10, oil (0.23 g; 95%); $[\alpha]_D=+41$ (*c* 1.1, MeOH); ^1H NMR ($CDCl_3$): δ 0.07; 0.11; 0.13 (3 s, 12H, CH_3Si); 0.91; 0.92 (2s, 18H, $(CH_3)C$); 3.55–3.77 (m, 1H, *H-4*); 3.80–3.90 (m, 2H, *H-5*); 4.25 (d, 1H, $J_{3,4}=3.0$ Hz, *H-3*); 4.32 (s, 2H, SCH_2-Ph); 4.70 (d, 1H, $J_{2,1}=5.4$ Hz, *H-2*); 6.09 (d, 1H, *H-1*); 7.20–7.35 (m, 5H, CH_{Ar}); ^{13}C NMR ($CDCl_3$): δ −4.6; −4.5; −4.3; −4.1; −3.8; −3.5 (CH_3Si); 18.1; 18.3 ($(CH_3)_3C$); 25.7; 26.0 ($(CH_3)_3C$); 36.5 (SCH_2-Ph); 59.9 (*C-5*); 74.9 (*C-3*); 79.8 (*C-4*); 88.8 (*C-2*); 99.6 (*C-1*); 127.7; 128.6; 129.0 (CH_{Ar}); 136.3 (*Cq*); 169.4 (*C*-S); IR (NaCl): 1609 cm^{-1} (C=N); MS IS *m*/*z*=510.5 $[M+H^+]$; HRMS: calcd for $C_{25}H_{43}NO_4SSi_2$ (509.2451), found (509.2452).

4.2.14. 2-Benzylthio-4,5-dihydro-(3′,5′,7′-tri-*O*-*tert*butyldimethylsilyl-1′,2′-dideoxy-β-D-glucofuranoso) [1,2-*d*]-oxazole 26. Eluent: petroleum ether–ethyl acetate 90/10, oil (0.23 g; 95%); $[\alpha]_D=+60$ (*c* 1.1, MeOH); ^1H NMR ($CDCl_3$): δ 0.09; 0.10; 0.11; 0.15; 0.17 (5s, 18H, CH_3Si); 0.88–0.93 (m, 27H, $(CH_3)C$); 3.55 (dd, 1H, $J_{4,3}=2.6$ Hz, $J_{4,5}=6.6$ Hz, *H-4*); 3.69 (dd, 1H, $J_{6a,6b}=10.9$ Hz, *H-6b*); 3.90 (dd, 1H, *H-6a*); 4.04–4.13 (m, 1H, *H-5*); 4.23 (d, 1H, SCH_2-Ph); 4.31–4.28 (m, 1H, *H-3*); 4.34 (d, 1H, SCH_2-Ph); 4.69 (d, 1H, $J_{2,1}=5.4$ Hz, *H-2*); 6.01 (d, 1H, *H-1*); 7.23–7.26 (m, 5H, CH_{Ar}); ^{13}C NMR ($CDCl_3$): δ −5.2; −5.1; −4.4; −4.2; 4.1; −3.4 (CH_3Si); 18.1; 18.3; 18.4 ($(CH_3)_3C$); 25.9; 26.1 ($(CH_3)_3C$); 36.5 (SCH_2-Ph); 65.2 (*C-6*); 71.5 (*C-5*); 75.0 (*C-3*); 80.2 (*C-4*); 87.2 (*C-2*); 99.1 (*C-1*); 127.6; 128.6; 129.0 (CH_{Ar}); 136.3 (*Cq*); 169.3 (*C*-S); MS IS *m*/*z*=654.5 $[M+H^+]$; HRMS: calcd for $C_{33}H_{51}NO_5SSi_2$ (629.3026), found (629.3031).

4.2.15. Generals protocols for cyclocondensation. *Method A*: The benzylthiooxazoline (1 equiv.) was dissolved in

ethanol, then molecular sieves 3 Å and the anthranilic acid derivative (1.3 equiv.) were added. The solution was refluxed overnight, then poured into an aqueous solution of $NaHCO_3$ (5%) and extracted with CH_2Cl_2 (3×50 mL). The organic phases were collected, washed with water, brine then dried over $MgSO_4$. The crude mixture obtained after drying in vacuo was purified by column chromatography.

Method B: The benzylthiooxazoline (1 equiv.) was dissolved in *tert*-butanol then molecular sieves 3 Å, camphorsulfonic acid (CSA) (1.1 equiv.), the anthranilic acid derivative (1.3 equiv.) were added. The solution was refluxed overnight, then poured into an aqueous solution of $NaHCO_3$ (5%) and extracted with CH_2Cl_2 (3×50 mL). The organic phases were collected, washed with water, brine then dried over $MgSO_4$. The crude mixture obtained after drying in vacuo was purified by column chromatography.

4.2.16. O^2,$O^{2'}$-Anhydro-3-(3′,5′-di-*O*-benzyl-β-D-arabinofuranosyl)-2,4-quinazolinedione 3. (Method B) Eluent: petroleum ether–ethyl acetate 70/30, yellow solid (2.62 g; 89%), mp=101–103 °C; $[\alpha]_D$=167 (*c* 0.59, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 3.33 (dd, 1H, $J_{5'a,4'}$=3.8 Hz, $J_{5'a,5'b}$=10.4 Hz, *H-5′a*); 3.76 (dd, 1H, $J_{5'b,4'}$=4.4 Hz, *H-5′b*); 4.17 (d, 1H, *J*=12.2 Hz, CH_2-Ph); 4.24 (d, 1H, CH_2-Ph); 4.38 (d, 1H, $J_{3',4'}$=2.2 Hz, *H-3′*); 4.41–4.47 (m, 1H, *H-4′*); 4.59 (d, 1H, *J*=11.6 Hz, CH_2-Ph); 4.65 (d, 1H, CH_2-Ph); 5.23 (d, 1H, $J_{2',1'}$=6.0 Hz, *H-2′*); 6.60 (d, 1H, *H-1′*), 6.68–7.07 (m, 2H, CH_{Ar}); 7.14–7.20 (m, 3H, CH_{Ar}); 7.27–7.41 (m, 6H, *H-6′*, 5×CH_{Ar}); 7.45 (dd, 1H, $J_{8,6}$=0.6 Hz, $J_{8,7}$=8.2 Hz, *H-8*); 7.64 (ddd, 1H, $J_{7,5}$=1.3 Hz, $J_{7,6}$=7.2 Hz, *H-7*); 8.31 (dd, 1H, $J_{6,5}$=8.2 Hz, *H-5*); ^{13}C NMR ($CDCl_3$): δ 69.0 (*C-5′*); 72.4; 73.4 (*C*H_2-Ph); 83.3 (*C-3′*); 85.5 (*C-4′*); 85.9 (*C-2′*); 87.7 (*C-1′*); 118.9 (*C-9*); 124.9 (*C-6*); 126.3 (*C-8*); 127.2 (*C-5*); 127.8; 127.9; 128.1; 128.3; 128.4; 128.7 (*C*H_{Ar}); 135.1 (*C-7*); 136.5; 137.1 (*Cq*); 149.1 (*C-10*); 156.7 (*C-2*) 160.2 (*C-4*); IR (NaCl): 1693 cm^{-1} (C=N); 1646 cm^{-1} (C=O); MS IS *m/z*=457.5 [M+H$^+$]; HRMS: calcd for $C_{27}H_{24}N_2O_5$ (456.1685), found (456.1690).

4.2.17. O^2,$O^{2'}$-Anhydro-3-(3′,5′-di-*O*-benzyl-α-L-arabinofuranosyl)-2,4-quinazolinedione 14. (Method A) Eluent: petroleum ether–ethyl acetate 70/30, yellow solid (79 mg; 79%); mp=101–103 °C; $[\alpha]_D$=−169 (*c* 0.55, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 3.35 (dd, 1H, $J_{5'a,4'}$=3.8 Hz, $J_{5'a,5'b}$=10.7 Hz, *H-5′a*); 3.39 (dd, 1H, $J_{5'b,4'}$=4.4 Hz, *H-5′b*); 4.19 (d, 1H, *J*=12.3 Hz, CH_2-Ph); 4.25 (d, 1H, CH_2-Ph); 4.39 (d, 1H, $J_{3',4'}$=2.2 Hz, *H-3′*); 4.43–4.48 (m, 1H, *H-4′*); 4.61 (d, 1H, *J*=11.9 Hz, CH_2-Ph); 4.67 (d, 1H, CH_2-Ph); 5.23 (d, 1H, $J_{2',1'}$=5.7 Hz, *H-2′*); 6.62 (d, 1H, *H-1′*), 6.99–7.07 (m, 2H, CH_{Ar}); 7.14–7.22 (m, 3H, CH_{Ar}); 7.28–7.42 (m, 6H, *H-6*, 5×CH_{Ar}); 7.47 (dd, 1H, $J_{8,6}$=0.9 Hz, *H-8*); 7.66 (ddd, 1H, $J_{7,5}$=$J_{7,6}$=7.2 Hz, $J_{7,5}$=1.6 Hz, *H-7*); 8,23 (dd, 1H, $J_{5,6}$=8.0 Hz, *H-5*); ^{13}C NMR ($CDCl_3$): δ 69.1 (*C-5′*); 72.5; 73.5 (*C*H_2-Ph); 83.6 (*C-3′*); 85.4 (*C-4′*); 86.0 (*C-2′*); 87.7 (*C-1′*); 119.0 (*C-9*); 125.0 (*C-6*); 126.4 (*C-8*); 127. (*C-5*); 127.9; 128.0; 128.2; 128.4; 128.5; 128.8 (*C*H_{Ar}); 135.2; 136.5 (*Cq*); 137.1 (*C-7*); 149.2 (*C-10*); 154.7 (*C-2*) 160.3 (*C-4*); IR (NaCl): 1693 cm^{-1} (C=N); 1646 cm^{-1} (C=O); MS IS *m/z*=457.0 [M+H$^+$]; HRMS: calcd for $C_{27}H_{24}N_2O_5$ (456.1685), found (456.1694).

4.2.18. O^2, $O^{2'}$-Anhydro-3-(3′,5′-di-*O*-benzyl-α-D-xylofuranosyl)-2,4-quinazolinedione 15. (Method A) Eluent: petroleum ether–ethyl acetate 50/50, yellow foam (144 mg; 75%); $[\alpha]_D$=−169 (*c* 0.55, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 3.77 (dd, 1H, $J_{5'a,4'}$=6.0 Hz, $J_{5'a,5'b}$=10.0 Hz, *H-5′a*); 3.84 (dd, 1H, $J_{5b,4}$=6.0 Hz, *H-5′b*); 4.21 (ddd, 1H, $J_{3',4'}$=3.5 Hz, *H-4′*); 4.32 (d, 1H, *H-3′*); 4.48 (d, 1H, *J*=12 Hz, CH_2-Ph); 4.55 (d, 1H, *J*=12 Hz, CH_2-Ph); 4.64 (d, 1H, *J*=12 Hz, CH_2-Ph); 4.73 (d, 1H, *J*=12 Hz, CH_2-Ph); 5.16 (d, 1H, $J_{2',1'}$=5.3 Hz, *H-2′*); 6.60 (d, 1H, *H-1′*); 7.23–7.38 (m, 11H, Ph-H, *H-6*); 7.46 -d, 1H, $J_{8,7}$=8.2 Hz, *H-8*); 7.64 (ddd, 1H, $J_{7,5}$=1.6 Hz, $J_{7,6}$=7.2 Hz, *H-7*); 8.17 (dd, 1H, $J_{5,6}$=7.8 Hz, *H-5*); ^{13}C NMR ($CDCl_3$): δ 66.8 (*C-5′*); 72.9 (*C*H_2-Ph); 73.7 (*C*H_2-Ph); 79.7 (*C-4′*); 80.4 (*C-3′*); 83.7 (*C-2′*); 86.5 (*C-1′*); 119.0 (*C-9*); 125.1 (*C-6*); 126.3 (*C-8*); 127.0 (*C-5*); 127.2; 127.9; 128.0; 128.3; 128.4; 128.7 (*C*H_{Ar}); 135.2 (*C-7*); 136.8; 137.7; 148.8 (*C-10*); 154.5 (*C-2*); 160.2 (*C-4*); IR (NaCl): 1659 cm^{-1} (C=N); 1701 cm^{-1} (C=O); MS IS *m/z*=457 [M+H$^+$]; HRMS: calcd for $C_{27}H_{24}N_2O_5$ (456.1685), found (456.1683).

4.2.19. O^2, $O^{2'}$-Anhydro-3-(3′,5′-di-*O*-benzyl-β-D-ribofuranosyl)-2,4-quinazolinedione 16. (Method A) Eluent: petroleum ether–ethyl acetate 70/30, yellow solid (1.66 g; 82%); mp=83–85 °C; $[\alpha]_D$=263 (*c* 0.55; $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 3.64 (dd, 1H, $J_{5'a,4'}$=3.2 Hz, $J_{5'a,5'b}$=11.3 Hz, *H-5′a*); 3.81 (dd, 1H, $J_{5'b,4'}$=1.9 Hz, *H-5′b*); 3.98–4.06 (m, 1H, *H-4′*); 4.24 (dd, 1H, $J_{3',2'}$=5.1 Hz, $J_{3',4'}$=8.5 Hz, *H-3′*); 4.48 (d, 1H, *J*=11.9 Hz, CH_2-Ph); 4.58 (d, 1H, CH_2-Ph); 4.63 (d, 1H, *J*=11.5 Hz, CH_2-Ph); 4.79 (d, 1H, CH_2-Ph); 5.11 (dd, 1H, $J_{2',1'}$=5.3 Hz, *H-2′*); 6.55 (d, 1H, *H-1′*), 7.24–7.42 (m, 11H, *H-6*, CH_{Ar}); 7.53 (d, 1H, $J_{8,7}$=7.7 Hz, *H-8*); 7.69 (ddd, 1H, $J_{7,5}$=1.3 Hz, $J_{7,6}$=7.2 Hz, *H-7*); 8.22 (d, 1H, $J_{5,6}$=8.0 Hz, *H-5*); ^{13}C NMR ($CDCl_3$): δ 67.1 (*C-5′*); 73.0; 73.7 (*C*H_2-Ph); 76.7 (*C-3′*); 78.6 (*C-2′*); 79.1 (*C-4′*); 86.4 (*C-1′*); 119.0 (*C-9*); 125.1 (*C-6*); 126.4 (*C-8*); 127.2 (*C-5*); 127.8; 127.9; 128.2; 128.4; 128.5; 128.6 (*C*H_{Ar}); 135.3 (*C-7′*); 136.9; 137.7 (*Cq*); 149.0 (*C-10*); 155.1 (*C-2*) 160.3 (*C-4*); IR (NaCl): 1656 cm^{-1} (C=N); 1702 cm^{-1} (C=O); MS IS *m/z*=457 [M+H$^+$]; HRMS: calcd for $C_{27}H_{24}N_2O_5$ (456.1685), found (456.1691).

4.2.20. O^2, $O^{3'}$-Anhydro-3-(1′,4′,6′-tri-*O*-benzyl-β-D-fructofuranosyl)-2,4-quinazolinedione 17. (Method B with 2 equiv. of CSA) Eluent: petroleum ether–ethyl acetate 80/20, pale yellow oil (90 mg; 57%); $[\alpha]_D$=−31 (*c* 0.74; $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 3.30 (dd, 1H, $J_{6'a,5'}$=3.6 Hz, $J_{6'a,6'b}$=10.7 Hz, *H-6′a*); 3.37 (dd, 1H, $J_{6'b,5'}$=4.2 Hz, *H-6′b*); 3.92 (d, 1H, $J_{1'a,1'b}$=10.4 Hz, *H-1′a*); 4.13 (d, 1H, *J*=12.3 Hz, CH_2-Ph); 4.19 (d, 1H, CH_2-Ph); 4.33 (dd, 1H, $J_{4,3}$=0.9 Hz, $J_{4',5'}$=2.5 Hz, *H-4′*); 4.45–4.71 (m, 6H, 2 CH_2-Ph, *H-1′b*, *H-5′*); 5.14 (s, 1H, *H-3′*); 6.95–7.03 (m, 2H, CH_{Ar}); 7.11–7.39 (m, 14H, *H-6*, CH_{Ar}); 7.43–7.50 (m, 1H, *H-8*); 7.36 (ddd, 1H, $J_{7,5}$=1.6 Hz, $J_{7,6}$=$J_{7,8}$=7.2 Hz, *H-7*); 8.20 (dd, 1H, $J_{5,6}$=8.0 Hz, *H-5*); ^{13}C NMR ($CDCl_3$): δ 68.5 (*C-6′*); 69.1 (*C-1′*); 72.2; 73.5; 73.7 (*C*H_2-Ph); 84.1 (*C-4′*); 86.3 (*C-5′*); 87.2 (*C-3′*); 100.7 (*C-2′*); 119.4 (*C-9*); 124.7 (*C-6*); 126.2 (*C-8*); 127.1 (*C-5*); 127.8; 127.9; 128.0; 128.3; 128.4; 128.5; 128.6; 128.7 (*C*H_{Ar}); 135.0 (*C-7*); 136.6; 137.1; 137.4 (*Cq*); 149.1 (*C-10*); 155.2 (*C-2*) 160.7 (*C-4*); IR (NaCl): 1695 (C=N); 1648 (C=O); MS IS *m/z*=577.5 [M+H$^+$]; HRMS: calcd for $C_{35}H_{32}N_2O_6$ (576.2260), found (576.2267).

4.2.21. *O*2³, *O* 3′-Anhydro-3-(1′,4′,6′-tri-*O*-benzyl-α-L-sorbofuranosyl)-2,4-quinazolinedione 18. (Method B with 2 equiv. of CSA) Eluent: petroleum ether–ethyl acetate 80/20, pale yellow oil (110 mg; 70%); $[\alpha]_D=-28$ (*c* 1.04; $CHCl_3$); ^1H NMR ($CDCl_3$): δ 3.40 (dd, 1H, $J_{6'a,5'}$=5.0 Hz, $J_{6'a,6'b}$=10.0 Hz, *H-6′a*); 3.79 (dd, 1H, $J_{6'b,5'}$=5.8 Hz, *H-6′b*); 3.80 (d, 1H, $J_{1'a,1'b}$=10.0 Hz, *H-1′a*); 4.19–4.27 (m, 2H, *H-4′*, *H-5′*); 4.43 (d, 1H, *J*=11.9 Hz, CH_2-Ph); 4.46 (d, 1H, *J*=12.3 Hz, CH_2-Ph); 4.47 (d, 1H, *J*=14.4 Hz, CH_2-Ph); 4.58 (d, 1H, CH_2-Ph); 4.62 (d, 1H, CH_2-Ph); 4.78 (d 1H, *H-1′b*); 5.01 (s, 1H, *H-3′*); 7.15–7.36 (m, 16H, *H-6*, CH_{Ar}); 7.49 (dd, 1H, $J_{8,6}$=0.6 Hz, $J_{8,7}$=7.9 Hz, *H-8*); 7.65 (ddd, 1H, $J_{7,5}$=1.6 Hz, *H-7*); 8.19 (dd, 1H, $J_{5,6}$=7.9 Hz, *H-5*); ^{13}C NMR ($CDCl_3$): δ 68.4 (*C-6′*); 67.7 (*C-1′*); 72.5; 73.6; 73.7 (*C*H_2-Ph); 80.4; 80.8 (*C-4′*, *C-5′*); 84.4 (*C-3′*); 99.7 (*C-2′*); 119.6 (*C-9*); 124.9 (*C-6*); 126.2 (*C-8*); 127.2 (*C-5*); 127.8; 127.9; 128.3; 128.4; 128.5; 128.7 (*C*H_{Ar}); 135.1 (*C-7*); 136.8; 137.4; 137.7 (*Cq*); 148.8 (*C-10*); 155.0 (*C-2*) 160.7 (*C-4*); IR (NaCl): 1699 (C═N); 1647 (C═O); MS IS *m*/*z*=577.5 [M+H⁺]; HRMS: calcd for $C_{35}H_{32}N_2O_6$ (576.2260), found (576.2263).

4.2.22. *O* 2′, *O* 2′-Anhydro-3-(3′,5′-di-*O*-*tert*butyldimethylsilyl-β-D-arabinofuranosyl)-2,4-quinazolinedione 23. (Method B without CSA) Eluent: petroleum ether–ethyl acetate 90/10, white solid (124 mg; 85%); mp: 111–112 °C; $[\alpha]_D=-193$ (*c* 0.45; $CHCl_3$); ^1H NMR ($CDCl_3$): δ 0.06; 0.20; 0.23 (3 s, 12H, CH_3Si); 0.80; 0.97 (2s, 18H, (CH_3)C); 3.52 (dd, 1H, $J_{5'a,4'}$=6.9 Hz, $J_{5'a,5'b}$=11 Hz, *H-5′a*); 3.67 (dd, 1H, $J_{5'b,4'}$=4.2 Hz, *H-5′b*); 4.14–4.22 (m, 1H, *H-4′*); 4.73 (dd, 1H, $J_{3',2'}$=1.3 Hz, $J_{3',4'}$=3.1 Hz, *H-3′*); 5.14 (dd, 1H, $J_{2',1'}$=5.6 Hz, *H-2′*); 6.62 (d, 1H, *H-1′*), 7.36 (ddd, 1H, $J_{6,8}$=1.2 Hz, $J_{6,5}=J_{6,7}$=7.2 Hz, *H-6*); 7.53 (dd, 1H, $J_{8,7}$= 8.2 Hz, *H-8*); 7.70 (ddd, 1H, $J_{7,5}$=1.5 Hz, *H-7*); 8.23 (dd, 1H, *H-5*); ^{13}C NMR ($CDCl_3$): δ −5.5; −5.4; −4.8; −4.7 (CH_3Si); 18.0; 18.2 ((CH_3)$_3$*C*); 25.7; 25.8 ((*C*H$_3$)$_3$C); 61.8 (*C-5′*); 75.9 (*C-3′*); 86.7 (*C-1′*); 88.4 (*C-2′*); 88.8 (*C-4′*); 118.9 (*C-9*); 125.1 (*C-6*); 126.4 (*C-8*); 127.2 (*C-5*); 135.2 (*C-7*); 149.0 (*C-10*); 154.2 (*C-2*) 160.1 (*C-4*); IR (NaCl): 1698 (C═N); 1647 (C═O); MS IS *m*/*z*=505.5 [M+H⁺]; HRMS: calcd for $C_{25}H_{40}N_2O_5Si_2$ (504.2475), found (504.2486).

4.2.23. *O* 2′, *O* 2′-Anhydro-3-(3′,5′-di-*O*-*tert*butyldimethylsilyl-β-L-arabinofuranosyl)-2,4-quinazolinedione 27. (Method B without CSA) Eluent: petroleum ether–ethyl acetate 90/10, white gum (82 mg; 85%); $[\alpha]_D=+144$ (*c* 1.0; CH_2Cl_2); ^1H NMR ($CDCl_3$): δ 0.06; 0.12; 0.32; 0.36 (4s, 12H, CH_3Si); 0.93; 1.10 (2s, 18H, (CH_3)C); 3.60–3.82 (m, 2H, *H-5′*); 4.27–4.39 (m, 1H, *H-4′*); 4.86 (d, 1H, $J_{3',4'}$=2.2 Hz, *H-3′*); 5.26 (d, 1H, $J_{2',1'}$=6.3 Hz, *H-2′*); 6.75 (d, 1H, *H-1′*), 7.47 (dd, 1H, $J_{6,5}=J_{6,7}$=7.8 Hz, *H-6*); 7.64 (d, 1H, $J_{8,7}$=8.0 Hz, *H-8*); 7.82 (dd, 1H, *H-7*); 8.34 (dd, 1H, *H-5*); ^{13}C NMR ($CDCl_3$): δ −5.5; −5.2; −4.6; −4.5 (CH_3Si); 18.2; 18.4 ((CH$_3$)$_3$*C*); 25.9 ((*C*H$_3$)$_3$C); 62.0 (*C-5′*); 76.1 (*C-3′*); 86.6 (*C-4′*); 88.6 (*C-2′*); 88.9 (*C-1′*); 123.7 (*C-9*); 126.1 (*C-6*); 127.8 (*C-8*); 129.4 (*C-5*); 130.8 (*C-7*); 137.5 (*C-10*); 143.5 (*C-2*) 160.9 (*C-4*); MS IS *m*/*z*=505.5 [M+H⁺]; HRMS: calcd for $C_{25}H_{40}N_2O_5Si_2$ (504.2475), found (504.2482).

4.2.24. *O* 2′, *O* 2′-Anhydro-3-(3′,5′-di-*O*-*tert*butyldimethylsilyl-β-D-xylofuraosyl-2,4-quinazolinedione 28. (Method B without CSA) Eluent: petroleum ether–ethyl acetate 90/10, white solid (124 mg; 99%); mp: 69–71 °C; $[\alpha]_D=+133$ (*c* 1.1; CH_2Cl_2); ^1H NMR ($CDCl_3$): δ 0.04; 0.06; 0.19; 0.22 (4s, 12H, CH_3Si); 0.88; 0.96 (2s, 18H, (CH_3)C); 3.82–3.92 (m, 1H, *H-5′*); 3.97–3.99 (m, 1H, *H-4′*); 4.55 (dd, 1H, $J_{3',2'}$=1.3 Hz, $J_{3',4'}$=3.2 Hz, *H-3′*); 5.04 (d, 1H, $J_{2',1'}$= 5.2 Hz, *H-2′*); 6.60 (d, 1H, *H-1′*), 7.30 (dd, 1H, $J_{6,5}=J_{6,7}$=8.0 Hz, *H-6*); 7.47 (d, 1H, $J_{8,7}$=8.2 Hz, *H-8*); 7.62 (dd, 1H, *H-7*); 8.23 (dd, 1H, *H-5*); ^{13}C NMR ($CDCl_3$): δ −5.5; −5.4; −4.8 (CH_3Si); 18.0; 18.2((CH$_3$)$_3$*C*); 25.7; 25.8 ((*C*H$_3$)$_3$C); 59.3 (*C-5′*); 74.0 (*C-3′*); 81.8 (*C-4′*); 86.2 (*C-2′*); 86.3 (*C-1′*); 118.9 (*C-9*); 124.9 (*C-6*); 126.2 (*C-8*); 127.0 (*C-5*); 135.0 (*C-7*); 148.8 (*C*-10); 154.2 (*C-2*); 160.1 (*C*-4); IR (NaCl): 1696 (C═N); 1651 (C═O); MS IS *m*/*z*=505.5 [M+H⁺]; HRMS: calcd for $C_{25}H_{40}N_2O_5Si_2$ (504.2475), found (504.2483).

4.2.25. *O* 2′, *O* 2′-Anhydro-3-(3′,5′,6′-tri-*O*-*tert*butyldimethylsilyl-β-D-glucofuranosyl)-2,4-quinazolinedione 29. (Method B without CSA) Eluent: petroleum ether–ethyl acetate 90/10, white solid (85 mg; 59%); mp: 71–74 °C; $[\alpha]_D=+140$ (*c* 1.0; CH_2Cl_2); ^1H NMR ($CDCl_3$): δ −0.11; −0.04; 0.06; 0.08; 0.18; 0.21 (6s, 18H, CH_3Si); 0.62; 0.84; 0.93 (3s, 27H, (CH_3)C); 3.82–3.92 (m, 2H, *H-6′*); 3.96 (dd, 1H, $J_{5',4'}$=4.2 Hz, *H-4′*); 4.06–4.09 (m, 1H, *H-5′*); 4.55 (d, 1H, $J_{3',4'}$=2.4 Hz, *H-3′*); 5.02 (d, 1H, $J_{2',1'}$=4.8 Hz, *H-2′*); 6.56 (d, 1H, *H-1′*), 7.33 (ddd, 1H, $J_{6,8}$=1.0 Hz, $J_{6,5}=J_{6,7}$=8.1 Hz, *H-6*); 7.50 (d, 1H, $J_{8,7}$=7.7 Hz, *H-8*); 7.64 (ddd, 1H, $J_{7,5}$=1.6 Hz, *H-7*); 8.20 (dd, 1H, *H-5*); ^{13}C NMR ($CDCl_3$): δ −5.8; −5.7; −4.3; −4.1; −4.0; −3.3 (CH_3Si); 18.1; 18.3 ((CH$_3$)$_3$*C*); 25.7; 25.8; 26.0 ((*C*H$_3$)$_3$C); 64.1 (*C-6′*); 70.7 (*C-5′*); 74.3 (*C-3′*); 81.7 (*C-4′*); 85.5 (*C-2′*); 86.0 (*C-1′*); 119.2 (*C-9*); 125.2 (*C-6*); 126.4 (*C-8*); 127.2 (*C-5*); 135.2 (*C-7*); 148.9 (*C-10*); 154.8 (*C-2*) 160.2 (*C-4*); IR (NaCl): 1701 (C═N); 1647 (C═O); MS IS *m*/*z*=505.5 [M+H⁺]; HRMS: calcd for $C_{32}H_{56}N_2O_6Si_3$ (648.3446), found (648.3457).

4.2.26. O², O²′-Anhydro-3-(3′,5′-di-*O*-benzyl-β-D-arabinofuranosyl)-6-methyl-2,4-quinazolinedione 30. (Method B) Eluent: petroleum ether–ethyl acetate 70/30, white solid (89 mg; 92%); mp: 125–128 °C; $[\alpha]_D=98$ (*c* 1; $CHCl_3$); ^1H NMR ($CDCl_3$): δ 2.41 (s, 3H, CH_3); 3.35 (d, 2H, $J_{5'a,5'b}$=4.4 Hz, *H-5′*); 4.18 (d, 1H, *J*=12.2 Hz, CH_2-Ph); 4.25 (d, 1H, CH_2-Ph); 4.37 (d, 1H, $J_{3',4'}$=2.2 Hz, *H-3′*); 4.40–4.47 (m, 1H, *H-4′*); 4.59 (d, 1H, *J*=11.9 Hz, CH_2-Ph); 4.64 (d, 1H, CH_2-Ph); 5,21 (d, 1H, $J_{2',1'}$=6.0 Hz, *H-2′*); 6.59 (d, 1H, *H-1′*), 6.69–7.08 (m, 2H, CH_{Ar}); 7.13–7.22 (m, 3H, CH_{Ar}); 7.27–7.41 (m, 6H, *H-8*, CH_{Ar}); 7.46 (dd, 1H, $J_{7,5}$=2.0 Hz, $J_{7,8}$=8.7 Hz, *H-7*); 7.98 (s, 1H, *H-5*); ^{13}C NMR ($CDCl_3$): 21.0 (*C*H$_3$); 69.0 (*C-5′*); 72.4; 73.4 (*C*H$_2$-Ph); 83.5 (*C-3′*); 85.2 (*C-4′*); 85.8 (*C-2′*); 87.6 (*C-1′*); 118.6 (*C-9*); 126.1 (*C-8*); 126.7 (*C-5*); 126.8; 126.9; 128.0; 128.3; 128.7 (*C*H$_{Ar}$); 134.9 (*C-7*); 136.4; 136.5 (*Cq*); 137.2 (*C-6*); 146.9 (*C-10*); 154.2 (*C-2*); 160.2 (*C-4*); IR (KBr): 1686 (C═N); 1643 (C═O); MS IS *m*/*z*=471.5 [M+H⁺], 493.5 [M+Na⁺]; HRMS: calcd for $C_{28}H_{26}N_2O_5$ (470.1841), found (470.1848).

4.2.27. *O* 2′, *O* 2′-Anhydro-3-(3′,5′-di-*O*-benzyl-β-D-arabinofuranosyl)-7-chloro-2,4-quinazolinedione 31. (Method B) Eluent: petroleum ether–ethyl acetate 90/10, white solid (91 mg; 86%); mp: 96–98 °C; $[\alpha]_D=-128$ (*c* 1; $CHCl_3$); ^1H

NMR ($CDCl_3$): δ 3.33 (dd, 1H, $J_{5'a,4'}$=3.3 Hz, $J_{5'a,5'b}$=10.5 Hz, *H-5'a*); 3.40 (dd, 1H, $J_{5'b,4'}$=3.9 Hz, *H-5'b*); 4.15 (d, 1H, *J*=12.2 Hz, CH_2-Ph); 4.22 (d, 1H, CH_2-Ph); 4.37 (d, 1H, $J_{3',4'}$=1.9 Hz, *H-3'*); 4.41–4.49 (m, 1H, *H-4'*); 4.59 (d, 1H, *J*=11.6 Hz, CH_2-Ph); 4.65 (d, 1H, CH_2-Ph); 5.24 (d, 1H, $J_{2,1}$=6.0 Hz, *H-2'*); 6.59 (d, 1H, *H-1'*), 6.96–7.05 (m, 2H, *H-6*, *H-8*); 7.12–7.43 (m, 10H, CH_{Ar}); 8.10 (d, 1H, $J_{5,6}$=8.5 Hz, *H-5*); ^{13}C NMR ($CDCl_3$): δ 69.1 (*C-5*); 72.5; 73.5 (*C*H_2-Ph); 83.7 (*C-3'*); 85.7 (*C-4'*); 86.1 (*C-2'*); 87.8 (*C-1'*); 117.4 (*C-9*); 125.4 (*C-6*); 126.0 (*C-8*); 127.8; 127.9; 128.1; 128.3; 128.4; 128.8 (*C-5*, *C*H_{Ar}); 136.4; 136.9 (*Cq*); 141.2 (*C-7*); 150.2 (*C-10*); 155.5 (*C-2*) 159.6 (*C-4*); IR (KBr): 1687 (C=N); 1647 (C=O); MS IS *m/z*=491 [M+H^+], 513 [M+Na^+]; HRMS: calcd for $C_{27}H_{23}ClN_2O_5$ (490.1295), found (490.1302).

4.2.28. O^2, O$^{2'}$-Anhydro-3-(3',5'-di-*O*-benzyl-β-D-arabinofuranosyl)-6-bromo-2,4-quinazolinedione 32. (Method B) Eluent: petroleum ether–ethyl acetate 90/10, white solid (109 mg; 94%); mp: 75–77 °C; $[\alpha]_D$=−167 (*c* 1.0; $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 3.24 (dd, 1H, $J_{5'a,4'}$=3.4 Hz, $J_{5'a,5'b}$=10.4 Hz, *H-5'a*); 3.30 (dd, 1H, $J_{5'b,4'}$=4.2 Hz, *H-5'b*); 4.06 (d, 1H, *J*=12.6 Hz, CH_2-Ph); 4.13 (d, 1H, CH_2-Ph); 4.28 (d, 1H, $J_{3',4'}$=1.7 Hz, *H-3'*); 4.32–4.40 (m, 1H, *H-4'*); 4.50 (d, 1H, *J*=11.6 Hz, CH_2-Ph); 4.56 (d, 1H, CH_2-Ph); 5.15 (d, 1H, $J_{2',1'}$=6.0 Hz, *H-2'*); 6,50 (d, 1H, *H-1'*), 6.88–7.33 (m, 11H, *H-8*, CH_{Ar}); 7.60 (dd, 1H, $J_{7,5}$=2.3 Hz, $J_{7,8}$=8.7 Hz, *H-7*); 8.21 (d, 1H, *H-5*); ^{13}C NMR ($CDCl_3$): δ 69.0 (*C-5'*); 72.5; 73,4 (*C*H_2-Ph); 83.6 (*C-3'*); 85.7 (*C-4'*); 86.1 (*C-2'*); 87.8 (*C-1'*); 118.0 (*C-9*); 120.5 (*C-6*); 127.8; 127.9; 128.0; 128.1; 128.4; 128.5; 128.7; 128.8 (*C-8*, *C*H_{Ar}); 129.6 (*C-5*); 136.4; 136.9 (*Cq*); 138.1 (*C-7*); 148.0 (*C-10*); 155.5 (*C-2*) 159.0 (*C-4*); IR (NaCl): 1694 (C=N); 1649 (C=O); MS IS *m/z*=537 [M+H^+]; 559 [M+Na^+]; HRMS: calcd for $C_{27}H_{23}BrN_2O_5$ (534.0790), found (534.0796).

4.2.29. *O*^{2}, *O*$^{2'}$-Anhydro-3-(3',5'-di-*O*-benzyl-β-D-arabinofuranosyl)-6-iodo-2,4-quinazolinedione 33. (Method B) Eluent: petroleum ether–ethyl acetate 70/30, white solid (98 mg; 78%); mp: 90–93 °C; $[\alpha]_D$=−173 (*c* 0.85; $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 3.32 (dd, 1H, $J_{5'a,4'}$=3.5 Hz, $J_{5'a,5'b}$=10.4 Hz, *H-5'a*); 3.38 (dd, 1H, $J_{5'b,4'}$=4.1 Hz, *H-5'b*); 4.14 (d, 1H, *J*=12.2 Hz, CH_2-Ph); 4,21 (d, 1H, CH_2-Ph); 4.36 (d, 1H, $J_{3',4'}$=2.2 Hz, *H-3'*); 4.41–4.48 (m, 1H, *H-4'*); 4.58 (d, 1H, *J*=11.9 Hz, CH_2-Ph); 4.64 (d, 1H, CH_2-Ph); 5.24 (d, 1H, $J_{2',1'}$=6.0 Hz, *H-2'*); 6.28 (d, 1H, *H-1'*), 6.96–7.04 (m, 2H, CH_{Ar}); 7.13–7.23 (m, 4H, *H-8*, CH_{Ar}); 7.26–7.40 (m, 5H, CH_{Ar}); 7.86 (dd, 1H, $J_{7,5}$=2.2 Hz, $J_{7,8}$=8.5 Hz, *H-7*); 8.48 (d, 1H, *H-5*); ^{13}C NMR ($CDCl_3$): δ 69.0 (*C-5'*); 72.5; 73.4 (*C*H_2-Ph); 83.6 (*C-3'*); 85.6 (*C-4'*); 86.1 (*C-2'*); 87.8 (*C-1'*); 88.3 (*C-6*); 120.8 (*C-9*); 127.8; 127.9; 128.1; 128.2; 128.3; 128.4; 128.7 (*C-8*, *C*H_{Ar}); 135.7 (*C-5*); 136.4; 136.9 (*Cq*); 143.6 (*C-7*); 148.5 (*C-10*); 155.1 (*C-2*) 158.8 (*C-4*); IR (KBr): 1691 (C=N); 1650 (C=O); MS IS *m/z*=583 [M+H^+], 605 [M+Na^+]; HRMS: calcd for $C_{27}H_{23}IN_2O_5$ (656.9623), found (656.9619).

4.2.30. *O*^{2}, *O*$^{2'}$-Anhydro-3-(3',5'-di-*O*-benzyl-β-D-arabinofuranosyl)-5,6-naphtyl-2,4-pyrimidinedione 34. (Method B) Eluent: CH_2Cl_2-MeOH 98/2, pale yellow solid (71 mg; 65%); mp: 97–100 °C; $[\alpha]_D$=−147 (*c* 0.64; $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 3.36 (dd, 1H, $J_{5'a,4'}$=3.6 Hz, $J_{5'a,5'b}$=10.4 Hz, *H-5'a*); 3.41 (dd, 1H, $J_{5'b,4'}$=4.4 Hz, *H-5'b*); 4.16 (d, 1H, *J*=12.3 Hz, CH_2-Ph); 4.25 (d, 1H, CH_2-Ph); 4.40 (d, 1H, $J_{3',4'}$=2.2 Hz, *H-3'*); 4.44–4.50 (m, 1H, *H-4'*); 4,62 (d, 1H, *J*=11.9 Hz, CH_2-Ph); 4.68 (d, 1H, CH_2-Ph); 5.25 (d, 1H, $J_{2,1}$=5.6 Hz, *H-2'*); 6.65 (d, 1H, *H-1'*), 6.99–7.06 (m, 2H, CH_{Ar}); 7.09–7.16 (m, 3H, CH_{Ar}); 7.29–7.43 (m, 5H, CH_{Ar}); 7.48 (ddd, 1H, $J_{8,6}$=1.3 Hz, $J_{8,7}$=6.6 Hz, $J_{8,9}$=8.2 Hz, *H-8*); 7.57 (ddd, 1H, $J_{7,9}$=1.3 Hz, $J_{7,6}$=6.6 Hz, *H-7*); 7.84–7.92 (m, 2H, *H-9*, *H-10*); 8.00 (d, 1H, *H-6*); 8.83 (s, 1H, *H-5*); ^{13}C NMR ($CDCl_3$): δ 69.1 (*C-5'*); 72.5; 73.5 (*C*H_2-Ph); 83.6 (*C-3'*); 85.4 (*C-4'*); 85.9 (*C-2'*); 87.5 (*C-1'*); 118.2 (*C-11*); 123.3 (*C-10*); 125.9 (*C-8*); 127.6 (*C-9*); 127.8; 127.9; 128.2; 128.4; 128.5; 128.8 (*C*H_{Ar}); 128.9 (*C-7*); 129.1 (*C-5*); 129.5 (*C-6*); 130.4 (*C-13*); 136.5 (*C-14*); 137.1; 137.3 (*Cq*); 143.5 (*C-12*); 154.0 (*C-2*) 160.8 (*C-4*); IR (KBr): 1690 (C=N); 1650 (C=O); MS IS *m/z*=507.5 [M+H^+], 529.5 [M+Na^+]; HRMS: calcd for $C_{31}H_{26}N_2O_5$ (506.1841), found (506.1843).

4.2.31. 3-(3',5'-Di-*O*-benzyl-β-D-arabinosyl)-2,4-quinazolinedione 35. The anhydro-nucleoside **3** (0.5 g; 1.1 mmol) dissolved in EtOH (40 mL) and HCl (2 M, 10 mL) was heated at 50 °C for 4 days. Ethanol was removed in vacuo then extraction with ethyl acetate - 5% aqueous solution of $NaHCO_3$ was performed. The organic fractions were collected and washed with H_2O then dried over $MgSO_4$. After evaporation, the residue was purified on column chromatography with petroleum ether–ethyl acetate (6/4). Compound **35** was isolated as a white solid (390 mg; 76%), mp: 90–92 °C; $[\alpha]_D$=−77 (*c* 0.59; $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 3.53 (d, 1H, $J_{OH,2'}$=11.0 Hz, O*H-2'*); 3.74 (dd, 1H, $J_{5'a,4'}$=3.1 Hz, $J_{5'a,5'b}$=10.4 Hz, *H-5'a*); 3.88 (dd, 1H, $J_{5'b,4'}$=7.5 Hz, *H-5'b*); 4.06–4.17 (m, 1H, *H-4'*); 4.29 (d, 1H, $J_{3',2'}$=5.7 Hz, $J_{3',4'}$=7.5 Hz, *H-3'*); 4.54 (d, 1H, *J*=11.9 Hz, CH_2-Ph); 4.60 (d, 1H, CH_2-Ph); 4.62–4.75 (m, 2H, *H-2'*, CH_2-Ph); 4.85 (d, 1H, *J*=11.9 Hz, CH_2-Ph); 6.79 (d, 1H, $J_{1',2'}$=7.9 Hz, *H-1'*), 6.95 (d, 1H, $J_{8,7}$=8.2 Hz, *H-8*); 7.08–7.39 (m, 11H, *H-6*, CH_{Ar}); 7.50 (ddd, 1H, $J_{7,5}$=1.3 Hz, $J_{7,6}$=8.5 Hz, *H-7*); 7.90 (dd, 1H, $J_{5,6}$=8.2 Hz, *H-5*); 9.75 (s, 1H, N*H*); ^{13}C NMR ($CDCl_3$): δ 70.9 (*C-5'*); 72.3; 73.3 (*C*H_2-Ph); 79.1 (*C-2'*); 79.2 (*C-4'*); 82.1 (*C-1'*); 85.9 (*C-3'*); 114.6 (*C-9*); 115.2 (*C-8*); 123.7 (*C-6*); 127.7; 127.8; 127.9; 128.0; 128.4; 128.6 (*C-5*, *C*H_{Ar}); 135.6 (*C-7*); 138.0; 138.1 (*Cq*); 138.4 (*C-10*); 152.0 (*C-2*); 163.2 (*C-4*); IR (KBr): 1661 (C=O); 1724 (C=O); MS IS *m/z*=475.5 [M+H^+], 497.5 [M+Na^+]; HRMS: calcd for $C_{27}H_{26}N_2O_6$ (474.1791), found (474.1789).

4.2.32. 3-β-D-Arabinosyl-2,4-quinazolinedione 36. The benzylated compound **35** (0.21 g; 0.44 mmol) was dissolved in acetic acid (5 mL) containing Pd/C 10% (0.2 g) and stirred overnight under hydrogen pressure at room temperature. The solution was filtered over Celite®, evaporated to give pure **36** (96 mg, 74%), mp: 178–183 °C; $[\alpha]_D$=27 (*c* 1.0; pyridine); ^{1}H NMR ($CDCl_3$): δ 3.55–3.68 (m, 3H, *H-4'*, *H-5'*); 4.18–4.28 (m, 2H, *H-2'*, *H-3'*); 6.55 (d, 1H, $J_{1',2'}$=7.5 Hz, *H-1'*); 7.08–7.22 (m, 2H, *H-6*, *H-8*); 7.59 (ddd, 1H, $J_{7,5}$=1.5 Hz, $J_{7,6}$=$J_{7,8}$=8.0 Hz, *H-7*); 7.85 (d, 1H, $J_{5,6}$=8.0 Hz, *H-5*);; ^{13}C NMR ($CDCl_3$): δ 62.1 (*C-5'*); 76.2 (*C-2'*); 76.9 (*C-3'*); 81.4 (*C-1'*); 83.1 (*C-4'*); 114.2 (*C-9*); 115.4 (*C-8*); 122.8 (*C-6*); 127.8 (*C-5*); 135.5 (*C-7*); 139.9 (*C-10*); 150.4 (*C-2*); 162.5 (*C-4*); IR (KBr): 1688 (C=O); 1744 (C=O); MS IS *m/z*=295 [M+H^+], 317 [M+Na^+];

HRMS: calcd for $C_{13}H_{14}N_2O_6$ (294.0852), found (294.0854); calcd for $C_{13}H_{14}N_2O_6$ (H 4.80, C 53.06, N 9.52), found (H 4.85, C 52.64, N 9.45).

4.2.33. 3-(3′,5′-Di-*O*-benzyl-β-D-ribosyl)-2,4-quinazolinedione 37. Compound **35** (136 mg; 0.29 mmol) was dissolved in CH_2Cl_2 (2 mL) then pyridine (162 μl; 2.01 mmol) and DMAP (4 mg; 0.03 mmol) were added. The solution was cooled to -78 °C, then triflic anhydride (218 μl, 0,86 mmol) was slowly added. The reaction was slowly brought to room temperature and stirred 1 h more. After treatment with water, the mixture was extracted twice with CH_2Cl_2. The organic phases collected were washed with aqueous solution of $NaHCO_3$ (5%), then water, and dried over $MgSO_4$. The solvent was removed. The crude residue was dissolved in DMF (1 mL), then sodium nitrite (91 mg, 1.32 mmol) was added. The solution was stirred overnight at room temperature. After hydrolysis with HCl 1 M (2.5 mL), extraction was performed with CH_2Cl_2. Collected organic phases were neutralized (5% $NaHCO_3$ aqueous solution) then washed with water and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified on silica gel to yield compound **37** (60 mg; 48%) as a white solid; mp: 61–64 °C; $[\alpha]_D=-112$ (*c* 0.5; $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 3.22 (d, 1H, $J_{OH,2'}$=4.1 Hz, O*H*-2′); 3.75 (d, 2H, $J_{5'a,5'b}$=5.0 Hz, *H*-5′); 4.21 (ddd, 1H, $J_{4',3'}$=7.2 Hz, *H*-4′); 4.53–4.68 (m, 5H, *H*-3′, CH_2-Ph); 4.79 (ddd, 1H, $J_{2',1'}$=2.5 Hz, $J_{2',3'}$=6.3 Hz, *H*-2′); 6,53 (d, 1H, *H*-1′), 7.02 (d, 1H, $J_{8,7}$=7.9 Hz, *H*-8); 7.13 (ddd, 1H, $J_{6,8}$=0.9 Hz, $J_{6,5}=J_{6,7}$=7.9 Hz, *H*-6); 7.22–7.37 (m, 10H, CH_{Ar}); 7.49 (ddd, 1H, $J_{7,5}$=1.3 Hz, *H*-7); 7.97 (dd, 1H, *H*-5); 10.37 (sl, 1H, N*H*); ^{13}C NMR ($CDCl_3$): δ 70.4 (*C*-5′); 71.4 (*C*-2′); 73.4; 73.5 (*C*H_2-Ph); 78.8 (*C*-3′); 80.9 (*C*-4′); 89.5 (*C*-1′); 114.8 (*C*-9); 115.3 (*C*-8); 123.5 (*C*-6); 127.7; 127.8; 128.2; 128.4; 128.8 (*C*-5, *C*H_{Ar}); 135.4 (*C*-7); 137.2; 138.1; 138.7 (*C*-10, *Cq*); 151.7 (*C*-2); 162.0 (*C*-4); IR (KBr): 1667 (C═O); 1723 (C═O); MS IS *m*/*z*=475.5 [M+H$^+$], 497.5 [M+Na$^+$]; HRMS: calcd for $C_{27}H_{26}N_2O_6$ (474.1791), found (474.1797).

4.2.34. 3-β-D-Ribosyl-2,4-quinazolinedione 38. The benzylated compound **37** (95 mg; 0.2 mmol) was dissolved in CH_3OH (5 mL) containing Pd/C 10% (0.1 g) and stirred overnight under hydrogen pressure at room temperature. The solution was filtered over Celite®, and purified by silica gel chromatography to give pure **38** (53 mg, 90%); mp: 220–222 °C; $[\alpha]_D=-124$ (*c* 1; DMSO); ^{1}H NMR ($CDCl_3$): δ 3.39–3.52 (m, 1H, *H*-5′*a*); 3.58–3.77 (m, 2H, *H*-4′, *H*-5′*b*); 4.17 (dd, 1H, $J_{3',2'}$=6.0 Hz, $J_{3',4'}$=6.3 Hz, *H*-3′); 4.48–4.68 (m, 2H, *H*-2′, O*H*-5′); 4.89 (d, 1H, $J_{OH,3'}$=6.6 Hz, O*H*-3′); 5.07 (d, 1H, $J_{OH,2'}$=4.7 Hz, O*H*-2′); 6.20 (d, 1H, $J_{1',2'}$=3.6 Hz, *H*-1′); 7.10–7.30 (m, 2H, *H*-6, *H*-8); 7.66 (ddd, 1H, $J_{7,5}$=1.3 Hz, $J_{7,6}$=8.5 Hz, $J_{7,8}$=8.2 Hz, *H*-7); 7.93 (d, 1*H*, $J_{5,6}$=7.5 Hz, *H*-5), 11.45 (sl, 1H, N*H*); ^{13}C NMR ($CDCl_3$): δ 62.4 (*C*-5′); 70.2 (*C*-3′); 71.1 (*C*-2′); 84.4 (*C*-4′); 88.1 (*C*-1′); 113.8 (*C*-9); 115.1 (*C*-8); 122,8 (*C*-6); 127.7 (*C*-5); 135.5 (*C*-7); 139.5 (*C*-10); 149.8 (*C*-2); 162.0 (*C*-4); IR (KBr): 1664 (C═O); 1724 (C═O); MS IS *m*/*z*=317 [M+Na$^+$]; HRMS: calcd for $C_{13}H_{14}N_2O_6$ (294.0852), found (294.0853); calcd for $C_{13}H_{14}N_2O_6$ (H 4.80, C 53.06, N 9.52), found (H 4.96, C 53.03, N 9.34).

4.2.35. 3-(3′,5′-Di-*O*-benzyl-2′-*O*-phenoxythiocarbonyl-β-D-arabinosyl)-2,4-quinazolinedione 39. Compound **35** (0.3 g; 0.63 mmol) was dissolved in CH_2Cl_2; DMAP (0.17 g, 1.38 mmol) then phenyl chlorothionoformiate (0.194 mL; 1.38 mmol) were added successively. The mixture was stirred overnight at room temperature, then NaOH (1 M) was added and extraction was performed with CH_2Cl_2. The collected organic phases were washed with HCl 1 M, water and finally dried over $MgSO_4$. After solvent removal, column chromatography purification (petroleum ether/AcOEt 6/4) afforded compound **39** (0.33 g, 85%) as a colourless gum; $[\alpha]_D=-17$ (*c* 1.0; $CDCl_3$); ^{1}H NMR ($CDCl_3$): δ 3.84 (dd, 1H, $J_{5'b,4'}$=3.1 Hz, $J_{5'b,5'a}$=10.4 Hz, *H*-5′*b*); 4.01 (dd, 1H, $J_{5'a,4'}$=7.9 Hz, *H*-5′*a*); 4.25–4.35 (m, 1H, *H*-4′); 4.53 (d, 1H, J_{gem}=11.9 Hz, CH_2-Ph); 4.62 (d, 1H, CH_2-Ph); 4.66 (d, 1H, J_{gem}=11.6 Hz, CH_2-Ph); 4.73 (d, 1H, CH_2-Ph); 4.96 (dd, 1H, $J_{3',2'}$=6.6 Hz, $J_{3',4'}$=7.9 Hz, *H*-3′); 6.10 (dd, 1H, $J_{2',1'}$=8.2 Hz, *H*-2′); 6.57–6.65 (m, 2H, CH_{Ar}); 6.90–7.40 (m, 16H, *H*-1′, *H*-6, *H*-8, CH_{Ar}); 7.51 (ddd, 1H, $J_{7,6}=J_{7,8}=J_{5,6}$=8.2 Hz, *H*-7); 8.04 (dd, 1H, $J_{5,7}$=1.3 Hz, *H*-5); 10.43 (s, 1H, N*H*); ^{13}C NMR ($CDCl_3$): δ 71.0 (*C*-5′); 73.1; 73.4 (*C*H_2-Ph); 79.6 (*C*-1′); 79.8 (*C*-4′); 82.4 (*C*-3′); 86.9 (*C*-2′); 114.6 (*C*-9); 115.2 (*C*-8); 121.3 (*C*H_{Ar}); 123.7 (*C*-6); 126.7; 127.9; 128.0; 128.1; 128.4; 128.6; 128.8; 129.6 (*C*-5′,*C*H_{Ar}); 135.6 (*C*-7); 137.7; 138.0; 138.5 (*Cq*); 151.4 (*C*-10); 153.1 (*C*-2); 161.6 (*C*-4); 193.7 (*C*═S); IR (KBr): 1225 (C═S); 1649 (C═O); 1730 (C═O); MS IS *m*/*z*=611,5 [M+H$^+$]; 633,5 [M+Na$^+$]; HRMS: calcd for $C_{34}H_{30}N_2O_7S$ (610.1774), found (610.1776).

4.2.36. 3-(3′,5′-Di-*O*-benzyl-2′-deoxy-β-D-ribofuranosyl)-2,4-quinazolinedione 40. Compound **39** (0.137 g; 0.29 mmol) dissolved in toluene (2 mL) was reacted with Bu_3SnH (80 μL; 0.3 mmol) and a catalytic amount of AIBN (0.1 equiv.) under reflux for 3 h. After toluene removal, the residue was dissolved in pentane (10 mL) then washed three times with acetonitrile (3×10 mL). The collected phases were washed twice with pentane, then evaporated and the residue was purified by column chromatography (petroleum ether/AcOEt 6/4) to yield **40** (63 mg; 62%) as a white gum; $[\alpha]_D=-29$ (*c* 0.8; $CDCl_3$); ^{1}H NMR ($CDCl_3$): δ 2.36 (ddd, 1H, $J_{2'b,3'}$=5.3 Hz, $J_{2'b,1'}$=9.0 Hz, $J_{2'a,2'b}$=13.4 Hz, *H*-2′*b*); 2.95 (ddd, 1H, $J_{2'a,1'}$=4.3 Hz, $J_{2'a,3'}$=7.9 Hz, *H*-2′*a*); 3.79 (dd, 1H, $J_{5'b,4'}$=4.9 Hz, $J_{5'b,5'a}$=10.2 Hz, *H*-5′*b*); 3.85 (dd, 1H, $J_{5'a,4'}$=7.0 Hz, *H*-5′*a*); 4.23–4.33 (m, 1H, *H*-4′); 4.47–4.69 (m, 5H, *H*-3′, CH_2-Ph); 6.94 (dd, 1H, *H*-1′); 7.01 (d, 1H, *H*-8); 7.10–7.44 (m, 11H, *H*-6, CH_{Ar}); 7.49 (ddd, 1H, $J_{7,5}$=1.3 Hz, $J_{7,6}=J_{7,8}$=8.5 Hz, *H*-7); 7.97–8.05 (m, 1H, *H*-5); 10.42 (s, 1H, N*H*); ^{13}C NMR ($CDCl_3$): δ 35.9 (*C*-2′); 71.2 (*C*-5′); 72.2; 73.3 (*C*H_2-Ph); 80.4 (*C*-3′); 82.4 (*C*-1′); 84.0 (*C*-4′); 115.0 (*C*-8, *C*-9); 123.5 (*C*-6); 127.6; 127.8; 127.9; 128.0; 128.4; 128.5; 128.6 (*C*-5, *C*H_{Ar}); 135.3 (*C*-7); 138.2; 138.3 (*Cq*); 138.6 (*C*-10); 151.6 (*C*-2); 162.0 (*C*-4); IR (KBr): 1655 (C═O); 1728 (C═O); MS IS *m*/*z*=459 [M+H$^+$]; 481 [M+Na$^+$]; HRMS: calcd for $C_{27}H_{26}N_2O_5$ (458.1841), found (458.1839).

4.2.37. 3-(2′-Deoxy-β-D-ribofuranosyl)-2,4-quinazolinedione 41. The solution was filtered over Celite®, and purified by silica gel chromatography to give pure **38** (53 Compound **40** (0.1 g; 0.22 mmol) was dissolved in MeOH (2 mL) containing Pd/C 10% (0.1 g) and stirred overnight under hydrogen pressure at room temperature. After

filtration over Celite® and evaporation, the residue was purified on silica gel (AcOEt/MeOH 95/5) to give **41** (38 mg; 62%) as a white solid; mp: 175–178 °C; $[\alpha]_D$=0 (*c* 1.0; DMSO); ^{1}H NMR (DMSO): δ 1.99 (ddd, 1H, $J_{2'b,3'}$= 4.7 Hz, $J_{2'b,1'}$=8.2 Hz, $J_{2'b,2'a}$=13.0 Hz, *H-2'b*); 2.79 (ddd, 1H, $J_{2'a,1'}$=6.0 Hz, $J_{2'a,3'}$=7.2 Hz, *H-2'a*); 3.43–3.56 (m, 1H, *H-5b*); 3.58–3.75 (m, 2H, *H-4'*, *H-5'a*); 4.30–4.45 (m, 1H, *H-3'*); 4.52–4.67 (m, 1H, O*H-5'*); 5.10 (d, 1H, $J_{OH,3'}$=4.7 Hz, O*H-3'*); 6.66 (dd, 1H, *H-1'*); 7.10–7.30 (m, 2H, *H-6*, *H-8*); 7.64 (ddd, 1H, $J_{7,5}$=1.3 Hz, $J_{7,6}$=$J_{7,8}$=8.3 Hz, *H-7*); 7.91 (dd, 1H, $J_{5,6}$=7.9 Hz, *H-5*); 11.38 (s, 1H, N*H*); ^{13}C NMR (DMSO): δ 36.8 (*C-2'*); 62.3 (*C-5'*); 71.2 (*C-3'*); 81.4 (*C-1'*); 87.5 (*C-4'*); 114.0 (*C-9*); 115.0 (*C-8*); 122.7 (*C-6*); 127.6 (*C-5*); 135.3 (*C-7'*); 139.4 (*C-10*); 149.7 (*C-2*); 162.0 (*C-4*); IR (KBr): 1658 (C═O); 1722 (C═O); MS IS *m*/*z*=279 [M+H$^+$]; 301 [M+Na$^+$]; HRMS: calcd for $C_{13}H_{14}N_2O_5$ (278.0802), found (278.0806); calcd for $C_{13}H_{14}N_2O_5$ (H 5.07, C 56.10, N 10.07), found (H 5.12, C 55.64, N 9.97).

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Stereospecific synthesis of urea-tethered neoglycoconjugates starting from glucopyranosyl carbamates

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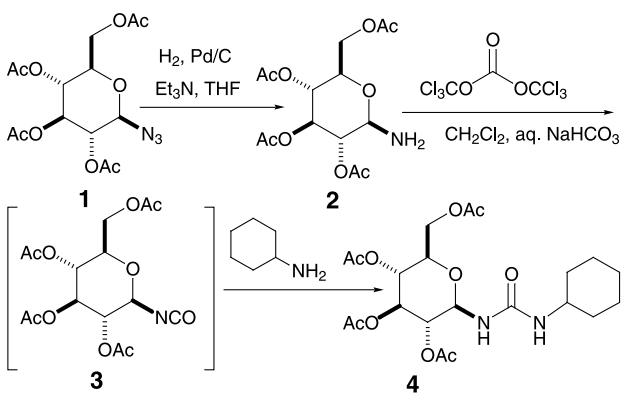
Abstract—Silyl-assisted elimination reaction of glucopyranosyl carbamates has been established for the synthesis of α- and β-D-glucopyranosyl isocyanates and ureas. This method proved to be useful for the synthesis of urea-tethered neoglycoconjugates.

1. Introduction

The importance of carbohydrates linked to the peptide backbone of protein (glycopeptides) has become increasingly appreciated in the bioorganic and/or medicinal research work due to their involvement in various biological events such as cellular recognition and adhesion.[1] Glycopeptides have two main classes of glycosidic linkage which involve either oxygen atom in the side chain of serine and threonine, or nitrogen atom in the side chain of asparagine.[2] Although synthetic chemists continue to explore the synthesis of accurately sequenced glycopeptides for biological and structural studies, total synthesis of the native glycopeptides still remain time-consuming and challenging tasks. In parallel, there are also much efforts toward the design and synthesis of glycopeptide mimetics which will supply homogeneous, stable and readily accessible glycopeptide analogues for biological studies and applications as potential therapeutic agents.[3] For example, *O*-glycosidic linkage is replaced by carbon–carbon,[4] carbon–sulfur[5] and carbon–aminooxy units.[6] With glycopeptide mimetics for *N*-glycosidic linkage, the amide group in *N*-glycosides was replaced by a retoamide subunit,[7] and alanine–hydroxylamine and alanine–hydrazine was employed as asparagine surrogates.[8] In addition to this rich area of glycopeptide mimetics, multivalent glycoconjugates such as glycoclusters and glycodendrimers have emerged as a new class of compounds which bear a structural resemblance to polysaccharides.[9] Such multivalent glycoconjugates are synthetically available and have exactly defined structure, which may be useful to explore the cluster effect of glycosides. Recently, we proposed a new approach to glycopeptide mimetics, which proposed urea glycosyl bond as the carbohydrate–peptide linkage.[10] The synthesis of urea glycosyl bond was planned to be constructed by the reaction of glycopyranosyl isocyanates with amines.[11]

During this research endeavor, a new synthetic method for the preparation of β-D-glucopyranosyl isocyanate **3** was established as represented in Scheme 1. Following the procedure reported by Ogawa,[12] catalytic hydrogenation of β-azide **1** gave β-amine **2**, treatment of which with triphosgene under Schotten–Baumann conditions afforded a solution of β-isocyanate **3**. Since isolation of pure **3** was unsuccessful due to the highly reactive nature of the isocyanate group,[13] the resulting reaction mixture was successively treated with cyclohexylamine to afford the stable and easily isolable urea glucoside **4** as crystals.

While β-urea **4** was obtained with this simple method, many attempts to prepare α-isomer using similar reaction sequence failed. In fact, hydrogenation of α-azide **5** gave



Scheme 1. Synthesis of β-glucopyranosyl isocyanate and urea by the reaction of β-glucopyranosyl amine with triphosgene.

Keywords: Carbamate; Carbohydrates; Neoglycoconjugates; Urea; Synthetic methods.
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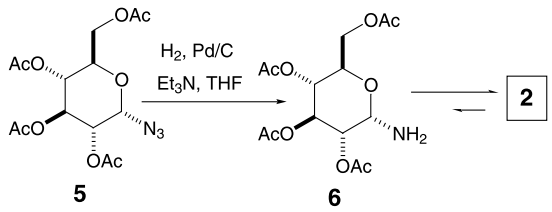
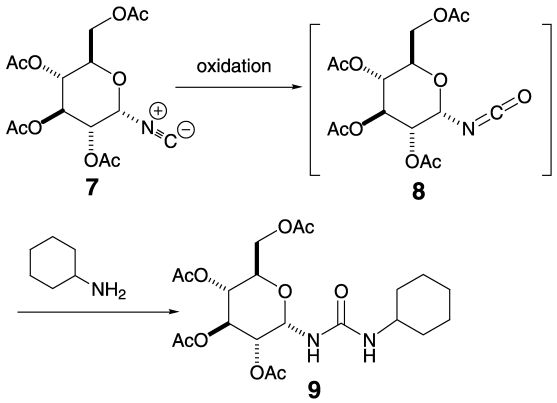
α-amine **6**, which rapidly isomerized into the thermodynamically more stable β-isomer **2** during work-up (Scheme 2). To avoid such an anomerization problem, we developed a method utilizing the oxidation of glucopyranosyl isonitrile **7** for the preparation of α-glucopyranosyl urea **9** (Scheme 3).



Scheme 2. A rapid anomerization of α-glucopyranosyl amine.

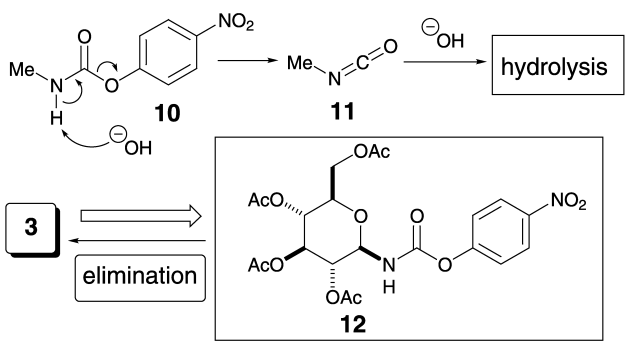


Scheme 3. Synthesis of α-glucopyranosyl isocyanate and urea starting from α-glucopyranosyl isonitrile.

While this protocol established a stereospecific synthesis of α- and β-D-glucopyranosyl isocyanates and ureas, we felt that more convenient method uncovered. Herein, we report the full detail of our second-generation synthesis of glucopyranosyl isocyanates and ureas starting from glucopyranosyl carbamates.[14]

2. Results and discussion

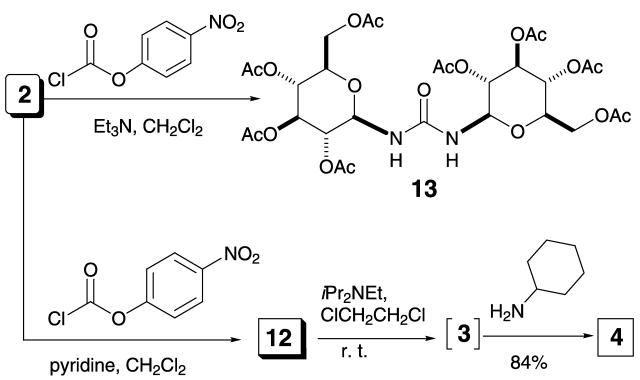
Bender proposed that *p*-nitrophenyl *N*-methylcarbamate **10** undergoes alkaline hydrolysis via elimination–addition mechanism, which involves methyl isocyanate **11** as an intermediate[15] (Scheme 4). This report inspired us to set



Scheme 4. Elimination–addition mechanism of carbamate hydrolysis and evolution of a new synthetic plan for glucopyranosyl isocyanate starting from glucopyranosyl carbamate.

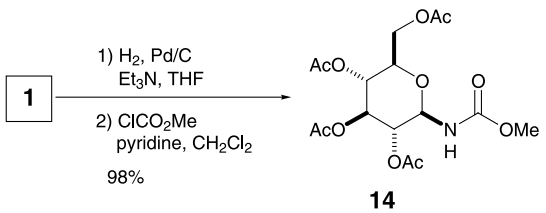
p-nitrophenyl β-*N*-glucopyranosyl carbamate **12** as a precursor to β-glucopyranosyl isocyanate **3**.

Initial attempts to synthesize **12** by the reaction of β-amine **2** with *p*-nitrophenyl chloroformate in the presence of triethylamine were unsuccessful; only bis-urea **13** was isolated (Scheme 5). We reasoned that use of triethylamine caused elimination of the initially formed *p*-nitrophenyl carbamate **12** to afford isocyanate **3**, which spontaneously reacted with the remaining amine **2**. This rationalization led us to employ a weaker base; the combination of *p*-nitrophenyl chloroformate and pyridine successfully suppress the elimination to furnish **12** as pale yellow crystals. As expected, base-catalyzed elimination of *p*-nitrophenyl carbamate **12** occurred quite readily; reaction of **12** in dichloroethane with diisopropylethylamine (iPr$_2$NEt) at room temperature spontaneously afforded an yellow solution containing β-isocyanate **3**, which was successively treated with cyclohexylamine to yield urea glucoside **4** in 84% yield for two steps. Although we were delighted with these results, we found the problem associated with **12**, which slowly decomposed even in a refrigerator. Moreover, purification of **12** by silica-gel chromatography was accompanied with partial formation of **13** to result in the decreased recovery of **12**.



Scheme 5. Synthesis of *p*-nitrophenyl glucopyranosyl carbamate and its use for the preparation of glucopyranosyl urea.

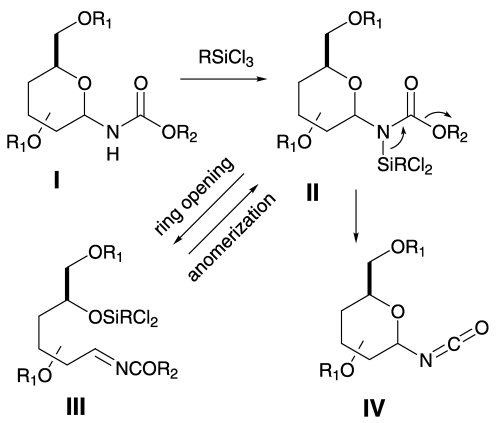
We next turned our attention to the more stable methyl carbamate **14**, which was prepared from **1** in 98% yield (Scheme 6).



Scheme 6. Synthesis of methyl glucopyranosyl carbamate.

Although **14** was sufficiently stable to be stored at room temperature for several weeks, the base-catalyzed elimination of methyl carbamate **14** (iPr$_2$NEt, 1,2-dichloroethane, reflux temperature, overnight) did not occur. To solve this problem, we explored the silyl-promoted elimination reaction of carbamates.[16] Although such elimination of carbamates are well-established transformations, no example of this reaction with α-alkoxy carbamate is

known. Accordingly, we were concerned about the behavior of the plausible intermediate, *N*-silylated species such as **II** (Scheme 7), which is critical to the origin of the stereoselectivity in this elimination reaction. If intermediate **II** is configurationally stable and undergoes the elimination reaction, complete retention of the anomeric stereochemistry in the starting material **I** will be observed. On the other hand, if equilibrium between **II** and *N*-carbamoylimine intermediate **III** occurs via reversible ring-opening reaction, then the product distribution will be determined by the relative stability of the α- and β-anomers **II** and/or the rates of their elimination and equilibration. In this sense, we were especially worried about the fate of **II** having α-anomer configuration, because α-*N*-glycosides are expected to be less stable than β-isomers.

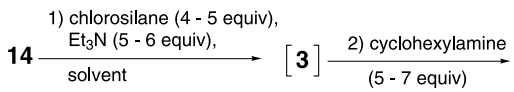


Scheme 7. A plausible reaction mechanism for the silyl-promoted elimination of glucopyranosyl carbamates.

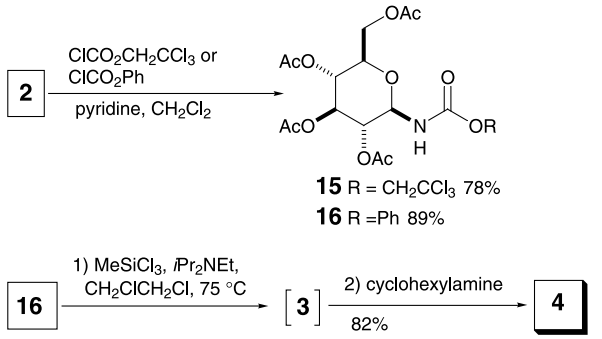
After screening several chlorosilanes and solvents, we have finally found that trichloromethylsilane (CH_3SiCl_3) and trichlorophenylsilane ($PhSiCl_3$) in 1,2-dichloroethane or acetonitrile are effective for this transformation as represented in Table 1. However, we soon realized a serious drawback; a large excess of cyclohexylamine (5 to 7 equiv.) was necessary to obtain a good yield of urea glucoside **4**. For example, when only 2 equiv. of cyclohexylamine was employed, the yield of isolated urea glucoside **4** dropped appreciably (ca. 30%). Since this problem appeared to arise from excess chlorosilane used which would interfere with the reaction of glucopyranosyl isocyanate **3** with cyclohexylamine, we turned our attention to the more reactive glucopyranosyl carbamates with moderate stability.

Since it is expected that the extent and rate of elimination depend on pK_a values of the leaving alkoxy substituents in the carbamates, we have prepared trichloroethyl (Troc) and phenyl carbamates **15** and **16** by treatment of **2** with 2,2,2-trichloroethyl chloroformate and phenyl chloroformate in 78 and 89% yields, respectively (Scheme 8). While elimination of the Troc carbamate **15** was sluggish and excess reagents were necessary, phenyl carbamate **16** underwent smooth elimination (1.5 equiv. of $MeSiCl_3$, 4.0–5.0 equiv. of iPr_2NEt, 1,2-dichloroethane, 75 °C, 5 h) to afford glucopyranosyl isocyanate **3**. Successive treatment of the reaction mixture containing **3** with cyclohexylamine (2.0 equiv.) afforded β-urea glucoside **4** in 82% yield after chromatographic purification.[17]

Table 1. Silyl-promoted elimination of β-methyl glucopyranosyl carbamate **14**

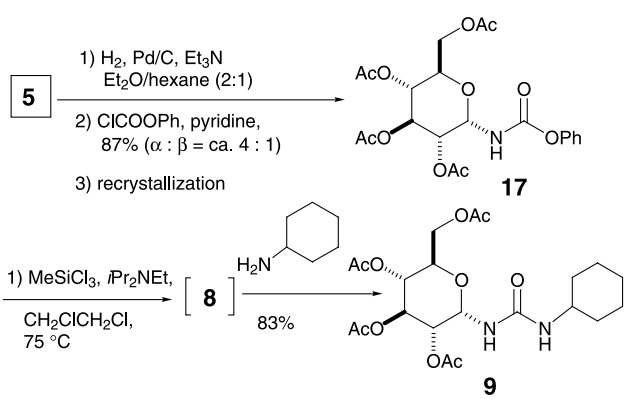


Entry	Chlorosilane	Solvent	Conditions	Yield (%)
A	$MeSiCl_3$	CH_2ClCH_2Cl	80 °C/4 h	90
B	$PhSiCl_3$	CH_3CN	45 °C/3 h	85
C	$MeSiCl_3$	CH_2ClCH_2Cl	80 °C/5 h	90
D	$PhSiCl_3$	CH_3CN	50 °C/6 h	89



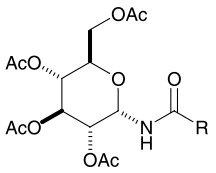
Scheme 8. Synthesis of Troc and phenyl glucopyranosyl carbamates and their use for the synthesis of β-urea glucoside.

Encouraged by this result, α-phenyl carbamate **17** was also prepared from α-azide **5** (Scheme 9). Catalytic hydrogenation of α-azide **5** followed by immediate treatment of the reaction mixture with phenyl chloroformate and pyridine afforded a 4:1 mixture of phenyl carbamates with the desired α-isomer **17** predominating in 87% yield. Although a mixture of these anomers could be separated by careful silica-gel chromatography, α-isomer **17** was much more conveniently purified by recrystallization.[18] Using a procedure similar to that given in Scheme 8, silyl-promoted elimination of α-carbamate **17** was carried out, and the corresponding α-urea glucoside **9** was isolated in 83% yield. According to ^1H NMR analysis of the crude reaction products, any β-isomer **4** has never been detected, which clearly showed that elimination of α-carbamate **17** proceeded stereospecifically without anomerization. It should be noted that while our previous method using glucopyranosyl isonitriles gave slightly better yields (Scheme 3) than the present procedure, both glucopyranosyl carbamates **16**

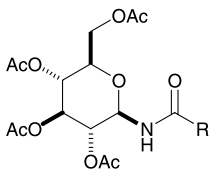


Scheme 9. Synthesis of α-phenyl glucopyranosyl carbamate and urea glucoside.

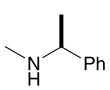
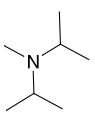
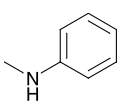
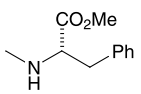
Table 2. Synthesis of urea-tethered neoglycoconjugates



18a-e



19a-e

Entry	A	B	C	D	E
R					
α-Urea glucosides (yield, %)[a]	**18a** (89%)[b]	**18b** (80%)[b]	**18c** (84%)[b]	**18d** (80%)[b]	**18e** (93%)[c]
β-Urea glucosides (yield, %)[a]	**19a** (82%)[b]	**19b** (78%)[b]	**19c** (82%)[b]	**19d** (81%)[b]	**19e** (94%)[c]

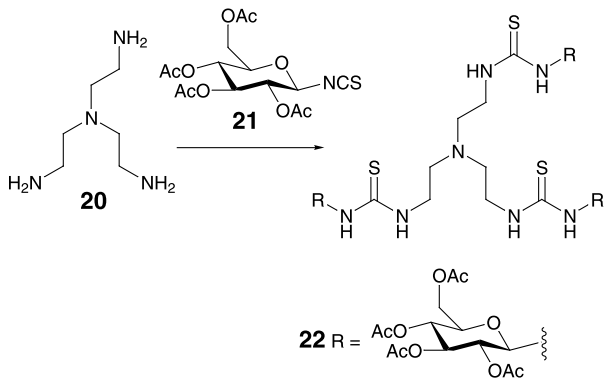
[a] Isolated yield after chromatographic purification.
[b] Glucopyranosyl carbamate (1.0 equiv.) and amine (2.0 equiv.) were employed. Yield based on glucopyranosyl carbamate.
[c] Glucopyranosyl carbamate (1.5 equiv.) and amine (1.0 equiv.) were used. Yield calculated based upon L-phenylalanine methyl ester hydrochloride.

and **17** can be readily prepared from glucopyranosyl azides in two steps using commercially available reagents. Moreover, a practical merit for the purification of α-phenyl glucopyranosyl carbamate **17** is noticed in its easy crystallinity.

With a new route to glucopyranosyl ureas established, we undertook to examine the utility of glucopyranosyl carbamates as glycosyl donors for the synthesis of urea-tethered neoglycoconjugates. The results are summarized in Table 2, in which a variety of urea-glucosides are prepared by the reaction with five different amines. It is notable that even sterically hindered amine, such as diisopropylamine (entry C), as well as low nucleophilic amine, such as aniline (entry D), gave satisfactory yields (>80%).

The first synthesis of both glucopyranosyl isocyanate **3** and isothiocyanate **21** was announced in 1914 by Fischer.[19] Although many syntheses of neoglycoconjugates using glucopyranosyl isothiocyanate has been reported,[20] little attention has been paid to glucopyranosyl isocyanate **3**. This miserable situation for **3** may be due to the difficulties associated with the preparation of the more reactive glucopyranosyl isocyanate **3**. Since a reliable synthetic method for the preparation of both α- and β-D-glucopyranosyl isocyanates has been established, we turned our attention upon comparing glucopyranosyl isocyanate with isothiocyanate counterpart in the context with the neoglycoconjugates synthesis. In this sense, we were interested in the report of Lindhorst,[21] who synthesized thio-bridged cluster of β-glucoside **22** by the reaction of tris(2-aminoethyl)amine **20** with β-glucopyranosyl isothiocyanate **21** (Scheme 10). In this case, the base-catalyzed O→N migration of acyl groups from the acetyl-protected glucosyl isothiocyanates onto the amino termini of the trivalent amine proved to be troublesome. To avoid this problem, reaction conditions using diluted solution and reflux temperature (CH_2Cl_2) were carefully employed.

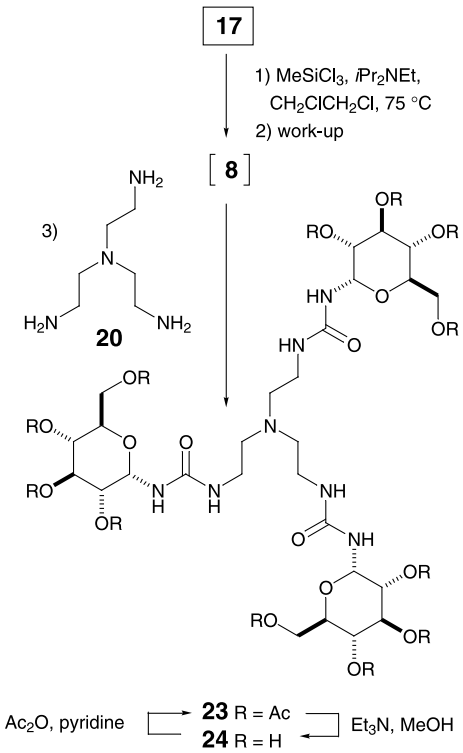
This report led us to examine the reaction of glucopyranosyl isocyanate with trivalent amine, which would offer an



Scheme 10. Lindhorst synthesis of thio-bridged cluster of β-glucoside.

opportunity to compare glucopyranosyl isocyanate with isothiocyanate counterpart. Furthermore, we expected that the synthesis of α-urea-bridged glucopyranosyl cluster appeared to be more appealing than the β-isomer synthesis, because the corresponding α-thiourea analogue is difficult to be synthesized.[22] Scheme 11 summarizes our approach to the urea-tethered α-glucopyranosyl cluster.

Using a procedure similar to that in Scheme 9, α-carbamate **17** was transformed into α-isocyanate **8**. Subsequent treatment of the resulting reaction mixture containing **8** with tris(2-aminoethyl)amine **20** resulted in low yields of product. After some experimentation, it was finally found that aqueous work-up was necessary. In fact, after silyl-promoted elimination of **17**, rapid and careful work-up gave the crude isocyanate **8**,[23] which was immediately dissolved in dichloroethane. Treatment of the resulting solution with **20** furnished the multivalent glucoside **23** in 89% yield.[24] It should be noted that any migration of acetyl group in **8** was not observed, which appears to reflect the more reactive nature of glucopyranosyl isocyanate. Further deprotection of **23** with a mixture of triethylamine and methanol gave water-soluble glucodendrimer **24**. Any anomerization of urea-glucoside linkage did not occur during hydrolysis of acetates in **23**, which was confirmed by acetylation of **24** to afford **23**.[25]



Scheme 11. Synthesis of urea-tethered cluster of glucoside with α-anomeric stereochemistry.

3. Conclusion

We have demonstrated that glucopyranosyl carbamates are valuable synthons for the preparation of urea-tethered neoglycoconjugates. The present method is especially useful for the synthesis of urea glycosides with α-stereochemistry. Studies to prepare mannopyranosyl and galactopyranosyl isocyanates and their use for the neoglycoconjugate synthesis is now in progress.

4. Experimental

4.1. General procedures

Melting points were recorded with a micro melting point apparatus and are not corrected. Optical rotations were measured on a JASCO DIP-370 digital polarimeter. Infrared spectra were recorded with a JASCO FT/IR-8300 spectrophotometer and are reported in wavenumbers (cm^{-1}). Proton nuclear magnetic resonance (^1H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded with Varian Gemini-2000 spectrometers. ^1H NMR chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane (TMS, δ=0.00 in $CDCl_3$), CHD_2OH (δ=3.31 in CD_3OH), and *t*-BuOH (δ=1.24 in D_2O) as internal standards. Data are reported as follows; chemical shift, integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, qn=quintet, sext=sextet, br=broadened, m=multiplet), coupling constants (*J*, given in Hz). ^{13}C NMR chemical shifts (δ) are recorded in parts per million (ppm) relative to $CDCl_3$ (δ=77.0), CD_3OD (δ=49.0), *t*-BuOH (δ=30.29, in D_2O) as internal standards. High-resolution mass spectra (HRMS) are reported in *m/z*. Elemental analysis was performed by Analytical Laboratory at Graduate School of Bioagricultural Sciences, Nagoya University. For thin-layer chromatography (TLC) analysis, Merck precoated TLC plates (silica gel 60 F_{254}, 0.25 mm) were used. Column chromatography was performed on silica gel (silica gel 60) supplied by E. Merck. Preparative TLC separation was made on plates prepared with a 2 mm layer of silica gel (Silica gel PF_{254}) obtained from E. Merck. Reactions were run under atmosphere of nitrogen when the reactions were sensitive to moisture or oxygen. Dichloromethane (CH_2Cl_2) was dried with molecular sieves 3 Å. Pyridine and triethylamine (Et_3N) were stored over anhydrous KOH. All other commercially available reagents were used as received.

4.1.1. Synthesis of *p*-nitrophenyl-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl carbamate 12 and its use for the preparation of glucopyranosyl urea. A solution of glucopyranosyl azide **1** (1.50 g, 4.02 mmol) and palladium on activated carbon (2%, 350 mg) in THF (100 mL) was vigorously stirred under hydrogen atmosphere for 3 h. The mixture was filtered through Celite and concentrated under reduced pressure. The resulting amine **2** (1.50 g) was dissolved in a mixture of pyridine (1.30 mL, 16.1 mmol) and CH_2Cl_2 (30.0 mL), and then treated with *p*-nitrophenyl chloroformate (1.62 g, 8.04 mmol) at room temperature. After being stirred for 30 min, the mixture was poured into aqueous saturated ammonium chloride solution, and the separating aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried (Na_2SO_4) and then concentrated. The resulting residue was passed through a short column of silica-gel (AcOEt–hexane, 2:1) to afford *p*-nitrophenyl glucopyranosyl carbamate **12** (1.97 g, 96%) as pale yellow solids. Since we have not succeeded in purifying **12**, the crude material was successively employed for the next reaction. IR (KBr) ν_{max}=3358, 1753, 1527, 1225; $\delta_H(CDCl_3)$; 2.05 (3H, s), 2.06 (3H, s), 2.10 (3H, s), 2.13 (3H, s), 3.87 (1H, ddd, *J*=10, 4.5, 2 Hz), 4.14 (1H, dd, *J*=12.5, 2 Hz), 4.35 (1H, dd, *J*=12.5, 4.5 Hz), 5.02 (1H, t, *J*=10, 9 Hz), 5.08 (1H, t, *J*=9 Hz), 5.12 (1H, t, *J*=10 Hz), 5.36 (1H, t, *J*=10 Hz), 6.26 (1H, d, *J*=9 Hz), 7.32–7.36 (2H), 8.24–8.27 (2H); $\delta_C(CDCl_3)$; 20.4, 20.5, 61.5, 67.9, 70.2, 72.5, 73.5, 80.8, 121.9, 125.2, 145.2, 152.5, 155.1, 169.6, 169.9, 170.6, 170.9.

To a solution of *p*-nitrophenyl glucopyranosyl carbamate **12** (100 mg, 0.20 mmol) dissolved in 1,2-dichloroethane (10.0 mL) was added diisopropylethylamine (175 μL, 0.98 mmol) at room temperature. The starting material disappeared immediately (TLC check), and the resulting yellow solution was treated with cyclohexylamine (30 μL, 0.26 mmol). After stirring for 10 min, the solution was poured into aqueous saturated ammonium chloride solution, and the aqueous layer was extracted with AcOEt. The combined organic layer was washed with brine, dried (Na_2SO_4), and then concentrated under reduced pressure. Purification of the resulting residue by silica-gel column chromatography (AcOEt–hexane, 2:1) gave β-urea **4** (79 mg, 87%).

4.1.2. Methyl-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl carbamate 14. A solution of **1** (500 mg, 1.34 mmol), Et_3N (0.19 mL, 1.40 mmol) and palladium on activated carbon

(2%, 0.20 g) in THF (20 mL) was stirred vigorously under hydrogen atmosphere for 90 min. The resulting solution was then filtered on Super Cell, and the filtrate was concentrated under reduced pressure until half volume. The resulting solution containing amine **2** was diluted with CH_2Cl_2 (10 mL), and then treated with pyridine (0.54 mL, 6.70 mmol) and methyl chloroformate (0.26 mL, 3.35 mmol) at room temperature. After stirring for 15 min, the mixture was poured into aqueous saturated sodium hydrogencarbonate solution, and aqueous layer was extracted with AcOEt. The combined organic layer was washed with brine, dried (Na_2SO_4), and then concentrated under reduced pressure. Purification of the resulting residue by silica-gel column chromatography (AcOEt–hexane, 1:1) afforded β-methyl carbamate **14** (535 mg, 98%); mp 104 °C; $[\alpha]_D^{22}$=+3.84 (*c* 1.00, $CHCl_3$); IR (KBr) ν_{max}=1753, 1541, 1370, 1237; $\delta_H(CDCl_3)$; 2.02 (3H, s), 2.04 (3H, s), 2.06 (3H, s), 2.09 (3H, s), 3.71 (3H, s), 3.76–3.84 (1H, m), 4.10 (1H, dd, *J*=12.5, 2 Hz), 4.31 (1H, dd, *J*=12.5, 4.5 Hz), 4.92 (1H, t, *J*=9.5 Hz), 5.03 (1H, bdt, *J*=9.5 Hz), 5.07 (1H, t, *J*=9.5 Hz), 5.30 (1H, t, *J*=9.5 Hz), 5.53 (1H, bd, *J*=9.5 Hz); $\delta_C(CDCl_3)$; 20.4, 20.5, 20.6, 52.6, 61.6, 68.1, 70.2, 72.8, 73.2, 80.8, 156.1, 169.6, 170.0, 170.7. Anal. Calcd for $C_{16}H_{23}NO_{11}$: C, 47.41; H, 5.72; N, 3.46. Found: C, 47.40; H, 5.54; N, 3.43.

4.2. General procedure for the preparation of glucopyranosyl urea

To a solution of **16** (120 mg, 0.26 mmol) and diisopropylethylamine (220 μL, 1.28 mmol) dissolved in 1,2-dichloroethane (6.0 mL) was added trichloromethylsilane (45 μL, 0.39 mmol). The reaction flask was sealed under nitrogen and then heated at 75 °C for 5 h. The resulting brown solution was treated with cyclohexylamine (58 μL, 0.51 mmol) at room temperature for 20 min. Usual work-up and purification by silica-gel chromatography (AcOEt–hexane, 2:3) afforded urea **4** (99 mg, 82%).

4.2.1. 2,3,4,6-Tetra-*O*-acetyl-*N*-(benzenaminocarbonyl)-α-D-glucopyranosylamine 18d. Mp 87 °C; $[\alpha]_D^{24}$=+135.2 (*c* 1.06, $CHCl_3$); IR (KBr) ν_{max}=3368, 1753, 1671, 1559, 1232,; $\delta_H(CDCl_3)$; 1.99 (3H, s), 2.03 (3H, s), 2.04 (3H, s), 2.07 (3H, s), 4.10–4.20 (2H), 4.24 (1H, dd, *J*=12, 5.5 Hz), 5.08 (1H, t, *J*=10 Hz), 5.17 (1H, dd, *J*=10, 5 Hz), 5.48 (1H, t, *J*=10 Hz), 5.76 (1H, t, *J*=5 Hz), 6.29 (1H, brd, *J*=4 Hz), 7.00–7.50 (5H); $\delta_C(CDCl_3)$; 20.43, 20.48, 61.8, 67.4, 68.3, 68.8, 69.9 76.7, 120.1, 123.9, 129.1, 137.9, 155.3, 169.3, 169.5, 170.3, 170.8. Anal. Calcd for $C_{21}H_{26}N_2O_{10}$: C, 54.07; H, 5.62; N, 6.01. Found: C, 54.31; H, 5.55; N, 5.99.

4.2.2. Methyl *N*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl-aminocarbonyl)-2(*S*)-phenylalanine 18e. A solution of **17** (200 mg, 0.43 mmol), trichloromethylsilane (75 μL, 0.64 mmol) and diisopropylethylamine (225 μL, 1.28 mmol) dissolved in 1,2-dichloroethane (10.0 mL) was sealed under nitrogen and then heated at 75 °C for 6.5 h. The resulting brown solution was treated with a solution of L-phenylalanine methyl ester hydrochloride (64 mg, 0.28 mmol) and diisopropylethylamine (65 μL, 0.36 mmol) in 1,2-dichloroethane (2.0 mL) at room temperature for 30 min. Usual work-up and purification by silica-gel chromatography (AcOEt–hexane, 1:3) afforded urea **18e** (143 mg, 93%). Mp 144 °C; $[\alpha]_D^{21}$=+112.3 (*c* 1.43, $CHCl_3$); IR (KBr) ν_{max}=3386, 1752, 1654, 1559, 1228; $\delta_H(CDCl_3)$; 2.01 (6H, s), 2.04 (3H, s), 2.06 (3H, s), 3.06 (1H, dd, *J*=14, 6.5 Hz), 3.26 (1H, dd, *J*=14, 6.5 Hz), 3.64 (1H, brdd, *J*=12.5, 1.5 Hz), 3.76 (3H, s), 3.93 (1H, dt, *J*=10, 1.5 Hz), 4.20 (1H, dd, *J*=12.5, 3.5 Hz), 4.77 (1H, q, *J*=6.5 Hz), 5.07 (1H, t, *J*=10 Hz), 5.10 (1H, dd, *J*=10, 5 Hz), 5.32 (1H, t, *J*=10 Hz), 5.50 (1H, t, *J*=5 Hz), 5.57 (1H, d, *J*=4 Hz), 5.73 (1H, d, *J*=7 Hz), 7.10–7.34 (5H); $\delta_C(CDCl_3)$; 20.37, 20.40, 20.43, 20.5, 37.8, 52.3, 53.8, 61.2, 67.1, 67.8, 68.6, 69.9, 76.7, 127.2, 128.6, 129.2, 135.9, 156.6, 169.2, 169.4, 170.3, 170.7, 172.7. Anal. Calcd for $C_{25}H_{32}N_2O_{12}$: C, 54.34; H, 5.84; N, 5.07. Found: C, 54.35; H, 5.85; N, 5.11.

4.2.3. Tris[2-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)urea-ethyl]amine (23). A solution of **17** (200 mg, 0.43 mmol), trichloromethylsilane (75 μL, 0.64 mmol) and diisopropylethylamine (260 μL, 1.46 mmol) dissolved in 1,2-dichloroethane (10.0 mL) was heated at 75 °C for 5 h. The resulting solution was diluted with CH_2Cl_2 (40 mL) and then carefully poured into water containing cracked ice. The resulting precipitate was quickly filtered on glass filter, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated. The resulting residue was immediately dissolved in 1,2-dichloroethane (10.0 mL) and then treated with a solution of tris(2-aminoethyl)amine (12 mg, 0.082 mmol) in 1,2-dichloroethane (1.5 mL). After stirring at room for 30 min, usual work-up and purification by silica-gel chromatography (AcOEt–2–PrOH, 10:1) afforded the multivalent glucoside **23** (92 mg, 89%); mp 134 °C; $[\alpha]_D^{21}$=+128.7 (*c* 1.00, $CHCl_3$); IR (KBr) ν_{max}=3377, 1752, 1663, 1236; $\delta_H(CD_3OD)$; 1.99 (9H, s), 2.01 (9H, s), 2.02 (9H, s), 2.05 (9H, s), 2.48–2.68 (6H), 3.12–3.28 (6H), 3.93–4.04 (6H), 4.26 (3H, dd, *J*=12, 5 Hz), 5.03 (3H, t, *J*=10 Hz), 5.09 (3H, dd, *J*=10, 5.5 Hz), 5.52 (3H, t, *J*=10 Hz), 5.80 (3H, d, *J*=5.5 Hz); $\delta_C(CDCl_3)$; 20.47, 20.56, 20.69, 20.7, 39.6, 55.5, 63.7, 68.3, 70.2, 70.4, 71.8, 76.8, 156.0, 171.4, 171.6, 171.8, 172.5. Anal. Calcd for $C_{51}H_{75}N_7O_{30}$: C, 48.38; H, 5.97; N, 7.74. Found: C, 48.38; H, 5.65; N, 7.45. HRMS (FAB) calcd for $C_{51}H_{76}N_7O_{30}$ $[M+H]^+$ 1266.4637, found 1266.4659.

4.2.4. Tris[2-(α-D-glucopyranosyl)urea-ethyl]amine 24. A solution of **23** (253 mg, 0.20 mmol) and Et_3N (2.0 mL) in methanol (12.0 mL) was stirred at room temperature overnight, and the reaction mixture was concentrated under reduced pressure. The resulting residue was washed with methanol to give **24** (151 mg, quantitatively) as a white amorphous solid; $[\alpha]_D^{23}$=+106.0 (*c* 0.57, H_2O); IR (KBr) ν_{max}=3352, 1652, 1560; $\delta_H(D_2O)$; 2.66 (6H, brt, *J*=6 Hz), 3.23 (6H, brt, *J*=6 Hz), 3.41 (3H, t, *J*=10 Hz), 3.53 (3H, ddd, *J*=10, 4, 2 Hz), 3.62 (3H, t, *J*=10 Hz), 3.68–3.84 (9H), 5.46 (3H, d, *J*=5.5 Hz); $\delta_C(D_2O)$; 38.4, 49.6, 54.3, 61.3, 70.2, 72.5, 73.9, 78.7 160.7. HRMS (FAB) calcd for $C_{27}H_{52}N_7O_{18}$ $[M+H]^+$ 762.3369, found 726.3339.

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23. This procedure appeared to remove the by-products derived from the silicon reagent which may interfere with the reaction of **8** with **20**.
24. While the conformational properties of α-cluster **23** resulted in line broadening of the ^{1}H NMR peaks measured in $CDCl_3$, only one set of moderately sharp signals for the sugar moieties due to the C_3-symmetric nature in **23** was detected with CD_3OD as solvent.
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Mercury(II) mediated cyclisation of *R*-1-(1′-hydroxyethyl)-2-(1″-propenyl)-3-alkoxy-4-methoxybenzenes to chiral isochromanes

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Abstract—A protocol has been established for the transformation of chiral *ortho* 1-hydroxyethyl propenyl benzenes under both anaerobic and oxidative mercury(II) mediated conditions to produce chiral isochromanes. Further transformations of the former products yielded chiral isochromanquinones, while the latter afforded the corresponding chiral 4-hydroxyisochromanquinones.

1. Introduction

Many naturally occurring quinones possessing either the naphthopyran or the isochromane nucleus demonstrate a wide spectrum of biological activity.[1–3] This has in major part been attributed to the positions of (a) the pyran ring oxygen atom (O-2), (b) the presence of a good leaving group at C-4 of the pyran ring.[4] Indeed we[5] and others[6,7] have had some success employing aspects of these ideas towards the synthesis of compounds containing these key features. Two substantive reviews on the isolation and structural determination of naphthopyranquinones[8] as well as their general syntheses[9] have recently appeared. Typical examples of these quinones include eleutherin **1**,[10] nanomycin D **2**,[11] erythrostominone **3**,[12] and granaticin **4**[13] (Fig. 1).

The pyran ring of these molecules generally contains either two, e.g., **1** and **3** or three, e.g., **2** and **4** stereogenic centres that have to be assembled in a stereocontrolled fashion. In this regard considerable efforts have been made in developing protocols for the synthesis of some enantiomerically pure naphthopyranquinones.[2,14–16]

As part of an ongoing research programme directed towards the synthesis of the chiral isochromanquinone nucleus, we have utilized Corey-Bakshi-Shibata asymmetric reductions of carbonyl precursors to provide what will ultimately be the stereogenic methyl substituent present at C-1 of the target compounds (Fig. 1). This has been described in previous reports from these laboratories.[17,18]

This paper describes the details of mercury(II) mediated cyclisations of these chiral benzylic alcohol precursors into chiral isochromanes and eventually into the corresponding quinones.

2. Results and discussions

2.1. Synthesis of racemic isochromanquinones

In order to validate the sequence of transformations envisaged for the synthesis of the required isochromanes in a racemic manner, the racemic alcohols **6a–c**[18] were treated, under established conditions,[19b] with 4 molar equivalents of potassium *t*-butoxide in DMF at 80 °C for 45 min to afford the corresponding *trans*-1,3-dimethylisochromanes **7a–c** in good yields. In all three products 3-H appeared as a multiplet at δ 4.00–3.98 which demonstrated that the relative stereochemistry of the methyl groups at C-1 and C-3 was *trans*.[19a]

The benzyl group was removed from isochromane **7c** by catalytic hydrogenolysis to afford the corresponding phenol **8** in 96% yield while boron tribromide at −78 °C was used to remove the isopropyl group in **7b** to produce the same racemic phenol **8** but in a reduced yield of 75%. Finally, phenol **8** was oxidized with Fremy's salt[20] to the bright yellow racemic *trans*-1,3-dimethylisochromanquinone **9** in 61% yield (Scheme 1).

Keywords: Isochromanes; Mercury(II) acetate; Quinones; Oxidative cyclisation.
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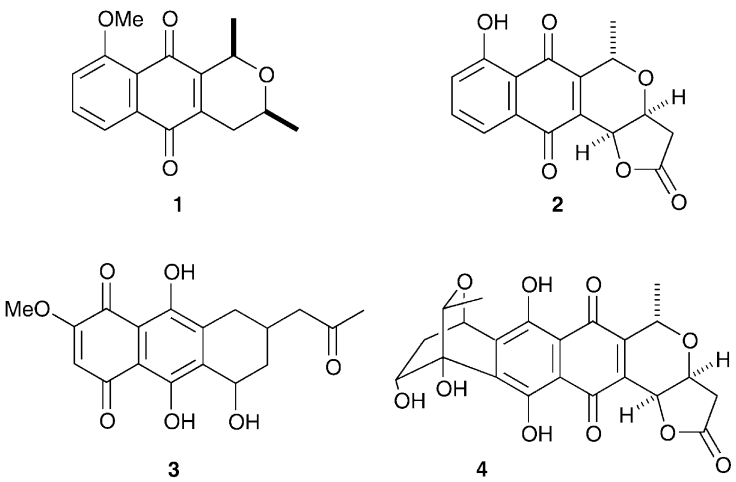
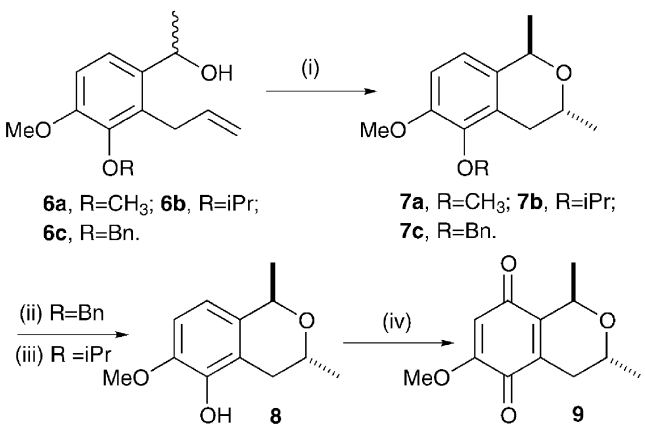


Figure 1.



Scheme 1. (i) KOBu^t, DMF, 80 °C, **7a**, 96%; **7b**, 90%; **7c**, 77%; (ii) H_2, 5% Pd/C, EtOAc, 96%; (iii) BBr_3/CH_2Cl_2, −78 °C, 75%; (iv) $K(SO_3)_2NO$, MeOH/phosphate buffer, 25 °C, 61%.

2.2. Synthesis of chiral isochromanes

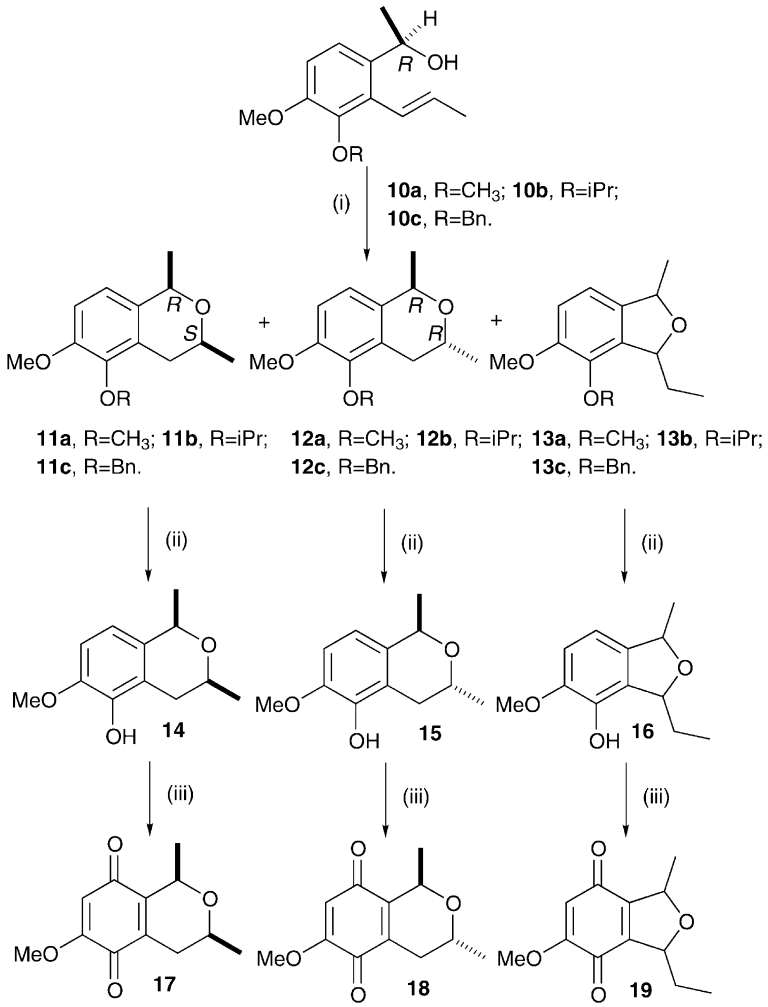
In turning our attention towards the transformation of the chiral alcohols **10a–c**[18] into the corresponding chiral isochromanes, either mercury(II) acetate[21] or potassium *t*-butoxide[19b] could be used since the former method affords both the *cis*- and *trans*-1,3-dimethylisochromanes non-diastereoselectively,[22,23] while the latter method was developed to provide a completely diastereoselective route to solely the *trans* compounds for the purposes of natural product synthesis.[24] In the present context the former method was chosen since it thus offered the potential for the additional *cis*-diastereoisomer to be produced. Furthermore, it is known that prolonged treatment by butoxide leads to some isomerisation of the *trans* isomer into its *cis* isomer.[19b] Since the precise mechanism of this latter isomerisation is not fully understood, its use would raise the unlikely possibility of racemisation of an asymmetric carbon.

Thus the *R*-alcohols **10**[18] (75% ee) in a THF–H_2O (1:1) solution were treated with mercury(II) acetate followed by aqueous sodium hydroxide and later by sodium borohydride to afford the separable diastereoisomeric mixtures of the pyrans **11** (1*R*, 3*S*) and **12** (1*R*, 3*R*) in a ratio of 1:1 and average yields of 60% together with trace quantities (~4%) of the benzofurans **13** as determined by ^{1}H NMR spectroscopy and GCMS as shown in Scheme 2.

Since the absolute configuration of the starting alcohol is known to be (*R*), assignment of the absolute configurations for pyrans **11** and **12** is based on the chemical shift for 3-H in the ^{1}H NMR spectra. For *cis*-pyran **11**, 3-H appeared as a multiplet at δ 3.71–3.75, while in *trans*-pyran **12** the same proton appeared as a multiplet at δ 3.98–4.00 similar to our earlier findings.[25] Benzofurans **13** could not be obtained pure enough at this stage for a complete structural assignment, since the R_f was similar to pyran **12**. However, the corresponding quinone **19** was isolated in pure form (vide infra).

Catalytic hydrogenolysis of the pyran mixture of **11c**, **12c** and **13c** afforded the corresponding phenolic mixture of **14**, **15** and **16** in 97% crude yield in the ratio of 47:47:6 by GCMS. Owing to the chemically sensitive nature of phenols, the mixture was not separated but immediately oxidized using Fremy's salt[20] to afford a mixture of the quinones **17**, **18**, and **19** in a crude yield of 70%.

Good separation was effected using radial chromatography to afford initially the benzofuranquinone **19** (6%) which apart from a molecular ion of *m*/*z* 222 in the mass spectrum had a strong C=O absorption at 1665 cm^{-1} in the infrared spectrum. The ^{1}H NMR spectrum showed, inter alia, a 3-proton triplet at δ 0.99 (J=7.2 Hz) coupled to a 2-proton multiplet at δ 1.71 (COSY) for the C-1 ethyl group; a 3-proton doublet at δ 1.47 (J=6.2 Hz) assigned to the C-3 methyl group; a 2-proton multiplet at δ 5.26 for 1- and 3-H which were confirmed by COSY cross peaks to both the 1-CH_3 and the CH_2 of the ethyl side chain at C-1. The next quinone to elute (26%) was assigned the absolute configuration of structure **17**, while the last to elute (28%) was assigned the absolute configuration of structure **18**. Assignment of the absolute configurations to these quinones is based on ^{1}H NMR data. For quinone **17**, the signal for 3-H appeared as a multiplet at δ 3.53 thus placing the C-1 and C-3 methyl groups *cis* to each other and di-equatorial; the signal for the 4-Ha appeared as a ddd at δ 2.13 with ^2J=18.4 to 4-H_e, ^3J=10.0 to 3-H_a and ^5J=4.0 to 1-H_a; the signal due



Scheme 2. (i) $Hg(OAc)_2$, NaOH, $NaBH_4$, THF/H_2O; for **11a** and **12a** 64%; for **11b** and **12b** 55%; for **11c** and **12c** 62%; trace quantities (~4%) of **11c**, **11b** and **11c** in each rxtn; (ii) BBr_3/CH_2Cl_2, −78 °C; or for **11c**–**13c** (R=Bn) (ii) H_2, 5% Pd/C, EtOAc, H^+, each 97%; (iii) $K(SO_3)_2NO$, MeOH/phosphate buffer, 25 °C; **14**→ **17**, 56%; **15**→ **18**, 59%; **16**→ **19**, 94%.

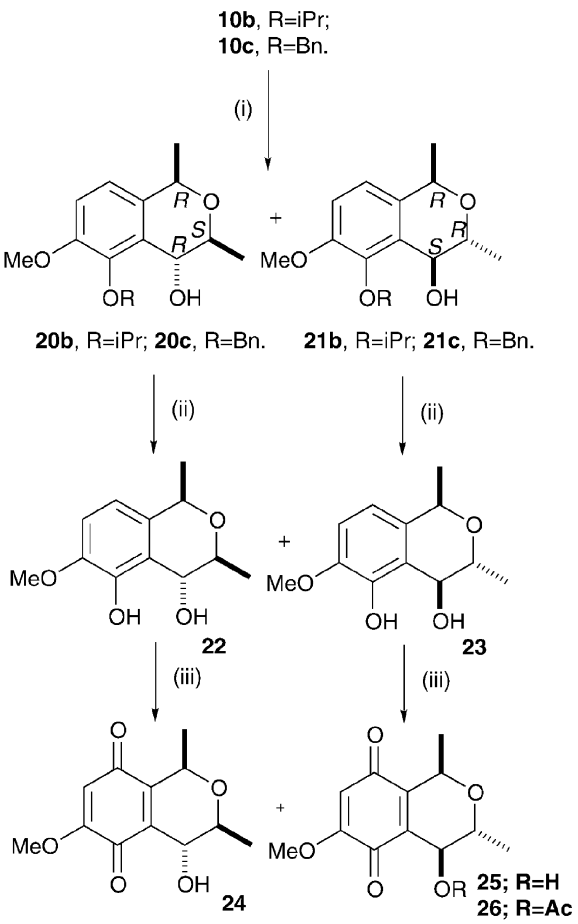
to 4-H_e appeared as a ddd at δ 2.61 with ^2J=18.4 to 4-H_a, ^3J=3.6 to 3-H_a and ^5J=1.0 to 1-H_a. Finally, the signal assigned to 1-H_a appeared as a ddq at δ 4.69 with ^3J=6.6 Hz and ^5J of 4.0 and 1.0 Hz. Assignment of the absolute stereochemistry for quinone **18** was based inter alia on the position of 3-H_a, which appeared as a multiplet at δ 3.92. Upon addition of 10 mol% of the lanthanide shift reagent, Eu(hfc)$_3$, all the signals experienced a strong deshielding effect, the most dramatic being 7-H from δ 5.83 to separate into two peaks at δ 7.04 and 6.99, which were used to determine the de values for **18** and **17** as 75%.

2.3. Synthesis of chiral 4-hydroxyisochromanes

Earlier, de Koning et al.[26] reported on an oxidative mercury(II) mediated ring closure procedure of *ortho* allyl hydroxymethyl benzene systems based on the work of Hill and Whitesides[27] during which the formed radical intermediate trapped oxygen specifically at the benzylic position. It was surmised that under similar conditions it might be possible to prepare chiral-4-hydroxy-1,3-dimethylisochromanes.

Initial attempts based upon the above protocol using chiral alcohol **10c** afforded only one product viz. **21c** (Scheme 3), but in a yield of 7% after 4 h, together with starting material. Increasing the reaction time to 12 h again afforded the hydroxypyran **21c** in 7% yield together with a new compound (11%) to which the dimeric structure **27** has been assigned (Fig. 2). Its HRMS indicated the molecular formula $C_{38}H_{42}O_6$. Four doublets in the ^{1}H NMR spectrum characterized the dimeric nature of the product viz., δ 1.28 and 1.35 (J=6.2 Hz) for the C-3 and C-3′ methyl groups and δ 1.50 and 1.55 (J=6.6 Hz) for the C-1 and C-1′ methyl groups. It is of interest to note that 3-H and 3′-H appear as two separate signals one at δ 3.98 and the other at δ 4.28 (dq, J=6.6 and 6.2 Hz for both), which would support the fact that the two methyl groups at C-1 and C-3 are *trans* to each other. The larger coupling of 6.6 Hz between 3-H and 4-H would suggest that these protons are *trans* and that the C-4, C-4′ bond is thus pseudoequatorial in both pyran rings. COSY spectroscopy supported the assigned structure as the 2-proton multiplet at δ 2.87 assigned to 4- and 4′-H showed two clear cross-peaks to the signals of 3- and 3′-H which in turn had cross-peaks to the C-3 and C-3′ methyl groups.

By employing a modification to the earlier method of cyclisation,[26,27] as outlined in Section 3, oxidative cyclisation



Scheme 3. (i) $Hg(OAc)_2$, NaOH, $NaBH_4$, O_2, DMF, R=iPr 50%; R=Bn, 75%; (ii) for **20c** and **21c** H_2, 5% Pd/C, EtOAc, H^+, 96%; (iii) $K(SO_3)_2NO$, MeOH/phosphate buffer, 25 °C, **25**, 35%, **24**, decomposed.

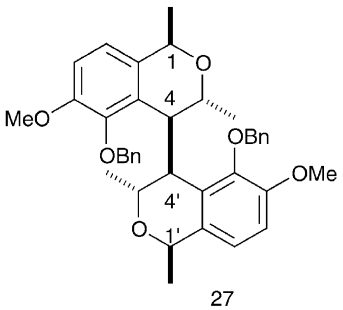


Figure 2.

was successfully effected on alcohol **10b** to afford **20b** and **21b** in 50% yield as a 1:1 mixture by GCMS while alcohol **10c** was oxidatively cyclised into a 1:1 mixture of **20c** and **21c** in an improved yield of 75% (Scheme 3). Isochromanes **20b** and **21b** proved extremely difficult to separate with only **20b** obtained pure; **21b** always had a trace (~5%) of **20b** present thus precluding optical measurements. Assignment of the absolute configurations for pyran **20b**, the 1*R*, 3*S*, 4*R* isomer, is based on the following ^{1}H NMR spectral data; a well-defined dq at δ 3.60 for 3-H clearly established the 1,3-diequatorial orientations of the two methyl groups from its chemical shift. The ^3J coupling constant of 6.2 Hz for the quartet corresponded to the coupling with the C-3 methyl group while a ^3J of 8.0 Hz to 4-H supported an approximately *trans* diaxial relationship between 3-H and 4-H and consequently the 4-OH is pseudoequatorial. Unfortunately, the signals due to 1-H, 4-H and the methine proton of the isopropyl group all overlapped at δ 4.70. On the other hand, compound **21b** exhibited a dq at δ 3.96 assigned to 3-H in the ^{1}H NMR spectrum. In this instance the chemical shift was consistent with a *trans* arrangement of the methyl substituents, while ^3J for the doublet was 6.6 Hz also demonstrating a *trans* diaxial relationship between 3-H and 4-H and thus supporting the orientation of 4-OH as pseudoequatorial. As further support for the assignment, the signal due to 4-OH appeared as a doublet at δ 4.10 (J=3.0 Hz) while 4-H appeared as a dd at δ 4.58 (J=6.6 and 3.0 Hz) and collapsed to a doublet (J=6.6 Hz) after D_2O washing.

Similarly pyrans **20c** and **21c** proved equally difficult to separate with only **20c** being obtained in pure form. Assignments were made using the same arguments as above. Pd/C catalyzed debenzylation of the pyran mixture of **20c** and **21c** yielded the expected mixture of the corresponding phenols **22** and **23**. Since these had the potential for instability,[14] they were immediately oxidized with Fremy's salt to afford a quinone mixture of **24** and **25** (60%) from which only one optically enriched diastereoisomer **25** was isolated (35%), the other undergoing decomposition.

Assignment of the configurations at the pyran ring carbons of **25** is based inter alia on the following signals in the ^{1}H NMR spectrum; a dq at δ 3.82 assigned to 3-H_a with ^3J to the C-3 methyl of 6.2 Hz and *trans* coupling of 7.8 Hz to 4-H_a; a D_2O exchangeable doublet at δ 3.42 (J=2.6 Hz) for 4-OH_e and a ddd at δ 4.34 assigned to 4-H_a with ^3J of 7.8 Hz to 3-H_a, ^3J of 2.6 to the 4-OH_e and ^5J of 1.0 Hz to 1-H_e. After a D_2O wash this signal collapsed to the expected dd (J=7.8 and 1.0 Hz). Since addition of the lanthanide shift reagent proved inconclusive to determine the de value for **25**, it was converted into the corresponding C-4 acetate **26** in pyridine and acetic anhydride. Addition of 10% $Eu(hfc)_3$ successfully caused the signal of the acetate group at δ 2.08 to become deshielded and split into two distinct signals at δ 2.86 and 2.79 which allowed the de to be determined as 70% (c=0.45; $CDCl_3$).

In conclusion, a method has been developed for the synthesis of chiral isochromanequinones in which a methoxy group is at position 6 for improved biological activity.[5] By a slight modification during the oxidative cyclisation step, a C-4 hydroxy group has been introduced stereoselectively to afford the corresponding 4-hydroxy isochromanequinones. Methods of improving the yields and ee's are currently under investigation.

3. Experimental

3.1. General

^{1}H- and ^{13}C spectra were recorded on a Varian 200 MHz spectrometer at 20 °C in deuterochloroform and J values are given in Hz. Assignments with the same superscript may be interchanged. Infrared spectra were measured as nujol mulls on a Perkin Elmer FT-IR 1000 PC spectrometer. Mass

spectra were recorded on a Finnigan Matt GCQ spectrometer or a VG 70E MS spectrometer. Melting points are uncorrected and were measured on a Fischer–John melting point apparatus. Elemental analysis was performed on a Carlo Erba 1500 NA analyser. Optical rotations were measured on a Perkin Elmer-Polarimeter 141, at 20 °C using the sodium D line. Preparative column chromatography was carried out on dry-packed columns using Silica Gel 60 (particle size 0.063–0.02 nm). The term 'residue obtained upon work-up' refers to the drying of the extract over magnesium sulfate, filtration and evaporation of the solvent.

3.1.1. General methodology for the base-induced cyclisation of racemic alcohols 6a, 6b and 6c. To a rapidly stirred solution of the alcohol **6** (2 mmol) in dimethylformamide (50 ml) under nitrogen at an oil bath temperature of 80 °C was added in one batch potassium *t*-butoxide (8 mmol) and the resulting mixture was stirred for 45 min. Water (200 ml) and ether (100 ml) were added to the cooled reaction mixture, which was exhaustively extracted with ether. The residue obtained upon work-up was purified by column chromatography using EtOAc/hexane (1:9) as the eluent to yield the racemic isochromanes as follows.

3.1.2. (±) *trans* 3,4-Dihydro-5,6-dimethoxy-1,3-dimethylbenzo[*c*]pyran 7a. Colourless oil (96%); δ_H 1.33 (3H, d, J=6.2 Hz, 3-CH_3), 1.49 (3H, d, J=6.6 Hz, 1-CH_3), 2.42 (1H, dd, J=16.8, 9.9 Hz, 4-Ha), 2.91 (1H, dd, J=16.8, 3.6 Hz, 4-He), 3.81 and 3.95 (each 3H, s, OCH_3), 4.00 (1H, m, 3-H), 5.00 (1H, q, J=6.6 Hz, 1-H), 6.75 (1H, d, J=8.4 Hz, 7-H), and 6.78 (1H, d, J=8.4 Hz, 8-H); δ_C 21.6 (3-CH_3), 22.4 (1-CH_3), 30.4 (C-4), 55.9 and 60.2 (OCH_3), 63.5 (C-3), 70.3 (C-1), 110.4 (C-7), 120.7 (C-8), 127.8 (C-8a)[a], 132.4 (C-4a)[a], 146.2 (C-5)[6], and 150.6 (C-6)[b]; MS (E1): *m*/*z* (%): 222 (M^+, 20), 207 (100), 189 (11), 176 (16). Calcd for $C_{13}H_{18}O_3$: C, 70.2; H, 8.2%; M 222. Found: C, 70.1; H, 8.2%.

3.1.3. (±) *trans* 3,4-Dihydro-5-isopropyloxy-6-methoxy-1,3-dimethylbenzo[*c*]pyran 7b. Colourless oil (90%); δ_H 1.25 [6H, d, J=6.2 Hz, CH(CH_3)$_2$], 1.29 (3H, d, J=6.2 Hz, 3-CH_3), 1.48 (3H, d, J=6.6 Hz, 1-CH_3), 2.42 (1H, dd, J=16.4, 9.4 Hz, 4-H_a), 2.91 (1H, dd, J=16.4, 3.4 Hz, 4-H_e), 3.81 (3H, s, OCH_3), 3.98 (1H, m, 3-H), 4.49 [1H, septet, J=6.2 Hz, C*H*(CH_3)$_2$], 5.00 (1H, q, J=6.6 Hz, 1-H), 6.72 (1H, d, J=8.4 Hz, 7-H), and 6.76 (1H, d, J=8.4 Hz, 8-H); δ_C 21.5 (3-C), 22.5 (1-C), 22.8 [×2, CH(*C*H_3)$_2$], 31.4 (C-4), 55.9 (OCH_3), 63.8 (C-3), 70.2 (C-1), 74.4 [*C*H(CH$_3$)$_2$] 110.4 (C-7), 120.1 (C-8), 128.5 (C-8a)[a], 132.4 (C-4a)[a], 144.1 (C-6)[b], and 150.8 (C-5)[b]; MS (EI): *m*/*z* (%): 250 (M^+, 19), 235 (29), 193 (100), 143 (13). Calcd for $C_{15}H_{22}O_3$: C, 71.95; H, 8.9%, M 250. Found: C, 72.1; H, 8.6%.

3.1.4. *trans* 3,4-Dihydro-5-benzoloxy-6-methoxy-1,3-dimethylbenzo[*c*]pyran 7c. White needles (77%), mp 85–87 °C (from hexane–ethyl acetate); δ_H 1.26 (3H, d, J=6.2 Hz, 3-CH_3), 1.48 (3H, d, J=6.6 Hz, 1-CH_3), 2.31 (1H, dd, J=16.8, 9.6 Hz, 4-H_a), 2.82 (1H, d, J=16.8, 3.4 Hz, 4-H_e), 3.87 (3H, s, OCH_3), 3.98 (1H, m, 3-H), 4.97 (1H, q, J=6.6 Hz, 1-H), 4.99 (2H, s, O*C*H_2Ph), 6.76 (1H, d, J=8.8 Hz, 7-H), 6.82 (1H, d, J=8.8 Hz, 8-H), and 7.38 (5H, m, aryl); δ_C 21.4 (3-CH_3), 22.5 (1-CH_3), 30.8 (C-4), 56.0 (OCH_3), 63.6 (C-3), 70.2 (C-1), 74.3 (O*C*H_2Ph), 110.5 (C-7), 120.8 (C-8), 127.9 (Ph), 128.0 (×2, Ph), 128.2 (×2, Ph), 128.4 (Ph), 132.4 (C-4a)[a], 138.0 (C-8a)[a], 145.0 (C-5)[b], and 150.7 (C-6)[b]; MS (EI): *m*/*z* (%): 298 (M^+, 31), 283 (73), 254 (46), 207 (14), 177 (20), 163 (53), 135 (17), 91 (100). Calcd for $C_{19}H_{22}O_3$: C, 76.5; H, 7.45%, M 298. Found: C, 76.4; H, 7.3%.

3.1.5. (±) *trans* 3,4-Dihydro-5-hydroxy-6-methoxy-1,3-dimethylbenzo[*c*]pyran 8. *Method A*. Pyran **7c** (123 mg; 0.41 mmol) in ethyl acetate (15 ml) containing 5% Pd on charcoal (15 mg) and 1 drop 10 M hydrochloric acid was hydrogenated. The residue obtained upon work-up was flash chromatographed using EtOAc/hexane (1:4) to yield the phenol **8** as a red oil (82 mg; 96%). ν_{max} 3472 cm^{-1} (bs, OH); δ_H 1.33 (3H, d, J=6.2 Hz, 3-CH_3), 1.49 (3H, d, J=6.6 Hz, 1-CH_3), 2.42 (1H, dd, J=16.8, 8.0 Hz, 4-H_a), 2.85 (1H, dd, J=16.8, 3.6 Hz, 4-H_e), 3.87 (3H, s, OCH_3), 4.12 (1H, m, 3-H), 4.99 (1H, q, J=6.6 Hz, 1-H), 5.69 (1H, bs, D_2O exchangeable, 5-OH), 6.54 (1H, d, J=8.4 Hz, 7-H), and 6.73 (1H, d, J=8.4 Hz, 8-H); δ_C 21.7 (3-CH_3), 22.6 (1-CH_3), 30.2 (C-4), 56.3 (OCH_3), 63.4 (C-3), 70.6 (C-1), 108.6 (C-7), 116.3 (C-8), 120.1 (C-4a)[a], 133.1 (C-8a)[a], 143.3 (C-5)[b], and 144.4 (C-6)[b]; MS (EI): *m*/*z* (%): 208 (M^+, 22), 193 (100), 161 (11), 143 (25), 133 (20). Calcd for $C_{12}H_{16}O_3$: C, 69.2; H, 7.6%; M 208. Found: C, 69.3; H, 7.4%.

Method B. Pyran **7b** (250 mg; 1 mmol) in dichloromethane (25 ml) at −78 °C under nitrogen was treated with boron tribromide (2.5 mmol) and allowed to stir for 1 h. The excess of reagent was destroyed with water (1 ml) and the residue obtained upon work-up was flash chromatographed as in Method A to yield phenol **8** as a red oil (158 mg; 75%) having identical spectral properties as measured earlier.

3.1.6. (±) *trans* 6-Methoxy-1,3-dimethylbenzo[*c*]pyran-5,8-dione 9. To 4.7 ml of an aqueous buffered solution (79 ml of 0.2 M sodium hydrogen phosphate and 171 ml of 0.2 M sodium dihydrogen phosphate) containing Fremy's salt (200 mg; 0.56 mmol)[20] was added in one batch a solution of phenol **8** (58 mg; 0.28 mmol) in methyl alcohol (0.4 ml). After stirring for 1 h, water (10 ml) was added and the reaction mixture extracted with dichloromethane. The residue obtained upon work-up was chromatographed using EtOAc/hexane (1:4) as eluent to yield the quinone **9** (38 mg; 61%), mp 134–136 °C (from hexane–ethyl acetate). Lit. mp 137–138 °C.[5]

3.1.7. (1*R*, 3*S*)-3,4-Dihydro-5,6-dimethoxy-1,3-dimethylbenzo[*c*]pyran 11a, (1*R*, 3*R*)-3,4-dihydro-5,6-dimethoxy-1,3-dimethylbenzo[*c*]pyran 12a and 6,7-dimethoxybenzofurans 13a. A solution of *R*-alcohol **10a**[18] (520 mg; 2.34 mmol) in tetrahydrofuran (17 ml) and water (17 ml) was treated with mercury(II) acetate (746 mg; 2.34 mmol) and stirred at 25 °C for 1 h. Aqueous sodium hydroxide (17 ml of a 3 M solution) was added and stirring was continued for a further 1 h. A further portion of aqueous sodium hydroxide (17 ml of a 3 M solution) and sodium borohydride (1.95 g; 51.5 mmol) were added and stirring continued for a further 1 h. The reaction mixture was exhaustively extracted with ethyl acetate and the residue chromatographed using EtOAc/hexane (1:4) as eluent to afford a (1:1) mixture of pyrans **11a** and **12a** together with

the benzofurans **13a** (332 mg; 64%) in a ratio of (48:48:4) by GC–MS. PLC purification of 50 mg of this sample using EtOAc/hexane (1:9) as eluent afforded the benzofurans **13a** (1.6 mg) followed by the *cis* dimethylpyran **11a** (21 mg) as an oil. δ_H 1.39 (3H, d, J=6.2 Hz, 3-CH_3), 1.52 (3H, d, J=6.6 Hz, 1-CH_3), 2.51 (1H, dd, J=17.0, 10.6 Hz, 4-H_a), 2.88 (1H, dd, J=17.0, 3.4 Hz, 4-H_e), 3.75 (1H, m, H-3a), 3.81 and 3.85 (each 3H, s, OCH_3), 4.91 (1H, q, J=6.6 Hz, 1-H), 6.76 (1H, d, J=8.4 Hz, 7-H), and 6.83 (1H, d, J=8.4 Hz, 8-H); δ_C 21.6 (3-CH_3), 22.4 (1-CH_3), 30.5 (C-4), 55.9 and 60.2 $(OCH)_3$, 63.5 (C-3), 70.3 (C-1), 110.4 (C-7), 120.7 (C-8), 127.8 (C-4a)[a], 132.4 (C-8a)[a], 146.2 (C-6)[b], 150.6 (C-5)[b]; MS (EI): *m/z* (%): 222 (M^+, 20), 207 (100), 189 (11), 176 (16). Calcd for $C_{13}H_{18}O_3$: C, 70.2; H, 8.2%; M 222. Found C, 70.1; H, 8.2%.

The next fraction to elute was the *trans* dimethylpyran **12a** (20 mg) as an oil with NMR spectral properties identical to the racemic pyran **7a**.

3.1.8. (1*R*, 3*S*)-3,4-Dihydro-5-isopropoxy-6-methoxy-1,3-dimethylbenzo[*c*]pyran 11b, (1*R*, 3*R*)-3,4-dihydro-5-isopropoxy-6-methoxy-1,3-dimethylbenzo[*c*]pyran 12b and the benzofurans 13b. Using an analogues synthetic protocol described for pyrans **11a** and **12a** the *R*-isopropoxy alcohol **10b**[18] (404 mg; 1.62 mmol, 75% ee) afforded a residue, which was chromatographed to yield a mixture of the pyrans **11b** and **12b** and the furans **13b** (220 mg; 55%) in the ratio of (47:47:6) by GC–MS. PLC of a 50 mg portion using EtOAc/hexane (1:9) afforded the benzofurans **13b** (2.5 mg) followed by the *cis* dimethylpyran **11b** (22 mg) as an oil. δ_H 1.26 [6H, d, J=6.2 Hz, $CH(CH_3)_2$], 1.34 (3H, d, J=6.2 Hz, 3-CH_3), 1.47 (3H, d, J=6.6 Hz, 1-CH_3), 2.40 (1H, dd, J=16.4, 9.8 Hz, 4-Ha), 2.89 (1H, dd, J=16.4, 3.2 Hz, 4-He), 3.71 (1H, m, 3-Ha), 3.81 (3H, s, OCH_3), 4.47 [1H, septet, J=6.2 Hz, $CH(CH_3)_2$], 4.77 (1H, q, J=6.2 Hz, 1-H), 6.73 (1H, d, J=8.4 Hz, 7-H), and 6.75 (1H, d, J=8.4 Hz, H-8); δ_C 21.5 (3-CH_3), 22.5 (1-CH_3), 22.7 (×2) [$CH(CH_3)_2$], 31.4 (C-4), 55.9 (CH_3), 66.3 (C-3), 70.2 (C-1), 74.4 [$CH(CH_3)_2$], 110.7 (C-7), 120.1 (C-8), 128.5 (C-4a)[a], 132.4 (C-8a)[a], 144.1 (C-6)[b] and 150.8 (C-5)[b]. MS (EI): *m/z* (%): 250 (M^+, 19), 235 (29), 193 (100), 143 (13). Calcd for $C_{15}H_{22}O_{33}$: C, 71.95; H, 8.9%; M 235. Found: C, 72.2; 8.4%. Further elution afforded the *trans* dimethylpyran **12b** (23 mg) as an oil with NMR spectra identical to the racemic pyran **7b**.

3.1.9. (1*R*, 3*S*)-5-Benzyloxy-3,4-dihydro-6-methoxy-1,3-dimethylbenzo[*c*]pyran 11c, (1*R*, 3*R*)-5-benzyloxy-3,4-dihydro-6-methoxy-1,3-dimethylbenzo[*c*]pyran 12c and the benzofurans 13c. Applying the same synthetic protocol as described above the *R*-benzyloxy alcohol **10c**[18] (375 mg; 1.26 mmol) afforded a residue, which was chromatographed using EtOAc/hexane (1:4) as eluent to produce a mixture of the pyrans **11c** and **12c** and furans **13c** (233 mg; 62%) in the ratio of (47:47:6) by GC–MS. PLC of a 50 mg portion using EtOAc/hexane (1:9) as eluent afforded the benzofurans **13c** (2.7 mg) followed by the *cis* dimethylpyran **11c** (20 mg) as an oil. δ_H 1.32 (3H, d, J=6.2 Hz, 3-CH_3), 1.46 (3H, d, J=6.2 Hz, 1-CH_3), 2.30 (1H, dd, J=16.8, 11.0 Hz, 4-H_a), 2.85 (1H, dd, J=16.8, 3.2 Hz, 4-H_e), 3.75 (1H, m, H-3_a), 3.87 (3H, s, OCH_3), 4.78 (1H, q, J=6.2 Hz, 1-H), 4.99 (2H, s, CH_2Ph), 6.78 (1H, d, J=8.8 Hz, H-7), 6.80 (1H, d, J=8.8 Hz, H-8), and 7.38 (5H, m, Ph); δ_C 21.3 (3-CH_3), 22.5 (1-CH_3), 30.8 (C-4), 56.0 (OCH_3), 63.6 (C-3), 70.2 (C-1), 74.3 (OCH_2Ph), 110.7 (C-7), 120.8 (C-8), 127.9 (aryl), 128.2 (×2, aryl), 128.3 (×2, aryl), 128.4 (aryl), 134.4 (C-4a)[a], 138.0 (C-8a)[a], 145.0 (C-5)[b], and 150.7 (C-6)[b]; MS (EI): *m/z* (%): 298 (M^+, 31), 283 (73), 254 (46), 207 (14), 177 (20), 163 (53), 135 (17), 91 (100). Calcd for $C_{19}H_{22}O_3$: C, 76.5; H, 7.45%; M 298. Found C, 76.6; H, 7.5%. Further elution afforded the *trans* dimethyl pyran **12c** (22 mg) as an oil with NMR spectral data similar to the racemic *trans* pyran **7c**.

3.1.10. (1*R*, 3*S*)-3,4-Dihydro-5-hydroxy-6-methoxy-1,3-dimethylbenzo[*c*]pyran 14, (1*R*, 3*R*)-3,4-dihydro-5-hydroxy-6-methoxy-1,3-dimethylbenzo[*c*]pyran 15 and the benzofurans 16. An isomeric mixture of the pyrans **11c**, **12c** and **13c** (988 mg; 3.32 mmol) in ethyl acetate (40 ml) containing palladium on charcoal (5%, 100 mg) and two drops of concentrated aqueous hydrogen chloride was hydrogenated for 15 h, filtered and removal of the solvent gave a mixture (670 mg; 97%) of phenols **14**, **15** and **16** in the ratio of 47:47:6 by GC–MS, as a red oil. ν_{max} 3500–3000 cm^{-1}; δ_H 1.30–1.54 (12H, 4×d, J=6.6, 6.2 Hz, 1- and 3-CH_3), 2.40 (2H, overlapping dd, J=17.0, 10.0 Hz, 4-H_a), 2.82 (2H, overlapping dd, J=17.0, 3.8 Hz, 4-H_e), 3.86 and 3.87 (each 3H, s, OCH_3), 3.90 and 4.12 (2H, m, 3-H of *cis* and *trans* isomers), 4.80 and 5.00 (2H, each q, J=7.6 Hz, 1-H), 5.78 (2H, bs, D_2O exchangeable, 5-OH), 6.65 (4H, overlapping pairs of d's, J=8.4 Hz, 7- and 8-H).

3.1.11. 1-Ethyl-6-methoxy-3-methylbenzo[*c*]furan-4,7-dione 19, (1*R*, 3*S*)-6-methoxy-1,3-dimethylbenzo[*c*]-pyran-5,8-dione 17 and (1*R*, 3*R*)-6-methoxy-1,3-dimethylbenzo[*c*]pyran-5,8-dione 18. To a buffered aqueous solution of 78.8 ml 0.2 M disodium hydrogen phosphate and 171.2 ml 0.2 M sodium dihydrogen phosphate (12 ml) containing Fremy's salt (773 mg; 1.44 mmol) was added a mixture of the phenols **14**, **15** and **16** (150 mg; 0.72 mmol) in methanol (1.0 ml) with rapid stirring which was continued for 1 h. Extraction of the reaction mixture with dichloromethane afforded a residue (112 mg; 70%) that was separated by radial chromatography using EtOAc/hexane (1:9) as eluent to give the furandione **19** (9 mg; 6%) as a bright yellow oil. ν_{max} 1665 cm^{-1}; δ_H 0.93 (3H, t, J=7.2 Hz, 2′-CH_3), 1.47 (3H, d, J=6.2 Hz, 1-CH_3), 1.71 (2H, m, 1′-CH_2), 3.83 (3H, s, OCH_3), 5.26 (2H, m, 1- and 3-H), 5.84 (1H, s, 5-H). δ_C 9.2 (2′-CH_3), 21.0 (1-CH_3), 27.4 (1′-CH_2), 56.8 (OCH_3), 79.8 (C-3), 83.8 (C-1), 107.6 (C-5), 142.6 (C-3a)[a], 148.3 (C-7a)[a], 159.7 (C-6), 178.7 (C=O), and 183.9 (C=O); MS (EI): *m/z* (%): 222 (M^+, 22), 193 (100), 165 (26). Calcd for $C_{12}H_{14}O_4$: C, 64.8; H, 6.4%; M 222. Found: C, 64.7; H, 6.5%.

The next product to elute was the benzopyrandione **17** (42 mg; 26%) as bright yellow crystals, mp 100–103 °C (from hexane–ethyl acetate). ν_{max} 1680 and 1666 cm^{-1}; δ_H 1.33 (3H, d, J=6.2 Hz, 3-CH_3), 1.48 (3H, d, J=6.6 Hz, 1-CH_3), 2.13 (1H, ddd, J=18.4, 10.0, 4.0 Hz, 4-H_a), 2.61 (1H, ddd, J=18.4, 3.6, 1.0 Hz, 4-H_e), 3.53 (1H, m, 3-H_a), 3.80 (3H, s, OCH_3), 4.69 (1H, ddq, J=1.0, 4.0, 6.6 Hz, 1-H), 5.83 (1H, s, 7-H); δ_C 21.1 (3-CH_3), 21.3 (1-CH_3), 29.9 (C-4), 56.3 (OCH_3), 68.8 (C-3), 69.9 (C-1), 107.8 (C-7), 138.3 (C-8a)[a], 144.8 (C-4a)[a], 158.3 (C-6), 181.3 (C=O),

and 186.5 (C=O); MS (EI): *m/z* (%): 222 (M^+, 28), 207 (100), 193 (28), 179 (37), 165 (28), 151 (26), 119 (13), 91 (14); $[\alpha]_D$=+97° (*c*=0.545, CH_2Cl_2); de 75% [Eu(hfc)$_3$]. Calcd for $C_{12}H_{14}O_4$: C, 64.8; H, 6.4%; M 222. Found: C, 64.6; H, 6.5%. The last product to elute was the benzopyrandione **18** (44 mg; 28%) as bright yellow crystals, mp 104–106 °C (from hexane–ethyl acetate). ν_{max} 1680 and 1665 cm^{-1}; δ_H 1.31 (3H, d, 6.2, 3-CH_3), 1.46 (3H, d, *J*=7.0 Hz, 1-CH_3), 2.12 (1H, ddd, *J*=19.0, 10.0, 2.2 Hz, 4-Ha), 2.60 (1H, dd, *J*=19.0, 3.2 Hz, 4-H_e), 3.81 (3H, s, OCH_3), 3.95 (1H, m, 3-H_a), 4.85 (1H, dq, *J*=2.2, 7.0 Hz, 1-H), and 5.85 (1H, s, 7-H); δ_C 19.9 (3-CH_3), 21.5 (1-CH_3), 29.3 (C-4), 56.3 (OCH_3), 62.7 (C-3), 67.2 (C-1), 107.4 (C-7), 137.4 (C-8a)[a], 144.7 (C-4a)[a], 158.5 (C-6), 181.4 (C=O), and 186.0 (C=O); MS (EI): *m/z* (%): 222 (M^+, 28), 207 (100), 193 (28), 179 (37), 165 (28), 151 (26), 119 (13), 91 (14); $[\alpha]_D$=−14 °C (*c*=0.720, CH_2Cl_2); de 75% [Eu(hfc)$_3$]. Calcd for $C_{12}H_{14}O_4$: C, 64.8; H, 6.4%; M 222. Found: C, 64.9; H, 6.4%.

3.1.12. (3*S*, 4*R*)-5-Benzyloxy-3,4-dihydro-4-hydroxy-6-methoxy-1,3-di-methylbenzo[*c*]pyran 20c and dimer 27. Treatment of (*R*)-alcohol **10c** (280 mg; 0.94 mmol) in tetrahydrofuran (25 ml) with mercury(II) acetate (400 mg; 1.25 mmol) at 25 °C with stirring for 2 h followed by the addition of sodium bromide (129 mg, 1.25 mmol) in hot methanol (10 ml) and stirring for another 2 h produced a residue upon removal of the solvents on a rotary evaporator at 40 °C. The residue was taken up in dimethylformamide (25 ml) and then added dropwise to a slurry of sodium borohydride (71 mg; 1.88 mmol) in dimethylformamide (12 ml) into which oxygen had previously been bubbled for 30 min. The resulting mixture was stirred at 25 °C with the passage of oxygen for 12 h. Removal of the solvents at 50 °C under reduced pressure afforded a greasy semi-solid material which was mixed with water (40 ml) and extracted with dichloromethane and the residue was chromatographed using ethyl acetate/hexane (3:7) as eluent to yield the dimer **27** (60 mg; 11%) as off-white crystals, mp 172–174 °C (from ethyl acetate–hexane); δ_H 1.28 (3H, d, *J*=6.2 Hz, 3-CH_3), 1.35 (3H, d, *J*=6.2 Hz, 3′-CH_3), 1.50 (3H, d, *J*=6.6 Hz, 1-CH_3), 1.51 (3H, d, *J*=6.6 Hz, 1′-CH_3), 2.87 (2H, m, 4- and 4′-H), 3.90 (6H, s, OCH_3), 3.98 (1H, dq, *J*=6.6, 6.2 Hz, 3-H), 4.28 (1H, dq, *J*=6.6, 6.2 Hz, 3′-H), 4.76 and 4.89 (2H, each a doublet, *J*=11.0 Hz; CH_2Ph), 4.90 (2H, m, 1- and 1′-H), 5.34 and 5.44 (2H, each doublet, *J*=11.0 Hz, CH_2Ph), 6.80 (4H, m, 7-, 8-, 7′ and 8′-H), 7.40 (10H, m, aryl); δ_C 21.7, 22.0, 22.3, 23.8, 55.9, 60.0, 67.1, 69.6, 73.2, 73.5, 75.8, 76.1, 76.4, 77.3, 110.0, 110.4, 120.5, 121.2, 128.8 (×2), 128.9 (×2), 129.0 (×4), 129.1 (×4), 129.8 (×2), 131.8 (×2), 136.9, 137.1, 150.7 and 151.0; HRMS calcd for $C_{38}H_{42}O_6$: 594.29813, C, 76.7; H, 7.1%; Found: 594.29788; C, 76.7; H, 7.3%). Further elution afforded the desired isochromanol **20c** (20 mg; 7%) as an oil. See spectral details vide infra.

3.1.13. (3*S*, 4*R*)-3,4-Dihydro-4-hydroxy-5-isopropoxy-6-methoxy-1,3-dimethylbenzo[*c*]pyran 20b and the (1*R*, 3*R*, 4*S*) diastereomer 21b. *R*-isopropoxy alcohol **10b** (250 mg; 1.0 mmol) was dissolved in tetrahydrofuran (30 ml) at 25 °C and water (30 ml) was added with vigorous stirring. Mercury(II) acetate (320 mg; 1.0 mmol) was added and the resulting mixture was stirred for 1 h after which aqueous sodium hydroxide (7.2 ml of 3 M solution; 21.6 mmol) was added and stirring continued for a further 1 h to then be followed by the addition of sodium bromide (103 mg; 1.0 mmol). After an additional 1 h stirring, oxygen was bubbled through for 1 h and then sodium borohydride (719 mg; 19.0 mmol) and additional aqueous sodium hydroxide (7.2 ml of a 3 M solution; 21.6 mmol) were added and oxygen was rapidly passed through this solution at 25 °C for 4 h after which period the solution was no longer gray. The residue obtained from extraction of the aqueous phase with ethyl acetate was purified by chromatography using ethyl acetate/hexane (15:85) to afford a pale yellow oily mixture of the isochromanes **20b** and **21b** (133 mg; 50%) in a ratio of 1:1 by GC–MS. A small amount of the mixture (40 mg) was subjected to PLC using ethyl acetate/hexane (1:9) as eluent to yield the pure benzopyranol **20b** (16 mg as an oil. ν_{max} 3506 cm^{-1}; δ_H 1.24 (3H, d, *J*=6.2 Hz, 3-CH_3), 1.43 (3H, d, *J*=5.8 Hz, 1-CH_3), 1.48 [6H, d, *J*=6.6 Hz, CH(CH_3)$_2$], 3.16 (1H, s, D_2O exchangeable, 4-OH), 3.60 (1H, dq, *J*=8.0, 6.2 Hz, 3-H_a), 3.84 (3H, s, OCH_3), 4.60–4.80 [3H, m, 1-, 4-, and C*H*(CH$_3$)$_2$], 6.80 (1H, d, *J*=7.8 Hz, 7-H) and 6.83 (1H, d, *J*=7.8 Hz, 8-H); δ_C 19.1 (3-CH_3), 21.7 (1-CH_3), 22.5 (CH_3 of isopropoxy), 23.2 (CH_3 of isopropyl), 55.9 (OMe), 70.7 (C-3)[a], 72.9 (CH of isopropyl)[a], 75.2 (C-1)[a], 75.7 (C-4)[a], 112.0 (C-7), 119.5 (C-8), 131.8 (C-4a)[b], 133.5 (C-8a)[b], 144.7 (C-5)[c] and 150.9 (C-6)[c]; MS (EI): *m/z* (%) 266 (9), 249 (11), 222 (64), 191 (100), 180 (60), 163 (22) and 133 (27); $[\alpha]_D$=+30.5° (*c*=1.11, CH_2Cl_2); de not possible due to inconclusive results with Eu(hfc)$_3$. Calcd for $C_{15}H_{22}O_4$: C, 67.6; H, 8.3%; M^+ 266. Found: C, 67.6; H, 8.3%.

The next band contained isochromane **21b** (18 mg) contaminated with a trace (5%) of pyran **20b** (by GC–MS) as an oil. ν_{max} 3510 cm^{-1}; δ_H 1.22 (3H, d, *J*=6.0 Hz, 3-CH_3), 1.34 [3H, d, *J*=6.6 Hz, CH(CH_3)$_2$], 1.42 (3H, d, *J*=6.2 Hz, 1-CH_3), 1.53 [3H, d, *J*=6.6 Hz, CH(CH_3)$_2$], 3.83 (3H, s, OCH_3), 3.96 (dq, *J*=6.0, 6.6 Hz, 3-H_a), 4.10 (1H, d, *J*=3.0 Hz, D_2O exchangeable, 4-OH), 4.58 (1H, dd, *J*=6.6, 3.0 Hz, 4-H_a), 4.69 [1H, m, C*H*(CH$_3$)$_2$], 4.89 (1H, q, *J*=6.2 Hz, 1-H), 6.72 (1H, d, *J*=8.2 Hz, 7-H), and 6.84 (1H, d, *J*=8.2 Hz, 8-H); δ_C 17.8 (3-CH_3), 21.9 (1-CH_3), 22.4 (CH_3 of isopropyl), 23.2 (CH_3 of isopropyl), 55.0 (OCH_3), 68.7 (C-3)[a], 69.2 (CH of isopropyl)[a], 69.4 (C-1)[a], 75.4 (C-4)[a], 112.4 (C-7), 120.2 (C-8), 130.3 (C-4a)[b], 132.6 (C-8a)[b], 145.2 (C-5)[c] and 150.8 (C-6)[c].

3.1.14. (1*R*, 3*S*, 4*R*)-5-Benzyloxy-3,4-dihydro-4-hydroxy-6-methoxy-1,3-di-methylbenzo[*c*]pyran 20c and its (1*R*, 3*R*, 4*S*) diastereomer 21c. By an analogues protocol describe vide infra *R*-alcohol **10c** (793 mg; 2.66 mmol) afforded a pale yellow oily mixture of the two diastereoisomers **20c** and **21c** (626 mg; 75%) in a 1:1 ratio by GC–MS. A small amount of the mixture (36 mg) was subjected to PLC and eluted with ethyl acetate/hexane (1:9) to provide benzopyranol **20c** (14 mg) as an oil. ν_{max} 3539 cm^{-1}; δ_H 1.42 (3H, d, *J*=5.8 Hz, 3-CH_3), 1.49 (3H, d, *J*=6.6 Hz, 1-CH_3), 3.59 (1H, d, *J*=8.8, 5.8 Hz, 3-Ha), 3.90 (3H, s, OCH_3), 4.14 (1H, *J*=1.6 Hz, D_2O exchangeable, 4-OH), 4.46 (1H, dd, *J*=8.8, 1.6 Hz, 4-H_a), 4.75 (1H, q, *J*=6.6 Hz, 1-H), 4.98 (1H, d, *J*=10.6 Hz, CH_2Ph), 5.24 (1H, d, *J*=10.6 Hz, CH_2Ph), 6.84 (1H, d, *J*=8.1 Hz, 7-H), 6.90 (1H, d, 8.1, 8-H), and 7.40 (5H, m, Ph); δ_C 19.2

(3-CH_3), 21.5 (1-CH_3), 56.0 (CH_3O), 70.0 (C-4)[a], 72.8 (C-1)[a], 75.2 (C-3)[a], 75.4 (CH_2Ph)[a], 112.1 (C-7), 120.0 (C-8), 128.1 (aryl), 128.6 (×2, aryl), 128.7 (×2, aryl), 131.5 (aryl), 133.7 (C-4a)[b], 137.0 (C-8a)[b], 145.9 (C-5)[c] and 150.9 (C-6)[c]; MS (EI): *m/z* (%): 314 (M^+, 2), 206 (44), 191 (100), 179 (28), 164 (31), 149 (13) and 91 (27); $[\alpha]_D$=+27.0° (*c*=0.690, CH_2Cl_2). Calcd for $C_{19}H_{22}O_4$: C, 72.6; H, 7.1%, M 314. Found: C, 72.4; H, 7.15%.

The next band provided mainly benzopyranol **21c** (19 mg) contaminated with ~5% of **20c** by GC–MS as an oil. ν_{max} 3539 cm^{-1}, 1.34 (3H, d, *J*=6.6 Hz, 3-CH_3), 1.46 (3H, d, *J*=6.6 Hz, 1-CH_3), 2.02 (1H, d, *J*=8.2 Hz, D_2O exchangeable, 4-OH), 3.90 (3H, s, OCH_3), 3.90 (1H, m, 3-H), 4.50 (1H, bd, *J*=8.0 Hz, 4-H), 5.04 (1H, q, *J*=6.6 Hz, 1-H), 5.07 (1H, d, *J*=10.6 Hz, CH_2Ph), 5.20 (1H, d, *J*=10.6 Hz, CH_2Ph), 6.78 (1H, d, *J*=8.0 Hz, 7-H), 6.89 (1H, d, *J*=8.0 Hz, 8-H), 7.39 (3H, m, 3′-, 4′- and 5′-H of aryl ring), and 7.44 (2H, m, 2′- and 6′-H of aryl ring); δ_C 17.0 (3-CH_3), 21.4 (1-CH_3), 56.2 (CH_3O), 63.5 (C-4)[a], 66.7 (C-1)[a], 70.9 (C-3)[a], 75.5 (CH_2Ph), 113.5 (C-7), 121.1 (C-8), 128.2 (aryl), 128.5 (×4, aryl), 131.6 (aryl), 131.9 (C-4a)[b], 137.8 (C-8a)[b], 146.0 (C-5)[c] and 151.1 (C-6)[c]; HRMS calcd for $C_{19}H_{22}O_4$: 314.1518. Found: 314.1518.

3.1.15. (1*R*, 3*R*, 4*S*)-3,4-Dihydro-4-hydroxy-6-methoxy-1,3-dimethyl-5,8-dioxybenzo[*c*]pyran 25. A mixture of hydroxypyrans **20c** and **21c** (150 mg; 0.48 mmol) in ethyl acetate (25 ml) containing palladium on C (21 mg of a 10% mixture) and one drop of concentrated aqueous hydrogen chloride was hydrogenated at 1 atm. for 15 h. The filtered solution afforded a residue on evaporation of the solvent and this was dissolved in methyl alcohol (3 ml) and added to 10 ml of the buffered solution (described earlier) containing Fremy's salt (0.99 g; 1.84 mmol). The residue obtained on work up (68 mg) was chromatographed to yield the isochromane quinone **25** (40 mg; 35%) as a bright yellow oil. ν_{max} (film) 3494 and 1672 cm^{-1}; δ_H 1.36 (3H, d, *J*=6.2 Hz, 3-CH_3), 1.52 (3H, d, *J*=7.0 Hz, 1-CH_3), 3.42 (1H, d, *J*=2.6 Hz, D_2O exchangeable, 4-OH), 3.82 (3H, s, OCH_3), 3.82 (1H, m, 3-H_a), 4.34 (1H, ddd, *J*=7.2, 2.6, 1.0 Hz, 4-H_a), 4.77 (1H, dq, *J*=7.0, 1.0 Hz, 1-H), 5.88 (1H, s, 7-H); δ_C 18.5 (3-CH_3), 19.2 (1-CH_3), 56.5 (CH_3O), 67.1 (C-3)[a], 67.2 (C-1)[a], 67.6 (C-4)[a] 107.8 (C-7), 137.1 (C-4a)[b], 146.1 (C-8a)[b], 158.8 (C-6), 183.0 (C=O) and 185.8 (C=O); MS (EI): *m/z* (%): 239 (M^++1, 1), 194 (81), 166 (100), 151 (84), 123 (13), 109 (15), 69 (12); $[\alpha]_D$=−69° (*c*=1.28, CH_2Cl_2). Calcd for $C_{12}H_{14}O_5$: C, 60.5; H, 5.9%, M 238. Found: C, 60.6; H, 5.8%.

3.1.16. (1*R*, 3*R*, 4*S*)-4-Acetoxy-3,4-dihydro-6-methoxy-1,3-dimethyl-5,8-dioxy-benzo[*c*]pyran 26. Pyranquinone **25** (12 mg; 0.05 mmol) was stirred in a mixture of pyridine (0.3 ml) and acetic anhydride (0.5 ml) for 2 h and then hydrolysed with water (20 ml). Extraction with ethyl acetate afforded a residue, which was chromatographed using ethyl acetate/hexane (3:7) as eluent to provide the acetate **26** (8 mg; 57%) as a yellow oil. ν_{max} (film) 1728 and 1675 cm^{-1}; δ_H 1.24 (3H, d, *J*=6.6 Hz, 3-CH_3), 1.54 (3H, d, *J*=6.8 Hz, 1-CH_3), 2.08 (3H s, $COCH_3$), 3.82 (3H, s, OCH_3), 4.04 (1H, dq, *J*=5.6, 6.6 Hz, 3-Ha), 4.76 (1H, dq, *J*=6.8, 1.8 Hz, 1-H_e), 5.61 (1H, dd, *J*=5.6, 1.8 Hz, 4-H_a), 5.90 (1H, s, 7-H); δ_C 17.0 (3-CH_3), 19.5 (1-CH_3), 20.9 (CH_3CO), 56.3 (CH_3O), 65.4 (C-1)[a], 65.5 (C-3)[a], 67.9 (C-4)[a], 107.6 (C-7), 133.7 (C-4a)[b], 147.6 (C-8a)[b], 158.6 (C-6), 170.0 ($COCH_3$), 179.6 (C=O) and 185.4 (C=O). HRMS calcd for $C_{14}H_{16}O_6$: 280.09469. Found: 280.09504; de 70% [Eu(hfc)$_3$].

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Palladium catalyzed Suzuki coupling reactions using cobalt-containing bulky phosphine ligands

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Abstract—Three bulky mono-dentate alkyne-bridged dicobalt-phosphine complexes $[(\mu\text{-}PPh_2CH_2PPh_2)Co_2(CO)_4](\mu,\eta\text{-}PhC{\equiv}CPPh_2)$ **4a**, $[(\mu\text{-}PPh_2CH_2PPh_2)Co_2(CO)_4](\mu,\eta\text{-}Me_3CC{\equiv}CPPh_2)$ **5a** and $[(\mu\text{-}PPh_2CH_2PPh_2)Co_2(CO)_4](\mu,\eta\text{-}Me_3SiC{\equiv}CPPh_2)$ **6a** were prepared from the reactions of the bis(diphenylphosphino)methylene (dppm) bridged dicobalt complex $Co_2(CO)_6(\mu\text{-}Ph_2PCH_2PPh_2)$ with $PhC{\equiv}CPPh_2$ **1**, $Me_3CC{\equiv}CPPh_2$ **2**, and $Me_3SiC{\equiv}CPPh_2$ **3**, respectively. These three metal-containing compounds **4a**, **5a** and **6a** were employed as ligands, replacing conventional organic phosphines, in the Suzuki cross-coupling reactions and have been proved to be effective, authentic mono-dentate phosphine ligands.

1. Introduction

Many studies have been focused on Suzuki's palladium-catalyzed cross-coupling reaction in recent years because of its exceptional competence in making sp^2–sp^2 carbon–carbon bond.[1] After several successful methodologies, still a great deal of efforts have been made on promoting the catalytic efficiency with the diversity by the ways of the modification of phosphine ligands,[2] the development of recyclable catalyst[3] and the application to aliphatic electrophiles.[4] It is well known that phosphine ligands play an important role in metal complexes catalyzed organic syntheses. Suitable phosphine ligands are always indispensable for their effective catalytic performance.[5] As established, the mechanism of the palladium-catalyzed cross-coupling reaction involves both oxidative addition and reductive elimination processes.[6] A phosphine with either electron-rich or bulky character is presumed to be able to accelerate the reaction rate and perceived as a potential candidate for an effectively catalytic performance.[7] Although a variety of organic phosphines have already been proved to be efficient in palladium-catalyzed processes, to our best knowledge, only few communications over metal-containing phosphine ligand were published lately.[8]

In our efforts in searching effective ligands for transition metal-catalyzed reactions, we are interested in developing a system that will allow us to straightforward access of a family of bulky phosphines, i.e., cobalt-containing phosphine ligands. The electron-donating capacities of the ligands are expected to be varied after adding cobalt fragment onto the organic moieties. These mono/bi-dentate phosphine ligands can be prepared starting from $Co_2(CO)_8$ with alkynyl phosphines, having the formula of $RC{\equiv}CPPh_2$ or $Ph_2PC{\equiv}CPPh_2$.[9]

Palladium-catalyzed Suzuki cross-coupling reactions of aryl halides with arylboronic acids represent one of the most powerful transformations in organic synthesis.[1b,c,10] In this work, we report some remarkable results of using new type of cobalt-containing mono-dentate phosphine ligands in Suzuki type catalytic coupling reactions. The efficiencies of these ligands are compared and discussed subsequently.

2. Results and discussion

2.1. Preparations of cobalt-containing phosphine ligands

Treatment of a dppm-bridged dicobalt compound $[Co_2(CO)_6(\mu\text{-}P,P\text{-}PPh_2CH_2PPh_2)]$ with one molar equivalent of alkynyl phosphines $R_1C{\equiv}CPPh_2$ (**1**: R_1=Ph; **2**: R_1=CMe_3; **3**: R_1=$SiMe_3$) in THF at 45 °C afforded alkyne-bridged dicobalt compounds $[(\mu\text{-}PPh_2CH_2PPh_2)\text{-}Co_2(CO)_4][\mu,\eta\text{-}R_1C{\equiv}CPPh_2]$ (**4a**: R_1=Ph; **5a**: R_1=CMe_3; **6a**: R_1=$SiMe_3$).[11] (Scheme 1). In addition, two oxidized complexes, $[(\mu\text{-}PPh_2CH_2PPh_2)Co_2(CO)_4](\mu,\eta\text{-}PhC{\equiv}CP(=O)Ph_2)$ **4b** and $[(\mu\text{-}PPh_2CH_2PPh_2)Co_2(CO)_4]\text{-}(\mu,\eta\text{-}Me_3CC{\equiv}CP(=O)Ph_2)$ **5b**, were also obtained along with **4a** and **5a** during the chromatographic processes. Compounds **4a**, **4b**, **5a** and **5b** were characterized by

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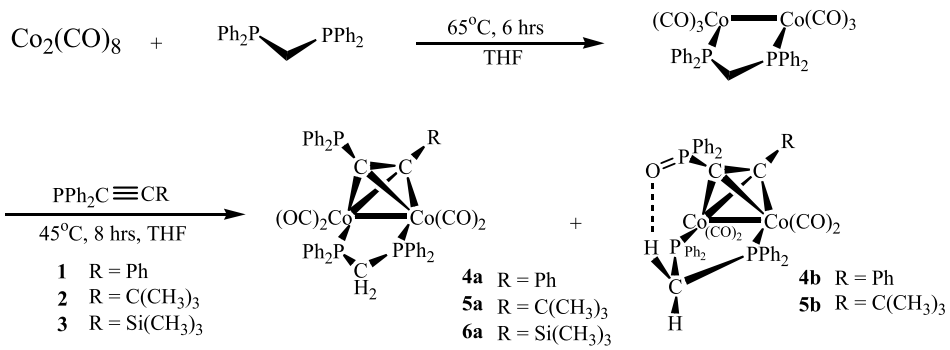


Scheme 1. Synthesis of cobalt-containing phosphine ligands.

spectroscopic means as well as by X-ray diffraction methods (Tables 1 and 2).

The ^{31}P NMR spectrum of **4a** displays two sets of singlet in the ratio of 2:1 at the chemical shifts of 37.5 and 6.8 ppm respectively for three phosphorous atoms. The corresponding signals are 34.7, −6.2 ppm and 34.7, −11.3 ppm for **5a** and **6a**, respectively. The upfield and downfield signals are assigned to the corresponding unbounded and coordinated phosphorous atoms respectively in all cases. The observed large discrepancies in chemical shifts of all three compounds in ^{31}P NMR for the unbounded phosphorous atoms is attributed to the slight difference in electron-donating capacities of these phosphorous atoms. In ^{1}H NMR, there are two distinct chemical shifts 3.32 and 4.25 ppm as well as 3.15 and 4.85 ppm are being observed for the methylene protons of **5a** and **6a**, respectively. Yet, only one set of triplet signal at 3.25 ppm is found for the matching protons in **4a**. It had demonstrated that the signal's outward appearance of the bridged dppm is greatly affected by the degree of its fluxional motion around the dicobalt framework.[9] Based on the ^{1}H NMR spectra, we conclude that the fluxional motion of the bridged dppm is much faster in **4a** than that of **5a** and **6a**.

Similar observations are perceived for the cases of **4b** and **5b**. The ^{31}P NMR spectrum of **4b** shows two singlets in the ratio of 2:1 at 35.7 and 28.4 ppm, respectively, for three phosphorous atoms; while the matching signals are observed at 35.8 and 28.2 ppm, respectively, for **5b**. Large downfield shifts are observed for the oxidized phosphorous atoms. In ^{1}H NMR, a large downfield shift for one of the methylene protons at 5.94 is observed for **4b**, while the matching signal is observed at 6.05 ppm for **5b**.

The selected bond distances and angles for **4a**, **4b**, **5a** and **5b** are displayed in the ORTEP diagrams presented in Figures 1–4. As presented in the figures, the phenyl rings of the bridged alkyne in all cases are pointed away from the center of the molecule to prevent severe steric hindrance. All of the coordinated carbonyl ligands are situated at the terminal positions. Interestingly, the coordinated dppm ligand and the substituent $-PPh_2$ are located on the same side of molecule in **5a**, while they are on the opposite side in **4a**. It can be expected due to the result of minimizing the steric effect among all the bulky groups. In the cases of **4b** and **5b**, the coordinated dppm ligand and the substituent $-P(=O)Ph_2$ are positioned on the same side of molecule. The structures of **4b** and **5b** showed the oxygen atom (of the

Table 1. Crystal data of **4a**, **4b**, **5a** and **5b**

Compound	4a	4b	5a	5b
Formula	$C_{49}H_{37}Co_2O_4P_3{\cdot}CH_2Cl_2$	$C_{49}H_{37}Co_2O_5P_3$	$C_{47}H_{41}Co_2O_4P_3{\cdot}CHCl_3$	$C_{47}H_{41}Co_2O_6P_3$
Formula weight	985.48	916.56	998.93	912.57
Crystal system	Monoclinic	Monoclinic	Monoclinic	Triclinic
Space group	*P*2(1)/*c*	*P*2(1)/*n*	*P*2(1)/*n*	P-1
a (Å)	13.0444(14)	18.431(3)	23.425(3)	11.2292(10)
b (Å)	19.232(2)	11.5373(17)	9.3966(13)	12.1443(10)
c (Å)	18.983(2)	21.411(3)	23.702(3)	17.4801(16)
α (°)	90(3)	90	90	96.014(2)
β (°)	101.294(2)	111.955(2)	118.080(3)	96.402(2)
γ (°)	90(2)	90	90	112.343(2)
V (Å^3)	4670.0(9)	4222.7(10)	4603.0(11)	2162.8(3)
Z	4	4	4	2
D_c (Mg/m^3)	1.402	1.442	1.441	1.401
λ (Mo Kα), Å	0.71073	0.71073	0.71073	0.71073
μ (mm^{-1})	0.971	0.947	1.402	0.926
θ range (°)	1.52 to 26.05	2.04 to 25.99	1.68 to 26.02	1.84 to 26.02
Observed reflections ($F>4\sigma(F)$)	1437	4760	2984	1753
No. of refined parameters	550	540	541	531
*R*1 for significant reflections[a]	0.0592	0.0319	0.0735	0.0574
*wR*2 significant reflections[b]	0.1149	0.0826	0.2001	0.1081
GoF[c]	0.828	0.518	0.895	0.853

[a] $R1 = |\sum(|F_o| - |F_c|)/|\sum F_o||$.
[b] $wR2 = \{\sum[w(F_o^2 - F_c^2)^2/\sum[w(F_o^2)^2\}\}^{1/2}$; $w = 0.0588$, 0.1009, 0.1508 and 0.0509 for **4a**, **4b**, **5a** and **5b**, respectively.
[c] $\text{GoF} = [\sum w(F_o^2 - F_c^2)^2/(N_{\text{rflns}} - N_{\text{params}})]^{1/2}$.

Table 2. Comparison of selected structural parameters of **4a**, **4b**, **5a** and **5b**

	Compound	
	4a	**4b**
Bond lengths (Å)		
Co(1)–C(2)	1.945(8)	1.966(2)
Co(1)–C(1)	1.996(8)	1.974(2)
Co(1)–P(2)	2.242(3)	2.2358(8)
Co(1)–Co(2)	2.4711(16)	2.4851(5)
Co(2)–C(1)	1.945(8)	1.952(2)
Co(2)–C(2)	1.961(8)	1.968(2)
Co(2)–P(3)	2.225(2)	2.2524(7)
P(1)–O(1)		1.5022(19)
P(1)–C(1)	1.770(8)	1.774(2)
P(2)–C(49)	1.855(7)	1.843(3)
P(3)–C(49)	1.810(8)	1.841(2)
C(1)–C(2)	1.371(10)	1.361(3)
C(2)–C(3)	1.485(10)	1.474(3)
Bond angles (°)		
C(2)–Co(1)–C(1)	40.7(3)	40.42(10)
P(2)–Co(1)–Co(2)	94.05(7)	96.81(2)
C(1)–Co(2)–C(2)	41.1(3)	40.62(10)
P(3)–Co(2)–Co(1)	100.44(8)	96.79(2)
C(49)–P(2)–Co(1)	111.8(3)	110.00(9)
C(49)–P(3)–Co(2)	109.8(3)	109.86(9)
C(2)–C(1)–P(1)	140.8(6)	139.1(2)
Co(2)–C(1)–Co(1)	77.6(3)	78.54(9)
C(1)–C(2)–C(3)	137.1(7)	142.4(2)
Co(1)–C(2)–Co(2)	78.5(3)	78.36(9)
P(3)–C(49)–P(2)	112.2(4)	109.94(12)
	5a	**5b**
Bond lengths (Å)		
Co(1)–C(2)	1.965(7)	1.984(5)
Co(1)–C(1)	2.006(7)	1.967(5)
Co(1)–P(2)	2.235(2)	2.2533(16)
Co(1)–Co(2)	2.4621(15)	2.4715(11)
Co(2)–C(1)	1.994(8)	1.998(5)
Co(2)–C(2)	1.991(8)	1.966(6)
Co(2)–P(3)	2.240(2)	2.2328(16)
P(1)–O(1)		1.489(4)
P(1)–C(1)	1.780(8)	1.772(5)
P(2)–C(47)	1.815(8)	1.817(6)
P(3)–C(47)	1.831(7)	1.814(5)
C(1)–C(2)	1.340(10)	1.357(7)
C(2)–C(3)	1.534(10)	1.511(7)
Bond angles (°)		
C(2)–Co(1)–C(1)	39.4(3)	40.15(19)
P(2)–Co(1)–Co(2)	95.41(7)	97.68(5)
C(1)–Co(2)–C(2)	39.3(3)	40.0(2)
P(3)–Co(2)–Co(1)	98.65(7)	95.59(5)
C(47)–P(2)–Co(1)	111.8(2)	109.32(19)
C(47)–P(3)–Co(2)	110.1(2)	109.8(2)
C(2)–C(1)–P(1)	154.7(6)	144.6(4)
Co(2)–C(1)–Co(1)	76.0(3)	77.10(18)
C(1)–C(2)–C(3)	146.6(7)	144.0(5)
Co(1)–C(2)–Co(2)	77.0(3)	77.45(19)
P(3)–C(47)–P(2)	111.6(4)	111.4(3)

oxidized phosphorus) points down toward the adjacent proton of the methylene. The distances between the oxygen and hydrogen atoms are 2.464 and 2.215 Å for **4b** and **5b**, respectively, which are within the normal range of hydrogen bonding.[12] The shorter bond distance in **5b** than **4b** is caused by the stronger repulsive force arose from the much bulkier –*t*Bu group from the back. The presumption of an intramolecular hydrogen bonding between the oxide and the adjacent methylene proton is also evidenced by the observation of a large downfield shift in ^{1}H NMR at 5.94 and 6.05 ppm for **4b** and **5b**, respectively. Consequently, the

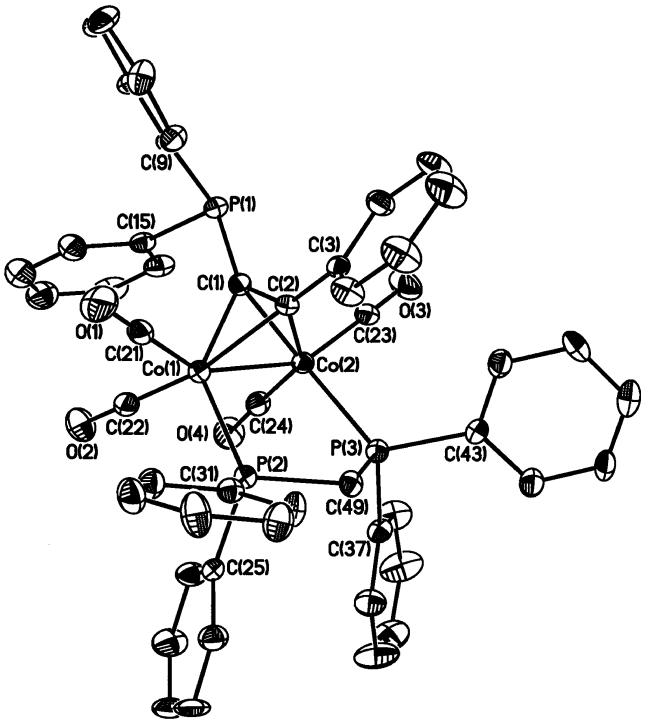


Figure 1. ORTEP drawing of **4a**. Hydrogen atoms are omitted for clarity.

effect of the intramolecular hydrogen bonding plays a crucial role in the arrangement of two bulky groups, dppm and –P(=O)Ph_2, in **4b** and **5b** ligands. The bond lengths of the bridged alkynes are 1.371(10), 1.361(3), 1.340(10) and 1.357(7) Å for **4a**, **4b**, **5a** and **5b**, respectively, which are close to the regular double bond range. The bond length values between two cobalt atoms are very close in all the ligands. They are 2.4711(16), 2.4851(5), 2.4621(15) and 2.4715(11) Å for **4a**, **4b**, **5a** and **5b**, respectively.

2.2. Suzuki reaction using cobalt-containing phosphine ligands 4a, 5a and 6a with Pd complexes

Suzuki type coupling reactions for arylbromide and phenylboronic acid were carried out by employing the newly made cobalt-containing phosphine ligands **4a**, **5a** and **6a**. The catalytic reaction is performed according to Wolfe's procedures.[7d] Table 3 summarizes the reaction conditions and results.

The cross-coupling reaction of phenylboronic acid with 2-bromothiophene was carried out by employing 1 mol% Pd catalyst (Pd/ligand=1/2) at the reaction temperature of 50 °C for 19 h. The yields are 33 and 42% using **4a** and **5a** as ligands, respectively (entries 1 and 2). These yields are improved to 63 and 75% by raising the temperature to 80 °C and reacting for 16 h (entries 3 and 4). The highest yields 86 and 91% are obtained for **4a** and **5a** ligands, when these reactions were carried out at 100 °C and for 16 h in toluene as solvent (entries 5 and 6). Under similar conditions, the yield is 87% using **6a** as phosphine ligand (entry 7). The results show that these cobalt-containing mono-dentate phosphines are efficient ligands for the Suzuki reactions. Similarly, the cross-coupling reaction was carried out for a less reactive substrate, aryl bromide, under the identical reaction conditions. Initially, the yield was poor (≤29%) in

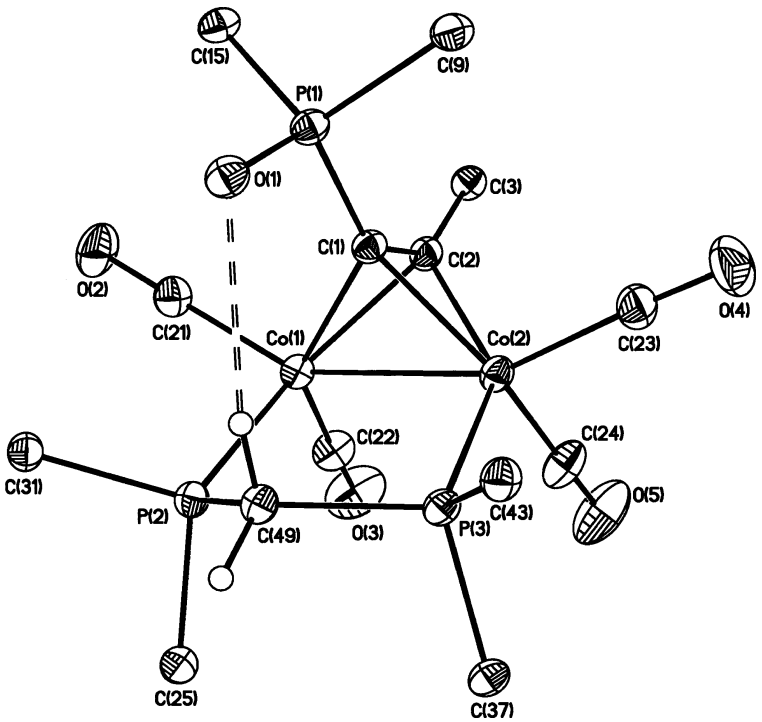


Figure 2. ORTEP drawing of **4b**. Some carbon and hydrogen atoms are omitted for clarity.

the absence of any phosphine ligand (entry 8). On the other hand, much better yields (≥91%) were observed when **4a**, **5a** and **6a** were employed as ligands (entries 9–11). These results are comparable to the data reported by Gladysz et al. using $CpRu(PEt_3)_2PPh_2$ as catalyst.[8c] It clearly shows that all these three compounds are competent phosphine ligands with fairly good activity in Suzuki reaction. Almost complete conversions were obtained using 4-bromobenzaldehyde as substrate, which is in consistence with the common observation for an aryl halide with an electron-withdrawing substituent[8g] (entries 12–14). The results observed in Table 2 echoes the observations of Buchwald and Fu stating that a phosphine ligand with a bulky $-t$Bu as substituent is more efficient than with a less bulky –Ph.[2,7d]

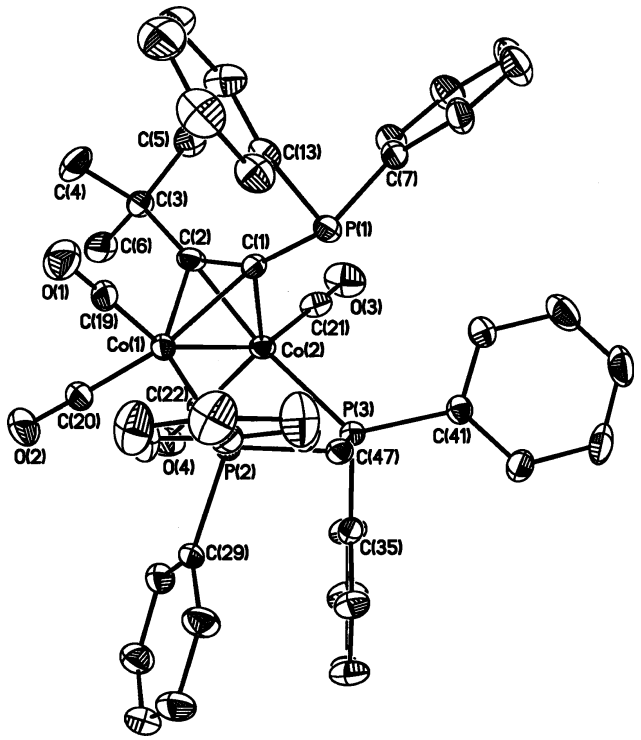


Figure 3. ORTEP drawing of **5a**. Hydrogen atoms are omitted for clarity.

3. Summary

We have demonstrated the preparations and reactivity studies of three new organometallic phosphine ligands **4a**, **5a** and **6a** designed for the palladium-catalyzed Suzuki cross-coupling reaction. Compound **5a** exhibited the highest catalytic efficiency among ligands **4a**, **5a** and **6a** for the cross-coupling reaction of aryl bromides with phenylboronic acid.

4. Experimental

4.1. General

All operations were performed in a nitrogen-flushed glove box or in a vacuum system. Freshly distilled solvents were used. All processes of separations of the products were performed by Centrifugal Thin Layer Chromatography (CTLC, Chromatotron, Harrison model 8924) or column chromatography. ^{1}H NMR spectra were recorded on 300 MHz Varian VXR-300S spectrometer. The chemical shifts are reported in ppm relative to internal standard $CHCl_3$ or CH_2Cl_2. ^{31}P and ^{13}C NMR spectra were recorded at 121.44 and 75.46 MHz, respectively. Some other routine ^{1}H NMR spectra were recorded over Gemini-200 spectrometer at 200.00 MHz or Varian-400 spectrometer at 400.00 MHz. IR spectra of samples using KBr were

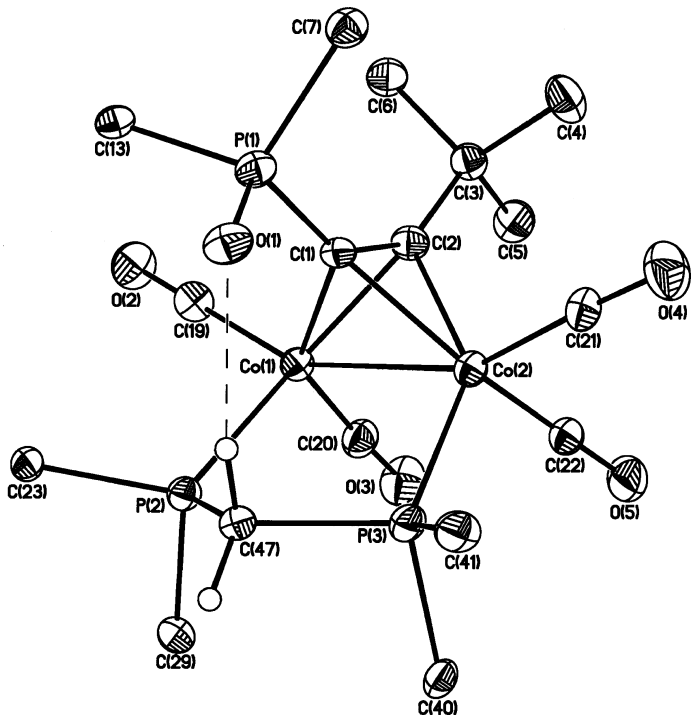
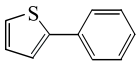
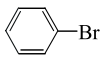
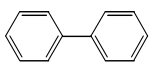
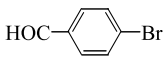
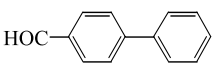


Figure 4. ORTEP drawing of **5b**. Some carbon and hydrogen atoms are omitted for clarity.

Table 3. Suzuki coupling reactions using cobalt-containing phosphine ligands[a]

Entry	Aryl halide	Product	Ligand	Time (h)	Yield (%)
1			**4a**	19	33[b]
2			**5a**	19	42[b]
3			**4a**	16	63[c]
4			**5a**	16	75[c]
5			**4a**	16	86
6			**5a**	16	91
7			**6a**	16	87
8			None	16	29
9			**4a**	16	93
10			**5a**	16	95
11			**6a**	16	91
12			**4a**	16	98
13			**5a**	16	99
14			**6a**	16	97

[a] Reaction conditions: 1.0 equiv. aryl bromide, 1.5 equiv. boronic acid, 2.0 equiv. K_3PO_4, 1 mol% $Pd(OAc)_2$, 2 mol% cat. ligand, toluene (1 mL/mmol aryl bromide), 100 °C; reaction times have not been minimized. Yields in the table are represented in isolated yields (average of two or more experiments) of compounds are estimated to be ≥95% pure as determined by ^1H NMR.
[b] The reaction was conducted at 50 °C using THF (1 mL/mmol aryl bromide) and KF (3.0 equiv.) in place of toluene and K_3PO_4.
[c] The reaction was conducted at 80 °C.

recorded on a Hitachi 270-30 spectrometer. Mass spectra were recorded on JOEL JMS-SX/SX 102A GC/MS/MS spectrometer. Elemental analyses were recorded on Heraeus CHN-O-S-Rapid.

4.2. Synthesis of $PhC{\equiv}CPPh_2$ 1 and $Me_3CC{\equiv}CPPh_2$ 2

The preparative procedure for the formation of **1** or **2** was modified to the method reported in literature.[13] Phenylacetylene (1.021 g, 10.000 mmol) and dimethylether (10 mL) were taken in a 100 mL round bottomed flask charged with magnetic stirrer. In a separate round bottomed flask, one molar equivalent of *n*-butyllithium (2.0 M in cyclohexane) dissolved in dimethylether (5 mL). The *n*-butyllithium solution is slowly added to the above mixture under stirring at −78 °C. The resultant mixture is continued to stir at −78 °C for more than 1 h, then one molar equivalent of diphenylchlorophosphine (2.206 g, 10.0 mmol) dissolved in 5 mL dimethylether (5 mL) was slowly added to it. The reaction mixture was then allowed to warm up to room temperature and then stirred for another 1 h. The solvent was removed under reduced pressure and toluene was added to precipitate the lithium chloride. After filtration, the resulted solution was further purified by chromatography. The solid obtained in white needles was identified as **1**.The isolated yield obtained in the reaction is

75.0% (2.147 g, 7.500 mmol). The same procedure was followed for the preparation of **2**.The reaction is started with 3,3-dimethyl-1-butyne (0.822 g, 10.000 mmol) as the alkyne source. The white colored compound obtained was identified as **2**.The isolated yield obtained in the reaction is 78.0% (2.077 g, 7.800 mmol).

4.2.1. Compound 1. ^{1}H NMR ($CDCl_3$, ppm): 7.70–7.22 (15H, arene). ^{31}P NMR ($CDCl_3$, ppm): −32.7 (s, 1P, C≡CP). IR (KBr, cm^{-1}): 2170 (s) (C≡C). MS (FAB): *m*/*z* 286 (M^+).

4.2.2. Compound 2. ^{1}H NMR ($CDCl_3$, ppm): 7.71–7.36 (10H, arene), 1.42 (s, 9H, CMe_3). ^{31}P NMR ($CDCl_3$, ppm): −33.6 (s, 1P, C≡CP). IR (KBr, cm^{-1}): 2171 (s), 2220 (s) (C≡C). MS (FAB): *m*/*z* 266 (M^+).

4.3. Synthesis of [(μ-$PPh_2CH_2PPh_2$)$Co_2(CO)_4$](μ,η-PhC≡CPPh_2) 4a, [(μ-$PPh_2CH_2PPh_2$)$Co_2(CO)_4$](μ,η-PhC≡CP(=O)Ph_2) 4b, [(μ-$PPh_2CH_2PPh_2$)$Co_2(CO)_4$]-(μ,η-Me_3CC≡CPPh_2) 5a and [(μ-$PPh_2CH_2PPh_2$)-$Co_2(CO)_4$](μ,η-Me_3CC≡CP(=O)Ph_2) 5b

1.0 mmol of dicobalt octacarbonyl, $Co_2(CO)_8$ (0.342 g), 1.0 mmol of dppm (0.385 g) and 10 mL of THF were taken in a 100 mL round bottomed flask charged with magnetic stirrer. The solution was stirred at 65 °C for 6 h, a yellow-colored compound, $Co_2(CO)_6$(μ-P,P–$PPh_2CH_2PPh_2$), was yielded. Without separation, the reaction flask was further charged with one molar equivalent of **1** (0.286 g) in 5 mL of THF and then the solution was allowed to stir at 45 °C for 8 h. The solvent was removed under reduced pressure and the resulted dark red-colored residue was separated by CTLC. A purple band was eluted out by mixed solvent (CH_2Cl_2–hexane=1:1) and the compound was identified as **4a** with the yield of 55.0% (0.495 g, 0.550 mmol). A small red band, followed by **4a** during the chromatographic process, was eluted out and the red-colored compound was identified as **4b** with the yield of 9.3% (0.085 g, 0.093 mmol). The similar procedure was followed for the preparations of **5a** and **5b** started with $Co_2(CO)_8$ (0.342 g, 1.000 mmol), dppm (0.385 g, 1.000 mmol) and **2** (0.266 g, 1.000 mmol). The first separated red-colored compound, which was eluted out by mixed solvent (CH_2Cl_2–hexane=1:1), was identified as **5a** with the yield of 60.0% (0.480 g, 0.600 mmol). The second red-colored compound was identified as **5b** with the yield of 6.1% (0.055 g, 0.061 mmol).

4.3.1. Complex 4a. ^{1}H NMR ($CDCl_3$, ppm): 7.54–6.92 (35H, arene), 3.30 (t, J_{P-H}=10.2 Hz, 2H, CH_2). ^{13}C NMR ($CDCl_3$, ppm): 132.3–127.8 (42C, arene), 36.6 (s, 1C, CH_2). ^{31}P NMR ($CDCl_3$, ppm): 37.5 (s, 2P, dppm), 6.8 (s, 1P, PPh_2). IR (KBr, cm^{-1}): 2020 (s), 1994 (s), 1967 (s) (C=O). MS (ESI): *m*/*z* 902 (M^++1). Anal. Calcd for $C_{49}H_{37}Co_2O_4P_3$: C, 65.35; H, 4.14. Found: C, 62.56; H, 3.86.

4.3.2. Complex 4b. ^{1}H NMR ($CDCl_3$, ppm): 7.78–7.04 (35H, arene), 6.02–5.94 (m, 1H, CH_2), 3.40–3.33 (m, 1H, CH_2). ^{13}C NMR ($CDCl_3$, ppm): 206.5, 200.8 (s, 2C, CO), 138.2–126.4 (42C, arene), 36.7 (t, J_{P-C}=78.0 Hz, 1C, CH_2). ^{31}P NMR ($CDCl_3$, ppm): 35.7 (s, 2P, dppm), 28.4 (s, 1P, PPh_2). IR (KBr, cm^{-1}): 2021 (s), 1995 (s), 1974 (s) (C=O). MS (FAB): *m*/*z* 918 (M^++1). Anal. Calcd for $C_{49}H_{37}Co_2O_5P_3$: C, 64.21; H, 4.07. Found: C, 61.50; H, 3.59.

4.3.3. Complex 5a. ^{1}H NMR ($CDCl_3$, ppm): 7.46–7.00 (30H, arene), 4.33–4.19 (m, 1H, CH_2), 3.39–3.28 (m, 1H, CH_2), 1.29 (s, 9H, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$, ppm): 207.8, 203.1 (s, 2C, CO), 138.5–127.4 (36C, arene), 37.6 (s, 1C, CH_2), 33.2 (s, 3C, $C(CH_3)_3$). ^{31}P NMR ($CDCl_3$, ppm): 34.7 (s, 2P, dppm), −6.2 (s, 1P, PPh_2). IR (KBr, cm^{-1}): 2009 (s), 1984 (s), 1962 (s) (C=O). MS (ESI): *m*/*z* 880 (M^+). Anal. Calcd for $C_{47}H_{41}Co_2O_4P_3$: C, 64.10; H, 4.69. Found: C, 63.92; H, 5.07.

4.3.4. Complex 5b. ^{1}H NMR ($CDCl_3$, ppm): 7.82–7.00 (30H, arene), 6.05 (brd, 1H, CH_2), 3.29 (brd, 1H, CH_2), 1.26 (s, 9H, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$, ppm): 209.6, 208.0 (s, 2C, CO), 138.5–125.1 (36C, arene), 38.0 (s, 1C, $C(CH_3)_3$), 35.4 (t, J_{P-C}=76.4 Hz, 1C, CH_2), 33.2 (s, 3C, $C(CH_3)_3$). ^{31}P NMR ($CDCl_3$, ppm): 35.8 (s, 2P, dppm), 28.2 (s, 1P, PPh_2). IR (KBr, cm^{-1}): 2016 (s), 1991 (s), 1960 (s) (C=O). MS (FAB): *m*/*z* 896 (M^+). Anal. Calcd for $C_{47}H_{41}Co_2O_5P_3$: C, 62.96; H, 4.61. Found: C, 63.83; H, 4.91.

4.4. General procedure for the Suzuki coupling reactions

Suzuki coupling reaction was performed according to Wolfe's procedure.[7d] The four reactants, $Pd(OAc)_2$ (2.200 mg, 0.010 mmol), phosphine ligand **4a** (or **5a**, **6a**) (L/$Pd(OAc)_2$=2/1), the boronic acid (0.183 g, 1.500 mmol) and K_3PO_4 (0.425 g, 2.000 mmol) were taken into a suitable oven-dried Schlenk flask. The flask was evacuated and backfilled with nitrogen before adding toluene (1 mL) and the aryl halide (1.000 mmol) through a rubber septum. The aryl halides being solids at room temperature were added prior to the evacuation/backfill cycle. The flask was sealed with Teflon screw cap and the solution was stirred at the required temperature for designated hours. Then, the reaction mixture was diluted with ether (30 mL) and poured into a separatory funnel. The mixture was washed with aqueous NaOH (1 M, 20 mL) and the aqueous layer was extracted with ether (20 mL). The combined organic layer were washed with brine (20 mL) and dried with anhydrous magnesium sulfate. The dried organic layer was concentrated in vacuo. The crude material was further purified by flash chromatography on silica gel.

4.4.1. 2-Phenylthiophene. ^{1}H NMR ($CDCl_3$, ppm): 7.69 (d, *J*=7.2 Hz, 2H), 7.44 (dd, *J*=7.8, 7.2 Hz, 2H), 7.44 (t, *J*=7.8 Hz, 1H), 7.37 (d, *J*=3.8 Hz, 1H), 7.33 (d, *J*=5.0 Hz, 1H), 7.13 (dd, *J*=5.0, 3.8 Hz, 1H).

4.4.2. Biphenyl. ^{1}H NMR ($CDCl_3$, ppm): 7.59 (t, *J*=11.2 Hz, 2H), 7.44 (m, *J*=46.8 Hz, 4H), 7.35 (d, *J*=8 Hz, 4H).

4.4.3. 4-Biphenylcarbaldehyde. ^{1}H NMR ($CDCl_3$, ppm): 10.01 (s, 1H, COH), 7.73 (d, *J*=8.2 Hz, 2H), 7.52 (d, *J*=8.2 Hz, 2H), 7.40 (d, *J*=8.4 Hz, 2H), 7.30–7.19 (m, *J*=23.4 Hz, 3H).

4.5. X-ray crystallographic studies

Suitable crystals of **4a**, **4b**, **5a**, and **5b** were sealed in

thin-walled glass capillaries under nitrogen atmosphere and mounted on a Bruker AXS SMART 1000 diffractometer. Intensity data were collected in 1350 frames with increasing ω (width of 0.3° per frame). The absorption correction was based on the symmetry equivalent reflections using SADABS program. The space group determination was based on a check of the Laue symmetry and systematic absences, and was confirmed using the structure solution. The structure was solved by direct methods using a SHELXTL package.[14] All non-H atoms were located from successive Fourier maps and the hydrogen atoms were refined using a riding model. Anisotropic thermal parameters were used for all non-H atoms and fixed isotropic parameters were used for H atoms.[15] Crystallographic data of **4a**, **4b**, **5a**, and **5b** are summarized in Table 1.

5. Supplementary information

Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Center, CCDC no. 216404-216407 for compounds **4a**, **4b**, **5a**, and **5b**, respectively. Copies of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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Regioselective hydroxylation of 2-hydroxychalcones by dimethyldioxirane towards polymethoxylated flavonoids

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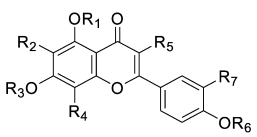
Abstract—The flavone nucleus is part of a large number of natural products and medicinal compounds. In this presentation the novel regioselective hydroxylation of hydroxyarenes with DMD is described. The results showed further that flavonoids with 5-hydroxy group were selectively oxyfunctionalized at the *para*-position C8 carbon atom by DMD. Finally, according to this methodology, the naturally occurring isosinensetin, tangeretin, sinensetin, nobiletin, natsudaidain, gardenin B, 3,3′,4′,5,6,7,8-heptamethoxyflavone, quercetin and its derivatives were synthesized.

1. Introduction

The flavone nucleus is part of a large number of natural products and medicinal compounds.[1] Quercetin (**7**) and kaempferol[2] are known as potential anti-tumor agents and human immunodeficiency virus (HIV) type 1 integrase inhibitors.[3] In addition, the polyphenol constituents of fruits, vegetables, and beverages are important contributors to health benefits including anticancer and antiviral activities and reduce the risk of coronary heart disease and stroke.[4] Recently much attention has focused on the protective biochemical function of naturally occurring antioxidants in biological systems, and on their mechanisms of action. Phenolic compounds were considered to play an important role for the prevention of oxidative damage in living systems.[5] Moreover, in capturing free radicals, their antioxidant activity is highly influenced by the presence of oxygenated groups (hydroxyls, methoxyls) on the aromatic rings. For instance, our previous investigation indicated that the CAPE analogues[6a–c] are therapeutically useful in analogy to the structural feature of an *ortho*-dihydroxy system.[7] In our observations,[6b] the ability of **7** and glycyrrhizin to scavenge free-radicals and block lipid peroxidation raises the possibility that they may act as protective factors against carcinogenesis, and it implies that **7** is better than glycyrrhizin as a chemopreventor against cytotoxicity and genotoxicity on co-exposure of cadmium and AA in V79 cells. Compound **7** is also consistent with structure and activity relationship that the aryl units contain at least one aryl ring required *ortho* bis-hydroxyl groups for significant inhibitory potency of antioxidants. Furthermore, Yano et al. have observed that six polymethoxylated flavonoids, namely, tangeretin (**2**), sinensetin (**3**), nobiletin (**4**), natsudaidain (**5**), gardenin B (**6**), and 3,3′,4′,5,6,7,8-heptamethoxyflavone (**8**), are important candidates for cancer-protective action.[8] In addition, Rio et al.[9] found that quercetogetin may play a protective role against pathogenic attack, and the biological activities of the polymethoxylated flavones are not well understood. Due to the medicinal imperatives, the scarcity of polyhydroxylated or polymethoxylated flavones and the clear need for a reliable supply, we are stimulated to synthesize polymethoxylated flavonoids **1**–**13**.



isosinensetin	**1** R_1=R_2=R_5=H,R_3=R_6=Me,R_4=R_7=OMe	**8** R_1=R_3=R_6=Me,R_2=R_4=R_5=R_7=OMe
tangeretin	**2** R_1=R_3=R_6=Me,R_2=R_4=OMe,R_5=R_7=H	**9** R_1=R_3=R_6=Me,R_2=R_4=H,R_5=R_7=OMe
sinensetin	**3** R_1=R_3=R_6=Me,R_2=R_7=OMe,R_4=R_5=H	**10** R_1=R_3=R_6=Me,R_2=R_4=H,R_5=OH,R_7=OMe
nobiletin	**4** R_1=R_3=R_6=Me,R_2=R_4=R_7=OMe,R_5=H	**11** R_1=R_2=R_4=H,R_3=R_6=Me,R_5=R_7=OMe
natsudaidain	**5** R_1=R_3=R_6=Me,R_2=R_4=R_7=OMe,R_5=OH	**12** R_1=R_2=H,R_3=R_6=Me,R_4=R_5=R_7=OMe
gardenin B	**6** R_1=R_5=R_7=H,R_2=R_4=OMe,R_3=R_6=Me	**13** R_1=R_3=R_6=Me,R_2=H,R_4=R_5=R_7=OMe
quercetin	**7** R_1=R_2=R_3=R_4=R_6=H,R_5=R_7=OH	

Keywords: Flavones; Hydroxylation; Dioxirane.
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We have developed syntheses of kaempferol and methylated kaempferols,[10] which has been worked on C3-hydroxylation of flavone by dimethyl dioxirane (DMD).[11] There are semisynthetic studies in the literature.[10] The reported results[10] and our preliminary study shows that the flavones can be synthesized from *o*-hydroxyketones or chalcones using the Allan-Robinson[10] or Algar-Flym-Oyamada[10] reaction, but in poor yields. Moreover, compared with other approaches for synthesizing polymethoxylated flavones, the oxidative reaction of the C-3 flavones was proved impossible to effect lithiolation with LDA or LHMDS, $B(OMe)_3$, and H_2O_2. Alternately, oxidative-hydroxylation of DMD has been reported by several groups.[12] Recently Bernini et al. claimed that aromatic ring hydroxylation of flavanones by DMD under acidic media.[13] However, the scope of this process appears to be limited. For example, the free hydroxy group of flavones affects the reaction, and it has a competition pathway between C3 hydroxylation and aromatic rings. Herein we report the regioselective hydroxylation of 2-hydroxylchalcones by DMD towards isosinensetin (**1**), **2**, **3**, **4**, **5**, **6**, **8**, **7** and its derivatives efficiently.

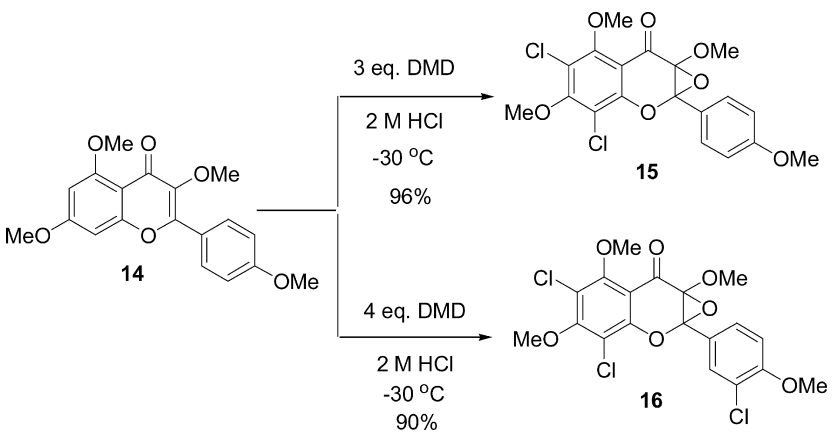
2. Results and discussion

In the beginning of our synthesis, the availability of methylated flavones prompted us to prepare polymethoxylated flavones from this compound. The synthetic compound **14**[10] was treated with 3 or 4 equiv. DMD (0.22 or 0.30 mmol) under 2 M HCl conditions to give the undesired chlorinated products **15** and **16** in excellent yield 96 and 90%, respectively (Scheme 1). The structures were analyzed by ^1H, ^{13}C NMR, and mass spectra. Thus, the utilization of acid media in DMD oxidation reactions on the methylated flavones cannot allow us to synthesize the polymethoxylated flavonoids.

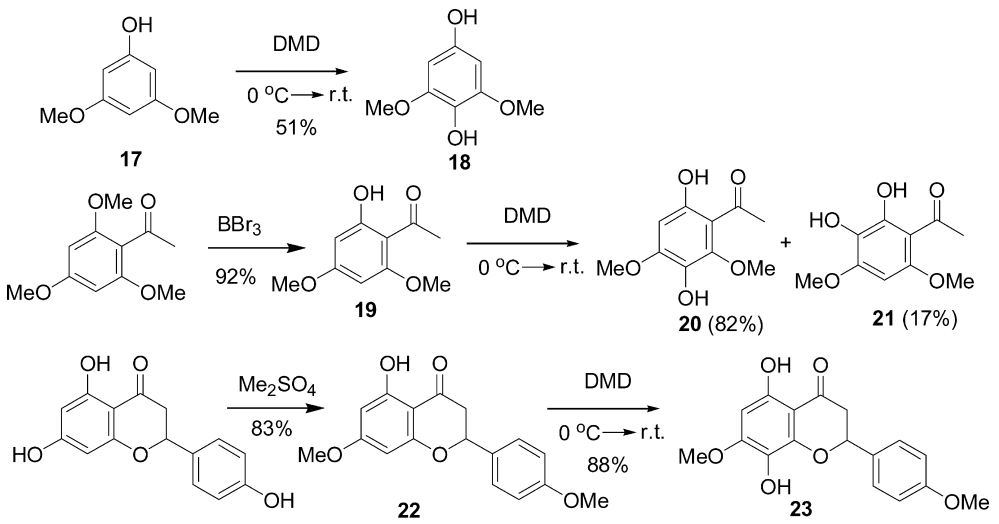
To evaluate this approach to hydroxyflavones, we tested simple aromatic compounds and 5-hydroxyflavonoids (**22**) and examine its versatility (Scheme 2). Insight into the scope of this reaction was initially gained in study with 3,5-dimethoxyphenol **17**. The hydroxybenzene **17** was treated with 1 equiv. DMD for 2 h to provide the dominated regiospecific product **18** in moderate yield 51%. Moreover, it can be smoothly obtained by the hydroxylation of **19** under previous conditions to afford the desired dihydroxyarene **20**. However, the adjacent hydroxyl **21** was accompanied in 17% yield. In a similar fashion, one interesting result had come from the reaction of 5-hydroxyflavanone **22** with DMD to provide the regiospecific hydroxylated product **23** in high yield 88%. The *regio*-structure of **20** was confirmed by use of X-ray crystallographic method.[14] Although, we do not know the detailed mechanism of the regioselective hydroxylation with DMD in the phenols. On the basis of these observations and Adam's[15] studies, the mechanistic route for the formation of the corresponding hydroxyl products involve an epoxide-intermediate **24**[15] at the first stage, and it then undergo a ring opening to obtain the regioselective *ortho*- and *para*-hydroxyl arenes (Scheme 3).

As a consequence of the biological and structural interest in polymethoxyl flavonoids, we initiated using this novel regioselective hydroxylation by DMD to prepare these substances, such as **1**, **7**, *tetra-O*-methylisoscutellarein (**27**), and kaempferols. It is worth noted that this oxyfunctional reaction may occur on the free 5-hydroxy group of flavones. The 5-hydroxy group could play a determining role in favoring C8-position oxyfunctionalized process. The C8 hydroxyl products obtained in this way appear useful starting materials to access polymethoxygenated flavonoids, known to be antioxidant and anti-tumor compounds. The results are shown in Scheme 4, which is manipulated by the treatment of 5-hydroxyflavones, **25**[10] and **26a**,[16] via the sequence of DMD and Me_2SO_4. For instance, compound **25** was readily performed by C8-hydroxylation with 1 equiv. DMD under neutral conditions and followed by methylation with 1 equiv. Me_2SO_4 to obtain the expected **27** in high yield (two steps 85%). Moreover, **26a** was also underway with 1 equiv. DMD to provide the C8-hydroxylation flavone, and followed by methylation to give **1** and **28** in 55 and 38% yield (two steps), respectively. On the other hand, the methylation of **26a** with Me_2SO_4 to provide the methylated flavone **26b** in excellent yield (97%), which could be converted by the sequence of C3-oxidative-hydroxylation and demethylation to afford kaempferol and quercetin derivatives **7**, **9**, **10**, and **11** as well.

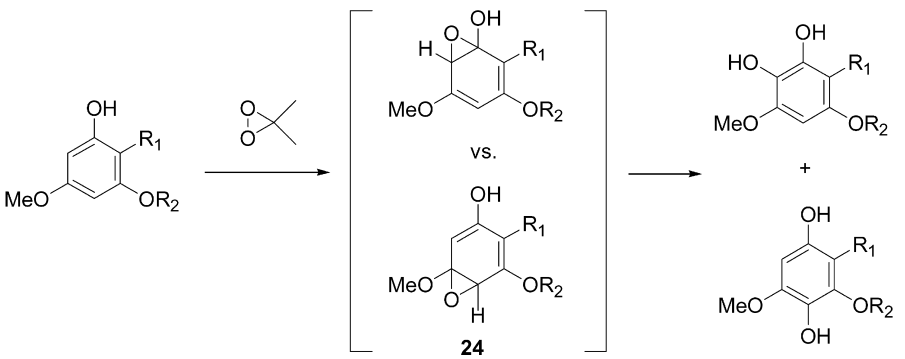
With the 5-hydroxy flavone **11** in hand, it can readily proceed with the regioselective oxidative-hydroxylation by DMD to afford the desired product **29** in high yield 89%



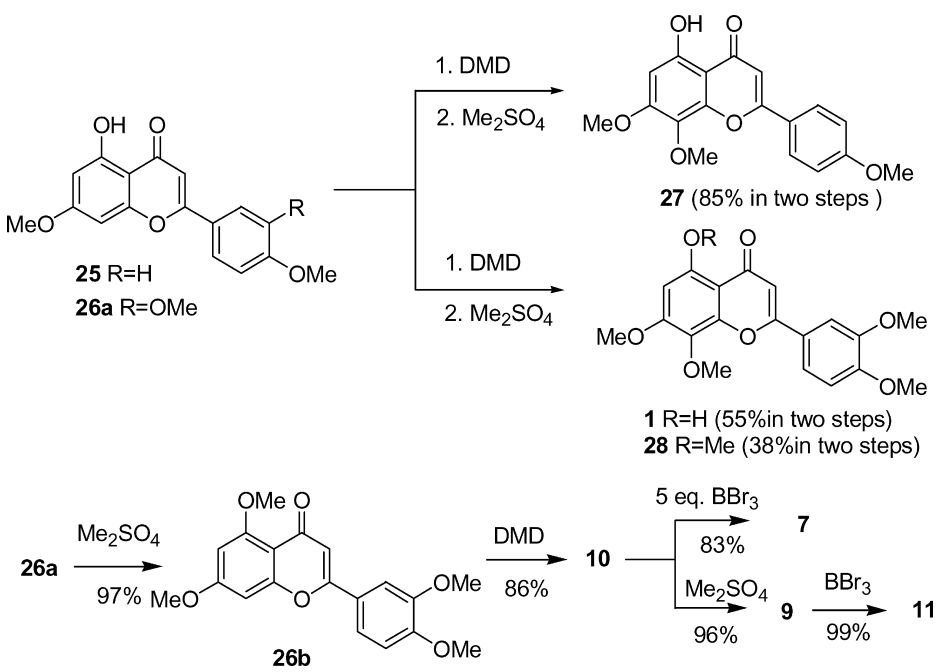
Scheme 1.



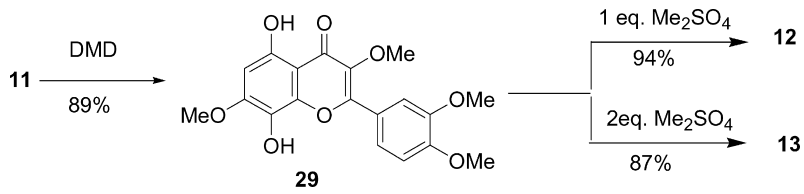
Scheme 2.



Scheme 3.



Scheme 4.

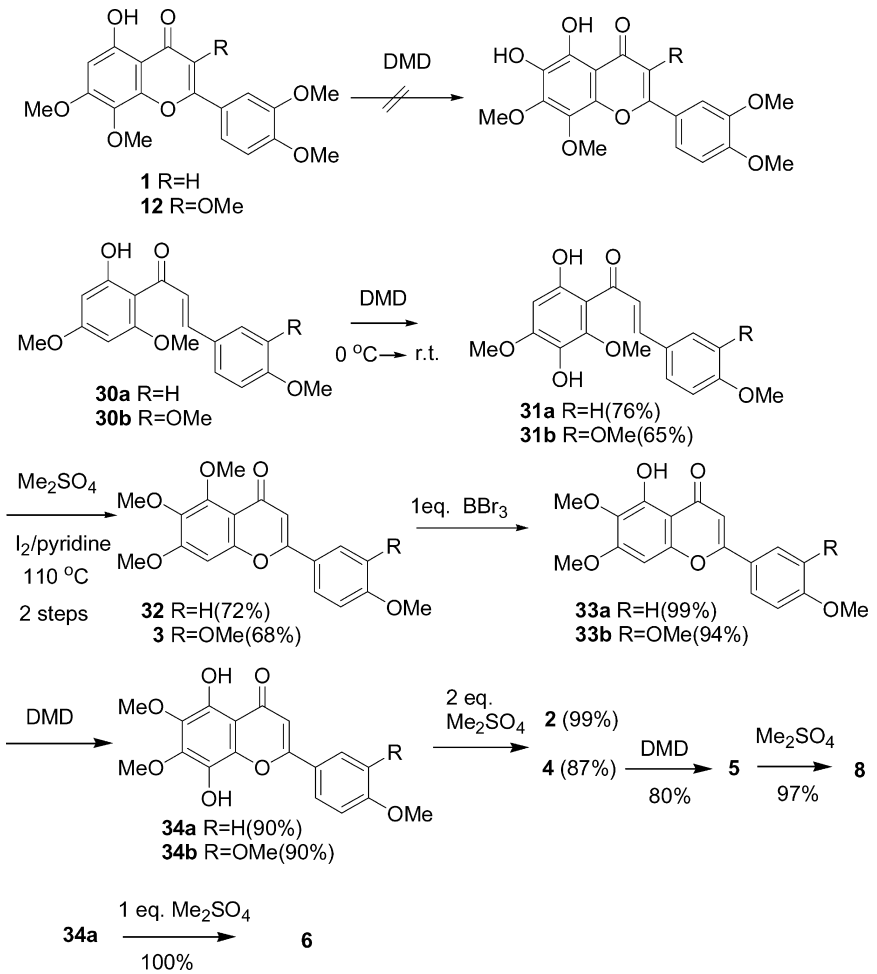


Scheme 5.

(Scheme 5). Sequentially, the dihydroxyl flavone **29** was treated with Me_2SO_4 to achieve the natural occurring product **12** in high yield (two steps 84% from **11**). The result also observed that **11** was transformed by the treatment of DMD and followed by methylation with 2 equiv. Me_2SO_4 to produce the polymethylated flavone **13** in good yield (two steps 77%).

Finally, we applied our strategy to the synthesis of the polymethoxyflavones **2**–**8**. Attempts to obtain 5,6-dihydroxyflavones from 5-hydroxyflavones with DMD and subsequent methylation with Me_2SO_4 (Scheme 6) were unsuccessful, and resulted in the B-ring opening and oxidative-degradation products, chalcones, ketones and aldehydes from 5-hydroxyflavones. An alternative procedure involving regioselective hydroxylation of 2-hydroxychalcones **30a** or **30b**, followed by a methylation and an oxidative-cyclization reaction on the resulting dihydroxychalcones **31a** or **31b** using Me_2SO_4 and I_2/pyridine gave good yields of the corresponding naturally occurring *tetra-O*-methylscutellarein **32** and **3**, respectively. The *regio*-structures of **31a**, **31b** and **32** were identified by use of X-ray crystallographic method.[14] With the key intermediates **3** and **32** in hand, it is manipulated by the treatment of polymethoxyflavones, **3** and **32**, via the sequence of BBr_3, DMD, and Me_2SO_4. For example, compounds, **3** and **32**, were readily employed by C5-demethylation with 1 equiv. BBr_3, and followed by the regioselective hydroxylation and methylation with DMD and Me_2SO_4 under standard conditions to obtain the naturally occurring **2**, **4** and **6** in a high yield 88, 74 and 89% (three steps from **3** and **32**), respectively. Furthermore, compound **4** could be converted by the sequence of C3-hydroxylation and methylation to afford **5** and **8** as well.

In summary, we have developed the versatility of DMD in



Scheme 6.

C3- and C8-hydroxylation of flavones and provided a practical method to synthesize the naturally occurring methylated flavones **1**–**13** starting with commercially available aldehyde. In addition, the key intermediates **3** and **32**, polymethoxyflavones, have efficiently been synthesized by cross-aldol condensation, DMD regioselective hydroxylation and I_2 oxidative promoting-cyclization. However, the regioselective C8-hydroxylation of aromatic ring, 5-hydroxyflavone, is predominated over the conjugated C3- or C6-position of flavones. Therefore, the mechanistic studies should be addressed in near future. Further polymethylated or polyhydroxylated flavones are currently underway to employ this strategy for supplying biological assays.

3. Experimental[17]

3.1. General procedure for hydroxylation with DMD

The required amount (5.0–150 mL) of the DMD (prepared according to Adam's method[11]) in acetone (0.01–0.05 M) was added rapidly to a cooled solution of flavones or aromatic compound under neutral conditions. Stirring was continued for various time, the reaction was monitored by TLC analysis. The solvent was removed and the residue was subjected to column chromatography to give the corresponding oxygenated or chlorinated products.

3.1.1. 1a,7a-Dihydro-3,5-dichloro-4,6-dimethoxy-1a-(4-methoxyphenyl)-7a-methoxy-7*H*-oxireno[b][1]benzopyran-7-one (15). A solution of **14** (25 mg, 0.073 mmol) in CH_2Cl_2 was cooled down to −30 °C under 2 M HCl (4.0 mmol), and then treated with DMD (22 mL, 0.22 mmol) for stirring 1 min. The solvent was removed in vacuo, and the residue was subjected to column chromatography (CH_2Cl_2/ether 2:1) to obtain the chlorinated product **15** (30 mg, 96%) as a white solid: mp 119–121 °C (acetone); ^{1}H NMR ($CDCl_3$) δ 3.53, 3.89, 4.03 and 4.19 (3H each, s, OMex4), 6.96 and 8.26 (2H each, d, J=9.0 Hz, 2,6-H, 3,5-H); ^{13}C NMR ($CDCl_3$) δ 53.4, 55.5, 61.3, 63.1, 107.0, 108.9, 109.0, 113.7, 115.7, 125.7, 133.4, 153.8, 161.7, 164.4, 165.8, 187.6, 189.8; HRMS (FAB+H) calcd for $C_{19}H_{17}O_7Cl_2$: 427.0351 [M+H], found: m/z 427.0351 $[M+H]^+$.

3.1.2. 1a,7a-Dihydro-3,5-dichloro-4,6-dimethoxy-1a-(3-chloro-4-methoxyphenyl)-7a-methoxy-7*H*-oxireno[b][1]benzopyran-7-one (16). Followed by previous procedures and conditions, a solution of **14** (25 mg, 0.073 mmol) in CH_2Cl_2 was treated with DMD (30 mL, 0.30 mmol) for stirring 1 min. The solvent was removed in vacuo, and the residue was subjected to column chromatography (CH_2Cl_2/ether 2:1) to obtain the chlorinated product **16** (30 mg, 90%) as an oil: ^{1}H NMR ($CDCl_3$) δ 3.53, 3.99, 4.03 and 4.19 (3H each, s, OMex4), 7.01 (1H, d, J=8.5 Hz, 5-H), 8.24 (1H, d, J=8.5 Hz, 6-H), 8.27 (1H, s, 2-H); ^{13}C NMR ($CDCl_3$) δ 53.5, 56.4, 61.3, 63.1, 107.0, 108.7, 108.7, 111.1, 115.9, 122.8, 126.2, 131.9, 132.9, 153.8, 159.6, 161.8, 165.7, 186.9, 189.4.

3.1.3. 2,6-Dimethoxybenzene-1,4-diol (18). The compound **17** (150 mg, 0.97 mmol) in CH_2Cl_2 was added DMD (5.0 mL) for stirring 50 min from 0 °C to room temperature. The purification was employed by column chromatography (hexane/ether 2:1) to provide the desired dihydroxy benzene **18** (84 mg, 51%) as a yellow solid: mp 253–255 °C (acetone) (lit.[18] mp 149 °C).

3.1.4. 3,6-Dihydroxy-2,4-dimethoxyacetophenone (20) and 2,3-dihydroxy-4,6-dimethoxyacetophenone (21). A solution of synthetic 2,4,6-trimethoxyacetophenone[10] (200 mg, 0.95 mmol) in CH_2Cl_2 was added BBr_3 (1 M, 1.0 mL, 1.0 mmol) solution dropwise at room temperature. The mixture was stirred under a nitrogen atmosphere for 20 min. The resulting solution was quenched by adding 4 M KOH (2.0 mL), and followed by extraction with CH_2Cl_2. The solvent was removed in vacuo to give a solid mixture which was subjected to column chromatography (SiO_2, hexane/ether 2:1) to obtain **19** (172 mg, 92%) as a white needle solid: mp 80–81 °C (hexane) (lit.[19a] mp 83–85 °C). According to previous general procedure for hydroxylation, the synthetic **19** (150 mg, 0.76 mmol) was treated with DMD (45 mL, 0.85 mmol) for stirring 10 min. The solvent was removed in vacuo, and the residue was subjected to column chromatography (SiO_2, CH_2Cl_2/ether 2:1) to provide the products **20** (133 mg, 82%) and **21** (27 mg, 17%), respectively. **20**: mp 156–158 °C (hexane) (lit.[19b] mp 162–162.5 °C); **21**: mp 161 °C (hexane) (lit.[19b] mp 161–165.5 °C); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.63 (3H, s, CH_3), 3.88 and 3.96 (3H each, s, OMex2), 6.01 (1H, s, 5-H).

3.1.5. 2,3-Dihydro-5-hydroxy-7-methoxy-2-(4-methoxyphenyl)-4-benzopyranone (22). To a mixture of 4,5,7-trihydroxyflavanone (500 mg, 1.8 mmol) and K_2CO_3 (2 equiv. 500 mg) in acetone (50 mL) was added Me_2SO_4 (0.40 mL, 4.2 mmol) dropwise at room temperature, and then refluxed for 6 h. The resulting solution was cooled and was added to H_2O (10 mL), and extracted with CH_2Cl_2 (3×100 mL). The organic layer was concentrated in vacuo, and the residue was subjected to column chromatography (SiO_2, CH_2Cl_2/ether 2:1) to afford the desired product **22** (459 mg, 83%) as a white solid: mp 167–168 °C (CH_2Cl_2) (lit.[20a] mp 164 °C).

3.1.6. 2,3-Dihydro-5,8-dihydroxy-7-methoxy-2-(4-methoxyphenyl)-4-benzopyranone (23). A solution of **22** (50 mg, 0.17 mmol) in CH_2Cl_2 was introduced with DMD (0.30 mL, 0.34 mmol) for 20 min to give the regioselective product **23** (47 mg, 88%) as an oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.88 (1H, dd, J=16.6, 3.8 Hz, 3-H), 3.11 (1H, dd, J=16.6, 12.5 Hz, 3-H), 3.82 (3H each, s, OMex2), 5.64 (1H, dd, J=12.5, 3.8 Hz, 2-H), 5.89 (1H, s, 6-H), 6.95 and 7.36 (2H each, d, J=8.7 Hz, 2,6-H, 3,5-H).

3.1.7. 5-Hydroxy-7-methoxy-2-(3,4-dimethoxyphenyl)-4-benzopyrone (26a). The **26a** was synthesized by our previous procedure[10] from **30b** (1.75 g, 5.1 mmol) in overall yield 97% (two steps) as a yellow solid: mp 169 °C (CH_2Cl_2) (lit.[20b] mp 161–162 °C).

3.1.8. 5-Hydroxy-7,8-dimethoxy-2-(4-methoxyphenyl)-4-benzopyrone (27). The 5-hydroxy-7-methoxy-2-(4-methoxyphenyl)-4-benzopyrone (**25**) was prepared according to our previous procedure.[10] A solution of **25** (150 mg, 0.50 mmol) in CH_2Cl_2 was added DMD (40 mL,

0.8 mmol) for 2 h to provide the desired 5,8-dihydroxy-7-methoxy-2-(4-methoxyphenyl)-4-benzopyrone (141 mg, 89%) as a solid: mp 269–271 °C (acetone) (lit.[21] mp 214–215 °C); ^{1}H NMR (200 MHz, DMSO) δ 3.96 and 4.00 (3H each, s, OMex2), 6.65 (1H, s, 6-H), 6.98 (1H, s, 3-H), 7.23 and 8.22 (2H each, d, J=8.8 Hz, 2,6-H, 3,5-H), 9.01 (1H, s, OH); HRMS (EI) calcd for $C_{17}H_{14}O_6$: 314.0790 [M], found: 314.0783 [M]$^+$. To a mixture of dihydroxyflavone (180 mg, 0.57 mmol) and K_2CO_3 (1.5 equiv. 120 mg) in acetone (10 mL) was added Me_2SO_4 (54 μL, 0.57 mmol) dropwise at room temperature, and then refluxed for 3 h. The resulting solution was cooled and was added H_2O (2 mL), and extracted with CH_2Cl_2 (3×20 mL). The organic layer was concentrated in vacuo, and the residue was subjected to column chromatography (SiO_2, CH_2Cl_2) to afford the desired product **27** (180 mg, 96%) as a white solid: mp 220.5 °C (CH_2Cl_2) (lit.[22] mp 220–221 °C); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.90, 3.94, and 3.95 (3H each, s, OMex3), 6.43 (1H, s, 6-H), 6.59 (1H, s, 3-H), 7.03 and 7.91 (2H each, d, J=8.8 Hz, 2,6-H, 3,5-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 55.5, 56.3, 61.6, 95.7, 103.8, 104.8, 114.5, 123.5, 128.1, 128.9, 149.4, 157.5, 158.4, 162.7, 163.9, 182.6.

3.1.9. 5,7,8-Trimethoxy-2-(3,4-dimethoxyphenyl)-4-benzopyrone (28) and isosinensetin (1). A solution of **26a** (100 mg, 0.30 mmol) in CH_2Cl_2 was treated with DMD (15 mL, 0.30 mmol) for 20 min to give the regioselective product 5,8-dihydroxy-7-methoxy-2-(3,4-dimethoxyphenyl)-4-benzopyrone (98 mg, 93%) as a yellow solid: mp 254–256 °C (acetone) (lit.[23a] mp 250–251 °C); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.97 and 3.99 (3H each, s, OMex3), 6.44 (1H, s, 6-H), 6.58 (1H, s, 3-H), 6.99 and 7.65 (1H each, d, J=8.4 Hz, 5,6-H), 7.51 (1H, s, 2-H). To a mixture of dihydroxyflavone (90 mg, 0.26 mmol) and K_2CO_3 (1.5 equiv. 54 mg) in acetone (5.0 mL) was added Me_2SO_4 (30 μL, 0.32 mmol) dropwise at room temperature, and then refluxed for 1 h. The resulting solution was cooled and was added H_2O (1 mL), and extracted with CH_2Cl_2 (3×10 mL). The organic layer was concentrated in vacuo, and the residue was subjected to column chromatography (SiO_2, CH_2Cl_2/ether 2:1) to afford the desired products **1** (55 mg, 59%) as a yellow solid and **28** (40 mg, 41%) as a white solid. **28**: mp 190–192 °C (acetone) (lit.[23b] mp 199–200 °C); HRMS (EI) calcd for $C_{20}H_{20}O_7$: 372.1209 [M], found: m/z 372.1216 [M]$^+$; **1**: mp 199–201 °C (CH_2Cl_2) (lit.[24] mp 207–208 °C); HRMS (EI) calcd for $C_{19}H_{18}O_7$: 358.1053 [M], found: 358.1051 [M]$^+$.

3.1.10. Quercetin (7). To a suspension of **26a** (1.5 g, 4.6 mmol) and K_2CO_3 (1.5 equiv. 0.95 g) in acetone (50 mL) was added Me_2SO_4 (0.65 mL, 6.9 mmol) dropwise at room temperature, and then refluxed for 2 h. The resulting solution was cooled and was added H_2O (10 mL), and extracted with CH_2Cl_2 (3×200 mL). The organic layer was concentrated in vacuo, and the residue was subjected to column chromatography (SiO_2, CH_2Cl_2/ether 2:1) to give the desired tetramethoxylflavone **26b** (1.5 g, 97%) as a white solid: mp 190–192 °C (CH_2Cl_2) (lit.[25a] mp 188–190 °C). The amount of DMD (50 mL) was added rapidly under N_2 to a cooled solution of methylated flavone **26b** (0.40 g, 1.2 mmol) in dried CH_2Cl_2 (50 mL). Stirring was continued for 30 min. The solvent was removed and the residue was subjected to column chromatography (SiO_2, CH_2Cl_2/ether 4:1) to provide the corresponding 3-hydroxy-5,7-dimethoxy-2-(3,4-dimethoxyphenyl)-4-benzopyrone (**10**) (0.36 g, 86%) as a yellow solid: mp 184–186 °C (CH_2Cl_2) (lit.[26] mp 197–198 °C); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.89, 3.92, 3.97, and 4.03 (3H each, s, OMex4), 6.33 and 6.53 (1H each, d, J=2.1 Hz, 6,8-H), 6.98 (1H, d, J=9.1 Hz, 5-H), 6.95 (1H, d, J=9.1 Hz, 6-H), 7.81 (1H, s, 2-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 56.5, 56.6, 56.7, 57.5, 93.1, 96.3, 106.8, 111.0, 111.5, 121.3, 124.4, 138.2, 142.8, 149.5, 150.9, 159.5, 161.2, 165.0, 172.5.

A sealed tube of **10** (0.30 g, 0.84 mmol) and BBr_3 (5 equiv. 1 M, 4.2 mL) in CH_2Cl_2 (10 mL) was refluxed for 6 h, and then cooled to room temperature. The brown mixture was dissolved in MeOH and subjected to column chromatography (SiO_2, EtOAc/CH_2Cl_2 1:4) to obtain **7** (0.21 g, 83%) as a yellow solid: mp 320 °C (acetone) (lit.[25b] mp 318–320 °C); ^{1}H NMR (300 MHz, $(CD_3)_2CO$+DMSO) δ 6.22 and 7.78 (1H each, d, J=2.1 Hz, 6,8-H), 6.46 (1H, d, J=1.8 Hz, 2′-H), 6.95 (1H, d, J=8.4 Hz, 5′-H), 7.64 (1H, dd, J=8.4, 2.1 Hz, 6′-H); ^{13}C NMR (75.47 MHz, $(CD_3)_2$-CO+DMSO) δ 92.6, 97.4, 102.2, 114.0, 114.4, 119.5, 121.8, 134.9, 144.2, 145.3, 146.7, 155.9, 160.4, 163.5, 174.8.

3.1.11. 3,5,7-Trimethoxy-2-(3,4-dimethoxyphenyl)-4-benzopyrone (9). To a mixture of **10** (1.0 g, 2.8 mmol) and K_2CO_3 (1.2 equiv. 0.46 g) in acetone (80 mL) was added Me_2SO_4 (0.32 mL, 3.3 mmol) dropwise at room temperature, and then refluxed for 1 h. The resulting solution was cooled and was added H_2O (10 mL), and extracted with CH_2Cl_2 (3×200 mL). The organic layer was concentrated in vacuo, and the residue was subjected to column chromatography (SiO_2, CH_2Cl_2/ether 4:1) to give the desired pentamethoxylflavone **9** (1.0 g, 96%) as a white solid: mp 154–155 °C (acetone) (lit.[27] mp 153–154 °C).

3.1.12. 5-Hydroxy-3,7-dimethoxy-2-(3,4-dimethoxyphenyl)-4-benzopyrone (11). A solution of **9** (1.0 g, 2.7 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 °C for 30 min, and added BBr_3 (1 equiv. 1 M 2.7 mL) into the solution dropwise. The brown mixture was stirred at 0 °C for 30 min, and then MeOH was introduced for quenching the reaction. The solvent was removed in vacuo, and the residue was subjected to column chromatography (SiO_2, CH_2Cl_2/ether 4:1) to afford the corresponding **11** (0.95 g, 99%) as a yellow solid: mp 158–159 °C (CH_2Cl_2) (lit.[28] mp 160–161 °C); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.85 and 3.96 (3H each, s, OMex4), 6.30 and 6.40 (1H each, d, J=2.1 Hz, 6,8-H), 6.96 (1H, d, J=8.5 Hz, 5-H), 7.66 (1H, s, 2-H), 7.72 (1H, d, J=8.5 Hz, 6-H); ^{13}C NMR (50 MHz, $CDCl_3$) 56.4, 56.6, 56.6, 60.7, 92.7, 98.4, 106.6, 111.4, 111.8, 122.7, 123.5, 139.5, 149.3, 152.0, 156.3, 157.2, 162.5, 166.0, 179.3.

3.1.13. 5,8-Dihydroxy-3,7-dimethoxy-2-(3,4-dimethoxyphenyl)-4-benzopyrone (29). The **11** (0.30 g, 0.84 mmol) in CH_2Cl_2 was added with DMD (25 mL, 1.0 mmol) for 50 min to obtain the regioselective product **29** (0.28 g, 89%) as a yellow solid: mp 238–240 °C (acetone) (lit.[29] mp 240–242 °C); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.87, 3.88, 3.97, and 3.98 (3H each, s, OMex4), 6.44 (1H, s, 6-H), 7.00 (1H, d, J=8.5 Hz, 5′-H), 7.79 (1H, d, J=1.9 Hz, 2′-H), 7.80 (1H, dd,

J=8.5, 1.9 Hz, 6′-H); HRMS (EI) calcd for $C_{19}H_{18}O_8$: 374.1004 [M], found: m/z 374.1002 $[M]^+$.

3.1.14. 5-Hydroxy-3,7,8-trimethoxy-2-(3,4-dimethoxyphenyl)-4-benzopyrone (12). To a mixture of **29** (0.24 g, 0.64 mmol) and K_2CO_3 (1.0 equiv. 89 mg) in acetone/CH_2Cl_2 (1:1 50 mL) was added Me_2SO_4 (61 μL, 0.63 mmol) dropwise at room temperature, and then refluxed for 4 h. The resulting solution was cooled and was added H_2O (1.0 mL), and extracted with CH_2Cl_2 (3×100 mL). The organic layer was concentrated in vacuo, and the residue was subjected to column chromatography (SiO_2, CH_2Cl_2/ether 4:1) to give the desired **12** (0.23 g, 94%) as a yellow solid: mp 152–155 °C (CH_2Cl_2) (lit.[30a] mp 161–162 °C); HRMS (FAB+H) calcd for $C_{20}H_{21}O_8$: 389.1236 [M+H], found: m/z 389.1233 $[M+H]^+$.

3.1.15. 3,5,7,8-Tetramethoxy-2-(3,4-dimethoxyphenyl)-4-benzopyrone (13). Followed by previous conditions from **29** (0.39 g, 1.0 mmol), K_2CO_3 (5.0 equiv. 0.73 g), and Me_2SO_4 (0.30 mL, 3.2 mmol) in acetone/CH_2Cl_2 (1:1 50 mL) to generate the corresponding **13** (0.36 g, 87%) as a white solid: mp 166–167 °C (acetone) (lit.[30b] mp 170 °C); HRMS (FAB+H) calcd for $C_{21}H_{23}O_8$: 403.1393 [M+H], found: m/z 403.1396 $[M+H]^+$.

3.1.16. 1-(2-Hydroxy-4,6-dimethoxyphenyl)-3-(4-methoxyphenyl)propenone (30a). The chalcone **30a** was synthesized by the known procedure.[10]

3.1.17. 1-(2-Hydroxy-4,6-dimethoxyphenyl)-3-(3,4-dimethoxyphenyl)propenone (30b). According to our previous procedures, a mixture of 2,4,6-trimethoxyacetophenone (4.3 g, 20 mmol) and 3,4-dimethoxybenzaldehyde (3.9 g, 23 mmol) in ethanol (200 mL) was stirred at room temperature for 20 min. A solution of 50% KOH (80 mL) was added dropwise, and then stirred at room temperature for 3 h. The resulting solution was neutralized by addition of 4 M HCl and extracted with CH_2Cl_2 (3×300 mL). The organic layer was concentrated in vacuo, and the residue was subjected to column chromatography (SiO_2, EtOAc/CH_2Cl_2 1:4) to give the desired 1-(2,4,6-trimethoxyphenyl)-3-(3,4-dimethoxyphenyl)propenone (7.1 g, 99%) as a yellow solid: mp 117 °C (CH_2Cl_2) (lit.[31a] mp 117 °C); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.79, 3.80, 3.86, 3.90, and 3.91 (3H each, s, OMex5), 6.17 (2H, s, 3,5-H), 6.84 and 7.29 (1H each, d, J=16.0 Hz, 2,3-C=H), 6.85 and 7.09 (1H each, d, J=8.0 Hz, 5′,6′-H), 7.07 (1H, s, 2′-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 55.3, 55.8, 55.8, 55.8, 90.6, 109.8, 110.9, 111.7, 122.8, 127.0, 127.7, 144.5, 149.0, 151.0, 158.5, 162.1, 194.3. A solution of 1-(2,4,6-trimethoxyphenyl)-3-(3,4-dimethoxyphenyl)propenone (2.4 g, 6.7 mmol) in CH_2Cl_2 (50 mL) was cooled to 0 °C for 30 min, and added BBr_3 (1 equiv. 1 M 6.7 mL) into the solution dropwise. The brown mixture was stirred at 0 °C for 30 min, and then MeOH was introduced for quenching the reaction. The solvent was removed in vacuo, and the residue was subjected to column chromatography (SiO_2, CH_2Cl_2/ether 1:1) to provide the corresponding **30b** (2.0 g, 90%) as a orange yellow solid: mp 154–156 °C (ether) (lit.[31b] mp 135–137 °C).

3.1.18. 1-(2,5-Dihydroxy-4,6-dimethoxyphenyl)-3-(4-methoxyphenyl)propenone (31a). The solution of **30a** (0.25 g, 0.80 mmol) in CH_2Cl_2 was added with DMD (45 mL, 0.90 mmol) for 1 h to give the regioselective product **31a** (0.20 g, 76%) as a red orange solid: mp 128–130 °C (hexane) (lit.[31c] mp 141–142 °C); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.86, 3.87, and 3.94 (3H each, s, OMex3), 6.33 (1H, s, 3-H), 6.94 and 7.60 (2H each, d, J=8.8 Hz, 2′,6′-H, 3′,5′-H), 7.86 (1H each, s, 2,3-C=H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 55.4, 56.3, 61.8, 96.2, 108.6, 114.4, 123.6, 128.0, 130.2, 131.7, 143.5, 146.8, 154.1, 159.6, 161.6, 192.5; HRMS (EI) calcd for $C_{18}H_{18}O_6$: 330.1103 [M], found: m/z 330.1110 $[M]^+$.

3.1.19. 1-(2,5-Dihydroxy-4,6-dimethoxyphenyl)-3-(3,4-dimethoxyphenyl)propenone (31b). Followed by general procedure for hydroxylation, a solution of **30b** (0.25 g, 0.73 mmol) in CH_2Cl_2 was added with DMD (40 mL, 0.80 mmol) for 1 h to produce the regioselective dihydroxychalcone **31b** (0.17 g, 65%) as a orange yellow solid: mp 171–172 °C (ether); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.87, 3.93, and 3.94 (3H each, s, OMex3), 6.33 (1H, s, 3-H), 6.91 (1H, d, J=8.3 Hz, 5′-H), 7.17 (1H, d, J=1.3 Hz, 2′-H), 7.24 (1H, dd, J=8.3, 2.0 Hz, 6′-H), 7.85 (1H each, s, 2,3-C=H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 56.4, 56.8, 62.3, 96.7, 109.1, 110.5, 111.7, 123.7, 124.4, 128.8, 132.4, 144.3, 147.4, 149.8, 151.9, 154.8, 160.1, 193.0; HRMS (EI) calcd for $C_{19}H_{20}O_7$: 360.1209 [M], found: m/z 360.1205 $[M]^+$.

3.1.20. 5,6,7-Trimethoxy-2-(4-methoxyphenyl)-4-benzopyrone (32). A mixture of **31a** (0.24 g, 0.73 mmol) and K_2CO_3 (1.2 equiv. 0.12 g) in acetone (50 mL) was added Me_2SO_4 (68 μL, 0.73 mmol), and then refluxed for 4 h. The resulting solution was cooled and added H_2O (1.0 mL), and extracted with CH_2Cl_2 (3×100 mL). The organic layer was concentrated in vacuo, and the residue was subjected to column chromatography (SiO_2, CH_2Cl_2/ether 4:1) to afford the corresponding 1-(6-hydroxy-2,3,4-trimethoxyphenyl)-3-(4-methoxyphenyl)propenone (0.24 g, 95%) as a yellow solid: mp 139–141 °C (hexane) (lit.[32] mp 142 °C); HRMS (EI) calcd for $C_{19}H_{20}O_6$: 344.1260 [M], found: m/z 344.1255 $[M]^+$. To a mixture of hydroxychalcone (0.24 g, 0.69 mmol) and I_2 (1 equiv. 0.69 mmol) in pyridine (10 mL) was refluxed for 4 h. After cooling, the solid was filtered and the filtrate was subjected to column chromatography (SiO_2, CH_2Cl_2/ether 1:1) to obtain the desired product **32** (0.18 g, 76%) as a white solid: mp 134–135 °C (hexane) (lit.[32] mp 141–142 °C); HRMS (EI) calcd for $C_{19}H_{18}O_6$: 342.1103 [M], found: m/z 342.1101 $[M]^+$.

3.1.21. Sinensetin (3). According to the previous preparation of **32**, a mixture of **31b** (0.25 g, 0.69 mmol) and K_2CO_3 (1.1 equiv. 0.11 g) in acetone (25 mL) was added Me_2SO_4 (70 μL, 0.74 mmol), and then refluxed for 6 h to afford the desired 1-(6-hydroxy-2,3,4-trimethoxyphenyl)-3-(3,4-dimethoxyphenyl)propenone (0.16 g, 95%) as a yellow solid: mp 135–136 °C (ether) (lit.[32] mp 140–142 °C); HRMS (EI) calcd for $C_{20}H_{22}O_7$: 374.1366 [M], found: m/z 374.1359 $[M]^+$. A mixture of hydroxychalcone (0.25 g, 0.67 mmol) and I_2 (1.1 equiv. 0.75 mmol) in pyridine (5 mL) was refluxed for 8 h. After cooling, the solid was filtered and the filtrate was subjected to column chromatography (SiO_2, CH_2Cl_2/ether 1:1) to obtain sinensetin **3** (0.16 g, 71%) as a white solid: mp 174–176 °C (acetone)

(lit.[22] mp 176–177 °C); HRMS (EI) calcd for $C_{20}H_{20}O_7$: 372.1209 [M], found: *m/z* 372.1219 $[M]^+$.

3.1.22. Tangeretin (2). A solution of **32** (0.10 g, 0.29 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 °C for 30 min, and added BBr_3 (1 equiv. 1 M 0.29 mL) into the solution dropwise. The brown mixture was stirred at 0 °C for 30 min, and then MeOH was introduced for quenching the reaction. The solvent was removed in vacuo, and the residue was subjected to column chromatography (SiO_2, CH_2Cl_2/ether 4:1) to afford the corresponding 5-hydroxy-6,7-dimethoxy-2-(4-methoxyphenyl)-4-benzopyrone (**33a**) (0.095 g, 99%) as a light yellow solid: mp 185–187 °C (CH_2Cl_2) (lit.[22] mp 185–186 °C); HRMS (EI) calcd for $C_{18}H_{18}O_6$: 328.0947 [M], found: *m/z* 328.0941 $[M]^+$. Followed by general procedure for hydroxylation, a solution of 5-hydroxyflavone **33a** (0.090 g, 0.27 mmol) was added with DMD (15 mL, 0.30 mmol) for 20 min to provide the regioselective 5,8-dihydroxy-6,7-dimethoxy-2-(4-methoxyphenyl)-4-benzopyrone (**34a**) (0.085 g, 90%) as a brown yellow solid: mp 194–196 °C (acetone) (lit.[33] mp 199–200 °C); HRMS (EI) calcd for $C_{18}H_{16}O_7$: 344.0896 [M], found: *m/z* 344.0895 $[M]^+$. To a mixture of dihydroxyflavone **34a** (0.075 g, 0.22 mmol) and K_2CO_3 (2.5 equiv. 0.076 g) in acetone/CH_2Cl_2 (1:1 10 mL) was added Me_2SO_4 (52 μL, 0.55 mmol) at room temperature, and then refluxed for 4 h. The resulting solution was cooled, and extracted with CH_2Cl_2 (3×20 mL). The organic layer was concentrated in vacuo, and the residue was subjected to column chromatography (SiO_2, CH_2Cl_2/ether 4:1) to give the desired **2** (0.080 g, 99%) as a white solid: mp 152.5–153 °C (hexane) (lit.[22] mp 153–154 °C); HRMS (EI) calcd for $C_{20}H_{20}O_7$: 372.1209 [M], found: *m/z* 372.1207 $[M]^+$; Anal. calcd for $C_{20}H_{20}O_7$: C 64.51; H 5.41; O 30.08. Found: C 64.22; H 5.81; O 29.91.

3.1.23. Nobiletin (4). To a solution of **3** (0.18 g, 0.48 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 °C for 30 min, and added BBr_3 (1 equiv. 1 M 0.48 mL) into the solution dropwise. The brown mixture was stirred at 0 °C for 30 min, and then MeOH was introduced for quenching the reaction. The solvent was removed in vacuo, and the residue was subjected to column chromatography (SiO_2, CH_2Cl_2/ether 1:1) to afford the corresponding 5-hydroxy-6,7-dimethoxy-2-(3,4-dimethoxyphenyl)-4-benzopyrone (**33b**) (0.16 g, 94%) as a light yellow solid: mp 190–192 °C (CH_2Cl_2) (lit.[22] mp 190–191 °C); HRMS (EI) calcd for $C_{19}H_{18}O_7$: 358.1053 [M], found: *m/z* 358.1057 $[M]^+$. Followed by general procedure for hydroxylation, a solution of 5-hydroxyflavone **33b** (0.16 g, 0.45 mmol) was added with DMD (25 mL, 0.50 mmol) for 20 min to provide the regioselective 5,8-dihydroxy-6,7-dimethoxy-2-(3,4-dimethoxyphenyl)-4-benzopyrone (**34b**) (0.15 g, 90%) as a brown yellow solid: mp 199–201 °C (acetone); ^1H NMR (200 MHz, $CDCl_3$) δ 3.97–4.15 (3H each, s, OMex4), 6.59 (1H, s, 3-H), 6.99 (1H, d, *J*=8.7 Hz, 5-H), 7.42 (1H, d, *J*=1.8 Hz, 2-H), 7.60 (1H, dd, *J*=8.4, 2.1 Hz, 6-H). To a mixture of dihydroxyflavone **34b** (0.15 g, 0.40 mmol) and K_2CO_3 (2.5 equiv. 0.14 g) in acetone/CH_2Cl_2 (1:1 10 mL) was added Me_2SO_4 (95 μL, 1.0 mmol) at room temperature, and then refluxed for 6 h. The resulting solution was cooled, and extracted with CH_2Cl_2 (3×20 mL). The organic layer was concentrated in vacuo, and the residue was subjected to column chromatography (SiO_2, CH_2Cl_2/ether 4:1) to give the desired **4** (0.14 g, 87%) as a white solid: mp 137–137.5 °C (acetone) (lit.[22] mp 138 °C); HRMS (EI) calcd for $C_{21}H_{22}O_8$: 402.1315 [M], found: *m/z* 402.1323 $[M]^+$.

3.1.24. Natsudaidain (5). A solution of **4** (78 mg, 0.20 mmol) was added with DMD (2.0 mL, 0.40 mmol) for 10 min to give the 3-hydroxylflavone **5** (28 mg, 80%) as a white solid: mp 130.9 °C (CH_2Cl_2) (lit.[30] mp 141–143 °C); HRMS (EI) calcd for $C_{21}H_{22}O_9$: 418.1264 [M], found: *m/z* 418.1272 $[M]^+$.

3.1.25. 3,5,6,7,8-Pentamethoxy-2-(3,4-dimethoxyphenyl)-4-benzopyrone (8). A mixture of **5** (40 mg, 0.11 mmol) and K_2CO_3 (1.0 equiv. 15 mg) in acetone (5 mL) was added Me_2SO_4 (13 μL, 0.13 mmol) at room temperature, and then refluxed for 1 h. The resulting solution was cooled, and extracted with CH_2Cl_2 (3×10 mL). The organic layer was concentrated in vacuo, and the residue was subjected to column chromatography (SiO_2, CH_2Cl_2/ether 4:1) to afford the desired **8** (46 mg, 97%) as a white solid: mp 129–130 °C (acetone) (lit.[24] mp 130–131 °C); HRMS (EI) calcd for $C_{22}H_{24}O_9$: 432.1420 [M], found: *m/z* 432.1416 $[M]^+$.

3.1.26. Gardenin B (6). To a mixture of **34a** (0.15 g, 0.44 mmol) and K_2CO_3 (1.0 equiv. 60 mg) in acetone/CH_2Cl_2 (1:1 10 mL) was added Me_2SO_4 (43 μL, 0.45 mmol) at room temperature, and then refluxed for 1 h. The resulting solution was cooled, and extracted with CH_2Cl_2 (3×20 mL). The organic layer was concentrated in vacuo, and the residue was subjected to column chromatography (SiO_2, CH_2Cl_2/ether 4:1) to give the desired **6** (0.16 g, 100%) as a yellow solid: mp 176 °C (ether) (lit.[22] mp 176–178 °C); MS (EI) *m/z* 211.1 (14.4), 343.3 (100), 358.4 (M^+, 94).

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Synthesis of podophyllotoxin analogues: δ-lactone-containing picropodophyllin, podophyllotoxin and 4′-demethyl-epipodophyllotoxin derivatives

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Abstract—Non-epimerizable *cis* and *trans* δ-lactone analogues of podophyllotoxin have been prepared. Thus the synthesis of the *cis* isomer **4** has been achieved in 8 steps and 4% overall yield from podophyllotoxin **1** via the reduction of the γ lactone ring into the *trans* diol, selective protection of the 4-OH and 11-OH as a benzylidene acetal, and Wittig elongation at C-13 with inversion of configuration at C-2. Same elongation at C-13 but via the formation of a mesylate and introduction of a cyano group, led to the *trans* δ-lactone **5** (7 steps from **1** and 6% overall yied) with a small amount of its C-4 epimer **6**. The synthesis of non-epimerizable δ-lactone analogues of 4′-demethyl-epipodophyllotoxin **7** and of 4-demethyl podophyllotoxin **8** are also reported. The synthesis of **7** and **8** was based upon the reduction of the γ-lactone ring of 4′-demethyl-4-epipodophyllotoxin followed by selective protection at C-11 and elongation at C-13. (8–15% and 4% overall yields). Compounds **4**, **5** and **7** did not display relevant cytotoxicity in vitro against L1210 murine leukemia.

1. Introduction

(−)-Podophyllotoxin **1** is a naturally occurring aryltetralin from *Podophyllum peltatum* and *P. emodi*.[1] Interest in podophyllotoxin has been heightened by its potent antimitotic activity.[2] Podophyllotoxin inhibits the assembly of tubulin protein into microtubules through tubulin binding at the colchicin site[3] but failed to advance in human clinical trials because of toxic side-effects. Extensive structure modifications have been performed since the 1950s, principally at Sandoz Laboratories[4] which led to the semi-synthetic etoposide (VP-16, **2**) and teniposide (VM-26, **3**). Both derivatives demonstrated significant activity and low toxicity in clinical trials (Fig. 1).

Despite the fact that they derived from podophyllotoxin, there was early evidence that these drugs did not share the same mechanism. In 1976, Loike and Horwitz made relevant observations[5] which ultimately led to the identification of DNA topoisomerase II as the intracellular target for the action of these drugs. Although etoposide has been used successfully in the clinic for many years in the treatment of small-cell lung cancer, testicular carcinoma, lymphoma, and Kaposi's sarcoma,[6,7] several problems still exist. Besides the poor solubility of etoposide and the development of drug resistance, the metabolism of etoposide results in inactivation by epimerisation of the *trans* lactone ring giving the *cis* isomer, the picropodophyllin analogue which is 100-fold less toxic.[8] A second metabolite

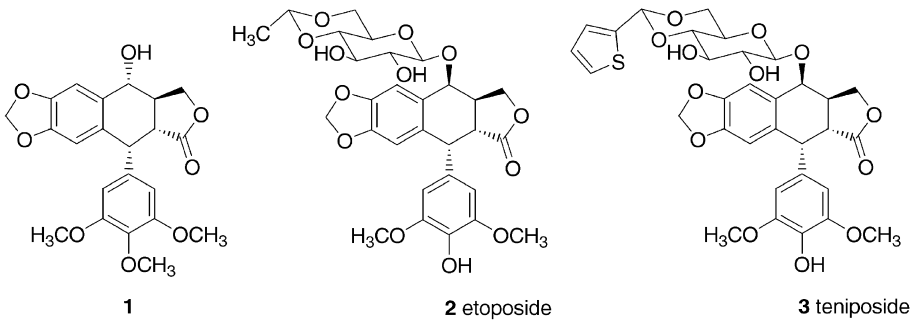

Figure 1.

Keywords: Podophyllotoxin analogues; δ-Lactones.
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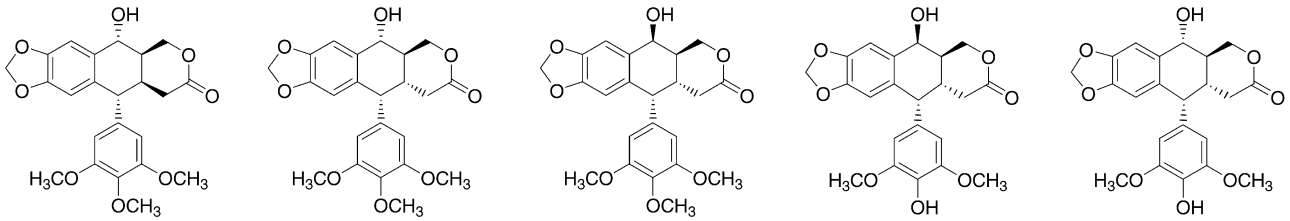


Figure 2.

is the *cis*-hydroxy acid which results from the opening of the lactone ring with subsequent epimerisation and which is 500-fold less cytotoxic than etoposide. In order to avoid or minimize the C-2 epimerization and/or the lactone ring opening, two main alternatives have been proposed. The first included the replacement of the γ-lactone with furan, thiolane, cyclopentane rings[9] whereas the second took advantage of the preparation of derivatives substituted at the 2-position such as methyl, halogeno, hydroxy[10,11] or nitrogen derivatives.[12] On the other hand, a few years ago, the groups of Gordaliza[13] and Subrahmanyam[14] have reported that podophyllotoxin analogues lacking the lactone ring are still endowed with relevant cytotoxic effects towards colon cancer cell lines. However, as no in vivo evaluation were reported in both cases, it remains to ascertain whether they present a relevant anti-tumour activity and lack of general toxicity.

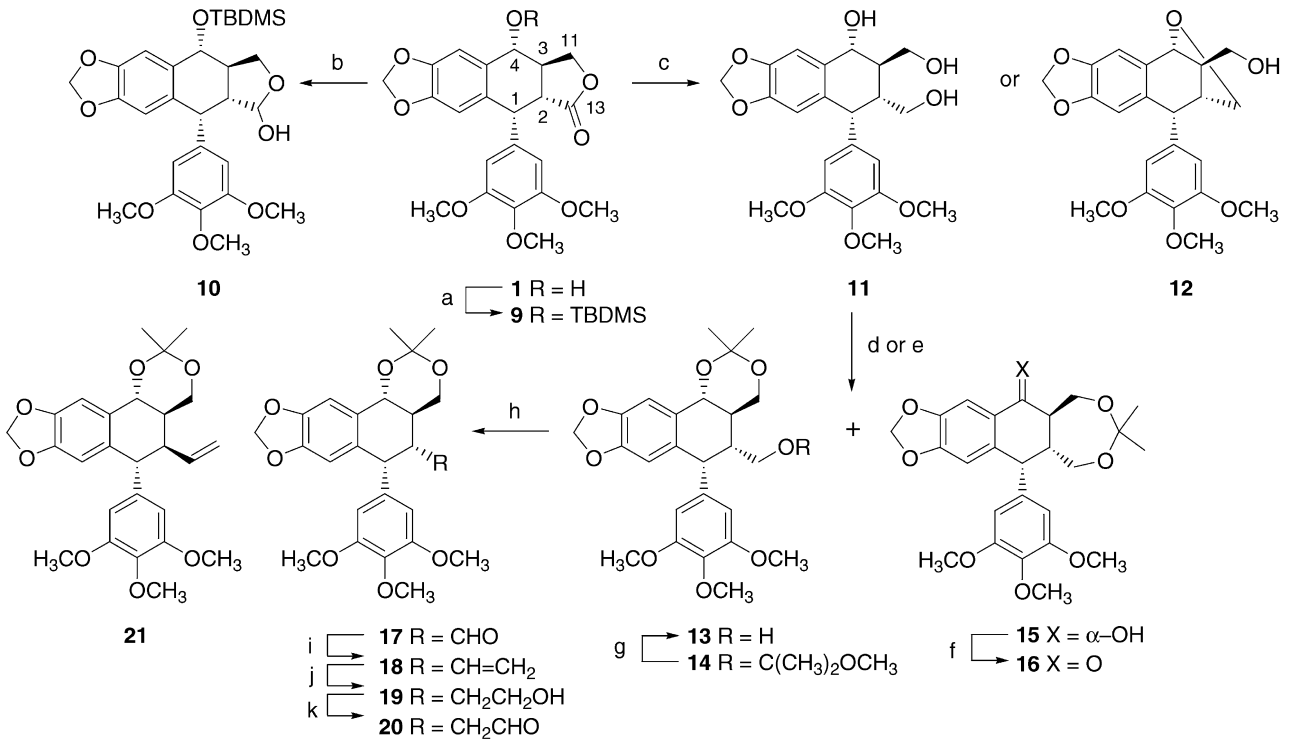
As part of our ongoing research program aimed at the synthesis and biological evaluation of new anti-tumour analogues[15–18] related to podophyllotoxin and etoposide, we have already been engaged in the synthesis of analogues including six-membered lactone ring since enhancement of the lactone ring may give access to more stable isomers. Thus we recently reported the synthesis of the δ-*cis*-lactone analogue of picropodophyllin[17] in which the carbonyl group was adjacent to the epimerizable C-2 as in natural lignans. Herein we describe the synthesis of non-epimerizable δ-lactone analogues of picropodophyllin **4** and of podophyllotoxin **5** and **6**, and the synthesis of non-epimerizable δ-lactone analogues of 4′-demethyl-epipodophyllotoxin **7** and of 4-demethyl podophyllotoxin **8**, possessing the carbonyl in β-position of the C/D ring junction. Exploratory evaluation of the biological activity of **4**, **5** and **7** is also presented (Fig. 2).

2. Results and discussion

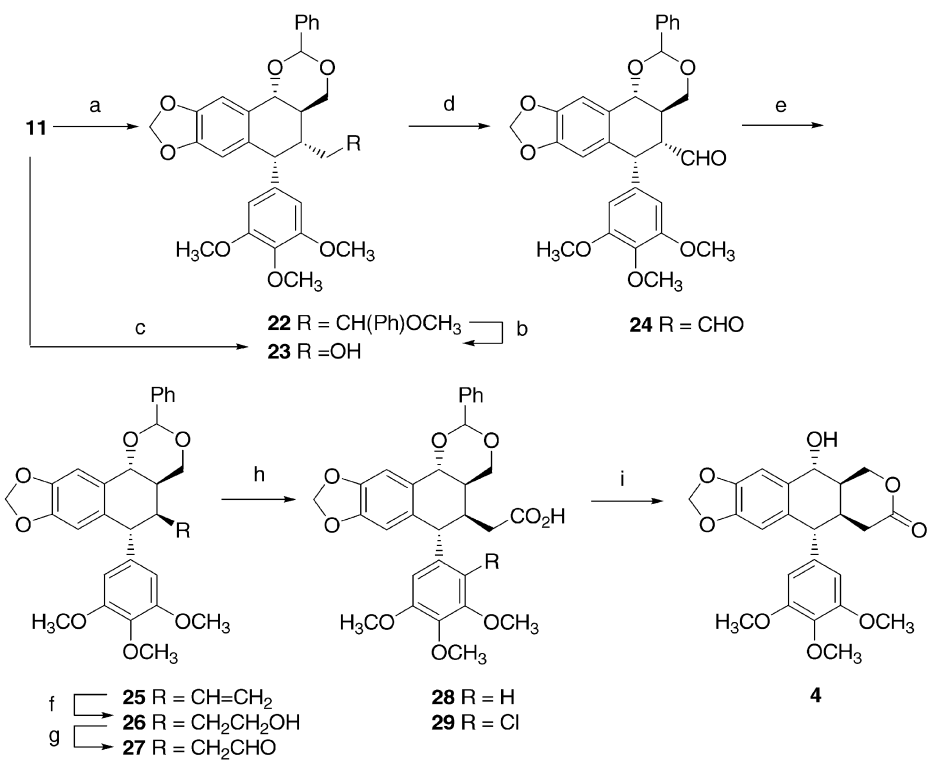
Our point of departure for the synthesis of **4**–**6** was the reduction of podophyllotoxin **1**: two different ways have been successively followed which consist in partial or total reduction of the lactone ring with retention of configuration at C-2 (Scheme 1). First, podophyllotoxin **1** was converted into silyl ether **9**[17] which was next reduced according to Lee et al.[19] in the presence of DIBAL-H to afford **10** in 87% yield. Unfortunately, subsequent attempts to introduce a side-chain via a Wittig reaction, using for example the ylide obtained from methoxymethyltriphenylphosphonium bromide,[20] did not succeed, even in the case of the free lactol at C-4. The same lack of reactivity of the lactol was observed when treated with 1,3-dithianyl anions prepared from 1,3-dithiane-2-yl-triphenylphosphonium chloride,[21] diethyl(1,3-dithian-2-yl)phosphonate,[22] or 2-trimethylsilyl-1,3-dithiane[23] for Wittig, Horner–Emmons and Peterson olefinations, respectively. Interestingly, the unprotected lactol reacted with methyl(triphenylphosphoranylidene)-acetate and pyridine in toluene at 90 °C to produce the expected α,β-unsaturated ester.[14b]

The alternative way involved the reductive cleavage of the lactone moiety into triol **11** by LAH. Indeed such a reductive method[24] is one among the few methods which allow the reductive opening of the lactone ring of podophyllotoxin with preservation of the 2,3-*trans* relationship[25] However, the crucial and immediate problem which is attached to this transformation is due to the fact that triol **11** is prone to dehydration during the work-up to readily afford the neoanhydropodophyllol **12**.[26]

Formation of this side-product has been contradictorily attributed to an acidic medium[24] and later to a basic medium[26] involved during the different work-up. In our laboratory, we observed that **12** is ineluctably formed upon addition of EtOAc and HCl, we decided to carefully remove the excess of hydride with successive addition of water and NaOH at low temperature.[27] Interestingly, under these conditions, triol **11** was obtained in 60% yield without any traces of **12**. The following step consisted in selectively protection of the C-11 hydroxyl by taking into account its vicinal situation with the C-4 hydroxyl to form a cyclic acetal. Moreover it was expected that treatment of **11** with α,α-dimethoxypropane would selectively afford a 6-membered isopropylidene. This acetonide protection have been previously used for the 1,3-diol system of the tetraline intermediate in the synthesis of (±)-podophyllotoxin.[28] In fact, such a treatment led to a mixture of three products which contained the expected isopropylidene acetal **13** along with the hemiketal derivative **14** and with the 7-membered acetal **15**, in 7, 62 and 28% yields, respectively. Additional amount of **13** could be obtained by selective deprotection at C-13 (AcOH, H_2O, MeOH, 88%) of **14**. Alternatively, addition of Et_3N (10 equiv.) to the crude reaction mixture, followed by concentration in vacuo and heating at 60 °C for 8 h in aqueous methanolic solution, afforded compounds **13** (54%) and **15** (15%) without any traces of the hemiketal **14**, allowing an easier purification of **13**. The structure of **15** was determined by ^1H NMR and by chemical means upon periodinane oxidation[29] of **15** leading to the corresponding keto-derivative **16** (74%). A compound having a similar skeleton had been already obtained by Pelter et al.[30]



Scheme 1. Reagents and conditions: (a) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 1.3 h, 92%; (b) DIBALH, toluene, −78 °C, 40 min, 87%; (c) LAH, THF, 0 °C, 4 h, then basic work up according Ref. 27 gave **11** (60%), or work up according Refs. 24 or 26 gave **12**; (d) α,α-DMP, PTSA, rt, 7 h, **13** (7%), **14** (62%) and **15** (28%); (e) α,α-DMP, PTSA, rt, 3.5 h, then Et_3N, MeOH/H_2O (10/1), 8 h, 60 °C, **13** (54%) and **15** (15%); (f) Dess–Martin periodinane, CH_2Cl_2, rt, 40 min, 74%; (g) AcOH/H_2O (1/1), MeOH, rt, 3.5 h, 88%; (h) Dess–Martin periodinane, CH_2Cl_2, rt, 30 min, 87%; (i) Ph_3PCH_3,Br, *n*-BuLi, THF, −78 °C, 45 min, 86%; (j) 9-BBN, THF, rt, 3.5 h, then H_2O_2 (30%), MeOH, pH 7.2 phosphate buffer, 74% (two steps); (k) Dess–Martin periodinane, CH_2Cl_2, rt, 1 h, 92%.



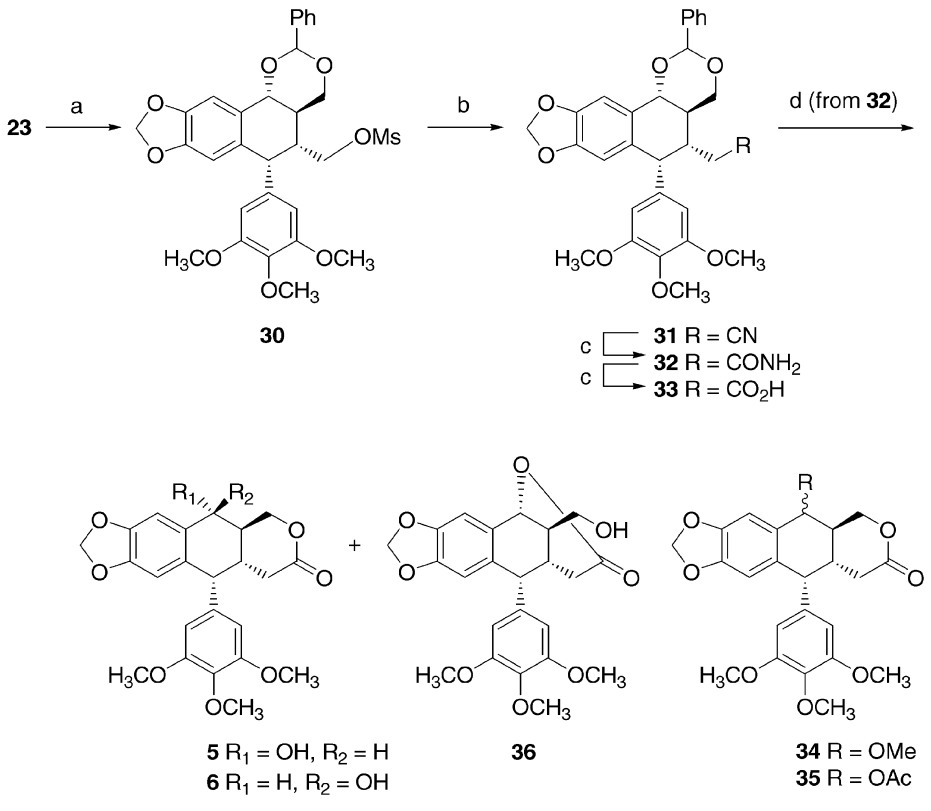
Scheme 2. Reagents and conditions: (a) α,α-dimethoxytoluene, PTSA, rt, 40 min, 73%; (b) AcOH/H_2O (1/1), MeOH, CH_2Cl_2, rt 5 days, 66%; (c) α,α-dimethoxytoluene, PTSA, CH_2Cl_2, rt, 10 min, **23** (37%), **22** (8%) and **12** (32%) (d) Dess–Martin periodinane, CH_2Cl_2, rt, 30 min, 87%; (e) Ph_3PCH_3,Br, K_2CO_3, 18-crown-6, THF, reflux, 19 h, 92%; (f) 9-BBN, THF, rt, 1.75 h, then H_2O_2 (30%), MeOH, pH 7.2 phosphate buffer, rt, 3 h, 80%; (g) Dess–Martin periodinane, CH_2Cl_2, rt, 1 h, 65%; (h) $NaClO_2$, NH_2SO_3H, *t*-BuOH/H_2O (2/1), rt, 25 min, 76%; (i) CSA, THF/H_2O (10/1), 80 °C, 6 h, 66%.

Once isolated, isopropylidene acetal **13** was oxidized in the presence of Dess–Martin reagent (87%) and the aldehyde derivative **17** (80 mg scale) was submitted to Wittig reagent to give **18**. The stereochemical assignment of **18** was based on $J_{3,4}$=(10.1 Hz) and $J_{1,2}$=(6.4 Hz) coupling constants, respectively consistent with 3,4-*trans* and 1,2-*cis* relationships, and a comparison with similar compounds.[28,31] Hydroboration followed by a second Dess–Martin oxidation of alcohol **19**, afforded **20** in 68% overall yield from **18**. On 500 mg scale for the synthesis of **13**, we noted the preponderant formation of the seven-membered during the first step (**13**:**15**=13:86 instead of 78:22). In addition, Wittig olefination of **17** (300 mg scale) provided an inseparable mixture of **18** and **21** which was attributed to the pronounced basic character of the ylide. This led us to consider the benzylidene protection for **11** (Scheme 2). This protective group was exploited in an exploratory approach towards podophyllotoxin[32] and epipodophyllotoxin.

Treatment of **11** with α,α-dimethoxytoluene, both as reagent and solvent, and PTSA exclusively afforded the six-membered benzylidene acetal **22** (73%) which was next converted into **23** by aqueous acidic hydrolysis (48% overall yield) (Scheme 3). Removal of α,α-dimethoxytoluene proved more troublesome than expected on larger scale. Alternatively, the use a stoichiometric amount of the reagent in dichloromethane led to a separable mixture of the desired acetal **23**, **22** and neoanhydropodophyllol **12**. Upon periodinane oxidation of **23**, the resulting aldehyde **24** was treated with the required ylide prepared in situ by deprotonation of methyl triphenylphosphonium bromide with potassium carbonate and 18-crown-6[33] to afford the *cis*-vinyl derivative **25** (92% yield). The assignment of the relative stereochemistry was based upon $J_{1,2}$ and $J_{2,3}$=(2.9 and 8.9 Hz). Note that the reaction of **24** with methylenetriphenylphosphorane (Ph_3PCH_3,Br, *n*-BuLi, THF, −78 °C, 1 h 30) furnished an inseparable stereoisomeric mixture of **25** and of the 2,3-*trans* isomer (30:70 ratio) in 81% yield. The same result was observed under various conditions of time, temperature, or in the presence of various ratios of the reagents versus the starting material. Furthermore, subsequent hydroboration of this mixture led to the separation problem again. Hydroboration of **25** gave alcohol **26** in 80% yield. Periodinane oxidation followed by sodium chlorite oxidation of aldehyde **27** led to the expected carboxylic acid **28** (76%) along with a small amount of **29** (8%) resulting from the chloration of the aromatic ring. Unfortunately, direct oxidation of the aformentioned vinyl or alcohol mixture at C-2 into the corresponding acids failed.[34] Acid hydrolysis of the benzylidene moiety of **28** took place without inversion[35] at C-4 ($J_{3,4}$=8.2 Hz) to provide the δ-lactone-containing picropodophyllin derivative **4** in 66% yield (e.g., 8 steps from **1** and 4% overall yield).

To obtain the corresponding *trans* isomer **5** of podophyllotoxin configuration (Scheme 3), compound **23** was first mesylated (99%) and mesylate **30** readily afforded the cyano derivative **31** (95%).

Next, hydrolysis of nitrile **31** was carried out in the presence of a large excess of NaOH (40 equiv.) in EtOH under reflux giving amide **32** in 83% yield. Carboxylic acid **33** could be obtained as a mixture with **32** by prolonging the reaction time to 16 h. Exposure of **32** to PTSA in MeOH led

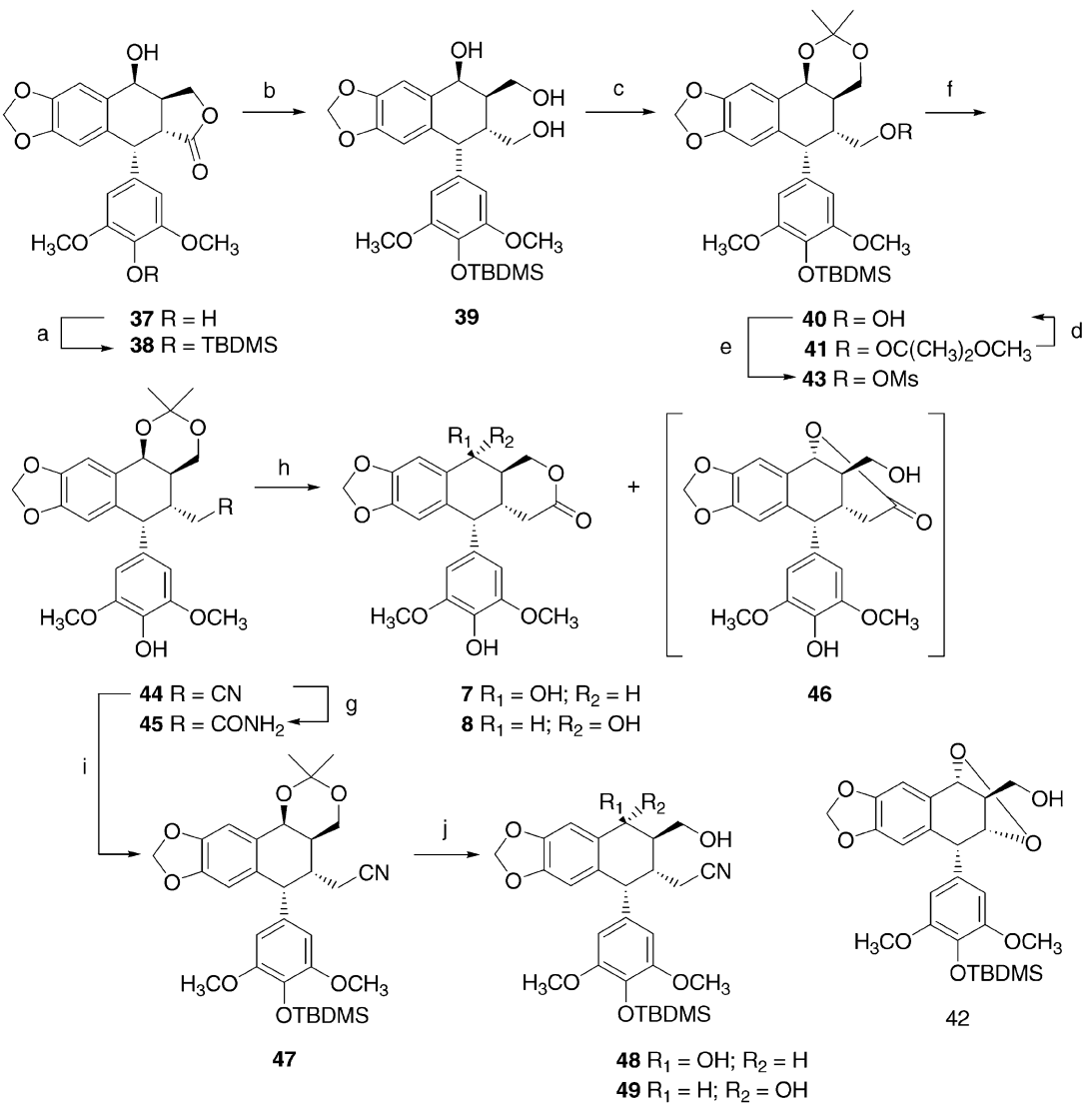


Scheme 3. Reagents and conditions: (a) MsCl, Et_3N, CH_2Cl_2, 0 °C, 30 min, 99%; (b) NaCN, DMF, 85 °C, 6 h, 95%; (c) NaOH (25%), EtOH, reflux, 7 h, **32** (83%)/reflux 16 h, mixture of **32** (24%) and **33** (47%); (d) CSA, THF/H_2O (1/1), 85 °C, 17 h, **5** (28%), **6** (7%) and **36** (13%).

exclusively to **34** as an epimeric mixture at C-4 whereas 80% aqueous AcOH gave **5**, **35** as an epimeric mixture, and **36**. To circumvent the problem of substitution at C-4, the reaction was carried out with CSA in THF/H_2O (1/1). Under these conditions, **32** was converted to the δ-lactone-containing podophyllotoxin derivative **5** (28%), along with a small amount of **6** (7%) and **36** (13%). Homolactone **5** showed a broad triplet at 4.51 ($J_{3,4}$=$J_{4,OH}$=7.6 Hz) and homolactone **6** showed a broad singlet at 4.76 due to H-4, respectively, indicating 3,4-*trans* and 3,4-*cis* relationships. The synthesis of **5** proceeds in 7 steps from **1** and in 6% overall yield.

The chemistry developed in the podophyllotoxin series was extended to 4′-demethyl-4-epipodophyllotoxin **37**. Protection of this latter as the *tert*-butyldimethylsilyl ether **38**, followed by treatment with LAH, afforded triol **39** (Scheme 4). Treatment of **39** with α,α-dimethoxypropane led to a mixture of three compounds which contained the expected isopropylidene acetal **40**, along with the hemiketal derivative **41** and with the 4′-demethyl-neoanhydropodophyllol derivative **42**. The 7-membered acetal was not detected. Prior to chromatographic isolation of **40**, the crude mixture was then treated in acidic medium to carry out selective deprotection at C-13. Under these conditions, **40** was more easily isolated (41%, 3 steps from **38**).

Mesylation of **40**, and cyanation with concomitant loss of the TBDMS group, gave **44** in 53% overall yield. Hydrolysis of nitrile **44** furnished amide **45** in acceptable (44%) albeit lower yield than in the podophyllotoxin series. One-pot deketalization and lactonization of **45** by a two-fold acidic treatment led to a mixture of three compounds: the expected δ-lactone **7** (31%), and an inseparable mixture of two other δ-lactone derivatives postulated from our previous results as being the epimer at C-4 **8** and the regioisomeric lactone **46**. Homolactone **7** showed a large singulet at 4.75 due to H-4 indicating a 3,4-*cis* relationship.



Scheme 4. Reagents and conditions: (a) TBDMSCl, imidazole, DMF, rt, 1.5 h, 89%; (b) LAH, THF, 0 °C, 1.5 h, 51%; (c) α,α-DMP, PTSA, rt, 35 min, (d) AcOH/H_2O (1/1), MeOH, rt, 6 h, **40** (41%, 3 steps from **38**); (e) MsCl, Et_3N, CH_2Cl_2, 0 °C, 50 min; (f) NaCN, DMF, 85 °C, 5 h, **44** (53%, 2 steps); (g) NaOH (25%), EtOH, 75 °C, 28 h, 44%; (h) (a) APTS, THF: H_2O (10/1), 45 °C, 7 h; (b) CSA, CH_2Cl_2, rt, 30 min, **7** (31%); (i) TBDMSCl, imidazole, DMF, rt, 2.5 h; (j) APTS, THF/H_2O (10/1), 70 °C, 25 h, **48** (29%) and **49** (36%).

The structure of **8** was confirmed from ^{1}H NMR comparison with **8** prepared otherwise (vide infra). Epimerization at C-4 occurred before the cyclization step as shown in the case of the cyano-derivative **47** which, under these reaction conditions, led to a mixture of **48** (29%) and **49** (36%). The conversion of methyl epipodophyllate into methyl podophyllate was obtained in a similar fashion during the asymmetric total synthesis of (−)-podophyllotoxin.[36] Hydrolysis of each cyano-derivative failed to furnish the corresponding amide.

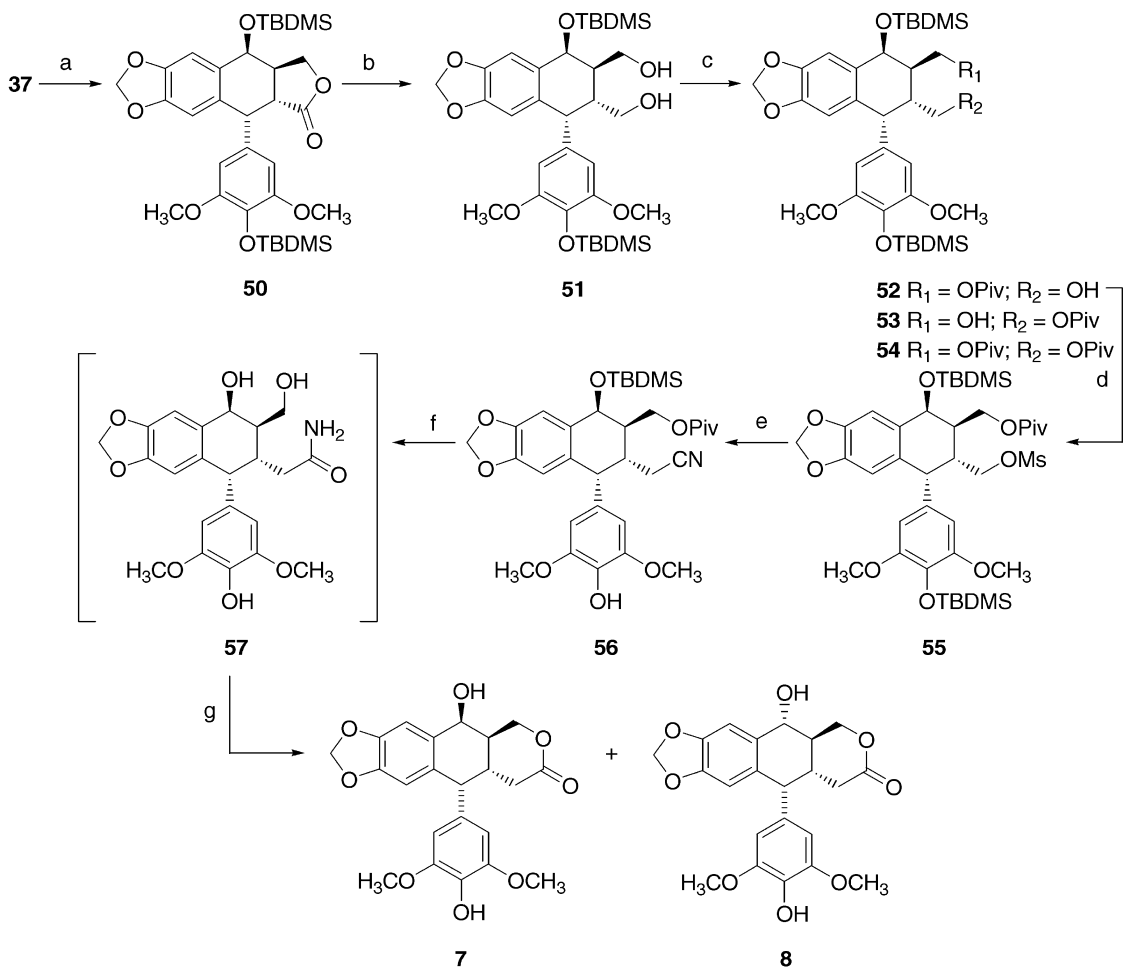
Our alternative synthesis of **7** involved the differential protection of the hydroxyl groups at C-4 and C-11.

As shown in Scheme 5, bis-silylation of **37** generated **50**[37] which was reduced as the diol **51**. Selective acylation with 2.5 equiv. of PivCl (Et_3N, cat. 4-DMAP) afforded a separable mixture of **52** (65%), **53** (27%) and **54** (8%). Mesylation of **52** and cyanation provided **56** (54%, 2 steps). Basic hydrolysis of the nitrile led to a polar compound—as judged by TLC—which was presumably **57** according to our knowledge in the podophyllotoxin series, and subsequent neutralization gave **7** (32–60%) and **8** (15%). The large coupling constant of **8** ($J_{3,4}$=8.4 Hz) is indicative of a 3,4-*trans* relationship. The syntheses of **7** and **8** proceeded in 8–15% and 4% overall yields from 4′-demethyl-epipodophyllotoxin **37**, respectively.

Exploratory evaluation of the biological activity of the six-membered lactone derivatives **4**, **5** and **7** were performed in vitro. None of these compounds exhibited relevant cytotoxicity against L1210 murine leukemia since the values of their IC_{50} were 73.9, 38 μM and>100 μM, respectively (**1**, IC_{50}=0.008 μM). The lack of cytotoxic effect may be due to the D-ring enhancement of the podophyllotoxin framework or more probably it means that the position of the carbonyl group on the lactone ring is important for activity.[17]

3. Conclusion

The synthesis of non-epimerizable δ-lactone analogues of picropodophyllin **4** and of podophyllotoxin **5** and **6** has been achieved. Analogues **4** and **5** did not display significant cytotoxicity in vitro against L1210. We have also completed the synthesis of non-epimerizable δ-lactone analogues of 4′-demethyl-epipodophyllotoxin **7** and of 4-demethyl podophyllotoxin **8**. Work toward the preparation of δ-lactone



Scheme 5. Reagents and conditions: (a) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 1 h, 81%; (b) LAH, THF, 0 °C to rt, 30 min, 92%; (c) PivCl, Et_3N, 4-DMAP, CH_2Cl_2, rt, 40 min, **52** 65%), **53** (27%) and **54** (8%); (d) MsCl, Et_3N, CH_2Cl_2, rt, 2 h; (e) NaCN, DMF, 85 °C, 24 h (54%, 2 steps); (f) NaOH (25%), EtOH, 85 °C, 7 h; (g) 1 N HCl (→pH 2–3), then work-up and stirring overnight of the combined organic phases. **7** (32–60%) and **8** (15%).

analogues having the carbonyl in α-position of the C/D ring junction is under investigation.

4. Experimental

4.1. Materials and methods

^{1}H NMR spectra were recorded on a Bruker AM-250 or a Brucker AC-300 instrument. IR spectra were recorded on a Perkin–Elmer 1710 infrared spectrophotometer. Optical rotations were measured with a Perkin–Elmer 241 polarimeter. Melting points were determined on either a Kofler hot-stage instrument or an Electrothermal digital melting point apparatus and are not corrected. Mass spectra (MS) were registered on a Nermag R10-10C mass spectrometer under chemical ionisation (CI) conditions. Elemental analyses were performed by the 'Service d'Analyse du CNRS, Vernaison, France'. All reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light and 7% ethanolic phosphomolybdic acid-heat as a developing agent. E Merck silica gel (particle size 0.040–0.063 mm) was used for flash column chromatography. All reactions were carried out using heat gun-dried glassware under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise noted. Yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated. Podophyllotoxin was purified by flash chromatography before use.

4.1.1. 4-*O*-(*tert*-Butyldimethylsilyl)-13-hydroxypodophyllotoxin (10). Compound **10** was prepared according to Lee et al.[19]

4.1.2. Podophyllol 11. To a suspension of LAH (18.44 g, 486 mmol) in THF (315 mL) at 0 °C was added podophyllotoxin **1** (24.26 g, 58.54 mmol) in THF (250 mL) over a period of 1.5 h. The mixture was stirred for an additional 2.5 h at the same temperature and under argon atmosphere prior to successive additions of water (18.5 mL), 15% aqueous solution of NaOH (18.5 mL) and water (56 mL). The crude mixture was filtered, washed with THF (4×100 mL) and the filtrate was concentrated under reduced pressure to c.a. 150 mL. The aqueous residue was extracted thrice with EtOAc (250 mL and then 2×150 mL) and the combined organic layers were washed with brine (2×250 mL), dried ($MgSO_4$) and concentrated in vacuo. The yellow solid residue was triturated with MeOH (75 mL) and the crystals were separated by precipitation to give podophyllol **11** (14.82 g, 60%) as a white powder, pure enough for the next step. Mp 178–179 °C (MeOH); $[\alpha]_D^{20}=-234.5$ (*c* 0.25, EtOH). [Lit.[25]: mp 179–181 °C; $[\alpha]_D^{18.5}=-179$ (*c* 0.27, $CHCl_3$); Lit.[26]: mp 186–188 °C (EtOAc); $[\alpha]_D^{19}=-203$ (*c* 0.25, EtOH)].

4.1.3. 4,11-*O*-Isopropylidene podophyllol (13), 11,13-*O*-isopropylidene podophyllol (15) and 4,11-*O*-isopropylidene-9-(2-methoxyisopropylether) podophyllol (14). *Procedure 1*. To a suspension of podophyllol **11** (224 mg, 0.53 mmol) in 2,2-dimethoxypropane (13 mL), *p*-toluenesulfonic acid monohydrate (10.2 mg, 53.5 μmol) was added. The reaction mixture was stirred at rt for 7 h, diluted with methylene chloride (20 mL) and with an aqueous saturated solution of sodium hydrogenocarbonate (15 mL). The aqueous layer was separated and washed with methylene chloride (15 mL). The combined organic layers were dried ($MgSO_4$), and.concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 3:1, then 2:1 and 1:1) successively gave **13** (17.2 mg, 7%) as a white solid, **15** (68.8 mg, 28%) as a white solid, and **14** (176 mg, 62%) as an amorphous solid.

Procedure 2. Podophyllol **11** (52.5 mg, 0.125 mmol) was treated as above but, after 3.5 h, as a tlc control indicated disappearance of **11** and appearance of **13**, **14** and **15**, Et_3N (20 μL, 0.143 mmol) was added to the mixture and, 15 min later, the reaction mixture was concentrated under reduced pressure. The solid was dissolved in MeOH (1.8 mL) and water (0.2 mL), and the solution was heated at 60 °C for 8 h. Work-up and flash chromatography as above led to isolation of **13** (31.1 mg, 54%), and **15** (8.7 mg, 15%).

Compound **13**. Mp 169–170 °C (CH_2Cl_2); $[\alpha]_D^{20}=-133$ (*c* 0.62, $CHCl_3$); IR ($CDCl_3$) 3620 (OH), 2939, 1590, 1505, 1482 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99 (s, 1H, H-5), 6.36 (s, 1H, H-8), 6.35 (s, 2H, H-2′, H-6′), 5.90 (d, 1H, *J*=1.4 Hz, OCH_2O), 5.88 (d, 1H, *J*=1.3 Hz, OCH_2O), 4.71 (d, 1H, *J*=9.2 Hz, H-4), 4.18 (d, 1H, *J*=5.4 Hz, H-1), 3.94 (dd, 1H, *J*=11.1, 4.2 Hz, H-11), 3.85 (m, 1H, H-11), 3.83 (s, 3H, OCH_3-4′), 3.78 (s, 6H, OCH_3-3′,5′), 3.51 (m, 1H, H-13), 3.41 (m, 1H, H-13), 2.24–2.05 (m, 2H, H-2, H-3), 1.60 (s, 3H, CH_3), 1.53 (s, 3H, CH_3); MS (DCI, NH_3) *m*/*z* 458 $[M]^+$, 476 $[M+NH_4]^+$.

Compound **14**. $[\alpha]_D^{20}=-139.5$ (*c* 0.63, $CHCl_3$); IR ($CDCl_3$) 2940, 1590, 1505, 1483 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.98 (s, 1H, H-5), 6.36 (s, 1H, H-8), 6.33 (s, 2H, H-2′, H-6′), 5.90 (d, 1H, *J*=1.4 Hz, OCH_2O), 5.88 (d, 1H, *J*=1.4 Hz, OCH_2O), 4.69 (d, 1H, *J*=9.1 Hz, H-4), 4.20 (d, 1H, *J*=5.6 Hz, H-1), 3.83 (m, 1H, H-11), 3.83 (s, 3H, OCH_3-4′), 3.77 (s, 6H, OCH_3-3′,5′), 3.77 (m, 1H, H-11), 3.17 (s, 3H, OCH_3), 3.05 (m, 2H, H-13), 2.16 (m, 2H, H-2, H-3), 1.61 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.26 (s, 3H, CH_3); MS (DCI, NH_3) *m*/*z* 530 $[M-H_2O+NH_4]^+$.

Compound **15**. Mp 150–152 °C (CH_2Cl_2); $[\alpha]_D^{20}=-199.5$ (*c* 0.75, $CHCl_3$); IR ($CDCl_3$) 3594 (OH), 2938, 1590, 1505, 1483 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 (s, 1H, H-5), 6.37 (s, 1H, H-8), 6.18 (s, 2H, H-2′, H-6′), 5.92 (s, 2H, OCH_2O), 4.31 (t, 1H, *J*=8.4 Hz, H-4), 4.10 (dd, 1H, *J*=11.6, 2.7 Hz, H-11), 3.82 (s, 3H, OCH_3-4′), 3.78 (s, 6H, OCH_3-3′,5′), 3.70 (m, 1H, H-11), 3.63 (m, 1H, H-13), 3.24 (m, 1H, H-13), 2.03 (m, 2H, H-2, H-3), 1.73 (d, 1H exch. D_2O, *J*=8.4 Hz, OH), 1.33 (s, 3H, CH_3), 1.20 (s, 3H, CH_3); MS (DCI, NH_3) *m*/*z* 458 $[M-H_2O+NH_4]^+$.

4.1.4. Ketone 16. Dess–Martin periodinane (26 mg, 61.5 μmol) was added to a solution of **15** (23.5 mg, 51 μmol) in methylene chloride (2 mL) at rt. After 40 min, the mixture was diluted with methylene chloride (3 mL), then a 10% aqueous $NaHSO_3$ solution (2 mL) and a saturated aqueous saturated $NaHCO_3$ solution (2 mL) were added. The aqueous layer was extracted with methylene chloride, and the combined organic layers were dried

($MgSO_4$), and concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 5:1) led to ketone **16** (17.3 g, 74%) as a syrup; IR ($CDCl_3$) 2941, 1669, 1590, 1505, 1480 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.49 (s, 1H, H-5), 6.52 (s, 1H, H-8), 6.15 (s, 2H, H-2′, H-6′), 6.02 (s, 2H, OCH_2O), 4.42 (dd, 1H, J=12.6, 3.7 Hz, H-11), 4.20 (d, 1H, J=4.6 Hz, H-1), 3.84 (dd, 1H, J=12.6, 9.8 Hz, H-11), 3.83 (s, H, OCH_3-4′), 3.76 (s, 6H, OCH_3-3′,5′), 3.72 (dd, 1H, J=11.9, 3 Hz, H-13), 3.40 (dd, 1H, J=11.9, 10.4 Hz, H-13), 2.88 (m, 1H, H-3), 2.52 (m, 1H, H-2), 1.32 (s, 3H, CH_3), 1.22 (s, 3H, CH_3).

4.1.5. Aldehyde 17. Periodinane (374 mg, 0.885 mmol) was added to a solution of **13** (338 mg, 0.737 mmol) in methylene chloride (35 mL) at rt. After stirring for 30 min, the reaction mixture was poured into a 10% aqueous $NaHSO_3$ solution (25 mL) and a saturated aqueous $NaHCO_3$ solution (25 mL). The aqueous layer was extracted with methylene chloride (25 mL), and the combined organic layers were washed with water (2×30 mL) and brine (30 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 4:1) led to aldehyde **17** (293 mg, 87%) as an amorphous solid; $[\alpha]_D^{20}=-116$ (c 0.05, $CHCl_3$); IR ($CDCl_3$) 2936, 1719, 1592, 1505, 1483 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.11 (d, 1H, J=3.9 Hz, CHO), 7.01 (s, 1H, H-5), 6.37 (s, 1H, H-8), 6.23 (s, 2H, H-2′, H-6′), 5.92 (s, 2H, OCH_2O),4.68 (d,1H, J=10 Hz, H-4), 4.40 (d, 1H, J=6.8 Hz, H-1), 3.94 (dd, 1H, J=11.5, 4.1 Hz, H-11), 3.82 (s, 3H, OCH_3-4′), 3.78 (s, 7H, OCH_3-3′,5′, H-11), 2.71 (m, 1H, H-2), 2.55 (m, 1H, H-3), 1.60 (s, 3H, CH_3), 1.55 (s, 3H, CH_3); MS (DCI, NH_3) m/z 457 $[M+H]^+$, 4.74 $[M+NH_4]^+$.

4.1.6. Vinyl 18. To a suspension of methyltriphenylphosphonium bromide (315 mg, 0.883 mmol) in tetrahydrofuran (4 mL) at −78 °C was added n-butyl lithium (2.5 M in hexane, 0.32 mL, 0.795 mol). After 5 min, a solution of **17** (80.6 mg, 0.177 mmol) in tetrahydrofuran (2 mL) was added and the resulting mixture was stirred at −78 °C for 45 min, quenched by addition of acetone (0.5 mL) and allowed to reach rt. Upon addition of methylene chloride (10 mL) and H_2O (10 mL), the aqueous layer was extracted with methylene chloride (10 mL). The combined organic layers were dried ($MgSO_4$), and concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 6:1) gave **18** (68.7 mg, 86%) as a syrup; $[\alpha]_D^{20}=-195.5$ (c 0.07, $CHCl_3$); IR ($CDCl_3$) 2926, 1592, 1505, 1483 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.00 (s, 1H, H-5), 6.36 (s, 1H, H-8), 6.19 (s, 2H, H-2′, 6′), 5.91 (d, 1H, J=1.4 Hz, OCH_2O), 5.89 (d, 1H, J=1.4 Hz, OCH_2O), 5.11–4.99 (m, 3H, 3H-vinyl), 4.67 (d, 1H, J=10.1 Hz, H-4), 4.03 (d, 1H, J=6.4 Hz, H-1), 3.83 (s, 3H, OCH_3-4′), 3.76 (s, 6H, OCH_3-3′,5′), 3.69–3.54 (m, 2H, H-11), 2.56 (m, 1H, H-2), 2.13 (m, 1H, H-3), 1.59 (s, 3H, CH_3), 1.53 (s, 3H, CH_3); MS (DCI, NH_3) m/z 455 $[M+H]^+$, 4.72 $[M+NH_4]^+$.

4.1.7. Alcohol 19. A solution of 9-BBN (0.5 M in THF, 1.2 mL, 0.6 mmol) was added to a solution of **18** (53.1 mg, 0.117 mmol) in anhydrous THF (3 mL) and the reaction mixture was stirred for 3.5 h at rt prior to addition of pH 7.2 phosphate buffer (1.5 mL), methanol (4.5 mL) and a 35% (weight) aqueous solution of hydrogen peroxide (3 mL). After further stirring for 2.5 h, the mixture was diluted with methylene chloride (15 mL) and poured into water (10 mL). The aqueous layer was extracted with methylene chloride (15 mL), and the combined organic layers were washed with water (2×20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 3:1, then 2:1) gave compound **19** (41 mg, 74%) as a syrup; $[\alpha]_D^{20}=-161.5$ (c 0.13, $CHCl_3$); IR ($CDCl_3$) 3690, 3629 (OH), 2934, 1590, 1505, 1482 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.97 (s, 1H, H-5), 6.34 (s, 1H, H-8), 6.28 (s, 2H, H-2′, 6′), 5.88 (s, 1H, OCH_2O), 5.86 (s, 1H, OCH_2O), 4.67 (d, 1H, J=8.8 Hz, H-4), 3.90 (dd, 1H, J=11.3, 3.7 Hz, H-11), 3.82 (s, 3H, OCH_3-4′), 3.77 (s, 6H, OCH_3-3′,5′), 3.80–3.70 (m, 3H, H-11, H-14), 2.22–2.10 (m, 2H, H-2, H-3), 1.59 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 1.31 (m, 3H, H-13, OH); MS (DCI, NH_3) m/z 490 $[M+NH_4]^+$.

4.1.8. Aldehyde 20. Dess–Martin periodinane (34 mg, 81 μmol) was added to a solution of **19** (31.5 mg, 66.7 μmol) in methylene chloride (5 mL) at rt. After 1 h, a 10% aqueous $NaHSO_3$ solution (2.5 mL) and a saturated aqueous $NaHCO_3$ solution (2.5 mL) were added. The aqueous layer was extracted with methylene chloride (5 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 4:1) provided **20** (28.9 mg, 92%) as a syrup; ^1H NMR (300 MHz, $CDCl_3$) δ 9.75 (s, 1H, CHO), 6.98 (s, 1H, H-5), 6.32 (s, 1H, H-8), 6.16 (s, 2H, H-2′, H-6′), 5.90 (d, 1H, J=1.3 Hz, OCH_2O), 5.88 (d, 1H, J=1.3 Hz, OCH_2O), 4.72 (d, 1H, J=9.9 Hz, H-4), 4.16 (d, 1H, J=6.2 Hz, H-1), 3.83 (s, 3H, OCH_3-4′), 3.77 (s, 6H, OCH_3-3′,5′), 3.75–3.65 (m, 2H, H-11), 2.66 (m, 1H, H-2), 2.18 (d, 2H, J=6.8 Hz, H-13), 2.10 (m, 1H, H-3), 1.60 (s, 3H, CH_3), 1.53 (s, 3H, CH_3); MS (DCI, NH_3) m/z 488 $[M+NH_4]^+$.

4.1.9. Hemiacetal 22. p-Toluene sulfonic acid monohydrate (8.7 mg, 0.046 mmol) was added to a suspension of podophyllol **11** (191 mg, 0.456 mmol) in benzaldehyde dimethylacetal (5 mL) at rt. After 40 min, the mixture was diluted with methylene chloride (20 mL) and poured into a saturated aqueous $NaHCO_3$ solution (10 mL). The aqueous layer was extracted with methylene chloride (10 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (cyclohexane then cyclohexane/EtOAc 95:5 then 90:10) gave **22** (210 mg, 73%) as a mixture of diastereoisomers at C-13 (ratio 60:40 from ^1H NMR data). Such a mixture was not purified further but, after MS control (DCI, NH_3 m/z 644 $[M+NH_4]^+$), engaged into the following step.

4.1.10. Alcohol 23. *From podophyllol* **11**. Benzaldehyde dimethylacetal (0.23 mL, 1.43 mmol) and p-toluenesulfonic acid monohydrate (22.7 mg, 0.12 mmol) were successively added to a suspension of podophyllol (500 mg, 1.19 mmol) in methylene chloride (30 mL). The reaction mixture was stirred for 10 min at rt, and then treated with a saturated aqueous $NaHCO_3$ solution (30 mL). After 30 min, the aqueous layer was extracted with methylene chloride (20 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 5:1 then 1:1 then 1:2)

successively afforded **22** (62 mg, 8%), **23** (224 mg, 37%) and **12** (153 mg, 32%).

From hemiacetal **22**. A solution of **22** (71 mg, 0.113 mmol) in a mixture of methylene chloride (6 mL), H_2O (0.6 mL) and acetic acid (0.6 mL) was stirred for 4 days at rt. After dilution with methylene chloride (10 mL), the organic layer was washed with a saturated aqueous $NaHCO_3$ solution (15 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 2:1) furnished **23** (37.7 mg, 66%) as a white solid. Mp 159–160 °C; $[\alpha]_D^{20}=-95.5$ (*c* 0.56, $CHCl_3$); IR ($CDCl_3$) 3621, 1590, 1505, 1484 cm^{-1}; ^1H NMR, (300 MHz, $CDCl_3$) δ 7.62–7.60 (m, 2H, Ar–H), 7.44–7.38 (m, 3H, Ar–H), 7.10 (s, 1H, H-5), 6.38 (s, 3H, H-8, H-2′, H-6′), 5.91 (s, 2H, OCH_2O), 5.81 (s, 1H, CHPh), 4.69 (d, 1H, *J*=9.8 Hz, H-4), 4.37 (dd, 1H, *J*=10.8, 4.1 Hz, H-11), 4.22 (d, 1H, *J*=6 Hz, H-1), 3.87 (t, 1H, *J*=10.8 Hz, H-11), 3.83 (s, 3H, OCH_3-4′), 3.79 (s, 6H, OCH_3-3′,5′), 3.54 (m, 1H, H-13), 3.46 (m, 1H, H-13), 2.41 (m, 1H, H-3), 2.19 (m, 1H, H-2); MS (DCI, NH_3) *m/z* 524 $[M+NH_4]^+$; Anal. Calcd for $C_{29}H_{30}O_8$: C, 68.76; H, 5.97. Found: C, 68.49; H, 6.01.

4.1.11. Aldehyde 24. Dess–Martin periodinane (2.9 g, 6.84 mmol) was added to a solution of **23** (2.31 g, 4.56 mmol) in methylene chloride (350 mL) at rt. After 20 min, a 10% aqueous $NaHSO_3$ solution (220 mL) and a saturated aqueous $NaHCO_3$ solution (220 mL) were added to the reaction mixture. After stirring for 30 min, the organic layer was washed with water (2×450 mL) and brine (450 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 4:1) led to **24** (1.95 g, 87%) as an amorphous solid; IR ($CDCl_3$) 2935, 1720, 1592, 1505, 1484 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.19 (d, 1H, *J*=3.3 Hz, CHO, 7.62–7.55 (m, 2H, Ar–H), 7.46–7.36 (m, 3H, Ar–H), 7.11 (s, 1H, H-5), 6.39 (s, 1H, H-8), 6.24 (s, 2H, H-2′, H-6′), 5.92 (s, 2H, OCH_2O), 5.81 (s, 1H, CHPh), 4.65 (d, 1H, *J*=8.5 Hz, H-4), 4.45 (d, 1H, *J*=5.7 Hz, H-1), 4.40 (dd, 1H, *J*=11, 3.5 Hz, H-11), 3.82 (s, 3H, OCH_3-4′), 3.77 (s, 6H, OCH_3-3′, 5′), 3.73 (t, 1H, *J*=11 Hz, H-11), 2.79–2.72 (m, 2H, H-2, H-3); MS (DCI, NH_3) *m/z* 505 $[M+H]^+$, 5.22 $[M+NH_4]^+$; Anal. Calcd for $C_{29}H_{28}O_8$: C, 69.04; H, 5.59. Found: C, 68.85; H, 5.62.

4.1.12. Vinyl 25. To a solution of methyltriphenylphosphonium bromide (1.03 g, 2.88 mmol) and anhydrous potassium carbonate (349.4 mg, 2.53 mmol) in tetrahydrofuran (20 mL) was added a solution of **24** (1.037 g, 2.055 mmol) in tetrahydrofuran (20 mL). The reaction mixture was refluxed for 19 h and, after cooling to rt, diluted with ethyl acetate (150 mL). The mixture was washed successively with 1 N HCl (50 mL), water (2×150 mL) and brine (150 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 6:1 then 5:1) afforded **25** as a white crystalline solid (0.95 g, 92%). Mp 162–163 °C; $[\alpha]_D^{20}=-37.5$ (*c* 0.25, $CHCl_3$); IR ($CDCl_3$) 2939, 1591, 1505, 1485 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.59–7.55 (m, 2H, Ar–H), 7.43–7.35 (m, 3H, Ar–H), 7.11 (s, 1H, H-5), 6.44 (s, 1H, H-8), 6.23 (s, 2H, H-2′, 6′), 5.93 (s, 2H, OCH_2O), 5.92 (m, 1H, H-vinyl), 5.72 (s, 1H, CHPh), 5.30 (br s, 1H, H-vinyl), 5.15 (br d, 1H, *J*=10.3 Hz, H-vinyl), 4.73 (d, 1H, *J*=10.6 Hz, H-4), 4.06–4.00 (m, 2H, H-1, H-11), 3.95 (t, 1H, *J*=10.4 Hz, H-11), 3.83 (s, 3H, OCH_3-4′), 3.77 (s, 6H, OCH_3-3′,5′), 2.53 (dd, 1H, *J*=8.9, 2.9 Hz, H-2), 2.39 (m, 1H, H-3); MS (DCI, NH_3) *m/z* 520 $[M+NH_4]^+$; Anal. Calcd for $C_{30}H_{30}O_7$: C, 71.70; H, 6.02. Found: C, 71.66; H, 6.07.

4.1.13. Alcohol 26. A solution of 9-BBN in THF (0.5 M, 10.8 mL, 5.4 mmol) was added to a solution of **25** (270 mg, 0.537 mmol) in anhydrous THF (25 mL) at rt. After stirring for 1.75 h, an aqueous solution of pH 7.2 phosphate buffer (8 mL), methanol (22 mL) and a 30% aqueous H_2O_2 solution (13.2 mL) were successively added to the reaction mixture. Further stirring was maintained for 3 h at rt, then the reaction mixture was diluted with ethyl acetate (40 mL). The aqueous layer was extracted with ethyl acetate (2×30 mL), and the combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 3:1) afforded **26** (223.6 g, 80%) as a syrup; IR ($CDCl_3$) 3614, 2933, 1590, 1505, 1485 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.59–7.56 (m, 2H, Ar–H), 7.42–7.37 (m, 3H, Ar–H), 7.11 (s, 1H, H-5), 6.45 (s, 1H, H-8), 6.23 (s, 2H, H-2′, 6′), 5.94 (d, 1H, *J*=1.3 Hz, OCH_2O), 5.92 (m, 1H, *J*=1.3 Hz, OCH_2O), 5.76 (s, 1H, CHPh), 4.77 (d, 1H, *J*=10.6 Hz, H-4), 4.09–3.90 (m, 5H, H-1, H-11, H-14), 3.83 (s, 3H, OCH_3-4′), 3.78 (s, 6H, OCH_3-3′,5′), 2.47–2.33 (m, 1H, H-2), 2.05 (m, 1H, OH), 1.90–1.80 (m, 1H, H-3), 1.68–1.50 (m, 2H, H-13).

4.1.14. Aldehyde 27. Dess–Martin periodinane (810 mg, 1.91 mmol) was added to a solution of derivative **26** (506 mg, 0.972 mmol) in methylene chloride (150 mL) at rt. After 1 h, a 10% aqueous $NaHSO_3$ solution (50 mL) and a saturated aqueous $NaHCO_3$ solution (50 mL) were successively added to the reaction mixture. After further stirring for 15 min, the organic layer was washed with brine (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 4:1) led to **27** (327.6 g, 65%) as a white foam; $[\alpha]_D^{20}=-10$ (*c* 0.25, $CHCl_3$); IR ($CDCl_3$) 2939, 1724, 1591, 1505, 1484 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.45 (s, 1H, CHO), 7.58–7.55 (m, 2H, Ar–H), 7.42–7.37 (m, 3H, Ar–H), 7.11 (s, 1H, H-5), 6.42 (s, 1H, H-8), 6.37 (s, 2H, H-2′, H-6′), 5.94 (s, 1H, OCH_2O), 5.93 (s, 1H, OCH_2O), 5.76 (s, 1H, CHPh), 4.69 (d, 1H, *J*=10.7 Hz, H-4), 4.03 (dd, 1H, H-1, *J*=10.9, 4 Hz, H-11), 3.93 (ls, 1H, H-1), 3.87 (t, 1H, *J*=10.9 Hz, H-11), 3.84 (s, 3H, OCH_3-4′), 3.84 (s, 6H, OCH_3-3′,5′), 3.81 (m, 1H, H-13), 2.72–2.60 (m, 2H, H-2, H-13), 2.46 (m, 1H, H-3); MS (DCI, NH_3) *m/z* 536 $[M+NH_4]^+$; Anal. Calcd for $C_{30}H_{30}O_8$: C, 69.49; H, 5.83. Found: C, 69.23; H, 5.86.

4.1.15. Carboxylic acid 28. Sulfamic acid (53.8 mg, 0.554 mmol) and sodium chlorite (49.2 mg, 0.435 mmol) were added to a suspension of **27** (205.3 mg, 0.396 mmol) in *tert*-butanol (16 mL) and H_2O (8 mL). The reaction mixture was stirred for 30 min at rt, at which point the reaction was poured into water (15 mL) and ethyl acetate (50 mL). The aqueous layer was extracted with ethyl acetate (3×20 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc/AcOH 2:1:0.1) successively gave **28**

(161 mg, 76%) as a syrup and **29** (18 mg, 8%) as a white solid.

Compound **28**. $[\alpha]_D^{20}=0$ (*c* 0.5, $CHCl_3$); IR ($CDCl_3$) 3679, 2929, 1709, 1591, 1505, 1485 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.58–7.55 (m, 2H, Ar–H), 7.42–7.36 (m, 3H, Ar–H), 7.11 (s, 1H, H-5), 6.44 (s, 1H, H-8), 6.33 (s, 2H, H-2′, H-6′), 5.95 (s, 1H, OCH_2O), 5.94 (s, 1H, OCH_2O), 5.76 (s, 1H, CHPh), 4.69 (d, 1H, *J*=10.5 Hz, H-4), 4.05 (m, 1H, H-11), 4.05 (br s, 1H, H-1), 3.92 (t, 1H, *J*=10.9 Hz, H-11), 3.83 (s, 3H, OCH_3-4′), 3.77 (s, 6H, OCH_3-3′,5′), 2.66–2.43 (m, 4H, H-2, H-3, H-13); MS (DCI, NH_3) *m/z* 552 $[M+NH_4]^+$.

Compound **29**. Mp 131–133 °C; $[\alpha]_D^{20}=0$ (*c* 0.6, $CHCl_3$); IR ($CDCl_3$) 3680, 2939, 1709, 1573, 1505, 1485 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.57–7.54 (m, 2H, Ar–H), 7.41–7.37 (m, 3H, Ar–H), 7.11 (s, 1H, H-5), 6.41 (s, 1H, H-8), 5.99 (s, 1H, H-6′), 5.95 (s, 1H, OCH_2O), 5.94 (s, 1H, OCH_2O), 5.77 (s, 1H, CHPh), 4.76 (d, 1H, *J*=10.5 Hz, H-4), 4.44 (br s, 1H, H-1), 4.08 (dd, 1H, *J*=10.9, 3.8 Hz, H-11), 3.97 (s and partially overlapped m, 4H, OCH_3, H-11), 3.86 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3) 2.73–2.41 (m, 4H, H-2, H-3, H-13); MS (DCI, NH_3) *m/z* 569 $[M+H]^+$, 586 $[M+NH_4]^+$.

4.1.16. Homolactone 4. CSA (34 mg, 0.146 mmol) was added to a solution of acid **28** (71.1 mg, 0.133 mmol) in THF (4 mL) and water (0.4 mL) at rt. The reaction mixture was heated at 80 °C for 6 h, then allowed to cool to rt. After dilution with ethyl acetate (10 mL) and water (5 mL), the aqueous layer was extracted with ethyl acetate (5 mL), and the organic layers were combined, dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 1:1) furnished **4** (37.5 mg, 66%) as a white solid. Mp 171–172 °C; $[\alpha]_D^{20}=+9.5$ (*c* 0.27, $CHCl_3$); IR ($CDCl_3$) 3624, 2939, 1739, 1592, 1504, 1482 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.02 (s, 1H, H-5), 6.36 (s, 2H, H-2′, H-6′), 6.29 (s, 1H, H-8), 5.93 (d, 1H, *J*=1.3 Hz, OCH_2O), 5.92 (s, 1H, *J*=1.3 Hz, OCH_2O), 4.65 (d, 1H exch. with D_2O, *J*=8.2 Hz, H-4), 4.49 (m, 2H, H-11), 3.87 (s, 3H, OCH_3-4′), 3.83 (s, 6H, OCH_3-3′,5′), 3.52 (d, 1H, *J*=9.3 Hz, H-1), 2.67 (m, 1H, H-2), 2.58 (dd, 1H, *J*=16.2, 6.1 Hz, H-13), 2.41 (dd, 1H, *J*=16.2, 6.1 Hz, H-13), 2.39 (m, 1H, H-3); MS (DCI, NH_3) *m/z* 446 $[M+NH_4]^+$; Anal. Calcd for $C_{23}H_{24}O_8$: C, 64.48; H, 5.65. Found: C, 64.27; H, 5.69.

4.1.17. Mesylate 30. To a cooled 0 °C solution of **23** (530 mg, 1.046 mmol) in methylene chloride (50 mL), were added successively triethylamine (1.45 mL, 10.46 mmol) and methanesulfonyl chloride (0.410 mL, 5.27 mmol). After stirring for 30 min at 0 °C, the reaction mixture was quenched with water (50 mL), and the organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 2:1) gave **30** (604 mg, 99%) as a white foam; $[\alpha]_D^{20}=-114$ (*c* 1, $CHCl_3$); IR ($CDCl_3$) 2937, 1590, 1505, 1484 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.61–7.58 (m, 2H, Ar–H), 7.46–7.39 (m, 3H, Ar–H), 7.09 (s, 1H, H-5), 6.38 (s, 1H, H-8), 6.32 (s, 2H, H-2′, H-6′), 5.92 (s, 1H, OCH_2O), 5.91 (s, 1H, OCH_2O), 5.81 (s, 1H, CHPh), 4.70 (d, 1H, *J*=8.7 Hz, H-4), 4.28–4.24 (m, 1H, H-11), 4.03–3.88 (m, 3H, H-11, H-13), 3.84 (s, 3H, OCH_3-4′), 3.79 (s, 6H, OCH_3-3′,5′), 2.97 (s, 3H, SO_2CH_3), 2.46 (m, 2H, H-2, H-3); MS (ES) *m/z* 607 $[M+Na]^+$.

4.1.18. Cyanide 31. A solution of sodium cyanide (25.8 mg, 0.526 mmol) in anhydrous dimethylformamide (15 mL) was added to a solution of mesylate **30** (153.7 mg, 0.263 mmol) ar rt. The reaction medium was heated at 85 °C for 6 h and, after cooling to rt, poured into water (75 mL). The mixture was extracted with ether (4×40 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 4:1) gave **31** (129 mg, 95%) as a white solid; $[\alpha]_D^{20}=-175$ (*c* 0.88, $CHCl_3$); IR ($CDCl_3$) 2933, 1591, 1506, 1485 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.60–7.57 (m, 2H, Ar–H), 7.46–7.39 (m, 3H, Ar–H), 7.09 (s, 1H, H-5), 6.41 (br s, 3H, H-8, H-2′, H-6′), 5.93 (s, 1H, OCH_2O), 5.92 (s, 1H, OCH_2O), 5.79 (s, 1H, CHPh), 4.67 (d, 1H, *J*=9.1 Hz, H-4), 4.31 (d, 1H, *J*=5.3 Hz, H-1), 4.21 (dd, 1H, *J*=10.6, 3.8 Hz, H-11), 3.84 (s and overlapped m, 4H, OCH_3-4′, H-11), 3.81 (s, 6H, OCH_3-3′,5′), 2.40 (m, 2H, H-2, H-3), 2.22 (dd, 1H, *J*=16.5, 3.9 Hz, H-13), 1.88 (dd, 1H, *J*=16.5, 10.6 Hz, H-13); MS (DCI) *m/z* 533 $[M+NH_4]^+$; Anal. Calcd for $C_{30}H_{29}NO_7$: C, 69.89; H, 5.67; N, 2.72. Found: C, 69.77; H, 5.71; N, 2.70.

4.1.19. Amide 32 and carboxylic acid 33. A solution of aqueous sodium hydroxide (6.25 M, 1.86 mL, 11.6 mmol) was added to a solution of **31** (143 mg, 0.277 mmol) in 95% ethanol (11 mL) at rt. The reaction mixture was heated at 80 °C for 7 h and then allowed to cool to rt. After quenching with 1 N HCl (11 mL), the reaction mixture was diluted with ethyl acetate (30 mL) and the aqueous layer was extracted with ethyl acetate (10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (methylene chloride/MeOH 97:3) afforded **32** (123 mg, 83%) as a white solid. Prolonged reaction time (16 h) gave a mixture of **32** (24%) and **33** (47%).

Compound **32**. Mp 140–142 °C; $[\alpha]_D^{20}=-118$ (*c* 1.02, $CHCl_3$); IR ($CDCl_3$) 3523, 3408 (NH_2), 2939, 1683, 1595, 1590, 1595, 1484 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.62–7.58 (m, 2H, Ar–H), 7.45–7.27 (m, 3H, Ar–H), 7.08 (s, 1H, H-5), 6.34 (s, 2H, H-8), 6.28 (s, 2H, H-2′, H-6′), 5.90 (d, 1H, *J*=1.4 Hz, OCH_2O), 5.89 (d, 1H, *J*=1.4 Hz, OCH_2O), 5.78 (s, 1H, CHPh), 5.38 and 5.33 (2 br s, 2H exch. D_2O, NH_2), 4.71 (d, 1H, *J*=9.7 Hz, H-4), 4.28 (d, 1H, *J*=6.1 Hz, H-1), 4.20 (dd, 1H, *J*=10.9, 4.2 Hz, H-11), 3.83 (s, 3H, OCH_3-4′), 3.77 (s and overlapped m, 7H, OCH_3-3′,5′, H-11), 2.71 (m, 1H, H-2), 2.32 (m, 1H, H-3), 2.01 (dd, 1H, *J*=16.3, 4.9 Hz, H-13), 1.82 (dd, 1H, *J*=16.3, 9.6 Hz, H-13); MS (DCI) *m/z* 551 $[M+NH_4]^+$.

Compound **33**. $[\alpha]_D^{20}=-130.5$ (*c* 0.78, $CHCl_3$); IR ($CDCl_3$) 3522, 3400–2500, 2939, 1708, 1590, 1505, 1484 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.621–7.57 (m, 2H, Ar–H), 7.44–7.39 (m, 3H, Ar–H), 7.09 (s, 1H, H-5), 6.35 (s, 2H, H-8), 6.23 (br s, 2H, H-2′, H-6′), 5.90 (br s, 2H, OCH_2O), 5.78 (s, 1H, CHPh), 4.69 (d, 1H, *J*=9.7 Hz, H-4), 4.22 (m, 2H, H-1, H-11), 3.83 (s, 3H, OCH_3-4′), 3.76 (s and overlapped m, 7H, OCH_3-3′,5′, H-11), 2.58 (m, 1H, H-2), 2.33 (m, 1H, H-3), 2.13 (m, 2H, H-13); MS (DCI, NH_3) *m/z* 552 $[M+NH_4]^+$.

4.1.20. Homolactones 5, 6 and 36. CSA (161 mg, 0.693 mmol) was added to a solution of amide **32** (246 mg, 0.462 mmol) in THF (15 mL) and water (15 mL) at rt. The reaction mixture was heated at 85 °C for 17 h, then allowed to cool to rt. The reaction mixture was poured into a saturated aqueous $NaHCO_3$ solution (15 mL) and extracted with ethyl acetate (30 mL). The organic layer was washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 6:4 then 1:1) gave **5** (55.4 mg, 28%), **6** (14 mg, 7%) and **36** (26 mg, 13%) as amorphous solids.

Compound **5**. $[\alpha]_D^{20}=118$ (*c* 0.77, $CHCl_3$); IR ($CDCl_3$) 3610, 2927, 1733, 1590, 1505, 1595, 1484 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.02 (s, 1H, H-5), 6.43 (s, 1H, H-8), 6.21 (s, 2H, H-2′, H-6′), 5.95 (s, 2H, OCH_2O), 4.79 (dd, 1H, *J*=11.3, 5.3 Hz, H-11), 4.51 (br t, 1H, *J*=7.6 Hz, H-4), 4.18 (dd, 1H, *J*=11.3, 10.1 Hz, H-11), 3.92 (d, 1H, *J*=5.4 Hz, H-1), 3.83 (s, 3H, OCH_3-4′), 3.79 (s, 6H, OCH_3-3′,5′), 2.62 (dd, 1H, *J*=17.4, 12, 5.6 Hz, H-13), 2.51–2.39 (m, 1H, H-2), 2.37–2.25 (m, 1H, H-3), 2.19 (d, 1H exch. with D_2O, *J*=7.6 Hz, OH), 2.09 (dd, 1H, *J*=17.4, 11.7 Hz, H-13); MS (DCI, NH_3) *m/z* 446 $[M+NH_4]^+$; Anal. Calcd for $C_{23}H_{24}O_8$: C, 64.48; H, 5.65. Found: C, 64.36; H, 5.67.

Compound **6**. IR ($CDCl_3$) 3597, 2927, 1733, 1506, 1595, 1485 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.84 (s, 1H, H-5), 6.45 (s, 1H, H-8), 6.06 (s, 2H, H-2′, H-6′), 5.96 (s, 1H, OCH_2O), 5.95 (s, 1H, OCH_2O), 4.76 (br s, 1H, H-4), 4.58–4.50 (m, 2H, H-11), 4.03 (d, 1H, *J*=6.2 Hz, H-10), 3.82 (s, 3H, OCH_3-4′), 3.77 (s, 6H, OCH_3-3′,5′), 2.90–2.80 (m, 1H, H-2), 2.67 (dd, 1H, *J*=17.8, 6.4 Hz, H-13), 2.40–2.30 (m, 1H, H-3), 2.08 (dd, 1H, *J*=17.8, 11.6 Hz, H-13); MS (DCI, NH_3) *m/z* 446 $[M+NH_4]^+$.

Compound **36**. $[\alpha]_D^{20}=-11.5$ (*c* 0.65, $CHCl_3$); IR ($CDCl_3$) 3608, 2927, 1735, 1590, 1504, 1485, 1484 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.80 (s, 1H, H-5), 6.51 (s, 1H, H-8), 6.48–6.10 (m, 2H, H-2′, H-6′), 5.97 (d, 1H, *J*=1.1 Hz, OCH_2O), 5.95 (d, 1H, *J*=1.1 Hz, OCH_2O), 5.24 (t, 1H, *J*=2.4 Hz, H-4), 4.28 (d, 1H, *J*=5.8 Hz, H-l), 3.86 (s, 3H, OCH_3-4′), 3.83–3.73 (m, 8H, OCH_3-3′,5′, H-11), 2.83 (m, 1H, H-3), 2.65–2.59 (m, 1H, H-2), 2.50–2.45 (m, 2H, H-13); MS (DCI, NH_3) *m/z* 446 $[M+NH_4]^+$.

4.1.21. 4′-*tert*-Butyldimethylsilanyloxy-podophyllol 39. To a suspension of $LiAlH_4$ (134 mg, 3.53 mmol) in THF (12 mL) cooled to 0 °C was added alcohol **38** (227 mg, 0.441 mmol) in solution in THF (7 mL). After 1.5 h at 0 °C, water (0.140 mL), a 25% NaOH aqueous solution (0.140 mL), and water (0.420 mL) were successively added to the reaction mixture. The precipitate was eliminated by filtration, and the filtrate was diluted with ethyl acetate (25 mL) and washed with Rochelle's salt saturated water (25 mL). The organic layer was washed with brine (25 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue, often directly used for the following reactions, could also be purified by flash chromatography (cyclohexane/EtOAc 1:2, 1:4), leading to **39** (117.4 mg, 51%) as a white solid. Mp 180–181 °C; $[\alpha]_D^{20}=-98.5$ (*c* 1, $CHCl_3$); IR ($CDCl_3$) 3600–3200, 2936, 1587, 1505, 1485 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.83 (s, 1H, H-5), 6.41 (s, 1H, H-8), 6.12 (s, 2H, H-2′, H-6′), 5.93 (d, 1H, *J*=1.3 Hz, OCH_2O), 5.91 (d, 1H, *J*=1.3 Hz, OCH_2O), 4.96 (d, 1H, *J*=3.1 Hz, H-4), 4.18 (d, 1H, *J*=5.5 Hz, H-1), 4.05 (dd, 1H, *J*=12, 1.9 Hz, H-11), 3.93 (dd, 1H, *J*=12, 4.1 Hz, H-11), 3.77 (dd, 1H, *J*=11, 4 Hz, H-13), 3.68 (s, 6H, OCH_3-3′,5′), 3.64 (m, 1H exch. with D_2O, OH), 3.46 (dd, 1H, *J*=11, 6.8 Hz, H-13), 3.08 (m, 1H exch. with D_2O, OH), 2.10 (m, 1H, H-3), 0.99 (s, 9H, $(CH_3)_3CSi$), 0.10 (s, 6H, $(CH_3)_2Si$); MS (ES) *m/z* (%) 541 $[M+Na]^+$.

4.1.22. (1α,2α,3β,4β)-4,11-*O*-Isopropylidene-4′-*tert*-butyldimethylsilanyloxy)-podophyllol 40. Monohydrated *p*-toluenesulfonic acid (51.1 mg, 0.269 mmol) was added to a solution of crude **39** (1.39 g, 2.68 mmol) in 2,2-dimethoxypropane (125 mL). After 35 min at rt, the reaction mixture was concentrated under reduced pressure until it reached a volume of 50 mL. A saturated aqueous $NaHCO_3$ solution (20 mL) and ethyl acetate (100 mL) were then added. The organic layer was washed with water (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure, affording a crude residue (1.65 g) as a beige foam, which was poured into methanol (85 mL). Water (1.2 mL) and acetic acid (1.2 mL) were then added. Stirring was maintained for 6 h at rt before addition of a saturated aqueous $NaHCO_3$ solution (35 mL) and ethyl acetate (100 mL). In order to obtain decantation, brine (100 mL) was added. The aqueous layer was extracted with ethyl acetate (80 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 4:1) afforded acetonide **40** (901 mg, 60%) as a white foam; $[\alpha]_D^{20}=-50$ (*c* 1, $CHCl_3$); IR ($CDCl_3$) 3564, 2931, 1586, 1506, 1485 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.75 (s, 1H, H-5), 6.43 (s, 1H, H-8), 6.22 (s, 2H, H-2′, H-6′), 5.92 (d, 1H, *J*=1.3 Hz, OCH_2O), 5.87 (d, 1H, *J*=1.3 Hz, OCH_2O), 4.94 (d, 1H, *J*=3.6 Hz, H-4), 4.20 (d, 1H, *J*=5.4 Hz, H-l), 4.07 (dd, 1H, *J*=12.3, 4.3 Hz, H-11), 3.89 (dd, 1H, *J*=12.3, 3.5 Hz, H-11), 3.82 (dt, 1H, $J_{gem}=11.7$ Hz, $J_{13,2}=J_{13,OH}=3$ Hz, H-13), 3.70 (s, 6H, OCH_3-3′,5′), 3.63 (m, 1H, H-13), 2.76 (m, 1H, H-2), 2.06 (m, 1H, H-3), 1.63 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 0.99 (s, 9H, $(CH_3)_3CSi$), 0.90 (dd, 1H exch. with D_2O, *J*=3, 9 Hz, OH), 0.10 (s, 6H, $(CH_3)_2Si$); MS (DCI, NH_3) *m/z* (%) 559 $[M+H]^+$; Anal. Calcd for $C_{30}H_{42}O_7Si$: C, 64.49; H, 7.58. Found: C, 64.28; H, 7.59.

4.1.23. Cyanide 44. Triethylamine (4 mL, 28.62 mmol) and methanesulfonyl chloride (0.57 mL, 7.182 mmol) were added to a solution of **40** (800 mg, 1.431 mmol) in methylene chloride (60 mL), cooled to 0 °C. After 50 min at 0 °C, water (60 mL) and methylene chloride (100 mL) were poured into the reaction mixture. The organic layer was washed with brine, acidified with 1 N HCl until pH 2, neutralized with water, dried ($MgSO_4$), and concentrated under reduced pressure to afford the crude mesylate **43** (939.6 mg). The latter was dissolved into anhydrous DMF (80 mL), and sodium cyanide (143.1 mg, 2.916 mmol) was added. The mixture was heated at 85 °C for 5 h, then allowed to reach rt. The reaction mixture was then poured into water (300 mL), the aqueous layer was extracted with ethyl acetate (3×150 mL) [Bad decantation can be remedied by addition of brine into the emulsion]. The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The remaining DMF traces were

eliminated by evaporation under high vacuum. Flash chromatography (cyclohexane/EtOAc 2:1) gave cyanide **44** (345.6 mg, 53% for the two steps) as a syrup; IR ($CDCl_3$) 3540, 2940, 1619, 1519, 1505, 1485 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.75 (s, 1H, H-5), 6.46 (s, 1H, H-8), 6.31 (br s, 2H, H-2′, H-6′), 5.94 (d, 1H, J=1.3 Hz, OCH_2O), 5.90 (d, 1H, J=1.3 Hz, OCH_2O), 5.44 (s, 1H exch. with D_2O, OH), 4.93 (d, 1H, J=3.6 Hz, H-4), 4.34 (d, 1H, J=5.1 Hz, H-1), 4.06 (dd, 1H, J=12.6, 4.1 Hz, H-11), 3.81 (s, 6H, OCH_3-3′, 5′), 3.68 (dd 1H, J=12.6, 3.4 Hz H-11), 3.04 (m, 1H, H-2), 2.56 (dd, 1H, J=16.5, 3.5 Hz, H-13), 1.94 (m, 1H, H-3), 1.87 (dd, 1H, J=16.5, 12 Hz, H-13), 1.62 (s, 3H, CH_3), 1.42 (s, 3H, CH_3); MS (DCI, NH_3) m/z 471 $[M+NH_4]^+$.

4.1.24. Amide 45. A 6.25 M sodium aqueous solution (0.181 mL, 1.13 mmol was added to a solution of **44** (12.2 mg, 26.9 mmol) in ethanol. The reaction mixture was heated at 75 °C for 28 h. After cooling, the mixture was neutralized with 1 N HCl. The aqueous layer was extracted with ethyl acetate (2×8 mL), and the combined organic layers were washed with brine (2×10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (methylene chloride/MeOH 97:3) gave **45** (5.8 mg, 44%) as a syrup; IR ($CDCl_3$) 3694, 3527, 3409, 2926, 1681, 1484 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.76 (s, 1H, H-5), 6.42 (s, 1H, H-8), 6.21 (s, 2H, H-2′, H-6′), 5.91 (d, 1H, J=1.3 Hz, OCH_2O), 5.87 (d, 1H, J=1.3 Hz, OCH_2O), 5.55 (br s, 1H exch. with D_2O, NH), 5.39 (s, 1H (d, 1H exch. with D_2O, OH), 5.35 (br s, 1H exch. with D_2O, NH), 4.92 (d, 1H, J=3.9 Hz, H-4), 4.34 (d, 1H, J=5 Hz, H-1), 4.01 (dd, 1H, J=12.3, 4.9 Hz, H-11), 3.80 (s, 6H, OCH_3-3′,5′), 3.74 (dd, 1H, J=12.3, 4.5 Hz, H-11), 3.03 (m, 1H, H-2), 2.30 (dd, 1H, J=15.7, 3.8 Hz, H-13), 2.01 (m, 1H, H-3), 1.86 (dd, 1H, J=15.7, 10.9 Hz, H-13), 1.62 (s, 3H, CH_3), 1.42 (s, 3H, CH_3); MS (DCI, NH_3) m/z (%) 489 $[M+NH_4]^+$.

4.1.25. Homolactones 7 and 8. *From cyanide* **44**. A solution of nitrile **44** (105 mg, 0.172 mmol) in 95% ethanol (14 mL) containing a 25% aqueous NaOH solution (1.15 mL, 7.2 mmol) was heated at 85 °C for 7 h. After cooling to rt, the reaction mixture was neutralized with 1 N HCl (7.2 mL) (the bright yellow color disappeared). A small excess of 1 N HCl (0.5 mL) was added to obtain pH 3–4, and after 10 min the mixture was poured into ethyl acetate (30 mL) and water (10 mL). The aqueous layer was extracted twice with ethyl acetate (2×10 mL), and the combined organic layers were stirred for 15 h, then washed with brine (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (methylene chloride/MeOH 98:2 then 97:3) afforded **7** (36.2 mg, 51%) as a white powder and **8** (8.5 mg, 12%) as a syrup.

From amide **45**. *p*.Toluenesulfonic acid (23 mg, 0.12 mmol) was added to a solution of **45** (48.6 mg, 0.1 mmol) in THF (5 mL) and water (0.5 mL). The reaction mixture was heated at 45 °C for 7 h and subsequently poured into brine (3 mL) and ethyl acetate (5 mL). The aquous layer was extracted twice with ethyl acetate (2×10 mL), and the combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue (56.1 mg) in anhydrous methylene chloride (3 mL) was treated with camphorsulfonic acid (3.7 mg, 0.016 mmol). After 30 min (TLC control showed the disappearance of polar compounds), the reaction was diluted with methylene chloride (8 mL), washed with brine (8 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Preparative chromatography on silica gel (methylene chloride/MeOH 95:5) led to **7** (12.8 mg, 31%) and to an inseparable mixture (7.2 mg) containing its 4-epimer **8** and the postulated bridged δ-lactone **46**.

Homolactone **7**. Mp 135–137 °C; $[\alpha]_D^{20}=-126$ (c 0.29, $CHCl_3$); IR ($CDCl_3$) 3544, 2917, 1734, 1619, 1519, 1485 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.83 (s, 1H, H-5), 6.44 (s, 1H, H-8), 6.07 (s, 2H, H-2′, H-6′), 5.95 (s, 2H, OCH_2O), 5.45 (s, 1H, exch. with D_2O, OH-4′), 4.75 (br s, 1H, H-4), 4.60–4.50 (m, 2H, H-11), 4.02 (d, 1H, J=6.1 Hz, H-1), 3.80 (s, 6H, OCH_3-3′,5′), 2.89–2.77 (m, 1H, H-2), 2.65 (dd, J=17.7, 6.3 Hz, H-13), 2.39–2.27 (m, 1H, H-3), 2.06 (dd, 1H, J=17.7, 11.3 Hz, H-13); HRMS (DCI, NH_3) m/z (%) Calcd: 415.1393 $[M+H]^+$. Found: 415.1384 $[M+H]^+$; Anal. Calcd for $C_{22}H_{22}O_8$: C, 63.76; H, 5.35. Found: C, 63.53; H, 5.31.

Homolactone **8**. IR ($CDCl_3$) 3541, 2898, 1729, 1620, 1517, 1484 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.01 (s, 1H, H-5), 6.42 (s, 1H, H-8), 6.22 (s, 2H, H-2′, H-6′), 5.94 (s, 2H, OCH_2O), 5.46 (s, 1H, exch. with D_2O, H-4′), 4.78 (dd, 1H, J=11.3, 5.3 Hz, H-11), 4.50 (br d, 1H, J=8.3 Hz, H-4), 4.18 (dd, 1H, J=11.3, 9.7 Hz, H-11), 3.91 (d, 1H, J=5.4 Hz, H-1), 3.83 (s, 6H, OCH_3-3′,5′), 2.60 (dd, 1H, J=17.5, 5.6 Hz, H-13), 2.49–2.37 (m, 1H, H-2), 2.34–2.24 (m, 1H, H-3), 2.07 (dd, 1H, J=17.5, 11.7 Hz, H-13); HRMS (DCI, NH_3) m/z (%) Calcd: 415.1393 $[M+H]^+$. Found 415.1386 $[M+H]^+$.

4.1.26. Cyanide 17. Imidazole (1.22 g, 8.94 mmol) and *tert*-butyldimethylsilyl chloride (1.35 g, 8.94 mmol) were added at rt to a solution of cyanide **44** (700 mg, 1.54 mmol) in anhydrous DMF (25 mL). After 2.5 h the reaction mixture was poured into water (100 mL) and ethyl acetate (50 mL) was added. The aqueous layer was extracted thrice (3×50 mL), and the combined organic layers were washed with brine (2×50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 5:1) gave cyanide **47** (537 mg, 61%) as a white foam. IR ($CDCl_3$) 2932, 1587, 1506, 1486 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.74 (s, 1H, H-5), 6.47 (s, 1H, H-8), 6.25 (s, 2H, H-2′, H-6′), 5.94 (d, 1H, J=1.3 Hz, OCH_2O), 5.89 (d, 1H, J=1.3 Hz, OCH_2O), 4.92 (d, 1H, J=3.4 Hz, H-4), 4.31 (d, 1H, J=5.1 Hz, H-1), 4.05 (dd, 1H, J=12.5, 4.1 Hz, H-11), 3.72 (s, 6H, OCH_3-3′,5′), 3.68 (dd, 1H, J=12.5, 3.5 Hz, H-11), 3.02 (m, 1H, H-2), 2.53 (dd, 1H, J=16.4, 3.5 Hz, H-13), 1.95 (m, 1H, H-3), 1.84 (dd, 1H, J=16.4, 11.9 Hz, H-13), 1.62 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.00 (s, 9H, $(CH_3)_3CSi$), 0.11 (s, 6H, CH_3Si); MS (DCI, NH_3) m/z (%) 585 $[M+NH_4]^+$.

4.1.27. Cyanides 48 and 49. Monohydrated *p*-toluenesulfonic acid (3.4 mg, 0.0176 mmol) was added to a solution of **47** (100 mg, 0.176 mmol) in a mixture of THF (10 mL) and water (1 mL), and the reaction mixture was heated at 70 °C for 25 h. The mixture was then diluted with water and ethyl acetate. The aqueous layer was extracted twice with ethyl acetate (2×10 mL) and the combined organic layers

were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (methylene chloride/MeOH 98:1) furnished a mixture of **48** (27 mg, 29%) and **49** (33.8 mg, 36%).

Compound **48**. Mp 144–145 °C; $[\alpha]_D^{20}=-182$ (*c* 0.59, $CHCl_3$); IR ($CDCl_3$): 3616, 2932, 1587, 1505, 1485 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.80 (s, 1H, H-5), 6.49 (s, 1H, H-8), 6.24 (s, 2H, H-2′, H-6′), 5.96 (d, 1H, *J*=1.1 Hz, OCH_2O), 5.95 (d, 1H, *J*=1.1 Hz, OCH_2O), 4.97 (t, 1H, *J*=3.7 Hz, H-4), 4.38 (d, 1H, *J*=5.3 Hz, H-1), 4.05 (br d, 1H, *J*=12 Hz, H-11), 3.71 (s, 6H, OCH_3-3′,5′), 3.67 (m, 1H, H-11), 3.05–2.90 (m, 2H, H-2, H-3), 2.79 (dd, 1H, *J*=16.3, 3.6 Hz, H-13), 2.09 (d, 1H exch. with D_2O, *J*=3.7 Hz, OH-4), 2.06 (m, 1H exch. with D_2O, OH-11), 1.85 (dd, 1H, *J*=16.3, 11.8 Hz, H-13), 0.99 (s, 9H, $(CH_3)_3CSi$), 0.10 (s, 6H, $(CH_3)_2Si$); MS (DCI, NH_3) *m/z* (%) 545 $[M+NH_4]^+$.

Compound **49**. Mp 100–102 °C; $[\alpha]_D^{20}=-215.5$ (*c* 0.66, $CHCl_3$); IR ($CDCl_3$): 3628, 2932, 1588, 1503, 1485 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.03 (s, 1H, H-5), 6.45 (s, 1H, H-8), 6.39 (s, 2H, H-2′, H-6′), 5.93 (s, 2H, OCH_2O), 4.80 (br d, 1H, *J*=8.4 Hz, H-4), 4.21 (d, 1H, *J*=4.6 Hz, H-1), 4.00 (br dd, *J*=10.6, 3.4 Hz, H-11), 3.73 (s, 6H, OCH_3-3′, 5′), 3.70 (m, 1H, H-11), 2.85 (br s, 1H exch. with D_2O, OH), 2.52 (dd, 1H, *J*=16.2, 4.3 Hz, H-13), 2.41 (m, 1H, H-2), 2.06 (m, 1H, H-3), 1.91 (dd, 1H, *J*=16.2, 10.7 Hz, H-13), 1.88 (m, 1H exch. with D_2O, OH), 1.00 (s, 9H, $(CH_3)_3CSi$), 0.13 (s, 6H, $(CH_3)_2Si$); MS (DCI, NH_3) *m/z* (%) 545 $[M+NH_4]^+$.

4.1.28. Alcohol 51. A solution of **50**[41] (6.7 g, 10.65 mmol) in THF (200 mL) was cooled to 0 °C, and lithium aluminium hydride (0.61 g, 16 mmol) was slowly added. After 15 min at 0 °C, the reaction mixture was warmed to rt for 15 min. The reaction was quenched by successive additions of water (0.6 mL), a 15% NaOH aqueous solution (0.6 mL) and water (1.8 mL). The precipitate was removed by filtration and the filtrate was concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 3:1) furnished diol **51** (6.22 g, 92%) as a white solid. Mp 156–158 °C (Lit.[37]: mp 160–162 °C); $[\alpha]_D^{20}=-50.5$ (*c* 1, $CHCl_3$); IR ($CDCl_3$) 3688, 3573, 2938, 1586, 1505, 1484 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.78 (s, 1H, H-5), 6.40 (s, 1H, H-8), 6.21 (s, 2H, H-2′, H-6′), 5.92 (s, 2H, OCH_2O), 5.01 (d, 1H, *J*=3.2 Hz, H-4), 4.16 (d, 1H, *J*=6.3 Hz, H-1), 3.85 (m, 2H, H-11), 3.70 (s, 6H, OCH_3-3′,5′), 3.67 (m, 2H, H-13), 2.66 (m, 1H, H-2), 2.32 (m, 1H, H-3), 1.00 (s, 9H, $(CH_3)_3CSi$), 0.88 (s, 9H, $(CH_3)_3CSi$), 0.20 (s, 3H, CH_3Si), 0.11 (s, 6H, $(CH_3)_2Si$), −0.02 (s, 3H, CH_3Si); MS (DCI, NH_3) *m/z* 650 $[M+NH_4]^+$; Anal. Calcd for $C_{33}H_{52}O_8Si_2$: C, 62.62; H, 8.28. Found: C, 62.38, H, 8.25.

4.1.29. Pivaloyls 52 and 53, and bis-pivaloyl 54. To a solution of **51** (5.71 g, 9.02 mmol) in methylene chloride (325 mL) were added, at rt, triethylamine (6.3 mL, 435.3 mmol), 4-DMAP (110 mg, 0.9 mmol) and pivaloyl chloride (2.8 mL, 22.5 mmol). After 25 min, the reaction mixture was poured into water (300 mL) and acidified with 1 N HCl until pH 2–3. The aqueous layer was extracted twice with methylene chloride (2×100 mL), and the combined organic layers were washed with brine (200 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 9:1 then 8:2) successively gave **52** (4.2 g, 65%), **53** (1.75 g, 27%) and **54** (0.5 g, 8%) as foams.

Compound **52**. $[\alpha]_D^{20}=-30.5$ (*c* 1, $CHCl_3$); IR ($CDCl_3$) 3630, 2931, 1719, 1587, 1507, 1483 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.80 (s, 1H, H-5), 6.44 (s, 1H, H-8), 6.27 (s, 2H, H-2′, H-6′), 5.91 (s, 2H, OCH_2O), 4.93 (d, 1H, *J*=3.4 Hz, H-4), 4.32–4.25 (m, 2H, H-1, H-11), 4.15 (dd, 1H, *J*=11, 7.5 Hz, H-11), 3.70 (s, 6H, OCH_3-3′,5′), 3.60 (dd, 1H, *J*=11.3, 5 Hz, H-13), 3.42 (dd, 1H, *J*=11.3, 7.2 Hz, H-13), 2.59 (m, 1H, H-2), 2.49 (m, 1H, H-3), 1.20 (s, 9H, $(CH_3)_3CCO$), 1.00 (s, 9H, $(CH_3)_3CSi$), 0.88 (s, 9H, $(CH_3)_3CSi$), 0.18 (s, 3H, CH_3Si), 0.12 (s, 6H, $(CH_3)_2Si$), 0.02 (s, 3H, CH_3Si); MS (DCI, NH_3) *m/z* 734 $[M+NH_4]^+$.

Compound **53**. IR ($CDCl_3$) 3629, 2930, 1718, 1603, 1507, 1484 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.84 (s, 1H, H-5), 6.46 (s, 1H, H-8), 6.18 (s, 2H, H-2′, H-6′), 5.92 (s, 2H, OCH_2O), 5.08 (d, 1H, *J*=4 Hz, H-4), 4.23 (d, 1H, *J*=6.1 Hz, H-1), 4.00–3.85 (m, 3H, H-11, H-13), 3.74 (m, 1H, H-13), 3.69 (s, 6H, OCH_3-3′,5′), 2.64 (m, 1H, H-2), 2.29 (m, 1H, H-3), 1.17 (s, 9H, $(CH_3)_3CCO$), 1.00 (s, 9H, $(CH_3)_3CSi$), 0.92 (s, 9H, $(CH_3)_3CSi$), 0.19 (s, 3H, CH_3Si), 0.13 (s, 6H, $(CH_3)_2Si$), 0.05 (s, 3H, CH_3Si); MS (DCI, NH_3) *m/z* 734 $[M+NH_4]^+$.

Compound **54**. IR ($CDCl_3$) 2932, 1722, 1587, 1504, 1483 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.77 (s, 1H, H-5), 6.42 (s, 1H, H-8), 6.15 (s, 2H, H-2′, H-6′), 5.91 (s, 2H, OCH_2O), 4.94 (d, 1H, *J*=3.3 Hz, H-4), 4.34 (dd, 1H, *J*=11.2, 6.6 Hz, H-11), 4.25 (d, 1H, *J*=5.8 Hz, H-1), 4.11 (dd, 1H, *J*=11.2, 7.6 Hz, H-11), 3.94 (dd, 1H, *J*=11.4, 6.3 Hz, H-13), 3.83 (dd, 1H, *J*=11.4, 7.6 Hz, H-13), 3.68 (s, 6H, OCH_3-3′,5′), 2.74 (m, 1H, H-2), 2.42 (m, 1H, H-3), 1.19 (s, 9H, $(CH_3)_3CCO$), 1.16 (s, 9H, $(CH_3)_3CCO$), 0.99 (s, 9H, $(CH_3)_3CSi$), 0.87 (s, 9H, $(CH_3)_3CSi$), 0.17 (s, 3H, CH_3Si), 0.11 (s, 6H, $(CH_3)_2Si$), 0.00 (s, 3H, CH_3Si); MS (DCI, NH_3) *m/z* 818 $[M+NH_4]^+$.

4.1.30. Cyanide 56. To a solution of **52** (4.2 g, 5.86 mmol) in methylene chloride (300 mL) were added, at rt, triethylamine (4.1 mL, 29.3 mmol) and methanesulfonyl chloride (1.14 mL, 14.64 mmol). After 2 h, the reaction was poured into water (250 mL) and acidified with 1 N HCl until pH 2–3. The aqueous layer was extracted twice with methylene chloride (2×100 mL), and the combined organic layers were washed with brine (200 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Sodium cyanide (860 mg, 17.54 mmol) was added to a solution of the crude mesylate **55** (4.65 g) in anhydrous DMF (300 mL) at rt, and the mixture was heated to 85 °C for 24 h. After cooling to rt, the mixture was concentrated under reduced pressure until to obtain a residual volume of 20 mL. Addition of water (100 mL) to this residue was followed by extraction with ethyl acetate (3×50 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 3:1) led to **56** (1.95 g, 54%) as a foam. Mp 83–85 °C; $[\alpha]_D^{20}=-88$ (*c* 1.01, $CHCl_3$); IR ($CDCl_3$) 3540, 2931, 1724, 1519, 1505, 1485 cm^{-1}; ^1H

NMR (300 MHz, $CDCl_3$) δ 6.77 (s, 1H, H-5), 6.44 (s, 1H, H-8), 6.29 (s, 2H, H-2′, H-6′), 5.93 (s, 2H, OCH_2O), 5.46 (s, 1H exch. with D_2O, OH), 4.93 (d, 1H, J=3.2 Hz, H-4), 4.39–4.34 (m, 2H, H-1, H-11), 4.03 (dd, 1H, J=11.2, 8 Hz, H-11), 3.82 (s, 6H, OCH_3-3′,5′), 2.89 (m, 1H, H-2), 2.45 (m, 1H, H-3), 2.38 (dd, 1H, J=16.7, 6 Hz, H-13), 1.87 (dd, 1H, J=16.7, 10.3 Hz, H-13), 1.16 (s, 9H, $(CH_3)_3CCO$), 0.89 (s, 9H, $(CH_3)_3CSi$), 0.22 (s, 3H, CH_3Si), 0.04 (s, 3H, CH_3Si); MS (DCI, NH_3) m/z 629 $[M+NH_4]^+$.

4.1.31. Homolactones 7 and 8 from 56. A 25% aqueous NaOH solution (1.15 mL, 7.2 mL) was added to a solution of nitrile **56** (105 mg, 0.172 mmol) in 95% ethanol (14 mL). The reaction mixture was heated at 85 °C for 7 h. Ater cooling to rt, the mixture was neutralized with 1 N HCl (7.2 mL) until the bright yellow color disappeared. A small amount of 1 N HCl (0.5 mL) was added until pH 3–4. After stirring for 10 min at rt, the mixture was poured into ethyl acetate (30 mL) and water (10 mL). The aqueous layer was extracted twice (2×15 mL), and the combined organic layer was stirred for 15 h. The latter was then washed with brine (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (methylene chloride/MeOH 98:2 then 97:3) led to **7** (36.2 mg, 51%) as a white powder and **8** (8.5 mg, 12%) as a syrup.

Acknowledgements

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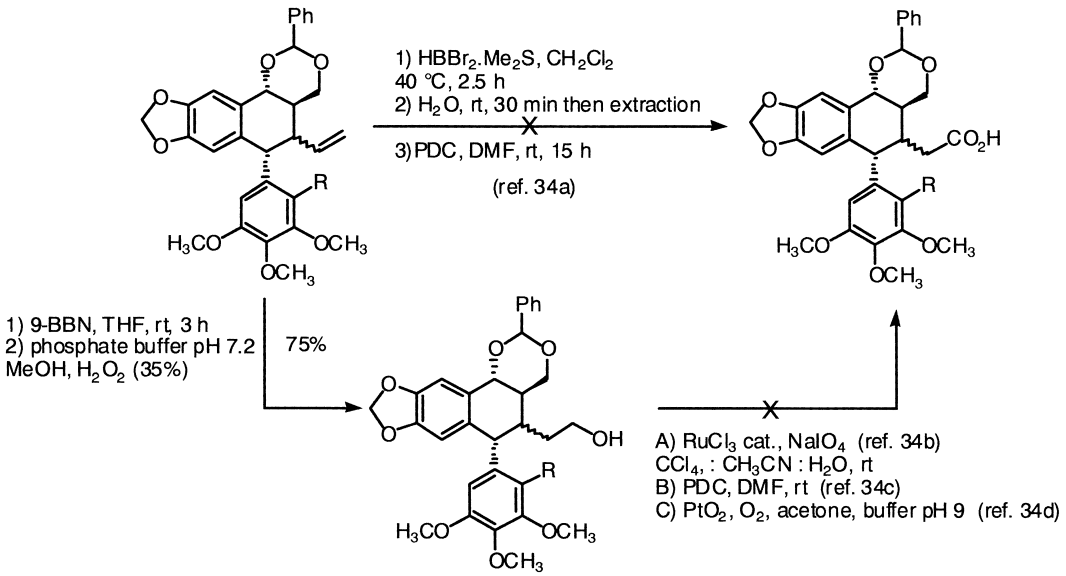

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Further observations on the rhodium (I)-catalysed tandem hydrosilylation-intramolecular aldol reaction

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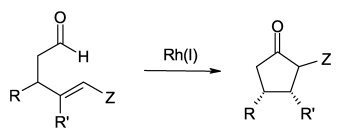
Abstract—The rhodium (I) catalysed tandem hydrosilylation-intramolecular aldol reaction provides a simple strategy for construction of a range of usefully functionalised five-membered rings from readily prepared 6-oxo-2-hexenoates in good yield and with good to excellent stereoselectivity. A series of silanes and rhodium catalysts have been investigated. Stereoselectivity proved to be highly dependant on the catalyst as well as on the substitution pattern of the parent substrate. The extension of this methodology for the synthesis of larger ring sizes has also been evaluated.

1. Introduction

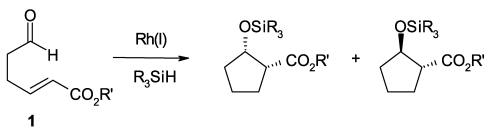
Highly stereoselective cyclisation methods provide a powerful tool for the construction of the carbocyclic skeletons found in both natural and non-natural molecules of biological importance. Moreover, the dictates of modern day organic synthesis also require that the overall process should be highly efficient in terms of atom economy. Within this context, the rhodium catalysed intramolecular hydroacylation reaction of 4-alkenals, first introduced by Sakai,[1] (Scheme 1, R=R′=alkyl, Z=H) provides a very good example of an extremely powerful method for the preparation of functionalised cyclopentanone derivatives,[2–9] especially in view of the *cis* stereoselectivities observed and the elegant studies by Bosnich[10] and Sakai[11] on the development of chiral catalysts for the asymmetric variant.



Scheme 1. General representation of the rhodium (**I**)-catalysed intramolecular hydroacylation of 4-alkenals.

On closer inspection, however, this protocol does suffer from some limitations, which include poorer yields for substrates either with heteroatom substituents or with additional groups located at the alkene terminus (Z), as well as in attempted cyclisations to give larger rings. Furthermore, competitive decarbonylation of the rhodium acyl complex generated after initial oxidative addition to the aldehyde can lead to undesired side reactions, and since the catalyst is then rendered inactive, relatively large amounts (20–50 mol%) have often been required for many examples.

In light of the above constraints, we therefore, sought to develop an alternative general methodology through the incorporation of ester functionality at the alkene terminus of the 4-pentenal unit (Scheme 1, Z=ester). The selection of a 6-oxo-2-hexenoate unit such as **1** then provides the opportunity for a tandem sequence involving transition metal mediated hydrosilylation followed by intramolecular aldol reaction as a route to substituted cycloalkanols (Scheme 2). Such an approach does of course find intermolecular precedent in terms of the sequential reductive aldol reaction which has witnessed spectacular development in recent years.[12] From the outset of our own study, even although it is often falsely assumed that an intramolecular variant of any given reaction will automatically follow on from its intermolecular congener, we were aware that chemoselectivity issues such as competing reduction of the aldehydic carbonyl group remained to be assessed, especially given that stepwise



Scheme 2. General representation of the rhodium (**I**)-catalysed tandem hydrosilylation-intramolecular aldol reaction of 6-oxo-2-hexenoates.

Keywords: Tandem hydrosilylation; Aldol; Rhodium; intramolecular; catalytic.
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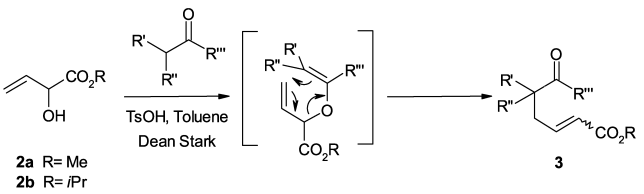
introduction of substrates is not possible in the intramolecular mode.

Within the large manifold of cascade reactions,[13] stereoselective tandem conjugate addition–cyclisation reactions have been extensively studied.[14] In particular, Michael addition followed by intramolecular aldolisation has proven to be a very useful strategy. Such ring closing reactions are believed to proceed via 1,4-addition of the organometallic or heteronucleophilic reagent to the enoate, with subsequent addition of the resultant enolate to the aldehyde.[15] Murphy[16] has recently reported a tandem Michael-intramolecular aldol mediated by secondary amines, thiols and phosphines. Lithium thiolates[14n] and $TiCl_4$–R_4NX combinations[17] have also been used to initiate such cyclisations; however, these heteronucleophiles remain covalently attached in the cyclisations products. There are also several examples in the literature of non-catalysed tandem Michael-intramolecular aldol reactions using stoichiometric amounts of organometallic hydrides such as Stryker's reagent $[(Ph_3P)CuH]_6$[18] and di-*n*-butyliodotin hydride (n-Bu_2SnIH).[19] We now report, in full detail[15] the results of our own study in which inexpensive and more environmentally benign organosilanes were selected for the initial conjugate addition step. An essentially contemporaneous parallel investigation by an American group[20] has also adopted a similar tandem-hydrosilylation intramolecular aldol sequence but chosen to investigate oxo-enone substrates and to use cobalt catalysts.

2. Results and discussion

2.1. Preparation of cyclisation substrates

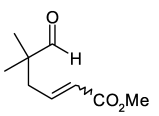
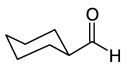
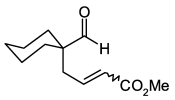
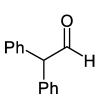
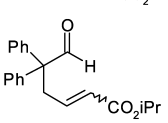
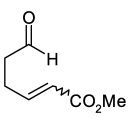
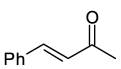
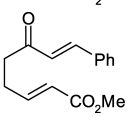
Substituted 6-oxo-2-hexenoate units such as **3** are proving to be especially valuable for a variety of tandem Michael addition-aldol processes and similar variants.[16,20] They are traditionally prepared either by Wittig olefination[21] or by relatively long multistep sequences.[22] For our present study, we elected to develop the simple atom efficient route[23] shown in Scheme 3 which requires acid catalysed condensation of a 2-hydroxy-3-butenoate ester with an aldehyde followed by in situ Claisen rearrangement of the allyl alkenyl ether intermediate (Scheme 3).



Scheme 3. General synthesis of substituted 6-oxo-2-hexenoates.

The required 2-hydroxy-3-butenoates **2a**–**b** were easily accessed from commercially available 2-acetoxy-3-butenenitrile using a literature method[24] involving dissolution in a saturated hydrochloric acid solution of the appropriate alcohol. A mixture of **2** with slightly more than one molar equivalent of the carbonyl compound was then refluxed in toluene for 48 h in the presence of a catalytic amount of *p*-toluenesulfonic acid and using a Dean and Stark trap for azeotropic removal of water. The corresponding 6-oxo-2-hexenoate products, produced as a mixture of geometric isomers, were then isolated by flash chromatography. Thus, as indicated in Table 1, aliphatic and aromatic 5,5-disubstituted 6-oxo-2-hexenoates **4**, **5a**, **5b** and **6** were obtained from the corresponding aldehydes in 49–64% yield in a 2:1 ratio (entries 1, 2 and 3). Synthesis of the parent unsubstituted derivative **7** was first attempted using acetaldehyde. However, this attempt was unsuccessful presumably due to the high volatility of acetaldehyde. However, when acetaldehyde was replaced by its less

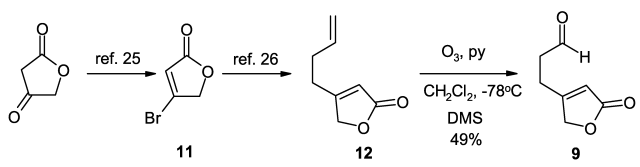
Table 1. Substituted 6-oxo-hexenoate derivatives produced via Scheme 3

Entry	Electrophile	Product		Yield (%)[a]	Ratio *E*/*Z*
1			**4**	53	2:1
2			**5a** (**5b**)	49 (61)[b]	1.5:1
3			**6**	64	2:1
4			**7**	46[c]	2.2:1
5			**8**	58	Only *E*

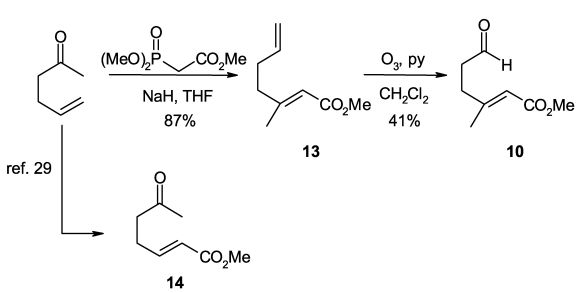
[a] Isolated yields.
[b] Yield of the correspondent isopropyl ester derivative starting from butenoate **2b**.
[c] The reaction was carried out using a Soxhlet extractor in the presence of 4 Å MS for the removal of ethanol.

volatile diethyl acetal congener, reaction proceeds to give **7** in 46% yield in a 2.2:1 ratio (entry 4). 6-Oxo-2,7-octadienoate **8** was also synthesised in 58% yield from benzylideneacetone as a single *E* diastereomer (entry 5). Additional examples and further preparative and stereochemical aspects on this [3,3] sigmatropic route have been discussed in our preliminary study.[23]

Substitution at *C*-3 was also sought and two different cyclisation substrates **9** and **10** were accordingly selected. Thus, 4-bromo-2(5*H*)-furanone **11** was prepared from tetronic acid following the procedure of Jas using oxalyl bromide and a catalylic amount of dimethylformamide in dichloromethane (Scheme 4).[25] Subsequent palladium-catalysed substitution reaction of **11** with a homoallylzinc reagent afforded **12** as described by Negishi.[26] Finally, 3-(5-oxo-2,5-dihydrofuran-3-yl)-propionaldehyde **9** was obtained in 49% yield by selective ozonolysis of the terminal double bond of alkene **12** in the presence of one volume percent of pyridine.[27] Methyl 3-methyl-6-oxo-2-hexenoate **10** was prepared from commercially available 5-hexen-2-one. We note parenthetically that the Horner–Wadsworth–Emmons olefination using trimethylphosphonoacetate and sodium hydride proceeded much more efficiently (87% vs. 43%) when the reaction was conducted in refluxing tetrahydrofuran rather than in 1,2-dimethoxyethane as previously reported for the corresponding ethyl ester.[28] Intermediate **13** was obtained as a 2:1 mixture of *E* and *Z* isomers, which were separated by chromatography (Scheme 5). Selective ozonolysis of **13** followed by reductive work up afforded **10** in 41% yield.



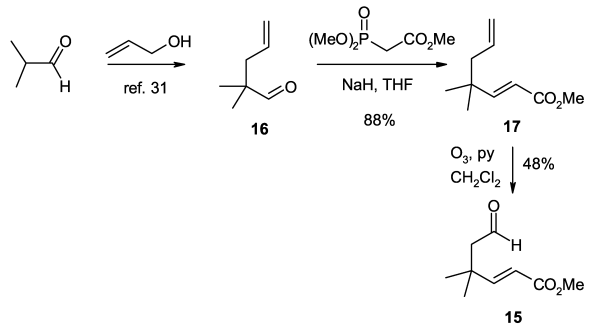
Scheme 4. Synthesis of 3-(5-oxo-2,5-dihydrofuran-3-yl)propionaldehyde.



Scheme 5. Syntheses of methyl (*E*)-3-methyl-6-oxo-2-hexenoate and methyl (*E*)-6-oxo-2-heptenoate from 5-hexen-2-one.

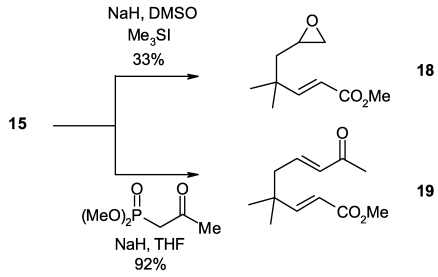
Methyl (*E*)-6-oxo-2-heptenoate **14** was also prepared from 5-hexen-2-one following a literature procedure.[29]

The synthesis of methyl 4,4-dimethyl-6-oxo-2-hexenoate **15** has already been reported by a multistep process which includes several protection and deprotection steps.[30] We have prepared it by an alternative procedure in three steps starting from isobutyraldehyde and allyl alcohol. Thus, 2,2-dimethyl-4-pentanal **16**, which is also commercially available, was synthesised by the method reported by Brannock from allyl alcohol and isobutyraldehyde via Claisen rearrangement of the allyl alkenyl ether intermediate.[31] Subsequent Horner–Wadsworth–Emmons olefination of the aldehyde with trimethylphosphonoacetate in the presence of sodium hydride afforded **17** in 88% yield as a single *E* diastereoisomer. Selective ozonolysis of the terminal alkene in **17** afforded compound **15** in 48% yield (Scheme 6). This method offers the advantage of permitting substituent variation at *C*-4 of the resulting 6-oxo-2-hexenoates of type **15** by a simple choice of the appropriate starting aldehyde.



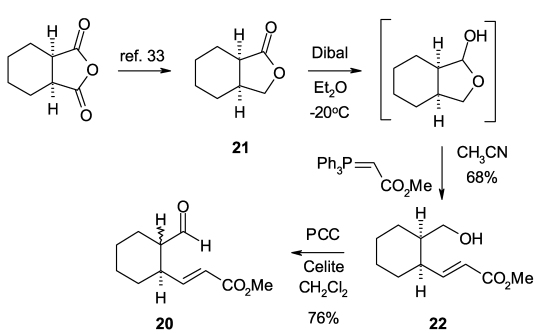
Scheme 6. Synthesis of methyl (*E*)-4,4-dimethyl-6-oxo-2-hexenoate.

Substrates **18** and **19** were also prepared from aldehyde **15** by Corey sulfur ylide epoxidation[32] and Horner–Wadsworth–Emmons olefination, respectively, (Scheme 7).



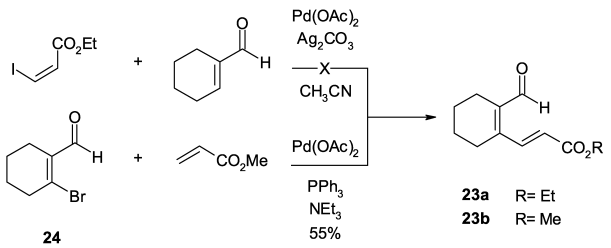
Scheme 7. Syntheses of methyl (*E*)-4,4-dimethyl- 5-oxiranyl-2-pentenoate and methyl (*E*)-4,4-dimethyl-8-oxo-2,6-nonadienoate.

In order to assess the feasibility of generating even more strained bicyclic systems in the tandem cyclisation sequence, substrate **20** was synthesised from commercially available *cis*-cyclohexane-1,2-dioic acid anhydride (Scheme 8). Lactone **21** was obtained in 70% yield by reduction of the corresponding anhydride with sodium borohydride, using the general procedure of Bailey and



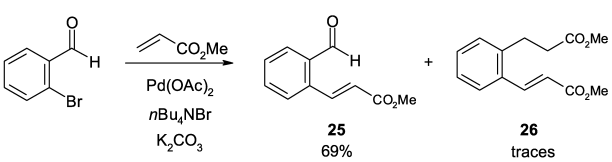
Scheme 8. Synthesis of methyl (*E*)-3-(2-formyl-cyclohexyl)-acrylate.

Johnson.[33] Treatment of lactone **21** with DIBAL in ether at −20 °C resulted in rapid and quantitative reduction to the lactol, which was subsequently reacted with methyl(triphenylphosphoranylidene)acetate in acetonitrile to afford alcohol **22** in an overall 68% yield as the single *E* isomer. Oxidation of alcohol **22** with pyridinium chlorochromate (PCC) gave the desired aldehyde **20** in 76% yield with some epimerization at the α centre of the newly formed aldehyde (*cis*/*trans*, 6:1). The viability of using a completely conjugated system in our cyclisation reaction was tested by selection of substrate **23** which was envisaged via a Heck strategy. In the first instance, 1-cyclohexene-1-carboxaldehyde and ethyl (*Z*)-3-iodo-propenoate, both commercially available, were stirred in acetonitrile at room temperature in the presence of 0.05 equiv. of palladium acetate and 1.5 equiv. of silver carbonate (Scheme 9). Coupling failed to occur and only starting material was recovered after 3 days. The yields and rates of reaction in Heck couplings are known to decrease with increasing size and number of substituents around the double bond in the olefin.[34] Coupling was, therefore, attempted between 2-bromo-1-cyclohexenecarboxaldehyde **24** and a monosubstituted olefin, methyl acrylate, in the presence of triethylamine and a catalytic amount of $Pd[(PPh_3)_3]_2(OAc)_2$ at reflux. In this way, the desired substrate **23b** was obtained in 55% yield as a single *E* diastereoisomer. The required aldehyde **24** was available from cyclohexanone by the bromo analogue of the Vilsmeier reaction according to the procedure of Arnold and Holy.[35]



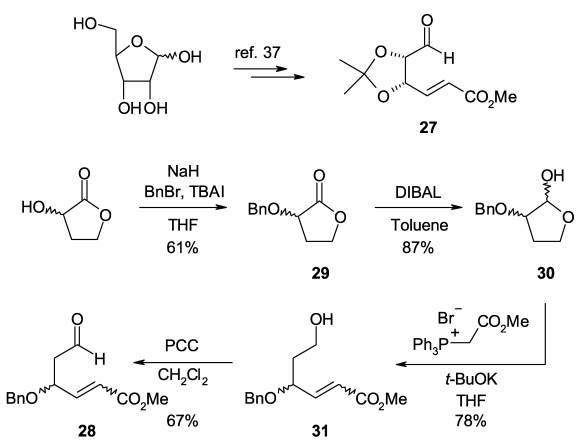
Scheme 9. Synthesis of methyl (*E*)-3-(2-formyl-cyclohex-1-enyl)-acrylate

Benzoannulated substrate **25** was then prepared from *o*-bromobenzaldehyde in order to investigate the compatibility of a 4,5-fused aromatic ring in the cyclisation reaction. Although Rodrigo[36] has observed that formation of the doubly substituted product **26** is favoured over the conventional Heck product **25** when the reaction is run in a concentrated solution in the presence of excess methyl acrylate (Scheme 10), the use of moderate amounts of methyl acrylate and more dilute solutions led to the optimum yield of our desired Heck product **25** which was obtained in 69% yield in pure form after chromatography.



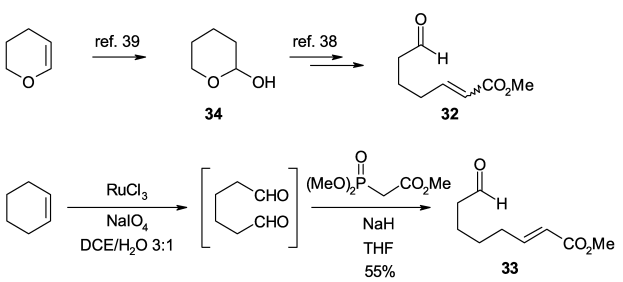
Scheme 10. Synthesis of methyl (*E*)-3-(2′-formylphenyl)-propenoate

Isopropylidene and benzyl ether functionalities were chosen to investigate whether tandem hydrosilylation cyclisation was compatible with heteroatomic substituents. Homochiral pentenal **27** was accessible from D-ribose by a literature procedure (Scheme 11).[37] Substrate **28** was prepared from commercially available racemic α-hydroxy-γ-butyrolactone, which was firstly protected using benzyl bromide in the presence of a catalytic quantity of tetrabutylammonium iodide. The resulting α-benzyloxy-γ-butyrolactone **29** was then reduced to the corresponding lactol **30** with DIBAL, which gave a mixture of *cis* and *trans* diastereoisomers in a 2:1 ratio. The observed *cis* selectivity presumably arises via subsequent equilibration which favours the *cis* lactol. Wittig olefination of lactol **30** with carbomethoxymethyltriphenylphosphonium bromide and potassium *tert*-butoxide gave **31** in 78% yield as a mixture of diastereoisomers. Subsequent oxidation of **31** with PCC afforded substrate **28** in 67% yield as two separable diastereoisomers.



Scheme 11. Methyl (4*S*, 5*S*)-6-oxo-4,5-isopropylidenedioxy-2-hexenoate and methyl 4-benzyloxy-6-oxo-2-hexenoate.

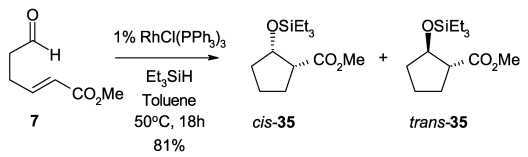
Finally, methyl 7-oxo-2-heptenoate **32** and its higher homologue **33** were prepared in order to explore the feasibility of constructing larger ring sizes. Thus, substrate **32** was prepared by a general route from 1-hydroxypyran **34**,[38] which was obtained by acid hydrolysis of commercially available 3,4-dihydropyran (Scheme 12).[39] Ruthenium trichloride catalysed oxidative cleavage of cyclohexene[40] followed by subsequent Horner–Wadsworth–Emmons olefination of resultant adipaldehyde, provided (*E*)-methyl 8-oxo-2-octenoate **33** in one step in 55% yield, accompanied by the doubly substituted diester (ca. 20%), which was easily separated by chromatography on silica gel.



Scheme 12. Methyl 7-oxo-2-heptenoate and methyl (*E*)-8-oxo-2-octenoate.

2.2. Cyclisation studies

In our preliminary study of the rhodium (I)-catalysed tandem hydrosilylation intramolecular aldol reaction, optimal conditions for the reaction of the model substrate methyl (*E*)-6-oxo-2-hexenoate (*E*)-**7** with Wilkinson's catalyst using triethylsilane as the hydride donor were first developed and these are summarized in Scheme 13 and Table 2 (entry 1). The significant observation was also made that the stereochemical outcome of the reaction was not altered when the (*Z*) geometrical isomer of **7** was employed as substrate in an otherwise identical reaction, thereby indicating that the initial alkene geometry does not play a crucial role in influencing the possible transition states adopted for the subsequent intramolecular aldol reaction. Since *E*/*Z* mixtures of α,β-unsaturated esters can, therefore, be used, this aspect is also clearly of preparative value.



Scheme 13. Rhodium (I)-catalysed tandem hydrosilylation-intramolecular aldol reaction of methyl (*E*)-6-oxo-2-hexenoate.

Table 2. Silane and catalyst screen

Entry	Silane[a]	Catalyst[b]	Ligand[c]	Yield[d] (%)	*c*-**35**/*t*-**35**
1	Et_3SiH	$RhCl(PPh_3)_3$	—	81	2.0:1.0
2	Me_2PhSiH	$RhCl(PPh_3)_3$	—	62	2.4:1.0
3	$MePh_2SiH$	$RhCl(PPh_3)_3$	—	49	2.8:1.0
4	Ph_3SiH	$RhCl(PPh_3)_3$	—	42	1.5:1.0
5	Et_3SiH	$[RhCl(C_8H_{14})_2]_2$[e]	PCy_3	79	2.5:1.0
6	Et_3SiH	$[RhCl(C_8H_{14})_2]_2$[e]	DIPHOS[f]	78	3.3:1.0
7	Et_3SiH	$[RhCl(C_8H_{14})_2]_2$[e]	$pTol_3P$	27	1.0:2.0
8	Et_3SiH	$[RhCl(C_8H_{14})_2]_2$[e]	$pTol_3P$	53	2.0:1.0
9	Et_3SiH	$[RhCl(C_8H_{14})_2]_2$[e]	pAn_3P[g]	61	1.0:1.6
10	Et_3SiH	$[RhCl(C_8H_{14})_2]_2$[e]	pAn_3P[g]	51	2.0:1.0
11	Et_3SiH	$RhH(PPh_3)_4$[h]	—	81	1.0:11.0

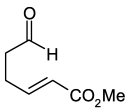
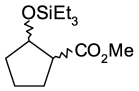
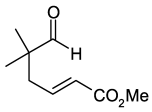
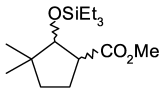
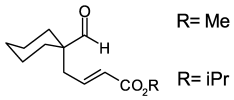
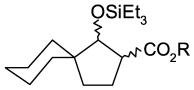
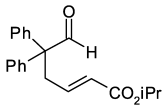
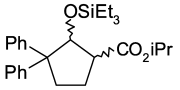
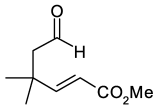
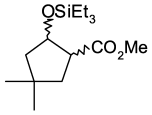
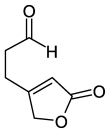
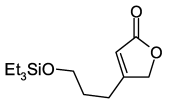
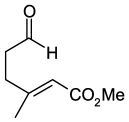
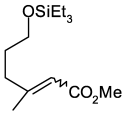
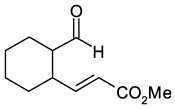
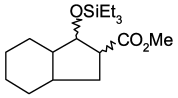
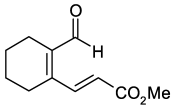
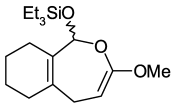
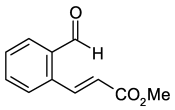
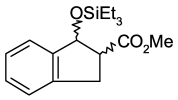
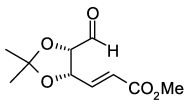
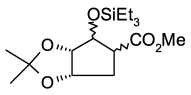
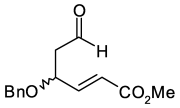
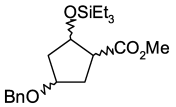
[a] 2.1 equiv. of silane used.
[b] 1 mol% catalyst unless otherwise stated.
[c] 4 equiv. ligand w.r.t. catalyst unless otherwise stated.
[d] Yield of isolated products.
[e] 2.5 mol% catalyst.
[f] 2 equiv. ligand w.r.t. catalyst, DIPHOS (1,2-bis(diphenylphosphino)ethane).
[g] An, anisole.
[h] Reaction complete after 6 h.

At this stage, examination of the results from a catalyst and silane screen (Table 2) revealed some useful trends. Thus, in reactions employing Wilkinson's catalyst, the use of silanes of increasing steric bulk (entries 1–4) led to reduced yields of the cyclopentanol **35**, even although the *cis* selectivity was maintained. Variation of the ancillary phosphine was also studied using triethylsilane and chlorobis(cyclooctene) rhodium (I) dimer (entries 5–10), and found to play a significant role, with the best combination of yield and *cis* stereoselectivity achieved through selection of the bidentate DIPHOS ligand (entry 6). The most intriguing observation of all, however, was that a complete reversal of stereoselectivity in favour of *trans*-**35** was noted when hydridotetrakis(triphenylphosphine) rhodium (I) was employed as the catalyst (entry 11). Although the observed preference in our preliminary study[15a] was relatively modest (*cis*/*trans*, 1:2) further work using carefully prepared rhodium catalyst now reproducibly favours the *trans* product in high yield and with excellent selectivity (*cis*/*trans*, 1.0:11.0).

We then elected to examine the synthetic utility of the reaction using both Wilkinson's catalyst[41] and hydridotetrakis(triphenylphosphine) rhodium (I).[42] The variety of variously functionalised substituted 6-oxo-2-hexenoate derivatives previously described were accordingly submitted to our optimised cyclisation conditions (2.1 M equiv. of triethylsilane and 1 mol% of rhodium catalyst in toluene at 50 °C) in order to probe such issues as chemoselectivity and the influence of the substitution pattern on the tandem sequence. The results are shown in Table 3.

Thus, comparison of entries 2–5 reveals that whilst geminal substitution at *C*-5 (entries 2–4) leads to a reduction in yield relative to the unsubstituted parent (entry 1) this is not necessarily the case for the *C*-4 *gem* dimethyl group (entry 5). Although all four cases might be anticipated to benefit from the Thorpe–Ingold effect,[43] it would, therefore, appear that the intramolecular aldol step is more sensitive to the presence of a neighbouring quaternary carbon atom than is the initial hydrosilylation step. Entry 3 also demonstrates that no significant difference in yield was observed when the methyl ester **5a** was replaced by its *iso*-propyl analogue in **5b**. Contrastingly, our examination of substrates possessing a trisubstituted α,β-unsaturated lactone or ester (entries 6 and 7) reveals that the incorporation of additional alkyl substitution at this site completely blocks the conjugate addition step and simple hydrosilylation of aldehydic functionality then becomes the dominant process. Comparison of entries 8, 9 and 10 reveals that the success of the intramolecular aldol addition step can be subject to very subtle conformational and stereoelectronic restrictions. Thus, whilst entries 8 and 10 provide a very encouraging basis for construction of the linearly fused bicyclo [4,3,0] system in both the hydrindane **42** (entry 8) and indane skeletons **44** (entry 10), the isolation of the hexahydrobenzo[*c*]oxepin **43** from the fully conjugated precursor **23b** was unexpected. In this latter instance, cyclisation of the ester enolate via oxygen to give the seven membered ring is clearly favoured, and formation of the silyl ether functionality in the product must be fast and hence preclude the reverse reaction. Finally, in view of the ever increasing importance of constructing carbocycles from the chiral pool of carbohydrates,[44–48] it was also of interest to examine substrates containing ancillary isopropylidene (entry 11) and benzyl ether (entry 12) functionality. The functional group tolerance exhibited in these latter two cyclisations provides an indication that this approach may be of promise for cyclopentanoid construction from carbohydrates. In terms of stereoselectivity, comparison of the two catalysts A and B reinforces the observation made in the parent system (entry 1) that the outcome can be significantly influenced by this choice. Thus, whilst Wilkinson's catalyst consistently exhibits a modest *cis* preference for formation of the β-triethylsiloxy ester unit, selection of hydridotetrakis(triphenylphosphine) rhodium (I) generally favours the *trans* congener. However, the diastereoisomeric ratios with the latter catalyst are evidently much more strongly

Table 3. Rhodium (I)-catalysed tandem cyclisation of substituted 6-oxo-2-hexenoate derivatives

Entry	Substrate		Product		Catalyst[a]	Yield (%)[b]	*cis*/*trans*[c]
1		**7**		**35**	A	81	3.0:1.0
					B	81	1.0:11.0
2		**4**		**36**	A	56	1.0:1.0
					B	62	6.4:1.0
3	 R= Me R= iPr	**5a**		**37a**	A	54	2.0:1.0
		5b		**37b**	B	59	1.0:2.0
4		**6**		**38**	B	68	1.0:2.5
5		**15**		**39**	A	93	2.2:1.0
					B	61	1.0:11.0
6		**9**		**40**	A	43	—
7		**10**		**41**	A	35	—
					B	39	—
8		**20**		**42**	B	81[d]	—
9		**23b**		**43**	B	88	—
10		**25**		**44**	A	61[e]	1.5:1.0
					B	69[e]	1.0:20.0
11		**27**		**45**	A	65	2.0:5.4:2.0:1.0[f]
					B	81	5.4:4.0:2.0:1.0[f]
12		**28**		**46**	A	81	1.7:1.5:1.0:1.0[g]
					B	72	1.2:1.0:1.2:1.7[g]

[a] A, $RhCl(PPh_3)_3$; B, $RhH(PPh_3)_4$.
[b] Isolated yields after chromatography on silica gel.
[c] Diastereomeric ratio in the crude material determined by ^1H NMR.
[d] Isolated as a complex mixture of diastereoisomers.
[e] Using 3 mol% of catalyst.
[f] See Figure 2 for assignment of the structures, *a*/*b*/*c*/*d*.
[g] Relative stereochemistry: OBn/$OSiEt_3$–$OSiEt_3$/CO_2Me; *trans*–*trans*/*cis*–*cis*/*cis*–*trans*; *trans*–*cis*.

influenced by the exact nature of the substrate substitution pattern and can, at times, be excellent (entries 1, 5 and 10).

In all cases, the structure of the major diastereoisomer was assigned on the basis of the values of coupling constants measured in ^{1}H NMR. In general, coupling constant $J(H^1-H^2)$=3.5–6.5 Hz indicates *cis* relative stereochemistry, whereas $J(H^1-H^2)$=5.5–9.5 Hz accounts for the *trans* isomer. This assignment could be confirmed by X-ray crystallographic analysis of compound **38**, since the minor *cis* diastereoisomer crystallised out of the mixture of isomers giving suitable crystals (Fig. 1).

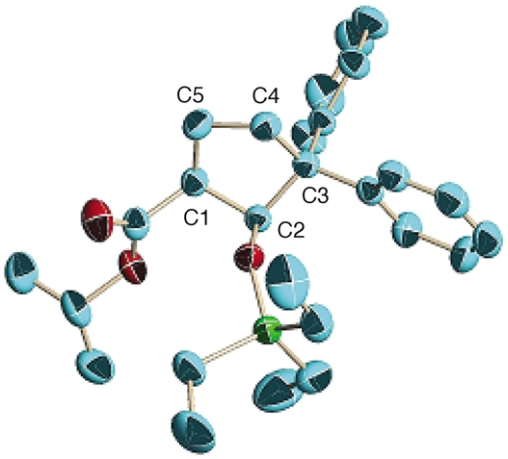


Figure 1. Crystal structure of compound **38**.

When more than two stereogenic centres are present, proton assignment and subsequent determination of all possible diastereoisomers by experimental means was extremely difficult. To our delight, however, careful column chromatography allowed the separation of three of the four possible isomers of substrate **45** and their structure and relative predominance (Table 3, entry 11) was determined by ^{1}H NMR (Fig. 2).

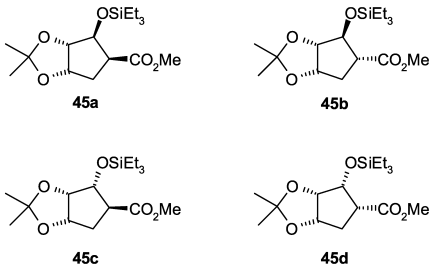


Figure 2. Structure of the four diastereoisomers of **45**.

A coupling constant $J(H_2-H_3)$=0.0–0.7 Hz was observed for both isomers **45a** and **45b**, indicating a dihedral angle close to 90 °C, which implies the equatorial configuration of H_2. The configuration of H_1 was assigned on the basis of NOE experiments (Fig. 3). A strong NOE effect between H_1 and H_{5eq} in **45a** indicates that H_1 occupies an axial position, whereas in **45b** the NOE effect was observed between H_1 and H_{5ax}, indicating that, in this case, it occupies an equatorial position.

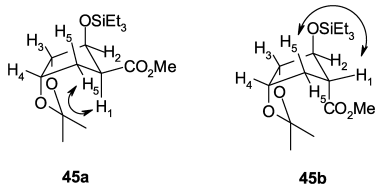


Figure 3. NOE mesurements of **45**.

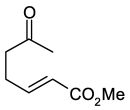
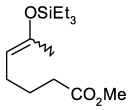
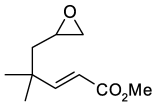
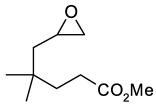
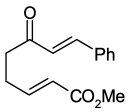
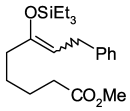
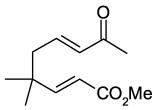
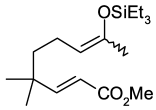
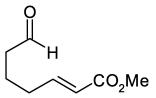
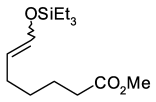
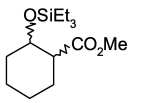
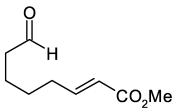
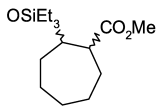
The structure of isomer **45c** was unequivocally assigned on the basis of a typical coupling constant $J(H_1-H_2)$=12.4 Hz for diaxial configuration. The minor isomer **45d** was not isolated but its structure was tentatively deduced as the all-*cis* isomer.

At this stage, in order to extend the scope of the reaction, cyclisation was also carried out on several substrates where the aldehyde functionality was replaced by alternative electrophilic acceptor groups. The construction of six- and seven-membered rings was also attempted. The results are shown in Table 4.

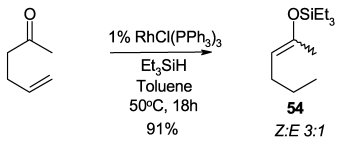
In the event, aldehyde functionality proved to be crucial in order to achieve cyclisation. Thus, as shown in entries 1 and 2, replacement of the aldehyde either by a methyl ketone or by an epoxide did not lead to the formation of cyclic products, even although the reduction of the acrylate unit by the silane in both cases implies formation of a hydrometallated ester enolate intermediate. In the case of the methyl ketone **14** (entry 1), the regiospecific and highly stereoselective formation of the silyl enol ether product was not anticipated but certainly of interest, especially since the control of regioselectivity in the case of unsymmetrical ketones[49] is always useful in organic synthesis. In order to understand this transformation commercially available 5-hexen-2-one was also subjected to the standard cyclisation conditions in the presence of Wilkinson's catalyst. As shown in Scheme 14, regiospecific silyl enol ether formation with concomitant double bond reduction occurred once again in excellent yield and with moderate stereoselectivity, thereby establishing that the ester group is not essential for this reaction to occur. A speculative intermediate is shown in Figure 4 and implies that substrate coordination around a silyl hydridorhodium intermediate may well direct the regiospecificity of the sequence and also produce molecular hydrogen for subsequent reduction of the double bond. At this stage, however, the reasons for the totally divergent behaviour of the aldehydic substrate **7** and its ketonic congener **14** still require further investigation.

The two enone substrates **8** and **19** shown in entries 3 and 4 were initially selected with the intention of probing a (non-rhodium catalysed) tandem hydrometallation–Michael addition sequence in which, as demonstrated by Evans[12a] for hydroboration, the α,β-unsaturated ketone unit should be the first point of attack. In the event, however, only acyclic products derived from 1,4-addition of the organosilane to the enones were isolated in the rhodium catalysed reactions and no evidence for a subsequent tandem Michael reaction was adduced. Interestingly, the use of Wilkinson's catalyst (entry 3) led to reduction of both the enone and the enoate whereas in the presence of hydridotetrakis(triphenylphosphine) rhodium (I) (entry 4) reduction occurred

Table 4. Rhodium (I)-catalysed tandem cyclisation of alternative acceptors and construction of larger ring sizes

Entry	Substrate		Product		Catalyst[a]	Yield (%)[b]	*cis*/*trans*[c]
1		**14**		**47**	A	83	5.0:1.0[d]
					B	61	5.0:1.0[d]
2		**18**		**48**	A	68	—
					B	60	
3		**8**		**49**	A	74	—
4		**19**		**50**	B	91	—
5		**32**		**51**	A	66	1.0:4.6
				**52**	B	65	1.0:3.0
6		**33**		**53**	B	68	2.5:1.0

[a] A, $RhCl(PPh_3)_3$; B, $RhH(PPh_3)_4$.
[b] Isolated yields after chromatography on silica gel.
[c] Diastereomeric ratio in the crude material determined by ^1H NMR.
[d] *Z*/*E* ratio.



Scheme 14. Formation of silyl enol ether **54** from 5-hexen-2-one.

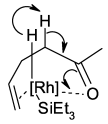


Figure 4. Speculative intermediate for the formation of **54** from 5-hexen-2-one.

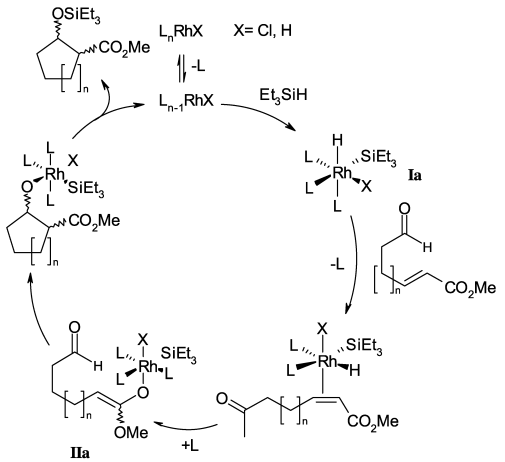
exclusively at the enone moiety. The contrasting behaviour of the two rhodium catalysts and the necessity for rigorous purification prior to their use was further highlighted in the case of 7-oxo-2-heptenoate **32** (entry 5). In our preliminary study,[15a] only a low yield of cyclised product was described using Wilkinson's catalyst. The results obtained under more stringent conditions reveal that, as in entry 1, the major product using Wilkinson's catalyst is the analogous reduced silyl enol ether **51**. To our delight, however, selection of hydridotetrakis-(triphenylphosphine) rhodium (I) affords the desired 2-carbomethoxycyclohexanol derivative **52** in 65% with *trans* selectivity. In similar fashion, octenoate **33** furnished the seven-membered ring analogue **53** in comparable yield (68%) but with a reversal in terms of stereoselectivity relative to the six-membered ring congener (entry 6). Significantly, and in contrast to the hydroacylation protocol, the applicability of this approach for the preparation of substituted five-, six- and seven-membered rings is, therefore, possible.

2.3. Mechanistic considerations and stereochemistry

From a mechanistic standpoint, it was of interest to determine whether the transformation described was indeed a consequence of intermolecular hydrosilylation followed by an intramolecular aldol reaction, and not in fact intramolecular hydroacylation followed by hydrosilylation. To this end, reduction of the ester, methyl-2-oxocyclopentane carboxylate, was attempted using an excess of triethylsilane in the presence of 1 mol% of Wilkinson's catalyst. Under identical conditions to those that yielded 81% of the products *c*-**35** and *t*-**35** from methyl (*E*)-6-oxo-2-hexenoate **7**, only traces of the β-triethylsiloxy ester were formed. We have also demonstrated that the *cis*-substituted cyclopentanol *c*-**35** was not interconverted to the *trans*-isomer *t*-**35** when resubmitted to the reaction conditions, neither in the presence of Wilkinson's catalyst nor in the presence of $RhH(PPh_3)_4$.

As in the intermolecular variant of this reaction using enones and aldehydes,[50] the intermediacy of an oxygen bound rhodium ester enolate of the type suggested by Heathcock[51] seems most likely. The influence of the ancillary phosphine ligands, and the replacement of the chlorine atom by a hydride ligand on the stereochemical outcome of our reactions both provide strong support for this possibility. A possible pathway for the catalytic aldol cycloreduction is depicted in Scheme 15. Thus, oxidative addition of the silane to the rhodium (I) catalyst provides the hydridosilyl rhodium (III) intermediate **Ia**. 1,4 hydride transfer of the hydridosilyl rhodium (III) species to the α,β-unsaturated ester then generates a rhodium ester enolate **IIa**. Intramolecular aldol reaction followed by reductive elimination liberates the carbocyclic silyl ether product with concomitant regeneration of the active catalyst. It is interesting that the rhodium complex may catalyse both, the 1,4-addition and the aldol reaction, in one catalytic cycle. The chemoselectivity for both steps is very high, the intermediates **Ia** and **IIa** reacting with the α,β-unsaturated ester and the aldehyde, respectively, with perfect selectivity.

The stereochemical outcome of this reaction can be formally rationalised in terms of the preferential formation of one stereoisomer of the rhodium ester enolate **55** (Scheme 16). Thus, (*Z*)-enolate **56** undergoes the intramolecular aldol reaction via a chelated transition state and provides the *cis*-carbocyclic product **58a** in which one of the substituents occupies an axial position. On the other hand, (*E*)-enolate **57** cyclises with an all-equatorial orientation leading to the *trans*-substituted product **58b**.



Scheme 15. Mechanism of rhodium (I)-catalysed tandem hydrosilylation-intramolecular aldol reaction.

Although in the first instance it could be argued that the two rhodium complexes used in this study might well have converged to a common catalytic intermediate through oxidative addition of the silane to Wilkinson's catalyst and subsequent reductive elimination of chlorotriethylsilane, the experimental observations clearly do not substantiate this hypothesis. Consequently, the presence or absence of the rhodium chlorine bond will clearly influence the outcome of the reaction both in terms of the polarity of the rhodium hydride bond and the stereochemical outcome in the initial hydrometallation step as well as altering the Lewis acidic nature of the chelated rhodium intermediate postulated for the intramolecular aldol step.

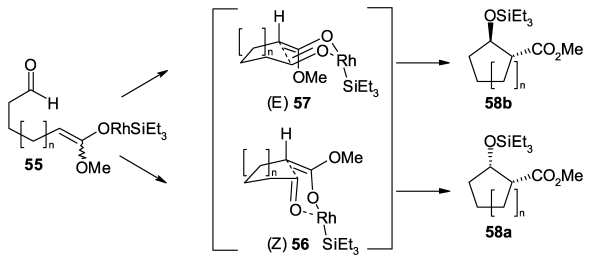
3. Conclusion

In summary, we have developed a highly stereoselective cyclisation sequence via a rhodium (I)-catalysed tandem hydrosilylation-intramolecular aldol reaction that can be used to prepare a range of usefully functionalised five-, six- and seven-membered rings in good yields under very mild conditions. Moreover, in many instances the required precursors can be easily prepared in a highly atom efficient way using the [3,3] sigmatropic rearrangement sequence. The scope and limitations of this novel reaction have been established. A range of substituents in the substrates is tolerated, however, aldehyde functionality proved to be crucial. The stereochemical outcome is highly dependant on the catalyst precursor, $RhH(PPh_3)_4$ is an efficient precatalyst for tandem hydrosilylation-aldol reaction and gave the best results in terms of selectivity. Further studies into the mechanism and stereochemistry of the tandem cyclisation and its applications in synthesis are ongoing.

4. Experimental

4.1. General

All cyclisations and air and/or moisture sensitive reactions were carried out in oven-dried glassware under a nitrogen atmosphere using standard Schlenk techniques. Unless otherwise noted, chemicals were commercially available and used without further purification. Solvents were distilled before use and degassed immediately prior to use. Toluene was distilled from sodium. Tetrahydrofuran and diethyl ether were distilled from sodium-benzophenone ketyl, methylene chloride and acetonitrile from calcium hydride and ethanol and methanol were used as supplied from Aldrich. $RhCl(PPh_3)_3$ was prepared according to



Scheme 16. Stereochemistry of rhodium (I)-catalysed tandem hydrosilylation-intramolecular aldol reaction.

Wilkinson's procedure[41] and $RhH(PPh_3)_4$ to Levison's procedure.[42]

Nuclear magnetic resonance spectra were recorded using a Bruker AMX-300 or a Bruker AMX-400 or a Bruker Avance 500. Chemical shifts (δ) are quoted in parts per million (ppm) relative to tetramethylsilane. The ^{1}H NMR spectra are reported relative to residual chloroform at 7.26 ppm. Coupling constants are reported in Hertz. ^{13}C NMR spectra were fully decoupled and are referenced to the middle peak of chloroform at 77.0 ppm. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and a combination of these. Melting points were determined using a Reichert hot stage or Electrothermal 9100 apparatus and are uncorrected. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter (using the sodium D line; 589 nm) and $[\alpha]_D^T$ are given in units of 10^{-1} deg dm^2 g^{-1}. IR spectra were recorded on a Perkin–Elmer 1605 FT-IR spectrometer as thin films on NaCl or as KBr discs and are reported in cm^{-1}. Mass spectra were recorded on a Micromass 70-SE spectrometer using a cesium ion gun for FAB. X-ray crystallography was performed using a Bruker Smart Apex, CDD diffractometer. Elemental analyses and accurate mass measurements were performed at Christopher Ingold Laboratories, University College London.

Column chromatography was performed using BDH silica gel (40–60 μm). Analytical thin layer chromatography was performed on pre-coated aluminium-backed plates (Merck Keisekgel 60 F_{254}) and visualised by 254 nm UV or by staining with basic potassium permanganate solution followed by heat.

4.2. General procedure A for the synthesis of cyclisation substrates via Claisen rearrangement

A mixture of methyl 2-hydroxy-3-butenoate **2a** (2.0 g, 17.2 mmol), isobutyraldehyde (1.86 g, 25.8 mmol) and a small amount of *p*-toluenesulfonic acid (10 mg) in 10 mL of toluene, was heated under reflux for 48 h with provision of a Dean and Stark apparatus for the removal of water. After evaporation of the solvent under reduced pressure, the crude oil was purified by flash column chromatography employing P.E. 30–40 °C/EtOAc (80:20) as eluant to afford the desired product **4** (1.54 g, 53%) as two single diastereomers in a *E*/*Z* 2:1 ratio as a colorless oil.

4.2.1. Methyl (*E*)-5,5-dimethyl-6-oxo-2-hexenoate ((*E*)-4). R_f 0.20 (P.E. 30–40 °C/EtOAc, 80:20); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (s, 6H, C(CH_3)$_2$), 2.41 (dd, J=7.8, 1.4 Hz, 2H, CH_2), 3.79 (s, 3H, OCH_3), 5.93 (dt, J=15.6, 1.4 Hz, 1H, =CHCO$_2$CH$_3$), 6.93 (dt, J=15.6, 7.8 Hz, 1H, CH=CHCO$_2$CH$_3$), 9.60 (s, 1H, CHO); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.8 (C(*C*H$_3$)$_2$), 39.7 (*C*H$_2$), 46.2 (*C*(CH$_3$)$_2$), 51.9 (O*C*H$_3$), 124.6 (=*C*HCO$_2$CH$_3$), 144.2 (*C*H=CHCO$_2$CH$_3$), 166.8 (*C*O$_2$CH$_3$), 205.0 (*C*HO); FTIR (film) ν 1803, 1730, 1645 cm^{-1}; LRMS (EI$^+$) *m*/*z* 171 (M$^+$+1, 50), 139 (100), 109 (79), 81 (73), 41 (33); HRMS (EI$^+$) calcd for $C_9H_{14}O_3$ (M$^+$) 170.09429, found 170.09400.

4.2.2. Methyl (*Z*)-5,5-dimethyl-6-oxo-2-hexenoate ((*Z*)-4). R_f 0.25 (P.E. 30–40 °C/EtOAc, 80:20); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (s, 6H, C(CH_3)$_2$), 2.83 (dd, J=7.8, 1.6 Hz, 2H, CH_2), 3.65 (s, 3H, OCH_3), 5.84 (dt, J=11.6, 1.6 Hz, 1H, =CHCO$_2$CH$_3$), 6.11 (dt, J=11.6, 7.8 Hz, 1H, CH=CHCO$_2$CH$_3$), 9.50 (s, 1H, CHO); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.7 (C(*C*H$_3$)$_2$), 35.9 (*C*H$_2$), 46.6 (*C*(CH$_3$)$_2$), 51.5 (O*C*H$_3$), 122.2 (=*C*HCO$_2$CH$_3$), 145.0 (*C*H=CHCO$_2$CH$_3$), 166.9 (*C*O$_2$CH$_3$), 205.5 (*C*HO); FTIR (film) ν 1797, 1724, 1656 cm^{-1}; LRMS (EI$^+$) *m*/*z* 170 (M, 8), 141 (58), 109 (87), 81 (70), 41 (100); HRMS (EI$^+$) calcd for $C_9H_{14}O_3$ (M$^+$) 170.09429, found 170.09417.

4.2.3. Methyl (*E*)-4-(1-formyl-cyclohexyl)-2-butenoate ((*E*)-5a). According to the general procedure A, reaction of methyl 2-hydroxy-3-butenoate **2a** (3.0 g, 25.8 mmol) and cyclohexanecarboxaldehyde (2.90 g, 25.8 mmol) gave, after purification by column chromatography eluting with P.E. 30–40 °C/EtOAc (80:20), the aldehyde **5a** (2.66 g, 49%) as two single diastereomers in a *E*/*Z* 1.5:1 ratio as a colorless oil. R_f 0.28 (P.E. 30–40 °C/EtOAc, 80:20); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24–1.50 (m, 4H, CH_2), 1.62–1.70 (m, 4H, CH_2), 1.96–2.00 (m, 2H, CH_2), 2.44 (dd, J=8.0, 1.3 Hz, 2H, CH_2CH=), 3.84 (s, 3H, OCH_3), 5.96 (dt, J=15.6, 1.3 Hz, 1H, =CHCO$_2$CH$_3$), 6.93 (dt, J=15.6, 8.0 Hz, 1H, CH=CHCO$_2$CH$_3$), 9.66 (s, 1H, CHO); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.6 (*C*H$_2$), 25.8 (*C*H$_2$), 31.4 (*C*H$_2$), 38.8 (*C*H$_2$), 50.1 (*C*Cy), 51.9 (O*C*H$_3$), 124.6 (=*C*HCO$_2$CH$_3$), 143.7 (*C*H=CHCO$_2$CH$_3$), 166.7 (*C*O$_2$CH$_3$), 206.1 (*C*HO); FTIR (film) ν 1799, 1732, 1656 cm^{-1}; LRMS (APCI$^+$) *m*/*z* 211 (M$^+$+H, 44), 179 (100), 149 (39); HRMS (CI$^+$) calcd for $C_{12}H_{19}O_3$ (M$^+$+H) 211.13341, found 211.13323.

4.2.4. *i*-Propyl (*E*)-4-(1-formyl-cyclohexyl)-2-butenoate ((*E*)-5b). As for general procedure A. Reaction of *i*-propyl 2-hydroxy-3-butenoate **2b** (3.0 g, 20.8 mmol) and cyclohexanecarboxaldehyde (2.33 g, 20.8 mmol) gave, after purification by column chromatography eluting with P.E. 30–40 °C/EtOAc (80:20), the aldehyde **5b** (3.02 g, 61%) as two single diastereomers in a *E*/*Z* 1.5:1 ratio as a colorless oil. R_f 0.58 (P.E. 30–40 °C/EtOAc, 80:20); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (d, J=6.3 Hz, 6H, OCH(CH_3)$_2$), 1.19–1.32 (m, 4H, CH_2), 1.39–1.57 (m, 4H, CH_2), 1.78–1.90 (m, 2H, CH_2), 2.24 (dd, J=7.8, 1.2 Hz, 2H, CH_2), 4.97 (m, 1H, OCH(CH$_3$)$_2$); 5.73 (dt, J=15.5, 1.2 Hz, 1H, =CHCO$_2$*i*Pr), 6.70 (dt, J=15.5, 7.8 Hz, 1H, CH=CHCO$_2$*i*Pr), 9.41 (s, 1H, CHO); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.2 (OCH(*C*H$_3$)$_2$), 22.6 (*C*H$_2$), 25.8 (*C*H$_2$), 31.2 (*C*H$_2$), 38.9 (*C*H$_2$CH=), 50.1 (*C*Cy), 68.1 (O*C*H(CH$_3$)$_2$), 125.6 (=*C*HCO$_2$*i*Pr), 143.0 (*C*H=CHCO$_2$-*i*Pr), 165.8 (*C*O$_2$*i*Pr), 206.2 (*C*HO); FTIR (film) ν 2934, 2856, 1798, 1719, 1655, 1452, 1273, 1200 cm^{-1}; LRMS (CI$^+$) *m*/*z* 239 (M$^+$+H, 58), 209 (83), 167 (100); HRMS (CI$^+$) calcd for $C_{14}H_{23}O_3$ (M$^+$+H) 239.16471, found 239.16435.

4.2.5. *i*-Propyl (*E*)-5,5-diphenyl-6-oxo-2-hexenoate ((*E*)-6). According to the general procedure A, reaction of *i*-propyl 2-hydroxy-3-butenoate **2b** (1.5 g, 10.4 mmol) and 2,2-diphenylacetaldehyde (2.04 g, 10.4 mmol) gave, after purification by column chromatography eluting with P.E. 30–40 °C/EtOAc (90:10), aldehyde **6** (2.15 g, 64%) as two isomers in a *E*/*Z* 2:1 ratio as a yellow oil. R_f 0.53 (P.E. 30–40 °C/EtOAc, 90:10); ^{1}H NMR (300 MHz, $CDCl_3$) δ

1.11 (d, J=6.3 Hz, 6H, CH(CH_3)$_2$), 3.11 (dd, J=7.4, 1.1 Hz, 2H, CH_2), 4.88 (m, 1H, CH(CH_3)$_2$), 5.62 (dt, J=15.6, 1.1 Hz, 1H, =$CH$$CO_2i$Pr), 6.62 (dt, J=15.6, 7.4 Hz, 1H, CH=CHCO$_2i$Pr), 7.08–7.33 (m, 10H, Ph), 9.74 (s, 1H, CHO); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.2 (CH(CH_3)$_2$), 37.4 (CH_2), 63.9 (CPh_2), 67.8 (CH(CH_3)$_2$), 125.4 (=CHCO$_2i$Pr), 128.1 (Ph), 129.3 (Ph), 139.3 (Ph), 144.1 (CH=CHCO$_2i$Pr), 165.9 (CO_2iPr), 197.9 (CHO); FTIR (film) ν 2982, 2936, 1796, 1720, 1656, 1277, 908, 735 cm^{-1}; LRMS (FAB$^+$) m/z 323 (M$^+$+H, 23), 307 (12), 263 (16), 245 (5), 167 (17), 154 (100); HRMS (FAB$^+$) calcd for $C_{21}H_{23}O_3$ (M$^+$+H) 323.16471, found 323.16428.

4.2.6. Methyl (*E*)-6-oxo-2-hexenoate ((*E*)-7). According to the general procedure A, methyl 2-hydroxy-3-butenoate **2a** (2.0 g, 17.2 mmol) and acetaldehyde diethyl acetal (3.05 g, 25.8 mmol) were heated under reflux using a Soxhlet extractor containing freshly conditioned 4 Å molecular sieves for 4 days. The sieves were replaced five times with a freshly conditioned batch. Purification by column chromatography eluting with P.E. 30–40 °C/EtOAc (60:40) gave the aldehyde **7**[52] (1.13 g, 46%) as two single diastereomers in a *E*/*Z* 2.2:1 ratio as a colorless oil. R_f 0.50 (P.E. 30–40 °C/EtOAc, 60:40); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.73–2.78 (m, 2H, CH_2CH=), 2.85 (t, J=7.3 Hz, 2H, CH_2CHO), 3.94 (s, 3H, OCH_3), 6.08 (dt, J=15.7, 1.5 Hz, 1H, =CHCO$_2$CH$_3$), 7.16 (dt, J=15.7, 6.7 Hz, 1H, CH=CHCO$_2$CH$_3$), 9.97 (s, 1H, CHO); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 24.8 (CH_2CH=), 42.2 (CH_2CHO), 51.9 (OCH_3), 122.4 (=CHCO$_2$CH$_3$), 147.0 (CH=CHCO$_2$CH$_3$), 167.0 (CO_2CH$_3$), 200.5 (CHO); FTIR (film) ν 2953, 2849, 2731, 1724, 1659, 1437, 1165 cm^{-1}.

4.2.7. Methyl (2*E*,7*E*)-6-oxo-8-phenyl-2,7-octadienoate (8). According to the general procedure A, reaction of methyl 2-hydroxy-3-butenoate **2a** (2.0 g, 17.2 mmol) and benzylideneacetone (2.48 g, 17.2 mmol) gave, after purification by column chromatography eluting with P.E. 30–40 °C/EtOAc (80:20), the ketone **8** (2.44 g, 58%) as a single *E*-diastereomer as a yellow oil. R_f 0.37 (P.E. 30–40 °C/EtOAc, 80:20); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.56 (qd, J=6.9, 1.4 Hz, 2H, CH_2CH=), 2.82 (t, J=6.9 Hz, 2H, CH_2CO), 3.70 (s, 3H, OCH_3), 5.86 (dt, J=15.6, 1.4 Hz, 1H, =CHCO$_2$CH$_3$), 6.72 (d, J=16.2 Hz, 1H, CH=CHPh), 6.99 (dt, J=15.6, 6.9 Hz, 1H, CH=CHCO$_2$CH$_3$), 7.37–7.54 (m, 5H, Ph), 7.60 (d, J=16.2 Hz, 1H, CH=CHPh); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 26.7 (CH_2CH=), 39.1 (CH_2CHO), 51.8 (OCH_3), 122.1 (=CHCO$_2$CH$_3$), 126.2 (CH=CHPh), 128.7 (Ph), 129.3 (Ph), 131.0 (Ph), 134.8 (Ph), 143.3 (CH=CHPh), 148.0 (CH=CHCO$_2$CH$_3$), 167.2 (CO_2CH$_3$), 198.4 (CO); FTIR (film) ν 3055, 1719, 1659, 1612, 1578, 1265, 739, 704 cm^{-1}; LRMS (FAB$^+$) m/z 245 (M$^+$+H, 100), 213 (78), 167 (39); HRMS (FAB$^+$) calcd for $C_{15}H_{17}O_3$ (M$^+$+H) 245.11776, found 245.11782.

4.3. General olefination procedure B for the synthesis of cyclisation substrates

A suspension of 80% sodium hydride dispersion in mineral oil (3.64 g, 121.2 mmol) in 100 mL of dry tetrahydrofuran under a positive nitrogen pressure was stirred in an ice bath while trimethylphosphonoacetate (22.07 g, 121.2 mmol) in 100 mL of dry tetrahydrofuran was added dropwise. The mixture becomes viscous near the end of the addition, but redissolved on continued stirring. After the addition was finished, the reaction mixture was stirred for further 1 h at 0 °C. Then, a solution of 5-hexen-2-one (10.0 g, 101.9 mmol) in 150 mL of dry tetrahydrofuran was added dropwise. The cold mixture was stirred for further 15 min after the addition. Then, it was slowly brought to reflux and stirred overnight. The clear ether layer was decanted from the oil. The remaining oil was dissolved in warm water and the upper organic layer was separated. The aqueous layer was extracted with ether. The combined organic layers were washed with saturated $NaHCO_3$, dried over Na_2SO_4, filtered and the solvents were removed in vacuo. Purification by flash column chromatography employing P.E. 30–40 °C/EtOAc (80:20) as eluant afforded the enoate **13** (13.67 g, 87%) as two single diastereomers in a *E*/*Z* 2:1 ratio as a colorless oil.

4.3.1. Methyl (*E*)-3-methyl-2,6-heptadienoate ((*E*)-13). R_f 0.73 (P.E. 30–40 °C/EtOAc, 80:20); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.09 (d, J=1.3 Hz, 3H, CH_3), 2.16–2.18 (m, 4H, CH_2), 3.61 (s, 3H, OCH_3), 4.89 (dq, J=10.1, 1.8 Hz, 1H, CH=CH_{cis}H), 4.96 (dq, J=17.1, 1.8 Hz, 1H, CH=CHH_{trans}), 5.60 (m, 1H, =CHCO$_2$CH$_3$), 5.66–5.78 (m, 1H, CH=CH$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.7 (CH_3), 31.4 (CH_2), 40.1 (CH_2), 50.7 (OCH_3), 115.3 (=CH$_2$), 115.4 (=CHCO$_2$CH$_3$), 137.2 (CH=CH$_2$), 159.4 (C=CHCO$_2$CH$_3$), 167.1 (CO_2CH$_3$); FTIR (film) ν 3078, 2926, 2853, 1720, 1651, 1435, 1225, 1151 cm^{-1}; LRMS (DCI$^+$) m/z 155 (M$^+$+H, 100), 139 (8), 123 (26), 95 (63); HRMS (DCI$^+$) calcd for $C_9H_{15}O_2$ (M$^+$+H) 155.10719, found 155.10696.

4.3.2. Methyl (*E*)-4,4-dimethyl-2,6-heptadienoate (17). According to the general procedure B, reaction of 4,4-dimethyl pentenal **16** (23.0 g, 205.0 mmol) with a mixture of 80% sodium hydride dispersion in oil (6.77 g, 225.6 mmol) and trimethylphosphonoacetate (41.0 g, 225.6 mmol) gave, after purification by column chromatography eluting with P.E. 30–40 °C/EtOAc (80:20), the enoate **17** (30.3 g, 88%) as a single *E*-isomer as a colorless oil. R_f 0.67 (P.E. 30–40 °C/EtOAc, 80:20); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (s, 6H, C(CH_3)$_2$), 2.04 (d, J=7.4 Hz, 2H, CH_2CH=), 3.66 (s, 3H, OCH_3), 4.92–5.02 (m, 2H, CH=CH_2), 5.56–5.72 (m, 1H, CH=CH$_2$), 5.66 (d, J=15.7 Hz, 1H, =CHCO$_2$CH$_3$), 6.88 (d, J=15.7 Hz, 1H, CH=CHCO$_2$CH$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 26.4 (C(CH_3)$_2$), 37.1 (C(CH$_3$)$_2$), 46.8 (CH_2), 51.8 (OCH_3), 117.9 (=CHCO$_2$CH$_3$), 118.2 (=CH_2), 134.6 (CH=CH$_2$), 158.3 (CH=CHCO$_2$CH$_3$), 167.9 (CO_2CH$_3$); FTIR (film) ν 2964, 2872, 1719, 1653, 1265 cm^{-1}; LRMS (APCI$^+$) m/z 169 (M$^+$+H, 10), 137 (10), 127 (63), 109 (100); HRMS (ES$^+$) calcd for $C_{10}H_{17}O_2$ (M$^+$+H) 169.1239, found 169.1232.

4.4. General ozonolysis procedure C for the synthesis of cyclisation substrates

A solution of 4-but-3-enyl-5*H*-furan-2-one **12** (0.6 g, 4.3 mmol) and pyridine (0.2 mL, 1% vol) in anhydrous dichloromethane (20 mL) was cooled to −78 °C. A stream of ozone was bubbled through the solution, and the reaction was carefully monitored by TLC. After consumption of the starting material the flask was flushed with nitrogen.

Dimethylsulfide was added (0.27 g, 43.4 mmol) and the mixture was allowed to warm to room temperature overnight. The solution was then extracted with dichloromethane. The combined organic layers were dried over Na_2SO_4, filtered and the filtrate concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography eluting with EtOAc to afford the aldehyde **9** (0.33 g, 49%) as a yellow oil.

4.4.1. 3-(5-Oxo-2,5-dihydrofuran-3-yl)propionaldehyde (9). R_f 0.35 (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.50–2.57 (m, 2H, CH_2CH$_2$CHO), 2.70 (t, J=7.4 Hz, 2H, CH_2CHO), 4.93 (d, J=1.5 Hz, 2H, OCH_2), 6.04–6.06 (m, 1H, =CHCO$_2$R), 9.79 (s, 1H, CHO); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.1 (*C*H$_2$CH$_2$CHO), 41.4 (*C*H$_2$CHO), 73.4 (O*C*H$_2$), 116.4 (=*C*HCO$_2$R), 168.7 (*C*=CHCO$_2$R), 173.8 (*C*O$_2$R), 199.4 (*C*HO); FTIR (film) ν 2853, 1744, 1636, 1391, 1182 cm^{-1}; HRMS (FAB$^+$) calcd for $C_7H_9O_3$ (M$^+$+H) 141.05516, found 141.05505.

4.4.2. Methyl (*E*)-3-methyl 6-oxo-2-hexenoate (10). According to the general procedure C, ozonolysis of methyl (*E*)-3-methyl-2,6-heptadienoate **13** (15.0 g, 97.3 mmol) gave, after purification by column chromatography eluting with P.E. 30–40 °C/EtOAc (90:10), the aldehyde **10**[53] (6.23 g, 41%) as a colorless oil. R_f 0.37 (P.E. 30–40 °C/EtOAc, 90:10); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.15 (d, J=1.3 Hz, 3H, CH_3), 2.45 (td, J=7.6, 1.1 Hz, 2H, CH_2CHO), 2.61 (td, J=7.6, 1.3 Hz, 2H, CH_2CH$_2$CHO), 3.65 (s, 3H, OCH_3), 5.61 (m, 1H, =CHCO$_2$CH$_3$), 9.77 (t, J=1.1 Hz, 1H, CHO); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.1 (*C*H$_3$), 33.0 (*C*H$_2$), 41.8 (*C*H$_2$), 51.3 (O*C*H$_3$), 116.4 (=*C*HCO$_2$CH$_3$), 157.7 (*C*=CHCO$_2$CH$_3$), 167.2 (*C*O$_2$CH$_3$), 200.8 (*C*HO); FTIR (film) ν 2951, 2845, 2729, 1719, 1649, 1437, 1362, 1229, 1153 cm^{-1}.

4.4.3. Methyl (*E*)-4,4-dimethyl-6-oxo-2-hexenoate (15). According to the general procedure C, ozonolysis of methyl (*E*)-4,4-dimethyl-2,6-heptadienoate **17** (30.0 g, 178.3 mmol) gave, after purification by column chromatography eluting with P.E. 30–40 °C/EtOAc (90:10), the aldehyde **15**[54] (14.57 g, 48%) as a colorless oil. R_f 0.28 (P.E. 30–40 °C/EtOAc, 90:10); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 6H, C(CH_3)$_2$), 2.52 (d, J=2.7 Hz, 2H, CH_2CHO), 3.83 (s, 3H, OCH_3), 5.89 (d, J=16.0 Hz, 1H, =CHCO$_2$CH$_3$), 7.13 (d, J=16.0 Hz, 1H, CH=CHCO$_2$CH$_3$), 9.84 (t, J=2.7 Hz, 1H, CHO); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.2 (C(*C*H$_3$)$_2$), 36.2 (*C*(CH$_3$)$_2$), 52.0 (O*C*H$_3$), 54.6 (*C*H$_2$), 118.9 (=*C*HCO$_2$CH$_3$), 155.9 (*C*H=CHCO$_2$CH$_3$), 167.3 (*C*O$_2$CH$_3$), 201.6 (*C*HO); FTIR (film) ν 2930, 2853, 2729, 1730, 1654, 1462 cm^{-1}; LRMS (APCI$^+$) *m*/*z* 171 (M$^+$+H, 8), 155 (46), 139 (100); HRMS (ES$^+$) calcd for $C_9H_{15}O_3$ (M$^+$+H) 171.1007, found 171.1011.

4.5. Synthesis of other cyclisation substrates

4.5.1. Methyl (*E*)-4,4-dimethyl-5-oxiranyl-2-pentenoate (18). A mixture of 60% sodium hydride dispersion in mineral oil (0.13 g, 3.2 mmol) and excess anhydrous dimethylsulfoxide (5 mL) was stirred under nitrogen at 75 °C until the evolution of hydrogen ceases (1 h). The solution was then cooled down to room temperature, diluted with an equal volume of dry tetrahydrofuran to avoid freezing and then cooled in an ice–salt bath. A solution of trimethyl sulfonium iodide (0.66 g, 3.2 mmol) in 3 mL of dry dimethylsulfoxide was added and the mixture stirred for 5 min. The aldehyde **15** was then added (0.5 g, 2.9 mmol) and stirring was continued at salt–ice temperature for further 15 min, then for 1 h at room temperature. The mixture was diluted with 3 volumes of water and extracted with ether. The combined organic layers were dried over Na_2SO_4, filtered and the filtrate concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography eluting with P.E. 30–40 °C/EtOAc (90:10) to afford the epoxide **18** (0.18 g, 33%) as a colorless oil. R_f 0.28 (P.E. 30–40 °C/EtOAc, 90:10); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.11 (s, 3H, CH_3), 1.20 (s, 3H, CH_3), 1.47–1.54 (m, 2H, CH_2), 2.34 (dd, J=5.0, 2.7 Hz, 1H, CH_aHO), 2.66 (dd, J=5.0, 4.1 Hz, 1H, CHH_bO), 2.80–2.82 (m, 1H, CHO), 3.67 (s, 3H, OCH_3), 5.67 (d, J=16.0 Hz, 1H, =CHCO$_2$CH$_3$), 6.93 (d, J=16.0 Hz, 1H, CH=CHCO$_2$CH$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 26.7 (*C*H$_3$), 27.3 (*C*H$_3$), 37.0 (*C*(CH$_3$)$_2$), 45.2 (*C*H$_2$), 47.0 (*C*H$_2$O), 49.4 (*C*HO), 51.9 (O*C*H$_3$), 118.3 (=*C*HCO$_2$CH$_3$), 157.6 (*C*H=CHCO$_2$CH$_3$), 167.7 (*C*O$_2$CH$_3$); FTIR (film) ν 3054, 2969, 2931, 2874, 1717, 1652, 1436, 1265 cm^{-1}; LRMS (FAB$^+$) *m*/*z* 185 (M$^+$+H, 66), 169 (8), 154 (100); HRMS (FAB$^+$) calcd for $C_{10}H_{17}O_3$ (M$^+$+H) 185.11775, found 185.11746.

4.5.2. Methyl (*E*)-4,4-dimethyl-8-oxo-2,6-nonadienoate (19). According to the general procedure B, reaction of methyl (*E*)-4,4-dimethyl-6-oxo-2-hexenoate **15** (1.5 g, 8.9 mmol) with a mixture of 80% sodium hydride dispersion in oil (0.26 g, 9.7 mmol) and dimethyl-(2-oxopropyl)-phosphonate (1.6 g, 9.7 mmol) gave, after purification by column chromatography eluting with P.E. 30–40 °C/EtOAc (90:10), the enoate **19**[55] (1.7 g, 92%) as a colorless oil. R_f 0.66 (P.E. 30–40 °C/EtOAc, 90:10); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (s, 6H, C(CH_3)$_2$), 2.22 (s, 3H, CH_3CO), 2.28 (dd, J=7.6, 1.2 Hz, 2H, CH_2CH=), 3.74 (s, 3H, OCH_3), 5.76 (d, J=16.0 Hz, 1H, =CHCO$_2$CH$_3$), 6.07 (dt, J=15.8, 1.2 Hz, 1H, =CHCOCH$_3$), 6.65 (dt, J=15.8, 7.6 Hz, 1H, CH=CHCOCH$_3$), 6.93 (d, J=16.0 Hz, 1H, CH=CHCO$_2$CH$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 26.8 (C(*C*H$_3$)$_2$), 27.5 (CO*C*H$_3$), 37.5 (*C*(CH$_3$)$_2$), 45.2 (*C*H$_2$), 51.9 (O*C*H$_3$), 118.7 (=*C*HCO$_2$CH$_3$), 134.3 (=*C*HCOCH$_3$), 143.6 (*C*H=CHCOCH$_3$), 156.9 (*C*H=CHCO$_2$CH$_3$), 167.5 (*C*O$_2$CH$_3$), 198.4 (*C*OCH$_3$); FTIR (film) ν 2964, 2845, 1724, 1655, 1628, 1437, 1367, 1256, 1171 cm^{-1}; LRMS (ES$^+$) *m*/*z*: 233 (M$^+$+Na, 96), 211 (M$^+$+H, 65), 179 (100); HRMS (ES$^+$) *m*/*z*: requires 211.1335 for $C_{12}H_{19}O_3$ (M$^+$+H), found 211.1334.

4.5.3. Methyl (*E*)-*cis*-3-(2-hydroxymethyl-cyclohexyl)-acrylate (22). To a stirred solution of hexahydro-isobenzofuran-1-one (5.5 g, 38.7 mmol) in 100 mL of anhydrous ether at −20 °C under positive nitrogen pressure, DIBAL (1.22 M solution in toluene) (33.3 mL, 40.6 mmol) was added dropwise over 1 h. The resulting solution was stirred at −20 °C for an additional 0.5 h, and was then quenched by the addition of methanol (30 mL). The solution was allowed to warm to room temperature and stirred overnight. The resulting suspension was diluted with 50 mL of 30% aqueous solution of Rochelle's salt and was stirred for 30 min. The organic layer was separated and washed with

30% aqueous solution of Rochelle's salt. The combined aqueous layers were extracted with ether. The organic layers were dried over Na_2SO_4, filtered and the filtrate concentrated under reduced pressure to afford the crude lactol that was added to a stirred solution of methyl(triphenylphosphoranylidene)acetate (18.55 g, 55 mmol) in 150 mL of dry acetonitrile and heated at reflux under a nitrogen atmosphere for 2 days. The heat was removed and most of the solvent was evaporated in vacuo. Ether (25 mL) was added and the mixture was stirred for an additional 2 h. The resulting mixture was filtered and the filtrate washed with 15 mL of ether. The solvent was removed in vacuo and 20 mL of 70% ether in pentane was added. After stirring for further 30 min, the suspension was filtered again and the filtrate concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography eluting with P.E. 30–40 °C/EtOAc (80:20) to afford the alcohol **22** (5.22 g, 68%) as a single *E* diastereoisomer as a colorless oil. R_f 0.33 (P.E. 30–40 °C/EtOAc, 80:20); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30–1.74 (m, 8H, CH_2), 1.86–1.97 (m, 1H, CHCH$_2$OH), 2.72–2.78 (m, 1H, CHCH=), 3.52 (d, J=7.2 Hz, 2H, CH_2OH), 3.80 (s, 3H, OCH_3), 5.95 (dd, J=15.6, 0.8 Hz, 1H, =CHCO$_2$CH$_3$), 7.23 (dd, J=15.6, 9.0 Hz, 1H, CH=CHCO$_2$CH$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.7 (*C*H$_2$), 25.1 (*C*H$_2$), 25.5 (*C*H$_2$), 30.7 (*C*H$_2$), 29.7 (*C*HCH$_2$OH), 43.0 (*C*HCH=), 51.8 (O*C*H$_3$), 65.3 (*C*H$_2$OH), 121.9 (=*C*HCO$_2$CH$_3$), 150.4 (*C*H=CHCO$_2$CH$_3$), 167.4 (*C*O$_2$CH$_3$); FTIR (film) ν 3423, 2928, 2858, 1707, 1649, 1437, 1375, 1271, 1238, 1172 cm^{-1}; LRMS (EI$^+$) *m*/*z* 198 (M$^+$, 3), 167 (53), 81 (95), 67 (100); HRMS (EI$^+$) calcd for $C_{11}H_{18}O_3$ (M$^+$) 198.12558, found 198.12538.

4.5.4. Methyl (*E*)-3-(2-formyl-cyclohexyl)-acrylate (20). To a stirred suspension of pyridinium chlorochromate (1.95 g, 9.1 mmol) and celite (2.1 g) in 15 mL of anhydrous dichloromethane, was added at room temperature and under a positive pressure of nitrogen, a solution of methyl (*E*)-*cis*-3-(2-hydroxymethyl-cyclohexyl)-acrylate **22** (1.2 g, 6.1 mmol) in 3 mL of dichloromethane. The reaction mixture was stirred for 2 h at room temperature and was then diluted with 50 mL of ether. The resulting suspension was filtered through a short pad of Florisil®, rinsed with several portions of ether and the solvent concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography eluting with P.E. 30–40 °C/EtOAc (80:20) to afford the aldehyde **20** (0.90 g, 76%) as a colorless oil. R_f 0.67 (P.E. 30–40 °C/EtOAc, 80:20); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.52–1.98 (m, 8H, CH_2, *cis*+*trans*), 2.28–2.37 (m, 1H, CHCHO, *trans*), 2.49–2.61 (m, 1H, CHCH=, *trans*), 2.64–2.67 (m, 1H, CHCHO, *cis*), 2.86–2.89 (m, 1H, CHCH=, *cis*), 3.79 (s, 3H, OCH_3, *trans*), 3.80 (s, 3H, OCH_3, *cis*), 5.91 (dd, J=15.8, 1.2 Hz, 1H, =CHCO$_2$CH$_3$, *trans*), 5.94 (dd, J=15.8, 1.3 Hz, 1H, =CHCO$_2$CH$_3$, *cis*), 6.94 (dd, J=15.8, 8.0 Hz, 1H, CH=CHCO$_2$CH$_3$, *trans*), 7.20 (dd, J=15.8, 7.3 Hz, 1H, CH=CHCO$_2$CH$_3$, *cis*), 9.64 (d, J=2.3 Hz, 1H, CHO, *trans*), 9.73 (s, 1H, CHO, *cis*); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.7 (*C*H$_2$, *cis*), 23.9 (*C*H$_2$, *cis*), 24.3 (*C*H$_2$, *cis*), 24.9 (*C*H$_2$, *trans*), 25.1 (*C*H$_2$, *trans*), 25.9 (*C*H$_2$, *trans*), 29.6 (*C*H$_2$, *cis*), 31.3 (*C*H$_2$, *trans*), 39.5 (*C*HCHO, *cis*), 40.5 (*C*HCHO, *trans*), 51.9 (O*C*H$_3$, *cis*+*trans*), 52.2 (*C*HCH=, *cis*), 54.2 (*C*HCH=, *trans*), 121.5 (=*C*HCO$_2$CH$_3$, *trans*), 122.0 (=*C*HCO$_2$CH$_3$, *cis*), 149.7 (*C*H=CHCO$_2$CH$_3$, *cis*), 151.0 (*C*H=CHCO$_2$CH$_3$, *trans*), 167.1 (*C*O$_2$CH$_3$, *cis*+*trans*), 203.6 (*C*HO, *trans*), 204.1 (*C*HO, *cis*); FTIR (film) ν 2937, 2858, 1719, 1655, 1437, 1277, 1175 cm^{-1}; LRMS (FAB$^+$) *m*/*z* 197 (M$^+$+H, 15), 181 (24), 165 (30); HRMS (FAB$^+$) calcd for $C_{11}H_{17}O_3$ (M$^+$+H) 197.11776, found 197.11916.

4.5.5. Methyl (*E*)-3-(2-formyl-cyclohex-1-enyl)-acrylate (23b). A mixture of 2-bromo-cyclohexene-1-carboxaldehyde **24** (1.5 g, 7.9 mmol), methyl acrylate (0.81 g, 9.5 mmol), triethylamine (0.96 g, 9.5 mmol), palladium acetate (18 mg, 0.079 mmol) and triphenylphosphine (42 mg, 0.158 mmol), was heated at reflux under a positive pressure of nitrogen for 3 days. The heat was removed and the reaction mixture was diluted with ether and filtered. The solids were washed several times with small portions of ether, and the filtrate was concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography eluting with P.E. 30–40 °C/EtOAc (90:10) to afford the aldehyde **23b** (0.85 g, 55%) as a colorless oil. R_f 0.39 (P.E. 30–40 °C/EtOAc, 90:10); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.54–1.67 (m, 4H, CH_2), 2.29–2.36 (m, 4H, CH_2), 3.73 (s, 3H, OCH_3), 6.07 (d, J=15.6 Hz, 1H, =CHCO$_2$CH$_3$), 8.22 (d, J=15.6 Hz, 1H, CH=CHCO$_2$CH$_3$), 10.35 (s, 1H, CHO); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.5 (*C*H$_2$), 22.0 (*C*H$_2$), 23.8 (*C*H$_2$), 27.3 (*C*H$_2$), 52.3 (O*C*H$_3$), 122.2 (=*C*HCO$_2$CH$_3$), 138.9 (*C*H=CHCO$_2$CH$_3$), 141.0 (=*C*CHO), 148.2 (*C*=CCHO), 167.2 (*C*O$_2$CH$_3$), 190.3 (*C*HO); FTIR (film) ν 2937, 2864, 1720, 1668, 1622, 1587, 1435, 1375, 1300, 1277, 1175 cm^{-1}; LRMS (EI$^+$) *m*/*z* 195 (M$^+$+H, 8), 165 (38), 135 (100); HRMS (EI$^+$) calcd for $C_{11}H_{15}O_3$ (M$^+$+H) 195.10210, found 195.10196.

4.5.6. Methyl (*E*)-3-(2′-formylphenyl)-propenoate (25). Tetrabutylammonium bromide (0.56 g, 1.7 mmol), potassium carbonate (0.80 g, 5.8 mmol), palladium acetate (156 mg, 0.69 mmol) and methyl acrylate (2.97 g, 34.8 mmol) were stirred for 5 min under nitrogen, forming a dark orange solution. A solution of *o*-bromobenzaldehyde (1.28 g, 6.9 mmol) in 4 mL of degassed dimethylformamide was then added and the reaction was stirred at 70 °C for 16 h. The resulting mixture was diluted with ethyl acetate and filtered through a short pad of celite. The filtrate was diluted with water and extracted with ethyl acetate. The combined organic extracts were dried over $MgSO_4$, filtered and the filtrate concentrated under reduced pressure. Purification by flash column chromatography eluting with P.E. 30–40 °C/EtOAc (90:10) enabled *o*-bromobenzaldehyde to be removed from the crude mixture, with the desired aldehyde being isolated in 69% yield (when adjusted for recovered starting material). All spectroscopic and analytical data were in agreement with the literature values.[36] R_f 0.32 (P.E. 30–40 °C/EtOAc, 90:10); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.85 (s, 3H, OCH_3), 6.40 (d, J=15.9 Hz, 1H, =CHCO$_2$CH$_3$), 7.56–7.91 (m, 4H, Ph), 8.55 (d, J=15.9 Hz, 1H, CH=CHCO$_2$CH$_3$), 10.31 (s, 1H, CHO); FTIR (film) ν 1728, 1699, 1621 cm^{-1}.

4.5.7. α-Benzyloxy-γ-butyrolactone (29). A suspension of 60% sodium hydride dispersion in mineral oil (2.15 g, 54 mmol) and α-hydroxy-γ-butyrolactone (5.0 g, 49 mmol) in dry tetrahydrofuran (50 mL) was stirred at 0–5 °C for

0.5 h. Benzyl bromide (7.3 mL, 61.3 mmol) and tetrabutylammonium iodide (1.18 g, 4.9 mmol) were then added. The resulting suspension was stirred at ambient temperature for 3 h, and then a saturated $NaHCO_3$ solution (50 mL) was cautiously added. The aqueous layer was extracted with dichloromethane and the combined organic extracts were dried over $MgSO_4$, filtered and the filtrate concentrated under reduced pressure. The resulting brown oil was purified by flash column chromatography eluting with P.E. 30–40 °C/EtOAc (60:40) to afford the product **29** (5.70 g, 61%) as a colorless oil. R_f 0.34 (P.E. 30–40 °C/EtOAc, 60:40); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.24–2.56 (m, 2H, CH_2CH$_2$O), 4.15–4.26 (m, 2H, OCH_2CH$_2$), 4.43 (t, J=8.0 Hz, 1H, OCHCH$_2$), 4.74 (d, J=12.0 Hz, 1H, PhCH_a-H$_b$O), 4.95 (d, J=12.0 Hz, 1H, PhCH$_a$$H_b$O), 7.30–7.42 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.9 (*C*H$_2$), 65.5 (*C*H$_2$OCO), 72.2 (O*C*H$_2$Ph), 72.5 (O*C*H), 128.1 (Ph), 128.2 (Ph), 128.6 (Ph), 137.0 (Ph), 175.0 (*C*O$_2$R); FTIR (film) ν 1781, 1175, 1142, 699 cm^{-1}; LRMS (ES$^+$) *m/z* 210 (M$^+$+NH$_4$, 100), 193 (M$^+$+H, 31), HRMS (ES$^+$) calcd for $C_{11}H_{13}O_3$ (M$^+$+H) 193.0852, found 193.0860.

4.5.8. α-Benzyloxy-γ-butyrolactol (30). DIBAL (1.22 M solution in toluene) (13.9 mL, 21 mmol) was added dropwise to a stirred solution of α-benzyloxy-γ-butyrolactone **29** (3.66 g, 19 mmol) in toluene (55 mL) at −75 °C under positive nitrogen pressure. The resulting solution was stirred at −70 °C for 3 h, and was then quenched by the addition of methanol (1.5 mL). The mixture was allowed to warm −10 to 0 °C, treated with 20% (w/v) aqueous solution of Rochelle's salt (50 mL) and the resulting mixture stirred at ambient temperature for 30 min. The biphasic mixture was separated, the aqueous layer extracted with toluene and the combined organic layers washed with water. The combined water washes were back extracted with toluene and the combined organics dried over Na_2SO_4, filtered and the filtrate concentrated under reduced pressure to afford a pale green oil of sufficient purity for further use (3.19 g, 87%). R_f 0.27 (P.E. 30–40 °C/EtOAc, 60:40); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.96–2.28 (m, 2H, CH_2CH$_2$O), 2.49 (d, J=2.5 Hz, 1H, O*H*), 3.80–3.86 (m, 1H, BnOC*H*CH$_2$, *trans*), 4.00–4.12 (m, 3H, BnOC*H*CH$_2$, *cis* and CH_2O), 4.57 (s, 2H, PhCH_2O, *cis*), 4.63 (d, J=6.0 Hz, 2H, PhCH_2O, *trans*), 5.35 (dd, J=17.0, 6.0 Hz, 1H, C*H*OH, *trans*), 5.45 (d, J=2.5 Hz, 1H, C*H*OH, *cis*), 7.25–7.40 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.9 (*C*H$_2$, *cis*+*trans*), 64.8 (*C*H$_2$O, *trans*), 67.0 (*C*H$_2$O, *cis*), 71.4 (O*C*H$_2$Ph, *cis*), 72.5 (O*C*H$_2$Ph, *trans*), 78.1 (O*C*H, *trans*), 83.4 (O*C*H, *cis*), 96.3 (HO*C*H, *trans*), 100.7 (HO*C*H, *cis*), 127.9 (Ph, *cis*), 128.1 (Ph, *trans*), 128.2 (Ph, *cis*+*trans*), 128.5 (Ph, *cis*), 128.6 (Ph, *trans*), 137.2 (Ph, *trans*), 137.9 (Ph, *cis*); FTIR (film) ν 3397, 1071, 739, 699 cm^{-1}; LRMS (ES$^+$) *m/z* 218 (M$^+$+NH$_4$), 195 (M$^+$+H), 177 (M$^+$−H$_2$O).

4.5.9. Methyl 6-hydroxy-4-benzyloxy-2-hexenoate (31). A solution of α-benzyloxy-γ-butyrolactol **30** (1.8 g, 9.3 mmol) in toluene (10 mL) was added to a stirred suspension of carbomethoxymethyl triphenylphosphonium bromide (4.25 g, 10 mmol) and potassium *t*-butoxide (1.12 g, 10 mmol) in dry tetrahydrofuran (40 mL) which were premixed at 0 °C for 30 min. The resulting suspension was heated at 80 °C for 3 h, then cooled to ambient temperature, diluted with water (30 mL), and extracted with dichloromethane. The combined organic extracts were dried over $MgSO_4$, filtered and the filtrate concentrated under reduced pressure. Purification of the pale green oil by flash column chromatography eluting with P.E. 30–40 °C/EtOAc (60:40) afforded the title compound as a mixture of *Z* and *E* isomers in a 1:4.3 ratio (1.89 g, 78%). R_f 0.29 (P.E. 30–40 °C/EtOAc, 60:40); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.82–1.88 (m, 2H, CH_2CH$_2$OH), 3.73–3.79 (m, 5H, CH_2OH and OCH_3), 4.23 (q, J=7.0 Hz, 1H, BnOC*H*, *E*), 4.41–4.57 (dd, J=11.0, 6.0 Hz, 2H, PhCH_2O, *Z*), 4.31–4.65 (dd, J=11.0, 6.0 Hz, 2H, PhCH_2O, *E*), 5.19–5.25 (q, J=7.0 Hz, 1H, BnOC*H*, *Z*); 5.95 (d, J=12.0 Hz, 1H, =C*H*CO$_2$CH$_3$, *Z*), 6.05–6.10 (d, J=17.0 Hz, 1H, =C*H*CO$_2$CH$_3$, *E*), 6.25 (dd, J=12.0, 6.0 Hz, 1H, C*H*=CHCO$_2$CH$_3$, *Z*), 6.90 (dd, J=17.0, 6.0 Hz, 1H, C*H*=CHCO$_2$CH$_3$, *E*), 7.28–7.38 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.2 (*C*H$_2$CH$_2$OH, *E*), 37.3 (*C*H$_2$-CH$_2$OH, *Z*), 51.7 (O*C*H$_3$, *Z*), 51.8 (O*C*H$_3$, *E*), 59.8 (*C*H$_2$OH, *E*), 60.0 (*C*H$_2$OH, *Z*), 71.4 (*C*HOBn, *E*), 71.7 (*C*HOBn, *Z*), 74.5 (Ph*C*H$_2$O, *Z*), 76.7 (Ph*C*H$_2$O, *E*), 121.3 (=*C*HCO$_2$-CH$_3$, *Z*), 122.0 (=*C*HCO$_2$CH$_3$, *E*), 127.9 (Ph, *E*), 128.0 (Ph, *Z*), 128.5 (Ph, *Z*), 128.6 (Ph, *E*), 137.6 (Ph, *E*), 137.7 (Ph, *Z*), 147.7 (*C*H=CHCO$_2$CH$_3$, *E*), 150.9 (*C*H=CHCO$_2$CH$_3$, *Z*), 166.5 (*C*O$_2$CH$_3$, *E*), 166.6 (*C*O$_2$CH$_3$, *Z*); FTIR (film) ν 3431, 1730, 738, 699 cm^{-1}; LRMS (ES$^+$) *m/z* 268 (M$^+$+NH$_4$, 38), 251 (M$^+$+H, 100), 233 (17), 210 (13); HRMS (ES$^+$) calcd for $C_{14}H_{22}NO_4$ (M$^+$+NH$_4$) 268.1549, found 268.1549.

4.5.10. Methyl 6-oxo-4-benzyloxy-2-hexenoate (28). To a stirred suspension of pyridinium chlorochromate (2.1 g, 9.6 mmol) in 10 mL of anhydrous dichloromethane, was added at room temperature and under a positive pressure of nitrogen, a solution of methyl 6-hydroxy-4-benzyloxy-2-hexenoate **31** (1.6 g, 6.4 mmol) in 10 mL of dichloromethane. The reaction mixture was stirred for 12 h at room temperature and the solvent removed under reduced pressure. The resulting crude oil was purified by flash column chromatography eluting with P.E. 30–40 °C/EtOAc (80:20) which allowed separation of *Z* and *E* isomers as clear oils (1.08 g, 67%).

Z isomer. R_f 0.48 (P.E. 30–40 °C/EtOAc, 80:20); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.60–2.84 (m, 2H, CH_2CHO), 3.75 (s, 3H, OCH_3), 4.45–4.63 (dd, J=12.0, 6.0 Hz, 2H, PhCH_2O), 5.50–5.63 (m, 1H, BnOC*H*CH$_2$); 6.00 (d, J=12.0 Hz, 1H, =C*H*CO$_2$CH$_3$), 6.80–6.95 (m, 1H, C*H*=CHCO$_2$CH$_3$), 7.25–7.38 (m, 5H, Ph), 9.75 (s, 1H, C*H*O); ^{13}C NMR (100 MHz, $CDCl_3$) δ 48.4 (*C*H$_2$CHO), 51.6 (O*C*H$_3$), 71.0 (*C*HOBn), 71.7 (Ph*C*H$_2$O), 121.5 (=*C*HCO$_2$CH$_3$), 127.9 (Ph), 128.4 (Ph), 137.7 (Ph), 149.7 (*C*H=CHCO$_2$CH$_3$), 166.1 (*C*O$_2$CH$_3$), 200.8 (*C*HO); FTIR (film) ν 2952, 1725, 698 cm^{-1}; LRMS (ES$^+$) *m/z* 514 (2M$^+$+NH$_4$, 43), 266 (M$^+$+NH$_4$, 100), 249 (M$^+$+H, 27), 210 (14); HRMS (ES$^+$) calcd for $C_{14}H_{17}O_4$ (M$^+$+H) 249.1116, found 249.1127.

E isomer. R_f 0.45 (P.E. 30–40 °C/EtOAc, 80:20); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.68–2.90 (m, 2H, CH_2CHO), 3.77 (s, 3H, OCH_3), 4.42–4.65 (dd, J=12.0, 6.0 Hz, 2H, PhCH_2O), 5.50–5.63 (m, 1H, BnOC*H*CH$_2$); 6.15 (d, J=17.0 Hz, 1H, =C*H*CO$_2$CH$_3$), 6.85–6.98 (m, 1H, C*H*=CHCO$_2$CH$_3$), 7.21–7.45 (m, 5H, Ph), 9.78 (s, 1H, C*H*O); ^{13}C NMR (100 MHz, $CDCl_3$) δ 48.4 (*C*H$_2$CHO),

51.8 (OCH_3), 71.5 (*C*HOBn), 73.0 ($PhCH_2O$), 122.7 (=*C*HCO_2CH_3), 127.9 (Ph), 128.5 (Ph), 137.3 (Ph), 146.2 (*C*H=CHCO_2CH_3), 166.3 (CO_2CH_3), 199.0 (*C*HO); HRMS (ES^+) calcd for $C_{14}H_{17}O_4$ (M^++H) 249.1116, found 249.1125.

4.5.11. Methyl (*E*)-8-oxo-2-octenoate (33). To a stirred mixture of cyclohexene (2.5 g, 30.4 mmol) and aqueous ruthenium trichloride stock solution (130 mg, 0.627 mmol, 0.035 M) in 1,2-dichloroethane (120 mL) and distilled water (90 mL), was added, in portions, sodium periodate (9.75 g, 45.7 mmol) over a period of 5 min at room temperature. The colour turned from black to yellow immediately. The reaction was monitored by TLC. After completion in 3 h, the reaction was quenched with a saturated aqueous solution of $Na_2S_2O_3$ and the two layers were separated. The aqueous layer was extracted with 1,2-dichloroethane (3×30 mL). The organic layers were dried over anhydrous Na_2SO_4, filtered and the filtrate containing the crude adipaldehyde was directly used without further purification. A suspension of 60% sodium hydride dispersion in mineral oil (0.49 g, 12.2 mmol) in 25 mL of dry 1,2-dichloroethane under a positive nitrogen pressure, was stirred in an ice bath while trimethylphosphonoacetate (2.22 g, 12.2 mmol) in 25 mL of dry 1,2-dichloroethane was added dropwise. After the addition was finished, the reaction mixture was stirred for further 1 h at 0 °C. Then, the solution of crude adipaldehyde in 1,2-dichloroethane was added dropwise. The cold mixture was stirred for further 15 min after the addition. Then, it was slowly brought to reflux and stirred overnight. The clear organic layer was decanted from the oil. The remaining oil was dissolved in warm water and the upper organic layer was separated. The aqueous layer was extracted with dichloromethane. The combined organic layers were washed with saturated $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered and the solvents were removed in vacuo. The resulting crude oil was purified by flash column chromatography eluting with P.E. 30–40 °C/EtOAc (80:20) to afford the aldehyde **33**[54] (2.85 g, 55%) as a colorless oil. R_f 0.66 (P.E. 30–40 °C/EtOAc, 80:20); ^1H NMR (300 MHz, $CDCl_3$) δ 1.38–1.46 (m, 2H, CH_2CH_2CH=), 1.55–1.62 (m, 2H, CH_2CH_2CHO), 2.17 (qd, J=7.1, 1.4 Hz, 2H, CH_2CH=), 2.39 (td, J=7.3, 1.5 Hz, 2H, CH_2CHO), 3.66 (s, 3H, OCH_3), 5.76 (dt, J=15.7, 1.4 Hz, 1H, =C*H*CO_2CH_3), 6.87 (dt, J=15.7, 7.1 Hz, 1H, C*H*=CHCO_2CH_3), 9.69 (t, J=1.5 Hz, 1H, C*H*O); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.9 (CH_2), 27.8 (CH_2), 32.2 (CH_2), 43.9 (CH_2), 51.8 (OCH_3), 121.8 (=*C*HCO_2CH_3), 149.0 (*C*H=CHCO_2CH_3), 167.4 (CO_2CH_3), 202.5 (*C*HO); FTIR (film) ν 2949, 2862, 2725, 1724, 1655, 1437, 1275 cm^{-1}; LRMS (ES^+) *m/z* 188 (M^++NH_4, 38), 171 (M^++H, 100), 139 (19).

4.6. Typical procedure for the rhodium catalysed tandem hydrosilylation-aldol reaction

Triethylsilane (0.86 g, 7.4 mmol, 2.1 equiv.) was added slowly to a stirred solution of methyl (*E*)-6-oxo-hexenoate (*E*)-**7** and tris(triphenylphosphine) rhodium (I) chloride (48 mg, 0.05 mmol, 1 mol%) in anhydrous, degassed toluene (20 mL) at ambient temperature. The resulting solution was heated for 16 h at 50 °C and then cooled to room temperature. The reaction mixture was diluted with 2 M aqueous sodium hydroxide (10 mL) and extracted with dichloromethane (60 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the filtrate concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography eluting with P.E. 30–40 °C/EtOAc (90:10) to afford the product **32** (0.73 g, 81%) as a 3:1 mixture of *cis* and *trans* diastereomers as a colorless oil. An identical procedure was followed when using hydridotetrakis(triphenylphosphine) rhodium (I).

4.6.1. 2-Triethylsilyloxy-cyclopentane carboxylic acid methyl ester (35). R_f 0.69 (P.E. 30–40 °C/EtOAc, 90:10); ^1H NMR (400 MHz, $CDCl_3$) δ 0.48–0.72 (q, J=6.0 Hz, 6H, OSiCH_2CH$_3$, *cis*+*trans*), 0.98–1.02 (t, J=6.0 Hz, 9H, OSiCH$_2$CH_3, *cis*+*trans*), 1.49–2.05 (m, 6H, CH_2, *cis*+*trans*), 2.70–2.81 (m, 1H, C*H*CO_2CH_3, *cis*+*trans*), 3.67 (s, 3H, OCH_3, *cis*), 3.68 (s, 3H, OCH_3, *trans*), 4.40 (q, J=6.0 Hz, 1H, C*H*OSi, *trans*), 4.50 (q, J=4.0 Hz, 1H, C*H*OSi, *cis*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.6 (OSi*C*H$_2$-CH$_3$, *trans*), 3.8 (OSi*C*H$_2$CH$_3$, *cis*), 5.6 (OSiCH$_2$*C*H$_3$, *trans*), 5.7 (OSiCH$_2$*C*H$_3$, *cis*), 21.7 (CH$_2$*C*H$_2$CH$_2$, *cis*), 22.7 (CH$_2$*C*H$_2$CH$_2$, *trans*), 23.4 (CH$_2$*C*H$_2$CH, *cis*), 28.1 (CH$_2$*C*H$_2$CH, *trans*), 34.5 (OCH*C*H$_2$, *cis*), 35.5 (OCH*C*H$_2$, *trans*), 50.5 (*C*HCO_2CH_3, *cis*), 50.6 (O*C*H$_3$, *cis*), 51.1 (O*C*H$_3$, *trans*), 53.1 (*C*HCO_2CH_3, *trans*), 74.3 (*C*HOSi, *cis*), 78.3 (*C*HOSi, *trans*), 172.3 (CO_2CH_3, *cis*), 174.6 (CO_2CH_3, *trans*); FTIR (film) ν 2955, 2878, 1738, 1200, 1007 cm^{-1}; LRMS (FAB^+) *m/z* 259 (M^++H, 5), 229 (10), 115 (40), 87 (100); HRMS (FAB^+) calcd for $C_{13}H_{27}O_3Si$ (M^++H) 259.1729, found 259.1710.

4.6.2. 3,3-Dimethyl-2-triethylsilyloxy-cyclopentane carboxylic acid methyl ester (36). R_f 0.63 (P.E. 30–40 °C/EtOAc, 90:10); ^1H NMR (500 MHz, $CDCl_3$) δ 0.55 (q, J=7.9 Hz, 6H, OSiCH_2CH$_3$, *cis*), 0.56 (q, J=7.9 Hz, 6H, OSiCH_2CH$_3$, *trans*), 0.87 (s, 3H, CH$_3$, *cis*), 0.92 (s, 3H, CH$_3$, *trans*), 0.93 (t, J=7.9 Hz, 9H, OSiCH$_2$CH_3, *cis*), 0.94 (t, J=7.9 Hz, 9H, OSiCH$_2$CH_3, *trans*), 0.97 (s, 3H, CH$_3$, *trans*), 0.98 (s, 3H, CH$_3$, *cis*), 1.50 (dd, J=7.4, 8.4 Hz, 2H, CH_2CH$_2$CH, *cis*+*trans*), 1.67–1.71 (dq, J=13.6, 7.4 Hz, 1H, CH_{eq}H$_{ax}$CHCO_2CH_3, *cis*), 1.69–1.72 (m, 1H, CH_{eq}-H$_{ax}$CHCO_2CH_3, *trans*), 1.97 (ddt, J=13.6, 10.8, 8.4 Hz, 1H, CH$_{eq}$H$_{ax}$CHCO_2CH_3, *cis*), 2.12–2.21 (m, 1H, CH$_{eq}$-H$_{ax}$CHCO_2CH_3, *trans*), 2.73 (dt, J=10.8, 7.4 Hz, 1H, C*H*CO_2CH_3, *cis*), 2.96 (td, J=10.4, 7.0 Hz, 1H, C*H*CO_2-CH$_3$, *trans*), 3.66 (s, 3H, OCH_3, *cis*), 3.67 (s, 3H, OCH_3, *trans*), 3.94 (d, J=10.4 Hz, 1H, C*H*OSi, *trans*), 3.94 (d, J=7.4 Hz, 1H, C*H*OSi, *cis*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 4.9 (OSi*C*H$_2$CH$_3$, *cis*), 5.0 (OSi*C*H$_2$CH$_3$, *trans*), 6.8 (OSiCH$_2$*C*H$_3$, *cis*), 6.9 (OSiCH$_2$*C*H$_3$, *trans*), 19.7 (*C*H$_2$CH, *trans*), 21.1 (*C*H$_3$, *cis*), 22.9 (*C*H$_3$, *trans*), 24.7 (*C*H$_2$CH, *cis*), 26.7 (*C*H$_3$, *cis*), 27.7 (*C*H$_3$, *trans*), 36.9 (*C*H$_2$CH$_2$CH, *cis*), 37.0 (*C*H$_2$CH$_2$CH, *trans*), 42.3 (*C*(CH$_3$)$_2$, *cis*), 43.7 (*C*(CH$_3$)$_2$, *trans*), 49.8 (*C*HCO_2CH_3, *trans*), 50.8 (*C*HCO_2CH_3, *cis*), 51.4 (O*C*H$_3$, *trans*), 51.5 (O*C*H$_3$, *cis*), 83.1 (*C*HOSi, *trans*), 83.5 (*C*HOSi, *cis*), 174.3 (CO_2CH_3, *trans*), 176.9 (CO_2CH_3, *cis*); FTIR (film) ν 1738 cm^{-1}; LRMS (FAB^+) *m/z* 287 (M^++H, 3), 257 (10), 255 (5), 155 (18), 125 (60), 95 (100); HRMS (CI^+) calcd for $C_{15}H_{31}O_3Si$ (M^++H) 287.20423, found 287.20397.

4.6.3. 2-Triethylsilyloxyspiro[4.5]decane carboxylic acid

methyl ester (37a). R_f 0.60 (P.E. 30–40 °C/EtOAc, 90:10); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.55–0.60 (q, J=7.8 Hz, 6H, OSiCH_2CH$_3$, *cis*+*trans*), 0.94 (t, J=7.8 Hz, 9H, OSiCH$_2$-CH_3, *trans*), 0.95 (t, J=7.8 Hz, 9H, OSiCH$_2$CH_3, *cis*), 1.23–1.31 (m, 6H, CH_2, *cis*+*trans*), 1.44–1.49 (m, 1H, CH_{eq}-H$_{ax}$CH$_2$CH, *cis*+*trans*), 1.53–1.58 (m, 4H, CH_2, *cis*+*trans*), 1.62–1.65 (m, 1H, CH$_{eq}H_{ax}$CH$_2$CH, *cis*+*trans*), 1.69–1.74 (m, 1H, CH_{eq}H$_{ax}$CHCO$_2$CH$_3$, *cis*), 1.75–1.81 (m, 1H, CH_{eq}H$_{ax}$CHCO$_2$CH$_3$, *trans*), 1.89–1.97 (m, 1H, CH$_{eq}H_{ax}$CHCO$_2$CH$_3$, *trans*), 2.12–2.20 (m, 1H, CH$_{eq}$-H_{ax}CHCO$_2$CH$_3$, *cis*), 2.74 (td, J=10.4, 7.9 Hz, 1H, CHCO$_2$-CH$_3$, *trans*), 2.99 (td, J=9.0, 5.3 Hz, 1H, CHCO$_2$CH$_3$, *cis*), 3.64 (s, 3H, OCH_3, *cis*), 3.65 (s, 3H, OCH_3, *trans*), 3.90 (d, J=7.9 Hz, 1H, CHOSi, *trans*), 3.98 (d, J=5.3 Hz, 1H, CHOSi, *cis*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 5.4 (OSiCH$_2$-CH$_3$, *trans*), 5.5 (OSiCH$_2$CH$_3$, *cis*), 7.0 (OSiCH$_2$$CH_3$, *trans*), 7.1 (OSiCH$_2$$CH_3$, *cis*), 22.8 ($CH_2$, Cy, *trans*), 23.3 ($CH_2$, Cy, *cis*), 23.7 ($CH_2$, Cy, *cis*), 23.9 ($CH_2$CH, *cis*), 24.2 ($CH_2$, Cy, *trans*), 25.0 ($CH_2$CH, *trans*), 26.8 ($CH_2$, Cy, *cis*), 26.9 ($CH_2$, Cy, *trans*), 30.0 ($CH_2$, Cy, *trans*), 31.9 ($CH_2$-CH$_2$CH, *trans*), 32.2 ($CH_2CH_2$CH, *cis*), 32.3 ($CH_2$, Cy, *cis*), 36.4 ($CH_2$, Cy, *cis*), 36.6 ($CH_2$, Cy, *trans*), 46.2 ($C$Cy, *trans*), 47.9 ($C$Cy, *cis*), 49.7 ($CHCO_2CH_3$, *cis*), 50.7 ($CHCO_2CH_3$, *trans*), 51.4 (OC$H_3$, *cis*), 51.7 (OC$H_3$, *trans*), 83.9 ($C$HOSi, *cis*), 84.4 ($C$HOSi, *trans*), 175.7 ($CO_2CH_3$, *cis*), 178.8 ($CO_2CH_3$, *trans*); FTIR (film) ν 1738 cm^{-1}; LRMS (CI$^+$) *m/z* 326 (M$^+$, 10), 298 (100), 195 (49), 135 (54); HRMS (CI$^+$) calcd for $C_{18}H_{34}O_3Si$ (M$^+$) 326.22771, found 326.22536.

4.6.4. 2-Triethylsilyloxyspiro[4.5]decane carboxylic acid *i*-propyl ester (37b). R_f 0.75 (P.E. 30–40 °C/EtOAc, 90:10); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.50–0.54 (q, J=7.8 Hz, 6H, OSiCH_2CH$_3$, *cis*+*trans*), 0.86–0.90 (t, J=7.8 Hz, 9H, OSiCH$_2$CH_3, *trans*), 0.95 (t, J=7.8 Hz, 9H, OSiCH$_2$CH_3, *cis*), 1.15–1.21 (m, 12H, CH_2, (CH_3)$_2$, *cis*+*trans*), 1.24–1.41 (m, 1H, CH_{eq}CH$_{ax}$CH$_2$CH, *cis*+*trans*), 1.42–1.56 (m, 4H, CH_2, *cis*+*trans*), 1.57–1.61 (m, 1H, CH$_{eq}$CH_{ax}CH$_2$CH, *cis*+*trans*), 1.64–1.71 (m, 1H, CH_{eq}H$_{ax}$CHCO$_2$*i*Pr, *cis*+*trans*), 1.85–1.93 (m, 1H, CH$_{eq}$-H_{ax}CHCO$_2$*i*Pr, *trans*), 2.07–2.12 (m, 1H, CH$_{eq}H_{ax}$CHCO$_2$-*i*Pr, *cis*), 2.60 (dt, J=10.4, 7.3 Hz, 1H, CHCO$_2$*i*Pr, *trans*), 2.84 (td, J=9.2, 5.2 Hz, 1H, CHCO$_2$*i*Pr, *cis*), 3.88 (d, J=7.3 Hz, 1H, CHOSi, *trans*), 3.89 (d, J=5.2 Hz, 1H, CHOSi, *cis*), 4.89 (m, 1H, OCH(CH$_3$)$_2$, *cis*), 4.91 (m, 1H, OCH(CH$_3$)$_2$, *trans*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 4.1 (OSiCH$_2$CH$_3$, *trans*), 4.2 (OSiCH$_2$CH$_3$, *cis*), 5.9 (OSiCH$_2$-CH$_3$, *trans*), 6.0 (OSiCH$_2$$CH_3$, *cis*), 20.0 ($CH_3$, *trans*), 20.8 ($CH_3$, *cis*), 21.6 ($CH_2$, Cy, *trans*), 22.0 ($CH_2$, Cy, *cis*), 22.3 ($CH_2$, Cy, *cis*), 22.6 ($CH_2$CH, *cis*), 22.7 ($CH_2$, Cy, *trans*), 24.1 ($CH_2$CH, *trans*), 25.3 ($CH_2$, Cy, *cis*), 25.5 ($CH_2$, Cy, *trans*), 27.9 ($CH_2$, Cy, *trans*), 30.9 ($CH_2CH_2$CH, *trans*), 31.1 ($CH_2CH_2$CH, *cis*), 33.1 ($CH_2$, Cy, *cis*), 34.8 ($CH_2$, Cy, *trans*), 35.4 ($CH_2$, Cy, *cis*), 45.0 ($C$Cy, *trans*), 46.2 ($C$Cy, *cis*), 48.9 ($CHCO_2$*i*Pr, *cis*), 50.0 ($CHCO_2$*i*Pr, *trans*), 66.4 (OCH(CH$_3$)$_2$, *cis*), 66.5 (OCH(CH$_3$)$_2$, *trans*), 82.3 (CHOSi, *trans*), 82.4 (CHOSi, *cis*), 171.8 (CO$_2$*i*Pr, *cis*), 174.7 (CO$_2$*i*Pr, *trans*); FTIR (film) ν 2934, 2858, 1717, 1452, 1375, 1107, 908 cm^{-1}; LRMS (CI$^+$) *m/z* 355 (M$^+$+H, 80), 313 (18), 283 (39), 223 (100); HRMS (CI$^+$) calcd for $C_{20}H_{39}O_3Si$ (M$^+$+H) 355.26683, found 355.26676.

4.6.5. 3,3-Diphenyl-2-triethylsilyloxy-cyclopentane carboxylic acid *i*-propyl ester (38). R_f 0.73 (P.E. 30–40 °C/EtOAc, 95:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.09–0.26 (q, J=7.8 Hz, 6H, OSiCH_2CH$_3$, *cis*+*trans*), 0.56 (t, J=7.8 Hz, 9H, OSiCH$_2$CH_3, *cis*), 0.59 (t, J=7.8 Hz, 9H, OSiCH$_2$CH_3, *trans*), 1.02 (d, J=6.3 Hz, 3H, CH_3, *trans*), 1.03 (d, J=6.3 Hz, 3H, CH_3, *cis*), 1.05 (d, J=6.3 Hz, 3H, CH_3, *trans*), 1.06 (d, J=6.3 Hz, 3H, CH_3, *cis*), 1.42–1.48 (m, 1H, CH_{eq}H$_{ax}$CHCO$_2$*i*Pr, *cis*), 1.49–1.54 (m, 1H, CH_{eq}H$_{ax}$-CHCO$_2$*i*Pr, *trans*), 1.79–1.86 (m, 1H, CH$_{eq}H_{ax}$CHCO$_2$*i*Pr, *trans*), 2.11–2.16 (m, 1H, CH$_{eq}H_{ax}$CHCO$_2$*i*Pr, *cis*), 2.17 (dt, J=12.9, 7.7 Hz, 1H, CH_{eq}H$_{ax}$CH$_2$CH, *trans*), 2.27 (ddd, J=12.9, 7.7, 5.9 Hz, 1H, CH$_{eq}H_{ax}$CH$_2$CH, *trans*), 2.29–2.32 (m, 1H, CH_{eq}H$_{ax}$CH$_2$CH, *cis*), 2.68 (ddd, J=12.0, 11.0, 9.2 Hz, 1H, CH$_{eq}H_{ax}$CH$_2$CH, *cis*), 2.70 (dt, J=11.0, 6.3 Hz, 1H, CHCO$_2$*i*Pr, *trans*), 2.89 (ddd, J=11.0, 7.4, 3.7 Hz, 1H, CHCO$_2$*i*Pr, *cis*), 4.74–4.82 (m, 1H, OCH(CH$_3$)$_2$, *cis*+*trans*), 4.85 (d, J=6.3 Hz, 1H, CHOSi, *trans*), 5.13 (d, J=3.7 Hz, 1H, CHOSi, *cis*), 6.93–7.19 (m, 10H, Ph, *cis*+*trans*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 5.2 (OSiCH$_2$-CH$_3$, *trans*), 5.4 (OSiCH$_2$CH$_3$, *cis*), 7.2 (OSiCH$_2$$CH_3$, *trans*), 7.4 (OSiCH$_2$$CH_3$, *cis*), 22.2 ($CH_3$, *trans*), 22.3 ($CH_3$, *cis*), 22.5 ($CH_2CH_2$CH, *cis*), 25.7 ($CH_2CH_2$CH, *trans*), 32.8 ($CH_2$CHCO$_2$*i*Pr, *cis*), 35.5 ($CH_2$CHCO$_2$*i*Pr, *trans*), 50.2 ($CHCO_2$*i*Pr, *cis*), 51.7 ($CHCO_2$*i*Pr, *trans*), 59.5 ($CPh_2$, *trans*), 61.7 ($CPh_2$, *cis*), 68.2 (OC$H$(CH$_3$)$_2$, *cis*), 68.3 (OC$H$(CH$_3$)$_2$, *trans*), 81.2 ($C$HOSi, *cis*), 82.1 ($C$HOSi, *trans*), 126.1 (Ph, *cis*+*trans*), 126.4 (Ph, *cis*+*trans*), 126.9 (Ph, *cis*), 127.8 (Ph, *trans*), 127.9 (Ph, *trans*), 128.0 (Ph, *trans*), 128.4 (Ph, *cis*), 128.6 (Ph, *cis*), 128.9 (Ph, *cis*), 129.8 (Ph, *trans*), 145.1 (Ph, *trans*), 145.8 (Ph, *cis*), 146.6 (Ph, *cis*), 146.8 (Ph, *trans*), 172.6 (CO$_2$*i*Pr, *cis*), 175.2 (CO$_2$*i*Pr, *trans*); FTIR (film) ν 3059, 3028, 2955, 2912, 2876, 1728, 1661, 1651, 1599, 1495, 1447, 1373, 1265, 1109 cm^{-1}; LRMS (FAB$^+$) *m/z* 439 (M$^+$+H, 33), 409 (42), 367 (25), 349 (38), 219 (77); HRMS (FAB$^+$) calcd for $C_{27}H_{39}O_3Si$ (M$^+$+H) 439.26680, found 439.26640; Crystal data for $C_{27}H_{38}O_3Si$,[56] M=438.66, triclinic, a=8.6086(11) Å, b=8.9819(12) Å, c=17.411(2) Å, U=1285.6(3) Å^3, T=293 K, space group $P\,1$, Z=2, μ(Mo Kα) 0.115 mm^{-1}, 11181 reflections measured, 5848 unique F^2 values used in refinement (R_{int}=0.0210), R_1[4707 with $F^2>2\sigma$]=0.0543, wR_2(all data)=0.1570.

4.6.6. 4,4-Dimethyl-2-triethylsilyloxy-cyclopentane carboxylic acid methyl ester (39). R_f 0.59 (P.E. 30–40 °C/EtOAc, 90:10); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.50–0.56 (q, J=7.9 Hz, 6H, OSiCH_2CH$_3$, *cis*+*trans*), 0.88–0.93 (t, J=7.9 Hz, 9H, OSiCH$_2$CH_3, *cis*+*trans*), 0.95 (s, 3H, CH_3, *cis*), 1.05 (s, 3H, CH_3, *trans*), 1.06 (s, 3H, CH_3, *trans*), 1.13 (s, 3H, CH_3, *cis*), 1.45 (dd, J=12.9, 7.2 Hz, 1H, CH$_{eq}H_{ax}$CHOSi, *trans*), 1.54 (dd, J=12.9, 7.7 Hz, 1H, CH_{eq}H$_{ax}$CHCO$_2$CH$_3$, *cis*), 1.56 (dd, J=13.3, 3.7 Hz, 1H, CH_{eq}H$_{ax}$CHOSi, *cis*), 1.58 (dd, J=12.9, 10.0 Hz, 1H, CH$_{eq}H_{ax}$CHCO$_2$CH$_3$, *trans*), 1.71 (dd, J=13.3, 5.7 Hz, 1H, CH$_{eq}H_{ax}$CHOSi, *cis*), 1.77 (dd, J=12.9, 7.2 Hz, 1H, CH_{eq}H$_{ax}$CHOSi, *trans*), 1.79 (dd, J=12.9, 8.9 Hz, 1H, CH_{eq}H$_{ax}$CHCO$_2$CH$_3$, *trans*), 2.09 (dd, J=12.9, 11.0 Hz, 1H, CH$_{eq}H_{ax}$CHCO$_2$CH$_3$, *cis*), 2.83 (ddd, J=10.0, 8.9, 7.2 Hz, 1H, CHCO$_2$CH$_3$, *trans*), 2.93 (ddd, J=11.0, 7.7, 5.7 Hz, 1H, CHCO$_2$CH$_3$, *cis*), 3.63 (s, 3H, OCH_3, *cis*), 3.65 (s, 3H, OCH_3, *trans*), 4.45 (q, J=7.2 Hz, 1H, CHOSi, *trans*), 4.53 (td, J=5.7, 3.7 Hz, 1H, CHOSi, *cis*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 4.4 (OSiCH$_2$CH$_3$, *cis*),

4.6 ($OSiCH_2CH_3$, *trans*), 6.4 ($OSiCH_2CH_3$, *cis*), 6.7 ($OSiCH_2CH_3$, *trans*), 27.3 (CH_3, *cis*), 30.3 (CH_3, *trans*), 36.6 ($C(CH_3)_2$, *cis*), 37.2 ($C(CH_3)_2$, *trans*), 40.6 (CH_2, *cis*), 43.0 (CH_2, *trans*), 50.1 (CH_2, *trans*), 50.5 (CH_2, *cis*), 50.8 ($CHCO_2CH_3$, *cis*), 51.2 (OCH_3, *cis*), 51.5 ($CHCO_2CH_3$, *trans*), 53.2 (OCH_3, *trans*), 75.4 (*C*HOSi, *cis*), 76.5 (*C*HOSi, *trans*), 173.1 (CO_2CH_3, *cis*), 175.9 (CO_2CH_3, *trans*); FTIR (film) ν 2955, 2876, 1740, 1460, 1435, 1171 cm^{-1}; LRMS (FAB^+) *m/z* 287 (M^++H, 3), 257 (10), 255 (5), 155 (18), 125 (60), 95 (100); HRMS (CI^+) calcd for $C_{15}H_{31}O_3Si$ (M^++H) 287.20423, found 287.20397.

4.6.7. 4-(3-Triethylsilanyloxy-propyl)-5*H*-furan-2-one (40). R_f 0.62 (EtOAc); ^1H NMR (300 MHz, CD_2Cl_2) δ 0.49 (q, *J*=7.8 Hz, 6H, $OSiCH_2CH_3$), 0.88 (t, *J*=7.8 Hz, 9H, $OSiCH_2CH_3$), 1.70–1.75 (m, 2H, CH_2CH_2OSi), 2.42 (td, *J*=7.9, 1.8 Hz, 2H, CH_2CH_2C=), 3.58 (t, *J*=7.8 Hz, 2H, CH_2OSi), 4.67 (d, *J*=1.8 Hz, 2H, =CCH_2O), 5.71–5.76 (m, 1H, =$CHCO_2R$); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 3.2 ($OSiCH_2CH_3$), 5.7 ($OSiCH_2CH_3$), 24.4 (CH_2CH_2OSi), 29.6 (CH_2CH_2C=), 60.8 (CH_2OSi), 72.4 (OCH_2C=), 114.3 (=$CHCO_2R$), 170.0 (C=$CHCO_2R$), 173.1 (CO_2R); FTIR (film) ν 2957, 2876, 1747, 1655, 1456, 1414, 1379, 1238, 1074 cm^{-1}; LRMS (DCI^+) *m/z* 257 (M^++H, 81), 227 (47), 197 (12), 115 (15); HRMS (DCI^+) calcd for $C_{13}H_{25}O_3Si$ (M^++H) 257.15728, found 257.15669.

4.6.8. Methyl (*E*)-3-methyl-6-triethylsilanyloxy-hex-2-enoate (41). R_f 0.70 (P.E. 30–40 °C/EtOAc, 95:5); ^1H NMR (300 MHz, $CDCl_3$) δ 0.52 (q, *J*=7.8 Hz, 6H, $OSiCH_2CH_3$), 0.89 (t, *J*=7.8 Hz, 9H, $OSiCH_2CH_3$), 1.60–1.65 (m, 2H, CH_2CH_2OSi), 2.09 (d, *J*=1.2 Hz, 3H, CH_3), 2.14 (td, *J*=7.8, 1.1 Hz, 2H, CH_2CH_2C=), 3.52 (t, *J*=6.5 Hz, 2H, CH_2OSi), 3.61 (s, 3H, OCH_3), 5.61–5.64 (m, 1H, =$CHCO_2CH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 3.5 ($OSiCH_2CH_3$), 5.7 ($OSiCH_2CH_3$), 17.8 (CH_3), 29.7 (CH_2CH_2OSi), 36.3 (CH_2CH_2C=), 49.7 (OCH_3), 61.1 (CH_2OSi), 114.2 (=$CHCO_2CH_3$), 159.0 (C=$CHCO_2CH_3$), 166.2 (CO_2CH_3); FTIR (film) ν 2876, 1728, 1651, 1435, 1360, 1101 cm^{-1}; LRMS (DCI^+) *m/z* 273 (M^++H, 100), 258 (5), 243 (34), 132 (28); HRMS (DCI^+) calcd for $C_{14}H_{29}O_3Si$ (M^++H) 273.18858, found 273.18821.

4.6.9. Methyl 1-triethylsilanyloxy-octahydro-indene-2-carboxylate (42). R_f 0.80 (P.E. 30–40 °C/EtOAc, 90:10); ^1H NMR (500 MHz, $CDCl_3$) δ 0.55–0.58 (q, *J*=7.8 Hz, 6H, $OSiCH_2CH_3$), 0.90–0.97 (t, *J*=7.8 Hz, 9H, $OSiCH_2CH_3$), 1.05–2.34 (m, 12H, CH_2 and CH), 2.58–3.10 (m, 1H, $CHCO_2CH_3$), 3.64–3.68 (s, 3H, OCH_3), 3.73–4.39 (m, 1H, CHOSi); ^{13}C NMR (125 MHz, $CDCl_3$) δ 3.4–3.9 ($OSiCH_2CH_3$), 5.7–5.8 ($OSiCH_2CH_3$), 19.9–33.5 (CH_2), 33.9–52.3 (CH, OCH_3), 75.6 (CHOSi), 77.7 (CHOSi), 78.2 (CHOSi), 78.3 (CHOSi), 78.5 (CHOSi), 80.2 (CHOSi), 172.9 (CO_2CH_3), 173.2 (CO_2CH_3), 173.6 (CO_2CH_3), 175.7 (CO_2CH_3), 176.2 (CO_2CH_3), 176.4 (CO_2CH_3); FTIR (film) ν 3053, 2930, 2878, 2855, 1732, 1435, 1265 cm^{-1}; LRMS (FAB^+) *m/z* 313 (M^++H, 8), 283 (100), 267 (5), 251 (31), 221 (34), 207 (25); HRMS (FAB^+) calcd for $C_{17}H_{33}O_3Si$ (M^++H) 313.21988, found 313.21948.

4.6.10. Triethyl-(3-methoxy-1,5,6,7,8,9-hexahydro-benzo[c]oxepin-1-yloxy)-silane (43). R_f 0.57 (P.E. 30–40 °C/EtOAc, 90:10); ^1H NMR (300 MHz, $CDCl_3$) δ 0.56 (q, *J*=7.9 Hz, 6H, $OSiCH_2CH_3$), 0.88 (t, *J*=7.9 Hz, 9H, $OSiCH_2CH_3$), 1.51–1.54 (m, 4H, $CH_2CH_2CH_2CH_2$), 1.90–1.94 (m, 2H, CH_2CH_2C=), 2.08–2.11 (m, 2H, CH_2CH_2C=), 2.95 (d, *J*=6.6 Hz, 2H, =CCH_2CH=), 3.59 (s, 3H, OCH_3), 5.35 (t, *J*=6.6 Hz, 1H, CH_2CH=), 6.02 (s, 1H, OCHOSi); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 4.8 ($OSiCH_2CH_3$), 6.8 ($OSiCH_2CH_3$), 28.5 (CH_2), 28.8 (CH_2), 31.9 (CH_2), 35.3 (CH_2), 37.3 (=CCH_2CH=), 51.8 (OCH_3), 116.2 (CH=$C(O)OCH_3$), 119.4 (CH_2C=CCH_2), 132.4 (OCHOSi), 138.4 (CH_2C=CCH_2), 174.1 (=$C(O)OCH_3$); FTIR (film) ν 2934, 2878, 1736, 1439, 1265, 1173 cm^{-1}; LRMS (ES^+) *m/z* 328 (M^++NH_4, 18), 311 (M^++H, 100), 246 (11); HRMS (ES^+) calcd for $C_{17}H_{31}O_3Si$ (M^++H) 311.2042, found 311.2439.

4.6.11. 2-Triethylsilyloxy-3,4-phenyl-cyclopentane carboxylic acid methyl ester (44). R_f 0.79 (P.E. 30–40 °C/EtOAc, 90:10); ^1H NMR (500 MHz, $CDCl_3$) δ 0.62 (q, *J*=7.9 Hz, 6H, $OSiCH_2CH_3$, *cis*+*trans*), 0.91 (t, *J*=7.9 Hz, 9H, $OSiCH_2CH_3$, *cis*+*trans*), 2.88 (dd, *J*=11.2, 7.8 Hz, 1H, $CH_{eq}H_{ax}CHCO_2CH_3$, *cis*), 2.98 (dd, *J*=15.0, 8.5 Hz, 1H, $CH_{eq}H_{ax}CHCO_2CH_3$, *trans*), 3.11 (dt, *J*=8.5, 6.7 Hz, 1H, $CH_2CHCO_2CH_3$, *trans*), 3.19 (dd, *J*=15.0, 8.5 Hz, 1H, $CH_{eq}H_{ax}CHCO_2CH_3$, *trans*), 3.28 (dt, *J*=7.8, 6.2 Hz, 1H, $CH_2CHCO_2CH_3$, *cis*), 3.47 (dd, *J*=11.2, 7.8 Hz, 1H, $CH_{eq}H_{ax}CHCO_2CH_3$, *cis*), 3.68 (s, 3H, OCH_3, *trans*), 3.73 (s, 3H, OCH_3, *cis*), 5.34 (d, *J*=6.2 Hz, 1H, CHOSiEt$_3$, *cis*), 5.51 (d, *J*=6.7 Hz, 1H, CHOSiEt$_3$, *trans*), 7.13–7.64 (m, 4H, Ph, *cis*+*trans*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 4.0 ($OSiCH_2CH_3$, *trans*), 5.7 ($OSiCH_2CH_3$, *trans*), 33.2 (CH_2, *trans*), 50.6 (OCH_3, *trans*), 53.6 ($CHCO_2CH_3$, *trans*), 78.2 (CHOSiEt$_3$, *trans*), 123.0 (Ph, *trans*), 123.4 (Ph, *trans*), 126.1 (Ph, *trans*), 127.5 (Ph, *trans*), 138.6 (Ph, *trans*), 142.9 (Ph, *trans*), 174.0 (CO_2CH_3); FTIR (film) ν 2955, 2877, 1731, 1637, 1437, 1351, 909 cm^{-1}; LRMS (ES^+) *m/z* 324 (M^++NH_4, 100), 307 (M^++H, 44), 246 (61), 175 (93); HRMS (ES^+) calcd for $C_{17}H_{27}O_3Si$ (M^++H) 307.1729, found 307.1735.

4.6.12. Methyl (1*S*,2*S*,3*S*,4*S*)-2-triethylsilyloxy-3,4-isopropylidene-dioxy-cyclopentane carboxylate (45a). R_f 0.53 (P.E. 30–40 °C/EtOAc, 95:5); ^1H NMR (500 MHz, $CDCl_3$) δ 0.51 (q, *J*=7.7 Hz, 6H, $OSiCH_2CH_3$), 0.86 (t, *J*=7.7 Hz, 9H, $OSiCH_2CH_3$), 1.21 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.89 (dd, *J*=13.8, 6.3 Hz, 1H, $CH_{eq}H_{ax}CHCO_2CH_3$), 2.24 (ddd, *J*=13.8, 10.7, 5.4 Hz, 1H, $CH_{eq}H_{ax}CHCO_2CH_3$), 3.02 (ddd, *J*=10.7, 6.3, 4.0 Hz, 1H, $CHCO_2CH_3$), 3.60 (s, 3H, OCH_3), 4.20 (d, *J*=5.4 Hz, 1H, CHCHOSiEt$_3$), 4.28 (d, *J*=4.0 Hz, 1H, CHOSiEt$_3$), 4.67 (t, *J*=5.4 Hz, 1H, CH_2CHO); ^{13}C NMR (125 MHz, $CDCl_3$) δ 3.7 ($OSiCH_2CH_3$), 5.7 ($OSiCH_2CH_3$), 22.8 (CH_3), 25.1 (CH_3), 30.8 (CH_2), 46.2 ($CHCO_2CH_3$), 50.4 (OCH_3), 76.8 (CHOSiEt$_3$), 78.2 (CH_2CHO), 84.9 (OCHCHOSiEt$_3$), 108.9 ($OC(CH_3)_2$), 171.1 (CO_2CH_3); FTIR (film) ν 2936, 2878, 1733, 1439, 1376, 1262, 902 cm^{-1}; LRMS (FAB^+) *m/z* 331 (M^++H, 20), 301 (100), 241 (15), 211 (10), 187 (10); HRMS (FAB^+) calcd for $C_{16}H_{31}O_5Si$ (M^++H) 331.19406, found 331.19408; $[\alpha]_D^{20}$: −20.7 (*c*=0.50, $CHCl_3$/MeOH 9:1).

4.6.13. 2-Triethylsilanyloxy-4-benzyloxy-cyclopentane carboxylic acid methyl ester (46a). R_f 0.68 (P.E. 30–40 °C/EtOAc, 90:10); ^1H NMR (500 MHz, $CDCl_3$) δ 0.54 (q, *J*=7.7 Hz, 6H, $OSiCH_2CH_3$), 0.90 (t, *J*=7.7 Hz, 9H,

OSiCH$_2$CH$_3$), 1.71 (ddd, J=13.6, 7.0, 6.6 Hz, 1H, CH$_{eq}$-H$_{ax}$CHOSiEt$_3$), 1.93 (ddd, J=13.3, 9.9, 6.5 Hz, 1H, CH$_{eq}$-H$_{ax}$CO$_2$CH$_3$), 2.09 (ddd, J=13.3, 8.1, 3.6 Hz, 1H, CH$_{eq}$H$_{ax}$CO$_2$CH$_3$); 2.31 (ddd, J=13.6, 7.2, 6.7 Hz, 1H, CH$_{eq}$H$_{ax}$CHOSiEt$_3$), 2.92 (ddd, J=9.9, 8.1, 7.8 Hz, 1H, CHCO$_2$CH$_3$), 3.64 (s, 3H, OCH$_3$), 3.95 (m, 1H, CHOBn), 4.29 (ddd, J=7.8, 7.2, 7.0 Hz, 1H, CHOSiEt$_3$), 4.42 (s, 2H, ArCH$_2$O); 7.29–7.42 (m, 5H, Ph); ^{13}C NMR (100 MHz, CDCl$_3$) δ 4.6 (OSiCH$_2$CH$_3$), 6.7 (OSiCH$_2$CH$_3$), 34.6 (CH$_2$), 42.0 (CH$_2$), 51.1 (OCH$_3$), 51.7 (CHCO$_2$CH$_3$), 70.7 (OCH$_2$Ph), 74.5 (CHOBn), 76.9 (CHOSiEt$_3$), 127.5 (Ph), 127.6 (Ph), 128.4 (Ph), 138.5 (Ph), 175.6 (CO$_2$CH$_3$); FTIR (film) ν 2953, 2912, 2876, 1739, 1496, 1455, 1436, 1354, 1116, 1058, 736, 697 cm^{-1}; LRMS (ES$^+$) m/z 382 (M$^+$+NH$_4$, 72), 365 (M$^+$+H, 100), 251 (10); HRMS (ES$^+$) calcd for C$_{20}$H$_{36}$NO$_4$Si (M$^+$+NH$_4$) 382.2414, found 382.2404.

4.6.14. 6-Triethylsilanyloxy-5-heptenoate (47). R_f 0.69 (P.E. 30–40 °C/EtOAc, 90:10); ^{1}H NMR (500 MHz, CDCl$_3$) δ 0.62–0.66 (q, J=8.0 Hz, 6H, OSiCH$_2$CH$_3$, *cis*+*trans*), 0.94–0.99 (t, J=8.0 Hz, 9H, OSiCH$_2$CH$_3$, *cis*+*trans*), 1.62–1.65 (m, 2H, CH$_2$CH$_2$CH$_2$, *cis*+*trans*), 1.71 (d, J=1.0 Hz, 3H, CH$_3$, *trans*), 1.77 (d, J=1.1 Hz, 3H, CH$_3$, *cis*), 1.95 (q, J=7.5 Hz, 2H, CH$_2$CH$_2$CH=, *trans*), 2.02 (q, J=7.2 Hz, 2H, CH$_2$CH$_2$CH=, *cis*), 2.29 (t, J=7.5 Hz, 2H, CH$_2$CO$_2$CH$_3$, *cis*+*trans*), 3.65 (s, 3H, OCH$_3$, *cis*), 3.66 (s, 3H, OCH$_3$, *trans*), 4.33 (tq, J=7.2, 1.1 Hz, 1H, CH=C(OSi)CH$_3$, *cis*), 4.60 (tq, J=7.5, 1.0 Hz, 1H, CH=C(OSi)CH$_3$, *trans*); ^{13}C NMR (125 MHz, CDCl$_3$) δ 4.9 (OSiCH$_2$CH$_3$, *cis*), 5.0 (OSiCH$_2$CH$_3$, *trans*), 6.4 (OSiCH$_2$CH$_3$, *cis*), 6.5 (OSiCH$_2$CH$_3$, *trans*), 17.6 (CH$_3$, *trans*), 22.6 (CH$_3$, *cis*), 24.6 (CH$_2$CH$_2$C=, *cis*), 25.6 (CH$_2$CH$_2$CH$_2$, *cis*+*trans*), 26.5 (CH$_2$CH$_2$C=, *trans*), 33.3 (CH$_2$CO$_2$CH$_3$, *trans*), 33.7 (CH$_2$CO$_2$CH$_3$, *cis*), 51.3 (OCH$_3$, *cis*), 51.4 (OCH$_3$, *trans*), 106.4 (CH=C(OSi)CH$_3$, *trans*), 107.0 (CH=C(OSi)CH$_3$, *cis*), 147.5 (CH=C(OSi)CH$_3$, *cis*), 148.7 (CH=C(OSi)CH$_3$, *trans*), 174.2 (CO$_2$CH$_3$, *trans*), 174.3 (CO$_2$CH$_3$, *cis*); FTIR (film) ν 3053, 2955, 2914, 2878, 1732, 1670, 1437, 1362, 1265 cm^{-1}; LRMS (CI$^+$) m/z 273 (M$^+$+H, 51), 243 (24), 103 (100); HRMS (CI$^+$) calcd for C$_{14}$H$_{29}$O$_3$Si (M$^+$+H) 273.18858, found 273.18830.

4.6.15. Methyl 4,4-dimethyl-5-oxiranyl-pentanoate (48). R_f 0.28 (P.E. 30–40 °C/EtOAc, 90:10); ^{1}H NMR (500 MHz, CDCl$_3$) δ 0.91 (s, 3H, CH$_3$), 0.93 (s, 3H, CH$_3$), 1.34–1.36 (m, 2H, CH$_2$CHOCH$_2$), 1.56–1.66 (m, 2H, CH$_2$CH$_2$CO$_2$CH$_3$); 2.20–2.27 (m, 2H, CH$_2$CH$_2$CO$_2$CH$_3$); 2.35 (dd, J=5.0, 2.7 Hz, 1H, CH$_a$HO), 2.69 (dd, J=5.0, 4.1 Hz, 1H, CHH_bO), 2.89–2.90 (m, 1H, CHO), 3.59 (s, 3H, OCH$_3$); ^{13}C NMR (125 MHz, CDCl$_3$) δ 26.8 (CH$_3$), 26.9 (CH$_3$), 29.3 (CH$_2$CH$_2$CO$_2$CH$_3$); 32.8 (CH$_2$CO$_2$CH$_3$); 36.6 (C(CH$_3$)$_2$), 44.4 (CH$_2$), 46.7 (CH$_2$O), 49.2 (CHO), 51.6 (OCH$_3$), 174.5 (CO$_2$CH$_3$); FTIR (film) ν 2958, 2924, 2850, 1730, 1463, 1436, 1264, 1172 cm^{-1}; LRMS (ES$^+$) m/z 187 (M$^+$+H, 100), 204 (M$^+$+NH$_4$, 25); HRMS (ES$^+$) calcd for C$_{10}$H$_{19}$O$_3$ (M$^+$+H) 187.1320, found 187.1328.

4.6.16. 7-Phenyl-6-triethylsilanyloxy-6-heptenoic acid methyl ester (49). R_f 0.76 (P.E. 30–40 °C/EtOAc, 90:10); ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.60 (q, J=7.8 Hz, 6H, OSiCH$_2$CH$_3$), 0.90 (t, J=7.8 Hz, 9H, OSiCH$_2$CH$_3$), 1.40–1.62 (m, 4H, CH$_2$CH$_2$CH$_2$CH$_2$), 1.96–2.02 (m, 2H, CH$_2$-C(OSiEt$_3$)=), 2.24 (t, J=7.2 Hz, 2H, CH$_2$CO$_2$CH$_3$), 3.31 (d, J=7.1 Hz, 1H, =CHCH$_2$Ph), 3.59 (s, 3H, OCH$_3$), 4.55 (t, J=7.1 Hz, 1H, =CHCH$_2$Ph), 7.09–7.28 (m, 5H, Ph); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ 5.7 (OSiCH$_2$CH$_3$), 7.2 (OSiCH$_2$CH$_3$), 27.0 (CH$_2$), 31.9 (CH$_2$), 34.6 (CH$_2$), 36.7 (CH$_2$), 51.9 (OCH$_3$), 54.8 (CH$_2$Ph), 107.0 (=CHCH$_2$Ph), 128.6 (Ph), 128.7 (Ph), 129.0 (Ph), 132.6 (Ph), 151.1 (C(OSiEt$_3$)=CH), 167.1 (CO$_2$CH$_3$); FTIR (film) ν 3051, 2930, 2876, 1736, 1435, 1264, 1016 cm^{-1}; LRMS (CI$^+$) m/z 363 (M$^+$+H, 30), 348 (28), 332 (19), 232 (14); HRMS (CI$^+$) calcd for C$_{21}$H$_{35}$O$_3$Si (M$^+$+H) 363.23553, found 363.23519.

4.6.17. (2*E*)-4,4-Dimethyl-triethylsilanyloxy-nona-2,7-dienoic acid methyl ester (50). R_f 0.79 (P.E. 30–40 °C/EtOAc, 90:10); ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.56 (q, J=7.9 Hz, 6H, OSiCH$_2$CH$_3$), 0.89 (t, J=7.9 Hz, 9H, OSiCH$_2$CH$_3$), 0.99 (s, 6H, C(CH$_3$)$_2$), 1.25–1.32 (m, 2H, CH$_2$CH$_2$CH=), 1.70 (s, 3H, CH$_3$C(OSiEt$_3$)=CH), 1.79–1.80 (m, 2H, CH$_2$CH=), 3.68 (s, 3H, OCH$_3$), 4.24 (t, J=6.6 Hz, 1H, CH$_2$CH=), 6.65 (d, J=15.8 Hz, 1H, =CHCO$_2$CH$_3$), 6.84 (d, J=15.8 Hz, 1H, CH=CHCO$_2$CH$_3$); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ 6.0 (OSiCH$_2$CH$_3$), 7.1 (OSiCH$_2$CH$_3$), 21.0 (CH$_2$CH$_2$CH=), 23.1 (CH=CCH$_3$), 26.6 (C(CH$_3$)$_2$), 37.2 (C(CH$_3$)$_2$), 42.6 (CH$_2$CH=), 51.8 (OCH$_3$), 108.5 (=CHCH$_2$), 117.7 (=CHCO$_2$CH$_3$), 147.2 (CH=CHCO$_2$CH$_3$), 159.0 (CH=C(CH$_3$)OSiEt$_3$), 167.5 (CO$_2$CH$_3$); FTIR (film) ν 2959, 2914, 2877, 1717, 1651, 1465, 1437, 1380, 902 cm^{-1}; LRMS (FAB$^+$) m/z 327 (M$^+$+H, 100), 297 (60), 253 (34), 225 (21), 185 (79); HRMS (CI$^+$) calcd for C$_{18}$H$_{35}$O$_3$Si (M$^+$+H) 327.23553, found 327.23496.

4.6.18. Methyl 7-triethylsilanyloxy-6-heptenoate (51). R_f 0.70 (P.E. 30–40 °C/EtOAc, 90:10); ^{1}H NMR (500 MHz, CDCl$_3$) δ 0.53–0.67 (q, J=7.9 Hz, 6H, OSiCH$_2$CH$_3$, *cis*+*trans*), 0.88–0.98 (t, J=7.9 Hz, 9H, OSiCH$_2$CH$_3$, *cis*+*trans*), 1.27–1.40 (m, 2H, CH$_2$CH$_2$CH=, *cis*+*trans*), 1.56–1.68 (m, 2H, CH$_2$CH$_2$CO$_2$CH$_3$, *cis*+*trans*), 1.83–1.92 (qd, J=7.4, 1.0 Hz, 2H, CH$_2$CH=, *trans*), 2.05–2.11 (qd, J=7.2, 1.3 Hz, 2H, CH$_2$CH=, *cis*), 2.25–2.35 (m, 2H, CH$_2$CO$_2$CH$_3$, *cis*+*trans*), 3.65 (s, 3H, OCH$_3$, *cis*+*trans*), 4.41 (q, J=7.2 Hz, 1H, =CHCH$_2$, *cis*), 4.96 (dt, J=12.0, 7.4 Hz, 1H, =CHCH$_2$, *trans*), 6.21 (d, J=7.2 Hz, 1H, =CHOSi, *cis*), 6.24 (d, J=12.0 Hz, 1H, =CHOSi, *trans*); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ 4.4 (OSiCH$_2$CH$_3$, *cis*), 5.4 (OSiCH$_2$CH$_3$, *trans*), 6.9 (OSiCH$_2$CH$_3$, *cis*), 7.1 (OSiCH$_2$CH$_3$, *trans*), 23.5 (CH$_2$), 24.7 (CH$_2$), 24.9 (CH$_2$), 27.3 (CH$_2$), 29.5 (CH$_2$), 30.3 (CH$_2$), 34.3 (CH$_2$), 34.4 (CH$_2$), 51.7 (OCH$_3$, *cis*+*trans*), 110.4 (=CHCH$_2$, *cis*), 111.3 (=CHCH$_2$, *trans*), 139.0 (=CHOSi, *cis*), 140.6 (=CHOSi, *trans*), 174.3 (CO$_2$CH$_3$, *cis*), 174.6 (CO$_2$CH$_3$, *trans*); FTIR (film) ν 2937, 2877, 1732, 1652, 1436, 907 cm^{-1}; LRMS (CI$^+$) m/z 273 (M$^+$+H, 25), 243 (19), 211 (12); 175 (60); HRMS (CI$^+$) calcd for C$_{14}$H$_{29}$O$_3$Si (M$^+$+H) 273.18858, found 273.18832.

4.6.19. Methyl 2-triethylsilyloxycyclohexanecarboxylate (52). R_f 0.55 (P.E. 30–40 °C/EtOAc, 90:10); ^{1}H NMR (500 MHz, CDCl$_3$) δ 0.50–0.57 (q, J=7.9 Hz, 6H, OSiCH$_2$-CH$_3$, *cis*+*trans*), 0.89–0.92 (t, J=7.9 Hz, 9H, OSiCH$_2$CH$_3$,

cis+*trans*), 1.15–1.90 (m, 8H, CH_2, *cis*+*trans*), 2.27–2.30 (m, 1H, CHCO_2CH_3, *cis*), 2.30–2.34 (ddd, *J*=9.7, 9.2, 3.5 Hz, 1H, CHCO_2CH_3, *trans*), 3.63 (s, 3H, OCH_3, *cis*), 3.64 (s, 3H, OCH_3, *trans*), 3.77 (dt, *J*=9.7, 4.3 Hz, 1H, CHOSi, *trans*), 3.96–4.00 (m, 1H, CHOSi, *cis*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 4.4 (OSiCH_2CH$_3$, *cis*), 4.9 (OSiCH_2-CH$_3$, *trans*), 6.5 (OSiCH$_2$$CH_3$, *cis*), 6.8 (OSiCH$_2$$CH_3$, *trans*), 19.7 ($CH_2$, *cis*), 22.0 ($CH_2$, *cis*), 24.3 ($CH_2$, *trans*), 24.4 ($CH_2$, *trans*), 24.5 ($CH_2$, *cis*), 28.6 ($CH_2$, *trans*), 33.6 ($CH_2$, *cis*), 35.2 ($CH_2$, *trans*), 48.4 ($CHCO_2CH_3$, *cis*), 51.2 (OCH$_3$, *cis*), 51.3 (OCH$_3$, *trans*), 52.5 ($CHCO_2CH_3$, *trans*), 68.2 ($C$HOSi, *cis*), 72.2 ($C$HOSi, *trans*), 174.3 ($CO_2CH_3$, *cis*), 175.6 ($CO_2CH_3$, *trans*); FTIR (film) ν 2937, 2876, 1740, 1435, 1173 cm^{-1}; LRMS (CI$^+$) *m*/*z* 272 (M$^+$, 14), 243 (35), 175 (10), 57 (100); HRMS (CI$^+$) calcd for $C_{14}H_{28}O_3Si$ (M$^+$) 272.18076, found 272.17809.

4.6.20. 2-Triethylsilyloxy-cycloheptane carboxylic acid methyl ester (53). R_f 0.70 (P.E. 30–40 °C/EtOAc, 90:10); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.54 (q, *J*=7.9 Hz, 6H, OSiCH_2CH$_3$, *cis*+*trans*), 0.92 (t, *J*=7.9 Hz, 9H, OSiCH$_2$-CH_3, *trans*), 0.93 (t, *J*=7.9 Hz, 9H, OSiCH$_2$CH_3, *cis*), 1.34–1.88 (m, 10H, CH_2, *cis*+*trans*), 2.50–2.55 (m, 1H, CHCO$_2$CH$_3$, *cis*+*trans*), 3.65 (s, 3H, OCH_3, *cis*), 3.66 (s, 3H, OCH_3, *trans*), 4.00 (dt, *J*=8.3, 3.6 Hz, 1H, CHOSi, *trans*), 4.00 (dt, *J*=6.8, 3.4 Hz, 1H, CHOSi, *cis*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 3.9 (OSiCH_2CH$_3$, *cis*), 4.0 (OSiCH_2-CH$_3$, *trans*), 5.7 (OSiCH$_2$$CH_3$, *trans*), 5.8 (OSiCH$_2$$CH_3$, *cis*), 21.0 ($CH_2$, *trans*), 21.3 ($CH_2$, *cis*), 22.3 ($CH_2$, *cis*), 25.1 ($CH_2$, *trans*), 25.6 ($CH_2$, *cis*), 26.3 ($CH_2$, *trans*), 26.8 ($CH_2$, *trans*), 27.4 ($CH_2$, *cis*), 35.1 ($CH_2$, *cis*), 35.6 ($CH_2$, *trans*), 50.3 (OCH$_3$, *cis*), 50.8 (OCH$_3$, *trans*), 50.9 ($CHCO_2CH_3$, *cis*), 53.6 ($CHCO_2CH_3$, *trans*), 70.7 ($C$HOSi, *cis*), 73.7 ($C$HOSi, *trans*), 174.1 ($CO_2CH_3$, *cis*), 175.4 ($CO_2CH_3$, *trans*); FTIR (film) ν 2937, 2878, 1734, 1458, 1437, 1007, 908 cm^{-1}; LRMS (FAB$^+$) *m*/*z* 287 (M$^+$+H, 18), 257 (100), 115 (45), 87 (69); HRMS (FAB$^+$) calcd for $C_{15}H_{31}O_3Si$ (M$^+$+H) 287.20420, found 287.20413.

4.6.21. Triethyl-(1-methyl-pent-1-enyloxy)-silane (54). R_f 0.86 (P.E. 30–40 °C/EtOAc, 90:10); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.61–0.68 (q, *J*=8.1 Hz, 6H, OSiCH_2CH$_3$, *cis*+*trans*), 0.86 (t, *J*=7.4 Hz, 3H, CH$_2$CH_3, *trans*), 0.87 (t, *J*=7.4 Hz, 3H, CH$_2$CH_3, *cis*), 0.93–0.97 (t, *J*=8.1 Hz, 9H, OSiCH$_2$CH_3, *cis*+*trans*), 1.27–1.34 (m, 2H, CH$_2$CH_2-CH$_3$, *cis*+*trans*), 1.71 (d, *J*=0.7 Hz, 3H, CH_3, *trans*), 1.77 (d, *J*=1.1 Hz, 3H, CH_3, *cis*), 1.87 (q, *J*=7.2 Hz, 2H, CH$_2$CH_2CH=, *trans*), 1.97 (q, *J*=7.3 Hz, 2H, CH$_2$CH_2-CH=, *cis*), 4.37 (tq, *J*=7.3, 1.1 Hz, 1H, CH=C(OSi)CH$_3$, *cis*), 4.63 (tq, *J*=7.2, 0.7 Hz, 1H, CH=C(OSi)CH$_3$, *trans*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 4.9 (OSiCH_2CH$_3$, *cis*), 5.0 (OSiCH_2CH$_3$, *trans*), 6.4 (OSiCH$_2$$CH_3$, *cis*), 6.6 (OSiCH$_2$-$CH_3$, *trans*), 13.6 ($CH_3$, *trans*), 13.9 ($CH_3$, *cis*), 17.6 ($CH_3$C=, *trans*), 22.7 ($CH_3$C=, *cis*), 23.0 (CH$_2$$CH_2CH_2$, *cis*), 23.6 (CH$_2$$CH_2CH_2$, *trans*), 27.4 (CH$_2$$CH_2$C=, *cis*), 29.3 (CH$_2$$CH_2$C=, *trans*), 107.7 ($C$H=C(OSi)CH$_3$, *trans*), 108.4 ($C$H=C(OSi)CH$_3$, *cis*), 146.6 (CH=$C$(OSi)CH$_3$, *cis*), 147.8 (CH=$C$(OSi)CH$_3$, *trans*); FTIR (film) ν 2957, 2878, 1670, 1460, 1240 cm^{-1}; LRMS (CI$^+$) *m*/*z* 215 (M$^+$+H, 21), 185 (41), 157 (14), 115 (68); HRMS (CI$^+$) calcd for $C_{12}H_{27}OSi$ (M$^+$+H) 215.18310, found 215.18272.

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56. Crystallographic data (excluding structure factors) for this structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 220626. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].