Total Synthesis of Balanol and Designed Analogues

K. C. Nicolaou,* Kazunori Koide and Mark E. Bunnage

Abstract: The total synthesis of balanol, a potent protein kinase C inhibitor isolated from the fungus *Verticillium balanoides*, is described. The hexahydroazepine fragment was prepared from D-serine through a sequence of reactions including the diastereoselective allylboration of a derived amino aldehyde and a base-induced 7-*exo-tet* ring closure as key steps. The benzophenone fragment was secured through the initial coupling of the two functionalised aromatic components through an ester linkage, followed by intramolecular nucleophilic attack of an aryl lithium derivative to form the desired ketone bridge. After coupling of the two balanol domains, the adoption of benzyl-derived protecting groups for the latent functionalities then allowed the liberation of balanol in a single step by catalytic hydrogenolysis. Finally, the newly developed synthetic strategy was applied to the synthesis of a variety of designed balanol analogues for biological evaluation.

Keywords
antitumour agents · balanol · enzyme inhibitor · natural product · total synthesis

Introduction

Recent years have witnessed an increasing awareness of the importance of protein kinases as pivotal mediators in an array of cellular events. Although the number of known protein kinases continues to expand, the interest associated with protein kinase C (PKC) remains unparalleled.[1] Protein phosphorylation mediated by PKC is known to lead to a range of cellular responses, including gene expression and cell proliferation,[1, 2] and activated PKC has been implicated in conditions as diverse as cancer, cardiovascular disorders, asthma, inflammation, diabetes, CNS dysfunction and HIV infection.[2] In particular, the observation that the tumour-promoting phorbol esters cause unfettered PKC activation[1d] has suggested that effective inhibitors of PKC could prove useful in cancer chemotherapy.

Balanol (**1**, Fig. 1),[3] a metabolite produced by the fungus *Verticillium balanoides*, represents a significant new development in the quest for effective inhibitors of PKC. Balanol has been found to inhibit the majority of PKC isozymes in the low nanomolar range and its novel structure serves as a new lead for the development of potent and selective PKC inhibitors. Such an endeavour may not only provide useful tools for illuminating signal transduction pathways involving PKC, but may also result in the introduction of novel drugs with considerable therapeutic value.[2] In this paper we present full details of our recent total synthesis of balanol,[4] and demonstrate the utility of the newly developed synthetic strategy by the preparation of a variety of balanol analogues for biological evaluation.

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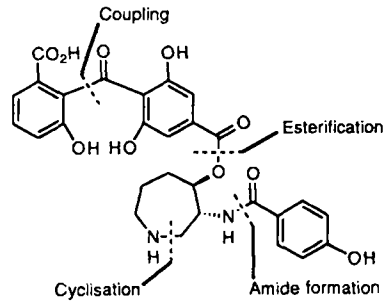

Fig. 1. Strategic bond disconnections of balanol.

1: balanol

Total Synthesis of Balanol

Retrosynthetic Analysis and Strategy: The structural features of balanol suggested the strategic bond disconnections illustrated in Figure 1. Balanol is in essence comprised of two major domains coupled through a central ester linkage. The hexahydroazepine-containing fragment can be simplified by removal of the 4-hydroxybenzoic acid segment through dissection of the amide moiety. We expected that the 7-membered hexahydroazepine ring could be secured through the intramolecular displacement of a suitable leaving group by an amino-derived nucleophile; this 7-*exo-tet* cyclisation is formally allowed according to Baldwin's rules.[5] Furthermore, the potential to generate the hexahydroazepine stereogenic centres through stereocontrolled addition of an appropriate nucleophile to a homochiral α-amino aldehyde derivative was attractive in view of the ready availability of potential homochiral amino acid precursors such as D-serine.

We envisioned synthesising the remaining benzophenone domain of the molecule through conventional Stille-type coupling

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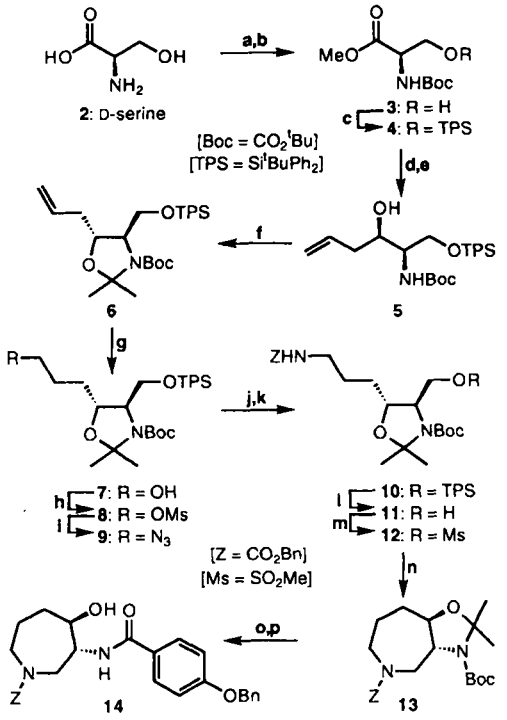
of the appropriately substituted acid chloride and arylstannane components suggested by the disconnection shown in Figure 1. It was anticipated that commercially available 4-bromo-3,5-dihydroxybenzoic acid could be simply elaborated to deliver the acid chloride fragment and a regioselective metallation of a 3-hydroxybenzoic acid surrogate was expected to provide its arylstannane counterpart.

Finally, the amino acid nature of balanol suggested the use of benzyl-derived protecting groups for the functional groups not involved in the coupling steps, since this should allow facile liberation of the natural product by hydrogenolysis.

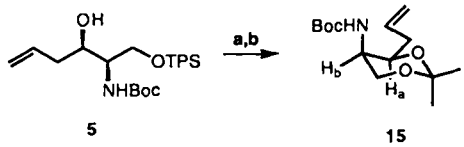
Synthesis of the Hexahydroazepine Domain: Our synthetic approach to the hexahydroazepine fragment is presented in Scheme 1. The readily available homochiral amino acid D-serine



Scheme 1. Synthesis of the hexahydroazepine ring system. Reagents and conditions: a) 1.2 equiv of $(Boc)_2O$, 2.1 equiv of NaOH, 1,4-dioxane, H_2O, 0 → 25 °C, 2 h, 100%; b) 1.1 equiv of K_2CO_3, 2.0 equiv of MeI, DMF, 0 → 25 °C, 2 h, 100%; c) 1.2 equiv of TPSCl, 1.4 equiv of imidazole, DMF, 25 °C, 14 h, 100%; d) 2.5 equiv of DIBALH, toluene, −78 °C, 1.5 h; e) 1.8 equiv of allyl-B(^{t}Ipc)$_2$, Et_2O, −78 °C, 3.5 h; ethanolamine; f) 5.0 equiv of 2,2-dimethoxypropane, 0.01 equiv of CSA, CH_2Cl_2, 25 °C, 3 h, 68% (3 steps); g) 2.2 equiv of 9-BBN, THF, 0 → 25 °C, 20 h; NaOH, H_2O_2, 0 → 25 °C, 5 h, 97%; h) 1.2 equiv of MsCl, 1.5 equiv of Et_3N, CH_2Cl_2, 0 °C, 10 min; i) 6.0 equiv of NaN_3, DMF, 25 °C, 24 h, 98% (2 steps); j) H_2, 0.1 equiv of Pd/C, THF, 19 h; k) 1.15 equiv of benzyl chlorocarbonate, 3.0 equiv of NaOH, 1,4-dioxane, H_2O, 0 °C, 15 min, 100% (2 steps); l) 1.2 equiv of TBAF, THF, 25 °C, 16 h, 96%; m) 1.2 equiv of MsCl, 1.5 equiv of Et_3N, CH_2Cl_2, 0 °C, 20 min; n) 1.2 equiv of KOtBu added over 1 h at 0.02 M, THF, 25 °C, 80% (2 steps); o) excess TFA, CH_2Cl_2, 25 °C, 1 h; p) 1.5 equiv of *p*-(benzyloxy)benzoyl chloride, 5.0 equiv of Et_3N, CH_2Cl_2, 0 → 25 °C, 1.5 h, 73% (2 steps). Boc = CO_2tBu; TPS = tBuPh$_2$Si; DIBALH = di-*i*-butylaluminium hydride; allyl-B(^{t}Ipc)$_2$ = *l*-allyldiisopinocampheylborane; CSA = (±)-camphorsulfonic acid; 9-BBN = 9-borabicyclo[3.3.1]nonane; Ms = $MeSO_2$; TBAF = tetra-*n*-butylammonium fluoride; TFA = CF_3CO_2H.

was first protected as its *N*-Boc derivative[6] by treatment with di-*tert*-butyl dicarbonate (Boc_2O) and then converted to the methyl ester **3** with methyl iodide and potassium carbonate.[6] The remaining hydroxyl group was then silylated to give the fully protected derivative **4** in quantitative overall yield.

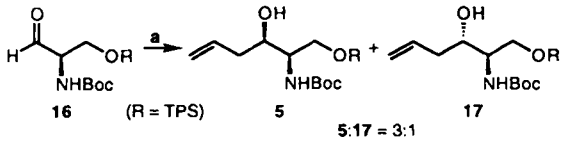
Reduction of **4** with excess DIBALH afforded the corresponding amino aldehyde,[6, 7] which was not isolated but instead treated in situ with Brown's diisopinocampheylborane reagent,[8] allyl-B(^{t}Ipc)$_2$, to yield a 12:1 mixture of amino alcohol diastereoisomers **5**. The stereochemical outcome of allylboration with diisopinocampheylborane is known to be mainly determined by the chirality of the reagent, with the stereodirecting effect due to the substrate being largely overridden.[8] We therefore effected allylboration using the reagent derived from (−)-α-pinene, since this was expected to deliver the desired *syn* amino alcohol arrangement.[8] Indeed, confirmation of the *syn* configuration of **5** was obtained by desilylation with TBAF and conversion to the known acetonide **15** (Scheme 2).[9] The cou-



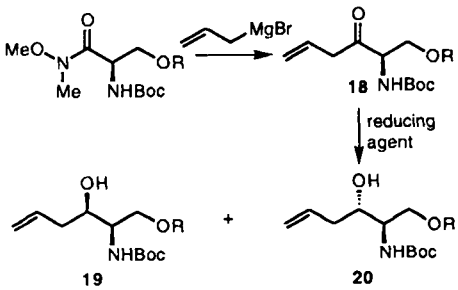
Scheme 2. Determination of configuration of compound **5**: for **15**, $J_{Ha,Hb}$ = 1.7 Hz (ref. [9] $J_{Ha,Hb}$ = 1.5 Hz). Reagents and conditions: a) 1.2 equiv of TBAF, THF, 25 °C, 16 h; b) excess 2-methoxypropene, 0.1 equiv of CSA, CH_2Cl_2, 25 °C, 1 h.

pling constant for the vicinal ring protons in **15** (J_{HaHb} = 1.7 Hz) correlated closely with that reported in the literature for this material (J_{HaHb} = 1.5 Hz)[9] and was inconsistent with that described for the acetonide derived from the alternative *anti* diastereoisomer (J_{HaHb} = 9.5 Hz).[9]

Although this allylation reaction was successful, we were also interested in the possibility of synthesising the *syn* β-amino alcohol **5** by a purely substrate-controlled nucleophilic addition. For example, the allylation of **16** was attempted by reaction with allyltrimethylsilane promoted by tin tetrachloride[10] (Scheme 3) but this approach only afforded the desired adduct **5** with poor *syn* selectivity (3:1) and in low yield (40%). We also investigated the potential for the diastereoselective reduction of a variety of protected α-amino ketones (Scheme 4). Unfortunately, despite extensive investigation, only poor to moderate *syn* selectivities were obtained (Table 1). Surprisingly, however, it did prove possible to achieve excellent *anti* selectivity in the reduction of ketone **18** with the tetramethylammonium triace-



Scheme 3. Allylation of amino aldehyde **16**. Reagents and conditions: a) 2.0 equiv of allyltrimethylsilane, 1.2 equiv of $SnCl_4$, CH_2Cl_2, −78 °C, 1 h, 40%.



Scheme 4. Reduction of allylic ketones **18**.

Table 1. Stereoselectivities of the reduction of ketones **18** (Scheme 4).

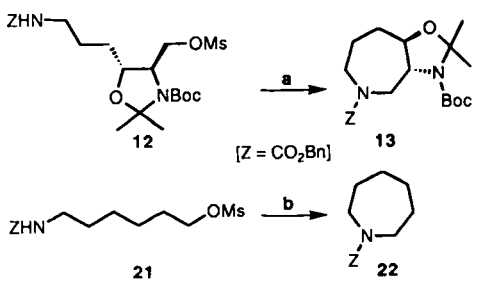
R	Reducing agent	Solvent	Yield (%) [a]	19:20
H	L-Selectride	THF	51	1:3
	$Me_4NB(OAc)_3H$	AcOH/MeCN	47	<5:>95
-C(OMe)Me_2	$LiAlH_4$	Et_2O	25	1:5
	$NaBH_4$	MeOH/THF	28	1:3
	$NaBH_4$ + $CeCl_3$	MeOH	73	1:4
	K-Selectride	THF	82	2:1
	L-Selectride	THF	70	4:1
	L-Selectride + TMEDA	THF	62	5:1
TBS	L-Selectride	THF	79	1:1
PMB	L-Selectride	THF	72	3:1

[a] For 2 steps from the corresponding Weinreb amide.

toxyborohydride reagent developed by Evans.[11] These experiments led us to conclude that the reagent-controlled allylboration reaction described above was the most convenient method for the generation of the stereogenic centres within balanol; we then concentrated on the conversion of **5** to the hexahydroazepine ring system (Scheme 1).

Firstly, amino alcohol **5** was protected as the corresponding acetonide (68% yield from **4**), and this material was then hydroborated with 9-BBN to deliver the alcohol **7** in 97% yield upon workup with alkaline hydroperoxide. This alcohol was then converted to the corresponding mesylate (**8**), which was subsequently displaced by sodium azide to furnish **9** in 98% overall yield. Reduction of the azide group over 10% Pd/C was followed by protection of the resultant amino moiety as its benzyloxycarbonyl (Z) derivative to deliver **10** in quantitative overall yield. In order to prepare for closure of the hexahydroazepine ring, the primary alcohol within **10** was exposed by desilylation with TBAF (96% yield), and then converted to the corresponding mesylate derivative (**12**). The *7-exo-tet* cyclisation was then effected by treatment of **12** with a slight excess of potassium *tert*-butoxide in THF at ambient temperature under moderately dilute conditions (0.02 M) to afford the protected hexahydroazepine fragment **13** in 80% overall yield. The alternative addition process, whereby the substrate was added to potassium *tert*-butoxide solution, afforded only a trace amount of the cyclised product.

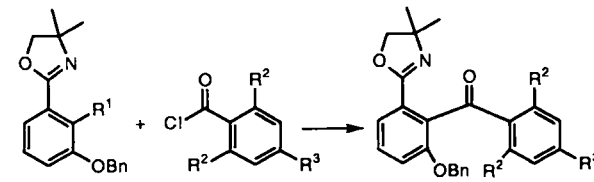
We selected a rigid acetonide protecting group for the precursor **12**, postulating that this would reduce the unfavourable entropy factors associated with *intramolecular* mesylate displacement and thus encourage cyclisation. To lend weight to this hypothesis, we examined the cyclisation of the unsubstituted hexahydroazepine precursor **21**. Interestingly, under an identical set of conditions, the cyclisation of **21** did lead to a somewhat lower yield of the corresponding hexahydroazepine (**22**) than that observed when **12** was used (Scheme 5).



Scheme 5. Comparison of hexahydroazepine ring system closures. Reagents and conditions: a) 1.2 equiv of KO*t*Bu, 0.05 M, THF, 25 °C, 1 h, 69%; b) 1.2 equiv of KO*t*Bu, 0.05 M, THF, 25 °C, 1 h, 46%.

Finally, conversion of **13** to the targeted fragment **14** was readily achieved by removal of the Boc and acetonide protecting groups with trifluoroacetic acid (TFA) and subsequent derivatisation of the resultant free amino alcohol by treatment with 4-benzyloxybenzoyl chloride (73% overall yield). Large quantities of the key balanol component **14** could thus be secured in 36% overall yield from D-serine by means of the above sequence of reactions.

Synthesis of the Benzophenone Domain: With the hexahydroazepine fragment of balanol successfully prepared, we anticipated that the remaining benzophenone domain could be synthesised by utilisation of a Stille coupling[12] of the appropriately functionalised acid chloride and arylstannane components suggested by the disconnection in Figure 1. Indeed, our initial efforts focussed upon attempts to couple the arylstannane **25** with the acid chloride **26** (Scheme 6). The generation of the acid



23: R^1 = H
24: R^1 = Li
25: R^1 = $SnBu_3$
26: R^2 = OBn, R^3 = CH_2OTPS
27: R^2 = R^3 = H
28: R^2 OBn, R^3 = CH_2OTPS
29: R^2 = R^3 = H

Scheme 6. Attempted Stille coupling approach to the benzophenone domain.

chloride fragment was smoothly achieved through treatment of the corresponding benzoic acid with oxalyl chloride and a catalytic amount of *N,N*-dimethylformamide (DMF). The acid itself was readily prepared, as anticipated, from 4-bromo-3,5-dihydroxybenzoic acid (vide infra).

Our choice of **25** as the arylstannane counterpart was based on the ready availability of the oxazoline **23**[13, 14] and its straightforward conversion to **25** through initial regioselective lithiation and subsequent transmetallation by treatment with tributyltin chloride.[15] Unfortunately, however, all attempts to couple **25** and **26** proved unsuccessful, despite the investigation of an extensive range of catalysts and conditions. Furthermore, although it has been reported that lithiated oxazolines related to **24** can react with acid chlorides to form the corresponding benzophenones directly,[16] we were unable to couple **24** with **26**. These results suggested that coupling was frustrated by an overpowering degree of steric congestion; the observation that both the aryllithium **24** and the arylstannane **25** could be coupled with benzoyl chloride (**27**) to provide **29** in good yield supports this contention. We therefore considered alternative methods to obtain the benzophenone. In particular, we wanted to ascertain whether an aryllithium species such as **31** would undergo intramolecular attack at the ester moiety[17] and thus generate the desired ketone linkage between the two aromatic components (Scheme 7). Indeed, such a rearrangement might be expected to prove very favourable in the light of the greater thermodynamic stability of the resultant alkoxide ion. In addition, we anticipated that the prerequisite aryllithium species would be readily obtainable from the corresponding aryl bromide by low temperature halogen–metal exchange with *n*-butyllithium since this reaction is known to proceed at a significantly greater rate than the alternative pathway of ester attack.[18] To test this methodology, the ester **30** was prepared from the corresponding com-

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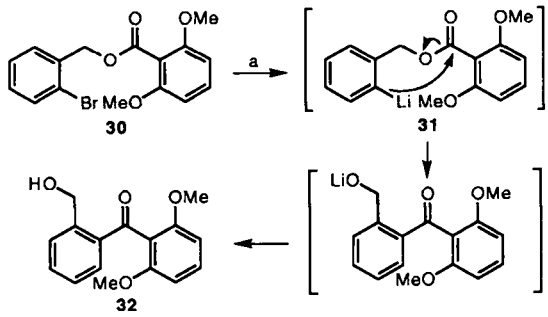
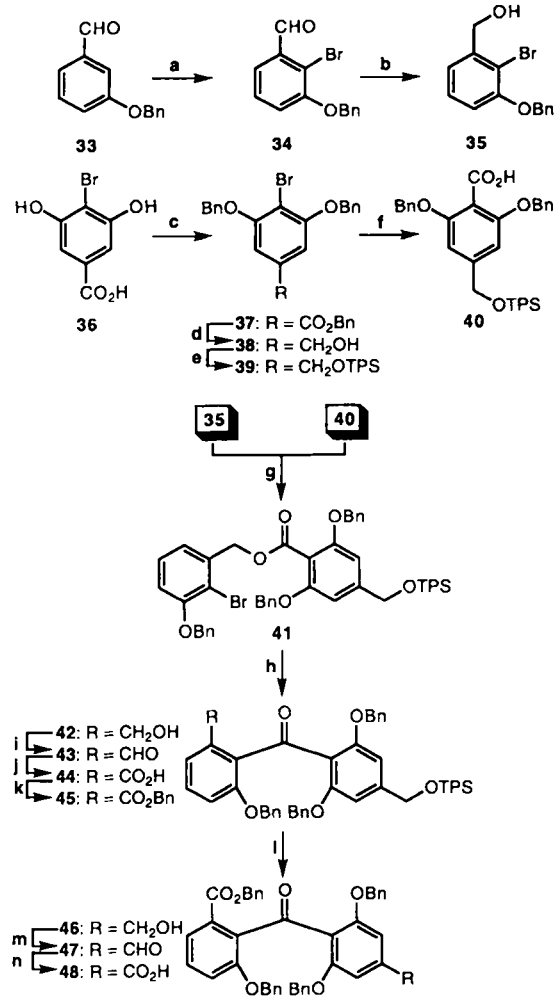


Scheme 7. Model study for new benzophenone strategy. Reagents and conditions: a) *n*BuLi, THF, −98 → −78 °C, 0.5 h; aq. NaHCO3, 87%.

mercially available carboxylic acid and alcohol. To our delight, treatment of **30** at low temperature (− 98 °C) with *n*-butyllithium followed by warming the reaction mixture to ambient temperature and protic workup resulted in the formation of the benzophenone **32**, which was isolated in 87% yield.

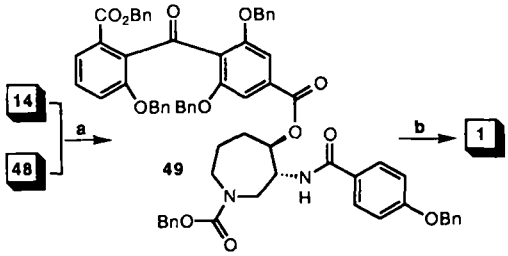
We then attempted to generate the targeted benzophenone **48** using this method. The necessary ester precursor **41** was prepared as follows (Scheme 8): firstly, the alcohol component (**35**) of ester **41** was prepared from 3-benzyloxybenzaldehyde (**33**) by a two-step sequence. Aldehyde **33** was subjected to regiospecific lithiation by the protocol developed by Comins,[19] and this aryllithium species was trapped with 1,2-dibromotetrafluoroethane[20] to deliver the bromide **34** as a single regioisomer in 77% yield. DIBALH reduction of this aldehyde then furnished the benzyl alcohol **35** in 96% yield. As indicated above, commercially available carboxylic acid **36** proved a convenient precursor for the acid component (**40**) of ester **41**. Tribenzylation of **36** with benzyl bromide and potassium carbonate in DMF occurred smoothly (96% yield) and the resultant benzyl ester **37** was reduced with DIBALH to the corresponding primary alcohol **38** (100% yield), which was finally silylated to afford **39** in 82% yield. This material was then subjected to lithium–halogen exchange with *n*-butyllithium, and the resulting aryllithium species was trapped with carbon dioxide to provide the desired carboxylic acid **40** in good yield (60% overall).

The coupling of **35** and **40** was most efficiently achieved by the Mitsunobu protocol,[21] which gave the target ester **41** in 93% yield. Interestingly, we found that mechanistically divergent methods of ester formation, namely those which proceed through attack of the alcohol at an activated acid derivative (e.g., DCC, acid chloride, etc.), resulted in poor yields of **41**, and this again presumably reflected the degree of steric congestion at the carbonyl centre. As anticipated, the aryllithium species resulting from the low temperature (− 98 °C) treatment of **41** with *n*-butyllithium successfully underwent the desired rearrangement to afford the corresponding alcohol (**42**) upon protic workup. Although this material could be isolated, it proved somewhat unstable, and direct oxidation to aldehyde **43** (65% yield from **41**) with TPAP/NMO[22] was generally more convenient. With this material in hand, we then employed sodium chlorite oxidation[23] to secure the carboxylic acid **44**, which was readily converted to the benzyl ester **45** in the normal manner (96% yield from **43**). Subsequent TBAF-mediated desilylation of **45** provided the alcohol **46** (95% yield), which was in turn subjected to TPAP/NMO oxidation to give the aldehyde **47** (70% yield). Finally, oxidation of this aldehyde with sodium chlorite proceeded smoothly (95% yield) to furnish the protected balanol benzophenone component **48**. Utilisation of the above approach thus allowed for the preparation of large quantities of the targeted benzophenone fragment in 17% overall yield from **36** (longest linear sequence).



Scheme 8. Synthesis of the benzophenone system **48**. Reagents and conditions: a) 1.03 equiv of *n*BuLi, 1.07 equiv of $MeNHCH_2CH_2NMe_2$, PhH, 0 → 25 °C, 0.5 h; aldehyde, 0 → 25 °C, 0.5 h; 3.0 equiv of PhLi, 0 → 25 °C, 7.5 h; 4.0 equiv of 1,2-dibromotetrafluoroethane, THF, −78 → 25 °C, 0.5 h; 0 °C, 77%; b) 1.2 equiv of DIBALH, CH_2Cl_2, −78 → 0 °C, 1 h, 96%; c) 3.3 equiv of BnBr, 5.0 equiv of K_2CO_3, DMF, 25 °C, 4 h, 96%; d) 2.4 equiv of DIBALH, CH_2Cl_2, −78 → 0 °C, 1 h, 100%; e) 1.2 equiv of TPSCl, 1.5 equiv of imidazole, DMF, 25 °C, 1 h, 82%; f) 1.1 equiv of *n*BuLi, THF, −98 → −78 °C, 0.5 h; excess CO_2, −78 → 25 °C, 0.5 h; aq. KHSO4, 60%; g) 1.1 equiv of DEAD, 1.1 equiv of Ph_3P, THF, 0 → 25 °C, 40 min, 93%; h) 1.05 equiv of *n*BuLi, THF, −98 → −78 °C, 0.5 h, 86%; i) 1.5 equiv of NMO, 0.05 equiv of TPAP, CH_3CN, 25 °C, 0.5 h, 75%; j) 3.0 equiv of $NaClO_2$, 3.0 equiv of NaH_2PO_4, 8.0 equiv of 2-methyl-2-butene, THF, *t*BuOH, H_2O, 25 °C, 8 h, 98%; k) 2.0 equiv of BnBr, 3.0 equiv of K_2CO_3, DMF, 25 °C, 1 h, 98%; l) 1.2 equiv of TBAF, THF, 25 °C, 10 min, 95%; m) 1.5 equiv of NMO, 0.05 equiv of TPAP, CH_3CN, 25 °C, 0.5 h, 70%; n) 3.0 equiv of $NaClO_2$, 3.0 equiv of NaH_2PO_4, 8.0 equiv of 2-methyl-2-butene, THF, *t*BuOH, H_2O, 25 °C, 1 h, 95%. Bn = $PhCH_2$; DEAD = diethyl azodicarboxylate; NMO = 4-methylmorpholine *N*-oxide; TPAP = tetra-*n*-propylammonium perruthenate(VII).

Coupling of Domains and Generation of Balanol: The union of the two protected components **14** and **48** was successfully accomplished by esterification by means of a modified Mukaiyama procedure[24] to give the fully protected balanol progenitor **49** in 79% yield (Scheme 9). The adoption of benzyl-derived protecting groups for the latent functionalities in this coupling step was rewarded here: mild palladium-catalysed hydrogenolysis of **49** at ambient temperature in formic acid resulted in the generation of balanol (**1**) as a yellow solid in quantitative yield (≥ 90% purity).[25] Final purification was achieved by a combi-



Scheme 9. Coupling of fragments **14** and **48** and generation of balanol (**1**). Reagents and conditions: a) 1.3 equiv of 2-chloro-1-methylpyridinium iodide, 2.0 equiv of Et_3N, 0.5 equiv of DMAP, CH_2Cl_2, 25 °C, 3 h, 79%; b) 2.8 equiv of Pd black, HCO_2H, 25 °C, 7 h, 80%. DMAP = 4-dimethylaminopyridine.

nation of normal-phase and reversed-phase preparative TLC to provide a sample of balanol in 80% yield which exhibited characterisation data consistent with the proposed structure and a ^1H NMR spectrum that correlated precisely with that of an authentic sample.[26] Furthermore, synthetic balanol proved to be as active an inhibitor of PKC as the natural product [IC_{50} = 4 nM; rat brain kinases (Ca^{2+} dependent)].[27]

Design and Synthesis of Balanol Analogues

Having accomplished the total synthesis of the natural product, we were now able to use the same strategies to prepare a variety of new balanoids for biological evaluation.[27] In particular, we wished to identify the functional group requirements for PKC inhibition, with the eventual aim of preparing a highly selective inhibitor of equal potency to balanol and even more synthetically accessible. We hypothesised that the inhibitory properties of balanol stemmed from its potential to mimic ATP at the PKC-catalytic domain, and designed analogues accordingly. These studies will be described in full detail elsewhere;[27] here we report the chemical synthesis of our designed balanoids.

At the outset of our analogue program we required access to model compounds for both the benzophenone and hexahydroazepine domains of balanol for individual testing. Consequently, compound **51** (Fig. 2) was selected as an ideal model of the benzophenone fragment and was readily prepared (Scheme 10) by conversion of the protected benzophenone domain **48** to the corresponding methyl ester (100% yield) followed by hydrogenolysis of the benzyl groups (92% yield). Similarly, the hexahydroazepine fragment **52** (Fig. 2) was readily prepared (Scheme 10) by the cleavage of the protecting groups in **14** (100% yield).

The finding that both domains were required for activity, together with results from molecular modelling studies,[27] led us to conclude that the balanol backbone should be retained. Furthermore, our modelling studies suggested that the analogues **73**, **74**, **75** and **76** (Fig. 2) would serve as useful indicators of the validity of our ATP-mimetic hypothesis, and they were therefore targeted for synthesis.

The dideoxybenzophenone fragment **62**, required for analogue **75**, was prepared in a similar manner (Scheme 11) to that described above for the natural fragment **48**. Commercially available ester **53** was first protected by silylation in the normal manner (100% yield) and then carefully hydrolysed to the corresponding carboxylic acid **55** (62% yield). Condensation of **55** with the previously prepared (vide supra) alcohol **35** then afforded the rearrangement precursor **56** in 96% yield. This material was rearranged and oxidised as described earlier to provide the aldehyde **57** in 57% overall yield for the two steps. The

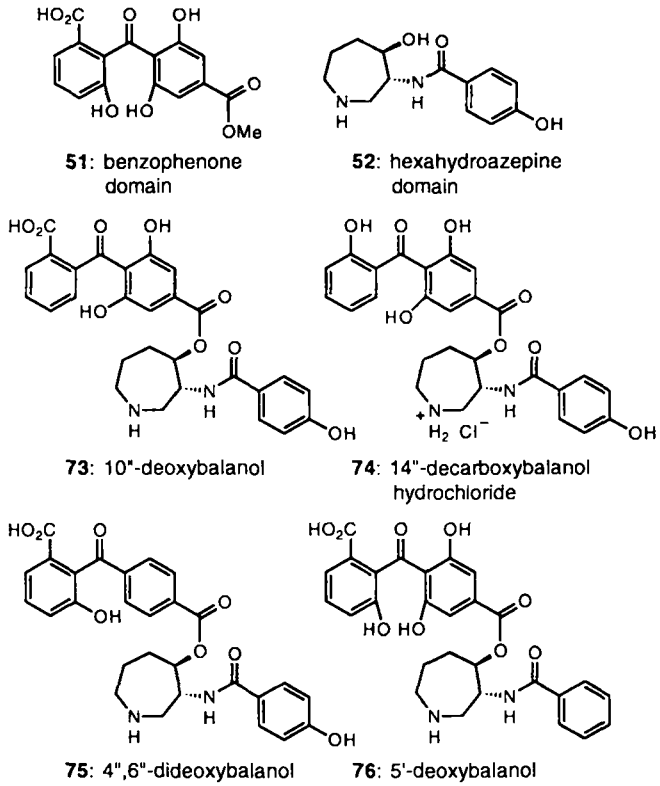
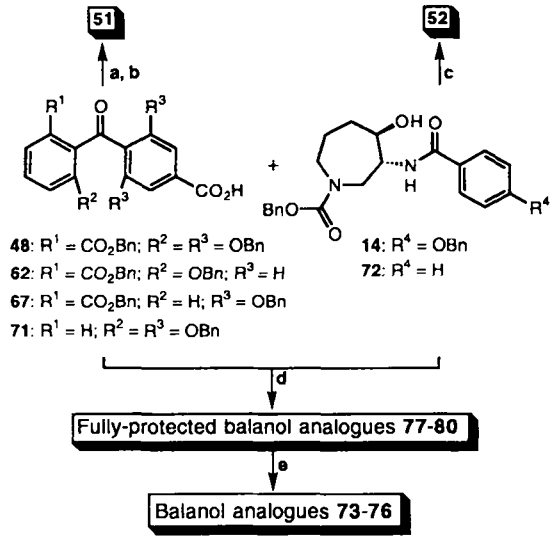


Fig. 2. Designed balanol analogues.



Scheme 10. Synthesis of balanol analogues. Reagents and conditions: a) 2.0 equiv of MeI, 1.2 equiv of K_2CO_3, DMF, 25 °C, 2 h, 100%; b) 0.25 equiv of Pd-black, H_2 (1 atm), THF, 25 °C, 12 h, 92%; c) 2.8 equiv of Pd-black, HCO_2H, 25 °C, 7 h, 100%; d) 1.3 equiv of 2-chloro-1-methylpyridinium iodide, 2.0 equiv of Et_3N, 0.5 equiv of DMAP, CH_2Cl_2, 25 °C, 3 h, 86–96%; e) 2.8 equiv of Pd-black, HCO_2H, 25 °C, 7 h, 90–97%.

conversion of **57** to the target carboxylic acid **62** was again achieved in an analogous fashion (48% overall yield) to that detailed above for the synthesis of **48**.

For the preparation of the benzophenone fragment required for the synthesis of analogue **73**, we wished to establish whether the rearrangement step could be omitted and the synthetic sequence thus shortened. We discovered that the anion derived

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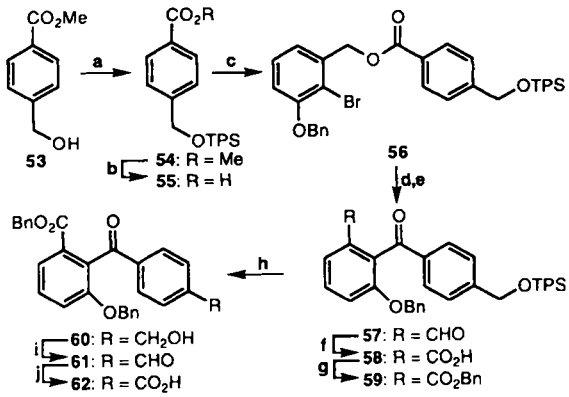
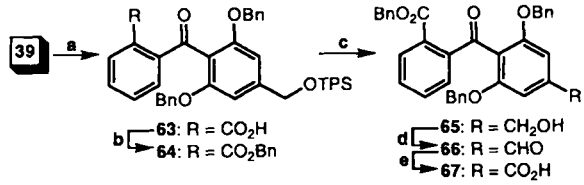


Scheme 11. Synthesis of the 4",6"-dideoxybenzophenone fragment. Reagents and conditions: a) 1.15 equiv of TPSCl, 1.5 equiv of imidazole, DMF, 0 → 25 °C, 2 h, 100%; b) 2.0 equiv of LiOH, 1,4-dioxane, H_2O, 25 °C, 24 h, 62%; c) 1.0 equiv of **35**, 1.1 equiv of DEAD, 1.1 equiv of Ph_3P, THF, 0 → 25 °C, 15 min, 96%; d) 1.1 equiv of *n*BuLi, THF, −98 → −78 °C, 0.5 h; e) 1.5 equiv of NMO, 0.05 equiv of TPAP, CH_3CN, 25 °C, 0.5 h, 57% (2 steps); f) 3.0 equiv of $NaClO_2$, 3.0 equiv of NaH_2PO_4, 8.0 equiv of 2-methyl-2-butene, THF, *t*BuOH, H_2O, 25 °C, 8 h, 94%; g) 1.6 equiv of BnBr, 1.6 equiv of K_2CO_3, DMF, 25 °C, 2 h, 98%; h) 1.2 equiv of TBAF, THF, 25 °C, 10 min, 92%; i) 1.5 equiv of NMO, 0.05 equiv of TPAP, CH_3CN, 25 °C, 0.5 h, 64%; j) 3.0 equiv of $NaClO_2$, 3.0 equiv of NaH_2PO_4, 8.0 equiv of 2-methyl-2-butene, THF, *t*BuOH, H_2O, 25 °C, 1 h, 89%.

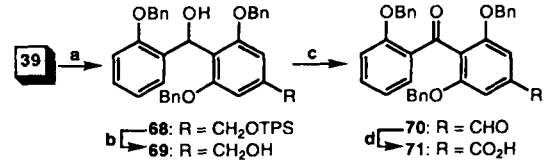
from lithium–halogen exchange of the previously prepared aryl bromide **39** could indeed react directly with phthalic anhydride to deliver the carboxylic acid **63** in 73% yield upon protic workup (Scheme 12). This acid was then protected as its benzyl ester derivative **64** (98% yield) before desilylation and oxidation to the target carboxylic acid **67** in the standard manner (58% yield for the three steps). The overall yield of **67** was thus 33% in just 7 steps compared to the 17% (12 steps) required for the naturally occurring component **48**.



Scheme 12. Synthesis of the 10"-deoxybenzophenone fragment. Reagents and conditions: a) 1.2 equiv of *n*BuLi, THF, −98 → −78 °C, 0.5 h; 1.3 equiv of phthalic anhydride, −78 → 25 °C, 0.5 h; $KHSO_4$, 73%; b) 2.0 equiv of BnBr, 3.0 equiv of K_2CO_3, DMF, 25 °C, 3 h, 98%; c) 1.2 equiv of TBAF, THF, 25 °C, 10 min, 92%; d) 1.5 equiv of NMO, 0.05 equiv of TPAP, CH_3CN, 25 °C, 0.5 h, 63%; e) 3.0 equiv of $NaClO_2$, 3.0 equiv of NaH_2PO_4, 8.0 equiv of 2-methyl-2-butene, THF, *t*BuOH, H_2O, 25 °C, 1 h, 100%. Bn = $PhCH_2$; TBAF = tetra-*n*-butylammonium fluoride; NMO = 4-methylmorpholine *N*-oxide; TPAP = tetra-*n*-propylammonium perruthenate(VII).

The benzophenone fragment required for the decarboxy analogue **74** was prepared in a related manner (Scheme 13). Thus the aryllithium derived from **39** was found to react with 2-(benzyloxy)benzaldehyde to furnish the carbinol **68** (67% yield). Desilylation of **68** mediated by TBAF afforded the diol **69** (99% yield), which was oxidised to the benzophenone **70** by TPAP/NMO (53% yield) and then finally to the desired carboxylic acid **71** with sodium chlorite (96% yield). Again, this approach proved significantly more direct than the previous rearrangement method.

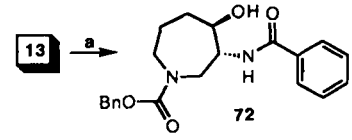
Finally, for the preparation of analogue **76**, a deoxygenated hexahydroazepine fragment was required. This material was



Scheme 13. Synthesis of the 14"-decarboxybenzophenone fragment. Reagents and conditions: a) 1.2 equiv of *n*BuLi, THF, −98 → −78 °C, 15 min; 1.5 equiv of 2-(benzyloxy)benzaldehyde, −78 → 0 °C, 1 h, 67%; b) 1.2 equiv of TBAF, THF, 25 °C, 10 min, 99%; c) 3.0 equiv of NMO, 0.1 equiv of TPAP, CH_3CN, 25 °C, 0.5 h, 53%; d) 3.0 equiv of $NaClO_2$, 3.0 equiv of NaH_2PO_4, 8.0 equiv of 2-methyl-2-butene, THF, *t*BuOH, H_2O, 25 °C, 1 h, 96%.

simply synthesised in 52% yield by deprotection of the hexahydroazepine **13** (vide supra) with TFA and treatment of the corresponding free amino alcohol with benzoyl chloride (Scheme 14).

With all the necessary fragments prepared, coupling was performed in the standard manner and the desired balanol analogues (**73**–**76**) were then liberated by hydrogenolysis in uniformly high yield (Scheme 10).



Scheme 14. Synthesis of the 5'-deoxyhexahydroazepine fragment. Reagents and conditions: a) excess TFA, CH_2Cl_2, 25 °C, 2 h; 2.0 equiv of benzoyl chloride, 10 equiv of Et_3N, CH_2Cl_2, 25 °C, 1 h, 52%. TFA = CF_3CO_2H.

Conclusion

The important role of protein kinase C in a variety of cellular processes has prompted a dramatic effort to identify novel and potent inhibitors of this enzyme. The recent isolation of balanol provides an important new lead in this regard, particularly in the light of its impressive activity and structural divergence from other known PKC inhibitors such as staurosporine.[28] The synthetic strategies outlined in this paper provide a direct and efficient synthesis of this natural product and allowed for the preparation of a variety of analogues for biological investigation. Studies concerning the biological action of balanol and its analogues will be reported elsewhere.[27]

Experimental Section

General techniques: All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Tetrahydrofuran (THF), diethyl ether (Et_2O) and benzene were distilled from sodiumbenzophenone, toluene was distilled from sodium, and methylene chloride (CH_2Cl_2) was distilled from calcium hydride. Yields refer to chromatographically and spectroscopically (^1H NMR) homogeneous materials, unless otherwise stated. All reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254), unless otherwise stated. UV light, 2.4% phosphomolybdic acid/1.4% phosphoric acid/5% sulfuric acid in water or 0.2% ninhydrin in ethanol and heat were used as developing agents. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on 0.50 or 1.00 mm E. Merck silica gel plates (60F-254) or E. Merck reversed phase plates ($RP\text{-}18F_{254}$).

NMR spectra were recorded on a Bruker AMX-500 instrument and calibrated with tetramethylsilane as an internal reference. The following abbreviations are used to indicate the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad. The balanol numbering system used herein is in accordance with that employed by Kulanthaivel et al.[3] IR spectra were recorded on a Perkin–Elmer 1600 series FT-IR spectrometer. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter. High resolution mass spectra (HRMS) were recorded on a VG ZAB-ZSE mass spectrometer under fast atom bombardment (FAB) conditions.

Silyl ether 4: A solution of D-serine derivative **3** [6] (42.18 g, 192.4 mmol) and imidazole (19.65 g, 248.4 mmol) in DMF (250 mL) was treated with tBuPh$_2$SiCl (60.0 mL, 230.9 mmol) at 0 °C and stirred at 25 °C for 14 h. The reaction was then quenched with MeOH (20 mL) and diluted with Et$_2$O/petroleum ether (3/1, 1000 mL). The resultant solution was washed with water (1000 mL) and the aqueous layer extracted with Et$_2$O/petroleum ether (3/1, 600 mL). The combined organic layers were washed with water (1000 mL × 2) and brine (500 mL) and then dried (Na$_2$SO$_4$), filtered and concentrated. Purification of the residue by flash chromatography (silica gel, 3 → 10% EtOAc in petroleum ether) afforded **4** (88.06 g, 100%) as a colourless oil: R_f = 0.33 (10% EtOAc in petroleum ether); $[\alpha]_D^{24} = -13.4$ (c = 0.62 in CHCl$_3$); IR (thin film): $\tilde{\nu}_{max}$ = 1749 (C=O), 1717 (C=O), 1496, 1165, 1110, 704 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$, 20 °C): δ = 7.61 (m, 4H; Ar), 7.44 (m, 2H; Ar), 7.39 (m, 4H; Ar), 5.42 (d, J = 8.8 Hz, 1H; NH), 4.40 (ddd, J = 8.8, 3.0, 2.9 Hz, 1H; 3-H), 4.07 (dd, J = 10.1, 2.9 Hz, 1H; 2-H), 3.89 (dd, J = 10.1, 3.0 Hz, 1H; 2-H'), 3.74 (s, 3H; CO$_2$CH$_3$), 1.46 (s, 9H; CO$_2t$Bu), 1.03 (s, 9H; SiPh$_2t$Bu); ^{13}C NMR (125 MHz, CDCl$_3$, 20 °C): δ = 171.2, 155.4, 135.52, 135.47, 132.9, 132.8, 129.9, 127.8, 79.9, 64.6, 55.5, 52.3, 28.3, 26.7, 19.3; FAB HRMS: calcd for C$_{25}$H$_{36}$NO$_5$Si (M + H$^+$): 458.2363, found: 458.2370.

Homoallylic alcohol 5: A solution of silyl ether **4** (21.72 g, 47.46 mmol) in toluene (220 mL) was cooled to −78 °C and treated with DIBALH (119.0 mL, 1.0 M in toluene) dropwise over 1 h. After the mixture had been stirred at −78 °C for 30 min, the reaction was quenched by the addition of MeOH (30 mL). The reaction mixture was then treated with 1 N HCl (500 mL) and stirred at 0 °C for 1.5 h. The organic layer was then separated and the aqueous layer extracted with EtOAc (500 mL). The combined organic layers were washed with 1 N HCl (300 mL), saturated NaHCO$_3$ (300 mL) and brine (300 mL) and then dried (Na$_2$SO$_4$), filtered and concentrated. The crude product was used in the next reaction without further purification.

A solution of (+)-*B*-methoxydiisopinocampheylborane (27.02 g, 85.43 mmol) in Et$_2$O (200 mL) was cooled to 0 °C and treated with allylmagnesium bromide (76.0 mL, 1.0 M in Et$_2$O). After stirring for 3 h at 25 °C, the resultant suspension was cooled to −98 °C and the crude aldehyde in Et$_2$O (50 mL × 2) was then added over 25 min. After stirring at −78 °C for 3.5 h, the reaction was quenched with ethanolamine (14.0 mL) and stirred for 24 h at 25 °C. The resultant mixture was filtered through Celite and washed with water (200 mL), and the aqueous layer extracted with Et$_2$O (300 mL). The combined organic layers were then washed with saturated aqueous NH$_4$Cl (300 mL) and brine (300 mL) and then dried (Na$_2$SO$_4$), filtered and concentrated. Purification of the residue by flash chromatography (silica gel, 5 → 12% EtOAc in petroleum ether) afforded **5** (27.37 g, crude) as a colourless oil. An analytical sample of **5** was obtained by PTLC (silica gel, 20% EtOAc in petroleum ether): R_f = 0.30 (15% EtOAc in petroleum ether); $[\alpha]_D^{24} = -6.0$ (c = 0.87 in CHCl$_3$); IR (thin film): $\tilde{\nu}_{max}$ = 3440 (OH), 1693 (C=O), 1500, 1169, 1109, 703 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$, 20 °C): δ = 7.64 (d, J = 6.4 Hz, 2H; Ar), 7.47–7.37 (m, 8H; Ar), 5.84 (m, 1H; 6-H), 5.18–5.10 (m, 3H; 7-H$_2$ and NH), 4.03 (m, 1H; 4-H), 3.84 (dd, J = 10.3, 4.3 Hz, 1H; 2-H), 3.80 (dd, J = 10.3, 3.4 Hz, 1H; 2-H'), 3.65 (m, 1H; 3-H), 3.00 (d, J = 1.7 Hz, 1H; OH), 2.29 (dd, J = 13.6, 7.3 Hz, 1H; 5-H), 2.24 (dd, J = 13.6, 6.0 Hz, 1H; 5-H'), 1.45 (s, 9H; CO$_2t$Bu), 1.06 (s, 9H; SiPh$_2t$Bu); ^{13}C NMR (125 MHz, CDCl$_3$, 20 °C): δ = 155.9, 135.54, 135.50, 134.3, 132.6, 132.5, 130.0, 127.9, 117.9, 79.3, 72.0, 66.6, 53.4, 38.5, 28.4, 26.8, 19.1; FAB HRMS calcd for C$_{27}$H$_{40}$NO$_4$Si (M + H$^+$): 470.2727, found: 470.2744.

Acetonide 6: A solution of crude homoallylic alcohol **5** (27.32 g) in CH$_2$Cl$_2$ (150 mL) was treated with 2,2-dimethoxypropane (23.3 mL, 189.8 mmol) and then camphorsulfonic acid (110 mg, 0.47 mmol). After stirring at 25 °C for 3 h, the reaction was quenched by the addition of triethylamine (1.0 mL, 7.2 mmol) and then concentrated in vacuo. Purification of the residue by flash chromatography (silica gel, 2 → 4% EtOAc in petroleum ether) afforded **6** (16.73 g, 69% for the 3 steps) as a colourless oil: R_f = 0.28 (4% EtOAc in petroleum ether); $[\alpha]_D^{24} = -13.9$ (c = 1.02 in CHCl$_3$); IR (thin film): $\tilde{\nu}_{max}$ = 1698 (C=O), 1384, 1109, 703 cm^{-1}; ^{1}H NMR (500 MHz, C$_6$D$_6$, 67 °C): δ = 7.97–7.76 (m, 4H; Ar), 7.26–7.21 (m, 6H; Ar), 5.90 (m, 1H; 6-H), 5.09 (d, J = 17.1 Hz, 1H; 7-H), 5.03 (d, J = 10.1 Hz, 1H; 7-H'), 4.47 (dd, J = 11.9, 6.0 Hz, 1H; 2-H), 4.11 (bs, 1H; 3-H), 3.97 (bd, J = 11.9 Hz, 1H; 2-H'), 3.81 (dt, J = 5.6, 3.8 Hz, 1H; 4-H), 2.40 (bt, J = 5.6 Hz, 2H; 5-H$_2$), 1.73 (bs, 3H; acetonide), 1.61 (s, 3H; acetonide), 1.37 (bs, 9H; CO$_2t$Bu), 1.17 (s, 9H; SiPh$_2t$Bu); ^{13}C NMR (125 MHz, C$_6$D$_6$, 70 °C): δ = 152.1, 136.2, 136.1, 134.8, 134.1, 134.0, 130.1, 117.3, 94.6, 79.5, 77.5, 63.3, 61.2, 39.6, 28.6, 27.4, 27.3, 27.1, 19.6; FAB HRMS calcd for C$_{30}$H$_{44}$NO$_4$Si (M + H$^+$): 510.3040, found: 510.3055.

Alcohol 7: A solution of acetonide **6** (16.73 g, 32.82 mmol) was cooled to 0 °C and treated with 9-BBN (144.4 mL, 0.5 M in THF). After stirring at 25 °C for 20 h, the solution was treated with MeOH (50 mL) and 40 mL of an aqueous solution of NaOH (3 N), and then cooled to 0 °C and treated dropwise with 30% H$_2$O$_2$ (40 mL). After this had been stirred at 25 °C for 5 h, the THF and MeOH were evaporated in vacuo and the aqueous residue was extracted with EtOAc (300 mL × 2). The combined organic layers were washed with saturated NaHCO$_3$ (300 mL) and brine (500 mL) and then dried (Na$_2$SO$_4$), filtered and concentrated. Purification of the residue by flash chromatography (silica gel, 15 → 25% EtOAc in petroleum ether) afforded **7** (16.77 g, 97%) as a colourless oil: R_f = 0.19 (20% EtOAc in petroleum ether); $[\alpha]_D^{23} = -14.7$ (c = 1.05 in CHCl$_3$); IR (thin film): $\tilde{\nu}_{max}$ = 3433 (broad, OH), 1694 (C=O), 1389, 1110, 703 cm^{-1}; ^{1}H NMR (500 MHz, C$_6$D$_6$, 75 °C): δ = 7.79–7.76 (m, 4H; Ar), 7.28–7.23 (m, 6H; Ar), 4.38 (m, 1H; 2-H), 4.10 (bs, 1H; 3-H), 3.98 (dd, J = 9.7, 2.4 Hz, 1H; 2-H'), 3.72 (ddd, J = 6.0, 6.0, 3.3 Hz, 1H; 4-H), 3.46 (t, J = 5.7 Hz, 2H; 7-H$_2$), 1.71 (bs, 3H; acetonide), 1.69–1.61 (bm, 4H; 5-H$_2$ and 6-H$_2$), 1.60 (s, 3H; acetonide), 1.38 (s, 9H; CO$_2t$Bu), 1.17 (s, 9H; SiPh$_2t$Bu); ^{13}C NMR (125 MHz, C$_6$D$_6$, 75 °C): δ = 152.2, 136.1, 136.1, 134.1, 134.0, 130.1, 128.6, 94.5, 79.6, 77.9, 63.9, 62.5, 61.4, 31.8, 29.8, 28.5, 27.4, 27.3, 27.1, 19.6; FAB HRMS calcd for C$_{30}$H$_{44}$NO$_5$SiCs (M + Cs$^+$): 660.2121, found: 660.2129.

Azide 9: A solution of alcohol **7** (16.26 g, 30.87 mmol) in CH$_2$Cl$_2$ (160 mL) was cooled 0 °C and treated with triethylamine (6.45 mL, 46.28 mL) and methanesulfonyl chloride (2.87 mL, 37.1 mmol). After stirring at 0 °C for 10 min, the reaction mixture was quenched with water (100 mL) and then concentrated in vacuo. The aqueous residue was extracted with EtOAc (300 mL × 2), and the combined organic layers were washed with water (300 mL) and brine (300 mL) and then dried (Na$_2$SO$_4$), filtered and concentrated. The crude product **8** was dissolved in DMF (160 mL) and treated at 25 °C with sodium azide (12.04 g, 185.2 mmol). The resultant suspension was stirred at 25 °C for 24 h and then diluted with water (800 mL) and extracted with Et$_2$O/petroleum ether (2/1, 400 mL × 2). The combined organic layers were washed with water (400 mL × 2) and brine (500 mL) and then dried (Na$_2$SO$_4$), filtered and concentrated. Purification of the residue by flash chromatography (silica gel, 4 → 6% EtOAc in petroleum ether) afforded **9** (16.72 g, 98%) as a colourless oil: R_f = 0.21(5% EtOAc in petroleum ether); $[\alpha]_D^{23} = -14.5$ (c = 1.12 in CHCl$_3$); IR (thin film): $\tilde{\nu}_{max}$ = 2095 (N$_3$), 1697 (C=O), 1387, 1110, 703 cm^{-1}; ^{1}H NMR (500 MHz, C$_6$D$_6$, 67 °C): δ = 7.76 (m, 4H; Ar), 7.28–7.23 (m, 6H; Ar), 4.28 (bs, 1H; 2-H), 4.06 (bs, 1H; 3-H), 3.96 (bd, J = 7.7 Hz, 1H; 2-H'), 3.67 (ddd, J = 5.8, 5.8, 3.4 Hz, 1H; 4-H), 2.89 (dd, J = 12.3, 5.9 Hz, 1H; 7-H), 2.84 (dd, J = 12.3, 6.4 Hz, 1H; 7-H'), 1.70 (s, 3H; acetonide), 1.60–1.45 (m, 4H; 5-H$_2$ and 6-H$_2$), 1.58 (s, 3H; acetonide), 1.38 (s, 9H; CO$_2t$Bu), 1.17 (s, 9H; SiPh$_2t$Bu); ^{13}C NMR (125 MHz, C$_6$D$_6$, 75 °C): δ = 152.0, 136.0, 134.0, 133.9, 130.1, 128.1, 94.6, 79.6, 77.5, 63.8, 61.3, 51.4, 32.3, 28.5, 27.4, 27.3, 27.1, 25.8, 19.6; FAB HRMS calcd for C$_{30}$H$_{44}$N$_4$O$_4$SiNa (M + Na$^+$): 575.3030, found: 575.3045.

Benzyloxycarbonylamine 10: A solution of azide **9** (9.80 g, 17.73 mmol) in THF (100 mL) was treated with 10% palladium on activated carbon (188 mg, 1.77 mmol), and the resultant mixture was stirred under an atmosphere of hydrogen for 19 h at 25 °C. The reaction mixture was then filtered and concentrated, and the crude product dissolved in 1,4-dioxane (94 mL). This solution was then cooled to 0 °C and treated with 3 N NaOH (17.7 mL, 53.1 mmol) and benzyl chloroformate (2.93 mL, 20.52 mmol). After stirring at 0 °C for 15 min, the reaction mixture was treated with saturated aqueous NH$_4$Cl (50 mL), and the 1,4-dioxane was then evaporated in vacuo. The residue was extracted with EtOAc (450 mL) and the organic layer was washed with brine (300 mL) and then dried (Na$_2$SO$_4$), filtered and concentrated. Purification of the residue by flash chromatography (silica gel, 10 → 20% EtOAc in petroleum ether) afforded **10** (11.56 g, 99%) as a colourless oil: R_f = 0.19 (15% EtOAc in petroleum ether); $[\alpha]_D^{23} = -11.9$ (c = 1.00 in CHCl$_3$); IR (thin film): $\tilde{\nu}_{max}$ = 3349 (NH), 1696 (C=O), 1391, 1110, 702 cm^{-1}; ^{1}H NMR (500 MHz, C$_6$D$_6$, 75 °C): δ = 7.77 (m, 4H; Ar), 7.32–7.11 (m, 10H; Ar), 7.07 (bt, J = 7.3 Hz, 1H; Ar), 5.10 (s, 2H; CO$_2$CH_2Ph), 4.28 (m, 2H; 2-H and NH), 4.10 (bs, 1H; 3-H), 3.93 (bd, J = 9.6 Hz, 1H; 2-H'), 3.64 (td, J = 6.0, 3.1 Hz, 1H; 4-H), 3.04 (bs, 2H; 7-H$_2$), 1.70 (s, 3H; acetonide), 1.60 (s, 3H; acetonide), 1.51–1.43 (m, 4H; 5-H$_2$ and 6-H$_2$), 1.38 (s, 9H; CO$_2t$Bu), 1.17 (s, 9H; SiPh$_2t$Bu); ^{13}C NMR (125 MHz, C$_6$D$_6$, 75 °C): δ = 156.4, 152.1, 138.0, 136.13, 136.11, 134.1, 134.0, 130.2, 128.2, 94.6, 79.6, 77.7, 66.7, 63.9, 63.3, 41.4, 32.3, 30.2, 28.6, 28.3, 27.3, 27.0, 19.6; FAB HRMS calcd for C$_{38}$H$_{52}$N$_2$O$_6$SiNa (M + Na$^+$): 683.3492, found: 683.3502.

Alcohol 11: A solution of benzyloxycarbonylamine **10** (11.29 g, 17.08 mmol) in THF (48 mL) was treated with tetrabutylammonium fluoride (20.5 mL, 1.0 M in THF) and stirred for 16 h at 25 °C. The reaction mixture was then concentrated and the residue purified by flash chromatography (silica gel, 1% MeOH and 50 → 90% Et$_2$O in petroleum ether) to afford **11** (6.93 g, 96%) as a colourless oil: R_f = 0.30 (1% MeOH and 80% Et$_2$O in petroleum ether); $[\alpha]_D^{23} = +1.1$ (c = 1.02 in CHCl$_3$); IR (thin film): $\tilde{\nu}_{max}$ = 3341 (broad, OH and NH), 1695 (C=O), 1396, 1256 cm^{-1}; ^{1}H NMR (500 MHz, C$_6$D$_6$, 70 °C): δ = 7.27 (d, J = 7.3 Hz, 2H; Ar(*ortho*)), 7.14 (dd, J = 7.3, 7.3 Hz, 2H; Ar(*meta*)), 7.08 (t, J = 7.3 Hz, 1H; Ar(*para*)), 5.09 (s, 2H; OCH_2Ph), 4.28 (bs, 1H; 3-H), 3.67–3.61 (m, 3H; 2-H$_2$ and NH), 3.51 (m, 1H; 4-H), 3.01–2.91 (m, 2H; 7-H$_2$), 1.58 (s, 3H; acetonide), 1.45 (s, 3H; acetonide), 1.41–1.32 (m, 4H; 5-H$_2$ and 6-H$_2$), 1.38 (s, 9H; CO$_2t$Bu); ^{13}C NMR (125 MHz, C$_6$D$_6$, 75 °C): δ = 156.6, 153.7, 137.9, 128.7, 128.6, 128.44, 128.37, 94.5, 80.5, 76.8, 66.7, 65.6, 64.3, 41.1, 31.2, 28.5, 28.2, 26.6; FAB HRMS calcd for C$_{22}$H$_{34}$N$_2$O$_6$Na (M + Na$^+$): 445.2315, found: 445.2331.

Hexahydroazepine 13: A solution of alcohol **11** (8.47 g, 20.05 mmol) in CH$_2$Cl$_2$ (85 mL) was cooled to 0 °C and treated with triethylamine (4.19 mL, 30.08 mL) and methanesulfonyl chloride (1.86 mL, 24.1 mmol). After stirring at 0 °C for 20 min, the solution was quenched by the addition of water (100 mL) and the organic solvent was then evaporated in vacuo. The aqueous residue was extracted with EtOAc (160 mL × 2) and the combined organic layers were washed with water (150 mL) and brine (150 mL) and then dried (Na$_2$SO$_4$), filtered and concentrated. The crude product was dissolved in THF (1003 mL, 0.02 M), and KOtBu (24.1 mL, 1.0 M in THF) was added dropwise over 50 min at 25 °C. After being stirred for a

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further 10 min, the reaction was quenched with saturated aqueous NH_4Cl (150 mL) and the organic solvent was then evaporated in vacuo. The aqueous residue was extracted with EtOAc (200 mL × 2), and the combined organic layers were washed with brine (300 mL) and then dried (Na_2SO_4), filtered and concentrated. Purification of the residue by flash chromatography (silica gel, 10 → 20% EtOAc in petroleum ether) afforded **13** (6.46 g, 80%) as a white solid. An analytical sample of **13** was prepared by recrystallisation from Et_2O/petroleum ether: M.p. 84–86 °C; R_f = 0.25 (20% EtOAc in petroleum ether); $[\alpha]_D^{23} = -104.6$ (c = 1.10 in $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}$ = 1697 (C=O), 1393 cm^{-1}; ^1H NMR (500 MHz, C_6D_6, 70 °C): δ = 7.26 (d, J = 7.3 Hz, 2H; Ar(*ortho*)), 7.12 (dd, J = 7.3, 7.3 Hz, 2H; Ar(*meta*)), 7.05 (t, J = 7.3 Hz, 1H; Ar(*para*)), 5.16, 5.09 (AB system, J = 12.8 Hz, 2H; CO_2CH_2Ph), 4.25 (bs, 1H; 3-H), 3.80–3.46 (bm, 4H; 2-H_2, 4-H and 7-H), 2.56 (bs, 1H; 7-H'), 1.93 (m, 1H; 5-H), 1.65 (s, 3H; acetonide), 1.51 (s, 3H; acetonide), 1.46–1.25 (m, 3H; 5-H' and 6-H_2); ^{13}C NMR (125 MHz, C_6D_6, 75 °C): δ = 155.8, 152.4, 137.9, 128.7, 128.6, 94.8, 79.9, 78.3, 74.3, 67.3, 62.5, 49.2, 45.4, 31.4, 28.6, 27.3, 26.0, 24.7, 24.1; FAB HRMS calcd for $C_{22}H_{33}N_2O_5$ (M + H^+): 405.2389, found: 405.2376.

Amide 14: A solution of hexahydroazepine **13** (4.00 g, 9.89 mmol) in CH_2Cl_2 (40 mL) was treated with trifluoroacetic acid (10 mL, excess) and stirred at 25 °C for 1 h. After dilution with benzene (120 mL), the solution was concentrated and the crude product was employed in the next reaction without further purification.
A suspension of *p*-benzyloxybenzoic acid (3.39 g, 14.84 mmol) in CH_2Cl_2 (34 mL) was cooled to 0 °C and treated with triethylamine (10.30 mL, 73.90 mmol) and oxalyl chloride (7.04 mL, 2.0 M in CH_2Cl_2). The reaction mixture was then warmed to 25 °C and stirred for 25 min. The crude aminoalcohol prepared above was dissolved in CH_2Cl_2 (40 mL) and treated with the freshly prepared solution of *p*-benzyloxybenzoyl chloride and triethylamine, and the resultant mixture was then stirred for 1.5 h at 25 °C. After quenching with MeOH (100 mL) and pyridine (20 mL), the reaction mixture was concentrated and then diluted with EtOAc (300 mL). This mixture was washed with 2 N HCl (150 mL × 2), water (150 mL), saturated aqueous $NaHCO_3$ (150 mL) and brine (150 mL) and then dried (Na_2SO_4), filtered and concentrated. Purification of the residue by flash chromatography (silica gel, 80 → 100% Et_2O in petroleum ether containing 1% MeOH) and recrystallisation of the product from EtOAc/*n*-hexane afforded **14** (3.42 g, 73% for the 2 steps) as white crystals: M.p. 123–124.5 °C; R_f 0.17 (3% MeOH in CH_2Cl_2); $[\alpha]_D^{23} = -73.0$ (c = 1.00 in $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}$ = 3345 (broad, OH and NH), 1680 (C=O), 1638 (C=O), 1608 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 20 °C): δ = 8.75 (d, J = 5.5 Hz, 1H; NH), 7.82 (ddd, J = 8.8, 2.8, 1.9 Hz, 2H; 3'-H and 7'H'), 7.45–7.29 (m, 10H; Ar), 7.02 (ddd, J = 8.8, 2.8, 1.9 Hz, 2H; 4'-H and 6'-H), 5.21, 5.18 (AB system, J = 12.3 Hz, 2H; CO_2CH_2Ph), 5.13 (s, 2H; 5'-OCH_2Ph), 4.19 (dd, J = 14.3, 3.8 Hz, 1H; 7-H), 4.15 (d, J = 15.4 Hz, 1H; 2-H), 4.10 (m, 1H; 3-H), 3.77 (ddd, J = 10.2, 6.1, 1.6 Hz, 1H; 4-H), 3.35 (dd, J = 15.4, 5.1 Hz, 1H; 2-H'), 2.79 (ddd, J = 14.3, 13.2, 3.5 Hz, 1H; 7-H'), 1.95–1.81 (m, 3H; 5-H_2 and 6-H), 1.66 (m, 1H; 6-H'); ^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): δ = 168.5, 161.5, 157.7, 136.3, 136.1, 129.1, 128.62, 128.56, 128.2, 128.1, 127.7, 127.4, 125.6, 114.6, 79.7, 70.0, 67.8, 60.7, 50.4, 50.2, 32.7, 27.3; FAB HRMS calcd for $C_{28}H_{31}N_2O_5$ (M + H^+): 475.2233, found: 475.2242.

Benzyl alcohol 32: A solution of ester **30** (124 mg, 0.354 mmol) in THF (2 mL) was cooled to −98 °C and treated with *n*BuLi (0.23 mL, 2.0 M in pentane). The reaction mixture was then allowed to warm to −78 °C over 10 min and stirring was continued for a further 20 min. The reaction was then quenched by the addition of saturated aqueous $NaHCO_3$, diluted with water (10 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were then dried (Na_2SO_4), filtered and concentrated. Purification of the residue by PTLC (silica gel, 1% Et_3N and 80% Et_2O in petroleum ether) afforded **32** (84 mg, 87%) as a white solid: M.p. 93.5–95.5 °C; R_f = 0.20 (60% Et_2O in petroleum ether); IR (thin film): $\tilde{\nu}_{max}$ = 3420 (broad, OH), 1663 (C=O),1593, 1472, 1252, 1110 cm^{-1}; ^1H NMR (500 MHz, [D$_6$]DMSO, 20 °C): δ = 7.85 (d, J = 7.7 Hz, 1H; 10''-H), 7.61 (t, J = 7.7 Hz, 1H; 2''-H), 7.40 (dd, J = 7.7, 7.7 Hz, 1H; 11''-H), 7.37 (d, J = 7.7 Hz, 1H; 13''-H), 7.29 (dd, J = 7.7, 7.7 Hz, 1H; 12''-H), 6.76 (d, J = 7.7 Hz, 2H; 3''-H and 7''-H), 5.34 (bt, J = 4.6 Hz, 1H; OH), 4.91 (d, J = 4.6 Hz, 2H; CH_2OH), 3.65 (s, 6H; 4''-OCH_3 and 6''-OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): δ = 196.6, 156.7, 144.8, 134.3, 132.8, 131.7, 131.0, 126.4, 126.2, 118.8, 104.5, 61.3, 55.9; FAB HRMS calcd for $C_{16}H_{17}O_4$ (M + H^+): 273.1127, found: 273.1137.

Bromide 34: A solution of *N,N,N'*-trimethylethylenediamine (4.97 mL, 39.09 mmol) in benzene (100 mL) was cooled to 0 °C and treated with *n*BuLi (18.81 mL, 2.0 M in pentane). After stirring at 25 °C for 30 min, the reaction mixture was recooled to 0 °C and 3-(benzyloxy)benzaldehyde **33** (7.75 g, 36.51 mmol) was added in one portion. The resultant solution was then stirred at 25 °C for 30 min and again recooled to 0 °C before treatment with PhLi (60.9 mL, 1.8 M in cyclohexane/Et_2O). This mixture was allowed to warm to 25 °C and then stirred for a further 7.5 h. The resultant dark purple solution was diluted with THF (100 mL), cooled to −78 °C and treated with 1,2-dibromotetrafluoroethane (17.5 mL, 146.0 mmol). The reaction mixture was subsequently allowed to warm to 25 °C over 30 min and the solvents were then evaporated in vacuo and the residue diluted with EtOAc (300 mL). The resultant mixture was washed with 1 N HCl (200 mL × 2), saturated aqueous $NaHCO_3$ (150 mL) and brine (150 mL) and then dried (Na_2SO_4), filtered and concentrated. Purification of the residue by flash chromatography (silica gel, 5–15% EtOAc in petroleum ether) and recrystallisation of the product from EtOAc/*n*-hexane afforded **34** (8.18 g, 77%) as white crystals: M.p. 130.5–132 °C; R_f = 0.38 (10% EtOAc in petroleum ether); IR (thin film): $\tilde{\nu}_{max}$ = 1679 (C=O), 1269, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 20 °C): δ = 10.37 (s, 1H; CHO), 7.54 (d, J = 7.5 Hz, 1H; 11''-H), 7.49 (d, J = 7.2 Hz, 2H; OCH_2Ph(*ortho*)), 7.42 (dd, J = 7.2, 7.2 Hz, 2H; OCH_2Ph(*meta*)), 7.35 (m, 2H; OCH_2Ph(*para*) and 12''-H), 7.17 (d, J = 7.9 Hz, 1H; 13''-H), 5.22 (s, 2H; OCH_2Ph); ^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): δ = 192.3, 155.3, 135.9, 134.9, 128.7, 128.24, 128.20, 127.0, 121.7, 118.7, 117.9, 71.2; FAB HRMS calcd for $C_{14}H_{11}O_2Br$ (M + H^+): 291.0021, found: 291.0025.

Benzyl alcohol 35: A solution of bromide **34** (7.19 g, 24.69 mmol) in CH_2Cl_2 (70 mL) was cooled to −78 °C and treated with DIBALH (29.6 mL, 1.0 M in CH_2Cl_2). The reaction mixture was then warmed to 0 °C and stirred for 1 h. After quenching with saturated aqueous NH_4Cl (8.3 mL) and dilution with Et_2O (100 mL), the mixture was stirred for 4 h at 25 °C. After addition of $MgSO_4$, the suspension was filtered through Celite and concentrated, and the resulting solid was recrystallised from EtOAc/*n*-hexane to afford **35** (6.95 g, 96%) as white crystals: M.p. 123.5–124.5 °C; R_f = 0.47 (30% EtOAc in petroleum ether); IR (thin film): $\tilde{\nu}_{max}$ = 3315 (broad, OH), 1457, 1283, 1030, 691 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 20 °C): δ = 7.49 (d, J = 7.3 Hz, 2H; OCH_2Ph(*ortho*)), 7.40 (dd, J = 7.3, 7.3 Hz, 2H; OCH_2Ph(*meta*)), 7.33 (t, J = 7.3 Hz, 1H; OCH_2Ph(*para*)), 7.26 (dd, J = 7.9, 7.9 Hz, 1H; 12''H), 7.11 (d, J = 7.9 Hz, 1H; Ar), 6.90 (d, J = 7.9 Hz, 1H; Ar), 5.18 (s, 2H; 10''-OCH_2Ph), 4.79 (d, J = 6.5 Hz, 2H; $ArCH_2OH$), 2.07 (t, J = 6.5 Hz, 1H; OH); ^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): δ = 154.9, 141.6, 136.5, 128.6, 128.1, 127.9, 127.0, 121.0, 112.8, 112.5, 70.9, 65.3; FAB HRMS calcd for $C_{14}H_{13}O_2Br$ (M^+): 292.0099, found: 292.0104.

Benzyl ester 37: A solution of 4-bromo-3,5-dihydroxybenzoic acid **36** (11.55 g, 49.56 mmol) in DMF (100 mL) was treated with K_2CO_3 (34.25 g, 247.8 mmol) and benzyl bromide (19.4 mL, 163.5 mmol) and stirred for 4 h at 25 °C. After dilution with water (1 L), the precipitates were filtered and then rinsed with water (500 mL × 2) and chilled EtOH (500 mL). The resultant solid was recrystallised from toluene to afford **37** (23.95 g, 96%) as white crystals: M.p. 131–132 °C; R_f = 0.25 (10% EtOAc in petroleum ether); IR (thin film): $\tilde{\nu}_{max}$ = 1717 (C=O), 1585, 1423, 1376, 1328, 1234, 1114, 738, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 20 °C): δ = 7.49 (d, J = 7.5 Hz, 4H; 4''-OCH_2Ph(*ortho*) and 6''-OCH_2Ph(*ortho*)), 7.42–7.37 (m, 9H; Ar), 7.34–7.31 (m, 4H; Ar), 5.34 (s, 2H; 2''-CO_2CH_2Ph), 5.20 (s, 4H; 4''-OCH_2Ph and 6''-OCH_2Ph); ^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): δ = 165.7, 156.2, 136.1, 135.8, 130.0, 128.6, 128.4, 128.2, 128.0, 127.1, 108.4, 107.4, 71.1, 67.1; FAB HRMS calcd for $C_{28}H_{23}O_4BrCs$ (M + Cs^+): 634.9834, found: 634.9841.

Benzyl alcohol 38: A solution of benzyl ester **37** (23.95 g, 47.58 mmol) in CH_2Cl_2 (240 mL) was cooled to −78 °C and treated with DIBALH (114.2 mL, 1.0 M in toluene). The reaction mixture was then warmed to 0 °C and stirred at 0 °C for 1 h. After quenching with saturated aqueous NH_4Cl (33 mL) and dilution with Et_2O (200 mL), the mixture was stirred for 4 h at 25 °C. After addition of $MgSO_4$, the suspension was filtered through Celite and concentrated, and the resulting solid was reprecipitated from EtOAc/petroleum ether to afford **38** (19.00 g, 100%) as a white solid: M.p. 119.5–120.5 °C; R_f = 0.33 (40% EtOAc in petroleum ether); IR (thin film): $\tilde{\nu}_{max}$ = 3363 (broad, OH), 1587, 1430, 1112, 737, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 20 °C): δ = 7.49 (d, J = 7.5 Hz, 4H; OCH_2Ph(*ortho*)), 7.39 (dd, J = 7.5, 7.5 Hz, 4H; OCH_2Ph(*meta*)), 7.32 (t, J = 7.5 Hz, 2H; OCH_2Ph(*para*)), 6.65 (s, 2H; 3''-H and 7''-H), 5.17 (s, 4H; 4''-OCH_2Ph and 6''-OCH_2Ph), 4.61 (d, J = 5.9 Hz, 2H; $ArCH_2OH$), 1.70 (t, J = 5.9 Hz, 1H; OH); ^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): δ = 156.3, 141.6, 136.5, 128.6, 127.9, 127.0, 104.8, 101.3, 70.9, 65.0; FAB HRMS calcd for $C_{21}H_{19}O_3BrCs$ (M + Cs^+): 530.9572, found: 530.9580.

Silyl ether 39: A solution of benzyl alcohol **38** (19.00 g, 47.58 mmol) and imidazole (4.86 g, 71.37 mmol) in DMF (100 mL) was cooled to 0 °C, treated with *t*BuPh$_2$SiCl (14.8 mL, 57.0 mmol), and then warmed to 25 °C and stirred for 1 h. The reaction was quenched by the addition of water (700 mL) and the aqueous residue was extracted with Et_2O (1200 mL). The organic layer was washed with water (600 mL × 2) and brine (600 mL) and then dried (Na_2SO_4), filtered and concentrated. The crude product was recrystallised from Et_2O/*n*-hexane to afford **39** (24.97 g, 82%) as white crystals: M.p. 98.5–99.5 °C; R_f = 0.43 (5% EtOAc in petroleum ether); IR (thin film): $\tilde{\nu}_{max}$ = 1588, 1429, 1109, 737, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 20 °C): δ = 7.63 (m, 4H; Si*t*BuPh_2(*ortho*)), 7.45 (d, J = 7.3 Hz, 4H; 4''-OCH_2Ph(*ortho*) and 6''-OCH_2Ph(*ortho*)), 7.42 (tt, J = 7.4, 1.4 Hz, 2H; Si*t*BuPh_2-(*para*)), 7.38–7.35 (m, 8H; Ar), 7.30 (tt ,J = 7.3, 2.1 Hz, 2H; 4''-OCH_2Ph(*para*) and 6''-OCH_2Ph(*para*)), 6.60 (s, 2H; 3''-H and 7''-H), 5.12 (s, 4H; $ArOCH_2Ph$), 4.67 (s, 2H; $ArCH_2OTPS$), 1.07 (s, 9H; *t*Bu); ^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): δ = 156.1, 141.8, 136.7, 135.5, 133.2, 129.8, 128.5, 127.81, 127.77, 126.9, 104.1, 100.4, 70.7, 65.2, 26.8, 19.3; FAB HRMS calcd for $C_{37}H_{37}O_3BrSiCs$ (M + Cs^+): 769.0750, found: 769.0768.

Carboxylic acid 40: A solution of silyl ether **39** (19.95 g, 31.28 mmol) in THF (200 mL) was cooled to −98 °C and treated with *n*BuLi (21.5 mL, 1.6 M in hexanes). The resultant mixture was then warmed to −78 °C and stirred for 30 min. Crushed dry ice (excess) was then added and the reaction mixture was warmed to 25 °C over 30 min. The solvent was then evaporated in vacuo and 1 N $KHSO_4$ (70 mL) and

CH_2Cl_2 (200 mL) were added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (150 mL × 2). The combined organic layers were washed with brine (300 mL) and then dried (Na_2SO_4), filtered and concentrated. Purification of the residue by flash chromatography (silica gel, 2–7% MeOH in CH_2Cl_2) and recrystallisation of the product from EtOH/*n*-hexane afforded **40** (11.31 g, 60%) as white crystals: M.p. 156.5–158 °C; $R_f = 0.22$ (5% MeOH in CH_2Cl_2); IR (thin film): $\tilde{\nu}_{max} = 1703$ (C=O), 1432, 1112, 736, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 20 °C): $\delta = 7.63$ (ddd, $J = 8.1$, 3.4, 2.0 Hz, 4H; Si*t*BuPh_2(*ortho*)), 7.44 (tt, $J = 7.3$, 2.3 Hz, 2H; Si*t*BuPh_2(*para*)), 7.42–7.26 (m, 14H; Ar), 6.64 (s, 2H; 3″-H and 7″-H), 5.12 (s, 4H; ArOCH_2Ph), 4.69 (s, 2H; ArCH_2OTPS), 1.08 (s, 9H; *t*Bu); ^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): $\delta = 168.5$, 157.3, 146.0, 136.3, 135.5, 133.1, 129.8, 128.6, 127.84, 127.81, 126.9, 110.6, 103.3, 70.6, 65.1, 26.8, 19.3; FAB HRMS calcd for $C_{38}H_{38}O_5SiCs$ ($M + Cs^+$): 735.1543, found: 735.1565.

Ester 41: A solution of carboxylic acid **40** (9.20 g, 15.26 mmol), benzyl alcohol **35** (4.47 g, 15.26 mmol) and triphenylphosphine (4.40 g, 16.78 mmol) in THF (76 mL) was cooled to 0 °C and treated with diethyl azodicarboxylate (2.64 mL, 16.78 mmol). The resultant mixture was then warmed to 25 °C and stirred for 40 min. The reaction mixture was concentrated and the residue passed through a short column (silica gel, 25% EtOAc in petroleum ether). The eluent was then concentrated and the residue purified by flash chromatography (silica gel, 7 → 12% EtOAc in petroleum ether) to afford **41** (12.44 g, 93%) as a colourless oil: $R_f = 0.35$ (15% EtOAc in petroleum ether); IR (thin film): $\tilde{\nu}_{max} = 1735$ (C=O), 1587, 1433, 1264, 1110, 738, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 20 °C): $\delta = 7.63$ (m, 4H; Si*t*BuPh_2(*ortho*)), 7.46 (d, $J = 7.3$ Hz, 2H; 10″-OCH$_2$*Ph*(*ortho*)), 7.43 (tt, $J = 7.4$, 2.2 Hz, 2H; Si*t*BuPh_2(*para*)), 7.42–7.24 (m, 17H; Ar), 7.07 (d, $J = 8.0$ Hz, 1H; Ar), 6.91 (dd, $J = 8.0$, 8.0 Hz, 1H; 12″-H), 6.81 (d, $J = 8.0$, Hz, 1H; Ar), 6.60 (s, 2H; 3″-H and 7″-H), 5.48 (s, 2H; 14″-CH_2), 5.13 (s, 2H; 10″-OCH_2Ph), 5.07 (s, 4H; 4″-OCH_2Ph and 6″-OCH_2Ph), 4.68 (s, 2H; ArCH_2OTPS), 1.07 (s, 9H; *t*Bu); ^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): $\delta = 166.1$, 156.5, 154.9, 145.0, 137.1, 136.6, 136.5, 135.5, 133.1, 129.8, 128.54, 128.48, 128.4, 127.9, 127.8, 127.0, 126.9, 112.9, 112.8, 112.2, 102.9, 70.8, 70.2, 66.6, 65.2, 26.8, 19.2; FAB HRMS calcd for $C_{52}H_{59}O_6BrSi$ ($M + H^+$): 877.2560, found: 877.2550.

Benzyl alcohol 42: A solution of ester **41** (6.39 g, 7.28 mmol) in THF (73 mL) was cooled to −98 °C and treated with *n*BuLi (4.78 mL, 1.6 M in hexanes). The resultant mixture was then warmed to −78 °C and stirred for 30 min. After the reaction was quenched with saturated aqueous $NaHCO_3$ (50 mL), the THF was evaporated in vacuo and the residue extracted with EtOAc (100 mL × 2). The combined organic layers were washed with brine (100 mL) and then dried (Na_2SO_4), filtered and concentrated. Purification of the residue by flash chromatography (silica gel, 1% MeOH and 20% EtOAc in petroleum ether) afforded **42** (4.98 g, 86%) as a white foam: $R_f = 0.13$ (20% EtOAc in petroleum ether); IR (thin film): $\tilde{\nu}_{max} = 3493$ (broad, OH), 1652 (C=O), 1584, 1429, 1266, 1110, 740, 700 cm^{-1}; ^1H NMR (500 MHz, [D$_6$]DMSO, 20 °C): $\delta = 7.61$ (ddd, $J = 8.1$, 3.4, 2.0 Hz, 4H; Si*t*BuPh_2(*ortho*)), 7.48 (tt, $J = 7.3$, 1.4 Hz, 2H; Si*t*BuPh_2(*para*)), 7.43–7.40 (m, 5H; Ar), 7.26–7.21 (m, 6H; Ar), 7.14 (t, $J = 7.3$ Hz, 1H; Ar), 7.07 (t, $J = 7.7$ Hz, 2H; Ar), 7.02–6.99 (m, 6H; Ar), 6.83 (d, $J = 7.1$, Hz, 2H; 10″-OCH$_2$*Ph*(*para*)), 6.59 (s, 2H; 3″-H and 7″-H), 4.97 (t, $J = 5.6$ Hz, 1H; OH), 4.77 (s, 2H; 10″-OCH_2Ph), 4.73 (s, 4H; 4″-OCH_2Ph and 6″-OCH_2Ph), 4.71 (s, 2H; ArCH_2OTPS), 4.51 (d, $J = 5.6$ Hz, 2H; ArCH_2OH), 1.03 (s, 9H; *t*Bu); ^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): $\delta = 195.2$, 156.4, 156.1, 143.9, 143.4, 136.6, 136.2, 134.9, 132.6, 130.6, 129.9, 128.6, 128.1, 127.90, 127.86, 127.8, 127.5, 127.34, 127.30, 126.7, 119.9, 118.6, 110.9, 102.5, 69.6, 69.0, 64.7, 60.2, 26.5, 18.7; FAB HRMS calcd for $C_{52}H_{50}O_6SiCs$ ($M + Cs^+$): 931.2431, found: 931.2445.

General procedure A for oxidation of benzyl alcohols to benzaldehydes: A suspension of the benzyl alcohol derivative (1 mmol), 4-methylmorpholine *N*-oxide (175.7 mg, 1.5 mmol) and activated 3 Å molecular sieves in acetonitrile (5 mL) was treated with tetrapropylammonium perruthenate(VII) (17.6 mg, 0.05 mmol) and stirred at 25 °C for 30 min. The reaction mixture was then diluted with EtOAc and filtered through a pad of silica gel. The filtrate was concentrated and the residue purified by flash chromatography (silica gel) to afford the corresponding aldehyde.

Benzaldehyde 43: Benzyl alcohol **42** (4.98 g, 6.24 mmol) was converted to **43** (3.73 g, 75%) according to general procedure A and isolated as white crystals by recrystallisation from EtOAc/*n*-hexane: M.p. 123–125 °C; $R_f = 0.30$ (20% EtOAc in petroleum ether); IR (thin film): $\tilde{\nu}_{max} = 1693$ (C=O), 1662 (C=O), 1583, 1430, 1263, 1110, 741, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 20 °C): $\delta = 9.93$ (s, 1H; CHO), 7.67 (dd, $J = 8.0$, 1.2 Hz, 4H; Si*t*BuPh_2(*ortho*)), 7.44 (tt, $J = 7.5$, 1.3 Hz, 2H; Si*t*BuPh_2(*para*)), 7.39–7.34 (m, 6H; Ar), 7.24–7.17 (m, 6H; Ar), 7.12 (t, $J = 7.5$ Hz, 2H; Ar), 7.08–7.02 (m, 6H; Ar), 6.90 (d, $J = 7.3$ Hz, 2H; 10″-OCH$_2$*Ph*(*ortho*)), 6.52 (s, 2H; 3″-H and 7″-H), 4.79 (s, 2H; ArCH_2OTPS), 4.72 (s, 6H; 4″-OCH_2Ph, 6″-OCH_2Ph and 10″-OCH_2Ph), 1.11 (s, 9H; *t*Bu); ^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): $\delta = 193.9$, 191.5, 157.6, 156.3, 145.8, 136.9, 136.2, 135.8, 135.6, 135.51, 135.47, 133.1, 130.5, 129.9, 128.3, 128.2, 127.84, 127.78, 127.7, 127.6, 127.1, 119.9, 119.1, 116.9, 102.5, 70.5, 70.1, 65.2, 26.8, 19.3; FAB HRMS calcd for $C_{52}H_{48}O_6SiCs$ ($M + Cs^+$): 929.2275, found: 929.2243.

General procedure B for oxidation of benzaldehydes to benzoic acids: A solution of the aldehyde (1 mmol) in THF (4.5 mL), *t*BuOH (4.5 mL) and water (1.5 mL) was treated with 2-methyl-2-butene (4.0 mL, 2.0 M in THF), NaH_2PO_4 (3.0 mL, 1.0 M in water) and 80% $NaClO_2$ (339 mg, 3.0 mmol). The reaction mixture was stirred at 25 °C until the oxidation was complete (8–12 h for 14″-aldehyde; 1 h for 2″-aldehyde), and the organic solvents were then evaporated in vacuo. The residue was then treated with $KHSO_4$ (10 mL, 0.5 M in water) and the resultant aqueous mixture was extracted with EtOAc (10 mL × 2). The combined layers were washed with water (10 mL), saturated Na_2SO_3 (5 mL) and brine (10 mL) and then dried (Na_2SO_4), filtered and concentrated. Purification of the residue by flash chromatography (silica gel, 0–5% MeOH in CH_2Cl_2) and recrystallisation of the product from EtOAc/*n*-hexane then afforded the corresponding carboxylic acid.

Carboxylic acid 44: Benzaldehyde **43** (3.71 g, 4.65 mmol) was converted to **44** (3.71 g, 98%) according to general procedure B and isolated as white crystals: M.p. 124–124.5 °C; $R_f = 0.12$ (5% MeOH in CH_2Cl_2); IR (thin film): $\tilde{\nu}_{max} = 1694$ (C=O), 1674 (C=O), 1606, 1580, 1429, 1271, 1110, 736, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 20 °C): $\delta = 8.54$ (s), 7.67–7.64 (m; Ar), 7.44 (m; Ar), 7.38–7.31 (m; Ar), 7.23–7.07 (m; Ar), 7.03–7.01 (m; Ar), 6.99 (d, $J = 7.5$, Hz; 10″-OCH$_2$*Ph*(*ortho*)), 6.95 (m; Ar), 6.91 (d, $J = 8.1$ Hz; Ar), 6.78 (s; Ar), 6.71 (d, $J = 7.3$ Hz; Ar), 6.59 (s; Ar), 6.56 (s; Ar), 5.11, 5.02 (AB system, $J = 11.3$ Hz; ArOCH_2Ph), 5.07, 5.00 (AB system, $J = 12.2$ Hz; ArOCH_2Ph), 4.78 (s), 4.74 (s; ArCH_2OTPS), 4.61, 4.36 (AB system, $J = 11.2$ Hz; ArOCH_2Ph), 1.09 (s, 9H; *t*Bu); ^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): $\delta = 192.3$, 169.7, 169.2, 158.7, 158.3, 157.0, 155.6, 152.5, 146.4, 144.2, 139.3, 136.5, 136.3, 136.2, 135.50, 135.46, 135.2, 135.1, 133.12, 133.06, 133.02, 130.7, 129.9, 129.8, 129.3, 128.9, 128.6, 128.34, 128.28, 128.25, 128.21, 127.9, 127.84, 127.75, 127.6, 127.5, 127.2, 127.0, 122.8, 116.8, 116.4, 116.3, 111.6, 105.6, 104.4, 103.9, 102.8, 72.6, 70.5, 70.36, 70.32, 69.6, 65.2, 64.9, 26.8, 19.3 [the equilibrium between ketocarboxylic acid and its hemiketal precluded a comprehensive assignment of all resonances]; FAB HRMS calcd for $C_{52}H_{48}O_7SiCs$ ($M + Cs^+$): 945.2224, found: 945.2236.

Benzyl ester 45: A solution of carboxylic acid **44** (3.70 g, 4.55 mmol) in DMF (40 mL) was treated with K_2CO_3 (1.89 g, 13.65 mmol) and benzyl bromide (1.08 mL, 9.10 mmol) and stirred for 1 h at 25 °C. The reaction was then quenched with water (350 mL) and the aqueous residue extracted with EtOAc (80 mL × 2). The combined organic layers were washed with water (80 mL × 2) and then dried (Na_2SO_4), filtered and concentrated. Purification of the residue by flash chromatography (silica gel, 15 → 20% EtOAc in petroleum ether) afforded **45** (4.03 g, 98%) as a white foam: $R_f = 0.28$ (20% EtOAc in petroleum ether); IR (thin film): $\tilde{\nu}_{max} = 1724$ (C=O), 1662 (C=O), 1605, 1581, 1429, 1273, 1110, 736, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 20 °C): $\delta = 7.67$ (m, 4H; Si*t*BuPh_2(*ortho*)), 7.44 (tt, $J = 7.5$, 1.3 Hz, 2H; Si*t*BuPh_2(*para*)), 7.38 (tt, $J = 7.0$, 1.1 Hz, 4H; Ar), 7.25–7.13 (m, 14H; Ar), 7.10 (tt, $J = 6.9$, 1.5 Hz, 2H; 4″-OCH$_2$*Ph*(*para*) and 6″-OCH$_2$*Ph*(*para*)), 7.05 (m, 4H; Ar), 6.97 (bd, $J = 7.2$ Hz, 2H; Ar), 6.91 (d, $J = 8.2$ Hz, 1H; Ar), 6.53 (s, 2H; 3″-H and 7″-H), 5.13 (s, 2H; CO_2CH_2Ph), 4.81 (s, 2H; 10″-OCH_2Ph), 4.73 (s, 4H; 4″-OCH_2Ph and 6″-OCH_2Ph), 4.71 (s, 2H; ArCH_2OTPS), 1.10 (s, 9H; *t*Bu); ^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): $\delta = 192.0$, 166.9, 159.0, 155.6, 146.2, 136.5, 136.3, 135.9, 135.5, 134.7, 133.2, 131.3, 129.9, 129.3, 128.3, 128.2, 127.8, 127.5, 127.4, 127.11, 127.05, 122.3, 118.2, 115.7, 102.8, 70.4, 70.2, 66.8, 65.3, 26.8, 19.3; FAB HRMS calcd for $C_{59}H_{54}O_7SiCs$ ($M + Cs^+$): 1035.2693, found: 1035.2736.

General procedure C for desilylation of *tert*-butyldiphenylsilylethers: A solution of the *tert*-butyldiphenylsilylether (1 mmol) in THF (10 mL) was treated with tetrabutylammonium fluoride (1.20 mL, 1.0 M in THF) and stirred for 10 min at 25 °C. The solution was then concentrated and the residue purified by flash chromatography (silica gel, 1% MeOH and 20 → 40% EtOAc in petroleum ether) to afford the corresponding benzyl alcohol.

Benzyl alcohol 46: Benzyl ester **45** (3.52 g, 3.90 mmol) was converted to **46** (2.46 g, 95%) according to general procedure C and isolated as white crystals by recrystallisation from EtOAc/*n*-hexane: M.p. 138.5–139.5 °C; $R_f = 0.26$ (1% MeOH and 40% EtOAc in petroleum ether); $\tilde{\nu}_{max} = 3448$ (broad, OH), 1722 (C=O), 1655 (C=O), 1605, 1580, 1431, 1274, 1118, 739, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 20 °C): $\delta = 7.24–7.16$ (m, 14H; Ar), 7.14 (tt, $J = 7.1$, 1.4 Hz, 2H; 4″-OCH$_2$*Ph* and 6″-OCH$_2$*Ph*(*para*)), 7.09–7.07 (m, 4H; Ar), 6.97 (bd, $J = 7.1$ Hz, 2H; Ar), 6.90 (dd, $J = 8.1$, 1.0 Hz, 1H; 11″-H), 6.50 (s, 2H, 3″-H and 7″-H), 5.13 (s, 2H; CO_2CH_2Ph), 4.78 (s, 4H; 4″-OCH_2Ph and 6″-OCH_2Ph), 4.77 (s, 2H; 10″-OCH_2Ph), 4.61 (d, $J = 6.0$ Hz, 2H; CH_2OH), 1.86 (t, $J = 6.0$ Hz, 1H; OH); ^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): $\delta = 192.2$, 166.9, 159.0, 155.7, 146.4, 136.4, 136.3, 135.9, 134.2, 131.5, 129.5, 128.24, 128.19, 128.1, 127.8, 127.6, 127.4, 127.2, 127.1, 122.2, 118.4, 115.7, 103.3, 70.4, 70.3, 66.8, 64.8; FAB HRMS calcd for $C_{43}H_{36}O_7Cs$ ($M + Cs^+$): 797.1515, found: 797.1527.

Benzaldehyde 47: Benzyl alcohol **46** (2.37 g, 3.57 mmol) was converted to **47** (1.66 g, 70%) according to general procedure A and isolated as white crystals by recrystallisation from EtOAc/*n*-hexane: M.p. 110–112 °C; $R_f = 0.47$ (30% EtOAc in petroleum ether); IR (thin film): $\tilde{\nu}_{max} = 1724$ (C=O), 1697 (C=O), 1667(C=O), 1581, 1434, 1278, 1114, 738, 695 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 20 °C): $\delta = 9.81$ (s, 1H; CHO), 7.34 (t, $J = 8.0$ Hz, 1H; Ar), 7.26–7.19 (m, 13H; Ar), 7.11–7.06 (m, 6H; Ar), 6.97 (dd, $J = 8.4$, 0.8 Hz, 1H; 11″-H), 6.90 (s, 2H; 3″-H and 7″-H), 6.83 (d, $J = 8.2$ Hz, 2H; Ar), 5.14 (s, 2H; CO_2CH_2Ph), 4.81 (s, 4H; 4″-

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OCH_2Ph and 6″-OCH_2Ph), 4.70 (s, 2H; 10″-OCH_2Ph); ^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): δ = 191.5, 191.4, 167.6, 158.2, 156.6, 138.1, 135.9, 135.7, 135.4, 133.4, 131.2, 131.1, 128.33, 128.29, 128.2, 127.94, 127.92, 127.7, 127.1, 125.3, 122.0, 115.1, 106.5, 70.6, 70.4, 67.2; FAB HRMS calcd for $C_{43}H_{34}O_7Cs$ (M + Cs^+): 795.1359, found: 795.1369.

Carboxylic acid 48: Benzaldehyde **47** (1.56 g, 2.35 mmol) was converted to **48** (1.51 g, 95%) according to general procedure B and isolated as white crystals: M.p. 158–160.5 °C; R_f = 0.30 (5% MeOH in CH_2Cl_2); IR (thin film): $\tilde{\nu}_{max}$ = 3000 (broad, OH), 1722 (C=O), 1690 (C=O), 1670 (C=O), 1581, 1424, 1278, 1115, 1039, 910, 737, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 20 °C): δ = 7.31 (dd, J = 8.0, 8.0 Hz, 1H; 12″-H), 7.25–7.21 (m, 15H; Ar), 7.13 (t, J = 7.9 Hz, 2H; 4″-OCH_2Ph and 6″-OCH_2Ph(*para*)), 7.07–7.05 (m, 4H; Ar), 6.96 (d, J = 8.2 Hz, 1H; 11″-H), 6.85 (d, J = 7.3 Hz, 2H; Ar), 5.14 (s, 2H; CO_2CH_2Ph), 4.79 (s, 4H; 4″-OCH_2Ph and 6″-OCH_2Ph), 4.71 (s, 2H; 10″-OCH_2Ph); ^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): δ = 191.6, 171.0, 167.5, 157.8, 156.4, 136.0, 135.7, 135.5, 133.1, 131.7, 131.6, 130.8, 128.3, 128.2, 127.9, 127.6, 127.2, 124.7, 122.0, 115.2, 107.2, 70.5, 70.4, 67.1; FAB HRMS calcd for $C_{43}H_{35}O_8$ (M + H^+): 679.2332, found: 679.2310.

General procedure D for ester formation: A suspension of the alcohol (1.00 mmol), the carboxylic acid (1.00 mmol) and 2-chloro-1-methylpyridinium iodide (332 mg, 1.30 mmol) in CH_2Cl_2 (10 mL) was treated with triethylamine (0.28 mL, 2.0 mmol) and then stirred at 25 °C for 30 min. 4-Dimethylaminopyridine (61.1 mg, 0.50 mmol) was then added to the mixture and stirring was continued at 25 °C for a further 3 h. The reaction mixture was then passed through a pad of silica gel and the filtrate concentrated in vacuo. Purification of the residue by PTLC (silica gel, 40% EtOAc and 10% CH_2Cl_2 in petroleum ether) then afforded the corresponding ester.

Fully protected balanol 49: Amide **14** (62.6 mg, 0.132 mmol) and carboxylic acid **48** (89.6 mg, 0.132 mmol) were coupled according to general procedure D to afford **49** (118.9 mg, 79%) as a colourless oil: R_f = 0.36 (20% EtOAc in benzene); $[\alpha]_D^{23}$ = −63.9 (c = 0.83 in $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}$ = 3377 (NH), 1712 (C=O), 1663 (C=O), 1604 (C=O), 1581 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 20 °C): δ = 7.80 (d, J = 7.8 Hz), 7.72 (d, J = 7.8 Hz), 7.42–7.03 (m), 6.91 (bdd, J = 7.1, 7.1 Hz), 6.82 (bd, J = 7.7 Hz), 5.27 (AB system, J = 12.5 Hz, OCH_2Ph), 5.24 (d, J = 12.5 Hz, OCH_2Ph), 5.19 (m, 4-H), 5.10 (s, OCH_2Ph), 5.05 (s, OCH_2Ph), 4.85, 4.82 (AB system, J = 11.9 Hz, OCH_2Ph), 4.68 (s, OCH_2Ph), 4.12 (bd, J = 5.5 Hz, 3-H), 3.42 (dd, J = 15.3, 5.5 Hz, 2-H), 2.90 (ddd, J = 14.5, 10.8, 4.4 Hz, 7-H), 2.09–1.76 (m, 6-H, 7-H′); ^{13}C NMR (125 MHz, C_6D_6, 75 °C) δ = 190.4, 167.7, 166.2, 166.0, 162.0, 159.0, 157.4, 137.5, 137.0, 136.7, 134.5, 130.5, 129.4, 128.9, 128.7, 128.6, 128.5, 128.4, 128.0, 127.8, 127.7, 127.7, 122.6, 116.0, 115.3, 108.6, 78.5, 71.4, 71.3, 70.4, 68.0, 67.3, 54.5, 49.2, 29.6 [the presence of rotamers precluded a comprehensive assignment of all proton and carbon resonances]; FAB HRMS calcd for $C_{71}H_{62}N_2O_{12}$ (M + Cs^+): 1267.3357, found: 1267.3306.

General procedure E for debenzylation: A solution of the fully protected balanol (derivative) (1.00 mmol) in formic acid (50 mL) was treated with palladium black (300 mg, 2.8 mmol) and then stirred for 7 h at 25 °C. The resultant mixture was filtered and concentrated and the residue purified by PTLC on silica gel (nBuOH/H_2O/AcOH = 5/1/1) followed by PTLC on C_{18}-reversed phase silica gel (40% MeCN in water) to afford balanol (analogue).

Balanol (1): Fully protected balanol **49** (70.0 mg, 61.7 μmol) was converted to balanol (**1**) (27.1 mg, 80%) as a yellow solid according to general procedure E: M.p. decomp. ≥ 180 °C; R_f = 0.64 (nBuOH/H_2O/AcOH = 4/1/1); $[\alpha]_D^{23}$ = −111.0 (c = 0.10 in MeOH); IR (thin film) $\tilde{\nu}_{max}$ = 3385 (NH), 1711 (C=O), 1628 (C=O), 1604, 1507 cm^{-1}; ^1H NMR (500 MHz, CD_3OD, 23 °C): δ = 7.60 (d, J = 8.7 Hz, 2H; 3′-H and 7′-H), 7.26 (d, J = 7.3 Hz, 1H; 13″-H), 7.17 (dd, J = 7.9, 7.9 Hz, 1H; 12″-H), 6.91 (s, 2H; 3″ H and 7″-H), 6.79 (d, J = 7.7 Hz, 1H; 11″-H), 6.76 (d, J = 8.7 Hz, 2H; 4′-H and 6′-H), 5.29 (m, 1H; 4-H), 4.33 (bm, 1H; 3-H), 3.44–2.98 (bm, 4H; 2-H_2 and 7-H_2), 2.11–1.85 (bm, 4H; 5-H_2, 6-H_2); ^{13}C NMR (125 MHz, CD_3OD, 23 °C): δ = 203.6, 174.8, 169.8, 166.5, 162.3, 161.3, 154.4, 139.2, 136.3, 132.2, 130.5, 130.2, 125.9, 120.8, 118.7, 118.5, 116.2, 109.7, 77.4, 54.5, 30.2, 23.4 [the carbon resonances for C_2 and C_7 are obscured by solvent peaks]; FAB HRMS calcd for $C_{28}H_{26}N_2O_{10}$ (M + H^+): 551.1666, found: 551.1684.

Methyl ester 50: A solution of carboxylic acid **48** (121 mg, 0.178 mmol) in DMF (2 mL) was treated with K_2CO_3 (30 mg, 0.214 mmol) and iodomethane (22 μL, 0.36 mmol) and stirred for 2 h at 25 °C. The reaction was then quenched with water (30 mL) and the resultant aqueous mixture was extracted with EtOAc (30 mL × 2). The combined organic layers were washed with water (30 mL × 2) and then dried (Na_2SO_4), filtered and concentrated. Purification of the residue by PTLC (silica gel, 40% EtOAc in petroleum ether) afforded **50** (123 mg, 100%) as a colourless oil: R_f = 0.20 (20% EtOAc in petroleum ether); IR (thin film): $\tilde{\nu}_{max}$ = 1774 (C=O), 1723 (C=O), 1668 (C=O), 1582, 1423, 1280, 1238, 1117, 1028, 739, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 20 °C): δ = 7.30–7.15 (m, 16H; Ar), 7.11 (t, J = 7.8 Hz, 2H; 4″-OCH_2Ph (*para*) and 6″-OCH_2Ph(*para*)), 7.07–7.05 (m, 4H; Ar), 6.94 (d, J = 8.2 Hz, 1H; 11″-H), 6.86 (d, J = 7.4 Hz, 2H; Ar), 5.12 (s, 2H; CO_2CH_2Ph), 4.79 (s, 4H; 4″-OCH_2Ph and 6″-OCH_2Ph), 4.71 (s, 2H; 10″-OCH_2Ph), 3.95 (s, 3H; CO_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): δ = 191.6, 167.4, 166.3, 157.9, 156.3, 136.1, 135.8, 135.7, 132.9, 132.6, 132.1, 130.6, 128.3, 128.2, 127.9, 127.8, 127.6, 127.5, 127.2, 123.8, 122.0, 115.2, 106.7, 70.5, 70.4, 67.1, 52.4; FAB HRMS calcd for $C_{44}H_{36}O_8Cs$ (M + Cs^+): 825.1465, found: 825.1478.

Carboxylic acid 51: A solution of methyl ester **50** (105 mg, 0.152 mmol) in THF (3 mL) was treated with palladium black (4.0 mg, 38 μmol) and stirred under an atmosphere of hydrogen for 12 h at 25 °C. The reaction mixture was filtered and concentrated and the residue purified by PTLC (C_{18}-reversed phase silica gel, 40% MeCN in water) to afford **51** (46.5 mg, 92%) as a yellow solid: M.p. 172–174 °C; R_f = 0.55 (C_{18}-reversed phase silica gel, 50% MeCN in H_2O); IR (thin film): $\tilde{\nu}_{max}$ = 3431 (broad, OH), 1701 (C=O), 1636 (C=O), 1599, 1424, 1251 cm^{-1}; ^1H NMR (500 MHz, CD_3OD, 20 °C): δ = 7.49 (d, J = 7.6 Hz, 1H; 13″-H), 7.27 (dd, J = 8.0, 7.6 Hz, 1H; 12″-H), 7.02 (d, J = 8.0 Hz, 1H; 11″-H), 6.89 (s, 2H; 3″-H and 7″-H), 3.87 (s, 3H; CO_2CH_3); ^{13}C NMR (125 MHz, CD_3OD, 20 °C): δ = 167.6, 163.2, 154.7, 137.2, 134.4, 129.9, 121.9, 120.7, 115.2, 108.8, 52.9; FAB HRMS calcd for $C_{16}H_{13}O_8$ (M + H^+): 333.0610, found: 333.0615.

Amine 52: A solution of amide **14** (49.2 mg, 0.104 mmol) in formic acid (2 mL) was treated with palladium black (11.0 mg, 0.103 mmol) and stirred for 1 h at 25 °C. The reaction mixture was filtered and concentrated and the residue purified by PTLC (C_{18}-reversed phase silica gel, 30% MeOH in 0.1 N HCl) to afford the hydrochloric acid salt of **52** (30.8 mg, 100%) as a white powder: M.p. decomp. ≥ 180 °C; R_f = 0.23 (nBuOH/H_2O/AcOH); $[\alpha]_D^{23}$ = −12.1 (c = 0.27 in MeOH); IR (KBr): $\tilde{\nu}_{max}$ = 3400 (broad, OH and NH), 1718 (C=O), 1608, 1508, 1273, 1177 cm^{-1}; ^1H NMR (500 MHz, [D_6]DMSO, 20 °C): 9.41 (bs, 1H), 9.08 (bs, 1H), 8.38 (d, J = 7.6 Hz, 1H; NHCO), 7.82 (d, J = 8.6 Hz, 2H; 3′-H and 7′-H), 6.82 (d, J = 8.6 Hz, 2H; 4′-H and 6′-H), 4.09 (ddd, J = 14.6, 7.6, 3.1 Hz, 1H; 3-H), 3.87 (bm, 1H; 4-H), 3.21–3.03 (m, 4H; 2-H_2 and 7-H_2), 1.93–1.73 (m, 4H; 5-H_2 and 6-H_2); ^{13}C NMR (125 MHz, [D_6]DMSO, 20 °C): δ = 166.0, 160.3, 129.4, 124.5, 114.6, 71.1, 53.5, 45.7, 45.6, 30.8, 19.3; FAB HRMS calcd for $C_{13}H_{19}N_2O_3$ (M + H^+): 251.1396, found: 251.1385.

Silyl ether 54: A solution of methyl 4-(hydroxymethyl)benzoate **53** (10.20 g, 60.16 mmol) and imidazole (6.14 g, 90.19 mmol) in DMF (90 mL) was treated with tBuPh_2SiCl (18.0 mL, 69.2 mmol) at 0 °C, warmed to 25 °C and stirred for 2 h. The reaction mixture was then treated with water (500 mL) and the resultant aqueous mixture was extracted with EtOAc (250 mL × 2). The combined organic layers were washed with water (500 mL × 2) and brine (300 mL) and then dried (Na_2SO_4), filtered and concentrated. Purification of the residue by flash chromatography (silica gel, 2 → 3% EtOAc in petroleum ether) afforded **54** (23.61 g, 100%) as a pale yellow oil: R_f = 0.38 (5% EtOAc in petroleum ether); IR (thin film): $\tilde{\nu}_{max}$ = 1722 (C=O), 1278, 1107, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 20 °C): δ = 8.01 (d, J = 8.2 Hz, 2H; 4″-H and 6″-H), 7.68 (m, 4H; SitBuPh_2(*ortho*)), 7.45–7.36 (m, 8H; Ar), 4.81 (s, 2H; ArCH_2OTPS), 3.92 (s, 3H; CO_2CH_3), 1.10 (s, 9H; tBu); ^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): δ = 167.1, 146.3, 135.5, 133.2, 129.8, 129.6, 128.7, 127.8, 125.6, 65.1, 52.0, 26.8, 19.3; FAB HRMS calcd for $C_{25}H_{28}O_3SiNa$ (M + Na^+): 427.1705, found: 427.1719.

Carboxylic acid 55: A solution of silyl ether **54** (23.47 g, 59.79 mmol) in 1,4-dioxane (225 mL) and water (75 mL) was treated with LiOH (2.86 g, 119.6 mmol) and the reaction mixture was stirred for 24 h at 25 °C. Saturated aqueous NH_4Cl (100 mL) was then added and the organic solvent was evaporated in vacuo. The aqueous mixture was acidified with $KHSO_4$ (240 mL, 0.5 M) and extracted with CH_2Cl_2 (250 mL × 3). The combined organic layers were washed with water (500 mL) and then dried (Na_2SO_4), filtered and concentrated. Purification of the residue by flash chromatography (silica gel, 0 → 5% MeOH in CH_2Cl_2) and recrystallisation of the product from EtOAc/n-hexane afforded **55** (14.04 g, 62%) as white needles: M.p. 123.5–124.5 °C; R_f = 0.44 (10% MeOH in CH_2Cl_2); IR (thin film): $\tilde{\nu}_{max}$ = 3000 (broad, OH), 1692 (C=O), 1427, 1287, 1112, 1086, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 20 °C): δ = 8.09 (d, J = 8.3 Hz, 2H; 4″-H and 6″-H), 7.69 (m, 4H; SitBuPh_2(*ortho*)), 7.46 (d, J = 8.3 Hz, 2H; 3″-H and 7″-H), 7.44 (tt, J = 7.4, 1.4 Hz, 2H; SitBuPh_2(*para*)), 7.38 (m, 4H; SitBuPh_2(*meta*)), 4.84 (s, 2H; ArCH_2OTPS), 1.11 (s, 9H; tBu); ^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): δ = 171.3, 147.4, 135.5, 133.1, 130.2, 129.8, 127.80, 127.76, 125.7, 65.1, 26.8, 19.3; FAB HRMS calcd for $C_{24}H_{25}O_3Si$ (M − H^+): 389.1573, found: 389.1568.

Ester 56: A solution of carboxylic acid **55** (10.99 g, 28.14 mmol), benzyl alcohol **35** (8.25 g, 28.14 mmol) and triphenylphosphine (8.12 g, 30.95 mmol) in THF (93 mL) was cooled to 0 °C and treated with diethyl azodicarboxylate (4.87 mL, 30.95 mmol). The resultant mixture was then warmed to 25 °C, stirred at 25 °C for 15 min and finally concentrated in vacuo. Purification of the residue by flash chromatography (silica gel, 7–10% EtOAc in petroleum ether) and recrystallisation of the product from EtOAc/n-hexane afforded **56** (17.60 g, 96%) as white needles: M.p. 105.5–106.5 °C; R_f = 0.58 (20% EtOAc in petroleum ether); IR (thin film): $\tilde{\nu}_{max}$ = 1722 (C=O), 1270, 1106, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 20 °C): δ = 8.08 (d, J = 8.3 Hz, 2H; 4″-H and 6″-H), 7.68 (m, 4H; SitBuPh_2(*ortho*)), 7.49 (d, J = 7.2 Hz, 2H; 10″-OCH_2Ph(*ortho*)), 7.44–7.36 (m, 10H; Ar), 7.33 (bt, J = 7.3 Hz, 1H; 10″-CH_2Ph(*para*)), 7.26 (dd, J = 7.9, 7.9 Hz, 1H; 12″-H), 7.13 (bd, J = 7.9 Hz, 1H; Ar), 6.93 (bd, J = 7.9 Hz, 1H; Ar), 5.48 (s, 2H; ArCH_2OCOAr), 5.18 (s, 2H; ArOCH_2Ph), 4.82 (s, 2H; ArCH_2OTPS), 1.10 (s, 9H; tBu); ^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): δ = 166.2, 155.3, 146.6, 137.3, 136.5, 135.5, 133.2, 129.8,

128.61, 128.57, 128.0, 127.8, 127.0, 125.7, 121.8, 113.6, 113.3, 71.0, 66.3, 65.1, 26.8, 19.3; FAB HRMS calcd for $C_{38}H_{37}BrO_4SiCs$ ($M + Cs^+$): 797.0699, found: 797.0665.

Benzaldehyde 57: A solution of ester **56** (10.82 g, 16.26 mmol) in THF (110 mL) was cooled to −98 °C and treated with *n*BuLi (11.2 mL, 1.6 M in hexanes). The resultant mixture was then warmed to −78 °C and stirred for a further 30 min. After quenching with saturated aqueous $NaHCO_3$ (50 mL), the THF was evaporated and the aqueous residue extracted with EtOAc (150 mL × 2). The combined organic layers were washed with brine (200 mL) and then dried (Na_2SO_4), filtered and concentrated. The crude product was then converted to **57** (5.42 g, 57% for the 2 steps) according to general procedure A and isolated as a colourless oil: $R_f = 0.24$ (20% EtOAc in petroleum ether); IR (thin film): $\tilde{\nu}_{max} = 1700$ (C=O), 1674 (C=O), 1462, 1269, 1113, 739, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 20 °C): $\delta = 9.91$(s, 1H; CHO), 7.80 (d, $J = 8.3$ Hz, 2H; Ar), 7.68 (m, 4H; Si*t*Bu*Ph*$_2$(*ortho*)), 7.59 (dd, $J = 7.7$, 1.1 Hz, 1H; 13″-H), 7.54 (t, $J = 7.7$ Hz, 1H; Ar), 7.43 (tt, $J = 7.3$, 1.5 Hz, 4H; Ar), 7.37 (m, 4H; Si*t*Bu*Ph*$_2$(*meta*)), 7.26–7.21 (m, 4H; Ar), 7.08 (dd, $J = 7.3$, 2.3 Hz, 2H; Ar), 5.08 (s, 2H; 10″-OCH_2Ph), 4.83 (s, 2H; ArCH_2OTPS), 1.10 (s, 9H; *t*Bu); ^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): $\delta = 195.4$, 190.4, 156.0, 147.2, 136.4, 135.9, 135.5, 133.1, 131.5, 130.6, 129.8, 129.3, 128.5, 127.9, 127.8, 126.7, 125.8, 123.0, 118.4, 70.5, 65.1, 26.8, 19.3; FAB HRMS calcd for $C_{38}H_{36}O_4SiCs$ ($M + Cs^+$): 717.1437, found: 717.1470.

Carboxylic acid 58: Benzaldehyde **57** (5.42 g, 9.27 mmol) was converted to **58** (5.24 g, 94%) according to general procedure B and isolated as white crystals: M.p. 175.5–177 °C; $R_f = 0.13$ (5% MeOH in CH_2Cl_2); IR (thin film): $\tilde{\nu}_{max} = 1700$ (C=O), 1664 (C=O), 1270, 1113, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 20 °C): $\delta = 7.75$ (d, $J = 8.0$ Hz, 2H; 4″-H and 6″-H), 7.71–7.67 (m, 5H; Ar), 7.43–7.39 (m, 5H; Ar), 7.36 (dd, $J = 7.5$, 7.5 Hz, 4H; Si*t*Bu*Ph*$_2$(*meta*)), 7.21–7.18 (m, 4H; Ar), 7.05 (m, 2H; Ar), 5.04 (s, 2H; 10″-OCH_2Ph), 4.82 (s, 2H; ArCH_2OTPS), 1.10 (s, 9H; *t*Bu); ^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): $\delta = 169.8$, 155.7, 146.4, 136.3, 136.0, 135.51, 135.47, 133.1, 129.8, 129.0, 128.6, 128.4, 127.8, 127.7, 126.7, 125.6, 123.3, 117.9, 70.5, 65.1, 26.8, 19.3; FAB HRMS calcd for $C_{38}H_{36}O_5SiCs$ ($M + Cs^+$): 733.1386, found: 733.1421.

Benzyl ester 59: A solution of carboxylic acid **58** (5.23 g, 8.71 mmol) in DMF (50 mL) was treated with K_2CO_3 (1.92 g, 13.9 mmol) and benzyl bromide (1.65 mL, 13.9 mmol) and stirred for 2 h at 25 °C. The reaction mixture was then treated with saturated aqueous NH_4Cl (300 mL) and the resultant aqueous mixture was extracted with EtOAc (120 mL × 2). The combined organic layers were washed with water (120 mL × 2) and then dried (Na_2SO_4), filtered and concentrated. Purification of the residue by flash chromatography (silica gel, 15–20% EtOAc in petroleum ether) afforded **59** (5.90 g, 98%) as a colourless oil: $R_f = 0.32$ (20% EtOAc in petroleum ether); IR (thin film): $\tilde{\nu}_{max} = 1721$ (C=O), 1678 (C=O), 1274, 1113, 740, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 20 °C): $\delta = 7.74$ (d, $J = 8.2$ Hz, 2H; 4″-H and 6″-H), 7.72–7.68 (m, 5H; Ar), 7.45–7.36 (m, 9H; Ar), 7.25–7.16 (m, 9H; Ar), 7.06 (dd, $J = 7.4$, 2.2 Hz, 2H; Ar), 5.14 (s, 2H; CO_2CH_2Ph), 5.05 (s, 2H; 10″-OCH_2Ph), 4.82 (s, 2H; ArCH_2OTPS), 1.11 (s, 9H; *t*Bu); ^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): $\delta = 195.4$, 165.2, 155.7, 146.3, 136.4, 136.1, 135.5, 135.1, 133.1, 132.1, 129.8, 129.6, 129.0, 128.40, 128.36, 128.3, 128.1, 127.8, 127.7, 126.7, 125.6, 122.8, 117.2, 70.5, 67.2, 65.1, 26.8, 19.3; FAB HRMS calcd for $C_{45}H_{42}O_5SiCs$ ($M + Cs^+$): 823.1856, found: 823.1821.

Benzyl alcohol 60: Benzyl ester **59** (5.90 g, 8.54 mmol) was converted to **60** (3.56 g, 92%) according to general procedure C and isolated as a colourless oil: $R_f = 0.28$ (40% EtOAc in petroleum ether); IR (thin film): $\tilde{\nu}_{max} = 3421$ (broad, OH), 1717 (C=O), 1670 (C=O), 1275, 753, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 20 °C): $\delta = 7.76$ (d, $J = 8.1$ Hz, 2H; 4″-H and 6″-H), 7.72 (d, $J = 8.0$ Hz, 1H; 13″-H), 7.42 (dd, $J = 8.0$, 8.0 Hz, 1H; 12″-H), 7.37 (d, $J = 8.1$ Hz, 2H; 3″-H and 7″-H), 7.29–7.26 (m, 3H; Ar), 7.23–7.16 (m, 6H; Ar), 7.07–7.05 (m, 2H; Ar), 5.13 (s, 2H; CO_2CH_2Ph), 5.03 (s, 2H; 10″-OCH_2Ph), 4.75 (s, 2H; ArCH_2OH); ^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): $\delta = 195.4$, 165.2, 155.7, 145.9, 136.9, 136.1, 135.1, 131.9, 129.9, 129.6, 129.2, 128.4, 128.3, 128.2, 127.8, 126.6, 126.5, 122.9, 117.3, 70.5, 67.2, 64.8; FAB HRMS calcd for $C_{29}H_{24}O_5Na$ ($M + Na^+$): 475.1521, found: 475.1540.

Benzaldehyde 61: Benzyl alcohol **60** (3.55 g, 7.85 mmol) was converted to **61** (2.25 g, 64%) according to general procedure A and isolated as a colourless oil: $R_f = 0.20$ (20% EtOAc in petroleum ether); IR (thin film): $\tilde{\nu}_{max} = 1716$ (C=O), 1704 (C=O), 1683, 1277, 751, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 20 °C): $\delta = 10.08$ (s, 1H; CHO), 7.89–7.85 (m, 4H; 3″-H, 4″-H, 6″-H and 7″-H), 7.74 (dd, $J = 8.0$, 0.8 Hz, 1H; 13″-H), 7.46 (dd, $J = 8.0$, 8.0 Hz, 1H; 12″-H), 7.28–7.17 (m, 9H; Ar), 7.05–7.03 (m, 2H; Ar), 5.13 (s, 2H; CO_2CH_2Ph), 5.03 (s, 2H; 10″-OCH_2Ph); ^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): $\delta = 195.0$, 191.8, 165.1, 155.7, 141.7, 138.7, 135.8, 134.8, 131.1, 130.4, 129.73, 129.69, 129.3, 128.5, 128.3, 128.0, 126.7, 122.9, 117.3, 70.6, 67.4; FAB HRMS calcd for $C_{29}H_{22}O_5Na$ ($M + Na^+$): 473.1365, found: 473.1387.

Carboxylic acid 62: Benzaldehyde **61** (2.25 g, 5.00 mmol) was converted to **62** (2.08 g, 89%) according to general procedure B and isolated as white crystals: M.p. 152.5–154 °C; $R_f = 0.23$ (5% MeOH in CH_2Cl_2); IR (thin film): $\tilde{\nu}_{max} = 3000$ (broad, OH), 1718 (C=O), 1685 (C=O), 1278 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 20 °C): $\delta = 8.09$ (d, $J = 8.5$ Hz, 2H; 3″-H and 7″-H), 7.81 (d, $J = 8.5$ Hz, 2H; 4″-H and 6″-H), 7.75 (dd, $J = 8.0$, 0.7 Hz, 1H; 13″-H), 7.46 (dd, $J = 8.0$, 8.0 Hz, 1H; 12″-H), 7.29–7.17 (m, 9H; Ar), 7.05–7.03 (m, 2H; Ar), 5.13 (s, 2H; CO_2CH_2Ph), 5.04 (s, 2H; 10″-OCH_2Ph); ^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): $\delta = 195.1$, 170.9, 165.1, 155.7, 141.4, 135.8, 134.8, 132.6, 131.2, 130.33, 130.28, 129.7, 128.7, 128.4, 128.3, 127.9, 126.7, 122.9, 117.3, 70.5, 67.4; FAB HRMS calcd for $C_{29}H_{23}O_6$ ($M + H^+$): 467.1495, found: 467.1512.

Carboxylic acid 63: A solution of silyl ether **39** (5.42 g, 8.50 mmol) in THF (56 mL) was cooled to −98 °C and treated with *n*BuLi (5.10 mL, 2.0 M in pentane). The reaction mixture was then warmed to −78 °C and stirred for 30 min. Phthalic anhydride (1.64 g, 11.07 mmol) was then added and the reaction mixture was warmed to 25 °C over 30 min. The resultant mixture was quenched with water (1 mL) and the organic solvents were evaporated in vacuo . $KHSO_4$ solution (30 mL, 0.5 M) was added and the mixture was extracted with CH_2Cl_2 (100 mL × 3). The combined organic layers were washed with water (60 mL × 2) and then dried (Na_2SO_4), filtered and concentrated. Purification of the residue by flash chromatography (silica gel, 5% MeOH in CH_2Cl_2) and recrystallisation of the product from EtOAc/*n*-hexane afforded **63** (4.39 g, 73%) as white crystals: M.p. 138.5–141 °C; $R_f = 0.46$ (10% MeOH in CH_2Cl_2); IR (thin film): $\tilde{\nu}_{max} = 1700$ (C=O), 1675 (C=O), 1607, 1576, 1429, 1113, 736, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 20 °C): $\delta = 7.85$ (bs, 1H; Ar), 7.65 (d, $J = 7.4$ Hz, 4H; Si*t*Bu*Ph*$_2$(*ortho*)), 7.53 (bs, 2H; Ar), 7.43 (t, $J = 7.4$ Hz, 2H; Si*t*Bu*Ph*$_2$(*para*)), 7.37 (dd, $J = 7.4$, 7.4 Hz, 4H; Si*t*Bu*Ph*$_2$(*meta*)), 7.23–7.18 (bs, 7H; Ar), 7.08 (m, 4H; Ar), 6.66 (s, 2H; 3″-H and 7″-H), 4.92 (s, 4H; 4″-OCH_2Ph and 6″-OCH_2Ph), 4.72 (s, 2H; ArCH_2OTPS), 1.09 (s, 9H; *t*Bu); ^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): $\delta = 196.0$, 157.7, 146.4, 136.2, 135.5, 133.1, 131.5, 130.4, 129.9, 128.4, 127.8, 127.7, 126.9, 116.8, 103.0, 70.3, 65.3, 26.8, 19.3; FAB HRMS calcd for $C_{45}H_{42}O_6SiNa$ ($M + Na^+$): 729.2648, found: 729.2612.

Benzyl ester 64: A solution of carboxylic acid **63** (4.38 g, 6.20 mmol) in DMF (40 mL) was treated with K_2CO_3 (2.27 g, 18.6 mmol) and benzyl bromide (1.47 mL, 12.4 mmol) and stirred for 3 h at 25 °C. The reaction was then quenched with water (320 mL) and the aqueous mixture was extracted with EtOAc (100 mL × 2). The combined organic layers were washed with water (100 mL × 2) and then dried (Na_2SO_4), filtered and concentrated. Purification of the residue by flash chromatography (silica gel, 10 → 15% EtOAc in petroleum ether) afforded **64** (4.84 g, 98%) as a colourless oil: $R_f = 0.45$ (20% EtOAc in petroleum ether); IR (thin film): $\tilde{\nu}_{max} = 1734$ (C=O), 1676 (C=O), 1607, 1577, 1429, 1286, 1260, 1114, 737, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 20 °C): $\delta = 7.65$ (m, 4H; Si*t*Bu*Ph*$_2$(*ortho*)), 7.59 (dd, $J = 7.6$, 1.0 Hz, 1H; 13″-H), 7.52 (dd, $J = 7.6$, 1.0 Hz, 1H; 10″-H), 7.47 (ddd, $J = 7.6$, 7.6, 1.3 Hz, 1H; 11″-H), 7.44 (tt, $J = 7.5$, 1.5 Hz, 2H; Si*t*Bu*Ph*$_2$(*para*)), 7.41–7.36 (m, 5H; Ar), 7.28–7.16 (m, 11H; Ar), 7.07–7.04 (m, 4H; Ar), 6.61 (s, 2H; 3″-H and 7″-H), 5.18 (s, 2H; CO_2CH_2Ph), 4.89 (s, 4H; 4″-OCH_2Ph and 6″-OCH_2Ph), 4.72 (s, 2H; ArCH_2OTPS), 1.09 (s, 9H; *t*Bu); ^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): $\delta = 193.5$, 169.1, 157.8, 145.9, 139.8, 136.4, 135.8, 135.5, 133.1, 132.8, 131.1, 130.2, 129.9, 129.7, 128.6, 128.2, 128.1, 127.8, 127.5, 126.8, 116.8, 103.0, 70.2, 67.3, 65.3, 26.8, 19.3.; FAB HRMS calcd for $C_{52}H_{48}O_6SiCs$ ($M + Cs^+$): 929.2275, found: 929.2311.

Benzyl alcohol 65: Benzyl ester **64** (4.78 g, 6.00 mmol) was converted to **65** (3.08 g, 92%) according to general procedure C and isolated as a colourless oil: $R_f = 0.28$ (5% MeOH in CH_2Cl_2); IR (thin film): $\tilde{\nu}_{max} = 3448$ (broad, OH), 1725 (C=O), 1670 (C=O), 1607, 1578, 1431, 1287, 1261, 1120, 737, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 20 °C): $\delta = 7.58$ (dd, $J = 7.6$, 1.3 Hz, 1H; 13″-H), 7.49 (dd, $J = 7.6$, 1.3 Hz, 1H; 10″-H), 7.47 (ddd, $J = 7.6$, 7.6, 1.3 Hz, 1H; 11″-H), 7.37 (ddd, $J = 7.6$, 7.6, 1.3 Hz, 1H; 12″-H), 7.33–7.18 (m, 12H; Ar), 7.09–7.05 (m, 3H; Ar), 6.63 (s, 2H; 3″-H and 7″-H), 5.18 (s, 2H; CO_2CH_2Ph), 4.94 (s, 4H; 4″-OCH_2Ph and 6″-OCH_2Ph), 4.66 (s, 2H; ArCH_2OH); ^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): $\delta = 193.7$, 169.0, 157.9, 146.2, 139.7, 136.3, 135.8, 132.8, 131.2, 130.2, 129.6, 128.6, 128.3, 128.2, 128.1, 127.9, 127.5, 126.8, 116.9, 103.5, 70.2, 67.2, 64.7; FAB HRMS calcd for $C_{36}H_{30}O_6Na$ ($M + Na^+$): 581.1940, found: 581.1950.

Benzaldehyde 66: Benzyl alcohol **65** (2.87 g, 5.14 mmol) was converted to **66** (1.80 g, 63%) according to general procedure A and isolated as a pale yellow oil: $R_f = 0.18$ (20% EtOAc in petroleum ether); IR (thin film): $\tilde{\nu}_{max} = 1728$ (C=O), 1700 (C=O), 1684 (C=O), 1578, 1432, 1261, 1118, 737, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 20 °C): $\delta = 9.90$ (s, 1H; CHO), 7.61 (dd, $J = 7.6$, 1.3 Hz, 1H; 13″-H), 7.54 (ddd, $J = 7.6$, 7.6, 1.3 Hz, 1H; 12″-H), 7.49 (dd, $J = 7.6$, 1.3 Hz, 1H; 10″-H), 7.40 (ddd, $J = 7.6$, 7.6, 1.3 Hz, 1H; 11″-H), 7.28–7.18 (m, 11H; Ar), 7.12 (s, 2H; 3″-H and 7″-H), 7.10–7.08 (m, 4H; Ar), 5.20 (s, 2H; CO_2CH_2Ph), 5.02 (s, 4H; 4″-OCH_2Ph and 6″-OCH_2Ph); ^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): $\delta = 192.5$, 191.2, 168.9, 157.9, 138.8, 137.9, 135.7, 135.6, 133.2, 132.0, 130.3, 130.0, 128.7, 128.4, 128.3, 128.2, 128.0, 127.8, 126.9, 123.6, 106.7, 70.6, 67.4; FAB HRMS calcd for $C_{36}H_{28}O_6Na$ ($M + Na^+$): 579.1784, found: 579.1761.

Carboxylic acid 67: Benzaldehyde **66** (1.33 g, 2.34 mmol) was converted to **67** (1.34 g, 100%) according to general procedure B and isolated as white crystals: M.p. 171–173 °C; $R_f = 0.21$ (5% MeOH in CH_2Cl_2); IR (thin film): $\tilde{\nu}_{max} = 3000$ (broad, OH), 1725 (C=O), 1685 (C=O), 1578, 1424, 1260, 1118, 734, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 20 °C): $\delta = 7.61$ (d, $J = 7.5$ Hz, 1H; 13″-H), 7.53 (dd, $J = 7.5$, 7.5 Hz, 1H; 12″-), 7.48 (d, $J = 7.5$ Hz, 1H; 10″-H), 7.40 (dd, $J = 7.5$, 7.5 Hz,

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1H; 11″-H), 7.38 (s, 2H; 3″-H and 7″-H), 7.29–7.24 (m, 5H; Ar), 7.21–7.18 (m, 6H; Ar), 7.10–7.08 (m, 4H; Ar), 5.20 (s, 2H; CO_2CH_2Ph), 5.01 (s, 4H; 4″-OCH_2Ph and 6″-OCH_2Ph); ^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): δ = 192.7, 170.8, 169.0, 157.4, 138.1, 135.8, 135.6, 133.2, 132.1, 131.9, 130.3, 130.0, 128.7, 128.4, 128.33, 128.27, 128.0, 127.8, 127.0, 123.1, 107.4, 70.5, 67.5; FAB HRMS calcd for $C_{36}H_{29}O_7$ ($M + H^+$): 573.1913, found: 573.1936.

Alcohol 68: A solution of silyl ether **39** (10.00 g, 15.68 mmol) in THF (75 mL) was cooled to −98 °C and treated with *n*BuLi (9.40 mL, 2.0 M in pentane). The resultant mixture was then warmed to −78 °C and stirred for 15 min. A solution of 2-(benzyloxy)benzaldehyde (4.99 g, 23.51 mmol) in THF (45 mL) was added and the reaction mixture was warmed to 0 °C over 1 h. The resultant mixture was then quenched with saturated aqueous NH_4Cl (100 mL) and the organic solvents were evaporated in vacuo. The aqueous residue was extracted with EtOAc (200 mL × 2) and the combined organic layers were washed with water (120 mL × 2) and then dried (Na_2SO_4), filtered and concentrated. Purification of the residue by flash chromatography (silica gel, 10 → 15% EtOAc in petroleum ether) afforded **68** (8.05 g, 67%) as a white foam: R_f = 0.30 (15% EtOAc in petroleum ether); IR (thin film): $\tilde{\nu}_{max}$ = 3555 (OH), 1587, 1428, 1222, 1112, 738, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 20 °C): δ = 7.67 (m, 4H; Si*t*BuPh_2(*ortho*)), 7.43 (tt, J = 7.4, 2.3 Hz, 2H; Si*t*BuPh_2(*para*)), 7.38–7.34 (m, 5H; Ar), 7.24–7.15 (m, 15H; Ar), 6.86–6.83 (m, 3H; Ar), 6.78 (d, J = 10.6 Hz, 1H; 8″-H), 6.60 (s, 2H; 3″-H and 7″-H), 5.04,4.93 (AB system, J = 12.3 Hz, 2H; 10″-OCH_2Ph), 4.92,4.86 (AB system, J = 11.8 Hz, 4H; 4″-OCH_2Ph and 6″-OCH_2Ph), 4.72 (s, 2H; ArCH_2OTPS), 4.13 (d, J = 10.6 Hz, 1H; OH), 1.09 (s, 9H; *t*Bu); ^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): δ = 157.1, 156.0, 141.9, 137.3, 136.7, 135.6, 133.3, 132.4, 129.8, 128.4, 128.3, 127.9, 127.8, 127.7, 127.4, 127.3, 127.1, 120.2, 117.8, 111.9, 103.1, 70.1, 69.8, 65.4, 64.9, 26.8, 19.3; FAB HRMS calcd for $C_{51}H_{50}O_3SiCs$ ($M + Cs^+$): 903.2482, found: 903.2520.

Diol 69: Alcohol **68** (7.88 g, 10.22 mmol) was converted to **69** (5.37 g, 99%) according to general procedure C and the diol was isolated as a white solid: M.p. 49.5–51.5 °C; R_f = 0.53 (Et_2O); IR (thin film): $\tilde{\nu}_{max}$ = 3412 (broad, OH), 1586, 1455, 1435, 1224, 1112, 737, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 20 °C): δ = 7.30 (dd, J = 7.6, 1.5 Hz, 1H; 14″-H), 7.26–7.14 (m, 16H; Ar), 6.84 (d, J = 8.2 Hz, 1H; 11″-H), 6.82 (dd, J = 7.6, 7.6 Hz, 1H; 13″-H), 6.78 (d, J = 11.0 Hz, 1H; 8″-H), 6.61 (s, 2H; 3″-H and 7″-H), 5.03,4.92 (AB system, J = 12.3 Hz, 2H; 10″-OCH_2Ph), 4.96,4.90 (AB system, J = 11.6 Hz, 4H; 4″-OCH_2Ph and 6″-OCH_2Ph), 4.62 (s, 2H; CH_2OH), 4.12 (d, J = 11.0 Hz, 1H; 8″-OH), 1.84 (s, 1H; CH_2OH); ^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): δ = 157.3, 156.0, 141.8, 137.3, 136.5, 132.1, 128.4, 128.3, 128.0, 127.8, 127.4, 127.3, 127.1, 120.2, 118.6, 111.9, 104.0, 70.3, 69.7, 65.3, 64.9; FAB HRMS calcd for $C_{35}H_{32}O_5Cs$ ($M + Cs^+$): 665.1304, found: 665.1335.

Ketoaldehyde 70: Diol **69** (5.37 g, 10.08 mmol) was converted to **70** (2.81 g, 53%) according to general procedure A with 0.1 equiv of tetrapropylammonium perruthenate(VII) and 3.0 equiv of 4-methylmorpholine *N*-oxide and isolated as white crystals by recrystallisation from EtOAc/*n*-hexane: M.p. 140.5–141 °C; R_f = 0.40 (30% EtOAc in petroleum ether); IR (thin film): $\tilde{\nu}_{max}$ = 1697 (C=O), 1656 (C=O), 1594, 1582, 1432, 1114, 735, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 20 °C): δ = 9.69 (s, 1H; CHO), 7.98 (dd, J = 7.8, 1.8 Hz, 1H; 14″-H), 7.53 (ddd, J = 8.3, 7.4, 1.8 Hz, 1H; 12″-H), 7.26–7.20 (m, 7H; Ar), 7.13–7.07 (m, 7H; Ar), 6.97 (d, J = 8.3 Hz, 1H; 11″-H), 6.83 (s, 2H; 3″-H and 7″-H), 6.80 (d, J = 8.2 Hz, 2H; Ar), 4.95 (s, 4H; 4″-OCH_2Ph and 6″-OCH_2Ph), 4.70 (s, 2H; 10″-OCH_2Ph); ^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): δ = 192.3, 191.4, 158.9, 156.3, 137.2, 136.3, 135.3, 134.5, 131.5, 128.4, 128.3, 128.1, 128.0, 127.8, 126.9, 120.9, 112.5, 106.7, 70.4, 70.2; FAB HRMS calcd for $C_{35}H_{28}O_5Na$ ($M + Na^+$): 551.1834, found: 551.1859.

Carboxylic acid 71: Ketoaldehyde **70** (2.35 g, 4.45 mmol) was converted to **71** (2.34 g, 96%) according to general procedure B and isolated as white crystals: M.p. 151–152 °C; R_f = 0.20 (5% MeOH in CH_2Cl_2); IR (thin film) $\tilde{\nu}_{max}$ = 3000 (broad, OH), 1689 (C=O), 1658 (C=O), 1594, 1423, 1115, 734, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 20 °C): δ = 7.96 (dd, J = 7.8, 1.8 Hz, 1H; 14″-H), 7.52 (ddd, J = 8.3, 7.8, 1.8 Hz, 1H; 12″-H), 7.27–7.12 (m, 15H; Ar), 7.07 (t, J = 7.8 Hz, 1H; Ar), 6.97 (d, J = 8.3 Hz, 1H; 11″-H), 6.85 (d, J = 7.3 Hz, 2H; Ar), 4.95 (s, 4H; 4″-OCH_2Ph and 6″-OCH_2Ph), 4.73 (s, 2H; 10″-OCH_2Ph); ^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): δ = 192.5, 171.1, 158.8, 155.9, 136.4, 135.5, 134.3, 131.5, 130.1, 128.4, 128.2, 128.1, 128.0, 127.9, 127.7, 127.0, 120.8, 112.6, 107.5, 70.5, 70.2; FAB HRMS calcd for $C_{35}H_{29}O_6$ ($M + H^+$): 545.1964, found: 545.1941.

Amide 72: A solution of hexahydroazepine **13** (303 mg, 0.749 mmol) in CH_2Cl_2 (3 mL) was treated with trifluoroacetic acid (1 mL, excess) and stirred at 25 °C for 2 h. After dilution with benzene (10 mL), the solution was concentrated and the crude product was employed in the next reaction without further purification.
A solution of the crude product in CH_2Cl_2 (3 mL) at 0 °C was treated with triethylamine (1.04 mL, 7.49 mmol) and benzoyl chloride (0.17 mL, 1.50 mmol) and the reaction mixture was stirred for 1 h at 25 °C. After quenching with MeOH (1 mL), the reaction mixture was concentrated and the residue purified by PTLC (silica gel, 80% EtOAc and 10% CH_2Cl_2 in petroleum ether) to afford **72** (144.6 mg, 52% for the 2 steps) as a white solid: M.p. 106–108 °C; R_f = 0.30 (70% EtOAc and 10% CH_2Cl_2 in petroleum ether); $[\alpha]_D^{21}$ = −48.9 (c = 0.67 in $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}$ = 3338 (broad, OH and NH), 1677 (C=O), 1639 (C=O), 1423 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 20 °C): δ = 8.87 (d, J = 5.2 Hz, 1H; NH), 7.86 (d, J = 7.4 Hz, 2H; 3′-H and 7′-H), 7.53 (t, J = 7.4 Hz, 1H; 5′-H), 7.46 (dd, J = 7.4, 7.4 Hz, 2H; 4′-H and 6′-H), 7.36–7.30 (m, 5H; $CO_2CH_2C_6H_5$), 5.40 (bs, 1H; OH), 5.22,5.18 (AB system, J = 12.3 Hz, 2H; NCO_2CH_2Ph), 4.21–4.11 (m, 3H; 2-H, 3-H and 7-H), 3.79 (ddd, J = 10.1, 6.0, 1.6 Hz, 1H; 4-H), 3.36 (dd, J = 15.4, 5.0 Hz, 1H; 2 H′), 2.80 (ddd, J = 13.9, 12.7, 3.6 Hz, 1H; 7 H′), 1.98–1.63 (m, 4H; 5-H_2 and 6-H_2); ^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): δ = 169.0, 157.7, 136.1, 133.0, 131.8, 128.6, 128.3, 127.8, 127.2, 79.6, 67.9, 60.8, 50.4, 50.2, 32.7, 27.3; FAB HRMS calcd for $C_{21}H_{25}N_2O_4$ ($M + H^+$): 369.1814, found: 369.1826.

Fully protected 10″-deoxybalanol (77): Amide **14** (70.5 mg, 0.149 mmol) and carboxylic acid **67** (100.8 mg, 0.149 mmol) were coupled according to general procedure E to afford fully protected 10″-deoxybalanol (**77**) (162.0 mg, 96%) as a pale yellow oil: R_f = 0.45 (20% EtOAc in toluene); $[\alpha]_D^{21}$ = −72.9 (c = 0.86 in $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}$ = 3368 (broad, NH), 1718 (C=O), 1708 (C=O), 1702 (C=O), 1685 (C=O), 1676 (C=O), 1499, 1423, 1252, 1116, 734, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 20 °C): δ = 7.80 (d, J = 7.6 Hz, 1H; 13″-H), 7.72 (d, J = 8.7 Hz, 2H; 3′-H and 7′-H), 7.58 (d, J = 7.4 Hz, 1H; 10″-H), 7.50 (td, J = 7.6, 1.1 Hz, 1H; 12″-H), 7.47–7.10 (m, 29H; Ar), 6.93 (d, J = 8.7 Hz, 2H; 4′-H and 6′-H), 5.25 (s, 2H; OCH_2Ph), 5.18 (s, 4H; 4″-OCH_2Ph and 6″-OCH_2Ph), 5.08 (s, 2H; OCH_2Ph), 5.05,5.01 (AB system, J = 12.4 Hz, 2H; CO_2CH_2Ph), 4.73 (bdd, J = 13.2, 7.3 Hz, 1H; 2-H), 4.14–4.08 (m, 2H), 3.43 (dd, J = 15.4, 5.8 Hz, 1H), 2.89 (m, 1H; 7-H), 2.05–1.74 (m, 4H; 5-H_2 and 6-H_2); ^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): δ = 192.9, 169.0, 166.0, 165.6, 161.3, 157.7, 157.3, 138.2, 136.3, 136.2, 136.1, 135.7, 133.1, 131.7, 130.2, 129.9, 128.8, 128.6, 128.2, 127.88, 127.85, 127.6, 127.4, 127.0, 126.6, 122.2, 114.6, 107.2, 78.4, 70.4, 70.0, 67.9, 67.4, 53.5, 50.8, 49.5, 29.1, 25.2 [the presence of rotamers precluded a comprehensive assignment of all proton and carbon resonances]; FAB HRMS calcd for $C_{64}H_{56}N_2O_{11}Cs$ ($M + Cs^+$): 1161.2938, found: 1161.2935.

10″-Deoxybalanol (73): Fully protected 10″-deoxybalanol (**77**) (55.0 mg, 53.4 μmol) was converted to 10″-deoxybalanol (**73**) (26.2 mg, 92%) according to general procedure E and isolated as a pale yellow solid: M.p. decomp. ≥ 180 °C; R_f = 0.40 (C_{18}-reversed phase silica gel, 60% MeOH in water); $[\alpha]_D^{22}$ = −186.4 (c = 0.25 in MeOH); IR (KBr): $\tilde{\nu}_{max}$ = 3200 (broad, OH and NH), 1717 (C=O), 1636, 1608, 1542, 1507, 1383, 1236 cm^{-1}; ^1H NMR (500 MHz, CD_3OD, 20 °C): δ = 7.81 (d, J = 7.5 Hz, 1H; 13″-H), 7.61 (d, J = 8.5 Hz, 2H; 3′-H and 7′-H), 7.44–7.39 (m, 2H; 11″-H and 12″-H), 7.10 (d, J = 7.5 Hz, 1H; 10″-H), 6.92 (s, 2H; 3″-H and 7″-H), 6.76 (d, J = 8.5 Hz, 2H; 4′-H and 6′-H), 5.37 (bm, 1H; 4-H), 4.27 (bm, 1H; 3-H), 3.41–3.16 (m, 4H; 2-H_2 and 7-H_2), 2.18–1.90 (m, 4H; 5-H_2 and 6-H_2); ^{13}C NMR (125 MHz, CD_3OD, 20 °C): δ = 203.7, 174.5, 170.3, 166.4, 162.5, 161.0, 145.0, 136.3, 130.9, 130.5, 129.9, 129.8, 126.0, 125.6, 117.6, 116.1, 109.5, 76.9, 53.8, 30.2, 21.8; FAB HRMS calcd for $C_{28}H_{27}N_2O_9$ ($M + H^+$): 535.1717, found: 535.1740.

Fully protected 14″-decarboxybalanol (78): Amide **14** (46.5 mg, 98.0 μmol) and carboxylic acid **71** (53.4 mg, 98.0 μmol) were coupled according to general procedure D to afford fully protected 14″-decarboxybalanol (**78**) (88.8 mg, 91%) as a white solid: M.p. 76–81 °C; R_f = 0.38 (40% EtOAc and 10% CH_2Cl_2 in petroleum ether); $[\alpha]_D^{21}$ = −83.9 (c = 0.40 in $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}$ = 3364 (broad, NH), 1700 (C=O), 1654 (C=O), 1595, 1498, 1422, 1233, 1114, 737, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 20 °C): δ = 7.87 (dd, J = 7.6, 1.8 Hz, 1H; 14″-H), 7.77 (d, J = 7.7 Hz, 1H; Ar), 7.72 (d, J = 8.7 Hz, 2H; 3′-H and 7′-H), 7.48 (ddd, J = 7.8, 7.8, 1.8 Hz, 1H; 12″-H), 7.44–7.02 (m, 27H; Ar), 6.92 (dd, J = 8.4, 2.9 Hz, 2H; Ar), 6.82(d, J = 8.7 Hz, 2H; 4′-H and 6′-H), 5.26,5.24 (AB system, J = 13.0 Hz, 2H; NCO_2CH_2Ph), 5.07 (s, 2H; 10″-OCH_2Ph), 4.98,4.95 (AB system, J = 12.3 Hz, 4H; 4″-OCH_2Ph and 6″-OCH_2Ph), 4.90 (bs, 1H; 4-H), 4.71 (s, 2H; 5′-OCH_2Ph), 4.15–4.09 (m, 3H; 2-H, 3-H and 7-H), 3.42 (dd, J = 15.1, 5.5 Hz, 1H; 2 H′), 2.90 (ddd, J = 14.9, 4.8, 4.5 Hz, 1H; 7-H), 2.05–1.76 (m, 4H; 5-H_2 and 6-H_2); ^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): δ = 192.8, 166.1, 165.7, 161.3, 158.6, 157.9, 155.9, 136.7, 136.4, 136.3, 135.6, 134.1, 131.5, 131.3, 128.8, 128.7, 128.32, 128.26, 128.1, 127.9, 127.8, 127.6, 127.5, 127.4, 126.9, 120.7, 114.6, 112.7, 107.2, 77.6, 70.3, 70.2, 70.0, 67.9, 53.5, 50.6, 49.3, 28.6, 24.8 [the presence of rotamers precluded a comprehensive assignment of all proton and carbon resonances]; FAB HRMS calcd for $C_{63}H_{56}N_2O_{10}Cs$ ($M + Cs^+$): 1133.2989, found: 1133.2935.

14″-Decarboxybalanol hydrochloride (74): Fully protected 14″-decarboxybalanol (**78**) (43.8 mg, 43.8 μmol) was converted to 14″-decarboxybalanol hydrochloride (**74**) (22.6 mg, 95%) according to general procedure E (50% MeOH in 0.1 N HCl was used as the eluent for reversed phase PTLC): M.p. decomp. ≥ 180 °C; R_f = 0.38 (*n*BuOH/H_2O/AcOH = 5/1/1); $[\alpha]_D^{22}$ = −79.5 (c = 0.67 in MeOH); IR (KBr): $\tilde{\nu}_{max}$ = 3400 (broad, OH and NH), 1718 (C=O), 1702 (C=O), 1624, 1236 cm^{-1}; ^1H NMR (500 MHz, CD_3OD, 20 °C): δ = 7.64 (d, J = 8.7 Hz, 2H; 3′-H and 7′-H), 7.49 (ddd, J = 8.3, 7.2, 1.6 Hz, 1H; 12″-H), 7.25 (dd, J = 8.0, 1.6 Hz, 1H; 14″-H), 7.02 (s, 2H; 3″-H and 7″-H), 6.97 (dd, J = 8.3, 0.8 Hz, 1H; 11″-H), 6.82 (ddd, J = 8.0, 7.2, 0.8 Hz, 1H; 13″-H), 6.80 (d, J = 8.7 Hz, 2H; 4′-H and 6′-H), 5.42 (m, 1H; 4-H), 4.58 (m, 1H; 3-H), 3.69 (dd, J = 5.0, 4.4 Hz, 1H; 7-H), 3.57 (dd, J = 5.0, 4.4 Hz, 1H; 7 H′), 3.48 (d, J = 5.7 Hz, 1H; 2-H), 2-H′ is obscured by solvent signal, 2.30 (m, 1H; 5-H), 2.14 (m, 1H; 5 H′), 2.11–2.04 (m, 2H; 6-H_2); ^{13}C NMR (125 MHz, CD_3OD, 20 °C): δ = 202.9, 166.7, 163.6, 162.6, 156.8, 137.8, 134.3, 133.6, 130.6, 125.5, 121.9, 120.2, 120.0, 118.6, 116.2, 108.9, 76.7, 73.5, 62.2, 53.2, 30.3, 21.3; FAB HRMS calcd for $C_{27}H_{27}N_2O_8$ ($M + H^+$): 507.1767, found: 507.1751.

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Fully protected 4″,6″-dideoxybalanol (79): Amide **14** (67.8 mg, 0.143 mmol) and carboxylic acid **62** (66.7 mg, 0.143 mmol) were coupled according to general procedure D to afford fully protected 4″,6″-dideoxybalanol (**79**) (118.6 mg, 91%) as a pale yellow oil: $R_f = 0.44$ (10% CH_2Cl_2 and 40% EtOAc in petroleum ether); $[\alpha]_D^{21} = -83.9$ ($c = 0.60$ in $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3362$ (broad, NH), 1715 (C=O), 1682 (C=O), 1276, 736, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 20 °C): $\delta = 8.02$ (d, $J = 8.3$ Hz, 2H; 3″-H and 7″-H), 7.77–7.68 (m, 5H; Ar), 7.47–7.14 (m, 20H; Ar), 7.01 (bs, 2H; Ar), 6.94 (d, $J = 8.7$ Hz, 2H; 4′-H and 6′-H), 5.26,5.22 (AB system, $J = 12.6$ Hz, 2H; NCO_2CH_2Ph), 5.10 (s, 2H; OCH_2Ph), 5.06 (s, 2H; OCH_2Ph), 5.01 (s, 2H; OCH_2Ph), 4.65 (bdd, $J = 6.0, 6.0$ Hz, 1H; 4-H), 4.16–4.08 (m, 2H; 2-H and 3-H), 3.87 (m, 1H; 7-H), 3.49 (dd, $J = 15.3, 5.0$ Hz, 1H; 2-H′), 3.00 (ddd, $J = 14.8, 9.4, 5.2$ Hz, 1H; 7-H′), 2.10–1.83 (m, 4H; 5-H_2 and 6-H_2); ^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): $\delta = 195.1, 166.2, 165.3, 165.1, 161.2, 157.9, 155.7, 140.7, 136.4, 136.3, 135.8, 134.8, 133.5, 131.3, 130.2, 129.8, 129.6, 128.9, 128.7, 128.6, 128.42, 128.39, 128.29, 128.25, 128.1, 127.9, 127.4, 126.7, 122.9, 117.3, 114.6, 70.5, 70.0, 67.9, 67.4, 53.7, 50.4, 49.0, 28.3, 24.3$ [the presence of rotamers precluded a comprehensive assignment of all proton and carbon resonances]; FAB HRMS calcd for $C_{57}H_{50}N_2O_{10}Cs$ ($M + Cs^+$): 1055.2520, found: 1055.2552.

4″,6″-Dideoxybalanol (75): Fully protected 4″,6″-dideoxybalanol (**79**) (11.9 mg, 13.1 μmol) was converted to 4″,6″-dideoxybalanol (**75**) (6.1 mg, 90%) according to general procedure E and isolated as a white solid: M.p. decomp. ≥ 180 °C; $R_f = 0.50$ (C_{18}-reversed phase silica gel, 40% MeCN in H_2O); $[\alpha]_D^{22} = -72.4$ ($c = 0.12$ in MeOH); IR (KBr): $\tilde{\nu}_{max} = 3400$ (broad, OH and NH), 1718 (C=O), 1636, 1508, 1387, 1278 cm^{-1}; ^1H NMR (500 MHz, CD_3OD/[D_6]DMSO (6/1), 20 °C): $\delta = 7.98$ (d, $J = 7.8$ Hz, 2H; 3″-H and 7″-H), 7.78 (d, $J = 7.8$ Hz, 2H; 4″-H and 6″-H), 7.60 (d, $J = 8.2$ Hz, 2H; 3′-H and 7′-H), 7.47 (d, $J = 7.2$ Hz, 1H; 13″-H), 7.31 (dd, $J = 7.2, 7.2$ Hz, 1H; 12″-H), 6.96 (d, $J = 7.2$ Hz, 1H; 11″-H), 6.76 (d, $J = 8.2$ Hz, 2H; 4′-H and 6′-H), 5.31 (bm, 1H; 4-H), 4.44 (bm, 1H; 3-H), either 2-H or 7-H is obscured by solvent signals, 3.10 (bs, 1H), 3.00 (bs, 1H), 2.60 (bs, 1H), 2.26–1.83 (m, 4H; 5-H_2 and 6-H_2); ^{13}C NMR (125 MHz, CD_3OD/[D_6]DMSO (6/1), 20 °C): $\delta = 169.3, 166.5, 162.1, 155.5, 143.7, 133.8, 130.7, 130.55, 130.52, 129.7, 126.0, 121.8, 118.6, 116.2, 77.6, 54.1, C_2$ and C_6 are obscured by CD_3OD peaks, 30.2, 22.7; FAB HRMS calcd for $C_{28}H_{27}N_2O_8$ ($M + H^+$): 519.1767, found: 519.1745.

Fully protected 5′-deoxybalanol (80): Amide **72** (65.4 mg, 0.178 mmol) and carboxylic acid **48** (120.5 mg, 0.178 mmol) were coupled according to general procedure D to afford fully protected 5′-deoxybalanol (**80**) (157.2 mg, 86%) as a white solid: M.p. 76.5–78 °C; $R_f = 0.38$ (5% MeOH in CH_2Cl_2); $[\alpha]_D^{21} = -51.3$ ($c = 0.97$ in $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3000$ (broad, NH), 1720 (C=O), 1711 (C=O), 1691 (C=O), 1677 (C=O), 1664 (C=O), 1423, 1279, 1232, 1116, 736, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 20 °C): $\delta = 7.92$ (d, $J = 7.7$ Hz, 1H; 13″-H), 7.77 (d, $J = 7.6$ Hz, 2H; 3′-H and 7′-H), 7.47–7.03 (m, 29H; Ar), 6.91 (d, $J = 8.1$ Hz, 1H; 11″-H), 6.82 (d, $J = 7.4$ Hz, 2H; Ar), 5.26 (s, 2H; 14″-CO_2CH_2Ph), 5.10 (s, 2H; OCH_2Ph), 5.03 (ddd, $J = 8.1, 8.1, 1.2$ Hz, 1H; 4-H), 4.86,4.82 (AB system, $J = 11.9$ Hz, 4H; 4″-OCH_2Ph and 6″-OCH_2Ph), 4.68 (s, 2H; OCH_2Ph), 4.15–4.10 (m, 3H; 2-H, 3-H and 7-H), 3.44 (dd, $J = 15.5$, 5.4 Hz, 1H; 2-H′), 2.91 (ddd, $J = 14.3, 9.6, 4.8$ Hz, 1H; 7-H′), 2.07–1.80 (m, 4H; 5-H_2 and 6-H_2); ^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): $\delta = 191.6, 167.3, 166.5, 165.6, 158.0, 157.8, 156.2, 136.3, 136.2, 135.74, 135.68, 134.0, 132.6, 132.3, 131.5, 130.4, 128.64, 128.56, 128.32, 128.25, 128.2, 127.89, 127.85, 127.7, 127.5, 127.3, 127.2, 127.0, 77.9, 70.4, 67.9, 67.0, 60.4, 53.6, 50.7, 49.4, 28.9, 25.0$ [the presence of rotamers precluded a comprehensive assignment of all proton and carbon resonances]; FAB HRMS calcd for $C_{64}H_{56}N_2O_{11}Cs$ ($M + Cs^+$): 1161.2938, found: 1161.2990.

5′-Deoxybalanol (76): Fully protected 5′-deoxybalanol (**80**) (95.3 mg, 92.6 μmol) was converted to 5′-deoxybalanol (**76**) (48.0 mg, 97%) according to general procedure E and isolated as a yellow solid: M.p. decomp. ≥ 180 °C; $R_f = 0.40$ (*n*BuOH/H_2O/AcOH = 5/1/1); $[\alpha]_D^{22} = -55.5$ ($c = 0.80$ in MeOH); IR (KBr): $\tilde{\nu}_{max} = 3300$ (broad, OH and NH), 1718 (C=O), 1636, 1603, 1384, 1236 cm^{-1}; ^1H NMR (500 MHz, CD_3OD, 20 °C): $\delta = 7.73$ (d, $J = 7.4$ Hz, 2H; 3′-H and 7′-H), 7.49 (tt, $J = 7.4, 1.2$ Hz, 1H; 5′-H), 7.42 (dd, $J = 7.9, 0.8$ Hz, 1H; 13″-H), 7.40 (dd, $J = 7.4, 7.4$ Hz, 2H; 4′-H and 6′-H), 7.23 (dd, $J = 7.9, 7.9$ Hz, 1H; 12″-H), 6.95 (dd, $J = 7.9, 0.8$ Hz, 1H; 11″-H), 6.89 (s, 2H; 3″-H and 7″-H), 5.41 (ddd, $J = 8.4, 8.4, 3.6$ Hz, 1H; 4-H), 4.51 (ddd, $J = 8.8, 5.0, 3.6$ Hz, 1H; 3-H), 3.49–3.46 (m, 2H; 2-H and 7-H), 3.27–3.20 (m, 2H; 2-H′ and 7-H′), 2.27–1.95 (m, 4H; 5-H_2 and 6-H_2); ^{13}C NMR (125 MHz, CD_3OD, 20 °C): $\delta = 175.5, 171.5, 170.5, 166.3, 162.6, 154.6, 136.7, 134.9, 133.6, 133.2, 133.1, 130.1, 129.7, 128.5, 121.6, 120.0, 116.3, 109.2, 76.7, 53.4, 48.2, 47.9, 30.2, 21.4$; FAB HRMS calcd for $C_{28}H_{27}N_2O_9$ ($M + H^+$): 535.1717, found: 535.1691.

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[1] a) A. C. Newton, *Annu. Rev. Biophys. Biomol. Struct.* **1993**, *22*, 1; b) A. Farago, Y. Nishizuka, *FEBS Lett.* **1990**, *268*, 350; c) S. Stabel, P. J. Parker, *Pharmac. Ther.* **1991**, *51*, 71; d) Y. Nishizuka, *Nature* **1988**, *334*, 661; e) Y. Nishizuka, *Science* **1986**, *233*, 305; f) Y. Nishizuka, *Nature* **1984**, *308*, 693; g) Y. Nishizuka, *Science* **1992**, *258*, 607.

[2] D. Bradshaw, C. H. Hill, J. S. Nixon, S. E. Wilkinson, *Agents Actions* **1993**, *38*, 135.

[3] a) P. Kulanthaivel, Y. F. Hallock, C. Boros, S. M. Hamilton, W. P. Janzen, L. M. Ballas, C. R. Loomis, J. B. Jiang, B. Katz, J. R. Steiner, J. Clardy, *J. Am. Chem. Soc.* **1993**, *115*, 6452; b) This molecule has also been isolated from an alternative genus of fungi and termed "azepinostatin"; see: Y. Ohshima, M. Yanagisawa, A. Katoh, T. Fujii, T. Sano, S. Matsukuma, T. Furumai, M. Fujiu, K. Watanabe, K. Yokose, M. Arisawa, T. Okuda, *J. Antibiot.* **1994**, *47*, 639.

[4] K. C. Nicolaou, M. E. Bunnage, K. Koide, *J. Am. Chem. Soc.* **1994**, *116*, 8402. Balanol has also been independently prepared by two other groups; see: a) J. W. Lampe, P. F. Hughes, C. K. Biggers, S. H. Smith, H. Hu *J. Org. Chem.* **1994**, *59*, 5147; b) N. Vicker, Rhône-Poulenc Rorer (U. K.), personal communication.

[5] J. E. Baldwin, *J. Chem. Soc. Chem. Commun.* **1976**, 734.

[6] P. Garner, J. M. Park, *Org. Synth.* **1991**, *70*, 18.

[7] J. Jurczak, A. Golebiowski, *Chem. Rev.* **1989**, *89*, 149.

[8] H. C. Brown, K. S. Bhat, R. S. Randad, *J. Org. Chem.* **1989**, *54*, 1570.

[9] A. Hafner, R. O. Duthaler, R. Marti, G. Rihs, P. Rothe-Streit, F. Schwarzenbach, *J. Am. Chem. Soc.* **1992**, *114*, 2321.

[10] J. V. N. Vara Prasad, D. H. Rich, *Tetrahedron Lett.* **1990**, *31*, 1803.

[11] D. A. Evans, K. T. Chapman, E. M. Carreira, *J. Am. Chem. Soc.* **1988**, *110*, 3560.

[12] a) J. W. Labadie, D. Tueting, J. K. Stille, *J. Org. Chem.* **1983**, *48*, 4634; b) D. Milstein, J. K. Stille, *J. Org. Chem.* **1979** *44*, 1613.

[13] The oxazoline was readily prepared from 3-benzyloxybenzoic acid under conditions reported for a related substrate; see: M. V. Sargent, A. B. Zwicky, *J. Chem. Soc. Perkin Trans. 1* **1990**, 1713.

[14] For a recent review of oxazoline chemistry see: T. G. Gant, A. I. Meyers, *Tetrahedron* **1994**, *50*,2297.

[15] For an analogous metallation–substitution sequence see ref. [13].

[16] K. J. Edgar, C. K. Bradsher, *J. Org. Chem.* **1982**, *47*, 1585.

[17] An analogous reaction has previously been reported; see: S. Horne, R. Rodrigo, *J. Chem. Soc. Chem. Commun.* **1992**, 164.

[18] W. E. Parham, Y. A. Sayed, *J. Org. Chem.* **1974**, *39*, 2053.

[19] D. L. Comins, J. D. Brown, *J. Org. Chem.* **1989**, *54*, 3730.

[20] H. Moorlag, A. I. Meyers, *Tetrahedron Lett.* **1993**, *34*, 6993.

[21] O. Mitsunobu, *Synthesis* **1981**, 1.

[22] W. P. Griffith, S. V. Ley, *Aldrichimica Acta* **1990**, *23*, 13.

[23] B. S. Bal, W. E. Childers, H. W. Pinnick, *Tetrahedron* **1981**, *37*, 2091.

[24] T. Mukaiyama, *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 707.

[25] THF was initially employed as the solvent for hydrogenation; however, this also led to the generation of an impurity identified as the balanol *N*-$(CH_2)_4OH$ derivative (resulting from attack of the free hexahydroazepine nitrogen atom onto THF). We are grateful to Dr. Nigel Vicker of Rhône-Poulenc Rorer (U. K.) for helpful discussions regarding this issue.

[26] An authentic sample of balanol was kindly provided by Nippon Roche K. K.

[27] K. Koide, M. E. Bunnage, L. Gomez Paloma, J. R. Kanter, S. S. Taylor, L. L. Brunton, K. C. Nicolaou, *Chem. Biol.* **1995**, in press.

[28] For the recent total synthesis of staurosporine and leading references, see: J. T. Link, S. Raghavan, S. J. Danishefsky, *J. Am. Chem. Soc.* **1995**, *117*, 552.

0947-6539/95/0107-0466 $ 30.00+.25/0